**THE SYNTHESIS OF CERTAIN PYRIDINE
DERIVATIVES OF BARBITURIC ACID**

by

Carl Sellner Kuhn, Jr.

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The advent of substituted barbituric acids among the organic medicaments followed the synthesis of veronal by E. Fischer and A. Dilthey in 1903.¹ They condensed diethyl ethyl malonate with urea in the presence of sodium ethylate in absolute alcohol at a temperature of 105-108° by employing an autoclave as the reaction vessel. This remains the most generally used synthesis of barbituric acid derivatives.

E. Fischer and v. Mering were the first to recognize these compounds as valuable hypnotics,² and since the discovery of veronal hundreds of barbituric acid derivatives have been prepared in an effort to find a safe but effective drug. It is curious to note that some of the closest approximations to the ideal hypnotic are found among these substituted barbituric acids prepared more than thirty years ago.³

The nucleus of these compounds, barbituric acid, has been synthesized in various ways. Baeyer⁴ prepared it from alloxan. Grimaux⁵ employed a method which is more generally applicable to the preparation of the acyl ureas, -- heating a mixture of the dicarboxylic acid, urea, and phosphorous oxychloride. However, the best procedure is the one worked out by Fischer and Dilthey as mentioned above.

It has been found that the hypnotic action of the

barbituric acid derivatives is most appreciably effected by altering the substitutions in the (5) position. Thus, the most common derivatives have groups on that carbon atom. Only this type of derivative will be considered in this paper.

The method of Fischer and Diltney makes necessary the preparation of substituted malonic esters to be used in the condensation with urea. Probably the most complete work on the simple alkyl derivatives of ethyl malonate is that of M. Conrad and C. A. Bischoff. They prepared the following ethyl malonates: isopropyl, ethyl-methyl, isobutyl, dioctyl, allyl, and benzyl-methyl. Together with the work of Fischer and Diltney this represents most of the fundamental research on the malonyl ureas.

As previously pointed out, the methods available for the synthesis of the barbituric acid nucleus are limited in number and application. On the other hand, there are at least six important methods for introducing groups into the (5) position. Obviously, any method which permits preparation of the substituted ethyl malonates may be considered as an intermediate stage in the synthesis of the (5) substituted barbituric acids. The other possible methods would then come under the heading of direct introduction of groups into the barbituric acid nucleus.

The indirect methods for placing groups on the (5) carbon atom of the barbituric acid nucleus are:

I. Addition of alkyl, aryl, or acyl halides to the sodium enolate of malonic esters, with subsequent condensation of the substituted malonic esters with urea.

II. Condensation of aldehydes with malonic acid or ester to give unsaturated compounds of the type $R'CH: C(CO_2R)_2$; cf. Riedel,¹ Knövenagel,² and Claisen.³ These may be reduced to the saturated derivatives if necessary. The resulting compounds are then condensed with urea. There are many variations to this type of synthesis which are beyond the scope of this paper; however, one of the more ingenious methods certainly deserves mention.

H. Ojiyama, Y. Hasegawa, and H. Matsumura¹⁰ used the following procedure: An aromatic aldehyde was condensed with the sodium salt of α -cyano acetic acid in the presence of alkali giving an acrylic acid derivative. This was reduced with 2% sodium-amalgam in water to the propionic acid derivative, and then by alkaline saponification converted to the malonic acid. By esterification of this acid and addition of an ethyl group, and finally by condensing the resulting ester with urea, the barbituric acid derivative was obtained.

III. Heating of compounds of the type $R'CH(COOR)(CO_2COOR)$ to give the corresponding ethyl malonate derivative $R'CH(CO_2R)_2$ which is condensed with urea in the usual manner. This type of synthesis ordinarily has the ester $R'CH_2COOR$

as the starting compound. The condensation with an ester of oxalic acid is the next step. Such a method is particularly useful in the preparation of malonic esters having an aromatic nucleus attached directly to the methylene carbon atom.

Rising and Stieglitz¹¹ were the first to use this method for the preparation of Luminal. Their synthesis follows:

The direct methods for introducing groups into the (5) position of the barbituric acid nucleus are:

I. Treating the silver salt of barbituric acid with an active alkyl, aryl, or acyl halide. It has been shown by

L. T. Thorne that the two hydrogen atoms in the (5) position are replaced by silver when barbituric acid is treated with the theoretical amount of silver nitrate. The method is limited in application, since only symmetrical disubstituted derivatives can be prepared. The action of the alkyl iodides on the silver salt is the only reaction that has been given much attention.

II. Condensing a barbituric acid having active hydrogen atoms in the (5) position with an aldehyde.¹³ This method is analogous to the condensation of an aldehyde with malonic acid or malonic ester as previously discussed. The resulting derivative has one group attached by an unsaturated linkage and, if desired, may be reduced to the saturated structure.¹⁰ This type of synthesis has been used to prepare furane derivatives of barbituric acid.

III. Treating 5-bromo barbituric acid with various organic bases. This method usually employs primary and secondary amines. The procedure for preparing piperidine derivatives of barbituric acid has been patented by the Chemische Fabrik von Heyden A. G.¹⁴

IV. Treating barbituric acid or its derivatives having one or two active hydrogen atoms in the (5) position with an active organic halide. This method is not usually resorted to when the same result may be obtained with the substituted malonic ester. However, a very recent patent obtained by the

Chemische Fabrik von Heyden A. G.¹⁵ makes use of this procedure in preparing pyridine derivatives of barbituric acid. The fact that experiments in our laboratory failed to show a reaction of ethyl ethyl malonate with α -bromo pyridine may explain why the above synthesis was developed.

The physical and chemical properties of barbituric acid and its many derivatives can be discussed only very briefly here, and the topic shall be considered mainly from the standpoint of barbituric acid itself.

Barbituric acid is a very strong organic acid, having a dissociation constant of 0.0105 at 25°C. Its strong acidity comes from the enolization of the methylene hydrogens to the adjacent carbonyl oxygen atoms. When these hydrogen atoms are replaced by alkyl groups as in 5-ethyl barbituric acid and 5,5-diethyl barbituric acid, the dissociation constant is considerably lowered, being 0.00383 and 0.0000073 respectively.¹⁶

Nearly all of the barbituric acids are white crystalline solids of high melting point, and are practically insoluble in cold water. They act as monobasic acids to form salts with the alkali metal hydroxides even when both methylene hydrogen atoms are replaced by unreactive groups. Obviously, this can be explained by the properties of the amide linkage. The two nitrogen atoms, however, cannot be equivalent since only the mono-sodium salt can be prepared.

Holle and Linaire¹⁷ fused these disubstituted barbituric acids with potassium hydroxide and obtained both ammonia and hydrogen cyanide as products. Marotta and Rosanova¹⁸ treated veronal with diazomethane and obtained two products. One of these was a crystalline solid identical with the product of the condensation of diethyl ethyl malonate with methyl urea, and the other was undoubtedly the methyl ether. The two are represented

These results can be interpreted to show that the sodium salt is probably formed from an active hydrogen in the (2) position by enolization from either the (1) or (2) positions. Such a configuration would be analogous to the methyl ether, making one nitrogen atom secondary and the other tertiary in nature.

Simple hydrolysis of the barbituric acids gives substituted malonic acids, ammonia, and carbon dioxide. Phosphorous oxychloride at 130-140°C gives 2,4,6-trichloro pyrimidine with barbituric acid. This compound reacts with an alcoholic solution of ammonia to give first (at 160°) the

2,4-diamino derivative, and finally (at 200°) the 2,4,6-triamino pyrimidine.¹⁹ Electrolytic reduction forms trimethylene urea and hydro uracil.²⁰ Oxidation with potassium permanganate gives hydric acid ($C_6H_5O_6N_4$).²¹

The use of the substituted barbituric acids as hypnotics was followed by their administration with various other drugs which enhanced their effectiveness. The analgesics and anti-pyretics are most commonly used for this purpose. Since practically all of these drugs are basic, such as the alkaloids and other heterocyclic nitrogen compounds, they will form very definite "molecular compounds" with the acidic barbituric acid derivatives. These are usually prepared by melting the two components together in the correct proportions as determined by mixed melting point curves. Barbituric acid compounds with pyrimidine²², pyrimidone²³, pyrazolone²⁴, morphine²⁵, sparteine²⁶, etc. have been prepared. One of the most important drugs of this type is described in a patent by F. Hoffmann-LaRoche and Co.²⁷ Its name is ALLONAL (Allional), and is prepared by melting together equimolecular portions of 5-allyl 5-isopropyl barbituric acid and 4-dimethylamino 1-phenyl 2,3-dimethyl 5-pyrazolone (pyrimidone). It is a definite compound, having a melting point of 92-93°C.

The success of these "molecular compounds" as drugs depends upon the correct ratio of the two substituents.

Many have been prepared whose hypnotic properties are no better than the barbituric acid derivatives they contain, while the analgesic or antipyretic action is increased. These compounds furnish a rather convenient method for preparing a homogeneous product.

The introduction of a heterocyclic residue in the (5) position presents a more difficult problem, since the active halides and the aldehydes of this group of compounds are limited in number and application. A review of the literature on (5) substituted barbituric acids shows that only eight different heterocyclic rings have been introduced, namely:

I. Pyrazole

5-(4-antipyrilimine) barbituric acid²⁹

5-(2,5-dihydro 5-keto 2,4-dimethyl 1-phenyl 3-pyrazolyl methyl) 5-ethyl barbituric acid²⁹

5-[p-(2,5-dihydro 5-keto 2,3-dimethyl 1-pyrazolyl) benzyl] 5-ethyl barbituric acid³⁰

II. Imidazole

5-(4-imidazole methyl) 5-n-butyl barbituric acid³¹

5-(4-imidazole methyl) 5-isocanyl barbituric acid³¹

III. Piperidine

5-(1-piperidyl) 5-ethyl 1-methyl barbituric acid¹⁴

5-(1-piperidyl) 5-ethyl barbituric acid¹⁴

5-(1-piperidyl) 1,3,5-trimethyl barbituric acid¹⁴

IV. Pyridine

5-(γ -pyridyl) 5-ethyl barbituric acid¹⁵

5-(η -pyridyl) 5-ethyl 1-methyl barbituric acid¹⁵

5-($\eta\eta$ -nitropyridyl) 5-ethyl barbituric acid¹⁵

V. Indole

5-(β -indolyl) 1,3-dimethyl barbituric acid¹³

VI. Thiazole

5-(2-methyl thiazole 4-methyl) 5-ethyl barbituric acid³²

5-(2-phenyl thiazole 4-methyl) 5-ethyl barbituric acid³²

VII. Tetrahydro-furane

5-(tetrahydro 2-furyl methyl) 5-ethyl barbituric acid³³

VIII. Furane

5-(α -furfuryl) barbituric acid³⁴

5-(α -furfuryl) 5-ethyl barbituric acid³⁴

The following aldehyde derivatives of furane have been condensed with 1,3-dimethyl barbituric acid:¹³

furfural

methyl furfural

hydroxy-methyl furfural

furylacrylaldehyde

ethoxy-methyl furfural

The condensation of 5-(hydroxy-methyl) 2-furaldehyde

with barbituric acid has also been carried out, giving

5-5'-[(oxydimethylene) di-2-fural] bis-barbituric acid.³⁵

Our laboratory has succeeded in adding four more barbituric acids to this list, all containing the pyridine nucleus. The attempts at preparing pyridine substituted barbituric acids by treating the sodium enolate of ethyl ethyl malonate with α -bromo pyridine³⁶ proved the stability of this halide to such a reaction. The Friedel-Craft's³⁷ and Ladenburg syntheses³⁸ were then tried, using bromo ethyl ethyl malonate³⁹ and pyridine in the presence of various catalysts. The decomposition of the bromo ethyl ethyl malonate at moderate temperatures and in the presence of catalysts prevented the success of this method.

It was found recently (1935)⁴⁰ that the pyridine nucleus could be substituted directly into the (5) position by treating barbituric acid or its derivatives with a halopyridine. Since the experimental work was covered in a French patent which was not available, no details of the procedure could be learned. It is possible that this unusual type of synthesis was resorted to after it was found that the halopyridines would not react with the sodium enolate of malonic ester.

After our failure to introduce the pyridine nucleus adjacent to the methylene carbon atom in ethyl malonate, it was decided to employ a more active halide in the form of β -picolyl bromide. From this compound it was possible to prepare four new barbituric acids. The instability of the

bromide was the only troublesome factor in the syntheses.

The β -picoline required for the preparation of the β -picolyl bromide was made by the method of P. Schwarz⁴⁰, and gives a product free from the α and γ isomers. Dry glycerine, ammonium phosphate, and phosphorous pentoxide are heated for fifty hours under reflux. The reaction is a curious one, taking place in several steps. The glycerol is first converted to acrolein in the presence of the phosphorous pentoxide. Two molecules of this aldehyde then condense with the ammonia furnished by the ammonium phosphate to give pure β -picoline. This condensation may be represented:

The halogenation of side chains in the alkyl pyridines has been given very little attention. The only reference found on this problem apparently represents all the work. The lack of investigation of the pyridine alkyl halides undoubtedly accounts for the very few derivatives of pyridine having functional groups on side chains. E. Dehn⁴¹ prepared β -picolyl bromide by dissolving β -picoline in concentrated hydrochloric acid and heating with two mole

of bromine at 150° in a sealed tube for ten hours. He describes the resulting material as a clear ruby-red liquid, which is exactly as noted in our work. The isolation of the bromide from the acid solution must necessarily be rapid and efficient as the compound is unstable even in the ether solution. Dehnelt made no attempt to examine the pure bromide as to physical properties or reaction, but converted it immediately to the picrate (m.pt. 114°). The instability of the pure bromide is marked, it probably condensing with itself to give a high molecular weight pyridinium compound. The ether solution is originally light yellow in color, but gradually turns a deep red and precipitates a heavy tar which will not redissolve. The difficulties in drying and handling the ether solution prior to treatment with the sodium enolate of a malonic ester were never satisfactorily overcome.

The % yields of the picolyl malonic esters could not be determined, since there were no means of finding the amounts of the β -picolyl bromide present in the ether solution. The esters were purified by first extracting them with dilute hydrochloric acid and then drying them in a vacuum distilling flask just below their boiling points. They were not distilled due to decomposition at their boiling points under a pressure of 2 m.m. Approximate boiling points were estimated by the action of the material in the distilling flask.

The crude esters were then condensed with urea to give the barbituric acid derivatives. The procedure was essentially that described in "An Advanced Laboratory Manual of Organic Chemistry" by M. Heidelberger (p.66).⁴²

The separation and purification of the picolyl barbituric acids required a somewhat different method than is usually employed due to their amphoteric properties. Precipitation with dilute hydrochloric acid from the aqueous solution of the sodium salt revealed an isoelectric point that differed for each derivative.

The barbituric acid derivatives having a picolyl group in the (5) position are new and should prove to have interesting physiological activities. The fact that nicotine contains the β -pyridyl residue leads one to believe this. Nicotine is an α -(β -pyridyl) N-methyl pyrrolidine.⁴³ The barbituric acids synthesized in our laboratory may be represented:

where R is ethyl, n-propyl, n-butyl, or isocamyl.

SYNTHESIS OF α -AMINO PYRIDINE

	M.W.	Mols	Gms.
Pyridine	79.06	0.653	50.0
Sodamide	39.02	1.26	50.0
Toluene	92.06	0.544	50.0
α -amino pyridine	94.06	0.653	59.5

The above reaction is commonly known as the Tschitschibabin reaction after A. E. Tschitschibabin. The mechanism is a curious one. The procedure is described in *J. Russ. Phys. Chem. Soc.*, 46, 1224 (1914);⁴⁴ but since this journal was not available, all of the experimental details were obtained from Abderhalden - "Handbuch der Biologischen Arbeitsmethoden".⁴⁵

All of the materials used in the above synthesis must be absolutely dry. The pyridine was dried over potassium hydroxide and distilled just before use. The toluene was dried with metallic sodium. A good grade of sodamide was obtained from the Eastman Kodak Company shortly before the experiments were carried out.

50 grams of the sodamide were cautiously pulverized

under dry toluene. Its marked activity with atmospheric moisture made this precaution necessary. After pulverization, it was placed together with 50 grams of dry toluene in a 1 liter round-bottom flask mounted with an efficient reflux condenser. The previously dried and distilled pyridine (50 grams) was then added. This represents 2 mols of sodamide to 1 mol of pyridine. An increase of sodamide over 2 mols has no advantage, and Tschitschibabin has shown that less than this amount lowers the yield of α -amine pyridine considerably. The mixture was shaken vigorously for a few minutes, and then heated in an oil bath at 120-130° for twelve hours. During this time a calcium chloride tube was kept in the top of the reflux condenser to exclude atmospheric moisture. The reaction proceeded very quietly for the first three hours and then became so violent that considerable quantities of material were thrown into the condenser. This vigorous period was of short duration, the reaction then progressing slowly the rest of the time.

After cooling, the resulting thick mass was treated with about 300 c.c. of water in small portions to convert the sodium salt of α -amine pyridine into the free compound and to decompose the remaining unreacted sodamide. The reactions were vigorous and therefore carried out slowly. Strong evolution of ammonia accompanied the process. The toluene

layer which separated was then removed and the aqueous layer saturated with potassium carbonate. Several extractions with ether removed all of the α -amine pyridine remaining in the aqueous layer. The toluene and ether solutions of the compound were then mixed and distilled. The lower boiling solvents were first removed carefully on the steam bath with the aid of the water pump. The remaining material was placed in a Claisen flask and the fraction boiling from 80° to 95° (2 m.m.) collected. The distillation was made difficult by the crystallization of the α -amine pyridine in the condenser. It was necessary to pass small quantities of steam into the condenser at intervals to keep the material mobile. 41.5 grams of a product melting 58-60° were obtained. This represents a yield of 70% of the theoretical. Tschitschibabin claims a maximum yield of 85%.

The α -amine pyridine is a white crystalline deliquescent compound having a peculiar fish-like odor.

SYNTHESIS OF α -BROMO PYRIDINE

	<u>M.W.</u>	<u>Mols</u>	<u>Gms.</u>
α -amine pyridine	94.06	0.212	20.0
Hydrogen bromide	80.92	0.59	47.6
Bromine	159.83	0.622	99.5
Sodium nitrite	69.01	0.53	36.6
Sodium hydroxide	40.01	1.99	80.0
α -bromo pyridine	157.95	0.212	33.5

The first satisfactory preparation of α -bromo pyridine by the diazotisation of α -amine pyridine was worked out by Tschitschibabin and Rjasanzew⁴⁶. However, their yields were not particularly good. A more complete study of the preparation of alpha-pyridyl halides from α -amine pyridine

by the diazo reaction was made by L. C. Craig,^{3c} and it was his procedure that was employed in our laboratory.

The hydrobromic acid used in the above reaction was made by the usual method, 87 c.c. of bromine, 100 c.c. of water, and 300 grams of broken ice were mixed together in a 2 liter flask, and sulfur dioxide passed into the mixture until the color changed to a light yellow. It was then distilled and the portion boiling 185-187° was collected. The yield was 480 grams of a product having a sp.gr. of 1.45 at 25°C. This corresponds to about 45% hydrobromic acid. In the article by Craig it is pointed out that the concentration of the acid does not seriously effect the yield of α -bromo pyridine, so no attempt was made to further concentrate it.

A three-necked 1 liter round bottom flask was fitted with a motor-driven stirrer, a dropping funnel, and a thermometer. 110 c.c. (0.59 mole) of the 45% hydrobromic acid were placed in the flask and 20 grams of α -amino pyridine added cautiously. The base dissolved immediately. 31.9 c.c. (0.622 mole) of bromine were then added slowly through the dropping funnel, during which time (35 minutes) the solid orange perbromide separated. The diazotization of this perbromide of α -amino pyridine was then immediately started. Sodium nitrite in aqueous solution (36.6 gms. in 60 c.c.) was added dropwise so that the temperature could not rise above 0°C. It required 45 minutes for the addition of the 60

c.c. of solution, and necessitated constant attention. As the last of the nitrite was being added a vigorous evolution of nitrogen and nitrogen dioxide took place, and the temperature increased to about 5°C. The compound was now in the form of the perbromide of α -bromo pyridine, and required treatment with alkali to liberate the free base. As a precaution against possible replacement of the alpha bromine atom, and to keep the reaction well under control, the flask was kept in the freezing mixture. 80 grams of sodium hydroxide in 200 c.c. of water were cautiously added, keeping the mixture well stirred and the temperature below 20°C. The mixture was then extracted with three 100 c.c. portions of ether and the ether solution fractionated. 14.5 c.c. (24 gms) of a product boiling 95-96° (38 m.m.) was obtained. This represents a yield of 71.8%. Craig claims a yield of 87%.

The compound is an oily liquid of characteristic pungent odor, and has a density of 1.65.

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A repetition of the above synthesis with the same molecular quantities gave a 72.1% yield of α -bromo pyridine. The same precautions were taken and the experimental details as worked out by Craig were followed implicitly.

SYNTHESIS OF ETHYL, n-PROPYL, n-BUTYL,
AND ISOMYL - ETHYL MALONATE.

The above equations represent the generally used synthesis of malonic ester derivatives as originally developed by Conrad⁶, where R is an alkyl radical and R·X is the corresponding alkyl halide. The method used in our laboratory, however, was essentially that described in "Organic Syntheses"⁴, and differs only in experimental details. The alkyl malonic esters - where R is ethyl, n-propyl, n-butyl, and isomyl - were prepared. The method was the same in every case, so it will suffice to discuss only one in detail. The following procedure was employed in the synthesis of ethyl ethyl malonate:-

Absolute ethyl alcohol was prepared by treating the commercial absolute alcohol with an excess of magnesium methyate and distilling under anhydrous conditions directly into the reaction flask. The three-necked round bottom flask was previously equipped with a motor-driven stirrer, reflux condenser and dropping funnel. The apparatus was then closed by placing a calcium chloride tube in the top of the condenser.

The theoretical amount of sodium (weighed under xylene) was dissolved slowly in the alcohol with necessary cooling of the reaction vessel during the process. After all of the sodium had reacted, the solution of sodium ethylate was cooled in ice-water to about 45° at which temperature some of the compound crystallized in long white needles. Previously dried and distilled ethyl malonate (105-107°/ 32 m.m.) was then added slowly through the dropping funnel while the mixture was vigorously stirred, allowing about 15 minutes after the addition to insure complete reaction. The ethyl iodide (72.5°) was now added through the dropping funnel over a period of one hour. After about one-third had been added the reaction proceeded vigorously, and necessitated cooling of the flask. A large amount of sodium iodide precipitated during the reaction, and a deep red color developed. The mixture was then allowed to reflux gently for two hours by heating in a water bath. At the end of this

time a neutral reaction was noted on moist litmus paper, indicating complete reaction of the sodium enolate. The alcohol was then removed on the steam bath and the mixture allowed to cool to room temperature. About twice the volume of water was added to dissolve the sodium iodide and the resulting insoluble layer removed in a separatory funnel. The aqueous solution was extracted once with ether and the ether solution added to the separated layer. This was carefully dried over anhydrous sodium sulfate and fractionated from a modified Claisen flask. The fraction 111-112° (23 m.m.) was collected after a systematic fractionation. The product was a colorless oil with a pleasant faint odor.

The following table shows the amounts of material used, the yields, and the boiling points of the four alkyl malonic esters prepared in the manner described:

	<u>Mols</u>	<u>Gms.</u>	<u>S.G.</u>	<u>Product:</u>
Ethyl iodide	0.66	105.0	53.5	Ethyl ethyl malonate
Ethyl malonate	0.60	96.0	90.5	Yield: 62 gms.
Sodium	0.60	13.8	----	55% theory
Ethyl alcohol	----	----	400.0	B.pt: 111-112° (23 m.m.)

	<u>Mols</u>	<u>Gms.</u>	<u>C.O.</u>	<u>Product:</u>
n-propyl bromide	0.37	46.0	35.0	n-propyl ethyl malonate
Ethyl malonate	0.34	54.5	54.5	Yield: 51 gms.
Sodium	0.34	7.8	----	74.3% theory
Ethyl Alcohol	----	----	95.0	B.pt: 151-155° (25 m.m.)
n-butyl bromide	0.37	50.6	39.6	n-butyl ethyl malonate
Ethyl malonate	0.34	54.5	54.5	Yield: 50.4 gms.
Sodium	0.34	7.8	----	69% theory
Ethyl alcohol	----	----	95.0	B.pt: 135-137° (25 m.m.)
isocamyl bromide	0.36	55.0	47.0	isocamyl ethyl malonate
Ethyl malonate	0.33	52.7	52.7	Yield: 55.5 gms.
Sodium	0.33	7.6	----	73.1% theory
Ethyl alcohol	----	----	95.0	B.pt: 142-145° (25 m.m.)

* * * * *

As may be seen from the above tables, an excess of the alkyl halide amounting to about 10% was used in every case. These were carefully dried over calcium chloride and distilled just before use. The fractionation of the alkyl malonic esters was carried out in a Vigreux column. The mixture of the mono- and di-ethyl derivatives of ethyl malonate were rather difficult to separate. The final product boiled 212°C (763 m.m.)

INVESTIGATION OF THE ACTION OF α -BROMO PYRIDINE
ON THE SODIUM ENOLATE OF ETHYL MALONATE

A number of experiments have shown that the more highly halogenated pyridines exhibit a marked activity toward alkalies with the displacement of at least one halogen atom. The simple mono-halogenated pyridines on the other hand show a high degree of stability toward such reagents. W. J. Sell and F. W. Deetsen⁴⁶ investigated the action of 2,3,4,5 - tetrachloro pyridine on ethyl sodiomalonate and found that the chlorine atom in the 4 position was easily replaced by the $-\text{CH}(\text{COOC}_2\text{H}_5)$ under ordinary conditions. Sell⁴⁶ also describes the replacement of the 2- and 4- chlorine atoms by methoxy groups when sodium methylate is allowed to react with the tetra-halogenated pyridine. Other alkalies, such as alcoholic or aqueous sodium hydroxide and ammonia, exhibit the same type of reaction. From these experiments one might expect the α and γ halo-pyridines to show similar reactivity, but such is not the case. However, a number of reactions have been performed on the mono-halogenated pyridines that led us to believe a replacement of the α halogen atom by $-\text{CH}(\text{COOC}_2\text{H}_5)$ could be accomplished. Markwald, Klemm, and Trebert⁴⁷ prepared the α and γ mercaptan derivatives of pyridine by heating α and γ halogen compounds with an alcoholic solution of potassium hydrosulfide

at 100° to 140°C. The methoxy derivatives were also prepared by the action of sodium methylate on the halogen derivatives at 100°. The high temperatures necessary in these experiments show the relative stability of the mono-halogenated pyridines. However, encouraged by even this moderate reactivity, we investigated the action of α -bromo pyridine on the sodium enolates of ethyl malonate and ethyl ethyl malonate under various conditions.

The α -bromo pyridine and ethyl ethyl malonate required in our experiments were freshly prepared as previously described, and were absolutely anhydrous. The ethyl alcohol was made anhydrous with magnesium methylate before each experiment.

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I.)	<u>Mols</u>	<u>Gms.</u>	<u>g. g.</u>
Ethyl ethyl malonate	0.043	7.9	7.9
Sodium	0.033	0.67	----
Ethyl alcohol	-----	-----	15.0
α -bromo pyridine	0.033	10.0	6.1

The sodium was dissolved in the absolute alcohol using a Pyrex Carius tube as the reaction vessel. After cooling this solution, the ethyl ethyl malonate was added slowly with vigorous shaking. The α -bromo pyridine was then

added. A red color developed almost immediately, but no heat of reaction could be detected. During these manipulations a calcium chloride tube was mounted in the open end of the Pyrex tube to exclude atmospheric moisture. Immediately after the introduction of the bromo pyridine the tube was sealed by pulling off the end in a gas-oxygen flame. It was then placed in an autoclave and heated at 125-130° for five hours, during which time it was impossible to observe the course of the reaction without opening the autoclave. After this period, the tube was removed and opened. No pressure had formed in the tube. A considerable amount of solid was present, which proved to be a mixture of sodium ethylate and various condensation and decomposition products of the ethyl ethyl malonate⁵². The contents were washed out with water; all of the solid dissolving and an oil layer separating to the bottom. The resulting mixture was treated with 10% sulfuric acid to remove all the basic pyridine compounds. The ethyl ethyl malonate was insoluble and was extracted with ether. The acid solution was then carefully neutralized with 20% sodium carbonate solution and saturated with sodium sulfate to "salt out" the free pyridine compounds. These were then extracted with ether and the ether solution dried and fractionated. Only a trace of unreacted α -bromo pyridine was recovered here, so the other ether extraction (from acid solution) was inves-

tigated in the same manner. Fractionation recovered the remainder of the bromo pyridine, and about three-fourths of the ethyl ethyl malonate, indicating that there was no reaction between the two compounds.

Since the extraction of the pyridine compounds with 10% sulfuric acid was unsuccessful, it was decided to use a 15% hydrochloric acid solution on the same mixture to test its "extractive power". In this case a nearly quantitative extraction of the α -bromo pyridine was obtained. The difficulty in forming pyridine sulfates in dilute acid solution when one or both alpha positions are occupied is marked.

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II.)	<u>Mols</u>	<u>Gms.</u>	<u>S.S.</u>
α -bromo pyridine	0.063	10.0	6.1
Ethyl ethyl malonate	0.0635	12.0	12.0
Sodium	0.063	1.5	-----

As before, a pyrex tube was used as the reaction vessel. The ethyl ethyl malonate was placed in the tube and the sodium added in small pieces. The reaction was very slow and the process required several hours with occasional heating on the steam bath to prevent the entire mass from solidifying. Excessive heating had to be avoided because of the tendency of the malonic ester to decompose or condense with

itself under such conditions. After the last bit of sodium had reacted the tube was sealed and placed in the autoclave, where it was heated at 125-130° for six and one-half hours. A red viscous material remained at the end of this time. Some solid was also present. The contents were removed from the tube by washing with water. The resulting mixture was acidified with hydrochloric acid (corresponding to about a 15% solution), and shaken vigorously. Extraction with ether removed all acidic and neutral organic compounds. The aqueous layer was neutralized with dilute sodium hydroxide and extracted with ether, thus removing all basic organic compounds. In both extractions with ether, any water soluble constituents remained in the aqueous layer in small amounts. This necessitated the investigation of the aqueous layer, especially after the failure to detect any pyridyl ethyl malonic ester in the ether solutions.

The material extracted from acid solution contained about 8 grams of unchanged ethyl ethyl malonate and a small amount of a white crystalline solid, which appeared in the distillate when the temperature of distillation reached about 109° (25 m.m.). The ethyl ethyl malonate was collected over a small range (108-110°/25 m.m.). The solid was filtered off (few milligrams) and investigated. It was very soluble in water and gave an acid reaction to moist litmus. It melted with decomposition at 197°(uncorr.), and burned without a residue on platinum foil. The fact that the material was

soluble in water led us to believe that more could be obtained for further investigation from the aqueous solution. However, no success was met with when this was attempted. The last of the material was used in an attempt to prepare a silver salt for analysis.

The other extractions from neutral (and alkaline) solution recovered about seven grams of the unreacted bromo pyridine as shown by distillation. A few milligrams of tar remained in the flask and was not investigated.

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III.)	Mols	Gms.	Ref.
α -bromo pyridine	0.095	15.0	9.1
Ethyl malonate	0.090	14.4	13.6
Sodium	0.090	2.1	----
Ethyl alcohol	-----	----	19.0

The failure to obtain the pyridyl malonic ester with or without ethyl alcohol as a solvent at 125-130° seemed to indicate that the conditions were unsatisfactory. To be certain that the reaction would not proceed under the usual conditions of a malonic ester synthesis, the materials were mixed as previously described (page 28) in a 200 c.c. round bottom flask mounted with a reflux condenser and calcium chloride tube, and heated for 15 hours

in an oil bath at 100-105°C. The material turned a deep red and some solid precipitated, which proved to be mainly sodium ethylate. The contents were cooled to room temperature and treated with 50 c.c. of water. All of the solid material dissolved and considerable heat was evolved from the reaction with sodium ethylate. This mixture was then worked up from acid and alkaline solutions in a manner described in the other experiments. Distillation of the material extracted from alkaline solution recovered the greater part of the α -bromo pyridine. No pyridyl malonic ester or other basic pyridine derivatives could be detected. Distillation of the ether extraction from acid solution gave as the main product the unchanged ethyl malonate. About one-half gram of a red viscous tar remained in the flask even when the temperature of the oil bath was raised to 200° (33 m.m.) This was removed with absolute alcohol and treated with urea and sodium ethylate in a sealed tube.

	Mole	Gms.	C.C.
Product (red tar)	0.0081	0.5	?
Sodium	0.0081	0.05	----
Urea	0.0081	0.15	----
Ethyl alcohol	-----	----	10.0

The above mixture was heated in the tube at 115° for 5 hours. When opened, a small pressure was detected

together with a faint odor of ammonia. The contents were washed out with water and the aqueous solution carefully neutralized with dilute hydrochloric acid. An emulsion of the original tar with water was formed, and a small amount of a red amorphous solid precipitated. All attempts to crystallize the solid met with failure, a highly discolored amorphous compound being the product in every case. A melting point showed decomposition at about 810°C . The obvious impurity of the sample made an analysis useless.

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IV.)	Mols	Gms.	gms.
α -bromo pyridine	0.048	7.5	4.6
Ethyl malonate	0.10	14.0	15.1
Sodium	0.10	2.3	----
Ethyl alcohol	----	----	20.0

In this attempt, two mols of the sodium enolate were used for one mol of α -bromo pyridine. The materials were introduced into the Pyrex tube as described in the previous experiments and the mixture heated in an electric oven at 165° for 4 hours. At the end of this time a solid orange mass remained in the tube and considerable pressure had developed. The evolved gas had a peculiar hydrocarbon-like odor and was probably a decomposition product of ethyl

malonate. Upon treatment with water, the mass dissolved with some evolution of heat and an alkaline oil layer separated. The mixture was treated with dilute hydrochloric acid as before and extracted with ether. The aqueous layer was then neutralized with dilute sodium hydroxide and the solution extracted. The first ether solution obtained was distilled and found to contain about 10 grams of unchanged ethyl malonate and a lower boiling constituent (77-85°/51-52 m.m.) which was probably some decomposition product. The ether extraction from alkaline solution recovered practically all of the α -bromo pyridine. It was contaminated with some impurity that discolored the distillate.

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From the experiments just described it will be noted that the conditions were altered each time, none being satisfactory for the addition of the bromo pyridine to the sodium enolate. An excess of the halide and of the ethyl malonate were employed without success. Temperatures as high as 165° were apparently not conducive to the desired reaction, but led to decomposition of the ethyl malonate. A similar decomposition occurred when the reaction was attempted without ethyl alcohol as a solvent. It is

probable that a combination of inherent difficulties in the method prevent the application of necessarily vigorous conditions of reaction to fairly inactive halides. It is for this reason that several other methods of synthesis have been developed. The synthesis of Luminal (page 4) is a good example of such a method. In our case, however, none of these could be applied, since the desired starting materials are unknown.

INVESTIGATION OF THE FRIEDEL-CRAFTS' REACTION ON PYRIDINE

In order to test the possibility of preparing the pyridyl ethyl malonate by the action of bromo ethyl malonate on pyridine in the presence of anhydrous aluminum chloride, a preliminary investigation of the Friedel-Crafts' reaction on pyridine with chloroacetic acid was made. No mention of this type reaction could be found in the literature, so the usual conditions of reaction with the aromatics were followed.⁵³ Two runs were made, one with carbon disulfide as the solvent, and one with nitrobenzene.

I. Solvent: carbon disulfide

	<u>Mols</u>	<u>Gms.</u>	<u>S.G.</u>
pyridine	0.5	39.5	39.9
chloroacetic acid	0.5	47.3	----
aluminum chloride	0.5	66.7	----

150 c.c. of freshly dried and distilled (46-47°) carbon disulfide was introduced into a 1 liter round-bottom flask. The chloroacetic acid, which had previously been dried over concentrated sulfuric acid in a vacuum, was then added. About 40 c.c. of dry pyridine was then slowly added. The reaction to the pyridinium salt proceeded with evolution of heat. A special grade (Schuchart) of anhydrous aluminum chloride was then carefully introduced. The entire

mass was now in solid form. It should be mentioned here that pyridine is capable of forming amine salts with any of the reactants, and probably assumed the most stable configuration. No reaction with evolution of hydrogen chloride could be detected even after the contents of the flask were heated on a water bath (50°) for one hour. In fact, no noticeable change had taken place. It was suspected that any hydrogen chloride formed in the reaction was combined as the hydrochloride of pyridine or pyridine acetic acid, so the mixture was investigated. It was first emptied into a beaker of ice and water to decompose the aluminum chloride and its salts with pyridine. Considerable heat was evolved in the process. A yellow oil layer separated, which was removed and distilled. It proved to be mainly carbon disulfide containing a trace of chloroacetic acid. The aqueous layer was distinctly acid, and was carefully neutralized with dilute sodium hydroxide so that no aluminum hydroxide precipitated. Extraction with ether gave a small amount of pyridine. The solution was then made distinctly alkaline with concentrated (40%) sodium hydroxide and again extracted with ether. This recovered practically all of the unreacted pyridine. Some time was spent in trying to find an isoelectric point at which some of the pyridine acetic acid might precipitate or be extracted, without success. Evaporation of small amounts of the neu-

tral solution to dryness and extraction of the residue with ether was also tried. No pyridine acetic acid or its betaine could be detected.

II. Solvent: nitrobenzene

The experiment was repeated in nitrobenzene with the same molecular quantities of material. In this case the pyridine was introduced into the solvent first, and the aluminum chloride added. Some heat was evolved in the reaction to form the complex salt with pyridine. The chloroacetic acid was then added in small quantities, but no reaction could be detected. Again the mixture turned to a pasty mass. It was heated in an oil bath at 200° for one hour, during which time no hydrogen chloride was evolved. The resulting mass was worked up as before without success.

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These preliminary experiments on the Friedel-Crafts' reaction confirmed our belief that in the case of pyridine it could not be satisfactorily carried out using the same conditions as for the aromatics. Thus, the plan to prepare the pyridyl ethyl malonate by this reaction had to be discarded.

SYNTHESIS OF BROMO ETHYL ETHYL MALONATE

	<u>Mols</u>	<u>Gms.</u>	<u>G.c.</u>
Ethyl ethyl malonate	0.115	21.3	21.2
Bromine	0.120	19.8	6.2
Carbon tetrachloride	-----	----	150.0

The method is described in "Organic Syntheses"²² for bromo ethyl malonate. 150 c.c. of carbon tetrachloride were placed in a 500 c.c. three-necked flask mounted with a reflux condenser, motor-driven stirrer, and dropping funnel. The ethyl ethyl malonate was then introduced. The bromine was added slowly through the dropping funnel while the mixture was stirred vigorously. The reaction proceeded rapidly as evidenced by the immediate decolorization of the bromine and the strong evolution of hydrogen bromide. The addition required about one hour. To complete the reaction, the mixture was heated at 90° (water bath) for an additional hour. Most of the dissolved hydrogen bromide was driven off in

this time. The contents of the flask were cooled and washed thoroughly with a 5% sodium carbonate solution to remove the last traces of unreacted bromine and the hydrogen bromide. The insoluble carbon tetrachloride layer was removed, dried over anhydrous sodium sulfate, and distilled. The first fraction distilled 132-137°/32 m.m., and contained some bromo ethyl malonate and ethyl ethyl malonate. The second fraction distilled 137-144°/32 m.m., and was mainly the bromo ethyl ethyl malonate. This was redistilled, and 21.0 grams of a product boiling 133-141°/32 m.m. was collected. The yield was 69.9% of the theoretical. The product was a colorless heavy oil with a faint disagreeable odor.

INVESTIGATION OF LADENBURG'S REARRANGEMENT METHOD
FOR THE SYNTHESIS OF
THE PYRIDYL ETHYL ETHYL MALONATE

A. E. Tschitschibabin and R. F. Rumschin³⁰ describe the preparation of α - and γ -benzyl pyridines by a modified Ladenburg method. They obtained good yields by using a little powdered copper or cuprous chloride as the catalyst in the reaction of benzyl chloride with pyridine at 265-275°C. This same type of procedure was tried with bromo ethyl ethyl malonate on pyridine.

	<u>Mols</u>	<u>Gms.</u>	<u>G. G.</u>
Bromo ethyl ethyl malonate	0.02	3.4	3.5
Pyridine	0.026	2.1	2.2
Copper powder	-----	0.1	---

The above mixture was heated in a 60 c.c. flask mounted with a reflux condenser. When the temperature of the oil bath reached about 150° the contents partially solidified and no refluxing was noted in the condenser from that point on. The temperature was gradually raised to 210° over a period of three hours, and was not carried higher due to decomposition. After cooling, the mass was treated with 80% sodium hydroxide and extracted with ether. About one-half of the pyridine was recovered together with

a trace of a black tar that was not further investigated. No pyridyl ethyl ethyl malonate was present, and none of the bromo ethyl ethyl malonate could be recovered.

The same procedure was carried out using cuprous chloride as the catalyst on the same molecular quantities of material. Again, much decomposition was noted and no pyridyl malonic ester was obtained from the resulting black tarry mass.

As was expected, the method is limited in application, since the halide employed must necessarily form a stable addition product with pyridine that will rearrange to the α or γ positions without decomposing. The bromo ethyl ethyl malonate did not meet these requirements. It is relatively unstable in the presence of alkalis at a high temperature, and decomposed far below the necessary rearrangement temperature (265-275°).

SYNTHESIS OF β -PICOLINE
(3-methyl pyridine)

	<u>Mols</u>	<u>Gms.</u>
Glycerol	3.40	313
Phosphorous pentoxide	1.76	250
Di-ammonium phosphate	1.09	125
β -picoline	1.70	158

The above synthesis of pure β -picoline was developed by P. Schwarz⁴⁰ and the experimental details were obtained from Vanino's - "Präparative Chemie".⁵⁴ The mechanism is a curious one and was previously discussed in the Introduction (page 12). The product is free from the other isomers by virtue of the one possible condensation of acrolein and ammonia to give a pyridine ring.

250 grams of phosphorous pentoxide were placed in a carefully dried 5 liter round bottom flask. A layer of 125 grams of dry di-ammonium phosphate was then added. The glycerol, which had previously been dried by heating at 150°, was carefully introduced through a large funnel. Before the

flask could be attached to the reflux condenser, a vigorous reaction began. The entire mass turned black, and yellow vapors (acrolein) were evolved. After the flask was mounted with the condenser, it was placed in a large sand bath where the mixture was heated for about 50 hours. The initial reaction (dehydration of glycerol to acrolein) had to be carefully controlled. The black tarry mass swelled to more than twice its original volume due to the quantities of gas evolved. The flame had to be repeatedly removed to allow the mass to subside. After about three hours, the reaction proceeded mildly and required little or no attention for the remainder of the heating process. It was noticed after about 10 hours that some water vapor had collected in the condenser. After the 50 hours of heating, the contents of the flask were reduced to about one-half their original volume, a black viscous material remaining.

The mass was allowed to cool to room temperature and then carefully made alkaline with 250 c.c. of previously cooled 50% sodium hydroxide solution. The neutralization reaction was a vigorous one and the precaution of adding the alkali through the condenser had to be observed. During the process large amounts of the sodium phosphates precipitated, but redissolved when the mixture was heated. The hot alkaline solution was then steam distilled from the same flask. The first 300 c.c. of distillate contained prac-

tically all of the β -picoline, but the distillation was continued until over a liter of distillate had been collected. This was saturated with solid sodium hydride, being careful to cool the solution during the process. The β -picoline separated from the aqueous alkaline solution and was removed in a separatory funnel. It was dried over solid potassium hydroxide and used without further purification. The crude product was a red-brown liquid with a characteristic fish-like odor. The yield was 16 grams, or about 10% of the theoretical.

The same synthesis was repeated twice, with yields of 12.7% and 13.6%. The literature reported a maximum yield of 20%.

SYNTHESIS OF β -PICOLYL BROMIDE

Investigation of the literature for a simple active halide containing the pyridine nucleus revealed only one such compound - β -picolyl bromide. The synthesis of this compound by E. Dehn¹ represents the only published work on a pyridine alkyl halide. He did not isolate the free bromide because of its marked instability, and attempted no reaction with it other than the preparation of the picrate. However, he did hydrolyse this picrate to the corresponding picrate of β -pyridyl carbinol. He describes the β -picolyl bromide in ether solution as being highly unstable and as having pronounced lachrimatory properties.

It was decided to study the action of this halide on the sodium enolate of various malonic esters as the first

step in the synthesis of 5-(β -picolyl) 5-alkyl barbituric acids. The preparation of β -picolyl bromide follows:

7 grams (8.2 c.c.) of the β -picoline were placed in a Pyrex tube and treated with 6.0 c.c. of 12 N hydrochloric acid to form the hydrochloride. 7.7 c.c. of bromine were then added dropwise through a long-stemmed funnel. Two layers appeared in the tube, a light yellow aqueous layer on top of a deep red bromine layer. The tube was then sealed and heated in an electric oven at 150° for 10 hours. After this time the tube was allowed to cool and the end very carefully extended just outside the iron pipe acting as the container. A non-luminous flame was then cautiously touched to the sealed point, causing the tube to open with explosive violence. Large quantities of hydrogen bromide issued through the small opening with a hissing noise for several seconds.* The resulting solution was homogeneous and of a deep ruby red color. It was removed by washing the tube with a small quantity of water. A red oil separated to the bottom. 50 c.c. of alcohol-free ether were then added to take up this material. The whole was then decolorized (to a light orange color) by passing in sulfur dioxide for a few minutes. 25 grams of sodium carbonate were slowly added to this mixture to liberate the bromide from the acid solution. The effervescence of carbon dioxide through the ether layer was somewhat troublesome as it caused considerable frothing. When the neutral

point was approached the evolution of gas subsided and the bromide began separating into the ether layer, which was finally removed in a separatory funnel. The aqueous layer was extracted with a small quantity of ether. The two ether solutions (about 75 c.c.) were mixed and thoroughly dried over anhydrous magnesium sulfate. During the transference of this solution from the separatory funnel and during the filtration from the magnesium sulfate some evaporation could not be avoided. The oil which remained from this evaporation was at first light yellow, but rapidly changed to a brown tar that would not redissolve in ether. Thus, the handling of the ether solutions of β -picolyl bromide presented a problem which was never satisfactorily overcome. Needless to say, it was essential that the compound be prepared immediately before use in each of the following reactions with the malonic esters. Its properties corresponded to those described by Dehnal. The yields were poor, and could not be determined due to its instability out of ether solution.

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* NOTE: The first two attempts at bromination of β -picoline met with failure. An explosion of the Pyrex tube destroyed the initial run, and in the second case the opening of the tube was followed by a spray of liquid along with the hydrobromic acid, causing loss of the material.

SYNTHESIS OF β -PICOLYL ETHYL ETHYL MALONATE

	<u>Mols</u>	<u>Gms.</u>	<u>C.C.</u>
β -picolyl bromide *	0.07	6.8	?
Ethyl ethyl malonate	0.07	13.2	13.2
Sodium	0.07	1.6	----
Alcohol	----	----	22.0

The method employed in this synthesis was essentially that used in the preparation of the mono-alkyl malonic esters. A 500 c.c. two-necked round bottom flask was fitted with an ice cooled condenser. Into this was placed about 22 c.c. of absolute alcohol, which had previously been made anhydrous with magnesium methyate and kept in sealed ampoules for this purpose. (The method allowed storage of small amounts of absolute alcohol for an indefinite length of time). The sodium (1.6 grams) was then dissolved slowly in the alcohol and the resulting sodium ethylate solution cooled to about 50°, 13.2 grams of dry ethyl ethyl malonate were then added dropwise through the side neck of the flask. Heating was then started

on the steam bath. The β -picolyl bromide, which had been prepared shortly before the above operations, was being kept over anhydrous magnesium sulfate in ether solution. The procedure to this point required about one-half hour. The ether solution of the bromide was now added as rapidly as possible to the sodium enolate solution. Most of the ether was volatilized through the neck of the flask during the addition. In a few minutes a large amount of sodium bromide precipitated, indicating a reaction involving the sodium enolate. At the end of an hour the remainder of the ether and the alcohol were distilled off. The mixture was allowed to cool and then treated with 50 c.c. of 15% hydrochloric acid. The sodium bromide dissolved and an oil separated which was extracted with ether. The aqueous acid layer was made definitely alkaline with 20% sodium hydroxide, and the resulting basic compounds of pyridine extracted with ether. The ether solution was dried over anhydrous magnesium sulfate and distilled. About 1.5 grams of a red viscous oil remained, and would not distill at 150° under a pressure of 2 m.m.. It apparently boiled when the temperature of the bath reached 145°, but due to the small amount of material and the obvious decomposition taking place, no attempt was made to distill the compound. The heating served to thoroughly dry the oil. It was removed from the flask with absolute alcohol for the condensation with urea to the cor-

responding barbituric acid. These were crystalline high-melting solids and proved to be excellent derivatives for each of the malonic esters prepared. The fact that the procedure was necessarily carried out on a small scale made the saving of every milligram of the products essential. The yield of the picolyl malonic ester could not be determined, since the limiting factor was the picolyl bromide which was present in unknown amount in the ether solution. If quantitative yields are assumed in every case, the yield of the malonic ester (crude) on the basis of β -picoline used would be about 7%. Obviously, the bromide yields were poor, and gave corresponding small amounts of the picolyl malonic esters.

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* NOTE: In order to estimate a necessary excess of the sodium enolate, a yield of 80% was assumed in the bromination of β -picoline. This, of course, is far above the actual yield.

SYNTHESIS OF 5-(β -PICOLYL) 5-ETHYL BARBITURIC ACID

	<u>Mols</u>	<u>Gms.</u>	<u>C.C.</u>
β -picolyl ethyl ethyl malonate	0.0056	1.5	-
Sodium	0.037	0.62	----
Ethyl alcohol	0.253	11.7	14.3
Urea	0.129	0.775	----

The synthesis of the above barbituric acid was carried out using the conditions described in "An advanced Laboratory Manual of Organic Chemistry" - Heidelberger.⁴² 10 c.c. of absolute alcohol were placed in a Pyrex tube, and 0.62 grams of clean sodium added. When this was completely dissolved, the alcoholic solution (5 c.c.) of the β -picolyl ethyl ethyl malonate was introduced. 0.75 gram of dry finely powdered urea was then dissolved in the mixture with gentle application of heat and vigorous shaking. The tube was sealed immediately thereafter, being careful to prevent the condensation of water vapor inside. The tube and contents were heated at 100° for 18 hours by placing in

an iron pipe through which a steady stream of steam was passed. At the end of this time, the tube was allowed to cool and then opened. No noticeable pressure had developed, but a faint odor of ammonia was discernable and some sodium carbonate had precipitated. The contents of the tube were washed out with water, and the greater part of the alcohol evaporated off on the hot plate (about 90°). The resulting aqueous solution was then carefully treated (dropwise addition) with 5% hydrochloric acid. At the neutral point (congealed) no precipitation took place, but when slightly acid an amorphous solid precipitated. This was crystallized from 95% ethyl alcohol several times. The resulting product was in the form of colorless crystalline plates which melted without decomposition at 213-214°.

The compound was soluble in dilute and concentrated alkali and in concentrated hydrochloric acid, showing its amphoteric character. It was practically insoluble in cold water, but slightly soluble in hot water. It readily dissolved in warm 95% ethyl alcohol, crystallizing in colorless plates on cooling. The yield was 0.65 gram or 49% of the theoretical based on the crude ester.

Micro-combustion analysis: $C_{19}H_{19}O_2N_3$ (247.10)

Sample ...	4.755 mg.		Calc.	Found
CO ₂ ...	10.243 mg.	% C	58.28	58.20
H ₂ O ...	2.430 mg.	% H	5.30	5.71

SYNTHESIS OF β -PICOLYL n-PROPYL ETHYL MALONATE

	<u>Mols</u>	<u>Gms.</u>	<u>S.S.</u>
β -picolyl bromide	0.053	9.0	7
n-propyl ethyl malonate	0.053	10.6	10.4
Sodium	0.053	1.2	----
Ethyl alcohol	-----	----	15.0

This malonic ester was obtained in the same manner as the β -picolyl ethyl ethyl malonate. The ether solution of the bromide was added in similar fashion to the sodium enolate of n-propyl ethyl malonate. Upon extraction of the aqueous alkaline solution with ether all of the unchanged alkyl malonic ester was removed together with the picolyl malonic ester. Treatment of an acid solution with ether removed the alkyl malonic ester alone, leaving the picolyl malonic ester in solution as a salt. Neutralization of the acid solution with alkali and subsequent extraction gave the desired compound. This was dried as before by heating just

below the boiling point at 8 m.m. pressure. The temperature at this point was approximately 180°. The resulting product was a viscous red oil. It was removed from the distillation flask with absolute alcohol immediately before the condensation with urea.

SYNTHESIS OF 5-(β -PICOLYL) 5-n-PROPYL BARBITURIC ACID

	<u>Mols</u>	<u>Gms.</u>	<u>S.C.</u>
β -picolyl n-propyl ethyl malonate	0.0188	4.0	-
Sodium	0.0411	0.95	----
Ethyl alcohol	0.586	17.8	22.6
Urea	0.0188	1.19	----

The above mixture was placed in a Pyrex tube in the same manner as described for the picolyl ethyl barbituric acid and heated for 6 hours in an autoclave at 107° . The contents of the tube were then treated in the same fashion as the previously outlined method. A white solid was obtained from slightly acid solution. It was recrystallized from 95% ethyl alcohol four times and gave a white micro-crystalline product that melted with decomposition at 250°C . Further recrystallization had no effect on the melting point. The yield was 0.52 gram or 14.6% of the theory based on the crude ester. The compound behaved toward aqueous acid and alkaline solu-

tions in a manner similar to the previously prepared picro-lyl ethyl barbituric acid. It was insoluble in cold and hot water, but dissolved readily in warm 95% ethyl alcohol.

Micro-combustion analysis: $C_{12}H_{18}O_5N_2$ (261.12)

sample ...	8.586 mg.		Calc.	Found
CO ₂ ...	18.854 mg.	% C	59.74	59.61
H ₂ O ...	4.451 mg.	% H	5.79	5.77

SYNTHESIS OF β -PICOLYL *n*-BUTYL ETHYL MALONATE

	<u>Mols</u>	<u>Gms.</u>	<u>G.C.</u>
β -picolyl bromide	0.053	9.0	?
<i>n</i> -butyl ethyl malonate	0.053	11.4	12.0
Sodium	0.053	1.2	----
Ethyl Alcohol	-----	----	15.0

As in the previous experiments, a maximum yield of β -picolyl bromide was assumed in order to have an excess of the sodium enolate present. The mixture was handled as before. However, it was heated only 15 minutes after the addition of the bromide in order to test the effect of length of heating on the yield. As well as could be told, there was little or no effect. The yield in this case was 2.5 grams of a red viscous oil that would not distill at 165° (2 m.m.), but apparently began to boil when the temp. of the oil bath reached 155°C.

The compound was removed from the distillation flask with absolute alcohol just before the condensation with urea.

SYNTHESIS OF 5-(β -PICOLYL) 5-n-BUTYL BARBITURIC ACID

	<u>Mols</u>	<u>Gms.</u>	<u>S.G.</u>
β -picolyl n-butyl ethyl malonate	0.0051	2.5	?
Sodium	0.0243	0.86	-----
Ethyl alcohol	0.228	10.5	13.8
Urea	0.0117	0.70	-----

This material was heated in a sealed tube at 100° for 12 hours and the contents worked up as before. A white solid precipitated from acid solution, and was crystallized from 95% ethyl alcohol in micro-platelets. Three crystallizations gave a product melting 218-219°C. The yield was 0.71 gram or 31.8% of the theory based on the crude ester.

Micro-combustion analysis: $C_{14}H_{17}O_3N_3$ (275.14)

sample ...	Calc.	Found
5.916 mg.		
CO ₂ ... 13.396 mg.	% C 61.06	61.79
H ₂ O ... 3.597 mg.	% H 6.83	6.81

SYNTHESIS OF β -PICOLYL ISOAMYL ETHYL MALONATE

	<u>Mols</u>	<u>Gms.</u>	<u>Q.C.</u>
β -picolyl bromide	0.053	9.0	?
isoamyl ethyl malonate	0.053	12.2	12.6
Sodium	0.053	1.3	----
Ethyl alcohol	-----	----	13.0

The same molecular quantities of material were used in this synthesis as in the previously discussed similar preparations. The picolyl isoamyl malonic ester was isolated from alkaline solution by extraction with ether after all of the unchanged mono-alkyl malonic ester had been removed. The ether solution was then distilled as before. About four grams of a viscous red oil remained in the distillation flask at 3 m.m. pressure and 170°C. The compound apparently boiled at approximately 165°. After cooling, the material was removed with absolute ethyl alcohol and condensed with urea in a sealed tube.

SYNTHESIS OF 5-(β PICOLYL) 5-ISOAMYL BARBITURIC ACID

	<u>Mole</u>	<u>Gms.</u>	<u>Q.Q.</u>
β -picolyl isoamyl ethyl malonate	0.0125	4.0	?
Sodium	0.0375	0.86	----
Ethyl alcohol	0.352	16.2	20.3
Urea	0.018	1.08	----

The dry alcoholic solution of the picolyl isoamyl malonic ester was placed in a Pyrex tube with the above materials. The tube was sealed and heated at 100° for 12 hours. As before, a white solid precipitated from acid solution and crystallized from 95% alcohol in micro-plates. Melting point - 229-230°. Yield: 1.4 grams or 25.9% of the theory.

Micro-combustion analysis: $C_{15}H_{19}O_3N_3$ (289.15)

sample ...	5.752 mg.		<u>Calc.</u>	<u>Found</u>
CO ₂ ...	13.296 mg.	% C	62.25	62.70
H ₂ O ...	3.639 mg.	% H	6.62	6.72

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