Synthesis of some Glycolaline derivatives

A

THESIS

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SYNTHESIS
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SOME GLYOXALINE DERIVATIVES
OF
BARBITURIC ACID
HISTORICAL INTRODUCTION
Barbituric acid itself has been prepared by several different methods. Baeyer (A. 1863, 127, 3, 229ff.) obtained it from alloxan. This method is no longer of interest today. Grimaux (B. 1879, 12, 378) synthesized it by heating a mixture of malonic acid, urea, and phosphoroxychloride, and thereby established a method later used to prepare a number of derivatives of barbituric acid. However, it is best obtained by boiling sodium malonic ester with urea in absolute alcohol. (Hatigrion-A. 6 22, 295 1893; Trubsbach-Ph. Ch. 16, 717 1895; Hantash, Voegelen-B. 35, 1006. 1902; Wood-Soc. 82, 1835, 1838 1906.)

In this thesis, the usual convention of numbering the positions of the barbituric acid ring will be followed; i.e.,

(6) \(\overset{0}{C} - \overset{0}{NH}\) (1)
(5) \(\overset{0}{NH} - C\) (2)
(4) \(\overset{0}{C} - \overset{0}{NH}\) (3)

Only those derivatives will be considered where the hydrogen atoms on the (5) carbon atom have been substituted.

In general the simpler derivatives have been made by:

I. Heating the substituted malonic acids with urea and phosphoroxychloride. A simple improvement was to convert the substituted malonic acid into a diacid
chloride with phosphorous pentachloride and then condense this with urea.

II. Treating the silver salt of barbituric acid with alkyl iodides. This method is limited to the preparation of disubstituted barbituric acid derivatives, since the silver salt contains two atoms of silver in the (5) position. It was definitely proven by L.T. Thorne (Soc. 1881, 32, 543) that in this method the two hydrogen atoms on the (5) carbon are substituted before those on the (1) and (3) positions. Tetrasubstituted products have been prepared by treating the silver salts of 5,5-disubstituted products with alkyl iodides.

Nearly all the simple derivatives prepared by different people using a variety of methods were re-synthesized by F. Fisher and A. Dilthey (A. 325, 334) who amplified the procedure employed by A. Michael (Journ. f. pract. Chem. 2 35, 456. 1887) to prepare barbituric acid. The method of Fisher and Dilthey consists in heating sodium malonic acid with urea in the presence of sodium etholate in absolute alcohol. Conrad (A. 204, 138) developed the general method of preparing substituted malonic esters by adding organic halides to sodium malonic ester dissolved in absolute alcohol, used by Fisher and Dilthey.
The following is a résumé of the different barbituric acid derivatives and their physiological effects.

Monomethyl barbituric acid is known. (R. 7, 22; D.R.P. 146,948 C 1904 1 68; A. 335, 355)

Monoethyl barbituric acid was first prepared by M. Conrad and M. Guthszeit (B. 15, 2845 1882) by the reaction of ethyl malonic ester with phosphoroxychloride and urea. It does not possess any special hypnotic effect.

Monopropyl barbituric acid was synthesized by Fisher and Dilthey (ibid.). It does not possess any special hypnotic effect. The same workers also prepared isopropyl barbituric acid.

Methyl propyl barbituric acid is known, due to the work of E. Merck (C. 1903 2 1484) and its physiological effect is uncertain.

Dimethyl barbituric acid was first prepared by M. Conrad and M. Guthszeit (B. 14, 1643) by heating the silver salt of barbituric acid with methyl iodide. It is without hypnotic effect.

Diethyl barbituric acid, commonly known as veronal or barbital, was discovered by Conrad and Guthszeit (B. 15, 2849) by heating the silver salt of barbituric acid and ethyl iodide. Its hypnotic action has been found to be very strong.
It is administered in doses of 0.3-0.5 gm, in the form of a powder and in solution. Its solubility in water is only one part in 160 and in alcohol one in 8. Its taste is faintly bitter. Apparently it produces sleep without any other effects. When the dose is large, however, poisoning may occur and then the sleep is marked by trembling and restlessness, sometimes interrupted by excitement and is long continued. The monosodium salt of barbital has also found extensive use as a hypnotic. It has the advantage of being much more soluble in water, but is objectionally bitter.

Dipropyl barbituric acid is due to E. Merck (ibid.). It possesses a very intensive hypnotic effect. Ethyl propyl, diisocamyl, dibenzyl and diisobutyl barbituric acids were also described by the same writer. The first is strongly hypnotic, comparing favorably with veronal, and diisobutyl barbituric acid produces heavy drunkenness and sleep. Diisocamyl barbituric acid does not produce sleep, its action being uncertain. Dibenzyl barbituric acid has no effect.

Methyl ethyl was first prepared by G. v. Niessen (C. 1903 II 778). This author also noted that in
the reaction of silver salts of barbituric acids with iodides, the monosubstituted derivatives gave disubstituted products in much higher yields than did unsubstituted barbituric acid. Methyl ethyl barbituric acid is rather weakly hypnotic.

Among compounds of more recent origin, the following are of interest:

Ethyl phenyl barbituric acid or luminal has been synthesized in the following rather interesting way by Rising and Stroglitz (J.A.C.S. 1916, 40, 723). Benzyl cyanide is treated with hydrochloric acid and methyl alcohol to convert it into methyl phenyl acetate, which, when condensed with methyl oxalate, gives dimethyl oxalyl phenyl acetate. By heating, the latter is caused to lose carbon monoxide to form methyl phenyl malonate which is then substituted with ethyl iodide and condensed with urea in the usual manner. Luminal is about twice as strong a hypnotic as barbital; whereas the ratio of lethal dose to therapeutic dose is greater than for veronal.

Dioethoxybarbituric acid was synthesized by D. J. v. Prooye (Rec. trav. chim. 1915, 34, 526-49).
The mercury salts of diethyl barbituric acid and ethyl phenyl barbituric acid have been made by Pio Lami (Boll. chim. farm. 1914, 53, 195-200).

A. Dox and L. Yoder (J. A. C. S. 1922, 44, 1141-5) have prepared a series of derivatives of benzyl barbituric acid. These derivatives were the methyl, ethyl, propyl, isopropyl, butyl, isobutyl, and iscamyl. Of these compounds, the benzyl ethyl derivative showed marked hypnotic powers, but instead of being anti-spasmodic, as hoped by the authors, its action was directly opposite.

A. Dox and L. Yoder (J. A. C. S. 1922, 44, 1578) also prepared a series of n-butyl derivatives of barbituric acid. They made the n-butyl barbituric acid, bromo, ethyl, and phenoxy, n-butyl barbituric acids. Of these only n-butyl ethyl barbituric acid proved to be a strong hypnotic.

H. A. Shoule and A. Homent (J. A. C. S. 1923, 45, 245-9) have prepared the isobutyl ethyl, iscamyl ethyl, n-butyl isopropyl, n-propyl isopropyl, iscamyl isopropyl, iscamyl propyl, and sec-butyl ethyl barbituric acids. Of these, the iscamyl ethyl barbituric acid was found to be the most active in its hypnotic
properties.

A. W. Dox and B. Houston (J. A. C. S. 1924, 46, 252) have prepared acetonyl barbituric acid by substituting directly on the (5) carbon atom of barbituric acid with the group CH₂CO-CH₂ as well as the bromine, chlorine, allyl, benzyl, ethyl, and diacetonyl derivatives. Four of these compounds, diacetonyl, acetonyl, benzyl, acetonyl ethyl, and acetonyl allyl barbituric acids were found to be rather weak in hypnotic action.

The ethyl, propyl, allyl, isobutyl, n-butyl derivatives of acetophenonyl barbituric acid were prepared by W. T. Keach and A. J. Hill (J. A. C. S., 1926, 49, 2743-5). These derivatives are quite toxic and, excepting the ethyl derivative, lack hypnotic properties.

All of the above described derivatives of barbituric acid are rather simple allyl or aryl substitution products. The best of them fall far short of being ideal hypnotics. On the other hand, very few heterocyclic substituted barbituric acids have been prepared, although some heterocyclic rings, such as the glyoxaline, are famous for their physiological effects.
These considerations made it appear worthwhile to synthesize barbituric acids containing the imidazol nucleus. It was decided to begin with the 4 (or 5)-chloromethyl glyoxaline hydrochloride

\[
\begin{align*}
\text{H} & \quad \text{C} = \text{C} - \text{CH}_2\text{Cl} \\
\text{H} & \quad \downarrow \quad \downarrow \\
\text{Cl} & \quad \text{C} \\
\text{H} & 
\end{align*}
\]

first prepared by Pyman (J. C. S. 1911, 92, 668) as an intermediate in his synthesis of histamine. This chloride had been demonstrated to possess a suitable reactivity and stability for malonic ester and acetoacetic ester condensations.

There are two general methods for the preparation of glyoxaline compounds. The first of these may be illustrated by the synthesis of glyoxaline (Debus-A., 1858, 107, 204) from glyoxal and ammonia,

\[
\begin{align*}
\text{CHO} + 2\text{NH}_2 + \text{C} = \text{H} & \rightarrow \text{CH} - \text{NH} \\
\text{CHO} & \quad \text{H} \quad \text{CHO} \\
\end{align*}
\]

the formaldehyde being a decomposition product of glyoxal. In the synthesis of other glyoxaline compounds from 1,2-dicarbonyl compounds, it is necessary to add the aldehyde.

The second general method may be illustrated
by the reaction

\[
\begin{align*}
\text{CH}_3\text{O} & + \text{HSN} \rightarrow \text{CH}_3\text{O}-\text{HN} \rightarrow \text{CH}_3\text{O}-\text{HN} \\
\text{CH}_2 & + \text{SH} \rightarrow \text{CH}_2\text{NH} \rightarrow \text{HO}_2
\end{align*}
\]

This method was discovered by Wohl and Harckwald (B. 1889, 22, 572, 1353; B. 1892, 25, 2354).

Glyoxaline is a very interesting compound in that it is both a secondary and tertiary amine and is unsaturated. It is strongly basic (K 1.2x10^{-7}) (Buchner-A. 1893, 273, 218) and yet it gives a precipitate with silver nitrate of C\text{H}_2\text{H}_2\text{Ag}.

In this thesis no attempt will be made to treat with all the known glyoxaline compounds, but only those bearing directly on the compounds described herein.

Byman (J.C.S. 1911, 29, 668) accomplished the synthesis of histamine by the following series of steps. He began with citric acid.
The 4 (or 5)-chloro methyl glyoxaline compound written above is a very reactive chloride. Thus it is
hydrolysed by hot water in a few minutes to the corresponding alcohol. Pyman (J. C. S. 1911, 29, 1386), therefore, condensed it with ethyl sodiomalonate to prepare ethyl 4(or 5)-glyoxalinemethyl malonate. By hydrolysis of this ester, he produced 4(or 5)-glyoxaline-methyl malonic acid. On heating, this compound loses one molecule of carbon dioxide to give 3-glyoxaline, 4(or 5)-propionic acid, previously prepared by Knoop and Windaus (Beitr. chem. Physiol. Path. 1905, 2, 144).

Similarly Pyman condensed the 4(or 5)-chloro-methyl glyoxaline with ethyl sodioacetocacetate and ethyl sodiomethylacetocacetate to obtain ethyl 4(or 5)-glyoxalinemethylacetoacetate and ethyl 4(or 5)-glyoxaline-methylmethylacetoacetate. By the same methods he prepared ethyl 4(or 5)-glyoxalinenethylchloromalonate I

\[
\text{CH}-\text{HN} \\
\text{C} \equiv \text{N}^\circ \text{CH} \\
\text{C} \equiv \text{O} \text{C}=\text{C}_\text{H}_\text{F} \\
\text{CH}_\text{F} \equiv \text{C}=\text{Cl} \\
\text{C}=\text{O} \text{C}=\text{C}_\text{H}_\text{F} 
\]

which when treated with 20\% boiling hydrochloric acid gives 3-\(\alpha\)-chloro 3-glyoxaline 4(or 5)-propionic acid II

\[
\text{CH}-\text{HN} \\
\text{C} \equiv \text{N}^\circ \text{CH} \\
\text{C} \equiv \text{O} \text{C}=\text{C}_\text{H}_\text{F} \\
\text{CH}_\text{F} \equiv \text{C}=\text{Cl} \\
\text{C}=\text{O} \text{C}=\text{C}_\text{H}_\text{F} 
\]


\[
\text{CH}-\text{HN} \\
\text{C} \equiv \text{N}^\circ \text{CH} \\
\text{C} \equiv \text{O} \text{C}=\text{C}_\text{H}_\text{F} \\
\text{CH}_\text{F} \equiv \text{C}=\text{Cl} \\
\text{C}=\text{O} \text{C}=\text{C}_\text{H}_\text{F} 
\]

III.
On treating with concentrated ammonia, this acid gave \( r - \) amino-\( \alpha \)-glyoxaline, \( 4 \) (or \( 5 \))-propionic acid III (\( r \)-histidine). By resolution the \( d \)-and \( l \)-forms were obtained.
EXPERIMENTAL PART
SYNTHESIS

OF

SOME GLYOXALINE DERIVATIVES

OF

BARBITURIC ACID
SYNTHESIS OF ACETONE DICARBOXYLIC ACID

\[
\text{HCOC-}H_2\text{C}_2\text{O}_\text{OC-COOH} + 2\text{SO}_3 + \text{H}_2\text{SO}_4
\]

\[
\begin{array}{ccc}
210.08 & 80.06 & 96.08 \\
12.143 & 2.05 & 749 \\
450 & 164.7 & 735.3
\end{array}
\]

\[
\text{HCOC-}H_2\text{C}_2\text{O}_\text{O=O} + 3\text{H}_2\text{SO}_4 + \text{CO} \uparrow
\]

\[
\begin{array}{c}
134.48 \\
2.143 \\
287.162
\end{array}
\]

This reaction was first described by Beckmann (A. 261, 155) and was later improved on by Koezeler and Henke (J. A. C. S., 40, 1717). Both procedures were tried in this laboratory and the latter one adopted. The citric acid containing one molecule of water of crystallization was crushed to a fine powder in a mortar and added to the 18% fuming sulfuric acid contained in a 5 l. round bottom flask. The powder was poured in during an interval of about ten minutes with no stirring at all. Vigorous effervescence took place and after several minutes, a cork having a glass tube through it was introduced into the neck of the flask and the carbon monoxide ignited.
After allowing the flask to sit quietly for fifteen minutes, it was clamped over a water bath maintained at 65-70°. The flask was not agitated. After about fifty-five minutes the GO flame went out, whereupon the flask was placed in water at room temp for about fifteen minutes and then placed in an ice and salt mixture. When the temperature reached near 0°, the addition of 500 c.c. of water was begun. By strong cooling, the temperature was maintained below 10° throughout the addition. After 200 c.c. is added, the acetone dicarboxylic acid begins to separate out. The resulting semi-solid mass was filtered on a glass funnel. It was necessary to continually press down the acetone dicarboxylic acid with a glass stopper to prevent it from channelling. 330 gms. of 80.3 acetone dicarboxylic acid were obtained.

This crude product was used without further purification for the synthesis of the diisonitrosoacetone.

Notes: The acetone dicarboxylic acid is unstable and begins to decompose after several hours. Hence, it was always converted into diisonitrosocetone the same day it
was prepared.

Due to the long time it took to filter the product, yields often contained much more than 20% of H$_2$SO$_4$. So that, in the nitrosation it was never necessary to add any HNO$_3$ as called for in the literature.
SYNTHESIS OF DIISOCITROSACETONE

\[
\begin{align*}
\text{CH-} & \text{C=O} \\
| & | \\
\text{C=O} & + 2\text{HNO}_2 \quad \rightarrow \quad \text{C=O} \quad + \quad \text{H}_2\text{O} \\
\text{CH-} & \text{C=O}
\end{align*}
\]

\[
\begin{array}{c|c|c}
134.48 & 47.016 & 4.21 \\
H 1.96 & 198 & \\
gms 264 & & \\
\end{array}
\]

Peckmann's original description (B. 19, 2465) was modified by Koessler and Henke somewhat. Both procedures were tried in this laboratory and the latter adopted.

The crude acetone dicarboxylic acid was dissolved in 660 c.c. of water in a 5 l. round bottom flask. The contents were stirred by means of an electric motor and cooled to about 0°. A concentrated solution of NaNO₂ was then added through a dropping funnel whose tip extended below the surface of the solution. This took about one and a half hours.

The yield was about 60 gms. or 26% theory.
NOTES: The diisonitrosoacetone is unstable and begins to decompose within several hours. Hence, it was necessary to convert it directly into the diaminoacetone chlorostannite the same day it was prepared.

The nitrosation of acetone dicarboxylic acid is a very difficult process. We never obtained as good a yield as that reported in the literature. It is best to maintain the temperature as low as possible with a salt and ice mixture. The NaNO₂ solution is added slowly and beneath the surface, thus giving the HNO a good chance to be absorbed.

Since it always contained an excess of H₂SO₄, Na₂SO₄ frequently precipitated out along with the diisonitrosoacetone. This did not hurt anything and was removed in the next stage. The amount of Na₂SO₄ can be estimated by treating a small amount of the product with ether and noting how much of it dissolves.

A recrystallization out of methyl alcohol gave m.p. 138°. Reported in literature 135°.
SYNTHESIS OF DIAminoAcetone Chlorostannite

\[
\begin{align*}
\text{CH}_2\text{NCO} + 5 \text{SnCl}_2 + 10 \text{HCl} &\rightarrow \text{CH}_2\text{NCO} \cdot \text{SnCl}_2 - 2\text{HCl} + 4\text{SnCl}_4
\end{align*}
\]

The method used was that of Kalischer (B_28, 1519) improved by Koessler and Henke.

The stannous chloride was mixed with 220 c.c. of concentrated HCl (which dissolved only a part of the salt) in a 5 l. round bottom flask fitted with an electric stirrer. 30 gms of the diisonitroacetone was slowly added during the course of an hour, the temp. being maintained at room temp. by means of a water bath. Then 220 c.c. more of concentrated HCl were added (which dissolved most of the remaining SnCl_2) and the remaining 30 gms of diisonitroacetone added during the course of another hour. Then 100 c.c. of concentrated HCl were added and the pale brown solution placed in the ice box overnight and filtered. The crystals were washed with concentrated HCl and then with 95% alcohol.

When dried in an oven at 90° for five hours weighed
136 gms or 83% theory.

In the above process, stannous chloride containing one molecule of water of crystallization was used in place of the anhydrous substance. Although the anhydrous salt will dissolve completely in concentrated HCl, the hydrated substance is partly hydrolyzed by its own water of crystallization to give a colloidal stannous oxychloride. This made the filtration of the tin double salt very tedious. By using filter paper containing large pores, the trouble was mainly avoided.

Contrary to the literature, no great evolution of heat was noticed in the reduction.

On allowing the mother liquors of the tin double salt to stand for several weeks, further crops amounting in one case to 13 gms were obtained.

This double salt is quite stable.
Preparation of Diaminoactone Hydrochloride

\[
\begin{align*}
\text{CH}_2\text{NH}_2\text{Cl} & \quad \text{CH}_2\text{NH}_2\text{Cl} \\
\text{C}_2\text{O} \cdot \text{SnCl}_2 + \text{H}_2\text{S} & \quad \rightarrow \quad \text{C}_2\text{O} \quad \rightarrow \quad \text{SnS} + 2\text{HCl} \\
\text{CH}_2\text{NH}_2\text{Cl} & \quad \text{CH}_2\text{NH}_2\text{Cl} \\
161.01 & \quad 161.01 \\
350.624 & \quad 350.624 \\
136 & \quad 136 \\
\text{gms} & \quad \text{gms} \\
338 & \quad 338 \\
62.4 & \quad 62.4
\end{align*}
\]

Kalischer originally added HCl to the double salt "to decompose it," and had great difficulty in getting rid of all the tin. Köessler and Henke pointed out that HCl is generated in the course of the reaction and that when it becomes concentrated enough, it will redissolve the SnS.

The tin double salt was dissolved in about 3,000 cc. of water and H$_2$S was passed in for about twenty hours. The SnS was then filtered off and the filtrate tested by passing H$_2$S through it for a short length of time. If the filtrate was free of tin, it was then distilled to dryness in a 5 l. round bottom flask at 40-50° over a boiling water bath. A very large goose neck (10-12 mm.) was used.

The residue weighed 62.4 gms which is 100% of the theory.
NOTES: Care should be exercised that the concentration of HCl is not too great. On one run this happened, and a colloidal solution of SnS resulted. Two weeks were spend on various vain attempts to break this sol, such as adding thallium nitrate, etc. Finally it was discovered that the simple expedient of dilution with distilled water would immediately cause the SnS to settle out.

It is best and most rapid to decant from the SnS. On one occasion when filtration was used, it was necessary to refilter through a collection of SnS. It was found that the filtrate always contained tin; the suction removed H₂S and the equilibrium was shifted so that some of the SnS dissolved.

The distillate was tested from time to time for any diaminoacetone that might have bumped over by adding saturated picric acid solution to a small portion of it. In the later stages care must be taken not to confuse the picric acid precipitated by the HCl with the diaminoacetone picrate.

It is best to lower the temperature of the water bath below 80° a little before the finish to prevent decomposition of the compound.
PREPARATION OF 2-THIOL, 4(OR 5)-AMINOMETHYLGLYXALINE HYDROCHLORIDE

The method used was that of Eyman (J.C.S. 29, 671) and improved by Kessinger and Henke. The diaminooacetone hydrochloride was dissolved in 58 c.c. of water heated on the boiling water bath. The sodium thiocyanate was added to the solution, one half immediately, and the rest in the course of twenty
After adding about two-thirds of the NaSCN, the 2-thiol, 4(or 5)-aminomethylglyoxaline hydrochloride began to separate out. After 60 min. of heating from the time all the NaSCN was added, the mixture was cooled on an ice bath for 2 hours and the 2-thiol, 4(or 5)-aminomethylglyoxaline hydrochloride was filtered off.

The crystals were washed with 50% alcohol in which they were not very soluble. When dried at 100° for 2 hours, the white crystals weighed 52.6 gms which corresponds to 82.5% of theory.

By distilling the combined mother liquor and 50% wash alcohol to dryness at 50° in vacuo, a product may be obtained that after extraction with 95% alcohol to remove thiocyanic acid, NaSCN, and coloring matter contains some 2-thiol, 4(or 5)-aminomethylglyoxaline hydrochloride mixed with a great deal of NaCl. This may be oxidized to form the picrate of the 4(or 5)-hydroxymethylglyoxaline hydrochloride exactly as the main product is.

NOTES: This is a very smooth and easy reaction.

It was found advisable to plug the neck of the round bottom flask with a reflux condenser during the time of heating on the water bath.
PREPARATION OF 4(OR 5)-HYDROXYMETHYLGLYOXALINE PICRATE

\[
\begin{align*}
\text{HCl} & \\
\text{HC} & \rightleftharpoons \text{N} \\
\cdots \text{C-SH} \quad & \text{HNO}_3 \\
\text{C} & \rightleftharpoons \text{N} \\
\text{CH}_2\text{NH}_3\text{Cl} & \\
\end{align*}
\]

\[
\begin{align*}
\text{HNO}_3 & \\
\text{HC} & \rightleftharpoons \text{N} \\
\cdots \text{C-S} & \rightleftharpoons \text{OH} \\
\text{C} & \rightleftharpoons \text{N} \\
\text{CH}_2\text{NH}_3\text{Cl} & \\
\end{align*}
\]

\[
\begin{align*}
\text{HNO}_3 & \\
\text{HC} & \rightleftharpoons \text{N} \\
\cdots \text{C-S} & \rightleftharpoons \text{OH} \\
\text{C} & \rightleftharpoons \text{N} \\
\text{CH}_2\text{OH} & \\
\end{align*}
\]

The 2-thiol, 4 (or 5)-aminomethylglyoxaline hydrochloride was dissolved in almost the least amount of water possible and was slowly added to a gently boiling solution of 97.2 o.c. of concentrated HNO₃ in 1,556 o.c. of water by means of a dropping funnel whose tip extended beneath the surface of the liquid contained in a 5 l. round bottom flask. There was vigorous effervescence of nitrous oxide. The resulting solution was then
boiled for one hour very vigorously to remove as much water as possible. The resulting solution was about 500 c.c., and after cooling, was neutralized with dry Na₂CO₃, and poured into a hot solution of 116.7 gms of picric acid in 1,056 c.c. of water. A heavy precipitate of the picrate of the 4(or 5)-hydroxymethylglyoxaline separated as the solution cooled. After being in the ice box overnight, the crystals were filtered off and when dried in air for 24 hours, weighed 114 gms which is 90% of the theory.

NOTE: This also is a very smooth reaction. On several runs the cooling and neutralization with Na₂CO₃ was omitted. It was found that this gave almost as good a yield of the picrate as by the above procedure, and it has the added advantage that in no possible way can any sodium picrate get mixed up with the alcohol picrate as sometimes happens when the solution is first neutralized with Na₂CO₃.

A little of the picrate was recrystallized out of alcohol and melted at 206°. The literature reports 207°.
PREPARATION OF 4(OR 5)-HYDROXYMETHYLGLOXALINE HYDROCHLORIDE

To a mixture of 114 c.c. of concentrated hydrochloric acid, 285 c.c. of water and 570 c.c. of benzene placed in a 2 l. round bottom flask and immersed in a water bath kept at 80°, 114 gms of 4(or 5)-hydroxymethyl-gloxaline picrate were added. The contents of the flask were then thoroughly shaken and mixed until all the solid went into solution. This took only a few minutes. Then the benzene solution, almost saturated with picric acid, was decanted and about 500 c.c. of fresh benzene were used for each of five more extractions conducted in a separatory funnel. The resulting pale yellow solution was treated with about 5 gms of Norite in the hot, and the solution well cooled before filtering through a hard, folded, water-soaked filter paper. This usually removed almost all of the remaining picric acid.

The residue benzene was left on the filter paper along with the charcoal and coloring matter. By distillation under 27 mm. pressure, the water and HCl were removed. Usually the temperature was about 40-45°, but never rose beyond 60-60°.

The white crystalline solid was loosened by means
of a glass rod and freed from the last traces of water and HCl by drying in vacuum over calcium oxide.

The last particles of product were removed from the flask by dissolving in a small amount of water and evaporating to dryness over calcium oxide. 45.6 gms of the 4(or 5)-hydroxymethylglyoxaline were obtained which is 97% of the theory.

NOTES: Here also in the distillation of the water and HCl from the product, the distillate was proven free of 4(or 5)-hydroxymethylglyoxaline hydrochloride by adding a few drops of saturated solution of picric acid to a small portion of it.

Koessler and Henke further purified their product by grinding in a mortar with acetone rapidly and filtering hurriedly on a Buchner funnel. The reason for the haste is that the 4(or 5)-hydroxymethylglyoxaline hydrochloride is hygroscopic and part of the product will go into solution in the water from the air and will be lost if this operation is not carried out rapidly. On real dry days the salt is not capable of taking moisture from the air as it is on wet days.

The above treatment with acetone was omitted in
this laboratory after the first time, because in the
preparation of 4(or 5)-chloromethylglyoxaline hydro-
chloride, the product is reocrystallized out of absolute
alcohol, and any picric acid still present is left be-
hind in the mother liquor.

A small amount of 4(or 5)-methylhydroxyglyoxaline
hydrochloride was dissolved in water and made alkaline
with Na₂CO₃. The residue obtained by evaporating this
solution was extracted with several c.c. of absolute
alcohol. The alcohol solution was filtered on a Hirsch
funnel and boiled to drive off most of the alcohol. The
free base alcohol finally crystallized on cooling in
ice. It was filtered on a Hirsch funnel, mashed fine,
and dried for several days over H₂SO₄. m.p. 89-91°.
Literature reports 93-4°.

In the above distillation to dryness, the water
bath may be kept boiling until a little before the pro-
duct begins to crystallize out, when it must be lowered
to below 80° to prevent decomposition of the substance.
PREPARATION OF 4 (OR 5)-CHLOROMETHYLGLYOXALINE HYDROCHLORIDE

\[
\begin{align*}
\text{HC} & = \text{C} - \text{CH}_2\text{OH} & \text{HC} & = \text{C} - \text{CH}_2\text{Cl} \\
\text{H} & \quad | & \quad \text{H} & \quad | \\
\text{H} & \quad \text{N} & \quad \text{N} & \quad \text{Cl} & \quad \text{Cl} & \quad \text{Cl} \\
\text{Cl} & \quad \text{H} & \quad + & \quad \text{PCl}_3 & \quad + & \quad \text{PCl}_3 \\
\text{C} & \quad \text{H} & & & & \\
\end{align*}
\]

134.529 152.978

H 339 339

gms 45.6 51.8

The 4(or 5)-hydroxymethylglyoxaline hydrochloride was added rapidly in small amounts to 72 gms of finely powdered phosphorous pentachloride in the course of a few minutes. If the day was moist, instantaneous reaction occurred, but on dry days it was necessary to place the 1 liter round bottom flask, containing the mixture, on a boiling water bath when the reaction began in a few minutes. As the mixture became hot, the components went into solution in the phosphoryl chloride.

Copious fumes of hydrochloric acid were evolved and the reaction mixture gradually solidified. About 60 c.c. of chloroform were then added to wash any phosphorous pentachloride into contact with unchanged glyoxaline alcohol.

After about half an hour, when the evolution of HCl had almost ceased, the flask was placed on the boiling
water bath for about 15 minutes. This removed most of the chloroform and a little of the phosphoryl chloride. The flask was then connected by means of a goose neck to a condenser and the pressure reduced to about 27 mm. Under these conditions the remaining phosphoryl chloride, chloroform and HCl distilled off.

The residue was then dissolved in 63 c.c. of absolute alcohol (prepared according to Smith—J.C.S., 1927, 1288) and filtered while hot to remove small traces of NaCl. On standing for several hours in a well stoppered flask, 42 c.c. of 4 (or 5)-chloromethylglyoxaline hydrochloride separated. This was filtered off as quickly as possible and placed immediately in a desiccator over calcium oxide. It was quite white and perfectly crystalline.

NOTE: The literature reports a m.p. 140-42°. The product obtained by us had m.p. 140-42°.

Care must be taken not to let the flask stay in the boiling water bath in the above distillation too long, as considerable charring will take place. At the best, the crude mixture is somewhat brown after the distillation.
This salt also is very hygroscopic. This, together with its great reactivity, makes it very difficult to handle. The water collecting on the surface from the air can in a few minutes hydrolyze the crystals to the 4(or 5)-hydroxymethylglyoxaline hydrochloride. In fact, Pyman found that the picrate of the chloride would, on dissolving in hot water, be converted into the picrate of the alcohol, and that this compound on cooling would crystallize out. He proved this by a melting point and mixed melting point determinations.

The mother liquor from the crystallization of the chloride contains considerable amounts of this compound and some unchanged alcohol. The liquors, therefore, from a number of runs were evaporated to dryness and the residue treated with HCI. A considerable quantity of the chloride was obtained in this way.
PREPARATION OF N-BUTYL MALONIC ESTER

\[
\begin{align*}
\ce{O} & \ce{\rightarrow} \ce{\rightarrow} \ce{\rightarrow} \\
\ce{\text{CH}} & \ce{\text{CH}} & \ce{\text{CH}} \\
\ce{\text{CH}} & \ce{\text{OH}} & \ce{\text{Na}} \\
\ce{\text{OH}} & \ce{\text{C}=\text{C}-\text{C}_2\text{H}_5} & \ce{\text{C}=\text{C}-\text{C}_2\text{H}_5} \\
\ce{\text{C}=\text{C}-\text{C}_2\text{H}_5} & & \ce{\text{C}=\text{C}-\text{C}_2\text{H}_5}
\end{align*}
\]

A three-neck, 2 L, round bottom flask fitted with a reflux condenser, electric stirrer, and dropping funnel was clamped over an oil bath. The bath was then heated to 150° and dry air drawn through the whole apparatus for one hour to insure perfectly dry conditions in the system. After cooling the flask below 50°, 780°C of absolute alcohol, prepared according to Smith (loc.cit.), were distilled directly into the 3 neck flask from the flask in which it was prepared.

Then through one of the necks, 36.2 gms of clean
Considerable heat was generated but the cool oil bath prevented the boiling from becoming too vigorous. After cooling to 50°C, the malonic ester was added over a period of about 15 min. with the stirrer going. The bath was then heated to about 100°C and the n-butyl bromide added slowly over a period of about 30 min. Considerable heat was generated and it was necessary to turn out the flame.

After two hours refluxing, the reaction mixture was neutral to moist litmus and the condenser was turned downward, gentle vacuum applied, and as much alcohol as possible distilled off.

Then the contents were transferred to a 2 l. separatory funnel and treated with 625 ml. of water. The upper layer of n-butyl malonic ester was separated off and dried over anhydrous Na2SO4 before distilling.

A 250 ml. Claisen flask, having a fractionating column in the side arm was used. Two distillations were necessary. The course of the distillation was followed by means of molecular refraction determinations. The accepted cut was made under the following conditions:

<table>
<thead>
<tr>
<th>Distillation temp.</th>
<th>Pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>73-74°C</td>
<td>0.3 mm, 0.2 mm</td>
</tr>
</tbody>
</table>
A molecular refraction on the first 15 c.c. of this cut is below.

\[ \text{R.I.} = 1.4230 \quad \text{d.} = 9761 \]

\[ M_p \text{ found} = 56.28 \]

\[ M_p \text{ calc.} = \frac{56.30}{0.02} \]

This corresponds to 0.1% malonic ester and is within the limits of experimental error.

The ethyl malonate used in the above reaction was distilled under 27 mm. over a 5° range. The n-butyl bromide was a 1° fraction.

The ratio of malonic ester to n-butyl bromide used above is the one recommended in "Chemical Synthesis," and a yield of 85-90% of the theory is claimed. In this laboratory, however, we were never able to get over a 50% yield due to approximately 25% of the n-butyl bromide reacting with monosubstituted malonic ester to give the dissubstituted ester, while the remaining ethyl malonate remained unchanged. We would, therefore, recommend using at least two moles of ethyl malonate to one of n-butyl bromide, rather than the almost one to one ratio given in "Chemical Synthesis."
THE PREPARATION OF 5-4(OR 5)-GLYCOLINEFATYL-N-BUTYL MALONIC ESTER

\[
\begin{align*}
\text{H}_3\text{C}=\text{C}-\text{CH}_2\text{Cl} & \quad \xrightarrow{\text{O}} \quad \text{C}-\text{O}-\text{C}_2\text{H}_5 \\
\text{H}_3\text{C}=\text{C}-\text{CH}_2\text{H} & + 2\text{Na} + \text{H}_3\text{C}_7\text{H}_7 & \xrightarrow{} & \text{C}-\text{O}-\text{C}_2\text{H}_5 \\
\text{C} & & \text{C}-\text{O}-\text{C}_2\text{H}_5 \\
\text{H} & & \text{H}
\end{align*}
\]

152.0  23  216.16

M  9686  32  0.515
gms 15  4.6  68

This reaction was carried out in a 3 neck, 1 liter round bottom flask, fitted with a return condenser, stirrer and dropping funnel.

As before the whole apparatus was thoroughly dried after being set up by drawing a stream of dry air through it and heating at the same time to 150° by means of an oil bath. Then after cooling to near room temp. 200 c.c. of absolute alcohol were distilled over into the flask and the sodium dissolved in it. About 1 hour was used to run in the n-butyl malonic ester.
after first cooling to about 50°. The condenser was then set downward and about 150 c.c. of alcohol distilled off into a 500 c.c. round bottom flask which had been dried in the same manner that the above apparatus was. The opening to the outside during the distillation was plugged with a CaCl₂ tube (as were all openings during the experiment). This 150 c.c. of alcohol was used to dissolve the 15 gms of 4(or 5)-chloromethylglyoxaline hydrochloride, which it did in the cold, although it was warmed to hasten the solution. The solution was slowly added during the course of about 4 hours, the temperature of the bath being about 105-120°, which was sufficient to keep the alcohol refluxing gently. Immediately after the first few drops of the chloride solution were added, a precipitate of NaCl began to form. After all the chloride had been added, the mixture was refluxed for two hours, and the alcohol distilled off under vacuo (not under 15 cm). The contents were transferred to 500 c.c. separatory funnel and treated with 150 c.c. of about 5% HCl and extracted three times with ether to remove all the non-nitrogen esters. Then it was made
alkaline with dry Na₂CO₃ when two kinds of oil separated. One was immiscible in both water and ether and was discarded. It was very black and tarry. The other oil was miscible in ether, but not in water. Two extractions with ether removed this completely from the water. After drying the ether solutions with anhy. Na₂SO₄ and evaporating to dryness, a pale brown liquid was obtained which poured readily when warmed, but was glassy when cold. It weighed 16.3 gms or 55.9% of the theory.

NOTE: The condensation of the glyoxaline chloride was tried with ethyl malonic ester before it was with any of the other substituted malonic esters. But due to the difficulty in getting very pure ethyl malonic ester (its boiling point being very close to malonic ester on the one side and diethyl malonic ester on the other) and due to the probability of the glyoxaline ethyl barbituric acid being less active physiologically than the butyl or isocamyl derivatives, the latter were made in preference to the former. Nevertheless, some interesting observations were made on these that deserve description.

First, an attempt was made to distill some of the impure ethyl-4(or 5)-glyoxaline methyl (diethyl) malonic ester. The pressure was reduced to about 0.3 mm. and the temperature of the bath raised to 200° when
a little yellow oil came over which partly solidified in the side arm and in the distilling flask. Decomposition in the distilling flask appeared to be taking place rapidly. The following tests were made on this oil-solid mixture.

It was found to be insoluble in water, and to contain nitrogen.

A little of the mixture was treated with ether when a white crystalline material was precipitated that was perfectly solid. When this was treated with dilute \( \text{HCl} \), it went into solution, but failed to come out when made alkaline with \( \text{Na}_2\text{CO}_3 \).

The ether precipitated material was recrystallized out of ethyl malonic ester.

These tests and others lead to the conclusion that the solid was a substituted malonic acid formed by the glyoxaline malonic ester losing one or both of its ethyl groups and, therefore, that it cannot be distilled.

The 5, 4(or 5)-glyoxaline methyl, 5n-butyl (diethyl) malonic ester was found to be rather hygroscopic and it was necessary to place it in vacuo three days over phosphorus pentoxide to get it perfectly dry. This was absolutely necessary before condensing it with urea.
A condensation of the glyoxaline chloride was conducted with the ethyl malonic ester under the following rather unusual conditions. The temperature was maintained at from 10^215^°. To about 25-35 c.c. of absolute alcohol in a 200 c.c. round bottom flask was added 1 gm. sodium and 8 gm. of ethyl malonic ester. Then 3 gms of the glyoxaline chloride, mashed fine, was added as a solid. After a few minutes NaCl began to separate out. During the course of 1 hour the temperature was allowed to rise to 0° with occasional shaking and finally to room temperature. The mixture was then treated with dilute HCl, extracted with ether, made alkaline with Na_2CO_3. Yield was about 40% theory.

A condensation of the glyoxaline chloride with n-butyl malonic ester was carried out under the following conditions. Five hours and 45 min. were taken for the addition of the glyoxaline chloride solution in absolute alcohol. It was added dropwise, as slowly as possible. Three molecular proportions of n-butyl malonic ester were used. After refluxing an hour, the contents were worked up as usual. A considerable amount of the black tar, immiscible in both water and ether, was found.

Some of the pale brown glyoxaline, n-butyl malonic
ester was dissolved in dilute hydrochloric acid and treated twice with Norite in the cold to remove the color, but was unsuccessful.

Another condensation of the glyoxaline chloride with the n-butyl malonic ester was carried out using twice the theoretical amount of sodium. It was thought it might be possible to push the equilibrium toward the desired compound by using an excess of sodium n-butyl malonic ester. This would follow, provided the tar formed in the reaction was due to the reaction of the glyoxaline chloride with itself, as it might well do considering that it is both a reactive chloride and amine. If, on the other hand, the tar were due to the decomposition of the glyoxaline malonic ester by the sodium n-butyl malonate, a poorer yield would be obtained by using more than an equivalent amount of sodium. Only 8.0 gms of the desired ester were obtained which is 36.8% theory. Hence, the origin of the tar is probably the glyoxaline n-butyl malonic ester and is caused by the sodium. It is best, therefore, to be careful to use exactly equivalent amounts and to add the glyoxaline chloride over a short period of time; e.g., 2 hours.
THE PREPARATION OF 5-4(OR 5)-GLYOXALINE METHYL,

5-N-BUTYL BARBITURIC ACID

\[
\begin{align*}
\text{HCO} &= \text{C-CH}_2-\text{C-C}_4\text{H}_9 + 3\text{Na} \rightarrow \text{C}=\text{O} + \text{C}_2\text{H}_5\text{OH} \\
\text{H}_2\text{C}&=\text{C-CH}_2-\text{C-C}_4\text{H}_9 + 3\text{Na} \rightarrow \text{C}=\text{O} + \text{C}_2\text{H}_5\text{OH}
\end{align*}
\]

80 c.c. of absolute alcohol was distilled into a pyrex tube (dried by heating with a luminous flame and drawing dry air through it) and the required sodium dissolved in it, atmospheric moisture being excluded by plugging the end with a CaCl_2 tube. Then the evaporating dish containing the glyoxaline n-butyl malonic ester was placed on the hot plate for about 10 min. At the end of this time the substance was sufficiently liquid to pour
through a short funnel into the tube. The evaporating dish and funnel were then washed out quickly with 10 c.c. of hot alcohol. Finely powdered urea, which had been dried in vacuo over concentrated \( \text{H}_2\text{SO}_4 \), was added and went into solution easily. The tube was then sealed off after washing the hydrogen gas, generated by the sodium and alcohol, out with dry air. If permitted to remain in the tube, it would have been ignited when the tube was sealed off, thus forming water that would have been absorbed by the alcohol. The contents were shaken thoroughly and then placed in an iron pipe and heated by a stream of steam through the pipe.

After the tube had been heated for 22 hours, it was removed from the pipe and opened. The contents of the tube were light brown in color. There were about 2 gms of a precipitate from which the liquid was decanted.

The latter was evaporated to near dryness under reduced pressure over concentrated \( \text{H}_2\text{SO}_4 \). A strong odor of ammonia gas was observed on opening the tube.

The precipitate was taken up in about 33 c.c. of water and extracted with ether to remove the unreacted malonic ester. It was then slowly made neutral with acetic acid, after being treated twice in the cold with
Norite. However, no precipitate was obtained, the initial precipitate presumably being nearly all Na₂CO₃.

The residue from the evaporation was dissolved in 80 c.c. of water and extracted twice with ether to recover the unchanged glyoxaline malonic ester. Not very much was obtained. Next the dark solution was treated three times in the cold with Norite. This did not clear the solution very much. Then dilute acetic acid (3-5 c.c. in 50 c.c. H₂O) was carefully added. On approaching the isoelectric point, a large amount of tar separated, but a slight cloudiness prevailed throughout the solution. It was filtered immediately and in the filtrate a fine powder gradually separated. This, after about 5 min., was filtered off. It was light brown in color and weighed about 0.1 gm. The tar was 3-5 times this much. This filtrate, on standing over night, deposited another gram of the powder.

This substance was recrystallized out of dilute alcohol and treated while dissolved with Norite, when it separated in snow white crystals.

On this material a micro-Dumas was run.
Sample = 5.964 mg.
Corrected volume $V_2 = 1.197$ c.c. at $29.6^\circ$ and 769.3 mm.
$V_2$ calculated = 21.21 \%
$V_2$ found = 22.00 \%

After another recrystallization out of dilute alcohol, the analysis was:
Sample = 5.412 mg.
Volume $V_2$ (cor.) = 1.104 c.c.
$V_2$ calculated = 21.21 \%
$V_2$ found = 21.98 \%

Still another micro-Dumas was run, and I think one is justified in regarding this as the most nearly correct value, since getting the right answer with micro-Dumas determinations is largely a matter of practice.
Sample = 4.738 mg.
Volume $V_2$ (cor.) = 0.953 c.c. at $29.4^\circ$ and 762.0 mm.
$V_2$ calculated = 21.21 \%
$V_2$ found = 21.72 \%

On attempting to determine the melting point of the compound it was found to decompose around $290^\circ$ and above to a black tarry material which did not resolidify on cooling. It was found to be practically insoluble in water and ether, but quite soluble in alcohol. It did not dissolve to any appreciable extent in $10\%$ HCl, but went in easily on heat-
ing to the boiling point to crystallize out in colorless needles. It was found to be easily soluble in concentrated HCl. When this solution is allowed to stand colorless needles, presumably the glyoxaline malonic acid, separates out.

NOTE: The first three or four times the glyoxaline malonic esters were condensed with urea, a black tar was obtained. It had the same solubility as the desired compound and, therefore, was assumed to be it.

Many experiments, of which only a few will be enumerated, were conducted to get a crystalline substance out of this tar.

Some of it was dissolved in water and made slightly acid with HCl and treated with picric acid. A fairly crystalline picrate separated out. This was not a suitable derivative, however, as picrate cannot be injected into the blood stream. This water solution, acidified with HCl, was also treated with BaCl₂, and acidified with acetic acid with lead acetate without obtaining a precipitate. Next about 5-10 c.c. of water containing the tar was mixed with 8 c.c. of 10% solution of chloroplatinic acid. Only the barest sort of a precipitate came down.

Next, some of the tar was dissolved in dilute HCl
(slight excess) and evaporated to dryness in an attempt to prepare the hydrochloride.

The result was a gummy brown mass with the crystal structure fairly well hidden. Some of the tar was dissolved in absolute alcohol and a drop of concentrated H₂SO₄ added when a fairly crystalline precipitate separated. It was very hygroscopic (as the tar and hydrochloride were), however, and changed to a glassy mass on the filter.

Another portion of the tar was dissolved in alcohol and cooled to about -50° (with solid CO₂) and ether slowly added. The material was precipitated out, but on filtering, proved to be little more crystalline than the original tar.

An attempt was made to prepare the benzoate by dissolving some of the tar in 80% alcohol, adding an excess of benzoic acid, neutralizing this excess with Na₂CO₃, and evaporating to dryness. The organic residue was then taken up with absolute alcohol and allowed to evaporate slowly in a desiccator. Only a tar was obtained.

Finally some of the tar was dissolved in dilute alcohol and allowed to spontaneously evaporate over CaO in a desiccator placed in an ice box. Again only tar resulted.

Also, some of the tar was dissolved in the calculated
amount of \(1/\text{H} \, \text{NaOH}\) and evaporated to dryness. A hygroscopic, fairly solid salt was obtained that would not wash white with chloroform. Some of it was dissolved in absolute alcohol and precipitated with ether without whitening it or getting it more crystalline.

Some of the tar was dissolved in \(\text{NaOH}\) and treated with Horite three times in the cold. It was then made acid with \(\text{HCl}\) and treated three times in the cold with Horite. On neutralization, the same black tar precipitated out.

Concerning the reason of the formation of the tar, it was found that the cause was heating too long. In experiments where the tube was heated \(36-40\) hours, the tar was formed to the exclusion of all else. With \(20\) hours some of the desired barbituric acid was obtained and on heating \(10\) hours, a still better yield was obtained. Presumably it was the sodium or sodium hydroxide which caused the trouble, since heat would not cause such marked decomposition alone. The optimum time of heating is about \(7\) hrs.

In order to oriente ourselves, the following control experiments were made:

First, an experiment identical to the condensation of the glyoxaline \(n\)-butyl malonic ester with \(\text{urca}\), omitting the glyoxaline malonic ester, was made. That is, the same
amounts of Na, urea, and alcohol were placed in the tube and heated for 10 hours. At the end of that time, the contents of the tube were almost white which showed that the brown color observed when the glyoxaline malonic ester was present was due to its decomposition or its products.

Next a synthesis of barbituric acid itself was carried out using the same proportions as with the glyoxaline experiments to check the conditions of heating, technique, absoluteness of the alcohol, etc. A yield of about 90% was obtained.
PREPARATION OF ISOCARYL (DIETHYL) MALONIC ESTER

\[
\begin{align*}
\text{CH}_3\text{C}=\text{O} & \quad \text{C}_2\text{H}_5 \\
\text{H}_2\text{C=O} & \quad \text{C}_2\text{H}_5
\end{align*}
\]

+ Na ➞

\[
\begin{align*}
\text{CH} & \quad \text{C}_2\text{H}_5 \\
\text{H}_2\text{C=O} & \quad \text{C}_2\text{H}_5
\end{align*}
\]

160.096  23
M  763  739
gms 122  16.997

\[
\begin{align*}
\text{CH}_3\text{C}=\text{O} & \quad \text{C}_2\text{H}_5 \\
\text{H}_2\text{C}=\text{O} & \quad \text{C}_2\text{H}_5
\end{align*}
\]

+ C\text{C}_\text{H}_2\text{Br} ➞

\[
\begin{align*}
\text{CH} & \quad \text{C}_2\text{H}_5 \\
\text{H}_2\text{C}=\text{O} & \quad \text{C}_2\text{H}_5
\end{align*}
\]

151.004  230.176
739  739
111.5  170.8

This synthesis was carried out similarly to that of n-butyl malonic ester.

The product was distilled twice. A molecular refraction determination on the first part of the accepted cut is as follows:

\[
\begin{align*}
\text{R.I.} &= 1.4262 \\
\text{d} &= 0.9640 \\
M_\text{p \ calculated} &= 60.92 \\
M_\text{p \ found} &= 61.19
\end{align*}
\]

Hence, this product is free from ethyl malonate.

NOTES: In preparing these esters, it was deemed very important to get them free of ethyl malonate since the glyco-
aline malonic ester produced was not purified by the usual distillation. Instead, the impure ester was condensed with urea; consequently if there was any malonic ester present, the desired barbituric acid would be impure due to the presence of some 5-, 4(or 5)-glyoxaline methyl barbituric acid. On the other hand, any disubstituted malonic ester present would not be important due to the fact that it could not be further substituted.
The reaction was carried out in a similar fashion to that for the preparation of 4-(or 5)-glyoxaline. It differed, however, in the following details. The chloride, dissolved in 100-120 c.c. of absolute alcohol, was added over a period of 2.5 hours rather than 4 hours and the temperature during the addition was maintained at 95-105° instead of 105-120°. Also, instead of refluxing for 2 hours, it was only refluxed ½ hour. This was justified in view of the experiment mentioned above which indicated that heat and alkali produce tar with glyoxaline compounds.
The mixture was worked up as was the n-butyl glycolaldehyde mononic ester and the yield was 12.8 gms corresponding to 52.3% theory.

The product, as before, was pale brown and very viscous when cold.
PREPARATION OF 5-,4-(OR 5)-GLYOXALINEMETHYL, 5-ISOALYL

BARBITURIC ACID

\[
\begin{align*}
\text{C}_6\text{H}_5\text{C}=\text{O} & + 1\text{H}_2\text{O} + 3\text{Na} \\
\text{C}_6\text{H}_5\text{C}=\text{O} \quad \text{NH}_2
\end{align*}
\]

\[
\begin{align*}
\text{C}_6\text{H}_5\text{C}=\text{O} \quad \text{NH}_2
\end{align*}
\]

The procedure in this case differed from that for the preparation of 5-,4-(or 5)-glyoxalinemethyl, 5-n-butyl barbituric acid in the time of heating. Whereas, before the tube was heated for 22 hours, the time was shortened to 10 hours. The amount of ammonia resulting from the hydrolysis of urea by sodium hydroxide was scarcely noticable. Part of the sodium salt of the barbituric acid had precipitated, but most of it was in solution.

The product, purified by several recrystallizations out of dilute alcohol, gave the following analysis by the micro-Dumas:
Sample = 4.899 mg

_{N_2} Corrected volume 325 at 762.0 mm and 30°

_{N_2} calculated = 20.15 %

_{N_2} found = 20.32 %

To exclude entirely the possibility of the compound being barbituric acid, a carbon and hydrogen determination was made that checked the formula O,\textsubscript{13} H,\textsubscript{5} O,\textsubscript{3} H,\textsubscript{4} within about 2%. The percents of carbon and hydrogen in barbituric acid are much lower than in the above described product.
PREPARATION OF ALLYL (D I T H Y L ) M A L O N I C E S T E R

\[
\begin{align*}
\text{CH}_2=CH & \xrightarrow{\text{Na}} \text{CH} \\
\text{C}-\text{O}-\text{C}_2\text{H}_5 & \xrightarrow{\text{Na}} \text{C}-\text{O}-\text{C}_2\text{H}_5
\end{align*}
\]

This experiment was in every way similar to that for the preparation of isocamyl (diethyl) malonic ester, except that it was necessary to fractionate three times instead of twice to get the product pure. The purity of the fraction was determined by an optical analysis.

\[
\begin{align*}
R.I. & = 1.4282 \\
\text{d} & = 1.025 \\
M_b \text{ calculated} & = 49.85 \\
M_b \text{ found} & = 50.34
\end{align*}
\]
PREPARATION OF 4 (OR 5)-GLYOXALINEMETHYL, ALLYL MALONIC ESTER

\[
\begin{align*}
\text{Na} & \quad \text{C} = \text{C} - \text{CH}_2 \text{H}_5 \\
\text{C} = \text{C} - \text{C}_2 \text{H}_5 \\
\text{H}_3 - \text{C}_2 \text{H}_5 + \text{Na} & \quad \text{C} = \text{C} - \text{C}_2 \text{H}_5 \\
\text{C} = \text{C} - \text{C}_2 \text{H}_5 \\
\text{C} = \text{C} - \text{C}_2 \text{H}_5 \\
\end{align*}
\]

200.138  23
M 252.06
gms 50.14  3.30

\[
\begin{align*}
\text{H} & \quad \text{H} \\
\text{C} = \text{C} - \text{C}_2 \text{H}_5 \\
\text{H}_3 - \text{C}_2 \text{H}_5 & \quad \text{H}_3 - \text{C}_2 \text{H}_5 \\
\text{C} = \text{C} - \text{C}_2 \text{H}_5 \\
\text{C} = \text{C} - \text{C}_2 \text{H}_5 \\
\text{C} = \text{C} - \text{C}_2 \text{H}_5 \\
\end{align*}
\]

152.976  275.136
0.0789  0.0789
12  21.7

The procedure employed to synthesise this compound differed from that used to prepare 4 (or 5)-glyoxalinemethyl isocamyl malonic ester in the following details. The time of addition of the glyoxaline chloride was shortened to 2 hrs. Then the mixture was treated with about 10% HCl rather than 5%. Yield was 13.8 gms or 62.4% of theory. This was the best yield obtained for this type synthesis.

The condensation of this product with urea did not turn out well due to the unfortunate presence of some water in the reaction mixture. Undoubtedly this was due to a hydric formation. Other experiments have indicated that the glyoxaline compounds are either extremely hygroscopic or form hydrates of great stability.
PREPARATION OF P-, 4(O R 5)-GLYOXALINEMETHYL AMINOBENZOIC ACID

\[
\begin{align*}
\text{HCl} & \quad \text{O} \\
\text{Cl} & \quad \text{O} \\
\text{H} & \quad \text{H} \\
\text{H} & \quad \text{N} \\
\text{C} & \quad \text{H} \\
\text{O} & \quad \text{Na}_2\text{CO}_3 \quad \longrightarrow \\
\text{H} & \quad \text{N} \\
\text{C} & \quad \text{H} \\
\end{align*}
\]

This compound was the product obtained when an attempt was made to synthesize 4(or 5)-glyoxalimethyl, p-aminobenzoate.

In about 5 c.c. of water the Na\textsubscript{2}CO\textsubscript{3} and p-aminobenzoic acid were dissolved. The solution was cooled to about 0° and the 4(or 5)-chloromethyl glyoxaline hydrochloride added. Vigorous foaming due to the evolution of carbon dioxide occurred and gradually over a period of several minutes the new compound separated in the form of a white hard powder. It was filtered off and had a m.p. 213°(uncorr.). It possessed on standing several days a yellow odor from which it was freed by dissolving in boiling water and filtering through Norite. It crystallized out in perfectly white crystals, m.p. 219° (corr.) with decomposition.

This new compound although nearly insoluble in cold water was very soluble in dilute NaOH which it should not be if it were an ester. To exclude the possibility of it being a very rapidly hydrolyzing ester, some of its solution in alkali acid was made and a melting point of the precipitated material taken. It was found to be a few degrees lower than the material dissolved. On the other hand, p-aminobenzoic acid melts at 186°.
The new compound was shown not to be an ester by dissolving it in NaOH and refluxing for 1.5 hours. Then the solution was neutralized with acetic acid and a precipitate, m.p. 209-10° (uncorr.), came down. Hence, the compound was not hydrolyzed. To demonstrate it not to be the benzoic acid salt of 4(or 5)-hydroxymethyl glyoxaline 0.5 g. of the glyoxaline chloride was refluxed with 0.349 g. Na₂CO₃ for a half hour. This necessarily converted all of the glyoxaline chloride into the alcohol and left the solution neutral. Then 0.45 g. of p-aminobenzoic acid was added and the mixture heated until the acid went into solution. On cooling a brown precipitate came down that had m.p. 180° (uncorr.). This in its state of impurity was about what p-aminobenzoic acid would be expected to melt. A mixed melting point was 161-2°.

A micro-Dumas was run on a sample that had been dried for several days over concentrated H₂SO₄ in vacuo. It took up water at an extremely fast rate when exposed to air.

Sample = 5.942
Corrected volume N₂ = 1.038 c.c. at 28.5 and 767.4 mm.
N₂ calculated (C₆H₅N₂O₂) = 19.34 %
N₂ found = 19.22 %

The only other possibility of a compound with this percent nitrogen and which is amphoteric is p-4(or 5)-glyoxalimethyl aminobenzoic acid.
This was somewhat unexpected, as one would expect the sodium atom to be much more reactive in a double decomposition than the hydrogen on the amino group. Still, it can be explained by assuming that the very active chloride has a greater tendency to add on the nitrogen, to form a quaternary ammonium salt, which would be easily decomposed by the alkali present, from hydrolysis of the sodium p-amino benzoate. Numerous other examples of the same type of reaction are reported in the literature 1,2.

1. B.5, 1038
2. Helv. 2, 245, 248