THE RICE INSTITUTE

SYNTHETIC APPROACHES TO POLYCYCLIC
BRIDGED RING COMPOUNDS

by

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INTRODUCTION

Despite a voluminous literature on the chemistry of the diterpenes,\(^1\) comparatively little work has been done on diterpenoid substances possessing bridged structures. Interest in substances of this type has been stimulated by the recent elucidation of the structures of the diterpene alkaloids garryine (I),\(^2\) veatchine (II),\(^2\) cuauuchichicine (III),\(^3\) the glycoside of *Stevia rebaudiana*, stevioside (IV),\(^4\) and atisine (V),\(^5\) an alkaloid of theaconite group in which the terminal ring structure is based on a bicyclo(2,2,2)octane, rather than on the bicyclo(1,2,3)octane, nucleus. It may be
noted further that the recent suggestion that lycoctonine (VI) is biogenetically derived from a precursor possessing the atisine skeleton provides the basis for a tentative correlation of the complex aconite and delphinium alkaloids with the simpler bridged diterpenes.

Of the compounds that have been considered thus far all but atisine and lycoctonine appear to be related to the hydrocarbon phyllocladene, for which structure VII has been proposed. Although certain details of the constitution of phyllocladene remain to be settled, the nature of the bridged C/D ring system is established with reasonable certainty. The presence of a vinylidene group attached to a five membered ring may be inferred from the infrared spectrum which shows characteristic vinylidene absorption at 3.36 (\(\text{C} = \text{C}_\text{H}\) stretching), 6.04 (\(\text{C} = \text{C}\) stretching) and 11.4\(\mu\) (\(\text{C} = \text{C}_\text{H}\) bending), and from the fact that the substance affords formaldehyde and the norketone VIII which exhibits cyclopentanone absorption in the infrared at 5.74\(\mu\). The presence of one methylene group adjacent to the carbonyl group in VIII has been deduced from intensity measurements of the infrared band at 7.12\(\mu\) which is assigned to methylene bending vibrations.
On treatment with acid phyllocladene yields isophyllocladene (IX), oxidizable to a keto acid for which structure X is proposed. The keto acid gives a positive iodoform test for a methyl ketone and on refluxing for 2½ hours with 4% methanolic hydrogen-chloride furnishes an isomeric keto acid, presumably by inversion of the acetyl group to give the more stable trans-arrangement of substituents. The failure of the carboxyl group to undergo esterification under these conditions is noteworthy and suggestive of its attachment to a quaternary carbon. When subjected to selenium dehydrogenation, X furnishes 1-methyl-7-ethylphenanthrene (XI). This fact, coupled with the observation that phyllocladene yields both retene (1-methyl-7-isopropylphenanthrene) and pimanthrene (1,7-dimethylphenanthrene) on dehydrogenation, establishes one point of attachment of the 5-membered D ring to ring C, the relation of the methylene group to this junction, the probable incorporation of rings A, B, and C in a hydrophenanthrene system, and the location of a substituent, presumably methyl, in ring A. Assuming that the hindered carboxyl group of X is attached to a quaternary carbon and assuming a disposition
of the two remaining methyl groups analogous to that in other diterpenes, structure VII follows for phyllocladene. This last assumption is supported by infrared evidence which indicates by intensity measurements the presence of one gem-dimethyl group (7.22 and 7.30μ) and one angular methyl group between two six-membered rings (7.24μ).

The question of the stereochemistry of phyllocladene and its relatives has thus far received slight attention. Wiesner and Edwards have discussed the problem as it relates to garryine and veatchine. Their conclusions, which are based upon consideration of the influences of steric factors on the basicity of these compounds and their derivatives, are expressed in formula XII.* A similar proposal for the stereochemistry of phyllocladene (see formula XIII) has been advanced by Wenkert in connection with a mechanistic interpretation of the conversions of rimuene and mirene, for which Wenkert suggests structures XIV and XV respectively, into isophyllocladene (XVII) in the presence of acid. The

* The configuration of the hydrogen atoms at the A/B and C/D bridge heads were not specified by Wiesner and Edwards but were apparently assumed to be as indicated.
non-classical carbonium ion XVI is postulated as a common intermediate for both transformations. Although the scheme possesses certain attractive features, the argument suffers considerably from lack of definite evidence on the structures and stereochemistry of rimuene and mirene. It is of interest to note that a related cyclization process has been observed in the conversion of limonene (XVIII) into bicycloisolimonene (XIX) when the former substance is passed over hot silicophosphoric acid\textsuperscript{12}.

The most recent evidence bearing on the stereochemistry of phyllocladene is that derived from rotatory dispersion measurements on the norketone VIII\textsuperscript{13}. The data has been interpreted by the use of some rather tenuous correlations as favoring the mirror image of structure XIII.
In evaluating methods for the stereo-specific synthesis of diterpenes related to phyllocladene, it appeared that the preparation of intermediates of type XX containing the B/C ring system in both cis and trans modifications with functional groups to permit elaboration of rings A and D would offer considerable advantage. Methods for the introduction of the angular methyl group and incorporation of the A ring (cf. XXI) have been thoroughly explored in the steroid series, and conversion of a product such as XXI into a derivative (XXII) possessing the typical geminal dimethyl structure finds ample analogy in the transformation of cholestenone into lanosterol.

Among the procedures that can be visualized for closure of ring D are the acyloin condensation and Arndt-Eistert homologation of the hindered carboxyl group, followed by pyrolytic cyclization of the resulting diacid. In each case the cyclization step is irreversible and hence more suited to the synthesis of a strained bridged system than a reversible one (i.e., Dieckmann ring closure). The present investigation was undertaken for the purpose of evaluating...
these two approaches. Since trans-decalin derivatives of the desired type are more readily obtained than the corresponding cis-decalins, the work recorded in this dissertation was carried out on trans-fused models.

The preparation of the starting diacid (XXVIII) was accomplished by the transformations contained in Chart I. Malonic ester was condensed in the Michael reaction with two molecules of acrylonitrile by a modification of the procedure employed by Hesse\textsuperscript{18} for monocynoethylation. Diethyl bis(2-cyanoethyl)-malonate (XXIII)\textsuperscript{18,19} was obtained in this way in 85% yield. The crystalline product was then hydrolyzed with concentrated hydrochloric acid and decarboxylated to XXIV\textsubscript{a} by heating to 200\textdegree. Esterification with methanol and sulfuric acid afforded 1,3,5-tricarbomethoxypentane (XXIV\textsubscript{b}) in an overall yield of 84% from (XXIII). Dieckmann cyclization of the triester by the method of Openshaw and Robinson\textsuperscript{20} proceeded smoothly, and the product (XXV) after preliminary distillation was obtained as large prisms melting at 44-45\textdegree. Attempts to condense the keto diester (XXV) with 4-diethylamine-2-butanone methiodide and sodium methoxide, a procedure that was successful when applied to 2-carbethoxy-cyclohexanone\textsuperscript{21,22} or with methyl vinyl ketone and triethylamine, gave only recovered starting material. The keto diester was hence converted into the corresponding sodium enolate with sodium hydride, and the salt was then allowed to react with 4-chloro-2-butanone.
CHART I

\[
\text{NCCH} = \text{CH}_2 + \text{CH}_2 + \text{CH} = \text{CH}_2 \text{CN} \rightarrow \text{RO}_2\text{CCH}_2\text{CH}_2\text{CH} - \text{CH}_2\text{CH}_2\text{CO}_2\text{R}
\]

\[\text{XXIII}\]

\[\text{XXIVa} \quad R = \text{H} \quad \text{CO}_2\text{R} \]

\[\text{XXIVb} \quad R = \text{CH}_3\]

\[\rightarrow \quad \text{XXV} \quad \text{CO}_2\text{CH}_3 \]

\[\rightarrow \quad \text{XXVI} \quad \text{CO}_2\text{CH}_3\]

\[\rightarrow \quad \text{XXVII} \quad \text{CO}_2\text{CH}_3 \]

\[\rightarrow \quad \text{XXVIII} \quad \text{CO}_2\text{H}\]
Formulation of the alkylation step as a simple displacement suggested that the chloroketone, being less hindered than the Mannich base methiodide at the site of substitution, might provide a more suitable reagent. The reaction proceeded rapidly with the separation of sodium chloride, and the crude product was employed directly for cyclization without purification. Attempts to effect ring closure with sodium methoxide and with sodium hydride failed, and in view of possible intervention of the reverse Michael reaction, attention was turned to the use of weak bases. Both triethylamine and piperidine acetate were tried without success. Cyclization was finally accomplished with p-toluene-sulfonic acid in catalytic amount. The reaction was carried out in benzene solution under a continuous water separator, and the oily material resulting from this treatment afforded crystalline bicyclic product (XXVI), m.p. 88-89°, \( \lambda \) max. 237 nm, \( \varepsilon \) 12,000, on crystallization from ether. The yield, while only about 20%, proved sufficient for study of the subsequent steps, and the reaction was not investigated further.

Hydrogenation of the unsaturated keto diester XXVI proceeded smoothly over palladized charcoal, furnishing the saturated \( \beta \)-decalone derivative (XXVII), m.p. 88-89°, in 90% yield.
The particular configuration assigned to this product is based on analogy to the corresponding reduction of $\Delta^{1,9}$-10-carbomethoxy-2-decalone (XXIX$\alpha$), which is known to yield the trans-fused product (XXIX)$\beta$, and

\[
\text{XXIX}_\alpha
\]
\[
\text{XXIX}_\beta
\]
on the assumption that the C.6 carbomethoxy group adopts the more stable equatorial orientation.

Hydrolysis of (XXVII) presented certain difficulties in view of the severity of the conditions required for removal of the hindered ester function. Prolonged treatment with 25% alcoholic potassium hydroxide at 80° gave amorphous material that could not be satisfactorily purified. Although the hydrolyzed product showed no conjugated carbonyl absorption in the ultra-violet or infrared which might arise from intermolecular aldol condensation, removal of the carbonyl group appeared to offer advantages in this as well as in the subsequent steps. The compound was, therefore, subjected to Wolff-Kishner reduction in diethylene glycol at 215°. Cleavage of the ester groups occurred concurrently with reduction of the carbonyl group and a crystalline diacid (XXVIII), m.p. 227-228°, neutral equivalent 113.6, was obtained in 60% yield.

It is of interest to note that Wolff-Kishner
reduction of (XXIX), which has been carried out under somewhat more vigorous conditions than those employed in the present case, gave a 32% yield of (XXX) together with 58% of the corresponding hydrazide (XXXI)\(^{22}\).

![XXX](image1)

![XXXI](image2)

Under conditions comparable to those of this investigation, (XXIX) furnishes 82% of crude (XXX)\(^{25}\). No attempt was made to isolate hydrazide from the reduction of (XXVII), and some of this product may well have been present.

In the hope that Arndt-Eistert homologation of the hindered carboxyl group in (XXVIII) might yield a product (XXXIII) susceptible to pyrolytic ring closure with inversion to yield the tricyclic ketone (XXXIV), the diacid (XXVIII) was converted into the crystalline half ester (XXXII) under the Freudenberg conditions\(^{26}\). Treatment of the latter product with thionyl chloride furnished an oily acid chloride showing characteristic infrared absorption at 5.60 (\(-\text{CO}\)) and 5.80 \(\mu\) (\(-\text{COCl}\)).
The acid chloride was then treated with excess diazomethane, and the material that was recovered after removal of the solvents was subjected to the conditions of the Wolff rearrangement (methanol and silver oxide). The product was finally saponified, and a crystalline acid was isolated which melted at 104-105°. The compound, however, gave a neutral equivalent of 240.8 and was readily identified as the half ester (XXXV) by comparison with an authentic sample derived from the amorphous dimethyl ester of (XXVIII) by partial hydrolysis.

\[
\text{XXXV}
\]

A re-investigation of the Arndt-Eistert sequence revealed that the acid chloride was inert to the action of diazomethane and that no diazoketone was formed. This fact was established in two ways. Material recovered from the diazomethane reaction showed infrared absorption characteristic of the starting acid chloride. Although the intensity of the 5.60μ band was somewhat reduced in this sample, no bands attributable to a diazoketone structure were detectable. Furthermore, treatment of the recovered product with aqueous sulfuric acid gave no evidence of nitrogen evolution and afforded material which gave a negative response in the Fehling test for α-ketols. Despite the
resistance of the acid chloride to the action of diazomethane, it is of interest to note that it undergoes methanolysis with reasonable facility.

A survey of the literature reveals at least two examples of hindered acid chlorides which fail to react with diazomethane, these being mesitoyl chloride (XXXVI) and the chloride (XXXVII) from the acid ester of homocamphoric acid. Although both these cases would appear to involve considerably more hindrance than the acid chloride derived from (XXXII), it should be noted that the angular substituent in (XXXII) bears an axial relationship to both rings, and that the methyl ester (XXXV) can be recovered unchanged after treatment with 3-4% potassium hydroxide in aqueous diethylene glycol at 145° for one hour.

With the failure of the Arndt-Eistert approach,* attention was next directed towards the acyloin reaction. For this purpose the cis-diester (XL)

* The possibility still exists that the Arndt-Eistert method might succeed with a cis-decalin derivative of type (XXXII) in which the angular carboxyl would be axial with respect to one ring, but equatorial with respect to the other. This matter has not been further investigated.
was deemed more suitable than the corresponding trans-diester to which reference has already been made, since the latter substance could undergo intramolecular cyclization only after inversion of the C.2 carbomethoxyl group. Preparation of the cis-diester was accomplished as follows. The trans-diacid (XXVIII) was converted into the anhydride (XXXVIII) by prolonged refluxing with acetic anhydride

```
XXVIII  \rightarrow
XXXVIII \rightarrow
XXXIX

\rightarrow
XL
```

and sodium acetate. Preliminary experiments in which sodium acetate was not employed gave poor yields of (XXXVIII) accompanied by large amounts of gummy material, the infrared spectrum of which (5.60, 5.75 μ) indicated the probable presence of polymeric anhydride. When sodium acetate was added (in order to catalyze the trans to cis inversion) (XXXVIII) was obtained as microscopic crystals, m.p. 88-89°, in 71% yield. The
Infrared spectrum of this material showed peaks at 5.55 and 5.68 \( \mu \) typical of a glutaric anhydride\(^2\). 

Hydrolysis of (XXXVIII) was carried out in aqueous acetone without a catalyst and furnished the cis-diacid (XXXIX), m.p. 229-230\(^\circ\), in 83%. A mixed melting point with the trans-diacid (XXVIII) was depressed to 206-209\(^\circ\), and the infrared spectra of the two compounds showed several distinctive differences. Esterification of (XXXIX) with diazomethane proceeded normally and furnished the desired diester (XL), m.p. 68-69\(^\circ\), in virtually quantitative yield.

Initial attempts to effect the acyloin condensation of XL with sodium in xylene under the usual conditions\(^3\) were unsuccessful. In one experiment carried out at 125\(^\circ\) for 5 hours, the only isolable product was identified as unchanged starting material. More prolonged treatment (12 hours) afforded an anomalous product which showed no hydroxyl or carbonyl absorption in the infrared. The material appeared to be chromatographically homogeneous and distilled at a bath temperature of 260\(^\circ\) at 1 mm. All attempts at crystallization were unsuccessful and the material was not further investigated.
Attention was next directed towards the possibility of effecting the acyloin condensation in liquid ammonia under conditions employed successfully by Sheehan and his associates in numerous cases involving the closure of a 5-membered ring. When the reaction was modified to the simultaneous slow addition of sodium and an ethereal solution of (XL) to the liquid ammonia solvent, a mixture of products was obtained, which on chromatography furnished approximately 23% of crude material, giving a positive test with Fehling's solution. On crystallization from petroleum ether a pure sample, m.p. 77°-78°, showed banded hydroxyl and 5-membered ring ketone absorption* at 2.80 and 5.78μ, respectively, in the infrared (carbon disulfide solution). Carbon - hydrogen analyses gave values corresponding to the formula C₁₂H₁₈O₂, and the

* Though normal 5-membered ring ketone absorption is 5.70 to 5.75μ, the presence of an α-hydroxyl group would be expected to increase the carbonyl absorption by about 0.04μ, presumably due to hydrogen bonding.
substance is, hence, formulated as indicated in structure (XLI). Insufficient material was available for investigation of the problem of the exact location of the carbonyl and hydroxyl groups, but it may be noted that this question is not particularly relevant to the conversion of (XLI) into the desired product (XXXIV). Prelog and coworkers\textsuperscript{32} have obtained ketones (XLIII) by treatment of various acyloins with hydrochloric acid and zinc, and Sheehan\textsuperscript{17b} has reported good results in the conversions indicated by transformations (XLII)\textsuperscript{→}(XLIV)\textsuperscript{→}(XLV).

Although there are numerous examples of the acyloin condensation yielding 5-membered rings,\textsuperscript{33} a literature search failed to reveal any other instance in which a bridged 5-membered ring system had been formed by this reaction. However, it is clear that
unless the yield of acyloin can be markedly improved
the process has little to offer as a synthetic route
to more complex molecules. Towards this goal,
several modifications of the original experiment
were tried without success. Thus, in one run lithium
was employed on the assumption that a less reactive
metal might favorably change the ratio of the re-
action products. Duplication of Sheehan's pro-
cedure as well as inverse addition of the sodium
to the cis-diester (XL) in a liquid ammonia - ether
solution showed no improvement in yield.
III
EXPERIMENTAL

Preparation of Diethyl bis-(2-cyanoethyl)-malonate (XXIII). - Sodium metal (4.6 g., 0.2 mole) was added slowly in small pieces to absolute ethanol under nitrogen. After the sodium had dissolved, the excess alcohol was removed under reduced pressure, and the residual slightly yellow sodium ethoxide was suspended in 300 ml. of dry ether. Diethyl malonate (160.2 g., 1 mole) was added and 106 g. of acrylonitrile (2 moles) was then introduced through a dropping funnel with mechanical stirring. Heat was evolved immediately, and the ether continued to reflux throughout the addition. After a further 15 hour reflux period, the reaction flask was cooled in an ice bath, and the solution was acidified with dilute hydrochloric acid. The resulting aqueous layer was separated and extracted with ether. The combined organic portions were then washed successively with cold, dilute sodium bicarbonate solution, water, and a saturated solution of sodium chloride. After drying over anhydrous sodium sulfate, the ether was removed under reduced pressure, affording 229 g. (86%) of a white crystalline product. Recrystallization from ethanol gave 220 g. of pure material, m.p. 61-62° (literature value, 61.5° 19).
Preparation of 1,3,5-Tricarbomethoxypentane (XXIVb). - Diethyl bis-(2-cyanoethyl)-malonate (133 g., 0.5 mole) was hydrolyzed by refluxing with 400 g. of concentrated hydrochloric acid. After evaporation to dryness under reduced pressure, the crude malonic acid derivative was decarboxylated by heating to 200° for 2 hours. The resulting tricarbonyl acid was then taken up in 100 ml. of methanol containing 20 ml. concentrated sulfuric acid. The water formed in the esterification reaction was removed by slow distillation with simultaneous addition of anhydrous methanol. After 1500 ml. of distillate had been collected, the boiling point had dropped to 65°. The residual solution was then diluted with water and extracted 4 times with ether. The combined ether extracts were washed with water and saturated sodium chloride solution, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. Distillation at a pressure of 2 mm. gave a small forerun, b.p. 132-138°, followed by the main fraction (98.5 g., 84%) boiling at 138-140° (literature value, 162° at 12 mm. 20).

Preparation of 2,4-Dicarbomethoxycyclohexanone (XXV). - The trimethyl ester (78.0 g., 0.33 moles) obtained in the preceding experiment was dissolved in 300 ml. of dry benzene. Sodium wire (9.0 g., 0.39 gr. atoms) and a few drops of methanol were added, and the
mixture was refluxed under a nitrogen atmosphere for 24 hours. Magnetic stirring was necessary towards the end of the reaction to avoid bumping caused by the accumulation of insoluble sodium salt. After cooling to room temperature, the mixture was poured into an excess of dilute hydrochloric acid and stirred vigorously with ice cooling. The aqueous phase was extracted twice with ether, and the combined organic layers were washed with dilute sodium bicarbonate solution, water, saturated sodium chloride solution, and finally dried with anhydrous sodium sulfate. Removal of the ether and vacuum distillation furnished 61.0 g. (86%) of a clear liquid, b.p. 130-132° at 2 mm. that crystallized on standing in the refrigerator. Recrystallization from ether-petroleum ether gave 56.0 g. (79%) of large prisms, m.p. 44-45° (literature value, 40-44° 20).

Preparation of 2-Keto-trans-6,10-dicarbomethoxy-\(\Delta^{1,9}\) - octahydronaphalene (XXVI). - To a reaction flask equipped with a mechanical stirrer, addition funnel, reflux condenser, and gas inlet tube, there was added 4.6 g. (0.2 moles) of sodium hydride and 25 ml. of dry benzene. A stream of dry nitrogen was passed through the flask, and a solution of 42.8 g. (0.2 moles) of 2,4-dicarbomethoxycyclohexanone in
50 ml. of dry benzene was added dropwise. The addition was accompanied by the evolution of hydrogen and was complete in 1 hour. Ten ml. portions of dry benzene were added from time to time to prevent caking of the sodium enolate that separated. After heating for an additional 2 hours on the steam cone, the reaction mixture was cooled and treated by dropwise addition with 21.5 g., (0.2 moles) of freshly distilled 4-chloro-2-butanone, prepared as described below. After standing for 12 hours at room temperature, the solution was acidified with dilute hydrochloric acid. The layers were separated and the aqueous phase was back-extracted with ether. The combined organic fractions were then washed with dilute sodium hydroxide, water, and saturated sodium chloride solution, and dried over anhydrous sodium sulfate. The ether was finally removed and the oily residue was taken up in 500 ml. dry benzene and treated with 4.0 g. of p-toluene-sulfonic acid monohydrate. The solution was then refluxed under a continuous water separator for 20 hours at the end of which time 3.4 ml. (theory, 3.6 ml.) of water had been collected. After thorough washing and drying, the solvent was removed, and the resulting orange oil was crystallized from ether at dry ice
temperature. The crude product obtained in this way amounted to 13.0 g. (24%). Two recrystallizations from ether-petroleum ether, followed by a third from cyclohexane gave 11.0 g. (20%) of product as clusters of long white needles, m.p. 88-89°, λ max. 237 mμ, ε 12,000.

Anal. Calcd. for C_{14}H_{18}O_5; C, 63.13; H, 6.82.
Found: C, 63.28; H, 6.85.

The compound furnished a semicarbazone, m.p. 215-217° from methanol, λ max. 268 mμ, ε 36,500.

Anal. Calcd. for C_{15}H_{21}O_5N_3; C, 55.72; H, 6.54; N, 13.00. Found: C, 55.92; H, 6.50; N, 13.10.

Preparation of 4-Chloro-2-butane. - A solution of 200 g. of methyl vinyl ketone (Chas. Pfizer, Inc.) in 500 ml. of benzene was saturated with anhydrous hydrogen chloride at 0° over a period of 4 hours. The brown solution was then washed with water, dilute sodium hydroxide, and saturated sodium chloride solution, and was dried over anhydrous sodium sulfate. After removal of the benzene at the water pump, the colorless product was purified by distillation, affording 145 g. (49%) of 4-chloro-2-butane, b.p. 48-52° at 18 mm. (literature value, 50-53° at 15 mm.)
Preparation of 6,10-trans-Dicarbomethoxy-trans-2-decalone (XXVII). - The bicyclic unsaturated keto diester (10.0 g.) obtained as described previously was hydrogenated at atmospheric pressure over 2.0 g. of 10% palladized charcoal in methanol. One mole equivalent of hydrogen was absorbed in 40 minutes. The catalyst was removed by filtration, and the product obtained after evaporation and crystallization from cold ether weighed 9.1 g. (90%), m.p. 88-89°. The infrared spectrum showed bands at 5.80 and 5.83 μ.

**Anal.** Calcd. for C_{14}H_{20}O_{5}: C, 62.67; H, 7.51. Found: C, 62.72; H, 7.46.

The semicarbazone was prepared in the usual manner and melted at 203-204°.

The ethylene ketal was prepared by refluxing the decalone, dissolved in a toluene-dioxane mixture, with ethylene glycol and a trace of p-toluene-sulfonic acid under a continuous water separator for 24 hours. After working up as usual, an infrared spectrum on the crude oily residue indicated only a single band at 5.80 μ.
Preparation of trans-Decalin-2,9-trans-dicarboxylic acid (XXVIII). - The saturated keto diester (10.0 g., 0.0373 moles) obtained in the preceding experiment was dissolved in 200 ml. of diethylene glycol and treated with 20.0 g. of 85% aqueous hydrazine hydrate and 10.0 g. of solid potassium hydroxide. The mixture was heated under reflux for 1 hour at 147° at the end of which time the condenser was removed and the temperature raised to 215° where it was maintained for an additional 3 hours. The pale yellow solution was then cooled in an ice bath, diluted with an equal volume of water, and acidified with concentrated hydrochloric acid. The white solid that separated was filtered off and recrystallized from aqueous acetone yielding 5.0 g. (60%) of crystals melting at 227-228° (sealed capillary). The melting point was not changed by further recrystallization.

**Anal.** Calcd. for C_{12}H_{18}O_{4}; C, 63.70; H, 8.02. Found: C, 64.00; H, 8.05. Neutral equivalent 113.6 (theory, 113.1).

Preparation of trans-2-Carbomethoxy-9-carboxy-trans-decalin (XXXII). - A solution of 972 mg. of the above diacid in 100 ml. of methanol was treated with 4 ml. of acetyl chloride and was allowed to stand at room temperature for 14 hours.
Removal of the solvent under reduced pressure furnished crystalline material, m.p. 130-135\(^\circ\), which was re-crystallized to a constant melting point, 143-144\(^\circ\), from aqueous acetone.

**Anal.** Calcd. for C\(_{13}\)H\(_{20}\)O\(_4\): C, 64.97; H, 8.39. Found: C, 64.63; H, 8.39. Neutral equivalent, 240.7 (theory, 240.3).

**Attempted Arndt-Eistert Homologation of trans-2-Carbomethoxy-9-carboxy-trans-decalin (XXXII).** The trans half ester (XXXII) (200 mg.) was dissolved in 6 ml. of dry benzene and treated with 1.0 ml. of purified thionyl chloride\(^{35}\). The resulting solution was allowed to stand overnight at room temperature, and was then heated to reflux temperature for 3 hours. Removal of the solvent and flushing of the residue with dry benzene to remove the last traces of thionyl chloride gave an oil showing infrared absorption maxima at 5.80 and 5.60\(\mu\), characteristic of the expected ester - acid chloride. No absorption attributable to a carboxyl group was detectable.

The ester - acid chloride was taken up in 6 ml. of ether and was allowed to stand for 24 hours with 4 equivalents of dry ethereal diazomethane. Removal of the solvent furnished an oil which showed an acid chloride band of somewhat reduced intensity at 5.60\(\mu\) in the infrared but no bands ascribable to the
desired diazoketone. The material was nevertheless subjected to the conditions employed for Wolff rearrangement (methanol and dry silver oxide at 55°). The product of this reaction was refluxed overnight with aqueous-alcoholic sodium hydroxide, and after routine work-up furnished 187 mg. of crystalline material, m.p. 104-105°, that was identified as trans-9-carbomethoxy-2-carboxy-trans-decalin (XXXV), by mixed melting point and infrared comparison with an authentic sample, prepared as described in the following experiment.

Preparation of trans-9-Carbomethoxy-2-carboxy-trans-decalin (XXXV).—Esterification of the above half ester (XXXII) with diazomethane gave the corresponding dimethyl ester as an oil that resisted all attempts at crystallization. The infrared spectrum of this material (CS₂) showed a single band in the carbonyl region at 5.80μ. Material showing identical infrared absorption characteristics was obtained by diazomethane esterification of the starting diacid (XXVIII).

Partial saponification of 500 mg. of diester in 6 ml. of methanol and 6 ml. of 0.5 N sodium hydroxide (1.33 equivalents) at room temperature (24 hours) afforded 365 mg. (79%) of material which melted at 104-105° after two recrystallizations from
aqueous alcohol. The infrared spectrum of this product showed bands with maxima intensity at 5.81 and 5.87μ.

**Anal.** Calcd. for C\textsubscript{13}H\textsubscript{20}O\textsubscript{4}; C, 64.97; H, 8.39. Found: C, 64.88; H, 8.25. Neutral equivalent, 240.8 (theory, 240.3).

**Preparation of trans-Decalin-2,9-cis-dicarboxylic Acid Anhydride (XXXVIII).** - A solution of the diacid (XXVIII) (2.07 g., 0.01 moles) in 200 ml. of freshly purified acetic anhydride\textsuperscript{35} containing 2.0 g. of sodium acetate was refluxed for 16 hours. The solvent was then removed at reduced pressure and the dark residue was taken up in ether and filtered to free it of sodium acetate. Concentration of the resulting ethereal solution and cooling to dry ice temperature resulted in the deposition of 1.36 g. (71%) of tan crystals. Recrystallization from cold ether furnished a sample, which after sublimation melted at 89-90°. The infrared spectrum (CS\textsubscript{2}) showed bands at 5.55 and 5.68μ characteristic of a glutaric anhydride.

**Anal.** Calcd. for C\textsubscript{12}H\textsubscript{16}O\textsubscript{3}; C, 69.21; H, 7.75. Found: C, 69.20; H, 7.75.
Preparation of trans-Decalin-2,9-cis-dicarboxylic Acid (XXXIX). - A solution of 1.34 g. of the above anhydride (XXXVIII) in 20 ml. of acetone and 30 ml. of water was heated under reflux until crystalline material began to separate. The mixture was then stirred at room temperature for 12 hours. Filtration afforded 1.23 g. (83%) of trans-decalin-2,9-cis-dicarboxylic acid, m.p. 229-230° (evacuated capillary). Several recrystallizations from aqueous ethanol did not change the melting point. A mixed melting point with trans-decalin-2,9-trans-dicarboxylic acid was depressed to 206-209°, and the infrared spectrum (Nujol mull) of the material showed a single band at 5.88 μ.

Anal. Calcd. for C_{12}H_{18}O_{4}: C, 63.70; H, 8.02. Found: C, 64.00; H, 8.11. Neutral equivalent, 113.0 (theory, 113.1).

Preparation of 2,9-cis-Dicarbomethoxy-trans-decalin (XL). - A neutral solution of 1.2 g. of cis-diacid (XXXIX) was treated with excess ethereal diazomethane. After standing for 3 hours the solvents were removed and the solid residue recrystallized from aqueous methanol, yielding 1.3 g. (quantitative) of cis-diester, m.p. 68-69°. The analytical sample
was obtained as plates, m.p. 68-69°, \( \lambda \) max. 5.88 \( \mu \), after two recrystallizations from the same solvent mixture.

**Anal. Calcd.** for \( C_{14}H_{22}O_4 \); C, 66.12; H, 8.72. **Found:** C, 66.33; H, 8.72.

**Attempted Acyloin Preparation by the Sodium-Xylene Method**  
- The cis-diester (XL), 400 mg. was dissolved in 100 ml. of dry xylene and added dropwise to 145 mg. (4 equivalents) of powdered sodium in 200 ml. of dry xylene with vigorous agitation ("Vibromischer") and under a steady flow of dry, purified nitrogen at 125°. After 3 hours the addition was complete and heating was continued (125°) for another 2 hours. After cooling to room temperature, the clear product was acidified with dilute alcoholic sulfuric acid, washed with water, dilute sodium hydroxide solution, saturated sodium chloride solution, and dried over anhydrous sodium sulfate. Removal of the solvent under reduced pressure gave a yellow oil with a negative Fehling's test. Chromatography on 16 g. of activated alumina afforded only 1 fraction, 96 mg., which was eluted with pure benzene. This crystalline product was identical in every respect to the starting diester (XL).
A second experiment in which the reaction period was increased to 12 hours, followed by stirring at room temperature for 6 hours, afforded no acyloin and no starting material was recovered.

**Preparation of the Acyloin (XLI) by the Sodium-Liquid Ammonia Process**

The cis diester (XL), 500 mg., was dissolved in 100 ml. of dry ether and added through a dropping funnel to a 3-neck flask, containing 150 ml. of liquid ammonia and 100 ml. dry ether and fitted with a dry ice condenser, mechanical stirrer, and inlet tube for a stream of dry, purified nitrogen. Sodium wire was added simultaneously in small portions, keeping the solution dark blue. An excess of 4 equivalents was required by the end of the addition (3 hours). The ammonia was evaporated under a vigorous flow of nitrogen, and the orange ethereal solution was treated with 2 ml. of methanol in 50 ml. of ether to destroy any unreacted sodium. Acidification with 50 ml. of 3% aqueous hydrochloric acid gave, after separation, washing with dilute sodium bicarbonate solution and working up in the usual manner, a brown oil (420 mg.) which was chromatographed on 20 g. of activated alumina, yielding crystalline material, 75 mg.,
which was eluted with 1:20 methanol-ether. Recrystallization from petroleum ether afforded 20 mg. of thin, clear plates, m.p. 77-78°, with a positive Fehling's test for \( \alpha \)-ketols. The infrared spectrum showed bands at 2.80 and 5.79\( \mu \), characteristic of hydroxyl and 5-membered ring ketone respectively.

**Anal.** Calcd. for \( C_{12}H_{18}O_2 \); C, 74.19; H, 9.34. Found: C, 74.07; H, 9.44.

A second experiment in which the sodium was added to the cis-diester (XL), 500 mg., in an ether-liquid ammonia solution gave, after chromatography, the following crude fractions: 36 mg. with pure benzene (cis-diester); 47 mg. with 1:1 ether-benzene (trans-diester); 110 mg. with 1:20 methanol-ether (acyloin); and 37 mg. with 1:1 methanol-ether (a dark tar). Infrared analysis on the 1:20 methanol-ether fraction indicated some acyloin was present but no crystalline material could be isolated.
REFERENCES


24. Huang-Minlon, ibid., 68, 2487 (1946); ibid., 71, 3301 (1949).


