The ethyl ketone in the dimethylamino series was found to be polymorphic. The melting point depended largely on the solvent used for crystallization. When recrystallized from an ethanol–isopropyl ether solution it melted at 86–88°, and when dried in an Abderhalden at 56° it melted at 114–116°. When recrystallized from ethanol or ethanol–ether it melted at 142–142.5° after sintering at 86°.

Bromination of Dialkylamino Ketone Hydrobromides.—The hydrobromide salts were dissolved in glacial acetic acid in the ratio of 3 liters of acetic acid per mole of salt and the solution maintained at approximately 50°. Dropwise addition of a solution of the theoretical amount of bromine in glacial acetic acid in the ratio of 1500 ml. of acetic acid per mole of bromine was carried out over two hours. The solvent was removed by distillation under reduced pressure leaving an orange oily residue. Trituration with ethyl acetate yielded crystalline products.

1,1-Dialkyl-4,4-diphenyl-3-piperidonium Bromides and 1,1,2-Trialkyl-4,4-diphenyl-3-piperidonium Bromides.—The solid bromination products were dissolved in 50% ethanol and an equal volume of ether was added. The mixture was kept cool, neutralized with sodium bicarbonate solution, shaken and the ether layer was separated quickly. In the case of the dimethylamino compounds, it was found that the product which came out of the ether solution was much easier to purify.

Pyrolyses of the Quaternary Salts.—The quaternary salts were placed in a 10-ml. Claisen flask fitted with a 10-ml. receiver flask and the evacuated system heated with an oil-bath. The piperidones distilled and were dissolved in ether; the ether solutions were treated with hydrogen chloride to give the hydrochlorides. The methiodides were prepared in the usual manner and the ethiodides by refluxing with ethyl iodide in isopropyl ether.

1,1-Dimethyl-4,4-diphenyl-3-piperidonium Iodide.—A mixture of 5 ml. of absolute ethanol, 5 ml. of acetone, 0.75 g. of 1,1-dimethyl-4,4-diphenyl-3-piperidonium bromide and 0.5 g. of sodium iodide was heated to the boiling point and then filtered. The product, which separated from the cooled filtrate, melted at 201.5–202° after recrystallization from absolute ethanol; mixed m.p. with methiodide of Ia was 201.5–202.5°.

Anal. Calcd. for $C_{19}H_{22}NOI$: N, 3.44. Found: N, 3.36, 3.39.

1,1,2-Trimethyl-4,4-diphenyl-3-piperidonium Iodide.—A mixture of 5 ml. of absolute ethanol, 5 ml. of acetone, 0.6 g. of 1,1,2-trimethyl-4,4-diphenyl-3-piperidonium bromide and 0.4 g. of sodium iodide was heated to the boiling point and then filtered. The product, which separated from the cooled filtrate, melted at 199–200.5° after recrystallization from absolute ethanol; mixed m.p. with the methiodide of Ib was 199–200°.

Anal. Calcd. for $C_{20}H_{24}NOI$: N, 3.32. Found: N, 3.26, 3.23.

Isolation of VII or VIII.—The mother liquors obtained from the purification of the hydrochloride of 1-ethyl-2-methyl-4,4-diphenyl-3-piperidone were concentrated under reduced pressure. The residue was taken up in acetone and treated with decolorizing charcoal. After filtration isopropyl ether was added until turbidity was produced. Crystals separated from the cooled solution which, after recrystallization from acetone, sintered at 100° and melted at 150–151°.

Anal. Calcd. for $C_{21}H_{28}ONCl$: Cl, 9.91. Found: Cl, 9.69.

Bromination of 6-Dimethylamino-4,4-diphenyl-3-hexanone Hydrobromide at Room Temperature.—A solution of 18.5 g. of the hydrobromide in 75 ml. of glacial acetic acid was shaken and a solution of 7.8 g. of bromine in 10 ml. of glacial acetic acid was slowly added. The bromine was absorbed very rapidly. Yellow crystals which melted at 99–100° with decomposition and weighed 22.4 g. (85%) separated gradually. The melting point of the product was lower after recrystallization from acetic acid. It gave the best analysis after being dried under 2 mm. pressure.

Anal. Calcd. for $C_{20}H_{26}ONBr_3$: C, 44.79; H, 4.89; N, 2.61; Br, 44.72. Found: C, 45.10; H, 4.88; N, 2.64; Br, 44.95.

3-Dimethylamino-1,1-diphenylpropane Hydrobromide.—To a solution of 14.6 g. (0.05 mole) of γ-diethylamino-α,α-diphenylbutyronitrile in 400 ml. of isopropyl alcohol there was added 40 g. (1.74 moles) of sodium. The mixture was allowed to reflux until most of the sodium had reacted. After refluxing for two hours the excess sodium was decomposed with a 50% solution of ethanol and water. The mixture was extracted with ether and the ether extract was dried over magnesium sulfate. The solution was filtered, the ether removed, and the residue was dissolved in 20 ml. of absolute ethanol and 48% hydrobromic acid was added until the mixture was acid to congo red paper. The solvent was removed under reduced pressure and the residue placed in an evaporating dish where crystallization occurred. After recrystallization from a mixture of absolute ethanol and isopropyl ether, the product melted at 136–137° and weighed 10.5 g.

Anal. Calcd. for $C_{19}H_{26}NBr$: N, 4.02; Br, 22.94. Found: N, 3.93; Br, 23.20.

A mixed melting point of this material with that obtained from the preparation of the diethylamino ketones showed no depression.

BETHLEHEM, PENNA.

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE JOHNS HOPKINS UNIVERSITY]

Anomalous Displacements in the Pyrrole Series[1]

BY ALSOPH H. CORWIN AND GEORGE G. KLEINSPEHN[2,3]

RECEIVED DECEMBER 19, 1952

In an attempt to prove the structure of 2-bromo-3-methyl-4-carbethoxypyrrole, the Gattermann hydrogen cyanide–hydrogen chloride formylation was employed. The principal product isolated was 2-chloro-3-methyl-4-carbethoxy-5-formylpyrrole, along with 2-formyl-3-methyl-4-carbethoxy-5-chloropyrrole and 2-formyl-3-methyl-4-carbethoxypyrrole. Formylation using hydrogen bromide gave 2-bromo-3-methyl-4-carbethoxy-5-formylpyrrole and 2-formyl-3-methyl-4-carbethoxypyrrole. Differentiation between the 2-chloro- and the 2-bromoaldehyde by the method of mixed melting points failed. Possible mechanisms for the anomalous displacements are advanced. These anomalies constitute a definite limitation to the usefulness of the Gattermann aldehyde synthesis. Other displacement reactions are also presented.

Recently initiated investigations in this Laboratory of a proposed new synthetic route to chlorophyll-type porphyrins posed the problem of preparing 2-bromo-3-methyl-4-carbethoxypyrrole (II). It was decided to attempt preparation of this intermediate by means of a selective monobromination of 3-methyl-4-carbethoxypyrrole (I),[4a,5a] a substance which is best obtained from 2,4-dicarb-

(1) Studies in the Pyrrole Series. XXIII. Paper XXII. K. W. Doak and A. H. Corwin, THIS JOURNAL, **71**, 159, 4165 (1949). A portion of this paper is taken from the doctoral dissertation of George G. Kleinspehn, The Johns Hopkins University, Baltimore, Md.

(2) du Pont Fellow in Chemistry, 1950–1951.

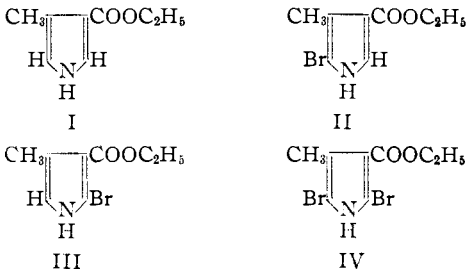
(3) Public Health Service Postdoctorate Research Fellow of the National Institutes of Health, 1951–1952.

(4) H. Fischer and O. Wiedemann, *Z. physiol. Chem.*, **155**, (a) 58, (b) 59 (1926).

(5) A. H. Corwin and P. Viohl, THIS JOURNAL, **66**, (a) 1145, (b) 1142 (1944).

ethoxy-3,5-dimethylpyrrole by the synthetic sequence of Corwin, Bailey and Viohl[6a] and of Corwin and Viohl.[6a]

CHART I



That a monobromination of I should be expected to yield the 2-bromo (II) rather than the 5-bromo isomer (III) follows both from electronic considerations and from the previous demonstration by Fischer and Wiedemann[4b] that electrophilic attack in the case of formylation does in fact lead to 2-formyl-3-methyl-4-carbethoxypyrrole (VII).[4b,5a]

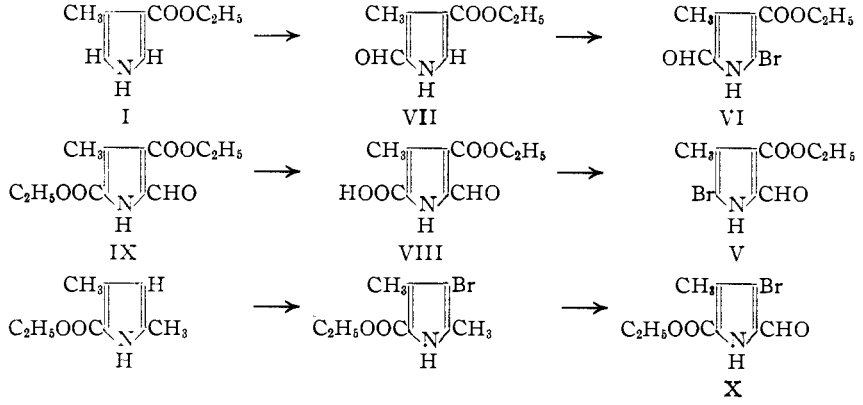
Reaction of I with two moles of bromine has been found to afford the anticipated 2,5-dibromo-3-methyl-4-carbethoxypyrrole (IV) in 50% yield. By carrying out a one-molar bromination at Dry Ice–ethanol temperatures it has been possible to isolate and to characterize a monobrominated 3-methyl-4-carbethoxypyrrole, which has been tentatively assigned structure II. Under these reaction conditions very little IV results. The mono- and dibrominated products may be conveniently separated with the aid of aqueous 1% sodium hydroxide, in which the latter is much more soluble. This solubility difference probably reflects the increase in acidity of the imino group engendered by the substitution of an additional bromine for hydrogen in the second α-position.

The work described in the succeeding portions of this paper was undertaken in order to elucidate the structure of the monobrominated pyrrole. However, two anomalous replacement reactions encountered during the course of the work have led to experimental results which, while favoring the conclusion that the monobrominated product is at least predominantly 2-bromo-3-methyl-4-carbethoxypyrrole (II), do not, nevertheless, constitute a rigorous proof of structure. In connection with this attempted structural proof several new displacements in the pyrrole series have been carried out, and these are now described.

It was initially proposed to formylate the monobromopyrrole to obtain an α-bromo-α'-formylpyrrole. Thus bromopyrrole II should have been expected to yield aldehyde V, while III should have given VI. Neither bromoaldehyde V nor VI had been previously reported. However, it has proved possible to prepare each by an independent method which in each instance clearly establishes structure. We have obtained bromoaldehyde VI, which melts at 166.5–167°, by bromination of 2-formyl-3-methyl-4-carbethoxypyrrole (VII). Bromoaldehyde V has been prepared by accomplishing a brominative decarboxylation of 2-carboxy-3-methyl-4-carbethoxy-5-formylpyrrole (VIII).[7a]

Prior to the present work no proof of structure for aldehyde acid VIII had been reported. This substance, first prepared by Fischer and Ernst,[7a] is obtained by the basic hydrolysis of 2,4-dicarbethoxy-3-methyl-5-formylpyrrole (IX),[6b,7b,8] and it was inferred by analogy with the behavior of other pyrryl diesters that alkaline saponification attacked the α- rather than the β-carbethoxy group to give the 2-acid and not the 4-acid. Through brominative decarboxylation it has now been shown that the aldehyde acid is in fact the 2-acid (VIII). One-molar bromination yields a product which analysis indicates to be a bromoaldehyde and which melts at 146–147°. Had the aldehyde acid been the 4-acid, bromination should have afforded 2-carbethoxy-3-methyl-4-bromo-5-formylpyrrole (X), which is a known substance.[7c,9,10] An authentic sample of X melting at 135–136° was prepared by the method of Corwin and Straughn[10] as shown in Chart II, and admixture with the bromoaldehyde obtained from the aldehyde acid caused a substantial melting point depression. Thus VIII represents the structure of the aldehyde acid, and the bromoaldehyde obtained from it must then be V.

CHART II



With the two authentic bromoaldehydes V and VI available as reference compounds, formylation of an analytically pure sample of the monobrominated 3-methyl-4-carbethoxypyrrole was undertaken. For this purpose the Gattermann method and modifications[11,12] of it were employed. The use of dry hydrogen chloride with liquid hydrogen cyanide, zinc cyanide or mercuric cyanide produced as the principal product in each instance a substance melting within the range 146–148°. This

(6) A. H. Corwin, W. A. Bailey and P. Viohl, THIS JOURNAL, **64**, (a) 1272, (b) 1271 (1942).

(7) H. Fischer and P. Ernst, *Ann.*, **447**, (a) 155, (b) 154, (c) 152 (1926).

(8) H. Fischer and P. Halbig, *ibid.*, **447**, 137 (1926).

(9) H. Fischer, H. Berg and A. Schormüller, *ibid.*, **480**, 155 (1930).

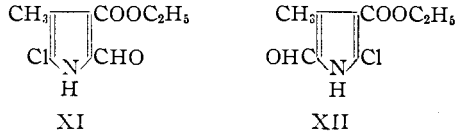
(10) A. H. Corwin and J. L. Straughn, THIS JOURNAL, **70**, 1420 (1948).

(11) R. Adams and I. Levine, *ibid.*, **45**, 2373 (1923).

(12) R. Adams and E. Montgomery, *ibid.*, **46**, 1518 (1924).

product showed no melting point depression when mixed with authentic 2-bromo-3-methyl-4-carbethoxy-5-formylpyrrole (V), but did depress markedly upon admixture with bromoaldehyde VI. However, carbon, hydrogen and ethoxy analytical data agreed not with the values calculated for a bromoaldehyde, but rather with values for an analogous chloroaldehyde. It has been reported[9] that mixtures of X with its chloroaldehyde analog similarly show no melting point depression. In order to confirm the presence of chlorine in the Gattermann formylation product, a qualitative analytical procedure for ascertaining the nature of the halogen was employed. The method consisted in combustion of a sample of the substance, reduction of the halogen thus formed to halide ion, then potentiometric titration of the resulting halide ion with silver acetate solution. By obtaining titration data both for a known chlorine-containing and a bromine-containing compound and comparing these with the titration data obtained for the formylation product, the presence of chlorine was established. Consequently, it was necessary to assign to this substance either structure XI or XII.

CHART III



XI XII

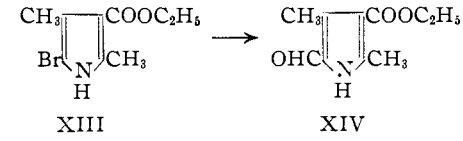
A second substance melting at 172–173° was isolated in much smaller amount from the runs in which zinc cyanide or mercuric cyanide was employed. Carbon and hydrogen analyses indicated that this latter product was also a chloroaldehyde.

While the mixed melting point data already cited indicated the probability that the lower-melting chloroaldehyde had the structure XI, actual assignment of a specific structure to each of these chloroaldehyde reaction products has been made possible by an independent synthesis of chloroaldehyde XII. This was prepared by chlorinating 2-formyl-3-methyl-4-carbethoxypyrrole (VII) with sulfuryl chloride and melts at 173.5–174.5° with previous sintering at 169–170°. Thus the lower-melting chloroaldehyde must be the isomeric 2-chloro-3-methyl-4-carbethoxy-5-formylpyrrole (XI).

In view of the anomalous halogen interchange attending the use of hydrogen chloride, Gattermann formylation of the monobrominated 3-methyl-4-carbethoxypyrrole was reattempted using hydrogen bromide and liquid hydrogen cyanide. In this case the two principal products were 2-formyl-3-methyl-4-carbethoxypyrrole (VII) and the bromoaldehyde V, and thus formylation was being accompanied by debromination. Aldehyde VII had already been isolated in one instance from a previous formylation run in which zinc cyanide and hydrogen chloride had been allowed to react with monobrominated 3-methyl-4-carbethoxypyrrole.

In order to establish an unambiguous instance in which the entering formyl group does in fact take up the position vacated by the bromine, the closely analogous 2-bromo-3,5-dimethyl-4-carbethoxypyrrole (XIII)[6b,13] was subjected to the Gattermann reaction. In this case the action of hydrogen chloride and zinc cyanide afforded a 37% yield of crude 2-formyl-3,5-dimethyl-4-carbethoxypyrrole (XIV).[14,15] The product was identified by a mixed melting point with a sample of the authentic aldehyde XIV which had been prepared by an independent method.[15]

CHART IV



XIII XIV

Both the halogen interchange and the dehalogenation described above constitute definite limitations to the usefulness of the Gattermann aldehyde synthesis. Analogy for the halogen interchange reaction is found in the work of King and Nord[16] who observed that considerable 2-chloro-5-formylthiophene is formed during formylation of 2-bromothiophene using N-methylformanilide and phosphorus oxychloride, although it has subsequently been demonstrated[17] that some of the expected 2-bromo-5-formylthiophene is formed simultaneously.

The reaction sequence shown below in Chart V represents a possible mechanism by which the two chloroaldehydes XI and XII as well as 2-formyl-3-methyl-4-carbethoxypyrrole (VII) might result from bromopyrrole II under the conditions of the Gattermann formylation.

Step (A) of this mechanism would seem entirely plausible in view of the results of a recent investigation[18] which indicated that in the presence of acid and of halide ion, both iodine and bromine of pyrroles of the type of II may be displaced by hydrogen. It is further known that bromine chloride is appreciable dissociated[19] at ordinary temperatures. Thus it is extremely likely that under the conditions of the Gattermann reaction there is present some free chlorine for chlorination of pyrrole I as shown in reaction (C). The resulting chloropyrrole XV could then undergo formylation to afford chloroaldehyde XI. It is doubtful that reaction (C) would be reversible, for the greater strength of the carbon–chlorine bond should make dehalogenation considerably more difficult here than in the case of the analogous bromopyrrole II. Alternatively the di-α-free pyrrole I formed in reaction (A) might undergo formylation to provide 2-formyl-3-methyl-4-carbethoxypyrrole (VII), some of which should be isolated from the reaction mixture, the remainder being chlorinated to give chloroaldehyde XII.

Two other displacements of synthetic interest were carried out in connection with the preparation

(13) H. Fischer and R. Bäumler, *Ann.*, **468**, 73 (1929).

(14) H. Fischer and W. Zerweck, *Ber.*, **55**, 1945 (1922).

(15) A. H. Corwin and J. S. Andrews, THIS JOURNAL, **58**, 1088 (1936).

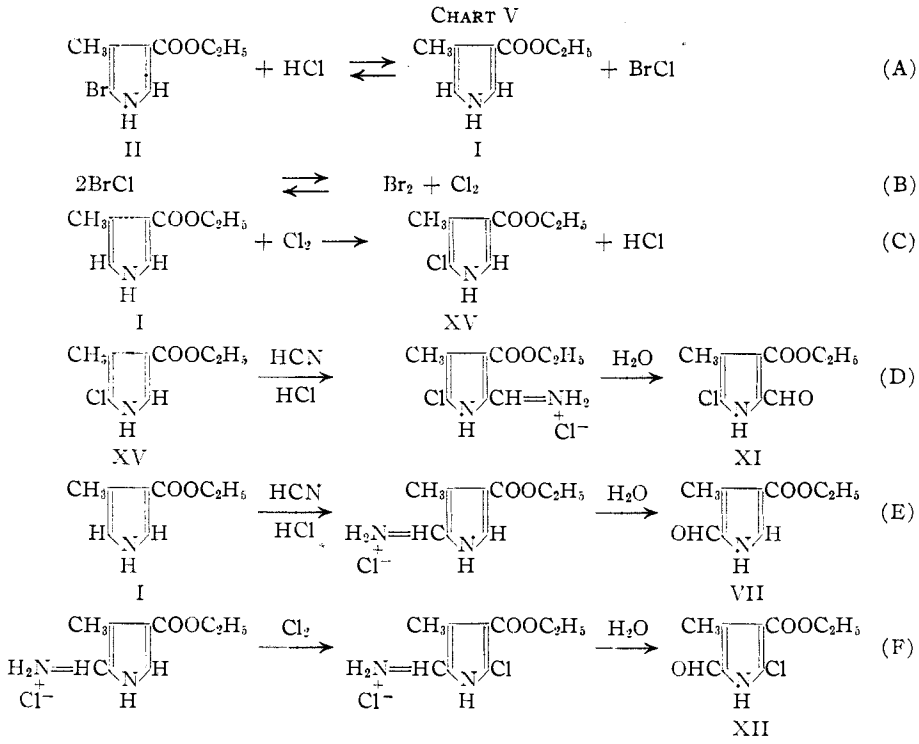
(16) W. J. King and F. F. Nord, *J. Org. Chem.*, **13**, 638 (1948).

(17) A. W. Weston and R. J. Michaels, THIS JOURNAL, **72**, 1423 (1950).

(18) K. W. Doak and A. H. Corwin, *ibid.*, **71**, 159, 4165 (1949); K. W. Doak, Dissertation, The Johns Hopkins University, pp. 85–86 (1942).

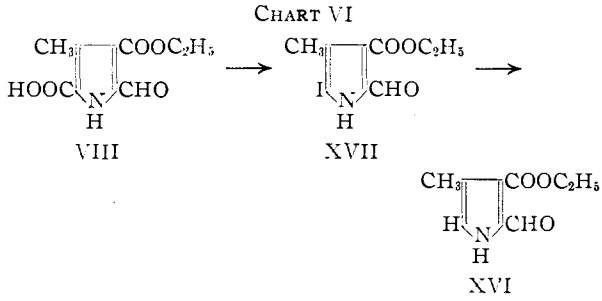
(19) N. V. Sidgwick, "The Elements and Their Compounds," Vol. II, Oxford University Press, New York, 1950, pp. 1149–1151.

CHART V



of 3-methyl-4-carbethoxy-5-formylpyrrole (XVI). This hitherto inaccessible isomer of aldehyde VII was obtained from 2-carboxy-3-methyl-4-carbethoxy-5-formylpyrrole (VIII) as shown in Chart VI. Aldehyde acid VIII underwent iodinative decarboxylation to give the iodoaldehyde XVII, which was in turn dehalogenated by catalytic hydrogenation to aldehyde XVI. Thus XVI was also available as a reference compound for comparison with the products obtained in the course of the previously described formylation studies.

CHART VI



Because of the complexities introduced by halogen interchange and by debromination, the Gattermann aldehyde synthesis has failed to provide a rigorous proof of structure in the case of monobrominated 3-methyl-4-carbethoxypyrrole. Consequently, an alternative method of structural proof has since been undertaken.

Experimental

3-Methyl-4-carbethoxypyrrole (I).[4a,5a]—This substance was prepared by the method of Corwin and Viohl.[5a] The crude product was purified by dissolving in minimum methanol at room temperature, adding an equal volume of water, then inducing crystallization from the oily mixture by shaking and cooling under the cold water tap. As soon as sufficient separation of solid product had taken place to dispel the turbidity, crystallization was completed in the refrigerator, m.p. 75–76°.[20]

Monobrominated 3-Methyl-4-carbethoxypyrrole.—Twenty milliliters of absolute methanol and 8.47 g. of once-recrystallized 3-methyl-4-carbethoxypyrrole were placed in a 250-ml. erlenmeyer flask equipped with a magnetic stirring bar. The pyrrole was dissolved by stirring, and the solution was then immersed in an ethanol-bath and cooled to Dry Ice–ethanol temperatures by gradual addition of Dry Ice to the cooling bath. Meanwhile 3.0 ml. of bromine was pipetted into a solution of 5.5 g. of anhydrous sodium acetate in 93 ml. of absolute methanol. The bromine solution, after being cooled rapidly to room temperature, was then added dropwise with stirring during 45 minutes to the pyrrole–methanol mixture (some solid pyrrole had separated from solution at Dry Ice–ethanol temperature). The low temperature of the bath was maintained by replenishing the Dry Ice when necessary. When addition was complete the still turbid reaction mixture was poured slowly and with stirring into 1125 ml. of ice-water. After a few hours refrigeration the resulting light yellow precipitate was filtered off, washed with water, pressed well on the filter, then taken up in 48 ml. of methanol at room temperature. A small amount of greenish insoluble impurity was removed by filtration, and the solution was then poured with stirring into a cold solution of 5.0 g. of sodium hydroxide in 440 ml. of water in order to free the product of any dibrominated pyrrole. After refrigerating the mixture for a few hours, the light yellow-green monobromopyrrole was filtered off and washed well with water. On the basis of the loss of weight which an aliquot of this material underwent on drying, the yield of thus purified product in the case of one run was estimated as 43%.

This crude monobromopyrrole was then taken up in 83 ml. of 3:1 (by volume) methanol–water at room temperature, treated with 0.8 g. of Norit A and filtered. A pale yellow-green crystalline product was obtained by adding water to the filtrate until the pyrrole had begun to separate, then refrigerating for several hours. One additional recrystallization carried out in the same manner afforded 2.54 g. of very nearly colorless analytically pure monobrominated 3-methyl-4-carbethoxypyrrole. The product was dried in a stream of dry air.

Anal. Calcd. for $C_8H_{10}O_2NBr$: C, 41.40; H, 4.34; C_2H_5O, 19.42. Found: C, 41.27, 41.40, 41.41; H, 4.42, 4.40, 4.44; C_2H_5O, 19.42, 19.57.

The analytically pure product does not melt on the Fisher–Johns melting point apparatus. Darkening commences at about 70° and decomposition proceeds until by 90° the material is very nearly black. Monobrominated 3-methyl-4-carbethoxypyrrole decomposes after a few days standing at room temperature, but may be kept for many weeks in a refrigerator in the absence of light.

2,5-Dibromo-3-methyl-4-carbethoxypyrrole (IV).—One and eight-tenths grams of anhydrous sodium acetate was added with stirring to a solution of 612 mg. of 3-methyl-4-carbethoxypyrrole in 3 ml. of absolute methanol. A solution of 1.30 g. of bromine in 5 ml. of methanol was then dropped in with stirring at room temperature. The addition was carried out during ten minutes and stirring was continued for five minutes more. Upon pouring the reaction mixture with stirring into 100 ml. of ice–water mixture, a general turbidity developed with separation of some brown-

(20) Determined on the Fisher–Johns melting point apparatus.

ish viscous oil. After refrigeration had brought about solidification of the crude product, it was filtered off, washed with water, then stirred for several minutes with 100 ml. of aqueous 1% sodium hydroxide. Norit A was added, the mixture was filtered, and after addition of ice to the filtrate, the dibromopyrrole was reprecipitated from the filtrate by acidification with glacial acetic acid to a *p*H of 5 (Hydrion paper). Upon refrigeration the resulting turbidity gave way to a flocculent precipitate. The crude product thus obtained weighed 621 mg. (50% yield) and melted at 119–122° with previous softening beginning at 103°.[20] Two recrystallizations from isoöctane at 60–75° successively lowered the melting point. However, two subsequent recrystallizations from methanol–water carried out in the manner described above for the monobromopyrrole afforded the analytically pure material melting with decomposition at 118–120° with previous development of a purple coloration beginning at 95–100°.[20]

Anal. Calcd. for $C_8H_9O_2NBr_2$: C, 30.89; H, 2.92; C_2H_5O, 14.49. Found: C, 30.96; H, 2.92; C_2H_5O, 14.66, 14.60.

By recrystallization from isoöctane of a sample of the dibromopyrrole which had been previously recrystallized from methanol–water, it has been possible to obtain analytically pure material melting at 127–128°,[20] little or no color development occurring until immediately after melting. Found for the dibromopyrrole melting with decomposition at 127–128°: C, 31.11; H, 2.95.

The dibromopyrrole exhibits a marked sensitivity to light, a property which precludes observation of its decomposition point on the brightly illuminated Köfler hot-stage. Like the monobromopyrrole it must be stored in a refrigerator in the absence of light.

2-Formyl-3-methyl-4-carbethoxypyrrole (VII).[4b,5a]—The Adams modification[11,12] of the Gattermann aldehyde synthesis was employed in the preparation of this pyrrylaldehyde.

To a solution of 2.74 g. of 3-methyl-4-carbethoxypyrrole in 85 ml. of anhydrous ether (filtered from sodium) was added 3.2 g. of technical zinc cyanide. After the mixture had been cooled by immersion in an ice–salt mixture, dry hydrogen chloride was bubbled through the suspension at such a rate that the temperature did not exceed 18°. Gas passage was continued for a total of 65 minutes, the separation of the aldimine salt commencing after about 25 minutes. The aldimine salt was filtered off, washed with dry ether, then heated briefly with 200 ml. of water to 50–55°. When the mixture had been cooled in an ice-bath, the crude aldehyde was filtered off, washed with water, then dried *in vacuo;* yield 2.37 g. or 73% of product melting at 125.5–126.5°.[21] One recrystallization from 40–50% ethanol (Norit A) raised the melting point to 127.5–128.5°.[21]

2-Formyl-3-methyl-4-carbethoxy-5-bromopyrrole (VI).—Three and one-tenth grams of sodium bicarbonate was added to solution of 3.1 g. of 2-formyl-3-methyl-4-carbethoxypyrrole in methanol. A solution of 0.95 ml. of bromine in 10 ml. of methanol was next added dropwise with stirring during 10 minutes. Stirring was continued for 5 minutes more, then 50 ml. of ice-water was dripped in. A dark oily product separated, and a few crystals of sodium thiosulfate was added to destroy any unreacted bromine. Upon immersion of the reaction mixture in a Dry Ice–ethanol-bath the dark-colored product solidified and was filtered off. Freezing, then thawing the filtrate followed by dilution with water to 250 ml., then refrigeration produced a second crop of crude product. To effect removal of colored tarry impurities, 120 ml. of aqueous tertiary sodium phosphate solution (sp. gr. 1.08) was added with stirring to a solution of the combined crudes in methanol. Norit A was added, and after filtration the filtrate was acidified to a *p*H of 6 (Hydrion paper) with hydrochloric acid, then refrigerated. The product was filtered off and washed with water. Seven recrystallizations from hot 60–70% ethanol afforded an analytically pure sample of the bromoaldehyde melting at 166.5–167°.[21]

Anal. Calcd. for $C_9H_{10}O_3NBr$: C, 41.56; H, 3.88; C_2H_5O, 17.32. Found: C, 41.67, 41.80; H, 3.90, 3.97; C_2H_5O, 17.39.

2-Carboxy-3-methyl-4-carbethoxy-5-formylpyrrole (VIII).[7a]—The partial hydrolysis of 2,4-dicarbethoxy-3-methyl-5-formylpyrrole (IX)[6b,7b,8] was first accomplished by Fischer and Ernst.[7a] The following procedure has been found most satisfactory.

In a 250-ml. erlenmeyer flask was placed 10 g. of potassium hydroxide and 100 ml. of alcohol. The mixture was warmed until the potassium hydroxide dissolved. Ten grams of the aldehyde diester IX was then introduced, and the mixture was boiled gently on the steam-bath for exactly 25 minutes, then precipitated immediately.

In an 800-ml. beaker was placed 300 ml. of water, 30 ml. of concentrated hydrochloric acid and sufficient ice to lower the temperature to 0°. The alcoholic solution of the pyrrole was added slowly together with enough ice to keep the temperature below 15°. The mixture was stirred until coagulation was complete, then filtered and washed with water. The crude acid was dissolved in an excess of alcohol, and the solution was poured into 300 ml. of cold water containing 20 g. of sodium bicarbonate. Charcoal was added, and the solution filtered and acidified with hydrochloric acid. The pyrrole was filtered off, washed with water, pressed and dried. It was then recrystallized from a minimum amount of toluene and washed with ligroin. The mother liquors were evaporated to obtain a second crop of crystals. A pure white product was obtained which melts at 204–205°[21] with decomposition; yield about 6.3 g. or 70%. A 50-g. lot gave 65% yield.

2-Bromo-3-methyl-4-carbethoxy-5-formylpyrrole (V).—Four and thirty-nine hundredths grams of 2-carboxy-3-methyl-4-carbethoxy-5-formylpyrrole was dissolved in 16 ml. of hot absolute methanol. After the addition with stirring of 5.5 g. of sodium bicarbonate, the mixture was cooled to 25°. Stirring was continued during the dropwise addition of a solution of 1.03 ml. of bromine in 8 ml. of methanol. The addition was completed in 10 minutes, the temperature rising to 34°, and the mixture was stirred for an additional 20 minutes. It was then poured into 230 ml. of ice-water. After refrigerating overnight the purplish-brown product was filtered off. A second crop of crude bromoaldehyde separated from the filtrate on further standing. Acidification of the final filtrate to a *p*H of 2 to 3 with hydrochloric acid resulted in precipitation of a considerable amount of unchanged aldehyde acid (51% recovery).

To separate the bromoaldehyde from tarry impurities, the crude colored product was stirred for more than an hour with 150 ml. of aqueous 1% sodium hydroxide. The mixture was filtered, and following one treatment with Norit A the filtrate was acidified to a *p*H of 5 with glacial acetic acid. The light-colored product was filtered off, and after two recrystallizations from hot ethanol–water a yield of 546 mg. (11%) of the bromoaldehyde was obtained. Analytically pure V melts at 146–147°[21] and is obtained by repeated crystallization from ethanol–water; mixed melting point with 2-formyl-3-methyl-4-carbethoxy-5-bromopyrrole (VI), 127–148°[21]; mixed melting point with 2-carbethoxy-3-methyl-4-bromo-5-formylpyrrole (X), 111–129°.[21]

Anal. Calcd. for $C_9H_{10}O_3NBr$: C, 41.56; H, 3.88; C_2H_5O, 17.32. Found: C, 41.72, 41.69; H, 3.91, 3.89; C_2H_5O, 17.43.

2-Carbethoxy-3-methyl-4-bromo-5-formylpyrrole (X).[7c,9,10]—This was prepared by the method of Corwin and Straughn.[10] The product melted at 135–136°.[21]

Formylation of Monobrominated 3-Methyl-4-carbethoxypyrrole.—In each of the experiments described below the monobromopyrrole used was of analytical purity as ascertained from carbon and hydrogen analysis of a sample of the material. The anhydrous ether used as solvent was in each case filtered from sodium just prior to use.

(A) **Using Hydrogen Cyanide and Hydrogen Chloride.**—Five milliliters of anhydrous liquid hydrogen cyanide was added to a solution of 1.00 g. of the monobromopyrrole in 30 ml. of anhydrous ether. After cooling the solution to −5° in an ice–salt-bath, dry hydrogen chloride was bubbled in for 80 minutes at such a rate that the temperature did not exceed 6°. Considerable precipitate began to form after the first 25 minutes. The ether was removed *in vacuo* and the residue was treated with 75 ml. of water. After heating briefly to 70–75°, the mixture was cooled in an ice-bath. The crude flesh-colored product was filtered off, washed with water, then stirred for 20 minutes with 150 ml. of aqueous 1% sodium hydroxide. After filtration the pyrrole was precipitated from the filtrate by acidification with acetic acid to a *p*H of 5 to 6. Following a period of refrig-

(21) Determined on the hot-stage of the Köfler micromelting point apparatus.

eration the colorless product was filtered, washed and dried; weight 653 mg. Three recrystallizations from 60–70% ethanol afforded the analytically pure 2-chloro-3-methyl-4-carbethoxy-5-formylpyrrole (XI), melting at 146.5–148°.[21]

Anal. Calcd. for $C_9H_{10}O_3NCl$: C, 50.13; H, 4.68; C_2H_5O, 20.90. Found: C, 49.86, 50.09; H, 4.75, 4.60; C_2H_5O, 20.74.

Three mixtures of widely varying composition were made with the analogous bromoaldehyde (V). The bromoaldehyde melted at 146–146.5°,[21] while the mixtures melted at 146–147°, 146–146.5° and 146–147.5°,[21] respectively.

In order to establish the presence of chlorine in the compound, the following qualitative analytical procedure was employed. Approximately 0.02 millimole of the substance was burned in a stream of oxygen at 800° in the presence of a platinum catalyst. Reduction of the liberated halogen to halide ion was accomplished by bubbling the gaseous combustion products through 2 ml. of 50% formic acid contained in a small spiral bubbler. After transferring the contents of the bubbler to a small beaker together with a few milliliters of distilled water, 1 ml. of 40% ammonium sulfate solution was added. The halide ion was then titrated potentiometrically with 0.002 *M* silver acetate solution using a silver electrode and a saturated calomel reference electrode with an ammonium sulfate salt bridge. Two standard halogen-containing compounds, *o*-chlorobenzoic acid (XVIII) and 2-bromo-3,5-dicarbethoxy-4-methylpyrrole (XIX),[6a,22] were carried through the above procedure, and the resulting titration data were compared with data obtained for the formylation product. The results given in Table I substantiate the presence in XI of chlorine.

TABLE I

Substance	Halogen present	Potential at start of titration, mv.	Potential at titration end-point, mv.
XVIII	Chlorine	146	293
XIX	Bromine	27	212
XI	Unknown	162	292

(B) **Using Mercuric Cyanide and Hydrogen Chloride.**—The formylation was carried out as described in the preceding preparation, using 501 mg. of the monobromopyrrole, 278 mg. of mercuric cyanide and 25 ml. of anhydrous ether. The total time of hydrogen chloride passage was 75 minutes, and the temperature was not permitted to exceed 13°. The reaction mixture was finally filtered to remove whitish solid A, while ether washes and filtrate were combined and evaporated to dryness *in vacuo* to give the buff-colored residue B. Solids A and B were worked up similarly, but separately, as follows. Each was hydrolyzed by heating briefly with a few milliliters of water, then cooled in an ice-water-bath. The aldehyde was filtered off, taken up in 1 to 2 ml. of boiling ethanol, then poured with stirring into about a twenty-fold volume of aqueous 1% sodium hydroxide. After treatment with a little Norit A, the mixture was filtered, and the filtrate was cooled by addition of a little ice, then acidified to a *p*H of 5 to 6 with glacial acetic acid. In each case the precipitated aldehyde was filtered off, washed and dried. Thus was obtained 32 mg. of product A and 156 mg. of product B.

After two recrystallizations from ethanol–water product A, 2-formyl-3-methyl-4-carbethoxy-5-chloropyrrole (XII), melted at 172–173°[21] with previous sintering.

Anal. Calcd. for $C_9H_{10}O_3NCl$: C, 50.13; H, 4.68. Found: C, 50.07; H, 4.85.

Product B was thrice recrystallized from ethanol–water to give pure 2-chloro-3-methyl-4-carbethoxy-5-formylpyrrole (XI), melting at 146–146.5°[21]; mixed melting points with bromoaldehyde V, 146–147°[21]; mixed melting point with bromoaldehyde VI, 129–143°.[21]

Anal. Calcd. for $C_9H_{10}O_3NCl$: C, 50.13; H, 4.68. Found: C, 50.01; H, 4.66.

(C) **Using Zinc Cyanide and Hydrogen Chloride.**—The formylation procedure was essentially that of the preceding two runs, this time using 500 mg. of the monobromopyrrole, 1.0 g. of technical zinc cyanide and 21 ml. of anhydrous ether. Dry hydrogen chloride was passed in for a total of one hour, during which time the temperature did not exceed 12°. After allowing the reaction mixture to warm to 15°, the ether was removed *in vacuo*. The residue was hydrolyzed with 30 ml. of hot water, and the crude product was purified as before by dissolving in minimum hot ethanol, pouring into 50 ml. of aqueous 1% sodium hydroxide and, after filtration, reprecipitating with acetic acid. Following an unsuccessful preliminary attempt to separate the resulting product into its pure component compounds, the product was reclaimed from aqueous basic solution, dried and recrystallized once from hot benzene. Three-fourths of the reclaimed material was stirred for 30 minutes with 75 ml. of carbonate–bicarbonate buffer (22.3 g. of sodium carbonate monohydrate and 25.3 g. of sodium bicarbonate per liter of water). The undissolved solid A was filtered off by gravity and further processed as described below. The filtrate upon acidification and refrigeration yielded a precipitate of product B, which was filtered off and after two recrystallizations from alcohol–water melted at 167–172.5°.[20] Thus product B was most likely 2-formyl-3-methyl-4-carbethoxy-5-chloropyrrole (XII).

To remove any aldehyde VII which may have been present in solid A, it was stirred for about 40 minutes with a solution of 4.7 g. of sodium carbonate monohydrate in 75 ml. of water. After filtration the crude chloroaldehyde was precipitated from the filtrate in the usual manner by acidification with acetic acid. The crude product was next dissolved in minimum hot ethanol, then poured with stirring into 10 ml. of the carbonate–bicarbonate buffer (composition given in the preceding paragraph). The resulting precipitate was filtered off, and after one recrystallization from ethanol–water afforded pure 2-chloro-3-methyl-4-carbethoxy-5-formylpyrrole (XI) melting at 146–147°.[21]

Anal. Calcd. for $C_9H_{10}O_3NCl$: C, 50.13; H, 4.68. Found: C, 50.07; H, 4.64.

From one formylation run in which zinc cyanide was used it was possible also to isolate 2-formyl-3-methyl-4-carbethoxypyrrole (VII) from among the products. This was identified by its melting point, 128.5–129°.[21] A mixed melting point with a sample of the authentic aldehyde showed no depression.

(D) **Using Hydrogen Cyanide and Hydrogen Bromide.**—Formylation was carried out by essentially the procedure of the three previous runs, this time using 1.00 g. of the monobromopyrrole, 5.2 ml. of liquid hydrogen cyanide, 30 ml. of anhydrous ether, and substituting dry hydrogen bromide for hydrogen chloride in order to eliminate the halogen interchange reaction. The hydrogen bromide was bubbled in for a total of 30 minutes, during which time the temperature did not exceed 0°. After allowing the reaction mixture to stand an additional one-half hour in the freezing mixture, the ether was removed *in vacuo*, and the residue was hydrolyzed as before with 50 ml. of water at 65°. The oily product solidified on cooling in an ice-bath, was filtered off, then was stirred for about 30 minutes with 150 ml. of aqueous 1% sodium hydroxide. After filtering the mixture, the *p*H of the filtrate was adjusted to 8 by addition of acetic acid; then 12 g. of sodium carbonate monohydrate was added. At the *p*H of the resulting mixture aldehyde VII is insoluble while the bromoaldehyde V remains in solution. After 90 minutes stirring the mixture was filtered and the insoluble residue A was worked up separately from product B, which separated from the filtrate upon neutralization with acetic acid to a *p*H of 7 and subsequent refrigeration.

Residue A was taken up in 3 to 4 ml. of hot ethanol and further purified by pouring with stirring into a solution of 3.1 g. of sodium carbonate monohydrate in 50 ml. of water. The resulting fibrous product which separated was filtered off, washed and dried; yield 211 mg. of crude 2-formyl-3-methyl-4-carbethoxypyrrole (VII). One recrystallization from ethanol–water afforded 149 mg. of a purer product melting at 128.5–129.5°[21]; mixed melting point with an authentic sample of aldehyde VII, 128–129°.[21]

Product B, after five recrystallizations from ethanol–water, afforded analytically pure 2-bromo-3-methyl-4-carbethoxy-5-formylpyrrole (V) melting at 146–146.5°[21]; mixed melting point with authentic V from the aldehyde acid VIII, 146.5–147°.[21]

Anal. Calcd. for $C_9H_{10}O_3NBr$: C, 41.56; H, 3.88. Found: C, 41.82; H, 3.91.

2-Formyl-3,5-dimethyl-4-carbethoxypyrrole (XIV).[14,15]—The formylation procedure was essentially that of the pre-

(22) H. Fischer and B. Pützer, *Ber.*, **61**, 1072 (1928).

ceding runs. One and thirty-one hundredths grams of analytically pure 2-bromo-3,5-dimethyl-4-carbethoxypyrrole prepared according to Corwin and Viohl,[5b] 2.0 g. of technical zinc cyanide and 55 ml. of dry ether (filtered from sodium) were used. Dry hydrogen chloride was passed through the reaction mixture for a total of 70 minutes, the temperature being held below 16°. After the reaction mixture had stood for a few additional minutes, the ether was removed *in vacuo* leaving a viscous red-brown sirup which was subsequently heated to 90° with 70 ml. of water, then cooled to 15°. The crude brown product was filtered, taken up in warm ethanol, then poured with stirring into 70 ml. of aqueous 2% sodium hydroxide. A bright red precipitate formed, and stirring was continued for some time to effect coagulation. The red substance was filtered off by gravity, suspended in a few ml. of ethanol and re-extracted twice more in the same manner with 2% sodium hydroxide solution. All three filtrates upon acidification with acetic acid to a *p*H of 6 to 7 gave precipitates of the aldehyde. After refrigeration the three crops were combined during filtration; weight of crude 2-formyl-3,5-dimethyl-4-carbethoxypyrrole (XIV), 385 mg. or 37% yield of material melting at 158–164.5°[20] with previous softening. Recrystallization from ethanol–water, then from isoöctane raised the melting point to 165.5–166°[21]; mixed melting point with authentic XIV prepared by the method of Corwin and Andrews,[15] 165–166°.[21]

2-Formyl-3-methyl-4-carbethoxy-5-chloropyrrole (XII).—To a solution of 1.34 g. of 2-formyl-3-methyl-4-carbethoxypyrrole in 6 ml. of glacial acetic acid at room temperature was added dropwise with stirring a solution of 0.65 ml. of sulfuryl chloride in 3 ml. of glacial acetic acid. The addition was carried out during 5 minutes, and the mixture was stirred for 5 more minutes, then poured cautiously with stirring into a solution of 20 g. of sodium bicarbonate in 100 ml. of water. After refrigerating briefly the light orange precipitate which had separated was filtered off, washed and pressed. To remove any starting aldehyde still present the crude product was taken up in minimum boiling ethanol, then poured with stirring into a solution of 5.1 g. of sodium carbonate monohydrate in 83 ml. of water. After a few minutes stirring the mixture was filtered to remove the reddish precipitate. The crude chloroaldehyde separated from the filtrate upon neutralization to a *p*H of 7 with acetic acid. After refrigerating for a short time the product was filtered off and washed. Repeated recrystallization from ethanol–water afforded the analytically pure chloroaldehyde XII melting at 173.5–174.5° with previous sintering at 169–170°.[21]

Anal. Calcd. for $C_9H_{10}O_3NCl$: C, 50.13; H, 4.68; C_2H_5O, 20.90. Found: C, 50.12; H, 4.63; C_2H_5O, 20.85.

2-Iodo-3-methyl-4-carbethoxy-5-formylpyrrole (XVII).—Two and five-tenths grams of 2-carboxy-3-methyl-4-carbethoxy-5-formylpyrrole was heated with 10 ml. of methanol to the boiling point. Three grams of sodium bicarbonate was then added, and the mixture was shaken to complete neutralization of the acid. Two and eight-tenths grams of iodine was then added, and the mixture was boiled for several minutes. Upon pouring into 100 ml. of ice-water a brown gummy mass separated. After addition of 1 g. of potassium iodide, the mixture was reheated to near boiling with frequent shaking, then cooled and allowed to stand overnight at room temperature. In order to effect purification of the crude brownish solid which had separated out, this material was filtered off and stirred for about one-half hour with 150 ml. of aqueous 1% sodium hydroxide, then filtered. Acidification of the filtrate with glacial acetic acid to a *p*H of 5 produced a precipitate of the iodoaldehyde. After filtration the crude product was dried *in vacuo*; yield 2.3 g. or 67%. One recrystallization from ethanol followed by two more from toluene–isoöctane gave the analytically pure iodoaldehyde melting at 178–179°[21] with previous sintering.

Anal. Calcd. for $C_9H_{10}O_3NI$: C, 35.20; H, 3.28; C_2H_5O, 14.67. Found: C, 35.20, 35.05; H, 3.31, 3.33; C_2H_5O, 14.42.

3-Methyl-4-carbethoxy-5-formylpyrrole (XVI).—Three hundred eighty-three milligrams of 2-iodo-3-methyl-4-carbethoxy-5-formylpyrrole, 156 mg. of magnesium oxide, 309 mg. of 5% palladium-on-carbon and 5 ml. of methanol were placed in a semi-micro hydrogenation vessel. Shaking was begun at a pressure of 17.5 lb. of hydrogen (2.8 lb. gage). Twenty-two hours later the hydrogen uptake had ceased and the reaction mixture was filtered to remove the catalyst. The catalyst was washed with 2 ml. of methanol, and a few drops of aqueous 0.1 *N* sodium thiosulfate were added to the filtrate to prevent reoxidation of iodide ion. Fifty milliliters of water was then added and the mixture was refrigerated. The crude aldehyde was filtered off and dried *in vacuo*; weight of product 83 mg. An additional 30 mg. separated from the filtrate on long standing; total yield 50%. The first crop of aldehyde was recrystallized for analysis from isoöctane, m.p. 143–144°.[21]

Anal. Calcd. for $C_9H_{11}O_3N$: C, 59.66; H, 6.12; C_2H_5O, 24.87. Found: C, 59.49, 59.54; H, 6.03, 6.06; C_2H_5O, 24.68.

BALTIMORE, MARYLAND

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA AND THE STERLING-WINTHROP RESEARCH INSTITUTE]

Synthesis of N-Methylmorphinane

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Isoquinoline has been converted to N-methylmorphinane by the reaction sequence outlined below.

The synthesis of N-methylmorphinane from isoquinoline as outlined below was begun by the senior author (C.F.K.) in March, 1947, and carried as far as the betaine, VI, before learning of Grewe's successful synthesis of X.[1] Experimental work was discontinued until the junior author became interested in this field and undertook to try the remaining steps. Because the recent successes of others[2] have made this synthesis chiefly of academic interest, time was not spent in improving yields. However, some of the steps may be of general interest.

The 5-hydroxyisoquinoline was prepared in 56% over-all yield from isoquinoline *via* the nitro and amino intermediates, but on a larger scale the preparation *via* the sulfonic acid, IIA, in 48% over-all yield was more convenient. Also it proved to be simpler to prepare VII directly from V rather than to prepare the betaine, which forms a hydrate that cannot be dehydrated without decomposition.[3]

Reduction of 1-benzyl-2-methyl-5-hydroxy-1,2,-3,4-tetrahydroisoquinoline (VIII) with hydrogen in the presence of Adams platinum oxide in acetic acid led to reduction of the unsubstituted benzene

(1) R. Grewe, *Naturwissenschaften*, **33**, 333 (1946). See also R. Grewe and A. Mondon, *Ber.*, **81**, 279 (1948).

(2) (a) O. Schnider and J. Hellerbach, *Helv. Chim. Acta*, **33**, 1437 (1950). (b) R. Grewe, H. Pohlmann and M. Schnoor, *Ber.*, **84**, 527 (1951). A convenient synthesis of N-methylisomorphinane has also been reported by M. Gates, R. Woodward, W. Newhall and R. Kunzli, THIS JOURNAL, **72**, 1141 (1950). The method has been applied to the synthesis of morphine by M. Gates and G. Tschudi, *ibid.*, **74**, 1109 (1952).

(3) A. Claus and C. Gutzeit, *J. prakt. Chem.*, [2] **52**, 10 (1895).