The substance decomposed at the boiling point of chloroform, so the molecular weight determination was unsatisfactory (found, 800 ±; calcd. for above formula, 1000).

G. Grignard Reactions.—These were all done in high-boiling solvents, *i. e.*, "forced conditions." α-Phenyl-α-(2,5-dimethyl-3,4-diphenylphenyl)-ethylene (XXI) was obtained from the benzophenone (XX); the other products were carbinols. The bimolecular product (IV) failed to react with phenylmagnesium bromide, but gave a quantitative yield of diol with phenyllithium. Their properties are collected in Table IV.

The phenylcarbinol, m. p. 107°, gave a chloride on refluxing for fifteen minutes in acetyl chloride; the chloride (85% yield) crystallizes in rods, m. p. 128°.

Anal. Calcd. for $C_{33}H_{29}Cl$: Cl, 7.6. Found: Cl, 7.4.

Summary

A considerable number and variety of compounds containing a carbonyl bridge have been prepared and their chemical behavior examined. Their synthesis was made possible by the discovery that one of them, a bimolecular product resulting from the dehydration of α,β-dimethylanhydroacetonebenzil, is partially dissociated in most solvents. In one type, the only functional group is the C=O.

A carbonyl group forming a bridge is no different from any other carbonyl group; its elimination as carbon monoxide on heating is in accord with Schmidt's double bond rule.

By heating to eliminate the bridge, and dehydrogenation, highly substituted aromatic compounds have been prepared.

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

Structural Investigations upon a Substituted Dipyrrylmethane. An Unusual Melting Point-Symmetry Relationship[1,2]

BY ALSOPH H. CORWIN, WILLIAM A. BAILEY, JR.,[3] AND PAUL VIOHL[4]

Dipyrrylmethanes have assumed great importance in the chemistry of pyrrole pigments because of the fact that they are degradation products of bile pigments and are intermediates in the synthesis of bile pigments and porphyrins as well. Substances of this type were first prepared by Pictet and Rilliet.[5] One of the most productive methods for their preparation is that from pyrryl carbinols discovered by Fischer and Nenitzescu.[6] This can be represented schematically by the equation

$$2RCH_2OH \longrightarrow RCH_2R + CH_2O + H_2O \quad (1)$$

The usefulness of this synthesis was further extended by Fischer and Halbig,[7] whose essential contribution was that pyrryl carbinols and their ethers could be produced from pyrrylmethyl halides.

By analogy with the course of many other pyrrole reactions, it has been assumed that the points of junction of the methylene bridge were the alpha carbon atoms and not the equally available nitrogens. Only fragmentary evidence exists to support this view[8] and, as a matter of fact, no general method is in existence for the unequivocal proof of the point. In this connection, it should be recalled that Pictet formulated his original dipyrrylmethane as involving N–C–N linkage. We report in this paper a method for the determination of the bridge structure of certain dipyrrylmethanes and a further study of the reaction of Fischer and Nenitzescu. The reactions involved in the structural argument are summarized in Chart I.

The preparation of methane IX from pyrrole II shows that it is a di-N-methylmethane. The stepwise conversion of methane VII to IX through VIII as an intermediate shows that the hydrogens open in VII are on the nitrogens. To test the possibility of intermediate rearrangements, methanes VII and VIII were regenerated from their mono-sodium salts.

The preferential methylation of the imine hydrogen over the hydroxyl hydrogen in compound V is a matter for comment. It is well known that the acidity of the imine hydrogens in pyrrole derivatives is of a different order of magnitude from

(1) Studies in the Pyrrole Series, VIII; Paper VII, Quattlebaum and Corwin, THIS JOURNAL, **64**, 922 (1942).

(2) The major portion of this paper is taken from the doctoral dissertation of William A. Bailey, Jr., The Johns Hopkins University, 1937.

(3) Present address, Shell Development Company, Emeryville, Calif.

(4) Present address, United States Rubber Company, Detroit, Mich.

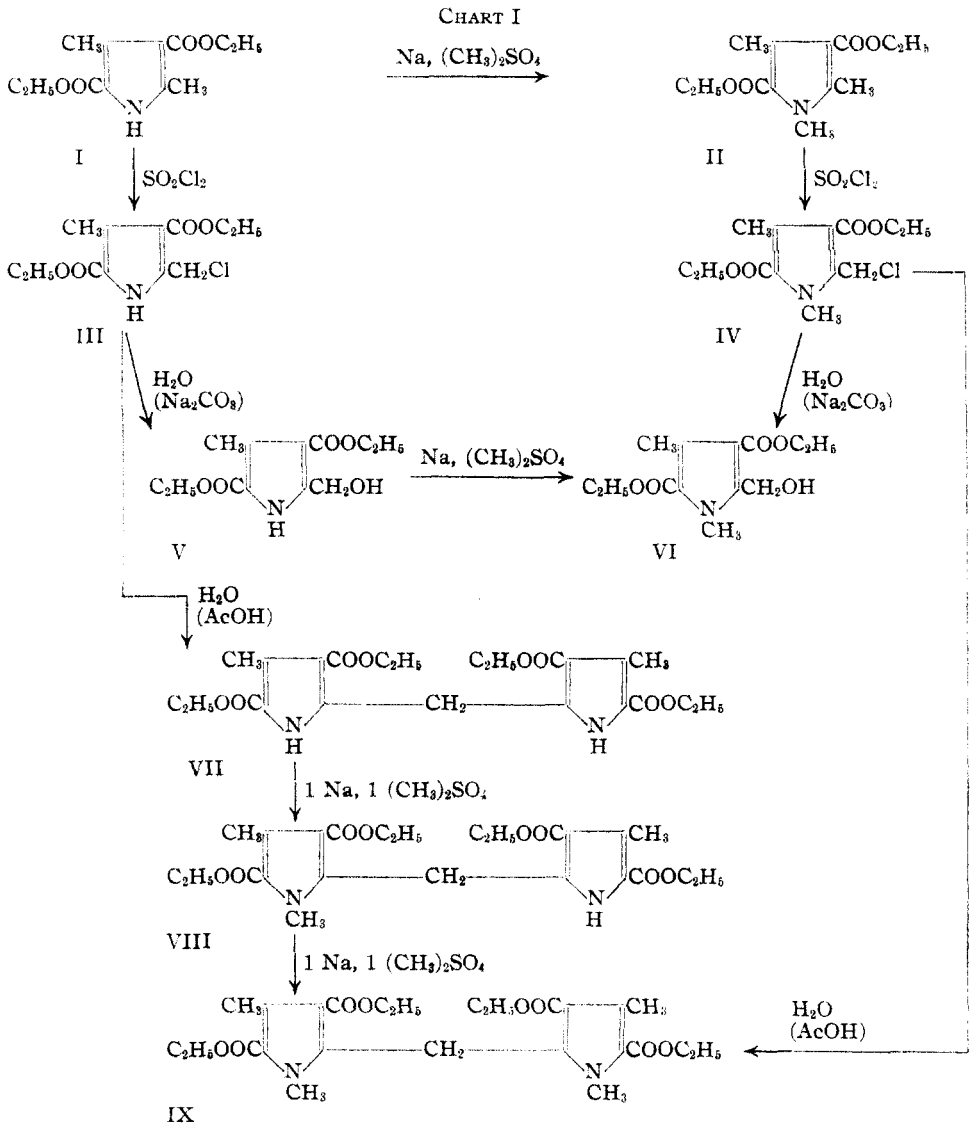
(5) Pictet and Rilliet, *Ber.*, **40**, 1170 (1907).

(6) Fischer and Nenitzescu, *Ann.*, **443**, 114 (1925).

(7) Fischer and Halbig, *ibid.*, **447**, 133 (1926).

(8) Feist, *Ber.*, **35**, 1647 (1902).

CHART I



those of aliphatic amines.[9] In compound V this tendency has proceeded so far that the sodium salt is formed by ionization of the imine hydrogen and subsequent methylation gives the N-methyl compound. It is possible that the inductive influence of the pyrrole ring also decreases the acidity of the hydroxyl group but at any rate the reaction demonstrates the reversal of the normal OH–NH acidity relationship.

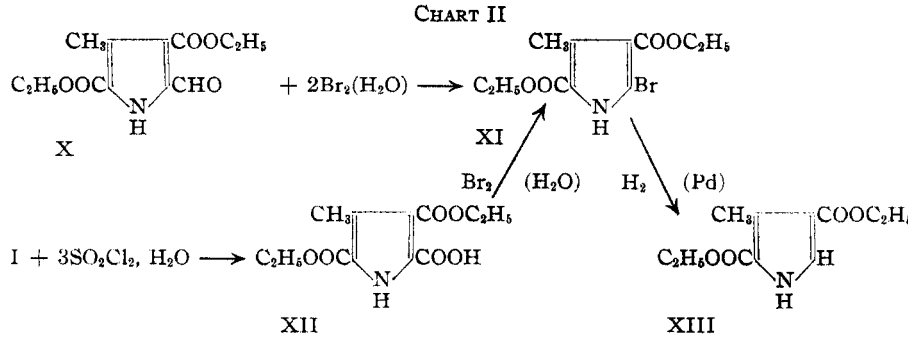
Methanes VII, VIII and IX exhibit melting point relationships which are at variance with at least two well-established regularities of behavior. In the preparation of numerous N-methylated pyrrole derivatives it has been invariably observed that the N-methyl homolog melts lower than the unmethylated compound.[1] This rule finds a reasonable theoretical explanation in the acidity of the pyrrole NH group. It seems logical to assume that pyrroles are associated through NH groups in a fashion similar to the association of alcohols whose acidity they resemble. N-Methylpyrroles, then, should be regarded as "iminoethers" and melting points lower than the NH compounds would be predicted as normal. Compound IX presents a contrast to this behavior, however, since its melting point is 144–145° whereas that of compound VII is 135°.

It is also the usual rule that a decrease in symmetry results in a lowering of the melting point of organic substances.[10] Compound VIII, the un-

(9) W. K. McEwen, THIS JOURNAL, **58**, 1124 (1936).

(10) See, for instance, Hückel, "Theoretische Grundlagen der organischen Chemie," Akad. Verlag, Leipzig, 1931, II Band, p. 185.

CHART II



symmetrical mono-N-methylmethane, melts at 139–140°, 4–5° higher than the symmetrical lower homolog, thus breaking both the symmetry rule and the N-methylation rule. We have no explanation of these anomalies to advance. It is possible that an X-ray study of the actual spatial arrangement of these molecules would reveal the source of the peculiarities.

The methylation procedure outlined above was attempted on the following dipyrrylmethanes without success: 3,5,4′-tricarbethoxy-4,3′,5′-trimethyl, 3,5,3′,5′-tetramethyl-4,4′-dicarbethoxy, and 1,4,3′,5′-tetramethyl-3,5,4′-tricarbethoxy. Attempts to force the reaction by the use of potassium instead of sodium were likewise unsuccessful. In the succeeding paper a more general method for preparing sodium salts will be given in detail and this will show that the negative result is not due to an alteration in structure.

The reaction represented by Eq. 1 and illustrated by the formation of compounds V and IX, involves an acid catalyzed C–C cleavage as well as a condensation. The simplest manner of formulating this reaction is to assume that the cleavage precedes the condensation

$$RCH_2OH \rightleftharpoons RH + CH_2O \qquad (2)$$

$$RCH_2OH + RH \longrightarrow RCH_2R + H_2O \qquad (3)$$

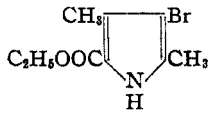
To test this assumed reaction sequence, it was necessary to prepare the compound RH or 2,4-dicarbethoxy-3-methylpyrrole (XIII). This was accomplished by a series of reactions given in detail in Chart II. That formaldehyde will condense with pyrrole XIII reversing reaction 2 was demonstrated by the preparation of methane VII from pyrrole XIII and formaldehyde under the conditions of reaction 1. It was also found that reaction 3 proceeds under the conditions of reaction 1. It is thus demonstrated that the proposed sequence is a possible one.

It should be noted in passing that the hydrolyses of the pyrrylmethyl halides III and IV both proceed in either acid or alkaline media and it seems logical to infer that these reactions are "solvolytic." It is thus possible that the methane condensation proceeding from the pyrrylmethyl halides does not go as far as the production of a carbinol but that an intermediate carbonium ion reacts with pyrrole XIII to form the methane. This possibility can be tested only by a thorough kinetic analysis of the course of the reaction.

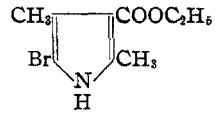
Although the acid-catalyzed C–C cleavage of reaction 2 is one with few proved analogies, acid catalyzed cleavages of pyrryl aldehydes followed by methene formation have been recorded frequently.[11] The cleavage of aldehyde X (Chart II), which is the oxidation product of carbinol V, does not proceed under the conditions which lead to the cleavage of those pyrryl aldehydes in which dipyrrylmethene formation is involved. On the other hand, there is some evidence that cleavage of this compound under the influence of bromine can take place. Two moles of bromine in water convert the aldehyde into the bromopyrrole XI.[12] This can also be accomplished by the use of one mole of bromine on the pyrrylcarboxylic acid XII whose preparation is now reported for the first time. The reactions involved in these transformations are summarized in Chart II.

The pyrrolecarboxylic acid XII differs from most of those which have been reported previously in that it is difficult to decarboxylate. No method has yet been discovered for accomplishing this directly without destroying the products of decarboxylation. Indirectly, however, it can be accomplished by the catalytic debromination of compound XI with hydrogen and palladium. This reaction seems to be quite general in the pyrrole series, having been successfully carried out on pyrryl bromides of reactivity varying as widely as XIV and XV in addition to XI. Such a reaction opens the door to the use of bromine instead of carboxyl as a protective group for the pyrrole nucleus.

(11) See Fischer and Zerweck, *Ber.*, **55**, 1943 (1922).
(12) Fischer and Pützer, *ibid.*, **61**, 1072 (1928)



XIV



XV

It is not possible to decide from the data now at hand whether the C–C cleavage by the action of bromine takes place only on acid XII, that is, whether aldehyde X is first oxidized or first cleaved. Which reaction takes place first is immaterial to the argument of analogy since both compounds X and XII are stable to temperatures above 200° unless treated with reagents capable of attacking the pyrrole ring. This is analogous to the reactions 2 and 3 in which the cleavage 2 cannot be made evident except under conditions which permit irreversible attack on the pyrrole ring as in reaction 3.

It may be concluded that our experimental examination has brought to light no evidence in conflict with the reaction sequence (reactions 2 and 3) proposed for the formation of dipyrrylmethanes from pyrryl carbinols.

Experimental Section

2-Chloromethyl-3,5-dicarbethoxy-4-methylpyrrole (III).—In a one-liter three-neck flask fitted with a mechanical stirrer, thermometer, gas-exit tube and dropping funnel is placed 84 g. of 2,4-dimethyl-3,5-dicarbethoxypyrrole and 670 cc. of glacial acetic acid. The solution is warmed with stirring until all the solid is dissolved. A solution of 54 g. (28.4 cc.) of sulfuryl chloride in 60 cc. of glacial acetic acid is then added as rapidly as possible between the limits of 50–60°. The reaction mixture is warmed to 70° for half an hour, then cooled slowly to 20° and kept at this temperature until no more solid separates out. It is filtered rapidly under the hood and most of the mother liquor sucked out while the solid is pressed. The crystals are washed on the funnel with hexane or ligroin until they are light pink and then dried in the air; m. p. 153.5–154°. The material is recrystallized from 200 cc. of benzene and 125 cc. of chloroform, raising the m. p. to 156°; yield after recrystallization, 68 g. or 71%.

Anal. Calcd. for $C_{12}H_{16}O_4NCl$: C, 52.65; H, 5.89. Found: C, 52.80; H, 5.92.

The 2-acetoxymethyl, 2-methoxymethyl and 2-ethoxymethyl derivatives were prepared by methods closely resembling the preparations from the corresponding 2-bromomethyl compound[13]; mixed m. p. with samples prepared by this older method gave no depressions.

2-Hydroxymethyl-3,5-dicarbethoxy-4-methylpyrrole (V).—In a 200-cc. round-bottom flask fitted with a reflux condenser is placed 15 g. of 2-chloromethyl-3,5-dicarbethoxy-4-methylpyrrole, 50 cc. of acetone and 10 cc. of water. To this is added a solution of 2.9 g. of sodium carbonate in 15 cc. of water. The solution is refluxed for nine hours and then poured into 150 cc. of ice-water. Colorless crystals separate which are filtered off, washed with water and dried in the air. The crystals are dissolved in 50 cc. of hot carbon tetrachloride and hexane is added to the point of cloudiness. The solution is cooled to below 10° and the precipitate filtered off and washed with cold hexane; yield, 12 g. or about 90%; m. p. 117.5–118.5° with decomposition. A further crystallization gave crystals melting with decomposition at 120–121°; remelt, 112–113°.

As noted by Fischer, Sturm and Friedrich,[14] this substance is difficult to identify by melting point. Repeated recrystallizations gave a product melting as high as 123° with decomposition. The higher the initial melting point observed, the greater the drop of melting point which is found upon remelting. The decomposition of the substance appears to be critically poised near these temperatures, however, since samples melting as low as 112–113° show very little further depression of melting point upon remelting even though they will undergo a further melting point lowering upon prolonged heating.

3,5,3′,5′-Tetracarbethoxy-4,4′-dimethyldipyrrylmethane (VII). (a) **From Monochloropyrrole (III).**—The recrystallized monochloropyrrole obtained from chlorination of 84 g. of 2,4-dimethyl-3,5-dicarbethoxypyrrole is dissolved in 84 cc. of glacial acetic acid and brought to a boil; 84 cc. of water is added and the solution refluxed for ninety minutes. The contents of the flask are allowed to cool and the oil which is first formed is permitted to solidify completely before filtering. The crude dipyrrylmethane is crystallized from the minimum amount of ethanol, filtered and dried; yield 54%. An additional 3% may be recovered from the alcoholic mother liquors; m. p. 135°.

(b) **From Hydroxymethylpyrrole (V) by Fusion.**—Five hundred milligrams of the hydroxymethylpyrrole is placed in a test-tube and heated in an oil-bath to 130°. A pinch of powdered potassium acid sulfate is added and rapid bubbling ensues with evolution of formaldehyde. The temperature is maintained at 130–135° for thirty minutes, 5 cc. of alcohol added to the melt and the mixture boiled until the solution is clear. It is filtered, a little water added and the solution cooled, filtered and dried; yield, 420 mg. or 93%, m. p. 135°.

(c) **From Hydroxymethylpyrrole (V) in Solution.**—Five hundred milligrams of the hydroxymethylpyrrole is dissolved in 15 cc. of xylene, a pinch of powdered potassium acid sulfate added and the mixture refluxed for three hours. Paraformaldehyde forms in the condenser. The solution is filtered hot, evaporated to dryness and the residue recrystallized from alcohol–water. The yield is practically quantitative; m. p. 135°.

1,4,4′-Trimethyl-3,5,3′,5′-tetracarbethoxydipyrrylmethane (VIII).—In a 200-cc. three-neck flask fitted with a mechanical stirrer, reflux condenser protected with a calcium chloride tube and a dropping funnel are placed 9.25 g. of 3,5,3′,5′-tetracarbethoxy-4,4′-dimethyldipyrrylmethane and 75 cc. of dry toluene. The solution is heated to 105° in an oil-bath and 470 mg. of sodium added in small portions with rapid stirring. The temperature is kept at 105–110° until the sodium reacts, usually requiring two hours. The reaction is accompanied by the evolution of hydrogen and the precipitation of the insoluble sodium salt

(13) Fischer and Halbig, *Ann.*, **447**, 139 (1926); Fischer and Scheyer, *ibid.*, **434**, 245 (1923).

(14) Fischer, Sturm and Friedrich, *ibid.*, **461**, 251 (1928).

of the methane. The temperature is allowed to fall to 90° and 2.0 cc. of redistilled dimethyl sulfate is added, followed by 10 cc. of toluene to wash the funnel. The mixture is refluxed for one hour and filtered hot to remove the sodium methyl sulfate, which is then washed with 20 cc. of hot toluene. The toluene is distilled off with steam, and the steam distillation stopped as soon as all the toluene is removed, since the N-methylmethane is somewhat volatile with steam. The residue is cooled, filtered off and crystallized from ethanol; yield, 90–95%; m. p. of the purified product, 139–140°; mixed m. p. with starting material, 133–134°.

Anal. Calcd. for $C_{24}H_{32}O_8N_2$: C, 60.47; H, 6.77. Found: C, 60.39; H, 6.84.

1,4,1′,4′-Tetramethyl-3,5,3′,5′-tetracarbethoxydipyrrylmethane (IX).—The methylation is similar to that described above except that 9.52 g. of the monomethyldipyrrylmethane is used in the reaction. The product is crystallized from 85% alcohol; yield, 9.5 g. of the recrystallized product or 97% of the theoretical; m. p. of the purified product, 144–145°; mixed m. p. with the mono-N-methyldipyrrylmethane, 131–132°; with the unmethylated methane, 128–130°.

The product may be prepared alternatively by dimethylating 3,5,3′,5′-tetracarbethoxy-4,4′-dimethyldipyrrylmethane without isolation of the mono-N-methylmethane. An excess of sodium and dimethyl sulfate is used and eight hours of refluxing allowed after the dimethyl sulfate has been added.

Anal. Calcd. for $C_{25}H_{34}O_8N_2$: C, 61.21; H, 6.99. Found: C, 61.13; H, 6.88.

Another alternative method for this preparation is described below.

1,2,4-Trimethyl-3,5-dicarbethoxypyrrole (II).—The purification of this product, which has been described previously,[15] can be improved by treating the toluene solution of the N-methylpyrrole with sodium metal at 100° after removal of the sodium methyl sulfate. The sodium salt of any unchanged starting pyrrole precipitates and is filtered off together with unreacted sodium metal.

1,4-Dimethyl-2-chloromethyl-3,5-dicarbethoxypyrrole (IV).—The preparation is essentially similar to that of 2-chloromethyl-3,5-dicarbethoxy-4-methylpyrrole except that 89.4 g. of 1,2,4-trimethyl-3,5-dicarbethoxypyrrole is used in the reaction and is dissolved in 500 cc. of glacial acetic acid. After the reaction is complete, the monochloropyrrole may be removed by cooling the acetic acid solution to 20° and adding water slowly enough to prevent the formation of an oil until all the solid is precipitated. The precipitate is then filtered off and air-dried. It may be crystallized from benzene; yield, 80%; m. p. 71–72°.

Anal. Calcd. for $C_{13}H_{18}O_4NCl$: C, 54.26; H, 6.31. Found: C, 54.35; H, 6.35.

1,4-Dimethyl-2-hydroxymethyl-3,5-dicarbethoxypyrrole (VI). **(a) By Methylation.**—In a 200-cc. three-neck flask fitted with a mechanical stirrer, reflux condenser and dropping funnel is placed 2.55 g. of 2-hydroxymethyl-3,5-dicarbethoxy-4-methylpyrrole and 75 cc. of dry toluene. The solution is heated to 100° in an oil-bath and 0.25 g. of sodium is added in small pieces. The mixture is stirred rapidly at 100° for three hours or until practically all the sodium has reacted. A solution of 1.2 cc. of redistilled dimethyl sulfate in 10 cc. of toluene is added and stirring continued at 100° for two hours or until all the sodium salt of the pyrrole has reacted, leaving transparent sodium methyl sulfate as the residue. The solution is filtered hot, the residue washed with a little hot toluene and the filtrate evaporated to dryness cold, leaving a brown mass of crystals which can be recrystallized from 20 cc. of 1:5 benzene–hexane solution; 2.15 g. of light brown crystals is obtained; m. p. 86–88°. Recrystallization from hexane, using Norite to decolorize the solution, gives colorless plates melting reversibly at 98°; yield 70%.

Anal. Calcd. for $C_{15}H_{19}O_6N$: C, 57.98; H, 7.11. Found: C, 58.33; H, 6.99.

(b) By Hydrolysis.—The procedure is essentially that described for 2-hydroxymethyl-3,5-dicarbethoxy-4-methylpyrrole, using 1,4-dimethyl-2-chloromethyl-3,5-dicarbethoxypyrrole as the starting material. The product after recrystallization melts at 96–97°; mixed m. p. with that described above, no depression.

1,4,1′,4′-Tetramethyl-3,5,3′,5′-tetracarbethoxydipyrrylmethane.—The procedure starting with 1,4-dimethyl-2-chloromethyl-3,5-dicarbethoxypyrrole is similar to the preparation of the corresponding di-NH-dipyrrylmethane (VII) described above. The di-N-methyldipyrrylmethane is first crystallized from 50% alcohol and then from 85% alcohol as described above; yield, 30%; mixed m. p., no depression.

3,5,4′-Trimethyl-4,3′,5′-tricarbethoxydipyrrylmethane.[16] —Ten and nine-tenths grams of 2-chloromethyl-3,5-dicarbethoxy-4-methylpyrrole and 6.7 g. of 2,4-dimethyl-3-carbethoxypyrrole are refluxed in 20 cc. of methanol for three hours. Upon cooling, 14.5 g. of colorless crystals precipitates. This may be recrystallized from ethanol; m. p. 157°.

Attempted Methylations of Dipyrrylmethanes.—The methylation procedure described above was tried upon the following dipyrrylmethanes without success: 3,5,4′-trimethyl-4,3′,5′-tricarbethoxy, 1,4,3′,5′-tetramethyl-3,5,4′-tricarbethoxy,[17] 3,5,3′,5′-tetramethyl-4,4′-dicarbethoxy. In unsuccessful attempts to force the reactions, potassium was substituted for sodium and dioxane for toluene as solvent. In dioxane the tetramethyltricarbethoxydipyrrylmethane gave a deep blue fluorescence with sodium which slowly disappeared upon methylation. An impure mixture was obtained from this reaction which softened at 173° and melted at 210–221°. Further recrystallization did not seem to improve the purity of this compound. This reaction has been subjected to close scrutiny and will be reported upon in a later communication.

2-Formyl-3,5-dicarbethoxy-4-methylpyrrole (X).[18]—In a 500-cc. three-neck flask equipped with a motor stirrer, thermometer, gas-exit tube and dropping funnel are placed 50 g. of 2,4-dimethyl-3,5-dicarbethoxypyrrole and 250 g. of glacial acetic acid. The reaction is carried out under a hood. The flask is heated to 50° and 56.6 g. (35.2 cc.) of

(15) Corwin and Quattlebaum, THIS JOURNAL, **58**, 1083 (1936).

(16) Fischer and Halbig, *Ann.*, **447**, 132 (1926).

(17) Quattlebaum and Corwin, THIS JOURNAL, **64**, 923 (1942).

(18) Fischer and Halbig, *Ann.*, **447**, 137 (1926); Fischer, Sturm and Friedrich, *ibid.*, **461**, 267 (1928); Fischer, Goldschmidt and Nüssler, *ibid.*, **486**, 50 (1931).

sulfuryl chloride in 70 cc. of glacial acetic acid is added between the limits of 50–60°. The solution is maintained at this temperature for several minutes and the flask then cooled to 20°. The precipitated aldehyde is filtered off under a hood and washed with hexane or ligroin. After drying the aldehyde may be recrystallized from the minimum amount of toluene. A colorless product is obtained melting at 124–125°. The mother liquors from the toluene may be evaporated down and a second crop of crystals obtained; yield 90%.

The aldehyde also may be prepared by using one mole of sulfuryl chloride and one of 2-chloromethyl-3,5-dicarbethoxy-4-methylpyrrole under identical conditions as would be expected.

2-Carboxyl-3,5-dicarbethoxy-4-methylpyrrole (XII).—The solution of 2,4-dimethyl-3,5-dicarbethoxypyrrole in acetic acid is made up exactly as described in the preceding preparation. The flask is then cooled by an ice-bath. At 14°, 33 g. (10.3 cc.) of bromine is added, taking only a few minutes. The addition of 84.8 g. (52.5 cc.) of sulfuryl chloride is started at 14° and the temperature allowed to fall as far as possible without congealing the acetic acid. During the first half of the addition of the sulfuryl chloride the temperature will not go below 11° but later it should be lowered to 0° by substituting a freezing mixture for an ice-bath. The addition of the sulfuryl chloride is attended by the evolution of much heat and it is necessary to add it very slowly if the maximum yield is to be obtained. The addition requires one and one-half to two hours. The mixture is held at 0–2° for six hours. Water at room temperature is then added drop by drop until the violence of the action diminishes and then more rapidly until the flask is full. The temperature is raised to 60° and held there for fifteen to thirty minutes. The solution is poured into two liters of cold water and stirred to complete the coagulation of the precipitate. The precipitate is filtered off under a hood, washed with cold water, dissolved in alcohol and warmed to 60°. Dry, powdered sodium bicarbonate is added to the alcoholic solution until no further evolution of carbon dioxide is noted. The solution is then poured very slowly and with constant stirring into five times its volume of cold water, the mixture allowed to stand with occasional stirring for at least an hour to ensure complete precipitation of the aldehyde which is formed as a by-product, the aldehyde removed by filtration and purified by recrystallization from toluene; yield 7–9 g. or 13–17%. The acid is precipitated with hydrochloric acid, filtered, washed and dried at 50°; yield 39–42 g. or 70–75%; m. p. 150°. The acid may be recrystallized from a mixture of alcohol and water.

Anal. Calcd. for $C_{12}H_{15}O_6N$: C, 53.50; H, 5.61. Found: C, 53.58; H, 5.68.

This pyrrylcarboxylic acid is unusual in its low melting point and its great stability to conditions which usually cause decarboxylation. It may be distilled with glycerol or with mineral oil boiling at 300° without decomposition. A mixture of quinoline or of the copper salt of the acid does not bring about decarboxylation. Heating in a silver-lined autoclave for five hours at 200° brought about extensive decomposition into carbon dioxide and tar but it was not possible to isolate a crystalline solid from the tar. A decarboxylation in the gas phase was also attempted in a flowing system. The substance was found to be stable to very brief exposure to 500° but at 525° decomposition into carbon dioxide and tar took place. Again it was impossible to isolate a crystalline solid. The only successful decarboxylation is the indirect one described below.

2-Bromo-3,5-dicarbethoxy-4-methylpyrrole (XI).[12]—In a two-liter three-neck flask equipped with a mechanical stirrer, dropping funnel, reflux condenser and thermometer are placed 40 g. of 2-carboxyl-3,5-dicarbethoxy-4-methylpyrrole and 400 cc. of glacial acetic acid. The pyrrole is dissolved by warming and 26.2 g. of bromine in 40 cc. of glacial acetic acid is added slowly at a temperature of 40–45° by means of the dropping funnel. This requires about twenty minutes. The solution is allowed to stand with stirring for fifteen minutes after which 300 cc. of water is added slowly. The temperature is maintained at 45°; this requires about an hour. The temperature is then slowly raised to 100° and held there until all the bromine color has disappeared. The hot solution is then poured into two liters of ice–water mixture. The bromopyrrole precipitates along with considerable unreacted starting material. The crude product is filtered off and washed with water. It is dissolved in 350 cc. of ethanol and treated with sodium bicarbonate at 40° until the evolution of carbon dioxide ceases. The bromopyrrole is then precipitated by pouring into 1500 cc. of ice–water. The purified bromopyrrole is filtered off and dried to constant weight; yield 35 g. or 77%. m. p. 143°.

The unchanged starting acid may be recovered from the final filtrate by acidification with hydrochloric acid and filtration; recovery, 8 g. or 20%.

The bromopyrrole may be recrystallized from alcohol–water or from carbon tetrachloride; m. p. 145°.

2,4-Dicarbethoxy-3-methylpyrrole (XIII).—In a 50-cc. hydrogenation flask is placed 1.48 g. of purest 2-bromo-3,5-dicarbethoxy-4-methylpyrrole and 30 cc. of methanol. The pyrrole is dissolved and 500 mg. of Norite A, 500 mg. of magnesium oxide and ten drops of 10% palladium chloride solution are added and the mixture shaken. The solution is hydrogenated for two hours at room temperature and a pressure of two atmospheres of hydrogen. When reduction is complete the mixture is heated to boiling and filtered. The catalyst is washed with two 10-cc. portions of hot methanol and the combined filtrates poured into 250 cc. of ice–water mixture. This is allowed to stand for several hours to ensure complete precipitation, after which the pyrrole is filtered off and washed with water; yield 1.02 g. or 92.5%; m. p. 90–91°. The product may be crystallized from alcohol–water, m. p. 91°.

Anal. Calcd. for $C_{11}H_{15}O_4N$: C, 58.65; H, 6.71. Found: C, 58.62; H, 6.74.

The procedure described above may be applied to the removal of bromine from other bromopyrroles. Hydrogenation of 2,4-dimethyl-3-carbethoxy-5-bromopyrrole gives 2,4-dimethyl-3-carbethoxypyrrole; m. p. 76°. Hydrogenation of 2,4-dimethyl-3-bromo-5-carbethoxypyrrole gives 2,4-dimethyl-5-carbethoxypyrrole; m. p. 124°.

As a structural confirmation, the hydrogenation process was reversed by bromination. In a 10-cc. Erlenmeyer flask, 225 mg. of 2,4-dicarbethoxy-3-methylpyrrole was dissolved in 1 cc. of glacial acetic acid; 0.52 cc. of a solution of bromine in glacial acetic acid (0.31 g./cc.) was added

and the mixture allowed to stand for one hour at room temperature. The solution was poured slowly with stirring into 50 cc. of ice–water. The precipitate was filtered off and washed with water; yield, 280 mg. or 92.5%; m. p. 138°. Recrystallization from alcohol–water raised the melting point to 144°. A mixed m. p. with 2-bromo-3,5-dicarbethoxy-4-methylpyrrole showed no depression.

Experiments upon the Formation of Dipyrrylmethane VII.—(a) In a 25-cc. Erlenmeyer flask fitted with a reflux condenser is placed 450 mg. of 2,4-dicarbethoxy-3-methylpyrrole, 4 cc. of glacial acetic acid, 0.70 cc. of concentrated hydrochloric acid and 1 cc. of 36% formaldehyde solution. The solution is refluxed for ninety minutes. After fifteen minutes, 0.5 cc. of formaldehyde is added. At the end of the refluxing period, 0.5 cc. of water is added and the solution allowed to cool slowly to room temperature. After standing in the ice-box overnight, the crystals which separate out are filtered off and washed with 5 cc. of 50% acetic acid. Recrystallization from alcohol–water gives 210 mg. (23%) of a material melting at 135°. Mixed m. p. with dipyrrylmethane VII showed no depression.

(b) In a 25-cc. Erlenmeyer flask with a condenser is placed 255 mg. of 2-hydroxymethyl-3,5-dicarbethoxy-4-methylpyrrole, 2 cc. of glacial acetic acid, 0.3 cc. of concentrated hydrochloric acid and 0.2 cc. of distilled water. The reaction is treated exactly as described under (a); yield, 127 mg. or 55%.

(c) One hundred twenty-eight milligrams of 2-hydroxymethyl-3,5-dicarbethoxy-4-methylpyrrole and 113 mg. of 2,4-dicarbethoxy-3-methylpyrrole are treated exactly as described under (b); yield, 90 mg. Since the yield from this amount of the 2-hydroxymethylpyrrole alone would be 63–64 mg., the remaining 26–27 mg. is the amount which cannot be formed from this reaction and is the minimum amount to be ascribed to the cross-reaction between the two pyrroles.

Summary

1. A method for the determination of the bridge structure of certain dipyrrylmethanes is described.

2. A pyrrole derivative is reported whose NH is more acidic than an OH in the same molecule.

3. Three dipyrrylmethanes which exhibit an anomalous melting point behavior are described.

4. 2-Carboxyl-3,5-dicarbethoxy-4-methylpyrrole has been prepared.

5. The catalytic debromination of a number of pyrrole derivatives has been accomplished.

6. A reaction sequence for the conversion of pyrryl carbinols to dipyrrylmethanes is proposed.

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[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

Sterols. CXLII. 17-Methyl-pregnan-3(β)-ol-20-one and Related Compounds*

BY RUSSELL E. MARKER AND R. B. WAGNER

Recently,[1] we have described the rearrangement of 17-bromo-pregnan-3(β)-ol-20-one into the methyl ester of 3(β)-hydroxy-17-methyl-*etio*-cholanic acid. This readily available material led to the preparation of 17-methyl compounds of the hormone series.

Treatment of the methyl ester of 3(β)-hydroxy-17-methyl-*etio*-cholanic acid (I) with excess methyl Grignard reagent gave an unsaturated compound, $C_{23}H_{38}O$. It is very likely that this substance resulted from the dehydration of an intermediate tertiary carbinol. Similar observation of a simultaneous addition and dehydration to give an unsaturated compound has been made by Brown, Heilbron and Spring.[2] They obtained 7-methylene-cholesterol from 7-keto-cholesteryl acetate. The analogous compound in our reaction would be 20-methylene-17-methyl-pregnan-3(β)-ol (II).

Catalytic hydrogenation of 20-methylene-17-methyl-pregnan-3(β)-ol (II) gave the corresponding saturated compound (III). Oxidation of the acetylated unsaturated compound (II) either by ozonolysis or with chromic anhydride in acetic acid gave 17-methyl-pregnan-3(β)-ol-20-one (VI) isolated as the free hydroxy ketone.

Hydrolysis of the methyl ester (I) gave 3(β)-hydroxy-17-methyl-*etio*-cholanic acid previously described by us[1] which was acetylated and treated with thionyl chloride. The acid chloride (V) was not isolated but was immediately treated with dimethylzinc. Hydrolysis of this product gave the same 17-methyl-pregnan-3(β)-ol-20-one (VI) previously obtained.

The acetylated acid chloride was treated with diazomethane to give (VII) and then with moist gaseous hydrochloric acid. Subsequent hydrolysis gave as the major product a substance, $C_{22}H_{36}O_3$. By analogy this compound is considered to be 21-hydroxy-17-methyl-pregnan-3(β)-ol-20-one (VIII), since Reichstein[3] similarly ob-

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(1) Marker and Wagner, THIS JOURNAL, **64**, 216 (1942).

(2) Brown, Heilbron and Spring, *J. Chem. Soc.*, 1274 (1936).

(3) Reichstein, *Helv. Chim. Acta*, **20**, 1164 (1937).