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

Preparation of Dipyrrylmethylpyrocolls. Catalytic Reduction of 3,5,4′-Tricarbethoxy-4,3′,5′-trimethylpyrromethene[1]

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Catalytic reduction of 3,5,4'-tricarbethoxy-4,3',5'-trimethylpyrromethene gave two dimeric products. The products are formulated as *cis* and *trans* isomers of a dipyrrylmethylpyrocoll derivative. Similar dipyrrylmethylpyrocoll derivatives were synthesized by other routes and have proved to exhibit properties similar to those of the compounds resulting from the reduction. Explanations are offered for the tendencies of these compounds to retain water and alcohol.

Catalytic hydrogenation of a pyrromethene usually yields the corresponding pyrromethane. We report conditions under which the catalytic hydrogenation of 3,5,4′-tricarbethoxy-4,3′,5′-trimethylpyrromethene (I) gives instead a pair of dimeric products. These products are designated compound A and compound B.

Compounds A and B were first prepared by Corwin and Andrews.[2] Ellingson[3] repeated the preparation, and his molecular weight data revealed that both compound A and compound B are formed from two molecules of pyrromethene.

The course of the reduction is affected by catalyst, acidity and concentration of pyrromethene. When Raney nickel catalyst is used the "usual" reduction product, 3,5,4′-tricarbethoxy-4,3′,5′-trimethylpyrromethane, is obtained from pyrromethene I. The pyrromethane was obtained in addition to compounds A and B by Ellingson,[3] who used platinum or palladium-on-charcoal and acid solutions. We employ palladium in the absence of acid to obtain good yields of A and B but no pyrromethane. Increasing the concentration of pyrromethene gives more B and less A, the total yield increasing somewhat. This variation remains unexplained. The course of the reduction is the same whether methanol, 95% ethanol or *n*-butyl alcohol be employed as the solvent.

The analytical data agree with the scheme

$$2(C_{21}H_{26}N_2O_6) + 2H_2 = C_{42}H_{56}N_4O_{12}$$

$$2 \text{ pyrromethene I} + 2H_2 \longrightarrow \text{compound A (or B)}$$

We have reversed the reaction through oxidation with bromine; both compound A and compound B give the starting pyrromethene.

Considering the facts outlined above and the pyrocoll syntheses described below, we propose that the first step of the reaction is reduction of the double bond connecting the bridge carbon to the pyrrolenine ring of I, giving structure II (Chart I). This leaves the ring in the pyrrolenine form, and the nitrogen retains its unshared electron pair. The double condensation of basic nitrogens on the carbonyl carbons of the α-carbethoxy groups then proceeds; structure III results. The α-hydrogens then shift (as protons) to the negatively-charged oxygens to give IV.

Structure IV is proposed as that of compounds A and B, the two compounds being *cis* and *trans* isomers. A decision as to which is *cis* and which is *trans* cannot be made on the basis of the data at hand. However, the somewhat more symmetrical *cis* form, which has a twofold axis of symmetry, might be expected to form the more stable, and therefore higher-melting, crystal lattice. Compound B, melting 41° above compound A, is provisionally assigned the *cis* configuration.

It is apparent that the reaction cannot proceed according to Chart I unless the N–H hydrogen of pyrromethene I is attached to the ring containing two methyl groups. Consideration of the substituents on the two rings indicates that the nitrogen of the ring containing the two methyl groups is indeed more basic than that of the other ring, and this has been demonstrated by methylations of the corresponding pyrromethane.[4] The assumption is made that the reduced pyrrolenine structure II is relatively stable, the stability probably resulting from its adhesion to the catalyst surface. If it were not stable, the hydrogen on the ring carbon would shift rapidly to nitrogen, and the remaining steps in the reaction could not occur. The difference in the course of the reaction when Raney nickel is used instead of the palladium catalyst is explained in terms of this reaction mechanism if it is supposed that the reduced intermediate II is released rapidly by the catalyst, thus preventing attack at the carbonyl by allowing the shift of hydrogen from carbon to nitrogen. The mechanism explains why Ellingson obtained pyrromethane in addition to compounds A and B. Ellingson's reaction mixture contained acid, and the salt form of the pyrromethene was not free to condense after reduction.

Synthesis of compounds A and B by another route has not yet been accomplished. However, compounds of quite similar structures have been synthesized, and their properties resemble closely those of A and B.

The simple pyrocolls (dipyrrolopyrazinediones) are formed by dehydrating pyrrole-α-carboxylic acids intermolecularly with acetic anhydride.[5] Pyrocolls similar to compounds A and B should result from the reaction of pyrromethane-α-carboxylic acids with acetic anhydride. For the sake of simplicity the 2-pyrrylmethyl compounds will be referred to as "methane pyrocolls" (V, VIII). They are characterized by (a) covalent binding of

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[1] Studies in the Pyrrole Series XXVIII. Paper XXVII, G. G. Kleinspehn, THIS JOURNAL, **77**, 1546 (1955). Taken from the doctoral dissertation of Bryant Harrell, The Johns Hopkins University, 1951.

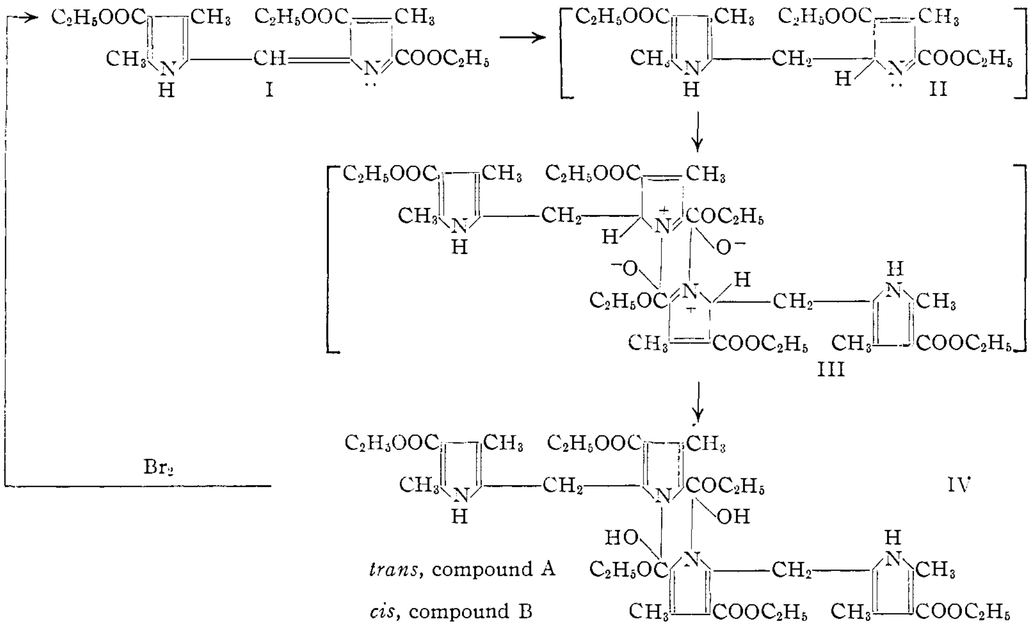
[2] A. H. Corwin and J. S. Andrews, THIS JOURNAL, **59**, 1977 (1937).

[3] R. C. Ellingson, Dissertation, The Johns Hopkins University, 1938, pp. 48, 110.

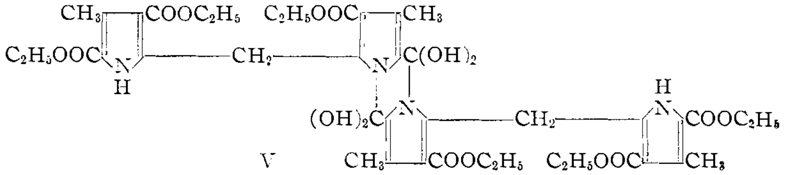
[4] A. H. Corwin and R. C. Ellingson, THIS JOURNAL, **64**, 2101 (1942).

[5] H. Fischer and H. Orth, "Die Chemie des Pyrroles," Band I, Akademische Verlagsgesellschaft m.b.H., Leipzig, 1934, p. 236.

CHART I



water to the carbonyl groups of the pyrazine ring in the manner of the hydrate of chloral and (b) physical binding of water within the crystals. A similar compound, which can be thought of as derived from a pyrromethene, is designated a "methene pyrocoll" (VII).



V

Methane pyrocoll V is prepared by refluxing 3,3′,5′-tricarbethoxy-4,4′-dimethyl-5-carboxypyrromethane with acetic anhydride. Refluxing 3,4′-dicarbethoxy-4,3′,5′-trimethyl-5-carboxypyrromethane in this way led to the formation of methene pyrocoll VII instead of the desired methane pyrocoll (VIII). VIII is more easily dehydrogenated than V because each of the two outlying pyrrole rings has lost the stabilizing influence of a carbethoxy group. Our attempts to reduce VII catalytically to give a methane pyrocoll have been unsuccessful.

A second route to methane pyrocoll VIII was employed in which a dibromomethylpyrocoll (VI, Chart II) was formed and then the outlying pyrrole rings attached by fusing it with 2,4-dimethyl-3-carbethoxypyrrole. This route gave methene pyrocoll VII as the major product, but a small amount of methane pyrocoll VIII was recovered. We were unable to obtain dibromomethylpyrocoll VI by the direct bromination of 1,3,6,8-tetramethyl-2,7-dicarbethoxypyrocoll. It was prepared by the reaction of 1,6-dimethyl-2,7-dicarbethoxy-3,8-diethoxymethylpyrocoll with hydrogen bromide.

Methene pyrocoll VII requires special consideration because of the fact that the product obtained from the pyrromethane-α-carboxylic acid held two molecules of water while that from dibromomethylpyrocoll VI held one molecule of water. The water was not removed from the dihydrate by heating 15 minutes under vacuum at 240°, though the compound gave evidence of beginning to decompose. Heating the monohydrate under vacuum 15 minutes at 205° did not remove the water. However, by using anhydrous conditions we have obtained anhydrous methene pyrocoll VII *via* the dibromomethylpyrrocoll route. Anhydrous VII, the monohydrate and the dihydrate have identical ultraviolet and infrared absorption spectra, proving that the absorbing entities are identical.

Of seven molecules of water retained by methane pyrocoll V, five are removed by heating the compound under vacuum. That the remaining two are bound across the pyrazinedione carbonyls is to be expected by analogy with compounds A and B, which retain the elements of ethanol across the pyrazinedione carbonyls. This expectation appears to be borne out by comparison of infrared absorption spectra. The spectra of a number of pyrrole derivatives substituted by carbethoxy and methyl groups have been compared in the carbonyl region (Table I). All absorb between 5.87 and 6.00 μ, except for the N-methyl- and N,N′-dimethyl-tetracarbethoxypyrromethanes which are unique in having three absorption bands, the third band falling at 5.82 μ. 1,3,6,8-Tetramethyl-2,7-dicarbethoxypyrocoll[6] exhibits a band at a still shorter wave length, 5.80 μ. The band at 5.80 μ we take to be due to the pyrazinedione carbonyls. Methane pyrocoll V, like compounds A and B, lacks this band at 5.80 μ, indicating that pyrazinedione carbonyls are not present. (The spectrum of VIII was not taken since it underwent considerable decomposition in the interval between its preparation and the taking of spectra.)

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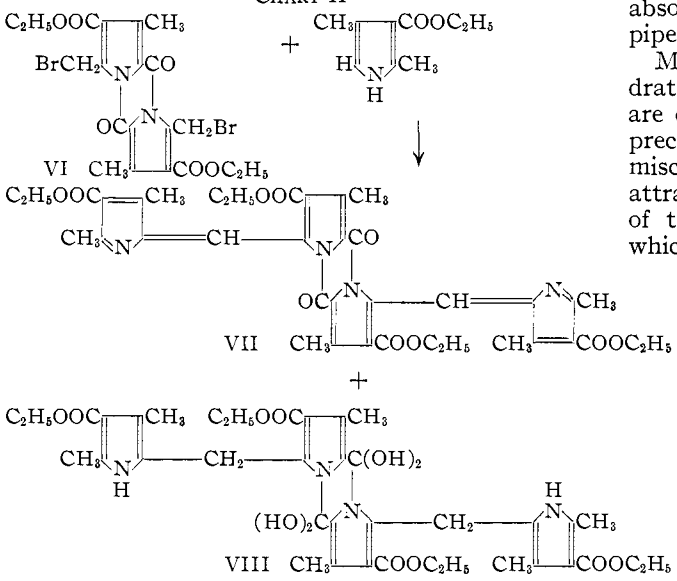
(6) G. Magnanini, *Ber.*, **21**, 2871 (1888).

The property of binding water covalently exhibited by methane pyrocoll V and the retention of ethanol by compounds A and B may be unique among the derivatives of piperazinedione. Water and alcohol are not bound by any of the simpler pyrocolls thus far prepared,[5] nor are they bound by the piperazinediones which result from condensation of esters of α-amino acids or dipeptides.[7]

CHART II



Cases are reported in which structurally similar compounds (similar to the pyrocolls in having a carbonyl group connecting pyrrole nitrogen to a double bond), derivatives of pyrrolizine (3H-pyrrolo[1,2-a]pyrrole), bind water covalently under the conditions of their preparation and purification.[8] When the double bond conjugated with the carbonyl group is saturated, the carbonyl group does not bind solvent.[9] It may be hypothesized that the weak electron-attracting powers of the pyrrole nitrogen on one side of the carbonyl and the double bond on the other side combine with the strained five-membered ring to render the carbonyl capable of binding water.

A similar explanation will not do for the pyrocolls. We are faced with the fact that the pyrocoll system does not of itself bind water covalently, yet the substitution of pyrrylmethyl groups on positions relatively far from the carbonyls in question causes such binding of water to occur. We offer the following as a tentative explanation:

A model[10] of either methane pyrocoll shows that the outlying pyrrole rings may be bent in from a number of directions so as to bring the carbonyls of the pyrazine ring into the force fields of the N–H hydrogens. We suggest that these hydrogens may act with the pyrocoll–pyrrole nitrogen and the ring double bond, to which each carbonyl is already attached, so as to effect the polarization of the carbonyl required in order for it to react with water.

In the case of methene pyrocoll VII the outlying rings are pyrrolenine rather than pyrrole, and there are no pyrrole N–H hydrogens available for hydrogen bonding. As the explanation leads us to expect, the hydrates of methene pyrocoll VII (like the anhydrous compound) have a strong absorption peak at 5.80 μ, indicating that the piperazinedione carbonyl groups are free.

Methane pyrocolls V and VIII form pentahydrates. These compounds, like pyrroles in general, are quite insoluble in water, and they are readily precipitated from their solutions by water (when miscibility permits). Thus it is not an inherent attraction of any of the structural components of the methane and methene pyrocolls for water which accounts for the formation of the hydrates. Rather it would appear to be some feature of the geometry of the molecules. We suggest that these hydrates may be similar to the clathrate compounds,[11] the water being held within a cage-like structure. A model of any of the methane pyrocolls may be easily arranged into the form of a boat or basket, keeping the pyrrole N–H hydrogens bent in toward the hydrated carbonyl groups. The space thus enclosed is sufficient to contain the five water molecules. Alternatively, it may be that several molecules participate in the formation of a tube, the space enclosed being occupied by water.

Again methene pyrocoll VII requires special attention. It would be expected that, because of the resonance of the pyrromethene systems, all

TABLE I

CARBONYL ABSORPTIONS (μ)

2-Carbethoxy-3-methylpyrrole			5.94
2,4-Dicarbethoxy-3,5-dimethylpyrrole		5.90	5.95
3,5,3'-Tricarbethoxy-4,4'-dimethylpyrromethane		5.88	5.93
3,5,4'-Tricarbethoxy-4,3',5'-trimethylpyrromethane		5.91	5.98
3,5,3',5'-Tetracarbethoxy-4,4'-dimethylpyrromethane		5.88	5.99
1,3,5,3',5'-Pentamethyl-4,4'-dicarbethoxypyrromethane		5.89	5.98
1,4,4'-Trimethyl-3,5,3',5'-tetracarbethoxypyrromethane	5.82	5.89	5.93
1,3,5,1',4'-Pentamethyl-4,3',5'-tricarbethoxypyrromethane		5.88	5.93
1,4,1',4'-Tetramethyl-3,5,3',5'-tetracarbethoxypyrromethane	5.82	5.89	5.94
3,5,3',5'-Tetramethyl-4,4'-dicarbethoxypyrromethene			5.87
3,5,4'-Tricarbethoxy-4,3',5'-trimethylpyrromethene			5.89
1,3,6,8-Tetramethyl-2,7-dicarbethoxypyrocoll		5.80	5.87
Compound A		5.92	6.00
Compound B		5.90	6.00
Methane pyrocoll V			5.87
Methene pyrocoll VII		5.80	5.89

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(7) E. Abderhalden, "Biochemisches Handlexikon," Band IV, Julius Springer, Berlin, 1911, p. 282 ff.

(8) (a) W. Küster, E. Brudi and G. Koppenhöfer, *Ber.*, **58**, 1019 (1925); (b) F. Micheel and W. Kimpel, *ibid.*, **69**, 1992 (1936).

(9) (a) H. Fischer and H. Neber, *Ann.*, **496**, 18 (1932); (b) W. Herz, K. Dittmer and S. J. Cristol, THIS JOURNAL, **70**, 506 (1948); (c) N. J. Leonard and E. H. Burk, Jr., *ibid.*, **72**, 2545 (1950).

(10) B. Harrell and A. H. Corwin, *J. Chem. Ed.*, **32**, 186 (1955).

(11) H. M. Powell, *J. Chem. Soc.*, 61 (1948).

four of the pyrrole rings would lie in the same plane. The model of this compound reveals that interference from the carbonyl groups or from carbethoxy groups prevents coplanarity, whichever of the four conceivable coplanar positions is attempted. The molecule assumes either the boat configuration, which we have suggested as explaining the methane pyrocoll hydrates, or a "chair" configuration. The fact that this pyrocoll does hydrate and the firmness with which the water is held lead to the expectation that the configuration is that of the boat. Comparison of the ultraviolet spectrum of methene pyrocoll VII with that of pyrromethene I confirms that the resonance of the pyrromethene system has been interfered with; the pyrromethene peak at 427 mμ has been suppressed until it is only a hump at approximately the same wave length (Fig. 1).

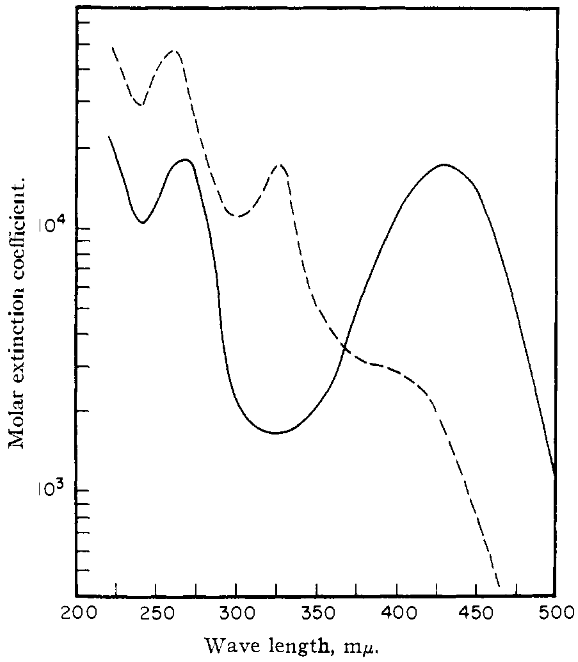

Figure 1.—Absorption curves: ———, 3,5,4'-tricarbethoxy-4,3',5'-trimethylpyrromethene (I); – – – – –, methene pyrocoll VII.

The arguments which have been adduced regarding the binding of water by V and VIII can be applied as well to compounds A and B. However, if A and B assume the boat configuration, three isomers are to be expected: one *trans*, one *cis* with the hydroxyls inside the boat and one *cis* with the ethoxyls inside the boat.[12] It must be assumed that only one of the two possible *cis* forms actually appears. Were A and B both *cis* it might be possible to convert A to B or *vice versa* through the use of conditions calculated to turn the boat inside out. The employment of strong heat, strong acid and strong alkali have failed to cause such a conversion up to the point at which gross decomposition of the compounds begins. The sharp melting points of A and B argue against either one being a mixture of isomers.

Support for the boat hypothesis for physically-bound water is found in the fact that compound B takes on two molecules of water of crystallization when recrystallized from dioxane–water below the boiling point and four molecules of water when recrystallized at the boil. This is explained as being due to a slight loosening at the boil of the forces holding the boat in shape, allowing the boat to expand somewhat and thus permitting the entrance of more water. The fact that compound A still retains only two molecules of water when recrystallized from boiling dioxane–water is in harmony with the suggestion above that A is the *trans* isomer. If compound B is *cis* with the hydroxyls inside the boat, compound A, having one ethoxyl group inside the boat, should have a smaller volume available for water.

Experimental[13]

***cis*- and *trans*-1,6-Dimethyl-2,7-dicarbethoxy-3,8-bis-(3,5-dimethyl-4-carbethoxy-2-pyrrylmethyl)-5,10-diethoxy-5,10-dihydroxydipyrrolo[a,d]pyrazine (Compounds B and A; IV).**—Catalyst: Five grams of Norit A and 1.5 ml. of 10% palladium chloride (in 10% HCl) were shaken with 100 ml. of 95% ethanol under 20 lb. of hydrogen for 1 hr. The palladium-on-charcoal was washed several times with ethanol. One gram of 3,5,4'-tricarbethoxy-4,3',5'-trimethylpyrromethene and several tenths of a gram of palladium catalyst were shaken with 25 ml. of 95% ethanol under 20 lb. of hydrogen for 3 hr. and the mixture was filtered. Hot water was added to the filtrate until it became cloudy, and it was then allowed to cool. The solid was filtered off, dissolved in 25 ml. of ethanol, filtered to remove traces of catalyst and precipitated as above. Glistening platelets of compound A (0.45 g.) were obtained, m.p. 145° (loses water). The product was recrystallized several times from ethanol–water and dried over NaOH pellets, m.p. 145°.

Anal. Calcd. for $C_{42}H_{56}N_4O_{12}\cdot 2H_2O$: C, 59.70; H, 7.15; C_2H_5O, 31.99. Found: C, 59.93, 60.60; H, 6.93, 6.96. Second sample, found: C, 59.95; H, 6.91; C_2H_5O, 32.19, 32.20.

A fresh sample was recrystallized several times from benzene and dried under vacuum at 160° for 15 min., m.p. 195–196.5°. *Anal.* Calcd. for $C_{42}H_{56}N_4O_{12}$: C_2H_5O, 33.42. Found: C_2H_5O, 33.42.

The mixture of catalyst and product from the original filtration was boiled with 10 ml. of acetic acid (or dioxane) and the solution was filtered. The filtrate was allowed to cool, and the solid was filtered off. The solid was dissolved in 15 ml. of hot dioxane, the solution was filtered to remove traces of catalyst, and hot water was added until the solution became cloudy. It was allowed to cool. Fine white needles of compound B were obtained, 0.40 g., m.p. 234–236°. A sample was dissolved in boiling dioxane. The heat was removed and water added until precipitation began, m.p. 236–237.5°.

Anal. Calcd. for $C_{42}H_{56}N_4O_{12}\cdot 2H_2O$: C_2H_5O, 31.99. Found: C_2H_5O, 31.72.

A fresh sample was dissolved in hot dioxane, and the solution was cooled to room temperature. Water was added until the solution became cloudy, and the solution was cooled in the refrigerator, m.p. 234.5–236°. *Anal.* Calcd. for $C_{42}H_{56}N_4O_{12}\cdot 2H_2O$: C_2H_5O, 31.99. Found: C_2H_5O, 31.77.

A fresh sample was dissolved in boiling dioxane, and water was dripped in, maintaining the boil, until precipitation began, m.p. 236–237°. *Anal.* Calcd. for $C_{42}H_{56}N_4O_{12}\cdot 4H_2O$: C_2H_5O, 30.68. Found: C_2H_5O, 30.61, 30.61.

A fresh sample was recrystallized several times from ethanol and dried under vacuum at 77° for 2 hr., m.p. 237–238°. *Anal.* Calcd. for $C_{42}H_{56}N_4O_{12}\cdot 2C_2H_5OH$: C, 61.31; H, 7.60. Found: C, 61.33; H, 7.38.

The sample from ethanol was dried under vacuum at 160° for 15 min., m.p. 237–238.5°. *Anal.* Calcd. for $C_{42}H_{56}N_4O_{12}$: C_2H_5O, 33.42. Found: C_2H_5O, 33.40.

A fresh sample was recrystallized several times from ben-

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[12] This was pointed out to us by Dr. Evans B. Reid.

[13] Melting points were taken in the capillary tube and are uncorrected. In every case the compounds melt with decomposition.

zene and dried under vacuum at 160° for 15 min., m.p. 237–238°. *Anal.* Calcd. for $C_{42}H_{56}N_4O_{12}$: C_2H_5O, 33.42. Found: C_2H_5O, 33.31.

The reduction was run as described above, using 5 g. of pyrromethene and varying the quantity of 95% ethanol:

125 ml. → 2.2 g. A + 2.1 g. B
100 ml. → 1.2 g. A + 3.5 g. B
75 ml. → 0.8 g. A + 4.2 g. B.

Oxidation of Compounds A and B to Pyrromethene I.—One hundred mg. of compound A was dissolved in 50 ml. of hot carbon tetrachloride, and the solution was cooled to room temperature. A solution of 40 mg. of bromine in 1 ml. of carbon tetrachloride was mixed with 100 ml. of isoöctane, and the solution containing compound A was stirred in. After about 20 seconds a precipitate appeared. After 2–3 min. the product was removed and dried at 70°. Seventy-one mg. of bright orange product was obtained, m.p. 138–141° (pyrromethene hydrobromide). The free base was prepared by grinding the solid in a mortar with a few drops of water until it was thoroughly wet. One or two ml. of concentrated aqueous ammonia solution was added, and the mixture was ground well. The solid was removed, washed well with water and dried at 70°. Fifty-five mg. of bright red-orange solid was obtained, m.p. 128–129°. There was no depression in melting point on mixing the product with 3,5,4'-tricarbethoxy-4,3',5'-trimethylpyrromethene.

The pyrromethene was prepared from compound B in exactly the same manner; 68 mg. of pyrromethene hydrobromide was obtained, m.p. 140–143°, which yielded 51 mg. of pyrromethene free base, m.p. 127–128°.

3,5,4'-Tricarbethoxy-4,3',5'-trimethylpyrromethane. (a) **By Reduction.**—One gram of 3,5,4'-tricarbethoxy-4,3',5'-trimethylpyrromethene and several tenths of a gram of Raney nickel catalyst were shaken with 40 ml. of 95% ethanol under 20 lb. of hydrogen for 1 hr. The mixture was brought to a boil and the catalyst filtered off. The pyrromethane was precipitated by adding hot water to the filtrate until it became cloudy and allowing the solution to cool. The precipitate was filtered off and washed with 50% ethanol to give 0.7 g. (70%) of product, m.p. 157–158°. There was no depression of the melting point on mixing with a sample of 3,5,4'-tricarbethoxy-4,3',5'-trimethylpyrromethane.

(b) **By Condensation.**—Two grams of 2,4-dimethyl-3-carbethoxypyrrole and 2.85 g. of 2-chloromethyl-3,5-dicarbethoxy-4-methylpyrrole[14] were mixed with 200 ml. of isoöctane. The mixture was refluxed for 7 hr. under a 40-cm. air condenser. Hydrogen chloride was evolved. The mixture was cooled to room temperature, and the precipitate was removed, the last of the solid being washed from the flask with isoöctane and dried at 80°. Four grams (95%) of light orange fibers was obtained, m.p. 155.5–156.5°. When the product was mixed with the starting chloromethylpyrrole, the melting point was depressed to 130°.

1,6-Dimethyl-2,7-dicarbethoxy-3,8-bis-(3,5-dicarbethoxy-4-methyl-2-pyrrylmethyl)-5,5,10,10-tetrahydroxydipyrrolo-[a,d]pyrazine (V).—Nine hundred seventeen mg. of 3,3',5'-tricarbethoxy-4,4'-dimethyl-5-carboxypyrromethane[15] was mixed with 0.1–0.3 g. of anhydrous sodium acetate and 10 ml. of acetic anhydride. The mixture was refluxed for 1 hr. and then cooled in the refrigerator. The solid was removed by filtration, washed well with ether, triturated with ether, refiltered and dried. Five hundred fifty-five mg. (54%) of pale yellow fibers was obtained, m.p. 195–196°. A sample was recrystallized twice from dioxane–water and dried at 90° to give glistening, pure white fibers, m.p. 203–204°.

Anal. Calcd. for $C_{42}H_{52}N_4O_{16}\cdot 5H_2O$: C_2H_5O, 28.19. Found: C_2H_5O, 28.15.

The same sample was dried under vacuum at 180° for 15 min., m.p. 203–204°. *Anal.* Calcd. for $C_{42}H_{52}N_4O_{16}\cdot 2H_2O$: C_2H_5O, 29.87. Found: C_2H_5O, 29.91.

The same sample was dried under vacuum at 195° for 30 min. The fibers were faintly yellow and slightly hygroscopic, m.p. 203–204°. *Anal.* Calcd. for $C_{42}H_{52}N_4O_{16}$: C_2H_5O, 31.12. Found: C_2H_5O, 30.76.

2-Ethoxymethyl-3-carbethoxy-4-methyl-5-carboxypyrrole.—Eight-tenths gram of sodium hydroxide was dissolved in 50 ml. of 95% ethanol with warming. Five grams of 2-ethoxymethyl-3,5-dicarbethoxy-4-methylpyrrole[16] was added to the solution, and the mixture was refluxed for 3 hr. The hot solution was stirred into 200 ml. of water, and 0.25 g. of unreacted starting material was removed by filtration. The filtrate was made acid with 2 ml. of concentrated hydrochloric acid. Stirring and scratching were necessary to start crystallization. The precipitate was removed and dried at 75°. Three and two-tenths grams (71%) of yellow solid was obtained, m.p. 138–139°. The purification of the compound for analysis was unusually difficult, and coloration of the sample persisted until the final crystallization from isoöctane. The sample was recrystallized twice from ethanol–water, twice from benzene–isoöctane, five times from dioxane–water and once from a large quantity of isoöctane. Drying was at 65° for 2 hr.; white powder, m.p. 147.5–149°.

Anal. Calcd. for $C_{12}H_{17}NO_5$: C, 56.47; H, 6.71; C_2H_5O, 35.30. Found: C, 56.46; H, 6.48; C_2H_5O, 34.80.

1,6-Dimethyl-2,7-dicarbethoxy-3,8-diethoxymethylpyrocoll.—Two grams of 2-ethoxymethyl-3-carbethoxy-4-methyl-5-carboxypyrrole was mixed with 1 g. of anhydrous sodium acetate and 40 ml. of acetic anhydride. The mixture was refluxed for 1 hr. The solid was removed and washed well with ether. The product was heated with 50 ml. of water, filtered off, washed well with water and dried. The gray solid weighed 0.4 g. (22%), m.p. 155.5–157.5°. This material, like the acid from which it was made, was very difficult to purify, and a completely pure sample was not obtained for analysis. It was recrystallized from dioxane–water, 95% ethanol and benzene–isoöctane. A benzene solution was then passed through a column of alumina, which removed most of the color. Recrystallization from ethanol gave white fibers which were dried under vacuum at 50° for 1 hr., m.p. 158–159.5°.

Anal. Calcd. for $C_{24}H_{30}N_2O_8$: C, 60.74; H, 6.37; C_2H_5O, 37.98. Found: C, 61.04; H, 6.30; C_2H_5O, 37.65.

1,6-Dimethyl-2,7-dicarbethoxy-3,8-dibromomethylpyrocoll (VI).—Two and fifty-five hundredths grams of 1,6-dimethyl-2,7-dicarbethoxy-3,8-diethoxymethylpyrocoll was mixed with 76 ml. of acetic acid and 4 ml. of 48% aqueous hydrogen bromide, and the mixture was refluxed for 30 min. Long needles appeared in the solution as it cooled. The precipitate was removed and washed with a little acetic acid; 2.66 g. (85%) of silvery needles was obtained, m.p. 205.5–207°. A sample was recrystallized from dioxane–water and dried at 70°, m.p. 205.5–207°.

Anal. Calcd. for $C_{20}H_{20}N_2O_6Br_2$: C_2H_5O, 16.56; Br, 29.37. Found: C_2H_5O, 16.57; Br, 29.01, 29.86, 29.39.

3,4'-Dicarbethoxy-4,3',5'-trimethyl-5-carboxypyrromethane.—The conditions of this experiment are those which are known to hydrolyze the α-carbethoxy groups of 1,4,1',4'-tetramethyl-3,5,3'-tricarbethoxypyrromethane,[15] 2-ethoxymethyl-3,5-dicarbethoxy-4-methylpyrrole (above) and similar α,β-carbethoxy-substituted pyrrole derivatives. Two grams of 3,5,4'-tricarbethoxy-4,3',5'-trimethylpyrromethane was mixed with 80 ml. of ethanol and 15 ml. of water. The mixture was brought to a boil, 5 ml. of 1.1 *N* sodium hydroxide added and refluxed for 5 hr. The solution was then transferred to a large glass dish and evaporated to dryness on the steam-bath. The residue was taken up in 150 ml. of water, and the mixture was brought to a boil. Filtering removed 0.13 g. of unreacted pyrromethane triester. The filtrate was made acid with hydrochloric acid and cooled on an ice-bath. The solid was filtered off, triturated with water, refiltered and dried; 1.57 g. of crude yellow product was obtained. This was boiled for several minutes with 225 ml. of acetone. The mixture was centrifuged at 2,000 r.p.m. for 15 min., decanted from a yellow solid and stirred into 450 ml. of water. The solution was cooled in the refrigerator and filtered. The solid was washed freely with water and dried at 75° to give 0.94 g. (50%) of the pyrromethane acid, m.p. 212–215° with bubbling. A sample was recrystallized three times from ethanol–water to give white, fibrous crystals, m.p. 225–225.5°.

Anal. Calcd. for $C_{19}H_{24}N_2O_6$: C_2H_5O, 23.94. Found: C_2H_5O, 23.98.

1,6-Dimethyl-2,7-dicarbethoxy-3,8-bis-(3,5-dimethyl-4-carbethoxy-2-pyrrolenylidenemethyl)-pyrocoll (VII). (a) **Dihydrate.**—Nine hundred sixty-five mg. of 3,4'-dicarbeth-

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[15] A. H. Corwin and S. R. Buc, *ibid.*, **66**, 1151–1156 (1944).

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oxy-4,3′,5′-trimethyl-5-carboxypyrromethane, 10 ml. of acetic anhydride and 0.1–0.3 g. of anhydrous sodium acetate were refluxed together for 1 hr. and the mixture then cooled on the ice-bath. The precipitate was filtered off, washed well with ether, triturated with ether, refiltered and dried at 75°; 770 mg. (80%) of orange, fibrous crystals was obtained, m.p. 262–265°. A sample was recrystallized five times from dioxane–water, m.p. 266.5–268°.

Anal. Calcd. for $C_{38}H_{40}N_4O_{10}\cdot 2H_2O$: C_2H_5O, 24.07. Found: C_2H_5O, 24.13.

(b) **Monohydrate.**—Two hundred fifty mg. of 1,6-dimethyl-2,7-dicarbethoxy-3,8-dibromomethylpyrocoll was mixed with 1.00 g. of 2,4-dimethyl-3-carbethoxypyrrole[17] in a 13 by 100 mm. test-tube. The mixture was heated on the oil-bath at 106° for 3–3.5 min. while agitating with the spatula. The mixture liquefied and then resolidified rapidly. When cool, the red-orange, gummy material was triturated with ether and filtered. It was again triturated with ether, filtered and dried at 70°; 525 mg. of bright orange solid was obtained. The solid was warmed with 25 ml. of chloroform until it dissolved, 75 ml. of isoöctane was added to the hot solution and the mixture was cooled. The orange precipitate was filtered off and dried at 70° (methane pyrocoll VIII was obtained from this filtrate); 266 mg. (79%) of the methene pyrocoll was obtained, m.p. 245–248°. A sample was recrystallized from dioxane–water four times, m.p. 266–267°.

Anal. Calcd. for $C_{38}H_{40}N_4O_{10}\cdot H_2O$: C_2H_5O, 24.66. Found: C_2H_5O, 24.76.

(c) **Anhydrous.**—The reaction was run as in (b) above, using the same quantities, except that the reactants were dried under vacuum at 50° for 2 hr., and the reaction was run in an atmosphere of dry hydrogen. After heating at 106° and allowing to cool, 3 ml. of ethanol was added. The product was triturated with ethanol, washed into a flask and refluxed with 80 ml. of ethanol for 30 min. The undissolved material was removed; 237 mg. (72%) was obtained, m.p. 256–258°. A sample was recrystallized four times from dioxane–ethanol and then dried 2.5 hours at 70°, m.p. 266.5–268°.

Anal. Calcd. for $C_{38}H_{40}N_4O_{10}$: C_2H_5O, 25.29. Found: C_2H_5O, 25.68.

1,6-Dimethyl-2,7-dicarbethoxy-3,8-bis-(3,5-dimethyl-4-carbethoxy-2-pyrrylmethyl)-5,5,10,10-tetrahydroxydipyrrolo[a,d]pyrazine (VII).—The filtrate from the preparation of methene pyrocoll VII·H_2O (b, above) was evaporated to a volume of 25 ml. in the air stream. A yellow scum had collected on the sides of the flask, and this was discarded. Needles collected on the bottom of the flask. The needles were removed and dried in the air overnight; 84 mg. (21%) was obtained, m.p. 124–125°, becoming orange. The crystals decomposed slowly over a period of months. A sample was recrystallized from chloroform–isoöctane, m.p. 126.5–128°.

Anal. Calcd. for $C_{38}H_{48}N_4O_{12}\cdot 5H_2O$: C_2H_5O: 21.38. Found: C_2H_5O, 21.33.

Ultraviolet absorption curves were taken of dioxane solutions in the Beckman DU spectrophotometer. Infrared absorption curves were taken of mineral oil mulls in the Perkin–Elmer 21 double-beam recording spectrophotometer without a compensating cell.

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Baltimore, Md.

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[Contribution from the Department of Chemistry of the University of Wisconsin]

Piperidine Derivatives. XXVIII. 1-Methyl-3-alkyl-4-phenyl-4-acyloxypiperidines

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1-Methyl-3-carbethoxy-4-piperidone has been C-benzylated and C-allylated in the 3-position with benzyl- and allyldimethylanilinium halides. The resulting piperidones were converted to two series of 1-methyl-3-alkyl-4-phenyl-4-acyloxypiperidines (IX and X). These compounds with the 3-benzyl substituent are completely inactive as analgesics; however, the members of the corresponding 3-propyl series are all quite active. The 4-propionoxy derivative (Xb) of this latter series is significantly more active than the homologous 4-acetoxy (Xa) or 4-butyroxy (Xc) compounds.

Several 1-alkyl-4-phenyl-4-acyloxypiperidines have been prepared and found to possess significant analgesic action.[2] Those compounds with the 4-propionoxy substituent appear to be the most potent analgesics. Ziering and Lee[3] found that further modification of this structure by the introduction of a 3-methyl substituent into the piperidine nucleus greatly enhanced the pharmacological activity, *e.g.*, one of the stereoisomeric forms of 1,3-dimethyl-4-phenyl-4-propionoxypiperidine showed analgesic action comparable to that of dihydrodesoxymorphine-D, which is 5–10 times as active as morphine.

The 1,3-dimethyl-4-piperidone required for the preparation of this analgesic was obtained by the Dieckmann cyclization of methyl-(β-carbomethoxyethyl)-(β-carbomethoxypropyl)-amine, which was prepared by the addition of methylamine to methyl methacrylate and the addition of the resulting secondary amino ester to methyl acrylate. While the 1,3-dimethyl-4-piperidone could be prepared satisfactorily by this procedure, it would appear to have some serious limitations as a general method for 1-methyl-3-alkyl-4-piperidones.

The C-alkylation of the enolate anion of a 3-carbalkoxy-4-piperidone and the decarbalkoxylation of the resulting keto ester seemed to offer another, and perhaps a more general, approach to the 3-alkyl-4-piperidones. This procedure has been utilized for the introduction of a 3-ethyl substituent into the 1-benzoyl-3-carbethoxy-4-piperidone[4a]; however, attempts to alkylate the 1-methyl-3-carbethoxy-4-piperidone anion (I) with an alkyl halide resulted in N- rather than C-alkylation.[4b]

In the work now reported it was found that the anion I can be C-alkylated to the 3,3-disubstituted

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(1) Wisconsin Alumni Research Foundation Research Assistant, 1953–1955.

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