Cycloalkapyrrolones *via* Decarboxylative Ring Closure of Pyrrole-3-alkanoic Acids and Derivatives

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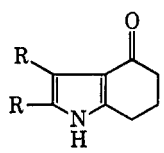
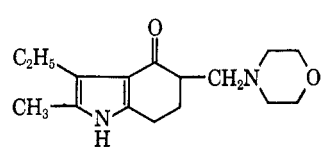
Acylation of pyrroles 1–2 with ω-(methoxycarbonyl)acyl chlorides followed by catalytic reduction produces 3-pyrrolealkanoic acid esters (**4a–d**) with chains bearing 3 and 4 methylene groups. Alkylation of malonic ester with quaternary salts of Mannich bases **10a–c** followed by hydrolysis and decarboxylation yields derivatives **4e–i** and **14a–b** with chains bearing 2 methylene groups. Treatment of these intermediates with polyphosphoric acid affords cycloalkapyrrolones of classes III and IV. One of these compounds, a 7-ketotetrahydroindole (**5**), was aromatized to produce the corresponding indol-7-ol **9**. The infrared and ultraviolet spectra and their relationship to structure are discussed.

Our interest in cycloalkapyrrolones stems from the finding that Mannich bases derived from 6,7-dihydroindol-4(5H)-ones (I) exhibit central nervous system depressant effects.[1] The morpholino Mannich base II (molindone) has been found to be a potent antipsychotic agent in man.[2]

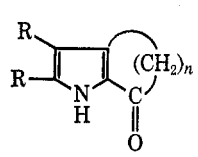


I

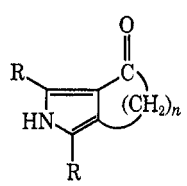


II

In order to study related systems we required appropriate cycloalkapyrrolones of classes III and IV.



III



IV

Although compounds of type I have been described,[3] little work has been done on systems included in III and IV.[4] In this paper we shall describe general synthetic routes to these latter systems.

It has been reported[5] that compounds **1a–b** undergo Friedel–Crafts acetylation. Accordingly, we found that acylations of **1a** and **2** with the acid chloride esters of succinic and glutaric acids give the keto diesters **3a–d** easily and in good yield (Scheme I).

The conversion of the esters **3a–d** to the subsequent intermediates **4a–d** requires selective reducing conditions. Ketopyrroles, which bear some chemical resemblance to vinylogous amides, are not reduced by sodium borohydrides. More drastic hydride reduction, as with diborane, can result in ester reduction as well as ketone reduction.[6,7]

Wolff–Kishner reduction, when applied to compounds of type **3** ($n = 2$), has been found to result in pyridazine formation.[8]

Catalytic hydrogenation under conditions of high temperature and pressure has been used to reduce ketopyrroles, some bearing ethoxycarbonyl groups on the pyrrole nucleus.[9] It seemed probable that the presence of electron-attracting ethoxycarbonyl groups would enhance the ketonic character of compounds **3a–d**, making such drastic conditions unnecessary.

Indeed, it was found that ketoalkanoic esters **3a–d** underwent very rapid reduction and hydrogenolysis to yield esters **4a–d** when subjected to the action of hydrogen at 50 psi at ambient temperatures in the presence of palladium on charcoal. In all cases the theoretical uptake of hydrogen was complete within 2 hr, whereupon the reaction ceased. Reduced products were obtained in high yield.

Regarding the cyclization of systems related to **4a–d**, it was found that polyphosphoric acid (PPA) was a superior agent for the conversion of indole-3-alkanoic acids into cycloalka[*b*]indolones.[10] Although indolealkanoic acids are stable materials, pyrrolealkanoic acids which lack electron-withdrawing substituents on the ring are relatively unstable compounds.[11] The preparation and isolation of these compounds was avoided by generating them from **4a–d** *in situ* in PPA at 130–140°. Ester cleavage, decarboxylation, and ring closure occurred in one step to yield the six- and seven-membered cycloalkapyrrolones **5–8**.

Previous workers[12] found that treatment of compounds of type I with Pd–C in high-boiling hydrocarbon

(1) K. Schoen, I. J. Pachter, and A. A. Rubin, Abstracts, 153rd National Meeting of the American Chemical Society, Miami, Fla., April 1967, No. M46.

(2) A. A. Sugerman and J. Herrmann, *Clin. Pharmacol. Ther.*, **8**, 261 (1967); G. M. Simpson and L. Krakov, *Curr. Ther. Res. Clin. Exp.*, **10**, 41 (1968).

(3) H. Stetter and R. Lauterbach, *Justus Liebigs Ann. Chem.*, **655**, 20 (1962); K. E. Schulte, J. Reisch, and H. Lang, *Chem. Ber.*, **96**, 1470 (1963); S. Hauptmann and M. Martin, *Z. Chem.*, **8**, 333 (1968); J. M. Bobbitt and C. P. Dutta, *Chem. Commun.*, 1429 (1968).

(4) (a) M. E. Flaugh and H. Rappaport, *J. Amer. Chem. Soc.*, **90**, 6877 (1968), have reported preparation of a 4,5-dihydrocyclopenta[*b*]pyrrol-6(1H)-one. (b) A. J. Castro, *et al.*, Abstracts, 158th Meeting of the American Chemical Society, New York, N. Y., Sept. 1969, No. ORGN 85, reported the isolation of 4,5-dihydroindol-7(6H)-one in very low yield from the reaction of pyrrolyl magnesium bromide with 4-chlorobutyronitrile. (c) The isolation of both 6,7-dihydroindol-4 (5H)-one and 4,5-dihydroindole-7(6H)-one from the cyclization of the mixed carbonic anhydride of 4-(2-pyrrolyl)butyric acid has been recently reported. The conversion of these compounds to the corresponding hydroxy indoles is also described: M. Julia, French Patent 1540484 (1968); *Chem. Abstr.*, **71**, 81163w (1969).

(5) H. Fischer and E. Fink, *Hoppe-Seyler's Z. Physiol. Chem.*, **283**, 152 (1948); H. Fischer and W. Kutscher, *Justus Liebigs Ann. Chem.*, **481**, 201 (1930).

(6) R. L. Hinman and S. Thodoropoulous, *J. Org. Chem.*, **28**, 3052 (1963), and references therein.

(7) K. M. Biswas and A. H. Jackson, *Tetrahedron*, **24**, 1145 (1967).

(8) H. Fischer, H. Bayer, and E. Zaucker, *Justus Liebigs Ann. Chem.*, **486**, 55 (1931); H. Fischer and W. Kutscher, *ibid.*, **481**, 193 (1930).

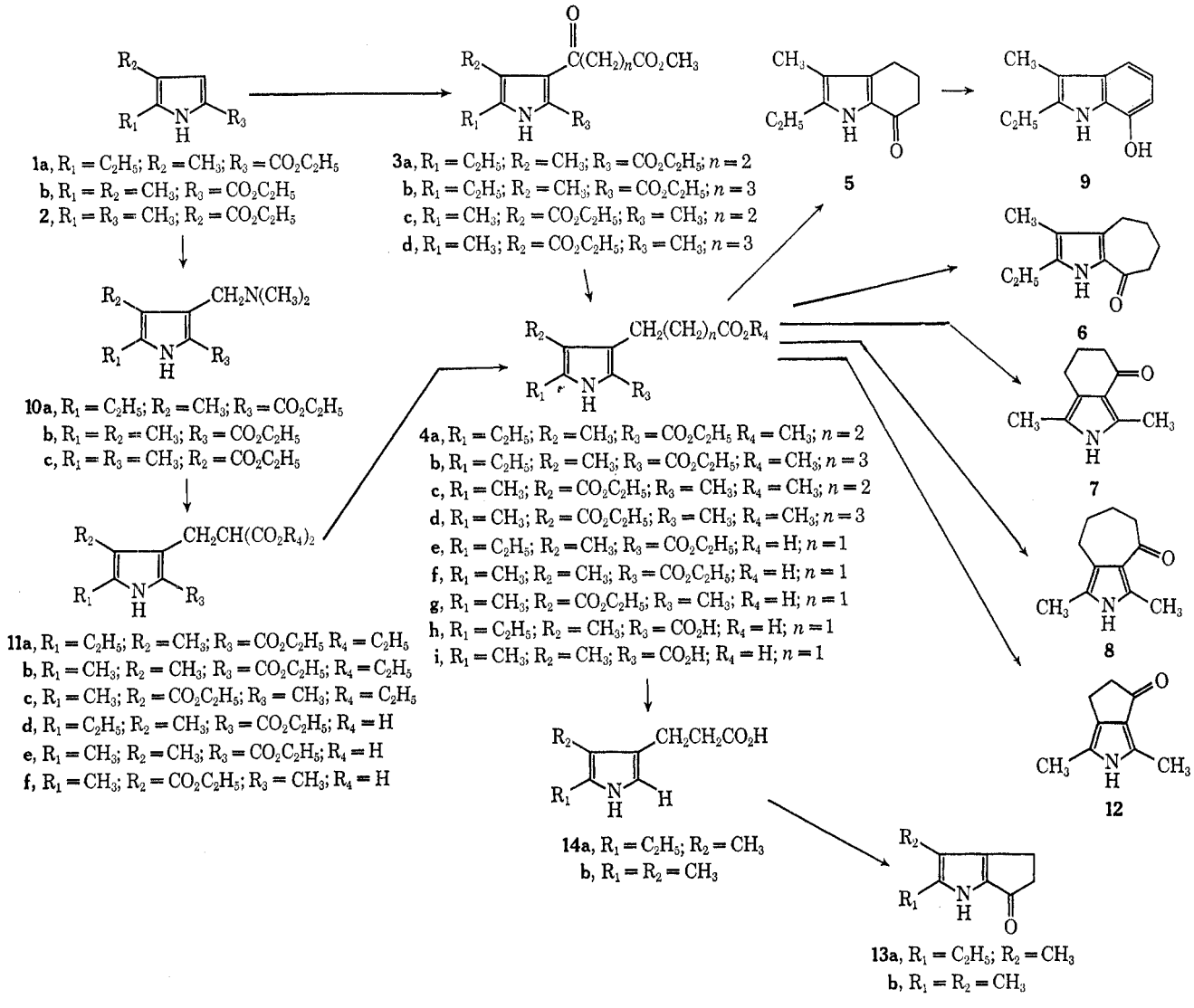
(9) F. K. Signaigo and H. Adkins, *J. Amer. Chem. Soc.*, **58**, 709 (1936); R. A. Nicolaus, G. Narni, M. Piatelli, and A. Vitale, *Rend. Accad. Sci. Fis. Mat., Naples*, **26** [**4**], 135 (1959); *Chem. Abstr.*, **55**, 14426*f* (1961).

(10) K. Ishizumi, T. Shioiri, and S. Yamada, *Chem. Pharm. Bull.*, **15**, 863 (1967).

(11) These compounds darken rapidly on exposure to air and/or light: *cf.* H. Fischer and H. Orth, "Die Chemie des Pyrrols," Akademische Verlag, Leipzig, 1934, pp 271–272.

(12) W. A. Remers and M. J. Weiss, *J. Amer. Chem. Soc.*, **87**, 5262 (1965); H. Pleininger and K. Klinga, *Chem. Ber.*, **101**, 2605 (1968).

SCHEME I



solvents afforded 4-hydroxyindoles. Similar treatment of **5** has been found to result in formation of the indol-7-ol **9**, suggesting a useful synthetic route to these compounds.[4c] Attempts to aromatize **7** were unsuccessful.

Next we undertook the synthesis of the cyclopentapyrrolones. In reactions related to those which gave **3a–d**, we found that **1a** with ethylmalonyl chloride resulted only in recovery of starting material. Consequently another method of elaborating the propionic acid side chain was sought.

The observation has been made[13a] that the ethoxycarbonyl group in compounds of the type **1a** and **1b** exhibits a profound deactivating effect on the free β position toward electrophilic attack. While a later report[13b] indicated that 2-methyl-5-carbethoxypyrrole-3-propionic acid underwent the Mannich reaction with piperidine (but not with diethylamine or dimethylamine), this reactivity was attributed to stabilization of the product by inner salt formation, since the ethyl ester failed to react. We have found that both **1a** and **1b** readily undergo the Mannich reaction to give **10a** and **10b** in good yield. Compound **2** has been reported to undergo the Mannich reaction with diethylamine and piperidine,[14] although the products were described only as their perchlorate salts. Attempts to free the bases from these salts were reported to be unsuccessful. In our hands no difficulty was experienced in preparing **10c** from **2**.

Quaternization of **10a–c** with methyl sulfate, followed by treatment with sodiomalonic ester gave the corresponding substituted malonic esters **11a–c**.[15] These esters could be selectively hydrolyzed to the free malonic acids **11d–f** by refluxing briefly with methanolic KOH. Decarboxylation to give **4e–g** was effected by heating above the melting point until cessation of gas evolution. Acid ester **4g** was converted directly to **12** by heating with PPA.

Hydrolysis of **4e** and **4f** to the dicarboxylic acids **4h** and **4i** was effected by heating with aqueous alkali. The diacids, which were isolated but not characterized, were decarboxylated by heating briefly in water on the steam bath to give the pyrrolepropionic acids **14a** and **14b**. This sequence of reactions for preparing these important pyrrole derivatives may be considered as an

(13) (a) S. F. MacDonald, *J. Chem. Soc.*, 4176 (1952); (b) A. Triebs and W. Ott, *Justus Liebigs Ann. Chem.*, **615**, 137 (1958).

(14) H. Fischer and C. Nenitzescu, *ibid.*, **443**, 113 (1925).

(15) W. Herz and R. L. Settine, *J. Org. Chem.*, **24**, 201 (1959).

TABLE I

CARBONYL STRETCHING FREQUENCIES OF CYCLOALKAPYRROLONES[a]

	Ring size	Compd	$\nu_{C=O}$, cm^{-1}
Cycloalka[*b*] series	5	**13a**	1657
	5	**13b**	1658
	6	**5**	1643, 1630
	7	**6**	1612
		2-Acetyl-3,4,5-trimethylpyrrole	1624[b]
		2-Acetyl-3,4-dimethyl-5-*n*-propylpyrrole	1630
Cycloalka[*c*] series	5	**12**	1690[c]
	6	**7**	1663
	7	**8**	1650
		3-Acetyl-2,4,5-trimethylpyrrole	1657[b]

[a] 5×10^{-3} *M* in CCl_4. [b] Reference 17. [c] 1.8×10^{-3} *M*.

TABLE II

ULTRAVIOLET SPECTRA OF CYCLOALKAPYRROLONES[a]

	Ring size	Compd	λ_{max}, mμ	$10^3\epsilon$	θ
Cycloalka[*b*] series	5	**13b**	292	20.2	0
			257.5	7.68	
	6	**5**	305.5	19.6	10
			268[b]	5.82	
	7	**6**	314	16.7	24
			270[b]	5.37	
		2-Acetyl-3,5-dimethyl-4-ethylpyrrole	308	19.6	10
			266[b]	4.70	
Cycloalka[*c*] series	5	**12**	305	3.81	0
			250	13.4	
	6	**7**	306	3.98	22
			254	11.5	
	7	**8**	302	3.73	35
			253.5	8.85	
		3-Acetyl-2,5-dimethyl-4-*n*-propylpyrrole	296	4.56	27
			253.5	10.7	

[a] Solvent ethanol. [b] Shoulder.

alternate to several described in the literature[13,16] which are very laborious and/or require difficultly accessible starting materials. The 2,3-dialkyl-5-ethoxycarbonylpyrroles required for our scheme are easily available.[5,9] PPA proved useful for the cyclization of **14a–b** and the five-membered cycloalkapyrrolones **13a–b** were synthesized.

It has been shown that[17] the carbonyl stretching frequency of 2-acylpyrroles in dilute carbon tetrachloride solution is appreciably lower than that of the 3-acyl derivatives. This effect is presumably due to intramolecular hydrogen bonding, and is shown by the cycloalkapyrrolones (Table I). In addition, a lowering of the carbonyl stretching frequency is noted in going from the five- to the seven-membered cycloalkapyrrolones. This behavior is parallel to that observed for a series of closely related cycloalka[*b*]indolones,[18a] as well as the benzocyclanones,[18b] and was attributed to changes in the C–O bond character with increasing bond angle.[18b] A splitting of the carbonyl band of the six-membered ketone **5** is observed. This behavior was also noted with the six-membered ketones in the indolone series.[18a]

The ultraviolet spectra of the cycloalkapyrrolones (Table II) show behavior which conforms to a general pattern previously established[19] for pyrroles substituted with –M substituents. In both series, the intensity of the major band is decreased with increasing ring size. This effect may be attributed to the inhibition of coplanarity of the carbonyl group with the pyrrole ring by nonbonded interactions in the saturated ring, which increase with increasing ring size. This effect has already been noticed in the previously mentioned cycloalka[*b*]indolones,[18a] which provides an interesting parallel to the present work.

By use of the $\cos^2\theta$ rule,[20] the angle θ by which the carbonyl group is twisted out of the plane of the aromatic ring may be approximated. For the cycloalka[*b*]pyrrolones these angles are considerably smaller than in the corresponding cycloalka[*b*]indolones.[18a] This may be rationalized by postulating that canonical forms of the cycloalka[*b*]pyrrolones such as V are important contributors to the total structure of III, whereas forms such as VI are not as important to the total

(16) (a) H. Plieninger, P. Hess, and J. Rupert, *Chem. Ber.*, **101**, 240 (1968); (b) F. Morsingh and S. F. MacDonald, *J. Amer. Chem. Soc.*, **82**, 4377 (1960).

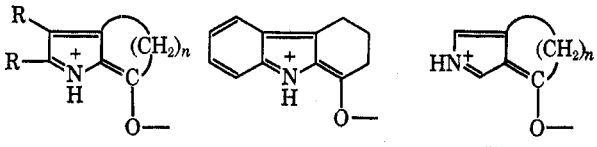
(17) R. W. Guy and R. A. Jones, *Aust. J. Chem.*, **19**, 107 (1966).

(18) (a) T. Shioiri, K. Ishizumi, and S. Yamada, *Chem. Pharm. Bull.*, **15**, 1010 (1967); (b) W. M. Schubert and W. A. Sweeney, *J. Amer. Chem. Soc.*, **77**, 4172 (1955).

(19) U. Eisner and P. H. Gore, *J. Chem. Soc.*, 922 (1958).

(20) $\cos^2\theta = \epsilon/\epsilon^\circ$, where ϵ° is the extinction coefficient for the planar homolog ($\theta = 0°$): E. A. Braude and F. Sondheimer, *J. Chem. Soc.*, 3754 (1955).

picture of the cycloalkaindolones since this structure requires disturbance of benzenoid resonance. This concept has already been employed to explain differences in chemical reactivity between pyrroles and indoles.[6] Application of the $\cos^2\theta$ rule to the cycloalka[*c*] series yields angles which are in the same range as those of the cycloalka[*b*]indolones, indicating that form VII is a less significant contributor to IV.



V VI VII

The absorption bands of the type III ketones exhibit concomitant bathochromic and hypochromic effects with increasing ring size, behavior typical of nonalternant aromatic systems.[21] However, the type IV ketones show spectral behavior which is more typical of alternant systems such as the benzocyclanones.[22] It is of interest to note that open-chain trisubstituted pyrrole ketones are also apparently twisted out of plane.

The nmr spectrum of compound **5** (see Experimental Section) was determined and appears consistent with the proposed structure.

Experimental Section[23]

Methyl 2-Ethoxycarbonyl-5-ethyl-4-methyl-γ-oxopyrrole-3-butyrate (3a).—Aluminum chloride (200 g, 1.5 mol) was added in large portions to a solution of ethyl 2-ethyl-3-methylpyrrole-5-carboxylate (136 g, 0.75 mol) and methyl 3-(chloroformyl)-propionate (Aldrich, 450 g, 3.0 mol) in 2.2 l. of carbon disulfide contained in a 5-l. 3-necked flask equipped with a mechanical stirrer and a reflux condenser topped with a $CaCl_2$ drying tube. The stirred mixture was gently heated at reflux for 4 hr during which time a gummy brown reaction complex separated. After cooling the mixture to room temperature, the CS_2 was decanted and the remaining complex decomposed with ice. The solid product which separated was filtered off, dissolved in benzene, and washed with Na_2CO_3 solution, then with saturated NaCl. The solution was then dried over $MgSO_4$, the solvent removed *in vacuo*, and the residue recrystallized from methanol–water to give 175 g (78%) of material: mp 70–72°; ir (Nujol) 5.75 (aliphatic ester), 5.89 (pyrrole ketone), 6.01 μ (pyrrole ester). *Anal.* Calcd for $C_{15}H_{21}NO_5$: C, 61.00; H, 7.17; N, 4.74. Found: C, 61.06; H, 7.08; N, 4.54.

Methyl 2-ethoxycarbonyl-5-ethyl-4-methyl-δ-oxopyrrole-3-valerate (3b) was prepared from **1a** and methyl 4-(chloroformyl)-butyrate as above in 84% yield. Colorless needles from hexane, mp 38–39.5°. *Anal.* Calcd for $C_{16}H_{23}NO_5$: C, 62.12; H, 7.49; N, 4.53: Found: C, 62.17; H, 7.51; N, 4.53.

Methyl 4-Ethoxycarbonyl-2,5-dimethyl-γ-oxopyrrole-3-butyrate (3c).—From **2** as described for **3a** in 75% yield. The compound was obtained as an oil which solidified to a crystalline material mp 53–56° upon standing in moist air. Attempts to dry the solid *in vacuo* at 25° resulted in reconversion to an oil. A satisfactory analysis could not be obtained.

Methyl 4-Ethoxycarbonyl-2,5-dimethyl-δ-oxopyrrole-3-valerate (3d).—From **2** in 95% yield as a yellow oil which failed to crystallize.

Methyl 2-Ethoxycarbonyl-5-ethyl-4-methylpyrrole-3-butyrate (4a).—A solution of **3a** (59 g, 0.2 mol) in 250 ml of abs ethanol was hydrogenated over 10 g of 10% Pd–C at 50 psi in a Parr apparatus at room temperature. Uptake of hydrogen (98% of theory) was complete after 2 hr. Catalyst was filtered off and the filtrate evaporated to give a colorless oil which soon solidified. Recrystallization from ether–petroleum ether (30–60°) gave white needles (35.5 g, 63%): mp 65–67°; ir (Nujol) 5.73 (aliphatic ester), 6.01 μ (pyrrole ester). *Anal.* Calcd for $C_{15}H_{23}NO_4$: C, 64.03; H, 8.24; N, 4.98. Found: C, 63.75; H, 8.30; N, 4.87.

Methyl 2-Ethoxycarbonyl-5-ethyl-4-methylpyrrole-3-valerate (4b).—From **3b** in 85% yield as white crystals from pentane, mp 34–36°. *Anal.* Calcd for $C_{16}H_{25}NO_4$: C, 65.06; H, 8.53; N, 4.74. Found: C, 64.89; H, 8.71; N, 4.67.

Methyl 4-Ethoxycarbonyl-2,5-dimethylpyrrole-4-butyrate (4c).—From **3c** in 78% yield as white crystals from ether, mp 85.5–86.5°. *Anal.* Calcd for $C_{14}H_{21}NO_4$: C, 62.90; H, 7.92; N, 5.24. Found: C, 62.91; H, 7.80; N, 5.18.

Methyl 4-Ethoxycarbonyl-2,5-dimethylpyrrole-3-valerate (4d). From **3d** in 71% yield as white crystals from benzene–hexane, mp 45.5–47.5°. *Anal.* Calcd for $C_{15}H_{23}NO_4$: C, 64.03; H, 8.24; N, 4.98. Found: C, 64.15; H, 8.22; N, 4.91.

Ethyl 3-(Dimethylamino)methyl-5-ethyl-4-methylpyrrole-2-carboxylate (10a).—A mixture of ethyl 5-ethyl-4-methylpyrrole-2-carboxylate (270 g, 1.5 mol), 36% aqueous formaldehyde (125 ml, 1.5 mol), and anhydrous dimethylamine (67.5 g, 1.5 mol) in 2 l. of ethanol was heated at 80–95° under a nitrogen atmosphere in a 3 l. steel bomb for 16 hr. The contents of the bomb were then evaporated *in vacuo*, the residue was taken up in ether and extracted with several portions of 2 *N* HCl. Work-up of the ether layer gave 81 g of recovered starting material.

The acid extracts were basified with NaOH, and the precipitated oil was extracted into ether. The extracts were washed with water, dried over anhydrous K_2CO_3, and evaporated to yield a dark oil which quickly crystallized. Recrystallization from pentane gave white needles (169.2 g), mp 76–78°. The recovered starting material was recycled to give another 67.3 g of product, total yield 66%. *Anal.* Calcd for $C_{13}H_{22}N_2O_2$: C, 65.51; H, 9.31; N, 11.76. Found: C, 65.57; H, 9.38; N, 11.86.

Ethyl 3-(Dimethylamino)methyl-4,5-dimethylpyrrole-2-carboxylate (10b).—From **1b** as above in 45% yield. Thick staffs from pentane, mp 87–89°. *Anal.* Calcd for $C_{12}H_{20}N_2O_2$: C, 64.25; H, 8.99; N, 12.49. Found: C, 64.19; H, 9.00; N, 12.35.

Ethyl 4-(Dimethylamino)methyl-2,5-dimethylpyrrole-3-carboxylate (10c).—From **2** as above in 68% yield. Pale yellow crystals from benzene–hexane, mp 111–113°. *Anal.* Calcd for $C_{12}H_{20}N_2O_2$: C, 64.25; H, 8.99; N, 12.49. Found: C, 64.43; H, 9.02; N, 12.59.

Diethyl [(2-Ethoxycarbonyl-5-ethyl-4-methylpyrrol-3-yl)methyl]-malonate (11a).—Dimethyl sulfate (126 g, 1.0 mol) was slowly added to a solution of **10a** (238 g, 1.0 mol) in 550 ml of ethanol. The solution warmed and was allowed to stand for 2 hr before adding a freshly prepared solution of sodio diethyl malonate (from sodium (28.6 g, 1.25 g-atom) and diethyl malonate (190 ml, 1.25 mol) in 500 ml of ethanol. The resulting mixture was then allowed to stand at room temperature for 3.5 days.

Alcohol was then removed *in vacuo*, and the residue treated with benzene and water. The benzene layer was separated, extracted with 1 *N* HCl, washed with water, and dried ($MgSO_4$). Removal of solvent left a pale yellow oil which soon solidified, and was recrystallized from pentane. Thusly was obtained 227 g (64%) of white needles, mp 46–48°. *Anal.* Calcd for $C_{18}H_{27}NO_6$: C, 61.17; H, 7.70; N, 3.96. Found: C, 60.94; H, 7.63; N, 3.87.

Treatment of this material (70.6 g) with 500 ml of 20% methanolic potassium hydroxide gave an initially clear solution, which began to deposit a voluminous white solid within 5 min at room temperature. This mixture was warmed at reflux for 15 min and the potassium salt filtered off, washed with some cold methanol and dissolved in 600 ml of water. A stream of SO_2 gas was passed into the solution until pH 3 was reached. The precipitated acid (**11d**) was filtered off and dried to give 48 g (81%) of white crystals, mp 170–171° dec; 80.5 mg required 5.72 ml of 0.1 *N* NaOH (neutral equiv 140.5, theory 148.5).

Diethyl [(2-Ethoxycarbonyl)-4,5-dimethylpyrrol-3-yl)methyl]-malonate (11b).—From **10b** in 69% yield. Needles from pentane, mp 55–56.5°. *Anal.* Calcd for $C_{17}H_{25}NO_6$: C, 60.16; H, 7.43; N, 4.13. Found: C, 60.18; H, 7.40; N, 4.16.

(21) H. H. Jaffe and M. Orchin, "Theory and Applications of Ultraviolet Spectroscopy," Wiley, New York, N. Y., 1962, pp 434–437.

(22) G. D. Hedden and W. G. Brown, *J. Amer. Chem. Soc.*, **75**, 3744 (1953).

(23) Melting points are uncorrected. Microanalyses were performed by the Spang Microanalytical Laboratory, Ann Arbor, Mich. Infrared spectra as Nujol mulls were determined on a Perkin-Elmer Model 137 Infracord. Solution spectra were determined in 1.0-mm matched NaCl cells on a Perkin-Elmer Model 221 spectrophotometer. Ultraviolet spectra were determined on a Cary 14 recording spectrophotometer. Nmr spectra were determined; courtesy of Dr. J. Swinehart of the Perkin-Elmer Laboratories, Norwalk, Conn. on a Model R-12 spectrometer.

This material was hydrolyzed to the corresponding malonic acid (**11e**), mp 169–170° dec, which was not further characterized.

Diethyl [(4-Ethoxycarbonyl-2,5-dimethylpyrrol-3-yl)methyl]-malonate (11c).—From **10c** in 51% yield. White crystals from 80% ethanol, mp 75–76°. *Anal.* Calcd for $C_{17}H_{25}NO_6$: C, 60.16; H, 7.43; N, 4.13. Found: C, 60.22; H, 7.41; N, 4.17.

Hydrolysis gave **11f**, mp 155–157° dec.

2-Ethoxycarbonyl-5-ethyl-4-methylpyrrole-3-propionic Acid (4e).—Decarboxylation of **11d** was effected by heating the compound (48 g) in an Erlenmeyer flask immersed in an oil bath at 190–200° until evolution of CO_2 was complete (10–15 min). The liquid product was allowed to solidify and was then scraped out of the flask, giving 40.2 g (98%) of crude **4e**.

An analytical sample was recrystallized from ethanol–water as long needles, mp 145.5–147.5°; ir (Nujol) 5.84 (COOH), 6.01 (pyrrole ester). *Anal.* Calcd for $C_{13}H_{19}NO_4$: C, 61.64; H, 7.56; N, 5.53. Found: C, 61.58; H, 7.57; N, 5.53.

2-Ethoxycarbonyl-4,5-dimethylpyrrole-3-propionic Acid (4f).—From **11e**. Needles from ethanol–water, mp 155–157°. *Anal.* Calcd for $C_{12}H_{17}NO_4$: C, 60.24; H, 7.16; N, 5.85. Found: C, 60.14; H, 7.09; N, 5.83.

4-Ethoxycarbonyl-2,5-dimethylpyrrole-3-propionic Acid (4g).—From **11f**. Needles from ethanol–water, mp 172–175°. *Anal.* Calcd for $C_{12}H_{17}NO_4$: C, 60.24; H, 7.16; N, 5.85. Found: C, 60.27; H, 7.23; N, 5.83.

2-Ethyl-3-methylpyrrole-4-propionic Acid (14a).—The above described crude **4e** was heated for 1 hr at reflux with 250 ml of 20% aqueous potassium hydroxide. The mixture was then cooled and diluted with 250 ml of water; a stream of SO_2 gas was passed into the solution until pH 3 was obtained. Precipitated solid (**4h**) was filtered off and the filtrate extracted with ether. The ether extracts were evaporated, leaving a yellow oil which was combined with the filtered solids, moistened with some water, and heated on the steam bath until gas evolution was complete. Water was removed from the resulting product on the rotary evaporator and the residue extracted with several portions of boiling hexane totalling 2.5 l. On cooling, long colorless needles of **14a** formed, which were filtered off and dried. There was obtained 24.4 g (85%) of product, mp 83–84.5° [lit.[24] mp 85–88°].

2,3-Dimethylpyrrole-4-propionic Acid (Haemopyrrolecarboxylic Acid, (14b).—Prepared as above from **4f**, mp 126.5–127.5 [lit.[16b] mp 127–129°].

2-Ethyl-4,5-dihydro-3-methylindol-7(6H)-one (5).—The diester **4a** (31 g) and 458 g of polyphosphoric acid were heated slowly to 125–130°. Frothing commenced at about 80° and the mixture was stirred vigorously with a glass rod to prevent overflow. The dark mixture was heated for 30 min after the frothing had ended, cooled to 60°, and poured into a large volume of cold water. After stirring to dissolve the polyphosphoric acid, the mixture was chilled in ice for 30 min; the solid product was filtered off and thoroughly washed with water. After drying, the highly colored crude product was sublimed at 125° (0.1 mm) to give white crystals (8.8 g, 45% yield). An analytical sample was recrystallized from ether–hexane, mp 135–136°; nmr ($CDCl_3$) δ 1.18 (t, 3, J = 7 Hz, CH_3–CH_2), 1.89 (s, 3, CH_3–), 1.96–2.82 (m, 8, combined $-CH_2-$). *Anal.* Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.44; C, 8.41; N, 7.93.

The following ketopyrroles were prepared as above using a 15 fold excess of PPA: **2-ethyl-4,5,6,7-tetrahydro-3-methylcyclohepta[*b*]pyrrol-8(1H)-one (6).** From **4b** in 17% yield. Needles from hexane, mp 120–121°. *Anal.* Calcd for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.30; H, 9.05; N, 7.35.

6,7-Dihydro-1,3-dimethylisoindol-4(5H)-one (7).—From **4c** in 65% yield. Crystals from methanol, mp 151–152° (lit.[25] mp 151–152°). *Anal.* Calcd for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.75; H, 7.97; N, 8.64.

5,6,7,8-Tetrahydro-1,3-dimethylcyclohepta[*c*]pyrrol-4(2H)-one (8).—From **4d** in 28% yield. Needles from hexane–benzene, mp 136–138°. *Anal.* Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.01°. Found: C, 74.56; H, 8.52; N, 6.90.

2-Ethyl-4,5-dihydro-3-methylcyclopenta[*b*]pyrrol-6(1H)-one (13a).—From **14a** in 62% yield. Rhombs from hexane, mp 179.5–181.5°. *Anal.* Calcd for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.55; H, 8.01; N, 8.64.

4,5-Dihydro-2,3-dimethylcyclopenta[*b*]pyrrol-6(1H)-one (13b).—From **14b** in 67% yield. Microcrystals from hexane, mp 223–223.5°. *Anal.* Calcd for $C_9H_{11}NO$: C, 72.45; H, 7.43; N, 9.39. Found: C, 72.53; H, 7.33; N, 9.40.

5,6-Dihydro-1,3-dimethylcyclopenta[*c*]pyrrol-4(2H)-one (12).—From **4g** in 38% yield. Feathers from toluene, mp 244–246° (lit.[25] mp 245–248° dec). *Anal.* Calcd for $C_9H_{11}NO$: C, 72.45; 7.43; N, 9.39. Found: C, 72.30; H, 7.62; N, 9.42.

2-Ethyl-3-methylindol-7-ol (9).—A mixture of **5** (3.8 g), 10% Pd–C (4.0 g), and 125 ml of cumene was heated with stirring at reflux under nitrogen for 20 hr. The hot reaction mixture was then filtered, and the solvent evaporated *in vacuo* to give a light orange residue (2.7 g) which solidified on trituration under pentane. Recrystallization from hexane gave white needles, mp 86–88°, soluble in 1 *N* NaOH and giving a violet color with $FeCl_3$ solution. Ultraviolet spectrum (MeOH): 293 (5075), 271 mμ (7884). *Anal.* Calcd for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.13; H, 7.55; N, 8.02.

Registry No.—**3a**, 25109-99-3; **3b**, 25110-00-3; **3c**, 25110-01-4; **4a**, 25110-02-5; **4b**, 25110-03-6; **4c**, 25110-04-7; **4d**, 25110-05-8; **4e**, 25110-06-9; **4f**, 25110-07-0; **4g**, 6315-16-8; **5**, 25110-09-2; **6**, 25158-24-1; **7**, 21770-35-4; **8**, 25110-11-6; **9**, 25158-25-2; **10a**, 25110-12-7; **10b**, 25110-13-8; **10c**, 25110-14-9; **11a**, 25110-15-0; **11b**, 25158-26-3; **11c**, 25158-27-4; **11d**, 25110-16-1; **12**, 21770-33-2; **13a**, 25110-18-3; **13b**, 25110-19-4; 2-acetyl-3,4,5-trimethylpyrrole, 22186-84-1; 2-acetyl-3,4-dimethyl-5-*n*-propylpyrrole, 25110-21-8; 3-acetyl-2,4,5-trimethylpyrrole, 19005-95-9; 2-acetyl-3,5-dimethyl-4-ethylpyrrole, 1500-91-0; 3-acetyl-2,5-dimethyl-4-*n*-propylpyrrole, 10594-44-2.

(24) V. L. Archibald, D. M. Walker, K. B. Shaw, A. Markovac, and S. F. MacDonald, *Can. J. Chem.*, **44**, 345 (1966).

(25) I. J. Pachter and W. Herz, U. S. Patent 3, 415, 843 (1968).