Tetrahedron Vol 23, pp 4499 to 4507. Pergamon Press Ltd 1967 Printed in Great Britain

ARYLPYRROLYLMETHENES[1]

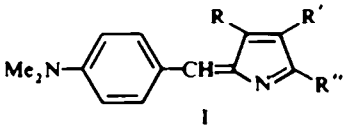
A. J. CASTRO, G. TERTZAKIAN,[2] B. T. NAKATA[3a] and D. A. BROSE[3b]

Department of Chemistry, San Jose State College, San Jose, California 95114

(*Received in USA* 10 *November* 1966; *accepted for publication* 21 *March* 1967)

Abstract—The synthesis of 2-*p*-hydroxyphenylmethylene-2H-pyrrolenine hydrobromides and their properties are described. The results of attempted synthesis of other "mixed" arylpyrrolylmethenes are discussed and an improved procedure for the synthesis of 2-ethoxycarbonyl-4-methoxypyrrole is reported. Deformylation and apparent self-condensation of pyrrole aldehydes were observed in a number of methene syntheses tried and a mechanism to account for this is presented.

THE highly colored 2,2'-dipyrrolylmethenes (2-pyrrol-2-ylmethylene-2H-pyrrolenines) and their salts are well known.[4a] In addition, the related tripyrrolymethenes[5–7] as well as bipyrrolylpyrrolylmethenes[8–15] and derivatives[16–19] have been studied to some extent. However, arylpyrrolylmethenes, in which one of the pyrrole rings of a dipyrrolylmethene is replaced by a non-pyrrole aromatic nucleus (e.g. I), have received almost exiguous attention.



I

Paramount in this regard is the well-known Ehrlich's test [4b] for pyrroles, which has

[1] This investigation was supported by a United States Public Health Service Research Grant CA-06255- (01-04) MCHA from the National Cancer Institute, for which we are grateful. We also wish to thank Michael P. Gardner and Jon F. Harbaugh[3a] for the synthesis of some of the compounds used.

[2] Present address: R & L Molecular Research, 8045 Argyll Road, Edmonton 29, Alberta, Canada.

[3] United States National Science Foundation Undergraduate Research Participant: [a] (NSF-G21628), [b] (NSF-GY81).

[4] H. Fischer and H. Orth, *Die chemie des Pyrrols*. Akademische Veragsgesellschaft, M.B.H., Leipzig [a] Vol. II, p. 1, 1 Hälfte (1937); [b] Vol. I, p. 66 (1934); [c] Ref. *a*, p. 39.

[5] H. Fischer and K. Gangl, *Z. physiol. Chem.* **267**, 201 (1941).

[6] A. Treibs and K. Hintermeier, *Liebigs Ann.* **605**, 35 (1957).

[7] A. J. Castro, A. H. Corwin, J. F. Deck and P. E. Wei, *J. Org. Chem.* **24**, 1437 (1959).

[8] F. Wrede and A. Rothhaas, *Z. Physiol. Chem.* **219**, 267 (1933).

[9] F. Wrede and A. Rothhaas, *Z. Physiol. Chem.* **226**, 95 (1934).

[10] G. Narni and R. A. Nicolaus, *Rend. Accad. Sci. Fis. Mat. (Soc. Nazl. Sci. Napoli)* **26**, 471 (1959).

[11] H. H. Wasserman, J. E. McKeon, L. Smith and P. Forgione, *J. Am. Chem. Soc.* **82**, 506 (1960).

[12] H. H. Wasserman, L. L. Williams and J. J. Keggi, *Angew. Chem.* **73**, 467 (1961).

[13] H. Rapoport and K. G. Holden, *J. Am. Chem. Soc.* **84**, 635 (1962).

[14] A. J. Castro, J. F. Deck, M. T. Hugo, E. J. Lowe, J. P. Marsh, Jr. and R. J. Pfeiffer, *J. Org. Chem.* **28**, 857 (1963).

[15] E. Bullock, R. Grigg, A. W. Johnson and J. W. F. Wasley, *J. Chem. Soc.* 2326 (1963).

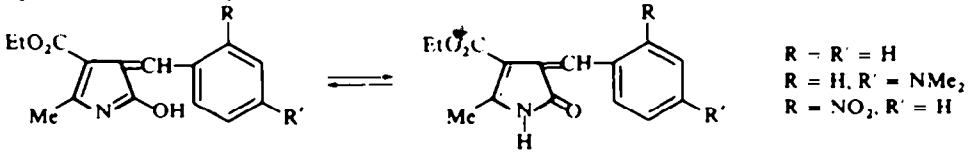
[16] A. W. Johnson, I. T. Kay and R. Rodrigo, *J. Chem. Soc.* 2336 (1963).

[17] R. Grigg and A. W. Johnson, *J. Chem. Soc.* 3315 (1964).

[18] J. H. Atkinson, A. W. Johnson and W. Raudenbusch, *J. Chem. Soc.* C: Org., 1155 (1966).

[19] A. Treibs and R. Zimmer-Galler, *Z. physiol. Chem.* **318**, 12 (1960).

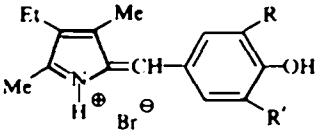
been shown[20] to yield compounds represented by formula I with several pyrroles having a free α-position.[21] The stability of such compounds is very pH dependent,[20a] and in the solid state these apparently exist only as the monoprotonated species of I. The only other phenylpyrrolylmethenes that have been reported are those claimed (II) as resulting from the reactions of benzaldehyde, *p*-dimethylaminobenzaldehyde and *o*-nitrobenzaldehyde with 2-methyl-3-ethoxycarbonyl-5-hydroxypyrrole in the presence of conc hydrochloric acid.[22]



IIa IIb

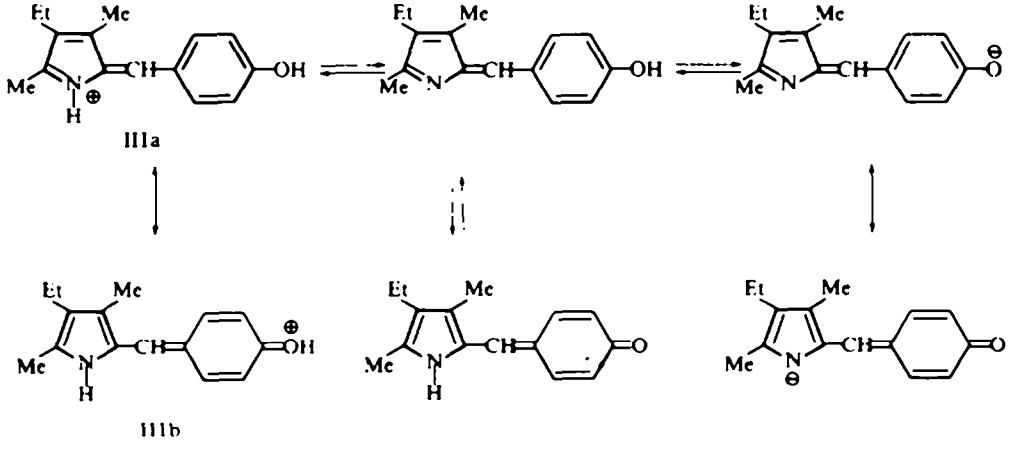
The simpler 2-hydroxypyrroles normally exist as their keto-tautomers (pyrrolinones)[23] and if the same situation exists here, these compounds should be represented by IIb rather than IIa.

We have now found that the condensations of *p*-hydroxybenzaldehyde, vanillin,



III: R = R' = H
IV: R = H, R' = OMe
V: R = R' = OMe

and syringic aldehyde with 2,4-dimethyl-3-ethylpyrrole (cryptopyrrole) yields red, crystalline phenylpyrrolylmethene hydrobromides III–V. Aqueous solutions of these compounds are yellow in acid or base, but become pink on neutralization. Similarly,



IIIa IIIb

[20] [a] A. Treibs and E. Herrman, *Z. physiol. Chem.* **299**, 168 (1955); [b] L. R. Morgan, Jr. and R. Schunior, *J. Org. Chem.* **27**, 3696 (1962). These workers also report a variation.

[21] Trisubstituted pyrroles having a free β-position and certain tetrasubstituted pyrroles occasionally have been found to give a positive Ehrlich test.[20a]

[22] H. Fischer and J. Müller, *Z. physiol. Chem.* **132**, 72 (1924).

[23] A. R. Katritzky and J. M. Lagowski, *Advances in Heterocyclic Chemistry* Vol. 2; p. 11 *et. seq.* Academic Press, New York, N.Y. (1963)

simple dilution of yellow concentrated aqueous solutions of the salts with ordinary distilled water yields intensely pink solutions. Although this could reflect a change such as degree of aggregation, it may again be nothing more than an expected change with pH. However, the existence of three stages of protonation, as shown for III, is supported directly by their different UV-visible spectra at pH 1, 6·86, and 13 (Fig. 1 and Table 1).

In sharp contrast with the facile synthesis of III V, the attempted condensation of benzaldehyde, *p*-nitrobenzaldehyde, and piperonal with cryptopyrrole led only to dark, intractable products. Hence a criterion for successful arylpyrrolylmethene synthesis among the congeners tried is the presence of a *p*-hydroxy substituent. This can be rationalized in terms of important resonance stabilization involving canonical forms like IIIa ·IIIb in the hydrobromides leading to charge delocalization between the two rings. This would not be possible in the first two of the other examples investigated and the contribution from analogous resonance forms of the third is evidently not as effective.

Some time ago Fischer and Schormüller[24] described the synthesis of the two unstable "mixed" heterocyclepyrrolylmethene hydrobromides of 2-fur-2-ylmethylene-3,5-dimethyl-4-ethyl-2H-pyrrolenine and 2-thien-2-ylmethylene-3,5-dimethyl-4-ethyl-2H-pyrrolenine from the condensation of furfural and thiophene-2-aldehyde with

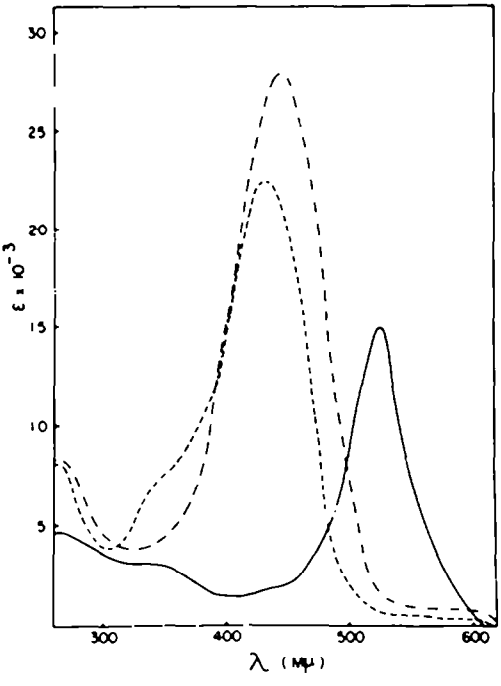


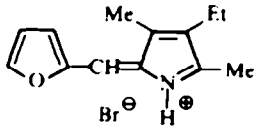
FIG. 1. UV-visible absorption spectra of 2-(3-methoxy-4-hydroxyphenyl)methylene-3,5-dimethyl-4-ethyl-2H-pyrrolenine hydrobromode (IV) in 0·1N HCl (· ···), Beckman buffer of pH 6·86 (— · — ·), and 0·1N NaOH (– –).

[24] H. Fischer and A. Schormüller, *Liebigs Ann.* **482**, 232 (1930).

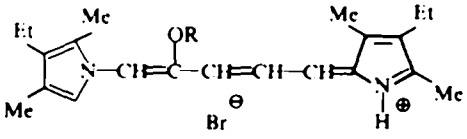
TABLE 1. UV ABSORPTION SPECTRA OF 2-*p*-HYDROXYPHENYLMETHYLENE-2H-PYRROLENINE HYDROBROMIDES

Compound	pH	λ_{max} mμ (ε × 10^{-3})							
	1	416	(25·12),	260	(9·12),	242	(2·43).		
III	6·86	509	(8·13),	320	(4·57),	281	(8·71),	220	(11·75).
	13	424	(25·12),	320	(9·77),	261	(2·61),	241	(2·65).
	1	438	(22·54),	355	(7·94),	271	(8·91),	262	(9·33).
IV	6·86	527	(15·00),	350	(3·24),	279	(2·34)		
	13	450	(27·94),	271	(8·32),	250	(7·59).		
	1	447	(19·05),	280	(7·08),	262	(8·51)		
V	6·86	553	(3·39),	361	(2·69),	269	(4·07)		
	13	470	(23·99),	370	(6·17),	272	(9·33),	255	(8·71)

cryptopyrrole. Piutti[25] later reported the synthesis of several furylpyrrolylmethenes. However, Strell *et al.*[26] have presented evidence that the assumed furylpyrrolylmethene structure VI assigned to the product from furfural and cryptopyrrole should be replaced by VII, resulting from ring cleavage of furfural. The condensation of formylpyridines with pyrroles was found [27] to lead to pyridyldipyrrolylmethanes and pyridylpyrrolylmethenes could only be observed spectroscopically, although a pyridylpyrrolylmethene zinc chloride complex has been prepared.[19] In our hands the



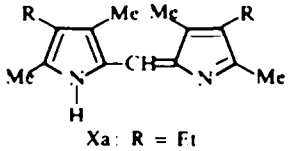
VI



R = H[28] and or Ac

VII

attempted hydrobromic acid catalyzed condensation of 2-formyl-3,5-dimethyl-4-ethylpyrrole (VIII), and of 2-formyl-3,5-dimethyl-4-ethoxycarbonylpyrrole (IX), with thiophene surprisingly gave the hydrobromides of the symmetrical methene Xa and b. Employing the reverse combination of 2-formylthiophene with cryptopyrrole, or 2,4-dimethyl-3-ethoxycarbonylpyrrole, yielded tars. With 4-formylimidazole[29] and cryptopyrrole, a yellow compound was isolated, which may have been the derived from deformylation of the pyrrole aldehyde as in the attempted condensations



Xa: R = Et
Xb: R = CO_2Et

[25] P. Piutti, *Gazz. Chim. Ital.* **66**, 265 (1936).
[26] M. Strell, A. Kalojanoff and L. Brem-Rupp, *Chem. Ber.* **87**, 1019 (1954).
[28] Keto form expected.
[27] M. Strell, A. Zocher and E. Kopp, *Chem. Ber.* **90**, 1798 (1957).
[29] F. L. Pyman, *J. Chem. Soc.* **109**, 186 (1916).

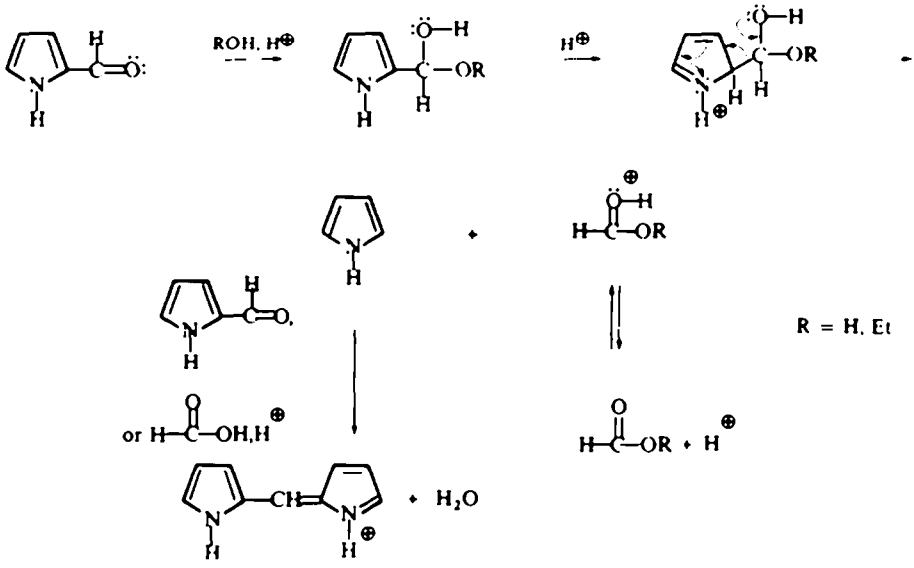
by its infrared spectrum, but because of its instability it was not further characterized. Using the alternate approach of aldehyde VIII and imidazole yielded Xa, the product derived from deformylation of the pyrrole aldehyde as in the attempted condensations with thiophene.

Dipyrrolylmethene formation through deformylation has been noted previously[4a, 15, 30, 31] and in addition to the different examples mentioned above the same type reaction has been noted by us in other attempted methene syntheses. Thus the attempted condensation of aldehyde IX with a mixture of 4-pyrrol-2-ylbutanenitrile (chiefly) and 4-pyrrol-3-ylbutanenitrile[32] in the presence of hydrobromic acid in ethyl alcohol yielded methene Xb. Likewise, both aldehydes VIII and IX with 2-ethoxycarbonyl-4-methoxypyrrole (XI) gave only the methenes derived from the aldehydes (Xa and b). It should be noted, however, that upon carrying out the condensation of 2-formyl-3-methoxy-5-ethoxy-carbonylpyrrole (XII) with cryptopyrrole in a chloroform ether mixture in the presence of hydrogen chloride, the mixed methene salt 2-(3-methoxy-5-ethoxycarbonylpyrrol-2-yl)methylene-3,5-dimethyl-4-ethyl-2H-pyrrolenine hydrochloride (XIII) was obtained. The analogous synthesis of 2-(3-methoxy-5-methoxycarbonylpyrrol-2-yl)methylene-4-pentyl-5-methyl-2H-pyrrolenine hydrobromide from 2-formyl-3-methoxy-5-methoxycarbonylpyrrole and 2-methyl-3-pentylpyrrole in ethyl alcohol has been described.[14]

It has been suggested, without supporting evidence, that formic acid is eliminated in the self-condensation of pyrrolealdehydes to dipyrrolylmethenes.[4a, 30] In this regard, it has been shown that several substituted benzaldehydes undergo deformylation by strong acid[33, 37] (and base)[38] yielding the parent benzene and formic acid[35, 38] or carbon monoxide[35] (the latter when concentrated acid is used). Following the frequently employed conditions for methene synthesis, 2-formylpyrrole, aldehyde VIII, and aldehyde IX were each boiled in ethanol with 48% hydrobromic acid. The only readily volatile organic compounds from the reaction mixture that were detectable were ethyl formate and the solvent. The appropriate symmetrical methene was also isolated in the cases where substituted pyrrole aldehydes were used. 2,2'-Dipyrrolylmethene, which would have been the expected product from 2-formylpyrrole, was not obtained since it is unstable. The isolation of ethyl formate permits considerations of its elimination from the pyrrole aldehyde hemiacetal, but it does not preclude initial loss of formic acid followed by esterification. The possibility of deformylation through the loss of carbon monoxide and its conversion into the ester seems unlikely in view of the usual conditions for the latter reaction.[39] Deformylation and methene salt formation may be envisaged as successive processes. Although, ethyl

[30] H. Fischer and W. Zerweck, *Ber. Deut. Chem. Ges.* **55**, 1942 (1922).
[31] H. Fischer and W. Zerweck, *Ber. Dtsch. Chem. Ges.* **56**, 519 (1923).
[32] A. J. Castro, J. F. Deck, N. C. Ling, J. P. Marsh, Jr. and G. E. Means, *J. Org. Chem.* **30**, 344 (1965).
[33] A. Bistrzycki and M. Fellman, *Ber. Deut. Chem. Ges.* **43**, 772 (1910).
[34] A. Bistrzycki and L. Ryncki, *Chem. Ztg.* **36**, 403 (1912).
[35] W. M. Schubert and R. E. Zahler, *J. Am. Chem. Soc.* **76**, 1 (1954).
[36] H. Burkett, W. M. Schubert, F. Schultz, R. B. Murphy and R. Talbott, *J. Am. Chem. Soc.* **81**, 3923 (1959).
[37] H. Burkett, F. Schultz and J. Cassady, *J. Org. Chem.* **26**, 2072 (1961).
[38] G. Lock, *Ber. Deut. Chem. Ges.* **66B**, 1527, 1759 (1933); **68B**, 1505 (1935); **69B** 2253 (1936).
[39] H. Henecka, *Methoden der Organischen Chemie* (4th Edition, edited by E. Müller) Vol. VIII; p. 509. Thieme Verlag, Stuttgart (1952).

formate may be the actual species eliminated in the deformylation of the aldehyde, it cannot participate directly in methene formation. This was clearly demonstrated by refluxing an acidic alcohol solution of the ester and 2,4-dimethyl-3-ethoxycarbonylpyrrole for four hours, during which there was no evidence of methene salt formation. Under the same conditions with formic acid, the methene is derived.[40,c] It is of



further interest to note that the reaction of 3-formyl-2,5-dimethyl-4-ethoxycarbonylpyrrole and 2,4-dimethyl-3-ethoxycarbonylpyrrole yields 2-(3,5-dimethyl-4-ethoxycarbonylpyrrol-2-yl)methylene-3,5-dimethyl-4-ethoxycarbonyl-2H-pyrrolenine hydrochloride[30] (Xb·HCl), wherein the pyrrole rings found in the methene salt are entirely from the starting pyrrole alone and that from the starting aldehyde is not represented.

2-Ethoxycarbonyl-4-methoxypyrrole (XI) has been synthesized[40] in one step by heating 1,2-diethoxycarbonyl-4,4-dimethoxypyrrolidine (XIV) with a large amount of palladium on charcoal catalyst, but in our hands this led to a mixture and none of XI. In the synthesis of a 4-alkoxypyrrole Kuhn and Osswald[41] report the formation of the intermediate 1,2-diethoxycarbonyl-4-ethoxy-Δ^4-pyrroline, through conversion of 1,2-diethoxycarbonyl-4-oxopyrrolidine to the diethyl ketal by reaction with ethyl sulfite, followed by pyrolysis of the reaction mixture. Apparently in an attempt to synthesize the 4-methoxy analog in the same way Rapoport and Willson[40] obtained a mixture of the isomeric methoxypyrrolines. We have found that ketal XIV can be smoothly pyrolyzed in refluxing hexyl ether solution to a single pyrroline XV in substantially a quantitative yield. Subsequent[41] bromination with *N*-bromosuccinnimide, dehydrobromination and hydrolysis led readily to the desired XI.

[40] H. Rapoport and C. D. Willson, *J. Am. Chem. Soc.* **84**, 630 (1962).
[41] R. Kuhn and G. Osswald, *Chem. Ber.* **89**, 1423 (1956).

EXPERIMENTAL

M.ps are uncorrected and have been determined on a Fisher-Johns apparatus. UV, IR and NMR spectra were obtained with Cary Model 14, Beckman IR-5 and Varian A-60 instruments, respectively. An Aerograph A-100C instrument was used for GLC.

2-p-Hydroxybenzylidene-2H-pyrrolenine hydrobromides

2-p-Hydroxybenzylidene-3,5-dimethyl-4-ethyl-2H-pyrrolenine hydrobromide (III). To a soln of 3-ethyl-2,4-dimethylpyrrole (0·6 g) and *p*-hydroxybenzaldehyde (0·6 g) in abs EtOH (7 ml), HBr (1 g, 48%) was added dropwise with shaking. The soln immediately became intensely red and a red crystalline ppt formed. The mixture was refrigerated for 1 hr and filtered yielding a red solid (1·3 g, 86%). Two recrystallizations from glacial AcOH gave analytically pure 2-*p*-hydroxybenzylidene-3,5-dimethyl-4-ethyl-2H-pyrrolenine. HBr as small maroon needles, m.p. 200–201° (dec). (Found: C, 58·39; H, 6·16; N, 4·58. $C_{15}H_{18}BrNO$ requires: C, 58·47; H, 5·89; N, 4·55%.) IR (Nujol mull): 3030 (m), 1635 (w), 1600 (s), 1575 (m), 1525 (w), 1225 (s) and 1175 cm^{-1} (s).

2-(3-Methoxy-4-hydroxybenzylidene)-3,5-dimethyl-4-ethyl-2H-pyrrolenine hydrobromide (IV). The above procedure was followed using 2,4-dimethyl-3-ethylpyrrole (0·615 g), vanillin (0·75 g) and the previously described quantities of alcohol and HBr. 2-(3-Methoxy-4-hydroxybenzylidene)-3,5-dimethyl-4-ethyl-2H-pyrrolenine. HBr (1·43 g, 86%) was obtained, which had a m.p. of 183° (dec) after two recrystallizations from glacial AcOH. (Found: C, 56·85; H, 6·12; N, 3·91. $C_{16}H_{20}BrNO_2$ requires: C, 56·81; H, 5·96; N, 4·14%.) IR (Nujol mull): 3070 (m), 1640 (m), 1595 (s), 1525 (m), 1260 (s) and 1140 cm^{-1} (m).

2-(3,5-Dimethoxy-4-hydroxybenzylidene)-3,5-dimethyl-4-ethyl-2H-pyrrolenine hydrobromide (V). The above procedure was followed using 2,4-dimethyl-3-ethylpyrrole (0·66 g) and syringic aldehyde (0·86) in abs EtOH (3·5 ml) and HBr (1 g). 2-(3,5-Dimethoxy-4-hydroxybenzylidene)-3,5-dimethyl-4-ethyl-2H-pyrrolenine. HBr (1·5 g, 86%) precipitated as a red solid which quickly darkened in air while moist. Three recrystallizations from small amounts of glacial AcOH yielded an analytical sample, m.p. 162–163·5° (dec), as tiny dark red needles. (Found: N, 3·72. $C_{17}H_{22}BrNO_3$ requires: N, 3·80%.) IR (Nujol mull): 3450 (m), 1635 (m), 1585 (m), 1515 (m), 1355 (s), 1270 (s), 1125 cm^{-1} (s). NMR ($CDCl_3$): pyrrole ethyl methyl protons (δ = 1·10, triplet, 3), pyrrole ethyl methylene and pyrrole β-methyl (2·40, singlet over quartet, 5), pyrrole α-methyl (2·88, singlet, 3), methoxyl methyl (4·12, singlet, 6), hydroxyl (ca. 5·5, singlet, 1), phenyl ring (7·48, singlet, 2), *meso*-methylidene (7·93, singlet, 1). NH (ca. 13·4, broad singlet, 1). The positions of the OH and NH proton signals are concentration dependent and disappear on shaking with D_2O.

Pyrroles and pyrrole aldehydes

2-Formyl-3,5-dimethyl-4-ethylpyrrole (VIII). This aldehyde was synthesized from cryptopyrrole[42] (9·86 g) and corresponding proportionate amounts of the other reagents essentially as described for the Vilsmeier Haack formylations of pyrrole and other substituted pyrroles.[14,43] The product (7·1 g) was collected as an oil, b.p. 130–132°/1·5 mm, which after crystallization gave 5·32 g (44%) of almost white crystals, m.p. 101·0–102·0° (lit.[44] 105–106°).

2-Formyl-3,5-dimethyl-4-ethoxycarbonylpyrrole (IX). 2,4-Dimethyl-3-ethoxycarbonylpyrrole[45] (10·0 g) dissolved in N, N-dimethylformamide (50 ml) was added to an ice cold soln of $POCl_3$ (6·2 ml) in the same amide (50 ml).[46] The mixture was stirred at 5° for 10 min, heated at 40° for 2 hr, and poured into a mixture of ice and water (125 g). After storage in a refrigerator for 2 days the product was collected, dried, decolorized in EtOH with Norite, and collected in 2 crops, m.p. 161·0–162·0° and 164·0–165·0° (lit.[30] 165°), as a tan to brown solid (10·4 g, 89%).

2-Ethoxycarbonyl-4-methoxypyrrole (XI). Ketal XIV[40] (42 g) in hexyl ether (55 ml) was refluxed in a slow stream of N_2 for 7 hr; the temp of the boiling soln, initially at 160–165°, rose to 230° in 2 hr. The solvent was evaporated (b.p. 90°/6 mm) and XV (36·6 g, 99%) distilled at 127°/1·2 mm. Gas chromatography of this product (Carbowax column) gave only one peak. IR (liquid film): ester C=O at 1750 (s) and 1725 (s); unconjugated C=C at 1670 cm^{-1} (m).

To a soln of XV (36·6 g) in CCl_4 (200 ml), N-bromosuccinimide (27 g) was added and the mixture was

[42] Aldrich Chemical Co., Inc., Milwaukee, Wisconsin.
[43] R. M. Silverstein, E. E. Ryskiewiez and C. Willard, *Org. Syn.* **36**, 74 (1956).
[44] H. Fischer and M. Schubert, *Ber. Deut. Chem. Ges.* **56**, 1202 (1923).
[45] L. Knorr, *Liebigs Ann.* **236**, 290 (1886).
[46] cf. A. Ermili, A. J. Castro and P. A. Westfall, *J. Org. Chem.* **30**, 339 (1965).

warmed with a trace of benzoyl peroxide on a steam bath until a vigorous exothermic reaction set in. The mixture became dark red and boiled from its own heat of reaction for about 10 min. A trace more of benzoyl peroxide was added, and the mixture was boiled for an additonal 10 min. Dry Et_3N (24 ml) was then added, the mixture was refluxed for 2 hr, filtered hot, and the solid residue was repeatedly washed with CCl_4. The combined red filtrate was washed with 2N H_2SO_4 (2 × 100 ml) and $NaHCO_3$ aq (150 ml), dried with $MgSO_4$, and evaporated under reduced press to yield a viscous red oil. Distillation yielded 1,2-diethoxycarbonyl-4-methoxypyrrole (16·6 g, 46%), b.p. 112–115°/0·25 mm, as a yellow oil. In another run, a 48% yield of the product was realized.

1,2-Diethoxycarbonyl-4-methoxypyrrole (16·6 g) was refluxed in a water–EtOH (8:70 ml) soln of KOH (4·6 g, 85% reagent grade) for 25 min. The reaction mixture was poured into water (300 ml), made acidic (pH 2) with 2N HCl and the resulting red oil was extracted with ether. The extracts were dried with $MgSO_4$ and evaporated to yield XI (10·3 g, 89%) as pale brown oily crystals. Recrystallization from hexane (charcoal) gave colorless prisms of XI, m.p. 44–46°. This product could be further purified by sublimation at 100°/0·20 mm, yielding a colorless solid, m.p. 58–60° (lit.,[40] m.p. 55–58°). NMR ($CDCl_3$): ester methyl (δ = 1·28, triplet, 3); methoxyl (3·62, singlet, 3); ester methylene (4·2, quartet, 2); pyrrole ring (6·40 and 6·44, singlets, 1 each); NH (11·22, broad singlet, 1).

2-Formyl-3-methoxy-5-ethoxycarbonylpyrrole (XII). Compound XI (2·77 g) was formylated as described for VIII to yield crude (XII (3·12 g, 97%), m.p. 108–115°. A sample, after decolorization with Norite in EtOH, crystallization, sublimation (100°/0·4 mm) and repeated crystallization from EtOH, gave practically white crystals, m.p. 131·0–131·3° (Found: C, 55·39; H, 5·66. $C_9H_{11}NO_4$ requires: C, 54·82; H, 5·62%.) NMR ($CDCl_3$): ester methyl (δ = 1·32, triplet, 3); methoxyl (3·78, singlet, 3); ester methylene (4·27, quartet, 2); pyrrole ring (6·31, singlet, 1); formyl (9·54, singlet, 1); NH (10·4, broad singlet, 1).

Attempted condensations of 2-formyl-3,5-dimethyl-4-ethylpyrrole (VIII)

With thiophene. A soln of VIII (1·00 g) and thiophene (0·689 g) in abs EtOH (25 ml) was warmed on a steam bath and HBr (0·95 ml) was added dropwise. The mixture was refluxed for 1 hr and crystals were observed to form in the mixture during this period. After cooling, Xa (1·00 g, 90%) was collected as red crystals with a blue reflex, m.p. 247·0–249·0° (dec) (lit.[47] 249–250°). The IR spectrum of this compound was identical with that of an authentic sample.

With imidazole. HBr (1 drop) was added to a warm soln of VIII and imidazole in abs EtOH (few ml). Red crystals of Xa, m.p. 244·5–247·0° (dec), deposited from the soln upon standing. These were further identified by their IR spectrum.

With 2-ethoxycarbonyl-4-methoxypyrrole (XI). HBr (1 ml) was added rapidly to a 95% EtOH soln (6 ml) of VIII (0·2793 g) and XI (0·3336 g) and the mixture was heated on the steam bath for 10 min. Compound Xa (0·2372 g, 76%), m.p. 244·0–245·0° crystallized as red crystals with a blue reflex from the reaction mixture and was isolated after cooling and washing with 95% EtOH. The IR spectrum confirmed the identity of the product.

Attempted condensations of 2-formyl-3,5-dimethyl-4-ethoxycarbonylpyrrole (IX)

With thiophene. To a refluxing soln of IX (6·96 g) and thiophene (3·0 g) in abs EtOH (125 ml), HBr (4·12 ml) was added dropwise. The resulting dark soln was heated to reflux for 3 hr, cooled in ice and the mixture was filtered. The solid collected (5·85 g) was recrystallized from chloroform–cyclohexane yielding Xb (4·75 g, 63%) as dark red crystals which were collected in 3 crops melting within the range 207·5–211·0° (dec) (lit.[48] 210·0–213·5°). A sample of Xb in chloroform, after reaction with ammonia and crystallization of the product from chloroform–cyclohexane, gave the free base as red needles, m.p. 189·7–191·0° (dec) (lit.[49] 190°), having an IR spectrum identical with an authentic sample of 2-(3,5-dimethyl-4-ethoxycarbonylpyrrol-2-yl)methylene-3,5-dimethyl-4-ethoxycarbonyl-2H-pyrrolenine.

With 4-pyrrolylbutanenitriles. From IX (0·975 g), a mixture of 4-pyrroly-2-ylbutanenitrile and 4-pyrrol-3-ylbutanenitrile[32] (chiefly the former, 0·75 g), and HBr (2 ml) in boiling abs EtOH (5 ml) there was isolated 0·53 g (50%) of red crystals of Xb. After recrystallization from chloroform–cyclohexane the product melted with decomposition, 207·5–209° (Found: C, 53·93; H, 5·81; N, 6·41. Calc. for $C_{19}H_{25}BrN_2O_4$:

[47] A. J. Castro, G. R. Gale, G. E. Means and G. Tertzakian, *J. Med. Chem.* **10**, 29 (1967).
[48] A. J. Castro, J. P. Marsh, Jr. and B. T. Nakata, *J. Org. Chem.* **28**, 1943 (1963).
[49] A. H. Corwin and K. J. Brunings, *J. Am. Chem. Soc.* **64**, 2106 (1942).

C, 53·65; H, 5·92; N, 6·59%.) The product was also found to have an IR spectrum identical with that of the authentic methene hydrobromide.

With 2-ethoxycarbonyl-4-methoxypyrrole (XI). HBr (1 ml) was added to a warm 95% EtOH soln (7·2 ml) of IX (0·3672 g) and XI (0·3377 g) and the mixture was heated on a steam bath. Maroon crystals with a blue reflex formed during this period resulting in bumping and some mechanical loss. Compound Xb (0·2216 g, 55%), bulk m.p. 211·0–215·0° (dec) was collected after washing with 95% EtOH. Recrystallization from chloroform–cyclohexene gave crystals m.p. 216·0–216·5° (dec), which showed the correct IR spectrum.

Acid catalyzed deformylation of pyrrolealdehydes

2-Formyl-3,5-dimethyl-4-ethylpyrrole (VIII). A soln of VIII (0·5 g) and HBr (1·0 g) in abs EtOH (10 ml) was boiled under reflux for 15 min. The mixture was then distilled using a small fractionating column and the distillate (2 ml, b.p. 50–65°) was analyzed by gas chromatography (Carbowax column). Two peaks were recorded. Authentic mixtures of ethyl formate and 95% EtOH were similarly chromatographed, both alone and admixed with the above distillate. In each case only the same two peaks were observed. The compound from the distillate which was first eluted from the chromatograph was collected in a trap containing CCl_4 cooled in a Dry Ice–acetone bath. After allowing the resulting soln to warm to room temp, the IR spectrum was recorded using a 1-mm cell with NaCl windows. This spectrum [2985 (m), 2915 (m), 1725 (s), 1186 (s) and 1155 cm^{-1} (s)] was superimposable on one obtained from an authentic sample of ethyl formate in the same solvent.

The deformylation reaction mixture was evaporated to half its volume, refrigerated, and the brown crystals (0·48 g, 86%) which separated were filtered off and recrystallized from chloroform–hexane to yield the hydrobromide of Xa, m.p. 249·0–250·0° (dec) with some decomposition setting in at 210·0°. (Found: C, 60·62; H, 7·02; N, 8·15. Calc. for $C_{13}H_{25}BrN_2$: C, 60·53; H, 7·47; N, 8·31%.) The IR spectrum of these crystals (Nujol mull) was superimposable on one from a sample, m.p. 249–250° (dec), made by the reaction of 3-ethyl-2,4-dimethylpyrrole with 2-formyl-3,5-dimethyl-4-ethylpyrrole in the presence of 48% HBr.

2-Formyl-3,5-dimethyl-4-ethoxycarbonylpyrrole (IX). This experiment was carried out in a manner identical to the above starting with IX (0·5 g). Besides the identification of ethyl formate, the hydrobromide of Xb (0·34 g, 65%) was obtained, which after recrystallization from chloroform–hexane (charcoal) melted at 208·0–210·0° (dec) and has an IR spectrum identical with that of an authentic sample.

2-Formylpyrrole. This experiment was identical to the above run except that the ethyl formate was identified only by its retention time on the gas chromatograph. The residue from the reaction mixture was an intractable black tar.

2-(3-Methoxy-5-ethoxycarbonylpyrrol-2-yl)methylene-3,5-dimethyl-4-ethyl-2H-pyrrolenine hydrochloride (XIII)

To a soln of XII (0·1985 g) and cryptopyrrole (0·1279 g) in chloroform (3 ml) there was added dropwise a solution of dry HCl (3·9) in anhydrous Et_2O (0·5 ml). The mixture rapidly became dark orange-red in color and after standing at room temp for about 5 min it was evaporated to dryness at reduced press. The residue was crystallized from a mixture of chloroform and cyclohexane yielding 2-(3-methoxy-5-ethoxycarbonylpyrrol-2-yl)-methylene-3,5-dimethyl-4-ethyl-2H-pyrrolenine hydrochloride (0·189 g, 55%), m.p. 158·0–160·0° (dec). A recrystallized sample of the methene melted at 159·0–159·5° (dec). The methene appears as very dark greenish-blue crystals to the naked eye. A microscopic examination of the crystals reveals blades which appear orange or green depending upon orientation in the light. (Found: C, 59·42; H, 6·89. $C_{17}H_{23}ClN_2O_3$ requires: C, 60·26; H, 6·84%.)