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Preparation and Properties of Ternary Iminium Salts of Pyrrole Aldehydes and Ketones. Synthesis of 4-Substituted Pyrrole-2-carboxaldehydes

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Ternary iminium salts were readily prepared from pyrrole aldehydes and methyl pyrryl ketones. Reaction of 1-(pyrrol-2-ylmethylene)pyrrolidinium perchlorate (1) with 1–3 equiv of bromine provides, after hydrolysis, 4-bromo-, 4,5-dibromo-, and 3,4,5-tribromopyrrole-2-carboxaldehydes. Reaction of 1 with sulfuryl chloride, acyl chlorides, and dichloromethyl methyl ether was found useful in preparing 4-chloro-, 4-acyl-, and 4-formylpyrrole-2-carboxaldehydes relatively free of 5 isomers. Conversion of acylated aldehydes to 3-acyl- and 3-alkylpyrroles is described.

The synthesis of β-substituted pyrroles is generally accomplished by ring closures, alkylations and acylations of metallopyrroles, and electrophilic substitution upon pyrroles bearing an electronegative substituent on the α position.[1] The first method is limited by the availability of suitably constituted acyclic precursors, while the other two methods are limited by concurrent and consecutive substitution reactions.

Our interest in preparing isoprenoid heterocyclics for screening as mimics of insect juvenile hormones led us to consider using an α substituent with a formal positive charge as a meta-directing group for electrophilic substitution on the pyrrole ring. We recently reported[2] that bromination of 1-(pyrrol-2-ylmethylene)pyrrolidinium perchlorate (**1**) at 0° gave a monobrominated product, **2**, in high yield. Conversion of this salt to 4-bromopyrrole-2-carboxaldehyde (**3**) with aqueous $NaHCO_3$ also proceeded in high yield. The product contained only ~0.5% of the 5-bromo aldehyde as inferred by glpc. We now report the preparation and physical properties of such ternary iminium salts and the investigation of the synthetic utility of **1** using some of the common electrophilic substitution reactions.

Preparation and Properties of the Salts.—Leonard and Paukstelis[3] described the preparations and properties of ternary iminium perchlorates from a variety of aldehydes and ketones. Some of the condensations they reported proceeded spontaneously with evolution of heat, whereas others required the removal of water to drive them to completion. The salts (Table I) were prepared under forcing conditions (benzene, reflux).[3] It was possible to prepare the pyrrolidinium perchlorate and use it directly in the condensation step. However, it was necessary to ensure alkalinity by adding a few drops of pyrrolidine prior to the condensation step in order to promote the condensation and to reduce the color of the product. Phenyl pyrryl ketones did not react with pyrrolidinium perchlorate under these conditions.

TABLE I

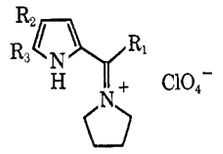
CHARACTERIZATION OF SALTS[a]

Compd	Yield, %	Mp, °C[b]	Spectral data[c]
1	>95	101–102.5	ir 3240, 1643 cm^{-1};[d] uv sh 260 (4.01), 289 (4.32);[e] nmr ref 2
6	9.5[f]	111–112	ir 3250, 1597; uv sh 273 (3.57), 323 (4.42)
7	90	155–157	ir 3200, 1712, 1643; uv 233 (4.11), 294 (4.23), 336 (3.97), sh 358 (3.45)
8	86	187–188	ir 3220, 1710, 1596; uv 238 (4.01), sh 297 (3.98), 332 (4.38), sh 354 (3.47)
9	86	209–211	ir 3350, 1717, 1640
10	90	256–258	ir 3430, 1620; uv 243 (4.21), 262 (4.13), 293 (4.17), sh 343 (2.80)

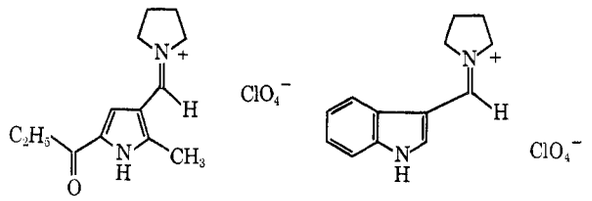
[a] Analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Satisfactory analytical data (±0.4% for C, H, N, Br, Cl, and I) were reported for all new compounds listed in the table: Ed. [b] Melting points were obtained with a Fisher-Johns apparatus and are uncorrected. [c] Infrared spectra were determined with Perkin-Elmer Models 137 and 521 infrared spectrophotometers; ultraviolet spectra were obtained in ethanol with a Carey 14 recording spectrophotometer; and nmr spectra were obtained with Varian T-60 and HA-100-A instruments. Chemical shifts are given in parts per million from TMS. Piperidine was added to facilitate NH exchange. [d] 1% in ethylene dichloride. [e] λ_{max}, mμ (log ε). [f] Recovered 65.3% of the ketone after 2-hr reflux in benzene.

The infrared spectra of the salts, taken as 1% solu-

(1) (a) K. Schofield, "Heteroaromatic Nitrogen Compounds. Pyrroles and Pyridines," Butterworths, London, 1967. (b) A. J. Castro, W. G. Duncan, and A. K. Leong, *J. Amer. Chem. Soc.*, **91**, 4304 (1969).
(2) P. E. Sonnet, *J. Org. Chem.*, **36**, 1005 (1971).
(3) N. J. Leonard and J. V. Paukstelis, *ibid.*, **28**, 3021 (1963).



Compd	R_1	R_2	R_3
1	H	H	H
6	CH_3	H	H
7	H	$CO_2C_2H_5$	CH_3
8	CH_3	$CO_2C_2H_5$	CH_3



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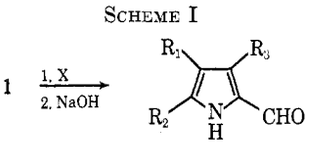
tions in ethylene dichloride, exhibited broad NH absorption due to hydrogen bonding. A comparison of the positions of the bands for compounds **1**, **6**, **7**, and **8** indicates that the carbethoxy groups in **7** and **8** increase the acidity of these two compounds, as evidenced by stronger hydrogen bonding. The C=N band is unaffected by its position on the ring or the presence of a carbethoxy group and appears at 1640–1643 cm^{-1} for PyCH=N<$^+$ and 1596–1597 cm^{-1} for PyC(CH_3)=N<$^+$.

Halogenation.—Treatment of **1** with 2 equiv of bromine followed by hydrolysis produced the 4,5-dibromo compound **11** (Scheme I, Table II). Nmr

SCHEME I



11–17

	X	R^1	R^2	R^3
11	$2Br_2$	Br	Br	H
12	$3Br_2$	Br	Br	Br
13	SO_2Cl_2	Cl	H	H
14	$2SO_2Cl_2$	Cl	Cl	H
15	SO_2Cl_2, then Br_2	Cl	Br	H
16	Br_2, then SO_2Cl_2	Br	Cl	H
17	$Tl(TFA)_3$, then KI	I	H	H

documented the loss of H-5 and a change in multiplicity of the aldehyde proton from the doublet of **3** caused by long-range splitting (J_{CHO-5} = 1.0 Hz) to a sharp singlet. The third equivalent of bromine reacted with the dibromo salt in refluxing acetic acid, and the tribromo compound, **12**, was obtained therefrom by hydrolysis.

The corresponding salt of furfural[3] was recovered unchanged after treatment with 1 equiv of bromine (ethylene dichloride, 24-hr reflux, and acetic acid, 3-hr reflux). This illustrated the deactivation of the furan ring by the positively charged substituent.

The reaction of sulfuryl chloride with pyrrole-2-carboxyaldehyde reportedly gave a complex mixture from which a 9% yield of the 5-chloro compound was obtained.[4] Sulfuryl chloride reacted with **1** in ethylene dichloride to produce the 4-chloride **13** in good yield contaminated by small amounts of the 4,5-dichloride

(4) P. Hodge and R. W. Rickards, *J. Chem. Soc.*, 459 (1965).

TABLE II

CHARACTERIZATION OF OTHER NEW COMPOUNDS[a]

Compd	Yield, %	Mp, °C	Spectral data
3	92	122.5–124.5	ir 3460, 1671; uv 253 (3.85), 298 (4.10)
11	>95	158–159.5	ir 3443, 3210, 1671; uv 250 (3.72), 303 (4.18); nmr (3:1 $CDCl_3$–DMSO-d_6) δ 6.92 (s, H-3), 9.43 (s, CHO)
12	>95	202 dec	ir 3432, ~3180, 1666; uv sh 270 (3.73), 308 (4.21); nmr (3:1 $CDCl_3$–DMSO-d_6) δ 9.52 (s, CHO)
13	82	129–129.5	ir 3467, 3260, 1672; uv 252 (3.84), 302 (4.16); nmr (3:1 $CDCl_3$–DMSO-d_6) δ 6.90 (d, J = 1.5 Hz, H-3), 7.12 (b s, H-5), 9.53 (b s, CHO)
14	85	143.5–145	ir 3444, 3210, 1671; uv 252 (3.61), 302 (3.70); nmr (3:1 $CDCl_3$DMSO-d_6) δ 6.93 (s, H-3), 9.47 (s, CHO)
15	71	149.5–150	ir 3444, 3190, 1670; uv 250 (3.68), 303 (4.20); nmr DMSO-d_6) δ 7.17 (s, H-3), 9.48 (s, CHO)
16	71[b]	148–149.5	ir 3445, 3200, 1671; uv 250 (3.71), 302 (4.18); nmr DMSO-d_6) δ 7.18 (s, H-3), 9.48 (s, CHO)
17	27	118–120	ir 3460, 3270, 1670; uv 257 (3.95), 303 (4.07); nmr (3:1 $CDCl_3$–DMSO-d_6) δ 7.03 (d, J = 1.4 Hz, H-3), 7.15 (b s, H-5) 9.55 (b s, CHO)
18	48[c]	70.5–71.5	ir 3210, 1630;[d] nmr ($CDCl_3$) δ 7.41 (m, H-2), 6.68 (m, H-4), 6.77 (m, H-5)[e]
19	89[c]	99.5–101.5	ir 3130, 1670;[d] nmr (3:1 $CDCl_3$–DMSO-d_6) δ 7.37 (m, H-2), 7.73 (m, H-5), 9.63 (b s, CHO)[e]
20	74[c]	81.5–83	ir 3150, 1630;[d] nmr (CCl_4) δ 6.58 (m, H-4), 6.75 (m, H-5), 7.45 (m, H-2)[e]
21	33[c]	59.5–60.5	ir 3150, 1620;[d] nmr (CCl_4) δ 6.58 (m, H-4), 6.75 (m, H-5), 7.45 (m, H-2)[e]
22	53[f]		ir 3380, 772, 704;[d,g] nmr (CCl_4) δ 5.95 (m, H-4), 6.37 (m, H-2), 6.48 (m, H-5)[e]
23	51[f]		ir 3380, 772, 707[d,g]
24	50[h]	160–162	ir 1690;[d] nmr (DMSO-d_6) δ 7.42 (s, H-3), 11.33 (b s, CO_2H, NH)[e]

[a] Footnotes *a–f* of Table I apply to this table except that infrared spectra were obtained as 10^{-3} M solutions in CCl_4. [b] All yields are of crude product which were generally >90% of the stated compound. In this case, **16** comprised ~58% of the crude product by glpc. [c] Yield calculated from **1**. [d] Nujol mull; values approximate. [e] No piperidine added to this solution. [f] Yield calculated from the ketone. [g] Infrared bands characteristic of 3-alkylpyrroles; ref 18. [h] Yield calculated from **1** after recrystallization from toluene.

and a material, probably the 5 isomer, showing a lesser retention time by glpc than **13**. Substitution in the 4 position was typically verified with the nmr spectral data, which showed the aldehyde proton split into a doublet and coupling of the remaining aryl protons of

the magnitude expected for cross-ring coupling.[5] Compound **14**, the dichloride, was easily prepared using 2 equiv of sulfuryl chloride, but the trichloroaldehyde could not be formed in refluxing ethylene dichloride.

Although the mixed dihalides **15** and **16** were successfully prepared, such reactions may incur displacement and rearrangement,[6,7] and the investigator is sometimes challenged with products that occur in the reaction mixtures as complexes[8] or have very similar physical properties which would thwart assignment of structure.[7a] When **1** was first chlorinated and then brominated, the crude product was primarily a mixed dihalide showing a glpc peak well separated from contaminants of shorter retention times, the principle one being the monochloropyrrole **13**. The sharp melting point of the purified dihalide and its glpc retention time suggested that it was a single compound and a simple pyrrole derivative to which we assigned the structure **15**.

Bromination of **1** followed by chlorination produced a mixed dihalide plus the 4,5-dibromide **11**, with the latter predominating. When the intermediate brominated salt was stripped of HBr and the reaction mixture was reconstituted with fresh solvent prior to the addition of sulfuryl chloride, the product was free of **11** and consisted mainly of a mixed dihalide with essentially the same melting point as **15** (undepressed on admixture) and its nmr and uv spectral properties as well as its glpc behavior were indistinguishable from those of **15**. However, the infrared spectra (Nujol mull and $CHCl_3$) showed a small but significant difference, namely, **15**, 993 and 997 cm^{-1}; **16**, 993 and 1002 cm^{-1}. In addition, the formation of **16** was almost completely inhibited by the addition of 2,6-diisopropylphenol in the chlorination step. Although dichlorination of **1** can be achieved at room temperature in ethylene dichloride, chlorination of the 4-brominated salt was much slower and, in fact, proceeded only to a slight extent in acetonitrile (64 hr). Thus the chlorination of the 4-brominated salt was apparently a free-radical reaction. Since reaction of a radical is expected to occur at position 5 on a pyrrole substituted in the 2 position with an electronegative substitutent,[8] this evidence of a radical pathway lends support to structure **16** (rather than rearrangement to **15**) for this dihalide.

Iodinations of **1** with iodine in acetic acid or iodic acid[9] were unsuccessful. The 4-iodopyrrole-2-carboxaldehyde **17** was prepared, albeit in low yield, by treatment with $Tl(TFA)_3$[10] followed by KI.

Spectra of the haloaldehydes in dilute solution revealed both free and intramolecularly hydrogen bonded NH stretching modes. In general a β halogen lowered the free NH band to 3460–3467 cm^{-1}, α plus β halogens shifted this band to 3443–3445 cm^{-1}, and the third halogen displaced it a like amount to 3432 cm^{-1}. The presence of halogen atoms has been reported to increase the acidity of pyrroles,[4] and the considerably greater power of an electronegative substituent (*e.g.*, NO_2) in the α position has been made the basis of the chemical separation of isomers.[11] The stretching frequencies of the hydrogen-bonded NH of these haloaldehydes underscored this fact. Each of the three 4-haloaldehydes, **3**, **13**, and **17**, absorbed most intensely at ~3260–3270 cm^{-1}. The 4,5-dihaloaldehydes and the tribromoaldehyde absorbed at ~3180–3210 cm^{-1}. The uv spectra of these compounds, excepting **12**, were all very similar. The 250-mμ band was shifted to 270 mμ in the tribromoaldehyde **12**. This band was seen at 265 mμ with 3,4-dichloropyrrole-2-carboxaldehyde.[8] A tentative explanation for this is a resonance interaction between the formyl group and the electron-donating ortho bromine atom. Such interaction is well documented for para-disubstituted benzene rings.[12]

Acylation.—The Friedel–Crafts alkylation of pyrrole-2-carboxyaldehyde with isopropyl bromide was reported to proceed cleanly to 4-isopropylpyrrole-2-carboxaldehyde in high yield.[13] We turned our attention, therefore, to acylation reactions instead. The acetylation of **1** has been reported to occur with greater success than the analogous reaction of pyrrole-2-carboxaldehyde.[2] The acetylated aldehyde was converted in good yield to the acid by oxidation with Ag_2O. An improvement in the method of decarboxylation would make this an excellent route for β-acylpyrroles. In fact, 3-palmitoylpyrrole (**18**) was prepared in greater than 40% yield from pyrrole. Acylation of **1** with palmitoyl chloride and oxidation of the resulting 4-palmitoylpyrrole-2-carboxaldehyde (**19**) to the acid proceeded well with some modification necessitated by the low solubility of **19**. The acid melted at 182–184° with gas evolution, and the decarboxylation was carried out easily at ~190–200°. Similarly, isopentyl pyrrol-3-yl ketone (**20**) (the nitrogen analog of perilla ketone[14]) and 3,7-dimethyloctyl pyrrol-3-yl ketone (**21**) were prepared. An attempt to improve the yield of methylpyrrol-3-yl ketone by heating the acid *in vacuo* at ~190–200° resulted in sublimation of the unreacted acid. The longer chains of the other acids lower their melting points considerably. Apparently a melt or its equivalent in molecular mobility is necessary for the decarboxylation. Because we were interested in screening the corresponding β-alkylpyrroles, **20** and **21** were reduced with $LiAlH_4$ to produce the air-sensitive **22** and **23**, respectively (Scheme II).

Acylation of **1** with α-methyl-$\Delta^{1,\alpha}$-cyclohexaneacetyl chloride failed. Reaction of the corresponding acid[15] with $SiCl_4$ followed by addition of **1** and $SnCl_4$, a method which successfully produced thiophenes with unsaturated isoprenoid side chains,[16] likewise failed. In both cases the infrared spectra of the crude products indicated that considerable γ-lactone had formed.

Formylation.—When **1** was subjected to the Vilsmeier–Haack formylation procedure there was es-

(5) S. Gronowitz, A. B. Hörnfeldt, B. Gestblom, and R. A. Hoffman, *Ark. Kemi*, **18**, 133 (1961).

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(9) H. O. Wirth, O. Konigstein, and W. Kern, *Justus Liebigs Ann. Chem.*, **634**, 84 (1960).

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(11) T. J. Rinkes, *Recl. Trav. Chim. Pays-Bas*, **53**, 1167 (1934).

(12) H. H. Jaffe and M. Orchin, "Theory and Applications of Ultraviolet Spectroscopy," Wiley, New York, N. Y., 1962, p 259.

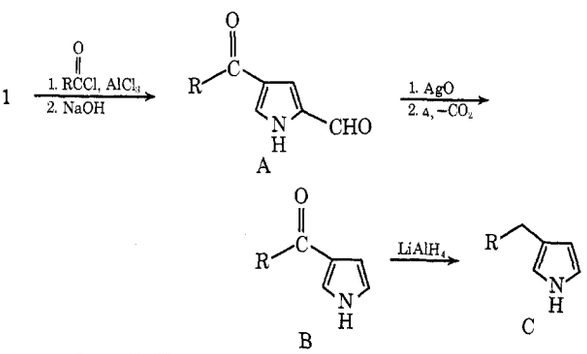
(13) H. J. Anderson and L. C. Hopkins, *Can. J. Chem.*, **44**, 1831 (1966).

(14) Y. Arata and K. Achiwa, *Kanazawa Daigaku Yakugakubu Kenkyu Nempo*, **8**, 29 (1958); *Chem. Abstr.*, **53**, 5228 (1959).

(15) H. S. Corey, Jr., J. R. D. McCormick, and W. E. Swenson, *J. Amer. Chem. Soc.*, **86**, 1884 (1964).

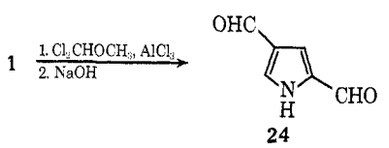
(16) Y. Yuryev, G. B. Elyakov, N. S. Zefirov, and A. N. Vysokosof, *J. Gen. Chem. USSR*, **26**, 3717 (1956).

SCHEME II



A, 19, R = $C_{15}H_{31}$
B, 18, R = $C_{15}H_{31}$
20, R = $CH_3CH(CH_3)CH_2CH_2$–
21, R = $CH_3CH(CH_3)CH_2CH_2CH_2CH(CH_3)CH_2CH_2$–
C, 22, R = $CH_3CH(CH_3)CH_2CH_2$–
23, R = $CH_3CH(CH_3)CH_2CH_2CH_2CH(CH_3)CH_2CH_2$–

sentially no reaction. The Friedel–Crafts formylation using dichloromethyl methyl ether and $AlCl_3$ gave yields of 40–50% of pyrrole-2,4-dicarboxaldehyde (**24**).[17] Other Lewis acid catalysts ($ZnCl_2$, $SnCl_4$, $BF_3 \cdot Et_2O$) provided only tars and unchanged starting aldehyde.



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Nitration.—The nitration of pyrrole-2-carboxaldehyde with acetyl nitrate has been described.[18] We found that nitration of this aldehyde with concentrated HNO_3 produced a greater quantity of crude product and the relative amounts of 4 and 5 isomers was 64:36 at −2°. The reaction of **1** under these conditions was much slower, but the ratio of mononitration products was not materially changed (67:33). The corresponding salt of the weaker base morpholine gave an even slower reaction producing a 64:36 product ratio. Evidently the salts are hydrolyzed to the aldehyde and it is this species which is nitrated. Reaction of the aldehyde with concentrated HNO_3 at −20° increased the ratio of 4:5 to 75:25.

Treatment of the aldehyde with acetyl nitrate at −2° in our hands gave a ratio of 37:63, indicating that protonation of the aldehyde in concentrated HNO_3 was responsible for a greater percentage of 4 isomer in the nitration product obtained therefrom. Nitration of benzaldehyde, for example, produces 72% *m*-nitrobenzaldehyde from fuming HNO_3 and 91% from oleum.[19] A nitration of pyrrole-2-carboxaldehyde in oleum resulted in a fire. Compound **1**, however, was converted to a dinitropyrrole-2-carboxaldehyde, which was characterized as the corresponding carboxylic acid, **24**. The assignment of the 4,5-dinitro structure is by analogy with the other electrophilic substitutions discussed. Apparently the salt is nitrated (it cannot hydrolyze to aldehyde first), but under these conditions dinitration occurs.

Miscellaneous Reactions.—Compound **1** gave no reaction under the usual conditions of the Mannich reaction,[20] nor did it react with formaldehyde under the influence of acid in ethanol to produce either a dipyrrylmethane or an alkoxymethylpyrrole. Moreover, **1** did not react with pyrrole (the production of a Mannich base, dipyrrolylmethane, was attempted). Both oxalyl chloride and phosgene failed to react with **1** in refluxing ethylene dichloride. Phosgenation with $AlCl_3$ produced tars, and phosgenation using *N*,*N*-dimethylaniline followed by treatment with methanol gave a crude mixture that probably contained primarily N-acylated material (1765 cm^{-1}). Chloromethylation with chloromethyl methyl ether and $AlCl_3$ gave only tarry material.

Summary.—The low reactivity of **1** limits electrophilic substitution reactions to only the more reactive electrophiles. However, considerably greater specificity for 4 substitution occurred as compared to analogous reactions of pyrrole-2-carboxaldehyde in the case of halogenation. Much better yields of acylation (4 isomer) and formylation (4 isomer) products can be obtained by using **1**. The iminium group is so deactivating that the salt derived from furfural could not be brominated.

The haloaldehydes may serve as sources of the otherwise not readily available halocarboxylic esters. These could serve as intermediates for the synthesis of, *e.g.*, pyoluteorin[21] and, in fact, we have found that the 4-haloaldehydes and corresponding methyl carboxylates are active as trail-marking chemicals for the Texas leaf-cutting ant, *Atta texana* (Buckley).[22] In addition the acylaldehydes are useful in preparing 3-acyl- and 3-alkylpyrroles.

Experimental Section

Gas chromatographic analyses were carried out with an Aerograph Model A-700 instrument employing principally an SE-30 column (5% on acid-washed Chromosorb W, 3.05 m × 0.32 cm) at 150–200°. Mention of a proprietary product in this paper does not constitute endorsement by USDA.

1-(Pyrrol-2-yl)ethylidenepyrrolidinium Perchlorate (6).—The preparation of 1 has been reported.[2] Typically, the methyl substituent slowed the condensation and an example of lowered yield and recovered starting material is given here. Pyrrolidinium perchlorate (0.02 mol), 0.02 mol of methyl pyrrol-2-yl ketone,[23] and 2 drops of pyrrolidine were heated under reflux in 50 ml of C_6H_6 for 2 hr using a Dean–Stark trap. The mixture was cooled and decanted, and the resiude was washed with Et_2O. Removal of the solvents from the washings yielded 1.4 g of the ketone. The residual oil was washed with H_2O, dissolved in ethylene dichloride, and dried (Na_2SO_4). Removal of solvent followed by crystallization from anhydrous Et_2O gave 0.50 g of **6**.

4,5-Dibromopyrrole-2-carboxaldehyde (11).—Bromine (1.60 g) in 10 ml of ethylene dichloride (EDC) was added dropwise to a solution of 1.25 g of 1 in 25 ml of EDC at 5–7°. The mixture was allowed to stand at room temperature overnight. The solvent was stripped to give the dibrominated salt, mp 158–159.5° (EDC). A mixture of 0.5 g of NaOH, 0.5 g of this salt, and 20 ml of EtOH (1:1) was swirled till homogeneous. After 1 hr, the mixture was acidified (HCl) and extracted with Et_2O; the extract was dried ($MgSO_4$) and concentrated to give 0.31 g of **11**.

3,4,5-Tribromopyrrole-2-carboxaldehyde (12).—The 4,5-dibromo salt (2.03 g) and 1 equiv of bromine were heated under re- the product was filtered with C_6H_6, giving 2.15 g (88.5%) of tribromo salt, mp ~245° dec (CH_3CN–Et_2O). A mixture of this salt (0.70 g), 0.50 g of NaOH, and 20 ml of EtOH–H_2O (1:1) was heated until the mixture became homogeneous (~10 min),

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(19) P. B. D. DeLaMare and J. H. Ridd, "Aromatic Substitution," Academic Press, New York, N. Y., 1959, p 83.
(20) W. Herz and U. Toggweiler, *J. Org. Chem.*, **29**, 213 (1964).
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(22) P. E. Sonnet and J. C. Moser, results to be published elsewhere.
(23) P. S. Skell and C. P. Bean, *J. Amer. Chem. Soc.*, **84**, 4655 (1962).

cooled to room temperature, and then worked up as described for **11**. The yield of **12** was 0.48 g.

4-Chloropyrrole-2-carboxaldehyde (13) and 4,5-Dichloropyrrole-2-carboxaldehyde (14).—The procedures for preparing these compounds were analogous to those employed for the bromo aldehydes, except that the sulfuryl chloride was substituted for bromine. The monochlorinated salt melted at 126–128° (EDC–Et_2O) and the dichloro salt at 209–214° (EDC–Et_2O).

5-Bromo-4-chloropyrrole-2-carboxaldehyde (15).—Chlorination was carried out on **1** in the usual way. After 1 hr the mixture was cooled and 1 equiv of bromine in EDC was added. The mixture was stirred overnight at ambient temperature and the product was hydrolyzed in the usual manner. Recrystallization twice from C_6H_6–petroleum ether (bp 30–60°) gave the product, mp 149.5–150°.

4-Bromo-5-chloropyrrole-2-carboxaldehyde (16).—The procedure was as for **15** except that the addition of halogenators was reversed and the intermediate bromo salt was freed of HBr by stripping the solvent. After hydrolysis the crude product was analyzed by glpc as 58% **16**, with the remainder mainly 4-bromo aldehyde. The crude product (1.6 g) was placed on 5 g of alumina and added to a 48-g column of alumina in C_6H_6–petroleum ether (1:1). The 4-bromoaldehyde (0.15 g) was obtained by elution with C_6H_6–Et_2O. The dihalide **16** was obtained with EtOAc–Et_2O and, finally, MeOH–C_6H_6 and weighed (0.80 g). Recrystallization twice from C_6H_6 gave product of 91% purity (glpc), mp 148.5–149.5°.

4-Iodopyrrole-2-carboxaldehyde (17).—To a suspension of 1.25 g of **1** in 10 ml of TFA was added 7.2 g of $Tl(TFA)_3$[10] and the mixture was heated under reflux overnight. The mixture was cooled and stripped of solvent. The product was treated with 6.5 g of KI in 25 ml of H_2O. After 15 min some $KHSO_3$ was added and the mixture was made alkaline with aqueous NaOH and filtered. The orange solid obtained was warmed on a steam bath with 1 g of NaOH in 10 ml each of H_2O and EtOH for 40 min. The mixture was cooled, filtered, acidified with HCl, and extracted with Et_2O. The extract was dried ($MgSO_4$) and concentrated to give 0.3 g of **17**. The glpc analysis revealed a minor component of low retention which may be the 5 isomer.

4-Palmitoylpyrrole-2-carboxaldehyde (19) and Similar Acylations of 1.—To a solution of 1.25 g of **1** in 25 ml of EDC was added 1.47 g of $AlCl_3$. To the resulting violet solution, cooled to 0°, was added 1.27 g of palmitoyl chloride in 5 ml of EDC. The mixture was kept at 0° overnight and then poured over crushed ice; 20 ml of H_2O containing 1 g of NaOH was added thereto, and the mixture was stirred vigorously for 15 min. It was then acidified (HCl) and extracted with $CHCl_3$. The extract was washed to neutrality, dried ($MgSO_4$), and concentrated, giving 1.48 g of **19**. Acylations of **1** with 4-methylvaleryl chloride and 4,8-dimethylnonanoyl chloride were carried out in a similar manner. The oily keto aldehydes obtained were oxidized directly to keto acids.

4-Palmitoylpyrrole-2-carboxylic Acid and Similar Oxidations of 4-Acylpyrrole-2-carboxaldehydes.—The crude aldehyde obtained above (2.96 g) was dissolved in 100 ml of EtOH to which was added a solution of 2.50 g of $AgNO_3$ in 35 ml of H_2O. The mixture was heated under reflux and a solution of 7.1 g of NaOH in 75 ml of H_2O was added in a slow stream. The mixture was heated for 1 hr with vigorous stirring and filtered by suction, and the precipitate was washed with H_2O. The filtrate was diluted with two volumes of H_2O and acidified (HCl). The crystalline acid (2.44 g) was collected by filtration, mp 182–184° dec (EtOH). Oxidations of the other keto aldehydes were carried out in the same way to give the crystalline acids: 4-(4-methylvaleroyl)pyrrole-2-carboxylic acid, mp 213–213.5° (aqueous EtOH), and 4-(4,8-dimethylnonanoyl)pyrrole-2-carboxylic acid, mp 181–183° (aqueous EtOH).

3-Palmitoylpyrrole (Pentadecyl Pyrrol-3-yl Ketone) (18) and Decarboxylations of 4-Acylpyrrole-2-carboxylic Acids to 20 and 21.—The 4-palmitoylpyrrole-2-carboxylic acid (2.0 g) was heated under N_2 at 190–200° with magnetic stirring for 5 hr. The mixture was cooled and extracted with hot benzene and the extract was filtered and stripped. The residue was recrystallized from hexane to give 1.30 g of **18**. Decarboxylation of 4-(4-methylvaleroylpyrrole-2-carboxylic acid (486 mg) was acflux in 20 ml of AcOH for 2.5 hr. The AcOH was stripped and complished by heating to melting (~215°) at 1 mm. After 1.25 hr, 325 mg of **20** was obtained from the condenser. Another 17 mg was obtained by working up the pot residue as above. Decarboxylation of 4-(4,8-dimethylnonanoyl)pyrrole-2-carboxylic acid was best conducted at atmospheric pressure. The product, however, was purified by passage through alumina with hexane–Et_2O; only 1.64 g of **21** was obtained from 5.00 g of the acid.

Reductions of 3-Acylpyrroles to 3-Alkylpyrroles 22 and 23.—The acylpyrrole **20** (1.24 g) was added in portions to a slurry of 0.5 g of $LiAlH_4$ in 40 ml of anhydrous Et_2O. The mixture was heated under reflux for 45 min and then worked up in the usual way. The product was subjected to short-path distillation, bp 58–60° (0.15 mm), 0.60 g (53%). Similarly, **21** was converted to **23**. The crude product was purified by distillation in a Hickman still, bath temperature 120–130° (0.05 mm), yield 51%.

Pyrrole-2,4-dicarboxaldehyde (24).—To a solution of **1** (1.25 g) and $AlCl_3$ (1.47 g) in 20 ml of EDC kept at 0° was added 0.86 g of Cl_2CHOCH_3. The mixture was stirred without cooling for 0.5 hr, decomposed with ice, and made alkaline with aqueus NaOH; after 5 min of vigorous stirring, it was acidified (HCl) and extracted continuously with ether for 16 hr. The crude product was dissolved in EtOAc and filtered through 10 g of alumina to give 0.26 g (43%) of **24**, mp 154° (lit.[17] mp 151.5–152°). The glpc trace showed this material to be virtually free of any isomer of lesser retention time, *i.e.*, 2,5-dialdehyde.

Nitration of 1 with Concentrated HNO_3.—The salt **1** (1.25 g) was added in portions to 20 ml of concentrated HNO_3 cooled to 0° and stirred magnetically. The mixture became homogeneous in ~15 min and was then stored at −20° overnight. The mixture was poured over ice and made alkaline with aqueous NaOH, and after 5 min was acidified (HCl) and extracted continuously with Et_2O for 5 hr. The solvent was stripped from the extract and the crude product was extracted with hot benzene. Removal of the benzene left 0.53 g of red solid. Recrystallization from benzene gave a product showing two glpc peaks (see text). Several preparations were combined and submitted to column chromatography using Brockman neutral alumina, activity I. Material corresponding to the longer retention glpc peak was eluted with Et_2O–C_6H_6. It was identical (glpc, ir) with a known sample of 4-nitroaldehyde, mp 140–141.5° (lit. mp 142°)[24] with no depression on admixture with an authentic sample.[25] A sample of the shorter retention component was obtained by elution with EtOAc–Et_2O, mp 181.5–183° (lit. mp 185°).[23]

Nitration of 1 in Oleum.—The salt **1** (5.0 g) was added in small portions to a vigorously stirred solution of 2 g of 90% HNO_3 in 9 ml of 30% SO_3–H_2SO_4 kept at <0° under N. The amber solution was stored at −2° for 16 hr. The mixture was poured over crushed ice and filtered to give 4.5 g of yellow solid. The aldehyde could not be freed of pyrrolidine and so this product (a salt) was oxidized directly to the acid **24**. The yellow solid, 1 g, was added to 220 ml of 1 *N* NaOH, and a solution of 1.1 g of $AgNO_3$ in 100 ml of H_2O was added thereto. The mixture was warmed to 40° and stirred for 0.5 hr. The mixture was filtered, brought to neutrality with dilute HCl, and extracted continuously with Et_2O for 16 hr. The extract was dried ($MgSO_4$) and concentrated to a yellow-brown solid (0.7 g). Extraction of this material with toluene gave 0.45 g of **24**, mp 160–162°.

Registry No.—**1**, 27521-94-4; **1** (dibromo derivative), 33515-46-7; **1** (tribromo derivative), 33515-47-8; **1** (monochloro derivative), 33515-48-9; **1** (dichloro derivative), 33515-49-0; **3**, 931-33-9; **6**, 33515-51-4; **7**, 33515-52-5; **8**, 33515-53-6; **9**, 33515-54-7; **10**, 33515-55-8; **11**, 932-82-1; **12**, 33515-57-0; **13**, 33515-58-1; **14**, 33515-59-2; **15**, 33515-60-5; **16**, 33515-61-6; **17**, 33515-62-7; **18**, 33515-63-8; **19**, 33578-91-5; **20**, 33515-64-9; **21**, 33545-28-7; **22**, 33515-65-0; **23**, 33515-66-1; **24**, 23999-91-9; 4-palmitoylpyrrole-2-carboxylic acid, 33515-68-3; 4-(4-methylvaleroyl)pyrrole-2-carboxylic acid, 33515-69-4; 4-(4,8-dimethylnonanoyl)pyrrole-2-carboxylic acid, 33515-70-7.

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