crystallize, therefore it was converted to the hydrochloride before analysis. The hydrochloride required 5 recrystallizations from absolute ethanol before a reasonable degree of purity was achieved. The melting point was 219–220° (dec.).

Anal. Calcd. for $C_{12}H_{28}N_4Cl_2O_2$: C, 43.5; H, 8.4; N, 16.9; Cl, 21.4. Found: C, 43.3; H, 8.2; N, 16.8; Cl, 21.7.

sym-Bis(3-methoxypropyl)oxamidine from 3-methoxypropylamine. A solution of 75 g. (0.833 mole) of 3-methoxypropylamine in 175 ml. of ethanol was treated with 19 g. (0.365 mole) of cyanogen. The yield of crude crystals was 54.5 g. (64.4% based on cyanogen). After recrystallization from ethanol with Norit the solid melted at 89–91°.

Anal. Calcd. for $C_{10}H_{22}N_4O_2$: C, 52.1; H, 9.5; N, 24.3. Found: C, 52.0; H, 9.1; N, 24.6.

The *hydrochloride* prepared as above, was recrystallized from ethanol and melted at 227–228° (dec.).

Anal. Calcd. for $C_{10}H_{24}N_4Cl_2O_2$: C, 39.9; H, 7.9; N, 18.4; Cl, 23.4. Found: C, 39.7; H, 7.7; N, 18.8; Cl, 23.7.

BUFFALO 14, N. Y.

[CONTRIBUTION NO. 487 FROM THE RESEARCH LABORATORIES OF HOFFMANN-LA ROCHE, INC.]

Syntheses in the Pyrrole Series

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A number of pyrryl ketones and their derivatives were prepared for screening for pharmacological and chemotherapeutic activity. For comparison purposes, some other related heterocyclic compounds were also prepared. A few of the pyrryl ketones, especially 3-propionylpyrrole, were active as muscle relaxants in the anti-strychnine test in mice and cats.

Extracts of Valerian root[1] (Valeriana officinalis) have been claimed to reduce blood pressure and have some cardiac and sedative action. The finding of 2-acetylpyrrole in such extracts,[2] and also the reported hypnotic activity of 2-isobutyl pyrryl ketone[3] suggested further examination of pyrrole ketones and related compounds in order to determine the range of their biological actions.

A number of new pyrrole ketones (Table I) were prepared and tested as muscle relaxants in the anti-strychnine[4] test in mice and cats. The following previously reported pyrrole ketones were also prepared using the Grignard reaction for comparison purposes: 2- and 3-propionylpyrroles, 1-methyl-2-propionylpyrrole, 2-pyrryl isobutyl ketone, 1-(2-pyrryl)-1,3-butadione, 2-furyl 2-pyrryl ketone, 2-phenylacetylpyrrole, 2,5-dimethyl-3-propionylpyrrole, and 2,5-dimethyl-3-acetylpyrrole. Although many of the pyrrole ketones exhibited some activity as muscle relaxants, 3-propionylpyrrole[5] only (m.p. 117°), was found to be of the order of Myanesin in this test, while interestingly, 2-propionylpyrrole (m.p. 54°) was inactive.

The reduction of 3-propionylpyrrole to 3-propylpyrrole, the partial reduction to α-ethyl-3-pyrrolemethanol, and methylation to yield 1-methyl-3-propionylpyrrole eliminated anti-strychnine activity.

The heterocyclic analogs of 3-propionylpyrrole, 3-propionylfuran, 3-propionylthiophene, and also 2-propionylpyrazine, were inactive in the anti-strychnine test. During the work on the *C*-propionylpyrroles, some errors in the literature were cleared up. 2-Propionylpyrrole readily formed the phenylhydrazone (m.p. 112–114°) but failed to yield a semicarbazone; while 3-propionylpyrrole gave a semicarbazone (m.p. 181°) but failed to yield a phenylhydrazone. Previous reports[6] on the ketone derivatives of *C*-propionylpyrroles undoubtedly described mixtures of the 2 and 3 isomers.

2-Propionylpyrrole yielded a hydrazone and oxime but 3-propionylpyrrole failed to give either.

The *C*-propionylpyrroles failed to react with acetylene in liquid ammonia using sodium, potassium, or lithium to yield the acetylenic alcohols. We were unable to prepare hydantoins or substituted glycidamides using a modified Darzens' reaction[7] with chloroacetamide. The failure of the modified Darzens' reaction is probably due to the acidic pyrrole hydrogen on the nitrogen.[8]

The mixed acycloins, α-hydroxybenzyl-2-pyrryl ketone, the 4-chlorbenzyl and the 2,4-dichlorbenzyl acycloins were prepared. The presence of a high band in the ultraviolet spectrum near 290 mμ (ε 16000) of the mixed acycloins suggested the possibility of an enediol structure. However, comparison with α-pyridoin[9] which is known to be a

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(8) M. E. Dullaghan and F. F. Nord, *J. Org. Chem.*, **17**, 1183 (1952).

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TABLE I

PYRRYL KETONES

Ketone	Formula	Cryst. from	M.P., °C.	Yield, %	Color	Analysis Calcd. N	Analysis Found N
4-Pyridyl 2-pyrryl	$C_{10}H_8N_2O$	Ethanol	127–128	6	Brown to purple	16.3	16.5[a]
4-Pyridyl 2-pyrryl hydrochloride	$C_{10}H_8N_2O\cdot HCl$	Ethanol	170–171	—	Greenish yellow	13.4	12.8
3-Pyridyl 2-pyrryl hydrochloride	$C_{10}H_8N_2O\cdot HCl$	Ethanol	187–188	[b]	Greyish green	13.4	13.3
2-Pyridyl 2-pyrryl hydrochloride	$C_{10}H_8N_2O\cdot HCl$	Ethanol + ether	>250	[c]	Violet	13.4	13.8[d]
2-Pyridyl 2,5-dimethyl-3-pyrryl	$C_{12}H_{12}N_2O$	Ethyl acetate–ether	118–120	20[e]	Yellow	14.0	13.3
2-Pyridyl 2,5-dimethyl-3-pyrryl hydrochloride	$C_{12}H_{12}N_2O\cdot HCl$	Ethyl acetate–pet. ether	208–210	—	Orange	11.8	11.1
3-Pyridyl 2,5-dimethyl-3-pyrryl	$C_{12}H_{12}N_2O$	Ethanol	166–168	12	Yellow	14.0	13.7
3-Pyridyl 2,5-dimethyl-3-pyrryl hydrochloride	$C_{12}H_{12}N_2O\cdot HCl$	Ethanol	203–204	—	Yellow	11.8	11.9
4-Pyridyl 2,5-dimethyl-3-pyrryl	$C_{12}H_{12}N_2O$	Ethanol	190–191	8	Light brown	14.0	13.7
4-Pyridyl 2,5-dimethyl-3-pyrryl hydrochloride	$C_{12}H_{12}N_2O$	Ethyl acetate–pet. ether	261–263	—	Orange	11.8	11.1
Diphenylmethyl 2-pyrryl	$C_{18}H_{15}NO$	Ether–pet. ether	104–106[f]	21	Colorless	5.4	5.9
Benzyl 2,5-dimethyl-3-pyrryl	$C_{14}H_{15}NO$	Ether–pet. ether	170–171	2	Light pink	6.6	6.4
Phenyl 2,5-dimethyl-3-pyrryl	$C_{12}H_{13}NO$	Ether–pet. ether	129–130	4	Yellow	7.0	6.9
2-Furyl 2,5-dimethyl-3-pyrryl	$C_{11}H_{11}NO_2$	Ether–pet. ether	96–97[g]	36	Light brown	7.4	7.2
Isobutyl 2,5-dimethyl-3-pyrryl	$C_{11}H_{17}NO$	Ether–pet. ether	90–91[h]	47	Light pink	7.8	7.4
Diphenylmethyl 2,5-dimethyl-3-pyrryl	$C_{20}H_{19}NO$	Ether	163–164	2	Light cream	4.9	4.9
2-Thienyl 2,5-dimethyl-3-pyrryl	$C_{11}H_{11}NOS$	Water or ether–pet. ether	110–112	19	Tan	[i]	
5-Methyl-3-isoxazolyl 2-pyrryl	$C_9H_8N_2O_2$	Ether	103–104	5	Yellowish red	15.9	15.6
4-Chlorophenyl 2-pyrryl	$C_{11}H_8ClNO$	Ether	110–111	15	Light pink	6.8	6.6[j]

[a] Calcd.: C, 69.8; H, 4.7. Found: C, 70.0; H, 4.8. On distillation at 2 mm. violet vapors were obtained. [b] The yield of the free base before conversion to the hydrochloride was 15%. The free base was reported by B. Oddo, *Gazz. chim. ital.*, **42**, I, 348 (1912). [c] Free base reported by Oddo[b] with a 75° m.p. We obtained a 7% yield with ethyl picolinate in the Grignard reaction, m.p. 72–74°. [d] Calcd. for $C_{10}H_8N_2O.HCl$: C, 57.9; H, 4.3. Found: C, 57.9; H, 4.4. [e] Ethyl picolinate was used in the Grignard reaction. The yield reported was the crude yield before recrystallization. [f] B.p. 230° at 5 mm. [g] B.p. 205° at 5 mm. [h] B.p. 163–165° at 3 mm. [i] Calcd.: C, 64.4; H, 5.4. Found: C, 64.4; H, 5.5. [j] Calcd.: Cl, 17.3. Found: Cl, 17.3.

stable enediol, eliminated this type of structure. Similarities in the infrared spectra of the mixed acycloins and a number of 2-substituted pyrrole ketones indicate that the carbonyl group in the acycloins is adjacent to the pyrrole moiety.

It was found in the preparation of benzopyroins that the ratio of 2-pyrrolecarboxaldehyde to the aromatic aldehydes affected yields significantly and that the length of time of heating was also critical.

Attempted "benzoin"-type condensations with 2-pyrrolecarboxaldehyde, under the best conditions for benzopyroin, failed to yield the desired product using the following aldehydes: 3,4-dichlorobenzaldehyde, 2,6-dichlorobenzaldehyde, *m*-nitrobenzaldehyde, 2-thiophenealdehyde, and furfural. The desired product was not obtained on self-condensation of 2-pyrrolecarboxaldehyde.

The reductive condensation using Raney nickel and hydrogen of 2-pyrrolecarboxaldehyde with diethyl malonate gave diethyl-α-(2-pyrrylmethyl)-malonate, while it has been shown that the use of platinum oxide as a catalyst yields the corresponding pyrrolidyl[10] compound. Diethyl-α-(2-pyrrylmethyl)malonate was converted to the diamide, the dihydrazide, and also reduced to the propanediol but failed to yield a 5-substituted barbituric acid on condensation with urea using sodium ethoxide as a condensing agent.

(10) G. R. Clemo, N. Fletcher, G. R. Fulton, and R. Raper, *J. Chem. Soc.*, 1140 (1950).

Nitration of 2-propionylpyrrole gave the 5-nitro compound from which the semicarbazone was prepared. The assignment of the nitro group to the 5-position is made by analogy with 5-nitro-2-acetylpyrrole[11] prepared in the same manner. In contrast, a semicarbazone could not be prepared from 2-propionylpyrrole itself.

Biologic findings. 3-Propionylpyrrole was of the order of activity of Myanesin as a muscle relaxant in the anti-strychnine test[4] in mice and cats. Isobutyl-2,5-dimethyl-3-pyrryl ketone, 3-pyridyl 2-pyrryl ketone hydrochloride, and 2-pyrryl 5-methyl-3-isoxazolyl ketone exhibited some activity in this test also. α-(2-Pyrrylmethyl)malonamide and 3-propionylpyrrole semicarbazone were active as stimulants in the spinal reflex[12] in cats. All the other compounds were without pharmacological or chemotherapeutic interest.

It was also observed that a number of the pyrrole compounds gave dark colored urines to the mice, rats and dogs.

EXPERIMENTAL[13]

Methyl 5-dimethylaminomethyl-2-pyrryl ketone hydrochloride. 2-Acetyl pyrrole (10 g.) was heated with 9 g. of dimethylamine hydrochloride and 10 g. of paraformaldehyde in 75 ml. of isoamyl alcohol for 7 hr. The solution was concentrated to a small volume and poured into cold water saturated with potassium carbonate. The product was separated by extraction with ether. The ether solution was dried with anhydrous sodium sulfate and decolorized with activated carbon. Addition of 6*N* HCl in ethanol gave an oily precipitate which crystallized at 4°. This was recrystallized from ethanol-ether; yield, 11 g., m.p. 170–171°.

Anal. Calcd. for $C_9H_{14}N_2O.HCl$: N, 14.0. Found: N, 14.2.

The assignment of structure was based on reaction in the Ehrlich test using *p*-dimethylaminobenzaldehyde in hydrochloric acid. In this test, pyrrole gives a deep red color, and 2-acetyl pyrrole a pink to light red. The compound described above gave a yellow color indicative of both α-positions being blocked.

α,α-Diethyl-2-pyrrolemethanol. This compound was prepared using the Grignard reaction with 2-propionylpyrrole and ethyl iodide. The hydrolyzed reaction product was extracted by ether and vacuum distilled at 200° at 3 mm. 2-Propionylpyrrole (12 g.) gave 8 g. of the tertiary alcohol which distilled as a colorless liquid but darkened rapidly on standing.

Anal. Calcd. for $C_9H_{15}NO$: N, 9.2. Found: N, 9.8.

Diethyl α-(2-pyrrylmethyl)malonate. 2-Pyrrolecarboxaldehyde (22.5 g.), 42 g. of diethyl malonate and 5 ml. of piperidine was allowed to stand for 2 days and then the condensation product was diluted with ethanol and reduced with Raney nickel and hydrogen at 500 p.s.i. for 1 hour at 60°. When a theoretical hydrogen uptake was obtained, the catalyst was removed by filtration and the solvent removed. The remaining oil was fractionated under vacuum to give 26 g. (46%) of diethyl pyrrylmethyl malonate, b.p., 137° at 2 mm., n_D^{22} 1.4871.

Anal. Calcd. for $C_{12}H_{17}NO_4$: C, 60.2; H, 7.1. Found: C, 60.2; H, 7.0.

α-(2-Pyrrylmethyl)malonamide. Diethyl-(α-pyrrylmethyl)-malonate (10 g.) was dissolved in 100 ml. of 25% NH_3 in methanol and heated at 100° for 6 hr. under 500 p.s.i. N_2 pressure. The reaction product was concentrated to a solid and crystallized from methanol yielding a light tan compound, m.p. 188–189°.

Anal. Calcd. for $C_8H_{11}N_3O_2$: N, 23.2. Found: N, 23.6.

(2-Pyrrylmethyl)malonic acid dihydrazide. Diethyl (2-pyrrylmethyl)malonate (24 g.) was treated with 6.5 g. of 85% hydrazine hydrate in 2-propanol at reflux temperature for 6 hr. Concentration under vacuum gave a solid which was crystallized from boiling water to yield a light brown product; yield, 4 g., m.p. 178–180°.

Anal. Calcd. for $C_8H_{15}N_6O_2$: C, 45.5; H, 6.2; N, 33.2. Found: C, 46.0; H, 6.2; N, 33.3.

2-(2-Pyrrylmethyl)-1,3-propanediol. Diethyl α-(2-pyrrylmethyl)malonate (20 g.) was dropped into a solution of 10.0 g. of $LiAlH_4$ in 300 ml. of dry ether, stirred for 3 hr. and stood at 25° overnight. The excess $LiAlH_4$ was decomposed with ethyl acetate and the complex was decomposed by the addition of 18 ml. of water. This was worked up in the usual manner and the oil was distilled at 160–170° at 2–4 mm.; yield, 3 g., $n_D^{24.5}$ 1.5283.

Anal. Calcd. for $C_8H_{13}NO_2$: C, 62.0; H, 8.4. Found: C, 62.3; H, 8.3.

The diol turned dark at 25° but remained a light yellow in color at 4°.

2-Propionylpyrrole oxime. 2-Propionylpyrrole (100 g.) was treated at 25° in aqueous ethanol with 70 g. of hydroxylamine hydrochloride and 85 g. of sodium acetate. The product crystallized from the solution and was recrystallized from ethanol; yield, 54 g., m.p. 125–126°.

Anal. Calcd. for $C_7H_{10}N_2O$: N, 20.3. Found: N, 20.2.

α-Hydroxybenzyl 2-pyrryl ketone (benzopyroin). Benzaldehyde (5 g.), 5 g. of 2-pyrrolecarboxaldehyde, 10 g. of KCN and 10 g. of water were added to 120 ml. of ethanol. The solution was heated at reflux temperature for 3 hr., diluted to 500 ml. with water, and chilled. The crude product crystallized and was obtained as a colorless compound by crystallization from ethanol or ethanol-water after decolorization with carbon; yield, 3 g., m.p. 157–158°.

Anal. Calcd. for $C_{12}H_{11}NO_2$: C, 71.6; H, 5.5; N, 7.0. Found: C, 71.5; H, 5.5; N, 6.8.

4-Chloro-α-hydroxybenzyl 2-pyrryl ketone. p-Chlorobenzaldehyde (37 g.) and 20 g. of 2-pyrrolecarboxylaldehyde in a typical benzoin condensation as described above gave 20 g. of a light yellow compound crystallizable from aqueous ethanol; m.p. 131–132°.

Anal. Calcd. for $C_{12}H_{10}ClNO_2$: Cl, 15.1. Found: Cl, 15.3.

2,4-Dichloro-α-hydroxybenzyl 2-pyrryl ketone. 2,4-Dichlorobenzaldehyde (10 g.) and 10 g. of 2-pyrrolecarboxaldehyde in the benzoin type condensation gave 8 g. of a pale cream colored compound, m.p. 138–139°.

Anal. Calcd. for $C_{12}H_9Cl_2NO_2$: N, 5.2; Cl, 26.3. Found: N, 4.6; Cl, 26.2.

Phenyl-2-pyrrylglyoxal. Pyridine (80 ml.), $CuSO_4 \cdot 5H_2O$ (82 g.), and 32 ml. of water were warmed and stirred until solution was obtained. To this solution was added 34 g. of α-hydroxybenzyl 2-pyrryl ketone and the solution heated at 80° for 3.5 hr. The solution was poured into water and chilled at 4° for 14 hr. The separated product was stirred with 10% hydrochloric acid for 0.5 hr., filtered, washed with water, and dried. The dried product was crystallized from ethyl acetate–*n*-hexane solution as yellow crystals; yield, 32 g., m.p. 101–102°.

Anal. Calcd. for $C_{12}H_9NO_2$: C, 72.3; H, 4.5. Found: C, 71.9; H, 4.3.

This compound did not condense with *o*-phenylenediamine and $NaHSO_3$ to give a substituted quinoxaline. The starting compound was recovered unchanged.

α-Methoxybenzyl N-methyl 2-pyrryl ketone. α-Hydroxybenzyl 2-pyrryl ketone (10 g.) was heated with 2.3 g. of sodium in 500 ml. of dry toluene. The sodium salt which formed as a suspension on vigorous stirring was treated with

(11) H. J. Anderson, *Can. J. Chem.*, **35**, 21 (1957).

(12) W. Koll and M. Ergang, *Arch. exptl. Pathol. Pharmakol.*, 199, 577 (1942); F. M. Berger, *Brit. J. Pharmacol.*, 2, 241 (1947); *Pharmacol. Revs.*, 1, 243 (1949).

(13) All melting points are corrected.

an excess of methyl iodide (50 ml.) and gently refluxed for 2 hr. The sodium iodide formed was filtered off and the toluene removed. The residual solid distilled at 150–160° at 2–3 mm.; yield, 4 g. The distillate solidified at 4° and on addition of ether crystallized. The colorless product was recrystallized from ether; m.p. 82–83°.

Anal. Calcd. for $C_{14}H_{15}NO_2$: C, 73.4; H, 6.6; *O*-methoxy, 13.5. Found: C, 73.2; H, 6.5; *O*-methoxy, 13.6.

Infrared analysis showed absence of —NH band indicating methylation on the pyrrole nitrogen.

5-(2-Pyrrylmethylidene)barbituric acid.[14] A solution of 4.7 g. of 2-pyrrolecarboxaldehyde in 25 ml. of 80° water was added to a solution of 12.8 g. of barbituric acid in 70 ml. of boiling water. On mixing, a solid product began to separate. The suspension was heated for one hour at 80° and then filtered and washed with hot water. The yellow product was practically insoluble in boiling water, hot ethanol, or hot ethyl acetate. It was recrystallized from acetic acid; yield, 9.2 g., m.p. >280°.

Anal. Calcd. for $C_9H_7N_3O_3$: C, 52.6; H, 3.4. Found: C, 52.6; H, 3.5.

3-Propylpyrrole. 3-Propionylpyrrole (7 g.) in 100 ml. of ether was added to 2.2 g. of $LiAlH_4$ in 100 ml. of ether. After reaction, destruction of excess $LiAlH_4$ with ethyl acetate, and decomposition of the complex with water, the solvent was removed from the separated ether layer and the residue distilled at 47–50° at 2 mm., to yield 5 g. of a dark yellow oil; n_D^{25} 1.4900.

Anal. Calcd. for $C_7H_{11}N$: C, 77.1; H, 10.1. Found: C, 76.8; H, 10.0.

2-(2-Pyrrylmethyl)furan. 2-Furyl 2-pyrryl ketone (16 g.) was reduced in dry ether using $LiAlH_4$ (3.8 g.) to give 6 g. of a dark yellow oil; b.p. 80–96° at 3 mm., n_D^{21} 1.5460.

Anal. Calcd. for C_9H_9NO: C, 73.6; H, 6.2. Found: C, 74.2; H, 6.8.

2,5-Dimethyl-3-(2,2-diphenylethyl)pyrrole. 2,5-Dimethyl-3-(diphenylacetyl)pyrrole (12 g.) was reduced in dry ether with $LiAlH_4$ (1.6 g.). The recovered product was distilled at 180–185° at 5 mm. The distillate crystallized and the light brown compound was recrystallized from ether–*n*-hexane; yield, 6 g., m.p. 95–96°.

Anal. Calcd. for $C_{20}H_{21}N$: C, 87.3; H, 7.6. Found: C, 87.2; H, 7.5.

α-Ethyl-3-pyrrolemethanol. $LiAlH_4$ (5.8 g.) in 100 ml. of ether was added dropwise to 24.5 g. of 3-propionylpyrrole in 150 ml. of dry ether. The solution was refluxed for 0.5 hr. The cooled material was decomposed with ice and the product worked up in the usual fashion. The residual oil was distilled in vacuum at 117–125° at 2–3 mm., giving a light yellow oil; yield, 5 g., n_D^{23} 1.5205.

Anal. Calcd. for $C_7H_{11}NO$: C, 67.1; H, 8.8; N, 11.2. Found: C, 66.3; H, 8.4; N, 11.6.

The isomeric 2 compound has been prepared by the same reversed addition procedure.[15]

3-Propionylpyrrole semicarbazone. 3-Propionylpyrrole (8 g.), 30 g. of semicarbazide hydrochloride, and 60 g. of sodium acetate in 200 ml. of water was heated for 0.5 hr. On concentrating to 100 ml. and addition of concentrated ammonia, a colorless crystalline material separated which was recrystallized from water containing ammonia; yield, 3 g., m.p. 180–181°.

Anal. Calcd. for $C_8H_{12}N_4O$: N, 31.1. Found: N, 30.7.

Ethyl 2-pyrryl ketone hydrazone. 2-Propionylpyrrole (30.5 g.) was treated in 2-propanol with 85% hydrazine hydrate (50 g.) at 80° for 6 hr. The solution was concentrated to a small volume and on cooling, the hydrazone crystallized. The colorless product was recrystallized from ether; yield, 22 g., m.p. 103–104°.

Anal. Calcd. for $C_7H_{11}N_3$: N, 30.7. Found: N, 31.3.

1-Methyl-3-propionylpyrrole. Metallic potassium (6.5 g.) was suspended in ligroin, b.p. 90–120°, and 3-propionylpyrrole (20 g.) was added in small portions during vigorous agitation. After the addition of the ketone, the suspension was refluxed for 0.5 hr. and the ligroin was decanted from the potassium salt of the ketone. Dry ethyl ether containing 50 g. of methyl iodide was added and the reaction was stirred for 15 hr. at reflux. The potassium iodide formed was filtered off and the ether solution concentrated to an oil which was distilled at 8–10 mm. at 135–142° to give a yellow liquid; yield, 10 g., n_D^{26} 1.5338.

Anal. Calcd. for $C_8H_{11}NO$: C, 70.0; H, 8.0. Found: C, 70.1; H, 8.1.

The known 1-methyl-2-propionylpyrrole[16] was also prepared by the above procedure using 2-propionylpyrrole and also by the action of propionyl chloride on 1-methylpyrrole in the Grignard reaction. 1-Methyl-2-propionylpyrrole had the physical constants, n_D^{27} 1.5282, b.p. 95° at 14 mm.

3-Propionylfuran.[17] To a Grignard solution prepared from 8.4 g. of magnesium and 38.5 g. of ethyl bromide in 500 ml. of ether was added 33 g. of pulverized $CdCl_2$ and the suspension stirred for 0.5 hr. Thirty g. of 3-furoyl chloride (b.p. 87° at 85 mm.) in ether was then added and the suspension refluxed for one hour. The cooled suspension was decomposed with ice and dilute sulfuric acid solution. The ether layer was washed with water, dilute sodium hydroxide solution, and finally with ice water. The dried ether solution was concentrated and the product distilled as a colorless oil at 70° and 4 mm. pressure; yield, 16.5 g., n_D^{26} 1.4770.

Anal. Calcd. for $C_7H_8O_2$: C, 67.8; H, 6.5. Found: C, 67.6; H, 6.5.

3-Propionylthiophene. A modified Grignard reaction,[17] as described above for 3-propionylfuran, gave 43 g. of crude ketone from 50 g. of 3-thiophenecarboxylic acid chloride (b.p. 120° at 60 mm.). The fraction (25 g.) boiling at 78–84° at 4 mm. was treated with 69 g. of Girard's reagent "T" in the usual procedure. The recovered ketone was vacuum-distilled at 125° at 42 mm.; yield, 10 g., n_D^{25} 1.5460.

Anal. Calcd. for C_7H_8OS: C, 60.0; H, 5.7. Found: C, 60.1; H, 6.0.

2-Propionylpyrazine. Pyrazinoic acid (42 g.) was converted to the acid chloride using thionyl chloride (500 g.) to give a violet colored liquid.[18] The acid chloride was used in the $CdCl_2$ modified Grignard reaction described for 3-propionyl furan above. Distillation of the ketone at 77–82° at 4 mm. gave a colorless liquid having a tar-oil odor which crystallized to a white solid at 4° but melted to a pale yellow liquid at 25°; yield, 2 g.

Anal. Calcd. for $C_7H_8N_2O$: C, 61.8; H, 5.9. Found: C, 61.9; H, 6.1.

2-Diethylaminoethyl α-(2-pyrryl) benzyl ether DL-*tartrate.* 2-Benzoyl pyrrole (66 g.) was reduced to the alcohol in 1 liter of ether solution by the reverse addition of $LiAlH_4$ (24 g.). The crude product (66 g.) was dissolved in xylene and reacted with 10 g. of sodium. After formation of the sodium salt, 80 g. of freshly prepared diethylaminoethyl chloride was added. The reaction mixture was stirred and heated at 100° for 6 hr. On completion of the reaction, the cooled suspension was extracted with dilute hydrochloric acid solution. The aqueous solution was made basic with dilute sodium hydroxide solution and extracted with ether. The ether extract was dried with anhydrous sodium sulfate, decolorized, and concentrated to an oil under high vacuum to remove traces of diethylaminoethyl chloride. The oil was dissolved in acetone and treated with an acetone

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saturated solution of DL-tartaric acid. The separated dark purple crystalline solid was recrystallized from hot acetone; yield, 24 g., m.p. 100–102°.

Anal. Calcd. for $C_{17}H_{24}N_2O.1.75C_4H_6O_6$: C, 53.9; H, 6.5; N, 5.3. Found: C, 53.9; H, 6.6; N, 5.3.

1-(3-Dimethylaminopropyl)-2-propionylpyrrole acid tartrate. Metallic potassium (3.5 g.) was suspended in toluene (200 ml.) at 65° and 10 g. of 2-propionylpyrrole in 100 ml. of toluene was added. After the reaction was completed, 12 g. of dimethylaminopropyl chloride in 50 ml. of toluene was added and the mixture heated at reflux for 6 hr. with efficient stirring. The cooled suspension was treated with ice water and the water layer saturated with sodium chloride. The separated toluene layer contained most of the product and the water layer was extracted with ether three times to remove residual product. The combined solvent layers were concentrated to an oil under high vacuum and the residual oil dissolved in acetone.

The acetone solution was decolorized and treated with a saturated solution of DL-tartaric acid in acetone. The separated light pink salt was purified by extraction with hot acetone; yield, 16 g. of light pink crystals, m.p. 116–117°.

Anal. Calcd. for $C_{12}H_{20}N_2O.C_4H_6O_6$: N, 7.8. Found: N, 7.8.

1-(3-Dimethylaminopropyl)-3-propionylpyrrole. This compound was prepared in the same manner as the 2-propionyl isomer above. Ten grams of 3-propionylpyrrole gave 10 g. of free base as a dark red oil; n_D^{27} 1.5144.

Anal. Calcd. for $C_{12}H_{20}N_2O$: N, 13.4. Found: N, 13.0.

3-Dimethylaminopropyl α-(2-pyrryl)benzyl ether ascorbate hydrate. The free base was prepared in the same manner as the 2-diethylaminoethyl-α-(2-pyrryl)benzyl ether described above. The free base was dissolved in ether and an ethanolic solution of ascorbic acid added. The ascorbate separated as a brown powder. The powder was dissolved in 95% ethanol and precipitated by ether as a very hygroscopic brown powder; yield, 8 g.

Anal. Calcd. for $C_{16}H_{22}N_2O.C_6H_8O_6.1^1/_2H_2O$: C, 57.2; H, 7.2; N, 6.1. Found: C, 57.3; H, 7.3; N, 5.5.

2,2'-[1,2-Bis(3-dimethylaminopropoxy)vinylene]bis(6-methylpyridine). 1,2-Di(6-methyl-2-pyridyl)-1,2-ethenediol[19] (24 g.) on treatment with sodium (5 g.) in toluene and then dimethylaminopropyl chloride (31 g.) as previously described, gave 11.8 g. of a red oil, b.p. 200–210° at 2 mm.

Anal. Calcd. for $C_{24}H_{36}N_4O_2$: C, 70.0; H, 8.8; N, 13.6. Found: C, 70.0; H, 9.0; N, 13.7.

The usual ketone–hydroxy benzoin type of structure has been assigned[19] to the self-condensation product of 6-methyl picolinaldehyde. However, the formation of the bis-3-dimethylaminopropoxy derivative justified the new enediol structure and name given above.

α-(3-Dimethylaminopropoxy)benzyl 2-pyrryl ketone. α-Hydroxybenzyl 2-pyrryl ketone (9 g.) on treatment with sodium (2.3 g.) in toluene, and then dimethylaminopropyl chloride (32 g.) as previously described gave 9.4 g. of an orange colored oil; b.p. 180–200° at 2–4 mm.

Anal. Calcd. for $C_{17}H_{22}N_2O_2$: C, 71.3; H, 7.7; N, 9.8. Found: C, 71.5; H, 8.0; N, 9.8.

5-Nitro-2-propionylpyrrole. 2-Propionylpyrrole (25 g.) in 150 ml. of acetic anhydride cooled to −10° was dropped into 22 g. of fuming nitric acid (d = 1.5) in 50 ml. of acetic anhydride cooled to −10°. The solution was cooled to −20° and stirred for 3 hr. and then poured into ice and water. On standing overnight, the product crystallized. The yellow compound was recrystallized from hot water; yield, 14 g., m.p. 100–101°.

Anal. Calcd. for $C_7H_8N_2O_3$: C, 50.0; H, 4.8; N, 16.7. Found: C, 50.0; H, 5.0; N, 17.1.

This compound failed to give a hydrazone, oxime, or guanylhydrazone under the usual conditions.

5-Nitro-2-propionylpyrrole semicarbazone. 5-Nitro-2-propionylpyrrole (10 g.) was dissolved in aqueous ethanol to which 10 g. of semicarbazide hydrochloride and 10 g. of sodium acetate were added. Overnight, a few yellow crystals separated. However, the solution was heated at 80° for two hours and then on standing for 3 days the product separated as crystalline yellow-orange needles. The separated crystals were recrystallized from boiling water; yield, 10 g., m.p. 203–204°.

Anal. Calcd. for $C_8H_{11}N_3O$: C, 42.7; H, 4.9. Found: C, 42.5; H, 4.8.

2,5-Dimethyl-3-pyrrolecarboxaldehyde. Dimethylformamide (500 g.) was cooled to 10° and 338 g. of phosphorus oxychloride dropped in. Aftter stirring for 15 min., 192 g. of 2,5-dimethylpyrrole, dissolved in 200 ml. of ethylenedichloride, was dropped in while the reaction solution was maintained at 0–5°. The solution was stirred for one hour at 10° and then heated to 40° for one hour. The completed reaction solution was mixed with 5 kg. of cracked ice and after stirring for 15 min., 600 g. of solid sodium hydroxide was stirred into the water solution, while ice was added to keep the temperature down. After 20 min., ice and concentrated hydrochloric acid was added to *p*H 7. The mixture was permitted to stand overnight and then extracted several times with ether. Concentration of the combined ether extracts gave a dark colored solid that could be crystallized from ethanol, m.p. 143°. The solid residue was distilled with sublimation at 2–4 mm. The distilled material was recrystallized to give buff-colored crystals, m.p. 144–145°; yield, 31 g.

Anal. Calcd. for C_7H_9NO: N, 11.4. Found: N, 11.1.

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