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New Reactions of Pyrroles. II. Preparation and Reactions of Pyrroleglyoxyloyl Derivatives

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Pyrroles treated with oxalyl chloride produced pyrroleglyoxyloyl chlorides. Unsubstituted and *C*-alkyl pyrroles gave products stable only at low temperatures. *N*-Substitution or presence on the ring of an electron withdrawing group (*e.g.* carbonyl) increased the stability of the glyoxyloyl chlorides considerably. Substitution occurred at the 2-position unless both 2 and 5 positions of the pyrrole nucleus were blocked. When this was the case substitution occurred slowly at position 3.

The similarity which pyrroles and indoles have in their susceptibility to electrophilic substitution was examined in part I of this series (1). This led to the preparation of a group of mono and di-pyridylethylated pyrroles. In the present paper the reaction of a second electrophilic reagent, oxalyl chloride, which has been of great value in indole chemistry (2,3), was applied to pyrroles and utilized for the synthesis of a number of derivatives of interest as potential therapeutic agents.

Oddo and Acuto (4) prepared 2,5-dimethylpyrrole-3-glyoxylamide by the reaction of the pyrrole-magnesium iodide reagent with ethyl oxalyl chloride, followed by ammonolysis of the ester.

In the present study it was found that treatment of pyrrole with oxalyl chloride at −50° produced pyrrole-2-glyoxyloyl chloride. At room temperature the reaction produced only intractable tars. Crystalline pyrrole-2-glyoxyloyl chloride (I) could be isolated, but was extremely unstable at temperatures above 0° as were ethereal solutions of the compound. It could be conveniently converted into amides by treatment of the reaction mixture at −50° with an excess of amine. In contrast to the pyridylethylation of pyrrole (1) there was no tendency to form a di-substituted product such as pyrrole-2,5-diglyoxyloyl chloride. Presumably the electron withdrawing character of a 2-glyoxyloyl chloride substituent deactivates the 5-position sufficiently to inhibit further reaction. When oxalyl chloride was added to a solution of pyrrole a mixture of bis-(pyrrol-2-yl)glyoxal (II) and pyrrole-2-glyoxyloyl chloride (I) was obtained. The formation of II could be avoided by adding a solution of pyrrole to excess oxalyl chloride.

Pyrrole-2-glyoxyloyl chloride was reacted, without isolation, with a variety of amines to provide the amides shown in Table I (III–VII). Pyrrole-2-glyoxyloyl chloride was also reacted with piperazine to give the bis-amide (VIII).

An *N*-substituted pyrrole, 1-(2-cyanoethyl)pyrrole was similarly treated with oxalyl chloride. This reaction was conducted in refluxing ether without apparent decomposition and the product (IX) was much more stable than I. Treatment of IX with ammonia and with piperidine provided the pyrroleglyoxylamides X and XI (Table I).

CHART A

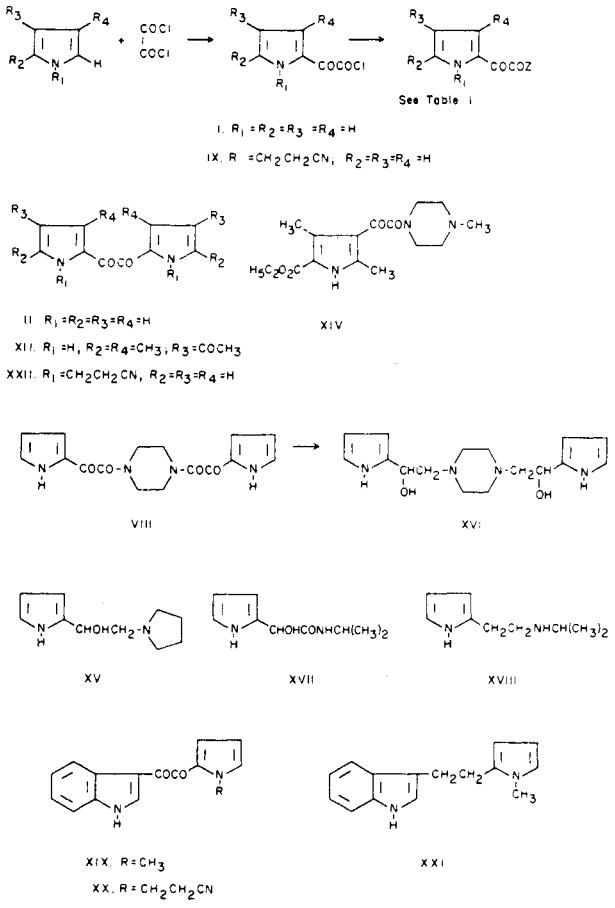
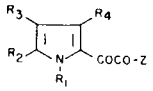
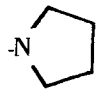
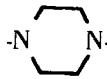
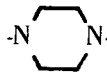


TABLE I

Pyrrol-2-glyoxylamides



	Z	R_1	R_2	R_3	R_4	M.P.	Recryst. from	Formula	Analysis Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
III	$-NH_2$	H	H	H	H	126–127°	a	$C_6H_6N_2O_2$	52.17	4.38	20.28	52.42	4.46	20.07
IV		H	H	H	H	111–112°	a	$C_{10}H_{12}N_2O_2$	62.48	6.29	14.58	62.70	6.57	14.60
V	$-NHCH(CH_3)_2$	H	H	H	H	120–123°	b	$C_9H_{12}N_2O_2$	59.98	6.71	15.55	59.81	6.87	15.66
VI	$-NHCH_2CH_2N(CH_3)_2$	H	H	H	H	116–117°	a	$C_{10}H_{15}N_3O_2$	57.40	7.23	20.08	57.13	7.06	19.80
VII		H	H	H	H	141–145°	d	$C_{16}H_{17}N_3O_2$	67.82	6.05	14.83	68.08	5.92	14.83
X	$-NH_2$	CH_2CH_2CN	H	H	H	133–134°	a	$C_9H_9N_3O_2$	56.54	4.75	21.98	56.53	4.72	22.21
XI		CH_2CH_2CN	H	H	H	70–71°	c	$C_{14}H_{17}N_3O_2$	64.84	6.61	16.21	65.02	6.43	16.00
XIII		H	CH_3	$COCH_3$	CH_3	212–213°	c	$C_{20}H_{23}N_3O_2$	67.97	6.65	11.89	68.14	6.34	12.11

a = water, b = ethanol, c = ether, d = benzene-*n*-hexane, e = acetone-water.

Two reactions between oxalyl chloride and pyrroles bearing electronegative substituents were next investigated. 3-Acetyl-2,4-dimethylpyrrole was treated with oxalyl chloride at room temperature, and reverse addition was not employed. In this case, bis-(3-acetyl-2,4-dimethylpyrrol-5-yl)glyoxal (XII) crystallized from the reaction mixture. Treatment of the filtrate, which contained the more soluble glyoxyloyl chloride, with *N*-phenylpiperazine afforded the amide (XIII, Table I). Although it had been found that ethyl 2,4-dimethylpyrrole-5-carboxylate could not be pyridylethylated (1) it did react slowly (18 hours) with oxalyl chloride at the 3 position. Treatment with *N*-methylpiperazine provided the amide (XIV).

Lithium aluminum hydride reductions of several of these pyrroleglyoxylamides were carried out. Reduction of the pyrrolidine derivative (IV) and the bis-piperazine derivative VIII yielded the 2-hydroxy-2-pyrrolylethylamines XV and XVI analogous to the reported reduction products of 1-alkylindole-3-glyoxylamides (5). However, reduction of *N*-isopropyl(pyrrole-2-glyoxyl)amide (V) gave a mixture of hydroxyamide (XVII) and the ethylamine (XVIII).

Following the preparation of the foregoing pyrroleglyoxyloyl chlorides it seemed of interest to explore the use of reactions of this type to link pyrrole and indole rings and provide novel indoleglyoxyloylpyrroles and indolylethylpyrroles. These compounds could presumably be obtained from reactions between pyrroleglyoxyloyl chlorides and indoles, followed by reduction. Alternatively, the the same products would result if indoleglyoxyloyl chlorides could be made to react with suitable pyrroles. The latter route was studied because of the greater stability of 3-indoleglyoxyloyl chlorides. Treatment of 3-indoleglyoxyloyl chloride with 1-methylpyrrole and with 1-(2-cyanoethyl)pyrrole readily provided XIX and XX. Lithium aluminum hydride reduction of XIX in tetrahydrofuran gave a light sensitive crude product whose I.R. spectrum showed OH absorption and thin layer chromatography showed eight spots. However, more vigorous conditions (refluxing 1,2-dimethoxyethane) provided the anticipated indolylethylpyrrole (XXI). The chemistry involved is summarized in chart A.

These compounds were screened for pharmacological activity. In general the compounds were mild central depressants. One (VIII) showed a degree of anti-inflammatory action.

EXPERIMENTAL

Pyrrole-2-glyoxylamides.

N-Isopropyl(pyrrole-2-glyoxyl)amide (V, Table I).

Pyrrole (26.8 g., 0.4 mole) in ether (100 ml.) was added slowly dropwise to a stirred solution of oxalyl chloride (40 ml., 0.425 mole) in ether (500 ml.) kept at -50° (dry ice-acetone bath). Stirring was continued for 1 hour, then the reaction mixture (while still at -50°) was poured slowly onto a stirred and cooled solution of isopropylamine (118 g.) in ether (500 ml.). The precipitate was filtered off and washed very thoroughly with methylene chloride. The combined ether filtrate and methylene chloride washings were evaporated *in vacuo* and the residue was crystallized from ethanol to provide V (47.0 g.), m.p. 120–123°. This and other examples prepared similarly are listed in Table I (III, IV, V, VI, VII).

1,4-Bis(pyrrole-2-glyoxyloyl)piperazine (VIII).

A solution of pyrrole-2-glyoxyloyl chloride was prepared from pyrrole (26.8 g.) and oxalyl chloride (40 ml.) in the same way as before. The reaction mixture, at -50°, was poured slowly into a vigorously stirred mixture of sodium bicarbonate (100 g.) in water (600 ml.) and piperazine (43 g.) in chloroform (400 ml.). The precipitate was collected and recrystallized from aqueous dimethylformamide to give the product as colorless needles (49 g., 75%), m.p. 237–238° dec.

Anal. Calcd. for $C_{16}H_{16}N_4O_4$: C, 58.53; H, 4.91; N, 17.07. Found: C, 58.60; H, 5.16; N, 17.31.

Amides Derived from 1-(2-Cyanoethyl)pyrrole-2-glyoxyloyl Chloride (IX).

A solution of 1-(2-cyanoethyl)pyrrole (24.0 g.) in ether (100 ml.) was added dropwise to a stirred solution of oxalyl chloride (20 ml.) in ether (300 ml.) under reflux. Stirring was continued for 1 hour, then the crystalline 1-(2-cyanoethyl)pyrrole-2-glyoxyloyl chloride (34.8 g., m.p. 99–101°) was collected.

The foregoing acid chloride was added slowly portionwise to a stirred solution of ammonia in water. Recrystallization of the resulting solid from water provided X (Table I).

A solution of the acid chloride in methylene chloride was basified with piperidine, washed with water (x2) and dried ($MgSO_4$). Evaporation under reduced pressure and recrystallization of the residual viscous oil from ether provided XI (Table I).

A preparation of 1-(2-cyanoethyl)pyrrole-2-glyoxyloyl chloride in which oxalyl chloride (20 ml.) was added to 1-(2-cyanoethyl)-pyrrole (24 g.) in ether (250 ml.) afforded a mixture of XXII and 1-(2-cyanoethyl)pyrrole-2-glyoxyloyl chloride (35.2 g., m.p. 94–102°). A solution of this material in methylene chloride was treated with excess piperidine, washed, dried, and evaporated as before. Crystallization of the residue from aqueous ethanol gave as a first crop, bis[1-(2-cyanoethyl)pyrrol-2-yl]glyoxal (XXII), m.p. 151–152°.

Anal. Calcd. for $C_{16}H_{14}N_4O_2$: C, 65.29; H, 4.80; N, 19.04. Found: C, 65.16; H, 4.79; N, 19.10.

Evaporation of the filtrate and crystallization of the residue from ether provided XI (Table I).

3-Acetyl-2,4-dimethyl-5-(4-phenyl-1-piperazinylglyoxyloyl)pyrrole (XIII, Table I), and Bis-(3-acetyl-2,4-dimethylpyrrol-2-yl)glyoxal (XII).

Oxalyl chloride (2.9 ml.) was added dropwise to a stirred solution of 3-acetyl-2,4-dimethylpyrrole (4.1 g.) in dry ether (500 ml.). After 1 hour the red crystals of XII, hemihydrate were collected (2.2 g.), m.p. 286–288° dec.

Anal. Calcd. for $C_{18}H_{20}N_2O_4 \cdot \frac{1}{2}H_2O$: C, 64.12; H, 5.99; N, 8.30. Found: C, 64.14; H, 5.98; N, 8.27.

The filtrate was mixed with *N*-phenylpiperazine (12 g.) and the resulting precipitate was collected, washed well with water and dried. Recrystallization from aqueous acetone gave XIII (3.75 g.), m.p. 212–213°.

Anal. Calcd. for $C_{20}H_{23}N_3O_3$: C, 67.97; H, 6.56; N, 11.89. Found: C, 68.14; H, 6.34; N, 12.11.

Ethyl 2,4-Dimethyl-3-(4-methyl-1-piperazinylglyoxyloyl)pyrrole-5-carboxylate (XIV).

Oxalyl chloride (0.75 ml.) was added dropwise to a stirred so-

lution of ethyl 2,4-dimethylpyrrole-5-carboxylate (1.3 g.) in ether (50 ml.) and the reaction mixture was left at room temperature for 18 hours. A solution of potassium bicarbonate (2.5 g.) in water (10 ml.) was added and the mixture was stirred while *N*-methylpiperazine (1.0 g.) in methylene chloride (50 ml.) was added. The organic layer was dried (magnesium sulfate) and evaporated and the residue was recrystallized from aqueous ethanol. The first crop was unchanged ethyl 2,4-dimethylpyrrole-5-carboxylate (0.3 g.), m.p. 118–121°. Concentration of the mother-liquor provided XIV as colorless needles (0.7 g.), m.p. 167–168°.

Anal. Calcd. for $C_{16}H_{23}N_3O_4$: C, 59.79; H, 7.21; N, 13.08. Found: C, 60.07; H, 7.07; N, 13.21.

2-(2-Pyrrolidino-1-hydroxy)ethylpyrrole (XV).

Thirty three g. of 1-(pyrrole-2-glyoxyloyl)pyrrolidine (IV) was added in portions to a stirred suspension of lithium aluminum hydride (17.0 g.) in tetrahydrofuran (1.25 l.). The mixture was refluxed for 2 hours, then kept at room temperature for 16 hours. Water (50 ml.) was added dropwise with stirring, then the inorganic material was filtered off and washed well with tetrahydrofuran. Evaporation of the filtrate and washings *in vacuo* gave a colorless solid which was recrystallized from ethanol to provide XV (19.0 g.), m.p. 118–120°.

Anal. Calcd. for $C_{10}H_{16}N_2O$: C, 66.63; H, 8.95; N, 15.54. Found: C, 66.86; H, 8.74; N, 15.34.

1,4-Bis-[2-hydroxy-2-(2-pyrrolyl)ethyl]piperazine (XVI).

1,4-Bis(pyrrole-2-glyoxyloyl)piperazine (VIII) was reduced with lithium aluminum hydride in the same way as in the preceeding example. Recrystallization of the crude product from aqueous dimethylformamide afforded XVI, m.p. 210° dec.

Anal. Calcd. for $C_{16}H_{24}N_4O_2$: C, 63.13; H, 7.95; N, 18.41. Found: C, 63.27; H, 7.96; N, 18.54.

N-Isopropyl-2-(2-pyrrolyl)-2-hydroxyacetamide (XVII) and 2-[2-(isopropylamino)ethyl]pyrrole (XVIII).

N-Isopropyl-(pyrrole-2-glyoxyl)amide (18 g.) was added portionwise to a stirred suspension of lithium aluminum hydride (9.7 g.) in tetrahydrofuran (500 ml.). The mixture was refluxed for 2 hours, then left overnight at room temperature. Water (30 ml.) was added dropwise and the precipitate was filtered off. Evaporation of the filtrate gave a light sensitive brown oil. Heating this with *n*-hexane gave an insoluble fraction which was twice recrystallized from ethyl acetate to provide 1.6 g. of XVII, m.p. 109–111°.

Anal. Calcd. for $C_9H_{14}N_2O_2$: C, 59.32; H, 7.74; N, 15.37. Found: C, 59.38; H, 7.75; N, 15.27.

The *n*-hexane filtrate was evaporated *in vacuo* and the residual black oil was distilled. The colorless, light-sensitive distillate, b.p. 60–120°/0.2 mm, (7.0 g.) crystallized on standing. Two recrystallizations from petroleum ether gave XVIII as colorless needles (4.2 g.), m.p. 56–58°.

Anal. Calcd. for $C_9H_{16}N_2$: C, 71.00; H, 10.59; N, 18.40. Found: C, 71.18; H, 10.67; N, 18.12.

Indol-3-yl(1-methylpyrrol-2-yl)glyoxal (XIX).

Freshly distilled 1-methylpyrrole (12.15 g.) was added dropwise to a stirred solution of 31.35 g. of 3-indoleglyoxyloyl chloride (5) in tetrahydrofuran (350 ml.). The mixture was left at room temperature for 1 hour, then *n*-hexane (600 ml.) was added and the mixture was allowed to cool. Recrystallization of the crude product from ethanol provided XIX (21.5 g.), m.p. 197–199°.

Anal. Calcd. for $C_{15}H_{12}N_2O_2$: C, 71.43; H, 4.80; N, 11.11. Found: C, 71.31; H, 4.78; N, 11.14.

Indol-3-yl[1-(2-cyanoethyl)pyrrol-2-yl]glyoxal (XX).

1-(2-Cyanoethyl)pyrrole (5.0 g.) in tetrahydrofuran (10 ml.) was added to a solution of 3-indoleglyoxyloyl chloride (8.5 g.) in tetrahydrofuran (90 ml.). The mixture was refluxed for 10 minutes, then *n*-hexane was added until crystallization commenced. Recrystallization of the crude product from ethanol provided XX (6.5 g.), m.p. 174–175°.

Anal. Calcd. for $C_{17}H_{13}N_3O_2$: C, 70.09; H, 4.50; N, 14.43. Found: C, 70.14; H, 4.45; N, 14.47.

3-[2-(1-methylpyrrol-2-yl)ethyl]indole (XXI).

The glyoxal XIX (5.0 g.) was added portionwise to a stirred suspension of lithium aluminum hydride (4.5 g.) in 1,2-dimethoxyethane (100 ml.) and the mixture was refluxed for 18 hours. Water (12 ml.) was added dropwise to the cooled reaction mixture then the inorganic material was filtered off. Evaporation of the filtrate *in vacuo*, and recrystallization of the residue from aqueous ethanol provided XXI (2.3 g.), m.p. 113–115°.

Anal. Calcd. for $C_{15}H_{16}N_2$: C, 80.32; H, 7.19; N, 12.49. Found: C, 80.17; H, 7.39; N, 12.33.

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