Preparation and Reactions of some 1,2,3,4-Tetrahydro-2,3-disubstituted 7(or 8)hydroxy-1,4-dioxopyrazino[1,2-*a*]indoles

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1,2,3,4-Tetrahydro-2,3-disubstituted 7(or 8)hydroxy-1,4-dioxopyrazino[1,2-*a*]indoles have been prepared by the condensation of 6(or 5)benzyloxyindole-2-carbonyl chloride with *dl*-*N*-alkylamino acid ethyl esters in the presence of triethyl amine followed by the hydrogenolysis over palladium-carbon. Methylation and alkaline hydrolysis of 1,2,3,4-tetrahydro-2-benzyl-1,4-dioxopyrazino[1,2-*a*]indole are discussed.

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Taylor *et al.*, (3) isolated 1,2,3,4-tetrahydro-2-methyl-3-methylene-6-hydroxy-1,4-dioxopyrazino[1,2-*a*]indole from the cultures of *Penicilium terlikowskii* and postulated 1,2,3,4-tetrahydro-1,4-dioxopyrazino[1,2-*a*]indoles as possible intermediates in the biosynthesis of antibiotics like gliotoxin. The only hydroxypyrazino[1,2-*a*]indoles synthesized by Johnson *et al.*, (4,5) have the hydroxy group at position 10. Since the introduction of the hydroxy group at the 4,5,6 and 7 positions of indole leads to interesting pharmacological properties, a number of 7 and 8-hydroxypyrazino[1,2-*a*]indoles have been prepared and their spectral data reported (Table I). 1,2,3,4-Tetrahydro-2-benzyl-1,4-dioxopyrazino[1,2-*a*]indole with its closed peptide structure is interesting enough in itself to study its chemical reactions and hence, in the present work, methylation and alkaline hydrolysis are reported.

1,2,3,4-Tetrahydro-2,3-disubstituted-1,4-dioxopyrazino-[1,2-*a*]indoles (**1,2**) were prepared by the condensation of indole-2-carbonyl chloride and *dl*-*N*-benzylamino acid ethyl esters in the presence of triethylamine under anhydrous conditions. The condensation product of indole-2-carbonyl chloride and *N*-methylglycine ethyl ester cyclizes to pyrazino[1,2-*a*]indole in the presence of an excess of *N*-methylglycine ethyl ester (4). 5(or 6)Benzyloxyindole-2-carboxylic acids (required for the preparation of 8(or 7)benzyloxypyrazino[1,2-*a*] indoles) were prepared following the procedures due to Bergel *et al.*, (6) and Burton *et al.*, (7), respectively. These acids were converted to the acid chloride followed by the condensation with *dl*-*N*-benzylamino acid ethyl ester, in the presence of triethylamine. The resulting 8(or 7)benzyloxypyrazino[1,2-*a*]indoles (**3-8**) on hydrogenolysis over palladium-carbon yield corresponding hydroxypyrazino[1,2-*a*]indoles (**9-14**). Our findings that the base catalyzed cyclizaiton takes place only when there is no active hydrogen on the amide nitrogen, is in agreement with the earlier reports (8,9). *dl*-*N*-Benzylamino acids, needed for the synthesis of the corresponding 2-benzylpyrazino[1,2-*a*]indoles, were prepared according to Quitt *et al.*, (10). The suspension of *dl*-*N*-alkylamino acid in absolute ethanol, on saturation with dry gaseous hydrogen chloride gave the respective ethyl ester hydrochloride which on treatment with potassium carbonate yielded the corresponding amino acid ethyl ester.

Characteristic absorption bands around 1700 and 1645 cm^{-1} for the indole N-C=O and amide carbonyl, respectively, were observed in the ir spectra of all the pyrazinoindoles (**1-14**). In the uv spectra, a remarkable bathochromic shift was noted in the case of 7-substituted pyrazino[1,2-*a*]indoles (**6-8,12-14**), which may probably be due to the *meta* position of the substituent with respect to the indole nitrogen. Nmr spectrum of **1** in carbon tetrachloride, clearly explained the presence of the two methylene groups at δ 4.19 and 4.74. The lower field signal represented the methylene protons adjacent to the carbonyl group. All of the aromatic protons appeared at δ 7.3 except that on position 10, which appeared at δ 8.2, strongly affected due to the conjugated carbonyl group.

Methylation of **1** with methyl iodide and sodium methoxide gave 1,2,3,4-tetrahydro-2-benzyl-3-methyl-1,4-dioxopyrazino[1,2-*a*]indole which was identified by the comparison of the ir spectrum and mixed melting point with those of a compound **2**, obtained by independent synthesis.

Scheme

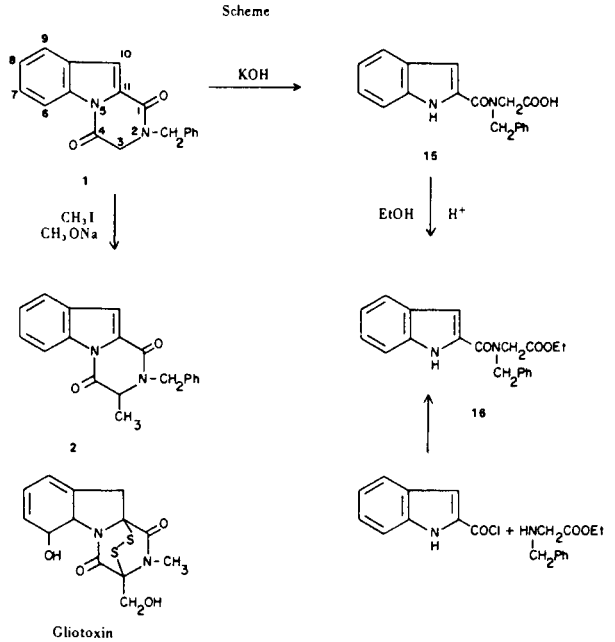
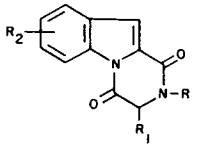


Table I

Physical and Spectral Data for



Compound (a)	R	R_1	R_2	M.p. °C	Yield %	Recrystallization solvent (b)	Ir (Potassium bromide) cm^{-1}	Uv max, nm (ϵ x 10^{-3}) (c)
1	CH_2Ph	H	H	157-158	66	A	1700, 1650, 1610, 1570, 1440	239 (19.50), 294 (17.38)
2	CH_2Ph	CH_3	H	123-124	65	B	1715, 1635, 1580, 1560, 1440	240 (22.91), 291 (18.62)
3	CH_2Ph	H	8-OCH_2Ph	197-198	62	C	1700, 1650, 1625, 1575, 1450, 1235, 1210	256 (26.92), 292 (18.62)
4	CH_2Ph	CH_3	8-OCH_2Ph	135	63	B	1695, 1640, 1600, 1585, 1435, 1240, 1210	257 (28.84), 292 (17.78)
5	CH_3	H	8-OCH_2Ph	201-202	64	A	1695, 1645, 1590, 1440, 1262, 1240	255 (27.54), 290 (19.05)
6	CH_2Ph	H	7-OCH_2Ph	170-171	63	C	1700, 1650, 1600, 1575, 1430, 1240	317 (22.39)
7	CH_2Ph	CH_3	7-OCH_2Ph	97	65	C	1700, 1630, 1600, 1585, 1440, 1250, 1200	317 (21.38)
8	CH_3	H	7-OCH_2Ph	227-228	65	D	1705, 1670, 1620, 1590, 1440, 1240	315 (22.39)
9	CH_2Ph	H	8-OH	252-254	78	A	3150, 1680, 1615	256 (22.91), 294 (16.6)
10	CH_2Ph	CH_3	8-OH	225-226	80	A	3100, 1670, 1610	257 (23.99), 294 (17.38)
11	CH_3	H	8-OH	256-257	78	A	3100, 1660, 1600	255 (23.44), 291 (16.98)
12	CH_2Ph	H	7-OH	315-317	80	A	3100, 1670, 1610	319 (20.89)
13	CH_2Ph	CH_3	7-OH	215-216	75	A	3150, 1670, 1625	321 (15.49)
14	CH_3	H	7-OH	276-277	80	A	3300, 1700, 1630	317 (22.39)

(a) Compounds **9-14**, first darken, then melt. (b) A = Ethanol, B = methanol, C = benzene-hexane, D = benzene. (c) Uv spectra were recorded in methanol except **1** (ethanol).

Table II

Elemental Analysis of the Compounds Listed in Table I

Compound No. (a)	Molecular formula		Elemental Analysis (%) C	H	N
2	$C_{19}H_{16}N_2O_2$	Calcd.	74.98	5.30	9.21
		Found	74.69	5.48	8.88
3	$C_{25}H_{20}N_2O_3$	Calcd.	75.74	5.09	7.07
		Found	75.46	5.04	7.14
4	$C_{26}H_{22}N_2O_3$	Calcd.	76.08	5.40	6.83
		Found	76.35	5.49	6.82
6	$C_{25}H_{20}N_2O_3$	Calcd.	75.74	5.09	7.07
		Found	76.04	5.40	7.29
7	$C_{26}H_{22}N_2O_3$	Calcd.	76.08	5.40	6.83
		Found	76.23	5.40	7.03
8	$C_{19}H_{16}N_2O_3$	Calcd.	71.24	5.03	8.75
		Found	70.99	5.28	8.48
9	$C_{18}H_{14}N_2O_3$	Calcd.	70.58	4.61	9.15
		Found	70.43	4.35	9.01
10	$C_{19}H_{16}N_2O_3$	Calcd.	71.24	5.03	8.75
		Found	71.32	5.09	8.62
12	$C_{18}H_{14}N_2O_3$	Calcd.	70.58	4.61	9.15
		Found	70.61	4.44	9.00
13	$C_{19}H_{16}N_2O_3$	Calcd.	71.24	5.03	8.75
		Found	71.38	5.09	8.46
14	$C_{12}H_{10}N_2O_3$	Calcd.	62.60	4.38	12.17
		Found	62.39	4.21	12.09

(a) Analytical data for the compouns **1**,**5** and **11** are reported in the experimental.

Alkaline hydrolysis of **1** yielded indole-2-carboxyl-*N*-benzylglycine (**15**) which was esterified to its ethyl ester (**16**). This ethyl ester (**16**) was identified by the comparison of ir and mixed m.p. with those of a sample synthesized independently, by condensing indole-2-carbonyl chloride with *N*-benzylglycine ethyl ester.

EXPERIMENTAL

Nmr spectrum was recorded on 60 MHz Varian spectrometer (using TMS as an internal standard), ir spectra on Perkin-Elmer infracord spectrophotometer and uv spectra on a Russian uv spectrophotometer. Melting points are uncorrected.

General Procedure for the preparation of *N*-Alkylamino Acid Ethyl Esters.

The suspension of *dl*-*N*-alkylamino acid in absolute ethanol was saturated with dry gaseous hydrogen chloride, ethanol was removed under reduced pressure on a steam bath and a small quantity of ethanol and dry ether was added. The hydrochloride of the amino acid ethyl ester separated out in 99% yield. A calculated quantity of the dried hydrochloride was dissolved in a minimum quantity of water, covered with ether and then potassium carbonate was added in small portions until it became semisolid. Ether was decanted and the thick paste was extracted with fresh ether. The combined ether extract was dried (potassium carbonate) filtered and then ether was removed under reduced pressure at 30° to obtain the title compound in 98% yield. In the case of *N*-methylglycine ethyl ester, the ether was concentrated to 100 ml. at atmosphere pressure and was used as such.

1,2,3,4-Tetrahydro-2-benzyl-1,4-dioxopyrazino[1,2-*a*]indole (**1**).

Compounds **2**-**4**, **6** and **7** (Table I) were prepared in an analogous fashion.

An etheral solution of indole-2-carboxylic acid (8.0 g., 0.05 mole) was treated with freshly distilled thionyl chloride (11.9 g., 0.1 mole) and the mixture was allowed to stand for 1 hour at room temperature. Ether and the excess of thionyl chloride were removed under reduced pressure at room temperature. The residue was flushed with fresh amounts of dry ether to remove the last traces of thionyl chloride. The semi-crystalline residue was dissolved in dry ether and treated with an etheral solution of *N*-benzylglycine ethyl ester (9.65 g., 0.05 mole) and triethylamine (10.1 g., 0.1 mole). The reaction mixture was kept for 1 hour at room temperature and then refluxed gently for 8 hours. Ether was removed from the reaction mixture and the residue was taken up in benzene, washed with 5% hydrochloric acid, water, dried (sodium sulfate). Solvent was removed and the residue was crystallized from ethanol, yellow needles, m.p. 157-158°, 6 g. (66%); ir (potassium bromide): 1700 (indole N-C=O), 1650 (amide C=O), 1610, 1570, 1440 cm^{-1} (indole ring); uv max (95% ethanol): 239 nm (ϵ, 19,500), 294 nm (ϵ, 17,300); nmr (60 MHz, carbon tetrachloride): δ 4.19 (s, 2H), 4.74 (s, 2H), 7.3 (m, 9H), 8.2 (m, 1H).

Anal. Calcd. for $C_{18}H_{14}N_2O_2$: C, 74.47; H, 4.86; N, 9.65. Found: C, 74.50; H, 5.05; N, 9.43.

1,2,3,4-Tetrahydro-2-methyl-8-benzylosy-1,4-dioxopyrazino-[1,2-*a*]indole (**5**).

Compound **8** was prepared by a similar procedure.

5-Benxyloxyindole-2-carbonyl chloride (prepared from 0.66g., 0.0025 mole of the corresponding acid) in ether was treated with an excess of *N*-methylglycine ethyl ester (prepared from 3.0 g., 0.2 mole of *N*-methylglycine ethyl ester hydrochloride). The reaction was worked up as before. The product was crystallized from ethanol, m.p. 201-202°, 0.51 g. (64%); ir (potassium bromide): 1695 (indole N-C=O), 1645 (amide C=O), 1590, 1440 (indole ring), 1262, 1240 cm^{-1} (aromatic C-O-C): uv max (methanol): 255 nm (ϵ, 27,540), 290 nm (ϵ, 19,050).

Anal. Calcd. for $C_{19}H_{16}N_2O_3$: C, 71.24; H, 5.03; N, 8.75. Found: C, 71.16; H, 5.28; N, 8.63.

1,2,3,4-Tetrahydro-2-methyl-8-hydroxy-1,4-dioxopyrazino[1,2-*a*]-indole (**11**).

Compounds **9**, **10**, **12-14** were prepared in an analogous fashion.

The benzyloxy compound **5** (0.22 g., 0.001 mole) in ethanol was debenzylated under hydrogen at 3 atmospheres pressure for 4 hours in the presence of 10% palladium-carbon (90 mg.). The catalyst was filtered off and the product was crystallized from ethanol, m.p. 256-257° (darkens at 235°); ir (potassium bromide): 3100 (phenol OH), 1660, 1600 cm^{-1}, uv max (methanol): 255 nm (ϵ, 23,440), 291 nm (ϵ, 6,980).

Anal. Calcd. for $C_{12}H_{10}N_2O_3$: C, 62.60; H, 4.38; N, 12.17. Found: C, 62.43; H, 4.08; N, 12.00.

Reaction of **1** with Methyl Iodide (**1** → **2**).

A mixture of **1** (2.9 g., 0.01 mole) in 10 ml. of benzene and methyl iodide (1.42 g., 0.01 mole) was added to a solution of sodium metal 30 mg. in absolute methanol (50 ml.). The reaction mixture was heated at 60° for 5 hours with efficient stirring. The solvent was distilled off and the residue was treated with dilute hydrochloric acid (10%, 50 ml.) in crushed ice. A light yellow powder separated, which was washed, dried and crystallized from methanol, 2.1 g. (69%); m.p. 123°, mixed m.p. with **2**, 123°; ir was found identical with that of **2**

Anal. Calcd. for $C_{19}H_{16}N_2O_2$: C, 74.98; H, 5.30; N, 9.21. Found: C, 74.81; H, 5.47; N, 9.07.

Reaction of **1** with Aqueous Potassium Hydroxide (**1** → **15**).

Compound **1** (0.5 g.) was heated with 10 ml. of 0.5 *N* potassium hydroxide, on a steam bath for 15 minutes. The cooled mixture was acidified with dilute hydrochloric acid. The white precipitate thus obtained was washed, dried and crystallized from ethanol, 0.47 g. (90%); m.p. 213° dec.; ir (potassium bromide): 3230 (carboxylic OH), 3000 (indole NH), 1700 (> C=O), 1630 (amide C=O), 1530, 1500, 1465 (indole ring).

Anal. Calcd. for $C_{18}H_{16}N_2O_3$: C, 70.11; H, 5.23; N, 9.09. Found: C, 69.80; H, 5.16; N, 8.71.

Preparation of the Ethyl Ester of **15** (**15** → **16**).

Compound **15** (0.25 g.) was refluxed with ethanol (25 ml.) for 24 hours in the presence of catalytic amount of sulfuric acid. After working up, the product was crystallized from ethanol and identified as indole-2-carboxyl-*N*-benzylglycine ethyl ester (**16**), m.p. 142°, 0.24 g. (90%); ir (potassium brmoide) was found to be identical with those of a sample obtained by independent synthesis, mixed m.p. with synthetic **16**, 141-142°.

Anal. Calcd. for $C_{20}H_{20}N_2O_3$: C, 71.41; H, 5.99; N, 8.33. Found: C, 71.31; H, 5.90; N, 8.27.

Independent Synthesis of Incole-2-carboxyl-*N*-benzylglycine Ethyl Ester (**16**).

An etheral solution of indole-2-carbonyl chloride (prepared from indole-2-carboxylic acid; 2.1 g., 0.0125 mole) was treated with *N*-benzylglycine ethyl ester (5 g., 0.025 mole) for 1 hour at room temperature. Ether was distilled off and the residue was washed, dried and crystallized from ethanol, 3.65 g. (95%); m.p. 141°, ir (potassium bromide): 3250 (indole NH), 1715 (ester C=O), 1625 (amide C=O), 1500, 1450 cm^{-1} (indole ring).

Anal. Calcd. for $C_{20}H_{20}N_2O_3$: C, 71.41; H, 5.99; N, 8.33. Found: C, 71.18; H, 5.83; N, 8.31.

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