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Received March 29, 1977

4*H*-Furo[3,2-*b*]indole (III) was prepared from deoxygenation of 2-(2-nitrophenyl)furan (II) with triethyl phosphite and thermolysis of 2-(2-azidophenyl)furan (VI). 4*H*- or 4-alkylfuro[3,2-*b*]indole-2-carboxaldehydes (VIII, IXa-c) were obtained by Vilsmeier formylation of the corresponding furo[3,2-*b*]indoles (III, VIIa-c). 4*H*-Furo[3,2-*b*]indole-2-carboxaldehyde (VIII) was submitted to the Cannizzaro, Wittig and reduction reactions. The Schiff's bases were obtained by the reaction of 4-ethylfuro[3,2-*b*]indole-2-carboxaldehyde (IXb) with amines.

*J. Heterocyclic Chem.*, 14, 975 (1977)

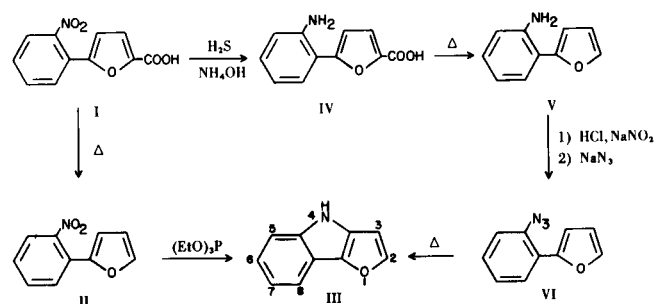
Recently the authors have prepared some furo[2,3-*d*]-pyridazine derivatives in order to study their possible biological activity (2). It is well known that many pharmacologically-active compounds such as serotonin, tryptamine, 3-indolylacetic acid, reserpine and yohimbine possess an indole moiety. Thus furoindoles were of interest to us for their potential biological activity. A search of the literature reveals furoindoles in which the furan ring is fused to the benzene ring of indole (3) and to the pyrrole ring of indole. Derivatives saturated at the 2,3-position (4) or 2,3,4,5-position (5) (structural analogs of physovenine) are reported. Fully aromatic furo[3,2-*b*]indoles or furo[2,3-*b*]indoles have not been reported. Consequently, 2-(2-nitrophenyl)furan appeared to be a useful intermediate for our research.

Cadogan, *et al.* (6) have studied the reaction of nitro and nitroso compounds with tervalent phosphorus reagents in detail. They reported that various carbazoles were conveniently obtained in good yield by deoxygenation of *o*-nitro- and *o*-nitrosobiphenyls by tervalent phosphorus reagents and have suggested a "nitrene" intermediate. Smith, *et al.* (7) have succeeded in preparing the carbazoles through thermolysis of *o*-azidobiphenyls. Similarly, Abramovitch, *et al.* (8) have obtained pyrid[1,2-*b*]indazole in good yields by thermolysis of 2-(2-azidophenyl)pyridine.

Consequently, we have attempted to prepare 4*H*-furo[3,2-*b*]indole (III) from 2-(2-nitrophenyl)furan (II) by using triethyl phosphite as a tervalent phosphorus reagent following the method of Cadogan, *et al.* (6). Compound II was prepared by decarboxylation of 5-(2-nitrophenyl)-2-furoic acid (I) which was synthesized by Meerwein arylation of *o*-nitroaniline and 2-furoic acid (9). Upon refluxing II with triethyl phosphite for five hours in an atmosphere of nitrogen, III was obtained in 34% yield. The structure of III was supported by spectral data and elemental analysis. Compound III was also prepared by thermal ring closure of 2-(2-azidophenyl)furan (VI) in improved yield. 5-(2-Aminophenyl)-2-furoic acid (IV) was

prepared from I with hydrogen sulfide in aqueous ammonia, followed by decarboxylation of IV to give 2-(2-amino-phenyl)furan (V). The diazonium salt of V reacted with sodium azide to give VI. Compound VI eliminated molecular nitrogen to give III upon heating in *o*-dichlorobenzene. This structure was identified with the compound prepared above by mixed melting point and ir spectrum. The synthesis of III (Scheme I) was accomplished in about 30% overall yield from I. Thermal ring closure of VI was better than deoxygenation of II (20%).

Scheme I



4-Alkyl derivatives (VIIa-c) of III were prepared, followed by formylation of III and VIIa-c to give the 2-formyl compounds (VIII and IXa-c) as shown in Scheme II. Thus, 4-alkylfuro[3,2-*b*]indoles (VIIa-c) were prepared from the reaction of substituted III by sodium amide with alkyl iodides (Table I). Vilsmeier formylation of III gave 4*H*-furo[3,2-*b*]indole-2-carboxaldehyde (VIII) in good yield. The position of the formyl group was established at the 2-position, and by the C<sub>3</sub>-proton singlet at  $\delta$  7.79. The Cannizzaro reaction of VIII gave 2-hydroxymethyl-4*H*-furo[3,2-*b*]indole (XII) and 4*H*-furo[3,2-*b*]indole-2-carboxylic acid (XIII) (10). Similarly, formylation of VIIa-c gave 4-alkylfuro[3,2-*b*]indole-2-carboxaldehydes (IXa-c), respectively (Table I). The 4*H*-furo[3,2-*b*]indole-2-vinylene derivatives (Xa-g) were prepared by the condensation of VIII with the corresponding Wittig reagent (Table II). 4-Ethylfuro[3,2-*b*]indole-2-carboxaldehyde

Table I  
*N*-Alkylfuro[3,2-*b*]indoles (VIIa-c) and the 2-Carboxaldehydes (IXa-c)

Compound	R	Appearance	B.p., °C (mm) [M.p., °C]	Yield %	Recrystallization Solvent	Empirical Formula	Calcd. % C H N	Found % C H N
VIIa	-CH <sub>3</sub>	Yellow oil	148-150 (7)	80	-	C <sub>11</sub> H <sub>9</sub> NO	77.17 5.30 8.18	77.10 5.16 8.32
VIIb	-CH <sub>2</sub> CH <sub>3</sub>	Yellow oil	158-160 (10)	63	-	C <sub>12</sub> H <sub>11</sub> NO	77.81 5.99 7.56	77.69 6.13 7.45
VIIc	-CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	Yellow oil	172-174 (14)	25	-	C <sub>13</sub> H <sub>13</sub> NO	78.36 6.58 7.03	78.51 6.60 7.12
IXa	-CH <sub>3</sub>	Blue needles	[104-105]	82	methanol	C <sub>12</sub> H <sub>9</sub> NO <sub>2</sub>	72.35 4.55 7.03	72.11 4.32 7.16
IXb	-CH <sub>2</sub> CH <sub>3</sub>	Yellow needles	[84-85]	85	ethanol	C <sub>13</sub> H <sub>11</sub> NO <sub>2</sub>	73.22 5.20 6.59	72.95 5.14 6.37
IXc	-CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	Yellow scales	[87-88]	72	ethanol	C <sub>14</sub> H <sub>13</sub> NO <sub>2</sub>	73.99 5.77 6.16	74.22 5.63 6.02

Table II

4*H*-Furo[3,2-*b*]indole-2-vinylene Derivatives (Xa-g)


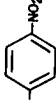

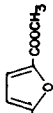
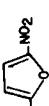

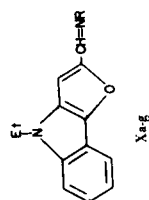
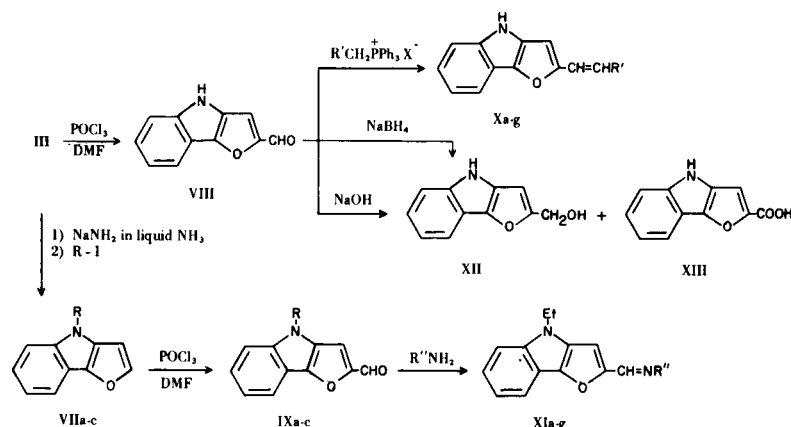
Compound	R	Appearance	M.p., °C	Yield %	Recrystallization Solvent	Empirical Formula	Calcd. % C H N	Found % C H N
Xa	-CONH <sub>2</sub>	Colorless scales	231-232	70	ethanol- water	C <sub>13</sub> H <sub>10</sub> N <sub>2</sub> O <sub>2</sub>	69.01 4.46 12.38	68.77 4.16 12.50
Xb		Yellow plates	193-194	30	ethanol	C <sub>18</sub> H <sub>13</sub> NO	83.37 5.05 5.40	83.15 4.79 5.13
Xc		Reddish needles	245-246	45	ethanol- chloroform	C <sub>18</sub> H <sub>12</sub> N <sub>2</sub> O <sub>3</sub>	71.04 3.98 9.21	71.00 3.76 8.92
Xd		Reddish needles	179-180	55	methanol	C <sub>19</sub> H <sub>12</sub> N <sub>2</sub> O	80.26 4.25 9.85	80.48 3.97 9.66
Xe		Yellow needles	247-248	58	chloroform	C <sub>18</sub> H <sub>13</sub> NO <sub>4</sub>	70.35 4.26 4.56	70.30 4.12 4.34
Xf		Golden crystals	201-202	28	methanol- dioxane	C <sub>16</sub> H <sub>10</sub> N <sub>2</sub> O <sub>4</sub>	65.30 3.41 9.52	65.19 3.05 9.80
Xg		Yellow scales	195-196	50	methanol- chloroform	C <sub>16</sub> H <sub>11</sub> NOS	72.42 4.18 5.28	72.20 3.92 4.99

Table III  
*N*-Ethylfuro[3,2-*b*]indole-2-carboxaldehyde Schiff's Bases (XIa-g)



Compound	R	Appearance	M.p. °C	Yield %	Recrystallization Solvent	Empirical Formula	Calcd. %		Found %		
							C	H	C	H	N
XIa	-OH	Brown crystals	130-131	93	benzene-petroleum benzin	C <sub>13</sub> H <sub>12</sub> N <sub>2</sub> O <sub>2</sub>	68.41	5.30	68.30	5.60	12.15
XIb	-NHCONH <sub>2</sub>	Yellow prisms	197-199	92	ethanol	C <sub>14</sub> H <sub>14</sub> N <sub>4</sub> O <sub>2</sub>	62.21	5.22	61.95	5.10	20.47
XIc	-NHCSNH <sub>2</sub>	Yellow prisms	209-210	91	ethanol	C <sub>14</sub> H <sub>14</sub> N <sub>4</sub> OS	58.72	4.93	58.73	4.86	19.34
XId		Yellow plates	129-130	65	ethanol	C <sub>22</sub> H <sub>20</sub> N <sub>2</sub> O <sub>3</sub>	73.31	5.59	73.03	5.71	7.98
XIe		Yellow prisms	226-227	94	acetone	C <sub>16</sub> H <sub>15</sub> N <sub>3</sub> O <sub>3</sub>	64.63	5.09	64.44	5.00	13.98
XIf		Yellow needles	204-205	90	ethanol	C <sub>19</sub> H <sub>16</sub> N <sub>4</sub> O <sub>2</sub>	68.66	4.85	68.40	4.69	16.60
XIg		Yellow	245-247	75	acetone	C <sub>24</sub> H <sub>22</sub> N <sub>2</sub> O <sub>4</sub>	72.34	5.57	72.50	5.54	13.84

Scheme II



Shiff's bases (XIa-g) were obtained from IXb with the corresponding amines (Table III). Also XII was prepared from VIII with sodium borohydride. The chlorination of XII with thionyl chloride was unsuccessful. An examination of the structure of XII suggests it be relatively unstable in acidic medium. Detailed chemical properties of the 4H-furo[3,2-b]indole ring system will be described in a forthcoming paper. The determination of the pharmacological activity of the compounds prepared are in progress.

#### EXPERIMENTAL

Melting points are uncorrected. The ir spectra were measured with a Jasco IRA-1 spectrometer and the nmr spectra were recorded on a JEOL-PS-100 spectrometer using tetramethylsilane as an internal standard. Mass spectra were taken with a Hitachi RMU-6 spectrophotometer.

**4H-Furo[3,2-b]indole (III).** Reaction of 2-(2-Nitrophenyl)furan (II) with Triethyl Phosphite.

A solution of 2 g. (0.011 mole) of II in 8.8 g. (0.053 mole) of triethyl phosphite was refluxed in an atmosphere of nitrogen for 5 hours. After evaporation of excess triethyl phosphite *in vacuo*, the residue was purified by column chromatography on silica gel. Elution with benzene gave 0.57 g. (34%) of III as colorless scales, m.p. 81-82°; ir  $\nu$  max (potassium bromide) cm<sup>-1</sup>: 3330 (NH); nmr  $\delta$  (deuteriochloroform): 7.53 (1H, d, J = 2 Hz, C<sub>2</sub>-H), 7.41 (5H, m, C<sub>5-8</sub>-H and NH), 6.52 (1H, d, J = 2 Hz, C<sub>3</sub>-H); ms (m/e): 157 (M<sup>+</sup>).

*Anal.* Calcd. for C<sub>10</sub>H<sub>7</sub>NO: C, 76.42; H, 4.49; N, 8.91. Found: C, 76.31; H, 4.49; N, 8.74.

**5-(2-Aminophenyl)-2-furoic Acid (IV).**

The mixture of 200 g. (0.858 mole) of 5-(2-nitrophenyl)-2-furoic acid (I) dissolved in 2000 ml. of 14% aqueous ammonia was saturated with hydrogen sulfide at such a rate that the temperature did not rise above 50°. The reaction mixture was then allowed to reflux for 5 hours. The mixture was filtered to remove sulfur and the filtrate was acidified with concentrated hydrochloric acid. The resulting product was filtered off and purified by recrystallization from ethyl acetate to give 123 g. (71%) of IV as brown prisms, m.p. 159-160°.

*Anal.* Calcd. for C<sub>11</sub>H<sub>9</sub>NO<sub>3</sub>: C, 65.02; H, 4.46; N, 6.89. Found: C, 65.31; H, 4.26; N, 6.59.

**2-(2-Aminophenyl)furan (V).**

A mixture of 100 g. (0.492 mole) of IV in 1000 ml. of xylene was refluxed for 10 hours with stirring. Evaporation of the solvent gave a brown oil, which was purified by distillation *in vacuo* to give 66 g. (85%) of V as yellow oil, b.p.<sub>6</sub> 134-136°; ir  $\nu$  max (film) cm<sup>-1</sup>: 3500, 3390 (NH<sub>2</sub>).

*Anal.* Calcd. for C<sub>10</sub>H<sub>9</sub>NO: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.56; H, 5.91; N, 9.01.

**2-(2-Azidophenyl)furan (VI).**

A mixture of 15.9 g. (0.1 mole) of V in 18 ml. of concentrated hydrochloric acid was cooled in an ice-salt-bath. To the cold solution was added 7.6 g. of sodium nitrite in 20 ml. of water. The cold reaction mixture was then allowed to stand with frequent stirring for 45 minutes and then to the cold diazonium solution was added dropwise a solution of 13 g. of sodium azide in 30 ml. of water. After all of the azide had been added, the solution was allowed to stand at room temperature for half an hour. The dark-reddish oil which formed was separated, and combined with the ether extracts of the water layer. Evaporation of the ether gave 15.2 g. (82%) of VI as dark-reddish oil; ir  $\nu$  max (film) cm<sup>-1</sup>: 2200 (N<sub>3</sub>); ms (m/e): 185 (M<sup>+</sup>).

**4H-Furo[3,2-b]indole (III).** Thermolysis of VI.

A solution of 14.8 g. (0.08 mole) of VI (not distilled) in 15 ml. of *o*-dichlorobenzene was added dropwise to 60 ml. of boiling *o*-dichlorobenzene with stirring. After 1 hour, the crystalline residue which was obtained by evaporation of the solvent *in vacuo* was extracted with boiling petroleum benzin 5 times and treated with charcoal, which gave 7.5 g. (60%) of III as colorless scales, which was identified by mixed melting point and ir with those of III prepared by deoxygenation of II.

**4-Alkylfuro[3,2-b]indoles (VIIa-c).**

To a 200 ml. of liquid ammonia containing 0.01 g. of ferric nitrate was added 0.25 g. (0.011 g.-atom) of sodium with vigorous stirring. After dissolution was complete, a solution of 1.57 g. (0.01 mole) of III in 5 ml. of ether was added slowly and then after an additional 10 minutes, a solution of 0.011 mole of alkyl iodide in an equal volume of ether was added dropwise. Stirring was continued for an additional 15 minutes. The ammonia was allowed to evaporate and 10 ml. of water was added followed by

20 ml. of ether. The ether layer was separated, the aqueous phase extracted with 20 ml. of ether, and the combined ether extracts washed with water and dried over magnesium sulfate. The solvent was removed and the crude oil was purified by distillation *in vacuo*, which gave VIIa-c (Table I).

#### 4*H*-Furo[3,2-*b*]indole-2-carboxaldehyde (VIII).

To a mixture of 3 g. (0.04 mole) of dimethylformamide and 1.7 g. (0.011 mole) of phosphorus oxychloride which was kept 0-5° for 20 minutes was added 1.57 g. (0.01 mole) of III in 3 g. of dimethylformamide with stirring at a rate such that the temperature of the reaction mixture did not rise above 20°. After the addition was complete, the mixture was kept at 0-5° for 1 hour and then at room temperature for 45 minutes. The reaction mixture was poured into 200 ml. of ice-water, neutralized with 3 g. (0.028 mole) of sodium carbonate and allowed to stand overnight. The resulting product was filtered off and purified by recrystallization from ethanol to give 1.5 g. (81%) of VIII as yellow-green scales, m.p. 180-181°;  $\nu$  max (potassium bromide)  $\text{cm}^{-1}$ : 3280 (NH), 1640 (C=O); nmr  $\delta$  (dimethyl sulfoxide- $\text{d}_6$ ): 10.64 (1H, br, NH), 9.61 (1H, s, CHO), 7.79 (1H, s, C<sub>3</sub>-H), 7.51 (4H, m, C<sub>5-8</sub>-H); ms ( $m/e$ ): 185 ( $\text{M}^+$ ).

*Anal.* Calcd. for  $\text{C}_{11}\text{H}_7\text{NO}_2$ : C, 71.35; H, 3.81; N, 7.56. Found: C, 71.45; H, 3.51; N, 7.46.

#### 4-Alkylfuro[3,2-*b*]indole-2-carboxaldehydes (IXa-c).

The procedure described for VIII was employed to convert VIIa-c to IXa-c as shown in Table I.

#### 4*H*-Furo[3,2-*b*]indole-2-vinylene Derivatives (Xa-g).

To a mixture of 1 g. (0.0054 mole) of VIII and equimolar triphenyl phosphonium salts in 40 ml. of methanol was added 0.29 g. (0.0054 mole) of sodium methoxide with stirring at room temperature. After 1 hour, the reaction mixture was treated as usual to give Xa-g (Table II).

#### 4-Ethylfuro[3,2-*b*]indole-2-carboxaldehyde Schiff's Bases (XIa-g).

To a solution of 1 g. (0.0047 mole) of IXb in a little ethanol was added equimolar amines and then 3 drops of acetic acid (sodium acetate was used on XIa and XIb which were used as the amines hydrochlorides) were added. After heating for 5 minutes, the reaction mixture was treated as usual to give XIa-g (Table III).

#### 2-Hydroxymethyl-4*H*-furo[3,2-*b*]indole (XII) and 4*H*-furo[3,2-*b*]indole-2-carboxylic Acid (XIII).

A mixture of 1.85 g. (0.01 mole) of VIII in 10 ml. of 33% sodium hydroxide solution was heated at 80° for half an hour. The reaction mixture was allowed to come to room temperature, and 10 ml. of water was added. The resulting product was filtered and purified by recrystallization from benzene to give 0.5 g. (27%) of XII as colorless scales, m.p. 109-110°;  $\nu$  max (potassium bromide)  $\text{cm}^{-1}$ : 3360 (NH, OH); nmr  $\delta$  (dimethyl sulfoxide- $\text{d}_6$ ): 10.78 (1H, br, NH), 7.32 (4H, m, C<sub>5-8</sub>-H), 6.65 (1H, s, C<sub>3</sub>-H), 5.36 (1H, t,  $J = 5.7$  Hz, OH), 4.58 (2H, d,  $J = 5.7$  Hz, CH<sub>2</sub>).

*Anal.* Calcd. for  $\text{C}_{11}\text{H}_9\text{NO}_2$ : C, 70.58; H, 4.85; N, 7.48. Found: C, 70.44; H, 4.72; N, 7.25.

The filtrate was acidified with 10% hydrochloric acid and the product filtered and purified by recrystallization from acetone to give 0.5 g. (25%) of XIII as colorless scales, m.p. 229-230°;  $\nu$  max (potassium bromide)  $\text{cm}^{-1}$ : 3410 (NH), 2990 (OH), 1660 (C=O); nmr  $\delta$  (dimethylsulfoxide- $\text{d}_6$ ): 11.15 (1H, br, NH), 7.56 (1H, s, C<sub>3</sub>-H), 7.48 (4H, m, C<sub>5-8</sub>-H).

*Anal.* Calcd. for  $\text{C}_{11}\text{H}_7\text{NO}_3$ : C, 65.67; H, 3.51; N, 6.96. Found: C, 65.83; H, 3.28; N, 6.72.

#### 2-Hydroxymethyl-4*H*-furo[3,2-*b*]indole (XII).

To a solution of 1.85 g. (0.01 mole) of VIII in 300 ml. of ethanol was added a solution of 0.2 g. (0.005 mole) of sodium borohydride in 23 ml. of 2*N* sodium hydroxide solution, and the mixture was then stirred for 1 hour. After evaporation of ethanol, the residue was poured into ice-water. The resulting product was filtered and purified by recrystallization from benzene to give 1.4 g. (75%) of XII as colorless scales, identified by mixed melting point and ir with XII prepared by the Cannizzaro reaction of VIII.

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- (10) We decided to describe the position of another formyl group in the latter paper. Namely, 4*H*-furo[3,2-*b*]indole-2-carboxylic acid (XIII) was identified with the compound synthesized *via* hydrolysis of ethyl 4*H*-furo[3,2-*b*]indole-2-carboxylate prepared from thermolysis of ethyl 5-(2-azidophenyl)-2-furoate by mixed melting point test and ir spectrum.