

## The Synthesis of Thiaolivacine and Related Compounds (I)

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1,5-Dimethylbenzothieno[2,3-*g*]isoquinoline (thiaolivacine) has been prepared from the nitrovinyl derivative of 4-methyl-3-dibenzothiophenecarboxaldehyde. Using the same aldehyde, 4-*des*-methylisothiaolivacine was prepared by formation of the Schiff's base with aminoacetaldehyde diethyl acetal followed by cyclization. Similar methods yielded the pyrido-*N*-isomer, 1-*des*-methylthiaolivacine, from 4-methyl-2-dibenzothiophenecarboxaldehyde. The thiaolivacine parent unsubstituted ring system, benzothieno[2,3-*g*]isoquinoline, was prepared from 2-dibenzothiophenecarboxaldehyde by the aminoacetaldehyde approach, as was the corresponding oxygen analog, benzofuro[2,3-*g*]isoquinoline, from 2-dibenzofurancarboxaldehyde. The 100 MHz spectra of these fused isoquinolines are recorded and correlated.

Interest has recently been shown in the antitumor properties of the indole alkaloids olivacine and ellipticine (2). Several analogs of these alkaloids have been prepared including a recent synthesis of thiaellipticine (1) (3) and isothiaellipticine (11) (2). The synthesis of analogs of these alkaloids is beneficial both as a means of searching for more active or specific antitumor compounds and as a means of developing or refining a theory explaining the mode of action of these compounds on tumors (4). A related series of compounds with these aims in mind has recently been reported from these laboratories (5).

Condensation of 4-methyl-3-dibenzothiophenecarboxaldehyde (IIIa) (6) with nitromethane yielded the nitrovinyl compound (IIIb) which was reduced with lithium aluminum hydride to 4-methyl-3-(2'-aminoethyl)dibenzothiophene (IIIc). Bischler-Napieralski cyclization of the derived acetamido compound (III'd) gave 1,5-dimethyl-3,4-dihydrobenzothieno[2,3-*g*]isoquinoline (IV). Dehydrogenation with palladium on charcoal gave 1,5-dimethylbenzothieno[2,3-*g*]isoquinoline (V) (thiaolivacine). Condensation of the same aldehyde (IIIa) with aminoacetaldehyde diethyl acetal gave the Schiff's base (IIIe) which was cyclized in 105% phosphoric acid to yield 11-methylbenzothieno[3,2-*g*]isoquinoline (VI) (4-*des*-methylisothiaolivacine). Similarly, treatment of the isomeric aldehyde, 4-methyl-2-dibenzothiophenecarboxaldehyde (VIIa) (6) with aminoacetaldehyde diethyl acetal yielded VIIIb which cyclized to 5-methylbenzothieno[2,3-*g*]isoquinoline (VIII) (1-*des*-methylthiaolivacine). In the latter case cyclization was shown to have occurred at the 3-position of the dibenzothiophene nucleus, yielding the linearly fused product, by the presence of a singlet at  $\delta$  8.2 in the 100 MHz nmr spectrum of VIII. This singlet, associated with H-11 is also present in thiaolivacine (V,  $\delta$  8.24). Had

cyclization occurred in the 1-position a singlet for H-3 (numbering for dibenzothiophene) would have been observed at  $\delta$  ca. 7.4 (7).

Benzothieno[2,3-*g*]isoquinoline (IX), the parent unsubstituted ring system of thiaolivacine, was prepared by condensation of 2-dibenzothiophenecarboxaldehyde (7) with aminoacetaldehyde diethyl acetal, followed by cyclization. This compound was again shown to possess linearly fused rings by the presence of sharp singlets in its 100 MHz nmr spectrum at  $\delta$  8.06 and 8.48 associated with H-5 and H-11. Had cyclization occurred in the 1-position doublets for H-3 and H-4 (numbering for dibenzothiophene) would have been observed. Bright yellow needles were formed when IX was treated with methyl iodide in ethanol; however, upon heating at its melting point (ca. 280°) the parent compound (IX) sublimed. This, coupled with the fact that in its mass spectrum only methyl iodide (*m/e* 142) and the parent compound (*m/e* 235) with its normal decay pattern could be observed suggests that the product is a molecular complex rather than a mono-methiodide salt.

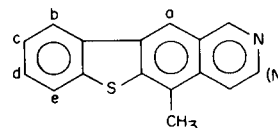
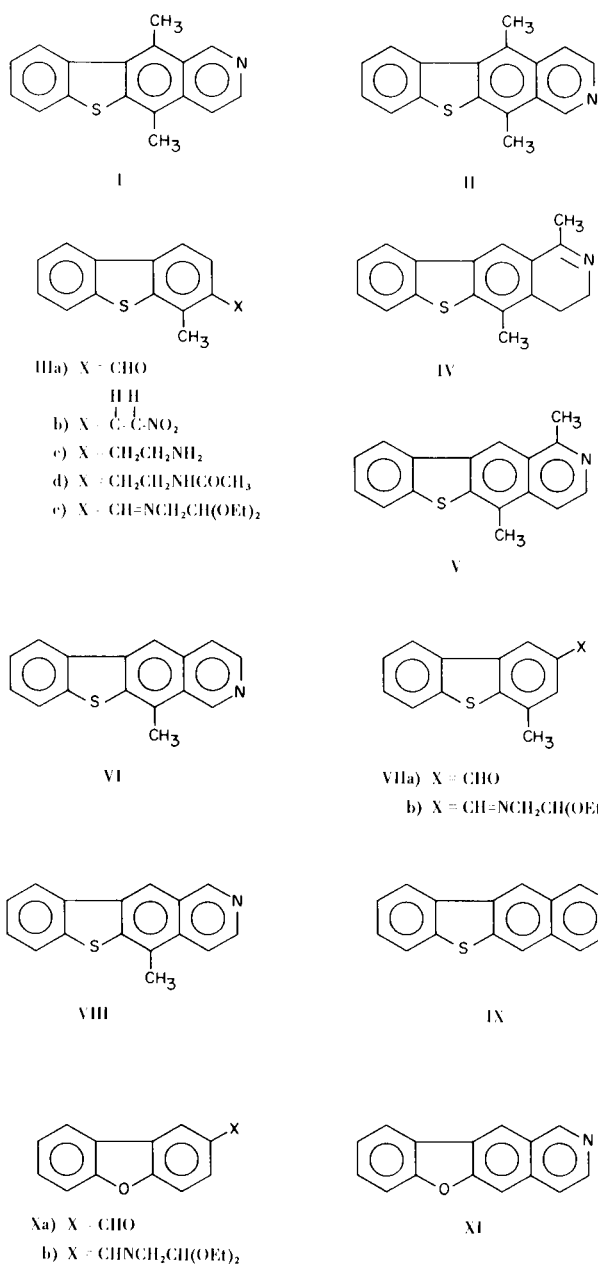


Figure 1

By comparison of the 100 MHz nmr spectra of compounds V, VI, VIII, and the published but not fully assigned spectra of 1 (3) and 11 (2) it is possible to distinguish between the pyrido-*N*-isomers of compounds substituted with a methyl group in the position shown in Figure 1. Reference to the spectra of V, VI and VIII

reveals that the resonance of proton a (Figure 1) occurs at *ca.*  $\delta$  8.2 irrespective of the position of the pyridine nitrogen. The methyl group resonance of such compounds (Figure 1) is however sensitive to changes in the pyridine nitrogen. In the series I, V, and VIII the average value for this resonance is  $\delta$  2.52; however in the *iso* compound VI this resonance occurs at  $\delta$  2.87, being deshielded by 45 Hz from the methyl resonance in 4-methyldibenzothiophene ( $\delta$  2.42). We have thus assigned the two methyl resonances in the published spectrum of II (2) as follows. The C-5 methyl group of II (position a in Figure 1)  $\delta$  2.75 and the C-11 methyl group  $\delta$  2.90. Thus the methyl resonance in



position a of compound I (3), II (2), and 1,4-dimethyldibenzothiophene (3) will remain constant at *ca.*  $\delta$  2.77 as was observed for a proton in this position, while the methyl group shown in Figure 1 will be deshielded by 42 Hz from 1,4-dimethyldibenzothiophene in isothiaellipticine (II).

2-Dibenzofurancarboxaldehyde (Xa) (8) was prepared from 2-bromodibenzofuran (9) by lithium exchange followed by treatment with *N,N*-dimethylformamide. Analysis of the 100 MHz nmr spectrum of Xa revealed a similar pattern to that observed for 2-dibenzothiophenecarboxaldehyde (7), in particular a broadened singlet ( $J_{1,3}$  2 Hz) at  $\delta$  8.41 associated with H-1. This would indicate that the nmr theory outlined recently for 2- and 3-substituted dibenzothiophenes (7) can be applied to dibenzofuran chemistry. Condensation of Xa with aminoacetaldehyde followed by cyclization yielded benzofuro[2,3-*g*]isoquinoline (XI) (10), the oxygen analog of IX. Again the linearity of the molecule was established by the presence of singlets at  $\delta$  7.76 and 8.4 in its 100 MHz nmr spectrum associated with H-5 and H-11 respectively.

#### EXPERIMENTAL

Melting points were determined on a Mel-Temp melting point apparatus and are corrected. Infrared spectra were measured on potassium bromide mulls on an Infracord Model 137-B spectrometer. The 100 MHz nmr spectra were determined in deuteriochloroform on a Varian HA-100 instrument at 20°, with TMS used as internal lock throughout. Proton integrations were carried out routinely and in all cases supported the structure assignments made. In reporting the nmr spectra the following abbreviations have been made: s = singlet; d = doublet; dd = double doublet; m = multiplet (refers to the center of the multiplet resonance). Ether solutions were dried with anhydrous magnesium sulfate. The 105% superphosphoric acid was prepared from 85% orthophosphoric acid (110 g.) and phosphorus pentoxide (56 g.), this gave 165 g. of 105% phosphoric acid (75%  $\text{P}_2\text{O}_5$ ).

#### 4-Methyl-3-(2'-nitrovinyl)dibenzothiophene (IIIb).

A mixture of IIIa (6) (0.18 g., 0.00079 mole), ammonium acetate (0.2 g.) and nitromethane (0.6 ml.) dissolved in 6 ml. of acetic acid was refluxed for 2 hours. The resultant yellow solid and solution was poured onto ice, filtered and dried (0.18 g., 84%), m.p. 213-225°. Crystallization from ethyl acetate gave the product as gleaming orange-yellow plates, m.p. 228°;  $\text{ir } \mu$  6.2 and 6.7 (nitro).

*Anal.* Calcd. for  $\text{C}_{15}\text{H}_{11}\text{NO}_2\text{S}$ : C, 66.9; H, 4.12; N, 5.20. Found: C, 66.8; H, 4.21; N, 5.14.

#### 4-Methyl-3-(2'-aminoethyl)dibenzothiophene (IIIc).

A solution of IIIb (2.69 g., 0.0111 mole) in anhydrous tetrahydrofuran (300 ml.) was added to an excess of lithium aluminum hydride in tetrahydrofuran (50 ml.) and the stirred mixture refluxed for 3.5 hours. Excess hydride was destroyed with ethyl acetate and the resultant suspension filtered. The filtrate was then poured into water (1 l.) and extracted with ether (2 x 200 ml.). Evaporation of the dried ethereal extracts gave the product as an oil (1.69 g., 70%);  $\text{ir } \mu$  3.1 (broad, NH). The hydrochloride was prepared by treating a solution of the amine in tetrahydrofuran with

a few drops of hydrochloric acid and filtering the resultant colorless solid. Crystallization from ethanol-water gave IIIc-HCl, m.p. 290-292°.

*Anal.* Calcd. for  $C_{15}H_{16}ClNS$ : C, 64.8; H, 5.80; N, 5.0; Cl, 12.7. Found: C, 64.4; H, 5.91; N, 4.8; Cl, 12.4.

#### 4-Methyl-3-(2'-acetamidoethyl)dibenzothiophene (III d).

A solution of IIIc (1.68 g., 0.00697 mole) in pyridine (20 ml.) was treated with acetic anhydride (1.68 ml.) on a steam bath for 25 minutes. The solvent was removed under reduced pressure and the resultant semi-solid triturated with acetic acid (1M, 15 ml.). The resultant solid was filtered, washed with water and dried (1.88 g., 95%), m.p. 123-127°. Recrystallization from ethanol-water gave an analytical sample, m.p. 128-130°;  $\text{ir } \mu$  3.1 (N-H), 6.1 and 6.4 (amide).

*Anal.* Calcd. for  $C_{17}H_{17}NOS$ : C, 72.0; H, 6.05; N, 4.9. Found: C, 72.2; H, 5.95; N, 4.7.

#### 1,5-Dimethyl-3,4-dihydrobenzothieno[2,3-g]isoquinoline (IV).

A solution of III d (1.88 g., 0.0063 mole) in toluene (120 ml.) was distilled for a few minutes to remove traces of moisture from the system. Phosphorus oxychloride (15 ml.) was then introduced and the mixture refluxed for 2 hours. Upon removing the solvent under reduced pressure a semi-solid was formed which was extracted with hydrochloric acid (18%; 2 x 100 ml.). Basification with sodium hydroxide and extraction with methylene chloride (3 x 100 ml.) gave, upon evaporation, 1.13 g. (65%) of IV, m.p. 174-178°. An analytical sample from ethanol-water had m.p. 178°;  $\text{ir } \mu$  6.15 (imine).

*Anal.* Calcd. for  $C_{17}H_{15}NS$ : C, 77.0; H, 5.69; N, 5.26. Found: C, 76.9; H, 5.65; N, 5.16.

#### 1,5-Dimethylbenzothieno[2,3-g]isoquinoline (Thiaolivacine) (V).

A mixture of IV (1.41 g., 0.0053 mole) and palladium on carbon (30%, 1.5 g.) in decalin (70 ml.) was refluxed for 3 hours. The solution was filtered hot and allowed to cool to room temperature. Hydrochloric acid (36%, ca. 0.5 ml.) was added to the rapidly stirred solution and the yellow hydrochloride filtered, stirred with 10% sodium hydroxide and extracted with methylene chloride (3 x 50 ml.). Removal of the solvent gave a solid which was crystallized from ethanol-water as needles (0.850 g., 61%) m.p. 124° (softens) 137-140°. Recrystallization from benzene gave material, m.p. 139-141°;  $\text{uv}$  (ethanol) 230, 239, 257, 270 (sh) 280, and 286  $\mu$  ( $\epsilon = 30,700, 29,800, 27,200, 42,100, 68,000$  and  $69,760$ );  $\text{nmr } \delta$  8.28 (d,  $J_{3,4} = 6$  Hz; H-3), 8.24 (s, H-11), 7.96 (m, H-10), 7.65 (m, H-7), 7.38 (m, H-4, 8 and 9), 2.92 (s, 1- $CH_3$ ) and 2.53 (s, 5- $CH_3$ ).

*Anal.* Calcd. for  $C_{17}H_{13}NS$ : C, 77.5; H, 4.97; N, 5.32; MW, 263. Found: C, 77.5; H, 4.90; N, 5.40; MW (mass spec.) 263.

#### 4-Methyl-3-(2',2'-diethoxyethylimino)methylidibenzothiophene (III e).

A mixture of 4-methyl-3-dibenzothiophenecarboxaldehyde (III a) (6) (7.00 g., 0.0309 mole) and aminoacetaldehyde diethyl acetal (5.92 g., 6.44 ml., 0.0443 mole) was heated at 95-100° for 2.5 hours. Four portions of benzene (10 ml.) were added and distilled to remove traces of water. Removal of the solvent left a solid which was crystallized as needles (8.30 g., 79%, m.p. 81-83.5°);  $\text{ir } \mu$  3.51, 6.16 (C=N), 6.97. Two further recrystallizations raised the m.p. to 85-86° for a sample of analytical purity.

*Anal.* Calcd. for  $C_{20}H_{23}NO_2S$ : C, 70.3; H, 6.80; N, 4.10. Found: C, 70.1; H, 6.91; N, 4.09.

#### 11-Methylbenzothieno[3,2-g]isoquinoline (VI).

4-Methyl-3-(2',2'-diethoxyethylimino)methylidibenzothiophene (III e) (6.00 g., 0.0175 mole) was added with stirring to 165 g. of freshly prepared superphosphoric acid at 140°. The mixture was kept between 135° and 136° for 25 minutes and then poured into water (250 ml.) with rapid stirring. The insoluble phosphate salt of the product was allowed to coagulate for one hour and filtered. The phosphate was then stirred into hydrochloric acid (250 ml., 18%) at 85°. The stirring was continued for 15 minutes and the bright yellow solution filtered hot. On cooling bright yellow crystals of the hydrochloride of the product separated (1.12 g., 22%), m.p. 240-245°. The reaction mixture was extracted with a further portion of hydrochloric acid (180 ml., 18%), filtered hot, basified with sodium hydroxide and extracted with methylene chloride (3 x 10 ml.). Removal of the solvent gave a light brown solid which was crystallized from aqueous methanol as needles (0.9 g., 20%), m.p. 155-157°. All filtrates and contaminated glassware were further extracted in 18% hydrochloric acid (4 l.) at 80° for 1 hour. The solution was filtered, basified, and extracted as before yielding a further crop of needles (1.00 g., 23%), m.p. 157-159°. The total yield of product was 65%;  $\text{uv}$  (ethanol) 230, 244, 267 and 269  $\mu$  ( $\epsilon = 24,900, 30,200, 45,400$  and  $68,900$ );  $\text{nmr } \delta$  9.50 (s, broad, H-1), 8.50 (d,  $J_{3,4} = 6$  Hz; H-3), 8.21 (s, H-5), 8.02-8.20 (m, H-6), 7.76 (m, H-9), 7.66 (d,  $J_{4,3} = 6$  Hz; H-4), 7.46 (m, H-7,8) and 2.87 (s, 11- $CH_3$ ).

*Anal.* Calcd. for  $C_{16}H_{11}NS$ : C, 77.1; H, 4.45; N, 5.62. Found: C, 77.0; H, 4.36; N, 5.76.

#### 4-Methyl-2-(2',2'-diethoxyethylimino)methylidibenzothiophene (VII b).

This was prepared from VII a (6) by the method used for III e. The product crystallized from hexane as needles (78%), m.p. 75.5-77.5°. A further recrystallization from hexane gave material of analytical purity, m.p. 78.5-80°;  $\text{ir } \mu$  3.49, 6.18 (C=N), 9.44.

*Anal.* Calcd. for  $C_{20}H_{23}NO_2S$ : C, 70.3; H, 6.80; S, 9.4. Found: C, 70.3; H, 6.86; S, 9.5.

#### 5-Methylbenzothieno[2,3-g]isoquinoline (VIII).

After adding VII b (1.50 g., 0.0044 mole) with stirring to 42 g. of freshly prepared 105% phosphoric acid at 145°, the mixture was kept at 138-140° for 25 minutes and poured into ice water with rapid stirring. The insoluble phosphate salt was allowed to coagulate for 1 hour and filtered. The phosphate was stirred into boiling 38% hydrochloric acid (100 ml.) and filtered while hot. The yellow solution was basified with 25% aqueous sodium hydroxide and the precipitate extracted with methylene chloride (3 x 75 ml.). Evaporation of the solvent gave a brown oil which slowly crystallized. Recrystallization from benzene gave the product as yellow needles (0.30 g., 27%), m.p. 126-127°. A further recrystallization raised the m.p. to 129.5-131°;  $\text{uv}$  (ethanol) 229, 240, 268, 278 and 285  $\mu$  ( $\epsilon = 35,000, 28,150, 40,800, 64,950, 71,100$ );  $\text{nmr } \delta$  9.21 (s, H-1), 8.44 (d,  $J_{3,4} = 6$  Hz, H-3), 8.20 (s, H-11), 8.01 (m, H-10), 7.85 (m, H-4,7), 7.38 (m, H-8,9) and 2.63 (s, 5- $CH_3$ ).

*Anal.* Calcd. for  $C_{16}H_{11}NS$ : C, 77.1; H, 4.45; N, 5.62. Found: C, 76.8; H, 4.64; N, 5.60.

#### 2-(2',2'-Diethoxyethylimino)methylidibenzothiophene.

This was prepared from 2-dibenzothiophenecarboxaldehyde (7) by the method used for III e (63%), m.p. 48-50°. An analytical sample from hexane had m.p. 54-54.5°;  $\text{ir } \mu$  6.1 (imine).

*Anal.* Calcd. for  $C_{19}H_{21}NO_2S$ : C, 69.7; H, 6.47; N, 4.28. Found: C, 69.6; H, 6.56; N, 4.35.

Benzothieno[2,3-*g*]isoquinoline (IX).

2-(2',2'-Diethoxyethylimino)methylidibenzothiophene (4.08 g., 0.013 mole) was added with stirring to freshly prepared 105% phosphoric acid (120 g.) at 140°. The mixture was kept at 135-140° for 25 minutes and poured with rapid stirring onto ice (250 g.). The insoluble phosphate was filtered and extracted with boiling hydrochloric acid (18%, 3 x 100 ml.). The acid solution was filtered hot and made basic with sodium hydroxide. The resultant cloudy solution was extracted with methylene chloride (3 x 100 ml.). Evaporation gave the product which was crystallized from isopropyl alcohol-water, m.p. 170-172° (1.168 g., 60%). An analytical sample from benzene had m.p. 174-175°; uv (ethanol) 231, 238, 268 (sh), 276 and 284 m $\mu$  ( $\epsilon = 41,200, 32,200, 41,200, 65,600$  and  $80,300$ ); nmr  $\delta$  9.32 (s, H-1), 8.48 (s, H-11), 8.44 (d, J<sub>3,4</sub> 6 Hz; H-3), 8.1 (m, H-10), 8.06 (s, H-5), 7.92 (m, H-7) and 7.5 (m, H-4, 8,9).

*Anal.* Calcd. for C<sub>15</sub>H<sub>9</sub>NS: C, 76.6; H, 3.86; N, 5.95. Found: C, 76.4; H, 3.97; N, 6.04.

The hydrochloride was prepared from the above product by treating a warm ethanolic solution (0.5 g. in 40 ml.) with a few drops of concentrated hydrochloric acid. The yellow product was filtered (0.56 g., 97%), m.p. 285-290°. An analytical sample from ethanol-water had m.p. 293° (soften) 320° dec.; ir  $\mu$  3.8 and 4.2 (N<sup>+</sup>H).

*Anal.* Calcd. for C<sub>15</sub>H<sub>10</sub>ClNS: C, 66.3; H, 3.69; Cl, 13.1. Found: C, 66.6; H, 3.99; Cl, 13.1.

## Reactions of IX with Methyl Iodide.

A warm solution of IX (640 mg., 0.00272 mole) in ethanol (12 ml.) and methyl iodide (6.5 ml.) was kept at room temperature for 30 minutes and cooled in an ice bath for 15 minutes. The resultant yellow crystals were filtered (550 mg.) m.p. 272-275° dec. Crystallization from a large volume of ethanol raised the m.p. to 284° dec.

*Anal.* Calcd. for C<sub>16</sub>H<sub>12</sub>INS (mono-methiodide): C, 50.9; H, 3.28; N, 3.80; I, 33.6. Found: C, 50.8; H, 3.39; N, 3.61; I, 35.8.

The mass spectrum showed strong peaks at 142 (CH<sub>3</sub>I) and 235 (parent compound) indicating the product to be a molecular complex. Heating a sample of this compound at 280° caused the parent compound (IX) to sublime, m.p. 174°.

## 2-Dibenzofurancarboxaldehyde (Xa) (8).

Butyllithium (37.7 ml., 0.0627 mole, 15% solution in hexane) was added with stirring to a solution of 2-bromodibenzofuran (9) (15.0 g., 0.607 mole) in 250 ml. of sodium-dried ether under a nitrogen atmosphere. After stirring for 2 minutes a solution of *N,N*-dimethylformamide (3.46 g., 5.45 ml., 0.0647 mole) in 100 ml. of sodium-dried ether was added, and the mixture refluxed for 2 hours. The resultant solution was hydrolyzed with 3*N* hydrochloric acid (60 ml.), extracted with ether (3 x 60 ml.) and the ether extracts combined and washed with 1*N* hydrochloric acid and sodium bicarbonate. The extract was dried and the solvent evaporated leaving a semi-solid which solidified under vacuum. Repeated recrystallization from light petroleum gave the product as a white powder (2.55 g., 21.5%), m.p. 66.5-68° (lit. (8) m.p. 68°): ir  $\mu$  3.7 and 5.98 (CHO) 12.4 and 13.45; nmr  $\delta$  8.41 (d, J<sub>1,3</sub> 2 Hz; H-1), 7.95 (rough doublet, H-9), 7.95 (d, J<sub>3,4</sub> 10 Hz; H-3), 7.6 (d, J<sub>4,3</sub> 10 Hz; H-4) and 7.4 (m, H-6,7, and 8).

## 2-(2',2'-Diethoxyethylimino)methylidibenzofuran (Xb).

This was prepared from Xa by the method used for IIIc (62%) m.p. 46-47° from hexane. An analytical sample had m.p. 46.5-47°; ir  $\mu$  6.15 (imine), 11.95 and 13.3 (unassigned).

*Anal.* Calcd. for C<sub>19</sub>H<sub>21</sub>NO<sub>3</sub>: C, 73.3; H, 6.73; N, 4.49. Found: C, 73.1; H, 6.70; N, 4.66.

Benzofuro[2,3-*g*]isoquinoline (XI) (10).

To 64.6 g. of freshly prepared superphosphoric acid at 140° was added with stirring 1.5 g. (0.00685 mole) of Xb. The mixture was kept at 135-136° for 25 minutes then poured into ice water (125 ml.) with rapid stirring. The insoluble phosphate salt of the product was allowed to coagulate overnight and then filtered. The phosphate was then stirred into hydrochloric acid (100 ml., 6*N*) at 85°. The stirring was continued for 15 minutes and the bright yellow solution was filtered hot. The reaction mixture was extracted with a further portion of hydrochloric acid (100 ml., 6*N*). The combined extracts were basified with sodium hydroxide and extracted with methylene chloride (3 x 150 ml.). Removal of the solvent gave a yellow solid which was recrystallized from aqueous methanol as a creamy yellow powder, m.p. 189-190°. Recrystallization from a 3:1 mixture of cyclohexane-tetrahydrofuran yielded XI (0.21 g., 20.1%), m.p. 192.5-193°; ir  $\mu$  3.3, 6.23 (aromatic C=C), 11.45 and 13.1 (unassigned); uv (ethanol) 220, 244, 267, 273 (sh) 324 and 338 m $\mu$  ( $\epsilon = 47,500, 31,500, 69,750, 59,400, 17,350$  and  $15,050$ ); nmr  $\delta$  9.3 (s, very broad, H-1), 8.4 (s, H-11), 8.02 (rough doublet, H-10), 7.76 (s, H-5) and 7.6 (m, H-4,7,8,9). The H-3 doublet is allowed for by integration between  $\delta$  8.2 and 8.88, however no definite resonance shape was discernible.

*Anal.* Calcd. for C<sub>15</sub>H<sub>9</sub>NO: C, 82.2; H, 4.14; N, 6.39. Found: C, 82.0; H, 4.17; N, 6.28.

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