Ellipticine Analogs: Oxygen and Sulfur Isosteres (1)

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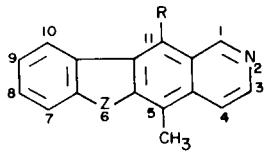
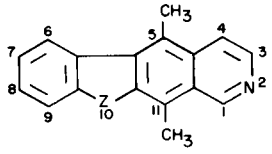
Oxaellipticine has been synthesized from 1,4-dimethyldibenzofuran, by converting it to the 2-aldehyde, forming the Schiff's base with aminoacetaldehyde diethyl acetal, and cyclizing this with 105% superphosphoric acid. Alternatively, tetrahydrodimethyldibenzofuran was formylated mainly at the 3-position, and the 3-(2-nitrovinyl) derivative of the 3-aldehyde, by hydride reduction, then Bischler-Napieralski cyclization of the 3-(2-formamidoethyl) derivative, afforded hexahydrooxaellipticine, which could be aromatized only in poor yield. Isooxaellipticine, the pyrido-*N* positional isomer, was similarly prepared from the nitrovinyl derivative of 1,4-dimethyl-2-dibenzofurancarboxaldehyde, through cyclization of the formamidoethyl intermediate and aromatization of the dihydro product. Likewise, isothiaellipticine was obtained from 1,4-dimethyl-2-dibenzothiophenecarboxaldehyde.

In a search for active analogs of the antitumor alkaloid, ellipticine (I) (2), we have previously prepared 11-desmethylellipticine (II) (3), isoellipticine (the pyrido-*N* positional isomer, V) (4), and recently, thiaellipticine (the *S*-isostere, III) (5). Initial biological tests have shown



I, Z = NH, R = CH_3
II, Z = NH, R = H
III, Z = S, R = CH_3
IV, Z = O, R = CH_3



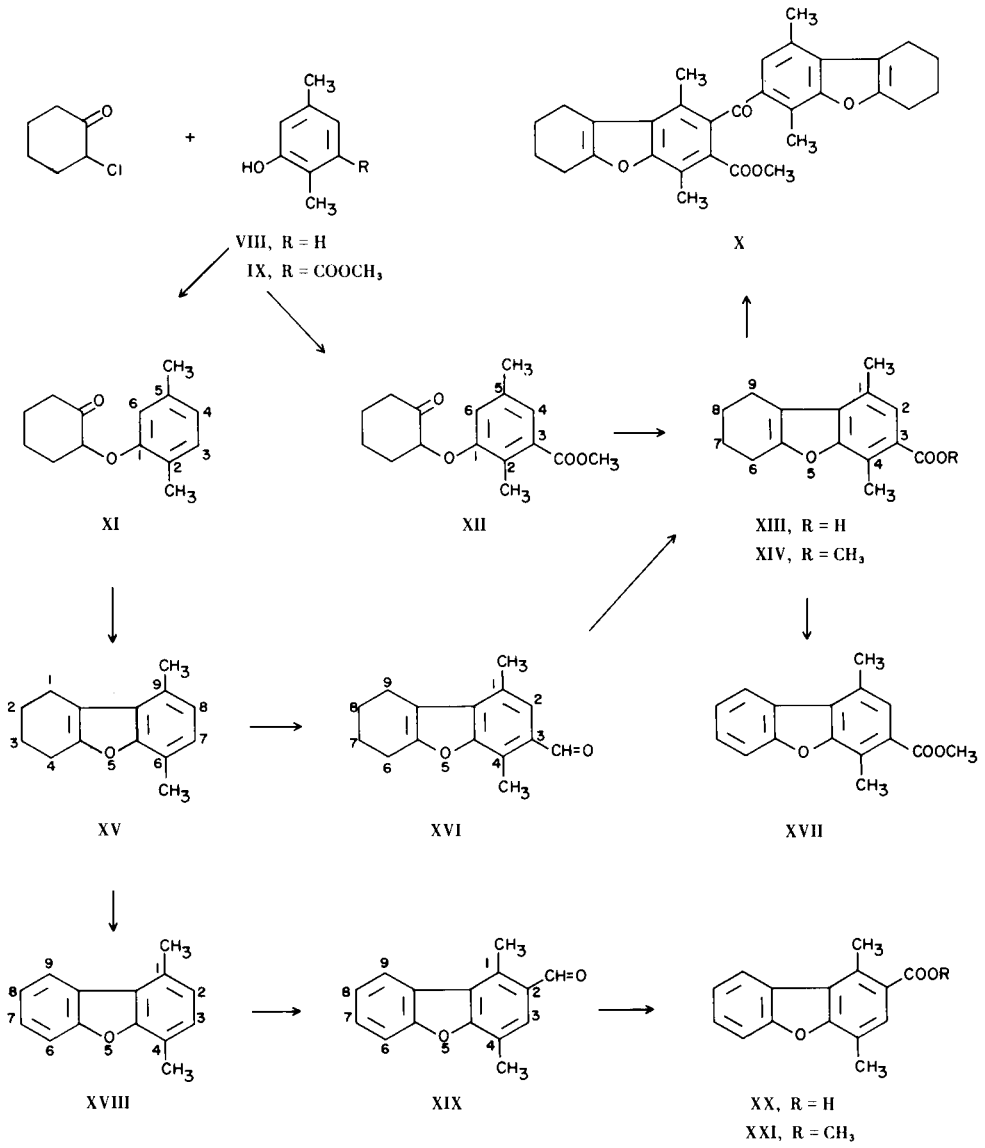
V, Z = NH
VI, Z = O
VII, Z = S

antitumor activity (6) for thiaellipticine; previously, desmethylellipticine was also active (3), but isoellipticine was not (4). These results suggested that activity might be expected in this series (7) so long as the pyrido-*N* was not shifted in position. The synthesis of oxaellipticine (IV) now completes the series of *NH*, *O*, and *S* isosteres. Unlike its isosteres, oxaellipticine was inactive (6). Isooxaellipticine (VI) and isothiaellipticine (VII) were prepared for comparison, and isooxaellipticine was also, more expectably, inactive; the testing of isothiaellipticine is pending.

The synthetic route for oxaellipticine was analogous to that for ellipticine (2) and thiaellipticine (5). 1,4-Dimethyldibenzofuran (XVIII, Scheme 1) (8) was prepared by the method of Trippett (9b), and converted to the 2-aldehyde (XIX). The Schiff's base (XXIII, Scheme 2) of XIX with aminoacetaldehyde acetal could then be cyclized with 105% superphosphoric acid to yield oxaellipticine (IV) in 40% yield. The dimethyldibenzofuran (XVIII) as intermediate had to be purified by chromatography to remove impurities which had accumulated in each step of its preparation. These difficulties were largely related to the poorer nucleophilicity of the phenoxide of 2,5-xylenol (VIII) (relative to the thiophenoxide as in the synthesis of thiaellipticine) in reacting with 2-chlorocyclohexanone, so that the phenoxy ketone (XI) formed was contaminated with hydroxyl-containing impurities. It was surprising that the phenoxy ketone also contained a little of its cyclization product, 1,2,3,4-tetrahydro-6,9-dimethyldibenzofuran (XV); this amount of XV was increased on distillation of XI (9a). Deliberate cyclization (of XI to XV) could be accomplished efficiently only with polyphosphoric acid (9b), however; treatment of the phenoxy ketone (XI) with methanolic hydrogen chloride had no effect, and concentrated sulfuric acid caused only partial cyclization. Chromatographic purification of the phenoxy ketone (XI) and the tetrahydro compound (XV), previously described (9b) as distillable syrups, showed them to be low-melting solids.

Both 1,4-dimethyldibenzofuran (XVIII) and the tetra-

SCHEME I



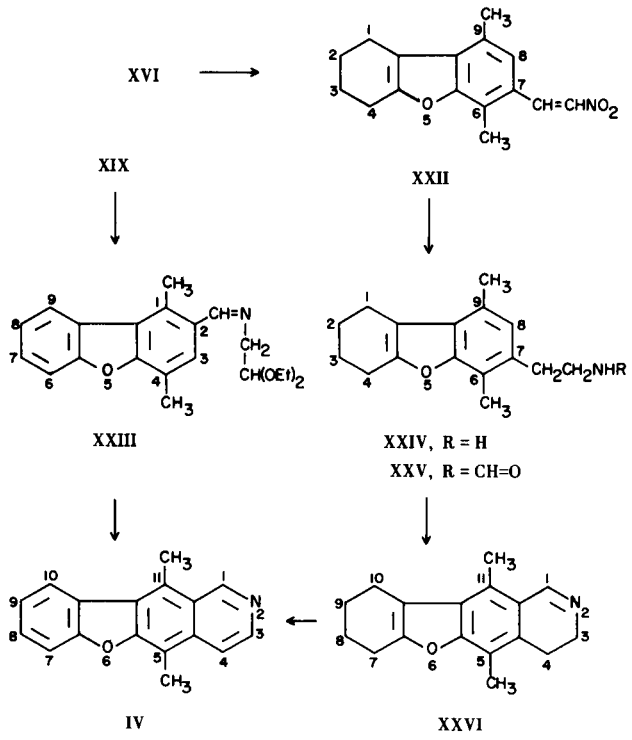
hydro precursor (XV) were converted to aldehydes in good yields, using butyl dichloromethyl ether and stannic chloride (10). The aromatic substitution patterns were those predicted from known reactions in the dibenzofuran series (11), substitution *para* to the hetero atom for the fully aromatic system, and *meta* for the 1,2,3,4-tetrahydro derivative. These patterns were like those found with the dibenzothiophene analogs (5); *i.e.*, the 2-aldehyde (XIX) was obtained from 1,4-dimethyldibenzofuran, whereas the tetrahydro compound XV gave a mixture in which the 3-aldehyde (XVI) predominated over the 2-isomer of XVI in a ratio of 80/20, determined from the nmr spectrum. When *N*-methylformanilide in phosphoryl chloride was the reagent, there was no contaminating 2-isomer, but the tetrahydrodibenzofuran afforded 3-aldehyde (XVI) in only 10% yield. The aldehyde structures could be determined chemically, by oxidation to the corresponding acids and conversion to the methyl esters. The tetrahydro aldehyde (XVI) afforded a pure tetrahydro 3-ester (XIV); apparently the contaminating 2-isomer was lost on recrystallization of the methyl ester or of the intermediate acid (XIII). This ester (XIV) was identified as methyl 6,7,8,9-tetrahydro-1,4-dimethyl-3-dibenzofurancarboxylate (XIV) by comparison with an authentic sample, prepared from methyl 2,5-dimethyl-3-hydroxybenzoate (IX) and 2-chlorocyclohexanone. This alternative synthesis of XIV was

practical only for small amounts. For example, IX had to be purified by fractional recrystallization (12) to remove the accompanying *para*-hydroxy isomer of IX (13). Furthermore, cyclization of the phenoxy ketone (XII) with polyphosphoric acid, even at 40°, to form the tetrahydrodibenzofuran 3-ester (XIV) was accompanied by formation of a dimer. Structure X was postulated for this dimer from the spectral evidence; there were two equally intense carbonyl bands in the infrared spectrum at 5.79 and 5.83 μ, and the nmr spectrum showed four singlets for aryl methyls but only one aryl proton and one methyl ester; it was clear that there was no uncyclized keto ether, from the absence of any signal for CO-CH-O- near 4.6 δ. At 80°, the reaction product was entirely dimer; presumably the process was an intermolecular acylation. Catalytic dehydrogenation of XIV afforded methyl 1,4-dimethyl-3-dibenzofurancarboxylate (XVII) (although some 1,4-dimethyldibenzofuran was apparently formed as by-product). The 3-ester (XVII) was compared with 1,4-dimethyl-2-dibenzofurancarboxylate (XXI), obtained from the 2-aldehyde (XIX) by oxidation and esterification, to show that the two were distinctly different. This verified that 1,4-dimethyldibenzofuran had formed the 2-aldehyde (substitution in the dimethyl ring, the more reactive of the two benzo rings, was established from the nmr spectrum of XIX, by the disappearance of the AB quartet for H-2 and H-3 in XVIII, and by the appearance, downfield, of a singlet for the one of these two protons remaining in XIX).

Whether the aldehyde and ester functions were substituted at C-2 or C-3 could also be inferred simply by studying the nmr spectra. As it was with analogous carbazoles (2) and dibenzothiophenes (5), the deshielding of an aryl methyl when a carbonyl function is introduced adjacent to it was a useful diagnostic tool. The observed downfield shift was 0.20-0.32 ppm, whereas non-adjacent methyls were barely affected. Consequently for the 2-derivatives in Scheme 1, the spacing of the two methyls was relatively wide; the 1-methyl (*i.e.*, in XV, the 9-methyl) was already the more downfield in the parent hydrocarbons (XV, XVIII), and this spread was increased by a 2-substituent. On the other hand for the 3-derivatives, spacing of the methyls was relatively close; deshielding of the 4-methyl (*i.e.*, in XV, the 6-methyl) moved it from above the 1-methyl to just downfield from it.

Completion of the oxaellipticine synthesis in two steps (Scheme 2) from 1,4-dimethyl-2-dibenzofurancarboxaldehyde (XIX) depended on the use of "105% superphosphoric acid" in the Pomeranz-Fritsch cyclization of the Schiff's base (XXIII). Polyphosphoric acid, a more common reagent, gave less than 10% of the product (IV), instead of 40%. The main side-reaction seemed to be hydrolysis of the Schiff's base back to XIX.

SCHEME 2

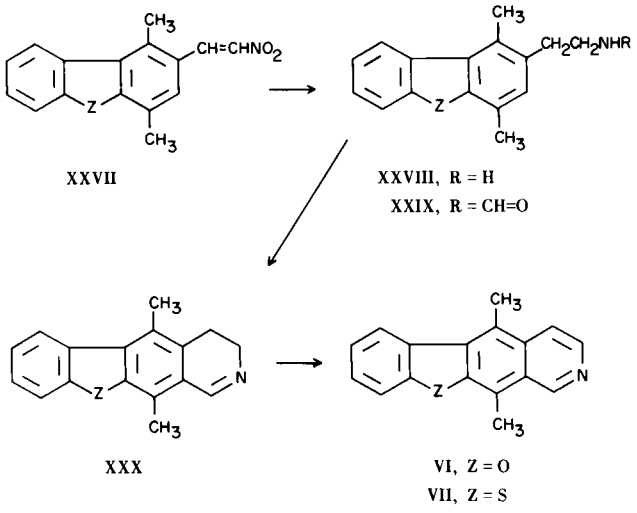


An alternative synthesis of oxaellipticine, the nitrovinyl → formamidoethyl → Bischler-Napieralski sequence, was pursued (Scheme 2) starting from the tetrahydro-3-aldehyde (XVI), but this was impractical owing to difficulties in aromatizing the hexahydro compound (XXVI). The nitrovinyl tetrahydrodibenzofuran (XXII) was readily purified by recrystallization, whereupon the isomer of XXII, formed from the 20% of isomeric 2-aldehyde contaminant in XVI, remained in the mother liquor. Lithium aluminum hydride reduction of XXII afforded the aminoethyl compound (XXIV); slow addition of hydride to the substrate in solution and control of the temperature at 25° was important, to minimize formation of a dimeric by-product. This dimer was removed by virtue of its insolubility in aqueous acetic acid. Cyclization of the formamide (XXV) afforded 64% of hexahydrooxaellipticine (XXVI). Catalytic dehydrogenation of XXVI was slow and incomplete, but a sample of oxaellipticine was obtained in low yield and was identical to IV from the cyclization of the Schiff's base (XXIII). These two syntheses were complementary, in demonstrating the structural relationship between the two starting aldehydes (XVI and XIX).

The nitrovinyl → formamidoethyl → Bischler-Napieralski sequence readily afforded isooxaellipticine (VI), when 1,4-dimethyl-2-dibenzofurancarboxaldehyde (XIX) was the

starting aldehyde (Scheme 3). Similarly, 1,4-dimethyl-2-dibenzothiophenecarboxaldehyde afforded isothiaellipticine (VII). Catalytic dehydrogenation of the dihydro intermediates (XXXa and b), in contrast to hexahydrooxaellipticine (XXVI), was complete in 2.5 hours at 210°.

SCHEME 3



series a, Z = O
series b, Z = S

EXPERIMENTAL

Methods.

Melting points were determined on a Fisher-Johns hot stage and are uncorrected. Uv spectra were determined with a Cary Model 11 recording spectrophotometer; ir spectra were determined in Nujol mull, and only those bands useful for structure assignments are recorded. Nmr spectra were determined in deuteriochloroform solutions with 2% tetramethylsilane as internal standard (δ 0.00), using Varian A-60 and HA-100 spectrometers. Accuracy is ± 0.05 ppm for chemical shifts. Signals are described as singlet (s), doublet (d), triplet (t), quartet (q), or multiplet (m).

Integrated signal ratios were determined routinely and were as expected from the structural assignments. Assignments of H-9 rather than H-6 to the proton farthest downfield in dibenzofurans (14) was by analogy with carbazole. Thin-layer chromatography (tlc) was done on silica gel and the spots detected under uv light. Solutions for preparative tlc were applied to plates with the Rodder streaker, Rodder Instrument Co., Los Altos, California. In processing reaction products, solutions were dried with magnesium sulfate, which was removed by filtration; solutions were concentrated *in vacuo*.

2-(2,5-Xylyoxy)cyclohexanone (XI).

This compound was prepared according to the procedure of Trippett (9b), using 2-chlorocyclohexanone conveniently in place of the 2-bromo analog. The procedure of Hurd and Perletz (15) for phenoxyacetone (used below for XII) could also be used, with essentially the same result. Distillation of the crude product at 116° (0.8 mm.) removed some hydroxy-containing impurities and afforded a mixture (50-55% yield) of XI (R_f 0.5 on tlc in 1% methanolic benzene) and the tetrahydrodimethyldibenzofuran (XV) (R_f 0.9) in a ratio of about 2:1, according to ir and nmr spectra (the ratio had been about 4:1 before distillation). The mixture could be resolved by column chromatography on silica gel (90-200 mesh) in benzene. First eluted was XV (12% yield; see below). It was followed by the phenoxy ketone (XI) (26%), m.p. 55-57°; ir μ 5.80 (ketone C=O), 6.19, 6.30, and 12.51 (aryl), with the absence of bands at 7.30 and 9.12 diagnostic for the absence of the tetrahydro compound (XV); nmr δ 6.94 d (H-3, $J_{3,4}$ = 7Hz), 6.62 broad d (H-4, $J_{3,4}$ = 7Hz, estimated $J_{4,6}$ = 2Hz), 6.45 broad s (H-6, estimated $J_{4,6}$ = 2Hz), 4.52 m (CO-CH-O-), 2.8-1.5 (ring CH_2), 2.24 s (2-CH_3 and 5-CH_3).

A sample recrystallized from ether-petroleum ether (b.p. 30-60°) melted at 58-58.5°.

Anal. Calcd. for $C_{14}H_{18}O_2$: C, 77.0; H, 8.31. Found: C, 77.0; H, 8.04.

1,2,3,4-Tetrahydro-6,9-dimethyldibenzofuran (XV).

Method A.

The sample from the above chromatogram melted at 30-31°; uv (ethanol) λ max mμ 257 (ε 13,600); ir μ 6.12 and 12.5 (aryl), with the absence of bands at 5.80, 6.19, and 6.30 diagnostic for the absence of XI; nmr δ 6.77 s (H-7 and H-8), 2.9-2.6 m (benzylic CH_2's at C-1 and C-4), 2.49 s (9-CH_3), 2.42 s (6-CH_3), 1.95-1.65 m (CH_2's at C-2 and C-3).

Anal. Calcd. for $C_{14}H_{16}O$: C, 84.0; H, 8.05. Found: C, 84.1; H, 8.01.

Method B.

Cyclization (9b) of chromatographically purified phenoxy ketone (XI) with commercial polyphosphoric acid at 80° afforded XV (93% yield) identical spectrally and chromatographically to the sample from Method A (R_f 0.9 on tlc in 1% methanolic benzene, R_f 0.5 in hexane).

1,4-Dimethyldibenzofuran (XVIII).

Aromatization (9b) of XV with 30% palladium-charcoal afforded a pure sample (16) in 80% yield; uv (ethanol) λ max mμ 224 (ε x 10^{-3}, 51.9), 247 (11.8), 255 (19.1), 279 (23.1), 294 (6.26), 306 (5.41); ir (film) 6.31, 12.45, 12.9, 13.4, 13.7 (aryl); nmr δ 8.02-7.90 m (H-9), 7.60-7.15 m (H-6, H-7, H-8), 7.08 d (H-3, $J_{2,3}$ = 7.5Hz), 6.93 d (H-2, $J_{2,3}$ = 7.5Hz), 2.71 s (1-CH_3), 2.53 s (4-CH_3). The R_f of XVIII on tlc was always the same as that of XV. Absence of any XV was clearly seen in the nmr spectrum, and in the ir spectrum by the absence of medium-intensity bands at μ 6.12, 7.10, 7.70, 10.45, 10.9, 11.68. The use, in some runs, of incompletely purified precursors (XI and XV) gave rise to chromatographically slow-moving impurities, which were removed by absorption on a column of silica gel in hexane, with the elution of XVIII.

6,7,8,9-Tetrahydro-1,4-dimethyl-3(and 2)dibenzofurancarboxaldehyde (XVI).

A stirred solution of 0-3° of 1.0 g. (5.0 mmoles) of 1,2,3,4-tetrahydro-6,9-dimethyldibenzofuran (XV) in 10 ml. of dichloromethane, protected from moisture, was treated with 0.70 ml. (6.0 mmoles) of anhydrous stannic chloride. To the dark red solution was added, with stirring, 0.85 ml. (6.0 mmoles) of butyl dichloromethyl ether (10). The ice bath was removed and

the mixture was stirred for 45 minutes, then poured with stirring onto 50 ml. of ice and water. The hydrolyzed mixture was extracted with two 50-ml. portions of dichloromethane. The combined extracts were washed with 100 ml. of water, 75 ml. of saturated sodium bicarbonate, two 75-ml. portions of water, and were dried. Concentration afforded a residual syrup (1.1 g., 95%) which crystallized on standing, m.p. 70-78°. Recrystallization from 10 ml. of hexane afforded 0.71 g. (62%), m.p. 75-78°, which was chromatographically homogeneous (R_f 0.4 on tlc in benzene, *vs.* R_f 0.9 for XV) and analytically pure; ir μ 3.72 (aldehyde CH), 5.95 (C=O).

Anal. Calcd. for $C_{15}H_{16}O_2$: C, 78.9; H, 7.06. Found: C, 78.7; H, 7.03.

The nmr spectrum indicated the product was a mixture of 3-aldehyde (XVI) and its 2-isomer in a ratio of about 80:20. The stronger nmr signals were identical to those of isomerically pure 3-aldehyde obtained (10% yield, isolated chromatographically) from XV with phosphoryl chloride and *N*-methylformanilide as reagent, δ 10.20 s (CH=O), 7.34 s (H-2), 2.9-2.6 m (benzylic CH_2's at C-6 and C-9), 2.74 s (4-CH_3), 2.55 s (1-CH_3), 2.0-1.7 m (CH_2's at C-7 and C-8). Weaker signals attributed to isomeric 2-aldehyde were at δ 10.23 (CH=O), 7.43 s (H-3), 2.82 s (1-CH_3), 2.47 s (4-CH_3). Examination of the hexane mother liquor revealed crude aldehyde of the same isomeric composition.

1,4-Dimethyl-2-dibenzofurancarboxaldehyde (XIX).

Chromatographically purified 1,4-dimethyldibenzofuran (XVIII) (2.94 g., 15.0 mmoles) in 37 ml. of dichloromethane was treated with 2.56 ml. (22.5 mmoles) of anhydrous stannic chloride and 3.11 ml. (21.9 mmoles) of butyl dichloromethyl ether (10) according to the procedure for XVI. The crude product weighed 3.20 g. (95%), m.p. 108-118°. Recrystallization from 9 ml. of benzene and 10 ml. of petroleum ether (b.p. 30-60°) afforded 2.45 g. (73%), m.p. 116-117°; ir μ 5.95 (C=O); nmr δ 10.28 s (CH=O), 8.06-7.83 m (H-9), 7.60 s (H-3), 7.60-7.10 m (H-6, H-7, H-8), 2.93 s (1-CH_3), 2.49 s (4-CH_3). Weak singlets at δ 2.74 and 2.67 could not be removed by further recrystallization of the sample from 2-propanol (m.p. 117-118°) and might have been from the methyls of about 3% of the isomeric 3-aldehyde, but there was no extraneous signal in the -CH=O region near δ 10 to support this. A sample for analysis, m.p. 115-118°, from another run showed about 5% of the extraneous signals.

Anal. Calcd. for $C_{15}H_{12}O_2$: C, 80.3; H, 5.39. Found: C, 80.4; H, 5.35.

1,4-Dimethyl-2-dibenzofurancarboxylic Acid (XX).

A stirred, refluxing solution of 0.224 g. (1.00 mmole) of the 2-aldehyde (XIX) in 15 ml. of acetone was treated, during 30 minutes, with a solution of 0.350 g. (2.21 mmoles) of potassium permanganate in 40 ml. of acetone and 10 ml. of water, then refluxed for 5 hours. Manganese dioxide was removed by filtration. The filtrate was further basified (*p*H 10-11) with 10% sodium hydroxide and was concentrated to remove acetone. Water (5 ml.) was added and the cloudy solution was purified by extraction with 20 ml. of dichloromethane and by filtration. Acidification of the filtrate with 6 *M* hydrochloric acid precipitated the acid, 0.194 g. (81%), m.p. 210-260°. Ethanol recrystallization afforded 0.135 g. (56%), m.p. 274-275°; ir μ 5.95 (acid C=O).

Anal. Calcd. for $C_{15}H_{12}O_3$: C, 75.0; H, 5.03. Found: C, 74.7; H, 4.99.

Methyl 1,4-Dimethyl-2-dibenzofurancarboxylate (XXI).

A suspension of the acid (XX) in saturated anhydrous methanolic hydrogen chloride (60 ml./g.) was refluxed for 3 hours (17). Gradual solution was followed by separation of the crystalline ester in nearly quantitative yield, m.p. 97-98°; uv (ethanol) λ max mμ 219 (ϵ x 10^{-3}, 45.3), 240 (43.3), 283 (10.5), 297 (4.07), 307 (1.67); ir μ 5.80 (ester C=O); nmr δ 8.10-7.83 m (H-9), 7.72 s (H-3), 7.65-7.15 m (H-6, H-7, H-8), 3.89 s ($COOCH_3$), 2.91 s (1-CH_3), 2.48 s (4-CH_3).

Anal. Calcd. for $C_{16}H_{14}O_3$: C, 75.6; H, 5.55. Found: C, 75.6; H, 5.52.

2-(3-Methoxycarbonyl-2,5-xylyloxy)cyclohexanone (XII).

A refluxing solution of 13.8 g. (76.6 mmoles) of methyl 2,5-dimethyl-3-hydroxybenzoate (IX; freed of 4-hydroxy isomer by fractional crystallization) (12) in 120 ml. of acetone was treated with 10.6 g. (76.6 mmoles) of potassium carbonate, added in several portions, along with a solution of 15.2 g. (115 mmoles) of 2-chlorocyclohexanone and 0.23 g. of potassium iodide in 45 ml. of acetone added dropwise over 2 hours, according to the procedure for phenoxyacetone (15). The solution was filtered, the filtrate was concentrated, and the residual syrup in 150 ml. of dichloromethane solution was extracted twice with 100-ml. portions of 5% sodium hydroxide, washed with water, and dried. Concentration afforded 19.1 g. (90%) of residual syrup; minor contamination was indicated by weak hydroxyl absorption in the infrared and by faint, slower-moving spots (relative to XII, R_f 0.7) on tlc in chloroform. Crystallization from an ether-petroleum ether (b.p. 30-60°) solution, followed by several recrystallizations, afforded 4.1 g. (19%), m.p. 73-75°. An analytical sample melted at 73.5-74°; uv (ethanol) λ max mμ 298 (ϵ x 10^{-3}, 2.31); ir μ 5.80 (C=O, ester and ketone); nmr δ 7.21 broad s (H-4, estimated $J_{4,6}$ = 2Hz), 6.63 s (H-6, estimated $J_{4,6}$ = 2Hz), 4.57 q (CO-CH-O-), 3.82 s ($COOCH_3$), 2.8-1.5 m (ring CH_2), 2.43 s (2-CH_3), 2.24 s (5-CH_3).

Anal. Calcd. for $C_{16}H_{20}O_4$: C, 69.5; H, 7.30. Found: C, 69.5; H, 7.21.

2-(4-Methoxycarbonyl-2,5-xylyloxy)cyclohexanone.

This compound was detected, by the extraneous aryl singlets, in the nmr spectra of samples of XII which had been prepared from methyl 2,5-dimethyl-3-hydroxybenzoate (IX) contaminated with the 4-hydroxy isomer. Once, when the syrupy product (XII) was a 65/35 mixture of isomers, crystals of the contaminating 4-carboxylate separated on standing, m.p. 113-120°, chromatographically identical to XII, ir μ 5.82 (C=O, ester and ketone); nmr δ 7.70 s (H-3), 6.40 s (H-6), 4.67 m (CO-CH-O-), 3.80 s ($COOCH_3$), 2.7-1.6 m (ring CH_2), 2.50 s (5-CH_3), 2.23 s (2-CH_3). Recrystallization from ether-hexane afforded a sample for analysis, m.p. 125-127°.

Anal. Found: C, 69.5; H, 7.31.

Methyl 6,7,8,9-Tetrahydro-1,4-dimethyl-3-dibenzofurancarboxylate (XIV).

Method A.

The phenoxy ketone 3-ester (XII, 0.73 g., 2.6 mmoles) was stirred with 12 g. of commercial polyphosphoric acid at room temperature until thoroughly mixed, then heated at 40° for 4 hours with stirring, and the yellow-brown mixture was hydrolyzed with crushed ice. The gummy white solid which separated was extracted with two 50-ml. portions of ether. The extracts were washed with 50 ml. of bicarbonate solution, 50 ml. of water, dried, and concentrated. The residual sticky solid (0.66 g., 96%) was crystallized from ether and ether-petroleum ether (b.p. 30-60°) to yield 0.27 g., m.p. 103-107°. Crystallization from 10

ml. of methanol afforded 0.20 g. (29%), m.p. 104-105°; uv (ethanol) λ max mμ 216 (ε x 10^{-3}, 19.7), 283 (18.1); ir μ 5.83 (ester C=O); nmr δ 7.50 s (H-2), 3.83 s ($COOCH_3$), 2.90-2.57 m (benzylic CH_2's at C-6 and C-9), 2.63 s (4-CH_3), 2.49 s (1-CH_3), 2.05-1.60 m (CH_2's at C-7 and C-8).

Anal. Calcd. for $C_{16}H_{18}O_3$: C, 74.4; H, 7.02. Found: C, 74.5; H, 6.96.

An additional 0.11 g. (total yield, 45%) was isolated by chromatography of the mother liquors (three 20 x 20-cm. plates, 2 mm. layers of silica gel, in benzene).

A *dimeric substance* (X), less mobile on tlc and detected in ir and nmr spectra of the crude product, was also isolated from the chromatographic plates (0.12 g.), m.p. 135-141°; ir μ 5.79 and 5.83 (C=O, assigned to ketone and ester of structure X); nmr δ 7.11 s (one aryl H), 3.76 s ($COOCH_3$), 3.0-2.5 m (benzylic CH_2's), 2.80 s, 2.68 s, 2.38 s, 2.34 s (four aryl CH_3's), 1.9-1.1 m (ring CH_2's); (presence of about 10% of the monomer was indicated in the nmr by weak singlets at δ 7.50 and 3.83). Structure X was postulated for this substance. The dimer upon recrystallization from 95% ethanol melted at 160-172°.

Anal. Calcd. for $C_{31}H_{32}O_5$: C, 76.8; H, 6.66; mol. wt., 485. Found: C, 77.0; H, 6.42; mol. wt. (osmometer), 480.

Method B.

Oxidation of the tetrahydro-3-aldehyde (XVI, containing about 20% of the 2-isomer) with potassium permanganate (as described for XX, above) and esterification of the resultant acid (XIII) with diazomethane gave a sample of XIV, m.p. 92-101°, identical in spectra and tlc to that from method A, except for the impurity arising from the use of diazomethane (17). Any 2-isomer which might have been carried through from XVI must have been lost during recrystallization of the acid (XIII) from ethanol or of ester (XIV) from petroleum ether, as there were no nmr signals for isomeric aryl H or aryl CH_3.

Methyl 1,4-Dimethyl-3-dibenzofurancarboxylate (XVII).

The tetrahydro ester (XIV; 115 mg., 0.44 mmole, from method A, above) was aromatized neat at 230-240° with 120 mg. of 30% palladium-carbon for 18 hours. The product was extracted from the catalyst with dichloromethane and purified chromatographically (one 20 x 20 cm. plate with 2.0 mm. of silica gel, in benzene) to yield 32 mg. (28%), m.p. 117-118°; uv (ethanol) λ max mμ 225 (ε x 10^{-3}, 38.8), 269 (14.2), 292 (26.9); ir μ 5.82 (C=O); nmr δ 8.05-7.94 m (H-9), 7.69 s (H-2), 7.7-7.2 m (H-6, H-7, H-8), 3.91 s ($COOCH_3$), 2.79 s (4-CH_3), 2.75 s (1-CH_3).

Anal. Calcd. for $C_{16}H_{14}O_3$: C, 75.6; H, 5.55. Found: C, 75.4; H, 5.36.

In one experiment, 38 mg. of syrupy by-product (R_f 0.9 on tlc in benzene, *vs.* R_f 0.6 for XVII) was also isolated from the chromatographic plate and identified as 1,4-dimethyldibenzofuran (44% yield) by its nmr spectrum.

1,4-Dimethyl-2-(2,2-diethoxyethylimino)methyldibenzofuran (XXIII).

As for the carbazole (2) and dibenzothiophene (5) analogs, XXIII was prepared from 5.0 g. (22 mmoles) of 2-aldehyde (XIX) and 3.7 ml. of aminoacetaldehyde diethyl acetal. Recrystallization from 18 ml. of hexane afforded 6.3 g. (84%), m.p. 77-79°. An analytical sample melted at 78-79°; uv (ethanol) λ max mμ 225 (ε x 10^{-3}, 20.7), 251 sh, 257 (46.0); ir μ 6.08 (C=N); nmr δ 8.73 s (CH=N, partly split into triplet, estimated J = 1Hz), 8.15-7.93 m (H-9), 7.87 s (H-3), 7.75-7.20 m (H-6, H-7, H-8), 4.88 t (-$CH(OEt)_2$, J = 5.5Hz), 3.98-3.43 m (=NCH_2, plus two CH_2's of Et's), 2.86 s (1-CH_3), 2.55 s (4-CH_3), 1.23 t (two CH_3's of Et's, J = 7 cps).

Anal. Calcd. for $C_{21}H_{25}NO_3$: C, 74.3; H, 7.42; N, 4.13. Found: C, 74.4; H, 7.54; N, 4.32.

5,11-Dimethylbenzofuro[2,3-*g*]isoquinoline (IV, Oxaellipticine).

Method A.

To 150 g. of 105% superphosphoric acid (18), stirred and heated at 140°, was added evenly over 2-3 minutes so as to prevent lumping, 6.8 g. (20 mmoles) of the iminoacetal (XXIII). The homogeneous dark mixture was stirred at 140° for 12 minutes, then poured onto 500 g. of crushed ice. The aqueous mixture was warmed on the steam bath until the product separated readily as a solid phosphate salt, which was collected on a filter. Trituration with three 35-ml. portions of dichloromethane removed 0.87 g. of dark gum, shown to be crude aldehyde (XIX) by inspection of the infrared spectrum. The insoluble phosphate salt was stirred with 80 ml. of 10% sodium hydroxide. The suspension gradually turned to a dark gum and finally to a solid, with continued stirring overnight. The solid free base (IV) was collected on a filter, triturated three times with 40 ml. of water, collected again, and dried to yield 3.8 g., m.p. 138-144°, of 65% purity (estimated from uv extinctions).

Trituration with four 25-ml. portions of hot methanol (the insolubles were probably polymeric) and concentration of the combined methanol filtrates afforded 2.5 g., m.p. 135-148°, of 92% purity (51% yield). Further purification was accomplished by solution in 60 ml. of hot 3 *M* hydrochloric acid, whereupon a little insoluble gum was removed by filtration. The acid filtrate on cooling deposited crystalline yellow hydrochloride, which was stirred with 50 ml. of 10% sodium hydroxide to regenerate the free base, 2.3 g., m.p. 145-150°. Recrystallization from 25 ml. of methanol and 3 ml. of water afforded 2.0 g. (40% yield), m.p. 150-151.5°. It was identical to an analytical sample, m.p. 151-152°, from another experiment, recrystallized from carbon tetrachloride and dried at 80° *in vacuo;* uv (ethanol) λ max mμ 264 (ε x 10^{-3}, 62.6), 269 (66.7), 273 (62.8), 283 (13.7), 333 (9.05), 349 (8.34); uv (0.1 *M* hydrochloric acid) mμ 229 sh, 283 (ε x 10^{-3}, 61.2), 332 (4.63); nmr δ 9.57 s (H-1), 8.48 d (H-3, $J_{3,4}$ = 6Hz), 8.05 m (rough doublet, H-10), 7.76 d (H-4, $J_{3,4}$ = 6Hz, verified by decoupling), 7.57-7.20 m (H-7, H-8, H-9), 3.02 s (11-CH_3), 2.68 s (5-CH_3). Every nmr spectrum showed an extraneous, field-dependent singlet, ranging between δ 6 and 3, which was exchangeable with deuterium oxide and was assigned to water, perhaps absorbed during preparation of the solution since elemental analysis showed no evidence of hydration in the dried solid.

Anal. Calcd. for $C_{17}H_{13}NO$: C, 82.6; H, 5.30; N, 5.66. Found: C, 82.4; H, 5.33; N, 5.75.

There was evidence for formation of an *acetic acid solvate* of IV, extractable into dichloromethane from aqueous acetic acid solution. A solution of 40 mg. of IV in 15 ml. of cold 3 *M* acetic acid was extracted with three 20-ml. portions of dichloromethane; concentration of the combined, dried extracts afforded 36 mg., m.p. 118-149°. The major ir absorption bands were the same as those of IV but there was additional bands at μ 4.1 and 5.1 (broad; acidic H) and at 5.8 (C=O of acetic acid; there were no bands at μ 6.3 and 7.0 to suggest ionic acetate). The only charges in the nmr spectrum, relative to that of IV, were the appearance of signals at δ 10.7 s (one H, acid OH) and 2.18 s (three H's, CH_3COO) and the considerable broadening of the H-1 and H-3 signals, with lesser broadening of H-4; chemical shifts were unchanged. The solubility and spectral data do not permit

interpretation of the substance as an acetic acid salt. Formation of an acetate salt by lyophilization of a glacial acetic acid solution of IV was attempted, but only unchanged IV could be recovered.

Method B.

A solution of 1.0 g. (4.0 mmoles) of the hexahydro precursor (XXVI) (see below) in 35 ml. of decalin was refluxed with 1.0 g. of palladium black for 6 days. After removal of the catalyst and concentration of the solution, 0.92 g. (95%) of gum was obtained. Its dichloromethane solution was extracted with 3 *M* hydrochloric acid, leaving 0.42 g. of unidentified neutral by-products in the organic layer. The acid extracts were basified, and 0.16 g. of free base was recovered by extraction with dichloromethane, m.p. 120-133°, of 75-80% purity according to uv extinctions. Purification through the crystalline hydrochloride, followed by recrystallization of the regenerated free base, as described in method A, afforded a sample, m.p. 149-150.5°, identical to the analytical sample in spectra and mixed melting point.

1,2,3,4-Tetrahydro-6,9-dimethyl-7-(2-nitrovinyl)dibenzofuran (XXII).

A mixture of 4.8 g. (21 mmoles) of 6,7,8,9-tetrahydro-1,4-dimethyl-3-dibenzofurancarboxaldehyde (XVI, containing about 20% of the 2-aldehyde), 0.90 g. (11 mmoles) of ammonium acetate, and 19 ml. of nitromethane was heated on the steam bath, while the resultant solution deposited the product. After 1 hour, the orange crystals were collected, washed with water, and dried to yield 4.3 g. (76%), m.p. 140-195°. Recrystallization from 160 ml. of hot 1-butanol afforded 3.2 g. (55%), m.p. 200-204°; ir μ 3.23 (vinyl CH), 6.17, 6.28, 10.30, 10.40 (C=C); nmr δ 8.37 d (C=CH-NO_2, J_{trans} = 13.5Hz), 7.51 d (aryl-CH=C, J_{trans} = 13.5Hz), 7.11 s (H-8), 2.95-2.40 m (benzylic CH_2's at C-1 and C-4), 2.54 s and 2.52 s (6-CH_3 and 9-CH_3), 2.05-1.70 m (ring CH_2's at C-2 and C-3).

Anal. Calcd. for $C_{16}H_{17}NO_3$: C, 70.8; H, 6.32; N, 5.16. Found: C, 70.9; H, 6.40; N, 5.24.

The recrystallization had removed a second isomer, which was enriched in the mother liquor, and was observed in the nmr spectrum along with a small amount of XXII. This isomer was assumed to be the 8-nitrovinyl compound (to be expected from the 2-aldehyde present in XVI) from the relatively wide spacing of the methyl resonances, at δ 2.63 (9-CH_3) and 2.48 (6-CH_3).

1,2,3,4-Tetrahydro-6,9-dimethyl-7-(2-aminoethyl)dibenzofuran (XXIV).

A stirred suspension of 1.25 g. (32.9 mmoles) of lithium aluminum hydride in 25 ml. of anhydrous tetrahydrofuran was treated dropwise at room temperature with a solution of 1.00 g. (3.70 mmoles) of nitrovinyl compound (XXII) in 50 ml. of anhydrous tetrahydrofuran. After stirring for 1 hour, the excess hydride was decomposed with 20 ml. of aqueous 50% tetrahydrofuran. The resultant gelatinous precipitate was removed on a filter and washed with solvent. Concentration of the combined filtrate afforded 0.885 g. (99%) of syrupy amine. A dimeric impurity was evidenced by a strong extraneous singlet at δ 1.43 in the nmr spectrum. Solution in 25 ml. of warm 3 *M* acetic acid removed the insoluble dimer (found, mol. wt. 401; calcd., 243 for monomeric XXIV), and basification of the filtrate with 10 *M* sodium hydroxide precipitated 0.672 g. (76%) of the amorphous amine; nmr δ 6.72 s (H-8), 3.0-2.5 m (benzylic CH_2's at C-1 and C-4), 2.49 s (9-CH_3), 2.39 s (6-CH_3), 2.25 broad s (NH_2, exchangeable), 2.0-1.7 m (CH_2's at C-2 and C-3). The ***hydrochloride*** was precipitated from an ether solution with ethereal hydrogen chloride, and was recrystallized from acetone-methanol, m.p. 269-279° dec.

Anal. Calcd. for $C_{16}H_{21}NO{\cdot}HCl$: C, 68.6; H, 7.92; Cl, 12.7; N, 5.01. Found: C, 68.4; H, 7.97; Cl, 12.4; N, 4.97.

1,2,3,4-Tetrahydro-6,9-dimethyl-7-(2-formamidoethyl)dibenzofuran (XXV).

A suspension of 6.8 g. (28 mmoles) of amine (XXIV) in 145 ml. of ethyl formate was heated in a sealed steel bomb at 100° for 2.5 hours. The resultant solution was concentrated to yield 7.4 g. (97%) of syrupy amide. Trituration with hexane and refrigeration of the suspension overnight afforded 7.2 g. of crystals, m.p. 75-90°. Recrystallization from 18 ml. of methanol and 5 ml. of water gave 5.8 g. (77%), m.p. 106-109°, of analytical purity. Another analytical sample melted at 112-113°, and other samples of equivalent purity according to spectral data melted at 100-101° and 101-103°. Infrared spectra disclosed the presence of two crystal forms in the solid phase (Nujol), one with a broad NH band and two C=O bands (μ 3.06 medium, 5.95 medium, 6.08 strong), the other with single sharp, strong NH and C=O bands (μ 3.02, 6.01); chloroform solution spectra of both forms showed single NH and C=O bands at μ 2.92 and 5.90. Nmr spectra were identical for all samples (100 cps, deuteriochloroform exchanged with deuterium oxide). δ 8.06 s (-CH=O), 6.67 s (H-8), 3.6-3.3 rough t (-CH_2N-, estimated J = 7Hz), 2.83 t (7-CH_2-, J = 7Hz), 2.9-2.55 m (benzylic CH_2's at C-1 and C-4), 2.45 s (9-CH_3), 2.36 s (6-CH_3), 1.9-1.7 m (CH_2's at C-2 and C-3). Without deuterium oxide exchange, the amide NH was a broad signal near δ 6.0, there was broadening of the singlet for -CH=O, and the multiplet for -CH_2N was a pentet. In every spectrum, there were weak extraneous signals at 7.83 d (J = 12Hz, collapsed to singlet on deuterium oxide exchange), 6.62 s, and 2.33 s; though the presence of an impurity (10-20%) could not be discounted as the explanation, this seemed unlikely, considering the homogeneity (R_f 0.6 by tlc in ethyl acetate) and analytical purity of the best samples, and it seemed that intermolecular association in solution might be responsible for the extraneous signals.

Anal. Calcd. for $C_{17}H_{21}NO_2$: C, 75.2; H, 7.80; N, 5.16. Found: C, 75.1; H, 7.83; N, 5.45.

3,4,7,8,9,10-Hexahydro-5,11-dimethylbenzofuro[2,3-*g*]isoquinoline (XXVI).

The formamide (XXV; 5.4 g., 20 mmoles) was stirred and mixed thoroughly with 250 g. of polyphosphoric acid at room temperature, then immersed in an oil bath at 115-120° and stirred and heated for 1.25 hours. The dark mixture was cooled and was hydrolyzed with *ca.* 400 g. of crushed ice. The acidic solution (containing the product as dissolved phosphate salt; in one run when less ice-water was added, some of the phosphate salt remained an insoluble gum and was triturated with base) was clarified by filtration and basified (with ice cooling) with 250-300 ml. of concentrated ammonium hydroxide. The free base (XXVI) separated, along with inorganic phosphates which were redissolved by adding 800 ml. of water and stirring. The solution was decanted from the product, which was dissolved in dichloromethane; the decantate was extracted with dichloromethane, and the combined dichloromethane solutions (750 ml.) were dried and were concentrated to yield 4.7 g., m.p. 137-148°. Recrystallization from hexane-dichloromethane (4:1), and reprecipitation from a solution in 30 ml. of warm 3 *M* acetic acid by adding ammonium hydroxide afforded 3.2 g. (64%) of yellow solid, m.p. 142-148°. Purity of 92% was estimated by comparison of the uv extinction with that of an analytical sample, obtained in another experiment after several recrystallizations and dried at 80° *in vacuo*, m.p. 144-154°; uv (ethanol) λ max mμ 249 (ϵ x

10^{-3}, 46.6); nmr δ 8.7 broad s (H-1), 3.8-3.5 broad m (=N-CH_2 at C-3), 3.0-2.6 m (CH_2's at C-4, C-7, C-10), 2.63 s (11-CH_3), 2.33 s (5-CH_3), 2.05-1.75 m (CH_2's at C-8 and C-9).

Anal. Calcd. for $C_{17}H_{19}NO$: C, 80.6; H, 7.56; N, 5.53. Found: C, 80.3; H, 7.37; N, 5.56.

1,4-Dimethyl-2-(2-nitrovinyl)dibenzofuran (XXVIIa).

A mixture of 2.23 g. (9.95 mmoles) of 1,4-dimethyl-2-dibenzofurancarboxaldehyde (XIX), 0.432 g. of ammonium acetate, and 8.8 ml. of nitromethane was heated on the steam bath, while the resultant solution slowly deposited the product. The orange crystals were collected after 3 hours, washed with water, and dried to yield 2.1 g. (81%), m.p. 195-204°. Recrystallization from 40 ml. of 1,2-dimethoxyethane afforded 1.7 g. (65%), m.p. 201-205°; uv (ethanol) λ max mμ 227 (ε x 10^{-3}, 30.4), 253 (15.9), 277 (22.4), 296 (11.4), 350 (16.1); ir μ 10.22, 10.45 (C=C); nmr δ 8.47 d (C=CH-NO_2, J_{trans} = 6.8Hz), 8.12-7.98 m (H-9), 7.65-7.10 m (H-3, H-6, H-7, H-8, and aryl-CH=C, probably a doublet at 7.48, J_{trans} = 6.8Hz), 2.82 s (1-CH_3), 2.53 s (4-CH_3).

Anal. Calcd. for $C_{16}H_{13}NO_3$: C, 71.9; H, 4.90; N, 5.24. Found: C, 72.0; H, 4.88; N, 5.11.

1,4-Dimethyl-2-(2-nitrovinyl)dibenzothiophene (XXVIIb).

This compound was similarly prepared and recrystallized; yields were 55-90%, m.p. 207-211°; ir μ 10.27, 10.38 (C=C).

Anal. Calcd. for $C_{16}H_{13}NO_2S$: C, 67.8; H, 4.63; N, 4.95. Found: C, 67.8; H, 4.46; N, 4.98.

1,4-Dimethyl-2-(2-aminoethyl)dibenzofuran (XXVIIIa).

As for the tetrahydroamine (XXIV), XXVIIIa was prepared as a syrup (70% yield) reprecipitated from acid solution; nmr δ 8.08-7.95 m (H-9), 7.65-7.10 m (H-6, H-7, H-8), 7.00 s (H-3), 2.88 s (2-CH_2CH_2N), 2.67 s (1-CH_3), 2.52 s (4-CH_3), 1.25 s (NH_2, exchangeable). The *hydrochloride* was recrystallized from 2-propanol-methanol, m.p. 288-300°.

Anal. Calcd. for $C_{16}H_{17}NO{\cdot}HCl$: C, 69.7; H, 6.58; Cl, 12.9; N, 5.08. Found: C, 69.2; H, 6.67; Cl, 12.9; N, 4.86.

1,4-Dimethyl-2-(2-aminoethyl)dibenzothiophene (XXVIIIb).

This compound was similarly prepared and purified; the yield was 78%; nmr δ 8.48-8.20 m (H-9), 7.95-7.70 m (H-6), 7.55-7.28 m (H-7, H-8), 7.03 s (H-3), 2.92 s (2-CH_2CH_2N), 2.77 s (1-CH_3), 2.49 (4-CH_3), 2.20 s (NH_2, exchangeable). A weak singlet at δ 1.42 was indicative of a few percent of dimeric contaminant, not removed by re-precipitation. The *hydrochloride* was recrystallized from ethanol-acetone (1:2; 50 ml./g.), m.p. 272-287°.

Anal. Calcd. for $C_{16}H_{17}NS{\cdot}HCl$: C, 65.8; H, 6.22; N, 4.80. Found: C, 66.1; H, 6.22; N, 4.85.

1,4-Dimethyl-2-(2-formamidoethyl)dibenzofuran (XXIXa).

The amine (XXVIIIa; 1.6 g., 6.7 mmoles) and 35 ml. of ethyl formate in a steel bomb were heated at 100° for 3 hours. The resultant solution was clarified by filtration, concentrated, and the residual product was recrystallized from 80% ethanol to yield 1.2 g. (69%), m.p. 144-145°; nmr (deuteriochloroform, exchanged) δ 8.10 s (-CH=O), 8.08-7.88 m (H-9), 7.65-7.15 m (H-6, H-7, H-8), 6.98 s (H-3), 3.7-3.3 broad m (-CH_2N), 3.1-3.75 m (2-CH_2-), 2.70 s (1-CH_3), 2.53 s (4-CH_3).

Anal. Calcd. for $C_{17}H_{17}NO_2$: C, 76.4; H, 6.41; N, 5.24. Found: C, 76.1; H, 6.58; N, 5.36.

1,4-Dimethyl-2-(2-formamidoethyl)dibenzothiophene (XXIXb).

Similarly prepared, the yield was 65%, m.p. 167-169° after recrystallization from 95% ethanol; nmr δ 8.55-8.25 (H-9), 8.03 s (-CH=O), 8.03-7.25 m (H-6, H-7, H-8), 7.07 s (H-3), 3.75-3.25 m (-CH_2N), 3.20-2.8 m (2-CH_2-), 2.85 s (1-CH_3), 2.53 s (4-CH_3).

Anal. Calcd. for $C_{17}H_{17}NOS$: C, 72.0; H, 6.05; N, 4.95. Found: C, 71.9; H, 6.03; N, 5.02.

3,4-Dihydro-5,11-dimethylbenzofuro[3,2-*g*]isoquinoline (XXXa).

The formamide (XXIXa, 1.1 g., 4.1 mmoles) was stirred with 31 g. of polyphosphoric acid and mixed thoroughly at room temperature, then immersed in an oil bath and heated at 135-140° (internal temperature) and stirred for 2 hours. The hydrolysate with 50 g. of crushed ice was stirred for 1.5 hours, while the phosphate salt of XXXa separated as a tan solid. It was collected, suspended in 50 ml. of water, basified with concentrated ammonium hydroxide, and stirred overnight, while the regenerated free base formed a brown solid, 0.98 g. (90% yield), m.p. 123-133°. Recrystallization from 20 ml. of carbon tetrachloride gave 0.51 g. (53%), m.p. 135-137°. Unlike the pyridocarbazole analog (4), drying at 80° *in vacuo* readily gave a solvent-free sample; uv (ethanol) λ max mμ 229 (ε x 10^{-3}, 7.95), 270 (8.36), 279 (10.9), 308 (28.8); nmr δ 8.65 broad s (H-1), 8.05-7.83 m (H-6), 7.60-7.10 m (H-9, H-8, H-7), 3.92-3.58 m (-CH_2N=), 2.90-2.62 m (benzylic CH_2 at C-4), 2.59 s and 2.52 s (1-CH_3 and 4-CH_3).

Anal. Calcd. for $C_{17}H_{15}NO$: C, 81.9; H, 6.06; N, 5.62. Found: C, 81.8; H, 6.14; N, 5.45.

3,4-Dihydro-5,11-dimethylbenzothieno[3,2-*g*]isoquinoline (XXXb).

By the same procedure, the amide (XXIXb) was cyclized at 140° for 3 hours. The regenerated free base was extracted into dichloromethane. Concentration of the washed and dried extract afforded 87% of a residual gum, which crystallized. A minor contaminant with amidic infrared absorption was removed upon solution of the product in 3 *M* acetic acid (20 ml./g.) and filtration; basification of the filtrate with sodium hydroxide regenerated 69% of XXXb, m.p. 93-116°. A sample recrystallized from carbon tetrachloride-petroleum ether (10:1) melted at 90-127° (dried at 80° *in vacuo*), but was chromatographically homogeneous (R_f 0.4 on tlc in benzene-methanol, 9:1) and analytically pure; nmr δ 8.69 t (H-1, $J_{1,3}$ = 2.4Hz), 8.47-81.3 m (H-6), 7.93-7.64 m (H-9), 7.55-7.27 (H-7, H-8), 3.90-3.57 m (-CH_2N=), 2.92-2.68 m (benzylic CH_2 at C-4), 2.63 s and 2.57 s (1-CH_3 and 4-CH_3).

Anal. Calcd. for $C_{17}H_{15}NS$: C, 76.9; H, 5.70; N, 5.28; S, 12.1. Found: C, 77.0; H, 5.54; N, 5.26; S, 12.4.

5,11-Dimethylbenzofuro[3,2-*g*]isoquinoline (VI, Isooxaellipticine).

A mixture of 1.51 g. (6.1 mmoles) of XXXa and 0.76 g. of 30% palladium-charcoal was heated under nitrogen at 210° for 2.5 hours. The catalyst was removed by dissolving the product in dichloromethane; concentration of the filtrate afforded 1.32 g. (89%) m.p. 145-154°. Recrystallization from carbon tetrachloride-dichloromethane (7:1) yielded 1.01 g. (68%), m.p. 154-156°. A sample for analysis melted at 155-157°; uv (ethanol) λ max mμ 221 (ε x 10^{-3}, 27.9), 264 (78.6), 293 sh, 305 (11.1), 318 (14.6), 356 (7.72); uv (0.1 *M* hydrochloric acid) λ max mμ 225 (ε x 10^{-3}, 23.9), 276 (49.9), 333 (13.4); nmr δ 9.40 broad s (H-1), 8.48 broad d (H-3, $J_{3,4}$ = 6Hz), 8.04-7.82 m (H-6), 7.70 d (H-4, $J_{3,4}$ = 6Hz), 7.53-7.08 m (H-9, H-8, H-7), 2.73 s and 2.71 s (1-CH_3 and 4-CH_3).

Anal. Calcd. for $C_{17}H_{13}NO$: C, 82.6; H, 5.30; N, 5.66. Found: C, 82.7; H, 5.30; N, 5.43.

5,11-Dimethylbenzothieno[3,2-*g*]isoquinoline (VII, Isothiaellipticine).

Similarly, aromatization of XXXb afforded VII in 57% yield after recrystallization from methanol (25 ml./g.), m.p. 146-149°; uv (ethanol) λ max mμ 243 (ε x 10^{-3}, 29.5), 267 (51.7), 276 (86.2), 302 (7.11), 312 (6.53); nmr (deuteriochloroform) δ 9.46 s (H-1; estimated $J_{1,3}$ = 0.5Hz), 8.53 d (H-3, $J_{3,4}$ = 6Hz), 8.43-8.22 m (H-6), 7.97-7.34 m (H-4, H-9, H-8, H-7), 2.90 s and 2.75 s (1-CH_3 and 4-CH_3).

Anal. Calcd. for $C_{17}H_{13}NS$: C, 77.5; H, 4.97; N, 5.32; S, 12.2. Found: C, 77.8; H, 4.98; N, 5.36; S, 12.5.

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(7) Olivacine (ref. 3) and 9-methoxyellipticine (ref. 2) may be cited along with I and II as active pyrido[4,3-*b*]carbazoles.

(8) The various systematic numberings of the structures are designated, so as to avoid confusion.

(9a) The authors are indebted to one of the referees for citing a paper by T. S. Osdene and P. B. Russell, *J. Org. Chem.*, 31, 2646 (1966) explaining these observations, and suggesting that the hydroxy-containing impurity is the hemiketal derived by reaction of 2-chlorocyclohexanone at the 6-position of 2,5-xylenol, followed by cyclization of the ketophenol. Dehydration of the hemiketal on distillation leads to compound XV; (b) S. Trippett, *J. Chem. Soc.*, 419 (1957).

(10) A. Rieche, H. Gross, and E. Höft, *Chem. Ber.*, **93**, 88 (1960).

(11) W. E. Parham, "Dibenzofuran," Chapter 3, "Heterocyclic Compounds," Vol. 2, R. C. Elderfield, Ed., John Wiley and Sons, New York, N. Y., 1951, p. 130 and p. 141.

(12) A. N. Fujiwara and E. M. Acton, to be published.

(13) Otherwise, of course, the reaction product (XII) with chlorocyclohexanone was contaminated by the *para*-oxy isomer of XII; in one run, this was isolated as a crystalline solid (see Experimental).

(14) P. J. Black and M. L. Heffernan, *Australian J. Chem.*, 18, 353 (1965).

(15) C. D. Hurd and P. Perletz, *J. Am. Chem. Soc.*, 68, 38 (1946).

(16) Comparison of uv extinctions indicates the sample in ref. 9 was about 80% pure.

(17) Esterification with ethereal diazomethane generally suffered from the introduction of an extraneous impurity, giving rise to broadening at 5.90-5.95 μ of the infrared carbonyl absorption, an unassigned singlet at δ 3.3 in the nmr spectrum, and lowered melting points, relative to samples obtained by other methods.

(18) According to FMC Corporation, Inorganic Chemicals Division, New York, N. Y., the phosphorus content is equivalent to 76% phosphorus pentoxide, distributed as 49% H_3PO_4, 42% $H_4P_2O_7$, 8% $H_5P_3O_{11}$, and 1% $H_6P_4O_{13}$. This reagent is also known as phospholeum. In contrast, the phosphorus content of commercial polyphosphoric acid is equivalent to 82-84% phosphorux pentoxide.

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