

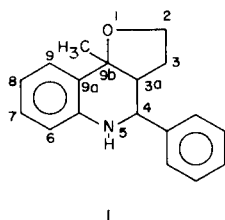
1,4-Cycloaddition Reactions. II. Preparation of *p*-Dioxino[2,3-*g*]furo[3,2-*c*]quinolines, *p*-Dioxino[2,3-*f*]furo[3,2-*c*]quinolines, and [1,3]Dioxolo[4,5-*g*]furo[3,2-*c*]quinolines from 2,3-Dihydro-5-methylfuran and Schiff Bases (1)

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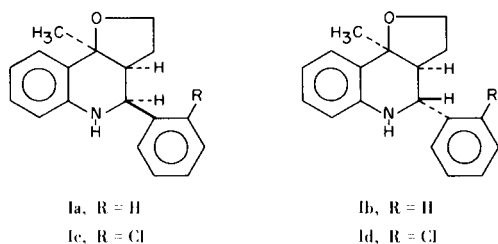
The boron trifluoride catalyzed 1,4-addition of 2,3-dihydro-5-methylfuran to *N*-(*p*-methoxybenzylidene)-1,4-benzodioxan-6-amine (II) gave 2 pairs of epimers, 2,3,3a,4,5,8,9,11b-octahydro-4-(*p*-methoxyphenyl)-11b-methyl-*p*-dioxino[2,3-*g*]furo[3,2-*c*]quinoline (IIIa and b) and 2,3,7,8,8a,9,10,11a-octahydro-8-(*p*-methoxyphenyl)-11a-methyl-*p*-dioxino[2,3-*f*]furo[3,2-*c*]quinoline (IVa and b). When *N*-(*p*-methoxybenzylidene)-3,4-methylenedioxyaniline (V) was condensed with 2,3-dihydro-5-methylfuran in an analogous manner, a mixture of 2 epimers of 2,3,3a,4,5,10b-hexahydro-4-(*p*-methoxyphenyl)-10b-methyl[1,3]dioxolo[4,5-*g*]furo[3,2-*c*]quinoline (VIa and b) was isolated. Treatment of this mixture with sulfur afforded 6-(*p*-methoxyphenyl)-8-methyl-1,3-dioxolo[4,5-*g*]quinoline-7-ethanol (VIII). Structural assignments for all of the products were made from NMR spectra. None of the compounds possessed appreciable biological activity.

2,3,3a,4,5,9b-Hexahydro-9b-methyl-4-phenylfuro[3,2-*c*]quinoline (I) was synthesized by Povarov and co-workers



(2) from 2,3-dihydro-5-methylfuran and *N*-benzylideneaniline and was described along with other 1,4-cycloaddition products derived from vinyl ethers and Schiff bases (3). These authors discussed the course of the reaction and reported that only one isomer of I was obtained (2). More recent studies in these laboratories provided additional data bearing on the structure of such adducts (1). In summary, contrary to the report of Povarov and co-workers (2), 2 epimers (Ia and b) were formed by the

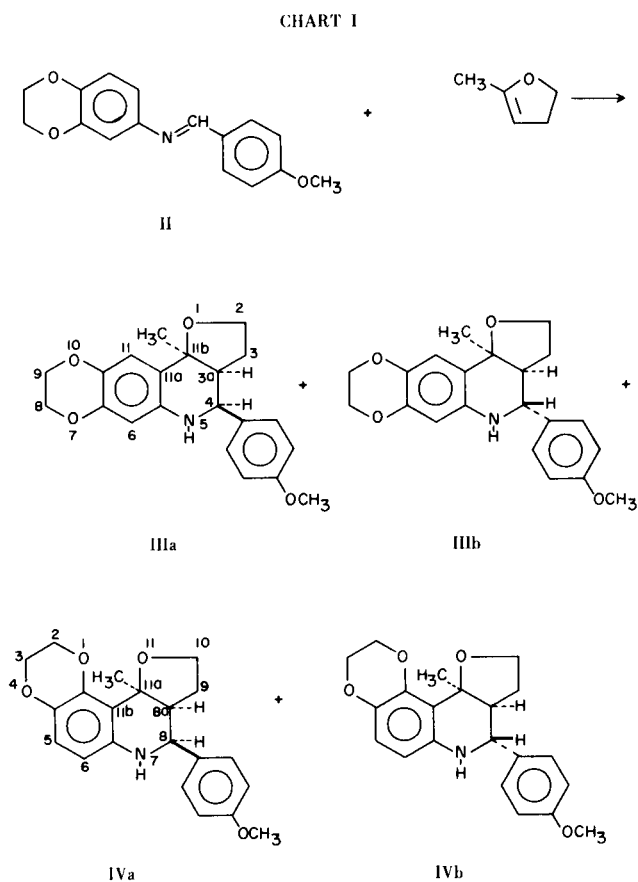
1,4-cycloaddition of 2,3-dihydro-5-methylfuran to *N*-benzylideneaniline. Two epimers (Ic and d) were also formed in the addition of 2,3-dihydro-5-methylfuran to *N*-(*o*-chlorobenzylidene)aniline (1). One of these *o*-chlorophenyl compounds gave a 1 proton doublet (4-H) at 5.11 with $J_{3a,4} = 2$ and a 3 proton singlet at 1.70 (9b-CH₃). The other gave a 1 proton doublet (4-H) at 4.62 with $J_{3a,4} = 8$ and a 3 proton singlet at 1.41 (9b-CH₃). Structure Ic, with the 3a,4-protons in the *cis* configuration, was then assigned to the compound with the smaller coupling constant, and structure Id with the 3a,4-protons *trans*, was assigned to the compound with the larger coupling constant (1). In the case of the epimers Ia and b, the higher melting compound gave a 1 proton doublet at 4.65 with $J_{3a,4} = 2$ (4-H) and a 3 proton singlet at 1.70 (9b-CH₃). The lower melting isomer gave a 3 proton singlet at 1.41 but the doublet due to the 4-proton was lost in other absorption in the range of 3.6-4.1. Structures Ia (higher melting isomer) and Ib (lower melting isomer) were, however, assigned on the basis of the correspondence of the signals from the 9b-methyl groups, and the J-value for the 4-proton of the *cis* isomer Ia (1).



Three other heterocyclic systems, namely *p*-dioxino[2,3-*g*]furo[3,2-*c*]quinolines (IIIa and b), *p*-dioxino[2,3-*f*]furo[3,2-*c*]quinolines (IVa and b), and [1,3]dioxolo[4,5-*g*]furo[3,2-*c*]quinolines (VIa and b) (Charts I and II), have now been synthesized utilizing the 1,4-cycloaddition of 2,3-dihydro-5-methylfuran to *N*-(*p*-methoxybenzylidene)-1,4-benzodioxan-6-amine (II) and *N*-(*p*-methoxybenzylidene)-3,4-methylenedioxyaniline (V). The first

two aforementioned ring systems are not listed in *Chemical Abstracts* or "The Ring Index" (4) and appear to be novel heterocyclic types. Structure assignments were based on spectral data.

It was anticipated that the 1,4-cycloaddition of 2,3-dihydro-5-methylfuran to *N*-(*p*-methoxybenzylidene)-1,4-benzodioxan-6-amine (II) might produce the 4 isomers IIIa and b and IVa and b. Indeed, an NMR curve of the crude gum initially obtained from the reaction gave peaks at 1.84, 1.64, 1.58, and 1.39 which were tentatively assigned to the angular methyl groups of these pairs of epimers. Column chromatography cleanly separated three



components with melting points of 203-205°, 226-227°, and 193-199°. The angular methyl groups of these compounds gave signals at 1.65, 1.86, and 1.56, respectively (Fig. 1). A fourth compound with the methyl peak at 1.38 was also obtained (Fig. 1), but was contaminated to the extent of approximately 25% with the product with the methyl peak at 1.86.

Microanalyses (C,H,N) for all four compounds were consistent with a 1:1 adduct, and each exhibited N-H absorption in the infrared spectra in accordance with previous work (1-3). Examination of the NMR curves (Fig. 1)

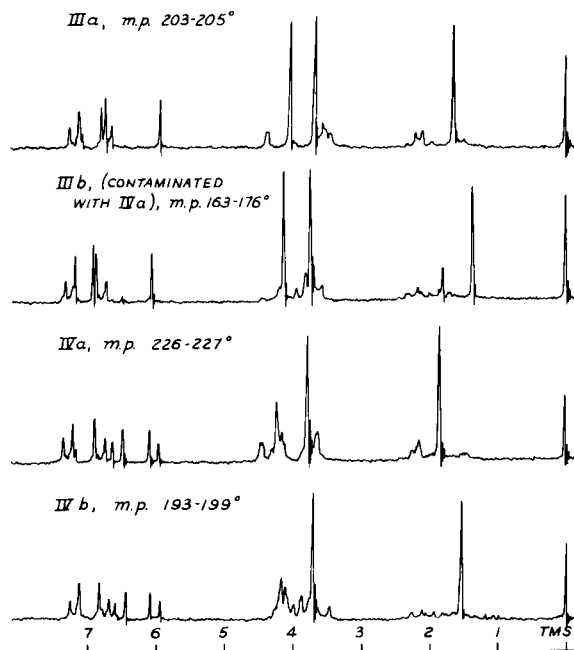


Figure 1. NMR Curves of the Products from the Boron Trifluoride Catalyzed Reaction of 2,3-Dihydro-5-methylfuran and *N*-(*p*-Methoxybenzylidene)-1,4-benzodioxan-6-amine.

showed that those components of m.p. 203-205° and 226-227° showed doublets with $J = 2$ at 4.45 and 4.50 respectively. These isomers were then assigned the *cis* configurations IIIa and IVa in correspondence with Ia (1). Further inspection of the NMR spectra showed that the isomer of m.p. 226-227° exhibited 2 typical AB patterns, a 4 proton pattern centered at 7.12 due to the *p*-methoxyphenyl group, and a 2 proton pattern centered at 6.36 with $J_{AB} = 8.5$ cps and $\Delta\nu_{AB} = 31.2$ cps, which was assigned to the 5,6-protons of IVa. In contrast, the isomer of m.p. 203-205° showed a 4 proton AB pattern centered at 7.12 due to the *p*-methoxyphenyl group, and two 1 proton singlets at 6.90 and 6.07 which were assigned to the *para* 6 and 11 protons of IIIa.

The remaining two components, with the pattern of the signals from the benzylic protons obscured due to absorption of other protons in the range of 3.5-4.5, were then assumed to be in the *trans* configurations IIIb and IVb. The isomer of m.p. 193-199° was assigned structure IVb on the basis of the similarity of the 2 AB patterns centered at 7.12 and 6.44 to those found for IVa. The fourth isomer (m.p. 163-176°) (IIIb) showed the AB pattern expected for the *p*-methoxyphenyl group, and singlets at 6.12 and 6.99 due to the *para* 6 and 11 protons (Chart I, Fig. 1).

The relative integration indicates that the absorption due to the N-H proton for all four isomers is hidden in the complex pattern in the 3.5-4.5 region. This area also contains signals from the 2, 8, 9, and OCH₃ protons of IIIa and b as well as the corresponding protons of IVa and b.

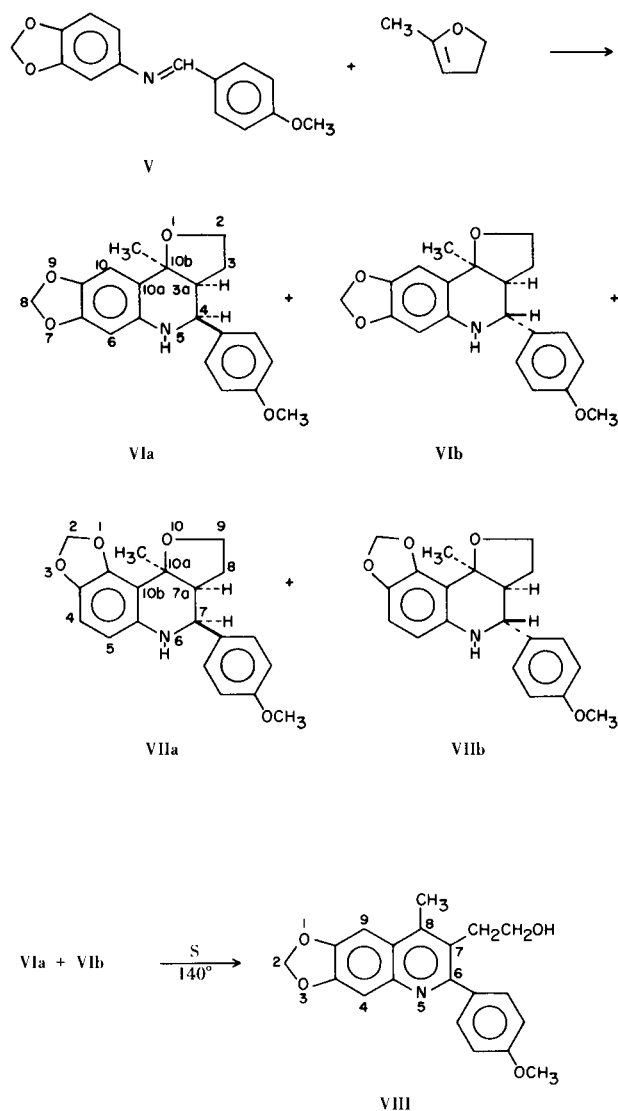
It is noteworthy that the NMR signals from the angular methyl groups of the *cis* compounds IIIa and IVa were located downfield from the signals from the respective *trans* compounds IIIb and IVb. Also, the pair of signals from the angular methyl groups from the dioxino[2,3-*f*]-furo[3,2-*c*]quinolines (IVa and b) was shifted slightly downfield from the corresponding signals from the dioxino[2,3-*g*]furo[3,2-*c*]quinolines (IIIa and b).

Inspection of the NMR spectrum of the crude reaction mixture from the addition of 2,3-dihydro-5-methylfuran to *N*-(*p*-methoxybenzylidene)-3,4-methylenedioxyaniline (V) (Chart II) revealed numerous peaks in the 1.0-2.0 region, suggesting that again four isomers (VIa and b, VIIa and b) corresponding to those obtained from the reaction of 2,3-dihydro-5-methylfuran and *N*-(*p*-methoxybenzylidene)-1,4-benzodioxan-6-amine were formed. However, recrystallization from ethanol gave a mixture (45% yield), which exhibited 1.5 proton singlets at 1.40 and 1.66, a 0.5 proton doublet at 4.55 with *J* = 2, 0.5 proton singlets at 6.11 and 6.16, a singlet at 6.97, and a typical AB pattern from the *p*-methoxyphenyl group in the NMR spectrum. This clearly indicated that this fraction was the mixture of epimers of 2,3,3a,4,5,10b-hexahydro-4-(*p*-methoxyphenyl)-10b-methyl[1,3]dioxolo[4,5-*g*]furo[3,2-*c*]quinoline (VIa and b). The signals from the 4-H of VIb and the N-H of VIa and b were obscured in other absorptions in the 3.4-4.5 region. No further work was undertaken in the isolation of additional reaction products, presumably VIIa and b, from the mother liquors or in the separation of VIa and b, due to the lack of appreciable biological activity for the mixture of VIa and b.

Aromatization of the mixture of VIa and VIb with sulfur to 6-(*p*-methoxyphenyl)-8-methyl-1,3-dioxolo[4,5-*g*]quinoline-7-ethanol (VIII) (Chart II) was achieved and the NMR spectrum examined. A three proton singlet at 2.61 was assigned to the 8-methyl group. The aromatic region exhibited two singlets at 7.26 and 7.44 which integrated for one proton each along with the AB pattern from the 6-*p*-methoxyphenyl group.

Representative compounds described in the present communication were tested in mice against an array of parasites, including *Plasmodium berghei*, *Schistosoma mansoni*, and a broad spectrum of helminths. The effects of various compounds on the central nervous system of mice, atherosclerosis in the rat, and the inhibition of ADP-induced thrombocyte aggregation *in vitro* were also evaluated. None of the compounds possessed appreciable biological activity in these test systems.

CHART II



EXPERIMENTAL (5)

dl-2,3,3a,4,5,8,9,11b-Octahydro-4-(*p*-methoxyphenyl)-11b-methyl-*p*-dioxino[2,3-*g*]furo[3,2-*c*]quinoline (IIIa and b) and *dl*-2,3,7,8,8a,9,10,11a-octahydro-8-(*p*-methoxyphenyl)-11a-methyl-*p*-dioxino[2,3-*f*]furo[3,2-*c*]quinoline (IVa and b) (Chart I).

To a solution of 25.0 g. (0.093 mole) of *N*-(*p*-methoxybenzylidene)-1,4-benzodioxan-6-amine (II) and 0.5 ml. of boron trifluoride etherate in 400 ml. of benzene was added dropwise a solution of 10.0 g. (0.12 mole) of 2,3-dihydro-5-methylfuran (6) in 40 ml. of benzene. The exothermic reaction raised the temperature from 26° to 31°. Stirring was continued for 4 hours at room temperature, and the solution was concentrated *in vacuo* to a gum. The gum was dissolved in 250 ml. of boiling 2-propanol. On cooling, a precipitate separated which was collected and crystallized from 2-propanol to give 5.5 g. of a white solid, m.p. 181.5-189°; infrared cm^{-1} , 3260 (N-H). The NMR spectrum showed peaks at

1.65 and 1.38, indicating a mixture of IIIa and b.

Anal. Calcd. for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96.
Found: C, 71.10; H, 6.36; N, 3.95.

The 2-propanol filtrate was concentrated *in vacuo* and 12.0 g. of the residue was dissolved in 5% ethyl acetate in benzene and chromatographed on alumina (Alcoa, grade F-20, 600 g.) with 5% ethyl acetate in benzene. Approximately 300 ml. fractions were taken. Fractions 18-20 were combined, and upon concentration and recrystallization from acetonitrile gave 0.5 g., m.p. 203-205°, of isomer IIIa; NMR signal, 1.65.

Anal. Calcd. for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96.
Found: C, 71.21; H, 6.50; N, 3.83.

In like manner fractions 22-24 gave 0.2 g., m.p. 226-227°, of isomer IVa; NMR signal, 1.86.

Anal. Calcd. for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96.
Found: C, 71.57; H, 6.55; N, 3.99.

Similarly, fractions 25-28 gave 0.6 g., m.p. 163-176°, of a mixture of isomer IIIb and isomer IVa; NMR signals, 1.38 and 1.86, with relative integrations of 3 to 1, respectively.

Anal. Calcd. for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96.
Found: C, 71.52; H, 6.69; N, 4.01.

Finally, fractions 42-48 on concentration and recrystallization from acetonitrile produced 0.2 g. of isomer IVb, m.p. 193-199°; NMR signal, 1.56.

Anal. Calcd. for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96.
Found: C, 71.51; H, 6.69; N, 3.89.

2,3,3a,4,5,10b-Hexahydro-4-(*p*-methoxyphenyl)-10b-methyl[1,3]-dioxolo[4,5-*g*]furo[3,2-*c*]quinoline (VIa and b) (Chart II).

To a solution of 40.0 g. (0.157 mole) of *N*-(*p*-methoxybenzylidene)-3,4-methylenedioxyaniline (V) and 0.5 ml. of boron trifluoride etherate in 500 ml. of benzene was added dropwise a solution of 18.7 g. (0.22 mole) of 2,3-dihydro-5-methylfuran (6) in 50 ml. of benzene. The exothermic reaction increased the temperature of the reaction mixture from 26° to 37°. After 4 hours the reaction mixture was concentrated to a gum which was triturated with 95% ethanol. The resultant solid was recrystallized from 95% ethanol to give 24.0 g. (45%) of a mixture of VIa and b, m.p. 126-129°, infrared spectrum, 3320 cm^{-1} (N-H).

Anal. Calcd. for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13.
Found: C, 70.47; H, 6.28; N, 4.08.

6-(*p*-Methoxyphenyl)-8-methyl[1,3]dioxolo[4,5-*g*]quinoline-7-ethanol (VIII, Chart II).

An intimate mixture of 7.0 g. (0.02 mole) of the mixture of VIa and b and 0.6 g. (0.02 mole) of sulfur was heated at melt (140° bath temperature). Hydrogen sulfide was evolved and the reaction mass solidified. The bath temperature was raised to 160° without remelting of the reaction mass. The solid was cooled and treated with boiling acetonitrile. The resultant crystals were collected and recrystallized from acetonitrile to give 4.9 g. (70%) of VIII as a pale yellow powder, m.p. 203-205°; infrared cm^{-1} (carbon tetrachloride, 1.0 cm. cell), 3637 (OH).

Anal. Calcd. for $C_{20}H_{19}NO_4$: C, 71.19; H, 5.68; N, 4.15.
Found: C, 71.06; H, 5.72; N, 4.23.

N-(*p*-Methoxybenzylidene)-1,4-benzodioxan-6-amine (II, Chart I).

1,4-Benzodioxan-6-amine (7) (15.0 g., 0.1 mole) was combined with *p*-anisaldehyde (13.6 g., 0.1 mole) in 300 ml. of benzene and a few crystals of *p*-toluenesulfonic acid were added as catalyst. The reaction mixture was heated at reflux while water was removed in a trap for 4 hours. The solution was concentrated to 100 ml.; petroleum ether (b.p. 30-60°) was added, and the resultant oil

solidified upon cooling and vigorous shaking. The solid was collected and the filtrate was concentrated to an oil which was crystallized from 2-propanol. These two crops were combined and recrystallized from 2-propanol to give 25.0 g. (93%), m.p. 78-79°.

Anal. Calcd. for $C_{16}H_{15}NO_3$: C, 71.37; H, 5.61; N, 5.20.
Found: C, 71.48; H, 5.61; N, 5.25.

N-(*p*-Methoxybenzylidene)-3,4-methylenedioxyaniline (V, Chart II).

3,4-Methylenedioxyaniline hydrochloride (8) (100 g., 0.575 mole) was treated with an excess of 20% aqueous sodium hydroxide and the solution extracted with three 75 ml. portions of benzene. The combined benzene solutions were washed with water (20 ml.), dried over anhydrous potassium carbonate, and filtered. The benzene solution was added to a solution of *p*-anisaldehyde (78.0 g., 0.575 mole) in one liter of benzene and a few crystals of *p*-toluenesulfonic acid were added as catalyst. This solution was heated at reflux while water was removed in a trap for 4 hours. The reaction mixture was concentrated to 300 ml., the residue cooled, and the resulting precipitate collected. Addition of petroleum ether (b.p. 30-60°) to the filtrate gave a second crop. These crops were combined and recrystallized from 2-propanol to give 86.0 g. (59%) of (V), m.p. 105-106°.

Anal. Calcd. for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13; N, 5.49.
Found: C, 70.79; H, 5.29; N, 5.44.

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