

1,4-Cycloaddition Reactions. IV.
Preparation of Cyclopenta[*g*]furo[3,2-*c*]quinolines, Cyclopenta-
[*f*]furo[3,2-*c*]quinolines, Benzo[*h*]furo[3,2-*c*]quinolines, and Furo-
[3,2-*c*]indeno[1,7-*gh*]quinolines from 2,3-Dihydro-5-methylfuran
and Schiff Bases (1)

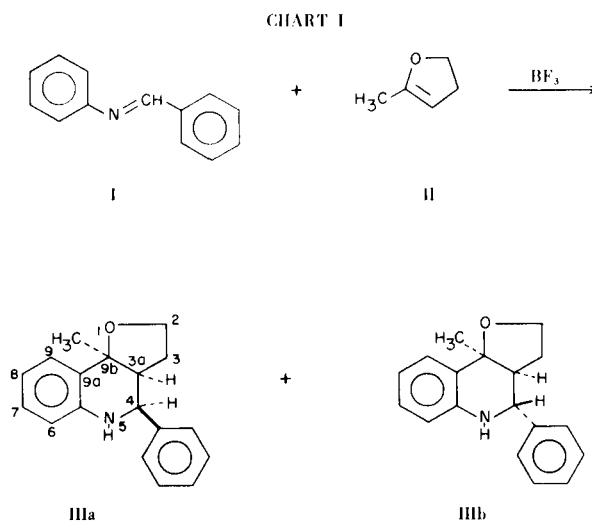
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The boron trifluoride catalyzed 1,4-addition of 2,3-dihydro-5-methylfuran to *N*-(*p*-methoxybenzylidene)-5-indanamine (VI) gave 2 pairs of epimers, *dl*-3,3a,4,5,7,8,9,10b-octahydro-4-(*p*-methoxyphenyl)-10b-methyl-2*H*-cyclopenta[*g*]furo[3,2-*c*]quinoline (VIIa and b) and *dl*-3,3a,4,5,8,9,10,10c-octahydro-4-(*p*-methoxyphenyl)-10c-methyl-2*H*-cyclopenta[*f*]furo[3,2-*c*]quinoline (VIIIa and b). When 4-(benzylideneamino)-1-naphthol (IXa) was condensed with 2,3-dihydro-5-methylfuran in an analogous manner, a mixture of two isomers of *dl*-1,2,2a,3,4,5a-hexahydro-5a-methyl-2-phenylbenzo[*h*]furo[3,2-*c*]quinolin-7-ol [Xa and b (R = H)] was obtained. Likewise, 4-[(*p*-hydroxybenzylidene)amino]-1-naphthol (IXb) and 4-(*p*-methoxybenzylidene)amino]-1-naphthol (IXc) gave a mixture of two isomers of *dl*-1,2,2a,3,4,5a-hexahydro-2-(*p*-hydroxyphenyl)-5a-methylbenzo[*h*]furo[3,2-*c*]quinolin-7-ol [Xa and b (R = OH)] and *dl*-1,2,2a,3,4,5a-hexahydro-2-(*p*-methoxyphenyl)-5a-methylbenzo[*h*]furo[3,2-*c*]quinolin-7-ol [Xa and b (R = OCH₃)], respectively. The condensation of *N*-(*p*-methoxybenzylidene)-5-acenaphthenamine (XI) with 2,3-dihydro-5-methylfuran afforded a mixture of two isomers of *dl*-2,3,3a,4,5,9,10,11b-octahydro-4-(*p*-methoxyphenyl)-11b-methylfuro[3,2-*c*]indeno[1,7-*gh*]quinoline (XIIa and b). Structural assignments for all of the products were made from NMR spectra. None of these compounds possessed appreciable biological activity.

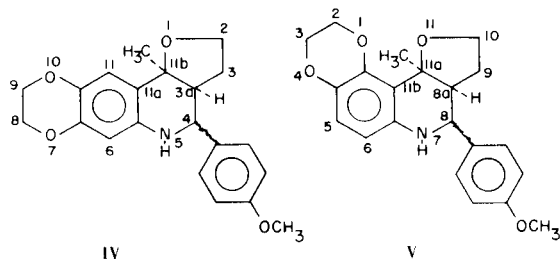
Pavorov and coworkers recently developed an elegant quinoline synthesis utilizing the cycloaddition of vinyl ethers to Schiff bases (2). Moreover, the condensation of the cyclic enol ether 2,3-dihydro-5-methylfuran (II) with *N*-benzylideneaniline (I) led to the formation of the interesting tricyclic derivative 2,3,3a,4,5,9b-hexahydro-9b-methyl-4-phenylfuro[3,2-*c*]quinoline in high yield (3). A reinvestigation of the latter reaction in these laboratories showed that the reaction of 2,3-dihydro-5-methylfuran (II) with *N*-benzylideneaniline (I) (Chart I) did not yield a single product but instead gave two epimers (IIIa and IIIb) in approximately equal amounts (4). The structures of these products were assigned primarily on the basis of their NMR spectra (4). A correspondence was demonstrated relating the position and coupling constant of the 4-proton peak in the *cis* (IIIa) and *trans* (IIIb) configurations with the chemical shift of the 9b-CH₃ signal.

Subsequently, several novel fused heterocyclic furoquinoline structures were prepared utilizing analogous 1,4-cycloaddition reactions (5). Among these were *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 (IV, 3a,4-protons *cis* and *trans*) 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 (V, 8,8a-protons *cis* and *trans*), prepared from 2,3-dihydro-5-methylfuran and *N*-(*p*-methoxybenzylidene)-1,4-benzodioxan-6-amine. Inspection of the NMR spectra showed an AB pattern in the aromatic region for the 5,6-protons of V and 2 singlets for protons 6 and 11 of IV which was cited as supporting data for the structure assignments (5). Thereby the angular methyl groups of these 4 products were related to the corresponding aromatic pattern as well as the 4(8)-proton signals.

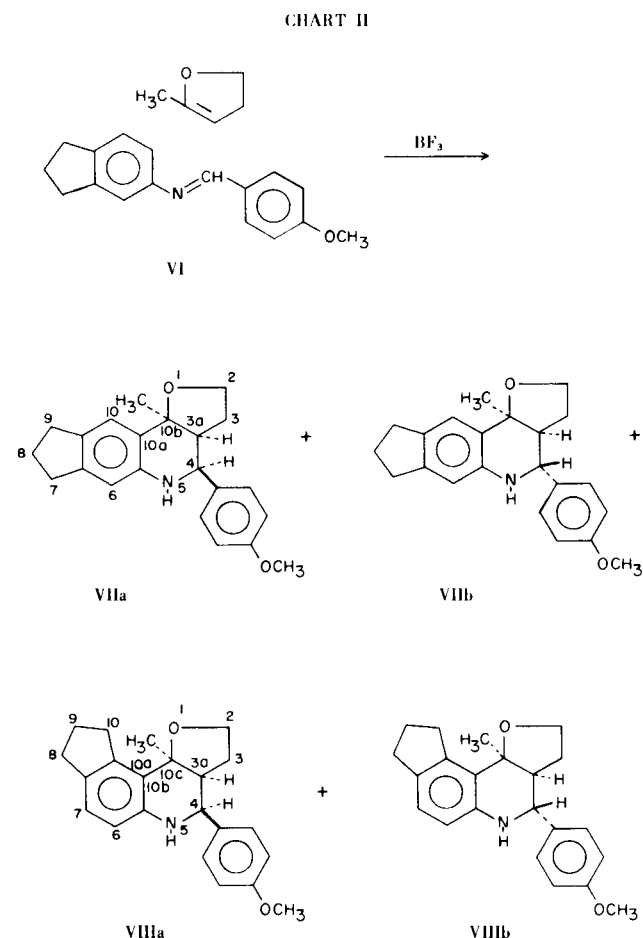


The present communication describes the synthesis and structure assignments of several furoquinolines which contain fused carbocyclic rings. Specifically, various cyclopenta[*g*]furo[3,2-*c*]quinolines (VII), cyclopenta[*f*]furo[3,2-*c*]quinolines (VIII), benzo[*h*]furo[3,2-*c*]quinolines (X), and furo[3,2-*e*]indeno[1,7-*gh*]quinolines (XII) have now been synthesized utilizing the 1,4-cycloaddition of 2,3-dihydro-5-methylfuran to *N*-(*p*-methoxybenzylidene)-5-indanamine (VI), 4-(benzylideneamino)-1-naphthol (IXa), 4-[(*p*-hydroxybenzylidene)amino]-1-naphthol (IXb), 4-[(*p*-methoxybenzylidene)amino]-1-naphthol (IXc), and *N*-(*p*-methoxybenzylidene)-5-acenaphthenamine (XI). Ring systems VII, VIII, and XII are not listed in *Chemical Abstracts* or "The Ring Index" (6) and appear to be novel heterocyclic types. Structure assignments are based on spectral data.

In general these condensations proceeded exothermically and gave moderate to high yields of crystalline products which elemental analysis indicated were 1:1 adducts. Moreover, the NMR spectra exhibited patterns consistent with previous experience in related series (1,4,5). Addition of 2,3-dihydro-5-methylfuran to *N*-(*p*-methoxybenzylidene)-5-indanamine (VI) under these conditions was expected to yield 2 pairs of epimers, while the 4-(benzylideneamino)-1-naphthols (IXa, b, and c) and *N*-(*p*-methoxybenzylidene)-5-acenaphthenamine (XI) were expected to give only one pair of epimers each.

When 2,3-dihydro-5-methylfuran was condensed with *N*-(*p*-methoxybenzylidene)-5-indanamine (VI) (Chart II), 3 crops of product were isolated with melting points of 191-196°, 155-164°, and 141-154°. Inspection of the NMR curve of the crop m.p. 191-196° showed a peak at δ 1.25 (with a small shoulder at 1.23) and an aromatic pattern consisting of two AB patterns, one integrating for

4 protons (*p*-methoxyphenyl protons), the other integrating for 2 protons [6,7-protons (VIIIa)]. Peaks at 1.25 and 1.58 were characteristic of the crop of m.p. 155-164° as well as a peak (0.3 proton) at 4.51 and an aromatic pattern consisting of two *p*-methoxyphenyl AB patterns and two pairs of singlets (6,10 protons). The NMR curve of the crop which melted from 141-154° showed a peak at 1.25 with a shoulder at 1.23 and a peak at 1.58 with a shoulder at 1.61, a peak at 4.52 (~0.5 proton), and an aromatic pattern with two *p*-methoxyphenyl AB patterns



and the same 2 pairs of singlets but of reversed relative integration. This data suggests that the peak at 1.58 is due to the *cis*-linear compound (VIIa) and the peak at 1.23 is due to the *trans*-linear compound (VIIb). Although the aromatic pattern demands that two peaks are superimposed at 1.23-1.25, the available instrument could not resolve these peaks sufficiently to allow relating these CH₃ signals to specific aromatic patterns, or even the assignment of chemical shifts with certainty.

Three Schiff bases were prepared from 4-amino-1-naphthol by condensation with benzaldehyde, *p*-hydroxybenz-

6.6 g. was obtained from the filtrate; recrystallization from 2-propanol and finally acetone gave 3.9 g., m.p. 191-196°; NMR 1.25, 1.23. A final crop of 8.4 g. was obtained from the reaction mixture and was similar to the first crop based on the NMR spectrum. These two crops were combined and recrystallized from the acetone filtrate of the crop of m.p. 191-196° to give two crops: 7.3 g., m.p. 155-164° (NMR, 1.25, 1.58), and 5.9 g., m.p. 141-154° (NMR, 1.23, 1.25, 1.58, 1.61). The total yield was 17.1 g. (64%).

Anal. Calcd. for $C_{22}H_{25}NO_2$: C, 78.77; H, 7.51; N, 4.18. Found: (crop, m.p. 191-196°) C, 78.67; H, 7.40; N, 4.19.

dl-1,2,2a,3,4,5a-Hexahydro-5a-methyl-2-phenylbenzo[*h*]furo[3,2-*c*]quinolin-7-ol [Xa and b (R = H)].

To a solution of 4-(benzylideneamino)-1-naphthol (IXa) (8) (30.0 g., 0.12 mole) in 300 ml. of dioxane was added 0.5 ml. of boron trifluoride etherate followed by the dropwise addition of 2,3-dihydro-5-methylfuran (10.5 g., 0.125 mole). An exothermic reaction produced a temperature rise to 49°. After 3 hours the reaction mixture was filtered and the precipitate was washed with acetonitrile to give 15.0 g. of product, m.p. 240-244°. The dioxane filtrate was concentrated to an oil which gave 13.0 g., m.p. 240-244°, of additional product after trituration with acetonitrile. A subsequent crop of 4.0 g., m.p. 210-212°, was obtained by concentration of the acetonitrile filtrates. A total yield of 32.0 g. (81%) was obtained; NMR 1.15, 1.71.

Anal. Calcd. for $C_{22}H_{21}NO_2$: C, 79.73; H, 6.39; N, 4.23. Found: (mixture of first 2 crops) C, 79.78; H, 6.14; N, 4.18.

dl-1,2,2a,3,4,5a-Hexahydro-2-(*p*-hydroxyphenyl)-5a-methylbenzo[*h*]furo[3,2-*c*]quinolin-7-ol [Xa and b (R = OH)].

To a solution of 4-[(*p*-hydroxybenzylidene)amino]-1-naphthol (IXb) (8) (20.0 g., 0.076 mole) in 300 ml. of dioxane was added 0.5 ml. of boron trifluoride etherate followed by the dropwise addition of 2,3-dihydro-5-methylfuran (6.5 g., 0.076 mole). The exothermic reaction produced a temperature rise to 45°. After 3 hours the reaction mixture was concentrated to 100 ml. and poured into 2800 ml. of ice and water. The supernatant was decanted and the residue crystallized from boiling acetonitrile to give 11.0 g., m.p. 278-284°. The aqueous supernatant gave a precipitate which was collected and recrystallized from acetonitrile, 1.5 g., m.p. 278-284°. A total yield of 12.5 g. (47%) was thus obtained; NMR 1.20, 1.68.

Anal. Calcd. for $C_{22}H_{21}NO_3$: C, 76.06; H, 6.09; N, 4.03. Found: C, 76.02; H, 6.07; N, 4.10.

dl-1,2,2a,3,4,5a-Hexahydro-2-(*p*-methoxyphenyl)-5a-methylbenzo[*h*]furo[3,2-*c*]quinolin-7-ol [Xa and b (R = OCH₃)].

To a solution of 4-[(*p*-methoxybenzylidene)amino]-1-naphthol (IXc) (8) (30.0 g., 0.108 mole) in 300 ml. of dioxane was added 0.5 ml. of boron trifluoride etherate followed by the dropwise addition of 2,3-dihydro-5-methylfuran (9.5 g., 0.112 mole). The exothermic reaction produced a temperature increase to 48°. After 3 hours the reaction mixture was concentrated to an oil which was crystallized from acetonitrile to give 18.0 g. (46%) of product, m.p. 204-212° with preliminary softening; NMR 1.19, 1.70.

Anal. Calcd. for $C_{23}H_{23}NO_3$: C, 76.43; H, 6.41; N, 3.83. Found: C, 76.55; H, 6.28; N, 3.90.

dl-2,3,3a,4,5,9,10,11b-Octahydro-4-(*p*-methoxyphenyl)-11b-methylfuro[3,2-*c*]indeno[1,7-*gh*]quinoline (XIIa and b).

To a solution of *N*-(*p*-methoxybenzylidene)-5-acenaphthenamine (9) (XI) (14.4 g., 0.05 mole) in 100 ml. of ethyl acetate was added 3 drops of boron trifluoride etherate followed by the dropwise addition of 2,3-dihydro-5-methylfuran (4.2 g., 0.05 mole). The exothermic reaction produced a temperature rise to 34°. Two

subsequent additions of boron trifluoride etherate and 2,3-dihydro-5-methylfuran at 2 hour intervals were made. TLC showed incomplete conversion after 22 hours. The reaction mixture was concentrated to an oil and the oil was placed on an alumina (Alcoa F-20, 1500 g.) column and eluted with benzene. Fractions of 500 ml. to 2 l. were taken and like fractions (by TLC) were combined and concentrated. Fractions 2-4 gave upon crystallization from acetonitrile 2.2 g. of product m.p. 181-185°; NMR 1.77 (deuteriochloroform). Fractions 5-8 likewise gave 1.9 g., m.p. 139-163°; NMR 1.48, 1.79 (deuteriochloroform). Fractions 9-25 afforded 3.6 g., m.p. 160-163°; NMR 1.45 (deuteriochloroform). A total yield of 7.7 g. (42%) was thus obtained.

Anal. Calcd. for $C_{25}H_{25}NO_2$: C, 80.83; H, 6.78; N, 3.77. Found: (crop m.p. 181-185°) C, 81.11; H, 6.88; N, 3.97; (crop m.p. 160-163°) C, 80.74; H, 6.84; N, 3.92.

N-(*p*-methoxybenzylidene)-5-indanamine (VI).

A mixture of 5-aminoindane (10) (24.4 g., 0.183 mole), *p*-anisaldehyde (25.0 g., 0.183 mole), and a few crystals of *p*-toluenesulfonic acid in 500 ml. of benzene was heated under reflux for 1 hour while 3.2 ml. of water was collected in a Dean-Stark trap. After cooling, the reaction solution was concentrated to dryness, and the residue was crystallized from 2-propanol to give 40 g. (87%), m.p. 69-71°.

Anal. Calcd. for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57. Found: C, 81.39; H, 6.83; N, 5.59.

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