

Tricyclic Heterocycles Derived from 4-Oxo-4,5,6,7-tetrahydrobenzo[*b*]furan

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As part of a program in exploring new pharmaceutical leads, we have prepared a variety of novel tricyclic heterocycles (1,2). This note describes tricyclic heterocycles derived from 4-oxo-4,5,6,7-tetrahydrobenzo[*b*]furans. Although none of them were interesting biologically, they do represent a number of ring systems hitherto unreported, including the furo[2,3-*g*]-1,2-benzisoxazole, furo[3,2-*e*]-benzothiazole, 1*H*-furo[2,3-*g*]indazole, and furo[2,3-*h*]-quinazoline systems.

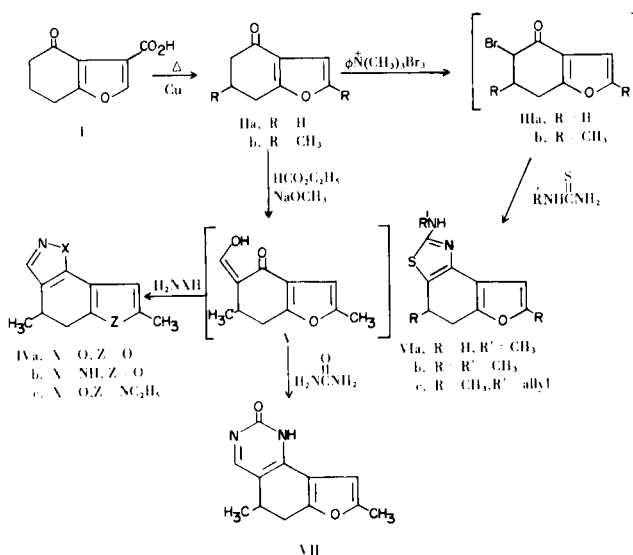
The parent 4-oxo-4,5,6,7-tetrahydrobenzo[*b*]furan (IIa) was prepared by decarboxylation of the corresponding 3-carboxylic acid I, which was derived from 1,3-cyclohexanedione according to the procedure of Stetter and Lauterbach (3). This route, which affords yields up to 60% of IIa from 1,3-cyclohexanedione, compares favorably with the previously reported route (30% yield) involving condensation of 1,3-cyclohexanedione with dichlorovinyl acetate (Feist-Benary reaction) (4). The 2,6-dimethyl analog (IIb) of IIa was prepared from 5-methyl-1,3-cyclohexanedione and bromoacetone by the known method (3).

Bromination of IIa or IIb gave the corresponding 5-bromo derivatives IIIa and IIIb. However, these oily products were contaminated with small amounts of dibromo derivatives and their purification was difficult due to instability. They were converted directly into 2-aminofuro[3,2-*e*]benzothiazoles IIIa-VIc upon condensation with *N*-methylthiourea or *N*-allylthiourea.

Treatment of IIb with ethyl formate and sodium methoxide furnished the corresponding 5-hydroxymethylene derivative V as a mobile oil which showed only one spot on tlc. It was used directly in the preparation of tricyclic heterocycles. Thus, condensation of V with hydroxylamine and with hydrazine gave 4,5-dihydro-4,7-dimethylfuro[2,3-*g*]-1,2-benzisoxazole (IVa) and 4,5-dihydro-4,7-dimethyl-1*H*-furo[2,3-*g*]indazole (IVb), respectively. Urea also condensed with V, furnishing 5,6-dihydro-5,8-dimethylfuro[2,3-*h*]quinazoline-2(1*H*)one (VII), but no single product could be isolated from the mixture obtained when V was treated with guanidine.

Two structures are possible for the product obtained

from V and hydroxylamine, the depicted IVa and the analog in which the positions of O and NH in the isoxazole ring are reversed. Structure IVa is preferred by analogy to the closely related compound IVc, which was prepared by parallel reactions from 1-ethyl-2,6-dimethyl-4-oxo-4,5,6,7-tetrahydroindole (5). The arrangement of the isoxazole ring in IVc was established by hydrolysis to the 5-cyano derivative (5).



## EXPERIMENTAL

Melting points are corrected. Solutions were concentrated under reduced pressure on a rotary evaporator. Microanalyses were determined by Midwest Microlab Ltd., Indianapolis, IN.

4-Oxo-4,5,6,7-tetrahydrobenzo[*b*]furan (IIa).

A mixture of 15 g. of I, prepared in 60-80% yields from 1,3-cyclohexanedione by the method of Stetter and Lauterbach (3), 90 g. of quinoline and 1.5 g. of copper powder was heated at reflux temperature for 6 hours, cooled, filtered, diluted with chloroform, and washed with portions of 6*N* hydrochloric acid to remove the quinoline. The chloroform solution was dried over magnesium sulfate and concentrated. Distillation of the viscous dark residual oil gave 8.34 g. (74%) of IIa as a yellow oil, b.p. 118-122° at 2 mm. It had  $n_{\text{D}}^{25}$  1.5344 (Lit. (4)  $n_{\text{D}}^{23}$  1.537) and gave a 2,4-dinitrophenylhydrazone with m.p. 247-249° (Lit. (4) 241°).

4,5-Dihydro-2-methylaminofuro[3,2-*e*]benzothiazole (VIa).

To a solution of 6.80 g. of IIa in 65 ml. of tetrahydrofuran was added 18.75 g. of phenyltrimethylammonium tribromide in small portions. After 5 hours the mixture was poured into 5% sodium bicarbonate solution. The liquid that separated was diluted with chloroform, dried over magnesium sulfate, and concentrated to give 11.89 g. of dark liquid. Thin-layer chromatography showed mainly IIIa, but a small spot corresponding to IIa was present. The mixture was used directly in the preparation of VIa.

A solution of 4.3 g. of IIa and 1.8 g. of *N*-methylthiourea in 200 ml. of ethanol was heated at reflux temperature for 5 hours, concentrated under reduced pressure, and the residual solid was washed with methanol. Recrystallization from ethanol gave 7.17 g. (50% from IIa) as the hydrobromide, m.p. 280-281°.

*Anal.* Calcd. for  $C_{10}H_{11}N_2OS \cdot HBr$ : C, 41.83; H, 3.86; N, 9.76; S, 11.16; Br, 27.82. Found: C, 41.90; H, 4.15; N, 9.60; S, 11.32; Br, 27.82.

4,5-Dihydro-4,7-dimethyl-2-methylaminofuro[3,2-*e*]benzothiazole (VIb).

A solution of 21.4 g. of IIb in 65 ml. of tetrahydrofuran was treated with 41.7 g. of pyridinium tribromide in 65 ml. of tetrahydrofuran, added in small portions during 1 hour. After 16 hours the mixture was filtered and concentrated. The residual liquid was diluted with dichloromethane, washed with 5% sodium bicarbonate, dried over magnesium sulfate, and concentrated. An amber liquid weighing 40.9 g. was obtained. Thin-layer chromatography showed small amounts of IIb and a third component, possibly a dibromide, present in addition to the main product IIIb. The mixture was used directly in the preparation of tricyclic heterocycles.

A mixture of 4.86 g. of IIIb, 1.80 g. of *N*-methylthiourea and 80 ml. of ethanol was heated at reflux temperature for 16 hours. Partial concentration gave white crystals which were washed with ethanol and then recrystallized from ethanol. This procedure gave 2.80 g. (42%) of VIb as the hydrobromide monohydrate, m.p. 298-300° dec.

*Anal.* Calcd. for  $C_{12}H_{14}N_2OS \cdot HBr \cdot H_2O$ : C, 43.24; H, 5.14; N, 8.41; Br, 23.97. Found: C, 42.82; H, 4.79; N, 8.05; Br, 24.14.

2-Allylamino-4,5-dihydro-4,7-dimethylfuro[3,2-*e*]benzothiazole (VIc).

This compound was prepared as its hydrobromide by the method described for VIb. From 4.86 g. of *N*-allylthiourea was obtained 2.7 g. (40%) of VIc as white crystals, m.p. 208-209°.

*Anal.* Calcd. for  $C_{15}H_{16}N_2OS$ : C, 49.26; H, 5.02; N, 8.21; Br, 23.41. Found: C, 49.46; H, 4.83; N, 8.10; Br, 23.53.

4,5-Dihydro-4,7-dimethylfuro[2,3-*g*]-1,2-benzisoxazole (IVa).

A suspension of 65 g. of sodium methoxide in 600 ml. of dry benzene, under nitrogen, was treated with 89 g. of ethyl formate in 300 ml. of benzene and with 49.2 g. of IIb in benzene. The mixture was stirred overnight at room temperature, cooled in an

ice bath, and extracted with 1.2 ℓ. of 5% sodium hydroxide. After separation of the layers, the benzene layer was extracted with 600 ml. more of 5% sodium hydroxide. The combined alkaline extracts were cooled in an ice bath, acidified to pH 2 with 6*N* hydrochloric acid and extracted with dichloromethane. The organic extract was washed with water, dried over magnesium sulfate and concentrated to give 51.3 g. of V as a yellow oil that showed only one spot on thin-layer chromatography. This oil was used directly in the preparation of tricyclic heterocycles.

A solution of 3.84 g. of V in 20 ml. of ethanol was heated on a steam bath and treated with 1.39 g. of hydroxylamine hydrochloride in 5 ml. of water. The mixture was heated to boiling, diluted to 50 ml. with water, and cooled, whereupon the product crystallized. Recrystallization from methanol-water gave 3.2 g. (85% from V) of IVa as white needles, m.p. 63-64°.

*Anal.* Calcd. for  $C_{11}H_{11}NO_2$ : C, 69.82; H, 5.86; N, 7.40. Found: C, 69.81; H, 5.75; N, 7.40.

4,5-Dihydro-4,7-dimethyl-1*H*-furo[2,3-*g*]indazole (IVb).

A mixture of 7.68 g. of V (prepared as described above), 4.0 ml. of hydrazine hydrate and 25 ml. of ethanol was heated at reflux temperature for 3 hours, cooled, and diluted with water, whereupon the product crystallized. Recrystallization from methanol-water gave 5.7 g. (76% from V) of IVb as white crystals, m.p. 155-156.5°.

*Anal.* Calcd. for  $C_{11}H_{12}N_2O$ : C, 70.19; H, 6.43; N, 14.88. Found: C, 70.44; H, 6.20; N, 15.06.

5,6-Dihydro-5,8-dimethylfuro[2,3-*h*]quinazoline-2(1*H*)one (VII).

A mixture of 3.84 g. of V (prepared as described above), 1.20 g. of urea and 40 ml. of ethanol was heated at reflux temperature for 26 hours and then cooled. The crystals that formed were washed with methanol and dried. This procedure gave 1.2 g. (26% from V) of VII as the monohydrate, pale yellow crystals, m.p. 234-237°.

*Anal.* Calcd. for  $C_{12}H_{12}N_2O_2 \cdot H_2O$ : C, 61.53; H, 6.02; N, 11.93. Found: C, 62.00; H, 6.11; N, 11.61.

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