Synthesis of Benzofuro[3,2-*e*][1,4]diazepines [1]

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A synthesis of 4-*N*-oxides and of 3-hydroxy derivatives of 1,3-dihydro-2*H*-benzofuro[3,2-*e*][1,4]diazepin-2-ones and of 2,3-dihydro-1*H*-benzofuro[3,2-*e*][1,4]diazepines is described. Condensation of 2-acetyl- and 2-benzoyl-3-ethoxycarbonylaminobenzofurans with acrylonitrile gave derivatives of 1,2-dihydro- and of 1,2,3,4-tetrahydrobenzofuro[3,2-*b*]pyridine.

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The preparation of some 5-aryl-1,3-dihydrobenzofuro-[3,2-*e*][1,4]diazepin-2-ones starting from 3-amino-2-aroylbenzofurans and following a known synthetic pathway [2] was recently reported by Ashby and Ramage [3].

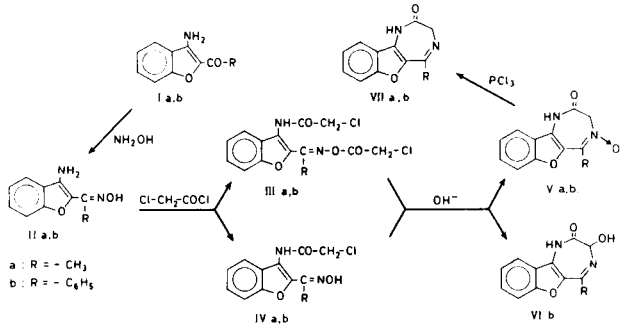
The easy preparation of 2-acyl-3-aminobenzofurans I with good yields [4] prompted us to carry on a study in this field in order to extend our researches on polycyclic nitrogen compounds containing the 1,4-diazepine moiety [5,6].

In the present paper we describe the synthesis of 1,3-dihydro-2*H*-benzofuro[3,2-*e*][1,4]diazepin-2-one 4-oxides V (R = -CH_3, -C_6H_5), of 3-hydroxy-1,3-dihydro-2*H*-benzofuro[3,2-*e*][1,4]diazepin-2-one VI (R = -C_6H_5) and of 1,3-dihydro-1*H*-benzofuro[3,2-*e*][1,4]diazepines XI (R = -CH_3, -C_6H_5).

The synthetic pathway to compounds V and VI are illustrated in Scheme 1 which starts from the oximes of 2-acyl-3-aminobenzofuran II (IIb resulted with lower yields only when Ib was allowed to react with hydroxylamine in refluxing concentrated aqueous alcoholic potassium hydroxide solution); II and chloroacetyl chloride in acetic acid led exclusively to the bis *N*- and *O*-chloroacetylated derivatives III, while in dioxane-pyridine the same reactants gave a 1:2 mixture of compounds III and of mono-*N*-chloroacetylated derivatives IV. Unlike their analogues *o*-aminobenzophenone oximes [7], no cyclization took place during these reactions. Compounds III and IV, instead, underwent smoothly a sodium hydroxide catalyzed cyclization at room temperature: while IIIa and IVa gave only the corresponding diazepinone 4-oxide, Va, IIIb and IVb afforded a 2:1 mixture of the 4-oxide Vb and of the 3-hydroxybenzofurodiazepinone VIb.

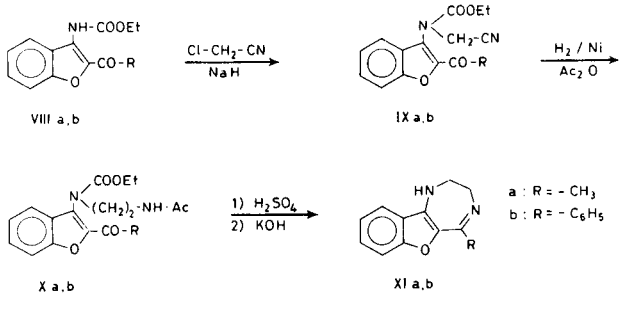
From the 4-oxides V by phosphorus trichloride oxygen removal the related 1,3-dihydro-2*H*-benzofuro[3,2-*e*][1,4]-diazepin-2-ones VII were obtained. In the Scheme 2 the synthesis of the 2,3-dihydro-1*H*-benzofuro[3,2-*e*][1,4]diazepines XI (R = -CH_3, -C_6H_5) is summarized. In this case, the starting materials were the *N*-ethoxycarbonyl derivatives VIII of the 2-acyl-3-aminobenzofurans I, which were submitted to *N*-cyanomethylation by treatment with sodium hydride/chloroacetonitrile in dimethylformamide at

Scheme 1



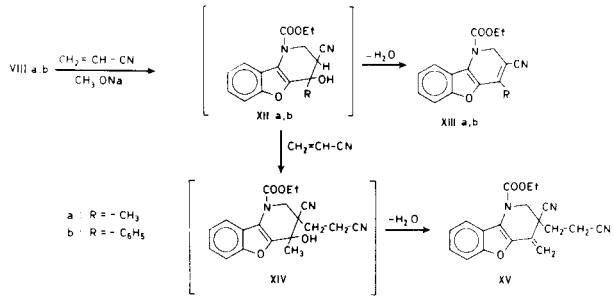
room temperature to give the corresponding 2-acyl-3-(*N*-ethoxycarbonyl)cyanomethylaminobenzofurans IX. The Raney nickel hydrogenation of the latter in the presence of acetic anhydride afforded the related 3-[*N*-(2-acetylaminoethyl)-*N*-ethoxycarbonyl]aminobenzofurans X, which were finally cyclized in 15% aqueous sulfuric acid. The resulting related crude *N*-ethoxycarbonylbenzofurodiazepines were then refluxed in alcoholic potassium hydroxide to yield the 2,3-dihydro-1*H*-benzofuro[3,2-*e*][1,4]diazepines XI.

Scheme 2



An attempted *N*-β-cyanoethylation of the 2-acyl-3-ethoxycarbonylaminobenzofurans VIII aimed at preparing intermediate compounds suitable for the preparation of benzofuro[3,2-*b*][1,5]diazocines gave the benzofuropyridines XIII and XV instead, possibly through the unisolated adducts XII and XIV (Scheme 3).

Scheme 3



EXPERIMENTAL

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. The ^{1}H-nmr spectra were determined on a T-60 Varian spectrometer with TMS as internal standard: chemical shifts are given in δ units. Electron ionization mass spectra were recorded on an LKB 2091 equipped with a digital PDP 11 data processing system; samples applied by direct inlet and probe usually heated from 25-200°, 70 eV. Column chromatographic separations were accomplished on Merck silicagel (70-230 mesh); Merck silicagel tlc plates were also used. The drying agent used was sodium sulfate. Yields, crystallization solvents, melting points and microanalytical data for all the compounds described herein are reported in Table 1.

Table 1

Compound No.	Yield % [a]	Mp °C	Recrystallized from	Molecular formula	Analyses % Found/(Calcd.) C	H	N
IIa	79	178-180	Ethanol	$C_{10}H_{10}N_2O_2$	62.97 (63.15)	5.17 (5.30)	14.92 (14.73)
IIb	40	168-169	Ethanol	$C_{15}H_{12}N_2O_2$	71.31 (71.41)	4.83 (4.79)	11.22 (11.10)
IIIa	87	135-138	Ethanol	$C_{14}H_{12}Cl_2N_2O_4$	49.11 (49.00)	3.58 (3.52)	7.76 (8.16)
IIIb	79	128-130	Ethanol	$C_{19}H_{14}Cl_2N_2O_4$	56.30 (56.31)	3.50 (3.48)	6.62 (6.92)
IVa	56	171-173	2-Propanol	$C_{12}H_{11}ClN_2O_3$	54.21 (54.04)	4.19 (4.16)	10.59 (10.50)
IVb	65	158-160	Benzene	$C_{17}H_{13}ClN_2O_3$	62.37 (62.11)	4.07 (3.99)	8.39 (8.59)
Va	91 [b]	255-258	Ethanol	$C_{12}H_{10}N_2O_3$	62.70 (62.60)	4.32 (4.38)	12.05 (12.17)
Vb	58 [b]	245-247	Ethanol	$C_{17}H_{12}N_2O_3$	69.55 (69.85)	4.12 (4.14)	9.50 (9.58)
VIb	25 [b]	220-222	Ethanol	$C_{17}H_{12}N_2O_3$	69.84 (69.85)	4.07 (4.14)	9.70 (9.58)
VIIa	86	218-220	Ethanol	$C_{12}H_{10}N_2O_2$	66.94 (67.28)	4.71 (4.71)	12.80 (13.08)
VIIb	90	261-263 lit [2] 264-266	Ethanol	$C_{17}H_{12}N_2O_2$	74.04 (73.90)	4.36 (4.38)	9.96 (10.14)
VIIIa	89	87-88	Ethanol	$C_{13}H_{13}NO_4$	63.07 (63.15)	5.27 (5.30)	5.82 (5.67)
VIIIb	84	102-104	Benzene	$C_{18}H_{15}NO_4$	69.72 (69.89)	4.76 (4.89)	4.45 (4.53)
IXa	49	98-100	Benzene-hexane 1:2	$C_{15}H_{14}N_2O_4$	63.13 (62.93)	4.91 (4.93)	9.68 (9.79)
IXb	57	106-107	2-Propanol	$C_{20}H_{16}N_2O_4$	69.11 (68.96)	4.67 (4.63)	7.98 (8.04)
Xa	52	137-139	Benzene	$C_{17}H_{20}N_2O_5$	61.61 (61.43)	6.09 (6.07)	8.57 (8.43)
Xb	62	173-175	Ethyl acetate-hexane 1:1	$C_{22}H_{22}N_2O_5$	66.71 (66.99)	5.71 (5.62)	6.92 (7.10)
XIa	67	200-202	Benzene	$C_{12}H_{12}N_2O$	71.94 (71.98)	6.07 (6.04)	14.11 (13.99)
XIb	75	177-179	Benzene-hexane 4:1	$C_{17}H_{14}N_2O$	77.67 (77.84)	5.63 (5.38)	10.77 (10.68)
XIIIa	11	131-133	Ethanol	$C_{16}H_{14}N_2O_3$	68.26 (68.07)	5.00 (5.09)	10.07 (9.92)
XIIIb	42	128-129	Ethanol	$C_{21}H_{16}N_2O_3$	73.11 (73.24)	4.68 (4.68)	7.98 (8.14)
XV	29	113-115	Ethanol	$C_{19}H_{17}N_3O_3$	68.26 (68.05)	5.10 (5.11)	12.53 (12.43)

[a] Calculated on the crude product. [b] Calculated on the compounds II employed.

3-Amino-2-(1-hydroxyimino)ethylbenzofuran (IIa) and 3-Amino-2-(α-hydroxyimino)benzylbenzofuran (IIb).

A mixture of Ia or Ib [4] (0.01 mole), hydroxylamine hydrochloride (2.8 g, 0.04 mole) and potassium hydroxide (2.3 g, 0.04 mole for Ia; 7.0 g, 0.125 mole for Ib) in 70% aqueous ethanol (50 ml) was refluxed for 4 hours. After cooling, water was added and the resulting precipitate collected and crystallized.

3-Chloroacetamido-2-(1-chloroacetoxyimino)ethylbenzofuran (IIIa) and 3-Chloroacetamido-2-(α-chloroacetoxyimino)benzylbenzofuran (IIIb).

To a warm stirred solution (50°) of IIa or IIb (0.01 mole) in glacial acetic acid (20 ml) chloroacetylchloride (2.8 g, 0.025 mole) was added dropwise; after addition, the mixture was heated at 50° for a further 15 minutes, then stirred for 2 hours at room temperature, water added and the obtained precipitate collected and crystallized.

3-Chloroacetamido-2-(1-hydroxyimino)ethylbenzofuran (IVa) and 3-Chloroacetamido-2-(α-hydroxyimino)benzylbenzofuran (IVb).

To a stirred solution of IIa or IIb (0.01 mole) in a mixture of anhydrous dioxane (30 ml) and pyridine (2 ml, 0.025 mole) chloroacetyl chloride (2.8 g, 0.025 mole) was added dropwise at room temperature. The mixture was stirred for a further 3 hours, then poured into water and extracted with ethyl acetate. After the solvent evaporation, the resulting residue was chromatographed on a silicagel column. Compound IIIa (0.8 g, 23%) and IVa (1.5 g, 56%) were obtained by elution with chloroform; IIIb (1.2 g, 30%) and IVb (2.1 g, 65%) were eluted with an ethyl acetate-*n*-hexane 1:3 mixture.

5-Methyl-1,3-dihydro-2*H*-benzofuro[3,2-*e*][1,4]diazepin-2-one 4-Oxide (Va).

The crude mixture of IIIa and IVa resulting from IIa (1.9 g, 0.01 mole) was dissolved in ethanol (80 ml), treated with sodium hydroxide 2*N* (20 ml) and stirred for 3 hours at room temperature. After water addition, the mixture was first neutralized with diluted hydrochloric acid, then extracted with chloroform and the solvent evaporated. Crude Va was obtained and crystallized; nmr (DMSO-d_6): δ 11.5 (broad, -NH-CO, 1H), 7.50 (m, aromatics, 4H), 4.46 (s, -CH_2-, 2H), 1.96 (s, -CH_3, 3H); ms: 230 (M^+, 100), 185 (42), 172 (25), 158 (29), 130 (38), 103 (26), 102 (19), 77 (23), 76 (26).

5-Phenyl-1,3-dihydro-2*H*-benzofuro[3,2-*e*][1,4]diazepin-2-one 4-Oxide (Vb) and 5-Phenyl-3-hydroxy-1,3-dihydro-2*H*-benzofuro[3,2-*e*][1,4]diazepin-2-one (VIb).

Following the procedure just described, a mixture of Vb and VIb was obtained from the crude mixture of IIIb and IVb resulting from IIb (2.5 g, 0.01 mole). The two products were separated by column chromatography (eluting solvent: ethyl acetate-*n*-hexane 1:3); Vb, 1.7 g (58%); VIb, 0.7 g (25%).

Compound Vb.

This compound had the following spectral data: (DMSO-d_6): δ 11.90 (broad, -NH-CO, 1H), 7.60 (m, aromatics, 9H), 4.90 (s, -CH_2-, 2H); ms: 292 (M^+, 100), 275 (35), 263 (28), 247 (30), 105 (42), 89 (22), 77 (34), 76 (27).

Compound VIb.

This compound had the following spectral data: (DMSO-d_6): δ 11.70 (broad, -NH-CO, 1H), 7.60 (m, aromatics, 9H), 6.43 (d, -CH-O*H*, 1H), 5.10 (d, -C*H*OH, 1H); ms: 292 (M^+, 15), 274 (27), 264 (21), 263 (100), 246 (51), 245 (48), 235 (38), 190 (19), 104 (31), 77 (42).

5-Methyl-1,3-dihydro-2*H*-benzofuro[3,2-*e*][1,4]diazepin-2-one (VIIa) and 5-Phenyl-1,3-dihydro-2*H*-benzofuro[3,2-*e*][1,4]diazepin-2-one (VIIb).

To a solution of Va or Vb (1 g) in chloroform (30 ml) phosphorus trichloride (1 ml) was added and the mixture refluxed for 2 hours. After cooling, the solvent was evaporated and the resulting residue treated with 20% aqueous potassium carbonate solution (10 ml). The solid thus obtained was collected by filtration and crystallized.

2-Acetyl-3-ethoxycarbonylaminobenzofuran (VIIIa) and 2-Benzoyl-3-ethoxycarbonylaminobenzofuran (VIIIb).

To a stirred cooled solution of 2-acyl-3-aminobenzofuran Ia or Ib (0.01 mole) in a mixture of anhydrous benzene (20 ml) and pyridine (6 ml) a solution of ethyl chlorocarbonate (2.8 ml, 0.03 mole) in anhydrous benzene (20 ml) was dropwise added and the resulting mixture was allowed to react at room temperature for 2 hours. The organic phase was then washed successively with water, diluted hydrochloric acid, 8% aqueous sodium hydroxide solution and finally with water. The benzene was evaporated and the obtained solid residue crystallized.

2-Acetyl-3-(*N*-ethoxycarbonyl)cyanomethylaminobenzofuran (IXa) and 2-Benzoyl-3-(*N*-ethoxycarbonyl)cyanomethylaminobenzofuran (IXb).

To a stirred suspension of sodium hydride (0.7 g, 50% oil dispersion, 0.015 mole) in anhydrous dimethylformamide (50 ml) a solution of VIIIa or VIIIb (0.01 mole) in dimethylformamide (20 ml) was added dropwise. After stirring 1 hour at room temperature, chloroacetonitrile (1.1 g, 0.015 mole) was added, the mixture stirred for 2 hours at room temperature, then poured into water and extracted with chloroform. The crude material resulting from the solvent evaporation was purified by column chromatography (eluting mixture: ethyl acetate-*n*-hexane 1:2).

2-Acetyl-3-[*N*-(2-acetylaminoethyl)-*N*-ethoxycarbonyl]aminobenzofuran (Xa) and 3-[*N*-(2-Acetylaminoethyl)-*N*-ethoxycarbonyl]amino-2-benzoylbenzofuran (Xb).

Each nitrile IXa or IXb (0.01 mole), dissolved in a mixture of tetrahydrofuran (50 ml) and acetic anhydride (20 ml), was hydrogenated with Raney nickel at 5 atmospheres of pressure and 40° for 5 hours. After filtration, the solvent was evaporated, the residue made alkaline with aqueous sodium bicarbonate solution and extracted with chloroform. Evaporation of the latter afforded the crude products X.

5-Methyl-2,3-dihydro-1*H*-benzofuro[3,2-*e*][1,4]diazepine (XIa) and 5-Phenyl-2,3-dihydro-1*H*-benzofuro[3,2-*e*][1,4]diazepine (XIb).

Each compound Xa or Xb (1 g) was boiled in 15% aqueous sulfuric acid (20 ml) until the starting material had disappeared (about 8 hours). The reaction was controlled by tlc. Eluting solvents were ethyl acetate for Xa, a 1:2 mixture of ethyl acetate-*n*-hexane for Xb. After cooling, the reaction mixture was diluted with water, made alkaline with potassium carbonate and extracted with chloroform. The solvent was then evaporated and the residue obtained was heated to reflux for 1 hour in a mixture of ethanol (10 ml) and 40% aqueous potassium hydroxide (1 ml). After cooling, water was added and the mixture was extracted with chloroform. After removal of the chloroform, the resulting crude product was purified by column chromatography on alumina (act. grade II-III) eluting with ethyl acetate.

Compound XIa.

This compound had the following spectral data: nmr (deuteriochloroform): δ 7.50 (m, aromatics, 4H), 4.53 (s, NH, 1H), 3.96 (m, -CH_2-N=, 2H), 3.40 (m, -NH-CH_2-, 2H), 2.40 (s, -CH_3, 3H); ms: 200 (M^+, 100), 199 (82), 185 (22), 172 (23), 171 (23), 170 (22), 144 (17), 115 (24), 28 (52).

Compound XIb.

This compound had the following spectral data: nmr (deuteriochloroform): δ 7.50 (m, aromatics, 9H), 4.23 (broad, NH, 1H), 4.06 (m,-CH_2-N=, 2H), 3.47 (m, -NH-CH_2-, 2H); ms: 262 (M^+,86), 261 (100), 234 (21), 233 (15), 130 (13).

1-Ethoxycarbonyl-3-cyano-4-methyl-1,2-dihydrobenzofuro[3,2-*b*]pyridine (XIIIa), 1-Ethoxycarbonyl-3-cyano-4-phenyl-1,2-dihydrobenzofuro[3,2-*b*]-pyridine (XIIIb) and 1-Ethoxycarbonyl-3-cyano-3-(2-cyanoethyl)-4-methylene-1,2,3,4-tetrahydrobenzofuro[3,2-*b*]pyridine (XV).

To a solution of VIIIa or VIIIb (0.01 mole) in acrylonitrile (30 ml), heated to 40-50°, sodium methoxide (0.3 g) was added and an exothermic reaction started immediately. After cooling (about 1 hour), the mixture was extracted with chloroform and the solvent evaporated. A mixture of XIIIa and XV, which was resolved by column chromatography (eluting solvent: a 1:2 mixture ethyl acetate-*n*-hexane), and respectively crude XIIIb were thus obtained.

Compound XIIIa.

This compound had the following spectral data: nmr (deuteriochloroform): δ 7.50 (m, aromatics, 4H), 4.66 (s, -N-CH_2, 2H), 4.37 (q, -CH_2-CH_3, 2H), 2.40 (s, -CH_3, 3H), 1.37 (t, -CH_2-CH_3, 3H); ms: 282 (M^+, 78), 253 (39), 237 (24), 209 (100), 208 (21), 29 (87).

Compound XIIIb.

This compound had the following spectral data: nmr (deuteriochloroform): δ 7.50 (m, aromatics, 9H), 4.86 (s, -N-CH_2, 2H), 4.43 (q, CH_2-CH_3, 2H), 1.44 (t, -CH_2-CH_3, 3H); ms: 344 (M^+, 62), 315 (28) 299 (14), 271 (100), 242 (13), 140 (19), 29 (54).

Compound XV.

This compound had the following spectral data: nmr (deuteriochloroform): δ 7.50 (m, aromatics, 4H), 5.50 and 5.40 (two s, C=CH_2, 2H), 4.60 and 3.62 (two d, AB system, -N-CH_2-, 2H), 4.32 (q, -CH_2-CH_3, 2H), 2.57 and 2.10 (two m, -CH_2-CH_2-CN, 4H), 1.33 (t, -CH_2-CH_3, 3H); ms: 335 (M^+, 100), 282 (32), 262 (40), 253 (30), 223 (67), 221 (43), 210 (40), 209 (97), 29 (95).

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