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Abstract

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SYNTHESIS OF SYMMETRICAL 3,4-BIS(DIALKYLAMINOMET

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In previous communications ([1],[2]) we described a method for the synthesis of symmetrical 2,5-bis(dialkylaminomethyl)furans, the diiodomethylates of which possess a clearly pronounced ganglion-blocking action ([3]). To determine the dependence of the physiological activity of the diiodomethylates on the position of the aminomethyl group in the furan nucleus, we synthesized symmetrical 3,4-bis(dialkylaminomethyl)furans containing no substituents in the 2 and 5 positions of the ring. Diamines of this structure have not been described in the literature; only 2,5-diphenyl-3,4-bis(dialkylaminomethyl)furans are known, obtained by Lutz et al. ([4]) by the action of secondary amines on 2,5-diphenyl-3,4-bis(chloromethyl)furan.

The method we developed for the synthesis of 3,4-bis(dialkylaminomethyl)furans is based on the use of 3,4-bis(oxymethyl)furan (I), which, under the action of thionyl chloride in the presence of pyridine, was converted into 3,4-bis(chloromethyl)furan (II). The reaction of dichloride (II) with secondary amines proceeded readily and led to 3,4-bis(dialkylaminomethyl)furans (III) (a, b, c, d, e) in yields of 55–91%.

$$\mathrm{HOCH_2\text{-}furan\text{-}CH_2OH} \xrightarrow[\mathrm{C_5H_5N}]{\mathrm{SOCl_2}} \mathrm{ClCH_2\text{-}furan\text{-}CH_2Cl} \xrightarrow{\mathrm{R_2NH}} \mathrm{R_2NCH_2\text{-}furan\text{-}CH_2NR_2}$$

(I) (II) (III) (a, b, c, d, e)

$\mathrm{NR_2}$ = a) $\mathrm{N(CH_3)_2}$; b) $\mathrm{N(C_2H_5)_2}$;

c) *N*-pyrrolidino; d) *N*-piperidino; e) *N*-morpholino.

In this way 3,4-bis(dimethylaminomethyl)-, (diethylaminomethyl)-, (N-pyrrolidinomethyl)-, (N-piperidinomethyl)-, and (N-morpholinomethyl)furans were obtained. It should be noted that 3,4-bis(chloromethyl)furan (II), in contrast to 2,5-bis(chloromethyl)furan, can be stored for a long time in the absence

of solvent even at room temperature. The 3,4-bis(dialkylaminomethyl)furans are also more stable than the corresponding 2,5-isomers.

We also studied the reduction of N,N-substituted diamides of furan-3,4-dicarboxylic acid, obtained by reaction of the dichloranhydride of this acid with amines, and in this way synthesized 3,4-bis(pyrrolidinomethyl)furan, identical with III c:

$$\text{ClOC-furan-COCl} \longrightarrow \text{R}_2\text{NOC-furan-CONR}_2 \longrightarrow \text{R}_2\text{NCH}_2\text{-furan-CH}_2\text{NR}_2$$

(V)

Experimental Part

3,4-Bis(oxymethyl)furan (I). A solution of 18 g of diethyl furan-3,4-dicarboxylate ([5],[6]) in 150 ml of absolute ether was added dropwise to 7.6 g of lithium aluminum hydride in 300 ml of ether; the mixture was boiled for one hour, left overnight, and decomposed with 200 ml of a 20% solution of Rochelle salt.

The ether layer was separated, and the aqueous layer was extracted for 30 h in an extractor with ether. After removal of the ether and distillation of the residue in vacuum, 9 g (83%) of the diol was obtained; it is a viscous colorless liquid, solidifying on cooling: b.p. 137–138° (3 mm); 129–130° (2 mm); n_D^{20} 1.5080; d_4^{20} 1.2390. MR_D 30.62. $C_6H_8O_3F_2$. Calculated MR_D 31.46. Literature data: b.p. 146–148° (6 mm); n_D^{25} 1.5021 (7); b.p. 120° (1 mm); n_D^{20} 1.4970 (8); b.p. 115–120° (1 mm); n_D^{27} 1.5073 (9).

3,4-Bis(chloromethyl)furan (II). To a solution of 12 g of (I) in 35 ml of abs. chloroform and 20 ml of pyridine, a solution of 21 ml of thionyl chloride in 15 ml of chloroform was added dropwise at $-5 \div -10°$. The mixture was kept for 1 h at 20° and poured onto ice. The chloroform layer was separated, washed twice with diluted (1:10) hydrochloric acid, with 3% sodium hydroxide solution in the presence of ice, and dried over potash. After removal of the solvent and distillation in vacuum under nitrogen, 8.4 g (54%) of dichloride II was obtained: a colorless liquid, crystallizing on cooling to colorless plates; readily soluble in benzene and chloroform, poorly soluble in ether; m.p. 28–29°; b.p. 86–87° (6 mm).

Found, %: C 43.84, 44.06; H 4.01, 4.02; Cl 43.56
$C_6H_6OCl_2$. Calculated, %: C 43.64; H 3.67; Cl 43.03

3,4-Bis(dimethylaminomethyl)furan (IIIa). To 15 g of dimethylamine in 75 ml of abs. ether and 2 g of powdered potassium hydroxide, 3.5 g of dichloride II in 20 ml of benzene was added. The mixture was boiled for 2 h, left overnight, and the precipitate was separated and washed with ether. After removal of the ether and distillation of the residue in vacuum under nitrogen, 3.2 g (82%) of

IIIa was obtained: a colorless mobile liquid with a characteristic amine odor: b.p. 81–82° (6 mm); n_D^{20} 1.4707; d_4^{20} 0.9427; MR_D 53.93, $C_{10}H_{18}ON_2F_2$. Calculated MR_D 54.77.

Found, %: C 65.76, 65.60; H 9.88, 10.04
$C_{10}H_{18}ON_2$. Calculated, %: C 65.89; H 9.95

Dipicrate: m.p. 139–140° (from alcohol), light-yellow lustrous crystals.

Found, %: C 41.58, 41.68; H 4.20, 4.13
$C_{22}H_{24}O_{15}N_8$. Calculated, %: C 41.25; H 3.75

Diiodomethylate: m.p. 234–235° (from aqueous alcohol), colorless needles.

Found, %: C 31.24; H 5.40
$C_{12}H_{24}ON_2J_2$. Calculated, %: C 30.90; H 5.15

3,4-Bis(diethylaminomethyl)furan (IIIb). From 2 g of dichloride II, 15 ml of freshly distilled diethylamine, and 1 g of potassium hydroxide, as described above, 1.5 g (54%) of IIIb was obtained: a colorless liquid; b.p. 114–115° (5 mm); n_D^{20} 1.4730; d_4^{20} 0.9201; MR_D 72.86, $C_{14}H_{26}ON_2F_2$. Calculated: MR_D 73.24.

Found, %: C 70.53, 70.80; H 11.03, 11.18
$C_{14}H_{26}ON_2$. Calculated, %: C 70.54; H 10.99

Dipicrate: m.p. 160–161° (from aqueous alcohol), light-yellow crystals.

Found, %: C 44.79, 45.00; H 4.77, 4.81; N 15.79, 15.69
$C_{26}H_{32}O_{15}N_8$. Calculated, %: C 44.83; H 4.63; N 16.09

Diiodomethylate: m.p. 175–176° (with decomposition, from absolute alcohol).

Found, %: C 36.73, 36.51; H 6.33, 6.29
$C_{16}H_{32}ON_2J_2$. Calculated, %: C 36.79; H 6.18

3,4-Bis(N-pyrrolidinomethyl)furan (IIIb). From 3 g of II and 4.5 g of pyrrolidine in 25 ml of benzene with 2 g of caustic potash, as described above, 3.9 g (89%) of IIIb was obtained: a colorless liquid fuming in air; b.p. 141–142° (5 mm); n_D^{20} 1.5070; d_4^{20} 1.0204; MR_D 68.49, $C_{14}H_{22}ON_2F_2$, calculated: MR_D 68.84.

Found %: C 72.09, 72.10; H 9.62, 9.79
$C_{14}H_{22}ON_2$. Calculated %: C 71.79; H 9.40

Dipicrate: m.p. 183–184° (from alcohol).

Found %: C 45.26, 45.30; H 4.22, 4.26; N 16.05, 15.93
$C_{26}H_{28}O_{15}N_8$. Calculated %: C 45.09; H 4.07; N 16.18

Diiodomethylate: m.p. 197–198° (with decomp., from alcohol).

Found %: C 37.23; H 5.51

$C_{16}H_{28}ON_2J_2$. Calculated %: C 37.06; H 5.40

3,4-Bis-(N-piperidinomethyl)furan (IIIc). From 1.3 g of II and 3.5 g of piperidine in 20 ml of abs. benzene with 1 g of caustic potash, as described above, 1.8 g (86%) of IIIc was obtained, distilling as a colorless liquid with b.p. 161–162° (5 mm), immediately crystallizing into colorless crystals; m.p. 26–27°.

Found %: C 73.30, 73.40; H 10.03, 9.81

$C_{16}H_{26}ON_2$. Calculated %: C 73.24; H 9.99

Dipicrate: m.p. 183–184° (from aqueous alcohol).

Found %: C 46.68, 46.85; H 4.54, 4.70

$C_{28}H_{32}O_{15}N_8$. Calculated %: C 46.67; H 4.48

Diiodomethylate: m.p. 223–224° (with decomp., from absolute alcohol), colorless needles.

Found %: C 39.83, 39.84; H 6.08, 5.90

$C_{18}H_{32}ON_2J_2$. Calculated %: C 39.95; H 5.91

3,4-Bis-(N-morpholinomethyl)furan (IIId). From 1.8 g of II and 5 g of morpholine with 2 g of caustic potash in benzene, as described above, 2.7 g (92%) of IIId was obtained: a colorless liquid crystallizing on cooling; b.p. 156–158° (3 mm); m.p. 40–41°.

Found %: C 62.94, 62.73; H 8.10, 8.36

$C_{14}H_{22}O_3N_2$. Calculated %: C 63.13; H 8.32

Dipicrate: m.p. 228–229° (with decomp., from aqueous alcohol).

Found %: C 42.80; H 4.28

$C_{26}H_{28}O_{17}N_8$. Calculated %: C 43.10; H 3.88

Diiodomethylate: m.p. 226–227° (from absolute alcohol).

Found %: C 35.07, 35.02; H 5.27, 5.19

$C_{16}H_{28}O_3N_2J_2$. Calculated %: C 35.56; H 5.19

Furan-3,4-dicarboxylic acid dichloride. To a suspension of 4.9 g of furan-3,4-dicarboxylic acid (m.p. 210–211°) (10) in 70 ml of abs. benzene, 20 ml

of thionyl chloride was added portionwise, and the mixture was boiled for 15 h. After removal of the solvent, 6.1 g (98%) was obtained; m.p. 71–72° (from petroleum ether); colorless shiny plates.

Found %: C 37.53, 37.49; H 1.10, 1.15
$C_6H_2O_3Cl_2$. Calculated %: C 37.31; H 1.03

3,4-Bis(N-pyrrolidinomethyl)furan (IIIb). To 15 ml of pyrrolidine in 50 ml of abs. ether, with cooling by ice water, by ···

4.8 g of dichloroanhydride in 50 ml of ether was added dropwise. The mixture was boiled for 2 h and left overnight. The precipitate of pyrrolidine hydrochloride was separated, and the ethereal solution of N,N′-bispyrrolidylamide of furan-3,4-dicarboxylic acid was added dropwise to a solution of 7 g of lithium aluminum hydride in 180 ml of absolute ether. The mixture was boiled for 5 h and decomposed with 200 ml of a 20% solution of Rochelle salt. The ethereal solution was dried with caustic potash. After removal of the solvent and distillation of the residue in vacuo, 1.7 g (40%) of IIIc was obtained: b.p. 129–131° (2 mm); n_D^{20} 1.5095. A mixed sample of the dipicrate with the dipicrate described above showed no depression of the melting point.

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Note: Figure translations are in progress. See original paper for figures.