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RESEARCHES ON FURANS

XL. Reaction of 3,4-Bis(chloromethyl) furan with Primary Amines

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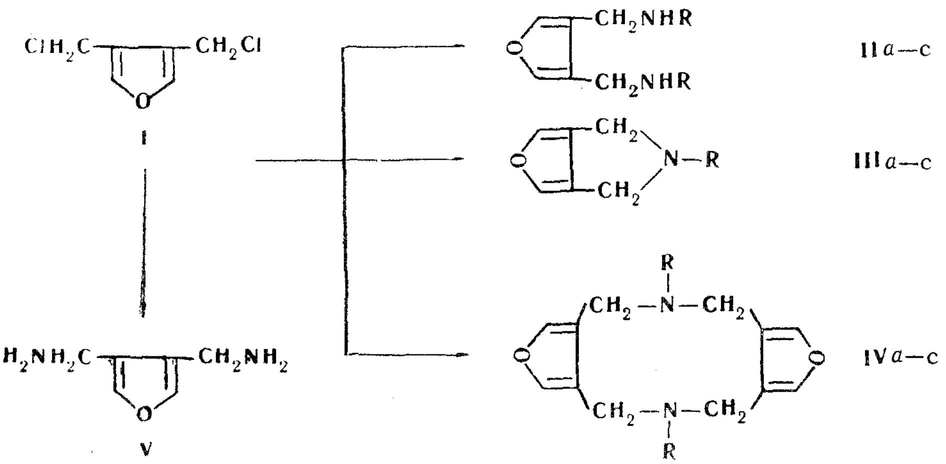
Study of the reaction of 3,4-bis(chloromethyl) furan with primary aliphatic amines showed that under the conditions chosen, the products are 3,4-bis(alkylaminomethyl) furans which have hitherto not been described in the literature, N-alkyl-4H, 6H-furo [3,4-c] pyrroles, which are types of compounds hitherto not known in the series, and diazecines which are 10-membered ring compounds with a furan ring.

Two of the present authors previously showed [1] that reaction of 2,5-bis(chloromethyl) furan with primary amines gives symmetrical 2,5-bis(aminomethyl) furans, along with more complex triamines which are formed from 3 moles of primary amine and 2 moles of dichloride. The action of secondary amines on 3,4-bis(chloromethyl) furan (I) gave high yields of 3,4-bis(dialkylaminomethyl) furans [2]. With regard to the reaction of primary amines with 3,4-bis(chloromethyl) furan, not only can the corresponding symmetrical diamines (II) be formed, but reaction can also lead to closing of new rings, and formation of two types of cyclic amines, N-alkylfuropyrroles (III) and their dimers, N, N'-dialkyldiazecines (IV), containing two furan rings:



$R = C_2H_5, C_3H_7, C_4H_9$

The present work showed that the action of primary aliphatic amines on 3,4-bis(chloromethyl) furan always gave all three possible kinds of reaction products, II, III, and IV.

Cyclization of vicinal dihalogenomethyl compounds is known with aromatic compounds. Thus primary amines convert 1,2-bis (bromoethyl)benzene into type III isoindoline structures, 1,2-bis(alkylaminomethyl)benzenes being also formed [3-5]. Primary amines and tetrachloro-substituted 1,2-bis (bromomethyl) benzene give mainly type IV 10-membered ring diazecine structures [6, 7].

Ya. L. Gol'dfarb and co-workers [8] have investigated cyclization of bishalogenomethyl compounds of the thiophene series. The action of primary amines on 2,5-dimethyl-3,4-bis(chloromethyl) thiophene was found to give the corresponding diamines (type II) and diazecines (type IV), but pyrroline systems were not formed. The authors believe that there is steric hindrance to formation of type III structures, the valence angle for the carbon atoms at positions 3 and 4 in the thiophene ring (124° 90') [9] being greater than in substituted benzene systems.

Though the valence angle for carbon atoms at positions 3 and 4 in the furan ring is even greater, being 127°40' [9], a furopyrroline structure III compound is, nevertheless, found. There is no doubt that the course of the reaction of vicinal bishalogenomethyl compounds with primary amines is greatly dependent on ratio of reactants and dilution.

The type II, III, and IV compounds which we have obtained occur in the mixture in a ratio 2:1:2, the amount of IV being slightly greater than that of II. The total reaction products yield is 40 – 80%.

By analogy with the synthesis of 2,5-bis(aminomethyl)furan [10], we used the improved phthalimide method for preparation of 3,4-bis(aminomethyl)furan (V) from I.

Experimental

Reaction of 3,4-bis(chloromethyl)furan (I) with primary amines.

Reaction with ethylamine. A 50 ml autoclave was charged with 3.3 g I [2], 2.24 g KOH, and 20 ml dry benzene, cooled to − 30° C, and 1.9 g ethylamine in 5 ml dry benzene added. The autoclave was held for 24 hr at 60° C, a further 2.7 g ethylamine added, and the whole then held for 48 hr at 85–90° C. Here and in subsequent runs, the end of the reactions were shown by a negative test for halogen. The contents of the autoclave were poured into 60 ml water, the benzene layer separated off, and the aqueous layer saturated (with cooling) with KOH, then thrice extracted with ether. The total extracts were dried over KOH, the solvent distilled off, and the residue vacuum-fractionated in a stream of nitrogen, to give 3 fractions: 1) bp 79–81° C (5 mm); 2) bp 86–90° C (1 mm), 3 bp 90–150°C (1mm). Freezing fraction 3 gave crystals of IVa. Fractions 1 and 2, and the filtrate after removing IVa, were bulked and thrice fractionally distilled to give IIa and IIIa.

N-Ethyl-4H, 6H-furo [3,4-c] pyrrole (IIIa), 0.2 g (8%), bp 67–68° C (4mm), d_4^{20} 0.9922, n_D^{20} 1.4972, MR_D 40.47, calculated for $C_8H_{11}NO$ with 2F, 39.39. Found: C 69.87, 69.75; H 8.32, 8.26%. Calculated for $C_8H_{11}NO$: C 70.04; H 8.08%. Colorless liquid with an ammonical odor, forming a viscous yellow oil after standing for 2–3 hr. Picrate (ex ether): mp 119–120° C (washed with ether), depressed mixed mp with picric acid. Found: C 45.68, 45.71; H 4.11, 4.12%: M 371*. Calculated for $C_8H_{11}NO$: C 45.90; H 3.85%; M 366.3.

3,4-Bis(ethylaminomethyl) furan. (IIa), 0.6 g (17%); bp 86–87° (1 mm), d_4^{20} 0.9919, n_D^{20} 1.4808; MR_D 52.27, calculated for $C_{10}H_{18}N_2O$ with 2 F, 51.59. Found: C 66.35, 66.46; H 9.80, 9.87%. Calculated for $C_{10}H_{18}N_2O$: C 66.05; H 9.96%. Colorless liquid, giving a viscous yellow mass on standing.

Dipicrate. (ex ether): mp 154–155°C (washed with ether). Found: N 17.55, 17.71%. Calculated for $C_{10}H_{18}N_2O \cdot 2C_6H_3N_3O_7$: N 17.49%.

1,9-Diethyl-5,13-dioxa-1,9-diazatricyclo [3-7,11-15] hexadecatetra-3,6,11,14-ene (IVa).** Yield 0.5 g (19%); mp 78–79° C (washed with ether); white crystals. Found: C 69.89, 69.70; H 8.08, 8.12; N 10.57, 10.47%; M 265***. Calculated for $C_{16}H_{22}N_2O_2$: C 70.04; H 8.08; N 10.02%; M 247.3. No crystalline picrate could be obtained.

Dimethiodide: mp 242–244° C (decomposition, ex dry ethanol). Found: C 36.68, 36.56; H 5.42, 5.46; I 42.32, 42.22%. Calculated for $C_{18}H_{28}I_2N_2O_2 \cdot 2H_2O$: C 36.38; H 5.43; I 42.71%.

Reaction with propylamine. 1.18 g propylamine in 20 ml dry benzene was added slowly to a mixture of 3.3 g I, 2.24 g KOH, and 20 ml dry benzene at 45° C, and the mixture stirred for 6 hr at 45° C. A further 1.82 g propylamine in 20 ml dry benzene was then added, the mixture stirred for 6 hr at 45° C, 1.18 g propylamine added, stirring continued for 4 hr longer, and the mixture then allowed to stand a week. 40 ml water was added, and the reaction product then extracted and worked up in the way described above. Fractional distillation then gave 3 fractions: 1) bp 52–54° (1 mm); 2) bp 91–130° (1 mm), 3) bp 130–170°C (1mm). Crystals of IVb were obtained by freezing fraction IVb. Repeated fractionation of fractions 1 and 2 and the filtrate from IVb gave IIb and IIIb.

N-Propyl-4H, 6H-furo [3,4-c] pyrrole (IIIb). Yield 0.3 g (10%), bp 52–54° C, (1 mm); d_4^{20} 0.9886; n_D^{20} 1.4920; MR_D 44.37; calculated for $C_9H_{13}NO$ with 2 F, 44.01. Found: C 71.12; H 8.64%. Calculated for $C_9H_{13}NO$: C 71.49; H 8.67%. Colorless liquid with the odor of an amine, after standing for some hours becomes a viscous yellow oil.

Picrate. (ex ether): mp 118–119°C (from benzene + petrol ether), gave depressed mixed mp with picric acid. Found: C 47.52, 47.47; H 4.27, 4.37; N 14.71%; M 398. Calculated for $C_9H_{13}NO \cdot C_6H_3N_3O_7$: C 47.37; H 4.24; N 14.73%. M 380.3.

3,4-Bis (propylaminomethyl) furan (IIb). Yield 0.9 g (21%); bp 113–115°C (1mm); d_4^{20} 0.9886; n_D^{20} 1.4920; MR_D 63.71; calculated for $C_{12}H_{22}N_2O$ with 2 F, 63.33. Found: C 68.25, 68.04; H 10.80, 10.60%. Calculated for $C_{12}H_{22}N_2O$: C 68.53; H 10.79%. Colorless readily mobile liquid, turning yellow on standing; did not give a crystalline picrate.

Dipicrolonate: mp 275–276° C (decomp), ex dry EtOH. Found: N 19.26%. Calculated for $C_{12}H_{22}N_2O \cdot 2C_{10}H_8N_4O_5$: N 18.96%.

1, 9 Dipropyl-5, 13-dioxa-1, 9-diazatricyclo [3–7, 11–15] hexadeca-3, 6, 11, 14-tetraene (IVb). Yield 0.8 g

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* The molecular weights of picrates IIIa, IIIb, and IIIc were determined spectrophotometrically [11].

** The naming of compounds IVa-c is in accordance with the nomenclature of A. P. Terent'ev and others [12].

*** The molecular weights of IVa, IVb, and IVc were found by isothermal distillation.

(27%); bp 165–167°C (1 mm); mp 47–48°C; white crystals. Found: C 71.33, 71.29; H 8.65, 8.84%; M 309. Calculated $C_{18}H_{26}N_2O_2$: C 71.49; H 8.67%; M 302.4. Did not give a crystalline picrate.

Dimethiodide: mp 267–268° C (decomp, ex dry EtOH). Found: C 40.74; H 5.98. Calculated for $C_{20}H_{32}N_2I_2O_2$: C 40.97; H 5.50%.

Reaction with butylamine. 4.38 g butylamine was added gradually to 3.3 g I, 2.24 g KOH, and 20 ml dry benzene (as described above); the reaction was effected at 55–56° C, and the mixture was kept 48 hr at 20° C. Treatment with water followed by vacuum-distillation gave 3 fractions: 1) bp 57–59° C (1 mm); 2) bp 110–130° C (1 mm); 3) bp 130–157° C (1 mm). Freezing the 3rd fraction gave crystals of IVc; fractional distillation of the filtrate from this, and fractions 1 and 2, gave:

N-Butyl-4H, 6H-furo [3, 4-c] pyrrole (IIIc). Yield 0.6 g (18%); bp 57–59° C (1 mm); d_4^{20} 0.9892; n_D^{20} 1.4962; MR_D 48.81. Calculated for $C_{10}H_{15}NO$ with 2 F, 48.63. Found: C 73.27, 73.32; H 9.09, 9.29%. Calculated for $C_{10}H_{15}NO$: C 72.69; H 9.15%. Colorless liquid with the odor of an amine, on standing it formed a heavy yellow oil.

Hydrochloride: mp 184–185° C (precipitated from EtOH with Et_2O). Found: Cl 17.72, 17.58%. Calculated for $C_{10}H_{15}NO \cdot HCl$: Cl 17.58%.

Picrate: mp 99–100° C (washed with ether). Found: C 48.84, 48.90; H 4.93, 4.92%; M 392. Calculated for $C_{10}H_{15}NO \cdot C_6H_3N_3O_7$: C 48.73; H 4.60%; M 394.3.

3, 4-Bis (butylaminomethyl) furan (IIc). Yield 1.3 g (28%); bp 110–112° C (1 mm), d_4^{20} 0.9409; n_D^{20} 1.4820; MR_D 72.92. Calculated for $C_{14}H_{26}N_2O$ with 2 F, 72.56. Found: C 70.26, 70.16; H 10.44, 10.24%. Calculated for $C_{14}H_{26}N_2O$: C 70.54; H 10.99%. Colorless liquid, did not give a picrate.

Dipicrolonate: mp 255–256° C (decomp. after washing with EtOH). Found: N 17.98, 18.01%. Calculated for $C_{14}H_{26}N_2O \cdot 2C_{10}H_8N_4O_5$: N 18.27%.

1, 9-Dibutyl-5, 13-dioxa-1, 9-diazatricyclo 3-7, 11-15 hexadeca-3, 6, 11, 14-tetraene (IVc). Yield 1 g (30%), mp 63–63.5° C (washed with EtOH), white crystals. Found: C 72.71, 72.74; H 9.48, 9.39; N 8.64, 8.67%; M 328. Calculated for $C_{20}H_{30}N_2O_2$: C 72.69; H 9.15; N 8.48%; M 330.5. Did not give a crystalline picrate.

Dimethiodide: mp 255–257° C (with decomp, ex EtOH). Found: C 43.42; H 6.13%. Calculated for $C_{22}H_{36}I_2N_2O_2$: C 43.00; H 5.90%.

3, 4-Bis (aminomethyl) furan (V). A mixture of 1.65 g I and 3.77 g dry K phthalimide in 15 ml freshly-distilled dimethylformamide was refluxed for 4 hr, when after cooling there was obtained 3.8 g (99%) 3, 4-bis (phthalimidomethyl) furan, bp 265–266° C (after vacuum-distilling), needles, colorless crystals. Found: C 68.28, 68.26; H 3.88, 3.89%. Calculated for $C_{22}H_{14}N_2O_5$: C 68.39; H 3.62%.

A mixture of 10.5 g 3, 4-bis (phthalimidomethyl) furan, 3.2 g 85% hydrazine hydrate, and 60 ml EtOH was refluxed for 6 hr. After cooling concentrated HCl was added (till strongly acid), the precipitate filtered off, and washed with EtOH. The total ethanol solutions were vacuum-distilled down to 50 ml, 60 ml water added, the precipitate separated off, and the filtrate vacuum-distilled to dryness. Yield 6.6 g dihydrochloride V, to which 10 g NaOH and 10 ml 40% NaOH solution were added, after which the oil which separated was thrice extracted with diethylamine. The extracts were dried over KOH, the amine distilled off, and 1 g (30%) diamine V was obtained, bp 111–113° C (6 mm), as a colorless liquid with the odor of an amine. On standing in a refrigerator it crystallized, mp 28–29° C. Found: C 57.39, 57.46; H 8.09, 8.12%. Calculated for $C_6H_{10}N_2O$: C 57.12; H 7.99%.

Dipicrate: mp 165–166° C (ex EtOH). N 19.14, 19.33%. Calculated for $C_6H_{10}N_2O \cdot 2C_6H_3N_3O_7$: N 19.18%.

3, 4-Bis (N-phenylureidomethyl) furan was prepared by treating diamine V with phenylisocyanate; mp 242–243° C (ex absolute EtOH), colorless crystals. Found: C 65.78, 65.73; H 5.46, 5.51%. Calculated for $C_{20}H_{20}O_3N_4$: C 65.92; H 5.53%.

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