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SYNTHESIS OF 1-AMINOPIPERAZINE-2,3-DIONE DERIVATIVES

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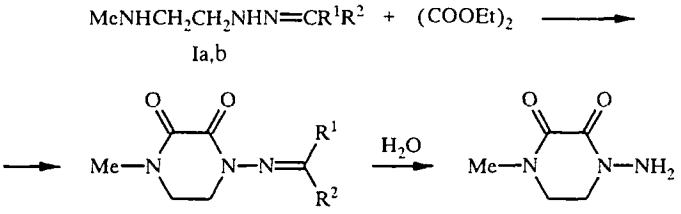
In connection with a study of the structure and properties of alkylidene derivatives of 2-aminoethylhydrazines [1,2], we resorted to the use of the mentioned compounds as starting materials in synthesis of heterocycles. 2-Aminoethylhydrazones of ketones exist exclusively in acyclic form and do not tend toward intramolecular cyclization with participation of the N–H and C=N bonds. They have two nucleophilic centers in 1 and 4 positions: amine and hydrazone nitrogen atoms. This suggests the possibility of interaction with 1,2-dielectrophiles, such as diethyl oxalate, with formation of six-membered heterocycles.

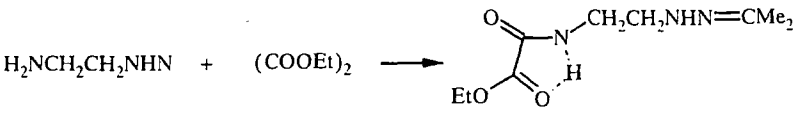


Ia,b IIa,b III

I, IIa $R^1 = R^2 = Me$; I, IIb $R^1 + R^2 = (CH_2)_5$

Hydrazones Ia,b react smoothly with diethyl oxalate at room temperature, forming piperazines IIa,b. Piperazine IIa is easily hydrolyzed, being converted to piperazine III, and it is not necessary even to use an acidic or basic catalyst.

Contrary to expectations, hydrazone Ic under the same conditions with diethyl oxalate forms only the monoacylation product IV, which has absolutely no tendency toward cyclization.



Ic IV

Formation of piperazine-2,3-dione does not occur either when heating compound IV or when treating it with base (sodium ethylate). Possibly the stability of the acylation product is due to stabilization (by the intramolecular hydrogen bond) of a conformation from which cyclization is impossible.

Synthesis of the starting aminoethylhydrazones is described in [1].

1-Isopropylideneamino-4-methylpiperazine-2,3-dione (IIa, $C_8H_{13}N_3O_2$). Solution of acetone methylaminoethylhydrazone Ia (6.45 g, 50 mmol) in 15 ml of benzene was added to solution of diethyl oxalate (7.30 g, 50 mmol) in 10 ml of benzene over a 10 min period. The reaction mixture was held for 2 days at room temperature. The benzene was distilled off in vacuum and the residue was recrystallized from toluene. Obtained: 6.59 g (36 mmol, 72%) of piperazine IIa; mp 134-135°C. PMR spectrum ($CDCl_3$): 1.90 (3H, s, C–Me); 2.13 (3H, s, C–Me); 3.13 (3H, s, N–Me); 3.65-3.75 ppm (4H, m, NCH_2CH_2N).

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1-Cyclohexylideneamino-4-methylpiperazine-2,3-dione (IIb, $C_{11}H_{17}N_3O_2$) was obtained similarly from cyclohexanone methylaminoethylhydrazone Ib. Yield 80%; mp 93-97°C. PMR spectrum ($CDCl_3$): 1.4-1.8 (6H, m, β,γ-CH_2); 2.1-2.5 (1H, m, α-CH_2); 3.08 (3H, s, N–Me); 3.55-3.75 ppm (4H, m, NCH_2CH_2N).

1-Amino-4-methylpiperazine-2,3-dione (III, $C_5H_9N_3O_2$). Solution of isopropylideneaminopiperazine IIa (5.50 g, 30 mmol) in 20 ml of 60% ethanol was placed in a distillation apparatus with reflux condenser and the acetone–ethanol mixture was slowly distilled off. After distilling off acetone, the solvent was evaporated under vacuum and the residue was crystallized from methanol. Obtained: 3 g (21 mmol, 70%) of piperazine III; mp 160°C. PMR spectrum (CD_3OD): 3.11 (3H, s, N–Me); 3.65-3.70 ppm (4H, m, NCH_2CH_2N).

Acetone 2-(Ethoxalylamino)ethylhydrazone (IV, $C_9H_{17}N_3O_3$). Obtained from diethyl oxalate (5.80 g, 40 mmol) and acetone aminoethylhydrazone Ic (4.60 g, 40 mmol) under conditions for synthesis of piperazine IIa: 6.05 g (28 mmol, 70%) of hydrazone IV; mp 58-60°C (2:1 toluene–heptane mixture). PMR spectrum ($CDCl_3$): 1.35 (3H, t, J = 7 Hz, $CH_2\underline{CH_3}$); 4.37 (2H, q, J = 7 Hz, OCH_2); 1.74 (3H, s, =CMe); 1.83 (3H, s, =CMe; 3.2-3.8 ppm (4H, m, NCH_2CH_2N).

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2. P. S. Lobanov, O. V. Solod, and A. A. Potekhin, *Zh. Org. Khim.*, **19**, 2310 (1983).