

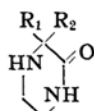
Synthesis of 3,3-Disubstituted-2-Piperazinones

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(Received May 10, 1958)

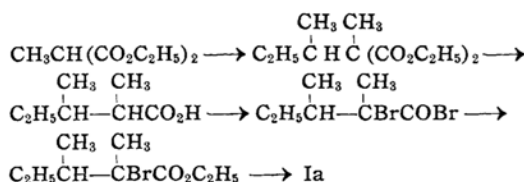
It was believed that 2-piperazinones containing a quaternary carbon atom adjacent to the carbonyl group might exhibit hypnotic activity. Several 3,3-disubstituted-2-piperazinones were therefore synthesized essentially by the method of Aspinall²⁾ although with some modification (see experimental section). Although the desired activity was present in several of the compounds, it did not appear sufficient for further extension.

The 3-methyl-3-*sec*-butyl compound Ia was prepared



- (I) a. $R_1 = \text{Me}$; $R_2 = \text{sec-Bu}$
 b. $R_1 = R_2 = \text{Ph}$
 c. $R_1 = \text{Ph}$; $R_2 = \text{Et}$

in accordance with the reaction scheme.



The 3,3-diphenyl derivative Ib was prepared by treatment of methyl α -bromodiphenylacetate resulting from treatment of methyl diphenylacetate with *N*-bromosuccinimide, with ethylene diamine.

The 3-phenyl-3-ethyl derivative (Ic) was prepared by bromination of methyl α -ethyl phenylacetate with *N*-bromosuccinimide followed by treatment of the resulting bromo-ester with ethylene diamine.

Experimental

Diethyl methyl-*sec*-butylmalonate was prepared in 73% yield by alkylation of diethyl methylmalonate³⁾ with 2-bromobutane, in the

presence of sodium ethoxide. The ester boils at 110–123°C/19 mmHg.

α -*sec*-Butylpropionic acid was prepared in 66% yield by refluxing the above ester with 20% aqueous ethanolic potassium hydroxide for 3 hrs., acidification with 10% hydrochloric acid, ether extraction and decarboxylation of the crude malonic acid at 200°C.

α -Bromo- α -*sec*-butylpropionyl bromide was obtained in 86% yield⁴⁾ by treating the above acid (6.8 g.) in the usual way with red phosphorus (0.68 g.) and bromine (6.8 ml.), b. p. 114–121°C/40 mmHg.

Ethyl α -bromo- α -*sec*-butylpropionate was prepared in 68% yield by the usual procedure from the freshly distilled acid bromide (25.5 g.) and dry ethanol (4.4 g.), b. p. 116°C/33 mmHg.

3-Methyl-3-*sec*-butyl-2-piperazinone (Ia).—A solution of ethyl α -*sec*-butylpropionate (15.4 g.) in dry ethanol (100 ml.) was added dropwise with stirring at room temperature during 3 hr. to a solution of ethylene diamine (50 g.) in dry ethanol (150 ml.). After 2 hr. longer at reflux temperature, a solution of sodium ethoxide (1.51 g.) of sodium in dry ethanol (30 ml.) was added to the boiling solution during 30 min. Refluxing was continued for two additional hours. Excess ethanol and ethylene diamine were removed at the water pump. Acetone was added to the residue and the colorless precipitate was filtered. The mother liquor was evaporated and acetone was again added and the residue was distilled in 0.2 mm. It crystallized on standing, m.p. 58–61°C (from petroleum ether).

Anal. Found: C, 63.35; H, 10.62; N, 17.13. Calcd. for $\text{C}_{19}\text{H}_{25}\text{N}_2\text{O}$: C, 63.49; H, 10.66; N, 16.46%. The hydrobromide had m.p. 203–206°C (from absolute ethanol-ether).

When an ether solution of the α -bromo-acid bromide was added to a solution of excess ethylene diamine in chloroform at 0°C, a colorless precipitate was formed. After refluxing for 3 hrs. a brown insoluble oil was obtained and this solidified on standing. Recrystallization from benzene gave a product, m.p. 172–174°C which was insoluble in water and gave a negative test with aqueous silver nitrate. Its analysis was unsatisfactory but there is indication that this product is the α,α -dibromo-bis-amide, $[\text{CH}_3\text{C}(\text{Br})(\text{sec-C}_4\text{H}_9)\text{CONHCH}_2]_2$.

Anal. Found: C, 44.30; H, 6.84; N, 7.13; Br, 34.73. Calcd. for $\text{C}_{18}\text{H}_{30}\text{O}_2\text{N}_2\text{Br}_2$: C, 43.44; H, 6.78; N, 6.35; Br, 36.19%.

Methyl diphenylacetate was prepared from

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2) S. R. Aspinall, *J. Am. Chem. Soc.*, **62**, 1202 (1940). cf. R. L. Hodgson, I. R. C. Bick and D. J. Cram, *ibid.*, **76**, 1138 (1954).

3) "Organic Syntheses", Coll. Vol. II, Wiley, New York, (1946), p. 279.

4) *Ibid.*, Vol. 33, Wiley, New York, (1953), p. 29.

diphenylacetic acid (25 g.), methanol (500 ml.) and concentrated sulfuric acid (25 ml.). The mixture was refluxed for 3 hrs., most of the methanol was removed at the water pump and the residue was poured into ice-water. The oil which soon solidified was recrystallized from aqueous ethanol, m.p. 60°C (24.8 g.). Lit.⁵⁾ m.p. 60°C.

Methyl α -bromodiphenylacetate.—A mixture of the above methyl ester (2.26 g.), carbon tetrachloride (15 ml.) and *N*-bromosuccinimide (1.82 g.) was refluxed for 6 hrs. After the usual workup the bromo-ester was obtained (2.77 g.; 91%) as an oil which was used in its crude form.

3,3-Diphenylpiperazinone (Ib).—A mixture of the crude bromoester (2.5 g.), ethylene diamine (1.2 g.) and dry chloroform (10 ml.) was refluxed for 4 hrs. After standing overnight the red oil which had separated solidified and appeared to be the hydrobromide of ethylene diamine. The chloroform solution was evaporated to dryness and the glassy residue was triturated with benzene, affording colorless crystals (2.3 g.; 96%), m.p. 163°C (from dry benzene; sinters 155–156°C). The product gives a picrate, m.p. 248–249°C (from ethanol).

Anal. Found: C, 76.20; H, 6.488; N, 11.18. Calcd. for $C_{16}H_{16}ON_2$: C, 76.16; H, 6.39; N, 11.10%.

Methyl α -phenylethylate was obtained in 91% yield by esterification of the acid as described above for methyl diphenylacetate. It had b.p.

225–228°C. Lit.⁶⁾ b.p. 225–226°C.

Methyl α -bromo- α -phenylethylacetate was obtained by bromination of the above ester (17.8 g.) with *N*-bromosuccinimide (20.8 g.) in carbon tetrachloride (100 ml.) during 4 hr. After the usual workup the crude ester (94% yield) was used in order to avoid dehydrobromination during distillation at a relatively high temperature.

3-Ethyl-3-phenylpiperazinone (Ic).—This was prepared in poor yield from the crude bromo-ester and ethylene diamine as described for the preparation of Ia. It was an oil, b.p. 140–160°C/0.4 mmHg. (1g. from 9.7g. bromo-ester).

Anal. Found: N, 14.01. Calcd. for $C_{12}H_{16}ON_2$: N, 13.72%.

Summary

Several 3,3-disubstituted-2-piperazinones have been synthesized for pharmacological testing as potential hypnotics.

One of the authors (T. K.) thanks Calanda Foundation for the award of Fellowship.

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5) P. Fritsch and F. Feldmann, *Ann.*, **306**, 81 (1899).

6) M. M. Rising and T. W. Zee, *J. Am. Chem. Soc.*, **50**, 1211 (1928).