

Reductive Cyclization of Hydrazones

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DURING investigation of the preparation of substituted hydrazines (I), as potential monoamine oxidase (MAO) inhibitors, we noted the facile reductive cyclizations of the hydrazones of several aliphatic γ - and δ -keto-carboxylic acids.

The compounds, listed in Table I, were prepared by the condensation of the appropriate keto-carboxylic acid with either ethyl carbazate (2), acetylhydrazine (3) or semicarbazide in a suitable solvent. The resultant hydrazones (I) were reduced catalytically to give excellent yields (71–95%) of the corresponding cyclized hydrazines (II). In general, the reaction conditions were similar, and a representative preparation is given in the experimental section.

Pharmacological testing of these cyclized hydrazines (II A-C) indicated LD₅₀s, p.o., in mice of greater than 1000 mg./kg. They exhibited no evidence of MAO inhibition, by the "reserpine-challenge" test (4), at doses up to 100 mg./kg.

EXPERIMENTAL

Ethyl 2-oxo-5-methyl-1-pyrrolidinecarbamate (IIC). A mixture of ethyl carbazate, levulinic acid and isopropyl alcohol

was refluxed for 6 hours. A yield of 183 grams (90%) of colorless crystals of IC, m.p. 108–110° was obtained. A sample was recrystallized for analyses, m.p. 109–110°. Anal. Calcd. for $C_8H_{14}N_2O_4$: C, 47.52; H, 6.98; N, 13.86. Found: C, 47.62; H, 7.10; N, 13.69.

A mixture of IC, isopropyl alcohol and PtO_2 (palladium on charcoal, 5%, has also been used successfully) was hydrogenated in a Paar apparatus until the theoretical amount of hydrogen was absorbed (2 hours; initial pressure, 3.5 atm.). The mixture yielded 18.6 grams (81%) of colorless crystals (IIC), m.p. 56–58°. Recrystallization yielded the analytical sample (see Table I).

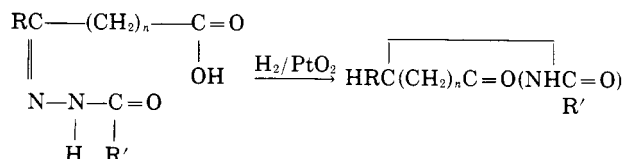
LITERATURE CITED

- (1) Anderson, F.E., Kaminsky, D., Dubnick, B., Klutcko, S.R., Cetenko, W.A., Gylys, J., Hart, J.A., *J. Med. Pharm. Chem.* **5**, 221 (1962).
- (2) Diels, O., *Ber.* **2183** (1914).
- (3) Curtius, T., Hofmann, T.S., *J. Prakt. Chem.* **53**, 513 (1896).
- (4) Chessin, M., Dubnick, B., Leeson, G., Scott, C.C., *Ann. N. Y. Acad. Sci.* **80**, 597 (1959).
- (5) Goss, F.R., Ingold, C.K., Thorpe, J.F., *J. Chem. Soc.* **1925**, p. 468.

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Table I. Properties of Hydrazones



	Hydrazone				Hydrazine		Carbon		Hydrogen		Nitrogen	
	M.P. ^a ° C.	R	R	n	M.P. ^a ° C.	Formula	Calcd.	Found	Calcd.	Found	Calcd.	Found
A	188-189 ^b	CH ₃	NH ₂	2	181-183	C ₆ H ₁₁ N ₃ O ₂	45.85	45.92	7.05	7.11	26.74	26.79
B	143-144	CH ₃	CH ₂	2	54-56	C ₇ H ₁₂ N ₂ O ₂	53.83	53.59	7.74	7.84	17.94	17.66
C	111-113	CH ₃	OC ₂ H ₅	2	59-60	C ₈ H ₁₄ N ₂ O ₃	51.60	51.68	7.58	7.49	15.04	15.02
D	- ^c	CH ₃	OC ₂ H ₅	3	48-50 ^d	C ₉ H ₁₆ N ₂ O ₃	53.98	54.08	8.06	8.07	13.99	14.16
E	153-155	C ₆ H ₅	OC ₂ H ₅	2	- ^e	C ₁₃ H ₁₆ N ₂ O ₃	62.89	63.15	6.50	6.56	11.28	11.45

^a Melting points taken on Hoover-Thomas apparatus and are corrected. ^b Reported (5) m.p. 191–2°. ^c Not isolated. ^d B.P. 105–7°/0.1 mm. ^e B.P. 192–5°/1.0 mm.; after standing for 1 year it did not crystallize.