Reductive Cyclization of Hydrazones

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DURING investigation of the preparation of substituted hydrazines (*1*), as potential monoamine oxidase (MAO) inhibitors, we noted the facile reductive cyclizations of the hydrazones of several aliphatic γ- and ζ-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 LD_{50}s, 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).

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LITERATURE CITED

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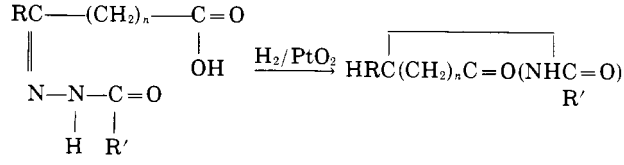
Table I. Properties of Hydrazones



	Hydrazone M.P.[a] °C.	R	R	n	Hydrazine M.P.[a] °C.	Hydrazine Formula	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
A	188–189[b]	CH_3	NH_2	2	181–183	$C_6H_{11}N_3O_2$	45.85	45.92	7.05	7.11	26.74	26.79
B	143–144	CH_3	CH_2	2	54–56	$C_7H_{12}N_2O_2$	53.83	53.59	7.74	7.84	17.94	17.66
C	111–113	CH_3	OC_2H_5	2	59–60	$C_8H_{14}N_2O_3$	51.60	51.68	7.58	7.49	15.04	15.02
D	–[c]	CH_3	OC_2H_5	3	48–50[d]	$C_9H_{16}N_2O_3$	53.98	54.08	8.06	8.07	13.99	14.16
E	153–155	C_6H_5	OC_2H_5	2	–[e]	$C_{13}H_{16}N_2O_3$	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.