

of the material by means of paper electrophoresis to a single component would lead to the speculation that the material was of the glycoprotein type.

Further characterization of the precise nature of the active agent will be presented after screening is completed.

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Monoamine Oxidase Inhibitors. Synthesis of a Series of Isopropylidene and Isopropyl Derivatives of Some Aryl and Arylalkyl Acid Hydrazides

By M. H. WEINSWIG and E. B. ROCHE*

Six isopropylidene hydrazides and six isopropyl hydrazides were prepared. This investigation was undertaken since recent derivatives of hydrazines and hydrazides have shown considerable activity as monoamine oxidase inhibitors. The hydrazides were synthesized from the aryl and arylalkylesters and hydrazine. From these hydrazides the isopropylidene derivatives were prepared by refluxing with acetone. Reduction of the isopropylidene hydrazides, using hydrogen and 5 per cent platinum-on-charcoal catalyst, gave the isopropyl hydrazides. The hydrazides prepared were of benzoic acid, phenylacetic acid, α -naphthoic acid, β -naphthoic acid, α -naphthylacetic acid, and β -naphthylacetic acid.

INTEREST in acyl hydrazine derivatives started in 1952 when Fox and Gibas (1) observed the tuberculostatic activity of isonicotinic acid hydrazides (isoniazid). Many derivatives of this compound were prepared, and one of these derivatives was 1-isonicotinyl-2-isopropyl hydrazide (iproniazid) (2) which was tested clinically as a tuberculostatic agent. During the investigation, it was noted (3) that iproniazid had a side effect of central nervous system stimulation. This effect appeared at the normal dosage levels used in the treatment of tuberculosis.

Further investigation by Zeller (4) in 1952 proved iproniazid to be an inhibitor of monoamine oxidase. The discovery of the clinical activity of iproniazid led to the modification of its structure (5) in an attempt to obtain a compound that would be more rapid in onset and of a lower toxicity.

The compounds chosen for synthesis in this study have the isopropyl hydrazine moiety in common with the monoamine oxidase inhibitor, iproniazid. The isonicotinyl portion has been replaced with aryl and arylalkyl groups.

The general synthesis of these compounds is shown in Scheme I.

The physical properties of the products obtained by this procedure are recorded in Tables I and II.

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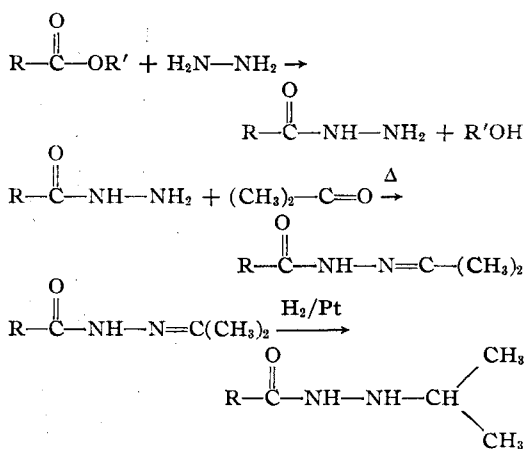
Abstracted from a thesis submitted by E. B. Roche to the Graduate School, Butler University, Indianapolis, Ind., in partial fulfillment of Master of Science degree requirements.

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EXPERIMENTAL


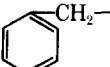
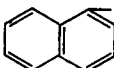
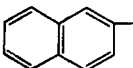
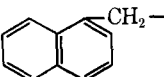
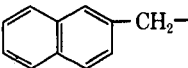
The preparation of most of the compounds prepared in this investigation were obtained through a four-step synthesis. This involved the preparation of methyl or ethyl esters of the various aryl and arylalkyl carboxylic acids. The procedure used was described by Vieth (6) by reacting the corresponding acyl chloride with absolute methyl alcohol with slight warming. The next step involved the preparation of the hydrazides, and for this the method employed by Fox and Gibas (1) was used. The esters of the aryl and arylalkyl carboxylic acids were refluxed in alcoholic solution with an excess of 95% hydrazine.

The isopropylidene derivatives were then pre-



Scheme I

TABLE I.—ANALYSES OF THE ISOPROPYLIDENE HYDRAZIDES

$\begin{array}{c} \text{O} \qquad \text{CH}_3 \\ \parallel \qquad \diagup \\ \text{R}-\text{C}-\text{NH}-\text{N}=\text{C} \\ \qquad \qquad \diagdown \\ \qquad \qquad \text{CH}_3 \end{array}$					
R	Yield, %	M.p., °C.	Empirical Formula	Anal., %	
				Calcd.	Found
	87	145–146	C ₁₀ H ₁₂ ON ₂	C, 68.16 H, 6.86 N, 15.90	68.05 6.87 15.80
	84	109–110	C ₁₁ H ₁₄ ON ₂	C, 69.44 H, 7.42 N, 14.73	69.53 7.64 14.52
	77	213.5	C ₁₄ H ₁₄ ON ₂	C, 74.31 H, 6.24 N, 12.38	74.16 5.93 12.31
	81	142–143	C ₁₄ H ₁₄ ON ₂	C, 74.31 H, 6.24 N, 12.38	74.49 6.55 12.58
	76	127–128	C ₁₅ H ₁₆ ON ₂	C, 74.97 H, 6.71 N, 11.66	74.86 6.63 11.22
	93	158	C ₁₅ H ₁₆ ON ₂	C, 74.97 H, 6.71 N, 11.66	74.63 6.61 11.75

pared by refluxing the respective aryl and arylalkyl hydrazides with acetone. The procedure, as interpreted by Royals (7), is essentially the addition of the electrophilic carbonyl carbon atom to the nucleophilic terminal nitrogen of the hydrazide. The isopropylidene hydrazides were finally reduced to the respective isopropyl hydrazides by catalytic hydrogenation with 5% platinum on powdered charcoal.

Details of a typical preparation are given in the following paragraphs.

Methyl β -Naphthoate (6).—Twenty-five grams (0.13 mole) of β -naphthoyl chloride was dissolved with the aid of heat in 100 ml. of methyl alcohol. The solution was cooled to room temperature, and 100 ml. of distilled water was added. The white solid that precipitated was collected by suction filtration, air dried, and powdered. The product was washed four times with 50-ml. portions of 5% sodium carbonate solution, and then with 100 ml. of water.

The product was recrystallized from methyl alcohol. The yield was 24.0 Gm. (99%) of white crystals. This compound melted at 77°. [Lit. (6) m.p. 77°.]

β -Naphthoic Acid Hydrazide (8).—In a round-bottom flask, 18.6 Gm. (0.10 mole) of methyl β -naphthoate was dissolved in 300 ml. of methyl alcohol. To this solution 40 ml. (1.00 mole) of 95% hydrazine was added. The flask was fitted with a reflux condenser, and the solution was refluxed for 5 hr. on a hot plate.

The solution was allowed to cool, and the solvent

and excess hydrazine were evaporated under reduced pressure. The resulting solid was recrystallized from 95% ethyl alcohol. The crystals were light gray in color, and the yield was 16.3 Gm. (88%). This compound melted at 147°. [Lit. (8) m.p. 147.5°.]

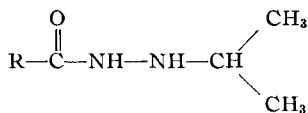
1- β -Naphthyl-2-isopropylidene Hydrazide.—In a round-bottom flask, 16.3 Gm. (0.09 mole) of β -naphthoic acid hydrazide was suspended in 200 ml. of freshly distilled acetone. The flask was fitted with a reflux condenser, and the reaction mixture was refluxed for 3 hr. over a water bath. The solid in the reaction mixture dissolved during the refluxing process.


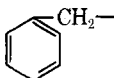
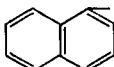
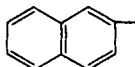
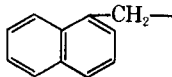
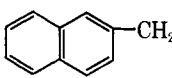
The solution was filtered while still hot, and the filtrate was placed in a refrigerator to cool. A solid precipitated and was recovered by suction filtration. The product was recrystallized from 95% ethyl alcohol. The yield of white crystals was 14.0 Gm. (71%). This compound melted at 142–143°.

Anal.—Calcd. for C₁₄H₁₄N₂O: C, 74.31; H, 6.24; N, 12.38. Found: C, 74.49; H, 6.55; N, 12.58.

1- β -Naphthyl-2-isopropyl Hydrazide.—Eleven and three-tenths grams (0.05 mole) of 1- β -naphthyl-2-isopropylidene hydrazide was dissolved in 300 ml. of 95% ethyl alcohol by warming on a water bath. The solution was transferred to the reaction vessel of a Parr low pressure hydrogenator. One-half gram of 5% platinum on powdered charcoal was added, and the vessel was attached to the hydrogenator. The system was flushed twice with hydrogen. The reduction was started at a pressure of 50 p.s.i. and a temperature of 50°. After 24 hr., the

TABLE II.—ANALYSES OF THE ISOPROPYL HYDRAZIDES



R	Yield, %	M.p., ^a °C.	Empirical Formula	Anal., %	Found ^b
	78	118–119	C ₁₀ H ₁₄ ON ₂	Calcd. C, 67.39 H, 7.91 N, 15.72	67.26 7.81 15.72
	76	81	C ₁₁ H ₁₆ ON ₂	C, 68.72 H, 8.39 N, 14.57	68.90 8.37 14.59
	74	137–138	C ₁₄ H ₁₆ ON ₂	C, 73.66 H, 7.06 N, 12.27	73.48 7.23 12.51
	80	140	C ₁₄ H ₁₆ ON ₂	C, 73.66 H, 7.06 N, 12.27	73.57 6.83 12.61
	83	130	C ₁₅ H ₁₈ ON ₂	C, 74.35 H, 7.49 N, 11.56	74.09 7.36 11.41
	74	135	C ₁₅ H ₁₈ ON ₂	C, 74.35 H, 7.49 N, 11.56	74.23 7.29 11.78

^a The melting points were taken on a Thomas-Hoover capillary melting point apparatus. ^b The carbon, hydrogen, and nitrogen analyses were obtained from the Weiler-Strauss Microanalytical Laboratory, Oxford, England.

required amount of hydrogen had reacted with the compound. The reaction vessel was removed from the hydrogenator, and the catalyst was recovered by filtration. The solution was filtered a second time through a medium grade sintered-glass filter to remove all traces of charcoal.

The solvent was evaporated under reduced pressure to give a white solid. The product was recrystallized from 50% ethyl alcohol. The yield of white crystals was 9.0 Gm. (80%). This compound melted at 140°.

Anal.—Calcd. for C₁₄H₁₆N₂O: C, 73.66; H, 7.06; N, 12.27. Found: C, 73.57; H, 6.83; N, 12.61.

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