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Indazole-3-carboxylic Acids and their Derivatives

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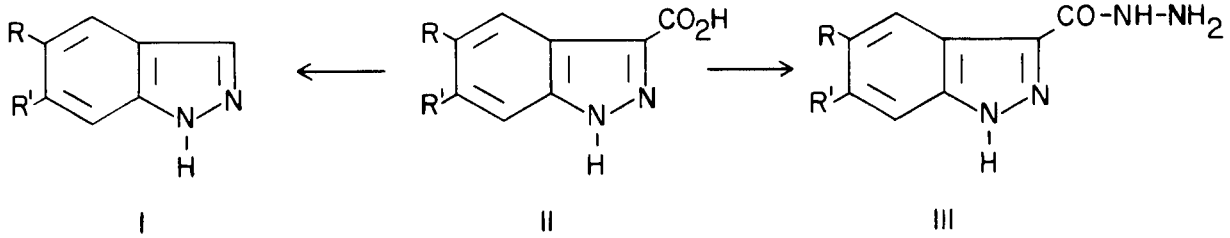
The preparation of indazole-3-carboxylic acids from the appropriate isatins by von Auwers' method has been investigated; these acids were used for acceding to the corresponding indazoles and for preparing hydrazides and hydrazones in the indazole series.

This work was prompted by two considerations: first, the need for a convenient source of indazole itself and several of its Bz-substituted derivatives whose structures were to be investigated by nuclear magnetic resonance spectroscopy (the results of this study have been published recently (1)); and secondly, the possibility that hydrazides and hydrazones derived from indazole-3-carboxylic acids might possess interesting biological properties. In this connection, it is known that *in vitro* tuberculostatic activity is not confined to isonicotinic acid hydrazide, but is also present to a lesser degree in a wide variety of hydrazides and hydrazones derived from other nitrogen heterocycles (2). Further, some hydrazides and hydrazones in the indazole series have recently been reported to produce a marked decrease in the food intake of cats, with no secondary incidents, thus suggesting the possibility of a therapeutic use for such compounds as anorexigenic agents in man (3).

The most convenient starting materials for preparing indazole-3-carboxylic acids were isatin and its substitution-products, which in the seven cases investigated, were readily converted into the corresponding indazolecarboxylic acids (II) by means of von Auwers' method involving the reduction of the diazo derivatives of the isatinic acids by stannous chloride (4). This procedure was applied to isatin and its 5-fluoro-, 5-chloro-, 5-bromo-, 5-iodo-, 5-methyl-, and 5,6-dimethyl- derivatives, with yields ranging from 50-60%; 5-methyl-, 5-fluoro-, and 5,6-dimethylisatin were conveniently prepared by applying the Sandmeyer chloral hydrate method (5) to the appropriate anilines, 5-chloro- and 5-bromoisatin were obtained by N-halosuccinimide substitution of isatin (6), and 5-iodoisatin was obtained by iodination of isatin with iodine monochloride in great excess (7). Heating the indazolecarboxylic acids above their melting points furnished the corresponding indazoles (I), except in the case of 5-iodoindazole-3-carboxylic acid, which underwent extensive decomposition with liberation of iodine. Several of the acids reported herein were previously unknown, as was 5,6-dimethylindazole; 5-fluoro- and 5-chloroindazole had earlier been prepared by a different route. Analytically, it was noted that several indazolecarboxylic acids tended to give poor elemental determinations, although their molecular weight could be determined by acidimetry; their methyl and ethyl esters, however, were readily prepared by direct sulfuric acid-catalyzed esterification with methanol and ethanol, and all these esters gave satisfactory analyses.

Hydrazides (III) of indazole-3-carboxylic acids were obtained in excellent yields by treating the corresponding esters with 99% hydrazine hydrate in 2-propanol; all reacted readily with aldehydes, ketones, and isatin to give poorly-soluble, high-melting hydrazones.

Tested *in vitro* against the five following microorganisms: *Staphylococcus aureus* (resistant strain), *Klebsiella pneumoniae*, *Trichomonas foetus*, *Candida albicans*, and *Trichophyton mentagrophytes*, none of the hydrazides or hydrazones prepared showed appreciable inhibitory activity. However, several hydrazones derived from indazole-3-carboxylic acid hydrazide showed distinct anorexigenic activity.



I II III

TABLE

Hydrazones (a) Derived from Hydrazides of Various Indazole-3-carboxylic Acids

Starting hydrazide	Carbonyl compound	Formula	M.p., °C	Nitrogen, % Calcd.	Found
II; R = R' = H (b)	4-hydroxybenzaldehyde	$C_{15}H_{12}N_4O_2$	303	20.0	20.3
II; R = R' = H	salicylaldehyde	$C_{15}H_{12}N_4O_2$	283	20.0	19.9
II; R = R' = H	piperonal	$C_{16}H_{12}N_4O_3$	312	18.2	18.1
II; R = R' = H	4-nitrobenzaldehyde	$C_{15}H_{11}N_5O_3$	352	22.6	22.5
II; R = R' = H	vanillin	$C_{16}H_{14}N_4O_3$	278	18.1	18.1
II; R = R' = H	4-acetaminobenzaldehyde	$C_{17}H_{15}N_5O_2$	358	21.9	22.0
II; R = R' = H	4-pyridinaldehyde	$C_{14}H_{11}N_5O$	340	26.4	25.9
II; R = R' = H	cyclooctanone	$C_{16}H_{20}N_4O$	284	19.7	19.5
II; R = R' = H	cyclododecanone	$C_{20}H_{28}N_4O$	273	16.5	16.4
II; R = R' = H	N-methyl-4-piperidone	$C_{14}H_{17}N_5O$	254	25.8	25.4
II; R = R' = H	N-benzyl-4-piperidone	$C_{20}H_{21}N_5O$	247	20.2	20.2
II; R = R' = H	isatin (c)	$C_{16}H_{11}N_5O_2$	>360	23.0	22.9
II; R = Cl, R' = H	4-dimethylaminobenzaldehyde	$C_{17}H_{16}ClN_5O$	349	20.5	20.6
II; R = Cl, R' = H	cyclopentanone	$C_{13}H_{13}ClN_4O$	336	20.3	20.4
II; R = Cl, R' = H	N-methyl-4-piperidone	$C_{14}H_{16}ClN_5O$	296	23.2	23.0

(a) All m.p.s taken on Maquenne block. (b) This hydrazide had m.p. 222°; Kirchner (3) gave m.p. 218-220°. (c) This hydrazone was recrystallized from butanol.

EXPERIMENTAL (8)

5-Fluoroindazole-3-carboxylic Acid (II; R = F, R' = H).

To a solution of 5.5 g. of sodium hydroxide in 100 ml. of water, 22 g. of 5-fluoroisatin prepared according to Yen, Buu-Hoi, and Xuong's technique (9) was added and the solution obtained was gently heated until it became pale yellow (formation of sodium 5-fluoroisatate); the solution was then cooled to 5° and treated, under stirring, with 10 g. of sodium nitrite (dissolved in 40 ml. of water). It was then poured, in small portions and with vigorous stirring, into aqueous sulfuric acid (8 ml. of acid, d = 1.84 in 300 ml. of water) cooled at 0°, and sulfur dioxide was bubbled through until most of the yellow precipitate which had formed was dissolved (sodium hydrogen sulfite can also be used for this purpose). The golden-yellow liquid obtained after filtration was poured into a solution of 48 g. of stannous chloride in 100 ml. of hydrochloric acid, and the mixture left for 5 hr. at room temperature. The precipitate obtained was collected, washed thoroughly with dilute hydrochloric acid, then with water, and recrystallized several times from acetic acid, giving cream-colored prisms, m.p. 299°, Yield, 60%.

Anal. Calcd. for $C_8H_5FN_2O_2$: Mol. weight (by acidimetry); 180. Found: 178.

The corresponding ethyl ester was prepared by refluxing for 3 hr. a mixture of 8 g. of the foregoing acid, 10 g. of ethanol and 9 g. of sulfuric acid; after cooling, ice-cooled water was added and the precipitate was collected, washed with dilute aqueous ammonia then with water, and recrystallized from aqueous ethanol, giving colorless needles, m.p. 169°.

Anal. Calcd. for $C_{10}H_9FN_2O_2$: N, 13.5. Found: N, 13.6.

5-Fluoroindazole (I; R = F, R' = H).

The acid was heated in a Claisen flask with powdered pumice stone above its melting point and the decarboxylation-product was distilled in vacuum and recrystallized from water, giving long colorless needles, m.p. 117°, lit. (10), m.p. 121°.

Anal. Calcd. for $C_7H_5FN_2$: N, 20.6. Found: N, 20.3.

5-Fluoroindazole-3-carboxylic Acid Hydrazide (III; R = F, R' = H).

A solution of 2 g. of ethyl 5-fluoroindazole-3-carboxylate and 2.5 g. of 99% hydrazine hydrate in a minimum of 2-propanol was refluxed for 5 hr. with one drop of acetic acid; the precipitate formed on cooling was recrystallized from ethanol, giving shiny colorless needles, m.p. 253°, Yield, 75%.

Anal. Calcd. for $C_8H_7FN_4O$: C, 49.5; H, 3.6; N, 28.9. Found: C, 50.0; H, 3.8; N, 28.4.

5-Chloroindazole-3-carboxylic Acid (II; R = Cl, R' = H).

Prepared from 5-chloroisatin, this acid crystallized from ethyl acetate in cream-colored needles, m.p. 337°.

Anal. Calcd. for $C_8H_5ClN_2O_2$: C, 48.8; H, 2.5; N, 14.3. Found: C, 49.0; H, 2.9; N, 14.5.

Thermal decarboxylation gave 5-chloroindazole (I; R = Cl, R' = H), crystallized from water in short colorless needles, m.p. 119°, von Auwers and Lange (11) gave m.p. 119-120° for the "labile" form of 5-chloroindazole; in our experiments however, no other form was isolated.

Methyl 5-Chloroindazole-3-carboxylate.

This compound crystallized from ethanol in colorless prisms, m.p. 207°.

Anal. Calcd. for $C_9H_7ClN_2O_2$: N, 13.3. Found: N, 13.2.

Ethyl 5-Chloroindazole-3-carboxylate.

Cream-colored microscopic prisms (from aqueous ethanol), m.p. 223° were obtained.

Anal. Calcd. for $C_{10}H_9ClN_2O_2$: N, 12.5. Found: N, 12.5.

5-Chloroindazole-3-carboxylic Acid Hydrazide (III; R = Cl, R' = H).

This compound crystallized from 2-propanol in silky colorless needles, m.p. 293°. This compound is significantly active *in vivo* against the tubercle bacilli (strain H37RV).

Anal. Calcd. for $C_8H_7ClN_4O$: C, 45.6; H, 3.3; N, 27.1. Found: C, 45.6; H, 3.4; N, 27.1.

5-Bromoindazole-3-carboxylic Acid (II; R = Br, R' = H).

This acid crystallized from acetic acid in cream-colored needles, m.p. 343°; decarboxylation gave 5-bromoindazole (I; R = Br, R' = H), crystallizing from water in long colorless needles, m.p. 126°; Bamberger (12) gave a m.p. of 124-125°, and von Auwers and Lange (11) gave a m.p. of 124° for the "labile" form. Ethyl 5-bromoindazole-3-carboxylate crystallized from aqueous ethanol in cream-colored needles, m.p. 142°. Treatment with hydrazine hydrate gave 5-bromoindazole-3-carboxylic hydrazide (III; R = Br, R' = H), crystallizing from 2-propanol in colorless needles, m.p. 297°, lit. (3), m.p. 300°.

5-Iodoindazole-3-carboxylic Acid (II; R = I, R' = H).

This acid crystallized from acetic acid in yellowish prisms, m.p. 375°; because of its high m.p., it underwent extensive decomposition on attempts at decarboxylation.

Anal. Calcd. for $C_8H_5IN_2O_2$: C, 33.3; H, 1.7; N, 9.7. Found: C, 33.3; H, 1.9; N, 9.7.

Methyl 5-Iodoindazole-3-carboxylate.

This compound crystallized from ethanol in fine cream-colored needles, m.p. 264°.

Anal. Calcd. for $C_9H_7IN_2O_2$: N, 9.3. Found: N, 8.9.

Ethyl 5-Iodoindazole-3-carboxylate.

This compound crystallized from ethanol in cream-colored needles, m.p. 231°.

Anal. Calcd. for $C_{10}H_9IN_2O_2$: N, 8.9. Found: N, 8.5.

5-Methylindazole-3-carboxylic Acid (II; R = Me, R' = H).

This acid crystallized from acetic acid in cream-colored leaflets, m.p. 343°; Shad (13) gave an apparently too-low m.p. (286°) for this compound. Our acid was identified by decarboxylation to 5-methylindazole (I; R = Me, R' = H), crystallizing from water in colorless prisms, m.p. 115° (lit. (13), m.p. 115°), and by formation of the methyl ester, crystallizing from aqueous ethanol in colorless needles, m.p. 184°; Piozzi and Ronchi (14) gave a m.p. of 181-182°. Ethyl 5-methylindazole-3-carboxylate crystallized from aqueous ethanol in colorless leaflets, m.p. 153°.

Anal. Calcd. for $C_{11}H_{12}N_2O_2$: N, 13.7. Found: N, 13.8.

5-Methylindazole-3-carboxylic Acid Hydrazide (III; R = Me, R' = H).

Prepared from the foregoing ester, this compound crystallized from dioxane in colorless prisms, m.p. 249°.

Anal. Calcd. for $C_9H_{10}N_4O$: C, 56.8; H, 5.3; N, 29.5. Found: C, 56.8; H, 5.2; N, 29.4.

5,6-Dimethylindazole (I; R = R' = Me).

5,6-Dimethylindazole-3-carboxylic acid crystallized from acetic acid in cream-colored microscopic needles, m.p. 332°; its thermal decarboxylation afforded 5,6-dimethylindazole, crystallizing from water in fine colorless needles, m.p. 173°, sublimable above 140°.

Anal. Calcd. for $C_9H_{10}N_2$: N, 19.2. Found: N, 19.1.

Methyl 5,6-dimethylindazole-3-carboxylate.

This compound crystallized from aqueous ethanol in yellowish prisms. m.p. 190°.

Anal. Calcd. for $C_{11}H_{12}N_2O_2$: N, 13.7. Found: N, 13.7.

Ethyl 5,6-dimethylindazole-3-carboxylate.

This compound crystallized from aqueous ethanol in yellowish prisms, m.p. 201°.

Anal. Calcd. for $C_{12}H_{14}N_2O_2$: N, 12.8. Found: N, 12.8.

5,6-Dimethylindazole-3-carboxylic Acid Hydrazide (III; R = R' = Me).

This compound crystallized from dioxane in cream-colored needles, m.p. 303°.

Anal. Calcd. for $C_{10}H_{12}N_4O$: N, 27.4. Found: N, 27.3.

Preparation of Hydrazones.

These, listed in the Table, were prepared by refluxing for 1 hr. an ethanolic solution of equimolar amounts of the corresponding hydrazine and the aldehyde or ketone; the hydrazones obtained, which were colorless or cream-colored (except for the derivative of isatin, which was orange-yellow), were collected and recrystallized from ethanol or 2-propanol. The hydrazones derived from N-methyl- and N-benzyl-4-piperidone were soluble in acid media.

Because of their ease of preparation, their nitrogen content, and their generally high and sharp melting points, the hydrazones derived from indazole-3-carboxylic acid hydrazide are good derivatives for the characterization of aldehydes and ketones.

Acknowledgment.

We thank Smith Kline and French Laboratories (Dr. Craig), Philadelphia, Pa., for the microbiological tests.

REFERENCES

(1) N. P. Buu-Hoi, J. P. Hoeffinger, and P. Jacquignon, *Bull. Soc. chim.* France, 2019 (1964).

(2) N. P. Buu-Hoi, M. Welsch, G. Dechamps, H. Le Bihan, F. Binon, and C. Mentzer, *Compt. rend.*, 234, 1925 (1952); N. P. Buu-Hoi, N. D. Xuong, F. Binon, and N. Hoan, *ibid.*, 235, 329 (1952); H. Offe, W. Siefken, and G. Domagk, *Naturwissenschaften*, 39, 118 (1952).

(3) F. K. Kirchner, U. S. Patent 3,007,938 (Nov. 7, 1961).

(4) K. von Auwers and R. Derser, *Ber.*, 52, 1345 (1919).

(5) P. Sandmeyer, *Helv. chim. Acta*, 2, 234 (1919).

(6) N. P. Buu-Hoi, *Rec. Trav. chim.*, 73, 197 (1954).

(7) N. P. Buu-Hoi and P. Jacquignon, *Compt. rend.*, 224, 768 (1957).

(8) All melting points are uncorrected.

(9) V. Q. Yen, N. P. Buu-Hoi, and N. D. Xuong, *J. Org. Chem.*, 23, 1858 (1958).

(10) I. K. Farben and H. Suschitsky, *J. Chem. Soc.*, 674 (1960).

(11) K. von Auwers and H. Lange, *Ber.*, 55, 1193 (1922).

(12) E. Bamberger, *ibid.*, 32, 1791 (1899).

(13) P. Shad, *ibid.*, 32, 1791 (1899).

(14) F. Piozzi and A. U. Ronchi, *Gazz. chim. Ital.*, 93, 2 (1963).

Received October 5, 1964

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