24 hr. The crystalline β,β-diethoxyacrylanilide was collected and recrystallized from a mixture of ethyl acetate and ether.

N-(β,β-Diethoxyacryl)-carbanilide.—A mixture of 23.8 g. (0.02 mole) of phenyl isocyanate and 11.6 g. (0.1 mole) of ketene diethylacetal was boiled under reflux for 8 hr. The resulting solution was concentrated under reduced pressure on the steam-bath. The residue was cooled and a small amount of solid crystallized which was recrystallized from ethyl acetate; yield 2 g. (4.5%), m.p. 148–149°.

Anal. Calcd. for $C_{20}H_{22}N_2O_4$: C, 67.78; H, 6.26; N, 7.91. Found: C, 67.66; H, 6.16; N, 7.96.

INDIANAPOLIS, INDIANA

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

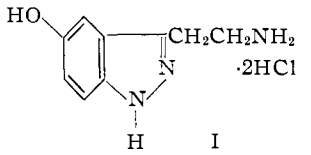
Substituted β-Aminoethylindazoles

BY C. AINSWORTH

RECEIVED SEPTEMBER 27, 1957

The synthesis of derivatives of 3β-aminoethyl-5-hydroxyindazole in which the side chain nitrogen is primary, secondary and tertiary is described, together with the preparation of the two isomeric N-substituted β-aminoethylindazoles. Some preliminary pharmacological findings on these compounds are included.

In a previous publication[1] it was reported that the indazole analog of serotonin, compound I, showed pronounced physiological activity paralleling the actions of serotonin. Included in the

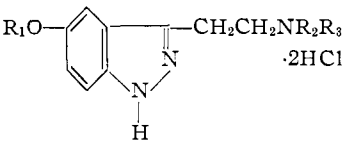


I

present communication is a description of the synthesis of a few selected derivatives of I. Five such compounds together with some preliminary pharmacological observations are listed in Table I.

TABLE I

SUBSTITUTED INDAZOLES,



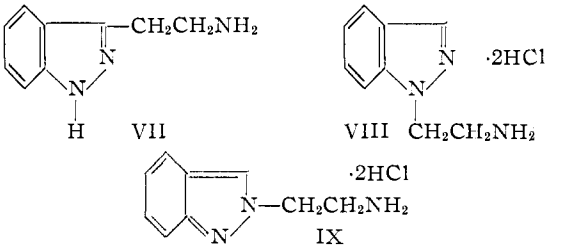
Compound	R_1	R_2	R_3	Pharmacological effects: Smooth muscle[b]		Blood pressure[d]	Ratio[e]
I	H	H	H	0.5γ	S[c]	0.5	1/10
II	H	CH_3	CH_3	2γ	S	0.1	1/2
III	H	H	$CH(CH_3)_2$	5γ	B	1.0	1/20
IV	R[a]	H	H	2γ	B	5.0	1/100
V	R[a]	CH_3	CH_3	2γ	B	1.2	1/25
VI	R[a]	H	$CH(CH_3)_2$	2γ	B	10.0	1/200

[a] R = benzyl. [b] Isolated rat uterus response, S = stimulation, B = block of serotonin stimulation. Values in column are concentration mg./l. Serotonin (5-hydroxytryptamine creatinine sulfate) is active at 0.2–0.4 γ. [c] The stimulating action of I on isolated rat uterus is blocked by a 1:20,000,000 dilution of lysergic acid diethylamide rather than the tenfold value reported in Ref. 1. [d] Concentration mg./kg. i.v. required to cause depressor effect in chloralose anesthetized cat. [e] Ratio of blood pressure effect compared with serotonin.

Compound IV, reported previously,[1] served as the starting material for the preparation of compounds III and VI. Ethyl 5-benzyloxy-3-indazole acetate[1] was converted to the corresponding dimethylamide, and this was reduced with lithium aluminum hydride to give compound V. The amine V was prepared also by reducing the ester to the corresponding alcohol that was converted with thionyl chloride to the β-chloroethyl compound. The latter intermediate upon reaction with dimethylamine gave compound V. Hydrogenolysis of compound V produced II.

5-Hydroxy-3-indazoleacetic acid, which would be an expected metabolite of compound I, was prepared by the hydrogenolysis of 5-benzyloxy-3-indazoleacetic acid.[1]

As an extension of our previous studies[2] on the indazole analog of tryptamine, compound VII, which was found to behave pharmacologically like tryptamine, it seemed of interest to prepare the two isomeric N-substituted β-aminoethylindazoles VIII and IX.



Indazole was alkylated with acrylonitrile at the 1-position as described by Rousseau and Lindwall.[3] The nitrile was hydrolyzed to the acid,[3] and this was converted directly with urea[4] to 1β-carbamylethylindazole. The amide yielded compound VIII when subjected to the Hofmann hypohalite reaction.

Surprisingly, when indazole was alkylated with acrylamide the 2-isomer was the predominant product together with about 15% of the 1-compound. Ultraviolet measurements readily distinguished the 1- and 2-substituted indazoles.[3] Treatment of 2β-carbamylethylindazole with sodium hypochlorite yielded compound IX. Compound IX was prepared also by the following scheme, RH → $RCH_2CO_2C_2H_5$ → RCH_2CONH_2 → RCH_2CN → IX, where the radical R is 2-indazole. The procedure of von Auwers[5] was followed to obtain ethyl 2-indazoleacetate which was con-

(1) C. Ainsworth, THIS JOURNAL, **79**, 5245 (1957).

(2) C. Ainsworth, *ibid.*, **79**, 5242 (1957).

(3) V. Rousseau and H. G. Lindwall, *ibid.*, **72**, 3047 (1950).

(4) E. Cherbuliez and F. Landolt, *Helv. Chim. Acta*, **29**, 1438 (1946).

(5) K. von Auwers and H. G. Allardt, *Ber.*, **59**, 95 (1926).

verted to the amide. The latter in turn was dehydrated[6] to the nitrile which afforded IX on reduction.

Compounds VIII and IX showed no appreciable pharmacological response in smooth muscle tests. Although the compounds listed in Table I had relatively high pharmacological effect on isolated muscle tests, the action was of short duration. It should be noted that the dimethyl derivative II, which is the indazole analog of bufotenine, was serotonin-like (in contrast to bufotenine) on isolated rat uterus response whereas the isopropyl compound III possessed an anti-serotonin action.

Acknowledgment.—The analyses were performed by H. L. Hunter and G. Beckmann. The author is grateful also to E. C. Powell and associates for the pharmacological data and to D. O. Woolf, Jr., and L. G. Howard for the physical measurements.

Experimental[7]

5-Benzyloxy-3-indazole-N,N-dimethylacetamide.—A solution of 4.6 g. (0.015 mole) of ethyl 5-benzyloxy-3-indazoleacetate,[1] 30 ml. of dimethylamine and 100 ml. of methyl alcohol was allowed to stand at room temperature for 7 days. After removal of the solvent the residue was recrystallized from an ethyl acetate–petroleum ether mixture, and 1.5 g. (33% yield) of 5-benzyloxy-3-indazole-N,N-dimethylacetamide was obtained, m.p. 163°; λ_{max} 254 mμ (log ε 3.65), 309 (3.71).

Anal. Calcd. for $C_{18}H_{19}N_3O_2$: C, 69.88; H, 6.19; N, 13.58. Found: C, 70.07; H, 6.28; N, 13.78.

5-Benzyloxy-3β-dimethylaminoethylindazole Dihydrochloride (V). (a) **Lithium Aluminum Hydride Reduction of 5-Benzyloxy-3-indazole-N,N-dimethylacetamide.**—To a mixture of 3.8 g. (0.1 mole) of lithium aluminum hydride and 100 ml. of dry tetrahydrofuran was added 2 g. (0.0065 mole) of 5-benzyloxy-3-indazole-N,N-dimethylacetamide dissolved in 200 ml. of dry tetrahydrofuran. The mixture was heated under reflux overnight and then was treated with 4 ml. of water, 3 ml. of 20% sodium hydroxide and finally 14 ml. of water. After removing the insoluble material by filtration, the filter cake was extracted with 500 ml. of hot ethyl acetate. The combined extracts were concentrated by heating under reduced pressure, and the oil that remained was dissolved in ethyl alcohol and treated with ether containing dry hydrogen chloride. The product what separated was recrystallized from ethyl alcohol–ether, and 1 g. (42% yield) of V was obtained, m.p. 185° (capillary); λ_{max} 253 mμ (log ε 3.67), 306 (3.71); pK_a' 8.4 (66% dimethylformamide).

Anal. Calcd. for $C_{18}H_{21}N_3O{\cdot}2HCl$: C, 58.70; H, 6.29; N, 11.41. Found: C, 58.75; H, 6.22; N, 11.13.

(b) **5-Benzyloxy-3β-chloroethylindazole Hydrochloride and Dimethylamine.**—A sample of 5-benzyloxy-3β-chloroethylindazole hydrochloride (see below) and dimethylamine was stored at 5° for 2 days. A little dilute sodium hydroxide was added, and the mixture was concentrated by heating on a steam-bath under reduced pressure. The residue was treated with dilute hydrochloric acid and again taken to dryness. The residue was extracted with absolute ethyl alcohol, and to this extract ether was added. The insoluble material that formed was recrystallized from ethyl alcohol–ether and shown by comparison of X-ray diffraction pattern to be identical with V prepared by procedure a.

3β-Dimethylaminoethyl-5-hydroxyindazole Dihydrochloride (II).—A mixture of 0.74 g. (0.002 mole) of 5-benzyloxy-3β-dimethylaminoethylindazole dihydrochloride, 0.7 g. of 5% palladium-on-carbon and 50 ml. of 50% aqueous ethyl alcohol was agitated with hydrogen at room temperature for about 5 hours. The catalyst was removed by filtration, and the filtrate was concentrated by heating under reduced pressure. The residue was recrystallized from an ethyl alcohol–ether mixture containing a small amount of hydrogen chloride, and 0.3 g. (54% yield) of II was obtained, m.p. 218° dec. (capillary); λ_{max} 254 mμ (log ε 3.61), 314 (3.73).

Anal. Calcd. for $C_{11}H_{15}N_3O{\cdot}2HCl$: C, 47.49; H, 6.16; N, 15.11. Found: C, 47.42; H, 6.22; N, 14.90.

5-Benzyloxy-3β-isopropylaminoethylindazole Dihydrochloride (VI).—A mixture of 2.7 g. (0.01 mole) of 3β-aminoethyl-5-benzyloxyindazole,[1] 2 ml. of acetone, 0.1 g. of Adams catalyst and 50 ml. of ethyl alcohol was reduced overnight with hydrogen in a Parr apparatus. The catalyst was removed by filtration, and the filtrate was concentrated by heating on a steam-bath. The residue solidified on standing and was recrystallized from ethyl acetate–petroleum ether to give 1 g. (32% yield) of 5-benzyloxy-3β-isopropylaminoethylindazole, m.p. 115°.

Anal. Calcd. for $C_{19}H_{23}N_3O$: C, 73.75; H, 7.49; N, 13.58. Found: C, 73.56; H, 7.60; N, 13.12.

The dihydrochloride was obtained in an ethyl alcohol–ether mixture containing hydrogen chloride, m.p. 233°; λ_{max} 253 mμ (log ε 3.68), 307 (3.71).

Anal. Calcd. for $C_{19}H_{23}N_3O{\cdot}2HCl$: C, 59.68; H, 6.59; N, 10.99. Found: C, 59.75; H, 6.63; N, 10.82.

5-Hydroxy-3β-isopropylaminoethylindazole Dihydrochloride (III).—A mixture of 1 g. of 5-benzyloxy-3β-isopropylaminoethylindazole, 1 g. of 5% palladium-on-carbon and 100 ml. of ethyl acetate was shaken overnight with hydrogen in a Parr apparatus. The catalyst was removed by filtration, and the filtrate was concentrated by heating on a steam-bath. The residue was dissolved in ethyl alcohol and treated with ether containing hydrogen chloride. Compound III was obtained in almost quantitative yield, m.p. 225° (capillary); λ_{max} 253 mμ (log ε 3.60), 313 (3.71). A sample, dried at 56° for 3 hours, analyzed for a monohydrate.

Anal. Calcd. for $C_{12}H_{17}N_3O{\cdot}2HCl{\cdot}H_2O$: C, 46.46; H, 6.82; N, 13.55. Found: C, 46.74; H, 7.14; N, 13.31.

5-Benzyloxy-3β-hydroxyethylindazole.—A mixture of 3.1 g. (0.01 mole) of ethyl 5-benzyloxy-3-indazoleacetate,[1] 3.8 g. (0.1 mole) of lithium aluminum hydride and 200 ml. of dry tetrahydrofuran was heated overnight under reflux. Successively, 4 ml. of water, 3 ml. of 20% sodium hydroxide and 14 ml. of water was added, and the mixture was filtered. The filter cake was extracted with 200 ml. of hot ethyl acetate, and the combined extracts were concentrated to dryness by heating on a steam-bath under reduced pressure. The solid that formed was recrystallized from ethyl acetate, and 2.5 g. (93% yield) of 5-benzyloxy-3β-hydroxyethylindazole resulted, m.p. 162°; λ_{max} 254 mμ (log ε 3.64), 307 (3.68).

Anal. Calcd. for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.39; H, 5.91; N, 10.15.

5-Benzyloxy-3β-chloroethylindazole Hydrochloride.—A mixture of 1.3 g. (0.005 mole) of 5-benzyloxy-3β-hydroxyethylindazole and 10 ml. of thionyl chloride was heated under reflux for 2 hours. About 200 ml. of dry ether containing a small amount of hydrogen chloride was added and the solid that separated was collected on a sintered glass funnel. It was recrystallized from a cold ethyl alcohol–ether mixture, and 0.35 g. (22% yield) of 5-benzyloxy-3β-chloroethylindazole hydrochloride was obtained, m.p. 140°; λ_{max} 254 mμ (log ε 3.68), 307 (3.72).

Anal. Calcd. for $C_{16}H_{15}ClN_2O{\cdot}HCl$: C, 59.45; H, 4.99; N, 8.67. Found: C, 59.49; H, 5.19; N, 8.52.

A sample of 5-benzyloxy-3β-chloroethylindazole hydrochloride was warmed with ethyl alcohol and ether was added. 5-Benzyloxy-3β-ethoxyethylindazole hydrochloride was obtained, m.p. 160°; λ_{max} 253 mμ (log ε 3.72), 306 (3.73).

Anal. Calcd. for $C_{18}H_{20}N_2O_2{\cdot}HCl$: C, 64.95; H, 6.36; N, 8.42. Found: C, 65.05; H, 6.66; N, 8.74.

5-Hydroxy-3-indazoleacetic Acid.—A mixture of 5.6 g. (0.02 mole) of 5-benzyloxy-3-indazoleacetic acid,[1] 5 g. of 5% palladium-on-carbon and 200 ml. of ethyl acetate was shaken overnight with hydrogen in a Parr apparatus. About 300 ml. of ethyl acetate was added, and the mixture was heated to boiling and filtered. An equal volume of petroleum ether was added to the filtrate, and 2.5 g. of product separated. It was recrystallized from 25 ml. of water or an ethyl acetate–petroleum ether mixture to give 2.0 g. (54% yield) of 5-hydroxy-3-indazoleacetic acid, m.p.

(6) The arylsulfonyl chloride method of C. R. Stephens, E. J. Bianco and F. J. Pilgrim, THIS JOURNAL, **77**, 1701 (1955), was used.

(7) The melting points were taken with a Fisher–Johns block and are uncorrected. The ultraviolet data were obtained in ethyl alcohol.

210° dec.; λ_{max} 253 mμ (log ε 3.65), 312 (3.73); pK'_a 7.0, 13.5 (66% dimethylformamide).

Anal. Calcd. for $C_9H_8N_2O_3$: C, 56.25; H, 4.20; N, 14.58. Found: C, 55.82; H, 4.33; N, 14.71.

2-Carbamylmethylindazole.—A solution of 20.4 g. (0.1 mole) of ethyl 2-indazoleacetate[5] dissolved in 50 ml. of methyl alcohol was added to 200 ml. of saturated ammoniacal methyl alcohol and allowed to stand at room temperature overnight. The solid that separated was collected and recrystallized from ethyl alcohol, m.p. 205°, λ_{max} 274 mμ (log ε 3.82); 6.5 g. (37%) yield.

Anal. Calcd. for $C_9H_9N_3O$: C, 61.70; H, 5.18; N, 23.99. Found: C, 61.66; H, 4.87; N, 24.24.

2-Cyanomethylindazole.—A solution of 8.8 g. (0.05 mole) of 2-carbamylmethylindazole, 9.5 g. (0.05 mole) of *p*-toluenesulfonyl chloride and 9 g. of pyridine was heated on a steam-bath for 0.5 hour. The solution was added to ice-water, and the solid that formed was washed with water and recrystallized from 50% aqueous ethyl alcohol. The solid (5 g.) that was deposited on cooling was air-dried and then recrystallized from ethyl acetate–petroleum ether to give 4 g. (50% yield) of 2-cyanomethylindazole, m.p. 82°, λ_{max} 274 mμ (log ε 3.81).

Anal. Calcd. for $C_9H_7N_3$: C, 68.77; H, 4.49; N, 26.74. Found: C, 68.84; H, 4.47; N, 26.77.

2β-Carbamylethylindazole.—A mixture of 11.8 g. (0.1 mole) of indazole, 7.1 g. (0.1 mole) of acrylamide, 1 ml. of 40% benzyltrimethylammonium hydroxide and 100 ml. of *t*-butyl alcohol was allowed to stand near a steam-bath (reaction temperature about 50°) overnight and then at room temperature for 2 days. The solid that formed was collected and air-dried. It melted over a range starting at 135°, and examination of the ultraviolet spectrum indicated about 15% of the 1-isomer. The product was recrystallized from ethyl alcohol and 9.5 g. (50% yield) of 95% pure 2-isomer melting near 165° was obtained. A sample was recrystallized from ethyl acetate and then ethyl alcohol to give pure 2β-carbamylethylindazole, m.p. 185–187°, λ_{max} 274 mμ (log ε 3.81).

Anal. Calcd. for $C_{10}H_{11}N_3O$: C, 63.47; H, 5.86; N, 22.21. Found: C, 63.36; H, 6.10; N, 22.58.

2-β-Aminoethylindazole Dihydrochloride (IX). (a) Reduction of 2-Cyanomethylindazole.—A mixture of 3.6 g. (0.023 mole) of 2-cyanomethylindazole, 0.1 g. of Adams catalyst and 25 ml. of acetic anhydride was shaken with hydrogen in a Parr apparatus. Following the theoretical uptake of hydrogen (about 6 hours) the catalyst was removed by filtration, water was added, and the solvents removed by heating under reduced pressure. The resulting oil was treated with excess picric acid in ethyl alcohol, and 3 g. (30% yield) of 2β-acetylaminoethylindazole picrate separated. It was recrystallized from ethyl alcohol, m.p. 182°.

Anal. Calcd. for $C_{17}H_{16}N_6O_8$: C, 47.22; H, 3.73; N, 19.44. Found: C, 47.27; H, 3.99; N, 19.63.

The above picrate was shaken for 5 minutes with a mixture of 50 ml. of nitrobenzene and 50 ml. of concentrated hydrochloric acid. The acid extract was warmed on a steam-bath for 5 hours and then concentrated to dryness by heating under reduced pressure. The residue was recrystallized from a methyl alcohol–ether mixture containing a small amount of hydrogen chloride. The yield of compound IX was 1 g. (60%), m.p. 212° dec. (capillary), λ_{max} 274 mμ (log ε 3.81), pK_a' 8.2 (66% dimethylformamide).

Anal. Calcd. for $C_9H_{11}N_3 \cdot 2HCl$: C, 46.17; H, 5.60; N, 17.95. Found: C, 46.31; H, 5.64; N, 18.23.

(b) **2β-Carbamylethylindazole and Sodium Hypochlorite.**—A mixture of 4 g. (0.02 mole) of 2β-carbamylethylindazole and 4 g. (0.1 mole) of sodium hydroxide in 30 ml. of ice-water containing 1.5 g. (0.02 mole) of chlorine was stirred at room temperature for 2 hours. Then the reaction was warmed on a steam-bath for 1 hour during which time solution was effected. The solution was extracted four times with 50 ml. of ethyl acetate, and the extracts were dried with anhydrous magnesium sulfate. Ether containing hydrogen chloride was added, and the mixture was allowed to stand for several days. The solid was collected and was recrystallized from ethyl alcohol to give 3 g. (64% yield) of IX, m.p. 215° dec. (capillary).

Anal. Calcd. for $C_9H_{11}N_3 \cdot 2HCl$: C, 46.17; H, 5.60; N, 17.95. Found: C, 46.33; H, 5.72; N, 17.66.

1β-Carbamylethylindazole.—A mixture of 7 g. (0.037 mole) of 1β-carboxyethylindazole[3] and 7 g. of urea was heated at 190° for 2 hours. After cooling about 50 ml. of 1 *N* sodium hydroxide was added, and the mixture was extracted with two 100-ml. portions of ethyl acetate. The ethyl acetate solution was dried and then concentrated to dryness by heating on a steam-bath. The solid that resulted was recrystallized from ethyl acetate to give 4 g. (57% yield) of 1β-carbamylethylindazole, m.p. 143°; λ_{max} 253 mμ (log ε 3.59), 290 (3.69).

Anal. Calcd. for $C_{10}H_{11}N_3O$: C, 63.47; H, 5.86; N, 22.21. Found: C, 63.85; H, 6.05; N, 22.07.

1β-Aminoethylindazole dihydrochloride (VIII) was prepared from 4 g. of 1β-carbamylethylindazole according to the second procedure described above for the preparation of compound IX. The product was recrystallized from alcohol–water mixture to give 3.7 g. (77% yield) of VIII, m.p. 180° dec. (capillary); λ_{max} 251 mμ (log ε 3.58), 289 (3.64); pK_a' 8.4 (66% dimethylformamide).

Anal. Calcd. for $C_9H_{11}N_3 \cdot 2HCl$: C, 46.17; H, 5.60; N, 17.95. Found: C, 46.43; H, 6.01; N, 18.05.

INDIANAPOLIS 6, INDIANA

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

Reinvestigation of the Fischer Indazole Synthesis

BY C. AINSWORTH

RECEIVED OCTOBER 23, 1957

The Fischer synthesis of 3-indazoleacetic acid has been reinvestigated, and the intermediate described as *o*-hydrazinocinnamic acid has been shown to be 2,3-dihydro-3-indazoleacetic acid. Sodium 2-(substituted phenyl)-hydrazinosulfonates have been found to undergo carbon–nitrogen cleavage under basic conditions.

Preliminary to the synthetic approach used for the preparation of 3β-aminoethyl-5-hydroxyindazole,[1] we reinvestigated some of the studies of Fischer and co-workers.[2] The work in question described the preparation of 3-indazoleacetic acid (I) from different intermediates obtained by the reduction of 2-(2-carboxyvinyl)-benzenediazonium chloride (II) as illustrated in the reaction scheme

(1) C. Ainsworth, THIS JOURNAL, **79**, 5245 (1957).

(2) (a) E. Fischer, *Ber.*, **14**, 478 (1881); (b) E. Fischer and H. Kuzel, *Ann.*, **221**, 261 (1883); (c) E. Fischer and J. Tafel, *ibid.*, **227**, 303 (1885).