stirring to anhydrous hydrazine (2.5 ml.). A large quantity of white solid deposited after stirring for 30 minutes. The mixture was evaporated to dryness *in vacuo* and the residue extracted with boiling benzene (100 ml.). The white solid which deposited from the extract was collected by filtration; yield 340 mg. (70%), m.p. 160–162°; $\tilde{\nu}_{max}$ in cm.$^{-1}$: 3125 (NH); 2960 and 2860 (CH); 1612 (NH); 1570, 1562 and 1528 (C=C, C=N); 1479 (CH); 1460 and 1374 (C-CH_3).

Anal. Calcd. for $C_7H_{10}N_6$: C, 47.19; H, 5.62; N, 47.19. Found: C, 47.16; H, 5.68; N, 48.35.

6-Dimethylamino-9-ethylpurine[5c] **(XI).**—A solution of 6-chloro-9-ethylpurine (500 mg., 2.74 mmoles) in aqueous dimethylamine (10 ml., 25%) was refluxed for 1 hr., evaporated to dryness *in vacuo* and the residue extracted with ether (3 × 25 ml.). The combined extracts were dried over magnesium sulfate, the drying agent removed by filtration and the filtrate evaporated to dryness; yield 390 mg.

Recrystallization of this material from Skellysolve C gave 380 mg. (73%) of a white solid, m.p. 82–84° (lit.[5c] 79–80°); $\tilde{\nu}_{max}$ in cm.$^{-1}$: 3065 and 2950 (CH); 1590, 1559 and 1547 (C=C, C=N); 1485 (CH); 1430 and 1370 (C-CH_3).

Anal. Calcd. for $C_9H_{13}N_5$: C, 56.54; H, 6.81; N, 36.65. Found: C, 56.87; H, 7.02; N, 36.39.

6-*n*-Butylamino-9-ethylpurine (XII).—After a solution of 6-chloro-9-ethylpurine (500 mg., 2.74 mmoles) in *n*-butylamine (10 ml.) was refluxed for 2 hr., the excess amine was removed *in vacuo* and the residue triturated with ether. The solid (*n*-butylamine hydrochloride) which deposited was removed by filtration. The residual oil obtained from the evaporation of the ether filtrate was dissolved in hydrochloric acid (8 ml., 1 *N*) by heating on a hot-plate for several minutes and the solution evaporated to dryness *in vacuo;* yield 400 mg.

Recrystallization (380 mg.) from methyl isobutyl ketone (75 ml.) gave 270 mg. (39%) of 6-*n*-butylamino-9-ethylpurine hydrochloride, m.p. 176–178°.

Anal. Calcd. for $C_{11}H_{17}N_5$·HCl: C, 51.66; H, 7.05; N, 27.45. Found: C, 51.67; H, 7.12; N, 27.45.

In a second run of 500 mg. of 6-chloro-9-ethylpurine, the oil obtained from the evaporation of the ether was distilled at approximately 164° (0.1 mm.). Crystallization of the distillate took place on standing overnight; yield 340 mg. (57%) of 6-*n*-butylamino-9-ethylpurine, m.p. 60–61.5°; $\tilde{\nu}_{max}$ in cm.$^{-1}$: 3265 (NH); 3030, 2917 and 2845 (CH); 1615 (NH); 1580, 1560, 1538 (C=C, C=N); 1487 (CH); 1469 and 1375 (C-CH_3).

Anal. Calcd. for $C_{11}H_{17}N_5$: C, 60.03; H, 7.76; N, 31.97. Found: C, 59.73; H, 7.70; N, 32.02.

BIRMINGHAM, ALABAMA

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

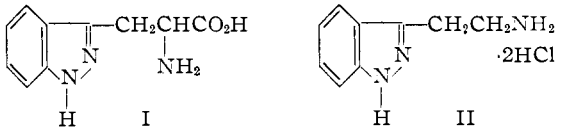
Indazole Analog of Tryptamine: A New Synthesis of Indazoles

BY C. AINSWORTH

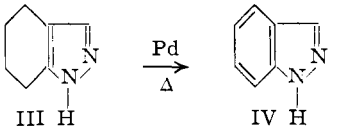
RECEIVED MAY 31, 1957

A new synthesis of indazoles involving the dehydrogenation of readily available tetrahydroindazoles, and the application of this method to the preparation of 3β-aminoethylindazole dihydrochloride (II) are described.

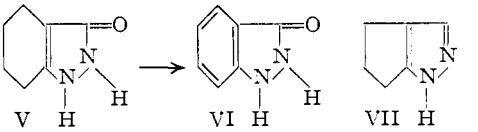
Indazole compounds have been known for a long time and have been synthesized in several different ways. In recent years there has been a certain interest in indazole analogs of some biologically important indole derivatives. For example, compound I, isosteric with tryptophane, has been reported.[1]



This paper describes a new and fairly general route to the synthesis of indazoles. In particular it describes the preparation of compound II, which is the indazole analog of tryptamine, by this new method. It has been found that indazole (IV) can be prepared easily and in good yield by the catalytic dehydrogenation of the readily available pyrazole compound III.

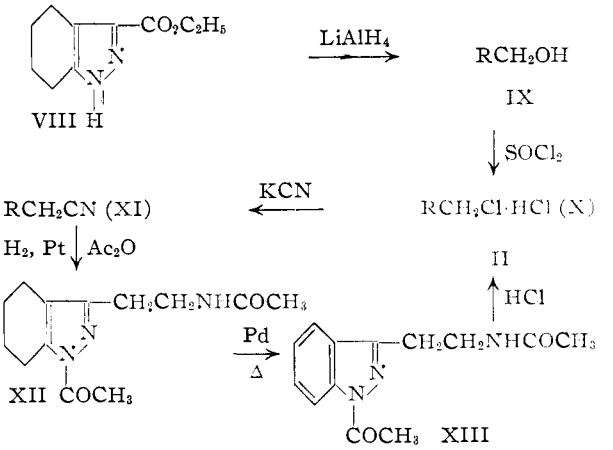


The reaction is carried out in boiling decalin using 5% palladium-on-carbon. Some related dehydrogenations were studied, and it was shown that 4,5-dihydronaphtho[1,2]pyrazole gave naphtho[1,2]-pyrazole, and compound V formed VI. However, the pyrazole derivative VII was recovered un-



changed when subjected to the dehydrogenation conditions.[2]

The method of synthesizing II is outlined by the following series of reactions.[3] Compound VIII



where the radical R is 4,5,6,7-tetrahydroindazole-3

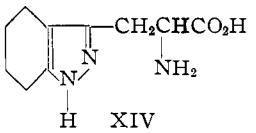
(1) H. R. Snyder, C. B. Thompson and R. L. Hinman, THIS JOURNAL, **74**, 2009 (1952).

(2) This observation is consistent with the finding of J. D. Roberts and W. F. Gorham, *ibid.*, **74**, 2278 (1952), that tetrahydropentalene failed to dehydrogenate to pentalene.

(3) This synthetic approach was proposed by Dr. Reuben G. Jones.

was prepared in good yield from ethyl cyclohexanone-2-glyoxalate and hydrazine hydrate, according to the method reported by von Auwers.[4] It was dehydrogenated with ease forming ethyl 3-indazolecarboxylate. The alcohol IX, however, lost the side chain when heated in decalin with 5% palladium-on-carbon and gave indazole.[5] The nitrile XI was recovered unchanged when subjected to conditions that satisfactorily brought about the dehydrogenation of compound XII to XIII. The position assigned to the ring-N-acetyl group of compound XII was not established but seems likely in view of previous acylation studies.[6] Compound XII was converted to 3β-aminoethyl-4,5,6,7-tetrahydroindazole dihydrochloride by acidic hydrolysis.

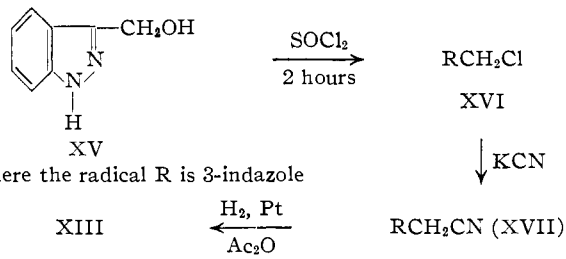
In the course of this work the α-aminocarboxylic acid XIV was prepared from X by the standard acylaminomalonic ester method.



XIV

No attempt was made to dehydrogenate XIV or its intermediate.

Compound XIII was prepared by an alternative method starting with the indazole alcohol XV. Snyder and his co-workers[1] reported that they did not obtain the chloride XVI by the reaction of the



where the radical R is 3-indazole

alcohol XV with thionyl chloride. They mentioned that a high melting solid was isolated. We observed a high melting solid when XV was warmed with thionyl chloride for a short time, but when the mixture was heated under reflux for two hours, compound XVI was formed. The chloromethyl compound XVI was converted to the nitrile XVII and this was reduced in acetic anhydride to give XIII. From these results it is apparent that both the indazole XVII and the tetrahydroindazole XI reacted with acetic anhydride on the same ring nitrogen.

Reductive alkylation of compound II using acetone in the presence of hydrogen and Adams catalyst formed 3β-isopropylaminoethylindazole.

3β-Aminoethylindazole dihydrochloride (II) has been tested for pharmacological action, and preliminary results indicate that it behaves much like tryptamine.[7] In phenobarbitalized dogs 1 mg. per kg. of II given intravenously raised blood pressure slightly for about five minutes. The compound showed slight stimulation of the isolated rabbit uterus and weak antiserotonin action on rat uterus. When administered orally to a denervated pouch dog at a dose of 15 mg. per kg. compound II showed no effect on gastric secretion. However, 3β-aminoethyl-4,5,6,7-tetrahydroindazole dihydrochloride at a dose of 1 mg. per kg. caused increased gastric flow.

Acknowledgments.—The author is grateful to W. L. Brown, H. L. Hunter, G. M. Maciak and G. Beckmann for the analyses, and to D. O. Woolf, Jr., and L. G. Howard for physical measurements. The pharmacological tests were carried out by C. E. Powell and associates, and Dr. T. M. Lin and associates.

Experimental[8]

Indazole (IV).—4,5,6,7-Tetrahydroindazole (III) was prepared from equimolar quantities of 2-hydroxymethylenecyclohexanone[9] and hydrazine hydrate.[10] It was recrystallized from petroleum ether, m.p. 82°; λ_{max} 223 mμ, log ε 3.65 (lit.[9] m.p. 84°).

A mixture of 5 g. (0.04 mole) of 4,5,6,7-tetrahydroindazole, 3.5 g. of 5% palladium-on-carbon and 100 ml. of dry decalin was heated under reflux for 24 hours. The hot mixture was filtered, and the filtrate was allowed to cool. After standing overnight the solid was collected and air-dried. The product weighed 3 g. (62%) and was essentially pure indazole, m.p. 145°; λ_{max} 250 mμ (log ε 3.65), 2.85 (3.66) (lit.[11] m.p. 146°).

3(1H)-Indazolone (VI).—A mixture of 1 g. of 4,5,6,7-tetrahydro-3(1H)-indazolone[12] (V) (λ_{max} 247, log ε 3.83), 0.5 g. of 5% palladium-on-carbon and 100 ml. of dry decalin was heated overnight under reflux. After cooling, the mixture was filtered, and the filter was extracted with 100 ml. of hot ethyl alcohol. The alcohol was evaporated, and the residue was recrystallized from nitromethane, m.p. 250°. An analytical sample was obtained by sublimation at 220° and 0.1 mm. pressure, m.p. 253–254°; λ_{max} 215 mμ (log ε 4.32), 306 (3.62) (lit.[13] m.p. 242° dec.).

Anal. Calcd. for $C_7H_6N_2O$: C, 62.68; H, 4.51. Found: C, 62.87; H, 4.62.

Naphtho[1,2]pyrazole.—4,5-Dihydronaphtho[1,2]pyrazole was prepared from equimolar quantities of 1-keto-2-hydroxymethylenetetrahydronaphthalene[14] and hydrazine hydrate.[9] It was recrystallized from ethyl acetate, m.p. 135°; λ_{max} 264 mμ, log ε 4.09 (lit.[14] m.p. 123°).

A mixture of 1 g. of 4,5-dihydronaphtho[1,2]pyrazole, 0.5 g. of 5% palladium-on-carbon and 50 ml. of dry decalin was heated overnight under reflux. The catalyst was removed by filtration and on cooling 0.6 g. (approximately 60% yield) of naphtho[1,2]pyrazole deposited, m.p. 160°; λ_{max} 243 mμ, log ε 4.62 (lit.[15] m.p. 158°).

Anal. Calcd. for $C_{11}H_8N_2$: C, 78.55; H, 4.79. Found: C, 78.71; H, 4.69.

Attempted Dehydrogenation of 4,5-Trimethylenepyrazole (VII).—4,5-Trimethylenepyrazole was made in a manner analogous to that described above for the preparation of 4,5,6,7-tetrahydroindazole.

(4) K. von Auwers, J. Conrad, A. Ernecke and B. Ottens, *Ann.* **469**, 57 (1929).

(5) This is similar to the observations of M. S. Newman and T. S. Bye, THIS JOURNAL, **74**, 905 (1952), in the tetrahydronaphthalene series.

(6) R. C. Elderfield, "Heterocyclic Compounds," Vol. V, John, Wiley and Sons, Inc., New York, N. Y., 1957, pp. 95, 182.

(7) C. E. Powell, E. E. Swanson and K. K. Chen, *J. Am. Pharm. Assoc. Sci. Ed.*, **44**, 399 (1955).

(8) Unless otherwise indicated the melting points were determined with a Fisher–Johns assembly and are reported as read. The ultraviolet absorption data were obtained in methanol.

(9) O. Wallach, A. Steindorff and W. Grimmer, *Ann.*, **329**, 109 (1903).

(10) This method was first employed in this Laboratory by Dr. N. Easton.

(11) E. F. M. Stephenson, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 475.

(12) W. Dieckmann and F. Coblitz, *Ann.*, **317**, 93 (1901).

(13) E. Fischer, *ibid.*, **212**, 316 (1882).

(14) K. von Auwers and C. Wiegand, *J. prakt. Chem.*, **134**, 82 (1932).

(15) V. Vesely, A. Medvedeva and E. Muller, *Collection Czechoslov. Chem. Commun.*, **7**, 228 (1935); *C. A.*, **29**, 5840 (1935).

A mixture of 1.5 g. of 4,5-trimethylenepyrazole, 0.5 g. of 5% palladium-on-carbon and 25 ml. of dry decalin was heated overnight under reflux. The catalyst was removed by filtration, and the filtrate was concentrated by heating under reduced pressure. The residue solidified on cooling. It was recrystallized from petroleum ether and shown to be unchanged 4,5-trimethylenepyrazole, m.p. 57°; λ_{max} 224 mμ, log ε 3.71 (lit.[9] m.p. 57–59°).

Ethyl 4,5,6,7-Tetrahydro-3-indazolecarboxylate (VIII).—A solution of 19.8 g. (0.1 mole) of crude ethyl cyclohexanone-2-glyoxalate[16] and 100 ml. of ethyl alcohol was treated with 5 ml. (0.1 mole) of hydrazine hydrate. Following the exothermic reaction the mixture was heated on the steam-bath for 0.5 hour. The solvent was removed, and the residue was distilled under reduced pressure, b.p. 190° (10 mm.). The product solidified on standing, m.p. 75°. A sample was recrystallized from light petroleum ether, m.p. 88°; λ_{max} 225 mμ, log ε 3.96 (lit.[4] m.p. 107°). The yield was 12 g. (62%).

Anal. Calcd. for $C_{10}H_{14}N_2O_2$: C, 61.83; H, 7.27; N, 14.42. Found: C, 62.00; H, 7.21; N, 14.42.

The picrate was recrystallized from water, m.p. 75°.

Anal. Calcd. for $C_{16}H_{17}N_5O_9$: C, 45.39; H, 4.05; N, 16.54. Found: C, 45.50; H, 4.43; N, 16.32.

Ethyl 3-Indazolecarboxylate.—A mixture of 9.7 g. (0.05 mole) of ethyl 4,5,6,7-tetrahydro-3-indazolecarboxylate, 3 g. of 5% palladium-on-carbon and 150 ml. of dry decalin was heated under reflux for 48 hours. The catalyst was removed by filtration, and on cooling 5.5 g. (58%) of product separated. It was recrystallized from ethyl alcohol and obtained as prisms, m.p. 139°; λ_{max} 393 mμ, log ε 3.95 (lit.[17] m.p. 137°). It was identical with ethyl 3-indazolecarboxylate prepared according to the method of von Auwers.[17]

3-Hydroxymethyl-4,5,6,7-tetrahydroindazole (IX).—To a stirred mixture of 7.6 g. (0.2 mole) of lithium aluminum hydride and 200 ml. of tetrahydrofuran was added dropwise a solution of 19.4 g. (0.1 mole) of ethyl 4,5,6,7-tetrahydro-3-indazolecarboxylate in 200 ml. of dry tetrahydrofuran. After heating under reflux for 1 hour the mixture was treated successively with 4 ml. of water, 3 ml. of 20% sodium hydroxide solution and 14 ml. of water. The solid was separated by filtration, and the filter cake was extracted with 500 ml. of hot ethyl acetate. The tetrahydrofuran and ethyl acetate extracts were combined, and the solvents were removed by heating under reduced pressure. The solid residue was recrystallized from ethyl acetate and obtained as needles, m.p. 129–130°; λ_{max} 226 mμ, log ε 3.71. The yield was 12 g. (79%).

Anal. Calcd. for $C_8H_{12}N_2O$: C, 63.13; H, 7.95; N, 18.41. Found: C, 63.30; H, 7.85; N, 18.30.

The hydrochloride salt was recrystallized from an ethanol–ether mixture, m.p. 155–157°.

Anal. Calcd. for $C_8H_{12}N_2O\cdot HCl$: C, 50.93; H, 6.95; N, 14.85. Found: C, 51.15; H, 7.12; N, 14.89.

A mixture of 1 g. of 3-hydroxymethyl-4,5,6,7-tetrahydroindazole, 0.5 g. of 5% palladium-on-carbon and 25 ml. of decalin was heated under reflux for 2 hours. The catalyst was removed by filtration, and on cooling the filtrate deposited only starting material. However, when the reactants were heated overnight under reflux, the solid (200 mg.) that separated following removal of the catalyst was shown to be indazole, m.p. 145°.

3-Chloromethyl-4,5,6,7-tetrahydroindazole Hydrochloride (X).—A mixture of 5 g. (0.03 mole) of 3-hydroxymethyl-4,5,6,7-tetrahydroindazole and 25 ml. of thionyl chloride was heated under reflux for 0.5 hour. About 200 ml. of dry ether was added, and the solid that formed was collected on a sintered glass funnel. The solid, 5.5 g. (80% yield), was dried over potassium hydroxide in a vacuum desiccator. A sample was recrystallized from a cold ethanol–ether mixture, m.p. 178–180° dec. (capillary); λ_{max} 232 mμ, log ε 3.81.

Anal. Calcd. for $C_8H_{11}ClN_2\cdot HCl$: C, 46.39; H, 5.84; N, 13.53. Found: C, 46.63; H, 5.88; N, 13.33.

(16) H. R. Snyder, L. A. Brooks and S. H. Shapiro, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 531.

(17) K. von Auwers and R. Dereser, *Ber.*, **52**, 1340 (1919).

3-Cyanomethyl-4,5,6,7-tetrahydroindazole (XI).—To a stirred solution of 6 g. of potassium cyanide in 6 ml. of water cooled to 10°, was added 2.1 g. (0.01 mole) of 3-chloromethyl-4,5,6,7-tetrahydroindazole hydrochloride dissolved in 20 ml. of ethyl alcohol. After stirring at room temperature for 6 hours, the salt was removed by filtration, and the filtrate was evaporated to dryness. The residue was extracted with 100 ml. of ether. The residue that remained after evaporation of the ether was recrystallized from benzene–petroleum ether. About 1 g. (62% yield) of 3-cyanomethyl-4,5,6,7-tetrahydroindazole was obtained as prisms, m.p. 109–110°; λ_{max} 225 mμ, log ε 3.72.

Anal. Calcd. for $C_9H_{11}N_3$: C, 67.05; H, 6.88; N, 26.07. Found: C, 67.16; H, 6.63; N, 25.85.

The picrate was recrystallized from water, m.p. 173°.

Anal. Calcd. for $C_{15}H_{14}N_6O_7$: C, 46.16; H, 3.62. Found: C, 46.27; H, 3.73.

A sample of 1 g. of 3-cyanomethyl-4,5,6,7-tetrahydroindazole and 0.5 g. of 5% palladium-on-carbon was heated overnight in boiling decalin and was recovered unchanged.

1-Acetyl-3β-acetylaminoethyl-4,5,6,7-tetrahydroindazole (XII).—A mixture of 3.2 g. (0.02 mole) of 3-cyanomethyl-4,5,6,7-tetrahydroindazole, 25 ml. of acetic anhydride and 0.5 g. of Adams catalyst was shaken in a Parr shaker with hydrogen. After the theoretical amount of hydrogen was taken up (about 4 hours) the catalyst was removed by filtration, and about 50 ml. of water was added to the filtrate. The solvents were removed by heating under reduced pressure, and the resulting residue was recrystallized from ethyl acetate. The yield of compound XII was 2.3 g. (46%), m.p. 154–155°; λ_{max} 246 mμ, log ε 4.12.

Anal. Calcd. for $C_{13}H_{19}N_3O_2$: C, 62.62; H, 7.68; N, 16.86. Found: C, 63.00; H, 7.92; N, 16.85.

3β-Aminoethyl-4,5,6,7-tetrahydroindazole Dihydrochloride.—A solution of 0.3 g. of 1-acetyl-3β-acetylaminoethyl-4,5,6,7-tetrahydroindazole and 25 ml. of 2.5 *N* hydrochloric acid was heated under reflux for 3 hours. The solvent was removed by heating under reduced pressure, and the residue was recrystallized from an ethanol–ether mixture, m.p. 210°; λ_{max} 226 mμ, log ε 3.71.

Anal. Calcd. for $C_9H_{15}N_3\cdot 2HCl$: C, 45.38; H, 7.20; N, 17.64. Found: C, 45.13; H, 7.34; N, 17.36.

1-Acetyl-3β-acetylaminoethylindazole (XIII).—A mixture of 1 g. of 1-acetyl-3β-acetylaminoethyl-4,5,6,7-tetrahydroindazole, 1 g. of 5% palladium-on-carbon and 50 ml. of dry decalin was heated overnight under reflux. The catalyst was removed by filtration, and on cooling 250 mg. (25% yield) of XIII separated. It was recrystallized from ethyl acetate, m.p. 139–140°; λ_{max} 232 mμ (log ε 4.26), 302 (3.92).

Anal. Calcd. for $C_{13}H_{15}N_3O_2$: C, 63.66; H, 6.16; N, 17.13. Found: C, 63.57; H, 6.25; N, 17.10.

1-Acetyl-3β-acetylaminoethylindazole was also obtained by the reduction of 3-cyanomethylindazole (XVII) (see below) using Adams catalyst and acetic anhydride. The products prepared by the two procedures showed identical absorption in the infrared.

3β-Aminoethylindazole Dihydrochloride (II).—A solution of 0.5 g. (0.002 mole) of 1-acetyl-3β-acetylaminoethylindazole and 25 ml. of 2.5 *N* hydrochloric acid was heated under reflux for 4 hours. The solvent was removed by heating under reduced pressure, and the residue was dissolved in 25 ml. of ethyl alcohol. About 25 ml. of ethyl acetate followed by 50 ml. of ether was added, and 0.3 g. (64% yield) of 3β-aminoethylindazole hydrochloride was obtained, m.p. 200–205° dec. (capillary); λ_{max} 253 mμ (log ε 3.49), 299 (3.61); pK'_a 9.28 (66% dimethylformamide).

Anal. Calcd. for $C_9H_{11}N_3\cdot 2HCl$: C, 46.17; H, 5.60; N, 17.95. Found: C, 46.40; H, 5.85; N, 17.99.

The monopicrate of 3β-aminoethylindazole was recrystallized from water, m.p. 230°.

Anal. Calcd. for $C_{15}H_{14}N_6O_7$: N, 21.53. Found: N, 21.62.

3β-Isopropylaminoethylindazole.—A mixture of 1.6 g. (0.01 mole) of 3β-aminoethylindazole, 0.1 g. of Adams catalyst and 2 ml. of acetone in 25 ml. of ethyl alcohol was shaken overnight with hydrogen in a Parr shaker. The catalyst was removed by filtration, and the filtrate was treated with 2.3 g. of picric acid dissolved in 25 ml. of warm

ethyl alcohol. On cooling, 3 g. (70% yield) of the monopicrate separated. It was recrystallized from 95% ethyl alcohol, m.p. 193°.

Anal. Calcd. for $C_{18}H_{20}N_6O_7$: N, 19.44. Found: N, 19.22.

The picrate salt was shaken with a mixture of 25 ml. of nitrobenzene and 25 ml. of concentrated hydrochloric acid. The hydrochloric acid layer was separated and concentrated by heating under reduced pressure, and the residue was recrystallized from ethyl alcohol–ether, m.p. 195° (capillary); λ_{max} 286 mμ, log ε 3.74.

Anal. Calcd. for $C_{12}H_{17}N_3 \cdot 2HCl$: C, 52.18; H, 6.93; N, 15.21. Found: C, 51.98; H, 7.20; N, 15.37.

3-Chloromethylindazole (XVI).—A solution of 2.2 g. (0.015 mole) of 3-hydroxymethylindazole[1] (λ_{max} 253 mμ (log ε 3.58), 286 (3.69)) and 25 ml. of thionyl chloride was heated under reflux for 2 hours. The excess thionyl chloride was removed by heating under reduced pressure, and dry ether was added to the residue. The solid that resulted was collected and recrystallized from a thionyl chloride–ether mixture. The 3-chloromethylindazole hydrochloride weighed 1.5 g. (50% yield) and melted over a temperature range near 240°. When the salt was dried at 78° and 1 mm. pressure, hydrogen chloride was lost and 3-chloromethylindazole base was obtained, m.p. 110°.

Anal. Calcd. for $C_8H_7ClN_2$: C, 57.68; H, 4.24; N, 16.82. Found: C, 57.47; H, 4.36; N, 16.46.

3-Cyanomethylindazole (XVII).—To a solution of 50 g. of potassium cyanide and 50 ml. of water was added 20 g. (0.1 mole) of 3-chloromethylindazole hydrochloride dissolved in 500 ml. of ethyl alcohol. After stirring at room temperature for 8 hours the mixture was filtered, and the filtrate was concentrated by heating under reduced pressure. The residue was extracted with ether. After drying the ether was evaporated and a residue of crude 3-cyanomethylindazole remained. (This material was used in the preparation of 1-acetyl-3β-acetylaminoethylindazole given above.) The residue was distilled under reduced pressure, and about 5 g. (32% yield) of pure product was obtained, b.p. 220° (1 mm.). The product solidified on standing and was recrystallized from benzene–petroleum ether, m.p. 75°; λ_{max} 253 mμ (log ε 3.61), 2.91 (3.69).

Anal. Calcd. for $C_9H_7N_3$: C, 68.77; H, 4.49; N, 26.74. Found: C, 68.46; H, 4.44; N, 24.48.

α-Amino-β-(4,5,6,7-tetrahydroindazole-3)-propionic Acid (XIV).—To a stirred mixture of 6.6 g. (0.033 mole) of diethyl formylaminomalonate, 3.3 g. (0.06 mole) of sodium methylate and 50 ml. of ethyl alcohol, cooled to 10°, was added 6.2 g. (0.03 mole) of 3-chloromethyl-4,5,6,7-tetrahydroindazole hydrochloride dissolved in 50 ml. of ethyl alcohol. Following addition the mixture was stirred at room temperature for 6 hours and then allowed to stand overnight. The salt was removed by filtration, and the filtrate was concentrated to dryness. The residue was dissolved in 300 ml. of hot ethyl acetate. This solution was concentrated to 100 ml. After cooling 4 g. (36% yield) of ethyl α-carbethoxy-α-formylamino-β-(4,5,6,7-tetrahydroindazole-3)-propionate separated, m.p. 165–167°; λ_{max} 226 mμ, log ε 3.79.

Anal. Calcd. for $C_{16}H_{23}N_3O_5$: N, 12.46. Found: N, 12.58.

The ethyl α-carbethoxy-α-formylamino-β-(4,5,6,7-tetrahydroindazole-3)-propionate was heated overnight on the steam-bath with 50 ml. of concentrated hydrochloric acid. After removing the acid by heating under reduced pressure the residue that remained was dissolved in 50 ml. of ethyl alcohol, and 1 ml. of aniline was added. The α-amino-β-(4,5,6,7-tetrahydroindazole-3)-propionic acid that separated was collected and recrystallized from water, m.p. 270–272° dec.; λ_{max} 226 mμ, log ε 3.73. The over-all yield was about 30%.

Anal. Calcd. for $C_{10}H_{15}N_3O_2$: C, 57.40; H, 7.23; N, 20.08. Found: C, 57.00; H, 7.25; N, 20.13.

INDIANAPOLIS 6, INDIANA

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

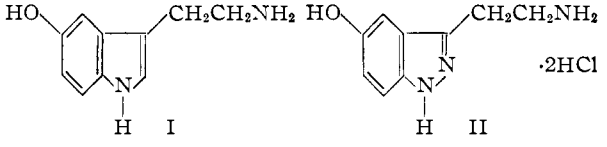
The Indazole Analog of Serotonin

BY C. AINSWORTH

RECEIVED MAY 31, 1957

The preparation of 3β-aminoethyl-5-hydroxyindazole dihydrochloride (II) together with some preliminary pharmacological findings is described.

Serotonin (5-hydroxytryptamine, I) has been examined in some detail as a physiological agent,[1,2] and indications are that it will continue to attract further investigation.[3] A number of indole derivatives have been synthesized[4] and found to possess varying degrees of serotonin and antiserotonin action in pharmacological tests. In this Laboratory we have been interested for some time in tryptamine compounds and recently have reported[5] the indazole analog of tryptamine. The present paper describes the synthesis of compound II, which is the indazole analog of serotonin.



(1) I. H. Page, *Physiol. Rev.*, **34**, 563 (1954).

(2) V. Erspamer, *Pharmacol. Rev.*, **6**, 425 (1954).

(3) I. H. Page and J. W. McCubbin, *Circulation*, **14**, 161 (1956), entitled their editorial "Serotonin or Tenure for the Pharmacologist."

(4) For a leading reference see E. Shaw, THIS JOURNAL, **77**, 4319 (1955).

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

The method of preparation of compound II is illustrated by the following series of reactions where R is benzyl. The ring-closure step involving the conversion of compound IV to VI is analogous to the reaction reported by Fischer and Tafel[6] for the preparation of 3-indazoleacetic acid from sodium 2-(2-carboxyvinyl)-phenylazosulfonate.

5-Benzyloxy-2-nitrobenzaldehyde was prepared according to the procedure reported by Ek and Witkop.[7] It was converted to the corresponding nitrocinnamic acid by the standard malonic acid method, and this was reduced with ferrous hydroxide to give 2-amino-5-benzyloxycinnamic acid. The amine was diazotized, and the resulting salt III was treated with sodium sulfite to form compound IV. The azo compound IV was warmed with dilute hydrochloric acid, and the indazole VI was formed in good yield. Compound V is proposed as an intermediate in the formation of compound VI from IV. It has the feature of being in the same oxidation state as compound VI.

(6) E. Fischer and J. Tafel, *Ann.*, **227**, 303 (1885).

(7) A. Ek and B. Witkop, THIS JOURNAL, **76**, 5579 (1954), footnote 44a.