drogenation was complete in less than 1 hr. The filtered solution was evaporated to a thick resin which was taken up in water, treated with alkali and extracted into ether. The dried ether extract was concentrated to a crystalline residue. Recrystallization from aqueous ethanol and then from benzene–Skellysolve B afforded 2.55 g. (56% yield) of XXI, m.p. 118–120°.

Anal. Calcd. for $C_{14}H_{18}N_2$: N (basic), 6.54. Found: N (basic), 6.24.

XXI hydrochloride showed m.p. 204–206° dec. after recrystallization from ethanol–ether.

Anal. Calcd. for $C_{14}H_{19}ClN_2$: C, 67.05; H, 7.64. Found: C, 66.89; H, 7.27.

C. **4-(2-Indolyl)-1-methylpiperidine (XXII).**—Similarly, 18.8 g. of XX methobromide was hydrogenated to yield, after recrystallization from ethanol, 9.2 g. (67%) of XXII in the form of colorless prisms, m.p. 183–187°.

Anal. Calcd. for $C_{14}H_{18}N_2$: N (basic), 6.54. Found: N (basic), 6.57.

XII hydrochloride formed glistening plates from aqueous methanol–acetone, m.p. 259–260° dec.

Anal. Calcd. for $C_{14}H_{19}ClN_2$: C, 67.05; H, 7.64; Cl, 14.14. Found: C, 66.85; H, 7.73; Cl (ionic), 13.89.

Condensation of Indoles with Pyridinecarboxaldehydes.—These reactions were carried out in acetic acid at room temperature. The products were relatively unstable, rapidly oxidizing in air to highly colored materials and were stored under nitrogen.

A. **4-(3,3′-Diindolylmethyl)-pyridine (XIII).**—To a solution of 32.1 g. (0.3 mole) of 4-pyridinecarboxaldehyde in 150 ml. of glacial acetic acid, cooled in an ice-bath, was added 70.2 g. (0.6 mole) of indole. The mixture was allowed to warm to room temperature. As the indole dissolved, a moderately exothermic reaction took place, and the resultant solution developed a deep purple color. After standing for 18 hr., the solution was diluted with aqueous hydrochloric acid to precipitate a purple hydrochloride salt which was recrystallized from ethanol–ether. Addition of aqueous alkali to an ethanol solution of the hydrochloride precipitated the base. This was crystallized from benzene–ethanol with the addition of Skellysolve B to provide 73 g. (75% yield) of yellow-orange crystals of XIII, m.p. 152–155° dec.

B. **4-[Bis-(1-methyl-3-indolyl)-methyl]-pyridine (XIV).**—Some heat was evolved on dissolving 5.0 g. (0.047 mole) of 4-pyridinecarboxaldehyde and 12.2 g. (0.094 mole) of 1-methylindole in 50 ml. of glacial acetic acid at room temperature. After standing for 21 hr. the deep purple solution was worked up as described above. The isolated base was recrystallized from benzene–Skellysolve B, affording 8.9 g. (54% yield) of flesh-colored crystals of XIV, m.p. 186–188° dec.

DECATUR, ILLINOIS

[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

Some Chlorinated 4-Indanols: Preparation and Proof of Structures[1]

BY J. S. BUCK,[2] R. A. CUTLER, F. C. NACHOD, R. G. POWLES, R. RAKOCZY, T. J. SLAUSON AND B. F. TULLAR

RECEIVED FEBRUARY 2, 1957

Chlorination of 4-indanol with sulfuryl chloride yields 5-chloro-4-indanol and 7-chloro-4-indanol. The structure assignment has been carried out by analysis of the infrared spectra as well as by unambiguous synthesis. It is shown that the OH stretching frequencies of the two isomeric chloro-4-indanols coincide with the corresponding frequencies of *o*-chloro- and *p*-chlorophenol. Chemical structure proof starts with *p*-chlorophenyl β-chloropropionate which rearranges with $AlCl_3$ to 5,β-dichloro-2-hydroxypropiophenone which in turn cyclizes to form 4-chloro-7-hydroxy-1-hydrindone. The latter compound is reduced with Zn in HCl to the corresponding 7-chloro-4-indanol.

The recent availability of 4-indanol[3] (I) from the coal hydrogenation process prompted us to investigate some of its chlorinated derivatives as potential antiseptic agents. The reaction of one equivalent of sulfuryl chloride on 4-indanol yielded a mixture from which two white crystalline products were isolated. The more abundant of the two melted at 91.0–93.7° and was assumed to be 7-chloro-4-indanol (III). This assumption was later proved correct by infrared studies and by synthesis by another route as outlined below (V → VI → VII → III). From the filtrates of the chlorination mixture there was obtained a smaller amount of a substance melting at 70.4–73.1° which appeared to be 5-chloro-4-indanol (II). Actual proof of this structure was supplied by infrared spectral analyses.

The reaction of 4-indanol (I) with two equivalents of sulfuryl chloride yielded a mixture from which a solid was isolated melting at 54.5–56.8°. That this product was indeed 5,7-dichloro-4-indanol (IV) was proved by showing that treatment of either 5-chloro- (II) or 7-chloro-4-indanol (III) with sulfuryl chloride yielded this same material.

(1) Presented before the Division of Organic Chemistry at the 131st meeting of the American Chemical Society, Miami, Fla., April, 1957.

(2) Deceased.

(3) Samples of 4-indanol were kindly supplied by Carbide and Carbon Chemicals Co.

Physicochemical Data.—The spectra of the two isomeric chloroindanols (II and III) and the unchlorinated starting material I in CS_2 solution are sufficiently different to permit differential assays. The 7-chloro-4-indanol (III) has a strong band at 12.35 μ while the 5-chloro analog II does not absorb in this region, which is used to estimate the former compound. In the 9.5 to 10.5 μ region both compounds show doublets, the 7-chloro-4-indanol absorbing at 9.98 and 10.11 μ and the 5-chloro-4-indanol at 9.98 and 10.05 μ. The intensity of the first and second maximum are reversed with respect to the pair. Distortion (in the case of 0.4 to 0.6 mole fraction of the 7-chloro compound) or peak ratio assays (in the case of 0.8 to 1.0 mole fraction of the 7-chloro compound) establish their relative concentration. Unchlorinated starting material shows a doublet at 12.97 and 13.12 μ where neither of the monochloro derivatives absorbs.

Structure Assignment of 5- and 7-Chloro-4-indanol *via* Infrared Spectra.—The two isomeric indanols can be compared with *o*- and *p*-chlorophenol with respect to the geometry of their substituents. The trimethylene bridge of the indanol should not influence the position of the OH stretching frequency to any extent just as it would not exert any marked effect upon the dipole moment of the molecules. Dipole–dipole interaction, *viz.*,

mixed (Cl···H–O) hydrogen bonding, should reduce the OH frequency for 5-chloro-4-indanol as it does for *o*-chlorophenol. The OH absorption maxima found were identical for the respective pairs of chlorophenol and chloroindanol; *p*-chlorophenol and 7-chloro-4-indanol in CS_2 solution absorb sharply at 2.786 μ while *o*-chlorophenol and 5-chloro-4-indanol under the same conditions absorb sharply at 2.823 μ. The damping of the OH frequency does indeed shift the absorption maximum to a longer wave length as postulated.

Acknowledgments.—The authors are indebted to Messrs. M. E. Auerbach and K. D. Fleischer and staff for the microanalyses and to Miss C. M. Martini and Mrs. M. Becker for assistance in the spectroscopical aspects of the work.

Experimental[4]

4-Chloro-7-indanol (III). Method A.—To a stirred solution of 194 g. (1.45 moles) of 4-indanol[5] and a small crystal of iodine in 100 ml. of glacial acetic acid was added 123 ml. (1.52 moles) of sulfuryl chloride over a period of ten minutes. External cooling was applied to keep the temperature below 55°. After an additional hour of stirring, the yellowish-orange solution was poured onto ice and made neutral to litmus with 35% sodium hydroxide solution. The solid which separated amounted to 230 g. (1.37 moles) (95%) and melted at 50–65°. Two recrystallizations from hexane, including treatment with charcoal in the first, gave 115 g. (47%) of white needles, m.p. 91.0–93.7°.

Anal. Calcd. for C_9H_9ClO: C, 64.10; H, 5.38; Cl, 21.03. Found: C, 64.59; H, 5.35; Cl, 20.90.

Method B (Chlorination without Solvent).—In a flask equipped with stirrer, thermometer, dropping funnel and gas vent, 469 g. (3.5 moles) of 4-indanol was melted by warming to 60°. After addition of a small crystal of iodine, 340 ml. (560 g., 4.2 moles) of sulfuryl chloride was added dropwise within 10 min. After an initial temperature surge to 75° the rate was such that it reached a level of about 65°. After complete addition, stirring and heating (70–75°) were continued for 1 hr. At that point 1.5 liters of water was added and heating and stirring (70–75°) were continued for an additional half hour. Slow cooling to 40° produced solidification of the mixture, and the product was filtered at room temperature and washed with cold water. Drying in a vacuum oven overnight yielded 583 g. of crude product (99%).

Infrared analyses (*vide infra*) indicated 88% of 7-chloro-4-indanol (III), 11% of 5-chloro-4-indanol (II) and 1% of unreacted starting material I. Recrystallization of this mixture from hexane gave a 75%[6] yield of 7-chloro-4-indanol, m.p. 90–92° (uncor.).

Isolation of 5-Chloro-4-indanol (II).—The solvent was removed by distillation from the hexane filtrates remaining after the purification of the 7-chloro-4-indanol (method A) to give 85 g. of dark oil. The latter was distilled at 2.5 mm. and four fractions of colorless oil collected. Crystallization of the first two fractions [b.p. range of 72–101° (uncor.)] from hexane yielded 12 g. of 5-chloro-4-indanol which melted at 70.4–73.1° after an additional recrystallization from hexane.

Anal. Calcd. for C_9H_9ClO: C, 64.10; H, 5.38; Cl, 21.03. Found: C, 64.02; H, 5.58; Cl, 20.75.

Crystallization of the third and fourth fractions from hexane gave additional amounts of 7-chloro-4-indanol.

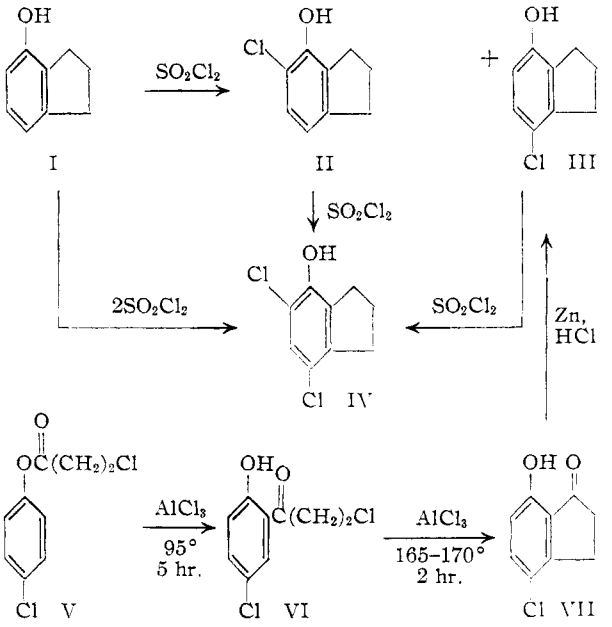
5,7-Dichloro-4-indanol (IV).—A stirred solution consisting of 40.5 g. (0.3 mole) of 4-indanol and a small crystal of iodine dissolved in 100 ml. of acetic acid was treated with 52 ml. (0.64 mole) of sulfuryl chloride and worked up similar to Method A above. A crude yield of 62 g. of low melting solid was obtained which gave 23 g. of pure 5,7-dichloro-4-indanol after two recrystallizations from pentane; m.p. 54.5–56.8°.

Anal. Calcd. for $C_9H_8Cl_2O$: Cl, 34.92; neut. equiv., 203.06. Found: Cl, 34.60; neut. equiv., 201.8.

The same product was obtained by the action of sulfuryl chloride on an acetic acid solution of either 7-chloro-4-indanol (III) or 5-chloro-4-indanol (II) according to the procedure outlined in Method A.

Chemical Proof of Structure of 7-Chloro-4-indanol (III).[7] ***p*-Chlorophenyl *β*-Chloropropionate (V).**—Molten *p*-chlorophenol was stirred and treated dropwise with an equimolecular amount of *β*-chloropropionyl chloride. After the addition was complete, the reaction mixture was allowed to stir for 3 hr. at room temperature and then heated for 1 hr. on a steam-bath. Distillation of the resulting oil gave a 90% yield of the desired product boiling at 152–156° (uncor.) at 11 mm., $n^{25}D$ 1.5306.

Anal. Calcd. for $C_9H_8Cl_2O_2$: Cl, 32.38. Found: Cl, 32.4.



4-Chloro-7-hydroxy-1-indanone (VII).[8]—A mixture of 150 g. (0.69 mole) of chlorophenyl *β*-chloropropionate with 350 g. of anhydrous aluminum chloride was heated 5 hr. at 95° and then 1 hr. at 160–170°. The mixture was quenched with ice and water. The product which separated was collected on a filter and washed well with water. Recrystallization from isopropyl alcohol, including treatment with charcoal, gave 45 g. (0.246 mole) (35.7%) of 4-chloro-7-hydroxy-1-indanone, m.p. 118–122° (uncor.).[9] By increasing the heating time at 165–170° to 2 hr., the yield of crude indanone (VII) was raised to 70% and none of the intermediate VI was recovered.

After recrystallization from ethyl acetate pure 4-chloro-

(4) All melting points are corrected unless otherwise specified.

(5) M.p. 45–47°.

(6) The increased yield over that of Method A is due mainly to the excess of sulfuryl chloride (20% employed.) When the reaction was run with no solvent and only a 5% excess of chlorinating agent was used, the yield was comparable to that obtained in Method A. Infrared analyses of the resulting crude product indicated that about 5% of it consisted of unchlorinated 4-indanol (I).

(7) The over-all procedure employed in this structure proof is similar to that used by R. A. Barnes, E. R. Kraft and L. Gordon, THIS JOURNAL, **71**, 3523 (1949), for the preparation of 7-bromo-4-indanol.

(8) F. Mayer, H. Phillipps, F. W. Ruppert and A. T. Schmitt, *Ber.*, **61B**, 1966 (1928), prepared this same compound (m.p. 122°) by the action of $AlCl_3$ on *β*-(2-chloro-5-methoxyphenyl)-propionyl chloride.

(9) From the liquors 30 g. of somewhat impure 5,*β*-dichloro-2-hydroxypropiophenone (VI) was recovered; m.p. 75–78° (uncor.). A 96% yield of this same compound was obtained by heating the *p*-chlorophenyl *β*-chloropropionate with one and one half times its weight of $AlCl_3$ at 120° for 20 minutes. After quenching in ice and two recrystallizations of the resulting solid from hexane the pure rearranged product VI was obtained as coarse white crystals; m.p. 89.8–90.6°. *Anal.* Calcd. for $C_9H_8Cl_2O_2$: C, 49.36; H, 3.68; Cl, 32.38. Found: C, 49.67; H, 4.17; Cl, 32.4.

7-hydroxy-1-indanone (VII) was obtained, m.p. 119.7–121.4°.

Anal. Calcd. for $C_9H_7ClO_2$: C, 59.20; H, 3.86; Cl, 19.42. Found: C, 59.16; H, 3.99; Cl, 19.50.

7-Chloro-4-indanol (III from VII).—A mixture of 450 g. (0.247 mole) of 4-chloro-7-hydroxy-1-indanone in 2 liters of toluene with 2 liters of acetic acid and 1500 g. of freshly amalgamated zinc (10 mesh) was heated with strong mechanical stirring under reflux at 90°, and 5 liters of hydrochloric acid was added during 4 hr. The heating and stirring were continued another 4 hr. with occasional additions of hydrochloric acid to a total of 7 liters.

The mixture was cooled and separated from undissolved zinc. The water layer was separated and washed with one liter of toluene. The combined toluene extracts were concentrated *in vacuo*. The residue was crystallized from 1 liter of "Skellysolve C" after decolorizing with charcoal yielding a 300 g. first crop of 7-chloro-4-indanole, m.p. 90–92°. By concentration and cooling and recrystallization a second crop of 35 g. was collected melting at the same point; total yield 335 g. (81%).

After recrystallization from 1.5 liters of ethylene dichloride, 310 g. of pure 7-chloro-4-indanol (II) was obtained, m.p. 91.2–92.8°.

Anal. Calcd. for C_9H_9ClO: Cl, 21.03. Found: Cl, 21.0.

A mixture melting point with the original sample of 7-chloro-4-indanol prepared by Method A was not depressed.

RENSSELAER, N. Y.

[CONTRIBUTION FROM THE LABORATORIES OF THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH]

Indole Carboxamidines and Aminomethylindoles as Antimetabolites of Serotonin

BY E. SHAW AND D. W. WOOLLEY[1]

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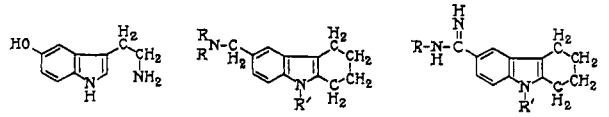
A number of antimetabolites of serotonin have been synthesized and studied in both isolated smooth muscles and in normal animals. These compounds were 1,2,3,4-tetrahydrocarbazoles (dialkylindoles) with $-CH_2-NR_2$ or $-C(=NR)-NH_2$ in the 6-position. Some had a benzyl group attached to the indole nitrogen as well. Methods for the synthesis of these compounds are described.

The early studies of the structural changes necessary to convert the hormone serotonin (I) into a specific antimetabolite of it had shown that one good way was to move the amino group from its position in the side chain of the hormone to position 5 in the indole nucleus.[2,3] The 5-amino-indoles, with alkyl groups in positions 3 (or 2 and 3) were active antiserotonins. However, they possessed the disadvantage that they were destroyed readily in living mammals. This defect apparently resided in the fact that they were substituted *p*-phenylenediamines which are liable to attack by some of the cytochrome-containing enzyme systems.[4] Since a basic group seemed to be needed somewhere in the molecule to confer high activity, the idea arose that the amino group of the aminoindoles might be protected from enzymic attack by placing a carbon atom between it and the indole nucleus. To test this postulate some 5-indolecarboxamidines and some 5-aminomethylindoles were synthesized and examined biologically for antiserotonin activity. These compounds contained either a $-C(=NH)-$ or a $-CH_2-$ between the basic nitrogen and the indole ring. For convenience in the practical syntheses, the alkyl groups in positions 2 and 3 were incorporated into a ring so that all of the compounds were 1,2,3,4-tetrahydrocarbazoles (II and III). Some of them proved to be relatively potent antimetabolites which were effective even in whole animals. Previous work had shown[5] that this was a rather rare property among antagonists of this hormone. The majority of existing antiserotonins were only effective on isolated tissues.



I II III

Experimental Part[6]

1,2,3,4-Tetrahydrocarbazole-6-carboxamide.—*p*-Aminobenzamide (7.0 g.) dissolved in water (55 ml.) and concentrated hydrochloric acid (20 ml.), was diazotized at −5° with sodium nitrite solution (3.5 g. in 25 ml. water). The filtered diazonium solution was poured into a cold solution of stannous chloride dihydrate (25 g.) in concentrated hydrochloric acid (25 ml.). After 15 minutes the tin complex was collected by suction filtration and converted to the hydrazine by treatment of a cold suspension in water (50 ml.) with 40% aqueous sodium hydroxide (20 ml.). *p*-Hydrazinobenzamide so obtained was combined with cyclohexanone in aqueous acetic acid in the usual manner. The crude hydrazone was refluxed in concentrated hydrochloric acid (20 ml. per g.) for 30 minutes. The resultant oil was dissolved in ethyl acetate which was washed with dilute alkali, dried and concentrated. The product crystallized in a yield of 45% (for the cyclization step) and had m.p. 217–219°.

Anal. Calcd. for $C_{13}H_{14}N_2O$: C, 72.89; H, 6.59; N, 13.08. Found: C, 73.41; H, 6.41; N, 12.83.

The intermediate hydrazine and hydrazone were too unstable to purify profitably.

1,2,3,4-Tetrahydrocarbazole-6-carboxhydrazide.—1,2,3,4-Tetrahydrocarbazole-6-carboxylic acid[7] was converted to the ethyl ester when refluxed for six hours with ten volumes of 2 *N* ethanolic hydrogen chloride. After recrystallization from ethanol, a 75% yield of ester, m.p. 117–119°, was obtained.

The ethyl ester (11.4 g.) was then refluxed in absolute alcohol (85 ml.) and 100% hydrazine hydrate (56 ml.) for 21 hours. The solution was concentrated in an air stream until crystals appeared; water was added and the product was filtered, washed with 50% aqueous alcohol and desiccated *in vacuo*. The material so obtained, 10.0 g. (93%), m.p. 197–199°, was used in the next step. An analytical sample crystallized from ethanol had m.p. 201–203°.

(1) With the technical assistance of C. Carter, G. Schaffner and E. Van Winkle.

(2) D. W. Woolley and E. Shaw, THIS JOURNAL, **74**, 2948 (1952).

(3) D. W. Woolley and E. Shaw, *J. Biol. Chem.*, **203**, 69 (1953).

(4) D. W. Woolley and E. Shaw, *J. Pharmacol. Exper. Therap.*, **108**, 87 (1953).

(5) E. Shaw and D. W. Woolley, *ibid.*, **116**, 164 (1956).

(6) M.p.'s are uncorrected. Analyses were performed by S. Theodore Bella.

(7) W. M. Collar and S. G. P. Plant, *J. Chem. Soc.*, 808 (1926).