place before closure of compound XIa upon heating with this acid. It is also possible that XIa contained a very small amount (about 1%) of a second tetrahydroxy compound which gives *dl*-asarinin.

Closure of Compounds XIc and XId.—Ring closure of XIc with the hydrochloric acid as described above, followed by chromatography of the product, yielded 68% of *dl*-sesamin and a minute amount of *dl*-asarinin. Similar treatment of XId gave a 61% yield of *dl*-sesamin and 11% of *dl*-asarinin. It is possible that XId, admittedly not pure, contained some of the tetrahydroxy compound which closes to *dl*-asarinin.

Because XIc and XId both gave mainly *dl*-sesamin upon closure, it is believed that they are polymorphic forms of XIa. Nujol mulls of XIc and XId gave infrared curves different from that of a mull of XIa. To determine whether these compounds are polymorphs, we determined their infrared absorption spectra in solution. The compounds were not soluble in non-polar solvents commonly employed in infrared work; hence spectra of their solutions in dimethylformamide between 9.5 and 15 μ were determined. In the curves of XIa, XIc and XId we could detect no differences; however, the curve for XIb in this solvent was also similar, so that the infrared studies did not conclusively prove or disprove that XIa, XIc and XId are polymorphic.[27]

Seeding experiments seemed to confirm that XId was polymorphic with XIa. For instance, XId (m.p. 199–200°) dissolved in pyridine–ether was seeded with XIa (m.p. 180–181°), but the crystals that deposited still melted at 199°. When XIa dissolved in pyridine–ether was seeded with XId, the crystalline product melted unsharply at about 195°. Not enough XIc remained to run similar experiments with it.

Closure of Compound XIb (from **Xb**).—Compound XIb (500 mg.) was treated with 5 ml. of 1% ethanolic hydrochloric acid as described for XIa. The product was chromatographed in the same manner with increasing concentrations of ethyl acetate in isoöctane. No substance was eluted until a zone (70 mg.) was removed with 10% ethyl acetate. Another zone (61 mg.) was eluted with 20% ethyl acetate. These fractions could not be crystallized or otherwise characterized. The column was then sectioned, and a fraction eluted from the center section crystallized after several weeks, m.p. 119.5–120° (XII) after recrystallization from benzene. In subsequent experiments it was possible to obtain the same compound directly after closure with the ethanolic hydrochloric acid as follows: The reaction mixture was neutralized with ammonia, water was added and the liquid was extracted several times with chloroform. The solution was dried over sodium sulfate, the chloroform evaporated and the residue taken up in hot benzene. On cooling, the solution was seeded and the compound crystallized out in 50% yield. Recrystallization from benzene gave the pure product XII. From its analysis only one molecule of water had been eliminated from XIb, therefore the compound probably has only one tetrahydrofuran ring.

Anal. Calcd. for $C_{20}H_{20}O_7$: C, 64.7; H, 5.40. Found: C, 64.65; H, 5.54; active hydrogen atoms (Zerewitinoff) per mole found, 2.03.

The acetate and benzoate of XII were not crystalline.

Oxidation of Compound XII.—To a solution of 20 mg. of compound XII in 4 ml. of acetone was added 120 mg. of potassium permanganate. After refluxing for two hours, water plus a few drops of 30% hydrogen peroxide were added to the cooled mixture. The manganese dioxide was filtered off and washed with hot water. The filtrate was made definitely alkaline with potassium hydroxide solution, washed three times with chloroform and the washings were discarded. The aqueous layer was acidified with hydrochloric acid and extracted three times with chloroform. The chloroform solution was dried and evaporated and the residue was crystallized from a hot water–alcohol solution. The product was filtered and dried, yield 4 mg. (22%), m.p. 226–228°, undepressed in admixture with an authentic sample of piperonylic acid.

Sesamin (20 mg.) was oxidized as described above and a negligible amount of impure product (0.2 mg.) was obtained.

Closure of Gums G-1 and G-2.—Similar closure of gum G-1 with 1% ethanolic hydrochloric acid followed by chromatography of the product gave a very small amount of sesamin along with gummy or oily fractions which we were unable to characterize. Similar treatment of gum G-2 likewise yielded compound XII (25%) plus small amounts of oily or gummy materials not readily characterized.

Acknowledgments.—We gratefully acknowledge the help of J. Carol and M. Dolinsky of the Food and Drug Administration in obtaining the infrared spectra. We are also indebted to E. F. Pratt of the University of Maryland and J. L. Hartwell of the National Institutes of Health for helpful discussions on this problem.

BELTSVILLE, MARYLAND

(27) Many of the infrared absorption peaks obtained in mulls or in non-polar solvents become weak or absent in dimethylformamide. (Communication from M. Dolinsky, U. S. Food and Drug Administration.)

[CONTRIBUTION FROM THE MOORE LABORATORY OF CHEMISTRY, AMHERST COLLEGE]

7-Azaindole. III. Syntheses of 7-Aza Analogs of Some Biologically Significant Indole Derivatives[1]

BY MICHAEL M. ROBISON AND BONNIE L. ROBISON

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A number of 3-substituted 7-azaindoles have been prepared for the purposes of testing their biological activities and comparing further the chemical reactivities of 7-azaindole and indole. Compounds synthesized include 7-azaindole-3-acetic acid, β-(7-aza-3-indolyl)-propionic acid, 7-azaindole-3-carboxylic acid and 7-azatryptamine, as well as certain of their derivatives. The bromination of 7-azaindole and its coupling reaction with benzenediazonium chloride also were studied.

7-Azagramine serves,[2] as does gramine itself,[3] to alkylate acetamidomalonic ester. Hydrolysis and decarboxylation of the resulting aza compound results in the formation of 7-azatryptophan[2] which has been found to be a fairly effective tryptophan inhibitor in *Tetrahymena pyriformis*.[4] It was therefore considered of interest to extend the transformations of 7-azaindole to other preparations of aza analogs of biologically significant indole compounds. A corollary aim of these endeavors was further to investigate the chemistry of the ring system, which is in many ways similar to that of in-

(1) This investigation was supported in part by a research grant, number C-2574, from the National Cancer Institute of the National Institutes of Health, Public Health Service.

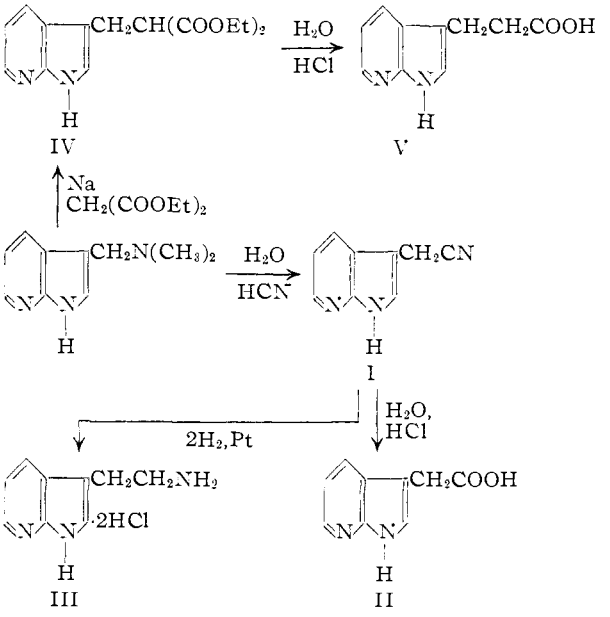
(2) M. M. Robison and B. L. Robison, THIS JOURNAL, **77**, 457 (1955).

(3) E. E. Howe, A. J. Zambito, H. R. Snyder and M. Tishler, *ibid.*, **67**, 38 (1945).

(4) G. W. Kidder and V. C. Dewey, *Biochim. et Biophys. Acta*, **17**, 288 (1955).

dole,[2] but which in some respects more closely resembles that of 2-aminopyridine.[5]

The properties of indole-3-acetic acid (heteroauxin) as a plant-growth hormone make desirable the study of analogs for possible inhibitory action. Of the variety of syntheses available for this compound, in the indole series the method of choice is the reaction of gramine with aqueous alcoholic sodium cyanide.[6] From 7-azagramine only resinous materials were obtained when the reaction was attempted under these conditions. It was found, however, that prolonged refluxing of the Mannich base with aqueous hydrogen cyanide produces respectable yields of 7-azaindole-3-acetonitrile (I). Since the azaindole ring is stable to acid,[2,7] the auxin analog II could be produced in high yield by hydrolysis of the nitrile in concentrated hydrochloric acid.



Compounds related to tryptamine and serotonin are of interest because of their possible effectiveness in the regulation of the blood pressure or in the study or treatment of certain mental disorders.[8] Accordingly, the preparation of 7-azatryptamine (III) was deemed desirable. This was readily accomplished by hydrogenation of the nitrile I at atmospheric temperature and pressure in the presence of Adams catalyst and hydrochloric acid, the product being isolated as the dihydrochloride.

β-(3-Indolyl)-propionic acid is also a plant hormone,[9] though less active than the acetic acid. Its aza analog V was synthesized by hydrolysis and decarboxylation of ethyl α-carbethoxy-β-(7-aza-3-indolyl)-propionate (IV), the latter being obtained on alkylation of malonic ester with 7-azagramine by methods developed in the indole series.[10]

(5) M. M. Robison and B. L. Robison, THIS JOURNAL, **77**, 6554 (1955).

(6) H. R. Snyder and F. J. Pilgrim, *ibid.*, **70**, 3770 (1948).

(7) O. Kruber, *Ber.*, **76**, 128 (1943).

(8) See E. Shaw, THIS JOURNAL, **77**, 4319 (1955), for leading references.

(9) R. H. F. Manske and L. C. Leitch, *Can. J. Research*, **14B**, 1 (1936).

(10) H. R. Snyder, C. W. Smith and J. M. Stewart, THIS JOURNAL, **66**, 200 (1944).

It has been found that β-(7-aza-3-indolyl)-propionic acid serves as an effective inhibitor of the growth of both normal and crown-gall tissue in *Parthenocissus*.[11] Detailed results will be reported elsewhere.

An uncompleted series of syntheses directed toward preparation of the tryptamine and acetic acid involved alkylation of nitromalonic ester with 7-azagramine. The ethyl α-nitro-α-carbethoxy-β-(7-aza-3-indolyl)-propionate was subjected to a few attempted reactions with aqueous base and with acetic acid–hydrochloric acid for the purpose of preparing 3-(β-nitroethyl)-7-azaindole, but these experiments were discontinued when the desired derivatives were obtained by the cyanide method.

Kruber[7] prepared a carboxylic acid derivative of 7-azaindole by treatment of the base with sodium and subsequent carbonation and proposed the structure 7-azaindole-3-carboxylic acid for the product. Since 7-azaindole-3-carboxaldehyde and other derivatives are available in which it has been demonstrated that the substituent groups are attached to the 3-position,[2] it was of interest to prepare the 3-carboxylic acid by an unequivocal synthesis for comparison with Kruber's product. This was done by three different routes. In the first experiments 7-azaindole-3-carboxaldehyde was converted to its oxime, which was dehydrated by acetic anhydride. Hydrolysis of the 1-acetyl-3-cyano-7-azaindole produced an acidic material which melted with decomposition about 10° higher than Kruber's compound and whose carbon–hydrogen analysis corresponded to that of the hemihydrate of the desired acid. It was considered possible at the time that the hydrolysis in strong aqueous acid had promoted some condensation or decomposition reaction and, accordingly, other preparative methods were sought. The nitrile was thus subjected to an ethanolysis reaction with ethanolic hydrogen chloride and the resulting 3-carbethoxy-7-azaindole on saponification in base yielded a product identical with that from the acid hydrolysis. Finally, the same material was obtained by the direct oxidation of 7-azaindole-3-carboxaldehyde with alkaline potassium permanganate. A repetition of Kruber's preparation provided material whose physical properties were identical with those of the products obtained from the other experiments. All of the samples on heating above their melting point produced 7-azaindole by decarboxylation.

Chlorine and bromine react vigorously with indole[12] and the extensive decomposition which results makes the direct halogenation of the unprotected ring impractical. 7-Azaindole, on the other hand, reacts readily with bromine in carbon tetrachloride to produce a monobromo derivative in high yield. By analogy to the course taken by other electrophilic substitutions, such as the Mannich reaction, in this series, the product is presumably 3-bromo-7-azaindole. The ultraviolet spectrum of the substance is also consistent with this structure, though such evidence is by no means conclusive. In chemical properties the halogen de-

(11) We wish to thank Drs. Henry T. Yost and Hope Robson of the Biological Laboratory, Amherst College, for performing these experiments.

(12) R. Weissgerber, *Ber.*, **46**, 651 (1913).

rivative resembles the supposed 3-bromoindole,[12] which has been prepared by bromination of N-benzoylindole. The aza analog is also unreactive toward nucleophilic reagents, such as sodium iodide in acetone, but does form a precipitate with alcoholic silver nitrate. No evidence of rearrangement to 7-azaoxindole was observed on warming the bromo derivative with dilute hydrochloric acid, however, though an analogous rearrangement is reported to take place with the des-aza compound.[12]

Indole undergoes a coupling reaction with benzenediazonium chloride in mild alkali to form a product substituted in the 3-position.[13] In a single experiment a similar product was isolated from a coupling reaction with 7-azaindole, though in low yield. It was not further investigated.

It may be noted that as in the indazole or (in the case of the aldehyde) the indole series, 3-substituted 7-azaindoles in which the carbon attached to the 3-position is also multiply bonded to oxygen or nitrogen are weak acids and are soluble in sodium hydroxide solution. This situation obtains, of course, only when the pyrrole nitrogen is unsubstituted, and is presumably due to the increased resonance possibilities in the anion.

Experimental[14,15]

7-Azaindole-3-acetonitrile (I).—To a mixture of 5.25 g. of 7-azagramine, 7.38 g. of sodium cyanide and 750 ml. of water was added 12.5 ml. of concentrated hydrochloric acid and the reaction mixture was refluxed under an efficient condenser for a period of 64 hours. After cooling, 25 g. of potassium carbonate was added to the liquid and it was chilled. The resulting light-tan solid was removed by filtration and dried, yield 2.30 g. (48.8%), m.p. 136–138°. The analytical sample was purified by recrystallizations from 1:1 benzene–cyclohexane and 1:9 ethanol–water; white crystals, m.p. 141.0–142.0°.

Anal. Calcd. for $C_9H_7N_3$: C, 68.77; H, 4.50; N, 26.73. Found: C, 68.50; H, 4.48; N, 26.99, 26.97.

In a number of other experiments in which the molar proportion of HCN was one-half that above and in which the reaction time was varied, either the yield or purity of the product was lower.

7-Azaindole-3-acetic Acid (II).—To 10 ml. of concentrated hydrochloric acid was added 785 mg. of the nitrile I and the solution was refluxed for 6 hours. The colorless liquid was evaporated to dryness, the residue was dissolved in a few milliliters of water and excess solid sodium bicarbonate was added. After a small quantity of insoluble material had been separated by filtration, the filtrate was acidified with excess acetic acid and chilled and the white product was separated by filtration and dried; weight 785 mg. (89.2%), m.p. 213–214° dec. The analytical sample was recrystallized from 1:1 ethanol–water; m.p. 214.5–215.0° dec.

Anal. Calcd. for $C_9H_8N_2O_2$: C, 61.35; H, 4.59; N, 15.90. Found: C, 61.61; H, 4.78; N, 15.98.

When a sample of the acid was heated for approximately 35 minutes at 240–250°, much tarry material was formed along with a small sublimate of 7-azaskatole.[2] After one recrystallization from cyclohexane this melted at 126.0–129.0° alone and at 128.0–130.5° on admixture with authentic 7-azaskatole, m.p. 131.5–133.0°. The samples of the compound from the two different sources also had the same R_f values on paper chromatography in *n*-butyl alcohol–acetic acid–water (60:15:25) as demonstrated by ultraviolet light.

β-(7-Aza-3-indolyl)-ethylamine Dihydrochloride (III).—The nitrile I (785 mg.) was dissolved in a mixture of 25 ml. of 95% ethanol and 1.5 ml. of concentrated hydrochloric acid and approximately 0.3 g. of reduced Adams catalyst was added. The mixture was stirred in the presence of hydrogen at atmospheric pressure and room temperature until approximately 99% of the hydrogen required for reduction of the nitrile group had been absorbed. After separation of the catalyst the yellow solution was evaporated to dryness *in vacuo* and the solid residue was collected and washed with absolute ethanol. There was thus obtained 631 mg. (53.9%) of slightly yellow amine dihydrochloride. For analysis a sample was purified by dissolution in boiling methanol (Darco) and precipitation by the addition of hot acetonitrile. The resulting white needles, which gave a positive ninhydrin test, had no characteristic melting point but browned gradually above 275° and decomposed completely between 290 and 300°.

Anal. Calcd. for $C_9H_{11}N_3 \cdot 2HCl$: C, 46.16; H, 5.61; N, 17.95. Found: C, 46.18; H, 5.38; N, 18.35.

In earlier experiments attempts were made to reduce the nitrile in the presence of Raney nickel[16] and ammonia. When 628 mg. of nitrile was stirred with hydrogen at atmospheric temperature and pressure in the presence of 25 ml. of 95% ethanol, 3.0 ml. of concentrated ammonium hydroxide, and an estimated 2–3 g. of catalyst, 86.6% of the theoretical hydrogen was absorbed in an 18-hour period. Filtration and evaporation of the solution left an oil which resisted crystallization. It was finally caused to solidify by the addition of acetone, but the resulting product was not 7-azatryptamine. On recrystallization from acetone and from benzene white plates were obtained, m.p. 141.0–143.0° dec. The analysis corresponded to a condensation product derived from one mole of acetone and one mole of azatryptamine with elimination of water.

Anal. Calcd. for $C_{12}H_{15}N_3$: C, 71.60; H, 7.53; N, 20.88. Found: C, 71.43; H, 7.30; N, 20.67, 21.09, 21.03.

The weight of product after one recrystallization, m.p. 141.0–144.5° dec., corresponded to a 27.0% yield on this basis. The substance is insoluble in cold water but readily gives a positive ninhydrin test on heating with this reagent in water. On standing the material gradually assumes a brown color.[17] It was not investigated further.

Ethyl α-Carbethoxy-β-(7-aza-3-indolyl)-propionate (IV).—A mixture of 0.87 g. of 7-azagramine and 2.4 g. of malonic ester was heated to 120° in a nitrogen atmosphere, a small chip of sodium was added and the reaction mixture was maintained at 120° for 6 hours. The red liquid was cooled, 8 ml. of 5% hydrochloric acid was added and unchanged malonic ester was separated by extraction into ether. The water layer was then made basic with solid sodium bicarbonate and the resulting oil was extracted into ether and dried. Evaporation of the ether left an oily, brown solid which was washed with carbon tetrachloride and recrystallized from a 1:1 mixture of carbon tetrachloride–*n*-hexane. There was thus obtained 0.74 g. (51%) of product, m.p. 110–113.5°. Further recrystallizations from the same solvent-pair and from water produced white crystals, m.p. 114.0–115.5°.

Anal. Calcd. for $C_{15}H_{18}N_2O_4$: C, 62.05; H, 6.25; N, 9.65. Found: C, 62.22; H, 6.15; N, 9.82.

β-(7-Aza-3-indolyl)-propionic Acid (V).—The substituted malonic ester (0.36 g.) was hydrolyzed and decarboxylated by refluxing with 5 ml. of concentrated hydrochloric acid for 6.5 hours. The solution was evaporated to dryness *in vacuo*, a few milliliters of water was added and the solution was neutralized with 5% sodium bicarbonate. The dried precipitate weighed 0.18 g. (76%) and melted at 205.5–206°. The compound was recrystallized from water for analysis; white needles, m.p. 205.0–206.5°.

Anal. Calcd. for $C_{10}H_{10}N_2O_2$: C, 63.14; H, 5.31; N, 14.73. Found: C, 62.80; H, 5.71; N, 14.5.

Ethyl α-Nitro-α-carbethoxy-β-(7-aza-3-indolyl)-propionate. The reaction was carried out by what was essentially the method of Weisblat and Lyttle.[18] 7-Azagramine (5.25 g.),

(13) W. Madelung and O. Wilhelmi, *Ber.*, **57**, 234 (1924).

(14) Melting points are corrected.

(15) Analyses by Weiler and Strauss, Oxford, England, and by J. F. Alicino, Metuchen, N. J., except for some nitrogen determinations which were carried out by a semi-micro Kjeldahl technique in this Laboratory.

(16) A. A. Pavlic and H. Adkins, THIS JOURNAL, **68**, 1471 (1946).

(17) NOTE ADDED IN PROOF.—The infrared spectrum of the azatryptamine-acetone condensation product (Baird spectrophotometer and KBr disk) showed a strong absorption band at 1655 cm.$^{-1}$, attributable to an imine carbon-nitrogen double bond (*cf.* L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, New York, N. Y., 1954, p. 223).

(18) D. I. Weisblat and D. A. Lyttle, THIS JOURNAL, **71**, 3079 (1949).

nitromalonic ester[17] (6.15 g.) and dry toluene (50 ml.) were heated to reflux with stirring under nitrogen and maintained at this temperature for 6 hours, stirring being discontinued after the first hour. After cooling, the dark red liquid was extracted with 150 ml. of 5% hydrochloric acid, the extract was washed with ether and the product was precipitated by the addition of solid sodium bicarbonate. The oil soon solidified to a sticky, dark-brown solid which was dissolved in benzene. The dried benzene solution was passed onto a column of alumina and the product eluted with benzene containing 5% absolute ethanol by volume. By this procedure some of the polymeric material was eliminated. There was thus obtained 4.10 g. (40.7%) of nitroester, m.p. 134–136°. The analytical sample was recrystallized from 1:3 benzene–cyclohexane (Darco) and was obtained as thick yellow needles, m.p. 136.0–137.0°.

Anal. Calcd. for $C_{15}H_{17}N_3O_6$: C, 53.72; H, 5.12; N, 12.53. Found: C, 53.76; H, 5.06; N, 12.4.

7-Azaindole-3-carboxaldehyde Oxime.—To a solution of 1.47 g. of 7-azaindole-3-carboxaldehyde[2] in 150 ml. of hot water were added 1.02 g. of hydroxylamine hydrochloride and 1.50 g. of sodium bicarbonate and the solution was heated on the steam-bath one hour, during which time a precipitate formed. After thorough chilling of the liquid the product was separated and dried, yield 1.50 g. (92.6%), m.p. 218–219° dec. The analytical sample on recrystallization from 1:2 ethanol–water formed white needles, m.p. 221.5–223.5° dec.

Anal. Calcd. for $C_8H_7N_3O$: C, 59.61; H, 4.39; N, 26.07. Found: C, 59.86; H, 4.66; N, 26.1.

Dehydration of the Oxime.—The oxime (0.80 g.) was added to 4 ml. of acetic anhydride and the mixture refluxed gently for 50 minutes. It was then cooled, 30 ml. of water was added and 0.91 g. of solid was separated by filtration. The melting range of the initial product was variable but a typical result was *ca.* m.p. 128–145°. This material was apparently impure 1-acetyl-3-cyano-7-azaindole. The substance was soluble in non-polar solvents and could be recrystallized from cyclohexane but a sharp melting point was not attained by this process. Recrystallization from water removed the acetyl group and produced 3-cyano-7-azaindole, which after recrystallization for analysis from water and from aqueous ethanol was obtained as white needles, m.p. 262–265° with some discoloration. It was insoluble in non-polar solvents.

Anal. Calcd. for $C_8H_5N_3$: C, 67.12; H, 3.52; N, 29.36. Found: C, 67.11; H, 3.69; N, 29.5.

Hydrolysis of 1-Acetyl-3-cyano-7-azaindole.—To 10 ml. of concentrated hydrochloric acid was added 0.70 g. of the crude acetyl derivative and the solution was refluxed 10 hours. The yellow liquid was evaporated to dryness and to the residue were added 5 ml. of water and excess solid sodium bicarbonate. Insoluble matter was separated by filtration and the filtrate was acidified with acetic acid. There was thus obtained 0.24 g. of crude acid (37%), m.p. 245° dec. Recrystallization from 1:1 ethanol–water produced rosettes of fine white needles whose melting point was approximately 254° dec., but which depended greatly on the rate of heating. Much difficulty was experienced in obtaining satisfactory analytical results for the various samples of the acid. It was eventually determined that these difficulties stemmed partly from the fact that the compound was unusually resistant to the Dumas nitrogen determination. In addition, although the material was usually separated as the hemihydrate, it was occasionally obtained in anhydrous condition even though the drying conditions were not apparently more severe. The decomposition melting point did not seem to be affected by the degree of hydration.

Anal. Calcd. for $C_8H_6N_2O_2 \cdot {}^1/_2H_2O$: C, 56.13; H, 4.13; N, 16.37. Found: C, 56.28; H, 4.33; N, 15.9.

After redrying this particular sample at 100° similar results were found, but on redrying to constant weight at 110° the water apparently was lost.

Anal. Calcd. for $C_8H_6N_2O_2$: C, 59.25; H, 3.74; N, 17.28. Found: C, 59.93; H, 3.66; N, 17.06.

3-Carbethoxy-7-azaindole.—Ten milliliters of 95% ethanol was saturated with hydrogen chloride, 0.55 g. of the crude acetyl derivative was added and the suspension was refluxed 4 hours, after which it was allowed to stand overnight at room temperature. Evaporation of the solvent and treatment of the residue with water and sodium bicarbonate produced 0.37 g. (65%) of tan solid, m.p. 154–158°. For analysis it was recrystallized from 1:3 ethanol–water (Darco) and from 1:1 benzene–cyclohexane as white needles, m.p. 163.0–164.0°.

Anal. Calcd. for $C_{10}H_{10}N_2O_2$: C, 63.14; H, 5.31; N, 14.73. Found: C, 62.97; H, 5.33; N, 14.9.

Saponification of 3-Carbethoxy-7-azaindole.—A mixture of 0.56 g. of the ester and 6 ml. of 20% sodium hydroxide was refluxed 1.5 hours, cooled and acidified with acetic acid. The precipitate was separated by filtration and dissolved in aqueous sodium bicarbonate. Filtration of the solution to remove a small quantity of insoluble matter followed by reacidification with acetic acid produced 0.38 g. (75%) of the acid, m.p. 235° dec. Purification as with the sample from the acid hydrolysis produced material with the same melting point, undepressed on admixture with the nitrile hydrolysis product.

Anal. Found: C, 56.50; H, 4.20; N, 16.13, 16.29.

Oxidation of 7-Azaindole-3-carboxaldehyde.—A solution of 146 mg. of aldehyde in 20 ml. of 0.1 *N* sodium hydroxide was maintained at 50–60° while a solution of 106 mg. of potassium permanganate in 75 ml. of water was added over a ten-minute period. The suspension of manganese dioxide was then heated to boiling, filtered and cooled after which the filtrate was saturated with carbon dioxide. The unreacted aldehyde was removed by filtration, weight 44 mg., m.p. 212.5–214.5°, undepressed on admixture with starting material. Acidification of the filtrate with acetic acid produced 59 mg. of the carboxylic acid, m.p. 234° dec. After recrystallization from ethanol–water the material melted at 258° dec., undepressed on admixture with the acid obtained from the saponification of the ester. The two samples of acid also had identical R_f values on chromatography in 60:15:25 butanol–acetic acid–water and in 8:1:1 isopropyl alcohol–ammonium hydroxide–water.

Carbonation of 7-Azaindole.—When 7-azaindole was treated with sodium and carbon dioxide by the method of Kruber[7] a product was obtained which, in our hands, melted at 257° dec. both alone and on admixture with the product from the alkaline saponification. Its R_f values were identical with those of the saponification product on chromatography in butanol–acetic acid–water and in isopropyl alcohol–ammonium hydroxide–water. Although the analytical sample (recrystallized as above) was only dried at 60°, it was found to be unhydrated.

Anal. Found: N, 17.07.

All of the above samples produced 7-azaindole on heating above their melting points as shown by the sodium nitroprusside test,[2] paper chromatography or both. In the case of the nitrile–hydrolysis product the base was isolated, m.p. 103.0–104.0°, undepressed on admixture with an authentic sample.

Bromination of 7-Azaindole.—A solution of 1.18 g. of 7-azaindole in 15 ml. of chloroform was chilled in an ice-bath and a solution of 1.60 g. of bromine in 19 ml. of carbon tetrachloride was added with swirling. The suspension was extracted with dilute hydrochloric acid and the water layer filtered and made basic with sodium hydroxide. The tan precipitate weighed 1.60 g. (81.2%) and melted at 177°. Recrystallization from benzene and from carbon tetrachloride (Darco) produced white needles, m.p. 188.0–188.5°. In cyclohexane solution the compound exhibited absorption maxima at 222 mμ (log ε 4.33), at 287 mμ (log ε 3.95) and at 294 mμ (log ε 3.89) and minima at 244 mμ (log ε 3.18) and 292 mμ (log ε 3.88).

Anal. Calcd. for $C_7H_5N_2Br$: C, 42.66; H, 2.56; N, 14.22; Br, 40.56. Found: C, 42.45; H, 2.62; N, 14.0; Br, 40.7.

When 0.20 g. of the bromo compound was warmed at 60–70° for 1 hour with 5 ml. of 5% hydrochloric acid, no reaction occurred. Evaporation of the solution followed by addition of water and sodium bicarbonate allowed recovery of 0.18 g. of starting material, m.p. 187.0–188.0°, undepressed on admixture with untreated bromo compound.

Reaction of 7-Azaindole with Benzenediazonium Chloride.—A solution of 0.59 g. of 7-azaindole in 8 ml. of methanol was added to a cold solution of benzenediazonium chloride, prepared from 0.46 g. of aniline, 1.5 ml. of concd. hydrochloric acid, 0.34 g. of sodium nitrite and 10 ml. of water. A precipitate gradually formed. After the mixture had been

allowed to stand overnight in the ice-box, the yellow precipitate, which consisted largely of 7-azaindole together with some product, was separated by filtration and triturated with 5% hydrochloric acid. The residue, which was only slowly soluble in this medium was recrystallized from 1:1 benzene–cyclohexane for analysis; fine yellow needles, m.p. 214.5–215.0°. It was later found that the compound, like its indole analog,[13] is soluble in dilute sodium hydroxide solution. The preparation was not repeated, but it is probable that the reaction would be more nearly complete at a higher *p*H.[13]

Anal. Calcd. for $C_{13}H_{10}N_4$: C, 70.25; H, 4.54; N, 25.21. Found: C, 70.50; H, 4.52; N, 25.0.

Ultraviolet Spectra.—Spectra were determined on a Beckman model DU quartz spectrophotometer at a concentration of 10^{-4} *M*.

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[CONTRIBUTION FROM THE COURTAULD INSTITUTE OF BIOCHEMISTRY]

Synthesis and Absorption Spectra of the Symmetrical Chloroindigos

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The ultraviolet and visible absorption spectra of the symmetrical chloroindigos were determined in tetrachloroethane solution. Contrary to earlier work[1,2] the degree of halogenation was not found to be paralleled by the extent of the bathochromic shift. In fact both bathochromic and hypsochromic shifts were found to occur, depending on the position of the substituents. A simple relationship was deduced between the absorption maxima of the four dichloroindigos and the more highly substituted compounds.

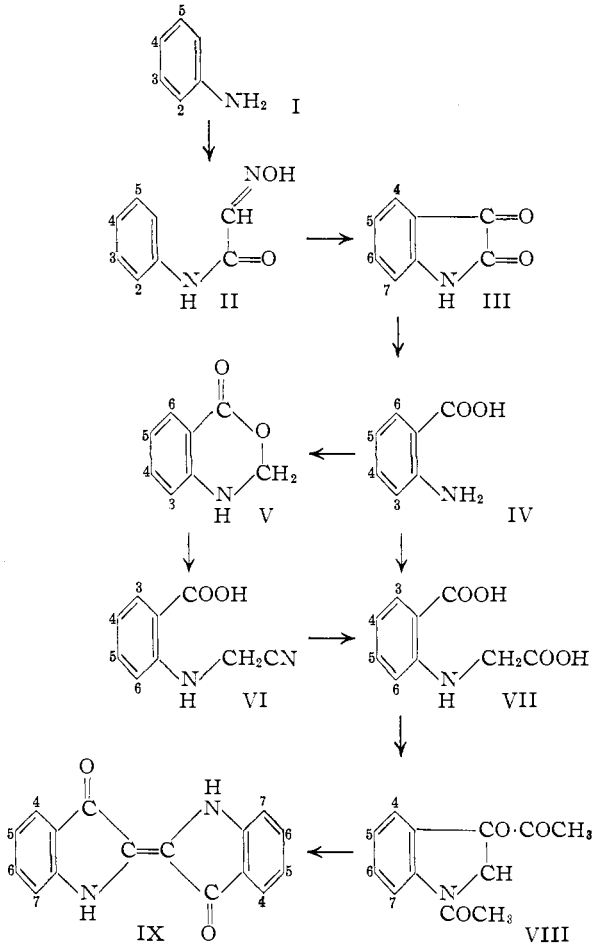
Introduction

As part of a larger program, relating absorption spectra to chemical constitution in indigoid dyes, the fifteen symmetrical chloroindigos were synthesized. All of the dyes were obtained from the corresponding diacetylindoxyl compounds by alkaline hydrolysis followed by aerial oxidation. Many of the chloroindigos previously prepared have been obtained by the direct chlorination of indigo, their configuration having been proved by degradation to known compounds; in this present work the synthetic route chosen has removed all ambiguity, as several known compounds occur as intermediates in the synthesis of each indigo, making the configuration of each dye certain.

Several of the chloroamines I which were used as starting materials were obtainable commercially,[3] with the exception of 3,5-dichloro,[4] 3,4,5-trichloro-[5] and 2,3,5-trichloroaniline[6] which were prepared and characterised by methods in the literature.

The substituted α-isonitrosoacetanilides II were prepared from the appropriate chloroamines I by the Sandmeyer synthesis,[7] using the Marvel–Hiers modifications.[8] The crude reaction products were extracted with warm 2 *N* sodium hydroxide (hot concentrated alkali decomposes the isonitrosoacetanilides) and filtered over "Hyflo-Supercel." Slow addition of 2 *N* hydrochloric acid precipitated the derivatives in a reasonably pure and often crystalline form. Aqueous ethanol was used for recrystallization. Details are listed in Table IV.

The isonitrosoacetanilides were cyclized to the isatins III in concentrated sulfuric acid,[7] the necessary modifications of temperature and duration of heating are given in Table V. In each case



the crude product was dissolved in the required amount of 2 *N* sodium hydroxide (water being added if necessary to prevent precipitation of the sodium isatinate), then filtered rapidly (charcoal) after making the hot solution faintly acid by the addition of glacial acetic acid. By this method a clear solution of the isatin was obtained, free from unchanged isonitrosoacetanilide and tarry by-

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