found to be very close to the polyethylene glycols in separating ability and retention time, but a sample of polypropylene glycol[14] was somewhat inferior in separating unsaturates. A silicone column (General Electric SF96-40) was found to be intermediate in retention time and separating ability between the polyglycol type and the paraffin type.

With Apiezon M, retention times generally followed boiling points, and the order of emergence of the allylic disulfides was reversed from that of the polar phases and separation was not complete. This stationary phase also had the disadvantage that higher disulfides and trisulfides had unusually long retention times. However, certain combinations not completely resolvable with the polar phases can be completely separated with Apiezon. Inspection of Table I or Table II shows that of the 16 disulfides and trisulfides listed, 9 pairs would probably not be completely separated on the polar substrates because the retention times are too close (< 15%). With the exception of the straight chain isomers, methyl-*n*-propyl disulfide and diethyl disulfide and the pair of corresponding trisulfides each of these pairs should be completely separable on Apiezon. This has been confirmed experimentally for several cases. In particular, the pairs dimethyl trisulfide and di-*n*-propyl disulfide, di-*i*-butyl disulfide and allyl-*n*-propyl disulfide, methyl-*n*-propyl trisulfide and di-*n*-butyl disulfide, and di-*i*-propyl disulfide and diethyl disulfide (or methyl-*n*-propyl disulfide) were incompletely resolved on Carbowax but were easily separated with Apiezon. This is merely one more example of the advantage of using two or more different stationary phases and in this case with a wide variation in polar character.

Acknowledgment. The authors thank Glen F. Bailey and Mrs. Edith Gong for infrared determinations.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES, NATIONAL DRUG CO.]

Synthesis in the 5-Hydroxyindole Series. *N*-Acetyl-5-hydroxytryptophan and Related Compounds

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Received August 22, 1958

A number of pharmacologically interesting 5-hydroxyindole derivatives, including *N*-acetyl-5-hydroxytryptophan (X), 5-hydroxyindole-3-acetamide (XVI) and 5-hydroxytryptophol (XIX) were synthesized. An improved process for the large scale preparation of 5-hydroxytryptophan was reported.

The importance of the physiological properties of indole derivatives has been emphasized again by the isolation of the powerful vasoconstrictor principle, serotonin.[2] The confirmation of its structure as 5-hydroxytryptamine[3,4] prompted us to initiate a study of 5-hydroxyindole derivatives. While our work was in progress, a few communications[3-5] on this subject appeared in the literature. This paper deals with the syntheses of *N*-acetyl-5-hydroxytryptophan, 5-hydroxytryptophol and related substances of potential pharmacological importance, and reports on improved methods for the large scale preparation of the important compound, 5-hydroxytryptophan.

The synthesis of 5-hydroxytryptophan by condensation of 5-benzyloxygramine with diethyl formaminomalonate, followed by saponification, decarboxylation, and hydrogenolysis has been reported.[4] Since large quantities of 5-hydroxytryptophan and related compounds were required by us, the commercially available diethyl acetamidomalonate, rather than the formamido analog, was employed for the condensation with the benzyloxygramine[6] (I). The reaction proceeded successfully to give the indole malonicester II in 78% yield. Catalytic debenzylation of II provided the 5-hydroxy-compound III. A combined decarboxylation and deacetylation of the acetaminomalonic acid IV, which was obtained by mild saponification of the corresponding ester II,

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(2) M. M. Rapport, A. A. Green, and I. H. Page, *Science*, **108**, 329 (1948); *J. Biol. Chem.*, **176**, 1243 (1948); M. M. Rapport, *J. Biol. Chem.*, **180**, 961 (1949).

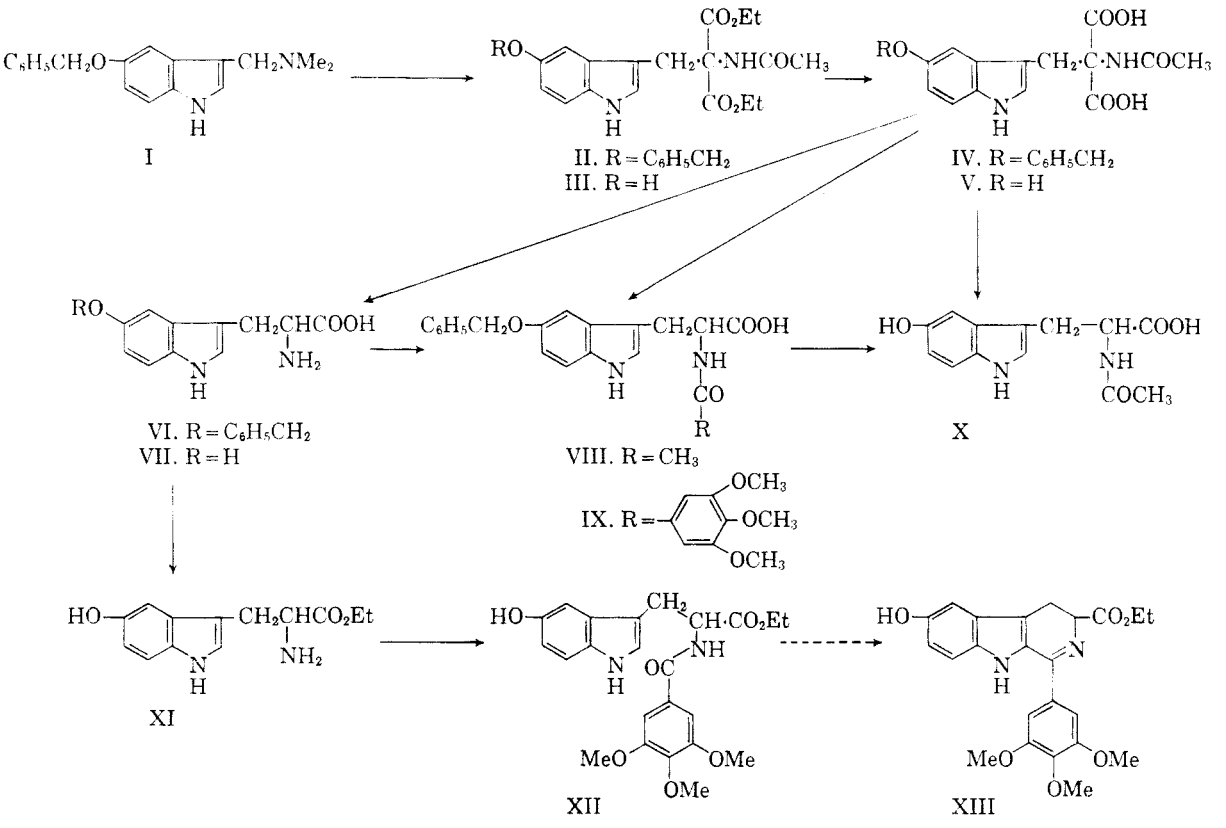
(3) K. E. Hamlin and F. E. Fischer, *J. Am. Chem. Soc.*, **73**, 5007 (1951).

(4) M. E. Speeter, R. V. Heinzelmann, and D. I. Weisblat, *J. Am. Chem. Soc.*, **73**, 5514 (1951).

(5) A. Ek and B. Witkop, *J. Am. Chem. Soc.*, **75**, 500 (1953).

(6) During our early experiments this compound was prepared by modification of the method of H. Kühn and O. Stein [*Ber.*, **70**, 567 (1937)], and later by the procedure of Ek and Witkop[7] with improved yields. We are indebted to Dr. B. Witkop for making available to us their procedure far in advance of publication.

(7) A. Ek and B. Witkop, *J. Am. Chem. Soc.*, **76**, 5579 (1954).



promptly gave 5-benzyloxytryptophan (VI) in excellent yield.

Acylation of VI with the appropriate acid chlorides, in the usual manner, gave the *N*-acetyl and *N*-3,4,5-trimethoxybenzoyl derivatives VIII and IX as expected. The *N*-acetyl-5-hydroxytryptophan (X) was produced by the catalytic reduction of VIII in ethanol without difficulty. Alternatively, two shorter and more convenient routes, which bypassed VI for the preparation of X, were also found. The first involves decarboxylation of IV in boiling water, without affecting the acetyl group, to yield VIII from which X was obtained as before. The second involves debenzylation of IV to give V, followed by rapid decarboxylation in hot ethyl acetate to provide X in a pure state. It is interesting to note that the carboxyl groups of the indolemalonic acid IV became much more unstable after debenzylation.

The high insolubility of 5-benzyloxytryptophan (VI) in many organic solvents caused its catalytic debenzylation to be difficult and incomplete,[8] especially when reasonably large amounts of material were used. However, after some experimentation, a convenient method was developed whereby relatively large quntities of VI, dissolved in dilute alkaline solution, were hydrogenolyzed rapidly and completely to afford VII in 91% yield. The 5-hydroxytryptophan was then converted to the ethyl ester (XI), which upon treatment with 3,4,5-trimethoxybenzoyl chloride in chloroform using potassium carbonate solution, produced the amide (XII).

Snyder and Werber[9] obtained two harmans in poor yields by the cyclization of *N*-formyl and *N*-acetyltryptophan with polyphosphoric acid and phosphorus oxychloride. However, the condensation of the ester, methyl α-formylamino-β-(3-indole)propionate, was unsuccessful. In the present instance, it seemed desirable to obtain the 3,4-dihydro-β-carboline derivative (XIII) from XII and numerous attempts were made to effect the cyclization with various agents including polyphosphoric acid. However, no pure product could be isolated.

5-Benzyloxyindole-3-acetamide[2] (XIV) and -acetic acid (XV) were simultaneously formed in equally good yields, without difficulty of separation,[10] by refluxing 5-benzyloxygramine (I) with sodium cyanide[11] in aqueous ethanol. Subsequently, they were readily debenzylated to give the corresponding 5-hydroxyindole-3-acetamide (XVI) and -acetic

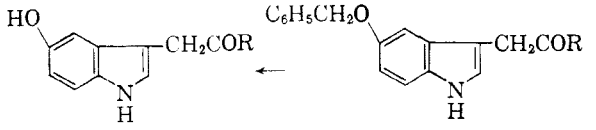
(8) After completion of our work, it was reported that the debenzylation of VI was carried out by suspension in equal parts of ethanol and water.[7] Independently, we tried both water and 95% ethanol as two of several solvents for this purpose. The results, however, were unsatisfactory.

(9) H. R. Snyder and F. X. Werber, *J. Am. Chem. Soc.*, **72**, 2962 (1950).

(10) Some difficulty in isolation of pure sample of XV from XIV was noted.[7] However, this was not observed by us.

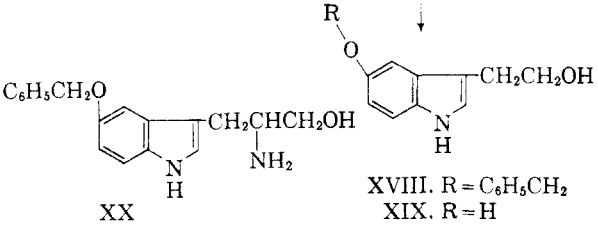
(11) H. R. Snyder and F. J. Pilgrim, *J. Am. Chem. Soc.*, **70**, 3770 (1948).

acid[12] (XVII), an important metabolic product of serotonin.[13]



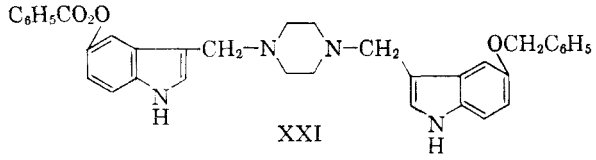
XVI. R = NH_2
XVII. R = OH

XIV. R = NH_2
XV. R = OH



XX

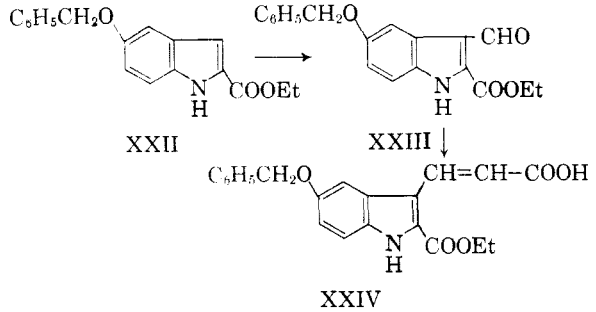
XVIII. R = $C_6H_5CH_2$
XIX. R = H



XXI

On the other hand, lithium aluminum hydride reduction of the indoleacetic acid XV gave the expected alcohol XVIII, which on hydrogenolysis afforded the very unstable compound, 5-hydroxytryptophol (XIX). β-Amino-α-(5-benzyloxy-3-indole) propanol (XX) was prepared by the analogous reduction of 5-benzyloxytryptophan. Condensation of 5-benzyloxygramine with piperazine yielded *N*,*N'*-bis(5-benzyloxyskatyl)piperazine (XXI).

In another series, ethyl 5-benzyloxyindole-2-carboxylate[14] (XXII) was converted in excellent yield to the 3-formyl derivative (XXIII) by modification of the method for preparation of 2-carbethoxyindole-3-carboxaldehyde.[15] It seems possible to decarbethoxylate[15] XXIII to yield 5-benzyloxyindole-3-carboxaldehyde which would be a useful intermediate for the preparation of many 5-hydroxyindole derivatives. However, this reaction was not attempted. Condensation of XXIII with malonic acid in the presence of a base[16] gave β-(2-carbethoxy-5-benzyloxy-3-indole)acrylic acid (XXIV).



XXII

XXIII

XXIV

EXPERIMENTAL[17]

5-Benzyloxygraminemethiodide. Ten g. of methyl iodide was added to a solution of 3 g. of 5-benzyloxygramine (I) in 75 ml. of ethyl acetate and the mixture allowed to stand at room temperature. After 5 hr. the ethyl acetate was decanted, and the residue was treated with acetone and then filtered. The yield of methiodide was 4 g. (88%), m.p. 173–175° dec.

Anal. Calcd. for $C_{19}H_{23}N_2OI$: N, 6.63. Found: N, 6.48.

Ethyl α-acetamino-α-carbethoxy-β-(5-benzyloxy-3-indole)-propionate (II). Powdered sodium hydroxide (1 g.) was added to a stirred, boiling mixture of 17.5 g. of 5-benzyloxygramine and 13.6 g. of ethyl acetaminomalonate in 80 ml. of dry toluene under nitrogen. The reaction was continued for 11 hr. The mixture was filtered hot through a Büchner funnel and the filtrate was cooled at 5° overnight. The precipitated, light brown crystalline solid, after filtration and washing with petroleum ether, weighed 22 g. (78.5%), and melted at 156–158°. A colorless sample for analysis was obtained by recrystallization of the crude material from aqueous ethanol, m.p. 166–168°.

Anal. Calcd. for $C_{25}H_{28}N_2O_6$: N, 6.19. Found: N, 6.28.

Ethyl α-acetamino-α-carbethoxy-β-(5-hydroxy-3-indole)-propionate (III). A solution of 8 g. of the crude ester (II) in 300 ml. of ethanol was hydrogenated at 40 p.s.i. pressure using 3 g. of 10% palladium-on-carbon as the catalyst. After 2 hr., the mixture was filtered and the filtrate concentrated to 35 ml. The crystalline product, which separated, weighed 6 g. (93%), m.p. 234–235°.

Anal. Calcd. for $C_{18}H_{22}N_2O_6$: N, 7.73. Found: N, 7.65, 7.70.

α-Acetamino-α-carboxy-β-(benzyloxy-3-indole)propionic acid (IV). A mixture of 20 g. of the crude ester (II) in 160 ml. of 10% sodium hydroxide was refluxed gently for 6 hr. The alkaline solution was treated with Norit and filtered. Cracked ice was added to the filtrate which was then acidified with excess hydrochloric acid. The resulting pink product was filtered off and washed twice with a little ice water. After drying, it weighed 15.5 g. (90%), m.p. 157–160°. Further purification was made by recrystallization twice from ethanol at 60° to yield small colorless needles, m.p. 162–163°.

Anal. Calcd. for $C_{21}H_{20}N_2O_6$: N, 7.07. Found: N, 6.98.

5-Benzyloxytryptophan (VI). A suspension of 15 g. of IV of IV in 80 ml. of water was refluxed with stirring for 4.5 hr. Then 40 ml. of 30% sodium hydroxide solution was added to the flask and refluxing was continued for another 24 hr. After treating with Norit, the alkaline solution was acidified with acetic acid. The light pink colored, heavy precipitate was filtered and recrystallized from 30% acetic acid to give 10.5 g. (90%) of almost colorless needles, m.p. 275–276° dec. (reported[5] m.p. 280°).

Anal. Calcd. for $C_{18}H_{18}N_2O_3$: N, 9.03. Found: N, 8.92.

N-Acetyl-5-benzyloxytryptophan (VIII). (*a*) *By acetylation of* VI. To a solution of 1 g. of the crude tryptophan (VI) in 15 ml. of 20% sodium hydroxide 3 ml. of acetic anhydride in several portions was added with vigorous shaking and occasional cooling. Acidification of the alkaline solution with acetic acid yielded a solid, weighing 1.1 g. (97%), m.p. 163–166°. It was recrystallized from aqueous ethanol to give colorless, small needles, m.p. 166–167°.

Anal. Calcd. for $C_{20}H_{20}N_2O_4$: N, 7.95. Found: N, 7.60.

(*b*) *By decarboxylation of* IV. The malonic acid (IV) (7 g.) was stirred and refluxed with 100 ml. of water for 3.5 hr.

(12) Our syntheses of compounds XIV, XV, and XVII were completed in 1953 and the paper was originally submitted for publication in 1954 before these three compounds were reported.[7] Thus, our findings confirm their work independently.

(13) E. Titus and S. Udenfriend, *Federation Proc.*, **13**, 411 (1954); A. Sjoerdsma, H. Weissbach, and S. Udenfriend, *Am. J. Med.*, **20**, 520 (1956).

(14) W. R. Boehme, *J. Am. Chem. Soc.*, **75**, 2502 (1953).

(15) A. C. Shabica, E. E. Howe, J. B. Ziegler, and M. Tishler, *J. Am. Chem. Soc.*, **68**, 1156 (1946).

(16) *Cf.* J. Koo, M. S. Fish, G. N. Walker, and J. Blake, *Org. Syntheses*, **31**, 35 (1951).

(17) All melting points are uncorrected.

The pale brown solid, which separated on cooling, was crystallized from dilute ethanol to yield 5.1 g. (82%) of needles, m.p. 165–166°. There was no m.p. depression with a sample obtained by method (a).

N-(3,4,5-Trimethoxybenzoyl)-5-benzyloxytryptophan (IX). A mixture of 5.1 g. of 5-benzyloxytryptophan (VI) and 4.1 g. of 3,4,5-trimethoxybenzoyl chloride in 50 ml. of pyridine was heated on a steam bath for 45 min. The resulting solution was then poured into ice water with stirring. The clear aqueous solution was separated from the small portion of dark, gummy material and acidified with hydrochloric acid. The colorless precipitate, after filtration and recrystallization from 80% ethanol, yielded 1.54 g. (19%) of colorless prisms, m.p. 202–204°.

Anal. Calcd. for $C_{28}H_{28}N_2O_7$: N, 5.55. Found: N, 5.51.

N-Acetyl-5-hydroxytryptophan (X). (*a*) *By hydrogenolysis of* VIII. A mixture of 5.2 g. of *N*-acetyl-5-benzyloxytryptophan (VIII) and 1 g. of 10% palladium-on-carbon catalyst in 100 ml. of absolute ethanol was hydrogenated at room temperature at 40 p.s.i. pressure for 3.5 hr. After filtering off the catalyst, the solvent was evaporated under reduced pressure below 40°. The light pink, crystalline solid residue was triturated with a little ethyl acetate and ether, filtered, and weighed 2.5 g. (64%) m.p. 202–205°. It was recrystallized from absolute ethanol–ether to yield colorless needles, m.p. 207–209°.

Anal. Calcd. for $C_{13}H_{14}N_2O_4$: N, 10.68. Found: N, 10.65.

(*b*) *By decarboxylation of* V. Three grams of crude V, dissolved in 100 ml. of ethyl acetate in a beaker, was heated gently to boiling on a steam bath for 20–30 min. after which some colorless crystals gradually separated. Adding petroleum ether and chilling the mixture, promptly yielded 2.3 g. (90%) of pure material, m.p. 207–208°. The mixed melting point with a sample from procedure (*a*) showed no depression.

α-Acetamino-α-carboxy-β-(5-hydroxy-3-indole)propionic acid (V). A mixture of 4 g. of the benzyloxyindole acid (III) and 1 g. of palladium-on-carbon catalyst in 60 ml. of absolute ethanol was hydrogenated at room temperature under 40 p.s.i. pressure for 3 hr. The catalyst was filtered off and the solvent was evaporated at 30° under reduced pressure. The resulting sirup was crystallized from ethyl acetate–ether without heating to give colorless small, unstable needles, melting at 156–157° with decomposition, resolidifying and then remelting at 200–205°.[18] Some decarboxylation accompanied the purification, thus rendering the preparation of an analytical sample difficult.

5-Hydroxytryptophan (VII). Fifty g. of VI was dissolved in 300 ml. of 5% sodium hydroxide solution and 10 g. of 10% palladium-on-carbon catalyst was added. The mixture was hydrogenated at room temperature and 40–50 p.s.i. pressure for 3 hr. After filtration of the catalyst, the aqueous phase was separated from the toluene layer, nearly neutralized with dilute hydrochloric acid, and finally acidified with dilute acetic acid. The pale pink solid which separated was filtered, washed with a small amount of ice water, and recrystallized from hot water to yield 32.2 g. (91%) of colorless prisms, m.p. 297–298° dec. (reported[5] m.p. 293–298°).

Anal. Calcd. for $C_{11}H_{12}N_2O_3$: N, 12.63. Found: N, 12.38.

Ethyl α-amino-β-(5-hydroxy-3-indole)propionate hydrochloride (XI). Five g. of 5-hydroxytryptophan (VII) suspended in 100 ml. of absolute ethanol was saturated with hydrogen chloride gas and the solution was allowed to stand at room temperature for 2 days. The alcoholic solution was concentrated at low temperature under reduced pressure to about 50 ml. after which dry ether was added. The colorless hydrochloride salt that separated was filtered, weighing 5.5 g. (85%), m.p. 234–235° dec.

Anal. Calcd. for $C_{13}H_{17}N_2O_3Cl$: N, 9.84. Found: N, 9.56.

Ethyl α-(3,4,5-trimethoxybenzoylamino)-β-(5-hydroxy-3-indole)propionate (XII). A stirred suspension of 5 g. of XI in 10 ml. of water was treated with 30 ml. of 20% sodium carbonate, then with 50 ml. of chloroform, and finally with 5 g. of 3,4,5-trimethoxybenzoyl chloride in 39 ml. of chloroform. The organic layer was separated, washed twice with water, dried over magnesium sulfate, and filtered. Concentration of the chloroform solution separated 6 g. (78%) of crystalline solid, m.p. 169–171°. It was recrystallized once from ethyl acetate–petroleum ether (65–75°) to yield a colorless material, m.p. 170–172°.

Anal. Calcd. for $C_{23}H_{26}N_2O_7$: N, 6.33. Found: N, 6.13.

5-Benzyloxyindole-3-acetamide (XIV). A mixture of 10 g. of 5-benzyloxygramine (I), 14 g. of sodium cyanide, 112 ml. of 95% ethanol, and 28 ml. of water was refluxed gently for 81 hr. After cooling, 50 ml. of cold water was added. The crystalline, colorless solid which precipitated was filtered, washed with cold water and dried, weighing 4.05 g. (40.5%), m.p. 155–157°. Recrystallization once from absolute ethanol yielded 3.65 g. of pure material, m.p. 156–157°. (reported[3] m.p. 158°).

Anal. Calcd. for $C_{17}H_{16}N_2O_2$: N, 9.99. Found: N, 9.88.

5-Benzyloxyindole-3-acetic acid (XV). The filtrate from the removal of the amide (XIV) was concentrated under reduced pressure to about half of its original volume, cooled with cracked ice, and then made acid to Congo red. The acid that separated was filtered, and weighed 4.2 g. (42%), m.p. 145–148°. A pure sample was obtained by recrystallization of the material from 50% ethanol to give colorless needles, m.p. 147–149°. (reported[7] m.p. 149–150.5°).

Anal. Calcd. for $C_{17}H_{15}NO_3$: N, 4.98. Found: N, 5.21.

5-Hydroxyindole-3-acetamide (XVI). A solution of 3 g. of 5-benzyloxy-3-indoleacetamide in 200 ml. of ethanol was reduced at 40 p.s.i. pressure in the presence of 2 g. of 10% palladium-on-carbon catalyst. After 4 hr. the catalyst was filtered and the filtrate evaporated under reduced pressure. The residue was dissolved in 2 l. of dry ether, filtered, and concentrated to 150 ml. The product which separated weighed 1.5 g. (74%), m.p. 164–165°.

Anal. Calcd. for $C_{10}H_{10}N_2O_2$: N, 14.73. Found: N, 14.73, 14.79.

5-Hydroxyindole-3-acetic acid (XVII). A solution of 5 g. of 5-benzyloxy-3-indoleacetic acid in 75 ml. of ethanol was reduced at 40 p.s.i. pressure with 2 g. of 10% palladium-on-carbon catalyst. After 3 hr. the catalyst was filtered and the filtrate evaporated to dryness under reduced pressure. The residue dissolved in 600 ml. of hot ether. Filtration and concentration to 500 ml. yielded 2 g. (59%) of pure product decomposing at 163–164°. (reported[7] m.p. 166°).

Anal. Calcd. for $C_{10}H_9NO_3$: N, 7.33. Found: N, 7.25.

5-Benzyloxytryptophol (XVIII). To a stirred suspension of 1.5 g. of lithium aluminum hydride in 200 ml. of anhydrous ether was added 4.2 g. of powdered 5-benzyloxy-3-indoleacetic acid (XV) in small portions during 1 hr. The mixture was heated under reflux for 6 hr. and the excess lithium aluminum hydride was carefully decomposed by dropwise addition of 10 ml. of ethyl acetate. Then 60 ml. of 10% sodium hydroxide solution was added with stirring. The ether layer was separated and the water layer was extracted once with ether. The combined ether solutions were washed with water, dried over magnesium sulfate, and evaporated at low temperature under reduced pressure. The remaining semisolid was recrystallized from benzene–petroleum ether; yield of colorless needles 2.85 g. (71%), m.p. 98–100°.

Anal. Calcd. for $C_{17}H_{17}NO_2$: N, 5.24. Found: N, 5.27.

5-Hydroxytryptophol (XIX). A mixture of 3 g. of 5-benzyloxytryptophol and 1 g. of 5% palladium-on-carbon catalyst in 60 ml. of absolute ethanol was hydrogenated at room temperature at low pressure for 2 hr. The catalyst was filtered off and the ethanol was evaporated at slightly above room temperature with reduced pressure. The residual, reddish oil was crystallized from ethyl acetate–petroleum ether. It separated as slightly pink needles upon standing several weeks in the refrigerator. The yield was 1.1 g. (55%) m.p. 111–113°. This unstable compound not only decomposed in

(18) Since m.p. of X was 207–209°, it seemed apparent that the compound first melted with decarboxylation to form X.

air, but also turned dark red in the solvent upon standing in the ice box.

Anal. Calcd. for $C_{10}H_{11}O_2$: C, 67.78; H, 6.26; N, 7.91. Found: C, 67.95; H, 6.05; N, 7.78.

β-Amino-α-(5-benzyloxy-3-indole)propanol (XX). 5-Benzyloxytryptophan (9 g.) was added portionwise to a stirred and refluxing mixture of 5 g. of lithium aluminum hydride in 500 ml. of dry ether during a 2-hr. period. The heating and stirring was continued for another 3 hr. and the mixture was allowed to stand overnight. The excess lithium aluminum hydride was carefully decomposed with 10 ml. of ethyl acetate and 200 ml. of 20% aqueous sodium potassium tartarate solution was then slowly added to the reaction mixture with stirring. The ether layer was separated and the water layer was extracted twice with small portions of ether. The combined ether solutions were washed with dilute sodium bicarbonate solution, water, and then dried over magnesium sulfate. Evaporation of the ether left 5.3 g. (61%) of a slightly reddish oil which soon solidified, m.p. 106–108°. It was recrystallized from benzene to give colorless small needles, m.p. 108–109°.

Anal. Calcd. for $C_{18}H_{20}N_2O_2$: N, 9.45. Found: N, 9.26.

N,N'-bis-(5-benzyloxyskatyl)piperazine (XXI). A solution of 7 g. of 5-benzyloxygramine and 0.9 g. of piperazine in 300 ml. of toluene was refluxed with stirring under nitrogen for 24 hr. Some of the product began to precipitate after a few hours. Filtration of the hot reaction mixture yielded 5.5 g. (80%) of the compound melting at 229–230°. Crystallization from dimethylformamide did not change this melting point.

Anal. Calcd. for $C_{36}H_{36}N_4O_2$: N, 10.07. Found: N, 10.01.

5-Benzyloxy-2-carbethoxy-3-indolecarboxaldehyde (XXIII). A mixture of 8 g. of *N*-methylformanilide and 9 g. of phosphoryl chloride was stirred for 15 min. under anhydrous conditions. Forty g. of ethylene dichloride was added to the mixture, followed by 14.2 g. of ethyl 5-benzyloxy-2-indolecarboxylate.[14] After stirring and refluxing for 1 hr. the reaction mixture was poured into a solution of 40 g. of sodium acetate in 80 ml. of ice water with stirring. The yellow paste which separated was triturated twice with water and once with ether to yield a finely divided solid, weighing 15 g. (96%), m.p. 240–242°. A pure sample was obtained by recrystallization of the crude material from ethylene dichloride to give light yellow, fine needles, m.p. 244–245°.

Anal. Calcd. for $C_{19}H_{17}NO_4$: C, 70.57; H, 5.30; N, 4.33. Found: C, 71.03; H, 5.25; N, 4.43.

The *oxime* was obtained by the following procedure: A mixture of 3 g. of indole aldehyde, 3 g. of hydroxylamine hydrochloride in 15 ml. of pyridine, and 15 ml. of absolute ethanol was heated gently on a steam bath for 2 hr. The excess solvent was evaporated and the residue was treated with cold water. The crude product was recrystallized from dilute ethanol to give 2.6 g. (83%) of colorless prisms, m.p. 220–221°.

Anal. Calcd. for $C_{19}H_{18}N_4O_4$: N, 8.28. Found: N, 8.12.

The *2,4-dinitrophenylhydrazone* was prepared in the usual manner and was recrystallized from ethyl acetate–ethanol to give a bright red material in almost theoretical yield, m.p. 278–280°.

Anal. Calcd. for $C_{25}H_{21}N_5O_7$: N, 13.91. Found: N, 13.63.

β-(2-Carbethoxy-5-benzyloxy-3-indole)acrylic acid (XXIV). Ten drops of piperidine was added to a solution of 1.5 g. of indole aldehyde (XXIII) and 3 g. of malonic acid in 15 ml. of pyridine. The solution was heated on a steam bath at 50–70° for 80 hr., then poured into ice water and acidified with dilute hydrochloric acid. The precipitate was filtered off and treated with 10% sodium hydroxide solution. The resulting insoluble material was filtered off and the filtrate was again acidified. The precipitate was recrystallized from 90% ethanol to yield 0.56 g. (31%) of pale yellow, cottony needles, m.p. 230° dec.

Anal. Calcd. for $C_{21}H_{19}NO_5$: C, 69.03; H, 5.24; N, 3.83. Found: C, 68.65; H, 5.15; N, 3.64.

PHILADELPHIA 44, PA.

[CONTRIBUTION FROM THE "LABORATORIO DE QUÍMICA BIOLÓGICA," FACULTAD DE CIENCIAS MÉDICAS, AND THE "LABORATORIOS DE INVESTIGACIÓN," E. R. SQUIBB & SONS ARGENTINA S.A.]

Reaction of Ammonia with Some Acetylated and Benzoylated Monosaccharides. VI. Derivatives of L-Arabinose, D-Xylose, and D-Ribose

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Received July 22, 1958

The tetraacetylated and tetrabenzoylated derivatives of L-arabinose, D-xylose and D-ribose gave, on treatment with methanolic ammonia, the *N,N'*-diacyl-pentosylidenediamines. By ammonolysis of tetrabenzoyl-L-arabononitrile and of tetrabenzoyl-D-xylononitrile, the *N,N'*-dibenzoyltetrosylidenediamines were obtained.

In our first papers[1] we described the action of methanolic ammonia on the pentaacetyl- and pentabenzoylhexoses, a reaction that leads, with opening of the pyranose or furanose ring, to the production as principal products, of the open chain *N,N'*-diacetyl-(I) or *N,N'*dibenzoylhexosylidenediamines (II). The reaction was afterwards applied to tetraacetyl and tetrabenzoyl-L-rhamnopyranose.[2] The products and yields almost duplicated the results with the corresponding D-mannose derivatives; while tetraacetyl-L-rhamnose produced only *N,N'*-diacetyl-L-rhamnosylidenediamine (III), tetrabenzoyl-L-rhamnose gave, as happened with pentabenzoyl-D-mannose, two products; the principal one was the open chain compound, *N,N'*-dibenzoyl-L-rhamnosylidenediamine (IV) and the secondary compound was a cyclic pyranose derivative, *N*-benzoyl-L-rhamnopyranosylamine.

(1) V. Deulofeu and J. O. Deferrari, *J. Org. Chem.*, **17**, 1087, 1093, 1097 (1952).

(2) J. O. Deferrari and V. Deulofeu, *J. Org. Chem.*, **22**, 802 (1957).