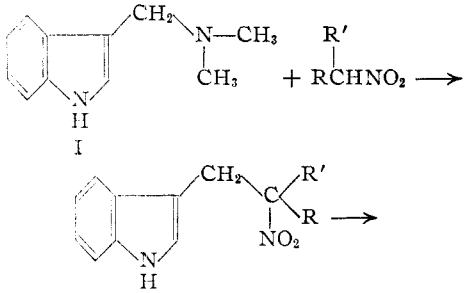
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

The Alkylation of Aliphatic Nitro Compounds with Gramine. A New Synthesis of Derivatives of Tryptamine[1,2]

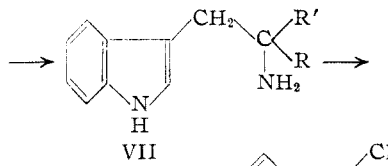
BY BY H. R. SNYDER AND LEON KATZ[3]

Derivatives of tryptamine are of interest not only because of the physiological activity of the parent base, but also because of the ease with which this base can be converted to substances containing the β-carboline nucleus.[4-9] Accordingly, it seemed profitable to examine the alkylation of aliphatic nitro compounds with gramine (I), a reaction which might be expected to yield nitro compounds of the type represented by II, reducible to substituted tryptamines. A similar

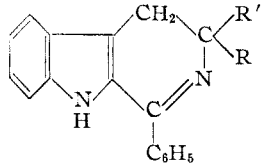


I

II R = R′ = CH_3
III R = H; R′ = C_2H_5
IV R = H; R′ = CH_3
V R = H; R′ = 3-indolemethyl
VI R = $CO_2C_2H_5$; R′ = 3-indolemethyl



VII



VIII R = H; R′ = C_2H_5

alkylation of nitromethane with Mannich bases obtained from acetophenones has been reported previously.[10]

The aliphatic nitro compounds which have been considered are nitromethane, nitroethane, 1-nitropropane, 2-nitropropane, 2-nitro-1-butanol and ethyl nitroacetate. Inasmuch as 2-nitropropane has only one active hydrogen atom it would be expected to give the simplest reaction with gramine. The reaction proceeded smoothly when a solution of gramine in an excess of 2-nitropropane was refluxed with solid sodium hydroxide as the catalyst, the crude condensation product being obtained in yields as high as 85%. 1-Nitropropane reacted similarly, producing the monosubstituted derivative (III) in yields as high as 95%. . Nitroethane and nitromethane both underwent dialkylation under these conditions; from the reaction of nitroethane the monoalkyl derivative (IV) was isolated in a yield of about 10%, but from trials with nitromethane only the dialkyl derivative (V) was obtained. Under similar conditions ethyl nitroacetate reacted with gramine methiodide[11] to give principally the disubstituted derivative (VI). The extensive dialkylation may have been a result of the low solubility of the sodium derivative of ethyl nitroacetate in the solvents chosen; this problem is under further study.[12]

Formaldehyde was evolved from the reaction mixture containing 2-nitro-1-butanol; this substance evidently reverts to 1-nitropropane and formaldehyde (in the presence of the alkali employed as a catalyst) too rapidly to permit the alkylation to proceed.

The various nitro compounds prepared were converted to amines by hydrogenation over Adams catalyst. The mixture obtained from ethyl nitroacetate on treatment with hydrogen chloride yielded a little of a substance which did not depress the melting point of the hydrochloride of the ethyl ester of tryptophan, the major product (isolated after hydrolysis to the amino acid) being the ester of di-(3-indolemethyl)-glycine. α,α-Dimethyltryptamine and α-ethyltryptamine, obtained by the reduction of the corresponding nitro compounds, did not yield acetyl derivatives on long boiling with glacial acetic acid; instead solid acetates were formed in good yields. These acetates were treated with phosphorus pentoxide according to the method used for the conversion of benzoyl tryptamine to 1-phenyl-3,4-dihydro-β-carboline,[8] but even under these conditions they were not dehydrated to amides and no cyclization occurred. The two tryptamines were readily converted to solid benzoyl derivatives by the use of benzoyl chloride and pyridine. The benzoyl de-

(1) Presented in part at the Tenth National Organic Symposium of the American Chemical Society, Boston, Mass., June 12, 1947.

(2) For the preceding paper in this series see Howe, Zambito, Snyder and Tishler, THIS JOURNAL, **67**, 38 (1945).

(3) Present address: Calco Chemical Division, American Cyanamid Co., Bound Brook, N. J.

(4) Akabori and Saito, *Ber.*, **63**, 2245 (1930).

(5) Spaeth and Lederer, *ibid.*, **63**, 124, 2102 (1938).

(6) Hahn and others, *ibid.*, **67**, 2031; **71**, 2163, 2175 (1938).

(7) Hahn, Barwald, Schales and Werner, *Ann.*, **520**, 107 (1935).

(8) Asahina and Osada, *Chem. Zentr.*, **98**, I, 1479 (1927).

(9) Tatsui, *ibid.*, **99**, II, 668 (1928).

(10) Reichert and Posemann, *Arch. Pharm.*, **275**, 67 (1937).

(11) This experiment was first carried out by Mr. F. J. Pilgrim.

(12) NOTE ADDED IN PROOF.—After this manuscript had been submitted, Lyttle and Weisblat [THIS JOURNAL, **69**, 2118 (1947)] reported the monoalkylation of ethyl nitroacetate with gramine.

TABLE I

Alkylation product										Amine prepared by hydrogenation					
						Analyses, %						Analyses, %			
						Calcd.		Found				Calcd.		Found	
Nitro compd.	Degree of alkylation	Yield, %	B. p., °C.	Pressure, mm.	M. p., °C.	C	H	C	H	Yield, %	M. p., °C.	C	H	C	H
1-Nitropropane	mono	82–95	157	0.2	90–91	66.08	6.42	66.32	6.33	58–65[a,b]	101–102	76.59	8.51	76.32	8.39
2-Nitropropane	mono	80–85	153–155	.05	66.5–68	66.08	6.42	66.47	6.53	67–75[c,d]	130–131	76.59	8.51	76.79	8.30
Nitroethane	mono	20	178–180	.5	171–172[e]	47.11[e]	3.46[e]	46.55[e]	2.70[e]	20	80–81	75.85	8.04	75.65	7.96
Nitromethane	di	20	.....	..	206	71.47	5.31	71.34	5.15	.....	.....	.....	.....	.....	.....
Ethyl nitroacetate	di	80	.....	..	142.5–143	67.50	5.41	67.49	5.54	.....	286[f]	72.05[f]	5.74[f]	71.88[f]	5.59[f]

[a] The acetate melted at 161°. *Anal.* Calcd. for $C_{14}H_{20}N_2O_2$: C, 67.74; H, 8.06. Found: C, 67.79; H, 8.19. [b] The benzoyl derivative melted at 101°. *Anal.* Calcd. for $C_{19}H_{20}N_2O$: C, 78.08; H, 6.85. Found: C, 78.02; H, 6.61. [c] The acetate melted at 204°. *Anal.* Calcd. for $C_{14}H_{20}N_2O_2$: C, 67.74; H, 8.06. Found: C, 67.48; H, 7.85. [d] The benzoyl derivative melted at 148°. *Anal.* Calcd. for $C_{19}H_{20}N_2O$: C, 78.08; H, 6.85. Found: C, 77.82; H, 6.67. [e] These figures refer to the picrate. [f] These figures refer to the amino acid.

rivative of α-ethyltryptamine gave the expected dihydro-β-carboline (VIII) on treatment with phosphorus pentoxide.

Experimental

(1) **Alkylation of Nitro Compounds with Gramine.**—The reaction with 1-nitropropane was carried out by refluxing a solution of 10 g. of gramine in 50 ml. of the redistilled nitropropane in the presence of 2.6 g. of solid sodium hydroxide. Nitrogen was passed through the system before the heating was begun. Dimethylamine was evolved copiously, and refluxing was continued for six to eight hours, or until the evolution of the amine had nearly ceased. The mixture was then cooled and acidified with 50 ml. of 10 % aqueous acetic acid. The resulting mixture was diluted with 200 ml. of ether and washed four times with 75-ml. portions of water. The solution then was shaken with Norit and filtered. The solvents were removed by distillation at room temperature, leaving a viscous brown oil; the analytical sample was prepared by distillation at approximately 0.2 mm. pressure (b. p. 157°). In a later preparation (by Mr. John P. Pellegrini) the condensation product was obtained as a solid, melting at 90–91°, which could be used to seed the older samples.

Most of the other preparations were carried out in essentially the same manner. The distilled product from nitroethane was converted to a solid picrate which was analyzed. The picrate of di-(3-indolemethyl)-nitromethane was prepared by treating the crude product with ethanolic picric acid; in this instance the nitro compound itself was isolated from a run carried out in ethyl cellosolve at 130°.

The experiment with ethyl nitroacetate was carried out in ethanol with equimolar quantities of gramine methiodide, ethyl nitroacetate and sodium ethoxide, the mixture being refluxed (for about fifteen hours) until the evolution of trimethylamine had ceased. The resulting mixture was filtered, concentrated, dissolved in ether, acidified with acetic acid and the crude product was recovered by removal of the ether from the dried solution. The resulting oil crystallized on standing for about a day, yielding 80% of crude VI melting at 136–139°.

(2) **Hydrogenation of the Nitro Compounds.**—A solution of 15 g. of the condensation product from 1-nitropropane in 150 ml. of ethanol was refluxed for fifteen minutes with ¼ teaspoonful of Raney nickel catalyst. The nickel was filtered from the cooled solution, which was then placed in a hydrogenation bottle with 0.2 g. of Adams catalyst. The hydrogenation was conducted at room temperature and under an initial pressure of about 50 lb., and it was allowed to proceed for about thirty-six hours. After filtration from the catalyst the solution was concentrated and the residue was dissolved in 200 ml. of benzene. The basic material recovered by extraction of the benzene solution with three 150-ml. portions of 2 *N* hydrochloric acid which were added to 500 ml. of 2 *N* sodium hydroxide weighed 8 g. and melted at 93–95°. The analytical sample (m. p. 101–102°) was prepared by crystallization from benzene.

Other preparations of amines were carried out in essentially the same manner. The hydrogenation of the product from ethyl nitroacetate was begun on a sample of the crude (oily) material before it was recognized as consisting largely of the dialkylated nitro ester (VI). A portion of the hydrogenated solution was treated with dry hydrogen chloride at −50°. The solid which separated, after recrystallization from ethyl acetate, melted at 224–226°, and this melting point was not depressed by addition of known hydrochloride of the ethyl ester of *dl*-tryptophan.[13] Another portion of the hydrogenation solution was concentrated and the residue was boiled with 10% aqueous sodium hydroxide. Acidification of the alkaline solution with acetic acid caused the immediate separation of a solid and the slow crystallization of a second fraction of m. p. 284–286°. This second fraction was amphoteric, melted at 286° after recrystallization from water, and had the composition of di-(3-indolemethyl)-glycine.

(3) **Derivatives of the Amines.**—The acetates of α-ethyltryptamine and α,α-dimethyltryptamine resulted when solutions of the amines in about four parts of glacial acetic acid were refluxed for five hours. The benzoyl derivatives of these two amines were prepared by benzoylation in pyridine solution.

1-Phenyl-3-ethyl-3,4-dihydro-β-carboline (VIII) was prepared by adding over a period of forty-five minutes a mixture of 12 g. of phosphorus pentoxide and 2.5 g. of Filter-Cel to a refluxing, stirred mixture of 0.8 g. of N-benzoyl-α-ethyltryptamine and 50 ml. of dry xylene. The mixture was refluxed for one and one-half hours after the completion of the addition. The cooled mixture was treated cautiously with 20 ml. of cold water and then with 25 ml. of 3 *N* hydrochloric acid. After filtration the solid was washed with 10 ml. of 3 *N* hydrochloric acid and the xylene was removed by steam distillation under diminished pressure. The product was recovered from the aqueous phase (volume about 50 ml.) by addition of 20% aqueous sodium hydroxide. The solid was collected, washed with water, and dried at 100° under 1 mm. pressure. The weight of material melting at 148–156° was 0.6 g. (80%). The analytical sample, m. p. 162°, was prepared by recrystallization from low-boiling petroleum ether containing a little benzene.

Anal. Calcd. for $C_{19}H_{18}N_2$: C, 83.21; H, 6.57. Found: C, 83.01; H, 6.53.

Summary

The nitropropanes are alkylated by the tertiary amine gramine, yielding nitro compounds which are reduced to derivatives of tryptamine. Similar alkylation occurs with nitroethane, but is accompanied by much dialkylation; only the product of dialkylation has been isolated from the reaction with nitromethane. Both monoalkylation and dialkylation occur when ethyl nitroacetate is

(13) The *dl*-tryptophan ethyl ester hydrochloride employed had been prepared by esterification of the amino acid with ethanol and hydrogen chloride at room temperature. It melted at 226–227° and had the composition: C, 58.23; H, 6.57 (Calcd.: C, 58.36; H, 6.32).

treated with gramine methiodide and sodium ethoxide in ethanol.

The synthesis of 1-phenyl-3-ethyl-3,4-dihydro-β-carboline is effected by alkylation of 1-nitropropane with gramine, reduction of the product, and cyclization of the benzoyl derivative of the resulting amine.

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NOTES

The Chlorination of Anthranilic Acid

BY EDWARD R. ATKINSON AND PARKER B. MITTON

The extension to a larger scale[1] of our earlier synthesis[2] of the resolvable *d,l*-4,6,4′,6′-tetrachlorodiphenic acid required the preparation of large amounts of 3,5-dichloro-2-aminobenzoic acid. The present paper describes the conditions we found best for the direct chlorination of anthranilic acid in either glacial acetic acid or in dilute hydrochloric acid. We have also identified three of the polychloro by-products which are formed in acetic acid solution, and which have not been isolated from this reaction mixture in previous work. The most interesting of these is 2,3,4,4,5,6-hexachloro-2,5-cyclohexadiene-1-one which has previously been prepared by the chlorination of a number of other aromatic substances and which recently has been introduced as an insecticide and fungicide.[3]

Experimental

Chlorination in Glacial Acetic Acid.—The method of Elion[4] did not give satisfactory results when used with 200 g. of anthranilic acid until important modifications were introduced. At least 25 cc. of commercial glacial acetic acid was used per gram of anthranilic acid; no change in results was noted when chlorination was performed under completely anhydrous conditions. When stirring of the reaction mixture was vigorous, the rate at which chlorine gas was introduced was not a critical factor. Dilution of chlorine with air prior to use did not increase the yield of the desired product. The reaction mixture was maintained at 15–20°. Chlorination was continued until the reaction mixture gained 1.0 g. to 1.4 g. per gram of anthranilic acid used. Further chlorination led to a marked diminution in yield with a corresponding increase in polychloro by-products. In all experiments these could be removed by leaching the crude with benzene as previously described[1] but we preferred to filter the solid mixture of crude mono- and dichloroanthranilic acids directly from the reaction mixture, the by-products remaining dissolved in the acetic acid filtrate. Their isolation and identification is described below.

The crude product was dried at temperatures under 40° then leached with boiling 15% hydrochloric acid, using 20 cc. of this acid per gram of crude. The insoluble portion was the desired 3,5-dichloro-2-aminobenzoic acid, m. p. 224–226°, obtained in over-all yields of 41–50%. 5-Chloro-2-aminobenzoic acid was recovered from the hydrochloric acid solution by raising the *p*H to 6.

Chlorination in Dilute Hydrochloric Acid.—Anthranilic acid was dissolved in 15% hydrochloric acid (20 cc. per gram) and chlorinated at 15–20° as above until the reaction mixture gained 1.0 to 1.2 g. per gram of anthranilic acid used. The crude product was filtered from the reaction mixture. It melted at 210–220° and was obtained in yields of 80%. In this method the 5-chloro-2-aminobenzoic acid by-product remained dissolved in the acidic reaction mixture. After appropriate dilution with water this acid solution could be used as solvent for a subsequent chlorination reaction.

Identification of Polychloro By-products.—These were easily isolated by pouring the filtrate from chlorinations in acetic acid into a large volume of water. For example when 20 g. of anthranilic acid was chlorinated until the reaction mixture had gained 38 g. in weight very little mono- and dichloroanthranilic acids were obtained. The filtrate was poured into 2 liters of water and a colorless emulsion was obtained. After four days a mass of yellow crystals imbedded in a red tar was separated by decantation. From this material there was isolated 5 g. of 2,3,4,-4,5,6-hexachloro-2,5-cyclohexadiene-1-one,[5] 1 g. of chloranil, 0.5 g. of pentachlorophenol and a red oil which must have consisted chiefly of the hexachlorocyclohexadienone since it gave 2 g. of pentachlorophenol on reduction with stannous chloride in acetic acid.[5]

In his original work on the chlorination of anthranilic acid in acetic acid solution Elion[4] poured the entire reaction mixture into a large volume of aqueous sulfite solution. No explanation for the use of sulfite was given. We have observed that if sulfite is used, hexachlorocyclohexadienone is not isolated, for this material is easily reduced by aqueous bisulfite to pentachlorophenol at room temperature.

(1) Atkinson, Morgan, Warren, Manning, THIS JOURNAL, **67**, 1513 (1945).

(2) Atkinson and Lawler, *Ibid.*, **62**, 1704 (1940).

(3) (a) Swingle, Phillips and Gahan, U. S. Dept. Agri., Bureau Entomol. Plant Quarantine E-621 (1944); (b) Wolcott, *Caribbean Forester*, **6**, 245 (1945); (c) Ter. Horst, U. S. Patent 2,378,597 (1945).

(4) Elion, *Rec. trav. chim.*, **44**, 1106 (1925).

(5) Biltz, *Ber.*, **37**, 4009 (1904).

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Extractives of Douglas Fir and Douglas Fir Lignin Residue

BY IRA L. CLARK, J. R. HICKS AND E. E. HARRIS

The appearance of wax-like materials of high boiling point in the hydrogenation product of lignin residue from the dilute acid hydrolysis of Douglas fir led to an investigation at the Forest Products Laboratory of the extractives present in this lignin residue and in the original wood-bark mixture. The lignin used was a residue of the Madison wood-sugar process[1] which treats sawmill waste with 0.5% sulfuric acid at 150°.

(1) E. E. Harris and E. Beglinger, *Ind. Eng. Chem.*, **38**, 890–895 (1946).