1067. N-*Alkylated* 5-*Fluorotryptamines.*

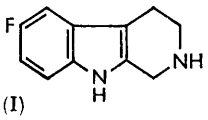
By Z. Pelchowicz, A. Kaluszyner, and M. Bentov.

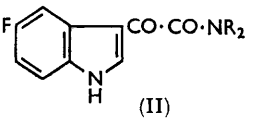
A new synthesis of 5-fluoroindole from 3-fluorotoluene is described. Through condensation with oxalyl chloride, reaction with secondary amines, and reduction, *N*-alkyl-5-fluorotryptamines have been prepared.

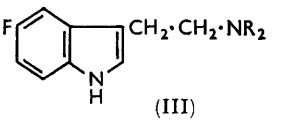
The biological properties of *N*-alkyl-tryptamines have recently aroused interest,[1] in particular, 5-hydroxy-*NN*-dimethyltryptamine (bufotenin) which produces hallucinations and intoxication. Seeds of *Piptadenia peregrina* and *macrocarpa* which contain this base and its hydroxyl-free analogue, have been used for centuries by the natives of South America for ceremonial purposes.[2] In view of the biological properties conferred upon

[1] See, *e.g.*, Hearst and Szara, *Amer. Psychologist*, 1960, **15**, 476; Gessner, McIsaac, and Page, *Nature*, 1961, **190**, 179.
[2] Manske, "The Alkaloids," Academic Press, New York and London, 1960, Vol. VII, p. 5.

tryptophan by $C_{(5)}$-fluorination,[3] *NN*-dialkyl derivatives (III) of 5-fluorotryptamine have been synthesised. 5-Fluorotryptamine,[4] upon treatment with formaldehyde and formic

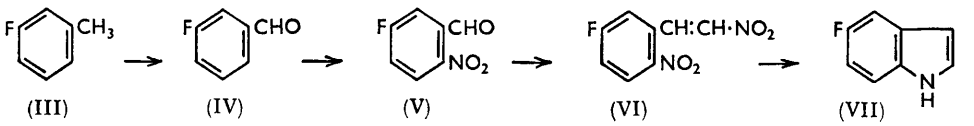

(I)


(II)


(III)

acid, did not yield a methyl derivative but a compound believed to be 6-fluoro-1,2,3,4-tetrahydronorharmaline (I), by analogy with the reaction between 5-fluorotryptamine and acetaldehyde [5] and in view of the similarity of the infrared spectra of the two substances. Speeter and Anthony's method [6] was, therefore, used for the synthesis of the tryptamine (III).* 5-Fluoroindole reacted smoothly with oxalyl chloride; the resulting chloride was treated with dimethylamine or diethylamine, and the products (II) were reduced with lithium aluminium hydride in ether–tetrahydrofuran. The desired bases (III; R = Me or Et) were isolated as their hydrochlorides.

The known methods for the synthesis of 5-fluoroindole (VII) [7,8] did not lend themselves to large-scale preparations. The following four-step method gave an overall yield of 29%, starting from 3-fluorotoluene:


(III) (IV) (V) (VI) (VII)

For the conversion of 3-fluorotoluene into 3-fluorobenzaldehyde (IV),[9] chlorination to 3-fluorobenzylidene chloride and subsequent hydrolysis appear to be preferable to oxidation with chromic anhydride. Nitration of the aldehyde [9] can be carried out either with nitric acid and sulphuric acid (at the stage of the diacetate) or with sulphuric acid and potassium nitrate; both of these methods are superior to the nitration with nitric acid in acetic anhydride. The reduction of 5-fluoro-2,ω-dinitrostyrene (VI), easily obtained from the nitrated aldehyde (V) and nitromethane,[10] is best carried out catalytically,[11] in ethyl acetate–acetic acid as solvent; inferior results were obtained with iron in acetic acid–ethanol.[12]

Experimental

6-Fluoro-1,2,3,4-tetrahydronorharmaline (I).—A mixture of 5-fluorotryptamine hydrochloride (10 g.), 36% formaldehyde solution (7·8 g.), 88% formic acid (6·0 g.), and sodium carbonate (2·5 g.) was refluxed gently for 5 hr., cooled, diluted, and neutralized. The *product* (8·5 g.) was insoluble in ether and water, soluble in hot hydrochloric acid, and had m. p. 226—228° (from ethanol) (Found: F, 10·4; N, 14·7. $C_{11}H_{11}FN_2$ requires F, 10·0; N, 14·7%).

3-Fluorobenzaldehyde (IV).—(*a*) A stream of chlorine was passed through boiling and strongly illuminated 3-fluorotoluene (110 g.), until *ca.* 70 g. were absorbed and the internal temperature had reached 195°. The resulting *3-fluorobenzylidene chloride* had b. p. 202—204°, n_D^{16} 1·5304, d_{16}^{16} 1·360, M_R, 40·70 (Calc.: 40·40) (Found: C, 46·6; H, 3·1; F, 10·7. $C_7H_5Cl_2F$ requires C, 46·9; H, 2·8; F, 10·6%). The crude 3-fluorobenzylidene chloride was refluxed for

* In a recent paper [5] we overlooked the fact that 7-methyltryptamine had been prepared by the same method before (Abramovitch *et al.*, *J.*, 1951, 847).

[3] See, *e.g.*, Sharon and Lipmann, *Arch. Biochem. Biophys.*, 1957, **69**, 219.
[4] Pelchowicz and Bergmann, *J.*, 1959, 847.
[5] Pelchowicz and Bergmann, *J.*, 1960, 4699.
[6] Speeter and Anthony, *J. Amer. Chem. Soc.*, 1954, **76**, 6208.
[7] Allen, Brunton, and Suschitzky, *J.*, 1955, 1283.
[8] Bergmann and Pelchowicz, *J.*, 1959, 1913.
[9] Schwarcz, Ph.D. Thesis, University of Buenos Aires, 1955.
[10] Huebner, Troxell, and Schroeder, *J. Amer. Chem. Soc.*, 1953, **75**, 5887.
[11] Benington, Morin, and Clark, *J. Org. Chem.*, 1960, **25**, 1542.
[12] A.Ek and B. Witkop, *J. Amer. Chem. Soc.*, 1954, **76**, 5579.

5 hr. with calcium carbonate (500 g.) and water (1·2 l.), and the organic material was steam distilled and then extracted with ether. The extract was washed with dilute sodium carbonate solution, dried, and distilled. The *aldehyde* (87 g.; 70%) boiled at 80—81°/30 mm. From the alkaline washings 3-fluorobenzoic acid (8 g., 6%), m. p. 123—125°, was isolated.

(*b*) To 3-fluorotoluene (71 g.), dissolved in a mixture of acetic anhydride (500 ml.) and acetic acid, sulphuric acid (230 g.) was added while cooling and stirring. The solution was cooled to −5°, and chromic anhydride (130 g.) added so that the temperature did not exceed 10°. The stirring was continued at room temperature for 1 hr. and the product poured into ice–water and filtered off. 3-*Fluorobenzylidene diacetate* (106 g., 73%) crystallized from light petroleum (b. p. 60—90°) and melted at 40° (Found: F, 8·1. $C_{11}H_{11}FO_4$ requires F, 8·4%).

5-*Fluoro*-2-*nitrobenzaldehyde* (V).—(*a*) *Acetic anhydride–nitric acid method.* A solution of 3-fluorobenzaldehyde (77·5 g.) in acetic anhydride (190 ml.) was slowly mixed with a cold solution of concentrated sulphuric acid (8 ml.) in acetic anhydride (380 ml.), and nitric acid (155 ml., *d* 1·50) added, dropwise and with stirring, at 20—30° during 40 min. The stirring was continued for 3 hr. and the solution then poured on crushed ice (2 kg.) and partially neutralized with 30% sodium hydroxide solution. The yellowish precipitate (105 g., 62%) was washed with cold water, triturated with cold ethanol, filtered off, and dried. 5-*Fluoro*-2-*nitrobenzaldehyde diacetate* (105 g., 62%), after recrystallization from ethanol, had 90—91° (Found: C, 48·2; H, 4·1; F, 6·9; N, 5·4. $C_{11}H_{10}FNO_6$ requires C, 48·7; H, 3·8; F, 7·0; N, 5·2%). The crude diacetate was hydrolysed by refluxing it for 1 hr. with concentrated sulphuric acid (30 ml.) in 50% ethanol (550 ml.). The solution was cooled and filtered to give 5-fluoro-2-nitrobenzaldehyde (V) (60·5 g., 57%), m. p. 94—95°.

(*b*) *Sulphuric acid–potassium nitrate method.* 3-Fluorobenzaldehyde (87 g.) was added dropwise at 0° to a stirred mixture of concentrated sulphuric acid (1 kg.) and powdered potassium nitrate (74·5 g.), and the resulting solution stirred for 15—20 min. and poured on ice–water (3 kg.). The white precipitate was washed thoroughly with cold water and dried. The aldehyde so obtained (108 g., 91%) melted at 93—95° and was sufficiently pure.

(*c*) *Sulphuric acid–nitric acid method.* 3-Fluorobenzaldehyde diacetate (70 g.) was added during 5 min. and with good agitation to concentrated sulphuric acid (250 ml.), cooled to −5°. The temperature rose to 2°. The stirring was continued for 10 min. and nitric acid (100 ml., *d* 1·52) added gradually between −10 and 0°. The temperature was permitted to reach 14° and the mixture was then poured on crushed ice. The product (48·5 g., 88%) formed yellowish needles (from dilute ethanol), m. p. 94°.

5-*Fluoro*-2,ω-*dinitrostyrene* (VI).—To a stirred mixture of the fluoronitrobenzaldehyde (V) (55 g.), nitromethane (18 g.), and methanol (80 ml.), cooled to −18°, sodium hydroxide (13·6 g.) in water (20 ml.) was added slowly so that the temperature did not exceed 10°. The stirring was continued for 1 hr. at 10—15° (if the solution had become too viscous, more methanol was added) and the mixture poured into ice–water (250 ml.). The clear solution was stirred quickly into a mixture of water (80 ml.) and concentrated hydrochloric acid (80 ml.). 1-(5-*Fluoro*-2-*nitrophenyl*)-2-*nitroethanol*, was filtered off. A sample was recrystallized from chloroform–light petroleum and melted at 93—94° (Found: C, 42·1; H, 3·0; F, 8·0. $C_8H_7FN_2O_5$ requires C, 41·8; H, 3·0; F, 8·3%).

The alcohol was refluxed for 5 min. with acetic anhydride (150 ml.) and sodium acetate (40 g.) and the solution poured into water (500 ml.) and kept until the practically pure *styrene* (46 g., 73%) solidified; recrystallization from light petroleum (b. p. 40—60°) raised the m. p. to 85—86° (Found: C, 45·7; H, 2·6. $C_8H_5FN_2O_4$ requires C, 45·3; H, 2·4%).

5-*Fluoroindole* (VII).—The styrene (VI) (20 g.), in a mixture of ethyl acetate (200 ml.) and glacial acetic acid (50 ml.), was hydrogenated in the presence of 10% palladium–charcoal at 40—50°/3 atm.; the theoretical quantity of hydrogen was absorbed within 10 min. The filtered solution was neutralized with solid sodium carbonate, filtered, and evaporated. 5-Fluoroindole (10·5 g., 83%) was best purified by steam distillation; it had m. p. 46—47°.

5-*Fluoro*-3-*indolylglyoxylyl Chloride*.—A solution of oxalyl chloride (17 ml.) in ether (60 ml.) was added with stirring and external cooling to 5-fluoroindole (13·5 g.) in ether (150 ml.). The yellow precipitate (19·0 g., 84%) was filtered off after 2 hr. and washed with a little ether. It could not be purified and was used directly for further experiments.

5-*Fluoro*-3-*indolylglyoxyl*-NN-*dimethylamide*. (II; R = Me).—A suspension of the chloride (9 g.) in ether (30 ml.) was slowly treated with dimethylamine (10 ml.) in ether. The *amide* (8·2 g., 88%) was collected, washed with water, and recrystallized from methanol; it formed

long needles, m. p. 201—202° (beginning to sublime) (Found: C, 61·8; H, 4·8; F, 8·1. $C_{12}H_{11}FN_2O_2$ requires C, 61·6; H, 4·7; F, 8·1%).

NN-*Diethyl-5-fluoro-3-indolylglyoxylamide* (II; R = Et) was prepared analogously in 82% yield; it formed needles, m. p. 208—210° (Found: C, 64·0; H, 5·9. $C_{14}H_{15}FN_2O_2$ requires C, 64·1; H, 5·8%).

5-*Fluoro*-NN-*dimethyltryptamine* (III; R = Me).—A solution of the glyoxylamide (II; R = Me) (7·0 g.) in tetrahydrofuran (150 ml.) was added dropwise to lithium aluminium hydride (8·5 g.) in ether (200 ml.). The mixture was refluxed with stirring for 1 hr., cautiously decomposed by successive addition of ethyl acetate and water, filtered, and concentrated. The residue was dissolved in ether, filtered, and treated with ethereal hydrogen chloride solution. The *hydrochloride* (2·8 g., 38%), crystallized from toluene–ethanol, had m. p. 175—176° (Found: C, 59·1; H, 6·9; F, 8·2. $C_{12}H_{16}ClFN_2$ requires C, 59·4; H, 6·6; F, 7·8). The picrate of the base melted at 180—181°.

NN-*Diethyl-5-fluorotryptamine* (III; R = Et).—The analogous treatment of the glyoxylamide (II; R = Et) (8·5 g.) in tetrahydrofuran (100 ml.) with lithium aluminium hydride (8·5 g.) in ether (200 ml.) gave the desired base (4·5 g., 59%) as a viscous oil, b. p. 160—165°/0·7 mm. In the crystallization of the *hydrochloride*, prepared as above, from toluene–ethanol, serious losses were sustained; the product had m. p. 192—193° (Found: C, 62·2; H, 7·6. $C_{14}H_{20}ClFN_2$ requires C, 62·1; H, 7·4%). The *picrate*, recrystallized from dilute ethanol, melted at 199—200° (Found: C, 51·9; H, 5·1. $C_{20}H_{22}FN_5O_7$ requires C, 51·8; H, 4·8%).

ISRAEL INSTITUTE FOR BIOLOGICAL RESEARCH,
NESS-ZIONA, ISRAEL.

[*Received, June 26th*, 1961.]