pyrrole ring by the thiophene ring is associated with a fall in stimulant activity. While XII inhibits the stimulant response to serotonin on the isolated rat fundus strip, the 2-aminopropyl compound XIII produced powerful contractions of the same tissue.

The presence of a 5-amino group and the side chain in the 2-position characterize the compounds of Group D which show very weak antagonism towards serotonin, histamine, and acetylcholine. With the exception of compound XV, serotonin-induced vasoconstriction was not antagonized but there was partial inhibition of epinephrine and norepinephrine vasoconstriction on the isolated perfused rat hindquarters.

The compounds of Group A exhibit the variability and nonselectivity in pharmacological properties characteristic of the corresponding indole derivatives.[21f,22] These features, the existence of both agonistic and antagonistic activity in the same compounds and the observed auto-inhibitory phenomena, make it difficult to draw any inferences concerning the influence on biological activity of replacing the indole by the benzo[*b*]thiophene ring system. These difficulties are further underlined by the lack of conclusive evidence that any specific serotonin receptor exists. An attempt to establish the nature of the interaction between the benzo[*b*]thiophene compounds and the hypothetical serotonin receptor, using Ariëns' technique on the rat jejunum, showed that I, VI, XI, XIV, XVI, and XVII possessed both agonistic and noncompetitively antagonistic properties, while the others exerted only a noncompetitive antagonism.[1b] It can be suggested, therefore, that the replacement of the –NH– group of the indole ring by sulfur leads to a reduction in the intrinsic activity.[23] The ability of the benzo[*b*]thiophene compounds to antagonize acetylcholine, histamine, and serotonin, and the ability of atropine, mepyramine, and lysergic acid diethylamide to antagonize the agonistic component of action of these compounds, where it exists, may have its explanation in a nonspecific affinity for additional receptor fields.[24]

The phenomenon of auto-inhibition was frequently observed in the compounds of Groups A and C, in which the response to the second and higher dose on the guinea pig ileum was observed to be less than that to the first. Moreover, larger doses stimulated the tissue but then rendered it insensitive to further additions of the drug. This effect has also been observed with acetylcholine, histamine, and serotonin.[25a,b]

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Synthesis and Pharmacological Activity of Fluorinated Tryptamine Derivatives

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The synthesis of several fluorinated tryptamine derivatives in which the fluorine atom occupies the 5- or 6-position is reported. The 5-fluoro and unsubstituted tryptamines are more active than the 6-substituted derivatives in inducing spontaneous locomotion when administered to reserpinized white mice. Both 6-fluoro-N,N-diethyltryptamine and N,N-diethyltryptamine exerted peripheral activity when tested in humans, but only the fluorine-free compound seemed to bear hallucinogenic properties. These results may be explained by change in the metabolic pathway of the tryptamines with substituted 6-position in the indole nucleus.

The 6-hydroxylation of various tryptamine derivatives was established in this laboratory as an important metabolic pathway.[3] Evidence was presented, using animal behavioral tests and human experiments, that this pathway might be important in producing pharmacologically active metabolites.[4,5] For further pharmacological and psychological studies it was of interest to prepare and compare the activity of structural isomers blocked in the 6-position, as this may render additional evidence for the proposed biological mechanism.

The fluorinated derivatives seemed to be particularly appropriate for this kind of study because of their stability and the availability of the starting 5- and 6-fluoroindoles.[6,7] Attempts were made to improve the synthesis of 6-fluoroindole since the oxidation of 4-fluoro-2-nitrotoluene (I) to the corresponding aldehyde was cumbersome. Addition of bromine to I at elevated temperature resulted in the introduction of two atoms of the halogen into the molecule, but subsequent hydrolysis yielded a bromine-containing organic acid. Nitration of *p*-fluorobenzyl chloride, alcohol, or acetate in acetic anhydride–nitric acid did not yield the expected nitro derivatives and in all cases only the acetate was recovered. The presence of sulfuric acid in this reaction brought about polymerization.

Nitration of *p*-fluorobenzyl cyanide did not yield either of the two expected isomers. The only compound isolated did not contain fluorine. The analytical data of this substance and derivatives support the

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(2) Name changed from A. Kaluszyner.

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(4) S. Szara, *Federation Proc.*, **20**, 885 (1961).

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(6) Z. Pelchowicz, A. Kaluszyner, and M. Bentov, *J. Chem. Soc.*, 5418 (1961).

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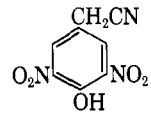
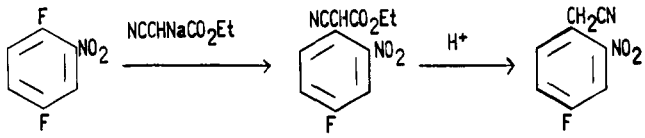
structure I. The compound was converted into the



I

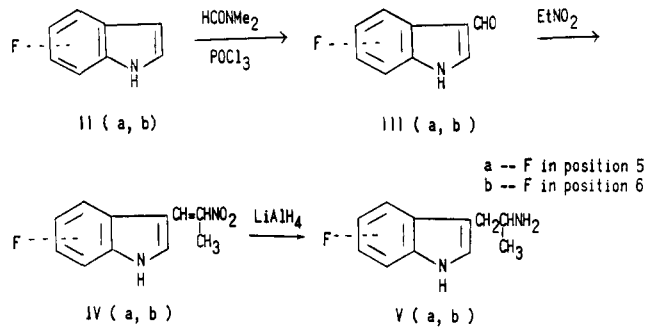
corresponding acid and its known ethyl ester.[8]

The 4-fluoro-2-nitrobenzyl cyanide was easily prepared according to the following sequence.



Reductive cyclization of 4-fluoro-2-nitrobenzyl cyanide with anhydrous stannous chloride[9] was unsuccessful. Reduction over palladium-on-charcoal in a Parr hydrogenation apparatus produced the desired 6-fluoroindole in low yield only.

The 5- and 6-fluoro-α-methyltryptamines were obtained by condensing appropriate aldehydes (prepared in turn from the fluoroindoles, dimethylformamide, and phosphorus oxychloride[10]) with nitroethane followed by lithium aluminum hydride reduction of the resulting nitrovinylindoles.[11]



Condensation of IIb with oxalyl chloride and treatment with diethylamine followed by reduction gave 6-fluoro-N,N-diethyltryptamine.[12]

Pharmacological Findings.—Compounds Va,b were tested on mice using reserpine-induced ptosis reversal and activity cage tests.[13] In these tests, (see Fig. 1 and 2) Va acted like the parent compound, α-methyltryptamine, but there was a marked decrease in activity especially in the locomotor test with the 6-fluoro derivative. The effect of 6-fluorodiethyltryptamine was compared with diethyltryptamine (DET) in six patients and one normal volunteer. Both drugs were given intramuscularly in 1 mg./kg. doses. DET produced sympathomimetic autonomic symptoms, perceptual disturbances, hallucinations, mood changes, and difficulties in thinking and speaking. The 6-fluoro analog in the same persons produced the autonomic symptoms and mood changes *without* the perceptual and thinking disturbances so characteristic of hallucinogenic drugs.

(8) J. H. Wilkinson, *Chem. Ind.* (London), 1352 (1955).
(9) H. Stephen, *J. Chem. Soc.*, **127**, 1874 (1925).
(10) P. N. James and H. R. Snyder, *Org. Syn.*, **39**, 30 (1959).
(11) E. H. P. Young, *J. Chem. Soc.*, 3493 (1958).
(12) M. E. Speeter and W. C. Anthony, *J. Am. Chem. Soc.*, **76**, 6208 (1954).
(13) A. Kalir and S. Szara, *Federation Proc.*, **21** (2), 337 (1962).

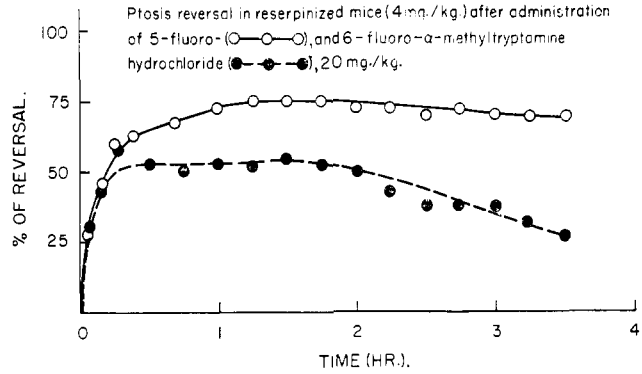


Figure 1.

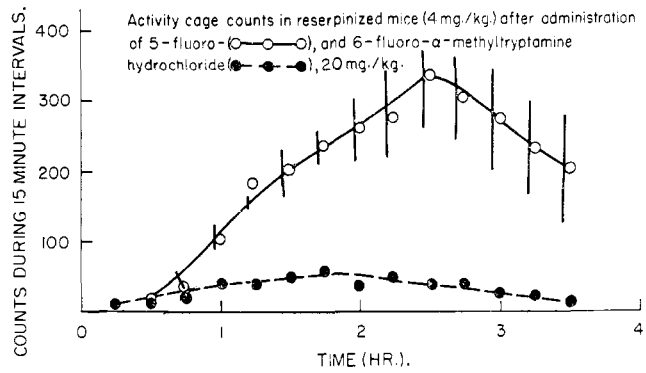


Figure 2.

In the urine of the patients treated with DET, various amounts of 6-hydroxy DET could be found (4.5–20.3% of the administered DET). In the case of the 6-fluoro analog, the urine contained large amounts of unchanged compound but no 6-hydroxy derivative could be detected.

These results indicate that the 6-fluoro substitution of the indole ring may represent an important structural change resulting in a different metabolic pathway, and quite possibly in a different pharmacological and psychological action of the compound.

Experimental[14]

2-Nitro-4-fluorotoluene.—*p*-Fluorotoluene (220 g., 2 moles) was mixed with 700 ml. of ice-cold concentrated sulfuric acid and treated at 5–10° with a mixture of 97 ml. of nitric acid (*d* 1.5) and 100 ml. of sulfuric acid. The stirring was continued for 1.5 hr., and the contents were poured onto crushed ice. The organic layer was separated, washed successively with water, sodium carbonate solution, again water, and dried ($MgSO_4$). The crude product (270 g.) was fractionated to give 190.5 g. of 2-nitro-4-fluorotoluene,[15] b.p. 107–109° (22 mm.), and 65 g. of a higher boiling fraction, which in turn was refluxed with 30 ml. of piperidine and 50 ml. of ethanol to remove the 3-nitro isomer, cooled, diluted with water, acidified, extracted with ether, and distilled to yield an additional 38 g. of 2-nitro-4-fluorotoluene; total yield, 228.5 g. (74%).

2-Nitro-4-fluorobenzaldehyde.—Oxidation of the 2-nitro-4-fluorotoluene with chromic acid–acetic anhydride[16] gave 27–32% of 2-nitro-4-fluorobenzaldehyde, m.p. 33–34° (after steam distillation).

Anal. Calcd. for $C_7H_4FNO_3$: C, 49.71; H, 2.38; F, 11.24. Found: C, 50.44; H, 2.91; F, 10.91.

(14) Melting points were determined on a Fisher-Johns apparatus and are not corrected.
(15) Y. Desirant, *Bull. Classe Sci., Acad. Roy. Belg.*, **19**, 325 (1933).
(16) S. M. Tsang, E. H. Wood, and J. R. Johnson, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 641.

4-Fluoro-2,β-dinitrostyrene, m.p. 67–68°, was obtained as described earlier,[7] and also in 55% yield by using a simpler procedure.[17]

6-Fluoroindole, m.p. 75°, was secured in 60–63% yield by reducing the 4-fluoro-2,β-dinitrostyrene in a Parr hydrogenation apparatus.[7]

Attempted Syntheses of 6-Fluoroindole and Starting Products. Bromination of 4-Fluoro-2-nitrotoluene.—Fluoro-2-nitrotoluene (39 g.) in 80 ml. of *o*-dichlorobenzene was irradiated with an ultraviolet lamp and slowly treated with 40 g. of bromine at 130–150°. After addition was completed, the precipitate was collected and washed with alcohol; yield 19 g., m.p. 228–230°. An analytical sample was sublimed at 0.5 mm., m.p. 230°.

Anal. Calcd. for $C_7H_4Br_2FNO_2$: C, 26.86; H, 1.50; Br, 51.07; F, 6.07; N, 4.48. Found: C, 28.50; H, 2.26; Br, 50.90; F, 6.06; N, 4.96.

The preceding compound (10.0 g.) was refluxed for 5 hr. with 20 g. of powdered calcium carbonate and 30 ml. of water. The liquid when filtered and acidified gave 2.0 g. of white needles, m.p. 240–242°, which is significantly higher than that of 4-fluoro-2-nitrobenzoic acid. Analysis revealed 38.7% of bromine, and the compound was not further investigated.

***p*-Fluorobenzyl Acetate.**—*p*-Fluorobenzyl chloride (Aldrich Chemical Co.) (100 g.) was refluxed for 2 hr. with 80 g. of potassium acetate in 140 ml. of acetic acid. The mixture was poured into water, extracted with benzene, dried, and distilled; yield 101.5 g. (87%), b.p. 90–92° (12 mm.), $n^{25}D$ 1.4883, d^{25} 1.161, MR found 41.75.

Anal. Calcd. for $C_9H_9FO_2$: C, 64.28; H, 5.39. Found: C, 64.32; H, 5.33.

Nitration of 4-Fluorobenzyl Acetate.—The foregoing ester (50.4 g.), in 250 ml. of acetic anhydride, was treated dropwise with 20 ml. of 90% HNO_3 at 30–35°. The solution was allowed to stand for 5 hr. at room temperature, then diluted with water and partially neutralized with sodium hydroxide. An oil separated (42 g., $n^{25}D$ 1.4894) that had the properties of the starting ester. Essentially the same result occurred during similar nitration of *p*-fluorobenzyl chloride or the corresponding alcohol.

When the ester (96 g.) was added to 250 ml. of 96% H_2SO_4 and 100 ml. of acetic acid and nitrated with 35 ml. of 90% HNO_3, a sticky material precipitated which was insoluble in common organic solvents.

Nitration of *p*-Fluorobenzyl Cyanide.—*p*-Fluorobenzyl cyanide (Aldrich Chemical Co.) (50 g.) was added to a mixture of 120 ml. nitric acid (*d* 1.42) and 120 ml. of concentrated sulfuric acid at 10–15°, stirred for 1 hr., and poured onto crushed ice.[18] An oil separated, which slowly solidified. The solid material was collected, triturated with alcohol, and recrystallized from ethyl acetate; yield 22 g. of yellow needles, m.p. 146–149°. An analytical sample was secured from methanol, m.p. 148–149°. Analytical data agree with those for 3,5-dinitro-4-hydroxybenzyl cyanide.

Anal. Calcd. for $C_8H_5N_3O_5$: N, 18.83. Found: N, 18.85.

3,5-Dinitro-4-hydroxyphenylacetic Acid.—The cyanide (2.3 g.) was heated to reflux with 6 ml. of concentrated sulfuric acid and 6 ml. of water. The mixture was cooled and diluted with water, and the pale-yellow precipitate was recrystallized from water; yield 2.2 g., m.p. 172–173°.

Anal. Calcd. for $C_8H_6N_2O_7$: C, 39.68; H, 2.50; N, 11.57. Found: C, 39.69; H, 2.55; N, 11.33.

Ethyl 3,5-Dinitro-4-hydroxyphenylacetate.—The foregoing acid (1.0 g.) was added to 15 ml. of absolute ethanol and 1.0 ml. of concentrated sulfuric acid. The precipitate disappeared slowly and on the third day the clear solution was diluted with cold water and treated with sodium acetate. The solid matter was collected and recrystallized from hexane, m.p. 68°; lit.[8] 71°.

Anal. Calcd. for $C_{10}H_{10}N_2O_7$: C, 44.45; H, 3.73; N, 10.37. Found: C, 44.68; H, 3.62; N, 10.48.

1,4-Difluoro-2-nitrobenzene.[19]—*p*-Difluorobenzene (Pierce Chemical Co.) (57 g., 0.5 mole) was stirred with 100 ml. of concentrated sulfuric acid and treated with a mixture of 27 ml. of 90% nitric acid and 25 ml. of 96% sulfuric acid at 30–35°. After 2 more hr. of stirring, the mixture was poured onto ice–water, extracted with ether, and distilled; yield 72.5 g. (91%), b.p. 74–75° (8 mm.).

Ethyl α-Cyano-4-fluoro-2-nitrophenylacetate.—Ethyl cyanoacetate (52 g.) in 100 ml. of absolute ethanol was added to sodium ethoxide solution (prepared from 10.3 g. of sodium metal in 200 ml. of absolute ethanol), followed by 46 g. of 1,4-difluoro-2-nitrobenzene. The solution was stirred and refluxed for 4 hr., cooled, poured into water, neutralized with diluted nitric acid, extracted with ether, and subjected to distillation. After a substantial forerun of unchanged starting material, there was obtained 44.5 g. (61%) of the desired compound, b.p. 160–170° (3 mm.). It was redistilled at 135–138° (0.8 mm.); $n^{25}D$ 1.5340.

Anal. Calcd. for $C_{11}H_9FN_2O_4$: C, 52.38; H, 3.60. Found: C, 53.02; H, 3.30.

4-Fluoro-2-nitrobenzyl Cyanide.—The preceding compound (20 g.) was refluxed for 3 hr. with 100 ml. of 70% acetic acid and 3 ml. of concentrated sulfuric acid, poured onto crushed ice, and partially neutralized with ammonia solution. A solid matter separated and was collected, washed with water, dried, and recrystallized from chloroform–hexane; yield 11 g. (77%), m.p. 46–47° (from hexane).

Anal. Calcd. for $C_8H_5FN_2O_2$: C, 53.34; H, 2.80; F, 10.54; N, 15.55. Found: C, 53.42; H, 3.01; F, 11.00; N, 15.85.

Cyclization of 4-Fluoro-2-nitrobenzyl Cyanide. (A).—Anhydrous stannous chloride (19 g.), in 100 ml. of absolute ether, was saturated with dry hydrogen chloride until liquid. A solution of 4.5 g. of 4-fluoro-2-nitrobenzyl cyanide in 75 ml. of ether was added slowly during 30 min. The mixture was stirred for 3 hr. more while a stream of hydrogen chloride was passed through. The upper ethereal layer was separated and the viscous, oily material treated with water, made alkaline, and subjected to water distillation. No organic material could be found in the distillate. The ethereal layer was evaporated and left only a trace of an oily substance.

(B).—A solution of 1.5 g. of the cyanide in 100 ml. of ethanol was hydrogenated for 90 min. in a Parr apparatus at 3.5 atm. (3.6 kg./cm.^{2}) and 45–50° in the presence of 1.5 g. of 10% palladium-on-charcoal catalyst. The resulting solution was strongly alkaline with a distinctive smell of ammonia. The solvent was removed and the remainder steam-distilled, yielding 0.8 g. (23%) of crude 6-fluoroindole, m.p. 58–70°.

N,N-Diethyl-6-fluoro-3-indoleglyoxylamide.—6-Fluoroindole (4.7 g.) in 50 ml. of ether was treated with 7 ml. of oxalyl chloride in 25 ml. of ether with stirring and cooling. A yellow precipitate formed and was collected, washed, transferred to another flask, slurried in 50 ml. of ether, and treated slowly with 17 ml. of diethylamine in 25 ml. of ether. A white substance which formed was filtered, washed with warm water, and recrystallized from methanol; yield 6.7 g. (77%), m.p. 188–190°.

Anal. Calcd. for $C_{14}H_{15}FN_2O_2$: N, 10.68. Found: N, 10.12.

6-Fluoro-N,N-diethyltryptamine.—A solution of 8.6 g. of N,N-diethyl-6-fluoro-3-indoleglyoxylamide in 220 ml. of tetrahydrofuran was added to 9.5 g. of lithium aluminum hydride in 250 ml. of tetrahydrofuran, refluxed for 4 hr., and cautiously decomposed by addition of 25 ml. of ethyl acetate, followed by wet tetrahydrofuran. After filtering and removing the solvent, the residue was acidified with dilute hydrochloric acid and extracted with benzene. The aqueous layer was rendered alkaline, the organic substance was taken up with ether, dried over potassium carbonate, concentrated, and distilled under reduced pressure. The yield was 5.4 g. (70%); b.p. 165–170° (0.8 mm.); m.p. 69–70° (from petroleum ether–ethyl acetate).

Anal. Calcd. for $C_{14}H_{19}FN_2$: C, 71.76; H, 8.17; F, 8.11; N, 11.96. Found: C, 71.59; H, 8.14; F, 8.01; N, 11.98.

The **picrate,** orange crystals, melted at 222–223° (methanol).

Anal. Calcd. for $C_{20}H_{22}FN_5O_7$: C, 51.86; H, 4.79; F, 4.10. Found: C, 51.01; H, 4.85; F, 3.90.

6-Fluoro-3-indolealdehyde.—6-Fluoroindole (5.8 g.), in 6 ml. of dimethylformamide, was added to a solution prepared from 5.5 ml. of phosphorus oxychloride and 18 ml. of dimethylformamide,[10] stirred for 75 min., and treated with 20 g. of crushed ice followed by 23.0 g. of sodium hydroxide in 65 ml. of water. The contents, heated to 100° (evolution of dimethylamine), poured into cold water, allowed to stand overnight and filtered, gave 5.3 g. (76%) of 6-fluoro-3-indolealdehyde, m.p. 173–176°. An analytical sample was sublimed, m.p. 178–179°.

Anal. Calcd. for C_9H_6FNO: N, 8.59. Found: N, 9.27.

The dark red **dinitrophenylhydrazone** melted at 315–318° dec.

Anal. Calcd. for $C_{15}H_{10}FN_5O_4$: C, 52.47; H, 2.94; N, 20.40. Found: C, 52.53; H, 3.47; N, 19.71.

6-Fluoro-3-(2-methyl-2-nitrovinyl)indole.—6-Fluoro-3-indolealdehyde (5.2 g.) was heated for 45 min. with 15 ml. of nitroethane

(17) D. E. Worrall, "Organic Syntheses," Coll. Vol. I, 1941, p. 413.
(18) G. R. Robertson, ref. 17, p. 396.
(19) F. Swarts, *Bull. Classe Sci., Acad Roy. Belg.*, 241 (1913).

and 2 g. of ammonium acetate at 95–100°, diluted with 50–60 ml. of methanol, and cooled, yielding 5.6 g. (80%) of orange-red needles, m.p. 229–230°. An analytical sample was sublimed at 0.5 mm.

Anal. Calcd. for $C_{11}H_9FN_2O_2$: C, 59.99; H, 4.12; F, 8.63; N, 12.73. Found: C, 60.23; H, 4.18; F, 8.65; N, 12.90.

6-Fluoro-α-methyltryptamine.—A solution of 5.6 g. of 6-fluoro-3-(2-methyl-2-nitrovinyl)indole in 100 ml. of tetrahydrofuran was added dropwise to 6.5 g. of lithium aluminum hydride in 150 ml. of tetrahydrofuran and refluxed for 2 hr. After the usual procedure, 3.0 g. (61%) of crystals were obtained, m.p. 102–105° (ethyl acetate–petroleum ether). An analytical sample was recrystallized from ethyl acetate, m.p. 104–106°.

Anal. Calcd. for $C_{11}H_{13}FN_2$: C, 68.73; H, 6.82; N, 14.57. Found: C, 68.39; H, 6.83; N, 14.22.

The **picrate,** red crystals from methanol–water, changed to orange-yellow when heated above 100–110°; m.p. 232–233° dec.

Anal. Calcd. for $C_{17}H_{16}FN_5O_7$: C, 48.46; H, 3.83; N, 16.63. Found: C, 49.03; H, 4.28; N, 16.77.

5-Fluoro-3-indolealdehyde.—A solution of 7.7 g. of 5-fluoroindole[6] added to 5.8 ml. of phosphorus oxychloride in 20 ml. of dimethylformamide, and processed as described for the 6-fluoro analog, afforded 7.5 g. (80%) of crystals, m.p. 170–171°.

Anal. Calcd. for C_9H_6FNO: C, 66.25; H, 3.71; F, 11.65. Found: C, 66.76; H, 4.22; F, 11.60.

5-Fluoro-3-(2-methyl-2-nitrovinyl)indole.—Reaction between 7.3 g. of 5-fluoro-3-indolealdehyde and 20 ml. of nitroethane in the presence of 2.3 g. of ammonium acetate, carried out as described in preceding sections, gave 6.1 g. (62%) of orange crystals, m.p. 186–186.5° (from methanol).

Anal. Calcd. for $C_{11}H_9FN_2O_2$: C, 59.99; H, 4.12; N, 12.73. Found: C, 60.25; H, 3.89; N, 12.45.

5-Fluoro-α-methyltryptamine.—The foregoing compound (5.8 g.), reduced exactly as described for the 6-fluoro isomer, was precipitated from an etheral solution as the hydrochloride, m.p. 228–230°; yield 4.9 g. (81%). An analytical sample was purified from toluene–ethanol; m.p. 233–234°.

Anal. Calcd. for $C_{11}H_{14}ClFN_2$: C, 57.77; H, 6.17; F, 8.31; N, 12.25. Found: C, 57.79; H, 6.48; F, 8.29; N, 12.27.

The yellow crystalline **picrate,** from methanol–water, melted at 234–235° dec.

Anal. Calcd. for $C_{17}H_{16}FN_5O_7$: C, 48.46; H, 3.83; F, 4.51; N, 16.63; Found: C, 48.73; H, 3.79; F, 3.99; N, 17.07.

Acknowledgment.—We are indebted to Mr. H. G. McCann of the Microanalytical Laboratory, National Institute of Arthritis and Metabolic Diseases, for analyses.

Acyltryptamines. II. Synthesis of Acyltryptamines, Indazoles, and Azepinoindoles from the Acylphenylhydrazones of 2,3-Piperidinedione[1]

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Received March 25, 1963

The 3-(*o*-, *m*-, and *p*-acylphenyl)hydrazones of 2,3-piperidinedione (I) were prepared by the Japp–Klingemann coupling of the corresponding acylbenzenediazonium salts with 2-oxo-3-piperidinecarboxylic acid. The acyl substituents were *o*-, *m*-, and *p*-acetyl, *o*-, *m*-, and *p*-benzoyl, *p*-propionyl, *p*-isonicotinoyl, and *p*-(4-chlorobenzoyl). The Fischer-indole cyclization of the *p*-acylphenylhydrazones gave 6-acyl-1,2,3,4-tetrahydro-1-oxo-β-carbolines (II) which on hydrolysis and decarboxylation yielded 5-acyltryptamines (IV). Cyclizations of the *m*-acylphenylhydrazones gave a mixture of 5- and 7-acyl-1,2,3,4-tetrahydro-1-oxo-β-carbolines (VI, V) which on hydrolysis and decarboxylation yielded azepino[5,4,3-*cd*]indoles (X) and 6-acyltryptamines (VIII), respectively. The *o*-acylphenylhydrazones on cyclization gave 3-methyl-2-(1,2,5,6-tetrahydro-2-oxo-3-pyridyl)-2H-indazole and 3-phenyl-2-(1,2,5,6-tetrahydro-2-oxo-3-pyridyl)-2H-indazole. These were reduced catalytically to the 3-methyl-2-(2-oxo-3-piperidyl)-2H-indazoles and 3-phenyl-2-(2-oxo-3-piperidyl)-2H-indazoles (XIII). Hydrolysis of the indazoles gave the corresponding derivatives of 5-amino-2-indazolylpentanoic acid (XV, XVI). The 5-acyltryptamines showed antiserotonin and hypotensive properties. The most active compound, 5-acetyltryptamine, which produced marked hypotensive effect in the anesthetized and unanesthetized dog, failed to elicit the same response in man when tested in the clinic.

The synthesis of tryptamines has been extensively pursued because of the biological activities of many naturally occurring substances containing this moiety. As a result of our investigations on the chemical modifications of indole alkaloids it became apparent to us that tryptamines, substituted in the benzene ring by acyl groups, had not previously been prepared. During the course of our synthesis in this area we encountered some interesting chemical and pharmacological findings which prompted us to expand our research to include indazoles and azepinoindoles.

The most feasible synthetic scheme appeared to be that utilized by Abramovitch and Shapiro[2] where substituted benzenediazonium salts are coupled with 3-carboxy-2-piperidone to give hydrazones which are cyclized to 1,2,3,4-tetrahydro-1-oxo-β-carbolines. Ring opening of the oxocarbolines followed by decarboxylation of the resulting 2-carboxytryptamines yields the tryptamines.[3]

Coupling of the *o*-, *m*-, and *p*-acylbenzenediazonium salts with 3-carboxy-2-piperidone gave the corresponding 3-(*o*-, *m*-, and *p*-acylphenyl)hydrazones of 2,3-piperidinedione Ia–i (Table I). Cyclization of the (*p*-acylphenyl)hydrazones of 2,3-piperidinedione Ia–d in refluxing 88% formic acid gave the 6-acyl-1,2,3,4-tetrahydro-1-oxo-β-carbolines (IIa–d, Table II). Hydrazone Ie, which resisted cyclization by formic acid, was successfully cyclized by polyphosphoric acid. Base-catalyzed hydrolysis of IIa–e gave the corresponding 5-acyl-2-carboxytryptamines (IIIa–e, Table III) which were decarboxylated in refluxing hydrochloric acid to the 5-acyltryptamines (IVa–e, Table IV).

(1) Presented in part as a Communication to the Editor, *J. Am. Chem. Soc.*, **84**, 881 (1962), and before the Division of Medicinal Chemistry at the 141st National Meeting of the American Chemical Society, Washington, D. C., March 26, 1962.

(2) R. A. Abramovitch and D. Shapiro, *Chem. Ind.* (London), 1255 (1955); *J. Chem. Soc.*, 4589 (1956).

(3) S. Keimatsu, S. Sugasawa, and G. Kasuya, *J. Pharm Soc. Japan*, **48**, 762 (1928).