the number of carbon atoms between the quaternary ammonium group and the phthalimide group was varied. In both series, activity was low until $n = 4$, at which point it abruptly rose until a broad maximum was reached at $n = 7$, 8, and 9. As the chain length was further increased, the activity gradually diminished. It appears, therefore, that there is no critical distance, other than the minimal, between the quaternary ammonium and phthalimide portions of the molecule. Although this does not rule out bond formation between the receptor site and the phthalimide portion of the molecule, the fit must be less specific than that of the *bis*-quaternary ammonium compounds related to *d*-tubocurarine whose nitrogen to nitrogen distance is much more critical.[10]

The "umbrella effect" to which Pfeiffer[11] ascribed the activity of *d*-tubocurarine may also afford a satisfactory explanation for the activity of these monoquaternary salts. The quaternary ammonium portion of the molecule may bond to the receptor sites in a manner similar to *d*-tubocurarine while the large phthalimide nucleus screens the surrounding receptor sites from the approach of the acetylcholine molecules.

Little difference is noted between piperidinomethyl and piperidinoethyl groups on the quaternary nitrogen. Substitution with the bulky benzyl group results in a series with diminished activity. A complete pharmacological report will be presented elsewhere.

(10) Barlow and Ing, *Brit. J. Pharmacol.*, **3**, 298 (1948).
(11) Pfeiffer, *Science*, **107**, 94 (1948).

EXPERIMENTAL[12]

N-(ω-bromononyl)-phthalimide. A mixture of 8.45 g. (0.05 mole) of potassium phthalimide, 57.2 g. (0.2 mole) of 1,9-dibromononane and 3.3 g. (5% by weight) of dimethylformamide was heated at 160° for 1.5 hrs. The solution was filtered to remove precipitated potassium bromide. The filtrate was heated to distill the dimethylformamide and the excess dibromononane removed under reduced pressure. The residue was fractionated under reduced pressure using a free flame and the solid portions of the distillate recrystallized from ethanol. With slight variations in procedure the yield of pure product varied from 40–78%. The analytical sample was first purified on alumina and then recrystallized repeatedly from ethanol, m.p. 37.5°.

Anal. Calc'd for $C_{17}H_{22}BrNO_2$: C, 57.96; H, 6.30. Found: C, 58.08; H, 6.17.

N-(ω-piperidinoalkyl)-phthalimides. A solution of 0.01 mole of the appropriate N-(ω-bromoalkyl)-phthalimide and 3.4 g. (0.04 mole) of piperidine in 30 ml. of benzene was heated on the steam bath for 1 hr. The benzene and excess piperidine were removed under reduced pressure and the residue dissolved in ether. The solution was filtered to remove piperidine hydrobromide and decolorized with charcoal. The dried solution was saturated with hydrogen chloride gas and the white crystalline salt collected on a funnel, washed with ether, and dried.

The free base was liberated from an aqueous solution of the hydrochloride salt with cold sodium carbonate solution. The product was recrystallized from 30–60° petroleum ether.

N-(ω-piperidinoalkyl)-phthalimide alkyl iodides. A solution of 0.005 mole of the N-(ω-piperidinoalkyl)-phthalimide and 0.05 mole of the appropriate alkyl iodide in 100 ml. of dry ether was allowed to stand overnight at room temperature. The precipitated quaternary salt was removed by filtration and the filtrate allowed to stand until no more product was formed. The quaternary salts were recrystallized from either absolute ethanol or isopropanol.

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(12) Analyses are by Du-Good Chemical Laboratory, St. Louis, Mo., and Clark Microanalytical Laboratory, Urbana, Ill. All melting points are corrected.

[Contribution from the Department of Organic Chemistry, University of Madras]

Synthesis of DL-α-Amino-β-(1-skatyl)propionic Acid

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Skatole has been found to undergo the Mannich reaction with formalin and dimethylamine to give 1-dimethylaminomethylskatole. The methiodide of this base alkylates ethyl acetamidocyanoacetate. The alkylated product after treatment with alkali furnishes DL-α-amino-β-(1-skatyl) propionic acid, a new methyl analog of tryptophan.

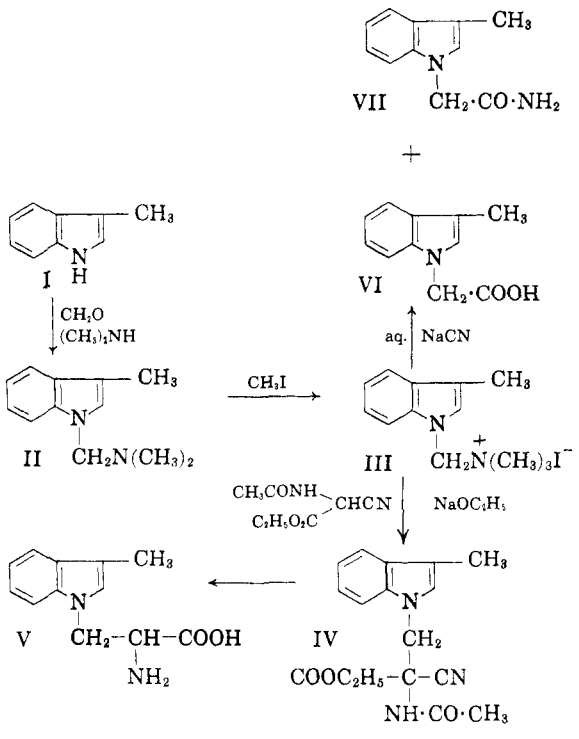
Since the elegant synthesis of tryptophan[1] by ethyl acetamidomalonate with gramine, many analogs of tryptophan have been synthesized with a view to studying their antimetabolite properties. Methyl tryptophans and methyl isotryptophans have been of particular interest in this connection and 1,2,4,5,6, and 7 methyl tryptophans[2a] and 6-methyl-2-isotryptophan[2b] have been prepared. It was of interest to synthesize 3-methyl-1-isotryptophan, *viz.*, α-amino-β-(1-skatyl)propionic acid (V) in

(1) Snyder and Smith, *J. Am. Chem. Soc.*, **66**, 350 (1944); Albertson, Archer, and Suter, *J. Am. Chem. Soc.*, **66**, 500 (1944).

(2a) Anderson, *Science*, **101**, 565 (1945); Jackman and Archer, *J. Am. Chem. Soc.*, **68**, 2105 (1946); Rydon, *J. Chem. Soc.*, 705 (1948); Snyder and Pilgrim, *J. Am. Chem. Soc.*, **70**, 3787 (1948); Snyder and Eliel, *J. Am. Chem. Soc.*, **70**, 3855 (1948); Boon, *J. Chem. Soc.*, S 231 (1949); Snyder, Beilfuss, and Williams, *J. Am. Chem. Soc.*, **75**, 1873 (1953); Jones and Kornfield, U.S. Patent 2621187 [*Chem. Abstr.* **47**, 10557 (1953)].

(2b) Snyder and Cook, *J. Am. Chem. Soc.*, **78**, 969 (1956)

which the amino acid side chain and the methyl group are attached to positions 1 and 3 of the indole nucleus, respectively. The synthesis was achieved as follows:



Skatole reacted with dimethylamine and formalin, according to the procedure of Kuhn and Stein,[3] to give 1-dimethylaminomethylskatole (II) in 71% yield. The base was characterized by its methiodide and picrate. The methiodide III reacted with sodium cyanide solution to furnish 1-skatylacetic acid (VI), 1-skatylacetamide (VII) and skatole. The structures of the acid VI and hence of the base II were confirmed by decarboxylation of the acid to 1,3-dimethylindole which was characterized by means of its picrate. As might be expected of a 1,3-disubstituted indole derivative,[5] VI gave a negative Ehrlich's test.

The methiodide III when reacted with ethyl acetamido-cyanoacetate furnished IV as a viscous liquid which could not be further purified. Treatment of crude IV with sodium hydroxide gave V in 33% yield based on III used. The analytical data for the amino acid revealed the presence of one molecule of water of crystallization which, however, could be removed by drying the sample *in vacuo* at 180°. The amino acid gave a positive ninhydrin test and a negative Ehrlich's test. The R_f value determined in butyl alcohol–acetic acid–water solution (4:1:5) was 0.81.

(3) Kuhn and Stein, *Ber.*, **70**, 567 (1937).

(4) Jackson and Manske, *Can. J. Research*, **13**, 170 (1935); *Chem. Abstr.*, **30**, 455 (1936).

(5) Giral and Laguna, *Ciencia*, **10**, 83 (1950); *Chem. Abstr.*, **44**, 10605 (1950).

Most of the derivatives of indole that have been reported so far to participate in the Mannich reaction do not carry any substituent in the 3 position. In these reactions, the dialkylaminomethyl group enters position 3, probably as a result of the activation of carbon 3 due to the lone pair of electrons on the nitrogen atom of the indole nucleus. Besides skatole, carbazole is the only other known derivative of indole which has been reported to give[6] an *N*-Mannich base. Evidently, when position 3 carries a substituent, the dialkylaminomethyl group gets linked to the nitrogen atom itslef. Electron releasing and electron attracting groups in the 3-position may be expected to favor or hinder the formation of *N*-dialkylaminomethyl Mannich bases. The fact that skatole gives the Mannich base II in good yield and under the same conditions as indole suggests that the electron releasing methyl group probably facilitates the reaction. Further work is in progress to correlate the character of a 3-substituent with the ease of formation of *N*-Mannich bases of indole derivatives.

The Mannich base II, like 1-methylgramine to which it bears a close structural resemblance, is a tertiary base incapable of effecting alkylations through a mechanism[7] of elimination and addition. The alkylations of ethyl acetamidocyanoacetate and sodium cyanide with III must therefore involve a direct substitution mechanism. In fact, some other alkylations which have been carried out with II and III, and which will be described in a later communication, bear out the anticipations based on their structural resemblance to 1-methyl gramine and its methiodide.

EXPERIMENTAL

Skatole was prepared by Fischer cyclization[8] of propionaldehyde phenylhydrazone. The original method was adapted as follows for large scale preparations:

A mixture of 3 g. of fused zinc chloride and 30 g. (0.2 mole) of crude propionaldehyde phenylhydrazone was placed in a 500-ml. round bottomed flask provided with a condenser and dropping funnel and heated in an oil bath. With the bath temperature at 220°, an additional portion (80 g.; 0.53 mole) of propionaldehyde phenylhydrazone was introduced at such a rate as to maintain a gentle reflux. After addition was over, the temperature of the bath was raised to and maintained at 240° for 0.5 hr. The reaction mixture was cooled, diluted with water and steam distilled to give 62.7 g. (64%) of skatole, m.p. 89–92°.

1-Dimethylaminomethylskatole (II). To 60 ml. of an ice-cold 16% solution of dimethylamine (0.21 mole) in water were added successively 40 ml. of glacial acetic acid and 20 ml. of 36% formalin (0.24 mole) at such a rate that the temperature did not rise above 0°. The solution was then mixed with 26.2 g. (0.2 mole) of skatole and the mixture stirred at room temperature. The skatole dissolved in the course of 2 hr. The reaction mixture was allowed to stand overnight in an ice chest and then made alkaline using 5 *N* sodium hydroxide solution. Extraction with ether furnished,

(6) Feldman and Wagner, *J. Org. Chem.*, **7**, 31 (1942); Hellmann and Löschmann, *Ber.*, **87**, 1684, 1690 (1954).

(7) Brewster and Eliel, *Org. Reactions*, **7**, 99 (1953).

(8) Fischer, *Ann.*, **236**, 137 (1886).

after removal of solvent, the product which was distilled *in vacuo* b.p. 146–150°/9 mm.; yield, 26.5 g. (71%).

The *picrate*, after two crystallizations from methanol, melted at 150–151°.

Anal. Calc'd for $C_{18}H_{19}N_5O_7$: C, 51.8; H, 4.6. Found: C, 52.0; H, 4.7.

The methiodide was obtained by mixing equimolar amounts of II and methyliodide in absolute methanol or ethanol solution. The analytical sample was prepared by repeated washing with absolute ethanol and ether, m.p. 210–220° (decomp.).

Anal. Calc'd for $C_{13}H_{19}IN_2$: C, 47.3; H, 5.8. Found: C, 47.4; H, 6.0.

1-Skatylacetamide (VII) and 1-skatylacetic acid (VI). A solution of 8.3 g. (0.025 mole) of III and 5 g. (0.1 mole) of sodium cyanide in 50 ml. of water was refluxed for 2.25 hr. Trimethylamine evolved steadily during this period. The reaction mixture was cooled in an ice-salt mixture and filtered. The semisolid obtained (3.7 g.) was extracted with hot benzene and the benzene extract when cooled deposited crystals of VII (1 g.); m.p. 164–166°. A crystallization from benzene furnished material m.p. 169–170°.

Anal. Calc'd for $C_{11}H_{12}N_2O$: C, 70.2; H, 6.4. Found: C, 70.4; H, 6.3.

The benzene extract was stripped of solvent and the residue sublimed at 100°/1 mm. The sublimed material (98 mg.) was identified as skatole by mixed melting point with an authentic sample and by preparation of the picrate.

The alkaline filtrate left after filtration of the crude amide when acidified deposited crystals (51 mg.) of VI; m.p. 171°. After two further crystallizations from benzene the m.p. was 174° (lit.[4] m.p. 178°).

Anal. Calc'd for $C_{11}H_{11}NO_2$: C, 69.8; H, 5.9. Found: C, 69.8; H, 5.9.

The same acid was obtained in 50% yield by hydrolysis of the amide with ethanolic potassium hydroxide solution.

Decarboxylation of VI to 1,3-dimethylindole. In a microdistillation flask 200 mg. of VI was heated in an atmosphere of nitrogen at 225–230° for 0.5 hr. The brown residual liquid was distilled at 17 mm. with the bath temperature at 170°. The distillate furnished a picrate, which after a crystallization from ethanol had m.p. 140–141°. This melting point was not depressed by admixture with an authentic sample of the picrate of 1,3-dimethylindole prepared as described by Snyder and Eliel.[9]

DL-*α-Amino-β-(1-skatyl) propionic acid (V).* To a solution prepared from 0.86 g. (0.037 g. atom) of sodium and 94 ml. of absolute ethanol were added 12.2 g. (0.037 mole) of III and 6.4 g. (0.038 mole) of ethyl acetamidocyanoacetate and the mixture was refluxed for 43 hr. The reaction mixture was then concentrated *in vacuo* and the residue diluted with water and extracted with ether. The ether extract furnished, after removal of solvent, 9.4 g. of the crude alkylated product IV. This was refluxed with 40 ml. of 15% sodium hydroxide solution for 25 hr. in a copper vessel. The mixture was cooled, filtered, and the filtrate extracted with ether to remove 1.3 g. of some unsaponifiable material. The aqueous solution was treated with animal charcoal and acidified with 9 ml. of glacial acetic acid. The crude amino acid which separated was collected and extracted with five 60-ml. portions of boiling water. The combined aqueous extracts when cooled deposited 2.9 g. of material m.p. 195–196°. The analytical sample (m.p. 217–218°) was obtained after seven recrystallizations from 50% methanol.

Anal. Calc'd for $C_{12}H_{14}N_2O_2 \cdot H_2O$: C, 61.0; H, 6.8. Found: C, 61.0; H, 7.2.

A sample of the amino acid hydrate when dried *in vacuo* for 6 hr. at 178° lost one mole of water of crystallization and had m.p. 214°. The anhydrous sample was analyzed.

Anal. Calc'd for $C_{12}H_{14}N_2O_2$: C, 66.0; H, 6.5. Found: C, 66.0; H, 6.8.

The picrolonate was readily obtained by mixing hot solutions of equal amounts of the amino acid and picrolonic acid in water and was crystallized from water; m.p. 145°.

Anal. Calc'd for: $C_{22}H_{22}N_6O_7 \cdot H_2O$: C, 52.8; H, 4.8. Found: C, 53.1; H, 4.6.

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MADRAS 25, INDIA

(9) Snyder and Eliel, *J. Am. Chem. Soc.*, **70**, 1703 (1948).

[CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, RADIUM INSTITUTE, UNIVERSITY OF PARIS]

Some 2,3-Polymethylene-indoles and -quinolines. An Attempt to Synthesize Large-Ring Nitrogen Heterocycles

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Several new 2,3-polymethylene-indoles and -quinolines have been prepared from various macrocyclic ketones by Fischer and Pfitzinger reactions. An attempt to use some of these compounds for the preparation of fully conjugated large-ring nitrogen-containing heterocycles was unsuccessful.

A possibility, at least theoretical, exists for the dehydrogenation of 2,3-polymethylenequinolines (I; R = H) with an even number (n) of methylene groups, to fully conjugated large-ring acridine analogs (II). Similarly, it is theoretically feasible to convert 2,3-polymethyleneindoles (III) bearing an odd number ($n + 1$) of methylene groups to fully conjugated macrocyclic analogs (IV) of 1-aza-2,3-benzazulene (VII). Treibs, Steinert and Kirchhof[1] did, in fact, succeed in preparing the latter substance by treating [(1′,2′-2,3)cyclohept-1′,2′-eno]indole (IIIb) with three moles of chloranil, a reagent frequently used for the aromatization of hydrogenated carbazoles[2] and acridines.[3]

(1) Treibs, Steinert, and Kirchhof, *Ann.*, **581**, 54 (1953).

(2) Barclay and Campbell, *J. Chem. Soc.*, 530 (1945); Buu-Hoï, Khôi, and Xuong, *J. Org. Chem.*, **14**, 492 (1949); **15**, 511, 957 (1950); **16**, 315 (1951).

(3) Buu-Hoï, Hoán, and Xuong, *J. Chem. Soc.*, 279 (1952)