Anal. Calcd. for $C_{16}H_{15}N_3O_3Cl$: C, 40.0; H, 3.14; N, 23.3. Found: C, 39.9; H, 3.16; N, 23.3.

Summary

1. The spontaneous decomposition of dibutylchloramine yields dibutylammonium chloride and a distillable fraction believed to be a mixture of N-*n*-butyl mono-, di- and trichlorobutanaldimines with the second of these compounds predominating. Other compounds seem to be present, but phenyl and dinitrophenylhydrazones and osazones of these three have been isolated.

2. Decomposition of dibutylchloramine in alcohols follows the same course, but hydrolysis of the aldimines occurs to give monobutylammonium chloride and ethylglyoxal.

3. Decomposition of dibutylchloramine in acetic acid or its anhydride gives also dibutylacetamide and, in the latter reagent, N-*n*-butylbutyramide.

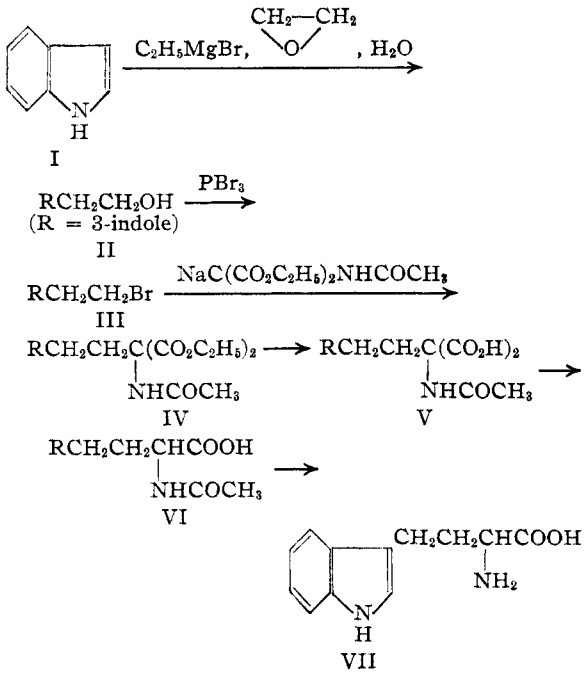
TORONTO, ONTARIO RECEIVED NOVEMBER 26, 1947

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

A Synthesis of *dl*-Homotryptophan

BY H. R. SNYDER AND FREDERICK J. PILGRIM

Homotryptophan [α-amino-γ-(3-indole)-butyric acid, VII] has been synthesized to permit physiological studies of the substance, particularly with reference to its possible action as an antimetabolite. The reactions employed in the synthesis are shown in the accompanying diagram.



Tryptophol (II) was prepared from indole (I) by the method of Oddo and Cambieri[1] which consists in the treatment of indole-magnesium bromide with ethylene oxide. Phosphorus tribromide was employed to convert tryptophol to the corresponding bromide (III) as described previously.[2] Alkylation of ethyl sodioacetylaminomalonate[3] by III was found to take place readily and in good yield (about 60%). The alkylation product, ethyl α-acetamino-α-carbethoxy-γ-(3-indole)-butyrate (IV), as obtained directly from the reaction mixture was of sufficient purity for conversion to V. Saponification of IV to the corresponding malonic acid, V, was effected by refluxing a mixture of IV with dilute sodium hydroxide solution; an almost quantitative yield of V was obtained.

Decarboxylation of the substituted malonic acid was brought about by refluxing an aqueous suspension of the material for several hours. *dl*-N-Acetylhomotryptophan (VI) was isolated from the mixture as the monohydrate. It was found convenient to purify the substance as the monohydrate; deacetylation of the pure monohydrate by hot dilute sodium hydroxide produced *dl*-homotryptophan (VII) in a state of high purity and in almost quantitative yield.

Experimental[4,5]

Ethyl α-Acetamino-α-carbethoxy-γ-(3-indole)-butyrate (IV).—To a solution prepared from 75 ml. of absolute ethanol and 0.58 g. of sodium were added 5.44 g. of ethyl acetaminomalonate and 5.50 g. of β-(3-indole)-ethyl bromide[2] (III). The reaction mixture was refluxed for fifteen hours with mechanical stirring. The hot mixture was filtered, the insoluble material on the filter was washed with 50 ml. of hot absolute ethanol, and the combined filtrate and washings were concentrated under reduced pressure to a small volume (about 20 ml.). The residue was cooled to 5° and filtered. The light yellow crystals on the filter were washed with 50 ml. of cold absolute ethanol to give a white product (IV), m. p. 161–163°; yield, 4.8 g. Concentration of the mother liquor to a few milliliters and addition of 30 ml. of anhydrous ether to the residue yielded a precipitate, mainly sodium bromide. Extraction of this precipitate with small portions of warm water left a residue of crude IV (0.3 g.), m. p. 153–156°. A dark oily residue was obtained when the mother liquor from the second crop of crude product was evaporated to dryness under reduced pressure. No additional product was isolated from the oily residue. The over-all yield of IV, sufficiently pure for conversion to V, was 5.1 g. (57.6%). A sample of pure IV, prepared for analysis by recrystallization from 95% ethanol, melted at 163–164°.

Anal. Calcd. for $C_{19}H_{24}O_5N_2$: N, 7.77. Found: N, 7.74.

(1) Oddo and Cambieri, *Gass. chim. ital.*, **69**, 19 (1939).

(2) Hoshino and Shimodaira, *Ann.*, **520**, 19 (1935).

(3) (a) Snyder, Shekleton and Lewis, THIS JOURNAL, **67**, 310 (1945); (b) Albertson and Archer, *ibid.*, **67**, 308 (1945).

(4) All melting points are corrected.

(5) Microanalyses by Miss Theta Spoor and Mr. Howard Clark.

α-Acetamino-α-carboxy-γ-(3-indole)-butyric Acid (V).—A reaction mixture consisting of 4 g. of IV, 2.2 g. of sodium hydroxide and 25 ml. of water was refluxed for four hours. The hot mixture was treated with Darco, filtered hot and the filtrate was then cooled to 5°. The addition of 5.7 ml. of cold concentrated hydrochloric acid to the filtrate caused precipitation of slightly pink crystals of V. The mixture, after standing fifteen hours at 5°, was filtered. The solid was washed with 50 ml. of ice-water and dried for two hours at 60°; m. p. 140–141°; yield 3.3 g. (97.5%) of material suitable for conversion to VI.

A sample of pure V, recrystallized from 30% ethanol, melted at 153–154°.

Anal. Calcd. for $C_{15}H_{16}O_5N_2$: N, 9.21. Found: N, 8.94.

α-Acetamino-γ-(3-indole)-butyric Acid (*dl*-N-Acetylhomotryptophan) (VI).—Decarboxylation of the substituted malonic acid V was readily effected by refluxing a suspension of 3.0 g. of V in 25 ml. of water for three hours. The homogeneous reaction mixture was cooled to 5° and made acidic (congo red paper) by the careful addition of 18% hydrochloric acid. The acetyl derivative (VI) separated from the acidic solution as an oil which slowly crystallized. The mixture was filtered and the crude product (2.0 g.) was recrystallized from 40% ethanol. The product isolated from this recrystallization was the monohydrate of VI, m. p. 112–113°; yield, 1.60 g. (58.3%).

Anal. Calcd. for $C_{14}H_{16}O_3N_2 \cdot H_2O$: N, 10.05. Found: N, 10.12.

For the above analysis the crystals were dried for two hours at 25° under 2 mm. pressure. When the crystals were finely pulverized and dried for an additional two hours at the same temperature and pressure the hydrate apparently decomposed to anhydrous VI.

Anal. Calcd. for $C_{14}H_{16}O_3N_2$: N, 10.77. Found: N, 10.53.

α-Amino-γ-(3-indole)-butyric Acid (*dl*-Homotryptophan) (VII).—Recrystallized *dl*-N-acetylhomotryptophan monohydrate (VI, 1.60 g.), sodium hydroxide (1.00 g.) and water (10 ml.) were combined and the solution was refluxed for twenty hours. The hot reaction mixture was treated with Darco, filtered and the filtrate was cooled to 5°. Glacial acetic acid (1.50 g.) was added to the filtrate which was then allowed to stand at 5° for twelve hours to ensure complete precipitation of the amino acid VII. The reaction mixture was filtered and the white solid was found to be almost pure *dl*-homotryptophan, m. p. 306–310°; yield 1.21 g. (96.5%). It was recrystallized from a large volume of 50% ethanol. The glistening platelets of pure VII melted sharply at 308° with decomposition.

Anal. Calcd. for $C_{12}H_{14}O_2N_2$: C, 66.0; H, 6.47; N, 12.84. Found: C, 66.15; H, 6.51; N, 13.16.

Summary

dl-Homotryptophan [α-amino-γ-(3-indole)-butyric acid] has been synthesized *via* the sequence: indole, tryptophol, β-(3-indole)-ethyl bromide, ethyl α-acetamino-α-carbethoxy-γ-(3-indole)-butyrate, α-acetamino-α-carboxy-γ-(3-indole)-butyric acid, α-acetamino-γ-(3-indole)-butyric acid, *dl*-homotryptophan.

URBANA, ILLINOIS RECEIVED JANUARY 2, 1948

NOTES

Correlation of Rates of Halogenation of Methylbenzenes

BY FRANCIS E. CONDON

The rate of chlorination of toluene relative to that of benzene is 345[1]; relative to that at only one position in benzene, it is 345 × 6 = 2070. The product has been reported to be 42% *p*- and 58% *o*-chlorotoluene.[2] Hence the partial relative rate of chlorination of toluene at the para position is 0.42 × 2070 = 870; similarly, the ortho partial relative rate is (0.58/2) × 2070 = 600. The meta partial relative rate may be approximated as 5, which seems reasonable in view of the value of 3 found for meta nitration.[3]

If each of the methyls in a polymethylbenzene exerts the same activating influence as the one in toluene, a partial relative rate of chlorination at each available nuclear position may be calculated as a product of two or more partial relative rates, each corresponding to a methyl and its position. The rate for the polymethylbenzene relative to that for benzene is then one-sixth the sum of the partial relative rates for all available positions.

TABLE I

RELATIVE RATES OF HALOGENATION OF POLYMETHYLBENZENES (BENZENE = 1)

	p-Xylene	*o*-Xylene	*m*-Xylene	Mesitylene	Pentamethylbenzene
Calculated	2.0×10^3	2.5×10^3	2.4×10^5	1.6×10^8	13×10^8
Experimental[1]	2.2×10^3	4.6×10^3	4.3×10^5	1.8×10^8	7.8×10^8
	Pseudocumene	**Hemimellitine**	**Durene**	**Prehnitene**	**Isodurene**
Calculated	7.4×10^5	8.7×10^5	3.0×10^6	4.4×10^7	5.2×10^8

In *p*-xylene, for example, each of the four available positions is influenced by two methyls, one ortho and one meta. The calculated partial rela-

(1) De la Mare and Robertson, *J. Chem. Soc.*, 270 (1943).

(2) Wertyporoch, *Ann.*, **493**, 153–165 (1932); *C. A.*, **26**, 2177 (1932).

(3) Ingold, Lapworth, Rothstein and Ward, *J. Chem. Soc.*, 1959 (1931).