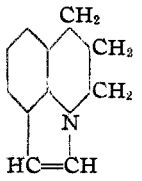
[CONTRIBUTION FROM THE DEPARTMENT OF MEDICAL CHEMISTRY OF THE UNIVERSITY OF EDINBURGH]

Synthesis of Polycyclic Indoles

BY GEORGE BARGER AND ELIZABETH DYER[1]

This research originated in an attempt to synthesize an indole, which had been obtained[2] by the degradation of the alkaloid calycanthine, and for which the following possible structure had been proposed



The synthesis of this indole was accomplished by condensing N-aminotetrahydroquinoline[3] with pyruvic acid, and converting the hydrazone thus obtained into 2-carboxy-1,8-trimethyleneindole by an application of the Fischer method.[4] Decarboxylation yielded the above 1,8-trimethyleneindole.

The structure of this indole was established by its conversion on reduction to 2,3-dihydro-1,8-trimethyleneindole or lilolidine, previously obtained by von Braun and co-workers through an independent synthesis.[5] The synthetic 1,8-trimethyleneindole was found to be not identical with the indole previously obtained from calycanthine. The properties of the calycanthine fragment differ also from those of the 3,4-trimethyleneindole described by Jacobs and Gould.[6]

The chemistry of polycyclic indoles of the type of 1,8-trimethyleneindole, a type which comprises both the tetrahydroquinoline and indole systems, was extended by the study of other members of the series. The 2-phenyl derivative of 1,8-trimethyleneindole was obtained from the hydrazone of acetophenone and N-aminotetrahydroquinoline. All attempts to prepare the corresponding 2-methyl derivative from the acetone hydrazone of N-aminotetrahydroquinoline were unsuccessful. A similar difficulty in preparing an indole from acetone-2-quinolyl hydrazone was experienced by Perkin and Robinson.[7]

With a view to applying the same type of reaction in the tetrahydrobenzoquinoline series, N-amino-1,2,3,4-tetrahydro-5,6-benzoquinoline was prepared. Although this readily formed a hydrazone with pyruvic acid, the corresponding indole could not be obtained. A similar resistance to indole formation was observed with the pyruvic acid hydrazone of N-amino-carbazole.

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Experimental Part

N-Amino-1,2,3,4-tetrahydroquinoline.—This substance was prepared from N-nitrosotetrahydroquinoline[8] by the method of Hoffmann and Königs.[3] To obtain 50% yields, care must be taken to keep the temperature of the reduction mixture between 60 and 75°. The product, purified by recrystallizing the sulfate, yielded a picrate (not previously described) which crystallized from alcohol as long, brownish-yellow needles, m. p. 140–141° with decomposition.

Anal. Calcd. for $C_{15}H_{12}O_7N_6$: N, 18.58. Found: N, 18.50.

Hydrazones.—The following table summarizes the successful methods of preparing the new hydrazones needed for indole syntheses. The hydrazones I and II were convertible to indoles, but all attempts to cyclize III, IV and V failed. The methods investigated included: heating with (a) zinc chloride at 100–130, 180–190° at 760 mm. or 110–120° at 12 mm.; (b) 10% aqueous hydrochloric acid at 50–60 or 80–100°; (c) dry hydrogen chloride gas in ethanol or *n*-butanol solution.

2-Carboxy-1,8-trimethyleneindole.—When a mixture of 2 g. of the pyruvic acid hydrazone of N-aminotetrahydroquinoline and 25 cc. of 10% hydrochloric acid was heated at 55° for one hour, the hydrazone gradually dissolved with the precipitation of the indole together with a dark impurity. The precipitate was filtered, dried, dissolved in ether and filtered from the small quantity of amorphous impurity. The ether solution was extracted with sodium carbonate, and 0.95 g. of the acid obtained on acidification of the basic extract (50% yield). For analysis the substance was recrystallized from benzene, from which it separated as needles, melting with decomposition at 210–212° when pure.

(1) Sarah Berliner Research Fellow of the American Association of University Women. Present address: Women's College, University of Delaware, Newark, Del.

(2) Unpublished work of Barger and Streuli, at the Department of Medical Chemistry of the University of Edinburgh.

(3) Hoffmann and Königs, *Ber.*, **16**, 730 (1883).

(4) Fischer and Hess, *ibid.*, **17**, 561 (1884).

(5) Von Braun, Heider and Wyczatkowska, *ibid.*, **51**, 1219 (1918).

(6) Jacobs and Gould, *J. Biol. Chem.*, **120**, 144 (1937).

(7) Perkin and Robinson, *J. Chem. Soc.*, **103**, 1974 (1913).

(8) Ziegler, *Ber.*, **21**, 862 (1888).

TABLE I

PREPARATION OF HYDRAZONES

	Hydrazine[a]	>CO Cpd.	Conditions	Cryst. form and recryst. solvent	% Yield	M. p., °C.	Analyses, % Calcd.	Found
I	4.4 g. A	3.2 g. pyruvic acid	Cold, dil. acetic acid	Hexagonal plates, 1:2 benzene-petroleum ether	92	98–99 dec.	N 12.85	12.56
II	3.0 g. A	2.4 g. acetophenone	Reflux 1 hr. in alc. with 5 drops conc. H_2SO_4	Needles, alc.-water	87	84.5–85.5	N 11.20	11.11
III	1.0 g. A	2 cc. acetone	Reflux 2 hr., distil		90	b. p. 153 at 12 mm.	C 76.50	76.37
							H 8.57	8.50
							N 14.89	14.68
	Picrate of III		Ethereal picric acid	Needles, alc.		138–140	N 16.78	16.71
IV	0.7 g. B	0.5 cc. pyruvic acid	Alc., reflux 5 min.	Plates, alc.	58	122–123	N 10.45	10.22
V	.5 g. C	.4 cc. pyruvic acid	Same as IV	Plates, alc.	85	148–150, dec.	N 11.12	11.37

[a] A = N-amino-1,2,3,4-tetrahydroquinoline; B = N-amino-1,2,3,4-tetrahydro-5,6-benzoquinoline; C = N-aminocarbazole.

Anal. Calcd. for $C_{12}H_{11}O_2N$: C, 71.61; H, 5.51; N, 6.97. Found: C, 71.49; H, 5.54; N, 7.02.

The substance was easily soluble in cold methanol and ethanol, and in acetone, moderately soluble in ether and practically insoluble in water. It gave a violet Ehrlich reaction on boiling.

1,8-Trimethyleneindole.—This indole was obtained in 68% yield from the corresponding acid by an adaptation of Reichstein's procedure for decarboxylation.[9] A mixture of 1.5 g. of 2-carboxy-1,8-trimethyleneindole, 0.4 g. of copper chromite[10] and 4 cc. of quinoline was heated at 180–190° in a stream of hydrogen. After one hour the absence of a further precipitate in a barium hydroxide trap indicated completion of the reaction. The mixture was diluted with ether, filtered from the copper chromite and extracted with 2 *N* hydrochloric acid until no more quinoline was removed. A further extraction with dilute sodium carbonate removed traces of the carboxy acid. The ether solution was dried, the solvent evaporated and the residue distilled with steam. The indole, obtained from the distillate by filtration, was recrystallized from a small volume of petroleum ether (b. p. 40–60°). The product separated as large, colorless plates, m. p. 86.5–88° when pure.

Anal. Calcd. for $C_{11}H_{11}N$: C, 84.01; H, 7.06; N, 8.92. Found: C, 84.11; H, 7.02; N, 9.31.

The indole is very soluble in alcohol, acetone, benzene, moderately soluble in petroleum ether and insoluble in water. It is a neutral substance, insoluble in acids and bases. It gives a purple coloration with the Ehrlich reagent in the cold.

An unstable picrate of the indole was obtained by treating a concentrated benzene solution of the substance with a benzene solution containing slightly less than one equivalent of picric acid. The resulting red solution, when diluted with cold petroleum ether to faint turbidity, deposited red needles, melting at 138–139°.

Anal. Calcd. for $C_{17}H_{14}O_7N_4$: N, 14.51. Found: N, 14.67.

The picrate is decomposed by boiling water, by hot alcohol and even by hot benzene and petroleum ether.

2,3-Dihydro-1,8-trimethyleneindole.—When 0.2 g. of 1,8-trimethyleneindole in alcohol solution was reduced with zinc dust and hydrochloric acid, according to the procedure of Schlieper[11] for α-naphthindole, an oil was obtained which boiled at about 140° at 12 mm., and which yielded a yellow picrate that precipitated from ether solution. When recrystallized from alcohol, it separated in two forms, plates and needles, which, however, were identical in mixed melting point. The twice recrystallized picrate sintered at 165°, and liquefied at 168–170° to a red oil, which soon effervesced. The same substance was obtained by reduction of the indole with tin and hydrochloric acid.

Anal. Calcd. for $C_{17}H_{16}O_7N_4$: C, 52.56; H, 4.16; N, 14.43. Found: C, 52.80; H, 4.14; N, 14.47.

This picrate was identical in analysis and properties with the picrate of lilolidine, which was prepared according to von Braun[5] by condensation of trimethylene chlorobromide with dihydroindole.[12] The product was carefully fractionated to separate any unchanged dihydroindole from the lilolidine. The picrate of the highest fraction, after two recrystallizations from alcohol, did not lower the melting point of the picrate from dihydro-1,8-trimethyleneindole. It is to be noted, however, that although the melting point of the picrate was unchanged by this recrystallization, it is higher than that reported by von Braun.[5] The substance gave no evidence of melting at 138°, although held at that temperature for fifteen minutes, but sintered at 165°, and melted to a red oil at 168–170°. A duplicate preparation of lilolidine gave the same results. We have communicated with Professor von Braun, who admits the identity of our reduction product with lilolidine, and states that his original preparation was done under very adverse circumstances.

(9) Reichstein, Zschokke and Grüssner, *Helv. Chim. Acta*, **15**, 1069 (1932).

(10) Adkins and Connor, THIS JOURNAL, **53**, 1092 (1931).

(11) Schlieper, *Ann.*, **239**, 229 (1887).

(12) Willstätter and Jaquet, *Ber.*, **51**, 777 (1918).

2-Phenyl-1,8-trimethyleneindole.—One gram of the hydrazone of N-aminotetrahydroquinoline and acetophenone was ground in a mortar with 5 g. of powdered anhydrous zinc chloride and the mixture was heated at 120° for one hour. The mass was then warmed with several small quantities of dilute hydrochloric acid to dissolve the zinc chloride. The residual gummy brown precipitate was filtered, dried, powdered and extracted with ether to separate the indole from brown ether-insoluble by-products. The residue obtained on evaporation of the extracts, when recrystallized from 10 cc. of alcohol, yielded 0.2 g. of the indole, m. p. 130–132° (22% yield). After two recrystallizations from alcohol, from which the substance separated as glittering, colorless leaves, it melted at 133–134°.

Anal. Calcd. for $C_{17}H_{15}N$: C, 87.50; H, 6.49; N, 6.01. Found: C, 87.32; H, 6.41; N, 5.91.

The substance gave with Ehrlich's reagent in the cold a violet color which turned blue on standing.

N - Amino-1,2,3,4-tetrahydro-5,6-benzoquinoline.—The necessary N-nitrosotetrahydrobenzoquinoline was prepared by the procedure of Bamberger and Müller.[13] Yields of 60–70% were obtainable if an adequate quantity of water was used to keep dissolved at 0° the rather insoluble salt of the tetrahydrobenzoquinoline.

The N-aminotetrahydrobenzoquinoline was prepared in yields of 35–40% by mild reduction of the nitroso compound with zinc dust and acetic acid in aqueous alcoholic solution, according to the procedure for N-aminotetrahydroquinoline. The product was isolated as the sulfate, which, after recrystallization from 0.6 N sulfuric acid, separated as glistening brown needles and leaves, m. p. 182° with decomposition.

(13) Bamberger and Müller, *Ber.*, **24**, 2644 (1891).

Anal. Calcd. for $C_{26}H_{30}O_4N_4S \cdot 4H_2O$: N, 9.90. Found: N, 10.15.

Anal. of salt after drying at 120°. Calcd. for $C_{26}H_{30}O_4N_4S$: N, 11.34. Found: N, 11.30, 11.35.

The free base, formed by decomposition of the sulfate in hot aqueous–alcoholic solution with dilute alkali, consisted of tan crystals which melted at 107–108° after two recrystallizations from ligroin.

Anal. Calcd. for $C_{13}H_{14}N_2$: N, 14.18. Found: N, 13.94.

This hydrazine was moderately soluble in alcohol, nearly insoluble in water. It reduced Tollens' solution rapidly in the cold, and Fehling's solution slowly on boiling.

Summary

1. The chemistry of a new tricyclic indole, 1,8-trimethyleneindole, has been studied. The 2-carboxy and 2-phenyl derivatives are also reported, but the 2-methyl derivative could not be obtained. The preparation of the intermediate hydrazones, the pyruvic acid, acetophenone and acetone hydrazones of N-amino-1,2,3,4-tetrahydroquinoline is reported.

2. N - Amino - 1,2,3,4 - tetrahydro - 5, 6- benzoquinoline and its pyruvic acid hydrazone have been prepared. The latter is inactive toward indolizing agents.

3. The pyruvic acid hydrazone of N-aminocarbazole is likewise not convertible to an indole.

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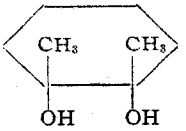
[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

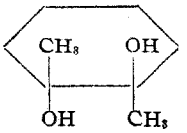
Inversion in the Pinacol Rearrangement of 1,2-Dimethylcyclopentanediol-1,2*

BY PAUL D. BARTLETT AND ABRAHAM BAVLEY

It has been pointed out[1] that in the pinacol rearrangement of the geometrical isomers of 1,2-dimethylcyclohexanediol-1,2 (I and II)



I



II

the methyl group migrates in preference to the ring carbon atom only in the *cis*-pinacol, in which the methyl group is, on a time average, remote from the hydroxyl which it displaces. Because the cyclohexane ring is non-planar and allows many different orientations of adjacent substituents with respect to each other, this example leaves something to be desired in exactness of interpretation. For this reason we have investigated the case of *cis*- and *trans*-1,2-dimethylcyclopentanediol-1,2, in which the planar nature of the five-membered ring makes the relative positions of the groups in space much more certain.

The assignment of configurations to the *cis*- and *trans*-isomers is made on the same basis as in the case of the analogous pinacols with six-membered rings. The *cis* isomer, a liquid boiling at 142–146° (20 mm.), is prepared by the action of potassium permanganate in cold aqueous acetone solution on 1,2-dimethylcyclopentene-1. The *trans* isomer, m. p. 99.5–101° (corr.), results

(*) Presented at the Milwaukee meeting of the American Chemical Society, September 6, 1938.

(1) Bartlett and Pöckel, THIS JOURNAL, **59**, 820 (1937).