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SOME DEGRADATIONS OF CALYCANTHINE*

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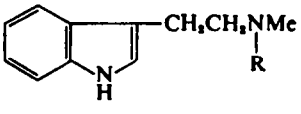
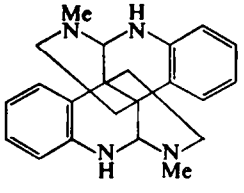
Abstract—Oxidation of benzoylcalycanthine (VI), yielded calycanine (III). Prolonged action of dil. HCl on calycanthine afforded an intermediate product VII, which gave 3-(2'-benzoylaminophenyl)-1-methyl-2-pyrroline (VIII) on benzoylation followed by pyrolysis. Dinitroso-calycanthine (IX) was converted into its diazonium salt by treatment with cold 4N HCl, and the latter underwent azo-coupling reactions with phenols.

BARGER[1] and Manske[2] suggested structures for calycanthine, and in 1954, Robinson and Teuber[3] proposed one of the β,β'-oxidatively coupled structures of two molecules of N-methyltryptamine (Ia). Recently, Woodward's[4] and Robertson's[5] groups presented the structure II, determined by means of X-ray analysis. This structure has only 6-membered and no 5-membered rings.



Ia, R = H
Ib, R = COPh



II

Pyrolysis of II with sodalime gave N-methyltryptamine (Ia).[1] 3-Methylindole, 3-ethylindole and calycanine (quino[4.3-c]quinoline) (III) were isolated from the zinc dust distillation products of II.[1] Selene dehydrogenation[6] afforded β-carboline, 4-methylquinoline and calycanine.

Späth and Eiter[7] found that dehydrogenation of calycanthine with silver acetate

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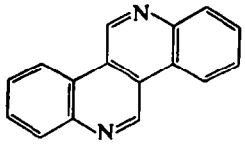
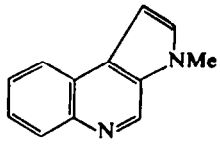
[1] G. Barger, J. Madiaveitia and P. Streuli, *J. Chem. Soc.* 510 (1939).
[2] R. H. F. Manske and L. Marion, *Canad. J. Res* B24, 224 (1946).
[3] R. Robinson and H. J. Teuber, *Chem. & Ind.* 783 (1954).
[4] R. B. Woodward, N. C. Yang and T. J. Katz, *Proc. Roy. Soc.* 76 (1960).
[5] T. A. Hamor, J. M. Robertson, H. N. Shrivastava and J. V. Silverston, *Proc. Roy. Soc.* 78 (1960); T. A. Hamor and J. M. Robertson, *J. Chem. Soc.* 194 (1962).
[6] R. H. F. Manske and L. Marion, *Canad. J. Res.* B17, 293 (1939).
[7] E. Späth, W. Stroh, E. Lederer and K. Eiter, *Monatsh.* 79, 11 (1948); K. Eiter and A. Nezval, *Ibid.* 81, 404 (1950).



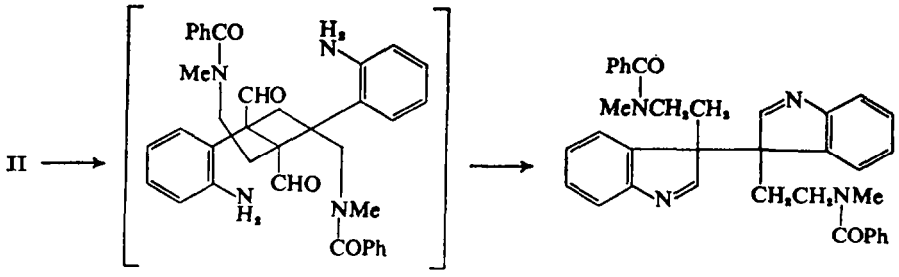
III



IV

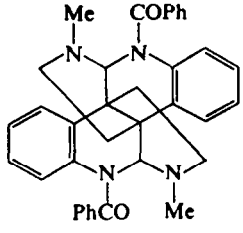
followed by hydrolytic fission with hydrochloric acid gave 1-methyl-pyrrolo[2.3-c]-quinoline (IV). The above cleavage reactions reveal that the degradations of calycanthine are always accompanied by rearrangement and formation of new ring systems not present in the original structure II.

The reaction of calycanthine with benzoyl chloride afforded, as reported by Manske,[8] a neutral benzoylation product which failed to crystallize. Its oxidation with potassium permanganate gave N-benzoyl-N-methyltryptamine (Ib).[8] We believe that during the course of benzoylation, the labile —N—C—N— bonds of II are cleaved and an intermediate thus formed cyclizes to give the observed product which most likely possesses the essential structural features found in Ib. The following scheme illustrates a possible reaction course and structure of the benzoylation product.



V

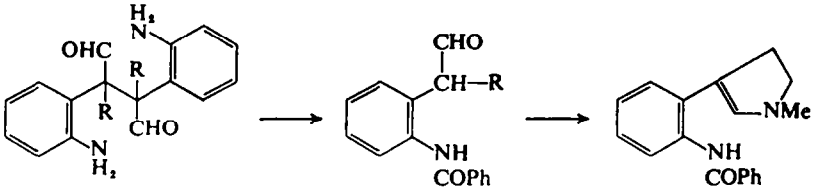
On the other hand, treatment of II with Grignard's reagent followed by methyl benzoate afforded benzoylcalycanthine (VI) which was believed to retain the original calycanthine skeleton. Oxidation of VI with potassium permanganate then gave calycanine (III). In the latter reaction two ethaneamine chains were eliminated without formation of a new ring system. These two reactions contrast with other known calycanthine reactions in that no rearrangement or formation of new ring systems occur, even when the two ethaneamine chains are eliminated.



VI

[8] R. H. F. Manske, *Canad. J. Res* B4, 275 (1939).

The acidic hydrolysis of calycanthine was thoroughly investigated. Prolonged treatment of calycanthine with dilute hydrochloric acid at 100° afforded an oily base VII. A successful azo coupling reaction of VII showed the presence of the aromatic primary amino group. Vacuum distillation (2 mm) of VII gave N-methyltryptamine (Ia) by dehydration and cleavage. On the other hand, vacuum distillation of the benzoylated derivative of VII afforded a new degradation product m.p. 113–114°. To this we assigned the structure, 3-(2′-benzoylaminophenyl)-1-methyl-2-pyrroline (VIII) on the basis of the molecular formula, $C_{18}H_{18}N_2O$ and the IR spectrum. The vacuum distillation includes not only purification, but also cleavage and ring closure.

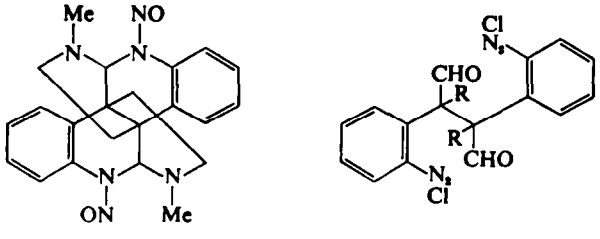


VII (R = —CH_2CH_2NHMe) VIII

When calycanthine was heated at 180° for 1 hr in dilute hydrochloric acid, N-methyltryptamine (Ia) was directly obtained. Treatment of II with dilute acetic acid at 120° and 180° also yielded VIII and Ia.

The structure of the intermediate base could not be determined, but the assignment of the structure VII is based on its transformation to Ia and VIII. It should be noted that the structure VII is the β,β'-oxidatively coupled intermediate in the biogensis of calycanthine.[4]

Gordon[9] reported that calycanthine gave a dinitroso derivative on treatment with nitrous acid. Dinitroso-calycanthine (IX) is insoluble in dilute hydrochloric acid but soluble in 4N HCl. Compound IX was gradually converted into a diazonium salt X when its acidic solution was allowed to stand in the cold.



IX X (R = CH_2CH_2NHMe·HCl)

The azo coupling reactions with phenols indicate that the imino group is attached directly to the benzene ring, and the ring opening by strong acid may be explained by the Woodward-Robertson's structure II, in which acid labile —N—C—N— bondings are present.

However, formation of Späth's compound, pyrrolo[2.3-c]quinoline ring system (IV), from II is difficult to understand. Saxton[10] suggested a mechanism for its formation, but the mechanism remains to be proved.

[9] H. M. Gordin, *J. Am. Chem. Soc.* **27**, 1426 (1905).
[10] J. E. Saxton, *Quarterly Rev.* 119 (1956).

EXPERIMENTAL

N-Benzoyl-N-methyltryptamine (Ib)

(i) Benzoylation and oxidation in accordance with experiments reported by Manske[8] yielded Ib, m.p. 198–199°.

(ii) *Hydrolysis by dil.* HCl *at* 180°. The solution of calycanthine (1 g) in 1·5N HClaq (4 ml) was heated at 180–185° for 1 hr in a sealed tube. The acidic solution with fluorescence was filtered with the aid of charcoal, made alkaline, and extracted with C_6H_6 several times. After removal of a small amount of insoluble material the benzene extract was treated with PhCOCl and NaOHaq under stirring overnight yielding Ib as a partly crystalline insoluble mass. Recrystallization from MeOH (charcoal), gave the product, m.p. 198–199°.

(iii) *Hydrolysis by dil. acetic acid at* 180–185°. Calycanthine (1 g) was dissolved in a minimum amount of dil. AcOH (0·5 ml and 2 ml, H_2O), heated at 180–185° for 3·5 hr. The acidic clear filtrate (charcoal) was neutralized with NaOHaq and extracted with warm C_6H_6 several times. The warm C_6H_6 layer was treated with PhCOCl (1 g) and K_2CO_3aq. The vacuum distillation of the C_6H_6 soluble and insoluble fractions afforded crystals, 0·4 g, m.p. 185°; recrystallization from MeOH, m.p. 198–199° (Ib).

Determination of the active hydrogen[11]

Calycanthine, 0·100 g and EtMgI resulted in the evolution of ethane, 13·1 ml (30°, 757·7 mm). (Found, active H_2, 1·84; $C_{22}H_{26}N_2$ requires; 2.)

Calycanine (III) *from benzoylcalycanthine* (VI)

Grignard's reagent obtained from EtI (1·2 g) and Mg (0·3 g) in dry ether, was evaporated on addition of dry C_6H_6. Calycanthine (1 g) was added to the C_6H_6 solution of EtMgI under stirring, and the effervescence of ethene was noted. After the addition of PhCOOEt (1 g) the mixture was refluxed for 4 hr, and after cooling, was poured into the mixture of ice and dil. AcOH. The C_6H_6 extract was washed with water and evaporated on a water bath. The residue was dissolved in acetone, treated dropwise with a solution of $KMnO_4$ (0·2 g) in acetone under magnetic stirring and allowed to stand overnight at room temp. The almost colourless solution was filtered, washed with acetone, and evaporated. The residue in dil. AcOH was extracted with C_6H_6. After washing with water drying with Na_2SO_4 and evaporation of the solvent, the extract was distilled *in vacuo* (2 mm). The higher boiling fraction gave crystals, m.p. 240° (from MeOH). By sublimation under atm. press. and the further recrystallization from MeOH (charcoal), needles, m.p. 308°, were obtained, which was identified as III by the mixed m.p. IR spectra.

3-(2′-*Benzoylaminophenyl*)-1-*methyl*-2-*pyrroline* (VIII)

(i) *Hydrolysis by* 2N HCl *at* 100°. Calycanthine (1 g) was heated with 2N HCl (15 ml) on a water bath 72 hr in a sealed tube. The acidic solution with blue fluorescence was treated with charcoal, and mixed with PhCOCl (1 g) and ether. Dil. NaOHaq was added dropwise gradually to the mixture in the cold, and the whole allowed to stand overnight under vigorous stirring. The ether soluble part was distilled *in vacuo* (2 mm) after removal of the solvent. The lower boiling fraction was crystallized from C_6H_6-pet. ether, m.p. 111–114° and recrystallization from MeOH as needles, m.p. 113–114° (VIII). The IR spectra showed the bands at 3440 (b) (—NH—) and at 1623 cm^{-1} (s) (=NCO—). (Found: C, 77·67; H, 6·52; N, 10·27. $C_{18}H_{18}N_2O$ requires; C, 77·67; H, 6·52; N, 10·07%).

The ether insoluble part yielded prisms, m.p. 198° (Ib) after vacuum distillation (2 mm) and recrystallization from MeOH.

(ii) *Hydrolysis dil. acteic acid at* 120–130°. Calycanthine (0·8 g) in AcOH (1 ml) and water (3 ml) was heated at 120–130° for 70 hr in a sealed tube. The acidic solution with blue fluorescene was mixed well with PhCOCl and ether, and then 2N NaOH added gradually in the cold with stirring. After drying and removal of solvent, the ethereal layer was distilled *in vacuo* (2 mm). The first distillate crystallized from C_6H_6–pet. ether, yield 40 mg, m.p. 111–113° and recrystallized from MeOH, m.p. 113–114° (VIII). The vacuum distillation (2 mm) of the ether insoluble part gave a small amount of crystals, m.p. 194° from MeOH (Ib).

[11] F. Pregl, *Quantitative Organische Mikroanalyse* (5 de Auflage). Wien, Springer-Verlag (1947).

If the acidic solution with fluoresence in i and ii is made alkaline, then PhCOCl added after some time VIII is not formed and Ib is the major product.

N,N-*Dinitrosocalycanthine* (IX)

To a magnetically stirred solution of calycanthine (1 g) in 1N HCl (20 ml) cooled in an ice bath was added gradually, 5 ml 10% $NaNO_2$aq. After stirring an additional 2 hr, the yellow precipitate was collected, washed thoroughly with water and dried in the air. The precipitate after crystallization from pyridine–MeOH gave dull yellow feathery needles, m.p. 175–176° (with effervescence) which has been described by Gordin, as the nitrosoamine, $C_{11}H_{12}N_2O$. (Found: C, 65·51; H, 6·12; N, 20·45. $C_{22}H_{24}N_4(NO)_2$ requires: C, 65·33; H, 5·98; N, 20·78%).

The dinitroso-derivative IX is insoluble in 1N HCl, but soluble in 4N HCl. After standing a short time in the cold, dilution with water again precipitated the dinitrosoamine. However, after allowing to stand 18 hr in a refrigerator (2°) no precipitate appeared on addition of water and during this period the brown colour changed to green.

The results of azo coupling reactions of the above green solution with phenols in the presence of alkali, are shown in the following Table.

	PhN_2Cl	X
PhOH	reddish yellow	greenish ochre
β-$C_{10}H_7OH$	reddish orange	pale brown
H acid	greenish purple	greyish purple

An acidic solution of IX in 8N HCl gave a dark brown mass on standing in cold.

Acknowledgement—We wish to thank Miss Yasuko Fujiyoshi for the microanalyses.