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SYNTHESIS OF CALYCANINE

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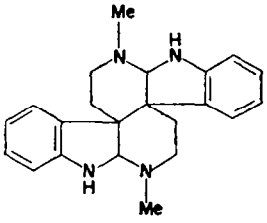
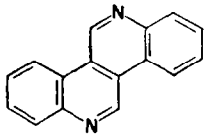
Abstract—Calycanine, the degradation product of the alkaloid calycanthine, has been synthesized.

THE alkaloid calycanthine isolated from various species of calycanthaceae has been assigned[1] structure (I). Dehydrogenation of calycanthine yields[2] a base, calycanine, $C_{16}H_{10}N_2$, formulated[1] as quinolino(4′:3′-3:4)quinoline (II). This structure has been reported[3] to have been confirmed by a synthesis from isoindigo by Clark and Woodward, but details have not been published. A new independent synthesis of calycanine has been devised and is reported here.



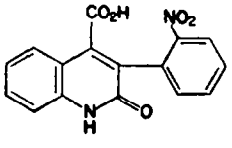
I



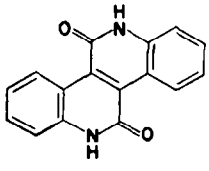
II

Aeschlimann[4] has condensed isatin with phenylacetyl chloride; the N-phenylacetyl isatin obtained underwent rearrangement in alkali to 3-phenyl-2-quinolone-4-carboxylic acid.

Isatin was condensed with *o*-nitrophenylacetyl chloride, but the N-acyl derivative could not be obtained pure. The crude product on treatment with alkali and subsequent acidification yielded 3-*o*-nitro-phenyl-2-quinolone-4-carboxylic acid (III), with infra-red bands at 5·95 (COOH) and 6·1 μ (amide). Catalytic hydrogenation in presence of Adams catalyst resulted in reduction of the nitro group and simultaneous lactamization yielding the diquinolone (IV) with infra-red absorption at 6·02 μ



III



IV

[1] R. Robinson and H. J. Teuber, *Chem. & Ind.* 783 (1954).
[2] R. H. F. Manske and H. L. Holmes, *The Alkaloids* Vol. II, p. 435. Academic Press (1952).
[3] Reference 17 in B. Witkop and R. K. Hill, *J. Amer. Chem. Soc.* **77**, 6592 (1955); J. E. Saxton, *Quart. Revs.* **10**, 119 (1956).
[4] J. A. Aeschlimann, *J. Chem. Soc.* 2902 (1926).

(amide), and the latter on distillation with zinc dust yielded quinolino(4′:3′-3:4)quinoline, identical with an authentic sample of calycanine.

EXPERIMENTAL

Infra-red spectra were measured as Nujol mulls in a Perkin–Elmer Infracord spectrophotometer by Mr. S. Selvavinayakam.

o-*Nitrophenylacetyl isatin.* A suspension of sodioisatin[5] (9·5 g) in benzene (60 ml) was treated (stirring) with a solution of *o*-nitrophenylacetyl chloride (from 10 g *o*-nitrophenylacetic acid) in benzene (40 ml). Stirring at 30° was continued for 1 hr and the mixture was then refluxed (stirring) for another hour. The solution was filtered and the residue washed with hot benzene. Evaporation of the combined filtrates yielded the crude *o*-nitrophenylacetyl isatin, used for the next step.

3-o-*Nitrophenyl-2-quinolone-4-carboxylic acid.* The above crude N-acyl isatin was repeatedly digested with warm 2 N NaOH until no more went into solution and then filtered, cooled, and acidified with HCl. The precipitated acid was filtered and crystallized from methanol (6·9 g), m.p. 322° (decomp) (Found: C, 61·9; H, 3·2. $C_{16}H_{10}O_5N_2$ requires: C, 61·9; H, 3·2%).

The diquinolone IV. The above acid (0·3 g) in alcohol (50 ml) was hydrogenated at 40–50 lbs/in² in presence of Adams catalyst (0·1 g) for 3 hr. The greenish solid was filtered, extracted with hot dimethylformamide and filtered. Dilution of the cooled filtrate with methanol yielded the *diquinolone* (0·2 g) as a yellow crystalline powder, which did not melt at 360°. The yield was considerably lowered if the reduction was carried out in larger batches. The analytical values for this compound agreed for the monohydrate after drying at 100°/2 mm (Found: C, 68·7, 68·7; H, 3·8, 3·9; N, 10·4. $C_{16}H_{10}O_2N_2 \cdot H_2O$ requires: C, 68·6; H, 4·3; N, 10·0%). After prolonged drying at 140° the following values were obtained (Found: C, 70·1; H, 3·7. $C_{16}H_{10}O_2N_2$ requires: C, 73·3; H, 3·8%).

Calycanine. The above diquinolone (0·1 g) was intimately ground with zinc dust (1·5 g) and the mixture covered with a layer of zinc dust (1·5 g). The mixture was heated and the sublimate (7 mg) collected on a cold thumb. The combined sublimate from four batches was crystallized from pyridine–methanol and again sublimed at atmospheric pressure to yield *quinolino*(4′:3′-3:4)*quinoline* (8 mg), m.p. and mixed m.p. with authentic calycanine 310°. Their infra-red spectra were also superposable. (Found: C, 83·0; H, 4·6. Calc. for $C_{16}H_{10}N_2$: C, 83·5; H, 4·3%).

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[5] G. Heller, *Ber. Dtsch. Chem. Ges.* **40**, 1291 (1907).