Tetrahedron, 1962, Vol. 18, pp. 813 to 814. Pergamon Press Ltd. Printed in Northern Ireland

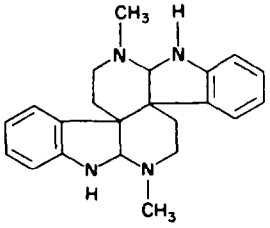
SYNTHESIS OF CALYCANINE

TEINOSUKE KOBAYASHI and RYOJI KIKUMOTO
Department of Chemistry, Gakushuin University, Mejiro, Tokyo, Japan

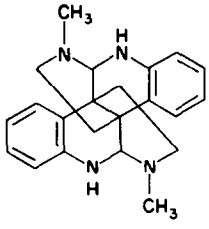
(*Received* 30 *January* 1962)

Abstract—Calycanine, the degradation product of the alkaloid calycanthine has been synthesized by heating *o*-aminoacetophenone (IV) and *o*-nitrophenylpyruvic acid (V) in the presence of zinc chloride.

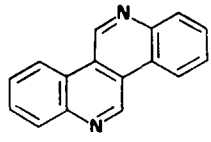
THE alkaloid calycanthine, isolated from the various species of Calycathaceae* was studied by Barger *et al.*[1] and for it the structure I was proposed by Robinson and Teuber.[2] Recently Woodward *et al.*[3] presented the revised structure (II), which was confirmed by the X-ray work performed in England.[4]



I



II



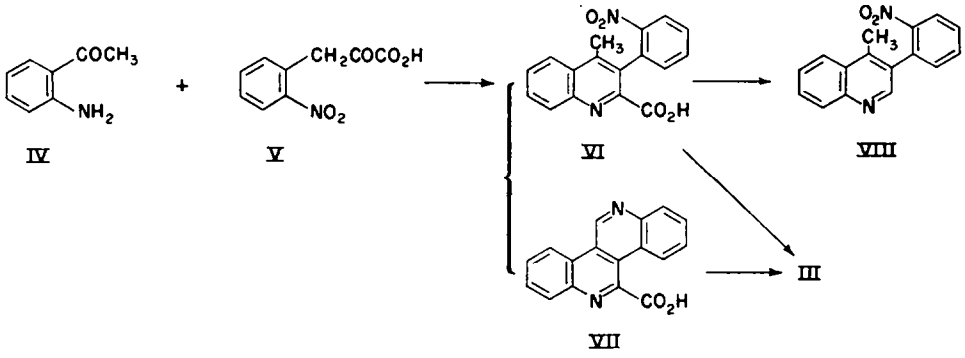
III

By dehydroge..ation of this compound Barger *et al.* obtained calycanine $C_{16}H_{10}N_2$, to which Robinson and Teuber assigned the structure of quinolino-(4',3'-3,4)-quinoline (III). This was synthesized from dihydroisoindigo by Clark and Woodward and recently from N-(*o*-nitrophenyl-acetyl)-isatin by Gopinath *et al.*[5] In this paper a new independent synthesis of calycanine is described. It has been reported that the condensation of *o*-aminophenylglyoxylic acid and phenylpyruvic acid in alkaline medium gives 3-phenylquinoline-2,4-dicarboxylic acid.[6] The condensation of *o*-aminophenylglyoxylic acid and *o*-nitrophenylpyruvic acid (V) and also of *o*-aminoacetophenone (IV) and *o*-nitrophenylpyruvic acid (V) in the same medium were, however, unsuccessful; probably due to steric hindrance of the *o*-nitro group.[7]

This reaction is successful if anhydrous zinc chloride in an inert solvent is used, i.e. equimolecular amounts of IV and V in boiling dry toluene react in the presence of zinc chloride to give quinolinoquinoline (III) (10 per cent). The intermediates, 3-(*o*-nitrophenyl)-lepidine-2-carboxylic acid (VI), quinolinoquinoline carboxylic acid (VII) and 3-(*o*-nitrophenyl)-lepidine (VIII) were identified. Quinolinoquinoline (III)

* References to earlier work by Gordion, by Späth and by Manske will be found in ref. 1.

[1] I. G. Barger, J. Madinaveitia and P. Streuli, *J. Chem. Soc.* 510 (1939).
[2] R. Robinson and H. I. Teuber, *Chem. & Ind.* 783 (1954).
[3] R. B. Woodward, *et. al.*, *Proc. Chem. Soc.* 76 (1960).
[4] T. A. Hamor, J. Monteath Robertson, H. N. Shrivastava and J. V. Silverton, *Proc. Chem. Soc.* 78 (1960).
[5] K. W. Gopinath, T. L. Govindachari and S. Rajappa, *Tetrahedron*, **8**, 291 (1960).
[6] W. Borsche and W. Noll, *Liebigs Ann.* **532**, 127 (1937).
[7] T. Kobayashi and R. Kikumoto, unpublished.



was also obtained by heating 3-(*o*-nitrophenyl)-lepidine-2-carboxylic acid (VII) with zinc chloride.

EXPERIMENTAL

Quinolino-(4′, 3′-3, 4)-quinoline (III)

(a) *From o-aminoacetophenone* (IV) *and o-nitrophenylpyruvic acid* (V). To a solution of *o*-aminoacetophenone (1·3 g) and *o*-nitrophenylpyruvic acid (2·1 g) in dry toluene (30 cc) pulverized anhydrous zinc chloride (3 g) was added and the mixture was heated in an oil bath for 3 hr at 140°–155° with frequent stirring. The dark oily product was dissolved in acetic acid (30 cc), treated with charcoal and the solution added to sodium hydroxide solution (130 cc, 30%). The resinous precipitate which partially solidified after standing over night was washed with water, dissolved in alcohol and the solution treated with charcoal. After removal of alcohol *in vacuo*, the product was distilled under red press (5 mm). The distillate, a pale yellow, mobile syrup, crystallized easily on heating with alcohol. It sublimed by heating at atm press and recrystallized from pyridine (1·7 g), colorless needles, m.p. 308°. (Found: C, 83·51; H, 4·21; N, 12·00. Calc. for $C_{16}H_{10}N_2$: C, 83·45; H, 4·38; N, 12·17%).

(b) *From 3-(o-nitrophenyl)-lepidine-2-carboxylic acid* (VI). To a solution of VI (0·1 g) in anhydrous benzene (30 cc) anhydrous pulverized zinc chloride (1 g) was added and the mixture heated on an oil bath for 3 hr with stirring while the temp was gradually raised to 160°. The dark oily product was dissolved in acetic acid (10 cc), decolorized with charcoal and the solution poured into a cold sodium hydroxide solution (40 cc, 30%). The residue was filtered, washed with water and distilled under red press (20 mm).

The distillate contained quinolinoquinoline (III) and *o*-nitrophenyllepidine (VIII) in smaller amount; the latter is more soluble in ethanol than the former. Recrystallization from ethanol and from pyridine gave white needles of quinolinoquinoline (III; 0·06 g), m.p. 308°. A solution of III in hot dil hydrochloric acid deposited on cooling long yellow needles of the *dihydrochloride*, m.p. above 350°. (Found: N, 9·49. $C_{16}H_{12}N_2Cl_2$ requires: N, 9·46%).

3-(*o-nitrophenyl*)-*lepidine-2-carboxylic acid* (VI) and *quinolinoquinoline carboxylic acid* (VII)

A solution of IV (1·3 g) and V (2·1 g) in dry benzene (30 cc) was refluxed on a water bath for 3 hr, then anhydrous pulverized zinc chloride (4 g) was added and the mixture refluxed for a further 4 hr with stirring. The reaction mixture was concentrated *in vacuo* to dryness and the residue dissolved in sodium hydroxide (30 cc, 20%) was treated with charcoal and filtered while hot. The solution was acidified with dil acetic acid and the resulting solid purified by the procedure mentioned above. This acid (0·5 g) recrystallized from dil acetic acid, prisms, m.p. 160° (decomp). Found: N, 9·14. $C_{17}H_{12}O_4N_2$ requires: N, 9·09%).

The filtrate of VI was evaporated on the water bath, some water added and allowed to stand overnight at room temp. The colorless crystals separated recrystallized from dil acetic acid (0·1 g), white needles, m.p. 150° (decomp). (Found: N, 10·32; $C_{17}H_{10}O_2N_2$ requires: N, 10·21%). The decarboxylation of this acid by distillation gave quinolinoquinoline (III), m.p. 308°.

3-(*o*-nitrophenyl)-lepidine-2-carboxylic acid (VI) was decarboxylated by distillation *in vacuo* (5 mm) and 3-(*o*-nitrophenyl)-lepidine obtained. (Found: C, 72·80; H, 4·43; N, 10·52. $C_{16}H_{12}O_2N_2$ requires: C, 72·71; H, 4·58; N, 10·60%).