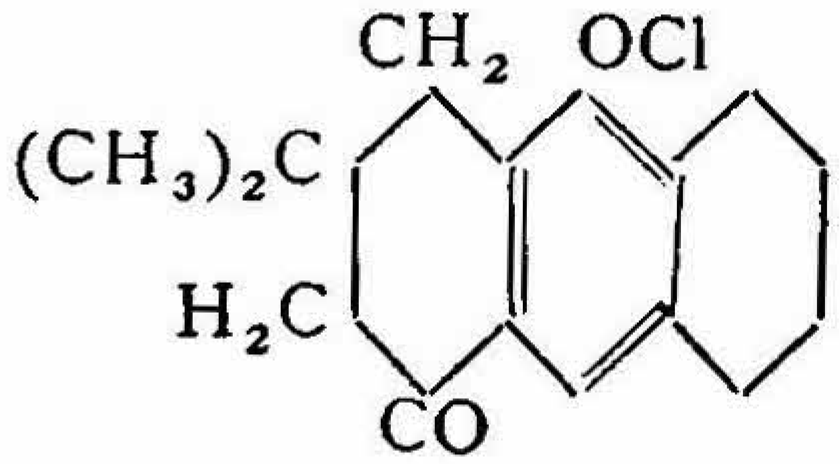
THE REACTIVITY OF DIMETHYLDIHYDRORESORCIN. PART II. BEHAVIOUR TOWARDS *ORTHO*-NITRO- AND *ORTHO*-AMINOBENZALDEHYDES.

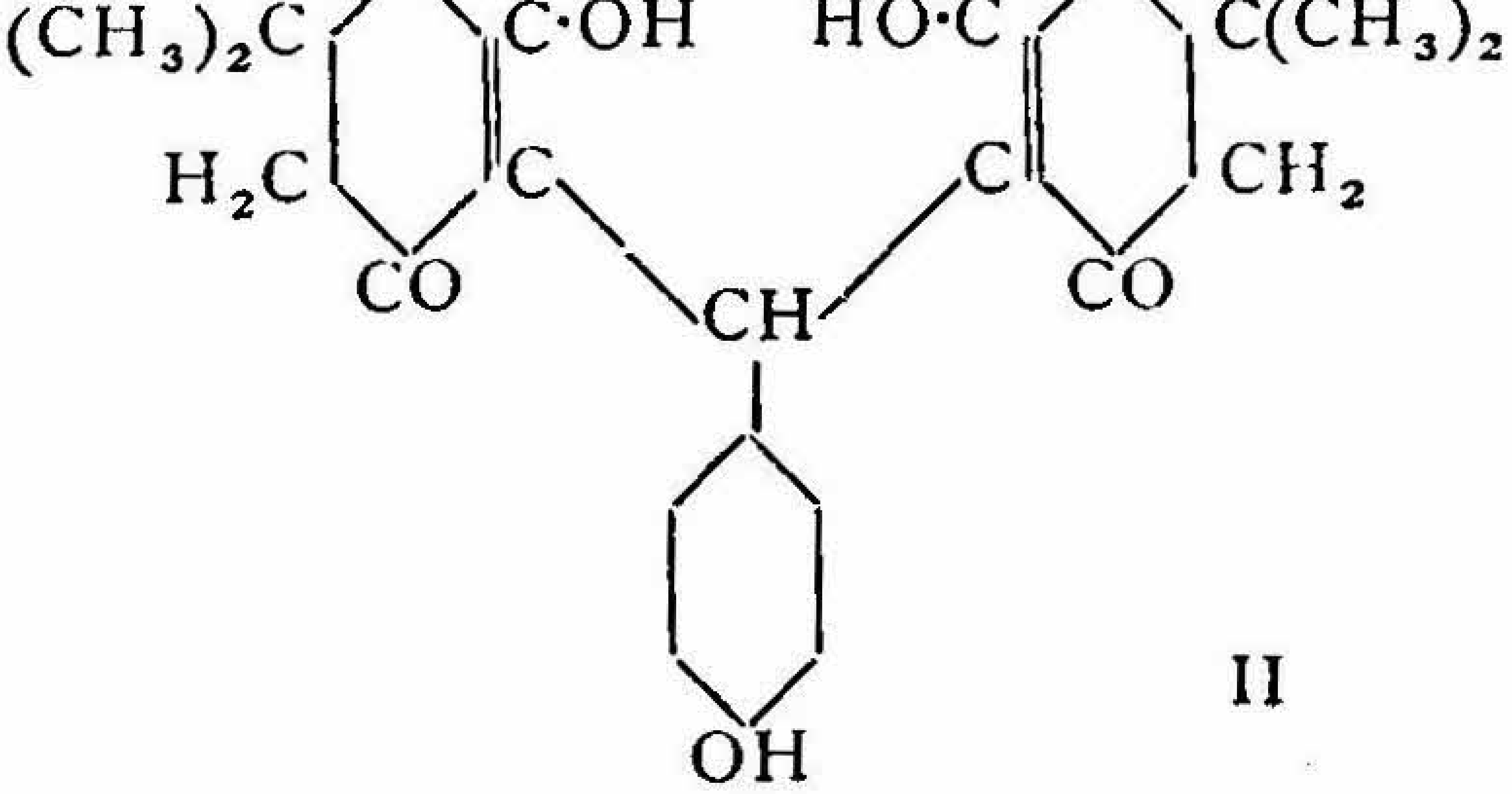
By B. H. Iyer and G. C. Chakravarti.

Chakravarti, Chattopadhyaya and Ghosh (Indian Science Congress Abstracts, 1929, 22), in condensing dimethyldihydroresorcin with aromatic aldehydes, have shown the various forms of ring closure taking place; the reactive methylene group between the two keto-groups gives dimethyldihydroresorcin great synthetic importance. This substance on condensation with *o*-hydroxybenzaldehyde in presence of dry hydrogen chloride gave 2-dimethyl-4-keto-tetrahydrobenzopyranol anhydrochloride (I),



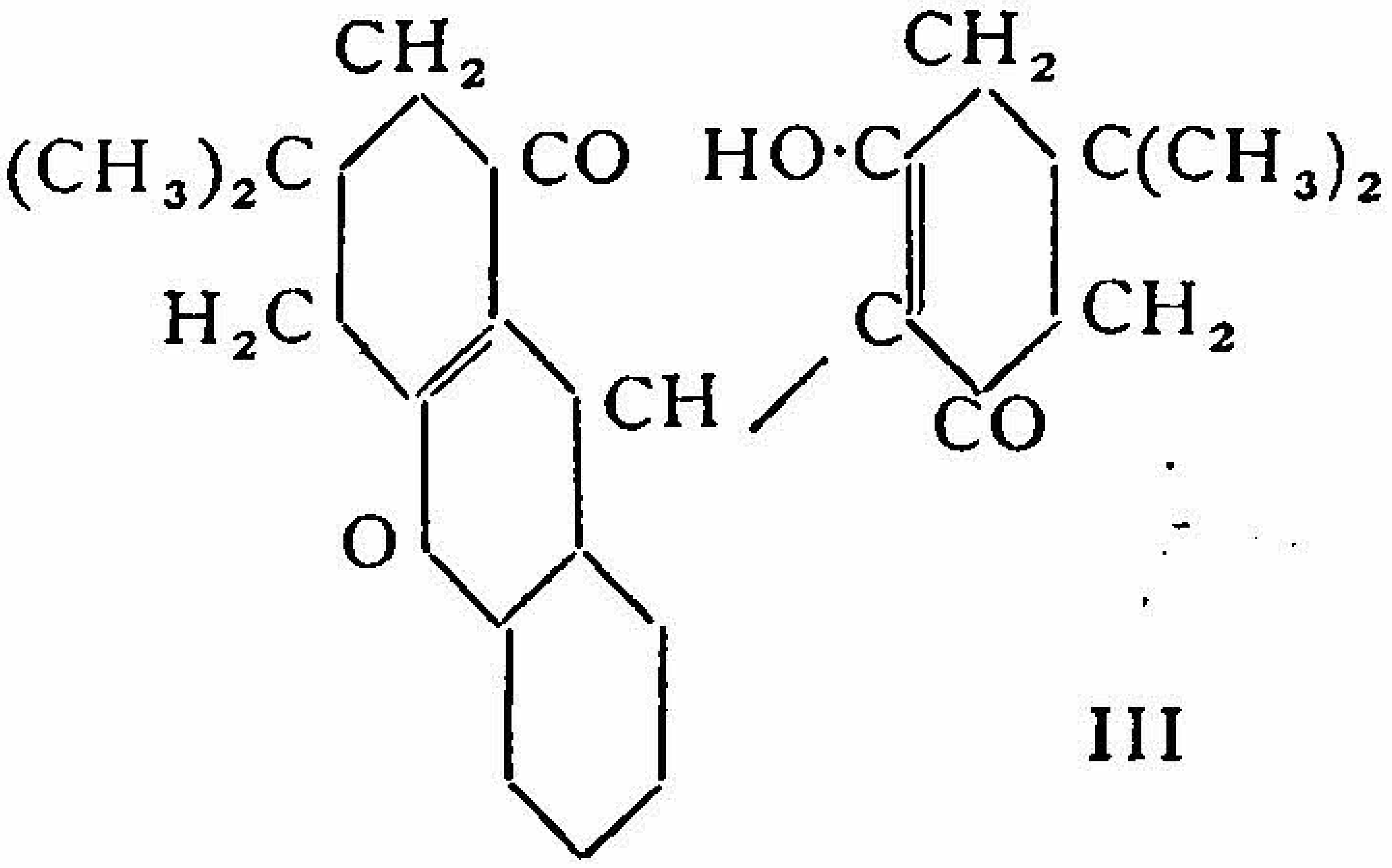
I

but condensation with salicylaldehyde in alcoholic potash gave compounds of the benzamarone type. Here two molecules of dimethyldihydroresorcin combined with one molecule of the aldehyde, whereas with hydrogen chloride only molecular proportions reacted. With *p*-hydroxybenzaldehyde, 4-hydroxybenzaldimethyldihydroresorcin (II) was obtained,



II

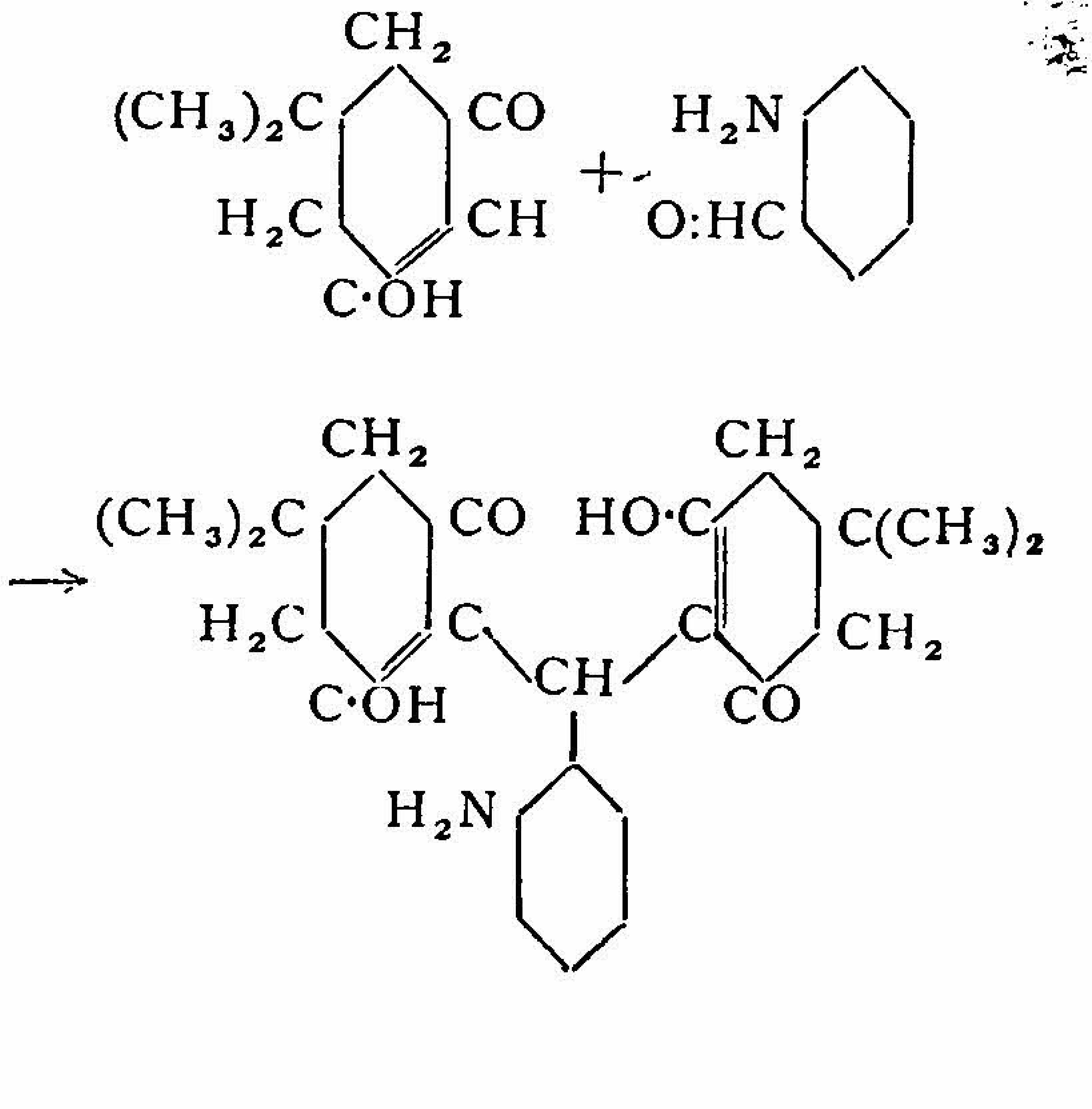
elimination of only one molecule of water taking place; but when the HO-group is in the *ortho*-position as in salicylaldehyde, two molecules of water are eliminated giving *o*-hydroxybenzaldimethyldihydroresorcin anhydride (III).

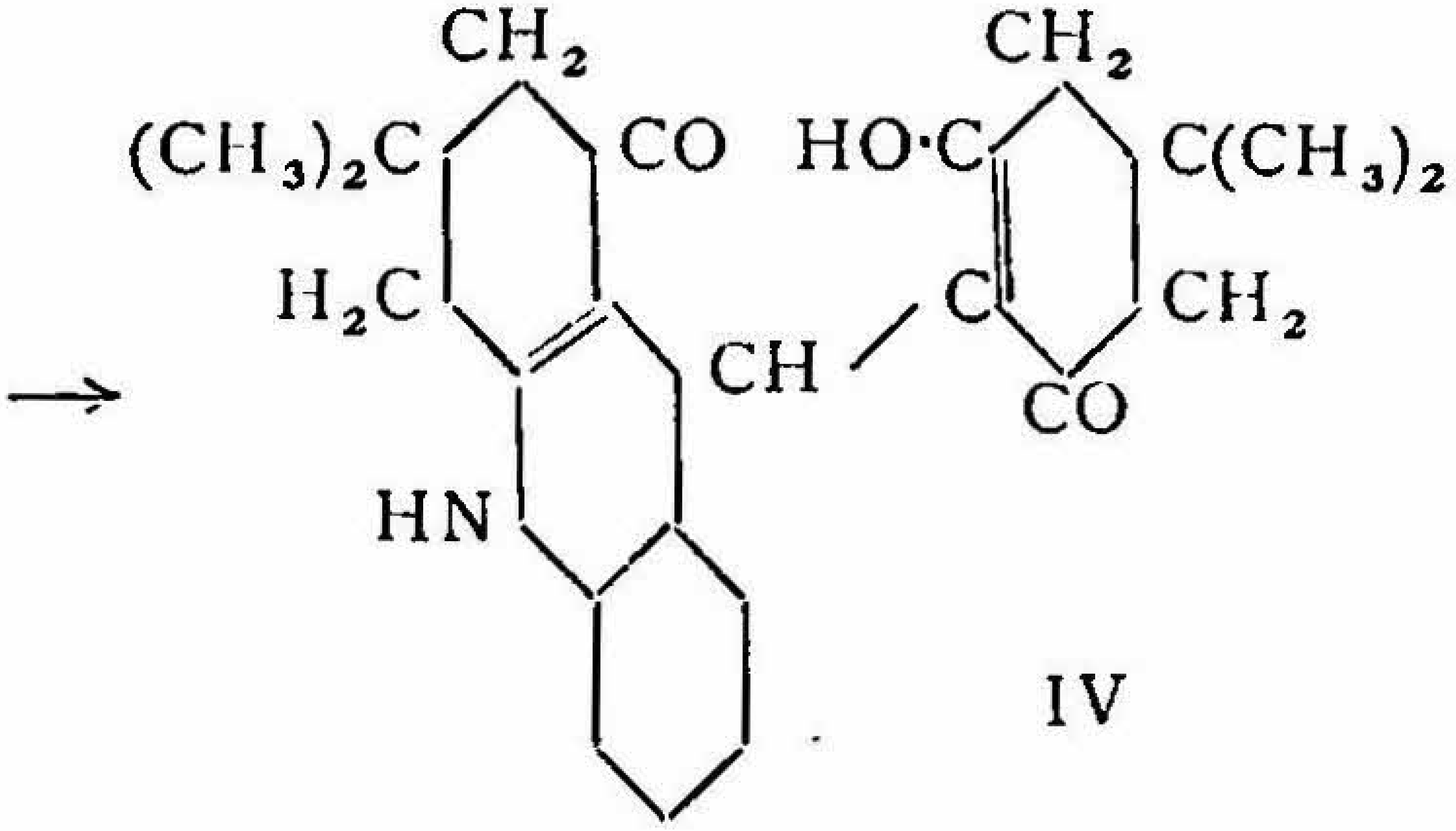


III

Owing to this interesting behaviour of the *o*-hydroxybenzaldehyde, it was thought that *o*-aminobenzaldehyde might give a dihydropyridine derivative of the type (IV).

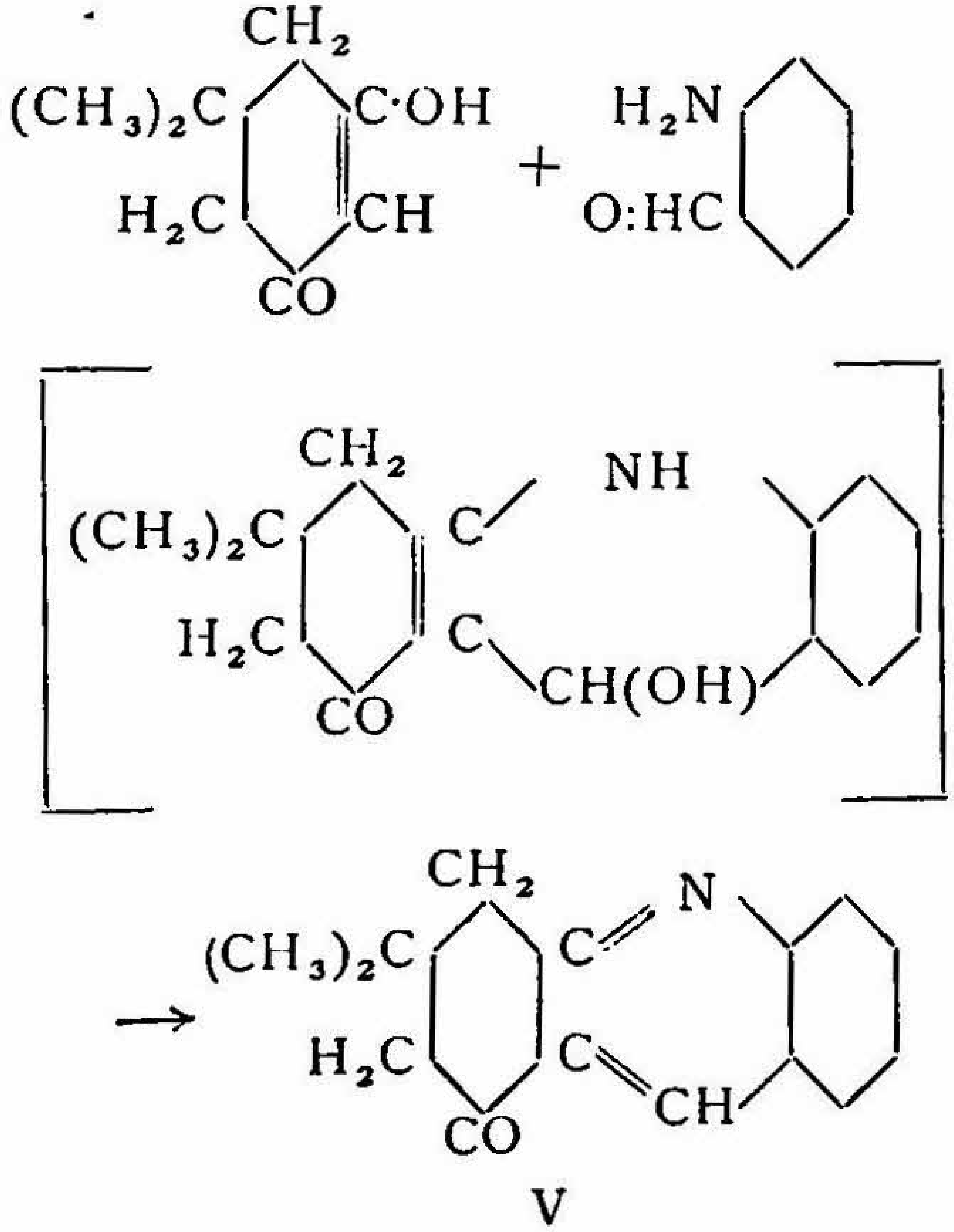
This product may be of great importance since it is likely to possess alkaloidal properties, having a reduced pyridine ring fused with hydroaromatic rings. The reaction was expected to take the following course:





IV

From the outset it was observed that *o*-aminobenzaldehyde and its derivatives behaved towards dimethyldihydroresorcin quite differently from the other aldehydes, only molecular proportions reacting. When dimethyldihydroresorcin was condensed with *o*-aminobenzaldehyde in alcoholic potash, only molecular proportions were involved and 1-keto-3-dimethyltetrahydroacridine (V) was formed by elimination of two molecules of water. The course of the reaction can be explained as follows :

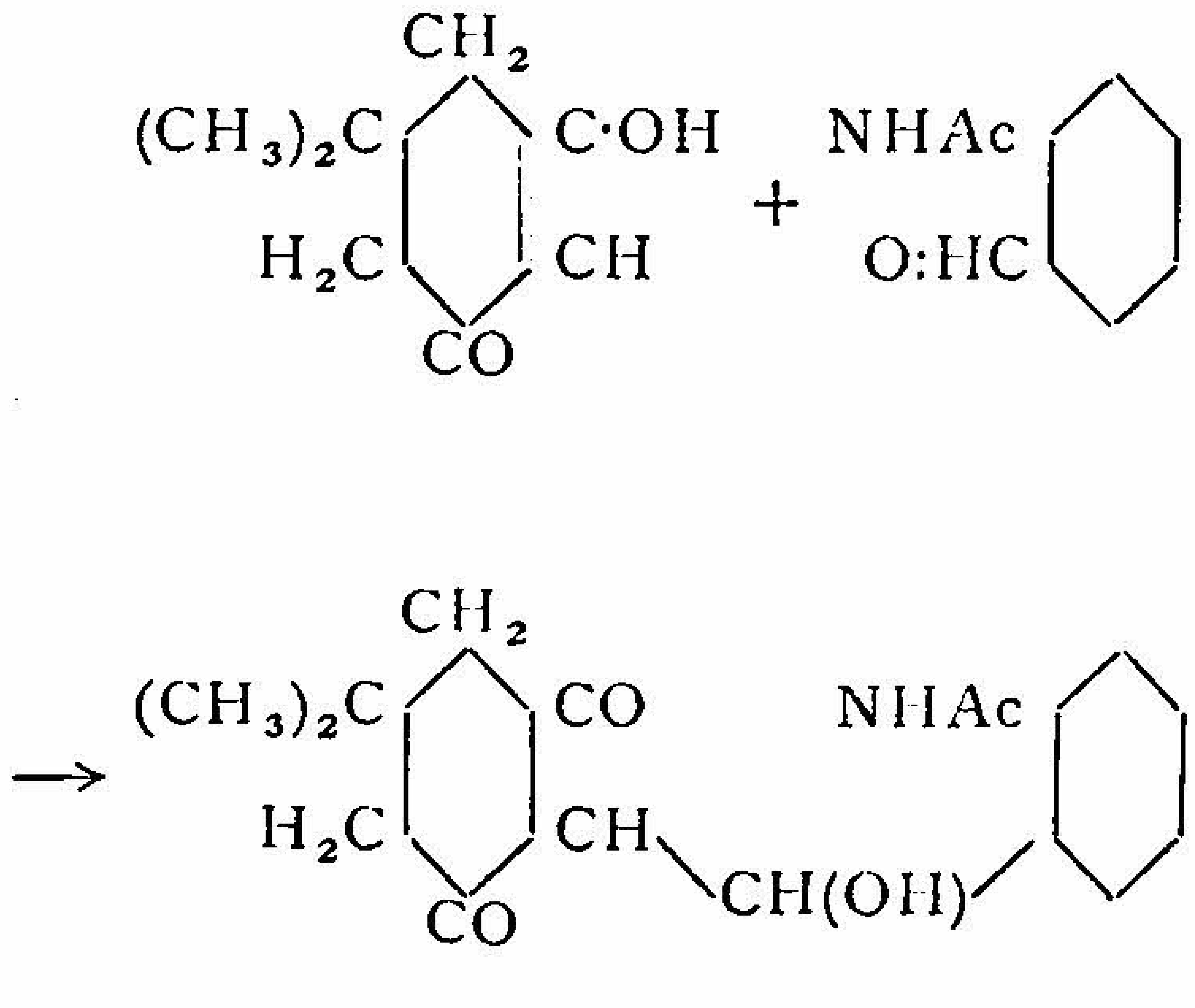


V

Elimination of water from the intermediate benzhydrol (not isolated) between the CH (OH) and NH-groups prevents a second molecule of dimethyldihydroresorcin from reacting.

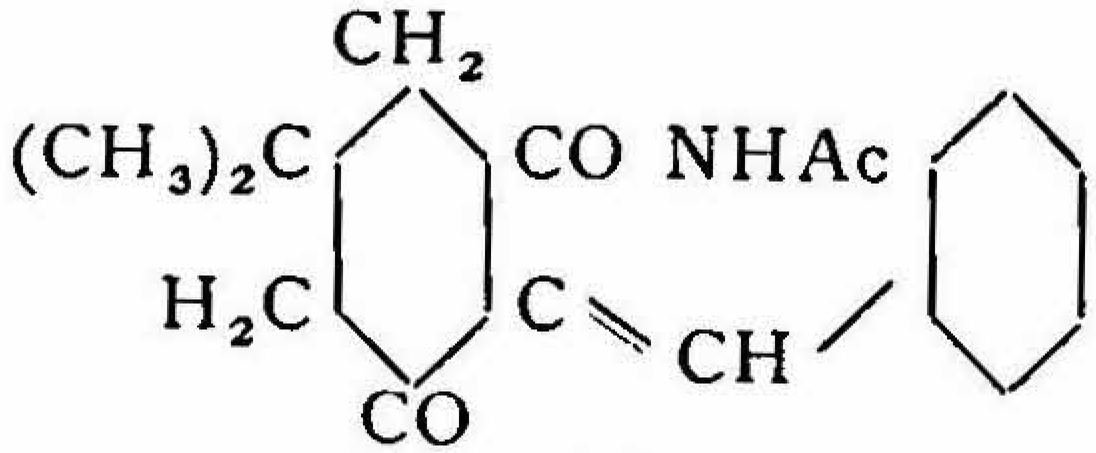
The above constitution for the product (V), namely, 1-keto-3-dimethyltetrahydroacridine, follows from, (1) Its tertiary basic properties indicated by non-formation of a nitroso- and acetyl derivative; (2) Negative colour test for the hydroxyl group with ferric chloride; (3) Formation of a methiodide, chloroplatinate and picrate. Moreover, when oxidised with concentrated nitric acid, it yields acridinic acid (2 : 3-quinolinedicarboxylic acid). With phenylhydrazine the product (V) yields the phenylhydrazones of dimethyldihydroresorcin and *o*-aminobenzaldehyde. Such behaviour has been observed in similar compounds by Sastry and Ghosh (*J.C.S.*, 1915, **107**, 1444) and in the case of oximes by Perkin and Robinson (*J.C.S.*, 1907, **91**, 1088)

To ascertain whether the NH_2-group was responsible for the non-formation of a pyridine derivative, it was protected by acetylation, but when dimethyldihydroresorcin was condensed with *o*-acetaminobenzaldehyde in alcoholic potash, the same acridine derivative was formed, owing to hydrolysis of the acetyl group. In absolute alcohol also only molecular proportions of the reactants combined; benzamarone condensation did not take place probably owing to steric hindrance by the acetamino-group in the ortho-position. The product was 2 : 6-diketo-4-dimethyl-2′-acetaminohexahydrobenzhydrol (VI), giving the acridine derivative (V) on hydrolysis with alcoholic potash.



VI

When the benzhydrol compound was heated at 105–110° for 15 to 20 hours, two molecules of water were eliminated with formation of 2-acetaminobenzylidenedimethyldihydroresorcin (VII).

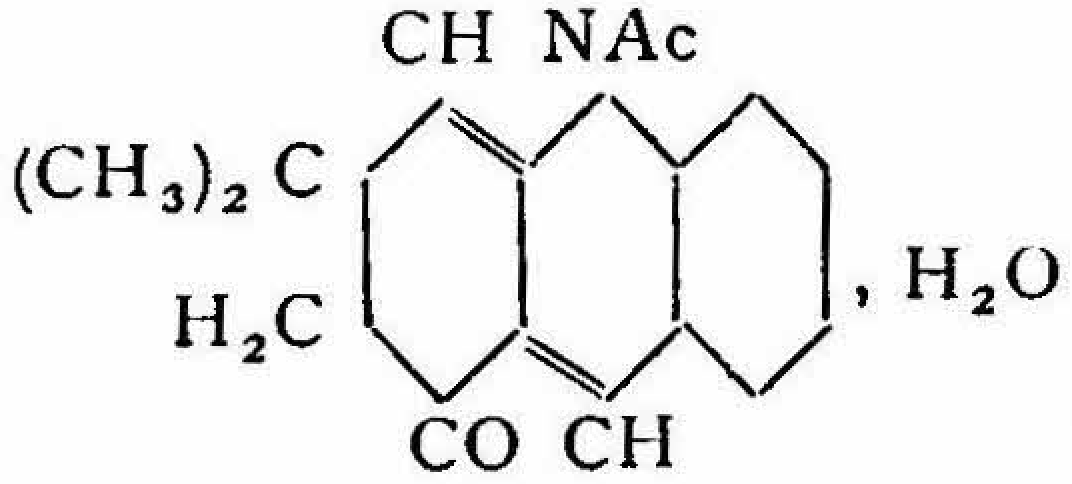


VII

The benzylidene derivative is colourless thus confirming the conclusion of Chakravarti, Chattopadhyaya and Ghosh (*J. Ind. Inst. Sci.*, 1931, **14A**, 141) that compounds of this structure should be colourless or very lightly coloured, although they were not synthesised. The *ortho*-quinonoid formula (I) for 2-dimethyl-4-ketotetrahydrobenzopyranol anhydrochloride was then suggested on account of the remarkable chromophoric character of the substance. This view necessitates that products similar to (VII) having a pair of double bonds in the *ortho*-position of a reduced benzene ring should be colourless. The observation therefore is strikingly in agreement with the theoretical forecast.

The next procedure was to condense the two substances in presence of a dehydrating agent and with a large excess of dimethyldihydroresorcin. Using fused zinc chloride, a product was obtained melting at 203–204° and having the composition $C_{17}H_{19}O_3N$. Even with six molecular proportions of dimethyldihydroresorcin, both dry (i.e. by fusion) and in absolute alcohol, combination of more than the molecular proportion never took place, definitely showing the impossibility of linking two molecules with one of the *o*-aminobenzaldehyde or its acetyl derivative, directly.

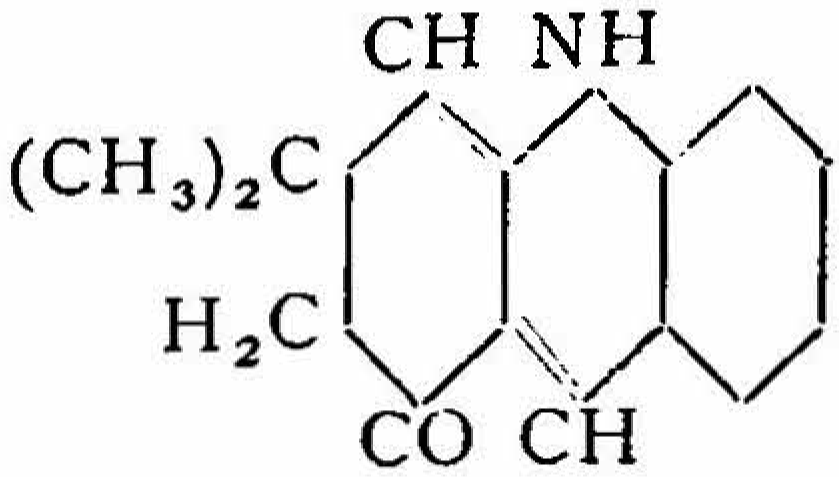
The compound $C_{17}H_{19}O_3N$ might be represented by either of the formulæ (VII) and (VIII),



VIII

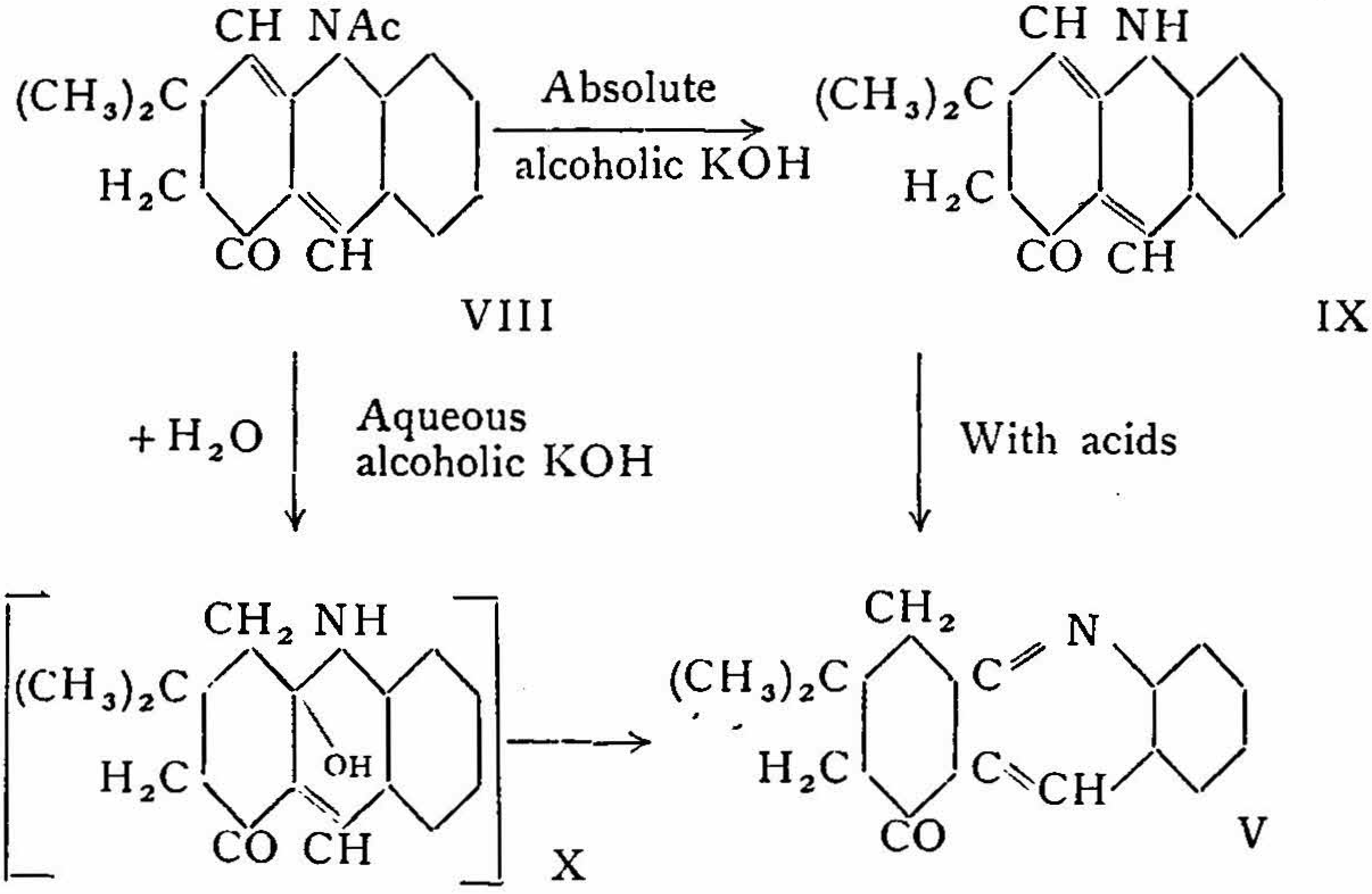
Whereas analytical results point to (VII), the authors prefer the formula (VIII) from a study of the chemical properties. When hydrolysed, both compounds are expected to give the acridine derivative

(V), and this is produced by aqueous alcoholic potash; but with potash and absolute alcohol, an isomeride melting at 245–250° (with decomposition) was formed. This is 2-dimethyl-4-ketotetrahydrobenzoquinoline (IX),



IX

changing into the acridine compound spontaneously during many days, more readily in contact with water and instantaneously on dissolution in acids and precipitation by alkali. The mechanism of the hydrolysis can best be explained as following from 2-dimethyl-4-keto-tetrahydro-*N*-acetylbenzoquinoline (VIII),

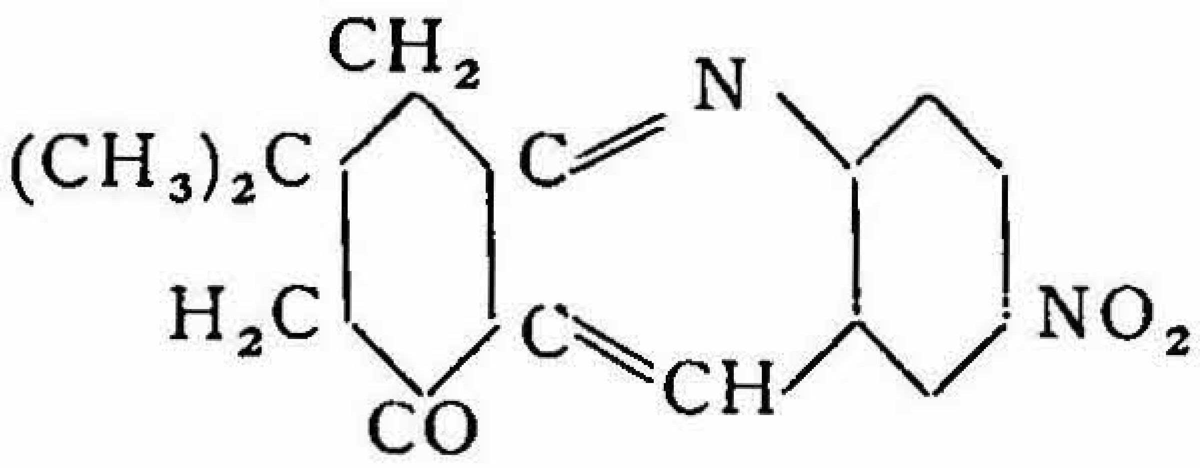


With aqueous alcoholic potash, one molecule of water is added to form the intermediate compound (X), not isolated; elimination of water would then give the acridine derivative (V).

The high melting hydrolysis product (IX) when treated with hydrochloric acid and sodium nitrite also gives the acridine compound, because the acid effects transformation before a nitroso-derivative can be formed.

The benzhydrol and the benzylidene compounds (VI and VII) when dissolved in concentrated sulphuric acid, warmed for half-an-hour and precipitated by water gave the benzoquinoline derivative (VIII). Thus the benzhydrol when heated loses the water of crystallisation and then another molecule of water to form the benzylidene compound, which when treated with sulphuric acid yields the benzoquinoline derivative by loss of another molecule of water; on the other hand, if the benzhydrol is treated with sulphuric acid, the benzoquinoline complex is directly formed without the intermediate benzylidene compound.

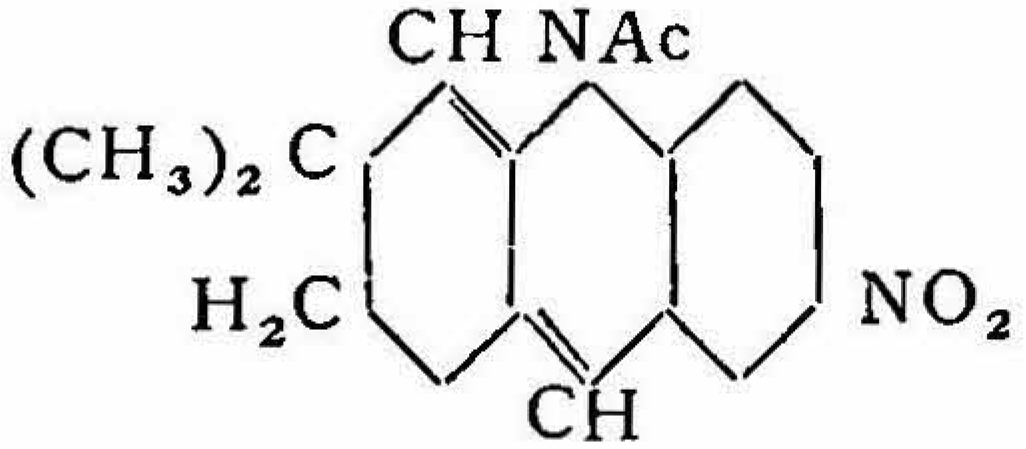
Similar condensations were conducted with 5-nitro-*o*-acetaminobenzaldehyde; when this was condensed with dimethyldihydroresorcin in alcoholic potash, 1-keto-3-dimethyl-7-nitrotetrahydroacridine (XI), m.p. 82–83° was obtained:



XI

In absolute alcohol no union took place, the materials being recovered almost quantitatively.

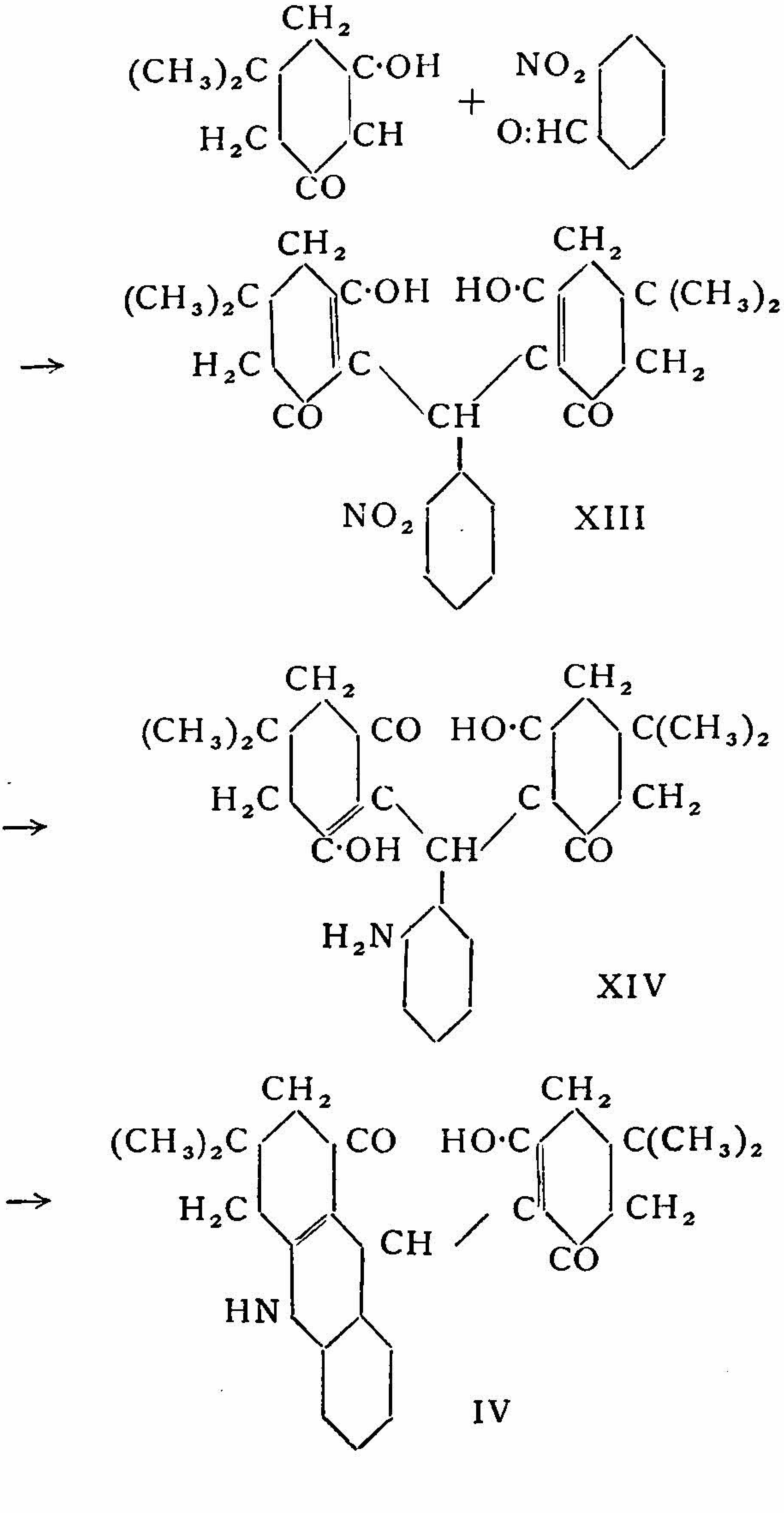
When 5-nitro-*o*-acetaminobenzaldehyde and dimethyldihydroresorcin were condensed in presence of fused zinc chloride without a solvent 2-dimethyl-4-keto-7-nitro-*N*-acetyltetrahydrobenzoquinoline (XII) was produced,



XII

and on hydrolysis with aqueous alcoholic potash readily gave the nitroacridine compound (XI).

When it was found that no benzamarone condensation could be brought about directly with *o*-aminobenzaldehyde or its acetyl derivative, dimethyldihydroresorcin was condensed with *o*-nitrobenzaldehyde with the intention of proceeding as follows:

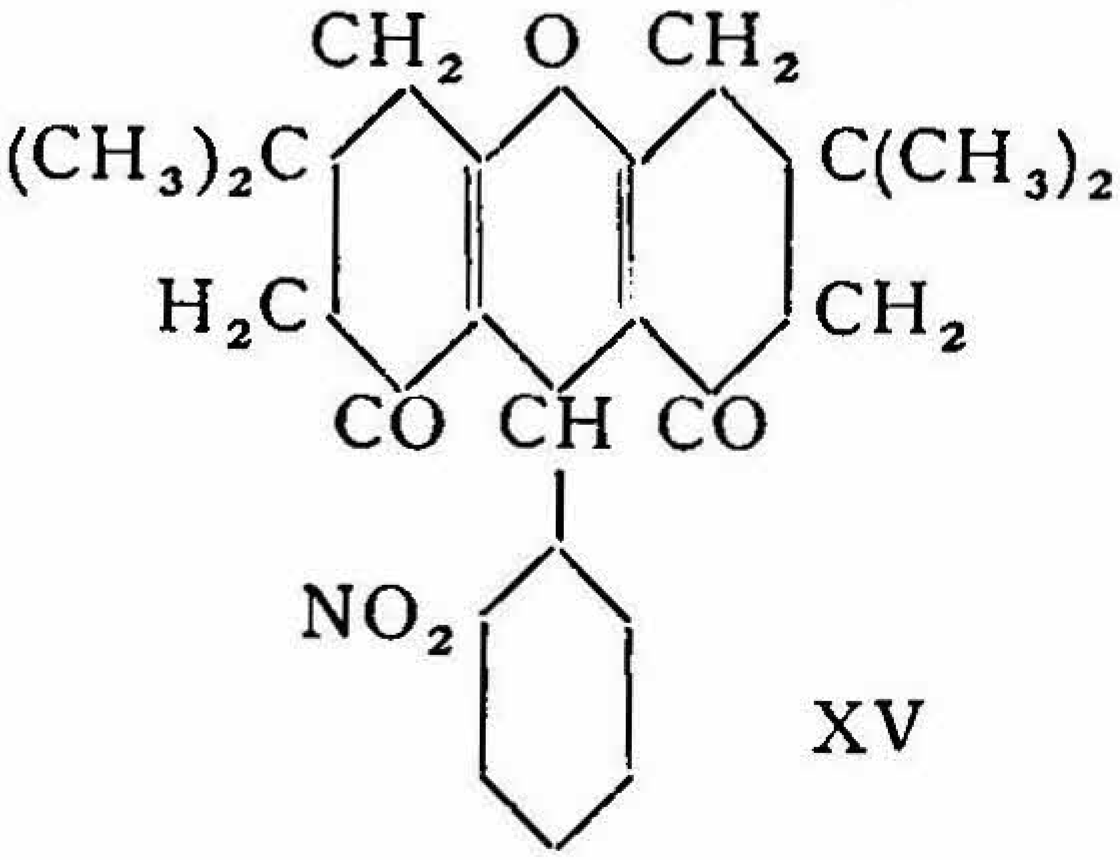


XIII

XIV

IV

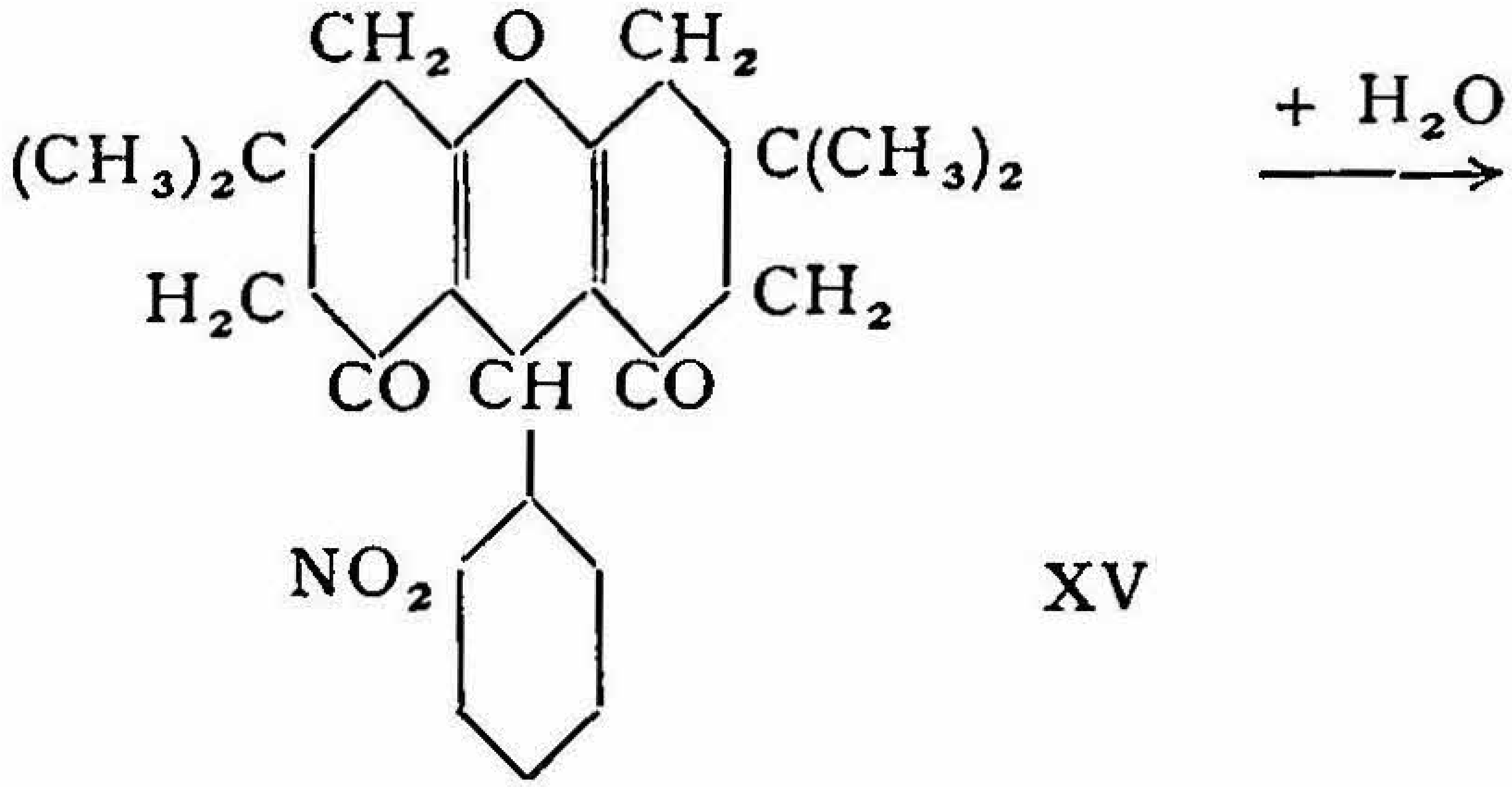
The 2-nitro-benzaldimethyldihydroresorcin (XIII) melts at 195° and gives a cherry-red coloration with ferric chloride, showing the presence of hydroxyl groups. When the condensation was conducted in absolute alcohol for a longer period, a mixture of compound (XIII) with 2 : 7-tetramethyl-4 : 5-diketo-*o*-nitrophenyloctahydroxanthene (XV), m.p. 253–254°, was obtained:



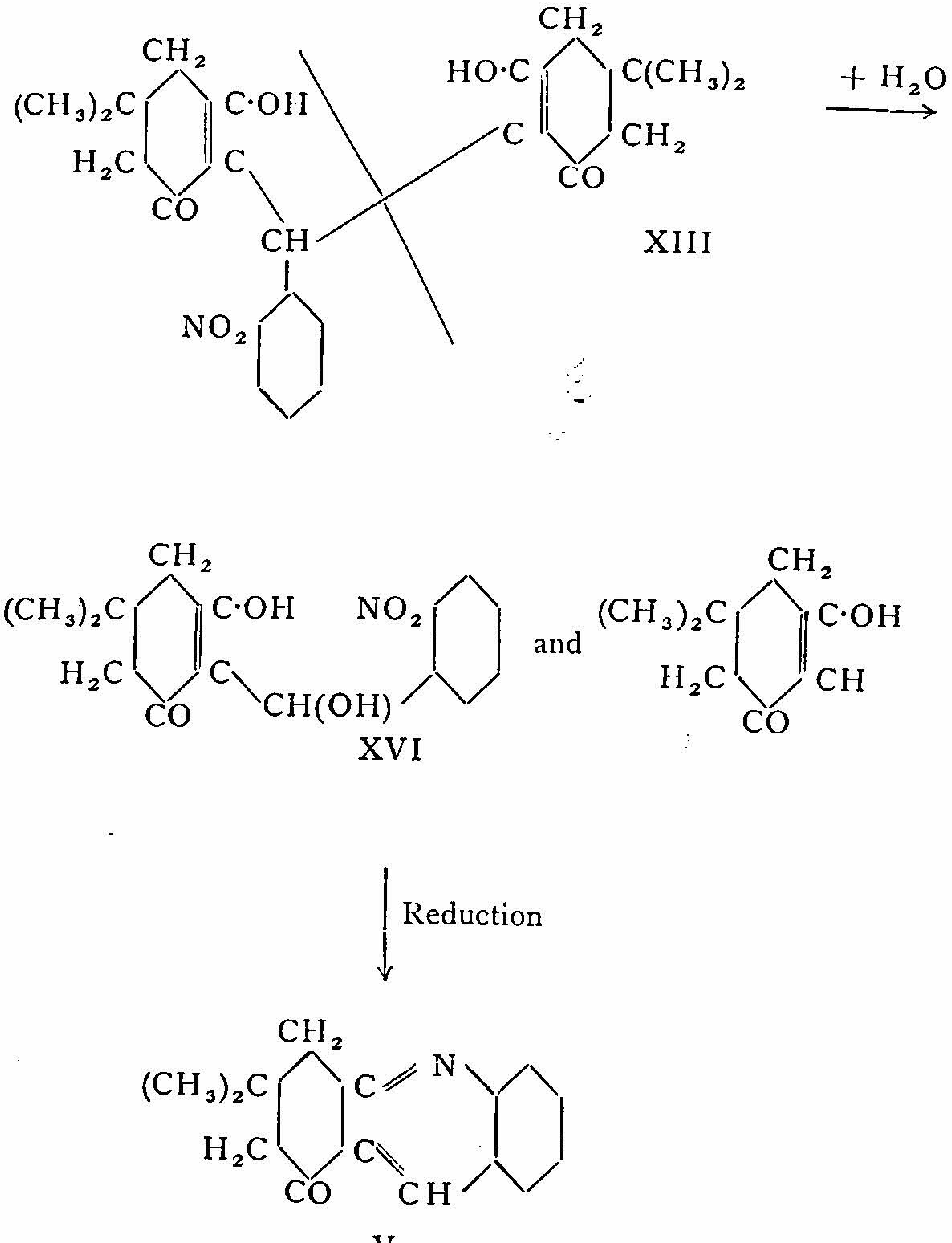
XV

This compound does not give a coloration with ferric chloride, and is separated by fractional crystallisation from alcohol, in which the benzal compound (XIII) is more soluble. When this is treated with concentrated sulphuric acid, it is converted quantitatively into the xanthene, which being more stable than the benzal compound was employed in the reduction experiments.

Reduction of (XV) was conducted with zinc dust in acetic acid containing a small quantity of hydrochloric acid. The product was a mixture of three or four compounds, the one melting at 246–249° being phototropic. The acridine derivative arises from hydrolysis of the molecule by hydrochloric acid, because in experiments without this acid the substance remained unchanged. First the xanthene derivative (XV) is converted into the benzal derivative (XIII) which is disrupted, forming the nitrobenzhydrol compound (XVI), which after reduction is transformed into the acridine compound:



XV



It is suspected that the product melting at 246–249° obtained by the reduction of the xanthene derivative (XV) is the one sought, and its investigation will be undertaken when a sufficient quantity has been prepared.

EXPERIMENTAL.

Preparation of *o*-aminobenzaldehyde by the method of Friedländer (*Ber.*, 1882, **15**, 2572) presented several difficulties. *o*-Nitrobenzaldehyde was first reduced by tin and glacial acetic acid to anthranil which was converted into the anthranil-mercuric chloride compound and reduced to aminobenzaldehyde by ferrous sulphate and ammonia. The process was tedious owing to the large quantity of steam distillate collected for extraction after saturation with common salt in both the stages of reduction, and the difficulty was augmented by the unstable nature of anthranil and *o*-aminobenzaldehyde. The former is an oil which changes into a solid melting above 200°, and *o*-aminobenzaldehyde, which ordinarily melts at 39°, simply on keeping changes into a compound melting above 250°. Both polymerides have been described in the literature.

Direct reduction of *o*-nitrobenzaldehyde by means of ferrous sulphate and ammonia was then tried according to Bamberger and Demuth (*Ber.*, 1901, **34**, 1330) who stated that 8 g. of *o*-nitrobenzaldehyde required only 55 c. c. of concentrated ammonia, whereas Bamberger (*Ber.*, 1927, **60**, 319) in a later communication found that 85 c.c. were needed. The present authors also required 80 to 85 c.c. to make the escaping vapours alkaline, which is the test for completion of the reduction. Until 55 c. c. of ammonia are added, the black precipitate of ferrous hydroxide changed after some time into yellow ferric hydroxide, but the escaping vapours were not alkaline; further addition of ammonia was controlled by the test of the escaping vapours and not by change in colour of the precipitate. Regulation of the quantity of ammonia is essential to the success of this preparation.

o-Acetaminobenzaldehyde was obtained according to Friedländer and Ghoring (*Ber.*, 1884, **17**, 456–461), while 5-nitro-*o*-acetaminobenzaldehyde was prepared by the method of Cohn and Springer (*Monatsh.*, 1903, **24**, 87–100).

Dimethyldihydroresorcin and o-*Aminobenzaldehyde.*

1-*Keto-3-dimethyltetrahydroacridine* (V).—*o*-Aminobenzaldehyde (3·7 g.) and dimethyldihydroresorcin (4 g.) were dissolved in the minimum quantity of absolute alcohol, and heated under reflux over a water-bath for 2 to 3 hours with caustic potash (2 g.) in water (4·4 c.c.). The mixture was then poured on ice, stirred, acidified with dilute hydrochloric acid, filtered and the filtrate kept overnight. Concentrated caustic soda produced a colourless crystalline precipitate, which was filtered, freed from dimethyldihydroresorcin by hot water and crystallised from alcohol and water, in faint, yellowish-green plates, m.p. 117° (Yield 3·4 g.). It crystallised from petrol ether (b.p. 40–60°) in needles (Found :

C, 79·78; H, 7·07; N, 6·48. $C_{15}H_{15}ON$ requires C, 80·00; H, 6·6; and N, 6·20 per cent.). The same compound was obtained by the alkaline hydrolysis of 2:6-diketo-4-dimethyl-2′-acetaminohexahydrobenzhydrol and 2-acetaminobenzylidenedimethyldihydroresorcin.

The picrate after crystallisation from alcohol melted at 197–198°, sintering at 184° (Found: N, 12·35; $C_{15}H_{15}ON, C_6H_2(NO_2)_3OH$ requires N, 12·36 per cent.).

The chloroplatinate was recrystallised from alcohol (Found: Pt, 22·40; Cl, 24·48. $(C_{15}H_{15}ON)_2PtCl_6$ requires Pt, 22·67; Cl, 24·77 per cent.).

The methiodide was best prepared by heating the substance sealed with large excess of methyl iodide in a boiling water-bath during over four hours. When cold, the large needles of methiodide were recrystallised from alcohol, m.p. 224–225°. The compound on standing decomposed slowly, hence an accurate estimation of the iodine content could not be made (Found: I, 35·72. $C_{15}H_{15}ON,MeI$ requires I, 34·7 per cent.)

Oxidation did not take place with potassium permanganate in neutral and alkaline solutions, either cold or hot; the acridine compound was therefore dissolved in concentrated nitric acid (8·4 parts, sp. gr. 1·42) and heated under reflux over a water-bath until evolution of nitrous fumes ceased, when the liquid was heated by an open flame until colourless. Water was added and the precipitate formed after some delay was filtered, washed thoroughly and recrystallised from hot water. The melting point rose to 272° indicating the formation of the aminocarboxylic acid produced on heating acridinic acid (Graebe and Caro, *Ber.*, 1880, **13**, 100). Analysis also proved that it was acridinic acid, but the yield was very poor (Found: N, 6·00. $C_{11}H_7O_4N$ $2H_2O$ requires N, 6·45 per cent.).

Dimethyldihydroresorcin and o-*Acetaminobenzaldehyde.*

2:6-*Diketo*-4-*dimethyl*-2′-*acetaminohexahydrobenzhydrol* (VI).—*o*-Acetaminobenzaldehyde (0·4 g.) and dimethyldihydroresorcin (0·35 g.) in the minimum quantity of absolute alcohol were heated under reflux on a water-bath for 45 minutes and poured into ice-water, the white precipitate weighing 0·6 g. The substance was freed from dimethyldihydroresorcin by boiling water and the crystals from alcohol and water contained one molecule of water of crystallisation. It is insoluble in ether and melts at 153–154° (Found: C, 63·5; H, 7·62; N, 4·35. $C_{17}H_{21}O_4N, H_2O$ requires C, 63·55; H, 7·17; N, 4·36 per cent.).

2-Acetaminobenzylidenedimethyldihydroresorcin.—The colourless benzhydrol (0·2637 g.) was heated at 105–110° for over 15 hours, becoming brownish and losing 10·5 per cent. The calculated percentage of water of crystallisation for the formula $C_{17}H_{21}O_4N,H_2O$, is 5·6 per cent., and for loss of two molecules of water, 11·2. The 2-acetaminobenzylidenedimethyldihydroresorcin (VII) thus formed melts at 197–199° (Found: C, 72·56; H, 7·81. $C_{17}H_{19}O_3N$ requires C, 71·6; H, 6·7 per cent.).

*2-Dimethyl-4-keto-*N*-acetyl-tetrahydrobenzoquinoline* (VIII).—*o*-Acetaminobenzaldehyde (2·3 g.) and dimethyldihydroresorcin (2 g.) dissolved in the minimum quantity of absolute alcohol with freshly fused zinc chloride (5 g.) were heated under reflux for about 3 hours, poured on ice, and the white precipitate crystallised from dilute acetic acid, forming long needles, m.p. 203–204°. It is very soluble in alcohol and is insoluble in ether, petrol ether, water and chloroform; slightly soluble in benzene, toluene and xylene; soluble in acetone, amyl alcohol and methyl alcohol. The same compound is obtained from the benzhydrol and the benzylidene compounds described above (Found: C, 71·42; 71·47; H, 7·26; 7·38; N, 5·16. $C_{17}H_{17}O_2N$, H_2O requires C, 71·58; H, 6·67; N, 4·92 per cent.). It retains the molecule of water of crystallisation even when heated at a high temperature for a very long period. Hydrolysis with aqueous alcoholic potash gives 1-keto-3-dimethyltetrahydroacridine, the colour changing through yellow and dull red to deep pink.

2-Dimethyl-4-ketotetrahydrobenzoquinoline (IX) was obtained by heating 2-dimethyl-4-keto-*N*-acetyltetrahydrobenzoquinoline dissolved in absolute alcohol with solid caustic potash under reflux for about three hours and immediately pouring on ice; the brown precipitate was crystallised from absolute alcohol, m.p. 245–250° with decomposition (Found: C, 79·82; H, 7·04. $C_{15}H_{15}ON$ requires C, 80·00; H, 6·6 per cent.).

Dimethyldihydroresorcin and 5-Nitro-o-Acetaminobenzaldehyde.

1-Keto-3-dimethyl-7-nitrotetrahydroacridine (XI).—5-Nitroacetaminobenzaldehyde (1 g.) and dimethyldihydroresorcin (0·8 g.) were dissolved in the minimum of absolute alcohol and heated under reflux for 2–3 hours with caustic potash (0·4 g.) in water (1 c. c.). When cooled, poured into ice-water, acidified with dilute hydrochloric acid and filtered, a small quantity of dimethyldihydroresorcin was recovered. The filtrate was then treated with concentrated alkali, giving a yellow precipitate (0·5 g.) which was filtered, washed and crystallised from alcohol and water, m.p. 82–83° (Found: N, 10·81. $C_{15}H_{14}O_3N$ requires N, 10·33 per cent.).

2-*Dimethyl*-4-*keto*-7-*nitro*-N-*acetyltetrahydrobenzoquinoline* (XII)—5-Nitro-2-acetaminobenzaldehyde (1 g.) and dimethyldihydroresorcin (0·8 g.) in the minimum of absolute alcohol with fused and powdered zinc chloride (3 g.) were heated under reflux on a water-bath for 2–3 hours, cooled and poured into ice-water; the light yellow precipitate (0·5 g.) was filtered, washed several times with boiling water and crystallised from alcohol, m.p. 171° (Found: N, 9·21. $C_{17}H_{16}O_4N_2$ requires N 8·97 per cent.).

Dimethyldihydroresorcin and o-*Nitrobenzaldehyde.*

Nitrobenzaldimethyldihydroresorcin (XIII) from dimethyldihydroresorcin (1 g.) and *o*-nitrobenzaldehyde (1 g.) in the minimum of absolute alcohol with caustic potash (0·4 g.) in water (1 c.c.), refluxed for 3–4 hours, was crystallised from alcohol and melted at 195°. It is insoluble in ether, petrol ether and benzene but very soluble in chloroform, acetone and methyl alcohol (Found: C, 66·73; H, 6·60; N, 3·89. $C_{27}H_{27}O_6N$ requires C, 66·81; H, 5·58; N, 3·4 per cent.). A small quantity of a high melting (253–255°) substance was also obtained.

2:7-*Tetramethyl*-4:5-*diketo*-o-*nitrophenyloctahydroxanthene* (XV).—Dimethyldihydroresorcin (5 g.) and *o*-nitrobenzaldehyde (4 g.) in absolute alcohol were heated under reflux for 4 to 5 hours when most of the alcohol was distilled; the diluted residue gave a precipitate (6 g.) which was washed with water and ether to remove unchanged materials. It melted at 190–195° and contained principally the benzal compound; so was dissolved in concentrated sulphuric acid, warmed for an hour and then poured into much water, when a quantitative yield of the xanthene derivative was obtained. This was crystallised from alcohol, m.p. 253–254° (Found: C, 69·64, H, 6·78; N, 4·23. $C_{23}H_{25}O_5N$, requires C, 69·86; H, 6·33; N, 3·54 per cent.).

Reduction of the xanthene derivative (XV).—The xanthene derivative (6 g.) was well mixed with zinc dust (4 g.) in a mortar, transferred to a conical flask and adding 90 c.c. of glacial acetic acid, this was boiled under reflux for half-an-hour; 100 c.c. of concentrated hydrochloric acid was added, and the heating continued for another 15 minutes, when the mixture was filtered hot and diluted with much water. Ammonia was added until the precipitated zinc hydroxide dissolved, and a slimy yellow precipitate formed. Extraction with ether and removal of the solvent left about 3 g. of yellow resinous substance which on retreatment with a small quantity of ether gave an ether-insoluble precipitate. Crystallisation from alcohol and water gave a light yellow substance, m.p. 246–249°, changing to orange-red on exposure to sunlight; the original colour was restored in darkness. As only a very small amount of this substance was obtained, it could not be analysed. The ether-soluble portion after driving off ether is repeatedly extracted with petrol ether and the product crystallised from alcohol and water, m.p. 116–117°. It was found to be identical with the acridine derivative. There was, in addition, a third product which was originally insoluble in ether.

The foregoing method of reduction was found to be superior to (1) alcoholic ammonium sulphide at 100° in a sealed tube: (2) iron and hydrochloric acid: (3) tin and acetic acid: and (4) tin and hydrochloric acid.

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