Reduction of Cyclohexanone 2-Nitrophenylhydrazone. Formation of Cyclohexane-3-spiro-3,4-dihydro-1,2,4-benzotriazine

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The structure of compound $C_{12}H_{15}N_3$, obtained by Perkin and Riley in 1923, through the reduction of cyclohexanone 2-nitrophenylhydrazone, was reexamined. This compound, considered originally as 3,4-cyclotetramethylene-4,5-dihydro-1,2,5-benzotriazepine (I) and later as 2-aminophenylazocyclohexene (II), is now defined through the nmr spectrum and chemical behaviour as cyclohexane-3-spiro-3,4-dihydro-1,2,4-benzotriazine (V). It is formed by spontaneous oxidation of the cyclic form of cyclohexanone 2-aminophenylhydrazone (namely, cyclohexane-3-spiro-1,2,3,4-tetrahydro-1,2,4-benzotriazine) obtained through amino group addition on the hydrazone double bond.

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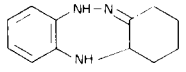
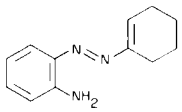
In 1923, the structure I of 3,4-cyclotetramethylene-4,5-dihydro-1,2,5-benzotriazepine was suggested by Perkin and Riley (1) for the yellow compound with an empirical formula $C_{12}H_{15}N_3$, which they obtained by sodium dithionite reduction of cyclohexanone 2-nitrophenylhydrazone.

This compound was reexamined in 1955 by the first of us during a general investigation on benzotriazepine derivatives of potential pharmacological interest (2). It gave a positive diazotisation reaction and on reduction with zinc and acetic acid yielded *o*-phenylenediamine, ammonia and cyclohexanone. On this basis, structure I was considered incorrect and that of 2-aminophenylazocyclohexene (II) was tentatively suggested. It is worth noting that dithionite reduction of cyclopentanone 2-nitrophenylhydrazone gave an analogous yellow compound, while from camphor 2-nitrophenylhydrazone,the colourless 2-aminophenylhydrazone was obtained (2).



I



II

The present note deals with a further examination of the structure of Perkin and Riley's substance, the outstanding stability of which does not agree with the high reactivity of arylazoenes, which has subsequently been demonstrated by Caglioti, *et al.* (3).

Nmr shows a broad singlet at δ 4.15 (1H) which collapses after exchange with deuterium oxide (NH), a multiplet (δ 7.67-6.42, 4H) connected with an *ortho*-disubstituted benzene ring and a very complex multiplet (δ 2.40-1.30 corresponding to 10H of a polymethylene ring. The evidence for only one proton on nitrogen ruled out structure II.

However, the formation of a red azo dye through diazotisation and coupling with β-naphthol is confirmed, but the obtained azo dye is now proven to be α-phenylazo-β-naphthol. Presumably, the NH function is sterically hindered and/or deactivated through a positive charge localisation as in VI. However, once the nitrosoamine is formed, the overcrowded molecule decomposes, resulting in the formation of phenyldiazonium salt.

In the absence of nitrous acid, Perkin and Riley's substance is resistant for several days to the action of hydrochloric acid not only at the diazotisation temperature but also at room temperature (25-28°). At boiling temperature, however, the compound splits up to give aniline and cyclohexanone. Steric hindrance on NH accounts for negative acylation reactions with acetic anhydride and pyridine at room temperature or acetyl chloride and triethylamine in refluxing benzene or with phenylisocyanate.

By catalytic hydrogenation, Perkin and Riley's substance absorbs only one mole of hydrogen with loss of the yellow colour. The product so obtained is rather unstable when exposed to the air giving place to the yellow starting material in high yield. Moreover, the same dihydroderivative of Perkin and Riley's substance is obtained directly by catalytic hydrogenation of cyclohexanone 2-nitrophenylhydrazone with absorption of three moles of hydrogen. These facts are easily explained assuming that cyclohexanone 2-aminophenylhydrazone, initially formed by catalytic or dithionite reduction, undergoes an intramolecular addition of the amino group to the hydrazone double bond providing a cyclic hydrazo-

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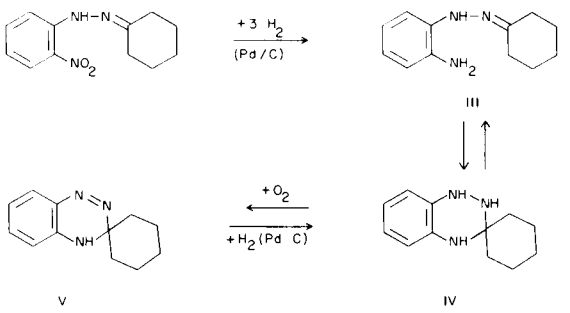
derivative IV, which is then oxidized in the air to give cyclohexane-3-spiro-3,4-dihydro-1,2,4-benzotriazine (V).



The protonated structures VIa through VIc make understandable the strong bathochromic shift observed for the longer wavelength absorption band (454 nm → 510 nm) when Perkin and Riley's substance is dissolved in 1*N* hydrochloric acid. The structure V also explains the peaks at m/e 173 and 144, which are much more intense than the molecular ion peak (m/e 201) in the mass spectrum. The first peak corresponds clearly to the loss of the azo group (201 − 28 = 173), while the second one could be connected with the ion $(C_7H_4N_3\text{-}CH_2)^+$, generated through aromatisation of the heterocyclic ring and loss of four methylene groups from the cyclohexane ring.

Finally, the suggested mechanism of formation of V justifies why, starting from camphor 2-nitrophenylhydrazone, the reaction doesn't go beyond aminophenylhydrazone formation; indeed, amino group addition on the hydrazone double bond is sterically hindered by the bicyclic structure and the three methyl groups of camphor.

Lacking steric hindrance, one could suppose that the dithionite reduction of 2-nitrophenylhydrazones of a wide variety of ketones (or still better the oxidation with oxygen of 2-aminophenylhydrazones obtained through catalytic hydrogenation) would give rise to a series of 3,4-dihydro-1,2,4-benzotriazines disubstituted on position 3. This has been effectively proven starting from several aliphatic, alicyclic and alkylarylketones. The compounds so obtained are described in a separate paper (4) together with results of their pharmacological investigation.

EXPERIMENTAL

Melting points are uncorrected. The uv spectra were recorded on a Unicam SP 700 spectrophotometer; nmr spectra were determined on a Hitachi Perkin-Elmer model R 24 spectrometer, using deuterochloroform as solvent and TMS as internal standard. Mass spectra were obtained with an AEI model MS 902 mass spectrometer. Elemental analyses were performed at Microanalytical Laboratory of the Istituto di Chimica Farmaceutica dell'Università di Padova.

Cyclohexanone 2-Aminophenylhydrazone.

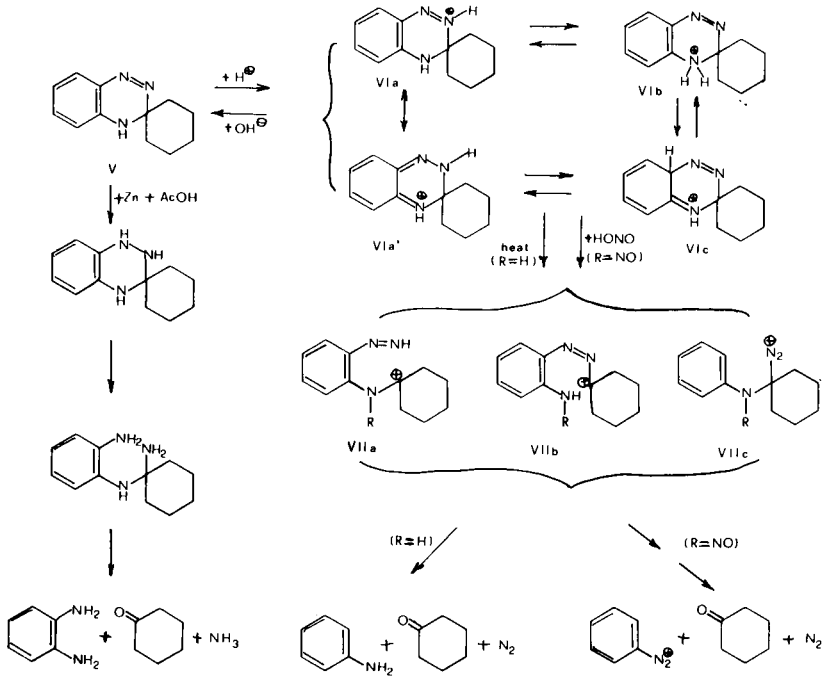
a)

A solution of 5 g. of 2-nitrophenylhydrazone (5) in tetrahydrofuran (20 ml.) was added to a suspension of 1.25 g. of 5% palladium on charcoal in 10 ml. of THF and hydrogenated at atmospheric pressure. The required volume of hydrogen (1650 ml., calcd. at 22.5° and 742 torr = 1598 ml.) was taken up in *ca.* 100 minutes. The catalyst was filtered and the solvent removed under reduced pressure giving white crystals melting at 83-85°; uv (ethanol): λ max 220, 252 and 305 nm.

As a consequence of easy oxidizability, no reproducible values for log ε were obtained. However, the shape of absorption curve is quite similar to that of camphor 2-aminophenylhydrazone.

b)

A solution of Perkin and Riley's substance (1) in tetrahydrofuran (1 g. in 16 ml.) was added to a suspension of 0.25 g. of 5% palladium on char-



coal in 4 ml. of THF previously saturated with hydrogen. At 21.5° and 743 torr, 124.5 ml. of hydrogen were absorbed (calcd. 123.5 ml.). Working up as above, white crystals melting at 87-90° were obtained; the mixed m.p. with the product prepared as above was 83-86°. The uv spectrum was identical with that obtained for the product described under a).

d-Camphor 2-Aminophenylhydrazone.

This compound was prepared from 2-nitrophenylhydrazone through both zinc and acetic acid reduction (2) and catalytic hydrogenation, as in the case of the former compound. White crystals were obtained with m.p. 113°; uv: λ max nm (log ε) 216 (4.36), 264 (4.06), 300 (3.86).

Cyclohexane-3-spiro-3,4-dihydrobenzo-1,2,4-triazine.

Cyclohexanone 2-aminophenylhydrazone prepared as above under a) was dissolved in methanol (~ 10 ml. per gram) and oxygen was bubbled through, following the reaction course by uv spectra. The methanolic solution was concentrated at reduced pressure and room temperature, yielding yellow crystals (68% yield calculated on the basis of the starting 2-nitrophenylhydrazone) melting at 140-142°, either alone or in admixture with the product prepared as described by Perkin and Riley (1); uv: (ethanol): λ max nm (log ε) 226 (4.33), 248 sh (4.02), 286 (3.35), 358 (3.34), 454 (3.04); (1*N* hydrochloric acid): 234 (4.12), 300 (sh (3.30), 345 (3.90), 510 (3.32).

After further concentration of the mother liquor, a dark brown oil, sometimes spontaneously decomposing with gas and heat evolution, was obtained.

Hydrolysis with Dilute Hydrochloric Acid.

A solution of 1 g. of cyclohexane-3-spiro-3,4-dihydrobenzo-1,2,4-triazine in 60 ml. of 2*N* hydrochloric acid was boiled for 90 minutes, under nitrogen, in a flask equipped with a short vertical air cooled condenser, the upper end of which was connected with a scrubber containing cold water. The condenser was washed with a little ethanol and water that were combined with the scrubber solution and extracted with ether. After removing the solvent, the oily residue (330 mg.) was allowed to react with semicarbazide hydrochloride and sodium acetate, giving white crystals (230 mg.), m.p. 160-163°, undepressed by an authentic sample of cyclohexanone semicarbazone. The acidic solution was made basic and steam distilled; ether extraction of the distillate gave an oil (100 mg.) which was heated with 0.2 ml. of acetic anhydride providing acetanilide melting at 112-113° either alone or mixed with an authentic specimen.

Nitrosation.

A solution of sodium nitrite (190 mg.) in 5 ml. of water was added dropwise, with cooling and stirring, to a solution of 0.5 g. of Perkin and Riley's substance in 2*N* hydrochloric acid (15 ml.). The solution was stirred for an additional 15 minutes and then poured into a solution of 360 mg. of β-naphthol in 15 ml. of 2*N* sodium hydroxide. The collected red precipitate was washed with water, 2*N* hydrochloric acid, again with water and finally dried (~ 0.5 g.) and recrystallized from ethanol, m.p. 129-131°, either alone or in admixture with a specimen of α-phenylazo-β-naphthol previously prepared (6); uv (ethanol): λ max nm (log ε) 228 (4.56), 258 sh (4.01), 312 (3.81), 420 (3.96), 484 (4.12).

Anal. Calcd. for $C_{16}H_{12}N_2O$: C, 77.40; H, 4.87; N, 11.28. Found: C, 77.34; H, 4.96; N, 11.33.

REFERENCES AND NOTES

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