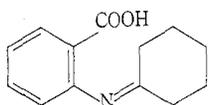


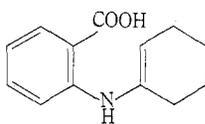
THE CONDENSATION OF CYCLOHEXANONE AND ANTHRANILIC ACID*

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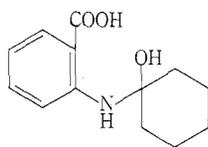
In 1909 Tiedtke¹ prepared 1,2,3,4-tetrahydro-5-acridone by heating a mixture of anthranilic acid and cyclohexanone at 120°C and then at 220°C. When the reaction mixture was maintained at 120°C, however, a nearly quantitative yield of an "intermediate" compound was obtained, and this was formulated as the anil (I). Repetition of the condensation under a variety of conditions has shown that the intermediate is rapidly formed under mild conditions, and that heating at 180°C (both with and without added solvent) generally leads to mixtures of the intermediate and tetrahydroacridone. Surprisingly, it was found that the supposed intermediate, when isolated and purified, cannot be converted into tetrahydroacridone by heating at 180°C; but conversion was achieved (with some loss) by heating in an inert solvent (such as diphenyl ether) to temperatures greater than 260°C.



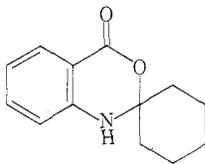
(I)



(II)



(III)



(IV)

The intermediate was obtained as a colourless crystalline solid, m.p. 155°C (lit.¹ 142–148°C), soluble in organic solvents and insoluble in water. It was insoluble in sodium bicarbonate. Alkaline and acidic solutions decomposed to yield anthranilic acid. Similarly bromination of the intermediate with bromine in chloroform gave 5-bromoanthranilic acid. Final evidence that the intermediate could not have the structure (I) was provided by its infrared spectrum which showed a strong band at 3300 cm^{-1} indicative of a NH group. The alternative structure (II) was also excluded by the insolubility of the intermediate in bicarbonate and by the absence of a band at 2500 cm^{-1} in the infrared region.

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¹ Tiedtke H. (1909).—*Ber. dtsh. chem. Ges.* **42**: 621.

The n.m.r. spectrum of the intermediate (in carbon tetrachloride, deuteriochloroform, or acetone) showed three areas of absorption. The first was a complex unresolved band system at τ 8.0–8.5 (10 protons), which is assigned to the alicyclic protons. Although not completely resolved, 4 protons were at a lower field than the other 6. A second band system was observed at τ 5.5. This was a broad peak and integrated for 1 proton. It is assigned to a NH proton, and this assignment was confirmed by the strong shift of the band to lower fields in acetone, relative to the position in carbon tetrachloride or deuteriochloroform (influence of hydrogen bonding). A third series of peaks was observed at τ 2.0–3.5. This was a doublet (1 proton), a triplet (1 proton) and a triplet (2 protons), and all peaks showed additional fine splitting. These bands are assigned to the aromatic protons, and the pattern is in agreement with an *ortho*-substituted benzene with different substituents.²

There seems little doubt therefore that the intermediate is 2-spirocyclohexane (4-oxo-1,2-dihydro-1,3-benzoxazine) (IV), and that it is formed by addition of anthranilic acid to the carbonyl group of cyclohexanone (to give III) followed by dehydration. It may be noted that the parent compound 4-oxo-1,2-dihydro-1,3-benzoxazine, has been prepared by reaction between anthranilic acid and formaldehyde.³ Moreover, reaction between salicylamide and cyclohexanone has been reported to give 2-spirocyclohexane-(4-oxo-2,3-dihydro-3,1-benzoxazine).⁴ It is concluded that (IV) is not a true intermediate in the formation of tetrahydroacridone under normal conditions. The true intermediate must be (III) which can suffer dehydration either to (IV) or to tetrahydroacridone.

² Jackman, L. M. (1959).—“Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry.” (Pergamon Press: London.)

³ Villiger, V. (1909).—*Ber. dtsh. chem. Ges.* **42**: 3534.

⁴ Horrom, B. W., and Zaugg, H. E., (1950).—*J. Amer. Chem. Soc.* **72**: 721.