Tetrahedron Letters No. 20, pp. 1277-1281, 1963. Pergamon Press Ltd.
Printed in Great Britain.

A DIRECT SYNTHESIS OF 4-AMINOQUINOLINES

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(Received 5 June 1963)

The formation of 4-hydroxyquinolines by cyclodehydration of ketones RCH_2COR' with anthranilic acid is a classical and practical preparative method[1]. The quinolones thus obtained may be converted via the chloro derivatives to 4-aminoquinolines, but the amination step can cause difficulty. In the preparation of 5-aminotetrahydroacridine (I) by this route, special conditions are required for the amination of the 5-chloro derivative, and yields are not high[2,3]. The growing pharmacological importance of I[4] prompted an effort to develop an improved synthetic procedure for I and related 4-aminoquinolines. It appeared that a convenient preparative route would be available if the amino group were introduced and maintained during the cyclization of a nitrogen-containing carboxyl function. This approach, using the nitrile

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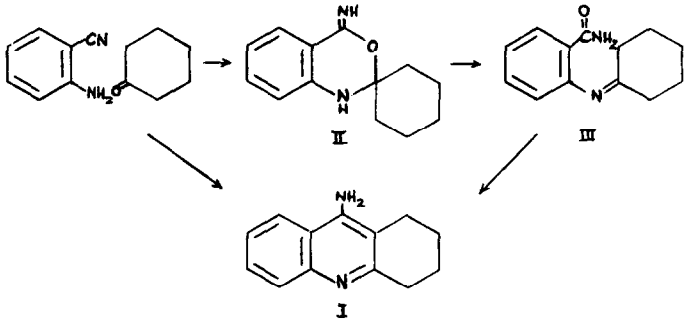
[1] St. v. Niementowski, Ber. 27, 1394 (1894).
[2] A. Albert and W. Gledhill, J. Soc. Chem. Ind. 64, 169 (1945).
[3] V. Petrow, J. Chem. Soc. 1947, 637.
[4] S. Gershon, Nature 186, 1072 (1960); Gershon and Olarin, J. Neuropsychiat. 1, 283 (1960).

group, has been employed in the preparation of 2,4-diaminopyrimidines by condensation of dicyandiamide and ketones[5].

In an effort to apply this reaction to the synthesis of I, a solution of anthranilonitrile in cyclohexanone was refluxed with a catalytic amount of Triton B; these are the conditions which were successfully used for the preparation of a related diaminopyrimidine[5]. After 80 hrs. 1.8% of I was isolated, in addition to unreacted nitrile. When the amount of quaternary ammonium catalyst was increased five-fold, a very rapid reaction ensued and a neutral compound, $C_{13}H_{16}ON_2$, separated from the cooled solution in 54% yield. Hydrolysis of the product furnished cyclohexanone and anthranilamide, and the structure III was confirmed by synthesis from anthranilamide and cyclohexanone. This facile transformation can be pictured simply as a cyclic transfer of the elements of



[5] E. J. Modest, S. Chatterjee and H. Kangur, J. Org. Chem. 27, 2708 (1962).

[6] Private communication, Dr. E. C. Taylor; J. Zoltewicz, Ph.D. Dissertation, Princeton University, 1960.

water, either directly or via an iminodihydrooxazine intermediate (II). An analogous cyclization to an iminooxazine intermediate and subsequent cleavage to formamidobenzamide has been proposed in the reaction of anthranilonitrile and dimethylformamide under acidic conditions[6].

The formation of the anil III suggested the requirement of an acidic medium for the efficient production of the amine I from the nitrile, and zinc chloride was found to fulfill this function very successfully. The reaction was conveniently carried out by heating a solution of the nitrile in cyclohexanone containing one molar equivalent of anhydrous zinc chloride. A 1:1 complex of the aminotetrahydroacridine with zinc chloride, m.p. 260-270° (dec), separated from the solution (in analytically pure form) in 96% yield after about 5 min. reaction time. The base was liberated by treatment of this complex with alkali and extraction with benzene, m.p. 183-184°.

The procedure was also applied to the reaction of anthranilonitrile and 2-butanone. In this case the crude zinc chloride complex was obtained in 75% yield after 2 hrs. reflux; the smaller yield was presumably due in part to the lower reaction temperature (85°). Decomposition of the complex gave a mixture of two bases which was separated by crystallization and alumina chromatography. Both compounds had the expected composition $C_{11}H_{12}N_2$; the structures were readily distinguished by the NMR spectra in $CDCl_3$. The major component (30%), m.p. 193-194° was 2,3-dimethyl-4-aminoquinoline (CH_3 peaks 2.20 and 2.63 ppm, broad NH_2 peak 4.63 ppm,

four-proton multiplet 7.23-8.03 ppm). A very small amount of the 2-ethyl isomer was isolated, m.p. 155-156° (CH_3 triplet 1.33 ppm, CH_2 quartet 2.87 ppm, NH_2 4.87 ppm, 3-H singlet 6.51 ppm, four proton multiplet 7.18-8.10 ppm).

The condensation provides a very satisfactory synthesis of I, but the rather tedious methods available for the preparation of anthranilonitrile detract somewhat from the utility of the method, and experiments were directed to the use of the relatively cheap anthranilamide. The anil III is obtained in 99% yield by distilling water from a solution of the amide in cyclohexanone containing a catalytic amount of zinc chloride, and thus represents a very attractive starting material. Cyclodehydration of III would be expected to require a temperature above 200°, a dehydrating medium, and a source of ammonia to prevent formation of the tetrahydroacridone. These conditions have been met by addition of III to a flux of zinc chloride and ammonium carbonate.

In a typical experiment, an intimate mixture of 96 g. of III and an equal weight of ammonium carbonate was added in several portions to a melt prepared by the addition of 90 g. of ammonium carbonate to 200 g. of molten zinc chloride, maintained at 220-250°. After the initially-formed layer of molten III changed to a crystalline precipitate the melt was poured into aqueous 10% acetic acid. The heavy precipitate was collected and treated with ammonia, giving a gum which quickly crystallized. This material was then basified with potassium hydroxide and extracted with benzene to furnish I in 55% overall yield. This procedure has the advantage that

the reaction temperature in the cyclization step is not limited by the boiling point of the ketone; the anil of anthranilamide and acetone on similar treatment gave 4-aminoquinaldine, m.p. 169-170°[7], in comparable yield.

The conditions described are the most satisfactory that have been found in a limited number of experiments. Only a small fraction of the added ammonium carbonate is absorbed by the hot zinc chloride; no attempt has been made to determine the exact composition of the melt since ammonia is evolved slowly throughout the fusion operation. The $ZnCl_2 \cdot 2NH_3$ complex is unsuitable as a reaction medium because of the higher m.p. and viscosity. With zinc chloride alone, the only product that has been isolated is tetrahydro-5-acridone; this is not converted to I with zinc chloride and ammonium carbonate, and thus appears not to be an intermediate in the ring closure of III. An unsuccessful attempt to prepare 5-methylaminotetrahydroacridine from the substituted amide suggests that the cyclization of III may proceed by initial dehydration to the nitrile.

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[7] J. Ephraim, Ber. 26, 2227 (1893).