THE MECHANISM OF THE CYCLIZATION OF β-(2-CARBOXYARYL)AMINOPROPIONIC ACIDS TO 1,2,3,4-TETRAHYDRO-4-OXOQUINOLINES

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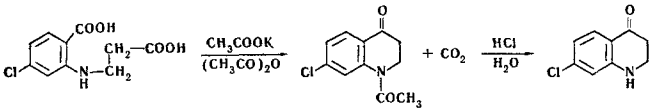
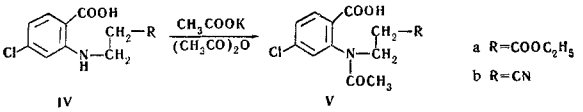
It is shown that cyclization of β-(2-carboxyaryl) aminopropionic acids to 1,2,3,4-tetrahydro-4-oxoquinolines in the presence of acetic anhydride and alkali metal acetates proceeds via the intermediate formation of the N-acetyl derivative of the monopotassium salt of the starting acid, which undergoes further conversion into the cyclic mixed anhydride. The latter decomposes with loss of CO_2 to give the corresponding 1,2,3,4-tetrahydro-4-oxoquinoline.

It has been shown previously [1] that β-(2-carboxyaryl) aminopropionic acids (I), on heating in acetic anhydride in the presence of alkali-metal acetates, undergo cyclization to 1,2,3,4-tetrahydro-4-oxoquinolines III.



I II III

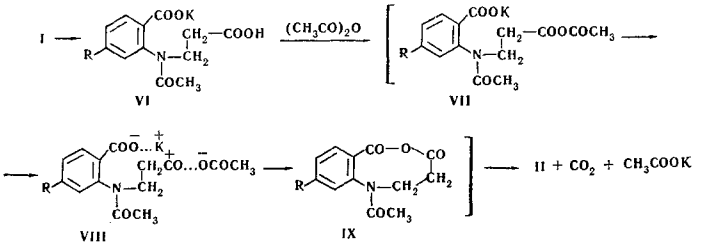
The suggestion that the formation of II from I proceeds by elimination of water between the aromatic carboxyl group and the α-methylene group in I, followed by decarboxylation of the resulting 1,2,3,4-tetrahydro-4-oxoquinoline-3-carboxylic acid is not supported by experiment. If, instead of the acid I, its aliphatic carboxy derivatives are used in the reaction, for instance the ester, or even the nitrile, which is a stronger electron acceptor, cyclization does not occur, only the corresponding N-acyl derivative V being formed.



IV V

a R=COOC$_2$H$_5$
b R=CN

Negative results were obtained even when concentrated sulfuric acid was used for the cyclization of I and IV. These results show that the hydrogen on the α-methylene group of I is insufficiently reactive, and that the presence of a free carboxyl group is necessary for the conversion of I into II. It is found that potassium acetate is a necessary ingredient, since cyclization of I in acetic anhydride in the absence of potassium acetate takes another path [2]. Examination of the conversion of I into II resulted in the isolation of the intermediate monopotassium salt of N-acetyl I (VI). Salt formation in the latter occurred at the aromatic carboxyl group on account of its greater acidity. On heating this salt in acetic anhydride, CO_2 was evolved, and II was formed in 82% yield. On heating the salt VI in other solvents (glacial acetic acid, isopentyl alcohol), cyclization failed to occur. These experiments demonstrate that the acetic anhydride plays an active part in the cyclization. The reaction appears to proceed by the following route:



VI VII VIII IX

The monopotassium salt **VI**, reacting further with acetic anhydride, gives the mixed anydride VII involving the aliphatic carboxyl group. Bearing in mind work on acylation with mixed anhydrides [3], it may be assumed that the acylium cation is formed at the aliphatic carboxyl group (VIII) in the polar solvent acetic anhydride. Alkali metal cations

facilitate ionization of aromatic groups with formation of the carboxylate ion. Subsequent reaction of the acylium cation with the aromatic carboxylate anion gives the mixed cyclic anhydride IX. The possibility of the formation of such a seven-membered ring is supported by a consideration of spatial models. Under the reaction conditions, IX decomposes further into II and CO_2. It has been found that, if the mixture is heated gradually until evolution of CO_2 has just started, the reaction mixture contains mainly the monopotassium salt VI and small amounts of II. A similar decomposition has been described for the internal anhydrides of adipic and pimelic acids, carbon dioxide being evolved to form the five- and six-membered cyclic ketones [4]. In a few other cases described in the literature [5], cyclic seven-membered mixed anhydrides are more stable, and can be isolated.

EXPERIMENTAL

Monopotassium salt of N-acetyl-β-(2-carboxy-5-chlorophenyl)aminopropionic acid (VI). A mixture of 2.5 g (0.01 mole) of I [6], 2 g (0.02 mole) of potassium acetate and 10 ml of acetic anhydride were heated gradually with stirring. A clear solution was obtained at 60° C, and at the same time the salt VI began to separate. The latter was filtered off and washed with acetone to give 3.1 g (94%) of VI, mp 253–254° C (decomp., from water), as a light-colored crystalline powder, soluble in water and acetic acid, but insoluble in alcohol, acetone, and benzene. Aqueous solutions of VI had an acid reaction (pH ~ 5). Found, %: K 11.65; 11.76; N 4.77; equiv. 323.1; 323.6. Calculated for $C_{12}H_{11}ClKNO_5$, %: K 12.07; N 4.32; equiv. 323.5. On boiling VI in glacial acetic acid or in isopentanol for 3 hr, no carbon dioxide was evolved, and distillation of the solvent left unchanged VI (mp 251–253° C).

N-Acetyl-7-chloro-1,2,3,4-tetrahydro-4-oxoquinoline (II). A) Eight grams of VI and 40 ml of acetic anhydride were boiled until the evolution of CO_2 ceased (30 min). The solution was worked up in the usual way to give 1.6 g (82%) of II, mp 140° C (from water).

B) A mixture of 24.4 g (0.1 mole) of I, 9.8 g (0.1 mole) of potassium acetate, and 50 ml of acetic anhydride were heated gradually with stirring to 60° C, complete solution being obtained at this temperature, followed quickly by separation of the salt VI. On raising the temperature to 110° C, evolution of CO_2 began and VI dissolved. The mixture was heated to 135° C until evolution of CO_2 was complete. Yield of II, 13.5 g (60.3%), mp 140° C (from water).

Ethyl β-(2-carboxy-5-chlorophenyl)aminopropionate (IVa). A mixture of 60.0 g (0.35 mole) of 4-chloroanthranilic acid, a solution of 14 g (0.35 mole) of NaOH in 90 ml of water, 42.5 g (0.42 mole) of ethyl acrylate, and 0.5 g of copper acetate was boiled for 17 hr. After working up and purifying in the usual manner, there was obtained 40.0 g (42%) of IVa, mp 121.5–122° C (from alcohol). Found, %: N 5.56, 5.58. Calculated for $C_{12}H_{14}ClNO_4$, %: N 5.15.

Ethyl ester and nitrile of N-acetyl-β-(2-carboxy-5-chlorophenyl)aminopropionic acid (Va and Vb). A mixture of 5.9 g (0.021 mole) of IVa, 2.5 g (0.25 mole) of potassium acetate, and 15 ml of acetic anhydride was heated at 100° C for 30 min to give 5.4 g (79%) of Va, mp 95–97° C (from benzene–light petroleum); readily soluble in most organic solvents, and moderately soluble in water. Found, %: N 4.84, 4.88. Calculated for $C_{14}H_{16}ClNO_5$, %: N 4.46.

Under the same conditions, the yield of Vb was 91%, mp 210–211° C (decomp., from alcohol). Found, %: N 10.64, 10.73. Calculated for $C_{12}H_{11}ClN_2O_3$, %: N 10.50.

Heating β-(2-carboxy-5-chlorophenyl)aminopropionic acid (I) with conc H_2SO_4. A mixture of 4.9 g of I and 13 ml of conc H_2SO_4 was heated for 30 min at 120–130° C. Dilution of the cooled mixture with water precipitated 2.8 g of starting material I, mp 188–189° C. If I is heated at 150° C, β-formation of 4-chloroanthranilic acid occurs.

β-(2-Carboxy-5-chlorophenyl)aminopropionamide (X). 4.8 g of IVb and 40 ml of conc H_2SO_4 were heated for 4 hr at 100° C. The mixture of amides X and I obtained was separated by fractional precipitation from caustic alkali solution The amide X separated at pH ~ 6 as colorless cyrstals, mp 200° C (decomp., from alcohol). Found, %: N 11.95, 11.44. Calculated for $C_{10}H_{11}N_2O_3$, % N 11.55. Acidification of the filtrate to pH ~4 precipitated I, mp 189–190° C.

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