SYNTHESIS OF BENZO[g]QUINOLINE DERIVATIVES

VI. The Mechanism of the Cyclization of β-(2-Carboxy-3-naphthylamino)propionic Acid into N-Acetyl-4-oxo-1, 2, 3, 4-tetrahydrobenzo[g]quinoline*

A. F. Bekhli, N. P. Kozyreva, and E. M. Peresleni

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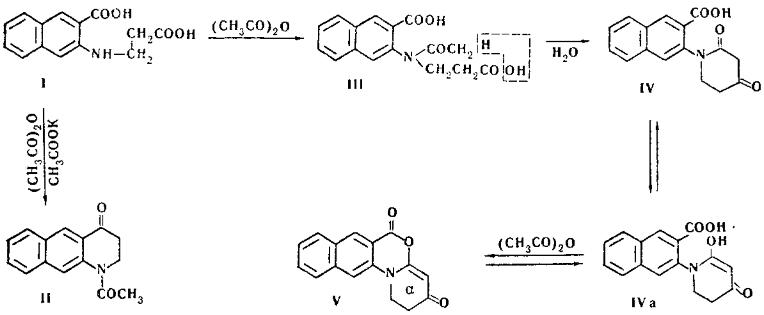
It has been established that the cyclization of β-(2-carboxy-3-naphthylamino)propionic acid into N-acetyl-4-oxo-1, 2, 3, 4-tetrahydrobenzo[g]quinoline takes place with the participation of acetic anhydride and an alkali metal acetate. In the absence of the alkali metal acetate cyclization takes place in a different direction. A mechanism for this reaction has been proposed as taking place through the formation of an internal mixed anhydride, which decomposes under the reaction conditions into N-acetyl-4-oxo-1, 2, 3, 4-tetrahydrobenzo[g]quinoline and carbon dioxide.

We have previously demonstrated the conversion of β-(2-carboxy-3-naphthylamino)propionic acid (I) into N-acetyl-4-oxo-1, 2, 3, 4-tetrahydrobenzo[g]quinoline (II), which takes place when I is heated with acetic anhydride and potassium acetate [2]. In this paper some questions connected with the mechanism of this reaction are considered.

The possibility of interaction between the aromatic carboxyl and the hydrogen atom attached to the α-carbon atom of acid I was rejected, since it was found that the reaction does not take place with other dehydrating agents (concentrated sulfuric acid) or with β-(2-carboxy-3-naphthylamino)propionitrile, which contains a nitrile group in place of the aliphatic carboxyl. In the nitrile, only its N-acetyl derivative (VI) is formed, and when this is heated with sulfuric acid, instead of cyclization, saponification of the nitrile group takes place with the formation of I. Thus, for the cyclization reaction to occur an aliphatic carboxyl group is necessary. In attempts to perform this reaction in other solvents in the presence of potassium acetate (glacial acetic acid and isopentyl alcohol), the starting materials were recovered; this showed the active role of the acetic anhydride.



To elucidate the importance of the alkali metal cation, acid I was heated with acetic anhydride in the absence of potassium acetate; this led to substance V, the properties of which were very different from those of II.

The proposed structure of V as the lactone of 3-(2, 4-dioxopiperidyl)-2-naphthoic acid is confirmed by cleavage of its ring in an alkaline medium to form acid IV, which on heating with acetic anhydride was reconverted into the lactone. The IR spectra of the crystals** (ν_{CO} of a δ-lactone at 1755 cm^{-1}, and ν_{CO} of ring *a* at 1655 cm^{-1}) also confirm the structure of the lactone as shown by formula V (figure).

The IR spectrum of acid IV has bands for the stretching vibrations of the hydroxyl and carbonyl of a carboxyl

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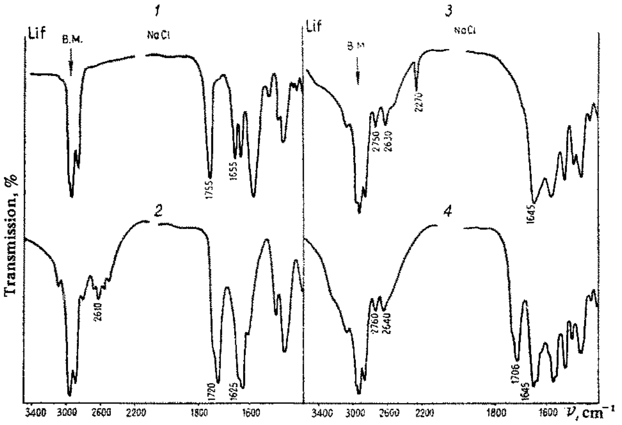
*For part V, see [1].

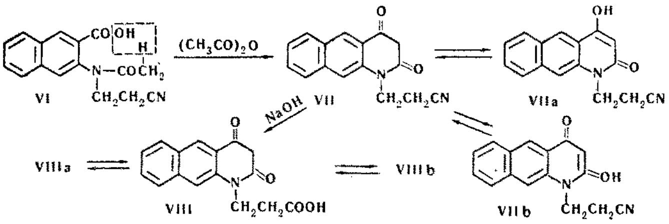
*Because of the poor solubility of the compounds, their spectra were not studied in solution.

group (2610, 1720 cm^{-1}) and also a strong broad band at 1625 cm^{-1} apparently due to the overlapping of the ν_{CO} and $\nu_{C=C}$ bands of the enolic form (**IVa**) (figure).



IR spectra in crystals: 1) lactone of 3-(2,4-dioxopiperidyl)-2-naphthoic acid (V), 2) 3-(2,4-dioxopiperidyl)-3-naphthoic acid (IV), 3) 1-β-cyanoethyl-2,4-dioxo-1,2,3,4-tetrahydrobenzo[g] quinoline (VII), and 4) 1-β-carboxyethyl-2,4-dioxo-1,2,3,4-tetrahydrobenzo[g]quinoline (VIII).

To confirm the participation of the aliphatic carboxyl in the formation of V, we studied the reaction of VI with acetic anhydride and found that cyclization took place with the aromatic carboxyl.

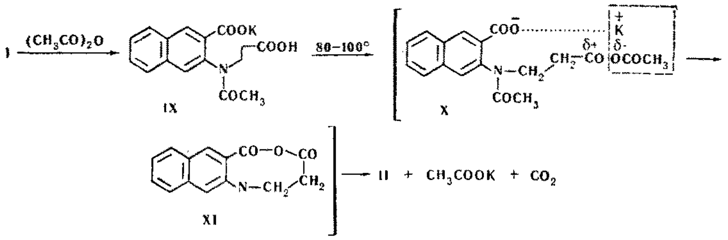


Similar reactions have been described for N-methyl-, N-phenyl-, and 4-chloroanthranilic acid [3,4], and also for β-(2-carboxy-5-chlorophenylamino)propionic acid [5]. The 1-(β-cyanoethyl)-2,4-ioxo-1,2,3,4-tetrahydrobenzo[g]-quinoline (VII) formed is soluble in dilute solutions of alkalis in the tautomeric enolic form, and it can be isolated from these solutions by acidification.

The IR spectrum of VII has bands for the stretching vibrations of hydroxyl, nitrile, and carbonyl groups (2750, 2630, 2270, and 1645 cm^{-1}). On saponification, VII is converted into the corresponding acid (VIII), whose IR spectrum has bands similar to those of VII (2760, 2640, and 1645 cm^{-1}) and also the ν_{CO} band of a carboxyl group at 1706 cm^{-1} (figure). The agreement of the spectral characteristics of VII and VIII with those of similar derivatives in the benzoic acid series and with literature data [6,7] gives support to our assumption that the compounds under investigation exist as mixtures of the hydroxy and oxo forms (VIIa and VIIb, and VIIIa and VIIIb). The difference in the properties of compounds IV and VIII shows that IV was formed by the reaction of the hydrogen of the acetyl group with the aliphatic hydroxyl, and VIII by its reaction with the aromatic carboxyl.

In view of the difference in the reactions of I with acetic anhydride when potassium acetate is present and when it is not as described above, and also the analogy with our previous investigations in the corresponding benzoic acid series [8], we assume that the cyclization of I takes place in the following manner.

When the cyclization process was carried out under mild conditions by heating 1 mole of I with 2 moles of potassium acetate, we were able to isolate the intermediate monopotassium salt of N-acetyl-β-(2-carboxy-3-naphthyl naphthylamino)propionic acid (IX). Apparently, the formation of the mono- and not the dipotassium salt, in spite of the presence of 2 moles of potassium acetate, involves only the aromatic carboxyl because of its greater acidity. From IX we obtained the N-acetyl derivative of I (III). When IX was heated with acetic anhydride, carbon dioxide split out and II was formed, i.e., IX is an intermediate in this reaction. The subsequent course of the process is accompanied



by the gradual dissolution of the IX, which originally separated out, and the formation of the mixed anhydride (X) by the reaction of the aliphatic carboxyl group with acetic anhydride. The presence of a partial positive charge on the carbonyl carbon of the aliphatic carboxyl group and the ionized aromatic carboxyl promotes the formation of the internal mixed anhydride (XI), accompanied by the splitting out of potassium acetate. The cyclic anhydride (XI) is unstable, and decomposes under the reaction conditions with the formation of II and the liberation of carbon dioxide.

Similar conversions into cyclic ketones via an eight-membered internal mixed anhydride with the splitting out of carbon dioxide have been described in the literature in individual cases [9]. When the starting material had a different structure and the reaction conditions were somewhat different, this cyclic compound proved to be stable and could be isolated from the reaction mixture [10].

Thus, the cyclization of β-(2-carboxy-5-chlorophenylamino)propionic acid [5] and that of β-(2-carboxy-3-naphthylamino)propionic acid in acetic anhydride in the presence or in the absence of potassium acetate take place in a similar manner.

EXPERIMENTAL

The IR spectra of the compounds in the form of mulls in paraffin oil were recorded on a UR-10 instrument.

N-Acetyl-β-(2-carboxy-3-naphthylamino)propionitrile (VI). A mixture of 12 g (0.05 mole) of β-(2-carboxy-3-naphthylamino)propionitrile, 9.8 g (0.1 mole) of potassium acetate, and 30 ml of acetic anhydride was heated with stirring for 1 hr, the temperature being raised gradually to 100° C, and then at 130° C for 30 min. The excess acetic anhydride was distilled off in vacuo, and water was added to the residue. The precipitate that deposited was filtered off and washed with water. The yield of VI was 13.2 g (94%), mp 219–220° C (from water); small lustrous cream-colored crystals aoluble in benzene, ethanol, acetone, and hot water. Found, %: N 10.0. Calculated for $C_{16}H_{14}N_2O_3$, %: N 9.9.

Lactone of 3-(2,4-dioxopiperidyl)-2-naphthoic acid (V). A) A mixture of 5.2 g (0.02 mole) of I and 50 ml of acetic anhydride was boiled with stirring for 30 min and cooled, and the precipitate that deposited was filtered off. The yield of V was 2.5 g (47%), mp 261–262° C (decomp, from aqueous dioxane); yellow powder readily soluble in hot dioxane, benzene, and acetone. A qualitative test with 2,4-dinitrophenylhydrazine and a test for the formation of hydroxamic acid were positive. Found, %: C 72.6; H 4.5; N 5.2. Calculated for $C_{16}H_{11}NO_3$, %: C 72.4; H 4.2; N 5.3. B) A mixture of 0.1 g of IV and 3 ml of acetic anhydride was boiled for 3 hr and cooled, and the precipitate that deposited was filtered off. The yield of V was 0.08 g (85%), mp 261–262° C (decomp, from aqueous dioxane); it was identical with the material obtained by method A.

3-(2,4-Dioxopiperidyl)-2-naphthoic acid (IV). A solution of 1.5 g of V in 15 ml of 10% NaOH was filtered with activated carbon and acidified; the oil that separated out was boiled with heptane, whereupon it solidified. The yield of IV was 1.0 g, mp 202–203° C (decomp, from water); small colorless crystals soluble in ethanol, acetone, dioxane, and hot water, giving a positive test for carbonyl group with 2,4-dinitrophenylhydrazine. Found, %: C 67.5; H 4.7; N 4.9. Calculated for $C_{16}H_{13}NO_4$, %: C 67.8; H 4.6; N 4.9.

1-(β-Cyanoethyl-2, 4-dioxo-1,2,3,4-tetrahydrobenzo[g]quinoline (VII). A mixture of 9.0 g of VI and 45 ml of acetic anhydride was heated at 115–120° C for 4 hr. The excess acetic anhydride was distilled off in vacuo, and the resinous residue was washed with water. After two reprecipitations from dilute alkali, the yield of VII was 2.7 g (29%), mp 285–287° C (from ethanol); cream-colored powder soluble in hot ethanol and dioxane, and sparingly soluble in water. Found, %: C 72.5; H 5.0; N 10.5. Calculated for $C_{16}H_{12}N_2O_2$, %: C 72.7; H 4.6; N 10.6. The mother liquor from the first reprecipitation, on acidification to pH 2, yielded 3.3 g of VI with mp 218–219° C.

1-(β-Carboxyethyl)-2,4-dioxo-1,2,3,4-tetrahydrobenzo[g]quinoline (VIII). A mixture of 1.8 g (0.007 mole) of VII, 0.7 g (0.017 mole) of caustic soda, and 5 ml of water was boiled until the evolution of ammonia ceased (10 hr), then it was acidified and the product that separated out was filtered off, reprecipitated twice from dilute alkali, and crystallized from water to give 0.5 g (26%) of VIII, mp 227–228° C; cream-colored powder soluble in hot ethanol, acetone, dioxane, and boiling water. Found, %: C 67.9; H 5.1; N 4.9. Calculated for $C_{16}H_{13}NO_4$, %: C 67.8; H 4.6; N 4.9.

N-Acetyl-β-(2-carboxy-3-naphthylamino)propionic acid (III) and its monopotassium salt (IX). With a stirring, a mixture of 9.8 g (0.38 mole) of I, 7.4 g (0.76 mole) of potassium acetate, and 23 ml of acetic anhydride was heated to 85° C, and then kept at 85° C for 15 min. The substance IX that deposited was filtered off and washed with dry acetone; yield 8.2 g mp 290–291° C (from aqueous acetone); cream-colored powder insoluble in organic solvents, readily soluble in water. Found, %: N 4.3. Calculated for $C_{15}H_{14}NO_5K$, %: N 4.1.

A mixture of 6.0 g of IX and 18 ml of acetic anhydride was heated for 1 hr 30 min, the temperature being raised slowly to 130° C; there was a vigorous evolution of carbon dioxide. The volatile products were distilled off in vacuo and the residue was treated with water, made alkaline, and extracted with benzene; and the benzene extract was evaporated. This gave 2.5 g (58%) of II, mp 148–149° C (from aqueous acetone).

A solution of 5.0 g of IX in water was acidified, and the oily product that separated out crystallized after being heated in water. This gave 2.0 g of III, mp 182–183° C (from water); white crystalline powder readily soluble in ethanol, acetone, and hot water. Found, %: N 5.1. Calculated for $C_{16}H_{15}NO_5$, %: N 4.6.

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Martsinovskii Institute of Medicinal Parasitology and
Tropical Medicine, Moscow

Ordzhonikidze Scientific-Research All-Union Chemical and
Pharmaceutical Institute, Moscow