KETO-ENOL TAUTOMERISM OF 4-HYDROXY-3-PHENYL-2-(2-CHLOROACETAMIDOPHENYL)-1-ISOQUINOLONE

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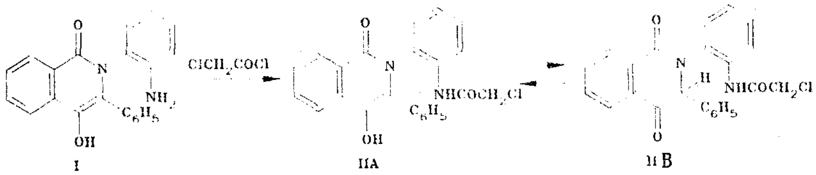
Three crystalline modifications of the N-chloroacetyl derivative were obtained in the chloroacetylation of 2-(2-aminophenyl)-4-hydroxy-3-phenyl-1-isoquinolone. It was established by IR spectroscopy that they differ with respect to isomeric composition and the character of the intermolecular hydrogen bonds. For the first time, both keto-enol tautomeric forms were isolated in individual form in the 4-hydroxy-1-isoquinolone series.

2,3-Disubstituted 4-hydroxy-1-isoquinolones, which are formed [1, 2] in the Wanag rearrangement [2-5] from 2-substituted 2-amino-1,3-indandiones, exist in the crystalline state in the 4-hydroxy form, whereas a tautomeric equilibrium between the 4-hydroxy and 4-oxo isomers is observed in solutions [2].

We have previously shown [6] that 2-(2-aminophenyl)-4-hydroxy-3-phenyl-1-isoquinolone (I) is formed in the reaction of 3-(α-bromobenzyl)-3-bromophthalide with o-phenylenediamine.

In the chloroacetylation of the amino group in I we obtained three crystalline modifications of 4-hydroxy-3-phenyl-2-(2-chloroacetamidophenyl)-1-isoquinolone (II) that differ with respect to the percentages of the isomers and the character of the intermolecular hydrogen bonds.



Compound IIA, with mp 136-141°C, was isolated from the reaction mixture. A broad melting-point range is characteristic for 2,3-disubstituted 4-hydroxy-1-isoquinolones. The IR spectrum of crystalline IIA is similar to the spectrum of starting isoquinolone I [6], and this confirms structure IIA. The presence of a broad OH band at 3080 cm^{-1} constitutes evidence for the formation of strong OH•••O=C intermolecular hydrogen bonds (quinolone) (see [6]). The IR spectrum of a freshly prepared solution of IIA in dioxane contains bands at 1701 (amide I), 1660 (quinolone C=O), 1625 (C=C), 1601 and 1586 (aromatic ring C–C), and 1522 cm^{-1} (amide II), which confirm the IIA structure in solution. However, the spectrum of the same solution (Fig. 1) recorded after 24 h provides evidence for a complete shift of the IIA ⇄ IIB equilibrium to favor the 4-oxo form: bands at 1710 [amide I + C$_{(4)}$=O] and 1682 cm^{-1} [C$_{(1)}$=O] are observed.

When we heated IIA in refluxing hexane, we obtained IIA' with the same elementary composition and mp 175-178°C. Its IR spectrum recorded for the crystalline state (Fig. 1) indicates a strong shift of the amide I band to the low-frequency side: Absorption at 1700 cm^{-1} is absent, and several bands at 1640-1660 cm^{-1} are observed. The character of the IR spectrum of crystalline IIA' makes it possible to assume that it is another crystalline modification of IIA in which the O–H•••O=C intermolecular hydrogen bonds are formed with the participation of the amide C=O group rather than the quinolone C=O group. This is also confirmed by the identical character of the IR spectra of freshly prepared solutions of IIA and IIA' in dioxane.

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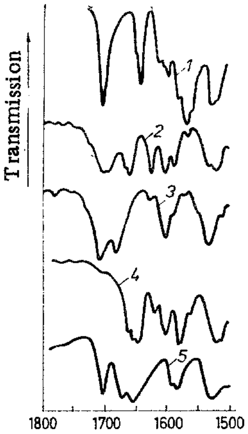

Fig. 1. IR spectra: 1) IIA; 2) freshly prepared IIA in dioxane; 3) the same solution after 24 h; 4) freshly prepared solution of IIA' in dioxane; 5) IIB recorded in Nujol.

After recrystallization of IIA' from benzene, we obtained IIB with mp 137-138°C. Amide I, ketone C=O, and quinolone C=O bands are observed in the IR spectrum of crystalline IIB. The IR spectrum of a freshly prepared solution of IIB in dioxane (Fig. 1), which contains the C=O bands of 4-oxo form IIB, does not change upon storage and is identical to the spectra of solutions of IIA or IIA' recorded 24 h after dissolving.

In the case of chloroacetamido derivative II we were, for the first time in the 2,3-disubstituted 4-hydroxy-1-isoquinolone series, able to isolate 4-oxo form IIB in crystalline form. We were unable to accomplish a similar transformation for 4-hydroxy-2,3-diphenyl-1-isoquinolone [2, 7], and it may therefore be assumed that crystalline form IIB is stabilized by intermolecular hydrogen bonds with the participation of the chloroacetamido group.

EXPERIMENTAL

The IR spectra of suspensions in Nujol or solutions in dioxane (c $3.3 \cdot 10^{-2}$ mole/liter) were recorded with a Specord 75-IR spectrometer.

4-Hydroxy-3-phenyl-2-(2-chloroacetamidophenyl)-1-isoquinolone (II). A 4.8-ml sample of chloroacetyl chloride was added to a suspension of 3 g of isoquinolone I [6] in 30 ml of anhydrous dioxane. After isoquinolone I had dissolved, the solution was filtered rapidly, and the filtrate was allowed to stand at room temperature. After 24 h, 2.86 g (78%) of lemon-yellow crystals of IIA, with mp 136-141°C, separated. IR spectrum in Nujol: 3260 (N—H), 3080 (broad band, O—H), 1706 (amide I), 1645, 1613, 1597, 1581, 1568, 1559, and 1527 cm^{-1}. Found, %: C 67.9, H 5.0, Cl 9.0, N 7.4. $C_{23}H_{17}ClN_2O_3$. Calculated, %: C 68.2, H 4.2, Cl 8.8, N 6.9. A suspension of 0.4 g of IIA in 10 ml of hexane was refluxed for 2.5 h, after which the mixture was cooled, and 0.37 g (92%) of light-yellow crystals of IIA', with mp 175-178°C, separated. IR spectrum in Nujol: 3305 (N—H), 3121 (broad band, O—H), 1658, 1653, 1644, 1618, 1600, 1578, and 1520 cm^{-1}. Found, %: C 69.5, H 4.6, Cl 8.7, N 6.9. $C_{23}H_{17}ClN_2O_3$. Calculated, %: C 68.2, H 4.2, Cl 8.8, N 6.9.

In the recrystallization of 0.26 g of IIA' from 10 ml of benzene, after rapid cooling, we observed the precipitation of a mixture of isomers (mp 125-140°C), which separated rapidly. The filtrate was allowed to stand in a refrigerator; after 24 h, 0.1 g of IIB, with mp 137-138°C, separated. IR spectrum in Nujol: 3348, 3228 (N—H), 1705 (amide I), 1674 (ketone C=O), 1654 (quinolone C=O), 1592, 1583 (aromatic ring C—C), 1529 cm^{-1} (amide II). Found, %: C 68.7, H 4.5, Cl 8.8, N 6.8. $C_{23}H_{17}ClN_2O_3$. Calculated, %: C 68.2, H 4.2, Cl 8.8, N 6.9.

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