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PYRIMIDINES

IV. Acetylation of 4-Phenylbenzo [h] Quinazoline Derivatives*

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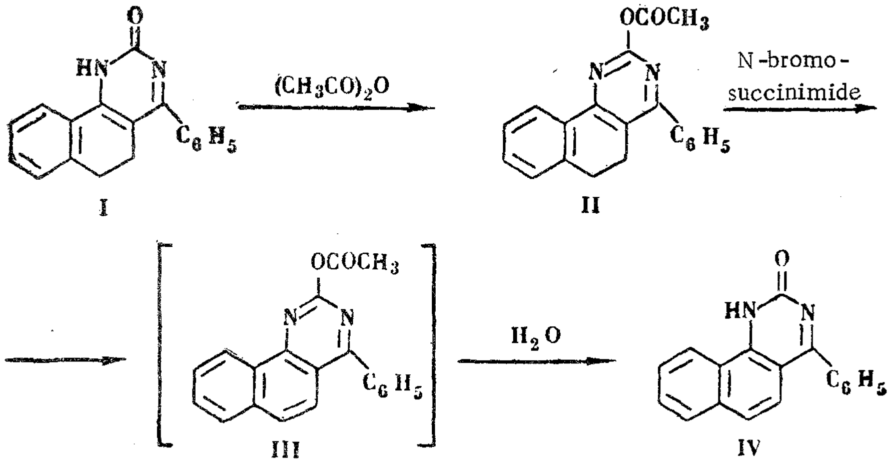
Some hydrogenation products of 2-hydroxy-4-phenylbenzo[h]quinazoline are acetylated with acetic anhydride. Mono and diacetyl derivatives are obtained, depending on the extent of hydrogenation of the quinazoline ring. From spectroscopic data structures are put forward for these compounds. Formation of a diacetyl derivative from 2-hydroxy-4-phenyl-3, 4, 5, 6-tetrahydrobenzo[h]quinazoline offers support for a previously advanced view regarding its structure.

A previous paper [1] dealt with the synthesis of a number of hydroxy derivatives of benzo[h]quinazoline. Extending that work to quinazolines, the acetylation of those compounds has been studied.

The existing literature deals mainly with acylation of dihydroxy and trihydroxypyrimidines [2-9]. The compounds prepared are regarded as N-acyl derivatives [3-6, 9], though some papers contain indications of O-acyl derivatives being formed [7].

Boiling 2-hydroxy-4-phenyl-5, 6-dihydrobenzo[h]quinazoline (I) with acetic anhydride gave a monoacetyl derivative, whose IR and UV spectra correspond to 2-acetoxy-4-phenyl-5, 6-dihydrobenzo[h]quinazoline (II).



In the IR spectra this is indicated by an absorption band at 1790 cm^{-1}, characteristic of the C=O group of phenyl esters (other bands at 1600-1800 cm^{-1} are lacking) and by the presence of an intense band at 1195 cm^{-1}, characteristic of the C–O–C bonds' valence vibrations in acetates [10].

The UV spectrum of the O-acetyl derivative I ought to be very like that of 4-phenyl-5, 6-dihydrobenzo[h]quinazoline V, as the two compounds have similar chromophoric systems. For the same reason the spectrum of the N-acetyl derivative should closely resemble the spectrum of I. Comparison of absorption maxima λ_{max} (lg ε): I 274-278 (410), 352-356 (3.97); II 240-244 (4.11), 294-298 (4.13), 314-320 (4.20); V[1] 230-232 (4.11), 290 (4.15), 308-310 (4.16) confirms that here the O-acetyl derivative II is formed. The small bathochromic shift of the absorption maxima of II in comparison with those of V can be put down to replacement of hydrogen by the acceptor acetoxy group.

As expected [9], II possesses acetylating properties, for example, aniline is 85% acetylated in dioxane solution. Dehydrogenation of II with N-bromosuccinimide was expected to give 2-acetoxy-4-phenylbenzo[h]quinazoline (III), but as the latter is very easily hydrolyzed, the main product isolated was 2-hydroxy-4-phenylbenzo[h]quinazoline (IV), and only a small quantity of a substance (probably III) which in the process of purification was also converted into IV.

There is very little information available regarding acylation of partly or fully hydrogenated monohydroxypyrimidine derivatives. Johnson and Folkers [11] showed that both mono and diacetyl derivatives can be formed, depending on the substituents and degree of hydrogenation (i.e., depending on the basicity of the compound).

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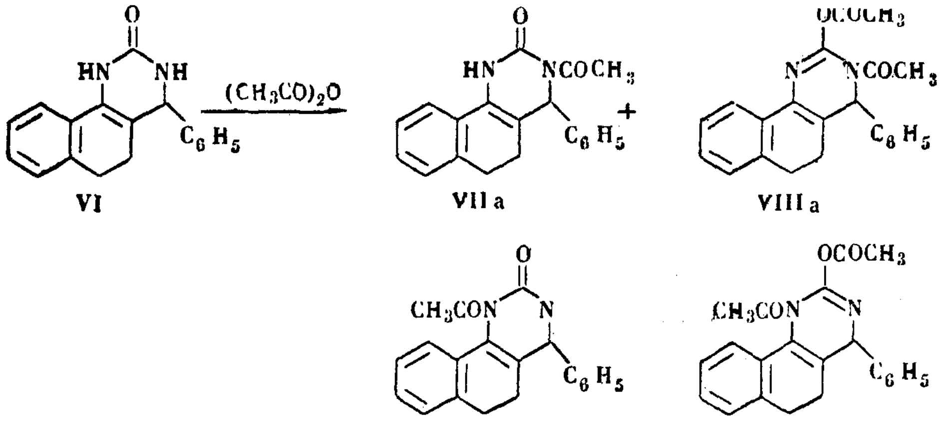
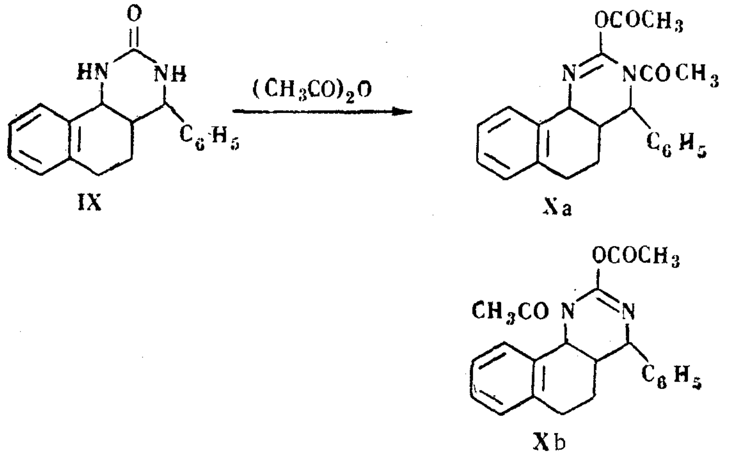
* For Part III see [1].

Acetylation of 2-hydroxy-4-phenyl-3, 4, 5, 6-tetrahydrobenzo[h]quinazoline (VI) gave two compounds, whose analyses corresponded to the mono and diacetyl derivatives of VI. The IR spectrum of the monoacetyl derivative contained an absorption band characteristic of the valence vibrations of the imino group =NH (3280 cm^{-1}); two bands of the C=O group (1690 and 1705 cm^{-1}), and the absorption band characteristic of the ester group C–O–C were lacking. These results corresponded to a structure N-acetyl-2-hydroxy-4-phenyl-3, 4, 5, 6-tetrahydrobenzo [h] quinazoline (VII). At the same time the IR spectrum of the diacetyl derivative was an intense absorption band at 1220 cm^{-1}, characteristic of the ester group C–O–C, and two valence vibrations of the C=O group at 1730 and 1710 cm^{-1}, corresponding to a structure N-acetyl-2-acetoxy-4-phenyl-3, 4, 5, 6-tetrahydrobenzo [h]quinazoline (VIII).



Further acetylation of VII with acetic anhydride converted it into VIII. Formation of the latter can be explained by the tendencies of VI and VII to go over to the lactim form. VII is readily hydrolyzed to VI with a solution of alkali, and VIII, with a sulfuric acid solution.

Acetylation of the fully hydrogenated quinazoline 2-hydroxy-4-phenyl-3, 4, 4a, 5, 6, 10a-hexahydrobenzo[h]quinazoline (IX) gave only one compound, a diacetyl derivative, converted by hydrolysis with 35% sulfuric acid to the starting compound IX. From IR spectra data (two bands at 1600-1800 cm^{-1}, 1710-1740 cm^{-1}, and a very intense band at 1205 cm^{-1}) the compound obtained is ascribed the structure N-acetyl-2-acetoxy-4-phenyl-3, 4, 4a, 5, 6, 10a-hexahydrobenzo [h] quinazoline (X) analogous to VIII.



The results obtained show that acetylation depends on the degree of hydrogenation [11], and also on the proneness of the compound to tautomerize. In the present work no special study was made of the question of the basicities of the nitrogen atoms, but from what is stated in the literature it can be assumed that the 3-N is the more basic, VI and IX also acetylating there. Further, in VI the conjugation of 1-N with the C=C double bond must lower its basicity in comparison with 3-N. On the other hand, formation of the lactim form of VI proceeds more readily when it involves 1-N, for then a conjugated system of double bonds is formed, whereas with 3-N the double bonds will be isolated ones, i.e., structure VIIIa for the diacetyl derivative seems more likely.

In preceding papers [1] it was recalled that the position of the double bond in condensation products from aromatic aldehydes, ureas, and compounds containing the $-CH_2-CO-$ group has not been established, for according to the literature [8] with acetoacetic ester the condensation products are mixed isomers with C=C and C=N bonds. However, it has been pointed out [1], that IR spectrum data and bromination data indicate that condensation product VI is a compound with a C=C bond. Results relating to the acetylation of VI (formation of compounds VII and VIII) support that view, since in the case of an isomer with a C=N bond, the diacetyl derivative VIII could not be formed, while the monoacetyl derivative VII would not contain the N–H bond (IR spectral data).

Experimental

UV spectra were determined with a SF-4 spectrophotometer, with alcohol as the solvent, solutions 10^{-4} M. IR spectra were recorded with a UR-10 spectrophotometer. Specimens were tabletted with KBr (5 mg compound and 800 mg KBr, range 1100-1900 cm^{-1} at concentration 1 mg compound per 800 mg KBr.)

2-Hydroxy-4-phenyl-5, 6-dihydrobenzo [h] quinazoline (I), 2-hydroxy-4-phenyl-3, 4, 5, 6-tetrahydrobenzo [h] quinazoline (VI), and 2-hydroxy-4-phenyl-3, 4, 4a, 5, 6, 10a-hexahydrobenzo [h] quinazoline (IX) were prepared as described in [1].

2-Acetoxy-4-phenyl-5, 6-dihydrobenzo [h] quinazoline (II). 0.25 g I was refluxed for 3 hr with 2.5 ml acetic anhydride, the latter then distilled off under reduced pressure, and the oil which remained triturated with water, when it crystallized, yield 0.27 g (98%) II, mp 141-143° (from alcohol). Found: C 76.2, 76.3; H 5.02, 5.07; N 9.02, 9.28%. Calculated for $C_{20}H_{16}N_2O_2$: C 76.0; H 5.06; N 8.86%.

Dehydrogenation of II. 0.50 g II was dissolved in 15 ml CCl_4, 0.27 g N-bromosuccinimide and 15 ml benzoyl peroxide added, and the whole refluxed for 1 hr 30 min. The precipitate formed was filtered off, and washed with a small amount of water, yield 0.22 g (58%) IV, mp 329-331° (from alcohol). Mixed mp and IR spectrum show it to be identical with an authentic specimen of IV [1]. The filtrate was evaporated, the residue washed with water. Yield 0.18 g III mp 120-130°. Recrystallization from alcohol gave 0.10 g IV mp 327-330°.

Acetylation of VI. 0.50 g VI in 5 ml acetic anhydride was refluxed for 5 hr, and the reaction products then allowed to stand for two days at room temperature. The precipitate formed was filtered off, washed with water, then with methanol, and finally with a large volume of ether. Yield 0.26 g VII (45%) mp 248.5-249.5° (from glacial acetic acid or pyridine). Found: C 75.8, 75.7; H 5.89, 5.76; N 8.80, 8.64%. Calculated for $C_{20}H_{18}N_2O_2$: C 75.5; H 5.69; N 8.80%. UV spectrum λ_{max}, mμ lg ε: 228-230 (4.43), 292-294 (3.80). The filtrate obtained after filtering off VII was evaporated, the residue treated with 10 ml water, and left overnight. The treated precipitate was filtered off, washed with water, and then with methanol. Yield 0.31 g (47%) VIII mp 183-186° (from alcohol). Found: C 73.7, 73.6; H 5.53, 5.64; N 7.87, 8.08%. Calculated for $C_{22}H_{20}N_2O_3$: C 73.3; H 5.59; N 7.77%. UV spectrum λ_{max}, mμ (lg ε): 266 (4.02), 274 (4.00).

Hydrolysis of VII. 0.20 g VII was refluxed for 6 hr with 6 ml 10% NaOH solution, the precipitate formed filtered off, washed with water, mp 256-258° (from alcohol), mixed mp with VI 256-259°.

Hydrolysis of VIII. 0.40 g VIII and 8 ml 47% H_2SO_4 were refluxed together for 1 hr 30 min. The precipitate was filtered off, and washed with methanol and ether. Yield 0.26 g VI mp 254-258° (from alcohol), mixed mp with VI 255-258°.

Acetylation of IX. 0.50 g IX was refluxed with 8 ml acetic anhydride for 4 hr 30 min. Excess anhydride was distilled off under reduced pressure, and the residue triturated with water. Yield 0.49 g (84%) X mp 162-164° (from methanol). Found: C 73.0, 72.9; H 6.16, 6.01; N 8.05, 8.00%. Calculated for $C_{22}H_{22}N_2O_3$: C 72.9; H 6.08; N 7.73%. UV spectrum λ_{max}, mμ (lg ε): 212-216 (4.33).

Hydrolysis of X. 0.10 g X was refluxed with 2.5 ml 30% H_2SO_4 for 1 hr 30 min. The precipitate was filtered off, mp 279-281°, shown by mixed mp and IR spectrum to be identical with IX.

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