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Formation of 3-Benzyl-4-quinazolinone from 4-Quinazolinone and 2-Amino-1-phenylpropanol. A Novel Reaction

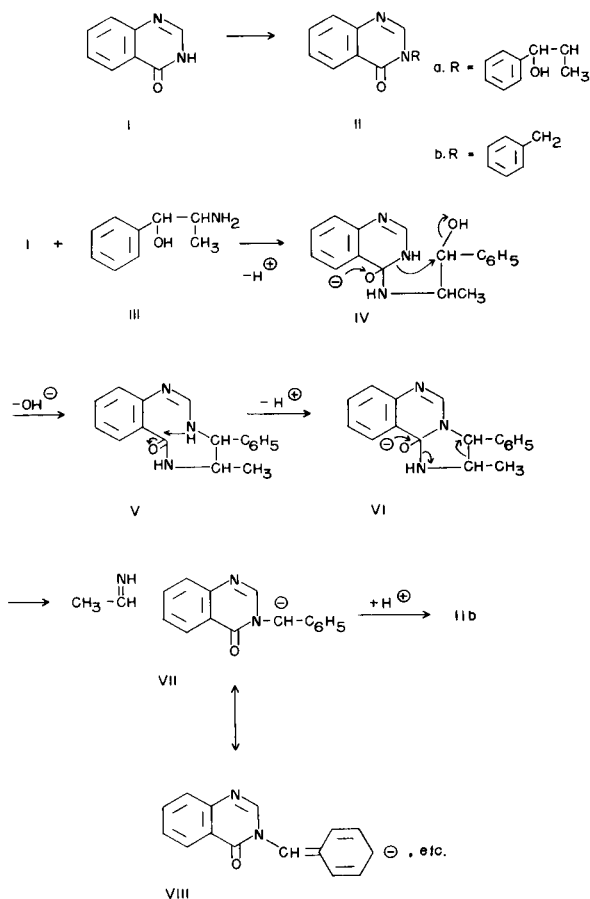
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The reaction of 4-quinazolinone (I) with primary amines yields 3-substituted 4-quinazolinones (1). The mechanism of this reaction, elucidated by Leonard and Curtin (1), involves addition of the primary amine to the carbonyl group, cleavage of the 3,4-bond, and restoration of the ring with the nitrogen of the primary amine replacing the original nitrogen atom at position 3, which is eliminated as ammonia.

In an attempt to prepare 3-(2-hydroxy-1-methyl-2-phenylethyl)-4-quinazolinone (IIa), it was found that when 4-quinazolinone (I) is heated at *ca.* 200° with approximately an equivalent amount of 2-amino-1-phenylpropanol (*dl*-norephedrine) (III) in ethylene glycol, a crystalline product was obtained. This product, however, was not the expected compound IIa. Elementary analysis indicated it differed from IIa by lacking the composition of acetaldehyde. The infrared spectrum suggested the product was 3-benzyl-4-quinazolinone (IIb), which had been prepared by Bogert and Geiger (2) and later by Baker *et al.* (3). It proved to be identical with a sample of IIb, which we prepared by condensing 4-quinazolinone (I) with benzylamine (1).

The direct formation of IIb from IIa by the expulsion of acetaldehyde appears unlikely. More probably, the elimination of acetaldehyde (or its equivalence) occurs during the reformation of the ring system.

The reaction of I and III is envisaged as proceeding in the following way. The amino group of III adds across the carbonyl group of I (1) to afford IV. The negative charge on oxygen facilitates rupture of the heterocyclic ring. Because of the proximity of N-3 to the benzyl hydroxyl group, a nucleophilic displacement of the latter group occurs, and a nine-membered ring intermediate, V, is formed. This in turn is converted to VI by a transannular reaction (4). Again, cleavage of a C-N bond is induced by the negatively charged oxygen. A shift of electrons results in the rupture of a C-C bond. The presence of the electron-withdrawing phenyl group promotes this rupture as it allows the resulting product to be stabilized by resonance (VII \leftrightarrow VIII). This fragmentation step finds a parallel in the base induced cleavage of 2,3-dimethyl-3-phenyl-2-pentanol to yield 2-phenylbutane and acetone (5). Protonation at the benzyl position of VII completes the transformation to give IIb together with the imine of acetaldehyde.



EXPERIMENTAL

Reaction of 4-Quinazolinone (I) with 2-Amino-1-phenylpropanol [*dl*-Norephedrine] (III).

A mixture of 5.00 g. (0.0331 mole) of 4-quinazolinone (I), 5.20 g. (0.0366 mole) of 2-amino-1-phenylpropanol (III), m. p. 96.5-100°, and 20 ml. of ethylene glycol was heated under reflux in an atmosphere of nitrogen for 22 hours. The dark reaction mixture was cooled and then poured into ice water. The resulting gum was extracted with ether. The combined ether extracts were washed with water, dried over anhydrous sodium sulfate, and distilled to dryness under reduced pressure. The residual oil was chromatographed on 500 g. of neutral alumina. The column was eluted with varying proportions of benzene and ethyl acetate. Elution with 10% ethyl acetate in benzene gave 1.33 g. of a solid. The solid was crystallized from ether-pentane to afford 0.64 g. (8%) of 3-benzyl-4-quinazolinone (IIb), m. p. 114.5-118.5°. The analytical sample of IIb was obtained as thick colorless

plates after another crystallization from ether-pentane, m. p. 119-120°, λ max (CHCl₃), 5.93, 6.20, 6.38 μ . The spectrum showed the absence of the hydroxyl group.

Anal. Calcd. for C₁₅H₁₂N₂O: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.25; H, 4.93; N, 12.08.

3-Benzyl-4-quinazolinone (IIb).

A solution of 4.00 g. (0.0265 mole) of I and 100 ml. (0.913 mole) of benzylamine was heated under reflux in an atmosphere of nitrogen for 19 hours. The reaction mixture was then concentrated to a small volume by distillation at atmospheric pressure. The residue was cooled, poured into ice water, and rubbed. The resulting semisolid was collected, washed well with water, and air-dried. Crystallization from ether-pentane gave 3.08 g. (49%) of IIb, m. p. 118.5-119.5° [lit. 116° (2), 112-114° (3)]; λ max (MeOH) 266-268 (ϵ , 8,150), 271.5-276.5 (ϵ , 7,460) (sh), 301 (ϵ , 3,620), 313 $m\mu$ (ϵ , 2,950); λ min (MeOH) 249-250 (ϵ , 4,600), 294-295 (ϵ , 2,930), 309 $m\mu$ (ϵ , 2,600). Its infrared spectrum was identical with that described above. A

mixture of the two samples of IIb showed no depression in the melting point.

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Received August 26, 1965

Chicago, Illinois 60680