[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

REACTIONS OF 4-QUINAZOLONE. III. REACTION WITH SECONDARY AMINES[1]

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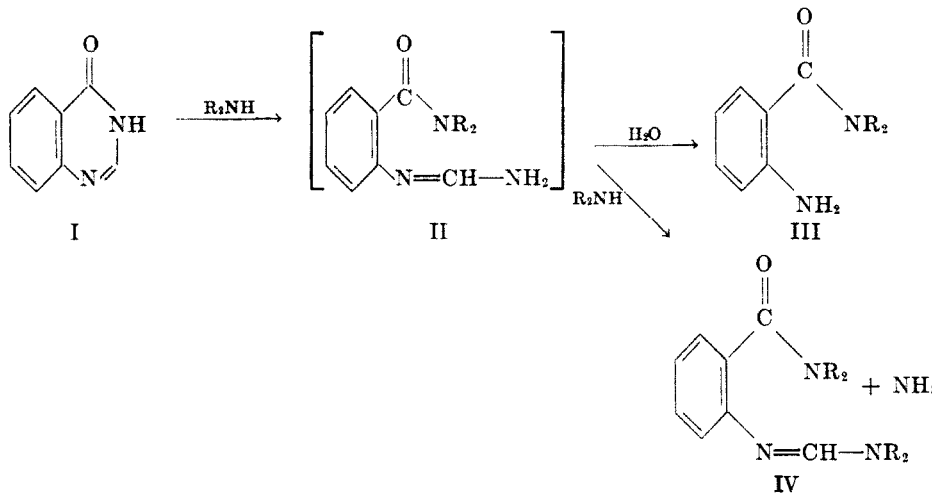
In order to test the hypothesis (1) that the reaction of 4-quinazolone (I) with amines proceeds by an initial ring-opening, the reaction of 4-quinazolone with secondary aliphatic amines was investigated. The nature of the products obtained indicates that ring-opening between the 3- and 4-position occurs initially and that the 3-N atom of 4-quinazolone is eliminated as ammonia.



I II III IV

In the course of the reaction of a secondary amine with 4-quinazolone, an amidine of type II would be the expected intermediate (1). Compound II could not undergo ring-closure to form a substituted 4-quinazolone but would be expected to yield the N-(2-aminobenzoyl)dialkylamine III on hydrolysis. Such a product was obtained from the reaction of 4-quinazolone with morpholine or piperidine when water was present in the reaction mixture. With morpholine containing water, the compound obtained was N-(2-aminobenzoyl)morpholine (III, R_2 = $-CH_2CH_2OCH_2CH_2-$), identified by mixed melting point with the reduction product of N-(2-nitrobenzoyl)morpholine. With moist piperidine, N-(2-aminobenzoyl)piperidine (III, R_2 = $-CH_2CH_2CH_2CH_2CH_2-$) was formed and was identified in a similar manner.

Under rigorously anhydrous conditions, the reaction of 4-quinazolone with piperidine produced a compound which had an elementary analysis, infrared

[1] For the first and second articles in this series, see Leonard and Curtin, *J. Org. Chem.*, **11**, 341, 349 (1946).

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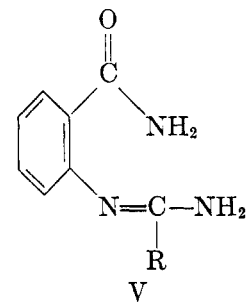
[3] Revised manuscript with additional experimental results received June 14, 1948.

absorption spectrum, and molecular weight consistent with the structure IV (R_2= —$CH_2CH_2CH_2CH_2CH_2$—). That compound IV might be formed from II by reaction with excess amine is not unlikely, as it is a well-established fact that certain amidines react with amines in this manner (2). An unequivocal synthesis of IV has not been accomplished although many attempts have been made. Compound IV was insoluble in water but soluble in dilute hydrochloric acid. When the compound was heated under reflux with twenty per cent hydrochloric acid or ten per cent aqueous-alcoholic sodium hydroxide it was unchanged. With sixty per cent sulfuric acid, compound IV was cleaved to piperidine (two moles per mole of IV), identified as the hydrochloride, and anthranilic acid. Treatment of IV with hot acetic anhydride gave N-(2-acetylaminobenzoyl)piperidine.

While the behavior of secondary aliphatic amines has demonstrated the occurrence of initial ring-opening of 4-quinazolone by amines, the identity of the postulated intermediate (II) has not been proved. Careful investigation of the reaction mixtures from many runs of 4-quinazolone with piperidine failed to reveal the presence of any compound II. During the reaction, piperidine evidently caused conversion to IV, or water, to III. In considering an N-arylformamidine as an intermediate in the ring-opening of 4-quinazolone by a primary alkylamine followed by ring-closure (of the N-arylformamidine or of the derived N-aryl-N′-alkylformamidine) to a 3-substituted 4-quinazolone (1), it should have been pointed out that amidines of closely analogous type have previously been described as intermediates in the synthesis of 2-substituted



V

4-quinazolones. The hydrochloride of the amidine V was suggested by Holljes and Wagner (3) to be the intermediate in the synthesis of 2-alkyl-4-quinazolones from anthranilamide hydrochloride and alkyl cyanides. The same workers proposed an amidine of type V as the intermediate in the reaction of anthranilic acid and acetonitrile in a sealed tube to give 2-methyl-4-quinazolone (4). It is of interest that no reference could be found in the literature to any N-arylformamidine (type II).

EXPERIMENTAL[4]

N-(2-Nitrobenzoyl)piperidine. The method of Franchimont, Van Rijn, and Friedmann (5) was adapted for this preparation. To 8.5 g. (0.1 mole) of piperidine and 5.25 g. (0.13

[4] All melting points are corrected. Microanalyses by Miss Theta Spoor. Infrared absorption spectra determinations by Mrs. James L. Johnson.

mole) of sodium hydroxide in 40 ml. of water, 2-nitrobenzoyl chloride (from 0.1 mole of 2-nitrobenzoic acid) was added dropwise with stirring during 30 minutes. The yellow oil which formed was separated from the aqueous layer, which was extracted with three 10-ml. portions of benzene. After the combined extracts and oil had been washed with water and dried over potassium carbonate, the benzene was removed, and the residue was recrystallized from benzene-petroleum ether. The yield was 11.5 g. (49% based on 2-nitrobenzoic acid) of crystals, m.p. 51–53° (lit., 56°). This material was reduced without further purification.

N-(2-Nitrobenzoyl)morpholine. This compound, which apparently has not been previously reported, was prepared by the same method as that used for N-(2-nitrobenzoyl)-piperidine. The yield from 16.8 g. (0.1 mole) of 2-nitrobenzoic acid was 15.5 g. (66%) of colorless prisms, m.p. 122–122.5°.

Anal. Calc'd for $C_{11}H_{12}N_2O_4$: C, 55.93; H, 5.12; N, 11.86.
Found: C, 55.79; H, 5.10; N, 11.82.

N-(2-Aminobenzoyl)piperidine. N-(2-Nitrobenzoyl)piperidine (6.25 g., 0.028 mole) was dissolved in 200 ml. of ethanol, 0.2 g. of platinum oxide catalyst was added, and the hydrogenation was carried out at 25° and 3–4 atmospheres. The catalyst and solvent were removed and crystallization of the residue was induced by trituration with petroleum ether. Recrystallization, first from ethanol, then from petroleum ether, gave 4.35 g. (79%) of colorless needles, m.p. 77–78°. The melting point was previously reported as 73–74° (3).

The *acetyl* derivative was prepared by heating under reflux with acetic anhydride. Recrystallization from petroleum ether gave colorless prisms, m.p. 132–132.5°, in 57% yield.

Anal. Calc'd for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.37; N, 11.38.
Found: C, 68.45; H, 7.39; N, 11.24.

N-(2-Aminobenzoyl)morpholine. This compound was obtained in analogous manner by the hydrogenation of N-(2-nitrobenzoyl)morpholine. Recrystallization from methanol, then from petroleum ether, gave colorless needles, m.p. 74–75°, in 53% yield.

The *acetyl* derivative was prepared by heating under reflux with acetic anhydride. Recrystallization from petroleum ether gave colorless elongated prisms, m.p. 133–135°, in 41% yield.

Anal. Calc'd for $C_{13}H_{16}N_2O_3$: C, 62.88; H, 6.50.
Found: C, 62.65; H, 6.42.

Reaction of 4-quinazolone with moist morpholine. A mixture of 7.0 g. (0.048 mole) of 4-quinazolone and 17 g. (0.0195 mole) of morpholine (containing *ca.* 3% water) was heated under reflux for 44 hours in an oil-bath maintained at 140–150°. Excess morpholine was removed by distillation under reduced pressure. The residual oil was shaken with 50 ml. of 2.5 *N* sodium hydroxide and 50 ml. of benzene and the layers were separated. The aqueous layer was extracted with three 25-ml. portions of benzene. When the aqueous layer was neutralized, no 4-quinazolone separated. The combined benzene extracts were dried over magnesium sulfate and the solvent was removed under reduced pressure. The residual oil crystallized slowly. Recrystallization from benzene-hexane yielded 5.11 g. (52%) of colorless needles, m.p. 74–75°.

Anal. Calc'd for $C_{11}H_{14}N_2O_2$: C, 63.75; H, 6.81; N, 13.52.
Found: C, 63.64; H, 6.87; N, 13.60.

The combined mother liquor from several recrystallizations was passed through a column of activated alumina. Successive elutions with 100 ml. of benzene and 100 ml. of ether yielded a further small quantity of the same material. The melting point was not depressed when the compound was mixed with N-(2-aminobenzoyl)morpholine, and the melting point of the *acetyl* derivative (133–135°) was not depressed when mixed with N-(2-acetylaminobenzoyl)morpholine.

Reaction of 4-quinazolone with moist piperidine. A mixture of 6.5 g. (0.044 mole) of 4-quinazolone and 18 g. (0.212 mole) of piperidine (containing *ca.* 5% water) was heated under reflux for 42 hours in an oil-bath maintained at 130–140°. Excess piperidine was removed by distillation under reduced pressure. The residual oil was shaken with 40 ml. of benzene and 25 ml. of 2.5 *N* sodium hydroxide. The layers were separated and the

aqueous layer was extracted with three 25-ml. portions of benzene. When the aqueous layer remaining was carefully neutralized with dilute hydrochloric acid, 2.87 g. of 4-quinazolone was obtained. The benzene extracts were dried over magnesium sulfate and the solvent was removed under reduced pressure. The residual oil crystallized slowly in a vacuum desiccator over concentrated sulfuric acid. The crude product was triturated with 200 ml. of hexane and then recrystallized repeatedly from hexane to give 1.65 g. (33% based on unrecovered 4-quinazolone) of colorless needles, m.p. 77.5–79°.

Anal. Calc'd for $C_{12}H_{16}N_2O$: C, 70.55; H, 7.90; N, 13.72.
Found: C, 70.69; H, 8.03; N, 13.78.

The hexane mother liquor was passed through a column of activated alumina. Elution with benzene yielded only a further quantity of the same material. The melting point was not depressed when the compound was mixed with N-(2-aminobenzoyl)piperidine, and the melting point of the *acetyl* derivative (132–132.5°) was not depressed when mixed with N-(2-acetylaminobenzoyl)piperidine.

When anthranilic acid was treated with piperidine and the crude product was worked up under scrupulously identical conditions throughout, no N-(2-aminobenzoyl)piperidine could be isolated and most of the anthranilic acid was recovered unchanged.

Reaction of 4-quinazolone with dry piperidine. The piperidine used in this experiment was dried over five changes of crushed potassium hydroxide and redistilled. The 4-quinazolone was dried to constant weight at 80° and kept in a desiccator.

A mixture of 15.0 g. (0.102 mole) of 4-quinazolone and 45 g. of piperidine (0.51 mole) was heated under reflux for forty-eight hours in an oil-bath maintained at 140°. Excess piperidine was removed by distillation under reduced pressure. The residue, which partially solidified on cooling, was digested with 75 ml. of boiling anhydrous ether. The solid was digested with 150 ml. of benzene, and the mixture was cooled and filtered. The residual solid material weighed 5.07 g. and melted at 213–215°. It was shown by mixed melting point to be 4-quinazolone. Evaporation of the benzene solution left a residue that was mostly 4-quinazolone (0.61 g.). Evaporation of the ether solution left 15.52 g. of viscous brown oil, which was triturated with a little high petroleum ether and placed in the refrigerator. Crystallization took place slowly. When the partially crystalline material was dissolved in 25 ml. of hot benzene and cooled briefly, more 4-quinazolone (0.39 g.) separated. The filtrate was concentrated to small volume and the residue was dissolved in hot benzene-petroleum ether mixture. The solvent was decanted from the viscous oil that separated upon preliminary cooling, and upon further cooling, light yellow prisms were deposited. Repetition of this process several times finally yielded 4.32 g. of colorless hexagonal prisms, m.p. 91.5–93°.

Anal. Calc'd for $C_{18}H_{25}N_3O$: C, 72.20; H, 8.42; N, 14.03; mol. wt., 299.
Found: C, 72.03; H, 8.30; N, 14.14; mol. wt. (Rast), 308.

In subsequent experiments it was found that the crystalline product could be isolated more conveniently if the unchanged 4-quinazolone was removed from the reaction mixture by extraction with alkali. Several grams of very viscous material remained after the isolation of the crystalline compound. This material resisted purification by recrystallization or distillation, and also resisted hydrolysis by refluxing with 20% hydrochloric acid.

The pure compound $C_{18}H_{25}N_3O$ was likewise resistant to hydrochloric acid hydrolysis. It was unchanged by refluxing with 20% hydrochloric acid or with 10% aqueous-ethanolic sodium hydroxide for two hours. It was readily soluble in alcohol, ether, and benzene, and insoluble in water and petroleum ether. It dissolved quickly in dilute hydrochloric acid, from which it separated upon neutralization with alkali. The hydrochloride could be formed in anhydrous ether solution, but it was very hygroscopic and appeared to lose hydrogen chloride rapidly.

Hydrolysis of $C_{18}H_{25}N_3O$ (IV) with sulfuric acid. A mixture of 8 ml. of 60% sulfuric acid and 1.01 g. of the compound $C_{18}H_{25}N_3O$ (IV) was heated under reflux for sixteen hours. After cooling, 10 ml. of water was added and the mixture was made distinctly alkaline with 20% sodium hydroxide solution (*ca.* 21 ml.). The mixture was distilled into 40 ml. of 10%

hydrochloric acid until about 15 ml. of distillate had been collected. Twenty ml. of water was added to the distilling flask, and 20 ml. more of distillate was collected. This process was repeated. The acid solution containing the distillate was evaporated to dryness. The residue, after drying *in vacuo*, weighed 0.99 g. and melted at 160–220°. After two recrystallizations from ether-ethanol, colorless needles were obtained which melted at 236–240°. This melting point was not depressed by admixture of the product with authentic piperidine hydrochloride. The yield was 0.65 g. or 79% of theoretical assuming the liberation of two moles of piperidine by hydrolysis of $C_{18}H_{25}N_3O$. The residue left after evaporation of the mother liquors consisted of impure aniline hydrochloride, which was converted to the base and thence to acetanilide, identified by melting point and mixed melting point, 114–115°.

In another hydrolytic cleavage of the compound $C_{18}H_{25}N_3O$, 0.5 g. was heated under reflux with 2 ml. of 60% sulfuric acid for four hours. Upon cooling, colorless leaflets separated, which were collected and washed with absolute ethanol and ether. When this substance, apparently the sulfate of anthranilic acid, was dissolved in a small quantity of water and the *p*H of the solution was adjusted to 5.0–5.5, anthranilic acid separated and was identified by melting point and mixed melting point, 143–144°. These hydrolytic products are consistent with the assignment of the structure N-(*o*-1-piperidylformiminobenzoyl)-piperidine to $C_{18}H_{25}N_3O$.

Reaction of $C_{18}H_{25}N_3O$ (IV) with acetic anhydride. One-half gram of the compound $C_{18}H_{25}N_3O$ was heated one-half hour under reflux with 2.5 ml. of acetic anhydride. The excess anhydride was decomposed by the addition of 10 ml. of water to the hot solution. After cooling, the solution was made alkaline and extracted with ether. The residue from the evaporation of the ether solution was recrystallized three times from petroleum ether (b.p. 60–90°). Small colorless prisms were obtained which were identified as N-(2-acetylaminobenzoyl)piperidine by melting point and mixed melting point, 131.5–132.5°.

Infrared absorption spectra. In the infrared absorption spectrum of N-(*o*-aminobenzoyl)-piperidine (III, R_2 = —$CH_2CH_2CH_2CH_2CH_2$—), the N—H stretching frequencies appear at 3437 and 3350 cm.$^{-1}$; the amide C=O stretching frequency, at 1613 cm.$^{-1}$; the characteristic phenyl frequencies, at 1586, 1554, and 1493 cm.$^{-1}$ and at 768 cm.$^{-1}$ in the long wavelength region of *o*-substituted phenyl. Comparison of the spectrum of N-(*o*-1-piperidylformiminobenzoyl)piperidine (IV, R_2 = —$CH_2CH_2CH_2CH_2CH_2$—) with that of III indicates that the proposed structure is probably correct. No absorption appears in the region of N—H or O—H stretching vibrations. The absorption band in the amide C=O region is strong and broad, between 1628 and 1616 cm.$^{-1}$. Since conjugated C=N stretching frequencies also would appear here, it seems likely that both are present. The characteristic phenyl frequencies are very close to those of III: 1587, 1564, 1492 cm.$^{-1}$ and at 757 cm.$^{-1}$ in the long wavelength region.

SUMMARY

In an extension of the study of the reaction of 4-quinazolone with amines, the nature of the products obtained with secondary aliphatic amines shows that initial ring-opening must occur.

URBANA, ILL.

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