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

REACTIONS OF 4-QUINAZOLONE. IV. REPLACEMENTS AT THE 3-POSITION

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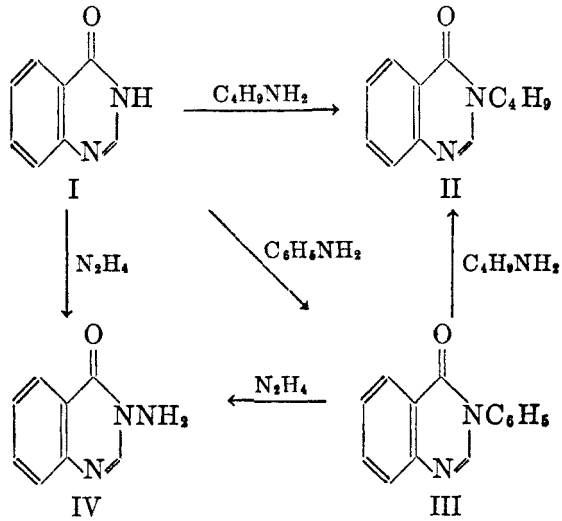
Since 4-quinazolone (I) has been found to react with primary and secondary alkylamines (1, 2), it was of interest to examine the reaction of 4-quinazolone with primary arylamines and other NH_2—functions and to determine the order of replacement of different groups at the 3-position.

The following facts were previously known. The 3-NH of 4-quinazolone could be replaced by NC_4H_9, through treatment of I with butylamine, to give II (1). The replacement of a 3-NH group by NNH_2 was discovered by Kunckell



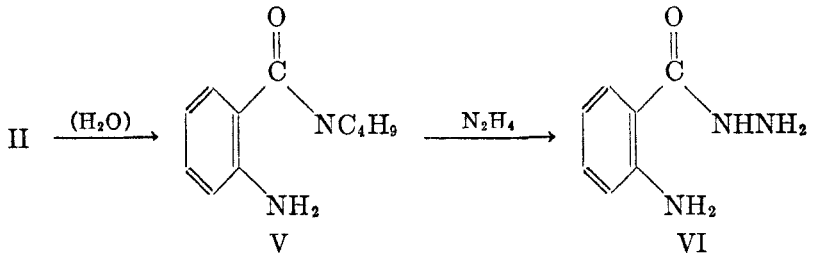
(3). He found that benzoyleneurea and hydrazine hydrate gave 3-amino-2,4-quinazolinedione (4) and that 1-methylbenzoyleneurea and hydrazine hydrate gave 3-amino-1-methyl-2,4-quinazolinedione (5). The replacement of the 3-NC_6H_5 in 3-phenyl-2,4-quinazolinedione by NNH_2 was also realized by Kunckell (5). The same replacement in 3-phenyl-4-quinazolone (III) was effected by Cairncross and Bogert (6), who identified their product, and thus the earlier product of Paal and Busch (7), as 3-amino-4-quinazolone (IV).

The replacement of 3-NC_6H_5 by NNH_2 (conversion of III to IV) has been repeated in order to show that a short period at the reflux temperature is just as effective (eighty-nine per cent yield) as lengthy heating in a sealed tube. The replacement of 3-NH by NC_6H_5 (conversion of I to III) has been shown to proceed to forty per cent yield. 3-Phenyl-4-quinazolone (III)[1] had been prepared

[1] Compound III was found to be about equal to aspirin in lowering the temperatures of febrile rats. We are grateful to Dr. K. K. Chen of the Lilly Research Laboratories for pharmacological testing.

previously by unequivocal methods (6, 8). The replacement of 3-NH by NNH_2 (conversion of I to IV) was effected readily when I was heated under reflux for thirty minutes with hydrazine hydrate, to give a seventy-five per cent yield of 3-amino-4-quinazolone (IV). The product had been synthesized previously by Thode (9). Finally, the replacement of 3-NC_6H_5 by NC_4H_9 (conversion of III to II) was effected when III was heated in a sealed tube with butylamine, to give a thirty-six per cent yield of 3-butyl-4-quinazolone (II). These interconversions were the only ones which could be realized within the group of 4-quinazolones I, II, III, and IV. Only the reactions indicated in the diagram could be forced to take place to any determinable degree. Since reversal of these replacements at the 3-position did not proceed (see Table I), the reaction between 4-quinazolones and amines appears not to be a simple equilibrium system.

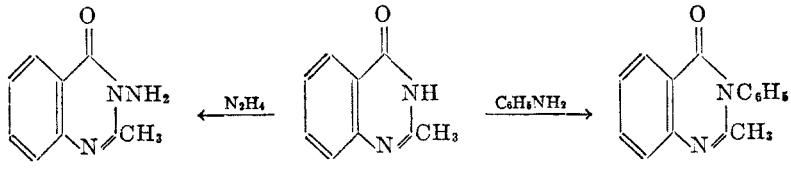
It has been established in these experiments that the order of replacement at the 3-position of 4-quinazolone is: NH, NC_6H_5, $\begin{Bmatrix} NNH_2 \\ NC_4H_9 \end{Bmatrix}$, wherein each group can replace the one (or two) preceding. The position of NNH_2 and NC_4H_9 with respect to each other is undecided. Hydrazine displaces ammonia and aniline from the quinazolones much more readily than does butylamine. Moreover, although butylamine gave no reaction with 3-amino-4-quinazolone, hydrazine hydrate in lengthy refluxing with 3-butyl-4-quinazolone (II) gave anthranilhydrazide (VI) and a small amount of N-(2-aminobenzoyl)butylamine (V).



V VI

In accounting for the formation of the hydrazide VI, the presence of a small amount of the amide V suggests that the displacement of butylamine occurred at this stage rather than in an initial reaction of hydrazine with 3-butyl-4-quinazolone.

In a series of reactions of amine functions with 2-methyl-4-quinazolone (VII), hydrazine was again found to be the most efficient in replacing the 3-NH group. The product was 3-amino-2-methyl-4-quinazolone (VIII).

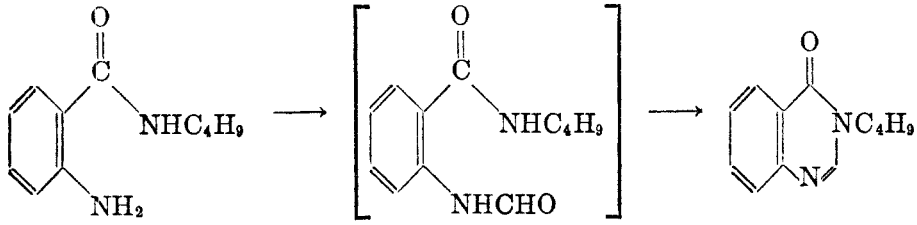


VIII VII IX

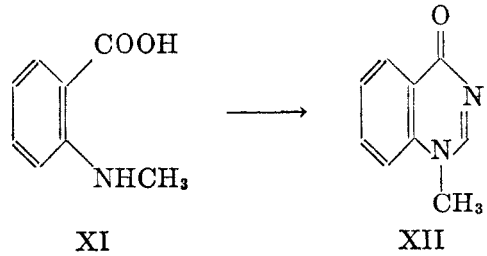
Aniline caused replacement of the 3-NH by NC_6H_5 to give 2-methyl-3-phenyl-4-quinazolone (IX), but butylamine caused no replacement of the 3-NH by NC_4H_9 under the conditions employed. The reaction of VII with piperidine, which would be expected to yield a more stable ring-opened intermediate than the reaction of I with piperidine (2), could not be forced to take place.

The unique effectiveness of hydrazine, in displacing ammonia from 4-quinazolone and 2-methyl-4-quinazolone and aniline from 3-phenyl-4-quinazolone, 3-phenyl-2,4-quinazolinedione, benzoyleneurea, and 1-methylbenzoyleneurea, probably lies in the preferential splitting out of ammonia or the amine after the hydrazine has added to the 4-carbonyl group. Analogous preferential splitting out of water occurs after the addition of hydrazine to carbonyl groups in the facile formation of hydrazones and azines.

It was found possible to make 3-butyl-4-quinazolone (II), which had been synthesized previously (1, 10) and which was used in the replacement studies, by a Niementowski reaction (11) from N-(2-aminobenzoyl)butylamine (V) and formamide. The conversion of V to II probably proceeds through N-(2-formylaminobenzoyl)butylamine (X), formed by the action of formamide as aquoammonoformic acid. Such a course for this reaction is consistent with the mechanism of the Niementowski ring-closure as established by Meyer and Wagner (12).



The Niementowski reaction was also shown to be applicable to the formation of a 1-alkyl-4-quinazolone from the corresponding N-alkylanthranilic acid. When N-methylanthranilic acid (XI) was heated with formamide under conditions which suffice for quinazolone formation in the usual Niementowski ring-closure (125°, four hours), most of the N-methylanthranilic acid was recovered unchanged. The reaction product, isolated in very small yield, was shown to be the N-methylanthranilic acid salt of 1-methyl-4-quinazolone.



By increasing the time of heating the reactants to eighteen hours, 1-methyl-4-quinazolone (XII), m.p. 136–137°, could be obtained in thirty per cent yield.

This compound had been prepared by Knape (13), from other reactants, in an amount insufficient for analysis and of a doubtful degree of purity, since he reported a lower melting point (123–124°).[2] Our product (XII) was further characterized by the formation of the hydrochloride and picrate.

EXPERIMENTAL[3]

The results of heating 4-quinazolones with various amine functions are assembled in Table I. Wherever the absence of a product is indicated, the only isolable substance was the starting material. Although the conditions of each reaction are included in Table I, it is also necessary to describe representative procedures in some detail because of the differing isolation problems encountered.

Reactions of 4-quinazolones with n-butylamine. The reaction of *4-quinazolone* with *n*-butylamine has been reported previously (1).

A mixture of 4.0 g. (0.018 mole) of *3-phenyl-4-quinazolone* and 11.1 g. (0.15 mole) of *n*-butylamine was heated in a sealed tube at 150° for twenty-four hours. There was no excess pressure in the tube when it was opened. The reaction mixture, which was a pale yellow liquid, was distilled at ordinary pressure until most of the *n*-butylamine had been removed. A second fraction distilled at 75–77° (15 mm.), 60–61° (6 mm.). This fraction weighed 0.60 g. (36%), and was identified as aniline by conversion to acetanilide. The residue from the distillation, which was a viscous oil, was extracted repeatedly with 10-ml. portions of boiling petroleum ether, (b.p. 40–60°). After several such extractions, the insoluble material solidified. Three recrystallizations of this solid from benzene-petroleum ether yielded 0.38 g. (10%) of *anthranilanilide*, m.p. 130–131°.

Anal. Calc'd for $C_{13}H_{12}N_2O$: C, 73.56; H, 5.70.
Found: C, 73.57; H, 5.84.

From the petroleum ether extracts, 1.33 g. (36%) of *3-butyl-4-quinazolone*, m.p. 71–72°, was obtained by fractional crystallization from petroleum ether. Approximately 1.5 g. of viscous oil was also obtained which could not be made to crystallize.

When *3-amino-4-quinazolone* and *2-methyl-4-quinazolone* were heated with *n*-butylamine under similar conditions, 96% and 92%, respectively, of the quinazolones were recovered unchanged. No other products were isolated.

Reactions of 4-quinazolones with aniline. A mixture of 5.0 g. (0.034 mole) of *4-quinazolone* and 9.5 g. (0.1 mole) of aniline was heated under reflux for twenty-four hours in an oil-bath maintained at 200–210°. Evolution of ammonia was observed. The crude mixture was worked up as with the earlier 4-quinazolone-amine reactions through the benzene extraction procedure (2). The combined benzene extracts were boiled five minutes with activated charcoal. The charcoal was removed and the benzene was distilled under reduced pressure. The residue was recrystallized from ether, then from ethanol, as colorless platelets, m.p. 136.5–137.5°. Clark and Wagner (8) reported the melting point 136–136.5° for *3-phenyl-4-quinazolone*.

The reaction of *3-butyl-4-quinazolone* with aniline was carried out in a similar manner. After removal of the aniline by distillation, a dark brown semi-solid mixture remained which was treated with activated charcoal and recrystallized from benzene-petroleum ether to give 67% recovery of 3-butyl-4-quinazolone as the only isolable compound.

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[2] Knape (13) reported the melting point 70–71° for 3-methyl-4-quinazolone. Bogert and Geiger (14) later showed that this material was actually the hydrate of 3-methyl-4-quinazolone, and that the anhydrous substance melted at 105°. Our tardy recognition of the corrective work of Bogert and Geiger allows us now to assign the 3-methyl-4-quinazolone structure to the "unknown" isomer, m.p. 103.5–105.5° obtained by Leonard and Curtin (1) along with 4-methoxyquinazolone in the treatment of 4-quinazolone with diazomethane.

[3] All melting points are corrected. Microanalyses by Miss Theta Spoor.

Similarly, from the reaction of *3-amino-4-quinazolone* with aniline, 57% of the starting material was isolated, but no other product.

When the reaction of *2-methyl-4-quinazolone* with aniline was carried out under similar conditions, *2-methyl-3-phenyl-4-quinazolone* was obtained and was identified by melting point and mixed melting point (145–146°) with the compound prepared by an unequivocal method (17).

Reactions of 4-quinazolones with hydrazine hydrate. A mixture of 20 g. (0.136 mole) of *4-quinazolone* and 55 g. of hydrazine hydrate (85% in water) was heated under reflux. The

TABLE I

REACTIONS OF AMINES WITH 4-QUINAZOLONES

AMINE	SUBSTITUTED 4-QUINAZOLONE	CONDITIONS*	PRODUCT	YIELD, %†	RECOVERY OF QUINAZOLONE, %
$C_4H_9NH_2$	4-Quinazolone	S, 150°, 24 hrs.	3-Butyl-4-quinazolone	36	?
$C_4H_9NH_2$	3-Phenyl-	S, 150°, 24 hrs.	3-Butyl-4-quinazolone	36 (36)	—
			Anthranilanilide	10	—
$C_4H_9NH_2$	3-Amino-	S, 150°, 24 hrs.	—	—	96
$C_4H_9NH_2$	2-Methyl-	S, 150°, 24 hrs.	—	—	92
$C_6H_5NH_2$	4-Quinazolone	R, 200°, 24 hrs.	3-Phenyl-4-quinazolone	26 (40)	34
$C_6H_5NH_2$	3-Butyl-	R, 200°, 24 hrs.	—	—	67
$C_6H_5NH_2$	3-Amino-	R, 200°, 24 hrs.	—	—	57
$C_6H_5NH_2$	2-Methyl-	R, 200°, 24 hrs.	2-Methyl-3-phenyl-4-quinazolone	17 (40)	58
$N_2H_4 \cdot H_2O$	4-Quinazolone	R, 120°, 0.5 hr.	3-Amino-4-quinazolone	75 (75)	—
$N_2H_4 \cdot H_2O$	3-Butyl-	R, 120°, 2 hrs.	—	—	95
		R, 120°, 24 hrs.	Anthranilhydrazide	37	—
			N-(2-Aminobenzoyl)butylamine	5	—
$N_2H_4 \cdot H_2O$	3-Phenyl-	R, 120°, 0.25 hr.	3-Amino-4-quinazolone	89 (89)	—
$N_2H_4 \cdot H_2O$	2-Methyl-	R, 120°, 2.5 hrs.	3-Amino-2-methyl-4-quinazolone	29 (39)	24
$C_5H_{10}NH$	2-Methyl-	S, 175°, 24 hrs.	—	—	91
α-C_5H_4N-NH_2	4-Quinazolone	S, 155°, 24 hrs.	—	—	68
α-$C_{10}H_7NH_2$	4-Quinazolone	S, 200°, 16 hrs.	—	—	56

* S = Sealed tube, R = reflux.

† Figure in parentheses is the yield based upon unrecovered starting quinazolone.

4-quinazolone dissolved quickly and after ten minutes white needles began to separate from the mixture, which soon became almost solid. The mixture was filtered and the filtrate was heated under reflux for twenty minutes. More of the product separated on cooling. The combined weight of the two crops was 16.2 g. (75%), m.p. 205–208°. Recrystallization from 95% ethanol gave glistening colorless needles of *3-amino-4-quinazolone*, m.p. 209–210° [reported by Cairncross and Bogert (6), 211°]. When this material was heated with benzaldehyde and the product was recrystallized from ethanol, shining colorless leaflets of 3-benzalamino-4-quinazolone, m.p. 127–128° were obtained [reported by Thode (9), 129°].

In the attempted reaction of 3-butyl-4-quinazolone with hydrazine hydrate under similar conditions (two hours under reflux) a 95% recovery of starting material was realized. However, when the reaction mixture was heated under reflux for twenty-four hours, *N-(2-aminobenzoyl)butylamine*, m.p. 85–86° (5% yield) and *anthranilhydrazide*, m.p. 121–122° (37% yield) were obtained.

A mixture of 1 g. of *3-phenyl-4-quinazolone* and 3 g. of hydrazine hydrate was heated under reflux for fifteen minutes. The crystals which separated were removed by filtration, washed with water, recrystallized from ethanol, and identified as *3-amino-4-quinazolone*, m.p. 209–210°. The presence of aniline in the aqueous ethanol filtrates was established by the formation of acetanilide.

When 1 g. of *2-methyl-4-quinazolone* was heated under reflux with 3 g. of hydrazine hydrate (85% in water) the 2-methyl-4-quinazolone dissolved slowly. After the mixture had been heated for two and one-half hours, it was cooled. Colorless needles separated which, after recrystallization, first from benzene then from ethanol, melted at 147–148° [reported for *3-amino-2-methyl-4-quinazolone* by Bogert and Gortner (15), 152°]; yield, 0.32 g. (39% based on unrecovered 2-methyl-4-quinazolone). The product was heated with benzaldehyde to obtain 3-benzalamino-2-methyl-4-quinazolone, m.p. 184–186° [reported by Bogert, Beal, and Amend (16), 187°].

N-(2-Nitrobenzoyl)butylamine. This compound, which apparently has not been previously prepared, was obtained by the same method as that used for N-(2-nitrobenzoyl)-piperidine (2). The yield from 50 g. (0.3 mole) of 2-nitrobenzoic acid was 48 g. (73%) of colorless prisms, m.p. 55–57°.

Anal. Calc'd for $C_{11}H_{14}N_2O_3$: C, 59.44; H, 6.40; N, 12.61.
Found: C, 59.56; H, 6.10; N, 12.41.

Satisfactory identification was established in the reduction of the nitro compound to the known amino compound.

N-(2-Aminobenzoyl)butylamine. This compound has been prepared previously but by a different method (8). N-(2-Nitrobenzoyl)butylamine (44.2 g., 0.2 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 hydrogen was absorbed rapidly and it was necessary to interrupt the shaking intermittently in order to prevent overheating. The catalyst and the solvent were removed and the residue was digested on a steam-bath for a few minutes with 100 ml. of low-boiling petroleum ether. The mixture was cooled and the voluminous mass of pink crystals was collected. The material retained on the filter was of a waxy nature and was very difficult to free from solvent. The yield of product, m.p. 84–86°, was 34.5 g. (90%). The pink color of the material was persistent and was not removed by recrystallization and attempted charcoal decolorization from either dilute ethanol or high-boiling petroleum ether. A colorless product was obtained by dissolving the material in dilute hydrochloric acid, treating with charcoal, filtering, and reprecipitating by the addition of aqueous sodium hydroxide. Recrystallization of the colorless material from high-boiling petroleum ether gave a pure product, m.p. 85–86°.

Reaction of N-(2-aminobenzoyl)butylamine with formamide. 3-Butyl-4-quinazolone. N-(2-Aminobenzoyl)butylamine (5 g., 0.026 mole) and formamide (3 g., 0.067 mole) were heated together for six hours in a large test-tube suspended in an oil-bath at 170°. Ammonia was evolved during this reaction period. Upon the addition of 20 ml. of water and 3–4 drops of ammonium hydroxide to the cooled mixture, a crystalline solid was obtained. The yield of crude product was 4.6 g. (88%). After two recrystallizations from 50% aqueous ethanol, the melting point was 72–73°. Bogert and May (10) reported the melting point 71–72° for 3-butyl-4-quinazolone. There was no depression of melting point when this product was mixed with an authentic sample of 3-butyl-4-quinazolone (1).

Reaction of N-methylanthranilic acid with formamide. 1-Methyl-4-quinazolone. A mixture of 10 g. (0.066 mole) of N-methylanthranilic acid and 6.25 g. (0.14 mole) of formamide was heated under an air condenser at 130° for eighteen hours. The reaction mixture was subjected to vacuum distillation (bath temp. 145°, 7 mm.) to remove excess formamide.

The residual oil partially crystallized on standing two days in the refrigerator. The mixture was triturated with 10 ml. of cold benzene and was filtered. The greyish gummy crystals were dissolved in a boiling mixture of 20 ml. of benzene and 5 ml. of ethanol. After cooling slightly, 15 ml. of petroleum ether (b.p. 40–60°) was added. The solvent layer was decanted from the oil which first separated, and was cooled slowly. The colorless needles which formed were recrystallized from benzene-ether; m.p. 132–135°. A final recrystallization from benzene gave 0.86 g. (8%) of colorless elongated prisms, m.p. 136–137°.

Anal. Calc'd for $C_9H_8N_2O$: C, 67.48; H, 5.03; N, 17.49.
Found: C, 67.31; H, 4.98; N, 17.62.

This compound was very deliquescent. It was soluble in water and ethanol and only slightly soluble in benzene, ether, and petroleum ether. It formed a *picrate* from ethanol solution as fine yellow needles, m.p. 246–247° (dec.).

Anal. Calc'd for $C_{15}H_{11}N_5O_8$: C, 46.28; H, 2.85.
Found: C, 46.28; H, 2.76.

The *hydrochloride* was prepared by treating the compound with concentrated hydrochloric acid, from which the salt separated as rectangular prisms. These were recrystallized from 95% ethanol; m.p. 245–246°.

Anal. Calc'd for $C_9H_9ClN_2O$: C, 54.97; H, 4.61.
Found: C, 54.82; H, 4.89.

Since it was impractical to isolate more of the pure 1-methyl-4-quinazolone from the mother liquors, these were converted—one portion to the hydrochloride (1.54 g., 12%), and the other to the picrate (2.68 g., 10%). The total yield of 1-methyl-4-quinazolone, its hydrochloride, and picrate was thus 30%.

In another experiment, 5 g. of N-methylanthranilic acid and 3 g. of formamide were heated at 125° for four hours. When the reaction mixture was cooled, greyish crystals formed, which were recrystallized from ethanol and then from benzene, m.p. 135–136°; yield, 0.72 g.

Anal. Calc'd for $C_{17}H_{17}N_3O_3$: C, 65.58; H, 5. 51; N, 13.50.
Found: C, 65.74; H, 5.71; N, 13.56.

The nature of the compound was indicated by the fact that a mixture of equimolar portions of N-methylanthranilic acid and 1-methyl-4-quinazolone started to melt below 100° but resolidified and melted completely at 134–135°. When the melt was recrystallized from benzene, its appearance and melting point were identical with those of the reaction product, m.p. 135–136°, and the melting point was not depressed by admixture of the two samples.

SUMMARY

1. It has been established that the order of replacement at the 3-position of 4-quinazolone is: NH, NC_6H_5, $\begin{Bmatrix} NNH_2 \\ NC_4H_9 \end{Bmatrix}$, wherein each group can replace the one (or two) preceding.

2. It has been shown that hydrazine can readily replace the 3-NH or 3-NC_6H_5 group in 4-quinazolone, 3-phenyl-4-quinazolone, and 2-methyl-4-quinazolone by NNH_2.

3. The Niementowski reaction has been extended to the synthesis of representative 1-alkyl- and 3-alkyl-4-quinazolones.

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