[Contribution from the Lederle Laboratories Division, American Cyanamid Co.]

# AN ANTIMALARIAL ALKALOID FROM HYDRANGEA. IV. FUNCTIONAL DERIVATIVES OF 3-ALKYL-4-QUINAZOLONES

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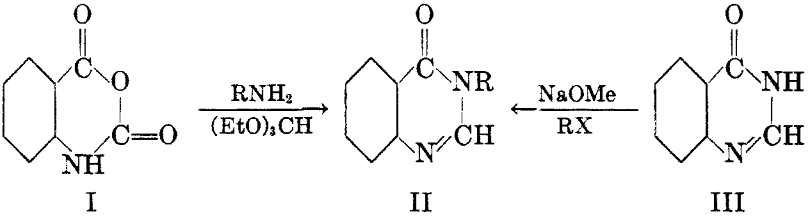
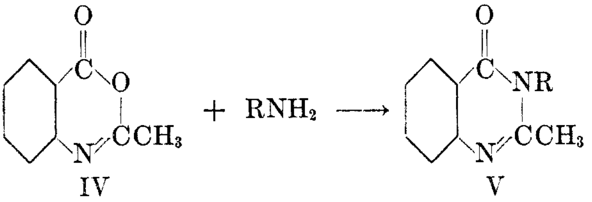
Early degradation experiments on the Hydrangea alkaloid (1) indicated that this molecule was a derivative of 4-quinazolone with a side chain on the 3-position containing one basic nitrogen and two oxygens. With this limited information on hand a number of 3-alkyl-4-quinazolones with functional groups in the side chain were synthesized in order to obtain (a) suitable models for degradation experiments (1), (b) compounds to be tested for antimalarial activity,[1] and (c) information on the synthesis and transformations of these functional groups.[2]

There are a number of methods described in the literature for the synthesis of molecules of this type, three of which were employed. Clark and Wagner (7) have heated primary aromatic amines with isatoic anhydride (I) and ethyl orthoformate to form 3-aryl-4-quinazolones (II). This procedure has now been found to work satisfactorily with primary aliphatic amines also, providing the amine is on a primary carbon. The alkylation of alkali metal salts of 4-quinazolone (III) with an alkyl halide or tosylate has been employed frequently (8). This method is also limited to the introduction of a primary alkyl group, which will be discussed later.





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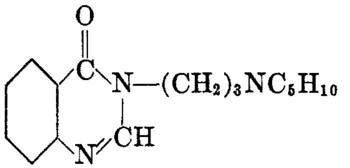
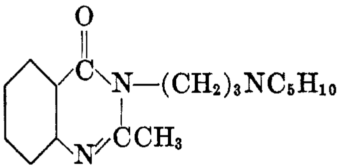
[1] The biological data will be published elsewhere.

[2] Although a large number of 3-alkyl-4-quinazolones have been reported in the literature, only a few with functional groups in the side chain have been described, namely, 3-allyl-4-quinazolone (2); 4-quinazolone-3-acetic acid, its methyl ester, and methylamide (3); the alkaloid Rutaecarpine (4); 3-benzamidomethyl-4-quinazolone and its 2-methyl derivative (5, 11); and 2-methyl-3-(5-diethylamino-2-pentyl)-7,8-dimethoxy-4-quinazolone (6).

For preparation of a 2-methyl-3-alkyl-4-quinazolone (V) the reaction of acetanthranil (IV) with a primary amine was employed (9, 13). This reaction proceeds satisfactorily when the primary amine is on either a primary or secondary carbon, such as Noval amine (6), but fails when the amine is on a tertiary carbon such as 2-methyl-2-amino-1,3-propanediol.

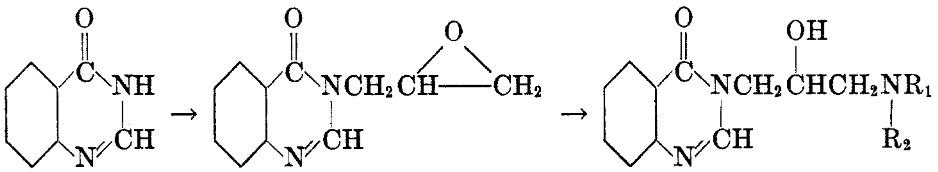
In order to establish whether or not the alkaloid was a 4-quinazolone substituted in the 2-position as well as the 3-position, the two model compounds,


VI


VII

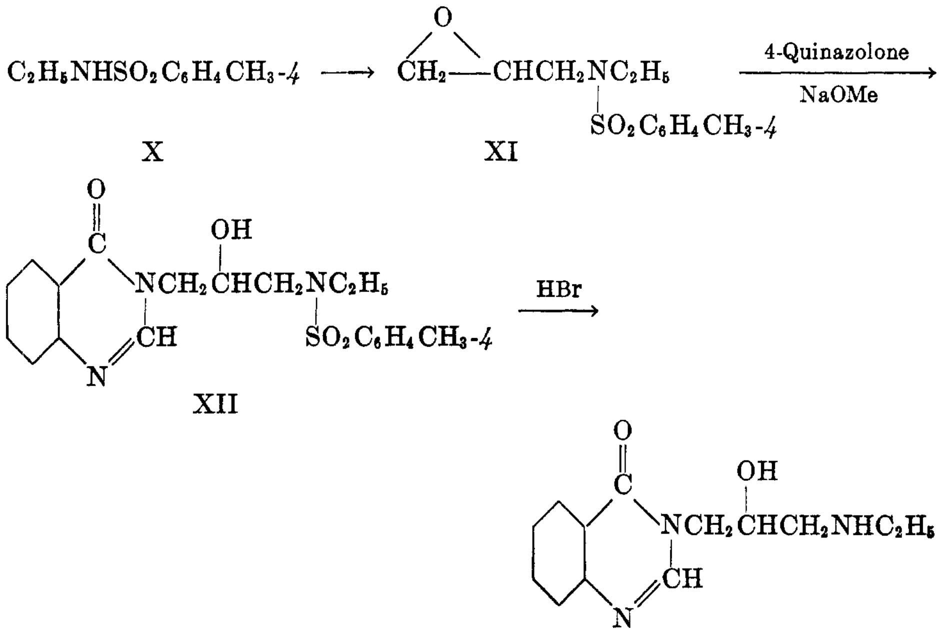
VI and VII, were prepared *via* the isatoic anhydride and acetanthranil methods, respectively, by reaction with γ-piperidinopropyl amine. Comparison of the u.v. spectra of these two compounds in 0.1 *N* sodium hydroxide revealed that the 3-(γ-piperidinopropyl)-4-quinazolone (VI) had essentially the same spectrum as the alkaloid with peaks at 265, 273, 302, and 313 mμ. On the other hand the corresponding 2-methyl derivative (VII) had peaks at 265, 273, 305, and 317 mμ, the latter two having been shifted.

A series of 3-*tert*-aminoalkyl derivatives related to VI and VII was prepared by these two methods by use of the appropriate amine. The isatoic anhydride method was also applicable to amino alcohols such as β-hydroxy-γ-piperidinopropyl amine for preparation of compounds of type IX. However, it was found more convenient to prepare these compounds by amine opening of the oxide


III VIII IX

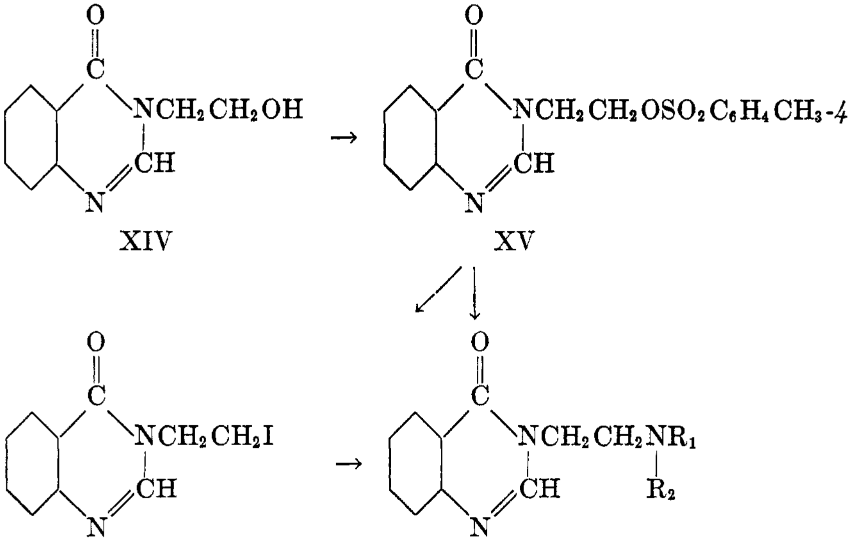
ring of 3-(β,γ-epoxypropyl)-4-quinazolone (VIII), obtainable from 4-quinazolone (III) and epichlorohydrin. When piperidine was employed to open the oxide ring, the product (IX) was identical with that obtained by the isatoic anhydride method, thus showing that the 4-quinazolone nucleus does not in this case influence the normal mode of opening (10). Primary (both aliphatic and aromatic) as well as secondary amines could be employed to give secondary or tertiary amino substituted side chains in IX, in contrast to the isatoic anhydride method which was unsuccessful with a primary-secondary diamine. The generality of this method was shown by the use of 2-methyl- or 6-chloro-4-quinazolone.

A somewhat similar method was also devised for the preparation of a β-hydroxy-γ-secondary-aminopropyl side chain. Treatment of N-ethyl-*p*-toluenesulfonamide (X) with excess epichlorohydrin in the presence of sodium methoxide gave a crude oxide, XI, which was condensed with 4-quinazolone in basic solution. The resultant product, XII, was hydrolyzed with difficulty with hydrobromic acid or 60% sulfuric acid to the desired amine, XIII.



X XI XII XIII

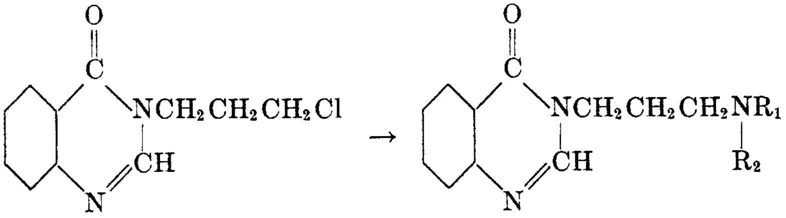
Since the isatoic anhydride method could not be employed for the preparation of a 3-alkyl-4-quinazolone containing a secondary amine on the side chain,



XIV XV XVI XVII

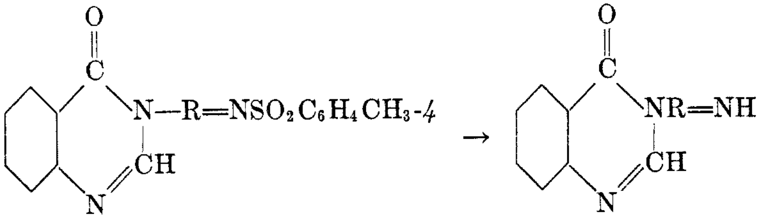
an indirect method was developed that was satisfactory for both alkylamino and arylamino side chains. 3-(β-Hydroxyethyl)-4-quinazolone (XIV) was readily obtained from ethanolamine by the isatoic anhydride-ethyl orthoformate procedure. Tosylation to XV followed by reaction with a primary or secondary amine gave the substituted amines, XVII. These amines could also be prepared by preliminary conversion to the iodoethyl derivative, XVI, with sodium odide, then reaction with the appropriate alkyl or aryl amine.

Similarly, γ-aminoalkyl side chains were synthesized by reacting 3-(γ-chloropropyl)-4-quinazolone (XVIIb) (obtained from 4-quinazolone and trimethylene chlorobromide) with primary or secondary amines. A 2-methyl or 6-chloro group on the 4-quinazolone did not change the course of the reaction.

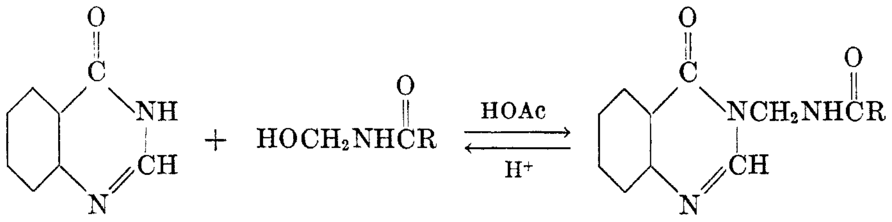

XVIIb XVIII

The last method, of course, was not applicable for synthesis of a 2- or 4-piperidylalkyl side chain. By tosylation of the proper amino alcohol, XIX, both the O and N groups were covered. The tosyl ester group of XX condensed with sodio 4-quinazolone to give XXI. The sulfonamide linkage was hydrolyzed with hydrobromic acid with difficulty with formation of XXII. The method was worked out with the commercially available ethylaminoethanol and successfully applied to 4-(γ-hydroxypropyl)piperidine. Although crystalline XX could be prepared from 2-(β-hydroxyethyl)piperidine, its condensation with 4-quinazolone failed. The reaction succeeded with 1-benzoyl-2-(β-chloroethyl)piperidine in poor yield.

$$\underset{\text{XIX}}{HOR{=}NH} \rightarrow \underset{\text{XX}}{4\text{-}CH_3C_6H_4SO_3{-}R{=}NSO_2C_6H_4CH_3\text{-}4} \rightarrow$$


XXI XXII

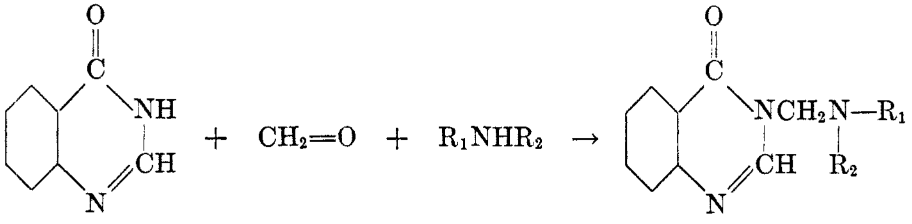
Since the alkaloid is stable to hot acid, but evolves ammonia with alkali (1), the 3-alkylaminomethyl side chain was investigated. The only compound of this type described in the literature (5) is 3-benzamidomethyl-4-quinazolone (XXIII, R = $C_6H_5$), prepared by condensation of methylolbenzamide with 4-



III XXIII

quinazolone. These authors claimed that acid hydrolysis gave 3-aminomethyl-4-quinazolone dihydrochloride. The condensation with methylolbenzamide has been repeated and also has been run with methylolchloroacetamide, the latter giving the typical u.v. spectrum of a 3-alkyl-4-quinazolone. However, acid hydrolysis in both cases did not lead to 3-aminomethyl-4-quinazolone, but caused a split to 4-quinazolone hydrochloride, m.p. 244°, identified by u.v. and mixed m.p.

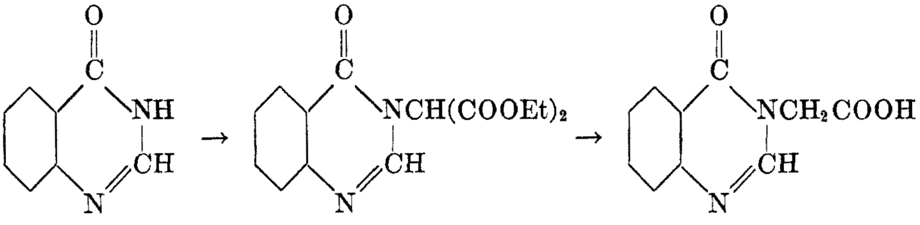
Monti and Simonetti (5) have described the Mannich reaction between 2-methyl-4-quinazolone, formaldehyde, and several amine hydrochlorides, the products being isolated as hydrochloride salts. Use of their procedure with 4-quinazolone gave 4-quinazolone hydrochloride as the only identifiable product.



III XXIV

The reaction did proceed, however, when the amine free base (piperidine or morpholine) was used in aqueous solution. The crystalline free bases (XXIV) separated on cooling. When either free base (XXIV) was treated with cold alcoholic hydrogen chloride, 4-quinazolone hydrochloride immediately separated, the reaction having reversed. That the free bases (XXIV) were actually 3-alkyl-4-quinazolones was shown by their typical u.v. spectra. It is doubtful that Monti and co-workers actually obtained a Mannich base. In view of the instability of this N—C—N linkage to acid, this possibility for the alkaloid was eliminated.

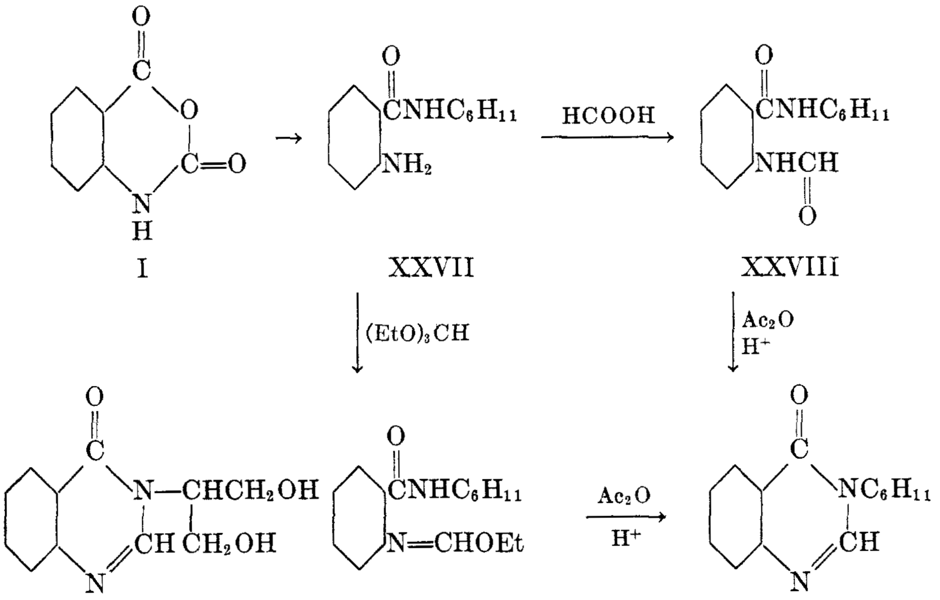
Oxidation of the alkaloid as well as of a number of appropriately substituted models led to 4-quinazolone-3-acetic acid (XXVI) (1). This posed the question as to whether or not 4-quinazolone-3-malonic acid could be a precursor as the result of branching on the $\alpha$-carbon of the side chain and whether this formed 4-quinazolone-3-acetic acid (XXVI) by decarboxylation. By fusion of dry sodio 4-quinazolone with ethyl bromomalonate the substituted malonic ester, XXV, was obtained. Its structure was demonstrated by acid hydrolysis to the known 4-quinazolone-3-acetic acid (XXVI) (3) in near quantitative yield. All attempts



III XXV XXVI

to prepare 4-quinazolone-3-malonic acid by alkaline hydrolysis led to the acetic acid, XXVI.

Since the malonic acid could not be obtained for oxidation studies, an appropriately substituted side chain which would lead to a malonic acid on oxidation was sought, such as XXXI. A search of the literature revealed that not even a simple α-branched 3-alkyl-4-quinazolone such as isopropyl or cyclohexyl had been synthesized. Attempted alkylation of 4-quinazolone (III) in the presence of methanolic sodium methoxide with isopropyl iodide, cyclohexyl bromide, or cyclohexyl tosylate led to propene or cyclohexene and the 4-quinazolone was recovered unchanged. Application of the isatoic anhydride-ethyl orthoformate procedure to cyclohexylamine did not give rise to the expected 3-cyclohexyl-4-quinazolone (XXX). The stepwise synthesis of XXX was then investigated to



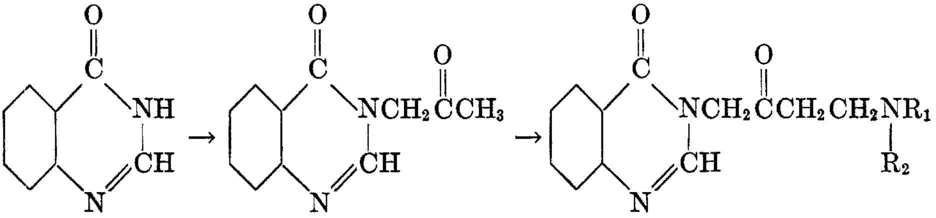
I XXVII XXVIII

XXXI XXIX XXX

determine which step might be sterically hindered. *o*-Amino-N-cyclohexylbenzamide (XXVII), prepared from isatoic anhydride and cyclohexylamine (7), was heated at 125° with ethyl orthoformate in the usual manner for making a 3-alkyl-4-quinazolone. The product formed appeared to be the intermediate ethoxymethyleneamine (XXIX) which had not cyclized. With boiling formic acid (90 or 99%) the substituted anthranilamide (XXVII) gave the intermediate formylamide, XXVIII, again ring closure not taking place. This contrasts with benzylamine which gave 3-benzyl-4-quinazolone directly by either procedure. The intermediate derivatives, XXVIII and XXIX, could be cyclized to 3-cyclohexyl-4-quinazolone (XXX) with boiling acetic anhydride, preferably with a catalytic amount of 85% phosphoric acid added. The formyl derivative (XXVIII) could also be cyclized by heating (2) to 225°, the minimum temperature at which reaction would take place, in less than 5% yield.

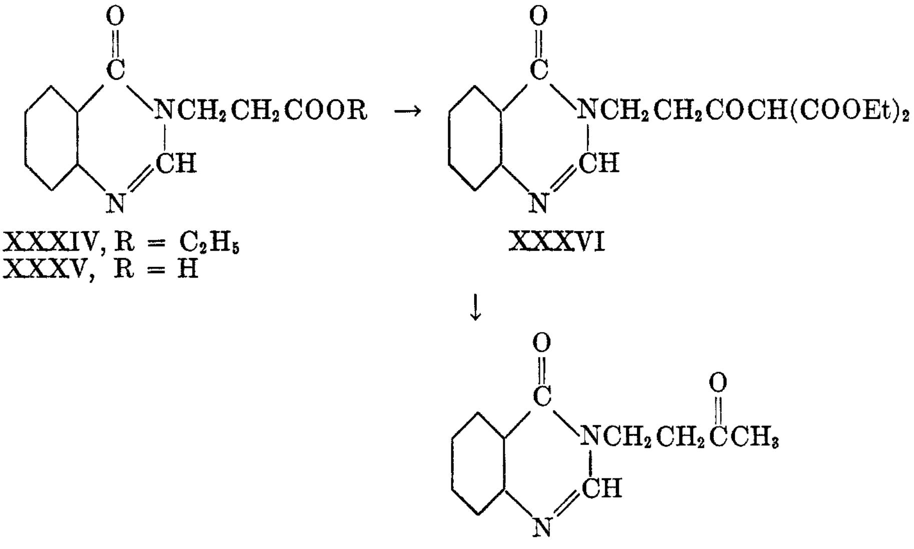
This series of reactions was then applied to 2-amino-1,3-propanediol without isolation of any intermediates, giving rise to the desired model compound, XXXI, for oxidation studies.

Treatment of sodio 4-quinazolone with chloroacetone formed 3-acetonyl-4-quinazolone (XXXII). Several attempts to prepare a Mannich base (XXXIII)



III XXXII XXXIII

were unpromising, but the reaction has not yet been extensively investigated Subsequently this ketone, XXXII, was found to be a pyrolysis product of the alkaloid (1). In view of the additional fact that the alkaloid evolved ammonia in alkaline solution, it seemed possible that 3-acetonyl-4-quinazolone (XXXII)



XXXIV, R = $C_2H_5$
XXXV, R = H

XXXVI

XXXVII

might evolve ammonia in some anomalous fashion on heating with dilute alkali. This was indeed found to be the case, indicating that the alkaloid had a ketone group on the β-position of the side chain. This observation was checked quantitatively (1).

As a further check 3-(γ-ketobutyl)-4-quinazolone (XXXVII) was synthesized and heated with alkali. Although this structure seemed a more plausible one to evolve ammonia, actually it was cleaved to 4-quinazolone and methyl vinyl ketone.

Attempted condensation of sodio 4-quinazolone with methyl β-bromopropionate led to methyl acrylate, and unchanged 4-quinazolone. However, the isatoic anhydride-ethyl orthoformate procedure with methyl β-alanate gave XXXIV which was acid hydrolyzed to the acid, XXXV. Condensation of the acid chloride of XXXV with magnesiomalonic ester and hydrolysis of the resultant keto malonate (XXXVI) gave the desired γ-ketone, XXXVII.

*Acknowledgement.* The authors are indebted to the late Dr. Y. SubbaRow for his interest in the problem. Thanks are given to Mr. Louis Brancone and his staff for the microanalyses and u.v. spectra.

## EXPERIMENTAL

*3-(γ-Piperidinopropyl-4-quinazolone* (VII) *dihydrochloride.* To 12 g. of isatoic anhydride (7) was added 11 g. of γ-piperidinopropylamine (12) followed by 13.2 cc. of ethyl orthoformate. The mixture was heated on the steam-bath for a few minutes until gas evolution subsided, then it was heated in a bath at 125° for one hour. The oil was crystallized as a dihydrochloride by treatment with 100 cc. of saturated absolute alcoholic hydrogen chloride; yield, 17.4 g. (69%), m.p. 222–225° dec. For analysis a sample was recrystallized from absolute alcohol to give white crystals, m.p. 230–232° dec.

Additional 3-substituted-4-quinazolones prepared in the same manner are listed in the tables under method A.

*2-Methyl-3-(γ-piperidinopropyl)-4-quinazolone dihydrochloride.* To 15.9 g. of γ-piperidinopropylamine (12) was added 17 g. of acetanthranil (13). There was considerable heat of reaction. After being heated in a bath at 125° for 30 minutes, the oil was dissolved in saturated absolute alcoholic hydrogen chloride and the solution diluted with ether to turbidity; yield, 10.2 g. (27%), m.p. 226–228° dec.

Other compounds prepared in a similar manner are listed in the tables under method B.

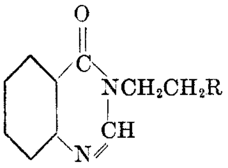
*3-(β,γ-Oxidopropyl)-4-quinazolone* (VIII). (A) A mixture of 1.0 g. of 4-quinazolone (14), 1 cc. of epichlorohydrin, and two drops of pyridine (15) was heated on the steam-bath for 15 minutes. The reaction was somewhat exothermic and the temperature was not allowed to go over 100°. The oil was crystallized from benzene by decanting several times from the gum which separated. The crude 3-(β-hydroxy-γ-chloropropyl)-4-quinazolone (240 mg., m.p. 128–130°), dissolved in 5 cc. of hot absolute alcohol, was treated with 0.1-cc. portions of 10% ethanolic sodium hydroxide until a permanent color was obtained with phenolphthalein (0.5 cc. total). The solution was heated an additional five minutes, then diluted with several volumes of water, saturated with salt, and extracted with chloroform. The combined dried extracts were evaporated and the residue crystallized from heptane; yield, 50 mg. of white crystals, m.p. 82–84°.

*Anal.* Calc'd for $C_{11}H_{10}N_2O_2$: C, 65.3; H, 4.97; N, 13.9.
Found: C, 65.1; H, 5.23; N, 13.8.

(B) To a solution of 2.0 g. of 4-quinazolone in 13.7 cc. of 1 *N* sodium methoxide was added 5 cc. of epichlorohydrin. After three hours the solution was separated from the salt and evaporated *in vacuo*. The residue was dissolved in chloroform, dried with magnesium sulfate, and the solution evaporated. Six extractions of the residue with hot heptane gave 0.57 g. (21%) of product, m.p. 78–80°, identical with preparation A.

TABLE I

FUNCTIONAL DERIVATIVES OF 3-ETHYL-4-QUINAZOLONES



| R | METHOD | M.P., °C. | YIELD, % | ANALYSIS Calc'd C | Calc'd H | Calc'd N | Found C | Found H | Found N |
|---|---|---|---|---|---|---|---|---|---|
| HO—[a, b] | A | 150–152 | 75 | 63.2 | 5.29 | 14.7 | 63.5 | 5.67 | 14.8 |
| Piperidino[c] | A | 220–222 d. | 58 | 54.6 | 6.42 | 12.7 | 54.2 | 6.79 | 12.9 |
| | E[e] | 223–225 d. | 77 | | | | | | |
| | E[f] | 228–230 d. | 87 | | | | | | |
| *n*-Butylamino[g] | E[l] | 100–130 d. | 30 | 50.0 | 6.30 | 12.5 | 50.2 | 6.84 | 12.2 |
| $HOCH_2CH_2NH$—[c] | E[e] | 203–205 d. | 10 | 47.2 | 5.60 | 13.7 | 47.0 | 6.30 | 13.5 |
| $C_6H_{11}NH$—[c] | E[e] | 242–244 d. | 55 | 55.8 | 6.75 | 12.2 | 55.2 | 7.23 | 12.1 |
| | E[f] | 230–232 d. | 66 | | | | | | |
| $HOCH_2C(CH_3)_2NH$—[c] | E[e] | 246 d. | 64 | 50.3 | 6.33 | 12.6 | 50.0 | 6.84 | 12.7 |
| Phthalimido[a] | E[h] | 207–209 | 54 | 67.7 | 4.12 | 13.2 | 68.0 | 4.31 | 13.4 |
| $NH_2$—[c] | [i] | 260 d. | 92 | 45.8 | 5.00 | 16.0 | 46.0 | 5.30 | 16.4 |
| $CH_3C(CH_2OH)_2NH$— | E[e] | [j] | 23 | 46.8 | 6.17 | 11.7 | 46.8 | 6.60 | 11.5 |
| 2-Pyridyl[c] | A | 222–223 d. | 49 | 55.8 | 4.64 | 13.0 | 56.0 | 4.53 | 12.9 |
| $\vert$<br>Tos $NC_2H_5$[k] | D[e] | 207–211 d. | 41 | 55.9 | 5.40 | 10.3 | 55.8 | 5.45 | 10.5 |
| $C_2H_5NH$—[l] | [m] | 220–221 d. | 67 | 46.8 | 6.73 | 13.6 | 47.2 | 6.55 | 14.0 |
| 2-Piperidyl[c] | D | 234–237 d. | 7[n] | 54.6 | 6.38 | 12.7 | 54.1 | 6.63 | 12.4 |

[a] Free base. [b] Crystallized from water. [c] Dihydrochloride crystallized from absolute alcoholic hydrogen chloride. [e] From tosylate. [f] From iodo compound. [g] Dihydrochloride monohydrate. [h] Reaction of the tosylate with potassium phthalimide in propyl alcohol at 100° for 75 minutes. [i] Hydrazine hydrolysis of phthalimido derivative in Methyl Cellosolve. [j] Hemihydrate of dihydrochloride, m.p. 160° (gas), resolidifies and remelts at 210° dec. [k] Monohydrochloride. [l] Dihydrochloride monohydrate. [m] Hydrolysis of preceding N-tosyl derivative by refluxing 1 g. with 10 cc. of 48% hydrobromic acid and 5 cc. of 30% hydrogen bromide in acetic acid for 16 hours. [n] Over-all yield obtained by benzoylation of 2-(β-chloroethyl)piperidine (18), condensation with 4-quinazolone by method D, and hydrolysis with hot 12 *N* HCl.

If a large excess of epichlorohydrin is not employed, considerable quantities of 1,3-bis-(4-quinazolone-3-)propanol-2 are formed as white crystals, m.p. 231–232°, when recrystallized from Methyl Cellosolve.

*Anal.* Calc'd for $C_{19}H_{16}N_4O_3$: C, 65.5; H, 4.65; N, 16.1.
Found: C, 65.7; H, 5.18; N, 15.9.

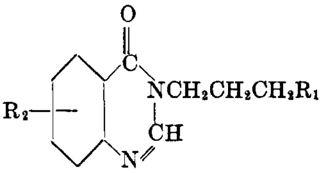
*2-Methyl-3-(β,γ-oxidopropyl)-4-quinazolone.* By fusion of 8 g. of acetanthranil with 4.3 g. of ammonium acetate at 170–180° (bath) for five minutes was obtained 4.7 g. (59%) of recrystallized 2-methyl-4-quinazolone, m.p. 234–236°. The method of Bogert and Botthelf (16) afforded 12% of a product, m.p. 230–232°. Condensation of 2 g. of 2-methyl-4-quinazolone in 13.2 cc. of 1 *N* sodium methoxide with 5 cc. of epichlorohydrin as described for 4-quinazolone gave 0.40 g. (14%) of white crystals, m.p. 90–92°.

*Anal.* Calc'd for $C_{12}H_{12}N_2O_2$: C, 66.7; H, 5.60; N, 13.0.

Found: C, 66.5; H, 6.02; N, 12.8.

TABLE II

FUNCTIONAL DERIVATIVES OF 3-PROPYL-4-QUINAZOLONES



| R₁ | R₂ | METHOD | M.P., °C. | YIELD, % | ANALYSIS | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Calc'd | | | Found | | |
| | | | | | C | H | N | C | H | N |
| Piperidino[a] | 2-Me | B | 226–228 d. | 38[b] | 54.3 | 7.23 | 11.1 | 54.7 | 6.53 | 10.7 |
| Piperidino[c] | H | A | 230–232 d. | 69 | 55.8 | 6.74 | 12.2 | 55.8 | 6.82 | 12.2 |
| Morpholino[d] | H | A | 220–222 d. | 73 | 50.8 | 6.28 | 11.8 | 50.9 | 6.44 | 11.4 |
| HO—[j] | H | A[g] | 162–164 | 37 | 54.9 | 5.44 | 11.6 | 54.8 | 6.19 | 11.5 |
| Tosyloxy[e] | H | [h] | 173–175 | 23 | 60.3 | 5.08 | | 60.0 | 4.63 | |
| $HOCH_2CH_2NH$—[d] | H | E | 170–180 d. | 56 | 47.4 | 6.15 | 12.7 | 47.2 | 6.29 | 12.6 |
| $C_6H_{11}NH$—[c] | H | E | 238–240 d. | 84 | 57.0 | 7.05 | 11.7 | 56.9 | 7.35 | 11.8 |
| $HOCH_2C(CH_3)_2NH$[c] | H | E | 215–217 d. | 71 | 51.7 | 6.67 | 12.1 | 51.5 | 7.37 | 11.9 |
| $CH_3CHOHCH_2NH$—[e] | H | E | 205–207 d. | 70 | 50.3 | 6.35 | 12.6 | 50.7 | 6.55 | 12.6 |
| Phthalimido[e] | H | D | 152–154 | 79 | 68.5 | 4.53 | | 68.5 | 5.18 | |
| $CH_3C(CH_2OH)_2NH$—[c] | H | E | 213–215 d. | 52 | 49.4 | 6.37 | 11.5 | 49.4 | 6.39 | 11.5 |
| Cl[e] | 6-Cl | D | 115–117 | 83 | 51.3 | 3.90 | 10.9 | 51.7 | 4.05 | 11.0 |
| $NH_2$—[c] | H | [i] | 250–252 d. | 51 | 47.8 | 5.48 | 15.2 | 47.6 | 5.55 | 15.4 |
| $C_6H_{11}NH$[a] | 6-Cl | E | 242–244 d. | 63 | 54.7 | 6.73 | 11.2 | 55.0 | 6.88 | 11.8 |
| Anilino[c] | H | E | 203–205 d. | 61 | 57.4 | 5.43 | 11.9 | 57.3 | 5.57 | 11.8 |
| Cl[f] | 6-$CH_3$ | E | 209–211 d. | 24 | | | 10.2 | | | 10.1 |
| 1-Tosyl-4-piperidyl[j] | H | D | 190–193 d. | 55 | 57.5 | 6.24 | 8.79 | 57.2 | 6.21 | 8.43 |
| 4-Piperidyl[l] | H | [k] | 228–231 d. | 35 | 54.3 | 6.85 | 11.9 | 54.3 | 7.59 | 11.7 |

[a] Dihydrochloride monohydrate which partially melts at 208°. [b] The dipicrate could also be isolated in 39% yield as yellow crystals, m.p. 147–149°. [c] Dihydrochloride. [d] Dihydrochloride hemihydrate. [e] Free base. [f] Monohydrochloride. [g] A yield of 43% obtained by method D using trimethylene chlorohydrin. [h] From the preceding hydroxy compound by tosylation in pyridine at 0°. [i] Hydrazine hydrolysis of the corresponding phthalimido derivative. [j] Monohydrochloride monohydrate. [k] See note *m*, Table I. [l] Dihydrochloride hemihydrate.

Similarly, *3-(β,γ-oxidopropyl)-6-chloro-4-quinazolone*, m.p. 152–155°, was prepared in 42% yield.

*Anal.* Calc'd for $C_{11}H_9ClN_2O_2$: C, 55.8; H, 3.81; N, 11.9.

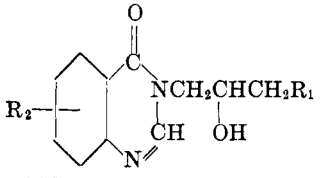
Found: C, 55.7; H, 3.75; N, 12.0.

*3-(β-Hydroxy-γ-cyclohexylaminopropyl)-4-quinazolone.* To 600 mg. of 3-(β,γ-oxidopropyl)-4-quinazolone (m.p. 78–80°) was added 1.4 cc. of cyclohexylamine. After the heat of reaction started to subside, the mixture was heated on the steam-bath for 30 minutes. Crystallization from benzene gave 700 mg. (78%) of product, m.p. 144–146°, as white crystals.

A much better over-all yield was obtained if the intermediate oxide was not purified. To a solution of 56 g. of 4-quinazolone in 384 cc. of 1 *N* sodium methoxide was added 140 cc. of epichlorohydrin. Initially the reaction mixture was cooled occasionally to keep the temperature from rising above 35°. After three hours the salt was removed and the filtrate evaporated to dryness *in vacuo*. The residue was dissolved in chloroform, dried with magnesium sulfate, and the solvent evaporated *in vacuo*. The crude oxide weighed 87 g.

TABLE III

FUNCTIONAL DERIVATIVES OF 3-β-HYDROXYPROPYL-4-QUINAZOLONES



| $R_1$ | $R_2$ | METHOD | M.P., °C. | YIELD, % | ANALYSIS |  |  |  |  |  |
|---|---|---|---|---|---|---|---|---|---|---|
|  |  |  |  |  | Calc'd |  |  | Found |  |  |
|  |  |  |  |  | C | H | N | C | H | N |
| H[d] | H | A | 196–198 d. | 70 | 55.0 | 5.46 | 11.7 | 55.0 | 5.85 | 11.9 |
| $Et_2N$—[a] | H | A | 217–219 d. | 59 | 51.7 | 6.67 | 12.1 | 51.5 | 6.83 | 12.1 |
| Piperidino[a] | H | A | 205–207 d. | 59 | 53.3 | 6.45 | 11.7 | 52.8 | 6.52 | 11.7 |
|  |  | C | 200–202 d. | 30 |  |  |  |  |  |  |
| $C_6H_{11}NH$—[b] | H | C | 144–146 | 54 | 67.8 | 7.70 | 14.0 | 67.5 | 7.86 | 14.1 |
| $HOCH_2CH_2NH$—[a] | H | C | 140–190 d. | 76 | 46.4 | 5.70 | 12.5 | 46.8 | 6.32 | 12.0 |
| $HOCH_2C(CH_3)_2NH$—[c] | H | C | 228–230 d. | 70 | 48.2 | 6.48 | 11.3 | 48.1 | 6.50 | 11.2 |
| $HOCH(CH_3)CH_2NH$—[a] | H | C | 160–170 d. | 63 |  |  | 12.0 |  |  | 11.6 |
| $NH_2$—[c] | H | C | 240–242 d. | 21 | 43.8 | 5.36 | 13.9 | 43.4 | 5.45 | 13.1 |
| *n*-$C_4H_9NH$—[d] | H | C | 238–240 d. | 55 |  |  | 13.5 |  |  | 13.2 |
| $C_6H_{11}NH$—[b] | 6-Cl | C | 160–162 | 34 |  |  | 12.5 |  |  | 12.5 |
| HO— | H | C[e] | 230–232 d. | 63 | 41.5 | 4.43 | 8.80 | 41.6 | 4.83 | 8.79 |
| Anilino[b] | H | C | 152–153 | 47 |  |  | 14.2 |  |  | 14.5 |
| $C_6H_{11}NH$—[b] | 2-$CH_3$ | C | 110–112 | 27 | 68.6 | 8.00 | 13.3 | 68.9 | 8.03 | 13.6 |
| $\vert$<br>Tos-N—$C_2H_5$[d] | H | F | 128 d. | 35[f] | 54.8 | 5.42 | 9.58 | 54.4 | 5.91 | 9.60 |
| $C_2H_5NH$—[c] | H | [g] | 213–216 d. | 39 | 47.6 | 5.83 | 12.8 | 47.7 | 5.59 | 12.6 |
| Allylamino[a] | H | C | 203–207 d.[h] | 56 | 53.1 | 6.00 | 13.2 | 53.4 | 6.17 | 13.2 |
| Morpholino[b] | H | C | 106–108 | 50 | 62.2 | 6.60 | 14.6 | 62.2 | 6.44 | 14.3 |
| $CH_3O$—[b] | H | D | 121–124 | 55 | 61.7 | 6.00 | 12.0 | 61.5 | 6.13 | 12.3 |
| Isopropylamino[d] | H | C | 209–212 d. | 38 | 56.3 | 6.77 | 14.1 | 55.6 | 6.90 | 14.4 |
| Piperidino[b] | 2-$CH_3$ | B | 120–122 | 40 | 67.8 | 7.63 | 13.9 | 68.1 | 7.80 | 14.0 |

[a] Dihydrochloride. [b] Free base. [c] Dihydrochloride hemihydrate. [d] Monohydrochloride. [e] By refluxing the crystalline oxide with 1 *N* $H_2SO_4$ for 3 hours. Product isolated as neutral sulfate. [f] Based on N-ethyl-*p*-toluenesulfonamide. [g] See note *m*, Table I. [h] The free base melted at 117–120°.

A mixture of 31.6 g. of this crude oxide was mixed with 42 cc. of cyclohexylamine. By treatment of the reaction mixture in the same manner as described above for the pure oxide there was obtained 33 g. (54% based on 4-quinazolone) of product, m.p. 140–142°.

Additional compounds prepared in a similar manner are described in Table III under method C.

*3-(β-Tosyloxyethyl)-4-quinazolone.* To a solution of 27 g. of *p*-toluenesulfonyl chloride in 270 cc. of reagent pyridine cooled to 5° was added 27 g. of 3-(β-hydroxyethyl)-4-quinazolone (Table I). After two hours in an ice-bath the mixture was poured into a large volume of ice-water to give 26.5 g. (55%) of white solid which decomposed at 160° without melting. The m.p. was unchanged when a sample was recrystallized from Methyl Cellosolve.

*Anal.* Calc'd for $C_{17}H_{16}N_2O_4S$: C, 59.3; H, 4.68; N, 8.15.
Found: C, 59.3; H, 4.92; N, 7.99.

*3-(β-Iodoethyl)-4-quinazolone.* A mixture of 23 g. of 3-(β-tosyloxyethyl)-4-quinazolone, 20 g. of sodium iodide, and 200 cc. of acetone was refluxed for 16 hours, then diluted with water containing some sodium bisulfite to give 17.5 g. (88%) of product, m.p. 121–124°. Recrystallization of a sample from alcohol gave white crystals, m.p. 124–125°.

*Anal.* Calc'd for $C_{10}H_9IN_2O$: C, 40.0; H, 3.00; N, 9.33.
Found: C, 40.5; H, 3.50; N, 9.48.

*3-(γ-Chloropropyl)-4-quinazolone.* To a solution of 60 g. of 4-quinazolone in 410 cc. of 1 *N* sodium methoxide was added 78 cc. of trimethylene chlorobromide. After being refluxed for six hours, the mixture was diluted with several volumes of water and extracted with chloroform. The dried extracts were evaporated *in vacuo* leaving an oil which was crystallized from dilute alcohol; yield, 62.5 g. (69%), m.p. 98–100°. Recrystallization of a sample from dilute alcohol did not raise the m.p.

*Anal.* Calc'd for $C_{11}H_{11}ClN_2O$: N, 12.6. Found: N, 12.5.

Other compounds prepared similarly are listed in the tables under method D. The reflux period varied from 6 to 17 hours.

Treatment with sodium iodide in Methyl Cellosolve at 100° for 17 hours converted the chloro compound to *3-(γ-iodopropyl)-4-quinazolone,* white crystals from dilute alcohol, m.p. 120–122°.

*Anal.* Calc'd for $C_{11}H_{11}IN_2O$: N, 8.92. Found: N, 8.84.

*3-(γ-Cyclohexylaminopropyl)-4-quinazolone dihydrochloride.* A mixture of 10 g. of 3-(γ-chloropropyl)-4-quinazolone, 20 cc. of cyclohexylamine, 0.5 g. of sodium iodide, and 30 cc. of Methyl Cellosolve was heated on the steam-bath under a condenser for 17 hours, diluted with water, basified with ammonium hydroxide, and extracted twice with chloroform. The combined dried extracts were evaporated to dryness *in vacuo.* Crystallization from absolute alcoholic hydrogen chloride gave 13.5 g. (84%) of product, m.p. 237–240° dec.

Additional compounds prepared in a similar manner are listed in the tables under method E.

*3-(N-Tosyl-β-hydroxy-γ-ethylaminopropyl)-4-quinazolone hydrochloride* (XII). A solution of 2 g. of N-ethyl-*p*-toluenesulfonamide and 3.9 cc. of epichlorohydrin in 10 cc. of 1 *N* sodium methoxide was allowed to stand for three hours, then diluted with water and extracted with chloroform. Evaporation of the extracts *in vacuo* gave 2.2 g. of N-(β,γ-oxidopropyl)-N-ethyl-*p*-toluenesulfonamide (XI) as an oil. This oil, dissolved in 9 cc. of methanol, was added to a solution of 1.25 g. of 4-quinazolone in 9.2 cc. of 1 *N* sodium methoxide. After 18 hours the mixture was diluted with water and extracted with chloroform. Evaporation of the extracts *in vacuo* gave an oil which was dissolved in absolute alcoholic hydrogen chloride and crystallized by the addition of ether. Further data are given in Table III under method F.

*1-Tosyl-4-(γ-tosyloxypropyl)piperidine.* To an ice-cooled solution of 32 g. of tosyl chloride and 11 cc. of triethylamine in 140 cc. of pyridine was added 11.3 g. of 4-(γ-hydroxypropyl)-piperidine (17) in portions at such a rate that the temperature did not rise above 12°. After two hours more in an ice-bath, the solution was poured into water to give 26.7 g. (74%) of product, m.p. 83–85°. Recrystallization of a sample from methanol resulted in white crystals, m.p. 88–90°.

*Anal.* Calc'd for $C_{22}H_{29}NO_5S_2$: C, 58.7; H, 6.50; N, 3.11.
Found: C, 58.7; H, 6.25; N, 3.37.

Similarly, ethylaminoethanol gave an 86% yield of *N-(β-tosyloxyethyl)-N-ethyl-p-toluenesulfonamide* as an oil except that the triethylamine was omitted. Treatment of 2-(β-hydroxyethyl)piperidine (18) with tosyl chloride in pyridine at 0–3° for 17 hours gave a 31% yield of *1-tosyl-2-(β-tosyloxyethyl)piperidine*, m.p. 60–65°. Recrystallization from dilute methanol gave white crystals, m.p. 72–75°.

*Anal.* Calc'd for $C_{21}H_{27}NO_5S_2$: C, 57.8; H, 6.18; N, 3.20.
Found: C, 57.9; H, 6.47; N, 3.18.

No crystalline product could be obtained by condensation of the latter compound with sodio 4-quinazolone.

*3-Chloroacetamidomethyl-4-quinazolone* (XXIII, R = $ClCH_2$-). A solution of 2.0 g. of 4-quinazolone and 1.5 g. of methylolchloroacetamide (19) in 20 cc. of acetic acid was refluxed for two hours. The solvent was removed *in vacuo* and the product crystallized by the addition of water; yield, 1.8 g. (53%), m.p. 172–174°. Recrystallization from methanol gave white crystals, m.p. 180–182°.

*Anal.* Calc'd for $C_{11}H_{10}ClN_3O_2$: C, 52.6; H, 3.80; N, 16.7.
Found: C, 52.3; H, 4.11; N, 17.0.

Similarly, 3-benzamidomethyl-4-quinazolone was prepared in 63% yield, m.p. 178–180°. Monti, Osta, and Piras (5) record m.p. 180–182°.

A solution of 500 mg. of 3-chloroacetamidomethyl-4-quinazolone in 5 cc. of 6 *N* hydrochloric acid was heated on the steam-bath for one hour. The odor of formaldehyde was perceptible. Evaporation *in vacuo* left a solid which was triturated with acetone to give 370 mg. (100%) of 4-quinazolone hydrochloride, m.p. 245–247° with dec. and sublimation. This was identified by mixed m.p. and u.v. spectra. Similar results were obtained with 3-benzamidomethyl-4-quinazolone.

*3-(Piperidinomethyl)-4-quinazolone* (XXIV). To a hot solution of 25 g. of 4-quinazolone and 18.8 cc. of piperidine in 250 cc. of water was added 14.3 cc. of 40% formalin. An oil separated. After being heated on the steam-bath for 15 minutes, the mixture was cooled in an ice-bath causing the oil to solidify; yield, 33 g. (78%), m.p. 104–105°. Recrystallization from heptane gave white crystals, m.p. 105°.

*Anal.* Calc'd for $C_{14}H_{17}N_3O$: N, 17.3. Found: N, 17.4.

When a sample was dissolved in cold acetone and treated with absolute alcoholic hydrogen chloride, white crystals of 4-quinazolone hydrochloride, m.p. 245–247° dec., immediately separated. This compound was identified by u.v. spectra and mixed m.p.

The use of morpholine in place of piperidine resulted in *3-morpholinomethyl-4-quinazolone*, m.p. 93–95°, in 40% yield.

*Anal.* Calc'd for $C_{13}H_{15}N_3O_2$: C, 63.3; H, 6.12; N, 17.1.
Found: C, 63.1; H, 6.80; N, 17.3.

*Ethyl 4-quinazolone-3-acetate.* To a stirred solution of 6.4 g. of sodium methoxide and 20 g. of 4-quinazolone (14) in 200 cc. of absolute alcohol was added 14.4 cc. of ethyl chloroacetate. The mixture was refluxed for two hours, decanted from the salt, concentrated to turbidity *in vacuo*, diluted with several volumes of water, and extracted twice with chloroform. The combined extracts, dried with magnesium sulfate, were evaporated to dryness *in vacuo*. Trituration of the hot residue with heptane followed by cooling gave 21.5 g. (68%) of product, m.p. 72–75°. Recrystallization of a sample from heptane afforded white crystals, m.p. 76–77°.

*Anal.* Calc'd for $C_{12}H_{12}N_2O_3$: C, 62.0; H, 5.18; N, 12.1.
Found: C, 62.2; H, 5.47; N, 12.5.

*4-Quinazolone-3-acetic acid* (XXVI). To a still warm solution of 44 g. of sodium hydroxide in 440 cc. of water was added 200 g. of ethyl 4-quinazolone-3-acetate. The mixture was heated on a steam-bath with stirring until solution was complete (five minutes) and then for an additional two minutes. The solution was cooled in an ice-bath and as soon as the temperature dropped to 50°, it was acidified with 92 cc. of 12 *N* hydrochloric acid and allowed to cool to 15°. The product was collected and washed with three 200-cc. portions of ice-water; yield, 167 g. (95%), m.p. 237–239°. This compound is readily soluble in hot water and somewhat soluble cold.

Späth and Nikawitz (3) recorded m.p. 235–237°.

*Ethyl 4-quinazolone-3-malonate* (XXV). A solution of 26 g. of 4-quinazolone and 10.4 g. of sodium methoxide in methanol was evaporated to dryness *in vacuo*. To the dry sodium salt was added 33 cc. of ethyl bromomalonate and the mixture was heated on the steam-bath. After the exothermic reaction had subsided, the mixture was heated one hour longer, then diluted with water and benzene. The separated organic layer was evaporated and the residue crystallized from benzene-petroleum ether; yield, 18.4 g. (34%), m.p. 63–66°. Recrystallization of a sample from aqueous methanol gave white crystals, m.p. 64–67°.

*Anal.* Calc'd for $C_{15}H_{16}N_2O_5$: C, 59.2; H, 5.28; N, 9.20.
Found: C, 59.3; H, 5.19; N, 9.40.

The *dihydrochloride* could be obtained in two different forms, (a) m.p. 208–209° dec. and (b) m.p. 143–145° dec.

*Anal.* Calc'd for $C_{15}H_{16}N_2O_5{\cdot}HCl$: C, 52.9; H, 4.99; N, 8.20.
Found: (a) C, 52.7; H, 4.99; N, 8.43.
(b) C, 53.2; H, 5.03; N, 8.47.

None of the malonate, XXV, could be isolated when the reaction was run in absolute ethanol in the usual manner of alkylating 4-quinazolone. Hydrolysis of the malonate by refluxing with 6 *N* hydrochloric acid for one hour gave a 90% yield of 4-quinazolone-3-acetic acid (XXVI), m.p. and mixed m.p. 227–231°. Careful alkaline hydrolysis still led to 4-quinazolone-3-acetic acid and the malonic acid could not be isolated.

*3-Cyclohexyl-4-quinazolone* (XXX). (A) A solution of 1.0 g. *o*-amino-N-cyclohexylbenzamide (7) in 10 cc. of 90% formic acid was heated on the steam-bath under a condenser for one hour, then evaporated to dryness *in vacuo*. The residue was refluxed with 10 cc. of acetic anhydride (containing 0.5% of 85% phosphoric acid) for one hour, then evaporated to dryness *in vacuo*. Crystallization from dilute alcohol gave 0.50 g. (47%) of product, m.p. 110–113°. Recrystallization from heptane formed white crystals, m.p. 111–113°.

*Anal.* Calc'd for $C_{14}H_{16}N_2O$: C, 73.9; H, 7.01; N, 12.3.
Found: C, 74.1; H, 7.14; N, 12.5.

The *dihydrochloride* was prepared by solution of the base in absolute alcoholic hydrogen chloride followed by concentration to a syrup, then addition of ether: white crystals, m.p. 224° dec.

*Anal.* Calc'd for $C_{14}H_{16}N_2O{\cdot}HCl$: C, 63.8; H, 6.45; N, 10.6.
Found: C, 63.9; H, 6.76; N, 10.4.

Omission of the phosphoric acid catalyst dropped the yield to 12%. Ordinarily 90% formic acid for one hour at 100° is sufficient to ring close an anthranilamide to a 4-quinazolone. For example, the N-benzylamide gave 3-benzyl-4-quinazolone in 67% yield. If the reaction mixture from the cyclohexylamide was worked up after formic acid treatment, *o*-formamido-N-cyclohexylbenzamide (XXVIII), m.p. 144–147°, was the only product which could be isolated.

*Anal.* Calc'd for $C_{14}H_{18}N_2O_2$: C, 68.2; H, 7.30; N, 11.4.
Found: C, 67.8; H, 7.46; N, 11.6.

(B) A solution of 1.0 g. of *o*-amino-N-cyclohexylbenzamide in 10 cc. of ethyl *o*-formate was refluxed for 2½ hours, then evaporated to dryness *in vacuo*. The residual crude ethoxymethylene derivative (XXIX), which solidified on cooling, was refluxed in 10 cc. of acetic anhydride (containing 0.5% of 85% phosphoric acid) for one hour and again evaporated to dryness *in vacuo*. Conversion of the residue to the hydrochloride as in part A gave 0.46 g. (38%) of product, m.p. 222–225° dec.

*3-(α-Methylol-β-hydroxyethyl)-4-quinazolone* (XXXI) *hydrochloride*. A mixture of 1.9 g. of 2-amino-1,3-propanediol (20), 20 cc. of absolute alcohol, and 3.4 g. of isatoic anhydride was refluxed for ten minutes when gas evolution was complete. Evaporation *in vacuo* gave an oil which was refluxed two hours with 50 cc. of ethyl *o*-formate, evaporated to dryness *in vacuo*, and refluxed with 50 cc. of acetic anhydride and 0.25 cc. of 85% phosphoric acid for one hour. Solvent was removed *in vacuo*. The residue was refluxed on the steam-bath for one hour with 50 cc. of absolute alcohol saturated with hydrogen chloride to hydrolyze any esterified hydroxyl groups. Addition of four volumes of acetone, then ether to turbidity gave 1.8 g. (33%) of product, m.p. 164–169°. Recrystallization from absolute alcohol by the addition of saturated absolute alcoholic hydrogen chloride gave white crystals, m.p. 172–174°.

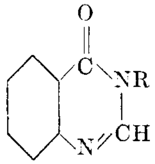
*Anal.* Calc'd for $C_{11}H_{12}N_2O_3 \cdot HCl$: C, 51.5; H, 5.12; N, 10.5.
Found: C, 51.4; H, 5.54; N, 10.8.

Other compounds prepared by this method are listed in the tables under G.

*3-(β-Carboxyethyl)-4-quinazolone* (XXXV) *hydrochloride.* A solution of 19.9 g. of 3-(β-carbethoxyethyl)-4-quinazolone (XXXIV) hydrochloride (Table IV) in 100 cc. of 6 *N* hydrochloric acid was refluxed for one hour. On being cooled the solution deposited 14.2 g. (79%) of product, m.p. 212–214° dec.

TABLE IV

VARIOUS 3-SUBSTITUTED-4-QUINAZOLONES



| R | METHOD | M.P., °C. | YIELD, % | ANALYSIS Calc'd C | Calc'd H | Calc'd N | Found C | Found H | Found N |
|---|---|---|---|---|---|---|---|---|---|
| $C_6H_5CH_2$—[a] | A | 112–114[b] | 83 | | | | | | |
| $CH_2{=}CHCH_2$—[c] | D[e] | 200–202 d.[d] | 45 | | | | | | |
| 2-Pyridyl—[a] | A | 132–134 | 49 | 70.4 | 4.04 | 18.8 | 69.9 | 4.35 | 18.7 |
| $CH_3COCH_2$—[a] | D[f] | 157–159 | 83 | 65.3 | 5.00 | 13.9 | 65.2 | 5.30 | 14.2 |
| —$CH_2CH_2COOC_2H_5$[c] | A | 177–179 | 63[g] | 55.2 | 4.96 | 9.94 | 55.1 | 5.63 | 10.2 |
| 2-Tetrahydrofuryl-methyl[c] | D[h] | 196–198 d. | 27 | 58.4 | 5.62 | 10.5 | 58.6 | 5.90 | 10.3 |
| 4-Ketopentyl—[a] | D[f] | 85–87 | 5 | 67.8 | 6.09 | 12.2 | 67.9 | 7.00 | 12.3 |
| Noval—[i] | G | 147–149 | 49 | 46.6 | 4.15 | 16.9 | 46.5 | 4.54 | 17.3 |
| $Br(CH_2)_6$—[c] | D[e] | 188–190 d. | 38 | 48.7 | 5.25 | 8.12 | 48.8 | 5.80 | 8.30 |
| $C_6H_{11}NH(CH_2)_6$—[j] | E | 211–213 d. | 51 | 60.0 | 7.77 | 10.5 | 60.1 | 7.73 | 10.2 |
| Piperidinobutyl—[a] | A | 118–120 | 43 | 71.6 | 8.13 | 14.8 | 71.3 | 8.29 | 14.8 |
| $CH_2{=}CBrCH_2$— | D[e] | 65–67 | 60 | 49.8 | 3.32 | 10.6 | 49.6 | 3.63 | 10.7 |

[a] Free base. [b] Bogert and Geiger (8) record m.p. 116° prepared by method D. [c] Monohydrochloride. [d] Free base, m.p. 64–65°; lit. (2), m.p. 67°. [e] Bromide employed. [f] Chloride employed. [g] Method D gave methyl acrylate. [h] Tosylate employed. [i] Dipicrate. [j] Dihydrochloride.

*Anal.* Calc'd for $C_{11}H_{10}N_2O_3 \cdot HCl \cdot H_2O$: C, 48.5; H, 4.76; N, 10.2.
Found: C, 49.1; H, 5.04; N, 10.1.

*3-(γ-Ketobutyl)-4-quinazolone* (XXXVII) *hydrochloride.* A mixture of 5 g. of 3-(β-carboxyethyl)-4-quinazolone (obtained by recrystallization of the hydrochloride from dilute alcohol) 12 cc. of reagent ether (containing 0.5% of pyridine), and 20 cc. of thionyl chloride was shaken for 30 minutes. The crude acid chloride hydrochloride was collected, washed with dry ether, and dried *in vacuo;* wt., 5.0 g., m.p. 165–170° dec. A similar preparation gave an 85% yield of anilide free base, m.p. 222–224°.

*Anal.* Calc'd for $C_{17}H_{15}N_3O_2$: N, 14.4. Found: N, 14.8.

The crude acid chloride was added to 61 cc. of 1.5 *M* ethoxymagesiomalonic ester in benzene, refluxed five minutes, acidified with 22 cc. of acetic acid, and washed with water.

The organic layer was evaporated and the excess ethyl malonate distilled out at 1 mm. The residue of crude keto malonate, XXXVI, (5.6 g.) was refluxed three hours with 56 cc. of 6 *N* hydrochloric acid, evaporated to dryness *in vacuo*, and the product crystallized from alcohol-ether; yield, 2.2 g. (48% over-all), m.p. 160–165° dec. Recrystallization from absolute alcohol-ether gave white crystals, m.p. 165–167° dec.

*Anal.* Calc'd for $C_{12}H_{12}N_2O_2 \cdot HCl$: N, 11.1. Found: N, 11.2.

The *phenylhydrazone* was prepared in dilute alcohol and formed white crystals, m.p. 148–150°.

*Anal.* Calc'd for $C_{18}H_{18}N_4O$: C, 70.6; H, 5.93; N, 18.3.
Found: C, 70.3; H, 6.17; N, 18.6.

A mixture of 500 mg. of 3-(γ-ketobutyl)-4-quinazolone and 5 cc. of 10% sodium hydroxide was heated on the steam-bath for ten minutes. The odor of methyl vinyl ketone was immediately perceptible but soon changed to that of a higher ketone. The solution was clarified by filtration through Celite, acidified with 1.5 cc. of acetic acid, and extracted twice with ethyl acetate. Evaporation of the dried extracts and trituration of the residue with benzene gave 150 mg. (52%) of 4-quinazolone, m.p. 202–205°, which was identified by mixed m.p.

*3-(β-Chloro-γ-methoxypropyl)-4-quinazolone hydrochloride.* To a refluxing solution of 16.4 g. of 3-(β-hydroxy-γ-methoxypropyl)-4-quinazolone (Table III) and 19.6 cc. of reagent pyridine in 190 cc. of chloroform was added 19 cc. of thionyl chloride over a period of five minutes. After being refluxed one hour, when gas evolution was complete, the solution was evaporated to dryness *in vacuo*. The residue was layered with chloroform and water, then basified with ammonium hydroxide. The aqueous layer was separated and extracted once more with chloroform. Evaporation of the combined extracts *in vacuo* and crystallization of the residue from absolute alcoholic hydrogen chloride gave 16.5 g. (82%) of product, m.p. 154–158° dec. Recrystallization of a sample from the same solvent gave white crystals, m.p. 166–169° dec.

*Anal.* Calc'd for $C_{12}H_{13}N_2O_2 \cdot HCl$: C, 49.8; H, 4.88; N, 9.68.
Found: C, 49.5; H, 5.06; N, 9.24.

If the pyridine was omitted, the hydroxy compound was recovered unchanged. Attempts to replace the chlorine with cyclohexylamino or piperidino were unsuccessful.

## SUMMARY

Over eighty functional derivatives of 3-alkyl-4-quinazolone have been synthesized in relationship to the antimalarial alkaloid from Hydrangea.

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