ture of the resulting partly purified 2-naphthylamine "acetone anil" and 0.8 g. of 10% palladium on carbon was heated at 270–285° (bath temperature) in the same apparatus for 2 hr. The reaction mixture was cooled, taken up in a minimum quantity of ether, filtered free of the catalyst, and transferred to a clean sublimation tube. After removal of the solvent under a gentle stream of nitrogen, the gummy residue was sublimed at 100–110° (0.01 mm.) over a period of 48 hr. Large sticky yellow crystals formed in the cool zone and were removed periodically. A total of 3.1 g. (91% based on crude 2-naphthylamine "acetone anil" used) was collected in this manner, but still appeared severely contaminated with 2-naphthylamine on the basis of its ultraviolet absorption spectrum. Efforts to purify the crude dehydrogenation product by resublimation or repeated recrystallization from aqueous ethanol were only partly successful, and were therefore abandoned in favor of the picrate–hydrochloride–free base route used in procedure A.

The picrate was prepared and found to melt sharply with decomposition at 231.5° after one recrystallization from absolute methanol. A mixture melting point with the picrate of authentic 1,3-dimethylbenzo[*f*]quinoline was undepressed.

Anal. Calcd. for $C_{21}H_{16}N_4O_7$: C, 57.79; H, 3.70; N, 12.84. Found: C, 57.38; H, 3.95; N, 12.63.

The hydrochloride was prepared in excellent yield from the picrate by metathetiel exchange, as in procedure A, and was found to decompose at approximately 285°, after recrystallization from dilute hydrochloric acid. The infrared spectrum of this hydrochloride was completely superimposable on that of authentic 1,3-dimethylbenzo[*f*]quinoline hydrochloride.

Anal. Calcd. for $C_{15}H_{13}N\cdot HCl$: C, 73.90; H, 5.80; N, 5.75. Found: C, 73.46; H, 6.27; N, 5.25.

Neutralization of an aqueous solution of the hydrochloride liberated the free base. Extraction into ether, drying, removal of solvent, and finally sublimation at 105° (0.4 mm.) furnished small white crystals, m.p. 125–126°. Infrared, ultraviolet, and n.m.r. spectra of the free bases prepared by procedures A and B were completely superimposable, and a mixture melting point was undepressed.

Anal. Calcd. for $C_{15}H_{13}N$: C, 86.91; H, 6.33; N, 6.76. Found: C, 86.79; H, 6.55; N, 6.69.

4,6-Diamino-2,2-dimethyl-1-(1-naphthyl)-1,2-dihydro-*s*-triazine Hydrochloride.—A mixture of 1-naphthylamine (43 g., 0.3 mole), dicyandiamide (27 g., 0.32 mole), and 25 ml. of concentrated hydrochloric acid in 40 ml. of acetone and 150 ml. of 95% ethanol was stirred under reflux for 16 hr. Nearly complete solution was achieved in 30 min., but solid began to deposit gradually. The reaction mixture was cooled in an ice bath and the product was collected, washed with acetone, and dried at 70°, yielding 49 g. (54%) of small colorless prisms, m.p. 231–239°. A 3-g. portion of this solid was crystallized from 25 ml. of water in 87% recovery. Two further crystallizations from water afforded analytically pure colorless prismatic rods, m.p. 220–222° (lit.[40] 226–228°). No high-melting material could be found under these conditions.

Anal. Calcd. for $C_{15}H_{17}N_5\cdot HCl$: C, 59.30; H, 5.97; N, 22.77. Found: C, 59.21; H, 6.06; N, 23.06.

N^2-(2-Naphthyl)acetoguanamine (IV).—A mixture of N^1-(2-naphthyl)biguanide (4.54 g., 0.02 mole), ethyl acetate (2.35 g., 0.0256 mole), and potassium hydroxide (0.37 g., 0.0066 mole) in 11.5 ml. of absolute methanol was stirred under reflux for 18 hr. and cooled to room temperature. The product was collected, washed with water and small portions of absolute methanol, and air-dried. The white, finely powdered solid weighed 1.75 g. (50%, allowing for 1.35 g. of starting material recovered from the mother liquor on dilution with water and further cooling) and melted at 195–200°. Purification by repeated crystallization from 50% aqueous ethanol gave product melting at 200–201°.

Anal. Calcd. for $C_{14}H_{13}N_5$: C, 66.91; H, 5.21. Found: C, 66.31; H, 5.40.

For the preparation of the hydrochloride salt of IV a solution of 72 mg. of free base in 5 ml. of *n*-propyl alcohol was saturated with dry hydrogen chloride gas and refrigerated briefly. The white solid that had formed was collected, washed with acetone, and crystallized from aqueous *n*-propyl alcohol, yielding colorless crystals, m.p. 232–238°.

Anal. Calcd. for $C_{14}H_{13}N_5\cdot HCl\cdot 0.5H_2O$: C, 56.57; H, 5.05; N, 23.74. Found: C, 56.12; H, 5.30; N, 23.62.

Acknowledgment.—The authors are indebted to Mr. James H. Gunnerson, Mr. Leo McCready, and Mr. Michael Botchan for assistance in obtaining infrared and ultraviolet absorption spectra in this investigation.

Investigations in Heterocycles. XVIII. The Synthesis of 1,2-Disubstituted 5,6,7,8-Tetrahydro-4-quinazolinethiones[1]

RICHARD W. J. CARNEY, JANICE WOJTKUNSKI, AND GEORGE DESTEVENS

Chemical Research Division, Ciba Pharmaceutical Company, Division of Ciba Corporation, Summit, New Jersey

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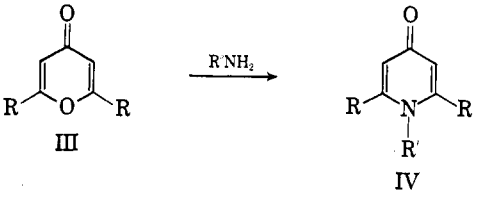
Two methods for the synthesis of 1,2-disubstituted 5,6,7,8-tetrahydro-4-quinazolinethiones are described: (a) the reaction of 5,6,7,8-tetrahydro-2-phenyl-4-benzoxazinethione with various primary amines and (b) the condensation of a N-monosubstituted enamine with an acylisothiocyanate. Some chemical transformations of this heterocyclic system are discussed.

Because of the continuing interest in our laboratories[2–4] in the synthesis of various heterocyclic systems for biological evaluation, our attention was recently drawn to the work of Hünig and Hübner who reported the formation of 5,6,7,8-tetrahydro-2-phenyl-4-benzoxazinethione (II) in 50% yield from the interaction of morpholinocyclohexene (I) with benzoylisothiocyanate (Scheme I, p. 2888).

Since 1,3-oxazine-4-ones can be considered to bear a formal resemblance to 1,4-pyrones with regard to the disposition of the double bonds, and, inasmuch as 1,4-pyrones (III) upon heating with primary amines can readily be transformed to 4-pyridones[6] (IV), it was of interest to us to explore the reactivity of II towards such amines.



III IV

(1) Presented in part before the Organic Chemistry Division at the 145th National Meeting of the American Chemical Society, New York, N. Y., Sept., 1963, Abstracts, p. 59Q.

(2) G. deStevens, B. Smolinsky, and L. Dorfman, *J. Org. Chem.*, **29**, 1115 (1964).

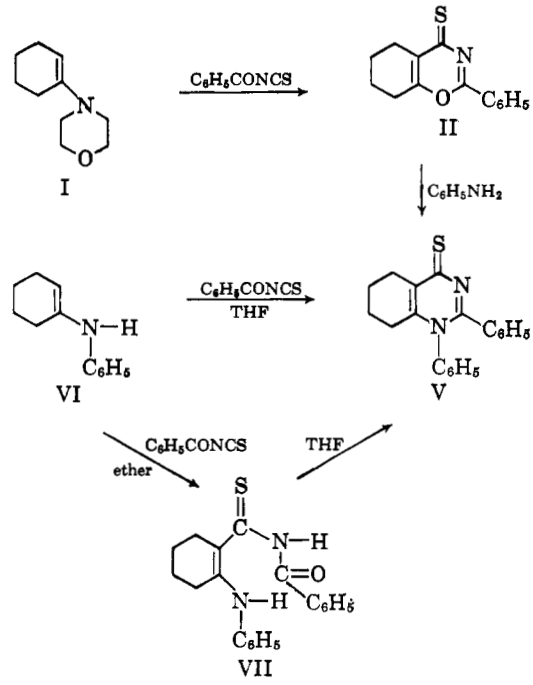
(3) G. deStevens, A. Halamandaris, M. Bernier, and H. M. Blatter, *ibid.*, **28**, 1336 (1963).

(4) G. deStevens, *Record of Chem. Progr.*, **23**, 105 (1962).

(5) S. Hünig and K. Hübner, *Chem. Ber.*, **95**, 937 (1962).

(6) L. F. Cavalieri, *Chem. Rev.*, **41**, 525 (1947).

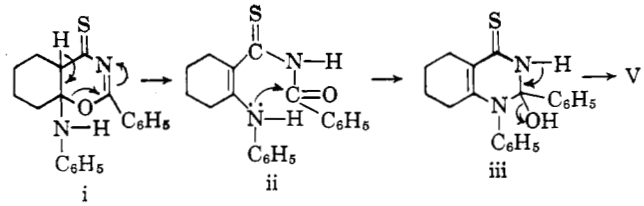
SCHEME I



When II was allowed to react in refluxing ethanol with excess aniline a yellow crystalline material (V) was obtained in 59% yield. Elemental analysis indicated that the product consisted of the combined reactants minus the elements of water. The ultraviolet absorption spectrum of this substance in ethanol showed a shoulder at 254 with a maximum at 342–345 mμ. This differed markedly from the spectrum of compound II which gave maxima at 228–230, 287, and 333–335 mμ in dioxane. Thus, it appeared that the chromophore of this latter heterocycle had been substantially altered. The absence of –NH, OH, or carbonyl absorption bands in the infrared further suggested that we were dealing with a heterocyclic compound rather than with a ring-opened, cyclohexenyl derivative. From the nature of the reaction[7] and from the analytical and spectral data, the compound was assigned structure V.

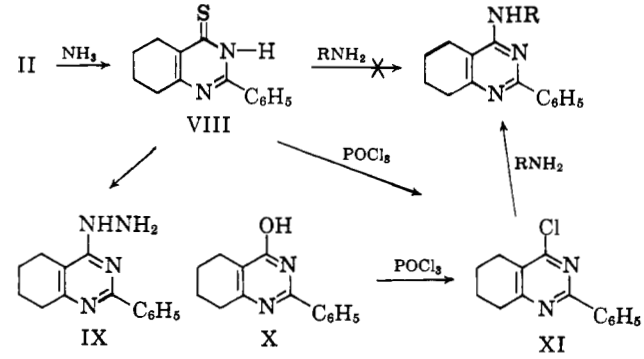
To substantiate this structural assignment, anilinocyclohexene (VI) was allowed to react with benzoyl isothiocyanate in tetrahydrofuran. Under these conditions a substance was obtained which corresponded in every respect with compound V. However, when this reaction was carried out in ethyl ether, the benzoylthiocarbamoyl derivative (VII) was obtained which, in turn, was converted to V in refluxing tetrahydrofuran. The isolation of VII and its subsequent conversion to V supports the mechanistic rationale already elaborated.[7]

(7) Mechanistically, the driving force of this reaction can be considered to be derived from the nucleophilic attack of the amino group on the carbocyclic double bond to form i. Prototropic shift followed by ring cleavage



can then lead to the benzoylthiocarbamoyl derivative ii which can undergo ring closure and dehydration to yield V.

SCHEME II



Following these results, the utility of II as an intermediate in the synthesis of 5,6,7,8-tetrahydroquinazolines was then explored extensively. A variety of primary amines has been allowed to react with II to give, in general, good yields of the 1-substituted 5,6,7,8-tetrahydro-2-phenyl-4-quinazolinethiones.

These substances could be readily oxidized by means of mercuric acetate[8] to the corresponding tetrahydro-4-quinazolinones. The data on these two heretofore unknown series of compounds are summarized in Tables I and II.

When ammonia gas was bubbled through a methanolic solution of II, a white crystalline solid was obtained which corresponded to VIII (Scheme II). The ultraviolet absorption in ethanol gave maxima at 244, 304, and 347 mμ while in basic medium the absorption maxima were observed at 254 and 301 mμ. Consequently, a specific tautomeric form cannot be assigned to this compound.

Condensation of VIII with hydrazine afforded IX in good yield; however, when substituted hydrazines were used, only starting material was isolated. On the other hand, VIII did not appear to undergo any change when treated with primary amines under reflux. However, chlorination of VIII with phosphorus oxychloride afforded an intermediate which readily reacted with amines to yield the 4-substituted amino derivatives (Table III). 4-Chloro-5,6,7,8-tetrahydro-2-phenylquinazoline (XI) could also be obtained from X.[5]

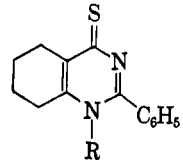
The versatility of Hünig's intermediate benzoxazine (II) is illustrated further in its application to the synthesis of tetrahydroquinazolinium salts (Scheme III). In the first case (a) reaction of II with methyl iodide yielded the oxonium salt XII which readily condensed with primary amines to form in good yields the 1,4-disubstituted tetrahydroquinazolinium iodide. The R groups at positions 1 and 4 in these compounds are identical. However, to prepare compounds in which the R groups at positions 1 and 4 are different, it was necessary to use sequence b. In this case, N_1-substituted 5,6,7,8-tetrahydroquinazolines were treated first with methyl iodide. The resulting methiodide salts were then condensed with a primary amine whose R function is different from that already incorporated at the 1-position of the heterocycle. These methods have not been extensively explored but they appear to be general.

Spectra Interpretation.—The ultraviolet absorption spectra for the 1,2-disubstituted tetrahydro-4-quinazo-

(8) L. Legrand and N. Lozac'h, *Bull. soc. chim. France*, 2088 (1960).

TABLE I

1-SUBSTITUTED 5,6,7,8-TETRAHYDRO-2-PHENYL-4-QUINAZOLINETHIONE

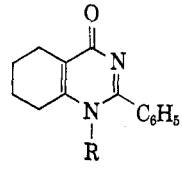


No.	R	M.p., °C.	Yield, %	Formula	Calcd., % C	H	N	S	Found, % C	H	N	S
1	$-C_6H_5$	268–270	59	$C_{20}H_{18}N_2S$	75.46	5.70	8.80	10.07	75.55	5.68	8.72	10.22
2	$-CH_2C_6H_5$	215–216	91	$C_{21}H_{20}N_2S$	75.86	6.06	8.43	9.65	75.52	5.97	8.69	9.77
3	$-CH_2CH_2-N\langle\rangle O$	195–197	51	$C_{20}H_{25}ON_3S$	67.56	7.09	11.82	9.02	67.78	7.19	11.68	9.27
4	$4\text{-}FC_6H_4-$	307–310	73	$C_{20}H_{17}N_2SF$	71.41	5.09	8.33		71.60	5.15	8.09	
5	$4\text{-}CH_3OC_6H_4-$	243–245	73	$C_{21}H_{20}N_2SO$	72.37	5.79	8.04		72.50	5.89	8.14	
6	$-CH_2CH_2NEt_2$	166–167	89	$C_{20}H_{27}N_3S$	70.33	7.97	12.30	9.39	70.30	7.98	12.10	9.62
7	$-CH_2CH_2NMe_2$	166–167	60	$C_{18}H_{23}N_3S$	68.98	7.40	13.41		68.71	7.38	13.14	
8	$-CH_2CH_2-N\langle\rangle$	158–159	65	$C_{20}H_{25}N_3S$	70.76	7.42	12.38	9.45	70.71	7.48	12.20	9.61
9	$-CH_2CH_2OH$	244–246	78	$C_{16}H_{18}N_2OS$	67.10	6.33	9.78	11.19	67.02	6.36	9.61	11.19
10	$-CH_2CH_2CH_2NEt_2$	174–175	72	$C_{21}H_{29}N_3S$	70.95	8.22	11.82		70.87	8.33	11.59	
11	$-CH_2CH_2CH_2OMe$	169–170	70	$C_{18}H_{22}N_2SO$	68.75	7.06	8.91		69.07	6.99	8.71	
12	$-(CH_2)_9CH_3$	155–156	85	$C_{24}H_{34}N_2S$	75.34	8.96	7.32	8.38	75.64	8.95	7.02	8.39
13	$-C_6H_{11}$	241–242	32	$C_{20}H_{24}N_2S$	74.02	7.45	8.63		74.10	7.52	8.45	
14	$3,4\text{-}(CH_3O)_2\text{-}C_6H_3CH_2CH_2-$	218–220[a]	54	$C_{24}H_{26}N_2O_2S$	70.91	6.45	6.89		70.97	6.52	6.71	
15	$4\text{-}CF_3C_6H_4-$	294–295[b,c]	55	$C_{21}H_{17}N_2SF_3$	65.27	4.44	7.25		65.10	4.31	7.16	
16	$3,4\text{-}(Cl)_2C_6H_3-$	330–332[d]	1	$C_{20}H_{16}N_2SCl_2$	62.02	4.16	7.24		61.99	4.36	6.94	

[a] Recrystallization solvent, acetone. [b] No reaction solvent. [c] Recrystallization solvent, acetonitrile. [d] Reaction solvent, tetrahydrofuran.

TABLE II

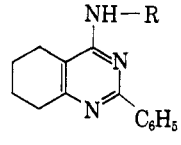
1-SUBSTITUTED 5,6,7,8-TETRAHYDRO-2-PHENYL-4-QUINAZOLINONE



No.	R	M.p., °C.	Yield, %	Formula	Calcd., % C	H	N	Found, % C	H	N
17	$-C_6H_5$	207–209	71	$C_{20}H_{18}N_2O$	79.43	6.00	9.27	79.40	6.02	9.25
18	$-CF_3C_6H_4$	207–209	46	$C_{21}H_{17}N_2OF_3$	68.09	4.63	7.56	67.91	4.52	7.69
19	$4\text{-}FC_6H_4-$	211–213	62	$C_{20}H_{17}N_2OF$	74.96	5.35	8.75	74.74	5.34	8.52

TABLE III

4-SUBSTITUTED AMINO-5,6,7,8-TETRAHYDRO-2-PHENYLQUINAZOLINE



No.	R	M.p., °C.	Yield, %	Formula	Calcd., % C	H	N	Found, % C	H	N
20	$-CH_2CH_2OH$	159–161	83	$C_{16}H_{19}N_3O$	71.34	7.11	15.60	71.54	7.33	15.58
21	$-CH_2CH_2NMe_2$	87–90	79	$C_{18}H_{24}N_4$[a]	72.92	8.16	18.91	73.00	8.01	18.86
22	$-CH_2CH_2-N\langle\rangle O$	109–110	87	$C_{20}H_{20}N_4O$[a]	70.99	7.74	16.56	70.67	7.76	16.72

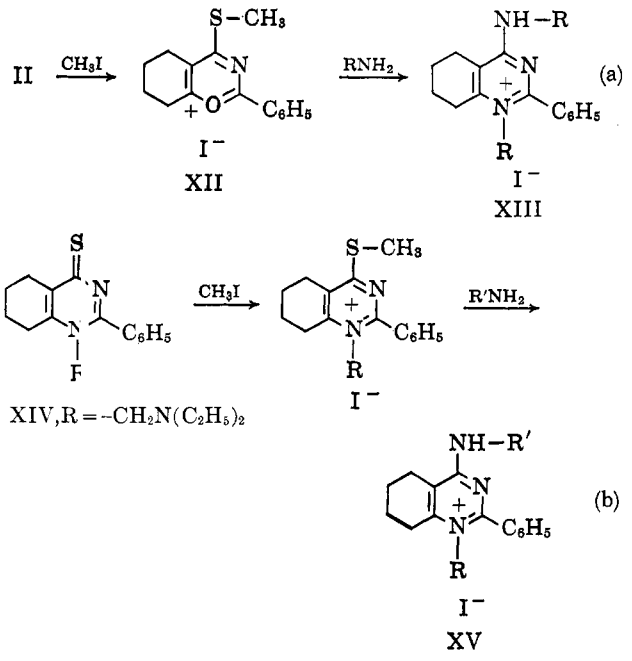
[a] Recrystallized from acetonitrile.

linethiones follow a pattern similar to the 1,2-disubstituted pyrimidines reported previously.[2] Substitution at position 1 with an aromatic group gives an absorption shoulder at 254–259 and a maximum at 341 to 345 mμ. When the substituent at position 1 is alkyl two bands are observed, one at 241–243 and the second at 341–345 mμ. Again this would illustrate the chromophoric nature of the 2-phenyl group in conjugation with the 4-thione through the C=N; however, a slight deviation occurs when R is changed from aromatic to alkyl. The oxygen derivatives of XIV (Table II) gave a single absorption band at 250 mμ.

Experimental

The ultraviolet absorption spectra were obtained from ethanol solutions using a Beckman recording spectrophotometer, Model

SCHEME III



DK. The infrared absorption spectra were run in Nujol mulls using a Perkin-Elmer Model 21 grating spectrophotometer. The melting points are corrected.

General Procedure for the Preparation of 1-Substituted 5,6,7,8-Tetrahydro-2-phenyl-4-quinazolinethione 5,6,7,8-Tetrahydro-1,2-diphenyl-4-quinazolinethione (V). Method A.—To 5,6,7,8-tetrahydro-2-phenyl-1,3-benzoxazine-4-thione (4.0 g., 0.017 mole) dissolved in 25 ml. of ethanol there was added 6 ml. (excess) of aniline. After refluxing this solution overnight, (time varied with amines used from 30 min. to several days) it was chilled for several hours. The resulting light yellow precipitate was collected and recrystallized from ethanol for analysis. See Table I for analytical data of this material.

Method B.—Cyclohexanone (50.0 g., 0.5 mole), aniline (70.0 g., 0.75 mole), and 200 ml. of benzene were combined and refluxed under a water separator until the reaction was complete as determined by the amount of water collected. The solvent was removed *in vacuo* and the residue was distilled. The portion collected at 106–111° (0.1 mm.) was satisfactory for the next step. The anilinocyclohexene (6.0 g., 0.034 mole) in 15 ml. of ether was added dropwise under nitrogen over 1 hr. to an ice-cooled, stirred solution of benzoyl isothiocyanate (5.5. g., 0.34 mole) in 25 ml. of ether. The orange precipitate was collected and washed with ether and methanol to give a nearly pure product (VII), m.p 87–8°.

Anal. Calcd. for $C_{20}H_{20}N_2OS$: C, 71.41; H, 5.99; N, 8.33. Found: C, 70.96; H, 5.78; N, 8.21.

This product when dissolved in tetrahydrofuran and refluxed for 3 hr. gave, on cooling, yellow needles which were collected and recrystallized. This corresponded to a substance identical with that obtained by method A.

This product could also be obtained directly from the condensation of anilinocyclohexene with benzoyl isothiocyanate in refluxing tetrahydrofuran.

5,6,7,8-Tetrahydro-2-phenyl-4-quinazolinethione (VIII).—Ammonia gas was bubbled for 1 hr. through a solution of 4.0 g. of II dissolved in 100 ml. of methanol. The solvent was removed and the white crystalline solid was crystallized from ethanol to give 3.4 g. (86%) of pure VIII, m.p. 199–201°.

Anal. Calcd. for $C_{14}H_{14}N_2S$: C, 69.39; H, 5.82; N, 11.57; S, 13.24. Found: C, 69.35; H, 6.00; N, 11.51; S, 13.14.

4-Hydrazino-5,6,7,8-tetrahydro-2-phenylquinazoline (IX).—Three grams of 5,6,7,8-tetrahydro-2-phenyl-4-quinazolinethione (VIII) was allowed to react under reflux with 12 ml. of hydrazine hydrate in 50 ml. of ethanol overnight. After cooling the solution, the crystals were filtered and recrystallized from ethanol to give pure white needles, m.p. 203–205° (90% yield).

Anal. Calcd. for $C_{14}H_{16}N_4$: C, 69.97; H, 6.71; N, 23.32. Found: C, 69.78; H, 6.74; N, 23.07.

4-Chloro-5,6,7,8-tetrahydro-2-phenylquinazoline (XI). Method A.—One gram of 5,6,7,8-tetrahydro-2-phenyl-4-quinazolinethione (VIII) was combined with 10 ml. of phosphorus oxychloride and refluxed for 1 hr. Upon cooling, the solution was poured onto ice, extracted with chloroform, and dried over magnesium sulfate; the solvent was removed *in vacuo*. Crystallization of the residue from ethanol gave a 71% yield of pure product, m.p. 105–108°.

Anal. Calcd. for $C_{14}H_{13}ClN_2$: C, 68.70; H, 5.36; N, 11.45. Found: C, 68.66; H, 5.26; N, 11.29.

Method B.—One gram of 5,6,7,8-tetrahydro-2-phenyl-4-quinazolinone (X) was allowed to react under reflux with 10 ml. of phosphorus oxychloride for 1 hr. Removal of solvent *in vacuo* and crystallization of the residue from ethanol yielded 0.70 g. (65%) of the desired compound (XI), m.p. 105–108°.

General Procedure for the Preparation of 1-Substituted 5,6,7,8-Tetrahydro-2-phenyl-4-quinazolinones. 5,6,7,8-Tetrahydro-1,2-diphenyl-4-quinazolinone.—5,6,7,8-Tetrahydro-1,2-diphenyl-4-quinazolinethione (4.2 g., 0.013 mole) and 8.3 g. (0.026 mole) of mercuric acetate were dissolved in 50 ml. of acetic acid and refluxed for 7 hr. and was allowed to stand overnight. The solution was filtered, and the filtrate was evaporated *in vacuo*. The resulting residue was taken up in chloroform and the extract was washed with water and dried over magnesium sulfate. Removal of the solvent *in vacuo* gave an oil which was crystallized from acetone to give the desired analytically pure compound, m.p. 207–209° (Table II).

General Procedure for the Preparation of 4-Substituted Amino 5,6,7,8-Tetrahydro-2-phenylquinazolines. 5,6,7,8-Tetrahydro-4-β-hydroxyethylamino-2-phenylquinazoline.—One gram of 4-chloro-5,6,7,8-tetrahydro-2-phenylquinazoline (XI) was refluxed for 2 hr. with 5 ml. of 2-aminoethanol. The solution was cooled, water was added, and the resulting precipitate was filtered. Crystallization of this material from ethanol afforded a white, analytically pure substance, m.p. 159–161° (Table III).

1-(2-Diethylaminoethyl)-4-(2-diethylaminoethylamino)-5,6,7,8-tetrahydro-2-phenylquinazolinium Iodide (XIII).—5,6,7,8-Tetrahydro-4-methylthio-2-phenyl-1,3-benzoxazinium iodide (XII) (3.0 g., 0.008 mole) was dissolved in 50 ml. of ethanol to which 2-(diethylamino)-ethylamine (2.8 g., 0.024 mole) was added. After refluxing the solution for 24 hr., the solvent was removed *in vacuo* to give the crude oily product. Crystallization of this material from ethyl acetate gave 3.2 g. (74%) of pure XII, m.p. 116–118°.

Anal. Calcd. for $C_{26}H_{42}IN_5$: C, 56.61; H, 7.67; N, 12.70. Found: C, 56.51; H, 7.63; N, 12.70.

1-(2-Diethylaminoethyl)-5,6,7,8-tetrahydro-2-phenyl-4-(*n*-propylamino)quinazolinium Iodide (XV).—To 1-(2-diethylaminoethyl)-5,6,7,8-tetrahydro-2-phenyl-4-quinazolinethione (XIV) (4.0 g., 0.11 mole) in 50 ml. of acetone there was added dropwise 2.4 g. (0.017 mole) of methyl iodide. After heating the reaction mixture for 40 min. the solvent was removed *in vacuo* to give a deep purple oil. The oil was dissolved in ethanol and 0.7 g. of *n*-propylamine was added. After refluxing the solution overnight, the solvent was removed *in vacuo* on the steam bath and the resulting oil crystallized on standing. Recrystallization of this substance with acetone yielded 2.4 g. (42%) of analytically pure XV, m.p. 170–172°.

Anal. Calcd. for $C_{23}H_{35}IN_4$: C, 55.86; H, 7.14; N, 11.33. Found: C, 56.00; H, 7.08; N, 11.20.

Acknowledgment.—We take this opportunity to thank Mr. Louis Dorfman for discussions concerning spectral data and the members of his staff for microanalytic and spectral determinations.