and treated with ice water. The product separated as a yellow solid, m.p. 81–86°. Recrystallization from ethanol gave 28 g. (80%) of colorless needles, m.p. 85–86°, λ^{KBr} 4.49 μ (med.).

Anal. Calcd. for $C_{13}H_{15}O_2N$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.82; H, 6.15; N, 6.31.

1-Cyano-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene (VII). A solution of 28 g. of the unsaturated nitrile VI in 100 ml. of methanol was shaken with 1 g. of 10% palladium-carbon catalyst for 10 hr. at 3 atm. hydrogen pressure. After removal of the catalyst and concentration the product crystallized as colorless plates, 23 g. (82%), m.p. 98–99°. Recrystallization from methanol raised the m.p. to 104–105°, λ^{KBr} 4.46 (med).

Anal. Calcd. for $C_{13}H_{16}O_2N$: C, 71.86; H, 6.96. Found: C, 72.06; H, 6.91.

1-Aminomethyl-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene (VIIIa). A. From VII. A solution of 23 g. of the saturated nitrile VIII in ether was refluxed for 5 hr. with excess lithium aluminum hydride. The excess reagent was decomposed with water and the inorganic solid filtered and washed with ether. The combined ether solutions were concentrated to a syrup which crystallized to give 19 g. of white needles, m.p. 86–87°.

B. From VI. A solution of 215 mg. of the unsaturated nitrile in 25 ml. of ethanol containing 0.16 ml. of concd. hydrochloric acid was stirred with 10% palladium-carbon catalyst for 10 hr. in a hydrogen atmosphere. The catalyst was filtered and the solution evaporated to a syrup which was dissolved in hydrochloric acid, decolorized and then made alkaline. The amine separated in white crystals, m.p. and mixed m.p. 83–85°.

1-Aminomethyl-5,8-dihydroxy-1,2,3,4-tetrahydronaphthalene hydrobromide (VIIIb). A solution of 15 g. of the dimethoxyamine in 350 ml. of 48% hydrobromic acid was refluxed for 2 hr. On cooling the salt of VIIIb crystallized as violet plates, which were recrystallized twice from ethanol to give 13 g. of nearly colorless crystals which decomposed above 150° without melting.

Anal. Calcd. for $C_{11}H_{16}O_2NBr$: C, 48.18; H, 5.88, N, 5.11. Found: C 48.53; H, 5.82; N, 5.38.

6-Hydroxy-1,3,4,5-tetrahydrobenz[cd]indole (IX). A solution of 1.23 g. of hydrobromide VIIIb in 100 ml. of water was shaken for 30 min. with freshly precipitated silver chloride and then filtered. To this solution of the hydrochloride of VIIIb was added in one portion a solution of 3.11 g. of potassium ferricyanide and 5 g. of sodium bicarbonate in 50 ml. of water. The solution immediately became magenta, and carbon dioxide was evolved for 2–3 min. The solution was then extracted with four 50-ml. portions of ether and the combined extracts were dried with magnesium sulfate; the drying agent immediately developed a brilliant azure color. The ether was then evaporated *in vacuo* to give 701 mg. of brown crystalline residue. A solution of this material in benzene was passed over a 1.5 x 20 cm. column of alumina. A band of dark violet material was retained at the top of the column; after elution of a small amount of oily material, increasing concentrations of chloroform eluted the indole, which crystallized as pale tan prisms, 452 mg., m.p. 117–118°. Sublimation furnished 406 mg. of sparkling white material. m.p. 125–126°, $\lambda_{max}^{C_2H_5OH}$ 276 μ (6000), 301 μ (4700). The Ehrlich reaction with *p*-dimethylaminobenzaldehyde gave a violet color.

Anal. Calcd. for $C_{11}H_{11}ON$: C, 76.27; H, 6.40; N, 8.09. Found: C, 76.25; H, 6.80; N, 8.41.

The *tosylate* was prepared by heating a solution of 100 mg. of IX and 300 mg. of *p*-toluenesulfonyl chloride in 5 ml. of pyridine at 50° for 26 hr. After pouring onto iced hydrochloric acid the product precipitated. It was recrystallized from ethanol-ether to give 121 mg. of colorless prisms, m.p. 164–165° and 25 mg., m.p. 162–163°.

Anal. Calcd. for $C_{18}H_{17}O_3NS$: C, 66.05; H, 5.24. Found: C, 66.15; H, 5.25.

In an attempted reduction, 100 mg. of the tosylate was refluxed with Raney nickel in ethanol with a stream of hydrogen for 6 hr. After removing the catalyst, evaporation of the solution furnished 65 mg. of the tosylate, m.p. 157–161°. None of the reduced indole was obtained by distillation of the mother liquor.

NEWARK, DEL.

[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, HOFFMANN LAROCHE, INC.]

Quinazolines and 1,4-Benzodiazepines. II.[1] The Rearrangement of 6-Chloro-2-chloromethyl-4-phenylquinazoline 3-Oxide into 2-Amino Derivatives of 7-Chloro-5-phenyl-3H-1,4-benzodiazepine 4-Oxide

L. H. STERNBACH AND E. REEDER

Received June 6, 1960

On treatment with ammonia or primary amines, 6-chloro-2-chloromethyl-4-phenylquinazoline 3-oxide (I) rearranges into 2-amino derivatives of 7-chloro-5-phenyl-3H-1,4-benzodiazepine 4-oxide (II, IX). Reaction of I with secondary amines proceeds without rearrangement with formation of the expected 6-chloro-2-aminomethyl-4-phenylquinazoline 3-oxides.

The structure determination of quinazoline 3-oxides was described in a preceding communication.[1] This paper is concerned with further reactions of these compounds.

In attempts to prepare secondary amino derivatives of quinazoline 3-oxides we treated 6-chloro-2-chloromethyl-4-phenylquinazoline 3-oxide (I)[1] with primary amines. In a few cases the expected products were formed, but in addition we obtained in all reactions compounds of a different character whose infrared and ultraviolet absorption spectra[2a] indicated a structural change. A closer study of the "abnormal" reaction products showed that a ring enlargement[2b] had occurred and that these compounds were 2-amino derivatives of 7-chloro-5-phenyl-3H-1,4-benzodiazepine 4-oxide.

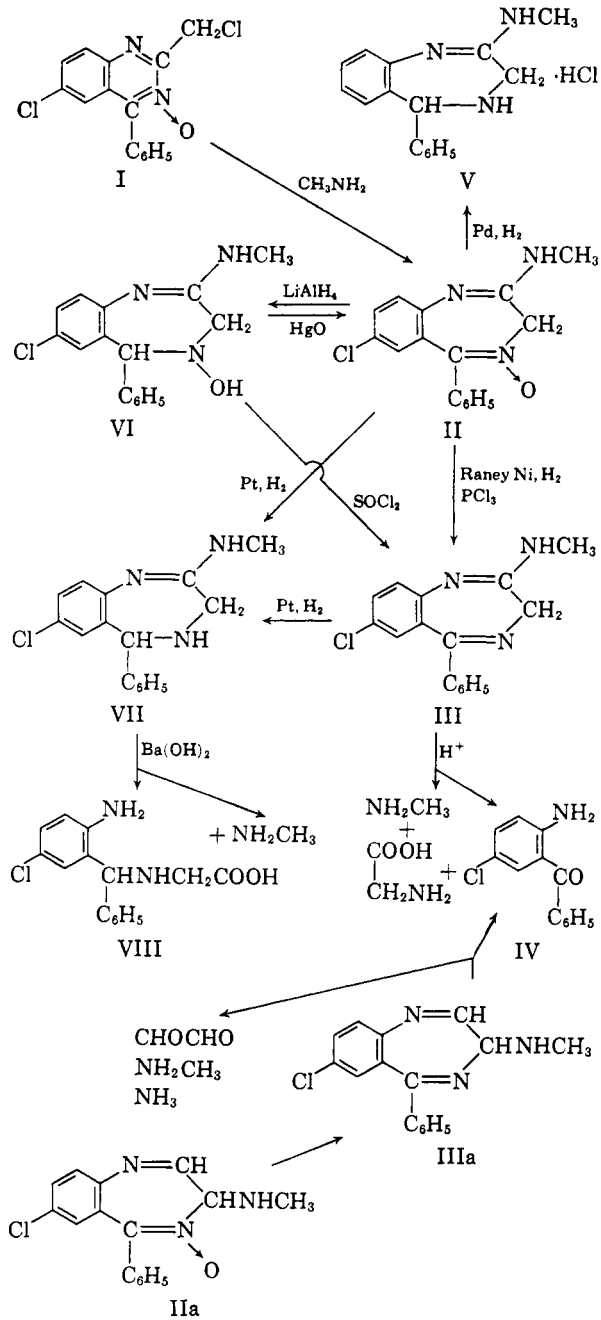
For the structure determination we chose the product formed on treatment of 6-chloro-

(1) Paper I. L. H. Sternbach, S. Kaiser, and E. Reeder, *J. Am. Chem. Soc.* 82, 475 (1960).

2-chloromethyl-4-phenylquinazoline 3-oxide with methylamine. This reaction yielded only the rearranged compound II[3] which was obtained in high yield (about 80%).

The product had the empirical formula $C_{16}H_{14}N_3OCl$ and was shown to be a base by its ability to form a stable hydrochloride. It had a hydrogen atom attached to the basic nitrogen as it could be easily acetylated to form a neutral monoacetyl derivative which in turn could be deacetylated and reconverted into the original base by mild alkaline hydrolysis. It proved to be an *N*-oxide, as it could be converted with excellent yield into a desoxy derivative by treatment with phosphorus trichloride or by hydrogenation with Raney nickel.[4] Both the *N*-oxide and the desoxy derivative yielded on hydrolysis 2-amino-5-chlorobenzophenone (IV) in almost quantitative yield which proved that on reaction with methylamine the 2-amino-5-chlorobenzophenone moiety of the molecule had remained unchanged. For the molecular weight determination we chose the dihydrodesoxy derivative $C_{16}H_{16}N_3Cl$, obtained from $C_{16}H_{14}N_3OCl$ by hydrogenation in the presence of a platinum catalyst. This compound was selected because it was soluble in the usual organic solvents whereas both the oxide and the desoxy derivative were not. The product was found to be a monomer by the Rast and the isothermic distillation methods.

Only structures II and IIa consistent with the above data could be proposed for this compound. To establish the correct one we studied the hydrolytic cleavage of the desoxy derivative III or IIIa. As degradation products, we expected in addition to the 2-amino-4-chlorobenzophenone (IV), glycine and methylamine, if structure II were correct. If IIa were the structure of the compound, glyoxal, ammonia, and methylamine would be the decomposition products. Energetic hydrolysis with dilute hydrochloric acid gave an almost quantitative yield of 2-amino-5-chlorobenzophenone (IV), which was extracted from the



acidic reaction mixture.[5] The aqueous solution was concentrated and the residue was treated with benzoyl chloride in the presence of alkali in order to convert the expected smaller basic fragments into their benzoyl derivatives. We obtained a yield of 55% of hippuric acid, formed from the glycine, and a 59% yield of benzoylmethylamine, formed from the methylamine. This proved conclusively structure II for our product and showed that 6-chloro-2-chloromethyl-4-phenylquinazoline 3-oxide (I) on treatment with methylamine undergoes a ring enlargement resulting in the formation of 7 - chloro - 2 - methylamino - 5 - phenyl - 3H - 1,4-

(2)(a) Characteristic for these compounds is a very strong maximum in the infrared spectrum at 1620–1605 cm.$^{-1}$ accompanied by a sharp peak of medium intensity at 1590–1580 cm.$^{-1}$ whereas the starting material and the normal reaction products showed only two sharp weak peaks at 1605 and 1550 cm.$^{-1}$ The ultraviolet spectra also showed characteristic differences. The starting material and the normal reaction products have two maxima at 230–234 mμ (ϵ, 25 000–30,000) and at 266–270 mμ (ϵ 27,000–32,000). The abnormal reaction products have two maxima at 243–247 mμ (ϵ 25,500–30,500) and at 263–267 mμ (ϵ 22,000–32,000) separated by a flat minimum (ϵ 25,000–29,000). (b) We have not yet established the mechanism of this rearrangement.

(3) The generic name of this compound is chlordiazepoxide and it is marketed under the trade name Librium.®

(4) The desoxy derivative was not a quinazoline as shown by the absence of the strong band at 1543–1539 cm.$^{-1}$ (see Ref. 1, footnote 15) in its infrared spectrum. The similarity of its infrared spectrum to that of the oxide from which it was obtained indicated that the removal of the oxygen atom had occurred without change in the ring structure.

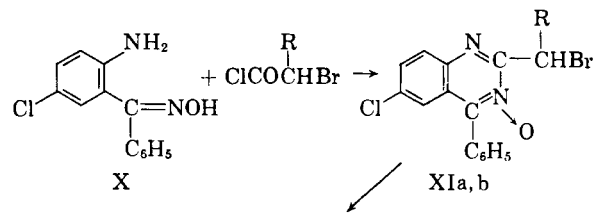
(5) Compound IV is not basic enough to form a salt with 3*N* hydrochloric acid.

benzodiazepine 4-oxide (II), a seven-membered cyclic compound.

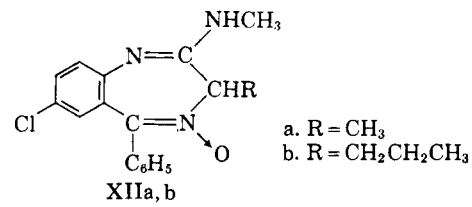
We also studied the hydrolytic degradation of the "dihydrodesoxy" derivative VII which was prepared by catalytic hydrogenation of II or III in the presence of platinum oxide. After acid hydrolysis we isolated methylamine hydrochloride but encountered difficulties in the purification of other degradation products. On hydrolysis with 1*N* barium hydroxide we observed the escape of a volatile base and isolated with excellent yield an insoluble, crystalline barium salt which was converted into a crystalline amino acid. Its composition, amphoteric character, and the presence of a primary aromatic amino group which was demonstrated by a positive diazo reaction pointed to structure VIII for this compound. The hydrolysis of VII to a compound of structure VIII corroborated the structures of II and III from which it was derived and in addition showed that the catalytic hydrogenation of III had resulted in the saturation of the double bond in the 4,5-position.

Further study of II led to the preparation of two additional reduction products. Hydrogenation in the presence of a palladium catalyst resulted in the removal of the oxygen and chlorine atoms, the addition of two hydrogen atoms, with the formation of V. The structure of this product was established by analysis, and by the similarity of the infrared and ultraviolet spectra of its free base with the spectra of VII. Reduction of II with lithium aluminum hydride yielded the hydroxylamine derivative VI.[6] The structure of this compound was proved by its reoxidation to II with mercuric oxide and by its dehydration with thionyl chloride to III.

Compound II showed, as found by L. O. Randall and co-workers,[7] interesting psychosedative properties. Therefore, a series of homologs and analogs of II was prepared by treating 2-chloromethyl-4-phenyl-6-chloroquinazoline 3-oxide (I) with ammonia and various primary amines in dioxane or methanol solutions. In all cases products were formed to which the benzodiazepine oxide structure IX was assigned on account of their characteristic infrared and ultraviolet spectra. The high melting points were also characteristic (in most cases above 200°) as well as the low solubility in acetone and methanol, and the sedative properties, which were observed only in compounds belonging to this group. Two homologs of II were also prepared as shown below (X → XI → XII):



X XIa,b

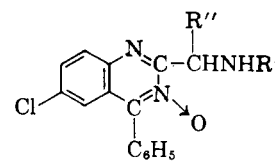


a. R = CH_3
b. R = $CH_2CH_2CH_3$

XIIa,b

The six amines IX a–f and the homolog XIIa showed sedative and muscle relaxant properties.[8] The primary amine IXa was about equally active, the others less active than II. The diamine IXg was pharmacologically inactive.

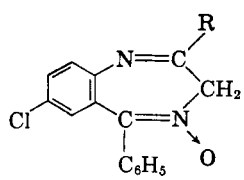
In four cases, the normal reaction products (XIII a–d) were isolated in addition to the rearranged compounds IXd–f and XIIb.[9]



XIII

XIIIa. R′ = $CH_2CH{=}CH_2$; R″ = H
b. R′ = CH_2CH_2OH; R″ = H
c. R′ = $CH_2CH_2OCH_3$; R″ = H
d. R′ = CH_3; R″ = $CH_2CH_2CH_3$

The reaction of I with secondary amines as described for the 2-chloromethyl-6,7-dimethyl-4-phenylquinazoline 3-oxide[1] yielded only the normal reaction products. Two compounds (XIV a and b) belonging to this series were synthesized.



IXa-g

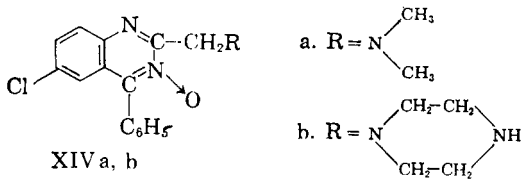
IXa. R = NH_2
b. R = NHC_2H_5
c. R = NHC_4H_9-*n*
d. R = $NHCH_2CH{=}CH_2$
e. R = $NHCH_2CH_2OH$
f. R = $NHCH_2CH_2OCH_3$
g. R = $NHCH_2CH_2NH_2$

(6) O. Exner [*Coll. Czech. Chem. Comm.*, **20**, 202 (1955)] discovered this interesting method for the reduction of nitrones to hydroxylamines.

(7) L. O. Randall, W. B. Schallek, G. A. Heise, E. F. Keith, and R. E. Bagdon, *J. Pharmac. and Experim. Therap.*, **129**, 163 (1960).

(8) Private communication from L. O. Randall.

(9) It is possible that in other reactions, compounds of type XIII were also formed, but no particular attempts were made to isolate them. The preparation of II, however, was thoroughly studied in order to find also the unrearranged reaction product (XIII, R = CH_3; R″ = H). We were, however, unable to demonstrate its presence; variations of the solvents used in this reaction did not result in its formation.



XIV a, b

EXPERIMENTAL

All melting points are corrected. The infrared and ultraviolet absorption spectra of starting materials and reaction products were compared wherever necessary in order to establish structural changes. The infrared spectra were determined in 1–5% chloroform solutions using a Perkin Elmer Model 21 spectrophotometer; the ultraviolet absorption spectra, in isopropyl alcohol and in 0.1*N* hydrochloric acid.

7-Chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine 4-oxide (II). Into 600 cc. of a cold 25% solution of methylamine in methanol was introduced with stirring 98 g. of the hydrochloride of 6-chloro-2-chloromethyl-4-phenylquinazoline 3-oxide (I).[1] The mixture was initially cooled to about 30° and then stirred at room temperature for 15 hr. The precipitated chemically pure reaction product (50 g.) was then filtered off. The mother liquor was concentrated *in vacuo* and the residue dissolved in methylene chloride. The methylene chloride solution was washed with water, dried with sodium sulfate, and concentrated *in vacuo*. The crystalline residue was triturated with a small amount of hot acetone to dissolve the more soluble impurities. The mixture was then cooled to 5° for 10 hr. and filtered, yielding 20.3 g. of almost chemically pure material. The total yield was 70.3 g. (82%). The product could be recrystallized from the fifteen-fold amount of boiling ethanol and formed then light yellow plates melting at 236–236.5°.

Anal. Calcd. for $C_{16}H_{14}N_3OCl$: C, 64.11; H, 4.71. Found: C, 64.38; H, 4.66.

Hydrochloride. A solution of the base in the calculated amount of 2*N* methanolic hydrochloric acid was diluted with ether and petroleum ether and the precipitated hydrochloride was filtered off. It could be recrystallized from methanol or a mixture of methanol and acetone and formed colorless water soluble plates melting at 215–216°. It discolored on exposure to light.

Anal. Calcd. for $C_{16}H_{15}N_3OCl_2$: C, 57.15; H, 4.50. Found: C, 57.20; H, 4.37.

Phosphate. To a stirred suspension of 13.2 g. (44.1 mmoles) of the base in 250 cc. of alcohol were added 44.1 mmoles of 85% phosphoric acid and as much water as necessary to keep the phosphate in solution. The solution was then concentrated to dryness *in vacuo* and the residue triturated with acetone. The crystalline phosphate (13.4 g.) was filtered off. It formed colorless plates melting at 206–207°.

Anal. Calcd. for $C_{16}H_{17}ClO_5P$: C, 48.31; H, 4.31. Found: C, 48.34; H, 4.23.

Bisulfate: To a suspension of 29.4 g. (98 mmoles) of the base in 55 cc. of methanol was added with stirring a solution of 98 mmoles of sulfuric acid in 25 cc. of methanol. The mixture was diluted with 100 cc. of acetone and the crystals formed (39.2 g.) were filtered off. The salt formed colorless plates melting at 214–215°.

Anal. Calcd. for $C_{16}H_{16}N_3O_5ClS$: C, 48.30; H, 4.05. Found: C, 48.81; H, 4.25.

Monoacetyl derivative. To a solution of 100 g. of the base in 1.2 l. of dry pyridine was added 600 cc. of acetic anhydride. The mixture was left at room temperature for 14 hr. and concentrated *in vacuo*. The residue was crystallized from a mixture of ether and petroleum ether (b.p. 30–60°) and yielded 93 g. (82%) of colorless prisms melting at 186–187°.

Anal. Calcd. for $C_{18}H_{16}N_3O_2Cl$: C, 63.25; H, 4.72; N, 12.30. Found: C, 62.96; H, 4.65; N, 12.26.

This compound reformed the base on mild alkaline hydrolysis: To a solution of 2 g. of the acetyl derivative in a mixture of 20 cc. of dioxane and 35 cc. of alcohol was added 25 cc. of 3*N* potassium hydroxide. The solution was left at room temperature for 20 days, diluted with water, and extracted with methylene chloride. The methylene chloride solution was concentrated *in vacuo* and the residue crystallized from a mixture of acetone, ether, and petroleum ether to yield 0.6 g. of the pure base II. It was identified by mixed melting point and infrared spectrum.

7-Chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine (III). A mixture of 20 g. of 7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine 3-oxide (II), 300 cc. of chloroform and 38 cc. of phosphorus trichloride was refluxed for 1 hr. and concentrated *in vacuo* to dryness. To this residue methylene chloride, an excess of 50% potassium hydroxide and ice were added. The mixture was stirred energetically to achieve complete decomposition and the precipitated reaction product was filtered off (12.2 g. m.p. 237–238°). The methylene chloride solution was then separated, dried with sodium sulfate, filtered and concentrated *in vacuo* to yield additional 5.9 g. of the product melting at 227–230°. The total yield was 95%. In other reactions, yields of about 80% were obtained. The product formed after recrystallization from acetone rhombic, yellowish plates melting at 240–241°.

Anal. Calcd. for $C_{16}H_{14}N_3Cl$: C, 67.72; H, 4.97; N, 14.81. Found: C, 67.68; H, 4.93; N, 14.78.

The same compound was obtained by catalytic hydrogenation of the *N*-oxide, II. A solution of 15 g. of II in 200 cc. of warm dioxane was cooled to room temperature and then hydrogenated at atmospheric pressure in the presence of about 20 g. of Raney nickel. After 2 hr. 1 mole of hydrogen was absorbed and the uptake came to an almost complete stop. The precipitated hydrogenation product was dissolved by heating and the Raney nickel removed by filtration. The product was isolated by crystallization in almost quantitative yield.

Hydrochloride. A methanol suspension of the base was neutralized with the calculated amount of 1*N* methanolic hydrochloric acid. The product was crystallized by the addition of ether and petroleum ether. It formed rosettes of plates melting at 260–261°.

Anal. Calcd. for $C_{16}H_{15}N_3Cl_2$: C, 60.02; H, 4.72. Found: C, 59.95; H, 4.63.

Acid hydrolysis of 7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine (II). *Isolation of a 2-amino-5-chlorobenzophenone* (IV), *glycine as hippuric acid, and methylamine as N-methylbenzamide.*

A solution of 2.83 g. (10 mmoles) of 7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine (II) in a mixture of 25 cc. of 3*N* hydrochloric acid and 15 cc. of alcohol was refluxed for 19 hr. The mixture was then cooled, diluted with water, and extracted with ether. The ether extract was dried and concentrated *in vacuo* yielding 2.0 g. (87%) of 2-amino-5-chlorobenzophenone,[5] which was identified by melting point and mixed melting point with an original sample.

The aqueous solution was concentrated *in vacuo* and the residue was dissolved in 30 cc. water. To the stirred and cooled solution were added in portions within 0.5 hr. 4.2 g. benzoyl chloride and about 25 cc. of 3*N* potassium hydroxide at such a rate as to maintain a *p*H of 6–7. The mixture was then made alkaline, heated to 60°, to destroy small amounts of unchanged benzoyl chloride, cooled, and extracted with ether. The ether solution containing the *N*-methylbenzamide was dried, concentrated *in vacuo*, and the *N*-methylbenzamide was extracted from the residual oil with boiling water. The aqueous extract was concentrated *in vacuo*, yielding 0.8 g. (59%) of crystalline *N*-methylbenzamide melting at 77–78°. The analysis sample was recrystallized from ether and formed plates melting at 78–79°. It gave no melting point depression with a synthetic sample.[20]

(20) The melting point reported in the literature is 80°.

Anal. Calcd. for C_8H_9NO: C, 71.09; H, 6.71. Found: C, 71.37; H, 6.79.

The alkaline aqueous solution, remaining after the removal of the *N*-methylbenzamide was acidified and concentrated *in vacuo* to a small volume until the hippuric acid started to crystallize. The mixture was then extracted with ethyl acetate. The extract was dried, concentrated *in vacuo*, and the crystalline residue was treated with hot benzene to dissolve the admixed benzoic acid. The undissolved hippuric acid (0.75 g.) was filtered off. The benzene solution deposited after partial concentration and cooling an additional amount (0.25 g.) of hippuric acid. The total yield was 55%. The hippuric acid was identified by melting point (187°), mixed melting point with an authentic sample, and analysis.

7-Chloro-2-methylamino-5-phenyl-3H-4,5-dihydro-1,4-benzodiazepine (VII). A) *From the desoxy compound* III. The desoxy compound III (2.83 g., 10 mmoles) was hydrogenated in acetic acid solution (20 cc.) at room temperature and atmospheric pressure in the presence of 0.3 g. prehydrogenated platinum oxide. After 1 hr., 10 mmoles of hydrogen was absorbed and the uptake had slowed down considerably. The catalyst was filtered off and the solution concentrated *in vacuo*. The residue was dissolved in ether and washed with ice cold 3*N* sodium hydroxide. The ether solution was dried, concentrated *in vacuo*, and the residue crystallized from a mixture of ether and petroleum ether, yielding 1.8 g. (63%) of crystalline material. The product formed colorless plates softening at 176° and melting at 179–180°.

Anal. Calcd. for $C_{16}H_{16}N_3Cl$: C, 67.24; H, 5.64; N, 14.71; Cl, 12.41; mol. wt., 285.77. Found: C, 66.84; H, 5.79; N, 14.79; Cl, 12.41; mol. wt., (Rast in exaltone) 282, 280; (isothermic distillation in acetone) 295, 302.

B) *From the N-oxide* II. *Isolation as dihydrochloride.* To 0.3 g. of prehydrogenated platinum oxide was added a solution of 2.99 g. (10 mmoles) of II in 40 cc. of acetic acid. The product was hydrogenated at room temperature and atmospheric pressure for 1.5 hr., until 20 mmoles of hydrogen were absorbed and the uptake came to a complete stop. The solution was filtered, concentrated *in vacuo*, and the residue dissolved in ether. The ether solution was washed with alkali, dried, and concentrated *in vacuo*. The residue was dissolved in 20 cc. of 1*N* methanolic hydrochloric acid. The solution was concentrated *in vacuo* and the residue crystallized from a mixture of methanol and ether. The yield was 2.4 g. 67%. The material can be recrystallized from a mixture of methanol and ether and forms then flat prisms or plates softening at 233° and melting at 236–238°. The analysis sample which was recrystallized from dilute hydrochloric acid, formed fine flat needles.

Anal. Calcd. for $C_{16}H_{18}N_3Cl_3$: C, 53.57; H, 5.06; Cl, 29.65. Found: C, 53.53; H, 5.05; Cl, 29.24.

The material could be converted into the above described base by treatment with alkali.

2-Amino-5-chloro-benzhydrylaminoacetic acid (VIII) *and its barium salt.* A solution of 2 g. (7 mmoles) of 7-chloro-2-methylamino-5-phenyl-3H-4,5-dihydro-1,4-benzodiazepine (VII) in a mixture of 30 cc. of methanolic 1*N* barium hydroxide and 10 cc. of water was refluxed for 6 hr. The mixture containing an appreciable amount of crystals was left at room temperature for 2 days and filtered. The precipitated barium salt (1.1 g., 3.07 mmoles) was filtered off, washed with some methanol, and recrystallized from water. It formed white needles melting at 207–208°.

Anal. Calcd. for $C_{30}H_{28}O_4N_4Cl_2Ba$: C, 50.26; H, 3.94; Ba, 19.16. Found: C, 50.54; H, 4.14; Ba, 19.27, 18.91.

The mother liquor containing the excess barium hydroxide and the rest of unchanged starting material was refluxed for 6 more hr., freed from barium ions with about 27 cc. of 1*N* sulfuric acid, filtered, concentrated *in vacuo*, diluted with a small amount of water, and extracted with ether. The free amino acid forming a crystalline precipitate (needles 0.3 g., 1 mmole) was filtered off and recrystallized from methanol or dilute methanol. The product formed needles or prisms softening at 191° and melting at 212–214°. It was soluble in acids and alkali. A strongly acidic solution gave after diazotation a positive color test with β-naphthol.

Anal. Calcd. for $C_{16}H_{15}O_2N_3Cl$: C, 61.96; H, 5.20; N, 9.64; Cl, 12.20. Found: C, 61.81; H, 5.22; N, 9.84; Cl, 12.13. The ether solution was concentrated *in vacuo* and yielded 0.6 g. (2 mmoles) of starting material. Thus 5 mmoles of hydrolyzed starting material yielded 3 mmoles of the barium salt of the amino acid and 1 mmole of the free amino acid.

2-Methylamino-5-phenyl-4,5-dihydro-3H-benzodiazepine hydrochloride (V). Six grams (20 mmoles) of 7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine 4-oxide (II) was hydrogenated at room temperature and atmospheric pressure in 200 cc. methanol with 2 g. of 10% palladium on charcoal as catalyst. After the absorption of about 50 mmoles of hydrogen (3.5 hr.) the reaction was stopped. The solution was filtered, concentrated *in vacuo*, and the residue crystallized from a mixture of alcohol, ether, and petroleum ether. The yield was 4.2 g. (*ca.* 70%). The pure material formed colorless plates melting at 240–242°.

Anal. Calcd. for $C_{16}H_{18}N_3Cl$: C, 66.77; H, 6.30. Found: C, 67.00; H, 5.76.

Base. The base was liberated from the hydrochloride with alkali and formed after crystallization from a mixture of ether and petroleum ether long prisms melting at 153–155°. The ultraviolet and infrared spectra of VII and this base showed a similarity which leaves no doubt as to the identity of their ring structures.

Anal. Calcd. for $C_{16}H_{17}N_3$: C, 76.46; H, 6.82. Found: C, 76.00; H, 6.45.

Dihydrochloride. The free base was dissolved in 2 moles of 1*N* methanolic hydrogen chloride. The solution was concentrated *in vacuo* and the salt crystallized from a mixture of methanol, ether and petroleum ether. It formed crystals melting like the monohydrochloride at 240–242°.

Anal. Calcd. for $C_{16}H_{19}N_3Cl_2$: C, 59.26; H, 5.91. Found: C, 59.37; H, 6.50.

7-Chloro-2-methylamino-4-hydroxy-5-phenyl-4,5-dihydro-3H-1,4-benzodiazepine (VI). A solution of 20 g. 7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine 4-oxide (II) in 200 cc. of dry tetrahydrofuran was added at room temperature in portions to a stirred suspension of 3.8 g. of lithium aluminum hydride in 250 cc. of tetrahydrofuran. The mixture was refluxed for 30 min., then the excess of lithium aluminum hydride was destroyed with ethyl acetate. Ice water was added and the reaction product extracted with ether. The ether solution was dried, concentrated *in vacuo*, and the residue crystallized from ether. The yield was 17 g. (85%). After recrystallization from acetone, the product formed rosettes of colorless needles melting at 183–184°.

Anal. Calcd. for $C_{16}H_{16}N_3OCl$: C, 63.68; H, 5.35; Cl, 11.75. Found: C, 63.65; H, 5.46; Cl, 11.46.

Dihydrochloride. A solution of the base in an excess of 1*N* methanolic hydrogen chloride was concentrated *in vacuo* to a small volume and diluted with ether. The precipitated dihydrochloride was recrystallized from a mixture of methanol and ether and formed then yellowish needles melting with decomposition at 166–170°.

Anal. Calcd. for $C_{16}H_{18}N_3OCl_3$: C, 51.29; H, 4.84. Found: C, 51.57; H, 5.21.

Diacetyl derivative. A solution of 3 g. of the base in a mixture of 48 cc. of pyridine and 24 cc. of acetic anhydride was left at room temperature for 16 hr. and then concentrated *in vacuo* to dryness. The residue was dissolved in ether; the solution was washed with ice cold dilute hydrochloric acid, dilute sodium carbonate solution and water. The dried ether solution was concentrated *in vacuo* and the residue crystallized from a mixture of ether and petroleum ether. It formed rosettes of plates melting at 133–134°.

Anal. Calcd. for $C_{20}H_{20}N_3O_3Cl$: C, 62.52; H, 5.22; acetyl, 22.36. Found: C, 62.54; H, 5.18; acetyl, 21.99.

Dehydration of VI to 7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine (III). To a warm solution of 0.5 g.

of 7-chloro-2-methylamino-4-hydroxy-5-phenyl-4,5-dihydro-3H-1,4-benzodiazepine (VI) in 25 cc. of chloroform was added 0.5 cc. of thionyl chloride. The mixture was refluxed for 10 min., poured on ice, and neutralized with 3*N* alkali. The organic layer was separated, dried, and concentrated *in vacuo*. The residue yielded after crystallization from acetone 0.2 g. of 7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine (III) which was identified by melting point, mixed melting point, and infrared spectrum.

Oxidation of VI *with mercuric oxide to 7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine 4-oxide* (II). A mixture of 1.5 g. of 7-chloro-2-methylamino-4-hydroxy-5-phenyl-4,5-dihydro-3H-1,4-benzodiazepine (VI), 2.1 g. of mercuric oxide, 30 cc. of acetone and 3 cc. of water was shaken at room temperature for 1.5 hr. Then methylene chloride was added and the mixture was filtered. The organic layer was separated, washed with water, dried and concentrated *in vacuo*. The residue was recrystallized from ethanol and yielded 0.2 g. of pure 7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine 4-oxide (II), which was identified by melting point, mixed melting point, and infrared spectrum. In addition, 0.6 g. of less pure lower melting material was obtained.

7-Chloro-2-amino-5-phenyl-3H-1,4-benzodiazepine 4-oxide (IXa). A suspension of 40 g. of 6-chloro-2-chloromethyl-4-phenylquinazoline 3-oxide (I) in 400 cc. of 15% alcoholic ammonia was stirred for 5 hr. at room temperature. The precipitated reaction product was then filtered off and washed with water and ether. The yield was 24 g. (60%), the melting point 245–246°. The product could be recrystallized from a large amount of methanol and formed then slightly yellowish prisms melting at 255–256°.

Anal. Calcd. for $C_{15}H_{12}N_3OCl$: C, 63.05; H, 4.23. Found: C, 63.22; H, 4.43.

Hydrochloride. A solution of the base in the calculated amount of 1*N* methanolic hydrochloric acid was diluted with ether and petroleum ether. The salt precipitated as colorless, water soluble plates melting at 245–246°.

Anal. Calcd. for $C_{15}H_{13}N_3OCl_2$: C, 55.91; H, 4.07. Found: C, 55.68; H, 3.97.

Monoacetyl derivative. To a solution of 0.45 g. of the base in 12 cc. of pyridine was added 12 cc. of acetic anhydride. The precipitated crystalline product (0.4 g.) was filtered off after 2 hr. and was purified by solution in warm pyridine and reprecipitation with acetic anhydride. The pure acetyl derivative forms fine white needles melting at 243–244°.

Anal. Calcd. for $C_{17}H_{14}N_3O_2Cl$: C, 62.29; H, 4.31; N, 12.82; acetyl, 13.13. Found: C, 61.80; H, 4.54; N, 12.96; acetyl, 12.84.

7-Chloro-2-ethylamino-5-phenyl-3H-1,4-benzodiazepine 4-oxide (IXb) was prepared in the same manner as IXa. 6-Chloro-2-chloromethyl-4-phenylquinazoline 3-oxide (I) gave after 14 hr. stirring with the five-fold amount of 33% alcoholic ethylamine a yield of 69%. After recrystallization from acetone the product formed slightly yellowish prisms melting at 231–233°.

Anal. Calcd. for $C_{17}H_{16}N_3OCl$: C, 65.07; H, 5.14. Found: C, 65.33; H, 5.00.

Hydrochloride. A solution of the base in the calculated amount of 1*N* alcoholic hydrochloric acid was diluted with ether and petroleum ether. The salt precipitated as colorless water soluble prisms melting at 208–209°.

Anal. Calcd. for $C_{17}H_{17}N_3OCl_2$: C, 58.29; H, 4.89. Found: C, 57.93; H, 4.72.

7-Chloro-2-butylamino-5-phenyl-3H-1,4-benzodiazepine 4-oxide (IXc) was prepared like IXb, using for 15 g. of I a mixture of 60 cc. of methanol and 30 cc. of *n*-butylamine. The yield was 50%. The pure compound crystallized from acetone in yellowish prisms melting at 202–203°.

Anal. Calcd. for $C_{19}H_{20}N_3OCl$: C, 66.76; H, 5.90. Found: C, 66.82; H, 5.82.

Hydrochloride. A solution of the base in the calculated amount of 1*N* methanolic hydrochloric acid was diluted with acetone, ether, and petroleum ether. The precipitated product was recrystallized from isopropyl alcohol with the addition of acetone and ether. It forms thin colorless plates melting at 171–173°. The product dissolved in water only on addition of dilute hydrochloric acid.

Anal. Calcd. for $C_{19}H_{21}N_3OCl_2$: C, 60.32; H, 5.60. Found: C, 60.09; H, 5.83.

7-Chloro-2-allylamino-5-phenyl-3H-1,4-benzodiazepine 4-oxide (IXd) *and 6-chloro-2-allylaminomethyl-4-phenylquinazoline 3-oxide* (XIIIa). A solution of 30 g. of 6-chloro-2-chloromethyl-4-phenylquinazoline 3-oxide (I) in a cooled mixture of 120 cc. of methanol and 60 cc. of allylamine was left at room temperature for 24 hr. The precipitated 7-chloro-2-allylamino-5-phenyl-3H-1,4-benzodiazepine 4-oxide (IXd) was filtered off (7 g. of prisms, m.p. 201–202°). The mother liquors were concentrated *in vacuo* and the residue dissolved in ice cold 1*N* hydrochloric acid. Neutral impurities were extracted with ether; the acid aqueous part was made alkaline with ice cold 3*N* alkali and the basic products were extracted with ether. The ether layer was dried with sodium sulfate, concentrated *in vacuo*, and the residue crystallized by the addition of acetone and petroleum ether yielding an additional 4.2 g. of IXd. The total yield was 35%. The material was recrystallized from methanol and formed then yellowish prisms melting at 202–204°.

Anal. Calcd. for $C_{18}H_{16}N_3OCl$: C, 66.36; H, 4.95. Found: C, 66.19; H, 4.93.

Hydrochloride. The base was dissolved in the calculated amount of 1*N* methanolic hydrogen chloride and the salt was precipitated by the addition of acetone, ether and petroleum ether. It formed colorless rosettes of plates, darkening at 180° and melting with decomposition at 221–227°. It was soluble in water only after addition of some hydrochloric acid.

Anal. Calcd. for $C_{18}H_{17}N_3OCl_2$: C, 59.68; H, 4.73. Found: C, 59.45; H, 4.96.

In other reactions also the isomeric 6-chloro-2-allylaminomethyl-4-phenylquinazoline 3-oxide (XIIIa) was isolated. It was separated from IXd by crystallization from methanol and acetone. The less soluble compound IXd crystallized and was filtered off. The mother liquors were partially concentrated, filtered again, then concentrated *in vacuo* to dryness. The residue was crystallized from a mixture of acetone and petroleum ether to yield compound XIIIa as yellowish needles melting at 135–136°.

Anal. Calcd. for $C_{18}H_{16}N_3OCl$: C, 66.36; H, 4.95. Found: C, 66.85; H, 5.23.

Hydrochloride. The base was dissolved in the calculated amount of 1*N* methanolic hydrochloric acid, and the salt precipitated by the addition of isopropyl alcohol and ether. After crystallization from a mixture of methanol and isopropyl alcohol, it formed needles melting at 168–169°.

Anal. Calcd. for $C_{18}H_{17}N_3OCl_2$: C, 59.67; H, 4.73. Found: C, 60.14; H, 5.04.

7-Chloro-2-ethanolamino-5-phenyl-3H-1,4-benzodiazepine 4-oxide (IXe) *and 6-chloro-2-ethanolaminomethyl-4-phenylquinazoline 3-oxide* (XIIIb). A suspension of 40 g. of 6-chloro-2-chloromethyl-4-phenylquinazoline 3-oxide in a mixture of 200 cc. of methanol and 100 cc. of ethanolamine was first cooled and then stirred at room temperature for 16 hr. The solution formed was concentrated *in vacuo* and the residue dissolved in 2*N* ice cold hydrochloric acid. Neutral impurities were extracted with methylene chloride, the aqueous part was cooled, made alkaline and mixed with a small amount of methylene chloride. The precipitated (17.7 g., 45%) benzodiazepine oxide (IXe)[2] was filtered off and recrystallized from methanol. It formed yellowish prisms melting at 216–218°. The methylene chloride mother liquor contained the isomer XIIIb which was isolated as described below.

Anal. Calcd. for $C_{17}H_{16}N_3O_2Cl$: C, 61.91; H, 4.89. Found: C, 62.18; H, 4.81.

Hydrochloride. A solution of the base in the calculated amount of 1*N* methanolic hydrochloric acid was diluted

with ether and petroleum ether. The precipitated hydrochloride was filtered off. It could be recrystallized from a mixture of methanol and ether and formed rosettes of needles melting at 210–211° dec.

Anal. Calcd. for $C_{17}H_{17}N_3O_2Cl_2$: C, 55.75; H, 4.68. Found: C, 55.84; H, 4.80.

The methylene chloride solution mentioned above was separated from the aqueous layer, dried and concentrated *in vacuo*. The residue yielded after crystallization from a mixture of methanol and ether 6.7 g. (17%) of the 6-chloro-2-ethanolaminomethyl-4-phenylquinazoline 3-oxide (XIIIb). It formed yellow needles melting at 149–150°.

Anal. Calcd. for $C_{17}H_{16}N_3O_2Cl$: C, 61.91, H, 4.89. Found: C, 61.87, H, 4.80.

7-Chloro-2-(2-methoxyethylamino)-5-phenyl-3H-1,4-benzodiazepine 4-oxide (IXf) and *6-chloro-2-(2-methoxyethylaminomethyl)-4-phenylquinazoline 3-oxide* (XIIIc). A solution of 12 g. of 6-chloro-2-chloromethyl-4-phenylquinazoline 3-oxide (I) in 70 cc. warm dioxane was cooled and combined with 30 cc. of β-methoxyethylamine containing 30% water. After 3 days, the mixture was concentrated *in vacuo* and the residue dissolved in ice cold 1*N* hydrochloric acid. Neutral impurities were extracted with ether; the acidic aqueous part was cooled, made alkaline, and the basic reaction products were extracted with ether. The ether layer was dried over sodium sulfate and quickly filtered, as one of the reaction products started to crystallize out. The filtrate was partially concentrated *in vacuo* and yielded two fractions of crystals, 5.7 g. melting at 160–190° and 1.7 g. melting at 115–116°. The higher melting less soluble product was isolated from these fractions by repeated crystallization from acetone, yielding finally 2.5 g. of pure 7-chloro-2-(2-methoxyethylamino)-5-phenyl-3H-1,4-benzodiazepine 4-oxide[3] (IXf) crystallizing in yellowish prisms melting at 225–226°. The mother liquors yielded the isomer (XIIIc) described below.

Anal. Calcd. for $C_{18}H_{18}N_3O_2Cl$: C, 62.88; H, 5.28. Found: C, 62.75; H, 5.29.

Hydrochloride. The base was dissolved in the calculated amount of 1*N* methanolic hydrochloric acid and the salt was crystallized by the addition of ether. The product forms prisms melting at 207–209°. It dissolved in water only on addition of hydrochloric acid.

Anal. Calcd. for $C_{18}H_{19}N_3O_2Cl_2$: C, 56.93; H, 4.77. Found: C, 57.00; H, 4.84.

The low melting product (m.p. 115–116°) and the mother liquors after the separation of IXf, containing the acetone soluble parts, were concentrated *in vacuo* and the residue was purified by repeated recrystallization from ether. The pure 6-chloro-2-(2-methoxyethylamino)-4-phenylquinazoline 3-oxide (XIIIc) thus obtained (3 g.) formed yellow needles melting at 127–130°.

Anal. Calcd. for $C_{18}H_{18}N_3O_2Cl$: C, 62.88; H, 5 28; N, 12.22. Found: C, 63.10; H, 4.77; N, 11.76.

7-Chloro-2-(2-aminoethylamino)-5-phenyl-3H-1,4-benzodiazepine 4-oxide (IXg) *dihydrochloride.* To a solution of 10 g. of 6-chloro-2-chloromethyl-4-phenylquinazoline 3-oxide (I) in 100 cc. of dioxane was added 10 cc. of ethylenediamine. The solution was left at room temperature for 2 hr. and then concentrated to dryness *in vacuo*. The residue was dissolved in an excess of ice cold 1*N* hydrochloric acid. Neutral impurities were extracted with methylene chloride; the aqueous part was made alkaline with the addition of ice and the basic reaction product was extracted with methylene chloride. The organic solution was separated, dried, concentrated *in vacuo*, and the residue was crystallized from a mixture of methylene chloride, ether, and petroleum ether. The base (4.7 g., 43%) formed yellowish prisms melting at 170–171°. The infrared spectrum proved the benzodiazepine 4-oxide structure.[3] The compound was dissolved in methanol and treated with 2 moles of 1*N* hydrochloric acid. The solution was concentrated *in vacuo* and the residue crystallized from a mixture of methanol and ether. The salt forms colorless plates melting at 219–220°.

Anal. Calcd. for $C_{17}H_{19}N_4OCl_3$: C, 50.82; H, 4.77. Found: C, 50.35; H, 4.61.

6-Chloro-2-(α-bromoethyl)-4-phenylquinazoline 3-oxide (XIa). A solution of 24.6 g. (0.1 mole) of the α-oxime of 2-amino-5-chlorobenzophenone (X)[1] in 120 cc. of warm glacial acetic acid was cooled, and 34.2 g. (0.2 moles) of α-bromopropionyl chloride was added while the temperature was kept at 30°. The mixture was left for 48 hr. at room temperature and then concentrated *in vacuo*. The residue was dissolved in methylene chloride, the solution was washed neutral with ice cold aqueous sodium carbonate, dried with sodium sulfate, and partly concentrated *in vacuo*. The crystalline reaction product (17.5 g.) was precipitated by the addition of ether and petroleum ether. It formed, after crystallization from a mixture of methylene chloride and petroleum ether, yellow needles or rhombic prisms melting at 183–184°.

Anal. Calcd. for $C_{16}H_{12}ON_2BrCl$: N, 7.70. Found: N, 7.73.

7-Chloro-2-methylamino-3-methyl-5-phenyl-3H-1,4-benzodiazepine 4-oxide (XIIa). A solution of 7 g. of 6-chloro-2-(α-bromoethyl)-4-phenylquinazoline 3-oxide (XIa) in 30 cc. warm dioxane was cooled and added to an ice cold 20% solution of methylamine in dioxane. The mixture was left at room temperature for 48 hr. and then concentrated *in vacuo*. The residue was mixed with ether and extracted with ice cold dilute hydrochloric acid. The acidic solution was made alkaline and the reaction product extracted with ether. The ether solution was dried, concentrated *in vacuo*, and the residue crystallized from acetone yielding 1.5 g. of yellowish prisms melting at 246–247°. A fairly large amount of basic material (most probably the normal reaction product) which remained in solution was not further investigated.

Anal. Calcd. for $C_{16}H_{16}N_3OCl$: C, 65.07; H, 5.14. Found: C, 65.56; H, 5.12.

Hydrochloride. The base was dissolved in the calculated amount of 1*N* methanolic hydrochloric acid, and the salt was crystallized by the addition of acetone, ether, and petroleum ether. After recrystallization from methanol with the addition of acetone and ether, it formed flat needles melting at 190–191°.

Anal. Calcd. for $C_{17}H_{17}N_3OCl_2$: N, 12.00. Found: N, 11.67.

2-(α-Bromobutyl)-4-phenyl-6-chloroquinazoline 3-oxide (XIb). To a cool solution of 7.4 g. (30 mmoles) of a mixture of the α- and β-oximes of 2-amino-4-chlorobenzophenone[1] (X) in 40 cc. of glacial acetic acid was added with cooling 6.0 g. (30 mmoles) of α-bromo-*n*-valeryl chloride. The mixture was kept at room temperature for 2 hr., saturated, with cooling, with hydrogen chloride, left at room temperature for 15 hr. and then concentrated *in vacuo*. The residue was dissolved in methylene chloride and washed neutral with ice cold sodium carbonate solution. The methylene chloride solution was dried and concentrated *in vacuo*. The residue crystallized on addition of ether yielding 5 g. of yellow crystals melting at 155–160°. After recrystallization from a mixture of methylene chloride and petroleum ether, the product formed yellow needles melting at 173–174°.

Anal. Calcd. for $C_{18}H_{16}N_2OClBr$: C, 55.19; H, 4.13. Found: C, 55.31; H, 3.93.

7-Chloro-2-methylamino-3-propyl-5-phenyl-3H-1,4-benzodiazepine 4-oxide (XIIb) *and 2-(α-methylaminobutyl)-4-phenyl-6-chloroquinazoline 3-oxide* (XIIId). A suspension of 14.4 g. of 2-(α-bromobutyl)-4-phenyl-6-chloroquinazoline 3-oxide (XIb) in 500 cc. of a 30% methylamine solution in methanol was stirred at room temperature for 1 hr. The solution formed was concentrated *in vacuo* and the residue dissolved in ice cold dilute hydrochloric acid. Neutral impurities were extracted with ether, the acidic aqueous solution was made alkaline with ice cold sodium hydroxide, and the reaction product extracted with ether. This ether solution was concentrated and treated with petroleum ether yielding the benzodiazepine *N*-oxide (XIIb)[3] in crystalline form. (The mother liquor contains the other isomer.) The crude material (3.6 g. m.p. 214–215°) was filtered off and recrystallized from a mixture of acetone and petroleum

ether. It formed yellowish small plates or large irregular prisms melting at 213–214°, resolidifying and melting again at 221–222°.

Anal. Calcd. for $C_{19}H_{20}N_3OCl$: C, 66.76; H, 5.90. Found: C, 66.28; H, 5.35.

Hydrochloride. A suspension of the base in methanol was neutralized with an equivalent amount of 5*N* methanolic hydrochloric acid. The solution was concentrated *in vacuo* and the residue crystallized from a mixture of methanol and separate ether. The hydrochloride formed colorless flat needles melting at 187–189°.

Anal. Calcd. for $C_{19}H_{21}N_3OCl_2$: C, 60.32; H, 5.60. Found: C, 60.28; H, 6.05.

The mother liquor after the separation of the benzodiazepine *N*-oxide (XIIb) described above was concentrated *in vacuo* and the residue crystallized from a mixture of ether and petroleum ether yielding 4 g. of yellowish crystals melting at 103–104°. After recrystallization from petroleum ether the quinazoline *N*-oxide (XIIId)[3] formed rosettes of yellowish needles melting at 106–107°.

Anal. Calcd. for $C_{19}H_{20}N_3OCl$: C, 66.76; H, 5.90. Found: C, 66.77; H, 6.11.

Hydrochloride. A suspension of the base in methanol was neutralized with the equivalent amount of 5*N* methanolic hydrochloric acid. The solution was concentrated *in vacuo* and the residue crystallized from a mixture of methanol, acetone, and petroleum ether. The hydrochloride formed fine white needles melting at 187–189°. It gave a melting point depression with the hydrochloride of the isomeric benzodiazepine *N*-oxide (XIIb).

Anal. Calcd. for $C_{19}H_{21}N_3OCl_2$: C, 60.32; H, 5.60. Found: C, 60.23; H, 5.54.

6-Chloro-2-dimethylaminomethyl-4-phenylquinazoline 3-oxide (XIVa). A solution of 100 g. of 6-chloro-2-chloromethyl-4-phenylquinazoline 3-oxide (I) in 250 cc. of dioxane was added to 150 cc. of a 50% solution of dimethylamine in dioxane. The mixture was left at room temperature for 20 hr., cooled with ice, acidified with 3*N* hydrochloric acid, and extracted with ether to remove neutral impurities. The aqueous layer was then made alkaline with 50% potassium hydroxide (ice was added to keep the mixture cold) and extracted with benzene. The benzene layer was dried with sodium sulfate, concentrated *in vacuo* to a small volume, and diluted with petroleum ether. The crystalline precipitate was recrystallized from a mixture of acetone and petroleum ether. It formed fine yellowish needles melting at 133–134°. The yield was 93 g. (90%).

Anal. Calcd. for $C_{17}H_{16}N_3OCl$: C, 65.07; H, 5.14. Found: C, 65.44; H, 4.86.

Hydrochloride monohydrate. A solution of the base in methanol was neutralized with 1*N* hydrochloric acid. The solution was concentrated *in vacuo* and the residue crystallized from a mixture of isopropyl alcohol and ether. The salt formed yellowish needles melting at 172–173°.

Anal. Calcd. for $C_{17}H_{19}N_3O_2Cl$: C, 55.45; H, 5.20. Found: C, 55.79; H, 5.30.

6-Chloro-2-(1-piperazinylmethyl)-4-phenylquinazoline 3-oxide (XIVb). A suspension of 15 g. of 6-chloro-2-chloromethyl-4-phenylquinazoline 3-oxide (I) in a solution of 30 g. of piperazine hydrate in 250 cc. of methanol was stirred for 20 hr. The precipitated reaction product was filtered off, the filtrate was concentrated *in vacuo*, combined with the precipitate, and dissolved in hydrochloric acid. The acidic solution was washed with methylene chloride and insoluble impurities were filtered off. The aqueous solution was cooled, made alkaline, and the reaction product extracted with methylene chloride. The organic solution was dried, partially concentrated *in vacuo*, and diluted with ether. The reaction product precipitated in yellowish prisms (10.2 g.) melting at 174–175°. After recrystallization from hot benzene with the addition of ether and petroleum ether, the product formed long flat prisms or plates melting at 175–176°. The infrared spectrum showed that the compound had the quinazoline 3-oxide structure.

Anal. Calcd. for $C_{19}H_{19}OClN_4$: C, 64.31; H, 5.40. Found: C, 64.60; H, 5.33.

Dihydrochloride. The base was dissolved in the calculated amount of 0.5*N* methanolic hydrochloric acid and the salt was precipitated by the addition of ether and petroleum ether. It can be recrystallized from methanol, containing a small amount of water, and ether. It formed colorless plates melting at 178–180°.

Anal. Calcd. for $C_{19}H_{21}OCl_3N_4$: C, 53.35; H, 4.95. Found: C, 52.88; H, 5.41.

Acknowledgment. We are indebted to Dr. L. O. Randall and his co-workers for the pharmacological information, to Dr. A. Motchane, Mr. S. Traiman, and Dr. V. Toome for the infrared and ultraviolet spectra, and to Dr. Al Steyermark and his staff for the microanalyses. Mr. L. A. Dolan was helpful in the preparation of larger amounts of starting materials and intermediates.

NUTLEY 10, N. J.

[CONTRIBUTION FROM THE DEPARTMENT OF PHARMACOLOGY, YALE UNIVERSITY SCHOOL OF MEDICINE]

New 5-Substituted 6-Azauracils[1]

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Received July 7, 1960

The 5-position of 6-azauracil (*asym*-triazine-3,5-dione) may be halogenated to yield the 5-chloro, 5-bromo, and 5-iodo derivatives. By reaction of 5-bromo-6-azauracil with molten ammonium acetate, 5-amino-6-azauracil was obtained. 5-Hydroxy-6-azauracil was prepared from the amino compound by basic hydrolysis or by reaction with nitrous acid. The acid dissociation constants, ultraviolet spectra, and infrared spectra were measured.

Recent work on the antitumor activity of 6-azauracil (*asym*-triazine-3,5-dione,1)[2,3] has suggested that its various derivatives substituted at the 5-position might have biological interest. For

(1) This work was supported by a grant (CY-2817) from the National Cancer Institute, Public Health Service. Presented in part before the Division of Medicinal Chemistry, 136th Meeting of the American Chemical Society, September 1959, Atlantic City, N. J.

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