[CONTRIBUTION FROM THE RESEARCH AND DEVELOPMENT DIVISION, WYETH LABORATORIES, INC.]

1,3-Dihydro-2*H*-1,4-benzodiazepine-2-ones and Their 4-Oxides

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Alcoholic sodium hydroxide converts 6-chloro-2-chloromethyl-4-phenylquinazoline 3-oxide (I) into 7-chloro-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepine-2-one 4-oxide (II). 7-Chloro-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepine-2-one (III) was prepared by reduction of II and by several alternate routes. A number of analogs were made.

The novel rearrangement that occurs upon treatment of 6-chloro-2-chloromethyl-4-phenylquinazoline 3-oxide (I) with primary aliphatic amines, affording 2-substituted amino-7-chloro-5-phenyl-3*H*-1,4-benzodiazepine 4-oxides, has recently been described by Sternbach and Reeder.[1] They found that the use of secondary amines and the weaker primary amines did not result in ring enlargement, but led to the expected 2-substituted aminomethyl-6-chloro-4-phenylquinazoline 3-oxides.[2] Similar requirements for ring enlargement have been observed in our laboratory.[3]

It has now been found that treatment of I with sodium hydroxide resulted in the formation of 7-chloro-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepine-2-one 4-oxide (II). That ring enlargement had occurred was indicated by the infrared absorption spectrum which showed a strong carbonyl band at 5.87 μ and no —OH deformation band in the 9.5-μ region. Hydrolysis of the compound with sodium hydroxide led to opening of the cyclic amide with the formation of *N*-(2-amino-5-chloro-α-phenylbenzylidene)glycine *N*-oxide (IV). II was recovered upon treatment with acid.

Compound II was reduced to 7-chloro-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepine-2-one (III) either by catalytic hydrogenation or by treatment with phosphorus trichloride or thionyl chloride. III had characteristics similar to II. Treatment of III with sodium hydroxide afforded the sodium salt of *N*-(2-amino-5-chloro-α-phenylbenzylidene)glycine (V) which upon acidification decomposed into glycine and 2-amino-5-chlorobenzophenone. Reduction of the sodium salt gave *N*-(2-amino-5-chloro-α-phenylbenzyl)glycine (VI). Compound III could be reconverted into II by peracetic acid. The structure of III was confirmed by its independent synthesis from 2-chloroacetamido-5-chlorobenzophenone and ammonia. The foregoing reactions are summarized in Fig. 1 along with two additional synthetic approaches to III.

2-Amino-5-chlorobenzophenone was acylated with *N*-(carbobenzoxy)glycyl chloride and the carbobenzoxy group was removed with hydrogen bromide. The intermediate 5-chloro-2-glycylamidobenzophenone was not isolated but was cyclized to give III. A similar preparation of III in satisfactory yield was accomplished from 2-amino-5-chlorobenzophenone and glycyl chloride hydrochloride. This reaction also afforded a small amount of a by-product, 3-amino-6-chloro-4-phenyl-2(1*H*)-quinolone (VIII). The structure of the by-product was established by deamination to 6-chloro-4-phenyl-2-(1*H*)-quinolone (IX) which was prepared unambiguously by condensing 2-amino-5-chlorobenzophenone with malonic ester, hydrolyzing the 3-carbethoxy-6-chloro-4-phenyl-2(1*H*)-quinolone (X) and decarboxylating the resultant acid.

An attempt to prepare III by treatment of 6-chloro-2-chloromethyl-4-phenyl-quinazoline with alcoholic sodium hydroxide was unsuccessful. 6-Chloro-2-ethoxymethyl-4-phenylquinazoline (XI) was the product of this reaction, illustrating again[3] the essential character of the *N*-oxide function in the ring enlargement. Another failure to prepare III arose from the treatment of 2-benzamido-4′-chloroacetanilide with polyphosphoric acid, only cleavage of the anilide bond occurring.

Both II and III reacted with alkylating agents in the 1-position under alkaline conditions. The point of alkylation in II was established by hydrolytic degradation of the methylated product (XII) to a compound that gave a negative diazo coupling test for a primary aromatic amino group and proved to be *N*-(2-methylamino-5-chloro-α-phenylbenzylidene)glycine *N*-oxide (XIII). The point of alkylation in III was established by independent synthesis of 7-chloro-1-methyl-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepine-2-one (XIV) from 5-chloro-2-methylaminobenzophenone (XV) by treatment with glycyl chloride hydrochloride. In addition XIV was obtained by reducing XII.

Methylation of III in the absence of base led to a quaternary salt (XVI). Sodium borohydride reduced this salt to 7-chloro-4-methyl-5-phenyl-1,3,4,5-tetrahydro-2*H*-1,4-benzodiazepine-2-one (XVII). A similar tetrahydro compound (XVIII) was also produced by catalytic hydrogenation of III, but in this case dechlorination at the 7-position took place simultaneously.

Compounds II and III had very potent actions on the central nervous system, showing sedative, anti-convulsant and anti-anxiety effects. In order

(1) L. H. Sternbach and E. Reeder, *J. Org. Chem.*, **26**, 1111 (1961).

(2) In some cases both types of product were obtained.

(3) S. C. Bell, C. Gochman, and S. J. Childress, *J. Med. Pharm. Chem., in press.*

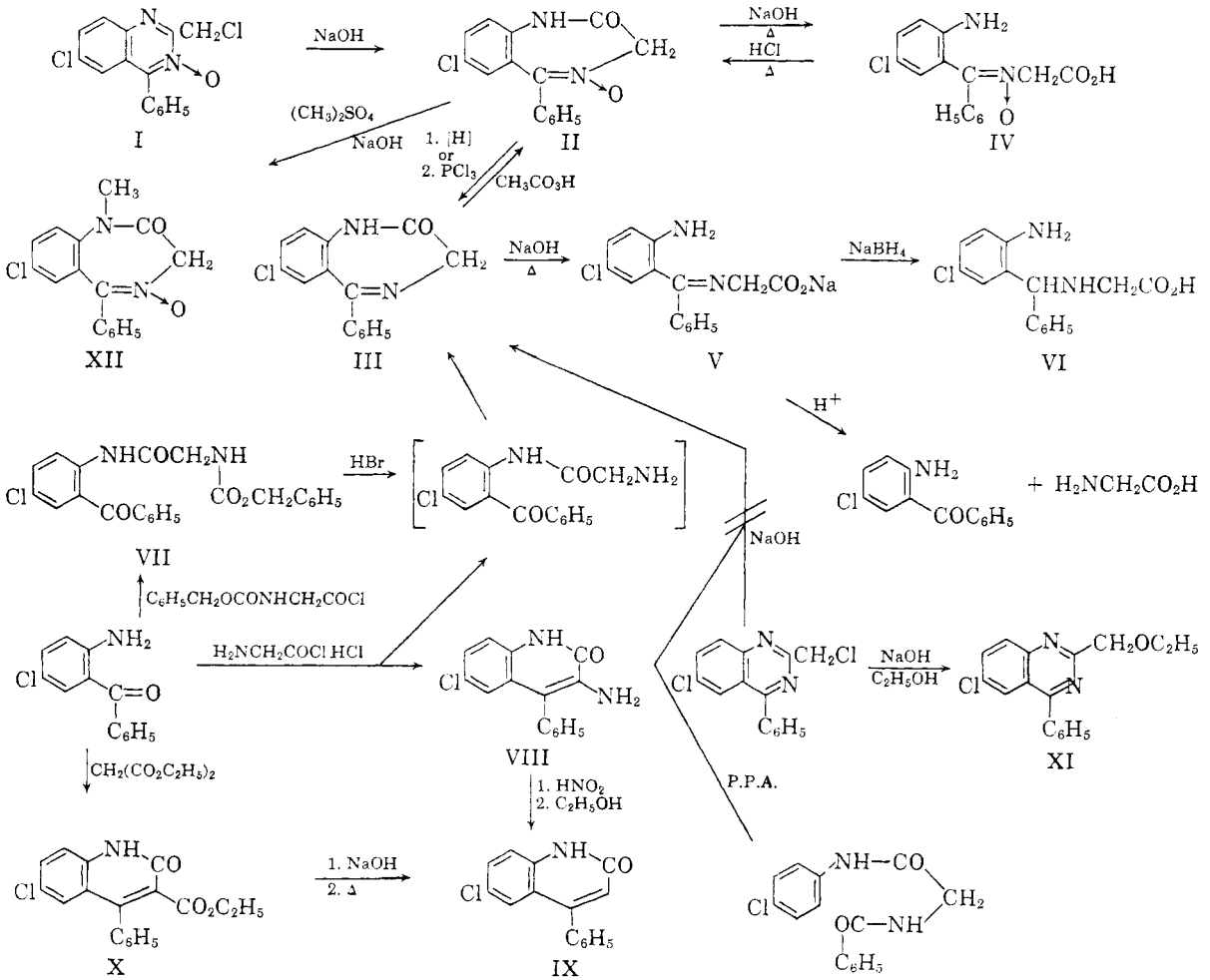


Figure 1

to study the structural requirements for these actions a number of analogs was synthesized, employing the routes illustrated in Fig. 1. The compounds that were made are listed in Table I. The most potent compound was 7-chloro-1-methyl-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepine-2-one (XIV). This material is undergoing clinical trial as Wyeth-3467.

EXPERIMENTAL[4]

The methods indicated below are those referred to in Table I. Intermediates for the compounds in Table I are either given below or will be found in references 1, 3 or 4.

7-Chloro-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepine-2-one 4-oxide (II). *Method A.* 6-Chloro-2-chloromethyl-4-phenylquinazoline 3-oxide (1.5 g.) was added with stirring to a solution of 2 g. of sodium hydroxide in 30 ml. of 85% alcohol. The mixture was stirred for 0.5 hr., diluted with 30 ml. of water and acidified with dilute hydrochloric acid. The product was collected and recrystallized from alcohol to give 1 g. of II, m.p. 238–239°.

When XXVII was prepared from 2-(α-bromoethyl)-6-chloro-4-phenylquinazoline 3-oxide using Method A, absolute ethanol was used as the solvent. In addition to XXVII, *7-chloro-2-ethoxy-3-methyl-5-phenyl-3H-1,4-benzodiazepine 4-oxide*, m.p. 156–157° (from hexane), was isolated in a yield of 22%.

(4) The melting points are uncorrected.

Anal. Calcd. for $C_{15}H_{17}ClN_2O_2$: C, 65.75; H, 5.21; Cl, 10.78; N, 8.52. Found: C, 65.93; H, 5.22; Cl, 10.55; N, 8.64.

Method B. A solution of 1 g. of III and 1 ml. of 40% peracetic acid in 25 ml. of acetic acid was kept at room temperature for 24 hr. Water (200 ml.) was added and the solution was neutralized with sodium carbonate. After recrystallization from alcohol there remained 0.5 g. of II, m.p. 238–239°.

7-Chloro-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepine-2-one (III). *Method C.* To a solution of 23 g. of 2-amino-5-chlorobenzophenone in 100 ml. of chloroform was added with stirring at room temperature 8.5 ml. of chloroacetyl chloride in 50 ml. of chloroform. After 1 hr. the solvent was removed and the residue recrystallized from alcohol giving 24 g. of *2-chloroacetamido-5-chlorobenzophenone*, m.p. 119–121°.

Anal. Calcd. for $C_{15}H_{11}Cl_2NO_2$: C, 58.45; H, 3.60; Cl, 23.01; N, 4.54. Found: C, 58.09; H, 3.30; Cl, 22.72; N, 4.49.

Five grams of the preceding product was added with stirring to 125 ml. of absolute alcohol saturated with ammonia and containing a trace of sodium iodide. While the mixture was stirring for 2 days, the solid dissolved. The solvent was removed *in vacuo* and water was added to the residue. The resultant solid was collected and extracted into dilute hydrochloric acid. Neutralization with ammonia afforded, after recrystallization from alcohol, 1.2 g. of III, m.p. 214–216°.

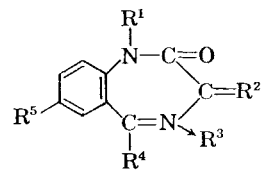
The *methiodide* (XVI), m.p. 250–251°, was prepared from methyl iodide in acetone.

Anal. Calcd. for $C_{16}H_{14}ClIN_2O$: C, 46.56; H, 3.43. Found: C, 46.32; H, 3.37.

7-Chloro-4-methyl-5-phenyl-1,3,4,5-tetrahydro-2H-1,4-benzodiazepine-2-one (XVII). Three grams of XVI in 300 ml. of water was treated dropwise with a solution of sodium boro-

TABLE I

1,3-DIHYDRO-2*H*-1,4-BENZODIAZEPINE-2-ONES



Compound No.	R¹	R²	R³	R⁴	R⁵	M.P.[a]	Method[b]	Recrystallization Solvent[c]	Yield	Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
XIX	H	H_2		CH_3	H	285–286	D	1	45	$C_{10}H_{10}N_2O\cdot HCl$[d]	57.01	5.27		56.55	5.87	
XX	H	H_2	0	CH_3	H	235–236	A	3	59	$C_{10}H_{10}N_2O_2$	63.15	5.29	14.73	63.20	5.19	14.61
XXI	H	H_2		C_6H_{11}	Cl	200–202	C	5	25	$C_{15}H_{17}ClN_2O$	65.03	6.19	10.13	64.92	6.08	10.26
XXII	H	H_2		C_6H_5	H	179–180[e]	D	4	55	$C_{15}H_{12}N_2O$	76.24	5.11	11.86	76.01	5.07	11.60
XXIII	H	H_2	0	C_6H_5	H	250	A	[f]	84	$C_{15}H_{12}N_2O_2$	71.40	4.80	11.11	71.05	4.79	11.36
XXIV	H	H_2		C_6H_5	CH_3	204–206	D	4	77	$C_{16}H_{14}N_2O$	76.77	5.64	11.19	76.99	5.62	11.05
XXV	H	H_2	0	C_6H_5	CH_3	235–236	A	2	90	$C_{16}H_{14}N_2O_2$	72.16	5.30	10.52	71.92	5.37	10.67
III	H	H_2		C_6H_5	Cl	214–216[g]	C, D, E, F, H	1	C: 27	$C_{15}H_{11}ClN_2O$	66.55	4.10	10.35	66.45	4.03	10.55
II	H	H_2	0	C_6H_5	Cl	238–239	A, B	1	A: 87	$C_{15}H_{11}ClN_2O_2$	62.81	3.84	9.77	63.01	4.09	9.83
XXVI	H	H, CH_3		C_6H_5	Cl	220–221[h]	C	1	30	$C_{16}H_{13}ClN_2O$	67.33	4.60	9.84	67.37	4.62	9.90
XXVII	H	H, CH_3	0	C_6H_5	Cl	268 dec.	A	1	27	$C_{16}H_{13}ClN_2O_2$	63.92	4.36	9.32	64.20	4.48	9.07
XXVIII	H	H_2	0	2-C_4H_3S	Cl	255–256	A	1	55	$C_{13}H_{11}ClN_2S$	53.35	3.10	9.57	53.66	3.20	9.09
XXIX	H	H_2		*p*-$CH_3OC_6H_4$	Cl	213–214	C	1	20	$C_{16}H_{13}ClN_2O_2$	63.92	4.36	9.32	64.09	4.50	9.18
XXX	H	H_2	0	*p*-ClC_6H_4	Br	260–261 dec.	A	1	67	$C_{15}H_{10}BrClN_2O_2$	49.27	2.76	7.66	49.29	2.63	7.65
XIV	CH_3	H_2		C_6H_5	Cl	122–124	F, G, H	6	H: 74	$C_{16}H_{13}ClN_2O$	67.33	4.60	9.84	67.44	4.70	9.79
XII	CH_3	H_2	0	C_6H_5	Cl	178–180	G	1	70	$C_{16}H_{13}ClN_2O_2$	63.92	4.36	9.32	63.67	4.23	9.38
XXXI	C_2H_5	H_2		C_6H_5	Cl	129–131	H	7	63	$C_{17}H_{15}ClN_2O$	68.40	5.06	9.39	68.34	4.88	9.25
XXXII	C_2H_5	H_2	0	C_6H_5	Cl	211–212	G	1	22	$C_{17}H_{15}ClN_2O_2$	64.87	4.80	8.91	65.02	4.80	8.68
XXXIII	$(CH_3)_2NCH_2CH_2$	H_2	0	C_6H_5	Cl	211–212	G	8	10	$C_{19}H_{20}ClN_3O_2\cdot HCl$	57.87	5.37	10.66	57.87	5.43	10.81
XXXIV	H	H, C_6H_5		CH_3	Cl	245–247	F	1	50	$C_{16}H_{13}ClN_2O$	67.49	4.60	9.84	67.61	4.88	9.96
XXXV	H	H, C_6H_5		C_6H_5	Cl	279 dec.	E	4	38	$C_{21}H_{15}ClN_2O$	72.72	4.36	8.08	72.45	4.33	7.83
XXXVI	H	$(CH_3)_2$		C_6H_5	Cl	209–211	F	1	8	$C_{17}H_{15}ClN_2O$	68.34	5.06	9.38	68.28	5.05	9.37
XXXVII	H	$-(CH_2)_4-$		C_6H_5	Cl	238–240	F	1	51	$C_{19}H_{17}ClN_2O$	70.26	5.28	8.63	70.16	5.25	8.88

[a] Uncorrected. [b] Experimental Section. [c] Solvents: 1, ethanol; 2, ethyl acetate; 3, water; 4, toluene; 5, acetonitrile; 6, cyclohexane; 7, methanol; 8, ethanol-ether. [d] Cl, Calcd., 16.83. Found: 16.43. [e] Hydrochloride: m.p. 251–253°. [f] Reprecipitated from alkali. [g] Hydrochloride: m.p. 251–252°. [h] Hydrochloride: m.p. 294–295°.

hydride in water until the yellow color was discharged. The product which had precipitated was removed by filtration and recrystallized from cyclohexane and from alcohol to afford 1.8 g. of white crystals, m.p. 206–208°.

Anal. Calcd. for $C_{16}H_{15}ClN_2O$: C, 67.00; H, 5.27; N, 9.77. Found: C, 67.25; H, 5.25; N, 9.85.

5-Phenyl-1,3-dihydro-2H-1,4-benzodiazepine-2-one (XXII). *Method D.* A suspension of 2.5 g. of XXIII in 120 ml. of 80% alcohol and 2 ml. of 6*N* hydrochloric acid was shaken with hydrogen in the presence of 1 g. of 5% palladium-charcoal until one mole of hydrogen was taken up. The filtered solution was concentrated *in vacuo*. Acetonitrile was added to the residue and the hydrochloride salt was separated and dissolved in water. The base was precipitated by addition of sodium carbonate solution. The product (1.3 g.) after recrystallization from benzene melted at 179–180°.

The same product (XXII) was isolated by catalytic hydrogenation of II, two moles of hydrogen removing the 7-chloro group as well as the 4-oxide. When a third mole of hydrogen was added saturation of the 4,5-double bond took place and *5-phenyl-1,3,4,5-tetrahydro-2H-1,4-benzodiazepine-2-one,* m.p. 145–146°, (from cyclohexane) was obtained in a yield of 50%.

Anal. Calcd. for $C_{15}H_{14}N_2O$: C, 75.60; H, 5.92; N, 11.76. Found: C, 75.47; H, 5.56; N, 11.64.

7-Chloro-3,5-diphenyl-1,3-dihydro-2H-1,4-benzodiazepine-2-one (XXXV). *Method E.* A solution of α-carbobenzoxamidophenylacetyl chloride, prepared from 10 g. of α-carbobenzoxamidophenylacetic acid and 7.9 g. of phosphorus pentachloride in 200 ml. of anhydrous ether, was quickly added to a solution of 8 g. of 2-amino-5-chlorobenzophenone in 75 ml. of chloroform. After standing overnight, *2-(α-carbobenzoxamidophenylacetamido)-5-chlorobenzophenone* was collected and recrystallized from alcohol. There was obtained 9.8 g. of product, m.p. 137°.

Anal. Calcd. for $C_{29}H_{23}ClN_2O_4$: C, 69.80; H, 4.65; Cl, 7.11; N, 5.62. Found: C, 70.02; H, 4.83; Cl, 7.20; N, 5.60.

Eight grams of the above product was dissolved in 25 ml. of acetic acid containing hydrogen bromide (30%). Gas evolution occurred and the mixture solidified within 10 min. The solid was separated after 1 hr., washed with ether, and dissolved in 100 ml. of aqueous methanol (75%). The solution was neutralized with ammonia and poured onto crushed ice. The solid—presumably 2-(α-aminophenylacetamido)-5-chlorobenzophenone—was separated and refluxed in toluene overnight. Upon cooling, XXXV crystallized. Recrystallization from toluene gave material melting at 279° dec.

2-(α-Carbobenzoxamidoacetamido)-5-chlorobenzophenone (VII) was made as in the preceding example and used in Method E to prepare III. The intermediate (VII) melted at 115–116° (from ethanol).

Anal. Calcd. for $C_{23}H_{19}ClN_2O_4$: C, 65.32; H, 4.53; Cl, 8.39; N, 6.53. Found: C, 65.58; H, 4.42; Cl, 8.44; N, 6.69.

7-Chloro-5-phenylspiro[3H-1,4-benzodiazepine-3,1'-cyclopentan]-2(1H)-one (XXXVII). *Method F.* A suspension of 12.9 g. of 1-aminocyclopentanecarboxylic acid, 40 g. of phosphorus pentachloride and 300 ml. of carbon tetrachloride was shaken vigorously in a stoppered bottle for 18 hr. The fine solid was filtered off, washed with carbon tetrachloride and with hexane. After drying in a vacuum desiccator, a quantitative yield (18.3 g.) of the acid chloride-hydrochloride, m.p. > 300°, was obtained. This product was suspended in a solution of 20 g. of 2-amino-5-chlorobenzophenone in 400 ml. of carbon tetrachloride and the mixture shaken overnight. The mixture was concentrated to dryness *in vacuo* and the residue was dissolved in methanol. After neutralization with ammonia, the solution was again evaporated *in vacuo,* the residue was extracted with 100 ml. of hot toluene and the extract was heated under reflux for 2 hr. The product, 13.5 g., was obtained on cooling. XXXVII (from alcohol) melted at 238–240°.

3-Amino-6-chloro-4-phenyl-2(1H)-quinolone (VIII) was obtained as a by-product in a yield of 15% when 2-amino-5-chlorobenzophenone and glycyl chloride hydrochloride were employed in Method F. After recrystallization from ethanol the product melted at 239–241°. Its structure was established by deamination (below).

Anal. Calcd. for $C_{15}H_{11}ClN_2O$: C, 66.55; H, 4.10; Cl, 13.10; N, 10.35. Found: C, 66.60; H, 4.14; Cl, 13.00; N, 10.46.

A mixture of 6 grams of VIII, 30 ml. of 95% alcohol and 6 ml. of sulfuric acid was heated on the steam bath to give a clear solution, then cooled to 5°. A solution of 4 grams of sodium nitrite in 10 ml. of water was added, keeping the temperature below 10°. The mixture was stirred for 20 min. after addition was completed. One gram of copper powder was added and the mixture was stirred vigorously and slowly heated to reflux. The reaction mixture was poured onto ice and made basic with ammonia. The solid was removed by filtration and extracted with hot ethanol. Upon cooling the extract afforded a solid, m.p. 260°. Recrystallization from ethanol gave 2.1 g. (37.5%) of product, m.p. 262°. A mixture-melting point with 6-chloro-4-phenyl-2(1*H*)-quinolone (IX) prepared below was not depressed.

3-Carbethoxy-6-chloro-4-phenyl-2(1H)-quinolone (X). Ten grams of diethyl malonate and 11.6 g. of 2-amino-5-chlorobenzophenone were mixed and heated at 150–160° for 1 hr. The mixture was cooled and triturated with hexane. The solid was separated by filtration. After recrystallization from alcohol, 9.5 g. (58%) of small, white needles was obtained, m.p. 235°.

Anal. Calcd. for $C_{18}H_{14}ClNO_3$: C, 65.96; H, 4.30; Cl, 10.82; N, 4.27. Found: C, 65.76; H, 4.28; Cl, 10.70; N, 4.25.

6-Chloro-4-phenyl-2(1H)-quinolone (IX). X (8 g.), 150 ml. of 20% sodium hydroxide solution, and 30 ml. of ethanol were heated under reflux for 1 hr. The mixture was cooled and acidified to give 7 g. (95%) of 3-carboxy-6-chloro-4-phenyl-2(1*H*)-quinolone as an off-white solid, m.p. 305°.

One and one-half grams of this acid was heated in 50 ml. of Dowtherm under reflux for 1 hr. The solution was cooled, diluted with an equal volume of hexane, and chilled. The fine precipitate was removed by filtration and recrystallized from ethanol. After drying, 1.1 g. (86.5%) of very fine needles was obtained, m.p. 262°.

Anal. Calcd. for $C_{15}H_{10}ClNO$: C, 70.45; H, 3.94; Cl, 13.87; N, 5.48. Found: C, 70.67; H, 3.93; Cl, 13.86; N, 5.44.

7-Chloro-1-methyl-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepine-2-one 4-oxide (XII). *Method G.* To a solution of 50.8 g. of II and 8.1 g. of sodium hydroxide in 1500 ml. of water and 300 ml. of alcohol was added dropwise with stirring 17.5 ml. of dimethyl sulfate. After 1 hr. the mixture was chilled and filtered. Recrystallization of the product from alcohol gave 36.5 g. of XII, m.p. 179–180°.

7-Chloro-1-methyl-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepine-2-one (XIV). *Method H.* A solution of 10 ml. of phosphorus trichloride in 10 ml. of benzene was slowly added to a solution of 12.5 g. of XII in 50 ml. of chloroform and 150 ml. of benzene. The reaction mixture became warm and a precipitate formed. The mixture was heated under reflux for 20 min., cooled, and slowly treated with a mixture of 3 ml. of ethanol and 10 ml. of benzene. The precipitate was separated, washed with benzene, and stirred in 300 ml. of water containing 3 ml. of hydrochloric acid. The insoluble matter was filtered off. Sodium carbonate solution precipitated the product from the filtrate. Recrystallization from cyclohexane gave 8.7 g. of crystals, m.p. 122–124°.

N-(2-Amino-5-chloro-α-phenylbenzylidene)glycine N-oxide (IV). A solution of 2 g. of II in 15 ml. of alcohol and 30 ml. of 5*N* sodium hydroxide was warmed on the steam bath for 10 min. The resultant sodium salt (m.p. 220–222°) was collected, dissolved in water, and the solution acidified with acetic acid. Recrystallization of the precipitate from acetonitrile gave 1 g. of IV, m.p. 150–151° dec.

Anal. Calcd. for $C_{15}H_{13}ClN_2O_3 \cdot {}^1/_2\ H_2O$: C, 57.42; H, 4.50; Cl, 11.30; N, 8.93; H_2O, 2.87. Found: C, 57.57; H, 4.57; Cl, 11.40; N, 9.14; H_2O, 2.70.

N-(2-Methylamino-5-chloro-α-phenylbenzylidene)glycine N-oxide (XIII) was prepared similarly. It melted at 150–151° dec.

Anal. Calcd. for $C_{16}H_{16}ClN_2O_2$: C, 60.29; H, 4.66; Cl, 11.12; N, 9.79. Found: C, 60.09; H, 4.50; Cl, 10.96; N, 9.62.

The two preceding compounds could be recyclized by heating for 5 min. in 3*N* aqueous alcoholic hydrogen chloride.

N-(2-Amino-5-chloro-α-phenylbenzylidene)glycine, sodium salt (V). A solution of 2 g. of III in 15 ml. of alcohol and 30 ml. of 5*N* sodium hydroxide was heated under reflux for 10 min., cooled and the resultant sodium salt (1.5 g.) filtered off and washed thoroughly with alcohol. This compound decomposed upon acidification, forming 2-amino-5-chlorobenzophenone and glycine. It was hygroscopic and gave variable carbon-hydrogen analyses.

Anal. Calcd. for $C_{15}H_{12}ClN_2O_2Na$: Na, 7.40. Found: Na, 7.50.

N-(2-Amino-5-chloro-α-phenylbenzyl)glycine (VI). A solution of 3 g. of V in 150 ml. of water was treated with a solution of 0.5 g. of sodium borohydride in 15 ml. of water. After 15 min. the reaction mixture was cautiously acidified with acetic acid, precipitating 2.5 g. of VI, m.p. 192–194°. Sternbach and Reeder[1] reported "softening at 191° and melting at 212–214°".

Anal. Calcd. for $C_{15}H_{15}ClN_2O_2$: C, 61.96; H, 5.20; Cl, 12.20; N, 9.64. Found: C, 61.81; H, 5.22; Cl, 12.00; N, 9.53.

2-Chloromethyl-4-methylquinazoline 3-oxide. A solution of 4.5 g. of 2-aminoacetophenone oxime in 50 ml. of acetic acid was treated overnight with 5 ml. of chloroacetyl chloride. The solvent was removed *in vacuo* and the residue was recrystallized from alcohol to give 4.6 g. of product, m.p. 169–170°.

Anal. Calcd. for $C_{10}H_9ClN_2O$: C, 57.54; H, 4.35; Cl, 16.99; N, 13.45. Found: C, 57.75; H, 4.50; Cl, 17.30; N, 13.39.

6-Bromo-2-chloromethyl-4-(p-chlorophenyl)quinazoline 3-oxide. p-Chlorobenzoyl chloride (100 g.) was cautiously added to 45 g. of *p*-bromoaniline and the mixture was heated to 180°. Fused zinc chloride (35 g.) was added over the course of 15 min. and heating was continued for 1.5 hr. The mixture was partially cooled and cautiously mixed into 300 ml. of alcohol. The solid so obtained was heated for four days in a mixture of 250 ml. of sulfuric acid, 250 ml. of water, and 300 ml. of alcohol. The unhydrolyzed material was filtered off and the filtrate was diluted with water to afford a yellow solid. Recrystallization from hexane gave 14 g. of *2-amino-5-bromo-4'-chlorobenzophenone*, m.p. 122–124°.

Anal. Calcd. for $C_{13}H_9BrClNO$: C, 50.27; H, 2.92; N, 4.51. Found: C, 50.11; H, 3.24; N, 4.53.

Oxime. M.p. 175–177° (from benzene).

Anal. Calcd. for $C_{13}H_{10}BrClN_2O$: C, 47.95; H, 3.09; N, 8.61. Found: C, 48.25; H, 3.14; N, 8.55.

Twelve grams of the foregoing oxime in 100 ml. of acetic acid was treated with 5.8 ml. of chloroacetyl chloride. Precipitation of a solid occurred. Hydrogen chloride was passed into the suspension with warming until solution took place. The solution was kept overnight at room temperature. Water was added to precipitate 6-bromo-2-chloromethyl-4-(*p*-chlorophenyl)quinazoline 3-oxide which after recrystallization from alcohol amounted to 6.6 g. and melted at 180–181°.

Anal. Calcd. for $C_{15}H_9BrCl_2N_2O$: C, 46.90; H, 2.36; N, 7.29. Found: C, 47.16; H, 2.35; N, 7.27.

The following intermediates were prepared as described in Method C for 2-chloroacetamido-5-chlorobenzophenone:

2-Chloroacetamido-5-chloro-4'-methoxybenzophenone, m.p. 138–140° (from alcohol).

Anal. Calcd. for $C_{16}H_{13}Cl_2NO_3$: C, 56.83; H, 3.87; N, 4.14. Found: C, 56.77; H, 3.84; N, 4.03.

2-Chloroacetamido-5-chlorophenyl cyclohexyl ketone, m.p. 116–118° (from alcohol).

Anal. Calcd. for $C_{15}H_{17}ClNO_2$: C, 57.32; H, 5.45; N, 4.46. Found: C, 57.51; H, 5.49; N, 4.20.

2-(α-Bromopropionamido)-5-chlorobenzophenone, m.p. 113–114° (from methanol).

Anal. Calcd. for $C_{16}H_{13}BrClNO_2$: C, 52.44; H, 3.57; N, 3.82. Found: C, 52.44; H, 3.52; N, 3.70.

6-Chloro-2-ethoxymethyl-4-phenylquinazoline (XI). Three grams of 6-chloro-2-chloromethyl-4-phenylquinazoline[5] was slowly added to a solution of 2 g. of sodium hydroxide in 45 ml. of absolute alcohol and the mixture stirred for 1 hr. After heating at 60° for 0.5 hr. the solution was cooled and kept overnight at room temperature. Water was added to precipitate the product. Recrystallization from acetonitrile afforded 1.6 g. of crystals, m.p. 94–96°.

Anal. Calcd. for $C_{17}H_{16}ClN_2O$: C, 68.39; H, 5.06; Cl, 11.86; N, 9.37. Found: C, 68.71; H, 5.04; Cl, 11.54; N, 9.04.

Attempted preparation of III *from 2-benzamido-4'-chloroacetanilide.* A mixture of 2 g. of 2-benzamido-4'-chloroacetanilide[6] and 50 ml. of polyphosphoric acid was heated on the steam bath with stirring for 1 hr. The solution was poured onto ice. The resultant solid, 0.9 g., was identified as hippuric acid.

2-Methylamino-5-chlorobenzophenone (XV). 2-Amino-5-chlorobenzophenone (23 g.) in 50 ml. of pyridine was treated with 21 g. of *p*-toluenesulfonyl chloride to give 36 g. of crude *2'-benzoyl-5'-chloro-p-toluenesulfonanilide.* A small portion recrystallized from alcohol melted at 115–116°.

Anal. Calcd. for $C_{20}H_{16}ClNO_3S$: C, 62.26; H, 4.18; Cl, 9.19; N, 3.63. Found: C, 63.00; H, 3.81; Cl, 8.94; N, 3.77.

The above product was dissolved in dilute sodium hydroxide. With vigorous stirring, 8 ml. of dimethyl sulfate was slowly added. A quantitative yield of crude *N-methyl-2'-benzoyl-5'-chloro-p-toluenesulfonanilide* precipitated. Recrystallization of a small portion from alcohol gave off-white crystals, m.p. 150–152°.

Anal. Calcd. for $C_{21}H_{18}ClNO_3S$: C, 63.07; H, 4.54; N, 3.50. Found: C, 62.86; H, 4.58; N, 3.60.

Thirty-five grams of the crude methylated product was dissolved in 100 ml. of concentrated sulfuric acid and the resultant solution was heated on the steam bath for 30 min. The solution was cooled, poured into 1 l. of water and made basic with ammonia. After recrystallizing the precipitate from hexane there remained 19 g. of XV, m.p. 94–96°.

Anal. Calcd. for $C_{14}H_{12}ClNO$: C, 68.42; H, 4.81; N, 5.70. Found: C, 68.63; H, 4.98; N, 5.81.

Reduction of II *with thionyl chloride.* II (0.5 g.) was placed in 5 ml. of thionyl chloride and heated under reflux for 10 min. The excess reagent was removed *in vacuo* and the residue was recrystallized from alcohol to give 0.3 g. of the hydrochloride of III (See Table I).

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