mixture was then heated under reflux for 2.5 hr., kept 16 hr.; the solid filtered, the filtrate cooled, and extracted with 750 ml. of cold 20% hydrochloric acid. With continued ice-cooling, the acid extract was made alkaline with solid potassium carbonate and the base extracted with ether. Concentration of the dried ether extract and distillation of the residue gave 142.3 g. (81% yield) of the *base*, b.p. 57–60° (1 mm.), $n^{22}D$ 1.4773.

Anal. Calcd. for $C_8H_{17}ClN_2$: Cl, 20.08. Found: Cl, 20.64.

A solution of the *base*, in ether, was cooled, treated with a slight excess of ethereal hydrogen chloride, the solid filtered, and recrystallized from isopropyl alcohol to give the dihydrochloride hemihydrate, m.p. 258–260°.

Anal. Calcd. for $C_8H_{17}ClN_2 \cdot 2HCl \cdot 0.5H_2O$: Cl (total), 41.13. Found: Cl (total), 41.13, 41.26.

Some Analogs of Chlordiazepoxide

S. C. BELL, C. GOCHMAN, AND S. J. CHILDRESS

Research and Development Division, Wyeth Laboratories, Inc., Radnor, Pennsylvania

Received August 29, 1961

Among some analogs of chlordiazepoxide that were prepared, only 2-amino-7-chloro-5-phenyl-3H-1,4-benzodiazepine and its 2-methylamino homolog showed activity approaching that of chlordiazepoxide.

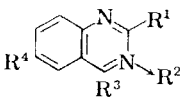
7-Chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine 4-oxide was disclosed by Sternbach[1] as the product of the action of methylamine upon 6-chloro-2-chloromethyl-4-phenylquinazoline 3-oxide. This compound subsequently has been used successfully as an antianxiety agent (chlordiazepoxide). In order to determine in our laboratories the effect of structural changes on the activity, we have prepared a number of related compounds. Those compounds not reported in the recent publications of Sternbach, Kaiser, and Reeder[2] and Sternbach and Reeder[3] are listed in Tables I and II.

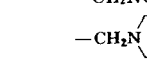
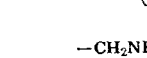
All of the compounds were prepared by known methods. We found, as did Sternbach and Reeder,[3] that secondary amines and

(1) L. H. Sternbach, U. S. Patent 2,893,992 (1959).
(2) L. H. Sternbach, S. Kaiser and E. Reeder, *J. Am. Chem. Soc.*, **82**, 475 (1960).
(3) L. H. Sternbach and E. Reeder, *J. Org. Chem.*, **26**, 1111 (1961).

TABLE I

QUINAZOLINES:

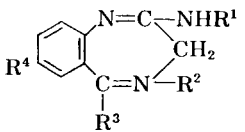


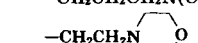
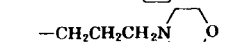
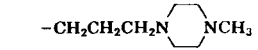
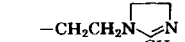
R¹	R²	R³	R⁴	M.p.,[a] °C.	Formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
—CH_2Cl	O	2-C_4H_3S	Cl	159–160	$C_{13}H_8Cl_2N_2OS$	50.17	2.59	9.00	50.53	2.78	9.13
—CH_2Cl	O	C_6H_{11}	Cl	131–132	$C_{15}H_{16}Cl_2N_2O$	57.89	5.18	9.00	58.12	5.06	8.93
—CH_2NHCH_3		C_6H_5	Cl	213–214 dec.	$C_{16}H_{14}ClN_3$·HCl	60.01	4.72	13.12	59.89	4.79	12.76
—$CH_2NHC_6H_5$	O	C_6H_5	Cl	171–173	$C_{21}H_{16}ClN_3O$·HCl	63.32	4.30	10.55	63.32	4.55	10.63
—$CH_2NC_5H_{10}$	O	C_6H_5	CH_3	149–151	$C_{21}H_{23}N_3O$	75.65	6.96	12.60	75.76	6.82	12.53
—$CH_2NC_5H_{10}$		C_6H_5	CH_3	89–90	$C_{21}H_{23}N_3$	79.44	7.30	13.23	79.44	7.21	12.98
	O	C_6H_5	Cl	178–179 dec.	$C_{20}H_{21}ClN_4O$	65.12	5.74	15.19	65.30	5.75	15.20
	O	C_6H_5	Cl	178–179[b]	$C_{21}H_{17}ClN_4O$·2HCl·C_2H_5OH	55.71	5.08	11.30	55.53	4.82	11.42
—$CH_2NHCH_2CH_2SCH_2C_6H_5$	O	C_6H_5	Cl	159–160	$C_{24}H_{22}ClN_3OS$·HCl	61.01	4.91	8.89	60.00	5.00	9.22
—$CH_2NHCH_2CONH_2$	O	C_6H_5	Cl	212	$C_{17}H_{15}ClN_4O$·HCl	53.83	4.25	14.77	53.56	4.32	14.67
—NH_2		C_6H_5	Cl	283	$C_{14}H_{10}ClN_3$·HCl	57.55	3.80	14.38	57.30	3.31	14.54
—$NHC(=NH)NH_2$		C_6H_5	Cl	309–310	$C_{15}H_{12}ClN_5$·HCl	53.91	3.92	20.96	53.45	3.74	20.96
—$CH_2[N(CH_3)_2NH_2]^+Cl^-$	O	C_6H_5	Cl	174–175	$C_{17}H_{18}Cl_2N_4O$	55.90	4.97	15.34	55.53	5.06	15.79
—$CH_2N(CH_3)NH_2$	O	C_6H_5	Cl	232–233	$C_{16}H_{16}ClN_4O$	61.05	4.80	17.80	61.49	4.80	17.91

[a] Uncorrected. [b] Dihydrochloride with ethanol of recrystallization.

TABLE II

3H-1,4-BENZODIAZEPINES:



						Analyses, %					
						Calcd.			Found		
R^1	R^2	R^3	R^4	M.p.,[a] °C.	Formula	C	H	N	C	H	N
—H		C_6H_5	Cl	236–237[b]	$C_{15}H_{12}ClN_3$	66.80	4.49	15.59	66.50	4.31	15.28
—CH_3		C_6H_5	Cl	242–245[c]	$C_{16}H_{14}ClN_3$	67.72	4.97	14.81	67.73	4.78	14.85
—CH_3	O	C_6H_5	H	216–218[d]	$C_{16}H_{15}N_3O$	72.44	5.70	15.84	72.57	5.59	15.90
—CH_3		C_6H_5	H	219–221	$C_{16}H_{15}N_3$	77.07	6.06	16.86	76.95	5.90	16.66
—CH_3		C_6H_5	CH_3	218–220	$C_{17}H_{17}N_3$	77.53	6.51	15.96	77.27	6.68	16.03
—CH_3	O	C_6H_{11}	Cl	239–241	$C_{16}H_{20}ClN_3O$	62.84	6.59	13.74	66.68	6.67	13.96
—CH_3		C_6H_{11}	Cl	218–220	$C_{16}H_{20}ClN_3$	66.30	6.96	14.50	66.26	6.77	14.61
—CH_3	O	2-C_4H_3S	Cl	256–257	$C_{14}H_{12}ClN_3OS$·HCl	49.13	3.83	12.28	48.92	3.73	12.37
—$CH_2C_6H_5$	O	C_6H_5	Cl	223–225	$C_{22}H_{18}ClN_3O$	70.30	5.10	11.18	70.49	4.95	11.06
—$CH_2CH_2N(CH_3)_2$	O	C_6H_5	Cl	262–263	$C_{19}H_{21}ClN_4O$·2HCl	53.10	5.39	13.04	52.71	5.11	12.82
—$CH_2CH_2N(C_2H_5)_2$	O	C_6H_5	Cl	237–238	$C_{21}H_{26}ClN_4O$·2HCl·0.5H_2O	54.02	6.04	12.00	53.93	5.88	12.03
—$CH_2CH_2CH_2N(CH_3)_2$	O	C_6H_5	Cl	242–243 dec.	$C_{20}H_{23}ClN_4O$·2HCl	54.12	5.68	12.63	54.24	5.61	12.88
	O	C_6H_5	Cl	277–278 dec.	$C_{21}H_{23}ClN_4O_2$·2HCl·H_2O	51.49	5.56	11.44	51.65	5.72	11.68
	O	C_6H_5	Cl	231–232 dec.	$C_{22}H_{25}ClN_4O_2$·2HCl	54.38	5.60	11.53	54.18	5.42	11.68
	O	C_6H_5	Cl	216–218	$C_{23}H_{28}ClN_5O$	64.85	6.63	16.44	64.83	6.58	16.18
	O	C_6H_5	Cl	245–246	$C_{21}H_{22}ClN_5O$·2HCl·0.5H_2O	52.78	5.27	14.66	52.80	5.25	14.66
—$C(=NH)NH_2$	O	C_6H_5	Cl	255–256 dec.	$C_{16}H_{14}ClN_5O$·HCl	52.76	4.15	19.23	52.69	4.23	19.45

[a] Uncorrected. [b] Hydrochloride, m.p. 264–265° dec. [c] Hydrochloride, m.p. 260° dec. [d] Ref. 1 gives m.p. 190–191°.

weak primary amines react with 6-chloro-2-chloromethyl-4-phenylquinazoline 3-oxide in a normal way, *i.e.*, replacement of chlorine without ring enlargement. These workers showed that in some cases both "normal" and "abnormal" reactions can take place, but no effort was made by us to isolate two products.

By treating 6-chloro-2-chloromethyl-4-phenylquinazoline with methylamine, 6-chloro-2-methylaminomethyl-4-phenylquinazoline was obtained, showing that no rearrangement occurred in the absence of the 3-oxide function. That the product had the quinazoline structure was shown by its difference from the material resulting from the catalytic deoxygenation of 7-chloro-2-methylamino-4-phenyl-3H-1,4-benzodiazepine 4-oxide, as well as its infrared absorption spectrum.

1,1-Dimethylhydrazine, upon treatment with 6-chloro-2-chloromethyl-4-phenylquinazoline 3-oxide, afforded 1-(6-chloro-4-phenyl-2-quinazolylmethyl)-1,1-dimethylhydrazonium chloride 3-oxide, but no benzodiazepine was isolated. The product easily lost methyl chloride on heating in alcohol, yielding 6-chloro-2-(1-methylhydrazinomethyl)-4-phenylquinazoline 3-oxide. A similar behavior of 1,1-dimethylhydrazine has been observed in its reaction with 4-chloro-6-methyl-1,3,3a,7-tetraazaindene.[4]

In a battery of tests[5] directed toward the central nervous system, those compounds having the quinazoline structure (Table I) were inactive. Of the compounds having the seven-membered ring structure (Table II), only 2-amino-7-chloro-4-phenyl-3H-1,4-benzodiazepine and its 2-methylamino homolog showed activity approaching that of chlordiazepoxide.

Experimental[6]

Only cursory directions for the preparation of the compounds in Tables I and II are given herewith, in case more detailed procedures are available in the publications of Sternbach, *et al.*[2,3] Compound preparations for which the general procedures are not applicable are given individually.

Reactions between 2-Chloromethylquinazoline 3-Oxides and Amines.—The

(4) G. A. Reynolds and J. A. VanAllan, *J. Org. Chem.*, **26**, 115 (1961).

(5) The tests included modifications of the anti-pentylenetetrazole test [G. M. Everett and R. K. Richards, *J. Pharmacol. Exptl. Therap.*, **81**, 402 (1944)], the rotabar test [W. J. Kinnard and C. J. Carr, *ibid.*, **121**, 354 (1957)], the orientational hypermotility test [J. Borsy, E. Csanyi and I. Lazar, *Arch. int. pharmacodyn.*, **124**, 180 (1960)], and the induced conflict test [I. Geller and J. Seifter, *Psychopharmacologia*, **1**, 482 (1960)].

(6) Melting points are not corrected.

appropriate 2-chloromethylquinazoline 3-oxide was added slowly to a large excess of the amine in alcohol and allowed to stand overnight at room temperature. The product was isolated by filtration, concentration of the solvent or dilution with water as seemed appropriate in each case. The product was recrystallized from alcohol. In some cases the hydrochloride was prepared by treatment of the base with one or two equivalents of alcoholic hydrogen chloride, affording the mono- or dihydrochloride, respectively.

2-Acetamido-5-chlorophenyl 2-Thienyl Ketone.—2-Thienylmagnesium bromide was prepared in 200 ml. of ether from 32.6 g. of 2-bromothiophene and 4.9 g. of magnesium. The Grignard reagent was added with stirring to a chilled suspension of 39 g. of 6-chloro-2-methyl-4H-3,1-benzoxazine-4-one in 300 ml. of benzene and the mixture was allowed to warm to 35°. The reaction mixture was decomposed with dilute hydrochloric acid and the ether layer was separated and washed with water and dilute sodium hydroxide. The ether was concentrated and diluted with hexane to afford 27 g. of crude product, m.p. 109–111°. Recrystallization of a portion from ethanol gave material melting at 112–113°.

Anal. Calcd. for $C_{13}H_{10}ClNO_2S$: C, 55.81; H, 3.60; Cl, 12.67; N, 5.01. Found: C, 55.96; H, 3.63; Cl, 12.76; N, 5.03.

2-Amino-5-chlorophenyl 2-Thienyl Ketone.—A solution of 20 g. of 2-acetamido-5-chlorophenyl 2-thienyl ketone in 200 ml. of alcohol and 50 ml. of hydrochloric acid was heated under reflux for 1.5 hr. The addition of 300 ml. of water to the cooled solution precipitated the product. Recrystallization from cyclohexane gave 12 g. of yellow needles, m.p. 97–98°.

Anal. Calcd. for $C_{11}H_8ClNOS$: C, 55.58; H, 3.39; Cl, 14.91; N, 5.89. Found: C, 55.34; H, 3.38; Cl, 14.72; N, 5.96.

2-Amino-5-chlorophenyl 2-Thienyl Ketoxime.—A solution of 16 g. of 2-amino-5-chlorophenyl 2-thienyl ketone and 16 g. of hydroxylamine hydrochloride in 75 ml. of pyridine was heated under reflux for 5 hr. The residue after concentration *in vacuo* was taken up in ether and washed with water. Evaporation of the ether gave 12 g. of product. A portion was recrystallized from carbon tetrachloride to afford crystals that melted at 140–141°.

Anal. Calcd. for $C_{11}H_9ClN_2OS$: C, 52.28; H, 3.59; Cl, 14.03; N, 11.09. Found: C, 52.14; H, 3.42; Cl, 14.20; N, 10.94.

6-Chloro-2-chloromethyl-4-(2-thienyl)-quinazoline 3-Oxide.—A solution of 13 g. of 2-amino-5-chlorophenyl 2-thienyl ketoxime in 100 ml. of acetic acid was treated with 4.2 ml. of chloroacetyl chloride and saturated with dry hydrogen chloride. After standing overnight, the solvent was removed *in vacuo* and the yellow product (8.2 g.) was recrystallized from acetonitrile giving material that melted at 159–160° (see Table I). It was possible to isolate 2-chloroacetamido-5-chlorophenyl 2-thienyl ketoxime, m.p. 175–176° (from toluene), by omitting the treatment with hydrogen chloride.

Anal. Calcd. for $C_{13}H_{10}Cl_2N_2O_2S$: C, 47.43; H, 3.06; Cl, 21.54; N, 8.51. Found: C, 47.45; H, 3.05; Cl, 21.42; N, 8.72.

When an attempt was made to form the quinazoline 3-oxide by using two equivalents of chloroacetyl chloride on the amino oxime (*cf.* Sternbach and Reeder[2]), the chloroacetate ester of 2-chloroacetamido-5-chlorophenyl 2-thienyl ketoxime resulted. Upon recrystallization from ethanol, it melted at 167–169°.

Anal. Calcd. for $C_{15}H_{11}Cl_3N_2O_3S$: C, 44.41; H, 2.73; N, 6.91. Found: C, 44.47; H, 2.83; N, 6.84.

2-Acetamido-5-chlorophenyl Cyclohexyl Ketone.—This ketone, m.p. 113–115°, was prepared in a yield of 50% by treatment of 6-chloro-2-methyl-4H-3,1-benzoxazine-4-one with cyclohexylmagnesium bromide as described above for the 2-thienyl analog.

Anal. Calcd. for $C_{15}H_{18}ClNO_2$: C, 64.38; H, 6.48; Cl, 12.67; N, 5.01. Found: C, 64.29; H, 6.35; Cl, 12.72; N, 5.07.

2-Amino-5-chlorophenyl Cyclohexyl Ketone.—Hydrolysis of 2-acetamido-5-chlorophenyl cyclohexyl ketone was accomplished as described above for the 2-thienyl analog; yield, 45%, m.p. 117–118° after recrystallization from aqueous alcohol.

Anal. Calcd. for $C_{13}H_{16}ClNO$: C, 65.68; H, 6.79; N, 5.89. Found: C, 65.72; H, 6.51; N, 5.97.

2-Amino-5-chlorophenyl Cyclohexyl Ketoxime.—This oxime, prepared in pyridine solution as described above, was recrystallized from alcohol and melted at 200–202°.

Anal. Calcd. for $C_{13}H_{17}ClN_2O$: C, 61.77; H, 6.78; Cl, 14.03; N, 11.09. Found: C, 61.70; H, 6.70; Cl, 13.85; N, 11.08.

6-Chloro-2-chloromethyl-4-cyclohexylquinazoline 3-Oxide.—Five grams of 2-amino-5-chlorophenyl cyclohexyl ketoxime in 50 ml. of acetic acid was treated overnight with 3.2 ml. of chloroacetyl chloride. The residue after evaporation was extracted with ether, the ether was removed and the product was recrystallized from aqueous alcohol giving crystals that melted at 131–132° (see Table I).

2-Amino-7-chloro-5-phenyl-3H-1,4-benzodiazepine.—A solution of 5.9 g. of 2-amino-7-chloro-5-phenyl-3H-1,4-benzodiazepine 4-oxide hydrochloride in 100 ml. of alcohol and 20 ml. of water was shaken with hydrogen in the presence of 1.2 g. of 5% palladium-on-charcoal until one equivalent of hydrogen had been consumed. The solution was filtered and diluted with 100 ml. of cold water to afford, upon treatment with ammonia and recrystallization from alcohol, 2.2 g. of 2-amino-7-chloro-5-phenyl-3H-1,4-benzodiazepine, m.p. 236–237° (see Table II).

The other deoxygenated compounds of Tables I and II were prepared in the same way or by use of phosphorus trichloride in chloroform as described by Sternbach, *et al.*[2,3]

6-Chloro-2-guanido-4-phenylquinazoline Hydrochloride.—2-Amino-5-chlorobenzophenone hydrochloride (8.1 g.) was fused with 2.5 g. of dicyandiamide at 140–150° for 3 hr.[7] The solid so obtained was washed with alcohol and recrystallized from aqueous alcohol containing a little hydrochloric acid. The pale yellow product, 2.0 g., melted at 309–310° (see Table I).

2-Amino-6-chloro-4-phenylquinazoline Hydrochloride.—2-Amino-5-chlorobenzophenone hydrochloride (8.1 g.) was warmed with 1.0 g. of cyanamide,[5] a vigorous reaction taking place. Alcoholic hydrogen chloride (80 ml.) was added to the cooled mixture and the product (4.0 g.) was filtered and recrystallized from alcohol. The product melted at 283° (see Table I).

(7) L. F. Theiling and R. L. McKee, *J. Am. Chem. Soc.*, **74**, 1834 (1952).

Acknowledgments.—We wish to thank Drs. Richard Tislow and Irving Geller and their associates for the pharmacological evaluations and Dr. Gordon Ellis and his group for the analytical data.

Indanols. IV.[1] Indanoxypropanolamines

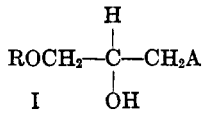
SEYMOUR L. SHAPIRO, VINCENT A. PARRINO, ELAINE S. ISAACS, AND LOUIS FREEDMAN

Research Laboratories, U. S. Vitamin & Pharmaceutical Corporation, Yonkers, New York

Received September 14, 1961

In a series of indanoxypropanolamines, $ROCH_2CHOHCH_2A$, compounds providing the best muscle relaxant activity have been found wherein R is 4-indanyl, and A is a relatively weak basic secondary amino group.

Indanoxypropanolamines of the type (I) have been synthesized and examined as central nervous system depressants. Related compounds have been evaluated as analgesics,[2,3] hypnotics,[4] anticonvulsants,[5,6] and muscle relaxants.[7,8]



I

R = 4 and 5-indanyl
A = dialkylamino substituted aminoalkylamino

The indanoxypropanolamines I (Table I) were obtained in fair

(1) Paper II in this series: S. L. Shapiro, K. Weinberg, T. Bazga, and L. Freedman, *J. Am. Chem. Soc.*, **80**, 3729 (1958).

(2) Y. M. Beasley, V. Petrow, and O. Stephenson, *ibid.*, **10**, 47, 103 (1958).

(3) V. Petrow, O. Stephenson, A. J. Thomas, and A. M. Wild, *ibid.*, **10**, 86 (1958).

(4) W. Schindler and F. Häfliger, U. S. Patent 2,948,719, Aug. 9, 1960.

(5) F. M. Berger, *J. Pharm. Exptl. Therap.*, **105**, 450 (1952).

(6) S. L. Shapiro, V. A. Parrino, and L. Freedman, *J. Am. Chem. Soc.*, **81**, 3996 (1959).

(7) C. D. Lunsford, R. P. Mays, J. A. Richman, Jr., and R. S. Murphey, *ibid.*, **82**, 1166 (1960).

(8) (a) J. Cheymol, P. Piganiol, P. Chabrier, and J. Seyden-Penne, *Compt. rend.*, **250**, 1498 (1960); (b) P. Piganiol, J. Cheymol, J. Seyden-Penne, and P. Chabrier, *Bull. soc. chim. France*, 255 (1961).