Experimental Section[14]

Amidoximes. General Procedure.—A mixture of 1 mole of alkyl or aryl cyanide and 1 mole of hydroxylamine hydrochloride was dissolved in 500 ml of 80% aqueous ethanol. One-half mole of K_2CO_3 was added, and following the evolution of CO_2 the solution was heated under reflux overnight. The solvent was removed under reduced pressure (steam bath), and the residue was twice extracted with 200 ml of absolute ethanol. The ethanol extract was concentrated to dryness, and the resulting amidoxime was recrystallized from benzene. Unless otherwise indicated, the amidoximes used are described in ref 2b.

3-Substituted 1,2,4-Oxadiazoles (Table I). General Procedure.—A mixture of 0.1 mole of appropriate amidoxime and 100 ml of triethyl orthoformate was heated under reflux for 2 hr, and the reaction mixture was then distilled under reduced pressure. If the product was a solid at room temperature, it was recrystallized from ethyl acetate–petroleum ether (60–70°) mixture. The nitrile corresponding to the starting material for the amidoxime was often a by-product of the reaction.[8]

3-*p*-Chlorophenyl-1,2,4-oxadiazole (14).—To 0.1 mole of DMF–$POCl_3$ complex[10] was added, with stirring, an ether solution of 0.05 mole of *p*-chlorobenzamidoxime. The temperature was maintained near 10° by means of an ice bath and the mixture was stirred for 10 min. After the solvent was removed at 60°, the residue was washed twice with 150 ml of ice water. The product was recrystallized from methanol and gave **14**, mp 100–102°, in 80% yield.

3,5-Disubstituted 4,5-Dihydro-1,2,4-oxadiazoles (Table IV). (a) General Procedure.—To 0.1 mole of appropriate amidoxime dissolved in 200 ml of 50% aqueous ethanol was added portionwise 0.15 mole of aldehyde. After the initial exothermic reaction had ended, the solution was allowed to stand at room temperature for 2 days and then was concentrated under reduced pressure (steam bath). The residue was recrystallized from ethanol–water if it was a solid, or was distilled using a spinning-band column if it was a liquid at room temperature.

(b) Spiro-4,5-dihydro-1,2,4-oxadiazoles (Table IV).—A mixture of 0.05 mole of the appropriate amidoxime and 20 ml of cyclohexanone[15] was heated under reflux for 2 hr. The mixture was concentrated under reduced pressure (steam bath) and the product was recrystallized from benzene.[16]

Acknowledgment.—The microanalyses were determined by W. L. Brown and associates, and D. O. Woolf, Jr., made the physical measurements. R. J. Boisvenue, M. C. Brandt, W. R. Agan, and E. L. Colestock assisted with the anthelmintic studies.

(14) Melting points were taken with a Fisher-Johns apparatus and are uncorrected.

(15) The reaction did not take place when cyclopentanone or cycloheptanone was used.

(16) In certain instances it was necessary to elute the product from an alumina column using benzene in order to obtain crystals.

Derivatives of 1-Hydroxybenzimidazoles and 1-Hydroxyindoles and Their Central Depressant Effects

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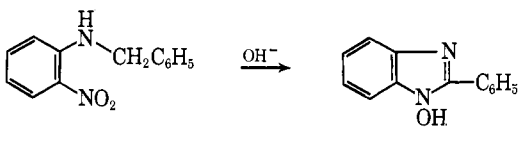
It has been noted that 1-(2-diethylaminoethoxy)-2-phenylbenzimidazole causes central nervous system depression in experimental animals. A variety of related compounds have been prepared and compared with this substance. In addition, corresponding derivatives of 1-hydroxy-2-phenylbenzimidazole 3-oxide and 1-hydroxy-2-phenylindole have also been synthesized and tested for CNS depression. A structure–activity relationship account is presented.

The first report on the synthesis of 1-hydroxybenzimidazoles was made by Niementowski[1] in 1910 who reduced *o*-nitroacetanilide with ammonium sulfide to form 1-hydroxy-2-methylbenzimidazoles. Fries and Reity[2] later were able to effect this reduction much more efficiently with sodium hyposulfite. Finally, in 1964 an alternate synthesis of this class of compounds was developed by Stacy, *et al.*,[3] which involved base-catalyzed cyclization of N-benzyl-*o*-nitroaniline. These authors also emphasized that the nmr spectrum strongly supports the assignment of the N-hydroxy form as the preferred tautomeric structure rather



I

than the N-oxide structure assigned by Kew and Nelson.[4] In addition, it was also shown by Takahushi and Kano[5] that the parent substance, 1-hydroxybenzimidazole, could be readily alkylated with methyl iodide to yield the 1-methoxy derivative. It thus occurred to us that a variety of 1-hydroxy-2-substituted benzimidazoles and their corresponding 1-alkoxy derivatives could be prepared for biological evaluation. This work was particularly prompted by the findings of Hunger,[6] *et al.*, who noted that 2-benzyl-1-(2-diethylaminoethyl)-5-nitrobenzimidazole exhibited potent analgetic effects. Thus, 1-alkoxybenzimidazoles related to this class of compounds were prepared from the corresponding 1-hydroxy heterocycle. The 1-hydroxy-2-arylbenzimidazoles and substituted derivatives were prepared according to the method of Stacy, whereas the 2-alkyl derivatives were synthesized by the procedure outlined by Fries and Reity.

Since substance 8 (Table I) showed good CNS depression in experimental animals, several modifications of the same were made in a structure–activity relationship study (*vide infra*). Besides the usual changes in the basic side chain, nuclear modifications at the 2 position, and substitutions on the benzene portion

(1) St. v. Niementowski, *Ber.*, **43**, 3012 (1910).

(2) K. Fries and H. Reity, *Ann.*, **527**, 38 (1937).

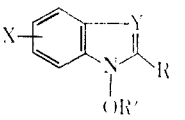
(3) G. W. Stacy, B. V. Ettling, and A. J. Papa, *J. Org. Chem.*, **29**, 1537 (1964).

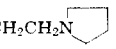
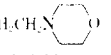
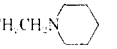
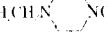
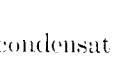
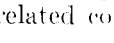
(4) D. J. Kew and P. F. Nelson, *Australian J. Chem.*, **15**, 792 (1962).

(5) S. Takahushi and H. Kano, *Chem. Pharm. Bull.* (Tokyo), **12**, 282 (1964).

(6) A. Hunger, H. Keberle, A. Rossi, and K. Hoffmann, *Helv. Chim. Acta*, **43**, 1032 (1960).

TABLE I
HETEROCYCLIC ETHERS



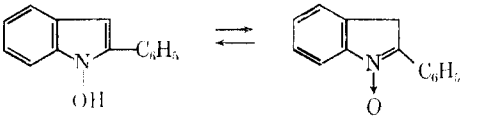
No.	Y	R	R′	X	Mp, °C	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
1	N	CH_3	$CH_2CH_2N(CH_3)_2$	H	187	$C_{12}H_{17}N_3O\cdot 2HCl$	49.32	6.29	14.38	49.20	6.60	14.01
2	N	CH_3	$CH_2CH_2N(C_2H_5)_2$	H	186	$C_{14}H_{21}N_3O\cdot 2HCl$	52.54	7.24	13.11	52.42	7.38	13.06
3	N	CH_3	$(CH_2)_3N(C_2H_5)_2$	H	186	$C_{15}H_{23}N_3O\cdot 2HCl$	53.89	7.53	12.57	54.26	8.02	12.23
4	N	CH_3	$CH_2CH_2N(CH_3)_2$	6-OCH_3	196	$C_{13}H_{19}N_3O_2\cdot 2HCl\cdot H_2O$	46.12	6.82	12.35	46.40	7.17	12.02
5	N	CH_3	$CH_2CH_2N(C_2H_5)_2$	6-OCH_3	204–205	$C_{15}H_{23}N_3O_2\cdot 2HCl$	51.43	7.19		51.22	7.30	
6	N	CH_3	$(CH_2)_3N(C_2H_5)_2$	6-OCH_3	143–145	$C_{16}H_{25}N_3O_2\cdot 2HCl$	51.43	7.50	11.24	51.12	7.86	11.34
7	N	C_6H_5	$CH_2CH_2N(CH_3)_2$	H	177–178	$C_{17}H_{19}N_3O\cdot 2HCl$	57.62	5.97		57.29	6.07	
8	N	C_6H_5	$CH_2CH_2N(C_2H_5)_2$	H	158–160	$C_{19}H_{23}N_3O\cdot 2HCl$	59.69	6.59	10.99	59.58	6.85	10.79
9	N	C_6H_5		H	187–188	$C_{19}H_{21}N_3O\cdot 2HCl$	62.30	6.33	7.65	62.28	6.30	7.66
10	N	*p*-Cl-C_6H_4	$CH_2CH_2N(C_2H_5)_2$	H	128–130	$C_{19}H_{22}ClN_3O\cdot 2HCl$	54.75	5.77	10.08	54.70	5.72	9.78
11	N	C_6H_5	$CH_2CH_2N(CH_3)_2$	6-Cl	192–193	$C_{17}H_{18}ClN_3O\cdot 2HCl$	52.52	5.19	10.81	52.23	5.49	10.55
12	N	C_6H_5	$CH_2CH_2N(C_2H_5)_2$	6-Cl	186–187	$C_{19}H_{22}ClN_3O\cdot 2HCl$	54.75	5.80	10.08	54.44	6.07	9.86
13	N	*p*-CH_3O-C_6H_4	$CH_2CH_2N(C_2H_5)_2$	H	143–145	$C_{20}H_{25}N_3O_2\cdot 2HCl$	55.54	6.84	9.69	55.81	7.02	9.36
14	N	C_6H_5	$CH_2CH_2N(CH_3)_2$	6-NO_2	200	$C_{17}H_{18}N_4O_3\cdot HCl$	56.27	5.29	15.44	56.09	5.39	15.52
15	N→O	C_6H_5	$CH_2CH_2N(CH_3)_2$	H	185–186	$C_{17}H_{19}N_3O_2\cdot HCl\cdot 2H_2O$	55.12	6.53	11.34	55.35	6.26	11.30
16	N→O	C_6H_5	$CH_2CH_2N(C_2H_5)_2$	H	123–124	$C_{19}H_{24}N_3O_2\cdot HCl\cdot 3H_2O$	54.98	7.26	10.02	54.97	7.38	9.82
17	N→O	C_6H_5	$CH_2CH_2CH_2N(CH_3)_2$	H	103–105	$C_{18}H_{21}N_3O_2\cdot HCl\cdot 3H_2O$	53.90	7.03	10.05	54.19	7.10	10.19
18	N→O	C_6H_5		H	200–202	$C_{19}H_{21}N_3O_3\cdot HCl\cdot 2H_2O$	57.79	6.09	10.57	57.21	6.06	10.20
19	CH	C_6H_5	$CH_2CH_2N(CH_3)_2$	H	164	$C_{18}H_{20}N_2O\cdot C_4H_4O_4$[a]	66.65	6.10	7.06	66.35	6.24	6.85
20	CH	C_6H_5	$CH_2CH(CH_3)N(CH_3)_2$	H	134–135	$C_{19}H_{22}N_2O\cdot C_4H_4O_4$	67.29	6.39	6.83	66.91	6.47	6.63
21	CH	C_6H_5	$CH_2CH_2N(C_2H_5)_2$	H	125	$C_{20}H_{24}N_2O\cdot C_4H_4O_4$	67.99	6.67	6.51	68.07	6.39	6.45
22	CH	C_6H_5		H	136–137	$C_{20}H_{22}N_2O\cdot C_4H_4O_4$	68.22	6.21	6.63	68.10	6.22	6.55
23	CH	C_6H_5		H	124–125	$C_{24}H_{24}N_2O\cdot C_4H_4O_4$	68.78	6.47	6.42	68.59	6.69	6.51
24	CH	C_6H_5		H	129–130	$C_{26}H_{22}N_2O_2\cdot C_4H_4O_4$	65.74	5.98	6.39	65.69	6.17	6.28
25	CH	C_6H_5		H	180–181	$C_{21}H_{25}N_3O\cdot 2C_4H_4O_4$	61.49	5.84	7.42	61.44	5.97	7.15

[a] $C_4H_4O_4$ indicates maleate salt.

of the heterocycle, other heterocyclic ring systems closely allied to 1-hydroxybenzimidazole were also synthesized.

For instance, the condensation of nitrosobenzene with benzonitrile oxide according to the method of Minisci and co-workers[7] afforded 1-hydroxy-2-phenylbenzimidazole 3-oxide. The appropriate 1-alkoxy derivatives of this and related compounds were accordingly prepared.

In addition, it was also of interest to synthesize 1-hydroxy-2-phenylindole, the carbon isostere of the prototype compound. This was done according to the method of Fischer and Hüty.[8] The alkylation of this compound, however, initially caused considerable difficulties. The procedure employed had proven successful in our previous studies, *i.e.*, the substance to be alkylated was dissolved in toluene or toluene–dimethylformamide and then treated with NaH to form the sodium salt which, in turn, was allowed to react with the appropriate alkylating agent. Under these conditions no homogeneous product could be isolated. Chromatograms of the crude isolated oils only revealed the presence of a multiplicity of products. This could be easily rationalized on the basis of the existence in solution of the following tautomers, each of which undergoes alkylation and probably side reactions.



A B

That isomers A and B indeed exist in equilibrium in certain solvents has been clearly demonstrated recently by Mousseron-Canet and Bora[9] by means of nmr studies. These investigators have shown that pyridine is one of the few solvents in which isomer A is exclusively present. Consequently, the desired

(7) F. Minisci, R. Galli, and A. Quilico, *Tetrahedron Letters*, **12**, 785 (1963).

(8) E. Fischer and H. Hüty, *Ber.*, **28**, 585 (1890).

(9) M. Mousseron-Canet and J. P. Bora, *Compt. Rend.*, **260**, 2851 (1965).

alkylation reaction was carried out in pyridine and in so doing good yields of the desired 1-alkoxy-2-phenylindoles were obtained. That alkylation had occurred at the 1 position rather that at position 3 became obvious from the nmr spectrum which showed a singlet at δ 6.3 for a CH signal associated with the proton at C-3.

CNS Depressant Effects.—In general, it was noted that benzimidazole ethers were more active than the ethers derived from 1-hydroxybenzimidazole 3-oxides and the 1-hydroxyindoles. The benzimidazole 3-oxide compounds (**16–18**) did show some CNS depressant action, but greater toxicity was associated with this effect. The indole compounds (**19–25**) were practically devoid of effects. Substitutions on the benzene ring and also at the 2 positions of compounds **16–25** were not made since it had already been determined in the benzimidazole group that such modifications did not afford improved activity. Within this group of compounds, the structural conditions for maximum tranquilizing muscle relaxant activity were somewhat specific.

Compound **8** [1-2-diethylaminoethoxy)-2-phenylbenzimidazole] was found to be the most effective in the series. Structural changes, however, led to no improvement of tranquilizing activity. For example, a 2-methyl substituent in place of 2-phenyl led to a lowering of the activity. Compound **8** was also more potent than **7** or **9**. Thus, the diethylaminoethoxy group appeared to be necessary for maximum activity. Substitutions on the 2-phenyl group as shown in **10** and **13** were of no advantage. Compounds **12** and **14** with substituents on the benzene ring fused to the hetero system showed diminished activity.

On the other hand, the neuropharmacological profile of **8** was of considerable interest. Depressant activity was produced by this compound in mice. Doses as low as 5.0 mg/kg sc decreased spontaneous motor activity in the jiggle cage test. For a 50% reduction in activity, 25 mg/kg of this compound subcutaneously was required as determined in the photoelectric activity cage.

In neurological dosage range studies at doses of 50–200 mg/kg sc or orally, it produced a quieting effect which was not like that produced by neuroleptics such as reserpine or chlorpromazine. There was no muscular incapacitation as noted with barbiturates or muscle relaxants such as mephenesin. Thus, this compound was described as a tranquilizer of the chlorodiazepoxide class. Further testing, however, proved that it had characteristics of all the above types of CNS depressants but did not satisfy all criteria of any single type.

Although **8** had a quieting effect in mice, at 20 mg/kg ip it had no effect in the monkey, whereas reserpine or chlorpromazine produce a marked effect at doses less than 5.0 mg/kg. In the cotton rat, it was ineffective at 100 mg/kg ip (approximately one-half the LD_{50} value), while chlorodiazepoxide had a taming effect at 25 mg/kg.

Elimination of the pinna reflex in 50% of the animals was obtained with a dose of 165 mg/kg sc in mice. Doses as high as 400 mg/kg by the same route had no effect on the corneal reflex of these animals. This selective effect of the drug on the pinna reflex is characteristic of muscle relaxants. However, as noted above, no incapacitation or lack of coordination was noted. Furthermore, in the chloralose–urethan anesthetized cat, doses as high as 25 mg/kg iv did not selectively depress polysynaptic reflexes, another characteristic of muscle relaxants.

Other pharmacological properties of **8** were also investigated. In the anesthetized dog at 9.0 mg/kg iv there was no significant effect on the blood pressure, heart rate, or respiration. A dose of 50 mg/kg subcutaneously (**8**) was inactive as an antiinflammatory drug in the rat granuloma pouch test. There was no effect on body growth following a dose of 20 mg/kg ip. The approximate LD_{50} values were 200 mg/kg ip and 600 mg/kg sc.

Experimental Section

Biological Methods.—The methods employed for determining the neurological and jiggle cage effects are herein recorded. Male albino mice (CF1) weighing 20–25 g were used. Drugs were given subcutaneously or orally at a concentration adjusted for an injection of 0.20 ml/20-g animal.

For neurological studies, animals were placed in individual metal 10-cm cube containers. A Plexiglass wall allowed constant observation of the animals. Following a 30-min control period, the animals were given the drug, three mice at each of five doses with the dosage range being 1.0–200.0 mg/kg. At regular intervals for 2 hr the animals were removed from the cages and a number of neurological reflexes tested (*e.g.*, righting, grasping, etc.). Notations were also made of the animals' motor activity, general appearance, and behavior.

Since the jiggle cage method depends upon the measurement of alteration of intensity of the motor activity produced in mice, a very sensitive activity-recording apparatus is required. The unit prepared by Anderson[10] is most satisfactory for this purpose. Its sensitivity depends upon the reduction of the inertia of the cage and its contained mice, the weight is nicely balanced by air pressure applied to a valve which is controlled by the suspended cage. Briefly, the apparatus consists of a spring-suspended cage attached to a pneumatic movement amplifier, which makes a kymographic tracing through a spring-loaded manometer. The manometer is kept on a steady base line by maintaining a constant air pressure within the recording system. Animal movements disturb the cage, upset the delicate balance, and permit the escape of air from the system. Escaping air lowers the pressure and causes the manometer with its attached writing point to record the activity on a kymograph. Most satisfactory results were obtained when three mice were placed together in the cage.

Animals were placed in the cages for 1 hr before injection. The initial dose for all drugs was 50 mg/kg sc and, if an effect was produced, lower doses (0.3 log interval) were used in subsequent experiments until the ineffective dose was obtained. The activity of the mice was recorded for 2 hr and compared with that of control mice tested concurrently.

Chemistry.[11] **1-Hydroxy-2-methyl-6-methoxybenzimidazole.**—4-Acetamido-3-nitroanisole (9 g) was dissolved in 250 ml of 10% aqueous NaOH and the resulting red-orange solution was treated slowly with vigorous stirring with 25 g of $Na_2S_2O_4$. The temperature of the reaction mixture during the addition was maintained at 50°. The mixture was then allowed to stir at room temperature overnight whereupon a fluffy amorphous precipitate was formed. This material was removed by filtration, and the filtrate was neutralized with concentrated HCl. This solution was chilled overnight whereupon a tan precipitate was formed which was collected, washed well with water, and dried *in vacuo*. One recrystallization from ethyl alcohol yielded 5.0 g of product, mp 215°.

Anal. Calcd for $C_9H_9N_2O_2$: C, 60.66; H, 5.66. Found: C, 60.76; H, 6.13.

1-Hydroxy-2-*p*-chlorophenylbenzimidazole.—N-*p*-Chlorobenzyl-*o*-nitroaniline (34.0 g, 0.60 mole) prepared by the condensation of *o*-nitrochlorobenzene with *p*-chlorobenzylamine

(10) F. F. Anderson and G. Wagle, *Federation Proc.*, **15**, 394 (1956).

(11) All melting points reported herein were obtained on a Thomas–Hoover capillary melting point apparatus and are corrected.

according to Gibson[12] was dissolved in 350 ml of CH_3OH containing 27.6 g of NaOH pellets. The mixture was heated under reflux for 5 hr and then cooled to room temperature. The supernatant liquid was poured off from the residue and brought to pH 7 with 20% HCl solution. After chilling this solution overnight, the light yellow crystals were collected on a filter and washed well with water. This material was recrystallized from ethyl alcohol–water (1:1) to give 16.0 g of white crystalline substance, mp 216–217°.

Anal. Calcd for $C_{13}H_9ClN_2O$: C, 63.81; H, 3.71; N, 11.45. Found: C, 63.57; H, 3.64; N, 11.32.

The following compounds were prepared in similar fashion.

1-Hydroxy-2-*p*-methoxyphenylbenzimidazole, mp 189–191°. *Anal.* Calcd for $C_{14}H_{12}N_2O_2$: C, 69.98; H, 5.04; N, 11.66. Found: C, 70.22; H, 5.12; N, 11.42.

1-Hydroxy-6-nitro-2-phenylbenzimidazole, mp 273° dec. *Anal.* Calcd for $C_{13}H_9N_3O_3$: C, 61.17; H, 3.55; N, 16.46. C, 61.25; H, 3.70; N, 16.43.

6-Chloro-1-hydroxy-2-phenylbenzimidazole, mp 241°. *Anal.* Calcd for $C_{13}H_9ClN_2O$: C, 63.81; H, 3.71; N, 11.45. Found: C, 63.68; H, 3.69; N, 11.38.

General Procedures for Preparation of Compounds in Table I. 1-(2-Diethylaminoethoxy)-2-phenylbenzimidazole Dihydrochloride (8).—1-Hydroxy-2-phenylbenzimidazole (25.0 g, 0.119 mole) was dissolved in 200 ml of dimethylformamide (DMF) containing 50 ml of toluene. Six grams (0.131 mole) of NaH (53% suspension in mineral oil) was added to this solution with vigorous stirring and the mixture was heated at 50° for 30 min. At the end of this time, the solution was cooled to room temperature and then treated with 91 ml of a toluene solution containing 0.177 g of 2-dimethylaminoethyl chloride/ml of solution and the resulting solution was heated at 60° for 3 hr. After cooling the solution to room temperature, 50 ml of ethyl alcohol was added to decompose any unreacted NaH. To this solution there was added 1 l. of ether, and the resulting precipitate was removed. The filtrate was evaporated to a viscous residue *in vacuo*. This was dissolved in a small amount of ethyl alcohol and the solution in turn was treated with saturated ethanolic HCl. After chilling the solution overnight, the copious precipitate was collected on a filter, washed well with ether, and then recrystallized twice from ethyl alcohol–ethyl ether (1:1) to yield 17.5 g of white crystalline product.

1-(2-Dimethylaminoethoxy)-2-phenylbenzimidazole 3-Oxide (16).—A slurry of 3.0 g (0.0132 mole) of 1-hydroxy-2-phenylbenzimidazole 3-oxide in 30 ml of DMF was allowed to react with 0.64 g (0.014 mole) of 53% NaH at steam bath temperature for 15 min. The mixture was then cooled to room temperature and allowed to react with 2.1 g (0.0155 mole) of 2-diethylaminoethyl chloride for 24 hr. The solution was filtered, and the filtrate was evaporated *in vacuo* to an oil to which was then added H_2O. This mixture was extracted well with ether and the ether extract was dried (Na_2SO_4). Removal of the drying salt by filtration and concentration of the ether solution on the steam bath gave a light yellow oil. Ethanolic HCl was added to the oil and the solution was chilled overnight. The resulting precipitate was collected on a filter and recrystallized from ethyl alcohol–ethyl ether (1:1).

1-(2-Diethylaminoethoxy)-2-phenylindole (21).—1-Hydroxy-phenylindole (4.0 g, 0.019 mole) was dissolved in 150 ml of dry pyridine and the solution was then treated with 0.85 g (0.018 mole) of 53% NaH. The mixture was stirred at room temperature for 1 hr, the solution changing in color from light yellow to dark brown. A toluene solution (25 ml) of 2-diethylaminoethyl chloride (100 mg/ml) was added and the solution stirred at room temperature overnight. The reaction mixture was added to 300 ml of H_2O whereupon an oil precipitated from solution. The oil was separated and any excess water and pyridine were removed by heating the oil at 40° *in vacuo* for 4 hr. The oil was dissolved in ether and dried (Na_2SO_4). This salt was then filtered off and the ether solution was evaporated to dryness. Again an oil was obtained from which the maleate salt was prepared in an ethyl alcohol solution. The product was recrystallized from ethyl alcohol–ethyl ether (1:1).

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A Series of Central Nervous System Stimulants Based on the 4-Substituted 3,3-Diphenyl-2-pyrrolidinone Skeleton. II

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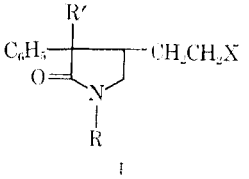
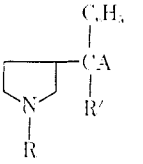
The previously described preparation of 4-(2-substituted ethyl)-3,3-diphenyl-2-pyrrolidinones by a rearrangement of (1-substituted 3-pyrrolidinyl)diphenylacetic acids has been expanded in order to observe structure-activity relationships. Variation of the ring and side-chain substituents has produced compounds of varying biological activity, generally central nervous system stimulants.

Part I[1] of this series described the synthesis of 1-alkyl-4-(2-substituted ethyl)-3,3-diphenyl-2-pyrrolidinones [I, R = lower alkyl, R′ = C_6H_5, X = Cl or Br (subsequently replaced by various basic residues)]. The key



I

intermediate 4-(2-haloethyl) compounds (I, X = Cl or Br, R′ = C_6H_5) were prepared from (1-alkyl-3-pyrrolidinyl)diphenylacetonitriles *via* a rearrangement of the corresponding acid chlorides (IIa → IIb → IIc → I; R = alkyl, R′ = C_6H_5, X = Cl or Br). In general



IIa, A = CN
b, A = COOH
c, A = COCl
d, A = $CONH_2$

the compounds stimulated the central nervous system. 1-Ethyl-4-(2-morpholinoethyl)-3,3-diphenyl-2-pyrrolidinone[2] (I, R = C_2H_5, R′ = C_6H_5, X = morpholino; VIa), selected for extensive study, proved to be a potent respiratory stimulant in animals and man.

Further variation of substituents on the 4-ethyl-2-pyrrolidinone nucleus is reported in the present work.

(1) C. D. Lunsford, A. D. Cale, Jr., J. W. Ward, B. V. Franko, and H. Jenkins, *J. Med. Chem.*, **7**, 302 (1964).

(2) Doxapram hydrochloride, Dopram®.