greatly influenced by the type of solvent system employed (20).

CONCLUSION

Both β-cyclodextrin and sodium deoxycholate are shown to interact with a variety of pharmaceutical compounds. While varying concentrations of sodium deoxycholate would be expected to have a measurable effect on the pH of systems at lower pH levels, no effect was observed in these investigations because of the elevated pH conditions employed. In general, greater complexing activity is observed between the smaller guest molecules and both complexing agents, illustrating the importance of molecular size and structure in these interactions. Compounds known to be too large for complete inclusion, such as morphine and reserpine, are seen to interact with β-cyclodextrin. The presence of certain functional groups in these large molecules, capable of interacting with or of being partially included by the cyclodextrin, could be responsible for the observed interactions. The high-formation constants determined for some of the β-cyclodextrin interactions indicate the formation of extremely stable complexes. Pure inclusion is described as an association taking place without intermolecular bonding between the guest and host components. Although in aqueous solution, the net interactions could result from both inclusion and intermolecular forces, particularly hydrogen bonding.

Similarities in the shapes of solubility isotherms obtained for interactions of both deoxycholic acid and its sodium salt with several pharmaceutical compounds could indicate similar mechanisms for these two complexing agents. Even though sodium deoxycholate, an anionic surfactant, is currently thought to exert its solubility effects through micelle formation, the possibility of total or even partial inclusion formation by this agent cannot be ignored. Multislopes obtained in the solubility isotherms for many of the sodium deoxycholate interactions could indicate a complex mechanism consisting of both micellar solubilization and inclusion formation, or they might represent the presence of higher order complexes. The complexity of these interactions is clearly shown in the studies dealing with the reserpine–deoxycholic acid interaction in various alcoholic solutions.

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Synthesis of *N*-Substituted Phenethylamines and Corresponding Cyclohexyl Analogs

Preliminary Evaluation as Bronchodilators

By JOHN B. DATA, MARTIN O. SKIBBE, T. LAMAR KERLEY, and LAWRENCE C. WEAVER

A series of *N*-substituted phenethylamines and their corresponding cyclohexyl analogs were prepared and tested pharmacologically for their effects on the duration of hexobarbital anesthesia in mice, and systemic blood pressure and bronchodilatory activity in dogs. Methods for the preparation of these compounds are described, and procedures used in pharmacological testing are indicated and the biological results tabulated. There were no consistent or appreciable bronchodilatory effects observed.

EPINEPHRINE (I) and isoproterenol (II) represent two potent and useful bronchodilators containing the catechol nucleus. Other structurally related substances which have been rated (1–3) as relatively potent bronchodilators are levarterenol (III), 3,4-dihydroxyephedrine (IV), and equine (V). A recently introduced adrenergic substance used in the management of bronchial asthma is the potent inhibitor, protokylol (VI).

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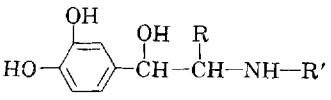
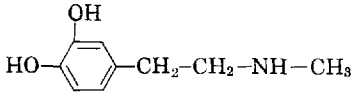


I, R is H; R′ is CH_3
II, R is H; R′ is $(CH_3)_2CH$
III, R is H; R′ is H
IV, R is CH_3; R′ is CH_3



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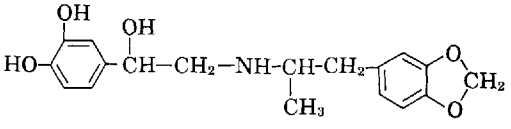
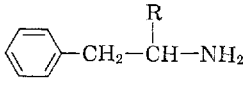


VI

These examples support the conclusion of Tainter and his co-workers (1, 2) and of Biel *et al.* (4) that the catechol nucleus appears to be essential for a high degree of bronchodilation efficiency.

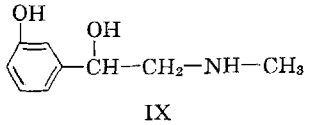
DISCUSSION

Mono-hydroxy and mono-methoxy derivatives of phenethylamine (VII) and 2-phenylisopropylamine (VIII) exhibit this same type of activity, although quantitatively not as great.

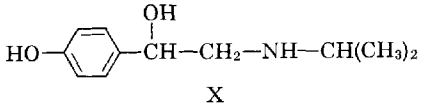


VII, R is H
VIII, R is CH_3

While phenylephrine (IX) has been reported as a fair (3) and a poor (2) bronchodilator, Konzett (5) reported that *p*-hydroxy-*α*-(isopropylaminomethyl)-benzyl alcohol (X) possesses marked activity; the corresponding *N*-methyl derivative is less active. Corrigan *et al.* reported (6) on the activity of additional hydroxy compounds in which the *N*-isopropyl group of X is replaced by other alkyl substituents. These in general were found to be active.

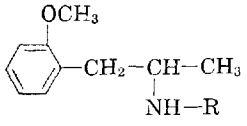


IX



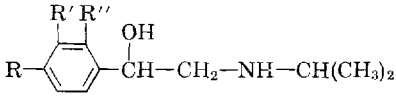
X

All possible mono-hydroxy derivatives of 2-phenyl-isopropylamine have been evaluated (7) for bronchial activity, but these isomers have shown no appreciable response; the corresponding mono-methoxy derivatives were tested by the same investigators, who concluded that the more active compounds were the methoxy derivatives. 2-(*o*-Methoxyphenyl)-isopropylamine (XI), the *N*-methyl, *N,N*-dimethyl, and *N*-benzyl derivatives have been shown (8) to possess a very high degree of specific bronchodilatory activity with little or no pressor effect. These latter studies may have been responsible for the introduction of the orally active and useful medicament, methoxyphenamine (XII).



XI, R is H
XII, R is CH_3

The quantitative difference in the ability of the hydroxyl and the methoxyl group to supply electrons to the conjugated ring system (9) suggests a means for correlating bronchial activity to chemical structure. The finding that isoprophenamine (XIII) is a potent bronchodilator (10) and, in addition has other physiological properties (11) qualitatively similar to methoxyphenamine, suggests that the chloro group, too, can be considered along with the hydroxyl and the methoxyl; while the chloro group is an electron withdrawing group, it can also release electrons to the conjugated ring system. This idea can be extended to include compounds which have two such groups as in the case of isoproterenol and dichloroisoproterenol (XIV), even though the latter is known to block the action of the former (12). While the exact role each group plays in broncho-



XIII, R is H; R′ is H; R″ is Cl
XIV, R is Cl; R′ is Cl; R″ is H

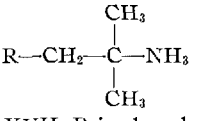
dilatory effect is unknown, the strength of the bond between the drug and receptor due to the magnitude of electron density in the phenyl ring because of the presence of these groups may be very important to explain and/or correlate the effect of a drug. Although from the standpoint of satisfying structural requirements for the same receptor site the chloro, the hydroxyl, or the methoxyl group may or may not be required, differences in pharmacological response may be due basically to difference in electron density created by these substituents. For example, isoproterenol and dichloroisoproterenol very likely possess the same structural requirements for the same *β*-receptor, even though the nature of the ring substituents are different. The difference in the ability of the chloro and the hydroxyl group to supply electrons to the phenyl ring would be evident in rates of release of the drug–receptor complex in a reversible reaction. Thus, the bond strength attributed to the difference in electron density can account, at least in part, for difference in pharmacological behavior of isoproterenol and dichloroisoproterenol. The reported pharmacology for these compounds bear out some of these points. For instance, Moran and Perkins (13) indicate that dichloroisoproterenol may be involved in an equilibrium type of blockade since the block can be reversed by excess of certain amines. Powell and Slater (14) report data which strongly support the

suggestion that the same β-receptors are involved, and they explain that the brief effects of isoproterenol are due to a rapid bio-transformation and/or weak bonding between drug and receptor; for dichloroisoproterenol they suggest the drug–receptor complex to be fairly stable.

Various types of substituents attached to the amino nitrogen have received considerable attention in the search for effective bronchodilators. Simple aliphatic groups from one to five carbons (4–6, 15–21), cycloalkyls (4, 15–17, 19), aralkyls (4, 18–20, 22), and cycloalkylalkyls (4) have been evaluated. The *N*-isopropyl derivative has been suggested for optimal activity in one series of compounds (16), and the *N*-butyl was found to be the most active in a second series (17). There does not appear to be any structural specificity for activity. These examples and the studies cited suffice to suggest that the kind of substitutions on the amino group is not crucial.

Effects of other substituents on the ethyl or isopropyl moiety of VII and VIII other than the amino group is not well documented. Studies designed to evaluate the importance of the hydroxyl group β to the amino are lacking. Seemingly, the literature records only three like pairs of compounds evaluated for their bronchial activity in which the β-OH group is the only variable. The first pair is epinephrine and equine; Pedden *et al.* (2) have rated these as excellent bronchodilators. The second pair is 2-phenylisopropylamine and α-(1-aminoethyl)benzyl alcohol (XV), which are reported (1) to act predominately as bronchoconstrictors, although Alles and Prinzmetal (23) reported slight bronchodilation for 2-phenylisopropylamine. The third pair is isoproterenol and *N*-isopropyl-3,4-dihydroxyphenethylamine (XVI); Siegmund *et al.* (21) indicate that the absence of a β-OH group in XVI causes very marked reduction in activity between this last pair of compounds. While these three pairs do not clearly indicate the effect of the β-OH group, Siegmund and his co-workers (21) concluded from their studies that the β-OH group is essential for bronchial activity.

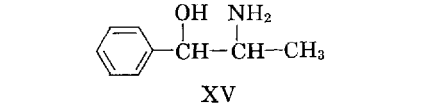
The lack of information on the effect of other substituents on the propyl moiety of 2-phenylisopropylamine prompted the authors to prepare and biologically evaluate as a matter of interest a series of *N*-substituted derivatives of α,α-dimethylphenethylamine (XVII) and their corresponding cyclohexyl derivatives (XVIII).



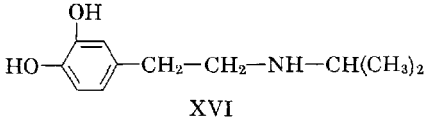
XVII, R is phenyl
XVIII, R is cyclohexyl

Except for α,α-dimethylphenethylamine (18) no one seems to have reported on the broncho-spastic relieving properties of these compounds. The only closely related study among the cyclohexylethylamines is the work of Lands *et al.* (24), who evaluated the spasmolytic activity of such compounds on isolated guinea pig ileum.

The α,α-dimethylphenethylamines and their corresponding cyclohexyl analogs were prepared by reducing with lithium aluminum hydride the formamides obtained by the Ritter reaction from 1,1-dimethyl-2-phenylethanol or its cyclohexyl analog and a nitrile as described under *Experimental.* (Scheme I.)



XV



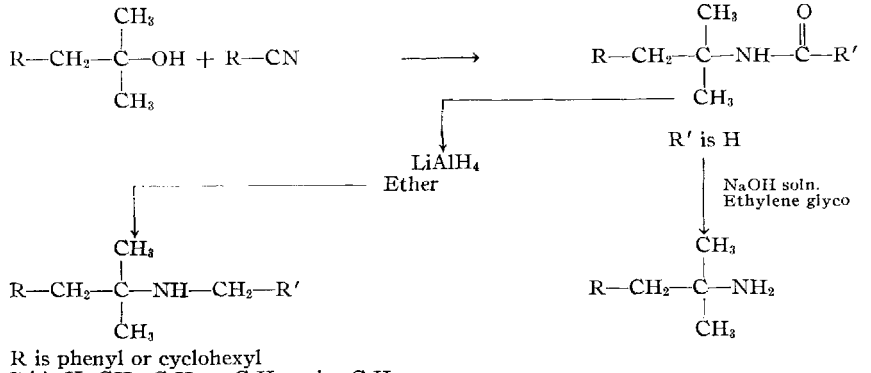
XVI

EXPERIMENTAL

All melting points are uncorrected. Chlorine was determined by the method of Blicke and Zienty (25), and the carbon and hydrogen analysis was performed by Galbraith Laboratories, Inc., Knoxville, Tenn. No attempt was made to improve yields obtained from the first trial.

Preparation of 1,1-Dimethyl-2-phenylethanol.—This product was prepared by the Grignard reaction for the synthesis of tertiary alcohols from esters.

Ethyl phenylacetate, 75.0 Gm. (0.455 mole), was added during 0.5 hr. to 600 ml. of an ethereal solution of methylmagnesium iodide prepared in the usual way from 24.3 Gm. (1.0 Gm. atom) of mag-



R is phenyl or cyclohexyl
R′ is H, CH_3, C_2H_5, *n*-C_3H_7 or iso-C_3H_7

Scheme I

nesium turnings and 150.0 Gm. (1.06 moles) of methyl iodide. The mixture was then refluxed for 3 hr., cooled, and poured onto about 300 Gm. of cracked ice, and then decomposed by the slow addition of 300 ml. of hydrochloric acid (10%). The organic layer was separated from the aqueous portion, which was then extracted 3 times with 100-ml. portions of ether. The combined ethereal extracts were washed successively with 100 ml. of sodium carbonate (5%) and 100 ml. of water. The ethereal solution was then dried over anhydrous potassium carbonate, filtered, the solvent removed under reduced pressure and the residue fractionated to give 59.2 Gm. (86.5%) of product distilling at 100–104° (14 mm.). [Reported (26) b.p. 103–105° (10 mm.).]

Preparation of 1,1-Dimethyl-2-cyclohexylethanol.—This product was prepared by the Grignard reaction for the preparation of tertiary alcohols from ketones.

The Grignard reagent was prepared in the usual fashion from 4.86 Gm. (0.2 Gm. atom) of magnesium and 35.4 Gm. (0.2 mole) of cyclohexylmethyl bromide dissolved in about 150 ml. of ether. To the reagent there was added during a period of about 0.5 hr. while stirring 11.6 Gm. (0.2 mole) of dry acetone in 50 ml. of ether. After 2 additional hr. of stirring and refluxing, the reaction mixture was hydrolyzed by the addition of about 100 Gm. of cracked ice and 75 ml. of hydrochloric acid (10%). The organic layer was separated from the aqueous portion, and the aqueous layer extracted 3 times with 30-ml. portions of ether. The ether extracts were then combined and washed successively with several 25-ml. portions of sodium carbonate (10%) and 25 ml. of water. The organic layer was dried with fused sodium sulfate, filtered, and fractionated. There was obtained 14.5 Gm. (46.5%) of a colorless oil distilling at 97–100° (16 mm.).

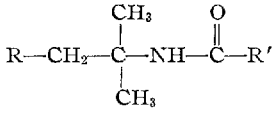
A second run twice as large gave 32.0 Gm. (51.2%) of product which distilled at 67–70° (2.2 mm.). The analytical sample distilled at 69° (2.2 mm.) and had a refractive index of 1.4650 at 20°.

Anal.—Calcd. for $C_{10}H_{20}O$: C, 76.92; H, 12.82. Found: C, 76.58; H, 12.60.

The alcohol gave a white, crystalline phenylurethan derivative which, when recrystallized 3 times from hexane, melted at 117–118°.

Anal.—Calcd. for $C_{17}H_{25}NO_2$: C, 74.18; H, 9.09. Found: C, 73.80; H, 9.09.

TABLE I. — *N*-(1,1-DIMETHYL-2-PHENYLETHYL)-AMIDES AND *N*-(1,1-DIMETHYL-2-CYCLOHEXYLETHYL)AMIDES



R	R′	M.p., C°.	Yield, %
C_6H_5	CH_3	89–91	80.5
C_6H_5	CH_3CH_2	95–97	84.5
C_6H_5	$CH_3CH_2CH_2$	62–64	60.7
C_6H_5	$(CH_3)_2CH$	111–113	79.5
C_6H_{11}	CH_3	80–82	81.3
C_6H_{11}	CH_3CH_2	59–61	85.4
C_6H_{11}	$CH_3CH_2CH_2$	79–81	87.7
C_6H_{11}	$(CH_3)_2CH$	105–106	89.0

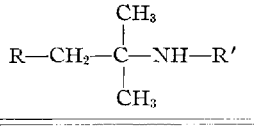
Preparation of 1,1-Dimethyl-2-cyclohexylethylamine (D-3-1)

N - (1,1 - Dimethyl - 2 - cyclohexylethyl)formamide.—This compound was prepared according to the method described by Ritter and Kalish (27) for the synthesis of *N-tert*-butylformamide.

Sodium cyanide, 19.6 Gm. (0.4 mole), and 50 ml. of glacial acetic acid was mixed with cooling and stirring. A solution of 100 Gm. of concentrated sulfuric acid in 50 ml. of glacial acetic acid was then added while continuing to stir the reaction mixture and maintaining the temperature at 20°. 1,1-Dimethyl-2-cyclohexylethanol, 62.4 Gm. (0.4 mole), was then added and the temperature permitted to rise spontaneously to 40–50°. The mixture was heated to 70° for 1 hr., stoppered, allowed to stand for 2 hr., diluted with 600 ml. of water, and neutralized with sodium carbonate. The formamide which separated as a viscous oil was extracted 3 times with 100-ml. portions of ether, dried over fused sodium sulfate, filtered, and the solvent removed under reduced pressure. The residue was fractionated to give 69.7 Gm. (95.5%) of product which distilled at 170–171° (15 mm.).

1,1 - Dimethyl - 2 - cyclohexylethylamine.—A mixture of 40.0 Gm. (1.0 mole) of sodium hydroxide in 60 ml. of water, 300 ml. of ethylene glycol, and

TABLE II.—*N*-SUBSTITUTED 1,1-DIMETHYLPHENETHYLAMINES AND *N*-SUBSTITUTED 1,1-DIMETHYL-2-CYCLOHEXYLETHYLAMINES



Code No.	R	R′	B.p., °C. (mm.)	Yield, %	Hydrochloride M.p., °C.	Formula	Cl, % Calcd.	Cl, % Found
D-3-2	C_6H_5	CH_3	114–120 (13)	95.0	176–177	$C_{11}H_{18}ClN$	17.78	17.80
D-3-4	C_6H_5	CH_3CH_2	107–109 (16)	61.8	214–215	$C_{12}H_{20}ClN$	16.61	16.60
D-3-6	C_6H_5	$CH_3CH_2CH_2$	119–121 (13)	91.2	205–206	$C_{13}H_{22}ClN$	15.59	15.68
D-3-8	C_6H_5	$CH_3(CH_2)_2CH_2$	131–132 (12)	58.7	160–161	$C_{14}H_{24}ClN$	14.70	14.68
D-3-10	C_6H_5	$(CH_3)_2CHCH_2$	126–128 (16)	51.7	209–210	$C_{14}H_{24}ClN$	14.70	14.88
D-3-3	C_6H_{11}	CH_3	96–99 (13)	71.0	155–156	$C_{11}H_{24}ClN$	17.20	17.14
D-3-5	C_6H_{11}	CH_3CH_2	103–106 (14)	60.0	220–221	$C_{12}H_{26}ClN$	16.12	16.15
D-3-7	C_6H_{11}	$CH_3CH_2CH_2$	115–116 (13)	54.3	189–190	$C_{13}H_{28}ClN$	15.18	15.10
D-3-9	C_6H_{11}	$CH_3(CH_2)_2CH_2$	133–136 (15)	72.0	173–174	$C_{14}H_{30}ClN$	14.32	14.32
D-3-11	C_6H_{11}	$(CH_3)_2CHCH_2$	130–139 (15)	48.8	174–175	$C_{14}H_{30}ClN$	14.32	14.37

TABLE III.—COMPARATIVE ACTIVITIES OF AMINES

Compd.	R	R′	Lethal Dose to Mice, mg./Kg.	Hexobarbital Anesthesia Mice, Ratio of Test/Control mg./Kg. 25	50	100	125	Blood Pressure Effect, % Change: Time After Drug, hr. 0	2	3	3.5	3.8	3.9	4	Atropine	Atropine and Vagotomy	Duration (min.) First Dose
D-3-2	C_6H_5	CH_3	200	0.81			0.57	−13/44[a]	−33	−32	−33	−28	−22	−21	−18	−22	1/60
D-3-4	C_6H_5	CH_3CH_2	400	1.0	0.8			−34/54	−25/62	−35/15	−38	−49	−50	—	−31	—	1/45
D-3-6	C_6H_5	$CH_3CH_2CH_2$	400	0.76	0.88			−22	−20	−22	−17	−19	−27	−35	−20	−23	1
D-3-8	C_6H_5	$CH_3(CH_2)_2CH_2$	200	1.08	0.83			−24	−26	−32	−34	−31	−35	−34	−35	−33	1
D-3-10	C_6H_5	$(CH_3)_2CHCH_2$	200	0.91	1.03			−21/6	−17/30	−13/28	−14/28	−19/11	−23/5	−26	−28	−26	1/15
D-3-1	C_6H_{11}	H	400	1.20	0.93			−29/51	−26/42	−17/37	−28/23	−31/2	−35/2	—	−44	−55	1/25
D-3-3	C_6H_{11}	CH_3	400		0.96	0.94		−40/39	−40/54	−33/23	−33/10	−37/5	−38	−37	−38	−42	2/35
D-3-5	C_6H_{11}	CH_3CH_2	400	0.73	0.58			−44/49	−40/34	−35/18	−44	−45	−43	−40	−42	−41	1/25
D-3-7	C_6H_{11}	$CH_3CH_2CH_2$	400	0.51	0.50			−51/7	−53/18	−40/4	−45	−38	−29	—	−46	−36	3/15
D-3-9	C_6H_{11}	$CH_3(CH_2)_2CH_2$	200	1.07	0.78			−15	−30	−32	−29	−31	−37	—	−41	−38	2
D-3-11	C_6H_{11}	$(CH_3)_2CHCH_2$	400	0.87	1.17			−69	−55	−51	−55	−43	−45	−45	−46	−44	2
Dextro-amphetamine			[b]					+60	−37	−35	−26	−30	−21	—	−19	−23	>45

[a] −13/44 = biphasic systemic blood pressure response; 13% decrease for 1 min., followed by a 44% increase for 60-min. duration. [b] LD_{50} in mice is 95 mg./Kg. [c] Ratios for 5 mg./Kg. were 1.0 and 0.93, while 10 mg./Kg. gave 1.21 and 0.61.

70.0 Gm. (0.382 mole) of *N*-(1,1-dimethyl-2-cyclohexylethyl)formamide was refluxed for 36 hr. It was then cooled and extracted 3 times with 100-ml. portions of ether. The combined ether extracts were washed with 50 ml. of water, dried over potassium carbonate, and distilled. The yield of product which boiled at 92–93° (17 mm.) was 48.2 Gm. (81.2%).

The base was dissolved in anhydrous ether and converted into the hydrochloride salt with gaseous hydrogen chloride in the usual way. The salt which was soluble in the ether–hydrogen chloride solution was obtained by evaporating off the ether. The crude product was recrystallized several times from ethyl acetate to give a pure product melting at 152–153°. [Reported (28) m.p. 147–148°.]

Anal.—Calcd. for $C_{10}H_{22}ClN$: Cl, 18.52. Found: Cl, 18.42, 18.30.

Preparation of *N*-Substituted 1,1-Dimethylphenethylamines and *N*-Substituted 1,1-Dimethyl-2-cyclohexylethylamines

N - (1,1 - Dimethyl - 2 - phenylethyl)amides and N-(1,1-Dimethyl-2-cyclohexylethyl)amides.—These amides were prepared by a slight modification of the method described by Ritter and Kalish (27). All amides listed in Table I were synthesized by the following procedure.

To a solution of 10.0 Gm. (0.1 mole) of concentrated sulfuric acid in 50 ml. of glacial acetic acid maintained at about 20° there was added portionwise 0.11 mole of the appropriate nitrile. One-tenth mole of 1,1-dimethyl-2-phenylethanol or 1,1-dimethyl-2-cyclohexylethanol, depending upon which of the amides was to be prepared, was added slowly. The mixture was stirred mechanically while raising the temperature to 50°, then stirred without heat for 0.5 hr. longer, during which time the temperature rose spontaneously to 60–80° leading to complete solution of the alcohol. The mixture was allowed to stand for 8 hr. and then diluted with 300 ml. of water to precipitate an oil which after several hours solidified to a crystalline mass. The solid was broken up, filtered, washed with water, and then air dried.

The yield and melting points for each *N*-substituted amide are listed in Table I. All products were recrystallized from dilute ethyl alcohol (50%).

N-Substituted 1,1-Dimethylphenethylamines and N - Substituted 1,1 - Dimethyl - 2 - cyclohexylethylamines.—For the preparation of these compounds a modified procedure of the method used by Moffett (29) for synthesizing 2,2-dimethylpyrrolidine was employed. All amines listed in Table II were prepared by the following procedure.

To a mixture of 3.8 Gm. (0.1 mole) of pulverized lithium aluminum hydride and 75 ml. of anhydrous ether, which had been refluxed gently for 1/4 hr. was added a solution of 0.05 mole of the amide in 150 ml. of anhydrous ether at such a rate that the solution refluxed gently without any further external heating. When the addition was complete and the initial reaction subsided, the mixture was stirred and refluxed for 15 hr. The reaction mixture was allowed to cool, and then 5 ml. of ethyl acetate was added slowly with vigorous stirring and, finally 50 ml. of 6 *N* hydrochloric acid was added in the same manner. The mixture was then steam distilled several minutes after the boiling point reached 100° and the

distillate discarded. The mixture in the flask was cooled and to it was added carefully with stirring 35 ml. of 12 *N* sodium hydroxide solution. The alkaline mixture was then steam distilled until the distillate was no longer basic (about 600 ml.). The amine was extracted from the distillate with three 100-ml. portions of ether, the combined ethereal extracts dried over potassium carbonate, filtered, and the solvent removed *in vacuo*. The residue was then fractionated under reduced pressure.

The base was dissolved in anhydrous ether and then precipitated as the hydrochloride salt by passing anhydrous hydrogen chloride into the solution in the usual way.

The yield and boiling points of each *N*-substituted amide are listed in Table II. The melting point for each *N*-substituted amine hydrochloride is listed in the same table. All amine salts were recrystallized from ethyl acetate–ethanol as solvent.

PHARMACOLOGY

Comparative pharmacological studies were conducted on all of the amine hydrochlorides prepared. Their effects were observed on the duration of hexobarbital anesthesia in mice and systemic blood pressure and bronchodilatory activity in dogs.

Groups of 10 male, albino Swiss-Webster mice were pretreated subcutaneously with the test compound 2 hr. before the intraperitoneal administration of a dose of 100 mg./Kg. of sodium hexobarbital. The end point was taken as that time when the mouse moved from a supine position. Similar groups of control mice were tested simultaneously, and the results presented as a ratio of the average duration of anesthesia of test mice to control mice. A ratio of 1.0 indicates the results were the same for both groups: a value less than 1.0 suggests antagonism of hexobarbital anesthesia. In addition, these compounds were administered orally in increasing doses to determine the degree and type of toxicity produced. The results are recorded in Table III. All test compounds were orally active as indicated by the fact that they were all lethal when administered orally to mice. Only compound D-3-5 and D-3-7 produced appreciable alteration in the hexobarbital anesthesia of mice. In both cases it was a decrease probably indicating central nervous system stimulation.

Adult mongrel dogs, unselected as to sex, were employed in the cardiovascular and bronchodilator experiments. Anesthesia was maintained by the judicious use of sodium pentobarbital. Solutions of test compounds were freshly prepared and injected intravenously. The ability of these compounds to alter systemic blood pressure at a constant dose of 4 mg./Kg. was investigated in 2 or 3 dogs for each compound and the results averaged. Furthermore, the same dose was repeated at various intervals to determine whether tolerance developed to the blood pressure effects. These results are also presented in Table III. For the phenyl derivatives the first dose of *N*-methyl (D-3-2) and *N*-ethyl (D-3-4) produced a pressor effect that became negligible after subsequent doses; with progressively longer chain length, including *N*-propyl (D-3-6), *N*-butyl (D-3-8), and *N*-isobutyl (D-3-10), no pressor activity was found. Similarly, for the cyclohexyl derivatives the magnitude of the pressor effect decreased with an increase in chain length of the *N*-substituent and completely disappeared with *N*-butyl (D-3-9). For some unexplained reason it was again present at *N*-isobutyl (D-3-11). As was expected tachyphylaxis developed readily to the pressor effect. The vasopressor effect following tachyphylaxis was not influenced by atropinization of the dog or by a combination of atropinization and bilateral midcervical vagotomy.

Changes in bronchiolar resistance of dogs were recorded by a modification of the method of Konzett and Rossler (30). In brief, under constant volume respiration variations in bronchiolar resistance were indicated by changes in the volume of air in excess of that required for adequate ventilation. Histamine, 10 mcg./Kg., or carbachol, 1 to 4 mcg./Kg., administered intravenously, were used as the bronchoconstricting agents. The ability of the test compound to block this bronchoconstriction was determined following intravenous administration of 2 and 4 mg./Kg. doses of the test compound. No consistent or appreciable bronchodilatory effect was observed.

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