N,N′-Disubstituted Compounds with Diverse Biological Activities

ROBERT P. MULL, CARL TANNENBAUM, MARY R. DAPERO, MARCEL BERNIER, WILLIAM YOST, AND GEORGE DESTEVENS

Chemical Research Division, CIBA Pharmaceutical Company, Division of CIBA Corporation, Summit, New Jersey

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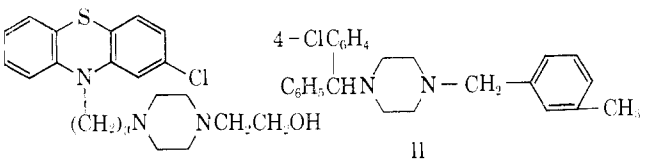
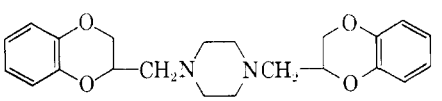
A large number of N,N′-disubstituted compounds were prepared for broad biological testing. Some N-phenylpiperazine derivatives were found to have antihypertensive, adrenolytic, and antiinflammatory properties. A structure–activity relationship study was carried out to separate these activities in single compounds and this has been accomplished.

A considerable body of literature is recorded on the biological effects of compounds containing the piperazine moiety. These substances have a plethora of activities and have led to some clinically useful drugs among which can be considered perphenazine (tranquilizer) (I), meclizine (antihistaminic) (II), dibozane (antihypertensive) (III), and diethylcarbamazine (anthelmintic) (IV). More recently, Wylie and Archer[1] have reported on the tranquilizing properties of 1-[(3-indolyl)-alkyl]-4-arylpiperazines in experimental animals.

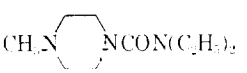


I

II

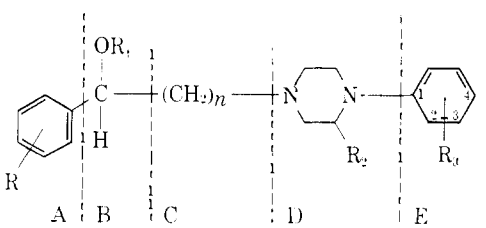


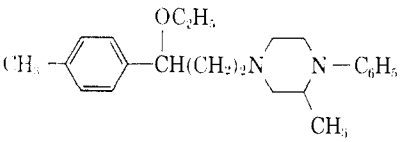
III



IV

Thus, it appeared that the piperazine grouping could serve as a useful platform for imparting biological activity to organic molecules. A new series of compounds containing this nitrogen heterocycle has been prepared in our laboratories and submitted for broad biological evaluation. The substances have the following basic structure. It was noted early in our work that 1-[(3-ethoxy-3-*p*-tolylpropyl]-3-methyl-4-phenylpiperazine (V) showed good adrenolytic effect, some weak but definite antihypertensive effect, and a moderate antiinflammatory activity at 50 mg./kg. s.c. in the granuloma pouch test in rats. This finding prompted us to study this class in depth, determining the effect on activity with appropriate changes from A to E in the general structure shown above. Each parameter was varied selectively, so that a minimum number of compounds would be prepared before choosing the compound or compounds with maximum biological effects. It was also essential that the adrenolytic, antihypertensive, and antiinflammatory effects be separated from one another. Before considering the structure–activity relationship, the general synthetic scheme employed in the preparation of these compounds will be considered.

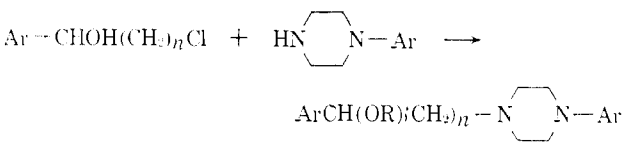




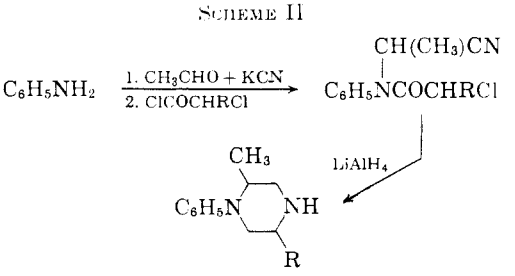
V

Chemistry.—The compounds to be described in this paper were prepared in most cases through condensation of the 1-alkoxyl-1-aralkyl chloride with the appropriate N-arylpiperazine (Scheme I). The aralkyl halide derivatives were prepared according to the method described by Duliere,[2] and Houben and Führer.[3] In addition, a new method was devised for the synthesis of 1-aryl-2-alkylpiperazines, 1-aryl-2,5-dialkylpiperazines, the corresponding homopiperazines (hexahydro-1,4-diazepine derivatives), and also octahydro-1,4-diazocine derivatives. This general method is described for 1-phenyl-2-methylpiperazine (Scheme II).

SCHEME I



SCHEME II



R = H, alkyl

Aniline was allowed to react with acetaldehyde and KCN to afford the nitrile derivative which then was condensed with an α-chloroacyl chloride to yield the appropriate amide. The latter compound on reduc-

(1) D. W. Wylie and S. Archer, *J. Med. Pharm. Chem.*, **5**, 932 (1962).

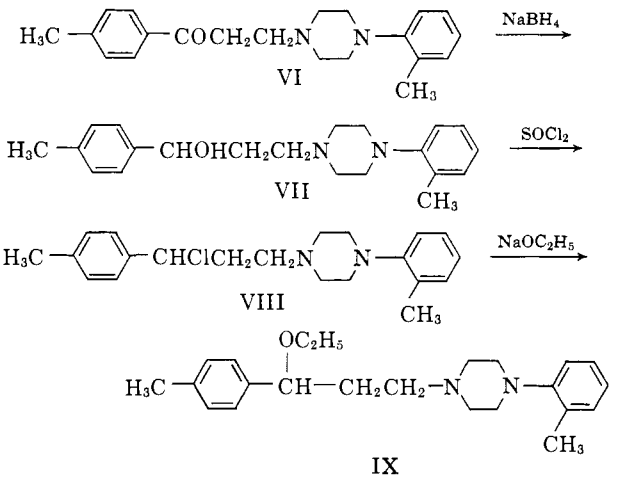
(2) W. Dudiere, *Bull. soc. chim. France*, **35**, 584 (1924).

(3) J. Houben and K. D. Führer, *Ber.*, **40**, 4990 (1907).

tion with lithium aluminum hydride gave rise to the desired 1-phenylpiperazine derivatives. The use of β-chloropropionyl chloride in the second step afforded hexahydro-2-methyl-1-phenyl-1,4-diazepine, where with γ-chloropropionyl chloride one obtains octahydro-2-methyl-1-phenyl-1,4-diazocine.

Since the most significant biological effects were seen with compounds in which $n = 2$ (see general structure), an alternative method of synthesis of these substances was developed (Scheme III).

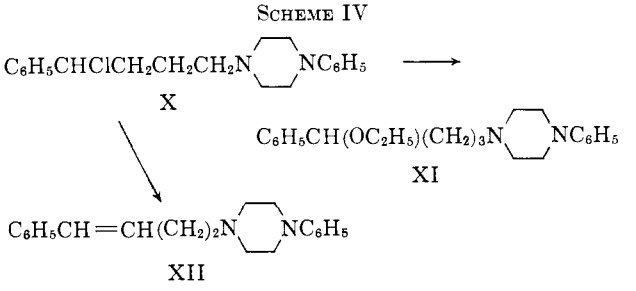
Scheme III



The Mannich base VI was reduced to the secondary alcohol VII with sodium borohydride. Treatment of VII with thionyl chloride formed [3-chloro-3-(*p*-tolyl)-propyl]-4-(*o*-tolyl)piperazine (VIII) which was then allowed to react with 1 equiv. of sodium ethoxide in ethyl alcohol solution forming [3-ethoxy-3-(*p*-tolyl)-propyl]-4-(*o*-tolyl)piperazine (IX). This was identical with the substance prepared by the previously described method, and the over-all yield from the Mannich base was 50%.

All attempts to convert X to XI by treatment with sodium ethoxide only gave rise to crystalline XII and a smaller amount of amorphous residue (Scheme IV).

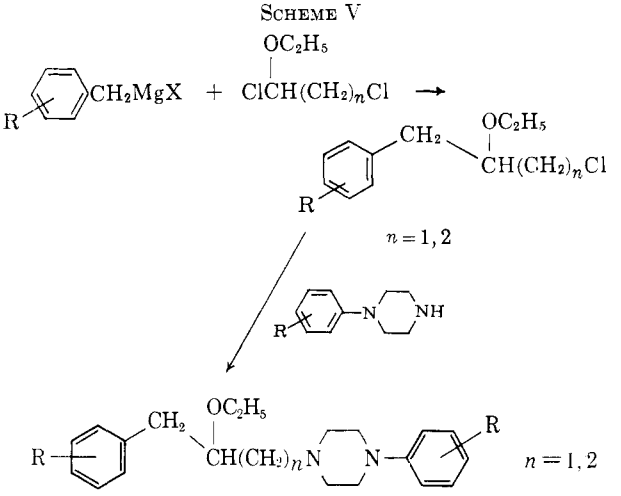
Scheme IV



Formation of XII is probably due to the neighboring group effect of piperazine nitrogen thus facilitating dehydrohalogenation.

Finally, in Scheme V is shown the synthesis of compounds in which the ethoxy group is at C-2 of the carbon chain. Dichloroethyl ethyl ether was allowed to react with the Grignard reagent to afford the corresponding chloropropane derivative which in turn was condensed with phenylpiperazines to yield the desired compounds. Condensation of the Grignard reagent with 2,3-dichloro-1-ethoxypropane afforded the corresponding butyl derivative.

Scheme V



Pharmacological Methods

The following methodology was employed in the testing of the compounds reported in this paper.

Adrenolytic Test.—This test was carried out by determining the effect of the compound in question on the pressor response of *l*-epinephrine in the anesthetized dog and, in addition, the effect on blood pressure as the parameter of the study. An active compound caused a reverse response to *l*-epinephrine and the degree of reversal was expressed from −1, equal to a mild effect, to −4, equal to a marked reversal.

Antihypertensive Test.—Drugs under study for possible hypotensive activity were first studied in anesthetized dogs. Several intravenous doses were administered in a semilog dose range and the effect of the drug on blood pressure was observed. In addition, the effects of various doses of the drug on the responses produced by the control drugs, *l*-epinephrine, *l*-norepinephrine, acetylcholine, histamine, angiotensin amide, and amphetamine, were noted. If the drug showed interesting hypotensive activity, it was then studied in anesthetized dogs for possible oral hypotensive activity.

Next the drug was studied in both renal and normotensive dogs for 12–14 days for possible oral hypotensive activity. At the same time the drug was studied in several groups of anesthetized dogs for its effect on cardiac output, coronary, renal, and femoral blood flow. The scale of activities was determined from values of +1 and +4, indicating a weak to a marked antihypertensive effect.

Antiinflammatory Test.—The procedure for producing the rat granuloma pouch is according to Robert and Nezamis.[4] Female rats weighing 140–155 g. were anesthetized with pentobarbital sodium. The hair on the dorsal surface was removed with electric clippers and the area was swabbed with 70% alcohol. Air (25 ml.) was injected beneath the skin to form the pouch. This was followed by the injection into the formed pouch of 0.5 ml. of 1% croton oil–corn oil solution. As soon as the animals recovered from the anesthesia, treatment with possible antiphlogistic agents was begun either by oral or parenteral administration and continued for the next 4 days. Approximately 48 hr. after formation of the pouches, the pouches were deflated by removing the air through a sterile needle attached by a rubber tube to a vacuum line. Two days following the removal of air, the animals were sacrificed, the exudate was removed through a cut in the skin, and the volume was measured in a graduated cylinder. Terminal body weight was then recorded and the animals were autopsied to obtain adrenal and thymus weights.

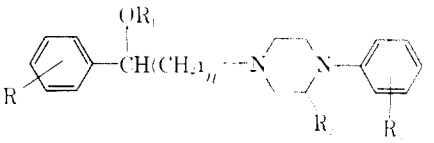
The scale of activities was determined by the per cent inhibition of exudate relative to control values: +1 = 25%, +2 = 25–50%, +3 = 50–75%, +4 = 75–100%.

Results

Structure–Activity Study.—The initial finding that V showed some degree of activity in the above described

(4) A. Robert and J. Nezamis, *Acta Endocrinol.*, **25**, 105 (1957).

TABLE I

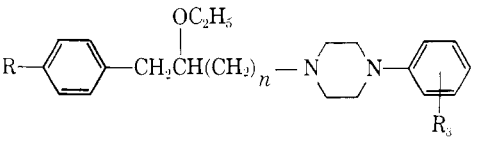


No.	R	R_1	n	R_2	R_3	M.p., °C.	Formula	Calcd., % C	Calcd., % H	Found, % C	Found, % H
1	H	C_2H_5	1	H	H	225–228	$C_{20}H_{26}N_2O_2 \cdot 2HCl$	62.72	7.37	62.77	7.48
2	H	C_2H_5	1	CH_3	H	230–235	$C_{21}H_{28}N_2O \cdot 2HCl$	63.48	7.56	63.20	7.80
3	H	C_2H_5	2	H	H	200	$C_{21}H_{28}N_2O \cdot 2HCl$	63.49	7.81	63.35	7.84
4	H	C_2H_5	2	CH_3	H	193–194	$C_{22}H_{30}N_2O \cdot 2HCl$	64.23	7.78	64.08	7.52
5	H	C_2H_5	1	H	2-Cl	200–203	$C_{20}H_{25}ClN_2O \cdot HCl$	63.04	6.88	62.58	6.92
6	H	C_2H_5	2	H	2-Cl	141–143	$C_{21}H_{27}ClN_2O \cdot 2HCl$	58.41	6.77	58.10	6.92
7	H	C_2H_5	2	H	4-Cl	158	$C_{21}H_{27}ClN_2O \cdot 2HCl$	58.41	6.77	58.20	6.80
8	H	C_2H_5	1	H	2-OCH_3	215–217	$C_{21}H_{28}N_2O_2 \cdot 2HCl$	61.07	7.32	61.03	7.39
9	H	C_2H_5	2	H	2-OCH_3	198	$C_{22}H_{30}N_2O_2 \cdot 2HCl$	61.82	7.58	61.71	7.61
10	H	C_2H_5	2	H	3-OCH_3	173	$C_{22}H_{30}N_2O_2 \cdot 2HCl$	61.82	7.58	61.52	7.83
11	H	C_2H_5	2	H	4-OCH_3	210–211	$C_{22}H_{30}N_2O_2 \cdot 2HCl$	61.82	7.58	61.45	7.47
12	H	C_2H_5	1	H	3-CH_3	197–199	$C_{21}H_{28}N_2O \cdot 2HCl$	63.53	7.62	63.41	7.90
13	H	C_2H_5	2	H	2-CH_3	179–180	$C_{22}H_{30}N_2O \cdot 2HCl$	64.23	7.78	68.87	7.93
14	H	C_2H_5	2	H	3-CH_3	153	$C_{22}H_{30}N_2O \cdot 2HCl \cdot 0.5H_2O$	62.85	8.15	62.68	8.24
15	H	C_2H_5	2	H	3-CF_3	173–174	$C_{22}H_{27}F_3N_2O$	61.59	6.57	61.88	6.44
16	H	C_2H_5	2	H	4-CH_3	200	$C_{22}H_{30}N_2O \cdot 2HCl$	64.23	7.78	64.12	7.72
17	H	C_2H_5	2	H	3-C_2H_5	186–188	$C_{23}H_{32}N_2O \cdot 2HCl \cdot 0.5H_2O$	63.58	8.12	63.56	8.18
18	4-CH_3	CH_3	2	H	H	200	$C_{21}H_{28}N_2O \cdot 2HCl$	63.47	7.61	63.62	7.56
19	4-CH_3	CH_3	2	CH_3	H	197–198	$C_{22}H_{30}N_2O \cdot 2HCl$	64.23	7.84	64.40	7.77
20	4-CH_3	C_2H_5	2	H	H	194	$C_{22}H_{30}N_2O \cdot 2HCl$	64.23	7.84	64.00	7.94
21	4-CH_3	$CH(CH_3)_2$	2	H	CH_3	171–173	$C_{24}H_{34}N_2O \cdot 2HCl$	65.58	8.26	65.21	8.28
22	4-CH_3	C_2H_5	2	H	2-CH_3	169–171	$C_{23}H_{32}N_2O \cdot 2HCl$	64.92	8.05	64.84	8.13
23	4-CH_3	C_2H_5	2	H	3-CH_3	165	$C_{23}H_{32}N_2O \cdot 2HCl$	64.92	8.05	64.54	8.15
24	4-CH_3	C_2H_5	2	H	4-CH_3	194–195	$C_{23}H_{32}N_2O \cdot 2HCl$	64.92	8.05	65.10	8.24
25	4-CH_3	C_2H_5	2	H	2-OCH_3	186–187	$C_{23}H_{32}N_2O_2 \cdot 2HCl$	62.56	7.76	62.74	7.78
26	4-CH_3	C_2H_5	2	H	2-Cl	150–152	$C_{22}H_{29}N_2O \cdot 2HCl$	59.26	7.01	59.21	7.26
27	4-CH_3	C_2H_5	2	H	3-Cl	168–170	$C_{22}H_{29}ClN_2O \cdot HCl$	64.50	7.39	64.56	7.47
28	4-CH_3	C_2H_5	2	H	4-Cl	271	$C_{22}H_{29}N_2O \cdot 2HCl$	59.26	7.01	59.15	7.16
29	4-Cl	C_2H_5	1	H	H	203–205	$C_{20}H_{25}ClN_2O_2 \cdot 2HCl$	57.46	6.51	57.37	6.79
30	4-Cl	C_2H_5	2	H	H	210	$C_{21}H_{27}ClN_2O \cdot 2HCl$	58.41	6.77	58.53	6.98
31	4-Cl	C_2H_5	2	H	H	170	$C_{21}H_{27}ClN_2O \cdot 2HCl \cdot 0.5H_2O$	57.22	7.09	57.25	7.08
32	4-Cl	C_2H_5	1	H	2-Cl	240–244	$C_{20}H_{24}Cl_2N_2O \cdot HCl$	57.81	6.06	57.84	6.05
33	4-Cl	C_2H_5	2	H	2-Cl	125	$C_{21}H_{26}Cl_2N_2O \cdot 2HCl$	54.09	6.05	54.08	6.26
34	4-Cl	C_2H_5	2	H	3-Cl	169	$C_{21}H_{26}Cl_2N_2O \cdot HCl$	58.68	6.33	58.87	6.49
35	4-Cl	C_2H_5	2	H	4-Cl	188	$C_{21}H_{26}Cl_2N_2O \cdot HCl \cdot H_2O$	56.32	6.53	56.21	6.36
36	4-Cl	C_2H_5	1	H	2-OCH_3	176–179	$C_{22}H_{28}ClN_2O_2 \cdot 2HCl \cdot H_2O$	55.05	7.20	55.04	7.00
37	4-Cl	C_2H_5	2	H	2-OCH_3	191–192	$C_{22}H_{29}ClN_2O_2 \cdot 2HCl$	57.20	6.76	56.89	6.88
38	3-Cl	C_2H_5	1	H	H	192–193	$C_{20}H_{26}ClN_2O \cdot 2HCl \cdot H_2O$	55.09	6.70	55.75	6.64
39	3-Cl	C_2H_5	1	H	2-OCH_3	213–217	$C_{21}H_{27}ClN_2O_2 \cdot 2HCl$	56.30	6.53	56.28	6.34
40	3,4-Cl_2	C_2H_5	1	H	H	211–213	$C_{20}H_{24}Cl_2N_2O \cdot 2HCl$	53.14	5.80	53.15	5.98
41	3,4-Cl_2	C_2H_5	1	H	2-OCH_3	221–225	$C_{21}H_{26}Cl_2N_2O_2 \cdot 2HCl \cdot 0.5H_2O$	51.37	5.95	51.30	6.14
42	4-Cl	C_2H_5	2	H	3-OCH_3	168–170	$C_{22}H_{29}ClN_2O \cdot 2HCl$	57.20	6.76	57.96	6.60
43	4-Cl	C_2H_5	2	H	4-CH_3	197	$C_{22}H_{29}ClN_2O \cdot 2HCl$	59.25	7.01	59.30	6.81
44	4-Cl	C_2H_5	2	H	3-CH_3	184	$C_{22}H_{29}ClN_2O \cdot 2HCl$	59.25	7.01	59.43	7.26
45	4-Cl	C_2H_5	1	H	3-CH_3	173–174	$C_{22}H_{29}ClN_2O \cdot 2HCl$	59.25	7.01	58.83	7.14
46	3-CF_3	C_2H_5	1	H	H	182–185	$C_{21}H_{25}F_3N_2O \cdot 2HCl \cdot 0.5H_2O$	54.83	6.14	54.90	6.53
47	4-F	C_2H_5	1	CH_3	H	224–228	$C_{21}H_{27}FN_2O \cdot 2HCl$	60.72	6.99	60.39	7.12
48	4-F	C_2H_5	1	H	3-CH_3	193–196	$C_{21}H_{27}FN_2O \cdot HCl \cdot 0.5H_2O$	65.00	7.55	65.03	7.65

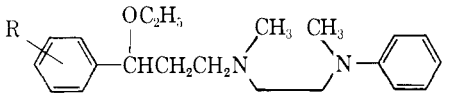
tests prompted us to investigate this series thoroughly (see Table I).

Considering the general structure already outlined, it was found that R_2 equal to CH_3 was not essential for any of the activities found. The R_1 function was also not critical since methyl, ethyl, and isopropyl did not alter the activity for any of the compounds. However, maximum biological effects were obtained with R_1 equal to ethyl. One compound was made with a homopiperazine moiety but this led to a marked diminution in adrenolytic, antiinflammatory, and antihypertensive effects. In addition, it was also observed that an N^4-methyl or -benzyl group also yielded weakly active compounds. An N^4-2-pyridyl group offered no advantage over the phenyl group. The compounds listed in Table II were also less effective in our tests. Open-chain derivatives of the piperazine [*e.g.*, N-methyl-N-phenyl-N′-methyl-N′-(3-*p*-chlorophenyl)-3-ethoxypropylethylenediamine, see Experimental] also were found to be weakly active in our tests. Thus, with the B and D portion of the molecule fixed and the E portion confined to phenyl and its derivatives, systematic changes were made at A and C to determine alterations in biological effects.

Table II



No.	R	n	R_3	M.p., °C.	Formula	Calcd., % C	Calcd., % H	Found, % C	Found, % H
49	H	1	H	172–175	$C_{21}H_{28}N_2O\cdot 2HCl$	63.53	7.62	63.98	8.11
50	H	1	2-OCH_3	198–201	$C_{22}H_{30}N_2O_2\cdot 2HCl$	61.88	7.55	62.10	7.77
51	4-Cl	1	H	179–183	$C_{21}H_{27}ClN_2O\cdot 2HCl\cdot H_2O$	56.05	6.94	55.87	6.63
52	4-Cl	1	2-OCH_3	176–179	$C_{22}H_{29}ClN_2O_2\cdot 2HCl\cdot H_2O$	55.05	7.20	58.84	7.00
53	4-Cl	2	H	178–179	$C_{22}H_{29}ClN_2O\cdot HCl\cdot 0.5H_2O$	63.39	7.42	63.51	7.85
54	4-Cl	2	2-OCH_3	217–218	$C_{23}H_{31}ClN_2O_2\cdot 2HCl$	58.05	6.95	57.93	7.20

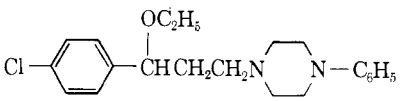


R = Cl, F

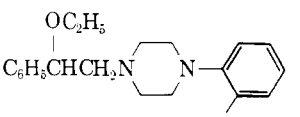
Adrenolytic Effects.—The selection of a compound with maximum adrenolytic action was facilitated when it was discovered that chain length (C) was quite important. Those compounds with $n = 1$ had a low order of activity and thus attention was confined to substances in which $n = 2$. Although R = H, R_3 = H or Cl at the 2-, 3-, or 4-positions gave compounds with a +2 effect, R = 4-CH_3 was responsible for compounds with increased adrenolytic activity. The most potent compound in this series with pronounced adrenolytic activity at 50 γ/kg. was found to be IX (**22**, Table I). Replacement of R_3 = 2-CH_3 for 2-OCH_3 had no favorable effect on activity, but the compound with R_3 = 2-, 3-, or 4-Cl gave only a −2 effect. More interestingly, a methyl or methoxyl group at position 3 or 4 in portion E with parts A, B, C, and D remaining fixed as in compound **20** gave less active substances.

Antihypertensive Effect.—Some of the compounds having an adrenolytic effect also were found to lower blood pressure. As previously indicated, V showed some antihypertensive effect, although transient. A more significant effect (+3) was noted for those compounds with R = R_2 = H and $n = 2$ with $R_1 = C_2H_5$. Those substances with $n = 1$ had insignificant antihypertensive activity. Thus, it appeared that the adrenolytic activity could be separated from the antihypertensive effect according to the nature of the substituent R; *i.e.*, the methyl group enhanced the adrenolytic effect, whereas an unsubstituted phenyl group at portion A of the molecule was responsible for increased hypotensive effect with minimum adrenolytic action. It now remained to determine the influence of R_3 on the blood pressure lowering action. Compounds with R_3 = Cl, either at the 2-, 3-, or 4-position, were weakly hypotensive. On the other hand, R_3 = 2-OCH_3 resulted in a substance with some hypotensive action (40 mm. decrease in blood pressure at 5 mg./kg.). However, at this effective dose the compound was also adrenolytic. A methoxyl group at the 3- or 4-position gave only weakly active substances. The methyl group for R_3 gave more definitively significant results; the 2- and the 4-methyl-substituted compounds gave a marked hypotensive response (60 mm. at 5 mg./kg.), but the effect was only transient with blood pressure returning to predrug level within 30 min. However, the 3-methyl derivative (Table I, **15**) markedly lowered the blood pressure (45 mm.) of unanesthetized dogs receiving doses of 4 mg./kg. orally for 12 days. Under these conditions, this substance produced a slight augmentation of the pressor response to intravenously administered *l*-epinephrine and a marked increase in the response produced by *l*-norepinephrine and angiotensin amide. A moderate bradycardia was also observed. At a dose of 6 mg./kg. administered orally to 12 unanesthetized dogs, this compound caused a 190% increase in water excretion, a 50% increase in sodium excretion, and a 30% increase in potassium excretion over control values in the 6-hr. period following the administration of the drug. It would appear that the substance inhibits antidiuretic hormone and preliminary experiments in this direction have confirmed this. Other members of this series, although hypotensive, do not show this diuretic action. The compound in which R_3 = 3-C_2H_5 gives a similar antihypertensive effect without any diuretic action.

Antiinflammatory Effects.—Again V furnished a useful lead in determining antiinflammatory effects of this series of compounds. Although several compounds showed antiinflammatory properties, this effect was accentuated in those substances where R = 4-Cl. These compounds did not show marked antihypertensive or adrenolytic effects. Substitution at the E portion of the general structure gave varying results. It was noted that compounds with +2 activity resulted with R_3 = H, 2-OCH_3, or 2-Cl. Substitution at the 3- or 4-position geneally led to weaker antiinflammatory substances. Also R_2 = H or CH_3 had little effect and the same was true for $n = 1$ or 2. Thus, of the vast number of compounds prepared the following two structures showed the most promising antiinflammatory action. These substances were 2–3 times more active



XIII



XIV

than phenylbutazone when tested orally in the granuloma pouch test and in the cotton pellet test. Although certain variations of these (*i.e.*, 2-OCH_3 in compound **30** and 4-Cl in compound **8**) led to potent antiinflammatory agents, the toxicity factor was also

increased by these changes. Disubstitution of the phenyl ring in portion A led to less active compounds. These substances were devoid of analgesic activity in experimental animals when tested according to the rat tail flick test.[5]

Experimental[6]

1-Substituted Piperazines.—These intermediates were obtained from commercial sources and also according to methods devised in our laboratory, examples of which are herein described.

1-Aryl-1-ethoxyethyl Chlorides.—These substances were prepared from the appropriately substituted phenyl compound according to the method of Duliere[2] and Houben and Führer.[3] 1-(4-Chlorophenyl)-1-ethoxyethyl chloride, b.p. 132–140° (12 mm.); 1-(3-trifluoromethylphenyl)-1-ethoxyethyl chloride, b.p. 108–110° (12 mm.); 1-(3,4-dichlorophenyl)-1-ethoxyethyl chloride, b.p. 152–159° (12 mm.); 1-(3-chlorophenyl)-1-ethoxyethyl chloride, b.p. 133–137° (12 mm.); 1-(4-fluorophenyl)-1-ethoxyethyl chloride, b.p. 110–115° (12 mm.); 3-ethoxy-3-(2-chlorophenyl)propyl chloride, b.p. 95–98° (12 mm.); 3-ethoxy-4-phenylbutyl chloride, b.p. 80–87° (0.05 mm.); and 3-ethoxy-4-(4-chlorophenyl)butyl chloride, b.p. 193–195° (0.05 mm.), have not been characterized previously.

3-Ethoxy-1-phenylpropyl chloride, 3-ethoxy-3-(4-tolyl)propyl chloride, 3-ethoxy-3-(4-chlorophenyl)propyl chloride were purchased from the Aldrich Chemical Co., Milwaukee, Wis.

General Method for the Synthesis of 1,4-Disubstituted Piperazines. 1-[2-(Ethoxy-2-phenyl)ethyl]-4-(2-methoxyphenyl)-piperazine.—A mixture of 26 g. (0.14 mole) of 1-phenyl-1-ethoxyethyl chloride, 27 g. (0.14 mole) of 1-(2-methoxyphenyl)-piperazine, and 20 g. of Na_2CO_3 in 400 ml. of butanol was refluxed for 28 hr. with vigorous stirring. The cooled solution was filtered and concentrated *in vacuo* to remove butanol. The residue was dissolved in ether, extracted with water, dried, and again concentrated *in vacuo*. The residue was fractionated to give 20 g. (42% yield) of the free base, b.p. 169–172° (0.1 mm.), which was converted to the dihydrochloride and recrystallized from ethanol; m.p. 215–217°. The characteristics for the other members of the series are listed in Table I; they were likewise obtained in yields of 40–45%.

1-[3-Ethoxy-3-(*o*-chlorophenyl)propyl]-4-methylpiperazine dihydrochloride was recrystallized from ethyl alcohol to give white crystals, m.p. 223–224°.

Anal. Calcd. for $C_{16}H_{27}Cl_3N_2O$: C, 51.97; H, 7.36. Found: C, 51.99; H, 7.33.

1-[3-Ethoxy-3-(*p*-tolyl)propyl]-4-benzylpiperazine dihydrochloride was recrystallized from ethyl alcohol to yield white powder, m.p. 300°.

Anal. Calcd. for $C_{23}H_{34}Cl_2N_2O$: C, 64.92; H, 8.05. Found: C, 64.86; H, 8.01.

1-[3-Ethoxy-3-(*p*-tolyl)propyl]-4-(2-pyridyl)piperazine dihydrochloride was recrystallized from ethyl alcohol to give white powder, m.p. 194–195°.

Anal. Calcd. for $C_{21}H_{31}Cl_2N_3O$: C, 61.16; H, 7.58. Found: C, 60.97; H, 7.42.

1-[3-Ethoxy-3-(*p*-tolyl)propyl]hexahydro-3-methyl-4-phenyl-1,4-diazepine had b.p. 150–152° (0.05 mm.).

Anal. Calcd. for $C_{24}H_{34}O$: C, 78.64; H, 9.34; N, 7.64. Found: C, 78.37; H, 9.17; N, 7.52.

1-[3-Keto-3-(*p*-tolyl)propyl]-4-(*o*-tolyl)piperazine Hydrochloride (VI).—A solution of 49.8 g. (0.20 mole) of 1-(*o*-tolyl)-piperazine dihydrochloride, 7.70 g. (0.255 mole) of paraformaldehyde, and 34.70 g. (0.255 mole) of *p*-methylacetophenone in 150 ml. of anhydrous ethanol was stirred under reflux for 22 hr. After cooling to −10° for 2 hr. the product was filtered, washed with three 30-ml. portions of cold acetone, and dried overnight *in vacuo* at 50°. The yield was 57.0 g. (79.5%) of colorless crystals melting at 210–214° dec. A sample was recrystallized from 5 vol. of methanol (m.p. 211–213°) (in 86% recovery).

Anal. Calcd. for $C_{21}H_{27}ClN_2O$: C, 70.27; H, 7.58; N, 7.81. Found: C, 70.93; H, 7.70; N, 7.74.

1-[3-Hydroxy-3-(*p*-tolyl)propyl]-4-(*o*-tolyl)piperazine (VII).—A solution of 39.5 g. (0.11 mole) of the keto-piperazine hydrochloride VI in 150 ml. of methanol was adjusted to pH 10 with 9 ml. of 50% aqueous NaOH. The resulting white suspension was stirred in an ice bath and treated with 5.65 g. of $NaBH_4$ over a 15-min. period, holding the temperature between 6 and 20°. When the ice bath was removed, the temperature rose to 33° within 5 min. The now thinner suspension was stirred at ambient temperature for 3 hr., cooled to 5°, and acidified to pH 2 with 32 ml. of concentrated HCl. After 20 min. of stirring, the pH was again raised to 12 with 50% NaOH, and the solution was diluted with 250 ml. of water and extracted with 150 ml. of $CHCl_3$, followed by two further extracts of 100 ml. each. After drying and removal of the solvent, the initially oily residue crystallized on standing to a colorless solid weighing 35.1 g. (98.3% yield) and melting at 80–83°. Recrystallization from 1 vol. of anhydrous ethanol gave a 92% recovery of material melting 85–86° (prior sintering).

Anal. Calcd. for $C_{21}H_{28}N_2O$: C, 77.74; H, 8.70; N, 8.63. Found: C, 77.66; H, 8.67; N, 8.90.

1-[3-Ethoxy-3-(*p*-tolyl)propyl]-4-(*o*-tolyl)piperazine Dihydrochloride (IX).—A solution of 16.22 g. (0.05 mole) of the piperazine alcohol VII in 125 ml. of benzene was treated with HCl gas until precipitation of the salt was complete (pH 2). A solution of 17.65 g. (0.15 mole) of thionyl chloride in 75 ml. of benzene was added over a period of 10 min. at room temperature, and the resulting suspension was heated to reflux during 30 min. and then refluxed with stirring for 3 hr. Benzene and excess thionyl chloride were distilled until 91 ml. of distillate had been collected, 50 ml. of fresh benzene was added, and the distillation continued to dryness. The tan residue was dissolved in 75 ml. of anhydrous ethanol and treated with a solution of 7.0 g. (0.304 g.-atom) of sodium in 150 ml. of anhydrous ethanol over a period of 10 min. with stirring and ice-bath cooling. The suspension was stirred and refluxed for 1 hr., cooled to room temperature, and left standing overnight. The solvent was removed *in vacuo*, the residue of 48.3 g. was treated with 500 ml. of water with ice-bath cooling, and the oily product was extracted into chloroform. The turbid extract was dried (Na_2SO_4), clarified with Darco, and evaporated to dryness *in vacuo*. The orange residual oil weighed 17.4 g. (98.5% yield).

A 13-g. portion of the above oil (0.03638 mole) was dissolved in 58 ml. of methanol and the solution was saturated with HCl gas without cooling. On cooling to room temperature, the product crystallized. It was filtered, washed with cold methanol, and dried in air overnight, yielding 8.99 g. of salt, m.p. 165–168°. A small second crop (0.86 g.) was obtained from the filtrate by cooling to −10° overnight. The 9.85 g. was recrystallized from 50 ml. of 2-propanol, with cooling to −10°, yielding 6.42 g. (44.1%) of material melting at 169–171° (prior sintering).

Anal. Calcd. for $C_{23}H_{34}Cl_2N_2O$: C, 64.93; H, 8.05; N, 6.58. Found: C, 64.88; H, 8.09; N, 6.55.

1-[4-Chloro-4-phenyl)butyl]-4-phenylpiperazine Dihydrochloride (X).—Twenty-five milliliters of 7–8 *N* ethanolic HCl was added to 5.31 g. (0.016 mole) of 1-[(4-hydroxy-4-phenyl)-butyl]-4-phenylpiperazine[7] dissolved in 25 ml. of ethyl alcohol. An immediate yellow coloration occurred followed by the formation of a white suspension. After refluxing this mixture for 3 hr., it was then filtered and the white solid was recrystallized from ethyl alcohol to yield 1.5 g. of pure product, m.p. 225–226°.

Anal. Calcd. for $C_{20}H_{27}Cl_3N_2$: C, 60.55; H, 6.91; N, 6.86. Found: C, 60.61; H, 6.97; N, 6.81.

Compound X (1.75 g., 0.002 mole) in 25 ml. of ethyl alcohol was added to 40 ml. of ethyl alcohol in which was dissolved 0.5 g. of sodium. The resulting mixture was stirred at room temperature overnight and then filtered. The filtrate was evaporated to dryness, the resulting brown solid was taken up in ether, and the amorphous residue was filtered off. The ether filtrate was evaporated to dryness again, and the residue was then recrystallized from a small amount of ether to give 0.15 g. of product, m.p. 96–98°.

Anal. Calcd. for $C_{20}H_{26}N_2$: C, 82.35; H, 8.23; N, 9.61. Found: C, 82.10; H, 8.15; N, 9.54.

N-Methyl-N'-phenylethylenediamine was prepared from N-methyl-N-phenylethylenediamine[8] *via* the N-formyl derivative by the method of Blicke and Lu[9]; yield 68%, b.p. 75–80° (0.3 mm.).

(5) H. G. Wolff, J. D. Hardy, and H. Goodell, *J. Clin. Invest.*, **20**, 63 (1941).

(6) All melting points are corrected.

(7) P. Adriaens and J. Janssen, U. S. Patent 2,997,474 (1961).

(8) H. E. Newman, *Ber.*, **24**, 2191 (1891).

(9) F. F. Blicke and C.-J. Lu, *J. Am. Chem. Soc.*, **74**, 3933 (1952).

Anal. Calcd. for $C_{10}H_{16}N_2$: C, 73.17; H, 9.76; N, 17.07. Found: C, 73.32; H, 9.54; N, 17.46.

N-Methyl-N-phenyl-N'-methyl-N'-(2-*p*-fluorophenyl-2-ethoxy)ethylethylenediamine.—A mixture of 7.45 g. (0.036 mole) of 1-*p*-fluorophenyl-1-ethoxyethyl chloride and 6 g. (0.036 mole) of N-methyl-N'-methyl-N'-phenylethylenediamine in 200 ml. of butanol containing 10 g. of Na_2CO_3 was refluxed with stirring for 96 hr. After filtration, the reaction mixture was concentrated *in vacuo* and the residual oil was fractionated *in vacuo* to give 6.1 g. (56%) of product, b.p. 170–180° (0.5 mm.).

Anal. Calcd. for $C_{20}H_{27}FN_2O$: C, 72.79; H, 8.25; N, 8.49. Found: C, 72.46; H, 8.26; N, 8.56.

N-Methyl-N-phenyl-N'-methyl-N'-(3-*p*-chlorophenyl)-3-ethoxypropylethylenediamine.—A mixture of 8.53 g. (0.036 mole) of 1-*p*-chlorophenyl-1-ethoxypropyl chloride and 6 g. (0.036 mole) of N-methyl-N'-methyl-N'-phenylethylenediamine in 200 ml. of butanol containing 10 g. of Na_2CO_3 was refluxed with stirring for 96 hr. After filtration and concentration *in vacuo*, the residual oil was fractionated *in vacuo* to give 8.5 g. (65%) of product, b.p. 180–195° (0.6 mm.).

Anal. Calcd. for $C_{21}H_{29}ClN_2O$: C, 69.86; H, 8.10; N, 7.76. Found: C, 70.01; H, 8.10; N, 7.64.

A New N-Phenylpiperazine Synthesis. 2-Anilinopropionitrile.[10]—To a solution of 83.0 g. (0.80 mole) of $NaHSO_3$ in 154 ml. of water was added 24.65 g. (0.56 mole) of acetaldehyde over a period of 25 min., maintaining the temperature between 60 and 70°. After an additional 0.5 hr. of stirring at this temperature, 77.0 g. (0.83 mole) of aniline was added over a 20-min. period. After 20 min. of stirring at 60–70°, a solution of 40.5 g. (0.80 mole) of NaCN in 90 ml. of water was added over 20 min. The product separated as an oil which crystallized on cooling to room temperature. After filtering, recrystallizing from 50% aqueous ethanol, and drying, it weighed 51.0 g. (62.4% yield), m.p. 90–92°.

Anal. Calcd. for $C_9H_{10}N_2$: C, 73.94; H, 6.90; N, 19.16. Found: C, 73.84; H, 7.12; N, 19.07.

2-Anilinoisobutyronitrile.[11]—In an analogous procedure 43.5 g. (0.75 mole) of acetone, 312.2 g. (3.0 moles) of $NaHSO_3$, 46.5 g. (0.5 mole) of aniline, and 29.5 g. (0.6 mole) of NaCN in a total of 655 ml. of water yielded 68.8 g. (86.0% yield) of the aminonitrile, m.p. 89–92°.

Anal. Calcd. for $C_{10}H_{12}N_2$: C, 75.0; H, 7.49; N, 17.49. Found: C, 74.91; H, 7.73; N, 17.30.

N-Phenyl-N-(1-cyanoethyl)chloroacetamide.—Sodium carbonate (154.6 g., 1.46 moles) was suspended in a solution of α-anilinoacetonitrile (213.0 g., 1.46 moles) in 2.0 l. of benzene. Chloroacetyl chloride (165.0 g., 1.46 moles) in 400 ml. of benzene was added over a 25-min. period at such a rate as to control the gas evolution, maintaining the temperature at 70°. The mixture was refluxed for 2 hr., cooled to room temperature, and filtered, and the inorganic salts were washed with benzene. Evaporation of the filtrate left a residue of 329.2 g. of oil which was crystallized from 400 ml. of anhydrous ethanol by cooling to −10° overnight. The colorless, crystalline product weighed 256.3 g. (78.8% yield), m.p. 69–71°.

Anal. Calcd. for $C_{11}H_{11}ClN_2O$: C, 59.33; H, 4.98; N, 12.58. Found: C, 59.00; H, 5.02; N, 12.56.

1-Phenyl-2-methylpiperazine.[12]—To a mixture of 11.93 g. (0.32 mole) of $LiAlH_4$ and 280 ml. of tetrahydrofuran in a 1-l. flask under N_2 was added a solution of N-phenyl-N-(1-cyanoethyl)chloroacetamide (22.26 g., 0.1 mole) in 85 ml. of tetrahydrofuran over a period of 17 min. maintaining the temperature below 25° with an ice bath. The mixture was then refluxed at 69° for 2 hr., cooled to 25°, decomposed with 18 ml. of water (stirring for 25 min.) and 12.3 ml. of 15% aqueous NaOH (stirring for 15 min.). The inorganic products were filtered and washed with tetrahydrofuran, and the filtrates were evaporated to dryness. The oily residue (13.3 g.) still contained halogen. It was refluxed overnight with 10.6 g. of Na_2CO_3 and 25 ml. of toluene. The toluene solution was filtered and evaporated to dryness, leaving 11.1 g. of halogen-free oil, which was distilled *in vacuo*. Material boiling at 115–117° (1.0 mm.) was collected (3.6 g., 20.4% yield) and converted to the phenylthiourea derivative, m.p. 158–160°. A mixture with phenylthiourea derivative of authentic 1-phenyl-2-methylpiperazine (m.p. 158–160°) melted at 159–160°.

Anal. Calcd. for $C_{18}H_{21}N_3S$: C, 69.50; H, 6.79; N, 13.48. Found: C, 69.36; H, 6.95; N, 13.47.

In a subsequent preparation, after addition of all reagents, tetrahydrofuran was distilled out and replaced with xylene until the temperature in the mixture reached 131°. It was then refluxed for 6.75 hr. and worked up as before. The fraction boiling at 114–120° (1.0 mm.) weighed 11.15 g. (63.4% yield). Replacement of tetrahydrofuran with toluene gave 48.7% after a 2-hr. reflux, and 58.5% after a 6-hr. reflux.

N-Phenyl-N-(1-cyanoethyl)-α-chloropropionamide.—In a procedure analogous to that used for the preparation of the corresponding acetanilide, α-chloropropionyl chloride gave a 70.4% yield of colorless crystalline product, m.p. 85–87°.

Anal. Calcd. for $C_{12}H_{13}ClN_2O$: C, 60.19; H, 5.49; N, 11.84. Found: C, 60.83; H, 5.45; N, 11.82.

1-Phenyl-2,5-dimethylpiperazine.—Reduction of N-phenyl-N-(1-cyanoethyl)-α-chloropropionamide with $LiAlH_4$ in toluene, refluxed for 6 hr., and worked up as in the first case, gave 57.4% of the oily piperazine, b.p. 117–125° (1.0 mm.).

Anal. Calcd. for $C_{12}H_{18}N_2 \cdot 0.75H_2O$: C, 70.72; H, 9.64; N, 13.75. Found: C, 70.83; H, 9.63; N, 13.61.

The **phenylthiourea** derivative melted at 163–165°.

Anal. Calcd. for $C_{19}H_{23}N_3S$: C, 70.15; H, 7.07; N, 12.92. Found: C, 69.74; H, 6.84; N, 12.77.

1-Phenyl-2,2-dimethylpiperazine.—Treatment of 19.2 g. (0.12 mole) of 2-anilinoisobutyronitrile with chloroacetyl chloride resulted in an oily amide which could not be crystallized. The crude product (27.3 g., 96.2% yield) was dissolved in 85 ml. of tetrahydrofuran and added over a 25-min. period to a solution of 12.0 g. (0.32 mole) of $LiAlH_4$ in 300 ml. of tetrahydrofuran at 25° under N_2. The mixture was refluxed for 6 hr. and worked up in the previously described way. The fraction boiling at 110–115° (1.0 mm.) weighed 3.7 g. (16.3% yield based on the anilinonitrile).

The **phenylthiourea** derivative melted at 193–195°.

Anal. Calcd. for $C_{19}H_{23}N_3S$: C, 70.15; H, 7.07; N, 12.92. Found: C, 69.93; H, 7.13; N, 12.71.

Hexahydro-2-methyl-1-phenyl-1,4-diazepine.—A mixture of 29.2 g. (0.20 mole) of α-anilinopropionitrile in 300 ml. of ethylene dichloride and 21.2 g. (0.20 mole) of Na_2CO_3 was treated with a solution of 27.7 g. (0.21 mole) of β-chloropropionyl chloride in 50 ml. of ethylene dichloride over a period of 34 min. at −15 to −20°. The mixture was stirred at −15° for 2.5 hr. and allowed to stand for 16.5 hr. at −35 to −40°. After removal of the inorganic salts and the ethylene dichloride *in vacuo* at room temperature, the residual oil (56.6 g.) showed a tendency to crystallize, and also to darken quickly on standing.

A 34.2-g. portion of this oil was dissolved in 150 ml. of tetrahydrofuran and added dropwise over a 38-min. period to 16.15 g. (0.44 mole) of $LiAlH_4$ in 400 ml. of tetrahydrofuran at 40° under N_2. The mixture was stirred at 37° for 21.5 hr., cooled to 20°, and worked up in the previously described way. The fraction boiling at 118–120° (1.0 mm.) weighed 7.8 g. (33.9% yield based on the anilinonitrile).

Anal. Calcd. for $C_{12}H_{16}N_2$: C, 75.79; H, 9.46; N, 14.75. Found: C, 75.63; H, 9.58; N, 14.32.

Octahydro-2-methyl-1-phenyl-1,4-diazocine.—A mixture of 30.0 g. (0.21 mole) of γ-chlorobutyryl chloride, 29.2 g. (0.20 mole) of α-anilinopropionitrile, and 21.2 g. (0.20 mole) of Na_2CO_3 in 325 ml. of benzene was refluxed for 1 hr., cooled to room temperature and stirred for 18 hr. After removal of the inorganic salts and the solvent, the oily residue (57.6 g.) was dissolved in 85 ml. of tetrahydrofuran and added over a 22-min. period to 14.8 g. (0.39 mole) of $LiAlH_4$ in 300 ml. of tetrahydrofuran at 25° under N_2. The mixture was then refluxed for 6 hr. and worked up in the previously described way. The fraction boiling at 138–142° (1.0 mm.) weighed 10.4 g. (25.5% yield based on the anilinonitrile).

Anal. Calcd. for $C_{13}H_{20}N_2$: C, 76.47; H, 9.79; N, 13.74. Found: C, 77.87; H, 9.74; N, 12.77.

An Improved Procedure for the Preparation of 1-Phenylpiperazine Derivatives. 1-(*m*-Ethylphenyl)piperazine.—To a mixture of β,β-dichloroethylamine hydrochloride (59.0 g., 0.33 mole) in 252 ml. of propyl alcohol, was added 40.0 g. (0.33 mole) of *m*-ethylaniline and then 24.7 g. of sodium iodide. Within a 15–20-min. period the temperature of the reaction mixture was brought to reflux temperature with vigorous stirring. The

(10) H. Bücherer, German Patent 157,910 (1905); *Chem. Zentr.*, **I**, 477 (1905).

(11) An alternative synthesis is given by R. A. Jackson, *J. Am. Chem. Soc.*, **67**, 1996 (1945).

(12) C. B. Pollard and T. H. Wicker, Jr., *ibid.*, **76**, 1853 (1954).

solution was heated under reflux for 3 hr. while 52.5 g. (0.495 mole) of Na_2CO_3 was added in small portions whereby vigorous foaming occurs. The reflux temperature was maintained for an additional 2 hr. and then the reaction mixture cooled to room temperature. The mixture was filtered, and the filtrate was evaporated to dryness. Aqueous acid was added to the residue and the resulting solution was extracted several times with chloroform. The acidic solution was then basified to pH 10 with 5 *N* NaOH solution and extracted well with ether. The ether extract was dried over Na_2SO_4. The drying salt was then filtered off, and the ether was removed on the steam bath. The oily residue was distilled *in vacuo* and the product was collected at 110–113° (0.15 mm.). The yield was 82%.

Anal. Calcd. for $C_{12}H_{18}N_2$: C, 75.74; H, 9.54; N, 14.72. Found: C, 75.61; H, 9.48; N, 14.34.

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Yohimbane Derivatives. II. The Synthesis and Psychopharmacological Properties of Yohimbane Derivatives with Halogen Substituents in Ring E

MAXIMILIAN VON STRANDTMANN, GEORGE BOBOWSKI, AND JOHN SHAVEL, JR.

Warner-Lambert Research Institute, Morris Plains, New Jersey

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17α-Fluoro-, -chloro-, and -bromoyohimbanes, 17β-fluoro- and 17β-chloro-16α-methylyohimbanes, 17β-chloro-16α-chloromethylyohimbane, and 16β-chloroyohimbane were prepared. On pharmacological evaluation, most of these compounds produced significant tranquilizing effects in untamed monkeys. The clinical evaluation of the 17α-haloyohimbanes, the most active of this series, was precluded by strong adrenolytic effects in dogs. A convenient n.m.r. method for conformational assignments of some cyclic alcohols is described.

The tranquilizing and hypotensive properties of reserpine have inspired considerable effort by various research groups to investigate the activity of other compounds having the pentacyclic yohimbanoid skeleton.[1] The resulting studies have centered mainly on the cardiovascular area leaving the pharmacology of the central nervous system largely unexplored. The scarce data available create the impression that *trans* C/D ring junction, opposite configuration at C-3, and other differences, as compared with reserpine, render derivatives of yohimbane devoid of sedative activity.[1a]

Our interest in this field arose from the observation[2] of significant analgesic and sedative properties in a group of previously described compounds, such as yohimbane (I), 16α-methylyohimbane (II),[3] epiyohimbol (III),[4] and 16α-methylyohimbol (IV).[3] This finding suggested the synthesis of a wide variety of compounds based on the yohimbane nucleus for evaluation of their central nervous system effects. The present study is concerned with the preparation of 16- and 17-haloyohimbanes and their pharmacological properties.

Two of the starting materials for this work, 17β-hydroxyyohimbane (III) and 17α-hydroxy-16α-methylyohimbane (IV), were readily accessible by procedures described in the literature.[3,4] The third, 16α-hydroxyyohimbane (XIX), was prepared by the KBH_4 reduction of 16-ketoyohimbane.[5] The ratio of the resulting epimers (XIX and XX), which was close to 1:1, did not permit any conclusions as to the configuration of the hydroxyl groups. The low solubility of one of the isomers (XX) in chloroform, pyridine, dimethyl sulfoxide, and other common solvents precluded steric studies by conventional infrared and n.m.r. methods. Configurational assignments were finally made on the basis of the observation that on warming in trifluoroacetic acid for 15–30 min. at 50° only epimer XX eliminated water. The dehydration reaction was most conveniently carried out in the n.m.r. sample tube, the formation of the olefin being detected by the appearance of a signal at 5.5 p.p.m. Application of this technique to model compounds with known configuration, showed definite stereochemical specificity. For example, in the case of 17α-hydroxy-16α-methylyohimbane and 17β-hydroxy-16α-methylyohimbane[6] only the former compound, in which the hydroxyl is axial, eliminated water to give rise to an olefinic signal at 5.25 p.p.m. This analogy, as well as the established concept that 1,2-elimination reactions are particularly facile if the two substituents are in a *trans* coplanar (diaxial) arrangement, led to the assignment of the 16β-OH (axial) configuration for the epimer XX which is easily dehydrated.

The tosylation of the alcohols III, IV, and XIX gave 17β-(*p*-toluenesulfonyloxy)yohimbane (V), 16α-methyl-17α-(*p*-toluenesulfonyloxy)yohimbane (VI), and 16α-(*p*-toluenesulfonyloxy)yohimbane (VII). When these compounds were allowed to react with a saturated solution of dry hydrogen halide in pyridine, substitution with inversion[7] took place to give 17α-fluoro-, 17α-chloro-,[8] and 17α-bromoyohimbane (VIII–X), 17β-fluoro-16α-methylyohimbane (XI), 17β-chloro-16α-methylyohimbane (XII), and 16β-chloroyohimbane (XIII) (see Table I).

The reactions involving hydrogen bromide were accompanied by partial elimination in the case of 17β-

(1) The subject was reviewed by: J. Kerwin, C. P. Balant, and G. E. Ullyot in "Medicinal Chemistry," A. Burger, Ed., 2nd. Ed., Interscience Publishers, Inc., New York, N. Y., 1960, p. 565; (b) R. A. Lucas, "Progress in Medicinal Chemistry," Butterworths, London, 1963, p. 149.

(2) We thank Mr. M. Chessin, Dr. J. F. Emele, and Dr. J. Gylys for their pharmacological studies.

(3) P. Karrer and R. Seamann, *Helv. Chim. Acta*, **35**, 1932 (1952).

(4) B. Witkop, *Ann.*, **554**, 83 (1943).

(5) R. K. Hill and K. Muench, *J. Org. Chem.*, **22**, 1276 (1957).

(6) J. Shavel, Jr., and M. von Strandtmann, U. S. Patent 3,096,245 (1963).

(7) Nucleophilic substitution of the *p*-toluenesulfonyloxy group has been shown by H. Phillips [*J. Chem. Soc.*, **123**, 44 (1923)] to proceed with inversion and very little racemization.

(8) After completion of this work, the conversion of epiyohimbol to 1X with $POCl_3$ was described by Y. Bao and O. Yonemitsu, *Tetrahedron Letters*, No. **5**, 181 (1962).