Isoxazoles. XVIII. Synthesis and Pharmacological Properties of 5-Aminoalkyl- and 3-Aminoalkylisoxazoles and Related Derivatives

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A number of 3-substituted 5-aminoalkyl- and 5-substituted 3-aminoalkylisoxazoles and some related amino alcohols have been prepared for pharmacological testings. Besides ordinary transformations of the corresponding alcohols and acetyl derivatives to the aminoalkyl derivatives and amino alcohols, a convenient synthetic method for the 5-aminoalkyl series which involves 1,3-dipolar cycloaddition of nitrile oxides to aminoalkynes has been developed. Several of the compounds proved to exhibit a wide spectrum of pharmacological properties which include potent hypothermic, analgesic, antiinflammatory, and antitussive activities.

In continuing a program of studies of chemistry and utilization of isoxazole derivatives,[2] we attempted to synthesize a series of 3-aryl-5-aminoalkyl- and 5-aryl-3-aminoalkylisoxazoles (I and II). The system I structurally resembles that of 3-aryl-5-aminoalkyl-1,2,4-oxadiazoles (III) which was reported to possess a variety of pharmacological activities: hypothermic, analgesic, antiinflammatory, and antitussive.[3] A number of compounds of type I were prepared by an extension of the elegant synthetic method of isoxazole derivatives which involves the 1,3-dipolar cycloaddition of nitrile oxides to triple-bonded compounds.[4] The requisite dipolarophiles for the synthesis of I, aminoalkynes (V), were prepared in two ways: by the method of Marszak, *et al.*[5] (amination of the corresponding bromides), and by the method of Campbell, *et al.*[6] (reaction of sodium acetylide with aminoalkyl bromides). Five known nitrile oxides (VI)[7] used as dipoles in the present cycloaddition are readily obtainable from the corresponding hydroxamyl chlorides (IV). However, these oxides are liable to dimerize into furoxan derivatives (VII).[7] In order to suppress this dimerization during the cycloaddition reaction, compounds IV were added to a solution of V and triethylamine in benzene by a modification of the method of Huisgen,[4] and the desired compounds were obtained in considerable yields. The compounds prepared by this procedure (method A) and their salts are listed in Table I.

All compounds of type II and some compounds of type I were prepared stepwise from the isoxazole alcohols (VIIIa–c and IXa–c) (method B, Table I). Chloroalkyl derivatives (VIIId–f and IXe, f) were obtained by the same procedure reported for the preparation of 3-chloromethyl derivative IXd.[8] Treatment of VIIId–f and IXd–f with appropriate secondary amines gave the desired products, I and II. However, with the chloroethyl derivatives, VIIIe and IXe, this reaction gave the corresponding vinyl derivatives as by-products. The compounds VIIIb and VIIIc were prepared by cycloaddition of VI with 1-butyn-4-ol[9] and 1-butyn-3-ol,[10] respectively, according to the procedure reported[11] for the preparation of VIIIa. The alcohols IXa–c were obtained by reduction of the corresponding esters (IXg[12]–i) with lithium aluminum hydride and the ester IXh was prepared in two ways: by esterification of the corresponding 3-acetic acid (IXj) which

VIIIa, R = CH_2OH
b, R = CH_2CH_2OH
c, R = $CH(CH_3)OH$
d, R = CH_2Cl
e, R = CH_2CH_2Cl
f, R = $CH(CH_3)Cl$

IXa, R = CH_2OH
b, R = CH_2CH_2OH
c, R = $(CH_2)_2CH_2OH$
d, R = CH_2Cl
e, R = CH_2CH_2Cl
f, R = $(CH_2)_2CH_2Cl$
g, R = $CO_2C_2H_5$[12]
h, R = $CH_2CO_2C_2H_5$
i, R = $CH_2CH_2CO_2C_2H_5$
j, R = CH_2COOH
k, R = $COCHN_2$

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(4) (a) A. Quilico in "The Chemistry of Heterocyclic Compounds," Vol. 17, R. H. Wiley, Ed., Interscience Publishers, Inc., New York, N. Y., 1962, p 19; (b) R. Huisgen, *Angew. Chem.*, **75**, 604 (1963).
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(7) (a) A. Werner and H. Buss, *Chem. Ber.*, **27**, 2197 (1894); (b) A. Werner and C. Block, *ibid.*, **32**, 1979 (1899); (c) C. R. Kinney, E. W. Smith, L. Wooley, and A. R. Willey, *J. Am. Chem. Soc.*, **55**, 3418 (1933); (d) R. Paul and S. Tchelitcheff, *Bull. Soc. Chim. France*, 2215 (1962).
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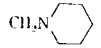
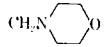
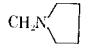
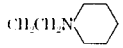
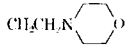
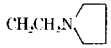
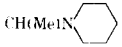
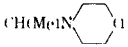
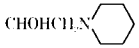
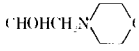
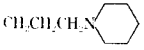
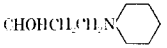
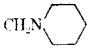
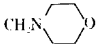
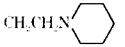
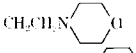
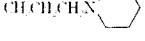
TABLE I

3-R-5-R′-ISOXAZOLES AND THEIR SALTS

No.	R	R′	Method	Yield, %	Bp (mm) or mp, °C of free	Mp, °C of salt	Recrystn solvent[a]	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
1	C_6H_5	CH_2NMe_2	B	83.3	123 (2)	207–208	E	$C_{12}H_{14}N_2O\cdot HCl$	60.37	6.33	11.74	60.58	6.31	11.46
2	C_6H_5	CH_2NEt_2	A B	47.2 87.0	130 (2)	117–118	E	$C_{20}H_{26}N_2O_8$[b]	56.86	6.20	6.63	56.89	6.26	6.27
3	C_6H_5		A B	45.1 85.7	150 (0.3)	225–226	E	$C_{15}H_{18}N_2O\cdot HCl$	64.62	6.87	10.05	64.42	7.00	10.10
4	C_6H_5		B	88.1	44–46	205–207	E	$C_{14}H_{16}N_2O_2\cdot HCl$	59.89	6.11	9.98	60.15	6.17	9.86
5	C_6H_5		B	80.4	160 (2)	189–190	E	$C_{14}H_{16}N_2O\cdot HCl$	63.51	6.47	10.58	63.70	6.49	10.25
6	C_6H_5	$CH_2CH_2NMe_2$	A	48.4	151 (4)	187–188	E	$C_{13}H_{16}N_2O\cdot HCl$	61.77	6.78	11.09	61.88	6.81	10.76
7	C_6H_5	$CH_2CH_2NEt_2$	A B	67.5 17.0	161 (5)	162–163	E	$C_{21}H_{28}N_2O_8$[b]	57.79	6.47	6.42	57.77	6.58	6.09
8	C_6H_5		A	54.1	55–56	124–125	E–K	$C_{22}H_{28}N_2O_8$[b]	58.92	6.29	6.25	58.69	6.33	6.42
9	C_6H_5		A B	69.0 18.8	70–71	251–253	E	$C_{15}H_{18}N_2O_2\cdot HCl$	61.11	6.50	9.50	61.29	6.61	9.46
10	C_6H_5		A	35.8	43–44	205–206	E	$C_{15}H_{18}N_2O\cdot HCl$	64.62	6.87	10.50	64.96	7.04	10.11
11	C_6H_5	$CH(Me)NMe_2$	B	76.0	126 (1)	187–187.5	K	$C_{13}H_{16}N_2O\cdot HCl$	61.78	6.73	11.09	61.87	6.91	10.89
12	C_6H_5		B	82.0	57.5–58.5	171–173	K	$C_{16}H_{20}N_2O\cdot HCl$	65.64	7.18	9.57	65.69	7.34	9.42
13	C_6H_5		B	54.6	107–108	199–200.5	K	$C_{15}H_{18}N_2O_2\cdot HCl$	61.12	6.45	9.51	60.76	6.48	9.45
14	C_6H_5		C	13.9	...	229–230	E	$C_{16}H_{20}N_2O_2\cdot HCl$	62.23	6.81	9.08	62.41	6.96	9.12
15	C_6H_5		C	69.5	119–120	200–204	E	$C_{15}H_{18}N_2O_3\cdot HCl$	57.97	6.16	9.02	58.18	6.32	9.19
16	C_6H_5		A	64.2	43–43.5	167–168	K	$C_{17}H_{22}N_2O\cdot HCl$	66.54	7.55	9.13	66.82	7.58	9.06
17	C_6H_5	$CHOHCH_2CH_2NMe_2$	C	50.0	88.5–90	145–147	K	$C_{14}H_{18}N_2O_2\cdot HCl$	59.47	6.73	9.91	59.60	6.95	10.21
18	C_6H_5		C	96.3	78–81	164–165.5	K–E	$C_{17}H_{22}N_2O_2\cdot HCl$	63.26	7.13	8.69	63.14	7.38	8.99
19	C_6H_5		C	93.0	88–89	151–153	K	$C_{16}H_{20}N_2O_3\cdot HCl$	59.16	6.51	8.63	59.22	6.65	8.55
20	p-ClC_6H_4	CH_2NEt_2	A	53.2	...	187–188	K	$C_{14}H_{17}ClN_2O\cdot HCl$	55.81	5.98	9.30	56.00	6.26	9.56
21	p-ClC_6H_4		A	49.2	...	246–247	E	$C_{15}H_{17}ClN_2O\cdot HCl$	57.47	5.75	8.94	57.57	5.86	8.80
22	p-ClC_6H_4		A	63.2	...	240–241	E	$C_{14}H_{15}ClN_2O_2\cdot HCl$	53.31	5.08	8.89	53.16	5.35	8.97
23	p-ClC_6H_4	$CH_2CH_2NMe_2$	A	50.9	160 (0.5)	206–207	E	$C_{13}H_{15}ClN_2O\cdot HCl$	54.36	5.57	9.76	54.35	5.69	9.58
24	p-ClC_6H_4		A	52.2	74–75	229–230	E	$C_{16}H_{19}ClN_2O\cdot HCl$	58.72	6.12	8.56	58.82	6.28	9.13
25	p-ClC_6H_4		A	64.2	123.5–125	233–234	E	$C_{15}H_{17}ClN_2O_2\cdot HCl$	54.68	5.47	8.51	54.91	5.71	8.45
26	p-ClC_6H_4		A	56.7	76–77	190–191	W	$C_{17}H_{22}ClN_2O\cdot HCl$	59.83	6.50	8.21	59.99	6.63	8.28

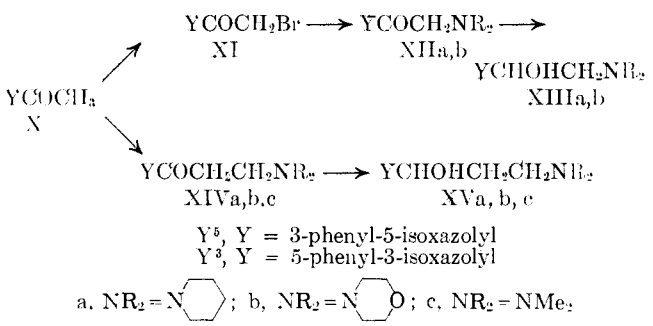
27	*p*-$MeOC_6H_4$	$CH_2CH_2NMe_2$	A	58.5	169 (3)	189–190	E	$C_{14}H_{18}N_2O_2 \cdot HCl$	59.46	6.77	9.91	59.94	6.91	9.69
28	*p*-$MeOC_6H_4$	$CH_2CH_2NEt_2$	A	65.8	181 (3)	175–176	E	$C_{16}H_{22}N_2O_2 \cdot HCl$	61.83	7.46	9.02	61.65	7.50	8.88
29	*p*-$MeOC_6H_4$		A	56.5	68–69	217–218	E	$C_{17}H_{22}N_2O_2 \cdot HCl$	63.25	7.18	8.68	62.96	7.18	8.58
30	*p*-$MeOC_6H_4$		A	70.0	106–107	222–224	E	$C_{16}H_{20}N_2O_3 \cdot HCl$	59.16	6.52	8.63	59.09	6.65	8.71
31	2-Pyridyl	$CH_2CH_2NMe_2$	A	46.1	126 (2)	110–111	K–M	$C_{18}H_{23}N_3O_8$[b]	52.81	5.66	10.27	52.32	6.03	9.98
32	2-Pyridyl	$CH_2CH_2NEt_2$	A	55.1	127 (1)	150–151	M	$C_{20}H_{27}N_3O_8$[b]	54.91	6.22	9.61	55.10	6.41	9.36
33	2-Pyridyl		A	38.9	153 (1)	218–219	E	$C_{15}H_{19}N_3O \cdot HCl$	61.32	6.86	14.30	61.10	7.00	14.17
34	3-Pyridyl	$CH_2CH_2NEt_2$	A	30.6	159 (3)	151–152	M	$C_{20}H_{27}N_3O_8$[b]	54.91	6.22	9.61	55.01	6.41	9.24
35	CH_2NMe_2	C_6H_5	B	70.0	132 (2)	223–225	E	$C_{12}H_{14}N_2O \cdot HCl$	60.37	6.33	11.74	60.25	6.67	11.11
36	CH_2NEt_2		B	78.2	144 (3)	163–164	E	$C_{14}H_{18}N_2O \cdot HCl$	63.51	7.23	10.59	63.19	7.28	10.47
37		C_6H_5	B	87.8	...	225–227	E	$C_{15}H_{18}N_2O \cdot HCl$	64.62	6.87	10.05	64.64	6.91	10.15
38		C_6H_5	B	94.6	91-92	217–219	E	$C_{14}H_{16}N_2O_2 \cdot HCl$	59.89	6.10	9.98	60.16	6.20	9.92
39		C_6H_5	B	24.0	150 (2)	190–191	E	$C_{14}H_{16}N_2O \cdot HCl$	63.51	6.47	10.58	63.73	6.51	10.31
40	$CH_2CH_2NMe_2$	C_6H_5	B	50.0	133 (4)	139–140	E	$C_{19}H_{24}N_2O_8$[b]	55.87	5.92	6.86	56.04	6.10	6.77
41	$CH_2CH_2NEt_2$	C_6H_5	B	61.0	146 (2)	145–146	K	$C_{21}H_{28}N_2O_8$[b]	57.79	6.47	6.42	57.82	6.56	6.38
42		C_6H_5	B	77.1	49–50	108–109	E	$C_{22}H_{28}N_2O_8$[b]	58.92	6.29	6.25	58.85	6.36	6.26
43		C_6H_5	B	66.0	95.5–96.5	223–224	E	$C_{15}H_{18}N_2O_2 \cdot HCl$	61.17	6.50	9.50	61.15	6.70	9.51
44		C_6H_5	B	45.2	...	188.5-190	E	$C_{15}H_{18}N_2O \cdot HCl$	64.62	6.87	10.05	64.84	6.93	10.32
45		C_6H_5	C	78.1	107–108	143–145	E	$C_{22}H_{28}N_2O_9$[b]	61.94	6.57	7.60	62.13	6.72	7.55
46		C_6H_5	C	60.0	139–140	189–190	E	$C_{15}H_{18}N_2O_3 \cdot HCl$	57.97	6.16	9.02	58.37	6.33	9.37
47		C_6H_5	B	47.4	...	189–190	K	$C_{17}H_{22}N_2O \cdot HCl$	66.54	7.55	9.13	66.39	7.67	9.29
48		C_6H_5	C	92.9	...	174–176	E	$C_{17}H_{22}N_2O_2 \cdot HCl$	63.25	7.18	8.68	63.14	7.37	8.56
49		C_6H_5	C	93.0	...	204–206	E	$C_{16}H_{20}N_2O_3 \cdot HCl$	59.17	6.52	8.63	59.42	6.62	8.70
50	CH_2NEt_2	Me	B	37.4	85 (0.1)	114–115	E	$C_{15}H_{24}N_2O_8$[b]	49.99	6.71	7.77	49.87	6.64	7.59
51		Me	B	33.8	90 (0.1)	188–190	E	$C_{10}H_{16}N_2O \cdot HCl$	55.42	7.91	12.93	55.44	7.80	12.72
52		Me	B	14.0	92 (0.1)	182–183	E	$C_9H_{14}N_2O_2 \cdot HCl$	49.43	6.91	12.81	49.54	6.98	12.64
53	$CH_2CH_2NEt_2$	Me	B	23.4	75 (0.5)	150–151	E	$C_{16}H_{26}N_2O_8$[b]	51.33	7.00	7.48	51.51	7.11	7.31
54		Me	B	44.1	104 (0.8)	195–196	E–K	$C_{11}H_{18}N_2O \cdot HCl$	57.26	8.30	12.14	56.90	8.52	12.46
55		Me	B	34.2	..	209–210	E	$C_{10}H_{16}N_2O_2 \cdot HCl$	51.61	7.37	12.04	51.45	7.52	12.29
56		Me	B	33.9	84 (0.7)	165–166	K	$C_{10}H_{16}N_2O \cdot HCl$	55.42	7.91	12.93	55.20	8.11	12.94

[a] E, Ethanol; K, Acetone; M, methanol; W, water. [b] Citrate.

was obtained from IXd *via* cyanation and subsequent hydrolysis, and by the Arndt–Eistert reaction with 5-phenyl-3-isoxazolecarbonyl chloride through the 3-diazoacetyl derivative (IXk). The ester IXi was obtained from IXe by a similar reaction sequence as used for the preparation of IXh from IXd.

For comparison of pharmacological activities, seven 5-methyl analogs were prepared from ethyl 5-methyl-3-isoxazolecarboxylate[13] in a method similar to that used for the 5-phenyl series.

As further structural variations of I and II, a series of 3-phenyl-5- and 5-phenyl-3-(α-hydroxy-ω-aminoalkyl)isoxazoles (XIII and XV) were synthesized. The corresponding 5- and 3-acetyl derivatives (X) were served as the pertinent starting compounds for the preparation of both XIII and XV. Compound X (Y = 3-phenyl-5-isoxazolyl) was prepared in good yield by oxidation of VIIIc although some other methods are available.[14] Another derivative of type X (Y = 5-phenyl-3-isoxazolyl) was prepared by the reaction of 5-phenylisoxazole-3-carboxy chloride with ethoxymagnesium diethylmalonate followed by decarboxylation of the resulting β-keto ester. Bromination of X with bromine gave the corresponding bromoacetyl derivatives (XI) which underwent reaction with piperidine and morpholine to give the amino ketones (XIIa and XIIb, respectively). The 3-chloroacetyl derivative obtained by treating IXk with HCl was also available in place of XI (Y = Y^3). Attempts to obtain dimethyl- and diethylamino analogs of XII failed owing to extensive tar formation. Mannich reactions with X gave the corresponding aminopropionyl derivatives (XIVa–c).



Finally the amino ketones, XIIa, b and XIVa–c, were reduced with sodium borohydride to yield the amino alcohols (XIIIa, b and XVa–c, respectively) (method C). Free bases of XII are unstable and XIIa (Y = Y^5) is especially liable to decompose into a tarry material; accordingly XIIa (Y = Y^5) was used in the subsequent reaction as its hydrochloride. The compounds prepared by method C were converted to their hydrochlorides and are listed in Table I.

Pharmacology

Methods.—Most of the compounds listed in Table I were evaluated by the following methods.

The acute toxicity was determined in mice. The subcutaneous LD_{50}'s were calculated by the Bliss method[15] on the basis of results obtained in 24 hr after the injection.

The hypothermic activity was studied by measuring the rectal temperature of the mouse every 30 or 60 min after a subcutaneous injection of the test compound. Mice were kept in individual cages in an air conditioned room (23°).

A modified Haffner's method[16] was used for estimating analgesic activity. The test compound and 3.5 mg/kg of morphine were simultaneously injected in the mouse subcutaneously. When the mouse did not attempt to remove a clip pinching its tail within 15 sec, it was considered that the test compound elicited a complete analgesic action. The ED_{50} was calculated by the up and down method of Brownlee, *et al.*[17]

For evaluating the analgesic–antiinflammatory activity, a foot licking method was devised in our laboratory.[18] As a phlogistic agent, 0.05 ml of 3.7% formaldehyde was subcutaneously injected into the dorsal part of hind paw of the rat. Since the animal frequently licked its inflamed paw in order to alleviate the pain, this syndrome was called the "foot licking response." The response frequency of the normal rat is usually 15–20 times for 50 min after formaldehyde injection. For the determination of analgesic–antiinflammatory activity, the test compound was injected subcutaneously, and 10 min later formaldehyde was injected into the dorsal part of the hind paw. The test compound was determined to be effective in the test when the frequency of licking was less than four times in 50 min of observation. The ED_{50} was calculated by the up and down method.[17]

The antiinflammatory activity was determined by measuring the thickness of the inflamed foot produced by an injection of 0.05 ml of 3.7% formaldehyde into the dorsal part of the hind paw of the rat. The thickness was measured by a microdial gauge. The detail procedure for evaluation was as follows. On the first day, the thickness of swelling of the left hind paw was measured at 1, 2, and 3 hr after the injection of formaldehyde without administration of any test compound and the mean value was used as the control. On the second day, the test compound was administered subcutaneously to the same animals. Thirty minutes later, formaldehyde solution was injected as the phlogistic agent into the right hind paw of each animal. The thickness of swelling was measured by the same procedure as on the first day. The antiinflammatory activity was calculated as the percentage inhibition by comparing the mean value obtained with the right paw on the second day with that obtained with the left paw on the first day in each individual animal.

The antitussive activity was studied on guinea pigs. The method was essentially that of Winter and Flataker.[19] Thirty minutes after subcutaneous injection of the test compound, the animal was placed into a transparent plastic box and inhaled NH_3 for 25 sec. Soon after removing the animal from the box, the antitussive activity was evaluated by observing whether a

(13) Reference 4a, p 86.

(14) (a) P. Grünanger and S. Mangiapan, *Gazz. Chim. Ital.*, **88**, 149 (1958); (b) L. Panizzi, *ibid.*, **73**, 99 (1943).

(15) C. P. Bliss, *Ann. Appl. Biol.*, **22**, 134, 307 (1935).

(16) M. Ogawa, *Folia Pharmacol. Japan.*, **54**, 195 (1958).

(17) K. A. Brownlee, J. L. Hodges, Jr., and M. Rosenblatt, *J. Am. Statist. Assoc.*, **48**, 262 (1953).

(18) K. Hirose, M. Eigyo, and R. Kido, unpublished work.

(19) C. A. Winter and L. Flataker, *J. Pharmacol. Exptl. Therap.*, **112**, 99 (1954).

TABLE II

ANALGESIC, ANTIINFLAMMATORY, AND ANTITUSSIVE PROPERTIES OF ISOXAZOLE DERIVATIVES[a]

No.	Acute toxicity (mouse) LD_{50}, mg/kg	Hypothermic test[b] (mouse) 100 mg/kg	Analgesic activity[c] (mouse) ED_{50}, mg/kg	Analgesic-antiinflammatory activity (rat) ED_{50}, mg/kg	Antiinflammatory activity[d] (rat) formalin edema 100 mg/kg	Antitussive activity[e] (guinea pig) ED_{50}, mg/kg
1		−1.7			8	
2	>1000	−0.6	156	>300	3	>110
3	600–700	−4.2	102	>300	4	>110
4	>1000	−2.9	147	200–300	17	>110
5	400	−4.3	72	166	19	>110
6	682	−1.2	>400	220	24	>110
7	350–400	−0.4	100		9	51
8	398	−4.3	78	79	34	54
9	700–800	−3.8	68	100–150	27	>110
10	411	−2.4	77	63	38	72
11	231	−3.4	32	150–200	33	
12	800–1000	−1.7	143	>300	4	
13	800–1000		71	>300	22	
14	400–600	−7.7	37	42	44	31
15	800–1000	−4.8	68	69	26	>65
16	186	−4.7	57	17	44[g]	28
17	600–800	−3.2	159	70–120	30	>65
18	407	−3.7	63	50–70	40[g]	45
19	800–1000	−3.7	134	100–200	40	>65
20	1000	−1.5	298	>330	3	52
21	768	−5.7	164	>330	7	>65
23	438	−1.7	128	94	24	>65
24	297	−7.0	61	72	25	42
27	325	−1.8	73	87	25	>65
28	417	−1.0	184	86	38	44
29	159	−1.7	>150	75	36	36
30	>1000	−4.2	181	207	29	>65
31	800–1000	−1.1	290	150–250	4	>65
32	700–900	−1.0	109	150–250	4	>65
33	200–300	−4.5	100	44	27	38
34	500–600	−0.4	177	100–150		
35	462	−2.5	113	135	31	>110
36	500–600	−1.4	55	185	22	>110
37	>500	−4.8	39	230	20	>110
38	>1000	−3.5	138	228	7	>110
39	212	−4.7	60	71	28	
40	460	−1.1	123	100–150	14	52
41	353	−1.5	133	40–60	31	30
42	443	−4.8	53	29	39	23
43	>800	−3.5	106	97	38	68
44	500–600	−3.0	93	33	35	29
45	416	−5.0	43	31	35	30
46	>600	−5.9	>100	42	30	
48	500	−2.5	73	43	35	21
49	970	−2.4	287	200–300	28	48
50	800–1000	−1.3	390–400	300–500	4	>110
51	135–142	−4.0[g]	65	50–100	20	71
53	614	−0.5	400	137	6	71
54	153	−4.5	77	23	57	48
Oxolamine[f]	672	−1.3	105	223	11	41
Aminopyrine	373	−4.1	102	110	22	...
Phenylbutazone	439	−0.2	...	200	15	...
Codeine	276	...	...	...	...	35

[a] All compounds were administered by the subcutaneous route. [b] Maximum fall in body temperature in °C. [c] Haffner method with morphine 3.5 mg/kg. [d] Per cent inhibition. [e] Chemical stimulation with NH_3. [f] Oxolamine = 3-phenyl-5-(β-diethylaminoethyl)-1,2,4-oxodiazole. [g] 50 mg/kg.

fit of coughing occurred within 5 min. The ED_{50} was calculated by the up and down method.[17]

Results.—The results of the pharmacological tests are demonstrated in Table II together with those of three known nonnarcotics (oxolamine, aminopyrine, and phenylbutazone) and an antitussive agent (codeine) for comparison. Most of the compounds tested showed more or less hypothermic, analgesic, and antiinflammatory activities and several of them also exhibited antitussive activity.

Among the 49 compounds listed in Table II, **14**, **16**, **42**, and **48** displayed relatively strong potencies. Their

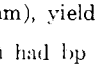
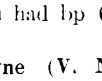
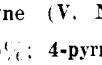
analgesic or antiinflammatory activities are 1.5–4 times, and their analgesic–antiinflammatory activities 3–13 times, those of the control analgesics. All four compounds showed slightly stronger antitussive activities than those of codeine and oxolamine. Except for **16**, the three others produced nearly the same toxicities as phenylbutazone.

Although the results obtained make it difficult to establish a clear relationship between chemical structure and biological activity, the potencies seem to be accentuated in those compounds which have a piperidino- and morpholinoalkyl side chain (n = 2 and 3). Replacement of the phenyl substituent by C_6H_4Cl-p, $C_6H_4OCH_3$-p, pyridyl, or methyl groups resulted in no significant advantage in potency. It is noticeable that **14**, which has an amino alcohol side chain is more potent and less toxic than the corresponding aminoalkyl derivative **8**.

Experimental Section

Melting points were taken on a Kofler hot stage and are uncorrected. Infrared spectra were recorded with a Koken infrared spectrophotometer, Model IR-S. Ultraviolet spectra were taken on a Hitachi recording spectrophotometer, EPS-2.

3-Dialkylaminopropynes (V, n = 1) were prepared in 50–80% yields from propargyl bromide in a procedure similar to that described for 3-dimethylaminopropyne;[5] **3-diethylaminopropyne** (V, NR_2 = NEt_2) had bp 72° (180 mm), yield 70%; **3-piperidinopropyne** (V, NR_2 = ) had bp 58–63° (20 mm), yield 50%; **3-morpholinopropyne** (V, NR_2 = ) had bp 70–74° (18 mm), yield 76.6%.

4-Dialkylamino-1-butynes (V, n = 2) were prepared in 40–60% yields from the corresponding 2-dialkylaminoethyl bromide hydrobromides and sodium acetylide in a manner similar to that for 4-diethylamino-1-butyne;[6] **4-dimethylamino-1-butyne** (V, NR_2 = NMe_2) had bp 105° (760 mm), yield 38.8%; **4-piperidino-1-butyne** (V, NR_2 = ) had bp 69–71° (13 mm), yield 41.1%; **4-morpholino-1-butyne** (V, NR_2 = ) had bp 99–101° (30 mm), yield 43.5%; **4-pyrrolidino-1-butyne** (V, NR_2 = ) had bp 75–80° (25 mm), yield 37.7%.

5-(2-Hydroxyethyl)-3-phenylisoxazole (VIIIb).—To a solution of benzohydroxamyl chloride[7] (4.7 g) and 1-butyn-4-ol[9] (4.3 g) in benzene (100 ml) was added NEt_3 (6.0 g) dropwise with stirring and cooling. The resulting mixture was stirred at 60° for 1 hr, then cooled and filtered. The filtrate was washed with water, dried ($MgSO_4$), and evaporated. The residue was crystallized from benzene–ligroin (bp 100–120°) as colorless plates (4.4 g), mp 56–57°, $\lambda_{max}^{95\%\ EtOH}$ 242 mμ (log ε 4.194).

Anal. Calcd for $C_{11}H_{11}NO_2$: C, 69.82; H, 5.86; N, 7.40. Found: C, 69.22; H, 6.1; N, 7.16.

5-(1-Hydroxyethyl)-3-phenylisoxazole (VIIIc).—To a solution of benzohydroxamyl chloride[7] (22.3 g) and 1-butyn-3-ol[10] (10.0 g) in benzene (160 ml) was added NEt_3 (21.7 g) dropwise with stirring and cooling. The mixture was treated as described above, and the resulting oil was distilled to give a pale yellow oil (18.1 g), bp 143–144° (0.3 mm).

Anal. Calcd for $C_{11}H_{11}NO_2$: C, 69.82; H, 5.86; N, 7.40. Found: C, 69.58; H, 5.90; N, 7.70.

5-Chloromethyl-3-phenylisoxazole (VIIId).—A solution of VIIIa[11] (9.7 g) and $SOCl_2$ (14.9 g) in dry ether (100 ml) was refluxed for 1 hr and then evaporated *in vacuo*. The resulting crystalline product was recrystallized from ligroin to give colorless prisms (8.4 g), mp 70–71° (lit.[7] mp 65–66°).

Anal. Calcd for $C_{10}H_8ClNO$: C, 62.02; H, 4.16; N, 7.24. Found: C, 62.18; H, 4.16; N, 6.96.

5-(2-Chloroethyl)-3-phenylisoxazole (VIIIe).—A solution of VIIIb (4.4 g) and $SOCl_2$ (5.0 g) in dry ether (15 ml) was treated as described above. Distillation of the residue gave a colorless oil (4.1 g), bp 134–136° (3 mm), which solidified on standing at room temperature. Recrystallization from ligroin afforded colorless plates, mp 39–40°.

Anal. Calcd for $C_{11}H_{10}ClNO$: C, 63.62; H, 4.85; N, 6.75. Found: C, 64.04; H, 4.90; N, 7.05.

5-(1-Chloroethyl)-3-phenylisoxazole (VIIIf).—A solution of VIIIc (18.9 g) and $SOCl_2$ (35.7 g) in dry ether (500 ml) was treated as described above. The resulting oil was distilled to afford a colorless oil (18.0 g), bp 128–130° (1.0 mm), which solidified on standing at room temperature. Recrystallization from petroleum ether (bp 60–70°) gave colorless plates, mp 56–57°.

Anal. Calcd for $C_{11}H_{10}ClNO$: C, 63.62; H, 4.85; N, 6.75. Found: C, 64.01; H, 4.91; N, 6.64.

Ethyl 5-Phenyl-3-isoxazoleacetate (IXh). **A.**—A solution of IXj (32.8 g) in absolute EtOH (330 ml) was refluxed with concentrated H_2SO_4 (33.0 g) for 2 hr and then concentrated *in vacuo*. The residue was poured onto ice and the resulting crystalline product was collected and washed with water. Recrystallization from petroleum ether (bp 30–50°) gave colorless needles (35.8 g) mp 49.5–50.5°, $\lambda_{max}^{95\%\ EtOH}$ 263 mμ (log ε 4.331).

Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.71; H, 5.82; N, 6.04.

B.—To a hot solution of IXk (1.07 g) in absolute EtOH (50 ml), Ag_2O (0.2 g) was added portionwise and the mixture was refluxed for 1.5 hr. After filtration, evaporation of the filtrate *in vacuo* gave the residue, which was taken up in hot petroleum ether. After cooling, the precipitated crystalline product was collected by filtration and recrystallized from petroleum ether (bp 30–50°) to give colorless needles (1.16 g), mp 48–50°, which were identified with the sample obtained above by comparison of their infrared spectra.

Ethyl 5-phenyl-3-isoxazolepropionate (IXi) was prepared from IXe in 19.2% yield by the same reaction sequence as for the preparation of IXh from IXd. The compound was recrystallized from petroleum ether (bp 60–70°) as colorless plates, mp 57–58°.

Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.55; H, 6.16; N, 5.71. Found: C, 69.03; H, 6.23; N, 5.71.

5-Phenyl-3-isoxazoleacetic Acid (IXj).—A mixture of IXd (20 g) and KCN (9.5 g) in 90% EtOH (260 ml) was refluxed for 2 hr and then evaporated *in vacuo*. After addition of $CHCl_3$, the $CHCl_3$ solution was washed with water and concentrated. The residue was refluxed with a solution of KOH (10 g) in 80% EtOH (280 ml) for 6 hr and then concentrated *in vacuo*. The solution, after addition of water, was washed with $CHCl_3$ and acidified with 6 *N* HCl to give colorless crystals (164 g). Recrystallization from 70% EtOH gave colorless needles, mp 171–172° dec, $\lambda_{max}^{95\%\ EtOH}$ 262 mμ (log ε 4.323).

Anal. Calcd for $C_{11}H_9NO_3$: C, 65.02; H, 4.46; N, 6.89. Found: C, 64.91; H, 4.54; N, 6.89.

3-Diazoacetyl-5-phenylisoxazole (IXk).—To a solution of diazomethane in dry ether (1 l.) which was freshly prepared from nitrosomethylurea (57 g) by the usual method, was added 5-phenyl-3-isoxazolecarbonyl chloride (30 g) portionwise with shaking and cooling. The resulting crystalline product, after standing overnight at room temperature, was collected by filtration (24 g) and recrystallized from benzene to give pale yellow plates, mp 162–163° dec.

Anal. Calcd for $C_{11}H_7N_3O_2$: C, 61.97; H, 3.31; N, 19.71. Found: C, 62.26; H, 3.31; N, 19.39.

3-Chloromethyl-5-phenylisoxazole (IXd).—A solution of IXg (63.0 g) in dry ether (150 ml) was added dropwise to a suspension of $LiAlH_4$ (8.0 g) in dry ether (270 ml) with shaking and cooling. The mixture was refluxed for 1.5 hr. After cautious addition of 2% aqueous H_2SO_4 under chilling, the ethereal phase was separated and the water layer was extracted with ether. The combined ethereal solution was washed with water, dried (Na_2SO_4), and evaporated to give crude crystals (44.8 g). They were dissolved in dry ether (100 ml) and treated with $SOCl_2$ (61.0 g) as described for VIIIa to yield a colorless oil (44.7 g), bp 153° (3 mm), which solidified on standing at room temperature. Recrystallization from ligroin gave colorless needles, mp 49.5–50° (lit.[3] mp 47.5–48.5°), $\lambda_{max}^{95\%\ EtOH}$ 263 mμ (log ε 4.319).

Anal. Calcd for $C_{10}H_8ClNO$: C, 62.02; H, 4.16; N, 7.24. Found: C, 62.41; H, 4.32; N, 7.30.

3-(2-Chloroethyl)-5-phenylisoxazole (IXe).—The ester IXh (28.0 g) was reduced with $LiAlH_4$ (3.7 g) in dry ether to give the corresponding alcohol, which was then treated with $SOCl_2$ (23 g). The resulting product was distilled *in vacuo* to give a colorless oil (13.5 g), bp 146° (3 mm), which solidified on standing at room temperature. Recrystallization from petroleum

ether (bp 30–50°) gave colorless prisms, mp 61–62°, $\lambda_{max}^{95\% EtOH}$ 262 mμ (log ε 4.325).

Anal. Calcd for $C_{11}H_{10}ClNO$: C, 63.62; H, 4.85; N, 6.75. Found: C, 63.26; H, 4.86; N, 6.51.

3-(3-Chloropropyl)-5-phenylisoxazole (IXf) was prepared from IXi in 18% yield by the same method as for IXe. The resulting crystalline product (1.9 g) was recrystallized from petroleum ether (bp 60–70°) as colorless needles, mp 55–56°.

Anal. Calcd for $C_{12}H_{12}ClNO$: C, 65.01; H, 5.46; N, 6.32. Found: C, 64.94; H, 5.55; N, 6.20.

3-(2-Chloroethyl)-5-methylisoxazole was prepared stepwise in 4.2% yield from ethyl 5-methyl-3-isoxazolecarboxylate[4] in a manner similar to that described for 5-phenyl analog; bp 102° (12 mm).

Anal. Calcd for C_6H_8ClNO: C, 49.50; H, 5.54; N, 9.62. Found: C, 48.83; H, 5.21; N, 9.21.

3-Substituted 5-Aminoalkyl- (I) and 5-Substituted 3-Aminoalkylisoxazoles (II) and Their Salts.—Forty-seven compounds in Table I were prepared by the following general procedures and the bases obtained were converted to their salts (hydrochloride or citrate) by the ordinary procedure.

Method A.—Hydroxyamyl chloride IV[7] (0.01 mole), dissolved in benzene (15 ml), was added to a solution of a dialkylaminoalkyne (0.01 mole) and triethylamine (0.02 mole) in benzene (15 ml) dropwise with stirring and cooling. The resulting mixture was stirred at 60° for 1 hr, then cooled and acidified with 3% aqueous HCl. The aqueous layer was separated and the benzene layer was extracted with water. The combined aqueous solution was washed with benzene and made alkaline with 20% aqueous NaOH. The resulting solution was extracted with ether. The extract was washed with water, dried (K_2CO_3), and evaporated to give the desired product I, which was purified by distillation *in vacuo* or by recrystallization from the appropriate solvent.

Evaporation of the benzene layer gave the corresponding 3,4-disubstituted furoxan which was identified by comparison of their infared spectra with those of an authentic sample.[7]

Method B.—A solution of 3- or 5-chloroalkylisoxazole (0.015 mole) and a secondary amine (0.045 mole) in toluene (20 ml) was heated at 110° for 8 hr (in a sealed tube if necessary), then cooled and acidified with 3% aqueous HCl. The water phase was separated, and the organic layer was extracted with water. The combined aqueous solution was treated as described for method A to yield the desired compounds, I and II.

5-Acetyl-3-phenylisoxazole (X, Y = Y[5]).—To a solution of VIIIc (22.8 g) in acetic acid (130 ml) was added a solution of CrO_3 (8.22 g) in acetic acid (120 ml) and water (10 ml) dropwise with stirring and cooling. After addition, the resulting mixture was stirred at room temperature for 2 hr, then kept at 50° for 30 min. After concentration *in vacuo* to *ca.* 50 ml, the mixture was poured on ice and the crystalline product was collected by filtration. Recrystallization from CCl_4 gave colorless plates (18.8 g), mp 106–107.5°, $\lambda_{max}^{95\% EtOH}$ 238 mμ (log ε 4.386). It was identified with authentic sample[14] by comparison of their infrared spectra.

Anal. Calcd for $C_{11}H_9NO_2$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.55; H, 4.88; N, 7.70.

3-Acetyl-5-phenylisoxazole (X, Y = Y[3]).—To a mixture of Mg turnings (5.4 g) and absolute EtOH (5 ml) was added CCl_4 (0.5 ml). After the reaction had proceeded for several minutes, a solution of diethyl malonate (35.2 g) and absolute EtOH (20 ml) in dry benzene (175 ml) was added dropwise with stirring at such a rate that rapid boiling was maintained. The mixture was heated under reflux for 1 hr to dissolve most Mg and after cooling at room temperature, 5-phenyl-3-isoxazolecarbonyl chloride (41.5 g) was added portionwise to the mixture. The mixture was refluxed for 1 hr, then cooled, and shaken with 20% aqueous H_2SO_4 until all of the solid dissolved. The benzene phase was separated and the aqueous layer was extracted with benzene. The combined benzene solution was washed with water and evaporated. The residue was refluxed with AcOH (72 ml) and concentrated H_2SO_4 (2.0 g) on an oil bath for 10 hr. After cooling, the mixture was poured on ice and the precipitated crystalline product (34.4 g) was collected by filtration. Recrystallization from petroleum ether (bp 60–70°) gave colorless scales, mp 98–99°, $\lambda_{max}^{95\% EtOH}$ 249 mμ (log ε 4.18). This was identified with an authentic sample[20] by comparison of their infrared spectra.

(20) A. Qualico and M. Simonetta, *Gazz. Chim. Ital.*, **76**, 148 (1946).

Anal. Calcd for $C_{11}H_9NO_2$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.84; H, 5.09; N, 7.59.

5-Bromoacetyl-3-phenylisoxazole (XI, Y = Y[5]).—To a solution of X (Y = Y[5]) (5.6 g) in CCl_4 (50 ml) was added bromine (4.8 g) dropwise with stirring. After stirring at room temperature for 6 hr, the precipitated crystalline product was collected by filtration and recrystallized from EtOH to give colorless plates (6.1 g), mp 116–117°, $\lambda_{max}^{95\% EtOH}$ 240 mμ (log ε 4.293).

Anal. Calcd for $C_{11}H_8BrNO_2$: C, 49.65; H, 3.30; N, 5.27. Found: C, 49.83; H, 3.11; N, 5.16.

3-Bromoacetyl-5-phenylisoxazole (XI, Y = Y[3]).—To a solution of X (Y = Y[3]) (21.7 g) in CCl_4 (300 ml) was added a solution of bromine (18.7 g) in CCl_4 (30 ml) in a similar way as above and the mixture was stirred for 3 hr. The resulting crystalline product (25.3 g) was recrystallized from benzene–petroleum ether (bp 60–70°) to give colorless prisms, mp 129–130°.

Anal. Calcd for $C_{11}H_8BrNO_2$: C, 49.65; H, 3.03; N, 5.26. Found: C, 49.40; H, 3.16; N, 5.42.

3-Chloroacetyl-5-phenylisoxazole.—Into a suspension of IXk (100 g) in $CHCl_3$ (2.0 l.) was passed dry HCl with stirring until no more N_2 was evolved. The resulting solution was concentrated to *ca.* 500 ml and petroleum ether (700 ml) was added to the solution. After cooling, the crystalline product was collected by filtration (95.7 g). Recrystallization from benzene–petroleum ether (bp 60–70°) gave colorless prisms, mp 131–132°.

Anal. Calcd for $C_{11}H_8ClNO_2$: C, 59.61; H, 3.64; N, 6.32. Found: C, 59.82; H, 3.65; N, 6.13.

5-Morpholinoacetyl-3-phenylisoxazole (XIIb, Y = Y[5]).—To a solution of XI (Y = Y[5]) (1.33 g) in benzene (50 ml) was added morpholine (1.10 g) and the resulting mixture was stirred at 40° for 15 min and then filtered. The filtrate was acidified with 25% ethanolic HCl and the precipitated hydrochloride was collected by filtration. The salt, suspended in water, was made alkaline with 20% aqueous NaOH to give colorless crystals (0.85 g). Recrystallization from MeOH gave pale yellow prisms, mp 137–138°, $\lambda_{max}^{95\% EtOH}$ 240 mμ (log ε 4.251).

Anal. Calcd for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29. Found: C, 66.30; H, 5.95; N, 10.10.

3-Piperidinoacetyl-5-phenylisoxazole (XIIa, Y = Y[3]).—The 3-bromoacetyl derivative XI (13.3 g), dissolved in acetone (160 ml), was added to a solution of piperidine (8.5 g) in acetone (85 ml) with stirring and cooling. After stirring at room temperature for 30 min, the precipitated piperidine hydrobromide was filtered off, and the filtrate was acidified with 25% ethanolic HCl. The precipitated hydrochloride was collected and recrystallized from MeOH–acetone to give colorless needles (12.9 g), mp 178–179° dec.

Anal. Calcd for $C_{16}H_{18}N_2O_2 \cdot HCl$: C, 62.63; H, 6.24; N, 9.13. Found: C, 63.03; H, 6.39; N, 9.03.

The hydrochloride was converted to the free base (9.96 g), mp 108–109°, which is unstable in solution.

Anal. Calcd for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.36. Found: C, 71.15; H, 6.83; N, 10.32.

3-Morpholinoacetyl-5-phenylisoxazole (XIIb, Y = Y[3]).—The 3-chloroacetyl derivative (11.0 g) dissolved in benzene (400 ml), was added to a solution of morpholine (15.0 g) in benzene (200 ml). After stirring at 55° for 2 hr, the precipitated morpholine hydrochloride was filtered off, and the filtrate was treated as the above. The resulting crystalline product (7.3 g) was recrystallized from MeOH to give pale yellow plates, mp 134–135°.

Anal. Calcd for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29. Found: C, 66.34; H, 5.99; N, 9.99.

5-(2-Piperidinopropionyl)-3-phenylisoxazole (XIVa, Y = Y[5]).—A mixture of X (Y = Y[5]) (1.87 g), piperidine hydrochloride (1.22 g), paraformaldehyde (0.45 g), concentrated HCl (0.03 ml), and dioxane (3 ml) was refluxed for 1 hr. After cooling, acetone was added and the precipitated hydrochloride was collected by filtration, washed with acetone, and dissolved in water. The solution was treated with aqueous NaOH as for XII and the resulting free base was crystallized from petroleum ether (bp 60–70°) to give colorless plates (1.76 g), mp 93–94°.

Anal. Calcd for $C_{17}H_{20}N_2O_2$: C, 71.80; H, 7.09; N, 9.85. Found: C, 71.87; H, 7.31; N, 9.88.

5-(2-Morpholinopropionyl)-3-phenylisoxazole (XIVb, Y = Y[5]).—A mixture of X (Y = Y[5]) (1.87 g), morpholine hydrochloride (1.24 g), paraformaldehyde (0.45 g), concentrated HCl (0.03 ml), and EtOH (3 ml) was treated as described above. The resulting crystalline product (1.29 g) was recrystallized from ligroin to give colorless prisms, mp 103–105°.

Anal. Calcd for $C_{16}H_{18}N_2O_3$: C, 67.11; H, 6.34; N, 9.78. Found: C, 67.42; H, 6.54; N, 9.50.

5-(2-Dimethylaminopropionyl)-3-phenylisoxazole (**XIVc**, Y = Y[5]) was obtained as unstable crystals in 23.3% yield in a similar manner as above. It was reduced with $NaBH_4$ without purification.

3-(2-Piperidinopropionyl)-5-phenylisoxazole (**XIVa**, Y = Y[3]). A mixture of X (Y = Y[3]) (3.75 g), piperidine hydrochloride (2.43 g), paraformaldehyde (0.90 g), concentrated HCl (0.05 ml), and dioxane (6 ml) was heated to reflux. After 1 hr, paraformaldehyde (0.45 g) was added and refluxing was continued for 2 hr. The reaction mixture was treated in a similar manner to yield colorless crystals (3.60 g). Recrystallization from petroleum ether (bp 60–70°) gave colorless plates, mp 94–96°.

Anal. Calcd for $C_{17}H_{20}N_2O_2$: C, 71.81; H, 7.09; N, 9.85. Found: C, 71.65; H, 7.18; N, 9.95.

3-(2-Morpholinopropionyl)-5-phenylisoxazole (**XIVb**, Y = Y[4]). —A mixture of X (Y = Y[3]) (3.75 g), morpholine hydrochloride (2.47 g), paraformaldehyde (0.90 g), concentrated HCl (0.1 ml), and EtOH (3 ml) was treated as the above. The resulting product consisted of colorless plates (3.22 g), mp 112–113°, when crystallized from benzene–petroleum ether (bp 60–70°).

Anal. Calcd for $C_{16}H_{18}N_2O_4$: C, 67.11; H, 6.34; N, 9.78. Found: C, 67.20; H, 6.43; N, 9.59.

Reduction of the Amino Ketones XII and XIV with $NaBH_4$ (Table I, Method B).—The amino ketone (0.5 mole) was treated with $NaBH_4$ (0.14 mole) in MeOH (1 l.) at 60° for 30 min. After cooling, the resulting solution was acidified with AcOH and evaporated *in vacuo*. After addition of 20% aqueous NaOH, the mixture was extracted with benzene and the extract was washed with water, dried over anhydrous K_2CO_3, and evaporated. The residue was dissolved in hot 1% aqueous HCl and the solution was treated with Norit and then made alkaline with 20% aqueous NaOH to give the corresponding 3-phenyl-5- or 5-phenyl-3-(α-hydroxy-ω-aminoalkyl)isoxazole (XIII or XV). The bases were converted to their hydrochlorides by the ordinary procedure.

Hydrochloride of 5-(1-Hydroxy-2-piperidinoethyl)-3-phenylisoxazole (**XIIIa**, Y = Y[5]). —A mixture of XI (Y = Y[5]) (2.0 g) and piperidine (1.6 g) in ether (100 ml) was treated as for XIIIb (Y = Y[5]). The resulting hydrochloride of XIIa (Y = Y[5]) (2.42 g) was added to a solution of $NaBH_4$ (0.5 g) and MeONa (0.5 g) in EtOH (80 ml) with stirring. The mixture, stirred at 50° for 1.5 hr, was cooled in an ice bath, acidified with 10% aqueous HCl, and evaporated *in vacuo*. The residue, after addition of 10% aqueous NaOH, was extracted with $CHCl_3$ and the extract was washed with water, and dried (K_2CO_3). Evaporation of the solvent left colorless crystals which gave its hydrochloride by the ordinary procedure.

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Phenylindenes and Phenylindans with Antireserpine Activity[1]

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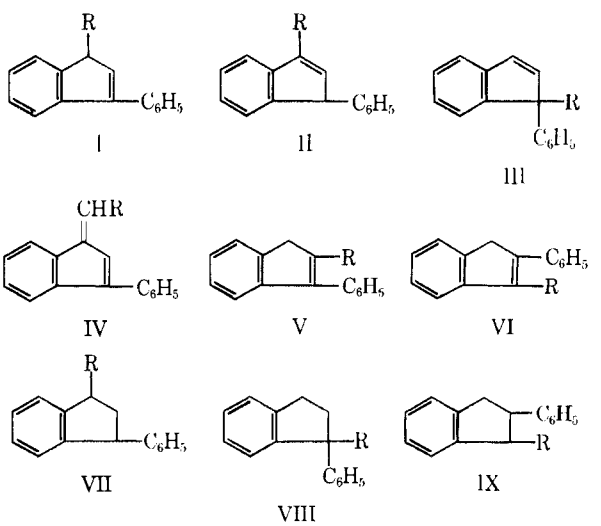
A series of aminoalkylphenylindenes and indans has been synthesized and pharmacologically evaluated. The majority of the phenylindene derivatives was prepared by the alkylation of phenylindene with aminoalkyl halides. A mixture of isomers is obtained when 3-phenylindene is alkylated by this procedure and the isomers of this mixture have been characterized. The final assignment of structure was based on nmr studies and these are reported in detail. An unequivocal synthesis of one isomer type, 1-aminoalkyl-1-phenylindene, is described. The indan derivatives were prepared by hydrogenation of the corresponding indenes. The indene derivatives, particularly 1-(2-dimethylaminoethyl)-1-phenylindene (**2**), were found to have potent activity in the prevention of reserpine-induced ptosis in mice, a test which has been used as a criterion for antidepressant activity. In addition, several of the indene and indan derivatives have exhibited significant antispasmodic and antiserotonin activity.

Aminoalkyl derivatives of diphenylmethane and its tricyclic analogs such as the phenothiazines have received considerable attention as useful pharmacological agents.[2a] The 1- and 3-phenylindene ring systems as well as the indan analogs also incorporate the diphenylmethane moiety. A series of aminoalkyl derivatives of phenylindene and phenylindan I–IX (R = aminoalkyl) was prepared and tested for a wide variety of activities associated with the diphenylmethane derivatives. Although compounds having the general formulas VI and IX are not diphenylmethane derivatives, we have included them for comparison purposes.

During the course of this investigation, the interesting pharmacological properties of the dibenzocycloheptenes were reported.[2b,c] Examination of molecular models



indicates that the two benzene rings in the phenylindenes and phenylindans can be spacially oriented in much the same manner as in the dibenzocycloheptenes

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