$CHCl_3$ (200 ml.) at 0°. The solution was stirred at room temperature for 60 min., refluxed for 4 hr., and then filtered. The filtrate was neutralized ($NaHCO_3$ solution), dried, and distilled to give N-(2-bromoethyl)-N-ethylaniline, b.p. 110–112° (0.1 mm.), in 45% yield.

Anal. Calcd. for $C_{10}H_{14}BrN$: Br, 35.08. Found: Br, 34.84.

N^4-(2-Bromoethyl)-N^4-ethylsulfanilamide was prepared, in 17% yield, from N-(2-bromoethyl)-N-ethylaniline according to the method of Benn, *et al.*[8] It had m.p. 130–131° (benzene).

Anal. Calcd. for $C_{10}H_{15}BrN_2O_2S$: C, 39.1; H, 4.92; Br, 26.02; N, 9.12. Found: C, 39.26; H, 5.1; Br, 25.98; N, 8.7.

N^1-Chloroacetyl-N^4-ethylsulfanilamide.—N-Chloroacetyl-N-ethylaniline[9] (10 g., 0.05 mole) in CCl_4 (25 ml.) was treated with chlorosulfonic acid (15 ml.) at 0°. The mixture was then maintained at 100–110° for 1 hr. and poured onto ice. The precipitate of N^4-chloroacetyl-N^4-ethylsulfanilyl chloride was filtered and dissolved in acetone (30 ml.) and added to NH_4OH (25 ml., *d* 0.88) and stirred for 10 min. Dilution with water and crystallization of the precipitate from benzene gave the sulfonamide as white plates, m.p. 138° (9.8 g., 70%), which were soluble in 10% NaOH.

Anal. Calcd. for $C_{10}H_{13}ClN_2O_3S$: C, 43.4; H, 4.73; Cl, 12.82; N, 10.12. Found: C, 43.27; H, 4.69; Cl, 12.90; N, 9.61.

Toxicity Determinations.—Male Holtzman rats (180–200 g.) and male Swiss mice (22–26 g.) were used. Compounds dissolved or suspended in cottonseed oil were administered by intraperitoneal injection to groups of 3 to 6 animals per dose level. Deaths within a 21-day period were recorded and approximate LD_{50} values were estimated graphically from per cent mortality/log dose plots.

Therapeutic Evaluation.—Murphy–Sturm lymphosarcoma and Walker carcinosarcoma 256 were implanted subcutaneously in the flank region of male Holtzman rats using a trochar and cannula. Five days later, when the tumors weighed 5–10 g., the compound was injected intraperitoneally daily for 5 days to groups of 6–10 rats. Control animals received injections of cottonseed oil. Changes in volume of the tumors were estimated from daily measurements taken by caliper.[10]

Development of leucopenia was determined from leucocyte counts performed 72 hr. after a single intraperitoneal injection of an LD_{50} dose.

Acknowledgment.—The authors acknowledge the able assistance of Mr. Paul L. Stanley in the biological testing.

(8) M. H. Benn, A. M. Creighton, B. J. Johnson, L. N. Owen, and G. R. White, *J. Chem. Soc.*, 3395 (1964).

(9) E. B. Kelsey, *J. Am. Chem. Soc.*, **46**, 1694 (1924).

(10) P. Hebborn and J. F. Danielli, *Biochem. Pharmacol.*, **1**, 19 (1958).

Basic Ethers of Guaiacol and Thymol with a Polyoxyethylenic Chain and Their Main Pharmacological Activities. New Antitussives

M. CARISSIMI, A. CATTANEO, R. D'AMBROSIO, V. DE PASCALE, E. GRIMELLI, E. MILLA, AND F. RAVENNA

Research Laboratories of Maggioni and Company, S.p.A., Milan, Italy

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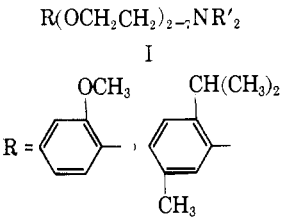
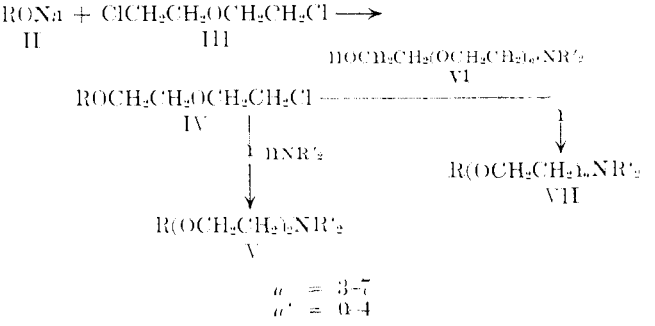
Among the compounds showing antitussive activity are found methoxypoly(ethyleneoxy)ethyl *p*-butylaminobenzoate (benzonatate) and 2-(diethylaminoethoxy)ethyl 1-phenylcyclopentyl-1-carboxylate (carbetapentane), both containing a polyoxyethylenic chain, which according to Bucher[1] seems to possess a selective affinity for the myelin surrounding the afferent pathways of stretch and tactile receptors. We synthetized two series of substances (I) by introducing such a chain ending with a basic group into two molecules, guaiacol and thymol, which are employed in the therapy of the respiratory apparatus. They were screened as antitussives.



Since the activity of many antitussive drugs such as codeine and its derivatives involves some more or less pronounced central effects (respiratory and circulatory impairments, general sedation, nausea, tolerance) as well as the inhibition of intestinal peristalsis and bronchoconstriction, and since several recently described thymol derivatives[2] showed marked sedative properties, we tried to determine the degree of such activities in our compounds in order to ascertain through a pharmacological profile as complete as possible the selectivity of their antitussive activity.

Chemistry.—The synthesis of the compounds listed in Table I was carried out according to Scheme 1.

SCHEME 1



2-Chloroethyl 2-aryloxyethyl ethers (IV) were prepared by condensing sodium guaiacolate or thymolate (II) with bis(2-chloroethyl) ether (III); IV reacted with a secondary amine in 1-hexanol in the presence of pyridine and gave compounds V (n = 2). For the synthesis of higher homologs (VII) the same compounds IV were condensed with a polyoxyethylenic amino alcohol (VI) in xylene in the presence of an alkali metal. Most of the amino alcohols VI used were prepared according to literature methods (see Table II) suitably improved when yields and purity of the products were unsatisfactory. Members where n' = 2, 3, and 4 were synthesized by treating 2-(2-aminoethoxy)-ethanols (VI, n' = 1) with ethylene oxide; in turn, compounds VI were prepared by condensation of 2-chloroethyl 2-acetoxyethyl ether with a secondary amine, followed by hydrolysis of the acetoxy group.

Experimental[3]

2-(2-Aminoethoxy)ethanols (Table II, 5 and 8–10).—2-Chloroethyl 2-acetoxyethyl ether[4] (300 g., 1.8 moles), 540 g. (5.4 moles) of 4-methylpiperazine or 1 equiv. wt. of the other heterocyclic

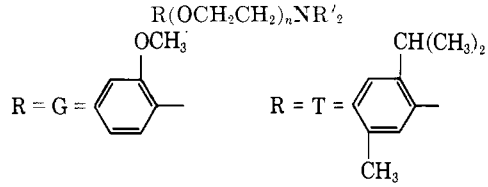
(1) K. Bucher, *Schweiz. Med. Wochschr.*, **86**, 94 (1956).

(2) A. Ashford, C. J. Sharpe, and F. F. Stephens, *Nature*, **197**, 969 (1963).

(3) Boiling and melting points are uncorrected, the work being completed before the announcement of the requirement for corrected data.

(4) F. F. Blicke and J. M. Biel, *J. Am. Chem. Soc.*, **76**, 3163 (1954).

TABLE I
GUAIACOL AND THYMOL DERIVATIVES
$R(OCH_2CH_2)_nNR'_2$



No.	R	n	NR'2	Yield, %	B.p., °C. (mm.)	Formula	Calcd., % C	H	N	O (Cl)	Found, % C	H	N	O (Cl)
1[a]	G	2	$N(C_2H_5)_2$	57	127–129 (0.5)	$C_{16}H_{25}NO_3$			5.24				5.18	
2	T	2	$N(C_2H_5)_2$	58	147 (0.5)	$C_{18}H_{31}NO_2$			4.77				4.72	
	T	2	$N(C_2H_5)_2$		89–90[b,c]	$C_{18}H_{31}NO_2 \cdot HCl$	65.52	9.77	4.24	(10.74)	65.35	9.50	4.35	(10.73)
3	G	3	$N(C_2H_5)_2$	40	153 (0.5)	$C_{17}H_{29}NO_4$	65.56	9.38	4.50		65.79	9.38	4.55	
4	T	3	$N(C_2H_5)_2$	33	154 (0.5)	$C_{20}H_{35}NO_3$	71.17	10.45	4.17		71.42	10.23	4.21	
5	G	4	$N(C_2H_5)_2$	24	182–184 (0.5)	$C_{19}H_{33}NO_5$	64.19	9.35	3.94	22.50	64.48	9.24	3.98	22.36
6	T	4	$N(C_2H_5)_2$	27	184 (0.5)	$C_{22}H_{39}NO_4$	69.25	10.30	3.67	16.77	69.11	10.00	3.71	16.63
7	G	5	$N(C_2H_5)_2$	23	209 (1)	$C_{21}H_{37}NO_5$	63.13	9.33	3.50	24.03	63.03	9.27	3.50	24.26
8	T	5	$N(C_2H_5)_2$	25	210 (1)	$C_{24}H_{43}NO_4$	66.72	10.18	3.29	18.79	67.70	10.13	3.26	19.06
9	G	6	$N(C_2H_5)_2$	23	215 (1)	$C_{23}H_{41}NO_7$	62.27	9.32	3.15	25.25	62.24	9.16	3.15	25.26
10	T	6	$N(C_2H_5)_2$	27	175–180 (1)	$C_{26}H_{47}NO_5$	66.49	10.08	2.98	20.44	66.62	10.30	2.96	20.65
11	G	7	$N(C_2H_5)_2$	23	187 (0.3)	$C_{25}H_{46}NO_8$	61.57	9.30	2.87	26.24	61.51	9.21	2.78	26.36
12	T	7	$N(C_2H_5)_2$	24	180 (0.3)	$C_{28}H_{51}NO_7$	65.46	10.00	2.72	21.80	65.39	9.87	2.76	21.98
13	G	2	Piperidino	77	145 (0.5)	$C_{16}H_{25}NO_3$	68.78	9.02	5.01		69.24	9.50	5.03	
14	T	2	Piperidino	58	157 (1)	$C_{19}H_{31}NO_2$			4.58				4.48	
	T	2	Piperidino		146[b,e]	$C_{21}H_{35}NO_6$[d]	63.77	8.41	3.54		63.99	8.28	3.81	
15	G	3	Piperidino	34	190–193 (0.5)	$C_{18}H_{29}NO_4$	66.84	9.03	4.33		66.94	9.15	4.30	
16	T	3	Piperidino	30	167–171 (0.5)	$C_{21}H_{35}NO_3$			4.00				3.92	
	T	3	Piperidino		89–90[b,f]	$C_{23}H_{37}NO_7$	62.84	8.48	3.18		63.24	8.46	3.15	
17	G	4	Piperidino	18	185 (1)	$C_{20}H_{33}NO_5$	65.36	9.05	3.81	21.77	65.62	8.93	3.90	22.04
18	T	4	Piperidino	27	180 (1)	$C_{23}H_{39}NO_4$	70.19	9.99	3.55	16.27	70.21	10.25	3.55	16.42
19	G	5	Piperidino	20	188 (0.3)	$C_{22}H_{37}NO_6$	64.20	9.06	3.40	23.32	64.02	8.99	3.41	23.49
20	T	5	Piperidino	28	190 (0.3)	$C_{25}H_{43}NO_5$	68.61	9.90	3.20	18.28	68.65	9.87	3.24	18.51
21	G	6	Piperidino	26	191 (0.3)	$C_{24}H_{41}NO_7$	63.26	9.07	3.07	24.58	63.13	8.96	3.09	24.81
22	T	6	Piperidino	29	190 (0.3)	$C_{27}H_{47}NO_6$	67.32	9.83	2.91	19.93	67.30	9.73	2.94	20.12
23	G	2	Morpholino	74	158 (0.5)	$C_{15}H_{23}NO_4$	64.03	8.24	4.98		64.23	8.26	4.98	
24	T	2	Morpholino	50	168–170 (1)	$C_{18}H_{29}NO_3$			4.55				4.53	
	T	2	Morpholino		147[b,e]	$C_{20}H_{31}NO_7$[d]	60.43	7.86	3.52		60.50	7.66	3.60	
25	G	3	Morpholino	25	184 (0.5)	$C_{17}H_{27}NO_5$	62.74	8.36	4.31		62.74	7.76	4.16	
26	T	3	Morpholino	19	178–180 (0.5)	$C_{20}H_{33}NO_4$			3.98				4.19	
	T	3	Morpholino		90–92[b,f]	$C_{22}H_{36}NO_8$[d]	59.94	7.99	3.17		59.70	7.90	3.18	
27	G	4	Morpholino	29	190 (1)	$C_{19}H_{31}NO_5$	61.76	8.45	3.79	25.98	61.80	8.44	3.79	26.21
28	T	4	Morpholino	35	180 (1)	$C_{22}H_{37}NO_5$	66.80	9.43	3.54	20.22	66.96	9.10	3.56	20.54
29	G	2	Pyrrolidino	78	140 (1)	$C_{15}H_{23}NO_3$	67.89	8.73	5.27		67.82	8.71	5.22	
30	T	2	Pyrrolidino	82	160 (1)	$C_{18}H_{27}NO_2$	74.69	9.40	4.84		74.83	9.55	4.74	
	T	2	Pyrrolidino		82–83[b]	$C_{24}H_{33}NO_9$[g]			2.91				2.85	
31	G	3	Pyrrolidino	20	178 (1)	$C_{17}H_{27}NO_4$	65.98	8.79	4.52		65.93	8.70	4.52	
32	T	3	Pyrrolidino	32	180 (0.5)	$C_{20}H_{33}NO_3$	71.60	9.91	4.17		71.56	9.88	4.15	
33	G	4	Pyrrolidino	26	185 (0.5)	$C_{19}H_{31}NO_6$	64.55	8.84	3.96	22.63	64.71	8.92	4.00	22.84
34	T	4	Pyrrolidino	28	187 (0.5)	$C_{22}H_{37}NO_4$	69.63	9.82	3.69	16.86	69.91	9.72	3.70	17.12
35	G	2	4-Methylpiperazino	31	170 (0.5)	$C_{16}H_{26}N_2O_3$	65.27	8.90	9.51		65.15	9.20	9.35	
	G	2	4-Methylpiperazino		215–217[b,e]	$C_{16}H_{26}N_2O_3 \cdot 2HCl$			7.66	(19.41)			7.63	(19.20)
36	T	2	4-Methylpiperazino	70	175 (0.5)	$C_{19}H_{32}N_2O_2$	71.20	10.06	8.74		71.41	9.84	8.47	
	T	2	4-Methylpiperazino		198–200[b,h]	$C_{19}H_{32}N_2O_2 \cdot 2HCl$			7.10	(18.02)			7.07	(18.01)
37	G	3	4-Methylpiperazino	21	180 (0.5)	$C_{18}H_{30}N_2O_4$	63.87	8.93	8.27		63.74	8.87	8.24	
	G	3	4-Methylpiperazino		87–91[b,i]	$C_{30}H_{46}N_2O_{18}$[i]			3.87				3.85	
38	T	3	4-Methylpiperazino	28	187 (0.5)	$C_{22}H_{36}N_2O_3$	70.17	9.63	7.44		70.07	9.73	7.55	
	T	3	4-Methylpiperazino		173–174[b,k]	$C_{22}H_{36}N_2O_3 \cdot 2HCl$			6.23	(15.77)			6.38	(16.05)
39	G	4	4-Methylpiperazino	24	190 (1)	$C_{20}H_{34}N_2O_5$	62.79	8.96	7.32	20.91	62.80	8.98	7.28	21.11
40	T	4	4-Methylpiperazino	31	195 (0.5)	$C_{23}H_{40}N_2O_4$	67.60	9.86	6.85	15.66	67.58	9.92	6.82	15.69

[a] This compound had been previously prepared by a different route by J. Moszew and A. Inasinski, *Roczniki Chem.*, **28**, 461 (1954); *Chem. Abstr.*, **50**, 221 (1956). [b] Melting point. [c] From dioxane + petroleum ether. [d] Acid oxalate. [e] From ethanol. [f] From 2-propanol. [g] Citrate. [h] From dioxane–ethanol (90:10). [i] Dicitrate. [j] From 2-propanol + ether. [k] From propanol + ether.

amines, and 450 ml. of anhydrous ethanol were heated to 125° in an autoclave for 18 hr. The solvent and the excess amine were removed under reduced pressure on a water bath and the residue was acidified with 7% HCl and extracted with ether. The aqueous layer was made basic with 40% NaOH, the resulting oil was collected, and the alkaline solution was extracted with ethyl acetate. The oily layer was dissolved in the combined extracts, and the solution was dried (Na_2SO_4). After removal of solvent under reduced pressure the residue was distilled, collecting the fraction boiling at 125–150° (18 mm.); this was boiled in 1 l. of 12% HCl for 4 hr. The cooled acid solution was extracted with ether and again made basic with 40% NaOH. The isolation of the reaction product was performed as described above. The oily residue was distilled under reduced pressure. By a similar procedure also were prepared 2-(2-N-piperidinoethoxy)ethanol (heating time in autoclave, 16 hr. at 150°), 2-(2-N-morpholinoethoxy)ethanol (18 hr. at 125°), and 2-(2-N-pyrrolidinoethoxy)ethanol (18 hr. at 125°).

1-(N-Piperidino)-8-hydroxy-3,6-dioxaoctane (Table II, 6) and 1-(N-Piperidino)-11-hydroxy-3,6,9-dioxaundecane (Table II,7).—Equimolar quantities of 2-(2-N-piperidinoethoxy)ethanol and ethylene oxide were heated to 100° in an autoclave for 1 hr. The reaction mixture was fractionated in a Todd-type fractionation column, packed with glass helices. The fraction boiling at 170–174° (16 mm.) is the dioxaoctane derivative, and the one boiling at 150–155° (0.5 mm.) is the dioxaundecane derivative. They were collected and distilled again in the same column. Boiling points of pure products are given in Table II.

2-Chloroethyl 2-Aryloxyethyl Ethers (IV).—A solution of 124 g. (1 mole) of guaiacol in 125 g. of ethylene glycol was treated with 42 g. of NaOH and warmed with stirring until it dissolved. After cooling, 256 g. (1.8 moles) of bis(2-chloroethyl) ether was added and the solution was gradually brought to 120°, at which temperature the burner was removed. Soon afterwards a vigorous reaction began. When it had subsided, the reaction mixture was heated to boiling for 2 hr. and poured into 5 vol. of water.

TABLE II

AMINO ALCOHOLS

$HOCH_2CH_2(OCH_2CH_2)_nNR'_2$

No.	NR'_2	n	Yield, %	B.p., °C. (mm.)	n_D^{20} (°C.)	% N Calcd.	% N Found
1[a]	$N(C_2H_5)_2$	1	...	...	...	...	...
2[b]	$N(C_2H_5)_2$	2	33	153 (16)	1.4513 (25)	6.82	6.78
3[b]	$N(C_2H_5)_2$	3	15	157 (2)	1.4552 (25)	5.62	5.57
4[b]	$N(C_2H_5)_2$	4	10	180 (1)	1.4570 (25)	4.77	4.65
5[c]	Piperidino	1	43	133 (18)	1.4741 (20)	8.08	8.08
6	Piperidino	2	25	170–71 (16)	1.4748 (20)	6.44	6.30
7	Piperidino	3	20	145–147 (0.3)	1.4751 (21)	5.36	5.26
8[c]	Morpholino	1	38	147 (16)	1.4718 (20)	7.97	7.99
9[b,c]	Pyrrolidino	1	38	126 (18)	1.4688 (25)	8.80	8.79
10	4-Methylpiperazino	1	56	150–155 (18)	1.4810 (20)	14.74	15.54

[a] See ref. 4. [b] A. J. W. Neadlee, A. R. Collet, and C. L. Lazzel, *J. Am. Chem. Soc.*, **55**, 1066 (1933). [c] H. Najer, P. Chabrier, and R. Giudicelli, *Bull. soc. chim. France*, 355 (1958). [d] W. Reppe, *Ann.*, **596**, 80 (1955). [e] R. B. Moffet, *J. Org. Chem.*, **14**, 862 (1949).

TABLE III

No.	Antitussive activity[a]	Acute toxicity (LD_{50})[b]	Analgesia (ED_{50})[c]	Local anaesthesia (ED_{50})[d]	Narcosis potentiation[e]
6[f,g]	++	191	133	230	...[h] (...)[i]
15	+++ +++[j] 130[k]	254	303	222	2.63
16[f,g]	+	233	128	363	3.27
17[g]	+ +	380	468	160	1.77
18[f]	+ + +	173	48.4	247	2.55
24	+ +	448	1115	1110	3.6 (1.52)[i]
26	+	517	324	682	3.1 (2.38)[i]
28[f,g]	-	278	223	444	...[h] (...)[i]
29[f,g]	+	264	327	535	1.94
30[f,g]	+ +	332	215	467	2.75
32[f]	-	244	200	300	...[h] (...)[i]
34[f]	- -	158	200	388	2.47 (1.10)[i]
35[g]	++	764	271	1100	2.13
37	+	827	780	1150	...[h] (2.03)[i]
Codeine	+++[l] +++[m] 128[k]				

[a] Activity index (stimulation of superior laryngeus nerve): +, cough inhibition by stimulation intensity up to 10 times the threshold value; ++, up to 20 times; +++, >20 times; dose = 25–30 μmoles/kg. Mean values of four experiments i.v. for all compounds and of 20 experiments i.v. and 12 experiments intraduodenally for **15**. [b] LD_{50} i.p. in μmoles/kg. in mice; fiducial limits ($P = 0.05$) not exceeding ±15–20% of reported values. [c] Dose in μmoles/kg. s.c. reducing 50% of the number of writhings in mice after phenylquinone injection[m] (for fiducial limits see *b*). [d] ED_{50}: concentration in μmoles/100 ml. of the injected solution (0.25 ml. intradermally reducing 50% of the pin prick responses in guinea pigs[8] (for fiducial limits see *b*). [e] Ratio between the mean sleep time of treated mice and that of controls (groups of 10 mice for each probe). Mean sleep time of controls treated with 30 mg./kg. i.p. of pentobarbital = 12 ± 3.47 min. [f] Blood pressure fall >40% and lasting more than 10 min. in the same cats employed for antitussive activity test. [g] Respiratory depression lasting longer than 10 min. after injection of the substance. [h] No potentiation. [i] In parenthesis ratio as in *c* for the corresponding guaiacol or thymol derivative (see Table I). [j] Activity index of **15** given intraduodenally (30–60 μmoles/kg.); mean of 10 essays. [k] Dose in μmoles/kg. s.c. injected in aerosolized guinea-pigs and chronically coughing rats giving a decrease of 50% of the control number of cough (significance test at $P = 0.05$). [l] Mean index of activity of 5 experiments i.v.; dose 25 μmoles/kg. [m] Mean index of activity of 5 experiments p.o.; dose 60 μmoles/kg.

The emulsion was extracted with CH_2Cl_2, and the extracts were washed with 2% NaOH solution and with water and finally dried (Na_2SO_4). The solvent was removed on a steam bath, and the residue was distilled under reduced pressure, collecting the fraction boiling at 184–187° (16 mm.) which became solid on standing; yield 120 g. (52%), m.p. 36°.

Anal. Calcd. for $C_{11}H_{15}ClO_3$: Cl, 15.38. Found: Cl, 15.25.

The corresponding thymol derivative was prepared in the same manner; yield 51%, b.p. 130–133° (1 mm.), $n^{22}D$ 1.5092.

Anal. Calcd. for $C_{14}H_{21}ClO_3$: Cl, 13.81. Found: Cl, 13.70.

Preparation of V.—A solution of 10 g. of 2-chloroethyl 2-(*o*-methoxyphenoxy)ethyl ether (or of the corresponding thymol derivative) and 30 ml. of the secondary amine, in a mixture of 50 ml. of 1-hexanol and 20 ml. of pyridine, was heated to 110° for 16 hr. The volatile fractions were distilled at reduced pressure on a steam bath, the oily residue was acidified with 7% HCl, and the mixture was extracted with ethyl acetate. The aqueous solution was made basic with a large excess of solid Na_2CO_3 and the base which separated was extracted with ethyl acetate. The extracts were dried (Na_2SO_4) and evaporated under reduced pressure. The oily residue was fractionated (see Table I).

Preparation of VII.—Sodium (2.3 g., 0.1 g.-atom) cut in small pieces was suspended in 40 ml. of dry xylene and heated to 120°, at which temperature 0.11 mole of the amino alcohol VI was dropped in. The mixture was heated to boiling until the sodium dissolved completely; this required a time varying from 3 to 20 hr. because the formation of the alcoholate became generally more difficult with increasing length of the polyoxyethylenic chain. The solution was cooled to 60° and 0.1 mole of 2-chloroethyl 2-(*o*-methoxyphenoxy)ethyl ether or of the corresponding thymol derivative (IV) was introduced. After stirring for 1 hr. the bath temperature was brought to 150° and kept there for 6 hr. The mixture was cooled, treated with 75 ml. of 7% HCl, and shaken. The xylene layer was separated, the aqueous solutions were extracted with ethyl acetate and then made basic with excess solid Na_2CO_3. The base separated and was taken up in ether or in ethyl acetate, and the solution was dried (Na_2SO_4)

and evaporated on a steam bath. The residue was fractionated under reduced pressure. The bases gave crystalline salts with difficulty; those which were obtained are described in Table I, after the respective base.

Pharmacology.—For all compounds, we evaluated (using codeine as reference substance) the antitussive activity on cats,[5,6] observing whether this was accompanied by hypotension and respiratory impairment, the acute LD_{50} in mice and albino rats,[7] and the local anesthetic[8] and analgesic activity.[9,10] The occurence of central sedation was measured through variations in the spontaneous motility and in the performance of the grip test, and through the influence exerted by the compounds on the duration of the barbiturate narcosis.[11] The spasmolytic activity was tested on the isolated rat and guinea pig ileum against histamine, acetylcholine, $BaCl_2$, and nicotine contractions.[12]

Compound **15** was studied as antitussive also on unanesthetized rats and guinea pigs[13,14] and further as an inhibitor of pentylenetetrazole seizures,[11] for its effect on peristalsis,[15] and on the bronchial and tracheal muscles *in vivo* and *in vitro*[16,17]; finally its influence upon the bronchial and tracheal secretion was examined.[18]

In Table III only the compounds appreciably active as antitussives are recorded with the results concerning their antitussive, local anesthetic, analgetic, narcosis-enhancing, hypotensive, and respiratory-depressing activities and the data about their acute toxicity.

A few observations relating the structure to the pharmacological activities are to be made. The antitussive as well as the other pharmacological activities listed are generally more pronounced in the thymol than in the guaiacol derivatives. The antitussive effect lasted for a time roughly proportional to the activity index (from 30 min. to 3–4 hr.) and was sometimes accompanied by a depression of the respiratory function. The compounds of both series containing a diethyl radical were inactive, whatever the length of the chain. In agreement with the literature,[19] the piperidine group seems to enhance this activity, as clearly shown by **15** (though a guaiacol derivative) and **18**, both being the most active of all our antitussives.

As spasmolytics the guaiacol derivatives were completely inactive, while the thymol derivatives were very weak inhibitors of acetylcholine contractions (less than 1% of atropine), and of about the same activity as papaverine against $BaCl_2$ contractions and hexamethonium against nicotine spasms.

The behavioral pattern,[20] body temperature, motility, and muscular tonus and force of the treated animals as well as the response to the hot plate test for analgesia were unaffected; the only signs (more evident in the thymol derivatives) of a certain trend to affect CNS functions were the analgesia detected in the phenylquinone test and the moderate prolongation of the barbiturate narcosis. These mild and unspecific effects on the CNS are in contrast with the marked sedative properties of some thymol derivatives described in literature.[2] Therefore, the observed antitussive effect does not seem to be bound to general analgesia or sedation, or to the intensity of the local anesthetic effect; in fact for some active compounds hypotensive and respiratory-depressing effects were lacking.

Compound **15** was studied particularly since it was the only one which showed a good degree of activity also by the oral route. Its antitussive activity is of same order of magnitude as that of codeine in the experiments on cats and seems to be fairly specific because of lack of side effects (respiratory and circulatory implications, inhibition of intestinal peristalsis, bronchoconstriction, and general sedation). No protection against pentylenetetrazole seizures and no change in the mucous tracheal secretion were observed. It did not produce tolerance; in cats injected daily for 4 weeks with 10 mg./kg. i.p., the inhibitory effect on the experimental cough[5,6] was obtained by the same doses which were active in cats not pretreated.

It does not appear that the hypotensive activity shown by several compounds is cause for concern. It is presumably bound to myocardic impairment as seen on the isolated rabbit heart, and to an intense and persistent peripheral vasodilatory effect, as also seen in the isolated rabbit ear vessels,[21] together with an adrenolytic effect; in any event, this was not observed on the blood pressure response to epinephrine.

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Insect Chemosterilants. II.[1] N-Carbamoylaziridines

ALEXEJ B. BOŘKOVEC AND CHARLES W. WOODS

Entomology Research Division, U. S. Department of Agriculture, Beltsville, Maryland

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Certain N-substituted aziridines are outstanding in their ability to interfere with insect reproduction. This type of biological activity can be found among other alkylating agents (*e.g.*, nitrogen mustards, alkyl alkanesulfonates), but the aziridines proved to be particularly useful because of their effectiveness in sterilizing male insects and their often wide toxicity–sterility margin.[2]

In general, the aziridine bases with no substituent on the ring nitrogen and the N-alkylaziridines have little or no activity as insect sterilants. Most of the screening and synthesis of aziridinyl chemosterilants centered on the compounds which had an unsaturated group attached to the ring nitrogen. The N-acyl and N-aroylaziridines exhibited the sterilizing activity in various degrees, but none of the compounds tested approached the high potency of tepa or other phosphorus-containing aziridines.[3]

It appeared desirable to increase the electron deficiency of the carbonyl carbon of N-acylaziridines by replacing the acyl group with a carbamoyl group. Several diaziridinyl compounds of this type were commercially available, and their testing and comparison with similar N-acylaziridines indicated substantially increased sterilizing properties. In our previous communication,[1] we have reported the synthesis of 1,1′-suberoylbisaziridine (I) and 1,1′-isophthaloylbisaziridine (II). The first compound exhibited no appreciable sterilizing properties when fed to house flies (*Musca domestica* L.) at 1% concentration and the second produced a 75% reduction in egg hatch when fed at 5% concentration. On the other hand, the two similar compounds N,N′-hexamethylenebis-1-aziridine-

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