radically in their preferred conformations and it has been suggested that this fact may have a bearing upon their more active enantiomers (of formally alike asymmetry) differing in configuration.[9] Conformational differences between methadols and their acetates are also likely to be of importance in this context and a study of this nature is presently in hand.

Experimental Section[10]

α-(±)-Methadol, mp 100–102° (lit.[11] mp 100–101°), was obtained from (±)-methadone and LAH; α-(+)-methadol hydrochloride, mp 187–188°, $[\alpha]^{26}D$ +33.5° (*c* 0.2, H_2O) [lit.[12] mp 169–171°, $[\alpha]^{25}D$ +34° (*c* 0.26, H_2O)], was obtained from (−)-methadone and Na–PrOH[1] (LAH gave racemic material).

6-Dimethylamino-4,4-diphenylhexan-3-ol (Normethadol).—Normethadone (26.7 g) was reduced with LAH (1.7 g) in the usual way[1] to give the amino alcohol (21 g), mp 100–101°, from EtOH. It formed a **hydrochloride**, mp 140–142°, from Me_2Co–Et_2O. *Anal.* ($C_{20}H_{25}ClNO$) C, H, N. **Methiodide**, mp 183–185°, from EtOH–Et_2O. *Anal.* ($C_{21}H_{30}INO$) C, H, N. **Bitartrate** [using (±)-tartaric acid], mp 146–148°, from EtOH. *Anal.* ($C_{24}H_{33}NO_7$) C, H, N.

Normethadol (14.85 g) and (+)-tartaric acid (7.5 g) were dissolved in hot 96% EtOH (30 ml) and the solution was stored at room temperature. The solid which separated was crystallized twice from the same solvent to give (+)-normethadol (+)-tartrate (7.8 g), mp 144–146°, $[\alpha]^{27}D$ +20° (*c* 2, H_2O). *Anal.* ($C_{24}H_{33}NO_7$) C, H, N.

3-Acetoxy-6-dimethylamino-4,4-diphenylhexane Hydrochloride.—A mixture of (±)-normethadol (3.5 g), EtOAc (80 ml), and AcCl (3 ml) was heated under reflux for 2 hr and then cooled. The solid which separated was recrystallized from EtOH–Et_2O to give (±)-**normethadyl acetate hydrochloride**, mp 104–106°, as a monohydrate (ν_{max} 3350 cm^{-1}). *Anal.* ($C_{22}H_{30}ClNO_2 \cdot H_2O$) C, H, N.

Acetylation of (+)-normethadol gave the (+)-acetoxy ester hydrochloride, mp 163–165°, from EtOH–Et_2O, $[\alpha]^{26}D$ +22.5° (*c* 2, H_2O). *Anal.* ($C_{22}H_{30}ClNO_2$) C, H.

(9) A. F. Casy and M. M. A. Hassan, *J. Pharm. Pharmacol.*, **19**, 114 (1967).

(10) Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

(11) E. L. May and E. Mosettig, *J. Org. Chem.*, **13**, 459 (1948).

(12) A. Pohland, F. J. Marshall, and T. P. Craney, *J. Am. Chem. Soc.*, **71**, 460 (1949).

7-Oxabicyclo[2.2.1]heptane-2,3-dicarboximides with Anticonvulsant Activity

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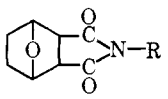
During an exploratory study of various derivatives of 7-oxabicyclo[2.2.1]heptane, we encountered marked anticonvulsant activity in the N-phenethyl-2,3-dicarboximide (I, R = phenethyl), a compound which may



I

be regarded as an elaborately substituted succinimide. Since its acute toxicity was relatively low, we undertook a study of the manner in which activity might be altered by variation of the R group.

Grogan and Rice[1] have described a number of imides of this sort. Some pharmacological testing was done, but revealed little significant activity. Beyond their work, only scattered examples of derivatives of this oxygen-bridged ring appear in the literature; it has been little used in the synthesis of potential drugs.

We prepared a series of imides (Table I) by heating primary amines with *exo,cis*-7-oxabicyclo[2.2.1]heptane-2,3-dicarboxylic acid or its anhydride, essentially according to published procedures.[1a] The products were considered to be *exo*, in conformity with the starting material. This assignment was confirmed by nmr examination in a number of instances; in no case was splitting of the signal for the protons at positions 2 and 3 of the cyclohexane ring by the protons at 1 and 4 observed ($J < 0.5$ cps).

Unexpectedly, two products, **46** and **47**, were obtained from 6-chloro-*o*-toluidine. Upon nmr examination, these were identified as rotationally isomeric forms of the expected imide, each containing 3–4% of the other rotamer. The signal for the protons at positions 2 and 3 was normally a single sharp line near δ 3.0. In the spectrum of **46**, it appeared as a pair of lines, a major one at 3.07 accompanied by a very small one at 3.02. For **47**, a similar but reversed pair appeared, the major line being at 3.05, the minor one at 3.09.

Confirmatory evidence of restricted rotation about the N-phenyl bond and consequent rotational isomerism among the phenylimides in general was afforded by the appearance of pairs of lines for the H-2,3 signal for those having only one *ortho* substituent, and for the protons of *o*-methyl groups, equal in size for the 2,6-xylylimide, unequal for *o*-tolylimides. Also, a small shift was seen between the two aromatic protons of the 2,4,6-trihalophenylimides, and in some cases two groups of lines could be seen for the protons at positions 1 and 4.

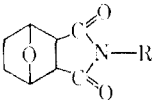
In pharmacological testing of the imides (Table II), considerable anticonvulsant activity was observed. Some of them showed potency in animal tests comparable to that of drugs currently used in therapy. Activity was essentially limited to compounds in which R was aryl or aralkyl with a one or two-carbon link between aryl group and imide N. Alkyl and heterocyclic imides had only feeble activity, if any.

Of the simple aralkyl derivatives, phenethyl (**4**) and benzyl (**3b**) were moderately active against both electroshock and pentylenetetrazole convulsions. β-Methylphenethyl (**8**) showed good activity in the electroshock test, but insertion of an α-methyl group (**6**, **7**) almost completely destroyed activity. Substitution on the phenyl ring tended to reduce potency.

The phenylimide (**3a**) was only feebly active. However, its monochloro derivatives were more active, and introduction of a second Cl or of an *o*-CH_3 substituent led to the most potent compounds of the series. The 2,3-dichlorophenylimide (**25**) showed the greatest overall activity. It was rivalled in potency against electroshock seizures by the 2,4- and 3,5-dichlorophenyl-, 3-chloro-*o*-tolyl-, and 2-chloro-5-trifluoromethylphenylimides (**26**, **30**, **48**, **52**) and against pentylenetetrazole seizures by the 2,5-dichlorophenyl- and 4-chloro-*o*-tolyl-

(1) (a) C. H. Grogan and L. M. Rice, *J. Med. Chem.*, **6**, 802 (1963); (b) L. M. Rice, C. H. Grogan, and E. E. Reid, *J. Am. Chem. Soc.*, **75**, 4911 (1953); (c) *ibid.*, **77**, 616 (1955).

TABLE I
exo,cis-7-OXABICYCLO[2.2.1]HEPTANE-2,3-DICARBOXIMIDES



Compd	R	Mp, °C	Yield, %	Formula[a]
1	*t*-C_4H_9	169–170	48	$C_{12}H_{17}NO_3$
2	Cyclohexyl	107–109	40	$C_{14}H_{19}NO_3$
3	$CH_3CHOHCH_2$	117–118	73	$C_{11}H_{15}NO_4$
4	$C_6H_5CH_2CH_2$	110–111[b]	86	$C_{16}H_{17}NO_3$
5	$C_6H_5(CH_2)_4$	99.5–100.5	74	$C_{18}H_{21}NO_3$[c]
6	$C_6H_5CH(CH_3)$	86–87	63	$C_{16}H_{17}NO_3$
7	$C_6H_5CH_2CH(CH_3)$	69–71	48	$C_{17}H_{19}NO_3$
8	$C_6H_5CH(CH_3)CH$	81–83	72	$C_{17}H_{19}NO_3$
9	$C_6H_5CH(C_2H_5)CH_2$	92–93	52	$C_{18}H_{21}NO_3$
10	$(C_6H_5)_2CH$	137–139	68	$C_{21}H_{19}NO_3$
11	$(C_6H_5)_2CHCH_2$	170–171	63	$C_{22}H_{21}NO_3$
12	$C_6H_5CH{=}CHCH_2$	106–107	32	$C_{17}H_{17}NO_3$
13	$C_6H_5OCH_2CH_2$	76–77	39	$C_{16}H_{17}NO_4$
14	$C_6H_5N(CH_3)$	140–141	75	$C_{15}H_{17}N_2O_3$
15	2-$CH_3C_6H_4$	166–167	76	$C_{15}H_{15}NO_3$
16	3-$CH_3C_6H_4$	160–161	58	$C_{15}H_{15}NO_3$
17	4-$CH_3C_6H_4$	182.5–183.5	62	$C_{15}H_{15}NO_3$
18	2-$C_2H_5C_6H_4$	123–125	41	$C_{16}H_{17}NO_3$
19	2,4-$(CH_3)_2C_6H_3$	180.5–181.5	57	$C_{16}H_{17}NO_3$
20	2,6-$(CH_3)_2C_6H_3$	186–188	65	$C_{16}H_{17}NO_3$
21	3,4-$(CH_3)_2C_6H_3$	169–170	77	$C_{16}H_{17}NO_3$
22	2-ClC_6H_4	163–164	79	$C_{14}H_{12}ClNO_3$
23	3-ClC_6H_4	153–154	71	$C_{14}H_{12}ClNO_3$
24	4-ClC_6H_4	194–195	90	$C_{14}H_{12}ClNO_3$
25	2,3-$Cl_2C_6H_3$	160–161	58	$C_{14}H_{11}Cl_2NO_3$
26	2,4-$Cl_2C_6H_3$	151–152	96	$C_{14}H_{11}Cl_2NO_3$
27	2,5-$Cl_2C_6H_3$	179–180	83	$C_{14}H_{11}Cl_2NO_3$
28	2,6-$Cl_2C_6H_3$	189–190	77	$C_{14}H_{11}Cl_2NO_3$
29	3,4-$Cl_2C_6H_3$	197–198	53	$C_{14}H_{11}Cl_2NO_3$
30	3,5-$Cl_2C_6H_3$	154–155	58	$C_{14}H_{11}Cl_2NO_3$
31	2,4,5-$Cl_3C_6H_2$	183–184	64	$C_{14}H_{10}Cl_3NO_3$
32	2,4,6-$Cl_3C_6H_2$	198–199	63	$C_{14}H_{10}Cl_3NO_3$
33	2-BrC_6H_4	159–160	36	$C_{14}H_{12}BrNO_3$
34	4-BrC_6H_4	206–208	58	$C_{14}H_{12}BrNO_3$
35	2,4,6-$Br_3C_6H_2$	210–211	22	$C_{14}H_{10}Br_3NO_3$[c]
36	2-HOC_6H_4	252–253	45	$C_{14}H_{13}NO_4$
37	4-HOC_6H_4	214–215	51	$C_{14}H_{13}NO_4$
38	2-$CH_3OC_6H_4$	149.5–150.5	76	$C_{15}H_{15}NO_4$
39	2-$C_2H_5OC_6H_4$	129–130	71	$C_{16}H_{17}NO_4$
40	4-$C_2H_5OC_6H_4$	173–174	86	$C_{16}H_{17}NO_4$
41	3-$CF_3C_6H_4$	196–198	71	$C_{15}H_{12}F_3NO_3$
42	3-$CH_3COC_6H_4$	183–184	41	$C_{16}H_{15}NO_4$
43	4-$(CH_3)_2NC_6H_4$	209–211	77	$C_{16}H_{18}N_2O_3$
44	2-Cl-4-$CH_3C_6H_3$	154–155	38	$C_{15}H_{14}ClNO_3$
45	2-Cl-5-$CH_3C_6H_3$	173–174	77	$C_{15}H_{14}ClNO_3$
	2-Cl-6-$CH_3C_6H_3$			
46	α-form	213–215	17	$C_{15}H_{14}ClNO_3$
47	β-form	216–218	7	$C_{15}H_{14}ClNO_3$
48	3-Cl-2-$CH_3C_6H_3$	155–156	87	$C_{15}H_{14}ClNO_3$
49	3-Cl-4-$CH_3C_6H_3$	203–204	70	$C_{15}H_{14}ClNO_3$
50	4-Cl-2-$CH_3C_6H_3$	173–174	64	$C_{15}H_{14}ClNO_3$
51	5-Cl-2-$CH_3C_6H_3$	175–176	83	$C_{15}H_{14}ClNO_3$
52	2-Cl-5-$CF_3C_6H_3$	138–139	80	$C_{15}H_{11}ClF_3NO_3$
53	2-$ClC_6H_4CH_2$	122–123	64	$C_{15}H_{14}ClNO_3$
54	4-$ClC_6H_4CH_2$	110.5–111.5	62	$C_{15}H_{14}ClNO_3$
55	2,4-$Cl_2C_6H_3CH_2$	144–145	24	$C_{15}H_{13}Cl_2NO_3$
56	3,4-$Cl_2C_6H_3CH_2$	122–123	92	$C_{15}H_{13}Cl_2NO_3$
57	4-$CH_3OC_6H_4CH_2$	109–110	73	$C_{16}H_{17}NO_4$
58	4-$C_2H_5OC_6H_4CH_2$	118–119	75	$C_{17}H_{19}NO_4$
59	4-$C_4H_9OC_6H_4CH_2$	88–89	73	$C_{19}H_{23}NO_4$
60	2-$ClC_6H_4CH_2CH_2$	82–83	31	$C_{16}H_{16}ClNO_3$
61	4-$ClC_6H_4CH_2CH_2$	143–145	56	$C_{16}H_{16}ClNO_3$
62	2,4-$Cl_2C_6H_3CH_2CH_2$	124–126	40	$C_{16}H_{15}Cl_2NO_3$
63	3-Pyridyl	160–161	45	$C_{13}H_{12}N_2O_3$
64	5-Cl-2-pyridyl	168–170	85	$C_{12}H_{11}ClN_2O_3$
65	2-Thiazolyl	185–186	22	$C_{11}H_{10}N_2O_3S$
66	2-Benzothiazolyl	252–254	18	$C_{16}H_{12}N_2O_3S$[d]

[a] Another crystalline form, mp 101–102°. [b] C: calcd, 72.21; found, 72.75. [c] C, H: calcd, 35.02, 2.10; found, 36.47, 1.45. [d] C: calcd, 60.01; found, 60.51. [e] All compounds were analyzed for C, H.

imides (**27**, **50**). Further substitution led to sharply decreased activity.

Many of the imides were also subjected to the amphetamine aggregation test. Three (**15**, **48**, **50**), all *ortho* substituted, gave complete protection at 200–400 mg/kg, but unfortunately none showed appreciable activity at lower doses.

A limited number of compounds were also tested for analgetic and antiemetic activity. Analgetic activity was apparent in a few, but their potency was not sufficient to justify further exploration. None showed antiemetic activity at the doses investigated.

Compounds listed in Table I but not in Table II showed little or no activity at the highest dose tested, usually 400 or 800 mg/kg.

Experimental Section[2]

N-(6-Chloro-*o*-tolyl)-7-oxabicyclo[2.2.1]heptane-2,3-dicarboximides (46, 47).—A mixture of 84 g of 6-chloro-*o*-toluidine and 111 g of *exo,cis*-7-oxabicyclo[2.2.1]heptane-2,3-dicarboxylic acid was heated gradually to 240–250° and held at this temperature for 2 hr, then cooled and recrystallized from EtOH. A first crop, largely prisms, formed at room temperature. The mother liquor was chilled and deposited a second crop, largely needles. The two crops were recrystallized separately from MeOH to constant melting point, yielding 27 g of prisms, mp 213–215° (α-form, **46**), and 14 g of needles, mp 216–218° (β-form, **47**). Nmr data are as follows: **20**, δ 2.10, 2.07 (3:3, CH_3); **44**, 3.04, 2.96 (1.2:0.8, H-2,3); **46**, 3.07, 3.02 (1.9:0.06, H-2,3), 2.15, 2.11 (1.9:0.06, CH_3); **47**, 3.05, 3.09 (1.9:0.08, H-2,3), 2.12, 2.15 (1.9:0.08, CH_3); **50**; 2.99, 2.94 (0.7:1.3, H-2,3), 4.93, 4.89 (0.7:1.3, H-1,4), 2.07, 2.10 (0.7:1.3, CH_3); mixture of **46** and **47** (2:1), 3.07, 3.03 (1.3:0.7, H-2,3), 4.98, 5.02 (1.3:0.7, H-1,4), 2.13, 2.09 (1.3:0.7, CH_3). Other peaks were as expected.

Pharmacological Methods.—Tests were performed in male albino Swiss–Webster mice which were allowed free access to food and water except during the testing period. Adult mongrel dogs unselected as to sex were used in the antiemetic studies. The compounds were administered as aqueous solutions or as fine suspensions in cellulose gums. Determinations of ED_{50} or LD_{50} and 95% confidence limits were made statistically.[3] When

(2) Melting points were determined in a Thomas–Hoover Unimelt apparatus and are uncorrected. Elemental analyses were performed by Clark Microanalytical Laboratory, Urbana, Ill., and Midwest Microlab, Indianapolis, Ind.; where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. Nmr spectra were obtained on a Varian A-60 spectrometer in 5–20% concentration in $CDCl_3$, using TMS as an internal reference.

(3) J. T. Litchfield, Jr., and F. Wilcoxon, *J. Pharmacol. Exptl. Therap.*, **96**, 99 (1949).

TABLE II

PHARMACOLOGICAL RESULTS[a]

Compd	LD_{50}, mg/kg	TD_{50}, mg/kg	Anticonvulsant ED_{50}, mg/kg			PAT[e] hr	dAA[f] % protection
			Met[b]	Mes[c]	SL[d]		
3a[g]	1165	510 (436–597)	>400[h]	400 (370–432)	>400	1	0
3b[i]	1240[h]	350 (297–413)	285[j] (197–413)	171 (143–205)	>400	2	0
4	>1600	600 (546–660)	168[k] (150–188)	154 (132–170)	>400	1	0
6	>1600	<800	>400	340 (272–425)	>400	3	0
8	>1600	<800	>200	132 (88–198)	>200	3	
12	>1600	<800	>400	220 (105–462)	>400	3	63
15	270 ip[h]		>800	260 (220-307)	>400	2	100
20	>1000	~500	>400	310 (227-356)	>400	3	0
22	1690	750 (581–958)	185[l] (170–202)	112 (101–124)	>240	1	38
23	>1200	1200 (500–2880)	280 (230–342)	260 (216–315)	>400	2	38
24	1450		>800	240 (191–306)	>400	5	13
25	>1600	565 (479–667)	52 (26–104)	27 (18–30)	>200	1	
26	1000	415 (319–540)	195[m] (160–238)	43.5 (30–62)	>400	3	0
27	>1600	<800	94 (73–149)	<200	>400	3	100
28	>1000		>400	280 (226–327)	>400	5	0
30	>800	<800	250 (227–295)	49 (20–118)	>200	3	50
32	>800		>400	175 (154–200)	>400	5	0
33	>1600	<800	315 (258–348)	<400	>400	3	40
38	595 ip		>800	505 (481–530)	>400	2	
39	410 ip[h]	700 (468–756)	>800[n]	296 (248–355)	>400	1	59
41	>1600	<800	>400	335 (211–533)	>400	3	71
42	>1600	>1600	>400	290 (234–360)	>400	1	59
48	<1600	<800	200 (141–284)	24.5 (17–36)	>200	1	100
50	>1000	280 (222–353)	90 (69–117)	105 (88–126)	>200	3	100
52	<400		>200	50 (40–63)	>200	5	67
53	1350 ip		>400	225 (188–269)	>400	3	60
54	600 ip		870 (725–1044)	251 (198–319)	>400	3	67
56	>2000	520 (260–1050)	>400	165 (131–208)	>400	3	50
60	>1600	<800	125 (106–148)	98 (78–113)	>200	1	0

[a] Oral administration unless otherwise indicated. [b] Pentylenetetrazole threshold seizure pattern test. [c] Maximal electroshock seizure pattern test. [d] Strychnine lethality test. [e] Peak activity time. [f] *d*-Amphetamine aggregation test. [g] R = phenyl [N. N. Mel'nikov and V. A. Kraft, *J. Gen. Chem. USSR*, **26**, 227 (1956); *Chem. Abstr.*, **50**, 13812 (1956)]. [h] Administered in Carbowax. [i] R = benzyl [J. Jolivet, *Ann. Chim.* (Paris), **5**, 1165 (1960)]. [j] Maximal pentylenetetrazole seizure pattern test (MMS): ED_{50} = 51 (38–68) mg/kg. [k] MMS: ED_{50} = 36 (23–56) mg/kg. [l] MMS: ED_{50} = 19 (15–24) mg/kg. [m] MMS: ED_{50} = 7.6 (6–9) mg/kg. [n] MMS: ED_{50} = 200 (143–280) mg/kg.

indicated, tests were performed at times of peak activity as determined during toxicity studies.

Determinations were made of 24-hr toxicities, using groups of ten mice at each dose level, of anticonvulsant activity against electroshock and pentylenetetrazole,[4] and of ability to protect against strychnine lethality[5] and amphetamine aggregation lethality,[6] the dose used in the latter test being the same as that in the strychnine test in nearly all cases. Representative compounds were also screened for analgetic[7] and antiemetic[8] activity.

Acknowledgment.—We are indebted to Dr. J. P. Heeschen, of the Chemical Physics Laboratory, The Dow Chemical Co., for determination and interpretation of nmr spectra.

(4) E. A. Swinyard, W. C. Brown, and L. S. Goodman, *J. Pharmacol. Exptl. Therap.*, **116**, 319 (1952).

(5) L. C. Weaver, W. R. Jones, and T. L. Kerley, *Arch. Intern. Pharmacodyn.*, **143**, 119 (1963).

(6) L. C. Weaver and T. L. Kerley, *J. Pharmacol. Exptl. Therap.*, **135**, 240 (1962).

(7) L. C. Weaver and B. E. Abreu, *J. Am. Pharm. Assoc., Sci. Ed.*, **49**, 298 (1960).

(8) R. W. Begley, W. R. Jones, and L. C. Weaver, *Arch. Intern. Pharmacodyn.*, **129**, 236 (1960).

Hypotensive Quaternary Ammonium Salts with a Guaiacol or Thymol Residue

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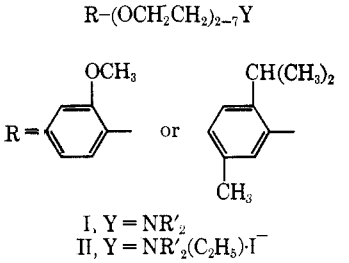
In a previous paper[1] we described a series of basic ethers of guaiacol and thymol with a polyoxyethylenic chain (I), some of which showed considerable antitussive activity; in addition, in almost all of the compounds of that series, we recorded hypotensive properties of short duration, probably originating in a direct action on the myocardium or the peripheral vasodilation. Quaternary ammonium salts often show a pronounced activity on neuromuscular or ganglionic transmission, which accounts for their properties of lowering blood pressure; this prompted us to transform the basic ethers previously described into quaternary ammonium salts (II), in order to see if the hypotensive activity of the former was enhanced.

The description of the new compounds, listed in Table I, and their pharmacological evaluation are the subject of the present note.



I, Y = NR'_2

II, Y = $NR'_2(C_2H_5)\cdot I^-$

Experimental Section

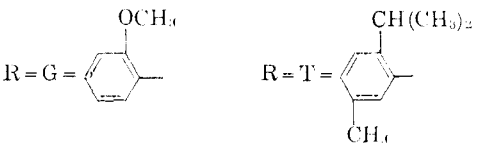
Where analyses are indicated only by symbols of the elements analytical results obtained for those elements were within ±0.4% of the theoretical values.

(1) M. Carissimi, A. Cattaneo, R. D'Ambrosio, V. De Pascale, E. Grimelli, E. Milla, and F. Ravenna, *J. Med. Chem.*, **8**, 542 (1965).

TABLE I

ETHIODIDES OF BASIC ETHERS OF GUAIACOL AND THYMOL

$R(OCH_2CH_2)_nNR'_2C_2H_5\cdot I^-$



No.	R	n	NR'_2	Formula[a]	Method	Yield, %
1	G	2	$N(C_2H_5)_2$	$C_{17}H_{30}INO_3$	A	67[b,c]
2	T	2	$N(C_2H_5)_2$	$C_{20}H_{36}INO_2$	A	73[c]
3	G	3	$N(C_2H_5)_2$	$C_{19}H_{34}INO_4$	B	75
4	T	3	$N(C_2H_5)_2$	$C_{22}H_{40}INO_3$	A	69[d]
5	G	4	$N(C_2H_5)_2$	$C_{21}H_{38}INO_5$	B	87
6	T	4	$N(C_2H_5)_2$	$C_{24}H_{44}INO_4$	B	69
7	G	5	$N(C_2H_5)_2$	$C_{23}H_{42}INO_6$	B	78
8	T	5	$N(C_2H_5)_2$	$C_{26}H_{48}INO_5$	B	79
9	G	6	$N(C_2H_5)_2$	$C_{25}H_{46}INO_7$	B	81
10	T	6	$N(C_2H_5)_2$	$C_{28}H_{52}INO_6$	B	80
11	G	7	$N(C_2H_5)_2$	$C_{27}H_{50}INO_8$	B	77
12	T	7	$N(C_2H_5)_2$	$C_{30}H_{56}INO_7$[e]	B	82
13	G	2	Piperidino	$C_{18}H_{30}INO_3$	B	81
14	T	2	Piperidino	$C_{21}H_{36}INO_2$	B	91
15	G	3	Piperidino	$C_{20}H_{34}INO_4$[f]	B	95
16	T	3	Piperidino	$C_{23}H_{40}INO_3$	B	92
17	G	4	Piperidino	$C_{22}H_{38}INO_5$	B	94
18	T	4	Piperidino	$C_{25}H_{44}INO_4$	B	89
19	G	5	Piperidino	$C_{24}H_{42}INO_6$	B	93
20	T	5	Piperidino	$C_{27}H_{48}INO_5$	B	90
21	G	6	Piperidino	$C_{26}H_{46}INO_7$	B	91
22	T	6	Piperidino	$C_{29}H_{52}INO_6$[g]	B	90
23	G	2	Morpholino	$C_{17}H_{28}INO_4$	B	50
24	T	2	Morpholino	$C_{20}H_{34}INO_3$[h]	B	32
25	G	5	Morpholino	$C_{19}H_{32}INO_5$	B	80
26	T	3	Morpholino	$C_{22}H_{38}INO_4$	B	73
27	G	4	Morpholino	$C_{21}H_{36}INO_6$	B	87
28	T	4	Morpholino	$C_{24}H_{42}INO_5$	B	79
29	G	2	Pyrrolidino	$C_{17}H_{28}INO_3$	B	96
30	T	2	Pyrrolidino	$C_{20}H_{34}INO_2$	B	95
31	G	3	Pyrrolidino	$C_{19}H_{32}INO_4$	B	72
32	T	3	Pyrrolidino	$C_{22}H_{38}INO_3$	B	87
33	G	4	Pyrrolidino	$C_{21}H_{36}INO_5$	B	93
34	T	4	Pyrrolidino	$C_{24}H_{42}INO_4$	B	86
35	G	2	4-Methylpiperazino	$C_{20}H_{36}I_2N_2O_3$	C	68
36	T	2	4-Methylpiperazino	$C_{23}H_{42}I_2N_2O_2$[i]	C	81[j]
37	G	3	4-Methylpiperazino	$C_{22}H_{40}I_2N_2O_4$	C	66
38	T	3	4-Methylpiperazino	$C_{25}H_{46}I_2N_2O_3$	C	60
39	G	4	4-Methylpiperazino	$C_{24}H_{44}I_2N_2O_5$[k]	C	86
40	T	4	4-Methylpiperazino	$C_{27}H_{50}I_2N_2O_4$	C	65

[a] Melting points were determined in a capillary tube and are not corrected. [b] Mp 94° from *i*-PrOH. [c] Mp 109° from *i*-PrOH–Et_2O. [d] Mp 66–68° (washed many times with ether). [e] I: calcd, 18.95; found, 18.46. [f] I: calcd, 26.47; found, 25.94. [g] I: calcd, 19.90; found, 20.35. [h] I: calcd, 27.38; found, 26.89. [i] Mp 163° from *i*-PrOH. [j] I: calcd, 40.12; found, 40.65. [k] I: calcd, 36.55; found, 37.17. [l] All compounds were analyzed for I, N.

Methods A and B.—The amine was dissolved with cooling in the same volume of EtI and, after standing 24 hr in the dark at room temperature, dry ether was added to the solution. Sometimes a solid precipitated (method A). This was filtered, washed with ether, and recrystallized. In most cases, however, an oil separated (method B) which was repeatedly slurried with ether and dissolved in 10 vol of acetone. After filtering with charcoal the solution was evaporated, yielding the quaternary salt as a clear water-soluble oil, which was dried at 60° (1 mm).

Method C.—The amine (5 mmoles), 5 ml of EtI, and 50 ml of dry MeOH were refluxed for 16 hr, after which time the solution was evaporated to dryness. The oily residue was slurried repeatedly with dry ether and dissolved in 20 ml of a saturated solution of $NaHCO_3$. This solution was extracted five times with 5 ml ($CHCl_3$) and evaporated at 35° (13 mm) to give a semisolid residue, from which the mineral salts were eliminated by extracting ing with 20-ml portions of hot *i*-PrOH and filtering from insoluble material. After evaporation of the solvent the oily quaternary salt was checked for the presence of mineral residue and extracted with *i*-PrOH until it was pure.