3-Substituted 9-Methyl-3,9-Diazabicyclo[3.3.1]nonanes

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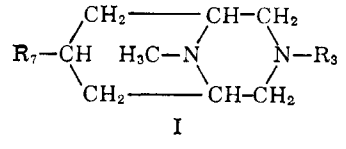
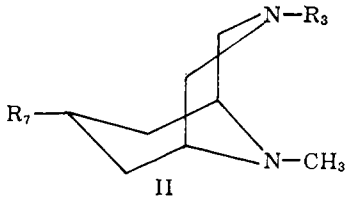
A variety of 3-substituted 9-methyl-3,9-diazabicyclo[3.3.1]nonanes was synthesized. 2,6-Lutidine was used as the starting material in the preparation of the requisite intermediates. In a similar sequence, chelidamic acid was transformed into 3-benzyl-7-methoxy-9-methyl-3,9-diazabicyclo[3.3.1]nonane. The compounds were selected on the basis of potential pharmacological actions.

Recently, Rubtsov and associates[2-5] have reported a series of 3,9-diazabicyclo[3.3.1]nonane derivatives. Quaternary salts of certain α,ω-bis[9-methyl-3,9-diazabicyclo[3.3.1]nonan-3-yl] alkanes were found to exhibit neuromuscular blocking activity resulting from depolarization at the motor end-plate. The publications of the Soviet group have constrained us to report our synthetic work on 3-substituted 9-methyl-3,9-diazabicyclo[3.3.1]nonanes. Although the entire program was completed some time prior to the appearance of the contributions cited,[2-5] intervening circumstances precluded our compilation of data until this time.

Prior to the time when our investigation of 3,9-diazabicyclo[3.3.1]nonane derivatives was begun, that ring system had received little attention.[6,7] This was surprising, for the possibilities of pharmacological activity inherent in such 2,6-trimethylenepiperazines appeared to be considerable. In addition to resemblance to the piperazines and to piperidines, stereochemical considerations of the structure evoked our attention. The 3-substituted 9-methyl-3,9-diazabicyclo[3.3.1]nonanes were chosen for synthesis because of similarity or relation to compounds known to have valuable pharmacological actions, *viz.*, 4-substituted 1-methylpiperazines, 1-substituted piperidines, and the pomegranate alkaloids. A considerable number of compounds was prepared in this program; in addition to a variety of 3-substituted 9-methyl-3,9-diazabicyclo-[3.3.1]nonanes, 3-benzyl-7-methoxy-9-methyl-3,9-diazabicyclo[3.3.1]nonane also was synthesized. Structures



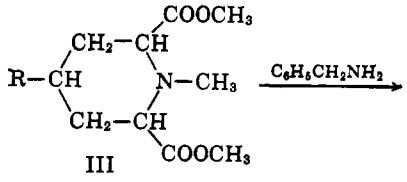
I



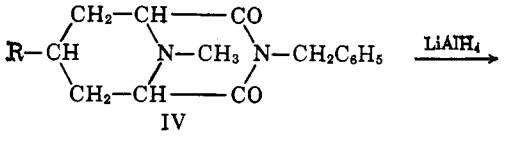
II

I and II show the planar and spatial aspects of the ring system investigated.

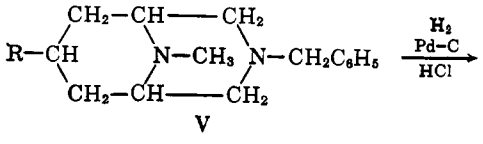
The scheme which we followed in the synthesis of the 9-methyl-3,9-diazabicyclo[3.3.1]nonanes was that reported by Barnes and Fales,[7] and which Rubtsov, *et al.*,[2] have also employed. It consisted of the preparation of the appropriate dimethyl 1-methyl-piperidine-2,6-dicarboxylate, conversion to the N-benzylimide, which was then reduced by lithium aluminum hydride to the 3-benzyl-9-methyl 3,9-diazabicyclo[3.3.1]nonane, which was then debenzylated. These steps are shown as III–VI, and are based on *cis* structures for III, after the remarks of Barnes and Fales.[7] The synthesis was readily adaptable to large-scale operations, as indicated in the Experimental. In agreement with Rubtsov, *et al.*,[2a] we found that rapid removal of methanol was desirable in the conversion of III to IV (R = H), but this was difficult in large batches. An over-all yield of 18.5–23% of 9-methyl 3,9-diazabicyclo[3.3.1]nonane was obtained from 2,6-lutidine. The series of transformations from chelidamic acid to 3-benzyl-7-methoxy methyl-9-methyl 3,9 - diazabicyclo[3.3.1]nonane gave only 16.4% yield. A particular cause for this low yield lay in the step proceeding from III to IV (R = OCH_3), for in this reaction there was always a considerable yield of the diamide, VII.



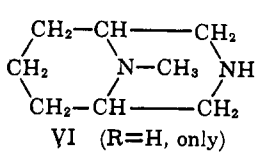
III



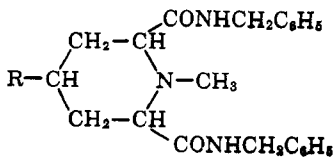
IV



V



VI (R=H, only)



VII (R = H, or OCH_3)

In Table I there have been assembled the 9-methyl 3,9-diazabicyclo[3.3.1]nonanes having an alkyl-type group in position 3. The substituents were chosen on

(1) Nalco Chemical Co., Chicago 38, Ill., to whom inquiries should be directed.

(2) E. S. Nikitsaya, V. S. Usovskaya, and M. V. Rubtsov, *Zh. Obshch. Khim.*, (a) **30**, 3306 (1960); (b) **31**, 3202 (1961); (c) **32**, 2886 (1962).

(3) M. V. Rubtsov, M. D. Mashkovskii, E. S. Nikitskaya, B. A. Medvedev, and V. S. Usovskaya, *J. Med. Pharm. Chem.*, **3**, 441 (1961).

(4) M. D. Mashkovskii and B. A. Medvedev, *Farmakol. Toksikol.*, **23**, 493 (1960).

(5) B. A. Medvedev, *ibid.*, **25**, 320 (1962).

(6) B. K. Blount and R. Robinson, *J. Chem. Soc.*, 2485 (1932).

(7) R. A. Barnes and H. M. Fales, *J. Am. Chem. Soc.*, **75**, 975 (1953).

TABLE I

3-ALKYL 9-METHYL-3,9-DIAZABICYCLO[3.3.1]NONANES

3-Substituent	Base or salt[a]	Yield, %[b]	Appearance[c]	Solvent[d]	M.p., °C.[e]	Analyses Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
Methyl[w]	2H	84.5	Needles	E	294–296 dec.[w]	47.58	8.87	31.21[f]	47.60	8.63	31.43[f]
Allyl	B	76.5	Col. liquid	(1.4950)	[55–57 (0.03)]			15.54[g]			15.47[g]
	C	96	Flakes	E–Eo	123.5–124.5 int.	54.82	7.58	7.52	54.92	7.48	7.57
Propargyl	C	83.5	Cryptocryst.	E	135 int.	51.9[h]	123.4[i]	7.57	51.53[h]	122.0[i]	7.43
Carbethoxymethyl	C	87.5	Platelets	M–Eo	107–109	51.66	7.23	6.70	51.71	7.34	6.38
(Carbo-2-diethylaminoethoxy)-methyl	B	65.5	Col. liquid	(1.4849)	[113–115 (0.02)]	64.61	10.51	14.13[g]	64.66	10.31	13.88[g]
Diethylcarbamylmethyl	B	84.5	Straw oil	(1.5000)	[100–103 (0.02)]			11.06[g]			10.92[g]
	P	89.5	Cryptocryst.	E–Eo	172–174				52.9[h]		47.2[j]
2-Hydroxyethyl	C	84.5	Cryptocryst.	E–Eo	114–116 int.	51.05	7.50	7.44	51.10	7.54	7.16
2-Methylmercaptoethyl	C	68:90	Cryptocryst.	E	137–138 int.	7.89[k]		6.89	8.08[k]		6.85
2-Dimethylaminoethyl[x]	3H	86	Rosettes, needles	E–Eo	236–237 dec.	44.93	8.80	33.17[f]	44.87	8.92	32.97[f]
	2Mb	76.5	Rods	E–Eo	276 dec.	39.84[f]		10.46	39.6[f]		10.24
3-Hydroxypropyl[x]	C	85	Needles	E–Eo	93–95 int.	52.29	7.75	7.18	52.05[l]	7.55	6.89[l]
3-(3,4,5-Trimethoxybenzoyl)-oxypropyl	C	83	Cryptocryst.	P–Eo	103–107 int.	55.47	6.90	4.79	55.56	6.98	4.69
3-Dimethylaminopropyl	B	88.5[m]	Col. liquid		[69–70 (0.08)]			18.65[g]			18.49[g]
	3C	76.5	Needles	P	232–233 dec.[n]	46.64	9.03	31.78[f]	46.83	8.90	31.56[f]
	2Mb	78	Microcryst.	E–Eo	282–283 dec.	43.38	8.01	10.12	43.31[o]	8.11	9.95[g]
4-Nitrobenzyl	B	72.5	Yellow needles	[p]	72–73	11.62[g]		10.17[g]	11.90[g]		10.08[g]
	C	88.5	Maize solid	[p]	178–179 int.	53.95	6.25	8.99	53.90	6.11	9.03
2,4-Dichlorobenzyl	B	74	Needles	[r]	63–64			9.36[g]			9.24[g]
	2H	89.5	Microcryst.	E–Eo	192–193 int.	19.01[f]		7.55	18.54[f,s]		7.48[s]
2-Chlorobenzohydryl	B	61	Yellow oil	(1.5942)	[90(3–4 μ)]	73.99	7.39	10.40[f]	73.65	7.86	10.24[f]
	C	81.5	Plates	E–Pe	112–113 int.	60.84	6.24	6.65[f]	60.67	6.31	6.49[f]
4-Chlorobenzohydryl	C	64.5	Cubic	E–Eo	113–115 int.	60.84	6.24	6.65[f]	60.84	6.31	6.45[f]
4-Butylmercaptobenzohydryl	C	58	Flakes	E	93–95 int.	63.46	7.22	4.78[g]	63.23[t]	7.46[t]	4.55[g,t]
2-(3,4,5-Trimethoxyphenyl)-ethyl	B	88.5	Straw col. liquid		[150–152 (0.01)]			8.38[g]			8.20[g]
	C	73	Microcryst.	E–A	144.5–146.5 int.	57.02	7.27	5.32[g]	56.61	7.25	5.28[g]
2-(4-Methyl-1-piperazinyl)ethyl	2 Mec	54.5	Prisms	E	194–195 dec.	52.25	5.75	8.41	52.49	5.75	8.28
3-(4-Carbethoxy-1-piperazinyl)-propyl	B	91[v]	Golden oil	(1.5074)	[v]	12.42[g]	9.45[u]	16.56	12.29[g]	9.80[u]	16.41
	4P	82.5	Prisms	E	181–182 dec.	29.60	6.35	53.67[h]	29.41	6.21	53.5[g]
2-(9-Carbazoyl)ethyl	B	74	Needles	E	115–117			12.99			12.64
	2H	86.5	Needles	E–Eo	239–240 dec.	17.45[f]		10.34	17.24[f]		10.35
1-Hydroxy-1,2,3,4-tetrahydro-2-naphthyl	B	79.5	Cryptocryst.	H	146.5–147.5			9.77[g]			9.63[g]
	C	63	Prisms	E	143–145 int.	60.23	7.16	5.86	60.23	7.21	5.56

[a] B, base; C, dihydrogen citrate; H, hydrochloride; 2H, dihydrochloride; 3H, trihydrochloride; 2Mb bis(methobromide); 2Mec, dimeconate; P, phosphate; 4P, tetraphosphate. [b] Purified products. When only a salt is listed, over-all yield is given. [c] Compounds were white unless otherwise stated. [d] Legend: A, acetone; B, benzene; Ch, cyclohexane; Eo, ether; H, hexane; Hp, heptane; M, methanol; P, 2-propanol; Pe, pentane; T, toluene. Numbers in parentheses refer to $n^{25}D$ of liquids. [e] dec. and int. indicate melting with decomposition or intumescence, respectively. Numbers given in brackets indicate boiling points (pressures) of bases which were distilled. [f] Halogen. [g] Basic nitrogen.[10] [h] Acid, %. [i] Neutral equivalent. [j] Base, %. [k] Sulfur. [l] Dry basis, corrected for 0.22% water. [m] Isolated from trishydrochloride; formed carbonate while refractive index was being done. [n] Evacuated capillary. [o] Dry basis, corrected for 1.75% water. [p] Obtained pure directly on isolation. [q] Oxygen. [r] Distilled, b.p. 90–92° (2 μ). [s] Dry basis, corrected for 1.8% alcohol content. [t] Predried samples used; original contained 1.04% water (K. Fischer method). [u] Oxygen. [v] Isolated from pure tetraphosphate; not distilled. [w] Reported by Rubtsov, *et al.* (ref. 2a), m.p. 275–276°. [x] Base described by Rubtsov, *et al.* (ref. 2a).

the basis of interesting profiles of pharmacological activity exhibited by related piperazines. Ordinarily, these were made by interaction of VI with an appropriate halide, but the 3,9-dimethyl compound was prepared by reductive alkylation of VI, and a Mannich reaction was used for the 3-(3-indolylmethyl) derivative. Of the series, only those having the 3-R group as methyl, 2-dimethylaminoethyl, and 3-hydroxypropyl were reported in the work of Rubtsov, *et al.*[2,3]

Table II lists various compounds prepared from VI in which the 3-substituent deprived the nitrogen in that position of its basic character. As in other instances, the choice was made on presumptions of pharmacological activity. Interestingly, none of this group of urea, thiourea, and amide types was reported by the Russian investigators.[2] The compounds were prepared by standard methods. 9-Methyl-3-phenylazo-3,9-diazabicyclo[3.31]nonane, not included in Table II, was made from VI and benzenediazonium chloride.

In addition to this compound, two examples of 3-aryl-9-methyl-3,9-diazabicyclo[3.3.1]nonanes were synthesized. This was achieved by reaction of III with aniline or with 3-chloro-4-methylaniline, then by reduction of the N-arylimide with lithium aluminum hydride. The yields were moderate.

Further, chelidamic acid was converted to dimethyl 4-methoxy-1-methylpiperidine-2,6-dicarboxylate (III, R = OCH_3), and thence to 3-benzyl-7-methoxy-9-methyl-3,9-diazabicyclo[3.3.1]nonane (V, R = OCH_3), in poor yield. The diamide VI (R = OCH_3) was a co-product in the synthesis.

Experimental[8]

A. 9-Methyl-3,9-diazabicyclo[3.3.1]nonane.—2,6-Lutidine was oxidized in 5-mole batches with potassium permanganate[9]; the yields of **dipicolinic acid** were 82–86%. The dipicolinic acid was converted to the **dimethyl ester** in 89–94% yield by the procedure of Barnes and Fales.[7] It was found to be expedient to reduce 2-mole batches of dimethyl dipicolinate with Raney nickel in methanol at 1700–2000 p.s.i. and 80° and then at once reductively methylate the filtered solution with formalin in the presence of 10% palladium on charcoal at 1200–1600 p.s.i. and

(8) All melting points are corrected values, whereas boiling points are uncorrected. Analyses were done in the Analytical Laboratories of this institute, under the direction of M. E. Auerbach and K. D. Fleischer.

(9) G. Black, E. Depp, and B. B. Corson, *J. Org. Chem.* **14**, 17 (1949).

TABLE II

3-SUBSTITUTED 9-METHYL-3,9-DIAZABICYCLO[3.3.1]NONANES

3-Substituent	Base or salt[a]	Yield, %[b]	Appearance[c]	Solvent[d]	M.p., °C.[e]	Analyses: Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
Carbamyl	B	74.5	Plates	T	177–178	58.99	9.35	22.93	58.88	9.34	22.82
Carbethoxy	B	81.5	Col. liquid	(1.4910)	[81–82 (0.5)]			6.52[f]			6.58[f]
	C	91.5	Amorphous	E–Eo	*ca.* 121 dec.	50.49	6.98	6.93	50.55	7.26	6.70
Diethylcarbamyl	C	74	Cryptocryst.	P–Eo	144–146 int.	52.89	7.71	9.73	52.72	7.38	9.49
Allylthiocarbamyl	C	69.5	Cryptocryst.	E; M	*ca.* 80–85 int.	7.43[g]		9.74	7.33[g]		9.53
Ethanesulfonyl	B	82	Needles	Pe	66–67	6.03[f]		12.06	6.07[f]		12.03
Dimethylsulfamyl	H	60.5	Needles	P	247.5–249 dec.	12.49[h]		14.81	12.61[h]		14.69
4-Methylphenylsulfonyl	B	88.5	Prisms	Hp	126–129			4.74[f]			4.68[f]
	C	92	Spherules	'	88–90 int.	6.59[g]		5.76	6.65[g]		5.64
4-Methoxyphenylsulfonyl	B	79.5	Blades	Hp	142.5–143.5	10.33[g]		9.03	10.50[g]		8.88
4-Chlorobenzylthiocarbamyl	B	78	Microcryst	B–Pe	144.5–145.5	9.91[g]		12.97	10.04[g]		12.73
4-Chlorobenzohydrylcarbamyl	B	86.5	Cryptocryst.	B	190–192			10.94			10.66
	C	78.5	Cryptocryst.	E–Eo	169.5–171 int.	22.22[j]		7.29	22.0[j]		7.24
4-Chlorobenzohydrylthiocarbamyl	B	93	Needles	Ch	114–115; 142–144[k]	3.50[f]		10.51	3.43[f]		10.38
	C	78	Microcryst.	E–Eo	140 dec.[l]	5.99[h]		7.10	6.09[h]		6.94
4-Butylmercaptobenzohydrylthiocarbamyl	B	87	Needles	Ch	85–87	68.85	7.78	3.09[f]	69.21	7.48	3.28[f]
	C	92	Amorphous	P–Eo	143–145 int.	9.93[g]		6.51	9.76[g]		6.32
4-Amino-2-methyl-6-quinolylthiocarbamyl	B	88.5	Rods	B	210–212	9.01[g]		7.87[f]	8.84[g]		7.85[f]
	P	97	Lemon microneedles	A	229.5–231 dec.				38.9[m]		60.2[n]

[a–e] See footnotes, Table I. [f] Basic nitrogen.[10] [g] Sulfur. [h] Halogen. [i] Obtained pure directly. [j] Oxygen. [k] Double melting point. [l] Instantaneous decomposition point. [m] Acid, %. [n] Base, %.

50°. The yield of distilled [99–101° (0.6 mm)] **dimethyl scopolinate** thus obtained from dimethyl dipicolinate amounted to 81–85%.

The method of Barnes and Fales[7] for the conversion of dimethyl scopolinate to **N-benzylscopolinimide**, and thence to 9-methyl-3,9-diazabicyclo[3.3.1]nonane, was modified for large scale operation. A mixture of 900.0 g. (4.2 moles) of dimethyl scopolinate and 1110 g. (10.2 moles) of benzylamine was heated (Glas-col mantle) at gentle reflux, with stirring, for 24 hr. At the end of this time, internal temperature was 120°. The mixture was then subjected to distillation, at atmospheric pressure, until the temperature of the liquid reached 140°. Refluxing was resumed for 24 hr., and then distillation carried out until the reaction mixture was at 200–205°. Some 500 g. of distillate was obtained totally. The golden, treacly residue often solidified on cooling, and it was expedient to transfer it to a beaker. The residue was extracted several times, using 3 l. of boiling hexane each time. Finally, the insoluble material (mostly N,N′-dibenzylisoscopolindiamide) was extracted in a Soxhlet apparatus with hexane, and the liquors were concentrated. N-Benzylscopolinimide was obtained in the form of white needles, m.p. 113–115° [lit. m.p. 113–115°,[2a] m.p. 116–118°[7]] in 50–53% yields (542–573 g). A sample was converted into the hydrochloride in ethanol solution; it separated from ethanol–ether as fine white needles, m.p. 209.5–210.5° dec.

Anal. Calcd. for $C_{15}H_{18}N_2O_2 \cdot HCl$: N, 9.51; Cl, 12.03. Found: N, 9.59; Cl, 12.04.

N-Benzylscopolinimide (3-benzyl-2,4-dioxo-9-methyl-3,9-diazabicyclo[3.3.1]nonane) was reduced with lithium aluminum hydride in more concentrated solution than reported by Barnes and Fales[7] (*cf.* ref. 2a). The imide (138.0 g., 0.53 mole) was added gradually to a well stirred suspension of lithium aluminum hydride (43.5 g.) in pure anhydrous ether (3 l.), under reflux. After stirring at room temperature (*ca.* 25°) for 72 hr., the excess of reducing agent was destroyed with 250 cc. of absolute ethanol, added during 1 hr.; it was followed by 1 l. of 35% sodium hydroxide to dissolve the salts. The layers were separated; aqueous phase was extracted well with ether; and ether solutions were united, dried, and concentrated. **3-Benzyl-9-methyl-3,9-diazabicyclo[3.3.1]nonane** was obtained as a bright golden oil of 92–94% purity based on titration for basic nitrogen by the method of Toennies and Callan[10] in yields of 90–95%. It was satisfactory for debenzylation without purification. A dihydrogen citrate was prepared readily in ethanol solution; it crystallized from ethanol–ether in the form of creamy platelets, m.p. 128–130°, with intumescence.

Anal. Calcd. for $C_{15}H_{22}N_2 \cdot C_6H_8O_7$: C, 59.70; H, 7.16; N, 6.63. Found: C, 59.60; H, 7.00; N, 6.44.

A Pfaudler-type autoclave was used in the debenzylation of 400 g. (1.59 moles) of 92% pure 3-benzyl-9-methyl-3,9-diazabicyclo[3.3.1]nonane in 19 l. of ethanol and 690 ml. of concentrated hydrochloric acid in the presence of 100 g. of 10% palladium-on-charcoal. Reduction was run at 46 p.s.i., 27°; 0.5 hr. was required for uptake of the theoretical amount of hydrogen. The catalyst was filtered off, washed with 8 l. of hot water, and then all liquors were concentrated *in vacuo* until a thick paste resulted.

Absolute ethanol (800 ml.) was added to the residue and the mixture refluxed to effect solution, then chilled at +2° for 3 days. The white, microcrystalline **9-methyl-3,9-diazabicyclo[3.3.1]nonane dihydrochloride** which separated (273.0 g., 81% yield) was of analytical purity as obtained; m.p. >300° (*cf.* ref. 2a and 7).

Anal. Calcd. for $C_8H_{16}N_2 \cdot 2HCl$: C, 45.08; H, 8.51; Cl, 33.27. Found: C, 45.04; H, 8.31; Cl, 33.6.

The base VI was readily obtained from the salt with a recovery of 99% of viscous, golden oil (*cf.* ref. 2a). Ordinarily, the base was not stored as such; however, benzene solutions of it were stable if kept under nitrogen. It formed a solid carbonate if this precaution were not observed.

B. Other Intermediates.—The following compounds were prepared by procedures essentially as reported in the literature: N,N-diethyl chloroacetamide,[11] 2-methylmercaptoethyl bromide,[12] *o*- and *p*-chlorobenzohydryl chlorides,[13,14] 2-bromo-1-tetralol,[15] 1-(2-chloroethyl)-4-methylpiperazine,[16] 9-(2-chloroethyl)carbazole,[17] 4-chlorobenzyl isothiocyanate,[18] dimethyl sulf-

(10) G. Toennies and T. P. Callan, *J. Biol. Chem.*, **125**, 259 (1938).

(11) S. A. Farmaceutici Italia, British Patent 745,028.

(12) E. Schneider, *Chem. Ber.*, **84**, 911 (1951).

(13) K. E. Hamlin, A. W. Weston, F. E. Fischer, and R. J. Michaels, Jr., *J. Am. Chem. Soc.*, **71**, 2732 (1949).

(14) J. F. Norris and J. T. Blake, *ibid.*, **50**, 1811 (1928).

(15) J. von Braun and G. Kirschbaum, *Chem. Ber.*, **54**, 611 (1921).

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amyl chloride,[19] 4-methoxyphenylsulfonyl chloride,[20] and 3,4,5-trimethoxybenzoyl chloride.[21]

The synthesis of **2-(3,4,5-trimethoxyphenyl) ethyl bromide** was carried out as a composite of several procedures used for the preparation of mescalin; much of the background literature lacked information on yields. Since the completion of this work, Major and Ohly[22] have reported a good method for preparation of 2-(3,4,5-trimethoxyphenyl)ethyl chloride. 2,6-Dimethoxyphenol was subjected to the Lederer-Manasse reaction as described by Jensch[23] and a 68.5% yield of 3,5-dimethoxy-4-hydroxybenzyl alcohol resulted; blades from ethyl acetate, m.p. 132–133°. The phenol was methylated by the action of methyl iodide and sodium ethoxide.[24] An 88% yield of 3,4,5-trimethoxybenzyl alcohol was obtained as a viscous oil, b.p. 132–134° (0.4 mm). The chloride was made by the action of hydrogen chloride on the alcohol in pentane at −5° to 0° (*cf.* ref. 25). A 78% yield of 3,4,5-trimethoxybenzyl chloride resulted; it separated from cyclohexane as leaflets, m.p. 58–60°. The nitrite was formed by the procedure described by Jensch[24]; the product (67.5% yield) crystallized from aqueous ethanol as needles, m.p. 74–76°. 3,4,5-Trimethoxyphenylacetic acid was made in 88.5% yield by alkaline hydrolysis of the nitrile, following aspects of work of Dankova, *et al.*[26] The compound (m.p. 118.5–120°) has been described by Slotta and Müller.[27] Reduction of the acid to 2-(3,4,5-trimethoxyphenyl) ethanol was effected by a procedure using lithium aluminum hydride (*cf.* ref. 28). 3,4,5-Trimethoxyphenyl acetic acid (36.0 g., 0.16 mole) was placed in a thimble of a Soxhlet apparatus wherein the flask contained 9.0 g. (0.23 mole) of 95% lithium aluminum hydride in 1.2 l. of absolute ether. The mixture was refluxed for 3 hr., cooled, then 100 ml. of water was added cautiously, followed by 360 ml. of 10% sodium hydroxide. The ether layer was separated, and the aqueous phase extracted well. A reddish oil remained after removing the solvent from the dried extracts; this was distilled at *ca.* 1 μ (bath, 115–120°) to obtain 31.5 g. (92%) of colorless, viscous oil; $n^{25}D$ 1.5365. This compound has been reported by Slotta and Müller.[27]

Anal. Calcd. for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.55; H, 7.71.

The conversion of the alcohol to the bromide was similar to a scheme used in another type of Reid, *et al.*[29] Thirty grams (0.14 mole) of 2-(3,4,5-trimethoxyphenyl)ethanol was dissolved in a mixture of 140 ml., each, of dry chloroform and ether, and a solution of 13.5 g. (0.15 mole) of phosphorus tribromide in 70 ml. of dry ether was added. The mixture was set aside overnight in a flask topped with a drying tube, and then it was washed with saturated salt solution, half-saturated sodium bicarbonate solution, and water. It was dried over sodium sulfate and distilled at 1 μ (bath 92–96°) to give **2-(3,4,5-trimethoxyphenyl)ethyl bromide** as a colorless fluid, $n^{25}D$ 1.5553. The yield was 29.7 g. (76.5%).

Anal. Calcd. for $C_{11}H_{15}BrO_3$: Br, 29.05. Found: Br, 28.84.

4-Butylmercaptobenzohydryl chloride was reported and used in a recent patent;[30] however there were neither preparative details nor physical constants of the compound. Butyl phenyl sulfide was made by the procedure of Ipatieff, *et al.*,[31] and was converted to 4-butylmercaptobenzophenone by a Friedel–Crafts reaction,[30] and then reduced by zinc and caustic[32] to give a 94% yield of the benzohydrol. A mixture comprised of 71.9 g. (0.265 mole) of 4-butylmercaptobenzohydrol, 190 ml. of hexane, 100 ml. of benzene and 75 g. of calcium chloride was chilled to −10°; then a stream of dry hydrogen chloride was conducted through it at −10° to −20° for 2.5 hr. The purplish mixture was stored at +2 to +5° for 3 days, and filtered. The filtrates were concentrated *in vacuo* with a bath temperature not exceeding 40°, and the residual oil (85.2 g.) was fractionated. 4-Butylmercaptobenzohydryl chloride (69.8 g., 91%) was collected as a pale yellow oil, b.p. *ca.* 150° (0.05 mm.), $n^{25}D$ 1.5990.

Anal. Calcd. for $C_{17}H_{19}ClS$: Cl, 12.19; S, 11.02. Found: Cl, 11.94; S, 10.72.

1-Carbethoxy-4-(3-chloropropyl)piperazine was prepared by alkylation of 1-carbethoxypiperazine. Seventy-eight grams (0.4 mole) of the piperazine derivative, in the form of the hydrochloride,[33] was added to a sodium methylate solution made from 9.21 g. (0.4 mole) of sodium and 300 ml. of methanol. The stirred mixture was diluted with 1.2 l. of benzene and 42.4 g. (0.4 mole) of sodium carbonate was added, followed by 188.4 g. (1.2 moles) of 1-bromo-3-chloropropane. The entire mixture was refluxed for 24 hr. with vigorous stirring prior to removal of 1 l. of solvent, meanwhile replacing it with a like volume of fresh benzene. It was mixed with 800 ml. of 15% sodium hydroxide solution, and the aqueous phase extracted with benzene. The combined extracts were shaken out with 6 *N* hydrochloric acid and the acidic liquors concentrated *in vacuo*. Ethanol (500 ml.) was added to the residues, chilled, and the solid collected; the filtrates were taken to near-dryness, the solids united, taken into 400 ml. of water, and made strongly basic. The product was extracted into ether and the dried extracts were fractionated. 1-Carbethoxy-4-(2-chloropropyl)piperazine (60.1 g., 64%) was obtained as a colorless oil, b.p. 87–89° (0.09 mm.), $n^{25}D$ 1.4840.

Anal. Calcd. for $C_{10}H_{19}ClN_2O_2$: N,[10] 5.98. Found: N,[10] 5.97.

4-Chlorobenzohydryl Isocyanate.—A well stirred mixture comprised of 42.6 g. (0.18 mole) of 4-chlorobenzohydryl chloride, 35.0 g. (0.23 mole) of silver cyanate, and *ca.* 0.1 g. of potassium iodide was refluxed in 400 ml. of dry toluene for 16 hr. The hot mixture was filtered and the solid extracted well with fresh solvent. Fractionation of the filtrates afforded 33.5 g. (76.5%) of straw colored oil, b.p. 111–113° (0.02 mm.), $n^{25}D$ 1.5871.

Anal. Calcd. for $C_{14}H_{10}ClNO$: Cl, 14.55; N, 5.75. Found: Cl, 14.39; N, 5.68.

4-Butylmercaptobenzohydryl isothiocyanate was made after the procedure described for the related 4-chloro compound. The yield of emerald green product, which boiled at *ca.* 155–158° (0.02 mm.), was 68.5%; $n^{25}D$ 1.6206.

Anal. Calcd. for $C_{18}H_{19}NS_2$: C, 68.97; H, 6.11; S, 20.46. Found: C, 69.19; H, 5.93; S, 20.53.

4-Amino-2-methyl-6-quinolyl isothiocyanate.—4,6-Diaminoquinaldine[34] (23.2 g., 0.135 mole) was dissolved in a mixture of 13.5 ml. of concentrated hydrochloric acid and 260 ml. of water, then 15.5 ml. of thiophosgene was added. The reaction mixture was allowed to cool to room temperature after 2 hr. of refluxing, and then it was chilled. The crude product was collected, suspended in 300 ml. of ice–water and rendered strongly basic with 35% sodium hydroxide, then set aside for 0.5 hr. prior to filtration. A 96.5% yield of crude, yellow isothiocyanate resulted. The decomposition point varied considerably with rate of heating as well as temperature of immersion, being *ca.* 180° decomposition with intumescence following immersion at 170°. The crude compound was refluxed with 2 l. of benzene for 0.5 hr. and filtered; filtrates were concentrated to *ca.* 300 ml. Upon cooling, rosettes of pale yellow blades separated from the benzene, and these were further crystallized for analysis. There was little change in the behavior on heating.

Anal. Calcd. for $C_{11}H_9N_3S$: N, 19.52; S, 14.89. Found: N, 18.99; S, 14.72.

C. 3-Alkyl-9-methyl-3,9-diazabicyclo[3.3.1]nonanes.—In Table I there have been assembled pertinent data concerning the 3-alkyl 9-methyl-3,9-diazabicyclo[3.3.1]nonanes which were prepared in connection with this work. The first member of the series, 3,9-dimethyl-3,9-diazabicyclo[3.3.1]nonane, was made by a procedure which differed from that used in the other instances, for it was prepared by reductive methylation. 9-Methyl-3,9-diazabicyclo[3.3.1]nonane was dissolved in methanol containing a slight excess of 37% formalin and reduced with use of a 5% palladium–charcoal catalyst at 25° under 1500-p.s.i. hydrogen

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pressure, followed by isolation of the hydrochloride. The preparation of 3-(carbo-2-diethylaminoethoxy) methyl-9-methyl-3,9-diazabicyclo[3.3.1]nonane was also an exception to the general scheme of alkylation. It was made from the 3-carbethoxymethyl compound by heating at 170–175° with 2-diethylaminoethanol hydrochloride for 125 hr. in following a method described by Donleavy and Condit.[35] 9-Methyl-3-[3(3,4,5-trimethoxybenzoyl)oxy]propyl-3,9-diazabicyclo[3.3.1]nonane was obtained by reaction of the alcohol with 3,4,5-trimethoxybenzoyl chloride in benzene.

The other examples were made by reaction of 9-methyl 3,9-diazabicyclo[3.3.1]nonane with the appropriate alkyl halide in the presence of a base. In the case of the more reactive halides, triethylamine was used, and the reactions were done in benzene solution. The greater number of cases were carried out in the presence of sodium carbonate with either toluene or butanol as solvent. There was no advantage, as shown by two comparisons of yields, in the use of an excess of the valuable compound VI. Ordinarily, the reaction mixtures were stirred and refluxed under nitrogen for 10–16 hr., filtered while hot, and stripped of solvent. The residue was then mixed with a little ice–water, excess of 50% sodium hydroxide added, and the product extracted with methylene chloride or benzene, dried, and distilled. In many cases, the crude residues were of sufficient purity to admit of conversion to satisfactory salts without need for prior purification. The greater number of the salts were made in ethanol–ether or propanol-2. In certain instances, the composition of the salts was not clearly stoichiometric, hence analyses were reported on composition in terms of base and acid.

3-(3-Indoyl)methyl-9-methyl-3,9-diazabicyclo[3.3.1]nonane was prepared by a Mannich reaction patterned on the procedure used by Kühn and Stein[36] for gramine types. An ice-cold solution of 9.9 g. (0.07 mole) of 9-methyl-3,9-diazabicyclo[3.3.1]nonane in a like weight of glacial acetic acid was treated with 5.85 g. (0.068 mole) of 37% formalin and then 8.1 g. (0.069 mole) of indole was added with stirring. The indole dissolved rapidly in an exothermic reaction (temperature rose to 43°); however, the mixture was kept at room temperature for 5 days. There was added 25 ml. each of ice–water and 50% sodium hydroxide, and 150 ml. of benzene; the whole was shaken well, the layers were separated, and the aqueous layer further was extracted twice. Extracts were dried by distillation to *ca.* 200 ml., and then refluxed gently while 300 ml. of pentane was added. Warty aggregates of microcrystals resulted; the liquors gave only an oil upon concentration. A crystallization from hexane afforded the pure Mannich base (8.4 g., 46% yield) as clusters of needles, m.p. 147.5–149.5°.

Anal. Calcd. for $C_{17}H_{23}N_3$: C, 75.80; H, 8.61; N,[10] 10.40. Found: C, 76.05 H, 8.64; N[10] 10.22.

D. Other 3-Substituted 9-Methyl-3,9-diazabicyclo[3.3.1]nonanes.—Table II gives the pertinent data on a variety of 3-substituted 9-methyl-3,9-diazabicyclo[3.3.1]nonanes wherein the nitrogen in position 3 has lost its basic character. The 3-carbamyl compound was obtained by reaction of VI with potassium cyanate in dilute acid, similar to a method in the literature (*cf.* ref. 37). All of the other thiourea and urea types listed in the Table were made by reaction of the requisite isothiocyanate (or isocyanate) with 9-methyl-3,9-diazabicyclo[3.3.1]nonane base in benzene, ordinarily using a 3-hr. reflux period. The compounds having a 3-carbethoxy and a 3-diethylcarbamyl grouping were prepared by a procedure closely akin to that used in the piperazine series by Kushner, *et al.*[38] A Schotten-Baumann method in methylene chloride was chosen for the dimethylsulfamyl, 4-methylphenylsulfonyl, and 4-methoxyphenylsulfonyl derivatives shown in Table II. The preparation of 3-ethanesulfonyl-9-methyl-3,9-diazabicyclo[3.3.1]nonane was patterned after one used for certain piperazines.[39]

9-Methyl-3-phenylazo-3,9-diazabicyclo[3.3.1]nonane.—Aniline (6.2 g., 0.067 mole) in dilute hydrochloric acid was diazotized in the usual way and stirred at 0° to +2° while a solution of 14.0 g. (0.066 mole) of 9-methyl-3,9-diazabicyclo[3.3.1]nonane dihydrochloride in aqueous sodium acetate (34 g., 0.25 mole of trihydrate in 50 ml. of water) was added during half an hour. The mixture was kept at 0° for 1 hr., then allowed to warm to 20° during 2 hr., and stored in refrigerator overnight. It was treated in the cold with 35% sodium hydroxide and a reddish brown oil separated; this was taken into ether and dried over potassium carbonate. Removal of the solvent left 14.3 g. (88%) of reddish brown residue which afforded 11.6 g. (71%) of viscous orange oil upon distillation at 7 μ (bath, 110–116°); $n^{25}D$ 1.6208.

Anal. Calcd. for $C_{14}H_{20}N_4$: C, 68.82; H, 8.25; N, 22.93. Found: C, 69.01; H, 8.39; N, 22.84; 22.97.

E. 3-Aryl-9-methyl-3,9-diazabicyclo[3.3.1]nonanes. 9-Methyl-3-phenyl-3,9-diazabicyclo[3.3.1]nonane.—A mixture including 21.5 g. (0.1 mole) of dimethyl scopolinate and 23.3 g. (0.25 mole) of aniline was refluxed gently under nitrogen for 48 hr. It was then steam-distilled to remove excess aniline; residues were extracted with ether and dried (sodium sulfate). A thick, treacly residue remained upon removal of solvent. It was extracted repeatedly with ethanol–hexane to give a whitish solid (m.p. 142–152°) which responded well to crystallization from 80% ethanol (charcoal). The white prisms (9.3 g., 38% yield) of 2,4-dioxo-9-methyl-3-phenyl-3,9-diazabicyclo[3.3.1]-nonane melted at 154–155°.

Anal. Calcd. for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N,[10] 5.73. Found: C, 68.89; H, 6.49; N[10] 5.67.

To a well stirred suspension of 3.55 g. (*ca.* 0.09 mole) of lithium aluminum hydride in 450 ml. of ether there was added 10.5 g. (0.043 mole) of 2,4-dioxo-9-methyl-3-phenyl-3,9-diazabicyclo-[3.3.1]nonane, and the mixture stirred at room temperature for 3 days. Excess hydride was destroyed with ethanol and a large quantity of 35% sodium hydroxide added to dissolve inorganic material. The ether layer and additional extracts were washed with saturated sodium chloride solution, dried, and solvent was removed, leaving 9.1 g. (97.5% yield) of pale amber oil. This was satisfactory for conversion to the dihydrogen citrate by reaction with citric acid in ethanol and separated with the addition of ether. The light tan solid was twice crystallized from ethanol–ether to give 13.3 g. (77.5% yield) of the salt as an amorphous white solid, m.p. 126.5–128.5°.

Anal. Calcd. for $C_{14}H_{20}N_2.C_6H_8O_7$: C, 58.81; H, 6.91; N, 6.86. Found: C, 58.97; H, 7.01; N, 6.58.

3-(3-Chloro-4-methylphenyl)-9-methyl-3,9-diazabicyclo[3.3.1]nonane.—Dimethyl scopolinate and 3-chloro-4-methylaniline were caused to react in the manner described for the use of aniline and the product isolated similarly. The yields of 3-(3-chloro-4-methylphenyl)-2,4-dioxo-9-methyl-3,9-diazabicyclo[3.3.1]nonane were 29.5–38%. It separated from ethanol (charcoal) as a cryptocrystalline, light tan solid, m.p. 143–146°.

Anal. Calcd. for $C_{15}H_{17}ClN_2O_2$: Cl, 12.11; N, 9.57. Found: Cl, 12.13; N, 9.33.

The reduction of the dioxo compound was effected with lithium aluminum hydride, and a 91.5% yield of 3-(3-chloro-4-methylphenyl)-9-methyl-3,9-diazabicyclo[3.3.1]nonane was obtained as a brownish oil. It was transformed into the dihydrogen citrate in ethanol–ether. The pure salt was isolated in 59.5% yield as an amorphous, light tan solid. It melted to a translucent mass at 128–130° and underwent intumescence at 139°.

Anal. Calcd. for $C_{15}H_{21}ClN_2.C_6H_8O_7$: C, 55.20; H, 6.40; N, 6.13. Found: C, 55.00; H, 6.54; N, 6.11.

F. 3-Benzyl-7-methoxy-9-methyl-3,9-diazabicyclo[3.3.1]-nonane. Dimethyl 4-Methoxypiperidine-2,6-dicarboxylate.—Dimethyl 4-methoxypyridine-2,6-dicarboxylate was synthesized by the procedure of Markees and Kidder.[40] The ester was reduced in methanol solution, using a 10% palladium–charcoal catalyst at 1600 p.s.i., 75°. A yield of 95.5% of straw colored oil was collected at 80–82° (0.02 mm.). Upon standing, the dimethyl 4-methoxypiperidine-2,6-dicarboxylate solidified to a mass of colorless needles, m.p. 37–39°.

Anal. Calcd. for $C_{10}H_{17}NO_5$: N,[10] 6.06. Found: N,[10] 6.08.

Dimethyl 4-Methoxy-1-methylpiperidine-2,6-dicarboxylate was obtained by reductive methylation of the piperidine type in methanolic formalin with use of a 10% palladium–charcoal catalyst at 60° under 1500 p.s.i. of hydrogen. A crude yield of 97% resulted, and following distillation at 116–117° (0.6 mm.), the yield of N-methyl compound was 91.5%. It solidified to a mass of prisms, m.p. 53–54°.

Anal. Calcd. for $C_{11}H_9NO_5$: N,[10] 5.71. Found: N[10], 5.72.

The hydrochloride was prepared in propanol-2-ether and crystallized from propanol-2 in the form of needles, m.p. 145.5–146.5°, with intumescence.

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Anal. Calcd. for $C_{11}H_{19}NO_5 \cdot HCl$: C, 46.89; H, 7.16; Cl, 12.59. Found: C, 47.20; H, 7.18; Cl, 12.56.

3-Benzyl-2,4-dioxo-7-methoxy-9-methyl-3,9-diazabicyclo[3.3.1]-nonane.—A stirred mixture of 125.9 g. (0.514 mole) of dimethyl 4-methoxy-1-methylpiperidine-2,6-dicarboxylate and 138.0 g. (1.29 moles) of benzylamine was heated to reflux (168°). Soon after refluxing had begun, the temperature began to fall, and was at 148° after half an hour. It was heated for 48 hr. The apparatus was then changed for distillation, and the mixture heated at 200° for 0.5 hr., again changed to refluxing, and heated at 140° for 5 hr., followed by heating at 200° for an hour. The hot material was transferred to a beaker; upon cooling, it assumed the appearance of cold honey. It was beaten twice each time with 200 cc. of saturated salt solution, and the organic layer was taken up in 1 l. of benzene. The solvent was removed from the dried solution, leaving 202.5 g. of an orange sirup which was extracted thrice with heptane, each time using 700 ml. of the solvent. The residual material (91.2 g.) solidified on cooling; this was the diamide type VII. Concentration of the liquors gave the impure imide as a viscous residue which solidified incompletely on standing. It was collected at the pump, and the oil expressed as completely as possible before it was dried on porous porcelain to yield *ca.* 74 g. of waxy solid. The pure compound (45.2 g., 30.2%) was obtained following several crystallizations from pentane, whence it separated as a cryptocrystalline mass, m.p. 66–68°.

Anal. Calcd. for $C_{16}H_{20}N_2O_3$: N,[10] 4.85. Found: N,[10] 4.86.

The hydrochloride of 3-benzyl-2,4-dioxo-7-methoxy-9-methyl-3,9-diazabicyclo[3.3.1]nonane could be obtained from the oily or waxy impure base. It was formed in, and crystallized from, propanol, from which it crystallized as fine needles, m.p. 172.5–173°, with intumescence.

Anal. Calcd. for $C_{16}H_{20}N_2O_3 \cdot HCl$: N, 8.63; N,[10] 4.32; Cl, 10.92. Found: N, 8.33; N, (basic[10]), 4.46; Cl, 11.09.

The crude residue of 2,6-bis(benzylcarbamyl)-4-methoxy-1-methylpiperidine, 91.2 g., was leached in the hot with cyclohexane and crystallized from ethanol. A rather amorphous product resulted, m.p. 103–105°.

Anal. Calcd. for $C_{23}H_{29}N_3O_3$: N, 10.63; N (basic[10]), 3.54. Found: N, 10.38; N (basic[10]), 3.51.

3-Benzyl-7-methoxy-9-methyl-3,9-diazabicyclo[3.3.1]nonane was prepared by lithium aluminum hydride reduction of the 2,4-dioxo compound. The yield of crude golden base was 93.5%. A dihydrogen citrate (m.p. *ca.* 125°, with intumescence) was formed in ether solution, although it became sticky upon attempts to purify it. The base was distilled and an 88% recovery of a pale yellow oil was obtained; b.p. 127–129° (0.02 mm.), $n^{25}D$ 1.5350. Values for carbon and hydrogen were consistently low in an erratic pattern.

Anal. Calcd. for $C_{16}H_{24}N_2O$: N, 10.77; O, 6.15. Found: N, 10.59; O, 6.47.

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Structural Determination of *cis*- and *trans*-1,3-Dibromocyclohexane[1]

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The structures of the *cis*- and *trans*-1,3 and 1,4-dibromocyclohexanes have heretofore been difficult to resolve because of the reaction of the corresponding diols with either hydrobromic acid or phosphorus tribromide results in a mixture of both *cis*- and *trans*-1,3 and 1,4-dibromocyclohexanes. All four isomers have been isolated and identified. Identification of the *cis*- and *trans*-1,4-dibromocyclohexanes has been achieved by dipole moment measurements. As both *cis*- and *trans*-1,3-dibromocyclohexanes have the same dipole moment, assignment of structure was made by variable temperature n.m.r. analysis. Thus the bromines of *cis*-1,3-dibromocyclohexane exist entirely in the diequatorial conformation and this isomer exhibits no significant change in its n.m.r. spectrum from −72° to 200°. The *trans*-1,3-dibromocyclohexane, which shows no change in its n.m.r. spectrum on heating, does exhibit a change in spectrum at −33°. At this temperature the chair–chair interconversion is sufficiently slow so that the C-2 hydrogens are no longer equivalent and the A_2X_2 multiplet is not exhibited.

The 1,3-dibromocyclohexanes have been described as a solid with a m.p. of 48–49°[3]; specifically, the 48–49° isomer has been assigned the *trans*-1,3 structure[4a] and the *cis*-1,3 structure.[4b] The *cis*-1,3 structure also has been assigned to a 112° isomer.[5a,b] The correct structures for the 1,4-dibromocyclohexanes (*trans*-1,4, m.p. 112°; *cis*-1,4, m.p. 48°) has been summarized by Cornubert, Rio, and Senechal[6a] and by Grob and Baumann.[6b] The individual 1,4-dibromocyclohexanes at times have been correctly identified,[4a,5a,6a,b,7] but the 1,3-dibromocyclohexanes have not been correctly characterized.

We have treated 1,3- and 1,4-cyclohexanediols with both aqueous hydrobromic acid and with phosphorus tribromide and have analyzed for the 1,3- and 1,4-dibromides by vapor phase chromatography. In order to ascertain the positional integrity of the diols, known derivatives of each of the diols were synthesized. Thus we could always be sure that the 1,3-diol was uncontaminated with any 1,4-diol and *vice versa*.

A purchased sample of 1,4-cyclohexanediol was identical to the diol prepared from reduction of 1,4-cyclohexanedione. The *cis*- and *trans*-ditosylates of 1,4-cyclohexanediol were prepared, separated, and the melting points compared with the known ditosylates.[8] This series of reactions confirmed the positional integrity of the 1,4-diol. The 1,4-diacetates also were made,[8,9] and the *cis*- and *trans*-isomers were detected by v.p.c. both before and after isolation. Similarly the 1,3-diacetates were synthesized[10] and the *cis*- and *trans*-isomers separated by v.p.c. The v.p.c. retention times of the *cis*- and *trans*-1,4 diacetates differed from those of the 1,3-diacetates. Although one of the 1,3-diacetates differed only slightly in retention time from *cis*-1,4-cyclohexanediol diacetate, these two compounds were shown to be different isomers by comparison of

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(2) Analytical Research Division, Esso Research and Engineering Co.

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