## Conformational Aspects of Acetylcholine Receptor Sites. The Isomeric 3-Trimethylammonium-2-acetoxy-*trans*-decalin Halides<sup>1</sup> and the Isomeric $\alpha,\beta$ -Dimethylacetylcholine Halides<sup>2</sup>

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The syntheses of the four possible isomeric 3-trimethylammonium-2-acetoxy-trans-decalins and of the isomeric  $\alpha_{\beta}\beta$ -dimethylacetylcholines are described. The results of muscarinic and cholinesterase assays are discussed.

The existence of receptor surfaces has been offered as an explanation for structure-activity relationships of various classes of drugs, their relative stimulatory and/or inhibitory properties, toxicity, and metabolic fate.<sup>5</sup> Steric differences have usually been studied without regard for the ability of a molecule to attach itself to a receptor in a form thermodynamically less stable than one which would exist in the greatest population under nonreceptor complex conditions.

If rotation about a carbon-carbon single bond can occur in a given drug, the possibility exists that the conformation which "fits" an effector site could differ from the conformation which is most desirable at the metabolic site, transport site, site of loss, etc., for a given biologically active agent. If this assumption is valid, a system in which the principal functions of attachment can be locked in conformationally rigid positions should give information concerning the absolute steric requirements of the individual receptor surfaces (effector, metabolic, etc.).

The 2,3-disubstituted *trans*-decalin molecule 1 and the 2,3-disubstituted butane molecule 2 were selected as model systems for a study of the conformational aspects of cholinergic, adrenergic, antihistaminic, and other biological agent induced responses since one system is rigid and the other represents a flexible system with definite preferred conformations.



In the application of the above stated hypothesis to the cholinergic receptors, one of the principal conformations (Figure 1) of acetylcholine should fit the nicotinic effector site more favorably than the muscarinic or acetylcholinesterase sites. With acetyl-



choline, the barrier to rotation about the carbon–carbon bond of the choline moiety is small with respect to the energy gained in attachment to the various receptor sites. If alkyl groups are placed on the  $\alpha$  or  $\beta$  carbons a variation in biological response can be noted (Table I)<sup>6</sup> but no unequivocal statement can be made as to the conformational preference of the receptor surface.

$\Gamma_{\Lambda}$	BLE	Ι
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<i></i>	Musca-	Nico-		
Compd	rinie	tinic	BuChE	
$CH_3COOCH_2CH_2N^+(CH_3)_3$	108)	100	+	
$CH_3COOCH_2CH(CH_3)N^+(CH_3)_3$	5	Ca.  100	÷	
$CH_3COOCH(CH_3)CH_3N^+(CH_3)_3$	50	()		

Steric differences of the neural hormone acetylcholine and its cogeners have been previously suggested to account for differences in muscarinic, nicotinic, and acetylcholinesterase activities but no conformational specificity existed in the molecules studied. Schueler<sup>7</sup> first brought attention to the flexibility of acetylcholine as a consideration for "collating structure with pharmacologic activity." Compounds **3** and **4**, which represent



<sup>(6) (</sup>a) A. Simonart, J. Pharmacol., 46, 157 (1932); (b) M. Wurzel. Experientia, 15, 430 (1959).

<sup>(1)</sup> Taken in part from the dissertation presented by W. L. Nelson, June 1965, to the Graduate School of the University of Kansas in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

<sup>(2)</sup> Taken in part from the dissertation presented by J. L. Day, March 1963, to the Graduate School of the Ohio State University in partial fulfillment of the requirements for the degree of Master of Science.

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<sup>(5)</sup> R. B. Barlow, "Introduction to Chemical Pharmacology," 2nd ed. John Wiley and Sons, Inc., New York, N. Y., 1964.

<sup>(7)</sup> F. W. Schueler, J. Am. Pharm. Assoc., Sci. Ed., 45, 197 (1956).

The validity of this comparison appears doubtful in the light of the disparity of skeletal arrangement of atoms in the two molecules.

Archer, *et al.*, prepared *cis-* and *trans-2-*acetoxytropine methiodides and found the *cis* compound to possess greater nicotinic activity and the *trans* compound greater muscarinic activity.<sup>8</sup>

In order to study steric requirements on a more exacting conformational basis 3(a)-dimethylamino-2(a)-acetoxy-trans-decalin methiodide (5), 3(a)-dimethylamino-2(e)-acetoxy-trans-decalin methiodide (6), 3(e)-dimethylamino-2(e)-acetoxy-trans-decalin methochloride (7), and 3(e)-dimethylamino-2(a)-acetoxy-trans-decalin methochloride (8) were prepared and preliminary biological testing was performed.



3(a)-Dimethylamino-2(a)-acetoxy-trans-decalin methiodide (5) was prepared from trans-decalin 2,3-oxide (9)<sup>9</sup> by allowing it to react with excess anhydrous dimethylamine affording 3(a)-dimethylamino-2(a)-transdecalol (10)<sup>10</sup> which was converted to 5 in two steps: acetylation and formation of the quaternary salt with methyl iodide. The nmr spectrum of 5 showed mul-



tiplets at 5.50 and 3.75 ppm with peak half-widths of 8 and 10 cps, respectively, which are consistent with equatorial protons at C-2 and C-3.

The addition of iodoisocyanate to  $trans-\Delta^2$ -octalin (11) afforded a route to 3(a)-dimethylamino-2(e)-ace-



(8) S. Archer, A. M. Lands, and T. R. Lewis, J. Med. Pharm. Chem., 5, 423 (1962).

(9) W. S. Johnson, V. J. Bauer, J. L. Margrave, M. A. Grisch, L. H. Dreger, and W. N. Hubbard, J. Am. Chem. Soc., 83, 606 (1961).

(10) (a) M. Tichý, J. Šipoš, and J. Sicher, Collection Czech. Chem. Commun.
 27, 2907 (1962); (b) M. P. Potin and R. Wylde, Bull. Soc. Chim. France, 69 (1962).

toxy-trans-decalin methiodide (6). Addition of this pseudohalogen has been shown to occur in a trans manner.<sup>11</sup>

The intermediate iodoisocyanate was not isolated but subjected to methanolysis affording 12 in 50% yield from trans- $\Delta^2$ -octalin. Pyrolysis of 12 produced cis-syntrans-decahydronaphth [2,3-d]oxazolin-2-one (13) in excellent yield. Alkaline hydrolysis of the carbamate afforded 3(a)-amino-trans-2(e)-decalol (14).<sup>10a</sup>

Reductive methylation with formaldehyde and formic acid, acetylation, and formation of the quaternary salt with methyl iodide afforded **6**. Its nmr spectrum showed multiplets at 5.67 and 3.93 ppm with peak half-widths of 13 and 9 cps, respectively, which are consistent with equatorial and axial disposition of protons at C-2 and C-3, respectively.

The successful synthesis of 3(e)-dimethylamino-2(e)acetoxy-*trans*-decalin (7) was accomplished utilizing 3(e)-carboxy-*trans*-2(e)-decalol.<sup>12</sup>

The conversion of the carboxydecalol to its hydrazide was accomplished in excellent yield by the preparation of the methyl ester utilizing diazomethane, followed by treatment with hydrazine. A Curtius rearrangement provided 3(e)-amino-2(e)-trans-decalol<sup>12a</sup> which was identical with an authentic sample.<sup>12b</sup> Reductive methylation with formaldehyde and formic acid, acetylation, and formation of the quaternary salt with methyliodide afforded a hygroscopic gum. The corresponding methochloride was prepared and its nmr spectrum confirmed the presence of 1 mole of water bound in the salt. Comparison of the integrated area of water before and after the addition of the sample (in  $D_2O$ ) showed an increase in area corresponding to two protons. Multiplets at 5.27 and 3.88 ppm, each with peak halfwidths of ca. 23 cps, indicated axial protons at C-2 and C-3.

Bromination of *trans*-2-decalone (15) provided 3(a)bromo-*trans*-2-decalone (16). Comparison of the infrared spectrum of the oil obtained with those of 3(e)bromo- and 3(a)-bromo-*trans*-2-decalone<sup>13</sup> confirmed axial introduction of the bromine atom. Treatment with anhydrous dimethylamine yielded an amino ketone 17, isolated as a picrate, which was converted to 3(e)-dimethylamino-2(a)-acetoxy-*trans*-decalin methochloride (8) in three steps. Catalytic hydrogena-



tion of the hydrochloride salt of the amino ketone 17 produced the hydrochloride salt of 3(e)-dimethylamino-2(a)-trans-decalol. The free amine was liberated, acetylated, and converted to its quaternary salt with

<sup>(11)</sup> A. Hassner and C. C. Heathcock, Tetrahedron Letters, 1125 (1964).
(12) (a) J. Sicher, M. Tichý, F. Šipoš, M. Svoboda, and J. Jonáš, Collection

Czech. Chem. Commun. 29, 1561 (1964); (b) J. Sicher, private communication.

<sup>(13)</sup> E. E. Smissman, T. L. Lemke, and O. Kristiansen, J. Am. Chem. Soc., 88, 334 (1966).

TAB	le II		
MUSCARINIC	ACTIVITIES <sup>a</sup>		
	Equipotent	Molar conen	Relative
OCH <sub>3</sub>	conen, µg/ml	$(10^{-4})$	potency

	Conformation		Equipotent	Molar concu	Relative
Compd	$N + (CH_3)_3$	OCOCH <sub>3</sub>	conen, µg/ml	(10-4)	potency
5	Axial <sup>b</sup>	Axial	50	1.3	0.06
6	Axial <sup>b</sup>	Equatorial	500-1000	13 - 26	0.003-0.006
7	Equatorial	Equatorial	Inactive at 1500	$>(51)^{d}$	
8	Equatorial	Axial	Inactive at 1800	$>(62)^{d}$	• • •
19	$erythro^{b}$ config		1.7	0.06	14
20	$threo^{b}$ config		67	2.3	0,036
Acetylcholine			0.0125	0.0084	100
chloride					

<sup>a</sup> All assays were performed on guinea pig ileum suspended in Tyrodes solution. Method was modified from E. J. Walaszek, R. D. Bünag, and C. G. Huggins, J. Pharmacol. Exptl. Therap., **138**, 139 (1962). <sup>b</sup> Iodides. <sup>c</sup> Chlorides. <sup>d</sup> The values in parentheses indicate that these compounds were inactive at these molar concentrations but, since higher concentrations were not tried, no definite value can be given.

TABLE III ACETYLCHOLINESTERASE HYDROLYSIS RATES<sup>4</sup>

			$\mu$ moles hvdrolyzed/	$\mu$ moles hydrolyzed/	
	Conformation		ml of enzyme	mg of enzyme	Relative
Compd	N +(C H <sub>3</sub> )3	OCOCH <sub>8</sub>	per min	protein per min	rates
5	Axial	Axial	43	26	13
6	Axial	Equatorial	<0.6	<0.4	<0.2
7	Equatorial	Equatorial	0	0	
8	Equatorial	Axial	0	0	
19	erythro config		0, <0.3	0, <0.2	
20	threo config		30, 29	18, 17	9
Acetylcholine	•••		336, 289	198, 172	100
$chloride^{b}$					
Ethyl acetate			0	0	

<sup>a</sup> Assay conditions: reaction was started by adding enzyme solution to substrate; 50  $\mu$ l of enzyme solution was added to 0.5 ml of substrated buffer solution: 0.1 *M* NaCl, 0.01 *M* MgCl<sub>2</sub>, and 0.02 *M* phosphate buffer pH 6.60  $\pm$  0.05; final substrate concn, 9.9  $\mu$ moles/ml; enzyme protein concentration, 1.7 mg/ml. <sup>b</sup> About 20–30% inhibition by product under conditions employed.

methyl iodide. The methochloride was prepared from its corresponding methoiodide salt utilizing a basic ion-exchange resin charged with chloride ion. Examination of the nmr spectrum of 8 confirmed the presence of 1 mole of water bound on crystallization. Multiplets at 5.78 and 3.80 ppm with peak half-widths of 9 and 18 cps, respectively, are consistent with an equatorial proton at C-2 and an axial proton at C-3.

In order to compare the biological action of an acyclic system, which would have definite preferred conformations, to the rigid decalin system, three- and erythro- $\alpha,\beta$ -dimethylacetylcholines (18) were prepared.

Ether cis- or trans-2-butene was allowed to react with HTH, a commercial form of calcium hypochlorite, to form the chlorohydrin. This was then converted to

# $\begin{array}{c} \mathrm{CH_3COOCH}(\mathrm{CH_3})\mathrm{CH}(\mathrm{CH_3})\mathrm{N}\,{}^+\!\mathrm{N}(\mathrm{CH_3})_3\\ 18\end{array}$

the oxide by treatment with potassium hydroxide.<sup>14</sup> Treatment with dimethylamine gave the amino alcohol which was converted to the quaternary salt with methyl iodide and acetylated with acetic anhydride to form the ester 18. The *threo* compound was obtained from the *cis* olefin; the *erythro* compound from the *trans* olefin. There is ample documentation for the steric course of these reactions.<sup>15,16</sup>

Infrared spectra of the amino alcohols in dilute carbon tetrachloride solution revealed that the compound derived from the *trans* oxide had a broad band in the region 3400–3450 cm<sup>-1</sup> (hydrogen-bonded OH) and a sharp band at approximately  $3625 \text{ cm}^{-1}$  (free OH) while the compound derived from the *cis* oxide did not exhibit the sharp, higher frequency band. This is consistent with the observations of Kanzawa<sup>17</sup> on the infrared spectra of N-methylephedrine, pseudoephedrine, and related compounds and confirms the stereoselectivity of the oxide ring opening.

**Biological Results.**—Table II lists the relative muscarinic potency of compounds 5–8 in the *trans*decalin series and 19 and 20 in the  $\alpha,\beta$ -dimethylacetylcholine system. Table III gives the initial hydrolysis rates of the same compounds compared to acetylcholine and ethyl acetate when subjected to true acetylcholinesterase isolated from the electric organ of the eel (*Electrophorus electricus*).<sup>18</sup>



The preliminary biological data indicate in the muscarinic assay that the completely staggered form,

<sup>(14)</sup> C. E. Wilson and H. J. Lucas, J. Am. Chem. Soc., 58, 2396 (1936).

<sup>(15)</sup> E. L. Eliel in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1965, Chapter 2.

<sup>(16)</sup> F. H. Dickey, W. Fickett, and H. J. Lucas, J. Am. Chem. Soc., 74, 944 (1952).

<sup>(17)</sup> T. Kanzawa, Bull. Chem. Soc. Japan, 29, 398, 379, 604 (1956).

<sup>(18)</sup> H. C. Lawler, J. Biol. Chem., 234, 799 (1959).

the trans-diaxial analog 5, is the most active of the decalins prepared. This correlates well with the fact that the *erythro* isomer of the  $\alpha,\beta$ -dimethylacetylcholine would have a preferred conformation 19 in which the acetoxy and the quaternary head are staggered and would be expected to fit a transoid receptor more facilely than would the *threo* isomer conformation 20. In the latter the system would tend to move away from a true staggered conformation for the functional groups.

Since the steric relationship between the two polar groups is dictated by assuming that they must be a given distance apart in order to interact with a receptor, the stability differences between various rotamers can be analyzed considering steric factors associated only with the nonreactive groups.

If it is assumed that H is a small (S) group,  $CH_3$  is medium (M), and the polar groups are large (L), and the *gauche* interactions between substituents are evaluated, *threo* I becomes LL, 2LM, 2MS, SS, and *threo* II becomes LL, 2LS, MM, 2MS. According to Mateos and Cram<sup>19</sup> threo I would be expected to be more stable. The two forms written for the *erythro* compound both give the same results (LL, LM, LS, MM, MS, SS) which would be expected to be less stable than *threo* I.



If the groups are required to be far apart at the time of interaction with a receptor, the active rotamers would be those indicated in **19** and **20**. In this case, the *erythro* compound is more stable than the *threo* (2LM, 2LS, 2MS vs. 2LM, 2LS, MM, SS).

In the decalin system, **5** would be expected to represent a stabilized conformational model of **20**. The activity of **5** is greater than **20** and this could be explained by the rigid conformation existing in **5**.

It is obvious that interference from the excessive bulk of the decalin system could occur. However, since the decalin system 5 has greater activity than the *threo* isomer 20, it is proposed that the activity of 19 is greater than that of 20 because of the more stable staggered conformation of the functional groups and greater than 5 because of diminished interaction of bulky alkyl functions which could diminish approach to the effector site.

The hydrolysis rates utilizing true acetylcholinesterase lead to the conclusion that the completely staggered

(19) J. L. Mateos and D. J. Cram, J. Am. Chem. Soc., 81, 2756 (1959).

conformation fits the degradation site best. As is noted in Table III the diaxial decalin system **5** is hydrolyzed more rapidly than any of the other acetylcholine analogs tested. However, the hydrolysis rate of the *erythro* isomer was negligible when compared to the threo isomer. This is postulated to be due to a hindrance of approach to the very specific enzyme surface by the methyl group on the carbon  $\alpha$  to the quaternary nitrogen. In conformation **19** and in the decalin system **5** both alkyl groups are on the same side of the molecule, whereas in conformation **20** the methyl groups are staggered.

Work is presently under way in these laboratories designed to check the above hypothesis. The decalin system 5 with methyl groups at the 2, the 3, and at both the 2 and 3 carbons are being synthesized. In order to obtain a transoid system with the quaternary nitrogen and acetoxy function fixed in such a manner as to resemble the *erythro* form **19** and for comparison to a similar compound in the *threo* series, the *trans* perhydro-



quinolines 21 and 22 are also being prepared. A definitive discussion of the biology will be the subject of a future publication.

#### **Experimental Section**<sup>20</sup>

trans-Decalin 2,3-Oxide (9).—The procedure used is essentially that of Hibbert and Burt.<sup>21</sup> To a cold solution (0°) of 9.60 g (0.069 mole) of perbenzoic acid in 120 ml of chloroform<sup>22</sup> was added cautiously 8.79 g (0.065 mole) of trans- $\Delta^2$ -octalin<sup>9</sup> (11) in 30 ml of CHCl<sub>3</sub>. The solution was maintained at 0° for 18 hr (after which time no peracid could be detected with NaI), then extracted with cold aqueous 5% NaOH solution, washed with water, and dried (MgSO<sub>4</sub>). The solvent was removed and the residual oil distilled affording 7.76 g (78.5%) of a colorless liquid: bp 136° (>30 mm); n<sup>22</sup>D 1.4828 [lit. bp 105° (21 mm), n<sup>22</sup>D 1.4835;<sup>9</sup> bp 92° (10 mm), n<sup>24</sup>D 1.4872<sup>23</sup>]; nmr (CDCl<sub>3</sub>),  $\delta$  3.23, 3.18 (singlets, methine protons).

**3(a)-Dimethylamino-***trans-2*(**a)-decalol.**—To a cold  $(-70^{\circ})$  150-ml capacity steel autoclave chamber was added 7.0 g (0.046 mole) of *trans*-decalin 2,3-oxide and 20.7 g (0.46 mole) of anhydrous dimethylamine. The autoclave was sealed and heated at 100° for 4 hr. After cooling to  $-70^{\circ}$  the autoclave was opened and the contents were removed. Excess dimethylamine was removed and distillation of the residue afforded 1.20 g of the starting epoxide, bp 60–62° (0.2 mm). The residual oil crystallized slowly on standing affording 5.51 g (74%) of the desired compound. The compound was recrystallized from petroleum ether (63–68°); mp 75.5–76.5° (lit. mp 74.5–75.5°, <sup>106</sup>, 77.5–78.5<sup>24,10a</sup>); infrared (CHCl<sub>3</sub>), 3.0 (broad), 3.45, 3.52, 3.63, 6.90,

(22) D. Swern, Org. Reactions, 7, 378 (1953).

(23) H. B. Henbest, M. Smith, and A. Thomas, J. Chem. Soc., 3293 (1958).

<sup>(20)</sup> Melting points were obtained on a calibrated Thomas-Hoover Unimelt and are corrected. Infrared data were recorded on Beckman IR5 and IR8 spectrophotometers. Nmr data were recorded on a Varian Associates Model A-60 spectrophotometer using  $Si(CH_2)_4$  or 3-(trimethylsilyl)-1-propanesulfonic acid sodium salt as internal standard. Gas chromatographic data were obtained on F and M 500 and 810 chromatographs. Microanalyses were conducted by Drs. G. Weiler and F. B. Strauss, Oxford, England, Huffman Microanalytical Laboratories, Wheatridge, Colo., and Alfred Bernhardt Mikroanalytiches Laboratorium, Max-Planck-Institut für Kohlenforschung, Mülheim (Ruhr), Germany.

<sup>(21)</sup> H. Hibbert and P. Burt, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p 494.

7.92, 9.70, 9.93, 10.32, 10.83, 11.40  $\mu$ ; nmr (CDCl<sub>3</sub>),  $\delta$  4.12 ( $W_{1/2} = 6$  cps, equatorial methine proton at C-2), 2.95 ( $W_{1/2} = 8$  cps, equatorial methine proton at C-3), 2.28 (singlet, N(CH<sub>3</sub>)<sub>2</sub>).

Anal. Calcd for  $C_{12}H_{23}NO$ : C, 73.04; H, 11.75; N, 7.10. Found: C, 72.79; H, 11.70; N, 6.94.

Hydrochloride, mp 207-209° (ethanol-ether) (lit.<sup>24</sup> mp 202.5-203.5°).

**3(a)-Dimethylamino-2(a)-acetoxy-***trans***-decalin.**—A mixture of 4.0 g (20.3 moles) of 3(a)-dimethylamino-*trans*-2(a)-decalol in a mixture of 20 ml each of pyridine and acetic anhydride was refluxed for 45 min. Excess pyridine and acetic anhydride were removed and the residual oil was mixed with 200 ml of aqueous  $3\frac{C}{C}$  HCl and allowed to stand 40 min. The acidic solution was washed with ether, make alkaline with aqueous  $10\frac{M}{20}$  NaOH solution, and extracted repeatedly with ether. The combined ether extracts were dried (MgSO<sub>4</sub>) and the ether was removed to give the crude ester (a yellow oil) which was taken to the next step without further purification; yield 4.75 g (93%); infrared (neat), 3.46, 3.53, 3.63, 5.76, 6.90, 7.30, 8.01, 8.25, 9.70  $\mu$ .

Hydrochloride, mp 238-240° (isobutyl alcohol-ether).

Anal. Caled for C<sub>14</sub>H<sub>28</sub>ClNO<sub>2</sub>: C, 60.96; H, 9.50; N, 5.08. Found: C, 60.55; H, 9.61; N, 5.04.

**3(a)-Dimethylamino-2(a)-acetoxy-***trans*-**decalin Methiodide** (5).—To 800 mg (3.33 mmoles) of crude 3(a)-dimethylamino-2(a)-acetoxy-*trans*-decalin was added 10 ml of methyl iodide and the mixture was allowed to stand for 5 hr. Anhydrous ether was added, and the resulting precipitate collected affording 850 mg (53%) of a white solid which was crystallized from methanolethyl acetate; mp 208-209.5°; infrared (KBr), 3.45, 3.53, 5.76, 6.76, 6.91, 7.29, 8.15, 8.32, 9.70, 9.77, 10.32  $\mu$ ; mmr (D<sub>2</sub>O),  $\delta$ 5.50 ( $W_{1/2} = 8$  cps, equatorial methine proton at C-2), 3.75 ( $W_{1/2} = 10$  cps, equatorial methine proton at C-3), 3.13 (singlet, N<sup>+</sup>(CH<sub>3</sub>)<sub>3</sub>), 2.13 (singlet, CH<sub>3</sub>COO).

Anal. Calcd  $C_{15}H_{18}INO_2$ : C, 47.25; H, 7.40; N, 3.67. Found: C, 47.11; H, 7.51; N, 3.68.

3(a)-Iodo-2(a)-carbomethoxyamino-trans-decalin (12).-To a cold  $(-15^{\circ})$  solution of 24.5 g (0.18 mole) of trans- $\Delta^2$ -octalin (11) in 540 ml of anhydrous ether was added 46.1 g (0.307 mole) of silver cyanate and 45.7 g (0.18 mole) of iodine. The mixture was allowed to warm to room temperature. After 6.5 hr the initially red solution had become a yellow slurry. The inorganic salts were removed by filtration and to the filtrate was added 45 ml of anhydrous methanol. The solution was refluxed for 4 hr and allowed to stand overnight. The ether solution was washed with aqueous 10% sodium sulfite solution and with water and dried (MgSO<sub>4</sub>). The ether was removed producing a yellowgreen solid. The solid was crystallized from methanol-chloroform affording 30.8 g (51%) of colorless crystals, mp 133–134.5° An analytical sample was prepared by sublimation at 90° (0.4 mm); mp 133.5-134.5°; infrared (CHCl<sub>3</sub>), 2.94, 3.44, 3.52, 5.80, 6.89, 7.44, 7.50, 8.1 (broad), 8.39, 9.69 µ; nmr (CDCl<sub>3</sub>), δ 5.32 (amide NH), 4.62 ( $W_{1/2} = 8$  cps; methine proton at C-3), 4.05 ( $W_{1/2} = 18$  cps, methine proton at C-2), 3.65 (singlet,  $OCH_3$ ).

Anal. Calcd for  $C_{12}H_{24}INO_2$ : C, 42.74; H, 5.98; N, 4.15. Found: C, 42.93; H, 5.97; N, 4.24.

cis-syn-trans-Decahydronaphth[2,3-d]oxazolin-2-one (13).— 3(a)-Iodo-2(a)-carbomethoxyamino-trans-decalin (10.4 g, 0.031 mole), was heated at 140° at 2 nm until the pressure dropped to 0.5 mm, about 15 min. The residual oil was crystallized from ethyl acetate after treatment with decolorizing carbon affording 5.79 g (94%) of colorless needles: mp 131–133°; infrared (CHCl<sub>8</sub>), 2.94, 3.10, 3.45, 3.52, 5.72, 6.90, 7.18, 7.61, 8.06, 8.06, 9.64, 9.82  $\mu$ .

Anal. Calcd for  $C_{11}H_{17}NO_2$ : C, 67.66; H, 8.78; N, 7.17. Found: C, 67.72; H, 8.90; N, 7.20.

**3(a)-Amino-***trans***-2(e)-decalol** (14).—A slurry of 1.80 g (9.35 mmoles) of *cis-syn-trans*-decahydronaphth[2,3-*d*]oxazolin-2-one in 80 ml of 1 N KOH in 10% aqueous ethanol was refluxed under nitrogen for 14 hr. The opaque aqueous solution was extracted with chloroform. The combined CHCl<sub>3</sub> extracts were dried (MgSO<sub>4</sub>), and the solvent was removed yielding 1.44 g (93%) of a white solid, mp 119–120°. The solid was crystallized from petroleum ether-ethyl acetate; mp 120–121.5° (lit.<sup>84</sup> mp 122.5-123.5°); infrared (CHCl<sub>3</sub>), 3.0 (broad), 3.45, 3.52, 6.90, 9.40, 9.57  $\mu$ ; nmr (CDCl<sub>3</sub>),  $\delta$  3.55 ( $W_{1/2}$  = 18 cps, methine proton at C-2), 3.13 ( $W_{1/2}$  = 9 cps, methine proton at C-3).

(24) S. Labodum, P. Potin, F. Winternitz, and R. Wylde, Bull. Soc. Chim. France, 111 (1965).

Anal. Caled for  $C_{10}H_{19}NO$ : C, 70.96, H, 11.32; N, 8.28. Found: C, 70.86; H, 11.26; N, 8.55.

**3(a)-Dimethylamino**-*trans*-2(e)-decalol. A mixture of 503 mg (2.98 mmoles) of 3(a)-amino-2(e)-*trans*-decalol and 1.8 g of formic acid and 1 ml of aqueous 40% formaldehyde solution was refluxed for 6 hr. The mixture was made alkaline with aqueous 20% NaOH solution and extracted three times with ether. The combined ether extracts were washed with water, with saturated NaCl solution, and dried (MgSO<sub>1</sub>). Evaporation of the solvent afforded 363 mg (62%) of a yellow oil: infrared (neat), 3.0 (broad), 3.46, 3.54, 3.63, 6.90, 9.35, 9.54, 9.69, 9.76  $\mu$ . The crude product was carried to the next step without further purification.

**3(a)-Dimethylamino-2(e)-acetoxy**-trans-decalin. A solution of 360 ml (1.83 mmoles) of 3(a)-dimethylamino-trans-2(c)decalol in a mixture of 2 ml of acetic anhydride and 2 ml of pyridine was refluxed for 1 hr. After cooling to room temperature the acetylation mixture was poured into 20 ml of aqueous  $3C_0^+$  HCl and allowed to stand for 1 hr. The aqueous mixture was washed with ether, made alkaline with aqueous  $10C_0^+$  Na<sub>2</sub>CO<sub>3</sub> solution, and extracted three times with ether. The combined ether extracts were dried (MgSO<sub>4</sub>), and the solvent removed affording 342 mg ( $83C_0^+$ ) of a light yellow oil; infrared (neat), 3.46, 3.54, 3.64, 5.76, 6.90, 7.30, 8.04, 8.19, 9.43, 9.58, 9.70, 10.32  $\mu$ . The product was carried to the next reaction without further purification.

Hydrochloride, mp 250-251° dec (isobutyl alcohol ether).

Anal. Caled for C<sub>14</sub>H<sub>26</sub>ClNO<sub>2</sub>; C, 60.96; H, 9.50; N, 5.08, Found: C, 60.64; H, 9.45; N, 5.21.

**3(a)-Dimethylamino-2(e)-acetoxy**-trans-decalin Methiodide (6). A solution of 340 mg (1.42 mmoles) of 3(a)-dimethylamino-2(e)-acetoxy-trans-decalin in 7 ml of methyl iodide was stoppered and shaken occasionally for 4 hr. Ether (5 ml) was added and the solvent was removed yielding 475 mg ( $88C_{\ell}$ ) of an oil which was obtained as a microcrystalline powder from methanol-ethyl acetate: mp 127–127.5°; infrared (KBr), 3.44, 3.53, 5.79, 6.75, 7.90, 7.27, 7.97, 8.07, 8.30, 9.56, 9.76, 10.30  $\mu$ ; mmr, as the methochloride (D<sub>2</sub>O),  $\delta$  5.67 ( $W_{1,2} = 13$  eps, axial methine proton at C-2), 3.93 ( $W_{1,2} = 9$  eps, equatorial methine proton at C-3), 3.23 (singlet, N(CH<sub>3</sub>)<sub>8</sub>), 2.20 (singlet, CH<sub>3</sub>COO).

Anal. Caled for C<sub>15</sub>H<sub>23</sub>INO<sub>2</sub>: C, 47.25; H. 7.40; N. 3.67. Found: C, 46.80; H, 7.52; N, 4.13.

trans-2-Decalone (15). trans-\beta-Decalol (0.350 g, 0.23 mmole) (Columbia Chemical Co., Columbia, S. C.), in 15 ml of acetone was treated with 2.67 M Jones reagent<sup>25</sup> until the orange color of Cr(VI) presisted. Excess oxidant was destroyed with a few drops of isopropyl alcohol. The acetone solution was partitioned between water and ether. The ethereal solution was dried  $(MgSO_4)$  and filtered and the solvent was evaporated under a nitrogen steam. The oil which remained was dissolved in acetone for examination by gas-liquid partition chromatography (1.22-m silicone rubber column operated isothermally). A single large peak was observed followed by a smaller one which represented less than  $5^{c_{\ell}}_{c}$  of the combined areas. Comparison of retention times and addition of authentic trans-2-decalone indicated this material was trans-2-decalone of 95% purity. This procedure was performed on a larger scale to give the desired compound as a liquid; bp 60-62° (0.18 mm);  $n^{23}$ p 1.4809 (lit.  $n^{25}$ p 1.4814<sup>26</sup> and  $n^{19}$ p 1.4809<sup>27</sup>); infrared (neat), 3.42, 3.50, 5.84, 6.91, 8.03, 8.20, 8.57, 9.71, 10.31 µ.

**3**(e)-**Carboxy**-*brans*-**2**-**decalone**. Potassium triphenylmethylide was prepared according to the method of Hauser.<sup>28</sup> To 300 ml of liquid NH<sub>3</sub> freshly distilled from sodium was added 7.8 g (0.2 g-atom) of potassium which had been freshly cut under dry xylene. Two small crystals of ferrie nitrate was added and the mixture was stirred until the blue color was displaced by a gray suspension of KNH<sub>2</sub>. A solution of 48.8 g (0.2 mole) of triphenyl methane in 300 ml of anhydrous ether was added as rapidly as refluxing NH<sub>3</sub> could be condensed efficiently. The mixture was added, and the mixture refluxed for 2 hr to rid the mixture of NH<sub>3</sub>. Ether was added to bring the volume up to approximately 500 ml and the mixture was cooled to 10°.

<sup>. . . . . . . . . .</sup> 

<sup>(25)</sup> C. Djerassi, R. R. Engel, and A. Bowers, J. Org. Chem., 21, 1547 (1956).

<sup>(26)</sup> E. E. van Tamelen and W. C. Proost, Jr., J. Am. Chem. Soc., 76, 3632 (1954).

<sup>(27)</sup> W. Huckel, Ann., 441, 4 (1925).

<sup>(28)</sup> L. Levin, E. Baumgarten, and C. R. Hauser, J. Am. Chem. Soc. 66, 1230 (1944)

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To a red suspension of potassium triphenylmethylide was added a 50% solution of trans-2-decalone in ether until the red color disappeared; 25.1 g (0.165 mole) of the ketone was utilized. The resulting suspension was poured over 300 g of Dry Ice and allowed to warm to 15°. Ether was added and the mixture was shaken with two portions of aqueous 10% NaOH solution which had been cooled to  $-9^{\circ}$ . The combined alkaline extracts were washed with ether and cooled to freezing (ca.  $-9^{\circ}$ ). Ether was added and the mixture was carefully acidified with aqueous 10% HCl cooled to  $-10^\circ$ . The aqueous layer was extracted with an additional portion of ether; the combined ether extracts were dried  $Mg(SO_4)$  and the solvent was removed to yield 28.0 g (88%) of a pink solid, mp 100-105° dec. The crude  $\beta$ -keto acid was reduced without further purification.

3(e)-Carboxy-trans-2(e)-decalol.—To a solution of 14.0 g (0.071 mole) of crude 3(e)-carboxy-trans-2-decalone in 800 ml of 2.5% aqueous Na<sub>2</sub>CO<sub>3</sub> solution was added 900 g of 3.3% sodium amalgam and the mixture allowed to stand for 3 days. The aqueous layer was decanted and aqueous  $10\%~\mathrm{HCl}$  was added to destory excess sodium. The solution was made acidic with concentrated HCl, saturated with NaCl, and extracted with three portions of ether. The combined ether extracts were dried  $(MgSO_4)$  and the solvent was removed affording 11.3 g (80%) of a slightly yellow solid which was crystallized from acetone; mp 173-175° (lit.<sup>12b</sup> 177.5-178°); mmp 175-177° with authentic 20;<sup>29</sup> infrared (KBr), 3.1 (broad), 3.42, 3.51, 3.7-4.1, 5.89, 6.93, 7.14, 7.77, 8.05, 8.78, 9.11, 9.46, 9.54, 9.69, 9.80, 10.30, 10.70, 11.12, 14.45  $\mu$ , identical with authentic 20;<sup>29</sup> nmr (CF<sub>3</sub>COOH),  $\delta$  4.30 ( $W_{1/2} = 24$  cps, axial methine proton at C-2), 2.7 (multiplet for one methine proton at C-3, partially obscured by the decalin ring envelope).

Anal. Caled for C11H18O3: C, 66.64; H, 9.15. Found: C, 66.91; H, 9.17.

3(e)-Carbomethoxy-trans-2(e)-decalol.—A solution of 1.50 g (7.7 mmoles) of 3(e)-carboxy-trans-2(e)-decalol in 150 ml of 50% ethanolic ether was treated with a solution of  $CH_2N_2$ , generated in ether, and diluted with an equal volume of alcohol, from 4.0 g (27.2 mmoles) of N-methyl-N-nitroso-N'-nitroguanidine (Aldrich Chemical Co., Inc., Milwaukee, Wis.). After 2 hr at room temperature aqueous 10% HCl was added dropwise to destroy excess diazomethane followed by anhydrous  $\mathrm{K_2CO_3}$  to neutralize and dry the solution. The desiccant was removed by filtration affording a pale yellow oil in quantitative yield which was carried to the next reaction without further purification.

3(e)-Carboxy-2(e)-trans-decalol Hydrazide.—The crude ester 21, from 1.50 g (7.7 mmoles) of 3(e)-carboxy-trans-2(e)-decalol, was dissolved in 20 ml of a solution of equal volumes of toluene and absolute ethanol. Twenty-five drops (ca. 0.7 g) of anhydrous hydrazine was added and the solution was heated at reflux for 12 hr. Precipitation of product occurred early in the course of the reaction. The mixture was cooled to  $0^{\circ}$  and filtered to give 1.50 g (94%) of the desired compound, mp 263-265°. The compound was recrystallized from ethanol; infrared (KBr), 2.9-3.1, 3.43, 3.51, 6.06, 6.55, 6.91, 7.87, 8.40, 8.85, 9.43, 9.78  $\mu$ .

Anal. Calcd for  $C_{11}H_{20}N_2O_2$ : C, 62.23; H, 9.50; N, 13.20. Found: C, 62.07; H, 9.46; N, 13.20.

3(e)-Amino-trans-2(e)-decalol.-To a cold (5°) solution of 1.80 g (8.5 mmoles) of 3(e)-carboxy-trans-2(e)-decalol hydrazide in a mixture of 70 ml of glacial acetic acid and 85 ml of aqueous 4% HCl was added 150 ml of ether. To this stirred, cold mixture was added over 20 min a solution of 2.0 g (29 mmoles) of NaNO<sub>2</sub> in 15 ml of water. Following the addition, the mixture was stirred for 20 min, then partitioned between ether and water. The aqueous layer was extracted twice with ether. The combined ether extracts were washed with aqueous 5% Na<sub>2</sub>CO<sub>3</sub> solution until no effervescence occurred, then with water, saturated NaCl solution, and dried (MgSO<sub>4</sub>). Approximately one-half (100 ml) of the ether was removed on a steam bath and 200 ml of absolute ethanol was added. The solution was heated until the boiling point had risen to 75° and then refluxed for an additional 3 hr. The solvent was removed and the crude carbamate ester was dissolved in a mixture of 3.0 g (54 mmoles) of KOH in 100 ml of ethanol and 10 ml of water and heated at reflux for 4 hr. The solvent system was removed and the solid residue was partitioned between water and ethyl acetate. The aqueous layer was extracted with two additional portions of ethyl acetate; the combined ethyl acetate extracts were extracted with aqueous

10% HCl. The combined aqueous extracts were washed with ethyl acetate, then made alkaline with aqueous 10% NaOH and extracted repeatedly with ethyl acetate. The combined organic layers were washed with water and dried (MgSO<sub>4</sub>), and the solvent was removed to yield 1.42 g (98%) of a white solid: mp  $125-127^{\circ}$ admixture with authentic material,<sup>29</sup> mp 125-127°; infrared (KBr), 3.05, 3.1-3.3, 3.45, 3.52, 6.30, 6.98, 7.19, 7.48, 8.76, 8.84, 9.18, 9.35, 9.45, 9.59, 9.70, 9.80, 10.05, 10.23, 10.72  $\mu$ .

Anal. Calcd for C<sub>10</sub>H<sub>19</sub>NO: C, 70.96; H, 11.32; N, 8.28. Found: C, 70.99; H, 11.18; N, 8.25.

3(e)-Dimethylamino-trans-2(e)-decalol.—To a solution of 803 mg (4.75 mmoles) of 3(e)-amino-trans-2(e)-decalol in 5 ml of 97% formic acid was added 5 ml of aqueous 40% formaldehyde solution. The mixture was refluxed for 6 hr and then made alkaline with aqueous 20% NaOH and extracted twice with ethyl acetate. The combined organic extracts were washed with water and dried  $(MgSO_4)$ , and the solvent was removed to afford 608 mg (64%)of an oil which crystallized on standing; mp 48-55°. An analytical sample was prepared by sublimation at  $45^{\circ}$  (0.01 mm); mp 51-53°; infrared (KBr), 2.9-3.1, 3.42, 3.51, 3.59, 6.90, 6.95, 7.73, 8.92, 9.17, 9.39, 9.54, 9.59, 9.69, 9.87, 11.99  $\mu$ ; nmr (CDCl<sub>3</sub>),  $\delta$  3.48 ( $W_{1/2} = 23$  cps, equatorial methine proton at C-2), 2.32 (singlet,  $N(CH_3)_2$ ), 3.82 (singlet, OH). Anal. Calcd for  $C_{12}H_{23}NO$ : C, 73.04; H, 11.75; N, 7.10.

Found: C, 73.08; H, 11.55; N, 7.31.

Methochloride, mp 247–249°

Anal. Calcd for C<sub>13</sub>H<sub>26</sub>CINO: C, 63.01; H, 10.58; Cl, 14.31; N, 5.65. Found: C, 62.81; H, 10.61; Cl, 14.24; N, 5.57.

3(e)-Dimethylamino-2(e)-acetoxy-trans-decalin.—A solution of 948 mg (4.8 mmoles) of 3(e)-dimethylamino-2(e)-trans-decalol in a mixture of 5 ml of acetic anhydride and 5 ml of pyridine was refluxed for 4 hr. The excess acetic anhydride and pyridine were removed. The residual oil was dissolved in 40 ml of 3% aqueous HCl and allowed to stand for 1 hr, then washed with ether, made alkaline with 10% aqueous NaOH, and extracted twice with ether. The combined ether extracts were dried (Mg- $\mathrm{SO}_4$ ) and the solvent was removed to yield 948 mg (90%) of a light yellow oil; infrared (neat), 3.42, 3.50, 3.60, 5.78, 6.90, 7.30, 8.06, 9.60, 9.77  $\mu$ ; nmr (CDCl<sub>3</sub>),  $\delta$  4.97 ( $W_{1/2} = 23$  cps, equatorial methine proton at C-2), 2.30 (singlet, N(CH<sub>3</sub>)<sub>2</sub>), 2.04 (singlet, CH<sub>3</sub>COO). The oil was not further purified.

3(e)-Dimethylamino-2(e)-acetoxy-trans-decalin Methochloride (7).—A mixture of 580 mg (2.65 mmoles) of 3(e)-dimethylamino-2(e)-acetoxy-trans-decalin and 2 ml of methyl iodide in 35 ml of dry acetone was allowed to stand at room temperature for 3 hr then heated at 50° for 3 hr. Acetone and excess methyl iodide were removed. The residue was taken up in 50 ml of a mixture of equal volumes of acetone and absolute ethanol and passed through a 25-cm column (1 cm diameter) of Dowex 1-X2, chloride form, 50-100 mesh. The volume of the solution obtained was reduced and the oil was dissolved in a mixture of acetone and ethyl acetate which deposited 593 mg (73%) of colorless plates: mp 136-138°; infrared (KBr), 2.92 (broad), 3.42, 3.50, 5.76, 6.70, 6.90, 7.30, 8.15, 9.75, 10.55, 11.20  $\mu$ ; nmr (D<sub>2</sub>O),  $\delta$  5.27  $(W_{1/2} = 23 \text{ cps}, \text{ equatorial methine proton at C-2}), 3.88 (W_{1/2} =$ 23 cps, equatorial methine proton at C-3), 3.27 (singlet, N+-(CH<sub>3</sub>)<sub>3</sub>), 2.23 (singlet, CH<sub>3</sub>COO). The presence of 1 mole of water in the crystalline salt was indicated after obtaining the nmr spectrum in D<sub>2</sub>O both before and after addition of the sample. The increase in the integrated areas of HOD corresponded to 2 protons when compared to other signals in the sample.

Anal. Calcd for C15H28ClNO2 · H2O: C, 58.52; H, 9.82; Cl, 11.52; N, 4.55. Found: C, 58.41; H, 9.83; Cl, 11.60; N, 4.38.

3(a)-Bromo-trans-2-decalone (16).-Pyridinium hydrobromide perbromide was prepared according to the method of Djerassi<sup>30</sup> in 82% yield, mp  $131-133^{\circ}$  (lit.<sup>30</sup> mp  $134^{\circ}$  with previous softening). To a solution of 6.0 g (0.04 mole) of *trans*-2-decalone in 150 ml of a mixture of equal volumes of chloroform and acetic acid was added 12.9 g (0.04 mole) of pyridinium hydrobromide perbromide over 20 min. Immediate loss of red color was noted with the addition of each portion. Near the end of the addition HBr was evolved. The mixture was warmed on a steam bath for 20 min, then poured into a mixture of 75 ml of petroleum ether and 500 ml of water containing 0.5% sodium sulfite. The layers were separated and the aqueous layer was extracted with two additional portions of ether. The organic layers were combined and washed with water, saturated NaCl solution, and dried (MgSO<sub>4</sub>). The solvent was removed affording 9.2 g (100%) of

<sup>(29)</sup> Acquired through the courtesy of J. Sicher. Academy of Science, Prague, Czechoslovakia.

<sup>(30)</sup> C. Djerassi and C. R. Scholz, J. Am. Chem. Soc., 70, 417 (1948).

a light tan oil. Upon comparison of the infrared spectra of this compound and an authentic sample<sup>13</sup> it was found that their spectra were identical: infrared (CHCl<sub>3</sub>), 3.42, 3.50, 5.85, 6.91, 7.02, 7.35, 7.41, 7.60, 7.81, 8.1–8.3, 8.51, 8.62, 9.13, 9.80, 10.28, 10.61, 10.80, 11.75  $\mu$ ; nmr (CDCl<sub>3</sub>),  $\delta$  4.37 ( $W_{1,2}$  = 6.5 cps, equatorial methine proton at C-3).

3(e)-Dimethylamino-trans-2-decalone (17).—To 12.0 g (0.052 mole) of crude 3(a)-bromo-trans-2-decalone cooled in a Dry Iceacetone bath was passed a stream of nitrogen for 0.5 hr. The nitrogen source was removed and 40 ml of anhydrous dimethylamine (at 0°) was added. The Dry Ice-acetone bath was removed and the mixture was allowed to reflux for 2.5 hr. The condenser was removed and the excess dimethylamine was allowed to evaporate. The residual oil was partitioned between water and ether. The ether layer was washed with three portions of water and then with aqueous 5% NaOH, followed by extraction with two portions of 10% aqueous HCl. The combined acid extracts were washed with ether, made alkaline with excess aqueous 10% NaOH, and extracted with three portions of chloroform. The combined CHCl<sub>3</sub> extracts were dried (MgSO<sub>4</sub>) and the solvent was removed. The crude amino ketone was dissolved in 20 ml of methanol and a hot solution of 12.5 g (0.054 mole) of picric acid in 80 ml of mixture of methanol-ether (7:3 by vol). The solution was allowed to reflux on a steam bath for 10 min and then refrigerated overnight depositing 6.40 g of the picrate: mp 160-163° dec; infrared (KBr), 3.3-4.2, 5.82, 6.0-7.0, 8.65, 8.90, 9.32, 9.48, 9.61, 9.95, 10.23, 10.32, 10.85, 11.00, 12.68, 13.47. 14.2 (broad)  $\mu$ .

Anal. Caled for  $C_{18}H_{24}N_4O_8$ ; C, 50.94; H, 5.70; N, 13.20. Found: C, 50.59; H, 5.45; N, 12.73.

**3(e)-Dimethylamino**-trans-2(**a**)-decalol.—A solution of 3.0 g (7.1 mmoles) of 3(e)-dimethylamino-trans-2-decalone picrate in 130 ml of absolute methanol was passed through a column (1-cm diameter) containing 20 g (72 mequiv) of Dowex 1-N2, chloride form, 50–100 mesh, followed by 120 ml of absolute methanol. The solvent was evaporated affording the hydrochloride salt which was dissolved in 70 ml of methanol and subjected to atmospheric hydrogenation over 500 mg of prereduced PtO<sub>2</sub>. After 12 hr, 104% of the theoretical amount of hydrogen had been absorbed, the catalyst was removed by filtration, and the methanol was removed affording 1.35 g (82%) of a white solid, mp 238–240°.

The hydrochloride salt was dissolved in water, washed with ethyl acetate, and made alkaline with aqueous 10% NaOH, then extracted with ethyl acetate. The combined ethyl acetate extracts were dried (MgSO<sub>4</sub>), and the solvent was removed affording an oil which crystallized on standing; mp 57-59°; infrared (neat), 3.1 broad, 3.45, 3.5-3.6, 6.85-7.0, 7.39, 7.73, 8.04, 8.21, 8.58, 8.89, 9.11, 9.70, 10.21, 10.35, 10.64, 10.89, 11.68, 14.40  $\mu$ ; mmr (CDCl<sub>3</sub>),  $\delta$  4.17 (W<sub>1.2</sub> = 8 cps, equatorial methine proton at C-2), 3.48 (singlet, OH), 2.57 (multiplet of methine proton at C-3, partially obscured by N-methyl signal), 2.37 (singlet, N(CH<sub>3</sub>)<sub>2</sub>). A sample for analysis was sublimed at 25° (0.05 mm), mp 59-61°.

Anal. Caled for  $C_{12}H_{33}NO$ : C, 73.04; H, 11.75; N, 7.10. Found: C, 73.19; H, 11.60; N, 7.05, 6.93.

3(e)-Dimethylamino-2(a)-acetoxy-trans-decalin.--A solution of 610 mg (3.1 mmoles) of 3(e)-dimethylamino-trans-2(a)-decalol in a mixture of 3 ml of acetic anhydride and 3 ml of pyridine was refluxed for 3 hr. The excess acetic anhydride and pyridine was removed. Aqueous  $3^{c_{\tau}}_{c_{\tau}}$  HCl (8 ml) was added, and the mixture allowed to stand at room temperature for 1 hr. The aqueous solution was washed with ethyl acetate, made alkaline with aqueous 10% NaOH, and extracted with several portions of ethyl acetate. The combined ethyl acetate extracts were washed with water and dried (MgSO<sub>4</sub>). The solvent was removed affording 628 mg (93%) of a pale oil; infrared (neat), 3.42, 3.50, 3.61, 5.76, 6.90, 7.32, 8.05, 8.30, 9.63, 9.75 (broad), 10.27, 10.58  $\mu$ : nmr (CDCl<sub>3</sub>),  $\delta$  5.50 ( $W_{1/2} = 8$  cps, equatorial methine proton at C-2), 2.4 (methine proton at C-3 obscured by N-methyl signal), 2.33 (singlet, N(CH<sub>3</sub>)<sub>2</sub>), 2.10 (singlet, CH<sub>3</sub>COO). The oil was not further purified.

3(e)-Dimethylamino-2(a)-acetoxy-trans-decalin Methochloride (8).—A solution of 620 mg (2.73 mmoles) of 3(e)-dimethylamino-2(a)-acetoxy-trans-decalin in 10 ml of methyl iodide was allowed to stand at room temperature for 1 hr. An additional 10 ml of methyl iodide was added. After an additional 2 hr excess methyl iodide was removed and the residual oil dissolved in a mixture of 10% methanol in ethyl acetate and anhydrous ether was added to precipitate an amorphous white powder. The crude methyl iodide was dissolved in 25 ml of methanol and passed through a column (1-cm diameter) containing 15 g (48 mequiv) of Dowex 1-X2, chloride form, 50–100 mesh. The eluent was collected, followed by 50 ml of methanol. The solvent was removed affording a colorless crystalline solid which was recrystallized from ethyl acetate-methanol to yield 390 mg (47 G) of 8: mp 149–152° dec; infrared (KBr), 3.0 broad, 3.42, 3.50, 5.76, 6.70, 6.91, 7.30, 8.15, 8.32, 9.75, 10.21, 10.38  $\mu$ ; mmr (D<sub>2</sub>O),  $\delta$  5.78 (W),  $\epsilon = 9$  cps, equatorial methine proton at C-2), 3.80 (W),  $\epsilon = 18$  cps, axial methine proton at C-3), 3.20 (singlet, N~(CH<sub>8</sub>)<sub>3</sub>), 2.20 (singlet, CH<sub>3</sub>COO). The presence of 1 mole of water in the crystalline salt was indicated after obtaining the nmr spectrum in D<sub>2</sub>O both before and after the addition of the sample. The increase in the integrated area of HOD corresponded to two protons when compared to the other signals in the sample.

Anal. Caled for  $C_{15}\dot{H}_{28}CINO_2(H_2O)$ ; C, 58.52; H, 9.82; Cl, 11.52; N, 4.55. Found: C, 58.59; H, 9.81; Cl, 11.52; N, 4.68. erythro- and three-3-chloro-2-butanol were prepared according to the procedure of Wilson and Lucas<sup>11</sup> from pure cis- and trans-2-butene (Matheson Co., Inc.).

cis- and trans-2-butene oxides were prepared from the appropriate 3-chloro-2-butanols by the method of Wilson and Lucas.<sup>11</sup> exythro-3-Chloro-2-butanol produced trans-2-butene oxide (yield  $80C_i$ ), bp 54–55°,  $n^{20}$ p 1.3715 (lit.<sup>14</sup> bp 53.6–54.1,  $n^{20}$ p 1.3736). three-3-Chloro-2-butanol produced cis-2-butene oxide (yield  $80C_i$ ), bp  $60-61^\circ$ ,  $n^{20}$ p 1.3815 (lit.<sup>14</sup> bp 59.9–60.4°,  $n^{20}$ p 1.3826).

erythro-3-Dimethylamino-2-butanol.—In a stainless steel reaction vessel were placed 50 g (0.69 mole) of trans-2-butene oxide, 50 ml (0.75 mole) of dimethylamine, and 75 of 0.1 N HCl. The vessel was sealed and nitrogen was introduced to a pressure of 70.03 kg/cm<sup>2</sup> (1000 psi). The mixture was maintained at a temperature of 200° for 3.5 hr while stirring. The contents of the reaction vessel were removed and neutralized (K<sub>2</sub>CO<sub>3</sub>). An excess of K<sub>2</sub>CO<sub>3</sub> was used to saturate the aqueous portion and the mixture was extracted with three 50-ml portions of ether. The ether extracts, after drying (MgSO<sub>4</sub>), were filtered, and the excess ether was removed under reduced pressure. The residue was fractionally distilled *in vacuo* to give 36.8 g (45.6%) of the desired product, bp 44-45° (6 mm),  $n^{20}$ b 1.4395 [lit.<sup>14</sup> bp 72.0-72.3° (30 mm)]; methiodide, mp 323-235° (absolute alcohol-ether).

*threo*-3-Dimethylamino-2-butanol.—The procedure was the same for the *erythro* isomer, except that the reaction mixture was heated for 1.5 hr to give 46.8 g (58%), bp 33–34° (6 mm),  $n^{29}$ D 1.4305 [lit.<sup>14</sup> 53.7–54.7° (30 mm)]: methiodide, mp 237–239° (absolute alcohol–ether).

crythro-3-Dimethylamino-2-butanol Acetate Methiodide (19). A mixture of crythro-3-dimethylamino-2-butanol methiodide (3.0 g, 0.012 mole) and acetic anhydride (10 ml) was heated at 110° for 6 hr. Anhydrous ether was then added to the cooled solution. The precipitate which formed was washed several times with ether and then dissolved in absolute alcohol. This solution was first decolorized with activated charcoal and the acetylated compound was reprecipitated by the slow addition of anhydrous ether. Recrystallization from absolute alcohol-ether gave 2.61 g (75.3%) of a white crystalline compound, mp 153.5– 154.5°.

Anal. Calcd for  $C_9H_{26}INO_2$ ; C, 35.89; H, 6.69. Found: C, 35.59; H, 6.60.

three-3-Dimethylamino-2-butanol acetate methiodide (20) was prepared by the procedure given for the *erythro* system but utilizing the methiodide salt of three-3-dimethylamino-2-butanol. Recrystallization from absolute alcohol-ether afforded 2.59 g (74.3%) of a white crystalline compound, mp 105-106°.

Anal. Calcd for C<sub>2</sub>H<sub>26</sub>INO<sub>2</sub>: C. 35.89; H. 6.69. Found: C. 36.38; H. 6.63.

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### Comparison of the Hypotensive Activities of Highly Hindered Open-Chain Amines and Their Cyclic Counterparts

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A number of cyclic hindered amines substituted on the  $\alpha$ -carbon with ethynyl and vinyl groups have been prepared by the addition of Grignard reagents to ternary iminium salts including: 2-ethynyl-1,2,5,5-tetramethylpyrrolidine, 2-ethynyl-1,2,6,6-tetramethylpiperidine, 2-ethynyl-1,2,6-trimethylpiperidine, and 1,2,5,5-tetramethyl-2-vinylpyrrolidine. Together with 1,2,2,5,5-pentamethylpyrrolidine and 2,2,5,5-tetramethylpyrrolidine, these comprised a series of cyclic compounds which were compared in antihypertensive properties with a closely related series of open-chain compounds, including  $\frac{1}{2}$ -(N-t-butylmethylamino)-3-methyl-1-butyne, (3-N-t-butylmethylamino)-3-methyl-1-butene, t-amyl-t-butylmethylamine, and t-amyl-t-butylamine. Within the two series studied, the open-chain compounds are generally more potent in their hypotensive effect than the cyclic compounds.

Change in pharmacological activity with difference in chemical structure is especially significant when the compounds differ only by ring formation, that is, one of the compounds is cyclic and the other is open chain. The Hennion synthesis of highly hindered acetylenic amines<sup>3,4</sup> and their hydrogenation products made available a large number of these compounds for pharmacological evaluation. At the same time, the synthesis of highly substituted pyrrolidines and piperidines by the mercuric acetate-iminium salt route<sup>5,6</sup> made it possible to obtain an analogous series of compounds in the monocyclic system. The purpose of this paper is to report on the pharmacological activities of these two series of compounds, especially with regard to their antihypertensive properties as found in rats made hypertensive by a modification of the Goldblatt procedure. The pyrrolidine II and the piperidine III can be visualized as the cyclic counterparts of 3-(N-tbutylmethylamino)-3-methyl-1-butyne (I). The vinylpyrrolidine V is analogous to the open-chain amine IV, and 1,2,2,5,5-pentamethylpyrrolidine (VII) is similar to the saturated open-chain tertiary amine VI. The final pair of compounds which were compared in this study were IX and VIII.

**Chemistry.**—The general reaction consisting of the attack of nucleophilic reagents on ternary iminium salts has been broadly applied.<sup>7</sup> Among the nucleophiles which have been utilized were representative Grignard reagents. The acetylenic-substituted pyrrolidine II, 2-ethynyl-1,2,5,5-tetramethylpyrrolidine, was made by the addition of ethynylmagnesium bromide to 1,2,5,5-tetramethyl- $\Delta^1$ -pyrrolinium perchlorate

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(X).<sup>5</sup> The reaction of an acetylenic Grignard reagent with a ternary iminium salt has also been exemplified by Ryan and Ainsworth<sup>8</sup> in the addition of ethoxyethynylmagnesium bromide to 1,2-dimethyl- $\Delta^1$ -tetrahydropyridinium perchlorate, and by Lednicer and Babcock<sup>9</sup> in the addition of ethynylmagnesium bromide to steroidal ternary iminium salts. The characterization of the product from X, 2-ethynyl-1,2,5,5-tetramethyl-



pyrrolidine (II), was based on the infrared spectra of the base and its hydrochloride salt, both of which showed characteristic maxima associated with  $\equiv$ C—H and C=C stretching.

The addition of vinyl Grignard reagent to 1,2,5,5tetramethyl- $\Delta^1$ -pyrrolinium perchlorate (X) represents the first example of this type of combination. The product of the reaction was 1,2,5,5-tetramethyl-2vinylpyrrolidine (V), which was characterized by the infrared spectrum of the base and by the nmr spectrum of the corresponding perchlorate salt.

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