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Chemistry and Structure-Activity Relationships of Mecamylamine and Derivatives

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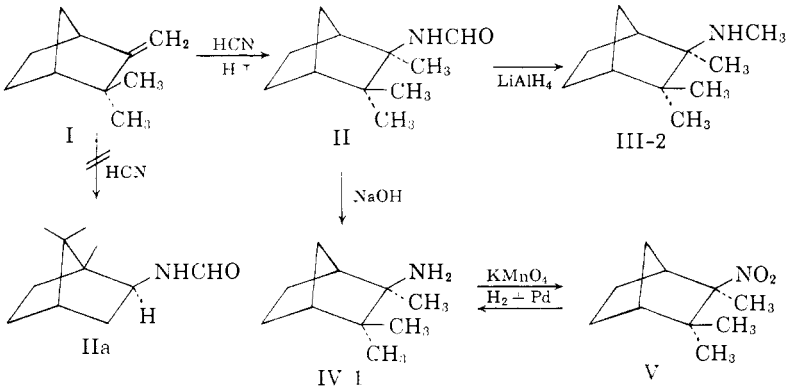
The synthesis, structure proof and resolution of mecamylamine are described. It has been established that mecamylamine is 3-methylamino-2,2,3-trimethylnorcamphane. A number of isomers of mecamylamine were made by the lithium aluminum hydride reduction of the corresponding 3-acylamino-2,2,3-trimethylnorcamphane and the catalytic reductive alkylation of the norcamphane-amine with the corresponding aldehyde ketone or alcohol. Several bicyclic analogs of mecamylamine were synthesized. Thus, 2,2-dimethyl-3-ethyl-3-methylaminonorcamphane and the *exo* and *endo* pairs of N-methylfenchylamine and 2,2-dimethyl-3-methylaminonorcamphane are described. The following monocyclic and aliphatic hindered amines were prepared: 1-N-dimethylcyclohexylamine; 1-formamido-1,2,2-trimethylcyclohexane; 3-methylamino-2,2,3-trimethylbutane, and 2,2-dimethyl-3-methylaminobutane. Structure-activity studies revealed that the angular methyl, at position 3, the methyl groups substituted at position 2 and the bridge methylenes all served as activity enhancing groups. Of the *exo–endo* pairs, the *exo* isomer was always somewhat more active. Methyl or dimethyl substitution on the amino group conferred maximum activity; all other substituents were less active. The data obtained were interpreted to indicate that actual hindrance of the amino group at position 3 was required for optimum activity.

Mecamylamine[1] (3-methylamino-2,2,3-trimethylnorcamphane, pre-

(1) G. A. Stein, M. Sletzinger, H. Arnold, W. Gaines and K. Pfister, *J. Am. Chem. Soc.*, **78**, 1514 (1956).

viously identified as 3-methylaminoisocamphane) (III-2) was the first of the sterically hindered secondary amines which exhibited a pronounced degree of ganglionic blocking action. This compound represented a marked departure in structure from the conventional bisquaternary ammonium drugs of the hexamethonium type. Notwithstanding its chemical dissimilarity, 3-methylamino-2,2,3-trimethylnorcamphane differs from these only in possessing a longer duration of action and almost quantitative absorption following oral administration. In order to correlate the relationship of structure to activity a study was undertaken to this effect. This paper is a summation of our work on the chemistry of the compounds synthesized, and the pharmacological testing and correlation of structure to activity.

Chemistry.—3-Methylamino-2,2,3-trimethylnorcamphane was made by treating racemic camphene (I) with hydrogen cyanide under strongly acidic conditions, differing somewhat from those described by Ritter and Minieri.[2] The 3-formamido-2,2,3-trimethylnorcamphane (II) thus produced was reduced with lithium aluminum hydride to mecamylamine (III-2).



This reaction of hydrogen cyanide with camphene to give the unrearranged norcamphane structure (II), rather than the isomeric N-formylisobornylamine (IIa), was unexpected since an examination of the reaction of other simple nitriles with camphene yielded in almost every case the Wagner-Meerwein rearranged product N-acylisobornylamine (IIa) as reported by Ritter and Minieri. Recently, Kochetkov, *et al.*[3] reported that trichloro- and dichloroacetonitrile also react with camphene to give the unrearranged product.

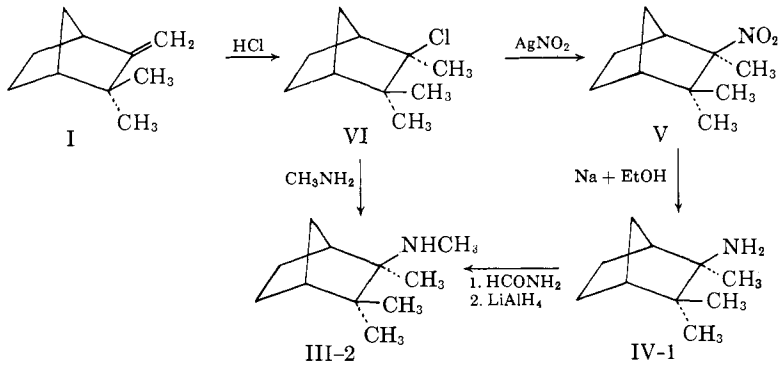
(2) J. J. Ritter and P. P. Minieri, *J. Am. Chem. Soc.*, **70**, 4045 (1948).

(3) N. K. Kochetkov, A. Ja. Khorlin and K. I. Lopatina, *J. Gen. Chem.*, U. S. S. R., **29**, 75 (1959).

The 3-amino-2,2,3-trimethylnorcamphane structure for mecamylamine was established by a direct comparison of the melting points of the formyl and the hydrochloride derivatives with the corresponding derivatives of the authentic bornyl and isobornylamines. In every case there were distinct differences. Further, the infrared spectra showed marked differences in the fingerprint region of the isomeric amines.

The oxidation of the primary amine (IV-1) with potassium permanganate[4] to the corresponding nitro derivative (V) and subsequent reduction back to IV-1 demonstrated the presence of a tertiary carbinamine structure. Since isobornylamine and bornylamine are not tertiary carbinamines, permanganate oxidation would not give rise to nitro derivatives. With all the above evidence it was clear that the structure of mecamylamine was that postulated as III-2.

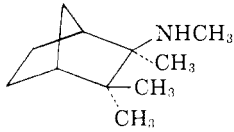
Since mecamylamine is asymmetric it was resolved by use of *d*-camphorsulfonic acid in acetone. Although racemic 3-amino-2,2,3-trimethylnorcamphane is not reported, Hückel and Nerdel[5] prepared an optically active isomer from (+)2-chloro-2,3,3-trimethylnorcamphane (VI) by the reaction with silver nitrite, followed by sodium and alcohol reduction of the nitro compound. Repetition of their work using racemic camphene gave the nitro compound V and amino compounds IV-1 and III-2 identical (infrared spectra and other physical constants) with those made *via* the Ritter reaction. Mecamylamine (III-2) also was made by treating VI with excess methylamine.



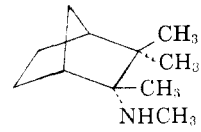
Since mecamylamine showed a very significant degree of ganglionic blocking activity it was of interest to establish some relationship of

(4) N. Kornblum and R. J. Clutter, *J. Am. Chem. Soc.*, **76**, 4494 (1954).
(5) W. Hückel and F. Nerdel, *Ann.*, **528**, 61 (1937).

structure to activity. The first group of compounds investigated were those which contained the original 3-amino-2,2,3-trimethylnorcamphane structure. Variations of the alkyl substituents on the amine were introduced by acylation with the desired acid chlorides or anhydrides. The acylated compound was then reduced with lithium hydride to the desired alkylated amine (Tables V and VI).

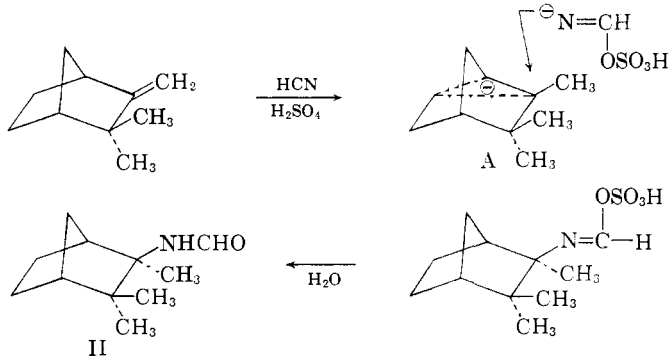


exo (III-2)



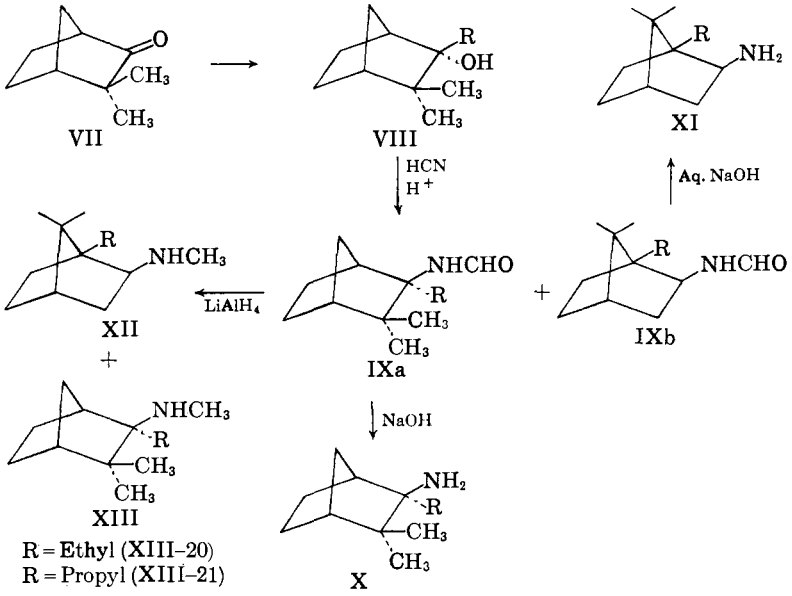
endo (III-26)

The problem of whether mecamylamine existed as the *endo* isomer (III-26) or the *exo* compounds (III-2) was of importance. Since the Ritter reaction of camphene and hydrogen cyanide gave only one product, the compound would either be the *endo* isomer (III-26) or the *exo* compound (III-2). If this reaction involved the participation of a non-classical carbonium ion (A) then the attacking negative fragment should approach from the bridgehead side to give the *exo* isomer (II). In all probability mecamylamine does possess the *exo* (III-2) configuration. However a more detailed confirmation of this point is still under investigation.

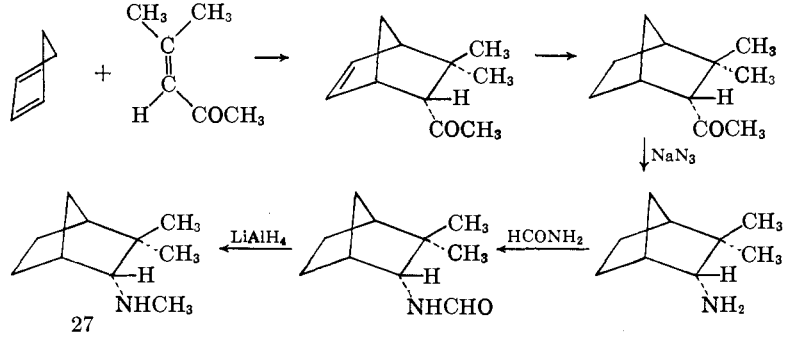


In order to further study the steric requirements necessary for biological activity in the norcamphane series it was necessary to prepare 2-amino-3,3-dimethyl-2-ethyl- and 2-amino-3,3-dimethyl-2-propylnorcamphanes. Camphenilone (VII) reacted with either ethyllithium or propyllithium to give 2-alkyl-3,3-dimethyl-2-hydroxynorcamphane (VIII). Upon treatment with hydrogen cyanide in strong acid two isomeric compounds (IXa) and (IXb) were ob-

tained. Reduction of this mixture with lithium aluminum hydride yielded the isomeric mixture of amines XII and XIII. Fractional crystallization of the hydrochlorides from methyl isobutyl ketone separated the components. The structure of the primary amine corresponding to X was differentiated from isomeric XI by permanganate oxidation using Kornblum's[4] procedure. Thus the primary amines



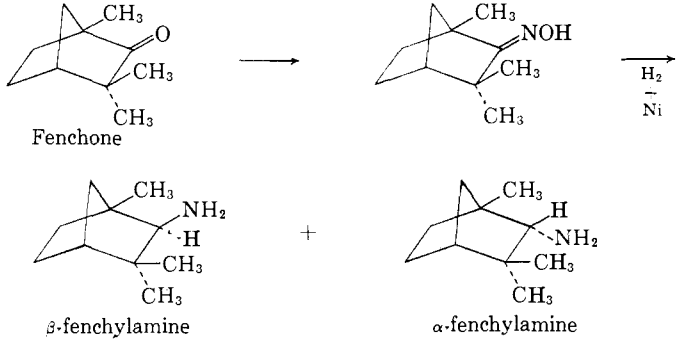
corresponding to structure X, which are *t*-carbinamines, yielded nitro compounds. The isomers were thereby distinguished since the nitro compounds were identified readily in the infrared, exhibiting the normal bands at 6.45 and 7.4 μ.



(6) W. R. Vaughan and R. Perry, Jr., *J. Am. Chem. Soc.*, **75**, 3168 (1953).

Another interesting pair of isomeric norcamphanes were the *endo*- and *exo*-3,3-dimethyl-2-methylaminonorcamphanes. The stereospecific syntheses of the parent amines have been reported previously in the literature. The procedure of Vaughan and Perry[6] was utilized for the preparation of *endo*-2-amino-3,3-dimethylnorcamphane utilizing a Diels–Alder condensation. This compound was then converted to 27 by the standard procedure. Hückel[9] synthesized a mixture of *endo* and *exo* isomers by the reduction of camphenilone oxime, with sodium and alcohol, which he separated by recrystallization of the benzoylated product. In our hands it appeared the *exo* isomer predominated in this sequence, since the ultimate product obtained was different from that of Vaughan and Perry[6] as determined by infrared spectra.

Another pair of isomeric sterically hindered bicyclic amines were those derived from fenchone. The fenchylamines were also first investigated by Hückel.[7] Utilizing the same procedure, the α (*endo*) and β (*exo*) fenchylamines were prepared. Since racemic fenchone was utilized in our work in contrast to the dextrorotary fenchone of Hückel, the results were not strictly comparable. However, on the basis of melting points, solubility and relative rate of hydrolysis of the N-benzoyl derivatives it was possible to assign the α and β configurations to the appropriate racemates. Thus the nickel catalyzed reduction of *dl*-fenchone oxime, followed by benzoylation, gave a mixture of N-benzoyl derivatives which was separated into a less soluble isomer, m.p. 188-189°, and a more soluble isomer, m.p. 99-100°. Hückel reported melting points of 164° (β) and 91° (α), respectively, for the N-benzoylfenchylamines prepared from (+)-fenchone oxime. Further, he found that the higher-melting β-N-benzoyl derivative underwent acid hydrolysis at a slower rate than the lower



(7) W. Hückel, H. Kindler and H. Wolowski, *Ber.*, **77**, 220 (1944).
(8) A. W. Ingersoll and H. D. Dewitt, *J. Am. Chem. Soc.*, **73**, 3360 (1951).

melting α isomer, which was true also for the isomers obtained from racemic N-benzoylfenchylamines.

The amine obtained from *dl*-fenchone *via* the Leuckart reaction was converted to the N-benzoyl derivative which was identical with the lower melting (99-100°) α isomer mentioned above. This is consistent with the results of Hückel[7] and Ingersoll[8] who found that the Leuckart reaction yielded the α isomer predominantly.

If the bridged methylene of the norcamphane structure were removed a cyclohexane derivative would result. Toward this end a number of substituted cyclohexylamine derivatives were synthesized. The procedures utilized for the synthesis of these compounds were either a Ritter reaction on the corresponding alcohol or unsaturated compound or a Leuckart reaction on the ketone.

The preparation of 3-methylamino-2,2,3-trimethylbutane and 2,2-dimethyl-3-methylaminobutane were undertaken as examples of simple aliphatic amines which could possibly have ganglionic blocking activity due to the largely hindered nature of their basic function. These compounds were made by a Ritter reaction on the corresponding alcohol or unsaturated compound.

Experimental

Structure-Activity Relationships.—As a measure of relative activity, the agents were studied for their ability to prevent the convulsive events due to a standard intravenous dose of nicotine by the procedure described in detail previously.[11] Briefly, several groups of 10 mice each were pretreated intraperitoneally with various doses of the compound under test 30 min. prior to the rapid intravenous injection of 0.84 mg. of nicotine base/kg. Immediately following the injection, each mouse was placed upon an elevated (610 cm.) platform, 21.3 × 27.9 cm. in dimension. If the injected mouse remained on this platform for 15 sec. it was considered protected from the excitatory and clonic convulsive phase of nicotine-induced convulsions. It is to be mentioned that (a) untreated mice injected with saline instead of nicotine remained on this platform indefinitely, (b) untreated mice injected with nicotine uniformly (100% of over 400 mice) ran off this platform within 5 sec. after being placed thereon and (c) that the proportion of treated mice remaining on the platform was directly related to the magnitude of the dose of protective agent.

The dose required to protect 50% of the mice from the excitatory and clonic convulsive events (measured as described) was calculated from the dose response line relating log dose and proportion of mice protected at each dose. The value (ED_{50}) was calculated by the moving average procedure of Thompson.[12]

As another index of ganglionic blocking activity, each compound was tested

(9) W. Hückel and W. Tappe, *Ber.*, **69**, 2769 (1936).

(10) K. E. Hamlin and M. Freifelder, *J. Am. Chem. Soc.*, **75**, 369 (1953).

(11) C. A. Stone, K. L. Meckelnburg and M. L. Torchiana, *Arch. int. Pharmacodyn.*, **117**, 419 (1958).

(12) W. R. Thompson, *Bact. Rev.*, **11**, 115 (1947).

for its ability to dilate the pupils of mice. The method employed was similar to that described by Pulewka[13] and has been described elsewhere.[11] Pupil diameters were measured with an ocular micrometer at 5, 10, 20, 40 and 80 min. after intraperitoneal administration of the compound under test. Regardless of the time interval at which it was found, the maximal (observed) dilatation was that used in subsequent potency determinations. Several doses of each drug were employed to encompass the entire dose response relationship, using 5 mice/level. The amount of agent required to dilate the pupils to 10 micrometer units (1 unit = 0.082 mm.) was estimated graphically from the dose response line and was designated the ED_{10}.

It is to be noted that the procedure adopted for measuring the effect of the compounds on the pupil allowed a reasonable estimate of the time after administration required for maximal activity. With each compound studied herein, this time was between 10 and 40 min., during which period the effects were well maintained. For this reason the nicotine convulsion studies described above were carried out 30 min. after administration of the test agents. Thus, the estimates of relative activity of the agents as determined by both methods were based upon measurements obtained at near maximal activity.

A limited number of the agents was studied with respect to their site of action. This was done by determining their effect on the contractions of the cat nictitating membrane induced by both pre- and postganglionic nerve stimulation. The contractions of both membranes of chloralosed cats (80 mg./kg. I.V.) were recorded simultaneously by appropriately weighted isotonic levels. Square wave stimuli delivered with maximal voltage were applied to the preganglionic cervical sympathetic nerve to the left membrane and to the postganglionic cervical sympathetic nerve to the right membrane. In each case, 10 per sec. pulses, each 5 msec. in duration, were delivered for 30 sec. at 5-min. intervals throughout the experiment. After appropriate control responses, the first dose of drug was injected and the effect was noted. Additional doses were given at 30-min. intervals so that the effects on preganglionically-induced contractions were reduced 20 to 80%. At least 2 cats were used with each agent studied.

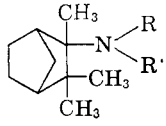
All experiments made in mice were performed using Carworth CF-1 females. All doses of all agents employed are in terms of the base weight. All derivatives of mecamylamine existing as geometric and/or optical isomers were in all probability of the *exo* configuration as the *dl* racemate unless otherwise identified.

Results.—1. Effect of Various Alkyl and Arylalkyl Substituents on the Amino Nitrogen.—As might be expected, substitution of various alkyl or arylalkyl substituents on the amino group modified activity. The data in Table I show that of the agents studied, one or two methyl groups on nitrogen (compounds 2 and 14) conferred the highest degree of activity, all other analogs being less active. Thus, mecamylamine, or its dimethylamino analog proved to be the most active members of these secondary and tertiary amines. It is clear from the data in Table I that, as the size of the alkyl substituent increases, activity decreases. This decrease in activity appeared to

(13) Pulewka, *Arch. exper. Path. u. Pharmakol.*, **168**, 307 (1932).

TABLE I

INFLUENCE OF VARIATION OF SUBSTITUENTS ON THE 3-AMINO GROUP OF MECAMYLAMINE



Compound	R	R'	Activity: Nicotine convulsions ED_{50}; mg./kg.[a] I.P.	Activity: Pupil dilatation ED_{10}; mg./kg[b] I.P.	Cat nictitating, effective dose[c] range mg./kg. I.V.
IV-1	H	H	2.8	5.2	—
III-2	H	CH_3 (mecamylamine)	0.78[d]	1.3[d]	0.25–1.0
3	H	C_2H_5	1.3	1.6	—
4	H	$(CH_2)_2CH_3$	6.4	7.5	—
5	H	$(CH_2)_3CH_3$	(toxic)	(toxic)	—
6	H	$(CH_2)_4CH_3$	11	>13.5	—
7	H	$CH(CH_3)_2$	4.9	5.2	—
8	H	$CH_2CH{=}CH_2$	5.8	8.5	—
9	H	$(CH_2)_2C(CH_3)_3$	26.5	43	—
10	H	C_6H_{13}	24	40	—
11	H	$C_6H_5CH_2$	48	83	—
12	H	$C_6H_5CH_2CH_2$	15	36	—
13	H	$C_6H_5(CH_2)_3$	45	37	—
14	CH_3	CH_3	0.71	1.5	0.25–1.0
15	C_2H_5	C_2H_5	3.2	3.8	—

[a] That dose required to antagonize the convulsions induced by a standard I.V. dose of nicotine in 50% of the mice. This value was based upon 10 mice at each of 4–5 dose levels and was calculated after Thompson.[14] See text for details.

[b] That dose required to dilate the pupils to 10 micrometer units (1 unit = 0.082 mm.). It was estimated graphically and based upon 5 mice at each of 4–5 doses.

[c] The dose range required to produce 20 to 80% reduction of contractions of the nictitating membrane induced by preganglionic nerve stimulation.

[d] The ED_{50} of mecamylamine is the average of 24 separate assays, each involving 10 mice at 4–5 dose levels. The ED_{10} is the average value of 5 assays, each involving 5 mice at 4–5 dose levels.

be the greatest with branched alkyl groups, cyclohexyl, benzyl, phenethyl and phenylpropyl (compounds 7-13).

Among the compounds in Table I, the *n*-butyl analog (compound 5) deserves special comment. A relatively high degree of toxicity prevented an estimation of activity in the nicotine convulsion assay or pupil procedure. The intravenous LD_{50} of this agent was found to be 2.5 mg./kg. (S. E. McKinney, personal communication). That this toxicity probably was associated with a neuromuscular blocking effect was demonstrated by the ability of compound 5 to block skeletal muscle contraction induced by indirect stimulation of the tibialis muscle in the dog. At the same time, however, the compound was capable of blocking nicotine-induced pressor responses (Stone, unpub-

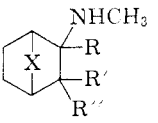
lished). This suggests that the compound does possess ganglionic blocking activity along with its neuromuscular paralyzing action, although the former cannot be estimated by the nicotine and pupil procedures.

2. Influence of Ring Methyls and Bridge Methylene Groups as Activity Enhancing Groups.—The data in Table II demonstrate that the angular methyl, the methyls at position 2 and the bridge methylene all possess an important function in terms of enhancing activity. The effect of the angular methyl may be seen by comparing compounds 16 and 17, 18 and 22, 19 and 23, and III-2 and 24. In each instance the angular methyl increased activity and produced a greater enhancement when there were fewer methyl substitutions on the other positions. Thus, there was only a minor effect of addition of the methyl to compound 24 to form compound III-2 (mecamylamine).

The enhancing activity of the methyl groups at position 2 is also evident in the data in Table II. There was a clear increase in ac-

TABLE II

INFLUENCE OF RING METHYL AND BRIDGE METHYLENE GROUPS ON ACTIVITY OF COMPOUNDS RELATED TO MECAMYLAMINE



Compound	X[e]	R	R'	R''	Activity: Nicotine convulsions[a] ED_{50}, mg./kg. I.P.	Activity: Pupil dilatation[b] ED_{10}, mg./kg. I.P.	Cat nictitating membrane effective dose range,[c] mg./kg. I.V
16	—	H	H	H	70	48	—
17	—	CH_3	H	H	6.6	21	—
18	—	CH_3	CH_3	H	1.1	3.1	—
19	—	CH_3	CH_3	CH_3	0.96	2.7	1.0 to 2.0
III-2	+	CH_3	CH_3	CH_3	0.78[d]	1.3[d]	0.25 to 1.0
XIII-20	+	CH_2CH_3	CH_3	CH_3	4.2	7.0	—
XIII-21	+	$CH_2CH_2CH_3$	CH_3	CH_3	39	50	—
22	—	H	CH_3	H	17	22	—
23	—	H	CH_3	CH_3	9.2	12	—
24	+	H	CH_3	CH_3	1.3	2.9	1.0 to 2.0

[a–d] Footnotes as in Table I. [e] —Denotes methylene bridge absent. + Denotes methylene bridge present.

tivity when one methyl was substituted at position 2, when the angular methyl was present (compounds 17 and 18), or absent (com-

pounds 16 and 22). Addition of a second methyl at position 2 effected only a slight to moderate increase in action. This can be seen by comparing the relative activities of compounds 18 and 19 and compounds 22 and 23.

The bridge methylene also acts as an activity enhancing group, as is evident by comparing compounds 19 and III-2 and compounds 23 and 24. However, it was more active as an enhancing group when the angular methyl was absent than when it was present.

The data in Table II indicate that any one of the three groups discussed is important from the viewpoint of enhancing activity. In addition, any one of three groups results in compounds with near maximal activity if supported by the presence of one of the other enhancing groups. Thus, near-maximal activity can be achieved by the presence of any two of the three groups. The importance of the group in the angular position is also shown by the fact that groups larger than methyl, such as ethyl (XIII-20) or propyl (XIII-21) result in a decrease in activity apparently proportional to the size of the group. Evidently, the group in the angular position must be of a critical size to assure its maximum influence.

3. Geometric and Optical Isomerism.—The availability of a number of geometric and optical isomers of mecamylamine and closely related structures allowed the assessment of such factors on activity within the series. Table III shows the pairs of geometric isomers examined. In each pair (compound 26 and 27 and 28 and 29) the β or *exo* isomer is somewhat more active than its corresponding α or *endo* isomer.

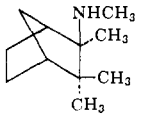
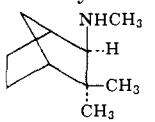
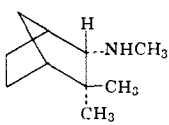
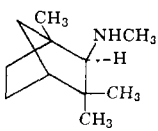
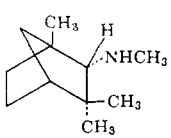
Only one optical isomer of mecamylamine was examined separately, namely, the *d* isomer (compound 25, Table III) which possessed an activity essentially equal to its corresponding racemate (mecamylamine, III-2). This result suggests that optical isomerism does not play a significant role in determining degree of activity. It is not known whether this holds true with respect to any other of the closely related analogs which possess asymmetric carbon atoms.

4. Partial Structures.—Two partial structures of mecamylamine were examined for activity by the procedures described. These are shown in Table IV and it is seen that one of these (compound 31) possesses a relatively high order of activity. This substance possesses two of the three important enhancing groups which are apparently responsible for its remarkable degree of activity for such a molecule.

Discussion.—The structure–activity relationships of mecamylamine and its various derivatives indicate that the highly basic amino

TABLE III

ACTIVITY OF GEOMETRIC AND STEREOISOMERS OF MECAMYLAMIN

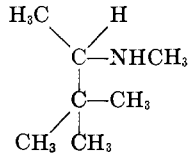
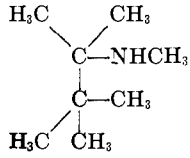
Compound	Configuration	Activity: Nicotine convulsions[a] ED_{50}; mg./kg. I.P.	Activity: Pupil dilatation ED_{50}; mg./kg. I.P.	Cat nictitating membrane effective dose range[c] mg./kg. I.V.
III-2 *d,l*-mecamylamine		0.78[d]	1.3[d]	0.25 to 10
25	*d*-mecamylamine	0.92	1.0	—
26		1.3	2.9	—
d,l exo form				
27		2.0	4.6	—
d,l-endo form				
28		1.0	2.2	0.5 to 1.0
d,l-exo form				
29		3.0	5.2	—
d,l-endo form				

[a] Footnotes as in Table I.

nitrogen must be hindered to a critical degree by the surrounding alkyl substituents. Of the hindering groups, the alkyl substituents in the angular position, the carbon adjacent to the nitrogen bearing carbon and the bridge methylene all are significant. It is clear from the data in this report that if hindrance is too great, as when the alkyl group in the angular position is large, then activity is diminished. The effect of critical hindrance is that it may give rise to optimal conditions for receptor fit. However, other factors such as differences in distribution, metabolism or excretion, or alteration of

TABLE IV

RELATIVE ACTIVITY OF PARTIAL STRUCTURES OF MECAMYLAMINE

Compound	Structure	Activity: Nicotine convulsions[a] ED_{50}, mg./kg. I.P.	Activity: Pupil dilatation[b] ED_{10}, mg./kg. I.P.	Cat nictitating membrane effective dose range[c] mg./kg. I.V.
III-2	mecamylamine	0.78[d]	1.3[d]	0.25 to 1.0
30		4.9	13.0	5.0 to 10.0
31		0.96	4.9	1.0 to 2.0

[a] Footnotes as in Table I.

the basicity of the nitrogen atom may also be involved to various degrees.

The difference in activity of the two geometric isomeric pairs may also be explained on the basis of critical hindrances. In the case of compounds 26 and 28 (*exo* isomers), the methylamino group lies in the same plane as the bridge methylene, whereas in the *endo* isomers (27 and 29) the methylamino group lies below the bridge methylene and, in fact, tends to lie within the cage created by the bridge. This suggests that the *endo* isomer is less active because the hindrance is more than optimum.

Bretherick, *et al.*[14] recently reported a structure-activity relationship study of pempidine and various derivatives. Their study indicated that the most important groups governing activity were the substituents on the carbons adjacent to the endocyclic nitrogen atom. Maximal or near-maximal activity was achieved by trimethyl or tetramethyl substitution, whereas dimethyl substitution resulted in nearly complete loss of activity. Thus, the results obtained with the pempidine series of compounds paralleled the data reported here on mecamylamine and derivatives.

A number of the compounds reported here have been studied for

(14) L. Bretherick, G. E. Lee, E. Lunt, W. R. Wragg and N. D. Edge, *Nature*, **184**, 1707 (1959).

ganglionic blocking activity by other workers.[15-18] While the methods of assessment have differed, the results obtained are in general agreement and support the conclusions reached in this investigation.

While the mydriatic effect of ganglionic blocking agents has been employed by several workers to assess activity[19] the antagonism of nicotine-induced convulsions has not been similarly employed to the same extent. Prior studies[11] however, have demonstrated that the ability to block such convulsions may be a general attribute of such drugs. This applies particularly when the index of protection was measured as described in this study since anticonvulsant, antitremor agents, depressants and other unrelated classes exerted only partial protection.[11] Moreover, the nonquaternary ammonium type of ganglionic blocking agents were much more effective against nicotine-induced convulsions than quaternary ammonium derivatives, such as pentolinium and hexamethonium.[11-20] Thus, within this series of nonquaternary ammonium derivatives of mecamylamine, the relative ability to antagonize nicotine-induced convulsions is most likely a true reflection of ganglionic blocking action. Further support for this concept may be seen in Figure 1 which shows the relationship between the activity of each compound with respect to dilating the pupil (ED_{10}) and antagonizing nicotine-induced convulsions (ED_{50}). It is clear that as activity decreases by one measure, the degree of activity by the other also decreases. The linear relationship depicted has a correlation coefficient of 0.95, which is highly statistically significant. It should be mentioned, however, that this type of correlation may not exist with widely divergent structures, especially if quaternary ammonium derivatives are compared with nonquaternary ammonium compounds.[11] Even with quaternary ammonium derivatives, however, a positive correlation may be obtained in a closely related homologous series.[11,21]

The use of the effects of compounds on the mouse pupil as a measure of inherent ganglionic blocking action is also open to certain reservations. First, a mydriatic effect may readily be produced by an atropine-like or by a sympathomimetic-like action. With all agents

(15) K. Rubinstein, J. G. A. Pedersen, J. Fakstorp and V. Roonnov-Jessen, *Experientia*, **14**, 222 (1958).

(16) M. Protiva, M. Rajsner, V. Trcka, M. Vanecek and Z. J. Vejdelek, *Experientia*, **15**, 54 (1959).

(17) Z. J. Vejdelek and V. Trcka, *Experientia*, **15**, 215 (1959).

(18) N. D. Edge, S. J. Corne, G. E. Lee and W. R. Wragg, *Brit. J. Pharmacol.*, **15**, 207 (1960).

(19) J. G. Blackman, F. M. Fastier, C. M. Patel and L. C. K. Wong, *Brit. J. Pharmacol.*, **11**, 282 (1956).

(20) S. J. Corne and N. D. Edge, *Brit. J. Pharmacol.*, **13**, 339 (1958).

(21) D. R. Laurence and R. S. Stacey, *Brit. J. Pharmacol.*, **7**, 80 (1952).

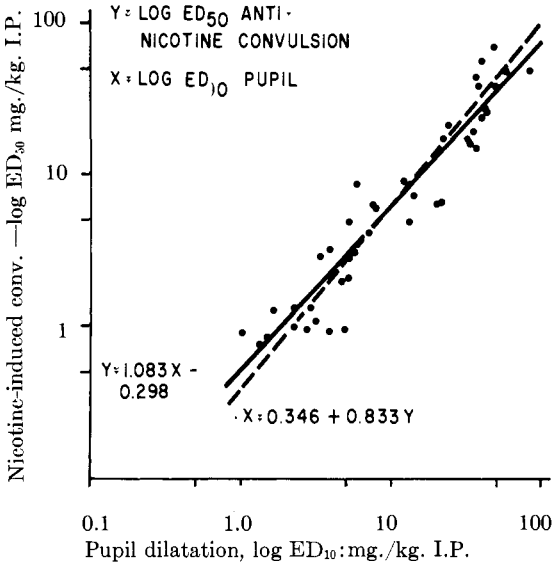


Fig. 1.—Relationship of potency of mecamylamine congeners measured by antagonism of nicotine-induced convulsions and by dilatation of the pupils in mice. The data include the values obtained with the compounds discussed in the text along with an additional 11 closely related structures not discussed. See text for explanation.

reported here, however, none was capable of antagonizing acetylcholine-induced contractions of the isolated rabbit intestine in concentrations 10,000 to 20,000 times greater than effective concentrations of atropine (Stone, unpublished). Sympathomimetic-like inhibition of the intestine also was not observed. From this it is unlikely that either activity biased the measurements reported.

Secondly, since analgesic substances have been demonstrated to dilate the pupils of mice it is conceivable that such activity (presumably central) could also be involved with some of the agents included in this study. This possibility seems remote because mecamylamine and several of the other agents were studied by the procedure of D'Amour and Smith[22] for analgesic activity and no such activity was found (Stone, unpublished). Nonetheless, the possibility remains that, with some of the agents, central actions resulting in pupillary dilatation could be involved.

That the nicotine convulsion and mouse pupil assay methods employed probably reflected ganglionic blocking activity was also sup-

(22) F. E. D'Amour and D. L. Smith, *J. Pharmacol. Exper. Therap.*, **72**, 74 (1941).

ported by the observations that of the seven agents examined for such activity using the cat nictitating membrane all proved to possess classical ganglionic blocking properties. The various compounds studied are identified in Tables I–IV in which are given the effective dose ranges required to reduce contractions induced by preganglionic nerve stimulation by 20 to 80%. In no case were postganglionic-induced contractions influenced. Thus, in each instance a site of action at the ganglia was established and an approximate correlation exists between the potency of the individual agents as measured by the mouse pupil and nicotine-convulsion assays with the effective dose range as established on the cat nictitating membrane. Thus, at least with the compounds studied by all three procedures the assays performed in mice yielded results predictive of ganglionic blocking action.

Experimental

Synthesis and Structure Proof of Mecamylamine. 3-Formamido-2,2,3-trimethylnorcamphane (II).—To a solution of 31.7 g. (0.23 mole) of camphene in 60 ml. of glacial acetic acid at 2° was added 10 ml. of liquid hydrogen cyanide. To this solution was added, with stirring at 0–3°, a solution of 63 ml. of concd. sulfuric acid, 58 ml. of glacial acetic acid, and 4 ml. of water over a period of 6 hr. The reaction was exothermic and good cooling was necessary. The mixture was stirred an additional hr. at 0–3°, then the temperature raised to 22°, and put under vacuum (25 mm.) for 10 min. in order to remove excess hydrogen cyanide. It was then quenched with cold water (500 ml.) keeping the temperature at 20°, extracted with chloroform and the organic layer washed with water and sodium bicarbonate until neutral. The chloroform layer was dried over anhydrous sodium sulfate, filtered, and concentrated on the steam bath at 25 mm. to dryness. The residue was diluted with 140 ml. of heptane and then refluxed and cooled. A white crystalline solid precipitated. This was filtered, washed with heptane and dried; yield 30.6 g.

3-Amino-2,2,3-trimethylnorcamphane (IV-1).—3-Formamido-2,2,3-trimethylnorcamphane (II) was hydrolyzed by dissolving 500 g. in 1 l. of methanol and then adding with stirring 180 g. of sodium hydroxide in 500 ml. of water. The mixture was refluxed for 20 hr. and the methanol distilled *in vacuo* until two phases separated. The residue was diluted with 1 l. of water and then extracted with 2 × 1 l. of ether. The ether extracts were dried over anhydrous magnesium sulfate, filtered and concentrated to dryness. The concentrate was practically pure 3-amino-2,2,3-trimethylnorcamphane. This was utilized for the preparation of other analogs listed in Table I. In order to prepare the hydrochloride the original ethereal solution was acidified with hydrogen chloride. The insoluble hydrochloride was filtered and dried; yield 379 g. (90%). For analysis the salt was recrystallized from 0.5 *N* aqueous hydrochloric acid.

The infrared spectrum of the above hydrochloride in chloroform was identical with that prepared by Hückel's[5] procedure from the reduction of the 3-nitro-2,2,3-trimethylnorcamphane. Further, the 3-amino-2,2,3-trimethylnorcamphane

hydrochloride prepared by Hückel's[5] procedure was formylated by heating with excess formamide at 156° for 16 hr. and after dilution with water and extraction with ether gave a compound identical with II by melting point and infrared spectra. Thus the infrared absorption spectra in carbon tetrachloride exhibited normal functional bands for N–H at 3.04 μ, C=O 5.90 μ and N–H bending at 6.5 μ, and identical bands in the fingerprint region.

dl-**Mecamylamine (III-2) (3-Methylamino-2,2,3-trimethylnorcamphane Hydrochloride).**—To a nitrogen purged solution of 4.55 g. of lithium aluminum hydride in 170 ml. of anhydrous ether was added slowly a solution of 11.0 g. of II in 120 ml. of anhydrous ether. The rate of addition was adjusted so that the ether refluxed gently. The mixture was then heated at reflux for an additional 4 hr. The excess lithium aluminum hydride was decomposed by cautious addition of 20 ml. of water. After filtration from the insoluble salt, the ethereal solution of base was acidified by the addition of 2-propanolic hydrogen chloride which precipitated the hydrochloride of 3-methylamino-2,2,3-trimethylnorcamphane. After filtering, washing with ether and drying, the product weighed 11.4 g. (92%). It was identical with the compound obtained by reducing 3-formamido-2,2,3-trimethylnorcamphane obtained by the Hückel procedure when the infrared spectra and melting points were compared.

Resolution of *dl*-mecamylamine.—To a cold solution of 25 g. of *dl*-methylamino-2,2,3-trimethylnorcamphane hydrochloride in 200 ml. of water was added 50 ml. of 2.5 *N* sodium hydroxide. The base was extracted with 2 × 100 ml. of ether. The ether extracts were dried over anhydrous magnesium sulfate, filtered and concentrated to give 21 g. of product. The optically-active salt was made by mixing a solution of the amine (21 g.) in 210 ml. of acetone with a solution of 26.5 g. of *d*-camphorsulfonic acid in 200 ml. of acetone. The first crop of crystals was filtered after standing for 2 hr. at 25°. The *d*-3-methylamino-2,2,3-trimethylnorcamphane *d*-camphorsulfonate salt melted at 213–214°, $[\alpha]^{25}D$ +31.2° (c = 0.8% in absolute ethanol). Recrystallization from acetone did not increase the specific rotation or m.p. of the salt.

d-3-Methylamino-2,2,3-trimethylnorcamphane was prepared by treating the *d*-camphorsulfonate salt with an equivalent of 2.5 *N* sodium hydroxide and extracting the liberated base with ether. The ether extract after drying over anhydrous magnesium sulfate and filtration was treated with ethereal HCl to precipitate the hydrochloride which after two recrystallizations from 2-propanol had $[\alpha]^{25}D$ +20.6 (c = 1.5% in $CHCl_3$), m.p. 262–264° dec.

In order to obtain the *levo* isomer, the original acetone mother liquors were concentrated to a point where crystallization occurred. The solution was cooled and filtered. The crude salt had a rotation of $[\alpha]^{25}D$ +23° (c = 1.5% in absolute ethanol). It was converted to the crystalline amine hydrochloride following the procedure illustrated above, $[\alpha]^{25}D$ −10° (c = 1.5% in $CHCl_3$), m.p. 258° dec. This hydrochloride was further purified by repeated crystallization from 2-propanol to rotation equal and opposite to the rotation of the *dextro*-rotating isomer, $[\alpha]^{25}D$ −20.6°.

Mecamylamine via Camphene Hydrochloride and Methylamine.—Camphene hydrochloride (10.0 g.) and a solution of 12 g. of methylamine in 50 ml. of ether were heated in a bomb at 50° for 18 hr. The mixture was concentrated to dryness and residue extracted thoroughly with ether. The insoluble methylamine hydrochloride was removed by filtration. The filtrate was acidified with ethereal hydrogen chloride. The precipitate was filtered, washed with ether and dried *in*

vacuo. Recrystallization from 2-propanol gave 0.59 g. (5%) of product, m.p. 246–247°. The melting point was not depressed on admixture with an authentic sample of mecamylamine hydrochloride (III-2). The infrared spectra of the product and an authentic sample were identical.

Oxidation of 3-Amino-2,2,3-trimethylnorcamphane (IV-1) to 3-Nitro-2,2,3-trimethylnorcamphane (V).—A solution of 5.0 g. of the amine (IV-1) in 25 ml. of benzene was added to 10.0 g. of potassium permanganate in 200 ml. of water. After stirring at room temperature for 18 hr., the mixture was heated at 50° for 6 hr., cooled and filtered through Supercel. The benzene layer was separated and the aqueous layer extracted with 2 × 20 ml. of benzene. The combined benzene extract was washed with 2.5 *N* hydrochloric acid and water and then dried and concentrated. The residue was then chromatographed on 40 g. of acid-washed alumina. The petroleum ether eluates were combined and, after evaporation of the solvent, the residue was fractionally sublimed twice to yield the nitro compound as white crystals, m.p. 199–200°.

Anal. Calcd. for $C_{10}H_{19}NO_2$: C, 65.51; H, 9.14; N, 7.64. Found: C, 65.44; H, 9.16; N, 7.43.

Infrared spectra in chloroform confirmed the nitro structure: bands at 6.45 and 7.4 μ.

COMPARISON OF THE N-FORMYL DERIVATIVES OF ISOBORNYLAMINE, BORNYLAMINE AND 3-AMINO-2,2,3-TRIMETHYLNORCAMPHANE[a] (II)

Derivatives	M.p., °C.	Infrared spectra in CCl_4, μ
N-Formylisobornylamine	68–69	NH, 3.04; CO, 5.90; N–H bending 6.5; differentiating bands 7.8, 8.2, 9.28.
N-Formylbornylamine	87.5	NH, 3.04; CO, 5.90; N–H bending 6.5; differentiating bands 8.70, 9.70, 11.18.
3-Formamido-2,2,3-trimethylnorcamphane (II)	170–174	NH, 3.04; CO, 5.90; N–H bending 6.5; differentiating bands 7.89, 8.87, 9.59.

[a] The difference in melting points, as well as in the fingerprint region of the infrared spectrum, shows that compound II does *not* possess an isobornyl or bornylamine type structure.

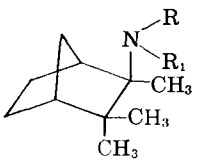
Preparation of 3-Alkylamino-2,2,3-trimethylnorcamphanes.—Table V gives a summation of all the 3-alkylamino-2,2,3-trimethylnorcamphanes synthesized. The methods of preparation are illustrated in the following generalized procedures.

General Procedure for Acylation of 3-Amino-2,2,3-trimethylnorcamphane (Table VI).—To 6.0 g. of 3-amino-2,2,3-trimethylnorcamphane with ice cooling was added 12 ml. of the acyl chloride in 3 ml. portions with stirring over 10 min. To this thick slurry was added slowly 60 ml. of 20% sodium hydroxide with stirring. After 2–3 hr. the reaction mixture was diluted with water (200 ml.) and extracted with 3 × 60 ml. benzene. The benzene extracts were washed with water, 2.5 *N* hydrochloric acid and finally with water. The benzene layer was dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was recrystallized.

3-Alkylamino-2,2,3-trimethylnorcamphane (Table V): A.—To 1.75 g. of lithium aluminum hydride in 300 ml. of anhydrous ethyl ether was added 0.025

TABLE V

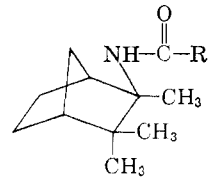
SUMMATION OF DATA FOR 3-ALKYLAMINO-2,2,3-TRIMETHYLNORCAMPHANES



·HCl

Compound	Prepn.	R	R_1	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	M.p., °C.	Solvent for recrystallization
IV-1		H	H	63.30	63.59	10.63	10.79	7.38	7.06	>300	0.5 *N* aq. HCl
III-2		H	CH_3	64.83	64.54	10.87	10.67	6.88	6.90	243–246	2-Propanol
3	A	H	C_2H_5	66.18	66.04	11.18	11.16	6.43	6.16	212.5–213	2-Propanol
4	A	H	*n*-C_3H_7	67.35	67.07	11.31	11.07	6.04	6.05	231–233	2-Propanol
5	A	H	*n*-C_4H_7	68.40	68.75	11.48	11.72	5.70	5.96	212–213	Methyl isobutyl ketone
6	A	H	*n*-C_5H_{11}	69.32	69.47	11.67	11.48	5.39	5.49	200–201	Methyl isobutyl ketone
7	C	H	*i*-C_3H_7	67.35	67.18	11.31	11.26	6.04	6.21	226–228	Aqueous HCl
8	B	H	C_3H_5 (allyl)	67.99	67.73	10.59	10.33	6.09	6.55	215–215.5	Methyl isobutyl ketone
9	A	H	$CH_2CH_2C(CH_3)_3$	70.16	70.25	11.78	11.86	5.12	5.31	233–234	Methyl isobutyl ketone
10	G	H	*n*-C_6H_{13}	70.68	71.10	11.13	11.22	5.15	4.56	212 dec.	Aqueous HCl
11	D	H	$C_6H_5CH_2$	72.96	72.90	9.37	9.25	5.01	5.28	197–198	Benzene
12	A	H	$C_6H_5(CH_2)_2$	73.56	73.14	9.60	9.52	4.77	4.91	220–222	Dioxane
13	A	H	$C_6H_5(CH_2)_3$	74.11	73.98	9.82	9.52	4.55	4.67	208–208.5	Water
14	F	CH_3	CH_3	66.18	66.17	11.11	10.81	6.43	6.54	166–169	Methyl isobutyl ketone
15	E	C_2H_5	C_2H_5	68.41	68.16	11.48	11.20	5.66	4.88	145–147	Benzene

TABLE VI



Compound R	M.p., °C.	—Carbon, %— Calcd.	Found	—Hydrogen, %— Calcd.	Found	—Nitrogen, %— Calcd.	Found
H[a]	170–174	70.96	70.67	11.31	11.03	8.28	8.53
CH_3	133–133.5	73.77	73.48	10.83	10.58	7.18	7.18
C_2H_5	95–97	74.59	75.02	11.07	10.94	6.71	7.08
n-C_3H_7	75–76.5	75.28	75.49	11.28	11.01	6.27	6.33
$(CH_3)_3CCH_2$	107–108.5	76.44	76.13	11.63	11.48	5.57	5.59
n-C_4H_9	55–58	75.89	75.86	11.47	11.16	5.90	5.64
$C_6H_5CH_2$	127–128	79.33	79.39	9.01	8.87	5.44	5.15
$C_6H_5CH_2CH_2$	90.5–92	79.95	80.23	9.54	9.35	4.90	5.20

[a] This compound was made by Ritter reaction on camphene with HCN. All the other compounds were made by acylation of the 3-amino-2,2,3-trimethylnorcamphane.

mole of acylated norcamphaneamine in 100 ml. of anhydrous ether over a period of 25 min. with stirring. After refluxing for 3 hr. the mixture was cooled and 8.3 ml. of water added with good agitation. The supernatant ether was filtered and washed with water, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated *in vacuo* to a small volume and the salt precipitated with ethereal hydrogen chloride. After filtering and washing with ether the solid was recrystallized from the appropriate solvent.

B.—A mixture of 3-amino-2,2,3-trimethylnorcamphane (3 g.), 20 ml. of ethanol, 5.04 g. of sodium bicarbonate and 1.9 ml. of allyl bromide was refluxed for 16 hr. with stirring. The reaction mixture was filtered and concentrated *in vacuo* to an oil. The residue was dissolved in ether and filtered from insolubles. The solution was treated with ethereal hydrogen chloride and the product deposited. After filtration and recrystallization from methyl isobutyl ketone pure product was obtained.

C.—A solution of 15.33 g. (0.1 mole) of 3-amino-2,2,3-trimethylnorcamphane in 100 ml. of 2-propanol was hydrogenated at 200° in the presence of Raney nickel catalyst at 14 kg./cm.^{2} for 6 hr. After filtration to remove catalyst the 2-propanol was distilled off and the crystalline slurry was heated at reflux in 50 ml. benzene. A total of 7.2 ml. benzaldehyde was added portionwise to the refluxing solution over a period of 4 hr. at the end of which time the amount of water collected became constant (0.7 ml.). After removal of benzene and benzaldehyde the N-benzal-N-isopropyl mixture was fractionally distilled. The 3-isopropylamino-2,2,3-trimethylnorcamphane[8] (1.585 g.) distilled at 50–60° (0.6–1.0 mm.), $n^{23}D$ 1.4745, whereas the N-benzal-derivative distilled at 130° (0.6–0.8 mm.), $n^{23}D$ 1.5543. The hydrochloride of the N-isopropyl derivative was formed by redissolving the free base in aqueous hydrochloric acid, extracting with benzene, and concentrating the aqueous solution to dryness; yield 1.285 g.

D.—A mixture of 3-amino-2,2,3-trimethylnorcamphane (10.0 g.), benzene (100 ml.) and benzaldehyde (6.9 g.) was refluxed for 2 hr. and 45 min. Water formed during the reaction was removed by a water separator. The reaction mixture, after hydrogenation at low pressure using 1.0 g. of 5% palladium-on-carbon catalyst, was filtered and concentrated *in vacuo* to a pale yellow oil (13.6 g., 95%). Precipitation of the product as the hydrochloride with ethereal hydrogen chloride, followed by recrystallization from hot benzene, afforded pure product (11-Table V) (6.90 g., 44.5%).

E.—3-Ethylamino-2,2,3-trimethylnorcamphane (19.0 g.) was acetylated with 76 ml. of acetic anhydride and 0.4 ml. of concentrated sulfuric acid by heating on the steam bath for 4 hr. After quenching in 600 ml. of water, filtering and washing, 17.5 g. (75%) of the (N-ethyl-N-acetyl)-2,2,3-trimethylnorcamphane was obtained, m.p. 83.5–85°. Reduction of this amide (18.38 g.) with lithium aluminum hydride (33.4 g.) in 1000 ml. of anhydrous ether for 68 hr. using normal procedure and precipitation of the hydrochloride yielded 20.26 g. (100%) of product.

F.—A mixture of 20 g. of 3-amino-2,2,3-trimethylnorcamphane, 150 ml. of water, 34 ml. of 40% formalin, 1.0 g. of sodium acetate and 2.0 g. of 5% palladium-on-charcoal was hydrogenated at room temperature and 2.8 kg./cm.^{2} for about 18 hr. After this time, the equivalent of 1 mole of hydrogen was absorbed and the reaction had slowed down considerably. Two grams of fresh catalyst was then added to the reaction mixture and hydrogenation continued for 24 hr. longer when another mole of hydrogen was absorbed. After filtering the catalyst, the colorless clear filtrate was concentrated *in vacuo* at 40–50° and the residual oil flushed several times with water and ethanol to remove excess formaldehyde. The partially crystalline residue was dissolved in 100 ml. of water and the solution rendered alkaline with 45 ml. of 2.5 *N* sodium hydroxide with ice cooling. The free amine was extracted with ether, washed with water and dried. After removal of the solvent the pale yellow oily residue (18 g.) was fractionally distilled *in vacuo;* yield 16.2 g. (85%), b.p. 65–66° (2 mm.), n^{25}D 1.4898.

The hydrochloride salt was precipitated from anhydrous ether with dry hydrogen chloride.

G.—A mixture of 7.63 g. of 3-amino-2,2,3-trimethylnorcamphane, 4.91 g. of cyclohexanone and 50 ml. of xylene was heated at reflux for 44 hr. removing water continuously. After removal of the xylene *in vacuo*, 75 ml. of ethanol was added and the mixture reduced with Raney nickel at 92.8 kg./cm.^{2} and 100°. The catalyst was removed by filtration and the solvent removed *in vacuo* to give 4.5 g. of crude product as an oil. A solution in 10% hydrochloric acid was extracted with ether and then concentrated *in vacuo* to 3.8 g. of crystalline mass. The residue was dissolved in 40 ml. of hot 2-propanol and the cooled solution filtered to remove a small amount of insolubles. After removal of the solvent, the residue was disssolved in 15 ml. of water, made alkaline and extracted with ether. The ether was washed with water, dried and evaporated to dryness. The residue was then redissolved in dilute hydrochloric acid, filtered and evaporated to give 550 mg. of 3-cyclohexylamino-2,2,3-trimethylnorcamphane.

Bicyclic Analogs and Isomers of Mecamylamine. 2,2-Dimethyl-3-ethyl-3-hydroxynorcamphane (VIII).—Five grams (0.036 mole) of camphenilone in 15 ml. of ether was added in 20 min. at 0–10° to freshly prepared ethyllithium (0.06 moles) in 200 ml. of ether. After 4 hr. at 25° the mixture was poured into 100 g. of ice, the ether separated and the aqueous layer extracted with 50 ml. of ether.

The ether solution was dried with magnesium sulfate and evaporated to give 6.4 g. of oil. Distillation gave 5.0 g., b.p. 89–93° (7 mm.), $n^{25}D$ 1.4872.

Anal. Calcd. for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found: C, 78.76; H, 11.57.

2,2-Dimethyl-3-ethyl-3-formamidonorcamphane (IXa) and 7,7-Dimethyl-1-ethyl-2-formamidonorcamphane (IXb).—To 25 ml. of glacial acetic acid was added 17.3 g. (0.354 mole) of sodium cyanide portionwise followed by 19.9 g. (0.118 mole) of 2,2-dimethyl-3-ethyl-3-hydroxynorcamphane (VIII) keeping the temperature below 20°. The mixture was allowed to warm to 25° and then heated at 60–70° for 3.5 hr. After standing overnight at 25° it was poured into 200 g. of ice, made alkaline with 30% caustic, and extracted with 200 ml. and 2 × 10 ml. of ether. The ether extract was washed with water, dried with magnesium sulfate and evaporated to give 23.7 g. of oil. Distillation gave 19.1 g., b.p. 139–143° (2 mm.), $n^{25}D$ 1.5074. This distillate was a mixture of isomers IXa and IXb.

Anal. Calcd. for $C_{12}H_{21}NO$: C, 73.79; H, 10.84; N, 7.17. Found: C, 73.26; H, 10.77; N, 7.13.

2,2-Dimethyl-3-ethyl-3-aminonorcamphane (X) and 2-Amino-7,7-dimethyl-1-ethylnorcamphane (XIII).—A mixture (18.7 g.) of formamido compounds IXa and IXb was dissolved in 130 ml. of ethylene glycol and 11.1 g. of potassium hydroxide was added. The mixture was heated at 200° for 2 hr., distilling the amines into 10% hydrochloric acid as they formed. After extracting the distillate with ether it was made alkaline and the amines were extracted with ether. The ether was evaporated and the residue distilled, giving 12.9 g. of an oil, b.p. 115–116° (25 mm.).

A mixture (37.6 g.) of amines (X and XI) was dissolved in 650 ml. of ether. Excess anhydrous hydrogen chloride gave 16.7 g. of salt which was recrystallized from 700 ml. of methyl isobutyl ketone to give 12.7 g. of isomer X. The ethereal mother liquors were concentrated to 150 ml. to give a second crop of 12.5 g. Recrystallization from 80 ml. of ethyl acetate gave 10.7 g. of isomer XI. Infrared analysis of the two isomers indicated the same functionality but showed differences in the fingerprint region. In order to prove the structure each isomer (X and XI) was converted to the free base by neutralization of 3.65 g. of the hydrochloride with 1 *N* sodium hydroxide and the free base extracted with benzene. The organic layer was then concentrated to 10 ml. and 25 ml. of water added. This solution was oxidized at 30° by slow addition of potassium permanganate (15 g.) until no more permanganate was consumed, and then heated at 60° for 7 hr. Unreacted permanganate was left at the end of the reaction. After filtration the product was extracted with ether, washed with dilute hydrochloric acid and water, dried and concentrated to an oil. The infrared spectrum of the product from isomer X showed nitro bands at 6.45 and 7.4 μ, whereas the oxidation product from the isobornyl isomer (XI) showed no indication of nitro groups.

2,2-Dimethyl-3-ethyl-3-methylaminonorcamphane (XIII-20).—2,2-Dimethyl-3-ethyl-3-aminonorcamphane (X) (1 g.) in 4 ml. of formamide was heated at 165° for 16 hr., poured into 50 g. of ice and extracted with ether to give 1 g. of an oil. The formyl compound was reduced with lithium aluminum hydride in ether in the usual manner to give 2,2-dimethyl-3-ethyl-3-methylaminonorcamphane, isolated as the hydrochloride salt, m.p. 285° dec.

Anal. Calcd. for $C_{12}H_{24}ClN$: C, 66.18; H, 11.11; N, 6.43. Found: C, 66.61; H, 10.94; N, 6.83.

Infrared analysis of this compound (XIII-20) showed bands at 9.4 μ, 10.1 μ, 11.3 μ and 12.1 μ in addition to the known functionalities.

2,2-Dimethyl-3-*n*-propyl-3-hydroxynorcamphane (VIII).—This compound was prepared from camphenilone (10 g.) with *n*-propyllithium as in Example VIII. The product was distilled to give an oil (10.4 g.), b.p. 81–85° (3 mm.), $n^{25}D$ 1.4840.

Anal. Calcd. for $C_{12}H_{22}O$: C, 79.06; H, 12.16. Found: C, 79.21; H, 12.49.

2,2-Dimethyl-3-formamido-3-*n*-propylnorcamphane (IXa) and 7,7-dimethyl-2-formamido-1-*n*-propylnorcamphane (IXb).—When subjected to the Ritter reaction with hydrogen cyanide, 10.1 g. of VIII gave a mixture of IXa and IXb which, upon distillation, yielded a viscous oil (9.6 g.), b.p. 144–148° (2 mm.)

Anal. Calcd. for $C_{13}H_{23}NO$: C, 74.59; H, 11.07; N, 6.69. Found: C, 74.56; H, 10.58; N, 6.32.

2,2-Dimethyl-3-methylamino-3-*n*-propylnorcamphane hydrochloride (XIII-21).—Lithium aluminum hydride reduction in ether of 9.0 g. of the mixture of 2,2-dimethyl-3-formamido-3-*n*-propylnorcamphane and 7,7-dimethyl-2-formamido-1-*n*-propylnorcamphane afforded 3.6 g. of a mixture of the hydrochlorides. Recrystallization from 175 ml. of ethyl acetate gave 800 mg. of 2,2-dimethyl-3-methylamino-3-*n*-propylnorcamphane hydrochloride, which was further purified by recrystallization from 300 ml. of ethyl acetate, yielding 400 mg., m.p. 299° dec.

Anal. Calcd. for $C_{13}H_{26}ClN$: C, 67.35; H, 11.30. Found: C, 67.12; H, 10.79.

The second crop (1.3 g. of impure 7,7-dimethyl-2-methylamino-1-*n*-propylnorcamphane hydrochloride) obtained by concentration of crop one mother liquors to 50 ml. was purified by recrystallization from 100 ml. of ethyl acetate to give 450 mg., m.p. 232–235°.

Anal. Calcd. for $C_{13}H_{26}ClN$: C, 67.35; H, 11.30. Found: C, 67.81; H, 10.92.

Infrared comparison of the *n*-propyl isomers in chloroform solution indicated identical functional bands. In addition, isomer XIII-21 showed specific bands at 10.4 μ and 10.85 μ. The isobornyl isomer had a differentiating band at 9.6 μ.

***endo*-2,2-Dimethyl-3-methylaminonorcamphane Hydrochloride (27).**—*endo*-2,2-Dimethyl-3-aminonorcamphane[6] (1.2 g.) was heated in 4 ml. of formamide for 6 hr. at 175–180° and then poured into 30 ml. of ice water. The N-formyl compound, which crystallized on standing, was recrystallized from Skellysolve C to give 670 mg., m.p. 108–112°. The *endo*-2,2-dimethyl-3-formamidonorcamphane was reduced with lithium aluminum hydride in ether, and the resulting amine isolated as the hydrochloride. The crude product was recrystallized from 2-propanol, m.p. above 300°.

Anal. Calcd. for $C_{10}H_{20}ClN$: C, 63.30; H, 10.63; Cl, 18.69. Found: C, 63.60; H, 10.41; Cl, 18.34.

***exo*-2,2-Dimethyl-3-methylaminonorcamphane hydrochloride (26).**—A mixture (5.5 g.) of the *endo* and *exo* isomers of 3-amino-2,2-dimethylnorcamphane obtained from the reduction[9] of camphenilone oxime with sodium and ethanol was heated with 15 ml. of formamide at 165–170° for 18 hr. The cooled reaction mixture was extracted with ether to give 4.5 g. of a mixture of the *exo* and *endo*-N-formyl compounds. This mixture (3.1 g.) was reduced in 75 ml. of ether using 3.0 g. of lithium aluminum hydride. After refluxing for 3 days, water was added to decompose excess hydride and the inorganic salts were removed by filtration. The resulting dried ether solution was acidified with ethereal hydrogen chloride and the hydrochloride filtered to give 4.4 g. (86%). Recrystallization of 3 g. from 2-propanol separated the isomers and yielded 1.8 g. of *exo* isomer (26), m.p. above 270°.

Anal. Calcd. for $C_{10}H_{20}ClN$: C, 63.30; H, 10.63; Cl, 18.69. Found: C, 62.87; H, 10.27; Cl, 18.52.

A comparison of this isomer with authentic *endo* isomer showed definite differences in infrared spectra. Both compounds exhibit the same functionality. The *exo* isomer had a strong 9.5 μ band and a moderately strong 10.2 μ band. The *endo* isomer had no absorption at 9.5 μ, a moderate 9.75 μ band, and a moderately strong 10.3 μ absorption. In addition, there were numerous minor differences in the fingerprint region.

α-N-Methylfenchylamine hydrochloride (29).—Fenchone was converted to the α-N-formylfenchylamine by the Leuckart reaction[8] and the product was recrystallized from petroleum ether to give material of m.p. 75–84°. Chromatography on alumina yielded material of m.p. 91–92°, eluted by ether, which corresponds to the reported melting point. A portion of the N-formylfenchylamine was hydrolyzed in acid to the free amine and then converted to the N-benzoyl derivative, m.p. 100.5–101.5°.

Anal. Calcd. for $C_{17}H_{23}NO$: C, 79.33; H, 9.01. Found: C, 79.64; H, 8.63.

This N-benzoylfenchylamine corresponds to low melting α-isomer of Hückel.[7]

Lithium aluminum hydride reduction of the α-N-formylfenchylamine (5 g.) in ether for 3.5 hr. at reflux followed by recrystallization of the amine hydrochloride from 35 ml. of 2-propanol gave 2.3 g. of α-N-methylfenchylamine hydrochloride, m.p. above 279°.

Anal. Calcd. for $C_{11}H_{22}ClN$: C, 64.83; H, 10.89; Cl, 17.4. Found: C, 64.70; H, 10.56; Cl, 17.6.

β-N-Methylfenchylamine (28).—Fenchone oxime (20 g.) was reduced catalytically in 60 ml. of methanol at 98 kg./cm.^{2} initial hydrogen pressure using 20 g. of Raney nickel catalyst. The reaction was complete in 4 hr. After removal of the catalyst and addition of caustic, the amines were extracted with ether and distilled; yield 16.5 g., b.p. 195–196°, $n^{25}D$ 1.4736.

To the mixed fenchylamines (16.45 g.) in 150 ml. of 20% sodium hydroxide at 20° was added 11.8 ml. of benzoyl chloride in 30 min. After stirring an additional 30 min., the product was extracted with ether and concentrated to a crystalline residue, 25.1 g., m.p. 103–148°.

The β-isomer was separated and purified by five recrystallizations, alternately using Skellysolve C and ether; yield 3.4 g. The purified β-N-benzoylfenchylamine had a m.p. 188–189°.

Anal. Calcd. for $C_{17}H_{23}NO$: C, 79.64; H, 9.01. Found: C, 79.44; H, 8.99.

This corresponds to the high melting β-isomer of Hückel.[7] The compound was essentially unchanged by refluxing in concentrated hydrochloric acid for 6 hr. The free β-fenchylamine was obtained by hydrolysis with concd. hydrochloric acid in a Carius tube at 175° for 6 hr. The more soluble α-N-benzoylfenchylamine was isolated from the mother liquors by fractional crystallization from petroleum ether; yield 4.0 g., m.p. 99–100°. This material was identical (infrared and mixture melting point) with the sample prepared *via* the Leuckart reaction.

β-Fenchylamine hydrochloride (1.3 g.) in 4 ml. of formamide was heated at 165° for 17 hr., cooled and poured into water. The oil which separated crystallized on standing. Recrystallization from petroleum ether gave 560 mg. of β-N-formylfenchylamine, m.p. 91–92°; mixture melting point with the α-isomer, 80–83°.

Lithium aluminum hydride reduction of 530 mg. of the formyl compound in 30 ml. of ether at reflux for 6 hr. followed by recrystallization of the hydrochloride

from 10 ml. of methyl isobutyl ketone gave 250 mg. of β-N-methylfenchylamine hydrochloride, m.p. above 250°.

Anal. Calcd. for $C_{11}H_{22}ClN$: C, 64.83; H, 10.89. Found: C, 64.37; H, 10.70.

Monocyclic Amines. **1-Methyl-1-N-methylcyclohexylamine** (17).—Ten grams (0.104 mole) of 1-methylcyclohexene was transformed to 1-formamido-1-methylcyclohexane by the procedure described for Example 19 using the following amounts of reactants: 10.2 g. (0.208 mole) of sodium cyanide in 26 ml. of glacial acetic acid and a mixture of 26 ml. of glacial acetic acid and 29 ml. of concd. sulfuric acid. The crude product obtained by chloroform extraction was fractionally distilled, yield, 9.53 g. (64.7%), b.p. 92° (0.3 mm.), $n^{25}D$ 1.4823. On standing the oil crystallized, m.p. *ca.* 27.5°.

Anal. Calcd. for $C_8H_{15}NO$: N, 9.92. Found: N, 9.55.

The infrared spectrum confirmed the formamide functionality. Reduction of 8.0 g. of the above formamide in anhydrous ether using 5.5 g. of lithium aluminum hydride in the usual manner afforded 6.0 g. (83.4%) of a yellow liquid which was dissolved in ether, and treated with ethereal hydrochloric acid to give 6.7 g. (72.2%) of crystalline hydrochloride, m.p. 147.5–149°. Recrystallization from hot methyl isobutyl ketone yielded 6.5 g. (69.7%) of pure compound, m.p. 149–159°. Infrared spectra were consistent with above structure.

Anal. Calcd. for $C_8H_{17}N \cdot HCl$: C, 58.70; H, 11.08; N, 8.56; Cl, 21.66. Found: C, 58.55; H, 10.87; N, 8.60; Cl, 21.80.

1,2-Dimethyl-1-methylaminocyclohexane (18). (a) **1,2-Dimethylcyclohexene-1.**—A solution of 15 g. of 2-methylcyclohexanone in 25 ml. of ether was added slowly at 0–5° to 0.27 mole of methylmagnesium iodide in 35 ml. of ether. The mixture was heated to reflux and then held at 25° for 16 hr. The cooled (0–5°) reaction mixture was hydrolyzed by the addition of 43.5 g. of ammonium chloride in 110 ml. of water. The ether layer was separated and the aqueous layer extracted with ether. The ether solution was washed with water, dried and concentrated. The residual carbinol (14.5 g.) was dehydrated on distillation (130–137°) to give 11 g. of 1,2-dimethylcyclohexene-1, $n^{25}D$ 1.4510.

(b) **1,2-Dimethyl-1-N-formamidocyclohexane.**—1,2-Dimethylcyclohexene (11 g.) was converted to the formamido compound (10 g. of yellow oil) *via* the Ritter reaction described in Example 19 using 5.4 g. of sodium cyanide in 13 ml. of glacial acetic acid and 25 ml. of sulfuric acid in 13 ml. of glacial acetic acid. The reaction mixture was heated at 50° for 3 hr. and then worked up as usual.

(c) **1,2-Dimethyl-1-methylaminocyclohexane.**—Lithium aluminum hydride reduction of 10 g. of 1,2-dimethyl-1-N-formamidocyclohexane in ether at reflux for 4 hr., followed by recrystallization from methyl isobutyl ketone, gave 1.65 g. of 1,2-dimethyl-1-methylaminocyclohexane, m.p. 180–182°.

Anal. Calcd. for $C_9H_{20}ClN$: C, 60.82; H, 11.35. Found: C, 60.66; H, 11.56.

This compound previously had been prepared by a different route.[10]

1-Methylamino-1,2,2-trimethylcyclohexane (19). (a) **1-Formamido-1,2,2-trimethylcyclohexane.**—Sodium cyanide (5.5 g.) was added to 14 ml. of glacial acetic acid at 10–15° and then of a solution of 16 ml. of sulfuric acid in 14 ml. of glacial acetic acid at 0°. At 0° in 25 min., 8.0 g. of 1,2,2-trimethylcyclohexanol was added and the reaction mixture maintained at 0° for 1.5 hr. The reaction mixture then was maintained at 25° for 1.5 hr. and quenched with 250 ml. of water at 20°. Extraction with chloroform gave 7.9 g. of product, m.p. 129–

131°. Vacuum sublimation (85–90°, 0.1 mm.) gave a 92% recovery of pure 1-formamido-1,2,2-trimethylcyclohexane, m.p. 134.5–135°.

Anal. Calcd. for $C_{10}H_{19}NO$: C, 70.96; H, 11.31; N, 8.28. Found: C, 70.67; H, 11.03; N, 8.53.

(b) **1-Methylamino-1,2,2-trimethylcyclohexane.**—Lithium aluminum hydride reduction of 5 g. of the formamido compound in ether at reflux for 16 hr. gave 4.4 g. of the free base as an oil, $n^{25}D$ 1.4658. Conversion to the hydrochloride in ethereal hydrogen chloride and recrystallization from 130 ml. of methyl isobutyl ketone gave pure material, m.p. 230–232°.

Anal. Calcd. for $C_{10}H_{22}ClN$: C, 62.64; H, 11.57; N, 7.31; Cl, 18.49. Found: C, 62.98; H, 11.31; N, 7.69; Cl, 18.85.

V. Aliphatic Amines. 3-Methylamino-2,2,3-trimethylbutane Hydrochloride (31). (a) **3-Formamido-2,2,3-trimethylbutane.**—2,2,3-Trimethylbutene-1 (10 g.) was converted to the formamido compound *via* the Ritter reaction using 5.5 g. of sodium cyanide in 13 ml. of glacial acetic acid and 25 ml. of sulfuric acid in 13 ml. of glacial acetic acid for 2 hr. at 40–50°. After quenching with ice the product was extracted with ether and the ether evaporated to give 12 g. of white solid, m.p. 135–140°. The corresponding alcohol (2,3,3-trimethyl-2-butanol) may also be used as a starting material.

(b) **3-Methylamino-2,2,3-trimethylbutane Hydrochloride.**—Eleven grams of 3-formamido-2,2,3-trimethylbutane was reduced with lithium aluminum hydride in refluxing ether for 5 hr. The product was isolated as the hydrochloride (10.7 g.) which was recrystallized from 40 ml. of 2-propanol (6.1 g.), m.p. 238–240°.

Anal. Calcd. for $C_8H_{20}ClN$: C, 57.98; H, 12.17. Found: C, 57.92; H, 12.38.

2,2-Dimethyl-3-methylaminobutane (30).[23]—Pinacolone (20 g.) was reductively aminated with methylamine (8.7 g.) in methanol using Raney nickel catalyst (2 g.) with 196 kg. of hydrogen/cm.^{2} for 8 hr. After removal of the catalyst the free base was isolated by extraction with ether and purified by distillation, yielding 4.7 g., b.p. 108–111°, $n^{25}D$ 1.4110; hydrochloride salt, m.p. 177–183°.

Anal. Calcd. for $C_7H_{18}ClN$: Cl, 23.4. Found: Cl, 23.3.

(23) H. Albers and S. Lange, *Chem. Ber.*, **85**, 278 (1952).

Veratrum Alkaloids. XLIX.[1] The Structures and Configurations of Sabine and Sabadine[2,3]

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Evidence is presented for assignment of structure and configuration VI to sabine and VII to its monoacetate ester, sabadine. Elementary analyses of a series of synthetic crystalline ester derivatives strongly support a $C_{27}H_{43}O_7N$ formula for sabine. Room temperature acetylation of sabadine with acetic