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Synthesis and Pharmacological Activity of gem-Dialkyl-9-azabicyclo[3,3,1]nonane Derivatives: New Anti-Cholinergic Agent

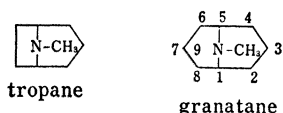
NAOTO YONEDA, TERUO ISHIHARA, TETSUJI KOBAYASHI,
KENTARO OKUMURA and MICHIO KOJIMA

Chemical Research & Development Laboratory, Tanabe Seiyaku & Co., Ltd.¹⁾

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6,6- and 7,7-dialkyl-9-alkyl-9-azabicyclo[3,3,1]nonan-3-one (V) and (IX), synthesized from 2,2- and 3,3-dialkylglutaraldehyde by the Robinson-Schöpf reaction, were reduced with NaBH₄ and Na-EtOH to afford the A- and B-isomers of the corresponding 6,6- and 7,7-dialkyl-9-alkyl-9-azabicyclo[3,3,1]nonan-3-ol (VI) and (X), respectively. Hydroxy groups on 3-position of A- and B-isomer of the alcohols were confirmed to be α - and β -configuration by the formation of a tetrahydrooxazine ring, respectively. Various ester and carbamate compounds of the alcohols (VI) and (X) were synthesized and their pharmacological activities were studied. Among their compounds several glycolate derivatives had a potent anti-cholinergic activity and showed high central specificity.

It is well known that granatane derivatives, a homologue of tropane *i.e.* 9-methyl-9-azabicyclo[3,3,1]nonane, have a potent anti-cholinergic activity.²⁾ It seems, however, that the derivatives have not been marketed upto now because of their strong side-effects accompanied by the main action.



The present paper describes the synthesis and pharmacological activity of 6,6- and 7,7-dialkyl-9-azabicyclo[3,3,1]nonane derivatives, where gem-dialkyl groups are introduced in 6- and 7-position on the carbon skeleton of 9-azabicyclo[3,3,1]nonane in order to improve the pharmacological activities.

As the 6,6-dialkyl derivatives, dimethyl and diethyl compounds were synthesized.

As shown in Chart 1, 6,6-dimethyl-9-alkyl-9-azabicyclo[3,3,1]nonan-3-one derivatives (Va—c) were synthesized by the following procedures: according to the method of Benzing,³⁾ isobutylaldehyde (I, R¹=CH₃) as a starting material was treated with piperidine or morpholine to obtain enamine (II), and then the corresponding dihydropyran compound (III) was afforded by the reaction of II with acrolein in ether according to the method of Opitz, *et al.*⁴⁾ Hydrolysis of III with hydrochloric acid gave 2,2-dimethylglutaraldehyde (IV), which was readily soluble in water, then the yield should be low because of difficult extraction with organic solvents. Therefore, III was treated with acidic ion exchange resin in an aqueous acetone to obtain the aqueous acetone solution of IV, which was used in next procedure without isolation, and thereby a total yields of Va—c were successfully increased.

The synthesis of 6,6-dimethylpseudopelletierine (Va) from IV by Robinson-Schöpf reaction was carried out by means of the synthetic method of pseudopelletierine.⁵⁾ Namely, acetone dicarboxylic acid and methylamine hydrochloride were added to the aqueous acetone solution of IV, and the pH of the solution was adjusted to about 4 by adding sodium acetate, and then it was allowed to stand for one or two days at room temperature. Thus, Va was

1) Location: *Kashima-cho, Higashiyodogawa-ku, Osaka.*

2) a) K. Satch and O. Dold, *Arzneim. Forsch.*, **15**, 856 (1965); b) A. Ribbentrop and W. Schaumann, *ibid.*, **15**, 857 (1965); c) *Idem, ibid.*, **13**, 1015 (1963).

3) E. Benzing, *Angew. Chem.*, **71**, 521 (1959).

4) G. Opitz and H. Holtmann, *Ann.*, **684**, 79 (1965); G. Opitz and I. Löschmann, *ibid.*, **72**, 523 (1960).

5) A.C. Cope, H.L. Dryden, Jr. and C.F. Howell, *Org. Synth.*, **37**, 73.

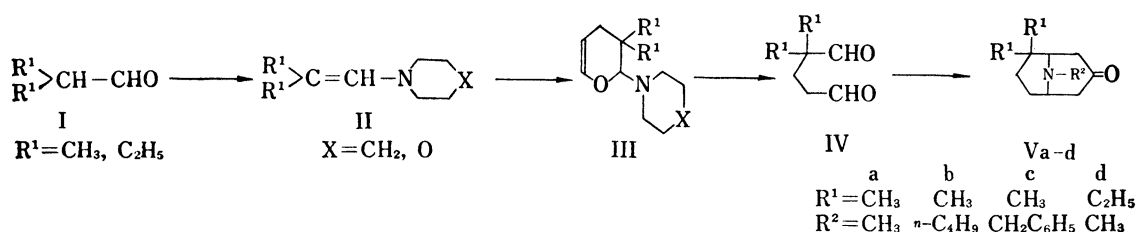
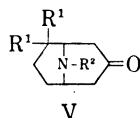


Chart 1

obtained in about 48% yield from III. Likewise, 9-*n*-butyl- and 9-benzyl-6,6-dimethyl-9-azabicyclo[3,3,1]nonan-3-one (Vb, Vc) were obtained by the reaction with *n*-butylamine and benzylamine used as primary amines instead of methylamine, respectively.

6,6-Diethylpseudopelletierine (Vd) was also obtained by the use of α -ethylbutylaldehyde (I, $R^1 = C_2H_5$) instead of isobutylaldehyde in the same manner. Table I represents the yield and physical constant of Va—d.

TABLE I. 6,6-Dialkyl-9-alkyl-9-azabicyclo[3,3,1]nonan-3-ones (V)



R ¹	R ²	Yield ^{a)} (%)	bp/mmHg (°C)	mp (°C)	Rec. ^{b)} solv	Formula	Analysis (%) Found (Calcd.)		
							C	H	N
a	CH ₃ CH ₃	48.0	93— 95/1.5	base 66— 68	A	C ₁₁ H ₁₉ ON	73.34 (72.87	10.70 10.57	7.83 7.73)
				HCl 243—245(decomp.)	C	C ₁₁ H ₂₀ ONCl	60.89 (60.68	9.44 9.26	6.43 6.44)
				Pic ^{c)} 213—214(decomp.)	B	C ₁₇ H ₂₂ O ₈ N ₄	50.13 (49.75	5.48 5.41	13.54 13.65)
b	CH ₃ n-C ₄ H ₉	15.1	106—110/0.5	HCl 216—217(decomp.)	B	C ₁₄ H ₂₆ ONCl	65.15 (64.72	10.24 10.09	5.37 5.40)
c	CH ₃ CH ₂ C ₆ H ₅	18.7	153—155/0.5	base 72— 73	A	C ₁₇ H ₂₃ ON	78.73 (79.32	9.00 9.01	5.48 5.44)
				Pic ^{c)} 182—183(decomp.)	B	C ₂₃ H ₂₆ O ₈ N ₄	56.82 (56.78	5.51 5.39	11.54 11.52)
d	C ₂ H ₅ CH ₃	38.5	130—132/4	base 57— 58	A	C ₁₃ H ₂₃ ON	74.51 (74.59	11.20 11.07	6.60 6.69)
				HCl 232—233(decomp.)	B	C ₁₃ H ₂₄ ONCl	63.87 (63.52	9.95 9.82	5.62 5.70)

a) Yields were based on dihydropyrans (III).

b) recrystallization solvent

A=*n*-hexane; B=EtOH; C=EtOH-H₂O (9:1 v/v)

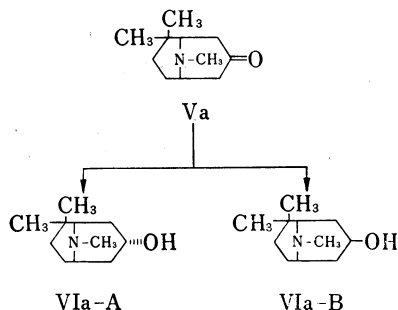
c) picrate

It has been reported that the selectivity of forming α - and β -isomers, on the basis of configuration of hydroxy group on 3-position, to be obtained by reduction of 9-azabicyclo[3,3,1]nonan-3-one derivatives is greater than that of tropinone.⁶⁾

As the model compound of 6,6-dialkyl ketone (V), Va was selected and reduced by the conditions indicated in Chart 2. The formation ratio of A-isomer and B-isomer of 6,6,9-

6) a) C.L. Zirkle, F.R. Gerns, A.M. Pavloff and A. Burger, *J. Org. Chem.*, **26**, 395 (1961); b) K. Alder and H.A. Dortmann, *Chem. Ber.*, **86**, 1544 (1953); c) W.H. Hartung and S.M. Gadekar, *J. Am. Pharm. Assoc. Sci. Ed.*, **42**, 715 (1953).

trimethyl-9-azabicyclo[3,3,1]nonan-3-ol (VIa) was determined by gas chromatography. The reduction product of Va with Na-EtOH was all VIa-B, while VIa-A formed selectively by the reduction with NaBH₄. Furthermore, reduction of Va with LiAlH₄ predominantly gave VIa-A which included a small amount of B-isomer as the by-product. The catalytic hydrogenation of Va in the presence of PtO₂ in acetic acid gave A-isomer only as the reduction product although the ketone (Va) was partly recovered. The selectivity to form A- and B-isomers was proved to be greater in 6,6-dimethyl derivatives than in pseudopelletierine in each reduction methods.

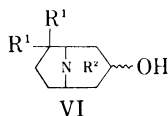


Reductn. method	Ratio of isomers (%)	
	A	B
Na-EtOH	—	100
NaBH ₄ in EtOH	100	—
LiAlH ₄ in ether	96	4
PtO ₂ /H ₂ in AcOH	100	—

G.C: Hyprose SP-80, 150°
 Rt: VIa—A=9 min 30 sec
 VIa—B=11 min 40 sec

Chart 2

TABLE II. 6,6-Dialkyl-9-alkyl-9-azabicyclo[3,3,1]nonan-3-ols (VI)



(VI)	R ¹	R ²	Config bp/mmHg		mp (°C)	Rec. ^{a)} Solv	Formula	Analysis (°%)			
			OH	(°C)				Found (Calcd.)	C	H	N
a-A	CH ₃	CH ₃	α	95— 97/1	base	81— 82	A	C ₁₁ H ₂₁ ON	72.10 (72.07)	11.80 11.55	7.63 7.64
					Pic ^{b)}	206—207 (decomp.)	B	C ₁₇ H ₂₄ O ₈ N ₄	49.47 (49.51)	5.97 5.87	13.42 13.59
a-B	CH ₃	CH ₃	β	113—115/3	base	77— 79	A	C ₁₁ H ₂₁ ON	72.37 (72.07)	11.60 11.55	7.53 7.64
					Pic ^{b)}	270—271 (decomp.)	B	C ₁₇ H ₂₁ O ₈ N ₄	49.54 (49.51)	5.94 5.87	13.54 13.59
b-A	CH ₃	<i>n</i> -C ₄ H ₉	α	133—135/3	Pic ^{b)}	174—175 (decomp.)	C	C ₂₆ H ₃₀ O ₈ N ₄	52.86 (52.85)	6.69 6.65	12.21 12.33
b-B	CH ₃	<i>n</i> -C ₄ H ₉	β	140—145/4	Pic ^{b)}	149—150 (decomp.)	B	C ₂₆ H ₃₀ O ₈ N ₄	52.95 (52.85)	6.74 6.65	12.31 12.33
c-A	CH ₃	CH ₂ C ₆ H ₅	α	145—150/0.2	Pic ^{b)}	172—173 (decomp.)	C	C ₂₃ H ₂₈ O ₈ N ₄	56.78 (56.54)	5.83 5.77	11.45 11.47
c-B	CH ₃	CH ₂ C ₆ H ₅	β	150—155/0.3	Pic ^{b)}	205—206 (decomp.)	B	C ₂₃ H ₂₈ O ₈ N ₄	56.75 (56.54)	5.77 5.77	11.80 11.47
d-A	C ₂ H ₅	CH ₃	α	131—132/2.5	Pic ^{b)}	199—200 (decomp.)	B	C ₁₉ H ₂₈ O ₈ N ₄	52.26 (51.81)	6.48 6.41	12.71 12.72
d-B	C ₂ H ₅	CH ₃	β	120—125/3	Pic ^{b)}	167—168 (decomp.)	C	C ₁₉ H ₂₈ O ₈ N ₄	51.98 (51.81)	6.47 6.41	12.57 12.72

^{a)} recrystallization solvent A=*n*-hexane; B=EtOH; C=*iso*-PrOH ^{b)} picrate

Reductions of Vb, Vc and Vd with NaBH₄ in ethanol and with Na-EtOH were carried out in the same manner, then A- and B-isomers of the corresponding alcohols were obtained. Their physical constant is shown in Table II.

The configuration of hydroxy groups on 3-position of two isomeric alcohols (VIa-A) and (VIa-B), obtained by reduction of Va, was identified by the formation of a tetrahydrooxazine. Thus as shown in Chart 3, two demethylated compounds 6,6-dimethyl-9-azabicyclo-[3,3,1]nonan-3 α -ol (VII-A) and 3 β -ol (VII-B) were obtained by the oxidative demethylation of VIa-A and VIa-B with KMnO_4 . In order to prove no occurrence of epimerization during demethylation, the original N-methyl derivatives (VIa-A) and (VIa-B) were recovered by methylation of VII-A and VII-B, respectively. When VII-B was reacted with *p*-nitrobenzaldehyde in chlorobenzene, a crystalline *p*-nitrophenyltetrahydrooxazine derivative (VIII) formed readily. On the other hand only tarry matter was obtained from the same reaction of VII-A.

From these results it was experimentally confirmed that VIa-B obtained by Na-EtOH reduction of Va was assigned β -configuration which has the hydroxy group on the same side as that of N-bridge, whereas VIa-A obtained by complex metal hydride reduction and catalytic hydrogenation showed α -configuration which has the hydroxy group on the opposite side to N-bridge.

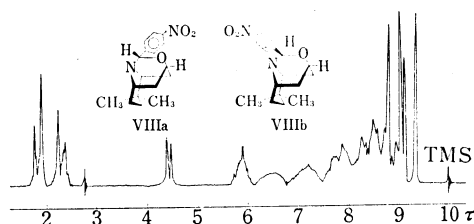
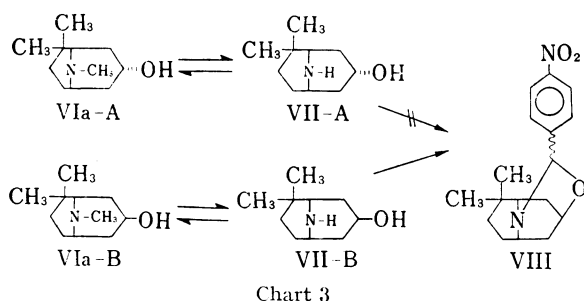


Fig. 1. NMR Spectrum of Tetrahydrooxazine (VIII) in CDCl_3 (60Mc)

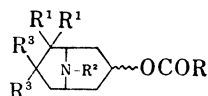
VIII was purified by recrystallization with ether followed by sublimation under reduced pressure. However its melting point was not sharp in the range of 98–108°, thus the existence of two diastereomers would be suggested. Although VIII indicated one component in gas chromatography and thin-layer chromatography it was proved to be a mixture of two isomers (VIIIa) and (VIIIb) by nuclear magnetic resonance (NMR) as shown in Fig. 1. The signal of gem-dimethyl group on 6-position appeared at 8.80, 9.03, 9.10, and 9.33 τ and the signal of H being interposed between N and O of tetrahydrooxazine ring appeared at 4.42 and 4.50 τ . The formation ratio of both isomers should be determined to be about one to one by NMR spectrum, but their isolation was not performed.

Subsequently, 7,7-dimethyl compounds were synthesized as the 7,7-dialkyl derivatives. 7,7-Dimethylpseudopelletierine (IX) was synthesized from 3,3-dimethylglutaraldehyde by the method of Meinwald, *et al.*⁷⁾ Then A- and B-isomers of 7,7,9-trimethyl-9-azabicyclo[3,3,1]nonan-3-ol (X) were selectively prepared by the reduction of IX with NaBH_4 and Na-EtOH respectively (Chart 4). The formation ratio of both isomers (X-A) and (X-B) was determined by gas chromatography after the acetylation of reduction products by acetic anhydride, since the original products appeared at the same retention time. The selectivity of reduction of IX was somewhat decreased, as compared with that of 6,6-dimethyl derivatives (Va), the reason for which was considered to be contribution of chair-boat conformation due to influence of gem-dimethyl group of 7-position.

The configuration of the hydroxy group of the alcohols (X-A) and (X-B) was identified by forming tetrahydrooxazine ring in the same manner as 6,6-dimethyl derivative (VIa). As seen in Chart 5, X-A and X-B were oxidatively demethylated by KMnO_4 to form two

7) J. Meinwald and P.C. Lee, *J. Am. Chem. Soc.*, **82**, 699 (1960).

TABLE III. Ester and Carbamate Derivatives of 6,6- and 7,7-Dialkyl-9-alkyl-9-azabicyclo[3,3,1]nonan-3-ol



Comp. No.	R ¹	R ²	R ³	R	OH	Method yield ^{a)} (%)	mp (°C) Recryst. Solv.	Formula	Analysis (%) Found (Calcd.)		
									C	H	N
1	CH ₃	CH ₃	H	CH ₃	α	A 87.7 EtOH	Pic ^{b)} 147—148 (decomp.)	C ₁₈ H ₂₆ O ₉ N ₄	50.02 (50.21)	5.84 5.77	12.17 12.33
2	CH ₃	CH ₃	H	CH ₃	β	A 86.0 EtOH	Pic 170—171 (decomp.)	C ₁₈ H ₂₆ O ₉ N ₄	50.15 (50.21)	5.87 5.77	12.11 12.33
3	CH ₃	CH ₃	H	C ₆ H ₅	α	B 82.3 EtOH-ether	HCl 253—254 (decomp.)	C ₁₈ H ₂₆ O ₂ NCl	66.61 (66.74)	8.18 7.78	4.21 4.32
4	CH ₃	CH ₃	H	C ₆ H ₅	β	B 77.7 EtOH-ether	HCl 239—240 (decomp.)	C ₁₈ H ₂₆ O ₂ NCl	66.69 (66.74)	8.19 7.78	4.29 4.32
5	CH ₃	CH ₃	H	CH(<i>n</i> -C ₃ H ₇) ₂	α	B 47.8 EtOH-ether	HCl 241—242 (decomp.)	C ₁₉ H ₃₆ O ₂ NCl · 1/3 H ₂ O	64.79 (64.84)	10.81 10.50	3.99 3.98
6	CH ₃	CH ₃	H	CH(<i>n</i> -C ₃ H ₇) ₂	β	B 44.4 EtOH-ether	HCl 215—216 (decomp.)	C ₁₉ H ₃₆ O ₂ NCl	66.22 (65.95)	10.72 10.49	3.86 4.05
7	CH ₃	CH ₃	H	CH(C ₆ H ₅) ₂	α	B 64.1 EtOH-ether	HCl 242—243 (decomp.)	C ₂₅ H ₃₂ O ₂ NCl	72.93 (72.52)	7.87 7.79	3.41 3.38
8	CH ₃	CH ₃	H	CH(C ₆ H ₅) ₂	β	B 82.0 EtOH-ether	HCl 226—227 (decomp.)	C ₂₅ H ₃₂ O ₂ NCl	72.05 (72.52)	8.07 7.79	3.36 3.38
9	CH ₃	CH ₃	H	C ₅ H ₄ N ^{c)}	α	A 44.3 EtOH-H ₂ O	2Pic 212—213 (decomp.)	C ₂₉ H ₃₀ O ₁₆ N ₈	46.92 (46.65)	4.11 4.06	15.05 15.01
10	CH ₃	CH ₃	H	C ₅ H ₄ N	β	A 42.0 EtOH-H ₂ O	2Pic 197—198 (decomp.)	C ₂₉ H ₃₀ O ₁₆ N ₈	46.74 (46.65)	4.09 4.06	15.05 15.01
11	CH ₃	CH ₃	H	C(C ₆ H ₅) ₂ OH	α	C 71.0 EtOH-ether	HCl 230—231 (decomp.)	C ₂₅ H ₃₂ O ₃ NCl · H ₂ O	67.12 (67.03)	7.51 7.65	3.20 3.13
12	CH ₃	CH ₃	H	C(C ₆ H ₅) ₂ OH	β	C 71.8 EtOH-ether	HCl 174—175 (decomp.)	C ₂₅ H ₃₂ O ₃ NCl · H ₂ O	67.19 (67.03)	7.63 7.65	3.11 3.13
13	CH ₃	CH ₃	H	C(C ₆ H ₅) ₂ Cl	α	E 70.0 EtOH-ether	HCl 226—227 (decomp.)	C ₂₅ H ₃₁ O ₂ NCl ₂	67.02 (66.95)	7.07 6.97	3.11 3.13
14	CH ₃	CH ₃	H	C(C ₆ H ₅) ₂ Cl	β	E 34.6 EtOH	HCl 255—256 (decomp.)	C ₂₅ H ₃₁ O ₂ NCl ₂	66.84 (66.95)	6.82 6.97	3.12 3.13
15	CH ₃	<i>n</i> -C ₄ H ₉	H	C(C ₆ H ₅) ₂ OH	α	C 76.9 EtOH	HCl 189—192 (decomp.)	C ₂₈ H ₃₈ O ₃ NCl · 1/2 H ₂ O	69.91 (69.91)	8.54 8.17	2.73 2.91
16	CH ₃	<i>n</i> -C ₄ H ₉	H	C(C ₆ H ₅) ₂ OH	β	C 50.0 EtOH-ether	HCl 201—202 (decomp.)	C ₂₈ H ₃₈ O ₃ NCl	71.46 (71.24)	8.10 8.11	2.90 2.97
17	CH ₃	CH ₂ C ₆ H ₅	H	C(C ₆ H ₅) ₂ OH	α	C 85.2 EtOH	HCl 220—221 (decomp.)	C ₃₁ H ₃₆ O ₃ NCl	73.69 (73.56)	7.16 7.17	2.75 2.77
18	CH ₃	CH ₂ C ₆ H ₅	H	C(C ₆ H ₅) ₂ OH	β	C 64.3 <i>n</i> -hexane	base 107—108	C ₃₁ H ₃₅ O ₃ N	79.57 (79.28)	7.55 7.51	3.02 2.98
19	C ₂ H ₅	CH ₃	H	C(C ₆ H ₅) ₂ OH	α	C 55.2 EtOH	HCl 223—225 (decomp.)	C ₂₇ H ₃₆ O ₃ NCl	70.88 (70.80)	7.99 7.92	3.00 3.06

Comp No.	R ¹	R ²	R ³	R	OH	Method yield ^{a)} (%)	mp (°C) Recryst. Solv.	Formula	Analysis (%) Found (Calcd.)		
									C	H	N
20	C ₂ H ₅	CH ₃	H	C(C ₆ H ₅) ₂ OH	β	C HCl	197—200 (decomp.)	C ₂₇ H ₃₆ O ₃ NCl	70.72 (70.80)	7.97 (7.92)	3.02 (3.06)
21	CH ₃	CH ₃	H	C(C ₄ H ₃ S) ₂ ^{d)} OH	α	C HCl	233—234 (decomp.)	C ₂₁ H ₂₈ O ₃ NS ₂ Cl	56.87 (57.06)	6.49 (6.38)	3.34 (3.17)
22	CH ₃	CH ₃	H	C(C ₄ H ₃ S) ₂ OH	β	C HCl	136—137 (decomp.)	C ₂₁ H ₂₈ O ₃ NS ₂ Cl · H ₂ O	54.77 (54.83)	6.40 (6.57)	3.21 (3.05)
23	CH ₃	CH ₃	H	C(C ₄ H ₃ S) ₂ OCH ₃	α	C HCl	228—230 (decomp.)	C ₂₂ H ₃₀ O ₃ NS ₂ Cl · 1/3 H ₂ O	57.31 (57.18)	6.69 (6.69)	3.02 (3.03)
24	CH ₃	CH ₃	H	C(C ₄ H ₃ S) ₂ OCH ₃	β	C HCl	203—205 (decomp.)	C ₂₂ H ₃₀ O ₃ NS ₂ Cl · 1/3 H ₂ O	57.50 (57.18)	6.62 (6.69)	3.00 (3.03)
25	C ₂ H ₅	CH ₃	H	C(C ₄ H ₃ S) ₂ OH	α	C HCl	219—220 (decomp.)	C ₂₃ H ₃₂ O ₃ NS ₂ Cl	58.67 (58.76)	6.94 (6.86)	3.03 (2.98)
26	C ₂ H ₅	CH ₃	H	C(C ₄ H ₃ S) ₂ OH	β	C HCl	196—198 (decomp.)	C ₂₃ H ₃₂ O ₃ NS ₂ Cl	58.95 (58.76)	6.86 (6.86)	2.97 (2.98)
27	C ₂ H ₅	CH ₃	H	C(C ₄ H ₃ S) ₂ OCH ₃	α	C HCl	210—212 (decomp.)	C ₂₄ H ₃₄ O ₃ NS ₂ Cl · 1/3 H ₂ O	58.53 (58.81)	7.28 (7.13)	2.78 (2.86)
28	C ₂ H ₅	CH ₃	H	C(C ₄ H ₃ S) ₂ OCH ₃	β	C HCl	202—204 (decomp.)	C ₂₄ H ₃₄ O ₃ NS ₂ Cl · 1/3 H ₂ O	59.16 (58.81)	7.16 (7.13)	2.79 (2.86)
29	CH ₃	CH ₃	H	C(C ₆ H ₅) ₂ OCOCH ₃	β	D HCl	232—233 (decomp.)	C ₂₇ N ₃₄ O ₄ NCl	56.84 (57.06)	6.29 (6.25)	2.99 (2.89)
30	CH ₃	CH ₃	H	C(C ₆ H ₅) ₂ OCOC ₂ H ₅	β	D HCl	208—210 (decomp.)	C ₂₈ H ₃₆ O ₄ NCl	57.87 (57.87)	6.50 (6.48)	2.71 (2.81)
31	CH ₃	CH ₃	H	C(C ₆ H ₅) ₂ OCOC _n C ₃ H ₇	β	D HCl	213—215 (decomp.)	C ₂₉ H ₃₈ O ₄ NCl	69.78 (69.65)	7.60 (7.66)	2.71 (2.80)
32	CH ₃	CH ₃	H	C(C ₄ H ₃ S) ₂ OCOCH ₃	β	D HCl	191—192 (decomp.)	C ₂₃ H ₃₀ O ₄ NS ₂ Cl	56.84 (57.06)	6.29 (6.25)	2.99 (2.89)
33	CH ₃	CH ₃	H	C(C ₄ H ₃ S) ₂ OCOC ₂ H ₅	β	D HCl	184—185 (decomp.)	C ₂₄ H ₃₂ O ₄ NS ₂ Cl	57.87 (57.87)	6.50 (6.48)	2.71 (2.81)
34	CH ₃	CH ₃	H	C(C ₄ H ₃ S) ₂ OCOC _n C ₃ H ₇	β	D HCl	180—181 (decomp.)	C ₂₅ H ₃₄ O ₄ NS ₂ Cl	58.49 (58.63)	6.75 (6.69)	2.89 (2.74)
35	H	CH ₃	CH ₃	CH ₃	α	A Pic	183—184 (decomp.)	C ₁₈ H ₂₆ O ₉ N ₄	50.22 (50.21)	5.84 (5.77)	12.44 (12.33)
36	H	CH ₃	CH ₃	CH ₃	β	A Pic	144—145 (decomp.)	C ₁₈ H ₂₆ O ₉ N ₄	50.20 (50.21)	5.82 (5.77)	12.47 (12.33)
37	H	CH ₃	CH ₃	C(C ₆ H ₅) ₂ OH	α	C HCl	224—225 (decomp.)	C ₂₅ H ₃₂ O ₃ NCl	69.66 (69.84)	7.39 (7.50)	3.11 (3.26)
38	H	CH ₃	CH ₃	C(C ₆ H ₅) ₂ OH	β	C base	124—125 (decomp.)	C ₂₅ H ₃₁ O ₃ N	76.15 (76.30)	7.82 (7.94)	3.42 (3.56)
39	CH ₃	CH ₃	H	NHC ₆ H ₅	α	F Pic	219—220 (decomp.)	C ₂₄ H ₂₉ O ₉ N ₅	54.44 (54.23)	5.58 (5.50)	13.09 (13.18)
40	CH ₃	CH ₃	H	NHC ₆ H ₅	β	F HCl	235—236 (decomp.)	C ₁₈ H ₂₇ O ₂ N ₂ Cl · H ₂ O	60.73 (60.56)	8.18 (8.19)	7.89 (7.85)

Comp No.	R ¹	R ²	R ³	R	OH	Method yield ^{a)} (%)	mp (°C) Recryst. Solv.	Formula	Analysis (%) Found (Calcd.)		
									C	H	N
41	CH ₃	CH ₃	H		α	F Pic 224—225 (decomp.) 66.0 EtOH		C ₂₁ H ₂₈ O ₉ N ₅ Cl	51.30 (50.93)	5.02 4.49	12.30 12.37
42	CH ₃	CH ₃	H		β	F HCl 247—248 (decomp.) 89.7 EtOH-ether		C ₁₈ H ₂₆ O ₂ N ₂ Cl ₂ · 1/2 H ₂ O	56.54 (56.54)	7.21 7.12	7.46 7.32
43	CH ₃	CH ₃	H	N(C ₂ H ₅) ₂	α	G HCl 224—226 (decomp.) 23.4 EtOH-ether		C ₁₆ H ₃₁ O ₂ N ₂ Cl	59.71 (60.25)	9.81 9.80	8.68 8.78
44	CH ₃	CH ₃	H	N(C ₂ H ₅) ₂	β	G HCl 232—234 (decomp.) 41.0 EtOH-ether		C ₁₆ H ₃₁ O ₂ N ₂ Cl	60.22 (60.25)	10.05 9.80	8.93 8.78
45	CH ₃	CH ₃	H		α	G Pic 207—208 (decomp.) 19.2 EtOH		C ₂₂ H ₃₁ O ₁₀ N ₅	50.66 (50.28)	6.05 5.95	13.47 13.33
46	CH ₃	CH ₃	H		β	G Pic 192—193 (decomp.) 37.4 EtOH		C ₂₂ H ₃₁ O ₁₀ N ₅	50.49 (50.28)	6.01 5.95	13.48 13.33
47	CH ₃	CH ₃	H		α	G Pic 197—198 (decomp.) 22.8 EtOH		C ₂₃ H ₃₃ O ₉ N ₅	53.09 (52.76)	6.59 6.93	13.58 13.38
48	CH ₃	CH ₃	H		β	G HCl 215—216 (decomp.) 32.7 EtOH-ether		C ₁₇ H ₃₁ O ₂ N ₂ Cl · 1/3 H ₂ O	60.66 (60.60)	9.48 9.47	8.45 8.32

a) crude product yield; b) picrate; c) 3-pyridyl-; d) C₄H₉S = 2-thienyl-

Reductn. method	Ratio of isomers (%)	
	A	B
Na-EtOH	4	96
NaBH ₄ in EtOH	92	8

G.C.: Hyprose SP—80, 150°

Rt: X-A-acetate = 7 min 30 sec; X-B-acetate = 5 min 30 sec

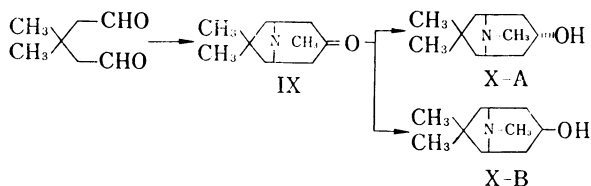


Chart 4

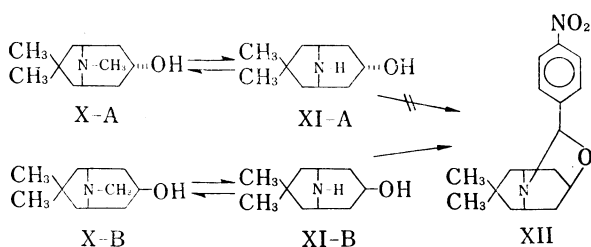


Chart 5

demethylated compounds 7,7-dimethyl-9-azabicyclo[3,3,1]nonan-3α-ol (XI-A) and 3β-ol (XI-B).

The corresponding tetrahydrooxazine derivative (XII) was readily obtained by the reaction of XI-B with *p*-nitrobenzaldehyde while XII could not be isolated in the case of XI-A. This fact indicates that XI-B has β-configuration while XI-A has α-configuration. Based on the result that

the original N-methyl derivatives (X-A) and (X-B) were recovered by the methylation of XI-A and XI-B, it was clearly proved that epimerization did not occur during demethylation.

Various ester and carbamate compounds were synthesized from α- and β-isomers of 6,6-dimethyl-, 6,6-diethyl- and 7,7-dimethyl-9-alkyl-9-azabicyclo[3,3,1]nonan-3-ols. The yield

TABLE IV. Pharmacological Activities of Ester and Carbamate Compounds

Comp No.	Anti-ACh. ^{a)} activity ED ₅₀ (g/ml)	Anti-Tre. ^{b)} activity ED ₅₀ (mg/kg)	Mydriatic ^{c)} activity ED ₅₀ (mg/kg)	Centr. ^{d)} Spec.
Atr. ^{e)}	6.0 × 10 ⁻⁹	1.4	0.22	0.16
3	>10 ⁻⁶	>10	>30	—
4	>10 ⁻⁶	>10	>30	—
5	>10 ⁻⁶	>10	>30	—
6	>10 ⁻⁶	>10	>30	—
7	1.8 × 10 ⁻⁶	8.9	>30	—
8	5.2 × 10 ⁻⁷	>10	>30	—
9	>10 ⁻⁶	>10	>30	—
10	>10 ⁻⁶	>10	>30	—
11	2.5 × 10 ⁻⁸	5.3	12.0	2.3
12	2.2 × 10 ⁻⁸	2.5	10.0	4.0
13	6.0 × 10 ⁻⁸	2.8	9.3	3.3
14	3.5 × 10 ⁻⁸	2.5	9.3	3.7
15	>10 ⁻⁶	>10	>30	—
16	>10 ⁻⁶	>10	>30	—
17	>10 ⁻⁷	>10	>30	—
18	>10 ⁻⁷	>10	>30	—
19	5.6 × 10 ⁻⁸	>10	>30	—
20	5.7 × 10 ⁻⁸	2.8	10.0	3.6
21	3.2 × 10 ⁻⁸	>10	4.0	—
22	6.4 × 10 ⁻⁹	0.5	1.3	2.6
23	4.2 × 10 ⁻⁷	>10	>30	—
24	5.0 × 10 ⁻⁸	3.3	20	6.0
25	2.9 × 10 ⁻⁸	>10	22	—
26	1.5 × 10 ⁻⁸	0.6	1.5	2.5
27	4.4 × 10 ⁻⁷	>10	>30	—
28	1.3 × 10 ⁻⁷	5.0	24	4.8
29	1.7 × 10 ⁻⁶	>10	>30	—
30	2.8 × 10 ⁻⁶	>10	>30	—
31	>10 ⁻⁶	>10	1.6	—
32	8.4 × 10 ⁻⁹	0.5	1.7	3.2
33	1.8 × 10 ⁻⁸	0.9	2.2	1.9
34	2.2 × 10 ⁻⁸	1.0	>30	2.2
37	9.1 × 10 ⁻⁸	>10	12.1	—
38	7.6 × 10 ⁻⁸	2.8	>30	4.3
39	>10 ⁻⁶	>10	>30	—
40	>10 ⁻⁶	>10	>30	—
41	>10 ⁻⁶	>10	>30	—
42	>10 ⁻⁶	>10	>30	—
43	>10 ⁻⁶	>10	>30	—
44	>10 ⁻⁶	>10	>30	—
45	>10 ⁻⁶	>10	>30	—
46	>10 ⁻⁶	>10	>30	—
47	>10 ⁻⁶	>10	>30	—
48	>10 ⁻⁶	>10	>30	—
49	6.3 × 10 ⁻⁹	0.61	0.24	0.39
50	3.9 × 10 ⁻⁹	0.33	0.18	0.55

a) anti-acetylcholine activity: A dose required to inhibit 50% of acetylcholine-induced contraction of the guinea-pig ileum.

b) anti-tremorine activity: A dose required to protect 50% of the mice from tremorine (15 mg/kg *i. p.*)-induced tremor.

c) A dose required to produce 0.9 mm increase in the pupil diameter. b) and c) were examined 30 min after intraperitoneal injections of the compounds to groups of 5 mice.

d) central specificity

e) atropine

and physical constant of ester derivatives and carbamate derivatives are shown in Table III.

Among the ester derivatives, (1), (2), (9), (10), (35), and (36) were synthesized by the reaction between the α - and β -isomers of the corresponding alcohols and acid anhydride (method A), while (3)—(8) were synthesized by reacting VIa-A and VIa-B with acid chloride (method B). Glycolate derivatives (11), (12), (15)—(28), (37), and (38) were obtained by the ester exchange reaction of the corresponding alcohols with the corresponding methyl glycolates in the presence of sodium catalyst (method C). O-Acylglycolate derivatives (29)—(34) were synthesized by acylation of the corresponding glycolates (method D), and chloride derivatives (13) and (14) were obtained by chlorination of the corresponding benzilates (method E). Carbamate compounds (39)—(48) were synthesized by reaction of VIa-A and VIa-B with the corresponding isocyanates (method F) and carbamoylchlorides (method G).

The pharmacological activities of the ester and carbamate compounds thus synthesized are represented in Table IV.

All of the compounds were tested for anti-acetylcholine activity on the isolated guinea-pig ileum. The compounds found to have some anti-acetylcholine activity were further tested for their anti-tremorine tremor and mydriatic activities in mice as a parameter of central anti-cholinergic activity and of side effects, respectively. Central specificity^{2b)} of the compounds was arbitrarily calculated as a ratio of (ED₅₀ of mydriatic activity)/(ED₅₀ of anti-tremorine activity), which would reflect the specificity of their central actions. The specificity of the gem-dialkyl compounds such as 11, 12, 20 and 38 was 4 to 10 times higher than that of 9-methyl-9-azabicyclo[3,3,1]non-3 α - and 3 β -yl benzilate (49) and (50).^{2b)}

The present results show that several glycolate derivatives had a potent central anti-cholinergic activity among the compounds tested, and that high central specificity was given by introducing gemdialkyl groups into the carbon skeleton of 9-azabicyclo[3,3,1]-nonane.

Experimental⁸⁾

2-Piperidino-3,3-dimethyl-4^h-dihydropyran (III, R¹=CH₃, X=CH₂)—To a solution of 1-isobutenylpiperidine⁹⁾ (II, R¹=CH₃, X=CH₂), prepared by dehydrating reaction of isobutylaldehyde (I, R¹=CH₃) and piperidine according to the method of Benzing,³⁾ (221.0 g, 1.59 moles) in ether (220 ml) was added dropwise freshly distilled acrolein (98.0 g, 1.75 moles) with stirring. The mixture was refluxed for 8 hr, then allowed to stand overnight at room temperature. The reaction mixture was concentrated and the residue was distilled to give III (242.5 g, 78.3%) as a colorless oil, bp₃ 83—87°.

6,6-Dimethylpseudopelletierine (Va)—A mixture of above obtained dihydropyran (III) (23.7 g, 0.121 mole), Amberlite IR-120 (H⁺) (100 ml) and 40% aqueous acetone (150 ml) was vigorously stirred at room temperature overnight. The resin was filtered off and washed with 50% aqueous acetone. To the combined solution, containing 2,2-dimethylglutaraldehyde (IV), were added CH₃NH₂·HCl (8.9 g, 0.132 mole) and acetone dicarboxylic acid⁹⁾ (20.0 g, 0.137 mole) and the resulting solution was adjusted to pH 4 with sodium acetate. After standing for 2 days at room temperature, the reaction mixture was made acidic with HCl and concentrated to remove most of the acetone. The acidic solution was made alkaline with NaOH and extracted with benzene. The extract was dried and evaporated, leaving a dark oily residue, which was distilled to yield Va (10.5 g, 48.2% based on III) as a pale yellow viscous oil, bp_{1.5} 93—95°. The product solidified on standing and was recrystallized from *n*-hexane to give colorless prisms, mp 66—68°. Hydrochloride: colorless prisms (from aqueous EtOH), mp 243—245° (decomp.).

Picrate: Yellow prisms (from EtOH), mp 213—214° (decomp.). Analytical results were shown in Table I.

6,6,9-Trimethyl-9-azabicyclo[3,3,1]nonan-3 α -ol (VIa-A)—To a solution of Va (100 g, 0.55 mole) in EtOH (600 ml) was added NaBH₄ (15.0 g, 0.396 mole) in small portions during 1 hr with stirring at room temperature and stirring was continued overnight. EtOH was removed *in vacuo*, the residue was mixed with ice-water and extracted with benzene. The benzene extract was dried and evaporated leaving an oily residue, which was distilled to give VIa-A (92.0 g, 91%) as a faint yellow viscous oil, bp₁ 95—97°. The product solidified immediately and was recrystallized from *n*-hexane to give colorless plates, mp 81—82°. Picrate: Yellow prisms (from EtOH), mp 206—207° (decomp.). Analytical data were shown in Table II.

8) All melting points were uncorrected.

9) R. Adams, H.M. Chiles and C.F. Rassweiler, *Org. Synth.*, **1**, 10.

6,6,9-Trimethyl-9-azabicyclo[3,3,1]nonan-3 β -ol (VIa-B)—6,6,9-Trimethyl-9-azabicyclo[3,3,1]nonan-3 β -ol (VIa-B) was prepared substantially by the same procedure employed for the pseudopelletierine.^{6b,10)} To a boiling solution of Va (60.0 g, 0.33 mole) in EtOH (800 ml) was added Na (68 g, 2.95 g-atoms) portionwise during 4 hr with gently stirring. Water was added to the cooled solution and most of the alcohol was distilled away under reduced pressure. The aqueous solution was saturated with NaCl and thoroughly extracted with benzene. The extract was dried and evaporated to leave an oily residue, which was distilled to yield VIa-B (51.7 g, 85%) as a pale yellow viscous oil, bp₃ 113–115°. The product solidified immediately and was recrystallized from *n*-hexane to give colorless needles, mp 77–79°.

Picrate: Yellow prisms (from EtOH), mp 270–271° (decomp.). Analytical results were shown in Table II.

6,6-Dimethyl-9-azabicyclo[3,3,1]nonan-3 α -ol (VII-A) and 3 β -ol (VII-B)—VII-A and VII-B were prepared according to the procedure of Zirkle, *et al.*^{6a)} for 3-oxagranatanin-7 β -ol and 7 α -ol. To a solution of VIa-A or IVa-B (1.5 g, 0.0082 mole) and KOH (1.5 g, 0.027 mole) in H₂O (100 ml) was added a solution of KMnO₄ (3.3 g, 0.021 mole) in H₂O (170 ml) dropwise during 45 min with stirring and ice-cooling. After standing overnight at room temperature, the mixture was filtered and the filtrate was made acidic with HCl and evaporated to dryness under reduced pressure. The residue was mixed with KOH-solution, extracted thoroughly with AcOEt and evaporated. Crude VII-A (1.0 g, 72%) was obtained from VIa-A, and was recrystallized from AcOEt to give colorless prisms, mp 90–91°. *Anal.* Calcd. for C₁₀H₁₉ON: C, 70.94; H, 11.31; N, 8.27. Found: C, 70.54; H, 11.08; N, 8.34.

From VIa-B there was obtained crude VII-B (1.1 g, 79.3%), which was recrystallized from AcOEt to give colorless needles, mp 164–165°. *Anal.* Calcd. for C₁₀H₁₉ON: C, 70.94; H, 11.31; N, 8.27. Found: C, 71.03; H, 11.57; N, 8.20.

Tetrahydrooxazine Derivative (VIII) of 6,6-Dimethyl-9-azabicyclo[3,3,1]nonan-3 β -ol (VII-B)—Following the procedure of Alder and Dortmann,^{6b)} tetrahydrooxazine derivative (VIII) (0.4 g, 93.2%) was prepared from VII-B (0.24 g, 0.0014 mole) and *p*-nitrobenzaldehyde (0.24 g, 0.0016 mole) in chlorobenzene (20 ml). After two recrystallizations from ether, followed by sublimation under reduced pressure, VIII was obtained as colorless minute prisms and melted in the range of 98–108°. *Anal.* Calcd. for C₁₇H₂₂O₃N₂: C, 67.51; H, 7.33; N, 9.27. Found: C, 67.40; H, 7.46; N, 9.00.

Under the same condition the epimer (VII-A) gave a dark brown tarry product, from which VIII was not obtained.

7,7-Dimethylpseudopelletierine (IX)—7,7-Dimethylpseudopelletierine (IX) was prepared according to the procedure of Meinwald and Lee.⁷⁾ From 3,3-dimethylglutaraldehyde, CH₃NH₂·HCl and acetonedicarboxylic acid there was obtained IX as a pale yellow viscous oil, bp₃ 88–101°, which solidified on standing.

Methiodide: Colorless scales (from MeOH), mp 233–234° (decomp.). Reported. mp 230–231° (decomp.).⁷⁾ *Anal.* Calcd. for C₁₂H₂₂ONI: C, 44.59; H, 6.87; N, 4.33; I, 39.26. Found: C, 44.76; H, 6.84; N, 4.09; I, 39.33.

7,7,9-Trimethyl-9-azabicyclo[3,3,1]nonan-3 α -ol (X-A)—To a solution of IX (2.1 g, 0.0116 mole) in EtOH (30 ml) was added NaBH₄ (1.0 g, 0.0263 mole) in small portions with stirring at room temperature. After standing overnight the reaction mixture was worked up as above for VIa-A to yield X-A (1.8 g, 85.0%) as a colorless viscous oil, bp₂ 94–96°, which solidified on standing.

Picrate: Yellow prisms (from EtOH), mp 203–204° (decomp.). *Anal.* Calcd. for C₁₇H₂₄O₈N₄: C, 49.51; H, 5.87; N, 13.59. Found: C, 49.64; H, 5.85; N, 13.43.

7,7,9-Trimethyl-9-azabicyclo[3,3,1]nonan-3 β -ol (X-B)—To a boiling solution of IX (3.0 g, 0.0166 mole) in EtOH (30 ml) was added Na (4.6 g, 0.2 g-atom) portionwise, and the reaction mixture was heated under reflux for 1.5 hr. On working up as usual, X-B (2.5 g, 82.5%) was obtained as a faint yellow viscous oil, bp₂ 96–98°, which solidified on standing.

Picrate: Yellow prisms (from EtOH), mp 215–216° (decomp.). *Anal.* Calcd. for C₁₇H₂₄O₈N₄: C, 49.51; H, 5.87; N, 13.59. Found: C, 49.40; H, 5.81; N, 13.39.

7,7-Dimethyl-9-azabicyclo[3,3,1]nonan-3 α -ol (XI-A) and 3 β -ol (XI-B)—XI-A and XI-B were prepared according to the procedure for above VII-A and VII-B. From X-B (0.5 g, 0.00262 mole) there was obtained crude XI-B (0.4 g, 86.5%) which was recrystallized from AcOEt to give colorless needles, mp 142–143°. *Anal.* Calcd. for C₁₀H₁₉ON: C, 70.94; H, 11.31; N, 8.29. Found: C, 71.02; H, 11.40; N, 8.29. Similarly, XI-A was obtained as colorless prisms, mp 119–120° (from AcOEt).

Tetrahydrooxazine Derivative (XII) of 7,7-Dimethyl-9-azabicyclo[3,3,1]nonan-3 β -ol (XI-B)—Tetrahydrooxazine derivative (XII) was prepared in the same manner for VII-B. From XI-B (0.15 g, 0.00089 mole) and *p*-nitrobenzaldehyde (0.14 g, 0.00093 mole) there was obtained crude XII (0.25 g, 93%), which was recrystallized from ether to form colorless prisms, mp 124–125°. *Anal.* Calcd. for C₁₇H₂₂O₃N₂: C, 67.51; H, 7.33; N, 9.27. Found: C, 68.02; H, 7.39; N, 9.28.

General Procedure of Ester and Carbamate Derivatives of 6,6- and 7,7-Dialkyl-9-alkyl-9-azabicyclo[3,3,1]nonan-3 α and 3 β -ol (Table III)—Method A. Esterification with Acid Anhydrides: Compound 1,

10) A.C. Cope and C.G. Overberger, *J. Am. Chem. Soc.*, **70**, 1433 (1948).

2, 35 and 36 were obtained by the acetylation of the corresponding alcohols. A mixture of 6,6,9-trimethyl- or 7,7,9-trimethyl-9-azabicyclo[3,3,1]nonan-3 α - or 3 β -ol and excess amount of Ac₂O was heated at 60–80° for 2–3 hr. After removal of Ac₂O, an acetate was distilled under reduced pressure and purified as picrate by recrystallization. Compound 9 and 10 were prepared from 6,6,9-trimethyl-9-azabicyclo[3,3,1]nonan-3 α -ol and 3 β -ol and nicotinic anhydride (1.5 mole ratio) in DMF solution by allowing at room temperature for 40 hr. A nicotinate was isolated and purified as a picrate.

Method B. Esterification with Acid Chloride: Compounds 3–8 were prepared by method B. A mixture of 6,6,9-trimethyl-9-azabicyclo[3,3,1]nonan-3 α -ol or 3 β -ol and the corresponding acid chloride in pyridine was refluxed for 2–4 hr and evaporated *in vacuo*. Ice-cold NaHCO₃ solution was added to the residue and the mixture was extracted with AcOEt or ether. From the organic solution a product was isolated as a hydrochloride which was purified by recrystallization.

Method C. Preparation of Glycolate Derivatives by Ester Exchange Reaction: Compounds 11, 12, 15–28, 37 and 38 were prepared by this method. A solution of the corresponding alcohol and the corresponding glycolic acid methylester (small excess amount of theoretical), such as methyl benzilate methyl thenilate and O-methyl methyl thenilate, was heated by distilling the formed MeOH for 3–4 hr in the presence of catalytic amount of metallic sodium or sodium hydride. After cooling the reaction mixture was extracted with dil. HCl. When a crystalline hydrochloride was separated, it was collected by filtration and recrystallized. Acidic layer was made alkaline with Na₂CO₃ and extracted with AcOEt. From the extract the corresponding glycolate was obtained by the usual way and purified as a hydrochloride.

Method D. Acylation of Glycolate Derivatives: Compounds 29–34 were prepared by the following procedure. A mixture of 6,6,9-trimethyl-9-azabicyclo[3,3,1]non-3 β -yl benzilate and the corresponding acid anhydride was stirred for 3–4 hr at room temperature in the presence of equimolar amount of conc. H₂SO₄. From the reaction mixture there was separated a crystalline mass, which was collected and added into ice-water. The mixture was made alkaline with NaHCO₃ and extracted with AcOEt. After removal of the solvent the product was isolated as a hydrochloride and recrystallized. Compounds 32–34 were obtained by acylation of 6,6,9-trimethyl-9-azabicyclo[3,3,1]non-3 β -yl thenilate and the corresponding acid anhydride in pyridine solution under the conditions at 60–80° for 10–20 hr.

Method E. Chlorination of Benzilate Derivatives: Compounds 13 and 14 were obtained by the chlorination of compounds 11 and 12 respectively. A solution of 6,6,9-trimethyl-9-azabicyclo[3,3,1]non-3 α - or 3 β -yl benzilate and SOCl₂ (excess amount) in CCl₄ was refluxed for 3 hr. After evaporating the solvent and an excess SOCl₂, the residue was mixed with ice-cold NaHCO₃ solution and extracted with AcOEt. From the extract a product was isolated as hydrochloride, which was recrystallized.

Method F. Preparation of Carbamate Derivatives with Isocyanates: Compounds 39–42 were prepared by method F. A solution of 6,6,9-trimethyl-9-azabicyclo[3,3,1]nonan-3 α -ol or 3 β -ol and the corresponding isocyanate (about 1.5 mole ratio) in benzene was refluxed for 3–4 hr. After cooling the mixture was extracted with dil. HCl. The acidic solution was made alkaline with Na₂CO₃ and extracted with AcOEt or ether. From the organic layer a carbamate derivative was obtained as a hydrochloride and which was purified by recrystallization.

Method G. Preparation of Carbamate Derivatives with Carbamoyl Chlorides: Compounds 43–48 were obtained by a reaction of alcohols with carbamoylchlorides. A mixture of 6,6,9-trimethyl-9-azabicyclo[3,3,1]nonan-3 α -ol or 3 β -ol, the corresponding carbamoyl chloride (1.2–1.5 mole ratio), a catalytic amount of metallic sodium and toluene was refluxed for 15–20 hr. After cooling the mixture was extracted with dil. HCl and then worked up as in above method F.

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