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

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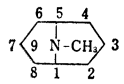
6,6- and 7,7-dialkyl-9-alkyl-9-azabicyclo[3,3,1]nonan-3-one (V) and (IX), synthesized from 2,2- and 3,3-dialkylglutaraldehyde by the Robinson–Schöpf reaction, were reduced with $NaBH_4$ and Na-EtOH to afford the A- and B-isomers of the corresponding 6,6- and 7,7-dialkyl-9-alkyl-9-azabicyclo[3,3,1]nonan-3-ol (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-chlolinergic 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.

tropane



granatane

The present paper describes the synthesis and pharmacological activity of 6,6- and 7,7-dialyl-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 shwon 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, $R^1=CH_3$) 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 yeilds 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. Forsh.*, **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.

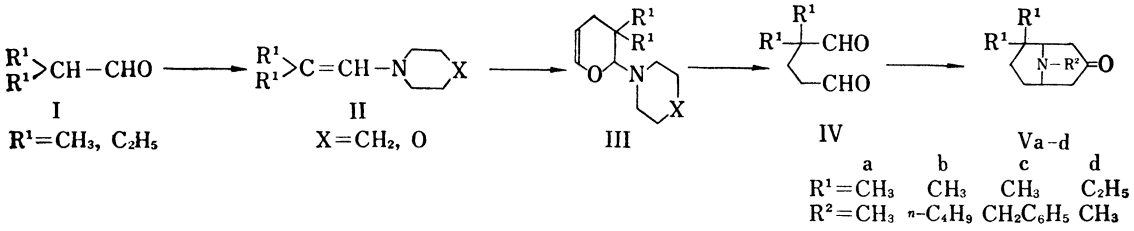
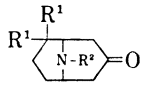


Chart 1

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-ethylbutyladehyde (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-aklyl-9-azabicyclo[3,3,1]nonan-3-ones (V)



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	$C_{17}H_{22}O_8N_4$	50.13 (49.75	5.48 5.41	13.54 13.65)
b	CH_3	n-C_4H_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	$CH_2C_6H_5$	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	$C_{23}H_{26}O_8N_4$	56.82 (56.78	5.51 5.39	11.54 11.52)
d	C_2H_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)

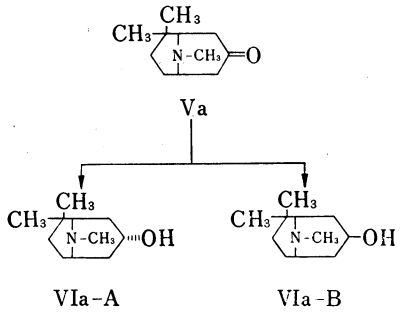
a) Yields were base on dihydropyrans (III). *b*) recrystallization solventt A=*n*-hexane; B=EtOH; C=EtOH-H_2O (9: 1 v/v)
c) picrate

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 $NaBH_4$. Furthermore, reduction of Va with $LiAlH_4$ 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 PtO_2 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.

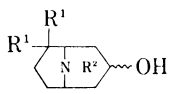


Reductn. method	Ratio of isomers (%) A	B
Na-EtOH	—	100
$NaBH_4$ in EtOH	100	—
$LiAlH_4$ in ether	96	4
PtO_2/H_2 in AcOH	100	—

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

(VI)	R^1	R^2	Config OH	bp/mmHg (°C)		mp (°C)	Rec.[a] Solv	Formula	Analysis (%) 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	$C_{17}H_{21}O_8N_4$	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	$C_{17}H_{21}O_8N_4$	49.54 (49.51	5.94 5.87	13.54 13.59)
b-A	CH_3	n-C_4H_9	α	133—135/3	Pic[b]	174—175 (decomp.)	C	$C_{20}H_{30}O_8N_4$	52.86 (52.85	6.69 6.65	12.21 12.33)
b-B	CH_3	n-C_4H_9	β	140—145/4	Pic[b]	149—150 (decomp.)	B	$C_{20}H_{30}O_8N_4$	52.95 (52.85	6.74 6.65	12.31 12.33)
c-A	CH_3	$CH_2C_6H_5$	α	145—150/0.2	Pic[b]	172—173 (decomp.)	C	$C_{23}H_{28}O_8N_4$	56.78 (56.54	5.83 5.77	11.45 11.47)
c-B	CH_3	$CH_2C_6H_5$	β	150—155/0.3	Pic[b]	205—206 (decomp.)	B	$C_{23}H_{28}O_8N_4$	56.75 (56.54	5.77 5.77	11.80 11.47)
d-A	C_2H_5	CH_3	α	131—132/2.5	Pic[b]	199—200 (decomp.)	B	$C_{19}H_{28}O_8N_4$	52.26 (51.81	6.48 6.41	12.71 12.72)
d-B	C_2H_5	CH_3	β	120—125/3	Pic[b]	167—168 (decomp.)	C	$C_{19}H_{28}O_8N_4$	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 $NaBH_4$ 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-3α-ol (VII-A) and 3β-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 reacton 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.

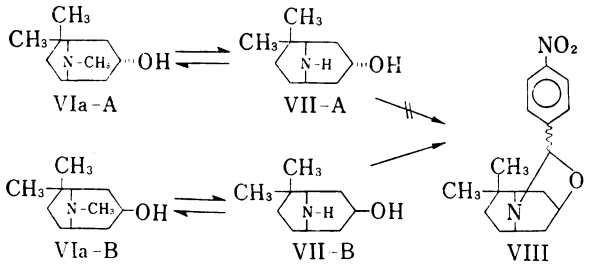


Chart 3

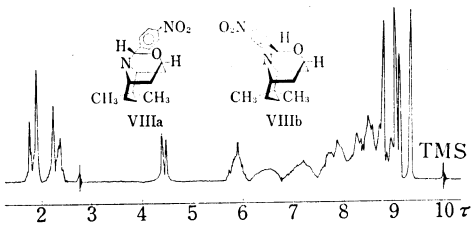


Fig. 1. NMR Spectrum of Tetrahydrooxazine (VIII) in $CDCl_3$ (60Mc)

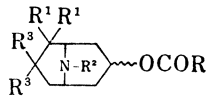
VIII was purified by recrystallization with ether followed by sublimation under reduced pressure. However its melting point was not sharp in the range of 98—108°, thus the existence of two diastereomers would be suggested. Although VIII indicated one component in gas chromatography and thin-layar chromatography 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	Pic[b] 87.7	147—148 (decomp.) EtOH	$C_{18}H_{26}O_9N_4$	50.02 (50.21	5.84 5.77	12.17 12.33)
2	CH_3	CH_3	H	CH_3	β	A	Pic 86.0	170—171 (decomp.) EtOH	$C_{18}H_{26}O_9N_4$	50.15 (50.21	5.87 5.77	12.11 12.33)
3	CH_3	CH_3	H	C_6H_5	α	B	HCl 82.3	253—254 (decomp.) EtOH–ether	$C_{18}H_{26}O_2NCl$	66.61 (66.74	8.18 7.78	4.21 4.32)
4	CH_3	CH_3	H	C_6H_5	β	B	HCl 77.7	239—240 (decomp.) EtOH–ether	$C_{18}H_{26}O_2NCl$	66.69 (66.74	8.19 7.78	4.29 4.32)
5	CH_3	CH_3	H	$CH(n\text{-}C_3H_7)_2$	α	B	HCl 47.8	241—242 (decomp.) EtOH–ether	$C_{19}H_{36}O_2NCl \cdot 1/3\ H_2O$	64.79 (64.84	10.81 10.50	3.99 3.98)
6	CH_3	CH_3	H	$CH(n\text{-}C_3H_7)_2$	β	B	HCl 44.4	215—216 (decomp.) EtOH–ether	$C_{19}H_{36}O_2NCl$	66.22 (65.95	10.72 10.49	3.86 4.05)
7	CH_3	CH_3	H	$CH(C_6H_5)_2$	α	B	HCl 64.1	242—243 (decomp.) EtOH–ether	$C_{25}H_{32}O_2NCl$	72.93 (72.52	7.87 7.79	3.41 3.38)
8	CH_3	CH_3	H	$CH(C_6H_5)_2$	β	B	HCl 82.0	226—227 (decomp.) EtOH–ether	$C_{25}H_{32}O_2NCl$	72.05 (72.52	8.07 7.79	3.36 3.38)
9	CH_3	CH_3	H	C_5H_4N[c]	α	A	2Pic 44.3	212—213 (decomp.) EtOH–H_2O	$C_{29}H_{30}O_{16}N_8$	46.92 (46.65	4.11 4.06	15.05 15.01)
10	CH_3	CH_3	H	C_5H_4N	β	A	2Pic 42.0	197—198 (decomp.) EtOH–H_2O	$C_{29}H_{30}O_{16}N_8$	46.74 (46.65	4.09 4.06	15.05 15.01)
11	CH_3	CH_3	H	$C(C_6H_5)_2$ | OH	α	C	HCl 71.0	230—231 (decomp.) EtOH–ether	$C_{25}H_{32}O_3NCl \cdot H_2O$	67.12 (67.03	7.51 7.65	3.20 3.13)
12	CH_3	CH_3	H	$C(C_6H_5)_2$ | OH	β	C	HCl 71.8	174—175 (decomp.) EtOH–ether	$C_{25}H_{32}O_3NCl \cdot H_2O$	67.19 (67.03	7.63 7.65	3.11 3.13)
13	CH_3	CH_3	H	$C(C_6H_5)_2$ | Cl	α	E	HCl 70.0	226—227 (decomp.) EtOH–ether	$C_{25}H_{31}O_2NCl_2$	67.02 (66.95	7.07 6.97	3.11 3.13)
14	CH_3	CH_3	H	$C(C_6H_5)_2$ | Cl	β	E	HCl 34.6	255—256 (decomp.) EtOH	$C_{25}H_{31}O_2NCl_2$	66.84 (66.95	6.82 6.97	3.12 3.13)
15	CH_3	$n\text{-}C_4H_9$	H	$C(C_6H_5)_2$ | OH	α	C	HCl 76.9	189—192 (decomp.) EtOH	$C_{28}H_{38}O_3NCl \cdot 1/2\ H_2O$	69.91 (69.91	8.54 8.17	2.73 2.91)
16	CH_3	$n\text{-}C_4H_9$	H	$C(C_6H_5)_2$ | OH	β	C	HCl 50.0	201—202 (dedomp.) EtOH–ether	$C_{28}H_{38}O_3NCl$	71.46 (71.24	8.10 8.11	2.90 2.97)
17	CH_3	$CH_2C_6H_5$	H	$C(C_6H_5)_2$ | OH	α	C	HCl 85.2	220—221 (decomp.) EtOH	$C_{31}H_{36}O_3NCl$	73.69 (73.56	7.16 7.17	2.75 2.77)
18	CH_3	$CH_2C_6H_5$	H	$C(C_6H_5)_2$ | OH	β	C	base 64.3	107—108 *n*-hexane	$C_{31}H_{35}O_3N$	79.57 (79.28	7.55 7.51	3.02 2.98)
19	C_2H_5	CH_3	H	$C(C_6H_5)_2$ | OH	α	C	HCl 55.2	223—225 (decomp.) EtOH	$C_{27}H_{36}O_3NCl$	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_2H_5	CH_3	H	$C(C_6H_5)_2$ OH	β	C 64.6	HCl 197—200 (decomp.) EtOH–ether	$C_{27}H_{36}O_3NCl$	70.72 (70.80	7.97 7.92	3.02 3.06)
21	CH_3	CH_3	H	$C(C_4H_3S)_2$[d] OH	α	C 47.8	HCl 233—234 (decomp.) EtOH	$C_{21}H_{28}O_3NS_2Cl$	56.87 (57.06	6.49 6.38	3.34 3.17)
22	CH_3	CH_3	H	$C(C_4H_3S)_2$ OH	β	C 63.6	HCl 136—137 (decomp.) 90% iso PrOH	$C_{21}H_{28}O_3NS_2Cl \cdot H_2O$	54.77 (54.83	6.40 6.57	3.21 3.05)
23	CH_3	CH_3	H	$C(C_4H_3S)_2$ OCH_3	α	C 44.3	HCl 228—230 (decomp.) EtOH	$C_{22}H_{30}O_3NS_2Cl \cdot 1/3\ H_2O$	57.31 (57.18	6.69 6.69	3.02 3.03)
24	CH_3	CH_3	H	$C(C_4H_3S)_2$ OCH_3	β	C 87.5	HCl 203—205 (decomp.) EtOH	$C_{22}H_{30}O_3NS_2Cl \cdot 1/3\ H_2O$	57.50 (57.18	6.62 6.69	3.00 3.03)
25	C_2H_5	CH_3	H	$C(C_4H_3S)_2$ OH	α	C 40.3	HCl 219—220 (decomp.) EtOH	$C_{23}H_{32}O_3NS_2Cl$	58.67 (58.76	6.94 6.86	3.03 2.98)
26	C_2H_5	CH_3	H	$C(C_4H_3S)_2$ OH	β	C 74.0	HCl 196—198 (decomp.) EtOH	$C_{23}H_{32}O_3NS_2Cl$	58.95 (58.76	6.86 6.86	2.97 2.98)
27	C_2H_5	CH_3	H	$C(C_4H_3S)_2$ OCH_3	α	C 66.1	HCl 210—212 (decomp.) EtOH	$C_{24}H_{34}O_3NS_2Cl \cdot 1/3\ H_2O$	58.53 (58.81	7.28 7.13	2.78 2.86)
28	C_2H_5	CH_3	H	$C(C_4H_3S)_2$ OCH_3	β	C 66.1	HCl 202—204 (decomp.) EtOH	$C_{24}H_{34}O_3NS_2Cl \cdot 1/3\ H_2O$	59.16 (58.81	7.16 7.13	2.79 2.86)
29	CH_3	CH_3	H	$C(C_6H_5)_2$ $OCOCH_3$	β	D 74.8	HCl 232—233 (decomp.) EtOH–ether	$C_{27}N_{34}O_4NCl$	56.84 (57.06	6.29 6.25	2.99 2.89)
30	CH_3	CH_3	H	$C(C_6H_5)_2$ $OCOC_2H_5$	β	D 79.7	HCl 208—210 (decomp.) EtOH–ether	$C_{28}H_{36}O_4NCl$	57.87 (57.87	6.50 6.48	2.71 2.81)
31	CH_3	CH_3	H	$C(C_6H_5)_2$ $OCOnC_3H_7$	β	D 81.4	HCl 213—215 (decomp.) EtOH–ether	$C_{29}H_{38}O_4NCl$	69.78 (69.65	7.60 7.66	2.71 2.80)
32	CH_3	CH_3	H	$C(C_4H_3S)_2$ $OCOCH_3$	β	D 33.5	HCl 191—192 (decomp.) EtOH–ether	$C_{23}H_{30}O_4NS_2Cl$	56.84 (57.06	6.29 6.25	2.99 2.89)
33	CH_3	CH_3	H	$C(C_4H_3S)_2$ $OCOC_2H_5$	β	D 10.5	HCl 184—185 (decomp.) EtOH–ether	$C_{24}H_{32}O_4NS_2Cl$	57.87 (57.87	6.50 6.48	2.71 2.81)
34	CH_3	CH_3	H	$C(C_4H_3S)_2$ $OCOnC_3H_7$	β	D 26.0	HCl 180—181 (decomp.) EtOH–ether	$C_{25}H_{34}O_4NS_2Cl$	58.49 (58.63	6.75 6.69	2.89 2.74)
35	H	CH_3	CH_3	CH_3	α	A 85.9	Pic 183—184 (decomp.) EtOH	$C_{18}H_{26}O_9N_4$	50.22 (50.21	5.84 5.77	12.44 12.33)
36	H	CH_3	CH_3	CH_3	β	A 88.8	Pic 144—145 (decomp.) EtOH	$C_{18}H_{26}O_9N_4$	50.20 (50.21	5.82 5.77	12.47 12.33)
37	H	CH_3	CH_3	$C(C_6H_5)_2$ OH	α	C 80.5	HCl 224—225 (decomp.) EtOH–ether	$C_{25}H_{32}O_3NCl$	69.66 (69.84	7.39 7.50	3.11 3.26)
38	H	CH_3	CH_3	$C(C_6H_5)_2$ OH	β	C 60.2	base 124—125 *n*-hexane–AcOEt	$C_{25}H_{31}O_3N$	76.15 (76.30	7.82 7.94	3.42 3.56)
39	CH_3	CH_3	H	NHC_6H_5	α	F 81.0	Pic 219—220 (decomp.) EtOH	$C_{24}H_{29}O_9N_5$	54.44 (54.23	5.58 5.50	13.09 13.18)
40	CH_3	CH_3	H	NHC_6H_5	β	F 91.1	HCl 235—236 (decomp.) EtOH–ether	$C_{18}H_{27}O_2N_2Cl \cdot H_2O$	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.)	$C_{24}H_{28}O_9N_5Cl$	51.30 (50.93	5.02 4.49	12.30 12.37)
						66.0	EtOH					
42	CH_3	CH_3	H		β	F	HCl	247—248 (decomp.)	$C_{18}H_{26}O_2N_2Cl_2$ ·1/2 H_2O	56.54 (56.54	7.21 7.12	7.46 7.32)
						89.7	EtOH–ether					
43	CH_3	CH_3	H	$N(C_2H_5)_2$	α	G	HCl	224—226 (decomp.)	$C_{16}H_{31}O_2N_2Cl$	59.71 (60.25	9.81 9.80	8.68 8.78)
						23.4	EtOH–ether					
44	CH_3	CH_3	H	$N(C_2H_5)_2$	β	G	HCl	232—234 (decomp.)	$C_{16}H_{31}O_2N_2Cl$	60.22 (60.25	10.05 9.80	8.93 8.78)
						41.0	EtOH–ether					
45	CH_3	CH_3	H		α	G	Pic	207—208 (decomp.)	$C_{22}H_{31}O_{10}N_5$	50.66 (50.28	6.05 5.95	13.47 13.33)
						19.2	EtOH					
46	CH_3	CH_3	H		β	G	Pic	192—193 (decomp.)	$C_{22}H_{31}O_{10}N_5$	50.49 (50.28	6.01 5.95	13.48 13.33)
						37.4	EtOH					
47	CH_3	CH_3	H		α	G	Pic	197—198 (decomp.)	$C_{23}H_{33}O_9N_5$	53.09 (52.76	6.59 6.93	13.58 13.38)
						22.8	EtOH					
48	CH_3	CH_3	H		β	G	HCl	215—216 (decomp.)	$C_{17}H_{31}O_2N_2Cl$ ·1/3 H_2O	60.66 (60.60	9.48 9.47	8.45 8.32)
						32.7	EtOH–ether					

a) crude product yield; *b*) picrate; *c*) 3-pyridyl-; *d*) C_4H_3S=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

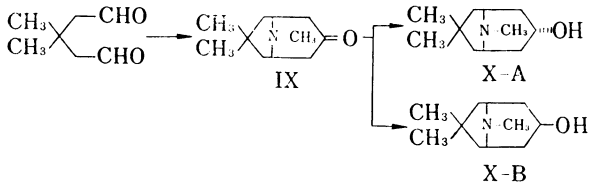


Chart 4

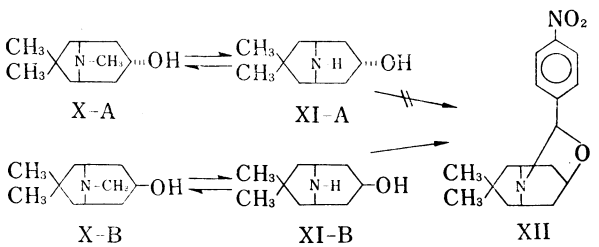


Chart 5

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 acetylchloline-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 (ED_{50} of mydriatic activity)/(ED_{50} 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-3α- and 3β-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.

Experimental[8]

2-Piperidino-3,3-dimethyl-Δ^5-dihydropyran (III, $R^1=CH_3$, $X=CH_2$)——To a solution of 1-isobutenyl-piperidine[3] (II, $R^1=CH_3$, $X=CH_2$), prepared by dehydrating reaction of isobutylaldehyde (I, $R^1=CH_3$) 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, bp_3 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 $CH_3NH_2 \cdot HCl$ (8.9 g, 0.132 mole) and acetone dicarboxylic acid[9] (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-3α-ol (VIa-A)——To a solution of Va (100 g, 0.55 mole) in EtOH (600 ml) was added $NaBH_4$ (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, bp_1 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-3β-ol (VIa-B)——6,6,9-Trimethyl-9-azabicyclo[3,3,1]nonan-3β-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) portionweise 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, bp_3 113—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-3α-ol (VII-A) and 3β-ol (VII-B)——VII-A and VII-B were prepared according to the procedure of Zirkle, *et al.*[6a] for 3-oxagranatanin-7β-ol and 7α-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 H_2O (100 ml) was added a solution of $KMnO_4$ (3.3 g, 0.021 mole) in H_2O (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 $C_{10}H_{19}ON$: 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 $C_{10}H_{19}ON$: 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-3β-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 $C_{17}H_{22}O_3N_2$: 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 be obtained.

7,7-Dimethylpseudopelletierine (IX)——7,7-Dimethylpseudopelletierine (IX) was prepared according to the procedure of Meinwald and Lee.[7] From 3,3-dimethylglutaraldehyde, $CH_3NH_2 \cdot HCl$ and acetonedicarboxylic acid there was obtained IX as a pale yellow viscous oil, bp_3 88—101°, which solidified on standing.

Methiodide: Colorless scales (from MeOH), mp 233—234° (decomp.). Reported. mp 230—231° (decomp.).[7] *Anal.* Calcd. for $C_{12}H_{22}ONI$: 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-3α-ol (X-A)——To a solution of IX (2.1 g, 0.0116 mole) in EtOH (30 ml) was added $NaBH_4$ (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, bp_2 94—96°, which solidified on standing.

Picrate: Yellow prisms (from EtOH), mp 203—204° (decomp.). *Anal.* Calcd. for $C_{17}H_{24}O_8N_4$: 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-3β-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) portionweise, 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, bp_2 96—98°, which solidified on standing.

Picrate: Yellow prisms (from EtOH), mp 215—216° (decomp.). *Anal.* Calcd. for $C_{17}H_{24}O_8N_4$: 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-3α-ol (XI-A) and 3β-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 $C_{10}H_{19}ON$: 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-3β-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 $C_{17}H_{22}O_3N_2$: 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-3α and 3β-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-3α- or 3β-ol and excess amount of Ac_2O was heated at 60—80° for 2—3 hr. After removal of Ac_2O, a 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-3α-ol and 3β-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-3α-ol or 3β-ol and the corresponding acid chloride in pyridine was refluxed for 2—4 hr and evaporated *in vacuo*. Ice-cold $NaHCO_3$ 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 distillating 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 Na_2CO_3 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-3β-yl benzilate and the corresponding acid anhydride was stirred for 3—4 hr at room temperature in the presence of equimolar amount of conc. H_2SO_4. From the reaction mixture there was separated a crystalline mass, which was collected and added into ice-water. The mixture was made alkaline with $NaHCO_3$ 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-3β-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-3α- or 3β-yl benzilate and $SOCl_2$ (excess amount) in CCl_4 was refluxed for 3 hr. After evaporating the solvent and an excess $SOCl_2$, the residue was mixed with ice-cold $NaHCO_3$ 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-3α-ol or 3β-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 Na_2CO_3 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-3α-ol or 3β-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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