1,6-dibromohexane in 100 ml of THF maintained under N_2 at *ca.* −9° was added dropwise over 0.75 hr a solution of 42.5 ml of 20% PhLi solution (70:30 C_6H_6-Et_2O). The resultant solution was allowed to come to room temperature over a 20-hr period. H_2O (50 ml) was slowly added to destroy the unreacted PhLi. The two phases were separated, the aqueous phase was discarded and the organic phase was washed (H_2O) and dried ($CaCl_2$). The solvent was evaporated under reduced pressure and the residue was distilled by means of a spinning-band column. The product, bp 79–81° (0.45 mm) [lit.[10] bp 160–161° (17 mm)], $n^{25}D$ 1.5252–1.5285, weighed 4.13 g (34%). *Anal.* ($C_{12}H_{17}Br$) Br.

Method B.—Equimolar quantities of an *N*-alkylaminoethyl halide hydrohalide and $Na_2S_2O_3 \cdot 5H_2O$ in H_2O or H_2O-EtOH, depending on the solubility of the former reactant, were heated on a steam bath for *ca.* 0.5 hr. When the reaction was complete, as indicated by failure of S to precipitate from a strongly acidified aliquot, the thiosulfuric acids crystallized from the cooled and, in some instances, concentrated reaction mixtures. The *N*-alkylaminoethanethiosulfuric acids which were recrystallized until they were free of halide ion showed characteristic peaks in the ir near 8.15, 8.40, and 9.80 μ.

2-(5-Phenylpentylamino)ethanethiosulfuric Acid.—The following exemplifies the procedure used when a carboxylic acid was the precursor of the *N*-alkyl group. A mixture of 100 g (0.56 mol) of 5-phenylvaleric acid and 34.3 g (0.56 mol) of 2-aminoethanol was heated gently at first, followed by a gradual increase in the application of heat until the temperature was maintained at 160–200°. The H_2O which formed in the course of the reaction was collected in a Dean–Stark trap fitted atop a Vigreaux column. The crude *N*-(2-hydroxyethyl)-5-phenylvaleramide was used in the next step without further purification.

A THF solution (200 ml) of the *N*-(2-hydroxyethyl)-5-phenylvaleramide was added over 2.5 hr to a cooled and stirred slurry of 22.8 g (0.6 mol) of LAH and 500 ml of THF. After the mixture was heated under reflux for 11 hr, 250 ml of H_2O was cautiously added to the cooled and stirred mixture to destroy excess LAH. The $Al(OH)_3$ which formed was filtered from the mixture and washed (Et_2O). The aqueous phase of the filtrate was extracted (Et_2O), the ether and THF solutions were combined, and dried ($MgSO_4$), and the solvents were evaporated on a rotary evaporator. The residue was distilled at reduced pressure to give 52 g (50%) of 2-(5-phenylpentylamino)ethanol. Treatment of the latter with 48% HBr by the method of Cortese[11] gave 58 g (69%) of 2-(5-phenylpentylamino)ethyl bromide·HBr which was converted into the thiosulfuric acid by the reaction with $Na_2S_2O_3 \cdot 5H_2O$ in 1:1 H_2O-EtOH.

Acknowledgments.—We thank Dr. T. R. Sweeney and Col. W. E. Rothe for many helpful suggestions. We are also grateful to Drs. W. F. Gilmore and S. Abdou-Sabet and Messrs. L. Hafner, J. D. White, J. Oliver, and P. L. Merkel for technical assistance.

(10) J. von Braun, *Ber.*, **44**, 2877 (1911).

(11) F. Cortese, "Organic Syntheses," Coll. Vol. II, John Wiley & Sons, Inc., New York, N. Y., 1943, p 91.

Antiviral Agents. I. Bicyclo[2.2.2]octan- and -oct-2-enamines

JOEL G. WHITNEY, W. A. GREGORY, J. C. KAUER, J. R. ROLAND, J. A. SNYDER, R. E. BENSON, AND E. C. HERMANN

Pharmaceuticals Division, Industrial and Biochemicals Department, and Central Research Department, E. I. DuPont De Nemours & Co., Inc., Wilmington, Delaware

Received June 30, 1965

The preparation of a number of bicyclo[2.2.2]octan- and -oct-2-enamines is described. Antiviral test data in mice are given and structure–activity relationships are discussed.

The discovery of antiviral activity for adamantan-1-amine (amantadine·HCl)[1] against several strains of influenza A virus in mice, chick embryos, and tissue culture[2] and the subsequent demonstration of its clinical efficacy against influenza A_2 in man[3] prompted us to synthesize other cage amines to explore their usefulness as antiviral agents.

This paper describes the synthesis of bicyclo[2.2.2]-octan-1-amines, bicyclo[2.2.2]oct-2-en-1-amines, bicyclo[2.2.2]octane-1-methylamines, and bicyclo[2.2.2]-oct-2-ene-1-methylamines[4] and presents a novel synthetic entry into the bicyclo[2.2.2]octane ring system. The results obtained from evaluation of these compounds as antiviral agents against influenza A/swine infections of mice are given.

Chemistry.—The syntheses of the required bicyclo[2.2.2]oct-2-ene- and -octane-1-carboxylic acids are outlined in Scheme I. Several of the alkyl α-pyrone-3-carboxylates (Ia,[5] Ic,[6] Id,[6] Ie, and If) were obtained by known methods.[5,6] The α-pyrones Ib,[6,7] Ig, and Ih were prepared by base condensation of the appropriate methyl ketone with diethyl ethoxymethylenemalonate, followed by cyclization of a postulated intermediate diethyl 3-acylethylidenemalonate. α-Pyrones Ic, If, and Ig were used without purification. The absorption bands of their spectra (ir) were as expected.

Reaction of the alkyl α-pyrone-3-carboxylates I with ethylene[8,9] at high pressure afforded the desired alkyl bicyclo[2.2.2]oct-2-ene-1-carboxylates II (see Scheme II). The esters (IV) were used without purification. Esters IIb and IIh have been reported previously.[9] In the reaction of ethylene with α-pyrones, the intermediate cyclohexadienes could usually be isolated by the use of lower temperatures or lower pressures.

We have observed that the ease of addition of ethylene to cyclohexadienes generally appears to increase

(1) Symmetrel®, E. I. DuPont De Nemours and Co.

(2) R. R. Grunert, J. W. McGahen, and W. L. Davies, *Virology*, **26**, 262 (1965). W. L. Davies, R. R. Grunert, R. F. Haff, J. W. McGahen, E. M. Neumayer, M. Paulshock, J. C. Watts, T. R. Wood, E. C. Hermann, and C. E. Hoffman, *Science*, **144**, 862 (1964). C. E. Hoffmann, E. M. Neumayer, R. F. Haff, and R. A. Goldsby, *J. Bacteriol.*, **90**, 623 (1965). E. M. Neumayer, R. F. Haff, and C. E. Hoffmann, *Proc. Soc. Exp. Biol. Med.*, **119**, 393 (1965). W. L. Davies, R. R. Grunert, and C. E. Hoffmann, *J. Immunol.*, **95**, 1090 (1966).

(3) For summaries see C. E. Hoffmann in "Annual Reports in Medicinal Chemistry," C. K. Cain Ed., Academic Press, New York, N. Y., 1967, p 118; 1968, p 117.

(4) J. C. Kauer, U. S. Patent 3,418,369 (1968). J. C. Kauer, Netherlands Patent Application 6,404,759 (1964); *Chem. Abstr.*, **62**, 14529 (1965).

(5) R. H. Wiley and A. J. Hart, *J. Amer. Chem. Soc.*, **76**, 1942 (1954).

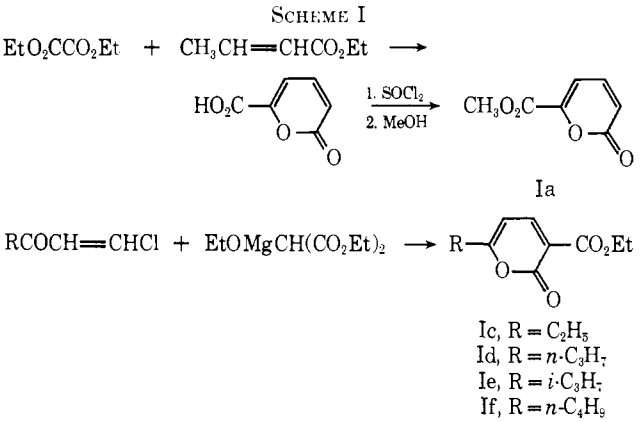
(6) N. K. Kochetkov and G. I. Kudryashov, *J. Gen. Chem. USSR*, **27**, 277 (1957).

(7) P. R. Hills and F. J. McQuillin, *J. Chem. Soc.*, 4060 (1953).

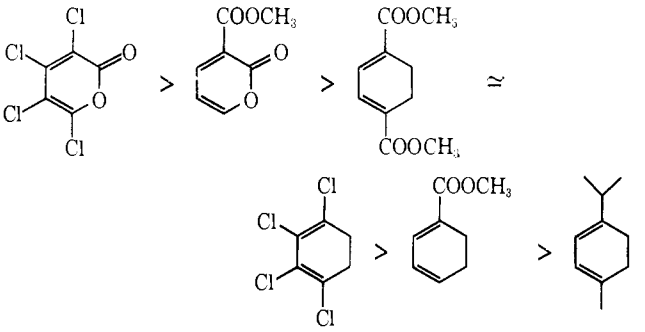
(8) J. C. Kauer, Netherlands Patent Application 6,507,979 (1965); *Chem. Abstr.*, **64**, 15772 (1966).

(9) F. W. Baker and L. M. Stock, *J. Org. Chem.*, **32**, 3344 (1967).

SCHEME I



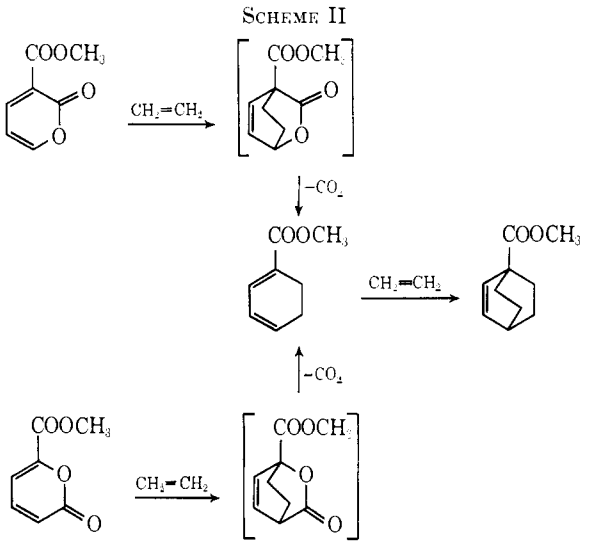
with the number of electronegative atoms or substituents on or in the ring. If α-pyrones are considered as disubstituted cyclohexadienes, they fit in the following sequence of reactivity.[10] We have previously



noted the tendency of ethylene to behave as an electron-rich dienophile in its reaction with dienes.[10a]

Hydrolysis with aqueous base of the unsaturated esters II gave the corresponding bicyclo[2.2.2]oct-2-ene-1-carboxylic acids III listed in Table I.

SCHEME II



Hydrogenation of the unsaturated esters II yielded the corresponding alkyl bicyclo[2.2.2]octane-1-carboxylates IV. The saturated esters were hydrolyzed without purification to the desired bicyclo[2.2.2]octane-1-carboxylic acids V (Table II). 4-Methylbicyclo[2.2.2]octane-1-carboxylic acid (Vb) was also prepared by HNO_3 oxidation of 1-isopropyl-4-methylbicyclo[2.2.2]octane, obtained by the addition of ethylene to α-terpinene followed by hydrogenation of the adduct (Scheme I).

Several bicyclo[2.2.2]oct-2-ene-1-carboxylic acids (IIIa, IIIb, IIId, and IIIg) were converted *via* a modified Curtius reaction[11] into the corresponding bicyclo[2.2.2]oct-2-en-1-amines **1**, **2**, **3**, and **4** (Table III). Conversion of bicyclo[2.2.2]oct-2-ene-1-carboxylic acids IIIa, IIIb, and IIIg into their mixed anhydrides with EtOCOCl followed by reaction with NH_3 and reduction of the amides formed with $LiAlH_4$[12] gave the corresponding bicyclo[2.2.2]oct-2-ene-1-methylamines **5**, **6**, and **7** (Table IV).

A large number of bicyclo[2.2.2]octan-1-amines 8 through **31** (Table IV) have been prepared. The bicyclo[2.2.2]octane-1-carboxylic acids Va through Vh were converted into bicyclo[2.2.2]octan-1-amines 8

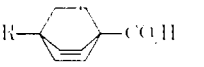
(10) (a) J. C. Kauer, R. E. Benson, and G. W. Parshall, *J. Org. Chem.*, **30**, 1431 (1965). (b) J. C. Kauer, U. S. Patent 3,256,329 (1966).

(11) J. Weinstock, *J. Org. Chem.*, **26**, 3511 (1961).

(12) A. C. Cope and E. Ciganek, *Org. Syn.*, **4**, 339 (1963).

TABLE I

BICYCLO[2.2.2]OCT-2-ENE-1-CARBOXYLIC ACIDS

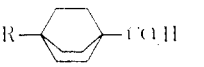


No.	R	Yield, %[a]	Solvent of cryst[b]	Mp, °C	Formula[c]
IIIa	H	39[d]		115.5–116.5[e]	$C_9H_{12}O_2$
IIIb	Me	27[b]	C_5H_{12}	143–144[f]	$C_{10}H_{14}O_2$
IIId	*n*-C_3H_7	56[b]	C_7H_{16}	173–173.5	$C_{12}H_{18}O_2$
IIIg	*t*-C_4H_9	42	EtOH	252.2–253.5	$C_{13}H_{20}O_2$

[a] All compounds were analyzed for C, H. [b] From the corresponding α-pyrone. [c] Lit.[g] mp 120–121°. [d] Lit.[g] mp 144–144.5°.

TABLE II

BICYCLO[2.2.2]OCTANE-1-CARBOXYLIC ACIDS

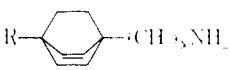


No.	R	Yield, %[a]	Solvent of cryst[b]	Mp, °C	Formula[c]
Va	H	40[d]		135–138[e]	$C_9H_{14}O_2$
Vb	CH_3[f]	33[b]	$MeNO_2$	182–183.5[g]	$C_{10}H_{16}O_2$
Vc	C_2H_5	40[d]	C_6H_{14}	178.5–179.5[g]	$C_{11}H_{18}O_2$[h]
Vd	*n*-C_3H_7	48[b]	$C_6H_5CH_3$	242–243	$C_{12}H_{20}O_2$
Ve	*i*-C_3H_7	20	$MeNO_2$	210–212	$C_{12}H_{20}O_2$
Vf	*n*-C_4H_9	2	C_7H_{16}	158–158.5	$C_{13}H_{22}O_2$
Vg	*t*-C_4H_9	45	EtOH	281–282	$C_{13}H_{22}O_2$
Vh	CF_3	88[d]	C_7H_{16}	222–223[e]	$C_{10}H_{13}F_3O_2$[i]

[a] From the corresponding α-pyrone. [b] J. D. Roberts, W. T. Moreland, and W. Frazer [*J. Amer. Chem. Soc.*, **75**, 637 (1953)] report mp 140.8–141.3°. [c] All compounds were analyzed for C, H, unless otherwise noted. [d] Adsorption bands of spectra (nmr) were as expected. [e] H. D. Holtz and L. M. Stock [*ibid.*, **86**, 5183 (1964)] report mp 187–188°. [f] Lit. mp 170.5–171°. [g] Not analyzed. [h] Lit.[g] mp 214–215.5°. [i] Analyzed for C, H, F.

TABLE III

BICYCLO[2.2.2]OCT-2-EN-1-AMINES AND 1-METHYLAMINES



No.	R	X	Yield, %[a]	Solvent of cryst[b]	Mp, °C	Formula	Analysis	λVis[c]
1	H[d]	0	80	*i*-PrOH, C_6H_{14}–C_6H_{14}	315.5–316.8	$C_8H_{13}N$·HCl	C, H, N	11
2	CH_3[e]	0	72		*b*	$C_9H_{15}N$	C, H, N	2.8
3	*n*-C_3H_7	0	31	6 *N* HCl	273–275	$C_{11}H_{19}N$·HCl	C, H, N	16
4	*t*-C_4H_9	0	18	6 *N* HCl	320–321	$C_{12}H_{21}N$·HCl	C, H, N	15
5	H	1	76	*c*	267–269 dec	$C_8H_{15}N$·HCl	Cl	18
6	CH_3	1	44	*c*	223–224.5	$C_9H_{17}N$·HCl	N, Cl	7.9
7	*t*-C_4H_9	1	38	*c*	265–275 dec	$C_{13}H_{25}N$·HCl	N, Cl	7.0

[a] Absorption bands of spectra (nmr) were as expected. [b] Bp 73–74° (80 mm); HCl salt, mp 315–316°, *i*-PrOH–C_6H_6–C_6H_{14}. [c] Precipitate from Et_2O.

through **15** *via* the Schmidt reaction.[13] Several of the N-substituted bicyclo[2.2.2]octan-1-amines (**18**, **25**, **27**, **29**, and **30**) were prepared by acylation of the appropriate bicyclo[2.2.2]octan-1-amine followed by reduction with LAH. 4,*N*,*N*-Trimethylbicyclo-[2.2.2]octan-1-amine hydrochloride (**19**) was prepared by alkylation of the corresponding amine **9** with MeI. Other *N*,*N*-dimethylbicyclo[2.2.2]octan-1-amines **20** through **24** were prepared by Eschweiler–Clarke[14] methylation of the corresponding primary amines **10** through **14**. 4-Cyclohexylbicyclo[2.2.2]octan-1-amine hydrochloride (**16**) was synthesized by catalytic hydrogenation of 4-phenylbicyclo[2.2.2]octan-1-amine.[15]

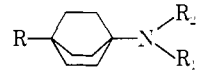
Conversion of bicyclo[2.2.2]octane-1-carboxylic acids V into their acid chlorides or into their mixed anhydrides with EtOCOCl followed by reaction with NH_3 or an amine and LAH reduction[12] of the amides afforded bicyclo[2.2.2]octane-1-methylamines **32** through **41** (Table V).

The α-methylbicyclo[2.2.2]octane-1-methylamines **42** and **43** (Table V) were prepared by reduction[16,17] of the oximes of the corresponding bicyclo[2.2.2]oct-1-yl methyl ketones VI. Reaction of the acids Va and Vb with MeLi[18] gave the methyl ketones VI which formed the required oximes on reaction with $H_2NOH \cdot HCl$[19] (Scheme III). Bicyclo[2.2.2]oct-1-yl methyl ketone and its oxime have been previously reported.[19]

(13) H. Wolff, *Org. React.*, **3**, 330 (1946).
(14) M. L. Moore, *ibid.*, **5**, 323 (1949).
(15) J. A. Snyder, U. S. Patent 3,362,878 (1968).
(16) C. A. Walter, *J. Amer. Chem. Soc.*, **7**, 5185 (1952).
(17) W. E. Rosen and M. J. Green, *J. Org. Chem.*, **28**, 2797 (1963).
(18) C. H. DePuy, G. M. Dappen, K. L. Eliers, and R. A. Klein, *ibid.*, **29**, 2813 (1964).
(19) H. P. Fischer and C. A. Grob, *Helv. Chim. Acta.*, **47**, 564 (1964).

TABLE IV

DERIVATIVES OF BICYCLO[2.2.2]OCTAN-1-AMINE

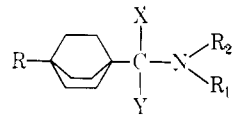


No.	R	R_1	R_2	Yield, %	Solvent of crystn	Mp, °C	Formula	Analyses	AVI[5]
8	H[a,b]	H	H	92	*c*	141.5–142.7	$C_{18}H_{15}N$	N	15.0
9	CH_3[a]	H	H	82	*d*	≡21 ≡20	$C_9H_{17}N$	C, H, N	2.2
10	C_2H_5	H	H	83	*e*	275–277	$C_{10}H_{19}N \cdot HCl$	C, H, N	2.0
11	*n*-C_3H_7	H	H	66.5	H_2O	318.5	$C_{11}H_{21}N \cdot HCl$	C, H, N	9.8
12	*i*-C_3H_7	H	H	84	$ClCH_2CH_2Cl$	298–299	$C_{11}H_{21}N \cdot HCl$	C, H, N	7.9
13	*n*-C_4H_9	H	H	80	H_2O	291–216	$C_{12}H_{23}N \cdot HCl$	C, H, N	Neg
14	*t*-C_4H_9	H	H	44	H_2O	>300	$C_{12}H_{23}N \cdot HCl$	C, H	5.6
15	CF_3[a]	H	H	81	*e*	>300	$C_9H_{14}F_3N \cdot HCl$	C, H, N, Cl	Neg
16	C_6H_{11}	H	H	55	*n*-BuOH	>300	$C_{14}H_{25}N \cdot HCl \cdot H_2O$	N, Cl	Neg
17	CH_3	CH=O	H	94		*f*	$C_{10}H_{17}NO$	N	
18	CH_3	CH_3	H	38	*i*-PrOH, C_6H_6	263.5–264.5[g]	$C_{10}H_{19}N \cdot HCl$	C, H, N, Cl	1.5
19	CH_3[a]	CH_3	CH_3	69	*i*-PrOH, C_6H_6	*h*	$C_{11}H_{21}N \cdot HCl$	C, H, N, Cl	3.1
20	C_2H_5	CH_3	CH_3	94	C_6H_6	208–209	$C_{12}H_{23}N \cdot HCl$	N	5.1
21	*n*-C_3H_7	CH_3	CH_3	32	Me_2CO	99–100	$C_{13}H_{25}N \cdot HCl$	C, H, N	Neg
22	*i*-C_3H_7	CH_3	CH_3	97	Dioxane	245–246	$C_{13}H_{25}N \cdot HCl$	C, H, N	16.0
23	*n*-C_4H_9	CH_3	CH_3	45	Me_2CO	209.5–212	$C_{14}H_{27}N \cdot HCl$	C, H, N	Neg
24	*t*-C_4H_9	CH_3	CH_3	36	EtOH, Me_2CO	287.5–288	$C_{14}H_{27}N \cdot HCl$	C, H, N	Neg
25	CH_3[a]	*n*-C_3H_7	*n*-C_3H_7	34[i]	*e*	189–196	$C_{15}H_{29}N \cdot HCl$	N, Cl	Neg
26	CH_3	C_2H_5CO	H	68	C_7H_{16}	115.5–116.5	$C_{21}H_{21}NO$	C, H, N	
27	CH_3	*n*-C_3H_7	H	47	6 *N* HCl	277–278	$C_{12}H_{23}N \cdot HCl$	C, H, N	Neg
28	CH_3	*i*-C_3H_7CO	H	86	C_6H_{14}	115–116	$C_{13}H_{23}NO$	N	
29	CH_3	*s*-C_4H_9	H	56	*e*	244–246	$C_{13}H_{25}N \cdot HCl$	C, H, N	Neg
30	CH_3	$C_6H_5CH_2$	H	31	EtOH	236 dec	$C_{16}H_{23}N \cdot C_4H_4O_4$	C, H, N	Neg
31	CH_3	C_6H_5CO	H	98		147.5–149	$C_{16}H_{21}NO$	C, H, N	

[a] Absorption bands of spectra (nmr) were as expected. [b] HCl salt (H. P. Fisher and C. A. Grob, *Helv. Chim. Acta*, **47**, 564 (1964)) [c] Sublimed. [d] Bp 84° (75 mm). [e] Precipitate from Et_2O. [f] Bp 300–302° (760 mm). [g] Free amine bp 69–71° (10 mm); $n^{25}D$ 1.4770; absorption bands of spectra (nmr) were as expected. [h] Free amine bp 87° (11 mm); $n^{25}D$ 1.4738. [i] From 27.

TABLE V

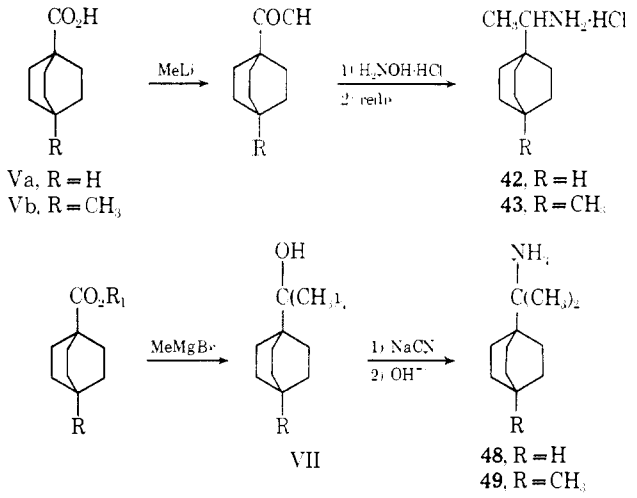
DERIVATIVES OF BICYCLO[2.2.2]OCTANE-1-METHYLAMINE



No.	R	R_1	R_2	X	Y	Yield, %	Solvent of crystn	Mp, °C	Formula	Analyses	AVI[50]
32	H	H	H	H	H	55	*a*	300–312 dec	$C_9H_{17}N \cdot HCl$	C, H, N, Cl	4.1
33	CH_3	H	H	H	H	41	6 *N* HCl	241	$C_{10}H_{19}N \cdot HCl$	C, H, N	3.1
34	CH_3	CH_3	H	H	H	89	*a*	284–287	$C_{11}H_{21}N \cdot HCl$	N	5.1
35	CH_3	CH_3	CH_3	H	H	54	*a*	258–259	$C_{12}H_{23}N \cdot HCl$	C, H, N	8.4
36	CH_3[b]	*n*-C_3H_7	*n*-C_3H_7	H	H	55	*a*	186.5–190	$C_{16}H_{33}N \cdot HCl$	C, H, N	Neg
37	C_3H_7	H	H	H	H	70	*a*	248–252	$C_{11}H_{23}N \cdot HCl$	N	23
38	C_3H_7	CH_3	H	H	H	66	*a*	277–293 dec	$C_{13}H_{25}N \cdot HCl$	C, H, N	Neg
39	C_3H_7	CH_3	CH_3	H	H	50.5	*a*	258–259 dec	$C_{14}H_{27}N \cdot HCl$	C, H, N	Neg
40	*t*-C_4H_9	CH_3	H	H	H	52	*a*	268–290 dec	$C_{14}H_{27}N \cdot HCl$	N, Cl	Neg
41	CF_3	H	H	H	H	62	*a*	276–277.5	$C_{10}H_{16}F_3N \cdot HCl$	C, H, N, Cl	Neg
42	H	H	H	CH_3	H	21	*a*	280–300 dec	$C_{10}H_{19}N \cdot HCl$	N	3.0
43	CH_3	H	H	CH_3	H	79	3 *N* HCl	322–324	$C_{11}H_{21}N \cdot HCl$	C, H, N, Cl	0.5
44	CH_3	CH=O	H	CH_3	H	72		85–88	$C_{12}H_{21}NO$	C, H, N	
45	CH_3	CH_3	H	CH_3	H	78	*a*	227–227.5 dec	$C_{12}H_{23}N \cdot HCl$	C, H, N	2.4
46	CH_3	*i*-C_3H_7CO	H	CH_3	H	77	CH_3CN	127–127.5	$C_{15}H_{27}NO$	C, H, N	
47	CH_3	*sec*-C_4H_9	H	CH_3	H	17	*a*	224–225	$C_{15}H_{29}N \cdot HCl$	C, H, N	Neg
48	H	H	H	CH_3	CH_3	47.5	*a*	*c*	$C_{11}H_{21}N \cdot HCl$	C, H, N, Cl	2.2
49	CH_3	H	H	CH_3	CH_3	42	*a*	290–308 dec	$C_{12}H_{23}N \cdot HCl$	C, H, N, Cl	1.3

[a] Precipitate from Et_2O. [b] Absorption bands of spectra (nmr) were as expected. [c] Sublimes 340–350°.

SCHEME III



Reaction of methyl bicyclo[2.2.2]octane-1-carboxylate and ethyl 4-methylbicyclo[2.2.2]octane-1-carboxylate with MeMgBr gave the corresponding α,α-dimethyl-1-methanols VII,[21] which were converted into the corresponding α,α-dimethyl-*N*-formylbicyclo[2.2.2]octane-1-methylamines *via* the Ritter reaction with NaCN.[21] Hydrolysis with base gave the α,α-dimethylbicyclo[2.2.2]octane-1-methylamines **48** and **49** (Table V). These synthesis are outlined in Scheme III.

The N-substituted derivatives **45** and **47** (Table V) of α,4-dimethylbicyclo[2.2.2]octane-1-methylamine (**43**) were prepared by acylation followed by LAH reduction.

There have been several reports recently which suggest that the methyl substituent, acting through space, may not exhibit its normal electron-donating effect, but rather exerts a weak, electron-withdrawing "field effect."[22] As has been pointed out by Roberts,[23] bridgehead-substituted bicyclo[2.2.2]octanes are ideal systems in which to study such subtle effects. The symmetrical, rigid, yet nearly unstrained bicyclo[2.2.2]octane nucleus holds the bridgehead substituents in a fixed spatial relationship, but unlike aromatic ring systems provides no pathway for the transmission of resonance effects.

In order to shed some light on the question of the electronegative methyl group we measured the pK_a of bicyclo[2.2.2]octan-1-amine (**8**) and its 4-methyl derivative **9**. We also measured the pK_a's of bicyclo[2.2.2]octane- (Va) and -oct-2-ene-1-carboxylic acids (IIIa) and their corresponding 4-methyl derivatives Vb and IIIb. The results are presented in Table VI. As can be seen, the effects are extremely small, the methyl group producing a slight acid-strengthening effect in the amine cations and no effect in the carboxylates. Stock has recently reported the dissociation constants of these acids in 50% (weight) EtOH-H_2O. For the bicyclo[2.2.2]octane acids he observed a small acid-weakening effect for the methyl group,[24a] but in the bicyclo[2.2.2]oct-2-ene series, a small acid-strengthening effect.[24b]

TABLE VI

DISSOCIATION CONSTANTS FOR BRIDGEHEAD-SUBSTITUTED BICYCLO[2.2.2]OCTANE AND BICYCLO[2.2.2]OCTENE DERIVATIVES

	$pK_a \pm$ 0.03	Temp, °C
Bicyclo[2.2.2]octan-1-amine (**8**)	10.22[a]	30
4-Methylbicyclo[2.2.2]octan-1-amine (**9**)	10.14[a]	30
Bicyclo[2.2.2]octane-1-carboxylic acid (Va)	6.68[b]	25
4-Methylbicyclo[2.2.2]octane-1-carboxylic acid (Vb)	6.71[b]	25
Bicyclo[2.2.2]oct-2-ene-1-carboxylic acid (IIIa)	6.31[b]	25
4-Methylbicyclo[2.2.2]oct-2-ene-1-carboxylic acid (IIIb)	6.32[b]	25

[a] Determined by Dr. H. K. Hall using the technique described in ref 22c. [b] Determined by 50% v/v EtOH-H_2O at 25° by Mrs. F. Younken using the procedure described by J. D. Roberts, E. A. McElhill, and R. Armstrong, *J. Amer. Chem. Soc.*, **71**, 2923 (1949). A Beckman 101900 Research pH meter, a standard glass electrode, and a Beckman 3502 frit-junction reference electrode were employed.

Since these effects are very small, a more sensitive probe such as the kinetic study recently undertaken by Schleyer and coworkers[22e] would be desirable in order to determine the nature of the field effect produced by alkyl substituents.

Antiviral Activity.—The antiviral dose$_{50}$ (AVI_{50}) screen was devised by R. R. Grunert of this laboratory to offer a quantitative comparison of the antiviral activity of a series of compounds tested at different times. The AVI_{50} dose is the amount of compound in milligrams per kilogram of body weight which causes a half-log (3.2-fold) increase in the infectivity of a 20-LD_{50} infecting dose of virus for mice. The test procedure and calculations for studies with influenza viruses were as follows: Swiss Webster mice 24–32 days of age were selected within a 3-day age and a 10% weight range. Infection was with 20 LD_{50} of virus in 0.05-ml inoculum administered intranasally to mice under light ether anesthesia. Thirty minutes prior to infection the mice (in groups of 10) were treated intraperitoneally with five twofold graded doses of test compound in 0.2 ml of 5% gum acacia–1% polyvinyl alcohol–saline vehicle. A control virus titration was made with 20, 10, 5, 2.5, and 1.25 LD_{50}'s of virus in mice receiving a comparable IP injection of vehicle. Daily mortality was recorded over a 10-day observation period. After the 10-day period the daily mortality data were converted to mean survival days (MSD) as follows:

$MSD = \Sigma\{f(d-1)\}/N$, where f equals the number of mice recorded dead on day d (survivors on day 10 were calculated as dead on day 11) and N is the number of mice in the group. The mean survival day data were then converted into an antiviral index (AVI) as follows: $AVI = (MSD_x - MSD_c)\,b$, where MSD_x is the mean survival days of the experimental (treated) group, MSD_c is the theoretical mean survival days of the control group calculated from the regression line of the control titration, and b is the slope of the regression line in the control titration.

(20) W. E. Bachmann and H. P. Hetzner, *Org. Syn.*, **3**, 839 (1955).

(21) J. J. Ritter and J. Kalish, *J. Amer. Chem. Soc.*, **70**, 4048 (1948).

(22) (a) H. Kwart and L. J. Miller, *Chem. Commun.*, **83**, 4552 (1961). (b) H. Kwart and T. Takeshita, *ibid.*, **86**, 1161 (1964). (c) H. K. Hall, Jr., *J. Org. Chem.*, **29**, 3135 (1964). (d) R. C. Fort, Jr., and P. von Schleyer, *J. Amer. Chem. Soc.*, **86**, 4194 (1964). (e) P. von R. Schleyer and C. W. Woodworth, *ibid.*, **90**, 6528 (1968).

(23) J. D. Roberts and W. T. Moreland, *ibid.*, **75**, 2167 (1953).

(24) (a) H. D. Holtz and L. M. Stock, *ibid.*, **86**, 5188 (1964). (b) C. W. Baker, R. C. Parrish, and L. M. Stock, *ibid.*, **89**, 5677 (1967).

From this the AVI_{50} dose was calculated by regression analysis of the straight-line portion of the dose–antiviral index response curve and the results were expressed as milligrams per kilogram of compound. The average AVI_{50} confidence limit, calculated from the regression data and expressed as a 90% confidence limit factor, was 2.1 (range 1.1–4.0).

The AVI_{50} doses for the bicyclo[2.2.2]octan- and -oct-2-enamines against influenza A/swine/S-15 are listed in Tables III, IV, and V. A negative result indicates an AVI_{50} of greater than 32 mg/kg.

The AVI_{50} for adamantan-1-amine is 4.6 and was calculated from results previously reported by us.[2]

Discussion

The unsaturated cage amines are similar in antiviral activity to their saturated counterparts. Substitution on the amino group with alkyl groups decreases antiviral activity. Large alkyl groups abolish activity. In the bicyclo[2.2.2]octan-1-amines optimal activity is achieved when R = Me (**9**) and decreases as R becomes larger or when R = H (**8**). In the bicyclo-[2.2.2]octane-1-methylamines maximal activity is obtained when R = Me (**33**) or H (**32**). The presence of α-alkyl groups in the bicyclo[2.2.2]octane-1-methylamine series enhances antiviral activity. The replacement of R = Me with CF_3 (**15** and **41**) abolishes antiviral activity.

Experimental Section[25]

Ethyl 6-Methyl-α-pyrone-3-carboxylate (Ib).—To 0.25 mol of NaOEt in 100 ml of $(MeOCH_2)_2O$ was added dropwise 54 g (0.25 mol) of diethyl ethoxymethylenemalonate. The reaction mixture was heated at reflux while 29.0 g (0.5 mol) of Me_2CO was added dropwise and then for a further 30 min. The reaction mixture was cooled and poured into 5 *N* HCl and the product extracted into C_6H_6. The C_6H_6 extracts were washed (aqueous NaCl) and concentrated to a red oil. A solution of the oil in 45 ml (49.75 g, 0.63 mol) of AcCl with a catalytic amount of DMF was heated at reflux for 2 hr. The AcCl was removed and the residue crystallized (EtOH) to afford 20.5 g (45%) of yellow crystals. One recrystallization (EtOH) gave an analytical sample; mp 82.5–83.5°; lit.[6,7] mp 86°; 87°. *Anal.* ($C_9H_{10}O_4$) C, H.

Ethyl 6-Trifluoromethyl-α-pyrone-3-carboxylate (Ih).—Similarly CF_3COCH_3 and diethyl ethoxymethylenemalonate gave Ih in 10% yield; mp 114–115°. *Anal.* ($C_9H_7F_3O_4$) C, H.

Ethyl 4-Methylbicyclo[2.2.2]oct-2-ene-1-carboxylate (IIb).—Compound Ib (40.0 g, 0.22 mol) was heated at 180° under C_2H_4 at a pressure of 3000 atm for 7.5 hr. The product was distilled to give IIb as a colorless oil.

4-Methylbicyclo[2.2.2]oct-2-ene-1-carboxylic acid (IIIb).—A mixture of 7.5 g (38.6 mmol) of IIb and 193 ml of 2 *N* aqueous NaOH was heated at reflux overnight. The solution was cooled and acidified with HCl to give 4.0 g of colorless solid, mp 139–142°. One recrystallization (heptane) afforded IIIb with the properties given in Table I.

4-Methylbicyclo[2.2.2]octane-1-carboxylic Acid (Vb).—IIb (35.1 g, 0.18 mol) was hydrogenated in EtOH with Pt–C to yield 32.47 g of crude saturated ester IV. Under conditions used to prepare IIIb, 18.47 g (94.2 mmol) of IV above gave 12.45 g of a colorless solid. One recrystallization ($MeNO_2$) gave Vb with the properties given in Table II.

1-Isopropyl-4-methylbicyclo[2.2.2]oct-2-ene.—α-Terpinene was heated to 180° under 100 atm of C_2H_4. After 10 hr the pressure was raised to 3000 atm for an additional 10 hr. The liquid was fractionally distilled to yield 80–90% of product, bp 92–94° (25 mm); $n^{25}D$ 1.4718. *Anal.* ($C_{12}H_{20}$) C, H.

(25) Melting points were determined in a Thomas-Hoover capillary melting point apparatus and are uncorrected. Where analyses are indicated only by symbols of the elements or functions, results obtained for these elements or functions were within ±0.4 of the theoretical values.

1-Isopropyl-4-methylbicyclo[2.2.2]octane.—A solution of 1-isopropyl-4-methylbicyclo[2.2.2]oct-2-ene in MeOH was hydrogenated under 3 atm of H_2 using a PtO_2 catalyst. The product was filtered and distilled to yield in almost quantitative yield 1-isopropyl-4-methylbicyclo[2.2.2]octane, bp 88–89° (19 mm); $n^{25}D$ 1.4666. *Anal.* ($C_{12}H_{22}$) C, H.

4-Methylbicyclo[2.2.2]octane-1-carboxylic Acid (Vb).—A solution of 60 g (0.36 mol) of 1-isopropyl-4-methylbicyclo[2.2.2]octane and 0.3 g of V_2O_5 in 500 g of 70% HNO_3 and 200 g of AcOH was heated on the steam bath for 8 hr. It was cooled and the crystalline precipitate (26 g) recrystallized (H_2O–Me_2CO) to yield 15.2 g (25%) of Vb, mp 183–184°. Similar results were obtained when a solution of 25 g of the hydrocarbon in 300 ml of 25% HNO_3 was heated to reflux for 3 days.

4-*n*-Propylbicyclo[2.2.2]oct-2-en-1-amine Hydrochloride (3).—To a solution of 6 g (30.9 mmol) of IIId in a minimum amount of H_2O–Me_2CO at 0° was added a solution of 5.02 ml (3.63 g, 35.9 mmol) of Et_3N in 87.5 ml of Me_2CO. A solution of 3.77 ml (4.29 g, 39.5 mmol) of $ClCO_2Et$ in 22.5 ml of Me_2CO was added at 0° over 5 min. The reaction mixture was stirred at 0° for 30 min, and then a solution of 3.04 g (46.7 mmol) of NaN_3 in 15 ml of H_2O was added dropwise over 10 min. Stirring at 0° was continued for 1 hr and then the reaction mixture poured into H_2O and the product extracted into Et_2O. The Et_2O extract was dried ($MgSO_4$) and concentrated to yield 6.0 g of the carboxylic acid azide as a pink oil. This was dissolved in 25 ml of C_6H_6Me and heated at reflux for 30 min, after which time N_2 evolution had ceased. Evaporation of the C_6H_6Me gave the isocyanate. This was heated at reflux with 45 ml of 6 *N* HCl overnight. Cooling the acid solution gave 1.85 g of **3**, as colorless crystals, with the properties given in Table III.

4-Methylbicyclo[2.2.2]oct-2-ene-1-methylamine Hydrochloride (6).—To a stirred solution at 0° of 2.47 g (14.9 mmol) of IIIb and 2.42 ml (1.75 g, 17.3 mmol) of Et_3N in 70 ml of $CHCl_3$ was added 1.82 ml (2.07 g, 19.0 mmol) of $ClCO_2Et$ over 5 min. The reaction mixture was stirred at 0° for 30 min and then treated with NH_3 at −10 to 0°. The solids were removed by filtration and the filtrate was concentrated to yield 1.88 g of 4-methylbicyclo-[2.2.2]oct-2-ene-1-carboxamide. The amide (1.88 g, 11.4 mmol) was placed in the cup of Soxhlet extractor and 1.56 g (41 mmol) of LAH was charged to 150 ml of Et_2O in the flask. The apparatus was operated overnight, and allowed to cool. The excess LAH was destroyed with H_2O and the solids were removed by filtration and washed with Et_2O. The Et_2O filtrate was dried (KOH and then $MgSO_4$) and gassed with HCl to give 1.24 g of **6** as a colorless solid with the properties given in Table III.

4-*t*-Butylbicyclo[2.2.2]octan-1-amine Hydrochloride (14).—To a stirred mixture of a solution of 14.0 g (67.3 mmol) of IIIg in 193 ml of $CHCl_3$ and 52.5 ml of H_2SO_4 at 50° was added portionwise 7.87 g (0.12 mol) of NaN_3 over 1 hr. The reaction mixture was stirred for 2 hr and then poured onto ice. A colorless solid was removed by filtration and washed with $CHCl_3$. The aqueous layer in the filtrate was separated and washed with $CHCl_3$. The combined solid and aqueous layer was made strongly basic with NaOH and extracted with Et_2O. The Et_2O extracts, after drying (Na_2SO_4), were treated with dry HCl to give 6.4 of **14** as a colorless solid with the properties given in Table IV.

***N*-Formyl-4-methylbicyclo[2.2.2]octan-1-amine (17).**—A 7.8-g (56 mmol) amount of **9** was heated with 2.88 g (62.6 mmol) of 98% HCO_2H in 500 ml of C_6H_6. The mixture was heated at reflux allowing the C_6H_6 to distil over and the residue was heated at reflux for 1 hr. The residue was then distilled at 760 mm to yield 8.8 g of **17** as a colorless oil with the properties given in Table IV.

4,*N*-Dimethylbicyclo[2.2.2]octan-1-amine Hydrochloride (18).—A THF solution of 8.8 g (52.7 mmol) of **17** was dropped into a solution of 3 g (79 mmol) of LAH in 125 ml of Et_2O at a rate sufficient to maintain reflux. The mixture was then stirred overnight at room temp and heated at reflux for 2 hr. The reaction was cooled and excess LAH was decomposed with saturated aqueous Na_2SO_4. The coagulated solid was removed by filtration, and the filtrate, A, was dried (NaOH). The solid, B, was extracted with Et_2O in a Soxhlet extractor. The Et_2O extract from this, C, was dried (NaOH). Distillation of Et_2O solutions A and C yielded 4.2 g (52%) of amine.

The amine was dissolved in Et_2O and treated with HCl gas and the precipitate was recrystallized from *i*-PrOH–C_6H_6 to yield 3.8 g of **18** as a colorless solid with the properties given in Table IV.

***N*-Isobutyryl-4-methylbicyclo[2.2.2]octan-1-amine (28).**—A

solution of 7.0 g (50 mmol) of **9** in 50 ml of C_5H_5N was treated dropwise with 11 g (0.1 mol) of isobutyryl chloride maintaining the temperature at less than 50° by cooling. The reaction mixture was heated reflux for 30 min, cooled, and then poured onto ice. Filtration gave 9.0 g of product, mp 90–92°. Recrystallization (C_6H_{14}) gave **28** with the properties given in Table IV.

4,*N*,*N*-Trimethylbicyclo[2.2.2]octan-1-amine Hydrochloride (19).—A mixture of 13.2 g (95 mmol) of **9**, 95 g (0.7 mol) of MeI, 26.2 g (0.31 mol) of $NaHCO_3$, and 150 ml of MeOH was stirred and refluxed for 16 hr. The solid salt, A, that precipitated was collected and the filtrate, B, was evaporated to dryness. The residue of B and the solid A were extracted with boiling $CHCl_3$ and the $CHCl_3$ extracts evaporated to give 30 g of the quaternary salt. The salt was refluxed with 57 g of ethanolamine for 15 min and then poured into 200 g of ice–H_2O. The resultant solution was extracted with Et_2O in a continuous extractor for about 16 hr. The Et_2O extract was dried (NaOH) and distilled to give 11.2 g of amine. The amine was dissolved in Et_2O and treated with HCl gas and the precipitate recrystallized from *i*-PrOH–C_6H_6 to give 12.0 g of **19** with the properties given in Table IV.

***N*,*N*-Dimethyl-4-ethylbicyclo[2.2.2]octan-1-amine Hydrochloride (20).**—A mixture of 5.26 g (28.0 mmol) of **10**, 8 ml of 98% HCO_2H, and 5 ml of 37% aqueous HCH=O was heated at reflux on a steam bath for 15 hr. After cooling, the mixture was made basic with aqueous NaOH and extracted with Et_2O and the extract dried (K_2CO_3). Dry HCl was passed into the solution to give 6.0 g of precipitate. Recrystallization (C_6H_6) gave 5.65 g of **20** with the properties given in Table IV.

4-Cyclohexylbicyclo[2.2.2]octan-1-amine Hydrochloride (16). 4-Phenylbicyclo[2.2.2]octan-1-amine[14] (11.65 g, 58.0 mmol), 10 g of 5% Ru on alumina, 10 g of NH_3, and 100 ml of dioxane were heated at 225° under 330 atm of H_2 for 1 hr. Insoluble materials were removed by filtration and the filtrate was vacuum evaporated to give a colorless crystalline solid. Recrystallization from aqueous HCl gave 10.72 g of crystals. Recrystallization from *n*-BuOH gave 7.65 g of **16** as colorless crystals with the properties given in Table IV.

4-Methylbicyclo[2.2.2]octane-1-carboxamide.—A solution of 2.5 g (14.9 mmol) of Vb in 10 ml (16.55 g, 0.139 mol) of $SOCl_2$ was refluxed 2 hr and then cooled to room temp. The excess $SOCl_2$ was removed at reduced pressure, leaving the acid chloride as a brown oil. The acid chloride in 100 ml of dry $CHCl_3$ was treated with NH_3 at −10°. The solvent was vacuum evaporated, and the residue was dissolved in 100 ml of C_6H_6. Insoluble NH_4Cl was removed by filtration and the filtrate concentrated to yield 3.13 g (100%) of a colorless solid. Recrystallization (C_6H_6–MeOH) gave an analytical sample, mp 190–192.5°. *Anal.* ($C_{10}H_{17}NO$) C, H, N.

4-Trifluoromethylbicyclo[2.2.2]octane-1-carboxamide.—Compound Vb (6.3g, 28.5 mmol) was converted into 6.3 g (100%) of the carboxamide using $ClCO_2Et$ followed by NH_3. Recrystallization (EtOH–H_2O) gave an analytical sample, mp 182–183°. *Anal.* ($C_{10}H_{14}F_3NO$) C, H, N.

α-4-Dimethylbicyclo[2.2.2]octane-1-methylamine Hydrochloride (43).—A solution of 27.2 g (0.162 mol) of Vb in 600 ml of THF was treated as rapidly as possible with 272 ml (0.34 mol) of 1.25 *M* MeLi in Et_2O under Ar. The reaction mixture was stirred and heated at reflux overnight, and then poured into H_2O. The organic layer was separated and the aqueous layer was extracted several times into Et_2O. The Et_2O extracts were dried ($MgSO_4$) and vacuum concentrated to produce 26.57 g (99%) of the ketone as a colorless oil: ir (1) 1700 cm^{-1} (C=O).

NaOH (30.0 g, 0.75 mol) was added portionwise to a solution of 25.15 g (0.162 mol) of the oil and 16.4 g (0.235 mol) of H_2NOH·HCl in a mixture of 100 ml of EtOH and 15 ml of H_2O. The reaction mixture was heated at reflux for 5 min, cooled, and then poured onto 2.5 *N* aqueous HCl. The product was collected by filtration (95%). Recrystallization (EtOH) gave an analytical sample: mp 172–173.5°. *Anal.* ($C_{11}H_{19}NO$) C, H, N.

A mixture of 20.0 g (0.11 mol) of oxime, 8.8 g (0.163 mol) of NaOMe, 20 g of Ra–Ni, and 175 ml of MeOH was shaken overnight under 3 atm of H_2 according to Rosen and Green.[15] The catalyst was removed by filtration and the filtrate was concentrated under vacuum. The residue was dissolved in Et_2O, which was washed with H_2O and then saturated with HCl gas. Evaporation of the Et_2O gave 18.75 g (84%) a colorless solid. Crystallization from 3 *N* HCl gave **43** with the properties given in Table V.

α,α,4-Trimethylbicyclo[2.2.2]octane-1-methylamine Hydrochloride (49).—A solution of 5.0 g (25.5 mmol) of ethyl 4-methylbicyclo[2.2.2]octane-1-carboxylate in 20 ml of Et_2O was added dropwise to 34 ml (0.102 mol) of 3 *M* MeMgBr in Et_2O. The reaction mixture was heated at reflux overnight, cooled, and poured into ice-cold 2 *N* H_2SO_4. The Et_2O layer was separated and the aqueous layer extracted several times with Et_2O. The Et_2O extracts were washed with 5% aqueous $NaHCO_3$ and then H_2O. The Et_2O was dried ($MgSO_4$) and then removed to afford 4.5 g (97%) of light yellow crystals: ir (Nujol) 3450 cm^{-1} (OH).

To a solution of 4.5 g (24.7 mmol) of the alcohol and 2.45 g (50 mmol) of NaCN in 3 ml of AcOH was added dropwise a mixture of 11 g of H_2SO_4 and 6 ml of AcOH at such an rate that the temperature was 50–60°. The reaction mixture was stirred overnight at room temperature and poured into H_2O and the product extracted into Et_2O. The Et_2O was dried ($MgSO_4$) and then evaporated to yield 4.84 g (95%) of light-yellow crystals: ir (Nujol) 1680 cm^{-1} (NHCH=O).

A mixture of 4.48 g (23.2 mmol) of the amide, 17 g (0.302 mol) of KOH, and 50 ml of MeOH in a polymer tube was shaken at 220° overnight. The product was extracted into Et_2O and then extracted from the combined Et_2O extracts into 3 × 35 ml (0.252 mol) of 2.4 *N* HCl. The combined acidic extracts were made strongly basic with 18.0 g (0.45 mol) of NaOH and the product was extracted into Et_2O. The Et_2O was dried (KOH) and then $MgSO_4$) and treated with HCl gas to give 2.29 g (45%) of **49** as a colorless solid, with the properties given in Table V.

Acknowledgments.—We wish to thank C. E. Hoffmann, R. R. Grunert, J. W. McGahen, and W. L. Davies for obtaining AVI$_{50}$ results for these compounds.