3-Substituted Tropane Derivatives. III. 3-Substituted Tropane Carbinols, Alkenes, and Alkanes

Charles L. Zirkle, Elvin L. Anderson, Paul N. Craig, Fred R. Gerns, Zena K. Indik, and Alex M. Pavloff

Research and Development Division, Smith Kline and French Laboratories, Philadelphia, Pennsylvania

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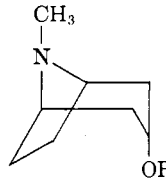
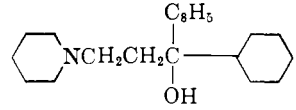
The synthesis of some 3-substituted tropane ketones (III), carbinols (IV), olefins (V, VI, VIII) and alkanes (VIII) is described. The *in vitro* cholinolytic activity of some of these derivatives equals or exceeds that of atropine.

During the past forty years hundreds or thousands of atropine (Ia) congeners have been synthesized and tested for parasympatholytic activity.[1,2]



Ia, R = $COCH(CH_2OH)C_6H_5$
b, R = H
c, R = $CH(C_6H_5)_2$



II

Until recently, most of these compounds were amino esters of substituted acetic acids in which the amino alcohol moiety of atropine, tropine (Ib), had been replaced with less complex acyclic or monocyclic amino alcohols. Since 1950, however, with 3-tropinones readily available as a result of developments in furan chemistry,[3] numerous tropane compounds derived from them have been prepared for phar-

(1) J. S. Pierce, in "Medicinal Chemistry," A. Burger, ed., Interscience Publishers, Inc., New York, N. Y., 1960, p. 463.

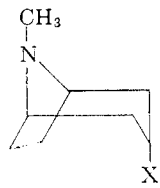
(2) R. R. Burtner, in "Medicinal Chemistry," Vol. I, C. M. Suter, ed., John Wiley and Sons Inc., New York, N. Y., 1951, p. 151.

(3) N. Elming, in "Advances in Organic Chemistry," Vol. 2, R. A. Raphael, E. C. Taylor, and H. Wynberg, editors, Interscience Publishers, Inc., New York, N. Y., 1960, p. 67.

macological evaluation. These synthetic compounds, as well as the tropane alkaloids, in most cases are derivatives of either the 3-tropanols[3,4] or 3-tropylamines.[5]

In extending the search for potential drugs in this field, we have synthesized some new types of 3-substituted tropane derivatives having structures IV (Table II), V, VI, VII (Table III), and VIII (Table IV). Some of these compounds, *e.g.*, IVe and VIIIc, are tropane analogs of trihexyphenidyl (II)[6-8] and benztropine (Ic),[9,10] respectively, which are parasympatholytic agents used clinically as antiparkinsonism drugs. Most of the derivatives prepared in this work have the α-configuration of tropine.

The tropane carbinols (Table II) in which R = R′ were synthesized from the corresponding tropane esters (IX)[11] and those in which R differs from R′ were prepared from the corresponding ketones (Table I). The latter derivatives, instead of the carbinols, were in

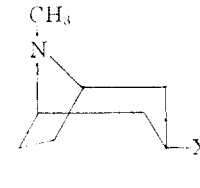


α-isomer

IXa, X = CO_2CH_3

b, X = $CH_2CO_2C_2H_5$

c, X = $(CH_2)_2CO_2C_2H_5$



β-isomer

most cases obtained as the chief products from the reactions of the tropane esters with Grignard reagents. Thus, when ethyl (3α-tropanyl)acetate[11b] (α-IXb) was treated with phenylmagnesium bromide in ether at room or reflux temperature, ketone IIIb was obtained in 75% yield. Only a small amount (8%) of the corresponding carbinol IVe was isolated. Similarly, the reactions of the same ester with 2-cyclohexylethylmagnesium bromide and of ethyl 3-(3α-tro-

(4) For examples see G. Fodor, in "The Alkaloids," Vol. VI, R. H. F. Manske, ed., Academic Press, New York, N. Y., 1960, p. 145.

(5) For examples see G. B. Payne and K. Pfister, U. S. Patent 2,678,317 (May 11, 1954); W. L. Archer, C. J. Cavallito, and A. P. Gray, *J. Am. Chem. Soc.*, **78**, 1227 (1956).

(6) J. J. Denton, W. B. Neier, and V. A. Lawson, *ibid.*, **71**, 2053 (1949).

(7) A. W. Ruddy and J. S. Buckley, Jr., *ibid.*, **72**, 718 (1950).

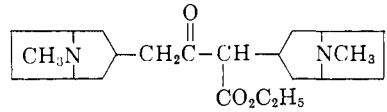
(8) D. W. Adamson, P. A. Barrett, and S. Wilkinson, *J. Chem. Soc.*, 52 (1951).

(9) R. F. Phillips, U. S. Patent 2,595,405 (May 6, 1952).

(10) L. J. Dosbay, *J. Am. Med. Assn.*, **162**, 1031 (1956).

(11) (a) C. L. Zirkle, T. A. Geissman, M. Bloom, P. N. Craig, F. R. Gerns, Z. K. Indik, and A. M. Pavloff, *J. Org. Chem.*, in press; (b) C. L. Zirkle, E. L. Anderson, F. R. Gerns, Z. K. Indik, and A. M. Pavloff, *ibid.*, in press.

panyl)propionate[11b] (α-IXc) with ethylmagnesium bromide proceeded smoothly at room temperature to give ketones IIId and IIIe, respectively, in good yields. Less satisfactory results were obtained from the reaction of ethyl (3α-tropanyl)acetate with cyclohexylmagnesium bromide. When the reaction was carried out at room temperature, ketone IIIc was obtained in only 17% yield, and 58% of the ester was recovered. In another experiment carried out at reflux temperature, the yield of ketone was increased to 35%, but a large amount of another product, a viscous, high-boiling oil, was obtained. Although this material was not fully characterized, its infrared spectrum indicated the presence of two carbonyl groups, and the analysis of its picrate salt was in agreement with the formula of the dipicrate of the keto ester X, which would be formed by self-condensation of the starting ester. The thienyl ketone IIIa was obtained in very poor



X

yield from the reaction of methyl tropane-3α-carboxylate[11a] (α-IXa) with 2-thienylmagnesium bromide at room temperature. Fifty per cent. of the ester was recovered and a small amount (*ca.* 9%) of the dithienyl carbinol (IVb) was also isolated. The low degree of reactivity of ester α-IXa under these conditions probably is due to hindrance of the ester group by the ethylene bridge of the tropane nucleus.

In their behavior toward Grignard reagents tropane esters α-IXb and α-IXc resemble acyclic amino esters $R_2N(CH_2)_nCO_2R'$ (XI), n = 3–10, which are reported[12] to yield ketones, not carbinols, as principal products. On the other hand, numerous examples of the Grignard reaction of esters XI, n = 2, in which carbinols are the predominant products are recorded in the literature.[13,14] Apparently the position of the amino group relative to that of the ester group is an important factor in determining the nature of the products of this reaction.

With the exception of compound IVb, all tropane carbinols (Table II) in which R = R′ were obtained from the reactions of the cor-

(12) P. A. Barrett, U. S. Patent 2,649,444 (August 18, 1953).
(13) D. W. Adamson, *J. Chem. Soc.*, S144 (1949).
(14) T. D. Perrine, *J. Org. Chem.*, **18**, 898 (1953).

TABLE I

3-SUBSTITUTED TROPANE KETONES (α-CONFIGURATION)

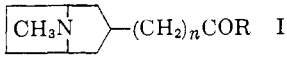
Compound No.	n	R[a]	Yield, %	B.p. °C.	B.p. Mm.	n_D^{25}	Salt	M.p., °C.
a	0	2-C_4H_3S	4.4	142–143	0.4		Picrate	259
b	1	C_6H_5	75	140–143	0.2[b]		HCl	231–232
c	1	C_6H_{11}	35	142–144	0.8[b]		Picrate	165–168
							CH_3Br	297–299
d	1	C_8H_{15}	74	157–164	0.7	1.5010	Picrate	148–150
e	2	C_2H_5	77	105–109	0.35	1.4870	Picrate	123–124.5

[a] 2-C_4H_3S = 2-thienyl; C_6H_{11} = cyclohexyl; C_8H_{16} = 2-cyclohexylethyl. A = ethanol, B = ether, C = water, D = acetonitrile.

TABLE II

3-SUBSTITUTED TROPANE CARBINOLS

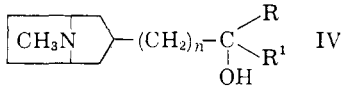
Compound[a] No.	n	R	R[1]	Configuration	Yield, %	Salt	M.p., °C.	Solvent[c]
a	0	CH_3	CH_3	β	84	...	...[b]	
						Picrate	167.5–169	A
						CH_3I	199–202	AB
b	0	2-C_4H_3S	2-C_4H_3S	α	8.0	...	157.5–159	C
c	0	C_6H_5	C_6H_5	α	47	...	185.5–186	C
						HCl	290	AB
						Citrate	112–118	FB
						Picrate	214–215.5	AD
						CH_3Br	309–310	A
d	0	C_6H_5	C_6H_6	β	86	...	182–184	C
						HCl	325	EB
						Picrate	230–231	F
e	1	C_6H_5	C_6H_6	α	76	...	147–148	C
						HCl	235	AB
						HBr	230	AB
						CH_3Br	282	AB
f	1	C_6H_5	C_6H_5	β	...	...	178–179	C
						HCl	253.5	AB
g	1	C_6H_{11}	C_6H_5	α	90	...	139–140.5	C
						HCl	254–255	AB
						CH_3Br	262	AB



III

Solvent[c]	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
D	$C_{19}H_{20}N_4O_8S$	49.13	49.21	4.24	4.17	12.06	12.25
AB	$C_{16}H_{22}ClNO$	68.68	68.61	7.93	7.93	5.01	5.27
A	$C_{22}H_{30}N_4O_8$	55.22	54.92	6.32	6.38	11.71	11.93
AB	$C_{17}H_{30}BrNO$	59.29	59.02	8.78	8.85	4.07	4.33
AC	$C_{24}H_{34}N_4O_8$	56.90	56.90	6.77	6.77	11.06	11.05
A	$C_{19}H_{28}N_4O_8$	52.05	52.17	5.98	6.25	12.78	12.80

[b] On standing the distillate gradually crystallized. [c] Recrystallization solvents:



IV

Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Relative activity, atropine = 1[d]
$C_{17}H_{24}N_4O_8$	49.51	49.67	5.87	5.78	13.59	13.87	
$C_{12}H_{24}INO$	44.31	44.13	7.44	7.61	4.31	4.29	
$C_{17}H_{21}OS_2$	63.91	63.93	6.63	6.46	4.38	4.25	
$C_{21}H_{25}NO$	82.04	82.02	8.20	8.34	4.56	4.64	
$C_{21}H_{26}ClNO$	73.34	73.20	7.62	7.80	4.07	4.26	
$C_{27}H_{33}NO_8$	64.91	64.94	6.66	6.47			0.001
$C_{27}H_{28}N_4O_8$	60.44	60.52	5.26	5.55			
$C_{22}H_{28}BrNO \cdot 0.25H_2O$	64.94	65.09	7.06	7.23			0.1
$C_{21}H_{25}NO$	82.04	81.87	8.20	8.50			
$C_{21}H_{25}NO$	73.34	73.04	7.62	7.53			0.001
$C_{27}H_{28}N_4O_8$	60.44	60.38	5.26	5.46			
$C_{22}H_{27}NO$	82.19	82.09	8.47	8.44	4.36	4.25	
$C_{22}H_{28}ClNO$	73.82	73.74	7.89	7.71	3.91	4.19	1
$C_{22}H_{28}BrNO$	65.67	65.65	7.01	6.78	3.48	3.53	
$C_{23}H_{30}BrNO \cdot 0.25H_2O$	65.62	65.67	7.30	7.22	3.33	3.64	0.1–1
$C_{22}H_{27}NO$	82.20	81.82	8.47	8.47			
$C_{22}H_{28}ClNO$	73.82	73.73	7.89	7.97	3.91	4.02	0.001
$C_{22}H_{33}NO$	80.68	80.49	10.16	10.42	4.28	4.32	
$C_{22}H_{34}ClNO$	72.60	72.60	9.42	9.67	3.85	4.30	0.1
$C_{23}H_{36}BrNO$	65.39	65.10	8.59	8.35	3.32	3.27	

TABLE II

Compound[a] No.		R	R′	Configuration	Yield, %	Salt	M.p., °C.	Solvent[b]
h	1	C_8H_{15}	C_6H_5	α	>66	...	104–106	C
						HCl	215–216	A
						Citrate	134–136	IE
						CH_3Br	263–265	AB
i	1	C_6H_5	C_2H_5	α	12	HCl	237	A
j	1	C_6H_5	2-C_5H_4N	α	64	...	117.5–118.5	C
						HI	194–196	AB
						Dipicrate	191–192	ID
						CH_3Br	268	A
k	1	C_6H_5	2-C_4H_3S	α	73	...	137.5–139	C
						Maleate	145–146	AB
						CH_3Br	256	A
l	1	2-C_4H_3S	2-C_4H_3S	α	69	...	138–140	C
						Acetate	189–190	..
						CH_3Br	245.5	A
m	2	C_6H_5	C_6H_5	α	92	...	142–143	GH
						HCl	249–250	EB
						CH_3Br	299	AB

[a] 2-C_4H_3S = 2-thienyl; C_6H_{11} = cyclohexyl; C_8H_{15} = 2-cyclohexylethyl; crystallized. [c] Recrystallization solvents: A = ethanol, B = ether, C = ethyl leum ether (b.p. 30–60°), I = acetone. [d] Cholinolytic activity, relative to that thonium iodide-induced spasms in isolated segments of rabbit ileum.

responding tropane esters with lithium reagents, and all derivatives in which R differed from R′, with one exception, were prepared in the same way from the ketones listed in Table I. The ethyl phenyl carbinol IVi was obtained by the action of ethylmagnesium bromide on ketone IIIb. Although a large excess of the Grignard reagent was employed, the yield of carbinol was only 12% and a considerable amount of ketone was recovered, a result consistent with those obtained in the ester reactions described above. As would be predicted on conformational grounds, equatorial ester β-IXa gave a diphenyl carbinol in higher yield than did its axial isomer α-IXa when the two esters were treated with phenyllithium under identical conditions (see compounds IVc and IVd, Table II).

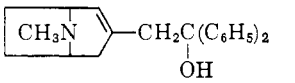
In addition to the carbinols listed in Table II, the unsaturated tropane carbinol XII also was prepared by the reaction of phenyl-

(*Continued*)

Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Relative activity, atripine = 1[d]
$C_{24}H_{37}NO$	81.07	80.64	10.49	9.99	3.94	4.00	
$C_{24}H_{38}ClNO$	73.53	73.21	9.77	9.90	3.57	3.61	0.01
$C_{30}H_{46}NO_8$	65.79	65.41	8.28	8.68	2.56	2.47	
$C_{25}H_{40}BrNO$	66.65	66.48	8.95	9.07	3.11	3.08	
$C_{18}H_{28}ClNO$	69.76	69.88	9.11	9.20			0.01–0.1
$C_{21}H_{28}N_2O\cdot H_2O$	74.08	74.07	8.29	8.47	8.23	8.11	
$C_{21}H_{27}IN_2O$	56.00	55.84	6.04	6.32	6.22	6.00	0.01
$C_{33}H_{32}N_8O_{15}$	50.77	50.72	4.13	4.02	14.36	14.42	
$C_{22}H_{29}BrN_2O$	63.30	62.99	7.00	7.07	6.71	6.46	
$C_{20}H_{25}NOS$	73.35	73.59	7.70	7.80	4.28	4.00	
$C_{24}H_{29}NO_5S$	64.99	65.07	6.59	6.83	3.16	3.09	1
$C_{21}H_{28}BrNOS$	59.71	59.73	6.68	6.96	3.32	3.14	
$C_{18}H_{23}NOS_2$	64.82	64.93	6.95	6.83	4.20	4.27	
$C_{20}H_{27}NO_3S_2$	61.03	61.10	6.92	7.15			1
$C_{19}H_{26}BrNOS_2$	53.26	53.36	6.12	5.86	3.27	3.09	
$C_{23}H_{29}NO$	82.34	82.27	8.71	8.84	4.18	4.20	
$C_{23}H_{30}ClNO$	74.27	74.35	8.13	8.26	3.77	3.75	0.01
$C_{24}H_{32}BrNO$	66.97	66.88	7.49	7.67	3.25	3.16	0.1

2-C_5H_4N = 2-pyridyl. [b] B.p. 116–119° (4 mm.); on standing the distillate acetate, D = water, E = methanol, F = 2-propanol, G = benzene, H = petro- of atropine, determined by means of the Magnus technique against furtre-

lithium with the corresponding unsaturated ester.[11b]



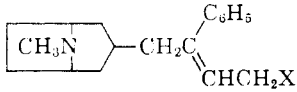
XII

In their ease of dehydration the tropane carbinols closely resembled related amino carbinols described by Adamson.[8,13,15,16] Although most of them were quite susceptible to dehydration in the presence of strong acids, mineral acid salts of most of the carbinols could be obtained if an excess of acid was avoided in their preparation. The thienyl carbinols IVb and IVl, however, dehydrated so readily (see below) that their hydrochloride salts could not be obtained.

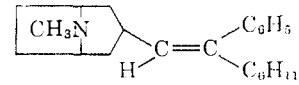
(15) D. W. Adamson, *J. Chem. Soc.*, 885 (1950).
(16) D. W. Adamson and J. W. Billinghurst, *ibid.*, 1039 (1950).

By heating a solution of the corresponding carbinol in a mixture of hydrochloric and acetic acids, the diphenyl olefins Va, VIa and VII, and the monophenyl olefins VIb, VIc, and VId were obtained readily. This treatment was too strenuous for the preparation of the thienyl compounds Vb, VIf, and VIg, since considerable decomposition of the products occurred, but under milder conditions of dehydration the olefins were obtained in good yields. The dithienyl carbinols IVb and IVl were dehydrated by passing hydrogen chloride into their solutions in chloroform at room temperature and the phenyl thienyl carbinol IVk was converted to the corresponding olefin by heating with aqueous oxalic acid solution. Although the pyridyl carbinol IVj was much more resistant to dehydration than the other members of the series, it gave olefin VIe in good yield when either 85% sulfuric acid or polyphosphoric acid was employed as the dehydrating agent.

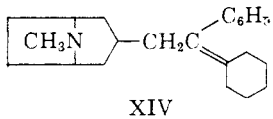
The olefins in which R differed from R′ may exist as pairs of isomers in which the R group is *syn* or *anti* to the tropane nucleus. Furthermore, the olefins listed in Table III as structures VId and VIc may actually be *syn* and/or *anti* forms of positional isomers XIIIa and XIIIb, respectively. We made no attempts to determine the iso-



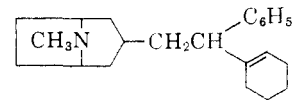
XIIIa, X = H
b, X = C_6H_{11}



VIb

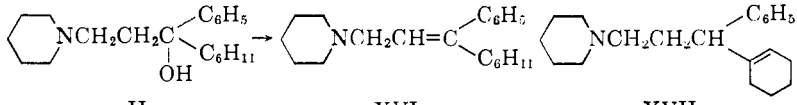


XIV



XV

meric composition or structures of any of the olefinic products. The fact that some of the crude bases and salts did not have sharp melting points suggests that some of the olefins, particularly those derived from the ethyl and 2-cyclohexylethyl carbinols, were indeed mixtures of the possible isomers discussed above. The crude hydrochloride of olefin VId melted over a very wide temperature range and no crystalline salts of olefin VIc could be prepared, yet ultraviolet spectra of both products exhibited absorption typical of phenyl-substituted olefins (λ_{max} 235–238 mμ).



II XVI XVII

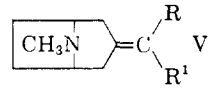
The olefin derived from cyclohexyl carbinol IVg, listed in Table III as structure VIb (*syn* or *anti* form), might actually have structure XIV or XV. One might expect the product to be VIb by analogy to results of Adamson,[8] who showed that the olefin obtained by dehydration of II with hydrochloric acid had structure XVI. Ruddy and Buckley,[7] however, found that treatment of II with hydriodic acid and phosphorus yielded two unsaturated bases, one of which was shown to have structure XVII.[17] Thus the corresponding tropane olefin might have structure XV. However, this possibility probably can be ruled out on the basis of the ultraviolet spectrum of the olefin. Although its spectrum exhibited none of the maxima found in the spectra of the other olefins, its absorption was considerably stronger than that expected for an unconjugated phenyl derivative. Thus the olefin probably has structure VIb or XIV. A comparison of molecular models of these two structures suggested that coplanarity of the double bond and benzene ring can be achieved much less readily in VIb than in XIV, the ultraviolet spectrum of which might be expected to show a typical absorption peak for a phenyl-substituted olefin. Furthermore, models of VIb and its isomer (phenyl *anti* to the tropane ring) indicate that a *syn* phenyl group can become coplanar with the double bond much less readily than an *anti* phenyl group. Therefore we tentatively assign structure VIb to the olefin derived from the cyclohexyl carbinol.

The tropane alkane derivatives listed in Table IV were obtained by reduction of the corresponding olefins. Olefin VII was hydrogenated smoothly over Raney nickel at room temperature and 4.2 kg./cm.^{2} hydrogen pressure, whereas reduction of olefins Va, VIa and VIb required more strenuous conditions (60° and 35 kg./cm.^{2} pressure). In one attempt to hydrogenate the pyridyl olefin VIe under similar conditions, reduction of the pyridine ring occurred to a considerable extent. We did not investigate this method further, since we found that selective reduction of the double bond could be achieved by the catalytic hydrogen exchange method[18] using a palladium-carbon

(17) M. Jackman, F. C. Nachod, and S. Archer, *J. Am. Chem. Soc.*, **72**, 716 (1950).
(18) E. A. Braude, R. P. Linstead, and P. W. D. Mitchell, *J. Chem. Soc.*, 3578 (1954).

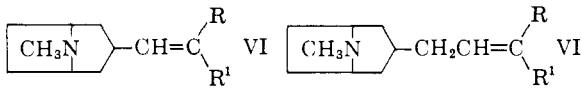
TABLE III

3-SUBSTITUTED TROPANE OLEFINS



Compound							
No.	R	R[1]	Config.	Yield, %	Salt	M.p., °C.	Solvent[b]
Va	C_6H_5	C_6H_5	..	..	HCl	275–278	AB
					Picrate	237–238	AC
					CH_3Br	281–285	DE
Vb	2-C_4H_3S	2-C_4H_3S	..	76	HCl	224–225	AB
VIa	C_8H_5	C_8H_6	α	100	...	111–112	E
					HCl	217–218	AB
					Picrate	186–188	A
					CH_3Br	286	AB
VIb	C_6H_{11}	C_6H_5	α	95	HCl	195–196	AB
					HI	222.5–224	FB
					CH_3Br	250–255	C
VIc	C_8H_{15}	C_6H_5	α	..	HCl		
VId	C_8H_5	C_2H_5	α	..	HCl	214–215	FB
VIe	C_6H_5	2-C_5H_4N	α	78	...	97.5–99.5	E
					Tartrate	165–167	AB
					Picrate	204–206	G
					CH_3Br	227–228	AB
VIf	C_6H_5	2-C_4H_3S	α	96	...	65–70	
					HCl	194–200	AB
					Tartrate	174–175	AB
					Picrate	209–210	EC
					CH_3Br	258–259	AB
VIg	2-C_4H_3S	2-C_4H_3S	α	76	HCl	230–232	AB
					Picrate	190–192	EC
					CH_3Br	252–253	AB
VII	C_6H_6	C_8H_5	α	70	Citrate	174	[c]
					CH_3Br	280	[c]

[a] 2-C_4H_3S = 2-thienyl; C_6H_{11} = cyclohexyl; C_8H_{15} = 2-cyclohexylethyl; C = water, D = 2-propanol, E = acetone, F = butanone, G = acetonitrile.



Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Relative activity, atropine = 1[d]
$C_{21}H_{24}ClN$	77.40	77.42	7.42	7.30			0.01
$C_{27}H_{26}N_4O_7$	62.54	62.41	5.05	5.25			
$C_{22}H_{28}BrN \cdot 0.25H_2O$	67.95	68.02	6.87	6.87			0.1–1
$C_{17}H_{20}ClNS_2$	60.42	60.33	5.97	6.25	4.15	4.05	
$C_{22}H_{26}N$	87.08	87.05	8.31	8.23	4.62	4.72	
$C_{22}H_{28}ClN$	77.74	77.54	7.71	7.89	4.12	4.25	1–10
$C_{28}H_{28}N_4O_7$	63.15	62.76	5.30	5.48	10.52	10.68	
$C_{23}H_{28}BrN$	69.34	69.14	7.09	7.24			0.1–1
$C_{22}H_{32}ClN \cdot 0.5H_2O$	74.43	74.39	9.37	9.16	3.95	4.08	1
$C_{22}H_{32}IN$	60.41	60.27	7.37	7.45	3.20	3.24	
$C_{23}H_{24}BrN$	68.30	67.83	8.47	8.42			
Extremely hygroscopic							
$C_{18}H_{26}ClN \cdot 0.25H_2O$	72.95	72.89	9.01	9.06			
$C_{21}H_{24}N_2$	82.85	82.88	7.95	8.08	9.20	9.20	
$C_{25}H_{30}N_2O_6$	66.06	65.68	6.65	6.73	6.16	6.29	
$C_{33}H_{30}N_8O_4$	51.97	52.04	3.97	4.23	14.69	14.89	
$C_{22}H_{27}BrN_2$	66.16	65.74	6.81	7.22	7.01	7.01	
$C_{20}H_{24}ClNS \cdot H_2O$	66.00	66.40	7.20	7.16	3.85	3.76	
$C_{24}H_{29}NO_6S$	62.72	62.72	6.36	6.56	3.05	2.92	0.1–1
$C_{26}H_{28}N_4O_7S$	57.98	58.03	4.87	5.22	10.41	10.23	
$C_{21}H_{28}BrNS$	62.37	62.49	6.48	6.35	3.46	3.51	
$C_{18}H_{22}ClNS_2$	61.42	61.55	6.30	6.22			1
$C_{24}H_{24}N_4O_7S_2$	52.93	53.15	4.44	4.29	10.29	10.33	
$C_{19}H_{24}BrNS_2$	55.60	55.35	5.89	6.00	3.41	3.22	
$C_{29}H_{36}NO_7 \cdot 0.25H_2O$	67.92	67.78	6.95	7.14	2.72	2.80	0.001
$C_{24}H_{30}BrN$	69.89	69.99	7.33	7.70	3.40	3.34	0.01

2-C_5H_4N = 2-pyridyl. [b] Recrystallization solvents: A = ethanol, B = ether, [c] Triturated with acetone. [d] Defined in Table II.

TABLE IV
3-SUBSTITUTED TROPANE ALKANES

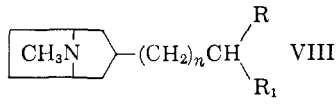
Compound[a]							
No.	n	R	R'	Config.	Salt	M.p., °C.	Solvent[d]
a	0	CH_3	CH_3	α[b]	...	...[c]	
					HCl	194–196	AB
					CH_3I	224–226	AB
b	0	C_6H_5	C_6H_5	α[b]	...	70–72	
					HCl	>310	AB
					CH_3Br	277–278	CA
c	1	C_6H_5	C_6H_5	α	HCl	244–245	AB
					CH_3Br	257–258	AB
d	1	C_6H_{11}	C_6H_5	α	HCl	167–168.5	DB
					Citrate	153–155	A
					Picrate	140–141	A
					CH_3Br	259–260	AB
e	1	C_8H_{15}	C_6H_5	α	HCl	198–200	E
f	1	C_6H_5	2-C_5H_4N	α	Tartrate	78–80	AB
					Picrate	201–203	E
g	2	C_6H_5	C_6H_5	α	Citrate	170	AB
					CH_3Br	277	AB

[a] C_6H_{11} = cyclohexyl; C_8H_{15} = 2-cyclohexylethyl; 2-C_5H_4N = 2-pyridyl. hydrogenation of the corresponding olefin, since other 3-substituted tropane predominantly α-isomers when reduced under these conditions (ref. 11). [c] B.p. B = ether, C = ethyl acetate, D = butanone, E = acetone. [e] Defined in Table

catalyst and cyclohexene as the hydrogen donor.

The cyclohexylethyl phenyl alkane VIIIe was prepared by reduction of the corresponding carbinol with red phosphorus and hydriodic acid. This method was unsuitable, however, for the preparation of the alkanes derived from carbinols IVe, IVg, and IVj. The products from the first two carbinols were mixtures in which the corresponding olefins predominated, and most of the starting material was recovered from the attempted reduction of the pyridyl carbinol IVj.

The *in vitro* cholinolytic activities of some of the tropane carbinols,



VIII

Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Relative activity, atropine = 1[e]
$C_{11}H_{22}ClN$	64.84	64.27	10.88	10.49			
$C_{12}H_{24}IN$	46.61	46.05	7.82	7.67			
$C_{21}H_{26}ClN$	76.92	76.52	8.00	8.00			0.01
$C_{22}H_{28}BrN \cdot 0.5H_2O$	66.83	66.98	7.39	7.55			0.1
$C_{22}H_{28}ClN$	77.28	77.21	8.25	8.14			1–10
$C_{23}H_{30}BrN$	68.99	68.76	7.55	7.44			1
$C_{22}H_{34}ClN \cdot 0.25H_2O$	74.96	75.18	9.87	9.84	3.97	4.02	
$C_{28}H_{41}NO_7$	66.77	66.64	8.21	8.30	2.78	3.00	0.1–1
$C_{28}H_{36}N_4O_7$	62.20	62.41	6.71	6.80	10.36	10.47	
$C_{23}H_{36}BrN$	67.96	67.79	8.93	8.93	3.45	3.71	
$C_{24}H_{38}ClN \cdot 0.25H_2O$	75.75	75.78	10.20	10.35	3.68	3.69	
$C_{25}H_{32}N_2O_8 \cdot 1.5H_2O$	62.09	61.85	7.30	6.87	5.80	5.38	
$C_{33}H_{32}N_8O_4$	51.83	51.59	4.22	4.07	14.66	14.74	
$C_{29}H_{37}NO_7 \cdot 0.25H_2O$	67.49	67.47	7.32	7.23	2.71	2.74	0.001–0.01
$C_{24}H_{32}BrN$	69.55	69.53	7.78	8.00	3.38	3.44	0.01

[b] Configuration assigned on the basis of the method of preparation, catalytic derivatives in which the 3-carbon atom is part of an unsaturated group yield 109–111° (29 mm.); n_D^{25} 1.4739. [d] Recrystallization solvents: A = ethanol, II.

olefins, and alkanes, relative to that of atropine, are presented in Tables II, III and IV.[19] A number of the derivatives in which two carbon atoms separate R and R′ from the tropane ring are quite active agents, equalling or exceeding atropine in potency, whereas the lower and higher homologs of these derivatives are relatively inactive. The β isomer (IVf) of the diphenyl carbinol IVe and the unsaturated

(19) We are indebted to Mr. Edward Macko and his associates, of the Pharmacology Section of these Laboratories, for supplying these data.

diphenyl carbinol XII (relative activity = 0.01–0.001) also showed little activity.

Since, in general, the more potent atropine-like agents contain an oxygen function in addition to the amino or quaternary ammonium group, the high activity of olefin VIa and alkane VIIIc, which have neither an oxygen function nor a quaternary ammonium group, is especially noteworthy. Alkane VIIIc, a methylene analog of benztropine (Ic), was found to be somewhat more active than atropine and as active as benztropine in the *in vitro* assay.

Experimental[20]

In general, the tropane ketones, carbinols, olefins and alkanes were prepared according to procedures described by Adamson.[8,13,15,18]

Tropane Ketones (Table I).—To a cooled ether solution of the Grignard reagent (prepared in the usual way from 2.5–4 g.-at. equivalents of magnesium and the appropriate halide (slight excess)) was added with stirring an ether solution of 1 mole equivalent of the tropane ester. The resulting mixture was stirred either at room or reflux temperature for 2–5 hr. To the cooled mixture was added slowly with stirring an aqueous solution of the tetrasodium salt of ethylenediaminetetraacetic acid[21] (40–42 g. of the salt per g. of magnesium), the ether layer was separated, and the aqueous layer was extracted with several portions of ether. The combined extracts were dried over sodium sulfate, the solvent was removed, and the residue was distilled *in vacuo*.

From the distillands from the distillation of ketones IIIa and IIIb small amounts (*ca.* 8%) of carbinols IVb and IVe, respectively, were obtained. The thick dark distilland from the distillation of the cyclohexyl ketone IIIc was transferred to a sausage flask and distilled *in vacuo*. The orange glassy distillate, b.p. *ca.* 210° 0.8 mm., formed a picrate in ethanol which melted at 241–242° after recrystallization from acetonitrile. The analysis of the salt was in agreement with the formula of the dipicrate of keto ester X.

Anal. Calcd. for $C_{34}H_{42}N_8O_{17}$: C, 48.92, H, 5.07; N, 13.42. Found: C, 49.20; H, 5.20; N, 13.69.

The infrared spectrum of the base showed peaks of about equal intensity at 5.82 and 5.87 μ with a shoulder at 5.75 μ.

Tropane Carbinols (Table II).—With the exceptions of carbinols IVb, referred to above, and IVi, all carbinols were prepared in the following way.

To a cooled ether solution of the organolithium reagent (prepared in the usual way from 3–5 g.-atom equivalents of the organic halide) was added with stirring an ether solution of 1 mole equivalent of the appropriate tropane ester or ketone.

(20) Microanalyses were performed by Mrs. Doris Rolston and co-workers of the Analytical and Physical Chemistry Section, Smith Kline and French Laboratories, and spectral data were obtained by Mr. E. S. Rump, Dr. Walter E. Thompson and their associates of the same section.

(21) Method for decomposing Grignard reaction mixtures described by J. Métivier, *Bull. soc. chim. France*, 965 (1952).

The resulting mixture was stirred for 2–5 hr. at either room or reflux temperature, and then the cooled mixture was hydrolyzed by addition of water. In many cases at this stage a high percentage of the carbinol product separated as a crystalline solid contaminated with the lithium derivative of the carbinol. The solid was collected on a filter and additional carbinol was isolated from the ether layer in the filtrate. To hydrolyze the lithium derivative of the carbinol present in the crude product, the latter was stirred vigorously for 2–3 hr. with a mixture of chloroform and water. The carbinol was then isolated from the chloroform layer in the usual way.

Carbinol IVf was prepared as described above from a mixture of ethyl (3β-tropanyl)acetate (β-IXb) and either methyl tropane-3β-carboxylate (β-IXa) or the corresponding ethyl ester.[11b] When water was added to the reaction mixture a colorless solid separated which was collected on a filter. Upon recrystallization of the solid from ethyl acetate, carbinol IVf was obtained as colorless crystals. From the ether layer in the filtrate from the crude carbinol was isolated a colorless solid, m.p. 156–167°. The infrared spectrum of this material, which could not be purified by recrystallization from ethyl acetate, indicated that it was a mixture of carbinols IVd and IVf.

Carbinol IVi was obtained from the reaction of ketone IIIb with ethylmagnesium bromide carried out as described above. Upon trituration of the crude oily product with ether, carbinol IVi was obtained as a colorless solid in 12% yield. From the filtrate, after evaporation of the ether and distillation of the residue *in vacuo*, 52% of ketone IIIb was recovered.

1,1-Diphenyl-2-[3-(Δ^2-tropidene)]ethanol (XII).—This carbinol was prepared by treatment of ethyl [3-(Δ^2-tropidene)]acetate[11b] with phenyllithium according to the procedure described above. The product, obtained in 72% yield, melted at 140–141° after recrystallization from ethyl acetate,

Anal. Calcd. for $C_{22}H_{25}NO$: C, 82.72; H, 7.89; N, 4.39. Found: C, 82.81; H, 7.92; N, 4.52.

The **citrate,** prepared in acetone and recrystallized from methanol, melted at 195–196°.

Anal. Calcd. for $C_{28}H_{33}NO_8$: C, 65.74; H, 6.50; N, 2.74. Found: C, 65.61; H, 6.64; N, 2.78.

Tropane Olefins (Table III).—Compounds Va, VIa, VIb, VIc, VId, and VII were obtained by heating a solution of the corresponding carbinol in a mixture of concd. hydrochloric and acetic acids (10 ml. of acetic acid and 3 ml. of hydrochloric acid/g. of carbinol) at 100° for 30 min. Upon evaporation of the solution to dryness *in vacuo* the hydrochloride of the olefin was obtained, usually as a crystalline solid.

The hydrochloride of the dehydration product of ethyl carbinol IVi was a hygroscopic mixture of salts, melting over a wide temperature range, from which, after several recrystallizations from butanone-ethanol, the hydrochloride of olefin VId or its isomer XIIIa was obtained in about 10% yield.

The **dithienyl olefins Vb and VIg** were prepared by passing hydrogen chloride into a solution of the corresponding carbinol until the solution was strongly acidic. The hydrochloride of the olefin was precipitated by addition of ether to the solution and the precipitate was collected on a filter.

To prepare the **phenyl thienyl olefin VIf,** a mixture of 9.7 g. of the corresponding carbinol, 19.4 g. of anhydrous oxalic acid, and 29 ml. of water was heated at the reflux temperature for 2 hr. The mixture was made alkaline by addition of 10% sodium hydroxide solution and extracted with chloroform. After evaporation of solvent from the dried extract, the crude olefin was obtained as a thick orange oil which crystallized on standing.

The pyridyl olefin VIe was obtained by heating a mixture of 0.5 g. of the corresponding carbinol and 2 ml. of polyphosphoric acid at 180° for 2 hr. The reaction mixture was made alkaline by addition of ammonium hydroxide solution, and the product was extracted with ether.

Approximately the same results were obtained when the carbinol was treated with 85% sulfuric acid according to the procedure of Adamson and Billinghurst.[16]

Tropane Alkanes (Table IV).—Compounds VIIIb, VIIIc, and VIIId were obtained by hydrogenation of the corresponding olefins over Raney nickel at 60° and 35 kg./cm.^{2} hydrogen pressure. Reduction of olefin VII to alkane VIIIg occurred smoothly at room temperature and 4.2 kg./cm.^{2} pressure.

Alkane VIIIa was prepared by heating a solution of carbinol IVa in 20 ml. of concd. hydrochloric acid at reflux for 4 hr. and then evaporating to dryness *in vacuo*. The residual salt was treated with concd. ammonium hydroxide solution and the resulting mixture was extracted with several portions of ether. From the dried extracts was obtained 1.3 g. of crude olefin, b.p. 116–124° (32 mm.), n_D^{23} 1.4910–1.4928. Without further purification the material was hydrogenated over Raney nickel to give 0.9 g. of alkane VIIIa.

The pyridyl alkane VIIIf was obtained from olefin VIe by heating a mixture of 0.2 g. of the latter compound, 0.3 g. of 20% palladium-carbon catalyst, and 5 g. of cyclohexene at reflux for 48 hr. After removal of the catalyst and evaporation of the cyclohexene, VIIIf was obtained as a colorless oil.

To prepare the cyclohexylethyl alkane VIIIe, a mixture of the corresponding carbinol (0.5 g.), 1 ml. of 47% hydriodic acid, 3 ml. of acetic acid, and 0.13 g. of red phosphorus was heated at reflux for 3.5 hr. The hot solution was filtered and the filtrate was diluted with hot water. From the solution the hydriodide of VIIIe separated as a dark oil which gradually crystallized.