TABLE V

OPTICAL ROTATIONS[a]

Compound No.[b]	$[\alpha]^{25}D$	10^2M_D
1	+27.2	62
3	+23.4	60
13	+52.2	123
15	+54.0	142
16	+51.2	141
18	+42.6	139
20	+58.2	165
21	+40.5	138
22	+48.6	142
24	+48.0	150
36	+32.7	129
41	+48.6	152
44	+43.8	139
49	+33.5	132
50	+21.0	91
16 (base)	+83.6	190

[a] Solvent: 90% ethanol-water; temperature: 25°; conc.: 0.5 g. in 15 ml. of solvent. [b] Compound numbers are those given in Tables I to IV and in experimental part. The compounds of Tables II and III were examined as hydrochlorides.

kept at 40–45° for 10 hr. After removing the solvents *in vacuo*, the residue was crystallized from acetone-ether in quantitative yield, m.p. 221°.

d-1,8,8-Trimethyl-3-azabicyclo[3:2:1]octane-3-spiropentamethylene ammonium tosylate (compound 49). To 2.8 g. of the amino alcohol (compound 16) in 50 ml. of triethylamine 2 g. of *p*-toluenesulfonyl chloride was added. The reaction mixture was warmed for 1 hr., when the flocculent precipitate that originally appeared changed to a waxy mass.

The solvent was removed *in vacuo* and the residue was triturated several times with ether to remove excess tosyl chloride and unchanged amino alcohol. This ether-insoluble material was extracted with a minimum amount of acetone and filtered off from acetone-insoluble triethylamine hydrochloride. The waxy product obtained on evaporation of acetone was subjected to high vacuum tubular[7] sublimation under 1 micron pressure at 100°: Traces of triethylamine hydrochloride sublimed. The residue was crystallized in quantitative yield from acetone-ether, m.p. 146–147°.

Anal. Calcd. for $C_{22}H_{35}NO_3S$: C, 64.8; H, 8.6. Found: C, 65.0; H, 8.8.

d-Spiro-3'-(methylaza)pentamethylene camphidinium tosylate (compound 50). This was prepared by the procedure outlined above in 80% yield, m.p. 195–200° for the sesquihydrate salt. Percentage moisture was determined gravimetrically by heating a sample for 3 hr. at 90° under 0.5 micron pressure.

Anal. Calcd. for $C_{22}H_{36}N_2O_3S \cdot 3/2\ H_2O$: C, 60.7; H, 8.9; H_2O, 5.67. Found: C, 60.4; H, 9.3; H_2O, 5.89.

TUCKAHOE, N. Y.

(7) N. B. Mehta and J. Zupicich, *Chemist-Analyst*, **50**, 84 (1961).

[CONTRIBUTION FROM THE RESEARCH AND DEVELOPMENT DIVISION, SMITH KLINE AND FRENCH LABORATORIES, AND THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA]

3-Substituted Tropane Derivatives. I. The Synthesis and Stereochemistry of the Tropane-3-carboxylic Acids and Their Esters. A Comparison of Positional Isomers in the Tropane Series[1]

CHARLES L. ZIRKLE,[2,3] T. A. GEISSMAN, M. BLOOM, PAUL N. CRAIG,[2] FRED R. GERNS, ZENA K. INDIK, AND ALEX M. PAVLOFF[2]

Received October 5, 1961

The α and β isomers of tropane-3-carboxylic acid and some related compounds were synthesized and their configurations established. Certain properties of these compounds are compared with those of tropane-2-carboxylic acid derivatives obtained from cocaine.

To provide intermediates for the preparation of new 3-substituted tropane derivatives of potential pharmacological interest[4] we investigated the synthesis and stereochemistry of tropane-3α- and 3β-carboxylic acids (IIIb) (Chart I) and related compounds.[5,6] In addition to the chemistry of these compounds, this paper records several noteworthy differences, observed in the course of our study, in the chemical behavior of esters of 3-tropane acids and of the corresponding 2-tropane esters derived from cocaine.

The isomeric tropane acids IIIb or their methyl esters IIIa were prepared from α-ecgonine methyl ester[7] (Ia) by two routes. One route, which permitted the preparation of both isomers of IIIa

(1) Taken in part from a Doctoral thesis submitted by Murray Bloom to the Graduate School of the University of California, Los Angeles.

(2) Smith Kline and French Laboratories.

(3) To whom inquiries concerning this paper may be addressed.

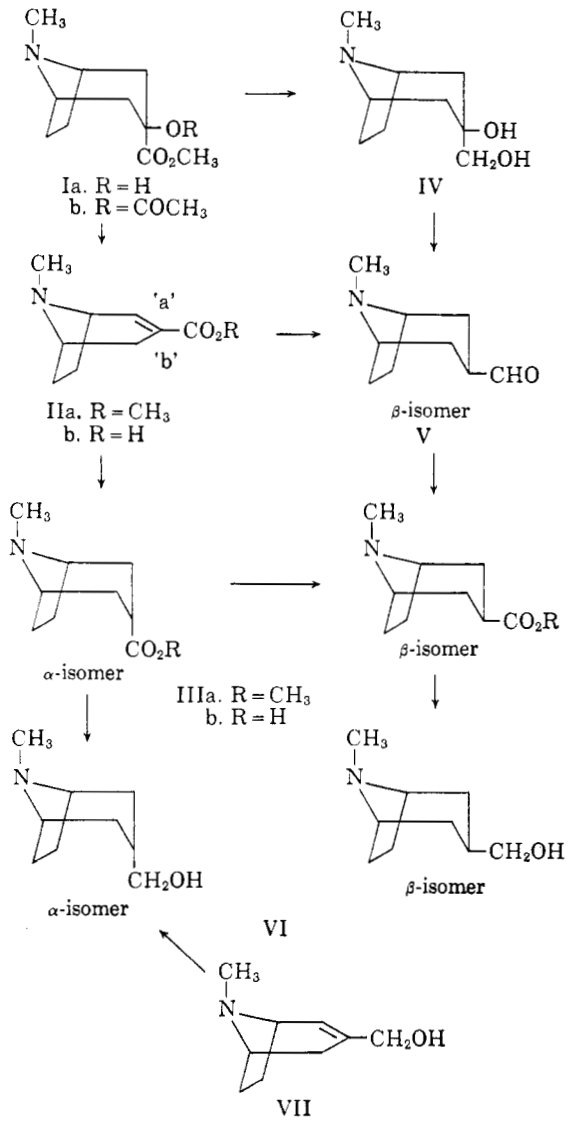
(4) Paper III of this series: C. L. Zirkle, E. L. Anderson, P. N. Craig, F. R. Gerns, Z. K. Indik, and A. M. Pavloff, *J. Med Pharm. Chem.*, **5**, 341 (1962).

(5) In naming these compounds we have adopted the nomenclature introduced by G. Fodor and K. Nador, *J. Chem. Soc.*, 721 (1953), to designate the configurations of isomers of other tropane derivatives.

(6) A preliminary account of part of this work has been presented elsewhere (C. L. Zirkle, P. N. Craig, T. A. Geissman, and M. Bloom, Congr. Handbook Vol. II, *16th Intern. Congr. Pure and Appl. Chemistry*, Paris, July 1957, p. 153).

(7) R. Willstätter, *Ber.*, 29, 1575, 2216 (1896).

CHART I

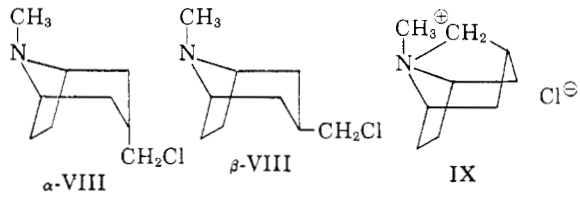


and IIIb, proceeded *via* the unsaturated ester IIa. Several attempts to prepare the latter compound by dehydration of Ia or its precursor, tropinone cyanohydrin, with acids, phosphorus oxychloride or thionyl chloride were unsuccessful. However, pyrolysis of the acetate Ib of α-ecgonine methyl ester (Ia) proceeded smoothly to give IIa in 66% yield.

Hydrogenation of unsaturated ester IIa over Raney nickel occurred stereoselectively to yield predominantly one epimer of methyl tropane-3-carboxylate (IIIa). The latter ester in the presence of sodium methoxide epimerized to the thermodynamically more stable isomer of IIIa. On conformational grounds, the more stable isomer may be assigned the β configuration in which the carboxyl group is equatorial to the piperidine ring when the latter is in the chair conformation.[8,8a] It follows that the chief product from the hydrogenation of IIa has the α configuration (carboxyl axial).

By fractional crystallization of their oxalate salts the pure α and β isomers of IIIa were obtained from the hydrogenation product and "equilibrated" ester, respectively. Infrared spectral data indicated that the mixture of isomeric esters from the hydrogenation of IIa contained 90% or more of the α epimer while the mixture from the epimerization of this isomer consisted of 90% or more of the β epimer.

Confirmatory evidence for the configurations of the esters assigned by conformational analysis was provided in the following way. The α ester IIIa and the β acid IIIb were converted to the corresponding tropane methanols VI by reduction with lithium aluminum hydride. Treatment of the α and β isomers of the amino alcohols VI with thionyl chloride gave the hydrochloride salts of the isomeric chloro amines VIII. The chloro amines were further characterized as their picrates which were prepared directly from the hydrochloride salts. When the salt of β-VIII was treated with alkali the product isolated was not the chloro amine but the tricyclic quaternary ammonium chloride



IX. This salt was also formed when the hydrochloride of β-VIII was heated above its melting point. IX was very hygroscopic but the quaternary ammonium ion could be characterized as its picrate and styphnate salts. That the salt formed from β-VIII was the cyclization product IX and not a quaternary ammonium dimer or polymer of β-VIII was shown by the elemental analyses of the picrate and styphnate obtained from IX and by the fact that the latter two salts gave a negative Beilstein test for halogen.

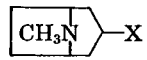
On the other hand, chloro amine α-VIII showed no tendency to form either intra- or intermolecular quaternary ammonium salts and could be distilled without change. The crude and distilled bases yielded identical picrates.

Due to the geometry of the tropane ring system, the cyclic ammonium salt IX can form from only the β-isomer of VIII and the isomer which does not cyclize must have the α configuration. Since the chloro amines were prepared from the isomeric

(8) For discussion of the conformation of tropane derivatives see G. Fodor in "The Alkaloids," Vol. VI, R. H. F. Manske, Ed., Academic Press, Inc., New York, 1960, p. 145.

(8a) After this work was completed, S. Archer *et al.*, *J. Am. Chem. Soc.*, **80**, 4677 (1958), reported the preparation of ester β-IIIa by a different route.

TABLE I



ISOMERIC TROPANE-3-CARBOXYLIC ACIDS AND RELATED COMPOUNDS

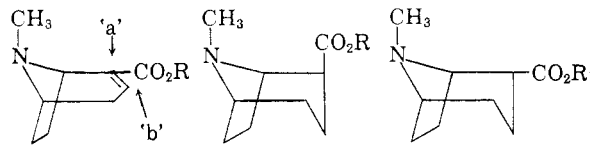
Compound			B.P.			Recryst.			Carbon, %		Hydrogen, %		Nitrogen, %	
No.	X	Config.	(mm.)	n_D (°C.)	Salt	Solv.[a]	M.P.	Formula	Calcd.	Found	Calcd.	Found	Calcd.	Found
IIIb	CO_2H	α			—	AB	233	$C_9H_{15}NO_2$	63.88	63.25[b]	8.94	9.05		
					HCl	CA	245–246	$C_9H_{15}NO_2 \cdot HCl$	52.55	52.58	7.84	7.98	6.81	6.99
IIIa	CO_2CH_3	α	108–109 (9)	1.4822 (24.6)	Picrate	D	171–172	$C_{10}H_{17}NO_2 \cdot C_6H_3N_3O_7$	46.60	46.70	4.89	4.65		
					Oxalate	CB	165.5–166	$C_{10}H_{17}NO_2 \cdot C_2H_2O_4$	52.74	52.79	7.01	7.24	5.13	5.34
					CH_3I	CB	221–222	$C_{11}H_{20}INO_2$	40.63	40.84	6.20	6.09	4.31	4.48
					CH_3Br	AB	275–278	$C_{11}H_{20}BrNO_2$	47.49	47.52	7.27	7.28	5.04	5.14
IIIb	CO_2H	β			—	E	219–220	$C_9H_{15}NO_2 \cdot H_2O$	57.73	57.66	9.15	9.29		
					HCl	F	246–247	$C_9H_{15}NO_2 \cdot HCl$	52.55	52.61	7.84	8.11	6.81	6.75
IIIa	CO_2CH_3	β	112–113 (9)	1.4789 (24.5)	Picrate	C	168.5–169.5	$C_{10}H_{17}NO_2 \cdot C_6H_3N_3O_7$	46.60	46.78	4.89	5.16	13.59	13.65
					Oxalate	C	150–152	$C_{10}H_{17}NO_2 \cdot C_2H_2O_4 \cdot 1/2\ H_2O$	49.48	49.26	7.27	6.75	4.81	4.49
					HCl	F	205	$C_{10}H_{17}NO_2 \cdot HCl$	54.66	54.73	8.26	8.32		
					CH_3I	A	229–230	$C_{11}H_{20}INO_2$	40.63	40.73	6.20	6.27	4.31	4.54
V	CHO	β	105–108 (11)	1.5013 (23.3)	Picrate	C	236	$C_9H_{15}NO \cdot C_6H_3N_3O_7$	47.12	47.15	4.75	5.18	14.66	15.02
VI	CH_2OH	α			—	B	75–76	$C_9H_{17}NO$	69.63	69.40	11.04	10.81		
					Picrate	G	204–205.5	$C_9H_{17}NO \cdot C_6H_3N_3O_7$	46.87	46.57	5.25	5.11	14.58	14.56
					CH_3I	C	356	$C_{10}H_{20}INO$	40.41	40.63	6.78	7.09	4.71	4.98
VI	CH_2OH	β	90–95 (1)	Hygroscopic solid										
					Picrate	C	193–194.5	$C_9H_{17}NO \cdot C_6H_3N_3O_7$	46.87	47.00	5.25	5.54		
					CH_3I	C	312–313	$C_{10}H_{20}INO$	40.41	40.44	6.78	6.75		
VIII	CH_2Cl	α	60–62 (0.2)	1.5035 (25)	Picrate	G	194–196	$C_9H_{16}ClN \cdot C_6H_3N_3O_7$	44.73	44.77	4.75	5.10	13.91	13.97
					HCl	G	168.5–169	$C_9H_{16}ClN \cdot HCl$	51.44	51.31	8.15	8.09	6.67	6.63
VIII	CH_2Cl	β	Base unstable		Picrate	A	165–167	$C_9H_{16}ClN \cdot C_6H_3N_3O_7$	44.73	44.46	4.75	4.68		
					HCl	CB	155–157.5	$C_9H_{16}ClN \cdot HCl$	51.44	51.30	8.15	8.13		

[a] Recrystallization solvents: A = methanol, B = ether, C = ethanol, D = water, E = 2-propanol, F = butanone, G = acetone. [b] The sample retained a small amount of water after drying for 12 hr. at 100° *in vacuo*.

esters IIIa by methods in which isomerization is known not to occur, each epimer of IIIa must have the configuration of the chloroamine derived from it.

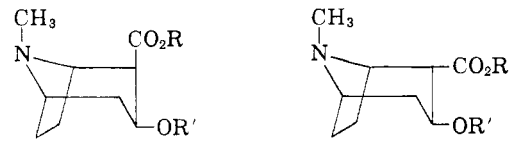
Data on the isomeric tropane acids, their esters and the compounds derived from them are presented in Table I.

The stereochemical course of reduction of IIa corresponds to that of the hydrogenation of tropinone.[9] In both cases hydrogen adds principally to the double bond from side "a" of the tropane ring (see formula II, Chart I) to give a preponderance of reduction products having the α configuration. In contrast, catalytic hydrogenation of anhydroecgonine and its esters (X)[10] follows an opposite course in which hydrogen adds chiefly from side "b" to form mainly tropane-2β-carboxylic acid (β-XIa) and its esters (β-XIb-c). Findlay,[10] in repeating work of von Braun and Müller,[11] hydrogenated Xb in ethanol over palladized charcoal to obtain a mixture of the two isomers of XIb in a ratio of roughly 6:1. The epimeric ester obtained in lesser amount was identical with that prepared by Willstätter[12] by



X a. R = H β isomer XI α isomer
b. R = C_2H_5
c. R = CH_3

esterification of the product from reduction of anhydroecgonine (Xa) with sodium and 1-pentanol. Although the configurations of the isomers of XIa have never been determined, they may be assigned readily by consideration of the conditions under which the acids or esters were formed. Willstätter's tropane-2-carboxylic acid (hydroecgonidine) should be an "equilibrated" product containing a preponderance of the thermodynamically more stable isomer of XIa. On conformational grounds this acid and its ethyl ester must have the α configuration in which the carboxyl group is equatorial to the piperidine ring. It follows that the predominant isomer obtained in the catalytic hydrogenation of Xb is the β epimer of XIb (carboxyl axial). Support for these assignments is provided by the fact that esters closely related to XIb, cocaine (XIIa) and ecgonine methyl ester (XIIb) whose β configurations are definitely established,[13,14] readily epimerize in the presence of strong base[13,15] to give pseudoecgonine (XIIIb) or its ester (XIIIa), indicating that in the series of tropane-2-carboxylic acid esters the α isomers are the more stable forms.



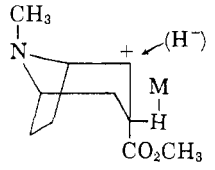
XII a. R = CH_3, R' = COC_6H_5
b. R = CH_3, R' = H
c. R = H, R' = H
d. R = H, R' = COC_6H_5
XIII a. R = CH_3, R' = H
b. R = H, R' = H

In the present work we found that catalytic reduction of unsaturated methyl ester Xc over Raney nickel under the conditions used to hydrogenate IIa also gave chiefly the β isomer, ester β-XI-c. That the predominant product was the β-isomer was demonstrated by its conversion by acid-catalyzed transesterification to ethyl ester β-XIb. Furthermore, the acid obtained from the methyl ester (see below) epimerized in the presence of sodium 1-pentoxide in refluxing 1-pentanol to acid α-XIa,[12] which was characterized as its methyl and ethyl esters α-XIc and α-XIb.[10,12,16] Thus, unsaturated esters Xb and Xc differ from IIa in that upon hydrogenation the former two yield predominantly β saturated esters while the latter gives mainly an α ester. For the β isomers to be the chief reduction products of Xb and Xc, hydrogen must have added to the double bond principally from side "b" of the tropane ring system rather than from side "a" as in the case of the isomeric unsaturated ester IIa.

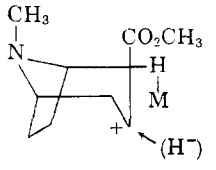
According to current concepts of the mechanism of catalytic hydrogenation,[17] addition of hydrogen to cyclic unsaturated compounds is predicted to occur from the less hindered side of the double bond. Therefore, an obvious rationalization of the different courses of hydrogenation followed by esters IIa and Xc is that side "a" of the double bond in the former and side "b" of the unsaturated linkage in the latter are more accessible to the catalyst than the other sides. However, a comparison of Courtald molecular models of the isomeric unsaturated esters did not show clear-cut steric differences between corresponding sides of the two molecules. An alternative explanation of the results is provided by consideration of possible transition states in the hydrogenation process. Perhaps the olefinic esters are absorbed on the catalyst to form complexes, having, for example, structures schematically represented by formulas XIV and XV similar to hypothetical intermediates

(9) L. C. Keagle and W. H. Hartung, *J. Am. Chem. Soc.*, **68**, 1608 (1946).
(10) S. P. Findlay, *J. Am. Chem. Soc.*, **75**, 1033 (1953).
(11) J. v. Braun and E. Müller, *Ber.*, **51**, 235 (1918).
(12) R. Willstätter, *Ber.*, **30**, 702 (1897).
(13) S. P. Findlay, *J. Am. Chem. Soc.*, **76**, 2855 (1954).
(14) Ref. in footnote 8.
(15) A. W. K. de Jong, *Rec. trav. chim.*, **56**, 186 (1937).
(16) For some unexplained reason, an attempt to obtain methyl ester α-XIc directly by epimerization of β-XIc with sodium methoxide in methanol was unsuccessful (see Experimental part).
(17) R. J. Wicker, *J. Chem. Soc.*, 2165 (1956).

proposed by Brewster[18] and by McQuillin,[19] in which the bulky surface of the catalyst assumes mainly an equatorial orientation to the ring minimizing steric repulsions in the transition states. In the formulas M represents the metallic catalyst



XIV



XV

and H refers to adsorbed hydrogen. Transference of hydrogen from the catalyst to the substrates leads in both instances to formation of the axial saturated esters, methyl tropane-3α- and 2β-carboxylates (α-IIIa and β-XIc).

Catalytic reduction of Δ^2-tropidine-3-carboxylic acid (IIb), obtained by hydrolysis of IIa in boiling water, also proceeded stereoselectively to yield chiefly tropane-3α-carboxylic acid (α-IIIb). The latter acid as its hydrochloride could also be obtained by hydrolysis of α-IIIa in 37% hydrochloric acid at room temperature. Under other, including quite mild, conditions of hydrolysis extensive epimerization occurred in the process resulting in the formation of β-IIIb as the predominant product. The latter acid was readily obtained by hydrolysis of its ester in hot aqueous solution.

The behavior of methyl tropane-3α-carboxylate under mild hydrolytic conditions differs markedly from that of esters of the tropane-2-carboxylic acids, cocaine, and related compounds, which do not epimerize under similar conditions. A more detailed discussion of the hydrolysis of both series of tropane esters will be presented in the sequel.

In a second route to tropane-3β-carboxylic acid (β-IIIb), α-ecgonine methyl ester (Ia) was reduced with lithium aluminum hydride to the diol IV. The latter has the configuration shown since Heusner[20] has established that its precursor, Ia, has this configuration. Diol IV in acid solutions underwent a pinacol rearrangement to tropane-3β-carboxaldehyde (V), characterized as its picrate and 2,4-dinitrophenylhydrazone. Oxidation of the aldehyde with silver oxide readily afforded the acid which was converted to its ester by Fischer esterification. The tropane acid and its ester obtained in this way were identical with the β acid and ester prepared by the first route.

Tropane-3β-carboxaldehyde (V) was also prepared, unexpectedly, by lithium aluminum hydride reduction of unsaturated ester IIa. In addition to the expected product, unsaturated alcohol VII, the aldehyde was obtained in 22% yield. The noteworthy feature of the reduction is the formation of saturated aldehyde under conditions—*viz.*, addition of unsaturated ester to excess metal hydride in refluxing ether—which usually lead, in the case of aliphatic and alicyclic α,β-unsaturated carbonyl compounds, to unsaturated alcohols and, in the case of cinnamic aldehydes, acids and esters, to saturated alcohols.[21] Furthermore, the ethyl ester of anhydroecgonine (Xa), the positional isomer of unsaturated acid IIb, is reported to yield under similar conditions only the unsaturated alcohol, 2-tropidine-methanol.[22] While this work was in progress Brüesch and Karrer[23] reported that reduction of apoyohimbine under similar conditions also gave a saturated aldehyde, dihydroapoyohimbal, as well as the unsaturated alcohol, "apoyohimbine alcohol." Perhaps it is no coincidence that the two compounds found to yield saturated aldehydes are amino α,β-unsaturated esters. The incomplete reduction of the ester group in these two instances is reminiscent of the fact that certain amino esters with excess Grignard reagent yield mainly the corresponding ketones instead of the tertiary carbinols.[4,24] Possibly in the course of both the reduction of the amino unsaturated esters and the reaction of amino ketones with Grignard reagents, metal complexes involving the amino group form at an intermediate stage preventing further reaction with the metallic reagents.

Further reduction of the β-aldehyde V and of the unsaturated alcohol VII by catalytic hydrogenation gave predominantly the β and α isomers, respectively, of the saturated tropane alcohol VI.

In the foregoing discussion of the isomeric methyl tropane-3-carboxylates (IIIa) we pointed out that the α isomer readily epimerizes during hydrolysis under conditions in which the tropane-2-carboxylic acid esters, cocaine (XIIa), and ecgonine methyl ester (XIIb), do not isomerize. Even when ester α-IIIa was hydrolyzed under very mild conditions, *i.e.*, in aqueous solution at room temperature, the acid obtained appeared to be almost exclusively the β isomer of IIIb. On the other hand, cocaine (XIIa), in boiling aqueous solution, hydrolyzes to benzoylecgonine (XIId)[13] and cocaine and ecgonine methyl ester (XIIb), in barium hydroxide solution at room temperature, is converted to ecgonine (XIIc).[25] In the presence of stronger bases these esters do epimerize to a considerable extent during hydrolysis to yield large amounts of pseudoecgonine (XIIIb).[13,15]

(18) J. H. Brewster, *J. Am. Chem. Soc.*, **76**, 6361 (1954).
(19) F. J. McQuillin, *Chem. and Ind. (London)*, 251 (1957).
(20) A. Heusner, *Z. Naturforsch.*, **12b**, 602 (1957).
(21) N. G. Gaylord, "Reduction with Complex Metal Hydrides," Interscience Publishers, Inc., New York, 1956, Chaps. 6–10.
(22) K. W. Rosenmund and F. Zymalkowski, *Ber.*, **85**, 152 (1952).
(23) J. Brüesch and P. Karrer, *Helv. Chim. Acta*, **38**, 905 (1955).
(24) P. A. Barrett, U. S. Patent **2,649,444** (August 18, 1953).
(25) R. Willstätter, O. Wolfes, and H. Mäder, *Ann.*, **434**, 111 (1923).

TABLE II

HYDROLYSIS OF METHYL TROPANE-2- AND 3-CARBOXYLATES IN AQUEOUS SOLUTION AT ROOM TEMPERATURE[a]

Ester					Acid Product	
Position of CO_2CH_3	Compound	Config.	Conform.	Time, Hr.	Compound	Yield, %
3	IIIa	α	a	3	β-IIIb	4.7
				6		12
				24		22
				48		45
				88		76
3	IIIa	β	e	3	β-IIIb	41
				24		85
				48		96
2	XI-c	β	a	3	β-XIa	4.3
				6		10
				24		22
				48		49
				168		89
2	XIc	α[b]	e	6	α-XIa	39
				24		63
				48		81
				88		96

[a] See Experimental part for procedure. [b] The sample of this ester contained 10–20% of its isomer β-XIc.

To investigate further the difference in behavior of the methyl tropane-2- and 3-carboxylates we studied, in a series of qualitative experiments, the hydrolysis in aqueous solution of esters α-XIc, β-XIc, α-IIIa, and β-IIIa. The results are summarized in Table II.

As indicated in the table, methyl tropane-3α-carboxylate (α-IIIa) underwent epimerization and hydrolysis readily at room temperature to give acid β-IIIb. Since esters epimerize much more readily than the corresponding acids,[13] α-IIIa most probably first isomerizes to ester β-IIIa which then hydrolyzes to the acid. The β ester could not be detected in the ester recovered from the hydrolysis mixture after forty-eight hours—a result consistent with data in Table II showing that the rate of hydrolysis of the β ester is quite high. The α ester was also recovered unchanged from a solution in dimethylformamide after three days and from a methanol solution after two weeks at room temperature.

In contrast to α-IIIa, methyl tropane-2β-carboxylate (β-XIc), like cocaine and ecgonine methyl ester, hydrolyzed without isomerization to yield the β-isomer of acid XIa. That isomerization did not occur was shown by the fact that the acid obtained formed an ethyl ester identical with that obtained by transesterification of the β-methyl ester.

Data in Table II show that the observed rates of hydrolysis of axial esters α-IIIa and β-XIc are about equal. However, since α-IIIa yields predominantly the β acid, the actual rate of hydrolysis of α-IIIa must be lower than the observed rate of amino acid formation which is really a rough measure of the epimerization rate of this ester. Thus the hydrolysis rate of β-XIc (axial) is higher than that of α-IIIa (axial), as would be predicted on steric grounds, and is about equal to the epimerization rate of α-IIIa. Since β-XIc hydrolyzes without isomerization, its rate of epimerization must be lower than its hydrolysis rate. Consequently, the rate of isomerization of β-XIc must be lower than that of α-IIIa under the conditions of these experiments. Therefore, a rationalization of the fact that hydrolysis of β-XIc in aqueous solution occurs with retention of configuration is found in both the higher rate of hydrolysis and the lower rate of epimerization of β-XIc relative to those of α-IIIa.

The simplest possible explanation of the epimerization of α-IIIa in aqueous solution is that the first step, enolization of the ester, is catalyzed by hydroxide ion formed in equilibrium (1). That epimerization does not occur in methanol may be due to the fact that, since this solvent is a weaker

$$R_3N + HOH \rightleftharpoons R_3N \cdots HOH \rightleftharpoons R_3\overset{\oplus}{N}H + OH^{\ominus} \quad (1)$$

$$R_3N + HOCH_3 \rightleftharpoons R_3N \cdots HOCH_3 \rightleftharpoons R_3\overset{\oplus}{N}H + OCH_3^{\ominus} \quad (2)$$

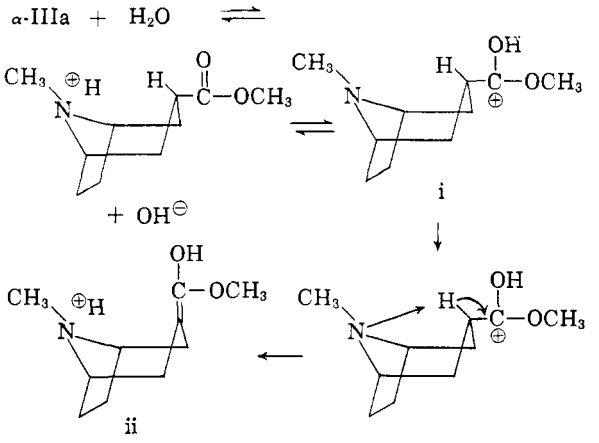
R_3N = tropane ester

acid than water, equilibrium (2) supplies a lower concentration of base, methoxide ion, then that provided by (1).[26]

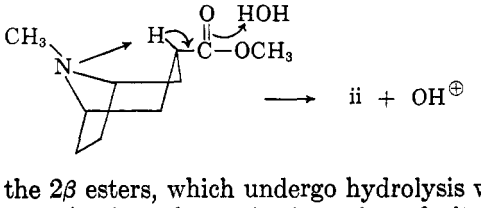
Another possibility, however, is suggested by the stereochemistry of the 3α- and 2β-tropane esters.

(26) Certain derivatives of lysergic acid epimerize readily in methanol solution (L. Marion in "The Alkaloids," Vol. II, R. H. F. Manske and H .L. Holmes, eds., Academic Press, Inc., New York, 1952, p. 375; J. E. Saxton, "The Alkaloids," R. H. F. Manske and H. L. Holmes, eds., Academic Press, Inc., New York, 1960, p. 9). However, in these compounds, which contain the system C=C—H, CCOX, the hydrogen atoms on the α carbon are considerably more labile than the corresponding hydrogen in α-IIIa.

In the 3α ester the hydrogen alpha to the carbonyl group is situated *syn* to the amino group and, conceivably, the latter could facilitate enolization of the ester by participating in the removal of the alpha proton.[27]



Another possibility is that protonation and enolization of the ester occurs by some concerted process such as that depicted below.



In the 2β esters, which undergo hydrolysis without epimerization, the *anti* orientation of nitrogen to the alpha hydrogen precludes enolization by this mechanism.

EXPERIMENTAL[28,29]

Methyl 3β-acetoxy-3α-tropanecarboxylate (Ib). A solution of 10.0 g. of α-ecgonine methyl ester[7] (Ia) in 50 ml. of acetic anhydride was heated at reflux temperature for 15 min. Excess acetic anhydride was removed *in vacuo*, the residue was added to 100 ml. of water, and the resulting mixture was extracted with three portions of ether. Upon evaporation of solvent and distillation of the residue, 10.6 g. (87%) of a colorless oil, b.p. 162–165° (15 mm.) was obtained, which on standing, crystallized as a white solid, m.p. 66–67°.

The picrate, recrystallized from dilute alcohol, melted at 215–217.5°.

Anal. Calcd. for $C_{18}H_{22}N_4O_{11}$: C, 45.96; H, 4.71. Found: C, 46.03; H, 4.87.

Methyl Δ²-tropidene-3-carboxylate (IIa). The acetoxy ester Ib (5 g.) was pyrolyzed by passage down a vertical 25 mm. × 18 in. Pyrex tube, packed for 8 in. of its length with 1/4 to 1/8 in. pieces of 7 mm. Pyrex tubing, heated to 420°. The ester was added during a 1.5-min. period. The crude product was dissolved in dilute hydrochloric acid, and the resulting solution was extracted with ether. From the ether extract was obtained 0.35 g. of neutral material having a terpene-like odor. The aqueous acid solution was neutralized and saturated with potassium carbonate and then extracted several times with ether. Distillation of the ether extracts gave 2.15 g. (57%) of pale yellow liquid, b.p. 131–134° (15 mm.); $n^{25.5}_D$ 1.4998.

The *picrate*, after recrystallization from water, melted at 207–208°.

Anal. Calcd. for $C_{16}H_{18}N_4O_9$: C, 46.83; H, 4.42. Found: C, 46.90; H. 4.28.

The *hydrochloride* was prepared in ether and recrystallized from alcohol–ether; m.p. 180–180.5°.

Anal. Calcd. for $C_{10}H_{16}NO_2Cl$: C, 55.17; H, 7.41; N, 6.43. Found: C, 55.02; H, 7.65; N, 6.32.

The *methobromide*, prepared in acetone, melted at 242–243°; it rapidly decolorized an aqueous solution of potassium permanganate.

Anal. Calcd. for $C_{11}H_{18}NO_2Br$: C, 47.84; H, 6.57. Found: C, 47.65; H, 6.65.

The infrared spectrum of ester IIa exhibited, in addition to a band at 5.80 μ (carbonyl), a strong peak at 6.08 μ indicative of a conjugated double bond. A peak at 218 mμ in the ultraviolet spectrum also demonstrated the presence of a conjugated ester grouping.

In another pyrolysis experiment, 29.4 g. of ester Ib was added to the column (420°) over a 7-min. period. From the reaction mixture were obtained 9.2 g. of unsaturated ester IIa and 11.5 g. of starting material. Pyrolysis of the latter at 440° over a 4-min. period gave an additional 5.4 g. of product. The total yield of unsaturated ester was 14.6 g. (66%).

Δ²-Tropidine-3-carboxylic acid (IIb). A solution of ester IIa in distilled water was heated at 100° for 2 hr. On evaporation of the solution to dryness under reduced pressure the amino acid, m.p. >350°, was obtained. The analytical sample, obtained by recrystallization of the acid from methanol, still contained a small amount of water of crystallization after drying at 100° *in vacuo* over phosphorus pentoxide for 12 hr.

Anal. Calcd. for $C_9H_{13}NO_2 \cdot 1/4\ H_2O$: C, 62.95; H, 7.75. Found: C, 62.95; H, 7.84.

Methyl tropane-3α-carboxylate (α-IIIa). The unsaturated ester IIa (124.8 g.) in 750 ml. of methanol was hydrogenated over Raney nickel (*ca.* 50 g.) at room temperature and an initial pressure of 600 p.s.i. After 7 hr. hydrogen uptake was 96% of the theoretical amount. Distillation of the product, after removal of catalyst and solvent, gave the mixture of of saturated esters, collected in two arbitrarily cut fractions: (1) 91 g., b.p. 72–77° (2 mm.), $n^{24.5}_D$ 1.4822; (2) 25.8 g., b.p. 77–80° (2 mm.), $n^{24.5}_D$ 1.4829. The yield was 93%.

In the infrared spectra of these fractions the 6.08 μ peak (double bond) was absent.

A mixture of oxalate salts was prepared from 37.5 g. of the pooled fractions of ester and 18.4 g. of oxalic acid in butanone. The crude oxalate weighted 52.3 g. (94%), m.p. *ca.* 150°. After two recrystallizations of this material from alcohol–ether, 42.3 g. of pure oxalate of methyl tropane-3α-carboxylate, m.p. 165.5–166°, was obtained.

From 20.0 g. of the oxalate 11.3 g. (84.5%) of pure α isomer of the amino ester was obtained. Data on it and its salts are presented in Table I.

The infrared spectrum of α-IIIa (natural film) showed characteristic bands at 10.10, 10.90, 11.65, and 12.30 μ.

In a known mixture of 90% of α-IIIa and 10% of its epimer β-IIIa the latter isomer was readily detected by the presence of bands at 9.96 and 10.76 μ (see below) in the spectrum of the mixture (natural film). In the spectrum of the mixture of esters obtained by catalytic hydrogenation of the unsaturated ester these bands were of lower intensity than those in the spectrum of the known mixture, indicating

(27) A referee has suggested the following mechanism for enolization of ester α-IIIa involving the protonated species i.

(28) We wish to thank Mrs. Doris Rolston and co-workers of the Analytical and Physical Chemistry Section, Smith Kline and French Laboratories, for the microanalyses, and Dr. Walter E. Thompson and co-workers of the same section for spectral data.

(29) We are indebted to Dr. George H. Connitt of the Organic Chemistry Section, Smith Kline and French Laboratories, for the large-scale preparation of intermediate IIa.

that the hydrogenation product consisted of 90% or more of α-IIIa.

Similar results were obtained when the hydrogenation of IIa was carried out at an initial pressure of 60 p.s.i.

Methyl tropane-3β-carboxylate (β-IIIa). A solution of 50.0 g. (0.273 mole) of ester α-IIIa and sodium methoxide (prepared from 0.63 g., 0.027 g.-atom of sodium) in 300 ml. of methanol was heated at reflux temperature for 8 hr. The methanol was evaporated *in vacuo*, a small volume of water was added to the residue, the resulting solution was saturated with potassium carbonate, and the mixture was extracted thoroughly with ether. From the ether extracts, dried over magnesium sulfate, was obtained 43 g. (86%) of distilled ester mixture, which was collected in two arbitrary fractions: (1) 30.5 g., b.p. 80–82° (3.5 mm.), n_D^{25} 1.4792; (2) 12.5 g., b.p. 82–84° (3.5 mm.), n_D^{25} 1.4798.

A mixture of oxalate salts, 20.6 g., m.p. 144–152°, was prepared, as described above, in 100% yield from 12.2 g. of the ester. After two recrystallizations of the salt from ethanol, 13.3 g. of pure oxalate of methyl tropane-3β-carboxylate, m.p. 150–152°, was obtained.

From this salt 4.77 g. (54%) of pure β-epimer of IIIa was obtained; data on it and its salts are listed in Table I.

The infrared spectrum of β-IIIa (natural film) exhibited characteristic peaks at 7.68, 9.96, 10.76, 11.76, 12.57, and 13.13 μ.

In the spectrum of a known mixture of 90% of β-IIIa and 10% of α-IIIa the band at 10.90 μ attributed to the latter epimer was easily recognized. Since this peak was less intense in the spectrum of the mixture of esters obtained from the epimerization of α-IIIa, the proportion of β-IIIa in this mixture was estimated to be 90% or more.

Tropane-3α-carboxylic acid (α-IIIb). A. Unsaturated acid IIb, 100 mg., in methanol was hydrogenated over platinum oxide (20 mg.) at 50 p.s.i. pressure at 25° to give 80 mg. of saturated acid, m.p. 233° dec.

The infrared spectrum of α-IIIb showed characteristic peaks at 8.40, 8.90, 9.45, 10.87, 11.09, 12.72, and 12.83 μ.

The *hydrochloride* was prepared by addition of an ether solution of hydrogen chloride to an ethanol solution of α-IIIb.

Its infrared spectrum exhibited characteristic bands at 8.50, 9.40, 10.88, 11.15, 12.75, and 14.00 μ.

B. A solution of 1.0 g. of ester α-IIIa in 10 ml. of 37% hydrochloric acid was allowed to stand at room temperature for 14 days. Upon evaporation of the solution to dryness *in vacuo* and trituration of the residue with acetone, 1.0 g. (91%) of amino acid hydrochloride, m.p. 237–241°, was obtained. The infrared spectrum of the crude salt was identical with that of the hydrochloride prepared from pure α-IIIb. The absence of bands at 11.01 and 13.40 μ (see below) indicated that little, if any, of the β-isomer was present. Upon recrystallization of the product from ethanol–methanol, 0.88 g. (80%) of pure α-IIIb hydrochloride was obtained.

Tropane-3β-carboxylic acid (β-IIIb). A. A solution of 0.2 g. of methyl ester β-IIIa in 5 ml. of distilled water was heated at reflux temperature for 3 hr. Upon evaporation of the water *in vacuo* the amino acid, m.p. 217–219°, was obtained in 100% yield. Recrystallization of the product from isopropyl alcohol gave the pure β isomer of the acid, m.p. 219–220°.

The infrared spectrum of β-IIIb showed characteristic bands at 8.64, 9.15, 10.98, and 13.01 μ.

The *hydrochloride* was prepared by addition of an ether solution of hydrogen chloride to β-IIIb dissolved in ethanol. After recrystallization from 2-butanone the salt melted at 246–247°.

The infrared spectrum of the hydrochloride exhibited characteristic peaks at 8.30, 8.40, 11.01, and 13.40 μ.

B. Ester α-IIIa was hydrolyzed in aqueous solution as described above for its β isomer. The crude amino acid obtained melted at 214–218°; its infrared spectrum, with the exception of somewhat more intense absorption bands in the 9.2–9.4-μ and 10.8–11.1-μ regions, was identical with that of the pure β acid. The product gave a hydrochloride identical with that prepared from β-IIIb.

In a second experiment a solution of 1.20 g. of the α ester in 5 ml. of distilled water was allowed to stand at room temperature for 48 hr. The solution was then extracted thoroughly with twelve portions of ether. From the ether extracts, dried over sodium sulfate, was recovered 0.70 g. (58%) of ester α-IIIa, b.p. 107–109° (9 mm.), $n_D^{24.3}$ 1.4828. The infrared spectra of the starting and recovered esters were identical. Upon evaporation of the aqueous solution to dryness *in vacuo*, 0.34 g. (31%) of amino acid, m.p. 213–218°, was obtained. Melting point and spectral data on this material and its hydrochloride showed that the hydrolysis product contained predominantly β-IIIb.

C. A solution of 1.0 g. of ester β-IIIa in 10 ml. of 37% hydrochloric acid was heated at reflux temperature for 24 hr. Upon evaporation of the solution to dryness *in vacuo* and recrystallization of the residue from 2-butanone, the hydrochloride of β-IIIb, having the properties described above, was obtained.

D. Ester α-IIIa was hydrolyzed in hot hydrochloric acid as described above for its β isomer to yield a crude amino acid hydrochloride, m.p. 241°, which according to its infrared spectrum, consisted mainly of the salt of β-IIIb. Slight absorption in the 10.8, 11.1, and 12.8 μ regions indicated the presence of a small amount of the α acid hydrochloride. Recrystallization of the crude product from 2-butanone gave the pure salt of β-IIIb.

Stability of ester α-IIIa *in dimethylformamide and methanol solutions.* A solution of α-IIIa in an equal volume of dimethylformamide was allowed to stand at room temperature for 3 days. The solution was diluted with 5 vol. of ether and divided into two portions. To one aliquot was added methyl iodide and to the other a saturated solution of picric acid in ether. The methiodide and picrate salts which precipitated were found to be identical with those of α-IIIa.

A solution of 1.0 g. of α-IIIa in 3 ml. of methanol was allowed to stand at room temperature for 2 weeks. The solution was distilled *in vacuo* to give 0.8 g. of ester which, according to its infrared spectrum and other physical properties and the melting points of its methiodide and picrate salts, was identical with pure α-IIIa.

3β-Hydroxy-3α-hydroxymethyltropane (IV). In a flask equipped with a stirrer and a Soxhlet extractor was placed 8.0 g. of lithium aluminum hydride and 500 ml. of ether. As the mixture was stirred and refluxed 28.2 g. of α-ecgonine methyl ester was washed from the Soxhlet thimble into the reaction flask. After the mixture was stirred and refluxed for 2 hr. it was decomposed by the gradual addition of first 16 ml. of water and then 12.8 ml. of 10% sodium hydroxide solution. The mixture was stirred for 2 hr., filtered, and the cake of inorganic solid was extracted thoroughly with chloroform. On removal of the solvents from the combined ether and chloroform solutions, 17.7 g. (79%) of white solid, m.p. 114–116°, was obtained. The analytical sample, obtained by sublimation of the product at 80° (0.5 mm.), melted at 115.5–116.5°.

Anal. Calcd. for $C_9H_{17}NO_2$: C, 63.12; H, 10.01; N, 8.18. Found: C, 63.10; H, 9.89; N, 8.39.

Tropane-3β-carboxaldehyde (V). A solution of 17.0 g. of the diol IV in 45 ml. of 85% phosphoric acid was heated at reflux temperature for 5.5 hr. The reaction mixture was made alkaline by addition of potassium carbonate solution and was continuously extracted with chloroform. Distillation of the extract (dried over sodium sulfate) gave 7.9 g. (57%) of colorless oil, b.p. 71–80° (1.5 mm.). The product on standing slowly changed into a very viscous gum.

The aldehyde was also obtained by heating a solution of 3.4 g. of diol in 10 ml. of 18*N* sulfuric acid at reflux temperature for 5 hr. (42% yield), and by allowing a solution of 3.4 g. of the diol in 10 ml. of concd. sulfuric acid to stand overnight at room temperature (35% yield).

The *picrate* was prepared in ether solution.

The *2,4-dinitrophenylhydrazone* was prepared according to Shriner and Fuson.[30] The first crop of crystals that separated from the mixture of the aldehyde and the 2,4-dinitrophenylhydrazine reagent melted at 177.5° dec. after recrystallization from ethanol. Analytical data on this material were in fair agreement with a formula for a mixed sulfate salt of tropane-3β-carboxaldehyde 2,4-dinitrophenylhydrazone and 2,4-dinitrophenylhydrazine.

Anal. Calcd. for $C_{21}H_{25}N_9O_8 \cdot H_2SO_4$: C, 40.06; H, 4.32; N, 20.02. Found: C, 40.81; H, 4.74; N, 19.85.

From the filtrate of the mixed salt the sulfate of the aldehyde hydrazone separated as yellow crystals which, after recrystallization from ethanol, melted at 201° dec.

Anal. Calcd. for $C_{15}H_{19}N_5O_4 \cdot H_2SO_4$: C, 41.76; H, 4.91. Found: C, 41.26; H, 5.18.

The sulfate salt, m.p. 201°, was also obtained by recrystallization of the mixed salt, m.p. 177.5°, from dilute alcohol containing a small amount of sulfuric acid.

When, in the process of recrystallizing the sulfate, m.p. 201°, the solution of the salt in absolute ethanol was boiled and concentrated inadvertently over a prolonged period of time, the salt obtained was not the original sulfate but the ethyl sulfate of the hydrazone, m.p. 176.5–177°.

Anal. Calcd. for $C_{15}H_{19}N_5O_4 \cdot C_2H_5OSO_3H$: C, 44.43; H, 5.49; N, 15.25. Found: C, 44.47; H, 5.78; N, 15.07.

The same *picrate* of the hydrazone was obtained from each of the salts described above *via* the free base. After recrystallization from acetone–ethanol it melted at 252° dec.

Anal. Calcd. for $C_{15}H_{19}N_5O_4 \cdot C_6H_3N_3O_7$: C, 44.84; H, 3.94; N, 19.92. Found: C, 44.68; H, 4.18; N, 19.98.

Oxidation of tropane-3β-carboxaldehyde (V) *to tropane-3β-carboxylic acid* (β-IIIb). To a stirred suspension of silver oxide (prepared from 0.08 mole of silver nitrate) in 300 ml. of water heated on a steam bath, 3.03 g. (0.02 mole) of freshly prepared aldehyde V was added. After a 5-hr. period of heating and stirring the mixture was filtered, and the filter cake was washed with hot water. Upon evaporation of the filtrates to dryness and recrystallization of the residue from methanol–ether, 2.56 g. (75%) of tropane acid was obtained. The product was identical with tropane-3β-carboxylic acid (β-IIIb) prepared by the procedures described above.

Tropane-3β-carboxaldehyde (V) *and* Δ²*-tropidine-3-methanol* (VII) *from reduction of methyl* Δ²*-tropidene-3-carboxylate* (IIa) *with lithium aluminum hydride.* A solution of 21.0 g. (0.116 mole) of unsaturated ester IIa in 190 ml. of ether was added to a stirred mixture of 8.8 g. (0.232 mole) of lithium hydride in 400 ml. of ether at such a rate that steady reflux of the solvent was maintained. A white precipitate rapidly formed as the ester was added. After the addition period (15 min.) the mixture was stirred at reflux temperature for 2.5 hr. and then was allowed to stand overnight. Excess lithium aluminum hydride was decomposed by addition of ethyl acetate and the resulting mixture was hydrolyzed by gradual addition with stirring of 16.7 ml. of water. The solid inorganic material was removed by filtration and washed thoroughly with ether. From the ether filtrates (dried over potassium carbonate) was obtained 14.4 g. of orange oil. Fractional distillation of the crude product through a 6-in. Vigreux column gave the following fractions: (1) 4.0 g. (23%) of mobile colorless liquid, b.p. 105–108° (11 mm.) n^{23}_D 1.5013; (2) 0.72 g. of a mixture distilling over a range of 108–140° (11 mm.), n^{23}_D 1.5089; (3) 7.3 g. of a viscous oil, b.p. 140–142.5° (11 mm.), n^{23}_D 1.5199.

The infrared spectrum (natural film) of fraction 1 showed peaks at 3.68 μ (C—H) and 5.78 μ (C=O) characteristic of aldehydes. The position of the carbonyl band and the absence of a peak in the 6.1 μ region (C=C) indicated that the compound was not an α,β-unsaturated aldehyde. That this fraction was chiefly tropane-3β-carboxaldehyde was demonstrated by the fact that it formed derivatives identical with those obtained from the product of rearrangement of the diol and by its conversion to tropane-3β-carboxylic acid by silver oxide oxidation.

Fraction 3 was shown to be unsaturated alcohol VII by the fact that upon catalytic hydrogenation it absorbed one mole equivalent of hydrogen to yield mainly 3α-hydroxymethyltropane (α-VI) (see below).

The *picrate,* prepared in ether solution and recrystallized from ethanol, melted at 209.5° dec.

Anal. Calcd. for $C_{10}H_{18}N_4O_8$: C, 47.12; H, 4.75; N, 14.66. Found: C, 46.92; H, 4.93; N, 14.80.

The *methiodide,* prepared in acetone, melted at 288° dec. after recrystallization from ethanol.

Anal. Calcd. for $C_{10}H_{18}NOI$: C, 40.69; H, 6.15; N, 4.75. Found: C, 40.75; H, 6.05; N, 4.72.

3α-Hydroxymethyltropane (α-VI). A. Ester α-IIIa (3.7 g.; 0.02 mole) was reduced with lithium aluminum hydride (0.8 g.) under the conditions described for reduction of unsaturated ester IIa to give 3.0 g. (97%) of colorless crystalline product. After recrystallization from ether the amino alcohol melted at 75–76°.

The *picrate* was prepared in ether and the *methiodide* in acetone.

B. Unsaturated alcohol VII (1.7 g.; 0.013 mole) in 15 ml. of ethanol was hydrogenated over platinum oxide catalyst (0.2 g.) at an initial pressure of 60 p.s.i. One mole equivalent of hydrogen was absorbed. Upon removal of the catalyst and solvent, 1.5 g. of white crystalline solid, m.p. 69–72°, was obtained. After two recrystallizations from ether the material melted at 74–76°. The picrate and methiodide of the product were identical with the corresponding salts of the alcohol prepared from ester α-IIIa.

3β-Hydroxymethyltropane (β-VI). A. Lithium aluminum hydride reduction of acid β-IIIb under conditions used in reducing the α isomer gave the β-amino alcohol, b.p. 90–95° (1 mm.). The colorless oil crystallized as a hygroscopic solid.

The *picrate* was prepared in ether and the *methiodide* in methanol.

B. Tropane-3β-carboxaldehyde (V) (0.8 g.) in 15 ml. of ethanol was hydrogenated over platinum oxide catalyst (0.15 g.) at an initial pressure of 50 p.s.i. One mole equivalent of hydrogen was absorbed. The product (0.5 g.) was a colorless oil, b.p. 86° (0.5 mm.), which formed salts identical with those of β-VI described above.

3α-Chloromethyltropane (α-VIII). Thionyl chloride (22 g., 0.17 mole) was added slowly to a stirred solution of 13 g. (0.084 mole) of amino alcohol α-VI in 50 ml. of chloroform, and the resulting mixture was heated at reflux temperature for 2 hr. Upon removal of solvent and thionyl chloride *in vacuo* and recrystallization of the residue from ethanol–ether (charcoal), 12 g. (69%) of tan solid was obtained. Recrystallization of this material from acetone gave the pure hydrochloride of α-VIII as colorless crystals, m.p. 168.5–169°.

The *picrate* was prepared by adding the hydrochloride to a saturated solution of picric acid in ethanol.

The chloroamine α-VIII liberated from its hydrochloride was a colorless oil which distilled without change. The picrate formed by the base was identical with that obtained from the hydrochloride salt.

3β-Chloromethyltropane (β-VIII). To a stirred solution of 0.83 g. of 3β-hydroxymethyltropane (β-VI) in benzene, 0.7 g. of thionyl chloride was added slowly. The reaction mixture was stirred at room temperature for 18 hr. and then evaporated to dryness *in vacuo.* Upon recrystallization of the residue from ethanol–ether the hydrochloride of β-VIII, m.p. 155–157.5°, was obtained.

The *picrate* of β-VIII was prepared by adding the hydrochloride to a saturated aqueous solution of picric acid.

Cyclic quaternary ammonium salt IX *from 3β-chloromethyl-*

(30) R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," Third Edition, John Wiley and Sons, Inc., New York, 1948, p. 171.

tropane (β-VIII). A. A mixture of 0.25 g. of the hydrochloride of β-VIII, 0.2 g. of anhydrous sodium carbonate and 25 ml. of ethanol was stirred and heated at reflux temperature for 2.5 hr. The inorganic salts were removed by filtration, and the filtrate was concentrated until crystals separated. The mixture was filtered, the filtrate was evaporated to dryness, and the residue was recrystallized from ethanol–ether. The salt obtained, 0.15 g. (73%), was an extremely hygroscopic, colorless solid which decomposed between 400–450°.

B. The hydrochloride of β-VIII (0.74 g.) was heated at 200° for 30 min. During this period hydrogen chloride was evolved and the melt crystallized. The product was identical with the quaternary ammonium chloride prepared by procedure A.

The *picrate* was prepared by adding IX to a saturated aqueous solution of picric acid; after recrystallization from water it melted at 345° dec. The salt gave a negative Beilstein test for halogen.

Anal. Calcd. for $C_9H_{16}N \cdot C_6H_2N_3O_7$: C, 49.18; H, 4.95; N, 15.30. Found: C, 49.30; H, 5.07; N, 15.35.

The *styphnate*, prepared in the same way and recrystallized from ethanol, melted at 250° dec.

Anal. Calcd. for $C_9H_{16}N \cdot C_6H_2N_3O_8$: C, 47.12; H, 4.75. Found: C, 47.26; H, 4.72.

Anhydroecgonine methyl ester (Xc). Anhydroecgonine (Xa) has been prepared by dehydration of ecgonine with phosphorus oxychloride[31] or hydrochloric acid.[15] Our preparation of Xa is based on the observation of de Jong[15] that cocaine and ecgonine, when treated with hydrochloric acid under similar conditions, yield about the same amount of the unsaturated acid.

A solution of 15.6 g. (0.046 mole) of cocaine hydrochloride in 125 ml. of 37% hydrochloric acid was refluxed for 17 hr. After the mixture was cooled in a refrigerator, the benzoic acid was collected and washed with a few milliliters of cold 37% hydrochloric acid. The benzoic acid weighed 5.3 g. (95%). The filtrate was evaporated to dryness and the white solid residue was triturated with several portions of ether to remove traces of benzoic acid. After drying *in vacuo* at 100° the crude anhydroecogonine hydrochloride, m.p. 233° (lit.,[31] m.p. 241°), weighed 8.8 g. (94%). The amino acid hydrochloride was dissolved in 200 ml. of methanol saturated with hydrogen chloride and the solution was allowed to stand at room temperature for 4 days. Upon evaporation of the solution *in vacuo*, treatment of the residue with alkali, and extraction of the mixture with ether, 5.2 g. (67%) of the methyl ester was obtained; b.p. 135–137° (23 mm.) (lit.,[32] b.p. 107° (7 mm.), $n^{24.5}_D$ 1.4996. The chloroaurate melted at 157° (lit.,[32] m.p. 152–153°).

The infrared spectrum (natural film) of Xc showed peaks at 5.82 (conjugated C=O) and 6.10 μ (conjugated C=C).

Methyl tropane-2β-carboxylate (β-XIc). The unsaturated ester Xc (3.5 g.) in methanol was hydrogenated over Raney nickel at 60 p.s.i. initial pressure to give 2.8 g. (80%) of colorless oil, b.p. 136–140° (31 mm.).

The spectrum of the product (natural film) showed a carbonyl peak at 5.75 μ (unconjugated C=O) and no absorption in the 6.1 μ region (C=C).

Treatment of the ester mixture in ether with hydrogen chloride gave a crude hydrochloride melting at 156–165°. Upon fractional crystallization of 2.2 g. of the salt from acetone, 1.6 g. of the hydrochloride of the β ester XIc was obtained as transparent prisms, m.p. 165–166°. The salt was hygroscopic and sublimed during an attempt to dry it *in vacuo* for analysis.

Methyl tropane-2β-carboxylate, liberated from its salt, distilled at 129–130° (21 mm.); $n^{25.5}_D$ 1.4791.

The *picrate*, prepared in ether sclution and recrystallized from ethanol, melted at 125–126°.

Anal. Calcd. for $C_{16}H_{20}N_4O_9$: C, 46.60; H, 4.89. Found: C, 46.47; H, 5.19.

The *methiodide*, prepared in acetone and recrystallized from ethanol–ether, melted at 232–233° dec.

Anal. Calcd. for $C_{11}H_{20}NO_2I$: C, 40.63; H, 6.20. Found: C, 40.65; H, 6.40.

The methyl ester was converted to the ethyl ester by allowing a solution of β-XIc in absolute ethanol saturated with hydrogen chloride to stand at room temperature for 3 days. Upon evaporation of the solution to dryness *in vacuo* the hydrochloride of the β-ethyl ester XIb was obtained as hygroscopic colorless crystals.

By addition of the salt to an aqueous solution of auric chloride the chloroaurate of ethyl ether β-XIb was obtained, m.p. 177–181° (lit.,[10] m.p. 177.5–181°).

The *picrate* of β-XIb, formed from the hydrochloride in saturated aqueous picric acid solution and recrystallized from ethanol, melted at 113.5° (lit.,[10] m.p. 113–114.5°).

Anal. Calcd. for $C_{17}H_{22}N_4O_9$: C, 47.89; H, 5.20. Found: C, 47.93; H, 5.14.

Tropane-2β-carboxylic acid (β-XIa). A solution of methyl ester β-XIc in water was heated at 90–95° for several hours and then evaporated to dryness *in vacuo*. The amino acid, m.p. 203–205°, was obtained in 90% yield. After recrystallization from isopropyl alcohol it melted at 203.5–205°. The analytical sample was dried at 100° *in vacuo* and then allowed to equilibrate with air.

Anal. Calcd. for $C_9H_{15}NO_2 \cdot H_2O$: C, 57.73; H, 9.15. Found: C, 57.60; H, 9.00.

The same acid was obtained by allowing an aqueous solution of β-XIc to stand at room temperature for several days (see below).

That isomerization had not occurred during hydrolysis was shown by the fact that the ethyl ester prepared by Fischer esterification of the amino acid gave chloroaurate and picrate salts identical with those of the ethyl ester obtained by transesterification of methyl ester β-XIc.

Epimerization of tropane-2β-carboxylic acid to tropane-2α-carboxylic acid (α-XIa). To a refluxing solution of 1.7 g. of tropane 2β-carboxylic acid in 20 ml. of dry 1-pentanol was added in several pieces 1.7 g. of sodium. The mixture was heated at reflux temperature overnight. To the cool solution was added 20 ml. of 20% hydrochloric acid and an equal volume of water. The pentanol layer was separated, the aqueous phase was evaporated to dryness, and the solid residue was extracted with several portions of ethanol. Upon evaporation of the ethanol extracts the crude amino acid hydrochloride was obtained. This material was converted to the methyl ester by the Fischer method. The ester, 0.8 g., distilled at 125–128° (25 mm.).

Upon hydrolysis of the ester (400 mg.) with hot water as described above for the 2β ester, 335 mg. of amino acid mixture was obtained as a hygroscopic white crystalline solid. Sublimation of the product (312 mg.) at 95° (0.5 mm.), conditions under which the β acid does not sublime, gave 257 mg. (82%) of tropane-2α-carboxylic acid as white, hygroscopic crystals which melted over a range starting at 150° (Willstätter[12] reported that the anhydrous acid melted at 200°). A residue of 54 mg. (17%) of the β acid remained after the sublimation of α-XIa.

The sublimed acid was converted to its methyl ester α-XIc by treatment with excess diazomethane in methylene chloride solution. The ester formed oily hydrochloride and picrate salts but gave a crystalline *methiodide* which melted at 182–183° after recrystallization from ethanol.

Anal. Calcd. for $C_{11}H_{20}NO_2I$: C, 40.63; H, 6.20. Found: C, 40.75; H, 6.04.

A solution of methyl ester α-XIc in anhydrous ethanol saturated with hydrogen chloride was allowed to stand at room temperature for 4 days. Upon evaporation of the solution to dryness *in vacuo* the crude hydrochloride of

(31) A. Einhorn, *Ber.*, **20**, 1221 (1887).

(32) J. R. Matchett and J. Levine, *J. Am. Chem. Soc.*, 63, 2444 (1941).

ethyl ester α-XIb was obtained as a gum. The picrate of α-XIb, prepared by addition of the hydrochloride to an aqueous picric acid solution, was an oil as reported.[10,12] The chloroaurate, formed by addition of an aqueous solution of auric chloride to an aqueous solution of α-XIb hydrochloride, melted at 121–122° after recrystallization from ethanol (lit., m.p. 122°,[12] 122.5°[10]).

Attempted epimerization of methyl tropane-2β-carboxylate (β-XIc). A solution of 2.8 g. of ester β-XIc and 0.3 g. of sodium methoxide in 15 ml. of methanol was heated at reflux overnight. The solvent was removed *in vacuo*, and the residue was extracted with ether. The ether insoluble material containing sodium methoxide weighed 0.6 g. Upon distillation of the ether solution, 2.0 g. of ester, b.p. 125–128° (24 mm.), was obtained. The hydrochloride of this material was fractionally crystallized from acetone to give 1.2 g. of the starting ester salt. From the mother liquors was obtained 1.2 g. of an oily mixture of salts from which the epimeric ester α-XIc could not be isolated.

Hydrolysis of esters α-IIIa, β-IIIa, α-XIc, *and* β-XIc *in aqueous solution at room temperature.* The data in Table II were obtained by the following procedure. All samples of esters were pure except the sample of α-XIc which contained 10–20% of its epimer.

A drop (15.0–25.0 mg.) of ester was weighed in a vial and a drop of distilled water (*p*H 6.0) was added. The vial was stoppered and the clear solution was allowed to stand at room temperature for the prescribed period of time. The vial was then placed in a drying pistol charged with phosphorus pentoxide and the solution evaporated at room temperature under 0.5 mm. pressure. (In preliminary experiments using freshly prepared solutions of the esters, it was shown by observation of the weight loss of the contents of the vial at various intervals of time that practically all of the water was removed after 15 min. leaving a film of ester on the wall of the vial. After drying for an additional 1.5 hr. all of the ester was evaporated.) After 2 hr. the pistol was heated and the amino acid residue was dried to constant weight. Acids α-IIIb, β-IIIb, and β-XIa were dried at 100° and acid α-XIa, which sublimed at this temperature, was dried at 60°. The yields of acids given in Table II are based on the amount of amino acid remaining in the vial after drying to constant weight.

PHILADELPHIA, PA.
LOS ANGELES, CALIF.

[CONTRIBUTION FROM THE RESEARCH AND DEVELOPMENT DIVISION, SMITH KLINE AND FRENCH LABORATORIES]

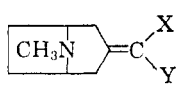
3-Substituted Tropane Derivatives. II. The Synthesis of 3α- and 3β-Tropaneacetic Acids, 3-(3α-Tropanyl)propionic Acid, and Related Compounds[1]

CHARLES L. ZIRKLE, ELVIN L. ANDERSON, FRED R. GERNS, ZENA K. INDIK, AND ALEX M. PAVLOFF

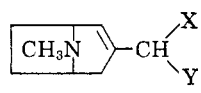
Received October 5, 1961

3α-Tropaneacetic and 3-(3α-tropanyl)propionic acids, and related compounds, were prepared from the products of the condensation of tropinone with malononitrile or ethyl cyanoacetate. The ethyl ester of 3β-tropaneacetic acid was obtained from tropane-3β-carboxylic acid by the Arndt-Eistert method.

In addition to the isomeric tropane-3-carboxylic acids, described in the preceding paper,[1] we prepared higher homologs of these acids as intermediates for the synthesis of new 3-substituted tropane derivatives of potential pharmacological interest,[2,3] This article reports the synthesis of 3α- and 3β-tropaneacetic acids (Vb and VIb), 3-(3α-tropanyl)propionic acid (Vg), and related compounds.

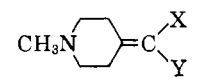


I

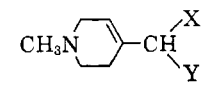


II

a. X = CN, Y = CN
b. X = CO_2H, Y = H
c. X = $CO_2C_2H_5$, Y = H
d. X = CN, Y = $CO_2C_2H_5$
e. X = CN, Y = CO_2H
f. X = CN, Y = H

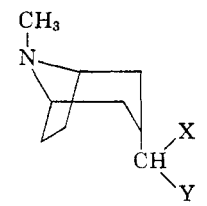


III

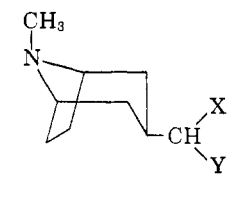


IV

a. X = CN, Y = $CO_2C_2H_5$
b. X = CN, Y = CN
c. X = CO_2H, Y = H



V



VI

a. X = $CO_2C_2H_5$, Y = CN
b. X = CO_2H, Y = H
c. X = $CO_2C_2H_5$, Y = H
d. X = CH_2OH, Y = H
e. X = CH_2Cl, Y = H
f. X = CH_2CN, Y = H
g. X = CH_2CO_2H, Y = H
h. X = $CH_2CO_2C_2H_5$, Y = H

(1) Paper I of this series: C. L. Zirkle, T. A. Geissman, M. Bloom, P. N. Craig, F. R. Gerns, Z. K. Indik, and A. M. Pavloff, *J. Org. Chem.*, 27, 1269 (1962).

(2) Paper III of this series: C. L. Zirkle, E. L. Anderson, P. N. Craig, F. R. Gerns, Z. K. Indik, and A. M. Pavloff, *J. Med. Pharm. Chem.*, 5, 341 (1962).

(3) A preliminary account of part of this work has been presented elsewhere (C. L. Zirkle, P. N. Craig, T. A. Geissman, and M. Bloom, Congr. Handbook, Vol. II, *16th Intern. Conar. Pure and Appl. Chemistry*, Paris, July 1957, p. 153).