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Camphoramic Acids, Aminoalkanols, and Spirocamphidinium Salts

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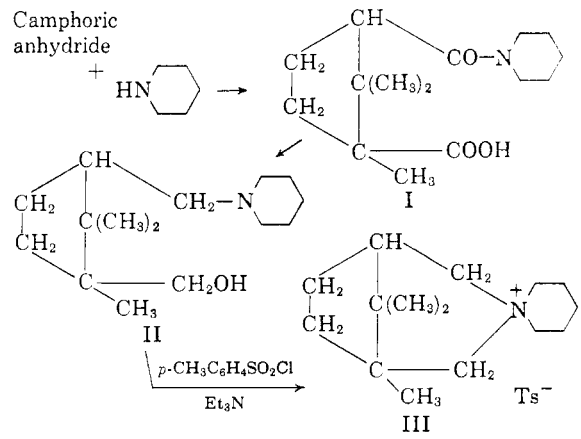
The reaction of amines with camphoric anhydride gave excellent yields of camphoramic acids. The aminoalkanols obtained on reduction, when treated with *p*-toluenesulfonyl chloride in triethylamine, were readily cyclized to camphidinium salts.

Rice and Grogan[2] have made extensive studies of the syntheses of a variety of azabicyclo systems. Among these, the preparation of camphidinium compounds has been carried out via camphorimides. Recently, Steck and Brundage[3] have prepared similar substituted camphidines through direct alkylation of the camphidine base. The scope of these procedures is limited by the nature of the alkylation reactions.

In our earlier studies[4] of the preparation of 3-azabicyclo[3.1.0]hexane - 3 - azaspiro quaternary salts we had encountered an extremely facile and specific ring closure from *cis*-substituted cyclopropanes. It seemed of interest to continue this approach with *cis*-1,3-substituted cyclopentanes, at once to ascertain if ease of cyclization was comparable, and to prepare azaspiro camphidinium salts such as III, not readily accessible by simple alkylation. An example of this consequent route is shown below.



The reaction of *d* or *dl*-camphoric anhydride with secondary aliphatic and alicyclic amines at their reflux temperatures for two to three hours gave excellent yields of *N*-substituted camphoramic acids (Table I). These were reduced with lithium aluminum hydride to the aminoalkanols (Table II) and crystallized from ether-pentane mixtures.

With benzylamine, at its reflux temperature, the reaction of *d*- or *dl*-camphoric anhydride gave a mixture of the amido acid and the corresponding camphorimide. However, when the reaction mixture

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(2) L. M. Rice and C. H. Grogan, *J. Org. Chem.*, 24, 7 (1959); 22, 185 (1957).

(3) E. A. Steck and R. P. Brundage, *J. Org. Chem.*, 24, 2021 (1959).

(4) R. Baltzly, N. B. Mehta, P. B. Russell, R. E. Brooks, E. M. Grivsky, and A. M. Steinberg, *J. Org. Chem.*, 27, 213 (1962).

TABLE I

N-SUBSTITUTED CAMPHORAMIC ACIDS[a]

No.	R, N, R′	M.P.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Isomer
1	$(CH_3)_2N$[b]	191	$C_{12}H_{21}NO_3$	63.4	63.7	9.3	9.0	*d*
2	$(CH_2)_4N$[c]	220	$C_{14}H_{23}NO_3$	66.4	66.5	9.1	9.0	*d*
3	$(C_2H_5)_2N$	174	$C_{14}H_{25}NO_3$	65.9	66.3	9.8	9.68	*d*
4	$(CH_2)_5N$[d]	220	$C_{15}H_{25}NO_3$	64.98	65.08	9.02	8.98	*d*
5	$(CH_2)_5N$[d]	190	$C_{15}H_{25}NO_3$	64.98	64.83	9.02	8.97	*dl*
6	$CH_3N(CH_2)_4N$[e]	217	$C_{15}H_{26}N_2O_3$	64.05	63.6	9.29	8.80	*d*
7	$CH_3N(CH_2)_4N$[e]	198	$C_{15}H_{26}N_2O_3$	64.05	64.0	9.29	9.2	*dl*
8	C_6H_5NH	200	$C_{16}H_{21}NO_3$	69.8	70.1	7.6	7.6	*d*
9	$C_2H_5N(CH_2)_4N$[f]	223	$C_{16}H_{28}N_2O_3$	64.9	65.02	9.46	9.39	*d*
10	$(n\text{-}C_3H_7)_2N$	174	$C_{16}H_{29}NO_3$	67.8	67.9	10.2	10.3	*d*
11	$C_6H_5CH_2NH$	150	$C_{17}H_{23}NO_3$	70.6	70.8	7.96	7.9	*d*
12	$C_6H_5CH_2NCH_3$	122	$C_{18}H_{25}NO_3$	71.4	71.4	8.3	8.4	*d*

[a] Crystallized from hot benzene. [b] Reported by K. Auwers and H. Schnell, *Ber.*, 26, 1517 (1893), m.p. 186–187°. [c] Pyrrolidino. [d] Piperidino. [e] 4-Methyl-1-piperazinyl. [f] 4-Ethyl-1-piperazinyl.

was heated for three hours below 100°, the amido acid was the sole product of the reaction.

The aminoalkanols were characterized as hydrochlorides (Table II) and quaternary salts (Table III). Acylation of the aminoalkanol hydrochlorides with acid chlorides in nitromethane at room temperature gave pure crystalline ester hydrochlorides in quantitative yields (Table IV).

When the tertiary aminoalkanols were warmed with *p*-toluenesulfonyl chloride, preferably in solution in triethylamine, the azaspirocamphidinium tosylates were formed in excellent yields. No tosyl esters of the amino alkanols were isolated. The ease of formation of the new six-membered ring suggests the extreme proximity of the unshared pair of electrons of the tertiary amino group to the hydroxyl-bearing carbon atom.

Optical rotations. Specific and molecular rotations were determined on *d* isomers of a number of examples in each class of compounds. Within these classes molecular rotations were fairly constant (variations within 2% are probably not significant). The amido acids (1, 3) had relatively low rotations while the amino alcohols (13,15,16,18,21,22, and 24), their esters (41,44), the quaternary salt (36), and the spiroquaternary salt (49) all showed molar rotations of 12–15,000°. The somewhat higher value shown by the anilino derivative (20) can be rationalized on the basis that considerable amounts of free base were present. In agreement with that, the free base of 16 has a considerably higher specific rotation. The methylpiperazino spiroquaternary salt (50) has a markedly lower rotation for which no obvious interpretation is apparent.

EXPERIMENTAL[5]

d-1,5,5-Trimethylcyclopentane-1,4-dicarboxylic acid-4-monopiperidide (compound 4). Ten grams (0.056 mole) of *d*-camphoric anhydride dissolved in an excess of freshly distilled piperidine was refluxed for 4 hr. The excess amine was removed *in vacuo* over a steam bath. The product was dissolved in 5% sodium hydroxide solution and filtered. On acidifying the reaction mixture, a white precipitate was obtained. It was twice crystallized from boiling benzene to give 13.8 g., of long hard needles in 95% yield, m.p. 220–221°.

Others in the series shown in Table I except compound 1 were prepared by the same procedure. For the volatile dimethylamine the following modification was employed.

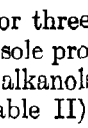
d-1,5,5-Trimethylcyclopentane-1,4-dicarboxylic acid monodimethyl amide (compound 1). To 10 g. (0.056 mole) of *d*-camphoric anhydride in 50 ml. of dry benzene in a pressure bottle 20 ml. of 30% dimethylamine in ether was added. The solution was kept at 40–45° for 12 hr., when a crystalline solid separated. The solvents and the excess amine were removed under reduced pressure and the product, 12 g., was crystallized from benzene, m.p. 191–192°.

d-1,5,5-Trimethyl-1-hydroxymethyl-4-piperidinomethylcyclopentane (compound 16). To a rapidly stirred solution of 10 g. (0.25 mole) of lithium aluminum hydride in 1 l. of anhydrous ether, 14 g. (0.052 mole) of the solid amido acid, compound 4, was added portionwise from an addition

(5) All melting points are uncorrected.

TABLE II

1,5,5-TRIMETHYL-1-HYDROXYMETHYL-3-AMINOMETHYLCYCLOPENTANES

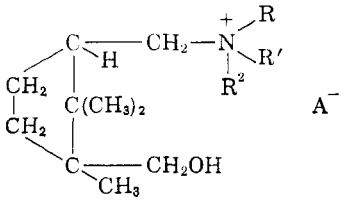


No.	R′	Isomer	Amino Alcohols M.P.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Hydrochlorides M.P.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
13	$(CH_3)_2N$	*d*	63	$C_{12}H_{25}NO$	72.4	72.3	12.5	12.3	267	$C_{12}H_{25}NO\cdot HCl$	61.1	61.0	10.3	10.1
14	$(CH_2)_4N^a$	*d*	73	$C_{14}H_{27}NO$	74.6	74.8	12.0	12.1	296 (dec.)	$C_{14}H_{27}NO\cdot HCl$	64.9	64.6	10.9	10.7
15	$(C_2H_5)_2N$	*d*	85	$C_{14}H_{29}NO$	74.1	74.4	12.8	12.7	250	$C_{14}H_{29}NO\cdot HCl$	63.8	64.1	11.4	11.4
16	$(CH_2)_5N^b$	*d*	85–86	$C_{15}H_{29}NO$	75.3	75.3	12.1	12.0	318 (dec.)	$C_{15}H_{29}NO\cdot HCl$	65.3	65.3	10.8	10.6
17	$(CH_2)_5N^b$	*dl*	175	$C_{15}H_{29}NO$	75.3	75.5	12.1	12.3	318–319	$C_{15}H_{29}NO\cdot HCl$	65.3	65.4	10.8	10.8
18	$CH_2N(CH_2)_4N^c$	*d*	86	$C_{15}H_{30}N_2O$	70.9	70.8	11.8	11.7	293	$C_{15}H_{30}N_2O\cdot 2HCl$	55.0	54.7	9.7	9.4
19	$CH_2N(CH_2)_4N^c$	*dl*	83	$C_{15}H_{30}N_2O$	70.9	71.0	11.8	11.7	278 (eff.)	$C_{15}H_{30}N_2O\cdot 2HCl\cdot 3H_2O$	47.3	47.5	9.9	9.7
20	C_6H_5NH	*d*							244	$C_{16}H_{25}NO\cdot HCl$	67.7	67.9	9.1	8.8
21	$C_2H_5N(CH_2)_4N^d$	*d*							303	$C_{16}H_{32}N_2O\cdot 2HCl$	56.3	56.3	10.0	10.0
22	$(n\text{-}C_3H_7)_2N$	*d*							248	$C_{16}H_{33}NO\cdot HCl$	65.8	65.5	11.6	11.5
23	$C_6H_5CH_2NH$	*d*							254–256	$C_{17}H_{27}NO\cdot HCl\cdot H_2O$	64.6	64.6	9.5	9.3
24	$C_6H_5CH_2NCH_3$	*d*							272	$C_{18}H_{29}NO\cdot HCl$	69.3	69.1	9.6	9.8

Footnote symbols *a–d* are defined in Table I as *c–f*, respectively. Chlorine analysis compound 13 salt: Calcd.: 17.8%; Found: 17.5. Dumas nitrogen analyses were obtained for the following compounds: no. 13 salt: Calcd.: 6.0% N; Found: 6.2. No. 21: Calcd.: 8.2% N; Found: 8.4. No. 22: Calcd.: 4.8% N; Found: 4.7. No. 23: Calcd.: 4.4% N; Found: 4.5. No. 24: Calcd.: 4.5% N; Found: 4.4.

TABLE III

QUATERNARY SALTS OF AMINOALKANOLS

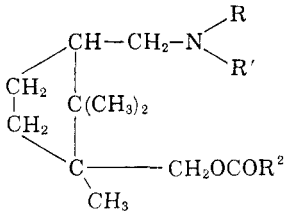


No.	R / N / R′	M.P.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	R^2A	Isomer
33	$(CH_3)_2N$	211	$C_{14}H_{30}NOI$	47.3	47.2	8.4	8.0	EtI	*d*
34	$(CH_2)_4N$[a]	258	$C_{16}H_{32}NOI$	50.4	50.2	8.4	8.3	EtI	*d*
35	$(C_2H_5)_2N$	240	$C_{16}H_{34}NOI$	50.4	50.2	8.8	8.8	EtI	*d*
36	$(CH_2)_5N$[b]	241–242	$C_{17}H_{34}NOI$	51.6	51.5	8.6	8.6	EtI	*d*
37	$(CH_2)_5N$[b]	241	$C_{17}H_{34}NOI$	51.6	51.7	8.6	8.8	EtI	*dl*
38	$C_2H_5N(CH_2)_4N$[d]	250 (dec.)	$C_{18}H_{37}N_2OI$	51.0	51.2	8.7	8.7	EtI	*d*
39	$(n\text{-}C_3H_7)_2N$	229–230 (dec.)	$C_{19}H_{40}NOI$	53.7	53.3	9.4	9.7	C_3H_7I	*d*
40	$(CH_2)_4N$[a]	203	$C_{21}H_{34}NOCl$	71.7	71.7	9.6	9.6	$C_6H_5CH_2Cl$	*d*

Footnote symbols *a–d* are defined in Table I as *c–f*, respectively. Dumas nitrogen analyses: no. 38: Calcd.: 6.6% N; Found: 6.4. No. 39: Calcd.: 3.3% N; Found: 3.7.

TABLE IV

1,5,5-TRIMETHYL-1-ACYLOXYMETHYL-3-AMINOMETHYLCYCLOPENTANES



No.	R / N / R′	M.P.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	R^2	Isomer
41	$(CH_3)_2N$	205 (eff.)	$C_{14}H_{27}NO_2\cdot HCl\cdot 2H_2O$	53.6	53.6	10.2	10.3	CH_3	*d*
42	$(CH_2)_4N$[a]	231	$C_{16}H_{29}NO_2\cdot HCl$	63.4	63.5	9.9	9.8	CH_3	*d*
43	$CH_3N(CH_2)_4N$[c]	290 (eff.)	$C_{17}H_{24}N_2O_2\cdot 2HCl\cdot H_2O$	52.7	52.4	9.3	9.1	CH_3	*d*
44	$(CH_2)_5N$[b]	221	$C_{17}H_{31}NO_2\cdot HCl$	64.2	64.2	10.0	9.8	CH_3	*d*
45	$(n\text{-}C_3H_7)_2N$	184	$C_{18}H_{35}NO_2\cdot HCl$	64.7	64.5	10.8	10.6	CH_3	*d*
46	$(CH_3)_2N$	212	$C_{19}H_{29}NO_2\cdot HCl$	67.2	67.0	8.8	8.7	C_6H_5	*d*
47	$(CH_2)_5N$[b]	205	$C_{22}H_{33}NO_2\cdot HCl$	69.5	69.4	8.9	8.6	C_6H_5	*dl*
48	$CH_3N(CH_2)_4N$[c]	289 (eff.)	$C_{22}H_{34}N_2O_2\cdot 2HCl\cdot 1/2\ H_2O$	60.0	59.7	8.4	8.5	C_6H_5	*d*

Footnote symbols *a–d* are defined in Table I as *c–f*, respectively. Chlorine analysis compound 48: Calcd.: 16.1%; Found: 15.9. Compound 43: Sample heated for 3 hr. at 93° under 0.1 micron pressure. Chlorine: Calcd.: 19.3%; Found: 19.5 for anhydrous salt.

funnel[6] at a rate rapid enough to maintain reflux conditions. After refluxing for 12 hr., it was decomposed by addition of water and then by 10 ml. of 5% sodium hydroxide solution. The clear ethereal extract was dried over potassium carbonate and concentrated. The crystalline product in 85% yield, m.p. 85°, was obtained.

Others in the series, shown in Table II, were prepared by the same procedure. The hydrochlorides of the bases were obtained by the addition of ethanolic hydrogen chloride solution to the dry ethereal solutions of the bases.

(6) N. B. Mehta and J. Zupicich, *Chemist-Analyst*, **50**, 55 (1961).

d-1,5,5-Trimethyl-1-hydroxymethyl-4-piperidinomethylcyclopentane ethiodide (compound 35). To 2 g. of the base, compound 16, dissolved in 50 ml. of ethanol, 10 g. of ethyl iodide was added and the solution refluxed for 1 hr. The solvent was removed *in vacuo* and the residue was dissolved in methanol and decolorized with charcoal. Crystallization from methanol–ethyl acetate gave 2 g. of prisms, m.p. 241–242°.

d-1,5,5-Trimethyl-1-acetoxymethyl-4-piperidinomethylcyclopentane hydrochloride (compound 44). To 2 g. of the amino alcohol hydrochloride (compound 16) dissolved in 25 ml. of nitromethane was added 5 ml. of acetyl chloride. The reaction mixture was placed in a pressure bottle and

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.

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(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]

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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).