197. *Some New Tropine Derivatives.*

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The α-methyltropic esters of tropine and ψ-tropine, together with their methiodides and decamethylene di-iodides, have been prepared. Some new derivatives of α-ecgonine methyl ester have also been made, *viz.*, its hexa- and deca-methylene di-iodides, its benziloyl and *p*-aminobenzoyl esters, and the hexa- and deca-methylene di-iodides of α-cocaine.

(—)-Hyoscyamine salts are readily racemized in solution and consequently atropine is normally used clinically although it is only half as active as (—)-hyoscyamine in most of its pharmacological properties. It was thought that the α-methyltropic esters of tropine and ψ-tropine, the optical isomerides of which should racemize much less readily than the tropic esters, were worthy of pharmacological investigation. The esters were obtained by transesterification of tropine and ψ-tropine with ethyl α-methyltropate; the corresponding methiodides and decamethylene di-iodides were also prepared. The pharmacology of these compounds will be reported elsewhere but preliminary results indicate that both esters and their methiodides possess atropine-like properties, but are less potent than atropine.

α-Methyltropic acid was prepared by the following series of reactions :

$$\mathrm{PhCH_2{\cdot}CN + Et_2CO_3 \xrightarrow{Na} PhCH(CN){\cdot}CO_2Et \xrightarrow{Na + MeI} PhCMe(CN){\cdot}CO_2Et}$$

$$\mathrm{\xrightarrow{H_2\text{-}Ni} PhCMe(CH_2{\cdot}NH_2){\cdot}CO_2Et \xrightarrow{HNO_2} PhCMe(CH_2{\cdot}OH){\cdot}CO_2Et \xrightarrow{Ba(OH)_2} PhCMe(CH_2{\cdot}OH){\cdot}CO_2H.}$$

All stages except the final hydrolysis gave good yields; in the fourth stage the hydrochloride of the amino-ester gave a poor yield (25%), but the neutral sulphate a 65% yield, with sodium nitrite.

Willstätter [1] stated that α-cocaine, which he synthesized from tropinone cyanohydrin, lacked local-anæsthetic properties. This claim, which rested solely upon the absence of a numbing effect when α-cocaine was applied to the tongue, has remained unchallenged for nearly 60 years. We have repeated Willstätter's synthesis and, in collaboration with Dr. Varagić, have shown that α-cocaine is a potent local anæsthetic when injected, but not when applied locally to the eye.[2] We have also prepared the benzilic and *p*-aminobenzoic esters of α-ecgonine methyl ester and the hexa- and deca-methylene di-iodides of α-cocaine and α-ecgonine methyl ester.

Willstätter [1] prepared α-ecgonine methyl ester by esterifying α-ecgonine; better yields are obtained by methanolysis of tropinone cyanohydrin. α-Ecgonine should exist in two stereoisomeric forms corresponding to tropine and ψ-tropine, but conventional methods, including paper chromatography, failed to reveal a second isomer in the product obtained by methanolysis of tropinone cyanohydrin.

Experimental

α-Methyltropic Acid.—Ethyl α-cyano-α-phenylacetate was prepared from benzyl cyanide and diethyl carbonate by the method described by Hessler; [3] the ester (yield, 55%) had b. p. 157°/14 mm. (Hessler reports b. p. 165°/20 mm.). Methylation of its sodio-derivative gave ethyl α-cyano-α-phenylpropionate (yield, 92%), b. p. 140°/10 mm. (Wideqvist [4] gives 133·5°/8 mm.). This ester (100 g.) in ethanol (800 ml.) was hydrogenated in presence of Raney nickel (20 g.) at 60°/75 atm. for 6 hr. After removal of the catalyst and solvent the residue was extracted with 2N-hydrochloric acid, and the acid solution washed with ether and then basified (K_2CO_3); the amino-ester was extracted with ether, dried (K_2CO_3), and fractionated. *Ethyl β-amino-α-methyl-α-phenylpropionate* (yield 70%) had b. p. 128°/3·5 mm., n_D^{20} 1·5123 (Found: C, 69·8; H, 8·3; N, 6·8. $C_{12}H_{17}O_2N$ requires C, 69·6; H, 8·2; N, 6·8%). The

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[1] Willstätter, *Ber.*, 1896, **29**, 2216.

[2] Foster, Ing, and Varagić, *Brit. J. Pharmacol.*, 1955, **10**, 436.

[3] Hessler, *Amer. Chem. J.*, 1904, **32**, 120.

[4] Wideqvist, *Svensk kem. Tidskr.*, 1943, **55**, 125.

amino-ester (50 g.) was dissolved in one equivalent of N-sulphuric acid, and one equivalent of sodium nitrite was added dropwise to the stirred solution at 0°. After 4 hr. the solution was extracted four times with ether, and the extract dried (Na_2SO_4) and evaporated. Fractionation of the residue gave *ethyl α-methyltropate* (yield, 65%), b. p. 110°/2 mm., n_D^{20} 1·4988 (Found: C, 68·9; H, 7·6. $C_{12}H_{16}O_3$ requires C, 69·2; H, 7·6%). A mixture of the ester (12 g.), barium hydroxide octahydrate (80 g.), and water (250 ml.) was boiled under reflux for 6 hr.; the solution was then acidified and extracted three times with chloroform; the extract was dried (Na_2SO_4) and evaporated; the residual oil solidified when scratched, and was recrystallized three times from benzene. *α-Methyltropic acid* forms feathery crystals (yield, 30%; m. p. 98°) easily soluble in cold water (Found: C, 66·7; H, 6·7. $C_{10}H_{12}O_3$ requires C, 66·7; H, 6·7%).

Tropine and ψ-Tropine α-Methyltropates.—Tropine or ψ-tropine (6—8 g.) in xylene (60 ml.) was treated with a solution of sodium methoxide [from sodium (0·12 g.) and methanol (10 ml.)]. The methanol was evaporated on the steam-bath, and ethyl α-methyltropate (10 g.) added. After removal of the xylene under reduced pressure at 90° the residue was heated at 130°/10 mm. for 4 hr. The product was dissolved in chloroform and extracted with N-hydrochloric acid. The free base was liberated by adding excess of potassium carbonate and extraction with chloroform; evaporation of the dried extract gave the free ester as a solid in 70—75% yield. The properties and analyses of the two esters and of their derivatives are given in the Table.

Ester	M. p.	Solvent	Formula	Found, % C	H	N	Reqd., % C	H	N
Tropine α-methyltropate [a]	84°	Petrol (60—80°)	$C_{18}H_{25}O_3N$	71·0	8·1	4·9	71·2	8·2	4·6
,, *perchlorate*	106—107	Dioxan	$C_{18}H_{25}O_3N,HClO_4$	53·6	6·6	—	53·6	6·4	—
,, *methiodide*	234	Ethanol	$C_{19}H_{28}O_3NI$	51·2	6·2	3·0	51·3	6·3	3·1
,, *decamethylene di-iodide* [b]	230	Ethanol	$C_{46}H_{70}O_6N_2I_2,H_2O$	54·2	7·1	2·7	54·2	7·1	2·7
,, *decamethylene dibromide* [c]	220	Petrol (60—80°) Ether–alcohol (7 : 3 v/v)	$C_{46}H_{70}O_6N_2Br_2$	60·6	7·8	3·1	60·9	7·7	3·1
ψ-Tropine α-methyltropate [a]	86·5	Petrol (80—100°)	$C_{18}H_{25}O_3N$	71·3	8·2	4·7	71·2	8·2	4·6
,, *hydrochloride*	213	Propanol	$C_{18}H_{25}O_3N,HCl$	63·7	7·6	4·2	63·6	7·7	4·1
,, *methiodide*	196	Ethanol	$C_{19}H_{28}O_3NI$	50·9	6·1	3·1	51·3	6·3	3·1
,, *decamethylene di-iodide* [b]	231	Ethanol	$C_{46}H_{70}O_6N_2I_2,H_2O$	54·0	7·0	2·9	54·2	7·1	2·7

(*a*) A mixture of the α-methyltropates of tropine and ψ-tropine had m. p. 58—65°.

(*b*) A mixture of the decamethylene di-iodides of tropine and ψ-tropine α-methyltropates had m. p. 220°.

(*c*) Found: Br, 17·6. Requires Br, 17·7%.

α-Ecgonine Derivatives.—Crude tropinone cyanohydrin[5] (100 g.) was washed with methanol (3 × 200 ml.) and covered with anhydrous methanol (1800 ml.). The suspension was stirred, cooled to 0°, and saturated with hydrogen chloride below 4°; after being left at room temperature for 5 days, the solution was boiled under reflux for 1 hr. while a rapid stream of hydrogen chloride was passed through it. The solvent was evaporated, water (200 ml.) and excess of potassium carbonate added, and the product extracted with chloroform. α-Ecgonine methyl ester, crystallized from light petroleum (b. p. 80—100°), had m. p. 114° (Willstätter[1] records m. p. 114°); the yield was 65% on tropinone. The following derivatives were made: *Hexamethylene di-iodide salt,* crystallized from methanol–ethanol (3 : 7 by vol.), m. p. 244° (Found: C, 42·0; H, 6·2; N, 4·0. $C_{26}H_{46}O_6N_2I_2$ requires C, 42·3; H, 6·2; N, 3·8%). *Decamethylene di-iodide salt,* crystallized from ethanol, m. p. 229° (Found: C, 45·5; H, 6·7; N, 3·5. $C_{30}H_{54}O_6N_2I_2$ requires C, 45·5; H, 6·7; N, 3·5%). α-Cocaine, prepared by Willstätter's method;[1] hydrochloride, crystallized from pentyl acetate, m. p. 180° (Found: C, 60·0; H, 6·6; N, 4·1. Calc. for $C_{17}H_{22}O_4NCl$: C, 60·1; H, 6·5; N, 4·1%). *Hexamethylenebis-α-cocainium di-iodide,* crystallized thrice from 90% methanol, m. p. 244° (decomp.) (Found: C, 50·6; H, 5·9; N, 2·8. $C_{40}H_{54}O_8N_2I_2$ requires C, 50·9; H, 5·7; N, 3·0%). *Decamethylenebis-α-cocainium di-iodide,* crystallized twice from ethanol, m. p. 182—185° (Found: C, 52·6; H, 6·3; N, 2·9. $C_{44}H_{62}O_8N_2I_2$ requires C, 52·8; H, 6·2; N, 2·8%). *Benziloyl-α-ecgonine methyl ester* was made by heating α-ecgonine methyl ester (10 g.) with α-chlorodiphenylacetyl chloride (14 g.) in dry

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[5] Willstätter, *Ber.*, 1896, **29**, 1575.

benzene (100 ml.) for 8 hr. Water (100 ml.) and excess of potassium carbonate were added to the cooled product, and the mixture was left overnight in order to effect hydrolysis of the α-chloro-group. The benzilic ester was extracted with chloroform (3 × 50 ml.), the solvents were evaporated, and the residual solid was crystallized from 70% ethanol; the ester (yield 20%) had m. p. 130° (Found: C, 70·2; H, 6·5; N, 3·2. $C_{24}H_{27}O_5N$ requires C, 70·4; H, 6·6; N, 3·4%). The *methiodide*, crystallized from *iso*propyl alcohol, had m. p. 196° (decomp.) (Found: C, 54·2; H, 5·7; N, 2·2. $C_{24}H_{27}O_5N,CH_3I$ requires C, 54·4; H, 5·4; N, 2·5%). p-*Nitrobenzoyl-α-ecgonine methyl ester*, obtained by heating α-ecgonine methyl ester (5 g.) and *p*-nitrobenzoyl chloride (10 g.) at 100° for 2 hr. and then with benzene (50 ml.) for 2 hr., crystallized from ethyl acetate or benzene (yield, 66%) had m. p. 138° (Found: C, 58·3; H, 5·9; N, 8·2. $C_{17}H_{20}O_6N_2$ requires C, 58·6; H, 5·7; N, 8·0%). Catalytic reduction of the nitrobenzoate (4·2 g.) in ethanol over Raney nickel at 3 atm. gave p-*aminobenzoyl-α-ecgonine methyl ester*, which after crystallization from ethanol had m. p. 158·5° (yield, 92%) (Found: C, 64·1; H, 6·9; N, 8·7. $C_{17}H_{22}O_4N_2$ requires C, 63·8; H, 7·0; N, 8·8%).

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