939. *The Preparation of Some Stereospecific Tropane and N-Alkylnortropane Derivatives*

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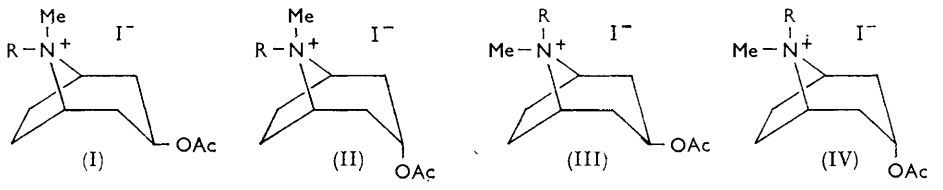
The tropane ring is a rigid structure and thus is a convenient ring system for studies of the effect of stereochemistry on pharmacological activity. As part of a study of the influence of stereochemistry upon enzyme-catalysed hydrolysis of esters it became necessary to prepare a series of stereospecific quaternary ammonium acetate esters. The following compounds were chosen and their preparation is reported here.



a: R = Me; b: R = Et; c: R = Pr^i

Convenient starting materials for such preparations are the parent ketones tropinone, *N*-ethylnortropinone, and *N*-isopropylnortropinone. Commercial tropinone was used and the remaining ketones were prepared by application of the method previously reported

by Elming [1] for the preparation of tropinone. This method, allowing the use of concentrated solutions at elevated temperatures to effect the condensation, is more convenient for the isolation of the product ketone than previously reported methods.[2,3]

Reduction of the ketones by (*a*) sodium in ethanol and (*b*) catalytic hydrogenation gave the *cis*- (equatorial hydroxyl group) and *trans*-isomers (axial hydroxyl group), respectively.[4] The resulting alcohols were separately esterified (using acetic anhydride in pyridine) and quaternised with the appropriate alkylating agent. The alkyl iodide was used except in the preparation of compounds (Ic) and (IIc) when di-isopropyl sulphate was employed and the resulting quaternary salt was then passed through a column of Amberlite IRA-400 (iodide form).

Stereochemistry of the Quaternary Tropane Derivatives.—(*a*) *Configuration at the quaternary nitrogen atom.* The configuration at the ring nitrogen atom in quaternary tropane derivatives has been shown to depend on the sequence in which the individual alkyl groups are introduced.[5-7] The alkyl group which entered last has been shown to enter the equatorial position. Thus, in tropane and in the quaternary tropane derivatives (Ia—c) and (IIa—c) the methyl group has the axial configuration whereas in compounds (IIIb, c) and (IVb, c) it adopts the equatorial configuration.

(*b*) *Stereochemistry of the ester group.* The hydroxyl group in pseudotropine has been shown, by means of infrared-spectral and dipole-moment measurements,[8] to adopt the equatorial conformation, and these results have been confirmed using N ⟶ O acyl migration reactions on norpseudotropine.[4,9] Thus, the acetoxy-group in compounds (Ia—c) and (IIIb, c) will have the equatorial (or β) configuration and this is confirmed by the infrared spectra (liquid film) of the acetate esters prepared in this work. Pesudotropine acetate and the *N*-alkylnorpseudotropine acetates show a sharp absorption peak at 1250 cm.$^{-1}$ (acyl–oxygen stretching vibration) whereas tropine acetate and the *N*-alkylnortropine acetates show broad absorption with maxima in the region 1250—1220 cm.$^{-1}$. This is in accord (though not directly comparable) with the infrared-spectral data reported by Chapman [10] for *cis*- and *trans*-4-t-butylcyclohexyl acetate in carbon tetrachloride solution.

Experimental.—Infrared spectra were determined, for liquid films, using a Unicam S.P. 200 double-beam spectrophotometer.

Acetonedicarboxylic acid was prepared by a known method.[11] Commercial 2,5-diethoxytetrahydrofuran was used [redistilled b. p. 165—167°/757 mm., $\nu_{max.}$ 1720w cm.$^{-1}$ (C=O) due to a trace of free succindialdehyde in the sample]. *N*-Phenyldihydropyridazine had m. p. 187—189° (from ether–chloroform) (lit.,[12] 183—184°) (Found: C, 75·8; H, 6·4. Calc. for $C_{10}H_{10}N_2$: C, 75·9; H, 6·4%).

Preparation of ketones. Commercial tropinone was used. Treatment of 2,5-diethoxytetrahydrofuran with acetonedicarboxylic acid and ethylamine hydrochloride by the method reported by Elming [1] for the preparation of tropinone yielded N-*ethylnortropinone* (72%), b. p. 108—112°/18 mm. $\nu_{max.}$ 1705 cm.$^{-1}$ (C=O) (Found: Equiv., 156·5. $C_9H_{15}NO$ requires Equiv., 153); picrate (from water), m. p. 192° (decomp.) (lit.,[2,13] 184—185°, 190°) (Found: C, 47·1; H, 4·6. Calc. for $C_{15}H_{18}N_4O_8$: C, 47·1; H, 4·7%).

N-*Isopropylnortropinone* (40% yield from 2,5-diethoxytetrahydrofuran, acetonedicarboxylic

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acid, and isopropylamine hydrochloride) had b. p. 117—120°/18 mm. (sets solid on cooling in ice), $\nu_{max.}$ 1705 cm.$^{-1}$ (C=O) (Found: Equiv., 177, unaltered by redistillation. $C_{10}H_{17}NO$ requires Equiv., 167); *picrate* (from water), m. p. 184—185° (Found: C, 48·3; H, 5·0. $C_{16}H_{20}N_4O_8$ requires C, 48·5; H, 5·05%).

N-*Alkylnorpseudotropines*. The following compounds were prepared by reduction of the appropriate ketone with sodium and dry isobutanol in toluene.[4]

Pseudotropine (67%), m. p. 107—107·5° (lit.,[4,14] 106—108°); *N*-ethylnorpseudotropine (46%), m. p. 85—87° (from ether) (lit.,[13] 87°) (Found: C, 69·6; H, 10·7. Calc. for $C_9H_{17}NO$: C, 69·7; H, 10·9%); picrate (from water), m. p. 182—184° (decomp.) (lit.,[13] 190°) (Found: C, 46·9; H, 4·9. Calc. for $C_{15}H_{20}N_4O_8$: C, 46·9; H, 5·2%); *N*-isopropylnorpseudotropine (52%), m. p. 118—119° (from ether) (lit.,[13] 120°) (Found: C, 70·7; H, 11·0. Calc. for $C_{10}H_{19}NO$: C, 71·0; H, 11·2%); *picrate* (from water), m. p. 158—160° (Found: C, 48·1; H, 5·5. $C_{16}H_{22}N_4O_8$ requires C, 48·2; H, 5·5%).

N-*Alkylnortropines*. Commercial tropine was used. *N*-Ethylnortropinone (15 g.) in ethanol (450 ml.), and platinum oxide (0·25 g.) were shaken with hydrogen (20 atm.) to give, after twice recrystallising from acetone–light petroleum (b. p. 40—60°), *N*-ethylnortropine (6·2 g., 41%), m. p. 75—77° (lit.,[5,13] 77—79°, 79°) (Found: C, 69·7; H, 10·9%). Similarly prepared was N-*isopropylnortropine* (39%), m. p. 113—115° (Found: C, 70·8; H, 11·1%).

N-*Alkylnorpseudo- and* N-*alkylnor-tropine acetates*. The appropriate alcohol was treated with acetic anhydride in pyridine following the method reported by Nickon and Fieser.[4] Pseudotropine acetate (70%) had b. p. 118—120°/17 mm., 116°/16 mm. (Found: Equiv., 183. Calc. for $C_{10}H_{17}NO_2$: Equiv., 183), $\nu_{max.}$ 1725 (C=O) and 1245 cm.$^{-1}$ (C–O stretch of acetate). *Tropine acetate* (65%) had b. p. 126—128°/25 mm. (Found: Equiv., 190), $\nu_{max.}$ 1720 (C=O) and 1260—1220 cm.$^{-1}$ (broad triple peak) (C–O); picrate (from water), m. p. 218—219° (lit.,[14] 217°) (Found: C, 46·6; H, 5·0. Calc. for $C_{16}H_{20}N_4O_9$: C, 46·6; H, 4·9%). N-*Ethylnorpseudotropine acetate* (60%) had b. p. 116°/11 mm., $\nu_{max.}$ 1730s (C=O) and 1240s cm.$^{-1}$ (C–O). (Found: Equiv., 196. $C_{11}H_{19}NO_2$ requires Equiv., 197); *picrate* (from water), m. p. 115—117° (Found: C, 47·85; H, 5·2. $C_{17}H_{22}N_4O_9$ requires C, 47·9; H, 5·2%). N-*Ethylnortropine acetate* (87%) had b. p. 100·5—101°/6 mm. $\nu_{max.}$ 1730s (C=O) and 1270—1220 cm.$^{-1}$ (broad triple peak) (C–O) (Found: Equiv., 196); *picrate* (from water), m. p. 189—191° (Found: C, 47·75; H, 5·1%). N-*Isopropylnorpseudotropine acetate* (69%) had b. p. 119—121°/13 mm., $\nu_{max.}$ 1730 (C=O) and 1250s cm.$^{-1}$ (C–O) (Found: Equiv., 208. $C_{12}H_{21}NO_2$ requires Equiv., 211); *picrate* (from water), m. p. 164—165° (Found: C, 48·95; H, 5·4. $C_{18}H_{24}N_4O_9$ requires C, 49·1; H, 5·4%). N-*Isopropylnortropine acetate* (91%), b. p. 120—122°/14 mm. $\nu_{max.}$ 1730 (C=O) and 1260—1220 cm.$^{-1}$ (broad triple peak) (C–O) (Found: Equiv., 211); *picrate* (from water), m. p. 205—207° (Found: C, 49·4; H, 5·6%).

Quaternary ammonium salts. The salts (Table) were prepared by reaction of the appropriate ester with the alkyl iodide and the product recrystallised from absolute ethanol.

Quaternary ammonium salts

Compound	Yield (%)	M. p.	Found (%) C	Found (%) H	Found (%) N	Formula	Required (%) C	Required (%) H	Required (%) N
(Ia)	75	191—192°	40·7	6·1	4·1	$C_{11}H_{20}INO_2$	40·6	6·15	4·3
(IIa)	50	282—283 *	40·4	6·0	4·7	$C_{11}H_{20}INO_2$	40·6 †	6·15 †	4·3 †
(IIIb)	49	199—201	42·6	6·4	3·75	$C_{12}H_{22}INO_2$	42·5	6·5	4·15
(IVb)	87	285—287 ‡	42·3	6·5	4·35	$C_{12}H_{22}INO_2$	42·5	6·5	4·15
(IIIc)	84	274·5—276·5	44·0	6·8	3·8	$C_{13}H_{24}INO_2$	44·1	6·8	4·0
(IVc)	78	294—295 §	44·35	6·8	3·95	$C_{13}H_{24}INO_2$	44·1	6·8	4·0
(Ib)		204—205	42·5	6·4	4·0	$C_{12}H_{22}INO_2$	42·5	6·5	4·15
(IIb)		284—286 ¶	42·2	6·3	4·05	$C_{12}H_{22}INO_2$	42·5	6·5	4·15

* Decomp. (lit.,[14] m. p. 278—280°). Mixed m. p. with compound (Ia) 183—188°. † Calc. ‡ Mixed m. p. with compound (IIIb) 183—210°. § Mixed m. p. with compound (IIIc) 264—268°. ¶ Decomp. Mixed m. p. with compound (Ib) 178—190°.

Pseudotropine acetate isopropiodide (Ic). Pseudotropine acetate (2·5 g.) was dissolved in dry isopropyl alcohol (4 ml.) and di-isopropyl sulphate [(4 ml.); prepared according to the method of Levaillant [15] in 25% yield, b. p. 48—50°/0·3 mm. (lit.,[15] 72—82°/3—4 mm.) n_D^{20} 1·406 (lit.,[15,16]

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1·409, 1·4057 at 25° (Found: C, 39·9; H, 7·9. Calc. for $C_6H_{14}O_4S$: C, 39·6; H, 7·7%)] added. The solution was set aside at room temperature for 4 weeks. The now almost solid reaction mixture was dried under reduced pressure without heat, the residue triturated with ether, and the ether discarded. The residual solid was dissolved in water (25 ml.) and added to a column of Amberlite IRA-400 (iodide form) (250 × 25 mm.) and the column slowly eluted with distilled water until the eluate did not give a positive test for iodide ions (700 ml.). The eluate was concentrated under reduced pressure to leave a gummy residue, the residue triturated with dry acetone and the crystals filtered off. The product was recrystallised three times from absolute ethanol to give a product (0·9 g.), m. p. 287—287·5° (decomp.) (Found: C, 42·9; H, 7·0. Calc. for $C_{13}H_{24}INO_2$: C, 44·1; H, 6·8%. Calc. for $C_{11}H_{22}INO$ (pseudotropine isopropiodide): C, 42·4; H, 7·1%).

The product (0·65 g.) was added to acetic anhydride (8 ml.) and the mixture heated on a steam-bath until the solid had dissolved and then for a further 16 hr. On cooling, the solution crystallised. The product was filtered, washed with ether, dissolved in absolute ethanol (200 ml.), and added to an ion-exchange column of Amberlite IRA-400 (iodide form in absolute ethanol). The column was slowly eluted with absolute ethanol and the eluate (3 l.) collected and evaporated to dryness under reduced pressure without heat to leave a white crystalline product which was twice recrystallised from ethanol, m. p. 251—253° (Found: C, 44·0; H, 6·9; N, 3·6%).

Tropine acetate isopropiodide (IIc). Tropine acetate (3·6 g.) was dissolved in dry isopropyl alcohol (5 ml.) and di-isopropyl sulphate (5 ml.) added. The mixture was set aside at room temperature for 30 days. The almost solid reaction mixture was dried under reduced pressure without heat, the residue triturated with ether, and the ether discarded. The residue was dissolved in water (40 ml.) and added to a column of Amberlite IRA-400 (iodide form) and the column eluted with distilled water until the eluate did not give a positive test for iodide ion (500 ml.). The eluate was evaporated under reduced pressure to a volume of 30 ml. and the solution then freeze-dried to yield a brown crystalline solid. The solid product was recrystallised three times from absolute ethanol and then finally purified by continuous extraction with chloroform to yield pale yellow flaky crystals, m. p. 289—290° (decomp.) (Found: C, 44·6; H, 7·1; N, 3·6%), mixed m. p. with pseudotropine acetate isopropiodide 230—247°.

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