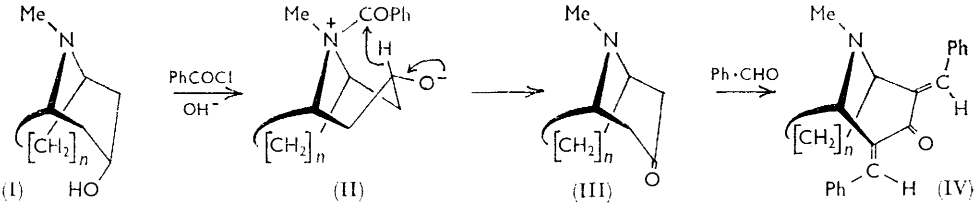
492. *Reactions of Tropine and Related Bases with Acid Chlorides*

By Barabara J. Calvert and J. D. Hobson

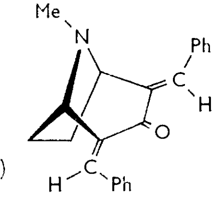
The oxidation of tropine to tropinone by the action of benzoyl chloride and aqueous alkali is described, together with some attempts to observe analogous hydrogen-transfer reactions. These reactions, and the dealkylations which occur under other conditions, are discussed in terms of the reactivity of tertiary *N*-acylammonium cations.

In the course of studies on nitrogen-bridged bicyclic compounds, we observed that appreciable quantities of 2,4-dibenzylidenetropinone (IVa) were formed when tropine (Ia) was merely shaken with benzoyl chloride and aqueous alkali. Our initial observations,[1] together with the results of related experiments, are now reported in greater detail.

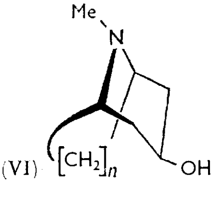
By using a large excess of benzoyl chloride, slowly added to tropine and 4N-sodium hydroxide, yields of the precipitated dienone (IVa) approaching the theoretical 50% (based on tropine) could be achieved. By interruption of the reaction at an early stage it was possible to isolate and characterise the precursors of this product, namely, tropinone (IIIa) and benzaldehyde. Entirely analogous behaviour was displayed by the higher homologue (Ib), which afforded the corresponding 2,4-dibenzylidene-ψ-pelletierine (IVb) under similar conditions, though no effort was made in this case to isolate its immediate precursors.



(I) (II) (III) (IV)

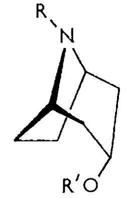


(V)



(VI)

a; $n = 2$ b; $n = 3$



(VII: R = Bz, R′ = H)
(VIII: R = R′ = Bz)
(IX: R = Me, R′ = Bz)

Originally, two isomeric dienones were obtained from the experiments with tropine, evidently a consequence of accidental exposure to light during isolation, since only the higher-melting of the two compounds results from the acid- or base-catalysed condensation of tropinone (IIIa) with benzaldehyde.[2] As expected,[3] irradiation of a benzene solution with ultraviolet light converted each pure compound into a mixture of the two, while the lower-melting form was quantitatively isomerised by dilute acid.

The main features of the nuclear magnetic resonance spectrum * of the higher-melting isomer were signals at 2·22 (singlet, 2 olefinic protons), 2·66 (apparent singlet, 10 aromatic

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* Measured for $CDCl_3$ solution with a Varian A-60 spectrometer; chemical shifts given on the τ scale using tetramethylsilane as internal reference.

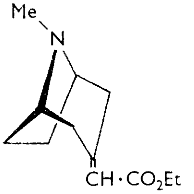
[1] B. J. Calvert and J. D. Hobson, *Proc. Chem. Soc.*, 1962, 19.

[2] (*a*) R. Willstätter, *Ber.*, 1897, **30**, 731, 2679; (*b*) W. A. M. Davies, J. B. Jones, and A. R. Pinder, *J.*, 1960, 3504.

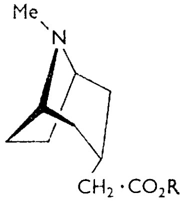
[3] R. E. Lutz and R. H. Jordan, *J. Amer. Chem. Soc.*, 1950, **72**, 4090; G. M. Wyman, *Chem. Rev.*, 1955, **55**, 37.

protons), 5·65 (broad unresolved multiplet, 2 bridgehead protons), and 7·72 (3-proton singlet, *N*-methyl). The spectrum of the lower-melting compound exhibited signals at 2·36—2·85 (10 aromatic and 1 olefinic protons), 3·43 (singlet, 1 olefinic proton), 5·70 and 6·18 (both broad unresolved multiplets, 1 bridgehead proton each), and 7·62 (3-proton singlet, *N*-methyl). Thus, in the latter spectrum, the appearance of one olefinic proton at higher field is accompanied by increased shielding of one bridgehead proton, consistent with the *cis*-orientation of one of the phenyl groups as in compound (V), compared with the symmetrical *trans,trans*-formulation (IVa) for the more stable compound.[4] It is perhaps worthy of note that the deshielding of the bridgehead protons by a *trans*-phenyl group requires that the aromatic nucleus be virtually coplanar with the dienone system.

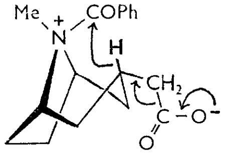
The oxidation–reduction process resulting in the formation of benzaldehyde and ketone is clearly of the Cannizzaro type, involving the transfer of a hydrogen atom complete with bonding electrons, from an alkoxide ion to an acceptor molecule.[5] However, the identity of the latter is less obvious, since the occurrence of such a reaction under simple Schotten–Baumann conditions is apparently without precedent. The presence of benzoylium cations can be excluded under these conditions,[6] as also can the possibility of an intermolecular hydrogen transfer to benzoyl chloride itself, since no products resulting from such a process could be detected in reactions with cyclohexanol or *N*-benzoylnortropine (VII). The fact that ψ-tropine (VIa) and *N*-methylgranatan-3β-ol (VIb) similarly remained unoxidised suggests that the particular relationship of the basic centre to the carbinol grouping present in the epimeric alcohols is a requirement for effective hydrogen transfer. We therefore conclude that in these cases the powerfully electrophilic carbonyl group [7] of the intermediate cation (II) is acting as acceptor, being favourably oriented for transannular capture of the hydride ion in the conformation shown. The transfer of the latter is almost certainly facilitated by prior or concerted removal of a proton from the hydroxyl group, as in other hydrogen-transfer reactions proceeding in strong base.[5]



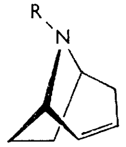
(X)



(XI: R = Et)
(XII: R = H)



(XIII)



(XIV: R = Me)
(XV: R = Bz)

The necessity for a high concentration of negative charge at the hydride source may account for the lack of reactivity of the carboxylic acid (XII). This compound, prepared from tropinone (IIIa) by reaction with the anion derived from diethyl ethoxycarbonylmethylphosphonate,[8] followed by catalytic reduction and hydrolysis of the unsaturated ester (X), might have been expected to undergo oxidative decarboxylation as indicated (XIII), in a type of hydrogen transfer originally suggested as a hypothetical possibility by Jackman.[9] However, no non-acidic material could be isolated from experiments in which the acid (XII) was exposed to prolonged treatment with a large excess of benzoyl chloride and alkali.

Although they have seldom been successfully isolated and characterised,[7] tertiary

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[4] D. N. Kevill, E. D. Weiler, and N. H. Cromwell, *J. Org. Chem.*, 1964, **29**, 1276.

[5] *Inter alia*, R. B. Woodward, N. L. Wendler, and F. J. Brutschy, *J. Amer. Chem. Soc.*, 1945, **67**, 1425; W. von E. Doering and T. C. Aschner, *ibid.*, 1949, **71**, 838; L. M. Jackman, *J.*, 1952, 3252.

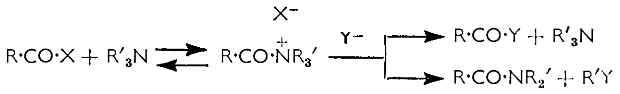
[6] H. K. Hall, *J. Amer. Chem. Soc.*, 1955, **77**, 5993.

[7] F. Klages and E. Zange, *Annalen*, 1957, **607**, 35.

[8] W. S. Wadsworth and W. D. Emmons, *J. Amer. Chem. Soc.*, 1961, **83**, 1733.

[9] L. M. Jackman in " Advances in Organic Chemistry," eds. R. A. Raphael, E. C. Taylor, and H. Wynberg, Interscience, New York, 1960, vol. II, p. 345.

N-acylammonium salts have been implicated as intermediates in many reactions involving acyl derivatives and aliphatic or heterocyclic tertiary bases. Apart from keten-forming eliminations, such species may suffer nucleophilic attack either at carbonyl, as in the tertiary amine-catalysed hydrolysis of esters [10,11] and acid chlorides,[12] or at a substituent alkyl group, in formal analogy with the Von Braun cyanogen bromide reaction: [13-15]



(XVI)

While the hydrogen-transfer reaction described above falls into the first category, the second mode of reaction apparently occurred when tropine and benzoyl chloride were heated together in the absence of solvent; appreciable quantities of *ON*-dibenzoylnortropine (VIII) were formed, in addition to the hydrochloride of the expected ester (IX). Similarly, *N*-benzoylnortropidine (XV) was obtained in low yield from tropidine (XIV). Such dealkylations have only rarely been observed with tertiary bases and benzoyl chloride, and appear to occur most readily in the fission of arylalkyl groups, *e.g.*, in the reported cleavages of nicotine,[13] apomorphine,[14] and *NN*-dimethylbenzylamines.[15] It has often been observed [16] that alkyl chloroformates are particularly effective in this type of cleavage, in spite of additional possible side-reactions; [17] presumably the stabilising effect of an adjacent alkoxyl group on the carbonyl group of the intermediate cation (XVI; R = O-alkyl) has a favourable influence on the pre-equilibrium. Thus, tropinone was smoothly dealkylated with ethyl chloroformate in dichloromethane solution at room temperature, giving *N*-ethoxycarbonylnortropinone in high yield. However, only starting material was recovered from experiments in which tropine was treated with ethyl chloroformate and aqueous alkali; evidently under these conditions neither hydrogen-transfer nor dealkylation is competitive with hydrolysis of the tertiary *N*-acylammonium intermediate.

EXPERIMENTAL

Reaction of Tropine with Benzoyl Chloride and Alkali.—(*a*) To a vigorously stirred solution of tropine (1·41 g., 0·01 mole) in 4N-sodium hydroxide (200 ml.) was slowly added freshly distilled benzoyl chloride (17·5 ml., 0·15 mole) at a rate sufficient to maintain the temperature of the mixture at 45—50°. After the addition (*ca.* 1 hr.), the mixture was shaken for 20 hr. at room temperature, whereafter the yellow precipitate was collected, washed with water, and recrystallised from methanol. Yellow needles, m. p. 153° (lit.,[2a] 153°) of *trans,trans*-2,4-dibenzylidenetropinone (IVa) (1·40 g.), $\lambda_{max.}$ (95% EtOH) 233 and 328 mμ (ε 15,000 and 26,300), $\nu_{max.}$ (Nujol) 1605 and 1666 cm.$^{-1}$ (Found: C, 83·7; H, 6·6; N, 4·6. Calc. for $C_{22}H_{21}NO$: C, 83·8; H, 6·7; N, 4·4%) were obtained, identical with material obtained by the condensation of tropinone and benzaldehyde.[2]

(*b*) Benzoyl chloride (12·5 ml.) was slowly added during 1 hr. to a solution of tropine (5 g.) in 2N-sodium hydroxide (300 ml.) vigorously stirred under nitrogen; the temperature of the mixture did not exceed 40° during the addition. Stirring was continued for a further 3 hr., whereupon the mixture was extracted with ether, first with two portions of 10 ml., and then continuously for 24 hr.; the two extracts were treated separately as follows.

[10] M. L. Bender, *Chem. Rev.*, 1960, **60**, 53.

[11] M. L. Bender and B. W. Turnquist, *J. Amer. Chem. Soc.*, 1957, **79**, 1656.

[12] I. Ugi and F. Beck, *Chem. Ber.*, 1961, **94**, 1839.

[13] A. Pinner, *Ber.*, 1894, **27**, 1053, 2861; K. Löffler and S. Kober, *Ber.*, 1909, **42**, 3431.

[14] R. Pschorr, B. Jaeckel, and H. Fecht, *Ber.*, 1902, **35**, 4377.

[15] G. Drehfahl, H. Lückert, and W. Köhler, *J. prakt. Chem.*, 1960, **11**, 341.

[16] J. Gadamer and F. Knoch, *Arch. Pharm.*, 1921, **259**, 135; J. Knabe, *ibid.*, 1956 **289**, 479; J. Knabe and U. R. Shukla, *ibid.*, 1962, **295**, 690; J. A. Campbell, *J. Org. Chem.*, 1957, **77**, 3104; E. H. Flynn, H. W. Murphy, P. F. Wiley, and K. Gerzon, *J. Amer. Chem. Soc.*, 1954, **76**, 3121; E. H. Flynn, H. W. Murphy, and R. E. McMahon, *ibid.*, 1955, **77**, 3104.

[17] W. Gerrard and F. Schild, *Chem. and Ind.*, 1954, 1232.

The first extract was shaken with 2N-hydrochloric acid, and after thorough washing with ether the aqueous layer was basified, liberating 2,4-dibenzylidenetropinone (1·84 g.), m. p. 153°. Evaporation of the ethereal layer gave an oil from which were prepared the 2,4-dinitrophenylhydrazone, m. p. 235°, and semicarbazone, m. p. 214°, of benzaldehyde.

The oily product isolated by continuous extraction crystallised under ether after being seeded with tropine. Additional crops of tropine (total recovery, 2·9 g.) were obtained by further concentration and seeding. From the oily mother-liquors crystals of tropinone (0·4 g.) eventually separated, identified by comparison (mixed m. p. and infrared spectra) of the compound, m. p. 41° (from ether), and its picrate, m. p. 216—217° (decomp.) [lit.,[18] 220° (decomp.)] with authentic samples.

Reaction of N-*Methylgranatan*-3α-*ol with Benzoyl Chloride and Alkali.*—The alcohol[19] (310 mg.) was treated with benzoyl chloride (3·5 ml.) and 4N-sodium hydroxide (40 ml.) as described in (*a*) above. The product (0·2 g.), recrystallised from methanol, had m. p. 198—199°, undepressed on admixture with a sample, m. p. 197—199° (lit.,[20] 200°) prepared by condensation of ψ-pelletierine with benzaldehyde.

cis,trans-2,4-*Dibenzylidenetropinone.*—A solution of *trans,trans*-2,4-dibenzylidenetropinone (m. p. 153°) (0·5 g.) in benzene (10 ml.) in Pyrex was irradiated for 8 hr. at 30 cm. from a Hanovia U.V.S. 500 A source. Evaporation of the solvent and extraction of the residue with a little warm light petroleum (b. p. 40—60°) gave the isomeric *dienone* (V) as yellow plates, (0·3 g.), m. p. 103°, $\lambda_{max.}$ (95% EtOH) 233 and 327 mμ (ε 14,400 and 20,600) (Found: C, 83·5; H, 6·6; N, 4·5%). Recrystallisation of the residue left after the extraction with light petroleum afforded starting material (0·08 g.), m. p. 153°.

Treatment of the lower-melting isomer (0·2 g.) in methanol (3 ml.) with one drop of acetic acid resulted in the separation of the higher-melting compound.

3-*Ethoxycarbonylmethylenetropane.*—Diethyl ethoxycarbonylmethylphosphonate (9 g.) in dry 1,2-dimethoxyethane (15 ml.) was added slowly to a suspension of sodium hydride (2 g. of a 50% oil dispersion) in 1,2-dimethoxyethane (50 ml.). After ½ hr., a solution of tropinone (5 g.) in 1,2-dimethoxyethane (15 ml.) was added during 1 hr., whereupon stirring was continued for 20 hr., after which the mixture was decomposed with ice–water and extracted with ether. The basic product was taken into 2N-hydrochloric acid, liberated with dilute alkali, and isolated with ether; the crude oil was fractionated under reduced pressure giving the colourless *ester* (4·75 g.), b. p. 128—129°/5 mm., n_D^{21} 1·4961, $\nu_{max.}$ (liquid film) 1725 and 1655 cm.$^{-1}$ (Found: C, 68·8; H, 9·3; N, 6·4. $C_{12}H_{19}NO_2$ requires C, 68·9; H, 9·15; N, 6·7%).

The ester afforded a *picrate*, obtained from ethanol as yellow needles, m. p. 151—153° (Found: C, 49·1; H, 4·7; N, 13·1. $C_{18}H_{22}N_4O_9$ requires C, 49·3; H, 5·1; N, 12·8%).

Tropane-3α-acetic Acid (XII).—The unsaturated ester (X) (4·6 g.) in methanol (50 ml.) was shaken with hydrogen (5 atm.) and Raney nickel (3 g.). The product was a colourless gum, from which was prepared 3α-ethoxycarbonylmethyltropane picrate, m. p. 141° (lit.,[21] 141—142°).

The crude ester (XI) (3·6 g.) was refluxed with 4N-hydrochloric acid (50 ml.) for 1 hr., and the gum obtained by evaporation *in vacuo* was dissolved in water (10 ml.) and passed down a column of Amberlite IR-4B resin. Evaporation of the aqueous eluate *in vacuo*, followed by recrystallisation from methanol–acetone, gave tropane-3α-acetic acid (3·1 g.) as colourless needles, m. p. 198—199° (lit.,[21] 195—196°) (Found: C, 60·1; H, 9·6; N, 7·3. Calc. for $C_{10}H_{17}NO_3,H_2O$: C, 59·7; H, 9·5; N, 7·0%).

Negative Experiments.—Reactions with cyclohexanol, *N*-benzoylnortropine (VII), ψ-tropine (VIa), *N*-methylgranatan-3β-ol (VIb),[19] and tropane-3α-acetic acid were carried out as described for tropine in (*a*) above, using equivalent proportions of reactants. Continuous ether extraction of the alkaline reaction mixture resulted in substantially complete recovery of starting material in the case of the alcohols, no significant amount of ketonic material being detectable by infrared spectroscopy; no non-acidic products were formed in the fifth experiment.

Demethylations with Benzoyl Chloride.—(*a*) Tropine (2 g.) was refluxed with freshly distilled benzoyl chloride (20 ml.) for 2 hr. under a stream of dry nitrogen. Addition of anhydrous

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[18] R. Willstätter, *Ber.*, 1896, **29**, 393.

[19] K. Alder and H. A. Dortmann, *Chem. Ber.*, 1953, **86**, 1544.

[20] A. Piccinini, *Gazzetta*, 1899, **29**, I, 408.

[21] C. L. Zirkle, E. L. Anderson, F. R. Gerns, Z. K. Indik, and A. M. Pavloff, *J. Org. Chem.*, 1962, **27**, 1279.

ether to the cooled solution precipitated *O*-benzoyltropine hydrochloride (0·9 g.) obtained from ethanol as colourless needles, m. p. 273° (lit.,[22] 275°). The ethereal mother-liquors were evaporated *in vacuo* giving a dark brown oil which crystallised under ether. Recrystallisation from ether gave ON-*dibenzoylnortropine* (1·4 g.), m. p. 134—136s, $\nu_{max.}$ (Nujol) 1730, 1640, and 1600 cm.$^{-1}$ (Found: C, 75·0; H, 6·3; N, 4·05. $C_{21}H_{21}NO_3$ requires C, 75·2; H, 6·3; N, 4·2%).

Saponification of the ester by refluxing with 10% aqueous ethanolic sodium hydroxide afforded *N*-benzoylnortropine (VII), crystallising from ether as colourless prisms, m. p. 127—128° (lit.,[23] 131—132°).

(*b*) A solution of tropidine (0·4 g.) and benzoyl chloride (0·85 ml.) in benzene (5 ml.) was refluxed for 24 hr., and the cooled mixture was poured into 4N-sodium hydroxide. After vigorous shaking for 1 hr., the mixture was extracted with ether and the organic layer was washed with dilute hydrochloric acid. The product, obtained by evaporation of the dried extract, crystallised from light petroleum (b. p. 60—80°) giving colourless needles, m. p. 91—93°, of N-*benzoylnortropidine* (XV) (85 mg.), $\nu_{max.}$ (Nujol) 1640 cm.$^{-1}$ (Found: C, 78·7; H, 7·1; N, 7·0. $C_{14}H_{15}NO$ requires C, 78·8; H, 7·1; N, 6·6%).

Demethylation of Tropinone with Ethyl Chloroformate.—A solution of tropinone (2·78 g., 0·02 mole) and freshly distilled ethyl chloroformate (3·3 g., 0·03 mole) in dichloromethane (20 ml.) was kept at 20° for 24 hr. Ether (40 ml.) was added, and the crystalline precipitate was collected and recrystallised from chloroform-ether; colourless prisms (0·4 g.), m. p. 206—208° (decomp.) [lit.,[18] 188—189° (decomp.)] of tropinone hydrochloride were obtained, from which the base, m. p. 41—42°, was recovered.

After being washed with N-hydrochloric acid and then with water, the ethereal filtrate was dried and evaporated, and the residue distilled; N-*ethoxycarbonylnortropinone* (3·1 g.) was obtained as a colourless oil, b. p. 152—153°/11 mm., n_D^{18} 1·4891, $\nu_{max.}$ (liquid film) 1697 cm.$^{-1}$ (broad) (Found: C, 61·1; H, 7·7; N, 7·0. $C_{10}H_{15}NO_3$ requires C, 60·9; H, 7·7; N, 7·1%). The 2,4-*dinitrophenylhydrazone* was obtained from ethanol as orange plates, m. p. 172° (Found: C, 50·5; H, 5·0; N, 18·7. $C_{16}H_{19}N_5O_6$ requires C, 50·9; H, 5·1; N, 18·6%).

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[22] H. A. D. Jowett and F. L. Pyman, *J.*, 1909, **95**, 1020.
[23] A. Nickon and L. F. Fieser, *J. Amer. Chem. Soc.*, 1952, **74**, 5566.