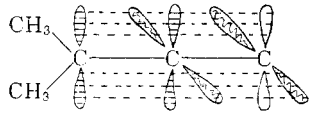
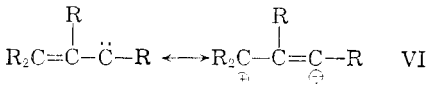
readily rationalized. The enhanced stability of I over methylene or alkyl carbenes may be attributable to overlap of the vacant p-orbital with the π-electrons of the β,γ-double bond (V). If this is the case, one can predict that β,γ-unsaturated carbenes (VI) in general will be considerably more stable than methylene.

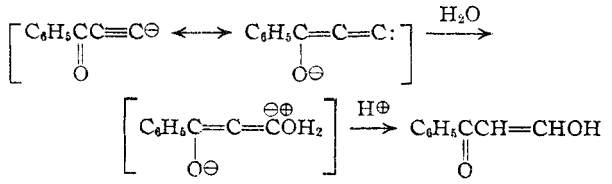


V



VI

The reactions of I with nucleophiles are unusual in that attack can occur at either the α- or γ-carbon atom. Thus, I undergoes reaction at the γ-carbon atom with alkoxide ions[1] and with amines[17] to give acetylenic ethers and amines, while it gives reaction at the α-carbon atom with olefins to give cyclopropanes. The choice between reaction paths for I is not simply related to the charge of the nucleophile or its relative nucleophilicity, for I (R = C_6H_5) reacts with acetylenic anions at the α-carbon atom to give cumulenes.[2] The ability of an alkenylidene carbene to react with a hydroxylic solvent at the α-carbon atom has been demonstrated in the formation of hydroxymethyleneacetophenone from the anion of benzoylacetylene.[18] No satisfactory explanation for the differentiation in reaction paths is available at present, and reactions of I with anions are currently under investigation.



(17) G. F. Hennion and K. W. Nelson, *J. Am. Chem. Soc.*, **79**, 2142 (1957).

(18) H. D. Hartzler and J. L. Warnell, unpublished work.

Experimental[19]

1-(2-Methylpropenylidene)-*cis*-2,3-dimethylcyclopropane (III).—The allene was prepared by the procedure previously given for the preparation of 7-(2-methylpropenylidene)-bicyclo[4,1,0]-heptane.[2] *cis*-2-Butene and 3-chloro-3-methyl-1-butyne gave a 23% yield of III, b.p. 80–82° at 66 mm., $n^{25}D$ 1.4830–1.4835.

Anal. Calcd. for C_9H_{14}: C, 88.45; H, 11.55. Found: C, 88.47; H, 11.66.

1-(2-Methylpropenylidene)-*trans*-2,3-dimethylcyclopropane (IV).—*trans*-2-Butene and the acetylenic chloride gave a 19% yield of IV, b.p. 66–68° at 54 mm., $n^{25}D$ 1.4792–1.4800.

Anal. Calcd. for C_9H_{14}: C, 88.45; H, 11.55. Found: C, 88.26; H, 11.70.

V.p.c. analysis of the reaction mixtures from *cis*- and *trans*-2-butene showed mainly the one isomer in each case. The analysis of the mixtures was done on the crude product, after filtration but before distillation. No detectable amount of IV was found in the reaction product from *cis*-2-butene. A trace of III was found in the reaction product from *trans*-2-butene. The amount was approximately equal to the amount of *cis*-2-butene present as a contaminant in the starting material. The column employed for analysis was 7 ft. × 0.25 in. copper tubing packed with Columpak firebrick coated with tris-cyanoethyl glyceryl ether and operated at 102° with a helium flow rate of 40 cm.^{3}/min. The retention time of IV was 4.3 minutes, while III eluted at 6.1 minutes. Separation was complete.

Competition Experiments.—The conditions used were comparable to those used in the preparative experiments.[2] Mixtures containing 0.10 mole each of cyclohexene and the competing olefin, and 0.010 mole of potassium *t*-butoxide were stirred at −10° under nitrogen. 3-Chloro-3-methyl-1-butyne (1.10 g., 0.010 mole) was added dropwise with the temperature maintained between −10 and 0°. The mixtures were stirred for 5 minutes, pentane (50 ml.) was added, and the mixtures were filtered. The crude filtrates were analyzed by v.p.c. In all cases separations between the two allenes were complete. The column and conditions employed were those used with the products from *cis*- and *trans*-2-butene.

(19) Boiling points are uncorrected.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF LEPETIT S.P.A., MILAN, ITALY]

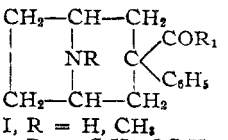
A New Synthesis of Tropane Derivatives

BY G. CIGNARELLA, G. G. GALLO AND E. TESTA

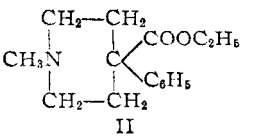
RECEIVED JUNE 20, 1961

A new synthesis of 3α-phenyltropane derivatives has been carried out starting from *cis*-2,5-dicarbethoxypyrrolidine (IV), 8-tosyl-3β-cyano-3α-phenylnortropane (VIII) being the intermediate product. 3α-Phenyl-3β-nortropanecarboxylic acid (XI) and its ethyl ester XIII, 3α-phenyltropane-3β-carboxylic acid (XII) and its ethyl ester XIV, 3α-phenyl-3β-nortropanyl phenyl ketone (XVI) and 3α-phenyl-3β-tropanyl phenyl ketone (XVII) have been synthesized and found identical by chemical and spectral properties with the compounds previously obtained from α-ecgonine.

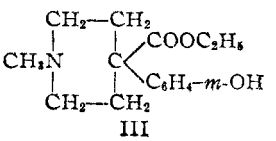
In connection with a research program directed toward the synthesis of a new class of bicyclic nitrogen compounds, which recently led one of us to the preparation of 3,8-diazabicyclo[3.2.1]octane and many its derivatives,[1,2] we were able to complete from suitable intermediates[3] a new synthesis



I, R = H, CH_3
R_1 = C_6H_5, OC_2H_5



II

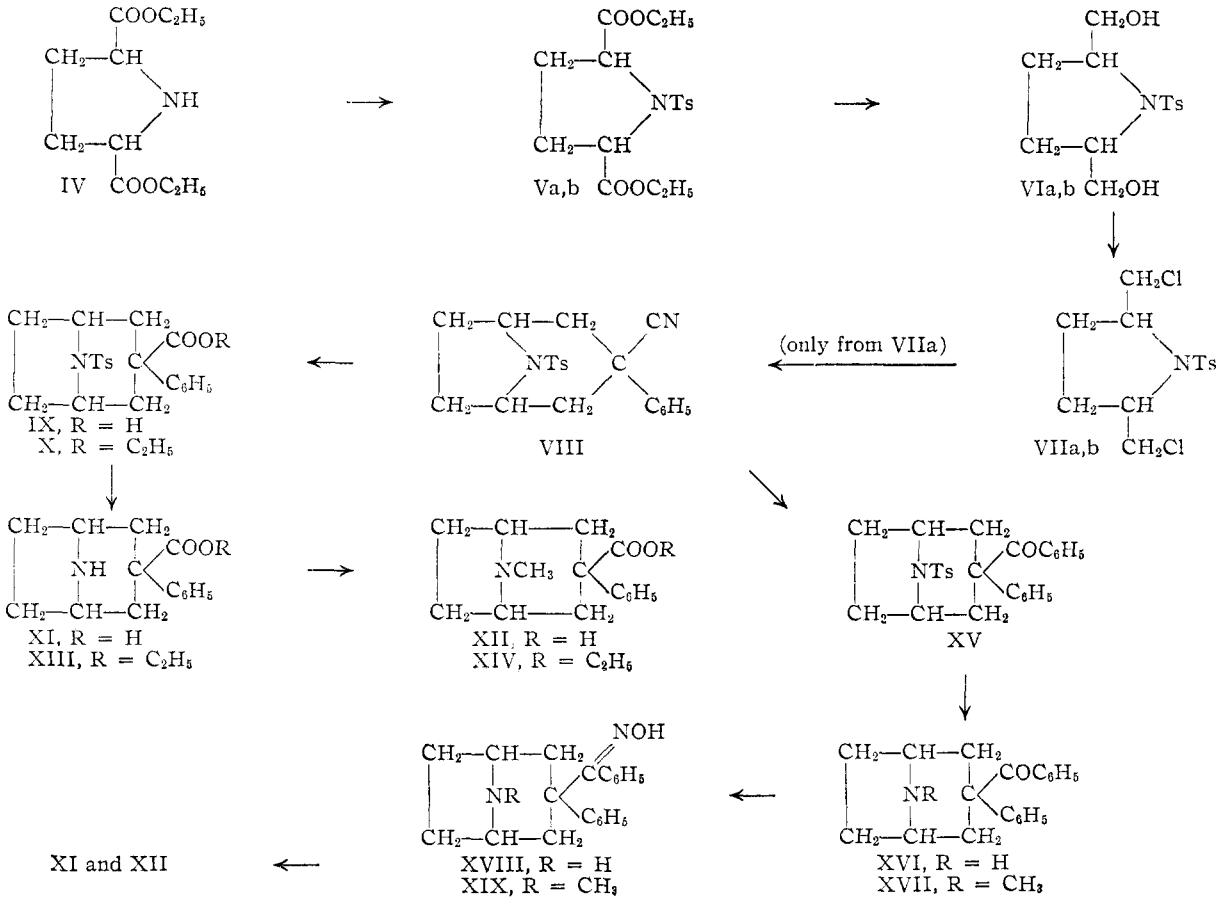


III

(1) G. Cignarella and G. G. Nathansohn, *J. Org. Chem.*, **26**, 1500 (1961).

(2) G. Cignarella, G. G. Nathansohn and E. Occelli, *ibid.*, **26**, 2767 (1961).

(3) G. Cignarella and G. G. Nathansohn, *Gazz. chim. ital.*, **90**, 1495 (1960).



of tropane derivatives, with potential pharmacological activity. The synthesis of the products I seemed to us of particular interest in view of the evident analogy with the analgesics meperidine (II), ketobemidone (III) and related compounds.

While this work was being carried out, a paper by Bell and Archer[4] appeared on the same subject. The authors described a synthesis of ethyl 3α-phenyltropane-3β-carboxylate starting from 3α-diphenylhydroxymethyl-3β-tropanol, obtained from α-ecgonine methyl ester.[5-7] Our starting material and synthetic routes are quite different from those mentioned above.

Our new synthesis of I starts from the already described[3] *cis*-2,5-dicarbethoxypyrrolidine (IV), which by tosylation in pyridine gave *cis*-N-tosyl-2,5-dicarbethoxypyrrolidine. Two forms of this compound could be separated by crystallization. The first (Va), obtained in pure state and in major amount, was reduced with lithium aluminum hydride in tetrahydrofuran to *cis*-N-tosyl-2,5-bis-(hydroxymethyl)-pyrrolidine (VIa). The second form (Vb), which could not be obtained in a pure state, was reduced, by analogous procedure, to a product (VIb) which could be isolated in pure state and which by elemental analysis and infrared spectrum was confirmed to be a steric isomer of VIa.

The isomer VIa was allowed to react with thionyl chloride in chloroform and gave *cis*-N-tosyl-2,5-bis-(chloromethyl)-pyrrolidine (VIIa); the same reaction carried out on VIb gave the isomer VIIb. Compound VIIa was condensed with benzyl cyanide and sodium amide in boiling toluene and gave N-tosyl-3-cyano-3-phenylnortropane (VIII). The same reaction was carried out on VIIb but did not yield any cyclic product. This suggests that Va, VIa and VIIa are indeed the *cis* isomers. The demonstration of the *trans* structure for the isomers Vb, VIb and VIIb is at present under investigation and will be the subject of a forthcoming paper. However, in this paper these isomers will be referred as *trans* forms. Saponification of VIII to the corresponding N-tosyl-3-phenylnortropane-3-carboxylic acid (IX) was unsuccessful using the usual procedures, but was achieved in high yield when the reaction was carried out in a boiling solution of KOH in ethylene glycol. Attempts to detosylate IX with H_2SO_4 in ethanol[8] failed and ethyl N-tosyl-3-phenylnortropane 3-carboxylate (X) was the only product obtained. Detosylation of IX proceeded very satisfactorily when carried out in a refluxed mixture of concd. hydrobromic acid, acetic acid and phenol[9] and gave in good yield 3-phenylnortropane-3-carboxylic acid (XI). This compound by methylation with formaldehyde and formic acid[10] was converted to 3-phenyltropane-3-carboxylic acid

(4) M. R. Bell and S. Archer, *J. Am. Chem. Soc.*, **82**, 4638 (1960).
(5) M. R. Bell and S. Archer, *ibid.*, **82**, 151 (1960).
(6) R. Willstätter, *Ber.*, **29**, 2216 (1896).
(7) A. Heusner, *Z. Naturforsch.*, **126**, 602 (1957).
(8) R. H. Thorp and E. Walton, *J. Chem. Soc.*, 559 (1948).
(9) J. Bornstein, S. C. Lashna and A. P. Boisselle, *J. Org. Chem.*, **22**, 1255 (1957).
(10) A. T. Clarke, H. B. Gillespie and S. Z. Weisshaus, *J. Am. Chem. Soc.*, **55**, 4571 (1933).

(XII). The hydrochloride of XI and of its ethyl ester XIII were identical (undepressed mixed melting point and infrared spectra) with samples of 3α-phenylnortropane-3β-carboxylic acid hydrochloride and its ethyl ester obtained from α-ecgonine,[11] thus suggesting for XI and XIII and consequently for VIII, IX, X and XII and XIV the same stereochemical structure of the analogous compounds synthesized from 3-tropinone.[4,5]

N-Tosyl-3β-cyano-3α-phenylnortropane was allowed to react with benzylmagnesium bromide and gave N-tosyl-3α-phenyl-3β-nortropanyl phenyl ketone (XV), which by detosylation gave 3α-phenyl-3β-nortropanyl phenyl ketone (XVI). The infrared and ultraviolet spectra of XVI are identical with those of the compound described by Bell and Archer.[5] N-Methylation with formaldehyde and formic acid of XVI yielded 3α-phenyl-3β-tropanyl phenyl ketone (XVII).

The infrared spectrum of XVII in methanol solution showed an absorption near 6 μ (assigned to the C=O stretching vibration) in contrast to that described by Bell and Archer[5]; however, our product (XVII) has been shown to be identical with that synthesized from α-ecgonine. In fact Dr. R. Bell subsequently confirmed (private communication) the exactness of our infrared result and the identity of the two products. The found divergence is probably due to the different used concentrations; we used a concentration of about 8% (0.045-mm. cell), while Bell and Archer used (private communication) a concentration of about 1% (0.0245-mm. cell).

The lack of any absorption near 6 μ of 3α-phenyl-3β-tropanyl phenyl ketone in methanol solution is one of the supporting points for the demonstration of the steric conformation of the compound. The hypothesis of Bell and Archer seems to be still valid, but this latter point should require further examination.

For a further identification of the compounds XVI and XVII, the corresponding ketoximes XVIII and XIX were prepared, which by the described procedure[4,5] yielded products that were found to be identical (infrared spectra) with XI and XII, respectively.

Acknowledgment.—The authors wish to express their appreciation to Dr. R. Pasqualucci for the infrared spectra, to Miss Dr. G. Pelizza for the functional analyses and to Mr. A. Restelli for the elementary microanalyses.

Experimental[12]

***cis*-N-Tosyl-2,5-dicarbethoxypyrrolidine (Va).**—To 154 g. (0.716 mole) of *cis*-2,5-dicarbethoxypyrrolidine[5] (IV) in 500 ml. of dry pyridine at 0° a solution of 172 g. (0.93 mole) of *p*-toluenesulfonyl chloride in 700 ml. of dry pyridine was added dropwise under stirring during 1 hour. The reaction mixture was warmed at 40° for 3 hours and kept at room temperature overnight. The precipitated pyridine hydrochloride was filtered off and the filtrate concentrated below 40°. The solid residue was slurried with 500 ml. of H_2O and acidified to *p*H 3 with concentrated HCl. The product (130 g.) was collected by filtration and washed with water. The filtrate was extracted with three 250-ml. portions of benzene and the extracts were added to the solid product. The resulting solution was dried over sodium sulfate, concentrated to about 300 ml. and petroleum ether (500 ml.) was added. After cooling, a slight yellow product was collected by filtration and the mother liquor was set aside; yield 160 g. (60.4%), m.p. 75–78°. A sample recrystallized from petroleum ether melted at 80–81°. The infrared spectrum in chloroform solution showed a broad band at 1730 cm.$^{-1}$ (> C=O) and two bands at 1350 and 1157 cm.$^{-1}$ (—SO_2—).

Anal. Calcd. for $C_{17}H_{23}NO_6S$: C, 55.27; H, 6.27; N, 3.79; S, 8.68. Found: C, 55.50; H, 6.40; N, 3.67; S, 8.91.

The stored mother liquor was shaken with 10% hydrochloric acid then with 10% sodium carbonate solution and finally with water. After drying over sodium sulfate, the solvent was evaporated, yielding 85 g. of a viscous oil, which failed to crystallize. The infrared spectrum in chloroform solution showed a band at 1728 cm.$^{-1}$ (> C=O) and two bands at 1350 and 1160 cm.$^{-1}$ (—SO_2—), but the comparison with the infrared spectrum of the pure *cis* form showed marked differences in the finger-print region, thus suggesting the presence in the oily product of the isomer N-tosyl-2,5-dicarbethoxypyrrolidine (Vb). The analytical data of the crude product were in sufficient agreement with the formula ($C_{17}H_{23}NO_6S$), but a sample distilled at 190–200° (0.3 mm.) failed to give a good elemental analysis. The product underwent partial decomposition during distillation.

***cis*-N-Tosyl-2,5-bis-(hydroxymethyl)-pyrrolidine (VIa).**—To a suspension of 47 g. (1.24 moles) of lithium aluminum hydride in 1700 ml. of anhydrous tetrahydrofuran at 0° a solution of 190 g. (0.514 mole) of *cis*-N-tosyl-2,5-dicarbethoxypyrrolidine (Va) in 1700 ml. of dry tetrahydrofuran was slowly added under stirring during 90 minutes. The mixture was stirred and refluxed for 1 hour, then cooled at 0–5° and cautiously decomposed with 180 ml. of water. After standing 1 hour at room temperature, the precipitate was removed by filtration. The combined filtrate and washings were dried over sodium sulfate and the solvent removed by distillation. The solid residue was slurried with 300 ml. of water, filtered and thoroughly dried to give 110 g. (75%) of crude *cis*-N-tosyl-2,5-bis-(hydroxymethyl)-pyrrolidine(VIa), m.p. 130–132°. One gram of crude product was crystallized from 10 ml. of ethyl acetate giving 850 mg. of VIa which, after drying, melted at 134–137°. The product is soluble in boiling water (1 g. in 20 ml.).

Anal. Calcd. for $C_{13}H_{19}NO_4S$: N, 4.91; S, 11.23. Found: N, 4.82; S, 11.31.

***trans*-N-Tosyl-2,5-bis-(hydroxymethyl)-pyrrolidine (VIb).**—Eighty grams of Vb was reduced as described for Va with 21.2 g. of lithium aluminum hydride in 1400 ml. of tetrahydrofuran; 50 g. of an oily product was obtained, dissolved in benzene and shaken with 10% hydrochloric acid. The organic layer was separated, dried over sodium sulfate and the solvent evaporated. The viscous oily residue (32 g.) was dissolved in 150 ml. of hot ethyl acetate and kept overnight at room temperature. A white precipitate (7 g.) was obtained. The precipitate was collected by filtration and identified by mixed melting point and infrared spectrum as *cis*-N-tosyl-2,5-bis-hydroxymethylpyrrolidine (VIa). The mother liquor was concentrated to half-volume and petroleum ether was added until cloudy. After cooling and scratching, 18.5 g. of solid product separated, which after drying melted at 108–112°. A sample recrystallized from water and dried *in vacuo* at 80° melted at 118–121°.

Anal. Calcd. for $C_{13}H_{19}NO_4S$: N, 4.91; S, 11.23. Found: N, 4.95; S, 11.18.

Comparison of this compound (VIb) with a sample of *cis*-diol VIa by mixed melting point (strong depression) and infrared spectra in Nujol and in chloroform solution showed that it is an isomer of VIa.

***cis*-N-Tosyl-2,5-bis-(chloromethyl)-pyrrolidine (VIIa).**—To a suspension of *cis*-N-tosyl-2,5-bis-(hydroxymethyl)-pyrrolidine (80 g., 0.28 mole) in 500 ml. of dry benzene 100 g. (0.84 mole) of thionyl chloride was added under stirring. The mixture was stirred for 2 hours at room temperature and for an additional hour at 40–50° to complete solution. When the gas evolution stopped, the solvent and the excess of thionyl chloride were eliminated *in vacuo*. The oily residue was distilled with an air-bath[13] and 87 g. (96%) of *cis*-

(11) The authors thank Dr. M. R. Bell of the Sterling-Winthrop Research Institute for his kindness in supplying samples of these products.

(12) All melting points are uncorrected.

(13) K. Ronco, B. Prijs and H. Erlenmeyer, *Helv. Chim. Acta*, **39**, 2088 (1956).

N-tosyl-2,5-bis-(chloromethyl)-pyrrolidine, b.p. 175–190° (0.5 mm.), was collected as a slightly yellow oil, which solidified after being slurried in petroleum ether. Compound VIIa was crystallized from ethyl ether; m.p. 70–73°.

Anal. Calcd. for $C_{13}H_{17}Cl_2NO_2S$: Cl, 22.00; N, 4.34; S, 9.94. Found: Cl, 21.80; N, 3.99; S, 10.11.

trans-N-Tosyl-2,5-bis-(chloromethyl)-pyrrolidine (VIIb. was prepared as described above for VIa from 5 g. (0.0175 mole) of *trans*-N-tosyl-2,5-bis-(hydroxymethyl)-pyrrolidine (VIb) and 6.25 g. (0.0525 mole) of thionyl chloride in 30 ml. of dry benzene yielding 4.7 g. of a slightly yellow oil, b.p. 190–200° (0.4 mm.). A sample was redistilled and the fraction 195–200° (0.4 mm.) was analyzed.

Anal. Calcd. for $C_{13}H_{17}Cl_2NO_2S$: Cl, 22.00; N, 4.34; S, 9.94. Found: Cl, 21.70; N, 4.11; S, 9.71.

8-Tosyl-3β-cyano-3α-phenylnortropane (VIII).—To a stirred suspension of 11.7 g. (0.3 mole) of sodium amide in 350 ml. of dry toluene a mixture of 32.2 g. (0.1 mole) of *cis*-N-tosyl-2,5-bis-(chloromethyl)-pyrrolidine (VIIa), 11.7 g. (0.1 mole) of benzyl cyanide and 250 ml. of dry toluene was slowly added at room temperature. During the addition the reaction temperature rose to 40°. After refluxing for 1 hour, the reaction flask was ice-cooled and 100 ml. of water was added cautiously. The aqueous layer was separated and the toluene solution was shaken with 10% hydrochloric acid and finally with water. On washing the organic phase, a viscous brown oil insoluble in both layers separated and was discarded. The toluene solution, after drying over sodium sulfate, was evaporated. The oily residue was dissolved in ether and cooled to furnish 9.5 g. of light brown crystalline product, m.p. 157–160°. The mother liquor was evaporated, the residue dissolved in a small volume of ethyl ether and cooled; 700 mg. of product, m.p. 159–161°, was obtained; total yield 10.2 g. (27.6%). A sample was recrystallized from benzene–ethyl ether and a white product was obtained, m.p. 167–170°.

Anal. Calcd. for $C_{21}H_{22}N_2O_2S$: C, 68.81; H, 6.05; N, 7.64; S, 8.74. Found: C, 69.01; H, 6.23; N, 7.70; S, 8.91.

8-Tosyl-3α-phenylnortropane-3β-carboxylic Acid (IX).—Ten grams of 8-tosyl-3β-cyano-3α-phenylnortropane (VIII) was dissolved in 300 ml. of a 5% solution of KOH in ethylene glycol and refluxed for 18 hours. The reaction mixture was cooled, diluted with 500 ml. of water and the cloudy solution filtered over Celite. After acidification the separated crude solid acid was collected, dissolved in hot 5% sodium bicarbonate and filtered from insoluble residue. The filtrate was acidified and 9.4 g. (89%) of 8-tosyl-3α-phenylnortropane-3β-carboxylic acid was obtained, m.p. 208–210°. A sample was crystallized from 95% ethanol; m.p. 210–212°.

Anal. Calcd. for $C_{21}H_{23}NO_4S$: C, 65.37; H, 6.00; N, 3.63; S, 8.31. Found: C, 65.28; H, 6.11; N, 3.55; S, 8.41.

Ethyl 8-Tosyl-3α-phenylnortropane-3β-carboxylate (X).—One gram of 8-tosyl-3α-phenylnortropane-3β-carboxylic acid (IX) was refluxed for 3 hours with 10 ml. of absolute ethanol and 0.6 ml. of concd. sulfuric acid. The reaction mixture was poured into 50 ml. of water. The viscous oil was decanted from the solution and solidified when slurried, with a small volume of ethyl ether. The product collected and crystallized from ethanol weighed 600 mg., white crystals, m.p. 162–164°.

Anal. Calcd. for $C_{23}H_{27}NO_4S$: C, 65.81; H, 6.78; N, 3.49; S, 7.98. Found: C, 65.98; H, 6.70; N, 3.30; S, 7.92.

3α-Phenyl-3β-nortropanecarboxylic Acid (XI).—(a) 8-Tosyl-3α-phenylnortropane-3β-carboxylic acid (IX) (5.4 g.) was dissolved in a hot mixture of acetic acid (40 ml.), 48% hydrobromic acid (40 ml.) and phenol (1.8 g.). The dark solution was refluxed for 3 hours. After concentration to half volume, under reduced pressure, the solution was cooled and extracted with ethyl ether. A crystalline solid insoluble in both layers, separated: it was collected, washed with water and dried, yielding 3.5 g. of 3α-phenylnortropane-3β-carboxylic acid hydrobromide, m.p. 257–258°. A sample crystallized from water gave a pink crystalline product, m.p. 260–261°.

Anal. Calcd. for $C_{14}H_{18}BrNO_2$: N, 4.49; Br, 25.60. Found: N, 4.39; Br, 25.75.

The acid layer, from which the hydrobromide was separated, was adjusted to *p*H 5 with sodium carbonate and 150 mg. of a white solid product separated. This was crystallized from water to give 100 mg. of 3α-phenylnortropane-3β-carboxylic acid (XI), m.p. > 300°.

Anal. Calcd. for $C_{14}H_{17}NO_2$: C, 72.68; H, 7.40; N, 6.05. Found: C, 72.71; H, 7.52; N, 6.01.

The hydrochloride of XI was prepared from the free base by dissolving the pure compound in alcoholic hydrogen chloride. The solvent was evaporated, the solid residue washed with ether and crystallized from ethanol–ethyl ether; m.p. 275–278°. This product was identical (undepressed mixed m.p. and infrared spectrum) with an authentic sample.[5]

Anal. Calcd. for $C_{14}H_{18}ClNO_2$: C, 62.78; H, 6.78; N, 5.23; Cl, 13.24. Found: C, 62.62; H, 6.73; N, 5.06; Cl, 13.05.

(b) 3α-Phenyl-3β-nortropanyl phenyl ketoxime (XVIII) hydrochloride, following the procedure of Bell and Archer,[4] was transformed to a product, m.p. 279–280°. The undepressed mixed melting point and infrared spectrum showed the compound to be identical with an authentic sample of the hydrochloride of XI.

3α-Phenyltropane-3β-carboxylic Acid (XII).—(a) A solution of 1.0 g. of 3α-phenyl-3β-nortropanecarboxylic acid (XI) in 2 ml. of 98% formic acid and 2 ml. of 38% formaldehyde was refluxed for 15 hours. After cooling, 1 ml. of concentrated hydrochloric acid was added and the reaction mixture was evaporated under reduced pressure. A white crystalline solid was collected and washed with acetone; 900 mg. of the hydrochloride of XII, m.p. 218–220°, was obtained. An analytical sample, after crystallization from methanol–ether, melted at 222–224° (reported[4] 226–227°).

Anal. Calcd. for $C_{15}H_{20}ClNO_2$: C, 63.93; H, 7.15; N, 4.97; Cl, 12.58. Found: C, 63.79; H, 7.40; N, 4.85; Cl, 12.38.

(b) 3α-Phenyl-3β-tropanyl phenyl ketoxime (XIX) hydrochloride according the mentioned procedure[4] was transformed to a product, m.p. 223–224°. The two samples prepared following both procedures showed no m.p. depression when mixed, and their infrared spectra were identical.

Ethyl 3α-Phenylnortropane-3β-carboxylate (XIII).—Following the described procedure,[4] 1.0 g. of 3-phenylnortropane-3-carboxylic acid was refluxed with thionyl chloride (10 ml.) for 2 hours. The excess of thionyl chloride was removed under reduced pressure and the residue treated with absolute ethanol. The obtained product (680 mg. of hydrochloride of XIII), after crystallization from ethanol–ethyl ether, melted at 228–230° (reported 222°). This product is identical (undepressed mixed m.p. and infrared spectrum) with an authentic sample.

Anal. Calcd. for $C_{16}H_{22}ClNO_2$: C, 64.94; H, 7.50; N, 4.73; Cl, 11.99. Found: C, 64.91; H, 7.70; N, 4.76; Cl, 11.80.

Ethyl 3α-Phenyltropane-3β-carboxylate (XIV).—The synthesis of this compound was performed following the same procedure used for the nortropane derivative XIII. The hydrochloride of XIV was crystallized from ethanol–ethyl ether and melted at 199–201° (reported 192.5–193.5°).

Anal. Calcd. for $C_{17}H_{24}ClNO_2$: C, 65.89; H, 7.81; N, 4.52; Cl, 11.44. Found: C, 65.91; H, 7.90; N, 4.70; Cl, 11.55.

8-Tosyl-3α-phenyl-3β-nortropanyl Phenyl Ketone (XV).—To 150 ml. of an ether solution of phenylmagnesium bromide prepared in the usual manner from 24.4 g. (0.155 mole) of benzyl bromide, a warm solution (50–60°) of 15 g. (0.0389 mole) of 8-tosyl-3β-cyano-3α-phenylnortropane (VIII) in 250 ml. of dry toluene was added under stirring. The ethyl ether was removed *in vacuo* and the stirred reaction mixture was heated at 90–100° for additional 6 hours. On cooling, 100 ml. of 10% hydrochloric acid was cautiously added and the mixture was heated at 60–70° for 30 minutes to ensure the complete hydrolysis of the intermediate ketimine. The toluene layer was separated and washed with water. On standing, a white crystalline product separated; yield 11.7 g. of XV, m.p. 202–204°. From the filtrate, by concentrating and cooling, an additional 2.3 g. of product, m.p. 197–199°, was obtained; total yield 77%. The infrared spectrum shows a carbonyl band at 1665 cm.$^{-1}$; the CN absorption band is lacking. A sample was recrystallized from ethanol; m.p. 203–205°.

Anal. Calcd. for $C_{27}H_{27}NO_3S$: C, 72.77; H, 6.10; N, 3.14; S, 7.19. Found: C, 72.85; H, 6.28; N, 3.12; S, 7.10.

3α-Phenyl-3β-nortropanyl Phenyl Ketone (XVI).—8-Tosyl-3α-phenyl-3β-nortropanyl phenyl ketone (4.5 g.) was suspended in a mixture of 50 ml. of propionic acid, 16 ml. of 48% hydrobromic acid and 1.34 g. of phenol and refluxed for 1 hour. The cooled solution was filtered from the insoluble, unreacted starting compound (1.1 g.) and concentrated to a small volume under reduced pressure. The residue was diluted with 50 ml. of water, filtered, and the filtrate extracted with ethyl ether. The aqueous layer was treated with 10% sodium hydroxide and the separated white crystalline product was collected and crystallized from ethanol yielding 1.57 g. (70.8%) of 3α-phenyl-3β-nortropanyl phenyl ketone, m.p. 206–208° (reported 208–212°). The infrared spectrum in bromoform solution of XVI showed no carbonyl band near 6μ and a hydroxyl band at 2.84 μ. The infrared spectrum in methanol solution of XVI hydrochloride showed no carbonyl band near 6μ.[5]

Anal. Calcd. for $C_{20}H_{21}NO$: C, 82.44; H, 7.27; N, 4.80. Found: C, 82.24; H, 7.40; N, 4.76.

The hydrochloride of XVI, after crystallization from ethanol–ethyl ether, melted at 280–282° (reported 297°).

Anal. Calcd. for $C_{20}H_{22}ClNO$: N, 4.27; Cl, 10.81. Found: N, 4.23; Cl, 11.00.

The oxime XVIII was prepared according the described[4] procedure. The hydrochloride after crystallization from water melted at 273–275° (reported 286°).

Anal. Calcd. for $C_{20}H_{23}ClN_2O$: N, 8.17; Cl, 10.34. Found: N, 7.90; Cl, 10.15.

3α-Phenyl-3β-tropanyl Phenyl Ketone (XVII).—3α-Phenyl-3β-nortropanyl phenyl ketone (1.45 g.) was dissolved in 3 ml. of 98% formic acid, then 2 ml. of 38% formaldehyde was added and the mixture was allowed to reflux for 7 hours. After cooling, 2 ml. of concentrated hydrochloric acid was added and the whole was concentrated under reduced pressure. On cooling, the oily residue was treated with 20% sodium hydroxide. The separated white product was collected by filtration, washed with water and dried yielding 1.10 g. (73) of XVII, m.p. 123–125°. A sample, after crystallization from hexane, melted at 125–126° (reported 121–122.5°).

Anal. Calcd. for $C_{21}H_{23}NO$: C, 82.57; H, 7.59; N, 4.58. Found: C, 82.51; H, 7.74; N, 4.60.

The hydrochloride of XVII, prepared by addition of alcoholic hydrogen chloride to an ethyl ether solution of the base, melted at 249–251° (after crystallization from absolute ethanol (reported 257–257.5°).

Anal. Calcd. for $C_{21}H_{24}ClNO$: N, 4.09; Cl, 10.37. Found: N, 4.24; Cl, 10.50.

The infrared spectrum of XVII in methanol solution showed a broad absorption with two peaks at 6.02 and 6.10 μ; in methylene chloride a band at 6.04 μ. The infrared spectrum of XVII hydrochloride in methanol solution showed a weak band at 6.00 μ.[5]

The oxime XIX hydrochloride was prepared according the described procedure[5]; m.p. 320–321° (reported 327°).

Anal. Calcd. for $C_{21}H_{25}ClN_2O$: N, 7.85; Cl, 9.94. Found: N, 7.75; Cl, 10.05.

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Synthesis of A-Norcholesterol

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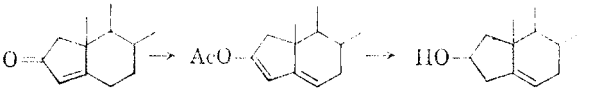
A-Norcholesterol (III) was prepared by a four-step procedure from A-norcoprostane-2,6-dione (IV). Attempts to prepare the sterol from A-norcholestenone (I) were unsuccessful.

The role of cholesterol in cardio-vascular diseases has attracted much interest in recent years, and the possible utilization of related steroids as dietary replacement factors has been investigated.[2] As it might be expected that any structural change in the immediate vicinity of the important C-3 hydroxyl function could affect the biological activity of a sterol, the preparation of A-norcholesterol (III) has been investigated.

With the recent availability of A-norcholestenone (I)[3,4] the standard method[5] used so successfully for the preparation of cholesterol from cholestenone was studied in the A-nor series. This method involves the conversion of a ring A enone (I) to the 2,5-dienol acetate (II) followed by reduction with sodium borohydride. Jacobs and Takahashi[3] have reported that preliminary attempts to prepare the dienol acetate II were unsuccessful. The preparation of II from A-norcholestenone (I) proved to be difficult in that under the usual reaction conditions employing isopropenyl acetate no reaction occurred.



I II III

Even when the forcing conditions used to prepare the enol acetate of A-norcholestane-2-one[4] were employed, II did not react with isopropenyl acetate.

It was found that when compound I was allowed to react for 24 hours with acetic anhydride containing a small amount of *p*-toluenesulfonic acid, there was obtained an oily product whose spectral features showed it to be the desired $\Delta^{2,5}$-A-norcholestadiene-3-ol acetate (II) contaminated with starting enone I. The dienol acetate could never be obtained pure and crystalline. Reduction of crude II with sodium borohydride in ethanol yielded an oily product which was treated with acid to dehydrate any allylic $\Delta^{3(5)}$-A-norcholestene-3-ol formed in the reaction. Chromatography of the resulting product gave only $\Delta^{2,5}$-A-norcholestadiene (IX), indicating the presence of only allylic alcohols in the reduction mixture. One reason for the failure of this method of preparation of β,γ-unsaturated alcohols from α,β-unsaturated ketones apparently could stem from the relatively slow rate of reduction of a cyclopentanone as compared to a cyclohexanone.[6]

(1) National Science Foundation Predoctoral Fellow, 1957–1958.

(2) For reviews, see *Ann. Rev. Biochem.*, **26**, 315 (1957); *Vitamins and Hormones*, **16**, 141 (1958); **17**, 233 (1959).

(3) T. L. Jacobs and N. Takahashi, *J. Am. Chem. Soc.*, **80**, 4865 (1958).

(4) W. G. Dauben, G. A. Boswell and W. H. Templeton, *ibid.*, **83**, 5006 (1961).

(5) B. Belleau and T. F. Gallagher, *ibid.*, **73**, 4458 (1951); W. G. Dauben and J. F. Eastham, *ibid.*, **73**, 4463 (1951).

(6) H. C. Brown and K. Ichikawa, *Tetrahedron*, **1**, 221 (1957).