could be obtained by dissolving the crude product in cold, 5% sodium hydroxide solution, treatment of the solution with charcoal followed by filtration, reacidification with acetic acid and recrystallization of the solid formed from a minimum of ethanol. Although the crude yields for the three runs were 44, 36 and 45%, the yields of pure material were quite variable, 8, 15 and 4%.

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[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE, RENSSELAER, N. Y.]

Ethyl 3α-Phenyltropane-3β-carboxylate and Related Compounds

BY M. R. BELL AND S. ARCHER

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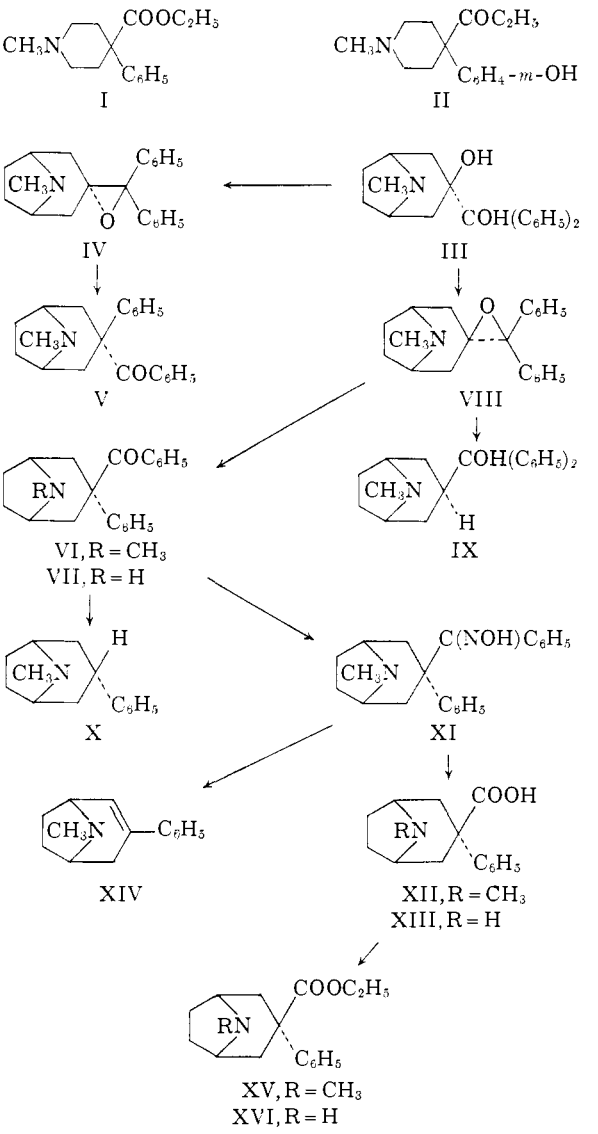
3α-Phenyl-3β-tropanyl phenyl ketoxime furnished 3α-phenyltropane-3β-carboxylic acid which on esterification gave the ethyl ester XV, the tropane analog of meperidine (I). The ketobemidone analog XXI was prepared from α-ecgonine amide by successive treatment with ethylmagnesium bromide and *m*-anisylmagnesium bromide, followed by treatment of the resulting diol with zinc chloride–acetic anhydride and then demethylation. Ethyl 3α-phenyltropane-3β-carboxylate (XV) was slightly more potent than meperidine as an analgesic.

Meperidine (I) and ketobemidone (II) are two members of the piperidine series of analgesics that have received some measure of clinical acceptance.[1] We thought it would be of interest to prepare the tropane analogs of these compounds and undertook the preparation of XV and XXI. If either of the new compounds showed interesting pharmacological properties we planned to replace the methyl group on the nitrogen of the tropane ring with a variety of larger radicals since it has been shown that such replacement of the N-methyl group of I resulted in a marked increase in potency.[2]

Previously we reported that 3α-diphenylhydroxymethyl-3β-tropanol (III) was converted to 3α-phenyl-3β-tropanyl phenyl ketone (VI) in the presence of zinc chloride and acetic anhydride.[3] We now find that brief exposure of III to this reagent results in the formation in good yield of the intermediate β-epoxide VIII. Assignment of this structure is based on the absence of hydroxyl and carbonyl absorption in the infrared spectrum and reductive cleavage with lithium aluminum hydride which furnished the known diphenyl-3β-tropanylcarbinol (IX).[3,4] Prolonged treatment of the epoxide with zinc chloride and acetic anhydride led to VI. The epoxide was assigned the β-configuration on the reasonable assumption that both the lithium aluminum hydride ring opening and the zinc chloride-catalyzed rearrangement occurred with inversion at C-3.

Boiling acetic anhydride converted III to the epimeric 3-benzhydrylidene tropane-α-epoxide (IV). The infrared spectrum of this product showed neither hydroxyl nor carbonyl absorption and the ultraviolet spectrum was virtually identical with that of the β-epoxide. The α-epoxide did not react with zinc chloride in acetic anhydride under the usual conditions at room temperature, but at 100° apparently 3β-phenyl-3α-tropanyl phenyl ketone (V) was formed. The infrared and ultraviolet



(1) O. J. Braenden and P. O. Wolff, *Bull. Wld. Hlth. Org.*, **10**, 1003 (1954); P. J. Braenden, N. B. Eddy and H. Halbach, *ibid.*, **13**, 937 (1955); N. B. Eddy, H. Halbach and O. J. Braenden, *ibid.*, **17**, 569 (1957).

(2) T. D. Perrine and N. B. Eddy, *J. Org. Chem.*, **21**, 125 (1956); J. Weijlard, *et al.*, THIS JOURNAL, **78**, 2342 (1956); B. Elpern, L. N. Gardner and L. Grumbach, *ibid.*, **79**, 1951 (1957).

(3) M. R. Bell and S. Archer, *ibid.*, **82**, 151 (1960).

(4) (a) C. L. Zirkle, U. S. Patent 2,800,478 (July 23, 1957); (b) S. Archer, M. R. Bell, T. R. Lewis, J. W. Schulenberg and M. J. Unser, THIS JOURNAL, **80**, 4677 (1958). 3-Benzoyltropane was first reported in ref. 4b and assigned the β-configuration by Bell and Archer (ref. 3). Since IX was prepared from this ketone (ref. 3) its configuration is as stated above.

spectra of this compound were characteristic of a normal alkyl phenyl ketone, in striking contrast to those of the isomer VI.[3] Unfortunately, the yield of this new ketone V was quite low.

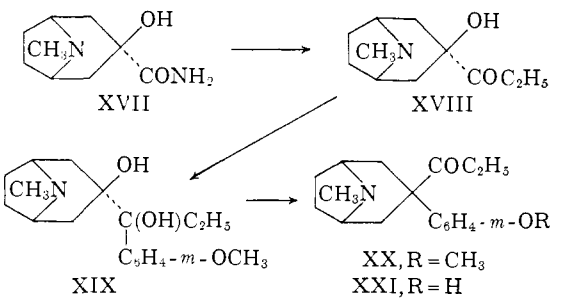
When the oxime XI[3] was subjected to the action of hydrogen chloride in hot acetic acid it was converted directly to 3α-phenyl-3β-tropanecarboxylic acid (XII) in good yield. Apparently the anilide, the expected product of a Beckmann rearrangement, was cleaved under these conditions since aniline was isolated from the reaction mixture. That the oxime was affected at all under these conditions is surprising since the piperidine analog is reported to be unchanged by such treatment.[5] Refluxing thionyl chloride converted XI to the known 3-phenyltropidine (XIV),[6] behavior which parallels that in the piperidine series.[5]

When the ketone VI was allowed to react with sodamide in boiling xylene, cleavage occurred to give 3α-phenyltropane (X).[7] The formation of both X and XIV showed that the tropane ring system was still intact and that the phenyl group was at C-3. Thus the proof of structure of VI is complete.[3]

Esterification of XII with alcoholic hydrogen chloride furnished the ester XV which was slightly more active than I as an analgesic.[8] Accordingly, we undertook the preparation of N-substituted analogs. The synthesis of the norester XVI from nortropinone[9] was similar to the one used for XV and proceeded uneventfully and in good yield. The norketone VII was identical with that prepared by demethylation of VI.[3]

A number of N-substituted derivatives of XVI were prepared by the usual procedures.[2] The groups introduced[10] were those which led to enhancement of activity in the meperidine series.[2] It was soon found that any departure from the N-methyl substituent led to a considerable decrease of activity.[8]

The ketobemidone analog XXI was prepared as indicated in the annexed scheme. The conversion



of α-ecgonine methyl ester to α-ecgonine amide was accomplished in almost quantitative yield with sodamide in liquid ammonia. This technique apparently was used first by Huebner[11] to convert methyl yohimbate to yohimbic acid amide.

(5) R. E. Lyle and G. G. Lyle, *J. Org. Chem.*, **18**, 1058 (1953).

(6) A. C. Cope and A. A. D'Addieco, THIS JOURNAL, **73**, 3419 (1951).

(7) A. M. Lands and S. Archer, *J. Med. and Pharm. Chem.*, in press.

(8) We wish to thank Dr. Leonard Grumbach for this information.

(9) R. Willstätter, *Ber.*, **29**, 1575 (1896); M. Polonovski and M. Polonovski, *Bull. soc. chim.*, **41**, 1190 (1927).

(10) M. R. Bell and S. Archer, unpublished.

(11) C. F. Huebner, *et al.*, THIS JOURNAL, **77**, 469 (1955).

Treatment of XVII with a large excess of ethylmagnesium bromide led to the hydroxyketone XVIII which afforded the diol XIX when allowed to react with *m*-anisylmagnesium bromide. When XIX was subjected to the action of zinc chloride and acetic anhydride, XX was obtained. A similar rearrangement in the cyclohexane series resulted in phenyl migration also.[12] The infrared spectrum of XX showed carbonyl absorption at 5.92 μ(CH_2Cl_2) in contrast to the prototype II which absorbed at 5.84 μ. Thus nitrogen–carbonyl interaction was present. The aromatic ketone 3α-phenyl-3β-tropanyl phenyl ketone (VI) absorbs at 6.03 μ in methylene chloride.[3]

Demethylation of XX with hydrobromic acid gave the desired XXI. The hydrochloride did not show carbonyl absorption in the infrared (D_2O, MeOH). Thus nitrogen–carbonyl reaction occurred with an aliphatic carbonyl as well as with an aromatic one.[3] In contrast to II which is a much stronger analgesic than I, XXI was much weaker than the ester XV.[8]

Experimental[13]

3-Benzhydrylidenetropane-β-epoxide (VIII).—A suspension of 10 g. of 3α-diphenylhydroxymethyl-3β-tropanol hydrochloride[3] and 10 g. of fused, powdered zinc chloride in 25 ml. of acetic anhydride was stirred at room temperature. After 80 minutes the dark brown solution was poured into a solution of 25 g. of sodium hydroxide in 200 ml. of water. The tan solid which had separated was collected, dried and leached with 250 ml. of boiling hexane. On concentration of the solvent to 100 ml. there separated 4.7 g. of a crystalline powder, m.p. 155–166°. Concentration of the filtrate yielded an additional 1.0 g., m.p. 150–161°. The crops were combined and recrystallized from 30 ml. of boiling methanol to give 4.3 g. of white plates, m.p. 166–166.5°.

Anal. Calcd. for $C_{21}H_{23}NO$: C, 82.55; H, 7.59; N, 4.59. Found: C, 82.32; H, 7.65; N, 4.04.

The **hydrochloride**, prepared by addition of alcoholic hydrogen chloride to an ether solution of the base, melted at 282° dec. after recrystallization from methanol–ether.

Anal. Calcd. for $C_{21}H_{24}ClNO$: C, 73.77; H, 7.07; N, 4.10. Found: C, 73.48; H, 6.74; N, 4.04.

Neither the base nor the hydrochloride showed either carbonyl or hydroxyl absorption in the infrared. In the ultraviolet the base showed λ_{max} 220 mμ, ε 13,400.

Reduction of 3-Benzhydrylidenetropane-β-epoxide (VIII) with Lithium Aluminum Hydride.—A solution of 1.0 g. of the epoxide and 0.5 g. of lithium aluminum hydride in 85 ml. of tetrahydrofuran was refluxed for 9 hours, stirred at room temperature for 9 hours and then decomposed by the addition of 2 ml. of water followed by 3 ml. of 35% sodium hydroxide. The solid material which had separated was leached with boiling benzene. The dried solution was evaporated to leave 1.1 g. of a waxy solid which afforded 0.38 g. of a crystalline material, m.p. 165–175° after trituration with hexane. After recrystallization from alcohol–water there was obtained 0.25 g. of white crystals, m.p. 175–180°. Further crystallization from the same solvent and then hexane raised the m.p. to 184–185.5°; the infrared spectrum was identical with that of 3β-tropanyldiphenylcarbinol (IX).[4]

3α-Phenyl-3β-tropanyl Phenyl Ketone (VI). A. From 3-Benzhydrylidenetropane-β-epoxide (VIII).—A mixture of the epoxide VIII hydrochloride (from 2.0 g. of the base), 2.0 g. of fused, powdered zinc chloride and 5 ml. of acetic anhydride was stirred at room temperature for 54 hours. The dark brown solution was poured into dilute sodium hydroxide. The solid that had separated was collected, dried and recrystallized from hexane to give 1.1 g. of white

(12) G. G. Lyle, R. A. Covey and R. E. Lyle, *ibid.*, **76**, 2714 (1954).

(13) All melting points are uncorrected. The ultraviolet spectra were determined in 95% ethanol unless otherwise specified. We are indebted to Dr. F. C. Nachod and his staff for the infrared and ultraviolet spectra and to Mr. K. D. Fleischer and his staff for the analyses.

needles, m.p. 119–122°. After one more recrystallization the product melted at 121–122°.

B. From 3α-Diphenylhydroxymethyl-3β-tropanol Hydrochloride.—This is an improved version of the previously described procedure.[3] A suspension of 10 g. of the diol hydrochloride and 23 g. of fused, powdered zinc chloride in 30 ml. of acetic anhydride was stirred for 24 hours at room temperature (solution complete in 20 minutes). It was poured into a solution of 60 g. of sodium hydroxide in 400 ml. of water. The tan crystalline solid which had separated was removed, washed with water and dried; weight 6.5 g., m.p. 118–122°.

The samples prepared by the two procedures showed no m.p. depression on admixture.

3-Benzhydrylidenetropane-α-epoxide (IV).—A mixture of 36.3 g. of 3α-diphenylhydroxymethyl-3β-tropanol hydrochloride and 500 ml. of acetic anhydride was refluxed for 20 hours, cooled to room temperature and diluted with 1200 ml. of ether, whereupon 20 g. of the **epoxide hydrochloride**, m.p. 265° dec., separated. Recrystallization of 6 g. from alcohol–ether afforded 4 g. of white microcrystals, m.p. 271° dec.

Anal. Calcd. for $C_{21}H_{24}ClNO$: C, 73.77; H, 7.07; Cl, 10.37. Found: C, 73.63; H, 7.19; Cl, 10.40.

The free base melted at 162–164.5° after recrystallization from hexane. *Anal.* Calcd. for $C_{21}H_{23}NO$: C, 82.55; H, 7.59. Found: C, 82.10; H, 7.71.

The m.m.p. with the β-epoxide resulted in a large depression and the infrared spectra were clearly different. No hydroxyl or carbonyl bands were present in the infrared of the α-epoxide. The ultraviolet spectrum showed λ_{max} 219 mμ, ε 12,700.

3β-Phenyl-3α-tropanyl Phenyl Ketone (V).—A stirred mixture of 2.0 g. of 3-benzhydrylidenetropane-α-epoxide hydrochloride, 2.0 g. of fused, powdered zinc chloride and 10 ml. of acetic anhydride was heated on the steam-bath for 30 minutes and then poured into excess aqueous sodium hydroxide. The mixture was extracted with methylene chloride and the extract was charcoaled before being evaporated to dryness. The clear brown oil which remained was dissolved in ether. The ether solution was concentrated to 25 ml. and filtered to remove 0.4 g. of an unidentified crystalline solid. Further concentration to 8 ml. followed by filtration served to remove 40 mg. more of insoluble material. The filtrate was concentrated to dryness and the residue in fresh ether was converted to the **hydrochloride** with alcoholic hydrogen chloride. The gum that separated furnished 240 mg. of a salt which crystallized under acetone, m.p. 280–290°. An additional 40 mg., m.p. 307°, was obtained from the filtrate. Recrystallization of the combined crops from methanol–ether furnished 210 mg., m.p. 314° dec. The analytical sample, m.p. 315° dec., crystallized as white needles from the same solvent. *Anal.* Calcd. for $C_{21}H_{24}ClNO$: C, 73.73; H, 7.07; Cl, 10.37. Found: C, 73.90; H, 7.04; Cl, 10.11. The infrared spectrum (KBr) showed a strong band at 5.99 μ and no hydroxyl absorption. The ultraviolet spectrum showed λ_{max} 249 mμ, ε 10,200; 320 mμ, ε 345.

3α-Phenyl Tropane-3β-carboxylic Acid (XII).—Dry hydrogen chloride was passed into a suspension of 15 g. of 3α-phenyl-3β-tropanyl phenyl ketoxime hydrochloride[3] (XI) in 100 ml. of glacial acetic acid. After a few minutes complete solution occurred and the whole was heated on the steam-bath while hydrogen chloride was passed slowly into the solution. After 2 hours the colorless solution was evaporated to dryness under reduced pressure. The crystalline residue was boiled with acetone to leave 7.8 g. of the white crystalline **amino acid hydrochloride**, m.p. 222–224° dec. The analytical sample melted at 226–227° dec. after recrystallization from methanol–ether.

Anal. Calcd. for $C_{15}H_{20}ClNO_2$: C, 63.93; H, 7.16; Cl, 12.58. Found: C, 63.80; H, 7.30; Cl, 12.55.

In another experiment, the acetone liquors were evaporated and the residue was treated with alkali and steam distilled. Aniline, characterized as benzanilide, was obtained from the distillate.

3-Phenyltropidine (XIV) from 3α-Phenyl-3β-tropanyl Phenyl Ketoxime.—A suspension of 1.0 g. of 3α-phenyl-3β-tropanyl phenyl ketoxime hydrochloride in 60 ml. of carbon tetrachloride containing 3 ml. of thionyl chloride was stirred at room temperature for 15 hours. The dark solution was stirred with 15 ml. of water for 1 hour and then the water layer was saturated with potassium carbonate before being extracted with methylene chloride. Evaporation of the methylene chloride left 0.9 g. of an oil with an odor of benzonitrile. This residue was dissolved in ether and treated with alcoholic hydrogen chloride to precipitate a gum that crystallized after trituration with fresh ether; weight 0.35 g., m.p. 219–225° dec. After recrystallization from acetonitrile–ether and then acetone–ether the hydrochloride (60 mg.) melted at 230–233° dec., identical by infrared and mixed melting point comparison with authentic 3-phenyltropidine hydrochloride.

3α-Phenyltropane (X) from 3α-Phenyl-3β-tropanyl Phenyl Ketone (VI).—Three grams of the ketone VI was refluxed with 1.6 g. of sodamide in 50 ml. of xylene for 16 hours. The cooled mixture was carefully treated with water and then ether. The organic phase was separated and the aqueous layer extracted with ether and then methylene chloride. The combined, dried (sodium sulfate) layers were evaporated to leave 2.0 g. of an oil which was converted to a gummy hydrochloride. Crystallization under acetone gave 100 mg. of the salt, m.p. 213–216°, which melted at 215–219° when admixed with an authentic specimen, m.p. 217–219°.[7] The infrared spectra of the two samples were indistinguishable.

Ethyl 3α-Phenyltropane-3β-carboxylate (XV).—A solution of 1.0 g. of 3α-phenyltropane-3β-carboxylic acid hydrochloride in 40 ml. of absolute ethanol saturated with hydrogen chloride was left at room temperature for 6 days. It was evaporated to dryness leaving a crystalline residue which was recrystallized from alcohol–ether to furnish 0.9 g. of the **hydrochloride** as white needles, m.p. 192.5–193.5°.

Anal. Calcd. for $C_{17}H_{24}ClNO_2$: C, 65.90; H, 7.81; Cl, 11.49. Found: C, 65.82; H, 7.81; Cl, 11.28.

The methobromide, prepared from the liberated base and methyl bromide in acetonitrile solution, melted at 206–207.5° after recrystallization from isopropyl alcohol–ether.

Anal. Calcd. for $C_{18}H_{26}BrNO_2$: C, 58.19; H, 7.12; Br, 21.70. Found: C, 58.44; H, 7.13; Br, 21.63.

Nor-α-ecgonine Methyl Ester.—A saturated aqueous solution of 243 g. nortropinone hydrochloride[9] was added rapidly with good stirring to a cold saturated aqueous solution of 107 g. of potassium cyanide while the temperature was maintained below 25°. The white slurry was stirred at room temperature for 1 hour, filtered and the crude cyanohydrin was pressed as dry as possible on the filter. The cake was added portionwise to 2 liters of concentrated hydrochloric acid with stirring while the temperature of the acid was kept below 25°. After 15 hours at room temperature the reaction mixture was evaporated to dryness under reduced pressure. The crude nor-α-ecgonine hydrochloride was dried by azeotropic distillation with benzene and finally at 100° (3 mm).

The solid was added to 2.5 l. of methanol and refluxed for 20 hours. During the first 5 hours dry hydrogen chloride was passed into the boiling mixture. The solvent was evaporated and the residue was dissolved in 550 ml. of water. The filtered solution was treated with 400 g. of potassium carbonate with cooling. The crystalline solid which separated was taken up in 2 × 1.5 l. of boiling chloroform. The dried extracts were evaporated to leave 135 g. of the ester, m.p. 142–146°. Further extraction of the aqueous phases furnished an additional 28 g., m.p. 137–144°.

The pure sample, m.p. 144–146°, after recrystallization from ethyl acetate was obtained as white prisms.

Anal. Calcd. for $C_9H_{15}NO_3$: C, 58.36; H, 8.16; N, 7.56. Found: C, 58.28; H, 8.14; N, 7.60.

3α-Diphenylhydroxymethyl-3β-nortropanol.—A solution of 100 g. of nor-α-ecgonine methyl ester in 1.5 l. of warm tetrahydrofuran was added to a stirred solution of phenyllithium (prepared from 594 g. of bromobenzene and 52.5 g. of lithium wire) in 1.5 l. of ether under nitrogen over a period of 30 minutes. The mixture was stirred and refluxed for 3 hours and then stirred at room temperature overnight. The deep red reaction mixture was decomposed with 600 ml. of water and the organic solvent was evaporated. The residue was dissolved in ether. The solution was decolorized with charcoal, dried and treated with a slight excess of alcoholic hydrogen chloride to give 157 g. of the **hydrochloride**, m.p. 258°. The analytical sample crystallized from 1-propanol as a solvate, m.p. 258°.

Anal. Calcd. for $C_{20}H_{23}NO_2 \cdot HCl \cdot {}^1/_3\ C_3H_8O$: C, 68.93; H, 7.34; Cl, 9.69; C_3H_7O, 5.38. Found: C, 69.24, 68.93; H, 7.84, 7.53; Cl, 9.69; C_3H_7O, 5.38.

3α-Phenyl-3β-nortropanyl Phenyl Ketone (VII).—A suspension of 10 g. of 3α-diphenylhydroxymethyl-3β-nortropanol hydrochloride and 20 g. of fused, powdered zinc chloride in 30 ml. of acetic anhydride was stirred at room temperature for 15 hours, poured into 200 ml. of water containing a few ml. of concentrated hydrochloric acid and the solution was warmed on the steam-bath until the odor of acetic anhydride was no longer detectable. More hydrochloric acid was added and the material that separated was taken up in methylene chloride. The organic phase was washed with sodium carbonate solution, dried and evaporated to leave 6.7 g. of yellow crystals, m.p. 197–207°. Recrystallization from 1-propanol afforded 4.2 g. of white plates, m.p. 209–212°, indistinguishable by means of mixed m.p. and infrared spectrum from the material prepared by demethylation of VI.

3α-Phenyl-3β-nortropanyl Phenyl Ketoxime.—A mixture of 10.0 g. of 3α-phenyl-3α-nortropanyl phenyl ketone, 10.0 g. of hydroxylamine hydrochloride, 35 ml. of pyridine and 250 ml. of 1-propanol was refluxed for 16 hours. After evaporation of the solvent, the residue was swirled with 25 ml. of water to give 6.3 g. of the **hydrochloride**, m.p. 281–283° dec. The filtrate on cooling in ice furnished an additional 2.2 g., m.p. 281° dec., and after standing overnight at room temperature, 2.0 g., m.p. 278–280° dec. After recrystallization from water the analytical sample melted at 286° dec.

Anal. Calcd. for $C_{20}H_{23}ClN_2O$: C, 70.06; H, 6.76; N, 8.17. Found: C, 69.95; H, 7.34; N, 7.94.

3α-Phenyl-3β-nortropanecarboxylic Acid (XIII).—A suspension of 81.3 g. of 3α-phenyl-3β-nortropanyl phenyl ketoxime hydrochloride in 1.5 l. of glacial acetic acid was heated for 5 hours on the steam-bath while hydrogen chloride was being passed into the solution. The solvent was evaporated and the residue was boiled with acetone. The insoluble **hydrochloride**, wt. 47 g., m.p. 281–282° dec., was recrystallized from methanol–ether, m.p. 283° dec.

Anal. Calcd. for $C_{14}H_{18}ClNO_2$: C, 62.80; H, 6.78; Cl, 13.24. Found: C, 62.81; H, 6.88; Cl, 13.18.

Ethyl 3α-Phenylnortropane-3β-carboxylate (XVI).—A suspension of 6.0 g. of 3α-phenylnortropane-3β-carboxylic acid hydrochloride in 300 ml. of thionyl chloride was refluxed for 75 minutes. The excess thionyl chloride was removed under reduced pressure on the water-bath at 30° and the residue was warmed for a few minutes with absolute ethanol. Addition of ether to the cooled solution caused the separation of the **hydrochloride**, m.p. 220–221° dec. wt. 5.8 g., which melted at 222° dec., after crystallization from ethanol–ether.

Anal. Calcd. for $C_{16}H_{22}ClNO_2$: C, 64.96; H, 7.50; Cl, 11.99. Found: C, 64.85; H, 7.15; Cl, 12.07.

Alternatively the acid may be esterified with alcoholic hydrogen chloride at room temperature for several days.

α-Ecgonine Amide (XVII).—A solution of 8.0 g. of α-ecgonine methyl ester and sodamide (from 8.0 g. of sodium) in 250 ml. of liquid ammonia was stirred at room temperature overnight during which time most of the solvent had evaporated. The residue was covered with 300 ml. of ether and decomposed with 60 ml. of water. The aqueous phase was separated and treated with a very large excess of potassium carbonate. The resulting sludge was extracted with chloroform. The united organic phases were evaporated to leave 7.0 g. of the white amide, m.p. 153–157°, raised to 156–157.5° after recrystallization from benzene, wt. 4.5 g.

Anal. Calcd. for $C_9H_{16}N_2O_2$: C, 58.67; H, 8.76; N, 15.21. Found: C, 58.85; H, 8.69; N, 15.19.

Ethyl 3β-Hydroxy-3α-tropanyl Ketone (XVIII).—A solution of 62.1 g. of α-ecgonine amide in 500 ml. of tetrahydrofuran was added to a stirred solution of ethylmagnesium bromide prepared from 368 g. of ethyl bromide and 82.2 g. of magnesium in 2 l. of ether and the clear solution was refluxed gently for 15 hours. The reation mixture was decomposed by addition of 800 ml. of concentrated hydrochloric acid followed by 500 ml. of 1:3 dilute hydrochloric acid. After standing at room temperature for 3 hr. the reaction mixture was treated with a large excess of solid potassium carbonate. The sludge was filtered and the wet filter cake was extracted twice with 3-l. portions of boiling chloroform. The aqueous filtrate was extracted several times with chloroform and the combined extracts were dried and evaporated to leave 72 g. of crystalline solid. This residue was boiled with two 750-ml. portions of hexane. Concentration of the filtered hexane extracts gave 29.5 g. of the ketone as white needles, m.p. 117.5–122°. Recrystallization of 4.5 g. from hexane gave 4 g. of white needles, m.p. 121.5–123.5°.

Anal. Calcd. for $C_{11}H_{19}NO_2$: C, 66.97; H, 9.71; N, 7.10. Found: C, 67.29; H, 9.61; N, 6.94.

3α-(*m*-Anisyl)-ethylhydroxymethyl-3β-tropanol (XIX).—A mixture of 118 g. of *m*-bromoanisole, 15.3 g. of magnesium and 200 ml. of ether was stirred vigorously under nitrogen at room temperature. The reaction began almost immediately and, after addition of 400 ml. of ether, proceeded smoothly with moderately vigorous reflux and without need of external heating or cooling. After 2 hours most of the magnesium had dissolved. Ether was added to bring the volume up to 800 ml. and then a solution of 15 g. of the hydroxyketone XVIII in 250 ml. of tetrahydrofuran was added rapidly causing a gentle reflux. The reaction mixture was refluxed for 4 hours, stirred at room temperature for 15 hours and then added slowly to a cold solution of 66 ml. of concentrated hydrochloric acid in 400 ml. of water followed by 100 ml. of concentrated acid. The layers were separated and the aqueous phase was made weakly basic by addition of solid potassium carbonate. After extraction with methylene chloride, drying and removal of the solvent there remained 18.8 g. of a dark brown, partly crystalline oil. It was dissolved in 125 ml. of acetone and a slight excess of alcoholic hydrogen chloride was added to precipitate the **hydrochloride**, m.p. 244–245° dec., wt. 14.5 g. The analytical sample melted at 245° dec. after crystallization from methanol–ether.

Anal. Calcd. for $C_{18}H_{28}ClNO_3$: C, 63.23; H, 8.25: Cl, 10.37. Found: C, 63.59; H, 8.17; Cl, 10.15.

3α-*m*-Anisyl-3β-tropanyl Ethyl Ketone (XX).—A mixture of 14.2 g. of the above hydrochloride and 28 g. of fused, powdered zinc chloride in 280 ml. of acetic anhydride was stirred at room temperature for 15 hours and then poured into excess sodium-hydroxide solution. The insoluble material was extracted with methylene chloride. Evaporation of the dried extracts left a residue which was converted to the **hydrochloride** in acetone; wt. 7.9 g., m.p. 234–236° dec. Recrystallization from isopropyl alcohol–ether gave the pure salt; wt. 7.3 g., m.p. 236–238°. The infrared spectrum (CH_2Cl_2 solution) showed a strong band at 5.92μ. Ketobemidone (II) showed a carbonyl band at 5.84 μ.

Anal. Calcd. for $C_{18}H_{26}ClNO_2$: C, 66.75; H, 8.09; Cl, 10.95. Found: C, 66.85; H, 8.30; Cl, 10.86.

3α-*m*-Hydroxyphenyl-3β-tropanyl Ethyl Ketone (XXI).—One gram of the above salt was refluxed with 25 ml. of 48% hydrobromic acid for 20 minutes under nitrogen and then evaporated to dryness under reduced pressure on the steam-bath. The residue was dissolved in water and treated with 4 ml. of 35% sodium hydroxide before being extracted with ether. The organic phase was discarded and the aqueous layer was made acidic and then saturated with potassium carbonate. This was followed by chloroform extraction. The dried extracts were evaporated and the residual gum was converted to the hydrochloride in acetone; wt. 0.78 g., m.p. 271.5–273°. Recrystallization from ethanol–ether gave white needles, wt. 0.67 g., m.p. 272.5–274°. The infrared spectrum in either methanol or deuterium oxide was transparent in the carbonyl region.[3]

Anal. Calcd. for $C_{17}H_{24}ClNO_2$: C, 65.90; H, 7.81; Cl, 11.44. Found: C, 66.23; H, 7.81; Cl, 11.25.