The low value of the molar refraction for ψ-tropine might be due to intramolecular hydrogen bonding contributed by configuration I.

The evidence reported here thus confirms the assignment of the *cis*-configuration for pseudotropine and the *trans* configuration for tropine as proposed by Fodor and Nádor.[4]

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Configuration of Tropine and Pseudotropine

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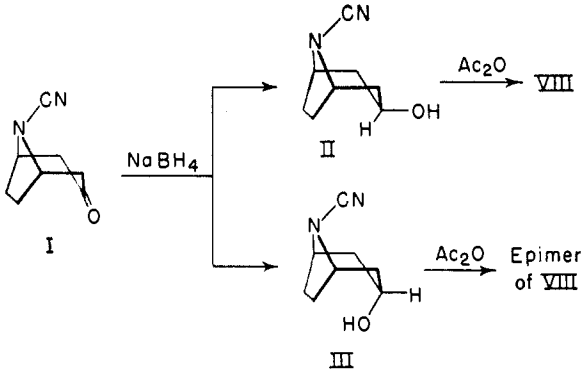
Attempts to establish the orientation of the hydroxyl group in tropine and pseudotropine by forming a bridge between oxygen and nitrogen in one or the other epimer were unsuccessful. In confirmation of recent work of Fodor and Nádor, we found a ready solution of the problem in the method of acyl migrations, which established that pseudotropine (XII) is cisoid and tropine transoid.

Willstätter[2,3] established that reduction of tropinone affords two isomeric alcohols, tropine (tropanol) and pseudotropine (pseudotropanol); both are readily oxidized to the original ketone[2,4] and dehydrated to tropidine.[5,6] The inference that the two alcohols are epimeric was examined critically and eventually accepted.[7,8] Since tropine is isomerized by boiling sodium amylate to pseudotropine,[2,8] the latter is the thermodynamically more stable epimer. Both alcohols have been isolated from plant sources, but tropine is the more abundant of the two; it is obtained readily by hydrolysis of *l*-hyoscyamine.[9]

The present work was undertaken with the objective of establishing the configurations of the epimeric alcohols. After trying various approaches we found a solution of the problem in application of the method of acyl migrations. Our work, however, has been anticipated by Fodor and Nádor,[10,10a] whose recent note reports application of the same method. We thus wish to present independent evidence confirming the conclusion of Fodor and Nádor that members of the pseudotropine series have the cisoid orientation of the hydroxyl group and nitrogen bridge (see IV) and that the tropine epimers are transoid.

Exploratory experiments to ascertain if hindrance of the hydroxyl group is markedly greater in one epimer than the other were carried out by ester interchange with ethyl acetoacetate.[11] Under the conditions employed, however, both tropine and pseudotropine were converted in high yield (94%) into their corresponding acetoacetates, isolated as the picrates. The obvious method of effecting cyclization between oxygen and nitrogen in one or the other of the epimers has been considered by Schöpf and Arnold,[12] who state in a footnote to a paper on another subject that attempts to effect ring closure in nortropine or norpseudotropine had met with no success. We first explored an approach starting with N-cyanonortropinone (I[13]), prepared from tropinone by the von Braun cyanogen bromide method. Although the cyanamide group ordinarily is susceptible to ready reduction, the bridging group in I proved resistant to sodium borohydride, which merely reduced the carbonyl group and gave a mixture of the epimeric alcohols II and III. The alcohols were separated by



chromatography and the higher melting epimer (m.p. 113–113.5°) was shown to belong to the tropine series by acetylation to a product identical with a sample of N-cyanonortropine acetate prepared by a reported procedure.[14] The lower melting alcohol (100–100.5°) on acetylation yielded N-cyanonorpseudotropine acetate (VIII), prepared unambiguously from pseudotropine.

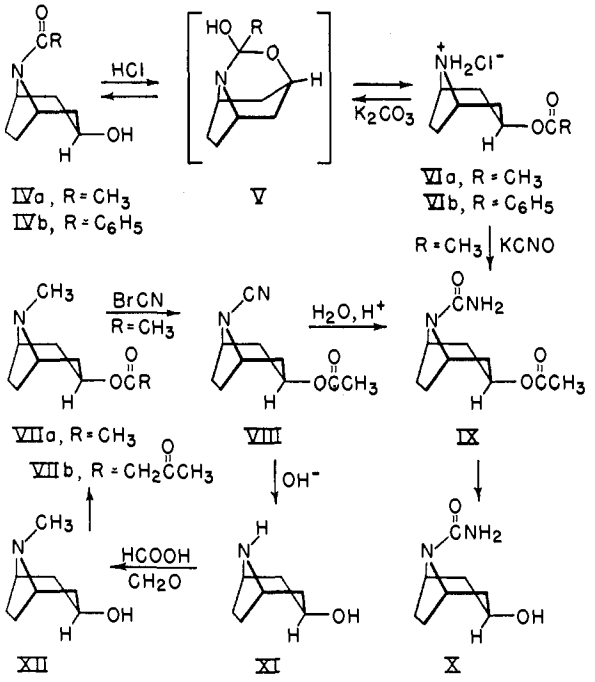
Each alcohol, II and III, was subjected to various

(1) National Institutes of Health Predoctoral Fellow, 1950–1952.
(2) R. Willstätter, *Ber.*, **29**, 936 (1896).
(3) R. Willstätter and F. Iglauer, *ibid.*, **33**, 1170 (1900).
(4) R. Willstätter, *ibid.*, **29**, 393 (1896).
(5) C. Liebermann and L. Limpach, *ibid.*, **25**, 927 (1892).
(6) A. Ladenburg, *Ann.*, **217**, 74 (1883).
(7) J. Gadamer, *Arch. Pharm.*, **239**, 294 (1901).
(8) M. Barrowcliff and F. Tutin, *J. Chem. Soc.*, **95**, 1966 (1909).
(9) For references, see R. H. F. Manske and H. L. Holmes, "The Alkaloids," Academic Press, New York, N. Y., 1950, Chapter VI.
(10) G. Fodor and K. Nádor, *Nature*, **169**, 462 (1952).
(10a) ADDED IN PROOF.—From the relative rates of hydrolysis of esters of tropine and pseudotropine and on the basis of assigned hindrance effects, F. L. J. Sixma, C. M. Siegmann and H. C. Beyerman, *Proc. K. Ned. Acad. Wet.*, **54B**, 432 (1951) [*Chem. Zentr.*, **36**, 5742 (1952)], attributed to the epimeric alkaloids configurations just the reverse of those established by Fodor and Nádor and by us; evidently their estimate of the relative hindrance effects was not valid.
(11) A. R. Bader, L. O. Cummings and H. A. Vogel, THIS JOURNAL, **73**, 4195 (1951).
(12) C. Schöpf and W. Arnold, *Ann.*, **558**, 109 (1947).
(13) The formulation of the piperidine ring in the chair conformation is purely arbitrary, as is the projected direction of the nitrogen substituent.
(14) German Patent 301,870 [*Chem. Zentr.*, I, **89**, 250 (1918)].

treatments in the attempt to effect internal addition of the hydroxyl group to the cyanamide function, but all such attempts failed. Contribution of a dipolar structure to the resonance of the cyanamide function in the sense

$$R_2N-C\equiv N \longleftrightarrow R_2\overset{+}{N}=C=\overset{-}{N}$$

may tend to keep the three atoms of the function colinear, and to a large extent coplanar with the ring residues, with the result that the nitrile and hydroxyl group are too remote in space for interaction. Attempts to cyclize N-carbamylnorpseudotropine (X, below) were also unsuccessful.



Acyl groups are known to migrate from nitrogen to oxygen under acid catalysis and in the reverse direction in the presence of bases, and recent studies of the mechanisms of the reactions have indicated that they probably proceed through cyclic intermediates.[15-18] This approach to the problem was investigated with the following results. N-Acetylnorpseudotropine (IVa) when refluxed in dioxane saturated with hydrogen chloride was converted in 87% yield to O-acetylnorpseudotropine hydrochloride (VIa), characterized by infrared absorption attributable to the ester group (5.77, 8.00 μ) and to the secondary amine hydrochloride group (6.21μ). The O-acetate rapidly reverts to the N-acetate (IVa) in aqueous potassium carbonate solution. N-Benzylnorpseudotropine[19] (IVb) on similar treatment with acid was isomerized to O-benzoylnorpseudotropine hydrochloride (VIb) in comparable yield; with base the latter similarly underwent O → N migration to regenerate IVb.

In sharp contrast, the corresponding amides of the tropine series, N-acetylnortropine and N-benzoylnortropine, proved inert to rearrangement under similar acid conditions and were largely recovered unchanged. That the acyl migrations of the pseudo compounds are intramolecular is indicated by the observation that the N → O benzoyl shift occurred equally well in the presence of ethanol and that the O → N rearrangement was not impeded by addition of diethylamine. Analogy to the work of van Tamelen[18] on stereospecific acyl migrations in the 2-aminocyclopentanol series suggests that the present migrations involve the cyclic intermediate V.

The following evidence establishes that the migrations occur with retention of configuration. First, O-benzoylnorpseudotropine hydrochloride (VIb), on treatment with ammonia to liberate the free base, followed by N-methylation, gave a product whose hydrochloride proved identical with a sample of the known tropacocaine hydrochloride, prepared for comparison from pseudotropine. Then O-acetylnorpseudotropine hydrochloride (VIa) on reaction with potassium cyanate was found to give N-carbamylnorpseudotropine acetate (IX). An identical substance was made from pseudotropine acetate (VIIa) by reaction in benzene with cyanogen bromide to form the N-cyano compound VIII; partial hydrolysis with sulfuric acid in acetic acid yielded the sulfuric acid salt of IX, from which IX was obtained on treatment with base. A similar sequence of reactions applied to N-cyanonortropine acetate afforded N-carbamylnortropine acetate. Conditions for effecting partial hydrolysis of the N-cyano compounds were defined in pilot experiments with the more readily available N-cyanonortropinone (I), which afforded the corresponding N-carbamyl derivative.

One compound encountered in this work, norpseudotropine (XI), differed markedly in properties from the material described by Willstätter.[19,20] By either reduction of nortropinone carbamate with sodium and alcohol[19] or alkaline permanganate oxidation of pseudotropine,[20] Willstätter obtained norpseudotropine as an oil that with carbon dioxide in ether–alcohol afforded a crystalline carbamate, melting at about 140° with evolution of carbon dioxide. Regeneration from the carbamate with cold alkali gave him the free base as fine crystals that absorbed moisture too rapidly for determination of melting point or analysis. In our work, vigorous saponification of N-cyanonorpseudotropine acetate (VIII) gave norpseudotropine as a non-hydroscopic solid that on vacuum sublimation was obtained as small white needles, m.p. 134.5–135°. The analysis and infrared spectrum were in agreement with structure XI, the material afforded pseudotropine (XII) on N-methylation, and melting points of the picrate, N-acetate, N-benzoate and N-carbamate corresponded to those reported. We repeated the oxidation of pseudotropine according to Willstätter, converted the crude oil to a carbamate identical in melting point and mixed melting point with that from our XI, and on regeneration of the base obtained non-hydroscopic, crystalline XI.

(15) G. Fodor and J. Kiss, THIS JOURNAL, **72**, 3495 (1950).
(16) L. H. Welsh, *ibid.*, **71**, 3500 (1949).
(17) A. P. Phillips and R. Baltzly, *ibid.*, **69**, 200 (1947).
(18) E. E. van Tamelen, *ibid.*, **73**, 5773 (1951).
(19) R. Willstätter, *Ber.*, **29**, 1636 (1896).
(20) R. Willstätter, *ibid.*, **29**, 2231 (1896).

Experimental[21]

Pseudotropine (XII).—This has been prepared various ways by Willstätter,[2] however we found the following modified Bouveault–Blanc method of Hansley[22] to be most convenient. Five grams of tropinone[23] was dissolved in a mixture of 10 cc. of anhydrous toluene and 3.3 g. of isobutanol in a dropping funnel mounted on a three-necked round bottom flask, equipped with stirrer and reflux condenser. The flask was charged with 10 cc. of dry toluene and 1.64 g. of sodium and heated to boiling. Vigorous stirring was then maintained while the contents of the funnel were gradually introduced over a period of 15 minutes. More toluene (10 cc.) was then added through the funnel and the mixture vigorously stirred and kept at a gentle reflux for 2 more hours. After cooling the flask in an ice-bath, 20 cc. of water was slowly added to decompose the reaction mixture and stirring was maintained an additional 10 minutes. The material was transferred to a separatory funnel, the toluene layer separated and the aqueous layer extracted with more toluene (or benzene). Evaporation of the combined extracts left an oil which was taken up in hot benzene, treated with a little charcoal and filtered. Petroleum ether (b.p. 30–60°) was added to the filtrate (until cloudy), which on standing deposited 3.6 g. (71%) of white needles, m.p. 106–108°.

Tropine (Epimer of XII).—This was obtained by catalytic reduction of tropinone according to Keagle and Hartung.[24]

Pseudotropine Acetoacetate (VIIb).—A solution (0.50 g.) of pseudotropine in ethyl acetoacetate (3 cc.)[11] was heated for 22 hours at a bath temperature of 100–110°. The ethyl acetoacetate was removed by vacuum distillation and the residue taken up in ether and filtered. The ether was replaced by 10 cc. of benzene and the solution added to 1.2 g. of picric acid dissolved in 10 cc. of warm benzene. Heating the mixture a few minutes and allowing to cool resulted in precipitation of the picrate as small yellow needles (1.52 g., 95% based on pseudotropine), m.p. 161.5–163°. Crystallization from 50% benzene–alcohol provided the analytically pure picrate of VIIb, m.p. 164°.

Anal. Calcd. for $C_{18}H_{22}O_{10}N_4$ (454.39): C, 47.58; H, 4.88. Found: C, 47.57; H, 5.10.

Tropine Acetoacetate (Epimer of VIIb).—Carried out exactly as for the pseudo compound, a 94% yield of the crude picrate (m.p. 171–174°) resulted. The pure yellow needles (from alcohol) melted at 179.5–180°.

Anal. Calcd. for $C_{18}H_{22}O_{10}N_4$ (454.39): C, 47.58; H, 4.88. Found: C, 47.70; H, 5.19.

N-Cyanonortropinone (I).—Tropinone (20.0 g.) dissolved in commercial anhydrous benzene (80 cc.) was slowly added (45 minutes) to a stirred solution of cyanogen bromide (18.0 g.) in benzene (80 cc.) maintained from 50–55°. Following addition the solution was stirred at 50° for 1.5 hours then allowed to stand at room temperature overnight. The mixture was filtered and the reaction flask rinsed with fresh portions of benzene. Evaporation of the combined filtrates left a residual oil which was taken up in 250 cc. of ether and again filtered. Concentration of the filtrate to one-half volume afforded 14.9 g. of white plates, m.p. 108–109°. A second crop (1.6 g.) melting at 103–108° was recovered by further evaporation of the mother liquor; total yield 76.5%. The analytical sample, after several crystallizations from anhydrous ether, melted at 116.5–117°; λ_{max}^{chf} 4.69, 5.87 μ.

Anal. Calcd. for $C_8H_{10}ON_2$ (150.18): C, 63.98; H, 6.71. Found: C, 63.60; H, 6.83.

N-Cyanonorpseudotropine (II) and N-Cyanonortropine (III).—To 500 mg. of I in 10 cc. of water was gradually added 40 mg. of sodium borohydride and the resulting solution allowed to stand at room temperature for 24 hours. It was then thoroughly extracted with several 10-cc. portions of chloroform. Evaporation of the combined extracts left an oil which crystallized on addition of a little ether, to yield 400 mg. (79%) of solid, consisting of a mixture of both epimers. Separation was effected by dissolving the mixture in benzene and chromatographing on alumina. Elution with solvents ranging from benzene–chloroform (7:1) to pure chloroform gave in the first few fractions the higher melting isomer III (crude m.p. about 105–110°) soon followed by II (crude m.p. about 97–99°), in a ratio of approximately 1:3.

For analysis, crude III was chromatographed twice more, retaining the highest melting fraction each time, after which it melted at 113–113.5°; λ_{max}^{chf} 2.78, 2.90, 4.62μ.

Anal. Calcd. for $C_8H_{12}ON_2$ (152.20): C, 63.13; H, 7.95. Found: C, 63.52; H, 8.05.

After similar purification the N-cyanonorpseudotropine (II) melted at 100–100.5°; λ_{max}^{chf} 2.78, 2.91, 4.62 μ.

Anal. Calcd. for $C_8H_{12}ON_2$ (152.20): C, 63.13; H, 7.95. Found: C, 63.18; H, 8.10.

Correlation of Configurations.—The lower melting alcohol II was related to the pseudo series by dissolving it in a mixture of acetic anhydride and anhydrous pyridine and allowing to stand overnight. Addition of excess water and ammonium hydroxide followed by extraction with chloroform and evaporation of the solvent provided white crystals which proved identical (m.p., mixed m.p. and infrared spectrum) with VIII prepared below. In a similar manner, III was acetylated and the product proved identical with N-cyanonortropine acetate previously reported[14] and also synthesized below.

N-Cyanonorpseudotropine Acetate (VIII).—Five grams of crude pseudotropine acetate (VIIa)[25] in 40 cc. of dry benzene was added during 30 minutes to a stirred solution of 5.0 g. of cyanogen bromide in 40 cc. of anhydrous benzene maintained at 60°. Warming was continued for 2 additional hours, after which the reaction mixture was allowed to stand overnight at room temperature. Filtration followed by evaporation of the solvent gave an oil which was taken up in 150 cc. of ether, warmed and rapidly filtered using partial suction. Concentration of the filtrate afforded 2.8 g. (m.p. 113–118°) of white crystals. A second crop (0.5 g.) melting at 110–114° was recovered from the mother liquor. The combined crops (3.3 g.) represented a 62% yield. Although the analytical sample (m.p. 118–118.5°) was obtained by several crystallizations from ether, a mixture of benzene and petroleum ether (b.p. 30–60°) was subsequently found to be more effective; λ_{max}^{chf} 4.64, 5.83, 8.03 μ.

Anal. Calcd. for $C_{10}H_{14}O_2N_2$ (194.23): C, 61.83; H, 7.27. Found: C, 61.44; H, 7.32.

N-Carbamylnortropinone.—To a solution of 0.80 g. of I in 8 cc. of glacial acetic acid (du Pont)[26] was added 0.5 cc. of concentrated sulfuric acid. After standing for at least one hour the sulfuric acid salt which had precipitated was collected on a Büchner funnel and washed well with anhydrous ether. The white crystals weighed 1.40 g. (98.5%) and decomposed at 151° (sealed tube).[27] Rapid crystallization from hot acetic acid improved its appearance but raised its decomposition point only to 151.5°.

Anal. Calcd. for $C_9H_{14}O_6N_2S$ (266.27): C, 36.08; H, 5.30. Found: C, 36.10; H, 5.01.

Liberation was effected by dissolving 1.0 g. of the sulfuric acid salt in 10 cc. of commercial anhydrous methanol and adding a solution of 0.41 g. (2 equivalents) of sodium methoxide in 10 cc. of methanol. After standing 30 minutes the sodium sulfate was filtered off, washed with a little anhydrous methanol and the filtrate evaporated to dryness to leave 0.62 g. (98%) of crude material decomposing at 197–199°. A solution of the latter in methanol was chromatographed on alumina, using methanol as eluent, to give a pure specimen which decomposed at 210–210.5° (vacuum) when

(21) All melting points are corrected. Those below 240° were taken with a Hershberg apparatus, those higher with an aluminum block. Microanalyses by Shirley Golden and by S. N. Nagy and associates. Acid-washed alumina kindly supplied by Merck and Co., Inc., was used for all chromatography.

(22) V. L. Hansley, *Ind. Eng. Chem.*, **39**, 55 (1947).

(23) We are indebted to Dr. Max Tishler of the Merck Laboratories for a generous supply of tropinone. It was purified by one crystallization from petroleum ether (b.p. 30–60°) followed by vacuum sublimation.

(24) L. R. Keagle and W. H. Hartung, THIS JOURNAL, **68**, 1508 (1946).

(25) G. Barger, W. F. Martin and W. Mitchell, *J. Chem. Soc.*, 1820 (1937).

(26) When a different brand of acetic acid (Mallinckrodt) was used a poorer yield was obtained unless one equivalent of water had been previously added.

(27) Some runs gave a product decomposing at about 157° undepressed when mixed with the 151° material.

introduced at 195° and heated at 2° per minute; λ_{max}^{chf} 2.83, 2.92, 5.87, 6.01, 6.28 μ.

Anal. Calcd. for $C_8H_{12}O_2N_2$ (168.19): C, 57.13; H, 7.19. Found: C, 56.96; H, 7.00.

N-Carbamylnorpseudotropine Acetate (IX).—To a solution of 100 mg. of VIII (m.p. 113–118°) in 1 cc. of glacial acetic acid was added 0.1 cc. of concentrated sulfuric acid and 0.01 cc. of water. The solution stood overnight and was then poured into 50 cc. of anhydrous ether. Scratching for a few minutes with a stirring rod crystallized the oil which first appeared. The yield of material (160 mg.) was quantitative and it decomposed at 123–130°. Since purification offered some difficulties a small amount was prepared for analysis as follows: to a little of pure VIII (m.p. 116–118.5°) dissolved in ordinary ether was added a few drops of concentrated sulfuric acid. On standing a few days, the sulfuric acid salt of IX precipitated in the form of fine needles, which were collected, washed well with anhydrous ether and analyzed without further purification (decomposed abruptly at 139–139.5° in a sealed tube).

Anal. Calcd. for $C_{10}H_{18}O_7N_2S$ (310.32): C, 38.70; H, 5.86. Found: C, 39.17; H, 5.79.

The free carbamyl compound (IX) was obtained in 75% yield from the crude sulfuric acid salt by dissolving in water, basifying with potassium carbonate and extracting with chloroform. The crude substance (m.p. 168–171°) obtained on removal of the solvent was purified by dissolving in benzene and passing over alumina using a 50% chloroform–ethyl acetate mixture as eluent. The best fractions were rechromatographed twice providing pure white crystals melting at 171.5–172°; λ_{max}^{chf} 2.85, 2.91, 5.82, 6.03, 6.28, 8.00 μ.

Anal. Calcd. for $C_{10}H_{16}O_3N_2$ (212.24): C, 56.59; H, 7.60; N, 13.20. Found: C, 57.11; H, 7.56; N, 13.08.

N-Carbamylnorpseudotropine (X).—A solution of 100 mg. of IX (m.p. 168–171°) in 3 cc. of anhydrous methanol was treated with 50 mg. of sodium methoxide in 3 cc. of dry methanol and allowed to stand for 5 minutes. Addition of 0.25 cc. of water followed by evaporation to dryness with a jet of air gave a residue which was extracted with 80 cc. of hot chloroform in 2–3 portions. The filtered extracts on evaporation provided 45 mg. (56%) of X melting at 182.5–185.5°. A solution in methanol when adsorbed on alumina and eluted with the same solvent yielded, in the best fraction, material with m.p. 186.5–188.5°.

Anal. Calcd. for $C_9H_{14}O_2N_2$ (170.21): C, 56.45; H, 8.29. Found: C, 56.74; H, 7.99.

N-Cyanonortropine Acetate (Epimer of VIII).—This substance has been reported[14] (m.p. 96°) but the experimental details were unavailable to us. Consequently the following procedure was employed for its preparation. A solution of crude tropine acetate[25] (5.9 g.) in 50 cc. of dry benzene was added with stirring during one hour to a gently refluxing solution of benzene (50 cc.) containing 6.0 g. of cyanogen bromide. The resulting red solution was refluxed an additional hour and let stand overnight. The benzene was removed by distillation and the remaining material extracted with three 50-cc. portions of hot ether. Concentration of the filtered (suction) extracts and addition of petroleum ether (b.p. 30–60°) forced out 4.7 g. (75%) of crude yellow tinged material melting about 70–75°. One crystallization from aqueous ethanol deposited white needles, m.p. 83–87°, used in most cases without further purification, λ_{max}^{chf} 4.64, 5.79, 8.02 μ.

N-Carbamylnortropine Acetate (Epimer of IX).—To a solution of 1.0 g. of crude N-cyanonortropine acetate (m.p. 83–87°) in 10 cc. of glacial acetic acid was added 1.0 cc. of concentrated sulfuric acid followed by 0.1 cc. of water. The mixture stood overnight and was then poured into 500 cc. of anhydrous ether while scratching the sides of the flask with a stirring rod. The oil first formed crystallized readily and the material was allowed to stand a few hours in the cold before filtration. The weight of sulfuric acid salt (decomposing at 133–135°) thus obtained was 1.4 g. This was directly dissolved in 10 cc. of water, made alkaline with saturated potassium carbonate solution, allowed to stand 15 minutes, then extracted with three 10-cc. portions of chloroform. The filtered extracts on removal of solvent produced 0.82 g. (75%) of white solid, m.p. 156–159°. Part of this was purified by dissolving in 50% benzene–chloroform and chromatographing on alumina using the same solvent mixture for elution. The purest fractions when combined and rechromatographed twice melted at 161.5–162°; λ_{max}^{chf} 2.85, 2.92, 5.78, 6.02, 6.26, 7.95 μ.

Anal. Calcd. for $C_{10}H_{16}O_3N_2$ (212.24): C, 56.59; H, 7.60. Found: C, 56.90; H, 7.70.

Norpseudotropine (XI) by Hydrolysis of VIII.—A solution of 3.0 g. of crude VIII (113–118°) in 30 cc. of water containing 3.0 g. of sodium hydroxide was refluxed 7.5 hours. After cooling, 4.5 g. of sodium hydroxide was dissolved in the solution after which it was transferred to a separatory funnel and extracted thoroughly with four 40-cc. portions of chloroform. Removal of solvent yielded 1.83 g. (93%) of material, m.p. 124–128°. Sublimation at 18 mm. (bath temperature about 110°) resulted in a recovery of 1.70 g. (86.5%) of XI, m.p. 132.5–134.5°; λ_{max}^{chf} 2.80–3.20 μ. Resublimation for analysis raised its melting point to 134.5–135°. Molecular weight determinations (Rast, camphor) gave 205, 207 in two independent runs.

Anal. Calcd. for $C_7H_{13}ON$ (127.18): C, 66.10; H, 10.30; N, 11.01. Found: C, 66.05; H, 9.86; N, 10.77.

Proof of Structure of XI. (a) Conversion to Pseudotropine (XII).—A mixture of 100 mg. of XI, 250 mg. of 87% formic acid and 250 mg. of 37% formaldehyde was refluxed 5 hours. The same amounts of formic acid and formaldehyde were again added to the solution and boiling was continued an additional 5 hours. Addition of concentrated hydrochloric acid followed by evaporation under an air jet left an oil which was taken up in a little water and basified with sodium hydroxide pellets. Chloroform extraction of the alkaline solution afforded 104 mg. of material which, when crystallized from benzene–petroleum ether (b.p. 30–60°), deposited 85 mg. (76.5%) of long white needles, m.p. 108.5–109°, undepressed by authentic pseudotropine. Its infrared spectrum, in chloroform, was superposable on that of genuine pseudotropine.

(b) Preparation of Picrate.—A benzene solution of picric acid was added to XI dissolved in benzene. The yellow precipitate which formed immediately, melted at 184–187°; reported for norpseudotropine picrate 187–188°.[28]

(c) Preparation of Carbamate.—Bubbling carbon dioxide through a solution of XI in a mixture of anhydrous ether–anhydrous ethanol (4:1) resulted in precipitation of pure white crystals melting at 143–144.5° (dec.) with some shrinking at 141°. Norpseudotropine carbamate is reported to melt with decomposition at about 140°.[19,20] When the carbamate was added to a cold concentrated solution of sodium hydroxide followed by extraction with chloroform, there was recovered on removal of solvent the original XI.

(d) Identity of N-Acetyl and N-Benzoyl Derivatives (IVa and IVb).—These compounds, prepared as described below, melted at 126–127° and 165.5–167°, respectively, in agreement with the literature values of 128°[29] and 166°.[19,20]

Norpseudotropine by Oxidation of XII.—Pseudotropine was oxidized according to Willstätter[20] and the oil thus obtained converted directly to its carbamate (as in c). One crystallization from ethanol–ether which had been saturated with carbon dioxide resulted in pure white crystals m.p. 142–144° (dec.), not depressed on admixture with the carbamate from c. Moreover, when either carbamate was treated with cold alkali and extracted with *ether* there remained, on evaporation, a viscous oil which, on drying in vacuum for several hours, crystallized and proved identical with XI. When the ether extracts were first dried with potassium hydroxide pellets, crystalline XI appeared directly on removal of solvent.

N-Acetylnorpseudotropine (IVa).—A solution of XI (320 mg.) in a mixture of 3 cc. of acetic anhydride and 3 cc. of anhydrous pyridine was allowed to stand 10 hours at room temperature then heated 4 hours on a steam-bath. Concentration to one-half volume followed by addition of 3 cc. of anhydrous ethanol and evaporation to dryness left the diacetylated material as a crude oil (λ_{max}^{chf} 5.79, 6.12, 8.00 μ). Partial saponification was effected by boiling for 5 hours in a solution of 10 cc. of commercial anhydrous ethanol containing 280 mg. of potassium hydroxide. The material was brought to a *p*H of 7 with dilute sulfuric acid and evaporated to dryness. On extraction of the residual solid with three

(28) H. King and L. L. Ware, *J. Chem. Soc.*, 331 (1941).

(29) M. Polonovski and M. Polonovski, *Bull. soc. chim.*, [IV] **43** 364 (1928).

15-cc. amounts of warm chloroform and subsequent removal of the solvent there was obtained 384 mg. of crude IVa melting at 110–120°. Upon adsorption on alumina and elution with chloroform an 82.5% yield (351 mg.) of pure material (m.p. 126–127°; λ_{max}^{chf} 2.94, 612 μ) was obtained. Polonovski and Polonovski reported an m.p. of 128° for the same compound prepared in a different manner.[29]

N-Benzoylnorpseudotropine (IVb).—This was prepared in a similar manner to that reported[19] using the following detailed procedure: to 40 mg. of XI in 1 cc. of H_2O was added 12.6 mg. (one equivalent) of sodium hydroxide in 0.2 cc. of water followed by 44 mg. (one equivalent) of benzoyl chloride in 0.2 cc. of dioxane. The mixture was vigorously shaken several minutes, after which 6.3 mg. (one-half equivalent) more of sodium hydroxide (in 0.1 cc. of water) was introduced and shaken 15 minutes longer. Extraction of the precipitate with chloroform followed by evaporation of the solvent left 65 mg. (89.5%) of IVb, m.p. 165.5–167°; λ_{max}^{chf} 2.94, 6.16, 6.28 μ.

Nortropine (Epimer of XI).—This was obtained in 95.5% yield from N-cyanonortropine acetate using the same procedure as in the pseudo series. Without purification it melted at 160–162° (reported 161°[30]); λ_{max}^{chf} 2.8–3.2 μ.

N-Acetylnortropine (Epimer of IVa).—Acetylation of nortropine followed by partial saponification as for the corresponding pseudo compounds afforded crude material (m.p. 106–110°); λ_{max}^{chf} 2.95, 6.12 μ. The literature value for the pure material is 124°.[30]

N-Benzoylnortropine (Epimer of IVb).—The same procedure was employed here as for the other series. The crude material (96.5% yield) when crystallized from benzene–ligroin (b.p. 60–90°) gave white crystals (71.5%) melting at 131–132°; λ_{max}^{chf} 2.93, 6.17, 6.29 μ. Willstätter reported 125° for the same compound.[31]

Acetyl Migration (N → O).—A solution of 25 mg. of IVa in 5 cc. of anhydrous dioxane was rapidly saturated with dry hydrogen chloride and refluxed for 8 hours. A jet of air was used to evaporate the solution to dryness. Crystallization of the residue from anhydrous ethanol–ether provided 27 mg. (87%) of VIa, m.p. 215–218° (slightly dependent upon rate of heating). Three recrystallizations from the same solvent mixture produced the analytical material melting at 226.5–227.5°,[32] when introduced at 200° and heated at 2° per minute. Its infrared spectrum (chloroform) exhibited strong bands at 5.77 and 8.00 μ and a sharp peak of slightly lower intensity at 6.21 μ.

Anal. Calcd. for $C_9H_{16}O_2NCl$ (205.68): C, 52.55; H, 7.84. Found: C, 52.67; H, 7.97.

Reverse Acetyl Migration (O → N).—A solution of VIa (20 mg.) in 1 cc. of water was treated with 50 mg. of potassium carbonate. After 10 minutes the material was warmed on a steam-bath for one-quarter hour, cooled and extracted with 5 one-cc. portions of chloroform. Filtration and evaporation of the extracts left 12.6 mg. (76%) of substance, m.p. 125.5–126° shown to be identical with IVa.

Conversion of VIa to IX.—A solution of 22 mg. of VIa and 30 mg. of potassium cyanate in 1 cc. of water was allowed to stand 15 minutes then warmed on a steam-bath for the same length of time. Chloroform extraction of the cooled solution provided 13.5 mg. (59%, m.p. 161–164°) of material identical in all respects with genuine IX.

Benzoyl Migration (N → O).—Dry dioxane (50 cc.) containing 326 mg. of IVb was saturated with dry hydrogen chloride and refluxed for 12 hours. Removal of solvent left a magma which was taken up in warm ethanol (anhydrous), the solution filtered and concentrated. Addition of anhydrous ether precipitated on cooling 325 mg. (86%) of VIb melting at 220–224° (vacuum).[32] Purification (ethanol–ether, anhydrous) raised its melting point to 232–233° (vacuum) when introduced at 200° and heated at 2° per minute. The pertinent infrared bands (chloroform) were located at 5.81, 6.20 and 7.85 μ.

Anal. Calcd. for $C_{14}H_{18}O_2NCl$ (267.75): C, 62.80; H, 6.78. Found: C, 62.43; H, 6.54.

The procedure was then repeated except that anhydrous ethanol (10 equivalent amounts) was added to the dioxane solution before refluxing. No alteration in results was observed. In this case we also observed the infrared spectrum of the material from the mother liquors of crystallizations and it proved to be essentially identical with the spectrum of the pure substance.

Reverse Benzoyl Migration (O → N).—Twenty milligrams of VIb (crude, m.p. 220–224°) in 2 cc. of water was treated with 60 mg. of potassium carbonate and warmed on the steam-bath for 2 hours. After an additional hour at room temperature the solution was extracted with chloroform to give 13 mg. (75%) of IVb.

A run was carried out in a similar manner except diethylamine (20 equivalent amounts) was added to the original mixture and the warming was extended to 3.5 hours. This resulted in an improved recovery (87%) of IVb melting at 165–167°.

Conversion of VIb to Tropacocaine Hydrochloride.—Crude VIb (25 mg.) was added to 3 cc. of concentrated ammonium hydroxide. Shaking for 2 minutes followed by extraction with chloroform provided the free amine of VIb (19.4 mg.) as a crude oil. N-Methylation was achieved in the same way as for norpseudotropine (see a, above). The crude pseudotropine benzoate (tropacocaine) thus obtained was dissolved in ether and converted directly to its hydrochloride salt with dry hydrogen chloride, m.p. (vacuum) 261–265° (dec.). A mixture with authentic tropacocaine hydrochloride[8] was not depressed, while considerable lowering was observed when admixed with the epimeric tropine benzoate hydrochloride.[8]

Attempted Migrations (N → O) in the Tropine Series.—N-Acetylnortropine was treated similary as for the corresponding compound of the pseudo family except that the residue after removal of dioxane was taken up in chloroform and subjected to infrared analysis. Its spectrum was essentially identical with that of the starting material with only a very minute peak appearing at 5.78 μ.

N-Benzoylnortropine received the same treatment except refluxing was maintained for 24 hours. Even under these conditions the starting material was quantitatively recovered.

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(30) M. Polonovski and M. Polonovski, *Bull. soc. chim.*, [IV] **41** 1190 (1927).

(31) R. Willstätter, *Ber.*, **29**, 1575 (1896).

(32) In their preliminary publication Fodor and Nádor (ref. 10) report the O-acetate as melting at 213–214°, and the O-benzoate at 214°. Analyses or states of purity are not given.