[CONTRIBUTION FROM STERLING-WINTHROP RESEARCH INSTITUTE]

Stereochemistry of the Tropines*

BY BERNARD L. ZENITZ, CATHERINE M. MARTINI, MICHAEL PRIZNAR AND FREDERICK C. NACHOD

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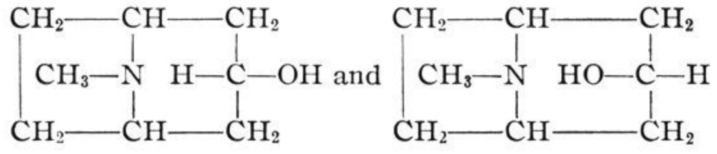
The evidence in the assignment of the steric relationship of tropine and pseudotropine has been amplified by using physico-chemical methods, leading to the *trans* assignment for tropine and the *cis* for pseudotropine.

The question of the assignment of *cis* or *trans* configurations to the N-methyl and hydroxyl groups in tropine and in pseudotropine was left open by Willstätter[1,2] and Barrowcliff.[3] Recently, Fodor and Nádor[4] have ascribed the *cis* configuration to pseudotropine and the *trans* to tropine based on their work with acyl migrations in the case of the N-benzoyl derivatives.

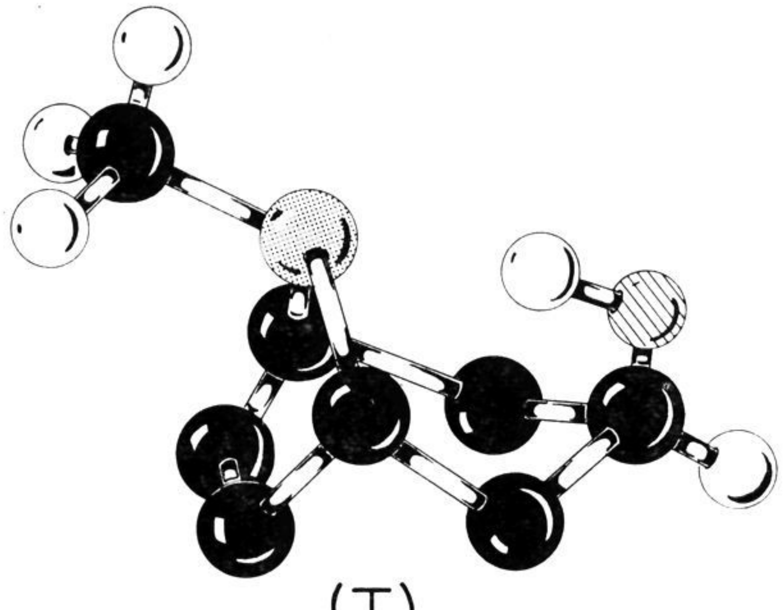


$$\begin{array}{lllll} CH_2 & —CH— & CH_2 & & \\ \mid\ CH_3—N & H—C—OH & & & \\ CH_2 & —CH— & CH_2 & & \end{array} \text{ and } \begin{array}{lll} CH_2 & —CH— & CH_2 \\ \mid\ CH_3—N & HO—C—H & \\ CH_2 & —CH— & CH_2 \end{array}$$

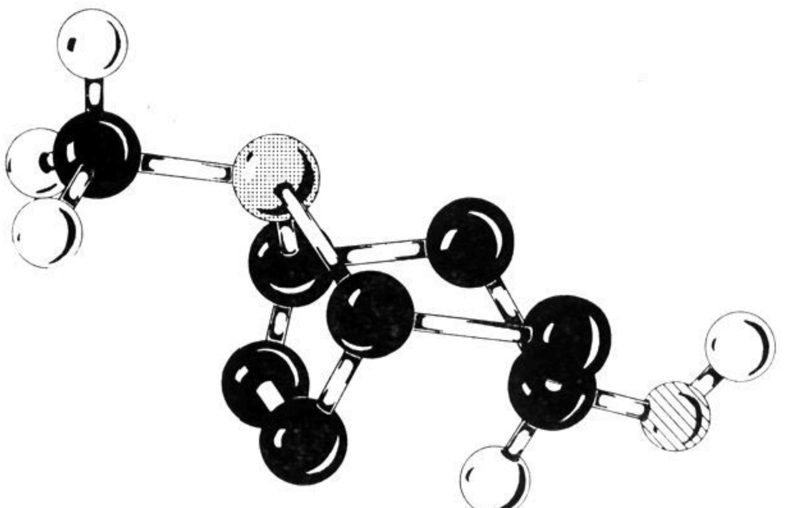
The purpose of this contribution is to use physico-chemical evidences in further establishing the stereochemical relationship. The approaches consisted of the measurement of the dipole moments, infrared spectra, densities and refractive indices.

The tropine (m.p. 64–66°) and the pseudotropine (m.p. 108.5–109.5°) used in these studies were synthesized in our laboratories by the reduction of tropinone which was obtained essentially following the procedures used by Robinson[5] and Hartung and Keagle.[6]

Each of the two epimers can exist in either the boat or the chair form which are shown in I to IV. The dipole moments for the two limiting conditions of the *cis* (I, II) and the *trans* (III, IV) forms were calculated, using group moments of 1.25 for the N-CH_3 group and 1.65 for the OH group as approximations and angles for the groups to the center of symmetry of 60, 135, 130 and 170° for I to IV, neglecting contributions of other portions of the molecule, following the vector



(I)



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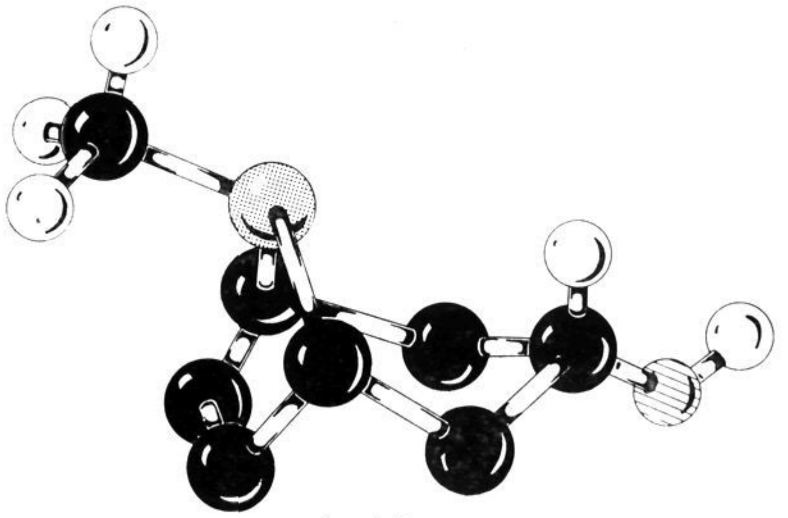
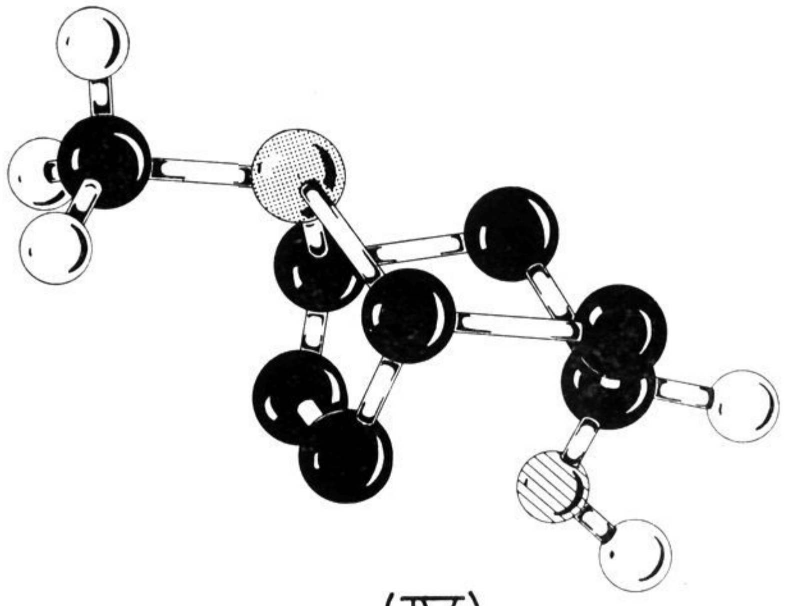


(III)



(IV)

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* Presented at the 122nd meeting of the American Chemical Society, Atlantic City, N. J., September 14–19, 1952.

(1) R. Willstätter and F. Iglauer, *Ber.*, **33**, 1170 (1900).

(2) R. Willstätter and M. Bommer, *Ann.*, **422**, 21 (1921).

(3) M. Barrowcliff and F. Tutin, *J. Chem. Soc.*, **95**, 1966 (1909).

(4) G. Fodor and K. Nádor, *Nature*, **169**, 462 (1952).

(5) R. Robinson, *J. Chem. Soc.*, 762 (1917).

(6) L. C. Keagle and W. H. Hartung, THIS JOURNAL, **68**, 1608 (1946).

addition method described by Smyth.[7] The calculated dipole moment limits for the two *cis* forms are 2.5 and 1.2 ± 0.5 *D;* and for the more compensated *trans* forms 1.3 and 0.5 ± 0.5 *D*, respectively. The measured moments (in benzene 25 ± 0.01°) were found to be 2.20 and 1.59 *D*, respectively, giving the expected higher value for the *cis-* or ψ-form, with a greater contribution from structure I.

The calculation of the moments in the present case is necessarily crude and only of a semi-quantitative nature. The large margin of error is a result of the fact that the position of the N-methyl group cannot be assigned on account of the low transition energy at the N–C bond angle of ±36°. This, as well as the assumptions above, accounts for ±0.3 *D* unit. In addition the rotation of the hydrogen at the hydroxyl group influences the result by about 0.1 *D* unit.[8] Increasing complexity in molecular arrangement frequently results in relatively large error limits[9] as has been pointed out by Brooker, *et al.*[10] Hence it was felt that in view of the many necessary assumptions the limits of ±0.5 *D* were justified.

The infrared spectra for the two compounds in the region 2 to 3.5 μ are shown in Fig. 1 as determined as solutions in CS_2. Apart from the OH band at 2.76 μ, strong hydrogen bonding is apparent from the bands 3.10 and 2.95 μ. It would appear that more complex and more extensive hydrogen bonding is present in pseudotropine than in tropine. It was reasoned that configuration I alone could show intramolecular hydrogen bonding whereas configurations II, III and IV could show only intermolecular hydrogen bonding. Since the former would be concentration independent and the latter concentration dependent the spectra were determined at three different concentrations. To show the extent of hydrogen bonding in each case and the concentration dependence, the curves were replotted as extinction coefficients, and the ratio of bonded OH to free OH for the integrated areas under the absorption maxima were calculated (Table I). These ratios show larger values, and therefore greater hydrogen bonding in the pseudotropine. It can also be shown, if the ratios are plotted against the concentration, that the curve for pseudotropine flattens out more quickly than that for tropine indicating less concentration dependence for the pseudo compound. Both pieces of evidence point to the presence of intra- as well as intermolecular hydrogen bonding for pseudotropine as would be expected for the *cis* configuration (structures I and II).

TABLE I

Concentrated g./l.	$\frac{\int A \text{ bonded OH}}{\int A_{OH}}$ (tropine)	$\frac{\int A \text{ bonded OH}}{\int A_{OH}}$ (ψ-tropine)
13.1	9.63	10.80
6.55	5.08	6.19
3.28	1.88	2.89

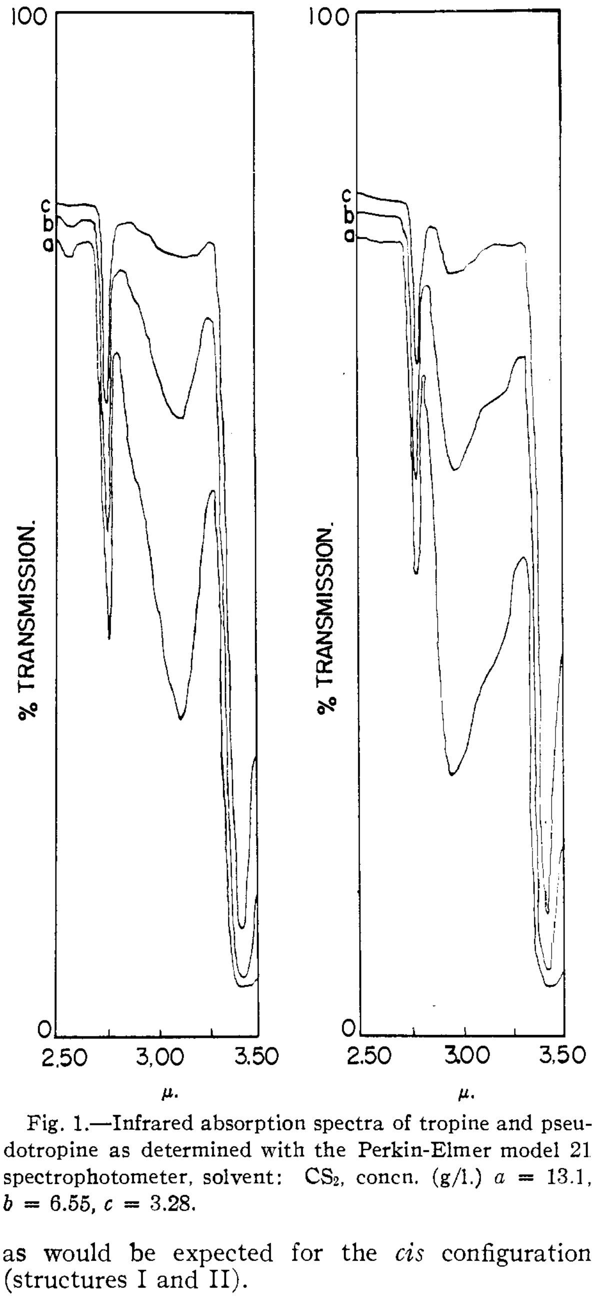

Fig. 1.—Infrared absorption spectra of tropine and pseudotropine as determined with the Perkin-Elmer model 21 spectrophotometer, solvent: CS_2, concn. (g/l.) *a* = 13.1, *b* = 6.55, *c* = 3.28.

We have also determined the densities and refractive indices (Table II) of the two solid epimers, since the only values available in the literature refer to liquids (tropine: $n^{99.8}_D$ 1.48113, $d^{99.8}_4$ 1.0161[11], d^{116}_{22} 1.001[12]; ψ-tropine: d^{116}_{22} 0.997[12]).

TABLE II

	Tropine	ψ-Tropine
Density d^{25}_4 (by displacement)	1.1154	1.1825
Refractive index[13]		
$n^{25}_D\ \sqrt[3]{n_\alpha n_\beta n_\gamma}$	1.552	1.566
Molar refraction (calcd. 40.21)	40.45	38.95

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[7] C. P. Smyth, Determination of Dipole Moments, in "Physical Methods of Organic Chemistry," ed. by A. Weissberger, Vol. I, pt. 2, 2nd edition, Interscience Publishers, New York, N. Y., 1949, p. 1617.

[8] W. C. Schneider. THIS JOURNAL, **70**, 627 (1948).

[9] Personal communication from Professor C. P. Smyth, Princeton University.

[10] L. G. S. Brooker, R. H. Sprague, C. P. Smyth and G. L. Lewis, THIS JOURNAL, **62**, 1116, 1122 (1940).

[11] K. von Auwers, *J. Prakt. Chem.*, **105**, 102 (1922); J. F. Eykman, *Ber.*, **25**, 3073 (1892).

[12] Smith, Ph.D. Thesis, University of Maryland, 1947.

[13] We are grateful to Dr. R. L. Clarke of these laboratories for the determination of the refractive indices. A more comprehensive crystallographic characterization of the two epimers is found in *Anal. Chem.*, **24**, 1516 (1951); *ibid.*, in press.

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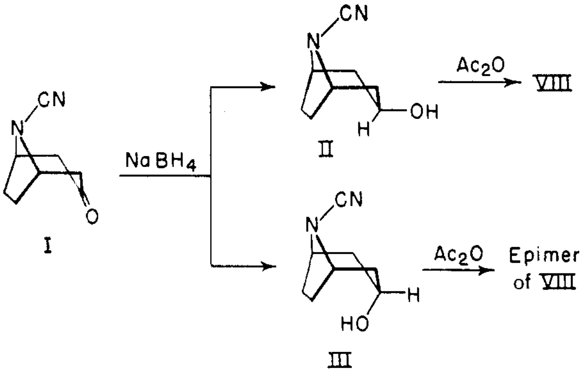
Attempts to establish the orientation of the hydroxyl group in tropine and pseudotropine by forming a bridge between oxygen and nitrogen in one or the other epimer were unsuccessful. In confirmation of recent work of Fodor and Nádor, we found a ready solution of the problem in the method of acyl migrations,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

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[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**, 452 (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)].