g.) suspended in 10% sodium hydroxide solution (4 ml.). The mixture was heated at 95° during a 7-hour period with occasional shaking, then cooled to 70° and treated with concd. nitric acid (6 ml.), stirred for an hour while cooling and finally extracted with ether. After drying and solvent removal, the crude furoic-α-C^{14} acid was purified to constant m.p. by repeated sublimation at 80–90° (1 mm.). The purified product weighed 112 mg. (30% based on xylose-1-C^{14}) and showed a specific radioactivity of 0.639 mc./mole. The radioactivity assay of the 2-furoic-α-C^{14} acid was thus about 23% higher than that of its D-xylose-1-C^{14} precursor, an observation for which we have no definitive explanation. It is well known[4] that hydrochloric acid converts 2-furaldehyde into amorphous, polymeric "humins" under the conditions of the xylose-2-furaldehyde transformation. If the conversion of our 2-furaldehyde-α-C^{14} partially into humic materials were accompanied by a large kinetic isotope effect, favoring the C^{12}-species, the unconverted 2-furaldehyde-α-C^{14} and its resulting 2-furoic-α-C^{14} acid would be expected to show a higher specific radioactivity than their D-xylose-1-C^{14} precursor. The present 23% discrepancy in the radioactivity assays in question, however, seems rather large to be explained only as an isotope effect.

Decarboxylation of 2-Furoic-α-C^{14} Acid.—The above 2 furoic-α-C^{14} acid (13.65 mg.) was neutralized with 0.1 *N* sodium hydroxide (4.88 mg. of NaOH) and the solution was treated with mercuric chloride (33.09 mg.) after the procedure of Gilman and Wright.[17] The mixture was placed in the customary combustion apparatus for carbon-14 assay[18] and heated under gentle reflux while sweeping the apparatus with helium. After several minutes the reaction mixture was cooled, whereupon the 2-chloromercuri derivative of furan crystallized.[17] This was collected, recrystallized twice from ethanol, dried and assayed for radioactivity. The specific radioactivity proved to be 0.0108 mc./mole, or approximately 1.7% that of the 2-furoic-α-C^{14} acid precursor.

Radioactivity assays were conducted by wet combustion of the above labeled samples to carbon dioxide[19] followed by counting[20] the latter in an ionization chamber with the aid of a Cary model 31 vibrating reed electrometer.

(17) H. Gilman and G. F. Wright, THIS JOURNAL, **55**, 3302 (1933).
(18) J. G. Burr, *Anal. Chem.*, **26**, 1395 (1954).
(19) O. K. Neville, THIS JOURNAL, **70**, 3501 (1948).
(20) V. A. Raaen and G. A. Ropp, *Anal. Chem.*, **25**, 174 (1953).

STANFORD, CALIF.

[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY, THE UNIVERSITY OF CHICAGO]

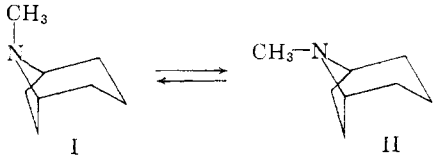
The Configurational Equilibrium of the N-Methyl Group in Some Tropane Deuteriohalides[1]

BY GERHARD L. CLOSS

RECEIVED APRIL 6, 1959

The non-equivalent methyl groups in pseudotropine methiodide give rise to proton magnetic resonance at slightly different fields and cause a doublet with a 6 c.p.s. separation. The occurrence of two doublets in the N-methyl region in the n.m.r. spectrum of an acidified aqueous solution of pseudotropine hydrochloride is interpreted as being caused by the presence of two isomers arising from the two possible configurations of the N-methyl group. As a consequence of rapid exchange of the nitrogen proton with the solvent, the two doublets coalesce into a single peak on adjusting the solution to *p*H 6. In acidified deuterium oxide solution two single peaks are obtained because of eliminated spin coupling. By measuring the ratio of the areas of the peaks, the equilibrium constant of the interconversion process is obtained in a semi-quantitative way. The resonance line at higher field is assigned to the isomer having the N-methyl group attached in an equatorial position relative to the piperidine ring. Equilibrium constants are reported for a number of deuteriohalides of tropane derivatives and the isomer with the equatorial methyl group was generally found to be the more stable one.

Because of the non-planar configuration of the nitrogen, tropane and its derivatives can exist in two stereoisomeric forms in which the methyl group is either oriented axial or equatorial relative to the piperidine ring (I and II). Since the inversion of



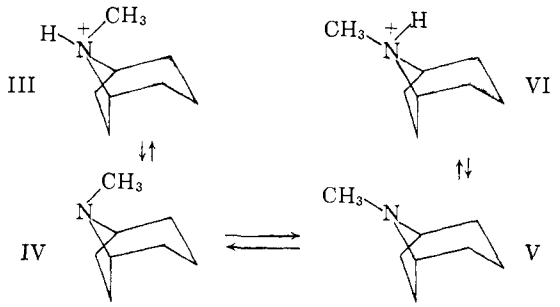
I II

substituents on trivalent nitrogen in relatively unstrained ring systems is known to be a process of low activation energy,[2] it can be expected that the two isomers exist in solution in a rapid equilibrium. Information about the position of this equilibrium and the magnitude of the equilibrium constant is of interest in connection with the recent observation of the stereoselective quaternization of tropane bases. In a series of publications Fodor and his group[3] have demonstrated that in nearly all cases they have studied, tropane derivatives yield on quaternization exclusively that isomer in which the entering substituent is located on the same side of the piperidine ring as the endoethylene bridge, or in other words occupies an equatorial position on the six-membered ring. In order to explain this stereospecificity the Hungarian workers argue that the amine with the methyl group axial relative to the piperidine ring is the more stable isomer because of smaller "Pitzer strain" in this configuration than in the isomer in which the methyl group is located in a quasi-axial position with regard to the pyrrolidine ring.

This argument does not seem to be a valid one because the stereochemical course of this rate-controlled alkylation does not give any information about the equilibrium of the much faster interconversion of the two isomeric amines.

Because of the fast rate of the inversion process no simple method is available to give direct information concerning this equilibrium. However, the conjugate acids of the tropane bases should exist in similar equilibria in which the interconversion of the two isomers proceeds *via* the free bases (III–VI). If one assumes in first approximation that this equilibrium is mainly determined by the difference of non-bonded interactions in the two isomers

(1) Presented in part at the 135th Meeting of the American Chemical Society, April, 1959, Boston, Mass.
(2) See, *e.g.*, A. T. Bottini and J. D. Roberts, THIS JOURNAL, **80**, 5203 (1958).
(3) For recent reviews see: G. Fodor, *Tetrahedron*, **1**, 87 (1957); G. Fodor, *Acta Chim. Acad. Sci. Hungar.*, **5**, 379 (1955); G. Fodor, *Experientia*, **11**, 129 (1955); compare also S. P. Findley, THIS JOURNAL, **75**, 3204 (1953); K. Zeile and W. Schulz, *Chem. Ber.*, **88**, 1078 (1955).



III and VI, one should expect the equilibrium of the conjugate acids to be qualitatively similar to the equilibrium of the free amines because the steric requirements of the lone electron pair on nitrogen should not differ very much from that of the proton.[4] However, the base-catalyzed interconversion of the conjugate acids can be slowed down considerably by keeping the base concentration low,[5] in contrast to the free bases.

It is the purpose of this paper to report how evidence for the existence of such an equilibrium can be obtained for a number of tropane salts and the equilibrium constant be estimated in a semi-quantitative way by nuclear magnetic resonance spectroscopy (n.m.r.). Throughout this paper isomers III and VI and their derivatives will be called the axial and equatorial isomers, respectively.

The method is based on the non-equivalence of the N-methyl groups in the two isomers. It can be expected that the methyl protons are shielded differently in each isomer and come into resonance at different applied fields. To test whether this difference in chemical shift of the two possible configurations of the methyl protons is large enough to permit resolution, the n.m.r. spectrum of pseudotropine methiodide (VII, R_1 = H, R_2 = CH_3) in aqueous solution was measured (Fig. 1A). The spectrum can be divided into three regions and assignments made on the basis of relative intensities and chemical shifts. The broad band at highest field is assigned to resonance of the methylene protons at carbons 2, 4, 6 and 7; the band at lowest field, located on the shoulder of the strong water band, constitutes a multiplet originating from resonance of the protons at carbons 1, 3 and 5, each of which is bound to an atom more electronegative than carbon. Small differences in shielding and spin coupling with protons on neighboring atoms cause complex multiplet structure which cannot be resolved and appears as broad band in each case. However, at 122 and 128 c.p.s. (relative to aromatic H in toluene at 40 mc.) there appears a sharp doublet with peaks of equal intensity that must be assigned to the N-methyl protons. Since there is no proton bound to the adjacent nitrogen, and spin coupling with 14N, which would lead to a triplet,[6] can be expected to be weak, the occurrence of a doublet can only be interpreted as resulting from the separate resonances of the non-equivalent methyl groups.

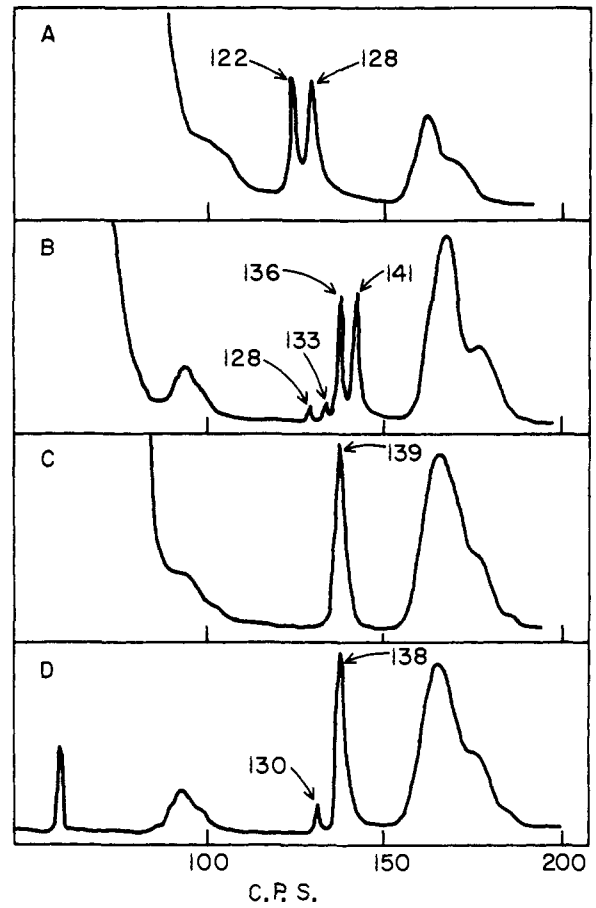


Fig. 1.—N.m.r. spectra of: A, pseudotropine methiodide (VII, R_1 = H, R_2 = CH_3) in water; B, pseudotropine hydrochloride (VII, R_1 = R_2 = H), in water at *p*H 1; C, pseudotropine hydrochloride (VII, R_1 = R_2 = H) in water at *p*H 6; D, pseudotropine deuteriochloride (VII, R_1 = R_2 = D) in deuterium oxide at *p*H 1 (c.p.s. relative to arom. H in toluene).

The observed dependence of the chemical shift on the configuration of the methyl group is large enough to encourage an attempt at detection of the isomeric hydrochlorides. Figure 1B shows the spectrum of pseudotropine hydrochloride (VII, R_1 = H, R_2 = H) in water at *p*H 1. As expected the broad band at high field shows little change compared to the equivalent peak of the methiodide spectrum. However, the N-methyl proton region shows one doublet at 136 and 141 c.p.s. and a much weaker doublet at 128 and 133 c.p.s. Because the proton on nitrogen interacts with the methyl protons by spin coupling, splitting of the methyl proton resonance into a doublet should be expected in the hydrohalides. The presence of a second doublet at lower field and much lower intensity can only be interpreted as arising from an isomer possessing a slightly less shielded N-methyl group. The reproducibility of the spectrum after careful purification of the pseudotropine excludes an impurity as the cause for the second doublet.

(4) Compare, however, M. Aroney and R. J. W. Fevre, *J. Chem. Soc.*, 3002 (1958), who found by molecular polarizability studies on piperidine that the volume requirement of a lone electron pair on ring nitrogen seems to exceed that of a covalently bound hydrogen atom.

(5) For effect of *p*H on exchange of protons on ammonium salts see: (a) A. I. Brodskii and L. V. Sulima, *Doklady Akad. Nauk. S.S.S.R.*, **74**, 513 (1950); (b) L. Kaplan and K. E. Wilzbach, THIS JOURNAL, **76**, 2593 (1954); (c) C. G. Swain, J. T. McKnight, M. M. Labes and V. P. Kreiter, *ibid.*, **76**, 4243 (1954).

(6) E. Grunwald, A. Loewenstein and S. Meiboom, *J. Chem. Phys.*, **27**, 641 (1957).

The 8 c.p.s. separation of the two doublets agrees well with the observed separation of 6 c.p.s. for the two configurations of the methyl groups in the quaternary salt. It is therefore reasonable to assume that the two doublets are caused by the N-methyl proton resonance of the two stereoisomers.

To support this view the spectrum of pseudotropine hydrochloride was measured at *p*H 6. At this *p*H the amine is still almost completely protonated.[7] However, the base-catalyzed exchange of the proton on nitrogen with the solvent should be too fast to allow spin coupling[8] to be observable and, similarly, the interconversion of the two stereoisomers should have grown to a rate at which independent signals for each isomer cannot be expected.[9] Figure 10 shows that in agreement with this consideration only one single peak is observed in the N-methyl resonance region. Spin coupling with the proton on nitrogen, responsible for the occurrence of doublets in the spectrum of the hydrohalides, can be effectively eliminated by exchanging the proton for a deuteron; one peak for each isomer should then be expected in acidified deuterium oxide solution. This was found to be the case (Fig. 1D). Use of deuterium oxide as solvent has the advantage that the areas of the singlets can be measured more accurately than the areas of doublets. The ratio of the areas should be equal to the ratio of the concentrations of the two isomers which is the equilibrium constant of the inversion process.

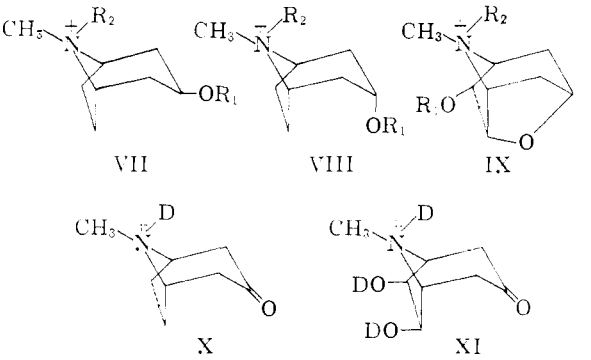
CHEMICAL SHIFTS AND RELATIVE INTENSITIES OF N-METHYL PROTON RESONANCE OF TROPANE DEUTERIOCHLORIDES IN DEUTERIUM OXIDE AT *p*H 1

Compound	Line I,[a] c.p.s.	Line II,[a] c.p.s.	$K = \frac{\text{area II}}{\text{area I}}$[b]
Tropane·DCl	136	143	15
Pseudotropine·DCl (VII, R_1 = R_2 = D)	130	138	9.5
Acetylpseudotropine·DCl (VII, R_1 = CH_3CO, R_2 = D)	132	141	11
Benzoylpseudotropine·DCl (VII, R_1 = C_6H_5CO, R_2 = D)	140	146	11
Tropine·DCl (VIII, R_1 = R_2 = D)	134	139	15
Acetyltropine·DCl (VIII, R_1 = CH_3CO, R_2 = D)	135	141	18
Benzoyltropine·DCl (VIII, R_1 = C_6H_5CO, R_2 = D)	140	145	20
Atropine·DCl (VIII, R_1 = $C_6H_5CH(CH_2OH)CO$, R_2 = D)	143	149	20
Scopoline·DCl (IX, R_1 = R_2 = D)	121[c]		
Benzoylscopoline·DCl (IX, R_1 = C_6H_5CO, R_2 = D)	131	134	1
2,2,4,4-Tetradeuteriotropinone·DCl (X)	126	134	4.2
2,2,4,4-Tetradeuterioteloidinone·DCl (XI)	123	128	1

[a] Chemical shifts are relative to aromatic H in toluene at 40 mc. [b] Average of ten determinations; estimated error: ±10%. [c] Cannot be resolved.

Table I summarizes the results obtained for various other tropane derivatives in acidified deuterium oxide. It can be seen that in all investigated derivatives of the deuteriochlorides of tropine (VIII, R_2 = D) and pseudotropine (VII, R_2 = D) the less intense peak is found at lower field. The two peaks of the deuteriochlorides of benzoylscopoline (IX, R_1 = COC_6H_5, R_2 = D) and 2,2,4,4-tetradeuterioteloidinone (XI) show about equal intensity. In order to study the equilibrium of tropinone (X) and teloidinone deuteriochloride the hydrogen atoms at carbons 2 and 4 had to be exchanged for deuterium because the neighboring carbonyl group lowers the shielding of these protons sufficiently to shift their resonance into the N-methyl region.

Without additional evidence it is not possible to assign one of the two isomers to the more intense N-methyl resonance because a sound prediction of the relative shielding of the methyl group in its two configurations cannot be made.[10] The fact that the equilibrium of the tetradeuterioteloidinone



deuteriochloride (XI) is shifted toward unity compared to the equilibrium of the tetradeuteriotropinone deuteriochloride (X) might be used as indication that the predominant isomer in the tropinone salt is the equatorial isomer. Additional nonbonded interaction of the two β-oriented hydroxyl groups in positions 6 and 7 with the equatorial methyl group would tend to destabilize this configuration in the teloidinone and make it comparable in stability to the isomer in which the methyl group is located axially on the piperidine ring. More direct evidence for the position of this equilibrium can, however, be obtained.

In his studies on the alkylation of the tropane bases Fodor showed that different stereoisomers of N-carboethoxymethylnorpseudotropine methiodide can be obtained depending on the order of the nitrogen alkylation. Structure XIII was assigned to the product obtained from the methylation of N-carboethoxymethyl norpseudotropine (XII) because it could be converted to the lactone XIV. Consistent with structure XVI the product from the reaction of pseudotropine (XV) with ethyl

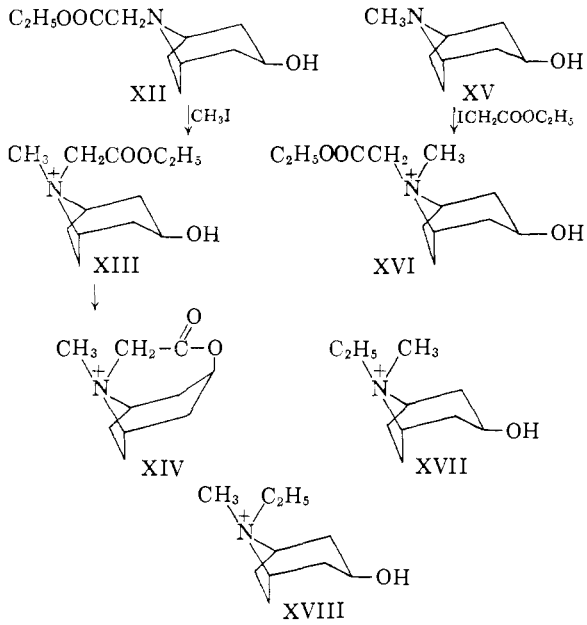
(7) The pK_b of pseudotropine was found to be 3.67 by P. F. Smith and W. H. Hartung, THIS JOURNAL, **75**, 3859 (1953).

(8) Compare the n.m.r. spectrum of methylammonium chloride in water as a function of *p*H; E. Grunwald, A. Loewenstein and S. Meiboom, *J. Chem. Phys.*, **27**, 630 (1957).

(9) For the influence of exchange of nuclei between two individual chemical environments on the n.m.r. spectrum see, *e.g.*, H. S. Gutowsky and D. W. McCall, *ibid.*, **21**, 279 (1953); H. S. Gutowsky and A. Saika, *ibid.*, **21**, 1688 (1953); H. S. Gutowsky and C. H. Holm, *ibid.*, **25**, 1228 (1956).

(10) R. U. Lemieux, R. K. Kullnig, H. J. Bernstein and W. G. Schneider, THIS JOURNAL, **80**, 6098 (1958), observed in acetylated sugars that the methyl protons of axial acetoxy groups usually give rise to resonance at lower field than when in the equatorial position. An inverse relation was found for the ring hydrogens.

iodoacetate could not be cyclized.[11] Since the carboethoxy group should have no direct bearing on the stereospecific course of this reaction, one should expect analogous results on alkylation with ethyl iodide. Ethylation of pseudotropine should yield the quaternary salt with the N-methy group in an axial position (XVII), whereas the methylation of N-ethylnorpseudotropine should produce the isomer bearing the methyl group in an equatorial orientation on the piperidine ring (XVIII).



Both alkylations were carried out and the n.m.r. spectra of the crude reaction products are presented in Fig. 2A and B. It can be seen that two different isomers are produced, but both reaction products are contaminated with small amounts of the other isomer. The predominant isomer of the ethylation of pseudotropine which should possess an axial N-methyl group gives rise to N-methyl proton resonance at lower field than the predominant ethylation product of N-methylnorpseudotropine with its equatorial methyl group. It seems permissible to extrapolate the results obtained for the quaternary ammonium halide to the deuteriochlorides and assign the peaks at higher field to the isomer with the equatorial N-methyl group. However, no definite assignments of the N-methyl peaks can be made in the cases of teloidinone and benzoylscopoline deuteriochlorides. It seems possible that the proximity of the oxygen atoms at carbon 6 to the equatorial methyl group may reduce its shielding enough to reverse the relation observed for pseudotropine.[12] Fortunately the equilibrium constants for these two compounds are close enough to unity that this assignment becomes irrelevant.

It can thus be stated that the more stable isomer of the 3-substituted tropane deuteriohalides is the one which bears the N-methyl group in an equatorial position. β-Substitution at carbons 6 and 7 tends to make both isomers about equal in stability. This result is in good agreement with the Stuart–Briegleb models which show clearly that the methyl group is almost unhindered in the equatorial position, whereas there is serious 1–3 interaction of the axial methyl group with the β-hydrogens at carbons 2 and 4.

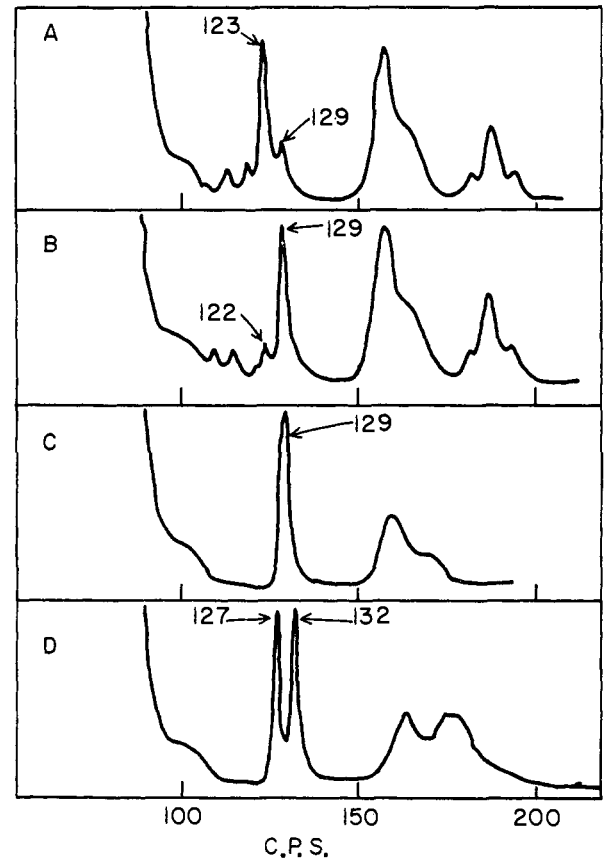


Fig. 2.—N.m.r. spectra of: A, pseudotropine ethiodide (XVII); B, N-ethylnorpseudotropine methiodide (XVIII); C, tropine methiodide (VIII, R_1 = H, R_2 = CH_3); D, tropane methiodide (c.p.s. relative to arom. H in toluene).

As already mentioned one can expect the equilibrium of the corresponding free bases to be qualitatively similar to those discussed above if one assumes that non-bonded interaction in both the amine and its conjugate acid are the determining factors for the equilibrium. It should be pointed out that the solvation of the positively charged deuteriochlorides can be expected to be much stronger than the solvent effect on the neutral amine. This may cause considerable difference between the magnitude of the equilibrium constants in the amine and its conjugate acid, respectively. However, inspection of models and conformational considerations seems to indicate that in the case of the amines too, the equatorial configuration of the methyl group is the more stable one.

Surprisingly, the n.m.r. spectrum of tropine methiodide[13] showed only one peak in the N-methyl

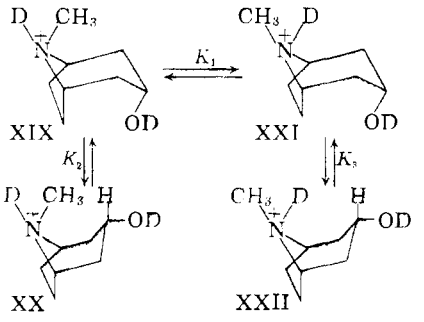
(11) G. Fodor, J. Toth and I. Vincze, *J. Chem. Soc.*, 3504 (1955); G. Fodor, Koczka and Lestyan, *Magyar Kem Folyoirat*, **59**, 243 (1953).

(12) W. D. Kumler, J. N. Shoolery and F. V. Brutcher, THIS JOURNAL, **80**, 2533 (1958), found a 12 c.p.s. shift toward low field in the spectrum of D$\alpha\alpha'$-dibromocamphor for one of the *gem*-methyl groups compared to the same methyl resonance in the endo-monobromo compound.

(13) Tropine methochloride and methobromide gave the same spectrum as the methiodide.

region instead of the expected doublet (Fig. 2C). Tropane methiodide behaved similarly to pseudotropine methiodide (Fig. 2D), exhibiting a doublet with a peak separation of 5 c.p.s. This inuflence of the orientation of the 3-hydroxyl group on the peak separation of the equatorial and axial N-methyl group may be accounted for by either of the two following explanations. The magnetic anisotropy of the hydroxyl group causes an angular dependence of its "long range" contribution to the total shielding of the two methyl groups.[14] It is conceivable that in the case of tropine methiodide this effect leads to the cancellation of the difference in shielding originating from other parts of the molecule. An alternative explanation is based on the assumption that the considerable mutual repulsion of the 3-hydroxyl group and the hydrogens at carbon atoms 6 and 7 forces the piperidine ring out of the normal chair conformation. A boat conformation seems even less favored because of strong interactions of the axial methyl group with the β-hydrogen at position 3. This should result in a slightly distorted piperidine ring which could lead to equal total shielding of the two methyl groups.

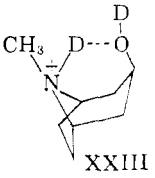
One apparent contradiction to these arguments appears in the fact that in acid solution all deuteriochlorides of tropine and its derivatives show the presence of a second, weaker, peak at lower field. That this second peak arises from the N-methyl proton resonance of an isomer could be demonstrated in the same way as described for pseudotropine. Again the two peaks coalesce into one on adjusting the pH to 6; the spectrum of the hydrochloride in acidified water showed two partially overlapping doublets of different intensities. On first sight this finding seems to be in disagreement with the observation made on tropine methiodide which indicated equal shielding for the N-methyl



protons in both configurations. A closer inspection of the conformational equilibria, however, can provide a satisfactory answer. Each of the isomeric tropine deuteriohalides can in principle exist in two conformations. The chair conformation of both isomers probably deviates slightly from a normal chair form of a piperidine ring for reasons just mentioned in the discussion of the tropine methiodide. The ratio of concentrations of boat and chair conformations present in the axial isomer (K_2) should be similar to the same ratio in the methiodide, and is probably small. In contrast the boat conformation of the equatorial isomer can be expected to be more stable because of much smaller interaction of the deuteron with the hydrogen at position 3. The conformational interconversions within the isomers occur very fast; consequently the average lifetime of the conformational isomers is much too short to cause separate n.m.r. signals. The chemical shift of the N-methyl protons of each configurational isomer will be found between the chemical shifts of this group in the conformations which contribute to it. The more predominant one conformation is the closer will the chemical shift of the isomer approach the chemical shift of this conformer. The shielding of the methyl protons in the axial isomer and in the chair conformation of the equatorial isomer XXI is probably very similar as indicated by the identical shielding of the two methyl groups in the methiodide. However, the shielding of the methyl protons in the conformation XXII will certainly be different. If the equatorial isomer exists predominately in the boat form, the two configurational isomers will have differently shielded methyl protons.

From Table I it can be seen that the equilibrium constants of the tropine series are generally larger than the constants obtained for the corresponding derivatives of pseudotropine. This may be regarded as additional evidence for a greater contribution of the boat form to the equatorial isomer of tropine deuteriohalides.

No support can be found for the boat form of pseudotropine deuteriochloride (XXIII) which might appear to be favored by deuterium bonding.[15]



XXIII

Since the deuterium bond can only be formed in the equatorial isomer, a larger equilibrium constant for pseudotropine than for its acetyl derivative should indicate the presence of this conformation. The constant for pseudotropine was found to be somewhat smaller than the constant for its acetate (Table I). This result is not surprising if one takes into account that the spectra were determined in deuterium oxide and considers deuterium bonding to the solvent to be more important.

Experimental

Compounds.—The tropane derivatives in Table I, Fig. 1 and Fig. 2 were prepared according to standard procedures described in the literature. All compounds were recrystallized several times and the physical constants agreed well with those reported in the literature.

2,2,4,4-Tetradeuteriotropinone.—Tropinone was dissolved in 10 times its weight of deuterium oxide and heated under nitrogen to 50° for 5 hours. The base was extracted with anhydrous ether and the ether evaporated. The residue was treated a second time with deuterium oxide. The deuterated tropinone was extracted from this solution with ether and recrystallized from pentane. The n.m.r. spectrum of the base in carbon tetrachloride indicated complete exchange of the hydrogens in positions 2 and 4 for deuterium.

(14) H. M. McConnell, *J. Chem. Phys.*, **27**, 226 (1957).

(15) Evidence for similar hydrogen bonding in pseudotropine in carbon tetrachloride could be demonstrated by infrared analyses by B. L. Zenitz, C. M. Martini, M. Priznar and F. C. Nachod, THIS JOURNAL, **74**, 5564 (1952).

2,2,4,4-Tetradeuterioteloidinone.—The procedure described for the preparation of tetradeuteriotropinone was used.

Ethylation of Pseudotropine.—Pseudotropine (1 g.) was dissolved in absolute ethanol (5 cc.). To this solution was added ethyl iodide (1.5 g.). The solution was allowed to stand 24 hours at room temperature. The precipitated crystals were filtered off (1.6 g.), washed with ethanol and dried at 100° (0.1 mm.), dec. p. 321°.

Anal. Calcd. for $C_{10}H_{20}O$ I N (297.19): C, 40.41; H, 6.78; N, 4.71. Found: C, 40.20; H, 6.91; N, 4.49.

Methylation of N-Ethylnorpseudotropine.—N-Ethylnorpseudotropine (0.5 g.) was treated with methyl iodide (0.7 g.) in ethanol (2.5 cc.). The resulting precipitate was filtered off after 24 hours (0.71 g.) and dried at 100° (0.1 mm.), dec. p. 325–328°.

Anal. Calcd. for $C_{10}H_{20}O$ I N (297.19): C, 40.41; H, 6.78; N, 4.71. Found: C, 40.14; H, 6.71; N, 4.32.

N.m.r. Spectra.—The spectra were measured at room temperature with a Varian V-4300 B spectrometer, equipped with superstabilizer, at 40 Mc. The positions of the bands were measured by the usual sideband technique. As reference toluene served in an external annulus. The spectra were measured in 20–25% (w./v.) solutions and the chemical shifts reported are not corrected to zero concentration. Values for the equilibrium constants were obtained by recording the spectra with a Varian G 10 recorder. The peak areas were cut out and measured by weighing. The values reported are the average of ten determinations for each compound.

CHICAGO 37, ILL.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA AT LOS ANGELES]

Electrophilic Fragmentation in the Tropilidene Series

BY KENNETH CONROW

RECEIVED MARCH 10, 1959

This paper reports the synthesis and characterization of a variety of functionally substituted alkyltropilidenes (7-alkylcycloheptatrienes). Of particular interest is the fact that electrophilic reagents in certain cases cause a fragmentation reaction which yields a tropylium (cycloheptatrienylium) ion and an aliphatic fragment which accounts for the alkyl substituent.

The unique stability of the tropylium ion[1,2] suggested that it might serve as a leaving group in electrophilic substitution and elimination reactions. Some support for this supposition was found in the reported isolation of tropylium bromide from ditropyl ether,[3] a reaction which may be considered an electrophilic displacement of a tropylium ion from oxygen by a proton. The quantitative conversion of tropyl isocyanate (or its homolog) to tropylium bromide (or its homolog) and cyanuric acid[4] is formally a similar displacement on nitrogen. The isolation of N-tropylbenzamide from ditropylamine and benzoyl chloride[3,5] could be the result of a displacement on nitrogen of the tropylium ion by the incipient benzoylium ion. The conversion of tropyl cyanide to tropylium salts under acid conditions[4] serves as an example in which the tropylium ion leaves a carbon atom.

On the basis of these reports of electrophilic displacements of tropylium ion, it was anticipated that properly constituted functionally substituted 7-alkyltropilidenes might provide additional examples in which tropylium ion could serve as a positively charged leaving group in electrophilic processes. Accordingly, an investigation of the synthesis and reaction of a series of representative compounds was undertaken.

Entry to the desired alkyltropilidenes was gained through the nucleophilic attack of various active methylene compounds on the tropylium ion. The reaction occurs rapidly and conveniently in pyridine as solvent and hydrogen bromide acceptor and gives good yields (46–83%) with the active methylene components used in spite of the use of crude tropylium bromide. The acetylacetone adduct is a solid; it was prepared from aqueous solution as well as from pyridine solution and appears to be a good derivative for isolating tropylium ion from aqueous solution. This type of condensation reaction was reported by Russian workers[6] shortly after its use was begun independently in this work.

Some interest was attached to the question of the structure of the condensation products. Three possibilities were considered: (1) a C-alkylation product, (2) an O-alkylation product and (3) an ionic product in which an anion related to the active methylene component has replaced the bromide ion of tropylium bromide. This last possibility was immediately eliminated on the basis of the solubility in benzene and ether and the volatility of the products, the ultraviolet spectra (which were identical with those of tropilidene and its simple derivatives rather than those of tropylium salts) and the unexceptional reactions of the products.

That C-alkylation is the predominant course of the reaction is evident from the functionality of the product. Thus the adduct from acetylacetone gives a bis-2,4-dinitrophenylhydrazone and a dioxime. The adduct from acetoacetic ester gives a mono-2,4-dinitrophenylhydrazone. None of these derivatives could be formed from reasonable O-alkylated adducts. The further transformations of these initial adducts offers incontrovertible evidence that C-alkylation occurs.

The possibility that ring contraction occurred[7] during the condensation reaction to give substi-

(1) W. von E. Doering and L. H. Knox, THIS JOURNAL, **76**, 3203 (1954).

(2) H. J. Dauben, Jr., E. A. Gadecki, K. M. Harmon and D. L. Pearson, *ibid.*, **79**, 4557 (1957).

(3) W. von E. Doering and L. H. Knox, *ibid.*, **79**, 352 (1957).

(4) M. J. S. Dewar and R. Pettit, *J. Chem. Soc.*, 2021, 2026 (1956).

(5) W. von E. Doering and H. Krauch, *Angew. Chem.*, **68**, 661 (1956).

(6) M. E. Vol'pin, I. S. Akhrem and D. N. Kursanov, *Izvest. Akad. Nauk S.S.S.R., Otdel Khim. Nauk*, 1501 (1957); *C. A.*, **52**, 7175c (1958).

(7) Ring contraction has been noted in oxidative processes on the tropylium ion[4] and in certain reactions of substituted tropilidenes.[3,5]