2200, 2140, 2110, 1615, 1410, 1320, 1295, 1175, 1140, 1120, 1095, 1070, 1020, 910, 850, and 620 cm^{-1}. The impurity in the azidostyrene was assumed to be another 1-substituted styrene: nmr (CCl_4) 5.60 (d, 1, J = 2.1 Hz) and 5.80 ppm (d, 1, J = 2.1 Hz).

The partially purified 1-azido-4′-trifluoromethylstyrene (**4g**) (4.6 g, 0.0216 mol) was refluxed in toluene (300 ml) until the evolution of nitrogen ceased (1 hr). The toluene was evaporated *in vacuo* and the residue was distilled yielding 2.8 g (70%) of 2-(4′-trifluoromethylphenyl)-1-azirine (**5g**): bp 42–44° (1.2 mm); nmr (CCl_4) 1.74 (s, 2) and 7.6–8.2 ppm (m, 4); ir (CCl_4) 1750, 1735, 1620, 1420, 1325, 1180, 1140, 1110, 1070, 1020, 995, 850, and 600 cm^{-1}.

Anal. Calcd for $C_9H_6NF_3$: C, 58.30; H, 3.26; N, 7.55. Found: C, 58.12; H, 3.20; N, 7.33.

The azirine **5g** also contained about 4 mol % of the same impurity (1-substituted styrene) which was present in the azidostyrene **4g**. The impurity could not be removed by repeated recrystallization of the azirine **5g** from petroleum ether at −40°.

Registry No.—**3a**, 29847-04-9; **4a**, 16717-64-9; **4g**, 32654-71-0; **5a**, 7654-06-0; **5b**, 32687-32-4; **5c**, 32687-33-5; **5d**, 32687-34-6; **5e**, 32687-35-7; **5f**, 17631-26-4; **5g**, 32687-37-9; **7**, 709-63-7; **9**, 32687-39-1; **10**, 32687-40-4.

Acknowledgments.—We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this work.

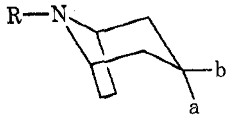
Stereochemistry of Tropane Quaternizations[1]

U. O. de la Camp,[2] A. T. Bottini,* C. C. Thut, J. Gal, and A. G. Bellettini

University of California, Davis, California 95616

Received December 7, 1970

In 1964, MacGillavry and Fodor[3] reported the results of an X-ray diffraction study of an N-ethyltropinium bromide which indicated that the major products from reactions of N-ethylnortropine (**1b**) and tropine (**1a**) with methyl and ethyl iodide, respectively, are formed by equatorial attack. Three years later, a group at Sheffield[4] questioned MacGillavry and Fodor's results and suggested that these major quaternization products, as well as the main products from other quaternizations of tropanes and 3-substituted tropanes,[5] are formed by axial attack. The following year, Fodor, Medina, and Mandava[6] reported that empirical correlations of nmr chemical shifts of exo α hydrogens indicated that the main products from reactions of tropine and pseudotropine (**2a**) with ethyl iodide are formed by different stereochemical pathways, namely, equatorial attack on tropine and axial attack on pseudotropine.[7] In that same year, two of us[11a] and Fodor and Mandava[11b] reported that hydrolysis of the lactone formed from pseudotropine bromoacetate gave the same N-carboxymethylpseudotropinium bromide as is formed by hydrolysis of the main product from quaternization of pseudotropine (**2a**) with ethyl bromoacetate. Because the lactone was formed by inter- rather than intramolecular reaction,[8] these results[11] led to the *erroneous conclusions* (1) that the N-carboxymethylpseudotropinium bromides were formed by axial attack on nitrogen and, therefore, (2) that the structural assignments originally made by Fodor, Koczka, and Lestyán[5] to the ethoxycarbonylmethylation products were incorrect.



1, a = OH; b = H **a**, R = CH_3
2, a = H; b = OH **b**, R = C_2H_5
3, a, b = O **c**, R = $PhCH_2$
4, a = b = H

Results described here and in a recent paper by Fodor and coworkers[8] establish conclusively that the predominant pathway for ethylation as well as methylation (or deuteriomethylation), alkoxycarbonylmethylation, and other quaternizations of tropine (**1a**), pseudotropine (**2a**), tropinone (**3a**), and several related compounds is by equatorial attack.

The major product from pseudotropine (**2a**) and ethyl bromide was obtained in >98% purity (nmr) by two crystallizations from methanol of the 74:26 mixture of diastereomers with δ_{NCH_3} 3.12 and 2.98 ppm, respectively.[12] The crystals are orthorhombic, space group *Pbca*, with unit cell dimensions a = 11.93, b = 14.15, c = 13.32 ± 0.004 Å, d_{obsd} (flotation) 1.45, d_{calcd} 1.45, Z = 8. A crystal was ground to a sphere of diameter 0.31 mm, and intensities were measured on a Picker automatic diffractometer using Ni-filtered Cu Kα radiation (λ 1.5418) and the θ–2θ scan mode to a value of 2θ = 133°. Out of 1952 measured reflections, 1648 were considered to be observed. The data were corrected for absorption effects (μR = 0.784) in addition to the usual data treatment. The position of the bromine atom was found from a three-dimensional Patterson map. A Fourier summation phased on the bromine atom immediately revealed the

---

(1) Supported in part by Grant CA-05528 from the National Cancer Institute, U. S. Public Health Service.

(2) Department of Chemistry, California State College at Dominquez Hills, Gardena, Calif. 90427.

(3) C. H. MacGillavry and G. Fodor, *J. Chem. Soc.*, 597 (1964); see also P. Benci, C. H. Stam, and C. H. MacGillavry, *Tetrahedron Lett.*, 243 (1971).

(4) D. R. Brown, R. Lygo, J. McKenna, J. M. McKenna, and B. G. Hutley, *J. Chem. Soc. B*, 1184 (1967).

(5) G. Fodor, K. Koczka, and J. Lestyán, *Magy. Kem. Foly.*, **59**, 242 (1953); *J. Chem. Soc.*, 1411 (1956).

(6) G. Fodor, J. D. Medina, and N. Mandava, *Chem. Commun.*, 581 (1968).

(7) This incorrect tentative conclusion concerning the stereochemistry of quanternization of pseudotropine with ethyl iodide resulted from misassignment of the band due to the hydroxyl group to the equatorial methyl group. In the solvent used for examination of the nmr spectra of the diastereomeric N-ethylpseudotropinium salts, the two N-methyl bands are coincident. Our results and those of Fodor, *et al.*,[8] confirm the conclusion reached by Closs[9] in 1959 that exo α hydrogens of N substituents in the equatorial configuration of tropane and 3-substituted tropane salts are more shielded than when in the axial configuration. The opposite is generally the case for piperidine salts.[10]

(8) G. Fodor, R. V. Chastain, Jr., D. Frehel, M. J. Cooper, N. Mandava, and E. L. Gooden, *J. Amer. Chem. Soc.*, **93**, 403 (1971). We thank Professor Fodor for informing us of their results prior to publication.

(9) G. L. Closs, *ibid.*, **81**, 5456 (1959).

(10) For examples, see (a) T. M. Moynehan, K. Schofield, R. A. Y. Jones, and A. R. Katritzky, *J. Chem. Soc.*, 218 (1962); (b) H. O. House and C. G. Pitt, *J. Org. Chem.*, **31**, 1062 (1966); (c) A. T. Bottini and M. K. O'Rell, *Tetrahedron Lett.*, 429 (1967).

(11) (a) C. C. Thut and A. T. Bottini, *J. Amer. Chem. Soc.*, **90**, 4752 (1968); (b) N. Mandava and G. Fodor, Abstracts, 51st Annual Conference of the Chemical Institute of Canada, Vancouver, B. C., June 1968, p 56.

(12) Both samples had mp >300°. The melting point is a poor criterion of purity for salts of **1a** and **1b**. *Cf.* S. P. Findlay, *J. Amer. Chem. Soc.*, **75**, 3204 (1953); G. Fodor, *Acad. Chim. Acad. Sci. Hung.*, **5**, 379 (1955). See also K. Zeile and W. Schulz, *Chem. Ber.*, **88**, 1078 (1955).

positions of the atoms heavier than hydrogen and showed that the ethyl group was equatorial. After three cycles of full-matrix least-squares refinement with independent isotropic temperature factors, the *R* index was 0.15.[13] A perspective drawing of the conformation of the molecule is shown in Figure 1.

Oxidation with ruthenium oxide[14] of the 74:26 mixture of *N*-ethylpseudotropinium bromides and of the 72:28 mixture of diastereomeric salts obtained from the reaction of ethyl bromide with tropine (δ_{NCH_3} 3.01 and 2.98 ppm, respectively, in dry DMSO-d_6; δ 3.02 ppm in D_2O) gave 74:26 and 71:29 mixtures of *N*-ethyltropinonium bromides with δ_{NCH_3} 3.32 and 3.18 ppm. Treatment of tropinone (**3a**) with a tenfold excess of ethyl bromide in acetonitrile gave a 75:25 mixture of the same salts, the major product being identical with the major product from the above oxidations. Thus, quaternizations with ethyl bromide of tropine and tropinone, as well as pseudotropine, occur predominantly by equatorial attack.

We have also related the stereochemistry of quaternizations of **1a**, **2a**, and **3a** with deuteriomethyl benzenesulfonate and with ethyl bromoacetate. The *ca.* 70:30 (δ_{NCH_3} 3.02 and 2.98 ppm in DMSO-d_6; 3.00 ppm in D_2O) and 72:28 (δ_{NCH_3} 3.18 and 3.03 ppm) mixtures obtained from tropine and pseudotropine, respectively, and deuteriomethyl benzenesulfonate gave on oxidation with ruthenium oxide corresponding mixtures of the *N*-deuteriomethyltropinonium benzenesulfonates with δ_{NCH_3} 3.38 and 3.21 ppm. The major product from each of these oxidations was identical with the major product obtained directly from tropinone and deuteriomethyl benzenesulfonate. Similar oxidations of the 92:8 (δ_{NCH_3} 3.25 and 3.16 ppm) and 91:9 (δ_{NCH_3} 3.38 and 3.00 ppm) mixtures of diastereomers obtained from tropine and pseudotropine, respectively, and ethyl bromoacetate gave 92:8 and 90:10 mixtures of the same salts with δ_{NCH_3} 3.57 and 3.34 ppm obtained directly from tropinone and ethyl bromoacetate in a ratio of 82:18.

We also examined quaternizations of tropine (**1a**), pseudotropine (**2a**), and tropane (**4a**) with ethyl brosylate, ethyl chloride, ethyl iodide, ethyl chloroacetate, and ethyl iodoacetate. Under otherwise identical reaction conditions, the stereochemical results of these alkylations did not differ significantly from those obtained when bromide was the leaving group. Further, under otherwise identical reaction conditions, the stereochemistry of these quaternizations was not changed significantly when the solvent was acetonitrile, benzene, or methanol.

Fodor and coworkers[8] carried out an X-ray crystal structure analysis of the dihydrate of *N*-carboxymethylpseudotropinium bromide prepared from the major product from pseudotropine and ethyl bromoacetate, and they found that the carboxymethyl group is equatorial. These workers also used chemical methods to correlate the stereochemistry of the predominant product from tropine and ethyl bromoacetate with that of the major products from pseudotropine (**2a**), tropinone (**3a**), and tropane (**4a**) with ethyl bromoacetate as well as the major products from **1a**, **2a**, and **4a** with ethyl bromide and **1a** with deuteriomethyl iodide.

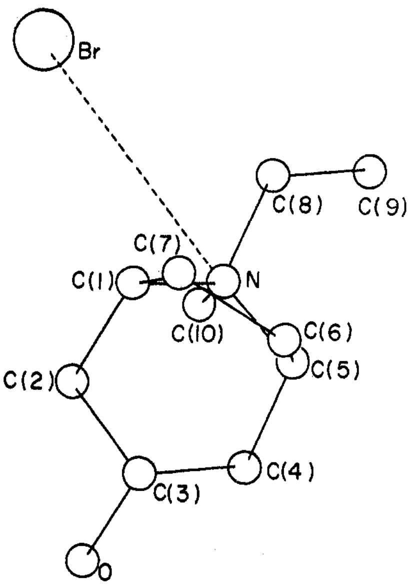


Figure 1.—Perspective of the major product from pseudotropine and ethyl bromide.

Thus, our results and the X-ray structural determination of Fodor and coworkers[8] confirm their chemical correlations of the stereochemistry of the major ethoxycarbonylmethylation and ethylation products. In addition, our results with the deuteriomethylation products, together with Fodor and coworkers' correlation by chemical means of the stereochemistry of the major products from tropine with deuteriomethyl iodide and ethyl bromoacetate,[8] establish that deuteriomethylation of pseudotropine and tropinone also occurs predominantly by equatorial attack.

During the course of this work, we observed that product ratios obtained from quaternizations of tropinone (**3a**) change as the reactions proceed. For example, quaternization of **3a** (0.5 *M*) with deuteriomethyl benzenesulfonate (0.5 *M*) at 30° in acetonitrile-d_3 gave a product ratio of 88:12 after 30 min, when the reaction was 70% complete, and this ratio decreased to a constant value of 77:23 after 24 hr, when the reaction was complete. Addition of either tropinone or pyridine resulted in a further gradual change of this ratio to 50:50. A possible mechanism for this and similar equilibrations involves opening of the bicyclic quaternary salt by the weak base[15] to the corresponding 6-dialkylamino-2-cycloheptenone, followed by Michael-type addition to give one or the other of the diastereomeric salts.[16] This mechanism gains support from the observation that dimethylamine hydrochloride, in the presence of dimethylamine, adds to 2,6-cycloheptadienone to give *N*-methyltropinonium chloride in good yield.[17]

Significantly, treatment with pyridine of the 87:13

---

[13] Listings of structure factors, conformational parameters, coordinates, and isotropic temperature factors will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Reprint Department, ACS Publications, 1155 Sixteenth Street, N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfilm.

[14] H. O. House and B. A. Tefertiller, *J. Org. Chem.*, **31**, 1068 (1966).

[15] Treatment with stronger base under more vigorous conditions gives a mixture of cycloheptadienones; see J. Meinwald, S. L. Emerman, N. C. Yang, and G. Büchi, *J. Amer. Chem. Soc.*, **77**, 4401 (1955).

[16] A possible alternative mechanism is mentioned briefly in ref 8.

[17] A. T. Bottini and J. Gal, *J. Org. Chem.*, **36**, 1718 (1971).

and 37:63 (δ_{NCH_3} 4.42 and 4.47 ppm) mixtures of diastereomeric salts obtained, respectively, from quaternizations of tropinone (**3a**) with benzyl brosylate and *N*-benzylnortropinone (**3c**)[17] with methyl brosylate gave the same 72:28 mixture, the predominant isomer being the major product of the benzylation. Essentially the same product ratio was obtained on addition of *N*-methylbenzylamine hydrochloride to 2,6-cycloheptadienone. If one allows that the *N*-benzyltropinonium salt with the benzyl group equatorial is the more stable, these results indicate that quaternizations of tropinone with benzyl brosylate and *N*-benzylnortropinone with methyl brosylate also occur predominantly by equatorial attack. As reactions of benzyl brosylate with tropine (**1a**), pseudotropine (**2a**), and tropane (**4a**) give product ratios (90:10) similar to that obtained with tropinone (**3a**), and, in view of the similar stereochemistry seen in alkoxycarbonylmethylations, deuteriomethylations, or ethylations of the four bases, it seems likely that the benzylations of **1a**, **2a**, and **4a** also occur mainly by equatorial attack.

Experimental Section[18]

Amines and quaternizing agents used were either obtained commercially or prepared following well-described procedures. Unless noted otherwise, quaternary salts were prepared at 30° from equimolar amounts of amine and quaternizing agent. Preparative runs were carried out in acetonitrile with initial concentrations of 0.2–0.5 *M*; for other runs, initial concentrations were 0.07–0.10 *M*.

Nmr spectra were determined with a Varian A-60A system of 10–20% solutions of the quaternary salts in deuterium oxide, dimethyl-d_6 sulfoxide, or equal volumes of these solvents containing 1% 3-trimethylsilyl-1-propanesulfonic acid sodium salt. Several reactions in acetonitrile containing 1% TMS were also followed directly by nmr. The ratio of the diastereomeric salts was taken as equal to the intensity ratio of the bands due to the *N*-methyl protons and, when possible, the *N*-benzyl protons. At least eight determinations of product compositions from reactions with high ($\gtrsim$7:1) and moderate ($\sim$3:1) degrees of stereoselectivity gave average deviations of 3 and 2%, respectively. Chemical shifts of the bands used for analysis were not changed significantly (±2 cps) when the anion was changed from bromide to chloride or iodide; change of anion from bromide to brosylate resulted in similar upfield shifts of these bands (*cf.* ref 10b and 10c). Assignment of bands in the nmr spectra of salts other than bromides was confirmed by examination of the spectra of mixtures of these salts and the corresponding bromides.

Ruthenium oxide solutions were prepared as described by House and Tefertiller,[14] and oxidations were carried out with approximately 200 mg of mixed quaternary salts. Yields of crude products, which were analyzed by nmr, ranged from 92–99%.

The *N*-benzyltropinonium brosylates and *N*-deuteriomethyl benzenesulfonates, as 0.3–0.5 *M* solutions, were equilibrated in 12–96 hr at 39° in 0.15 *M* solutions of pyridine in either acetonitrile-d_3 or deuterium oxide. Attempts to equilibrate the *N*-ethoxycarbonylmethyltropinonium bromides with pyridine in acetonitrile-d_3 were complicated by rapid saponification, as indicated by the appearance in the nmr spectrum of the upfield bands due to ethanol.

N-Benzyltropinonium chloride was prepared in 67% yield by allowing a mixture prepared from 206 mg (1.9 mmol) of 2,6-cycloheptadienone, 300 mg (1.9 mmol) of *N*-methylbenzylamine hydrochloride, 20 µl of *N*-methylbenzylamine, and 1 ml of methanol to stand at room temperature for 58 hr.

Registry No.—**1a**, 120-29-6; **2a**, 135-97-7; **3a**, 532-24-1; **2a** reaction product with ethyl bromide, 32515-65-7.

---

[18] For details of most of the work summarized here, see C. C. Thut, Ph.D. thesis, University of California, Davis, 1970.

A Nuclear Magnetic Resonance Study of 2,4-Dinitrohalobenzenes and 2,4-Dinitrohalonaphthalenes

John D. Reinheimer* and A. H. Kappelman[1]

Severance Chemical Laboratory, The College of Wooster, Wooster, Ohio 44691

Received July 6, 1971

The three spin system of trisubstituted benzenes has been extensively studied,[2] but little data on substituted naphthalenes have appeared. The spectra of 2,4-dinitrohalobenzenes are simple first-order spectra which may be compared to the classic data of the halobenzenes. We anticipated finding more complex AB-CD spectra for the 2,4-dinitrohalonaphthalenes and looked for similar comparisons with the halobenzene spectra.

Experimental Section

The 2,4-dinitrohalobenzenes were samples prepared for previous work.[3] Similarly, the preparation and purification of the 2,4-dinitrohalonaphthalenes are described.[4] The nmr spectra of the 2,4-dinitrohalobenzene series were observed with a Varian T-60, in 10% solution (acetone solvent) with TMS as an internal standard. The T-60 was calibrated against the Jungnickel[5] standard solution. The naphthalene series spectra were observed on a Varian HA-100.[6] The naphthalene samples were run in degassed dioxane solution; the solutions were less than 10% by weight. The chemical shifts and coupling constants were calculated on a control Data Corp. computer, CDC-6400 with the LAOCN3 program, as modified by J. T. Gerig.[7]

Results and Discussion

The calculated chemical shifts and coupling constants are presented in Tables I, II, and III. Comparison of our data with that of Smith and Ihrig indicates that there is reasonable agreement (Table III). We believe that the maximum error in absolute chemical shift will be ±1 Hz. The benzene series gave first-order spectra, but the napthalene series gave complex spectra.

TABLE I

CHEMICAL SHIFTS FOR 1-X-2,4-DINITRONAPHTHALENES IN DIOXANE

Proton no.	Chemical shift from dioxane at 100 Mc, Hz X = Cl	X = Br	X = I
3	512.60 ± 0.00	504.7 ± 0.00	493.3 ± 0.00
5	494.80 ± 0.02	419.35 ± 0.02	483.21 ± 0.02
6	436.23 ± 0.03	433.23 ± 0.02	428.77 ± 0.03
7	431.97 ± 0.03	429.98 ± 0.02	424.09 ± 0.03
8	506.67 ± 0.02	503.07 ± 0.02	496.10 ± 0.02

---

[1] Taken (in part) from the Senior Independent Study Thesis of A. H. Kappelman, The College of Wooster, 1970.

[2] L. M. Jackman and S. Sternhell, "Applications of NMR Spectroscopy to Organic Chemistry," Pergamon Press, Elmsford, N. Y., 1969, pp 94, 173, 205, 306.

[3] J. D. Reinheimer, R. C. Taylor, and P. E. Rohrbaugh, *J. Amer. Chem. Soc.*, **83**, 835 (1961).

[4] R. C. Krauss and J. D. Reinheimer, *Can. J. Chem.*, **45**, 77 (1967).

[5] J. L. Jungnickel, *Anal. Chem.*, **35**, 1985 (1963).

[6] We gratefully acknowledge the support of Dr. Brian Kieth and Dr. Henry Sable of Case Western Reserve for these spectra.

[7] LAOCN3, A. A. Bothner-By and S. M. Castellano, as modified by J. T. Gerig, personal communication.