tion of *syn*-Ic and an acid equilibration of *anti*-Id were carried out. These attempts were not successful since the desired isomerization did not occur due to unknown side reactions that prevail even under mild conditions. On an alumina (Brockman activity 1) or on a silicic acid column, isomerization of *anti*-Ic and *syn*-Ib did not take place to an extent[14] that could be detected by means of nmr spectroscopy.

It is shown now that base-catalyzed oximation of α-*t*-aminoacetophenone[4] gives predominantly the *anti* isomer of the corresponding oximes. Thus *anti* isomers of α-piperidino-, α-2-methylpiperidino-, and α-3-methylpiperidinoacetophenone oximes (*anti*-Ia, -Ib, and -Ic) are readily prepared by the oximation process eliminating laborious separation procedures required in the photoaddition route. By this oximation, however, only one isomer of VII is obtained for which *anti* configuration is assigned as discussed before.

Superficially the *anti* isomers of I–IV appear to possess higher melting points than the corresponding *syn* isomer while this trend is reversed in VIII series. The assignment of *syn–anti* isomers in VIII series have been worked out previously by Fischer and Grob,[8] the correctness of which is now further substantiated by nmr data and tlc behavior.

Experimental Section

The nmr spectra were recorded in $CDCl_3$ solution with TMS as an internal standard on a Varian A56/60 spectrometer. The tlc plates were prepared with Gelman aluminum oxide by the standard method. The melting points were recorded on a Fischer-Johns hot stage and were uncorrected.

Photoaddition of Nitrosamines to Olefins.—The photoaddition was carried out following the procedure described in a previous publication.[1] Pure samples of *syn*-VIIIc (from N-nitrosopyrrolidine and styrene), *syn*-VIIId, and *anti*-VIIId (from N-nitrosodimethylamine and styrene) were obtained in this manner.

Oximation of α-Aminoacetophenones.—The α-aminoacetophenones required were prepared fresh each time according to the procedure described.[4] The crude acetophenone prepared in this manner was taken up in 5% sodium hydroxide in methanol containing 2 equiv of hydroxylamine hydrochloride. After refluxing the solution for 20–30 min, the methanol was evaporated and the product extracted with ether. Gy this method, a mixtur of the *syn* and *anti* isomers richer in the latter was usually isolated. The pure specimens of *anti*-Ia, *anti*-Ib, *syn*- and *anti*-VIIIb, *anti*-VIIIc, and *anti*-VIIId were prepared by this method.

Equilibration of *syn*- and *anti*-Oximes.—A pure smple of *syn*-Ic (500 mg) was refluxed for 30 min in methanol (60 ml) containing sodium hydroxide (2 g). After working up in the usual manner, the recovered residue (250 mg) showed infrared and nmr spectra identical with that of *syn*-Ic.

In a methanol solution 0.5 N in hydrochloric acid, *anti*-Ib (340 mg) was dissolved and set aside at room temperature overnight. The recovered crystalline material (135 mg) was shown to be *anti*-Ib by the identical nmr spectrum.

A sample of *anti*-Ic (155 mg) was taken up in chloroform and was absorbed on an alumina column (Brockman activity) for 3 days. The recovered sample (125 mg), washed with 10% methanol in chloroform, showed infrared and nmr spectra identical with *anti*-Ic.

The same experiments performed with *anti*-Ib (340 mg) in a silicic acid column gave the unrearranged *anti*-Ib (324 mg).

Registry No.—*syn*-Ia, 16451-58-4; *anti*-Ia, 16451-59-5; *syn*-Ib, 16451-60-8; *anti*-Ib, 16451-61-9; *syn*-Ic, 16451-62-0; *anti*-Ic, 16451-63-1; *syn*-Id, 16451-64-2; *anti*-Id, 16451-65-3; *anti*-Ie, 16451-66-4; *syn*-II, 16451-67-5; *anti*-II, 16451-68-6; *syn*-III, 16451-69-7; *anti*-III, 16451-70-0; *syn*-IV, 16451-71-1; *anti*-IV, 16451-72-2; *anti*-Va, 16462-51-4; *anti*-Vb, 16451-73-3; *anti*-Vc, 16451-74-4; *anti*-Vd, 16451-75-5; *anti*-VI, 16451-76-6; *anti*-VII, 16451-77-7; *syn*-VIIIb, 16451-78-8; *anti*-VIIIb, 16451-79-9; *syn*-VIIIc, 16451-80-2; *anti*-VIIIc, 16451-81-3; *syn*-VIIId, 16451-82-4; *anti*-VIIId, 16451-83-5.

Acknowledgment.—The authors thank the National Research Council of Canada for their generous support of this work.

(14) Our earlier report[3] that *anti*-Ia was isomerized to *syn*-Ia on a silicic acid column was now shown to be wrong in that the starting material itself was a mixture of *anti*-Ia and *syn*-Ia. In general, *anti*-Ia and other *anti* isomers were isolated by column chromatographs in lesser yields than that indicated by the nmr spectra of the crude mixture. This misled us to state erroneously that *anti*-Ia was isomerized to *syn*-Ia.

Stereospecific Methods of Forming Ethers by Nucleophilic Reactions of 3α-Substituted Tropanes

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Despite the great pharmacological importance of tropine esters, little information is available on chemistry of the ethers of tropine (tropan-3α-ol). Until now, only the benzhydryl ether of tropine and some of its derivatives had been investigated.[1] This prompted the synthesis and the investigation of the properties of other tropine ethers. In the course of this investigation it became evident that the "methyl ether" of tropine described earlier[2] is actually not an O–methyl, but an N-methyl derivate, or in other words it is not an ether but a quaternary salt (methoiodide) of tropine.[3]

Willstätter[4] attempted to synthetize tropine ethers but the reaction of 3α-bromotropane with sodium ethoxide yielded tropene-2, exclusively. We also found that the conventional methods of ether-forming reactions were not applicable to the synthesis of tropine ethers.

It was possible, however, to produce various alkyl and aryl ethers of tropine and pseudotropine (tropan-3β-ol) with stereospecific reactions not previously applied to the synthesis of these compounds. The description of these methods and the stereochemistry of these reactions are the purpose of this short communication.

Tropane 3β-phenyl ether (2) can be obtained stereochemically pure from 3α-mesyloxytropane (tropine methanesulfonate) (1) and sodium phenoxide (see Figure 1).

The reaction of 1 with sodium thiophenoxide led to tropane 3β-phenyl thioether. The formation of this thioether proves that the oxygen of 2 originally came from the phenoxide anion. (For arguments for the β

(1) (a) R. F. Philips, U. S. Patent 2,595.405 (1952); (b) C. H. Nield and W. X. F. Bosch, U. S. Patent 2,782,200 (1956).
(2) Chem. Fabr. Schering, German Patent 106.492 (1900).
(3) K. Nádor, unpublished data.
(4) R. Willstätter, *Ann.*, **326**, 32 (1903).

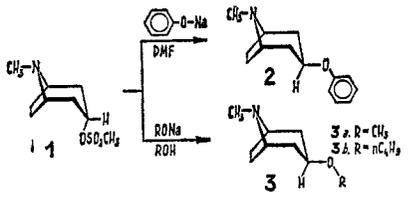

Figure 1.

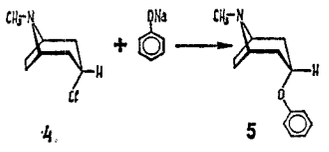

Figure 2.

configuration, see below.) Displacement and elimination of the mesylate group in **1** occurred simultaneously. This was also confirmed by the presence of tropene-2 as the by-product of the reaction.

The synthesis of tropane 3β-alkyl ethers was also carried out. The synthesis of these alkyl ethers from **1** and sodium methoxide and butoxide, respectively, gave significant amounts of tropene-2 as a by-product.

The formation of **2** occurs with the inversion of the mesyloxy group and its substitution by the phenoxy group. Although the rate of reaction depends on the concentrations of both **1** and phenoxide, it is not a pure second-order reaction. The kinetic data (see Table I)

TABLE I

RATE OF REACTION OF TROPINE METHANESULFONATE WITH SODIUM PHENOXIDE IN DMF AT 60.0° [a]

Time, sec	x/a[b]	10^2k_2,[c] l. M^{-1} sec^{-1}	10^2, k_2[d] l M^{-1} sec^{-1}
360	0.239	6.96	6.87
480	0.297	7.05	6.87
600	0.346	7.04	6.90
960	0.458	7.04	6.83
1200	0.515	7.09	6.87
1560	0.579	7.06	6.83
1800	0.617	7.16	6.90
2100	0.653	7.18	6.90
2400	0.685	7.24	6.96
3000	0.731	7.26	6.90
3600	0.768	7.35	6.96

[a]The first-order rate constant, k_1 of solvolysis of the tropine methanesulfonate in DMF at 60.0° is 1.85×10^{-5} sec^{-1}. This value was taken from another of our measurements. [b]a = 0.0125 and also all initial concentrations of both reactants are 0.0125 M. [c]Calculated from the equation $k_2^* = (1/at)[x/(a-x)]$. [d]Calculated[5] from the equation $k_2 = (k_1/a)[\alpha/(1-\alpha)]$, where $\alpha = [e^{-k_1t} + (x/a) - 1]/[(x/a)e^{-k_1t}]$.

suggest a reaction of the SN2 type with simultaneous solvolysis. The second-order rate constants (k_2^*) were corrected for the solvolysis,[5] and the values of k_2 obtained are of rather good constancy. Therefore, the reaction is a combination of a bimolecular substitution and a unimolecular solvolysis.

(5) E. Tommila and I. P. Pitkänen, *Acta Chem. Scand.*, **20**, 937 (1966).

The relative configuration of the C-3 atom at **3a** and **b** was determined by cleavage with hydroiodic acid. The product of this reaction was tropan-3β-ol verified by its melting point and by its ir spectrum. Tropan-3α-ol does not react with hydroiodic acid under similar conditions.

Tropane 3α-phenyl ether was obtained from 3α-chlorotropane (**4**) in contrast with the previous observations[4] (see Figure 2). The reaction of **4** with sodium phenoxide in alcoholic solution yields **5**. Tropane 3α-phenyl thioether was also obtained stereochemically pure from **4** and sodium thiophenoxide.

Compound **4** is converted into **5** with retention of configuration (see below). This indicates that this reaction occurs by nitrogen participation *via* an SN1 process in the same way as suggested earlier by Archer[6] for the reaction of 3α-chlorotropane with potassium cyanide.

The two methods found for the synthesis of tropine ethers are stereospecific. The treatment of **1** with sodium phenoxide together with 50% tropene-2 gives nearly 50% tropine phenyl ether. The *in toto* glpc analysis of the reaction compositions has shown that the crude reaction product contained 94–96% β-phenyl ether and 4% α ether. In the case of phenyl ether synthesis from **4**, tropene-2 formation was not detected; in compliance with the gc analysis the crude reaction product contained 80% α- and 20% β-phenyl ether.

The relative configuration of the C-3 atom and the conformation of the isomers **2** and **5** mentioned above were determined by physical–chemical methods.

The ir absorption curves of both **2** and **5** show peaks at 1045 and 1245 cm^{-1}. These bands correspond to the C–O linkages. The main difference between the ir spectra of the two compounds is similar to that of the tropine–pseudotropine system.[7] In the ir spectrum of **2** there is a peak at 1009 cm^{-1}, whereas in that of **5** a peak is at 946 cm^{-1}. As a band at 1020 cm^{-1} appears in the spectrum of pseudotropine and one appears at 958 cm^{-1} in that of tropine, it can be concluded, by analogy, that the configuration of the C-3 atom of **2** is in agreement with the configuration of C-3 of pseudotropine,[8] and the configuration of C-3 of **5** is the same as in tropine. Therefore, **2** is a 3β ether and **5** is a 3α ether.

The nmr spectra of **2** and **5** are markedly different. The hydrogen resonance spectra of **2** and **5** consists of lines at 5.52 and 5.35 ppm., respectively, on the τ scale for the proton attached to the C-3 atom. The band possessing the greater τ value corresponds to the hydrogen attached axially to the C-3 atom. If the position of the hydrogen belonging to the C-3 atom is known, the relative position of the ether linkage can be deduced. These nmr studies also indicated, in agreement with the results of the ir studies, that **2** and **5** have an equatorial (β) and an axial (α) ether linkage, respectively.

Data on the conformations of **2** and **5** were obtained through the determination of their dipole moments. The dipole moments in benzene at 25.00° were 2.15 D

(6) S. Archer, M. R. Bell, T. R. Lewis, J. W. Schulenberg, and M. J. Unser, *J. Amer. Chem. Soc.*, **80**, 4677 (1958).

(7) A. H. Beckett, N. J. Harper, A. D. J. Balon, and T. H. E. Watts, *Tetrahedron*, **6**, 319 (1959).

(8) (a) G. Fodor, and K. Nádor, *J. Chem. Soc.*, 721 (1953); (b) A. Nickon and L. F. Fieser, *J. Amer. Chem. Soc.*, **74**, 5566 (1952).

and 0.94 D for **2** and **5**, respectively. For the calculation of the dipole moment[9] of the possible conformations the following bond moments were used: $\mu_{C-N} = 0.92$ D, $\mu_{C_{Ar}-O} = 1.00$ D, $\mu_{C_{Al}-O} = 1.22$ D. If it is assumed that the piperidine ring in the tropane skeleton has a chair conformation and that the methyl group is attached equatorially to the nitrogen,[10] it is possible to conclude that the conformations of the two ethers are represented by the formulas **2** and **5**; this conclusion is confirmed by the calculated dipole moment values of 2.06 and 0.96 D for **2** and **5**, respectively.

Finally, there is a typical difference between the basicity of **2** and **5**; the pK values determined in methyl Cellosolve–water solution (80:20 w/w)[11] at 25° are 8.06 and 8.42, respectively. Others[12,13] found a similar difference between the pK values of tropine and pseudotropine.

The configurations of the tropane 3α- and 3β-phenyl thioethers are based by analogy for the corresponding 3α- and β-phenyl ethers.

Experimental Section

Melting points are corrected. The given yields refer to analytically pure compounds. The infrared spectra were taken on pressed potassium bromide pellets with a Zeiss Model UR 10 spectrophotometer. Nmr spectra were measured in deuteriochloroform solution at 60 Mc/sec. using tetramethylsilane as an internal reference on an AEI spectrometer. Dipole moments measurements were taken on a Dipolmeter DM 01 instrument; a detailed account will be described in a forthcoming article. For gas chromatographic experiments an Aerograph HY-FI Model 600 apparatus was used. Elemental analyses were carried out by our microanalytical laboratory.

Tropane 3β-Phenyl Ether(2).—To 65.7 g (0.3 mol) of tropine methanesulfonate[6] in 250 ml of DMF was added 36.0 g (0.31 mol) of sodium phenoxide in 250 ml of DMF. The solution was heated on the steam bath for 3 hr. The sodium methanesulfonate was then separated by filtration, washed with ethanol and dried to give 35 g of a white crystalline product. The DMF solution was acidified with 6 N hydrochloric acid to congo red and the DMF was removed by distillation at reduced pressure. To the residue was added 200 ml of water and the solution was extracted several times with ether to remove any nonbasic material. The aqueous layer was saturated with potassium carbonate and extracted three times with 100 ml of chloroform. The chloroform extracts were combined and dried over anhydrous sodium sulfate, and then the solvent and the main part of the by-product tropene-2 were evaporated at reduced pressure. The residue was distilled, bp 103° (0.06 mm), and was largely solidified, mp 42–46°. The yield of tropane 3β-phenyl ether was 28.75 g (44.2%). Several recrystallizations from petroleum ether (bp 60–80°) gave a colorless substance, mp 51°. The product was shown to be pure by gas chromatography.

Anal. Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.59; H, 8.91; N, 6.76.

For the hydrochloride of **2** the melting point was 282° dec from ethanol–ether.

Anal. Calcd for $C_{14}H_{20}ClNO$: C, 66.26; H, 7.94; N, 5.52; Cl, 13.97. Found: C, 66.32; H, 8.16; N, 5.58; Cl, 13.90.

Tropane 3β-Methyl Ether (3a).—Sodium (13.8 g) was dissolved in 300 ml of methanol and 109 g (0.5 mol) tropine methanesulfonate in 500 ml of methanol was added. The solution was refluxed for 4 hr. A yield of 59 g of sodium methanesulfonate separated from the solution, a value which corresponds to the amount calculated theoretically. The remaining work-up of the preparation was the same as that for **2**. The tropane 3β-methyl ether after distillation was a colorless oil (29.2 g, 26.6%): bp 90° (15 mm); $n^{20}D$ 1.4776. The usual reaction with hydroiodic acid yielded pseudotropine, mp and mmp 107–108°.

Anal. Calcd for $C_9H_{17}NO$: N, 9.03. Found: N, 9.31.

The hydrochloride melted at 242–243° after recrystallization from ethanol–ether.

Anal. Calcd for $C_9H_{18}ClNO$: C, 56.39; H, 9.47; N, 7.31; Cl, 18.49. Found: C, 56.66; H, 9.56; N, 7.15; Cl, 18.41.

Tropane 3β-n-Butyl Ether (3b).—Its preparation from 0.3 mol of sodium n-butoxide and 43.8 g (0.2 mol) of tropine methanesulfonate in 200 ml of n-butyl alcohol was similar to that of **3a**. The tropane 3β-n-butyl ether was a colorless oil (bp 77–78° (0.4 mm); $n^{20}D$ 1.4708); the yield was 8.3 g (21%). The usual reaction with hydroiodic acid yielded pseudotropine only, mp and mmp 107–108°.

Anal. Calcd for $C_{12}H_{23}NO$: N, 7.10. Found: N, 7.27.

For the p-toluenesulfonic acid salt the melting range was 165–165.5°, from ethanol–ether.

Anal. Calcd for $C_{19}H_{31}NO_4S$: C, 61.76; H, 8.46; N, 3.97. Found: C, 61.65; H, 8.46; N, 3.85.

Tropane 3β-Phenyl Thioether.—To 43.8 g (0.2 mol) of tropine methanesulfonate was added 57 g (0.4 mol) of sodium thiophenoxide in 800 ml of DMF. The mixture was heated for 3 hr. The sodium methanesulfonate that separated from the solution corresponds to the amount calculated theoretically. The preparation was the same as for **2**. The thioether was obtained as a colorless oil (22.6 g, 48.5%): bp 144° (0.4 mm); $n^{20}D$ 1.5798.

Anal. Calcd for $C_{14}H_{19}NS$: C, 72.05; H, 8.21; N, 6.00; S, 13.74. Found: C, 72.27; H, 8.25; N, 6.37; S, 13.45.

The hydrochloride melted at 230–231° after recrystallization from ethanol–ether.

Anal. Calcd for $C_{14}H_{20}ClNS$: C, 62.32; H, 7.47; N, 5.19; S, 11.88; Cl, 13.14. Found: C, 62.32; H, 7.76; N, 5.42; S, 11.57; Cl, 12.90.

Tropane 3α-Phenyl Ether (5).—Sodium phenoxide (69.6 g, 0.6 mol) and 3α-chlorotropane (47.8 g, 0.3 mol) were mixed in 200 ml of ethanol and refluxed for 16 hr. The preparation of **5** was processed similarly to that of **2**. The tropane 3α-phenyl ether (**5**) was distilled at 112–116° (0.3 mm); the yield was 31.0 g (47.6%) and solidified (mp 53°) shortly after recrystallization from n-hexane. This tropine ether was shown to be pure by gas chromatography.

Anal. Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.55; H, 8.99; N, 6.25.

The hydrochloride of **5** had mp 213°, from ethanol–ether.

Anal. Calcd for $C_{14}H_{20}ClNO$: C, 66.26; H, 7.94; N, 5.52; Cl, 13.97. Found: C, 66.80; H, 8.42; N, 5.38; Cl, 13.75.

Tropane 3α-phenyl thioether was prepared from 47.1 g (0.163 mol) of sodium thiophenoxide and 25.2 g (0.16 mol) of 3α-chlorotropane in 125 ml of alcohol. After refluxing for 5 hr the mixture was processed according to the method described for **2**. The 3α thioether was obtained as a colorless oil in 33.6% yield (12.5 g): bp 125–130° (0.2 mm); $n^{20}D$ 1.5812.

Anal. Calcd for $C_{14}H_{19}NS$: C, 72.05; H, 8.21; N, 6.00; S, 13.74. Found: C, 72.31; H, 8.46; N, 6.17; S, 13.36. The hydrochloride had mp 214–216°, from ethanol–ether.

Anal. Calcd for $C_{14}H_{20}ClNS$: C, 62.32; H, 7.47; N, 5.19; S, 11.88; Cl, 13.14. Found: C, 62.48; H, 7.28; N, 4.85; S, 12.03; Cl, 12.85.

Kinetic Measurement.—The course of the reaction of tropine methanesulfonate with sodium phenoxide was followed through the measurement of the conductivity of the solution. The increase of the conductivity was proportional to the change in concentration of the reactants. The conductivity was measured with a Metrohm Konduktoskop Type E 365. Further details will be published later.

Registry No.—**2**, 16487-31-3; **2**·HCl, 16487-32-4; **3a**, 16487-33-5; **3a**·HCl, 16487-34-6; **3b**, 16487-35-7; **3b**, p-toluenesulfonic acid salt, 16487-36-8; **5**, 16487-37-9; **5**·HCl, 16487-38-0; tropane 3α-phenyl thioether, 16487-39-1; tropane 3α-phenyl thioether hydrochloride, 16487-40-4; tropane 3β-phenyl thioether, 16487-41-5; tropane 3β-phenyl thioether hydrochloride, 16487-42-6.

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(10) R. J. Bishop, G. Fodor, A. R. Katritzky, F. Sóti, L. E. Sutton, and F. J. Swinbourne, *J. Chem. Soc., Sect. C*, 74 (1966).

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