allowed to come to room temperature over a period of 60 min. The solution was evaporated and the organic products were extracted from the solid residue with chloroform. Evaporation gave a colorless oily solid. Two recrystallizations from chloroform gave analytically pure 2-methyl-1,3-dithiane 1-oxide (VI): yield 0.043 g (0.286 mmol), 14%; mp 93–94°.

Anal. Calcd for $C_5H_{10}S_2O$: C, 39.97; H, 6.71; S, 42.68. Found: C, 40.25; H, 6.89; S, 42.79.

2-Benzyl-1,3-dithiane 1-Oxide (VII).—Benzyl bromide (0.69 g, 4.05 mmol) was added to a solution of the carbanion produced from 0.500 g (3.68 mmol) of 1,3-dithiane 1-oxide (II). After stirring for an additional 4 hr, the reaction mixture was poured into water (75 ml) and acidified with hydrochloric acid. Extraction of this mixture with chloroform gave a solution that was dried over anhydrous sodium sulfate and treated with decolorizing carbon. Concentration of the solution gave an oil (0.90 g) that was purified by preparative thin layer chromatography (5% ethanol in chloroform) to give an oil that slowly crystallized: mp 51–65°; yield 0.202 g (0.888 mmol), 24%. The analytical sample (mp 95–96°) was prepared using cyclohexane–chloroform as solvent.

Anal. Calcd for $C_{11}H_{14}OS_2$: C, 58.36; H, 6.23; S, 28.33. Found: C, 58.70; H, 6.32; S, 28.50.

1-Benzoyl-1,3-dithiane 1-Oxide (VIII).—To a solution of the carbanion I produced from 1.00 g of the sulfoxide (7.36 mmol) was added ethyl benzoate (0.55 g, 3.67 mmol). After stirring for 20 min the reaction mixture was poured into water (50 ml) and carefully acidified to pH 3. Extraction with chloroform produced a yellow solution which was washed with water, dried over sodium sulfate, and filtered. The chloroform was removed to leave a yellow oil (1.01 g) that was purified *via* preparative thin layer chromatography (5% ethanol in chloroform): yield 0.45 g (1.90 mmol), 52%, off-white crystals; ir ($CHCl_3$) 1050 cm^{-1}, broad (S→O), 1670 (C=O), 3430 (enol). Two recrystallizations from ethyl acetate–cyclohexane gave the analytical sample, mp 134–136°.

Anal. Calcd for $C_{11}H_{12}S_2O_2$: C, 54.96; H, 5.03; S, 26.68. Found: C, 55.21; H, 4.99; S, 26.71.

2-(Phenylhydroxymethyl)-1,3-dithiane 1-Oxide (IX).—A solution of the carbanion I in tetrahydrofuran was prepared in the usual manner from 0.50 g (3.68 mmol) of the sulfoxide. To this solution was added, over a 3-min period, a solution of benzaldehyde (0.47 g, 4.42 mmol) in tetrahydrofuran. The reaction mixture was stirred for 15 min (−5°) and the product (0.48 g, 2.0 mmol, 54%, mp 120–170°) isolated as for VII. The analytical sample (mp 185–191° dec) was prepared from chloroform–cyclohexane.

Anal. Calcd for $C_{11}H_{14}O_2S_2$: C, 54.51; H, 5.82; S, 26.46. Found: C, 54.71; H, 5.90; S, 26.21.

2-(Diphenylhydroxymethyl)-1,3-dithiane 1-Oxide (X).—To the solution of the carbanion (2.0 mmol) as prepared above was added a solution of benzophenone (0.34 g, 1.9 mmol) in dry tetrahydrofuran (2 ml). After stirring for 20 min, the product (0.49 g, 1.5 mmol, 79%, mp 158–162°) was again isolated as for VII. Several recrystallizations from chloroform–cyclohexane gave the analytical sample, mp 155–156° with decomposition.

Anal. Calcd for $C_{17}H_{18}O_2S_2$: C, 64.12; H, 5.70; S, 20.14. Found: C, 63.86; H, 5.65; S, 20.23.

1,3-Oxathiane 3-oxide (V) was prepared by the sodium metaperiodate oxidation (see preparation of II) of 1,3-oxathiane: 78%; bp 139–141° (0.6 mm); nmr ($CDCl_3$), δ 4.63 (q, 2, $-S(\rightarrow O)CH_2O$), 3.85 (t, 3, OCH_2-), 3.1 (m, 2, $-S(\rightarrow O)CH_2-$), 2.0 (m, 2, $-CH_2-$).

Anal. Calcd for $C_4H_8O_2S$: C, 39.98; H, 6.71; S, 26.68. Found: C, 40.01; H, 6.87; S, 26.84.

1,3-Oxathiane is a new compound[10] formed by the reaction of 3-mercapto-1-propanol with dimethoxymethane in boron trifluoride etherate–acetic acid.[11] Isolation of the crude product was effected by washing a chloroform solution of the reaction mixture several times with water and subsequent steam distillation from 10% potassium hydroxide. Vacuum distillation gave pure 1,3-oxathiane: 48%; bp 96–100° (100 mm.); nmr (pure liquid), δ 4.72 (S, 2, SCH_2O), 3.75 (t, 2, OCH_2-), 2.82 (t, 2, SCH_2-), 1.8 (m, 2).

Anal. Calcd for C_4H_8OS: C, 46.12; H, 7.74; S, 30.78. Found: C, 46.43; H, 7.89; S, 30.81.

Registry No.—II, 16487-10-8; VI, 16452-25-8; VII, 16452-26-9; VIII, 16452-27-0; IX, 16452-28-1; X, 16452-29-2; V, 16452-30-5.

Acknowledgments.—Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and to the Graduate School of the University of Minnesota for support of this work.

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The *syn-anti* Isomerism of *α-t*-Aminoalkanone Oximes

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The formation of *α-t*-aminoalkanone oximes in the photoaddition of N-nitrosamines to olefins led us to investigate the separation and identification of *syn* and *anti* isomers in the product (Chart I).[1] These photoadditions, as carried out under acidic conditions, usually gave exclusively or preferentially one isomer.[1-4] In cases where two geometric isomers were formed and could be isolated in the pure states, the assignment of *syn* or *anti* structures was often possible from comparison of their physical properties, although the evidence was tenuous.[3,4] Where only one isomer was isolated, however, assignment was no more than a reasonable guess since there were no general rules available.[1-4] In view of recent interest in the α-substituted (methoxy, mercapto, and halogeno groups) alkanone oximes,[5-7] it is desirable to establish a method by which *syn* and *anti* isomers can be identified rapidly. To this end, a systematic study has been carried out on the *α-t*-aminoalkanone oximes and is reported in this communication. In the sequel it is shown that compounds V and VI must possess the *anti* configuration, contrary to our original suggestion.[1,3]

The compounds examined (I–VII) were available from the previous preparative work.[1-4] The compounds of VIII series were prepared by the oximation of the appropriate α-aminoacetophenone[4] and/or by a photoaddition of the appropriate nitrosamine to styrene[3] followed by extensive chromatography. The melting points of all isomers in VIII series correspond to those prepared by different routes as reported by Fischer and Grob[8] with the exception of *anti*-VIIIc which is a new compound. These compounds can be conveniently divided into two groups; those in which

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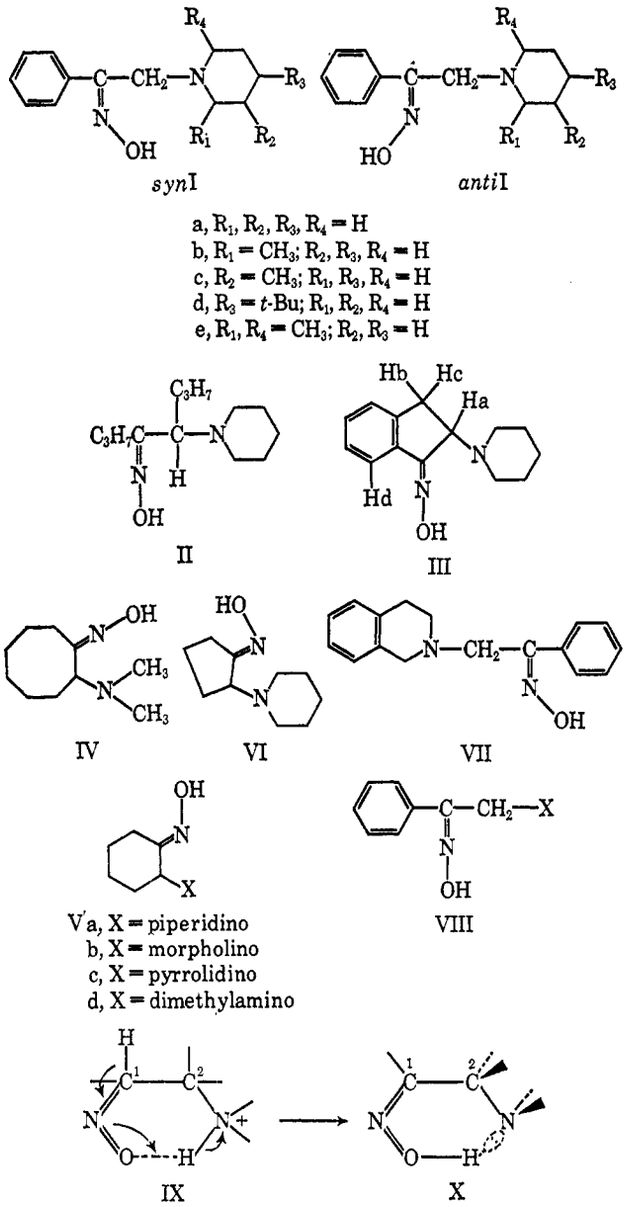
CHART I



both isomers are available (I–IV and VIII) and those in which only one isomer is available.

The particular structural features of α-aminoalkanone oximes permit one to speculate on *syn* and *anti* configurations based on logical deduction of hydrogen bonding properties and anisotropic effects of the oximino group.[9-12] Thus if both *syn* and *anti* isomers are available, differentiation of isomers and correlation of properties with structure may be made with data obtained from techniques such as infrared and nmr spectroscopy, chromatography, and solubility and melting point determinations. Identification of some similar *syn* and *anti* isomers by means of a color test and by ultraviolet spectroscopy has been reported.[8] Both methods suffer from obvious disadvantages; namely, (i) in the former the pure sample is required and (ii) the correlation is limited to α-aminoacetophenone oximes in the latter.

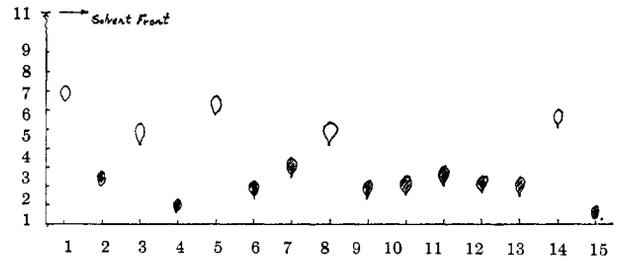


Figure 1.—The thin layer chromatograms of the oximes on alumina with 1.5% MeOH in $CHCl_3$: 1, *syn*-Ib; 2, *anti*-Ib; 3, *syn*-Ic; 4, *anti*-Ic; 5, *syn*-Id; 6, *anti*-Id; 7, *anti*-VII; 8, *syn*-IV; 9, *anti*-IV; 10, *anti*-Va; 11, *anti*-Vb; 12, *anti*-Vc; 13, *anti*-VI; 14, *syn*-II; 15, *anti*-II.

From the structural point of view the major difference between the *syn* and *anti* isomers of these oximes appears to be caused by hydrogen bonding. Thus the *syn* isomer should favor intramolecular hydrogen bonding, while the *anti* isomer can only undergo intermolecular hydrogen bonding. This argument is well validated by the following general observations; namely, (i) the *syn* isomer is always more soluble in nonpolar solvents (*e.g.*, cyclohexane and benzene) than the corresponding *anti* isomer, (ii) the *syn* isomer is invariably less strongly adsorbed than the corresponding *anti* isomer in column or thin layer chromatography (see Figure 1), and (iii) *syn*-III (2-piperidinoindanone oxime) is readily sublimed under conditions where *anti*-III cannot be sublimed.

Direct observation of inter- and intramolecular hydrogen bonding in the 3200–3600-cm^{-1} region employing dilution techniques does not afford an unequivocal answer since oximino hydroxyl groups of both *syn* and *anti* isomers show a broad peak at the 3250-cm^{-1} region and sharp peak at the 3590-cm^{-1} region in CCl_4 solution. It is, however, worth mentioning that the 3250-cm^{-1} peaks of *syn* isomers are usually less intense and attenuate more quickly on dilution. The usefulness of this technique is, however, severely reduced by the limited solubility of some oximes.

Nmr spectroscopy is, however, a more amenable physical method for distinguishing the *syn* and *anti* isomers owing to two salient facts; namely, (i) drastic downfield shift of the intramolecularly hydrogen bonded OH signal in comparison with an intermolecularly hydrogen bonded one[9] and (ii) the distinct anisotropic effects of the oximino group on the neighbouring proton signals.[10-12] The former point is well borne out by the downfield shift of OH signals of *syn*-oximes in comparison to those of the corresponding *anti*-oximes (Table I).

From nmr studies by various groups[8-11] the long-range shielding effects of an oximino group on α-hydrogen atoms are now fairly well understood. Thus the proton α to both the oximino and the amino group is expected to resonate at a lower field in the *syn*-oxime than in the *anti*-oxime.[10] Although the agreement displayed in Table I is excellent within each pair, a systematic correlation of the chemical shifts of the *syn* and *anti* isomers cannot be made. This failure clearly reflects the very subtle change of the magnetic environment experienced by the proton in question as controlled by a small change in conformation. Further

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TABLE I

2-*t*-AMINOALKANONE OXIME

Compound	Mp, °C	OH	Chemical shifts (τ value)[a] NCH_2- or NCH-
syn-Ia	117–117.5	−3.3	6.26
anti-Ia	133–134	−0.8	6.67
syn-Ib	73–76	−2.0	6.18[c]
anti-Ib	Liquid	0.9	6.59[c]
syn-Ic	97–99	−2.0	6.29
anti-Ic	...	...	6.72[d]
syn-Id	171–174	−1.1	6.26
anti-Id	...	...	6.68[d]
anti-Ie	161–164	...	5.91[b]
syn-II	Liquid	1.3	7.06[e]
anti-II	Liquid	2.7	7.23[e]
syn-III	101–103	−2.6	5.54[f]
anti-III	171–174	−0.02	5.83[f]
syn-IV	71–73	−0.65	6.77[e]
anti-IV	84–85	0.60	7.22[e]
anti-Va	118–120	0.5	7.28[g]
anti-Vb	113–114	0.7	7.25[g]
anti-Vc	123	0.6	7.22[g]
anti-Vd	120–121[i]	0.7	7.34[g]
anti-VI	152–154	1.3	6.55[e]
anti-VII	135–136	−0.5	6.11
syn-VIIIb	146–149[h]	−2.1	6.27
anti-VIIIb	116–119[h]	0.6	6.64
syn-VIIIc	110–111	−0.5	6.13
anti-VIIIc	69–71[h]	2.0	6.51
syn-VIIId	117–119[h]	...	6.35[b]
anti-VIIId	80–83[h]	...	6.58[b]

[a] The nmr spectra were taken in $CDCl_3$ solution with internal TMS standards unless specified otherwise and melting points were recorded with a Fisher-Johns hot stage. [b] The nmr spectra were recorded in pyridine solution. [c] The coupling patterns are AB quartet where δ = 35 cps, J = 15.5 cps for *syn*-Ib and δ = 34 cps, J = 14 cps for *anti*-Ib. All other corresponding signals in I series and VIII series are singlets. [d] These values were obtained from nmr spectra of mixtures. [e] Unsymmetrical triplets. [f] The X proton of the ABX system. [g] These signals are not well-defined multiplets with the width at the half-height ranging 8–10 cps. [h] The reported melting points in ref 8 are *syn*-VIIIb 147–149°, *anti*-VIIIb 116–120°, *anti*-VIIIc 78–79°, *syn*-VIIId 118–120°, and *anti*-VIIId 82–84°. [i] This melting point was erroneously given as 111–113° in our previous publication (ref 3).

useful information obtainable from the nmr data is the chemical shifts of the proton *ortho* to the oximino group in the *syn–anti* pair of III. Here the *anti*-III has the OH group oriented *cis* to the *ortho* proton (H_d) which is therefore more deshielded than the corresponding proton in *syn*-III. Such differential shielding on *ortho* protons in *syn* and *anti* isomers is not observed in the I and VIII series possibly due to the difficulty of the benzene ring assuming a conformation coplanar with the oximino group in these compounds.

Owing to scattering of the chemical shifts in the nmr correlation and the difficulty of reproducing the exact conditions in thin layer chromatography (tlc), neither method provides a direct assignment of a *syn* or an *anti* configuration where only one isomer is available. Nevertheless, advantage is taken of the fact that a *syn* and *anti* isomeric pair shows widely separated spots in many solvent systems on a thin layer chromatogram and that the *syn* isomers show yellow spots while the *anti* show dark brown spots on interaction with iodine vapor. Since 2-piperidino- (Va), 2-morpholino- (Vb), 2-pyrrolidino- (Vc), and 2-dimethylaminocyclohexanone oximes (Vd)[13] and 2-piperidinocyclopentanone oxime (VI) are structurally very similar to 2-dimethylaminocyclooctanone oximes (IV), the tlc behavior of the lone isomer of the former group can be compared with the last pair of isomers (*syn*- and *anti*-IV) under the same conditions. The tlc results indicate that these lone isomers move with similar R_f values and show the same coloration as *anti*-IV and therefore must be assigned the *anti* configuration. It is also obvious now that the previously published nmr data[1] of V can be rationalized unequivocally with the *trans* configuration. The similar tlc comparison of the lone isomer of α-(1,2,3,4-tetrahydroisoquinolino)acetophenone oxime[4] (VII) with *syn*- and *anti*-Ia (α-piperidinoacetophenone oxime) fails to give clear-cut indication by R_f value but the coloration with iodine no doubt identifies this compound as the *anti* isomer. It should be mentioned further that due to a complication from steric factors the nmr method could not afford a distinction between *syn* and *anti* configuration[4] of Id. This assignment, however, is neatly resolved on the basis of the tlc mobilities of the two isomers.

Assignment of V and IV to the *anti* configuration brings us to consider the steric factor in the tautomerization of the corresponding C-nitroso compounds IX. The major factors controlling the thermodynamic stabilities of the *syn* and *anti* configurations of these α-amino ketoximes are (i) the steric effects attending at the vicinity of the oximino group and (ii) the strength of intramolecular hydrogen bonding between OH and the lone pair electrons of the amino moieties (see X). The mechanism of intramolecular proton transfer *via* a cyclic transition state, which gives a *syn* configuration, should possess a transition state very similar to the conformation of a *syn*-oxime. Inspection of Dreiding models reveals that for *syn* isomers of IV and V (and larger ring analogs) to assume a conformation capable of hydrogen bonding (see X) the N-alkyl groups are in the eclipsing position with the other two bonds of C-2. This nonbonded interaction no doubt counterbalances the energy gain in intramolecular hydrogen bonding to give a net destabilization of the *syn* configuration. Such destabilization is most obvious in the conformationally less flexible cyclohexanone derivative giving only *anti* isomers. As the ring sizes increase (and, therefore, the flexibility increases) to an eight-membered ring and then to the freely flexible acyclic amino oxime (such as II), the yield of *syn* isomer also increases since the nonbonded interaction can be lessened by twisting the C–N (amine) bond slightly. This twisting also causes a weakening of the intramolecular hydrogen bonding since the lone pair electrons have to rotate away from the C=N–OH plane. These two factors counterbalance each other to yield a net result of the observed *syn–anti* ratio.[3] Owing to the ring strain imposed on the conformation of a five-membered system, the oximino OH and the piperidine in VI are too far apart to make any effective intramolecular hydrogen bonding. The geometry of the transition state in this case is therefore solely decided by steric factors which favor the *anti* isomer as the product in the tautomerization. With the hope of elucidating the relative importance of these two factors, a basic equilibra-

(13) It is pertinent to point out that Fischer and Grob[8] have assigned *anti* configuration to this compound based on steric reasons.

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

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