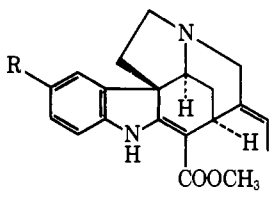
Structure and Absolute Configuration of Strictamine and Strictalamine from *Rhazya stricta*. Stereochemistry of the *Picralima* Alkaloids

Yusuf Ahmad,*[1a] Kaniz Fatima,[1a] Atta-ur-Rahman,[1b] John L. Occolowitz,[1c] Barbara A. Solheim,[1d] Jon Clardy,*[1d] Robert L. Garnick,[1e] and Philip W. Le Quesne*[1e]

Contribution from the P.C.S.I.R. Laboratories, Lahore-16, Pakistan, H.E.J. Postgraduate Institute of Chemistry, University of Karachi, Karachi-32, Pakistan, Lilly Research Laboratories, Indianapolis, Indiana 46206, Ames Laboratory and the Department of Chemistry, Iowa State University, Ames, Iowa 50011, and the Department of Chemistry, Northeastern University, Boston, Massachusetts 02115. *Received September 7, 1976*

Abstract: Strictamine (**4**), strictalamine (**6**), and nor-*C*-fluorocurarine (**8**) have been isolated from *Rhazya stricta*. X-ray structure determination and chemical correlation establish the structures and absolute configurations of **4**, **6**, and also, by extension, of the *Picralima* bases, especially with respect to the configurations of the 16-carbomethoxy group and the ethylidene group.

Continuing our studies of alkaloidal constituents of *Rhazya stricta*,[2,3] we have investigated several components of the ether-soluble extractives remaining after removal of sewarine (**1**; R = OH).[3] From these fractions we have isolated first, an



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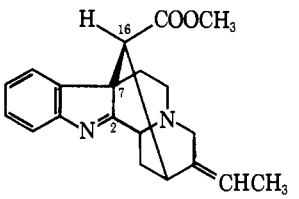

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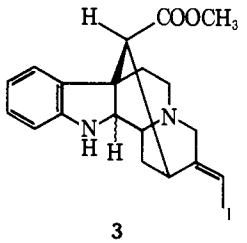

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alkaloid, $C_{20}H_{22}N_2O_2$, mp 114–115 °C, whose properties are generally in accord with those reported for strictamine, to which structure **2** has been assigned by Biemann, Chatterjee, and their co-workers.[4,5] A second alkaloid, which we name strictalamine, has been obtained in small amount. The mass spectrum of strictalamine shows mol wt 292, and the UV spectrum an indolenine chromophore (λ_{max}^{EtOH} 218, 265 nm). A formyl group (ν_{max} 2820, 2720, 1720 cm^{-1}; NMR ($CDCl_3$) δ 8.51, $-CHO$), and an ethylidene group (δ 1.8, 3 H, doublet; 5.5, 1 H, multiplet) are present. Important daughter ions in the mass spectrum are at *m/e* 264 (M − 28) and 263 (M −29). These data together suggested the molecular formula $C_{19}H_{20}N_2O$ for strictalamine. The close resemblances between the infrared spectra of the two alkaloids indicated their structural similarity and suggested that structural and stereochemical correlation between them might readily be achieved. However, it was necessary first to re-examine strictamine, since no firm stereochemical conclusions could be drawn from the earlier work and since another alkaloid ("Base A", = desacetyldesformylakuammiline), isolated from *Rauvolfia vomitoria* and having different melting point and optical rotation, has been assigned the same structure.[6]

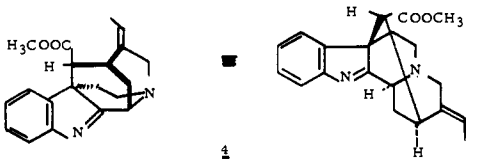
Chemical examination of strictamine generally corroborated the earlier findings,[4] although the indolenine function was found to be reducible with sodium borohydride in sodium methoxide–methanol or methanolic acetic acid; the product was the same dihydro derivative as previously obtained catalytically and assigned structure **3**. The high resolution mass spectra of strictamine and this dihydro derivative were completely in accord with earlier work and with the gross structure **2**.

Stereochemically, the points of interest in strictamine are chiral centers C-7, C-16, and the configuration of the ethylidene group (see below). An x-ray crystallographic examination was therefore undertaken. Crystalline strictamine, mp 114–115 °C, was found to be the monohydrate and to form colorless cubes in the orthorhombic crystal system. Precise measurement of 2θ for 15 high angle reflections gave a = 11.212 (3), b = 8.266 (2), and c = 19.034 (3) Å, while systematic extinctions ($h00$, absent if $h = 2n + 1$; $0k0$, absent if $k = 2n + 1$; $00l$, absent if $l = 2n + 1$) indicated space group $P2_12_12_1$. All unique diffraction maxima with $2\theta \leq 114°$ were recorded on a Syntex $P2_1$ diffractometer using graphite monochromated Cu Kα radiation (1.54178). A total of 1404 unique reflections were measured, and after correction for Lorentz, polarization, and background effects, 1159 (82%) were judged observed ($F_o^2 \geq 3\sigma(F_o^2)$).

The structure was solved by use of a multisolution, weighted tangent formula approach.[7] Full-matrix least-squares refinement with anisotropic temperature factors for nonhydrogen atoms and isotropic temperature factors for hydrogen have converged to a standard crystallographic residual of 0.037 for the observed reflections.[8]

Figure 1 shows a drawing of the x-ray model. The water of crystallization forms a H bond to N(4) with N···H of 1.90 Å and O–H of 0.99 Å. All bond distances and angles agree well with generally accepted values and there are no substantial peaks on a final difference electron density synthesis.[9]

This work shows strictamine to have structure and relative configuration **4** (also absolute configuration, see below). It



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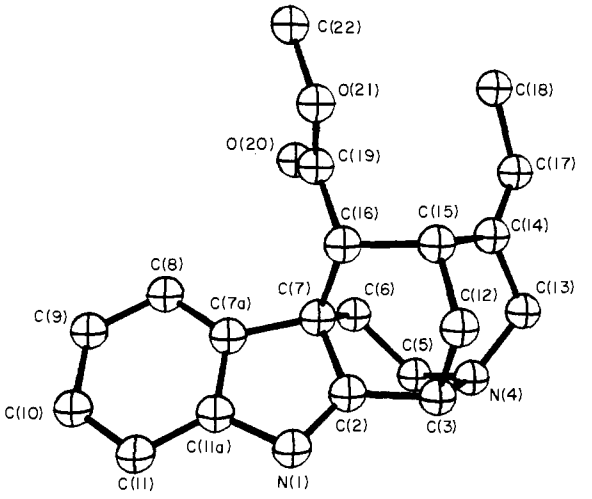
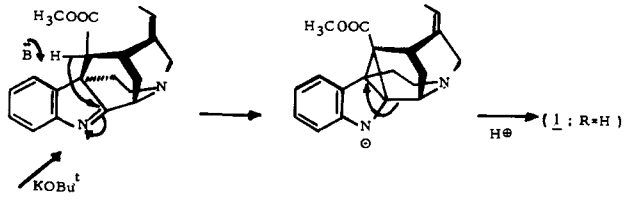


Figure 1. A computer-generated perspective drawing of strictamine (**4**). For clarity, hydrogen atoms are not shown. The absolute configuration depicted is that of the naturally occurring compound.

corroborates the tentative stereochemical proposals made previously for strictamine,[4] and defines the remaining stereochemical features of the molecule. The identity of "Base A" from *Rauwolfia vomitoria,* to which the same structure has also been assigned,[6] is now open to some speculation. Both its optical rotation and melting point ([α]D +133°, mp 140 °C) are different from those of strictamine ([α]D +103°, mp 114–115 °C), although the NMR data appear very similar. Strictamine crystallizes in apparently at least two hydrated forms, which are not reported for Base A. Whereas Base A with potassium *tert*-butoxide in benzene gives (−)-akuammicine (**1**; R = H) in readily isolable yield,[6] for strictamine the analogous reaction was initially equivocal,[4] and in our hands, while giving (−)-akuammicine, did so in very low yield. The mechanism proposed for such a conversion by the French workers[6] is in complete accord with structure **4** for strictamine.



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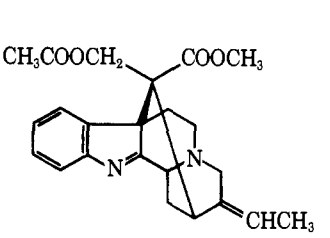
The fact that strictamine, the ethylidene group of which is now found to have the configuration depicted in **4**, is converted into akuammicine gives strong support to this, or a similar, mechanism.[10] An unusual feature of the NMR spectrum of strictamine is the downfield position of the signal from H-16, attached to the carbomethoxy group (δ 4.78). This was ascribed[4] to the deshielding effect of the indolenine system. Dreiding models of structure **4** show the C-16 H to be rather remote (ca. 2.5 Å) from the indolenine system;[4] in our view an equally important influence on the chemical shift of this proton may be the nearness of the carbomethoxy group, whose free rotation is restricted by the ethylidene methyl group and the C-8 aromatic proton. The model also reveals that the indolenine double bond should be accessible to hydride attack (cf. akuammiline **5**[11]).

The structure of strictamine being settled, we considered that strictalamine would likely be **6**, the formyl analogue of strictamine. This was established by reduction of strictamine with lithium aluminum hydride to the alcohol **7**, which on modified Oppenauer oxidation (potassium *tert*-butoxide-fluorenone)[11] gave a compound identical with strictalamine.



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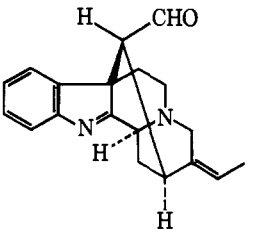

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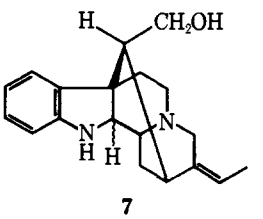

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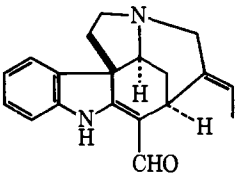
This establishes the structure **6** for strictalamine. Reduction of natural and synthetic strictalamine with lithium aluminum hydride gave only **7**, showing maintenance of stereochemical integrity. The other Oppenauer product was (−)-nor-*C*-fluorocurarine (**8**).[11,12] The formation of **8** during this reaction



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defines the absolute stereochemistry of strictamine (**4**) and strictalamine (**6**). The alcohol **7** had [α]D −113° (MeOH) (cf. [α]D −103° (MeOH) for the corresponding alcohol derived from Base A, and [α]D −108° (MeOH) for desformopicralinol, with which the alcohol from Base A is identical).[6] Since these samples are all amorphous and would be susceptible to occlusion of solvents, we consider these rotations to be the same within experimental error. Our work, taken together with previous investigations,[6,10] thus defines the absolute stereochemistry of the *Picralima* alkaloids at all points, including the ethylidene group. The proposed configurations at C-16 are now firm, and strictamine and strictalamine are linked with the *Picralima* group. It seems likely that strictamine and Base A[6] are the same chemical species.

In view of the formation of strictalamine (**6**) and (−)-nor-*C*-fluorocurarine (**8**) from the modified Oppenauer oxidation of alcohol **7**, it is of interest that we have also isolated **8** from *R. stricta,* although in small amount. It is thus possible that this reaction may be biomimetic for pathways operative in *R. stricta* and *Picralima nitida,* and thus may represent an origin for akuammicine alkaloids alternative to that proposed through geissoschizine oxindole in, for example, *Vinca rosea.*[13] The possible existence of such an alternate pathway, in vivo, first envisaged by Wenkert and Wickberg some years ago,[14] would be of interest to establish experimentally.

Experimental Section

UV absorption spectra were measured on a Cary 14 spectrophotometer and IR spectra with a Perkin Elmer 567 spectrophotometer. NMR spectra were taken with a Varian T-60 spectrometer in $CDCl_3$ with Me_4Si as internal standard. Mass spectra were taken with a Nuclide I-90G instrument and optical rotations with a Perkin-Elmer 140 polarimeter. Thin layer chromatography was performed on Eastman Chromagram silica gel plates in 90:10 dichloromethane–acetone unless otherwise specified. TLC plates were visualized with long-wavelength UV light and with a spray of saturated solution of Ce(IV) sulfate in 50% aqueous sulfuric acid.

Isolation of Strictamine. Air-dried *Rhazya stricta* leaves (12 kg) were extracted three times with ethanol (118 L). The dark green extract was concentrated at 25 °C under reduced pressure until a green solid separated. This solid was filtered and washed with ethanol. The filtrate was concentrated to a viscous mass and digested with distilled water (4 L) wherein most of the material dissolved (clarified with charcoal). The clear brown cooled solution was basified with ammonia, at which point a thick yellow-brown precipitate was obtained. This precipitate was exhaustively extracted with ethyl acetate (4 L). The ethyl acetate extract was washed with water, dried (Na_2SO_4), and concentrated to one-quarter of its original volume, at which point sewarine (**1**; R = OH) (1.8 g), mp 244–245 °C, crystallized. The ethyl acetate solution was evaporated to dryness (148 g). The powdered product (30 g) was divided into ether-soluble and -insoluble fractions. The ether-soluble fraction (10 g) was chromatographed on a column of neutral alumina (Woelm, activity I, 350 g) eluted with petroleum ether–benzene in gradients up to 1:1. Quebrachamine, mp 141–142 °C, was eluted initially, followed by a mixture of three or four other alkaloids. The solvent was then changed to benzene–chloroform and the chloroform concentration slowly increased to 1:1.

Strictamine was obtained from later fractions as a colorless crystalline compound, mp 98–100 °C (0.21 g). Crystallization from acetone raised the melting point to 114–115 °C. Strictamine[4] has $[\alpha]^{20}D$ +103° (EtOH); γ_{max}^{EtOH} 213 nm (ϵ 13 600), 262 (ϵ 3740); IR (film) 1740, 1630, 1610 cm^{-1}; NMR δ 7.1–7.8 (m, 4 H), 3.78 (s, 3 H, OCH_3), 1.56 (d of d, 3 H, ethylidene methyl); *m/e*, M^+ 322.1681 (calcd for $C_{20}H_{22}N_2O_2$, 322.168). Strictamine gave a colorless reaction to the Ce(IV) spray.

Isolation of Strictalamine (6). The ether-soluble portion (50 g) of the ethanol extract of *R. stricta*, after removal of sewarine (**1**; R = OH) was dissolved in tartaric acid solution (2% aqueous; 500 mL). After removal of an insoluble fraction (4.5 g) the filtrate was adjusted to pH 4 with ammonia and extracted with light petroleum, benzene, chloroform, and ethyl acetate successively. The chloroform extract (5.4 g) was chromatographed on neutral alumina (E. Merck; activity III). Elution with light petroleum gave material (31 mg) which was homogeneous by TLC (silica gel; ethanol–benzene, 1:9). Recrystallization of this material gave strictalamine as needles; mp 152–154 °C; λ_{max} 218, 265 nm; IR ν (film) 2820, 2720, 1720, 1615, 1590 cm^{-1}; NMR δ 8.75 (s, 1 H, -CHO (aldehyde)), 7.1–7.8 (m, 4 H), 5.4 (m, 1 H), 4.8 (d, 1 H), 1.6 (d, 3 H, (ethylidene methyl)); MS, *m/e* 292 (100, M^+), 264 (20.5), 263 (69.4), 234 (26.6) (cf. compound **7**, ref 11). Elution with more polar solvents gave a complex mixture of compounds (3.6 g) which is under investigation.

Isolation of (−)-Nor-*C*-fluorocurarine (8). A solution of the above mixed alkaloidal extractives (20 g) in 2% tartaric acid solution (250 mL) was basified to pH 3.5 with ammonia and extracted with ethyl acetate. Chromatography of the extract (3.1 g) on neutral alumina (Merck activity III, 200 g) using chloroform as eluent gave, in fractions 24–41 of a series of 50-mL fractions, (−)-nor-*C*-fluorocurarine (221 mg), identical with that prepared synthetically below. Mixtures of components eluted later from this column are under investigation.

Reduction of Strictamine (4) with Sodium Borohydride (Acidic Methanol). Strictamine (32 mg, 0.1 mmol) was stirred at 20 °C for 24 h with sodium borohydride (Ventron, 200 mg) in methanol (1 mL) to which had been added 1 drop of glacial acetic acid. Concentrated ammonia (1 mL) was then added and the reaction mixture extracted with chloroform (three 25-mL portions). The chloroform extracts were combined, dried over K_2CO_3, and concentrated under reduced pressure to yield 30 mg of a dark oil. Preparative plate chromatography (E. Merck SiO_2 gel, 0.5 mm, 3% $CHCl_3$–MeOH) and excision of the band at R_f 0.8 gave the dihydro derivative **3** as a pale yellow powder (from light petroleum, mp 135 °C dec): MS M^+ 324.1838; calcd for $C_{20}H_{24}N_2O_2$, 324.1883; 309 (50), 251 (80), 194 (90), 144 (82), 143 (82), 130 (80), 122 (80), 121 (85). The dihydro compound **3** gave an orange color with Ce(IV) spray.

An analogous experiment was also performed with strictamine and $NaBH_4$ in freshly prepared 20% sodium methoxide–methanol. TLC indicated formation of the dihydro compound **3** after 24 h.

Reduction of Strictamine 4 to the Alcohol 7 (cf. ref 11). Strictamine (100 mg, 0.33 mmol) was dissolved in ether–tetrahydrofuran (1:1) (25 mL) in a 50-mL flask attached to a Soxhlet extractor. Lithium aluminum hydride (100 mg) was placed in the Soxhlet thimble and the reaction mixture heated under reflux for 5 h. The reaction mixture was worked up by the addition of water (100 mL), 2 N NaOH (100 mL), and water (300 mL). Filtration of the insoluble aluminum salts, followed by subsequent washing with Et_2O, gave an Et_2O layer which was then dried with K_2CO_3. Final concentration of the Et_2O under reduced pressure yielded 92 mg of alcohol **7**, with identical IR and mass spectra with those obtained by Biemann, Chatterjee et al.;[4] $[\alpha]^{24}D$ −113° (*c*, 1.19. MeOH).

Modified Oppenauer Oxidation of Alcohol 7 to Strictalamine and (−)-Nor-*C*-fluorocurarine. Alcohol **7** (92 mg), dried in an Abderhalden pistol dryer (KOH, 65 °C) for 24 h was dissolved in anhydrous C_6H_6 (50 mL), together with fluorenone (1 g, freshly sublimed). Potassium *tert*-butoxide (0.75 g) was added, and the reaction mixture refluxed for 2.5 h. After addition of 1 N HCl (100 mL), the aqueous solution was basified with dilute ammonia and extracted with chloroform (three 50-mL portions). The chloroform extracts were combined and dried over K_2CO_3. (TLC indicated two products, R_f 0.4 (green color with Ce(IV)); R_f 0.5 (colorless with Ce(IV).) The $CHCl_3$ extracts were concentrated and placed on a preparative TLC plate (E. Merck SiO_2 gel, 0.5 mm, developed in acetone). This did not separate the two products, but did effect the removal of residual fluorenone. Excision of the alkaloidal bands followed by Soxhlet extraction with methanol gave a mixture of the two alkaloidal components. Sublimation at 0.01 mmHg and 160 °C gave a sublimate enriched in (−)-nor-*C*-fluorocurarine, **8**, from which **8** crystallized, using acetone, in long needles. The synthetic (−)-nor-*C*-fluorocurarine had mp 186–187 °C $[\alpha]^{24}D$ −1018° ($CHCl_3$); λ_{max} 245, 301, 364 nm (ϵ 20 800, 8000, 40 000); *m/e* 292 (145) (M^+), 263 (13), 249 (22.5), 194 (15.3), 121 (100) (cf. ref 11; mp 182 °C $[\alpha]D$ −1084° ($CHCl_3$)). The mother liquors, enriched in strictalamine (**6**), were subjected to a prolonged sublimation at 156 °C (0.01 mmHg). This yielded a crystalline compound whose IR, mass spectrum, NMR, R_f, and Ce(IV) spray reaction all were identical with those of natural strictalamine.

Lithium Aluminum Hydride Reduction of Natural and Synthetic Strictalamine. Natural strictalamine (1 mg) and synthetic strictalamine (1 mg) were each reduced to alcohol **7** by lithium aluminum hydride (10 mg) in ether–tetrahydrofuran (1:1) (0.5 mL). The reductions were carried out in a Soxhlet extractor system and worked up by Fieser's method.[15] TLC (SiO_2 gel, 10% acetone–dichloromethane) indicated identical R_f and Ce(IV) spray colors (bright orange) for the two single identical products. Furthermore, TLC comparison with alcohol **7** prepared directly from strictamine also showed identity.

Rearrangement of Strictamine to Akuammicine. Strictamine (43 mg) was dissolved in anhydrous benzene (3 mL), and potassium *tert*-butoxide (100 mg, freshly sublimed) added. The reaction mixture was refluxed for 2.5 h, then worked up by the addition of water (10 mL), followed by extraction with chloroform (three 25-ml portions). The chloroform extracts were combined, dried over K_2CO_3, filtered, and concentrated under reduced pressure. Preparative plate chromatography (E. Merck SiO_2 gel, 0.25 mm, developed in 10% acetone–chloroform), followed by excision of the band at R_f 0.1 yielded akuammicine, whose R_f and unmistakable Ce(IV) spray color (deep blue) were identical with those of an authentic sample. The optical rotation of this sample (less than 0.1 mg) was extremely negative.

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Relative Reactivities of Phenoxides with Methylating Agents

Edward S. Lewis* and Steven Vanderpool

Contribution from the Department of Chemistry, Rice University, Houston, Texas 77001. *Received September 14, 1976*

Abstract: The relative reactivities of substituted phenoxide ions toward a range of methylating agents are determined competitively from the yields of substituted anisoles, as well as by direct rate measurement, and show that the selectivity between different phenoxides increases for CH_3X in the order $(CH_3)_3O^+$ (2.8), $CH_3OSO_2CF_3$ (3.5), $CH_3(OSO_3CH_3)$ (5.0), $CH_3O\text{-}P^+CH_3(OCH_3)_2$ (9.5), CH_3OTs (9.6), CH_3I (28). The parenthetical numbers are relative rates of sodium phenoxide and sodium *p*-nitrophenoxide measured competitively in sulfolane solution at total sodium ion concentration of about 0.3 M. The relative rates increase with dilution, by substitution of potassium salts for sodium salts, and by addition of crown ethers, but the difference between methyl trifluoromethanesulfonate and methyl iodide remains substantial. Accuracy is limited by the instability of sodium or potassium phenoxide solutions in sulfolane, but the observed differences in selectivities cannot be attributed to this error. Some absolute rates in other solvents are presented.

Characterization of nucleophilic reactivity has been of interest for many years in a variety of systems. Reasonably successful attempts have been made to correlate rates of nucleophilic substitution on carbon with one another,[1] with basicity alone,[2] or combined with polarizability,[3,4] as well as by calculation.[5] Nucleophilic character has also been assigned by Ritchie[6] on the basis of rates of combination with electrophiles, such as carbonium ions. The current study is concerned with the reaction,

$$Y^- + RX \rightarrow YR + X^- \qquad (1)$$

with the further limitation that the only concern is with the clearly one-step or S_N2 reactions, thus avoiding many of the problems associated with intermediate carbonium ions. Although it has been suggested[7] that ion pairs are intermediate even in S_N2 reactions, there is little question that there is for classical S_N2 examples, a single rate-determining step with a negatively charged transition state containing Y, R, and X in a linear array. Thus the possible existence of a lower energy potential minimum for an R^+X^- ion pair before this transition state is reached is fortunately without relevance to the problem of rate or transition state structure or energy, and this possible complication can be safely ignored. By limiting the structure of R to methyl the S_N2 mechanism is assured and steric interactions are made nearly constant. Furthermore, the methyl is the smallest organic group. Thus substitution on methyl, or "methyl transfer", is a close analogue to the proton transfer reaction, which has been so extensively studied in both rate and equilibrium.[8]

The further rationale for studying reactions of CH_3X is that since much of the early work on nucleophilic reactivity of various compounds RX, a number of very reactive reagents, such as $(CH_3)_3O^+$ and $CH_3OSO_2CF_3$ ("methyl triflate", CH_3OTf) have become available. It appeared of interest to compare these reactive ones with the more conventional methylating agents; perhaps the high reactivity is associated with a low selectivity among different nucleophiles.

Methods and Results

The majority of the experimental work consists in the measurement of relative rates of the reactions

$$MeX + C_6H_5O^- \xrightarrow{k_H} C_6H_5OMe + X^- \qquad (2)$$

$$MeX + p\text{-}O_2NC_6H_4O^- \xrightarrow{k_{NO_2}} p\text{-}NO_2C_6H_4OMe + X^- \qquad (3)$$

by allowing a mixture of the two phenoxides to compete for an insufficiency of MeX, and then determining the apparent rate constant ratio, denoted as $R_{NO_2}{}^H$, from the relative yields of anisole and *p*-nitroanisole, as measured gas chromatographically, using the equation

$$R_{NO_2}{}^H = \frac{(p\text{-}NO_2C_6H_4O^-)_0\, A_{PhOMe} S_H}{(C_6H_5O^-)_0\, A_{p\text{-}NO_2C_6H_4OMe} S_{NO_2}} \qquad (4)$$

in which the concentrations are initial concentrations, the A's are integrated areas of the GC peaks of anisoles, and the S's are the relative GC molar sensitivities with the detector used. This equation actually represents the ratio of the bimolecular rate constants, k_H/k_{NO_2}, for reactions 2 and 3 only if certain assumptions are made: (1) The GC analysis actually gives the correct ratio of the two anisoles in the reaction mixture. This assumption is by no means automatically true, but problems such as the instability, especially of *p*-nitroanisole, on the GC system, fractionation of the anisoles during concentration, and interference of the solvent sulfolane with the analysis were successfully overcome, as shown by control experiments. (2) The relative concentrations of the two phenoxides do not change during the reaction. By choosing initial concentrations