Nucleophilic Heteroaromatic Substitutions. XXXVII.[1] Aryloxyls as Leaving Groups in Nucleophilic Heteroaromatic Substitution with Piperidine. Structural and Hydrogen Isotope Effects

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The reactivity of a number of 2- and 4-quinolyl aryl ethers with neat piperidine was examined. Product analysis showed that the compounds generally underwent substitution at both the heteroaryl and aryl carbons. The factors favoring the reaction at the aryl carbon are discussed. Where the dearylation reaction could be neglected, the kinetics of the heteroaromatic substitution were carried out. In such cases the kinetic hydrogen isotope effects by the use of *N*-deuteriopiperidine were also determined, k_H/k_D values as large as 1.96 and 2.46 being obtained for the γ-(2-methyl-4-nitrophenoxy) and the γ-(3-nitrophenoxy) derivative, respectively. The results indicate that the detailed reaction mechanism depends on whether the heteroaromatic substitution takes place at a position α or γ to the aza group. Structure dependence of the isotope effect at the position γ is interpreted in terms of transition-state symmetries.

Primary kinetic hydrogen isotope effects in nitro-activated nucleophilic aromatic substitutions by protic amines have been found to occur only when the leaving group is a rather poor one and the reaction is subject to base catalysis.[2] The reverse, however, is not always true, since some reactions, though subject to base catalysis, do not display a measurable isotope effect.[3]

As pointed out in a preceding paper in this series,[4] the tendency for the kinetic isotope effect to occur would seem to increase as the ease of separation of the leaving groups from the saturated carbon decreases. With the aim to test this hypothesis and to correlate kinetic isotope effects to the structure of the groups, we planned to examine the reactivity of a number of α- and γ-aryloxyquinolines, HET-OAr, with piperidine and *N*-deuteriopiperidine.

Although the work turned out to suffer from certain experimental limitations, it offered additional points of interest, such as the influence of the structure of the oxygen leaving group on the duality of attack of the reagent on either side of the oxygen bridge, and the comparison of reactivity between α and γ positions of the pyridinoid ring for the type of leaving groups under investigation.

Results and Discussion

The investigated aryloxyquinolines are listed in Table I. They have been obtained by the reaction of the parent chloroquinoline with either the appropriate sodium phenoxides in dimethyl sulfoxide solution or, more generally, the neat phenol. By the latter, straightforward procedure the occurrence of side reactions (autoquaternization) was kept to a minimum due to the protic nature of the medium and the H-bonding accepting properties of the heterocyclic substrate, especially 4-chloroquinoline.[5,6] Details are reported in the Experimental Section.

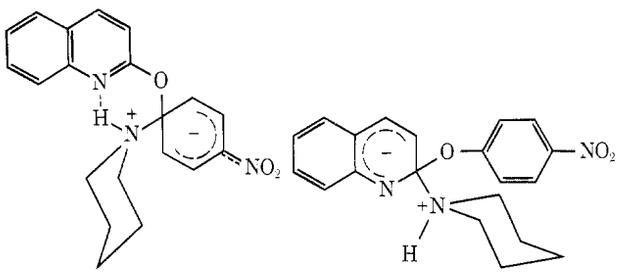
Product Analysis. The reaction of the heteroaryl aryl ethers, HET-OAr, with piperidine was generally found to involve attack on either side of the oxygen bridge (reactions 1 and 2). In order to ascertain whether a kinetic

$$\text{HET-OAr} + (CH_2)_5NH \longrightarrow \text{HET-N}(CH_2)_5 + \text{ArOH} \quad (1)$$

$$\text{HET-OAr} + (CH_2)_5NH \longrightarrow \text{HET-OH} + \text{Ar-N}(CH_2)_5 \quad (2)$$

study of reaction 1 was feasible or not, a product analysis was carried out first and gave the results shown in Table I. The dearylation reaction 2 was found to compete with reaction 1 to varying extents in the case of the *o*-nitrophenoxy and *p*-nitrophenoxy members of both quinoline series. The results are consistent within each series and are explained by the higher conjugative ability of the nitro group to accommodate a negative charge as compared to the aza group.[7] The presence of an *o*-methyl group on the aryl side of the oxygen bridge was expected[8] to exert a rate-depressing steric effect on reaction 2, rather than on reaction 1. Accordingly, the formation of the quinolone was suppressed or greatly reduced in the case of the 2-methyl-4-nitrophenoxy compounds.

A peculiarity of the product analysis data should be noted. The competing reaction 2 is more important in the 2-aryloxy than in the 4-aryloxy series, despite the fact that the reactivity of 2-X-quinolines with piperidine is higher than that of the corresponding 4-X isomers (see ref 6 and next section). A possible explanation for this effect is a stabilizing, concerted interaction in the transition state for the first step leading to such a cyclic adduct as **1**.



1 **2**

A similar interaction would neither be so favorable for the attack of piperidine on the heteroaryl side (no six-membered pseudocyclic structure would obtain, structure **2**) nor be at all possible for the reaction of the 4-X isomer. Such an interaction would also be compatible with the relative importance of the observed steric effect of the *o*-methyl group when reactions 1 and 2 are compared.

Reaction Kinetics On the basis of the above results, the rate determinations were carried out only for the substrates which did not undergo extensive dearylation reaction, *i.e.*, the phenoxy, the 3-nitrophenoxy, and the 2-methyl-4-nitrophenoxy members of the investigated series. The reactions with neat piperidine and with its N-deuterated analog were all found to follow pseudo-first-order kinetics. In the case of the reaction of 4-(2-methyl-4-nitrophenoxy)quinoline, which was accompanied by appreciable dearylation, the rate constants were determined by the method of initial rates. The rate constants at 121° and the activation parameters are reported in Table II (for the rate constants at the other temperatures, see the Experimental Section).

Table I
Piperidinolysis of Some 2- and 4-Aryloxyquinolines. Product Analysis[a]

Quinoline	Refluxing time, days	% Piperidinoquinoline	% quinolone
2-Phenoxy (40515-82-0)	20	100 (46708-03-6)	None
2-(*o*-Nitrophenoxy) (51248-08-9)	1	27	73 (493-62-9)
2-(*m*-Nitrophenoxy) (51248-09-0)	5	100	None
2-(*p*-Nitrophenoxy) (51248-10-3)	6	None	100
2-(2-Methyl-4-nitrophenoxy) (51248-11-4)	8	100	None
4-Phenoxy (30696-04-9)	60	100 (14157-04-1)	None
4-(*o*-Nitrophenoxy) (15248-12-5)	0.5	42	58
4-(*m*-Nitrophenoxy) (51248-13-6)	6	100	None
4-(*p*-Nitrophenoxy) (51248-14-7)	3	26	74 (529-37-3)
4-(2-Methyl-4-nitrophenoxy) (51248-15-8)	4	71	29

[a] Registry no. are found in parentheses under compound.

From these data first of all we note that for any given aryloxy leaving group, out of each isomeric pair, the α isomer is more reactive than the γ isomer, the α/γ reactivity ratio being 6.67, 7.42, and 17.2 for the phenoxy, 3-nitrophenoxy, and 2-methyl-4-nitrophenoxy groups, respectively. This behavior is analogous to that previously described for chlorine as the leaving group under the same medium conditions, which may indicate the occurrence of proximity *aza* effects with the aryloxyquinolines similar to those observed for the chloroquinolines.[6]

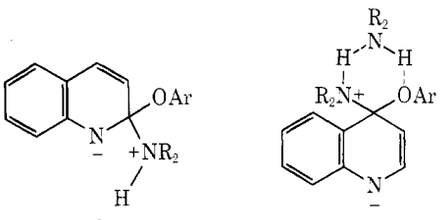
Secondly, we have an opportunity to compare, though in a limited set of structures, the oxygen leaving group effect with the basicity of the related aryloxide ion. An aryloxyl is expected to be a better leaving group as the related aryloxide ion becomes less basic. This is indeed the case for the nitrophenoxy groups when compared to the unsubstituted phenoxy group.[9] However, the leaving group order is irregular within the nitrophenoxy groups (3-nitrophenoxy and 2-methyl-4-nitrophenoxy), presumably as a consequence of a retarding steric effect of the 2-methyl-4-nitrophenoxy group.

As to the kinetic hydrogen isotope effect arising from the use of *N*-deuteriopiperidine as reagent as well as medium, there is a general tendency of the oxygen leaving groups to display positive effects (Table II), as expected from poor leaving groups.[2a,c,e,4] Such effects are assumed to be primary and caused by a rate-limiting hydrogen transfer during the decomposition of the intermediate adduct in a two-step mechanism.[2c,e,4]

$$\text{HET-OAr} + \text{pip} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \sigma\text{adduct} \xrightarrow{k_2} \text{products}$$

Secondary isotope effects on the electron-donor properties of the amine are expected to be small and inverse.[12] Solvent isotope effects are probably relatively unimportant in each of the two sets of results to be discussed below.

At the α position, displacement reactions by piperidine are known to have relatively little sensitivity to solvent[6] and to depend on built-in solvation phenomena.[6] The small observed isotope effect at this position, ranging from 1.25 to 1.46, is probably due to a slow, not necessarily concerted, hydrogen transfer from a partially neutralized charge from the α-ammonium nitrogen of adduct **3** to ei-



3 **4**

ther the adjacent aza nitrogen or to the solvent. It is of interest to note that these isotope effects are rather insensitive to the structure of the oxygen leaving group and to the reactivity of the substrate.

The overall picture is quite different at the γ position. Despite the lower spread of the reactivity (see Table II), fairly higher isotope effects (1.96 and 2.46), in fact the highest known so far for these reactions, are observed in two out of the three examined substrates (nitrophenoxy compounds) and *no* isotope effect is observed in the third one. A modified mechanism may explain the different behavior. In the absence of proximity effects, a concerted mechanism may be required to speed up the reaction. A possible path may involve a second molecule of amine and a cyclic transition state which can be visualized as deriving from an adduct of type **4**.[13] The isotope effect would be a function of the symmetry of the concerted change. The absence of an isotope effect for 4-phenoxyquinoline is obviously ambiguous, as it may simply result from a suppression of the decomposition of the intermediate adduct as a rate-limiting process; nevertheless, it may also imply a sufficient deviation from symmetry as to cause a *decrease* of the isotope effect.[14] The latter view, that we favor, would be supported by the higher entropy of activation observed for the unsubstituted phenoxy quinoline (see Table II) and by the state of self-association of liquid amines.[15]

To sum up, we may say that, although the oxygen groups are poor leaving groups, they do not necessarily cause primary kinetic hydrogen isotope effects greater than the ones observed for better leaving groups in heteroaromatic or aromatic nucleophilic substitution with *N*-

Table II
Rate Constants at 121°,[a] Kinetic Hydrogen Isotope Effects, and Activation Parameters for the Piperidinolysis Reaction of Some α- and γ-Aryloxyquinolines

Quinoline derivative	$10^6 k_H$[b]	$10^6 k_D$	k_H/k_D	E_a, kcal mol^{-1}	$-\Delta S^*$, eu
α-Phenoxy	0.714	0.538[c]	1.32	18.3	42.8
α-(*m*-Nitrophenoxy)	16.9	13.5[c]	1.25	13.3	49.2
α-(2-Methyl-4-nitrophenoxy)	13.4	9.17[c]	1.46	13.9	48.2
γ-Phenoxy	0.107	0.103[b]	~1	16.6[d]	50.9[d]
γ-(*m*-Nitrophenoxy)	2.28	0.925[c]	2.46	9.9	61.7
γ-(2-Methyl-4-nitrophenoxy)	0.778	0.397[c]	1.96	11.5	59.8

[a] k, sec^{-1}. [b] Calculated from activation parameters. [c] Mean value from duplicate runs. [d] For the reactions in [1-^{2}H]piperidine E_a = 15.9 kcal mol^{-1}, ΔS^* = −52.6 eu.

deuterioamines. Isotope effects may decrease or disappear either as a consequence of changing relative specific rates in the two-step mechanism or because the symmetry of a concerted change has been more than offset.

Experimental Section

Materials. Melting points and boiling points are uncorrected. Microanalyses were performed by A. Bernhardt, Elbach über Engelskirchen (West Germany).

Piperidine (Erba-RP) for use in the kinetic measurements and product analyses was refluxed for 3 hr over sodium metal and then fractionated over potassium metal through a 42-plate Todd column under nitrogen (reflux ratio 1:25); bp 105.5°.

Piperidine-*1-d* was prepared by the method of Foster and Horman;[16] it was at least 97% deuterated (nmr spectroscopy). 2-Chloroquinoline, 4-quinolone, phenol, and *o*-nitro-, *m*-nitro-, and *p*-nitrophenol were commercial chemicals.

4-Chloroquinoline[17] (mp 28–29°), 2-methyl-4-nitrophenol[18] (mp 95.5–96.5°), 2-chloro-5-nitrotoluene[19] (mp 42.5–43.5°), 2-piperidinoquinoline[20] (mp 48–49.5°), 4-piperidinoquinoline[21] (mp 86–87°), carbostyryl[22] (mp 198–199°), *N*-(*o*-nitrophenyl)piperidine[23] (mp 80–81°), *N*-(*p*-nitrophenyl)piperidine[24] (mp 104.5–105.5°), 2-phenoxyquinoline[25] (mp 62–62.5°), and 4-phenoxyquinoline[26] [bp 170–171° (6 mm), picrate (mp 176–177°)] were prepared as described in the given references. Their purity was checked by tlc.

***N*-(2-Methyl-4-nitrophenyl)piperidine.** 2-Chloro-5-nitrotoluene[19] (0.8 g, 4.7 mmol) was refluxed with piperidine under a nitrogen atmosphere for 90 min. The excess piperidine was removed under reduced pressure, the oily residue treated with a little 6 *N* sulfuric acid, diluted with ice-cold water, neutralized with aqueous ammonia, and extracted with ether. From the extracts 0.6 g (57.5%) of an orange product was obtained, which, after recrystallization from *n*-hexane, melted at 39–40°.

Anal. Calcd for $C_{12}H_{16}N_2O_2$: C, 65.43; H, 7.32; N, 12.72. Found: C, 65.56; H, 7.04; N, 12.78.

2- and 4-Aryloxyquinolines. These compounds were prepared by methods A and B as described below and purified by recrystallization from ligroin (bp 80–100°) to constant melting point. Method of preparation, melting points, yields, and analytical data are collected in Table III.

Method A. A 0.05-mol sample of the dry sodium aryl oxide (prepared from the parent phenol and sodium ethoxide in ethanol) and the equivalent amount of the chloroquinoline in 60 ml of anhydrous dimethyl sulfoxide were heated for about 4 days at 140 ± 5°. At the end of the reaction (tlc test), the reaction mixture was poured into ice-water; the precipitate was collected, thoroughly washed with water, and dried. This procedure proved to be unsuitable for the preparation of 4-(*p*-nitrophenoxy)quinoline, 4-(2-methyl-4-nitrophenoxy)quinoline, and 4-(*o*-nitrophenoxy)quinoline.

Method B. The chloroquinoline and a slight excess of the required phenol were intimately mixed and heated in a closed vessel at 120° up to disappearance (tlc test) of the starting chloroquinoline (usually overnight). The reaction mixture was then ground twice with 20 ml of ligroin (bp 80–100°), once with 20 ml of ether, and finally dissolved in chloroform. After extraction of the excess phenol with aqueous sodium hydroxide (20%) and drying over anhydrous Na_2SO_4, the solvent was removed under reduced pressure. This method proved to be generally applicable.

Product Analyses. The reactions were carried out by refluxing a solution of a weighed amount (1–2 g) of the aryloxyquinoline in 30 ml of dry piperidine in a dry N_2 atmosphere to complete disappearance of the starting material (tlc test). The excess piperidine was removed under reduced pressure; the residue was treated first with a few milliliters of dilute sulfuric acid, then made alkaline with aqueous ammonia (32%), and extracted with ether. The aqueous layer was evaporated under reduced pressure, and the residue was freed from moisture by azeotropic distillation with benzene and, then, extracted in a Soxhlet apparatus with dry propanol. These extracts essentially consisted of the phenol and varying amounts of the quinolone. The separation of any quinolone from the phenol was effected by chromatography on silica gel. The residue from the ethereal layer was chromatographed on silica gel, a mixture of benzene and ethyl acetate (1:1) being the eluent. The amount of the recovered material, which was identified by comparison (tlc, mixture melting points, ir spectrum) with authentic specimens, quantitatively accounted for the starting aryloxyquinoline in all cases. The results are collected in Table I.

Table III
2- and 4-Aryloxyquinolines[a]

Quinoline	Prepn method	Yield, %[b]	Mp, °C
2-(*o*-Nitrophenoxy)	B	33.5	108–109
2-(*m*-Nitrophenoxy)	A, B	60	116–117
2-(*p*-Nitrophenoxy)	A	40	159–160
2-(2-Methyl-4-nitrophenoxy)	A, B	50	164–165
4-(*o*-Nitrophenoxy)	B	51.5	136–137
4-(*m*-Nitrophenoxy)	A, B	83	104–105
4-(*p*-Nitrophenoxy)	B	77	103–104
4-(2-Methyl-4-nitrophenoxy)	B	87	139–140

[a] Satisfactory analyses (C, H, N ±0.35%) were obtained for all the compounds listed: Ed. [b] After recrystallization to constant melting point.

Kinetic Measurements. The kinetic runs were performed by dispensing 2.00 ml of the reaction mixture (50 ml, initial concentration *ca.* 10^{-2} *M*) into ampoules, which were then sealed and immersed all at once in the constant temperature bath. In the case of the reaction with piperidine-*1-d*, the ampoules were filled and sealed under dry nitrogen. At suitable time intervals the tubes were chilled and, on transferring the contents into a 250-ml volumetric flask, were rinsed with water–dioxane (2:1, v/v). The reaction rates were followed by measuring the increase in absorbance (Beckman *DU spectrophotometer*) due to the following species (wavelengths in parentheses): 2-piperidinoquinoline (354 nm) for the reactions of 2-phenoxy- and 2-(*m*-nitrophenoxy)quinoline; 2-methyl-4-nitrophenoxide ion (421 nm) for the reactions of 2- and 4-(2-methyl-4-nitrophenoxy)quinoline) 4-piperidinoquinoline (340 nm) for the reaction of 4-phenoxyquinoline. Owing to some overlap of the absorption bands of the reactants and products in the case of the piperidinolysis reaction of 4-(*m*-nitrophenoxy)quinoline, the concentration of the 4-piperidinoquinoline had to be measured by an indirect method.[27] The increase in absorbance due to the 4-piperidinoquinoline and to the *m*-nitrophenol was recorded at two different wavelengths, 350 and 360 nm. From the system of equations

$$A_{350} = c_1\epsilon'_{350} + c_2\epsilon''_{350}$$
$$A_{360} = c_1\epsilon'_{360} + c_2\epsilon''_{360}$$

the following expression

$$c_2 = \epsilon'_{360}A_{350} - \epsilon'_{350}A_{360}/\epsilon'_{360}\epsilon''_{350} - \epsilon'_{350}\epsilon''_{360}$$

is obtained, where c_1 = concentration of *m*-nitrophenol; c_2 = concentration of 4-piperidinoquinoline; ϵ'_{350} = 830, molar extinction coefficient for *m*-nitrophenol at 350 nm; ϵ'_{360} = 100, molar extinction coefficient for *m*-nitrophenol at 360 nm; ϵ''_{350} = 2800, molar extinction coefficient for 4-piperidinoquinoline at 350 nm; ϵ''_{360} = 750, molar extinction coefficient for 4-piperidinoquinoline at 360 nm.

All runs afforded linear plots of log $(A_\infty - A_t)$ *vs.* time, whose slope was calculated by the least-squares method in order to evaluate the *k*'s as usual. The infinity absorbances were in reasonable agreement (±5%) with those expected for a quantitative conversion into products. When the kinetics were complicated by dearylation, as with 4-(2-methyl-4-nitrophenoxy)quinoline, the reaction was stopped before the side reaction became evident (25–30%), and the rate constants were determined graphically from concentration *vs.* time plots by the initial rate method described by Livingston.[28] The estimated uncertainty is ±5%. The rate constants (10^6k, sec^{-1}) at diverse temperatures (given in parentheses as °C) are reported below in addition to those presented in Table II. 2-Phenoxyquinoline: 0.325 (109.1), 1.33 (130.6), 2.31 (140.1), 3.19 (150.3). 4-Phenoxyquinoline: 0.101 (120.3), 0.214 (131.8), 0.290 (140.1), 0.490 (151.6). 2-(*m*-Nitrophenoxy)quinoline; 9.90 (109.2), 16.2 (120.4), 26.8 (130.8), 35.5 (140.0). 4-(*m*-Nitrophenoxy)quinoline: 1.55 (109.0), 2.18 (120.1), 2.94 (130.0), 4.19 (140.0). 2-(2-Methyl-4-nitrophenoxy)quinoline: 7.93 (109.2), 12.5 (120.4), 20.0 (130.6), 30.9 (140.1). 4-(2-Methyl-4-nitrophenoxy)quinoline: 0.482 (109.1), 0.778 (120.3), 1.07 (130.0), 1.52 (140.1). 4-Phenoxyquinoline + [1-^{2}H]piperidine: 0.128 (122.6), 0.181 (130.0), 0.435 (150.6), 0.702 (160.0).

The Arrhenius activation energies, E_a, were calculated by the least-squares method and the activation entropies, ΔS^*, from the

appropriate equation.[29] The values of ΔS^*, as reported in Table II, were averaged from those obtained by this equation at all the temperatures used for each substrate. The probable errors in the rate constants lie between 2 and 5%, the probable errors in E_{act} between 0.5 and 1.2 kcal, and the probable errors in ΔS^* between 1.5 and 3 eu.

Registry No.—*N*-(2-methyl-4-nitrophenyl)piperidine, 51248-16-9; 2-chloro-5-nitrotoluene, 13290-74-9; piperidine, 110-89-4.

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Nucleic Acid Related Compounds. 12. The Facile and High-Yield Stannous Chloride Catalyzed Monomethylation of the Cis-Glycol System of Nucleosides by Diazomethane[1]

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Stannous chloride has been found to catalyze monomethylation of the cis-glycol system of nucleosides by diazomethane. With compounds having no acidic proton on the base, such as adenosine and cytidine, quantitative monomethylation occurs rapidly. Purine nucleosides gave a mixture of 2′-*O*-methyl and 3′-*O*-methyl isomers with the 3′ product in somewhat greater proportion. Pyrimidine nucleosides gave a mixture in which the 2′-*O*-methyl isomer predominates significantly. It has been found that even nucleosides which contain an acidic proton on the base can be monomethylated on the sugar by raising the concentration of catalyst and slowly adding a dilute solution of diazomethane. The 2′-*O*- and 3′-*O*-methyl ethers of adenosine, 6-chloropurine riboside, tubercidin, formycin, guanosine, cytidine, 4-methoxy-1-β-D-ribofuranosyl-2-pyrimidinone, uridine, and pseudouridine have been directly prepared in this manner. Thus, 2′-*O*-methyl nucleosides isolated from ribonucleic acids (as well as their 3′-*O*-methyl isomers) are now readily available by this route. Mass spectroscopy is shown to be a convenient and useful tool for the investigation of the isomeric structures.

Although 2′-*O*-methyl ethers of the "major" nucleosides are ubiquitous "minor components" of various ribonucleic acids,[3] routes to their syntheses have often been rather laborious. Several indirect approaches have been employed involving multistep procedures, especially for compounds containing an acidic hydrogen on the heterocyclic base. No generally applicable direct route has been available previously.

Ribonucleic acids (RNA's) containing 2′-*O*-methylnucleosides give rise to di- (and higher) nucleotide fragments containing these molecules upon digestion with sodium hydroxide,[4] since intermediate 2′,3′,5′-*O*-phospho triester formation necessary for cleavage to 2′(3′)-mononucleotides is blocked by the 2′-methyl ether function. Certain 2′-*O*-methyl-5′-nucleotides formed upon venom diesterase hydrolysis of RNA's were reported to be resistant to snake venom 5′-nucleotidase.[4,5] Hydrolase and phosphorylase enzymes which catalyze cleavage of the sugar–base linkage of nucleosides were found to have no effect on 2′-*O*-methyluridine[5] or the synthetic 3′-*O*-methyluridine.[6] Various 2′-*O*-methyl polynucleotide systems have been prepared and studied[7] in order to evaluate effects of the 2′-hydroxyl group in "normal" polynucleotides, effects on helix complementarity, hydrophobic contributions, etc. The possibility of employing these altered enzymatic and chemical properties in the design of nucleoside "drugs" with enhanced or protected (against catabolism and degradation) biological properties has been discussed.[8-12]

Broom and Robins[13] first exploited diazomethane for the selective sugar methylation of nucleosides by treating a hot aqueous solution of adenosine with diazomethane in glyme (1,2-dimethoxyethane). They reported isolation of 2′-*O*-methyladenosine in some 40% yield. Gin and Dekker[14] reported similar results but also isolated 3′-*O*-methyladenosine in 11% yield plus other minor methylated products. Reese and coworkers[15] reported analogous re-