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Direct Acylamination of Pyridine 1-Oxides[1a]

R. A. Abramovitch* and G. M. Singer

Departments of Chemistry, University of Alabama, University, Alabama 35486, and University of Saskatchewan, Saskatoon, Saskatchewan, Canada

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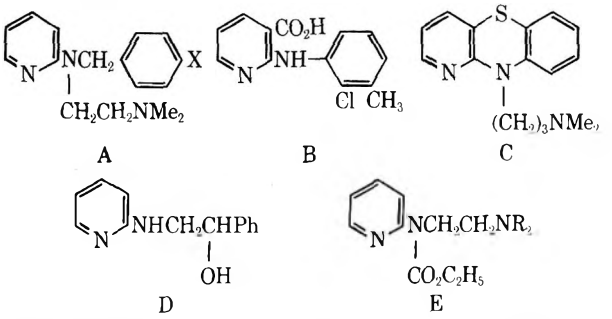
Treatment of a pyridine 1-oxide with an imidoyl chloride results in the introduction of a tertiary amide function into the α position of the pyridine ring with concomitant deoxygenation of the *N*-oxide. A nitrilium salt may be used instead of the imidoyl chloride. The scope and limitations of the reaction are discussed in terms of the structural requirements in the imidoyl chloride and nitrilium salt. Some less reactive compounds which are structurally related to imidoyl chlorides did not give the desired substitution products. The main features of the mechanism of this reaction have been elucidated, and involve initial nucleophilic attack by the *N*-oxide on the imidoyl chloride or nitrilium salt, followed by intramolecular nucleophilic addition of the nitrogen atom of the imidoyl chloride or nitrilium salt to the α position of the pyridine 1-oxide and aromatization. Other possible mechanisms have been discounted. The formation of 3-chloropyridines and other products is discussed and explained.

2-Aminopyridine derivatives are of great importance in medicinal chemistry. For example, the tertiary amines tripellenamine (A, X = H) and pyrilamine (A, X = OMe) are antihistamines, B has antiinflammatory properties, prothypendil (C) is a sedative and a tranquilizer, pheniramidol (D) is an analgesic and muscle relaxant, and E is said to be a powerful analgesic.



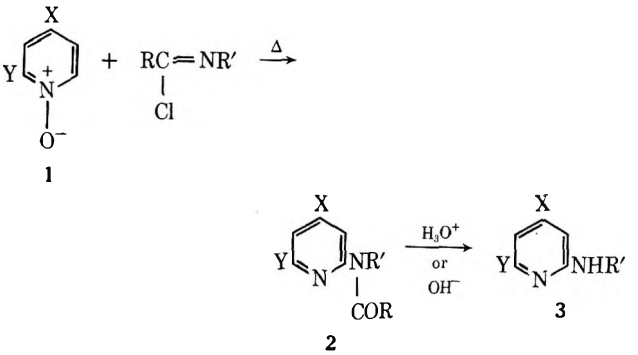
While primary 2-aminopyridines are usually readily available from the parent pyridine by the Tschitschibabin reaction, substituted amines are less readily available. Vajda and Kovacs[1b] extended the Tschitschibabin reaction to permit the use of alkylamines, but yields were generally low and the reaction failed for benzylamine and arylamines. Better yields of 2-alkylaminopyridines were reported when a pyridine was heated with a three- to fourfold excess of a primary aliphatic amine in the presence of finely divided sodium metal.[2] Secondary amines may also be prepared from aminopyridine and alkyl halides or from halopyridines and a primary amine.[3] Tertiary amines are usually available from either the secondary amine, or the halopyridine and a secondary amine.[3] The disadvantage of these methods is the relative difficulty of obtaining readily the appropriately substituted halopyridine precursor.

We have sought a method which would make available substituted secondary and tertiary aminopyridines from the parent pyridine, and would thus complement the Tschitschibabin reaction. We now report such a convenient reaction which starts with the appropriate five- or six-membered heteroaromatic *N*-oxide and an imidoyl chloride or the corresponding nitrilium salt.

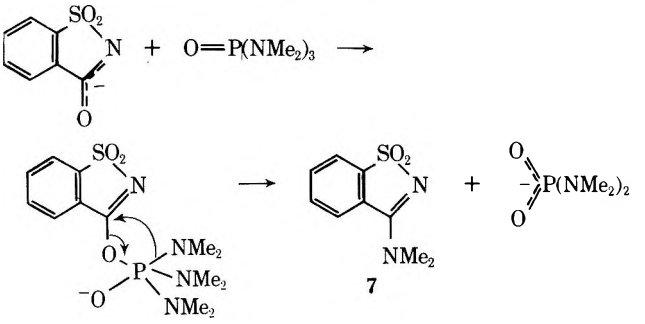
Initially the desired nitrilium salt was generated *in situ* by the thermal decomposition of aryldiazonium salts in nitrile solvents.[4] Thus, when benzenediazonium tetrafluoroborate was decomposed in acetonitrile containing pyridine 1-oxide and the reaction mixture saponified, 2-anilinopyridine was obtained in low yield. If the saponification step was omitted, 2-*N*-acetylanilinopyridine could be isolated, together with 2-anilinopyridine and acetanilide.

It was found to be much more convenient, and to lead to a considerable improvement in the yields of products, to use preformed nitrilium salts, or their precursors, the N-substituted imidoyl chlorides. Thus, when pyridine 1-oxide was boiled under reflux with a solution of *N*-phenylbenzimidoyl chloride in ethylene chloride, 2-*N*-benzoylanilinopyridine was obtained in respectable yield, together with some benzanilide. Hydrolysis of the reaction mixture without prior isolation of the amide gave 2-anilinopyridine directly.

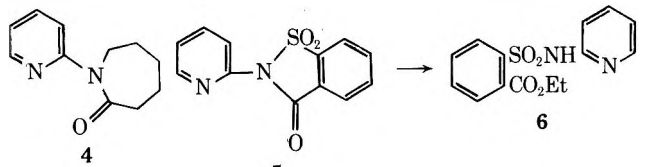
The reaction appears to be quite general, the only pyridine 1-oxide having failed to react to date being 4-nitropyridine 1-oxide (**1**, X = NO_2). In this paper, we report the



Scheme I



reactions with **1** (X = H or CH_3; Y = H). R and R′ can also vary widely, both alkyl and aryl groups giving the desired tertiary amide **2**. In the cases where R′ is an aryl group bearing an electron-withdrawing substituent, *e.g.*, *p*-NO_2, the reaction in boiling ethylene chloride becomes much more sluggish, and either a higher boiling solvent, for example chlorobenzene, was used or the more reactive preformed nitrilium salt was added to the *N*-oxide. R and R′ could be part of a ring, as illustrated by the synthesis of *N*-2-pyridylcaprolactam (**4**) from caprolactam pseudochloride. Also of great interest is the synthesis of *N*-2-pyridylsaccharin (**5**) by this route from saccharin pseudo-

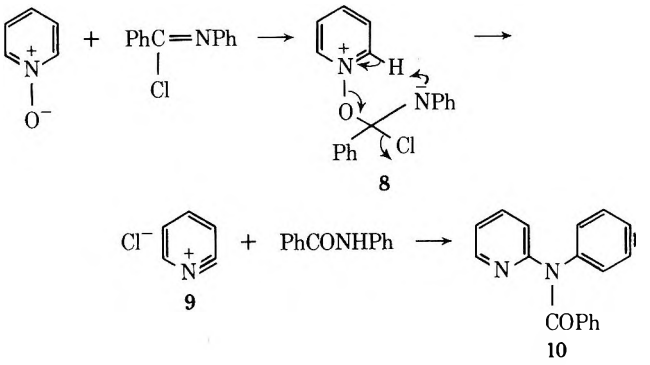


chloride. This amide could not be obtained from sodium saccharinate and 2-bromopyridine. When this latter reaction was attempted in hexamethylphosphoramide the only product formed was 3-dimethylaminobenzoisothiazole 1,1-dioxide (**7**). A plausible pathway to **7** is as shown in Scheme I. A very low yield of authentic **5** (0.65%) was obtained from 2-fluoropyridine and sodium saccharinate. When **5** was heated in ethanol it was slowly converted to *N*-2-pyridyl-*o*-carbethoxybenzenesulfonamide.

In sharp contrast, only *N*-benzoylbenzenesulfonamide was obtained from the open-chain analog of saccharin pseudochloride, *N*-benzenesulfonylbenzimidoyl chloride, and none of the desired 2-*N*-benzoylbenzenesulfonamidopyridine[5] or 2-benzenesulfonamidopyridine[6] were detected. No substitution product was formed from this imidoyl chloride and 4-ethoxypyridine 1-oxide either.

An attempt to use an imidate ester instead of the imidoyl chloride failed in the one case studied: when *O*-methyl-ε-caprolactim was heated with pyridine 1-oxide even in boiling chlorobenzene, most of it was recovered unchanged, and no **4** was detected. The nmr spectrum of **4** deserves some comment. In all of the aminopyridines prepared in this study and in 2-*N*-benzoylanilino-4-methylpyridine (**2**, X = Me; Y = H; R = R′ = Ph) and 2-*N*-benzoylcyclohexylaminopyridine (**2**, X = Y = H; R = Ph; R′ = C_6H_{11}) the chemical shift of H_3 is in the range δ 6.26–6.87, the higher field resonances corresponding to R′ = alkyl. On the other hand, H_3 in **4** resonates at δ 7.63, which is appreciably lower than in the other examples. One possible explanation of this is that in **4** the amide carbonyl may get close enough to C_3 H to deshield it, whereas in the *N*-benzoyl derivatives steric interactions between the aromatic nuclei cause twisting of the molecule so that the carbonyl group is away from C_3 H. Other examples of unhindered amide carbonyl groups at C_2 deshielding a pyridine β proton are known.[7] Thus, C_3 H in

Scheme II

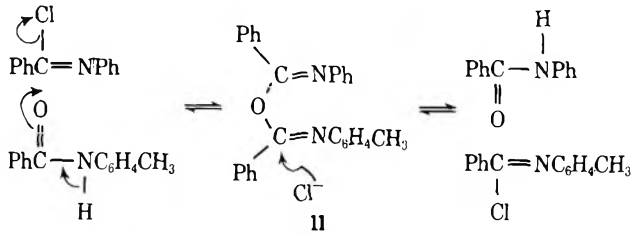


2-acetamidopyridine resonates 1.52 ppm lower than does the corresponding proton in 2-*N*-piperidinopyridine.

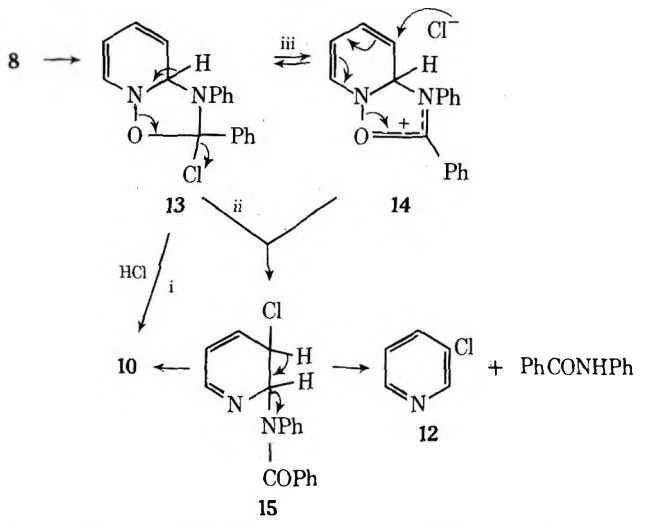
A perplexing question was the origin of the benzanilide which was obtained in all of the reactions involving *N*-phenylbenzimidoyl chloride, even when scrupulously dried reagents and solvents were used in a drybox. That this did not arise from the hydrolysis of the imidoyl chloride during the reaction was shown by the fact that the chloride was recovered when the reaction conditions were duplicated but pyridine 1-oxide was omitted. Since pyridine 1-oxides and pyridinium salts are known to undergo ready base-catalyzed proton abstraction from the α positions,[8] the initial assumption was made that intermediate **8**, resulting from the *N*-oxide attack upon the imidoyl halide, underwent intramolecular proton abstraction with the elimination of benzanilide and the formation of a 1,2-pyridynium ion (**9**). The latter might then add benzanilide to give the observed product (**10**) or the two fragments could diffuse apart, thus leading to the isolation of benzanilide (Scheme II). If this were so, it should be possible to add a different, and possibly more nucleophilic, amide to **9** and thus obtain a crossover product. Indeed, when *N*-benzoyl-*p*-toluidine was added to a mixture of pyridine 1-oxide and *N*-phenylbenzimidoyl chloride and the reaction was repeated, a mixture was obtained containing 2-*N*-benzoyl-*p*-toluidinopyridine and 2-*N*-benzoylanilinopyridine in an approximate 1:1 ratio. It thus appeared as though **9** had indeed been formed and trapped. When, however, **9** was generated from 1*H*-1,2,3,5-thiatriazole[5,4-*a*]pyridine 3-oxide[9] in the presence of benzanilide or *N*-benzoyl-*p*-toluidine, no 2-*N*-benzoylanilinopyridine derivative was obtained (reaction carried out by Dr. E. M. Smith). When *N*-benzoyl-*p*-toluidine and *N*-phenylbenzimidoyl chloride were heated together, the infrared spectrum of the product was identical with that obtained from benzanilide and *N*-*p*-tolybenzimidoyl chloride under the same conditions. The mass spectrum of the reaction mixture indicated the presence of both amides and both imidoyl chlorides in these reaction mixtures. Thus, the equilibria illustrated in Scheme III, involving the as yet unknown imidoyl anhydride **11**, appear to be set up under these reaction conditions, so that the formation of the two acylaminated pyridines from each of the individual imidoyl chlorides—or from the mixed imidoyl anhydride—would account nicely for the observations without the necessity of invoking the formation of **9**. The latter, in any case, does not give the observed product, as shown above.

This leaves the formation of benzanilide in substantial amounts still unexplained. The acylamination of pyridine 1-oxide by *N*-phenylbenzimidoyl chloride in ethylene chloride was therefore repeated and the reaction mixture was analyzed by gas chromatography without any work-up other than filtration of the pyridine 1-oxide hydrochloride formed. A 57% yield of **10** was thus obtained, together

Scheme III

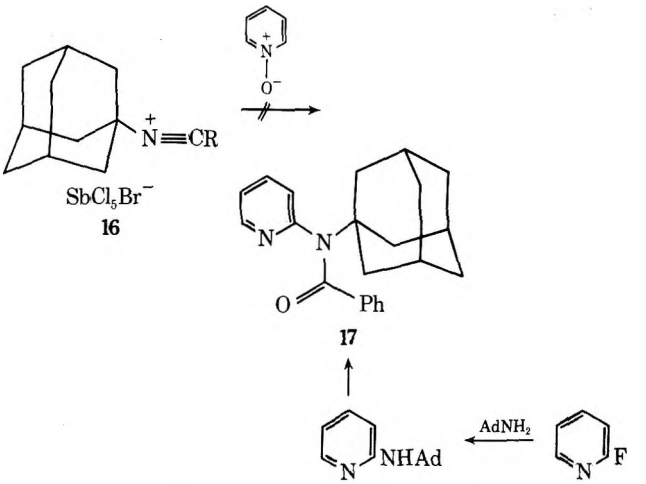


Scheme IV

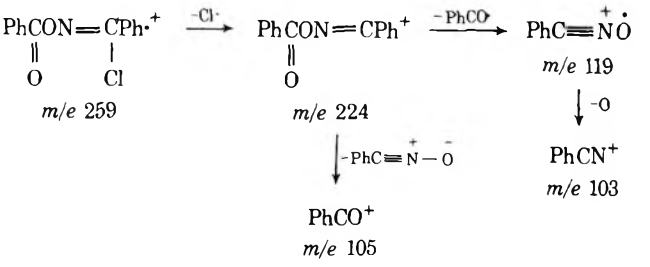


with benzanilide (36.8%) and 3-chloropyridine (**12**, 28%). Small amounts of two products, tentatively identified as 2-anilinopyridine (3.1%) and 3-benzoyloxypyridine (1.2%) on the basis of their relative retention times only, were also observed. We shall discuss the significance of these last two in a forthcoming publication. The observation that 3-chloropyridine is formed in appreciable amounts in this reaction allows us to suggest a mechanism which would account for the formation of the three major products observed (Scheme IV). The dihydro intermediate **13** (in one conformation of which the chlorine atom lies below the pyridine β position) can undergo (i) aromatization with elimination of HCl and the formation of the acylaminated product, and either (ii) intramolecular attack at C_3 or C_5 by the chlorine atom to give the 2,3-dihydropyridine derivative **15**, or (iii) ionization to give the delocalized carbonium ion **14** which undergoes intermolecular attack by Cl^- at C_3 or C_5 to give **15**. The latter can now eliminate HCl to give **10**, or eliminate benzanilide to yield 3-chloropyridine. The alternative extreme pathways ii and iii above may actually be merged so that the transition state involves appreciable stretching of the C–Cl bond, but the free carbonium ion **14** is not necessarily completely formed. The carbonium ion **14** appears, however, to be a necessary intermediate in the reaction of pyridine 1-oxides with nitrilium salts. That C–Cl bond breakage is important in the rate-determining step is shown by the fact that the addition of external chloride ion to the reaction mixture slows the reaction down considerably (likely owing to a common ion effect) and little 3-chloropyridine is formed.[10] Nucleophilic addition to a 1,2-dihydropyridine with concurrent departure of the group at nitrogen and the formation of a 2,3-dihydropyridine has already been postulated[11] to explain the formation of 2,5-diphenylpyridine from pyridine and phenylcalcium iodide,[12] and of a 3,5-disubstituted pyridine from 3-picoline and o-tolyllithium.[13] The formation of 3-tosyloxypyridine from pyridine 1-oxide and tosyl chloride[14] involves a similar intramolecular attack at the β position of a 1,2-dihydropyridine.[15]

The only nitrilium salts which failed to give the desired 2-acylaminopyridine were *N*-1-adamantylacetonitrilium bromopentachloroantimonate (**16a**) and *N*-1-adamantylbenzonitrilium bromopentachloroantimonate (**16b**). The latter, for example, on heating with pyridine 1-oxide gave none of the desired amide **17** (which was obtained from 2-fluoropyridine and 1-adamantanamine followed by benzoylation). The only products isolated were *N*-benzoyl-1-adamantanamine, benzonitrile, and the 1-adamantyl halides (the last two by thermal cleavage of the nitrilium salt).

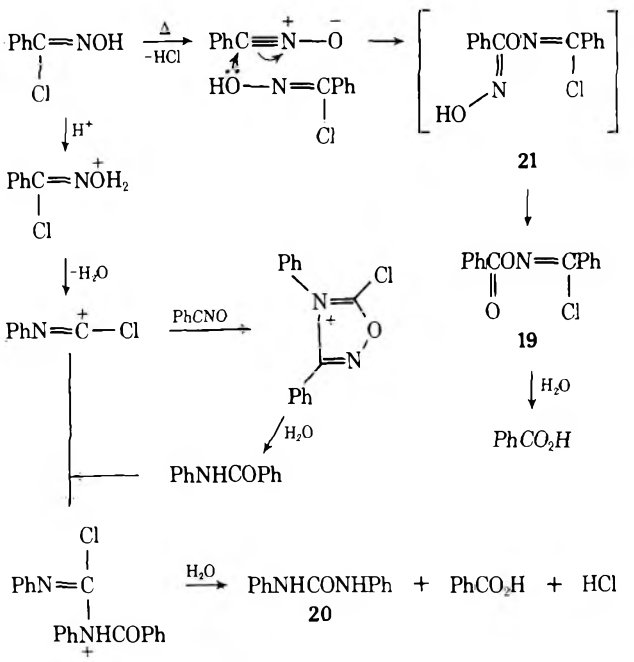


It was hoped that the acylamination reaction could be extended to the α-chloroaldoximes, which would have been expected to yield 2-pyridylhydroxylamine derivatives. Reaction of pyridine 1-oxide with α-chlorobenzaldoxime gave none of the desired *N*-2-pyridylhydroxamic acid (**18**). Instead, the *N*-oxide appeared to function as a weak base in this reaction and most of the products appear to be derived from benzonitrile oxide (α-chlorobenzaldoxime eliminates HCl in boiling chlorobenzene[16]). The major product (30%) was identified (literature melting point, nmr, ir, mass spectrum) as *N*-benzoyloxybenzimidoyl chloride (**19**).[17a] Benzanilide (11.4%) carbanilide (*N,N'*-diphenylurea, **20**, 7.6%), and benzoic acid (7%) were also isolated. The nmr spectrum of **19** consisted of two complex multiplets at δ 8.25–8.00 and 8.67–8.35 in the area ratio of 4:6 (ortho protons:meta and para protons). The mass spectrum exhibited a weak molecular ion [M^+ (^{35}Cl) at *m/e* 259] which lost Cl· to give a peak at *m/e* 224. The base peak was at *m/e* 105 ($PhCO^+$). A peak at *m/e* 103 may be attributed to $PhCN^{\cdot+}$. Carbanilide gave



the expected nmr and mass spectra and was identical with an authentic sample. Possible routes to these products are illustrated in Scheme V. Conversion of **21** to **19** probably occurs on chromatographic work-up, as does the hydrolysis of **19** to benzoic acid. The formation of benzanilide requires a Beckmann rearrangement, perhaps of the protonated oxime, and a speculative route to it and to

Scheme V

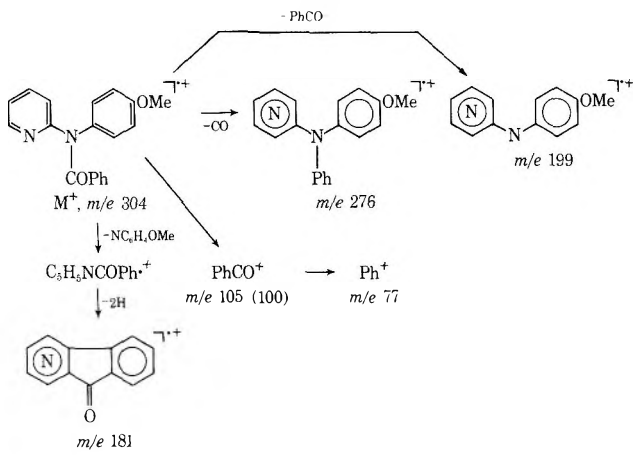


carbanilide is sketched. It is not clear at present why, if a nitrilium ion is formed as an intermediate, it would not react with pyridine 1-oxide. Blocking the hydroxyl function in the original oxime should prevent this degradation and perhaps cause the desired acylamination to occur. This is under investigation.

Mass Spectra of the 2-Acylaminated Pyridines. These were similar to that of *N*-benzoyldiphenylamine and the behavior of 2-(*N*-benzoyl-*p*-methoxyanilino)pyridine (Scheme VI) is typical. In all cases, the base peak is $PhCO^+$ while the second most prominent one is due to $C_6H_5^+$. All the other processes are minor. While loss of benzoyl from *N*-benzoyldiphenylamine is not detectable, formation of fluorenone (or its equivalent) by loss of the equivalent of aniline is (*m/e* 180). The latter process could involve a Fries-type rearrangement to give an anilinobenzophenone ion (precedent for such a rearrangement *in solution* exists[17b]) *followed by loss of an arylnitrene* fragment and cyclization.

When R′ in 2 is alkyl, the base peak is no longer at *m/e* 105. For example, when R = $PhCH_2$, the base peak is at *m/e* 43. When R′ = 1-adamantyl, the base peak is the adamantyl cation (*m/e* 135), and $PhCO^+$ and Ph^+ give rise to very intense fragments. In *N*-2-pyridylcaprolactam the base peak is the pyridinium radical cation (*m/e* 79). The mass spectrum of *N*-2-pyridylsaccharin is characterized

Scheme VI



by consecutive losses of SO_2 and CO. The base peak is at *m/e* 43. A similar fragmentation occurs in 2-substituted benzimidazoles.[18] More detailed discussion of these mass spectra does not seem warranted in the absence of high-resolution, isotopic-labeling, and metastable-peak data.

Experimental Section

Reagents and Solvents. These were, in general, of reagent grade and were used without further purification. Solvents for reactions requiring anhydrous conditions were dried and distilled prior to use. Halocarbons were dried with phosphorus pentoxide, ethers and hydrocarbons with sodium wire, and pyridines with potassium hydroxide pellets. Amine oxides were completely dehydrated by azeotroping with benzene followed by distillation, and were kept under anhydrous conditions. They were distilled in the drybox again just before use.

Drybox experiments were carried out under a nitrogen atmosphere maintained at positive pressure and with phosphorus pentoxide as desiccant.

Thin layer chromatography was carried out on silica gel (Camag Kieselgel DS-5) and column chromatography on Baker silica gel powder (60–200 mesh).

Nmr spectra were recorded on a Varian HA-100 spectrometer and infrared spectra on a Perkin-Elmer 337 or 257 spectrometer. Melting points are uncorrected.

Benzenediazonium tetrafluoroborate, *p*-chlorobenzenediazonium tetrafluoroborate, and *p*-nitrobenzenediazonium tetrafluoroborate were prepared according to the procedure of Roe.[19]

N-Phenylbenzimidoyl chloride was prepared from benzanilide by boiling under reflux for 90 min with phosphorus pentachloride (1 molar equiv) or, preferably, with thionyl chloride (1.1 molar equiv). The mixture was distilled to give *N*-phenylbenzimidoyl chloride (*ca.* 90% yield), bp 100° (0.05 mm) [lit.[4] bp 174–176° (12 mm)], mp 34–35° (lit.[4] mp 40°).

N-*p*-Tolylbenzimidoyl chloride, bp 104° (0.005 mm) [lit.[20] bp 106–109° (0.02 mm)], *N*-*p*-anisylbenzimidoyl chloride, bp 154–160° (0.53 mm) [lit.[20] bp 198–200° (20 mm)], *N*-*p*-chlorophenylbenzimidoyl chloride, bp 123° (0.01 mm) (lit.[21] mp 63–65°), and *N*-*p*-nitrophenylbenzimidoyl chloride, mp 110–111° (lit.[20] mp 114–116°), were prepared similarly.

N-Benzylbenzimidoyl chloride was prepared from *N*-benzoylbenzylamine (4.22 g, 0.92 mol) and phosphorus pentachloride (4.16 g, 0.02 mol). These were boiled under reflux until hydrogen chloride evolution ceased. The mixture was immediately distilled *in vacuo* to remove phosphorus oxychloride and any benzonitrile and benzyl chloride which had formed from the decomposition of the imidoyl chloride. The clear, yellow residue (3.33 g, 70%) of *N*-benzylbenzimidoyl chloride was used immediately without further purification.

N-Cyclohexylbenzimidoyl chloride was prepared from *N*-benzoylcyclohexylamine and thionyl chloride and had bp 84–86° (0.07 mm) [lit.[20] bp 110–112° (1 mm)]. Saccharin pseudochloride had mp 138–140° (lit.[22a] mp 143°). *N*-Phenylbenzonitrilium hexachloroantimonate was obtained from freshly prepared and distilled *N*-phenylbenzimidoyl chloride and antimony pentachloride in anhydrous ethylene chloride (drybox).[22b]

Amidation of Pyridine 1-Oxide. 2-Anilinopyridine and 2-*N*-Benzoylanilinopyridine. A. From Benzenediazonium Tetrafluoroborate. 1. A solution of benzenediazonium tetrafluoroborate (3.84 g, 0.02 mol) and pyridine 1-oxide (1.90 g, 0.02 mol) in dry (P_2O_5) acetonitrile (15 ml) was stirred at 50–60° for 1 hr. The acetonitrile was distilled *in vacuo* and the residue was boiled under reflux with 5% aqueous sodium hydroxide (50 ml) for 0.5 hr. The basic solution was steam distilled to give 2-anilinopyridine (0.63 g, 18.6%), mp 104–106° (lit.[23] mp 108°), identical with an authentic sample.

2 (Experiment Carried Out by Mr. F. F. Gadallah). A solution of benzenediazonium tetrafluoroborate (2.4 g) in acetonitrile (12 ml) containing pyridine 1-oxide (0.95 g) was heated for 8 hr at 65°. The excess acetonitrile was evaporated and the residue was chromatographed on a column of alumina (14 × 0.25 in.). Elution with benzene–ethanol (85:15 v/v) gave a fraction which, on glc on a column (4 ft × 0.25 in.) of 20% ethylene glycol adipate on Chromosorb W at 170°, gave six small peaks, the fourth one corresponding to 2-phenylpyridine. A subsequent fraction gave rise to three peaks on glc. These were collected and characterized. The first corresponded to acetanilide, mp 113–114°, the second to 2-anilinopyridine, mp 109–110°. The third component had bp 136° (0.6 mm), ir (KBr) 1670 cm^{-1} (s), and was identical with an au-

thentic sample of **2-*N*-acetylanilinopyridine** (prepared in 85% yield from 2-anilinopyridine, acetic anhydride, and 2 drops of perchloric acid).

Anal. Calcd for $C_{13}H_{12}N_2O$: C, 73.58; H, 5.66; N, 13.21. Found: C, 73.47; H, 5.78; N, 13.47.

Quantitative analysis (on duplicate runs) was effected by glc using a 3.5 ft × 0.25 in. column packed with 20% ethylene glycol adipate on Gas-Chrom P at 170° with a helium flow rate of 90 ml/min and using 2-o-bromophenylpyridine as the internal standard. The yields thus obtained follow: acetanilide, 20.7 ± 0.1%; 2-anilinopyridine, 7.7 ± 0.2%; and 2-*N*-acetylanilinopyridine, 5.7 ± 0.1%.

B. From *N*-Phenylbenzimidoyl Chloride. In a drybox, a solution of *N*-phenylbenzimidoyl chloride (2.45 g, 0.0114 mol) and pyridine 1-oxide (2.17 g, 0.0228 mol) in ethylene chloride (25 ml) was boiled under reflux for 10 hr. After cooling to room temperature, the reaction mixture was filtered to remove pyridine 1-oxide hydrochloride (1.10 g, 42%), mp 179.5–182° (lit.[24] mp 180°). One-half of the filtrate was evaporated and boiled under reflux for 0.5 hr with 5% aqueous sodium hydroxide. Steam distillation of the basic solution provided 2-anilinopyridine (0.44 g, 47%), mp 105–107° (lit.[23] mp 108°), identical with an authentic sample. Benzanilide (0.51 g, 45%), mp 162–163° (lit.[25] mp 163°), crystallized from the distillation residue.

The other half of the original filtrate was also evaporated. The residue was fractionally crystallized from ethanol to afford **2-*N*-benzoylanilinopyridine** (0.73 g, 47%): mp 163–167°; ir (KBr) identical with that of an authentic sample prepared from 2-anilinopyridine and benzoyl chloride in benzene; ir (KBr) 1660 cm^{-1}; nmr ($CDCl_3$) δ 8.30 (d of d, 1 H, $J_{5,6}$ = 5, $J_{4,6}$ = 1 Hz, H_6), 7.55–6.80 (m, 13 H, aromatic H); mass spectrum (70 eV) *m/e* (rel intensity) 274 (8, M^+), 246 (15), 245 (10), 106 (13), 105 (100), 78 (11), 77 (96).

Recrystallization from ethanol gave the analytical sample, mp 167–169°.

Anal. Calcd for $C_{18}H_{14}N_2O$: C, 78.81; H, 5.14; N, 10.21. Found: C, 78.92; H, 5.26; N, 10.43.

Benzanilide (0.43 g, 40%) was also obtained from the fractional crystallization and was identified by its infrared spectrum.

C. From *N*-Phenylbenzonitrilium Hexachloroantimonate. *N*-Phenylbenzonitrilium hexachloroantimonate (3.90 g, 0.0076 mol) was suspended in ethylene chloride (40 ml) (drybox). A solution of pyridine 1-oxide (1.44 g, 0.0152 mol) in ethylene chloride (20 ml) was added dropwise over a period of 5 min. All of the suspended nitrilium salt dissolved as the *N*-oxide was added. The reaction mixture was stirred at room temperature for 10 hr. The reaction mixture was concentrated and chromatographed on a column of silica gel (100 g). Elution with chloroform gave first benzanilide and then 2-*N*-benzoylanilinopyridine (0.39 g, 34%), identical with an authentic sample (melting point, ir).

Detailed Study of the Reaction of Pyridine 1-Oxide with *N*-Phenylbenzimidoyl Chloride. The reaction of pyridine 1-oxide with *N*-phenylbenzimidoyl chloride was carried out as described in B above. After removal of the pyridine 1-oxide hydrochloride, the reaction mixture was analyzed by glc [20% SE-30 on Chromosorb W (60–80 mesh), 6 ft × 3/16 in., He carrier gas, flow rate 60 ml/min, column temperature 100°]. 3-Chloropyridine was identified by its retention time (4.73 min) and, after collection, by its infrared and nmr spectra. The column temperature was raised to 250°. Four more compounds were detected. Benzanilide (6.80 min) and 2-*N*-benzoylanilinopyridine (17.77 min) were identified on the basis of respective retention times, melting points, and infrared and nmr spectra. The other two components, present in very low concentrations, had retention times identical with those of 2-anilinopyridine (3.15 min) and 3-benzoyloxypyridine (3.55 min).

In a separate experiment, weighed amounts of 2-bromopyridine and *N*-benzoyl-*p*-toluidine were added to serve a internal standards. Relative molar response factors of two minor components were assumed to be equal to 1.0 (The error introduced by this assumption is less than the experimental error.) Glc conditions were the same as given above. The yields were as follows: 3-chloropyridine, 28.1%; 2-*N*-benzoylanilinopyridine, 57.2%; benzanilide, 36.8%; 2-anilinopyridine, 3.1%; and 3-benzoyloxypyridine, 1.2%. The last two were only tentatively identified.

2-*N*-Benzoyl-*p*-toluidinopyridine. A. From *N*-*p*-Tolylbenzimidoyl Chloride. *N*-*p*-Tolylbenzimidoyl chloride (1.70 g, 0.00742 mol) and pyridine 1-oxide (1.41 g, 0.0144 mol) were dissolved in ethylene chloride (25 ml). The solution was boiled under reflux for 10 hr. After cooling to room temperature, the solution was filtered to remove pyridine 1-oxide hydrochloride (0.65 g, 68%). The filtrate was concentrated and chromatographed on silica gel (100 g). Elution with chloroform produced *N*-benzoyl-*p*- toluidide (0.66 g, 42%), mp 157–159° (lit.[25] *mp 158°*), identical with an authentic sample. Further elution gave **2-*N*-benzoyl-*p*-toluidinopyridine** (1.23 g, 57%), mp 149–151°, identical with an authentic sample (melting point, ir).

Anal. Calcd. for $C_{19}H_{16}N_2O$: C, 79.14; H, 5.59. Found: C, 79.45; H, 5.95.

B. Authentic 2-*N*-Benzoyl-*p*-toluidinopyridine. 2-*p*-Toluidinopyridine (0.46 g, 0.0025 mol) was treated with benzoyl chloride (0.7 g, 0.005 mol) in boiling benzene to give 2-*N*-benzoyl-*p*-toluidinopyridine (0.33 g, 46%): mp 148–151.5°; ir (KBr) 2990 (aromatic CH_3) and 1660 cm^{-1} (amide C=O); nmr ($CDCl_3$) δ 8.30 (d of d of d, 1 H, $J_{5,6}$ = 4.8, $J_{4,6}$ = 1.8, $J_{3,6}$ = 0.8 Hz, H_6), 7.7–6.9 (m, 12 H, aromatic H), 2.27 (s, 3 H, CH_3); mass spectrum (70 eV) *m/e* (rel intensity) 288 (9, M^+), 260 (9), 105 (100), 77 (48), 43 (35).

2-*p*-Toluidinopyridine. A solution of *N*-*p*-tolylbenzimidoyl chloride (2.99 g, 0.01 mol) and pyridine 1-oxide (1.90 g, 0.1 mol) in ethylene chloride (30 ml) was boiled under reflux for 11 hr. After cooling to room temperature, the solution was filtered to remove pyridine 1-oxide hydrochloride (0.72 g, 56%). The filtrate was evaporated and the residue was boiled under reflux for 4 hr with 5% aqueous sodium hydroxide (30 ml). After cooling to room temperature, the basic solution was filtered to remove a solid (1.90 g), mp 90–95°. Fractional crystallization from methanol afforded *N*-benzoyl-*p*-toluidide (0.23 g, 11%) and **2-*p*-toluidinopyridine** (1.48 g, 80%), mp 108–109°, identical with an authentic sample (melting point, ir).

Anal. Calcd for $C_{12}H_{12}N_2$: C, 78.23; H, 6.57. Found: C, 77.88; H, 6.65.

An authentic sample was prepared as follows. 2-Bromopyridine (3.32 g, 0.02 mol) and *p*-toluidine (2.0 g, 0.02 mol) were boiled together under reflux for 45 min. The mixture was dissolved in 2 *N* hydrochloric acid (15 ml). Basification with 20% aqueous sodium carbonate gave 2-*p*-toluidinopyridine (3.56 g, 97% crude). Recrystallization from aqueous ethanol gave pure material (2.44 g, 67%): mp 105–106°; ir (KBr) 3230 (free NH), 3180 (hydrogen-bonded NH), 1610, 1540, 1470, 1460, 1340, 995, and 775 cm^{-1}; nmr ($CDCl_3$) δ 8.48 (br s, 1 H, exchangeable with D_2O, NH), 8.00 (br d, 1 H, $J_{5,6}$ = 5 Hz, H_6), 7.36–6.90 (m, 5 H, pyridyl H_4 and phenyl H), 6.70 (d, 1 H, $J_{3,4}$ = 8 Hz, H_3), 6.46 (d of d, 1 H, $J_{4,5}$ = 8, $J_{5,6}$ = 5 Hz, H_5), 2.25 (s, 3 H, CH_3); mass spectrum (70 eV) *m/e* (rel intensity) 185 (8, M^+), 184 (52), 183 (100), 182 (6), 181 (6), 169 (6), 168 (12), 97 (14), 95 (12), 93 (6), 91 (13), 85 (7), 83 (13), 81 (13), 79 (14), 78 (17), 77 (12), 71 (12), 69 (19), 67 (23), 65 (13), 57 (21), 56 (8), 55 (26), 53 (7), 52 (9), 51 (17), 44 (10), 43 (23), 41 (28), 40 (22), 39 (18). The following were prepared similarly.

2-*N*-Benzoyl-*p*-chloroanilinopyridine (53%): mp 123.5–125° (EtOH); ir (KBr) 2890 (OCH_3), 1650 cm^{-1} (CO); nmr ($CDCl_3$) δ 8.22 (d of d of d, 1 H, $J_{5,6}$ = 5, $J_{4,6}$ = 2, $J_{3,6}$ = 1 Hz, H_6), 7.7–6.7 (m, 12 H, aromatic H), 3.69 (s, 3 H, OCH_3); mass spectrum *m/e* (rel intensity) 304 (9, M^+), 276 (6), 181 (11), 106 (6), 105 (100), 78 (7), 77 (35), 69 (6), 57 (6), 55 (6), 52 (12), 43 (7), 41 (8).

Anal. Calcd for $C_{19}H_{16}N_2O_2$: C, 74.98; H, 5.30. Found: C, 74.66; H, 5.62.

This, on acid-catalyzed hydrolysis, gave 2-*p*-anisidinopyridine, mp 87.5–88.5° (lit.[26] mp 85–86°), identical with an authentic sample (melting point, ir).

2-*N*-Benzoyl-*p*-chloroanilinopyridine (53%): mp 123.5–125° (EtOH); ir (KBr) 1650 cm^{-1} (CO); nmr ($CDCl_3$) δ 8.34 (d, 1 H, H, $J_{5,6}$ = 5, $J_{4,6}$ = 1.5 Hz, H_6), 7.7–7.0 (m, 12 H, aromatic H); mass spectrum *m/e* (rel intensity) 307 (5), 280 (6), 106 (9), 105 (100), 77 (42), 75 (7), 51 (10), 43 (13).

Anal. Calcd for $C_{18}H_{13}ClN_2O$: C, 70.02; H, 4.24. Found: C, 70.14; H, 4.17.

Acid-catalyzed hydrolysis of the amide gave 2-*p*-chloroanilinopyridine, mp 112–115° (lit.[27] mp 116°), identical with an authentic sample.

2-*N*-Benzoylbenzylaminopyridine (54%): mp 111–113° (EtOH); ir (KBr) 1650 cm^{-1} (CO); nmr ($CDCl_3$) 8.34 (d, 1 H $J_{5,6}$ = 5 Hz, H_6), 7.4–6.4 (m, 13 H, aromatic H), 5.30 (s, 2 H, $PhCH_2$); mass spectrum *m/e* (rel intensity) 288 (0.15, M^+), 287 (0.1), 259 (0.7), 212 (8), 211 (48), 210 (17), 105 (14), 77 (9), 58 (32), 43 (100).

Anal. Calcd for $C_{19}H_{16}N_2O$: C, 79.14; H, 5.59. Found: C, 79.45; H, 5.95.

Hydrolysis of the amide with 2 *N* HCl gave 2-benzylaminopyridine, mp 95–96° (lit.[2] mp 94–95°), identical with authentic sample.

2-*N*-Benzoylcyclohexylaminopyridine (64%): mp 132.5–134°

(lit.[28] mp 129–130°); ir (KBr) 1640 cm^{-1} (CO); nmr ($CDCl_3$) δ 8.40 (d of d, 1 H, $J_{5,6}$ = 5, $J_{4,6}$ = 2 Hz, H_6), 7.5–6.9 (m, 7 H, aromatic H), 6.75 (d of d, 1 H, $J_{3,4}$ = 8, $J_{3,5}$ = 2 Hz, H_3), 2.5–1.0 (m, 11 H, C_6H_{11}); mass spectrum *m/e* (rel intensity) 280 (6, M^+), 198 (13), 197 (21), 176 (15), 175 (100), 121 (22), 106 (7), 105 (89), 78 (18), 77 (55), 55 (5), 51 (5), 51 (11), 41 (8).

Hydrolysis with 2 *N* HCl gave 2-cyclohexylaminopyridine, mp 125–127° (lit.[28] mp 123–125°), *m/e* (rel intensity) 189 (19, M^+).

p-Nitroanilinopyridine. A. *N*-*p*-Nitrophenylbenzimidoyl chloride (2.30 g) and pyridine 1-oxide (1.68 g) in chlorobenzene (30 ml) were boiled under reflux for 32 hr. The cooled solution was filtered to remove pyridine 1-oxide hydrochloride (0.70 g, 61%), and the filtrate was concentrated and chromatographed on a silica gel column (200 g). Elution with benzene–chloroform (1:4 v/v) gave *N*-benzoyl-*p*-nitroaniline (0.42 g, 19%), mp 198–200° (lit.[25] mp 199°), identical with an authentic sample. Further elution with the same solvent gave **2-*N*-benzoyl-*p*-nitroanilinopyridine** (0.94 g, 33%) as a yellow oil, ir (film) 1670 (CO), 1510, 1340 cm^{-1} (NO_2). Attempted crystallization of the oil resulted in its hydrolysis to 2-*p*-nitroanilinopyridine and the amide was never obtained analytically pure.

The amide could either be hydrolyzed, or the concentrated reaction solution itself could be saponified with 5% aqueous NaOH for 3 hr to give 2-*p*-nitroanilinopyridine (71%, based on imidoyl chloride), mp 174–175° (lit.[29] mp 174–175°), identical with an authentic sample: nmr (acetone-d_6) δ 8.23 (d of d of d, 1 H, $J_{5,6}$ = 5.0, $J_{4,6}$ = 1.8, $J_{3,6}$ = 1.0 Hz, H_6), 8.10 (d, 2 H, J_o = 9.5 Hz, phenyl H_3, H_5), 7.92 (d, 2 H, J_o = 9.5 Hz, phenyl H_2, H_4), 7.51 (d of d of d, 1 H, $J_{3,4}$ = 8.7, $J_{4,5}$ = 7.5, $J_{4,6}$ = 1.8 Hz, H_4) 6.93 (d of d of d, 1 H, $J_{4,5}$ = 7.5, $J_{5,6}$ = 5.0, $J_{3,5}$ = 1.0 Hz, H_5), 6.87 (d of d of d, 1 H, $J_{3,4}$ = 8.7, $J_{3,5}$ = 1.0, $J_{3,6}$ = 1.0 Hz, H_3).

B. *N*-*p*-Nitrophenylbenzimidoyl chloride (1.76 g) in ethylene chloride (30 ml) was treated with antimony pentachloride (2.02 g) at room temperature in a drybox. The deep orange solution was treated dropwise with a solution of pyridine 1-oxide (1.29 g) in ethylene chloride (10 ml). A pale precipitate formed which gradually dissolved as the addition continued. The solution was then boiled under reflux for 17 hr, the solvent was distilled off *in vacuo*, and the residue was hydrolyzed with 2 *N* HCl to give 2-*p*-nitroanilinopyridine (1.30 g, 89%), identical with an authentic sample.

***N*-2-Pyridylcaprolactam.** Phosgene (3.2 g, 0.036 mol) was dissolved in chloroform (10 ml). A solution of caprolactam (3.68 g, 0.036 mol) in chloroform was added dropwise over a period of 1 hr. The oil heating bath was maintained at 38°. (There was an exothermic reaction as the addition proceeded and a gas was evolved which turned litmus paper red, although the literature[30] indicates that caprolactam pseudochloride hydrochloride is the substance produced. All attempts to isolate this hydrochloride failed.) The reaction mixture was kept at 55° for 4.25 hr and was then used as such. It was boiled under reflux while a solution of pyridine 1-oxide (9.3 g, 0.0978 mol) in chloroform (20 ml) was added over a period of 10 min. The addition caused an exothermic reaction, the solution became orange, and a white solid precipitated. After 15 hr the reaction mixture was cooled and pyridine 1-oxide hydrochloride was collected (2.60 g, 61%). The filtrate was evaporated and the residue was chromatographed on a column of silica gel (100 g). Elution with chloroform–benzene (1:1 v/v) gave ***N*-2-pyridylcaprolactam** as an oil (0.76 g, 11%): bp 106° (0.05 mm); ir (film) 2930 and 2850 (aliphatic CH) and 1665 cm^{-1} (amide C=O); nmr ($CDCl_3$) δ 8.37 (d of d of d, 1 H, $J_{5,6}$ = 5, $J_{4,6}$ = 1.5, $J_{3,6}$ = 1.3 Hz, H_6), 7.63 (m, 2 H, H_3, H_4), 7.00 (d of d of d, 1 H, $J_{4,5}$ = 6, $J_{5,6}$ = 5, $J_{3,5}$ = 2.3 Hz, H_5), 4.04 (br m, 2 H, $COCH_2$), 2.72 (br m, 2 H, NCH_2), 1.90 (br s, 6 H, aliphatic CH); *m/e* (rel intensity) 190 (34, M^+).

Anal. Calcd for $C_{11}H_{14}N_2O$: C, 69.44; H, 7.42. Found: C, 69.21; H, 7.58.

The picrate had mp 133–135° (from ethanol).

Anal. Calcd for $C_{17}H_{17}N_5O_8$: C, 48.69; H, 4.09. Found: C, 48.32; H, 3.67.

***N*-2-Pyridylsaccharin. A. Reaction of Pyridine 1-Oxide with Saccharin Pseudochloride.** 1. A solution of saccharin pseudochloride (0.35 g, 0.0017 mol) and pyridine 1-oxide (0.16 g, 0.0017 mol) in chlorobenzene (10 ml) was boiled under reflux for 18 hr. Tlc (2.5 and 5% MeOH–$CHCl_3$) showed the absence of saccharin pseudochloride and saccharin. There were two major components (R_f *ca.* 0.89 and 0.76) and several slower moving components (R_f 0.22 and 0.11) present. The solution was concentrated to 5 ml and chromatographed on a column of silica gel (50 g). The first fraction, eluted with 1% methanol–chloroform and crystallized from ethanol, was ***N*-2-pyridyl-*o*-carbethoxybenzenesulfonamide** (0.54 g, 10.4%): mp 170–172°; ir (KBr) 3250 (NH), 1750 (ester C=O), 1660, 1630, 1330 (SO_2), 1160 (SO_2), 1140, and 605 cm^{-1}; nmr ($CDCl_3$) δ 8.81 (br d, 1 H, $J_{5,6}$ = 5.5 Hz, pyridyl H_6), 8.57 (d of d, 1 H, $J_{5,6}$ = 8, $J_{4,6}$ = 4 Hz, phenyl H_6), 8.3–7.6 (m, 6 H, aromatic H and NH), 7.33 (d of d, 1 H, $J_{4,5}$ = 8, $J_{5,6}$ = 5.5 Hz, pyridyl H_5), 4.34 (q, 2 H, J_{vic} = 7 Hz, CH_3CH_2–), 1.30 (t, 3 H, J_{vic} = 7 Hz, CH_3CH_2–); mass spectrum (70 eV) *m/e* (rel intensity) 306 (2, M^+), 261 (17), 260 (30), 241 (13), 213 (26), 196 (64), 185 (93), 169 (100), 168 (54), 121 (38), 104 (25), 93 (28), 78 (50), 77 (28), 76 (61), 69 (10), 65 (38), 51 (32), 50 (45), 45 (27), 43 (37).

Anal. Calcd for $C_{14}H_{14}N_2O_4S$: C, 54.89; H, 4.61. Found: C, 54.88; H, 4.67.

The second fraction, eluted with 5% methanol–chloroform, was pyridine 1-oxide (0.062 g, 39%).

2. A solution of saccharin pseudochloride (0.60 g, 0.0030 mol) and pyridine 1-oxide (0.57 g, 0.0060 mol) in chlorobenzene (20 ml) was boiled under reflux for 50 hr. After cooling to room temperature, the solvent was decanted from a residual water-soluble, brown oil. This gave a positive halogen test with aqueous silver nitrate solution and was presumably pyridine 1-oxide hydrochloride. The solvent was evaporated from one-half of the reaction mixture and the semicrystalline residue was fractionally crystallized from aqueous ethanol to give ***N*-2-pyridylsaccharin** (0.30 g, 38.4%): mp 210–211°; ir (KBr) 1740 (five-membered lactam C=O), 1360 (SO_2), 1330, 1310, 1190 (SO_2), 1145, 774, and 580 cm^{-1}; nmr ($CDCl_3$) δ 8.58 (d of d, 1 H, $J_{5,6}$ = 5.5, $J_{4,6}$ = 1 Hz, pyridyl H_6), 8.1–7.6 (m, 6 H, aromatic H), 7.26 (d of d of d, 1 H, $J_{4,5}$ = 6, $J_{5,6}$ = 5.5, $J_{3,5}$ = 1 Hz, pyridyl H_5); mass spectrum *m/e* (rel intensity) 260 (25, M^+), 197 (7), 196 (42), 195 (6), 196 (7), 168 (29), 97 (9), 95 (9), 93 (9), 92 (9), 81 (9), 79 (8), 78 (24), 77 (31), 76 (30), 69 (12), 58 (32), 57 (13), 55 (16), 51 (20), 50 (22), 44 (10), 43 (100), 42 (8), 41 (16).

Anal. Calcd for $C_{12}H_8N_2O_3S$: C, 55.38; H, 3.10. Found: C, 55.52; H, 2.93.

The second half of the reaction mixture was concentrated and chromatographed on a column of silica gel (50 g). Elution with 1% methanol–chloroform and crystallization from ethanol gave *N*-2-pyridyl-*o*-carbethoxybenzenesulfonamide (0.096 g, 21%), ir identical with that of the product described above.

B. Preparation of Authentic *N*-2-Pyridylsaccharin. 1. A warm solution of sodiosaccharinate (1.03 g, 0.005 mol) in hexamethylphosphoramide (HMPA, 5 ml) was stirred while a solution of 2-bromopyridine (0.79 g, 0.005 mol) in HMPA (5 ml) was added dropwise. The solution was boiled under reflux for 10 min. After partial cooling, water (10 ml) was added. The mixture was cooled to room temperature and filtered to give 3-*N*,*N*-dimethylaminopseudosaccharin (0.85 g, 85%), mp 298–299°. One recrystallization from acetonitrile gave the analytical sample: mp 301–306° (lit.[31] mp 273–274°); ir (KBr) 2980 (NCH_3) and 1630 cm^{-1} (C=N); nmr, insufficiently soluble; mass spectrum *m/e* (rel intensity) 210 (22, M^+), 146 (10), 145 (61), 104 (10), 103 (46), 102 (14), 76 (14), 44 (100), 43 (12), 42 (12).

Anal. Calcd for $C_9H_{10}N_2O_2S$: C, 51.41; H, 4.79. Found: C, 51.72; H, 4.92.

2. Sodiosaccharinate (2.05 g, 0.01 mol) and 2-fluoropyridine (1.94 g, 0.02 mol) were boiled under reflux for 15 hr. The mixture was cooled and poured into water (10 ml) to dissolve any remaining sodiosaccharinate. The solution was extracted with chloroform (2 × 25 ml), and the extract was dried (Na_2CO_3) and evaporated. The residue was crystallized from aqueous ethanol to give *N*-2-pyridylsaccharin (0.017 g, 0.65%), identical with the material obtained above.

***N*-2-Pyridyl-*o*-carbethoxybenzenesulfonamide from *N*-2-Pyridylsaccharin.** *N*-2-Pyridylsaccharin (0.1 g) was boiled in ethanol under reflux for 10 hr. Undissolved *N*-2-pyridylsaccharin (0.067 g, 67%) was recovered from the cooled mixture. Evaporation of the solvent gave *N*-2-pyridyl-*o*-carbethoxybenzenesulfonamide (0.013 g, 11%), mp 170–172°, identical with the compound obtained above.

Reaction of Pyridine 1-Oxide, *N*-Phenylbenzimidoyl Chloride, and *N*-Benzoyl-*p*-toluidine. A solution of the *N*-oxide (1.68 g) in ethylene chloride (20 ml) and a suspension of *p*-benzotoluidide (3.8 g, 0.018 mol) in ethylene chloride (35 ml) were added to freshly prepared and distilled *N*-phenylbenzimidoyl chloride (1.9 g, 0.0085 mol) and the mixture was boiled under reflux for 8 hr. Pyridine 1-oxide hydrochloride (0.45 g, 39%) separated from the cooled solution. The filtrate was concentrated and analyzed by glc (5 ft × 0.25 in. column packed with 20% SE-30 on Gas-Chrom

Q at 250°, *N*-benzoyl-*p*-anisidine internal standard) and the products were collected and characterized. In addition to small amounts of the secondary amines, the following were formed: 2-*N*-benzoylanilinopyridine (23.6%); 2-*N*-benzoyl-*p*-toluidinopyridine (24.7%).

Reaction between *N*-Phenylbenzimidoyl Chloride and *N*-Benzoyl-*p*-toluidine (Work with Dr. E. M. Smith). In a drybox, a solution of *N*-benzoyl-*p*-toluidine (1.9 g, 0.009 mol) in ethylene chloride (25 ml) was added to freshly prepared and distilled *N*-phenylbenzimidoyl chloride (1.9 g, 0.009 mol) and the solution was boiled under reflux for 3.5 hr. The solvent was distilled *in vacuo* and the solid residue was examined by mass spectrometry with minimum exposure to the atmosphere (70 eV, direct inlet, 50°). Molecular ions were observed at *m/e* 229, 215, 211, and 197, corresponding to *N*-*p*-tolylbenzimidoyl chloride, *N*-phenylbenzimidoyl chloride, *N*-benzoyl-*p*-toluidine, and benzanilide, respectively. The first two M^+ peaks showed the cluster characteristic of an ion containing one Cl atom. The relative intensities of the *m/e* 229 and 215 ions were 229:215 = 1.66:1.

The above solid had an infrared spectrum identical with that obtained when a mixture of benzanilide and *N*-*p*-tolylbenzimidoyl chloride was heated under the same conditions.

2-*N*-Benzoylanilino-4-picoline. A solution of *N*-phenylbenzimidoyl chloride (3.9 g, 0.018 mol) and 4-picoline 1-oxide (3.83 g, 0.036 mol) in ethylene chloride (35 ml) was boiled under reflux for 3 hr. The reaction mixture was concentrated and chromatographed on a column of silica gel (200 g). Elution with chloroform–benzene (1:4 v/v) gave benzanilide (1.28 g, 36%), mp 164–165°. Elution with chloroform–benzene (1:1 to 3:1 v/v) yielded 2-*N*-benzoylanilino-4-picoline (1.32 g, 45%): mp 158.5–159.5° (from EtOH): ir (KBr) 2900 (aromatic CH_3), 1650 cm^{-1} (amide C=O); nmr ($CDCl_3$) δ 8.21 (d, 1 H, $J_{5,6}$ = 5 Hz, H_6), 7.5–7.0 (m, 11 H, aromatic H), 6.87 (d of d, 1 H, $J_{5,6}$ = 5 Hz, H_5), 2.27 (s, 3 H, CH_3); mass spectrum *m/e* (rel intensity) 288 (5, M^+), 260 (12), 259 (11), 106 (7), 105 (100), 77 (60), 51 (10).

Anal. Calcd for $C_{19}H_{16}N_2O$: C, 79.14; H, 5.59. Found: C, 79.20; H, 5.69.

2-Anilino-4-picoline. 2-*N*-Benzoylanilino-4-picoline (0.200 g, 0.00069 mol) was boiled under reflux with 2 *N* hydrochloric acid for 12 hr. After cooling to room temperature, the solution was filtered to remove benzoic acid (0.31 g, 37%). Basification with 5% aqueous sodium hydroxide produced 2-anilino-4-picoline (0.095 g, 74%): mp 118.5–119.5° (lit.[32] mp 119°); ir (KBr) 3220 (NH), 1615, and 1595 cm^{-1}; nmr ($CDCl_3$) δ 8.09 (d, 1 H, $J_{5,6}$ = 5 Hz, H_6), 7.4–7.0 (m, 6 H, phenyl H and NH), 6.72 (d, 1 H, $J_{3,5}$ = 1 Hz, H_3), 6.56 (d of d, 1 H, $J_{5,6}$ = 5, $J_{3,5}$ = 1 Hz, H_5), 2.27 (s, 3 H, CH_3); mass spectrum *m/e* (rel intensity) 185 (6, M^+), 184 (45), 183 (100), 182 (9), 97 (9), 95 (11), 93 (8), 92 (11), 91 (12), 83 (9), 81 (12), 80 (13), 79 (8), 77 (16), 71 (8), 69 (14), 67 (11), 65 (13), 57 (15), 55 (22), 51 (14), 43 (16), 41 (25), 40 (16), 39 (20).

Attempted Reaction of Pyridine 1-Oxide with Benzenesulfonylbenzimidoyl Chloride. A solution of *N*-benzenesulfonylbenzimidoyl chloride (0.35 g) and dry pyridine 1-oxide (0.24 g, freshly azeotroped with dry benzene) in chlorobenzene (5 ml) was boiled under reflux for 15 hr. Pyridine 1-oxide hydrochloride (0.1 g, 59%) sublimed in the condenser. The filtered solution was concentrated and chromatographed on a column of silica gel (50 g). Elution with chloroform gave *N*-benzoylbenzenesulfonamide (0.1 g, 31%), mp 145–146° (lit.[33] mp 147°). Two minor fractions eluted with 5% MeOH in $CHCl_3$ were not identified but were different from authentic 2-*N*-benzoylbenzenesulfonamidopyridine or from 2-benzenesulfonamidopyridine.

Reaction of Pyridine 1-Oxide with α-Chlorobenzaldoxime. A solution of pyridine 1-oxide (1.90 g) and α-chlorobenzaldoxime (1.55 g) in chlorobenzene (25 ml) was boiled under reflux for 12 hr. A white sublimate (0.4 g) formed in the condenser. The dark red solution was concentrated and chromatographed on a column of silica gel (100 g). Elution gave *N*-benzoyloxybenzimidoyl chloride (0.40 g, 30%): mp 109–110° (lit.[17a] mp 109°); ir (KBr) 1750 (C=O), 1250 cm^{-1}; nmr ($CDCl_3$) δ 8.25–8.00 (m, 4 H, ortho H), 7.65–7.35 (m, 6 H, meta and para H); *m/e* (rel intensity) 259 (0.09, M^+), 105 (100). Further elution gave benzanilide (0.10 g, 11.4%), mp 163.5–164.5°, identical with an authentic sample. The third product to elute was carbanilide (0.081 g, 7.6%), mp 247–248° (from EtOH) (lit.[25] mp 238°), identical with an authentic sample: nmr (DMSO-d_6) δ 9.02 (br s, 2 H, exchangeable with D_2O, NH), 7.9–7.5 (m, 8 H, ortho and meta H), 7.32 (t, 2 H, $J_{m,p}$ = 6.5 Hz, para H); *m/e* (rel intensity) 213 (2, M^+), 93 (100). Further elution gave benzoic acid (0.087 g, 7.1%), mp 120–121°. No derivatives of pyridine were isolated.

In a control experiment omitting the pyridine 1-oxide, tlc (10% benzene–chloroform) indicated the presence of *N*-benzoyloxybenzimidoyl chloride and a second minor unidentified compound. No α-chlorobenzaldoxime and carbanilide were present in the reaction mixture after it had been boiled under reflux for a period of 22 hr.

Reaction of *N*-Benzoyl-1-adamantanamine with Thionyl Chloride. A. Neat. *N*-Benzoyl-1-adamantanamine (2.04 g) was heated gently with thionyl chloride (1.3 ml) until HCl evolution ceased. The mixture was distilled under vacuum to remove HCl, SO_2, and $SOCl_2$, the residue was dissolved in ethylene chloride (15 ml), and a solution of pyridine 1-oxide (1.9 g) in ethylene chloride (20 ml) was added. The solution was boiled under reflux for 10 hr. On cooling the solution pyridine 1-oxide hydrochloride (0.30 g, 23%) separated. Tlc ($CHCl_3$) analysis indicated the presence of benzonitrile, 1-chloroadamantane, and pyridine 1-oxide, but no 2-*N*-benzoyl-1-adamantanamnopyridine.

B. In Ether. The chlorination of *N*-benzoyl-1-adamantanamine with thionyl chloride was carried out as above except in ether (30 ml) solution. The results were the same as in the reaction carried out in the absence of solvent.

Phosgene did not effect the chlorination of *N*-benzoyl-1-adamantanamine either at room temperature or at 50°.

Reaction of Pyridine 1-Oxide with an *N*-Adamantylacetonitrilium Salt. A solution of pyridine 1-oxide (0.95 g) was added to a suspension of 1-adamantanamine (1.51 g) in acetonitrile (35 ml). The suspension was stirred at room temperature while isoamyl nitrite (1.28 g) was added dropwise over a period of 5 min. There was no gas evolution at room temperature. Gentle heating on the steam bath produced quantitative gas evolution within 20 hr. The solution was concentrated (*ca.* 10 ml) and poured into water (50 ml). The organic layer was extracted with chloroform, and the chloroform layer was dried (Na_2CO_3) and evaporated to give 1-acetamidoadamantane (1.35 g, 70%): mp 147–148° (lit.[34] mp 149°); ir (KBr) 3260 (NH), 1640 cm^{-1} (CO); *m/e* (rel intensity) 193 (14, M^+).

***N*-1-Adamantylacetonitrilium Bromopentachloroantimonate.** In a drybox, antimony pentachloride (3.0 g) was added to a solution of acetonitrile (0.41 g) in chlorobenzene (15 ml) to form a bright yellow precipitate. A solution of 1-bromoadamantane (2.25 g) in chlorobenzene (10 ml) was added dropwise and a voluminous precipitate formed in an exothermic reaction. The precipitate was collected and washed thoroughly with chlorobenzene and petroleum ether to afford bright yellow ***N*-1-adamantylacetonitrilium bromopentachloroantimonate** (4.0 g, 72%); ir (Nujol) 2360 cm^{-1} (C≡N$^+$).

Anal. Calcd for $C_{12}H_{18}BrCl_5NSb$: C, 25.96; H, 3.27. Found: C, 25.88; H, 3.31.

***N*-1-Adamantylbenzonitrilium Bromopentachloroantimonate.** From $SbCl_5$, PhCN, and 1-bromoadamantane in *o*-dichlorobenzene, the benzonitrilium salt (53–75%) was obtained, ir (Nujol) 2330 cm^{-1}.

Anal. Calcd for $C_{17}H_{20}BrCl_5NSb$: C, 33.08; H, 3.27. Found: C, 33.07; H, 3.45.

Attempted Reaction of Pyridine 1-Oxide with *N*-1-Adamantylbenzonitrilium Bromopentachloroantimonate. The above salt (6.2 g) was suspended in ethylene chloride (75 ml), and the suspension was stirred at room temperature (drybox) while a solution of pyridine 1-oxide (1.90 g) in ethylene chloride (20 ml) was added. All of the salt dissolved during the addition of the *N*-oxide. The solution was boiled under reflux for 8 hr, cooled, and stirred with water. The mixture was filtered and the organic layer was separated and concentrated when pyridine 1-oxide–$SbCl_5$ adduct (1.0 g, 26%), mp 195–202° (lit.[35] mp 195–196°), crystallized. The filtrate was further concentrated and chromatographed on a column of silica gel. The only products isolated (identified by tlc and ir) were the 1-adamantyl halide (mixture of chloro and bromo), benzonitrile, and *N*-benzoyl-1-adamantanamine.

2-(1-Adamantanamino)pyridine. 2-Fluoropyridine (3.88 g) and 1-adamantanamine (3.01 g) were boiled together under reflux for 16 hr. The mixture was dissolved in 2 *N* HCl (10 ml) and the solution was basified with 5% aqueous NaOH to give a solid consisting of a mixture of the starting amine and of the desired product . Chromatography on a silica gel column (50 g) gave 2-(1-adamantanamino)pyridine (0.41 g, 8.9%): mp 165–166.5° (chloroform–light petroleum); ir (KBr) 3345 cm^{-1} (NH); nmr ($CDCl_3$) δ 8.00 (d of d of d, 1 H, $J_{5,6}$ = 4.5, $J_{4,6}$ = 2, $J_{3,6}$ = 1 Hz, H_6), 7.28 (d of d of d, 1 H, J = 7.8, 7.5, $J_{4,6}$ = 2 Hz, H_4), 6.44 (m, 2 H, H_3 and H_5), 4.38 (br s, 1 H, exchangeable with D_2O, NH), 2.04 and 1.70 (15 H, aliphatic H); *m/e* (rel intensity) 229 (14, M^+), 171 (100).

Anal. Calcd for $C_{15}H_{20}N_2$: C, 78.90; H, 8.83. Found: C, 79.15; H, 9.09.

2-*N*-Benzoyl-1-adamantanaminopyridine. This was obtained (84%) by benzoylation of the above amine in benzene: mp 210–212° (EtOH); ir (KBr) 1670 cm^{-1} (CO); *m/e* (rel intensity) 333 (9, M^+), 135 (100).

Anal. Calcd for $C_{22}H_{24}N_2O$: C, 79.48; H, 7.28. Found: C, 79.33; H, 7.53.

Acknowledgments. Part of this work was carried out during the tenure (by G. M. S.) of a University of Saskatchewan Teaching Fellowship (1967). The rest was supported by a grant from the National Institutes of Health (GM 16626), whom we thank. Pyridine 1-oxides were a gift from Reilly Tar and Chemical Co., to whom we are also grateful. We also wish to thank Dr. Elizabeth M. Smith for carrying out some of the experiments described herein.

Registry No.—Pyridine 1-oxide, 694-59-7; benzenediazonium tetrafluoroborate, 369-57-3; 2-*N*-acetylanilinopyridine, 51263-25-3; *N*-phenylbenzimidoyl chloride, 4903-36-0; 2-*N*-benzoylanilinopyridine, 20107-78-2; *N*-phenylbenzonitrilium hexachloroantimonate, 51293-24-4; 2-*N*-benzoyl-*p*-toluidinopyridine, 51263-26-4; *N*-*p*-tolylbenzimidoyl chloride, 15999-95-8; 2-*p*-toluidinopyridine, 51263-27-5; 2-*N*-benzoyl-*p*-anisidinopyridine, 51263-28-6; 2-*N*-benzoyl-*p*-chloroanilinopyridine, 51263-29-7; 2-*N*-benzoylbenzylaminopyridine, 24244-29-9; 2-*N*-benzoylcyclohexylaminopyridine, 51263-30-0; *p*-nitroanilinopyridine, 24068-29-9; *N*-*p*-nitrophenylbenzimidoyl chloride, 34918-79-1; 2-*N*-benzoyl-*p*-nitroanilinopyridine, 51263-31-1; caprolactam, 105-60-2; *N*-2-pyridylcaprolactam, 51263-32-2; *N*-2-pyridylcaprolactam picrate, 51263-33-3; *N*-2-pyridylsaccharin, 51263-34-4; saccharin pseudochloride, 567-19-1; *N*-2-pyridyl-*o*-carbethoxybenzenesulfonamide, 51263-35-5; 3-*N*,*N*-dimethylaminopseudosaccharin, 22716-43-4; *N*-benzoyl-*p*-toluidine, 582-78-5; 2-*N*-benzoylanilino-4-picoline, 51263-36-6; 4-picoline 1-oxide, 1003-67-4; 2-anilino-4-picoline, 19933-06-3; *N*-benzoyl-1-adamantanamine, 19026-84-7; thionyl chloride, 7719-09-7; *N*-1-adamantylacetonitrilium bromopentachloroantimonate, 51263-54-8; *N*-1-adamantylbenzonitrilium bromopentachloroantimonate, 51263-56-0; 2-(1-adamantanamino)pyridine, 22947-50-8; 2-fluoropyridine, 372-48-5; 1-adamantanamine, 768-94-5; 2-*N*-benzoyl-1-adamantanaminopyridine, 51263-37-7.

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Direct Acylamination of 3-Substituted Pyridine 1-Oxides. Directive Effect of the Substituent[1a]

R. A. Abramovitch* and Richard B. Rogers

Department of Chemistry, University of Alabama, University, Alabama 35486

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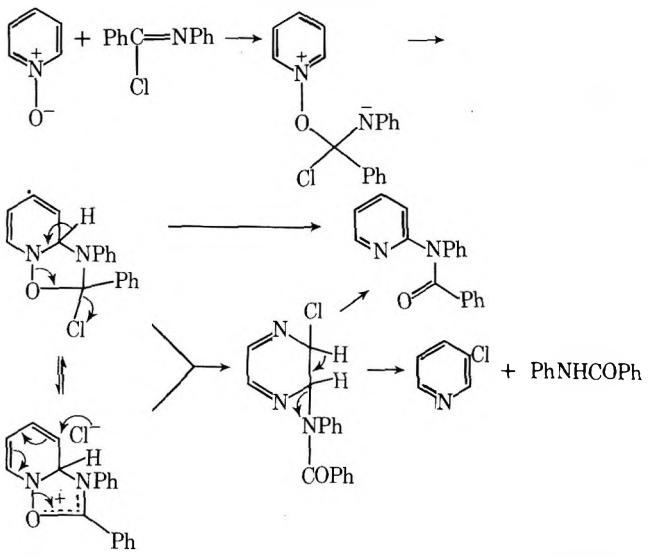
The effect of a 3 substituent upon the orientation of the entering group in the direct acylamination of pyridine 1-oxides with *N*-phenylbenzimidoyl chloride has been studied, and a possible explanation of the results is proposed. In the case of electron-attracting substituents (CN, CO_2Me) the formation of substantial amounts of 5-chloro derivative complicates the interpretation. With a 3-mesylamino substituent it is the 6-chloro compound that is formed as a by-product, and the intermediate 2-acylaminated product cyclizes to 2,3-diphenyl-3*H*-imidazo[4,5-*b*]pyridine.

The direct acylamination of pyridine 1-oxides by imidoyl chlorides or nitrilium salts has been reported.[1b] The main by-products formed were 3-chloropyridine and benzanilide (from *N*-phenylbenzimidoyl chloride), and the

Table I
Authentic New 2-Anilinopyridines (7) and 2-*N*-Benzoylanilinopyridines (3 and 4)

Compd	Yield, %	Mp, °C	Molecular formula	Calcd, % C	Calcd, % H	Found, % C	Found, % H
7, R = 3-Me	52	123–125	$C_{12}H_{12}N_2$	78.26	6.52	78.33	6.72
7, R = 5-Me	61	114–116	$C_{12}H_{12}N_2$	78.26	6.52	78.16	6.42
3a	63	122–123	$C_{19}H_{16}N_2O$	79.16	5.56	79.20	5.81
4a	80	104–105	$C_{19}H_{16}N_2O$	79.16	5.56	79.21	5.74
7, R = 3-CO_2Me	80	Oil, picrate mp 192–194 (EtOH)	$C_{13}H_{12}N_2O_2 \cdot C_6H_3N_3O_7$	49.89	3.28	49.86	3.48
7, R = 5-CO_2Me	40	119–120	$C_{13}H_{12}N_2O_2$	68.42	5.25	68.15	5.18
4b	77	116–117	$C_{20}H_{16}N_2O_3$	72.29	4.82	72.11	4.97
7, R = 3-F	9	69–70	$C_{11}H_9FN_2$	70.21	4.79	70.02	4.94
7, R = 5-F	42	99–100	$C_{11}H_9FN_2$	70.21	4.79	70.05	4.94
3d	65	123.5–124.5	$C_{18}H_{13}FN_2O$	73.97	4.54	74.00	4.63
4d	70	142–144	$C_{18}H_{13}FN_2O$	73.97	4.54	73.99	4.59
7, R = 3-OMe	45	Oil, picrate mp 190–192 (EtOH)	$C_{12}H_{12}N_2O \cdot C_6H_3N_3O_7$	50.35	3.50	50.44	3.60
3f	40	177–178	$C_{19}H_{16}N_2O_2$	75.00	5.26	75.08	5.38

Scheme I



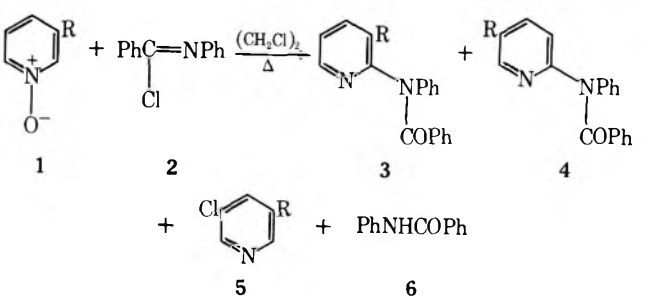
mechanism outlined in Scheme I was proposed to explain the formation of the products.

In seeking to examine the scope of this novel acylamination we have extended the reaction to 3-substituted pyridine 1-oxides. 3-Substituted 2-anilinopyridines are of potential pharmaceutical interest. Several 2-anilinonicotinic acid derivatives are reported to exhibit analgesic,[2,3] antiinflammatory,[2,3] antiphlogistic,[4] and antineoplastic[5] properties. Likewise, 6-anilinonicotinic acid derivatives and 6-anilino-3-nitro- and 6-anilino-3-aminopyridines have been found to have antineoplastic,[5] antiinflammatory,[3] and antiphlogistic[6] properties. Such compounds have been available in the past only through multistep synthetic schemes. The above one-step procedure could make available conveniently and economically a variety of substituted derivatives of these useful compounds.

We now report a quantitative study of the effect of a 3 substituent upon orientation in the intramolecular acylamination using *N*-phenylbenzimidoyl chloride. Attack can take place either at the 2 or the 6 position to give **3** and **4**, respectively, and in most cases both isomers were formed, at least initially (Scheme II).

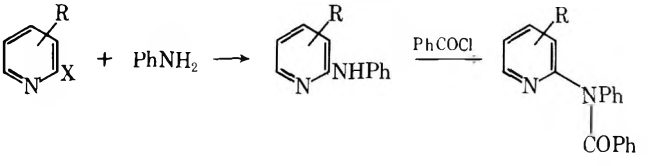
Quantitative analyses were performed using gas chromatography of the reaction mixtures following a minimum amount of manipulation and contact with the atmosphere. The products were resolved by preparative chromatography and characterized by their spectral properties and by comparison (melting point, ir, retention times)

Scheme II



R
a CH_3
b CO_2Me
c CN
d F
e $NHSO_2$Me.
f OCH_3

with authentic samples in most cases. Authentic substituted anilinopyridines were prepared from aniline and the appropriately substituted 2-chloro- or 2-bromopyridine, followed by benzoylation. The properties of new com-



pounds so prepared are summarized in Table I. This comparison with authentic samples was made necessary because in some instances the nmr spectra of the products did not allow unambiguous assignments of orientation. Thus, H_6 in **4f** consisted of a narrow triplet of unevenly spaced lines (para H–H coupling with C_3 H[7]) at δ 8.38 while the signal for H_6 in **3f** was a barely resolved doublet of doublets at δ 8.34 with the coupling between H_6 and H_5 (4 Hz) being almost the same as that between H_6 and H_4 (3 Hz). In 2-chloro-3-methoxypyridine as well, the ortho coupling constant is smaller than expected (4 Hz) while the meta one is larger (3 Hz). Again, H_6 in **4d** appeared as a broad doublet which, on scale expansion, turned out to be a multiplet, probably arising by the further splitting of the expected doublet of doublets (coupling with H_4 and with F) by H_3. On the other hand, both 2-bromo-5-fluoropyridine and 2-anilino-5-fluoropyridine exhibited only a doublet (J = 3 Hz) for H_6 with no evidence of H–F cou-

Table II
Products Formed on Acylamination of 3-R-Pyridine 1-Oxide with *N*-Phenylbenzimidoyl Chloride

R	Yield, % 3	4	5	6
CH_3	6.8	82.3	5	12.3
CO_2CH_3	Trace	53.2[a]	36.6	40.1
CN	33.4	19.8	30.6	36.7
F	25.9	55.9		10
$NHSO_2CH_3$	39[b]	36.5	10[c]	26.5
OCH_3	76.2	18.9	Trace	4.2

[a] 2-Anilino-5-carbomethoxypyridine was also isolated. [b] The product isolated was 2,3-diphenyl-3*H*-imidazo[4,5-*b*]-pyridine. [c] The product isolated was 2-chloro-5-(*N*-methanesulfonamido)pyridine.

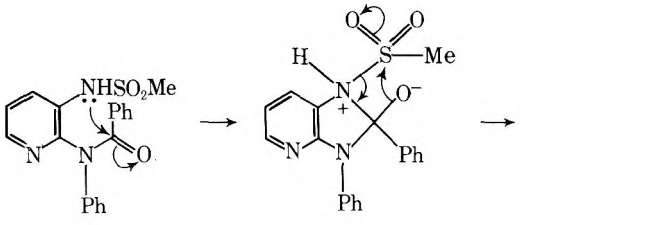
pling. This is in marked contrast to the known ortho H–F coupling constants (6.2–10.1 Hz) in fluorobenzene[8] derivatives. The expected meta coupling between H_3 and the fluorine atom ($J_{3,F}$ = 3.5 Hz) was observed in 2-anilino-5-fluoropyridine; this is smaller than in fluorobenzenes ($J_{m\text{-}H,F}$ = 6.2–8.3 Hz)[8] and 2-fluoropyridine.[9]

The products **3c** and **4c** from 3-cyanopyridine 1-oxide were characterized on the basis of their spectral and analytical data, and by their hydrolysis to either the 2- or the 6-anilinonicotinic esters, identical with authentic samples.

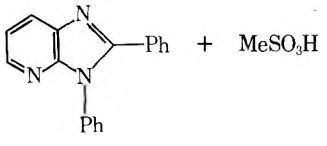
The quantitative (glc analysis except for R = $NHSO_2CH_3$) results of the acylaminations are summarized in Table II.

No 5-chloro-3-fluoropyridine (**5**, R = F) was detected in the run with 3-fluoropyridine 1-oxide. From the limited experience to date, it appears that the highest yields of **5** are obtained with **1** (R = H)[1] and with *N*-oxides bearing electron-withdrawing substituents at C_3. Some unexpected products were obtained with **1** (R = $NHSO_2Me$). The halogenated product proved to be 2-chloro-5-(*N*-methanesulfonamido)pyridine (**8**) rather than the corresponding β-chlorinated derivative. Its formation can be rationalized as in Scheme III.

Also, no 2-(*N*-benzoylanilino)-3-(*N*-methanesulfonamido)pyridine (**3e**) was isolated; instead, 2,3-diphenyl-3*H*-imidazo[4,5-*b*]pyridine (**9**) was formed, undoubtedly from **3e**, perhaps as follows.



3e



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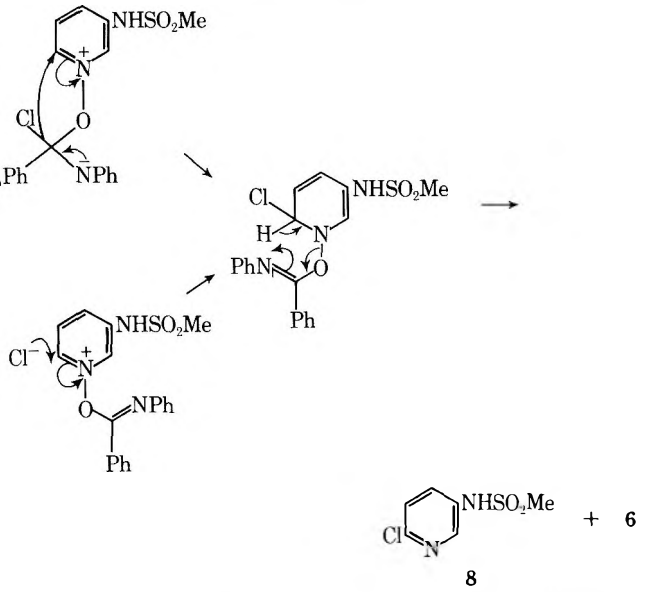
A similar compound, dipyrido[1,2-*a*:3′,2′-*d*]imidazole, was isolated from the reaction of 3-acetamidopyridine 1-oxide with 2-bromopyridine[10] and is probably formed from *N*-(3-acetamido-2-pyridyl)-2-pyridone.

Both electronic and steric effects have to be taken into account in any explanation of the influence of the 3 substituent upon orientation in the intramolecular cyclization. Approach of the α position by the nucleophile cannot be made from a direction perpendicular to the ring because of the geometric limitations enforced by the intramolecular mode of attack, so that one might expect steric

Scheme III



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and through-space electronic interactions between the nucleophile approaching C_2 and a substituent at C_3 to be larger than if approach by the nucleophile were initially perpendicular to the ring.

The effects of the three electron-donating substituents studied (CH_3, OMe, $NHSO_2Me$) are in agreement with predictions made on the basis of straightforward electronic and steric concepts. By virtue of its inductive and steric effect one would expect a 3-methyl group to deactivate C_2 more than C_6, this influence not being compensated by the weak hyperconjugative effect which would be expected to deactivate C_6 more than C_2. In intermolecular nucleophilic attacks by strong nucleophiles (RLi or $NaNH_2$) these effects are overshadowed by strong ion-dipole or London-type attractive forces between the approaching nucleophile and the 3-Me group.[11] In intramolecular nucleophilic substitutions, however, this is not the case and attack takes place predominantly at C_6, as for instance in the Emmert reaction.[12] In the present acylaminations, the inductive and steric effects of the methyl group direct substitution mainly to C_6 (Table II). The methoxyl group, on the other hand, is smaller than methyl[13] and its mesomeric effect is stronger than its inductive effect ($\sigma^n_{p\text{-MeO}}$ = −0.175). Mesomeric effects are known[14] to be more effective at the para than at the ortho positions (*p*-quinonoid contributing structure more stable than *o*-quinonoid ones). On that basis then, it would be predicted that a 3-methoxy substituent would deactivate C_6 more than C_2, and indeed this appears to be the case (Table II). A similar argument can be made concerning the methanesulfonamido group, though its size relative to methyl has not been determined; it would be anticipated that its electron-donating mesomeric effect would be less than that of the methoxyl group while its inductive (and field) effect should be greater. It is not surprising, therefore, that this group leads to only a slight preference for attack at C_2 over C_6.

The situtation with the three overall electron-withdrawing substituents studied (CN, CO_2CH_3, F) is not as clear-cut. The steric requirements of the linear nitrile group are small. It has been shown previously that nucleophilic attack at C_2 in 3-cyanopyridinium salts[15] or at the C_2 proton in 3-cyanopyridine methiodide[16] is faster than the corresponding attack at C_6. This is now also seen to be the case in the acylamination. The steric effect of the carbomethoxyl group is much larger, which could account for the predominant attack at C_6 in this case. A similar re-

versal was observed in the alkaline ferricyanide oxidation of 3-cyano- and 3-carbomethoxypyridinium salts.[15b] A major problem in the interpretation of these latter isomer ratios is the formation of substantial amounts of the 5-chloro derivatives (**5b** and **5c**) in these reactions, since it is not known whether they arise intra- or intermolecularly by the attack of chloride selectively at C_3 or C_5 of the 1,2-dihydropyridine intermediate (Scheme I). Further discussion of these is therefore not warranted until more is known about the mechanism of chlorination. The orientation with the 3-fluoropyridine derivative is difficult to rationalize simply. A fluorine substituent is electron withdrawing in the ground state (σ_p^n = +0.062), and fluorine is smaller than methyl so that its steric effect should not be of consequence. A small repulsive influence by the electronegative fluorine upon the nucleophile approaching C_2 could explain the isomer ratio, though other factors may well come into play.

Experimental Section

Reactants and solvents were purified prior to use either by recrystallization or distillation. Solvents were dried and distilled prior to use. Thus, all halocarbon solvents were boiled under reflux for 12 hr over phosphorus pentoxide and then distilled. Anhydrous diethyl ether was used directly from freshly opened cans. Tetrahydrofuran was purified by distillation from calcium hydride and then from lithium aluminum hydride. Light petroleum refers to that fraction with a boiling range of 60–110°, unless specified otherwise.

All nuclear magnetic resonance spectra were determined using a Varian Associates Model HA-100 spectrometer. Mass spectra were recorded on a C. E. C. Model 21-104 spectrometer, usually at an ionizing voltage of 70 eV. Infrared spectra were recorded on a Perkin-Elmer Model 337 spectrometer. Solid compounds were run as KBr disks while liquids were run as liquid films. Each spectrum was calibrated using polystyrene as a reference at 1944 and 906 cm^{-1}. Melting points are uncorrected. Gas chromatographic analyses were carried out using either a Varian Associates Model 200 or Model 1700 gas chromatograph with helium as the carrier gas. They were performed using one or, in some cases, both sets of conditions described below, using the internal standard technique.

(A) The analysis was performed using a Varian Aerograph Model 200 gas chromatograph equipped with dual columns (7 ft × 3/16 in.) packed with 20% SE-30 on Gas-Chrom Q (60–100 mesh).

(B) The analysis was performed using a Varian Aerograph Model 1700 gas chromatograph equipped with dual columns (6 ft × 3/16 in.) packed with 20% OV-17 on Gas-Chrom Q (60–100 mesh).

In all cases each peak was identified by collecting the compound as it eluted from the chromatograph and comparing its infrared spectrum with that of an authentic sample. The per cent yields are based on starting imidoyl chloride.

The aromatic amine oxides were prepared using either peracetic or permaleic acid. The latter procedure is illustrated below for the preparation of 3-fluoropyridine 1-oxide. The *N*-oxides were azeotroped if necessary, distilled, and redistilled just before use to ensure that they were completely anhydrous.

3-Fluoropyridine 1-Oxide. 3-Fluoropyridine (7.0 g, 0.072 mol) was added to a stirred solution of permaleic acid (9.9 g, 0.075 mol, from maleic anhydride and 90% H_2O_2) in $CHCl_3$ (100 ml) at 0°. The mixture was stirred at 0° for 1 hr, then at 25° for 45 min. A white solid precipitated. A paste of K_2CO_3 and water was added and the mixture was stirred for 1 hr. The organic layer was filtered, dried (K_2CO_3), and evaporated. The residual oil was distilled, bp 78–80° (0.3 mm), to give the *N*-oxide (3.1 g, 38%), mp 63–64° (lit.[17] mp 64°).

3-*N*-Methanesulfonamidopyridine 1-Oxide. Prepared from 3-*N*-methanesulfonamidopyridine[18] and permaleic acid, it was obtained in 45% yield: mp 187–188°; mass spectrum *m/e* (rel intensity) 189 (6.4), 188 (52, M^+), 187 (100, $M - 1^+$).

Anal. Calcd for $C_6H_8N_2O_3S$: C, 38.30; H, 4.26. Found: C, 38.48; H, 4.46.

N-Phenylbenzimidoyl chloride was prepared from benzanilide (0.058 mol) and thionyl chloride (0.10 mol) and was distilled before use. It had bp 104–107° (0.25 mm) [lit.[19] bp 174–176° (12 mm)].

Authentic samples of 2-anilinopyridines (Table I lists the new ones) were prepared either from the 2-chloro- or 2-bromopyridine derivative and aniline. The following are typical examples.

2-Anilino-3-methylpyridine. A mixture of 2-bromo-3-methylpyridine[20] (6.63 g, 0.039 mol) and freshly distilled aniline (3.58 g, 0.039 mol) was heated at 180° for 30 min. The gum was dissolved in 2 *N* HCl (50 ml), cooled in ice, and basified with 6 *N* NaOH to give dark crystals. Chromatography on silica gel (200 g, 4 ft × 1.5 in.) and elution with chloroform gave pale yellow crystals of the amine (3.81 g, 52%): mp 123–125° (from benzene); ir (KBr) 3305 cm^{-1} (NH); nmr ($CDCl_3$) δ 7.97 (br d, 1 H, $J_{5,6}$ = 5 Hz, $J_{4,6}$ not resolved, H_6), 7.30 (m, 5 H, ArH), 6.81 (t, 1 H, $J_{4,5}$ = 7 Hz, $J_{4,6}$ not resolved, H_4), 6.53 (d or d, 1 H, $J_{4,5}$ = 7, $J_{5,6}$ = 5 Hz, H_5), 6.0 (br s, 1 H, NH), 2.11 (s, 3 H, CH_3).

2-Anilino-5-methylpyridine was similarly prepared from 2-bromo-5-methylpyridine: nmr ($CDCl_3$) δ 7.98 (br s, 1 H, H_6), 7.49 (br s, 1 H, NH exchangeable), 7.32–6.84 (m, 7 H), 6.76 (d, 1 H, $J_{3,4}$ = 8 Hz, H_3), 2.14 (s, 3 H, CH_3).

2-Anilino-3-fluoropyridine. A mixture of 2-chloro-3-fluoropyridine[21] was heated with aniline as above and the products were chromatographed. Elution with $CHCl_3$ gave the product (9%): mp 69–70° (from light petroleum); ir (KBr) 3440 cm^{-1} (NH); nmr ($CDCl_3$) δ 7.94 (d of d, 1 H, $J_{5,6}$ = 5, $J_{4,6}$ = 0.8 Hz, H_6), 7.67–7.45 (m, 2 H), 7.35–7.10 (m, 3 H), 7.09–6.80 (m, 2 H), 6.71–6.45 (m, 1 H, H_5).

The authentic *N*-benzoyl derivatives were made by Schotten–Baumann benzoylation of the secondary amines. An example is given below.

2-(*N*-Benzoylanilino)-3-methoxypyridine. Benzoyl chloride (0.14 g) was added to a solution of 2-anilino-3-methoxypyridine (0.20 g) in pyridine (2 ml). The solution was heated at 90° for 1 hr, water (10 ml) was added, and the mixture was cooled in the refrigerator overnight to give the *N*-benzoyl derivative (0.12 g, 40%), mp 177–178°, identical with the material obtained from 3-methoxypyridine 1-oxide as described below.

2-Bromo-5-fluoropyridine. Ethyl nitrite (0.12 mol) was slowly bubbled into a solution of 5-amino-2-bromopyridine (7.3 g, 0.042 mol) in ethanol (40 ml) and tetrafluoroboric acid (37%, 24 ml) at 0° over a 10-min period. The diazonium salt precipitated. Ether (60 ml) was added, and the salt was filtered and washed with cold ether and then with light petroleum. The damp diazonium salt was suspended in *n*-heptane (50 ml) and the mixture was boiled under reflux for 4 hr; concentrated HCl (10 ml) was added and the solvent was evaporated *in vacuo*. The dark oily residue was basified with 30% aqueous NaOH and then steam distilled to give 2-bromo-5-fluoropyridine (1.1 g, 15%): bp 80–83° (44 mm): mp 27.5–29°; nmr ($CDCl_3$) δ 8.21 (d, 1 H, $J_{4,6}$ = 3 Hz), 7.53–7.11 (m, 2 H); mass spectrum *m/e* (rel intensity) 177 (46), 175 (48, M^+), 96 (100).

Anal. Calcd for C_5H_3BrFN: C, 34.11; H, 1.71. Found: C, 34.12; H, 1.69.

Reaction of 3-Methylpyridine 1-Oxide with *N*-Phenylbenzimidoyl Chloride. Preparative Run. A solution of 3-methylpyridine 1-oxide (3.30 g, 0.03 mol) in dry 1,2-dichloroethane (50 ml) was added to a freshly prepared solution of *N*-phenylbenzimidoyl chloride (3.23 g, 0.015 mol) in dry 1,2-dichloroethane (30 ml). The mixture was boiled under reflux for 6 hr and cooled in an ice bath, and the precipitated 3-methylpyridine 1-oxide hydrochloride (1.9 g, 85%) was filtered. Its infrared spectrum was identical with that of an authentic sample. The filtrate was evaporated and the residue was chromatographed on a column of silica gel (200 g, 4 ft × 1.5 in.) using light petroleum–acetone (9:1 v/v) as the eluent. Benzanilide (0.10 g, 30%), mp 160–163° (lit.[22] mp 162–163°), eluted first. Its infrared spectrum was identical with that of an authentic sample. The second product, which overlapped somewhat with the third, was recrystallized from ethanol and gave **2-(*N*-benzoylanilino)-5-methylpyridine (4a,** 1.95 g, 47%): mp 104–105°; ir (KBr) 1660 cm^{-1} (amide C=O); nmr ($CDCl_3$) δ 7.93 (br d, 1 H, $J_{4,6}$ = 2 Hz, H_6), 7.44–6.88 (m, 12 H), 2.15 (s, 3 H, CH_3); mass spectrum *m/e* (rel intensity) 288 (4, M^+), 105 (100, $PhCO^+$); identical (ir, melting point) with an authentic sample (Table I).

The last product to elute was **2-(*N*-benzoylanilino)-3-methylpyridine (3a,** 0.043 g, 1%): mp 122–123°; ir (KBr) 1650 cm^{-1} (amide C=O); nmr ($CDCl_3$) δ 8.25 (d of d, 1 H, $J_{5,6}$ = 4.2, $J_{4,6}$ = 1.5 Hz, H_6), 7.57–7.35 (m, 3 H), 7.27–6.97 (m, 9 H), 2.24 (s, 3 H, CH_3); mass spectrum *m/e* (rel intensity) 288 (9, M^+), 260 (5.5), 105 (100); identical with an authentic sample.

The quantitative analyses (results summarized in Table II) were carried out after heating 2 equiv of the *N*-oxide with 1 equiv of *N*-phenylbenzimidoyl chloride for 14–16 hr. A typical example is given below.

Reaction of 3-Methylpyridine 1-Oxide with *N*-Phenylbenzimidoyl Chloride. Quantitative Analysis. A solution of 3-methylpyridine 1-oxide (2.30 g, 0.024 mol) and *N*-phenylbenzimidoyl chloride (2.303 g, 0.0107 mol) in 1,2-dichloroethane (15 ml) was boiled under reflux for 14 hr. The mixture was cooled, transferred quantitatively to a volumetric flask (25 ml), and made up to volume with 1,2-dichloroethane. Exactly 2.5 ml of this solution was added to *n*-octadecane (0.0754 g, 2.97×10^{-4} mol), and the solution was extracted with aqueous potassium bicarbonate, dried, and analyzed by gas chromatography under both conditions A and B.

Reaction of Methyl Nicotinate 1-Oxide with *N*-Phenylbenzimidoyl Chloride. Preparative Run. A solution of 3-carbomethoxypyridine 1-oxide[23] (6.0 g) in dry 1,2-dichloroethane (70 ml) was added in one portion to a solution of *N*-phenylbenzimidoyl chloride (4.25 g) in 1,2-dichloroethane (30 ml). The mixture was boiled under reflux for 6 hr, the solvent was evaporated *in vacuo*, and the residue was chromatographed on silica gel (350 g, 6 ft × 1.5 in.) using light petroleum–acetone (9:1 v/v) as eluent. The first product to elute was 5-carbomethoxy-3-chloropyridine (0.31 g, 18%): mp 86–87° (from light petroleum) (lit.[24] mp 88–89°); ir (KBr) 1735 cm^{-1} (ester C=O); nmr ($CDCl_3$) δ 9.03 (d, 1 H, $J_{4,6}$ = 2 Hz, H_6), 8.69 (d, 1 H, $J_{2,4}$ = 2.2 Hz, H_2), 8.21 (t, 1 H, H_4), 3.92 (s, 3 H, CH_3); mass spectrum *m/e* (rel intensity) 173 (20), 171 (55, M^+), 140 (100); identical (ir, melting point) with an authentic sample. Benzanilide (1.96 g, 51%), mp 162–163°, eluted next. Overlapping slightly with benzanilide, **2-(*N*-benzoylanilino)-5-carbomethoxypyridine (4b,** 1.79 g, 28%), followed: mp 116–117° (ethanol); ir (KBr) 1735 (ester C=O), 1685 cm^{-1} (amide C=O); nmr ($CDCl_3$) δ 8.85 (d, 1 H, $J_{4,6}$ = 2 Hz, H_6), 8.14 (d of d, 1 H, $J_{3,4}$ = 8.5, $J_{4,6}$ = 2 Hz, H_4), 7.54–7.02 (m, 11 H, aromatic protons), 3.81 (s, 3 H, ester CH_3); mass spectrum *m/e* (rel intensity), 332 (5.6, M^+), 227 (5.6), 105 (100); identical with an authentic sample (Table I).

When a portion of the original reaction mixture was subjected to gas chromatographic analysis, a small additional peak was found. The compound was collected (an oil) and found to be **2-anilino-3-carbomethoxypyridine** (*ca.* 1%): ir (KBr) 3340, 3295 (NH), 1695 cm^{-1} (C=O); nmr (CCl_4) δ 10.15 (br s, 1 H, NH), 8.28 (d of d, 1 H, $J_{5,6}$ = 5, $J_{4,6}$ = 2 Hz, H_6), 7.96 (d of d, 1 H, $J_{4,5}$ = 8, $J_{4,6}$ = 2 Hz, H_4), 7.64 (br d, 2 H, J = 7 Hz, ortho protons on phenyl ring), 7.16 (br t, 2 H, J = 7 Hz, meta protons on phenyl ring), 6.85 (br t, 1 H, J = 7 Hz, para proton on phenyl ring), 6.44 (d of d, 1 H, $H_{4,5}$ = 8, $J_{5,6}$ = 5 Hz, H_5), 8.70 (s, 3 H, ester CH_3); mass spectrum *m/e* (rel intensity) 229 (11), 228 (67, M^+), 227 (75), 168 (100). It was identical with an authentic sample prepared from 2-anilinonicotinic acid[25] and diazomethane. The oil formed a picrate, mp 192–194° (ethanol).

Anal. Calcd for $C_{13}H_{12}N_2O_2 \cdot C_6H_3N_3O_7$: C, 49.89; H, 3.28. Found: C, 49.86; H, 3.48.

The crude reaction mixture for another run was hydrolyzed with boiling 6 *N* NaOH solution (100 ml) for 3 hr, the solution was acidified with 6 *N* HCl and cooled to −10°, and the precipitate was filtered. The solid was added to an excess of a solution of diazomethane in ether and, when N_2 evolution had ceased, the solution was filtered from NaCl and subjected to gas chromatography on a 10 ft × 0.25 in. column packed with 15% Apiezon N on Anakrom at 230°. The products were collected and identified (relative retention times and ir). In order of elution these were methyl benzoate, 3-carbomethoxy-5-chloropyridine, methyl nicotinate 1-oxide, benzanilide, 2-anilino-3-carbomethoxypyridine (<1%), and 2-anilino-5-carbomethoxypyridine.

Hydrolysis of 2-(*N*-Benzoylanilino)-5-carbomethoxypyridine. A solution of 2-(*N*-benzoylanilino)-5-carbomethoxypyridine (0.234 g) in concentrated HCl (1.30 g) and methanol (6.4 g) was boiled under reflux for 12 hr, water (30 ml) was added, and the mixture was concentrated to about 15 ml. The concentrate was basified with 10% aqueous sodium bicarbonate and the resulting 2-anilino-5-carbomethoxypyridine was filtered, dried, and recrystallized from benzene (0.106 g, 66%): mp 119–120°; ir (KBr) 3250, 3195 (NH), 1710 cm^{-1} (ester C=O); nmr ($CDCl_3$) δ 8.84 (d, 1 H, $J_{4,6}$ = 2.5 Hz, H_6), 8.06 (d of d, 1 H, $J_{4,6}$ = 2.5, $J_{3,4}$ = 9 Hz, H_4), 7.88 (br s, 1 H, NH), 7.63–7.03 (m, 5 H, aromatic protons), 6.8 (d, 1 H, $J_{3,4}$ = 9 Hz, H_3), 3.85 (s, 3 H, CH_3); mass spectrum *m/e* (rel intensity) 229 (8.2), 228 (54, M^+), 277 (100); identical with an authentic sample (Table I).

Reaction of 3-Cyanopyridine 1-Oxide with *N*-Phenylbenzimidoyl Chloride. Preparative Run. A suspension of 3-cyanopyridine 1-oxide (7.55 g, 0.064 mol) in 1,2-dichloroethane (60 ml) was added to *N*-phenylbenzimidoyl chloride (7 g, 0.032 mol) and the mixture was heated under reflux for 12 hr. After cooling to room temperature, 3-cyanopyridine 1-oxide (1.6 g) precipitated. The solvent was evaporated and the residue was chromatographed on silica gel (100 g/g of solvent-free product mixture). Elution with light petroleum–acetone (9:1 v/v) gave four products. The first was 3-chloro-5-cyanopyridine (**5c,** 25%): mp 98–99° (lit.[25] mp 60°); ir (KBr) 2240 cm^{-1} (C≡N); nmr ($CDCl_3$) δ 8.77 (t, 2 H, $J \cong 1$ Hz, H_2, H_6), 7.96 (t, 1 H, $J \cong 1$ Hz, H_4); mass spectrum *m/e* (rel intensity) 140 (34), 138 (100, M^+); identical (melting point, ir) with an authentic sample. (On hydrolysis followed by esterification with diazomethane it gave methyl 3-chloro-5-pyridinecarboxylate.)

Anal. Calcd for $C_6H_3ClN_2$: C, 51.99; H, 2.09. Found: C, 52.11; H, 2.08.

Benzanilide (33%) eluted next (ir).

The third product obtained was **2-(*N*-benzoylanilino)-5-cyanopyridine (4c,** 15%): mp 155–157° (EtOH); ir (KBr) 2240 (C≡N), 1685 cm^{-1} (amide C=O); nmr ($CDCl_3$) δ 8.51 (d, 1 H, $J_{4,6}$ = 2.1 Hz, H_6), 7.86 (d of d, 1 H, $J_{4,6}$ = 2.1, $J_{3,4}$ = 9 Hz, H_4). 7.60–7.06 (m, 11 H, H_3 and phenyl protons); mass spectrum *m/e* (rel intensity) 299 (10, M^+), 194 (9.6), 105 (100).

Anal. Calcd for $C_{19}H_{13}N_3O$: C, 76.26; H, 4.27. Found: C, 76.48; H, 4.58.

The fourth product, which overlapped slightly with the third, was **2-(*N*-benzoylanilino)-3-cyanopyridine (3c,** 30%): mp 139–141° (EtOH); ir (KBr) 2240 (C≡N): 1655 cm^{-1} (amide C=O); nmr ($CDCl_3$) δ 8.45 (d of d, 1 H, $J_{5,6}$ = 5, $J_{4,6}$ = 2 Hz, H_6), 7.85 (d of d, 1 H, $J_{4,5}$ = 8, $J_{4,6}$ = 2 Hz, H_4), 7.76–7.58 (m, 2 H, H_5 and phenyl proton in the deshielding region of C≡N), 7.27–6.98 (m, 9 H, phenyl protons); mass spectrum *m/e* (rel intensity) 299 (7.5, M^+), 105 (100).

Anal. Calcd for $C_{19}H_{13}N_3O$: C, 76.26; H, 4.37. Found: C, 76.44; H, 4.59.

Hydrolysis products of the amides were obtained if the reaction mixture was resolved by chromatography on alumina (100 g/g of solvent-free product mixture). Thus, from an alumina column using benzene as eluent were obtained the following compounds (in order of their elution): 3-chloro-5-cyanopyridine, mp 97–98°; **2-anilino-3-cyanopyridine** [mp 131–132° (EtOH); ir (KBr) 3340, 3250 (NH), 2225 cm^{-1} (C≡N); nmr ($CDCl_3$) δ 8.27 (d of d, 1 H, $J_{5,6}$ = 5, $J_{4,6}$ = 2 Hz, H_6) 7.65 (d of d, 1 H, $J_{4,6}$ = 2, $J_{4,5}$ = 7.8 Hz, H_4), 7.59–6.92 (m, 6 H, phenyl and NH), 6.65 (d of d, 1 H, $J_{5,6}$ = 5, $J_{4,5}$ = 7.8 Hz, H_5); mass spectrum *m/e* (rel intensity) 195 (45, M^+), 194 (85), 105 (100)].

Anal. Calcd for $C_{12}H_9N_3$: C, 73.33; H, 5.13. Found: C, 73.54; H, 4.89.

Benzanilide eluted third.

Eluting fourth was **2-anilino-5-cyanopyridine:** mp 180–181° (from ethanol); ir (KBr) 3245, 3190 (NH), 2220 cm^{-1} (C≡N); nmr ($CDCl_3$) δ 8.44 (d, 1 H, $J_{4,6}$ = 2 Hz, H_6), 7.62 [d of d (partially obscured by phenyl protons), 1 H, $J_{4,6}$ = 2, $J_{3,4}$ = 9 Hz, H_4], 7.60–7.04 (m, 6 H, phenyl and NH), 6.77 (d, 1 H, $J_{3,4}$ = 9 Hz, H_3); mass spectrum *m/e* (rel intensity) 195 (47, M^+), 194 (100).

Anal. Calcd for $C_{12}H_9N_3$: C, 73.33; H, 5.13. Found: C, 73.55; H, 4.92.

Hydrolysis of 2-(*N*-Benzoylanilino)-5-cyanopyridine. A solution of 2-(*N*-benzoylanilino)-5-cyanopyridine (0.10 g) in ethanol (10 ml) and water (10 ml) containing sodium hydroxide (0.40 g) was boiled under reflux for 4 hr, and the solution concentrated to *ca.* one-half of its original volume and carefully acidified with 6 *N* HCl. At pH 5–6 the solution became cloudy and when it was cooled in a methanol–ice solution (−15°) a solid precipitated. This was filtered and added to a solution of diazomethane in ether. The excess diazomethane was distilled, the remaining ether solution was dried ($MgSO_4$) and filtered, and the ether was removed *in vacuo*. The residue was recrystallized from benzene to give 2-anilino-3-carbomethoxypyridine, identical (ir, melting point) with an authentic sample (Table I).

Hydrolysis of 2-(*N*-Benzoylanilino)-3-cyanopyridine. Using a procedure identical with that described for the hydrolysis of the corresponding 2,5 isomer, **4c** was hydrolyzed and esterified. A yellow, viscous oil was obtained which could not be made to crystallize. Gas chromatography (5 ft × 0.25 in. column packed with 15% Apiezon M on Anakrom, operated at 230°) gave only one peak. The infrared spectrum of this compound was identical with

that of authentic 2-anilino-3-carbomethoxypyridine (Table I).

Similar results were obtained when 2-anilino-3- and -5-cyanopyridine were hydrolyzed and esterified with diazomethane.

Reaction of 3-Fluoropyridine 1-Oxide with *N*-Phenylbenzimidoyl Chloride. Preparative Run. A solution of 3-fluoropyridine 1-oxide (3.0 g) and *N*-phenylbenzimidoyl chloride (2.87 g) in dry 1,2-dichloroethane (50 ml) was boiled under reflux for 48 hr. The solvent was removed *in vacuo* and the residue was chromatographed on silica gel (300 g, 6 ft × 1.5 in.) using a mixture of light petroleum–acetone (9:1 v/v) as eluent. Three compounds were obtained. Benzanilide (0.30 g, 12%) eluted first. The second compound was **2-(*N*-benzoylanilino)-5-fluoropyridine (4d,** 1.72 g, 44%): mp 142–144° (from aqueous EtOH); ir (KBr) 1675 cm^{-1} (amide C=O); nmr ($CDCl_3$) δ 8.14 [br d (m on expansion), 1 H, J = 2 Hz, H_6], 7.55–6.95 (m, 12 H); mass spectrum m/e (rel intensity) 292 (3.6, M^+), 105 (100); identical with an authentic sample (Table I). The final product obtained was **2-(*N*-benzoylanilino)-3-fluoropyridine (3d,** 0.83 g, 20%): mp 123.5–124.5° (EtOH); ir (KBr) 1670 cm^{-1} (amide C=O); nmr ($CDCl_3$), δ 8.28 (q, 1 H, $J_{5,6}$ = 4.5, $J_{4,6}$ = 2 Hz, H_6), 7.56–6.0 (m, 12 H); mass spectrum (70 eV) m/e (rel intensity) 292 (9.6, M^+), 105 (100); identical with an authentic sample (Table I).

Reaction between 3-Methoxypyridine 1-Oxide and *N*-Phenylbenzimidoyl Chloride. Preparative Run. A solution of 3-methoxypyridine 1-oxide (1.5 g) in 1,2-dichloroethane (20 ml) was added to freshly distilled *N*-phenylbenzimidoyl chloride (1.13 g) in 1,2-dichloroethane (20 ml). The mixture was heated under reflux for 8 hr and the solvent was evaporated. The residue was chromatographed on a silica gel column (200 g, 4 ft × 1.5 in.) using light petroleum–acetone (9:1 v/v) as eluent. Three compounds were obtained. Benzanilide (0.26 g, 26%) eluted first. The second compound off the column was **2-(*N*-benzoylanilino)-5-methoxypyridine (4f,** 0.114 g, 7.3%): mp 102–103° (light petroleum–$CHCl_3$); ir (KBr) 1650 cm^{-1} (amide C=O); nmr ($CDCl_3$) δ 8.38 (d, 1 H, $J_{4,6}$ = 1.5 Hz, H_6), 7.85–7.30 (m, 12 H), 3.86 (s, 3 H, CH_3); mass spectrum m/e (rel intensity) 304 (4.5, M^+), 105 (100).

Anal. Calcd for $C_{19}H_{16}N_2O_2$: C, 75.00; H, 5.26. Found: C, 74.97; H, 5.40.

The final product obtained was **2-(*N*-benzoylanilino)-3-methoxypyridine (3f,** 0.784 g, 50%): mp 177–178° (from light petroleum–chloroform); ir (KBr) 1650 cm^{-1} (C=O); nmr ($CDCl_3$) δ 8.34 (overlapping d of d, 1 H, $J_{5,6}$ = 2.8 Hz, H_6), 7.85–7.29 (m, 12 H), 3.71 (s, 3 H, CH_3); mass spectrum m/e (rel intensity) 304 (4.5, M^+), 105 (100); identical with an authentic sample (Table I).

Reaction of 3-(*N*-Methanesulfonamido)pyridine 1-Oxide with *N*-Phenylbenzimidoyl Chloride. To a solution of freshly distilled *N*-phenylbenzimidoyl chloride (1.2 g) in 1,2-dichloroethane (50 ml) was added 3-(*N*-methanesulfonamido)pyridine 1-oxide (1.1 g) and the mixture was heated under reflux for 13 hr. The solution was allowed to cool to room temperature, and it was then chromatographed on a column of silica gel (300 g, 6 ft × 1.5 in.) using chloroform as eluent. The first product was benzanilide (0.30 g, 26.6%). The second compound obtained was **2,3-diphenyl-3*H*-imidazo[4,5-*b*]pyridine** (0.612 g, 40%): mp 159.5–160° (light petroleum); ir (KBr) no C=O, NH, or S=O bands; nmr ($CDCl_3$) δ 8.33 (d of d, 1 H, $J_{5,6}$ = 5, $J_{4,6}$ = 1.7 Hz, H_6), 8.10 (d of d, 1 H, $J_{4,5}$ = 8, $J_{4,6}$ = 1.7 Hz, H_4), 7.64–7.10 (m, 11 H); mass spectrum (70 eV) m/e (rel intensity) 272 (6.4), 271 (45), 270 (72), 77 (100); mass spectrum (10 eV) m/e (rel intensity) 272 (20), 271 (100), 270 (12); identical with an authentic sample.

Anal. Calcd for $C_{18}H_{13}N_3$: C, 79.70; H, 4.80. Found: C, 79.50; H, 4.91.

The third compound to elute was **2-chloro-5-(*N*-methanesulfonylamino)pyridine (5e,** 0.12 g, 10%): mp 131–132° (from water); ir (KBr) 3125 (NH), 1155 cm^{-1} (S=O); nmr (acetone-d_6) δ 8.86 (br s, 1 H, NH, exchangeable with D_2O), 8.31 (d, 1 H, $J_{4,6}$ = 3 Hz, H_6), 7.77 (d of d, 1 H, $J_{4,6}$ = 3, $J_{3,4}$ = 8.5 Hz, H_4), 7.37 (d, 1 H, $J_{3,4}$ = 8.5 Hz, H_3), 3.05 (s, 3 H, CH_3); mass spectrum m/e (rel intensity) 208 (9.7), 207 (3.2), 206 (24), 129 (29), 127 (100); identical with an authentic sample prepared from 5-amino-2-chloropyridine[26] and methanesulfonyl chloride in pyridine (69% yield).

Anal. Calcd for $C_6H_7ClN_2O_2S$: C, 34.87; H, 3.39. Found: C, 34.96; H, 3.59.

The last compound to elute was **2-(*N*-benzoylanilino)-5-(*N*-methanesulfonylamino)pyridine (4e,** 0.779 g, 37.5%): mp 175.5–177° (EtOH); ir (KBr) 3150 (NH), 1650 (C=O), 1155 cm^{-1} (S=O); nmr ($CDCl_3$) δ 8.13 (d, 1 H, $J_{4,6}$ = 2.8 Hz, H_6), 7.93 (br s, 1 H, NH, exchangeable with D_2O), 7.54 (d of d, 1 H, $J_{4,6}$ = 2.8, $J_{4,5}$ = 8.5 Hz, H_4), 7.50–6.94 (m, 11 H), 2.90 (s, 3 H, CH_3); mass spectrum m/e (rel intensity) 367 (1.7), 366 (7.3), 105 (100).

Anal. Calcd for $C_{19}H_{17}N_3O_3S$: C, 62.13; H, 4.36. Found: C, 61.98; H, 4.61.

2,3-Diphenyl-3*H*-imidazo[4,5-*b*]pyridine. A solution of 3-amino-2-anilinopyridine[27] (0.50 g) and benzoyl chloride (0.39 g) in pyridine (10 ml) was boiled under reflux for 4 hr and cooled, and water (50 ml) was added. The precipitate was filtered and recrystallized from light petroleum to give 2,3-diphenyl-3*H*-imidazo[4,5-*b*]pyridine (0.48 g, 63%), identical (melting point, ir) with the sample obtained above.

Acknowledgments. This work was carried out with the financial support of an NIH grant (GM 16626) for which we are grateful. We also wish to thank Reilly Tar and Chemical Corp. for the gift of pyridine derivatives.

Registry No.—**1a,** 1003-73-2; **1b,** 15906-18-7; **1c,** 14906-64-0; **1d,** 695-37-4; **1e,** 51269-71-7; **1f,** 14906-61-7; **2,** 4903-36-0; **3a,** 51269-72-8; **3c,** 51269-73-9; **3d,** 51269-74-0; **3f,** 51269-75-1; **4a,** 51269-76-2; **4b,** 51269-77-3; **4c,** 34941-75-8; **4d,** 51269-78-4; **4e,** 51269-79-5; **4f,** 51269-80-8; **5b,** 51269-81-9; **5c,** 51269-82-0; **5e,** 51269-83-1; **7** (R = 3-Me), 43191-22-6; **7** (R = 5-Me), 43191-23-7; **7** (R = 3-CO_2Me), 51269-84-2; **7** (R = 3-CO_2Me) picrate, 51269-85-3; **7** (R = 5-CO_2Me), 51269-86-4; **7** (R = 3-F), 51269-87-5; **7** (R = 5-F), 51269-88-6; **7** (R = 3-OMe), 51269-89-7; **7** (R = 3-OMe) picrate, 51269-90-0; **7** (R = 3-CN), 16344-18-6; **7** (R = 5-CN), 15871-89-3; **9,** 51269-91-1; 3-fluoropyridine, 372-47-4; 3-*N*-methanesulfonamidopyridine, 51269-92-2; benzanilide, 93-98-1; thionyl chloride, 7719-09-7; 2-bromo-3-methylpyridine, 3430-17-9; aniline, 62-53-3; 2-bromo-5-methylpyridine, 3510-66-5; 2-chloro-3-fluoropyridine, 17282-04-1; benzoyl chloride, 98-88-4; 2-bromo-5-fluoropyridine, 41404-58-4; 5-amino-2-bromopyridine, 13534-97-9.

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1,4-Benzodioxanes. I. A Synthesis Involving the Reaction of α-Halo Michael Acceptors with Catechol

A. R. Martin,* S. K. Mallick, and J. F. Caputo

College of Pharmacy, Washington State University, Pullman, Washington 99163

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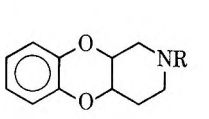
α-Halo Michael acceptors react with catechol in aprotic solvents in the presence of potassium carbonate to form 2-substituted 1,4-benzodioxanes. Cis β-alkyl and β-alicyclic α-halo Michael acceptors yield primarily cis 2,3-disubstituted 1,4-benzodioxanes, whereas trans 2,3-disubstituted isomers predominate when catechol is treated with trans β-alkyl α-halo Michael acceptors. It is therefore inferred that the reaction proceeds *via* a cis Michael addition of catechol monoanion, followed by intramolecular nucleophilic displacement of halide from the newly generated sp^3 α carbon by the remaining catechol oxygen. Ethyl 1,4-bromobut-2-enoate, formed by isomerization of ethyl 2-bromobut-2-enoate during the course of the reaction of the latter with catechol, is believed to be the source of the isomeric ethyl 1,4-benzodioxanyl-2-acetate isolated as a minor product.

2-Substituted 1,4-benzodioxanes represent a series of compounds of considerable medicinal importance.[1-5] As a part of a program directed toward investigation of relationships between conformational and pharmacological properties of this class of compounds, the preparation of tricyclic derivatives of types **1** and **2** was desired. General methods for the synthesis of 1,4-benzodioxanes, *e.g.*, reaction of catechol with vicinal dibromide[6] or an epihalohydrin,[7] did not appear to be efficient procedures for preparing tricyclic analogs. Hence, the reactions of catechol with α-halo Michael acceptors **3**–**7** were investigated.[8] In this report the scope, stereochemical consequences, and probable mechanism of this general reaction are described.

Some time ago, Koo, *et al.*,[6a] reported the "condensation" of catechol with ethyl 2,3-dibromopropanoate (**8**) in the presence of anhydrous potassium carbonate to form ethyl 1,4-benzodioxane-2-carboxylate (**10**). Similarly, a mixture of **12a** and **12b** of undetermined isomer composition was later obtained from the reaction of catechol with ethyl 2,3-dibromobutanoate (**9**).[6b] It seemed likely to us that, under the conditions employed for these reactions (K_2CO_3, 55°, 16 hr), elimination of hydrogen bromide from **8** and **9** to give the α-bromo olefinic esters **3** and **5** would occur more rapidly than would nucleophilic displacement of bromide ion by catechol monoanion. Indeed, when **8** (a mixture of diastereoisomers) was allowed to react under the above conditions for 12 hr in the absence of catechol, ethyl *cis*-2-bromobut-2-enoate (**5a**) was obtained in good yield. Less than 5% of the trans isomer **5b** was obtained. Thus, it is very probable that **10** and **12** are formed from the α-halo Michael acceptors **3** and **5a**, respectively, in the reactions reported by Koo, *et al.*



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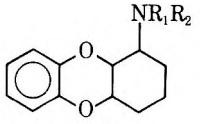

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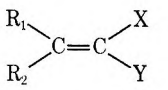
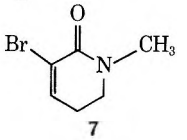
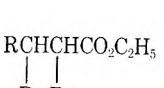
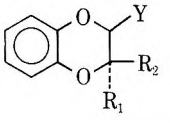


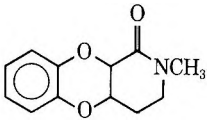


7

3, $R_1 = R_2 = H$; X = Br; Y = CO_2Et
4, $R_1 = R_2 = H$; X = Cl; Y = CN
5a, $R_1 = H$; $R_2 = CH_3$; X = Br; Y = CO_2Et
b, $R_1 = CH_3$; $R_2 = H$; X = Br; Y = CO_2Et
6, $R_1 = R_2 = CH_3$; X = Br; Y = CO_2Et





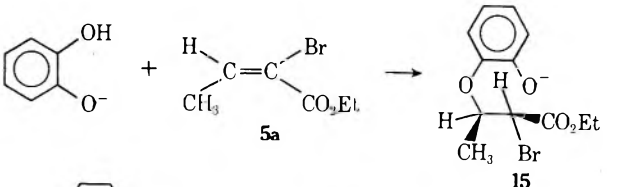


8, R = H
9, R = CH_3

10, $R_1 = R_2 = H$; Y = CO_2Et
11, $R_1 = R_2 = H$; Y = CN
12a, $R_1 = H$; $R_2 = CH_3$; Y = CO_2Et
b, $R_1 = CH_3$; $R_2 = H$; Y = CO_2Et
13, $R_1 = R_2 = CH_3$; Y = CO_2Et

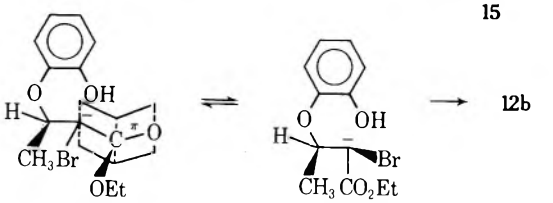
14a, cis
b, trans

Reference to per cent yield data (Table I) provides an indication of the scope of the title reaction. Increasingly poorer yields were obtained as the size and number of β substituents in the α-halo Michael acceptor were increased. Of perhaps greater interest are the stereochemical consequences of the reaction investigated by nmr analysis of product ratios (Table I) obtained from the reactions of catechol with **5a**, **5b**, and **7**. It is noted that reactions of the cis Michael acceptors **5a** and **7** with catechol yield predominantly the thermodynamically less stable *cis*-1,4-benzodioxanes **12a** and **14a**, respectively, while the trans isomer **5b** gives primarily the *trans*-1,4-benzodioxane **12b**. These observations best support the hypothesis that the reaction proceeds primarily by a cis Michael addition of catechol anion (*e.g.*, to **5a**) to form the intermediate **15**, wherein a proton (from catechol) is added from the same side, followed by intramolecular nucleophilic displacement of bromide ion to form **12a** as shown. Inversion of the intermediate carbanion (**16** ⇌ **17**), prior to proton attack, accounts for the **12b** formed.



5a

15



16 **17** **12b**

The analogous reaction of catechol with the ring compound **7**, wherein the barrier to inversion of the intermediate carbanion should be much higher than in the acyclic case, favors the cis isomer over the trans isomer **14b** by a 20:1 ratio. Comparatively few studies relevant to stereochemical aspects of the Michael reaction have been reported.[9] The general consensus of those investigations involving six-membered ring Michael acceptors[9-12] supports

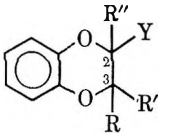
Table I
1,4-Benzodioxanes. Yields and Product Ratios

Michael acceptor	Principal product(s)	Yield, %
3	**10**	74
4	**11**	86
5a	60% **12a**, 40% **12b**	28
5b	28% **12a**, 72% **12b**	32
6	**13?**	<5
7	95% **14a**, 5% **14b**	17

overlap should otherwise be greater in **19** than in **18**), thus reducing the contribution of maximal overlap to stabilizing the intermediate carbanion.

In addition to **12a** and **12b**, relatively small amounts (10–20%) of the isomeric ester **20** (*m/e* 222) were isolated in reactions of catechol with either **5a** or **5b**. It is assumed that **20** arises from the reaction of catechol with ethyl 4-bromo-2-butenoate (**21a**), the latter being formed by aniontropic 1,3 shift of halide involving **21b**,[17] formed by tautomerism of **5a** (or **5b**).[18] Not surprisingly, **20** became

Table II
Nmr Data for 1,4-Benzodioxane Ring Protons (in $DCCl_3$)



10, R = R′ = H; Y = CO_2Et $\delta H_2 = 4.50$ $J = 3.5$ Hz; $\delta H_3 = 4.06$

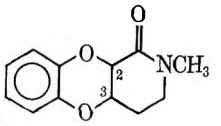
11, R = R′ = H; Y = CN $\delta H_2 = 4.91$ $J_{trans} = 3.8$ Hz; $\delta H_3 = 4.33$ $J_{cis} = 2.7$ Hz; $J_{3,3'} = -11.8$ Hz

12a, R = H; R′ = CH_3; Y = CO_2Et $\delta H_2 = 4.67$ $J = 2.6$ Hz; $\delta H_3 \cong 4.5$

12b, R = CH_3; R′ = H; Y = CO_2Et $\delta H_2 = 4.41$ $J = 5.5$ Hz; $\delta H_3 \cong 4.5$

20, R = R′ = H; Y = CH_2CO_2Et $\delta H_2 = 4.62$ $J_{2,3} = 7.08$ Hz; $\delta H_3 = 4.01$ $J_{2,3'} = 2.21$ Hz; $\delta H_3' = 4.31$ $J_{3,3'} = -12.53$ Hz

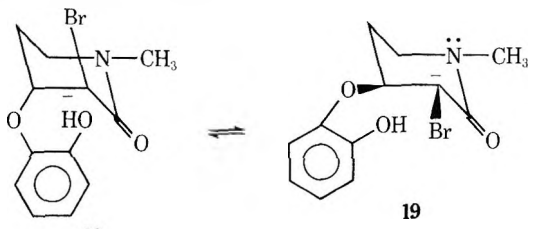
22, R = R′ = H; R″ = CH_3; Y = CH_2CO_2Et $\delta H_3 = 3.78$ $J_{3,3'} = 11.4$ Hz; $\delta H_{3'} = 4.11$



14a $H_2 = 4.66$ $J = 2.8$ Hz; $H_3 = 4.57$

14b $H_2 = 4.35$ $J = 9.5$ Hz; $H_3 = 4.18$

the view that the reaction is characterized by a trans antiparallel attack of the donor to the predominant conformation of the Michael acceptor, wherein both the attacking nucleophile and the proton enter from the axial side. It must be emphasized that in each of these cases the reactions were performed in protic solvents. Thus, the addition of a proton (from solvent) occurs most favorably from the least hindered axial side. Michael reactions involving diprotic donors (*e.g.*, catechol) carried out in aprotic solvents (*e.g.*, acetone, dioxane) appear to represent a special case in which the intramolecular addition of the proton to the equatorial face of the intermediate carbanion is favored. In the case of **7**, equatorial attack of a proton to conformer **18** would be favored over axial attack to conformer **19**, since the latter is destabilized by steric and dipo-



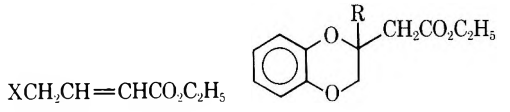
18 19

lar 1,2 interaction[13,14] of the carbonyl oxygen and the equatorial bromine atoms and (possibly) a 1,3 interaction between the carbanion and nitrogen lone pairs.[15,16] Furthermore, amide resonance may effectively compete with delocalization of the carbanion into the carbonyl group (π

the major product when either potassium iodide or bromide were added to the reaction mixture. Furthermore, direct reaction of catechol with **21a** gave good yields of **20**. Similarly, the isomeric ester **22** (not the expected **13**) was obtained when catechol was treated with ethyl 2-bromo-3-methyl-2-butenoate in the presence of K_2CO_3 and KI (thus, the reported preparation of **13** *via* the reaction of catechol with ethyl α,β-dibromovalerate by Augstein, *et al.*,[4] is no doubt in error).

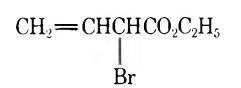
Yet a fourth compound, the lactone **23**, was obtained as the major product when catechol was treated with **5a** or **5b** at 25° with KI present. No **23** was isolated when the halide was omitted from the reaction. It was concluded, therefore, that halide ion facilitates isomerization of the double bond to the β,γ position to give **21b**. Nucleophilic attack at the highly activated α carbon by catechol, followed by intramolecular transesterification of the carbethoxy group by the remaining catechol oxygen and migration of the double bond into conjugation with the lactone carbonyl group, then provides **23** (it is entirely possible that transesterification precedes double-bond migration and nucleophilic attack, of course). The geometry of **23**, which according to its nmr spectrum, melting point, and tlc behavior appears to be a single compound, has not been established. Catalytic reduction of **23** gave 3-ethyl-2-oxo-1,4-benzodioxane, confirming that **23** is not the isomeric seven-membered ring isomer.

Proton magnetic resonance data for the 1,4-dicxane ring protons of the compounds prepared are listed in Table II.

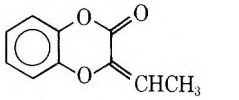


21a, X = Br or I

20, R = H
22, R = CH_3



21b



23

Although approximate coupling constants for the tricyclic isomers **14a** and **14b** had previously been obtained from Eu(fod)$_3$-shifted 60-MHz spectra,[19] accurate $J_{2,3}$ and δ values required the use of 220-MHz spectra for resolution of 2 H and 3 H resonances. $J_{2,3}$ values for **14a** and **14b** provide a reasonable standard for J_{ae} (average) and J_{aa} in 1,4-benzodioxanes and are in good agreement with values reported by previous workers.[20-23] Mixtures of 2-carbethoxy-3-methyl-1,4-benzodioxanes **12a** and **12b** were not separated, but their ratios were estimated by both integration of the ring methyl protons in Eu(fod)$_3$-shifted spectra and the sums of peak heights for the 2 H ring doublets. The ring protons of **20** form the AA'B part of an AA'BXX' spectrum. This five-spin system was subjected to computer analysis using the LAOCOON III program.

Experimental Section

Nmr spectra were determined on Varian T-60 and HA-100 spectrometers and, in the case of **12a** and **12b** (mixtures), **14a**, and **14b**, an HR-220 spectrometer in $CDCl_3$ with tetramethylsilane as an internal standard. Melting points were obtained using a Thomas-Hoover melting point apparatus and are corrected.

Ethyl *cis*-2-bromobut-2-enoate (5a) was obtained by refluxing a mixture of 27.4 g (0.1 mol) of ethyl 2,3-dibromobutanoate and 41.4 g (0.3 mol) of anhydrous K_2CO_3 in dry acetone under a stream of N_2 for 12 hr. After removal of the acetone (aspirator), water and methylene chloride were added to the residue. The methylene chloride was then separated and extracted, in turn, with 5% NaOH, 5% HCl, and saturated NaCl solutions, dried over anhydrous Na_4SO_4, and evaporated. Vacuum distillation of the residue gave 13.9 g (79%) of **5a**: bp 83–84° (20 mm) [lit.[24] bp 82–83° (20 mm)]; nmr ($CDCl_3$) δ 5.66 (q, 1, J = 7.1 Hz, CH=C), 4.43 (q, 2, J = 8.4 Hz, OCH_2), 1.93 (d, 3, J = 7.1 Hz, C=CCH_3), 1.33 (t, 3, J = 8.4 Hz, CH_3).

Ethyl *trans*-2-bromobut-2-enoate (5b) was prepared by refluxing 27.4 g (0.1 mol) of ethyl 2,3-dibromobutanoate and 12.7 g (0.15 mol) of freshly distilled pyridine in 100 ml of dry toluene for 8 hr. The mixture was cooled and fitered, and the filtrate was evaporated to remove the toluene and excess pyridine. The residue was taken up in methylene chloride, extracted with 5% HCl and saturated NaCl solutions, and dried over anhydrous Na_2SO_4, the methylene chloride was evaporated, and the residue was distilled, giving 2.5 g (14%) of **5b**, bp 67–70° (14 mm), and 12.8 g (72%) of **5b**: bp 78–79° (14 mm) [lit.[25] bp 78–79° (14 mm)]; nmr ($CDCl_3$) δ 6.60 (q, 1, J = 7.8 Hz, CH=C), 4.25 (q, 2, J = 7.4 Hz, OCH_2), 1.93 (d, 3, J = 7.8 Hz, C=CCH_3), 1.33 (t, 3, J = 7.4 Hz, CH_3).

1-Methyl-2-piperidone was obtained by treating the sodium salt of 2-piperidone (formed by reaction of 2-piperidone with an equimolar quantity of sodium hydride) with a 10% excess of methyl iodide.

3,3-Dibromo-1-methyl-2-piperidone was prepared by treating 1-methyl-2-piperidone with bromine in the presence of phosphorus pentachloride and zinc chloride according to the procedure of Wineman, *et al.*,[26] for the α,α-dibromination of ϵ-caprolactam. Combustion data indicated that the product, mp 74–75° after several recrystallations (95% ethanol), was contaminated with traces of α-chlorinated product. It was not purified further. *Anal.* Calcd for $C_6H_9Br_2NO$: C, 26.56; H, 3.32; Br, 59.04; N, 5.16. Found: C, 28.09; H, 3.17; Br, 52.86; N, 5.42.

1-Methyl-3-bromo-1,2,5,6-tetrahydro-2(2*H*)-pyridone (7) was obtained by heating a mixture of impure 1-methyl-3,3-dibromo-2-piperidone and an equimolar quantity of anhydrous calcium carbonate in dimethylformamide at 80–85° for 20 hr. The majority of the dimethylformamide was removed by vacuum distillation at 10–15 mm and the residue was taken up in methylene chloride and extracted with water. The combined methylene chloride extracts were washed with 5% HCl and saturated NaCl solutions and dried over anhydrous Na_2SO_4. After removal of the solvent, distillation of the residue gave 7, bp 94–95° (2 mm), which solidified on standing to give brownish plates, mp 44–47° (aqueous ethanol). Combustion analysis indicated the presence of impurity, assumed to be 1-methyl-3-chloro-1,2,5,6-tetrahydro-2(2*H*)-pyridone (based on the nmr spectrum), which could not be separated by attempted fractional distillations and recrystallizations. The nmr spectrum ($CDCl_3$) of the mixture gave δ 7.01 (t, 0.67, J = 4.3 Hz, BrC=CH), 6.67 (t, 0.33, J = 4.6 Hz, ClC=CH), 3.53 (t, 2, J = 7.4 Hz, NCH_2), 3.01 (s, 3, NCH_3), 2.5 (m, 2, CH_2). *Anal.* Calcd for a mixture containing 67% C_6H_8BrNO and 33% C_6H_8ClNO: C, 41.72; H, 4.54; N, 8.11. Found: C, 41.55; H, 4.78; N, 8.29.

Reactions of catechol with α-halo Michael acceptors were carried out using essentially identical procedures in every case. Therefore, one representative example will be described in detail and only physical data for the remaining compounds will be described.

Ethyl 1,4-Benzodioxane-2-carboxylate (10). A mixture of 12 g (0.11 mol) of catechol, 17.9 (0.1 mol) of ethyl 2-bromopropenoate (3), and 41.4 g (0.3 mol) of anhydrous K_2CO_3 was refluxed in 200 ml of dry acetone for 18 hr. After the acetone was removed (aspirator) the residue was taken up in methylene chloride, extracted (in turn) with water, 5% NaOH, 5% HCl, and saturated NaCl solutions, and dried over anhydrous Na_2SO_4. Evaporation of the solvent and distillation of the residue afforded 15.4 g (74%) of **10**: bp 106–108° (0.14 mm) [lit.[6a] bp 105–107° (0.15 mm)]; nmr ($CDCl_3$) δ 6.84 (m, 4, aromatic), 4.50 (t, 1, J = 3.5 Hz, ring OCH), 4.06 (d, 2, J = 3.5 Hz, ring OCH_2), 4.23 (q, 2, J = 7.0 Hz, ester OCH_2), 1.28 (t, 3, J = 7.0 Hz, CH_3).

2-Cyano-1,4-benzodioxane (11) was obtained from the reaction of catechol with α-chloroacrylonitrile (4) in 86% yield as a solid: mp 57° (toluene–petroleum ether) [lit.[20] bp 93–94° (0.2 mm)]; nmr ($CDCl_3$) δ 6.90 (s, 4, aromatic), 4.91 (t, 1, J_{trans} = 7.8, J_{cis} = 2.7, $J_{3,3}$ = −11.8 Hz, OCH), 4.33 (d, 2, J_{trans} = 3.8, J_{cis} = 2.7, $J_{3,3}$ = −11.8 Hz, OCH_2).

Mixtures of ethyl *cis*- and *trans*-3-methyl-1,4-benzodioxane-2-carboxylate (12a and 12b) and ethyl 1,4-benzodioxanyl-2-acetate (20) were obtained under the conditions described above as follows: from ethyl 2,3-dibromobutyrate (9), 53% **12a**, 38% **12b**, and 9% **20** (30% yield); from ethyl *cis*-2-bromobut-2-enoate (**5a**), 54% **12a**, 36% **12b**, and 10% **20**; and from ethyl *trans*-2-bromobut-2-enoate (**5b**), 26% **12a**, 66% **12b**, and 8% **20**. Chromatography of the mixture obtained from **5b** on neutral alumina with benzene–dichloromethane separated **20** out as a pure fraction, but failed to separate **12a** and **12b**. Distillation of the mixture of **12a** and **12b** gave a colorless oil, bp 96–98° (0.1 mm) [lit.[6b] bp 96–97° (0.1 mm)]. In the 220-MHz nmr spectrum of the mixture, doublets were observed at δ 1.40 (J = 7.1 Hz) and 1.36 ppm (J = 7.2 Hz), respectively. Resonances of the C-3 OCH, aromatic, and ester protons for the two isomers overlapped.

Ethyl 1,4-Benzodioxanyl-2-acetate (20). A. From 5b. When catechol was treated with **5b** (or **5a**) in the presence of an equimolar quantity of KI, a 30% yield of **12a**, **12b**, and **20** was obtained in a ratio of 20% **12a** and **12b** to 80% **20**.

B. From Ethyl 4-Bromo-2-butenoate (21a). Reaction of catechol with **21a** gave an 82% yield of **20**: bp 108–110° (0.1 mm) [lit.[27] bp 168–171° (7 mm), lit.[28] mp 100–101°]; acid mp 100–101°; nmr ($CDCl_3$) δ 6.84 (m, 4, aromatic), 4.62 (m, 1, $J_{2,3}$ = 7.08, $J_{2,3}$ = 2.21, $J_{2\alpha}$ = 6.32, $J_{2\alpha}$ = 6.89 Hz, OCH), 4.01, 4.31 (m, $J_{2,3}$ = 7.08, $J_{2,3}$ = 2.21, $J_{3,3}$ = −12.53 Hz, OCH_2), 2.63, 2.77 (m, 2, $J_{2\alpha}$ = 6.32, $J_{2\alpha}$ = 6.89, $J_{\alpha,\alpha}$ = −16.03 Hz, CH_2CO), 4.21 (q, 2, J = 7.2 Hz, CH_2CH_3), 1.28 (t, 3, J = 7.2 Hz, CH_3).

Ethyl 3,3-Dimethyl-1,4-benzodioxane-2-carboxylate (13). The nmr spectrum of the residue obtained from the work-up of the reaction of catechol with ethyl 3-methyl-2-bromo-2-butenoate showed less than 5% of **13** (from aromatic and ring CH_3 absorptions). Further purification was not attempted.

Ethyl 2-Methyl-1,4-benzodioxanyl-2-acetate (22). A. From Ethyl *cis*-2-Bromobut-2-enoate (5a). Reaction of **5a** with catechol in the presence of an equimolar amount of KI gave **22** (26%), bp 120–122° (0.2 mm).

From the reaction of ethyl 4-bromo-3-methyl-2-butenoate[26] with catechol, a 78% yield of **22** was obtained: bp 121–122° (0.2 mm); nmr ($CDCl_3$) δ 3.94 (q, 2, J = −11.5 Hz, ring CH_2), 2.52 (s, 2, CH_2CO), 1.29 (s, 3, CH_3), 1.08 (t, 3, J = 7.2 Hz, ester CH_3), 0.00 (m, 4, aromatic). *Anal.* Calcd for $C_{13}H_{16}O_4$: C, 66.08; H, 6.83. Found: C, 65.92; H, 6.60.

3-Ethylidino-2-oxo-1,4-benzodioxane (23). Reaction of catechol with **5b** at 25° for 72 hr in the presence of KI gave **23** (18% yield): mp 74–75° (95% ethanol); nmr ($CDCl_3$) δ 6.99 (s, 4, aromatic), 6.29 (q, 1, J = 7.6 Hz, CH=), 1.88 (d, 3, J = 7.6 Hz, CH_3). *Anal.* Calcd for $C_{10}H_8O_3$: C, 68.18; H, 4.54. Found: C, 67.96: H, 4.51. The nmr spectrum of the crude reaction mixture indicated the presence of about 20–25% of a mixture of **12a** and **12b** and 30% of unreacted **5b**, which were removed by fractional distillation.

cis- **and** *trans*-**1-methyl-1,2,3,4,5,6-hexahydrobenzo[*b*]-*p*-dioxino[3,4-*e*]pyrid-2(2*H*)-one (14a and 14b)** were prepared by treating catechol with 1-methyl-3-bromo-1,2,5,6-tetrahydro-2(2*H*)-pyridone (7) in the usual manner. Column chromatography of the residue following work-up on neutral alumina with benzene–dichloromethane gave **14b**: mp 218° after recrystallizations from acetone; 220-MHz nmr ($CDCl_3$) δ 6.93 (m, 4, aromatic), 4.35 (d, 1, J = 9.4 Hz, C-2 OCH), 4.18 (m, 1, C-3 OCH), 3.39 (m, 2, NCH_2), 2.99 (s, 3, NCH_3), 2.45, 2.13 (m, 2, CH_2). *Anal.* Calcd for $C_{12}H_{13}NO_3$: C, 65.75; H, 5.97; N, 6.87. Found: C, 65.67; H, 5.92; N, 6.66.

Subsequent fractions gave **14a**: mp 136–137° after recrystallizations from benzene; nmr ($CDCl_3$) δ 6.93 (m, 4, aromatic), 4.66 (d, 1, J = 2.8 Hz, C-2 OCH), 4.57 (m, 1, C-3 OCH), 3.62, 3.25 (m, 2, NCH_2), 2.93 (s, 3, NCH_3), 2.37, 2.38 (m, 2, CH_2). *Anal.* Calcd for $C_{12}H_{13}NO_3$: C, 65.75; H, 5.97; N, 6.87. Found: C, 65.76; H, 5.96; N, 6.29.

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Registry No.—**3,** 5459-35-8; **4,** 920-37-6; **5a,** 51263-38-8; **5b,** 51263-39-9; **7,** 51263-41-3; **9,** 609-11-0; **10,** 4739-94-0; **11,** 1008-92-0; **12a,** 51263-58-2; **12b,** 51263-59-3; **14a,** 35528-83-7; **14b,** 35528 84-8; **20,** 51263-60-6; **21a,** 6065-32-3; **22,** 51263-61-7; **23,** 51263-62-8; 2-piperidone, 675-20-7; 1-methyl-2-piperidone, 931-20-4; 3,3-dibromo-1-methyl-2-piperidone, 49785-78-6; 1-methyl-3-chloro-1,2,5,6-tetrahydro-2(2*H*)-pyridone, 51263-48-0; catechol, 120-80-9; ethyl 4-bromo-2-methyl-2-butenoate, 51263-63-9.

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1,4-Benzoxathians. 1. Reactions of *o*-Mercaptophenol with α-Halo Michael Acceptors

A. R. Martin* and J. F. Caputo

College of Pharmacy, Washington State University, Pullman, Washington 99163

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α-Halo Michael acceptors react with *o*-mercaptophenol in the presence of potassium carbonate to form substituted 1,4-benzoxthians, wherein the S atom may be α or β to the activating function. α-S substitution predominates when there are β-alkyl substituents present in the α-halo Michael acceptor, while β-S substitution occurs when the α carbon is unsubstituted. Both α- and β-S-substituted products were obtained in the reaction of o-mercaptophenol with 3-bromo-1,2,5,6-tetrahydro-2(2*H*)-pyridone, the α-S-substituted product having a trans configuration and the β-S-substituted product a cis configuration.

As part of a continuing investigation of the base-catalyzed (anhydrous K_2CO_3) reactions of dibasic nucleophiles with α- and γ-halo Michael acceptors,[1,2] reactions of *o*-mercaptophenol with **1–5** were examined. Because of the greater nucleophilicity of sulfur as compared with oxygen and the greater acidity of thiophenols as compared with phenols,[3,4] it was anticipated that the thiophenolate anion generated in an alkaline medium would preferentially attack the double bond of an α-halo Michael acceptor. This would be followed by nucleophilic displacement of halide at the newly generated sp^3-hybridized α carbon to yield, preferentially, 1,4-benzoxathians wherein the S atom is β to the activating group. This prediction is supported by the work of Tsai, *et al.*,[5] who recently reported

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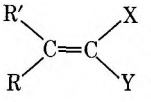
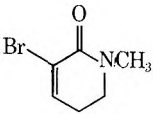
Table I
1,4-Benzoxathians. Yields and Product Ratios

Michael acceptor	Principal product(s)	Yield, %
1	**6**	78
2	**7**	90
3a	35% **8a**, 65% **8b**	44
3b	35% **8a**, 65% **8b**	54
4	**9**	65
5	80% **10a**, 20% **11b**	38

that ethyl 1,4-benzoxathian-2-carboxylate was the only isomer isolated from the reaction of ethyl 2,3-dibromopropanoate with o-mercaptophenol. Since we have strong evidence that this reaction proceeds through the intermediacy of ethyl α-bromoacrylate,[1] its selectivity is thus explained by the mechanism outlined above.

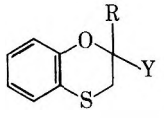
Reactions of o-mercaptophenol with the α-halo Michael acceptors **1** and **2** did, indeed, yield solely the anticipated 2-carbethoxy- and 2-cyano-1,4-benzoxathians **6** and **7**. However, when β-methyl and β,β-dimethyl substituents were present in the α-halo Michael acceptor, as in **3** and **4**, the 3-carbethoxy-1,4-benzoxathians **8** and **9** were obtained. Furthermore, the same mixture (Table I) of cis and trans 1,4-benzoxathians, **8a** and **8b**, respectively, was obtained from either **3a** or **3b**. This result contrasts with the stereoselectivity observed in reactions of catechol with **3a** and **3b**.[1]

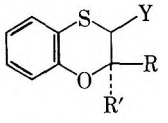




5

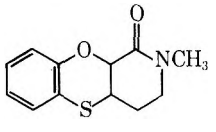
1, R = R′ = H; X = Br; Y = CO_2Et
2, R = R′ = H; X = Cl; Y = CN
3a, R = CH_3; R′ = H; X = Br; Y = CO_2Et
b, R = H; R′ = CH_3; X = Br; Y = CO_2Et
4, R = R′ = CH_3; X = Br; Y = CO_2Me

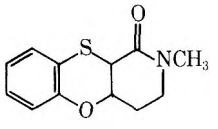




6, R = H; Y = CO_2Et
7, R = H; Y = CN

8a, R = CH_3; R′ = H; Y = CO_2Et
b, R = H; R′ = CH_3; Y = CO_2Et
9, R = R′ = CH_3; Y = CO_2Me



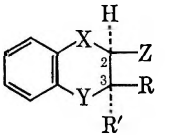


10a, cis
b, trans

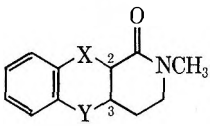
11a, cis
b, trans

A number of alternative mechanisms may be offered to explain both the formation of 3-carbethoxy-1,4-benzoxathians (instead of the expected 2-carbethoxy isomers) from **3a** and **3b** and the lack of stereoselectivity observed in these reactions. It is possible that β-alkyl substitution sufficiently hinders nucleophilic attack of the larger thiophenolate anion at the β carbon, but permits attack by the smaller phenolate ion to occur preferentially. Once **8a** and **8b** are formed, the α proton may be sufficiently acidic to allow equilibration between them, creating the observed isomer ratio. We do not favor this explanation, since **3** and **4** give good yields of **8** and **9**,[6] respectively, even at 25°, while much lower yields of the isomeric ethyl 3-methyl-1,4-benzodioxane-2-carboxylates are obtained from **3** and only a trace of ethyl 3,3-dimethyl-1,4-benzodioxane from **4** can be isolated from the corresponding catechol reactions at 55°.[1]

Table II
Nmr Data for 1,4-Benzoxathian Ring
(Protons in $CDCl_3$)



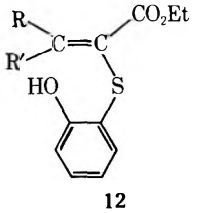
Compd	X	Y	Z	R	R′	δH_2	δH_3	$J_{2,3}$
6	O	S	CO_2Et	H	H	4.66	3.03	4.2
7	O	S	CN	H	H	6.13	2.83	5.4
8a	S	O	CO_2Et	CH_3	H	3.89	4.3[a]	2.4
8b	S	O	CO_2Et	H	CH_3	3.69	4.3[a]	6.0
9	S	O	CO_2Me	CH_3	CH_3	3.72		



Compd	X	Y	δH_2	δH_3	$J_{2,3}$
10a (cis)	O	S	4.67	3.63	3.2
11b (trans)	S	O	4.00	4.18	9.4
19a (cis)	O	O	4.66	4.57	2.8
19b (trans)	O	O	4.35	4.18	9.5

[a] Overlapping resonances in mixture of two isomers prevents measurement of accurate chemical shifts of the H_3 protons of the respective isomers.

Alternatively, we propose that the formation of **8** and **9** may occur through the intermediate **12**. This intermediate could be formed by a direct nucleophilic substitution of bromide ion by o-mercaptophenol on the intermediate **13** (formed by prior migration of the double bond to the β,γ position[7]), followed migration of the double bond back into conjugation with the carbonyl group.[8] Or **12** could arise from the episulfonium ion intermediate **14**.[9] Since only the "normal" Michael addition products **6** and **7** are obtained from the α-halo Michael acceptors **1** and **2** lacking a β-methyl group, it appears unlikely that the "abnormal" products **8** and **9** result from a direct nucleophilic displacement[10] of bromide ion by o-mercaptophenol at the sp^2-hybridized carbon atom of **3** or **4**.



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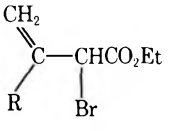
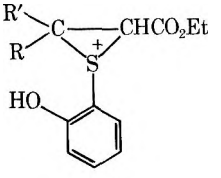


13



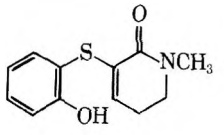
14

R = H; R′ = CH_3
R = R′ = CH_3

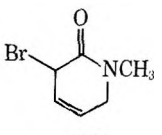
A 4:1 mixture of **10a** and **11b** was obtained in the reaction of o-mercaptophenol with **5**.[11] This somewhat curious result can be explained on the basis of two separate processes. It is likely that the major product **10a** is formed by the *axial* attack of the thiophenolate anion to the β carbon of **5**, followed by intramolecular *equatorial* addition of a proton to the α carbon and intramolecular nucleophilic

displacement of bromide in a manner analogous to the catechol reaction.[1] The minor product **11b** is probably formed from the intermediate **15**, which could either arise from the reaction of o-mercaptophenol with the β,γ-unsaturated amide **16**[12] followed by double-bond migration, or *via* the episulfonium ion intermediate **17**.[9] It has been suggested that the normal product **10a** could be formed directly from **17**[9] stereospecifically.

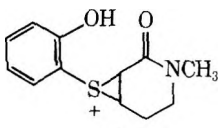
Attempts to epimerize either **10a** or **11b** in base failed. However, nmr evidence for the formation of the ring-opened compounds **15** and **18**, respectively, was obtained when **11b** and **10a** were each treated with potassium *tert*-butoxide in *tert*-butyl alcohol. Thus, **15** exhibited a triplet at δ 6.48 ppm (J = 5.2 Hz) and **18** gave a triplet at δ 6.12 ppm (J = 4.2 Hz).[13]



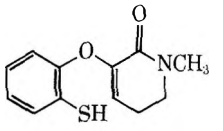
15



16



17



18

Nmr data for the ring protons of 1,4-benzoxathians **7–13** and the tricyclic 1,4-benzodioxanes **19a** and **19b** are summarized in Table II. Chemical shift (δ) values for H_2 and H_3 permit unambiguous assignment of the positions of sulfur and oxygen atoms relative to the activating group (nitrile, ester, or amide) in all cases, since protons on carbon atoms adjacent to oxygen experience greater deshielding than those on carbon atoms adjacent to sulfur. Thus, δH_2 (doublet) for **6** is 4.66 ppm, while δH_2 doublets for **8a** and **8b** are 3.89 and 3.69 ppm, respectively, clearly establishing that H_2 is adjacent to oxygen in **6** and adjacent to sulfur in **8a** and **8b**. The coupling constants $J_{2,3}$ of 2.4 and 6.0 Hz are consistent with cis and trans geometries of **8a** and **8b**, respectively.

Comparison of chemical shift values δH_2 and δH_3 of **10a** and **11b** with the corresponding tricyclic cis and trans 1,4-benzodioxanes **19a** and **19b** compels reversal of the assignment of the positions of oxygen and sulfur atoms in the cis isomer **10a** *vs.* the trans isomer **11b**. Thus, δH_2 is virtually the same for the cis isomers **10a** and **19a** (4.67 and 4.66 ppm, respectively), while δH_3 for **10a** is 3.63 ppm compared to 4.57 ppm for **19a**. Cis geometries of **10a** and **19a** can be confidently assigned on the basis of coupling constants $J_{2,3}$ of 3.2 and 2.8 Hz, respectively. Likewise, $J_{2,3}$ values of 9.4 and 9.5 Hz, respectively, clearly establish trans geometries for **11b** and **19b**. The δH_3 multiplets for **11b** and **19b** have the same value of 4.18 ppm, indicating that in both H_3 is adjacent to oxygen and in an *axial* orientation. On the other hand, δH_2 for **11b** is in the relatively shielded position of 4.00 ppm, as compared to 4.35 ppm for **19b**, establishing the position of H_2 as adjacent to sulfur.

Experimental Section

Nmr spectra were determined on a Varian HA-100 spectrometer and (in special cases) on a Varian HR-220 spectrometer in $CDCl_3$ solution using tetramethylsilane as an internal standard. Chemical shift values are accurate to 0.01 ppm at 100 MHz and to 0.005 ppm at 220 MHz. Melting points were determined on a Thomas-Hoover melting point apparatus and are corrected.

Reactions of o-mercaptophenol with α-halo Michael acceptors were carried out using esentially identical procedures in every case. Therefore, one representative example will be described in detail and only physical data for the remaining compounds will be given.

Ethyl 1,4-Benzoxathian-2-carboxylate (6). A mixture of 6.9 g (0.055 mol) of o-mercaptophenol (Polysciences), 8.9 g (0.05 mol) of ethyl 2-bromopropenoate[1] (**1**), and 20.7 g (0.15 mol) of anhydrous K_2CO_3 in 200 ml of dry acetone was stirred under a blanket of nitrogen for 18 hr. After the acetone was removed the residue was taken up in methylene chloride, extracted (in turn) with water, 5% NaOH, 5% HCl, and saturated NaCl solutions, and dried over anhydrous Na_2SO_4. Evaporation of the residue afforded 9.6 g (78%) of **6**: bp 121–122° (0.2 mm) [lit.[5] bp 130° (0.5 mm)]; nmr ($CDCl_3$) δ 6.5 (m, 4, ArH), 4.66 (t, 1, J = 4.2 Hz, OCH), 4.21 (q, 2, J = 7.0 Hz, OCH_2), 3.03 (d, 2, J = 4.2 Hz, SCH_2), 1.22 (t, 3, J = 7.0 Hz, CH_3).

2-Cyano-1,4-benzoxathian (7) was obtained from the reaction of o-mercaptophenol with α-chloroacrylonitrile (Aldrich) under the above conditions in 90% yield as pale yellow flakes: mp 61–62° (acetone); nmr ($CDCl_3$) δ 6.9 (m, 5, ArH), 6.13 (t, 1, J = 5.4 Hz, OCH), 2.83 (d, 2, J = 5.4 Hz, SCH_2).

Anal. Calcd. for C_9H_7NOS: C, 61.01; H, 3.95; N, 7.90; S, 18.07. Found: C, 61.07; H, 3.96; N, 7.88; S, 18.19.

Mixtures of ethyl *cis*- and *trans*-2-methyl-1,4-benzoxathian-3-carboxylate (8a and 8b) were obtained from the reaction of o-mercaptophenol with ethyl *cis*-2-bromobut-2-enoate[1] (**3a**), 44% yield (35% **8a**, 65% **8b**); ethyl *trans*-2-bromobut-2-enoate[1] (**3b**), 54% yield (35% **8a**, 65% **8b**); and ethyl 2,3-dibromobutanoate, 48% yield (35% **8a**, 65% **8b**). Distillation of the mixture of **8a** and **8b** gave a colorless oil, bp 110–120° (0.12 mm). In the nmr spectrum of the mixture, doublets were observed at δ 3.89 (J = 2.4 Hz) and 3.69 ppm (J = 6.0 Hz) for the C-3 protons of **8a** and **8b**, respectively. Resonances for the C-3 methyl groups of **8a** and **8b** were observed as doublets at δ 1.45 (J = 6.4 Hz) and 1.48 ppm (J = 6.2 Hz), and the ester methyl groups were at δ 1.25 (J = 7.1 Hz) and 1.27 ppm (J = 1.27 Hz), respectively. Resonances of the aromatic and ester methylene protons of the two isomers overlapped.

Anal. Calcd for $C_{12}H_{14}O_3S$: C, 60.48; H, 5.92; S, 13.46. Found: 60.62; H, 6.03; S, 13.40.

Methyl 2,2-Dimethyl-1,4-benzoxathian-3-carboxylate (9). Reaction of o-mercaptophenol with methyl 3-methyl-2-bromo-2-butenoate[1] (**4**) gave a 65% yield of **9** as colorless needles after recrystallizations from acetone: mp 61–62°; nmr ($CDCl_3$) δ 6.8 (m, 4, ArH), 3.72 (s, 1, SCH), 3.74 (s, 1, OCH_3), 1.49, 1.51 [d, 2, $C(CH_3)_2$].

Anal. Calcd for $C_{12}H_{14}O_3S$: C, 60.48; H, 5.92; S, 13.46. Found: C, 60.77; H, 6.06; S, 13.90.

***cis*-2-Methyl-3,4,4a,10a-tetrahydropyrido[3,4-*b*][1,4]benzoxathian-1(2*H*)-one (10a) and *trans*-2-methyl-3,4,4a,10a-tetrahydropyrido[4,3-*b*][1,4]benzoxathian-1(2*H*)-one (11b)** were prepared by treating o-mercaptophenol with a mixture of 1-methyl-3-bromo- and 1-methyl-3-chloro-5,6-dihydro-2(1*H*)-pyridone[1] (**5**) in the usual manner. Recrystallizations of the crude residue following work-up from the acetone gave a mixture consisting of 80% **10a** and 20% **11b** (38% total yield). Column chromatography of the mixture on neutral alumina with benzene–dichloromethane gave **11b**: mp 154–155° after recrystallization from acetone; nmr ($CDCl_3$) δ 6.94 (m, 4, ArH), 4.18 (m, 1, OCH), 4.00 (d, 1, J = 9.5 Hz, SCH), 3.43 (m, 2, NCH_2), 2.97 (s, 3, NCH_3), 2.48, 2.08 (m, 2, NCH_2).

Anal. Calcd for $C_{12}H_{13}NO_2S$: C, 61.27; H, 5.53; N, 5.95; S, 13.61. Found: C, 61.38; H, 5.47; N, 6.01; S, 13.70.

Subsequent fractions gave **10a**: mp 140–141° after recrystallizations from benzene; nmr ($CDCl_3$) δ 7.17 (m, 4, ArH), 4.67 (d, 1, J = 3.2 Hz, OCH), 3.63 (m, 1, SCH), 3.40 (m, 2, NCH_2), 2.90 (s, 3, NCH_3), 2.26 (m, 2, CH_2).

Anal. Calcd for $C_{12}H_{13}NO_2S$: C, 61.27; H, 5.53; N, 5.95; S, 13.61. Found: C, 61.04; H, 5.42; N, 5.76; S, 13.88.

Acknowledgment. We thank the National Institutes of Health for a Special Fellowship (GM54229), and the American Foundation of Pharmaceutical Education for a Gustavus A. Pfeiffer Memorial Fellowship for 1972–1973 to A. R. M. We are also grateful to Professor A. R. Katritzky of the School of Chemical Sciences of the University of East Anglia, Norwich, England, for graciously providing research facilities of that institution to A. R. M., who performed a portion of the work while on leave. The

220-MHz nmr spectra were measured by the Physico-Chemical Measurements Unit, Harwell Didcot, Berkshire, England.

Registry No.—**1**, 5459-35-8; **2**, 920-37-6; **3a**, 51263-38-8; **3b**, 51263-39-9; **4**, 51263-40-2; **5**, 51263-41-3; **6**, 35143-10-3; **7**, 51263-42-4; **8a**, 51263-43-5; **8b**, 51263-44-6; **9**, 51263-45-7; **10a**, 51263-46-8; **11b**, 51263-47-9; **19a**, 35528-83-7; **19b**, 35528-84-8; *o*-mercaptophenol, 1121-24-0; ethyl 2,3-dibromobutanoate, 609-11-0; 1-methyl-3-chloro-5,6-dihydro-2(1*H*)-pyridone, 51263-48-0.

References and Notes

(1) A. R. Martin, S. K. Mallick, and J. F. Caputo, *J. Org. Chem.*, **39**, 1808 (1974).
(2) J. F. Caputo and A. R. Martin, *Tetrahedron Lett.*, 4547 (1971).
(3) G. Swarzenbach and H. Egli, *Helv. Chim. Acta*, **17**, 1176 (1934).
(4) F. G. Bordwell and H. M. Anderson, *J. Amer. Chem. Soc.*, **75**, 6019 (1953).
(5) C. S. Tsai, U. S. Shah, H. B. Bhargava, R. G. Zaylskie, and W. H. Shelver, *J. Pharm. Sci.*, **61**, 229 (1972).
(6) The higher isolated yield of **9** as compared with the mixture of **8a** and **8b**, although theoretically unexpected, probably resulted from the fact that **9** was isolated as a solid while the mixture of **8a** and **8b** was purified by distillation. As yet, attempts to separate **8a** and **8b** have been unsuccessful. Nmr of the reaction mixtures prior to purification failed to detect β-S-substituted reaction products.
(7) Although the α,β-unsaturated isomer is thermodynamically favored over the β,γ-unsaturated isomer, the ΔG° for the equilibrium is not large.
(8) The formation of unexpected products in the reaction of catechol with α-bromocrotonate esters has also been explained by these phenomena (see ref 1).
(9) We thank one of the reviewers for suggesting this intriguing possibility. Mechanistic studies are underway and will constitute the subject of a future report from our laboratory.
(10) G. Modena, *Accounts Chem. Res.*, **4**, 73 (1971).
(11) The failure to isolate **10b** and **11a** from the reaction mixture does not rule out their possible formation in small quantities (undetected by nmr).
(12) Similar double-bond migrations have been observed in 6-hydroxyhexenoic lactones [C. G. Overberger and H. Kaye, *J. Amer. Chem. Soc.*, **89**, 5640 (1967)] and in tetrahydro-2*H*-azepin-2-ones [H. K. Reimschuessel, J. P. Siblia, and J. V. Pascale, *J. Org. Chem.*, **34**, 959 (1969)].
(13) The isolation, characterization, and Michael-type ring closure reactions of **15** and **18** will be subject of a future publication from this laboratory.

Synthesis of ω-1,3-Dithianyl Carboxylic Acids *via* Cleavage of Cyclic α-Diketone Monothioketals

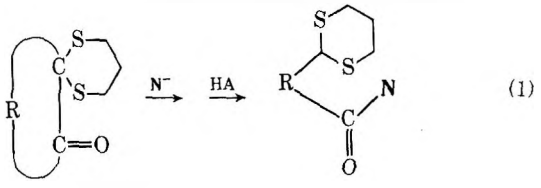
James A. Marshall* and David E. Seitz

Department of Chemistry, Northwestern University, Evanston, Illinois 60201

Received February 6, 1974

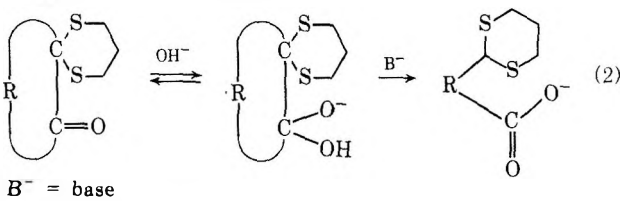
A number of cyclic (C_6–C_8) α-diketone monothioketals were prepared *via* hydroxymethylation of the parent monoketone followed by treatment with 1,3-propanedithiol ditosylate. Cleavage of these simple cyclic systems took place readily in KOH-*tert*-butyl alcohol to give, after acidification, ω-1,3-dithianyl carboxylic acids in 88–95% yield. The attempted cleavage of an α′,α′-dimethylated cyclohexane-1,2-dione monothioketal with KOH-*tert*-butyl alcohol failed, apparently because of steric hindrance to carbonyl addition. A thioketal ketone derived from an α,β-unsaturated cyclohexanone likewise failed to cleave. In this case enolization took place leading to the β,γ-unsaturated ketone derivative. Methanolic sodium methoxide or methanolic potassium hydroxide were ineffective in the cleavage reaction. These findings are consistent with a mechanism involving hydroxide addition to the carbonyl followed by proton abstraction by *tert*-butoxide leading to a reactive dialkoxy anion which undergoes C–C bond cleavage.

In a preliminary report we described the apparent nucleophilic cleavage of α-diketone monothioketals to give ω-dithianyl carboxylic acid derivatives (eq 1).[1] Subsequent studies indicated that the above cleavage reaction most likely proceeds in two stages with initial attack by hydroxide on the carbonyl followed by subsequent proton abstraction of the presumed adduct (eq 2).[2] The essential features of eq 2 had previously been proposed by Gassman in connection with his studies on the Haller–Bauer-type cleavage of nonenolizable ketones.[3] Employing his reaction conditions (NaOH, NaO-*t*-Bu, *t*-BuOH, ether) we succeeded in obtaining ω-dithianyl carboxylic acids from certain unhindered decalones in over 90% yield.[2] We have now completed more definitive studies on this cleavage reaction which shed light on its scope and synthetic potential.



(1)

N = nucleophile



(2)

B^- = base

As noted above, Gassman's work and our own experience[2] indicated that a combination of hydroxide plus a strong (alkoxide) base afforded the highest yields of cleavage products. In an effort to simplify the experimental procedure we investigated the use of powdered potassium hydroxide in *tert*-butyl alcohol, a base system previously employed by Meyers, *et al.*[4] As shown below (Chart I), under appropriate conditions excellent results could be obtained using this base system with various cyclic α-diketone monothioketals. Optimum yields were realized when the temperature was maintained near 60°. Higher temperatures led to colored decomposition products and lower temperatures prolonged the required reaction times.

In contrast to the results obtained with decalone **9** and its angular methyl counterpart,[2] the dimethyldecalone **11** afforded only recovered starting material (98%) after 8 hr of reaction time. Evidently steric effects retard the postulated addition step of the cleavage reaction in this case. The apparent lesser reactivity of the cycloheptanone **3** and particularly the cyclooctanone **5** may be similarly explained. Likewise the conjugated keto thioketal **12** failed to yield a cleavage product. In this case a substantial pro-

JOC-114-1

Experimental Section[6]

Thioketal Ketones

2,2-(Propane-1,3-dithio)cyclohexanone (1). - A solution of 1.64 g (13 mmol) of the hydroxymethylene ketone obtained (74%) from cyclohexanone by the procedure of Ainsworth[7], 7.08 g (17 mmol) of propane-1,3-dithiol di-*p*-toluenesulfonate[8] and 5 g of potassium acetate in 100 ml of absolute ethanol was heated at reflux for 10 hr according to the procedure of Woodward.[9] The ethanol was removed *in vacuo* from the cooled reaction mixture. Water was added to the residue and the products were isolated with ether. The crude product was filtered through 70 g of Fisher alumina with 250 ml of benzene. Removal of the solvent afforded crystalline material which was recrystallized from ethanol affording 1.68 g (64%) of thioketal ketone 1. Recrystallization from ethanol and sublimation at 46° (0.02 mm) afforded material of mp 54-55°; λ_{max}^{KBr} 5.88 (CO), 6.98, 7.08, 7.88, 8.18, 8.98, 9.29, 10.52, 11.00, 11.44, 12.63, 13.61 μm.

Anal. Calcd for $C_9H_{14}OS_2$: C, 53.43; H, 6.97; S, 31.69. Found: C, 53.30; H, 6.94; S, 31.53.

2,2-(Propane-1,3-dithio)cycloheptanone (3). - The procedure outlined above for the preparation of thioketal ketone 1 was followed using 1.70 g of the hydroxymethylene ketone obtained (86%) from cycloheptanone by the procedure of Ainsworth.[7] The crude product was filtered through 70 g of Fisher alumina with 250 ml of benzene. Removal of the solvent afforded crystalline material which was recrystallized from ethanol affording 1.64 g (64%) of thioketal ketone 3. Recrystallization from ethanol and sublimation at 62° (0.02 mm) afforded material of mp 76.5-77.5°; λ_{max}^{KBr} 5.90 (CO), 6.90, 7.02, 7.65, 7.90, 8.10, 8.67, 8.81, 10.68, 11.05, 11.60, 11.80 μm.

Anal. Calcd for $C_{10}H_{16}OS_2$: C, 55.51; H, 7.45; S, 29.64. Found: C, 55.48; H, 7.48; S, 29.88.

2,2-(Propane-1,3-dithio)cyclooctanone (5). - The procedure outlined above for the preparation of thioketal ketone 1 was followed using 2.00 g of the hydroxymethylene ketone obtained (82%) from cyclooctanone by the procedure of Ainsworth.[7] The crude product was filtered through 70 g of Fisher alumina with 250 ml of benzene. Removal of the solvent afforded crystalline material which was recrystallized from ethanol affording 2.04 g (66%) of thioketal ketone 5. Recrystallization from ethanol and sublimation at 62° (0.02 mm) afforded material of mp 80-81°; λ_{max}^{KBr} 5.91 (CO), 6.85, 6.95, 7.01, 7.60, 7.81, 8.30, 8.61, 8.75, 9.00, 9.39, 11.00, 11.23, 11.78, 12.70 μm.

Anal. Calcd for $C_{11}H_{18}OS_2$: C, 57.35; H, 7.87; S, 27.83. Found: C, 57.28; H, 8.05; S, 27.70.

2,2-(Propane-1,3-dithio)-4-cyclohepten-1-one (7). - The procedure outlined above for the preparation of thioketal ketone 1 was followed using 2.35 g of the hydroxymethylene ketone obtained (88%) from 4-cycloheptenone[10] by the procedure of Ainsworth.[7] The crude product was filtered through 70 g of Fisher alumina with 250 ml of benzene. Removal of the solvent afforded crystalline material which was recrystallized from ethanol affording 2.40 g (66%) of thioketal ketone 7. Recrystallization from ethanol and sublimation at 66° (0.02 mm) afforded material of mp 83.5-84.5°; λ_{max}^{KBr} 5.90 (CO), 6.06, 7.01, 7.68, 7.89, 8.42, 8.86, 11.15, 11.50, 12.40, 13.52 μm; δ $\overset{CDCl_3}{TMS}$ 5.81 ppm ($\overset{H}{}\!\!>\!C\!=\!C\!<\!\!\overset{H}{}$ multiplet).

Anal. Calcd for $C_{10}H_{14}S_2O$: C, 56.04; H, 6.58; S, 29.92. Found: C, 56.23; H, 6.66; S, 30.06.

3,3-(Propane-1,3-dithio)-10-methoxymethyl-*trans*-2-decalone (9). The procedure outlined above for the preparation of thioketal ketone 1 was followed using 4.50 g of the hydroxymethylene ketone obtained (94%) from 10-methoxymethyl-*trans*-2-decalone[3] by the procedure of Turner.[11] The crude product was filtered through 90 g of Fisher alumina with 500 ml of benzene. Removal of the solvent afforded crystalline material which was recrystallized from ethanol affording 5.32 g (89%) of thioketal ketone 9. Two additional recrystallizations from ethanol afforded material of mp 100-101°; λ_{max}^{KBr} 5.89 (CO), 6.70, 6.90, 7.08, 8.10, 8.55, 9.08, 9.95, 10.56, 11.01 μm; δ $\overset{CDCl_3}{TMS}$ 3.52 (2H, s) and 3.30 ppm (3H, s).

Anal. Calcd for $C_{15}H_{24}O_2S_2$: C, 59.96; H, 8.05; S, 21.34. Found: C, 60.13; H, 8.19; S, 21.45.

3,3-(Propane-1,3-dithio)-1,1-dimethyl-*trans*-2-decalone (11). - The procedure outlined above for the preparation of thioketal ketone 1 was followed using 2.70 g of the hydroxymethylene ketone obtained (93%) from 1,1-dimethyl-*trans*-2-decalone by the procedure of Turner.[11] The crude product was filtered through 70 g of Fisher alumina with 250 ml of benzene. Removal of the solvent afforded crystalline material which was recrystallized from ethanol affording 3.03 g (83%) of thioketal ketone 11. Two additional recrystallizations from ethanol afforded material of mp 95.5-97°; λ_{max}^{KBr} 5.92 (CO), 6.95, 7.05, 7.29, 7.39, 7.85, 9.48, 10.30, 11.05, 11.50, 12.55 μm; δ $\overset{CDCl_3}{TMS}$ 1.22 and 1.13 ppm (C-1 gem dimethyl).

Anal. Calcd for $C_{15}H_{24}OS_2$: C, 63.33; H, 8.50; S, 22.54. Found: C, 63.37; H, 8.65; S, 22.76.

3,3-(Propane-1,3-dithio)-10-methyl-1(9)-octal-2-one (12). The procedure outlined above for the preparation of thioketal ketone 1 was followed using 2.50 g of the hydroxymethylene ketone obtained (91%) from 10-methyl-1(9)-octal-2-one by the procedure of Turner.[11] The crude product was filtered through 70 g of Fisher alumina with 250 ml of benzene. Removal of the solvent afforded crystalline material which was recrystallized from ethanol affording 2.30 g (66%) of thioketal ketone 12. Two additional recrystallizations from ethanol afforded material of mp 127-128°; λ_{max}^{KBr} 6.09 (CO), 6.20, 7.05, 7.70, 7.90, 8.20, 8.40, 9.11, 10.51, 11.08, 11.55 μm; δ $\overset{CDCl_3}{TMS}$ 5.68 (1H, s) and 1.42 ppm (C-10 CH_3).

Anal. Calcd for $C_{14}H_{20}OS_2$: C, 62.64; H, 7.51; S, 23.89. Found: C, 62.42; H, 7.64; S, 23.78.

Cleavage Reactions

6,6-(Propane-1,3-dithio)hexanoic Acid (2). - To a stirred solution of thioketal ketone 1 (606 mg, 3 mmol) in 8 ml of *t*-butyl alcohol was added 504 mg (9 mmol) of powdered potassium hydroxide.[4] The reaction mixture was heated at 60° for 8 hr. Water was added and the aqueous phase was extracted with ether and acidified with cold conc hydrochloric acid. The acidic product was isolated by ether extraction affording 642 mg (97%) of crystalline solid. Recrystallization from ether-hexane yielded 615 mg (93%) of thioacetal acid 2. Recrystallization from ether-hexane and sublimation at 86° (0.02 mm) afforded material of mp 90-91.5°; λ_{max}^{KBr} 2.95-4.10(COOH), 5.91 (CO), 6.90, 7.03, 7.60, 7.89, 8.01, 8.20, 8.35, 8.52, 11.08, 13.15 μm; δ $\overset{CDCl_3}{TMS}$ 11.38 (COOH, s) and 4.01 ppm (1H, t, J=6 Hz).

Anal. Calcd for $C_8H_{14}O_2S_2$: C, 49.06; H, 7.32; S, 29.10. Found: C, 49.17; H, 7.20; S, 29.24.

The identical material was obtained in 92% yield by treatment of thioketal ketone 1 with a 3-fold excess of KO*t*-Bu (0.3 *M*) to which an equivalent amount of water was added prior to stirring at 60° for 8 hr.

7,7-(Propane-1,3-dithio)heptanoic Acid (4). - The procedure outlined above for the preparation of thioacetal acid 2 was followed using 648 mg of thioketal ketone 3. The reaction mixture was heated at 60° for 10 hr. The crude product (699 mg, 99%) was recrystallized from ether-hexane yielding 667 mg (95%) of thioacetal acid 4. Recrystallization from ether-hexane and sublimation at 68°(0.02 mm) afforded material of mp 74-75°; λ_{max}^{KBr} 3.02-4.10 (COOH), 5.89 (CO), 6.88, 7.02, 7.15, 7.88, 8.07, 11.06 μm; δ $\overset{CDCl_3}{TMS}$ 10.80 (COOH, s) and 4.00 ppm (1H, t, J=6 Hz).

Anal. Calcd for $C_{10}H_{18}O_2S_2$: C, 51.25; H, 7.74; S, 27.36. Found: C, 51.18; H, 7.66; S, 27.37.

8,8-(Propane-1,3-dithio)octanoic Acid (6). - The procedure outlined above for the preparation of thioacetal acid 2 was followed using 960 mg of thioketal ketone 5. The reaction mixture was heated at 60° for 48 hr. The isolation procedure afforded 993 mg (96%) of crude acid. Part (120 mg) of the crude acid was chromatographed on 10 g of silica gel with ether as eluant yielding 109 mg of thioacetal acid 6. Recrystallization from ether-hexane afforded material of mp 90-91°; λ_{max}^{KBr} 2.80-4.10 (COOH), 5.85 (CO), 6.80, 6.99, 7.10, 8.00, 8.10, 8.20, 11.00, 12.25 μm; δ $\overset{CDCl_3}{TMS}$ 9.41 (COOH, s) and 4.00 ppm (1H, t, J=6 Hz).

Anal. Calcd for $C_{11}H_{20}O_2S_2$: C, 53.19; H, 8.12; S, 25.82. Found: C, 53.42; H, 8.19; S, 25.80.

(Z)-7,7-(Propane-1,3-dithio)-4-heptenoic Acid (8). - The procedure outlined above for the preparation of thioacetal acid 2 was followed using 642 mg of thioketal ketone 7. The reaction mixture was heated at 60° for 10 hr. The crude product (699 mg, 100%) was recrystallized from ether-hexane yielding 648 mg (93%) of thioacetal acid 8. Recrystallization from ether-hexane and sublimation at 52° (0.02 mm) afforded material of mp 57-58°; λ_{max}^{KBr} 2.85-4.10 (COOH), 5.89 (CO), 7.05, 7.15, 7.78, 7.90, 8.30, 10.80, 12.90 μm; δ $\overset{CDCl_3}{TMS}$ 11.59 (COOH, s), 5.50 (2H, t, J=5 Hz) and 4.02 ppm (1H, t, J=6 Hz).

Anal. Calcd for $C_{10}H_{18}S_2O_2$: C, 51.92; H, 6.54; S, 27.72. Found: C, 51.66; H, 6.75; S, 27.65.

1-[2,2-(Propane-1,3-dithio)ethyl]-cis-1-methoxymethylcyclohex-2-yl Acetic Acid (10). - The procedure outlined above for the preparation of thioacetal acid 2 was followed using 600 mg of thioketal ketone 9. The reaction mixture was heated at 60° for 12 hr. The crude product (664 mg, 100%) was recrystallized from ether-hexane yielding 585 mg (92%) of thioacetal acid 10. An additional recrystallization from ether-hexane afforded material of mp 97-97.5°; λ_{max}^{KBr} 2.80-4.10 (COOH), 5.88 (CO), 6.95, 7.09, 7.71, 7.89, 8.08, 8.40, 9.05, 10.68, 11.02 μm; δ $\overset{CDCl_3}{TMS}$ 11.80 (COOH, s), 4.00 (1H, t, J=6 Hz) and 3.22 ppm (5H, s).

Anal. Calcd for $C_{15}H_{26}O_3S_2$: C, 56.75; H, 7.94; S, 20.20. Found: C, 56.93; H, 8.24; S, 19.91.

Attempted Cleavage of Thioketal Ketone 11. - The procedure outlined above for the preparation of thioacetal acid 2 was followed using 426 mg of thioketal ketone 11. The reaction mixture was heated at 60° for 8 hr. The neutral extracts afforded 417 mg (98%) of starting material.

Attempted Cleavage of Thioketal Ketone 12. - The procedure outlined above for the preparation of thioacetal acid 2 was followed using 402 mg of thioketal ketone 12. The reaction mixture was heated at 60° for 8 hr. The neutral extracts afforded 379 mg (94%) of a mixture of starting material (20%) and the β-γ-unsaturated isomer 13 (80%) of the starting material as determined by analysis of the infrared and nmr spectra.

Attempted Cleavage of 2-Thiophenylcyclohexanone (14).[12] - The procedure outlined above for the preparation of thioacetal acid 2 was followed using 618 mg of α-thiophenyl ketone 14. The reaction mixture was heated at 60° for 20 hr. The neutral extracts afforded 615 mg (99%) of starting material.

Attempted Cleavage of 2-Methyl-2-thiophenylcyclohexanone (15).[13] - The procedure outlined above for the preparation of thioacetal acid 2 was followed using 440 mg of α-thiophenyl ketone 15. The reaction mixture was heated at 60° for 10 hr. The neutral extracts afforded 439 mg (100%) of starting material.

6,6-bis-Thiophenylhexanoic Acid (17). - The procedure outlined above for the preparation of thioacetal acid 2 was followed using 785 mg of 2,2-bis-thiophenylcyclohexanone (16).[12] The reaction mixture was heated at 60° for 10 hr. The isolation procedure afforded 573 mg (69%) of crude acid. A 245-mg sample of this material was chromatographed on 20 g of silica gel with ether as eluant yielding 232 mg of thioacetal acid 17 which was distilled at 185° (bath temp) and 0.01 mm; λ_{max}^{film} 2.80-4.10 (COOH), 5.87 (CO), 6.31, 6.79, 6.99, 9.20, 9.40, 9.79, 13.50, 14.55 μm; δ $\overset{CDCl_3}{TMS}$ 10.20 (COOH, s), 6.90-7.55 (10H, m) and 4.30 ppm (1H, t, J=6 Hz).

Anal. Calcd for $C_{18}H_{20}O_2S_2$: C, 65.03; H, 6.06; S, 19.29. Found: C, 65.09; H, 6.17; S, 19.09.

References

6. The apparatus described by W. S. Johnson and W. P. Schneider ["Organic Syntheses," Coll. Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1963, p. 132] was used to maintain an argon atmosphere. The isolation procedure consisted of thorough extractions with the specified solvent, washing the combined extracts with saturated brine solution, and drying the extracts over anhydrous magnesium sulfate. The solvent was removed from the filtered extracts under reduced pressure on a rotary evaporator. Microanalyses were performed by Micro-Tech Laboratories, Inc., Skokie, Illinois. Infrared spectra were obtained with a Perkin-Elmer 137 spectrophotometer. Infrared absorption are reported in wavelengths (μm) and are standardized with reference to the 6.24-μm peak of polystyrene. Nuclear magnetic resonance spectra were recorded with a Varian T-60 spectrometer. Signals are reported as the chemical shift downfield from tetramethylsilane (TMS) in parts per million (ppm) of the applied field. The multiplicity of the peak is abbreviated: singlet s, doublet d, triplet t, quartet q and multiplet m. Coupling constants are reported in hertz (Hz). Melting points were determined on a calibrated Thomas capillary melting point apparatus. Melting points are not corrected.
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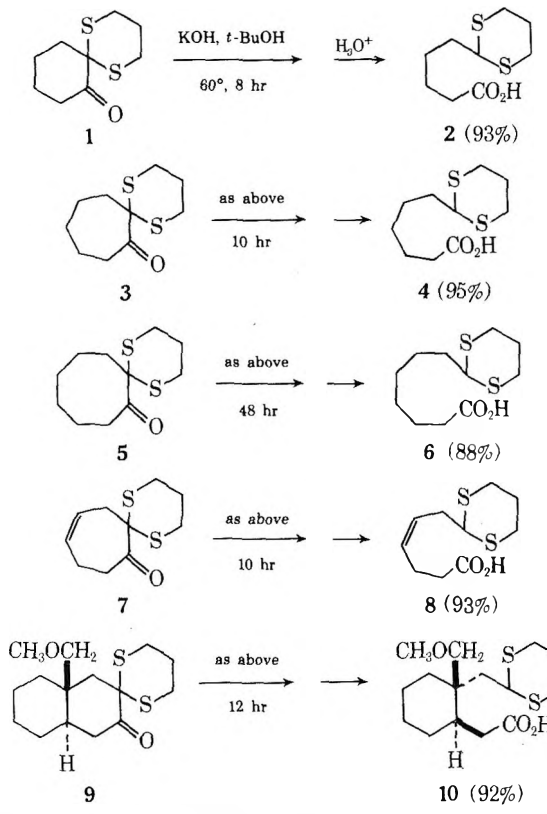
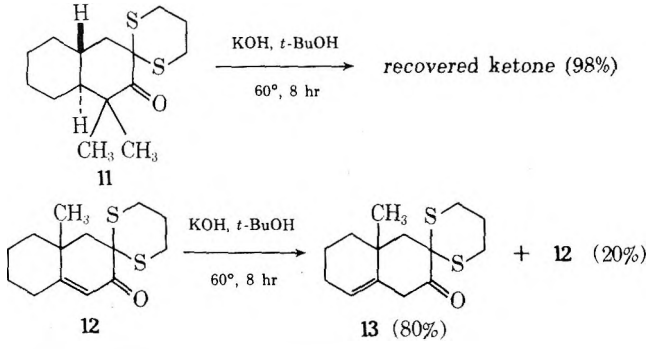
Chart I

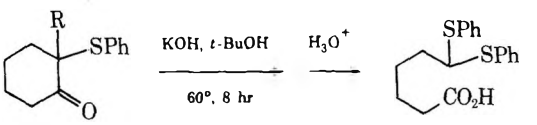


portion of the recovered material appeared to be the β,γ-unsaturated isomer **13**. Thus, enolate formation evidently



retards addition to the conjugated carbonyl group. Neither of the above uncooperative keto thioketals **11** or **12** could be induced to yield acidic cleavage products. Prolonged reaction times merely led to their gradual destruction.

Attempts to extend the cleavage reaction to α-thiophenyl ketones did not appear promising. Both cyclohexanone derivatives **14** and **15** were unaffected by the KOH–*t*-BuOH treatment. However with 2,2-bis(thiophenyl)cyclohexanone (**16**) cleavage did take place to give the acid **17** in 66% yield.



14, R = H
15, R = CH_3
16, R = SPh

Trost and coworkers have recently described the facile cleavage of the thioketal derivatives of cyclobutane-1,2-diones and the related alcohols with methanolic sodium methoxide to give β-1,3-dithianyl esters and ketones.[5] Under these conditions both the thioketal ketone **1** and the alcohol obtained upon addition of methyllithium to ketone **1** were recovered unchanged after 10 hr at reflux. Thus, as noted by Trost, ring strain must provide substantial driving force for the cyclobutane cleavage reactions.

Finally, cleavage of the thioketal ketone **1** to acid **2** also took place efficiently (92% yield) upon treatment with excess potassium *tert*-butoxide in *tert*-butyl alcohol to which the equivalent amount of water was added. Interestingly, with methanolic potassium hydroxide only starting thioketal ketone **1** was recovered after 8 hr at 60°.

Acknowledgment. Support from the National Institutes of Health (Research Grant 2RO1 CA 11089) and the National Science Foundation (Research Grant GP-33276X) is gratefully acknowledged.

Registry No.—**1**, 51310-03-3; **2**, 51310-04-4; **3**, 51310-05-5; **4**, 51310-06-6; **5**, 51310-07-7; **6**, 51364-41-1; **7**, 51364-42-2; **8**, 51310-08-8; **9**, 42836-58-8; **10**, 51310-09-9; **11**, 51310-10-2; **12**, 51310-11-3; **13**, 51310-12-4; **16**, 35874-99-8; **17**, 51310-13-5; cyclohexanone hydroxymethylene derivative, 823-45-0; cycloheptanone hydroxymethylene derivative, 934-20-3; cyclooctanone hydroxymethylene derivative, 936-65-2; 4-cycloheptenone hydroxymethylene derivative, 51310-14-6; 10-methoxymethyl-*trans*-2-decalone hydroxymethylene derivative, 51310-15-7; 1,1-dimethyl-*trans*-2-decalone hydroxymethylene derivative, 51310-16-8; 10-methyl-1(9)-octal-2-one hydroxymethylene derivative, 5240-82-4.

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α-Halosulfonamides. Synthesis and Base-Induced Reactions

John C. Sheehan,* Uri Zoller, and D. Ben-Ishai

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

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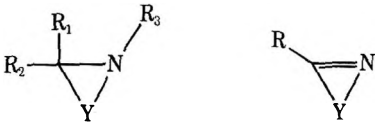
The syntheses of α-halosulfonamides by two methods are described. Base-induced reactions of α-halosulfonamides resulted in dimerization (**8a**), elimination-dimerization (**8g$_2$**), or cyclization (**8g**, **8h$_2$**).

Although no three-membered ring with two heteroatoms had been prepared before 1950, isolable compounds incorporating two nitrogens (diazirines, diaziridines),[1] or both nitrogen and oxygen (oxaziranes)[1,2] are known to date. Recently, the syntheses of three-membered ring systems comprised solely of heteroatoms (oxadiaziridines and thiadiaziridine 1,1-dioxides)[3] have been reported. However, nothing is known about such systems comprised of sulfur, nitrogen, and carbon (**1** and **2**).



1 **2**

a, Y = S
b, Y = SO_2

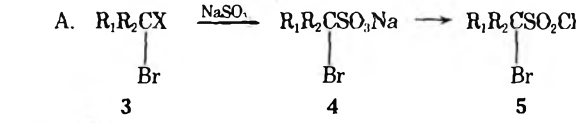
Three-membered heterocycles have been prepared by a variety of cyclization reactions.[4] α-Halosulfonamides would appear to be the most convenient and promising precursors for the synthesis of either the α-sultam or α-sultem (azathiirane dioxide **1b** and azathiirene **2b**, respectively).

The objective of this study was the synthesis of α-halosulfonamides (**8**) and the investigation of possible cyclization reactions leading to **1b**, **2b**, or degradation products.

Results and Discussion

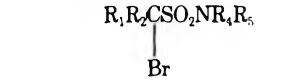
α-Halosulfonamides have been synthesized in two ways as shown in Scheme I.

Scheme I



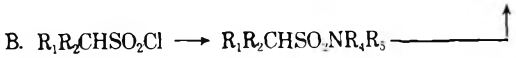
3 **4** **5**

a, $R_1 = R_2 = H$
b, $R_1 = CH_3$; $R_2 = H$
c, $R_1 = H$; R_2 = *tert*-butyl
d, $R_1 = H$; R_2 = *tert*-butyl; X = I
e, $R_1 = H$; $R_2 = p$-NO_2Ph
f, $R_1R_2 = -(CH_2)_5-$



8

a$_1$, R_4 = *tert*-butyl; $R_5 = H$
a$_2$, R_4 = *n*-propyl; $R_5 = H$
a$_3$, R_4 = cyclohexyl; $R_5 = H$
a$_4$, $R_4 = R_5 = CH_3$
a$_5$, $R_4R_5 = -(CH_2)_5-$
b, R_4 = *tert*-butyl; $R_5 = H$
g$_1$, R_4 = *tert*-butyl; $R_5 = H$
g$_2$, R_4 = *tert*-butyl; $R_5 = Cl$
h$_1$, R_4 = *tert*-butyl; $R_5 = H$
h$_2$, $R_4 = R_5 = H$



6 **7**

g, R_1 = Ph; $R_2 = H$
h, R_1 = Ph; R_2 = Br

Method A involves the Strecker reaction[5] of an alkyl halide with sulfite anion. This method was useful for the conversion of **3a** and **3b** to **4a** and **4b**[6] (X = Br). However, the more hindered *gem*-dihalides **3c–f** and **3h** were not converted to the α-halosulfonates even on treatment with sodium sulfite in refluxing aqueous ethanol or aqueous ethylene glycol. Use of this method with **3g** gave benzaldehyde as the main product. Thus it seems this type of reaction (**3** → **4**) is successful only if $R_1 = H$ and $R_2 = H$ or a linear alkyl group.[5b]

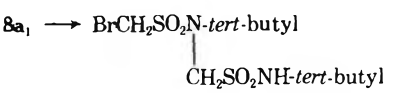
The selective α-halogenations of method B were achieved through radical-type reactions. *N*-Bromosuccinimide and molecular bromine were successfully applied for the benzylic brominations leading to the benzylsulfonamides **8g** and **8h**. In contrast to the easy α-halogenations of carbonyl compounds, α-halogenations of sulfonyl compounds are not facile using conventional ionic halogenation agents.[7] Such halogenations have been effected by reaction of a sulfonyl carbanion (prepared from the reaction of the parent sulfone with a strong base) with a source of X^+.[8] This method, however, was reported to be unsuccessful in some cases,[7] unless a very unusual source of X^+ (bromomethylmalonylacetonide) was applied. Primary or secondary sulfonamides would be expected to afford *N*-halo rather than *C*-halo products by this method.

The *N*-halosulfonamide **8g$_2$** was prepared from **7g** (R_4 = *tert*-butyl, $R_5 = H$) with *tert*-butyl hypochlorite.

The effects of bases on α-halosulfones, α,α-dihalosulfones, and α,α′-dihalosulfones have been studied extensively,[9-13] both mechanistically and synthetically. Two studies on the effect of alkali on α-chloromethanesulfonamides[12a,14] suggest the Ramberg–Bäcklund mechanism[12a] to be operative in these cases.

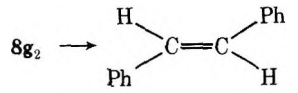
The intermediacy of episulfones and their vinylogs (thiirene dioxides) in the Ramberg–Bäcklund reaction of α-halosulfones and α,α-dichlorosulfones, respectively, has been established.[10-13] Furthermore, stable thiadiazirine 1,1-dioxides[3b] and thiirene dioxide[6a] were recently isolated by the treatment of substituted *N*-chlorosulfonylureas and α,α-dibromobenzyl sulfone, respectively, with bases. Therefore, the three-membered heterorings **1b** and **2b** might be accessible through the treatment of α-halosulfonamides **8a**, **8g**, and **8h** with a base.

Reaction of **8a$_1$** with metallic sodium in ether solution or with potassium *tert*-butoxide in ether or tetrahydrofuran afforded the dimer **9**. Compound **8a$_1$** was chosen as a representative of the α-bromoalkylsulfonamide series.



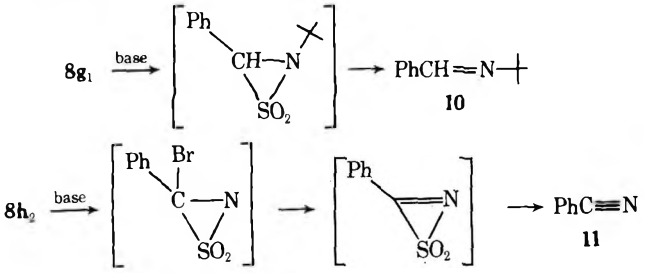
9

Treatment of the *N*-chloro compound **8g$_2$** with triethylamine in methylene chloride or with potassium *tert*-butoxide in ether gave **7g** (R_4 = *tert*-butyl; $R_5 = H$). Use of Baumgarten's procedure[15] for *in situ* generation of **8g$_2$** gave *trans*-stilbene.



Reaction of $8g_2$ with *n*-butyllithium followed by molecular bromine also gave *trans*-stilbene.

The α-halobenzylic sulfonamides $8g_1$ and $8h_2$ in the presence of thiethylamine in benzene or potassium *tert*-butoxide in ether gave products suggesting the intermediacy of an α-sultam.



Both episulfones and thiirene dioxides readily lose sulfur dioxide under Ramberg–Bäcklund reaction conditions.[9-13] Therefore **1b** and **2b** (the sulfo analogs of the α-lactam system[15,16] and the aza analogs of the thiirene dioxides, respectively) could behave similarly under comparable conditions.

The structures of the minor products from the reaction of $8h_2$ have not yet been established. In contrast to the isolated products from the rearrangement of the analogous α-halosulfones,[11,13] they were shown not to be derivatives of sulfonic acids.

The fact that $8g_2$ required hours whereas $8a_1$ required days for reaction with potassium *tert*-butoxide probably reflects the relative ease of displacement of benzyl bromine compared to alkyl bromine in α-bromosulfonamides.

Experimental Section

Melting points were obtained on a Reichert micro heating stage. Infrared spectra were recorded on a Perkin-Elmer 237 spectrophotometer. Nmr spectra were obtained on a Varian T-60 and are reported in parts per million downfield from TMS or sodium 2,2-dimethyl-2-silapentane-5-sulfonate (in D_2O) as internal standards. Mass spectra were obtained on a Hitachi Perkin-Elmer RMU-6. Microanalyses were performed by S. M. Nagy, Belmont, Mass., and Galbraith Laboratories Inc., Knoxville, Tenn.

α-Bromosulfonyl Chlorides. α-Bromosulfonates were prepared according to a known procedure[6a] and treated with excess phosphorus pentachloride to obtain the sulfonyl chlorides.

Sulfonamides. General Procedure. A solution of the sulfonyl chloride (**5**, **6**, 0.05 mol) in 50 ml of methylene chloride was dropped into a solution of the amine (0.2 mol) in 200 ml of methylene chloride with stirring at 0°. The mixture was stirred at 0° for 2 hr and at 25° for 1 hr. The solution was washed with water, 5% hydrochloric acid, water, 10% sodium bicarbonate, and water. The organic layer was dried and evaporated. In most cases the sulfonamide obtained was pure enough for further synthetic use. Otherwise it was recrystallized from 90% ethanol. The following sulfonamides were obtained: *N*-*tert*-butyl-α-bromomethanesulfonamide ($8a_1$), 72%, mp 65–67°; *N*-propyl-α-bromomethanesulfonamide ($8a_2$), 48%, mp 31.5–33.5°; *N*-cyclohexyl-α-bromomethanesulfonamide ($8a_3$), 70%, mp 68–70°; *N*,*N*-dimethyl-α-bromomethanesulfonamide ($8a_4$) (the amines used were dimethylamine hydrochloride and triethylamine), 46%, mp 94–96°; *N*,*N*-cyclopentyl-α-bromomethanesulfonamide ($8a_5$), 63%, mp 100–102°; *N*-*tert*-butyl-α-bromoethanesulfonamide (**8b**), 77%, mp 103.5–105.5°; *N*-*tert*-butyl-α-toluenesulfonamide (**7g**), 94%, mp 107.5–109.5°.

α-Bromination of Sulfonamides. *N*-*tert*-Butyl-α-bromo-α-toluenesulfonamide ($8g_1$) and *N*-*tert*-Butyl-α,α-dibromo-α-toluenesulfonamide ($8h_1$). A suspension of **7g** (2.273 g, 10 mmol) and *N*-bromosuccinimide (3.56 g, 20 mmol) was refluxed with stirring in 150 ml of carbon tetrachloride under a nitrogen atmosphere for 18 hr with irradiation by a sun lamp (Westinghouse, 275 W). The reaction mixture was cooled and filtered and the solvent was evaporated to give a brown, viscous oil. The oil was dissolved in ether and the solution was washed with water, dried, and evaporated. The residue was chromatographed on SilicAR cc-7 (100–200 mesh) with benzene to give $8h_1$ (0.76 g, 20%) and $8g_1$ (1.27 g, 41%). Recrystallization from chloroform–pentane gave $8g_1$, mp 101–102°, and $8h_1$, mp 138.5–141°.

α,α-Dibromo-α-toluenesulfonamide ($8h_2$). Bromine (17.6 g, 0.10 mol) was added to a suspension of α-toluenesulfonamide[17] (6.85 g, 40 mmol) in 300 ml of carbon tetrachloride. The solution was refluxed for 28 hr under a sun lamp (Westinghouse, 275 W). Filtration of the cooled reaction mixture gave a solid, which was recrystallized from chloroform to give 9.2 g (70%) of $8h_2$, mp 168–170°.

***N*-Chloro-*N*-*tert*-butyl-α-toluenesulfonamide ($8g_2$).** *tert*-Butyl hypochlorite (3.0 g, 27 mmol) was added dropwise to a solution of **7g** in 50 ml methylene chloride (5.68 g, 25 mmol) over 30 min. The solution was stirred for 16 hr and evaporated to give $8g_2$, 95%, mp 52–55.5°.

Base-Induced Reactions. Dimerization. A solution of $8a_1$ (1.28 g, 5.67 mmol) in 25 ml of ether was added to a suspension of sodium (0.138 g, 5.67 mmol) in 15 ml of ether. The mixture was stirred at 25° for 3 days under nitrogen. The solution was evaporated and the residue was taken up in water and chloroform. The solution was acidified with 1 *N* hydrochloric acid and the organic layer was dried and evaporated to give 0.87 g of an oil. Spectral analysis showed the oil to be a mixture of $8a_1$ and the dimer **9**. The dimer was isolated and recrystallized from hexane–ethyl acetate to give 0.11 g (10%), mp 124–125.5°.

Treatment of $8a_1$ with potassium *tert*-butoxide in ether for 1 week gave 14% of the dimer **9**.

***trans*-Stilbene.** The method of Baumgarten[15] was used to generate $8g_2$ from **7g** (2.27 g, 10 mmol). Unreacted α-toluenesulfonamide (60%) and *trans*-stilbene (40%) were isolated. *trans*-Stilbene was identified by comparison with an authentic sample.

Base-Induced "Cyclizations." A. With Triethylamine. A solution of $8g_1$ (308 mg, 1.007 mmol) and triethylamine (102 mg, 1.008 mmol) in 6.5 ml of benzene was refluxed with stirring for 42 hr. The reaction mixture was cooled and filtered. The precipitate of triethylammonium hydrobromide (70.8% recovery) was washed with benzene, and the washings were combined with the filtrate. Removal of benzene *in vacuo* gave a yellow-brown oil which was shown by ir and nmr to consist of unreacted $8g_1$ and the Schiff base **10**. Nmr integration showed the yield of **14** to be 78.7%. The mixture was separated by chromatography on SilicAR cc-7, using either benzene or methylene chloride as eluent.

The Schiff base **10** was found to be identical with an authentic sample. No other products were observed.

B. With Potassium *tert*-Butoxide. To a stirred solution of $8g_1$ (300 mg, 0.98 mmol) in 20 ml of ethyl ether under nitrogen was added in one portion 110 mg (0.98 mmol) of potassium *tert*-butoxide (MSA sublimed). The temperature of the reaction mixture was kept at −12 ± 3° for 2 hr. Centrifugation of the reaction mixture gave a white precipitate of KBr, which was washed with ether, and the washings were combined with the main portion of the decanted etheral solution. Removal of ether *in vacuo* gave a solid shown to be a mixture of $8g_1$ and **10**. Nmr integration showed the yield of **10** to be 65.1%. The remainder was starting material. No other products were observed and **10** could be separated from $8g_1$ by chromatography as described previously.

Reactions of $8h_2$ with triethylamine or potassium *tert*-butoxide were carried out as described above. Benzonitrile (62%) was isolated and found to be identical with an authentic sample.

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Registry No.—**5a**, 10099-08-8; **5b**, 14403-02-2; **6g**, 1939-99-7; **6h**, 51270-34-9; **7g**, 51270-35-0; $8a_1$, 51270-36-1; $8a_2$, 51270-37-2; $8a_3$, 51270-38-3; $8a_4$, 51270-39-4; $8a_5$, 51270-40-7; **8b**, 51270-41-8; $8g_1$, 51270-42-9; $8g_2$, 51270-43-0; $8h_1$, 51270-44-1; $8h_2$, 51270-45-2; **9**, 51270-46-3; *tert*-butylamine, 75-64-9; propylamine, 107-10-8; cyclohexylamine, 108-91-8; dimethylamine hydrochloride, 506-59-2; piperidine, 110-89-4; *N*-bromosuccinimide, 128-08-5; *tert*-butyl hypochlorite, 507-40-4.

Supplementary Material Available. Spectral and analytical data for compounds 8 will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155

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2-Amino-2-thiazoline. VII.[1] Unequivocal Structure Assignment of the Products of the Reaction of 2-Amino-2-thiazoline and Its Analogs with Carbethoxy Isothiocyanate

Daniel L. Klayman* and Thomas S. Woods

Division of Medicinal Chemistry, Walter Reed Army Institute of Research, Washington, D. C. 20012

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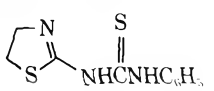
The reaction of 2-amino-2-thiazoline (**1**) with carbethoxy isothiocyanate (**3**) was found to give 2,3,6,7-tetrahydro-4*H*-thiazolo[3,2-*a*]-*s*-triazin-2-one-4-thione (**5**), the structure of which was confirmed by an X-ray crystallographic study. The reaction of **3** with 2-amino-5,6-dihydro-4*H*-1,3-thiazine (**15**), with 2-amino-4,4-dimethyl-2-thiazoline (**17**), and with 2-amino-2-selenazoline (**20**) also gave the analogous heterobicycles, 2,3,7,8-tetrahydro-4*H*,6*H*-thiazino[3,2-*a*]-*s*-triazin-2-one-4-thione (**16**), 2,3,6,7-tetrahydro-6,6-dimethyl-4*H*-thiazolo[3,2-*a*]-*s*-triazin-2-one-4-thione (**19**), and 2,3,6,7-tetrahydro-4*H*-selenazolo[3,2-*a*]-s-triazin-2-one-4-thione (**21**), respectively. The product **19** showed magnetic nonequivalence of the two methyl groups. Treatment of **5** with diazomethane gave two products, the result of both S- and N-methylation.

The differing nucleophilic character of the exocyclic and endocyclic nitrogen atoms of 2-amino-2-thiazoline (**1**) has been the subject of many studies. Reactions at the exocyclic nitrogen atom have been noted with nitrous acid,[2] acyl chlorides,[3] and cyanate ion,[4] whereas reactions with the endocyclic nitrogen have been reported in alkylations[2,5] and sulfonylations.[6] The condensation of **1** and isothiocyanates has been surrounded by some controversy. Fromm and Kapeller-Adler[7] reported that the reaction of **1** with phenyl isothiocyanate gave the product resulting from attack on the ring nitrogen when conducted at low temperature, but the exocyclic thiourea product at higher temperature. Klayman and coworkers,[8] who were able to isolate only a single monoadduct regardless of conditions, demonstrated by chemical and physicochemical means that the exocyclic nitrogen atom of **1** reacted with phenyl isothiocyanate, giving 1-(2-thiazolinyl)-3-phenyl-2-thiourea (**2**). Their work was confirmed by an X-ray crystallographic study.[9]



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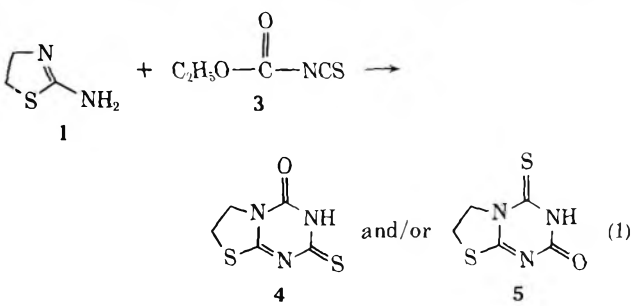
Carbethoxy isothiocyanate (**3**) is a useful reagent for the preparation of heterocyclic compounds through its reaction with amidines,[10] thiopseudoureas,[10] pseudoureas,[10] guanidines,[10] 2-aminopyridines,[11] 3-aminopyridazines,[12] 3-aminopyrazole,[13] 2-aminooxazoline,[13] 3-amino-1,2,4-triazoles,[13-15] 2-aminothiazoles,[16-18] enamines,[19] 2-amino-2-cyanoacetamide,[20] and 2-aminoacetonitrile.[21]

The reaction of **1** with carbethoxy isothiocyanate (**3**), studied by Capuano and Schrepfer,[13] could lead to either



1 **3** **4** **5**

(1)

or both of two possible products, **4** and **5** (eq 1). In fact, a single isomer is produced in the reaction, one to which Capuano and Schrepfer[13] assigned structure **4**; however, these workers presented no evidence for their structure assignment. The later work of Nagano, *et al.*,[16-18] indicated that 2-aminothiazole reacts with **3** to give, among other products, a heterobicycle resulting from attack of **3** on the endocyclic aromatic nitrogen atom. Extending the analogy to the case of **1**, the endocyclic attack could be favored, and structure **4**, proposed by the previous workers,[13] would thus be incorrect.

The present investigation was consequently undertaken to differentiate unequivocally between structures **4** and **5**,

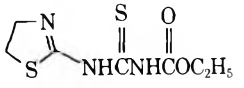
and to probe the steric and electronic requirements of the reaction of 1 with 3. Furthermore, the investigation included the study of the products of a previously reported methylation reaction, the structural assignments of which were suspect.

Results and Discussion

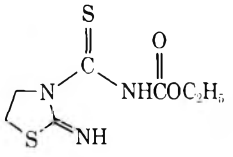
2-Amino-2-thiazoline (1). Two general procedures were employed to prepare the heterobicycles for study. The more convenient procedure (method A), based on that reported by Goerdeler and Neuffer[10] for the reaction of 3 with various acyclic ureas and their analogs, was to neutralize a hydrohalide salt of the starting material with aqueous sodium hydroxide, while a benzene solution of 3 was simultaneously added. In the second (method B), 3, generated *in situ*, was utilized in the reaction with the free base form of the starting thiazoline or related material.

The reaction of 2-amino-2-thiazoline (1) with 3 led to similar yields of the bicyclic product 4/5 by method A and method B. That the product was the same compound as that isolated by Capuano and Schrepfer[13] was shown by its elemental analysis and by the proximity of its melting point (281–283°) to that found by these earlier workers (275°).

The initial reaction of 1 with 3 could lead to two possible intermediates, 6 or 7. Steric considerations and the



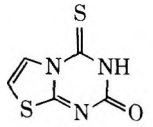
6



7

previously discussed indications that the isothiocyanate group preferentially attacks the exocyclic nitrogen atom of 1[8,9] would tend to favor the intermediate 6; however, in view of the duodirectional attack which 1 may undergo, 7 also could be the intermediate in the cyclization.

The ir spectrum of 4/5 was compared with those reported for 8 and 9, prepared by Nagano, *et al.*,[17a] which possess the same ring structure but with an additional C–C double bond in the five-membered ring. Compound 8 was formed directly on treatment of 2-aminothiazole with 3, and 9 was prepared by thermolysis of 1-(2-thiazolyl)-3-



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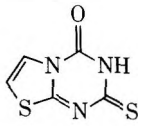


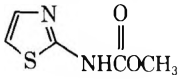
9

carbethoxy-2-thiourea (10, eq 2), which was also present in the reaction mixture. The structures of 8 and 9 were

10

$$\xrightarrow{180\text{–}190^\circ} \mathbf{9} \qquad (2)$$

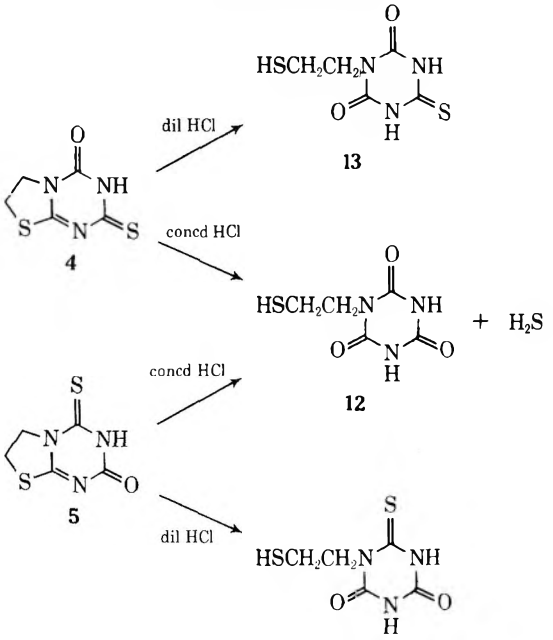
confirmed by conversion of 8 to the independently synthesized methyl *N*-(2-thiazolyl)carbamate (11) on treatment



11

with refluxing methanol, a process which would have given a thioncarbamate if the structure were 9; however, 4/5 was inert to these conditions. The spectrum of the model compound 8 shows an intense band at 1680 cm^{-1}, and that of 9 contains absorptions at 1755 and 1740 cm^{-1}.

Scheme I
Possible Acid-Catalyzed Hydrolytic Pathways for the Heterobicyclic Product 4/5



4 13 12 5 14

The ir spectrum of 4/5 shows, however, a strong carbonyl band at 1672 cm^{-1}. On this basis, compound 4/5 appears to be structured similarly to 8, which, in turn, is related to 5.

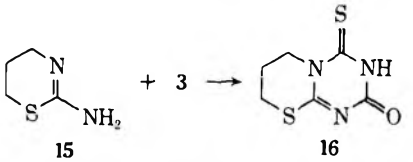
Klayman and Milne[1] have reported that the dihydrothiazolo ring of the 2,3,6,7-tetrahydro-4*H*-thiazolo[3,2-*a*]triazine system is labile to acid and opens to give a mercaptoethyltriazine compound. In concentrated acid, accompanying hydrolysis of the thiocarbonyl group of 4 or 5 would give 1-(2-mercaptoethyl)-1,2,3,4,5,6-hexahydro-*s*-triazine-2,4,6-trione (12, Scheme I). This experiment was conducted, and 12 was indeed obtained from the heterobicycle in high yield. The nmr spectrum of 12 showed the ring NH protons appearing at δ 11.55 in addition to complex upfield signals due to the mercaptoethyl side chain. An appropriate model for the magnetic environment of the NH protons of 12 could be provided by that of cyanuric acid, the nmr signal of which has been shown to appear at δ 11.1.[1]

Treatment of 4/5 with dilute acid opened the thiazoline ring but left the thiocarbonyl group intact (Scheme I). The ir spectrum of the product was similar to that of 12 except for the 1100–1300-cm^{-1} region, in which new bands, perhaps attributable to C=S stretching, appeared. Support for the correct *s*-triazine structure, 13 or 14, for this product could be provided by nmr spectrometry if exchange between the ring NH protons were slow on the nmr time scale. The spectrum of the hydrolyzed product showed, in addition to the upfield aliphatic region, a single broad absorption centered at δ 12.47. Thus the structure of the product could not be assigned, nor the structure of 4/5 inferred, by this technique, since the equivalent ring protons of 13 and exchange-averaged ring hydrogens of dissymmetric 14 would each appear as a single band.

Unequivocal evidence was provided by X-ray crystallography[22] that the structure of 4/5 is 2,3,6,7-tetrahydro-4*H*-thiazolo[3,2-*a*]-*s*-triazin-2-one-4-thione (5). The original structural assignment of Capuano and Schrepfer[13] is consequently shown to be incorrect. By extension of this finding, then, the structure of the product of the dilute acid-catalyzed hydrolysis of 5 is the unsymmetrical compound 1-(2-mercaptoethyl)-1,2,3,4,5,6-hexahydro-*s*-tria-

zine-4,6-dione-2-thione (14), the exchange between the ring protons of which must be too rapid to detect on the nmr time scale. The good agreement of the carbonyl stretching frequency of 5 with that of the analogous compound 8 indicates that such comparisons might be fruitful in diagnostic studies of structures of products of carbethoxy isothiocyanate (3) and bifunctional compounds in which the direction of attack may not be deduced *a priori*.

Other Analogs of 2-Amino-2-thiazoline. Treatment of 2-amino-5,6-dihydro-4*H*-1,3-thiazine (15) with carbethoxy isothiocyanate (3) gave the cyclized product 2,3,7,8-tetrahydro-4*H*,6*H*-thiazino[3,2-*a*]-*s*-triazin-2-one-4-thione (16) in 55 and 45% yields by methods A and B, respectively (eq 3). The relative positions of the carbonyl and thio-

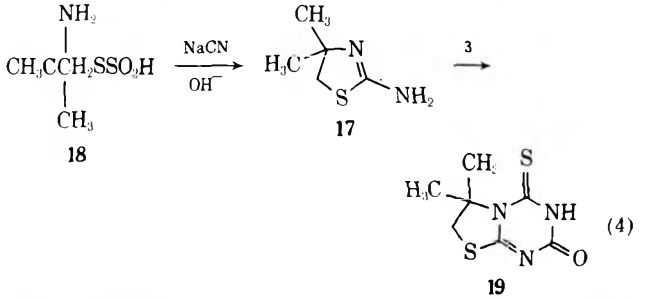


(3)

15 16

carbonyl groups of 16 and subsequently discussed analogs are assigned by analogy to 5 and by the similarity of their ir carbonyl stretching frequencies to that of 5. Whereas molecular models show the 2-amino-2-thiazoline ring to be essentially flat with only a slight pucker, the more flexible six-membered ring may assume a pseudo-chair or pseudo-boat conformation and their intermediate variations. In all of these conformations, the lone pair of electrons on the imino nitrogen atom, which must interact with the carbonyl carbon of the intermediate analogous to 7 to affect cyclization, is forced out of the quasi-plane of the SC=N moiety. This aspect of the ring system requires a more hindered arrangement of the atoms of the side chain than in the five-membered ring case; consequently, the cyclization step might be expected to be less favorable than in the case of 1; however, no significant difference in yield of 16 compared to that of 5 was obtained.

The steric effect of substitution in the 4 position of the thiazoline ring was investigated by beginning with 2-amino-4,4-dimethyl-2-thiazoline (17), prepared from 2-amino-2-methylpropanethiosulfuric acid (18) by treatment with alkaline sodium cyanide. Reaction of 17 with 3 gave the cyclized product 2,3,6,7-tetrahydro-6,6-dimethyl-4*H*-thiazolo[3,2-*a*]-*s*-triazin-2-one-4-thione (19) in 67% yield (method A) (eq 4), similar to the yield obtained from 1. The product 19 could not be obtained by the free base method (method B).



(4)

18 17 19

Compound 19 exhibits some interesting physical properties. For example, 19, obtained as tiny yellow needles, is the only colored compound of the series. The uv spectrum of 19 shows a 17-nm bathochromic shift of the 282-nm shoulder noted in the spectrum of 5, with formation of a new maximum at 299 nm. The electron-releasing effect of the large hydrocarbon portion at position 6 of 19 could raise the energy of its ground electronic state, causing a lower energy transition relative to that of 5. This considerable steric bulk could alternatively disrupt the energy levels of 19 relative to those of 5 by requiring hybridization changes. Separation of steric and electronic effects in these cases is tenuous at best. The most interesting physical property of 19, however, is the magnetic nonequivalence of the methyl groups in the 6 position. The two groups appear separated by 0.21 ppm at δ 1.67 and 1.88. A Fisher–Hirschfelder–Taylor molecular model of 19 (see Figure 1) shows that one methyl is held relatively rigidly in the diamagnetically anisotropic region of the thiocarbonyl group in position 4, whereas the other methyl group is below the plane formed by the two rings. Inversion of the dihydrothiazolo ring is sterically inhibited, and thus the magnetic environments of the two methyl groups are not averaged. This observed phenomenon provides a classic example of the diamagnetic anisotropy effect of the thiocarbonyl group, as has been noted in thioureas.[23]

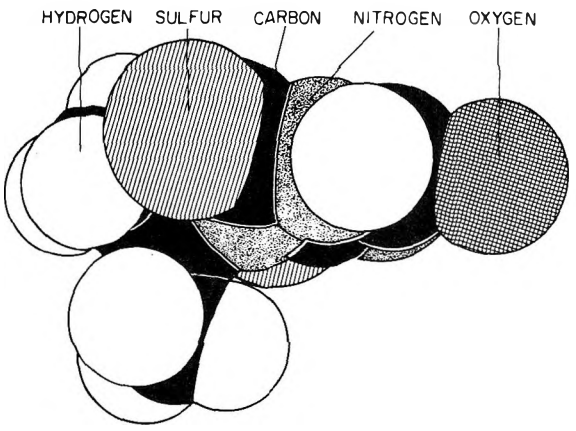
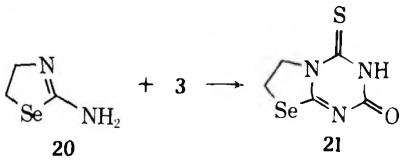


Figure 1. Fisher–Hirschfelder–Taylor model of 2,3,6,7-tetrahydro-6,6-dimethyl-4*H*-thiazolo[3,2-*a*]-*s*-triazin-2-one-4-thione (19).

Since the 8-oxygen analog of 5 had previously been prepared,[13] though by analogy with 5 the structure assignment was incorrect, it was decided to study the electronic effect of placing the next higher member of group 6a, selenium, into the starting material. Thus, 2-amino-2-selenazoline (20) was treated with 3 to give the product, 2,3,6,7-tetrahydro-4*H*-selenazolo[3,2-*a*]-*s*-triazin-2-one-4-thione (21), in 83 and 37% yields by methods A and B, respectively (eq 5), which indicated that the presence of the less electronegative selenium atom did not alter the reaction appreciably.



(5)

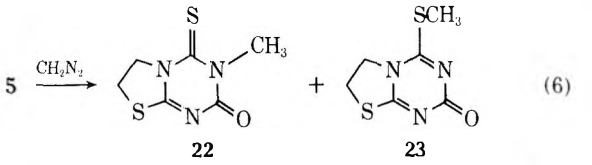
20 21

In conclusion, carbethoxy isothiocyanate (3) shows great promise in the preparation of heterocyclic compounds, the formation of which probably proceeds by a two-step dielectrophilic addition mechanism. The direction of attack of 3 on dinucleophiles may not be predicted with certainty, however, and structural assignments should be made circumspectly. The initial position of reaction may be influenced by steric and/or electronic factors; thus, further studies would be useful in developing diagnostic criteria for these reactions.

It appears that the physiological properties of carbethoxy isothiocyanate (3) have not been investigated. On exposure to the vapor of 3, three workers in this laboratory experienced its toxic effects, which included respiratory distress, headaches, and heart palpitations, the severity of which increased on repeated exposure. The reagent, therefore, should be handled with great caution in well-ventilated areas.

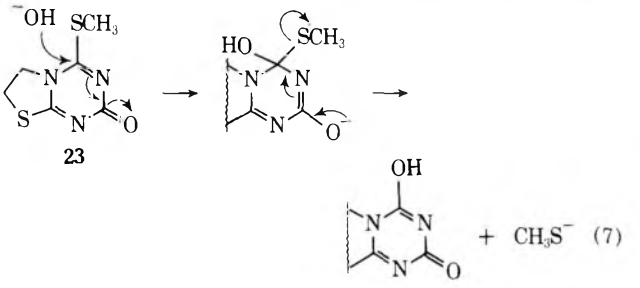
Reaction of 5 with Diazomethane. Capuano and

Schrepfer[13] treated **5** (believed by them to have structure **4**) with an excess of ethereal diazomethane and reported the isolation of solely the *N*-methyl product corresponding to **22**, mp 213°. When we repeated this reaction under the identical conditions, however, we obtained both the *N*-methyl (**22**, mp 149–150°) and the *S*-methyl (**23**, mp 218.5–219°) products (eq 6), which were separable by fractional crystallization. Thus, it appears that Capuano and Schrepfer not only failed to isolate the second product in the reaction, but also mistakenly assumed that N-methylation rather than S-methylation had occurred to give the 213° melting material.



22 23

The structures of **22** and **23** were assigned on the following bases. *Compound* **23** *gives a strong* nitroprusside test for thiol,[24] indicating displacement of methanethiolate ion from **23** (eq 7) under the strongly alkaline conditions of the test. No nitroprusside test was obtained from **22**, nor does the starting material **5** give such indication; consequently, production of thiol in strong base from **23** does not arise by opening of the dihydrothiazolo ring by hydroxide ion. Spectroscopic evidence also confirms the assignments. The carbonyl absorption in the ir spectrum of **23** appears at 1661 cm^{-1}, whereas that of **22** appears at 1701 cm^{-1}. It would be expected that the juxtaposition of the two carbon–nitrogen double bonds and the carbonyl of **23** would cause it to appear at lower frequency. The nmr spectrum of **23** shows a methyl absorption at δ 2.57, as opposed to a similar signal at δ 3.57 for **22**. The deshielding effects of the adjacent carbonyl and thiocarbonyl of **22** would cause the observed lower field signal in its spectrum. In addition, *N*-methyl signals generally appear at lower field than do *S*-methyl absorptions, though there is some overlap in the ranges.[25] The uv spectrum of **23** (λ_{max} 231 nm) is very different from that of **22** (λ_{max} 260 and 210 nm), which in turn is similar to that of the starting material **5** (λ_{max} 262 and 206 nm), as would be expected considering the analogous electronic structures of **5** and **22**. Finally, the base peak in the mass spectrum[26] of **23** appears at *m/e* 154, corresponding to a loss of 47 mass units ($\cdot SCH_3$) from the molecular ion (*m/e* 201). No such peak appears in the spectrum of **22**. Thus, these data indicate that the compound isolated by Capuano and Schrepfer[13] was in fact **23**, and that the *N*-methyl isomer **22** was also produced in the reaction.



23

Experimental Section

Infrared spectra were determined on a Beckman IR-5 spectrophotometer in KBr pellets unless otherwise indicated. Nuclear magnetic resonance spectra were taken on a Varian Associates A-60 spectometer using TMS as the internal standard. Mass spectra were run on a Hewlett-Packard 5930 A mass spectometer, and ultraviolet spectra were taken on a Beckman DB-G recording spectrophotometer. Melting points were determined on a Kofler hot stage and are corrected. Microanalyses were performed by the analytical staff of the Stanford Research Institute, Menlo Park, Calif. 94025, and by Dr. Harry Agahigian of the Baron Consulting Company, Milford, Conn. 06477.

Reaction of Carbethoxy Isothiocyanate (3) with Amino Heterocycles. Method A. A procedure similar to that reported by Goerdeler and Neuffer[10] was employed. To a mixture of 10 mmol of the hydrohalide salt of the starting 2-amino heterocycle in 10 ml of water and 40 ml of benzene was added, simultaneously with vigorous stirring, 10 ml of a benzene solution of 1.8 g (14 mmol) of carbethoxy isothiocyanate (**3**)[10,27] and 10 ml of 1 *N* NaOH over 15 min. An additional 10 ml of 1 *N* NaOH was then added, and stirring was continued for 1 hr. The aqueous layer was separated; the benzene solution was extracted with 10 ml of 1 *N* NaOH, and the combined aqueous extracts were made acidic with 6 *N* H_2SO_4. The precipitated product was collected, washed with water, and recrystallized from aqueous DMF.

Method B. Ethyl chloroformate (4.34 g, 40 mmol) and 4.1 g (42 mmol) of potassium thiocyanate in 100 ml of acetone were heated on a steam bath for 15 min, and the precipitated KCl was removed by filtration through Celite. To the filtrate was added a solution of 10 mmol of the free base form of the starting heterocycle in 200 ml of CH_2Cl_2, and the resulting mixture was heated for 0.5 hr. The precipitated product was collected, and the filtrate was concentrated to give a second crop. The combined batches were washed with water to remove unreacted KSCN and recrystallized from aqueous DMF.

2,3,6,7-Tetrahydro-4*H*-thiazolo[3,2-*a*]-*s*-triazin-2-one-4-thione (5). Compound **5** was prepared from 2-amino-2-thiazoline (**1**) in 65 (method A) and 70% yields (method B) and was obtained as colorless plates: mp 281–283° (lit.[13,28] mp 275°); ir (KBr) 3040 (NH), 2900 (CH), 1672 (C=O), and 1540 cm^{-1} (NH); nmr (DMSO-d_6) δ 3.57 and 4.63 (m, A_2B_2, 4, SCH_2CH_2N), and 12.78 (broad s, 1, NH); uv (C_2H_5OH) 282 nm (sh, ϵ 10,400), 262 (max, 14,900), 245 (sh, 12,000), and 206 (max, 11,500); mass spectrum (70 eV) *m/e* (rel intensity) 187 (100), 128 (76), 86 (22), 82 (16), 60 (63), 59 (26), and 58 (13).

Anal. Calcd for $C_5H_5N_3OS_2$: C, 32.07; H, 2.69; N, 22.44; S, 34.25. Found: C, 32.19; H, 2.94; N, 22.47; S, 34.45.

A suspension of 1.87 g (10.0 mmol) of **5** in 100 ml of CH_3OH was heated under reflux for 18 hr. The undissolved solid was collected and dried to give 1.74 g (93% recovery) of **5**, mp 278–280°, ir (KBr) identical with that of **5**.

2,3,7,8-Tetrahydro-4*H*,6*H*-thiazino[3,2-*a*]-s-triazin-2-one-4-thione (16). Compound **16** was prepared from 2-amino-5,6-dihydro-4*H*-1,3-thiazine (**15**) hydrochloride[29] in 55 (method A) and 45% yield (method B) as colorless needles: mp 247–249°; ir (KBr) 3040 (NH), 2890 (CH), 1661 (C=O), and 1520 cm^{-1} (NH); nmr (DMSO-d_6) δ 2.29 (m, 2, CCH_2C), 3.30 (t, J = 6 Hz, 2, CH_2CH_2S), 4.38 (t, J = 5.5 Hz, 2, CH_2CH_2N), and 12.72 (broad s, 1, NH); uv (C_2H_5OH) 290 nm (sh, ϵ 8670), 270 (max, 19,900), 239 (sh, 12,100), and 206 (max, 15,200); mass spectrum (70 eV) *m/e* (rel intensity) 201 (48), 142 (100), 127 (13), 114 (81), 86 (57), 74 (11), and 59 (19).

Anal. Calcd for $C_6H_7N_3OS_2$: C, 35.81; H, 3.51; N, 20.88; S, 31.86. Found: C, 35.70; H, 3.60; N, 20.89; S, 31.66.

4,4-Dimethyl-2-amino-2-thiazoline (17). Using the procedure developed by Klayman and Milne,[28] a solution of 25.0 g (0.135 mol) of 2-amino-2-methylpropanethiosulfuric acid (**18**),[30] 5.6 g (0.14 mol) of NaOH, and 8.33 g (0.17 mol) of NaCN in 200 ml of water was stirred at room temperature for 16 hr. The solvent was removed under reduced pressure, and the residue was triturated with four 50-ml portions of $CHCl_3$. Evaporation of the dried $CHCl_3$ extracts gave a yellowish oil which crystallized on cooling. Trituration and recrystallization of the material from hexane gave 14.6 g (83%) of **17** as large prisms: mp 74–74.5°; ir (KBr) 3460 (NH_2), 2950 (CH), 1660 (C=N), 1590 (NH_2), and 1445 cm^{-1} (CH); nmr ($CDCl_3$) δ 1.32 (s, 6, 2 CH_3), 3.16 (s, 2, CH_2S), and 5.68 (s, 2, NH_2).

Anal. Calcd for $C_5H_{10}N_2S$: C, 46.12; H, 7.74; N, 21.51; S, 24.62. Found: C, 46.31; H, 7.81; N, 21.54; S, 24.80.

2,3,6,7-Tetrahydro-6,6-dimethyl-4*H*-thiazolo[3,2-*a*]-s-triazin-2-one-4-thione (19). Compound **19** was prepared by method A from 4,4-dimethyl-2-amino-2-thiazoline (**17**) in 67% yield as tiny yellow needles: mp 192–193°; ir (KBr) 3100 (NH), 2920 (CH), 1695 (C=O), and 1545 cm^{-1} (NH); nmr (DMSO-d_6) δ 1.67 (s, 3, CH_3), 1.88 (s, 3, CH_3), 3.48 (s, 2, CH_2S), and 12.67 (broad s, 1, NH); uv (C_2H_5OH) 299 nm (max, ϵ 10,100), 262 (max, 13,300), and 205 (max, 13,000); mass spectrum (70 eV) *m/e* (rel intensity) 215 (98), 200 (25), 156 (31), 141 (100), 88 (19), 86 (29), 73 (19), and 55 (23).

Anal. Calcd for $C_7H_9N_3OS_2$: C, 39.05; H, 4.21; N, .52; S, 29.79. Found: C, 38.82; H, 4.27; N, 19.58; S, 29.70.

2,3,6,7-Tetrahydro-4*H*-selenazolo[3,2-*a*]-*s*-triazin- :ne-4-thione (21). Compound **21** was prepared from 2-amino-2 lenazo-line (20) hydrobromide[31] in 83 (method A) and 37% yi (meth-od B) as colorless needles: mp 255–258° dec; ir (KBr) 3) (NH), 2910 (CH), 1675 (C=O), and 1535 cm^{-1} (NH); nmr (D O-d_6) δ 3.56 and 4.71 (m, A_2B_2, 4, SCH_2CH_2N) and 12.33 (l ıd s, 1, NH); uv (C_2H_5OH) 277 nm (max, ϵ 19,500), 251 (sh, 1)0), and 206 (max, 14,400); mass spectrum (70 eV) *m/e* (rel int ity) 237 (17), 236 (11), 235 (63), 234 (12), 233 (34), 232 (15), 2 17), 178 (12), 176 (44), 175 (12), 174 (25), 173 (15), 172 (14), 1 23), 109 (12), 108 (100), 107 (28), 106 (57), 105 (30), and 104 (29).

Anal. Calcd for $C_5H_5N_3OSSe$: C, 25.65; H, 2.15; N 7.95, S, 13.69; Se, 33.72. Found: C, 25.97; H, 2.34; N, 18.26; S 3.84; Se, 33.4.

Acid-Catalyzed Hydrolysis of 5. A stirred suspens of 2.00 g (10.7 mmol) of **5** in 100 ml of 18% HCl was heated er reflux under an argon atmosphere for 6.5 hr, during which e consid-erable H_2S evolution was detected with lead(II) ac e paper. Cooling gave, on filtration, 1.53 g of analytically pu -(2-mer-captoethyl)-1,2,3,4,5,6-hexanhydro-*s*-triazine-2,4,6-tr (**12**). Evaporation of the filtrate and addition of 5 ml of gave an additional 0.37 g for a total yield of 94% of **12**: mp -258°; ir (KBr) 3100 (NH), 2760 (CH), 2551 (SH), 1727 and (C=O), and 1460 cm^{-1} (NH); nmr (DMSO-d_6) δ 2.64 (m H_2S + SH), 3.90 (m, 2, CH_2N), and 11.55 (s, 2, 2 NH).

Anal. Calcd for $C_5H_7N_3O_3S$: C, 31.74; H, 3.73; , 22.21; S, 16.95; SH, 17.48. Found: C, 31.68; H, 3.85; N, 22.07; , 16.64; SH, 17.4.

Dilute Acid Hydrolysis of 5. A stirred suspension of 0.50 g (2.67 mmol) of **5** in 78 ml of 0.46 *N* HCl was heated under reflux for 20 min under an argon atmosphere, whereupon traces of H_2S evolution could be detected with lead(II) acetate paper. The reaction flask was immediately immersed in an ice bath, causing 0.485 g (89%) of 1-(2-mercaptoethyl)-1,2,3,4,5,6-hexahydro-*s*-triazine-4,6-dione-2-thione (**14**) to crystallize as fine needles: mp 172–174°; ir (KBr) 3110 (NH), 2750 (CH), 2551 (SH), 1748 and 1715 (C=O), 1485 (NH), 1255, 1215, 1165, and 1153 cm^{-1} (NH, C=O, and C=S combination bands); nmr (DMSO-d_6) δ 2.81 (m, 3, CH_2S + SH), 4.46 (m, 2, CH_2N), and 12.47 (broad s, 2, 2 NH).

Anal. Calcd for $C_5H_7N_3O_2S_2$: C, 29.25; H, 3.44; N, 20.47; S, 31.34; SH, 16.11. Found: C, 29.42; H, 3.42; N, 20.39; S, 31.06; SH, 16.6.

Treatment of 5 with Diazomethane. The experiment was conducted by repeating the conditions of Capuano and Schrepfer[13] as follows. To approximately 250 ml of an ethereal solution of diazomethane generated from 7.5 g of Diazald (Aldrich) was added 1.5 g (8.0 mmol) of **5** moistened with 1 ml of CH_3OH. The mixture was stirred for 26 hr in a loosely corked flask, and the solid phase (1.10 g, 69%), mp 150–211°, was collected. Concentrating the filtrate gave an additional 0.20 g, bringing the total yield of methylated product to 81%. An nmr spectrum of the crude mixture (DMSO-d_6) indicated the presence of both NCH_3 and SCH_3 isomers (approximate ratio NCH_3:SCH_3 = 3:2). Three recrystallizations of the mixture from CH_3CN gave colorless needles of 6,7-dihydro-4-methylthio-2*H*-thiazolo[3,2-*a*]-*s*-triazin-2-one (**23**), which gave a strong nitroprusside test: mp 218.5–219° (lit.[32] mp 213°); ir (KBr) 2990 (CH), 1661 (C=O), 1580 (C=N), and 1460 cm^{-1} (CH); nmr (DMSO-d_6) δ 2.57 (s, 3, SCH_3), 3.57 and 4.39 (m, A_2B_2, 4, SCH_2CH_2N); uv (C_2H_5OH) 236 nm (sh, ϵ 21,000) and 231 (max, 21,100); mass spectrum (70 eV) *m/e* (rel intensity) 201 (29), 154 (100), 128 (87), 94 (36), 86 (86), 69 (12), 60 (85), 59 (31), 58 (16), 47 (13), 46 (18), 45 (34), and 44 (11).

Anal. Calcd for $C_6H_7N_3OS_2$: C, 35.81; H, 3.51; N, 20.88; S, 31.86. Found: C, 35.81; H, 3.85; N, 20.96; S, 32.07.

The colorless solid isolated by evaporation of the first CH_3CN filtrate was recrystallized three times from CH_3OH to give very fine, colorless needles of 2,3,6,7-tetrahydro-3-methyl-4*H*-thiazolo-[3,2-*a*]-*s*-triazin-2-one-4-thione (**22**), which gave a negative nitroprusside test: mp 149–150°; ir (KBr) 2980 (CH), 1701 (C=O), 1580 (C=N), and 1455 cm^{-1} (CH); nmr (DMSO-d_6) δ 3.57 (s, 3, NCH_3), 3.62 and 4.68 (m, A_2B_2, 4, SCH_2CH_2N); uv (C_2H_5OH) 271 nm (sh, ϵ 14,600), 260 (max, 19,800), and 210 (max, 14,000); mass spectrum (70 eV) *m/e* (rel intensity) 201 (55), 129 (17), 128 (48), 86 (21), 74 (13), 73 (19), 72 (15), 60 (100), 59 (21), 58 (11), 45 (23), 28 (17), and 27 (12).

Anal. Calcd for $C_6H_7N_3OS_2$: C, 35.81; H, 3.51; N, 20.88; S, 31.86. Found: C, 35.92; H, 3.79; N, 20.89; S, 31.87.

Acknowledgment. We are grateful to Mrs. Judith L. Flippen, Naval Research Laboratory, Washington, D. C., for the X-ray determination. We also thank Dr. T. Scott Griffin for valuable suggestions, Dr. James A. Kelley for the mass spectra, and Mr. Robert L. Runkle for technical assistance.

Registry No.—**1**, 1779-81-3; **3**, 16182-04-0; **5**, 51270-92-9; **12**, 51270-93-0; **14**, 51270-94-1; **15** hydrochloride, 2799-74-8; **16**, 51270-95-2; **17**, 51270-96-3; **18**, 4039-24-1; **19**, 51270-97-4; **20** hydrobromide, 2697-62-3; **21**, 51270-98-5.

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(26) The mass spectra of all of the compounds mentioned here are under further study.
(27) An ir spectrum of the carbethoxy isothiocyanate ($CHCl_3$) showed peaks at 1930 (N=C=S) and 1735 cm^{-1} (C=O).
(28) Capuano and Schrepfer (ref 13) assigned the 4-one-2-thione structure **4** to this compound.
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Synthesis of Novel Spiro Heterocycles. 2-Amino-7-oxa-3-thia-1-azaspiro[5.5]undec-1-enes[1]

Noal Cohen,* Bruce L. Banner, John F. Blount, Giuseppe Weber, Moujau Tsai, and Gabriel Saucy

Chemical Research Department, Hoffmann-La Roche Inc., Nutley, New Jersey 07110

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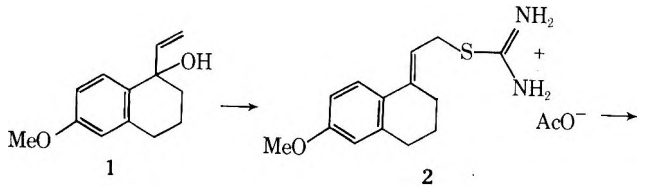
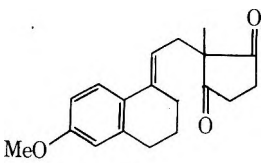
Reaction of the vinyl 4-hydroxyalkyl ketones **4a–d** with thiourea in acetic acid gave epimeric mixtures of the 8-substituted 2-amino-7-oxa-3-thia-1-azaspiro[5.5]undec-1-enes **15a–d** (major) and **16a–d** (minor). The relative stereochemistry of these epimers was deduced using nmr spectroscopy. These adducts were selectively monoacylated in series **a–c**, giving the derivatives **17** and **18**. The unsubstituted amino spirothiazinepyran **24** was prepared by treatment of the Mannich base **23** or the diol **31e** with thiourea. An X-ray crystal structure determination of the *p*-bromobenzoyl derivative **35** confirmed the structures of these novel heterocycles. These compounds exhibit facile ring-open-chain isomerism under acidic conditions, certain manifestations of which are described. Reaction of the aminothiazine mixtures **15b, 16b** and **15d, 16d** with 2-methyl-1,3-cyclopentanedione in the presence of aqueous acid led, in modest yields, to the dienes **8b** and **8d**, respectively. The latter compounds have previously been shown to be useful in certain total syntheses of 19-norsteroids and related compounds.

The allylic isothiuronium salt **2** was first synthesized by Kuo, Taub, and Wendler[2] and shown to be of utility in a variation of the Torgov-Smith[3-5] estrone total synthesis. This material is produced in high yield by treatment of the conventional intermediate,[3-5] vinyl carbinol **1**, with thiourea in acetic acid and couples efficiently with 2-methyl-1,3-cyclopentanedione giving the dione **3**. Related isothiuronium salts have been prepared and used as intermediates for the synthesis of thiasteroids,[6] oxasteroids,[7] and steroid analogs.[8]



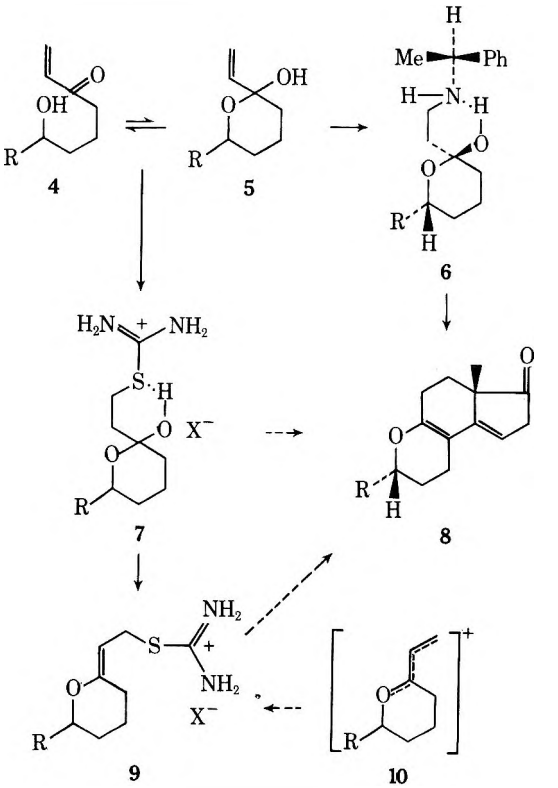
1 **2**



3

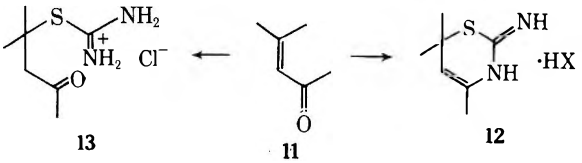
In our own laboratories, several efficient schemes for the total synthesis of optically active 19-norsteroids have been developed which utilize vinyl 4-hydroxyalkyl ketones such as **4** as key intermediates.[9] Addition of optically active α-methylbenzylamine to these vinyl ketones gives a mixture of diastereomeric Mannich bases which can be separated by recrystallization of the oxalic acid salts.[10] The resultant diastereomer **6** (or related derivatives) on condensation with 2-methyl-1,3-cyclopentanedione then yields the key steroidal precursor, dienol ether **8**, with substantial asymmetric induction at C_{13} being observed.

The vinyl ketones **4** exist in equilibrium with the hemiketal form **5**, a species which bears a structural resemblance to the carbinol **1**. For this reason we felt that a study of the reaction of thiourea with compounds such as **4** would be of interest in determining whether novel intermediates, capable of optical resolution and useful for the total synthesis of 19-norsteroids (by facile conversion into the dienes **8**), could be produced. We envisioned, for example, formation of the adduct **7**, an intermediate which potentially fulfills these requirements and which possesses structural features in common with both the Mannich bases **6** and the isothiuronium salt **2**. The salt **7** could arise from vinyl ketone **4** *via* conjugate addition of thiourea. Alternatively, the enol ether **9**, another potentially useful intermediate, could be formed under acidic conditions either by dehydration of **7** or from the hemiketal **5** *via* coupling of thiourea with the resonance-stabilized carbocationic species **10**.[11]



4 **5** **6** **7** **8** **9** **10**

The reaction of thiourea with simple, α,β-unsaturated ketones has been studied.[12-16] The products are generally those derived from conjugate addition of the sulfur atom to the double bond of the enone followed by cyclodehydration. Mesityl oxide (**11**), for example, was reported to give the 2-imino-2,3-dihydro-6*H*-1,3-thiazine salt **12** on treatment with thiourea in the presence of mineral acid.[13-15]



13 **11** **12**

Table I[a]
8-Substituted 2-Amino-7-oxa-3-thia-1-azaspiro[5.5]undec-1-enes

Compd	Yield, %[b]	Mp, °C	Crystd from[c]	Ir, cm^{-1}[d]	Nmr[e] NH_2[f]	Nmr[e] C_8H	Formula[k]
15a	71(74)	Oil[a]		3500, 3400, 1630, 1620, 1580	4.55	4.13[h]	$C_9H_{16}N_2OS$
16a		144–145	B–A	3500, 3400, 1650, 1625, 1580	4.67	3.67[h]	
15c	74(75)	102–103	B–H	3500, 3400, 1630, 1580	4.50	5.07[i,j]	$C_{14}H_{18}N_2OS$
16c		166–167	A	3500, 3400, 1670, 1650, 1610	6.00[g]	4.60[i]	
15d	79	126–127	A	3500, 3400, 1640, 1580	4.58	3.85[h]	$C_{15}H_{23}N_3O_2S$
16d		153–154	B–H	3500, 3400, 1640, 1620, 1580	4.39	3.50[h]	

[a] Elemental analyses (C, H, N, S) for all compounds except **15a** were submitted to the reviewers and found to be within acceptable limits. Compound **15a** was analyzed as the maleate salt, which is described in the experimental section. [b] Based on lactones **14**. The figures in parentheses are the yields starting from the Mannich bases **26a** and **26c**. [c] B = benzene, A = acetonitrile, H = hexane. Colorless solids were obtained. [d] NH_2 and C=N absorptions measured in $CHCl_3$ solution. [e] Measured in $CDCl_3$ solution (unless otherwise noted) with TMS as an internal standard. Chemical shifts (δ) reported in parts per million. [f] Two-proton singlet resonances except for **16c**. [g] Broad envelope measured in DMSO-d_6. [h] One-proton multiplet ($CDCl_3$). [i] Broadened, one-proton doublet, J = 10 Hz (DMSO-d_6). [j] One-proton doublet of doublets, J = 2, 12 Hz, centered at δ 5.11 in $CDCl_3$. [k] All compounds gave molecular ions in the low-resolution mass spectra corresponding to these molecular formulas. M − 28 peaks[22] were exhibited by all compounds except **15c**.

Willems and Vandenberghe,[16] on the other hand, claimed that interaction of **11** with isothiuronium chloride produced the open-chain isothiuronium salt **13**.

Results

Our initial studies were carried out utilizing the readily available, racemic, monosubstituted δ-lactones **14a**,[17] **14b**,[18] **14c**,[19] and **14d**[20] (Scheme I) as starting materials. These compounds were treated with vinylmagnesium chloride at −50 to −60°[21] giving the vinyl ketones **4a–d**. The latter intermediates, without purification, were treated with thiourea in glacial acetic acid at room temperature,[2] producing, in each series, not the desired adducts **7** or **9** but rather mixtures of two isomeric spirocyclic products **15a–d** and **16a–d** in overall yields of 63–79% based on starting lactone. The epimers **15** and **16** were readily distinguished using thin layer chromatography, the major epimer **15** (see below) being the more mobile component. Separation of these mixtures was difficult but could be accomplished in series **a**, **c**, and d using a combination of dry-column chromatography and recrystallization.

Assignment of the novel spirothiazinepyran structures **15** and **16** to the adducts rests on the following data. These compounds were all found to be strong bases which on the basis of microanalytical and mass spectral data were derived from addition of thiourea to the vinyl ketones **4** followed by loss of a molecule of water. The infrared spectra showed strong bands in the NH_2 and C=N regions consistent with the presence of an aminothiazine ring. Resonance peaks near 4.5 ppm in the pmr spectra also indicated the presence of the NH_2 group. The ultraviolet spectra exhibited no absorption above 205 nm except that due to the chromophores in the substituents R (**c** and **d** series). The mass spectra of the adducts generally showed M − 28 peaks corresponding to loss of ethylene from the thiazine ring *via* a retro Diels–Alder process. This mode of fragmentation is characteristic of 2-amino-5,6-dihydro-4*H*-1,3-thiazines.[22]

A comparison of the pmr spectra of each pair of adducts revealed that, in every series, the resonance due to the axial C_8 proton (H–C–O) of the major epimer occurred at lower field than the corresponding resonance arising from the minor epimer. Treatment of the thiazine mixtures in series **a–c** with acetic anhydride–pyridine gave the corresponding mixtures of acetyl derivatives **17** and **18** (R′ = CH_3; uv max 260–265 nm, see below) which, in contrast to the parent amines, could be readily separated by chromatography on silica gel. As in the case of the parent thiazines, the resonance band due to the C_8 proton in the pmr spectrum of the major acyl derivative was detected at lower field than that due to the minor epimer. These data are summarized in Tables I and II. By integration of the *N*-acetyl peak areas due to **17c** and **18c** in the crude mixture, it was possible to estimate that the ratio of parent amines was approximately 3:1.

It would be expected that the epimer in which the C_8 proton encounters a 1,3-diaxial interaction with the nitro-

Scheme I

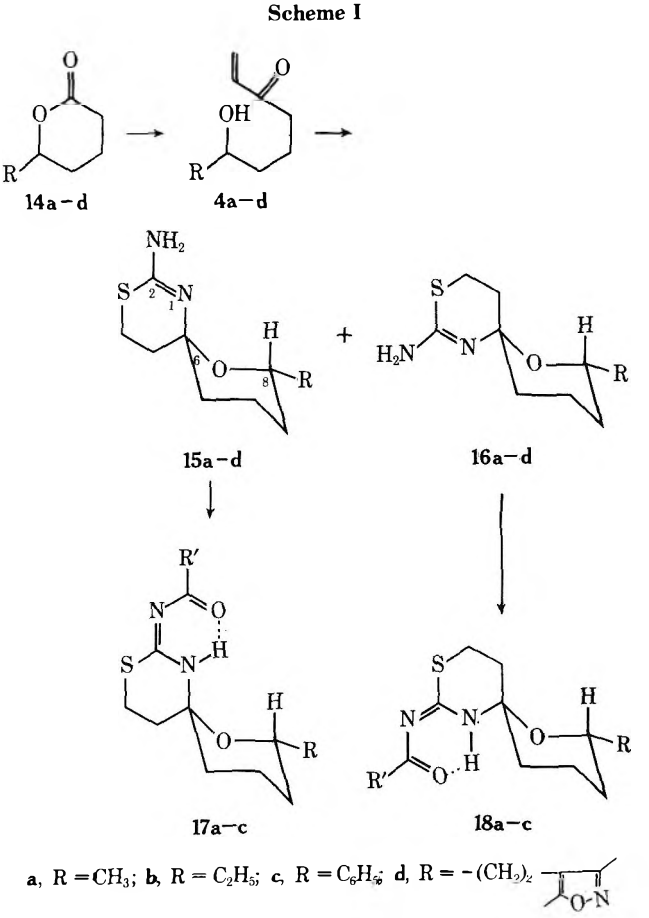


Table II[a]
2-Acylimino-7-oxa-3-thia-1-azaspiro[5.5]undecanes

Compd	R′	Mp, °C	Crystd from[b]	Uv max (ε) 95% EtOH; 0.1 *N* HCl	Ir, cm^{-1} [c]	Nmr[e] C_4 H	Nmr[e] C_8 H	Formula[n]
17a	CH_3	113–114.5	H	220 (6250), 238 (6650), 266 (13,800); 225 (11,000), 245 (11,800)	3400–3100, 1700 (w), 1595, 1550	3.53[f] 2.72[g]	3.78[h]	$C_{11}H_{18}N_2O_2S$
18a	CH_3	106–107	H–B	222 (6650), 239 (7150), 264 (14,020); 223 (11,000), 245 (12,180)	3400–3100, 1710 (w), 1600, 1550	3.19[i] 2.67[j]	3.61[h]	
17b	CH_3	79–80	H–B	222 (7250), 238 (7380), 265 (15,900); 225 (11,350), 246 (12,600)	3400–3100, 1700 (w), 1595, 1550	3.54[f] 2.72[g]	3.54[h]	$C_{12}H_{20}N_2O_2S$
18b	CH_3	98–99	H–B	223 (6450), 243 (7150), 265 (14,950); 224 (11,100), 247 (12,000)	3400–3100, 1595, 1555	3.24[i] 2.68[j]	3.33[h]	
17c	CH_3	Oil		208 (13,980), 235 (7250), 262 (11,650); 224 (11,500), 244 (12,200)	3400–3100, 1700 (w), 1595, 1550	3.51[f] 2.75[g]	4.76[k]	$C_{16}H_{20}N_2O_2S$
18c	CH_3	144–145	H–B	210 (10,500), 240 (7300), 264 (14,250); 226 (11,500), 245 (12,120)	3400–3100, 1710 (w), 1600, 1550	3.21[i] 2.77[j]	4.56[l]	
17c	*p*-C_6H_4Br	126.5–127.5	E	258 (15,200), 296 (29,600); 268 (26,350)	1590, 1550[d]	3.62[f] 2.72[g]	4.73[k]	$C_{21}H_{21}BrN_2O_2S$
18c	*p*-C_6H_4Br	157–157.5	E	256 (16,100), 295 (29,600); 267 (26,350)	1595, 1555[d]	3.27[i] 2.77[j]	4.47[l]	
35	*p*-C_6H_4Br	128.5–129	H–B or E	257 (15,100), 295 (30,200); 220 (10,600), 267 (27,000)	1595, 1555[d]	3.62[f] 2.79[g]	3.73[m]	$C_{15}H_{17}BrN_2O_2S$
36	*p*-C_6H_4F	150.5–151.5	H–B or E	249 (11,200), 290 (26,300); 213 (8840), 258 (23,600)	1595, 1555[d]	3.67[f] 2.83[g]	3.83[m]	$C_{15}H_{17}FN_2O_2S$

[a] Elemental analyses (C, H, N, S) for all compounds were submitted to the reviewers and found to be within acceptable limits. [b] B = benzene, E = ethanol, H = hexane. Colorless solids were obtained. [c] Bands due to NH (broad H-bonded), C=N, and C=O functions ($CHCl_3$). [d] NH bands not detectable in 3% $CHCl_3$ solution but could be detected in KBr disk spectra. [e] Measured in $CDCl_3$ solution with TMS as an internal standard. Chemical shifts (δ) reported in parts per million. [f] One-proton doublet of triplets, J = 4, 12 Hz, axial C_4 H. [g] One-proton doublet of triplets, J = 4, 12 Hz, equatorial C_4 H. [h] One-proton multiplet. [i] One-proton multiplet approximating a doublet of triplets with average J = 3, 13 Hz. [j] Two-proton multiplet including one of C_5 protons. [k] One-proton doublet of doublets, J = 2, 12 Hz. [l] One-proton, broadened doublet, J = 10 Hz. [m] Two-proton multiplet. [n] All compounds gave molecular ions in the low-resolution mass spectra corresponding to these molecular formulas. M − 28 peaks[22] were exhibited by all compounds except **17b** and **17c** (R′ = CH_3).

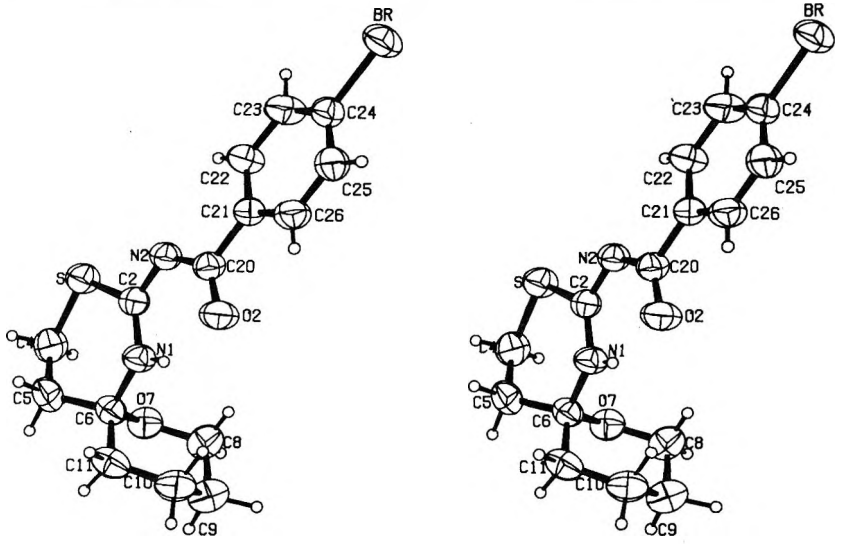
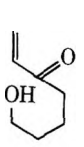


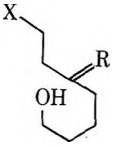
Figure 1. Stereoview of **35**.

gen atom of the thiazine ring and is thus more strongly deshielded would exhibit the relatively lower field C_8-H resonance.[23] Therefore, we have assigned structure **15** to the major epimer and **16** to the minor epimer in each series. This assignment is consistent with the anomeric effect,[24] on the basis of which it would be predicted that epimer **15**, in which both heteroatoms attached to the spiro center can assume an axial conformation, should predominate.

In order to synthesize the parent aminothiazine in this series, the vinyl ketone **19** or an appropriately disguised derivative such as **20** (which can easily generate **19**) was



19

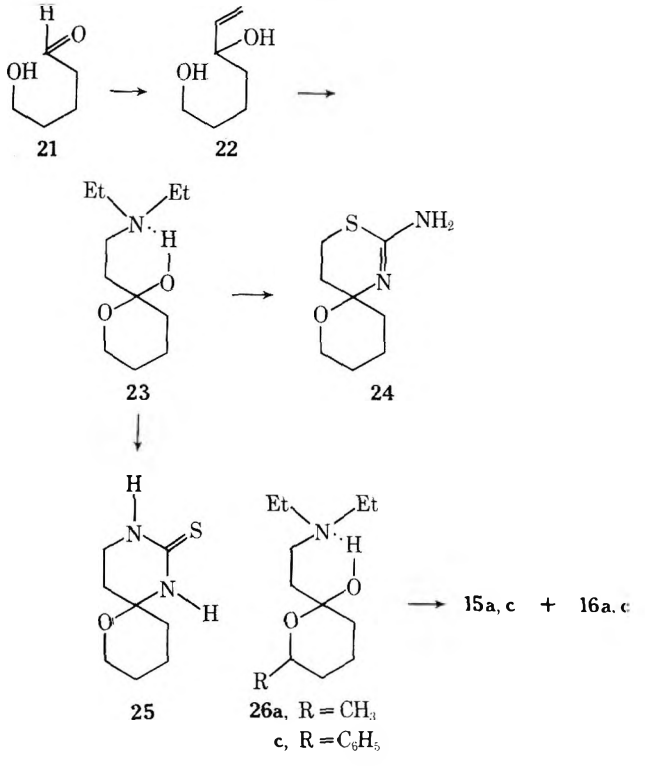


20, X = NEt_2, OH, halogen, etc.
R = O, $-OCH_2CH_2O-$

required. In contrast to the behavior of the 5-substituted δ-lactones **14**, δ-valerolactone itself was not converted into **19** upon treatment with vinylmagnesium chloride at low temperature.[25] We therefore turned our attention to the preparation of intermediates such as **20**. Reaction of 5-hydroxypentanal (**21**)[26] (Scheme II) with vinylmagnesium chloride gave the diol **22**,[27] which yielded the required Mannich base **23** (**20**, X = NEt_2, R = O)[10] in 51% overall yield upon selective oxidation with manganese dioxide in the presence of diethylamine.[21] Condensation of **23** with thiourea in refluxing toluene–acetic acid produced the desired spirothiazinepyran **24** in 45–55% yield. It was subsequently found that condensation of the Mannich bases **26a** and **26c** (prepared from **4a** and **4c** by addition of diethylamine) with thiourea under these conditions afforded the same mixtures of epimeric amino thiazines **15a**, **16a** and **15c**, **16c** as were obtained directly from **4a** and **4c**.

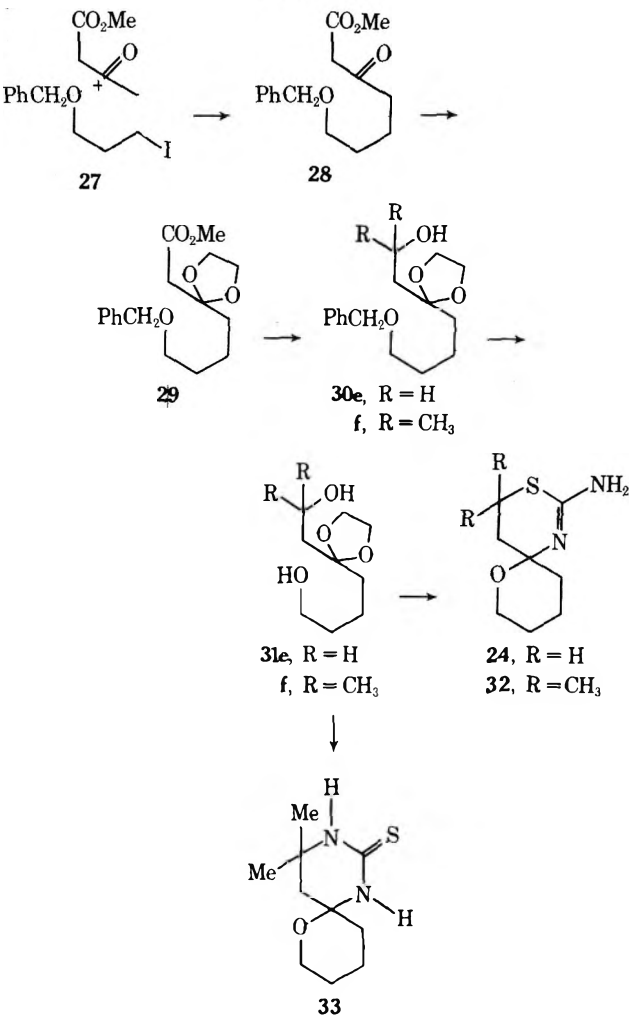
It is interesting to note that, when **23** was first quaternized with methyl iodide and the resulting salt was heated with thiourea in pyridine, a compound isomeric with

Scheme II



24 was isolated in 24% yield. We have assigned the pyrimidinethione structure **25** to this material on the basis of its spectral properties, most notably the absorption in the ultraviolet at 244 nm characteristic of thioureas.[28] The formation of related pyrimidinethiones from the reaction of thiourea with α,β-unsaturated ketones has been reported previously.[12,14,16]

Scheme III

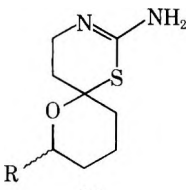


An alternative synthesis of **24** is shown in Scheme III. Alkylation of the dianion of methyl acetoacetate[29] with 3-benzyloxypropyl iodide (**27**)[30] gave the β-keto ester **28** in 60% yield. Formation of the corresponding ethylene ketal **29** was followed by lithium aluminum hydride reduction, yielding the hydroxy ketal **30e**. Removal of the benzyl protecting group by catalytic hydrogenolysis then furnished the diol **31e** (**20**, X = OH; R = $-OCH_2CH_2O-$), which, in turn, produced **24** (isolated as the maleic acid salt in 55% overall yield based on **28**) upon reaction with thiourea in refluxing aqueous sulfuric acid.

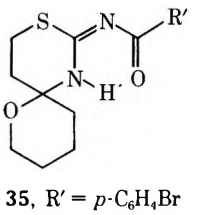
An attempt was made to extend this scheme to the synthesis of compound **32**, the 4,4-dimethyl analog of **24**. Thus, treatment of ketal ester **29** with methyllithium gave the carbinol **30f**, which was subjected to catalytic hydrogenolysis affording diol **31f**. Unfortunately, reaction of **31f** with thiourea in aqueous acid gave a complex mixture from which none of the expected thiazine **32** could be isolated. Instead, the only characterizable compound produced in this reaction was the isomeric pyrimidinethione **33**, which was obtained in very low yield.

It was of interest to confirm the structures of these novel spirothiazinepyrans. In particular, we wished to exclude definitively the isomeric thiazines represented by

34, which, although less likely to be formed on the basis of precedent,[2,12-16] were nonetheless conceivable products from the reaction of thiourea with our vinyl ketones or vinyl ketone precursors. To this end, an X-ray analysis of compound 35, the *p*-bromobenzoyl derivative of 24, was carried out. A view of the molecule is shown in Figure 1. Besides confirming the expected placement of the heteroatoms, two other important structural features of the crystal structure determination should be noted. First of all, it is evident that the amidine proton resides on the endocyclic nitrogen atom and is strongly hydrogen bonded to the carbonyl oxygen atom. The uv maxima and virtual lack of normal carbonyl absorption in the ir spectra exhibited by these compounds are consistent with this structural arrangement.[31] Secondly, in the solid state, this molecule assumes the expected[24] conformation in which the thiazine ring nitrogen is axial with respect to the pyran ring and the pyran ring oxygen is axial with respect to the thiazine ring.[34]



34



35, R′ = *p*-C_6H_4Br
36, R′ = *p*-C_6H_4F

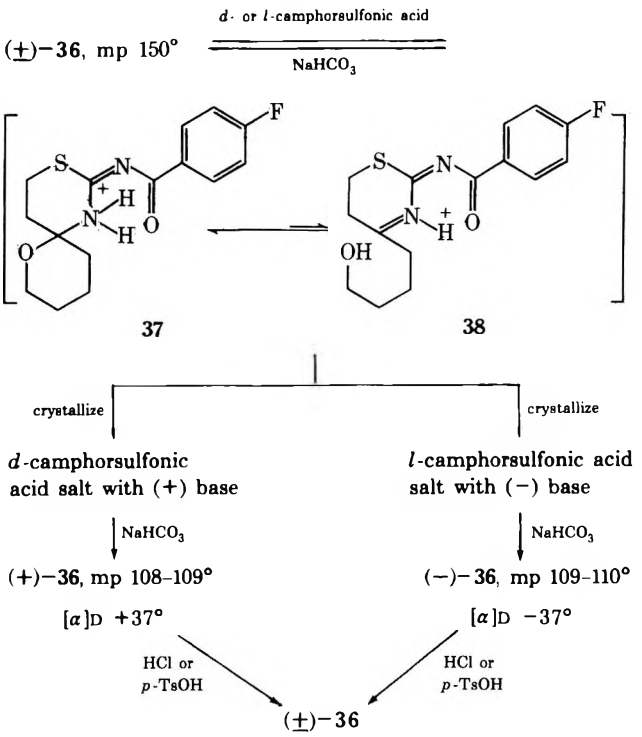
During the course of this work, we studied the optical resolution of the *p*-fluorobenzoylimino derivative 36[35] (Scheme IV). Thus, treatment of this substance with *d*-(+)-10-camphorsulfonic acid in ethanol gave rise to a salt which was usually isolated in yields considerably greater than theoretical for one enantiomer. Basification of this salt gave an enantiomer of 36 showing $[\alpha]D$ + 37°. Similar results were obtained when *l*-(−)-10-camphorsulfonic acid[36] was employed, in which case the negatively rotating antipode was isolated. It was found that the enantiomers racemized readily on mild treatment with achiral acids such as hydrochloric or *p*-toluenesulfonic acid, regenerating (±)-36. When a solution of the resolved thiazine camphorsulfonic acid salt was neutralized with bicarbonate before crystallization could occur, the base obtained was racemic.

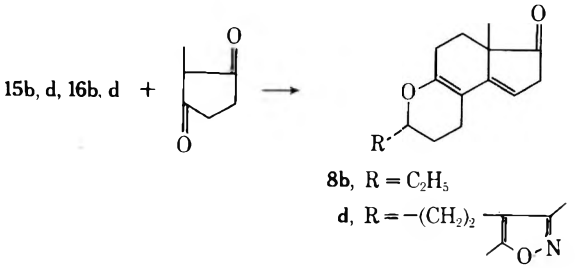
It soon became apparent that these molecules undergo facile ring-open-chain isomerism in the presence of acids, giving rise to a small concentration of an achiral species such as 38[37] (or a tautomer) which is in rapid equilibrium with the spirocyclic cation 37 (or a tautomer). Fortuitously, in the presence of optically active camphorsulfonic acid, a salt precipitates which contains only one enantiomer of the spiro compound. As a practical consequence of this phenomenon, the enantiomers of 36 could be produced from the racemic modification in weight yields exceeding 80%.

A further manifestation of this ring-open-chain isomerism was observed when the pure 8-methyl epimer 17a (R′ = CH_3) was hydrolyzed in aqueous hydrochloric acid. This reaction produced the mixture of epimeric amines 15a and 16a, indicating that equilibration of the 8-methyl group had taken place again *via* facile ring opening and reclosing. Reacetylation of this mixture gave a mixture of 17a and 18a with the former predominating as evidenced by nmr and tlc analysis.

We stated at the outset that the original aim of this work was a search for novel intermediates of potential utility in steroid total synthesis. Although the spirothiazinepyrans obtained were not the intermediates envisioned, they nonetheless seemed to be potentially capable of conversion into the dienes 8. In the event, it was found that the reaction of the thiazine mixture 15d and 16d with 2-methyl-1,3-cyclopentanedione in the presence of aqueous acid was slow owing to the stability of the spiro compounds under these conditions. When these components were heated in refluxing aqueous dioxane containing *p*-toluenesulfonic acid for 92 hr, and the crude, neutral product was dehydrated with *p*-toluenesulfonic acid in benzene, the desired diene (±)-8d[20] was produced in 40% yield. In addition, 33% of the starting base mixture was recovered. Diene (±)-8d has previously been converted into racemic estr-4-ene-3,17-dione.[20] In a similar manner, diene (±)-8b[38] was produced in 33% yield from the mixture of spiro compounds 15b and 16b. The relatively low yields observed and stringent conditions required for the conversion of 15 and 16 to 8 indicate that these amino spirothiazinepyrans are inferior in utility to the Mannich bases 6 as intermediates in our steroid total synthesis. For this reason, optical resolution of the 8-substituted spiro bases and their conversion into the optically active dienes 8 was not investigated.

Scheme IV





Experimental Section[39,40]

δ-Lactones 14a-d. (±)-5-Hydroxyhexanoic acid lactone (14a) was prepared by sodium borohydride reduction of 4-acetylbutyric acid followed by acidification in 86% yield, as a colorless liquid, bp 100–103° (10 mm) [lit.[17] bp 87–89° (7 mm)]. (±)-5-Hydroxyheptanoic acid lactone (14b) was synthesized in 76% yield by alkaline cleavage of 2-methyl-1,3-cyclohexanedione followed by sodium borohydride reduction of the crude keto acid and acidification, as a colorless liquid, bp 106–110° (6–7 mm) [lit.[18] bp 68–69° (1 mm)]. (±)-δ-Phenyl-δ-valerolactone (14c) was prepared as de-

scribed[19] by sodium borohydride reduction of 4-benzoylbutyric acid. The lactone, mp 72–74° (lit.[19] mp 74–76°), was obtained in 62% yield. (±)-7-(3,5-Dimethyl-4-isoxazolyl)-5-hydroxyheptanoic acid lactone (**14d**)[20] was provided by Dr. John W. Scott, Hoffmann-La Roche Inc., Nutley, N. J.

Vinyl Ketones 4a–d. These materials were prepared by treatment of the corresponding δ-lactones **14a–d** with vinylmagnesium chloride, in THF, at −50 to −60°, using the general procedure described previously.[9,20,21] The crude, oily vinyl ketones were used immediately, without purification.

(±)-2-(2-Diethylaminoethyl)-6-methyltetrahydropyran-2-ol (26a).[41] The crude vinyl ketone from 2.03 g (0.018 mol) of lactone **14a**, in ether solution, was treated with 10 ml of diethylamine. After standing at room temperature for 0.5 hr, the solution was concentrated at reduced pressure and the residue was partitioned between cold 1 *N* aqueous HCl and ether. The aqueous acidic solution was made alkaline with 20% aqueous KOH, saturated with salt, and worked up with ether, giving 2.6 g (68%) of Mannich base as a colorless oil: ir ($CHCl_3$) 3625–3125 (broad H-bonded OH), 1705 cm^{-1} (weak ketone C=O of open form); nmr ($CDCl_3$) δ 4.08 (m, 1, C_6 H), 1.15 (d, J = 7 Hz, C_6 CH_3), 1.10 ppm (t, CH_3CH_2N); mass spectrum m/e 197 (M − H_2O).

(±)-2-(2-Diethylaminoethyl)-6-phenyltetrahydropyran-2-ol (26c). This material was prepared as in the preceding experiment. From 1.75 g (0.01 mol) of lactone **14c** there was obtained 1.55 g (55%) of Mannich base as a yellow oil: ir (film) 3600–3050 (broad H-bonded OH), 1705 cm^{-1} (weak ketone C=O of open form).

Preparation of the Racemic 8-Substituted 2-Amino-7-oxa-3-thia-1-azaspiro[5.5]undec-1-enes 15 and 16. A. From the Vinyl Ketones 4. Solutions (1.0–1.6 *M*) of the crude, freshly prepared vinyl ketones **4a–d** in glacial acetic acid containing 1 molar equiv of thiourea (based on starting lactone **14**) were stirred at room temperature for 16–20 hr and then concentrated at reduced pressure. The residues were treated with ether and dilute (1–3 *N*) aqueous HCl. In series **a** and **d** the aqueous acidic layer was separated, washed once with ether (the ether layers were discarded), and then made alkaline with 10% aqueous NaOH. Extraction with dichloromethane yielded the mixtures of products **15** and **16**. In series **b**, a crystalline hydrochloride salt was obtained from the acidic aqueous solution, which was filtered and washed with ice-water. After drying, an almost colorless solid, mp 213–214.5° dec, was isolated in 22.4% yield. Tlc analysis (system A) indicated that the free base derived from this salt was largely the major, less polar epimer **15b**. The filtrate and washes were combined and made alkaline with concentrated NH_4OH. Extraction with dichloromethane gave the mixture of amines **15b** and **16b** as a viscous, brown oil, in 41% yield. The minor epimer **16b** was never isolated in pure form. A sample of the above salt was recrystallized from water to give an analytical specimen as a slightly off-white solid, mp 211–212°.

Anal. Calcd for $C_{10}H_{18}N_2OS \cdot HCl$: C, 47.89; H, 7.64; N, 11.17; S, 12.78. Found: C, 48.12; H, 7.75; N, 11.44; S, 12.31.

In the **c** series, addition of ether and 1 *N* aqueous HCl to the crude product after removal of the acetic acid led to the formation of a dense precipitate of HCl salt. The solid was filtered and the aqueous portion of the filtrate was separated from the ether layer and combined with the solid HCl salt before being made alkaline with 10% aqueous NaOH. Isolation with dichloromethane gave the mixture of epimers **15c** and **16c** as an orange semisolid.

In all four series, tlc analysis (system A) of the crude, basic product showed two spots, R_f ~0.4 (major, **15**) and ~0.13 (minor, **16**). Separation of the isomers was carried out using the following procedures.

Series a. The crude reaction product was triturated with benzene and the resulting solid, which was largely **16a** (tlc), was filtered off. The benzene mother liquor was concentrated and the residue was purified by dry-column chromatography on 500 parts by weight of Woelm grade III neutral alumina. After development with 9:1 ethyl acetate–triethylamine, elution with methanol gave pure **15a** as a viscous oil. This material could not be induced to crystallize but was treated with 0.58 g of maleic acid and the resulting salt was recrystallized from ethyl acetate and then acetonitrile, giving a colorless solid, mp 139–141°.

Anal. Calcd for $C_9H_{16}N_2OS \cdot C_4H_4O_4$: C, 49.36; H, 6.37; N, 8.86; S, 10.12. Found: C, 49.47; H, 6.50; N, 8.75; S, 10.14.

Series c. The crude base mixture was triturated with ethyl acetate and filtered, giving essentially pure **16c** as a colorless solid. The mother liquor was diluted with ethyl acetate, stirred with approximately 25 parts by weight of Woelm grade I neutral alumina, and then filtered. Concentration of the filtrate gave pure **15c** as an oil which crystallized on standing.

Series d. Repeated recrystallization of a sample of the crude semisolid base mixture from acetonitrile gave pure **15d**. Dry-column chromatography of a sample of this base mixture on 400 parts by weight of Woelm grade III neutral alumina, developing with 9:1 benzene–triethylamine, furnished a nearly pure sample of **16d** (eluted with methanol).

B. From the Mannich Bases 26. A mixture of 10 g (0.0465 mol) of Mannich base **26a**, 3.65 g (0.048 mol) of thiourea, 35 ml of glacial acetic acid, and 105 ml of toluene was stirred and heated at reflux for 75 min. The resulting solution was cooled, extracted with 3 *N* aqueous HCl, and discarded. The aqueous acidic extract was made alkaline with 10% aqueous NaOH and worked up with ether, giving 6.9 g of semisolid product, tlc analysis of which indicated that it was identical with the crude mixture of **15a** and **16a** derived from vinyl ketone **4a**.

Using essentially the same procedure, the Mannich base **26c** (1.55 g, 0.0056 mol) was treated with thiourea (0.44 g, 0.0058 mol). The reaction mixture was cooled, diluted with ether, and treated with 3 *N* aqueous HCl. The resulting precipitated hydrochloride salt was filtered and then treated with 10% aqueous NaOH. Extraction with dichloromethane gave 1.1 g of the mixture **15c** and **16c**. Tlc analysis showed the same two spots in approximately the same proportion as exhibited by the crude product derived from **4c**.

Physical properties and microanalytical, spectral, and yield data for the amino thiazines are presented in Table I.

6-Heptene-1,5-diol (22). A 2.91 *M* solution of vinylmagnesium chloride in THF (970 ml) was stirred efficiently while a solution of 96 g (0.94 mol) of 5-hydroxypentanal[26] in 250 ml of THF was added dropwise over a 30-min period. Ice-bath cooling was employed to maintain the internal temperature at 30°. The resultant gelatinous yellow-brown mixture was stirred at room temperature for 2 hr, then again cooled in an ice bath, and cautiously hydrolyzed with 500 ml of saturated aqueous NH_4Cl. It should be noted that, after the addition of approximately 20 ml of the NH_4Cl solution, a white, viscous mass formed and the remainder of the solution had to be added with *extreme care* until the mixture thinned and the mechanical stirrer was again able to operate smoothly. When the hydrolysis was complete, the suspension was filtered and the salts were washed several times with ether. The filtrate and washes were combined, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Distillation of the residue gave 90 g (74%) of diol **22** as a colorless liquid, bp 100–105° (0.3 mm) [lit.[27] bp 105–107° (0.6 mm)].

2-(2-Diethylaminoethyl)tetrahydropyran-2-ol (23). A solution of 90 g (0.69 mol) of diol **22** in 2500 ml of 1,2-dichloroethane (shaken with anhydrous K_2CO_3 and filtered before use) and 400 ml of diethylamine was stirred efficiently with ice-bath cooling while 750 g of activated manganese dioxide[21,42] was added in portions over a 15-min period. The resulting slurry was stirred for 24 hr at room temperature and then the solids were filtered and washed thoroughly with benzene. The filtrate and washes were combined and concentrated at reduced pressure, giving 110 g of dark brown oil. This material was dissolved in 150 ml of ethyl acetate and the resulting solution was cooled in an ice bath while 700 ml of 1.2 *N* aqueous HCl was slowly added with stirring. The mixture was then extracted with three 300-ml portions of ethyl acetate and the ethyl acetate extracts were combined, washed with saturated brine (300 ml), and then discarded. The aqueous solutions were combined and made alkaline by the cautious addition, with cooling, of approximately 150 ml of 10 *N* aqueous NaOH, and then the product was isolated by benzene extraction. This afforded 96.4 g (69%) of Mannich base **23** as a brown oil. A sample was chromatographed on 50 parts of Woelm grade III neutral alumina. Elution with benzene gave pure (tlc, system A) **23**, ir (film) 3100–3600 (H-bonded OH), 1715 cm^{-1} (w, C=O of open form).

Anal. Calcd for $C_{11}H_{23}NO_2$: C, 65.63; H, 11.52; N, 6.96. Found: C, 65.80; H, 11.52; N, 6.69.

3-Benzyloxy-1-propyl Iodide (27). 3-Benzyloxy-1-propanol was prepared from trimethylene glycol and converted into 3-benzyloxy-1-propyl chloride with thionyl chloride and *N,N*-dimethylaniline using the procedures described by Bennett and Hock.[43] The iodide was obtained in 94% yield by treatment of the chloride with excess sodium iodide in refluxing 2-butanone, as a yellow liquid, bp 96–110° (0.2–0.5 mm) [lit.[30] bp 112–113° (1.1 mm)].

Methyl 3-Oxo-7-benzyloxyheptanoate (28). The procedure of Weiler[29] was employed. A slurry of sodium hydride from 8.1 g

(0.169 mol) of 50% sodium hydride–mineral oil dispersion washed free of mineral oil with hexane, in 300 ml of dry THF was stirred with ice-bath cooling while a solution of 17.4 g (0.15 mol) of methyl acetoacetate in 30 ml of THF was added dropwise during 20 min (H_2 evolution). Stirring was continued for 20 min at 0–5°, whereupon 68 ml (0.162 mol) of 2.38 *M* butyllithium in hexane was added dropwise over 25 min, keeping the temperature around 10°. The orange mixture was stirred for 10 min with ice-bath cooling and then a solution of 45 g (0.163 mol) of 3-benzyloxypropyl iodide (**27**) in 45 ml of THF was added during 25 min, keeping the temperature below 20°. The ice bath was removed and stirring was continued for 45 min; then the reaction mixture was cautiously poured into a mixture of ice and 3 *N* aqueous HCl. The organic materials were isolated with ether (the combined ether extracts were additionally washed with aqueous sodium bisulfite), giving 45.8 g of an orange liquid. This material was chromatographed on 400 g of silica gel. Elution with 9:1 hexane–ether gave 13.5 g (30%) of recovered iodide. Elution with 4:1–1:3 hexane–ether furnished 23.7 g (59.7%) of pure keto ester **28** as a yellow liquid.

In another run a sample of keto ester prepared in this way was evaporatively distilled, giving a pale-yellow liquid: bp 150–190° (bath, 0.05 mm); ir ($CHCl_3$) 1745 (ester C=O), 1720 cm^{-1} (ketone C=O); nmr ($CDCl_3$) δ 7.27 (s, 5, C_6H_5–), 4.45 (s, 2, $C_6H_5CH_2O$–), 3.67 (s, 3, $-CO_2CH_3$), 3.45 (m, 2, C_7H), 3.38 (s, 2, C_2 H), 2.53 (m, 2, C_4 H), 1.65 ppm (m, 4, C_5 H, C_6 H); mass spectrum *m/e* 264 (M^+), 91 (base).

Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.33; H, 7.80.

Methyl 7-Benzyloxy-3,3-ethylenedioxyheptanoate (29). A mixture of 2.65 g (0.01 mol) of keto ester **28**, 1 g (0.0162 mol) of ethylene glycol, 0.06 g of *p*-toluenesulfonic acid monohydrate, and 30 ml of benzene was stirred and heated at reflux for 2.5 hr. A Dean-Stark trap was employed to collect water (0.35 ml). After cooling, the mixture was diluted with ether and washed with saturated aqueous sodium bicarbonate solution and brine, and then the organic solution was dried, filtered, and concentrated at reduced pressure, giving 3.05 g (98.7%) of ketal **29** as a yellow oil: ir ($CHCl_3$) 1740 cm^{-1} (ester C=O); nmr ($CDCl_3$) δ 7.28 (s, 5, C_6H_5–), 4.45 (s, 2, $C_6H_5CH_2O$–), 3.91 (s, 4, $-OCH_2CH_2O$–), 3.63 (s, 3, $-CO_2CH_3$), 3.45 (t, 2, J = 6 Hz, C_7 H), 2.26 (s, 2, C_2 H), 1.66 ppm (m, 6, C_{4-6} H); mass spectrum *m/e* 308 (M^+), 235, 145 (base), 91.

3,3-Ethylenedioxy-7-benzyloxyheptan-1-ol (30e). A solution of 2.6 g (8.45 mmol) of ketal ester **29** in 50 ml of dry ether was added dropwise over a 20-min period to a stirred mixture of 0.65 g (17.1 mmol) of lithium aluminum hydride in 50 ml of dry ether, with ice-bath cooling. Stirring was continued at 0–5° for 20 min and then at room temperature for 80 min. The reaction mixture was again cooled in an ice bath and cautiously decomposed by the addition of 1.3 ml of water and 1 ml of 10% aqueous NaOH. After stirring at room temperature for 45 min, the mixture was filtered and the solids were washed well with ether. The filtrate and washes were combined and concentrated at reduced pressure, giving 2.25 g (95.2%) of **30e** as a pale-pink oil. The crude alcohol could be used in the ensuing reactions without purification.

This material was chromatographed on 100 g of silica gel. Elution with 1:1 benzene–ether gave 1.95 g (82.5%) of pure **30e** as a pale-yellow oil: ir ($CHCl_3$) 3550 cm^{-1} (OH); nmr ($CDCl_3$) δ 7.31 (s, 5, C_6H_5–), 4.48 (s, 2, $C_6H_5CH_2O$–), 3.93 (s, 4, $-OCH_2CH_2O$–), 3.73 (m, 2, C_1 H), 3.47 (m, 2, C_7 H), 2.75 (m, 1, –OH), 1.90 (t, J = 6 Hz, 2, C_2 H), 1.58 ppm (m, 6, C_{4-6} H); mass spectrum *m/e* 280 (M^+), 117 (base).

Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.55; H, 8.63. Found: C, 68.60; H, 8.46.

3,3-Ethylenedioxy-1,7-heptanediol (31e). A 1.6-g (5.72 mmol) sample of alcohol **30e** was hydrogenated in 30 ml of ethanol over 0.2 g of preequilibrated 5% palladium on carbon catalyst at ~1 atm. After 1.5 hr, hydrogen uptake ceased. A total of 141 ml of hydrogen was consumed (143 ml theory). The catalyst was filtered on a Celite pad and washed with ethanol. Concentration of the combined filtrate and washes gave 1.02 g (94.3%) of diol **31e** as an almost colorless oil, ir ($CHCl_3$) 3625, 3500 cm^{-1} (OH); the ir, nmr, and mass spectra indicated the absence of the benzyl group.

(±)-2-Amino-7-oxa-3-thia-1-azaspiro[5.5]undec-1-ene (24). A. From Mannich Base 23. A solution of 60 g (0.298 mol) of the Mannich base **23** and 22.8 g (0.3 mol) of thiourea in 940 ml of toluene and 300 ml of glacial acetic acid was stirred and heated at reflux for 3 hr, using a Dean-Stark trap to remove water. At the end of this time, 15 ml of water–acetic acid layer had been collected and essentially no more water was being formed. The resulting dark red solution was cooled and the solvents were removed at 50–60°, under aspirator pressure and finally high vacuum. The oily residue was stirred rapidly and cooled in an ice bath while 500 ml of 10% aqueous NaOH was slowly added. After the addition was complete (pH 11–12), the mixture was stirred rapidly for 10 min with ice-bath cooling and then filtered with suction. The solid was washed with water and then dried under high vacuum, giving 35.9 g of crude **24** as a tan solid. Recrystallization from about 200 ml of ethyl acetate gave 25.9 g (46.8%) of large, tan crystals, mp 137.5–139°. Tlc analysis (system A) showed essentially a single spot, R_f 0.25. Several repetitions of this procedure gave yields in the range of 45–55%. An analytical specimen of **24** was obtained by further recrystallization of a sample from ethyl acetate, as a colorless solid: mp 139–140.5°; ir (KBr) 3375, 3300, 3250, 3150 (NH), 1640, 1590 cm^{-1} (C=N); nmr (DMSO-d_6) δ 3.90 ppm (m, C_8 H); mass spectrum *m/e* 186 (M^+), 158 ($M - C_2H_4$).

Anal. Calcd for $C_8H_{14}N_2OS$: C, 51.60; H, 7.58; N, 15.04; S, 17.19. Found: C, 51.68; H, 7.70; N, 15.25; S, 17.44.

The maleic acid salt was obtained as a colorless solid, mp 164–165°, by recrystallization from ethanol.

Anal. Calcd for $C_8H_{14}N_2OS \cdot C_4H_4O_4$: C, 47.68; H, 6.00; N, 9.27; S, 10.59. Found: C, 47.41; H, 5.78; N, 9.19; S, 10.71.

B. From Diol Ketal 31e. A solution of 0.954 g (5 mmol) of diol **31e** and 0.4 g (5.26 mmol) of thiourea in 25 ml of 0.5 *N* aqueous H_2SO_4 was stirred and heated at reflux for 2 hr. After cooling, the reaction mixture was made alkaline with 10% aqueous NaOH and saturated with salt and the product was isolated by extraction with dichloromethane, giving 0.762 g (82%) of crude **24** as a pale-yellow solid. This material was dissolved in hot ethanol and treated with 0.475 g of maleic acid. There was obtained 0.93 g (61.6%) of colorless, crystalline salt, mp 160–163°.

(±)-7-Oxa-1,3-diazaspiro[5.5]undecane-2-thione (25). A solution of 5 g (0.0249 mol) of Mannich base **23** in 20 ml of acetone was treated with 5 ml of methyl iodide and allowed to stand overnight at room temperature. The solvents were removed under reduced pressure, giving 8.9 g of gummy methiodide. To this was added 1.9 g (0.025 mol) of thiourea and 35 ml of pyridine. The reaction mixture was stirred and heated at 100° for 4 hr, then the pyridine was removed at reduced pressure. The residue was treated with 30 ml of water, basified to pH 11 with 10% aqueous NaOH, and worked up with chloroform, giving a brown gum which crystallized on trituration with ethyl acetate. Digestion with boiling acetonitrile gave 1.1 g (23.8%) of off-white solid, mp 202–203°. Tlc analysis (system A) showed a single uv spot, R_f 0.33. An analytical specimen was prepared by recrystallization of a sample from methanol–ether, giving a colorless solid: mp 204–205°; ir (KBr) 3200, 3100 (NH), 1560, 1500 cm^{-1} (thiourea C=S); uv max (95% EtOH) 244 nm (ϵ 14,900); nmr (DMSO-d_6) δ 8.25 (m, 2, NH); mass spectrum *m/e* 186 (M^+).

Anal. Calcd for $C_8H_{14}N_2OS$: C, 51.60; H, 7.58; N, 15.04; S, 17.19. Found: C, 51.50; H, 7.62; N, 15.05; S, 17.37.

Attempted Preparation of (±)-2-Amino-4,4-dimethyl-7-oxa-3-thia-1-azaspiro[5.5]undec-1-ene (32). A solution of 1 g (3.25 mmol) of ketal ester **29** in 20 ml of dry ether was added dropwise, over 10 min to 8 ml (13.2 mmol) of stirred 1.65 *M* ethereal methyllithium, with ice-bath cooling. Stirring was continued for 10 min at 0–5° and then at room temperature for 1.75 hr. At the end of this time, the reaction mixture was poured into ice water and worked up with ether, giving 0.95 g (95%) of yellow, oily 8-benzyloxy-4,4-ethylenedioxy-2-methyloctan-2-ol (**30f**): ir (film) 3500 cm^{-1} (OH); nmr ($CDCl_3$) δ 7.32 (s, 5, C_6H_5–), 4.50 (s, 2, $C_6H_5CH_2O$–), 4.13 (s, $-OCH_2CH_2O$–), 3.48 (m, C_8 H), 1.92 (s, –OH), 1.24 ppm [s, $(CH_3)_2C$–].

A 0.883-g (2.87 mmol) sample of this crude alcohol was hydrogenated in 30 ml of ethanol, over 0.3 g of preequilibrated 5% palladium on carbon, at approximately 1 atm. A total of 87 ml of hydrogen was absorbed during 15 min (72 ml theory). The catalyst was filtered and washed with ethanol and the combined filtrate and washes were concentrated at reduced pressure, giving 0.571 g of colorless, oily diol **31f**, ir (film) 3375 cm^{-1} (OH).

A solution of 1.24 g (5.69 mmol) of diol **31f** prepared in this way, 0.435 g (5.72 mmol) of thiourea, 0.18 ml of water, and 25 ml of glacial acetic acid was stirred at room temperature for 0.5 hr then at reflux for 3.25 hr, and again at room temperature for 14 hr. The resulting solution was concentrated at reduced pressure, giving 2.1 g of yellow oil the ir spectrum of which showed strong bands at 1740 and 1245 cm^{-1}, indicating the presence of acetate esters.

This material was treated with 5 ml of 10% aqueous NaOH so-

lution and 15 ml of methanol and the resulting solution was stirred at room temperature for 1.25 hr and then poured into brine, whereupon the organic materials were isolated by extraction with dichloromethane. This afforded 1.0 g of a yellow, semisolid product which was treated with ether and 1 *N* aqueous H_2SO_4. The resulting solid was filtered, washed with ether and water, and dried, giving 0.19 g of crude (±)-4,4-dimethyl-7-oxa-1,3-diazaspiro[5.5]undecane-2-thione (**33**) as a colorless solid.

A 0.211-g sample of **33** prepared in this way was chromatographed on 10 g of silica gel. Elution with chloroform gave 0.16 g of pure **33** as a colorless solid which was recrystallized from ethanol, yielding colorless crystals (0.122 g): mp 196.5–198°; ir (KBr) 3225 (NH), 1560, 1510 cm^{-1} (thiourea C=S); uv max (95% EtOH) 247 nm (ϵ 15,800); nmr (DMSO-d_6) δ 8.28 (m, 1, -NH), 8.11 (m, 1, -NH), 3.55 (m, 2, C_8 H), 1.26 (s, C_4 CH_3), 1.17 ppm (s, C_4 CH_3); mass spectrum *m/e* 214 (M^+, base), 139.

Anal. Calcd for $C_{10}H_{18}N_2OS$: C, 56.04; H, 8.47; N, 13.07; S, 14.96. Found: C, 56.09; H, 8.49; N, 13.18; S, 14.96.

The above aqueous sulfuric acid solution was made alkaline with aqueous NaOH and the organic materials were isolated with dichloromethane. This gave 0.385 g of a yellow gum, tlc analysis of which indicated a complex mixture.

Acylation of the 2-Amino-7-oxa-3-thia-1-azaspiro[5.5]undec-1-enes. The following general procedure was employed for preparation of **17a–c** and **18a–c** (R′ = CH_3). A solution of 0.05 mol of the mixture of amines **15** and **16** in 10 ml of pyridine and 5 ml of acetic anhydride was kept at room temperature for 3–20 hr and then concentrated at reduced pressure. The residue was dissolved in ether and the ether solution was washed three times with 1 *N* aqueous HCl. The aqueous acid extracts were combined and washed once with ether (the ether solutions containing neutral impurities were discarded), then made alkaline with 10% aqueous NaOH and saturated with NaCl. The products were then isolated by ether extraction and showed two spots on tlc analysis (system B), R_f ~0.30 (**17**) and ~0.20 (**18**). These mixtures were separated by column chromatography on 50 parts by weight of silica gel. Elution with 4:1 benzene–ether gave the less polar epimer **17** (R′ = CH_3), whereas elution with 1:1 benzene–ether and ether furnished **18** (R′ = CH_3). In the 8-phenyl series, acetylation of the crude amine mixture **15c** and **16c** by this procedure gave the corresponding mixture of derivatives **17c** and **18c** (R′ = CH_3). The nmr spectrum exhibited acetyl methyl singlets at δ 2.13 (**17c**) and 2.08 ppm (**18c**) in a ratio, by integration, of approximately 3:1, respectively.

The benzoylimino derivatives **17c** and **18c** (R′ = *p*-C_6H_4Br), **35**, and **36** were prepared by stirring a 0.3–0.8 *M* pyridine solution of the amine **24** or amine mixture **15c** and **16c** at 0° while the aroyl chloride (1 equiv) was added. The resulting mixture was stirred at room temperature for 3–6 hr and then treated with saturated aqueous $NaHCO_3$. Work-up with ether or dichloromethane gave the products, which were purified by chromatography on silica gel and/or recrystallization. The mixture of epimers **17c** and **18c** (R′ = *p*-C_6H_4Br) was separated by chromatography on 50 parts by weight of silica gel. Elution with 1:1 hexane–ether gave the major and less polar epimer **17c** (R′ = *p*-C_6H_4Br) (tlc, R_f 0.45, system C). Elution with 1:2 hexane–ether afforded the minor epimer **18c** (R′ = *p*-C_6H_4Br).

Physical properties and microanalytical and spectral data of the acyl derivatives are presented in Table II.

(+)-2-*p*-Fluorobenzoylimino-7-oxa-3-thia-1-azaspiro[5.5]undecane [(+)-36] *d*-(+)-Camphorsulfonic Acid Salt. A mixture of 10.1 g (0.032 mol) of racemic 2-*p*-fluorobenzoylimino-7-oxa-3-thia-1-azaspiro[5.5]undecane [(±)-36], 7.6 g (0.0328 mol) of *d*-(+)-camphorsulfonic acid, and 250 ml of ethanol was heated until all the solids had dissolved and then concentrated to a volume of approximately 70 ml at reduced pressure. After standing at room temperature for 2 hr and at 0° for 16 hr the solid was filtered, washed with ethanol and dried, giving 8.9 g (50.3%) of colorless solid, mp 149.5–151°. Two recrystallizations from ethanol gave colorless crystals, mp 149.5–151°, $[\alpha]^{25}D$ −22.61° (c 0.9862, $CHCl_3$).

Anal. Calcd for $C_{15}H_{17}FN_2O_2S \cdot C_{10}H_{16}O_4S$: C, 55.54; H, 6.15; N, 5.18; S, 11.86. Found: C, 55.66; H, 6.30; N, 5.19; S, 11.93.

In a subsequent experiment, carried out on the same scale, reduction of the amount of ethanol used in the initial crystallization to 50 ml allowed isolation of this salt in two crops of 12.6 g (mp 147.5–149.5°) and 1.8 g (mp 142–147°) for a total weight yield of 82%.

(+)-2-*p*-Fluorobenzoylimino-7-oxa-3-thia-1-azaspiro[5.5]undecane [(+)-36]. A 0.3-g sample of the salt prepared in the previous experiment was shaken with saturated aqueous $NaHCO_3$ and the liberated base was extracted with dichloromethane, giving 0.169 g of colorless solid (+)-**36**, mp 108.5–109.5°, $[\alpha]^{25}D$ +36.71° (c 0.9780, $CHCl_3$). The spectral and tlc properties of this material were essentially identical with those of the racemic form.

Anal. Calcd for $C_{15}H_{17}FN_2O_2S$: C, 58.43; H, 5.56; N, 9.08; S, 10.40. Found: C, 58.58; H, 5.69; N, 9.14; S, 10.27.

(−)-2-*p*-Fluorobenzoylimino-7-oxa-3-thia-1-azaspiro[5.5]undecane [(−)-36] *l*-(−)-Camphorsulfonic Acid Salt. A mixture of 8.0 g (0.026 mol) of (±)-**36**, 6.2 g (0.027 mol) of *l*-(−)-camphorsulfonic acid,[36] and 100 ml of ethanol was heated until all the solids had dissolved and then concentrated at reduced pressure. The residue was recrystallized from approximately 45 ml of ethanol. This gave 9.5 g (67.7%) of colorless solid, mp 148.5–150°. Another recrystallization from ethanol (30 ml) gave 7.2 g of colorless solid salt, mp 148.5–150°, $[\alpha]^{25}D$ +19.57° (c 1.017, $CHCl_3$).

Anal. Calcd for $C_{15}H_{17}FN_2O_2S \cdot C_{10}H_{16}O_4S$: C, 55.54; H, 6.15; N, 5.18; S, 11.86. Found: C, 55.53; H, 6.23; N, 5.15; S, 11.71.

In a subsequent experiment, 10 g of (±)-**36** and 7.7 g of *l*-(−)-camphorsulfonic acid crystallized from 35 ml of ethanol gave 14.4 g (82%) of salt, mp 147.5–150°.

(−)-2-*p*-Fluorobenzoylimino-7-oxa-3-thia-1-azaspiro[5.5]undecane [(−)-36]. A 6.4-g sample of the salt prepared in the previous experiment was shaken with excess aqueous saturated $NaHCO_3$ and the mixture was extracted with dichloromethane, giving 3.45 g of (−)-**36** as a colorless solid, mp 109–110°, $[\alpha]^{25}D$ −36.76° (c 1.020, $CHCl_3$). The spectral and tlc properties of this material were essentially identical with those of the racemic form and the (+) enantiomer.

Anal. Calcd for $C_{15}H_{17}FN_2O_2S$: C, 58.43; H, 5.56; N, 9.08; S, 10.40. Found: C, 58.23; H, 5.64; N, 9.10; S, 10.14.

Racemization of (+)-36. A. A solution of 0.15 g of (+)-**36** [$[\alpha]^{25}D$ +33.27° (c 1, $CHCl_3$)] and 0.01 g of *p*-toluenesulfonic acid monohydrate in 5 ml of ethanol was heated on a steam bath for 10 min and then poured into saturated aqueous $NaHCO_3$ solution. The resulting mixture was extracted with dichloromethane, giving 0.142 g of colorless solid (±)-**36**, mp 147–149°, $[\alpha]^{25}D$ 0° (c 1, $CHCl_3$). No impurities were detected by tlc analysis (system B).

B. A suspension of 0.15 g of (+)-**36** ($[\alpha]^{25}D$ +33.27°) in 15 ml of 0.1 *N* aqueous HCl was stirred at room temperature for 3 days and then treated with excess aqueous $NaHCO_3$. Extraction with dichloromethane gave 0.13 g of colorless solid (±)-**36**, mp 145.5–148°, $[\alpha]^{25}D$ +0.83° (c 1, $CHCl_3$). Tlc analysis showed that no impurities were present.

C. A 0.3-g sample of (+)-**36** (+)-camphorsulfonic acid salt was dissolved in hot ethanol (15 ml) and the warm solution was poured into excess saturated aqueous $NaHCO_3$ solution. The liberated base was isolated by extraction with dichloromethane, giving 0.169 g of the pure (tlc) (±)-**36** as a colorless solid, mp 147–149°, $[\alpha]^{25}D$ 0° (c 1, $CHCl_3$).

Acid Hydrolysis of 17a (R′ = CH_3). A mixture of 1.57 g (6.52 mmol) of pure (tlc) **17a** (R′ = CH_3) and 20 ml of 2 *N* aqueous HCl was stirred and heated at reflux for 2 hr. After cooling, the reaction mixture was made alkaline with 10% aqueous NaOH and the products were isolated by extraction with dichloromethane. This gave 1.2 g of the amine mixture **15a** and **16a** as a yellow oil [tlc two spots, R_f 0.07 (minor, **16a**) and 0.25 (major, **15a**), system A]. This material was acetylated as described above, giving an oily mixture of **17a** and **18a** (R′ = CH_3) in 89% yield. Analysis by tlc (system B) showed two spots with the less polar component (**17a**) predominating. The pmr spectrum ($CDCl_3$) showed two acetyl methyl singlets at δ 2.11 (**17a**) and 2.07 ppm (**18a**) in a ratio of approximately 3:2, respectively.

(±)-*trans*-3-[2-(3,5-Dimethyl-4-isoxazolyl)ethyl]-6a-methyl-1,2,3,5,6,6a-hexahydrocyclopenta[*f*][*b*]benzopyran-7 (8*H*)-one [(±)-8d]. A solution of 0.927 g (3 mmol) of a mixture of amino thiazines **15d** and **16d** (mp 119–122°, predominantly **15d**), 0.375 g (3.34 mmol) of 2-methylcyclopentane-1,3-dione, and 0.12 g of *p*-toluenesulfonic acid monohydrate in 5 ml of water and 10 ml of dioxane was stirred and heated at reflux for 92 hr. The resulting solution was cooled, poured into dilute aqueous HCl, and then worked up by ether extraction (the ether extracts were additionally washed twice with saturated aqueous sodium bicarbonate solution; the aqueous acidic solution was saved for recovery of starting material), giving 0.57 g of an orange oil. This material was stirred and heated at reflux in 15 ml of benzene containing 29 mg of *p*-toluenesulfonic acid monohydrate for 40 min. A Dean-Stark trap was used to remove water. The resulting green solution was treated with aqueous $NaHCO_3$ and worked up with ether, yielding 0.47 g of crystalline product. Chromatography of this material on 25 g of silica gel afforded 0.398 g (40.6%) of essentially pure (tlc,

system B), crystalline diene (±)-8d, eluted with 19:1 benzene–ether. Recrystallization from 2-propanol gave 0.307 g of yellow crystals: mp 107–110°; uv max (95% EtOH) 253 nm (ε 20,100) [lit.[20] mp 113–116°; uv max (95% EtOH) 252 nm (ε 18,200)]. This material was essentially identical with an authentic sample of (±)-8d by tlc, ir, and nmr comparisons.

The aqueous acidic solution which had been set aside was made alkaline with 10% aqueous NaOH and extracted with ether, giving 0.31 g (33.4%) of recovered starting thiazine mixture.

(±)-*trans*-3-Ethyl-6a-methyl-1,2,3,5,6,6a-hexahydrocyclopenta[*f*][*l*]benzopyran-7(8*H*)-one [(±)-8b]. This material was obtained from reaction of the amino thiazine mixture **15b** and **16b** with 2-methyl-1,3-cyclopentanedione using the procedure described in the preceding experiment. From 1.25 g (5.84 mmol) of the thiazine mixture there was obtained 0.454 g (33.5%) of pure (tlc, system B) diene (±)-8b after chromatographic purification. Recrystallization from hexane–ether gave orange crystals: mp 101–103.5°; uv max (95% EtOH) 254 nm (ε 18,200) [lit.[38] mp 105–105.5°; uv max (95% EtOH) 254 nm (ε 17,600)]. The starting thiazine mixture recovered amounted to 41.2%.

Crystallography. Crystals of **35** are monoclinic, space group $P2_1/a$, with a = 11.142 (6), b = 14.117 (3), c = 10.643 (4) Å, β = 108.51 (4)°, d_{obsd} (aqueous KI) = 1.53, d_{calcd} = 1.544 g cm^{-3} for Z = 4.

The intensity data were measured on a Hilger-Watts Model Y290 diffractometer by a θ–2θ technique. Ni-filtered Cu Kα radiation and pulse height discrimination were used. Of the 3158 accessible reflections with $2\theta < 140°$, 2097 had intensities significantly greater than background and these data were used for the structure analysis. The approximate size of the crystal used was 0.15 × 0.15 × 0.3 mm. The data were corrected for absorption (μ = 51.1 cm^{-1}).

The structure was solved by the heavy-atom method. The positions of the hydrogen atoms were obtained from a difference Fourier calculated after preliminary refinement of the heavier atoms. The final refinement was carried out by block diagonal least squares in which the crystal was partitioned into four blocks. Anisotropic thermal parameters were used for the heavier atoms and isotropic temperature factors for the hydrogen atoms. The positioned and thermal parameters of the hydrogen atoms were refined. The final discrepancy index, $R = \Sigma||F_o| - |F_c||/\Sigma|F_o|$, is 0.032 for the 2097 observed data.[44]

Acknowledgments. We wish to express our gratitude to the personnel of the Physical Chemistry Department of Hoffmann-La Roche Inc., Nutley, N. J., in particular Dr. W. Benz, Dr. T. Williams, Mr. S. Traiman, Dr. V. Toome, and Dr. F. Scheidl and their associates, for carrying out many of the spectral and microanalytical determinations required in this work. The technical assistance provided by Miss Roxanna Yang is also greatly appreciated.

Registry No.—**4a**, 51270-07-6; **4b**, 35313-18-9; **4c**, 51270-08-7; **4d**, 28867-67-6; **8b**, 35313-19-0; **8d**, 34769-94-3; **14c**, 51348-52-8; **15a**, 51270-09-8; **15a** maleate, 51270-10-1; **15b**, 51270-11-2; **15c**, 51270-12-3; **15d**, 51270-13-4; **16a**, 51270-14-5; **16c**, 51270-15-6; **16d**, 51270-16-7; **17a**, 51348-53-9; **17b**, 51348-54-0; **17c** (R′ = CH_3), 51348-55-1; **17c** (R′ = *p*-C_6H_4Br), 51348-56-2; **18a**, 51348-57-3; **18b**, 51348-58-4; **18c** (R′ = CH_3), 51348-59-5; **18c** (R′ = *p*-C_6H_4Br), 51348-60-8; **22**, 51270-17-8; **23**, 51270-18-9; **24**, 51270-19-0; **24** maleate, 51270-20-3; **25**, 51270-21-4; **26a**, 41323-55-1; **26c**, 41323-48-2; **27**, 5375-00-8; **28**, 51270-22-5; **29**, 51270-23-6; **30e**, 51270-24-7; **30f**, 51270-25-8; **31e**, 51270-26-9; **31f**, 51270-27-0; **33**, 51364-40-0; **35**, 51348-61-9; (±)-**36**, 51348-62-0; (+)-**36**, 51370-99-1; (+)-**36** *d*-(+)-camphorsulfonic acid salt, 51371-95-0; (−)-**36**, 51348-63-1; (−)-**36** *l*-(−)-camphorsulfonic acid salt, 51446-40-3; diethylamine, 109-89-7; thiourea, 62-56-6; 5-hydroxypentanal, 4221-03-8; methyl acetoacetate, 105-45-3; ethylene glycol, 107-21-1; *d*-(+)-camphorsulfonic acid, 3144-16-9; *l*-(−)-camphorsulfonic acid, 35963-20-3; 2-methylcyclopentane-1,3-dione, 765-69-5.

Supplementary Material Available. Listings of atomic parameters will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-1824.

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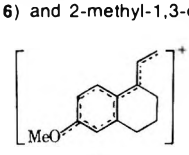
(10) These amine adducts exist preponderantly in the pseudo-spirocyclic, hydrogen-bonded hemiketal form, a factor which may be responsible for their relative ease of resolution.
(11) The related, stabilized carbenium ion i has been postulated as an intermediate species in the coupling of salt **2** with 2-methyl-1,3-cyclopentanedione.[2] Similarly, it is conceivable that the ion **10** may be involved in the reaction between the vinyl ketones **4** (or related derivatives such as **6**) and 2-methyl-1,3-cyclopentanedione, giving rise to the dienes **8**.



i

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(34) A comparison of the pmr spectra of **35** and the major, 8-substituted, acylated epimers **17** reveals similarities most notably with regard to the thiazine ring proton resonance patterns, which strongly suggest that these compounds all have analogous conformations. In contrast, the minor epimers **18** show resonance patterns due to the same protons which are consistent but substantially different from **17** and **35** (Table II). Since basic principles of conformational analysis mandate that the 8 substituents will prefer the relatively less energetic equatorial conformation in both epimers, again the conclusion is reached that the major epimers **17** (and the corresponding parent amines **15**) will have the relative stereochemistry in which the substituent R and the thiazine ring nitrogen atom are in a trans relationship. We have assumed, in drawing this conclusion, that the conformation of compound **35** is the same in solution (nmr) as in the solid state (X-ray).
(35) This substance and many of its analogs, including **35**, show biological activity a description of which will be published elsewhere.
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(37) Efforts to confirm the intermediacy of this or alternative open-chain species either by spectroscopic means or trapping experiments were unsuccessful. It is also conceivable, although seemingly less likely, that ring opening could occur *via* cleavage of the C_6–N_1 bond.

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(39) Unless otherwise noted, reaction products were isolated by addition of NaCl or saturated brine and extraction with the specified solvent. Organic extract solutions were combined, washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under water aspirator pressure at 40–50° on a rotary evaporator. The crude reaction products were then dried under high vacuum to constant weight. Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. All reactions except hydrogenations were carried out under an atmosphere of nitrogen. Unless otherwise noted, column chromatography was performed using Merck (Darmstadt) silica gel, 0.05–0.2 mm. Thin layer chromatography was performed using Brinkmann silica gel G plates with uv indicator. Plates were developed with one of the following systems: A, 9:1 benzene–triethylamine; B, 1:1 benzene–ethyl acetate; C, 1:1 hexane–ethyl acetate. Spots were detected with uv light, iodine vapor, or *p*-toluenesulfonic acid spray followed by heating. Varian A-60, HA-100, or Jeolco C-60H spectrometers were used to obtain the pmr spectra. Chemical shifts are reported relative to TMS as an internal standard. Infrared spectra were recorded on Beckman IR-9 or Perkin-Elmer 621 spectrophotometers. The ultraviolet spectra were recorded on a Cary Model 14M spectrophotometer. Low-resolution mass spectra were obtained on CEC 21-110 or JMS-01SG instruments. Optical rotations were measured on a Perkin-Elmer Model 141 polarimeter. Tetrahydrofuran (THF) and pyridine were dried by slurrying over Woelm grade I neutral alumina just prior to use.

(40) In naming the spiro compounds having an 8 substituent, we suggest that relative stereochemistry be designated by c and *t* to denote a cis or trans relationship to some reference (*r*) substituent. *Cf.* J. A. Marshall and P. C. Johnson, *J. Org. Chem.*, **35**, 192 (1970); Beilstein, "Handbuch der Organischen Chemie," E III, Vol. VI, Part 7, p x. Thus, for example, compound **15a** would be named (±)-2-amino-8*t*-methyl-(6*r*N^1)-7-oxa-3-thia-1-azaspiro[5.5]undec-1-ene and the epimer **16a**, (±)-2-amino-8*c*-methyl-(6*r*N^1)-7-oxa-3-thia-1-azaspiro[5.5]undec-1-ene. With regard to the acyl derivatives, compound **17a** (R′ = CH_3), for example would be named (±)-2-acetylimino-8*t*-methyl-(6*r*N^1)-7-oxa-3-thia-1-azaspiro[5.5]undecane.

(41) This preparation was carried out by Mrs. Angela Duggan.

(42) *Cf.* N. Cohen, B. L. Banner, J. F. Blount, M. Tsai, and G. Saucy, *J. Org. Chem.*, **38**, 3229 (1973), for a description of the preparation of the manganese dioxide used in this oxidation.

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(44) See paragraph at end of paper regarding supplementary material.

The Reaction of 3-Diazo-3*H*-indazole with Reactive Methylene Compounds and Formation of Indazolo[3,2-*c*]-1,2,4-triazines

D. Fortuna, B. Stanovnik, and M. Tišler*

Department of Chemistry, University of Ljubljana, 61000 Ljubljana, Yugoslavia

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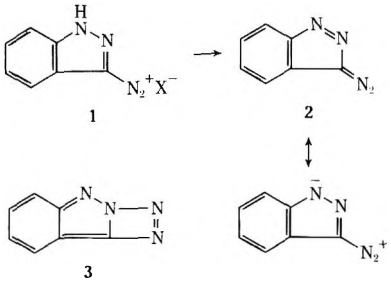
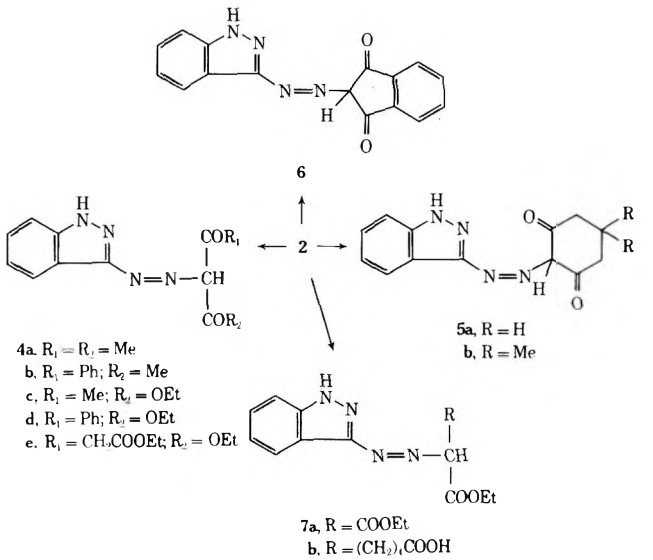
3-Diazo-3*H*-indazole reacts with 1,3-diketones, β-keto esters, or diethyl malonate and coupling occurs at the methylene group. The resulting products can be cyclized thermally or under the influence of acid into derivatives of indazolo[3,2-c]-1,2,4-triazine.

3-Aminoindazole, when diazotized, forms a diazonium salt (**1**) which can be converted upon treatment with alkali into the diazo compound. 3-Diazo-3*H*-indazole was the first heterocyclic diazo compound and was formulated by Bamberger[2] as indazolotriazolene (**3**), but later the diazo structure (**2**) was proposed.[3] 3-Diazo-3*H*-indazole exhibits



in solid state an ir absorption band at 2119 cm^{-1}, typical for diazo compounds,[4,5] and on the other hand it couples with phenols to give azo compounds or the diazo group can be replaced with halogens. So far, no other reactions of **2** have been investigated.

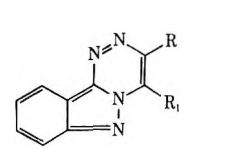
The reactivity of 3-diazo-3*H*-indazole was of interest in conjunction with our previous investigations on azido- and tetrazoloazines.[6-8] An ethanolic solution of **2**, when treated with a 1,3-dicarbonyl compound, a β-keto ester, or diethyl malonate, formed easily at room temperature the corresponding azo compound of the type **4**, **5**, **6**, or **7a**. Cyclic β-diketones, like cyclohexane-1,3-dione, its 5,5-dimethyl analog, or indan-1,3-dione, also reacted readily. For all compounds of this type several tautometric forms can be written. For example, compounds of the type **4** can be regarded as azo compounds or as hydrazones, and the carbonyl part can be written in the keto or enolized form. For compounds resulting from coupling of diazonium salts at a methyl or methylene carbon,[9] the hydrazone structure was postulated.[10] No attempt has been made to examine in detail the structures of our products.



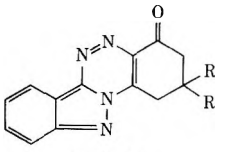
Compound **5a**, from 3-diazo-3*H*-indazole and 2-carbethoxycyclohexanone, reacted in ethanolic solution at room temperature to afford **7b** after 48 hr, indicating that ring opening of the cyclohexanone ring occurred during

the reaction. The reaction is comparable to the known Japp-Klingemann reaction[11] in which coupling of diazonium salts and cyclic β-keto esters gives ring-opened products.[12,13]

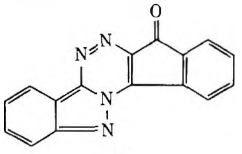
The azo compounds were transformed at widely differing rates into derivatives of indazolo[3,2-c]-1,2,4-triazine (**8, 9, 10**), a new heterocyclic system. In some cases cyclization occurred in hot ethanolic solution; with other compounds, temperatures around their melting point were required, whereas compound **6** was transformed into **10** only at 240°. These cyclic products are obtained rapidly at room temperature by acidification of an ethanolic solution of the azo compounds.



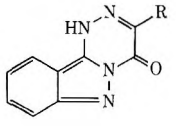
8a, R = COMe; R_1 = Me
b, R = COMe; R_1 = Ph
c, R = COOEt; R_1 = Me
d, R = COOEt; R_1 = Ph
e, R = COOEt; R_1 = CH_2COOEt



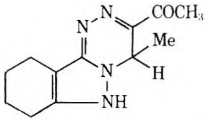
9a, R = H
b, R = Me



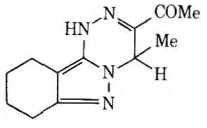
10



11a, R = COOEt
b, R = H



12a



12b

Thermal cyclization of compound **7a** was unsuccessful, but upon heating in polyphosphoric acid at 140° for 3 hr it was transformed into a cyclic product which was identified as **11b**. The reaction can be explained as the result of ring closure, hydrolysis of the carbethoxy group, and decarboxylation. However, acid-induced cyclization afforded the anticipated cyclic product **11a**. The reaction could be followed also in a nmr probe and progression of the elimination of ethanol was detected.

Compound **8a** could be easily reduced over palladized carbon at room temperature to give a hexahydro derivative which from its ir and nmr spectrum can be formulated as either **12a** or **12b**.

Finally, it should be mentioned that a solution of 3-diazo-3*H*-indazole in chloroform with dimethyl acetylenedicarboxylate gave a low yield of indazole after 10-hr reflux. Indazole was also obtained when a methanolic solution of **2** was irradiated; the reaction may be postulated to proceed through a carbene intermediate. On the other hand, treatment of either **8** or **4** with hydrazine hydrate or with a 5% aqueous solution of potassium hydroxide resulted in the formation of 3-aminoindazole. Under the influence of the base the heterocyclic ring of **8** is cleaved, as concluded from nmr evidence. Furthermore, as already mentioned, compounds of the type **4** can be regarded as hydrazones,[10] and therefore a base-induced N–N cleavage can be anticipated, which is consistent with previous observations of similar cases.[14,15]

Experimental Section

Melting points were taken on a Kofler micro hot stage and are corrected. Infrared spectra were recorded on a Perkin-Elmer 137 Infracord as KBr disks, nmr spectra were taken on a JEOL JNM-C-60HL spectrometer (TMS as internal standard), and mass spectra were recorded on a Hitachi Perkin-Elmer RMU-6L mass spectrometer. 3-Diazo-3*H*-indazole was obtained from 3-aminoindazole[16] according to the procedure described in literature.[2]

General Procedure for the Preparation of Coupling Products from 3-Diazo-3*H*-indazole and 1,3-Dicarbonyl Compounds. A solution of 3-diazo-3*H*-indazole (0.01 mol) in ethanol (2 ml) was treated with the corresponding 1,3-diketone, β-keto ester, or diethyl malonate (0.001 mol) at room temperature. The separated product was filtered off and crystallized. In this manner the following compounds were prepared.

Compound **4a** in 86% yield: mp 173–173.5° (from ethanol-*N,N*-dimethylformamide, 4:1); mass spectrum M$^+$ *m/e* 244; nmr (DMSO-d_6) τ 2.60 (m, H_4, H_5, H_6, H_7), 7.66 and 7.57 (s, CH_3), 6.50 (broad, NH).

Anal. Calcd for $C_{12}H_{12}N_4O_2$: C, 59.01; H, 4.95; N, 22.94. Found: C, 59.29; H, 5.09; N, 23.28.

Compound **4b** in 82% yield: mp 153°; ir 1639 cm^{-1} (CO); mass spectrum M$^+$ *m/e* 306; nmr (DMSO-d_6) τ 7.43 (s, CH_3), 2.50 (m, C_6H_5 and H_4, H_5, H_6, H_7), 6.50 (broad, NH or OH).

Anal. Calcd for $C_{17}H_{14}N_4O_2$: C, 66.65; H, 4.61; N, 18.29. Found: C, 66.81; H, 5.10; N, 18.72.

Compound **5a** in 68% yield: mp 162°; ir 1695, 1664 cm^{-1} (CO); mass spectrum M$^+$ *m/e* 256; nmr (DMSO-d_6, 65°) τ 6.40 (m, 4′-CH_2), 7.95 (m, 5′-CH_2), 7.24 (m, 6′-CH_2), 2.0 (m, H_4, H_5, H_6, H_7).

Anal. Calcd for $C_{13}H_{12}N_4O_2$: C, 60.93; H, 4.72; N, 21,87. Found: C, 60.76; H, 4.56; N, 21.80.

Compound **5b** in 90% yield: mp 175° (from EtOH); at the melting point the compound cyclized and melted again at 235°; mass spectrum M$^+$ *m/e* 284; nmr (DMSO-d_6) τ 7.40 (s, 4′-CH_2, 6′-CH_2), 8.92 (s, 5′-CH_3), 2.60 (m, H_4, H_5, H_6), 1.75 (m, H_7).

Anal. Calcd for $C_{15}H_{16}N_4O_2$: C, 63.36; H, 5.67; N, 19.71. Found: C, 62.97; H, 5.82; N, 19.23.

Compound **6** in 83% yield: mp 240–241° (from ethanol-*N,N*-dimethylformamide, 4:1); ir 1695, 1667 cm^{-1} (CO); mass spectrum M$^+$ *m/e* 290; nmr (DMF-d_7) τ 2.07 (s, $H_{4'}$, $H_{5'}$, $H_{6'}$, $H_{7'}$), 2.60 (m, $H_{4'}$, $H_{5'}$, H_6), 1.65 (m, H_7), 6.50 (broad, NH or OH).

Anal. Calcd for $C_{16}H_{10}N_4O_2$: C, 66.20; H, 3.47. Found: C, 66.67; H, 3.60.

Compound **4c** in 62% yield: mp 167–168° (from ethanol); mass spectrum M$^+$ *m/e* 274; ir 1639 cm^{-1} (CO); nmr (DMSO-d_6) τ 7.57 (s, CH_3), 8.62 (t, CH_2CH_3), 5.65 (q, CH_2CH_3) 2.55 (m, H_4, H_5, H_6), 1.87 (m, H_7), J_{Et} = 7.5 Hz.

Anal. Calcd for $C_{13}H_{14}N_4O_3$: C, 56.93; H, 5.15. Found: C, 57.03; H, 5.00.

Compound **4d** in 83% yield: mp 195–197° (from ethanol-*N,N*-dimethylformamide, 3:1); ir 1706, 1698 cm^{-1} (CO); mass spectrum M$^+$ *m/e* 336; nmr (DMSO-d_6) τ 8.23 (t, CH_2CH_3), 5.63 (q, CH_2CH_3), 2.50 (m, C_6H_5 and H_4, H_5, H_6, H_7), −2.5 (broad, NH or OH), J_{Et} = 7.5 Hz.

Anal. Calcd for $C_{18}H_{16}N_4O_3$: C, 64.27; H, 4.80; N, 16.66. Found: C, 64.14; H, 4.95; N, 16.35.

Compound **4e** in 61% yield: mp 138–139° (from ethanol); ir 1730, 1695 cm^{-1} (CO); mass spectrum M$^+$ *m/e* 346; nmr ($CDCl_3$) τ 8.54 (t, $CO_2CH_2CH_3$), 5.75 (q, $CO_2CH_2CH_3$), 8.67 (t, $CH_2COOCH_2CH_3$), 5.78 (q, $CH_2COOCH_2CH_3$), 5.95 (s, CH_2COOEt), 2.75 (m, H_4, H_5, H_6), 1.65 (m, H_7), −0.5 (broad, NH or OH), J_{Et} = 7.5 Hz.

Anal. Calcd for $C_{16}H_{18}N_4O_5$: C, 55.48; H, 5.25; N, 16.18. Found: C, 55.78; H, 5.19; N, 16.20.

Compound **7a** in 55% yield: mp 142–142,5° (from EtOH); mass spectrum M$^+$ *m/e* 304; ir 1701 cm^{-1} (COOEt); nmr ($CDCl_3$) τ 8.51 (t, CH_2CH_3), 5.58 (q, CH_2CH_3), 8.57 (t, CH_2CH_3), 2.70 (m, H_4, H_5, H_6), 1.60 (m, H_7), 0.0 and −3.1 (broad, two exchangeable protons), J_{Et} = 7.5 Hz.

Anal. Calcd for $C_{14}H_{16}N_4O_4$: C, 55.25; H, 5.30; N, 18.41. Found: C, 55.43; H, 5.36; N, 18.75.

Compound **7b** in 63% yield after 48 hr: mp 200–202° (from ethanol-*N,N*-dimethylformamide, 2:1); mass spectrum M$^+$ *m/e* 332; nmr (DMSO-d_6, 65°) τ 8.66 (t, OCH_2CH_3), 5.80 (q, OCH_2CH_3), 7.46 (t, CH), 8.35 (m, CH_2), 7.7 (t, CH_2), 2.6 and 1.7 (m, H_4, H_5, H_6, H_7), 5.8 (broad, OH), J_{OEt} = 7.0 Hz.

Anal. Calcd for $C_{16}H_{20}N_4O_4$: C, 57.82; H, 6.07; N, 16.86. Found: C, 58.16; H, 6.06; N, 16.33.

3-Acetyl-4-methylindazolo[3,2-*c*]-1,2,4-triazine (8a). Compound **4a** (0.21 g) was heated in a sublimation tube at 170° until the evolution of water had ceased (about 15 min). The residue was crystallized from ethanol-*N,N*-dimethylformamide (3:1), yield 0.18 g (93%), mp 187°. The same compound could be pre-

pared from **4a** after an ethanolic solution (2 ml) was acidified with hydrochloric acid: ir 1692 cm^{-1} (CO); mass spectrum M^+ m/e 226; nmr ($CDCl_3$) τ 7.02 (s, 3-CH_3), 6.78 (s, 4-CH_3), 2.40 (m, H_7, H_8, H_9), 1.55 (m, H_{10}).

Anal. Calcd for $C_{12}H_{10}N_4O$: C, 63.70; H, 4.46; N, 24.77. Found: C, 63.48; H, 4.69; N, 24.95.

3-Acetyl-4-phenylindazolo[3,2-c]-1,2,4-triazine (8b). The product was obtained after a solution of **4b** (0.25 g) in ethanol was heated under reflux for a few minutes. The same reaction took place if compound **4b** was dissolved in 2 ml of ethanol and the solution was acidified with hydrochloric acid at room temperature. The product was crystallized from ethanol: yield 0.21 g (90%); mp 198.5–199°; ir 1664 cm^{-1} (CO); mass spectrum M^+ m/e 288; nmr (DMSO-d_6) τ 7.0 (s, 3-CH_3), 2.60 (m, 4-C_6H_5), 2.70 (m, H_7, H_8, H_9), 1.45 (m, H_{10}).

Anal. Calcd for $C_{17}H_{12}N_4O$: C, 70.82; H, 4.20; N, 19.44. Found: C, 70.70; H, 4.30; N, 19.55.

8,9,10,11-Tetrahydroindazolo[3,2-c]-1,2,4-benzotriazin-8-one (9a). Compound **5a** (0.175 g) was dissolved in ethanol (2 ml) and the solution was heated under reflux for 5 min. The same conversion took place if the above solution was acidified with HCl at room temperature. The separated product was filtered off and crystallized from ethanol-*N,N*-dimethylformamide (2:1): yield 0.15 g (92%); mp 215–216°; ir 1689 cm^{-1} (CO); mass spectrum M^+ m/e 238; nmr (DMF-d_7, 75°) τ 6.45 (m, 9-CH_2), 6.87 (m, 10- and 11-CH_2), 2.40 (m, H_2, H_3, H_4), 1.60 (m, H_5).

Anal. Calcd for $C_{13}H_{10}N_4O$: C, 65.53; H, 4.23; N, 23.52. Found: C, 65.74; H, 4.36; N, 23.75.

10,10-Dimethyl-8,9,10,11-tetrahydroindazolo[3,2-c]-1,2,4-benzotriazin-8-one (9b). Compound **5b** (0.215 g) was heated in a sublimation tube at 220° for about 15 min until all water was evolved. Alternatively, a solution of the same amount in ethanol (2 ml) was acidified with hydrochloric acid. The product was crystallized from ethanol: yield 0.19 g (95%); mp 235°; ir 1695 cm^{-1} (CO); mass spectrum M^+ m/e 266; nmr ($CDCl_3$) τ 6.42 (s, 9-CH_2), 7.16 (s, 11-CH_2), 8.67 (s, 10,10-CH_3), 2.35 (m, H_2, H_3, H_4), 1.53 (m, H_5).

Anal. Calcd for $C_{15}H_{14}N_4O$: C, 67.65; H, 5.30; N, 21.04. Found: C, 67.83; H, 5.39; N, 20.75.

8*H*-Indazolo[3,2-c[indeno[1,2-e]-1,2,4-triazin-8-one (10). Compound 6 (0.24 g) was heated in a tube at 240° for about 30 min. The residue was sublimed at 239° (1 mm): yield 0.21 g (93%); mp >300°; ir 1730 cm^{-1} (CO); mass spectrum M^+ m/e 272; nmr ($CDCl_3$) τ 2.25 (m, H_2, H_3, H_4, H_5, H_9, H_{10}, H_{11}, H_{12}).

Anal. Calcd for $C_{16}H_8N_4O$; C, 70.58; H, 2.96; N, 20.58. Found: C, 70.52; H, 3.08; N, 20.75.

3-Carbethoxy-4-methylindazolo[3,2-c]1,2,4-triazine (8c). Compound **4c** (0.170 g) was heated in a tube at 167° for about 15 min. Alternatively, an ethanolic solution was treated with hydrochloric acid. The product was crystallized from ethanol: yield 0.15 g (94%); mp 150°; ir 1721 cm^{-1} (CO); mass spectrum M^+ m/e 256; nmr ($CDCl_3$) τ 6.78 (s, 4-CH_3), 8.50 (t, CH_2CH_3), 5.45 (q, CH_2CH_3), 2.4 (m, H_7, H_8, H_9), 1.5 (m, H_{10}), J_{Et} = 7.2 Hz.

Anal. Calcd for $C_{13}H_{12}N_4O_2$: C, 60.93; H, 4.72; N, 21.87. Found: C, 60.70; H, 4.90; N, 22.35.

3-Carbethoxy-4-phenylindazolo[3,2-c]-1,2,4-triazine (8d). Compound **4d** (0.28 g) was heated in a tube at 200° for 15 min. The same conversion took place after addition of HCl to an ethanolic solution. The product was crystallized from ethanol: yield 0.24 g (91%); mp 148°; ir 1721 cm^{-1} (COOEt); mass spectrum M^+ m/e 318; nmr ($CDCl_3$) τ 8.82 (t, CH_2CH_3), 5.65 (q, CH_2CH_3), 2.4 (m, 4-C_6H_5), 2.4 (m, H_7, H_8, H_9), 1.40 (m, H_{10}).

Anal. Calcd for $C_{18}H_{14}N_4O_2$: C, 67.91; H, 4.43; N, 17.60. Found: C, 67.55; H, 4.65; N, 17.62.

3-Carbethoxy-4-carbethoxymethylindazolo[3,2-c]-1,2,4-triazine (8e). Compound **4e** (0.21 g) was heated in a tube at 140° for about 15 min. Alternatively, an ethanolic solution was acidified with hydrochloric acid and heated under reflux for 5 min. The product was crystallized from ethanol–water (3:1): yield 0.18 g (90%): mp 114–115°; ir 1745, 1727 cm^{-1} (CO); mass specfrum M^+ m/e 328; nmr ($CDCl_3$) τ 8.48 (t, $COOCH_2CH_3$), 5.40 (q, $COOCH_2CH_3$), 8.75 (t, $CH_2COOCH_2CH_3$), 5.77 (q, $CH_2COOCH_2CH_3$), 5.02 (CH_2COOEt), 1.35 (m, H_{10}), 2.25 (m, H_7, H_8, H_9), J_{Et} = 7.2 Hz.

Anal. Calcd for $C_{16}H_{16}N_4O_4$: C, 58.53; H, 4.91; N, 17.07. Found: C, 58.29; H, 5.00; N, 17.50.

3-Carbethoxyindazolo[3,2-c]-1,2,4-triazin-4(1*H*)-one (11a). Compound **7a** (0.17 g) was dissolved in ethanol (2 ml), acidified with hydrochloric acid, and heated under reflux for 30 min. The separated product was filtered off and crystallized from ethanol–*N,N*-dimethylformamide (3:1); yield 0.12 g (83%); mp 165°; ir 1739 cm^{-1} (COOEt); mass spectrum M^+ m/e 258; nmr (DMSO-d_6, 88°) τ 2.58 (t, CH_2CH_3), 5.55 (q, CH_2CH_3), 2.50 (m, H_7, H_8, H_9), 1.55 (m, H_{10}), J_{Et} = 7.2 Hz.

Anal. Calcd for $C_{12}H_{10}N_4O_3$: C, 55.81; H, 3.90; N, 21.70. Found: C, 55.98; H, 4.08; N, 21.95.

Indazolo[3,2-c]-1,2,4-triazin-4(1*H*)-one (11b). A mixture of compound **7a** (0.17 g) and polyphosphoric acid (1 g) was heated at 140° for 3 hr. The cooled mixture was treated with water and the separated product was filtered off and sublimed at 270° (1 mm): yield 0.09 g (90%); mp 315°; ir 1712 cm^{-1} (CO); mass spectrum M^+ m/e 186; nmr (DMSO-d_6) τ 2.65 (m, H_7, H_8, H_9), 2.0 (m, H_{10}), 3.85 (broad, NH), H_3 was exchanged.

Anal. Calcd for $C_9H_6N_4O$: C, 58.06; H, 3.25. Found: C, 58.28; H, 3.55.

Hydrogenation of Compound 8a into 12. A mixture of **8a** (0.5 g), methanol (50 ml), and palladized carbon (0.2 g of 10%) was stirred in an atmosphere of hydrogen at room temperature for about 50 hr. Upon filtration the solution was evaporated to dryness and the residue was crystallized from ethanol: yield 0.45 g (90%); mp 260°; mass spectrum M^+ m/e 232; ir 1658 cm^{-1} (CO); nmr (DMSO-d_6) τ 8.69 (d, $CHCH_3$), 4.87 (q, CH), 7.68 (s, $COCH_3$), 7.65 (m, 7,10-CH_2), 8.36 (m, 8,9-CH_2), 6.70 (broad, NH), J_{CHMe} = 7.0 Hz.

Anal. Calcd for $C_{12}H_{16}N_4O$: C, 62.05; H, 6.94; N, 24.12. Found: C, 62.18; H, 7.08; N, 24.45.

Reaction between 3-Diazo-3*H*-indazole and Dimethyl Acetylenedicarboxylate. A solution of **2** (0.144 g) in chloroform (5 ml) was treated with dimethyl acetylenedicarboxylate (0.108 g) and the reaction mixture was heated under reflux for 10 hr. The solvent was evaporated to one-third of its original volume, and after addition of petroleum ether and cooling the product separated. It was identified as indazole. The same compound could be obtained when a methanolic solution of **2** was irradiated with a wavelength of 300 nm: yield 0.02 g (17%); mp 145–148° (lit.[17-19] mp *ca.* 145–148°); nmr ($CDCl_3$) τ 2.85 (s, H_3), 2.6 (m, H_4, H_5, H_6, H_7).

Reaction between Indazolo[3,2-c]-1,2,4-triazines and a Base. A suspension of the corresponding indazolo[3,2-c]-1,2,4-triazine (0.001 mol) in ethanol (5 ml) was treated with hydrazine hydrate (0.5 ml of 80%) (or 0.5 ml of a 5% aqueous solution of potassium hydroxide can be used) and the mixture was heated under reflux until no more of the starting compound was present. The latter was slowly dissolved and the progression of the reaction can be followed by tlc; 1–2 hr are necessary for a complete conversion. The reaction mixture was evaporated to dryness (if KOH is used, the solution is first neutralized) and the residue was treated with water (15 ml) and extracted with chloroform (3 × 10 ml). The combined extracts were dried over anhydrous sodium sulfate and upon evaporation of the solvent the product was identified as 3-aminoindazole, identical with an authentic specimen[16,20] (yields were 80–90%).

3-Aminoindazole was obtained similarly if compounds of the type **4**, **5**, **6**, or **7a** were treated with a base.[21]

Registry No.—**2**, 2596-89-6; **4a**, 51271-52-4; **4b**, 51271-53-5; **4c**, 51271-54-6; **4d**, 51271-55-7; **4e**, 51271-56-8; **5a**, 51271-57-9; **5b**, 51271-58-0; **6**, 51271-59-1; **7a**, 51271-60-4; **7b**, 51271-61-5; **8a**, 51293-26-6; **8b**, 51271-62-6; **8c**, 51271-63-7; **8d**, 51271-64-8; **8e**, 51271-65-9; **9a**, 51271-66-0; **9b**, 51271-67-1; **10**, 51271-68-2; **11a**, 51271-69-3; **11b**, 51271-70-6; **12**, 51271-72-8; 2,4-pentanedione, 123-54-6; 1-phenyl-1,3-butanedione, 93-91-4; 1,3-cyclohexanedione, 504-02-9; 5,5-dimethyl-1,3-cyclohexanedione, 126-81-8; 1,3-indandione, 606-23-5; ethyl 3-oxobutyric acid, 141-97-9; ethyl 3-oxobenzenepropanoic acid, 94-02-0; diethyl 3-oxopentanedioic acid, 105-50-0; diethyl malonate, 105-53-3; diethyl heptanedioate, 2050-20-6; dimethyl acetylenedicarboxylate, 762-42-5; indazole, 271-44-3.

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Studies on Organic Fluorine Compounds. XIV.[1] Syntheses and Reactions of (Trifluoromethyl)indoles[2]

Yoshiro Kobayashi,* Itsumaro Kumadaki, Yoshibumi Hirose, and Yuji Hanzawa

Tokyo College of Pharmacy, Kitashinjuku 3-chome, Shinjuku-ku, Tokyo, Japan

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To compare the reactivity of (trifluoromethyl)indoles with that of (trifluoromethyl)quinolines, 2- and 3-(trifluoromethyl)indoles (**12** and **13**) were synthesized from 3- and 4-(trifluoromethyl)quinoline in four steps: N-oxidation, oxidative cyanation using potassium cyanide and potassium ferricyanide, photomigration reaction to benzoxazepine derivatives, and recyclization with hydrogen chloride to indoles. Reactions of **12** and **13** with nucleophiles (sodium ethoxide, lithium aluminum hydride, sodium borohydride, and sodium amide) were examined, and **12** and **13** were found to undergo SN1-type reaction and the trifluoromethyl group in **13** was more reactive than that in **12**. These results were discussed.

A trifluoromethyl group on an aromatic ring is generally a very stable substituent,[3] and there has been little study of the reactions of the trifluoromethyl group on the heterocyclic ring. In previous papers[4] we have reported a study of the reactivity of the trifluoromethyl group on the quinoline ring with nucleophilic reagents and found three types of reactions: SN2 substitution of fluoride, elimination of fluoride, and displacement of the trifluoromethyl carbanion. Typical examples are shown in Scheme I.

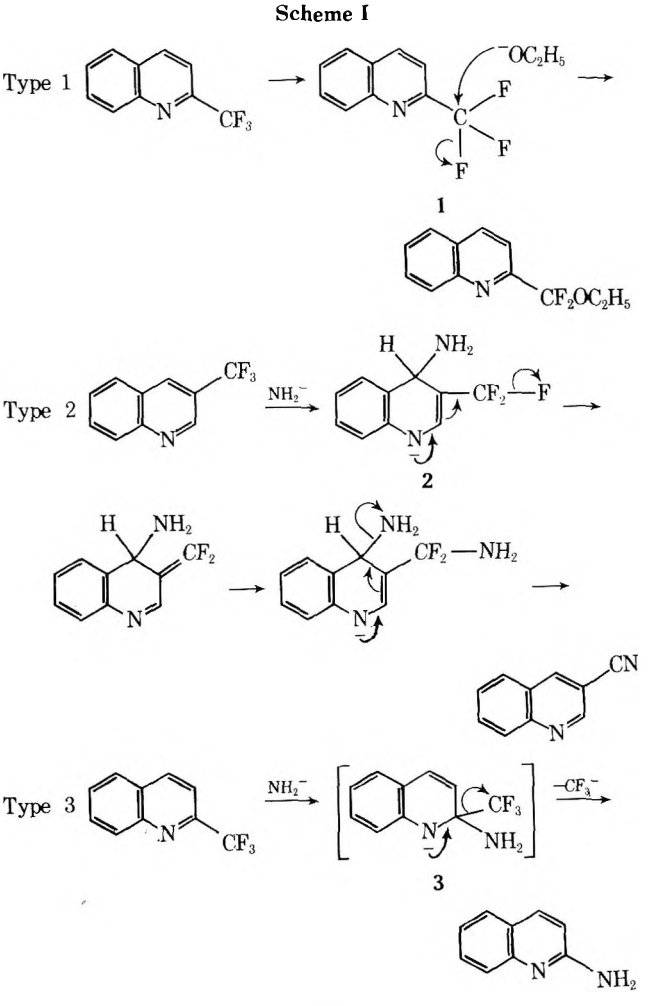
Since the trifluoromethyl group on the π-deficient quinoline ring shows unusual reactivity to nucleophilic reagents, it was of interest to examine the reactivity of this group on the π-electron excess indole ring. Indoles with a trifluoromethyl group on the pyrrole ring have not been reported to date. We have devised a synthetic route to such indoles from (trifluoromethyl)quinoline by the series of reactions shown in Scheme II.

In this method, 3- or 4-(trifluoromethyl)quinoline (**4** or **5**), obtained with sulfur tetrafluoride[5] or copper powder–trifluoromethyl iodide,[6] was converted into its *N*-oxide (**6** or **7**) by acetic acid–hydrogen peroxide.[7] A cyano group was introduced into the 2 position of **6** or **7** with retention of the *N*-oxide group by oxidative cyanation with potassium ferricyanide and potassium cyanide.[8] The resultant compound (**8** or **9**) was photoirradiated in an aprotic solvent to produce a benzoxazepine derivative (**10** or **11**), and the corresponding 2- or 3-(trifluoromethyl)indole (**12** or **13**) was successfully synthesized by ring opening and then closure with dry hydrogen chloride gas in methanol. When photoirradiation was carried out in methanol, the *N*-methoxycarbonylindole derivative (**14** or **15**) was obtained as a by-product. However, hydrolysis of **14** (or **15**) to **12** (or **13**) was unsuccessful; this may be due to the carbamate group of **14** (or **15**), which was stabilized by the electronic effect of the indole ring, and to the fact that indole itself is unstable to acids.

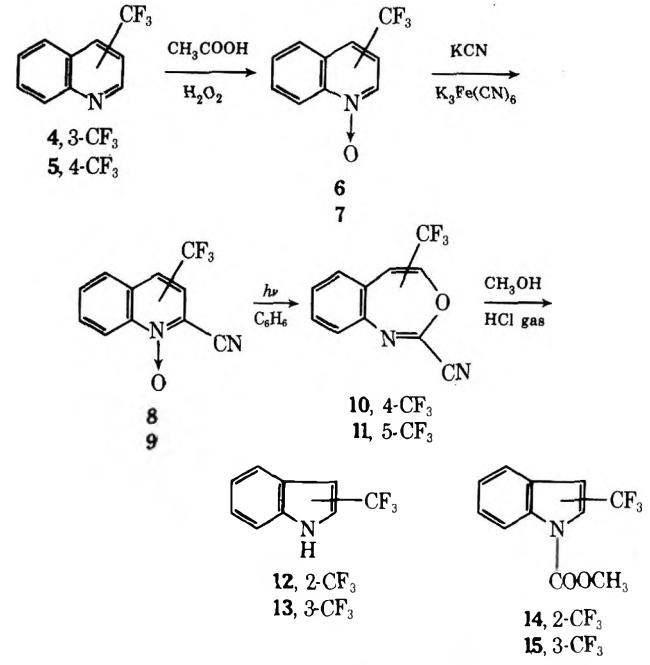
Next, we examined the reaction of **12** or **13** with nucleophilic reagents. We used sodium ethoxide and sodium amide; we also used metal hydrides to examine the reduction, since they attack as the hydride anion. These results are shown in Scheme III.

The fact that benzotrifluoride was recovered in these reaction conditions shows that susceptibility of the trifluoromethyl group to nucleophilic attack is increased by the electronic effect of the indole ring. This suggests that the carbon–fluorine bond in the trifluoromethyl group is cleaved in SN1-like manner. Further investigation of the results from **12** and **13** shows a considerable difference in their reactivity. Both compounds undergo alcoholysis when refluxed with sodium ethoxide in ethanol. With the

Scheme I

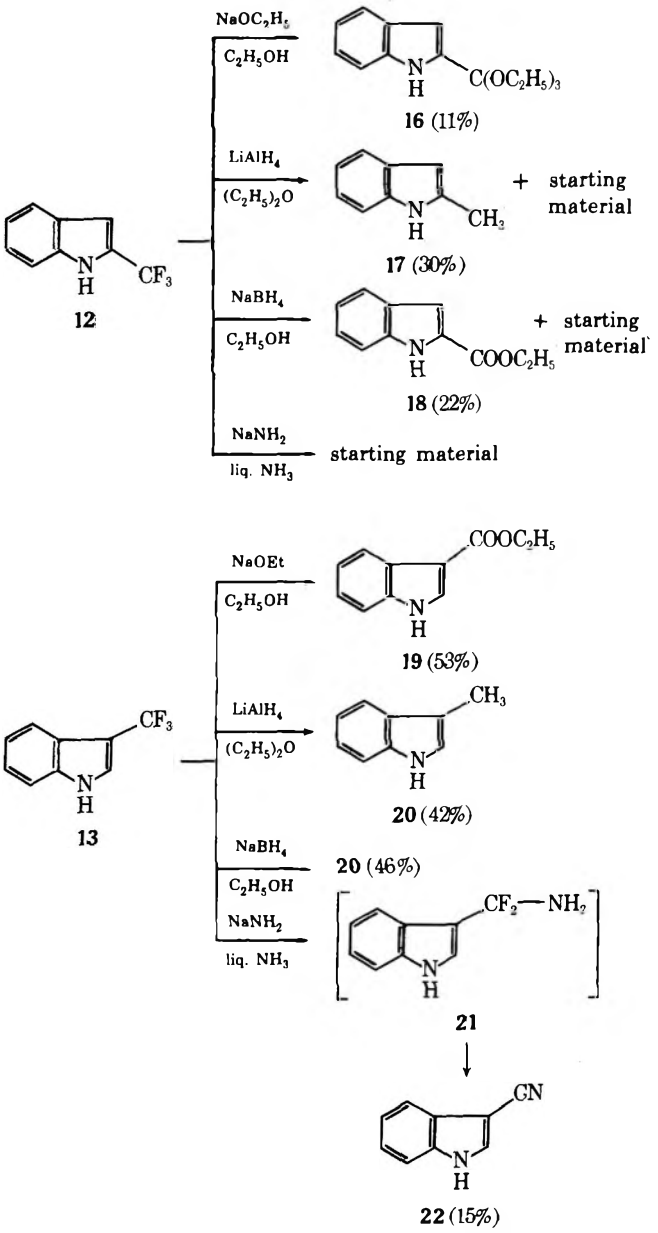


Scheme II



4, 3-CF_3
5, 4-CF_3
6
7
8
9
10, 4-CF_3
11, 5-CF_3
12, 2-CF_3
13, 3-CF_3
14, 2-CF_3
15, 3-CF_3

Scheme III



β-trifluoromethyl compound (**13**), the ortho ester, which should have been produced in the first step, was partially hydrolyzed to an ester (**19**). This may have been due to the higher electron density at the β position than at the α position in the indole ring. When refluxed with lithium aluminum hydride in ether, **13** easily gave skatole (**20**), while **12** required a much longer reaction time than **13** and a considerable amount of the starting material was recovered even then. The greater reactivity of **13** became more apparent in the reaction with sodium borohydride. When refluxed with sodium borohydride in ethanol, **13** gave **20**, while most of **12** was recovered with an ester (**18**) as a by-product in 22% yield.

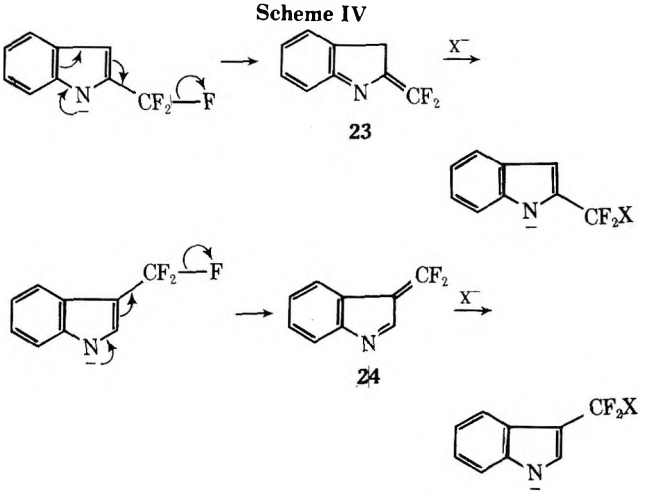
This may be explained as follows. The rate of reduction is much greater for **13** than for **12** and the rate of decomposition of sodium borohydride is significantly greater for the latter. Accordingly, sodium ethoxide produced by the decomposition of sodium borohydride attacks the trifluoromethyl group and gives the ester **18**. Therefore, this reaction also shows that the β-trifluoromethyl compound has a greater reactivity than the α compound.

The difference in reactivity between **12** and **13** was also observed with sodium amide. Although **12** was recovered unchanged, **13** gave a cyano derivative (**22**), which was produced by the substitution of one fluorine atom with an amino group followed by dehydrofluorination.

In these reactions the excess π-electron density of the indole ring appears to promote the SN1-like cleavage of the carbon–fluorine bond. The concept that the difference between reactivities of **12** and **13** is explained by the difference between stabilities of **23** and **24** (Scheme IV) has been recognized with methylene analogs.[9] The fact that the β position has a higher electron density than the α position from MO calculation of the indole ring in the literature[10] also supports the assumption that SN1-like cleavage of the carbon–fluorine bond is promoted more strongly in the β-trifluoromethyl compound than in the α-trifluoromethyl compound.

In contrast to the SN2-like reactions of 2- and 4-(trifluoromethyl)quinolines, which showed the electron-withdrawing effect of the ring, SN1-like reactions occurred in the present case with a π-electron excess system. The interesting point is that the results of 3-(trifluoromethyl)indole correspond with those of 3-(trifluoromethyl)quinoline, which we reported in the preceding paper.[4] Moreover, the intermediate proposed for 3-(trifluoromethyl)indole is quite similar to that proposed for this quinoline, namely, both have the same enamine conjugation.

Scheme IV



Experimental Section

Photoreaction of 2-Cyano-3-(trifluoromethyl)quinoline 1-Oxide[8] (8). A. A solution of 300 mg (1.25 mmol) of 8 dissolved in

300 ml of benzene was irradiated with a high-pressure mercury lamp (Ushio UM-102, 100 W) under a stream of nitrogen in a Pyrex vessel for 30 min. After evaporation of benzene, the residue was purified by silica gel column chromatography and **10** was obtained from the hexane eluate. Recrystallization from hexane gave yellow prisms: mp 88°; yield 273 mg (91%); ir (KBr) 2280 (C≡N), 1193 and 1150 cm^{-1} (broad, CF_3); nmr ($CDCl_3$) δ 6.42 (1 H, s, 5-H); mass spectrum *m/e* 238 (M^+). *Anal.* Calcd for $C_{11}H_5F_3N_2O$: C, 55.47; H, 2.12; F, 23.93; N, 11.76. Found: C, 55.41; H, 2.26; F, 23.31; N, 11.52.

B. A solution of 300 mg of **8** dissolved in 300 ml of MeOH was irradiated in the same manner as in A. MeOH was evaporated and the residue was recrystallized from benzene to give yellow crystals (**14**): mp 204°; yield 104.1 mg (34%); ir (KBr) 1676 (C=O) and 1126 cm^{-1} (broad, CF_3); nmr ($CDCl_3$) δ 3.86 (3 H, s, OCH_3); mass spectrum *m/e* 243 (M^+), 228 ($M^+ - CH_3$); high mass on *m/e* 228 ($M^+ - CH_3$), 228.025 (calcd, 228.027).

Recrystallization of the residue from mother liquor and hexane gave **10**, yield 96 mg (32%).

Photoreaction of 2-Cyano-4-(trifluoromethyl)quinoline 1-Oxide[8] (9). A. A solution of 300 mg of **9** dissolved in 300 ml of benzene was treated as in the case of **8**. After evaporation of benzene, the residue was purified by being passed through a silica gel column in hexane solution. The effluent was recrystallized from hexane to give yellow crystals (**11**): mp 59–60°; yield 291 mg (97%); ir (KBr) 2240 (C≡N), 1305, 1140 cm^{-1} (broad, CF_3); nmr (CCl_4) δ 6.93 (1 H, s, 4-H); mass spectrum *m/e* 238 (M^+). *Anal.* Calcd for $C_{11}H_5F_3N_2O$: C, 55.47; H, 2.12; F, 23.93; N, 11.76. Found: C, 55.22; H, 2.38; F, 23.07; N, 11.48.

B. A solution of 300 mg of **9** dissolved in 300 ml of MeOH was treated as in the case of **8**. The residue obtained after evaporation of MeOH was recrystallized from benzene to give yellow crystals (**15**): mp 238.5°; yield 24.5 mg (8%); ir (KBr) 1670 (C=O) 1156, 1120 cm^{-1} (CF_3); nmr (DMSO-d_6) δ 3.91 (3 H, s, OCH_3); mass spectrum *m/e* 243 (M^+), 228 ($M^+ - CH_3$); high mass on *m/e* 228 ($M^+ - CH_3$) 228.026 (calcd, 228.027).

The residue obtained by evaporation of the mother liquor was purified by silica gel column chromatography in hexane solution to give 144 mg (48%) of **11**.

2-(Trifluoromethyl)indole (12). HCl gas was passed through a solution of 300 mg of **10** dissolved in 15 ml of MeOH with stirring for 10 min and the reaction mixture was poured into ice water. This mixture was neutralized with Na_2CO_3 and extracted with Et_2O. The Et_2O solution was washed with H_2O and dried over Na_2SO_4. The residue obtained by evaporation of Et_2O was passed through a column of silica gel in hexane solution. The effluent was recrystallized from hexane and gave colorless plates (**12**): mp 102°; yield 144.5 mg (62%); ir (KBr) 3410 (NH), 1165, 1100 cm^{-1} (CF_3); nmr ($CDCl_3$) δ 6.94 (1 H, s, 3-H), 8.32 (1 H, broad, NH); mass spectrum *m/e* 185 (M^+). *Anal.* Calcd for $C_9H_6F_3N$: C, 58.42; H, 3.27; F, 30.80; N, 7.57. Found: C, 58.70; H, 3.33; F, 30.16; N, 7.24.

3-(Trifluoromethyl)indole (13). The same treatment of 300 mg of **11** as in the case of **10** gave colorless plates (**13**): mp 110°; yield 149 mg (64%): ir (KBr) 3440 (NH), 1183, 1120, 1087 cm^{-1} (CF_3); nmr ($CDCl_3$) δ 8.37 (1 H, broad, NH); mass spectrum *m/e* 185 (M^+). *Anal.* Calcd for $C_9H_6F_3N$: C, 58.42; H, 3.27; F, 30.80; N, 7.57. Found: C, 58.48; H, 3.50; F, 30.42; N, 7.73.

Alcoholysis of 12. A solution of 150 mg of **12** dissolved in 20 ml of absolute EtOH was added dropwise into a solution of 150 mg of Na dissolved in 20 ml of absolute EtOH, with stirring, and the mixture was refluxed for 5 hr. The cooled reaction mixture was poured into ice water and extracted with Et_2O, and the extract was dried over Na_2SO_4. The residue obtained by evaporation of Et_2O was purified by being passed through a silica gel column in CH_2Cl_2 solution. Recrystallization of the effluent from hexane gave crystals (**16**): mp 163°; yield 23.5 mg (11%); mass spectrum *m/e* 263 (M^+); high mass *m/e* 263.152 (calcd for $C_{15}H_{21}NO_3$, 263.152). **16** was partially hydrolyzed to **18** and was identified.

Alcoholysis of 13. The same treatment of 150 mg of **13** as in the case of **12** and recrystallization of the residue from the Et_2O extract from CCl_4 gave **19**, mp 124–126°, yield 81.2 mg (53%). It was identified with the authentic sample.[11]

Reaction of 12 with $LiAlH_4$. A solution of 200 mg of **12** dissolved in 20 ml of absolute Et_2O was added dropwise, with stirring, into 110 mg of $LiAlH_4$ suspended in 20 ml of absolute Et_2O, and the mixture was refluxed for 10 hr with stirring. Stirring was continued at room temperature for 2 days, but some **12** was still detected by tlc. Et_2O saturated with H_2O was added dropwise to decompose excess $LiAlH_4$ and the precipitate was filtered off. After being dried over Na_2SO_4, the filtrate was concentrated and the residue was purified through silica gel in hexane solution. The effluent was recrystallized from hexane to give 2-methylindole (**17**), mp 58.5°, yield 45.2 g (30%). It was identified with the authentic sample by comparison of their ir spectra.

Reaction of 13 with $LiAlH_4$. Treatment of 200 mg of **13** in the same way as **12**, except that refluxing was stopped as soon as **13** was no longer detected by tlc, and recrystallization of the residue obtained by evaporation of Et_2O from hexane gave skatole (**20**), mp 90–92°, yield 59.5 mg (42%).

Reaction of 12 with $NaBH_4$. A solution of 150 mg of **12** dissolved in 20 ml of EtOH was added dropwise with stirring into a solution of 200 mg of $NaBH_4$ dissolved in 20 ml of EtOH, and the mixture was refluxed for 30 hr. The cooled reaction mixture was poured into ice water and extracted with Et_2O, and the extract, after being dried over Na_2SO_4, was evaporated. The residue was chromatographed over silica gel.

From the first effluent with hexane 69 mg (46%) of the starting material (**12**) was recovered. The second effluent was recrystallized to give **18**, mp 123–125° (hexane), yield 33.7 mg (22%). **18** was identified with the authentic sample[12] by comparison of ir spectra and by a mixture melting point determination.

Reaction of 13 with $NaBH_4$. **13** (150 mg) was treated as in the case of **12**, but refluxing was continued for only 5 hr. The residue obtained by the evaporation of Et_2O was purified by silica gel chromatography in CH_2Cl_2 solution. The effluent was recrystallized from hexane to give **20**, mp 91–93°, yield 48.9 mg (46%). It was identified with the authentic skatole.

Reaction with Sodium Amide. Into about 30 ml of liquid NH_3, 0.1 g of $Fe(NO_3)_3$ crystals was added, and then 1.2 g of Na. When Na dissolved completely, 500 mg of **13** dissolved in 10 ml of absolute Et_2O was added dropwise with stirring. After 3 hr of stirring, NH_3 was evaporated and $NaNH_2$ was decomposed by a slow addition of hydrated Et_2O. The precipitate was collected by filtration and washed with Et_2O. The Et_2O layer was washed with H_2O and dried over Na_2SO_4. The residue obtained by evaporation of Et_2O was purified through a silica gel column in CH_2Cl_2 solution. The effluent was recrystallized from benzene to give 3-cyanoindole (**22**), mp 182–183°, yield 57.6 mg (15%). It was identified with the authentic sample.[13]

12 was recovered (75%) in this reaction and no product was isolated.

Registry No.—**8**, 35666-36-5; **9**, 35666-38-7; **10**, 51310-52-2; **11**, 51310-53-3; **12**, 51310-54-4; **13**, 51310-55-5; **14**, 51310-56-6; **15**, 51310-57-7; **16**, 51310-58-8; **17**, 95-20-5; **18**, 3770-50-1; **19**, 776-41-0; **20**, 83-34-1; **22**, 5457-28-3.

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Synthesis of Ortho-Substituted Benzonitriles by Nitro Displacement

James R. Beck,* Ronald L. Sobczak, Robert G. Suhr, and Joseph A. Yahner

Lilly Research Laboratories, Greenfield, Indiana 46140

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Novel ortho-substituted benzonitriles are synthesized by nitro displacement from o-nitrobenzonitriles and 2,6-dinitrobenzonitriles. The displacing nucleophiles include alkoxides, thiol anions, amines, and azide, chloride, and hydroxide ions.

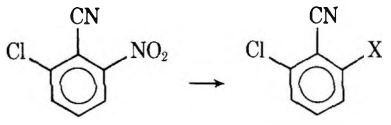
In a recent paper[1] we reported a facile synthesis of 3-aminobenzo[*b*]thiophene-2-carboxylate esters from *o*-nitrobenzonitriles. We now wish to describe the preparation of ortho-substituted benzonitriles, again by a process involving nucleophilic displacement of nitro groups activated by adjacent cyano functions. The nucleophilic lability of activated nitro groups has been well established by Bunnett and coworkers[2] and also by Bolto and Miller.[3] These authors studied the nucleophilic displacement of various functions activated by ortho and para nitro groups. The relative rate of nitro displacement by piperidine was reported to be more than 200 times that of chlorine and nearly equal to that of fluorine.

Numerous examples of activated nitro displacements in substituted benzenes are found in the chemical literature, although most cases involve intramolecular displacement.[4] The synthetic utility of intermolecular displacements of nitro functions, which are activated by ortho or para cyano groups, has received little attention. Ringer[5,6] reported the synthesis of *o*-anisonitrile and *p*-anisonitrile from *o*-nitrobenzonitrile and *p*-nitrobenzonitrile, respectively, by treatment with methoxide ion. Holmes and Loudon[7] reported examples of similar displacements using piperidine and benzyl mercaptan anion as nucleophiles. Another example is found in the synthesis of 2,6-dimethoxybenzonitrile (**2**)[8] from *m*-dinitrobenzene, but the overall yield was reported to be only 17%. We have obtained the same product (Table I) in 81% yield by the reaction of 2,6-dinitrobenzonitrile (**1**)[1] with 2 mol of sodium methoxide in refluxing methanol. Similarly, 6-nitro-o-anisonitrile (**3**) was prepared from **1** (80% yield) utilizing 1 mol of methoxide in DMF–methanol (room temperature). When **3** was allowed to react with excess methanethiol anion in aqueous DMF (0°), 6-(methylthio)-o-anisonitrile (**4**) was formed in 85% yield. Finally, the reaction of **1** with excess methanethiol anion under similar conditions gave 2,6-bis(methylthio)benzonitrile (**5**) in 75% yield. The nucleophilic lability of a nitro function *vs.* a

1

2, X = Y = OCH_3
3, X = NO_2; Y = OCH_3
4, X = OCH_3; Y = SCH_3
5, X = Y = SCH_3

chlorine atom is illustrated by the synthesis of compounds **7–9** from 2-chloro-6-nitrobenzonitrile (**6**). In each instance

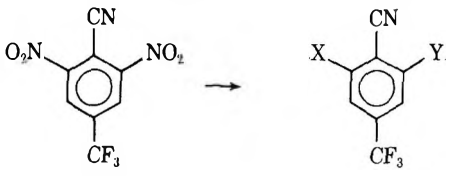


6

7, X = OCH_3
8, X = SCH_3
9, X = N_3

the nitro group is displaced preferentially and the yields are high.

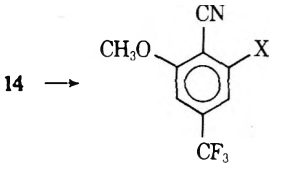
The versatility of the reaction is demonstrated by the synthesis of ortho-substituted benzonitriles obtained from α,α,α-trifluoro-2,6-dinitro-*p*-tolunitrile (**10**).[1] Both nitro groups can be displaced by the same nucleophile, and examples of this are compounds **11–13.** The conditions are



10

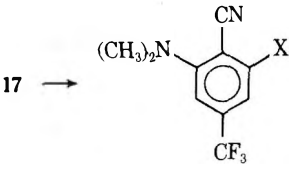
11, X = Y = OCH_3
12, X = Y = SCH_3
13, X = Y = N_3
14, X = OCH_3; Y = NO_2
15, X = N_3; Y = NO_2
16, X = $NHCH_3$; Y = NO_2
17, X = $N(CH_3)_2$; Y = NO_2
26, X = Cl; Y = NO_2
27, X = OH; Y = NO_2

quite mild and the yields are again high. The bisazide **13** was extremely light sensitive, and this might explain its lower yield. Compounds **14–17** illustrate the control of the reaction in displacing only one of the nitro functions present. Compounds **18–21** demonstrate the utility of the reac-



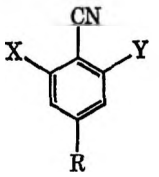
18, X = SCH_3
19, X = OCH_2CH_3
20, X = N_3
21, X = $NHCH_3$

tion in, first, displacement of one nitro group by a nucleophile, namely methoxide ion, and, second, displacement of the remaining nitro group by a different nucleophile. It is thus possible to synthesize mixed ethers, as in the case of **19**, which would be difficult to prepare by other routes. The same principle applies to the synthesis of compounds **22–25**, except that the initial displacement is by dimethylamine.



22, X = OCH_3
23, X = SCH_3
24, X = N_3
25, X = $N(CH_3)_2$

Table I
Synthesis of Ortho-Substituted Benzonitriles[a]



Compd	Reactant	Method of prepn	Mp, °C	Yield, %	Crystn solvent[b]	Reaction conditions
2	1	I	120–121[c]	81	B	65°, 43 hr
3	1		175–177[d]	80	B	
4	3	II	120–121	85	B	0°, 0.5 hr; 25°, 2 hr
5	1	II	167–169	75	B	0°, 0.5 hr; 25°, 2 hr
7	6		115–116[e]	67	B	
8	6	II	118–119	83	B	0°, 0.5 hr
9	6	III	101–102	74	B	25°, 22 hr
11	10	I	113–115	78	A	0°, 0.5 hr; 25°, 1.5 hr
12	10	II	133–134	85	B	0°, 5 min
13	10	III	94–95	58	B	0°, 1.5 hr
14	10	I	82–83.5	83	A	0°, 5 min
15	10	III	51–52	50	A	0°, 10 min
16	10	IV	164–165.5	63	B	0°, 2 hr
17	10		68–69	78	C	
18	14	II	113–114	77	B	0°, 0.5 hr; 25°, 2.5 hr
19	14		61.5–63	92	C	
20	14	III	84–85.5	73	B	25°, 3 hr
21	14	IV	143–145	72	B	100°, 1 hr
22	17	I	80–81	74	B	0°, 1.5 hr; 65°, 1 hr
23	17	II	74–74.5	76	B	0°, 0.5 hr; 25°, 2 hr
24	17	III	77–78	90	C	0°, 0.5 hr; 100°, 3 hr
25	17		111.5–113	66	B	
26	10		52–53	74	C	
27	10		194–196	65	D	

[a] Satisfactory analytical data (±0.3% for C, H, N) were reported for all new compounds listed in the table. [b] A = Methanol–water; B = alcohol; C = alcohol–water; D = water. [c] Lit.[8] mp 117–118°. [d] Lit.[9] mp 173°. [e] Lit.[10] mp 114.5°.

Related examples are the synthesis of the chloronitrile **26** and the salicylonitrile **27**. The reaction of hydrogen chloride with **10** in DMF yields **26**. Compound **27** is formed by the reaction of hydroxide ion with **10** in moist refluxing DMF. This reaction appears to be catalyzed by fluoride ion.

In conclusion, we have shown the synthetic utility of nucleophilic displacements of nitro groups activated by adjacent cyano functions. The procedure can be utilized for a variety of nucleophiles, including alkoxides, thiol anions, amines, and azide, chloride, and hydroxide ions. The procedure has failed with hindered alkoxides, hindered amines, thiocyanate ion, and ammonia. Electron-withdrawing groups in the 4 or 6 position of the starting *o*-nitrobenzonitrile appear to accelerate the displacement rates, as is evident from the reaction conditions in Table I. Readily available starting materials, coupled with the many known transformations of the nitrile function, make this method attractive for the synthesis of uniquely substituted benzene derivatives.

Experimental Section[11]

Materials. 2-Chloro-6-nitrobenzonitrile was obtained from the Aldrich Chemical Co. 2,6-Dinitrobenzonitrile[1] and α,α,α-trifluoro-2,6-dinitro-*p*-tolunitrile[1] were prepared by procedures described in the literature.

General Procedure I. To a cold solution (ice bath) containing 20 mmol of reactant (Table I) in 50 ml of methanol was added dropwise a solution containing a 20–50% molar excess (equimolar quantity in the preparation of 14) of sodium methoxide in 25 ml of methanol. The mixture was stirred at the temperature and for the time shown in Table I. It was then poured into ice water, and the product was collected and crystallized from the appropriate solvent (Table I).

General Procedure II. To a cold solution (ice bath) containing 20 mmol of reactant (Table I) and 5–10 ml of methanethiol (excess) in 50 ml of DMF was added dropwise a solution containing 2 g of potassium hydroxide in 10 ml of water. The mixture was stirred at the temperature and for the time shown in Table I. It was then poured into ice water and the product was isolated as in procedure I.

General Procedure III. To a cold solution (ice bath) containing 20 mmol of reactant (Table I) in 50 ml of DMF was slowly added portionwise a 20% molar excess of sodium azide. The mixture was stirred at the temperature and for the time shown in Table I. It was then poured into ice water and the product was isolated as in procedure I.

General Procedure IV. To a cold solution (ice bath) containing 20 mmol of reactant (Table I) in 50 ml of DMF was added dropwise 10 ml of 40% aqueous methylamine solution. The mixture was stirred at the temperature and for the time shown in Table I. It was then poured into ice water and the product was isolated as in procedure I.

6-Nitro-*o*-anisonitrile (3). To a cold solution (ice bath) containing 30 g (0.156 mol) of 2,6-dinitrobenzonitrile in 250 ml of DMF was added dropwise a solution containing 9 g (0.166 mol) of sodium methoxide in 75 ml of methanol. The mixture was stirred in the cold for 0.5 hr and then poured into ice water. The crude product was collected and crystallized from alcohol to yield 23.5 g of product, mp 175–177° (lit.[9] mp 173°).

6-Chloro-*o*-anisonitrile (7). Sodium methoxide (1.8 g, 33 mmol) was added portionwise to a cold solution (ice bath) con-

taining 5.5 g (30 mmol) of 2-chloro-6-nitrobenzonitrile in 60 ml of DMF. The mixture was stirred in the cold for 0.5 hr and then poured into ice water. The crude product was collected and crystallized from alcohol to yield 3.4 g of product, mp 115–116° (lit.[10] mp 114.5°).

2-Dimethylamino-α,α,α-trifluoro-6-nitro-p-tolunitrile (17). To a cold solution (ice bath) containing 10.4 g (40 mmol) of α,α,α-trifluoro-2,6-dinitro-*p*-tolunitrile and 5 g (62 mmol) of dimethylamine hydrochloride in 80 ml of DMF was added dropwise a solution containing 6 g of potassium hydroxide in 20 ml of water. The mixture was stirred in the cold for 1.5 hr and then poured into ice water. The solid was collected and crystallized from alcohol–water to yield 8.1 g of product, mp 67–69°. An analytical sample, mp 68–69°, was recrystallized from alcohol–water.

2-Ethoxy-α,α,α-trifluoro-6-methoxy-p-tolunitrile (19). To a cold solution (ice bath) containing 4.9 g (20 mmol) of 6-nitro-4-trifluoromethyl-o-anisonitrile (14) in 60 ml of absolute alcohol was added dropwise a solution containing 2 g of potassium hydroxide in 15 ml of water. The mixture was stirred in the cold for 0.5 hr and at room temperature for 2 hr and then poured into ice water. The solid was collected and crystallized from alcohol–water to yield 4.5 g of product, mp 61.5–63°.

2,6-Bis(dimethylamino)-α,α,α-trifluoro-p-tolunitrile (25). A solution containing 5.2 g (20 mmol) of 2-dimethylamino-α,α,α-trifluoro-6-nitro-*p*-tolunitrile (17), 4.5 g (55 mmol) of dimethylamine hydrochloride, and 7 g of anhydrous potassium carbonate in 50 ml of DMF was heated at steam-bath temperature for 68 hr and then poured into ice water. The crude product was collected and crystallized from alcohol to yield 3.4 g of product, mp 111.5–113°.

2-Chloro-α,α,α-trifluoro-6-nitro-p-tolunitrile (26). Hydrogen chloride gas was bubbled into a warm solution containing 15 g (58 mmol) of α,α,α-trifluoro-2,6-dinitro-*p*-tolunitrile in 60 ml of DMF. An exothermic reaction occurred at about 100°, and the solution was heated to reflux for 10 min and then poured into ice water. The solid was collected and crystallized from alcohol–water to yield 9.7 g of product, mp 52–53°.

6-Nitro-4-trifluoromethylsalicylonitrile (27). A solution containing 25 g (96 mmol) of α,α,α-trifluoro-2,6-dinitro-*p*-tolunitrile and 10 g of moist potassium fluoride in 100 ml of DMF was heated to reflux for 1 hr and then poured into ice water. The crude product was collected, but was not washed with water since it appeared to dissolve, and crystallized from water to yield 14.5 of product, mp 194–196°.

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Registry No.—**1**, 35213-00-4; **2**, 16932-49-3; **3**, 38469-85-1; **4**, 51271-32-0; **5**, 51271-33-1; **6**, 6575-07-1; **7**, 6575-10-6; **8**, 51271-34-2; **9**, 51271-35-3; **10**, 35213-02-6; **11**, 51271-36-4; **12**, 51271-37-5; **13**, 51364-43-3; **14**, 51271-38-6; **15**, 51271-39-7; **16**, 51271-40-0; **17**, 51271-41-1; **18**, 51271-42-2; **19**, 51271-43-3; **20**, 51271-44-4; **21**, 51271-45-5; **22**, 51271-46-6; **23**, 51271-47-7; **24**, 51271-48-8; **25**, 51271-49-9; **26**, 51271-50-2; **27**, 51271-51-3.

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Synthesis of Several Phenanthridines and a Quinazoline from Ortho-Substituted Arenediazonium Salts and Organic Nitriles[1]

R. C. Petterson,* J. T. Bennett, D. C. Lankin, G. W. Lin, J. P. Mykytka,[2] and T. G. Troendle[2]

Department of Chemistry, Loyola University (New Orleans), New Orleans, Louisiana 70118

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The thermal decomposition of 2-biphenyldiazonium tetrafluoroborates **3a** (R′ = H) and **3b** (R′ = NO_2) in the presence of representative aliphatic or aromatic nitriles is shown to afford the substituted phenanthridines **4a–g**. Little competition from the Baltz–Schiemann reaction was noted and in only one case was the competitive Meerwein quinazoline-forming reaction observed. The infrared spectrum of all phenanthridines studied exhibited two very strong absorption bands at 720–730 and 750–765 cm^{-1}, probably characteristic of this ring system.

The thermal decomposition of arenediazonium tetrafluoroborate salts (**1**) in the presence of organic nitriles results in the formation of *N*-arenenitrilium tetrafluoroborate salts (**2**). In several cases, it has been possible to isolate these salts and characterize them.[3,4] Infrared studies[5,6] on **2** have shown that *N*-alkyl- and *N*-arylnitrilium ion derivatives exhibit carbon–nitrogen triple bond stretching frequencies between 2300 and 2400 cm^{-1} while nmr investigations[6] of *N*-alkyl- and *N*-H nitrilium salts also indicate that only the linear nitrilium ions **2a** are present in detectable amounts. The imino carbocation form of the nitrilium ions **2b** can contribute very little to the reso-

$$\underset{\mathbf{1}}{ArN_2^+BF_4^-} \qquad \underset{\mathbf{2}}{\left[ArN\equiv CR \longleftrightarrow ArN{=}\overset{+}{C}R\right]BF_4^-}$$
$$\mathbf{2a} \qquad \mathbf{2b}$$

nance hybrid. However if the *N*-arylnitrilium ion could react with an adjacent substituent either as **2** or as a true carbocation, with which it might be in equilibrium (the angular form shown in **7**), then a new synthetic route to various N heterocycles would become available. We describe here the use of this approach as applied to the synthesis of phenanthridines.

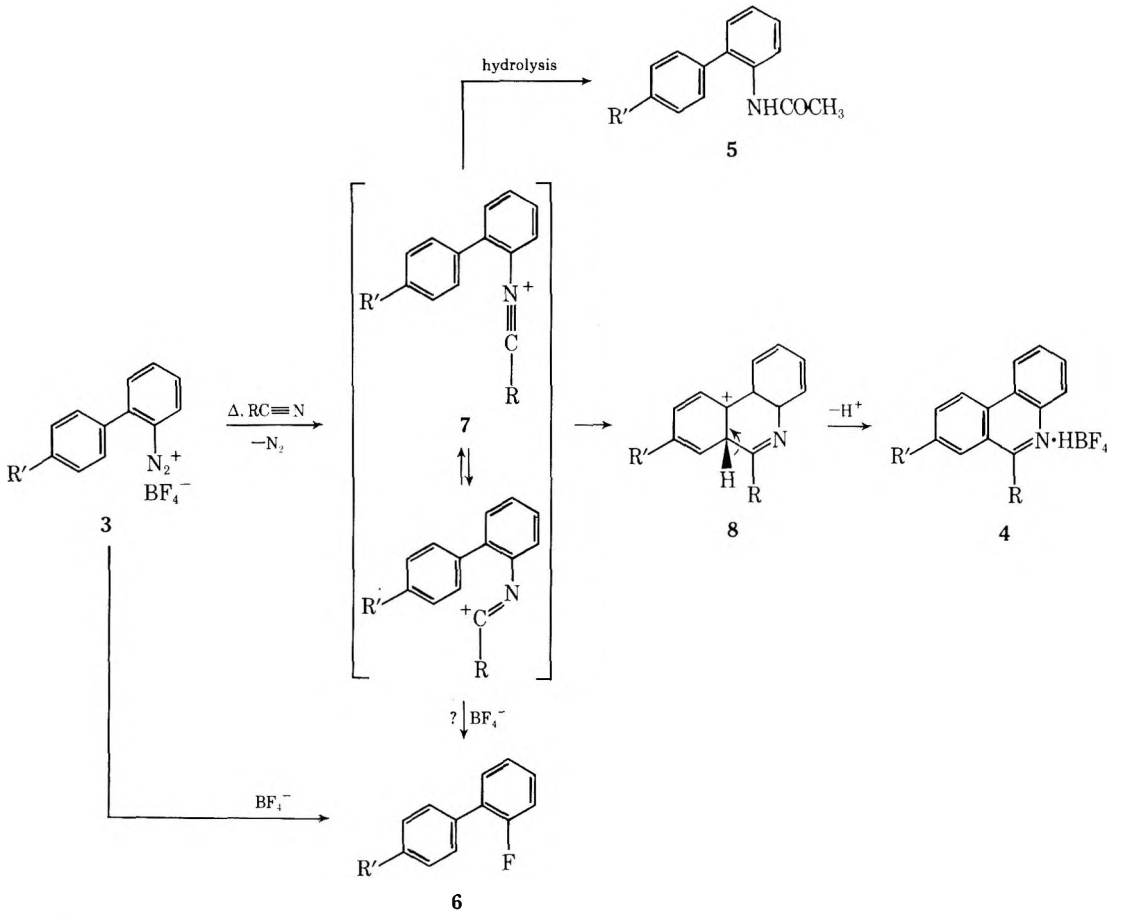
Phenanthridines. The thermal decomposition of the 2-biphenyldiazonium tetrafluoroborates **3a** (R′ = H) and **3b** (R′ = NO_2) in anhydrous aliphatic or aromatic nitriles leads to the formation of 6-substituted phenanthridines (**4a–g**). The yield of these phenanthridines was sensitive to both the time and temperature of the reaction. Thus, for example, the addition of **3a** to boiling acetonitrile over a 1-hr period, followed by hydrolysis, gave the 6-methyl derivative **4a** in 20% yield. The formation of **4a** was accompanied by a considerable amount of 2-acetamidobiphenyl (**5**) from hydrolysis of unreacted nitrilium ions. When the reaction time was increased to 12 hr, **4a** was obtained in 86% yield. In this case none of the amide **5** was

Table I
Synthesis of Phenanthridines

Registry no.	Phenanthridine obtained	R	R′	RC≡N/3, ml/g	Temp, °C	Time, hr	Work-up method	Yield, %[b] Picrate	Free base	2-Fluorobiphenyl
3955-65-5	**4a**	CH_3	H	23	82	12	A		86	4.5
13362-58-8	**4b**	C_2H_5	H	39	97	24	B	60[c]	43	
51381-75-0	**4c**	n-C_3H_7	H	26	117	96	B	71		
		n-C_3H_7	H	26	100	47	B	45		
2720-93-6	**4d**	C_6H_5	H	12	100	48	B	40[d]	36	7
		C_6H_5	H	12	100	24	B	32	22	
		C_6H_5	H	12	100	12	B	25	14	11[e]
46493-82-7	**4e**	CH_3S	H	25	100	48	B	53[f]	52	
		CH_3S	H	25	132	48	B	57	32	
51381-78-3	**4f**	CH_3	NO_2	25	82	96	B	35[g]	33	
51381-80-7	**4g**	C_2H_5	NO_2	25	97	72	A		9	

[a] Method of work-up: A, conventional acid extraction; B, picration. [b] Yields are based on the quantity of starting diazonium fluoroborate. [c] Registry no., 51381-74-9. [d] Registry no., 51381-76-1. [e] Registry no., 321-60-8. [f] Registry no., 51381-77-2. [g] Registry no., 51381-79-4.

Scheme I

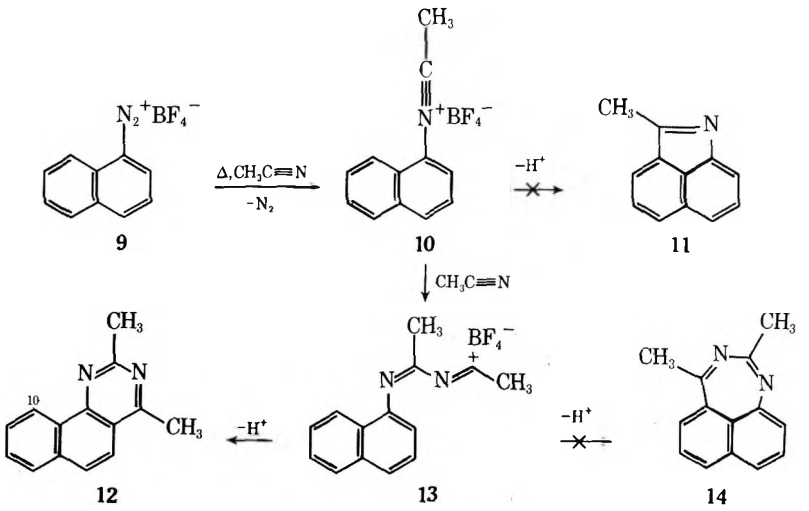


detected; a little (4.5%) 2-fluorobiphenyl (**6**) was the only low molecular weight by-product observed. The beneficial effect of increasing the reaction time is dramatically demonstrated in the synthesis of the 6-phenyl derivative **4d** from **3a** and benzonitrile. The effect of temperature is particularly notable in the synthesis of the methylthio derivative **4e**; an increase of 32° causes a decrease in yield of 20%. Table I summarizes the results which have been obtained for the decompositions of **3a** and **3b** while dissolved in various nitriles.

The isolation of the phenanthridines was accomplished using two isolation procedures: (A) acid extraction and (B) isolation *via* its picrate ("picration"). The latter method (B) proved to be the more useful one. Most of the phenanthridines described here are such weak bases that even several extractions with mineral acids does not assure complete removal of the heterocycle. However, all of the phenanthridines involved in this study formed picrates rapidly and quantitatively. The picrates were generally quite pure and the free bases could easily be recovered from them, usually in a high state of purity.

The formation of the phenanthridines, outlined in Scheme I, may be viewed as a two-step process. The first step is considered to involve replacement of the $-^+N{\equiv}N$ group of the diazonium salt **3** by RC≡N, which leads to the formation of the nitrilium salt **7**. This step is presumed to be fast, since evolution of the theoretical quantity of nitrogen is usually complete within a few minutes at the temperatures employed. The nitrilium salt **7** then cyclizes in a slower step to give the ion **8**, which after loss of a proton affords the phenanthridine **4** as an HBF_4 salt. That the cyclization reaction is the slow step in the for-

Scheme II



mation of the new ring is demonstrated by the fact that in two cases in which the effect of time was evaluated (**4a** and **4d**, Table I) the longer the reaction time, the better the yield of the phenanthridine. The isolation of amide **5**, which must result from hydrolysis of uncyclized nitrilium ion **7** (R = CH_3, R′ = H) in the decomposition of **3a** after 1 hr, provides additional support for this interpretation. Electronic stabilization of the nitrilium salt **7** and/or steric requirements imposed on the ring-closure reaction (**7** → **8**) may be factors retarding the rate of this second step. The formation of 2-fluorobiphenyl (**6**) is accounted for by competition of BF_4^- (Baltz-Schiemann reaction) with RC≡N for diazonium salt **3**, although the reaction of BF_4^- with nitrilium salt **7** has not been ruled out as a source of **6**.

Quinazolines. To further test the scope and limitations of this heterocyclization reaction, the thermal decomposition of 1-naphthalenediazonium tetrafluoroborate (**9**) in acetonitrile was investigated. A solution of **9** in refluxing acetonitrile gave as the major reaction product (56%) a new compound which was shown to be 2,4-dimethylbenzo[*h*]quinazoline (**12**). The structure assigned to **12** rests on its elemental analysis and an examination of its spectral properties. Its nmr spectrum showed a 1 H singlet at δ 9.30 and two 3 H singlets at δ 2.97 and 2.94, in addition to a 5 H multiplet centered at δ 7.80. The signal at δ 9.30 is assigned to the proton at C-10. This unusually low-field absorption must be caused by the anisotropic deshielding effect of the nitrogen at N-1. A very similar deshielding effect on the C-10 proton in the closely related compound benzo[*h*]quinoline by the spacially proximate nitrogen at N-1 has been noted.[7]

The formation of quinazoline **12** (Scheme II) is accounted for by reaction of the nitrilium salt **10** with a second molecule of acetonitrile to give the salt **13**, which then attacks the 2 position of the naphthalene ring to give the quinazoline **12**. It is interesting to note that compounds **11** and **14**, which might be formed by ring closure of **10** and **13**, respectively, at the 8 position (peri position), were not detected.

This synthesis of the dimethylquinazoline **12** has precedent in the literature.[4b] It is significant, however, that a reasonable yield of **12** is obtained. In the earlier studies[4b] of aryldiazonium tetrafluoroborate decompositions in acetonitrile solutions, only low and erratic yields of the desired 2,4-dimethylquinazolines were obtained. The apparent discrepancy between the earlier studies and the results described here is tentatively ascribed to the facts that in these previous studies only alkyl- and *p*-chlorobenzenediazonium salts were employed, and the decomposition of these salts in acetonitrile solution was further complicated by the fact that the methyl-substituted quinazolines formed underwent secondary condensation reactions at rates comparable with those of their formation. It appears that electron-donating groups on the aromatic ring tend to promote the reaction of *N*-arylnitrilium ions with a second molecule of nitrile. Electron-withdrawing substituents such as phenyl and *m*-nitrophenyl groups appear to slow the rate of attack of the nitrilium ion on another nitrile group to the point that the slow phenanthridine-forming reaction becomes dominant. Although considerable starting material is unaccounted for in some of our experiments, it is unlikely that more than minute amounts of it went to quinazolines; if so the phenanthridine picrates would have been contaminated with troublesome quantities of quinazoline picrates and this was not the case. The best single experimental fact[4b] supporting these speculations is the observation that benzenediazonium tetrafluoroborate in methyl thiocyanate was converted to 2,4-bis(methylthio)quinazoline (41%) in only 5 min at 110° but no quinazoline was formed in our synthesis of **4e** (48 hr, 100°).

The only other general method of phenanthridine synthesis is the classical Morgan–Walls reaction of *o*-amidobiphenyls with $POCl_3$;[8] a few modifications of it have been found useful.[9] It is perhaps surprising and certainly fortunate that, although both methods probably involve the same intermediate carbocation (as in **7**), the environment of the cation is so different that the yields of heterocycles do not change in a parallel manner as the R group of RCN is altered. Instead the methods tend to be complimentary. For example the original Morgan–Walls method[8] affords a much better yield (85%) of the 6-phenyl isomer than our procedure (36%). On the other hand, no more than a trace of the 6-methyl-8-nitro compound **4f** could be obtained by the standard Morgan–Walls method,[9] while our approach provides at least a 33% yield; the best yield reported in the literature[9] for **4f** is 25% and a special variation of the Morgan–Walls reaction had to be employed.

The synthetic method described here was discovered[1b] at almost the same time by Schmidt and his students,[10] who reported obtaining good yields of the HBF_4 salts of four 6-substituted phenanthridines by merely heating very concentrated solutions of diazonium salt **3a** in nitriles at 80° until all gas evolution ceased. We attempted to duplicate the synthesis of 6-phenylphenanthridine following their procedure as closely as possble but obtained the free

base **4d** only in low yield. It was accompanied by sizable amounts of 2-benzoylamidobiphenyl and 2-fluorobiphenyl.

The fact that we found reaction times much longer than those reported by Schmidt and his students to be necessary for good yields might be explained if considerable water were present in all our reaction mixtures, hydrolyzing nitrilium ions to amides. The amides might cyclize slowly in an HBF_4-catalyzed Morgan–Walls reaction. This possibility is excluded by the reproducibility of our yields as well as by the fact that no phenols could be found in the two cases where we sought them assiduously. It is probable that even a little water would compete with the nitriles for the diazonium ions and give detectable quantities of phenols. We are at a loss to explain the differences between our results and those of the German group. As noted previously in this work and in other related work,[11] it has been our experience that cyclization of nitrilium ions to phenanthridines is a slow process and that high concentrations of diazonium fluoroborates leads to significant competition from the Balz–Schiemann reaction.

Phenanthridine Ir Bands. It is noteworthy that without exception the ir spectrum of each of the seven substituted phenanthridines studied was dominated by two very strong absorption peaks, one at 720–730 and the other at 750–765 cm^{-1}, which may well be characteristic of this particular heterocyclic system.

Experimental Section[12]

Preparation of Phenanthridines (4a-g). 6-Methylphenanthridine (4a). Method A. A solution of 2-biphenyldiazonium tetrafluoroborate[13] (**3a** 1.07 g) in acetonitrile (25 ml) was heated to reflux for 12 hr. Care was taken to protect the refluxing solution from moisture. Nitrogen evolution was complete in a few minutes. After cooling, the unreacted acetonitrile was evaporated and the solid residue was treated with chloroform (15 ml) and 5% aqueous sodium hydroxide. The organic layer was extracted with 8% phosphoric acid (3 × 15 ml). The combined extracts were washed with chloroform, neutralized (NaOH solution), and then extracted with chloroform. Upon drying (anhydrous Na_2SO_4) and evaporation of the chloroform, there remained 0.66 g (86%) of **4a** (R = CH_3; R′ = H), mp 84° (lit.[14] mp 84°). Glpc analysis revealed that 2-fluorobiphenyl (**6**) was present in 4.5% yield.

6-Ethylphenanthridine (4b). Method B. A solution of **3a** (R′ = H, 0.649 g) in propionitrile (25 ml) was heated to reflux for 24 hr, cooled, and treated with saturated aqueous $NaHCO_3$. This mixture was then extracted with CH_2Cl_2 (6 × 35 ml) and the combined extracts were dried (anhydrous Na_2SO_4) and evaporated, which provided a brown oil. To an ethanol (5 ml) solution of the oil was added 15 ml of saturated alcoholic picric acid, which thus afforded 0.63 g (60%) of **4b** picrate, mp 211–212° (lit. mp 210–211°). A portion of the picrate (0.115 g) was decomposed by heating it for 5 min with 2 *N* NaOH (25 ml) on a steam bath. The aqueous solution was extracted with $CHCl_3$, washed with saturated aqueous Na_2SO_4, dried (anhydrous Na_2SO_4), and evaporated to give 87.7 mg (70%) of **4b** (R = C_2H_5; R′ = H) as an oil which crystallized when seeded, mp 51–53°. Recrystallization from ether gave pure **4b**, mp 53–54° (lit. mp 51–53°,[15] 54–55°[16]), ir (Nujol) 725 s, 750 cm^{-1} vs.

The following compounds were prepared according to methods A or B as indicated in Table I.

6-Propylphenanthridine (4c). From 1.0 g of diazonium salt **3a** was obtained 0.772 g of the picrate of **4c**, mp 194–201° dec (lit.[17] mp 196–197.5°). Decomposition of this picrate generated **4c** as an oil.

6-Phenylphenanthridine (4d). Method B was followed with the following modification. When 1.0 g of diazonium salt **3a** was decomposed in a benzonitrile (25 ml) solution, most of the unreacted benzonitrile was vacuum distilled prior to picration. The crude picrate, mp 246–251° dec (lit.[18] mp 251° dec), was decomposed to give the free base, mp 102–105°. Recrystallization from ligroin gave pure **4d**: mp 105–107° (lit.[18] mp 106°); ir (Nujol) 780 s, 765 vs, 755 vs, 695 cm^{-1} (C_6H_5 and phenanthridine ring bands). The by-product **6** in the mother liquor of the picrate was estimated by glpc.

6-(Methylthio)phenanthridine (4e). Decomposing 1.01 g of diazonium salt **3a** in a methyl thiocyanate solution gave, by method B, the picrate of **4e**, mp 190–192° dec, as analytically pure material.

Anal. Calcd for $C_{20}H_{14}N_4O_7S$: N, 12.33. Found: N, 12.36.

From the picrate, the free base **4e**, mp 58–62°, was obtained in 99% yield. Recrystallization from ethanol gave pale yellow needles of **4e**: mp 68–70° (lit.[19] mp 70–71°); ir (Nujol) 720 vs, 755 cm^{-1} vs; nmr ($CDCl_3$) δ 8.55–7.15 m (8 H, aromatic), 2.76 s (3 H, $-SCH_3$).

Preparation of 4′-Nitrobiphenyl-2-diazonium Tetrafluoroborate (3b). 4′-Nitro-2-biphenylamine (1.5 g), obtained from 2-biphenylamine by the method of Scarborough and Waters,[20] was dissolved in hot 48% HBF_4 and cooled to 20°, and to this stirred solution was added, dropwise, an aqueous solution of $NaNO_2$ (1.5 g) in 4 ml of water. Stirring was continued for 10 min. The colorless diazonium salt crystals were filtered, washed with cold 10% HBF_4 and then with 10 ml of ether, dried under vacuum, and recrystallized once from cold methanol–ether, affording 1.23 g (56%) of the diazonium salt **3b**, mp 89–91° dec.

Anal. Calcd for $C_{12}H_8BF_4N_3O_2$: C, 46.04; H, 2.58. Found: C, 46.23; H, 2.45.

6-Methyl-8-nitrophenanthridine (4f). Method B was followed with a 1.00-g sample of the diazonium salt **3b**. The crude product (0.87 g) was dissolved in boiling absolute ethanol (100 ml) and to this solution was added 50 ml of saturated alcoholic picric acid. Heating was continued for an additional 30 min. Cooling afforded 0.53 g (35%) of the picrate of **4f** as yellow needles, mp 220–226° dec. The pure picrate melted at 229–231° dec.

Anal. Calcd for $C_{16}H_{13}N_5O_9$: N, 12.15. Found: N,12.11.

The free base **4f** was isolated from the picrate in essentially quantitative yield (0.59 g): mp 243–246° (lit.[9] mp 242–243°); ir (Nujol) 730 vs, 765 vs, 785 m, 900, 1110 w, 1325 vs, 1590 cm^{-1} m; nmr ($CDCl_3$) δ 9.06 m (7 H, aromatic protons), 3.07 (3 H, CH_3).

6-Ethyl-8-nitrophenanthridine (4g). Method A was followed with the modification that extractions with both 10% HCl and 8% H_3PO_4 were used. From 1.0 g of the diazonium salt **3b** was obtained **4g**, mp 172°, in 9% yield: nmr ($CDCl_3$) δ 9.00–7.15 m (7 H, aromatic protons), 3.34 q (2 H, J = 7.5 Hz, $-CH_2-$), 1.54 t (3 H, J = 7.5 Hz, $-CH_3$).

Anal. Calcd for $C_{15}H_{12}N_2O_3$: C, 71.41; H, 4.79. Found: C, 71.24; H, 4.47.

The yellow picrate of **4g**, mp 214–217°, was prepared.

Anal. Calcd for $C_{21}H_{15}N_5O_9$: N, 14.54. Found: N, 14.28.

2,4-Dimethylbenzo[*h*]quinazoline (10). A solution of 1-naphthalenediazonium tetrafluoroborate (0.75 g) in acetonitrile (15 ml) was heated to reflux for 30 hr. After cooling, the mixture was neutralized with 20% aqueous NaOH and extracted with ether. The organic fraction was dried and evaporated, and the resulting solid was sublimed (120°, 0.1 Torr), affording 0.37 g (57%) of **10**, mp 110–114°. Recrystallization from ethanol gave colorless crystals of **10**: mp 119–121°; nmr ($CDCl_3$) δ 9.30 m (1 H), 7.80 m (3 H, aromatic protons), 2.97 s (3 H, $-CH_3$), 2.94 s (3 H, $-CH_3$).

Anal. Calcd for $C_{14}H_{12}N_2$: C, 80.74; H, 5.81; N, 13.45. Found: C, 81.03; H, 5.90; N, 13.33.

Synthesis of 6-Phenylphenanthridine (4d) under the Conditions of Schmidt and Coworkers.[10] A mixture of diazonium fluoroborate **3a** (4.44 g) and dry benzonitrile (12 ml) in a flask equipped with a tube leading to an oil-filled inverted cylinder to follow gas evolution was swirled for 5 min and then lowered into an 80° bath. Gas evolution ceased completely after 15 sec, after which the heating bath was removed and 30 ml of cyclohexane was added. No crystallization of the HBF_4 salt of phenanthridine **4d** being observed upon cooling, the mixture was perforce worked up by our method B. After removal of the CH_2Cl_2 and distillation of unreacted benzonitrile *in vacuo*, a subliminate of 2-fluorobiphenyl, mp 70–72° (0.114 g, 4%), was collected (the yield of this by-product was probably higher, since a 12% yield of the fluoro compound was obtained in a similar experiment). The picrate of 6-phenylphenanthridine, mp 249–251°, obtained weighed 1.34 g (16%, lit.[10] 56%, as HBF_4 salt). The picrate mother liquor afforded 1.86 g (41%) of 2-benzoylamidobiphenyl, mp 87–91° (lit.[21] 95°), ir (Nujol) 3415 vw and 3250 m (NH), 1640 s and 1575 m (amide I and II).

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Registry No.—**3a**, 51381-71-6; **3b**, 51381-73-8; **4g** picrate, 51381-81-8; **9**, 28912-93-8; **12**, 51464-55-2.

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(12) Melting points were taken on a Fisher-Johns block unless otherwise stated and are uncorrected. Ir spectra were taken on a Perkin-Elmer Model 337 spectrometer. Nmr spectra were run on a Varian A-60 nmr spectrometer and are reported in parts per million downfield from tetramethylsilane internal standard. Nitriles were normally dried by distillation from phosphorus pentoxide just prior to use. Apparatus used in cyclization experiments was dried at 120° or above before assembly.
(13) G. Schiemann and W. Roselius, *Chem. Ber.*, **62**, 1805 (1929). We often used a variation of their method in which the only acid present was HBF_4.
(14) M. M. Coombs, *J. Chem. Soc.*, 3454 (1958).
(15) C. L. Arcus and E. A. Lucken, *J. Chem. Soc.*, 1634 (1955).
(16) A. Pictet and A. Hubert, *Ber.*, **29**, 1182 (1896).
(17) H. Gilman and J. Eisch, *J. Amer. Chem. Soc.*, **79**, 4423 (1957).
(18) C. L. Arcus and M. M. Coombs, *J. Chem. Soc.*, 4319 (1954).
(19) D. A. Peak and F. Stansfield, *J. Chem. Soc.*, 4067 (1952).
(20) H. A. Scarborough and W. A. Waters, *J. Chem. Soc.*, 89 (1927).
(21) J. V. Braun, *Chem. Ber.*, **43**, 2880 (1910).

Mass Spectroscopy of Indolo[2,3-a]quinolizidines. I. Fragmentation Patterns of C-3, C-4, C-6, C-7, and C-12b Deuterated Derivatives

Gordon W. Gribble*[1] and Randall B. Nelson[2]

Department of Chemistry, Dartmouth College, Hanover, New Hampshire 03755

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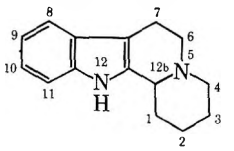
The mass spectra of the C-3, C-4, C-6, C-7, and C-12b deuterated derivatives of the indole alkaloid 1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine (**1**). (*Dracontomelum mangiferum*) show that the P − 1 (base) peak at 70 eV is a mixture of four discrete ions, resulting from loss of C-4 H, C-6 H, C-7 H, and C-12b H. The labeling results show that the previously proposed structure for *m/e* 197 arising from a retro Diels–Alder reaction of *m/e* 225 only accounts for about 20% of *m/e* 197. The revised structure accounting for most of *m/e* 197 arises from a stepwise fragmentation from the parent ion (*m/e* 226). New fragmentation pathways and ion structures are also proposed and supported for the peaks at *m/e* 184, 156, 144, 97, 83, and 69.

Since its first application to indole alkaloids,[3] mass spectrometry has become a very important technique for the elucidation of the structure of alkaloids and other natural products.[4,5]

Although mass spectrometry has been applied to several members of the *Corynanthe-Yohimbe* family,[4-6] there is no consensus and little direct support for the various proposed fragmentation pathways for this class of indole alkaloids.[7] The indole alkaloid 1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine (**1**)[8] is the simplest structure for



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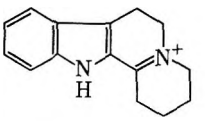
which a mass spectral fragmentation pattern representative of the *Corynanthe-Yohimbe* class of indole alkaloids may be expected.[6] The mass spectrum of **1** has been previously published,[6] but without direct support for the proposed fragments. We now report a mass spectral study of selected deuterated derivatives of **1**.

Results and Discussion

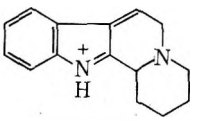
The 70-eV mass spectra of **1** is reproduced in Figure 1 and each of the main fragment clusters will be discussed in turn.

Parent Ion Cluster. It has been widely assumed[6,9-11] that the P − 1 (base) peak (*m/e* 225 for **1**) observed in the mass spectra of *Corynanthe-Yohimbe* indole alkaloids and other tetrahydro-β-carboline alkaloids is due to the loss of C-12b H leading to **2**. Only in systems where for steric reasons a C-12b iminium ion cannot form have alternate P − 1 ions been suggested.[12]

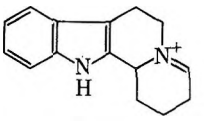
Our results (Table I) show that the P − 1 ion is a *mixture* of ions **2**–**5**, arising by hydrogen loss from C-12b, C-7,



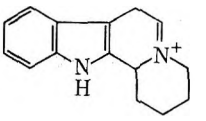
2 (*m/e* 225)



3 (*m/e* 225)



4 (*m/e* 225)



5 (*m/e* 225)

C-4, and C-6, respectively. For example, P − 2 (*m/e* 225, loss of D) is intense in the spectrum of 1-*7*-d_2 and P − 1 (*m/e* 226, loss of H) is intense in the spectrum of **1**-*12b*-d_1, both indicating the importance of other ions tc P − 1. In contrast, 1-*3*-d_2 (statistically adjusted for isotopic inhomogeneity) shows complete retention of deuterium in the

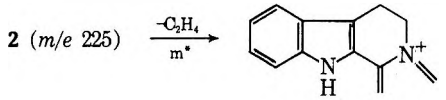
P − 1 ion. A quantitative analysis of the data, assuming 100% specific deuterium incorporation, gives the result that most of the P − 1 peak is comprised of **2** (37%) and **3** (32%), and the rest is due to **4** (13%) and **5** (19%) (see Sample Calculation).

Loss of C-7 H to give **3** has analogy in the mass spectrum of 3-methylindole,[13] where P − 1 is the base peak, arising from loss of a methyl hydrogen. Such ions have also been implicated in the solution chemistry of indoles.[14]

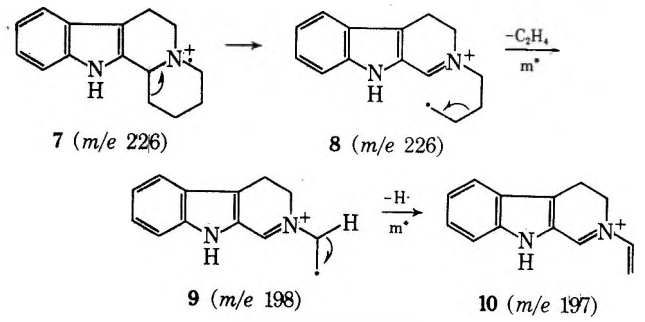
Loss of deuterium from C-4 in **1**-*4*-d_1 and **1**-*4*-d_2 is about the same (17% *vs.* 13%). We ascribe this to the trans-axial orientation of the deuterium and the nitrogen lone pair in **1**-*4*-d_1; this geometry is the much preferred one for loss of hydrogen (deuterium) (*i.e.*, in **1**-*4*-d_1 there is little preference for loss of hydrogen from C-4, even with an isotope effect working against deuterium loss). The axial deuterium in **1**-*4*-d_1 is so assigned because the 2040-cm^{-1} C-D stretch in the infrared spectrum[15] is a C-D "Bohlmann band."[16] By comparison, the infrared spectrum of **1**-*4*-d_2 with an axial and equatorial deuterium shows 2050 and 2190 cm^{-1} for the two C-D stretches, respectively.

We conclude that the facile loss of one hydrogen from **1** is much less specific than previously believed, loss of hydrogen from C-12b, C-7, and C-4-C-6 each representing about one-third of the P − 1 peak.

m/e **197 Cluster.** The peak at *m/e* 197 (28%) in the mass spectrum of **1** and many other indole alkaloids has been assigned to **6** and is proposed to arise by a retro Diels–Alder loss of ethylene from **2**.[6] This pathway is also implicated in quinolizidine itself.[11] A high-resolution measurement shows *m/e* 197 to have a molecular formula due entirely to $C_{13}H_{13}N_2$.



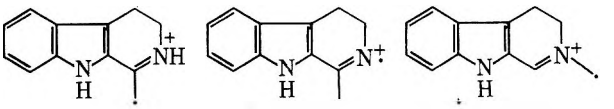
Our results (Table II) require that an additional structure be written for *m/e* 197. This new species must retain hydrogen on C-12b and C-3, and one-half of the hydrogen on C-4. The precursor to this ion, at *m/e* 198 (8%) and previously unexplained, must retain *all* of the hydrogen on C-3, C-4, and C-12b. We propose **9** as the *m/e* 198 ion and **10** as the other *m/e* 197 ion, with the following sequence accounting for their formation.



Metastables are found for both routes to *m/e* 197. In the deuterated derivatives the metastables corresponding to the stepwise process **7** → **10** are usually more pronounced than those for the retro Diels–Alder route.

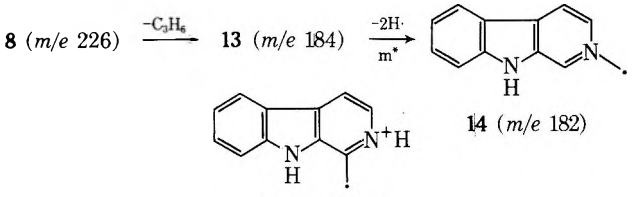
The clusters observed for **1**-*3*-d_2 and **1**-*12b*-d_1 at *m/e* 197, 198, 199, and 200 were used to calculate the contributions of the pathways leading to *m/e* 197. In the **1**-*3*-d_2 spectrum the *m/e* 199 peak will uniquely reflect the contribution of **10** and *m/e* 197 will be the contribution from **6**. After correction for isotopic distribution the intensity of these two peaks relative to the total *m/e* (197 + 199) intensity is 20% for **6** and 80% for **10**. A similar analysis for **1**-*12b*-d_1 gives 16% for **6** and 84% for **10**.

m/e **184 Cluster.** The cluster of three peaks at *m/e* 184 (7%), 183 (7%), and 182 (7%) has been ascribed[6,17,18] to two sets of ions, **11**–**12** or **13**, with the latter generally favored[17,18] and being supported by deuterium labelling (ajmalicine).[18] A high-resolution measurement shows *m/e* 184 to have a molecular formula due entirely to $C_{12}H_{12}N_2$.

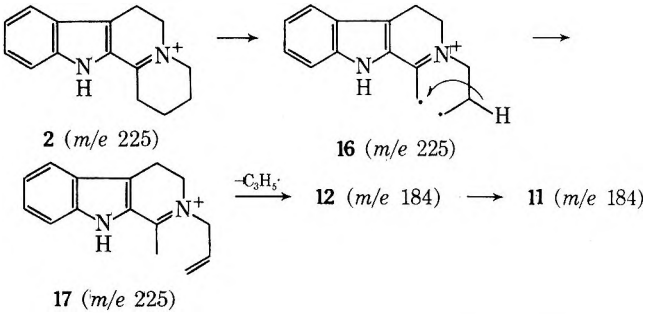


Our results (Table III) indicate that *both* sets of ions are contributors to the *m/e* 184 cluster. For **1**-*4*-d_2, the *m/e* 186 peak will be due primarily to fission of the C-12b–C-1 bond and subsequent loss of the carbon fragment (**13**). The *m/e* 184 peak will consist of ions from aromatization of *m/e* 186 (*i.e.*, loss of 2 H to give **14**) and **11**–**12**. Knowing the relative frequency of aromatization of both **11**–**12** and **13** in forming **15** and **14**, respectively, one can, by adjusting *m/e* 184 by the ratio *m/e* 184/182, determine the percentages to be 76% for **13** and 24% for **11**–**12**.

The formation of **13** and its cluster partners at *m/e* 183 and 182 can be viewed as arising from **8** with loss of cyclopropane or propene. Loss of C_3H_6 from the ion corresponding to **8** from quinolizidine itself is supported by a metastable peak.[11] We see a metastable for *m/e* 226 → 182 at 147.0 (calcd 146.6).



The formation of **11**–**12** might be visualized as involving C-1–C-2 cleavage followed by H migration and loss of allyl radical. The H migration from C-3 in **16** is supported by the increased peak at *m/e* 185 in **1**-*3*-d_2.



Such rearrangements are proposed to occur in the mass spectra of simple cyclic amines.[19,20]

At 20 eV *m/e* 183 and 182 are much less intense than at 70 eV (Table III), indicating that these fragments are formed from *m/e* 184 by successive hydrogen loss. At low ionization energy *m/e* 184 does not have enough residual energy to lose one or two hydrogens and it tends to accumulate.

m/e **170 Cluster.** The cluster of two peaks at *m/e* 170 (24%) and 169 (33%) has been previously assigned[17,18] to **18** and **19**, respectively, and these fragments are supported by a deuterium label at C-12b in ajmalicine, each being shifted to one higher mass unit.[18] The lesser peaks

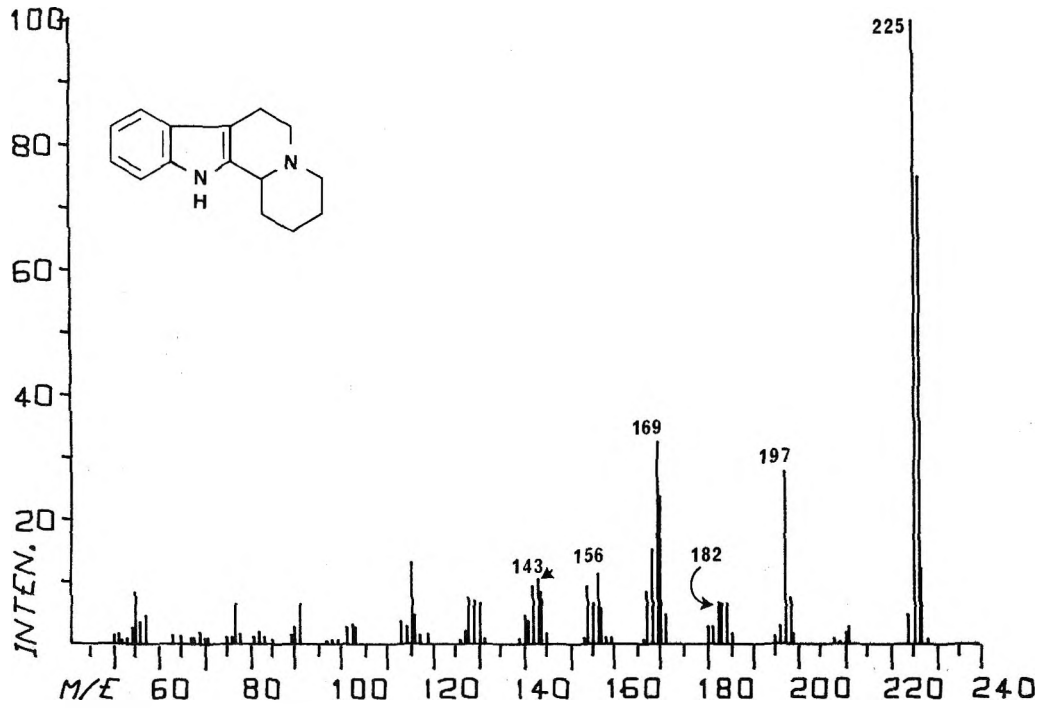
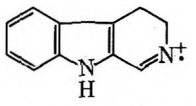
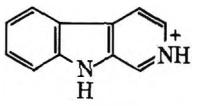


Figure 1. Mass spectrum (70 eV) of **1**.

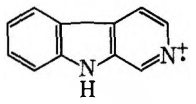
at *m/e* 168 (15%) and 171 (15%) are assigned to **20** and **21**, respectively. A high-resolution measurement shows *m/e* 170 to have a molecular formula due entirely to $C_{11}H_{10}N_2$.



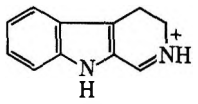
18 (*m/e* 170)



19 (*m/e* 169)



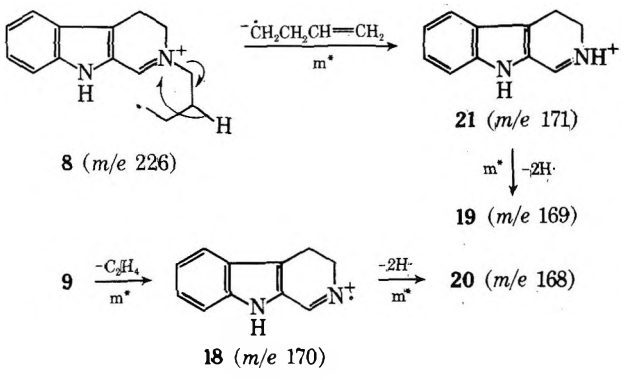
20 (*m/e* 168)



21 (*m/e* 171)

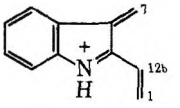
Our results (Table IV) support these assignments. As expected, the mass spectrum of 1-*3*-d_2 shows complete deuterium loss from this cluster. The increase by 20% in the *m/e* 170 peak in 1-*4*-d_2 may indicate that the origin of the hydrogen on N-5 in **19** and **21** is at least partly C-4. The spectrum of 1-*12b*-d_1 shows retention of deuterium in all four fragments (**18**–**21**). 1-*7*-d_2 shows a surprisingly large *m/e* 171 that may be due to **19** containing deuterium at both C-7 and N-5.

The formation of these fragments may proceed as shown below. Quinolizidine shows a similar loss of ethylene to

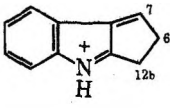


give a fragment corresponding to *m/e* 170 (**18**), and is supported by a metastable.[11]

m/e **156 Cluster.** The peak at *m/e* 156 (12%) has been previously assigned both to **22** and **23**. A high-resolution measurement shows *m/e* 156 to have a molecular formula due entirely to $C_{11}H_{10}N$.



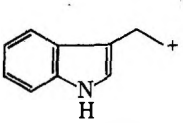
22 (*m/e* 156)



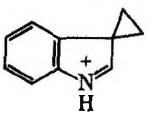
23 (*m/e* 156)

Our results (Table V) show that *both* **22** and **23** are present. The data for 1-*3*-d_2, 1-*4*-d_1, and 1-*4*-d_2 indicate clearly that C-3 and C-4 are not retained in the *m/e* 156 fragment. C-6 is retained but to a lesser extent than C-7 and C-12b, indicating a mixture of fragments **22** and **23**. An analysis of the data gives the relative contributions of each: **22**, 48%; **23**, 52%.

m/e **144 Cluster.** The cluster at *m/e* 144 (9%), 143 (11%), and 142 (10%) has previously been represented as **24** (or **25**) but this was in a study of oxindole alkaloids[18] and may not be the structure of the *m/e* 144 fragment from **1**. A high-resolution measurement shows *m/e* 144 to have a molecular formula due entirely to $C_{10}H_{10}N$.



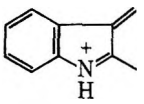
24 (*m/e* 144)



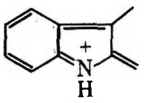
25 (*m/e* 144)

Our data (Table VI) indicate that the *m/e* 144 cluster cannot only be due to **24**. Carbons C-3 and C-4 are clearly not present in the *m/e* 144–142 fragments, nor is hydrogen transferred from these carbons to the fragments. The data for 1-*3*-d_2, 1-*4*-d_1, and 1-*4*-d_2 are self-consistent, but the small increase in *m/e* 145 in these three spectra compared to that for **1** is difficult to rationalize. It is clear from the data that both hydrogens on C-7 are retained but that only one from C-6 is retained in the fragments. The hydrogen on C-12b is retained to the extent of about 75%.

This suggests that the m/e 144 peak is due both to **24–25** (55%) and **26–27** (45%).



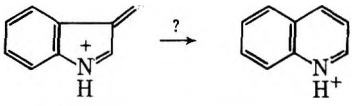
26 (m/e 144)



27 (m/e 144)

These ions have been proposed to occur in the fragmentation of quebrachamine.[21]

m/e 130 Cluster. The cluster of four peaks at m/e 130 (7%), 129 (7%), 128 (8%), and 127 (2%) has previously been ascribed[18] to **28** and subsequent ions. A high-resolution measurement shows m/e 130 to have a molecular formula due entirely to C_9H_8N.

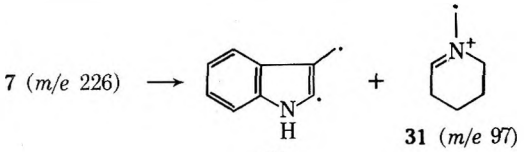


28 (m/e 130) **29** (m/e 130)

Fragment **28** is invariably found in the mass spectra of simple indoles,[13,18,22] but it is still not clear whether it has indole structure **28** or quinoline structure **29**,[23-25] even though ring expansion has been proposed to be significant in the fragmentation of 2-methylindole.[23,25]

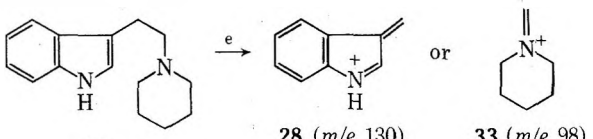
Our results (Table VII) show that C-3, C-4, and C-6 are not present in the m/e 130 fragment, as expected. Furthermore, it is clear that hydrogens from C-7 and C-12b are present in the fragment, supporting **28** (or **29**) as the m/e 130 structure. The m/e 129 and 128 fragments both appear to retain at least some hydrogen from C-7 and C-12b, but it is difficult to postulate appropriate structures.

The other ion formed in the fragmentation leading to m/e 130 appears at m/e 97 (1%). Our data (not tabulated) show that C-3, C-4, C-6 and C-12b, but not C-7, are retained in the ion. This is consistent with **7** → **30** + **31**.



7 (m/e 226) **30** **31** (m/e 97)

The tricyclic amine **32** shows in its mass spectrum the fragments **28** (3%) and **33** (100%),[26] indicating the facile cleavage of the "tryptamine bond."[22]



32 **28** (m/e 130) **33** (m/e 98)

Quinolizidine shows a very intense m/e 97 peak which has been assigned to **31**.[11]

Summary. It is clear that the mass spectral fragmentation pattern of indole alkaloid **1**, and probably most of the *Corynanthe-Yohimbe* alkaloids, is more complex than previously believed. All of the important high molecular weight fragments are shown to be mixtures of different ions. The main points of this work are summarized as follows.

(1) The P − 1 peak (m/e 225) consists of a mixture of four ions, **2–5**, arising from loss of hydrogen at C-12b, C-7, C-4, and C-6, respectively. Three of these ions result when ionization occurs at N-5, while the fourth (**3**) occurs when an electron is lost from the aromatic ring, presumably from N-12.

(2) The large molecular weight fragments at m/e 197, 184, and 170 arise principally from parent ion **7** by cleavage of the C-12b–C-1 bond and subsequent loss of two, three, and four carbons, respectively.

(3) The m/e 197 fragment is a mixture of two ions, **6** and **10**. The previously proposed retro Diels–Alder reaction from **2** (m/e 225) accounts for at most 20% of m/e 197 (**6**).

(4) The fragments that appear at m/e 184, 156, and 144 are each due to a mixture of at least two discrete ions (**11–13**, **22–23**, and **24–27**, respectively) arising from different fragmentation pathways.

(5) When hydrogen loss within a cluster at high ionization energy (70 eV) is important, at low ionization energy (≤ 20 eV) it is greatly retarded. This results in the accumulation of certain ions (*e.g.*, m/e 198, 171, 158, and 145) that are not easily seen at high ionization energy.

(6) Hydrogen loss from a carbon α to a nitrogen (*i.e.*, C-4, C-6, and C-12b in **1**) is more favorable when the hydrogen is trans diaxial to the nitrogen lone pair. This interesting observation, seen in the present work (*cf.* **1**-*4*-d_1 and **1**-*4*-d_2) and in our earlier work[16a] with the *cis*- and *trans*-2-*tert*-butyl derivatives of **1**, should be generally applicable to the problem of determining stereochemistry and ring fusion in *Corynanthe-Yohimbe* and other quinolizidine alkaloids.

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Registry No.—**1**, 4802-79-3; **1**-*3*-d_2, 51263-49-1; **1**-*4*-d_2, 51263-50-4; **1**-*6*-d_2, 51263-51-5; **1**-*7*-d_2, 51263-52-6; **1**-*12b*-d_1, 34388-09-5.

Supplementary and Miniprint Material Available. The 70-eV mass spectra of the deuterated derivatives of **1** will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material and full-sized photocopies of the miniprinted material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the miniprinted and supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $4.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-1845.

JOC-13-1

Table I. Relative Intensities for the Parent Ion Cluster at 70 eV[a]

Compound	m/e 224	225	226	227	228	229
1	5	100	75	12		
1-3d_2		4	16	100	70	11
1-4d_1	7	21	100	94	16	2
1-4d_2		6	15	100	93	19
1-6d_2	3	8	23	100	81	13
1-7d_2	6	11	47	100	92	17
1-12bd_1		58	100	97	16	
1[b]	3	29	100	17		
1[c]			100	17.6	1.4	

[a] Uncorrected for isotopic composition at 20 eV. [b] Calculated isotopic abundance (^{13}C, ^{15}N).

JOC-13-2

Table II. Relative Intensities of the m/e 197 Cluster at 70 eV[a]

Compound	m/e 195	196	197	198	199	200
1	5	10	100	28	7	
1-3d_2	7	6	20	32	100	30
1-4d_1	8	13	58	100	32	5
1-4d_2	8	19	30	96	100	47
1-6d_2	8	12	39	37	100	23
1-7d_2	11	19	56	64	100	28
1-12bd_1	5	8	20	100	30	3
1[b]	13	10	100	56	7	
1[c]			100	15.3	1.1	

[a] Uncorrected for isotopic composition at 20 eV. [b] Calculated isotopic abundances (^{13}C, ^{15}N).

JOC-13-3

Table III. Relative Intensities of the m/e 184 Cluster at 70 eV[a]

Compound	m/e 180	181	182	183	184	185	186	187
1	42	42	100	99	97	28	3	
1-3d_2	15	29	46	71	100	43	30	5
1-4d_1	25	34	70	93	100	70	14	2
1-4d_2	17	31	49	44	100	48	59	13
1-6d_2	32	36	90	84	100	82	65	13
1-7d_2	28	52	80	80	80	80	100	35
1-12bd_1	18	35	55	95	100	85	17	3
1[b]			20	50	100	22		
1[c]					100	14.2	0.9	

[a] Uncorrected for isotopic composition at 20 eV. [b] Calculated isotopic abundance (^{13}C, ^{15}N).

JOC-13-4

Table IV. Relative Intensities for the m/e 170 Cluster at 70 eV[a]

Compound	167	168	169	m/e 170	171	172	173
1	26	47	100	74	15	2	
1-3d$_2$	21	39	100	85	22	9	2
1-4d$_1$	24	48	100	78	17	3	1
1-4d$_2$	17	41	100	93	18	8	2
1-6d$_2$	27	42	54	100	43	81	16
1-7d$_2$	18	29	47	70	100	76	18
1-12bd$_1$	12	24	46	100	72	12	2
1[b]	5	11	14	100	20	7	
1[c]				100	13.1	0.8	

[a] Uncorrected for isotopic composition. [b] At 20 eV. [c] Calculated isotopic abundance (^{13}C, ^{15}N).

JOC-13-5

Table VI. Relative Intensities for the m/e 144 Cluster at 70 eV[a]

Compound	141	142	143	m/e 144	145	146	147
1	36	90	100	81	18	2	
1-3d$_2$	28	78	100	86	41	16	8
1-4d$_1$	30	75	100	95	30	10	5
1-4d$_2$	29	73	100	82	39	15	11
1-6d$_2$	49	82	100	82	88	70	20
1-7d$_1$	55	82	73	100	100	91	37
1-12bd$_1$	26	27	86	100	50	14	5
1[b]		100	100	75	33		
1[c]				100	11.6	0.6	

[a] Uncorrected for isotopic composition. [b] At 20 eV. [c] Calculated isotopic abundance (^{13}C, ^{15}N).

JOC-13-6

Table VIII. Calculation of Ion Distribution in the Parent Cluster for 1-12bd$_1$

m/e	observed relative intensities	expected P+1 contribution	corrected intensities
225	58	0	58
226	100	10	90
227	97	17	80
228	16	17	0

The percent total intensities for the uncorrected and corrected intensities are then calculated using the relationship: %X = X/(X+Y+Z) where X, Y, and Z represent the intensities of different peaks in a cluster. For example, the m/e 225 calculations for 1-12bd$_1$ using uncorrected and corrected values give 37% and 39%, respectively, for the percent of m/e 225 in the parent cluster. This difference of 2% is less than the 5% precision assumed to obtain in the mass spectral measurements.

Table V. Relative Intensities for m/e 156 Cluster at 70 eV[a]

Compound	154	155	156	m/e 157	158	159	160
1	83	58	100	50	10	10	
1-3d$_2$	62	46	100	60	19	8	
1-4d$_1$	60	48	100	62	22	8	
1-4d$_2$	51	44	100	58	28	12	
1-6d$_2$	61	60	100	53	60	39	10
1-7d$_2$	43	57	86	71	100	57	24
1-12bd$_1$	33	60	53	100	40	13	
1[b]		14	51	100	43		
1[c]			100	12.7	0.7		

[a] Uncorrected for isotopic composition. [b] At 20 eV. [c] Calculated isotopic abundance (^{13}C, ^{15}N).

Table VII. Relative Intensities for the m/e 130 Cluster at 70 eV[a]

Compound	127	128	129	m/e 130	131	132	133
1	30	100	94	88	13	6	4
1-3d$_2$	52	100	95	77	38	17	10
1-4d$_1$	57	100	87	57	39	14	7
1-4d$_2$	56	100	78	86	39	22	6
1-6d$_2$	50	92	100	75	42	22	20
1-7d$_2$	36	60	96	100	90	60	38
1-12bd$_1$	77	78	89	100	56	13	6
1[b]				100	10.4	0.5	

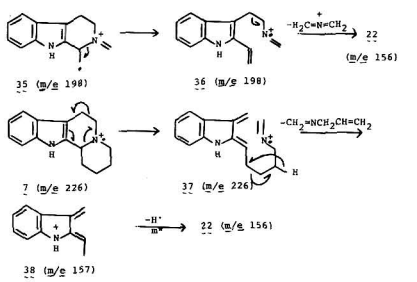
[a] Uncorrected for isotopic composition. [b] Calculated isotopic abundance (^{13}C, ^{15}N).

JOC-13-7

tion of m/e 198 relative to m/e 197 at low eV since less residual energy is available to be dissipated. It is not reasonable to suppose that the 4→10 pathway would be important when our results do show that the 2→6 pathway accounts for only 20% of m/e 197.

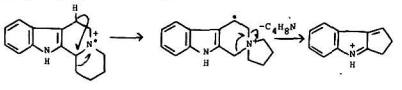
The much less intense peak at m/e 197 in the mass spectra of yohimbine and ajmalicine[6] compared to that in the mass spectrum of 1 supports the stepwise mechanism rather than the retro-Diels-Alder reaction as the main pathway for the formation of 6 (m/e 197).

A possible scheme for the formation of the m/e 156 fragment (22) is depicted below.



35 (m/e 198) 36 (m/e 198) 22 (m/e 156)
7 (m/e 226) 37 (m/e 226)
38 (m/e 157) 22 (m/e 156)

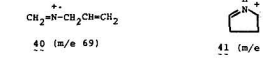
The fragmentation leading to retention of C6 as in 23 is shown below and resembles the mechanism proposed by Coutts[7] for tetrahydro-β-carbolines. This pathway is consistent with the fact that both C7 hydrogens are retained in m/e 156.



7 (m/e 226) 39 (m/e 226) 23 (m/e 156)

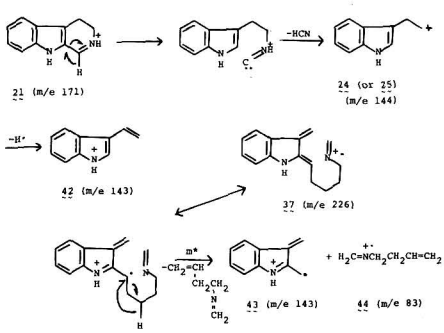
JOC-13-8

The other ion formed in m/e 226→157 (37→38) appears in a cluster of peaks at m/e 68, 69, and 70 (all <1%). A high resolution measurement shows m/e 69 to have a molecular formula due entirely to C_4H_7N. Our data (not tabulated) show that both 37→38 + 40 and 39→23 + 41 are operating since some loss of hydrogen from C6 is seen.



40 (m/e 69) 41 (m/e 70)

A possible scheme for the formation of the m/e 143 fragments is shown below.

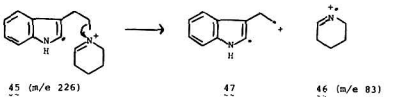


21 (m/e 171) 24 (or 25) (m/e 144)
42 (m/e 143) 37 (m/e 226)
43 (m/e 143) 44 (m/e 83)

JOC-13-9

Loss of HCN from 21 (m/e 171) has been proposed to occur in the fragmentation of tetrahydro-β-carbolines.[7]

The other ion formed in m/e 226→143 (37→43) appears in a cluster of peaks at m/e 82, 83, 84 and 85 (all <1%). A high resolution measurement shows m/e 83 to have a molecular formula due entirely to C_5H_9N. Our data (not tabulated) show that C3, C4, and some C6, but not C7, are retained in this ion. Therefore, both 37→43 + 44 and 45→46 + 47 are probably occurring.



45 (m/e 226) 47 46 (m/e 83)

Experimental Section

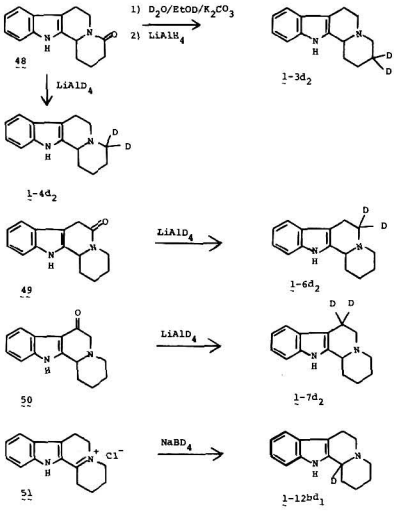
Deuterated Compounds. - The synthesis of the deuterated compounds 1-3d$_2$, 1-4d$_2$, 1-6d$_2$, 1-7d$_2$ and 1-12bd$_1$ is summarized in Scheme I. Compounds 1-4d$_1$ and 1-12bd$_1$ have been previously described,[15] although in the present study iminium ion 51 was prepared according to the method of Martel and Costerousse.[27] Lactams 48[28] and 49,[29,30] and ketone 50[30,31] are known compounds.

The isotopic purity of 1-4d$_1$, 1-4d$_2$, 1-6d$_2$, 1-7d$_2$, and 1-12bd due to the method of preparation should reflect the purity of the metal deuteride reducing agent,[32] whereas the preparation of 1-3d$_2$ involving aqueous exchange and a metal hydride reduction could give material having a much lower deuterium content.[33]

Analysis of the parent-ion clusters at 20 eV and 9 eV using a computerized version of published "parent" and "parent-1" procedures[34] gave unreasonably low values of deuterium content, even though the (P+1)/P isotopic ratios (at 20 eV) indicated high isotopic purity. Additional measurements at 25 eV showed the parent cluster to have the same relative intensities as at 70 eV, indicating very facile P-1 processes. Nonetheless, the "parent-1" procedure[34] should have corrected for this facile P-1 fragmentation at low ionization potential. Failure to do so indicated that the underlying assumptions[34] of the program were not applicable in the present case.

JOC-13-10

Scheme I



48 1-3d$_2$ 1-4d$_2$ 49 1-6d$_2$ 50 1-7d$_2$ 51 1-12bd$_1$

JOC-13-11

Visual examination of the data revealed that more than one species was contributing to the P-1 peak. Indeed, loss of hydrogen (deuterium) from C4, C6, C7, and C12b occurs at low and high ionization potential, making the "parent" and "parent-1" procedures unusable. The analysis of 1-3d$_2$ is acceptable using this method, since deuterium loss from C3 is insignificant, and it gives an isotopic composition of 86% d$_2$, 11% d$_1$, and 3% d$_0$.

Mass Spectra. - The mass spectra were determined by Mr. H. A. Kirst, Mr. J. W. Suggs, and Mr. H. E. Ensley at Harvard University on an associated Electronics Industries MS9 mass spectrometer at source temperatures of 150-200°. For the exact mass determinations perfluorotri-n-butyl amine was the calibration standard, the minimum resolution was 90 ppm, and the precision was ±5 ppm.

3,3-Dideuterio-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine (1-3d$_2$). - A mixture of 2.0 g (0.0083 mol) of lactam 48,[28] 0.5 g of anhyd K_2CO_3, 15 ml of D_2O, and 32 ml of EtOD was refluxed. After one day an additional 20 ml of EtOD and 1.0 g of K_2CO_3 were added. After 3 days an additional 10 ml of EtOD and 0.5 g of K_2CO_3 were added. After 13 days of reflux the mixture was allowed to cool and the white solid was collected by filtration. The filtrate was diluted with H_2O and extracted with $CHCl_3$. This afforded, after H_2O washing and drying (K_2CO_3), on concentration in vacuo 0.27 g of white solid. This material was stirred with 0.4 g (0.0095 mol) $LiAlH_4$ in 75 ml of dry THF at 25° (after 1 hr at 0°) under N_2 for 10 hr and then refluxed for 48 hr. The cooled mixture was cautiously quenched with H_2O and diluted with 2N NaOH. The THF layer was separated, the salts were further extracted with Et_2O, and the combined extracts were water washed, dried (K_2CO_3), and concentrated in vacuo to give 0.27 g of 1-3d$_2$ as a white solid. Recrystallization from Et_2O-hexane gave tiny crystal clusters, mp 150-152°. The tlc behavior was identical to that of 1.

4,4-Dideuterio-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine (1-4d$_2$). - A mixture of 2.0 g (0.0083 mol) of lactam 48[28] and 2.0 g (0.048 mol) of $LiAlD_4$ in 150 ml of dry THF was stirred under N_2 at 25° (after 1 hr at 0°) for 24 hr and then refluxed for 68 hr.

JOC-13-12

The cooled mixture was cautiously quenched with water and diluted with 2N NaOH. The usual workup (vide supra) gave 1.64 g (86%) of 1-4d$_2$ as a white solid. Recrystallization from Et_2O-hexane gave tiny colorless crystals, mp 152-153.5°. The tlc behavior was identical to that of 1.

6,6-Dideuterio-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine (1-6d$_2$). - A mixture of 2.0 g (0.0083 mol) of lactam 49[29,30] and 1.0 g (0.024 mol) of $LiAlD_4$ in 50 ml of dry THF was stirred under N_2 at 25° (after 1 hr at 0°) for 22 hr and then refluxed for 3 hr. The usual workup gave a yellow solid. Chromatography over 60 g of activity III basic Woelm alumina gave, with benzene elution, 1.53 g (81%) of 1-6d$_2$ as a white solid, mp 151-153°. Recrystallization from ether gave pure material as colorless crystals. The tlc behavior was identical to that of 1.

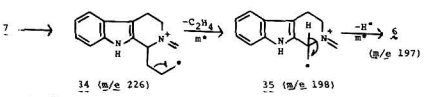
7,7-Dideuterio-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine (1-7d$_2$). - A mixture of 0.26 g (0.0011 mol) of ketone 50[30,31] and 0.13 g (0.0031 mol) of $LiAlD_4$ in 50 ml of dry THF was stirred under nitrogen at 25° (after 1 hr at 0°) for 20 hr and then refluxed for 1 hr. The usual workup and chromatography gave 0.082 g (33%) of 1-7d$_2$ as a white solid, mp 149-151°. The tlc behavior was identical to that of 1.

12b-Deuterio-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine (1-12bd$_1$). - To a solution of 0.20 g (0.0048 mol) of $NaBD_4$ in 20 ml of abs EtOH was added 1.2 g (0.0046 mol) of iminium chloride 51.[27] After 15 min the mixture was concentrated in vacuo and diluted with benzene. Chromatography over activity III basic Woelm alumina gave, with benzene elution, 0.93 g (89%) of 1-12bd$_1$ as an off-white solid. The tlc behavior was identical to that of 1.

Sample Calculation. To calculate the true intensities of peaks, the observed intensities are scaled for the most intense peak to 100%. The expected P+1 contributions are calculated by multiplying the peak intensity of, for example, m/e 225, 226, and 227 in succession by 17.6 (the calculated ((P+1)/P)100 for m/e 225, 226, and 227 using 1.107% ^{13}C, 0.366% ^{15}N, and 0.015% ^{2}H) to get the expected P+1 contributions of each peak. The expected P+1 contributions are then subtracted from the observed relative intensities of the peak to which they contribute to obtain the corrected values (Table VIII).

Fragmentation Appendix

The cleavage of the C1-C12b bond has been suggested to occur in the fragmentation of ajmalicine and related alkaloids,[10] as well as quinolizidine itself.[11] A similar stepwise mechanism can account for 6 but its precursor ion 35 does not satisfy the requirement that m/e 198 retain hydrogen at C3 and C12b. In addition, fragment 34 does not benefit from the extra stability of 8 where the positive charge can be shared by both nitrogens.



7 34 (m/e 226) 35 (m/e 198) 6 (m/e 197)

Another possibility for the formation of 10 is a retro-Diels-Alder loss of ethylene from 4 (m/e 225). Although our data cannot rule out the 4→10 pathway, the mass spectra at 20 eV show a more intense m/e 198 (56%) relative to m/e 197 (100%) than at 70 eV which suggests the importance of 9 in the formation of 10. One would expect an accumula-

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Photochemistry of Polycyclic 5-Acylnorbornenes[1]

Ronald R. Sauers* and Thomas R. Henderson

School of Chemistry, Rutgers University, New Brunswick, New Jersey 08903

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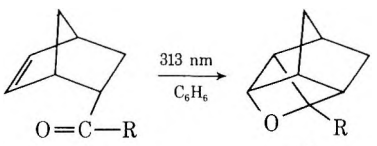
Ketones **3X**, **3N**, **4X**, and **4N** were synthesized and irradiated with ultraviolet light. Compounds **3X** and **3N** gave products, enal **6** and oxetane **5**, respectively, which are believed to have been formed from n,π* states of the carbonyl groups. Ketones **4X** and **4N** gave products, **8** and **7**, respectively, which were probably formed from π,π* states of the double bonds.

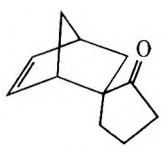
Earlier studies of the photochemistry of simple *endo*-5-acylnorbornenes[2,3] (**1**) have revealed a photocycloaddition reaction of significant synthetic versatility as well as one which involves intriguing mechanistic subtleties. It has been shown[4] that oxetanes of structure **2** are formed from **1** with quantum efficiencies ranging from 0.10 to 0.22 and



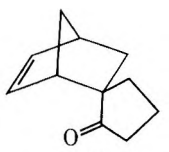
1 **2**

that essentially no other products are produced. In particular, type I and type II cleavages were not competitive even in favorable cases, *e.g.*, R = *t*-C_4H_9, *i*-C_5H_{11}.[4] Preliminary studies with *exo*-5-acylnorbornenes did not yield well-defined product mixtures, on the other hand. Thus, these results raised several questions concerning the factors which control the efficiency of oxetane formation and the general structural limitations of this reaction. In addition, the behavior of the exo systems was perplexing and a more detailed investigation was clearly of interest in view of the paucity of data on the behavior of constrained γ,δ-unsaturated ketones.[5]

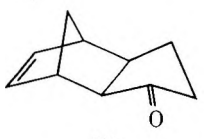
To these ends, an investigation of the synthesis and photochemistry of the following four ketones was initiated: **3X**, **3N**, **4X**, and **4N**.



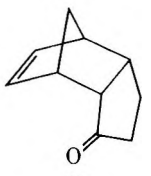
3X



3N

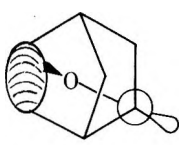


4X

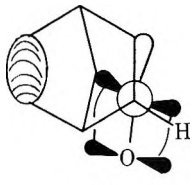


4N

The choice of these systems was governed by the relatively fixed geometrical orientations of the chromophores. From the drawings shown below, it can be seen that only



3N



4N

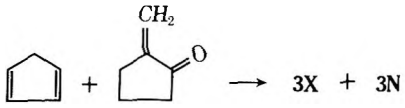
in **3N** is the n orbital of the carbonyl group suitably positioned with respect to the double bond to permit the mode of interaction proposed for exciplex formation in the

oxetane reaction.[6] On the other hand, the situation in **4N** is such that only the π orbitals of the carbonyl group can interact with the double bond. The behavior of the two exo isomers **3X** and **4X** was of intrinsic interest (see above) in the realm of photochemistry of unsaturated carbonyl systems and it was instructive to use them as model systems for the corresponding endo systems.

We report here the major chemical consequences of irradiations of these four ketones, and assign some tentative mechanistic schemes to rationalize the observed products.

Results

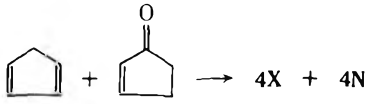
Syntheses. The spiro ketones **3X** and **3N** were conveniently prepared as a 10:1 mixture by the reaction of cyclopentadiene with the Mannich base of cyclopentanone.[7] Presumably, this reaction involves the intermediacy of α-methylenecyclopentanone, which undergoes a Diels–Alder reaction with the diene (eq 1). In agreement with recent



(1)

studies of the stereochemistry of Diels–Alder reactions of methylated dienophiles,[8] we assign the endo stereochemistry to the minor isomer **3N**. Our structural assignment was also based on nmr data which pertains to the chemical shifts of the 3-endo protons in these isomers. This proton in the exo isomer **3X** appeared as a four-line multiplet centered at δ 0.80. The larger coupling (J = 10.7 Hz) is attributed to geminal splitting and the smaller one (J = 2.8 Hz) is the result of long-range coupling with the anti C-7 proton.[9] The origin of the upfield shift of this proton has been attributed[9] to the anisotropy of the carbon–carbon bond at C-2.[10]

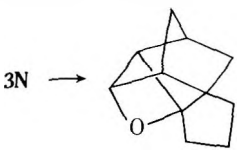
Similarly, the ketones **4X** and **4N** were obtained *via* a Diels–Alder reaction between 2-cyclopentenone and cyclopentadiene (eq 2). It was advantageous to use aluminum



(2)

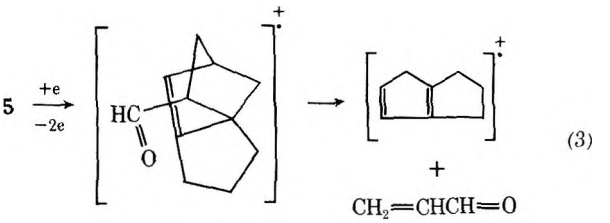
chloride as a catalyst in this sequence, since the yield was doubled under milder reaction conditions.[11] The predominant isomer (80%) was identified as the endo ketone (**4N**) by spectral comparisons with data from an authentic sample.[12]

Irradiations. All four ketones were irradiated in deoxygenated benzene with Pyrex-filtered light. Two volatile products in the ratio 98:2 were produced from **3N**. The major component showed no hydroxyl or carbonyl absorptions in the infrared region and no nmr absorptions below δ 4.48. The latter absorption appeared as a one-proton doublet of doublets and is typical[2] of oxetanes of structure **2**. In view of the earlier precedent, structure **5** is assigned to this photoproduct. Further evidence in support of this



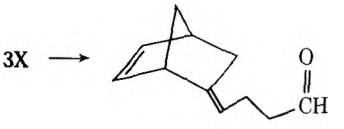
5

assignment was deduced from the mass spectral cracking pattern of **5**. The base peak at m/e 106 corresponds to the molecular ion less the elements of acrolein. The breakdown may be rationalized in terms of oxetane cleavage followed by a reverse Diels–Alder reaction[13] (eq 3).



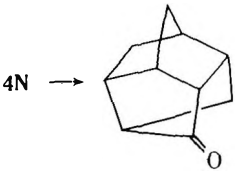
(3)

Compound **3X** led to a five-component product mixture, two components of which were shown to be **3N** (6.5%) and **5** (17%). The other two minor products totaled 5% and were not examined. The major product (72%) displayed absorptions attributable to aldehydic and olefinic groups in both the nmr and ir spectra. This data, the microanalytical results, and the mass spectrum all support the enal structure **6** for this product.



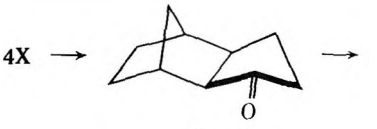
6

Irradiation of **4N** gave a product which was neither an oxetane nor an enal as evidenced by the absence of unsaturation and the presence of a carbonyl group at 5.67 μ. Attempts to define the structure of this compound by various chemical and spectral means failed to point to an unambiguous answer. The crystalline 2,4-dinitrophenylhydrazone derivative was therefore subjected to X-ray crystallographic analysis.[14] This procedure led only to structure **7**, a finding which is consistent with all other data.



7

The last ketone to be studied, **4X**, was found to produce as many as nine products upon irradiation in benzene. Since isolation and identification of these products did not appear feasible, other conditions were examined. Irradiation in methanol proceeded more cleanly to produce one major product which was further degraded on longer irradiation. The initial photoproduct was isolated and identified as the saturated ketone **8** and the degradation products as **9** and **10**. This overall sequence (**8** → **9** → **10**) had been observed in an earlier study[15] and was confirmed in this work.



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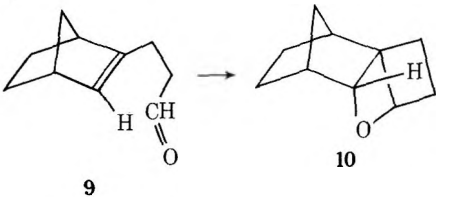


9 **10**

Discussion

The notable features of these results may be best appreciated by comparisons of behavior within the two main structural and stereochemical groups, *i.e.*, **3X** *vs.* **3N**, **3X**

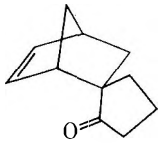
Table I
Quantum Yield and Quenching Data for 4N → 7

Determination	4N, *M*	Norbornene, *M*	ϕ[a]
Consumption of 4N	0.139	0	0.26 ± 0.03
	0.139	1.445	0.20 ± 0.02
Formation of **7**	0.139	0	0.095 ± 0.005
	0.139	1.445	0.026 ± 0.003
Formation of exo,-trans,endo dimer of norbornene[b]	0.139	1.445	0.009 ± 0.002

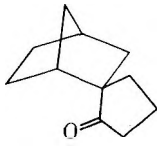
[a] Conversions varied from 9 to 14%. [b] Other dimers were formed to a minor extent.

vs. **4X**, etc. In this way the influence of the effect of structure and stereochemistry on the photoreactions may be assessed.

Thus, in the exo, endo pair **3X**, **3N**, it is clear that the proximity and accessibility of the double bond is the decisive factor which diverts the endo ketone away from type I cleavage. Since the efficiency of oxetane formation (0.21) equaled that of ketone loss, it is concluded that rapid exciplex formation[6,16] followed by oxetane formation and radiationless decay account for the fate of most of the excited state(s) of **3N**.[6,16] It is pertinent to note that the absorption spectrum of **3N** exhibits an enhanced intensity characteristic of systems in which the n orbital interacts with the π system.[17] Interestingly, the n → π^* absorption

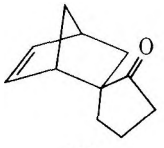


3N λ_{max} (C_6H_{12}) 307 nm (ϵ 54.4)

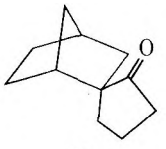


11 λ_{max} (C_6H_{12}) 302 nm (ϵ 27.4)

of the exo isomer **3X** also shows enhanced intensity and a red shift. These chromophores have a relative geometry



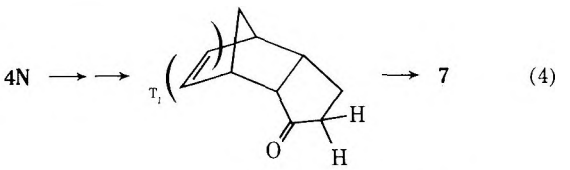
3X λ_{max} (C_6H_{12}) 301, 215 nm (sh) (ϵ 55,3200)



12 λ_{max} (C_6H_{12}) 300 nm (ϵ 26.9)

which is ideally suited for σ coupling as defined by Cookson and coworkers.[18] Although the overall course of the reaction **3X** → **6** is not abnormal, the consequences of σ interactions may not be apparent until one takes into account all of the parameters which define excited-state behavior.

Neither of the fused ketones **4X** and **4N** undergoes reactions typical of cyclopentanones, *e.g.*, type I cleavage or photoreduction, in contrast to the behavior of the saturated analogs.[15] The observed reactions both involved reduction of the double bond, a process which is characteristic of π,π^* states of strained olefins.[19] In these systems a likely sequence of events would entail energy transfer steps from the T_1 state of the excited carbonyl groups to the ground-state olefins.[20] There is precedent in both cases for the requisite subsequent processes. Thus, the triplet olefin in **4N** could undergo intramolecular abstraction followed by cyclization (eq 4) in a fashion analogous to that observed by Scharf[21] (eq 5).



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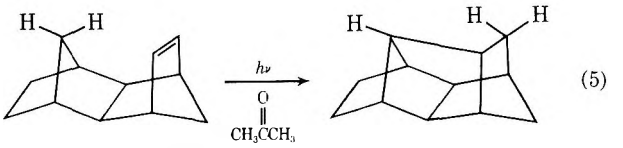
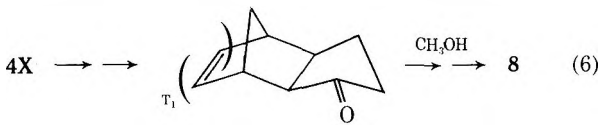


(5)

The overall reaction **4N** → **7** could be quenched by added norbornene with the concurrent production of dimers. From the data in Table I it can be seen that most of the product (**7**) arises from the quenchable state (ϕ_0/ϕ = 3.6). The most straightforward interpretation of this data involves competitive excitation transfer from triplet carbonyl to norbornene or **4N**.[22] The data also demand that a nonquenchable state is involved in those other processes which consume **4N** but which do not lead to **7**.

In the exo system **4X**, energy transfer is followed by a series of radical abstraction reactions[19] which ultimately produce the saturated ketone 8 (eq 6). This sequence par-



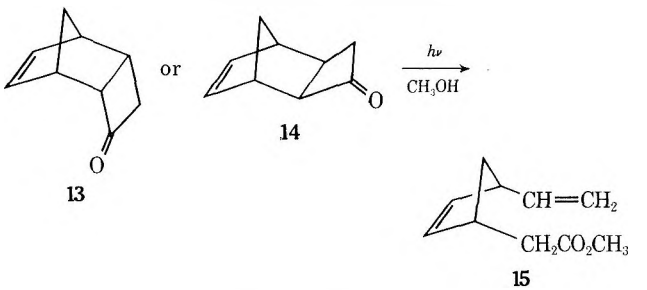
(6)

allels the photoreduction of norbornenes, which can be sensitized by acetone or aromatic donors.[23]

The contrast in behavior between **3N** and **4N** is instructive in the context of the overall behavior of *endo*-5-acylnorbornene photochemistry. On the one hand, **3N** rapidly forms an oxetane in competition with what must be a facile type I cleavage. On the other hand, the behavior of ketone **4N** resembles that of an isolated carbonyl system. Thus, in constrast to simple *endo*-5-acylnorbornenes, quenchable triplet states of **4N** are formed. We conclude that the singlet state is relatively long lived as a consequence of weak or negligible exciplex formation. These results lend support to the ideas[6] discussed above concerning the geometrical requirements for exciplex formation.

The contrasting behavior between **3X** and **4X** is probably the result of differences in ease of α cleavage toward tertiary and secondary centers.[24] These differences in turn are the deciding factors which control the extent of energy transfer to the ground state molecules.

The results of a related study in which the behavior of **13** and **14** was studied was recently reported.[25] It was



found that irradiation of both isomers produced ester **15**, but that chemical yields were significantly lower in the case of **14**. Conceivably, these reactions may involve ener-

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EXPERIMENTAL SECTION

Infrared spectra were determined on a Perkin-Elmer Model 137 spectrometer. Nuclear magnetic resonance spectra (in CCl_4 or $CDCl_3$) were obtained from Varian A-60 or T60 spectrometers and chemical shifts are relative to internal tetramethylsilane. Ultraviolet spectra were determined on a Cary 14 spectrophotometer. Preparative and analytical gas chromatography was carried out on Aerograph A-90-P instruments using the following columns: A, 16% QF-1: 4% Carbowax 20M (6 ft x 0.25 in); B, 4% QF-1: 1% Carbowax 20M (12 ft x 0.18 in); C, 4% QF-1: 1% Carbowax 20M (15 ft x 0.18 in); D, 45% QF-1: 3% Carbowax 20M (15 ft x 0.18 in); E, 3% QF-1: 2% Carbowax 20M (12 ft x 0.18 in); F, 4% QF-1: 1% Carbowax 20M (18 ft x 0.18 in). Mass spectra were recorded on an Hitachi Perkin-Elmer RMU-7 spectrometer.

endo, exo-5-Norbornen-2-spiro-1'-cyclopentan-2-one (3N and 3X). The Mannich base was prepared from cyclopentanone, formaldehyde, and dimethylamine hydrochloride.[26] A solution of 36.6 g (0.26 mol) of the Mannich base and 1.0 g of hydroquinone in 25.8 g (0.39 mol) of freshly prepared 1,3-cyclopentadiene was heated in a sealed tube at 125° for 4 hr. The crude product was dissolved in ether which was washed with dilute hydrochloric acid, aqueous sodium carbonate, dried, and evaporated. The residue (36.6 g) was distilled to give 19.8 g (47%) of a 9:91 mixture of isomers, bp 69° (4.5 mm) (lit., bp 74-74.5°/12 mm). The isomers were separated by partition chromatography on silica gel (Baker 60-200 mesh) using benzene as an eluent.

The endo-ketone (minor component) 3N showed the following properties: nmr (CCl_4) δ 5.9 (octet, 2H), complex absorption from δ 2.9 to 1.3 (12 H); ir (film) 5.78 (C=O) and 13.98 (HC=CH) μ; mass spectrum m/e 162 (0.19, molecular ion), 97 (0.40), 66 (1.0); $\lambda^{C_6H_{12}}_{max}$ 307 nm (ε 54.4), $\lambda^{C_6H_6}_{max}$ 305 nm (ε 76); semicarbazone mp 188.5-189° (dec).

Anal. Calcd for $C_{12}H_{17}N_3O$: C, 65.73; H, 7.81; N, 19.16
Found: C, 66.00: H, 8.02; N, 19.09.

The exo-isomer 3X showed the following properties: nmr δ 6.15 (m, 2H), complex absorption between δ 3.0 to 1.0 (11 H), and a one proton quartet centered at δ 0.80 (J = 2.8, 10.7 Hz); ir (CCl_4) 5.80 (C=O) and 13.89 (s, HC=CH) μ; mass specrrum m/e 162 (0.02, molecular ion), 96 (0.21), and 66 (1.0); $\lambda^{C_6H_{12}}_{max}$ 301 nm (ε 55.3), $\lambda^{C_6H_6}_{max}$ 298 nm (ε 93); semicarbazone mp 211-212° (dec).

Anal. Found: C, 65.86; H, 7.84; N, 19.10.

The saturated ketones 11 and 12 were prepared by hydrogenation[7] of the pure ketones 3N and 3X in methanol using 10% palladium on carbon as the catalyst. Ketone 11 showed the following properties: ir (CCl_4) 5.79 (C=O) μ; mass spectrum m/e 164 (molecular ion), 97 (base peak); $\lambda^{C_6H_{12}}_{max}$ 302 nm (ε 27.4). Ketone 12 showed the following properties: ir (CCl_4) 5.79 (C=O) μ; mass spectrum m/e 164 (molecular ion), 97 (base peak); $\lambda^{C_6H_{12}}_{max}$ 300 nm (ε 26.9).

exo, endo-Tricyclo[5.2.1.$0^{2,6}$]dec-8-en-3-one (4X, 4N). A solution of 8.2 g (0.1 mol) of 2-cyclopentenone[27] in 100 ml of dry methylene chloride was

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added slowly to a stirred, ice-cooled suspension of 13.35 g (0.1 mol) of anhydrous aluminum chloride in 100 ml of dry methylene chloride. After the exothermic reaction subsided, the ice bath was removed and 33.0 g (0.5 mol) of freshly distilled cyclopentadiene in 100 ml of dry methylene chloride was added over a period of 30 min. The reaction mixture was cooled and treated with 300 ml of 1N hydrochloric acid. The organic phase was separated and washed with water, dried (Na_2SO_4) and evaporated to give 35.5 g of a dark oil. The benzene soluble material was chromatographed on silica gel. Elution with benzene gave 6.03 g (41%) of a 20:80 mixture of 4X and 4N, respectively.

The endo- isomer was purified further by sublimation, mp 93-94° (lit., mp 100-103°) and showed ir and nmr spectra identical with those of an authentic sample;[12] $\lambda^{C_6H_{12}}_{max}$ 306 nm (ε 18.9), $\lambda^{C_6H_6}_{max}$ 304 nm (ε 21.4); the 2,4-dinitrophenylhydrazone derivative had mp 180.5-181° after crystallization from ethanol.

Anal. Calcd for $C_{16}H_{16}N_4O_4$: C, 58.53; H, 4.91; N, 17.06
Found: C, 58.55; H, 4.90; N, 16.99.

The exo- ketone (4X) had the following properties: bp 51-52° (0.5 mm); nmr δ 6.2 (t, 2H), 3.2-1.2 (complex absorptions, 10 H)); ir (CCl_4) 5.79 (C=O) and 13.60 (HC=CH) μ; mass spectrum m/e 148 (molecular ion); $\lambda^{C_6H_{12}}_{max}$ 307 nm (ε 39.3), $\lambda^{C_6H_6}_{max}$ 304 nm (42.8); the 2,4-dinitrophenylhydrazone derivative had mp 201-201.5° after crystallization from ethanol-ethyl acetate.

Found: C, 58.52; H, 5.06; N, 17.03.

Photolyses. Irradiations were carried out in nitrogen-purged solvents with a 450 watt Hanovia mercury lamp (Type L). Pyrex filters were used for irradiations of 3X, 3N, and 4N, and a Corex filter was used with 4X. The benzene used was purified by washing with concentrated sulfuric acid, water, aqueous sodium carbonate and water. After drying over $CaCl_2$ it was distilled from P_2O_5. Spectroquality methanol was used in the case of 4X. Internal standards were purified in a similar manner to benzene.

Tetracyclo[5.2.1.$0^{2,6}$.$0^{4,9}$]decan-3-one (7). A solution of 1.481 g (0.010 mol) of ketone 4N in 225 ml of benzene was irradiated for 93 hr. Gc analysis (b) revealed four componenets in the photolysate.

The major constituent (86.5%) was isolated by column chromatography on silica gel (benzene eluent) and had mp 174-175°, yield 0.713 g (48%); nmr[28] δ 1.22 (d,d, J = 12,6 Hz, 1H), 1.42 (d,d J = 12,5.5 Hz, 1H), 1.52 (d, J = 1.8 Hz, 2H), 1.83-1.99 (m, 4H), 2.25 (q, J = 6 Hz, 1H), 2.36 (q, J = 5 Hz, 1H), 2.43-2.59 (m, 2H); ir (CCl_4) 5.67 (C=O); mass spectrum m/e 148 (molecular ion); 2,4-dinitrophenylhydrazone derivative, mp 190-192°.

Anal. Calcd for $C_{16}H_{16}N_4O_4$: C, 58.53; H, 4.91; N, 17.06
Found: C, 58.43; H, 5.20; N, 17.41.

Irradiations of 4X. Benzene. After 14 hr of irradiation of a solution of 4X in benzene (0.060 g in 120 ml) there was observed nine volatile products on gc analysis (D, 82-160°). No single product was prominent enough to render isolation feasible.

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Methanol. A solution of 0.120 g (0.0068 mol) of ketone 4X in 120 ml of methanol was irradiated for 29 hr. Concurrently, the irradiation of a similar solution of ketone 8 was initiated. The gc retention time (D, 84-160°) of the initial product from 4X coincided with that for 8. Gradually, ketone 8 produced 9 and 10 in both cases. Preparative gc and ir comparisons confirmed the identity of the products from 4X.

12-Oxapentacyclo[8.2.1.$0^{1,5}$.$0^{2,9}$.$0^{7,11}$]dodecane (5). Irradiation of a solution of 0.500 g (0.00338 mol) of 3N in 110 ml of benzene for 29 hr gave a photosylate which showed two products bn the gc (B, 120°). The major product was isolated by preparative gc (A, 121°) as a colorless oil, yield 0.22 g (44%); nmr δ 4.48 (d,d, J = 3.9, 2.1 Hz, 1H), 3.25 (t, J = 3.9 Hz, 1H), 1.2-2.5 (m, 12H);[29] ir 9.14, 9.56, 9.80, 10.32, 11.16, 11.36 (all m) μ; mass spectrum m/e 162 (0.54, molecular ion), 106 (1.0), 91 (0.83).

Anal. Calcd for $C_{11}H_{14}O$: nuclidic mass 162.1044
Found: nuclidic mass 162.1045.

Irradiation of 3X. Irradiation of a solution of 0.648 g (0.0040 mol) of ketone 3X in 110 ml of benzene for 9.5 hr gave a five component product mixture as shown by gc (B). The identity of the products and their relative proportions are given as follows: 5 (.17), 3N (0.065), two unidentified peaks (0.045) and 6 (0.72). Aldehyde 6 had the following characteristics: nmr δ 9.66 (m, H-C=O), 1H); 6.04 (m, HC=, 2H), 5.2 (m, HC=, 1H), 1.2-3.5 (m, 10 H); ir 3.72 (HCO), 5.82 (C=O), 14.05 (HC=CH) μ; $\lambda^{C_6H_{12}}_{max}$ 295 nm (ε 37); mass spectrum m/e 162 (molecular ion); 2,4-dinitrophenylhydrazine, mp 107.5-109°.

Anal. Calcd for $C_{17}H_{18}N_4O_4$: C, 59.64; H, 5.30; N, 16.37
Found: C, 59.40; H, 5.39; N, 16.46.

Quantum Yield Determinations. All determinations were run in duplicate in 13 x 100 mm Pyrex test tubes which had been degassed by four freeze-thaw cycles and sealed under vacuum (5 x 10^{-3} Torr). A potassium chromate-sodium carbonate filter solution was placed in a reaction flask which surrounded the immersion lamp. Solutions to be irradiated were optically dense over 1 cm at 313 nm; concentrations of ketones ranged from 0.0915 to 0.139 M. The actinometer system used was the photocyclization reaction of 1 (R=CH_3) to 2 for which a quantum yield of 0.14 has been measured[4] using benzophenone-benshydrol actinometry.

These analyses were carried out using gc and known concentrations of an appropriate internal standard, usually, a saturated straight chain hydrocarbon. Norbornene dimers were a gift from P. v. R. Schleyer, Princeton University.

In addition to the data in Table I, the following results were obtained:

Φ_{-3N} 0.25 ± 0.03, Φ_5 0.21 ± 0.02;

Φ_{-3X} 0.31 ± 0.03, Φ_6 0.29 ± 0.03.

gy transfer steps which compete to differing extents with the type I cleavages.

Summary. The widely disparate behavior of these four ketones exemplifies the subtleties implicit in the photochemistry of complex molecules. We have rationalized the results in terms of reasonable assumptions about the relative magnitudes of the rates of competing processes. In any case, these results have led to a better understanding of the geometrical requirements for exciplex and oxetane formation and to a useful synthesis of a new tetracyclic ring system (7).[30]

Acknowledgments. The authors wish to acknowledge the financial support in the form of a Traineeship to the National Aeronautics and Space Administration.

Registry No.—*endo*-**3**, 51263-64-0; *endo*-**3** semicarbazone, 51263-65-1; *exo*-**3**, 51269-20-6; *exo*-**3** semicarbazone, 51269-21-7; *endo*-**4**, 22981-84-6; *endo*-**4** 2,4-dinitrophenylhydrazone, 51263-66-2; *exo*-**4**, 51269-22-8; *exo*-**4** 2,4-dinitrophenylhydrazone, 51263-67-3; **5**, 51263-68-4; **6**, 51263-69-5; **6** 2,4-dinitrophenylhydrazone, 51263-70-8; **7**, 51263-71-9; **7** 2,4-dinitrophenylhydrazone, 51263-72-0; **11**, 51263-73-1; **12**, 51269-23-9.

Miniprint Material Available. Full-sized photocopies of the miniprinted material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the miniprinted and supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-1850.

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A Synthesis of Tulipalin A and B and the Acylglucoside, Tuliposide A, Fungitoxic Agents from *Tulipa gesneriana*. Carbon-13 Nuclear Magnetic Resonance Analysis of Anomeric Configuration in Acylglucosides[1]

Charles R. Hutchinson

Section of Medicinal Chemistry and Pharmacognosy, School of Pharmacy, University of Connecticut, Storrs, Connecticut 06268

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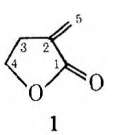
A synthesis of the plant antifungal agents, tulipalin A (1), tulipalin B (2), and pentaacetyl tuliposide A (5), the 1-acylglucoside of γ-hydroxy-α-methylenebutyric acid, is presented. The key steps of the syntheses involve the reductive amination of α-formyl-γ-butyrolactone (8) with dimethylamine and sodium cyanohydridoborate, indicative of a general route to α-methylenelactones. A C-13 nuclear magnetic resonance analysis of 1, 5, pentaacetyl α- and β-D-glucose, and the carbohydrate moiety of secologanin tetraacetate also is discussed. The results are indicative of a diagnostic carbon chemical shift for the anomeric carbon of peracetylated glucosides.

Among the many secondary natural products with biological activity that have been isolated from higher plants, there has been considerable interest recently in compounds that contain an α-methylene-γ- or -δ-lactone functional unit owing to their demonstrated cytotoxicity and tumor-inhibitory properties.[2] The simplest examples of naturally occurring α-methylene-γ-lactones are represented by tulipalin A (1) and B (*S*-2),[3] which occur



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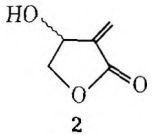

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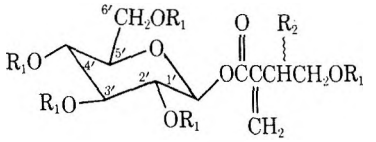


3, $R_1 = R_2 = H$
4, $R_1 = H$; $R_2 = OH$
5, $R_1 = Ac$; $R_2 = H$
6, $R_1 = R_2 = Ac$

in the common tulip *Tulipa gesneriana* L. as the 1-acylglucoside of their analogous γ-hydroxy acids, tuliposide A (3) and B (*S*-4).[4] These two lactones and perhaps also the glucosides appear to function as defensive agents against infection of the tulip plant by common pathogenic soil fungi, such as *Fusarium oxysporum*[5] and species of *Botrytis*.[6]

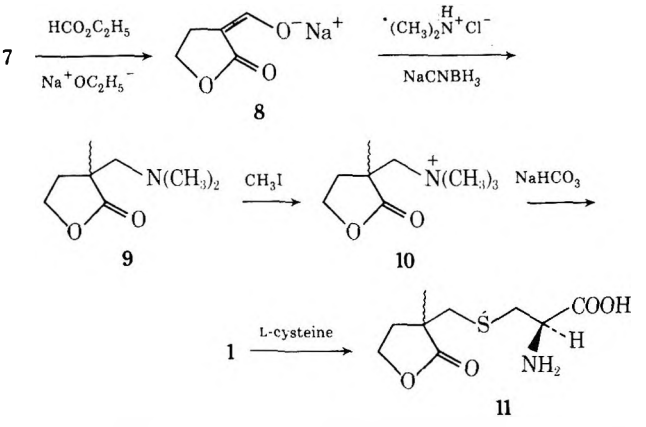
In view of the structural novelty of these glucosides[7] and a need for quantities of them for biological testing and for completion of a study of their biogenesis,[8] their synthesis was undertaken, arising out of our recently developed method for the conversion of γ- and δ-lactones to their α-methylene analogs.[1b] With the known instability of 3 and 4 to acid and base[3,4] in mind, it was decided at the outset to synthesize the glucosides as their acetates (*e.g.*, 5), which would satisfy our requirements and avoid the problem of acylglucosylating an unprotected γ-hydroxy acid with some form of D-glucose.[16]

It also was considered of interest to examine the ^{13}C nmr spectra of these novel compounds (a) to see if ^{13}C nmr assignments could allow the distinction of anomeric configuration in acylated glucosides, and (b) to establish the carbon chemical shifts of the α-methylene-γ-lactone unit.

Results and Discussion

Two syntheses of 1 had been reported at the outset of this work.[9] Jones, *et al.*,[10a] had prepared 1 in moderate yield from the reaction of but-3-yn-1-ol with nickel carbonyl in ethanol–acetic acid–water at 80°; McGraw[10b] had prepared α-hydroxymethyl-γ-butyrolactone from α-formyl-γ-butyrolactone (8) by high-pressure hydrogenation

Scheme I



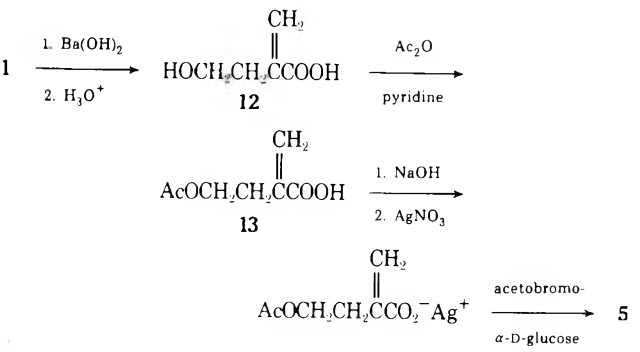
over Raney Ni, whence 1 was obtained in moderate yield by passage of the hydroxymethyl lactone over activated alumina at 340–350° to effect dehydration.

One synthesis of 1 was developed, analogous to that of McGraw.[11] However, the capricious nature of the high-pressure Raney Ni reduction and the only moderate overall yield of 1 led me to consider an alternative route that would be compatible with the instability of 1 to mineral acids and heat.[10,11] The recent discovery of the unique reductive properties of sodium cyanohydridoborate by Borch, *et al.*,[12] in particular its rapid reduction of imines and enamines at mildly acidic pH's thereby permitting a technically easy reductive amination of β-keto esters, prompted me to investigate a synthesis of 1 as shown in Scheme I.

γ-Butyrolactone (7) was formylated by standard techniques to give the sodium salt of α-formyl-γ-butyrolactone (8).[13] The dried sodium salt of 8 was reductively aminated with dimethylamine–dimethylamine hydrochloride and sodium cyanohydridoborate in dimethoxyethane at *ca.* pH 6 to give α-dimethylaminomethyl-γ-butyrolactone (9) in good yield. Quaternization of 9 with methyl iodide gave 10, which readily eliminated trimethylamine on treatment with aqueous sodium bicarbonate at room temperature to give 1 in an overall yield of 70% from 7. The nmr and ir spectral values of 1 were in complete agreement with those reported by Bergman, *et al.*[14] Although the Michael adduct (11) of 1 with L-cysteine was readily prepared as a stable, crystalline solid, an analogous reaction with 4-bromothiophenol gave a crystalline solid (mp 89–91°) that reverted to the starting materials on attempted drying *in vacuo*.

The most direct route to 2 appeared to be *via* selenium dioxide oxidation of 1 in view of the recent work of Bhal-

Scheme II



erao and Rapoport[15] on the allylic oxidation of trisubstituted olefins. A modest yield of **2** was obtained by oxidation of **1** with 1 equiv of selenium dioxide in refluxing dioxane, whereas 0.5 equiv of selenium dioxide led to considerable recovery of unreacted **1** and 2.0 equiv gave less than a 5% yield of **2** plus many other products. No reaction of **1** with selenium dioxide was seen after 24 hr in refluxing ethanol, in contrast to the greater reactivity of the *gem*-dimethyl olefins investigated by Bhalerao and Rapoport. The physical constants of **2**, purified by preparative gas chromatography, were in excellent agreement with those reported by Tschesche, *et al.*,[4] for tulipalin B, except that the C-3 and C-4 protons of **2** were seen as an AA′BB′XX′ system ($J_{AA'} = J_{BB'} = J_{XX'} \leq 0.4$ Hz) due to the racemic center at C-3.

Because of the low yield of **2** obtained by oxidation with selenium dioxide, other synthetic routes to it have been investigated. Attempted allylic bromination of **1** with *N*-bromosuccinimide gave a white, bromine-containing solid whose properties were suggestive of a polymer, in accord with the reported ease of free radical induced polymerization of **1**.[10] A similar attempted oxidation of the methyl ester of **13** (Scheme II) gave in low yield several products, none of which appeared to be the desired secondary allylic bromide.

The synthesis of **5** was achieved analogously to the recent general glycoside synthesis of Wulff, *et al.*,[16] as shown in Scheme II. Hydrolysis of **1** with barium hydroxide followed by careful acidification to pH 4 and extraction with diethyl ether gave γ-hydroxy-α-methylenebutyric acid (**12**). Acetylation of **12** with pyridine–acetic anhydride gave the γ-*O*-acetate **13**, the silver salt of which (**14**) was allowed to react with α-acetobromo-D-glucose in dry benzene at room temperature to give **5** in an excellent yield. The nmr spectral values (60 MHz) of **5** agreed well with those given for the pentaacetate of tuliposide A by Tschesche, *et al.*;[17] additional physical constants (melting point, ir, accurate mass, $[\alpha]^{26}D$) were obtained, as well as ^{13}C nmr data (*vide infra*), to fully confirm the structure of **5** and, consequently, the presence of the 1-acylglucosidic bond in naturally occurring tuliposide A. An analogous sequence of reactions aimed at obtaining **6** from **2** has not been successfully carried out thus far with the limited amount of **2** available. Apparently, the presence of traces of selenium and/or selenium oxides in samples of **2** have led to its complete, rapid decomposition on attempted acetylation, *p*-bromobenzoate derivatization, or basic hydrolysis.

The foregoing reaction sequence was anticipated to result in a β configuration at the anomeric carbon of the glucose moiety. Somewhat surprisingly, the optical rotation of **5** was negative at 589 nm, whereas the unacetylated tuliposides have positive rotations [*A* = +64° (c 1.0, H_2O); B = +56° (c 1.0, H_2O)][4] and most β-D-glycosides give plane positive ORD curves.[18] The ORD curve of **5** confirmed the negative rotation, and showed a negative Cotton effect with one maximum at 225 nm [$\Phi = -5.85 \times 10^3$°]. The nmr spectrum (100 MHz) of **5** revealed that the coupling constant of the anomeric proton at δ 5.78 was about 6 Hz, indicative of a β configuration;[4] however, clean resolution of its signal from that of the upfield vinyl proton was not possible at 100 MHz, thus making a definite decision impossible.

The power of ^{13}C nmr in assigning anomeric configuration among various sugars has been well documented.[19] In particular, the anomeric carbon of β-D-glucose resonates at 96.8 ppm downfield from TMS *vs.* 93.0 ppm for α-D-glucose.[20a] In both cases the resonances of the anomeric carbons fall downfield from all the other signals in the proton noise-decoupled ^{13}C nmr spectra. Hall and Johnson[20b] have shown that the anomeric center of several sugars (*e.g.*, D-glucose, D-galactose, and D-mannose) and their 1-*O*-methyl ethers has a diagnostic carbon chemical shift directly related to either the α or β anomer. The chemical shifts of the constituent carbons of **1**, **5**, α-D-glucose pentaacetate (**15**), and β-D-glucose pentaacetate (**16**) are shown in Table I. Carbons 1′–5′ of both **15** and **16** show a pronounced upfield shift, δ_c −2.5 to −4.9, which is in accord with the observed shielding of the β carbon in the alkyl group on acetylation of alcohols.[21] Carbon 6′ of **15** and **16** does not experience such a large upfield shift; the δ_c of −0.3 and −0.2, respectively, is probably indicative of some residual γ effect, however, for a small deshielding α effect (1.0–2.5 ppm) would have been anticipated.[21] If the assumption can be made that the relative δ_c of each carbon in **15** and **16** upon acetylation is of similar magnitude, then the assignments for carbons 2′, 3′, and 5′ follow as shown in Table I. Some small differences in the relative magnitude of δ_c for these carbons of **15** must occur, as two of the resonances were superimposed (tentatively, C-3′ and C-5′) at 69.9 ppm whereas in α-D-glucose they appear at 72.5 and 72.3 ppm, respectively.[22] Thus, the assignments for C-2′, C-3′, and C-5′ in **15** and **16** must be regarded as tentative. Analogous conclusions were reached by Dorman and Roberts.[20d] C-1′ of **15** has a 1.0 ppm smaller δ_c than C-1′ of **16**, which could be due to a diminished γ effect of its C-2′ acetoxyl group because of the latter's steric interaction with the axial acetoxyl at C-1′. Since the γ effect of an acetyl group has been attributed to through-space interaction, *i.e.*, shielding, of the carbonyl oxygens with the β carbon of the alkyl chain,[21] this is a reasonable explanation. Comparison of the chemical shifts for the carbohydrate moiety of **15**, **16**, and **5** shows that **5** has the anticipated β configuration at its anomeric center, for the chemical shifts of C-1′–C-6′ of **16** and **5** are within ±0.2 ppm of each other, whereas C-2′, C-3′, and C-5′ of **15** do not have such close similarity to the corresponding carbons of **5**, regardless of their relative assignments. Carbon 1′ of **5** appears at 0.5 ppm downfield of C-1′ of **16**. Although a direct explanation for this deshielding effect does not seem possible from available data,[21] some support for both the shift direction and magnitude is given by a comparison of the methyl ester carbon resonance of methyl acetate (51.0 ppm)[21] and methyl propionate (50.8 ppm)[21] to that of methyl methacrylate (51.5 ppm).[23] The downfield shift (0.5 ppm) of the latter compound from methyl acetate compares well that seen on going from the acetyl of **16** to the 4-acetoxy-2-pentenyl group of **5**.

The assignments for the carbon resonances of **1** were obtained directly from consideration of chemical shift theory and off-resonance decoupling data. They appear reasonable and are substantiated by the assignments given recently to the corresponding carbons of the trans-fused α-methylene-γ-lactone functionality of the germacranolide

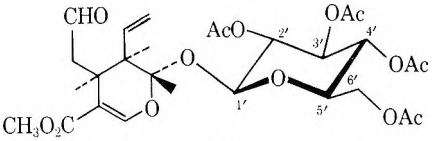
Table I

Compd	Chemical shifts, ppm[a] (δ_c)[b] C-1	C-2	C-3	C-4	C-5	C-1′	C-2′	C-3′	C-4′	C-5′	C-6′	CH_3
15						89.1 (−3.9)	69.3[c] (−2.6)	69.9[c] (−4.5)	68.0 (−2.6)	69.9[c] (−2.4)	61.5 (−0.3)	20.6
16						91.9 (−4.9)	70.5[c] (−4.7)	72.9[c] (−3.8)	68.1 (−2.5)	72.9[c] (−3.8)	61.6 (−0.2)	20.5
5	164.3	135.5	31.3	62.3	129.6	92.4	70.3[c]	72.8[c,d]	68.0	72.8[c,d]	61.5	20.5
1	170.7	134.3	27.4	65.5	121.4							
17						96.0	70.8[c]	72.6[c,e]	68.4	72.6[c,e]	61.8	20.6

[a] In $CDCl_3$, relative to internal TMS = 0; 0.2–0.5 *M* solutions. [b] $\delta_c = \delta_{OAc} - \delta_{OH}$; δ_{OH} for α-D-glucose and β-D-glucose from ref 19, p 461. [c] Tentative assignments (see Results and Discussion). [d] Center of two resonances separated by *ca.* 0.1 ppm. [e] Center of two resonances separated by 0.16 ppm.

sesquiterpene, melampodin B.[24] The chemical shifts for the corresponding carbons of **5** were assigned from consideration of those for **1** and methyl methacrylate.[23]

In order to examine the generality of the carbon chemical shifts for anomeric configuration among acetylated glucosides, the ^{13}C nmr assignments for the glucose moiety of secologanin tetraacetate (**17**) are given in Table I.



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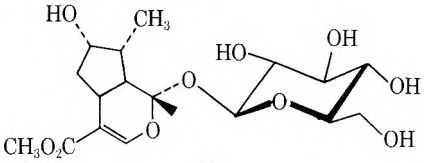

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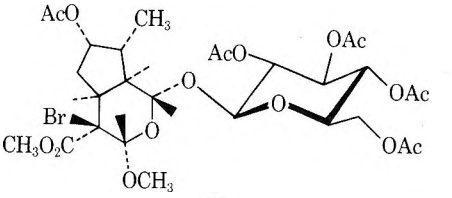
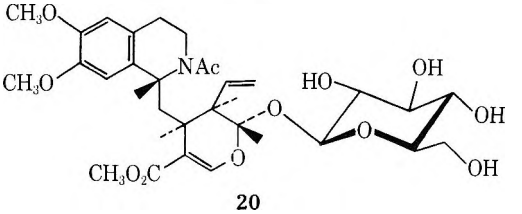
This compound has been shown to have the β configuration at its anomeric center by chemical means[25] and by correlation with loganin (**18**), whose absolute stereochemistry has been established by chemical[26] and X-ray[27] analysis. Since the chemical shifts for C-2′–C-6′ of **17** and **16** are within ±0.3 ppm, it appears that there is some generality among carbon chemical shifts for the carbohydrate moiety of acetylated β-D-glucosides. This is in complete agreement with the indications from work done in Hall's laboratory, particularly their recent INDOR study of several acetylated, anomeric *O*-methoxy pyranosides.[20c] Carbon 1′ of **17** has been shifted 0.8 ppm upfield from β-D-glucose. An upfield shift (0.2–0.3 ppm) of the anomeric carbon of α-D-glucose has been observed in the ^{13}C nmr spectra of sucrose, raffinose, and stachyose, wherein the glucose is linked α-1,2 to fructose.[28] The somewhat larger upfield shift for C-1′ of **17** most likely is due to the more pronounced γ effect of the dihydropyranyl oxygen. The X-ray crystallographic structures of loganin pentaacetate methoxybromide (**19**)[27] and *O,O*-dimethylipecoside (**20**)[29] both indicate that in the crystalline state conformation this oxygen would be close enough in **17** to sterically compress the carbon–proton bond at C-1′. The effect is similar to that of the axial hydroxyl in α-D-glucose on carbons 2, 3, and 5, which appear at higher fields than corresponding ones of β-D-glucose.[19] Obviously the conformation of **17** in solution may bear little similarity to that in the crystalline state, but the foregoing analysis seems reasonable in light of existing data. It also should be kept in mind that relative chemical shifts of such a small magnitude can be due to solvent-induced shifts.[30]



19



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Experimental Section[31]

α-Formyl-γ-butyrolactone (8). Sodium hydride dispersion in mineral oil (57%, 44.0 g, 1.05 mol), contained in a dry 2-l. three-necked flask to which an addition funnel, condenser, and mechanical stirrer were attached, was washed three times with dry hexane and suspended in diethyl ether (1 l., freshly distilled from $LiAlH_4$) under nitrogen. A mixture of γ-butyrolactone (7, 86 g, 1 mol) and ethyl formate (74 g, 1 mol, dried over K_2CO_3 and distilled from P_2O_5) was slowly added to the stirred suspension, immediately following the addition of absolute ethanol (5 ml), at a rate that maintained a gentle reflux of the reaction solvent. After stirring overnight the reaction mixture was rapidly filtered by suction and the resulting solid material was washed well with dry diethyl ether and dried *in vacuo* to give the sodium salt of 8 as a light tan powder (136 g, 100%). Tlc analysis [silica gel, chloroform–methanol (9:1)] of an acidified (acetic acid) sample of this material showed only one spot (R_f 0.50).

A portion of the sodium salt was added to a vigorously stirred mixture of ice-cold 0.5 *N* HCl and diethyl ether, the resulting two phases were separated, and the aqueous phase was extracted twice with more diethyl ether. The combined organic phases were washed with saturated aqueous sodium chloride, dried (Na_2SO_4), and evaporated *in vacuo* to a pale amber, viscous oil. Rapid distillation of this oil at reduced pressure gave 8, bp 83–85° (1 mm) (lit.[10b] bp 83–85°), as a colorless, viscous liquid in low yield, which slowly solidified on standing at 0–5°. Later distillation fractions contained γ-butyrolactone (boiling point) and the odor of formic acid could be detected in the distillation residue.

α-Dimethylaminomethyl-γ-butyrolactone (9). The sodium salt of 8 (275 mg, 2 mmol) and dimethylamine hydrochloride (325 mg, 4 mmol) were suspended in dry dimethoxyethane (20 ml, distilled from $LiAlH_4$) containing Linde 3A molecular sieves (*ca.* 0.25 g). $NaCNBH_3$ (130 mg, 2 mmol[32]) was added and the reaction mixture was stirred magnetically with protection from atmospheric moisture for 24 hr. The resulting brown slurry was filtered through a Celite pad, the solid material was washed with methanol (10 ml), and the combined filtrate and wash were acidified to pH *ca.* 2 with concentrated hydrochloric acid (hood!). The resulting acidic solution was concentrated *in vacuo* to a viscous oil containing some colorless, crystalline material. The total residue was partitioned between water (15 ml) and dichloromethane (2 × 20 ml). The remaining aqueous phase was basified with solid Na_2CO_3 (pH 8.5) and extracted with ethyl acetate (3 × 25 ml), then taken to pH 10 with solid KOH and reextracted with ethyl acetate (3 × 25 ml). The combined organic phases were dried (Na_2SO_4) and evaporated *in vacuo* to give 9 as a faintly yellow liquid:[33] 231 mg (81%); bp 72–73° (0.05 mm); $n^{25}D$ 1.4565; ir (neat) 1770 cm^{-1} (lactone); nmr (60 MHz) δ 2.24 (s, 6 H), 2.40–2.80 (m, 5 H), and 4.30 (m, 2 H); hydrochloride, recrystallized from methanol–diethyl ether, mp 190–190.5°.

Anal. Calcd for $C_7H_{14}NO_2Cl$: C, 46.80; H, 7.86; N, 7.80. Found: C, 46.91; H, 7.84; N, 7.87.

α-Trimethylaminomethyl-γ-butyrolactone iodide (10) was prepared quantitatively by allowing 9 to react with excess methyl iodide in methanol at 25° for 24 hr. The resulting colorless, shiny plates, obtained by filtration of the reaction mixture, were recrystallized from methanol. This caused a slow decomposition to give 1 (tlc analysis). The best melting point obtained was 206–206.5°; however, the melting point ranged from 200 to 207°, regardless of number of recrystallizations. Microanalysis was not attempted.

Tulipalin A (α-Methylene-γ-butyrolactone 1). The methiodide 10 (1.96 g, 7 mmol) was added to a separatory funnel containing a mixture of 5% aqueous $NaHCO_3$ (13 ml, 1.1 equiv) and dichloromethane (20 ml). The mixture was shaken until all the solid had dissolved and the organic layer was removed; the aqueous phase was extracted with more dichloromethane (5 × 20 ml), saturated with sodium chloride, and reextracted with dichloromethane (5 × 20 ml). The combined organic extracts were dried ($MgSO_4$) and evaporated *in vacuo* at *ca.* 5° to a yellowish liquid. Percolation of this crude product, dissolved in a small volume of dichloromethane, through a short silica gel column followed by evaporation of the effluent gave 1 as a faintly amber liquid: 0.66 g (97%): ir (neat) 1765 (lactone), 1668 (C=C), and 810 cm^{-1} (C=CH_2); nmr (60 MHz) δ 2.98 (m, 2 H), 4.37 (t, J = 7 Hz, 2 H), 5.64 (t, J = 3 Hz, 1 H), and 6.13 (t, J = 3 Hz, 1 H); mass spectrum m/e (rel intensity) 98 (M^+, 79), 68 (M − CH_2O, 100). An analytical sample was obtained by gas chromatography on SE-30 at 150°.

Anal. Calcd for $C_5H_6O_2$: C, 61.21; H, 6.17. Found: C, 61.24; H, 6.21.

The spectral values agreed quite well with those of the literature[4] for naturally occurring tulipalin A.

Michael Adduct of 1 with L-Cysteine (11). L-Cysteine (120.7 mg, 1 mmol) was dissolved in hot water (0.6 ml), 1 (100 mg, 1 mmol) dissolved in ethanol (0.7 ml) was added along with more water (0.3 ml), and the solution was stored at 0–5° until the formation of a white solid was complete (*ca.* 1 hr). The mixture was centrifuged and, after the supernatant was discarded, the solid was washed with acetone (2 ml); the mixture was recentrifuged, and the supernatant was again discarded; the yield was quantitative. Repeated recrystallization from water–ethanol–acetone, then water–ethanol–absolute ethanol and drying (1 mm, 61°) for several hours gave the pure L-cysteine adduct of 1 as short, colorless needles: mp 192–193°; ir (KBr) 1758 cm^{-1} (lactone).

Anal. Calcd for $C_8H_{13}O_4NS$: C, 43.78; H, 5.99; N, 6.39. Found: C, 43.21; H, 5.85; N, 6.29.[34]

(*RS*)-Tulipalin B (α-Methylene-β-hydroxy-γ-butyrolactone 2). 1 (190 mg, 1.9 mmol) was dissolved in dry dioxane (25 ml, distilled from $LiAlH_4$), SeO_2 (225 mg, 2 mmol) was added, and the reaction mixture was heated at reflux for 2 hr. The warm reaction mixture was filtered through a Celite pad to remove precipitated Se and the filtrate was evaporated *in vacuo* to a dark reddish-brown gum. Plc of this crude product on silica gel in chloroform–methanol (95:5), two times, showed two major bands that turned yellow on spraying with 1% aqueous $KMnO_4$–$KHCO_3$: R_f 0.7–0.8 (starting material) and 0.3–0.4. Elution of the lower running band with chloroform–methanol (80:20) and evaporation of the solvents *in vacuo* gave a reddish-yellow, viscous oil (141 mg). Plc of this material on silica gel in chloroform–methanol (90:10) showed a major pale yellow band (R_f 0.4) contaminated with at least three minor absorbing bands. Elution of the major band as before gave crude 2 (95 mg) as a pale yellow, viscous oil. A portion of this material was purified by preparative gas chromatography on a 0.5 in × 5 ft glass column containing 15% OV-17 on Chromosorb A AW/DMCS, 45–60 mesh, at 175° and He flow of 100 ml/min; 2 was the major component (retention time 9.3 min) but four other peaks were seen, the most abundant of which was 1 (retention time 3.7 min). The spectral and analytical data were obtained on 15.9 mg of pure 2 thus obtained: ir ($CHCl_3$) 3410 (OH), 1760 (lactone), 1672 (C=C), and 830 cm^{-1} (C=CH_2, neat sample); nmr (100 MHz) δ 3.36 (br s, 1 H), 4.24 (δ_B, J_{AB} = −10, J_{BX} = 4.4 Hz, 1 H), 4.30 (δ_A, J_{AX} = 7.6 Hz, 1 H), 4.90 (δ_X, m, 1 H), 5.95 (d, J = 1.5 Hz, 1 H), and 6.34 (d, J = 2 Hz, 1 H); mass spectrum m/e (rel intensity) 114.0315 (calcd for $C_5H_6O_3$, 114.0327) (M^+, 1), 115 (M + 1, 4), 96 (M − H_2O, 15), and 84 (M − CH_2O, 100).

γ-Hydroxy-α-methylenebutyric acid (12) was prepared from 1 (150 mg, 1.5 mmol) by the procedure of Tschesche, *et al.*:[4] 80 mg (46%); colorless needles from chloroform; mp 66–66.5° (lit.[4] mp 65°).

γ-Acetoxy-α-methylenebutyric Acid (13). 12 (75 mg, 0.65 mmol) was acetylated with acetic anhydride (0.3 ml) and pyridine (0.3 ml) at 3° overnight. The reagents were removed by evaporation *in vacuo* (1 mm), the residue was reevaporated with water (5 ml) and then toluene (2 × 5 ml) to azeotropically remove the remaining traces of reagents, and the resulting gum was percolated through a short silica gel column as a chloroform solution. Evaporation of the column effluent *in vacuo* gave 13 as a colorless, viscous oil: 75 mg (73%); ir ($CHCl_3$) 1730 (CH_3COO), 1697 (COOH), and 1628 cm^{-1} (C=C); nmr (60 MHz) δ 2.03 (s, 3 H), 2.68 (t, J = 7 Hz, 2 H), 4.25 (t, J = 7 Hz, 2 H), 5.75 (d, $J \leq 1$ Hz, 1 H), and 6.39 (d, $J \leq 1$ Hz, 1 H); p-bromophenacyl ester, recrystallized from methanol–water, mp 76.5–77° (lit.[10a] mp 76°).

Silver Salt of 13 (14). 13 (75 mg, 0.47 mmol) was dissolved in a mixture of acetone (5 ml) and water (1 ml). The solution was adjusted to pH 7.0 (pH meter) with 0.1 *N* NaOH. Silver nitrate (87 mg, 0.5 mmol) dissolved in water (2 ml) was added to the magnetically stirred solution of the sodium salt of 13 in the dark. After 30 min the resulting suspension was cooled to ice-bath temperatures and 14 was removed by filtration, washed with ethanol (10 ml) and then diethyl ether (10 ml), and dried (25°, 0.5 mm): shiny, colorless plates; 86 mg (69%); mp 191–192° dec. An additional quantity (15 mg) of less pure 14 was obtained on concentration of the filtrate.

Tuliposide A Pentaacetate (5). 14 (47 mg, 0.18 mmol) was suspended in dry benzene (10 ml) by magnetic stirring. α-Acetobromo-D-glucose[35] (78 mg, 0.19 mmol) was added and the reaction mixture was stirred at 25° for 23 hr in the dark. The insoluble solids were removed by filtration and washed with chloroform (10 ml). Evaporation of the combined filtrates *in vacuo* gave crude 5 as a light amber oil. Plc of this oil on silica gel in chloroform–methanol (8:2) and elution of the major band (R_f 0.7) with chlo-

roform–methanol (3:1) resulted in **5** as a colorless gum: 45 mg (51%, yields of 80% were seen on larger scale runs); ir ($CHCl_3$) 1748 (ester) and 1628 cm^{-1} (C=C); nmr (60 MHz) δ 2.00 and 2.04 (s, 15 H), 2.64 (dd, J = 6 and ~1 Hz, 2 H), 4.19 (t + m, J = 7 Hz, 4 H), 5.19 (m, 3 H), 5.78 (broadened s + t, $J \cong 6$ Hz, 2H), and 6.34 (broadened s, 1 H); mass spectrum m/e 488.1504 (calcd for $C_{21}H_{27}O_{13}$, 488.1521); $[\alpha]^{26}D$ −120° (c 0.02, MeOH); ORD (c 0.0004, MeOH) [Φ] (26°) −366° (500 nm), −488° (400 nm), −732° (300 nm), −2318° (250 nm), −4392° (235 nm), −5856° (225 nm), and −5368° (220 nm).

Recrystallization of **5** from diethyl ether–hexane gave long, colorless needles, mp 97–97.5°.

Anal. Calcd for $C_{21}H_{27}O_{13}$: C, 51.62; H, 5.57. Found: C, 51.64; H, 5.59.

Acknowledgments. I would like to thank Mr. R. J. Kubarek for technical assistance and Mr. A. D. Harmon for certain experimental details. I am indebted to Professor J. A. Glasel, University of Connecticut Health Center, for his invaluable time in instruction on the use of the JEOL PFT-100 nmr spectrometer. Both of us are grateful to the NIH (RR 00639-01A2) and JEOL, Inc., for making this nmr facility available.

Registry No.—**1**, 547-65-9; **1** L-cysteine adduct, 51270-63-4; **2**, 51348-66-4; **5**, 20075-86-9; **7**, 96-48-0; **8**, 42023-16-5; **8** sodium salt, 51270-64-5; **9**, 42023-17-6; **10**, 42023-18-7; **12**, 24923-76-0; **13**, 51270-65-6; **14**, 51270-66-7; ethyl formate, 109-94-4; dimethylamine hydrochloride, 506-59-2; α-acetobromo-D-glucose, 572-09-8.

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(32) Used directly as obtained from Alfa Inorganics.
(33) Physical and spectral constants of **9** were obtained from larger scale runs.
(34) **11** as well as the L-cysteine adducts of other α-methylenelactones (A. D. Harmon and C. R. Hutchinson, unpublished observations) recrystallized as well-formed needles with melting ranges of 1°; however, tlc analysis [cellulose, 2-propanol–HCOOH–water (80:4:20)] frequently showed at least two spots, presumably due to sulfoxide formation. Consequently, microchemical analyses were not within the acceptable ±0.4% limits.
(35) Sigma Chemical Co., $[\alpha]^{26}D$ +186° (c 2, $CHCl_3$).

Conformation of Acyclic Derivatives of Sugars. XI. Conformations of the D-Aldopentose Diethyl and Diphenyl Dithioacetals in Solution[1]

Derek Horton* and Joseph D. Wander

Department of Chemistry, The Ohio State University, Columbus, Ohio 43210

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The conformations of the unsubstituted aldopentose diethyl and diphenyl dithioacetals having the D-ribo [1 (Et), 2 (Ph)], D-arabino [3 (Et), 4 (Ph)], D-xylo [5 (Et), 6 (Ph)], and D-lyxo [7 (Et), 8 (Ph)] configurations have been examined in methanol-d_4 solution by pmr spectroscopy at 100 MHz. Complete sets of proton–proton spin-coupling constants were determined for 2 (in a mixed solvent), 3 (in the presence of 0–100 mequiv of $PrCl_3 \cdot 6D_2O$), 6, 7, and 8; partial spin-coupling data were obtained for the remainder. Clearly preponderant conformations are indicated for 3, 7, and 8 (all planar zigzag), for 2 and 5 [a sickle ($_3G^+$) form derived by rotation of the carbon chain about the C-3–C-4 bond] and, to a somewhat lesser extent, for 1 [a sickle ($_2G^-$) form generated by rotation of the chain about the C-2–C-3 bond]; $J_{1,2}$ values for 4 are consistent with the extended conformation, whereas the xylo derivative 5 is manifestly in a state of conformational instability. Variations in the solvent appear to exert no major influence upon these conformations. Conclusions from previous studies on acetylated derivatives are compared in an effort to assess the relative importance of 1,2 and 1,3 interactions in determining the stability of conformers. Attempts to describe quantitatively the conformational behavior of acyclic carbohydrates in terms of simple substituent-interaction parameters are not considered justifiable.

An extended, planar zigzag arrangement of carbon atoms, corresponding to maximal staggering of large substituents along each carbon–carbon bond, is considered[2] to be the favored conformation in polymethylene chains. Extension of this conformational concept to alditols was invoked in an effort to interpret the course of reactions leading to cyclic acetals.[3] In the latter study, the influence of thermodynamic control upon the product distribution was, however, not taken into account.[4]

Pmr data have indicated[5] that various isotactic vinyl polymers, such as polypropylene, in which the extended zigzag conformation would generate nonbonded interactions between parallel substituents on β-related carbon atoms, adopt, by internal carbon–carbon bond rotation, a conformation wherein these interactions are minimized at the expense of establishing a gauche disposition of carbon substituents along a carbon–carbon bond. Similar parallel interactions, between β-related hydroxyl groups, would exist in a tetrahydroxybutyl chain having the ribo or xylo stereochemistry were it to adopt the extended, zigzag conformation.

Numerous reports[1a,6-22] appearing during the past 6 years have described the use of pmr-spectral techniques [predicated on the premise[23-25] that small (~3 Hz) vicinal proton–proton couplings indicate a gauche (~60°) and large (~8 Hz) ones an antiparallel (~180°) dihedral relationship of the respective protons] to probe the influence of stereochemical configuration on the conformational properties of various polysubstituted acyclic chains that are present in open-chain sugar derivatives (see Table I). Slight liberties of reinterpretation have been taken for the sake of uniformity of presentation in a summary.

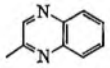
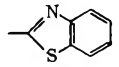
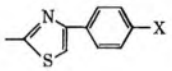
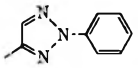
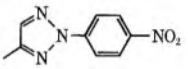
It is at once apparent from Table I that arabino, and to a somewhat lesser extent lyxo, side chains exhibit the anticipated predisposition for the planar, zigzag conformation; it is likewise manifest that the conformational behavior of both ribo and xylo systems is virtually devoid of clear patterns, save for the general tendency for them to exhibit conformational instability and to avoid planar, zigzag forms as favored conformations. However, three additional examples, 3,4-di-*O*-acetyl-1,2:5,6-bis(thioanhydro)-D-mannitol, -D-glucitol, and -L-iditol, have been examined by pmr spectroscopy and it was concluded[29] that *all three* adopt a $_3G^-$ (see footnote *a*, Table I) conformation that includes *parallel eclipsed interactions between both acetoxyl groups and the respective remote epithio rings*, so that there is considerable evidence to dictate caution in the formulation of hard and fast rules to predict conformational behavior in these acyclic molecules; it has been suggested,[27] moreover, from studies[30] of the conformationally simpler pentopyranose acetates, that specific interactions may exist between ester groups within the molecule.

Investigations on the conformations in solution of the nonacylated analogs of acylic compounds such as those listed in Table I are warranted for two reasons in particular. First of all, acylated carbohydrates are rare in biological systems, whereas nonacylated forms are ubiquitous; information on the favored shapes and conformational dynamics of simple polyhydroxyalkyl chains is of direct relevance for gaining insight into numerous biological processes. Secondly, the additional complication of possible acyl-group interaction is absent from the unsubstituted compounds, and correlation with solid-state X-ray crystallographic data is facilitated; such data are much more abundant in the literature for the unsubstituted derivatives than for the acylated analogs, which offer considerably greater procedural difficulty. Although X-ray crystallographic studies have indicated[31] that the conformations of such unsubstituted acyclic sugar derivatives as the alditols are governed by factors similar to those set out for the molecules in solution, specific examples of solid-state crystallographic data and detailed pmr data for the same molecules in solution are notably lacking. One such comparison has been described in a recent report,[1a] where it was shown that 2-*S*-ethyl-2-thio-D-mannose diethyl dithioacetal adopts in the crystal an extended conformation closely analogous to that postulated from pmr data as the favored form in acetone-d_6 solution; the corresponding tetraacetate in chloroform-*d* solution likewise adopts a very similar conformation of the backbone chain, as judged from pmr-spectral data.

Fragmentary data have been reported for some unsubstituted phenylosotriazoles,[19,20] quinoxalines,[21] and benzylphenylhydrazones[22] in solution and a recent report[12] indicates that the 2-(tetrahydroxybutyl)benzothiazole isomers having the D-ribo, D-arabino, and D-xylo stereochemistry adopt a partially unstable $_2G^-$, a virtually exclusive planar zigzag, and a completely unstable conformation, respectively, in almost exact correspondence with their respective acetates.

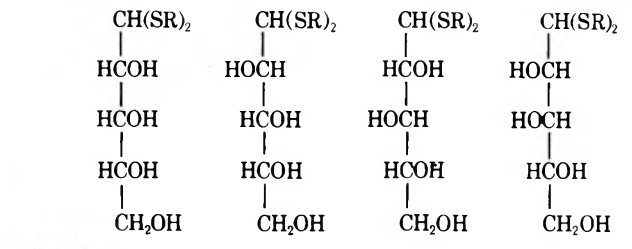
The present report describes the conformation in solu-

Table I
Favored Conformations of 1,2,3,4-Tetraacetoxybutyl Derivatives [R(CHOAc)$_3$CH$_2$OAc] in Solution as Determined by Pmr Spectroscopy

R	Favored conformation[a] D-ribo	D-arabino	D-xylo	D-lyxo	Ref
$-CH(SPh)_2$				**P** ($_4G^-$)	4
	$_3G^+$	P^b	$_3G^+$		5
$-CH(SEt)_2$	Unstable	**P**	Unstable	P^b	6
$-CH(OMe)_2$	[$_2G^-$]	P^b	Unstable	P^b	3
$-CH(NHCR')_2$ (R'=O)	[$_2G^-$]	**P**	$_3G^+$	$\mathbf{P}^b$	7
$-CH_2OAc$	Unstable	**P**	Unstable	*d*	9
$-CCH_2OAc$ (=O)	$_2G^-$	**P**	$_3G^+$		14
$-CO_2CH_3$[e]	$_2G^-$	**P**	Unstable	*P*	14
$-CHO$	$_2G^-$ ($_4G^-$)	**P**	Unstable	Unstable	4
$-CSNH_2$		**P** ($_4G^-$)[f]	$_3G^+$		13
$-C\equiv N$	$_2G^-$ ($_4G^-$)	*P* ($_4G^-$)[g]	$_3G^+$	Unstable	11
$-C(H)=CH(NO_2)$	$_2G^-$ ($_4G^-$)	**P** ($_4G^-$)	Unstable[h]		12
$-CHOAcC(H)=CH(NO_2)$		*P*		$\mathbf{P}^i$	10
		P^i	Unstable	*P*	17
	[$_2G^-$]	*P*	[$_3G^+$]		8
		*P*	[$_2G^-$][c]		13
 (5-deoxy)		*P* ($_4G^-$)	$_2G^-$[f]	*P*	2
		Unstable[f]			2
 (5-deoxy)		*P*	$_3G^+$[c,f]	*P*	2
		[$_2G^+$ $_4G^+$][f]			2

[a] *P* denotes planar, zigzag preponderates; **P** denotes planar, zigzag is virtually exclusive form; [*P*] indicates slight preference for the planar, zigzag (or other) conformation, but modest conformational instability and large contribution by two or more states to the conformational equilibrium;[26] $_2G^-$ denotes[27] the sickle obtained by 120° clockwise rotation of the remote atom along the C-2–C-3 bond; $_3G^+$ denotes[27] the sickle form obtained by 120° counterclockwise rotation of the remote atom along the C-3–C-4 bond; unstable signifies that there is no single, identifiable, favored conformation and indicates a high degree of conformational instability. [b] There is some instability about the C-1–C-2 bond. [c] There is some instability about the C-4–C-5 bond. [d] Identical with D-arabino; the symmetry of this derivative precludes conclusions about D-ribo and D-xylo conformations. [e] The $-CH_2OAc$ terminus is replaced by $-C(=O)CH_2OAc$. [f] Data are reported for the enantiomorph. [g] Data for this compound are reported also in ref 13. [h] Data for this compound are reported also in ref 28. [i] Rotation occurs about the C-1–C-2 axis to remove the nonextended C-1 substituent from 1,3 interaction with O-3. [j] Data for this compound are reported also in ref 15.

tion (methanol-d_4), as determined by analysis of 100-MHz pmr coupling constants, of two configurationally complete series of acyclic D-aldopentose derivatives having tetrahedrally hybridized end groups, namely D-ribose diethyl[32] (1) and diphenyl dithioacetal[9] (2), D-arabinose diethyl[33] (3) and diphenyl dithioacetal[9] (4), D-xylose diethyl[34] (5) and diphenyl dithioacetal[9] (6), and D-lyxose diethyl[35] (7) and diphenyl dithioacetal[8] (8).



Experimental Section

Compounds 1–8 had physical constants in agreement with published values. After exchange of the hydroxyl protons in D_2O, 100-MHz spectra of each compound [20 ± 2 mg in 0.3 ml of methanol-d_4 (Stohler) containing 3% Me_4Si as a lock signal and internal calibrant] were recorded on a Varian HA-100 spectrometer in the frequency-swept mode at a probe temperature of ~30°. Additions of pyridine-d_5 or of a solution (0.01 molar equiv per drop) of $PrCl_3 \cdot 6D_2O$ in methanol-d_4 were dropwise, with regular spectral scanning to monitor the effect of each addition. $PrCl_3 \cdot 6D_2O$ was prepared from the hexahydrate (Alfa-Ventron) by three repetitions of a cycle consisting of heating in two volumes of D_2O for 1 hr followed by lyophilization.

Table II
Pmr-Spectral Parameters Determined at 100 MHz for Solutions (~0.5 *M*) of Dithioacetals 1–8 in Methanol-d_4 at ~30°

H_i or $J_{i,j}$	Chemical shifts of H_i, τ, and coupling constants $J_{i,j}$, Hz							
	D-ribo		D-arabino		D-xylo		D-lyxo	
	Ethyl (1)	Phenyl[a] (2)	Ethyl[b] (3)	Phenyl[c] (4)	Ethyl[d] (5)	Phenyl (6)	Ethyl (7)	Phenyl (8)
$J_{1,2}$	8.0	1.6	9	8[e]	2.2	5.5	1.9	1.3
$J_{2,3}$	3.6	7.9	2		8.5	4.2	8.5	8.6
$J_{3,4}$	3.6[e]	3.6	8		4.5[e]	4.0	1.3	2.5
$J_{4,5}$		2.6	4			1.8	6.0	6.0
$J_{4,5'}$		7.2	6.5			9.1		
$J_{5,5'}$		10.3	12			11.6		
H-1	5.96	4.48	5.88	5.10	5.72	5.23	5.72	4.96
H-2	6.22	5.51	6.12	6.02	6.04	6.05	5.98	5.89
H-3	5.94	5.40	5.95			5.84	6.21	6.09
H-4	~6.28	5.71	6.19			6.27	6.05	6.03
H-5	~6.32	5.86	6.01			6.36	6.36	6.39
H-5′	~6.40	5.91	6.33	6.62	6.32	6.41	6.36	6.39
CH_2	7.29		7.23, 7.22		7.30, 7.26		7.31, 7.28	
CH_3	8.77		8.76, 8.75		8.74, 8.73		8.78, 8.76	
Ph		2.40–2.75		2.49–2.76		2.39–2.77		2.43–2.75

[a] Spectrum determined in 1:1 methanol-d_4–pyridine-d_5. [b] *J* values were determined in the presence of varying amounts of Pr^{3+}; chemical shifts were estimated by extrapolation back to zero concentration of the lanthanide. [c] In methyl sulfoxide-d_6; $J_{1,2}$ was unchanged in pyridine-d_5. [d] *J* values were determined in the presence of 30 millimolar equiv of $PrCl_3 \cdot 6D_2O$. [e] Measured spacings from X portion of presumed second-order systems.

Nmr Spectra. The 100-MHz pmr spectra of ~0.2 *M* solutions of the (hydroxyl proton-exchanged) dithioacetals 1–3 and 5–8 in methanol-d_4 at ~30° confirmed that the compounds were essentially free from contaminants and from hydroxylic protons; the insolubility of compound 4 in this solvent necessitated the use of methyl sulfoxide-d_6 or of pyridine-d_5 to obtain data on 4. The diphenyl dithioacetals 2, 4, 6, and 8 showed at lowest field between τ 2.40 and 2.75 a complex, ten-proton multiplet corresponding to the protons of the arylthio groups; at high field in the spectra of the corresponding diethyl dithioacetals are two three-proton triplets of identical or nearly identical chemical shift (near τ 8.75) and two two-proton quartets exhibiting similar chemical-shift relationships near τ 7.25, which are assigned to the methyl and methylene resonances, respectively, of the ethyl groups. The spectra of 1–3 and 5–8 are otherwise largely dissimilar, having the H-1 resonance at lowest field (near τ 5.8 for 1, 3, 5, and 7 or near τ 5.0 for 2, 6, and 8), generally as a doublet, and the remaining five resonances in the region from τ ~5.8 to ~6.4; the details of the skeletal proton resonances are discussed individually. A singlet near τ 5.2 in all these spectra is attributed to residual hydroxylic protons present in the solvent and the sample.

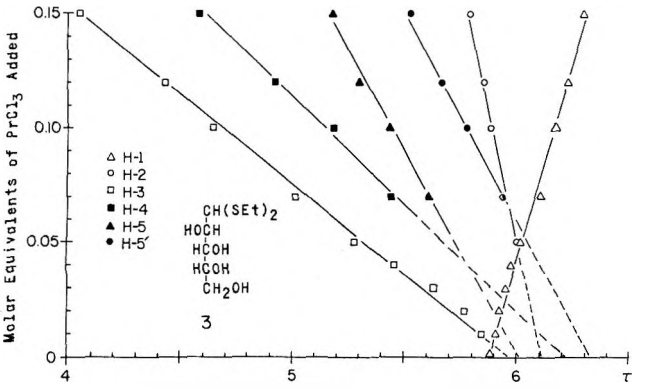


Figure 1. Plot of the chemical shifts of the proton resonances of D-arabinose diethyl dithioacetal (3) *vs.* the relative concentration of $PrCl_3 \cdot 6D_2O$ added. Values for the unperturbed chemical shifts were estimated by extrapolation back to zero concentration of Pr^{3+}.

Discussion

General Considerations Underlying the Deduction of Conformational Dispositions from Spin-Coupling Data. As in earlier studies,[4,6] it is assumed that interconversion between rotameric states is rapid, and that a pure antiparallel or a pure gauche relationship between vicinal pairs of protons gives rise to a coupling constant of ~9 or ~2 Hz, respectively. The latter assumption is reasonable, in that the effective electronegativity of the hydroxyl oxygen atom should be only slightly greater than that in the acetylated analog.

D-Arabinose Diethyl Dithioacetal (3). Compound 3 in methanol-d_4 gives a single, connected multiplet from τ 5.8 to 6.4 for the six skeletal-proton resonances. Incremental additions of $PrCl_3 \cdot 6D_2O$ in methanol-d_4 caused the identifiable separation of various signals in the spectrum at different lanthanide-ion concentrations (at the expense of some line broadening), and it was possible to measure the splittings of each resonance as it emerged from the envelope; at the low relative concentrations of Pr^{3+} employed, it appears that no significant alteration of conformation is caused by complexation[36] with the cation. Chemical-shift values were estimated by extrapolation of the approximately linearly dependent, paramagnetically altered field positions to zero concentration of added lanthanide, as illustrated in Figures 1 and 2. It is noteworthy that the lanthanide causes progressive downfield shifts for all protons except H-1: the signal of the latter undergoes moderate upfield shifts as the concentration of lanthanide increases.

The coupling parameters thus derived (Table II) accord with a dominant contribution to the conformational equilibrium[26] by a conformer having H-1 antiparallel to H-2, H-2 gauche to H-3, H-3 antiparallel to H-4, and an equilibrium about the C-4–C-5 bond between the forms having O-5 in the extended position (major) and in the gauche position remote from O-3 (minor), as shown by the planar zigzag representation **3a** and the derived conformation **3b**.

D-Arabinose Diphenyl Dithioacetal (4). Compound 4 is so insoluble in D_2O that hydroxyl-proton exchange could be accomplished only under extended refluxing, and it is also insoluble in methanol-d_4. The nmr spectra of solutions of 4 in pyridine-d_5 or methyl sulfoxide-d_6 exhibited gross similarity to those observed for the other seven examples in this study, displaying a well-separated H-1 doublet (from which $J_{1,2}$ was estimated) located between the aromatic resonances at low field and an effectively featureless, broadened envelope of signals from H-2 to H-5′; the addition of relatively enormous amounts of Pr^{3+} to these and similar solutions succeeded only in producing further broadening and negligible (~0.2 ppm/mol of Pr^{3+}) dislocations of the resonance positions, owing (presum-

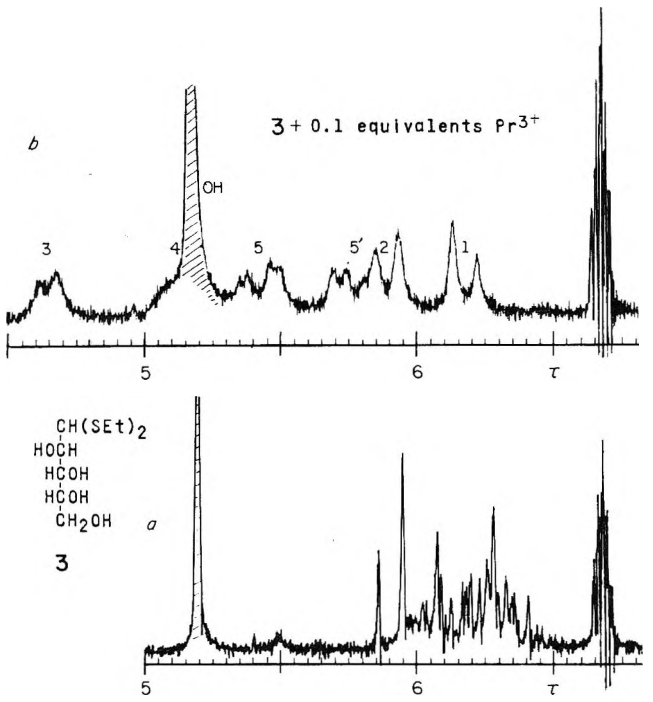


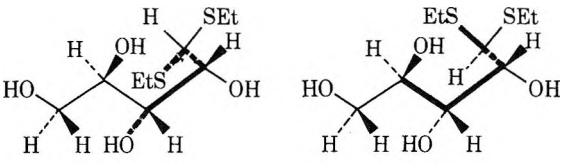
Figure 2. Pmr spectrum at 100 MHz of the chain protons of 3 in methanol-d_4 in the presence of (*a*) 0 and (*b*) 100 mequiv of $PrCl_3$; the signal to highest field is due to the solvent.

ably) to extremely efficient competition by the solvents for the cation.

As dominance of the conformational equilibrium of 4 by the planar, zigzag form is predicted by analogy with most of the examples in Table I, the preponderant extended conformation may be assumed[19-22] with reasonable confidence, even though only the $J_{1,2}$ value is available experimentally.

D-Lyxose Diethyl (7) and Diphenyl Dithioacetals (8). Closely similar spectra and conformations are observed for both 7 and 8. The H-1 resonance is observed at low field as a doublet ($J_{1,2} > 2$ Hz), followed, in turn, by the H-2, H-4, and H-3 signals and a doublet for the fortuitously equivalent, terminal methylene protons. The values in Table II were secured by approximate second-order analysis;[37] addition of $PrCl_3 \cdot 6D_2O$ or of $EuCl_3 \cdot 6D_2O$ failed to produce any spectral simplification. The values for $J_{1,2}$, $J_{2,3}$, and $J_{3,4}$ are clearly extreme ones, so that, despite the fact that the anisochronous methylene protons at C-5 resonate at the same field position and thus obscure any information contained in $J_{4,5}$ and $J_{4,5'}$, a conformational equilibrium may be specified (for both 7 and 8) that is absolutely dominated by the planar, zigzag form.

D-Ribose Diethyl Dithioacetal (1). The spectrum of 1 in methanol-d_4 is only partly separated and attempted simplification by additions of paramagnetic ions or of second solvents generally failed; observable H-1 and H-2 signals, however, allowed the determination of $J_{1,2}$ and $J_{2,3}$, and an estimation of $J_{3,4}$ (Table II). These values accord with the $_2G^-$ sickle conformation **1a**, which complements the elucidation of this arrangement for eight of nine examples in Table I, although the tendency toward intermediacy in the coupling magnitudes is suggestive of some degree of conformational nonuniformity (that is, instability). This observation points up a trend in the ribo column of Table I, which reveals that trigonally (or linearly) hybridized R groups seem to favor enhanced stability in the $_2G^-$ conformation compared to tetrahedral termini. Examination of the $_2G^-$ representations **1a** and **1b** (with particular reference to the intensified bonds) reveals that

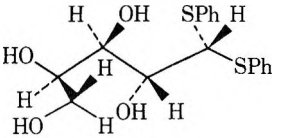


1a **1b**

these sickle forms are *not* totally free of parallel, eclipsed interactions where R is tetrahedral and disubstituted so that this trend in Table I can thus be rationalized. The slightly low $J_{1,2}$ value may also reflect some distortion of **1b** away from exact staggering about the C-1–C-2 bond in order to alleviate the parallel, C-4–S interaction.

D-Ribose Diphenyl Dithioacetal (2). The spectrum of 2 in methanol-d_4 was only partially resolved and, although sequential additions of either Pr^{3+} or Eu^{3+} failed to imporve signal separation before excessive line broadening prevailed, it was found that the addition of pyridine-d_5 (up to 50% of the final solvent mixture) effected sufficient spectral dispersion to permit second-order calculation by using the LAOCN3 program. The magnitude of $J_{1,2}$ was observed to be relatively solvent independent, as are other examples of this type.

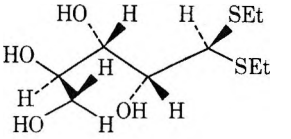
Coupling constants in Table II support a $_3G^+$ (sickle) conformation (**2a**) for 2 generated from the planar, zigzag



2a

form by counterclockwise rotation about the C-3–C-4 bond in order to place O-4 in the extended position formerly occupied by C-5; this conformation, which *is* free of eclipsed 1,3 interactions, has been reported for only one previous[9] example, the corresponding acetate. The possibility exists of an attractive interaction between the two aromatic groups, especially in methanol-d_4, although such an effect should serve to decrease, rather than increase, the effective size of the sulfur atoms.

D-Xylose Diethyl Dithioacetal (5). The addition of 30 mequiv of $PrCl_3 \cdot 6D_2O$ to a solution of 5 in methanol-d_4 produced the most informative spectrum of this compound, allowing measurement of $J_{1,2}$ and $J_{2,3}$ and estimation of $J_{3,4}$. The values of the former two coupling constants, 2.2 and 8.5 Hz, respectively, indicate a substantial energetic preference for the $_3G^+$ conformer **5a**, whereas



5a

the intermediacy of the somewhat uncertain $J_{3,4}$ (4.5 Hz) offers the possibility of a moderate degree of instability about the C-3–C-4 bond. The unavailability of coupling information for H-4–H-5 interactions precludes speculation about the C-4–C-5 rotameric state.

D-Xylose Diphenyl Dithioacetal (6). The spectrum of 6 in methanol-d_4, which is unique in this series of derivatives in having all of its resonances completely separated, is presented in Figure 3 to illustrate the resolution available in this solvent. In contrast to the preceding examples, the conformational behavior of 6 appears to feature extreme instability about the C-1–C-2–C-3 portion of the molecule, for which no discrete conformation can be identified as an important contributor to the rotameric equilibrium, but to exhibit almost total uniformity of confor-

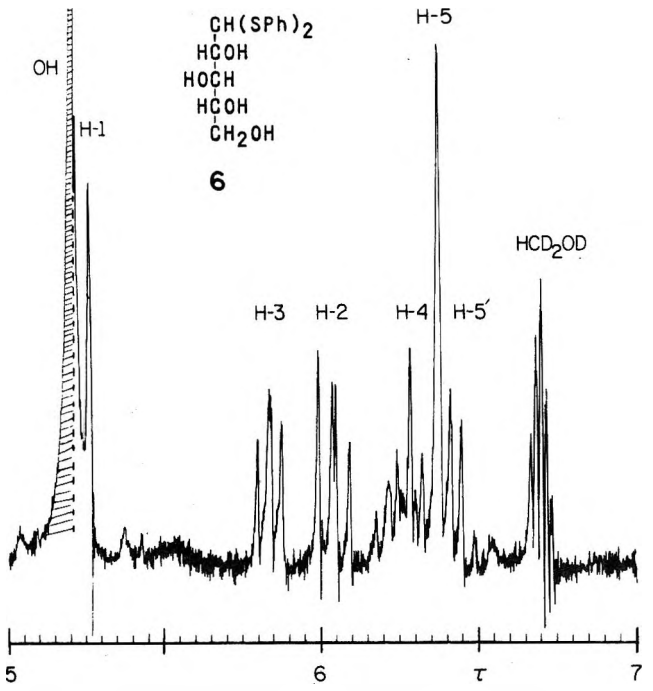


Figure 3. Pmr spectrum at 100 MHz of D-xylose diphenyl dithioacetal (6) in methanol-d_4.

mation in the C-3–C-4–C-5 segment. A decrease in effective size[38] of the arylthio sulfur atom, as anticipated (but not observed) for the xylo analogs, would act to minimize parallel, eclipsed interactions involving the sulfur atoms and O-3 or C-4 and might thus increase the relative stability of the zigzag and the $_2G^-$ conformations,[38] although no rationalization is immediately apparent for the seeming reversal of this effect in the ribo compounds **1** and **2**.

Summarizing, compounds **1**–**8** appear to follow the broad generalization that conformations incorporating eclipsed, 1,3 interactions between pairs of large groups tend to be relatively destabilized, so that, within the limits of their general validity, the conclusions drawn from studies of acetylated analogs can be extended with some degree of confidence to the unacylated carbohydrates. Quantitative, conformational predictions, either for acetylated or for unsubstituted acyclic carbohydrates, are currently out of the question, and, although a direct demonstration such as that presented[26c] to establish that conformations of the comparatively simpler aldopentopyranosyl derivatives are not amenable to quantitative correlation to simple, substituent-interaction parameters cannot be mustered, the prospect of such a simple correlation's evolving for the acyclic series is not optimistic.

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Registry No.—**1**, 7152-47-8; **2**, 6748-71-6; **3**, 1941-50-0; **4**, 6838-07-9; **5**, 13263-74-6; **6**, 28712-17-6; **7**, 6838-08-0; **8**, 30571-60-9.

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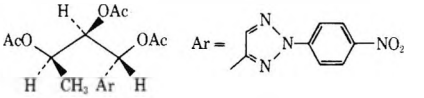
(38) The concept of effective size was invoked[6] originally to formulate the rationalization that the observed $_2G^-$ $_4G^-$ (enantiomorphic to $_2G^+$ $_4G^+$ in the D series) conformation of tri-*O*-acetyl-6-deoxy-L-*arabino*-hexulose *p*-nitrophenylosotriazole corresponds to a planar, zigzag form if the effective size of the methyl and heterocyclic substituents that represent the termini of the backbone in the Fischer projection is smaller than that of the two acetoxyl groups (O-2 and O-4 in the convention of Table I) occupying the extended positions of the reported conformation. The sensitivity of the conformation of this molecule to the presence of the physically remote nitro group highlights the weaknesses in arguments seeking to describe[17] this phenomenon quantitatively.



Isolation, Characterization, and Synthesis of *trans*-Pilosine Stereoisomers Occurring in Nature. Circular Dichroism and Mass Spectral Studies[1]

Enzo Tedeschi, Julia Kamionsky, Dov Zeider, and Simon Fackler

Plantex Ltd., The Dr. O. P. Pfeffer Industrial Center, Natanya

Shalom Sarel,* Varda Usieli, and Joseph Deutsch

Department of Pharmaceutical Chemistry, The Hebrew University School of Pharmacy, Jerusalem, Israel

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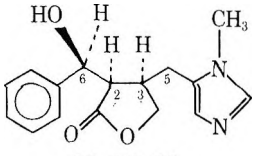
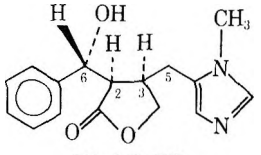
"Pilosine" of $[\alpha]^{20}D$ +83.9° is shown to be a 1:1 mixture of pilosine and isopilosine. Data on pure pilosine are described. The isolation and assignment of structure of a new pilosine constituent in *Pilocarpus jaborandi* are herein presented. From circular dichroism measurements it is concluded that pilosine, isopilosine, and epiisopilosine are of 2*R*,3*R*,6*S* (**1**), 2*S*,3*R*,6*S* (**4**), and 2*S*,3*R*,6*R* configurations (**3**), respectively. Optimal conditions for the production of **3**, **4**, and the fluoro derivatives (**3a** and **3b**), *via* aldol condensation between benzaldehyde, 2- and 4-fluorobenzaldehydes, and (3*R*)-pilosinine, in the presence of lithium methoxide, have been worked out. Effects of stereochemistry on trends of mass spectral fragmentations are discussed in terms of abundances of M − H_2O and *m/e* 223 ions being higher in the spectrum of the cis (**1**) than in that of the trans (**4**) isomer and in terms of [M − 1]/[M] ratios.

Until recently, only two of the four theoretically possible isomers (1–4) of (3*R*)-pilosine, namely, pilosine and isopilosine, were known to occur in nature. The synthesis[2] and the occurrence in nature of a 6 epimer of isopilosine has been reported lately.[1,3] According to Oberhansli,[4] pilosine, isopilosine, and epiisopilosine are assigned the 2*R*,3*R*,6*R*, 2*S*,3*R*,6*R*, and 2*S*,3*R*,6*S* configurations, respectively.



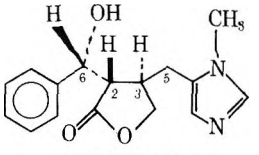
2*R*, 3*R*, 6*S*

1



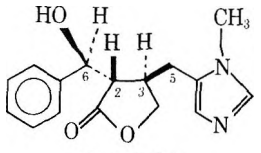
2*R*, 3*R*, 6*R*

2



2*S*, 3*R*, 6*R*

3



2*S*, 3*R*, 6*S*

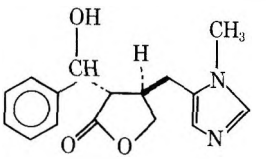
4

This paper gives an account of the isolation, characterization, and synthesis of the newly discovered naturally occurring imidazole alkaloid from a *Pilocarpus* species, shown to be epiisopilosine. Evidence is also adduced showing that the common crystalline pilosine of mp 176–178°, $[\alpha]D$ +83.9°[5], is in fact a "molecular compound" comprised of pilosine and isopilosine in equimolar ratio.

Later in this paper we shall show that carbon 6 in (−)-epiisopilosine should be assigned the *R* configuration rather than the *S* configuration as suggested above.[4] Accordingly, (+)-pilosine, (+)-isopilosine, and (−)-epiisopilosine should be assigned the 2*R*,3*R*,6*S* (**1**), 2*S*,3*R*,6*S* (**4**), and 2*S*,3*R*,6*R* (**3**) structures, respectively. This sense will be used throughout this paper when referring to pilosine.

The nmr spectrum (in DMSO) of "pilosine" prepared according to literature[5] was found to be complex. It appeared as spectra of two closely related compounds superimposed one on another, suggesting that the sample is in fact comprised of a 1:1 isomeric mixture (see Table I). To attain the desired genuine pilosine we set out to separate the two isomers, by first converting "pilosine" into the respective mixture of nitrates and then allowing it to undergo partial crystallization. This resulted in quick separation of isopilosine nitrate, leaving in solution the highly soluble pilosine nitrate. After neutralization and removal of precipitating "pilosine," the free base of genuine pilosine could be induced to crystallize as a dihydrate melting at 102–104°, $[\alpha]^{20}D$ +118°. The anhydrous form of pilosine was obtained by heating the dihydrate to 105° under high vacuum. When mixed with an equimolar quantity of isopilosine, the resulting material behaved as a typical "molecular compound" rather than a simple mixture and displayed identity in all respects with the starting "pilosine."

In the course of experiments aimed at extracting isopilosine from large leaves of *Pilocarpus jaborandi* we isolated a new constituent in 8.5% of the total alkaloid mixture which is in the range of 0.8–1.3% of the dried leaves. Other components characterized by tlc and spectroscopic methods were pilocarpine (70%) and isopilosine (10–18%). Whereas isopilosine gives on tlc plate a violet color on reaction with iodoplatinic acid, the new substance yields a blue color with the same reagent. Typically, pilosine exhibits double ir absorption at 1753 and 1765 cm^{-1}, whereas isopilosine and the new substance show single bands only, at 1765 and 1753 cm^{-1}, respectively. The uv absorption at 262.5 mμ is observed in the new substance only. The crystalline form of the new substance was analyzed as a $C_{16}H_{18}N_2O_3$ compound, and displayed an optical rotation of similar value but of opposite sign to that of isopilosine. On treatment with aqueous 20% KOH the new

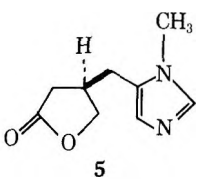


(+)-isopilosine or
(−)-epiisopilosine

base

retro aldol reaction

C_6H_5CHO +



5

(+)-(3*R*)-pilosinine

compound underwent aldol cleavage to yield pilosinine (**5**) and benzaldehyde. These data strongly suggested that the new substance must be a 6 epimer of isopilosine. This was

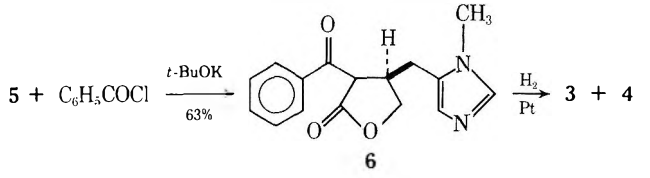
Table I
Characteristic Data of Isomeric Pilosines and Derivatives

Alkaloid	Mp, °C	$[\alpha]^{25}D$,[a] deg	Nmr, τ[b]	
"Pilosine" according to literature (ref 5)	176–178	+84	–CH(OH) –OCH_2– –NCH_3	d 4.82, d 5.0 d 6.30, d 6.08; d 5.91, d 5.50 s 6.72, s 6.55
Pilosine	172	+136.8	–CH(OH) –OCH_2 –NCH_3	d 4.82, J = 3 Hz d 6.30, d 5.50 s 6.72
Isopilosine	182.0–182.5	+33.5	–CH(OH) –OCH_2– –NCH_3	d 5.0, J = 3 Hz d 6.08, J = 5 Hz d 5.91, J = 5 Hz s 6.55
Epiisopilosine	182–184	−44.8	–CH(OH) –OCH_2– –NCH_3	d 4.76, J = 2 Hz d 6.08, J = 6.5 Hz d 5.64; J = 7.0 Hz s 6.95
6-Deoxypilosine	136–138	+98.3 +73.2[c]	–OCH_2– –NCH_3	d 5.75, d 6.20 s 6.70
o-Fluoroepiisopilosine	207–210	−39.9	–CH(OH)– –OCH_2– –NCH_3	d 4.56 d 6.02; J = 27 Hz d 5.58 J = 27 Hz s 6.80
p-Fluoroepiisopilosine	165–168	−28.2	–CH(OH)– –OCH_2– –NCH_3	d 4.75 d 6.08; J = 27 Hz d 5.65 J = 27 Hz s 6.83

[a] In ethanol (*c* 1). [b] In dimethyl sulfoxide, 60 MHz, Me_4Si as internal standard. [c] In water (c 1).

finally established by its comparison with a sample of epiisopilosine produced by synthesis.

A two-step synthesis of (−)-epiisopilosine in 17% overall yield has been recently reported by Link and Bernauer.[2] It involves an initial benzoylation of **5** in a stereoselective manner to yield **6**, followed by catalytic reduction in a nonstereoselective manner to yield (+)-isopilosine and (−)-epiisopilosine, each in approximately 25% yield.



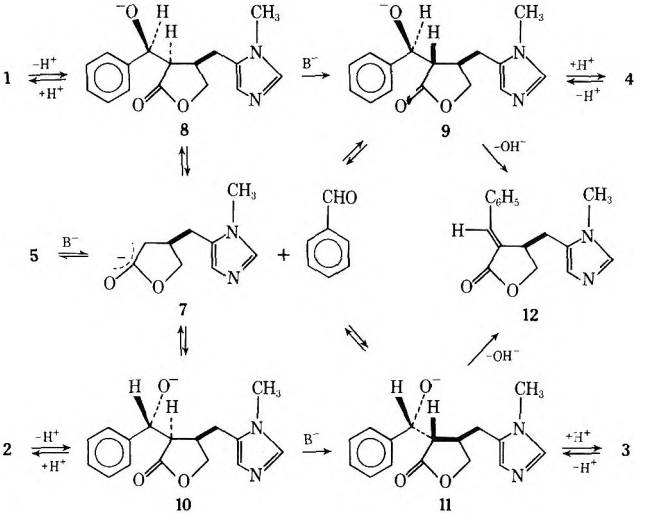
6

As part of a project aimed at total synthesis of pilosine and isopilosine we set to study the aldol reaction between **5** and benzaldehyde. This involved a study of the four reaction variables, catalyst, solvent, temperature, and time, on product distribution. Early in this study it became apparent that 20% alkali hydroxide favored the retrograde process. Alkali metal hydrides, on the other hand, although manifesting high potency in pushing the aldol reaction forward (**7** → **8** + **9** → **4** and **7** → **10** + **11** → **3**), promote also the concurrent path which involves a loss of hydroxide anion from the presumed anionic species **9** and **11** to yield anhydropilosine (**12**) (see Scheme I).

We then turned our attention to the use of alkali alkoxides in alcohols to catalyze this reaction. The total yield of pilosines was found to increase in the order $Mg(OCH_3)_2$ < $LiOCH_3$ < $NaOCH_3$ and, in parallel, the isomer ratio epiisopilosine/isopilosine increased from 0.8 to 1.6 to 2.7, reaching a top value of 14.0 in the case of potassium *tert*-butoxide in *tert*-butyl alcohol (compare expt 15 in Table II). The latter, however, is characterized by lower yields of pilosine stereoisomers, and by a significant increase in yields of **12** at the expense of the former (compare expt 12, 15, and 19 in Table II).

Analysis of product distribution as a function of reaction variables indicates that the ratio **12**/(**3** + **4**) is sensitive to proton concentration in the medium. For example, in presence of $LiOCH_3$–*t*-BuOH the ratio (**12**/(**3** + **4**) increases with the progress of reaction, but decreases remarkably on adding small amounts (5%) of methanol (expt 11). This suggests that the tendency of the less basic alkoxides, **9** and **11**, to lose a hydroxide ion (**9** → **12**, **11** → **12**) or to pick up a proton (**9** → **4**, **11** → **3**) is determined by the acid–base equilibrium existing in the system.

Scheme I



From product study it appears that the formation of epiisopilosine is governed by kinetic factors and isopilosine seems to be the thermodynamically controlled product. The nonobservance of the 2,3-cis isomers, **1** and **2**, among the reaction products is probably due to their instability in basic media; they are isomerized to the 2,3-trans isomers as soon as formed, as delineated in Scheme I (**8** → **9** → **4** and **10** → **11** → **3**).

With this background, we tried to react *o*- and *p*-fluorobenzaldehyde with **5** in presence of lithium methoxide in *t*-BuOH–MeOH at room temperature. In each case the

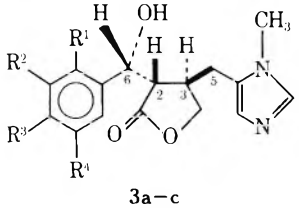
Table II
Effects of Reaction Conditions on Product Distribution Resulting from Base-Catalyzed Condensation between (+)-Pilosinine (5) and Benzaldehyde

Expt	Catalyst: Formula	Catalyst: Molar equiv	Solvent	Temp, °C	Time, hr	Product distribution, %: 5	4[a]	3[b]	12
1	KOH	0.5	H_2O	80	96	70	15		15
2		0.5	Dry EtOH	80	96	70	15		15
3	$Mg(OMe)_2$	2.0	MeOH	25	2	20	36	30	14
4		4.0	MeOH	25	48	10	80		10
5	LiOMe	2.0	MeOH	5	48	10	70		20
6		2.0	MeOH	25	0.5	75	20		5
7		2.0	*t*-BuOH	60	2	100			
8		2.0	*t*-BuOH	85	0.25	75	20		5
9		2.0	*t*-BuOH	85	2	70	20		10
10		2.0	*t*-BuOH	85	5	30	30		40
11		2.0	5% MeOH–95% *t*-BuOH	25	2	9.5	31	51	8
12	NaOMe	2.0	*t*-BuOH	25	2	0	26.5	73.4	0
13		1.0	*t*-BuOH	80	96	70	30		0
14		1.0	C_6H_6	80	168	30	40		30
15	$KOC(CH_3)_3$	2.0	*t*-BuOH	25	2	0	5	70	25
16	LiH	1.2	*t*-BuOH	40	0.5	0	25	20	55
17	NaH	1.2	DMSO	25	3	0	20	17	63
18		1.0	DMF	−5	2	0	70		30
19		1.0	*t*-BuOH	25	2	0	65		35
20		1.0	*i*-AmOH	5	18	10	60		30
21		1.0	C_7H_8	25	24	100	0		0

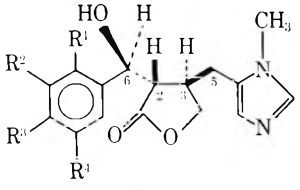
[a] Isopilosine. [b] Epiisopilosine.

stereoisomer which displays a strong negative Cotton effect at around 220 mμ could be isolated from the reaction mixture, and consequently these isomers were assigned the 6*R* configuration (see Experimental Section).

For biological testing we became interested in preparing 3′,4′,5′-trimethoxyisopilosine (**4c**) and 3′,4′,5′-trimethoxyepiisopilosine (**3c**), which bear a stereoelectronic resem-



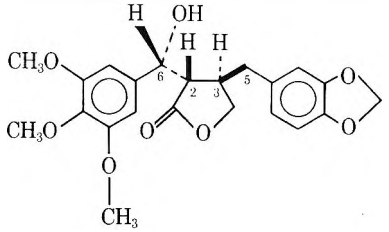
3a–c



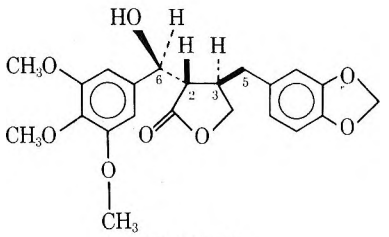
4a–c

a, $R^1 = F$; $R^2 = R^3 = R^4 = H$
b, $R^3 = F$; $R^1 = R^2 = R^4 = H$
c, $R^4 = H$; $R^2 = R^3 = R^4 = OCH_3$

blance to podorhizol (**13a**) and epipodorhizol (**13b**), respectively. Toward this end we allowed 3,4,5-trimethoxy-



2*S*, 3*S*, 6*R*.
13b

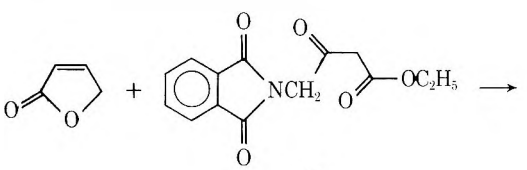


2*S*, 3*R*, 6*S*
13a

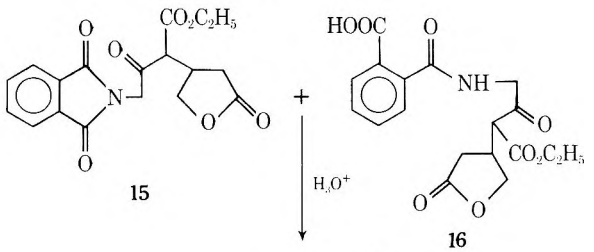
benzaldehyde to react with (3*R*)-pilosinine under various aldol reaction conditions but as yet with no success.

The various pathways to total synthesis of racemic (*rac*-**5**) and (3*R*)-pilosinine (**5**)[2] are well documented.[6-8] They are all characterized by poor yields. The key substance toward *rac*-**5** appears to be aminomethyl homopilosinyl ketone (**17**), which is amenable to a smooth reaction with methyl isothiocyanate followed by oxidation with ferric chloride.[7] We succeeded here in producing **17** in higher yields by allowing γ-crotonolactone to enter into Michael reaction with ethyl phthalimidoacetoacetate (**14**) in the presence of sodium ethoxide, followed by acid hydrolysis of the adduct mixture **15** and **16**.

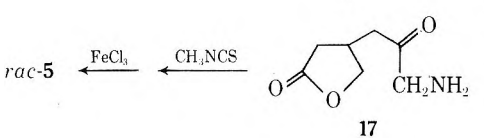
Since the optical resolution of *rac*-**5** is known, we regard the sequence **14** → *rac*-**5** → **5** → **3** + **4** described here as a new total synthesis of pilosines.



14



15 **16**



17

Anhydropilosine (**12**) can be hydrogenated to yield the *cis*-2,3-butyrolactone, 6-deoxypilosine (**18**). This stereochemistry is expected from addition of hydrogen to the less hindered side, in analogy with the reduction of anhy-

Table III
Relative Abundances of Prominent Peaks in the Mass Spectral Fragmentation of Isomeric Pilosines and Derivatives

m/e	Pilosine, %	Isopilosine, %	Epiiso-pilosine, %	*o*-Fluoroepiiso-pilosine, %	*p*-Fluoroepiiso-pilosine, %	Anhydro-pilosine, %
83	28.7	48.3	35.1	25.2	22.1	
95	100	100	100	100	100	100
96	47.0	57.2	53.2	45.0	42.0	9.7
105	24.5	28.6	25.6			
106	20.4	27.5	24.1			
123	20.4	12.1	11.0	37.9	31.5	
124				28.0	26.6	
137	10.2	4.4	8.3	14.9	3.9	
138	12.2	5.5	9.6	14.3	5.5	
180	6.1	6.6	8.3	7.7	7.7	
223	6.1	1.1	2.7			
241				2.9	1.1	
M − H_2O	6.1	2.2	5.4	6.7	2.8	5.1
M·+	5.1	4.4	8.9	6.1	3.3	
[M − 1]/[M]	0.27	0.43	0.30			

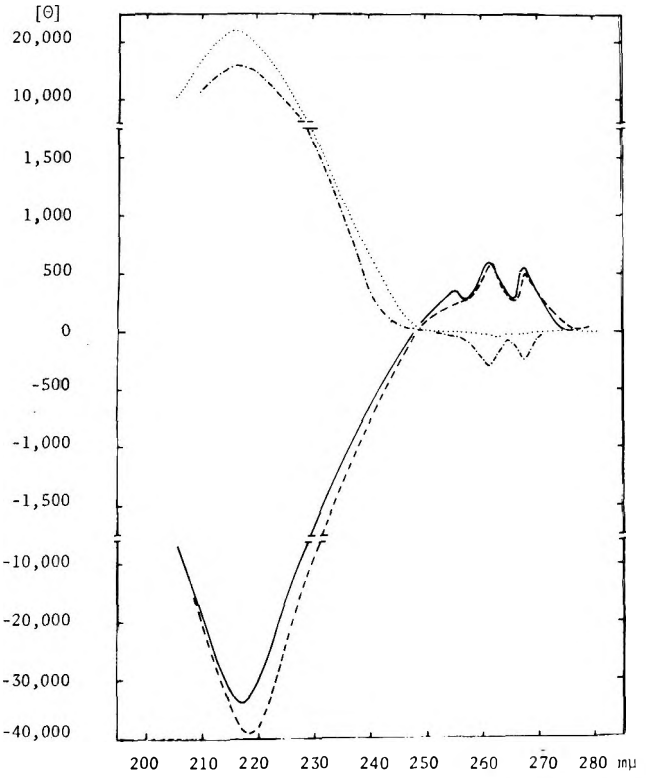
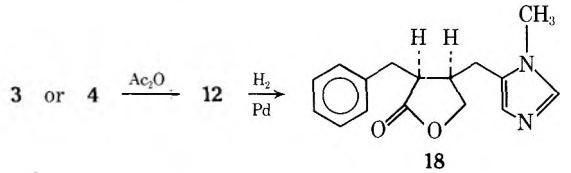


Figure 1. CD spectra of pilosine (. . . . .), isopilosine (- - - - - -), natural epiisopilosine (——), and synthetic epiisopilosine (- - - - -) in ethanol.

dropodorhizol to dihydroanhydropodorhizol[9] and that of hibalactone to isohinkinin.[10,11]



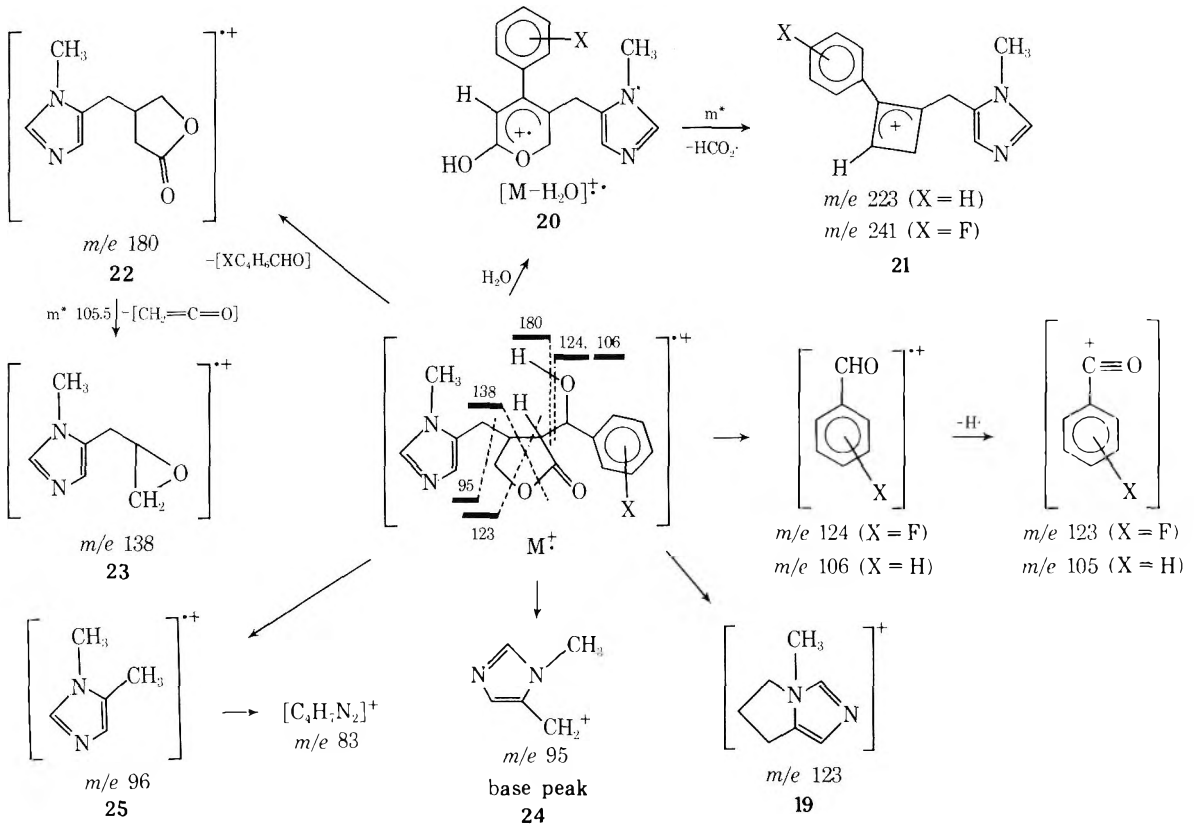
18

Circular Dichroism. The most striking difference between isopilosine and epiisopilosine is reflected in the signs of their optical rotations. It is positive for the former and negative for the latter. Furthermore, the circular dichroism curves of the two isomers are of the mirror image type (see Figure 1). Since these mirror image type bands around 220 and 260 mμ are associated with the phenyl absorptions, this indicates that the isomers are indeed epimeric at carbon 6. Moscowitz, Rosenberg, and Hansen[12a] have established the existence of optically active aromatic absorption bands for aromatic amino acids: the sign of the high-wavelength transition (^1L_b) of the phenyl group around 270 mμ is negative and the sign at the low-wavelength phenyl transition (^1L_a) around 220 mμ is positive for compounds with *S* configuration.[13] Following this consideration, pilosine and isopilosine, which exhibit positive dichroic bands in the low-wavelength region, should be assignd the 6*S* configuration and should therefore be formulated as structures **1** and **4**, respectively. Epiisopilosine, on the other hand, should be assigned the 2*S*,3*R*,6*R* configuration and be represented by formula **3**. Indeed, these are not in harmony with Oberhänsli's results as cited by Link and Bernauer.[2] It is not possible to draw firm conclusions on this matter before further proof, *e.g.*, chemical correlations, is produced.[14]

The two fluoro pilosine isomers described here should be assigned the same chirality, 2*S*,3*R*,6*R*, since both have negative CD bands around 218 mμ the amplitudes of which significantly compare with that of **3**.

Mass Spectra. The main modes of mass spectral fragmentation for pilosine and related compounds are shown in Scheme II. Examination of mass spectral data assembled in Table III reveals that the ion of highest intensity is the 1-methyl-5-imidazolylmethyl cation (**24**, *m/e* 95), which is accompanied by one or more of the tautomeric forms of 1,5-dimethylimidazolium cation (**25**, *m/e* 96). Other prominent peaks are the molecular ion and the ionic fragments corresponding to M − H_2O, M − H_2O − HCO_2, M − XC_6H_4CHO, M − XC_6H_4CHO − C_2H_2O, M − $C_9H_7O_3$, ionized corresponding benzaldehyde, and benzoylium ion. This suggests that there are five principal electron impact induced fragmentations of the pilosines, comprising three modes of C-C bond ruptures and two of C-O. These involve (a) cleavage of the 2,6 bond with retention of charge by either moiety [*m/e* 180 (**22**) ← M^+· → *m/e* 106 or 124]; (b) cleavage of the 3,5 bond, with or without hydrogen rearrangement, but with retention of the charge on the imidazole substituent (M^+· → **24** and **25**) which could transform into its valence tautomer, *N*-methylpyrimidinium ion; (c) rupture of the lactone ring at two sites, (i) between carbons 2 and 3, and (ii) between carbon 4 and the ring oxygen to yield an ionic species of structure **19**; (d) loss of water involving a hydrogen at C-3, to yield an ion of structure **20** rather than that of **12**, since the ionic distribution in the mass spectra of pilosine stereoisomers (**1**-**4**) is entirely different from that of **12** (see Table III). The 2.8- and 5.6-fold greater abundances of the respective ions **20** and **21** in the mass spectrum of the 2,3-cis (pilosine) as compared to that of the trans isomer

Scheme II



(isopilosine) (see Table III) suggests that the primary reaction $M^{+\cdot} \rightarrow$ **20** could be of considerable diagnostic importance.

Of particular interest, because of its variation with the stereochemistry, is another primary mass spectral reaction featured by the loss of hydrogen from the parent molecular ion (M). Thus, the [M − 1]/[M] ratio in isopilosine is 1.6-fold greater than in pilosine, and 1.4-fold greater than in epiisopilosine. This observation merits further work to establish whether it would be possible to deduce the stereochemistry in the imidazole alkaloids, and in related lactones of the Podophyllum-Lignane series,[10] by mass spectrometry.

Experimental Section

Ir spectra were recorded on a Perkin-Elmer Model 237 spectrometer, uv spectra on a Unicam Model Sp 800A spectrometer, nmr spectra on a 60-MHz Varian spectrometer with TMS as internal standard, optical rotations on a Perkin-Elmer polarimeter, CD spectra with a Cary 60 recording spectropolarimeter, and mass spectra on a Varian MAT CH-5 spectrometer using the direct inlet system. The electron energy was maintained at 70 eV and the ionization current was maintained at 20 μA. The abundances of ions from primary fragmentations are given in percentages relative to the *m/e* 95 ion peak and assembled in Table III. Thin layer chromatographies were performed on silica gel plates.

γ-Crotonolactone, bp 102–107° (24 mm), was prepared according to the literature.[15]

Ethyl γ-phthalimidoacetoacetate (14), mp 111–113° (lit.[16] mp 110°), was obtained in 63% yield by steam-induced hydrolysis of diethyl phthalimidacetomalonate (mp 66–68°, 65% yield) according to Mehrotra and Verma.[16]

Isolation of Pilosine According to Voigtlander and Rosenberg.[5] The title product (recrystallized from ethanol), mp 176–178°, $[\alpha]^{25}D$ +84 ± 1° (*c* 1, EtOH) ("pilosine"), was isolated (0.8–1.3%) from the weak acidic mother liquor left after recrystallization of pilocarpine nitrate which was obtained from the leaves of *Pilocarpus microphyllus* according to the literature.

Separation of "Pilosine" into Pure Forms of Pilosine and Isopilosine. To a suspension of "pilosine" (23 g), $[\alpha]^{20}D$ +82° (*c* 1, EtOH), in 35 ml of water, concentrated nitric acid was added dropwise until pH 3 was reached. While the acid was being added, the suspension gradually turned into a clear solution. After a few crystals of isopilosine nitrate were added and scratching was performed to initiate crystallization, the solution was kept at 0° for more than 2 days. The crystalline isopilosine nitrate thus obtained was collected by filtration (10 g, 35% yield), mp 77–82°. The free base was recovered from the nitrate salt in the usual way: ir (KBr) 1765 cm^{-1}; uv (C_2H_5OH) λ_{max} 214, 249, 253, 259, 265, 269 mμ (ϵ21,700. 110, 144, 180, 143, 75); CD (C_2H_5OH) λ_{max} 217 ± 1, 261, 267 mμ (θ +15,660 ± 11.5%, −325, −250).

After neutralization of the mother liquor with 10% NaOH and filtration, 14.7 g of a solid was obtained. Recrystallization from 10 volumes of EtOH yielded 9.2 g of crystals, mp 180°, $[\alpha]^{20}D$ +89° (*c* 1, EtOH). The mother liquor was concentrated to ⅓ of the volume and kept at 0° for 2 days. Pilosine dihydrate (2.5 g) crystallized out, mp 101–103°, $[\alpha]^{20}D$ +116.7° (*c* 1 EtOH). Further purification was carried out by recrystallization from absolute EtOH, mp 101–104°, $[\alpha]^{20}D$ +118° (*c* 1, EtOH). By high-vacuum drying of the purified compound while gradually raising the temperature to 105°, anhydrous pilosine was obtained: uv (C_2H_5OH) λ_{max} 212, 249, 254, 259, 265, 269 mμ (ϵ 15,399, 121, 157, 193, 154, 86); CD (C_2H_5OH) λ_{max} 217, 262, 267 mμ (θ_{max} +21,740, −50, −25); ir (KBr) 1753 and 1763 cm^{-1}.

Isolation of Epiisopilosine from Leaves of *Pilocarpus macrophyllus.* Ground dry leaves (1 kg) of *Pilocarpus jaborandi* were soaked in 800 ml of 6% Na_2CO_3 solution for 1–2 hr. The leaves were then extracted six or seven times, each time with 6 l of benzene at 50–55° for 45 min, until complete extraction of alkaloids was effected. The alkaloids were extracted from the benzene with 5% H_2SO_4, and after decolorization the aqueous layer was gradually basified to pH 9 (5% NH_4OH) while being successively extracted with CH_2Cl_2. The organic extracts were dried on Na_2SO_4 and after evaporation of the solvent 15 g of an oily residue was obtained. To the residue dissolved in acetone (15 ml), dry gaseous HCl was added at a temperature below 15° until a pH of 5.0–5.5 was obtained. The solution was kept at 5° for 24 hr and the crystalline pilocarpine hydrochloride (11–12 g) thus obtained was separated by filtration, washed with acetone, and dried.

The mother liquor was evaporated to yield an oil, which was dissolved in water, decolorized, and neutralized to pH 7.2 with 5% NH_4OH. The aqueous layer was successively extracted with CH_2Cl_2 while the pH was gradually increased to 9. The organic extracts were dried on Na_2SO_4 and the solvent was evaporated. To the residue 1.5 volumes of acetone was added and the suspension thus obtained was kept at 5° for 8–10 hr and then filtered to

yield 0.6–1.0 g epiisopilosine, $[\alpha]D$ −42° (*c* 1, EtOH). The epiisopilosine was further purified by recrystallization from 7 volumes of dry ethanol: R_f 0.50 (blue spot with iodoplatinic acid) with $CHCl_3$–MeOH (9:1) as eluent, R_f 0.76 with $CHCl_3$–MeOH (7:3); ir (KBr) 1753 cm^{-1}; uv (C_2H_5OH) 212, 249, 254, 259, 262.5, 265.5, 269 mμ (ε 13,600, 114, 149, 181, 156, 142, 106); CD (C_2H_5OH) λ_{max} 218 ± 1, 255. 261.5, 267 mμ (θ_{max} −39,200 ± 9%, +375, +600, +550).

The mother liquor was kept at 5° for an additional 48 hr after a few crystals of isopilosine were added. A mixture of pilosine and isopilosine (1.3–2.0 g) was obtained, $[\alpha]D$ +45–+65° (*c* 1, EtOH).

Anhydropilosine (12), mp 133–134° (lit.[5] mp 131–132°), $[\alpha]^{25}D$ +68.8° [lit.[5] $[\alpha]$ +62.3° (*c* 2, EtOH)], ν_{KBr} 1735 cm^{-1} (C=O), uv (C_2H_5OH) 285 mμ (ε 1.8 × 10^4), was prepared by the acetic anhydride induced dehydration of isopilosine according to the literature:[5] CD (C_2H_5OH) λ_{max} 212, 227, 241, 274.5 314.5 mμ (θ_{max} +8840, −6765, +2080, −4720, +2010.

6-Deoxypilosine (18) Nitrate. Anhydropilosine (**12**, 16 g) was dissolved in 180 ml of ethanol, 1 g of 10% Pd/C was added, and the mixture was agitated under atmospheric hydrogen for 2 hr. After removal of catalyst and solvent, the oily residue was dissolved in a 6:1 mixture of methyl ethyl ketone and ethanol, concentrated nitric acid was added to pH 4.5, and the resulting 6-deoxypilosine nitrate (80%) was allowed to recrystallize from dry ethanol: $\nu_{C=O}$ ($CHCl_3$) 1760–1770 cm^{-1}; uv (C_2H_5OH) λ_{max} 233, 249, 254, 260, 263, 266, 269 mμ (ε 1400, 140, 150, 170, 140, 120, 86); CD (C_2H_5OH) λ_{max} 217, 255, 261.5, 268, 272 mμ (θ_{max} +23,280, +550, +990, +1100, −110); mass spectrum *m/e* 270 (M^+), 123, 96, 95 (base peak), 83.

Aldol Cleavage of Epiisopilosine to (3*R*)-Pilosinine (5) and Benzaldehyde. Epiisopilosine (1 g) was dissolved in 40 ml of 20% aqueous potassium hydroxide and allowed to reflux for 8 hr, until benzaldehyde ceased to evolve. After neutralization with dilute sulfuric acid, the precipitating starting material which remained intact was removed, the filtrate was extracted with chloroform, and then solvent was evaporated, leaving behind 780 mg of crystalline (3*R*)-pilosinine (**5**): mp 78–79° (from anhydrous acetic acid); $[\alpha]^{17}D$ +17.1° (*c* 1, EtOH) [lit.[5] $[\alpha]^{25}D$ +14.35° (*c* 4, in H_2O)]; ir (KBr) 1758, 1770 cm^{-1}; uv (C_2H_5OH) λ_{max} 224 (sh), 232 mμ (ε 90, 900); CD (C_2H_5OH) 221 mμ, $[\theta]_{max}$ −1485.

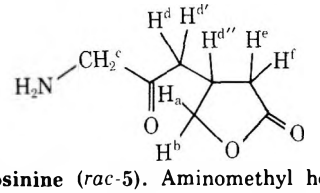
Michael Addition of 14 to γ-Crotonolactone. To a cold solution of sodium ethoxide (17 mmol) in dry ethanol (prepared by dissolving 0.4 g of sodium metal in 40 ml of dry ethanol) was added dropwise with stirring during 8 hr a solution containing a mixture of 10.5 g (125 mmol) of γ-crotonolactone and 13.8 g (50 mmol) of **14** in dry ethanol (40 ml) and the resulting mixture was kept for 24 hr at 50°. Stirring was continued for an additional 24 hr at room temperature, and the resulting precipitate of adduct was filtered, dissolved in benzene, washed with dilute acid, and dried. After the benzene solution was concentrated, the adduct, ethyl α-[3-butyryllactone-γ-(phthalimido)]acetoacetate (**15**), crystallized out (6.1 g): mp 134–135° (from benzene); R_f 0.7 [tlc, MeOH–C_6H_6 (9:1)]; ir ($CHCl_3$) 1783, 1758 (phthalimide), 1728 cm^{-1} (ester).

Anal. Calcd for $C_{18}H_{17}O_7N$: C, 60.16; H, 4.78; N, 3.90. Found: C, 59.90; H, 4.70; N, 3.80.

Further concentration of mother liquor afforded 1 g of the corresponding half-amide (**16**): mp 142–144° (from benzene); R_f 0.2 [tlc, MeOH–C_6H_6 (9:1)]; ir ($CHCl_3$) 1735 (phthalamide), 1725 (ester), 1695 (COOH), 1645 cm^{-1} (internal hydrogen bond).

Anal. Calcd for $C_{18}H_{19}O_8N$: C, 57.30; H, 5.08; N, 3.70. Found: C, 57.10; H, 5.0; N, 3.65.

Acid Hydrolysis of 15 + 16. Formation of Aminomethyl Homopilosinyl Ketone (17). A mixture of **15** (6.1 g) and **16** was dissolved in 20% hydrochloric acid (100 ml) and refluxed for 5 hr, the precipitated phthalic acid was removed by filtration and ether extraction, and the water solution was evaporated to dryness, providing 3.2 g (84%) of the amino ketone hydrochloride **17**: mp 140–143°; ir (KBr) 3420, 1755 (lactone), 1720 cm^{-1} (ketone); nmr (D_2O) τ 5.1–5.3 (1 H, dd, H^a), 5.6–5.9 (1 H, dd, H^b), 5.8 (2 H, s, H^c), 6.9 (3 H, m, H^d + $H^{d'}$ + $H^{d''}$) 7.15 (1 H, dd, H^e), 7.40 (1 H, dd, H^f).



Racemic Pilosinine (*rac*-5). Aminomethyl homopilosinyl ketone (**17**) was treated first with methyl isothiocyanate and then with ferric chloride according to the method of Preobrashensky[7] to yield racemic pilosinine (45%): mp 69–71°; nitrate mp 116–118° (lit.[8] mp 116°); ir (KBr) 1778 cm^{-1} (lactone).

Aldol Condensation between (3*R*)-Pilosinine (5) and Benzaldehyde. The procedure given in the following describes in outline the optimal conditions for the production of pilosine stereoisomers from (3*R*)-pilosinine (**5**) and benzaldehyde. Benzaldehyde (10.6 g, 100 mmol) and (3*R*)-pilosinine (1.8 g, 10 mmol) were mixed and stirred with 60 ml of the appropriate solvent containing 10–40 mmol of the base catalyst, at temperatures and durations of time as indicated in Table II. The reaction mixture was then poured on crushed ice and acidified with hydrochloric acid to pH 1, excess benzaldehyde was removed by extraction with chloroform, and the aqueous phase was first heated for 30 min to accomplish lactonization and then cooled. It was then neutralized to pH 7.2 with the aid of 10% sodium hydroxide, and the resulting precipitate containing reaction products was collected and finally subjected to analysis.

The percentage of anhydropilosine (**12**) was estimated by means of uv spectroscopy, and that of isopilosine and epiisopilosine from both nmr spectroscopy and optical rotations.

Preparation of (−)-Epiisopilosine with the Aid of Lithium Methoxide in Dry *tert*-Butyl Alcohol–Methanol. A mixture of (3*R*)-pilosinine (18 g) and benzaldehyde (106 g) was added with shaking to a solution of lithium methoxide (7.6 g) in a mixture of *tert*-butyl alcohol (400 ml) and methanol (20 ml), allowed to shake for 2 hr at room temperature, and then processed as described above. The reaction product (15 g, $[\alpha]D$ −23.7°) consisted of 27% isopilosine and 73% epiisopilosine. After two recrystallizations from dry ethanol (7 volumes) the optical rotation of the purified form was found to be constant, $[\alpha]D$ −44.8° (*c* 1, EtOH).

***o*-Fluoroepiisopilosine (3a) and *p*-Fluoroepiisopilosine (3b).** To a solution of lithium methoxide (2.22 g) in a mixture composed of 150 ml of *tert*-butyl alcohol and 12 ml of methanol was added with stirring (3*R*)-pilosinine (5.4 g, 30 mmol) and o-fluorobenzaldehyde (10 g) and the mixture was allowed to shake at room temperature for 24 hr and then processed as described above. Recrystallization from 20 volumes of 95% ethanol yielded 4.3 g of **3a**: ir (KBr) 1757 cm^{-1} (lactone); uv (C_2H_5OH) λ_{max} 211, 256, 261, 267, mμ (ε 7900, 430, 560, 520); CD (C_2H_5OH) λ_{max} 217 ± 1, 245, 252.5, 255, 261, 265, 267 mμ (θ_{max} −34,530 ± 10%, −918, −1570, −1628, −2309, −1598, −1865). From the mother liquor, 2.4 g of a mixture of isomers could be obtained.

Anal. Calcd for $C_{16}H_{17}O_3N_2F$: C, 63.1; H, 5.6; N, 9.2; mol wt, 304. Found: C, 62.6; H, 5.3; N, 9.0; mol wt, 304 (mass spectrum).

In a similar way, epiiso-*p*-fluoropilosine (**3b**) was produced in 47% yield: ir (KBr) 1765 cm^{-1}; uv (C_2H_5OH) λ_{max} 210, 265, 271 mμ (ε 12,500, 800, 740); CD (C_2H_5OH) λ_{max} 218 ± 1, 265, 295 $m\mu_{max}$ (θ_{max} −22,080 ± 6.3%, +190, −266).

Anal. Found for $C_{16}H_{17}O_3N_2F$: C, 62.8; H, 5.3; N, 9.1; mol wt, 304.

Attempted Condensation between 3,4,5-Trimethoxybenzaldehyde and 5. A mixture of (3*R*)-pilosinine (2.7 g, 15 mmol) and 3,4,5-trimethyoxybenzaldehyde (9.8 g, 50 mmol) was added with stirring to a solution of lithium methoxide (1.2 g) in a mixture of *tert*-butyl alcohol (75 ml) and methanol (6 ml) and allowed to stand overnight at room temperature. After processing of the reaction mixture in a fashion described above the starting materials were recovered unchanged.

Registry No.—**1**, 13640-28-3; **3**, 38993-92-9; **3a**, 51240-45-0; **3b**, 51240-46-1; **4**, 491-88-3; **4** nitrate, 51268-51-0; **5**, 38993-86-1; *rac*-**5**, 38993-85-0; *rac*-**5** nitrate, 51240-47-2; **12**, 51222-06-1; **14**, 13855-80-6; **15**, 51240-48-3; **16**, 51240-49-4; **17** hydrochloride, 51240-50-7; **18** nitrate, 51240-52-9; benzaldehyde, 100-52-7; γ-crotonolactone, 497-23-4; o-fluorobenzaldehyde, 446-52-6; *p*-fluorobenzaldehyde, 459-57-4.

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(14) (−)-Mandelic acid and its (−) derivatives which have been shown by chemical means [P. Pratesi, A. La Manna, A. Campiglio, and V. Ghislandi, *J. Chem. Soc.*, 2069 (1958); 4062 (1959)] to belong to the *R*-(D) series exhibit negative Cotton effects around 220 mμ. Caution was suggested[13] when ring substituents are present, since both (*S*)-(+)-3,4-methylenedioxy- and (*S*)-(+)-4-methoxymandelic acid appear to have positive CD bands around 274 mμ. On the other hand, the (*S*)-(+)-bromo acid acts like (*S*)-(+) parent acid in showing a small negative maximum at 283 mμ.
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Synthesis of *O*-Methyl-L-serine and N^{α}-*tert*-Butyloxycarbonyl-*O*-methyl-L-serine

Robert S. Hodges*[1] and R. B. Merrifield[2]

The Rockefeller University, New York, New York 10021

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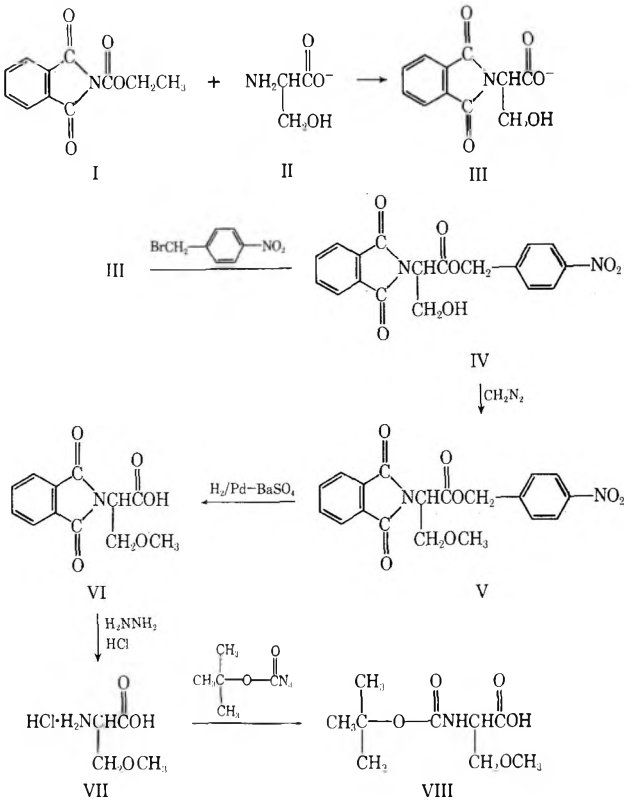
O-Methyl-L-serine and N^{α}-tert-butyloxycarbonyl-*O*-methyl-L-serine were synthesized from L-serine *via* the intermediate N^{α}-phthaloyl-L-serine *p*-nitrobenzyl ester. The ether was made with diazomethane and protecting groups were removed by catalytic hydrogenolysis and hydrazinolysis. Optical purity of the *O*-methyl-L-serine was established. The methyl ether function was stable to the conditions used for acid hydrolysis of peptide bonds and to the acidic conditions used in solid-phase peptide synthesis.

O-Methyl-L-serine was required as an amino acid analog of serine and threonine in the solid-phase peptide synthesis of some new derivatives of ribonuclease A. It was of interest because the hydroxyl groups of serine and threonine can act either as proton donors or acceptors in hydrogen bond formation in proteins, while the methoxyl group of *O*-methyl-L-serine should function only as a proton acceptor. *O*-Methyl-DL-serine was prepared by Schlitz and Carter[3] *via* mercuration of methyl acrylate. Resolution into *O*-methyl-L-serine and N^{α}-acetyl-*O*-methyl-L-serine was achieved by hydrolysis of the N^{α}-acetyl derivative with hog renal acylase.[4] In addition, *N*-phthaloyl-*O*-methyl-L-serine was prepared by Fles and Belenović[5] by resolution of *N*-phthaloyl-*O*-methyl-DL-serine *via* the brucine salt. This paper is concerned with the development of a more convenient synthetic route starting with L-serine.

Four routes were examined: first, a two-step synthesis in which L-serine was acylated to Boc-L-serine followed by methylation of the alcoholic function with methyl iodide in sodium–liquid ammonia at −40°; second, a three-step synthesis in which Boc-L-serine was converted to the *p*-nitrophenyl ester and then methylated with diazomethane (this would have the advantage that the nitrophenyl ester could be used directly for peptide synthesis); third, a four-step synthesis in which Boc-L-serine was converted to the *p*-nitrobenzyl ester with *p*-nitrobenzyl bromide, then methylated with diazomethane, and finally hydrogenated to give Boc-*O*-methyl-L-serine. In preliminary experiments these first three methods were generally unsatisfactory, resulting in poor yields and giving products that were difficult to purify.

The fourth synthesis involved six steps from L-serine but the high yields and easy purification made it the procedure of choice (Scheme I). Phthaloylation of L-serine (II) was carried out in good yield and with retention of optical purity by the method of Nefkens[6,7] using *N*-ethoxycarbonylphthalimide (I) in aqueous sodium carbonate. The *N*-phthaloyl-L-serine (III) was converted to the *p*-nitrobenzyl ester (IV) by a procedure similar to that used by

Scheme I



Shields and Renner[8] for the synthesis of *N*-benzyloxycarbonyl-L-serine *p*-nitrobenzyl ester. IV was methylated under mild conditions with diazomethane in the presence of fluoroboric acid as catalyst[9,10] to give V, which was converted to *N*-phthaloyl-*O*-methyl-L-serine (VI) by catalytic hydrogenolysis. *O*-Methyl-L-serine hydrochloride (VII) was obtained in 53% overall yield from L-serine by hydrazinolysis with hydrazine hydrate and precipitation of the phthalylhydrazide with HCl. Finally, N^{α}-Boc-*O*-

methyl-L-serine (VIII) was prepared from Boc-azide by the Schwyzer[11] method.

The O-methyl-L-serine prepared by this procedure was shown to be optically pure (<0.1% of D isomer) by the chromatographic method of Manning and Moore.[12] The methyl ether was stable to treatment with 1:3 (v/v) trifluoroacetic acid–methylene chloride for 72 hr at 25° and to HF for at least 4 hr at 0°. Such stability is important if peptides containing this analog are to be synthesized by the solid-phase method. The methyl ether was also stable to hydrolysis by 3 N p-toluenesulfonic acid under conditions where proteins are completely hydrolyzed. O-Methyl-L-serine can be separated and quantitated on the ion-exchange column of the amino acid analyzer.

Experimental Section

Melting points were obtained on a Thomas-Hoover melting point apparatus and are uncorrected. Thin layer chromatography was performed with Analtech silica gel GF plates (0.25 mm); compounds were visualized with 254-nm light or spraying with ninhydrin in acetone followed by heating. Nuclear magnetic resonance (nmr) spectra were measured with a Varian Associates A-60 spectrometer; chemical shifts are expressed in parts per million (ppm) downfield from internal standard tetramethylsilane.

N-Phthaloyl-L-serine (III). L-Serine (18.9 g, 0.18 mol) and 19.1 g (0.18 mol) of sodium carbonate were dissolved in 135 ml of water, followed by 41.6 g (0.19 mol) of N-carboethoxyphthalimide (I). The reaction mixture was stirred at room temperature for 2.5 hr. After filtration, 6 N HCl was added to pH 1.8 and phthaloyl-L-serine (III) was extracted with ethyl acetate. The organic phase was washed with cold water and a saturated solution of sodium chloride, dried over anhydrous $MgSO_4$, and filtered. Thin layer chromatography of the filtrate on silica gel [solvent I, chloroform–methanol–acetic acid (85:10:5), or solvent II, 1-butanol–formic acid–water (75:15:10)] showed a single ninhydrin-positive and ultraviolet-absorbing spot corresponding to N-phthaloyl-L-serine. R_f values from thin layer chromatography of N-phthaloyl-L-serine and L-serine were 0.32 and 0.06 for solvent I and 0.88 and 0.50 for solvent II, respectively.

N-Phthaloyl-L-serine p-Nitrobenzyl Ester (IV). p-Nitrobenzyl bromide (41.0 g, 0.19 mol) was dissolved in the ethyl acetate solution (1 l.) of N-phthaloyl-L-serine from the above reaction and 25.0 ml (0.18 mol) of triethylamine was added. The solution was refluxed for 20 hr, let cool to room temperature, and stored at −20° overnight. The solution was filtered on a Büchner funnel and the crystalline product was washed with 1 N sodium bicarbonate and water and dried under high vacuum, yield 43.1 g (65%), mp 179.5–180.8°. An analytical sample was dried under vacuum at 100° over P_2O_5 for 20 hr, $[\alpha]^{25}D$ −46.1° (c 0.8, DMF).

Anal. Calcd for $C_{18}H_{14}N_2O_7$: C, 58.38; H, 3.81; N, 7.57. Found: C, 58.38; H, 3.91; N, 7.52.

R_f values from thin layer chromatography on silica gel: solvent I, chloroform–acetic acid (95:5), N-phthaloyl-L-serine p-nitrobenzyl ester, 0.59; N-phthaloyl-L-serine, 0.19; p-nitrobenzyl bromide, 0.94; solvent II, chloroform–methanol (50:1), N-phthaloyl-L-serine p-nitrobenzyl ester, 0.54.

N-Phthaloyl-O-methyl-L-serine p-Nitrobenzyl Ester (V). To 800 ml of ether, 200 ml of 40% KOH was added and mixture was cooled to 5°. To this solution 66 g of N-nitroso-N-methylurea[10] was added in small portions over a period of several minutes with continued cooling and stirring. The deep yellow ether layer was decanted into 200 ml of ether containing KOH pellets and allowed to stand for 3 hr at 5° to remove dissolved water. The ether solution, containing approximately 0.4 mol of diazomethane, was decanted and used without distillation. The N-phthaloyl-L-serine p-nitrobenzyl ester (11.5 g, 0.031 mol) was dissolved in a minimum volume of dichloromethane at 5° (approximately 2 l.). Fluoroboric acid (0.1 ml) was diluted to 5 ml with ether. A 0.75-ml aliquot (0.22×10^{-3} mol) was added to the reaction mixture. The diazomethane solution was added in 250-ml aliquots (about 0.1 mol) every 5 hr.

The extent of the reaction was followed by thin layer chromatography on silica gel [solvent, chloroform–methanol (50:1); R_f values, N-phthaloyl-L-serine p-nitrobenzyl ester, 0.54; N-phthaloyl-O-methyl-L-serine p-nitrobenzyl ester, 0.79]. Starting material was absent after 20 hr. The solution was evaporated to dryness; the resulting oil was triturated with ether, reevaporated to dryness, and dried under high vacuum over P_2O_5 for 20 hr to give a white powder (11.9 g, 100%). An analytical sample was twice crystallized from ether–petroleum ether and dried for 16 hr under high vacuum at 100° to furnish the methyl ether V as a white powder: mp 126.2–126.8°; $[\alpha]^{25}D$ −48.4° (c 1.0, CH_2Cl_2); nmr ($CDCl_3$) 3.34 (s, 3 H, OCH_3), 4.11 (d, 1 H, J = 6.4 Hz, $CH^{\beta 1}$), 4.15 (d, 1 H, J = 8.8 Hz, $CH^{\beta 2}$), 5.27 (d of d, 2 H, $J_{\alpha,\beta 1}$ = 6.4, $J_{\alpha,\beta 2}$ = 8.8 Hz, CH^{α}), 5.31 (s, 2 H, CO_2CH_2), 7.47 (d, 2 H, J = 8.5 Hz, aromatic near CH_2), 7.81 (AB quartet, 4 H, J = 4 Hz, phthalimide), and 8.17 ppm (d, 2 H, J = 8.5 Hz, aromatic near NO_2).

Anal. Calcd for $C_{19}H_{16}N_2O_7$: C, 59.37; H, 4.20; N 7.29. Found: C, 59.37; H, 4.36; N, 7.29.

N-Phthaloyl-O-methyl-L-serine (VI). The ester V (10.0 g) was dissolved in 300 ml of glacial acetic acid. To this solution was added 2 g of 5% palladium on $BaSO_4$. Hydrogenation was carried out for 24 hr at a pressure of 50 psi. The catalyst was filtered off and washed several times with 50% acetic acid and the combined filtrates were evaporated to dryness *in vacuo* at 40°. Water (25 ml) was added to the residue and the solution was reconcentrated. This procedure was repeated several times. The residue was dissolved in 500 ml of ethyl acetate and extracted with seven 100-ml portions of a saturated sodium bicarbonate solution. The combined aqueous phase was acidified to pH 2.0 with 6 N HCl and extracted with five 200-ml portions of ethyl acetate. The combined organic phase was dried over anhydrous $MgSO_4$, filtered, and evaporated to dryness to give an oil. An analytical sample was crystallized from hot water and dried under high vacuum over P_2O_5 for 20 hr at 65° to give long, needle-like, white crystals: mp 98.0–99.0° (lit.[5] mp 101–102°); $[\alpha]^{25}D$ −66.9° (c 1.0, ethyl acetate) [lit.[5] $[\alpha]^{20}D$ −48.1° (c 2.0, ethanol)].

Anal. Calcd for $C_{12}H_{11}NO_5$: C, 57.83; H, 4.45; N, 5.46. Found: C, 57.78; H, 4.58; N, 5.58.

R_f values from thin layer chromatography on silica gel: solvent I, chloroform–methanol (50:1), N-phthaloyl-O-methyl-L-serine p-nitrobenzyl ester, 0.89; N-phthaloyl-O-methyl-L-serine, 0.11; solvent II, chloroform–acetic acid (95:5), N-phthaloyl-O-methyl-L-serine, 0.40.

O-Methyl-L-serine Hydrochloride (VII). The oily N-phthaloyl-O-methyl-L-serine (about 0.026 mol) obtained in the above reaction was dissolved in a minimum volume of methanol (about 300 ml) and 1.75 ml (0.052 mol) of hydrazine hydrate (95%) was added. The solution was stirred at room temperature for 20 hr, at which time the absence of an N-phthaloyl-O-methyl-L-serine spot was observed on thin layer chromatography on silica gel [solvent, chloroform–methanol–acetic acid (85:10:5)]: R_f values phthaloyl hydrazide, 0.57; N-phthaloyl-O-methyl-L-serine, 0.65 (both observed as ultraviolet-positive spots); O-methyl-L-serine hydrochloride, 0.01 (ninhydrin positive). The solution was filtered to remove phthaloyl hydrazide and the filtrate was evaporated to dryness *in vacuo*. The residue was dried for 16 hr under high vacuum over concentrated H_2SO_4 to remove the last traces of hydrazine. The phthaloyl hydrazide was precipitated by addition of 150 ml of 0.5 N HCl. After cooling for 2 hr at 4° the solution was filtered and the filtrate was freeze-dried to a white powder. The residue was triturated with 500 ml of acetone, let stand at −20° overnight, and filtered. The solid material was washed with cold acetone and dried under high vacuum, yield of O-methyl-L-serine hydrochloride after hydrogenolysis and hydrazinolysis 3.30 g (82%), overall yield from L-serine 53%. An analytical sample was twice crystallized from absolute ethanol–ether and dried under high vacuum over P_2O_5, first at room temperature and then at 56° for 10 hr, mp 197° dec, $[\alpha]^{25}D$ +17.9° (c 0.4, methanol).

Anal. Calcd for $2(C_4H_9O_3N)\cdot HCl$: C, 34.98; H, 6.97; N, 10.19; Cl, 12.91. Found: C, 35.47; H, 6.94; N, 10.24; Cl, 12.71.

R_f value from thin layer chromatography on silica gel [solvent, 1-butanol–acetic acid–water (65:15:20)], O-methyl-L-serine hydrochloride, 0.36.

Nmr analysis in trifluoroacetic acid showed 3.60 (s, 3 H, OCH_3), 4.18 (d, 2 H, J = 4.0 Hz, OCH_2), and 4.7 ppm (m, 1 H, CH).

Optical Purity of O-Methyl-L-serine. L-Leucine-N-carboxyanhydride was coupled[12] with O-methyl-L-serine and O-methyl-DL-serine and the separation of the diastereomeric dipeptides was performed on a 0.9 × 60 cm column of Beckman AA 15 resin on the Beckman 120B amino acid analyzer at a flow rate of 66 ml/hr at 56°. A 0.2 N sodium citrate buffer, pH 3.20, was used for column elution. This buffer was prepared by addition of concentrated HCl to the pH 3.49 buffer concentrate supplied by Beckman. The elution time of the dipeptides and amino acids are shown in Table I. Less than 0.1% of D isomer was present in the synthetic O-methyl-L-serine.

Acid Stability of O-Methyl-L-serine. The use of O-methyl-L-

Table I
Elution Conditions of Dipeptides and Amino Acids

Dipeptide	Elution pH	Peak position, min
L-Leu-L-Ser(Me)	3.20	264
L-Leu-D-Ser(Me)	3.20	222
L-Leu	3.20	325
DL-Ser(Me)	3.20	72

Table II
Recovery of *O*-Methyl-L-serine after Acid Hydrolysis with 3 *N* Toluenesulfonic Acid Containing 0.2% Indole

Hydrolysis time, hr	Recovery of *O*-methyl-L-serine, %
0	100
22	97.5
48	94.2
72	91.6

serine in peptide synthesis requires that the methyl ether be acid stable. The stability to various acidic conditions was determined by quantitative amino acid analysis. After a 72-hr exposure to 25% trifluoroacetic acid–75% dichloromethane at 25°, 100% of the methyl ether was recovered. Anhydrous HF for 1 hr at 0° is generally sufficient for cleavage of peptides from resin supports. Recovery of the methyl ether was 100% after treatment with HF for 4 hr at 0°.

O-Methyl-L-serine was heated in 6 *N* HCl for 24 hr at 110°. Amino acid analysis indicated a 64% hydrolysis of the methyl ether to serine. However, hydrolysis at 110° with 3 *N* *p*-toluenesulfonic acid containing 0.2% indole as described by Liu and Chang[13] resulted in very small losses of *O*-methyl-L-serine (Table II) under conditions where proteins are completely hydrolyzed. Currently 4 *N* methanesulfonic acid[13,14] at 110° for 22 hr is being used routinely for this purpose.

Chromatographic Separation of *O*-Methyl-L-serine. The *O*-methyl-L-serine hydrochloride cochromatographed with the *O*-methyl-DL-serine standard on the Beckman AA 15 resin in a 0.9 × 60 cm column of the amino acid analyzer under two sets of conditions. *O*-Methyl-L-serine elutes in the identical position of threonine using the standard conditions of amino acid analysis, that is, 56° and a first buffer of pH 3.49. To separate *O*-methyl-L-serine from threonine, the incorporation of 1-propanol in the first buffer is required. The first six amino acids of the standard amino acid mixture, aspartic acid, threonine, serine, glutamic acid, and proline, are separated from each other and from *O*-methyl-L-serine using a temperature of 76° and a 0.2 *N* sodium citrate buffer, pH 2.90, containing 7% by volume 1-propanol. This buffer was prepared by addition of concentrated HCl to the pH 3.49 buffer concentrate supplied by Beckman and addition of alcohol during dilution. The conditions for the complete amino acid analysis of protein hydrolysates containing *O*-methyl-L-serine will be reported in subsequent papers on the solid-phase synthesis of *O*-methyl-L-serine-containing peptides.

N^{α}-*tert*-Butyloxycarbonyl-*O*-methyl-L-serine (VIII). A mixture of *O*-methyl-L-serine hydrochloride ($C_4H_9O_3N \cdot \frac{1}{2}HCl$, 1.56 g, 11.4 mmol), Boc azide (2.90 ml, 20 mmol), magnesium oxide (1.2 g, 30 mmol), dioxane (30 ml), and water (15 ml) was stirred at 40–45° for 36 hr. The reaction mixture was cooled and the magnesium oxide was removed by filtration and washed twice with 50 ml of water. The combined filtrate and washings were extracted three times with ether. The aqueous phase was chilled with ice and acidified with 0.5 *N* HCl to pH 2.0 on the pH-Stat. The aqueous phase was extracted with six portions of ethyl acetate (75 ml). The combined organic phase was washed with a saturated sodium chloride solution, dried over anhydrous $MgSO_4$, and evaporated to dryness *in vacuo*. The residue was dissolved in 50 ml of ethyl acetate, cyclohexylamine was added, and the N^{α}-*tert*-butyloxycarbonyl-*O*-methyl-L-serine cyclohexylamine salt was crystallized by the addition of ether. The product was filtered and dried over P_2O_5 for 20 hr under high vacuum: yield 2.5 g (80%); mp 153.4–154.5; $[\alpha]^{25}D$ + 19.8° (*c* 1.0, methanol).

Anal. Calcd for $C_{15}H_{30}N_2O_5$: C, 56.58; H, 9.50; N, 8.80. Found: C, 56.69; H, 9.48; N, 9.01.

R_f values from thin layer chromatography on silica gel [solvent, chloroform–methanol–acetic acid (85:10:5)]: N^{α}-Boc-L-serine (CH_3), 0.76; N^{α}-Boc-L-serine, 0.45.

Registry No.—I, 22509-74-6; II, 56-45-1; III, 4702-14-1; IV, 51293-43-7; V, 51293-44-8; VI, 51293-45-9; VII, 51293-46-0; VIII cyclohexylamine salt, 51293-48-2; *p*-nitrobenzyl bromide, 100-11-8; *N*-nitroso-*N*-methylurea, 684-93-5.

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(2) Supported in part by Grant AM 01260 from the U. S. Public Health Service and by a grant from the Hoffmann-La Roche Foundation.
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A Synthesis of Aromatic Steroids

Marcel Harnik,* Roza Szpigielman, Ya'akov Lederman, and Joseph Herling

Ikapharm Research Department, Ramat-Gan, Israel

Ze'ev V. I. Zaretskii

The Daniel Sieff Research Institute, The Weizmann Institute of Science, Rehovoth, Israel

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Starting with the allyl derivative **2**, the diketo acid **1a** was prepared. Reaction of its acyl chloride **1c** with the enamines **4a** and **4b** furnished the tetrones **5a** and **5b**, respectively. Enol benzoylation followed by hydrogenation afforded the triones **7**, **8**, and **9**, which could be correlated with **10**, the key internediate in Torgov's total synthesis of steroids. Treatment of **9** with *p*-toluenesulfonic acid in boiling toluene led to a mixture of six crystalline compounds, the structure of four of which is presented. Two of these, **14a** and **15a**, are known tetracyclic structures having the 14β configuration.

Described herein is a relatively short synthesis of aromatic steroids, proceeding through the intermediates **2**, **1**, **5**, **6**, and **9**—connected by heavy arrows in Chart I—and leading, among others, to the known racemic 11-oxygenated compounds **14a** and **15a**.

The novelty of this synthesis stems from the use of the hitherto unknown diketo acid **1a**, which we obtained from 2-allylcyclopentane-1,3-dione (**2**)[1] by treatment with permanganate followed by scission with periodic acid. Some reactions of this eight-carbon fragment of rings C and D were next investigated. The methyl ester **1b** was unreactive in Claisen-type reactions: no condensation with α- or β-tetralone, or self-condensation, in the presence of sodium hydride, took place. Also the anhydride **3** and the chloride **1c** were unreactive in Friedel–Crafts condensations with aromatic compounds (naphthalene, 1,7-dimethoxynaphthalene) in the presence of aluminum chloride.

Synthetic uses of the pyrrolidine enamines **4a** and **4b** have been previously reported,[2,3] especially in conjunction with preparation of heterocyclic steroids.[4] We have now found that in the 3-deoxy series the acid chloride **1c** monoacylates the enamine **4a**, and after aqueous work-up the β-diketone **5a** could be obtained, exhibiting the expected positive ferric chloride color reaction. In the 3-methoxy series the acyl chloride **1c** reacted in an analogous manner with the enamine **4b** to give the β-diketone **5b**.

Further elaboration of the steroid skeleton required that the carbonyl oxygen at C_8 be removed from the β-diketone moiety. One approach suggested preferential enol thio ether formation at this site and subsequent treatment with deactivated Raney nickel.[5] However, selective attack of **5b** by methanethiol at position 8 could not be achieved. An alternative solution was sought by selective enol acylation at this position. With acetic anhydride the results were not encouraging, but the enol benzoate **6** could be satisfactorily obtained by the action of benzoyl chloride in pyridine.

The benzoate **6** was then subjected to hydrogenation in methanol in the presence of 5% palladium on charcoal and three compounds were obtained: (a) the known trione **7**, mp 113–116°, (b) its Δ^8 derivative **9**, mp 118–122°, and (c) the 8ξ-hydroxy derivative **8**, mp 142–144°, all of which were further interrelated as follows. Compound **8** (*m/e* 330) was dehydrated with *p*-toluenesulfonic acid in boiling benzene to the unsaturated ketone **9**, and this, in turn, could be readily hydrogenated to the triketone **7** (*m/e* 314). From the evidence at hand it is not clear whether the transformation of the enol benzoate **6** into the trione **7** proceeds only through the intermediates **8** and **9**, or if direct hydrogenolysis of **6** into **7** is also taking place.

At this stage we had occasion to confirm the identity of **7** by direct comparison with a sample which we prepared according to Zakharychev and collaborators,[6] and also Daniewski, *et al.*[7] The former treated **10** (Chart II), the key intermediate in the Torgov total synthesis of estrogens, with mercuric acetate, and the latter group used the more convenient peracid oxidation of **10**. In both cases the product was the hemiacetal **11b**, which in solution is in equilibrium with the tautomeric open-chain structure **11a**. The hemiacetal **11b** and its 14-acetate were converted[6,7] by *p*-toluenesulfonic acid in boiling benzene into the trione **7**. In a restudy of the epoxidation reaction of **10** with *m*-chloroperbenzoic acid, using slightly different experimental conditions, we were able to isolate not only **11b**, but also the alcohol **8**, which must be the product of further epoxidation of **11** followed by an acid-catalyzed rearrangement. We found the ketol **11** to be unreactive toward the Jones reagent and also perchloric acid at room temperature, but hydrogenation followed by Jones oxidation furnished the saturated trione **7**. Finally, treatment of **11** with *N*-bromosuccinimide and perchloric acid yielded the unsaturated triketone **9**, accompanied by small amounts of **7** and the known[8] naphthalenic trione **12**.

The next stage of the synthesis was concerned with attempts to cyclize the trione **9** to tetracyclic structures. Cyclodehydration with *p*-toluenesulfonic acid proceeded much more sluggishly than in the 11-deoxy series. In boiling toluene a complex mixture of air-sensitive compounds was obtained, some of which were products of disproportionation. Thus after a 6-hr reflux an oily mixture was obtained, which on careful chromatography yielded the trione **12**; after a 16-hr reflux five additional products were isolated. One was *rac*-11-keto-14-isoequilenin-3-methyl ether (**14a**), mp 158–160°, reported by Birch and Subba Rao.[9] Another identified cyclization product was *rac*-11-keto-8-dehydro-14-isoestrone-3-methyl ether (**15a**), mp 174–176°, identical with a sample obtained by Jones oxidation of the known 17β-ol analog **15b**.[10]

The structure of the next three isolated compounds is less certain. One, melting at 125–128° (*m/e* 294), contained three oxygen atoms and exhibited a single carbonyl maximum at 5.82 μ, but no hydroxyl absorption. A doublet centered at 6.0 ppm points to a H–C–O moiety, probably at position 11. These data, including maxima at 230 and 302 nm, are compatible with the oxido structure **13**. The two remaining compounds, mp 164–166 (*m/e* 294) and 192–193° (*m/e* 312), contain a hydroxyl group and are at present under investigation. See Table I for nmr spectra.

Mass Spectrometry. One of us has previously shown[11] that the mass spectral behavior of 8(14)-seco estrone de-

Chart I

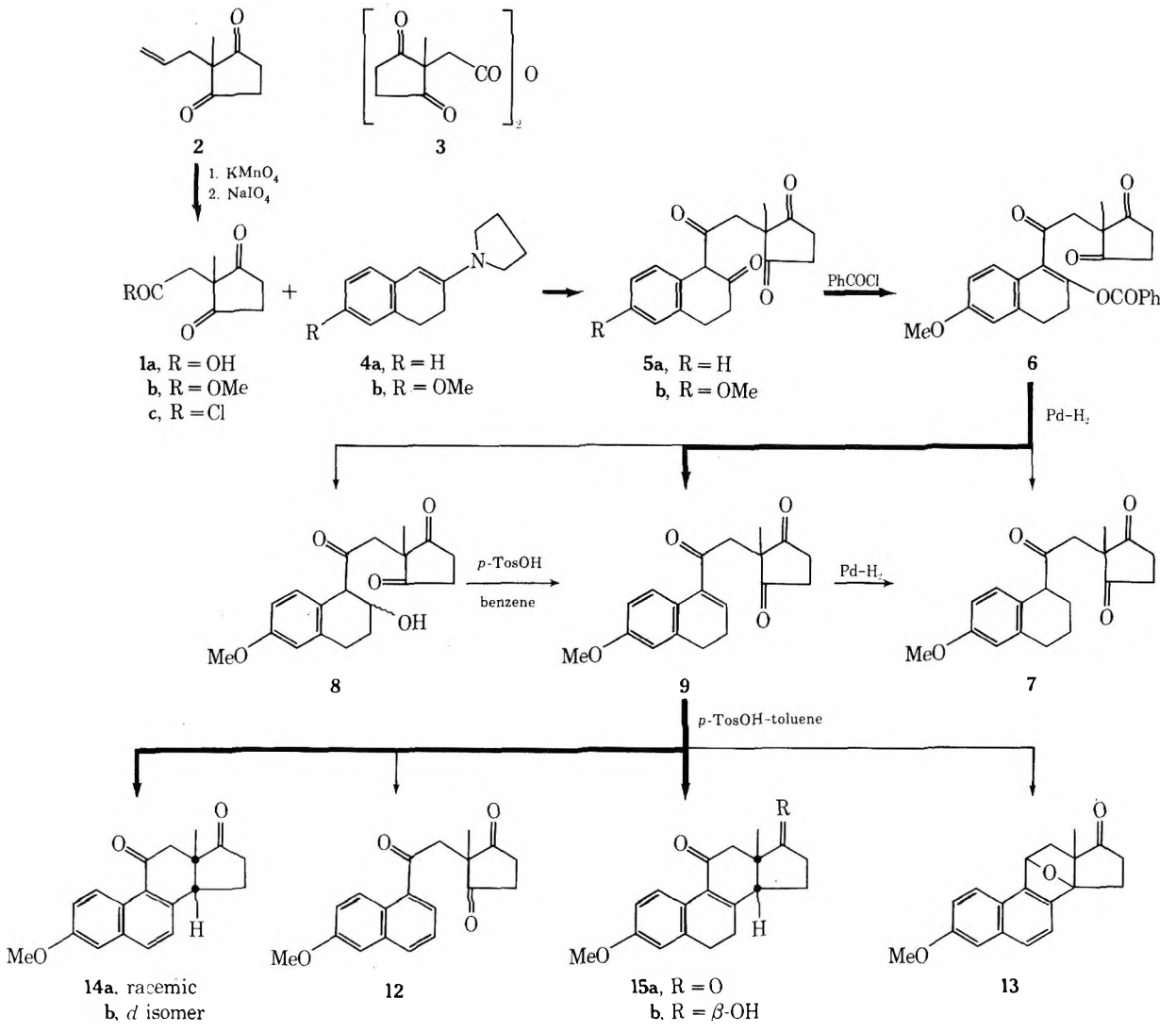
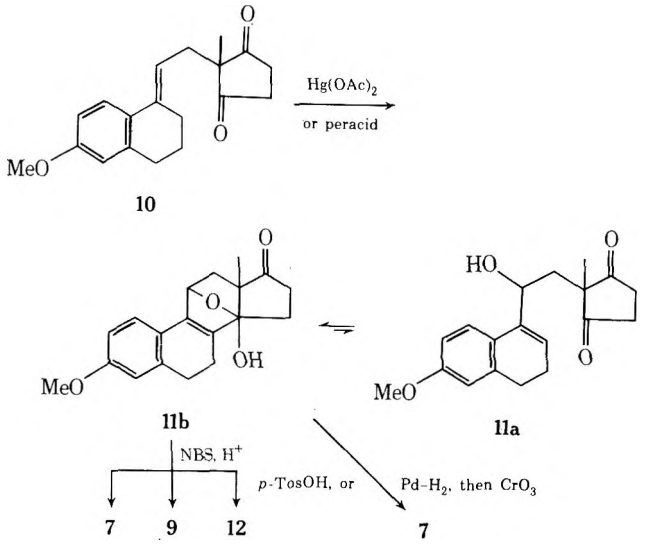


Chart II



rivatives is characterized by the formation of the bicyclic ion a (Chart III), which gives rise to the base peak in the spectrum of 8(14)-seco-14-keto-D-homoestrone-3-methyl ether. The present study shows that the seco ketones **5**, **7**, **8**, and **9** undergo the same type of decomposition on electron bombardment, the most intense fragmentation reaction being the cleavage of the benzylic 9–11 bond and the formation of the ions a, b, c, and h, respectively. In triketones **7**, **8**, and **9** a simple cleavage of this bond takes place, whereas the formation of the ion h from the molecular ion of **5b** is accompanied by migration of a hydrogen

Chart III

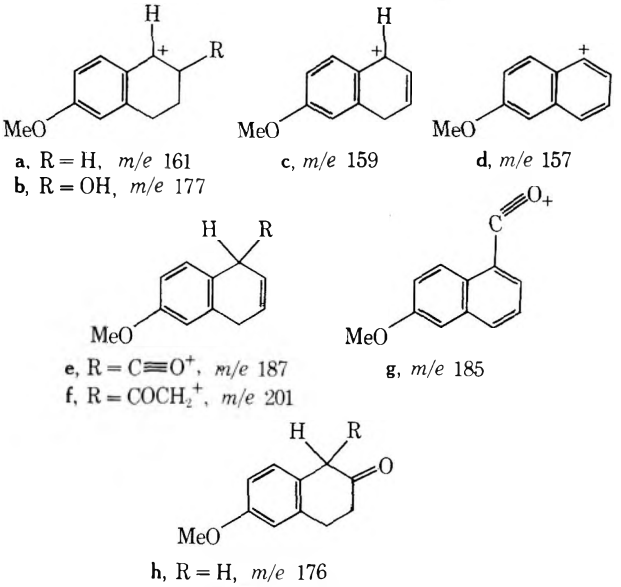
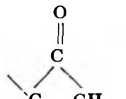


Table I
Nmr Spectra[a]

Compd	CH_3-(C_{18})		CH_2-(C_{12})	OCH_3-(C_3)	Phenyl (H_1)	Phenyl (H_2 + H_4)		CH_2-$COOCH_3$	OCH_3
1b	1.08	2.90						2.97	3.63
5b	1.11	2.93	3.46	3.83	7.25	6.75			
6	1.00	2.91	3.50	3.81	6.8	6.9	Benzoate 7.6 and 8.1		
7	1.01	2.88	3.19, d J = 3 Hz	3.77	6.68	6.82			
8	1.03	2.93	3.18	3.80	6.7	6.82			
9	1.13	2.98, d J = 3 Hz	3.6	3.8	7.1	6.8	7.5, d J = 9 Hz		
11b (*in* DMSO)	0.97			3.70	6.5	6.7			
13	1.4	2.9		3.9	7.2, 7.7 (5 H, m), 6.0 (1 H, C_{11}, d, J = 16 Hz)				
mp 164°	2.5 (!)			3.72	6.5–7.8 [3 H, m, + vinyl proton (?)]				
mp 192°	1.26		3.73		6.8 (2 H, m, aromatic) 7.1 (1 H, m, aromatic)				

[a] In parts per million.

Table II
Relative Intensities of the Characteristic Peaks in the Mass Spectra of Compounds 5b, 7, 8, 9, and 12

Compd	M^+	a	b	c	d	e	f	g	h	i	k
						m/e (rel intensity)					
5b	328								176	203	217
	(71)								(100)	(21)	(0.5)
7	314	161									
	(13)	(100)									
8	330		177	159		187	201				
	(1.1)		(100)	(4.3)		(1.4)	(1)				
9	312			159		187	201				
	(90)			(100)		(44)	(25)				
12	310				157			185			
	(43)				(34)			(100)			

atom to the charged fragment (Table II). Unlike ketones **7** and **8**, the seco compounds **9** and **12** containing the unsaturated ring B show intense formation of the ions e and g, respectively. Interestingly, in the tetrone **5b** there is a substantial peak at m/e 203 (ion i), also arising from the cleavage of the 11–12 bond. It is possible that at least partial enolization of the 8-CO group occurs under mass spectrometric conditions, leading to the formation of the 8-hydroxy analog of the trione **9** with an 8–9 double bond. Possibly this double bond hinders the vinylic cleavage of the 9–11 bond, and this, in turn, increases the probability of the competitive α-cleavage on the opposite side of the 11-keto group, in the order **5b** < **9** < **12**. Indeed, in the mass spectra of the ketones **5b** and **9** the relative intensities of the respective ions (i and e) are 21 and 44%, whereas in the equilenin derivative **12** the same cleavage of the 11–12 bond is even more intense: the respective ion g is the base peak of the spectrum.

Experimental Section

Melting points are uncorrected. Nmr spectra were recorded on a Varian Associates A-60 instrument in $CDCl_3$, using TMS as internal standard. Mass spectra were determined at 70 eV and 120–130° on an Atlas CH4 spectrometer equipped with a TO-4 source, using a direct inlet system. Comparison of samples was done with aid of ir, uv, and nmr spectra, as well as the consistent use of tlc (Merck A.G. silica gel plates F-254, with benzene–ethyl acetate mixtures ranging from 6:1 to 1:1; visualization of spots with phosphomolybdic acid followed by sulfuric acid).

α-(1,3-Diketo-2-methylcyclopentane)acetic Acid (1a). A solution of 60 g of potassium permanganate in 516 ml of water and 2400 ml of acetone was added, over a 30-min period, into a mechanically stirred solution of 30 g of the allyl derivative **2**[1] in 900 ml of acetone containing 12 ml of acetic acid and cooled in an ice–salt bath. After stirring with continued cooling for an additional 30 min, a solution of 30 g of sodium metabisulfite in 300 ml of water was dropped in over a 10-min period. The mixture was filtered with suction through a large sintered glass funnel, the manganese dioxide was washed with acetone, and the combined filtrates were concentrated at 50° to a volume of 900 ml and treated with a solution of 90 g of sodium metaperiodate in 1620 ml of water. The following morning the fine red-brown precipitate was removed by filtration through a pad of Celite and the filtrate was continuously extracted for 40 hr with ethyl acetate. Evaporation of the solvent gave 17 g of a solid, which on recrystallization from ether afforded a total of 15 g of the acid **1a**: mp 180–182°; λ_{max} (KBr) 5.7 (w), 5.8–5.9, 6.86, 7.02, 7.13, 7.54, 7.65, 8.25, 8.63, 9.30, 9.95, 11.15, and 12.40 μ; m/e 170.

Anal. Calcd for $C_8H_{10}O_4$: C, 56.46; H, 5.92. Found: C,56.71; H, 5.90.

The methyl ester **1b** (diazomethane) had mp 94–95° (petroleum ether); λ_{max} (KBr) 5.78 μ; m/e 184.

Anal. Calcd for $C_9H_{12}O_4$: C, 58.69; H, 6.57. Found C, 58.62; H, 6.37.

The anhydride **3** was prepared by treatment of a solution of 690 mg of the acid **1a** in 40 ml of dry ether with 515 mg of dicyclohexylcarbodiimide. The swirled solution rapidly deposited dicyclohexylurea, followed by **3**. After 48 hr the solid was filtered off and extracted with methylene chloride. Evaporation of solvent and trituration with dry benzene afforded a total of 537 mg of **3**: mp 162–165°; λ_{max} (KBr) 5.55 and 5.84 μ; m/e 322.

Anal. Calcd for $C_{16}H_{18}O_7$: C, 59.62; H, 5.63. Found C, 59.88; H, 5.55.

***rac*-8(14)-Seco-1,3,5(10)-estratriene-8,11,14,17-tetrone (5a).** The acid chloride **1c** was prepared by refluxing 2 g of **1a** with 40 ml of thionyl chloride for exactly 15 min and evaporation of the solvent *in vacuo*. Addition of 10 ml of dry benzene and evaporation *in vacuo* was carried out three times.

The residual oily **1c** was treated with a solution of 2 g of the enamine **4a**[3] in 60 ml of dry benzene and the mixture was refluxed with stirring for 1 hr. The resulting suspension was cooled

and worked up with ice–water and ether. The aqueous phase was allowed to stand at room temperature for 2 days (solution A). The organic phase was washed with water, evaporated, and chromatographed on a "dry" column of 190 g of silica gel ("Kieselgel 60," 70–230 mesh ASTM). Elution with cyclohexane–ethyl acetate (3:1) gave a total of 450 mg of **5a**: mp 117–119° (methylene chloride–ether); λ_{max} (KBr) 5.75 and 6.3 μ; *m/e* 298; λ_{max} (EtOH) 248 nm (ϵ 11,000), shifting on addition of alkali to 268 nm, followed by rapid decomposition; ferric chloride test, positive.

Solution A deposited 350 mg of a solid which upon crystallization from methylene chloride–ether yielded an additional 195 mg of **5a**, mp 117–119°.

Anal. Calcd for $C_{18}H_{18}O_4$: C, 72.46; H, 6.08. Found C, 72.59; H, 5.90.

rac-**3-Methoxy-8(14)-seco-1,3,5(10)-estratriene-8,11,14,17-tetrone (5b).** The acid **1a** (8.5 g) was converted into its chloride **1c** as described above, and treated with a solution of 8.5 g of the enamine **4b**[3] in 170 ml of dry benzene. The mixture was refluxed with mechanical stirring for 1 hr, cooled in ice, and treated dropwise over a 10-min period with 80 ml of water. The aqueous phase was reextracted with benzene and ether, and after several days, when additional oily material has separated from it, with methylene chloride. The combined extracts were evaporated to a gum which was chromatographed on 600 g of "Kieselgel 60." Elution with petroleum ether furnished 2 g of 6-methoxy-2-tetralone, and with 10 and 30% ethyl acetate in petroleum ether 4.8 g of the tetrone **5b** was obtained. Recrystallization from ether yielded a total of 3.8 g: mp 140–143°; λ_{max} (KBr) 5.55 (w) and 5.8 μ; *m/e* 328; λ_{max} (EtOH) 246, 282, and 330 nm (ϵ 13,800, 7500, and 4300).

Anal. Calcd for $C_{19}H_{20}O_5$: C, 69.50; H, 6.14. Found: C, 69.26; H, 6.30.

rac-**8-Benzoyloxy-3-methoxy-8(14)-seco-1,3,5(10),8-estratetraene-11,14,17-trione (6).** To an ice-cooled solution of 5.24 g of **5b** in 52 ml of dry pyridine was added 12 ml of benzoyl chloride. The reaction mixture was allowed to stand overnight at room temperature, whereupon ice and water were added up to a volume of 250 ml and the mixture was then stirred for 2 hr. The aqueous layer was decanted from the half-solid, which was washed with water and treated with 20 ml of ether. The resulting benzoate weighed 4.54 g, mp 127–129°. Usual work-up of the aqueous phase with ethyl acetate and chromatography over Florisil (30% ethyl acetate in petroleum ether) furnished an additional 1.9 g of the same material. The pure sample had mp 128–130° (ether); λ_{max} (KBr) 5.77, 5.87, and 5.94 μ (w); *m/e* 432; λ_{max} (EtOH) 228 and 260 nm (ϵ 21,200 and 13,700).

Anal. Calcd for $C_{26}H_{24}O_6$: C, 72.21; H, 5.59. Found: C, 72.01; H, 5.33.

Hydrogenation of the Enol Benzoate 6. A solution of 6 g of the benzoate **6** in 1 l. of methanol was hydrogenated for 10 hr at atmospheric pressure in the presence of 10 g of 5% palladium on charcoal. The oily product was carefully chromatographed on 300 g of Florisil. With 10% ether in benzene solid fractions were obtained, the first ones being pure *rac*-**3-methoxy-8(14)-seco-1,3,5(10)-estratriene-11,14,17-trione (7)**: mp 113–116° (methanol); λ_{max} (KBr) 5.81, 5.87, 6.20, and 6.64 μ; λ_{max} (EtOH) 278 and 285 nm (ϵ 1900 and 1660) (reported mp 120–122°,[6] 116–117°[7]). Ir, mass, and nmr spectra were identical with those reported. Further elution with 10% ether in benzene gave solid mixtures containing **7** and *rac*-**3-methoxy-8(14)-seco-1,3,5(10),8-estratetraene-11,14,17-trione (9).** By means of laborious fractional crystallizations from methanol it was possible to separate **7** and **9**, the latter as a solvate having a characteristically wide melting point of about 76–86°, rising to 118–122° after drying *in vacuo* at 70°: λ_{max} (KBr) 5.80, 6.05, and 6.21 μ; *m/e* 312; λ_{max} (EtOH) 244 and 287 nm (ϵ 14,000 and 4300).

Anal. Calcd for $C_{19}H_{20}O_4$: C, 73.06; H, 6.45. Found: C, 72.79; H, 6.71.

The weights of pure **7** and **9** isolated were 1.27 and 1.26 g, respectively. Elution with 50% ether in benzene furnished a third crystalline substance. Its solution in ether was filtered to remove an accompanying high-melting impurity and then concentrated to afford a total of 0.45 g of *rac*-8ξ-**hydroxy-3-methoxy-8(14)-seco-1,3,5(10)-estratriene-11,14,17-trione (8)**: mp 142.5–144° (ether); λ_{max} (KBr) 2.90, 5.70 (sh), 5.84, 6.23, and 6.65 μ; *m/e* 330; λ_{max} (EtOH) 275 and 282 nm (ϵ 1720 and 1610).

Anal. Calcd for $C_{19}H_{22}O_5$: C, 69.07; H, 6.71. Found: C, 68.80; H, 6.65.

Dehydration of the Ketol 8. A solution of 8 mg of **8** in 25 ml of benzene containing 200 mg of *p*-toluenesulfonic acid was refluxed for 30 min. The cooled solution was washed with water, bicarbonate, and water and then evaporated to furnish the tetraene **9**. Recrystallization from methanol gave 5 mg, mp 75–93°, identical with the solvated sample isolated from hydrogenation of **6**.

Hydrogenation of the Tetraene 9. A solution of 9 mg of **9** in 10 ml of ethyl acetate was hydrogenated for 3 hr at atmospheric pressure in the presence of 50 mg of 5% palladium on charcoal. The product was crystallized from methanol to give 7 mg of the trione **7**, mp 113–117°, identical with a sample isolated from hydrogenation of the benzoate **6**.

Treatment of *rac*-3-Methoxy-8(14)-seco-1,3,5(10),9(11)-estratetraene-14,17-dione (10) with *m*-Chloroperbenzoic Acid. A solution of 10.6 g of the tetraene **10**[12] in 125 ml of chloroform was treated at 0° with a cold solution of 7.8 g of *m*-chloroperbenzoic acid (80% pure) in 125 ml of chloroform. After standing overnight at room temperature the solution was washed with 5% potassium hydroxide solution and evaporated. The residue crystallized on addition of warm ether to furnish 4.84 g of *rac*-**14-hydroxy-3-methoxy-11,14-oxido-8(14)-seco-1,3,5(10),8-estratetraen-17-one (11b)**: mp 154–155.5°; λ_{max} (KBr) 3.05, 5.75, 6.22, 6.40, and 6.70 μ; λ_{max} (EtOH) 268 nm (ϵ 13,000) [reported[7] mp 156–157°, λ_{max} (MeOH) 269 nm (ϵ 12,350)]. In most cases treatment of the main filtrate with perchloric acid–dioxane–water (0.6:25:3 ml) overnight at room temperature afforded additional amounts of the same compound. Chromatography of the residue on silica gel, using ethyl acetate–cyclohexane (1:1) as the eluting agent, furnished at first minute amounts of **11b**, followed by **8**. Recrystallization of the latter from methylene chloride–ether yielded 0.50 g, mp 140–141°, identical with a sample obtained from the hydrogenation of **6**.

Conversion of 11b into 7. A solution of 200 mg of **11b** in 10 ml of ethyl acetate was hydrogenated for 3 hr in the presence of 200 mg of 5% palladium on charcoal. The ultraviolet spectrum of the resulting gum showed that saturation of the 8–9 bond had taken place. A portion (40 mg) of this mixture of stereoisomeric alcohols was dissolved in 10 ml of acetone and treated at 0° with 0.3 ml of the Jones reagent. Usual work-up gave an oil which was chromatographed on Florisil. Elution with benzene and 2% ether in benzene afforded at first crystals of an unknown nature, mp 74–75°, followed by the trione **7** (10 mg).

Treatment of 11b with *N*-Bromosuccinimide and Acid. A warm solution of 4.74 g of the hemiketal **11b** in 150 ml of acetone was concentrated to 80 ml, cooled in an ice–salt bath, and treated with 2.62 g of *N*-bromosuccinimide, followed by 8.5 ml of 10% perchloric acid. After the solution was allowed to stand at 0° for 2 hr, several milliliters of aqueous bisulfite solution was added, followed by water and methylene chloride. The organic phase was washed with bicarbonate solution and evaporated to an oil which was dissolved in 40 ml of hot methanol and seeded with the ketone **9**. There was obtained 2.1 g of the solvated product having the characteristically wide melting point of 78–92°, identical with that of authentic material. The concentrated filtrate deposited on storage at room temperature for 3 days a crop of 0.55 g of the saturated trione **7**, mp 113–114°. Chromatography of the residue on silica gel furnished, with benzene–ethyl acetate (4:1), 0.2 g of *rac*-**3-methoxy-8(14)-seco-1,3,5(10),6,8-estrapentaene-11,14,17-trione (12)**, mp 110–112° (ether or methanol), identical in all respects with an authentic sample prepared by treatment of **7** with DDQ, for which mp 115° was reported.[8]

Treatment of 9 with *p*-Toluenesulfonic Acid in Toluene. A. A solution of 1 g of **9** and 1.5 g of *p*-toluenesulfonic acid monohydrate in 100 ml of toluene was refluxed for 6 hr, using a Dean–Stark water collector. The cooled reaction mixture was washed with water and bicarbonate, and the gum obtained after evaporation of the solvent was chromatographed on 50 g of Florisil. With 1% ether in benzene there was obtained 100 mg of a soft solid, which after two recrystallizations from ether melted at 110–112°; it was identical with the naphthalenic trione **12** obtained above. Elution with more polar solvents gave mixtures of materials described below.

B. A solution of 2.8 g of **9** and 5.3 g of *p*-toluenesulfonic acid in 280 ml of toluene was refluxed for 15 hr. The oily product was chromatographed on 140 g of Florisil. With 1% ether in benzene there was obtained 10 mg of a product assumed to be *rac*-**11,14-oxidoequilenin-3-methyl ether (13)**: mp 125–128° (methanol); λ_{max} (KBr) 5.82 μ; *m/e* 294; λ_{max} (EtOH) 230 and 302 nm (ϵ 24,000 and 6100).

Anal. Calcd for $C_{19}H_{18}O_3$: C, 77.53; H, 6.16. Found: C, 77.59; H, 6.30.

Continued elution with 1% ether in benzene furnished a solid which after crystallization from methanol afforded 50 mg of *rac*-

11-keto-14-isoequilenin-3-methyl ether (14a), mp 158–160°,[13] *m/e* 294, whose identity was confirmed by comparison of its ir in potassium bromide with that of the optically active form **14b**, mp 187–189°, obtained by methylation of 11-keto-14-isoequilenin[14,15] with diazomethane.[18]

Elution with 5% ether in benzene yielded a solid which after recrystallization from methanol and then ether furnished 52 mg of a material, mp 164–166°, *m/e* 294. Its spectrum exhibited a hydroxyl and a peak at 5.90 μ, λ_{max} (EtOH) 222, 254, and 327 nm (ϵ 35,000, 13,000, and 3500), shifting on addition of alkali to 244 and 380 nm (ϵ 29,000 and 4000), reversible on acidification to the original wavelengths. The location of the methyl peak at 2.5 ppm shows unsaturation at the adjacent carbon atom.

Further elution with 5% ether in benzene furnished a mixture of solids, which on recrystallization from ethanol deposited 25 mg of *rac*-**11-keto-8-dehydro-14-isoestrone-3-methyl ether (15a)**: mp 174–176°; *m/e* 296; λ_{max} (KBr) 5.75 and 6.05 μ; λ_{max} (EtOH) 245, 295, and 315 nm (ϵ 17,000, 4800, and 4810). The identity of this compound was established by the Jones oxidation of an authentic sample of the corresponding 17β-ol analog **15b**,[10] and direct comparison of the product with our sample. The nonidentity with its 14α epimer, mp 161–163°, was confirmed by direct comparison with a sample of the latter.[17]

The next crop from crystallization of **15a** provided yet another material. Recrystallization furnished 53 mg, mp 192–193°, *m/e* 312, exhibiting a hydroxyl absorption and a carbonyl at 5.75 μ, λ_{max} (EtOH) 275 and 281 nm (ϵ 1500 and 1400), and a peak at 3.73 ppm.

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Registry No.—**1a**, 51270-51-0; **1b**, 51270-52-1; **1c**, 51270-53-2; **2**, 26828-48-8; **3**, 51270-54-3; **4a**, 21403-95-2; **4b**, 20915-80-4; **5a**, 51270-55-4; **5b**, 51270-56-5; **6**, 51270-57-6; **7**, 51270-58-7; **8**, 51270-59-8; **9**, 51270-60-1; **10**, 899-79-6; **11b**, 24421-61-2; **12**, 41021-02-7; **13**, 51270-61-2; **14a**, 26584-94-1; **15a**, 26435-94-9; **16**, 51270-62-3; *m*-chloroperbenzoic acid, 937-14-4.

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(13) We assume that the mp 160–171° reported for **14a**[9a] should read 160–161°, since in the preliminary communication[9b] mp 158–160° was reported.
(14) "Inactive 11-oxoequilenin" described[15] is in fact 11-keto-14-isoequilenin, for hydrogenolysis of its 3-methyl ether for 4 hr at room temperature in acetic acid solution, in the presence of 5% palladium on charcoal and perchloric acid, afforded 14-isoequilenin-3-methyl ether, mp 116–118° (lit.[16] mp 119° and, for equilenin-3-methyl ether, mp 193–194°). Furthermore, the above methyl ether, mp 187–189°, was not changed by heating with hydrochloric acid–acetic acid (1:4) for 1 hr at 100°, treatment which might be expected to cause isomerization of 11-ketoequilenin-3-methyl ether to **14b**.
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(17) Kindly provided by Dr. Richard W. Rees of the Wyeth Laboratories, Inc.
(18) Note Added in Proof. We have now prepared **14a** also by polyphosphoric acid cyclization of the pure "unnatural" stereoisomer of *rac*-5-(6-methoxy-2-naphthyl)-1-methyl-2-oxocyclopentane-1-acetic acid, mp 151–153° [E. G. Brain, F. Cassidy, M. F. Constantine, J. C. Hanson and D. J. D. Tidy, *J. Chem. Soc. C*, 3846 (1971)], kindly provided by Dr. Brain of the Beecham Laboratories. The product, mp 158–159°, was identical with **14a** described above.

Nonbenzenoid Aromatic Systems. X.[1a] Formation, Nuclear Magnetic Resonance Spectral Identification, and Reactions of Both Meisenheimer Type and Methyleneazulenate Anions

Richard N. McDonald,* Herbert E. Petty,[1b] N. Lee Wolfe, and Joseph V. Paukstelis

Department of Chemistry, Kansas State University, Manhattan, Kansas 66502

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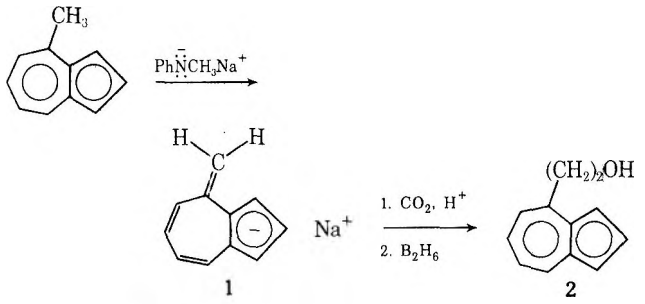
The reaction products from azulene and certain methylazulenes with several nucleophilic strong bases have been observed and identified by nmr spectroscopy. With azulene, lithium dicyclohexylamide (**3**) and tritylsodium (**18**) yield exclusively products of nucleophilic addition to the ring 6 position, 6-X-6*H*-azulenate anions, while, with lithium dimethylamide (**15**), methyllithium (**23**), and sodium methylsulfinylmethide (**27**), products derived from nucleophilic addition to both the azulene ring 4 (predominant) and 6 positions are observed. The Meisenheimer type of addition complexes formed with the amide nucleophiles (**3** and **15**) and azulene were shown to thermally equilibrate while those complexes resulting from ring addition by the carbon nucleophiles (**18**, **23**, and **27**) were thermally stable. Competitive nucleophilic addition and methyl group proton abstraction reactions were examined with some of these nucleophilic bases and 4,6,8-trimethylazulene (**31**). Exclusive proton abstraction was observed in the reaction of sodium *N*-methylanilide, **18**, or **27** with **31** to yield mixtures of the methyleneazulenate anions **32** and **33**. However, amide **15** reacted with **31** by nucleophilic addition to the 4 and 6 positions, the initially formed mixture being thermally equilibrated. Carbonation of lithium 6-dicyclohexylamino-6*H*-azulenate (**20**) yields a mixture of azulene mono- (1 and 2), di- (1,2 and 1,3), and tricarboxylic (1,2,3) acids. Carbonation of a mixture of lithium 6-dimethylamino-6*H*-azulenate and its 4 isomer yields only azulene. Other related reactions are presented, and discussions of the involved processes are given.

Our investigations of the effects of the five nonequivalent azulene ring positions on the solvolysis of β-azulylethyl arenesulfonates have thus far dealt with the ethyl side chain attached to the azulene 1,[2] 4,[3] and 6 positions.[3] 2-(1-Azulyl)ethanol was synthesized by electrophilic substitution of azulene.[4] The 2-(4- (**2**) and 2-(6-azulyl)ethanol

were prepared by carbonation of the 4- (1) and 6-methyleneazulenate anions,[5] respectively, followed by reduction of the corresponding acetic acids. The present work begins with our attempts to utilize the latter procedure to produce 2-(5-azulyl)ethanol.



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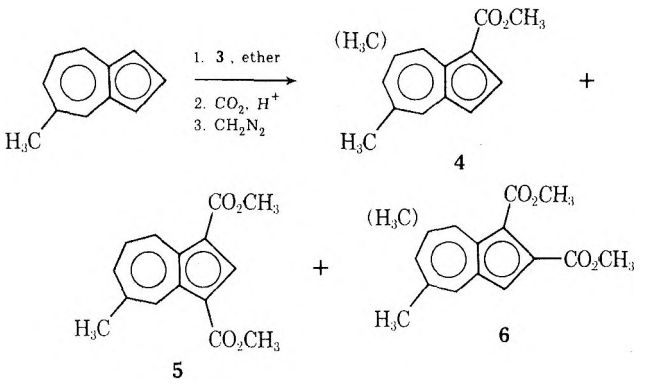
Products from Reactions of Azulenate Anions. The number of known 5-substituted azulenes which might be converted to 2-(5-azulyl)ethanol is very limited. Since the methyl group of 5-methylazulene is not activated toward proton abstraction as are those of 4- and 6-methylazulene,[6] it was felt that proton abstraction might result if a strong, sterically hindered base were employed.[7] The base chosen for this purpose was lithium *N,N*-dicyclohexylamide (**3**).[8]

Reaction of **3** and an excess of 5-methylazulene in ether resulted in no visible color change. Carbonation of the reaction mixture produced base-soluble products but nmr spectral analysis of the acidic product showed that the desired 5-azulylacetic acid had *not* been formed. Reaction with diazomethane and chromatography gave a mixture of methyl 5- (7-) methyl-1-azulenecarboxylate (**4**, 17.0%, 42.3% net), dimethyl 5-methyl-1,3-azulenedicarboxylate (**5**, 2.2%, 5.5% net), and dimethyl 5- (7-) methyl-1,2-azulenedicarboxylate (**6**, 0.9%, 2.3% net).



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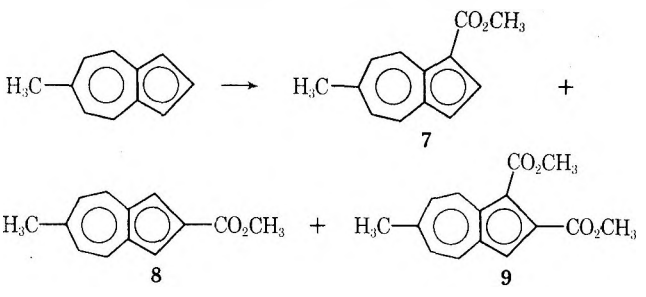
When **3** was allowed to react with 6-methylazulene in ether and the resulting yellow solution was carbonated followed by conversion of the acids to their methyl esters, a mixture of methyl 6-methyl-1-azulenecarboxylate (**7**, 8.3%, 32% net), methyl 6-methyl-2-azulenecarboxylate (**8**, 3.3%, 12.8% net), and dimethyl 6-methyl-1,2-azulenedicarboxylate (**9**, 5.0%, 19.2% net) was obtained. This result was unexpected since reacion of 6-methylazulene with sodium *N*-methylanilide in ether followed by carbonation produced 6-azulylacetic acid.[3,5]



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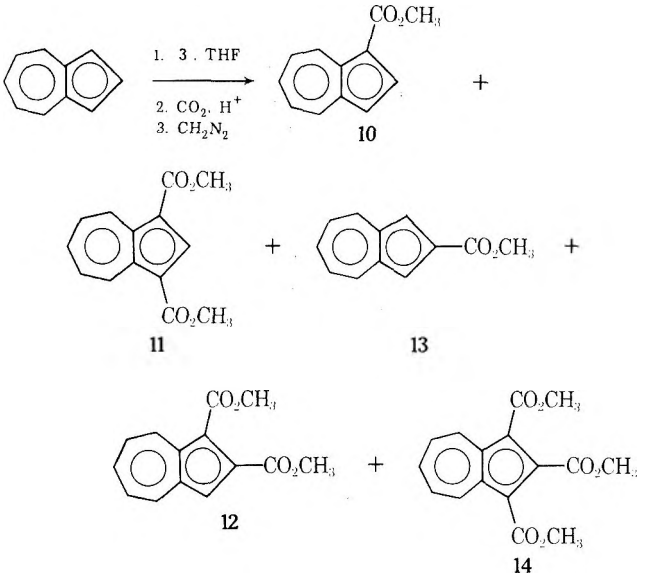
A solvent effect was noted in the reaction of **3** with 6-methylazulene. In tetrahydrofuran, the results of carbonation gave 36% of recovered 6-methylazulene and 39% of 6-azulylacetic acid. Similar conditions with 4-methylazulene yielded 22% recovered 4-methylazulene and a 70% yield of 4-azulylacetic acid.

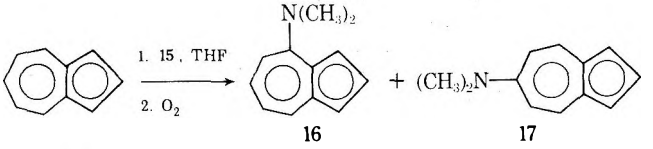
To demonstrate that the methyl groups of 5- and 6-methylazulene were not involved in formation of the nuclear carbonation products, azulene was similarly allowed to react with **3** in ether followed by carbonation and conversion of the acidic products to their methyl esters. The mixture of esters was composed of methyl 1-azulenecarboxylate (**10**, 13.7%, 71% net), dimethyl 1,3-azulenedicarboxylate (**11**, 2.3%, 13.5% net), and dimethyl 1,2-azulenedicarboxylate (**12**, 1.4%, 7.5% net). When this reaction was run on a larger scale with tetrahydrofuran as solvent the ester product mixture contained 11% (23% net) **10**, 5% (10% net) methyl 2-azulenecarboxylate (**13**), 4% (8% net) **11**, 5% (11% net) **12**, and 1% (2% net) trimethyl 1,2,3-azulenetricarboxylate (**14**).



10 11 13 12 14

When lithium dimethylamide (**15**) was allowed to react with azulene in ether, the color of the solution immediately changed from blue to yellow. Addition of carbon dioxide to this yellow solution regenerated the azulene blue color. When water was added effervescence resulted and work-up of the reaction yielded only recovered azulene. Substitution of methanol (a proton source) for carbon dioxide or changing the solvent to tetrahydrofuran or benzene produced the same result.

To establish the gross structure of the adduct(s) from reaction of **15** and azulene, the reaction mixture was treated with oxidizing agents. Bubbling oxygen through the reaction mixture at −70° produced no color change, but as the temperature was slowly increased the solution turned blue. Work-up of the resulting mixture gave 4- (**16**, 8%) and 6-*N,N*-dimethylaminoazulene (**17**,[12] 12%). When the reaction mixture from **15** and azulene was allowed to equilibrate at 25° and oxygen was added, the two amines **16** and **17** were isolated in 4 and 18% yields, respectively.



16 17

Table I
Visible λ_{max} for Certain 4- and 6-Substituted Azulenes

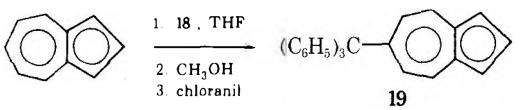
Compd	Solvent	λ_{max}, nm	Ref
Azulene	Cyclohexane	580	9
4-CH_3Az	Cyclohexane	568	9
6-CH_3Az	Cyclohexane	565	9
4-H_2NAz	CH_2Cl_2	510	10
4-$(CH_3)_2$NAz (**16**)	Cyclohexane	546	This work
6-H_2NAz	CH_3OH	465	11
	C_2H_5OH	470	
6-$(CH_2)_2$NAz (**17**)	CH_3OH	472	12, this work
	Cyclohexane	486	
6-$(C_2H_5)_2$NAz	CH_3OH	476	12

With chloranil as the oxidizing reagent, only amine **16** was isolated.

The λ_{max} of the visible spectra of **16** and **17** deserve comment. For many 4 and 6 substituents on the azulene ring, $\Delta\lambda_{max}$ is essentially constant, *e.g.*, the 4- and 6-methylazulenes in Table I. Generally, electron-donating substituents cause a hypsochromic shift and electron-withdrawing substituents result in a bathochromic shift of this absorption band. However, as can be seen from the data in Table I, the λ_{max} values for the azulylamines are quite different. The difference, $\Delta\lambda_{max}$, between **16** and **17** of +60 nm is attributed to a steric interaction between the 4-dimethylamino group and the peri-C_3 hydrogen[9] in **16** which is not present in **17**. This results in a steric inhibition of conjugation between the azulene ring and the nitrogen nonbonded pair of electrons. The stable conformation of **16** would probably have the peri-C_3 hydrogen roughly bisecting the nonbonded electron pair–nitrogen–methyl angle. It is interesting to note that 4-*N*-acetylaminoazulene has λ_{max} (CH_2Cl_2) 560 nm.[10a] In this case, the reduced availability of the nitrogen nonbonded electron pair for conjugation with the ring is probably electronic rather than steric.

An orange solution resulted when azulene was allowed to react with tritylsodium (**18**) in tetrahydrofuran at −70°. Addition of methanol produced a colorless solution which when dehydrogenated with chloranil gave a blue solution. From this solution a blue, crystalline solid was isolated which failed to yield sharp-melting crystals even after repeated column chromatography and recrystallizations.[13]

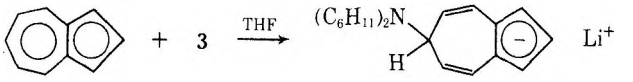
This blue solid is believed to be 6-tritylazulene (**19**) on the basis of the reaction which produced it and the spectral data. The nmr spectrum showed only the presence of aromatic protons; integration of the downfield doublet attributed to the azulyl C_4 and C_8 protons and the remaining 20 protons gave a 2:19 ratio. The mass spectrum gave M^+ at *m/e* 370 (50%) with strong ion abundances for *m/e* 243 (24%) and 127 (11%); however, ions at *m/e* 244 (10%) and 128 (6%) may be due to triphenylmethane and azulene contamination.[13] The visible spectrum had λ_{max} (cyclohexane) 579 nm, which was about that predicted for **19**.[14]



19

Nmr Spectral Investigation of Azulenate Anion Structures. The ability to produce the diverse mono-, di-, and trinuclear carbonation products **10–14** by carbonation of the product derived from reaction of azulene and the lithium dicyclohexylamide (**3**) prompted us to investigate the structure of this product and those derived from reactions involving other strongly basic nucleophiles and azulene. To obtain structural information on such reactive species, nmr spectroscopy appeared to be particularly suited to the task.

To a tetrahydrofuran solution of azulene in an nmr tube at 0° was added dropwise with shaking a solution of **3** in tetrahydrofuran until a yellow color resulted (small molar excess of **3** required). The spectrum is reproduced in Figure 1a and is interpreted as the exclusive production of lithium 6-*N,N*-dicyclohexylamino-6*H*-azulenate[16] (**20**). See Table II for a numerical listing of the proton absorptions and their assignments.[17,18] No change in the spectrum of this Meisenheimer type complex was observed after 36 hr at 33°.



20

The simplicity of the spectrum readily allows structural assignments to the three distinct spectral patterns, the C_1, C_2, and C_3 protons contributing to the broadened singlet at δ 5.61, the C_4 and C_8 protons absorbing at δ 6.24 as a doublet ($J_{4,5}$ = 10.5 Hz), and the C_5 and C_7 protons absorbing at δ 4.86 as a doublet of doublets ($J_{4,5}$ = 10.5 and $J_{5,6}$ = 4.5 Hz). The cyclohexyl and C_6 ring protons would be further upfield under the solvent absorptions.

When equimolar amounts of tetrahydrofuran solutions of azulene and lithium dimethylamide (**15**) were mixed at −70° the solution color immediately turned to a light yellow. The nmr spectrum recorded at −20° was interpreted as showing the presence of lithium 4-*N,N*-dimethylamino-4*H*-azulenate (**21**) and lithium 6-*N,N*-dimethylamino-6*H*-azulenate (**22**). Integration of the C_5 and C_7 protons of **22** and the C_5 proton of **21** gave the **21:22** ratio as about 4:1. (See Figure 1 and Table II for the proton assignments.)

21 22

Warming the solution of **21** and **22** to −10° and then to 0° produced no change in the spectrum. With the sample at 10° the doublet at δ 6.71 at lower temperatures was observed as a pair of doublets and integration gave the **21:22** ratio as 7:3. Warming the sample to higher temperatures (Figure 1c) produced further changes in the **21:22** ratio (33°, 3:7; 50°, 1:4). The observed changes in the **21:22** ratio as a function of temperature will be dealt with further in the Discussion.

Hafner[19] reported that addition of methyllithium (**23**) to azulene followed by protonation and dehydrogenation of the dihydro product with chloranil produced only 4-methylazulene.[20] When azulene (in tetrahydrofuran) was allowed to react with an equimolar amount of **23** (in ether) at −70° a yellow-green solution resulted. The nmr spectrum was recorded at −33° (Figure 2a) and was analyzed as a mixture of lithium 4-methyl-4*H*-azulenate (**24**) and lithium 6-methyl-6*H*-azulenate (**25**) in approximately a 9:1 ratio, respectively. The spectrum showed no change on standing for 24 hr at 25°. Addition of **23** to azulene at 25 or 50° produced the same **24:25** ratio as that found at −70°. The five-membered ring proton chemical shifts of **24** and **25** were readily verified by carrying out the reaction with azulene-*1,3-d*$_2$.

Table II
Nmr Spectral Data for the Meisenheimer-Type Complexes of Azulenate Anions[a,i]

Reactants	Nmr solvent	Product	Proton positions: 1,3	2	4	8	5	7	6	Other
Azulene + $(C_6H_{11})_2NLi$ (3)[b,e]	THF	20	5.61[f] s		6.24 d $J_{4,5}$ = 10.5		4.86 d of d $J_{4,5}$ = 10.5 $J_{5,6}$ = 4.5		[g]	
Azulene + $(CH_3)_2NLi$ (15)[b,e]	THF	21	5.83 d $J_{1,2}$ = 2.0	5.57 t $J_{1,2}$ = 2.0	[g]	6.71 d $J_{7,8}$ = 10.5	5.18 *d of d* $J_{5,6}$ = 10.5 $J_{4,5}$ = 7.5	5.32 *d of d* $J_{7,8}$ = 10.5 $J_{6,7}$ = 7.5	6.07 *d of d* $J_{5,6}$ = 10.5 $J_{6,7}$ = 7.5	
		22	5.85[f] m		6.65 d $J_{4,5}$ = 10.5		4.97 d of d $J_{4,5}$ = 10.5 $J_{5,6}$ = 4.5		[g]	
Azulene + CH_3Li (23)[b,e]	THF	24	5.20 d $J_{1,2}$ = 2.5	5.54 t $J_{1,2}$ = 2.5	[g]	6.60 d $J_{7,8}$ = 10.5	5.10 d of d $J_{5,6}$ = 10.5 $J_{4,5}$ = 5.2	5.36 d of d $J_{6,7}$ = 6.2 $J_{7,8}$ = 10.5	5.65 d of d $J_{5,6}$ = 10.5 $J_{6,7}$ = 6.2	
		25	5.51–5.61[f] m		6.26 d of d $J_{4,5}$ = 9.5 $J_{4,6}$ = 1.5		4.62 d of d $J_{4,5}$ = 9.5 $J_{5,6}$ = 4.0		[g]	
Azulene-*1,3*-d_2 + CH_3Li (23)[b,e]	THF	24		5.48 s	[g]	6.56 *d* $J_{7,8}$ = 10.5	5.10 *d of d* $J_{5,6}$ = 10.5 $J_{4,5}$ = 5.2	5.37 *d of d* $J_{7,8}$ = 10.5 $J_{6,7}$ = 6.2	5.62 *d of d* $J_{5,6}$ = 10.5 $J_{6,7}$ = 6.2	
		25		h	6.25 d of d $J_{7,8}$ = 9.5 $J_{6,8}$ = 1.5		4.61 d of d $J_{5,6}$ = 4.0 $J_{4,5}$ = 9.5		[g]	
Azulene + CH_3Li (23)[c,d]	DMSO-d_6	24	5.19 d $J_{1,2}$ = 2.5	5.56 t $J_{1,2}$ = 2.5	3.14 "t" J_{4,CH_3} = 6.5	6.62 d $J_{7,8}$ = 10.5	4.60–5.05 m			4-CH_3 1.97 d J_{4,CH_3} = 6.5
Azulene + $(C_6H_5)_3CNa$ (18)[b,e]	THF	26	5.88[f] s		6.49 d $J_{4,5}$ = 9.5		4.79 d of d $J_{4,5}$ = 9.5 $J_{5,6}$ = 4.0		[g]	
Azulene + CH_3SOCH_2Na (27)[b,e]	DMSO-d_6	28	5.54 *d* $J_{1,2}$ = 2.5	5.13 *t* $J_{1,2}$ = 2.5	3.57 *d* $J_{4,5}$ = 6.5	6.55 *d* $J_{7,8}$ = 10.5	4.98 *d of d* $J_{4,5}$ = 6.5 $J_{5,6}$ = 10.0	[h]	5.67 d of d $J_{6,7}$ = 7.0 $J_{5,6}$ = 10.0	
		29	5.50–5.60[f] m		6.34 d $J_{4,5}$ = 9.5		5.90 d $J_{4,5}$ = 9.5			
4,6,8-Trimethylazulene + $(CH_3)_2NLi$ (15)[b,e]	THF	34	6.00 d $J_{1,2}$ = 4.2	5.86 one line of the t			5.91 s	5.07 s		
		35	5.81 d $J_{1,2}$ = 4.2	5.57 t $J_{1,2}$ = 4.2			5.41 s			

[a] Chemical shifts are in δ and coupling constants are given in hertz. [b] Internal TMS standard. [c] Internal DMSO-d_5 standard. [d] Recorded on a T-60 spectrometer. [e] Recorded on XL-100 spectrometer. [f] Signals could not be resolved. [g] Signals could not be observed because of overlap with solvent absorptions. [h] Signals could not be observed because of overlap with signals of the major isomer. [i] s = singlet, d = doublet, t = triplet, and m = multiplet.

Table III
Nmr Spectral Data for the Methylenazulenate Anions[a,b]

Reactants	Nmr solvents	Product	Proton positions 1,3	2	5	7	CH_3	CH_2
4-Methylazuiene + $C_6H_5N(CH_3)Na$ (**30**)[c,d]	DMSO-d_6	**1**	—5.40–6.20[f]— m		—4.90–5.30[f]— m			3.91 and 4.42 d's J_{gem} = 3.7
4,6,8-Trimethylazulene + $C_6H_5N(CH_3)Na$ (**30**)[c,d]	DMSO-d_6	**32**	6.02 d $J_{1,2}$ = 3.2	*f*	5.93 s	5.03 s	2.24 and 2.02	3.81 and 4.32 d's J_{gem} = 3.7
		33	5.86 d $J_{1,2}$ = 3.2	5.56 t $J_{1,2}$ = 3.2	—5.22— s		2.08 s	3.83 s
4,6,8-Trimethylazulene + CD_3SOCD_2Na (**27**)[b,e]	DMSO-d_6	**32**	6.22 d $J_{1,2}$ = 3.2	*f*	6.12 s	5.28 s	*g*	4.03 and 4.55 d's J_{gem} = 6.0
		33	6.06 d $J_{1,2}$ = 3.2	5.80 t $J_{1,2}$ = 3.2	—5.61— s		2.33 s	4.06 s
4,6,8-Trimethylazulene + $(C_6H_5)_3CNa$ (**18**)[b,e]	THF	**32**	6.09 broad s	*f*	5.97 s	5.13 s	*f*	3.95 and 4.53 s's
		33	5.94 d $J_{1,2}$ = 3.0	5.68 t $J_{1,2}$ = 3.0	—5.45— s		*g*	3.98 s

[a] Chemical shifts are in δ and coupling constants are given in hertz. [b] Internal TMS standard. [c] Internal DMSO-d_5 standard. [d] Recorded on a T-60 spectrometer. [e] Recorded on a XL-100 spectrometer. [f] Signals could not be resolved. [g] Signals could not be observed because of overlap with solvent absorptions. [h] s = singlet, d = doublet, t = triplet, and m = multiplet.

24 **25**

When the solvent was removed from the mixture of **24** and **25** and the residue was dissolved in dimethyl sulfoxide-d_6, only the nmr spectrum of **24** could be observed. While we do not believe that **24** and **25** can equilibrate, we can only guess that a trace of water was introduced into the system during the exchange of solvents, causing destruction of **25**. However, the proton absorptions from its conjugate acid were not observed.

Addition to azulene by the bulky carbon nucleophile tritylsodium (**18**) also occurred. A tetrahydrofuran solution of azulene was "titrated" with **18** until the color of the solution was orange. The nmr spectrum (Figure 2b) was quite similar to that of **20** and indicated the presence of a single addition product, sodium 6-trityl-6*H*-azulenate (**26**) (see Table II for the proton assignments).

26

The third carbon nucleophile investigated was sodium methylsulfinylmethide (**27**). Mixing equimolar amounts of azulene and **27**-d_5 in DMSO-d_6 at 25° produced a yellow solution. Analysis of the nmr spectrum of this solution showed that it contained a mixture of sodium 4-methylsulfinylmethyl-d_5-4*H*-azulenate (**28**) and sodium 6-methylsulfinylmethyl-d_5-6*H*-azulenate (**29**) in a 9:1 ratio (Figure 2c). The **28**:**29** ratio did not change with time at 25°.

28 **29**

In each of the above cases, both nitrogen bases (**3** and **15**) and the three carbon bases (**18**, **23**, and **27**) reacted with azulene by addition to the ring 4 and/or 6 positions, yielding azulenate anions. It was of interest to us to determine how this addition reaction (a type of Meisenheimer complex formation) would compete with proton abstraction from the methyl groups of 4- and 6-methylazulene which yield the corresponding methyleneazulenates (*e.g.*, **1**).

To standardize our analysis of the nmr spectra of such methyleneazulenates, **1** was prepared by reaction of 4-methylazulene and sodium *N*-methylanilide (**30**) in tetrahydrofuran. Replacing this solvent with DMSO-d_6 and analysis of the nmr spectrum determined in the latter solvent produced the results given in Table III for **1**.

4,6,8-Trimethylazulene (**31**) reacted with **30** in tetrahydrofuran at 25° to produce a yellow solution. The solvent was replaced with DMSO-d_6 and the nmr spectrum was recorded at 33°; see Table III. The spectrum can be accounted for as a mixture of sodium 6,8-dimethyl-4-methyleneazulenate (**32**) and sodium 4,8-dimethyl-6-methyleneazulenate (**33**); the spectrum was not integrated. Carbonation of the mixture gave a 79% yield of a mixture of 6,8-dimethyl-4-azulylacetic acid (45%) and 4,8-dimethyl-

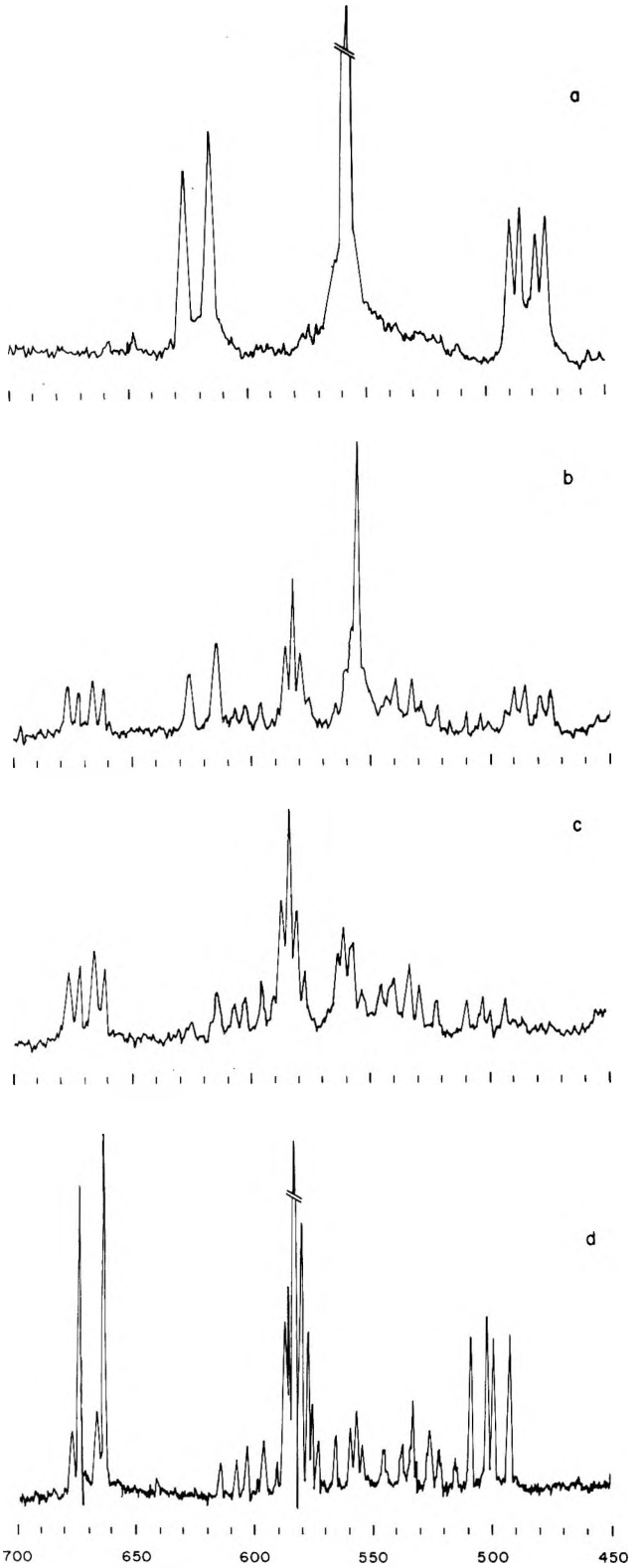


Figure 1. XL-100 spectra at −20° of (a) lithium 6-*N,N*-dicyclohexylamino-6*H*-azulenate (**20**) in THF, (b) THF solution of lithium dimethylamide added to (a) after 18 min at −20° giving a mixture of **20**, lithium 4-dimethylamino-4*H*-azulenate (**21**), and lithium 6-dimethylamino-6*H*-azulenate (**22**), (c) same as (b) but after 75 min at −20°, and (d) after 90 min at −20° and 20 min at 33°; scale in hertz.

6-azulylacetic acid (55%). Carrying out the formation of **32** and **33** at 25° and carbonation at −70 and −30° had only a negligible effect on the acid product composition.

When equimolar amounts of **31** and **27**-d_5 were allowed to react in DMSO-d_6 at 25° an orange solution resulted. While the seven-membered ring proton assignments of **32**

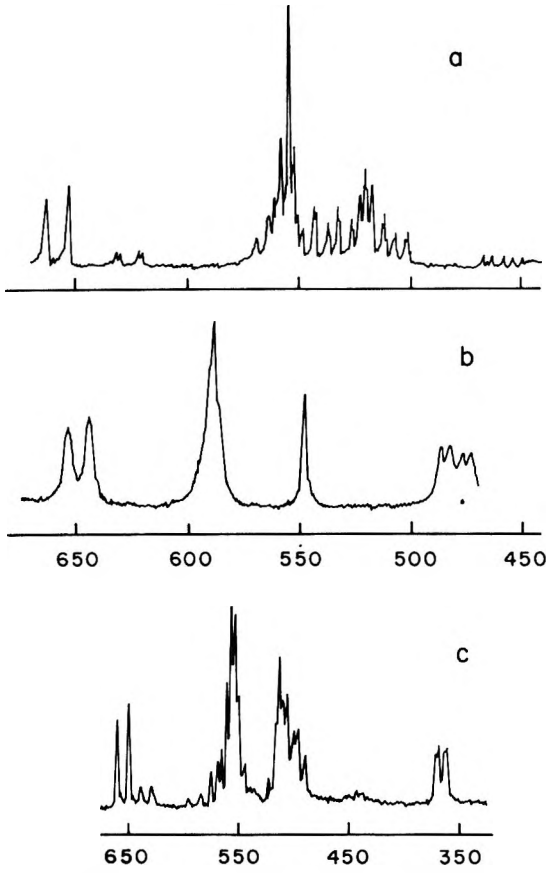
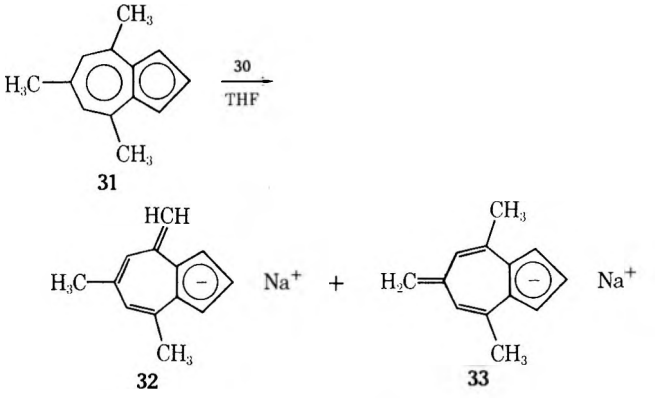


Figure 2. XL-100 spectra of (a) a mixture of lithium 4-methyl-4*H*- (**24**) and lithium 6-methyl-6*H*-azulenate (**25**) in THF, (b) sodium 6-trityl-6*H*-azulenate (**26**) in THF (peak at 546 Hz is Ph_3CH), and (c) a mixture of sodium 4-methylsulfinylmethyl-d_5-4*H*- (**28**) and sodium 6-methylsulfinylmethyl-d_5-6*H*-azulenate (**29**) in DMSO-d_6; scale in hertz.



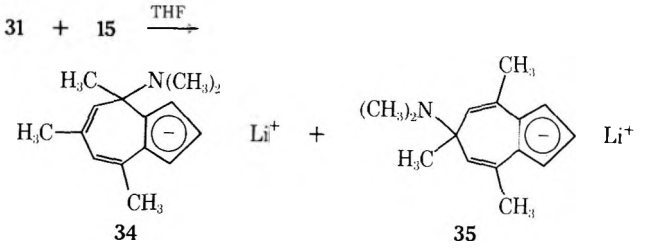
in this medium are tentative (Table III), the nmr spectrum indicated that the product of this reaction was a mixture of **32** and **33** formed by proton abstraction. Integration of C_6 methylene *vs.* the C_5 and C_7 ring protons of **33** indicated about 28% deuterium exchange of the C_6-methylene protons with solvent after standing for 2 hr at 25°. Repeating this reaction with **27** in DMSO and integration of the δ 4.55 C_4-methylene proton of **32** *vs.* the C_2 proton of **33** gave the **32:33** ratio of 1:3.

Reaction of **31** and **18** in tetrahydrofuran at 25° gave an orange solution. The nmr spectrum was recorded (Table III), and integration of the C_1 and C_3 protons of **32** *vs.* those of **33** showed that these two anions were produced in a **32:33** ratio of 1:3, the same ratio as that found from the reaction of **31** and **27**.

As was pointed out in the previous section, **3** appeared to add exclusively to 6-methylazulene in ether solvent, but in tetrahydrofuran this reaction resulted in proton ab-

straction from the methyl group to yield lithium 6-methyleneazulenate. The latter reaction mode was also apparently followed in the reaction of 4-methylazulene and 3 in tetrahydrofuran producing lithium 4-methyleneazulenate.

However, when 15 was allowed to react with hydrocarbon 31, no evidence for methyl group proton abstraction was found; instead the products of nucleophilic addition were observed (see Table II). The nmr spectrum of the yellow solution resulting from reaction of 15 and 31 in tetrahydrofuran at 25° was interpreted as that of a mixture of lithium 4,6,8-trimethyl-4-dimethylaminoazulenate (34) and lithium 4,6,8-trimethyl-6-dimethylaminoazulenate (35). Integration of the C_7 and C_2 protons of 34 and 35, respectively, gave a 34:35 ratio of 3:1. The relative

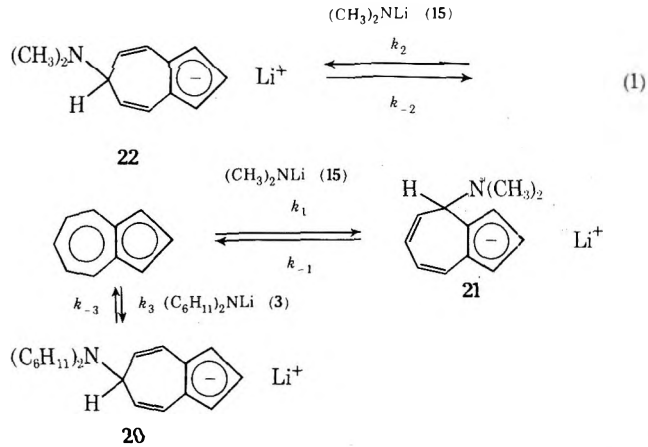


34 35

amount of 35 increased as a function of time when the sample was maintained at 25° as seen in the changes in the 34:35 ratio: 15 min, 3:2, 30 min, 1:1; and 3 hr, 3:7. No signals for anions 32 or 33 were observed.

Discussion

Reactions with Nitrogen Bases. The temperature dependency of the product compositions from the addition reactions of azulene and trimethylazulene 31 with 15 suggests that the ring C_4 position was the site of kinetically controlled nucleophilic addition while addition to the ring C_6 position led to the product of thermodynamic control. The mechanism by which the Meisenheimer type complexes 21 and 22 (34 and 35) are equilibrated (K_1 and K_2) might involve a small (unobservable by nmr) concentration of azulene present in the mixture or an S_N2' type of displacement on 21 or 22 by external nucleophile. The latter mechanistic possibility, however, would require an ionic attack on an anion and is believed to be less likely than the former suggested mechanism involving free azulene.



Although a similar equilibrium between azulene + 3 ⇄ 20 could not be established directly, the results of the following experiment lead us to conclude that k_{-3} is present. Equivalent amounts of azulene and 3 in tetrahydrofuran were mixed at 33° and the nmr spectrum was recorded, showing the presence of 20 along with a small amount of unreacted azulene. To this solution was added an equivalent amount of 15 in tetrahydrofuran at −10°. The nmr spectrum was immediately recorded and revealed the presence of a new pair of doublets at δ 6.71 and 6.65 attributed to 21 and 22. While it was not possible to accurately determine the relative amounts of 20, 21, and 22 owing to overlapping absorptions, the spectra showed that the amount of 20 decreased and 21 and 22 concentrations increased on standing at −10°. After 1 hr at −10° only a trace of 20 could be observed.

Accepting our proposed mechanism for the formation and equilibration of 20–22, the above result says that K_1 and K_2 are larger than K_3 by factors of 20–100. This is qualitatively the same conclusion reached from considering the equivalents of base needed to completely react with azulene. This probably reflects the increased steric size of the cyclohexyl groups in 20 compared to methyl groups in 22. However, we presently have no direct way of knowing if this influences only the forward (k_1, k_2, and k_3) or reverse (k_{-1}, k_{-2}, and k_{-3}) steps, or both. This also gives no information of the relative magnitudes of forward and reverse rate constants involved in yielding 20–22 except that we know that $k_1 > k_2$ from equilibration studies. From the observations that both nitrogen nucleophiles, 3 and 15, "immediately" decolorized azulene solutions with rapid mixing we know that k_1, k_2, and k_3 are large bimolecular rate constants. Assuming a steric effect in the additions of 3 and 15 to the azulene ring 4 and 6 positions we would expect $k_1 > k_2 > k_3$.

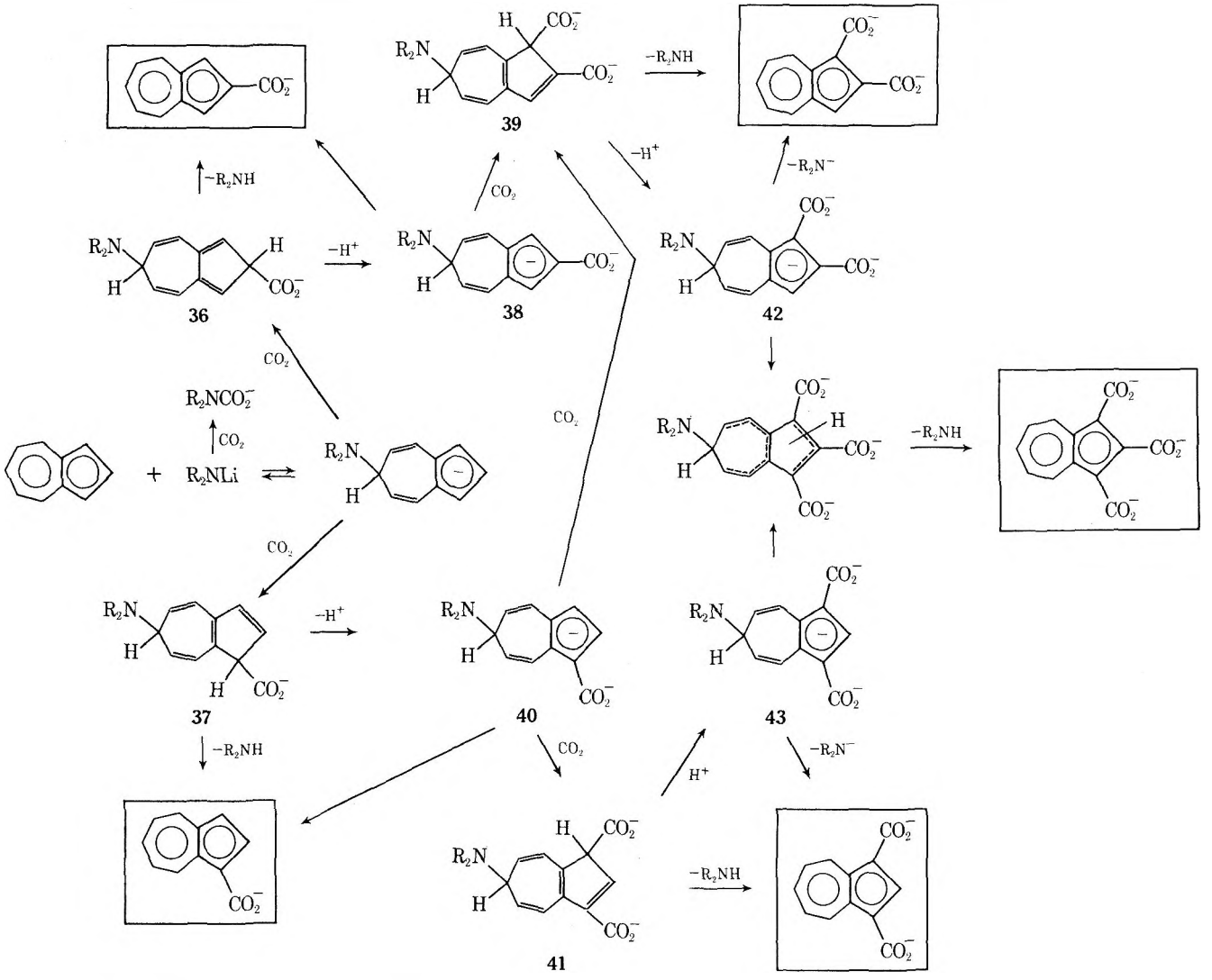
Qualitatively, there appears to be a definite difference in the rates of reaction of 3 and 15 with carbon dioxide. Bubbling carbon dioxide into a solution of 15 in ether resulted in immediate formation of a white precipitate, probably lithium dimethylcarbamate. Similar treatment of an ether solution of 3 required 30–40 sec before a precipitate was observed which slowly increased in amount. Ignoring any gross solubility differences in the two salts, we take this to mean that 15 reacts considerably faster with carbon dioxide than does 3.

Having identified the products from the reaction of azulene and 3 and 15 as Meisenheimer-type complexes 20, and 21 and 22, we can proceed to discuss the suspected processes resulting in the formation of the nuclear carbonation products from reaction of 20 with carbon dioxide as well as reasons why related results fail to occur on carbonation of 21 and 22. The proposed pathways leading from 20 to the five nuclear carbonation products 10–14 are given in Scheme I. Carbonation of 20 leading to the monocarboxylated products (10 and 13) involving loss of the elements of dicyclohexylamine from their respective intermediates, 36 and 37, is straightforward. However, to form the di- and tricarboxylated products we believe requires that the loss of a proton from 36 and 37 (39 and 41) yielding cyclopentadienidecarboxylates 38 and 40 (42 and 43) must compete with total loss of the amine. Intermediates 38, 40, 42, and 43 may also eject dicyclohexylamide to yield their respective carboxylic acid salts.

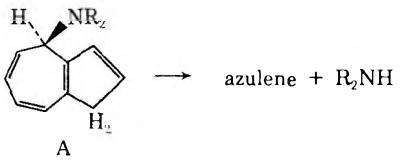
In each of the reactions of 5- and 6-methylazulene and azulene with 3 followed by reaction with carbon dioxide, substantial amounts of the starting azulene were recovered even though the azulene had been totally (by nmr) converted to its Meisenheimer-type complex prior to carbonation. This might result in at least three ways: (1) competitive carbonation of 3 in equilibrium with the azulene, (2) carbonation at a bridgehead center with that product reverting to the azulene during work-up, and/or (3) a ready proton exchange between the initially formed adduct and the carbonation products generating anions such as 38 and 40 and A.[21]

While we believe that this mechanistic scheme accounts for the variety of products derived from carbonation of 20, we must now deal with the fact that *only* starting azulene is found (generally 90+%) when mixtures of 21 and 22 and 34

Scheme I
Mechanistic Pathways for Formation of the Five Nuclear Carbonation Products from Azulene[a]



[a] For convenience the cations have been omitted.



and 35 are carbonated. Since the rates of five-membered ring carbonation of 20 and 22 should be approximately the same, the reason for the anomalous behavior of 22 must then lie in the relative rates of previous steps. We suggest that the explanation may be in the rates defined by k_{-1} and k_{-2} being at least equal to but probably greater than k_{-3} in eq 1. Taken together with the apparently much faster rate of reaction of carbonation of 15 compared to 3 could then account for the observed results. If this is correct then k_2 must be much greater than k_3 in general agreement with the analysis of k_1, k_2, and k_3 given above. This may simply reflect solvation energy differences in the amides 3 and 15, and their respective adducts 20, and 21 and 22.

It is again interesting to note the solvent effect in the type of reaction product from 6-methylazulene and 3; in ether ring addition was observed while in tetrahydrofuran proton abstraction exclusively took place. When the amide is the dimethyl derivative 15 and it was allowed to react with 4,6,8-trimethylazulene (31) in tetrahydrofuran only the products (34 and 35) of addition to the ring were observed in the nmr spectrum. These results appear to demonstrate the better nucleophilic *vs.* basic character of 15 in these reactions compared to 3. A probable major factor in this increased ease of nucleophilic addition by 15 is the much larger steric requirements for nucleophilic attack at the ring sites by 3.

Reactions with Carbon Bases. In marked contrast with the results of the nitrogen bases, when the carbon bases (18, 23, and 27) added to the 4 and/or 6 positions of the azulene ring the products were thermally stable and in the case with 23 the product mixture was invariant over the addition temperature range investigated. If we accept the premise that these product distributions are formed under kinetic control, such studies with carbon nucleophiles of varying structure could give a clear relationship between the steric size of the nucleophile and the $\Delta\Delta F^*$'s for attack at the two ring positions. The extreme with the bulky nucleophile, 18, is to yield exclusive addition to the 6 position while with the small nucleophiles, 23 and 27, the preference (9:1) is to add to the ring 4 position. Thus with both carbon (kinetic) and nitrogen (kinetic and thermodynamic) nucleophiles, steric bulk of the attacking base is important in determining the ring position to be attacked.

As was the case with the nitrogen bases, the carbon bases show different nucleophilic *vs.* basic characters. Hafner[19] reported that 23 added to 4-methylazulene and

after protonation and dehydrogenation the product 4,8-dimethylazulene was isolated in 52% yield. However, the reaction between **31** and **18** or **27** yields only the products of proton abstraction from the methyl groups.[5a] The dynamics involved with the carbon nucleophiles, however, were not as well investigated as were those with the nitrogen bases.

Experimental Section[22]

Lithium Dicyclohexylamide (3). Using a dry syringe, 4.39 g (0.0242 mol) of twice-distilled dicyclohexylamine was injected into a flame-dried three-necked flask containing 25 ml of dry ether (distilled from $LiAlH_4$) under a nitrogen atmosphere. With continous stirring, the solution was cooled to −20° and 20 ml of a 1.22 *M* solution of methyllithium in ether was slowly injected into the solution (vigorous bubbling). The solution was allowed to stir for 0.5 hr as the solution warmed to room temperature. Titration of two aliquots of this solution with standard hydrochloric acid indicated the solution to be 0.519 *M* in amide.

Solutions of lithium dimethylamide (**15**) were prepared by this method also.

Reaction of 3 with 5-Methylazulene Followed by Carbonation and Methylation. To a flame-dried flask under a nitrogen atmosphere was added 426 mg (3.00 mmol) of 5-methylazulene in 10 ml of dry ether. The contents of the flask were cooled to −20° and 5.70 ml of the 0.519 *M* **3** solution was slowly injected into the solution by means of a syringe. With stirring the solution was allowed to come to room temperature over 20 min with no visible color change. Dry carbon dioxide (passed through sulfuric acid and Na_2CO_3-Drierite) was bubbled through the solution for 0.5 hr with the formation of a red-violet precipitate in the flask. The reaction mixture was diluted with 50 ml of cold 5% aqueous sodium hydroxide and extracted with ether. The ether layer containing unreacted 5-methylazulene was washed with six 50-ml portions of 5% aqueous sodium hydroxide, water, two 100-ml portions of 10% hydrochloric acid, and water. The ether layer was dried ($MgSO_4$), the solvent volume was reduced, and the residue was chromatographed on 50 g of basic alumina with 9:1 hexane–dichloromethane to yield 0.255 g of 5-methylazulene.

The sodium hydroxide solutions were combined, acidified, and extracted with 250 ml of ether. This ether layer was washed with water and dried ($MgSO_4$). To this solution was added an excess of an ether solution of diazomethane. After standing for 5 min, the ether layer was washed with two 100-ml portions of 5% aqueous sodium bicarbonate and water and dried ($MgSO_4$). After solvent reduction, the products were chromatographed on 70 g of basic alumina.

CCl_4–CH_2Cl_2 (3:1) eluted a violet band containing 102 mg (17%, 42.3% net) of a mixture of methyl 5- and 7-methyl-1-azulenecarboxylate (**4**) as a violet oil: ir (film) 5.91 μ (s, C=O); nmr (CCl_4, internal TMS) τ 0.36 (broad s, 0.7), 0.46 (d, 0.3), 1.71–3.00 (m, 5), 6.11 (s, CO_2CH_3, 3), 7.25 (s, CH_3, 0.7), 7.35 (s, CH_3, 0.3); visible-uv (cyclohexane) 657 nm (log ε 2.23), 598 (2.61), 552 (2.65), 372 (4.03), 358 (3.87), 342 (3.86), 301 (4.71), 290 (4.65), and 240 (4.32).

Anal. Calcd for $C_{13}H_{12}O_2$: C, 77.98; H, 6.04. Found: C, 78.20; H, 5.92.

CCl_4–CH_2Cl_2 (1:1) eluted a red band containing 19 mg (2.2%, 5.5% net) of a red oil identified as dimethyl 5-methyl-1,3-azulenedicarboxylate (**5**) on the basis of its visible spectrum (cyclohexane): 606 (O.D. 0.361), 554 (0.902), and 519 nm (0.978).

A violet-blue band was eluted with CCl_4–CH_2Cl_2 (1:3) containing 7 mg (0.9%, 2.3% net) of a mixture of dimethyl 5- and 7-methyl-1,2-azulenedicarboxylate (**6**) as a violet-blue oil based on the visible-uv spectra: ir (film) 5.83 (s, C=O) and 5.94 μ (s, C=O); visible-uv (cyclohexane) 588 nm (log ε 2.64), 368 (3.61), 350 (3.68), 303 (4.60), 293 (4.57), and 242 (4.35).

Reaction of 3 with 6-Methylazulene Followed by Carbonation and Methylation. Using the above procedure, 426 mg (3.00 mmol) of 6-methylazulene was allowed to react with 5.70 ml (2.95 mmol) of 0.519 *M* **3**. Upon warming to −10°, the color of the solution changed to yellow-black. To the solution was added an additional 25 ml of dry ether and dry carbon dioxide was bubbled through the solution at a moderate rate for 0.5 hr. From the base-insoluble fraction was recovered 315 mg of 6-methylazulene.

The acids were methylated with diazomethane and chromatographed on 70 g of basic alumina. CCl_4–CH_2Cl_2 (3:1) eluted a violet band containing 50 mg (8.3%, 32% net) of methyl 6-methyl-1-azulenecarboxylate (**7**) as red-violet prisms: mp 77–79°; ir (KBr) 5.92 μ (s, C=O); nmr (CCl_4, internal TMS) τ 0.54 (d, *J* = 10.0 Hz, C_8 H, 1), 1.81 (d, *J* = 10.0 Hz, C_4 H, 1), 1.85 (d, *J* = 4.0 Hz, 1), 2.50–3.00 (m, 3), 6.11 (s, CO_2CH_3, 3), and 7.36 (s, CH_3, 3); visible-uv (cyclohexane) 629 nm (log ε 2.17), 601 (2.22), 573 (2.56), 547 (2.57), 531 (2.61), 370 (4.02), 355 (3.89), 344 (3.85), 304 (4.81), 297 (4.71), 292 (4.72), 262 (3.87), 255 (3.96), and 235 (4.34); mass spectrum (70 eV, heated inlet) *m/e* (rel intensity) 200 ($M^{\cdot+}$, 58) and 169 (100).

Anal. Calcd for $C_{13}H_{12}O_2$: C, 77.98; H, 6.04. Found: C, 78.00; H, 6.30.

CCl_4–CH_2Cl_2 (1:1) eluted a blue band containing 20 mg (3.3%, 13% net) of blue plates, mp 108–110°, of methyl 6-methyl-2-azulenecarboxylate (**8**) based on spectral evidence: ir (KBr) 5.86 μ (s, C=O); nmr (CCl_4, internal TMS) τ 1.77 (d, *J* = 10.5 Hz, C_4 and C_8 H, 2), 2.34 (s, C_1 and C_3 H, 2), 2.96 (d, *J* = 10.5 Hz, C_5 and C_7 H, 2), 6.08 (s, CO_2CH_3, 3), and 7.35 (s, CH_3, 3); visible-uv (cyclohexane) 704 nm (log ε 2.23), 694 (2.19), 637 (2.53), 592 (2.52), 362 (3.85), 348 (3.73), 336 (3.67), 296 (4.72), 285 (4.75), 266 (4.20), and 240 (4.17); mass spectrum (70 eV, heated inlet) *m/e* (rel intensity) 200 ($M^{\cdot+}$, 64) and 169 (100).

A second violet band was eluted with CCl_4–CH_2Cl_2 (1:3) and contained 39 mg (5.0%, 19% net) of violet needles, mp 69–71°, of dimethyl 6-methyl-1,2-azulenedicarboxylate (**9**) based on spectral evidence: ir (KBr) 5.80 (s, C=O) and 5.91 μ (s, C=O); nmr (CCl_4, internal TMS) τ 0.80 (d, *J* = 10.5 Hz, C_8 H, 1), 1.79 (d, *J* = 10.5 Hz, C_4 H, 1), 2.50–2.90 (m, 3), 6.10 (s, CO_2CH_3, 3), 6.11 (s, CO_2CH_3, 3), and 7.84 (s, CH_3, 3); visible-uv (cyclohexane) 563 nm (log ε 2.67), 368 (3.62), 352 (3.77), 305 (4.78), 294 (4.72), and 423 (4.26); mass spectrum (70 eV, heated inlet) *m/e* (rel intensity) 258 ($M^{\cdot+}$, 61), 227 (100), 200 (9), and 197 (12).

Reaction of 3 with Azulene Followed by Carbonation and Methylation. A. In Ether. Following the above procedure, 384 mg (3.0 mmol) of azulene in 10 ml of ether was allowed to react with 5.70 ml (2.95 mmol) of a 0.519 *M* ether solution of **3** at −20°. The solution was warmed to room temperature with no visible color change. Dry carbon dioxide was bubbled through the solution for 0.5 hr. From the base-insoluble fraction 310 mg of azulene was obtained.

The acids were methylated with diazomethane and chromatographed on 70 g of basic alumina. CCl_4–CH_2Cl_2 (3:1) eluted a violet band containing 76 mg (14%, 71% net) of methyl 1-azulenecarboxylate (**10**) as violet needles: mp 54–55° (lit.[10a] mp 56–57°); ir (KBr) 5.93 μ (s, C=O); nmr (CCl_4, internal TMS) τ 0.30 (broad d, C_8 H, 1), 1.62 and 1.70 (two superimposed d, 2), 2.00 and 2.80 (m, 4), and 6.10 (s, CO_2CH_3, 3); visible-uv (cyclohexane) 645 nm (log ε 2.19), 612 (2.21), 588 (2.55), 561 (2.54), 542 (2.60), 368 (4.04), 350 (4.03), 338 (3.96), 298 (4.78), 292 (4.68), 286 (4.69), 255 (3.88), 249 (4.03), and 236 (4.35).

CCl_4–CH_2Cl_2 (1:1) eluted a red band containing 17 mg (2.3%, 12% net) of red needles of dimethyl azulene-1,3-dicarboxylate (**11**): mp 171–173° (lit.[23] mp 171°); ir (KBr) 5.89 μ (s, C=O); nmr ($CDCl_3$, internal TMS) τ 0.05 (broad d, C_4 and C_8 H, 2), 1.07 (s, C_2 H, 1), 2.12 (m, 3), and 6.02 (s, CO_2CH_3, 3); visible-uv (cyclohexane) 598 nm (log ε 2.21), 547 (2.64), 511 (2.70), 374 (4.03), 370 (4.05), 366 (3.99), 361 (4.00), 330 (3.71), 303 (4.71), 296 (4.60), 292 (4.58), 268 (4.52), 263 (4.40), 249 (4.15), and 235 (4.63).

A second violet band was eluted with CCl_4–CH_2Cl_2 (1:3) containing 10 mg (1.4%, 7% net) of dimethyl 1,2-azulenedicarboxylate (**12**) as a violet oil: ir (film) 5.80 (s, C=O) and 5.91 μ (s, C=O); nmr (CCl_4, internal TMS) τ 0.55 (broad d, C_8 H, 1), 1.55 (broad d, C_4 H, 1), 1.98–2.80 (m, 4), and 6.06 and 6.07 (two overlapping s, CO_2CH_3, 6); visible-uv (cyclohexane) 578 nm (log ε 2.66), 364 (3.68), 347 (3.85), 300 (4.72), 290 (4.69), and 238 (4.35).

Anal. Calcd for $C_{14}H_{12}O_4$: C, 68.84; H, 4.95. Found: C, 68.95; H, 5.21.

B. In Tetrahydrofuran. To a solution of 750 mg (5.9 mmol) of azulene in 10 ml of dry tetrahydrofuran (distilled from $LiAlH_4$) cooled to −30° under a nitrogen atmosphere was added 5.9 ml (5.9 mmol) of 1 *M* **3** in tetrahydrofuran. There was no apparent color change and the solution was warmed to 25°, where it took on a green cast. Carbon dioxide was bubbled in and produced a blue solution. Carbon dioxide addition was continued for 10 min and then 100 ml of water was added which produced effervescence. An additional 400 ml of water and 100 ml of 10% potassium hydroxide were added and the basic solution was extracted with three 100-ml portions of ether. The ether layer was acidified with 10% hydrochloric acid and dicyclohexylamine hydrochloride precipitated. This white precipitate was filtered, and the ethereal filtrate was washed with three 100-ml portions of water and dried ($MgSO_4$). Concentration of the solvent followed by chromatogra-

phy on basic, activated alumina gave on elution with carbon tetrachloride 389 mg (52%) of starting azulene.

The violet, basic solution was acidified with cold 20% hydrochloric acid and extracted with 900 ml of ether. The violet ether solution was washed with three 100-ml portions of water and dried ($MgSO_4$). The carboxylic acids were converted to their methyl esters using diazomethane in ether and chromatographed on neutral activity II Woelm alumina.[24] CCl_4 eluted 122 mg (11%, 23% net) of methyl 1-azulenecarboxylate (**10**), mp 54–55°, followed by 51 mg (5%, 10% net) of methyl 2-azulenecarboxylate (**13**): mp 109–110° (lit.[25] mp 110–111°); ir (KBr) 5.82 μ (C=O); nmr ($CDCl_3$, internal TMS) τ 1.4–3.2 (m, Az H's, 7) and 6.03 (s, CH_3); visible-uv (cyclohexane) 724 nm (log ϵ 2.35), 654 (2.68), 605 (2.66), 356 (3.52), 344 (3.72), 330 (3.63), and 284 (4.72). Elution with CCl_4–CH_2Cl_2 (3:1) gave 53 mg (4%, 8% net) of dimethyl 1,3-azulenedicarboxylate (**11**), mp 174.5–176°. With CCl_4–CH_2Cl_2 (1:1), 76 mg (5%, 11% net) of dimethyl 1,2-azulenedicarboxylate (**12**) was eluted which crystallized; recrystallization from hexane gave violet-blue crystals, mp 46.5–47.5° (lit.[26] oil). Elution with CH_2Cl_2 gave 14 mg (1%, 2% net) of trimethyl 1,2,3-azulenetricarboxylate (**14**), which was recrystallized from CH_2Cl_2–petroleum ether to give red crystals: mp 155–156°; ir (KBr) 5.73 (C=O) and 5.92 μ (C=O); nmr ($CDCl_3$, internal TMS) τ 0.0–2.4 (m, Az H's, 5), 5.97 (s, CH_3, 3), and 6.07 (s, CH_3, 6); visible-uv (CH_2Cl_2) 500 nm (log ϵ 2.83), 368 (3.75), 335 (3.74), 304 (4.64), 294 (sh), and 272 (4.42).

Anal. Calcd for $C_{16}H_{14}O_6$: C, 63.58; H, 4.67. Found: C, 63.41; H, 4.53.

Reaction of Azulene with 15 in Tetrahydrofuran and Quenching with Methanol. To 200 mg (1.56 mmol) of azulene dissolved in 5 ml of dry tetrahydrofuran (distilled from $LiAlH_4$) under a nitrogen atmosphere and cooled to 0° was added 70 mg of dimethylamine in 5 ml of dry tetrahydrofuran followed by 1 ml (1.5 mmol) of 1.5 *M* methyllithium in ether dropwise. The solution turned from blue to yellow with the addition of the final drops of methyllithium. After cooling to −70°, 0.1 ml of absolute methanol was added, at which time the yellow solution was washed with three 100-ml portions of water and dried ($MgSO_4$). Evaporation of the solvent gave 195 mg (98%) of starting azulene.

Reaction of Azulene with 15 in Tetrahydrofuran Followed by Addition of Carbon Dioxide. To a solution of 100 mg (0.78 mmol) of azulene dissolved in 10 ml of dry tetrahydrofuran (distilled from $LiAlH_4$) under a nitrogen atmosphere and cooled to −30° was added 0.78 ml (0.78 mmol) of 1 *M* lithium dimethylamide in tetrahydrofuran. The solution immediately turned light green and was allowed to warm to room temperature. Carbon dioxide was bubbled into the solution, which turned blue. Carbon dioxide addition was continued for 10 min followed by the addition of 100 ml of water, which produced effervescence; 10 ml of 10% potassium hydroxide and 100 ml of ether were added. The ether layer was separated and washed with three 100-ml portions of water and dried ($MgSO_4$). Chromatography over basic alumina on elution with CCl_4 gave 94 mg (94%) of starting azulene.

Reaction of 4-Methylazulene with 15 Followed by Addition of Carbon Dioxide. This reaction was carried out as described above starting with 100 mg (0.70 mmol) of 4-methylazulene, 2 ml of dry tetrahydrofuran (distilled from $LiAlH_4$), and 2 ml (1.20 mmol) of 0.60 *M* lithium dimethylamide in tetrahydrofuran at −70°. The yellow solution was diluted with 10 ml of ether and allowed to warm to 25°. With the addition of carbon dioxide, which was continued for 10 min, the solution turned blue and a white precipitate formed. The addition of 100 ml of water produced effervescence and the white precipitate dissolved. Ether (100 ml) was added, and the colorless, basic, aqueous layer separated. Work-up as above gave 93 mg (93%) of starting 4-methylazulene.

When this reaction was carried out in tetrahydrofuran or benzene as solvent, the recoveries of 4-methylazulene were 87 and 92%, respectively.

Reaction of Azulene with 15 Followed by Oxidation with Oxygen. To a solution of 200 mg (1.56 mmol) of azulene in 5 ml of dry tetrahydrofuran under a nitrogen atmosphere and cooled to −70° was added 2.6 ml (1.6 mmol) of 0.60 *M* lithium dimethylamide in tetrahydrofuran. The color changed from blue to light green with the addition of the base. Oxygen was bubbled into this solution at −70° for 5 min but no color change was noted. The solution was allowed to warm to 25° and oxygen addition was continued for 20 min. To the reaction mixture was added 100 ml of water and 100 ml of ether. The ether layer was separated, washed with three 100-ml portions of water, and dried (Na_2SO_4). Chromatography over basic, activity I–II alumina[24] gave on elution with carbon tetrachloride 83 mg (42%) of starting azulene. Continued elution with carbon tetrachloride gave 21 mg (8%, net 13.5%) of 4-*N*,*N*-dimethylaminoazulene (**16**) as an unstable purple oil: ir (neat film) 3.51 (CH), 6.47, 7.46, and 10.93 μ; nmr ($CDCl_3$, internal TMS) τ 1.8–3.7 (m, Az H's, 7), 6.72 (s, CH_3, 6); visible-uv (cyclohexane) 715 nm (log ϵ 1.17), 546 (2.59), 308 (4.05), and 274 (4.51).

Anal. Calcd for $C_{12}H_{13}N$: C, 84.15; H, 7.67. Found: C, 84.31; H, 7.56.

Elution with methylene chloride gave 33 mg (12%, net 21.3%) of 6-*N*,*N*-dimethylaminoazulene (**17**) as a yellow solid: mp 169–170° (lit.[12] mp 163–164.5°); ir (KBr) 3.50, 6.35, 7.38, and 12.20 μ; nmr ($CDCl_3$, internal TMS) τ 1.8–3.7 (m, Az H's, 7) and 6.81 (s, CH_3, 6); visible-uv (cyclohexane) 505 nm (log ϵ 2.59), 486 (2.60), 475 (sh), 390 (4.72), 382 (4.61), and 316 nm (4.79).

When the above reaction of azulene (100 mg) and **15** was carried out at −70°, the mixture allowed to warm to room temperature, and then the oxygen bubbled into the solution, work-up gave a trace of recovered azulene, 9 mg (7%) of **16**, and 18 mg (14%) of **17**. Using chloranil in place of oxygen in this sequence gave only 15 mg (11%) of **16** as a pure product.

Reaction of 4,6,8-Trimethylazulene (31) and 15 in Tetrahydrofuran Followed by Addition of Carbon Dioxide. This reaction was carried out as described above starting with 200 mg (1.18 mmol) of 4,6,8-trimethylazulene in 10 ml of dry tetrahydrofuran at −70°. With the addition of 3.90 ml (2.34 mmol) of 0.60 *M* lithium dimethylamide in tetrahydrofuran the solution turned from purple to yellow. The solution was warmed to 25° and addition of carbon dioxide for 10 min gave a purple solution. Addition of 50 ml of water and extraction with 50 ml of ether left a colorless, basic, aqueous solution. Work-up of the ether layer gave on chromatographic elution with carbon tetrachloride 168 mg (84%) of the starting 4,6,8-trimethylazulene.

When the above reaction mixture was quenched with water, 97% of the starting 4,6,8-trimethylazulene was recovered.

Reaction of Azulene and Tritylsodium. To a solution of 100 mg (0.78 mmol) of azulene dissolved in 10 ml of dry tetrahydrofuran (distilled from $LiAlH_4$) under a nitrogen atmosphere was added 1.5 ml of an approximately 0.7 *M* solution of tritylsodium in ether. To the resulting orange solution cooled to −70° were added 1 ml of absolute methanol and 1 g of chloranil. The mixture was diluted with 100 ml of ether and stirred at 25° for 24 hr. The excess chloranil was removed by filtration and the ether solution was washed with water and dried ($MgSO_4$). The solvent was concentrated and the residue was chromatographed over basic, activated alumina, where elution with carbon tetrachloride gave a blue oil. On standing in ether a white precipitate formed and was filtered. The filtrate was concentrated and crystallization from carbon tetrachloride–petroleum ether gave a blue solid which could not be purified by further crystallization or repeated chromatography: mp 205–215°; ir (KBr) 6.41, 6.76, 7.09, and 7.35 μ; nmr (CCl_4, internal TMS) τ 1.90 (d, C_4 and C_8 H, 2), 2.1–3.2 (m, Az H's and phenyl H's, integrated for 19 instead of 20); visible-uv (cyclohexane) 696 nm (O.D. 0.120), 658 (0.138), 632 (0.276), 604 (0.278), 579 (0.035), 557 (0.254), 348 (0.102), 341 (0.098), 333 (0.092), 299 (0.979), 289 (0.885), and 284 (0.923); mass spectrum (70 eV) *m*/e (rel intensity) 370 ($M\cdot^+$, 50), 243 (241), and 127 (11).

It was noted that on standing in petroleum ether in the light or in the dark at −20° a white precipitate formed in a period of several days. The solution showed no color change.

Reaction of 6-Methylazulene and 3 in Tetrahydrofuran Followed by Addition of Carbon Dioxide. Following the procedure described above, 200 mg (1.41 mmol) of 6-methylazulene and 1.41 ml (1.41 mmol) of 1 *M* lithium dicyclohexylamide in tetrahydrofuran were added to 10 ml of dry tetrahydrofuran at −30° and the golden-colored solution was warmed to 25°. Carbon dioxide addition and the same work-up as described above gave 71 mg (36%) of recovered 6-methylazulene and 103 mg (39%) of 6-azulylacetic acid.[3]

Reaction of 4-Methylazulene with 3 in Tetrahydrofuran Followed by Addition of Carbon Dioxide. A solution of 274 mg (1.93 mmol) of 4-methylazulene in 10 ml of dry tetrahydrofuran (distilled from $LiAlH_4$) under a nitrogen atmosphere was cooled to −30°. When 1.93 ml (1.93 mmol) of 1 *M* lithium dicyclohexylamide was added the solution turned yellow. After warming to 25° carbon dioxide was added for 10 min; the initial addition produced a blue solution. To this was added 100 ml of water and 20 ml of 10% potassium hydroxide. The basic, aqueous layer was washed with two 100-ml portions of ether. The combined ether layers were worked up as described above to yield 59 mg (22%) of starting 4-methylazulene.

The aqueous, basic layer was acidified with 10% hydrochloric acid and extracted with three 100-ml portions of ether. Concentration gave 252 mg (70%) of 4-azulylacetic acid.[3]

Reaction of 4,6,8-Trimethylazulene and 3 Followed by Addition of Carbon Dioxide at 25°. Following the procedure described previously, 100 mg (0.59 mmol) of 4,6,8-trimethylazulene in 10 ml of dry tetrahydrofuran cooled to −50° was allowed to react with 0.59 ml (0.59 mmol) of 1 *M* lithium dicyclohexylamide in tetrahydrofuran and the solution turned brown. It was then allowed to warm up to 25° and stirred for 1 hr before carbon dioxide was added. The reaction mixture was worked up as described above and gave 16 mg (16%) of the starting 4,6,8-trimethylazulene and 99 mg (79%) of a mixture of acids. The acid mixture, as determined by nmr integration of the methylene protons, consisted of 45% 6,8-dimethyl-4-azulylacetic acid and 55% 4,8-dimethyl-6-azulylacetic acid.

The reaction was repeated with carbonation at −30° and gave a 65% yield of a mixture of acids which consisted of 44% 6,8-dimethyl-4-azulylacetic acid and 56% 4,8-dimethyl-6-azulylacetic acid.

The reaction was repeated with carbonation at −70° and gave a 43% yield of a mixture of acids consisting of 47% 6,8-dimethyl-4-azulylacetic acid and 53% 4,8-dimethyl-6-azulylacetic acid.

Reaction of 4,6,8-Trimethylazulene and Sodium *N*-Methylanilide in Tetrahydrofuran Followed by Addition of Carbon Dioxide at −10°. The reaction was carried out as described earlier starting with 100 mg (0.59 mmol) of 4,6,8-trimethylazulene in 50 ml of dry tetrahydrofuran cooled to −15°. To this was added 0.61 ml (0.59 mmol) of 0.97 *M* sodium *N*-methylanilide in tetrahydrofuran. The solution turned a golden color on warming to −10°. Carbon dioxide was bubbled in for 10 min, which immediately caused the solution to turn purple. Work-up as described earlier gave 112 mg (89%) of a mixture of 6,8-dimethyl-4-azulylacetic acid and 4,8-dimethyl-6-azulylacetic acid. Integration of the nmr spectrum of this mixture for the C_4 and C_6 methylene protons showed the mixture to be composed of 68 and 32%, respectively, of these two acids.

Reaction of 4,6,8-Trimethylazulene and Tritylsodium in Ether. Following the procedure outlined above, 100 mg (0.59 mmol) of 4,6,8-trimethylazulene in 10 ml of ether cooled to −15° was allowed to react with 2.2 ml of approximately 0.5 *M* tritylsodium (excess) in ether. The addition of carbon dioxide at 0° and work-up gave only base-soluble material. The acids were converted to their methyl esters and analysis of the nmr spectrum indicated that the mixture contained methyl 6,8-dimethyl-4-azulylacetate, methyl 4,8-dimethyl-6-azulylacetate, and methyl triphenylacetate: nmr (CCl_4, internal TMS) τ 2.2–3.1 (m, Ar and Az H's), 5.95–6.38 (group of singlets which are α-methylene and ester methyl protons), and 7.19–7.39 (three singlets, Az methyls).

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Registry No.—**1**, 51381-34-1; **3**, 4111-55-1; **4** (5-methyl), 51381-35-2; **4** (7-methyl), 51381-36-3; **5**, 51381-37-4; **6** (5-methyl), 51381-38-5; **6** (7-methyl), 51381-39-6; **7**, 51381-40-9; **8**, 51381-41-0; **9**, 51381-42-1; **10**, 14659-03-1; **11**, 51381-43-2; **12**, 39479-45-3; **13**, 14658-96-9; **14**, 51381-44-3; **15**, 3585-33-9; **16**, 51381-45-4; **17**, 2048-68-2; **18**, 4303-71-3; **20**, 51381-46-5; **21**, 51381-47-6; **22**, 51381-48-7; **23**, 917-54-4; **24**, 51381-49-8; **25**, 51381-50-1; **26**, 51381-51-2; **27**, 51464-52-9; **28**, 51381-52-3; **29**, 51381-53-4; **30**, 5000-15-7; **31**, 941-81-1; **32**, 51381-54-5; **33**, 51381-55-6; **34**, 51381-56-7; **35**, 51381-57-8; azulene, 275-51-4; 5-methylazulene, 1654-55-3; 6-methylazulene, 1654-52-0; 4-methylazulene, 17647-77-7; methyl 6,8-dimethyl-4-azulylacetate, 26157-18-6; methyl 4,8-dimethyl-6-azulenylacetate, 51381-58-9; methyl triphenylacetate, 5467-21-0.

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(13) It was observed that from hexane solutions of this blue solid a white precipitate slowly formed when the solutions were stored in laboratory light at 25° or in a freezer (dark) at −20°.
(14) A trityl group in the 1 position of azulene [1-tritylazulene, λ_{max} (C_6H_6) 602 nm, and 1,3-ditritylazulene, λ_{max} (C_6H_6) 619 nm][15] causes a +20 nm change in λ_{max} from azulene. A 6-alkyl group has $^2/_3$ of the absolute magnitude of $\Delta\lambda_{max}$ as does a 1-alkyl group. Assuming that this ratio holds for the trityl groups we would predict **19** to have λ_{max} 570 nm. Considering the differences in solvent and crudeness of the comparison, the agreement is quite good.
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(22) Melting points were determined on a Kofler hot stage and are uncorrected. Spectra were determined with commercial instruments (ir, Perkin-Elmer 137; nmr, Varian T-60; visible-uv, Cary 1; mass, AEI MS-9). Nmr spectral data are listed as centers except for multiplets where the range of the signals is given. All alumina is F-20 Alcoa, basic alumina, activity I assumed, unless otherwise specified.
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Nucleophilic Heteroaromatic Substitutions. XXXVII.[1] Aryloxyls as Leaving Groups in Nucleophilic Heteroaromatic Substitution with Piperidine. Structural and Hydrogen Isotope Effects

Fabio Fiorani, Gabriello Illuminati,* and Giancarlo Sleiter*

Istituto Chimico, Università di Roma, and Centro C.N.R. dei Meccanismi di Reazione, 00185 Roma, Italy

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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.

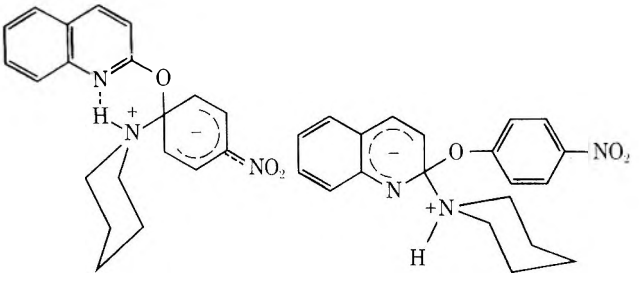
Product Analysis. The reaction of the heteroaryl aryl ethers, HET-OAr, with piperidine was generally found to involve attack on either side of the oxygen bridge (reactions 1 and 2). In order to ascertain whether a kinetic

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

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

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	% Piperidino-quinoline	% 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]

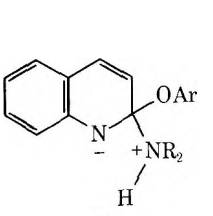
Secondly, we have an opportunity to compare, though in a limited set of structures, the oxygen leaving group effect with the basicity of the related aryloxide ion. An aryloxyl is expected to be a better leaving group as the related aryloxide ion becomes less basic. This is indeed the case for the nitrophenoxy 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 either 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.



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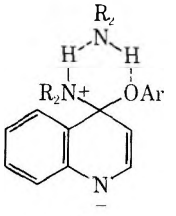

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The overall picture is quite different at the γ position. Despite the lower spread of the reactivity (see Table II), fairly higher isotope effects (1.96 and 2.46), in fact the highest known so far for these reactions, are observed in two out of the 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]

Morris J. Robins,* S. R. Naik,[2] and Alan S. K. Lee

Department of Chemistry, The University of Alberta, Edmonton, Alberta, Canada T6G 2G2

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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-

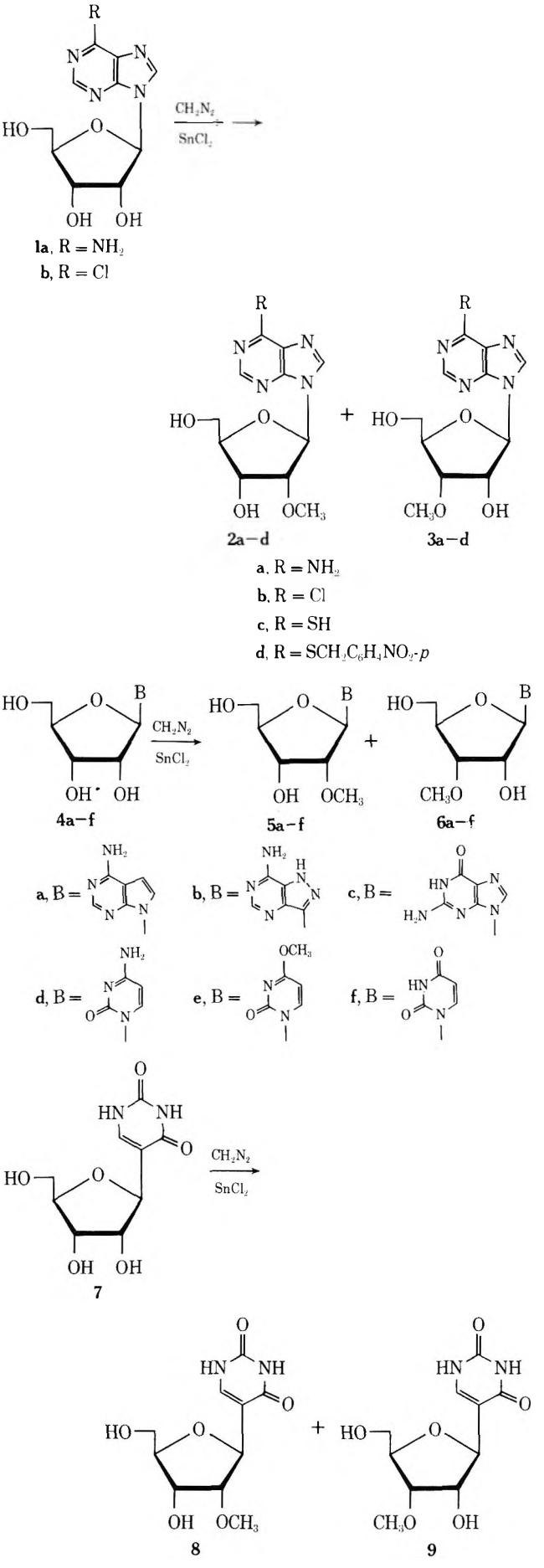
sults, with 2′-*O*- and 3′-*O*-methyladenosine being isolated in about 40% combined yield and a ratio of ~3:1, respectively. Cytidine was methylated by this procedure to give 2′-*O*-methylcytidine in less than 20% yield plus some 3′-*O*-methylcytidine after a rather extensive work-up procedure.[15] Deamination of these derivatives gave an indirect synthesis of 2′-*O*- and 3′-*O*-methyluridine in low overall yields. Methylation of ditrityluridine derivatives and separation of 2′-*O*- and 3′-*O*-methyluridine from the corresponding *N*,*O*-dimethyl products has been reported.[6] A recent multistep sugar synthesis and base coupling procedure gave 2′-*O*-methyluridine and its N^3-coupled isomer.[16] Methylation of 2-amino-6-chloro-9-β-D-ribofuranosylpurine and conversion of the heterocyclic moiety has been reported as a route to 2′-*O*-methylguanosine.[17] A multistep sugar synthesis, base coupling, and subsequent heterocyclic conversion was used to synthesize 3′-*O*-methylguanosine.[18] Recently, Shugar and coworkers have investigated the direct alkylation of cytosine nucleosides with dialkyl sulfates in strong aqueous alkali.[10-12] A similar approach was employed by Ts'o to effect 2′-O-alkylation of adenosine and cytidine 3′,5′-cyclic phosphates.[7c] This procedure leads to mixtures of alkylated products, and the separation of all possible combinations of even sugar alkylation products is an involved task. Certain isomers predominate, however, and apparently have fortuitous separation properties.[12] The yield of any one product is low to moderate unless exhaustive alkylation of suitably blocked precursors is employed.[7c,12]

We wish to describe a very facile and high yield procedure for the monomethylation of the cis-glycol system of nucleosides[19] using diazomethane with stannous chloride dihydrate as catalyst in methanolic (and other organic solvents) solution.[20] Interestingly, boron trifluoride etherate is ineffective in this system, although other metal salts give pronounced effects.[21]

Treatment of a suspension of adenosine (**1a**) in methanol containing 10^{-3} *M* stannous chloride dihydrate with a solution of diazomethane in glyme gave quantitative reaction with accompanying solubility of products. Evaporation of volatiles and chromatography of the residue on Dowex 1-X2 (OH^-)[22] gave 61% of 3′-*O*-methyladenosine (**3a**) and 38% of 2′-*O*-methyladenosine (**2a**) as pure crystalline solids.

Analogous reaction of 6-chloro-9-β-D-ribofuranosylpurine (**1b**) gave 6-chloro-9-(2-*O*-methyl-β-D-ribofuranosyl)purine (**2b**, 30%) and 6-chloro-9-(3-*O*-methyl-β-D-ribofuranosyl)-purine (**3b**, 38%) as analytically pure crystalline solids after preparative thin layer chromatographic (tlc) separation. The noncatalyzed methylation of **1b** with diazomethane has been reported, but **2b** was not purified or characterized and no investigation of the 3′-*O*-methyl isomer (**3b**) was mentioned.[17] Quantitative conversion of samples of **2b** and **3b** to the corresponding adenosine compounds **2a** and **3a** using liquid ammonia[23] confirmed the structure assignments. Treatment of **2b** and **3b** with hydrosulfide gave 9-(2-*O*-methyl-β-D-ribofuranosyl)purine-6-thione[17] (**2c**) and 9-(3-*O*-methyl-β-D-ribofuranosyl)purine-6-thione[18] (**3c**), respectively. Paterson and coworkers[24] have used *p*-nitrobenzylthio-substituted nucleosides as inhibitors of nucleoside transport across cell walls. Sulfur alkylation of **2c** and **3c** with *p*-nitrobenzyl bromide proceeded readily to give 6-*p*-nitrobenzylthio-9-(2-*O*-methyl-β-D-ribofuranosyl)purine (**2d**) and 6-*p*-nitrobenzylthio-9-(3-*O*-methyl-β-D-ribofuranosyl)purine (**3d**) for transport binding studies.

The nucleoside antibiotic tubercidin (**4a**) exerts strong biological inhibition in various systems and several molecular mechanisms have been investigated.[25] Catalyzed methylation gave 2′-*O*-methyltubercidin [4-amino-7-(2-*O*-methyl-β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine, **5a**, 53%] and 3′-*O*-methyltubercidin [4-amino-7-(3-*O*-methyl-



β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine, **6a**, 39%] after separation on the Dekker[22] column. Nmr and mass spectral (see later discussion) trends follow the adenosine case. However, in order to obtain conclusive proof of the isomer structures, each compound was acylated with trifluoroacetic anhydride and subjected to nmr double resonance analysis. The 2′-*O*-methyl nucleoside gives a 3′,5′-bis(*O*-trifluoroacetyl) derivative and the 3′-*O*-methyl isomer the 2′,5′-bis(trifluoroacetate). The primary alcoholic protons ($H_{5',5''}$) are shifted downfield by over 1δ in both cases confirming a free 5′-OH. The $H_{2'}$ of the 2′-*O*-methyl derivative is shifted only slightly upon trifluoroacetylation, whereas the $H_{3'}$ is shifted downfield ~0.9δ. Similarly, $H_{2'}$ of the 3′-*O*-methyl derivative is shifted ~0.9δ downfield, while $H_{3'}$ remains essentially unchanged. Irradiation of the nonshifted ($H_{2'}$ or $H_{3'}$) peak and observation of the collapse (2′-*O*-methyl isomer) of the anomeric ($H_{1'}$) proton doublet to a singlet or its ($H_{1'}$) invariance (3′-*O*-methyl isomer), respectively, verified the structures as assigned.

Formycin (**4b**) is another nucleoside antibiotic of considerable current interest.[26] Owing to its "glycosidic" linkage at C_3, an acidic proton (pK_a = 9.5)[27] is present on N_1 of the pyrazole moiety. In the presence of stannous chloride, however, the sugar was selectively monomethylated in good yield with only minor quantities of additionally methylated products detected. The products were separated by preparative tlc to give 2′-*O*-methylformycin [7-amino-3-(2-*O*-methyl-β-D-ribofuranosyl)pyrazolo[4,3-*d*]pyrimidine, **5b**] and 3′-*O*-methylformycin [7-amino-3-(3-*O*-methyl-β-D-ribofuranosyl)pyrazolo[4,3-*d*]pyrimidine, **6b**]. Nmr and mass spectral trends were analogous to those of the adenosine isomers and, again, trifluoroacetylation and proton double resonance experiments confirmed the isomer structure assignments.

Guanosine (**4c**) is readily methylated at N_7 by diazomethane;[28] additional methylation of the guanine base during 2′-deoxyguanosine treatment with diazomethane has been reported.[29] Indeed, attempted sugar methylation of 2-amino-6-benzyloxy-9-β-D-ribofuranosylpurine using diazomethane in aqueous glyme was reported to give N_7-methylation and imidazole ring opening.[17] However, careful treatment of a solution of guanosine (**4c**) and stannous chloride dihydrate in *N,N*-dimethylformamide gave 2′-*O*-methylguanosine (**5c**) and 3′-*O*-methylguanosine (**6c**) in ~50% combined yield. Separation of **5c** and **6c** from other methylated products was effected using silica gel column chromatography. The isomers, **5c** and **6c**, were cleanly resolved (3′ isomer again eluting first[30]) on a Dowex 1-X2 (Cl^-) column using an ammonium chloride–ammonium hydroxide buffer (pH 10.0). This anion exchange system[30] also separated 2′-*O*-methyl- and 3′-*O*-methylinosines (which can be prepared directly under analogous conditions but in lower yield) and would appear to be a useful procedure to consider for separation problems involving closely related isomers with an acidic ring proton in this general pH range.

Cytidine (**4d**) gave 2′-*O*-methylcytidine (**5d**, 74%) and 3′-*O*-methylcytidine (**6d**, 15%) as analytically pure crystalline products after chromatographic resolution,[22] in contrast with low yields reported in the absence of catalyst.[15]

Earlier studies in our laboratory[8] on the uncatalyzed methylation of 4-methoxy-1-β-D-ribofuranosyl-2-pyrimidinone (**4e**) resulted in isolation of 4-methoxy-1-(2-*O*-methyl-β-D-ribofuranosyl)-2-pyrimidinone (**5e**) in only 37% yield. Formation of 4-methoxy-1-(3-*O*-methyl-β-D-ribofuranosyl)-2-pyrimidinone (**6e**) and the 2′,3′-di-*O*-methyl nucleoside were noted, but **6e** was not isolated or characterized. The present catalyzed methylation of **4e** gave **5e** (74%) and **6e** (15%) as pure crystalline products. Thus, these useful intermediates for the preparation of 4-substituted 2-pyrimidinone nucleosides[8] are now readily available.

Treatment of a methanolic solution of uridine (**4f**) with diazomethane in glyme gives high yields of 3-*N*-methyluridine analogously to reported findings.[31] This result may be anticipated, since uridine has an acidic proton (pK_a = 9.2)[32] on N_3. However, treatment of **4f** and stannous chloride dihydrate in methanol with diazomethane in glyme gave 2′-*O*-methyluridine (**5f**, 58%) and 3′-*O*-methyluridine (**6f**, 28%) after preparative tlc separation. These yields and ease of direct reaction again stand in marked contrast with previous routes to 2′-*O*-methyluridine.[6,12,15,16,44]

The isolation of minute quantities of 2′-*O*-methylpseudouridine (**8**) from tRNA has been reported,[33] but no synthetic sample has been available previously for comparison. Careful treatment of pseudouridine (**7**) gave an ~80% combined crude yield of 2′-*O*-methylpseudouridine [5-(2-*O*-methyl-β-D-ribofuranosyl)uracil, **8**] and 3′-*O*-methylpseudouridine [5-(3-*O*-methyl-β-D-ribofuranosyl)-uracil, **9**]. Silica gel column chromatography gave partial resolution of the two isomers, and pure samples of **8** (27%) and **9** (10%) were obtained. Conditions were not investigated for the optimization of these procedures owing to the cost of **7**. The isomeric structures of **8** and **9** were again indicated by nmr and mass spectral trends and verified by trifluoroacetylation and nmr decoupling experiments. It is amazing that the catalytic enhancement is sufficient to allow sugar hydroxyl (pK_a > 13)[34] methylation to occur preferentially in the presence of the two acidic (pK_a ~ 8.9)[34] uracil ring protons (N_1 H and N_3 H) of ψ(**7**). The advantages of such a direct procedure are accentuated in the preparation of this natural product **8**, since transformation of other naturally occurring nucleosides to the pseudouridine system is precluded and *C*-glycoside coupling is not presently inviting.[35]

An examination of ^1H nmr data (see Table I) reveals that the anomeric proton ($H_{1'}$) is uniformly at lower field in the 2′-*O*-methyl isomer than in the 3′-*O*-methyl isomer as previously noted by Reese.[15] It is interesting that the $-OCH_3$ resonance is at lower field for the 3′ isomer in the purine and purine-like (tubercidin and formycin) compounds whereas this trend is uniformly reversed (2′-OCH_3 at lower field than 3′-OCH_3) in the pyrimidine series, including the pseudouridines.

Selected mass spectral fragmentation patterns (see Table II) show several trends. As previously noted,[36,37] the purine ring seems better able to stabilize charge localization in the base relative to the pyrimidine ring. This effect is seen in the lower abundance of the molecular ion (M) [and various other ions containing the heterocyclic base (B) plus a sugar fragment] in the pyrimidine compounds. The pseudouridine isomers (**8** and **9**) had extremely weak M peaks and the M + 1 intensity was always about fourfold greater. The uridine products **5f** and **6f** also had significant M + 1 peaks. Pseudouridine[38] gave an M + 1 peak of higher intensity than the M ion in several spectra obtained on our equipment. This was not noted in previously reported spectra[39,40] and its cause is unknown.

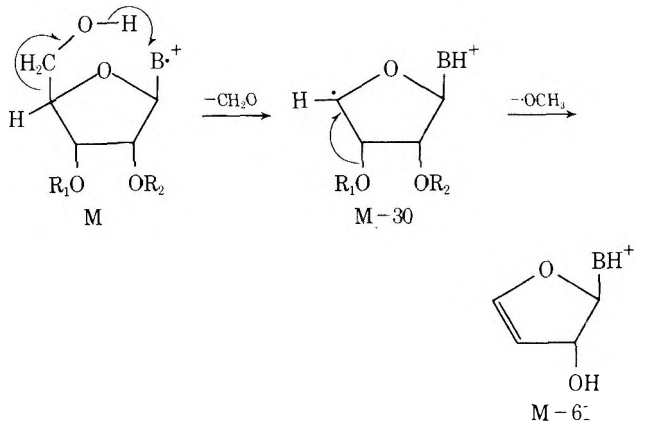
A peak at M − 15, presumably demethylation of the molecular ion, was noted in the purine and purine-like compounds except **2d**. This fragmentation was essentially absent from all the pyrimidine derivatives and was of lower intensity in the 2′ isomers except **5b**.

A peak at M − 30 is observed in all these nucleosides. This ion was proposed[36] to arise by loss of the hydroxymethyl function (with 5′-OH hydrogen transfer to base) as formaldehyde to give the M − 30 ion shown.

Table I
Characteristic ^{1}H Nmr Bands of the Methylated Nucleosides[a]

Compd	Solvent[b]	2′-OCH$_3$[c]	3′-OCH$_3$[c]	H$_{1'}$[d]	Base protons
2a	A	3.49		6.05 (5.6)	8.04 (s, H$_2$), 8.22 (s, H$_8$)
3a	A		3.60	6.01 (5.8)	8.05 (s, H$_2$), 8.25 (s, H$_8$)
2b	A	3.37		6.09 (4.8)	8.54 (s), 8.58 (s); H$_2$, H$_8$
3b	A		3.48	6.02 (5.1)	8.53 (s), 8.59 (s); H$_2$, H$_8$
2c	B	3.28		5.95 (5.0)	8.16 (s), 8.51 (s); H$_2$, H$_8$
3c	B		3.36	5.83 (5.4)	8.19 (s), 8.52 (s); H$_2$, H$_8$
2d	B	3.32		6.10 (5.0)	8.75 (s), 8.80 (s); H$_2$, H$_8$
3d	B		3.37	5.96 (5.5)	8.72 (s), 8.74 (s); H$_2$, H$_8$
5a	A	3.24		6.02 (6.3)	6.36 (d, H$_5$), 7.11 (d, H$_6$) (J_{5-6} = 4.0 Hz), 7.87 (s, H$_2$)
6a	A		3.42	5.94 (6.2)	6.36 (d, H$_5$), 7.13 (d, H$_6$) (J_{5-6} = 3.9 Hz), 7.85 (s, H$_2$)
5b[e]	A	3.39		5.28 (6.5)	8.38 (s, H$_8$)
6b[e]	A		3.45	5.15 (6.3)	8.31 (s, H$_8$)
5c	B	3.28		5.77 (5.8)	7.93 (s, H$_8$)
6c	B		3.34	5.63 (6.0)	7.88 (s, H$_8$)
5d	A	3.55		5.98 (3.3)	6.05 (d, H$_5$), 7.88 (d, H$_6$) (J_{5-6} = 7.5 Hz)
6d	A		3.48	5.89 (3.9)	6.04 (d, H$_5$), 7.84 (d, H$_6$) (J_{5-6} = 7.5 Hz)
5e	A	3.58		6.02 (2.7)	6.27 (d, H$_5$), 8.25 (d, H$_6$) (J_{5-6} = 7.5 Hz)
6e	A		3.47	5.93 (2.5)	6.26 (d, H$_5$), 8.22 (d, H$_6$) (J_{5-6} = 7.3 Hz)
5f	A	3.53		5.98 (3.6)	5.90 (d, H$_5$), 7.92 (d, H$_6$) (J_{5-6} = 8.3 Hz)
6f	A		3.45	5.87 (4.8)	5.89 (d, H$_5$), 7.88 (d, H$_6$) (J_{5-6} = 8.2 Hz)
8	A	3.46		4.73 (4.8)	7.64 (s, H$_6$)
9	A		3.39	4.68 (5.3)	7.58 (s, H$_6$)

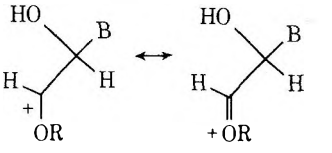
[a] Chemical shifts given in δ (parts per million from external TMS for D_2O solutions and internal TMS for DMSO-d_6). [b] A = D_2O; B = DMSO-d_6. [c] Sharp singlets. [d] Doublets; number in parentheses is $J_{1'-2'}$. [e] Spectrum taken on the monohydrochloride salt.



This fragmentation was observed to be uniformly more intense for the 2′ isomers (R_1 = H; R_2 = CH_3), although differences are often insignificant. An ion at M − 61 (not observed in the pyrimidine spectra) is seen to be much more intense in the 3′ isomers of the purine and purine-like compounds. Loss of a methoxyl radical from the M − 30 ion to produce the dihydrofuran derivative (M − 61) shown has been suggested.[41]

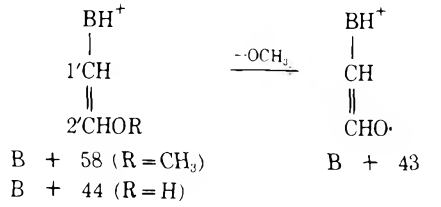
Loss of a methoxyl radical[37] from the molecular ion is presumed to give the M − 31 peak seen in all of these spectra. This is a low-intensity ion, especially in the pyrimidine and guanine nucleosides. A peak at M − 32 (essentially absent in the purine and purine-like compounds) appears characteristic of 2′-O-methylation in pyrimidine nucleosides. In certain other pyrimidine nucleoside pairs (to be published), only the 2′-*O*-methyl isomer has a significant M − 32 peak also. The 1′,2′ elimination of methanol would give a dihydrofuran derivative. Such extended conjugation could be advantageous in stabilizing the presumed less favorable charge localization[37] in the pyrimidine bases.

The B + 74 and B + 60 peaks correspond to ions suggested previously.[36,37] Although originally proposed to



arise *via* (and require) labile hydrogen transfer from a 3′ heteroatom,[36] an analogous peak was observed in permethylated nucleosides.[37] As seen in Table II this fragmentation is *not* uniformly diagnostic of the isomeric pairs.

The B + 58 and B + 44 ions are presumed to arise primarily by the pathway postulated by McCloskey.[36] These



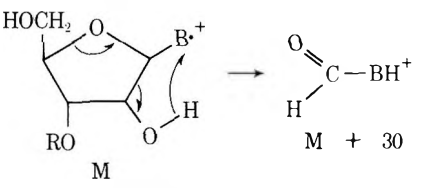
ions are seen to be uniformly diagnostic for all the isomeric pairs. The B + 58 peak is significantly more intense than the B + 44 peak for the 2′-*O*-methyl products, while the B + 44 peak is greater than the B + 58 peak for the 3′-O-methyl isomers (2′-hydroxyl free). Thus, inspection of the abundances of these two peaks in the spectrum of a compound specifies which isomer it is. It may be noted

Table II. Selected Mass Spectral Ions, *m/e* (Relative Intensity)

Compd	Temp, °C	M	M − 15	M − 30	M − 31	M − 32	M − 61	B + 74	B + 60	B + 58	B + 44	B + 30	B + 2H	B + H	*m/e* 146	*m/e* 87	Other ions
2a	180	281 (6.7)	266 (0.4)	251 (24)	250 (6.6)		220 (1.4)	208 (2.9)	194 (0.6)	192 (73)	178 (2.6)	164 (51)	136 (96)	135 (100)	(54)	(18)	
3a	170	281 (4.3)	266 (13)	251 (11)	250 (2.8)		220 (23)	208 (0.1)	194 (1.4)	192 (2.2)	178 (26)	164 (92)	136 (100)	135 (96)	(0.8)	(14)	
2b	145	300 (1.3)	285 (0.4)	270 (41)	269 (4.8)		239 (2.8)	227 (0.9)	213 (24)	211 (74)	197 (3.2)	183 (27)	155 (69)	154 (8.5)	(100)	(63)	
3b	135	300 (4.4)	285 (5.3)	270 (15)	269 (1.4)		239 (17)	227 (0.8)	213 (6.7)	211 (4.0)	197 (26)	183 (95)	155 (100)	154 (7.0)	(3.8)	(25)	
2c	160	298 (3.7)	283 (1.1)	268 (11)	267 (3.0)		237 (0.7)	225 (0.5)	211 (1.6)	209 (25)	195 (3.0)	181 (13)	153 (50)	152 (100)	(40)	(31)	
3c	200	298 (3.0)	283 (3.1)	268 (3.6)	267 (0.5)		237 (5.0)		211 (0.5)	209 (1.1)	195 (8.6)	181 (33)	153 (59)	152 (100)	(1.3)	(28)	
2d	150	433 (22)		403 (2.1)	402 (0.3)		372 (0.2)		346 (0.4)	344 (7.1)		316 (1.3)	288 (11)	287 (50)	(9.1)	(25)	136 (100, $C_7H_6NO_2$)
3d	190	433 (32)	418 (0.6)	403 (0.3)	402 (1.3)		372 (3.5)			344 (0.2)	330 (4.3)	316 (5.0)	288 (22)	287 (100)	(0.9)	(36)	136 (26, $C_7H_6NO_2$)
5a	200	280 (8.5)	265 (0.3)	250 (4.6)	249 (2.5)	207 (1.3)	219 (0.5)	193 (0.2)	191 (23)	177 (1.1)	163 (17)	135 (31)	134 (100)	134 (100)	(12)	(16)	
6a	200	280 (4.8)	265 (2.9)	250 (2.1)	249 (1.2)		219 (5.6)	193 (0.3)	191 (1.6)	177 (9.8)	163 (55)	135 (39)	134 (100)	134 (100)	(0.3)	(7.3)	
5b	190	281 (2.2)	266 (4.8)	251 (7.1)	250 (3.9)		220 (1.7)	208 (1.1)	194 (1.1)	192 (100)	178 (22)	164 (74)	136 (4.9)	135 (11)	(1.5)	(3.6)	
6b	220	281 (5.2)	266 (1.8)	251 (1.7)	250 (2.0)		220 (3.2)	208 (1.3)	194 (1.0)	192 (16)	178 (34)	164 (100)	136 (2.3)	135 (3.9)	(1.2)	(4.5)	
5c	190	297 (6.8)	282 (0.2)	267 (2.2)	266 (0.4)		236 (0.3)	256 (0.3)	242 (0.3)	208 (14)	194 (0.7)	180 (2.4)	152 (19)	151 (100)	(7.2)	(54)	
6c	240	297 (7.3)	282 (0.8)	267 (0.7)	266 (0.7)		236 (5.1)	256 (0.4)		208 (0.1)	194 (6.6)	180 (9.0)	152 (26)	151 (100)	(1.9)	(19)	
5d	225	257 (0.7)		227 (2.7)	226 (1.4)	225 (1.8)		184 (1.6)	170 (0.1)	168 (11)	154 (1.9)	140 (20)	112 (100)	111 (15)	(42)	(33)	151 (74)
6d	200	257 (0.7)		227 (1.6)	226 (0.6)				170 (25)	168 (1.1)	154 (6.4)	140 (24)	112 (100)	111 (9.8)	(0.8)	(13)	151 (12)
5e	175	272 (0.5)		242 (1.5)	241 (0.6)	240 (2.5)		199 (1.8)	185 (4.5)	183 (9.5)	169 (3.1)	155 (13)	127 (100)	126 (4.2)	(24)	(69)	166 (47)
6e	180	272 (0.5)		242 (0.7)	241 (0.3)				185 (22)	183 (1.6)	169 (6.1)	155 (11)	127 (100)	126 (2.8)	(0.4)	(21)	166 (7.7)
5f	165	258 (0.8)		228 (0.8)	227 (0.8)	226 (3.5)		185 (2.1)	171 (0.1)	169 (2.1)	155 (0.3)	141 (1.9)	113 (13)	112 (2.7)	(24)	(100)	147 (21, sugar)
6f	225	258 (0.5)		228 (0.6)	227 (0.6)	226 (0.6)		185 (1.7)	171 (9.1)	169 (1.6)	155 (9.0)	141 (2.6)	113 (38)	112 (81)	(8.2)	(100)	147 (27, sugar)
8	200	258 (0.1)		228 (2.3)	227 (1.5)	226 (4.4)		185 (0.5)	171 (0.3)	169 (8.7)	155 (2.2)	141 (48)	113 (2.1)	112 (2.9)	(0.1)	(100)	259 (0.4, M + 1) 208 (8.8, furan derivative)
9	220	258 (0.2)		228 (1.2)	227 (0.9)	226 (1.9)		185 (0.4)	171 (13)	169 (5.9)	155 (12)	141 (82)	113 (0.3)	112 (0.6)	(0.2)	(100)	259 (0.5, M + 1) 208 (4.2, furan derivative)

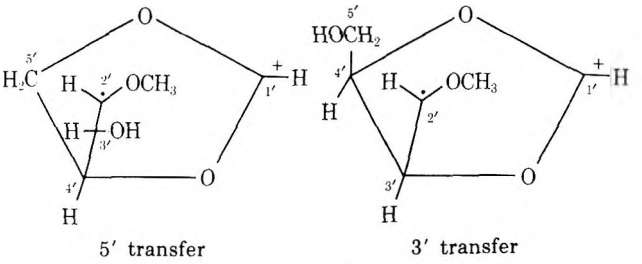
that rather minor differences in intensity in the same peak may exist when comparing a pair of isomers (*e.g.*, the B + 58 ion in **5f** and **6f**). Loss of the $O_{2'}$-methyl radical from the B + 58 ion to give a B + 43 ion was previously noted[36] with 2′-*O*-methyladenosine (**2a**). This step was suggested[36] to be unique to 2′-O-methylated compounds. However, the intensities of the B + 43 peak under our conditions were 4.1% for the 2′ isomer (**2a**) and 2.2% for the 3′ isomer (**3a**). This peak was absent or of less than 1% relative intensity in several 2′ isomers and was more intense in the 3′-*O*-methyluridine (**6f**) and pseudouridine (**9**) isomers.

The B + 30 ion, which contains $C_{1'}$, $H_{1'}$, and $O_{4'}$, arises by hydrogen transfer from sugar to base and $C_{4'}$–$O_{4'}$ and $C_{1'}$–$C_{2'}$ bond cleavages.[36] The suggested mechanism involving 2′-OH hydrogen transfer[36] is supported



by the greater intensity of this ion in the 3′-*O*-methyl isomers (free 2′-OH) of the purine and purine-like compounds only.

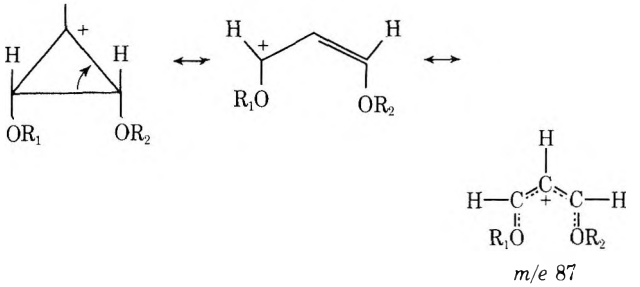
A significant peak at *m/e* 146 is observed for all 2′-*O*-methyl N-linked nucleosides, even constituting the mass spectral base peak (100% relative intensity) for **2b.** These



m/e 146

ions were postulated to arise from $C_{1'}$–$C_{2'}$ bond cleavage followed by 3′-OH or 5′-OH proton transfer to the base (B) with $C_{1'}$–base cleavage.[36] This peak is of low intensity in the 3′-*O*-methyl isomers and C-linked nucleosides, as predicted by the proposed mechanism.[36]

A significantly intense peak at *m/e* 87 was observed in the spectra of all these nucleosides, which was the mass spectral base peak for all four uridine (**5f** and **6f**) and pseudouridine (**8** and **9**) derivatives. Exact mass measurement gave *m/e* 87.0448 (calcd for $C_4H_7O_2$, 87.0446) in agreement with the highly stabilized allylic cation.



m/e 87

R_1 or R_2 = H, CH_3

An analogous species was observed in the mass spectra of permethylated nucleosides,[37] and an ion of *m/e* 73 (corresponding in mass to the above ion with $R_1 = R_2 = H$, $C_3H_5O_2$) was noted as a significant sugar fragmentation product of uridine.[40] Plausible mechanisms are difficult to

envision which would explain why the C-linked formycin compounds (**5b** and **6b**) give low-abundance *m/e* 87 peaks whereas the C-linked pseudouridines (**8** and **9**) have *m/e* 87 (100%). The high and sometimes nearly equal abundances of this ion in certain isomer pairs make consideration of fragmentations leading to a symmetrical intermediate (such as a cyclopropyl cation) involving the 2′ and 3′ carbons plus one additional CH group attractive.

Specific miscellaneous ions of note include the nitrobenzyl (or nitrotropylium) ion ($C_7H_6NO_2$) in the spectra of **2d** and **3d**, the strong sugar ion (*m/e* 147) in the uridine isomers, and the 5-(5-hydroxymethyl-2-furyl)uracil ion[40] (*m/e* 208) in **8** and **9**. The mass spectral base peak for 2′-*O*-methylformycin (**5b**) is the B + 58 ion (analogous to 2′-deoxyformycin[30]) while that for 3′-*O*-methylformycin (**6b**) is the B + 30 ion (as in 3′-deoxyformycin[30]). This is in accord with the preferred B + 58 fragmentation mechanism[36] and again[30] demonstrates that the B + 30 peak will *not necessarily* be the mass spectral base peak for a *C*-nucleoside, as had been suggested previously[42] and reemphasized very recently.[43]

This powerful catalytic system for monomethylation of nucleoside cis glycols makes direct access to the "minor component"[3] 2′-*O*-methylnucleosides (and their 3′ isomers) readily available. Mass spectral fragmentation trends are diagnostically useful for these isomers and provide results which support certain previously proposed mechanisms and preclude preferential or exclusive operation of others. Application of this general procedure to other products,[19] investigation of other catalysts,[21] and study of certain factors involved in the reaction will be reported separately.

Experimental Section

Melting points were determined on Fisher-Johns and Mel-Temp apparatus and are uncorrected. Uv spectra were recorded on Cary 14 or 15 spectrometers. Optical rotations were determined with a Perkin-Elmer Model 141 polarimeter using a 10-cm 1-ml microcell. Nmr spectra were recorded on Varian A-60, 56/60, and HA-100 spectrometers. Mass spectra were determined by the mass spectroscopy laboratory of this department on AEI MS-2 and MS-9 instruments at 70 eV using a direct probe for sample introduction at the specified temperature. Elemental analyses were determined by the microanalytical laboratory of this department and Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. Evaporations were effected using Büchler rotating evaporators under aspirator or mechanical oil pump vacuum at 40° or lower. Chromatography was effected on dry-packed columns of silica gel A (J. T. Baker 3405) or B (Mallinckrodt 2847). Preparative tlc plates were prepared using 110 g of Brinkmann PF 254 silica gel per 300 ml of water (slurry) or 300 g of Brinkmann PF 254 Type E alumina per 320 ml of water. These slurries produced four 20 × 40 cm plates of 0.8–1-mm thickness unless otherwise specified. Analytical tlc was run on Eastman silica gel sheets (13181).

Diazomethane Stock Solutions. Solution A. To an ice-cold mixture of 100 ml of 40% aqueous KOH and 150 ml of 1,2-dimethoxyethane (glyme) was slowly added 15 g of *N*-nitroso-*N*-methylurea with vigorous stirring. Stirring was continued for an additional 20 min at 0° and the phases were allowed to separate. The upper organic layer was decanted and dried over KOH pellets. The dried solution was filtered before use. Standardization of the diazomethane solution using 0.2 *N* benzoic acid in glyme and back titration with 0.1 *N* NaOH gave an average value of 0.43 *N* CH_2N_2 in glyme.

Solution B[17] was prepared in the above manner using 25 g of *N*-nitroso-*N*-methylurea, 62 ml of 40% aqueous KOH, and 130 ml of glyme.

General Methylation Procedure. A round-bottom flask with a magnetic stir bar was charged with solvent, catalyst, and starting material. The mixture was stirred at room temperature (except guanosine at 50°). Diazomethane stock solution was added slowly and progress of the reaction was monitored by tlc. When all starting material disappeared or when further diazomethane failed to increase the yield of desired products, the reaction was terminated and the mixture was evaporated to dryness.

General Trifluoroacetylation Procedure. The compound was added to 2 ml of dried methylene chloride and 1 ml of trifluoroacetic anhydride and stirred for 3 days [20 hr in the case of 2′-*O*-methylpseudouridine (**8**)] at 5° while protected from moisture. The resulting clear solution was evaporated to dryness *in vacuo* and the residue was dissolved in dry solvent for nmr spectroscopy.

2′-*O*-Methyladenosine (2a) and 3′-*O*-Methyladenosine (3a). A suspension of 0.8 g (0.003 mol) of **1a** in 180 ml of a 10^{-3} *M* solution of $SnCl_2 \cdot 2H_2O$ in MeOH was treated with 44 ml of CH_2N_2 stock solution B by the general methylation procedure. The resulting residue was dissolved in 20 ml of EtOH–H_2O (2:1) and applied to a column (50 × 2 cm, 110 ml) of Dowex 1-X2 (OH^-) packed in the same solvent. The same solvent was used to develop the column and 10-ml fractions were collected. Fractions 21–30 were pooled and evaporated to give 0.30 g (38%) of crystalline **2a**, which was recrystallized from absolute EtOH to give product: mp 202–203.5°; $[\alpha]^{22}D$ − 58° (*c* 1, H_2O); uv (H_2O) max 259 nm (ε 14,500), min 226 nm (ε 2100) (see ref 13–15 and 17 for comparisons).

Anal. Calcd for $C_{11}H_{15}N_5O_4$: C, 47.00; H, 5.30; N, 24.90. Found: C, 47.16; H, 5.36; N, 24.61.

Fractions 41–70 were combined and evaporated to give 0.53 g (61%) of **3a**, mp 174–176°. This material was recrystallized from absolute EtOH to give **3a**: mp 177–178°; $[\alpha]^{22}D$ − 59° (*c* 1, H_2O); uv (H_2O) max 259 nm (ε 15,300), min 226 nm (ε 2200) (see ref 14, 15, and 18 for comparisons).

Anal. Found: C, 46.82; H, 5.22; N, 24.98.

6-Chloro-9-(2-*O*-methyl-β-D-ribofuranosyl)purine (2b) and 6-Chloro-9-(3-*O*-methyl-β-D-ribofuranosyl)purine (3b). A solution of 0.58 g (0.002 mol) of **1b** and 0.030 g (0.0001 mol) of $SnCl_2 \cdot 2H_2O$ in 120 ml of absolute EtOH was methylated with CH_2N_2 stock solution A by the general procedure. The residue obtained was dissolved in 10 ml of EtOH, and 4 g of silica gel (A) was added. This slurry was evaporated to dryness and the impregnated adsorbent was added to a column (2.2 cm diameter, 20 g) of the same silica gel. The column was developed with *i*-PrOH–$CHCl_3$ (4:96) and the major homogeneous fractions containing **2b** and **3b** were combined and evaporated to give a colorless, solid foam. This material was dissolved in absolute EtOH and applied to eight alumina preparative tlc plates (40 × 20 cm, 0.5 mm thick). The plates were air dried and were then developed in the lower layer of $CHCl_3$–Me_2CO–H_2O (3:2:1, to which 1 ml of EtOH per 100 ml of solution was added) for 6 hr. This procedure was repeated two or three times as needed to ensure clean separation of **2b** and **3b**.

The more rapidly migrating of the two major bands was scraped from the plates, powdered, packed into a 5-cm diameter column, and eluted with about 150 ml of absolute EtOH. This solution was evaporated and the resulting gum was dissolved in a minimum amount of absolute EtOH. Approximately 3 volumes of Skellysolve B was added and the solution was allowed to stand (at 4°). Over a period of time, 0.16 g of crystals, mp 151–153°, separated and an additional crop of 0.06 g, mp 150–153°, was obtained upon concentration of the mother liquor: total yield of **3b** 0.22 g (38%); $[\alpha]^{23}D$ −37.4° (*c* 0.96, MeOH); uv (H_2O) max 264 nm (ε 9000), min 227 nm (ε 2000).

Anal. Calcd for $C_{11}H_{13}ClN_4O_4$: C, 44.03; H, 4.37; Cl, 11.78; N, 18.66. Found: C, 44.27; H, 4.61; Cl, 11.74; N, 18.47.

The slower moving major band was treated in the same manner to provide 0.17 g (30%) of crystalline **2b**: mp 144–146°; $[\alpha]^{23}D$ −29.3° (*c* 0.99, MeOH); uv (H_2O) max 263 nm (ε 9000), min 227 nm (ε 2200).

Anal. Found: C, 43.81; H, 4.65; Cl, 11.74; N, 18.89.

9-(2-*O*-Methyl-β-D-ribofuranosyl)purine-6-thione[17] **(2c).** A stirred solution of 0.15 g (0.0005 mol) of **2b** in 5 ml of MeOH was treated with 1.5 ml of 1 *N* NaSH in MeOH and the reaction mixture was gently refluxed for 15 min. After cooling to room temperature, the solution was evaporated to dryness and the 0.18 g of residue obtained was dissolved in about 2 ml of hot H_2O. The pH was adjusted to 4.5 by dropwise addition of HOAc and 0.13 g (88%) of **2c** was obtained by filtration and drying at 0.1 mm. Crystalline **2c** had mp 248–249° dec; $[\alpha]^{25}D$ −56.6° (c 0.88, 0.1 *N* NaOH); uv (MeOH) max 226, 323 nm (ε 8100, 24,000), min 256 nm (ε 260) [lit.[17] mp >200° dec; $[\alpha]^{22}D$ −53.5° (c 0.42, 0.1 *N* NaOH)].

Anal. Calcd for $C_{11}H_{14}N_4O_4S$: C, 44.29; H, 4.73; N, 18.78; S, 10.75. Found: C, 44.34, H, 4.92; N, 18.80; S, 10.52.

9-(3-*O*-Methyl-β-D-ribofuranosyl)purine-6-thione[18] **(3c).** A 0.15 g (0.0005 mol) portion of **3b** was treated exactly as in the conversion of **2b** to **2c** above to give 0.13 g (87%) of crystalline **3c**:

mp 215–218° dec; $[\alpha]^{25}D$ −77.6° (*c* 0.84, 0.1 *N* NaOH); uv (MeOH) max 226, 323 nm (ε 9100, 22,000), min 256 nm (ε 620) [lit.[18] mp 200–201° dec; $[\alpha]^{23}D$ −77° (*c* 1.0, 0.1 *N* NaOH)].

Anal. Calcd for $C_{11}H_{14}N_4O_4S$: C, 44.29; H, 4.73; N, 18.78; S, 10.75. Found: C, 44.12; H, 4.80; N, 18.89; S, 10.66.

6-*p*-Nitrobenzylthio-9-(2-*O*-methyl-β-D-ribofuranosyl)purine (2d). To a stirred solution of 0.175 g (0.00058 mol) of **2c** and 0.11 g of anhydrous Na_2CO_3 in 5 ml of dry DMF was slowly added a solution of 0.13 g (0.0006 mol) of α-bromo-*p*-nitrotoluene (*p*-nitrobenzyl bromide) in 3 ml of glyme. Stirring was continued for 2 hr at room temperature, the mixture was filtered, the filtrate was evaporated to dryness, and the residue was coevaporated with EtOH and then 5 ml of xylene. The resulting foam was dissolved in MeOH and applied to a silica gel preparative tlc plate (20 × 20 cm) which was developed in MeOH–$CHCl_3$ (10:90). The major band was scraped from the plate, extracted with MeOH, filtered, and evaporated to give an oil which was crystallized from EtOAc–cyclohexane. The analytically pure sample of **2d** (0.145 g, 57%) after drying at 0.1 mm had mp 125.5–128°; $[\alpha]^{25}D$ −38.9° (*c* 1.03, DMF); uv (MeOH) max 284 nm (ε 26,900), min 242 nm (ε 8400); uv (0.1 *N* HCl in MeOH) max 291 nm (ε 23,300), min 243 nm (ε 8700); uv (0.1 *N* NaOH in MeOH) max 284 nm (ε 26,400), min 243 nm (ε 8300).

Anal. Calcd for $C_{18}H_{19}N_5O_6S$: C, 49.87; H, 4.41; N, 16.15; S, 7.39. Found: C, 49.56; H, 4.65; N, 16.27; S, 7.47.

6-*p*-Nitrobenzylthio-9-(3-*O*-methyl-β-D-ribofuranosyl)purine (3d). A 0.18-g (0.0006 mol) portion of **3c** was treated as in the conversion of **2c** to **2d.** The resulting oil was crystallized from MeOH–cyclohexane plus a few drops of EtOAc to give 0.15 g (58%) of **3d:** mp 173–174°; $[\alpha]^{25}D$ −45.4° (*c* 1.0, DMF); uv (MeOH) max 284 nm (ε 27,000), min 240 nm (ε 5400); uv (0.1 *N* HCl in MeOH) max 292 nm (ε 22,700), min 240 nm (ε 5700); uv (0.1 *N* NaOH in MeOH) max 284 nm (ε 25,600), min 243 nm (ε 8000).

Anal. Calcd for $C_{18}H_{19}N_5O_6S$: C, 49.87; H, 4.41; N, 16.15; S, 7.39. Found: C, 49.83; H, 4.51; N, 15.99; S, 7.34.

4-Amino-7-(2-*O*-Methyl-β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (2′-*O*-Methyltubercidin, 5a) and 4-Amino-7-(3-*O*-methyl-β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (3′-*O*-Methyltubercidin, 6a). A solution of 0.8 g (0.003 mol) of **4a** in 200 ml of a 10^{-3} *M* solution of $SnCl_2 \cdot 2H_2O$ in MeOH was treated with about 45 ml of CH_2N_2 stock solution B according to the general methylation procedure. The residue from evaporation was dissolved in 5 ml of EtOH–H_2O (2:1) and applied to a column (75 × 3 cm) of Dowex 1-X2 (OH^-) resin packed in and developed with the same EtOH–H_2O (2:1) solvent mixture. Fractions (6 ml) 21–45 contained a small amount of unidentified material. Fractions 131–200 were combined and evaporated to give a colorless, solid foam (0.45 g, 53%) which did not crystallize under several conditions. A solution of 0.1 g of this material in 10 ml of absolute EtOH was treated with 10 ml of 0.05 *N* HCl in absolute EtOH and evaporated to dryness. The residue was coevaporated twice with absolute EtOH and then crystallized from this solvent to give 0.1 g (90%) of **5a** monohydrochloride: mp 222–224°; $[\alpha]^{26}D$ −44° (c 1, H_2O); uv (H_2O) max 270 nm (ε 12,700), min 239 nm (ε 2400); uv (0.1 *N* HCl) max 270, 227 nm (ε 12,400, 25,300), min 244, 213 nm (ε 5000, 16,000); uv (0.1 *N* NaOH) max 270 nm (ε 13,200), min 240 nm (ε 4200).

Anal. Calcd for $C_{12}H_{17}ClN_4O_4$: C, 45.50; H, 5.37; Cl, 11.19; N, 17.69. Found: C, 45.78; H, 5.35; Cl, 11.04; N, 17.66.

A 0.02-g sample of **5a** was trifluoroacetylated with 2 ml of trifluoroacetic anhydride in 3 ml of methylene chloride at 0° for 0.5 hr, evaporated, and dried at 0.1 mm for 15 hr. The resulting solid foam gave nmr ($CDCl_3$, TMS internal) δ 3.36 (s, 1, 2′-OCH_3), 4.52 ("q," $J_{2'-1'} = J_{2'-3'} = 6$ Hz, 1, $H_{2'}$), 4.63 (m, 2, $H_{5',5''}$), 5.52 ("q," $J_{3'-2'} = 6$, $J_{3'-4'} = 4$ Hz, 1, $H_{3'}$), 6.18 (d, $J_{1'-2'} = 6$ Hz, 1, $H_{1'}$). Irradiation at δ 6.18 ($H_{1'}$) caused the "quartet" at δ 4.52 ($H_{2'}$) to collapse to a doublet ($J_{2'-3'} = 6$ Hz). Irradiation at δ 4.52 ($H_{2'}$) caused the "quartet" at δ 5.52 ($H_{3'}$) to collapse to a singlet (simultaneous irradiation of $H_{4'}$) and the doublet at δ 6.18 ($H_{1'}$) to collapse to a singlet.

Fractions 220–320 were combined and evaporated to dryness to give 0.33 g (39%) of solid, which was crystallized from H_2O to give the analytical sample of **6a:** mp 194–195°; $[\alpha]^{26}D$ −76.7° (*c* 1, H_2O); uv (H_2O) max 270 nm (ε 11,500), min 239 nm (ε 2900); uv (0.1 *N* HCl) max 270, 227 nm (ε 11,300, 23,900), min 244, 213 nm (ε 4900, 15,200); uv (0.1 *N* NaOH) max 270 nm (ε 11,700), min 240 nm (ε 4100).

Anal. Calcd for $C_{12}H_{16}N_4O_4$: C, 51.42; H, 5.75; N, 19.99. Found: C, 51.68; H, 5.74; N, 19.80.

This product (20 mg) was trifluoroacetylated exactly as **5a** above to give a product with nmr ($CDCl_3$, TMS internal) δ 3.42 (s, 1, 3′-OCH_3), 4.30 (m, 2, $H_{3'}$, $H_{4'}$), 4.48–4.81 (m, 2, $H_{5',5''}$), 5.83 ("q," $J_{2'-3'} = 5$, $J_{2'-1'} = 3$ Hz, 1, $H_{2'}$), 6.28 (d, $J_{1'-2'} = 3$ Hz, 1, $H_{1'}$). Careful irradiation at δ 6.28 ($H_{1'}$) caused collapse of the peak at δ 5.83 ($H_{2'}$) to a doublet ($J_{2'-3'} = 5$ Hz). Careful irradiation at δ 5.83 ($H_{2'}$) caused collapse of the peak at δ 6.28 ($H_{1'}$) to a singlet and sharpening of the band at δ 4.30 ($H_{3'}$). Irradiation at δ 4.30 ($H_{3'}$) had no effect on the δ 6.28 ($H_{1'}$) band but collapsed the δ 5.83 ($H_{2'}$) band to a doublet ($J_{2'-1'} = 3$ Hz).

7-Amino-3-(2-*O*-methyl-β-D-ribofuranosyl)pyrazolo[4,3-*d*]pyrimidine (2′-*O*-Methylformycin, 5b) and 7-Amino-3-(3-*O*-methyl-β-D-ribofuranosyl)pyrazolo[4,3-*d*]pyrimidine (3′-*O*-Methylformycin, 6b). A suspension of 0.40 g (0.0015 mol) of **4b** in 100 ml of 10^{-3} *M* $SnCl_2 \cdot 2H_2O$ solution was stirred while 15 ml of CH_2N_2 stock solution B was slowly added (further additions gave rise to more of the faster tlc migrating material, presumably dimethylated products). The residue obtained upon evaporation was treated with 5 ml of H_2O and filtered. The clear filtrate was applied to four silica gel preparative tlc plates (20 × 40 cm, 1 mm thick) which were thoroughly dried and then developed using $CHCl_3$–Me_2CO–EtOH–MeOH (20:10:1.5:1.5). The plates were dried and redeveloped three to four times in the same solvent system to effect splitting of the second fastest migrating band into two bands. The faster of these two bands was removed from the plates, extracted with MeOH, filtered, and evaporated to give 0.14 g (33%) of **5b** contaminated with a trace of **6b.** This solid did not crystallize readily and was dissolved in 3 ml of absolute EtOH and treated with 5 ml of 1 *N* HCl in absolute EtOH. This solution was evaporated to dryness and the residue was coevaporated twice and then crystallized using absolute EtOH to give 81 mg (17%) of **5b** monohydrochloride: mp 205–210° dec; $[\alpha]^{26}D$ −30.3° (c 0.98, H_2O); uv (H_2O) max 294 nm (ε 11,700), min 252 nm (ε 3300); uv (0.1 *N* HCl) max 296, 234 nm (ε 11,700; 10,000), min 269, 224 nm (ε 5600, 8900); uv (0.1 *N* NaOH) max 304, 234 nm (ε 8900, 17,800) min 272, 227 nm (ε 3700, 15,900).

Anal. Calcd for $C_{11}H_{16}ClN_5O_4$: C, 41.58; H, 5.08; Cl, 11.17; N, 22.04. Found: C, 41.93; H, 5.27; Cl, 11.15; N, 21.90.

A 20-mg sample of this product was trifluoroacetylated by the general procedure outlined to give nmr ($CDCl_3$, TMS internal) δ 3.35 (s, 3, 2′-OCH_3), 4.38–4.80 (m, 4, $H_{2'}$, $H_{4'}$, $H_{5',5''}$), 5.48 (d, $J_{1'-2'} = 7$ Hz, 1, $H_{1'}$), 5.60 ("q," $J_{3'-2'} = 5$, $J_{3'-4'} = 4$ Hz, 1, $H_{3'}$). Irradiation at δ 4.68 ($H_{2'}$) collapsed the δ 5.48 ($H_{1'}$) band to a singlet and the band at δ 5.60 ($H_{3'}$) to a broad singlet (simultaneous irradiation of $H_{4'}$ as well as $H_{2'}$). Careful irradiation at δ 5.48 ($H_{1'}$) raised a rough doublet at δ 4.7 ($H_{2'}$).

The slower of the two bands separated above by preparative tlc was treated exactly as **5b** to give 0.21 g (50%) of amorphous **6b.** This product was analogously converted into 0.2 g (85%) of crystalline **6b** monohydrochloride: mp 231–233°; $[\alpha]^{26}D$ −38.3° (*c* 1.1, H_2O); uv (H_2O) max 294 nm (ε 10,500), min 253 nm (ε 3000); uv (0.1 *N* HCl) max 295, 235 nm (ε 13,500, 8500) min 268, 224 nm (ε 4000, 6700); uv (0.1 *N* NaOH) max 305, 234 nm (ε 7800, 16,200), min 272, 226 nm (ε 3000, 14,000).

Anal. Calcd for $C_{11}H_{16}ClN_5O_4$: C, 41.58; H, 5.08; Cl, 11.17; N, 22.04. Found: C, 41.69; H, 4.95; Cl, 11.26; N, 21.99.

A 20-mg sample of this product was trifluoroacetylated by the general procedure to give nmr ($CDCl_3$, TMS internal) δ 3.42 (s, 3, 3′-OCH_3), 4.38 (m, 2, $H_{3'}$, $H_{4'}$), 4.48–4.78 (m, 2, $H_{5',5''}$), 5.70 (d, $J_{1'-2'} = 2.5$ Hz, 1, $H_{1'}$), 6.00 ("q," $J_{2'-1'} = 2.5$, $J_{2'-3'} = 4$ Hz, 1, $H_{2'}$). Careful irradiation at δ 5.70 ($H_{1'}$) collapsed the peak at δ 6.00 ($H_{2'}$) to a rough doublet. Careful irradiation at δ 6.02 ($H_{2'}$) collapsed the peak at δ 5.70 ($H_{1'}$) to a rough singlet. Irradiation at δ 4.41 ($H_{3'}$) collapsed the peak at δ 6.02 ($H_{2'}$) to a rough doublet but had no effect on the δ 5.70 ($H_{1'}$) peak.

2′-*O*-Methylguanosine[17] (5c) and 3′-*O*-Methylguanosine[18] (6c). A stirred mixture of 1.5 g (0.0053 mol) of **4c** and 0.25 g (0.0011 mol) of $SnCl_2 \cdot 2H_2O$ in 500 ml of DMF at 50–55° was treated dropwise with 26 ml of CH_2N_2 stock solution A over a 6-hr period. At this point only traces (tlc) of **4c** remained and the solution was cooled and evaporated to about 15 ml. MeOH was added until the solution became turbid, and 15 g of silica gel (A) was added. The mixture was evaporated to dryness and the impregnated powder was applied to a column (52 × 3.5 cm, 100 g) of the same silica gel. The column was eluted with 1000 ml of $CHCl_3$ followed by MeOH–$CHCl_3$ (15:85) at a rate of 1.7 ml/min and 15-ml fractions were collected. Fractions 101–170 contained only **5c** and **6c.** This combined fraction was evaporated to dryness to give 0.5 g of solid. Fractions 86–100 were combined, evaporated, absorbed on silica gel, and rechromatographed on a column (1.8 cm diameter, 20 g) of the same silica gel. $CHCl_3$ containing 1% ammonia was used to elute the more rapidly migrating impurity.

MeOH–MeOAc (1:1) was used to elute 0.075 g of chromatographically homogeneous **5c** and **6c**. Fractions 171–250 were treated as fractions 86–100 [except that MeOH–MeOAc (1:1) was the only elution solvent] to provide an additional 0.18 g of **5c** and **6c** for an overall combined yield of 0.755 g (48%).

A column (150 × 3.5 cm, 1000 ml) of Dowex 1-X2 (Cl^-) 200–400 mesh) packed in distilled H_2O was washed with 500 ml of 2 *N* NH_4OH. A solution of 0.6 g of **5c** and **6c** in 5 ml of 2 *N* NH_4OH was applied to the column followed by 100 ml of 2 *N* NH_4OH. The column was developed with 0.02 *N* NH_4Cl brought to pH 10.00 ± 0.03 by the addition of 6.62 ml of concentrated NH_4OH per 1000 ml of 0.02 *N* NH_4Cl solution. The flow rate of the buffer through the column was 1.95 ml/min and 24.5-ml fractions were collected. Fractions 1–180 contained minor spots (tlc) and were discarded. Fractions 181–1710 were uv transparent and were discarded. Fractions 1711–1960 contained **6c**. Fractions 1961–2100 were uv transparent and were discarded. Fractions 2101–2470 contained **5c**.

Pooled fractions 1711–1960 were stirred for 15 hr with 1.25 g of activated charcoal (Barnebey-Cheney AU-4 prewashed with 6 *N* HCl and distilled H_2O and dried). The mixture was filtered, the uv-transparent filtrate was discarded, and the charcoal was continuously extracted with 450 ml of EtOH–concentrated NH_4OH (7:3) for 24 hr in a Soxhlet apparatus. Two additional 24-hr extractions with fresh solvent were effected and the pooled extracts were evaporated to give 0.18 g (14% overall from **4c**) of crystalline **6c**. A sample was recrystallized from MeOH to give fine needles: mp >258° dec; $[\alpha]^{25}D$ −74.7° (c 0.36, 0.1 *N* NaOH); uv (H_2O) max 253 nm (ε 14,000), min 223 nm (ε 3800) [lit.[18] mp 263–300° dec; $[\alpha]^{25}D$ −69° (*c* 1, 0.1 *N* NaOH)].

Anal. Calcd for $C_{11}H_{15}N_5O_5$: C, 44.44; H, 5.09; N, 23.56. Found: C, 44.30; H, 5.19; N, 23.50.

Fractions 2101–2470 from the Dowex 1-X2 (Cl^-) column were pooled, stirred with 2 g of activated charcoal, and continuously extracted with four 150–200-ml portions of EtOH–concentrated NH_4OH (7:3) as described above for **6c**. Evaporation of the extracts gave 0.19 g (15% overall from **4c**) of crystalline **5c**. A sample was recrystallized from MeOH to give **5c**·MeOH: mp 234–236° (resolidified and darkened at >240°); $[\alpha]^{25}D$ −52.0° (*c* 0.35, 0.1 *N* NaOH); uv (H_2O) max 254 nm (ε 13,400), min 224 nm (ε 2400) [lit.[17] mp 218–220°; $[\alpha]^{22}D$ − 38.4° (c 0.595, H_2O)].

Anal. Calcd for $C_{11}H_{15}N_5O_5 \cdot CH_3OH$: C, 43.76; H, 5.81; N, 21.27. Found: C, 43.54; H, 5.54; N, 21.73. The presence of CH_3OH was verified by integration of the methyl signal in the nmr spectrum.

2′-*O*-Methylcytidine[12,15] (5d) and 3′-*O*-Methylcytidine[12,15] (6d). A mixture of 0.49 g (0.002 mol) of **4d** and 0.013 g of $SnCl_2 \cdot 2H_2O$ in 120 ml of MeOH was treated with 9 ml of CH_2N_2 stock solution B according to the general methylation procedure. The evaporation residue was dissolved in 5 ml of H_2O and applied to a column (58 × 2.5 cm) of Dowex 1-X2 (OH^-). The column was packed and eluted with distilled H_2O and 5-ml fractions were collected at about 1 ml/min. Fractions 141–155 contained **5d**, 156–173 were uv transparent and were discarded, and 174–220 contained **6d**.

Fractions 141–155 were pooled and evaporated to give 0.38 g (74%) of crystalline **5d**, mp 251–254°. A sample was recrystallized from EtOH to give **5d**: mp 255–257°; $[\alpha]^{22}D$ 72.3° (c 1.1, H_2O); uv (H_2O) max 271 nm (ε 9000), min 250 nm (ε 6300); uv (0.1 *N* HCl) max 279 nm (ε 13,200), min 240 nm (ε 1800); uv (0.1 *N* NaOH) max 271 nm (ε 9500), min 250 nm (ε 6600).

Anal. Calcd for $C_{10}H_{15}N_3O_5$: C, 46.70; H, 5.80; N, 16.30. Found: C, 46.99; H, 5.87; N, 16.31.

Analogous work-up of fractions 174–220 gave 0.083 g (15%) of **6d**: mp 210–211°; $[\alpha]^{22}D$ 58.2° (*c* 1, H_2O); uv (H_2O) max 270 nm (ε 8600), min 248 nm (ε 5900); uv (0.1 *N* HCl) max 279 nm (ε 13,400), min 239 nm (ε 1500); uv (0.1 *N* NaOH) max 270 nm (ε 9200), min 248 nm (ε 6500).

Anal. Found: C, 46.63; H, 5.70; N, 16.26.

(See ref 12 and 15 for comparisons.)

4-Methoxy-1-(2-*O*-methyl-β-D-ribofuranosyl)-2-pyrimidinone[8] (5e) and 4-Methoxy-1-(3-*O*-methyl-β-D-ribofuranosyl)-2-pyrimidinone (6e). Method A. A solution of 0.52 g (0.002 mol) of **4e** in 120 ml of 10^{-3} *M* $SnCl_2 \cdot 2H_2O$ in MeOH was treated with 12 ml of CH_2N_2 stock solution B. The evaporation residue was crystallized directly from dry, acid-free EtOAc to give 0.31 g (57%) of pure **5e**, mp 171– 172°, identical in every respect with a known analytically pure sample.[8]

Method B. A solution of 1 g (0.004 mol) of **4e** and 0.08 g (0.0004 mol) of $SnCl_2 \cdot 2H_2O$ in 300 ml of MeOH was treated with 50 ml of CH_2N_2 stock solution A according to the general methylation procedure. The evaporation residue was dissolved in a small volume of MeOH, and 5 g of silica gel (A) was added. The mixture was evaporated and the impregnated powder was applied to a column (1.8 cm diameter, 50 g) of silica gel (B). The column was developed with MeOAc–*n*-C_5H_{12}–MeOH (84:14:0.5) at a rate of 0.33 ml/min and 5-ml fractions were collected. Fractions 101–200 contained pure **5e** and were evaporated to give 0.55 g of crystalline **5e**, mp 170–173°. Fractions 201–400 contained **5e** and **6e** and were evaporated to give 0.48 g of gum. The 0.48 g of mixed isomers was dissolved in MeOH and applied to four silica gel preparative tlc plates (20 × 20 cm). The plates were developed in MeOAc–*n*-C_5H_{12}–MeOH (84:14:0.5) three times for 1 hr each time with 15 min of drying between each development. The more rapidly migrating band was scraped off, extracted with MeOH, and evaporated to give 0.23 g of crystalline **5e**, mp 170–174°, total yield of **5e**[8] 0.78 g (74%).

The slower band was treated analogously to give 0.16 g (15%) of crystalline **6e**, mp 127–130°. This product was recrystallized from EtOH–Skellysolve B to give **6e**: mp 142–144°; $[\alpha]^{23}D$ 107.9° (*c* 1, H_2O); uv (H_2O) max 274 nm (ε 6900), min 238 nm (ε 1200); uv (0.1 *N* HCl) max 274 nm (ε 7000), min 237 nm (ε 1800); uv (0.1 *N* NaOH) max 275 nm (ε 7000), min 241 nm (ε 1900).

Anal. Calcd for $C_{11}H_{16}N_2O_6$: C, 48.53; H, 5.92; N, 10.29. Found: C, 48.23; H, 5.76; N, 10.39.

2′-*O*-Methyluridine[6,8,12,15,16] (5f) and 3′-*O*-Methyluridine[6,12,15] (6f). A solution of 0.73 g (0.003 mol) of **4f** and 0.068 g (0.0003 mol) of $SnCl_2 \cdot 2H_2O$ in 300 ml of MeOH was treated dropwise with 110 ml of CH_2N_2 stock solution A over a period of 2 hr according to the general methylation procedure. The evaporation residue was dissolved in MeOH and applied to six alumina preparative tlc plates (20 × 40 cm). The plates were developed in $CHCl_3$–MeOH–Me_2CO–H_2O (120:60:23:14) for 8 hr, dried for 15 min, and redeveloped for 2 hr in the same solvent system. The more rapidly migrating major band was scraped off and continuously extracted with 200-ml portions of MeOAc–MeOH (4:1) in a Soxhlet apparatus three times for 24 hr each. The combined extracts were evaporated to give 0.45 g (58%) of **5f**, mp 155–158°. A sample was recrystallized from EtOH–EtOAc to give **5f**, mp 159–161°, identical with a known sample.[8]

Anal. Calcd for $C_{10}H_{14}N_2O_6$: C, 46.50; H, 5.47; N, 10.38. Found: C, 46.22; H, 5.65; N, 10.52.

The slower migrating major band was treated analogously to give 0.22 g (28%) of **6f** as a tlc-homogeneous glass with all spectral properties corresponding to this structure (see Tables I and II). Several attempts to crystallize this product were unsuccessful, as also noted by Shugar.[12] The conversion to its crystalline diacetyl derivative in high yield verified the purity of this glassy sample of **6f** as follows.

3′-*O*-Methyl-2′,5′-di-*O*-acetyluridine. A solution of 2 ml of pyridine and 10 ml of Ac_2O was added to 0.16 g (0.006 mol) of glassy **6f** and the resulting solution was stirred at room temperature for 1 hr. The reaction was shown to be complete by tlc and was evaporated to dryness *in vacuo*. The residue was dissolved in $CHCl_3$ and applied to a silica gel preparative tlc plate (20 × 20 cm). The plate was developed with $CHCl_3$–EtOAc (2:1), and the band was scraped off, extracted with MeOAc, and evaporated. The resulting glass was crystallized in two crops from EtOH–Skellysolve B to give 0.20 g (94%) of anytically pure 3′-*O*-methyl-2′,5′-di-*O*-acetyluridine: mp 150–152°; $[\alpha]^{23}D$ 34.7° (c 0.96, MeOH); uv (MeOH) max 258 nm (ε 9500), min 227 nm (ε 2100); uv (0.1 *N* HCl in MeOH) max 258 nm (ε 9300), min 227 nm (ε 1800); uv (0.1 *N* NaOH in MeOH) max 260 nm (ε 6600), min 237 nm (ε 4700); nmr ($CDCl_3$, TMS internal) δ 2.13 and 2.17 (s and s, 3 and 3, 2′- and 5′-$OCOCH_3$), 3.39 (s, 3, 3′-OCH_3), 3.92 ("t," $J_{3'-2'}$ = 5, $J_{3'-4'}$ = 7.5 Hz, 1, $H_{3'}$), 4.18 (m, 1, $H_{4'}$), 4.35 ("d," 2, $H_{5',5''}$), 5.37 ("q," $J_{2'-1'}$ = 3.5, $J_{2'-3'}$ = 5 Hz, 1, $H_{2'}$), 5.64 (d, J_{5-6} = 8 Hz, 1, H_5), 5.81 (d, $J_{1'-2'}$ = 3.5 Hz, 1, $H_{1'}$), 7.40 (d, J_{6-5} = 8 Hz, 1, H_6), 8.71 (br s, 1, N_3-H).

Anal. Calcd for $C_{14}H_{18}N_2O_8$: C, 49.12; H, 5.30; N, 8.18. Found: C, 48.95; H, 5.44; N, 7.93.

5-(2-*O*-Methyl-β-D-ribofuranosyl)uracil (2′-*O*-Methylpseudouridine, 8) and 5-(3-*O*-Methyl-β-D-ribofuranosyl)uracil (3′-*O*-Methylpseudouridine, 9). To a stirred mixture of 0.24 g (0.001 mol) of 7[38] and 0.046 g of $SnCl_2 \cdot 2H_2O$ in 135 ml of MeOH was added a total of 49 ml of diazomethane stock solution A dropwise at such a rate that yellow color did not persist. Complete reaction was indicated (tlc) and a 1-g portion of silica gel (B) was added. The mixture was evaporated to dryness and the impregnated powder was applied to a column (1.2 cm diameter, 16 g) of the same absorbent. The column was developed with MeOAc–$CHCl_3$–EtOH (10:1:0.1) at a rate of 1.5 ml/min. Fractions of 3.2

ml were collected. Fractions 5–110 contained multiply methylated products (tlc) which were not identified. Fractions 141–180 were found (upon standing) to contain 0.012 g of slender needles of **8**, mp 214–217°, which were collected by decantation of solvent and scratching from the test tubes. The adhering crystals were dissolved in MeOH, pooled, evaporated, and crystallized from EtOH–EtOAc to give 0.034 g of needles, mp 209–212°. The mother liquor was combined with the decanted elution solvent and evaporated to dryness. Crystallization of this residue from EtOH–EtOAc gave 0.023 g of **8**, mp 200–210°, total collected yield of **8** 0.069 g (27%). The needles of **8**, mp 214–217°, had $[\alpha]^{23}D$ 22.2° (*c* 0.93, H_2O); uv (H_2O) max 263 nm (ϵ 7800), min 232 nm (ϵ 1500); uv (0.1 *N* HCl) max 263 nm (ϵ 8100), min 232 nm (ϵ 2000); uv (0.1 *N* NaOH) max 287 nm (ϵ 8100), min 246 nm (ϵ 2500).

Anal. Calcd for $C_{10}H_{14}N_2O_6$: C, 46.50; H, 5.47; N, 10.38. Found: C, 46.62; H, 5.70; N, 10.30.

A 9-mg sample of **8** was trifluoroacetylated using 0.5 ml of trifluoroacetic anhydride and 2 ml of dry CH_2Cl_2 at 5° for 20 hr by the general procedure to give a residue which had nmr (Me_2CO—d_6, TMS internal) δ 3.40 (s, 3, 2-OCH_3), 4.50 (m, 2, $H_{2'}$ and $H_{4'}$), 4.73 (m, 3, $H_{1'}$ and $H_{5',5''}$), 5.59 ("t," $J_{3'-2'} \cong J_{3'-4'}$ = 5.5 Hz, 1, $H_{3'}$), 6.48 (br s, 2, N_1 H and N_3 H), 7.67 (s, 1, H_6). Irradiation at δ 5.58 ($H_{3'}$) simplified the high-field multiplet ($H_{2'}$ and $H_{4'}$ but did not affect the multiplet centered at δ 4.73 ($H_{1'}$ and $H_{5',5''}$). Irradiation at δ 4.72 ($H_{1'}$ and $H_{5',5''}$) did not affect the "triplet" at δ 5.59 ($H_{3'}$). Irradiation at δ 4.54 ($H_{2'}$ and $H_{4'}$) collapsed the triplet at δ 5.59 to a singlet and simplified the multiplet at δ 4.73 to two peaks.

Fractions 181–340 from the above column contained both **8** and **9** and were pooled and evaporated to a small volume. A 1-g portion of silica gel (B) was added and the mixture was evaporated to dryness. The impregnated powder was applied to a similar column, which was developed with MeOAc–$CHCl_3$–EtOH (10:1:0.2). Fractions (3.2 ml) 31–110 contained 0.11 g (43%) of mixed **8** and **9** (as a dried solid after evaporation of solvents). Fractions 111–220 were pooled and evaporated to give 0.026 g (10%) of crystalline **9**: mp 225–228° dec; uv (H_2O) max 262 nm (ϵ 6500), min 232 nm (ϵ 1900); uv (0.1 *N* HCl) max 262 nm (ϵ 6900), min 233 nm (ϵ 2500); uv (0.1 *N* NaOH) max 287 nm (ϵ 6500), min 246 nm (ϵ 2300); mass spectrum *m/e* 259.0930 [calcd for $C_{10}H_{15}N_2O_6$ (M + 1), 259.0916].

Anal. Calcd for $C_{10}H_{14}N_2O_6$: C, 46.50; H, 5.47; N, 10.38. Found: C, 46.63; H, 5.64; N, 10.27.

A 10-mg sample of **9** was trifluoroacetylated by the general procedure. The evaporation residue gave nmr (Me_2CO-d_6, TMS internal) δ 3.37 (s, 3, 3′-OCH_3), 4.15 (m, 1, $H_{4'}$), 4.17 (d, $J_{3'-2'}$ = 4 Hz, $J_{3'-4'}$ small, 1, $H_{3'}$), 4.68 (m, 2, $H_{5',5''}$), 4.93 (d, $J_{1'-2'}$ = 3 Hz, $H_{1'}$), 5.74 ("q," $J_{2'-1'}$ = 3, $J_{2'-3'}$ = 4 Hz, 1, $H_{2'}$), 7.57 (br s, 1, H_6). Irradiation at δ 5.78 ($H_{2'}$) caused collapse of the doublet at δ 4.93 ($H_{1'}$) to a singlet and that at δ 4.17 ($H_{3'}$) to a singlet. Irradiation at δ 4.95 ($H_{1'}$) caused collapse of the band at δ 5.74 ($H_{2'}$) to a doublet ($J_{2'-3'}$ = 4 Hz). Irradiation at δ 4.19 ($H_{3'}$) caused collapse of the band at δ 5.74 ($H_{2'}$) to a doublet ($J_{2'-1'}$ = 3 Hz) but had no effect on the δ 4.93 ($H_{1'}$) doublet. Irradiation at δ 4.71 ($H_{5',5''}$) raised a singlet at δ 4.12 ($H_{4'}$), confirming the coupling of these bands.

Registry No.—**1a**, 58-61-7; **1b**, 5399-87-1; **2a**, 2140-79-6; **2b**, 51293-29-9; **2c**, 13039-46-8; **2d**, 51293-30-2; **3a**, 10300-22-8; **3b**, 51293-31-3; **3c**, 10300-25-1; **3d**, 51293-32-4; **4a**, 69-33-0; **4b**, 6742-12-7; **4c**, 118-00-3; **4d**, 65-46-3; **4e**, 34218-77-4; **4f**, 58-96-8; **5a** monohydrochloride, 51293-33-5; **5a** trifluoroacetate, 51293-34-6; **5b** monohydrochloride, 51293-35-7; **5b** trifluoroacetate, 51364-38-6; **5c**, 2140-71-8; **5d**, 2140-72-9; **5e**, 34218-78-5; **5f**, 2140-76-3; **6a**, 51293-36-8; **6a** trifluoroacetate, 51293-37-9; **6b** monohydrochloride, 51364-39-7; **6b** trifluoroacetate, 51293-38-0; **6c**, 10300-27-3; **6d**, 20594-00-7; **6e**, 34202-79-4; **6f**, 6038-59-1; **7**, 1445-07-4; **8**, 2140-68-3; **8** trifluoroacetate, 51293-39-1; **9**, 51293-40-4; **9** trifluoroacetate, 51293-41-5; 3′-*O*-methyl-2′,5′-di-*O*-acetyluridine, 51293-42-6.

References and Notes

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(44) Note Added in Proof. D. Wagner, J. P. H. Verheyden, and J. G. Moffatt, *J. Org. Chem.*, **39**, 24 (1974), have reported the methylation of a tin derivative of uridine with methyl iodide. However, the overall yield of a nearly equal mixture of **5f** and **6f** was 70% and no separation of the isomers was achieved.

Investigation of the Mechanism of Reductive Dehalogenation of Haloanisoles under Aryne-Forming Conditions[1a]

Edward R. Biehl,* Susan Lapis,[1b] and Perry C. Reeves

Department of Chemistry, Southern Methodist University, Dallas, Texas 75275

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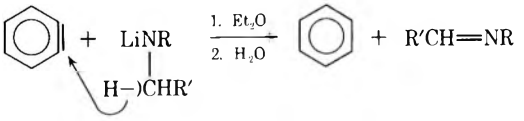
Separation of the reductive dehalogenation mechanism proceeding *via* aryne (mechanism A) from direct halogen displacement mechanisms (mechanisms B and C) has been achieved. In the presence of large excesses of di-*n*-propylamine as compared with lithium di-*n*-propylamide and haloanisole, aryne reduction is essentially eliminated. With the exception of *o*- and *p*-iodoanisole, haloanisole appears to undergo nonaryne reduction *via* mechanism B, hydride attack on ring halogen. Mechanism C, amide ion nucleophilic attack on ring halogen, most likely operates in the reduction of *o*- and *p*-iodoanisole. An explanation in terms of the influence of the methoxy group on (a) the relative benzenoid hydrogen atom acidities and (b) the relative stabilities of possible carbanion intermediates is presented.

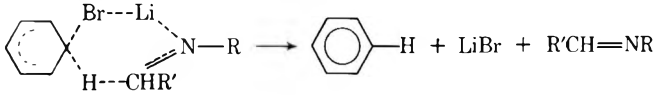
Three mechanisms have been proposed for the reduction of haloaromatic compounds under aryne-forming conditions. Mechanism A, introduced by Wittig,[2] postulates the reduction of aryne *via* a hydride transfer from the α-carbon atom of the appropriate lithium dialkylamide. In support of this mechanism, aryne intermediates have been trapped by furan,[3] and reduction does not occur in the presence of bases lacking α-hydrogen atoms, such as lithium diphenylamide.[4]

mechanism A



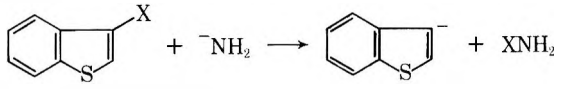
Benkeser and DeBoer[4] have proposed a direct displacement of aromatic halogen by a similar hydride transfer (mechanism B) on the basis that certain haloaromatic compounds containing no hydrogen atom ortho to halogen are reduced under aryne-forming conditions.[5]

mechanism B



Recently, Reinecke[6] and deBie[7] have suggested a third mechanism (mechanism C) to account for the reduction of

mechanism C



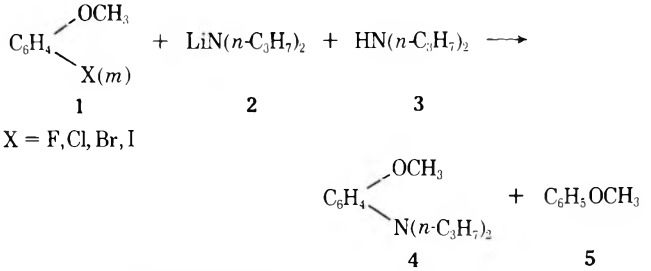
certain halothianaphthenes with metal amides. In this mechanism, halothianaphthenes are reduced by direct nucleophilic attack of amide onto ring halogen with subsequent formation of haloamine and thianaphthene anion. In support of this mechanism, 1,1′-bipiperidine—the expected product from the reaction of *N*-bromopiperidine and metal piperidide—can be isolated from the reaction of halothiaphenes with metal piperidide and piperidine.[6]

Wittig[3] has shown, by product analysis, that the mechanism of reduction of *p*-iodo- and *p*-fluorotoluene is dependent upon the halogen atom. On the basis of the relative polarizability and electronegativity of these two halogen atoms, *p*-fluorotoluene appears to be reduced *via* the corresponding 4-toluyne (mechanism A). However, the *p*-iodo isomer is reduced *via* direct displacement of iodine (mechanism B and/or C). We[8] have recently established a method for determining the extent of reduction occurring *via* the aryne and the direct displacement pathways by comparing the anisole–*m*-(*N*,*N*-di-*n*-propyl)anisidine product distribution from the reaction of *o*-haloanisole with lithium di-*n*-propylamide in varying amounts of di-*n*-propylamine. As the amount of amine was increased relative to haloanisole and dialkylamide, less of the 3-methoxybenzyne was converted to anisole since free amine does not reduce aryne.[9] At very large excess of amine, nearly all aryne formed dialkylanisidine instead of anisole. Consequently, at high amine/amide concentrations, reduction occurred chiefly by the direct displacement mechanism (B and/or C). The extent of reduction varied as the haloanisole was varied along the series I (76%) > F (9%) ~ Br (10%) > Cl (5%).

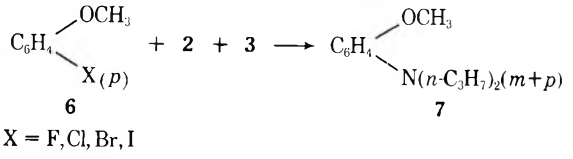
This paper reports the extension of this method to the reaction of *m*- and *p*-haloanisole in order to obtain more information on the role of the halogen atom. In addition, the influence of the position of the nonhalogen substituents on the mechanism of reduction under these reaction conditions will be studied.

Results

Table I lists the product distribution as % anisole (**5**)/% *N*,*N*-di-*n*-propyl-*m*-anisidine (**4**) from the reaction of *m*-haloanisole and lithium di-*n*-propylamide (**2**) with varying molar excesses of di-*n*-propylamine (**3**). Similarly, Table II



lists the product distribution as % **5**/*N*,*N*-di-*n*-propyl-*m*- and -*p*-anisidines (**7**) from the reaction of *p*-haloanisole (**6**) and **2** with varying molar excesses of **3**.



A high-boiling, acid-soluble residue was formed in those reactions conducted in the absence of amine **3**. This residue has not been fully identified but appears to be a mixture of higher phenylated aryne products as indicated by infrared, nmr, and mass spectra. The amount of residue, however, rapidly decreases with increasing amounts of **3**, no appre-

Table I
Product Distribution as % Anisole (5)/% *N,N*-Di-*n*-propyl-*m*-anisidine (4) from *m*-Haloanisoles

	Ratio % 5/% 4			
1:2:3 X =	F	Cl	Br	I
1:2:0	18/69	14/72	17/72	19/69
1:2:1	13/80	13/85	10/83	13/84
1:2:2	12/86	10/89	10/86	12/87
1:2:4	8/89	6/92	7/91	8.2/90
1:2:6	6/90	3.5/95	5.0/92	6.4/90
1:2:8	6/90	3.2/96	4.6/92	6.5/89

Table II
Product Distributions as % Anisole (5)/% Di-*n*-propylanisidine (7) from *p*-Haloanisoles

	Ratio % 5/% 7			
6:2:3 X =	F	Cl	Br	I
1:2:0	20/52	25/53	26/46	45/32
1:2:1	16/69	17/70	19/69	37/48
1:2:2	13/73	15/76	15/78	35/55
1:2:4	10/80	12/84	10/83	29/65
1:2:6	7.4/83	11/88	10/85	29/65
1:2:8	7.4/83	10/87		

Table III
Partitioning of Methoxyaryne[a]

1 or 6:2:3	*m*-F	*m*-Cl	*m*-Br	*m*-I	*p*-F	*p*-Cl	*p*-Br	*p*-I
1:2:2	0.07	0.08	0.06	0.06	0.08	0.07	0.06	0.11
1:2:4	0.02	0.03	0.03	0.02	0.03	0.02	0	0

[a] Results expressed as ratio per cent anisole *via* mechanism A *vs.* per cent **4** or **7**. Per cent anisole calculated by subtracting residual yield of amine from total yield of anisole for a particular reaction listed in Tables I and II.

ciable residue being observed for reactions employing 2 or more molar equiv of **3**.

In general, reductive dehalogenation of haloanisoles (**1** or **6**) to anisole **5** decreased, and their conversion to anisidines (**4** or **7**), *via* the corresponding methoxybenzyne intermediates, increased as the quantity of amine was increased. The extent of reductive dehalogenation of *m*-haloanisoles appears to be independent of the halogen atom since the four meta isomers yielded similar **5**/**4** product distributions for a given quantity of **3**. For example, **5**/**4** ratios of 12/86 (F), 10/89 (Cl), 10/86 (Br), and 12/87 (I) were obtained using a 2 molar excess of **3**. A similar relationship appears to hold for the *p*-bromo, -chloro, and -fluoro isomers of **6**. However, the **5**/**4** product ratios listed in Table II indicate that *p*-iodoanisole was reduced to a larger extent than the other *p*-haloanisoles. In addition, comparison of **5**/**4** product ratios for a particular halogen atom and a given molar excess of **3** indicates that reduction occurred to a greater extent with *p*- than with *m*-haloanisoles. For example, *p*-iodoanisole was converted to anisole (**5**) in 35% yield whereas the corresponding meta isomer afforded **5** in 12% yield in the presence of a 2 *M* excess of **3**.

The anisole/anisidine yield ratio was observed to reach a limiting value in all systems, indicating that reduction *via* aryne (mechanism A) was essentially eliminated in the presence of large (>4) molar excesses of **3**. Further, the amount of reductive dehalogenation *via* aryne should be approximated by subtracting the limiting yield of anisole *via* mechanism B and/or C from the yield of anisole for a particular reaction. Accordingly, the ratio of yield of anisole *via* aryne to yield of dialkylanisidine for a given molar ratio of **2** and **3** should be an indication of the partitioning of methoxyaryne, and should be independent of the halogen atom in the starting material. As shown in Table III, this appears to be approximately the case in all reactions studied.

Discussion

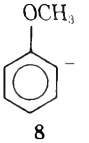
The relative reactivity of haloanisoles toward aryne formation and direct reduction of the carbon–halogen bond is influenced by the position of the methoxy group. Deuterium exchange experiments have shown that the 2-hydrogen atom in anisole is much more acidic than the 3- and 4-hydrogen atoms.[10] Consequently, the enhanced acidity of the 2-hydrogen atom in *m*-haloanisoles results in aryne formation with subsequent conversion to anisole or anisidines predominating over direct reduction of the carbon–halogen bond. The strong influence of the methoxy group is further demonstrated in the directing effect, since nucleophilic attack by **3** occurred solely at the meta position of 3-methoxybenzyne.

The hydrogen atom ortho to the halogen is farther from the electron-withdrawing methoxy group in *p*-haloanisoles than in the corresponding meta isomers, and is thus less acidic. Consequently, less aryne is formed and more nonaryne reduction occurs in the para system than in the meta system. The directing effect of the methoxy group is also weakened by distance in 4-methoxybenzyne as compared to 3-methoxybenzyne, and this results in the production of a mixture of meta and para anisidines.

A partial assessment of the relative amounts of reduction *via* mechanisms B and C in the o-, *m*-, and *p*-haloanisole series can be made by considering the variation in the anisole yield as a function of the halogen atom at limiting conditions in which only nonaryne reduction occurs. Mechanism C, nucleophilic attack on halogen, suggests that anisole formation would be greatest for the iodo isomer. Also its rate of formation would decrease as the halogen is varied along the series I, Br, Cl, F, on the basis of the relative polarizabilities of the halogen atoms. Similar considerations are not possible for mechanism B since the relative extents of (a) carbon–halogen bond breaking, (b) carbon–hydrogen bond making, and (c) lithium–halogen bond making in the corresponding transition states are not known. Since (a) would be expected to operate in the opposite direction of (b) and (c), a small change in anisole yield as the halogen atom is varied along the series, F, Cl, Br and I would not be unreasonable. Accordingly, the small variation observed in this study for meta and para isomers of fluoro-, chloro-, and bromoanisoles and the corresponding ortho isomers in a previously reported investigation[8] are in accordance with mechanism B.

In addition, whereas *m*-iodoanisole is reduced to approximately the same extent as the other *m*-haloanisoles, o-iodo- and, to a lesser extent, *p*-iodo- are considerably more reduced than the other o- and *p*-haloanisoles. This indicates that *m*-iodoanisole is probably undergoing reduction *via* mechanism B; however, the ortho and possibly para iodo isomers are being reduced in part by mechanism C.

The much larger yield of anisole (76%) as compared to aryne product **4** (14%), observed previously for o-iodoanisole,[8] probably reflects the greater tendency by the dialkylamide ion (**2**) to attack the iodine atom (mechanism C) rather than the ortho hydrogen atom of o-iodoanisole. Methoxyphenyl carbanion (**8**), produced in the former case, would be stabilized by the methoxy group to a larger extent than iodoanisole anion (**9**) formed in the latter case. In con-



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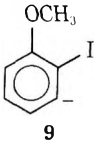
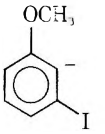


9

trast, amide ion **3** would be expected to attack the ortho hydrogen atom to a greater extent than the iodine atom in *m*-anisole since the former yields a more stable iodoanisole anion, **10**, than the carbanion, **11**, produced by the latter.



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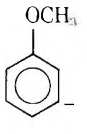

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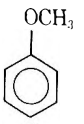
The decreased acidity of the hydrogen atom in *p*-iodoanisole as compared to that of *m*-iodoanisole apparently allows amide ion attack on iodine to compete with aryne formation. However, that the yield of anisole is less for *p*-iodoanisole (28%) than for o-iodoanisole (76%) is a result of the lower stability of carbanion **12** as compared to carbanion **8**.



12

Experimental Section

Glpc analyses were performed on a Beckman GC-5 chromatograph using nitrogen as carrier gas at a flow rate of 60 ml/min, inlet temperature of 150°, detection temperature of 200°, and column temperature of 100°. A 10 ft × 0.125 in. i.d. column packed with 10% SE-30 (silicone rubber) on Chromosorb W, acid-washed, 80–100 mesh, was used to analyze anisole. Nmr spectra were obtained using a Perkin-Elmer R-12B nmr spectrophotometer.

Materials. Di-*n*-propylamine was obtained from Eastman Kodak Co. and was dried, distilled, and then stored over anhydrous potassium carbonate. *n*-Butyllithium, 1.9–2.2 *M* in hexane, was obtained from Alfa Inorganics Inc., and was manipulated in a nitrogen-atmosphere glove bag. *m*- and *p*-fluoroanisoles were procured from Pierce Chemical Co.

m- and *p*-iodoanisoles,[11] *m*-bromoanisole,[12] and *m*- and *p*-chloroanisoles[13] were synthesized according to literature procedures.

General Procedure. The reactions were carried out using oven-dried glassware and under a nitrogen atmosphere. In a typical reaction, 0.05 mol of *n*-butyllithium was added dropwise to a stirred solution containing 25 ml of anhydrous ether and the appropriate amount of di-*n*-propylamine, and the solution was refluxed for 10 min to ensure complete amide formation. After 0.025 mol of haloanisole followed by 25 ml of anhydrous ether was added, the solution was refluxed (overnight) for at least 18 hr. The reaction was then quenched by the dropwise addition of water until the brightly colored solution changed to cloudy white. The ether solution was washed with water, extracted three times with 10% hydrochloric acid (25 ml each) to remove the basic aryne products, dried ($CaCl_2$), and concentrated by careful evaporation of ether to yield anisole. Anisole was quantitatively analyzed by vpc using phenetole as internal standard. The acidic aqueous extracts were combined, made basic with 10% sodium hydroxide, and extracted with three 25-ml portions of ether. After the basic ether extracts were combined, dried ($MgSO_4$), and concentrated, an oily residue was obtained which yielded the appropriate aryne amine product(s) upon vacuum distillation. *m*-haloanisoles yielded *N,N*-di-*n*-propyl-*m*-anisidine in these reactions, whereas the para isomeric anisoles gave a mixture of the corresponding meta and para isomeric anisidines. Infrared and nmr spectra were consistent with proposed structures. Nmr spectrum of the meta anisidine showed a singlet at τ 6.35 corresponding to the methoxy hydrogen atoms, whereas in the spectrum of the meta–para mixture two singlet peaks were observed in this region.

A higher boiling by-product, which was present in reactions with no excess amine solvent as a residue after vacuum distillation of the normal anisidine product, was pooled from a number of reactions and vacuum distilled, bp 153–154 (0.3 mm). The nmr spectrum was not clearly resolved, indicating a mixture, but showed aromatic hydrogens (τ 2.5–3.7), methoxy group (τ 6.3–6.4), and aliphatic hydrogens (τ 6.6–9.3). Mass spectrographic analysis was difficult to interpret due to polymerization. Infrared spectrum contained no N–H bands.

References and Notes

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Solvolysis of Arylvinyl Bromides and Tosylates

Keith Yates* and Jean-Jacques Périé

Lash Miller Chemical Laboratories, University of Toronto, Toronto, Ontario, Canada M5S 1A1

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The bromides and tosylates of the 1-(4-methylphenyl)vinyl, 1-(2,4-dimethylphenyl)vinyl, and 1-(2,4,6-trimethylphenyl)vinyl systems have been prepared and their rates of solvolysis measured in alcohol–water mixtures and in acetic acid in the temperature range 35–88°. Rate enhancements of up to 4 × 10^5 over the parent 1-phenylvinyl systems have been obtained, with ortho-methyl substitution leading to significant steric acceleration of these normally slow solvolytic reactions. The kinetics, medium effects, and leaving-group effects are all in accord with a simple SN1 type solvolysis mechanism leading to vinyl cation intermediates. However, the Winstein–Grunwald *m* values, Schleyer *Q* values, and insensitivity to solvent nucleophilicity all point to a weak nucleophilic assistance component in these vinyl solvolyses. Solvent effects in these solvolytic reactions are compared with those in electrophilic additions leading to analogous cationic intermediates.

In connection with some previous work of one of us,[1] concerning the relative ease of formation of carbonium ions and vinyl cations, as well as solvation effects on these species in electrophilic additions, we have been interested in investigating the rates and solvent effects of related solvolytic reactions leading to similar vinyl cationic intermediates. A second objective was to obtain more quantitative information about the reactivity of vinylic substrates,

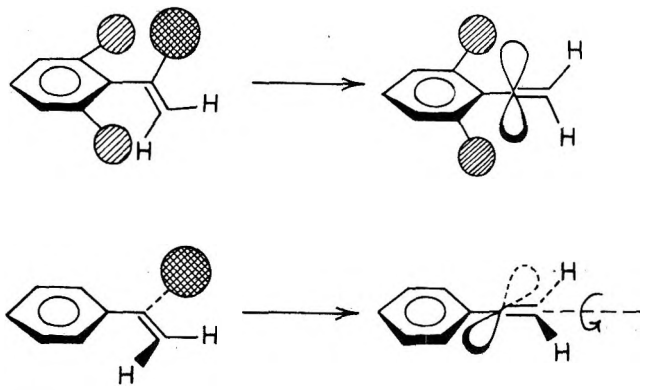
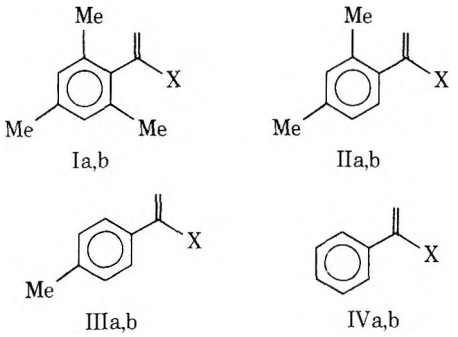


Figure 1.

since it is well known that such compounds generally show very sluggish solvolytic behavior. This has been ascribed to reactant stabilization, since a C(sp^2)-X bond is of lower energy than a corresponding C(sp^3)-X bond. However, other factors which could be important in producing this low reactivity are less effective backside solvation of the developing vinyl cation intermediate and the high energy of such a cation[2] compared with that of an analogous trisubstituted or "normal" carbonium ion.

We have therefore investigated these two points in the solvolysis and acetolysis of several arylvinyl bromides and tosylates by comparing the relative reactivities of differently substituted compounds, as well as solvation effects on these reactions. The compounds investigated were the following.



Ia,b IIa,b

IIIa,b IVa,b

a, X = Br
b, X = OTs

If we consider the model compound I and compare this with the parent system IV it can be predicted from an examination of molecular models that substitution in the neighborhood of the leaving group would produce two effects, as shown in Figure 1.

(1) Steric hindrance to coplanarity produced by the two ortho substituents should essentially destroy the conjugation between the phenyl and vinyl π systems and thus increase the initial state energy of I relative to IV. (This difference can be estimated to be of the order of 4–5 kcal based on enthalpies of hydrogenation.)

Examination of molecular models for Ib indicates that, because of the bulk of the tosylate group, the two π systems are probably very nearly orthogonal. Even for the less bulky bromide the interplanar angle between phenyl and vinyl in Ia is probably around 60–70°.

(2) As the system approaches the transition state during solvolysis, the vacant p orbital which develops at the π carbon as the leaving group departs can be directly conjugated with the phenyl ring in system I with little necessity for rotation about the C_α-phenyl bond. In the case of system IV, where the two π systems are initially coplanar, this conjugation could not be achieved until after the transition state had been reached.

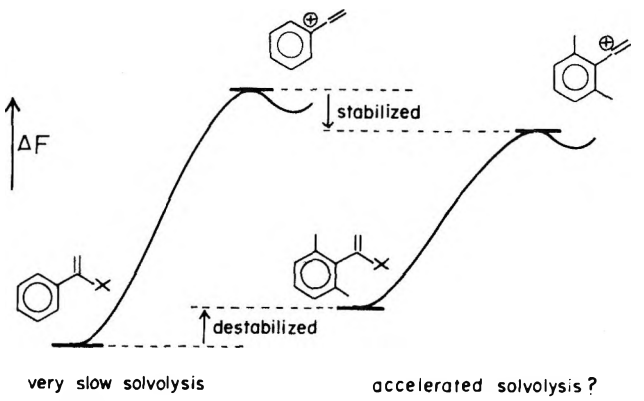


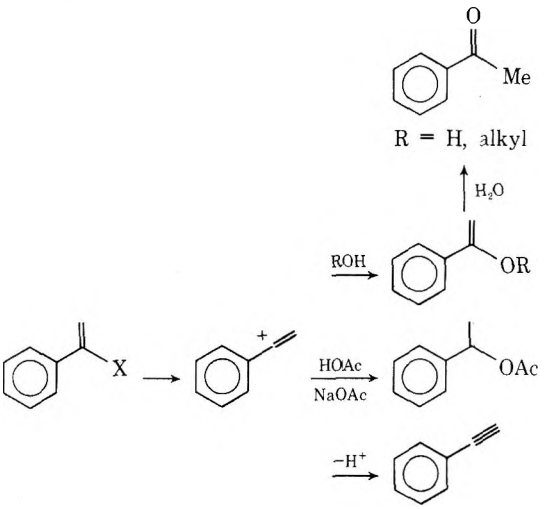
Figure 2.

Thus it would be expected that the total activation energy in the first case should be significantly lowered relative to that of the parent phenylvinyl system, as shown in Figure 2. Therefore, systems like I should solvolyze at reasonable rates at moderate temperatures, even with normal leaving groups, without requiring the use of highly polar leaving groups such as triflate, which have been used recently to obtain conveniently measurable solvolysis rates in vinyl systems.[3] In this way the solvolytic reactivity of arylvinyl bromides and tosylates can be more directly compared with the wealth of information available on the solvolysis of analogous saturated substrates,[4] and also with electrophilic additions to arylacetylenes.[1]

Results and Discussion

Although the SN1 mechanism has been observed in most previous studies of vinyl solvolysis, other possible solvolytic processes cannot automatically be excluded. Other observed processes have been nucleophilic addition followed by elimination,[5] electrophilic addition and elimination in acidic solution,[6] and E2-type elimination.[7] The SN2 mechanism is another possibility, although theoretical calculations suggest that it is energetically unfavorable for vinyl systems.[8] Therefore it is important to establish that the arylvinyl substrates studied here do in fact follow simple SN1 type processes.

Evidence for an SN1 Mechanism. This mechanism can be established from product analysis and kinetic measurements in the following way. Firstly, product analysis based on either solvolysis in alcohol–water mixtures or acetolysis in acetic acid–sodium acetate shows in all cases



that the ketone (or acetate) is the major product. The minor product (10–30%) in all cases is the corresponding arylacetylene, presumably formed by proton loss from the vinyl cation intermediate. (The proportions of product

formed from each substrate are given in the Experimental Section.)

The kinetics in each case are simple first order in substrate, and the rate constants obtained are independent of the concentration of added nucleophile or base, as illustrated in Table I. Even when sodium hydroxide is used in tenfold excess of the concentration of the starting tosylate, there is a negligible change in the observed rate constant. This is consistent only with an SN1 process.

It is well known that the effect of a change in leaving group on solvolytic rate is a good criterion for distinguishing between SN1 and SN2 processes.[4] For example, if the ratio k_{OTs}/k_{Br} for ROTs and RBr solvolysis is close to unity, this indicates an SN2 type process, whereas, if the ratio is of the order of 200 or greater, this indicates an SN1 mechanism. The results in Table II for the solvolysis of Ia,b and IIa,b clearly indicate an SN1 mechanism for these vinyl substrates. We will show later, when discussing solvation effects, that the rates of these arylvinyl-X solvolyses are significantly increased (by more than 10^2) by increasing the ionizing ability of the solvent (as from acetic acid to water). This is also much more consistent with an

Table I
Effect of Added Base on the Solvolysis of Ib in 80:20 Ethanol–Water at 36.5°

$[ROTs]_0$	Base (M)	[Base]/[ROTs]	$10^4 k_{obsd}$, sec^{-1}
10^{-4}	NaOAc (1.5×10^{-4})	1.5	2.08
10^{-4}	NaOAc (5×10^{-4})	5	2.02
10^{-4}	NaOAc (10^{-3})	10	2.01
10^{-4}	NaOH (10^{-3})	10	2.20

Table II
Leaving-Group Effects on Arylvinyl Solvolysis

Substrate	k, sec^{-1}	Reaction conditions	k_{OTs}/k_{Br}
Ia	$1.80 \pm 0.02 \times 10^{-5}$	E/W 80:20[a]	335
Ib	$6.03 \pm 0.01 \times 10^{-3}$	$T = 67.8°$	
IIa	$2.60 \pm 0.04 \times 10^{-6}$	E/W 80:20[a]	400
IIb	$1.05 \pm 0.01 \times 10^{-3}$	$T = 88.0°$	

[a] Ethanol–water.

From these two sets of data, and particularly from the tosylate data, it can be seen that the effect of methyl substitution in the para position, which gives only polar effects, is significantly less than that of ortho substitution. Substitution at the ortho position, and particularly at both, produces rate enhancements larger than would be expected from the additive polar effects of several methyl substituents. Thus, even though the measured rate enhancements are the sum of polar and steric accelerations, the results show that the latter contributes a large proportion of the observed enhancement of the vinyl solvolysis rate.

These results are in good agreement with the predictions based on the energy profile diagram of Figure 2 and show that the reactivity of vinyl substrates can be greatly enhanced by this type of substitution, without the need for highly polar leaving groups such as triflate. It is interesting to compare the effects of similar substitution on the rates of SN1 solvolysis of corresponding saturated compounds, such as the 1-phenylethyl chlorides studied by Charlton and Hughes.[10] These effects are shown in Table V.

In comparing the rate effects of methyl substitution in Tables III–V, the polar effect of a 4-methyl is expected to be roughly similar whether a carbonium ion or vinyl cation type of transition state is being produced, and in fact this is found to be the case. However, further substitution in the ortho positions produces rate accelerations which are less than cumulative[11] for the saturated series, but more than cumulative for the vinyl series. Thus steric effects in the saturated series are retarding, since they prevent carbonium ion delocalization into the phenyl group, but in the corresponding vinyl substrates they are accelerating, since they permit or even enforce vinyl cation delocalization. This comparison between the saturated and unsaturated series of solvolysis reactions supports the description given earlier of steric effects in the arylvinyl systems.

Solvent Effects. It is of interest to obtain more information about solvent participation in the solvolysis of vinyl compounds, partly to determine whether the low reactivity of such compounds is related to less effective solvation of vinyl cation intermediates and transition states,

Table III
Rates of Solvolysis of Arylvinyl Tosylates in MeOH–H_2O (50:50) at 36.5.

System	Ib	IIb	IIIb	IVb
k,[a] sec^{-1}	7.95×10^{-3}	1.39×10^{-4}	4.36×10^{-7}	1.90×10^{-8} [b]
k_{rel}	4.2×10^5	7.3×10^3	23	1
	(1.8×10^4)	(320)	(1)	

[a] $[ROTs]_0 = 10^{-4}$ M; $[NaOAc] = 5 \times 10^{-4}$ M. [b] Value extrapolated to 36.5° from data in ref 7 using activation parameters.

Table IV
Rates of Solvolysis of Arylvinyl Bromides in EtOH–H_2O (80:20) at 88.0.

System	Ia	IIa	IIIa	IVa
k,[a] sec^{-1}	1.54×10^{-4}	2.60×10^{-6}	3.5×10^{-8}	8.7×10^{-10} [b]
k_{rel}	1.8×10^5	3×10^3	40	1
	(4.5×10^3)	(75)	(1)	

[a] $[RBr]_0 = 10^{-4}$ M; $[NaOAc] = 5 \times 10^{-4}$ M. [b] Value extrapolated to 88.0° from data in ref 9 using activation parameters and $\rho\sigma^+$ relationships.

SN1 process, since SN2 processes are known to be relatively insensitive to changes in solvent polarity.

Effects of Substitution. The solvolysis rate enhancements which result from methyl substitution in the phenyl ring are shown by the two sets of data in Tables III and IV for the phenylvinyl tosylates and bromides, respectively.

Table V
Relative Rates of Solvolysis of Substituted 1-Phenylethyl Chlorides in EtOH at 34.8.

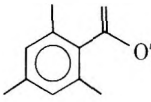
Substituent (registry no.)	2,4,6-Trimethyl (51270-90-7)	2,4-Dimethyl (51270-91-8)	4-Methyl (2362-36-9)	
k_{rel}	1440	560	40	1
	(36)	(14)	(1)	

and partly to compare solvent effects on the rates of solvolytic reactions with those observed for electrophilic additions generating analogous cationic intermediates. Two methods used to assess solvent effects were the Winstein-Grunwald treatment[12] and the more recent approach of Schleyer.[13]

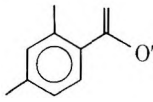
Determination of the effect of changing the solvent on the solvolytic rates of Ia and IIa gives the results shown in Table VI. These values can be used to calculate the parameter m, which is a measure of the sensitivity of the reaction to changes in solvent polarity (Y) according to the relation below.

$$\log k/k_0 = mY$$

Good linear plots were obtained in each case, yielding values of m at the reaction temperatures involved. The empirical relationship $m_1/m_2 = T_2/T_1$ [14] can then be used to correct these values to the standard temperature of 25°, for direct comparison with other available m values. This yields the values shown.



$m^{25°} = 0.62$



$m^{25°} = 0.65$

Compared with m values previously obtained for typical SN1 reactions,[12] these values are low, although they are comparable in magnitude to those found for the trianisylvinyl system.[15] To assess whether these low m values could be due to a less effective nucleophilic assistance component of the solvent participation, the complete Winstein-Grunwald equation

$$\log k/k_0 = mY + lN$$

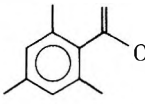
was used to try to determine the extent of partial SN2 character in these vinyl solvolyses. Unfortunately, the range of solvent nucleophilicity parameters (N) available is not large, but the contribution of the term lN can be determined[4] by using this equation in differential form

$$\mathrm{d} \log k = \left(\frac{\partial \log k}{\partial Y}\right)_N \partial Y + \left(\frac{\partial \log k}{\partial N}\right)_Y \partial N$$

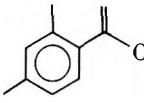
and by measuring the ratio of rate constants obtained in two solvents of the same Y value ($\partial Y = 0$) but with considerably different nucleophilicities ($\partial N \neq 0$). Two such solvents are ethanol-water (98:2) and acetic acid, for which $Y = -1.68$ in each case. The results obtained in these two solvents are shown in Table VII. From the rate ratios $k_{KOAc}/k_{E/W}$ it is clear that a significant change in nucleophilicity of the solvent[13] produces no significant change in rate (*i.e.*, $\mathrm{d} \log k/\partial N \cong 0$) compared with the changes obtained for typical SN2-type reactions (which show rate enhancements of 3×10^2 to 1.3×10^4 in changing from acetic acid to ethanol[16]). These results point to a very important aspect of the solvolysis of vinyl compounds, the absence of any significant rear-side nucleophilic assistance by solvent molecules or external nucleophiles. It is probable that the low values of m obtained using the simple Winstein-Grunwald equation result partly from the fact that these systems are poorly solvated from the rear side as they approach the transition state, compared with the solvation in typical SN1 processes of saturated systems.

Relative Ease of Solvolytic Formation of Vinyl Cations and Carbonium Ions. From the m value of 0.62 obtained for Ia and Charlton and Hughes' results[10] for the corresponding 1-arylethyl chloride, an estimate can be made of the relative solvolytic reactivity of vinyl and saturated systems. For the vinyl system I k_{EtOH} (Ia) = 1.90×10^{-5} sec^{-1} at 36.5° and using the ratio $k_{OTs}/k_{Br} = 335$ determined in this work, with the ratio $k_{Br}/k_{Cl} = 60$ obtained for other vinylic substrates,[15] it can be estimated that k_{RCl} (vinyl, 36.5°) = 9.5×10^{-10} sec^{-1}. From previous results[10] k_{RCl} (satd, 36.5°) for the 1-(2,4-6-trimethylphenyl)ethyl chloride is 1.35×10^{-3} sec^{-1}. Thus $(k_{RCl})_{satd}/(k_{RCl})_{vinyl} \cong 1.4 \times 10^6$. Previous estimates in the literature of saturated *vs.* vinyl solvolytic reactivity are of the same order of magnitude, although more approximations were required. It is worth pointing out that the above rate factor of $\sim 10^6$ is a lower limit, since steric effects on the saturated compound are unfavorable to solvolysis, as shown earlier. It seems very likely that 1-phenylethyl chloride itself would solvolyze at least 10^8 times as fast as 1-phenylvinyl chloride.

Determination of the Schleyer Q Parameter. The importance of rear-side nucleophilic assistance can also be assessed using the recently developed treatment of Schleyer,[13] which seems to have received little application so far despite its potential utility. The treatment is based on a comparison of solvent effects on the reaction of a tosylate of interest with the corresponding solvent effects in two extreme cases, that of methyl tosylate solvolysis, which is taken as a good model for strong nucleophilic assistance ($Q = 0$), and the case of 2-adamantyl tosylate, which is an excellent model for no rear-side nucleophilic assistance ($Q = 1.0$). Values of Q were determined using the solvent pair ethanol-water (80:20) as standard solvent, and methanol-water (50:50). The Q values obtained are



$Q = 0.67$ ($T = 36.5°$)



$Q = 0.76$ ($T = 67.6°$)

These values show that arylvinyl systems are much more adamantyl-like in terms of nucleophilic assistance to

Table VI
Rates of Solvolysis in Ethanol-Water Mixtures

System EtOH-H_2O	98:2	90:10	80:20	70:30	60:40	50:50
Ib	2.20×10^{-5} [a]	7.03×10^{-5}	2.02×10^{-4}	3.71×10^{-4}	9.81×10^{-4}	2.32×10^{-1}
IIb	1.38×10^{-5} [b]	3.96×10^{-5}	1.04×10^{-4}	2.65×10^{-4}	4.38×10^{-4}	1.13×10^{-3}

[a] Measured at 36.5°. [b] Measured at 67.6°.

Table VII

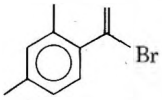
System	k, sec^{-1}, in HOAc	k, sec^{-1} in E/W (98:2)	$k_{HOAc}/k_{E/W}$
Ib	2.76×10^{-5} [a]	2.20×10^{-5} [a]	1.25
IIb	1.57×10^{-5} [b]	1.38×10^{-5} [b]	1.13

[a] At 36.5°. [b] At 67.6°.

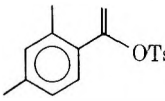
solvolysis than methyl-like; in other words, that solvent participation from the rear side of the developing vinyl cation is weak. This is in good accord with the results obtained from the extended Winstein-Grunwald equation. The above Q values can be compared with the values obtained by Schleyer[13] for saturated substrates, and are in the range of those determined for systems like cyclohexyl and 3-octyl tosylate, where rear-side nucleophilic assistance to solvolysis is expected to be weak because of steric hindrance to rear-side attack.[14]

Another advantage of the Q parameters is that they can be used to calculate rate constants in other solvents, which are used to estimate rates in solvents where data are not experimentally accessible. For example using Q = 0.67 for Ia, the calculated rate constant for this substrate in acetic acid at 36.5° is $k_{calcd} = 1.12 \times 10^{-5}$ sec^{-1}, which compares reasonably with the experimental value of 1.57×10^{-5} sec^{-1}.

In this way we are able to estimate rate constants in pure water, and so obtain the ratio $k_{H_2O}/kAcOH$, which cannot be experimentally determined for solubility reasons. Examples are given below.



$k_{H_2O}/k_{AcOH} = 384$ (at 36.5°)



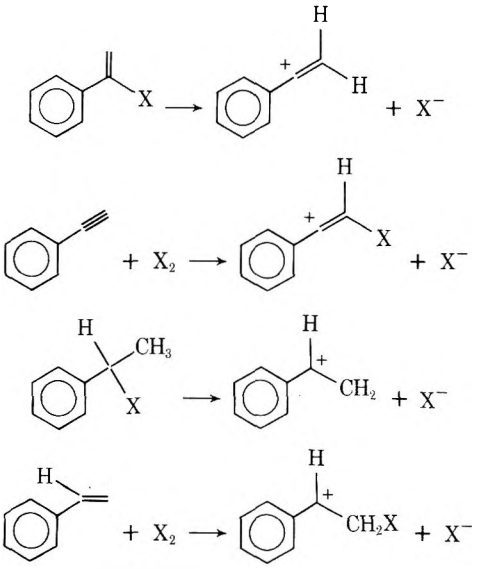
$k_{H_2O}/k_{AcOH} = 1.15 \times 10^3$ (at 67.7°)

These solvent effects will be compared later with those for other systems.

Activation Parameters. Rate measurements were made at several temperatures for some of the substrates, in an attempt to rationalize the observed rate enhancements in terms of changes in ΔH^* and ΔS^* values produced both by substitution and by solvent polarity changes. The activation parameters obtained are listed in Table VIII.

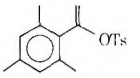
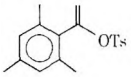
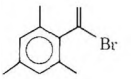
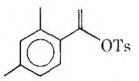
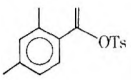
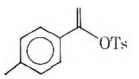
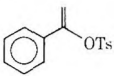
Comparing the values for Ib, IIb, and IIIb (all in 50:50 methanol-water) it can be seen that ΔS^* remains essentially constant with methyl substitution, and that the observed rate enhancements (1.8×10^4:320:1) are mainly due to a lowering of ΔH^* by about 3 kcal for each ortho methyl group. A similar trend is found by comparing the values for Ib and IIb in 80:20 ethanol-water. A change in solvent from 80:20 ethanol-water to 50:50 methanol-water produces a lower ΔH^* (by about 2-3 kcal) and a somewhat more negative (and compensating) value of ΔS^*. This can be seen by comparing the values for Ib or IIb in the two solvents. These changes are not unreasonable for an increase in solvent polarity leading to a modest rate enhancement of the magnitude observed. The major difference between the tosylate (Ib) and the bromide (Ia) is a significantly lower ΔH^* for the better leaving group, with the ΔS^* values being almost the same. The above results are interesting mainly in that they show there are no striking or anomalous changes in ΔS^* with the introduction of either one or two ortho methyl substituents. Thus the transition states in the rate-enhanced systems appear to be no more restricted compared with their initial states than are the unsubstituted systems. Thus the enhancements observed are mainly due to enthalpy changes produced by more favorable electronic stabilization in the nonplanar arylvinyl systems.

Solvent Stabilization of Vinyl Cation *vs.* Normal Carbonium Ion Intermediates. The values previously estimated for the rate ratios k_{H_2O}/k_{HOAc} for arylvinyl solvolysis are of the order of 10^3. These ratios are of the same order as, or less than, would be expected for the solvolysis rates of the corresponding saturated substrates in the same two solvents (since the m values for arylvinyl solvolysis appear to be somewhat low for SN1-type reactions). Thus the large rate ratios of the order of 10^6-10^8 which can be estimated for k_{satd}/k_{vinyl} in solvolytic reactions involving the same leaving groups would not be expected to decrease significantly with an increase in solvent polarity (such as from acetic acid to water), and would if anything be expected to increase. This is in marked contrast to the relative rates of electrophilic addition to typical olefins and acetylenes, which show a dramatic decrease with such a change in solvent. For example, it has been shown[1] that $k_{styrene}/k_{phenylacetylene}$ changes from 2.6×10^3 to 0.6 for brominations in acetic acid and water, respectively. Thus, despite the fact that the cationic intermediates being generated in the two types of reaction are formally very similar in structure (as shown), the solvent stabilization of the



vinyl cation intermediates in solvolysis must be much less effective than vinyl cation stabilization in electrophilic

Table VIII
Activation Parameters for Vinyl Solvolysis

Solvent	Compd		ΔH^*	ΔS^*
E/W 80:20		(Ib)	21.8	−5
M/W 50:50		(Ib)	18.4	−8
E/W 80:20		(Ia)	25.2	−7
E/W 80:20		(IIb)	23.4	−1
M/W 50:50		(IIb)	21.4	−10
M/W 50:50		(IIIb)	24.5	−8
M/W 50:50		(IVb)	24.2[a]	−18[a]

[a] From ref 7.

Table IX

Bromide	Ia	IIa	IIIa
Bp, °C (0.05 mm)	44	42	49
Ir ($\nu_{C=C}$), μ	6.13	6.13	6.20
Nmr (CCl_3, TMS), δ	2.21 s (3 H)	2.28 s (3 H)	2.33 s (3 H)
	2.25 s (6 H)	2.34 s (3 H)	5.62 d (1 H) J = 2 Hz
	5.50 d (1 H) J = 2 Hz	5.58 d (1 H) J = 2 Hz	5.97 d (1 H) J = 2 Hz
	5.78 d (1 H) J = 2 Hz	5.74 d (1 H) J = 2 Hz	6.95–7.50
	6.68] (2 H)	6.8–7.2 m (3 H)	
Analysis, %			
Calcd C	58.69	56.89	54.85
Found C	59.88	57.25	54.23
Calcd H	5.78	5.21	4.57
Found H	5.95	5.80	4.95
Calcd Br	35.52	37.88	40.53
Found Br	33.79	37.20	39.72
Mass spectra, m/e	226, M (^{81}Br)	212, M (^{81}Br)	198, M (^{81}Br)
	224, M (^{79}Br)	210, M (^{79}Br)	196, M (^{79}Br)
	145[a] (M − Br)	131[a] (M − Br)	117[a] (M − Br)

[a] Relative intensity 100.

Table X

Tosylate	Ib[a]	IIb[a]	IIIb[a]
Mp, °C	88	65	59
Ir ($\nu_{C=C}$), μ	5.98	6.08	6.12
(ν_{OTs}), μ	8.35, 8.45	8.40, 8.50	8.35, 8.45
Nmr (CCl_3, TMS), δ	2.16 s (9 H)	2.18 s (3 H)	2.25 s (3 H)
	2.35 s (3 H)	2.22 s (3 H)	2.42 s (3 H)
	4.72 d (1 H) J = 2 Hz	2.38 s (3 H) J = 2 Hz	4.96 d (1 H) J = 2 Hz
	5.40 d (1 H) J = 2 Hz	4.83 d (1 H) J = 2 Hz	5.22 d (1 H) J = 2 Hz
	6.73 s (2 H)	5.18 d (1 H)	6.90–7.80 m (8 H)
	7.03–7.60 m (4 H)	6.8–7.8 m (7 H)	
Mass spectra, m/e	316 (M)	302 (M)	288 (M)
	144[b] (M − OTs)	130[b] (M − OTs)	116[b] (M − OTs)

[a] Satisfactory combustion analytical data for C, H, and S (±0.7%) were reported for these compounds. [b] Relative intensity 100.

addition, relative to that of the corresponding trisubstituted or "normal" carbonium ion intermediates in each case. The reason for this difference in effectiveness of solvent stabilization of vinyl cations in solvolytic and addition reactions is difficult to understand, but it must be connected with the less effective nucleophilic participation in vinyl solvolysis, as evidenced by the low m and high Q values for these reactions, and their insensitivity to solvent or solute nucleophilicity, as shown earlier. It remains a striking fact that although typical vinyl systems must ionize to give cationic intermediates which are among the least stable carbonium species known in solvolysis reactions, they appear to do so by SN1-like processes in all solvents.

Experimental Section

Melting points are corrected; boiling points are not. Solvents were purified using standard procedures. Nmr spectra were recorded on a Varian T-60 spectrometer and chemical shifts are given in δ units relative to TMS. Infrared and ultraviolet spectra were obtained using Perkin-Elmer 337 and Cary 16 instruments, respectively. Kinetic measurements were made using either a Unicam SP-800 or Cary 16 spectrophotometer, using constant wavelength and scale expansion. Gc analyses were performed on a Carlo-Erba Model 61 chromatograph.

Preparation of Arylvinyl Bromides. Compounds Ia, IIa, and IIIa were prepared from the corresponding acetophenones, which are commercially available. These were first converted into the vinyl chlorides using a reported procedure.[18,19] The chlorides were dehydrochlorinated using sodium amide in liquid ammonia[19] and the resulting arylacetylenes were converted into the desired bromides using the following typical procedure. Through a solution of 10.0 g (0.074 mol) of 2,4-dimethylphenylacetylene in 120 ml of ethanol-free $CHCl_3$, gaseous, anhydrous HBr was bubbled for 30 min. (The course of the reaction was followed by the disappearance of the nmr signal of the acetylenic proton.) The solution was then washed ($NaHCO_3$, then H_2O) and dried over $MgSO_4$. Evaporation of solvent gave 14.5 g (94% yield) of a yellow material, whose nmr spectrum showed the presence of little impurity. Further purification was achieved by vacuum distillation. The results for all three bromides are summarized in Table IX.

Preparation of Arylvinyl Tosylates. The tosylates (Ib, IIb, and IIIb) were obtained by reaction of the above bromides with silver tosylate in acetonitrile using the following procedure, as for compound Ib. To a solution of 7.5 g (0.033 mol) of Ia in 50 ml of dry acetonitrile was added 11 g (0.04 mol) of silver tosylate in 120 ml of acetonitrile. (The commercial silver salt had been recrystallized from 1:1 acetonitrile–ether and dried under vacuum for 2 hr at 80°.) The mixture was kept at 80° for 30 min. After cooling, the silver bromide was filtered off and the solvent was evaporated. The solid residue was washed with pentane, and then CCl_4 was added. The resulting solution was dried ($MgSO_4$) and the solvent was evaporated. The remaining solid (7.6 g, 73% yield) was recrystallized from pentane–chloroform (9:1), giving crystals melting at 88°. The same procedure was used for IIb but the reaction was slower (reaction time 5 hr, yield 52%). The bromide IIIa does not react under the above conditions, and it was necessary to heat the acetonitrile solution at 120° for 3 hr in a sealed ampoule (yield 38%). The results for all three tosylates are summarized in Table X.

Product Analysis. Solvolysis. A 300-mg portion of the compound (bromide or tosylate) was dissolved in the appropriate alcohol–water mixture, with the corresponding amount of sodium acetate as base, and kept at the selected temperature for 10 half-lives in a sealed ampoule. The solvent was then removed by evaporation, and the product was extracted with ether and dried with magnesium sulfate. After removal of the solvent the products (Table XI) were analyzed by gas chromatography; quantitative analysis was achieved by integration after standardization with authentic samples, and by nmr.

Acetolysis. The same procedure was used, with acetic acid as solvent. The solvent was removed by evaporation and the solid residue was extracted with carbon tetrachloride, washed with an aqueous solution of sodium bicarbonate, then with water, and dried over magnesium sulfate. The product analysis was achieved by gas chromatography and nmr as previously. The acetates

Table XI
Solvolysis Products

Compd	Products, % Ketone	Acetylenic	Acetate
Ia or Ib (EtOH–H_2O, NaOAc)	65	35	
Ib (HOAc, NaOAc)		30	70
In (HOAc, without NaOAc)	100		
IIa or IIb (EtOH–H_2O, NaOAc)	70	30	
IIb (HOAc, NaOAc)		20	80
IIIa or IIIb (EtOH–H_2O, NaOAc)	90	10	

Table XII

Compd	Ia	IIa	IIIa	Ib	IIb	IIIb
λ, nm (solvolysis)	235	231	256	233	234	233
(acetolysis)				256	253	

formed were identified by comparison of their nmr and ir spectra with those of authentic samples obtained by reaction of silver acetate in glacial acetic acid on the corresponding bromide following the procedure of Rappoport.[20]

Kinetic Measurements. All kinetic runs were followed spectrophotometrically, using the change in absorbance at the most suitable wavelength (Table XII).

All runs were made at least in duplicate. For those up to 85°, the cell was thermostated with a water bath, with continuous recording of the absorbance for fast reactions, or by periodical recording for the slower runs. For the runs above 85°, Grob's technique of sealed ampoules in an oil bath was used.[9] The ampoules were filled with a syringe to avoid any evaporation and thus avoid changes in concentration leading to irreproducibility in the uv measurements. The samples were sealed after cooling in acetone–Dry Ice bath. First-order rate coefficients, *m* values, and activation parameters were calculated by least-squares treatment of the experimental data. In most cases an infinity absorbance value was used, except for acetolysis, for which the Guggenheim method was applied.

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Registry No.—Ia, 51270-84-9; Ib, 51270-85-0; IIa, 51270-86-1; IIb, 51270-87-2; IIIa, 51270-89-4; IIIb, 51270-88-3; IVa, 98-81-7; IVb, 26190-67-0.

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On the Mechanism of the Alkylative Decarboxylation of N-Carbalkoxypyrazoles

Joseph J. Wilczynski and H. W. Johnson, Jr.*

Department of Chemistry, University of California, Riverside, California 92502

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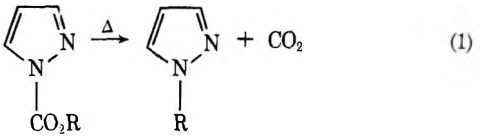
The alkylative decarboxylation of N-carbalkoxypyrazoles reported by van Auwers has been shown to require a polar aprotic solvent and to be subject to catalysis by nucleophiles, *e.g.*, halide ions. The halide ion catalyzed reaction is first order in ester and in halide ion in DMSO solvent. The relative rates of reaction of the methyl, ethyl, and isopropyl esters of 4-bromo-3,5-dimethyl-1-pyrazolecarboxylic acid are 17.2, 1, and 0.0401, respectively, in DMSO at 99.85° with chloride ion catalyst. The relative rates of reaction for Cl^--, Br^--, and I^--catalyzed alkylative decarboxylations of 4-bromo-1-carbomethoxy-3,5-dimethylpyrazole are 5.12, 3.02, and 1, respectively, in DMSO. The same mixture of 30% 1,3-dimethyl-5-phenylpyrazole and 55% 1,5-dimethyl-3-phenylpyrazole is obtained from the decarboxylation of the isomeric 1-carbomethoxy-3-methyl-5-phenylpyrazole and 1-carbomethoxy-5-methyl-3-phenylpyrazole. The mechanism of the halide ion catalyzed reaction appears to involve rate-determining nucleophilic attack of halide ion on the alkoxy α-carbon atom to yield alkyl halide, pyrazolyl anion, and carbon dioxide. A rapidly decarboxylating N-pyrazolecarboxylate anion may intervene. Attack of pyrazolyl anion on the alkyl halide (or, more slowly, on the parent ester) leads to N-alkylpyrazole and halide ion (or N-alkylpyrazole, pyrazolyl anion, and carbon dioxide, if attack occurs on the ester). Methyl p-nitrophenylcarbonate and dimethyl malonate were shown to yield p-nitroanisole and methyl acetate, respectively, upon heating with sodium iodide in similar reactions.

This study was undertaken to determine the pathway by which carbon dioxide and N-alkylpyrazoles are generated thermally from N-carbalkoxypyrazoles (eq 1), a reaction originally described by von Auwers.[1] Although decarboxylation is a common reaction of acids, esters are not normally considered to undergo this reaction.[2] A few reactions of esters occur in which the major products of reaction result from alkylative decarboxylation.[3-13]



(1)

A variety of mechanisms were available *a priori*. Among others, internal nucleophilic attack *via* four- or five-center cyclic transition states, external attack by a nucleophile (or radical) at the carbonyl carbon atom or the α-carbon atom of the alkoxyl group, and electrophilic attack at one of the ring nitrogen atoms were possible. The reaction has been described only in the melt, and preliminary studies were necessary to define the gross character of the reaction.

The volume of carbon dioxide produced was used as the initial probe. The ester, the solvent, and any additional reagent were added to a Pyrex reaction vessel equipped with a mercury-filled gas burette in a constant temperature bath; rates of carbon dioxide evolution were reproducible to ±3%. The esters used were 1-carbomethoxy-3,5-dimethylpyrazole (**1**) and 4-bromo-1-carbomethoxy-3,5-dimethylpyrazole (**2**).

In both triglyme and dibutyl phthalate (DBP) at 195° 50% of the theoretical yield of carbon dioxide was evolved from **1** after 7 hr, while in mineral oil 6% of the CO_2 was formed after 23 hr. At 110°, reaction in dimethyl sulfoxide (DMSO) yielded 50% of carbon dioxide after 22 hr from **2** while in DBP no discernable reaction occurred. The solvent order in facilitating the reaction was DMSO ≫ DBP ≈ triglyme ≫ mineral oil. A polar mechanism seems likely.

Benzoyl peroxide, benzoquinone, and oxygen had no effect on the rate of decomposition of **2** in DBP at 195°. It is considered unlikely that radical intermediates are involved in this reaction.

Results obtained from the decarboxylation of **2** in the presence of other reagents are collected in Table I. The ester concentration was 0.6–0.7 *m* and the concentration of added reagent was 0.06–0.07 *m*. The time required for production of 50% of the theoretical yield of carbon dioxide in DBP at 195° with no added reagents was 900 min. Benzylamine gave a moderate increase in rate while tri-*n*-butylamine, iodide ion, and chloride ion effected large increases in the rate. The uncatalyzed decarboxylation of **2** in DMSO at 110° yielded 50% CO_2 after 22 hr, while addition of iodide ion (10% of the ester concentration) reduced this time by a factor of 17 and chloride ion reduced the "half-life" by a factor of 90 under the same conditions.

Decarboxylation of **2** in DBP at 195° had a "half-life" of 900 min; however, this reaction time included a 225-min induction period during which no carbon dioxide was evolved. Added nucleophiles eliminated the induction period. These data and the solvent dependence suggest a nucleophilic ionic mechanism. The induction period presumably reflects the time required to produce a nucleophile by secondary decomposition of the ester.

Having ascertained the gross character of the reaction, a more detailed study of the kinetics of the halide ion catalyzed reaction was undertaken. Rates of alkylative decarboxylation of esters of 4-bromo-3,5-dimethylpyrazole-1-carboxylic acid were determined by ultraviolet spectroscopy. The solution of catalyst ($1–5.5 \times 10^{-2}$ *M*) in DMSO was equilibrated in a constant temperature bath. Then 50–100 μl of a 0.2 *M* ester–DMSO solution was added to the catalyst solution through a stopcock *via* syringe. Samples were removed from the reaction vessel by syringe through the stopcock at intervals, and the absorbance of the solution was measured. All glassware and reagents were dried, since water and other protic species change the reaction products yielding quantities of unalkylated parent pyrazole. Reactions were usually run under pseudo-first-order conditions with 50–100-fold excess catalyst. In two experiments the volume of carbon dioxide produced was measured as described earlier. In these last two reactions, the molar catalyst to ester concentration ratio was 1:10, and both reactions yielded good pseudo-first-order kinetics to 60% reaction. The reaction studied by uv absorption yielded good pseudo-first-order kinetics to 70–80% completion. In reactions followed by carbon

Table I
Effect of Reagents on the Alkylative Decarboxylation of 4-Bromo-1-carbomethoxy-3,5-dimethylpyrazole[a]

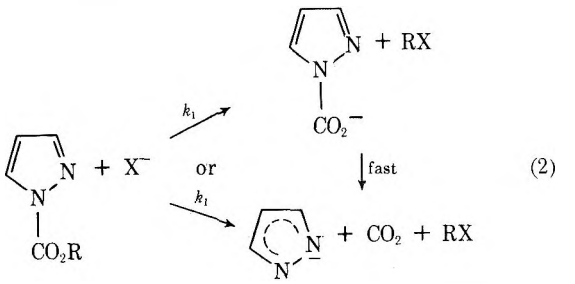
Reagent[b]	Solvent[c]	Temp, °C	$t_{1/2}$, min[d]
Tri-*n*-butylamine	DBP	195	11.5
I^- [e]	DBP	195	1
I^- [e]	DMSO	110	75
Cl^- [e]	DMSO	110	14
None	DMSO	110	1320
None	DBP	195	900

[a] Initial concentration, 0.6–0.7 *m*. [b] Initial concentration of added reagents, 0.06–0.07 *m*. [c] DBP, di-*n*-butyl phthalate; DMSO, dimethyl sulfoxide. [d] Time to yield 50% of theoretical carbon dioxide. [e] Tetra-*n*-butylammonium salts.

dioxide evolution, essentially quantitative recovery of unchanged halide was made after 80% reaction. The good pseudo-first-order plots obtained indicate that the assumption of constant halide ion concentration during these reactions is justified.

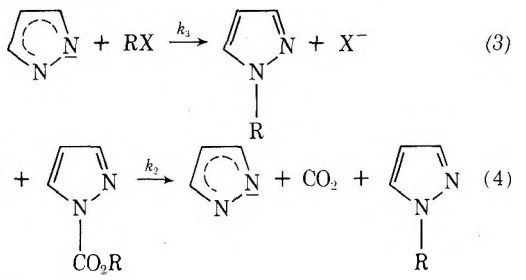
Table II contains data derived from the rate constants calculated for **2** at varying concentrations of sodium chloride. The data indicate that the reaction is first order in halide ion. Table III presents data with differing halide catalysts which suggest nucleophilic attack at the alkoxyl α-carbon atom. The ratio of the second-order rate constants k_{X^-}/k_{I^-}, was 5.12, 3.02, and 1.00 for the ions Cl^-, Br^-, and I^-, respectively, paralleling the relative nucleophilicities found in the displacement of tosylate from *n*-propyl tosylate in DMSO: Cl^-, 5.18; Br^-, 3.19; and I^-, 1.00.[14] The rate constant for the iodide-catalyzed reaction had to be determined by following the evolution of carbon dioxide rather than by uv because of the strong uv absorption of iodide ion, and molal concentrations were used. Data at 111 and 99.85° were combined to obtain these ratios; the assumption that k_{X^-}/k_{I^-} does not vary over the 11° range is implicit in this argument.

Changes in the structure of the alkoxyl group should have less effect on the rate of nucleophilic attack at the carbonyl carbon atom than on the rate of attack at the α-carbon atom of the alkoxyl function. In water or in 70% acetone–water, hydroxide ion attack on a series of alkyl acetates shows a very small change in the rate of reaction with changes in the alkoxy group. The relative rates of reaction of the series of acetates, methyl, ethyl, isopropyl, and benzyl, are all within a factor of 8 of each other in water.[15] Relative values are found in Table IV. In saponifications of the methyl and ethyl esters of aromatic acids in DMSO, the methyl ester reacted only 2.5 times faster than the ethyl ester.[16] Table IV also contains Streitwieser's values for the average relative rates of substitution (SN2) for compounds with changes in groups directly bonded to the reaction site. The ratio of rates of displacement from methyl, ethyl, and isopropyl halides was found to be 30:1:0.025.[17] The second-order rate constants for the reaction of the methyl, ethyl, isopropyl, benzyl, and (*R*)-(−)-α-methylbenzyl esters of 4-bromo-3,5-dimethyl-1-pyrazolecarboxylic acid with chloride ion in DMSO at 99.85° are given in Table IV. Comparison of the data in Table IV again suggests chloride ion attack at the α-carbon atom of the alkoxyl group (eq 2) rather than attack at the carbonyl carbon atom. The retardation of attack of chloride ion by successive methyl substitution at the α-carbon atom is of the order of magnitude seen in typical SN2 displacement reactions and larger than that of nucleophilic attack at the carbonyl carbon. Similar attack has been proposed by Warren and Williams[18] for the iodide-catalyzed decarboxylation of $(C_6H_5)_2POCO_2CH_2C_6H_5$.



(2)

The rate-determining step in the reaction is most likely attack of the nucleophile at the α-carbon atom of the alkoxyl group, yielding pyrazolyl anion, carbon dioxide, and alkylated nucleophile either in a concerted manner or *via* an intermediate *N*-pyrazolecarboxylate anion (eq 2). It is not possible to differentiate positively between the two modes of decarboxylation with the data at hand. The final product forming step in the reaction is probably SN2 attack of the pyrazolyl anion on R–X or ester (eq 3 or 4). If



(3) (4)

reaction proceeds through a *N*-pyrazolecarboxylate anion,[19] decarboxylation of this intermediate may potentially occur during or after a reaction with RX. In either of these schemes, an ester of an unsymmetrically substituted *N*-pyrazolecarboxylic acid would yield one *N*-alkylpyrazole (eq 5) while, if reaction of RX occurs with a pyrazolyl anion, two *N*-alkylpyrazoles will be formed (eq 6).

The iodide ion catalyzed decarboxylations of 1-carbomethoxy-3-methyl-5-phenylpyrazole (**3**) and 1-carbomethoxy-5-methyl-3-phenylpyrazole (**4**), in DMSO at 111°, gave two *N*-alkyl products in the same ratio: 30% 1,3-dimethyl-5-phenylpyrazole (**5**) and 55% 1,5-dimethyl-3-phenylpyrazole (**6**) from both **3** and **4**. The structures of compounds **3**–**6** were determined by von Auwers and Stuhlmann[1b] and the nuclear magnetic resonance (nmr)

Table II
Effect of Chloride Ion on the Rate of Decarboxylation of 4-Bromo-1-carbomethoxy-3,5-dimethylpyrazole in DMSO at 100°[a]

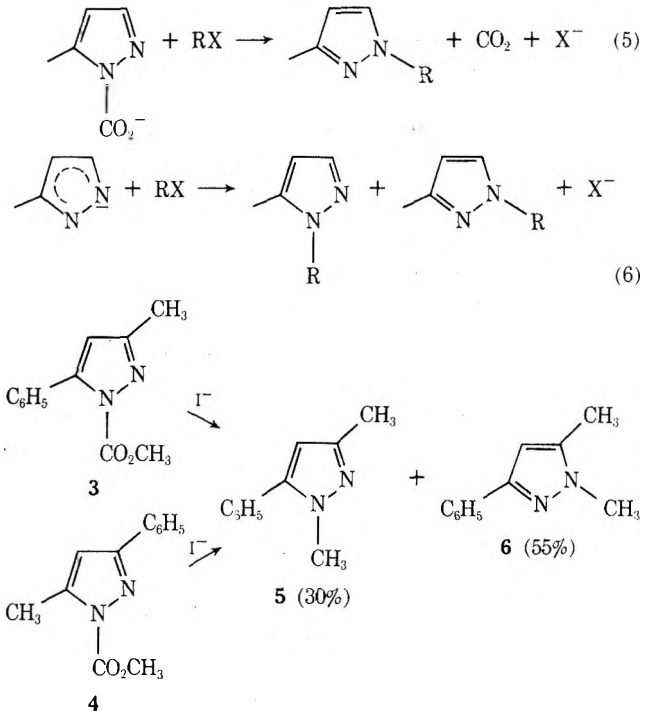
[NaCl], *M*	[$NaBF_4$],[b] *M*	k[c]	$k_l = k/[Cl^-]$
5.42×10^{-2}	0	2.06×10^{-4} sec^{-1}	3.80×10^{-3} M^{-1} sec^{-1}
4.06×10^{-2}	1.355×10^{-2}	1.43×10^{-4} sec^{-1}	3.51×10^{-3} M^{-1} sec^{-1}
2.710×10^{-2}	2.710×10^{-2}	1.01×10^{-4} sec^{-1}	3.73×10^{-3} M^{-1} sec^{-1}
			Av 3.68×10^{-3} M^{-1} sec^{-1}
0	5.42×10^{-2}	0[d]	

[a] Temperature, 99.85 ± 0.04°; initial ester concentrations, 5–10 $\times 10^{-4}$ *M*. [b] $NaBF_4$ was used to keep the ionic strength constant. [c] Observed pseudo-first-order rate constant. [d] No reaction was observed after 4 hr.

Table III
Second-Order Rate Constants for the Decarboxylation of 4-Bromo-1-carbomethoxy-3,5-dimethylpyrazole in DMSO Catalyzed by Halide Ions

Halide	Temp, °C	Method of analysis	k_1[a]
Cl^-	99.85	Loss of uv absorption	3.80×10^{-3} M^{-1} sec^{-1}
Br^-	99.85	Loss of uv absorption	2.24×10^{-3} M^{-1} sec^{-1}
Cl^-	111	Evolution of CO_2	1.28×10^{-2} m^{-1} sec^{-1}
I^-	111	Evolution of CO_2	2.50×10^{-3} m^{-1} sec^{-1}

[a] Observed pseudo-first-order rate constant divided by halide ion concentration.



spectra of these compounds reconfirm their assignments (see Experimental Section, Table VII). The esters and products were shown to be stable to isomerization under the reaction conditions.[20,21]

The formation of **5** and **6** in the same ratio from both of the esters **3** and **4** suggests strongly that an intermediate common to both esters is produced during the reaction. Further, since ester **3** decarboxylates 3.2 times faster than does ester **4**, the common intermediate must be formed after or during the rate-determining step. The pyrazolyl anion is probably this intermediate. These results also exclude intramolecular reactions *via* cyclic transition states, mechanisms largely excluded by kinetic studies as well.

The final N-alkylation step may occur by reaction of the pyrazolyl anion with RX (eq 3) or with ester (eq 4). The relative importance of these reactions in the mechanisms may be estimated in the chloride ion catalyzed reaction. The pseudo-first-order rate constant for the chloride ion catalyzed alkylative decarboxylation of **2** was found to be 2.06×10^{-4} sec^{-1} at 99.85° in DMSO at 5.42×10^{-2} *M* chloride ion concentration. The pseudo-first-order rate constant for disappearance of ester is equal to k_1[chloride] + k_2[pyrazolyl anion] if eq 4 is also an important step in the mechanism. If step 4 is important, then the term k_2[pyrazolyl anion] must contribute an appreciable fraction to the pseudo-first-order rate constant. The value of k_2 may be determined from the rate of reaction of 4-bromo-1-carbomethoxy-3,5-dimethylpyrazole with independently prepared 4-bromo-3,5-dimethylpyrazolyl anion (as the sodium salt). This pseudo-first-order rate constant (k_2[pyrazolyl anion]) was 2.55×10^{-4} sec^{-1} at 99.85° in DMSO at a pyrazolyl anion concentration of 4.83×10^{-3} *M*. The value of k_2 derived from this rate constant is 5.29×10^{-2} l./(mol sec), 14 times greater than the value of k_1 calculated in Table II. To determine the contribution of k_2[pyrazolyl anion] to the pseudo-first-order rate constant for the chloride ion catalyzed reaction, an estimate of the pyrazolyl anion concentration must be made. The quantity of the pyrazolyl anion in solution cannot exceed the amount of the ester which has reacted. Since the kinetics were determined at a maximum ester concentration of 10^{-3} *M*, the concentration of the pyrazolyl anion cannot exceed 10^{-3} *M* in these solutions. Even at this concentration, the calculated value of k_2[pyrazolyl anion] is only 5.29×10^{-5} sec^{-1} or 25.7% of the observed pseudo-first-order rate constant of 2.06×10^{-4} sec^{-1}. At more reasonable lower concentrations of the intermediate anion, the contribution of k_2[pyrazolyl anion] to the total reaction rate should be negligible. The rate of reaction of methyl chloride with the pyrazolyl anion in DMSO was too fast to measure with conventional methods even at room temperature. The mechanism of the halide-catalyzed alkylative decarboxylation of *N*-carbalkoxypyrazoles therefore involves principally initial attack by the halide ion on the alkoxyl α-carbon atom of the ester with formation of an alkyl halide, carbon dioxide, and pyrazolyl anion. The attack of the pyrazolyl anion on the alkyl halide with formation of *N*-alkylpyrazole and regeneration of the halide ion completes the sequence.

Table IV
Effect of Ester Structure on Rates of Nucleophilic Attack

Ester	k_R[a]	k_R/k_{Et}[b]	k_R/k_{Et}[c]	k_R/k_{Et}[d]
Methyl	3.80×10^{-3}	17.2	30	2.32
Ethyl	2.21×10^{-4}	1	1	1
Isopropyl	8.86×10^{-6} [e]	0.0401	0.025	0.151
Benzyl	2.94×10^{-3}	13.3	120	
α-Methylbenzyl[f]	1.28×10^{-3}	5.79		

[a] Rate of chloride ion catalyzed decarboxylation of 4-bromo-3,5-dimethyl-1-pyrazolecarboxylic acid ester, DMSO, 99.85°, M^{-1} sec^{-1}, this work. [b] Rate ratio for pyrazole ester decarboxylation relative to ethyl ester, this work. [c] Streitwieser's average values for displacement for SN2 displacements from alkyl halides, ref 17. [d] Relative rates of saponification of acetic acid esters in 70% acetone–water, ref 15. [e] Followed to 18% reaction. See Table V. [f] (*R*)-(−)-α-Methylbenzyl. See Table V.

Though the reaction of the pyrazolyl anion with the ester was unimportant in the halide ion catalyzed decarboxylation of *N*-carbalkoxypyrazoles, this reaction is thought to be the major pathway for the production of *N*-alkylpyrazole and carbon dioxide from the esters in the uncatalyzed reaction. The rate of decarboxylation of the methyl ester of 4-bromo-3,5-dimethyl-1-pyrazolecarboxylic acid (**2**) is very slow in DMSO, yielding only 50% of the theoretical amount of carbon dioxide after 22 hr. Assuming eq 4 to be the rate-determining step, the concentration of the pyrazolyl anion necessary to achieve this rate is 5×10^{-5} *m* or 0.008% of the initial ester concentration. It seems reasonable that this concentration of anion may be produced through a secondary decomposition of the ester during the induction period mentioned previously. Thus, the uncatalyzed reaction may involve a chain mechanism in which the pyrazolyl anion attacks the ester, forming *N*-alkylpyrazole, carbon dioxide, and a second pyrazolyl anion.

Table V
Product Yields for the Halide Ion Catalyzed Decarboxylation of Esters of 4-Bromo-3,5-dimethyl-1-pyrazolecarboxylic Acid

Ester	Solvent	*N*-Alkyl-pyrazole, %	4-Bromo-3,5-dimethyl-pyrazole, %	Other products
CH_3	DMSO[a]	70–80	20–30	Dimethyl carbonate (10%)
CH_2CH_3	DMSO	70–80	20–30	
$(CH_3)_2CH$	DMSO	0	100[c]	
$PhCH_2$	DMSO	10	90	Benzaldehyde (90%)
$PhCHCH_3$	DMSO	1	99	Acetophenone (99%)
CH_3	DBP[b]	80–90	10–20	Dimethyl carbonate (5%)
CH_2CH_3	DBP	70–80	20–30	

[a] DMSO = dimethyl sulfoxide. [b] DBP = di-*n*-butyl phthalate. [c] At 18% total reaction.

Products. The products of alkylative decarboxylation of the *N*-carbalkoxypyrazoles in DMSO in the presence of halide ion are carbon dioxide, *N*-alkylpyrazole, the parent unalkylated pyrazole, and other products; see Table V. The yields of *N*-methyl- and *N*-ethylpyrazole from the respective esters are normally 70–90% under these conditions with unalkylated parent pyrazole forming the residue. In the case of the isopropyl ester, the nitrogen-containing product was solely the parent unalkylated pyrazole at 18% total reaction. When carried out in the presence of water or other proton donors, no *N*-alkylpyrazole was detected; all of the product was found as the parent unalkylated pyrazole. For example, decarboxylation of 4-bromo-1-carbomethoxy-3,5-dimethylpyrazole with chloride ion in 2.5% H_2O–DMSO gave no 4-bromo-1,3,5-trimethylpyrazole and 100% 4-bromo-3,5-dimethylpyrazole. The production of the unalkylated pyrazole presumably involves protonation of the intermediate pyrazolyl anion, and the yield of this product in the absence of added water probably reflects the concentration of the trace amounts of water in these reaction mixtures.

Further qualitative evidence for the premise that the production of unalkylated pyrazole depends on the presence of proton donors is found in Table VI. The yields of *N*-alkylpyrazoles are high (90%) when the methyl, ethyl, isopropyl, and benzyl esters of 4-bromo-3,5-dimethyl-1-pyrazolecarboxylic acid are heated at 200–300° with dry sodium iodide. When this reaction is carried out with moist sodium iodide (moisture derived from the atmosphere during storage) the yields of the *N*-alkylpyrazoles are reduced. As the alkyl groups increased in size, the SN2 displacement of iodide by the pyrazolyl anion will be retarded and more of the anion will react with water. Thus, the yield of *N*-alkylpyrazole from the isopropyl ester should be the lowest in the series methyl, ethyl, and isopropyl as it is.

In Table V, the yields of some other products are also given. The decarboxylations of the benzyl and the α-methylbenzyl esters give very high yields of benzaldehyde and acetophenone, respectively, together with high yields of the unalkylated pyrazole in DMSO. The reaction between water and the intermediate pyrazolyl anion cannot account for all of the unalkylated pyrazole. Benzylic halides react with dimethyl sulfoxide and base to produce carbonyl compounds and dimethyl sulfide.[22] This reaction could account for the production of both the carbonyl compounds and the unalkylated pyrazole in the decarboxylations of the benzyl and the α-methylbenzyl esters. The lack of formation of carbonyl compounds in the decarboxylations of the other alkyl esters is probably due to the relatively low reactivity of the intermediate alkyl halides with dimethyl sulfoxide.

Table VI
Products of the Decarboxylation of 4-Bromo-3,5-dimethyl-1-pyrazolecarboxylic Acid Esters[a]

Ester	Catalyst	*N*-Alkyl-pyrazole, %	Parent pyrazole, %
CH_3	NaI (dry)	90–100	0–10
CH_2CH_3	NaI (dry)	90–100	0–10
$(CH_3)_2CH$	NaI (dry)	80–90	10–20
$PhCH_2$	NaI (dry)	90–100	0–10
CH_3	NaI (moist)	78	22
CH_2CH_3	NaI (moist)	72	28
$(CH_3)_2CH$	NaI (moist)	41	59

[a] These reactions were carried out by heating the ester (1 g) and NaI (0.1 g) in a test tube over an open flame for 5–15 min without solvent.

In several of the reactions in which the methyl ester was decarboxylated, dimethyl carbonate was observed in the collected gases by glc and infrared spectroscopy. When *N*-pyrazole (carboxylic acid) methyl esters are treated with sodium methoxide in the DMSO solution, high yields of dimethyl carbonate are produced, based upon the quantity of methoxide added. The formation of dimethyl carbonate from the methyl ester in this reaction is almost surely due to attack of the methoxide ion on the carbonyl carbon atom of the ester, followed by elimination of a pyrazolyl anion. The formation of methoxide ion (and subsequently dimethyl carbonate) from the methyl ester in the absence of added methoxide ion could arise from the analogous attack of trace hydroxide ion at the carbonyl with production of the methoxide, the unalkylated pyrazole, and carbon dioxide.

The stability of the anionic residue from decarboxylation of the acid fragment of the ester is of prime importance in the prediction of alkylative decarboxylation reactions. An unrelated ester predicted on this basis to undergo alkylative decarboxylation catalyzed by nucleophiles is methyl *p*-nitrophenylcarbonate. This ester, when heated with tetra-*n*-butylammonium iodide (TBAI) above 200° without solvent, decarboxylates to give *p*-nitroanisole in 95% yield.[23] This result is consistent with the premise that the stability of the intermediate anion is important in the alkylative decarboxylation reactions but does not distinguish between attack at the carbonyl carbon atom or the methyl carbon atom.

Another ester which might alkylatively decarboxylate is dimethyl malonate. Refluxing dimethyl malonate with TBAI leads to the formation of carbon dioxide and methyl acetate instead of the expected methyl propionate. It is probable that the anion of methyl acetate formed initially reacts with the dimethyl malonate in a proton exchange to yield methyl acetate and the anion of dimethyl malonate.

Summary. The mechanism of the halide ion catalyzed alkylative decarboxylation of *N*-carbalkoxypyrazoles in polar aprotic solvents appears to involve initial rate-determining attack of halide ion at the α-carbon atom of the alkoxyl group of the ester, producing an alkyl halide, carbon dioxide, and a pyrazolyl anion either in a concerted manner or in a two-step process involving an intermediate *N*-pyrazolecarboxylate anion. The final step in the mechanism appears to be nucleophilic attack of the pyrazolyl anion on the alkyl halide to form the primary reaction product, *N*-alkylpyrazole, and to regenerate the catalyst halide ion. A secondary product, unalkylated pyrazole, was formed by pyrazolyl anion abstraction of a proton from trace amounts of water in the solution or by abstrac-

Table VII
Nmr[a] Data on Pyrazole Derivatives

Derivative	Pyrazole ring position 3	5	1	4	Registry no.
3,5-Dimethylpyrazole	7.76 (s)	7.76 (s)	−3.07 (s)	4.33 (s)	67-51-6
4-Bromo-3,5-dimethylpyrazole	7.78 (s)	7.78 (s)	−2.41 (s)		3398-16-1
3(5)-Methyl-5(3)-phenylpyrazole	7.80 (CH_3, s)	2.36 (Ph, m), 2.72 (Ph, m)	−2.55 (s)	3.78 (s)	3440-06-0
Derivatives of 4-Bromo-3,5-dimethylpyrazole					
1-Carbomethoxy-	7.82 (s)	7.55 (s)	6.05 (OCH_3, s)		28188-06-9
1-Carbethoxy-	7.80 (s)	7.55 (s)	5.60 (OCH_2, q), 8.57 (CCH_3, t)		51108-47-5
1-Carboisopropoxy-	7.79 (s)	7.50 (s)	4.87 (OCH, m), 8.60 (CCH_3, d)		51108-48-6
1-Carbobenzoxy-	7.80 (s)	7.50 (s)	4.66 (OCH_2, s), 2.62 (Ph, m)		51108-49-7
(*R*)-(−)-1-α-Methylbenzoxy-	7.81 (s)	7.56 (s)	4.07 (OCH, q), 8.32 (CCH_3, d), 2.71 (Ph, m)		51108-50-0
1-Methyl-	7.82 (s)	7.90 (s)	6.32 (NCH_3, s)		15801-69-1
1-Ethyl-	7.80 (s)	7.89 (s)	6.03 (NCH_2, q), 8.67 (CCH_3, t)		51108-51-1
1-Isopropyl-	7.81 (s)	7.88 (s)	5.70 (NCH, m), 8.62 (CCH_3, d)		51108-52-2
1-Benzyl-	7.86 (s)	8.04 (s)	5.02 (NCH_2, s), 2.93 (Ph, m)		51108-53-3
Derivatives of 3-Methyl-5-phenylpyrazole					
1-Carbomethoxy-	7.70 (CH_3, s)	2.69 (φ, s)	6.14 (OCH_3, s)	3.90 (s)	51108-54-4
1-Methyl-	7.80 (CH_3, s)	2.54 (φ, m)	6.38 (NCH_3, s)	4.05 (s)	10250-58-5
Derivatives of 5-Methyl-3-phenylpyrazole					
1-Carbomethoxy-	2.43 (Ph, m)	7.47 (CH_3, d)	6.05 (OCH_3, s)	3.65 (q)	51108-55-5
1-Methyl-	2.54 (Ph, m)	8.00 (CH_3, s)	6.48 (NCH_3, s)	3.88 (s)	10250-60-9

[a] Nmr spectra were obtained on CCl_4 solutions with internal tetramethylsilane standard reference using a Varian Associates Model A-60 analytical nmr spectrometer at ambient temperatures. The numbers in the table are chemical shifts in τ units relative to tetramethylsilane. The letters in parentheses refer to the multiplicity of the resonance as: s = singlet; d = doublet; t = triplet; q = quartet; and m = unresolved multiplet. All of the τ values given in the table are the centers of the resonances and all of the resonances integrated to the correct relative area.

tion of an α proton from an intermediate sulfoxonium salt formed by reaction of activated alkyl halides (benzylic halides) with the solvent, dimethyl sulfoxide. A carbonyl compound and (presumably) dimethyl sulfide were also formed in the latter case. Dimethyl carbonate was formed during the reactions of the methyl esters which produced some parent unalkylated pyrazole and was attributed to the formation of trace amounts of bases through reaction of the intermediate pyrazolyl anion with water in the reaction medium.

The uncatalyzed alkylative decarboxylation of *N*-carbalkoxypyrazoles appears to involve an initial induction period in which a small concentration of pyrazolyl anion is formed followed by a chain mechanism in which pyrazolyl anion attacks the *N*-carbalkoxypyrazole at the α carbon of the alkoxyl group yielding *N*-alkylpyrazole, carbon dioxide, and a second pyrazolyl anion.

Experimental Section

Acetylacetone and hydrazine hydrate were obtained from Matheson Coleman and Bell; methyl iodide, ethyl iodide, isopropyl iodide, methyl chloroformate, and ethyl chloroformate were obtained from the Aldrich Chemical Co. Phosgene was obtained from the Matheson Co. and (*R*)-(+)-α-methylbenzyl alcohol from Norse Laboratories. These reagents were used without further purification.

A Perkin-Elmer Model 137 sodium chloride spectrophotometer was used for ir spectra using films for liquids and Nujol mulls for solids. A Varian Associates Model A-60 analytical nmr spectrometer was used for nmr spectra of carbon tetrachloride solutions with internal tetramethylsilane at ambient temperatures. Melting points were obtained with a Thomas-Hoover capillary melting point apparatus. Gas chromatograms were obtained on a F & M Model 700 laboratory gas chromatograph (dual column) with columns of 20% Apiezon "L" on 60–80 Firebrick and 20% SE-20 on 100–120 Chromosorb W.

Nmr data on pyrazole derivatives appear in Table VII.

3,5-Dimethylpyrazole. The procedure of Knorr and Rosengarten[24] was used to prepare 3,5-dimethylpyrazole from acetylacetone and hydrazine hydrate: mp 106–108° (lit.[24] 107°).

4-Bromo-3,5-dimethylpyrazole. The procedure of Morgan and Ackerman[25] was used to prepare 4-bromo-3,5-dimethylpyrazole by the bromination of 3,5-dimethylpyrazole: mp 124–125°.[25]

3(5)-Methyl-5(3)-phenylpyrazole. The procedure of van Auwers and Breyhan[1c] was used to prepare 3(5)-methyl-5(3)-phenylpyrazole from benzoylacetone and hydrazine hydrate: mp 126–127° (lit.[1c] 128°).

Preparation of 4-Bromo-1-carbalkoxy-3,5-dimethylpyrazoles. A modified procedure of van Auwers and Breyhan[1c] was used to prepare 4-bromo-1-carbalkoxy-3,5-dimethylpyrazoles from 4-bromo-3,5-dimethylpyrazole and the respective alkyl chloroformate. To a solution of 0.037 mol of the alkyl chloroformate in 100 ml of benzene was added 3.0 g (0.017 mol) of 4-bromo-3,5-dimethylpyrazole dissolved in 50 ml of benzene. The solution was stirred for 2 hr and 6 g of sodium bicarbonate was added. The solution was allowed to stand at room temperature overnight and was then washed with two 100-ml portions of water. The benzene solution was dried over sodium sulfate and concentrated *in vacuo*. The residue was distilled (if liquid) and sublimed (if solid) at 1–2 Torr. The solid esters were then recrystallized from cyclohexane. Yields of esters based upon the quantity of pyrazole used ranged from 50 to 90%. The four esters prepared by this method follow.

4-Bromo-1-carbomethoxy-3,5-dimethylpyrazole: mp 63–64.5°; ir ν 1750, 1350, 1130, 1060 cm^{-1}. *Anal.* Calcd for $C_7H_9BrN_2O_2$: C, 36.08; H, 3.89; N, 12.02; Br, 34.29. Found: 36.10; H, 3.85; N, 11.92; Br, 34.75.

4-Bromo-1-carbethoxy-3,5-dimethylpyrazole: mp 32.5°; ir ν 1750, 1340, 1120, 1060 cm^{-1}. *Anal.* Calcd for $C_8H_{11}BrN_2O_2$: C, 38.89; H, 4.49; N, 11.34; Br, 32.34. Found: C, 38.76; H, 4.44; N, 11.17; Br, 32.86.

4-Bromo-1-carboisopropoxy-3,5-dimethylpyrazole: mp 31–33°; ir ν 1750, 1375, 1105, 1055 cm^{-1}. *Anal.* Calcd for

$C_9H_{13}BrN_2O_2$: C, 41.39; H, 5.02; N, 10.73; Br, 30.60. Found: C, 41.58; H, 4.80; N, 10.86; Br, 30.30.

4-Bromo-1-carbobenzoxy-3,5-dimethylpyrazole: mp 107–108°; ir ν 1740, 1340, 1270, 1120, 1060, 1010 cm^{-1}. *Anal.* Calcd for $C_{13}H_{13}BrN_2O_2$: C, 50.50; H, 4.24; N, 9.06; Br, 25.85. Found: C, 50.99; H, 4.49; N, 9.25; Br, 25.74.

(*R*)-(−)-4-Bromo-1-carbo-α-methylbenzoxy-3,5-dimethylpyrazole. To a solution of 3.7 g (0.03 mol) of (*R*)-(+)-α-phenylethanol ($[\alpha]^{20}D$ +37.5°, 93% optically pure) was added a solution of 6 g (0.06 mol) of phosgene in 100 ml of benzene. Dry nitrogen was bubbled through the solution for 2 hr, and the solution was warmed to remove excess phosgene. A solution of 5.3 g (0.03 mol) of 4-bromo-3,5-dimethylpyrazole dissolved in 50 ml of benzene was added and the solution was stirred at room temperature for 2 hr. To the solution was added 6 g of sodium bicarbonate. The mixture was stirred overnight at room temperature, washed with two 100-ml portions of water, dried over sodium sulfate, and concentrated *in vacuo*. Attempted distillation of the residue led to decomposition. The residue was chromatographed on silica gel and was eluted with dichloromethane. The yield of ester was 4 g of pale yellow liquid. This material was used in kinetic experiments without further purification: ir ν 1730, 1370, 1340, 1270, 1055, 760 cm^{-1}.

Preparation of 1-Carbomethoxy-5-methyl-3-phenylpyrazole. The modified procedure of van Auwers and Breyhan[1c] was used to prepare 1-carbomethoxy-5-methyl-3-phenylpyrazole from 3(5)-methyl-5(3)-phenylpyrazole and methyl chloroformate: mp 63–65° (lit.[1c] 74.5°); ir ν 1750, 1350, 1290, 1110, 947, 770, 693 cm^{-1}. The melting point difference is not resolved.

Preparation of 1-Carbomethoxy-3-methyl-5-phenylpyrazole. The procedure of van Auwers and Breyhan[1c] was used to prepare 1-carbomethoxy-3-methyl-5-phenylpyrazole from benzoylacetone and carbomethoxyhydrazine: mp 57.5–58.5° (lit.[1c] 58.9°); ir ν 1750, 1340, 1290, 1120, 830, 825, 778, 765, 727, 702, 678 cm^{-1}.

Preparation of 1-Alkylpyrazole Derivatives. The synthesis of 1-alkyl-4-bromo-3,5-dimethylpyrazoles and 1-methyl derivatives of 3(5)-methyl-5(3)-phenylpyrazole was accomplished through reaction of the sodium salt of the pyrazole with the alkyl halide in tetrahydrofuran solution. To a solution of 0.017 mol of the pyrazole in 50 ml of dry tetrahydrofuran (THF) was added 0.50 g (0.021 mol) of sodium hydride which had been previously washed with dry THF. The solution of 0.021 mol of the appropriate alkyl halide was added and the solution was stirred for 5 hr. The solution was filtered to remove the sodium halide and the solution was concentrated *in vacuo*. The residue was distilled at 1 Torr and compared spectrally with the respective products of the decarboxylations of the respective *N*-carbalkoxypyrazole. Compounds prepared are listed below.

4-Bromo-1,3,5-trimethylpyrazole: mp 34–36° (reported[26] liquid).

4-Bromo-3,5-dimethyl-1-ethylpyrazole: bp 56–57° (0.05 Torr). *Anal.* Calcd for $C_7H_{11}N_2Br$: C, 41.40; H, 5.46; N, 13.80; Br, 39.35. Found: C, 41.53; H, 5.46; N, 13.55; Br, 39.25.

4-Bromo-3,5-dimethyl-1-isopropylpyrazole: bp 65° (0.05 Torr). *Anal.* Calcd for $C_8H_{13}N_2Br$: C, 44.26; H, 6.04; N, 12.91; Br, 36.81. Found: C, 44.65; H, 6.31; N, 13.11; Br, 36.43.

1-Benzyl-4-bromo-3,5-dimethylpyrazole: bp ~210° (0.05 Torr). *Anal.* Calcd for $C_{12}H_{13}N_2Br$: C, 54.35; H, 4.94; N, 10.57; Br, 30.14. Found: C, 54.62; H, 5.19; N, 11.03; Br, 30.10.

Isolation of TBAI from Decarboxylation of Reaction Mixtures. Tetra-*n*-butylammonium iodide (TBAI) was recovered from two reaction mixtures by the following procedure. After 80% evolution of carbon dioxide from 0.131 g (5.65×10^{-4} mol) of 1-carbomethoxy-4-bromo-3,5-dimethylpyrazole catalyzed by 0.0561 g (1.52×10^{-4} mol) of TBAI at 110° in 1.884 g of dibutyl phthalate solvent, the reaction tube was removed from the constant temperature bath. To the reaction solution was added 10 ml of ligroine (bp 30–60°). The solution was washed into a beaker and was diluted with ligroine to a volume of 50 ml. The precipitated TBAI was collected by filtration and was washed with 10 ml of ligroin (bp 30–60°). The solution was washed into a beaker and 140–145° (authentic material melts at 145–146°); the ir spectrum (Nujol mull) was identical with that of authentic TBAI.

By the same procedure, 0.18 g (91% recovery) of TBAI was isolated from a decarboxylation involving 0.1989 g (5.40×10^{-4} mol) of TBAI and 0.934 g (4.325×10^{-3} mol) of 1-carbomethoxy-5-methyl-3-phenylpyrazole in 7.245 g of DBP and heated at 110°.

Kinetics. The constant temperature bath was of conventional design utilizing 5 gallons of Union Carbide L-45 silicone oil (200 cSt) as the bath liquid. Temperature control was ±0.04° at 100°. Ultraviolet spectra were recorded with a Beckman Model DB spectrophotometer equipped with a Sargent Model SRL recorder. The kinetic data were analyzed using a least-squares fit to the best straight line using an Olivetti Underwood Programma 101 desk computer.

Volumetric Kinetic Determinations. A weighed quantity of dry catalyst was placed in a 100 × 20 mm Pyrex test tube equipped with inner and outer standard taper joints. A weighed ester solution of known molal concentration in the appropriate solvent was added to the catalyst. The reaction tube was placed in a neck of a three-necked 500-ml flask in which 300 ml of toluene was vigorously refluxing. An insulated mercury gas buret was immediately attached to the reaction tube and the change in the volume of gas in the buret was measured as a function of time. Changes in room temperature and pressure during any kinetic run were negligible and variations in temperature (3°) and pressure (5 Torr) could have only produced a 1% error in the volume of gas which was observed. Volumes were corrected for the initial expansion of air in the reaction tube and for the initial temperature equilibration period. Duplicate runs were reproducible to ±3%.

Ultraviolet Kinetic Determinations. Kinetic experiments using ultraviolet maxima of the esters were conducted in DMSO solution. The esters exhibited a sharp absorption at 258 mμ where none of the products absorbed. Extinction coefficients of the esters were in the range 2×10^3–2.8×10^3 l./(mol cm).

A 20-ml portion of the halide catalyst solution (0.0543 *M*) was thermally equilibrated in the reaction vessel for 30–60 min at 99.85°. Then 50–100 μl of a 0.2000 *M* ester solution was added through the stopcock *via* a syringe. The initial ester concentration was in the range 5.0–10×10^{-4} *M* and the initial absorbance of the solution at 258 mμ was approximately 1.2. Samples of 1–2 ml were removed periodically from the reaction solution through the stopcock *via* syringe. The samples were cooled to room temperature, and the ultraviolet spectrum of the aliquot was recorded at least three times; the average of these values was used in the determination of the rate constant of the reaction. Reactions were followed for at least 2 half-lives with six to twelve samples being taken. Rate constants were reproducible to 1–2%, and all of the esters studied showed good first-order kinetics.

In the decomposition of the benzyl ester, one of the major products, benzaldehyde, absorbs at 258 mμ. The products were unalkylated pyrazole and benzaldehyde, and the ratio of the concentrations of the ester at time t to the initial concentration of the ester, $[E]_t/[E]_0$, was obtained from the expression

$$[E]_t/[E]_0 = (A_t - A_0)/(A_0 - A_\infty)$$

where A_∞ is the absorbance of the solution at infinite time and A_0 is the initial absorbance of the solution. Products are shown in Table V.

The kinetic reactions of the alkylative decarboxylation of the methyl ester catalyzed by the sodium salt of 4-bromo-3,5-dimethylpyrazole were followed by determining the change in the uv absorption of the solution as a function of time as were the halide-catalyzed reactions.

The sodium salt of the pyrazole was prepared by the reaction of 4-bromo-3,5-dimethylpyrazole with an excess of sodium hydride in tetrahydrofuran (THF) solution. A solution of the pyrazole salt resulted from this reaction, and, after filtration of the solution to remove the excess sodium hydride, the solution was concentrated *in vacuo*. The residual salt was then dried of residual THF in a bell jar at room temperature at 0.3 Torr for 2 days prior to use. The reaction solution of the catalyst was prepared just prior to use by dissolving 20.0 mg of sodium 4-bromo-3,5-dimethylpyrazole in 21.0 ml of dry DMSO to yield a 5.29×10^{-3} *M* solution. The reaction was then carried out exactly as were the halide-catalyzed reactions. A small amount of decomposition of the solution occurred but little problem was caused in determining the rate constant for the reaction. Analysis of the final reaction mixture showed essentially quantitative conversion of the 4-bromo-1-carbomethoxy-3,5-dimethylpyrazole to 4-bromo-1,3,5-trimethylpyrazole. The quantity of 4-bromo-3,5-dimethylpyrazole found after work-up was accountable to the hydrolysis of the sodium salt during the work-up procedure.

The kinetics of the decarboxylation of the (*R*)-(−)-α-methylbenzyl ester were determined by following the optical rotation of a DMSO solution. The instrument used was a Japan Spectroscopic Co., Ltd., Model ORD/UV-5 optical rotary dispersion spectrophotometer.

Into a 10-mm quartz curvette was placed 3.0 ml of the stock sodium chloride–DMSO solution. The curvette was capped with a

tight-fitting Teflon stopper and was then placed into the cell compartment of the ORD. The cell compartment was thermostated at 99.80 ± 0.5° through the use of an ethylene glycol filled circulating pump obtained from the Precision Scientific Co. The solution was allowed to equilibrate at this temperature for 30 min while the instrument was set at zero rotation at the sodium D line (5893 Å). The neat ester (5–15 mg) was introduced *via* a capillary tube and was stirred for 2 sec. The optical rotation of the solution was recorded continuously for a period of 6 hr (*ca.* 2 half-lives of reaction) and the rotation was found to decrease exponentially to a value of 0.00 after 20 hr. The products were acetophenone and 4-bromo-3,5-dimethylpyrazole in 99% yields by nmr and glc. A least-squares fit to the best straight line of ln (rotation) *vs.* time indicated that the decomposition of the ester was first order with a rate constant reproducible to ±3%.

Methyl 4-Nitrophenylcarbonate. Into the reaction vessel used for volumetric rate determinations was placed 0.540 g of methyl 4-nitrophenylcarbonate and 50 mg of tetra-*n*-butylammonium iodide. The reaction vessel was then placed into a flask containing vigorously boiling ethylene glycol (195°) and the gas buret was immediately attached to the reaction vessel. After 5 min 68 ml of carbon dioxide (identified by ir) was evolved, corresponding to 90% reaction. The reaction mixture was cooled to room temperature, and ether was added. The ether solution was washed with two 10-ml portions of water, dried over sodium sulfate, and concentrated *in vacuo*. The residue (0.375 g, 91% yield) was identified as 4-nitroanisole by comparison of the infrared and nmr spectra and melting point with those of authentic material.

Dimethyl Malonate Decarboxylation. Into a 50-ml round-bottom distilling flask was placed 25 g of dimethyl malonate and 1 g of tetra-*n*-butylammonium iodide. The mixture was heated with a heating mantle at atmospheric pressure with stirring. Near the boiling point of the malonate, evolution of carbon dioxide began and, after 30 min, methyl acetate began to distill from the reaction mixture. After 2.5 hr, 5 g of methyl acetate was collected (35% yield). The methyl acetate was identified by comparison of the ir and nmr spectra with those of authentic material.

Registry No.—Methyl chloroformate, 79-22-1; ethyl chloroformate, 541-41-3; isopropyl chloroformate, 108-23-6; benzyl chloroformate, 501-53-1; (*R*)-(+)-α-phenylethanol, 1517-69-7.

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Kinetics and Mechanism for Chloromercuriolactonization of Esters of γ,δ-Unsaturated Acids[1]

Omar A. El Seoud,[2] Antonia T. do Amaral,[2] M. Moura Campos, and Luciano do Amaral*

Instituto de Quimica da Universidade de São Paulo, Caixa Postal, 20.780, São Paulo, SP, Brazil

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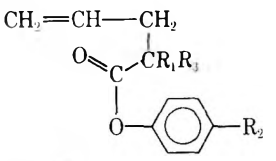
The kinetics of the reaction of phenyl allylphenylacetate (I), phenyl allyl-*p*-tolylacetate (II), phenyl *p*-methoxyphenylacetate (III), phenyl allyl-*p*-chlorophenylacetate (IV), phenyl allyl-*p*-fluorophenylacetate (V), phenyl allyl-*p*-nitrophenylacetate (VI), phenyl allylacetate (VII), *p*-tolyl allylacetate (VIII), *p*-methoxylphenyl allylacetate (IX), *p*-bromophenyl allylacetate (X), *p*-nitrophenyl allylacetate (XI), and phenyl allyldiphenylacetate (XII) with mercuric chloride have been studied in 50% aqueous ethanol. The reaction follows the expression rate = k_2[ester][$HgCl_2$]. Rate constants for the reaction are increased by electron-withdrawing substituents in the phenyl allyl para-substituted phenylacetate moiety (compounds I–VI) and by electron-donating substituents in the para-substituted allylacetate moiety (compounds VII–XI). A mechanism is postulated and discussed in terms of the kinetic data.

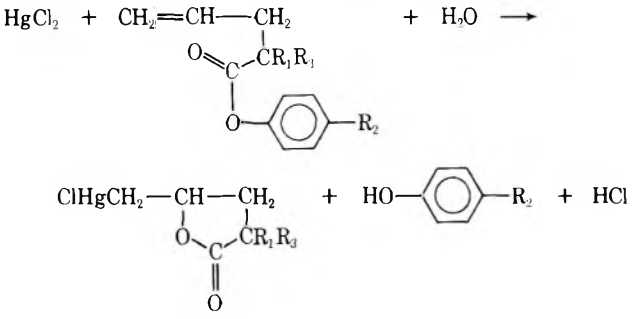
In the course of a search for new mercurials of diuretic action, we have prepared δ-chloromercuri-γ-lactones by the reaction of various allyl para-substituted acids with mercuric chloride in 50% aqueous ethanol. The structure of these chloromercurilactones were established by chemical and spectroscopic means. Aside from the pharmacological importance of these products, we were interested in studying the reaction itself to determine its kinetic expression and the effect of structural changes on its rate. Such a kinetic study was particularly interesting because of the surprisingly small amount of kinetic data available on this reaction. We have therefore prepared several phenyl esters of allyl para-substituted phenylacetate acids (compounds I to VI) and several para-substituted phenylic esters of the allylacetic acid (compounds VII to XI). See Chart I for general structure of compounds I–XII. These esters react with mercuric chloride in ethanol–water solution to give δ-chloromercuri-γ-lactones and the corre-

Chart I



Compd	R_1	R_2	R_3
I	C_6H_5	H	H
II	p-$C_6H_4CH_3$	H	H
III	p-$CH_6H_4OCH_3$	H	H
IV	p-C_6H_4Cl	H	H
V	p-C_6H_4F	H	H
VI	p-$C_6H_4NO_2$	H	H
VII	H	H	H
VIII	H	CH_3	H
IX	H	OCH_3	H
X	H	Br	H
XI	H	NO_2	H
XII	C_6H_5	H	C_6H_5

sponding phenol. The reaction rate was studied spectrometrically by observing the formation of the phenols.



Experimental Section

Ir spectra (in cm^{-1}) were measured on a Perkin-Elmer Model 337 grating spectrometer and Raman spectra on a Jarrel-Ash 25-300 spectrometer. Nmr spectra were measured on a Perkin-Elmer R-10 spectrometer. Chemical shifts (τ) in ppm were measured from an internal TMS reference. A Perkin-Elmer Model 180 instrument was used for glc analysis. In all chromatographic analysis of the esters a 3% SE-30 column was used, with nitrogen as the carrier gas. Mass spectra were recorded on a single focus Perkin-Elmer 200, operating at an ionizing potential of 70 eV. Melting points were determined on a Kofler hot stage apparatus and are uncorrected.

Preparation of Allyl Para-Substituted Phenylacetic Acids. A solution of 24 mmol of n-butyllithium (solution 2 M in hexane) was added to a solution of 24 mmol of diisopropylamine in 20 ml of THF at −5°. The acid (phenylacetic, p-tolylacetic, p-methoxyphenylacetic, p-chlorophenylacetic, p-fluorophenylacetic, or diphenylacetic), 11.3 mmol in 10 ml of THF, was added slowly. After 5 min, 5 ml of HMPT was added, and the solution stirred at 0° for 15 min. Allyl bromide (15 mmol) was then added in one portion. After stirring at room temperature for 2 hr, followed by distillation of the solvent, the residue was poured into water and extracted with ether. After removal of the ether, the crude acid was obtained (Table I).

Allyl p-nitrophenylacetic acid was synthetized as follows. Diethyl p-nitrophenylmalonate was prepared according to the method of Bourdais and Mahieu,[3] yield 47%, mp 56° (lit.[3] mp 56°). The ester was alkylated with allyl bromide in *tert*-butyl alcohol using potassium *tert*-butoxide as base to give diethyl allyl-p-nitrophenylmalonate, in 85% yield. The required acid was obtained by hydrolysis with dilute aqueous sodium hydroxide (2.8%), followed by acidification and decarboxylation: yield 73%, mp 89–90°, ν_{max} (KBr) 1710 (CO), 1525, 1340 (NO_2). *Anal.* Calcd: C, 59.72; H, 5.10. Found: C, 59.91; H, 5.21.

Preparation of Phenyl Allyl Para-Substituted Phenylacetates and Para-Substituted Phenyl Allylacetates. Phenyl allylphenylacetate (I), phenyl allylacetate (VII), p-tolylallylacetate (VIII), p-methoxyphenyl allylacetate (IX), p-bromophenyl allylacetate (X), p-nitrophenyl allylacetate (XI), and phenyl allyldiphenylacetate (XII) were prepared by heating 0.1 mol of the corresponding acid with 0.2 mol of thionyl chloride until the evolution of gases ceased. After the excess thionyl chloride was removed by distillation, 0.12 mol of the corresponding phenol was added and the mixture heated for 2–3 hr. The product was washed with cold 10% sodium hydroxide solution and water and extracted with ether; the solvent was evaporated. The residual oil was distilled to give the required ester [compound: yield, elemental analysis (calcd); boiling point; ir absorption (film)]. I: 67%; C 80.40 (80.90), H 6.66 (6.39); 127–129° (0.3 Torr); 1745, 1640, 1280–1190. VII: 52%; C 74.89 (74.85), H 7.09 (6.80); 96–100° (3 Torr); 3060, 1760, 1540, 1500, 750, 680. VIII: 64%; C 75.32 (75.76), H 7.49 (7.42); 114–118° (6–7 Torr); 3060, 1640, 1580, 1220, 840. IX: 56%; C 69.84 (69.88), H 7.04 (6.84); 103–105° (0.15 Torr); 3100, 2850, 1760, 1650–1590, 1500, 1460–1440, 1220, 1020, 840. X: 79%; C 52.21 (51.79), H 4.85 (4.35); 136–140° (0.15 Torr); 3100, 1760, 1660, 1490, 1220, 1015, 840, 520. XI: 55%; C 60.32 (59.72), H 5.04 (5.01); 130–140° (0.15 Torr); 3060, 1765, 1640, 1610–1580, 1340, 1220, 1010, 850. XII: 47%; C 84.07 (84.12), H 6.24 (6.14). Phenyl allyl-p-tolylacetate (II), phenyl allyl-p-methoxyphenylacetate (III), phenyl allyl-p-chlorophenylacetate (IV), phenyl allyl-p-fluorophenylacetate (V), and phenyl allyl-p-nitrophenylacetate (VI) were prepared by the following method. A mixture of 100 ml of DMF and 0.1 mol of thionyl chloride was heated at 40–50° for 20 min; 0.1 mol of the acid was added. The mixture was heated at 60° for 2 hr after which 0.13 mol of phenol was introduced and mixture heated for an additional 3 hr. After addition of 10% HCl solution, and extraction with ether, the combined ethereal extracts were washed with 10% HCl solution, water, and cold 10% NaOH, and then dried and the solvent evaporated. The residual oil was distilled to give the required ester [compound; yield; elemental analysis (calcd); boiling or melting point; ir absorptions]. II: 88%; C 80.90 (81.17), H 6.76 (6.81); bp 118–20° (0.8 Torr); (film) 1730, 1620, 1300–1070. III: 75%; C 68.59 (68.88), H 5.01 (5.09); bp 142–44° (0.3 Torr); (film) 1730, 1620, 1300–1050. IV: 86%; C 70.97 (71.20), H 5.21 (5.27); bp 120–122° (0.4 Torr); (film) 1748, 1630, 1250–1050. V: 86%; C 75.39 (75.54), H 5.65 (5.59); bp 120–122° (0.5 Torr); (film) 1752, 1650, 1300–1100. VI: 61%; C 68.59 (68.88), H, 5.01 (5.09); mp 45.5–46.5°; (KBr) 1730, 1530, 1340, 1250–1050.

Preparation of the δ-Chloromercuri-γ-lactones. (a) From the Corresponding Acids. Equimolar amounts of the appropriate acid and mercuric chloride were dissolved in an 80% methanol-water mixture.[4] After 6 hr the solvent was evaporated with hot air and the amorphous viscous material obtained was crystallized from ethanol, with the exception of chloromercuri-γ-valerolactone which was crystallized from chloroform–petroleum ether. The results are summarized in Table II.

(b) From the Corresponding Esters. Equimolar amounts of the appropriate esters and mercuric chloride were dissolved in an 80% methanol-water mixture. After 2 days the solvent was evaporated with hot air and the amorphous, viscous material obtained

Table I
Yield in Allylation of $R_1R_3CHCO_2H$, Employing LiDiPA as Base, in THF–HMPT Solution, and Characterization of the $CH_2{=}CHCH_2C(R_1)(R_3)CO_2H$ Formed

Registry no.	Compd	R_1	R_3	Yield, %	Mp, °C	Ir[c] ν_{max}, cm^{-1}	Nmr[e]
1575-70-8	**1**	H	C_6H_5	81	*a*	1690, 1620[d]	2.83, 4.39, 5.03, 6.47, 7.55,
51230-90-1	**2**[f]	H	p-$CH_3C_6H_4$	80	91–92	1720, 1620	2.83, 4.32, 4.96, 6.42, 7.40, 7.77
51230-91-2	**3**[f]	H	p-$CH_3OC_6H_4$	78	81–81.5	1690, 1640	2.83, 4.20, 4.90, 6.22, 6.49, 7.29
51230-92-3	**4**[f]	H	p-ClC_6H_4	83	94–95	1715, 1630	2.67, 4.42, 4.69, 6.39, 7.40
51230-93-4	**5**[f]	H	p-FC_6H_4	80	67–69	1720, 1650	2.79, 4.34, 4.92, 6.39, 7.29
6966-03-6	**6**	C_6H_5	C_6H_5	81	141–142[b]	1705, 1640	2.79, 4.49, 5.22, 6.89

[a] Bp 146–147° (15 Torr) [lit.[16] 113–117 (1 Torr)]. [b] Lit.[7] 138–140. [c] KBr. [d] Film. [e] Taken in carbon tetrachloride for compounds I and VI and in acetone-d_6 for compounds II, III, IV, and V. [f] Satisfactory combustion analytical data for C and H (±0.4%) were reported for these compounds. Ed.

Table II
Yields of the Reaction of CH_2=$CHCH_2C(R_1)(R_3)CO_2H$ and Mercuric Chloride, and Characterization of the δ-Chloromercuri-γ-lactones Formed

Registry no.	R_1	R_3	Yield, %	Mp, °C	Ir ν_{max}, cm^{-1}
51230-94-5	H	H	57	81–82[a]	1745 (CO), 530 (C–Hg)
51230-95-6	H	C_6H_5	56	172.5–173.5[b]	1740 (CO), 560 (C–Hg)
51230-96-7	H	p-$CH_3C_6H_4$	77	165–166.5[b]	1700 (CO), 553 (C–Hg), 300 (Hg–Cl)
51230-97-8	H	p-$CH_3OC_6H_4$	77	177–178.5[b]	1745 (CO), 560 (C–Hg), 300 (Hg–Cl)
51230-98-9	H	p-ClC_6H_4	80	149–150[b]	1740 (CO), 565 (C–Hg), 308 (Hg–Cl)
51271-05-7	H	p-FC_6H_4	75	180–181.5[b]	1735 (CO), 1200, 1100(C–F), 552 (C–Hg), 305 (Hg–Cl)
51230-99-0	H	p-$NO_2C_6H_4$	51	142–143[b]	1745 (CO), 1520 1350 (NO_2), 560 (C–Hg), 315 (Hg–Cl)
51231-00-6	C_6H_4	C_6H_4	82	203–204[c]	1754 (CO), 568 (C–Hg)

[a] Lit.[6] 81–82°. [b] Satisfactory combustion analytical data for C, H (±0.4%) were reported for these compounds. Ed. [c] Lit.[6] 203–204°.

from esters I, II, III, IV, V, and VI was crystallized from ethanol, and from esters VII, VIII, IX, X, and XI were crystallized from chloroform and petroleum ether (starting ester, yield): I, 40%; II, 54%; III, 51%; IV, 61%; V, 58%; VI, 33%; VII, VIII, IX, X, XI, *ca.* 10%.

Dehalomercuration of the δ-Chloromercuri-γ-lactones. The method of Brown, *et al.*,[5] was used, with the exception that the sodium borohydride (in 3 *M* sodium hydroxide solution without free alkali) was added to a THF–water solution of chloromercurilactones. The following results were obtained. (1) The reduction of δ-chloromercuri-γ-valerolactone gave allylacetic acid, identified by its ir spectrum.[6] (2) The reduction of the α-phenyl-δ-chloromercuri-γ-valerolactone gave an 85% yield of α-phenyl-γ-valerolactone; bp 154–156° (3 Torr); ir (film) 1775 (CO). *Anal.* Calcd: C, 74.97; H, 6.68. Found: C, 74.86; H, 6.79. The reduction of the α,α-diphenyl-δ-chloromercuri-γ-valerolactone gave an 80% yield of α,α-diphenyl-γ-valerolactone: mp 113–114° (lit.[7] 113–114°); ir (Nujol) 1760 (CO).

Kinetic measurements were carried out spectrophotometrically with the aid of a Zeiss PMQ II spectrometer equipped with a cell holder through which water from a thermostated bath was continuously circulated. The required reaction temperature was measured inside the cell with an accuracy of ±0.05°. All reagents were Merck R.G. grade and doubly distilled water was used throughout the work. Reagent solutions were prepared in 50% ethanol–water mixture and had the following concentrations: ester solutions, 4.0×10^{-4} *M*; mercuric chloride, 3.0×10^{-1} *M*; and sodium perchlorate, 1.0 *M*. Kinetic runs were carried out as follows. All reagents, except the ester solution, were pipetted into reaction tube, mixed, and then left in the water bath for 30 min. At zero time, a measured quantity of the ester solution was added to the mixture, which was then shaken and transferred rapidly to the reaction cell. The reaction kinetics were monitored by following the appearance of the liberated phenol at the appropriate wavelength until a constant reading was reached. In all cases a sufficient excess of mercuric chloride was used to ensure pseudo-first-order kinetic behavior. An ionic strength of 0.10 was obtained by addition of sodium perchlorate solution. Observed first-order rate constants, k_{obsd}, were evaluated from plots of log $(OD_\infty - OD_t)$ against time and the expression $k_{obsd} = 0.693/t_{1/2}$. Second-order rate constants, k_2, were determined by dividing k_{obsd} by the mercuric chloride concentration.

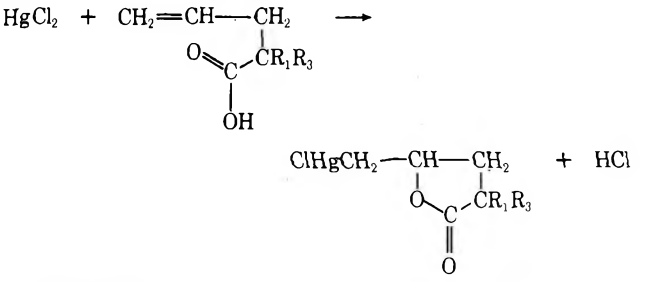
Results

Preparation of the Allylphenylacetic Acids. The usual method for preparing allylphenylacetic acids involves the hydrolysis and decarboxylation of disubstituted malonic esters. The latter compounds may be obtained by known procedures.[8]

In addition to the multistep nature of this method of synthesis, low overall yields are usually obtained (35–40%).

We have prepared several allyl para-substituted phenylacetic acids; *viz.* allylphenylacetic acid, allyl-*p*-tolylacetic acid, allyl-*p*-methoxyphenylacetic acid, allyl-*p*-chlorophenylacetic acid, and allyl-*p*-fluorophenylacetic acid as well as allyldiphenylacetic acid by direct allylation of the appropriate phenylacetic acids, employing the bulky base lithium diisopropylamide.[9] Metal amides have been used as strong bases for metalation; however, only metal alkylamides can be used with carbonyl compounds to avoid the undesirable addition of the amide ion.[10] This base results in rapid formation of the dianion of the acid at room temperature, and its use seems more advantageous in both reaction conditions and yields than the less bulky dimethyl- or diethylamine.[10] Alkylation with allyl bromide gave excellent yields of the monoalkylated acid (Table I). No dialkylated compounds could be detected by glc or nmr.

Preparation of the Chloromercurilactones. The allylphenylacetic acids, prepared as described above, were treated with mercuric chloride, producing the corresponding δ-chloromercuri α-substituted γ-lactones.



The reaction was carried out in methanol–water solution, as addition of mercuric chloride to the unsaturated acids under anhydrous conditions led to simple double bond addition, with no lactone formation.[11] It seems possible, therefore, that water participates in the transition state formed by the intramolecular attack of the carbonyl oxygen to the mercurinium ion. The chloromercurilactones were prepared in high yields (Table II).

Structure of the Lactone Ring. The ir absorption for the carbonyl group of chloromercurilactones varied between 1754 and 1735 cm^{-1}. This range corresponds to a δ-lactone (reported 1750–1735 cm^{-1})[12] rather than a γ-lactone (reported range 1780–1760 cm^{-1});[12] however, the lactones derived from γ,δ-unsaturated acids were reported to be γ-lactones.[13,14] The origin of this difference was investigated. If the observed frequencies of the lactones in the study originate from an interaction between the electropositive mercury atom and the carbonyl group, then dehalomercuration should result in a blue shift to the ν_{max} value reported for the carbonyl group in γ-lactones. This dehalomercuration was affected by sodium borohydride reduction in alkaline solution, and the results were as follows. (1) For the chloromercurilactones of allylacetic acid, it was not possible to effect reduction without regenerating the starting allylacetic acid. (2) Reduction to the chloromercurilactone derived from allylphenylacetic acid resulted in a blue shift from 1740 to 1775 cm^{-1}. (3) For allyldiphenylacetic acid, the lactone obtained by direct lactonization of the acid by concentrated sulfuric acid and by reduction of the chloromercurilactone showed the characteristic absorption of a γ-lactone (1760 cm^{-1}).

Table III
Mass Spectra of δ-Chloromercuri-α-p-chlorophenyl-γ-lactone

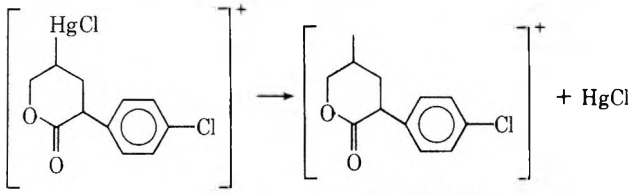
m/e	Abund., %	m/e	Abund., %	m/e	Abund., %	m/e	Abund., %
41	8	89	15	130	48	169	58
43	6	113	16	138	10	171	20
51	14	115	20	141	33	199	13
63	11	125	33	143	10	209	8
75	13	127	28	165	100	211	2
77	16	129	51	167	30		

Table IV
Second-Order Rate Constants for the Reaction of Phenyl Allyl Para-Substituted Phenylacetates and Mercuric Chloride, in 50% Ethanol–Water with Ionic Strength of 0.10

Registry no.	Substituent	$k_2 \times 10^3$, M^{-1} min^{-1} T = 25°	T = 35°	T = 45°
51231-01-7	OCH_3	8.2	18.7	38.5
51231-02-8	CH_3	7.9	18.9	43.0
51231-03-9	H	6.3	15.8	35.0
51231-04-0	F	6.5	15.4	33.4
51231-05-1	Cl		12.5	29.6
51231-06-2	NO_2		5.6	16.6

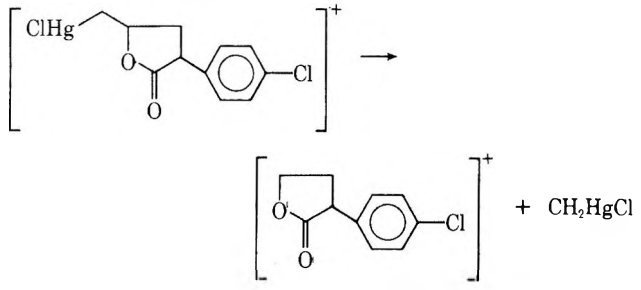
The mass spectrum of δ-chloromercuri-α-p-chlorophenyl-γ-lactone was taken in an attempt to confirm the structure of the lactone ring, since simply substituted γ- and δ-lactones give a base peak of m/e 85 and 99, respectively.[15,16] The results are shown in Table III.

However, this method of differentiation was not effective in this case because of the very low abundance of peaks with m/e 85 and 99 (2%). The parent peaks in the mass spectrum of this compound are at m/e 211 and 209, corresponding to the loss of HgCl. This loss is readily explained in the case of a δ-lactone by γ-fission.



m/e 211, 209

A similar γ-fission on the case of a γ-lactone would give rise to loss of CH_2HgCl

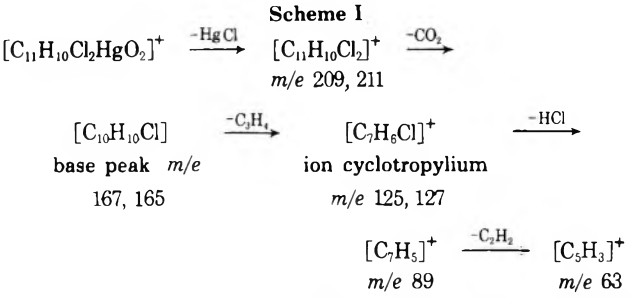


m/e 197, 195

The low abundance of peaks with m/e 197 and 195, however, does not rule out the existence of a γ-lactone since the weaker C–Hg bond should cleave more readily than C–C bond.

The ease with which the C–Hg bond breaks is demonstrated in the mass spectrum of Me_2Hg where the heat of formation, $\Delta H_f°$ of $HgCH_3^+$ (C–Hg breakage), is almost equal to that of $Hg(CH_3)_2^+$ (two-electron loss). After losing HgCl, the resulting ion loses CO_2 to produce base peaks m/e 167 and 165. Scheme I shows the prominent peaks obtained and a possible fragmentation route.

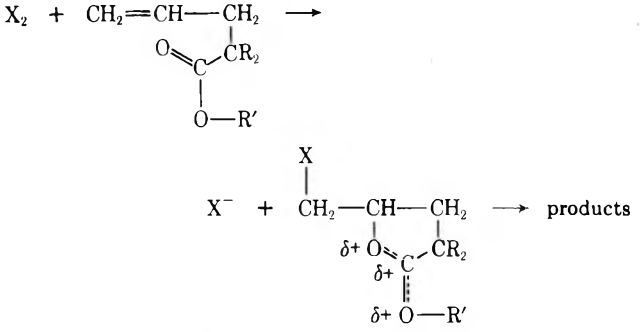
Scheme I



Kinetic measurements established the rate law as being rate = k_2[ester][$HgCl_2$]. The reaction is therefore second-order overall.

Several oxymercuration reactions have established the same kinetic behavior.[4-6,17]

Table IV shows the results obtained at different temperatures for the reaction of phenyl allyl para-substituted phenylacetates (esters I to VI) and mercuric chloride in 50% ethanol–water solution with an ionic strength 0.10. It can be seen that the presence of electron-withdrawing groups in the para position of the phenyl ring decrease the reaction rate, whereas the opposite is true with electron-donating substituents. This behavior can be explained by considering the general mechanism for the reaction of electrophilic reagents with γ,δ-unsaturated acids and esters.[20]



In general, the addition of mercuric chloride to a double bond proceeds *via* an alkenemercurinium ion, followed by a trans attack of the nucleophilic species.[18-21] This step is rapid and reversible.[21] In the chloromercuriolactonization the nucleophilic attack is made intramolecularly by the neighboring oxygen of the carbonyl group, leading to ring formation. The rate of this step is dependent on the electronic density of the carbonyl group. The presence of electron-withdrawing groups in the para position of phenyl ring decreases in the reaction rate while the presence of electron-donating groups at the same position increases the electron density of the carbonyl group and causes a rate increase.

The importance of the polar factor on chloromercuration of the γ,δ-unsaturated esters can be determined by the application of the Hammett equation. In Figure 1, values of rate constants are plotted against σ^n substituent constants.[22] A satisfactory straight line relationship is obtained, with a ρ^n value of −0.43. The rate constants are better correlated by σ^n than by σ values. This is explained by the fact that the interaction between para groups in the phenyl allyl para-substituted phenylacetates and the reaction center is believed to be purely polar since the substituents are removed by one atom from the carbonyl group. The negative sign of ρ^n indicates that the reaction rate is increased by increasing the electron density at the reaction center, *i.e.*, by electron-releasing groups. The small value of ρ^n arises from the fact that the substituents are distant from the reaction center. The activation energy E_a was determined by a least-squares analysis of a plot of log k_2 *vs.* $1/T$ (Table V).

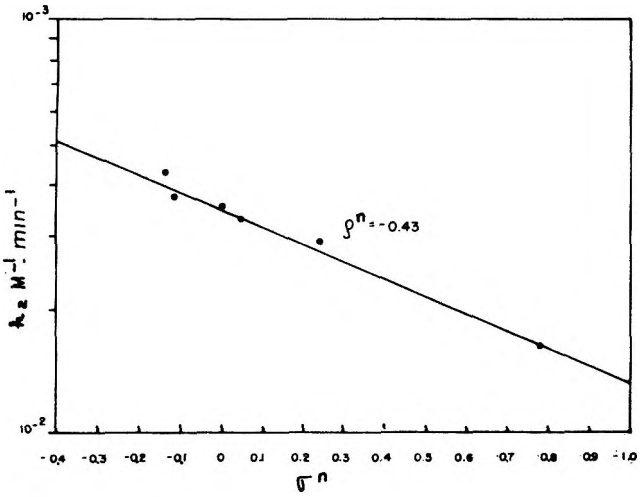


Figure 1. Logarithms of the second-order rate constants for the reaction of phenyl allyl para-substituted phenylacetates and mercuric chloride, in 50% aqueous ethanol, at 45° and an ionic strength of 0.10, plotted against σ^n substituent constants. The compounds employed and the numerical values of the rate constants are listed in Table IV.

The enthalpy of activation, ΔH^*, was obtained by subtracting RT from E_a. The entropy of activation, ΔS^*, was calculated from the formula given by Schaleger and Long.[23] It can be seen that the enthalpy of activation (ΔH^*) and the free energy of activation (ΔG^*) are higher for electron-withdrawing groups. This clearly shows the contribution of the polar effect of the substituents to the reaction rate. The values of the entropy of activation (ΔS^*) are almost constant, supporting the idea that only the polar effect is operating. The reported negative values of the entropy of activation are clearly due to the formation of a solvent shell around the ionic species in the reactions.[24]

Table VI shows the results obtained for the reaction of para-substituted phenyl allylacetates (esters VII–XI) and mercuric chloride in 50% ethanol–water solution with an ionic strength of 0.10 at 45°. It can be seen that electron-attracting groups increase the reaction rate whereas electron-releasing groups have an opposite effect. This result is the reverse of that obtained for the first series of esters

Table V
Activation Parameters for the Reaction of Phenyl Allyl Para-Substituted Phenylacetates and Mercuric Chloride, in 50% Ethanol–Water and an Ionic Strength of 0.10

Substituent	ΔE^*, kcal mol^{-1}	ΔH^*, kcal mol^{-1}	ΔS^*, eu	ΔG^*, kcal mol^{-1}
OCH_3	14.1	13.4	−75.1	37.3
CH_3	16.0	15.4	−74.9	39.2
H	15.5	14.9	−75.4	38.9
F	15.1	14.5	−75.4	38.5
Cl	16.8	16.2	−75.6	40.2
NO_2	21.3	20.7	−76.6	45.1

Table VI
Second-Order Rate Constants for the Reaction of Para-Substituted Phenyl Allylacetate and Mercuric Chloride in 50% Ethanol–Water and an Ionic Strength of 0.10 at 45°

Registry no.	Substituent	$k_2 \times 10^3$, M^{-1} min^{-1}
51231-07-3	OCH_3	6.2
51231-08-4	CH_3	6.9
51231-09-5	H	8.3
51231-10-8	Br	15.4
51231-11-9	NO_2	112

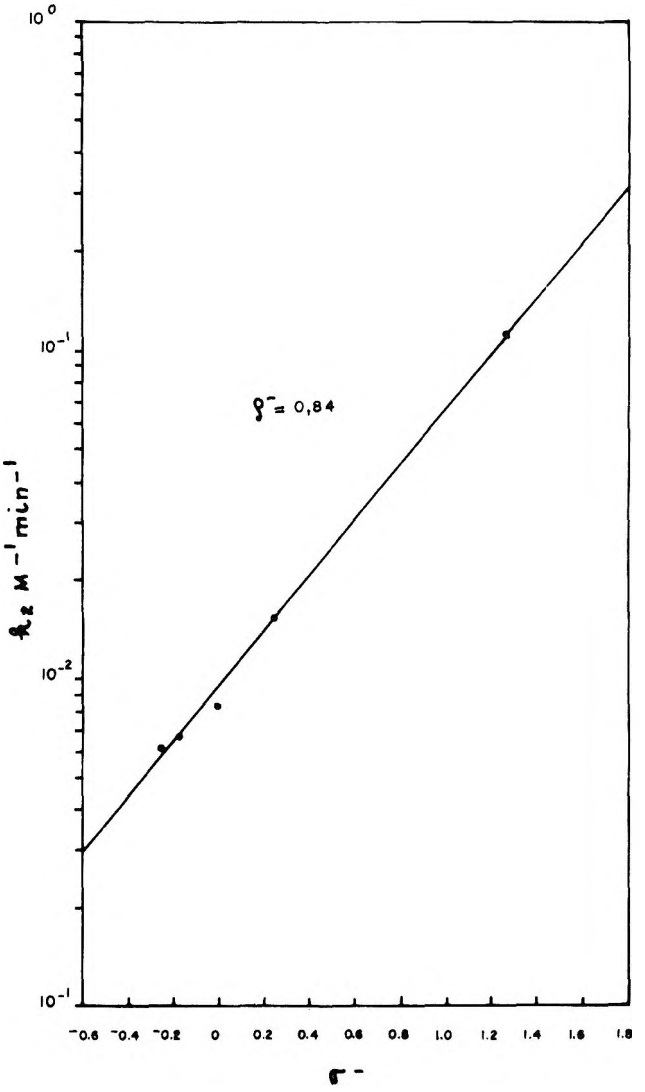


Figure 2. Logarithms of second-order rate constants for the reaction of para-substituted phenyl allylacetates and mercuric chloride, in 50% aqueous ethanol at 45° and an ionic strength of 0.10, plotted against σ^- substituent constants. The compounds employed and the numerical values of the rate constants are listed in Table VI.

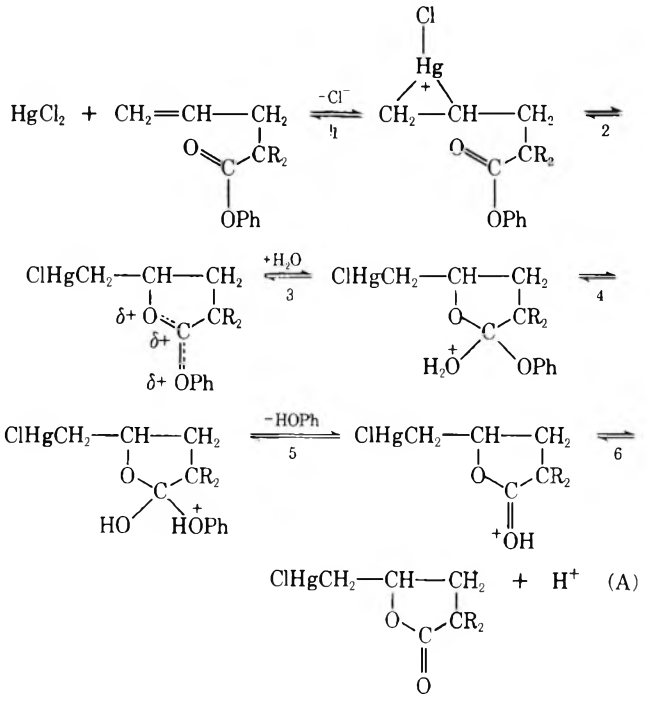
(esters I–VI) and can be explained by assuming that the reaction rate is being controlled by the ease of departure of the leaving group. Electron-attracting groups in the para-substituted phenyl allylacetates make the phenol a better leaving group, thus increasing the rate of the reaction, in accordance with the results obtained.

In Figure 2 the values of the rate constants are plotted against the σ^- substituent constants,[25] giving a ρ^- value of 0.84.

Discussion

On the basis of our results we propose mechanism A for the chloromercuriolactonization of phenyl esters of γ,δ-unsaturated esters, in ethanol–water solution. The fact that carbonyl oxygen is the one involved in the ring formation has been established previously for the same type of reaction.[26,27] Steps 1, 3, 4, and 6 are rapid.[21] The rate-determining step may be, therefore, step 2, in which intramolecular nucleophilic attack by the carbonyl oxygen leads to ring formation, or step 5, in which the phenol departs. It can be shown easily that the form of the kinetic equation obtained in either case is essentially the same.

With the para-substituted phenyl allylacetates (esters VII–XI) the rate of the reaction increases when the substituent is an electron-attracting group and decreases



when the substituent is an electron-releasing group. This suggests that the rate-determining step is the departure of the phenol (step 5), since a better leaving groups departs quicker. If the rate-determining step were the nucleophilic attack of the carbonyl oxygen on the mercurinium ion (step 2), the velocity of the reaction would decrease when the substituent is an electron-attracting group and increase when the substituent is an electron-releasing group. The experimental observations do not support the latter statement.

With the phenyl allyl para-substituted phenylacetates esters the presence of electron-withdrawing groups in the para position of the phenyl ring decreases the rate of the reaction while the presence of electron-donating groups at the same position causes an increase in the reaction rate. In these esters the leaving group remains the same, but step 2 is shifted to the right by the increase in the electron density of the carbonyl group. This further supports the postulate that the rate-determining step for the chloromercuriolactonization reaction is the loss of the substituted phenol.

Registry No.—$HgCl_2$, 7487-94-7; phenyl allyldiphenylacetate, 51231-12-0.

References and Notes

(1) Supported in part by the Fund for Overseas Research Grants and Education.
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Mercuric Chloride Promoted and Cobaltous Chloride Promoted Reactions of 1-Phenylethyl Chloride[1,2]

Carlos Monge, Jr., John L. Palmer, and A. F. Diaz*

Department of Chemistry, University of California, San Diego, La Jolla, California 92037

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The ionization of 1-phenylethyl chloride in anhydrous acetone is efficiently promoted by $HgCl_2$ and $CoCl_2$. The reactions measured by loss of optical activity and radiochlorine exchange provide results which are consistent with the intervention of ion-pair intermediates. In the case with $HgCl_2$ the kinetics are complicated and are consistent with the presence of two molecules of $HgCl_2$.

In the previous papers of this series we described the $HgCl_2$-promoted reactions of fairly reactive alkyl chlorides which ionized to form cations with intermediate stability such as the benzhydryl[3a] and the norbornyl[3b,c] cations. In these cases, the reactions are well behaved, showing a clean first-order dependence on the $HgCl_2$ concentration, and the importance of ion-pair intermediates was stressed. It seemed appropriate to extend this study to alkyl chlorides whose ionization reactions are more endothermic and where the cation is relatively less stable, especially since previous reports on studies with compounds of this type bring out the fact that the kinetic dependence of the reaction on $HgCl_2$ is complicated.[4-6] Thus, the hydrolysis and accompanying loss of optical activity of 1-phenylethyl chloride in aqueous acetone shows complicated kinetics and the two reactions are reported to proceed *via* different reaction pathways.[5] We now wish to present the results of a study on the $CoCl_2$-promoted and $HgCl_2$-promoted reactions of 1-phenylethyl chloride (RCl).

Table I
Summary of k Values for 1-Phenylethyl Chloride[a] in Acetone Containing $CoCl_2$ at 50.0°

$[CoCl_2]$, 10^2 M	10^6 k, sec^{-1}		10^4 k, M^{-1} sec^{-1}	
	k_α	k_e	k_α	k_e
0.853	31.7		37.2	
0.900		21.1 ± 2.0		23.5
1.003	37.2 ± 0.4		37.2	
1.160		28.1 ± 1.4		24.3
1.640		37.2 ± 3.4		23.1
2.002		54.9 ± 0.9		27.5
2.098	82.8 ± 0.6		39.5	
3.556	131		37.1	
			Av 37.8 ± 0.8	24.6 ± 1.4
			k_α/k_e = 1.54 ± 0.09	

[a] *Ca.* 0.09 and 0.01 M RCl used for k_α and k_e measurements, respectively.

Table II
Summary of k Values for 1-Phenylethyl Chloride[a] in Acetone

Temp, °C	$[H_2O]$, M	$[HgCl_2]$, 10^2 M	10^6 k, sec^{-1}			k_{rac}/k_e
			k_α	k_e	k_t	
50.0		0.204		0.788 ± 0.014		
50.0		0.530		2.66 ± 0.27		
50.0		1.00	8.23 ± 0.4	5.60 ± 0.35		1.47
50.0		1.00	8.20[b]			
50.0		5.00	54.3 ± 1.2	47.2 ± 2.2		1.15
50.0		10.1	153 ± 4	129 ± 3		1.19
50.0		10.0	134[b]			
50.0	2.22	2.50	42.3 ± 1.7	20.3 ± 0.3	10.6 ± 1.2	1.56
			(k_{rac})'31.7			
50.0	2.22	5.00	104 ± 9	41.5 ± 1.5	39.7 ± 3.1	1.54
			(k_{rac}) 64.3			
25.0	2.22	120.0		~2.5[d]	~950[d]	
20.0[c]	2.78	30.0	95.0 ± 5.1		90.1 ± 2.2	
20.0[c]	2.78	120.0	1050 ± 30		905 ± 40	

[a] [RCl] was 0.02–0.1 M for exchange runs and 0.1–0.3 M for polarimetric runs. [b] Calculated from Satchell's data (ref 4). [c] Recalculated values using the data of Read and Taylor (ref 5). [d] Good values are difficult to measure at these experimental conditions.

Results

Cobaltous Chloride. Optically active 1-phenylethyl chloride was prepared from the resolved carbinol with thionyl chloride. The prepared solution in acetone was placed in an all-glass 1-dm cell thermostated at 50.0°, and the rate of loss of optical activity was measured using a Perkin-Elmer polarimeter, Model 141.

$$\left.\begin{array}{ll} d\text{-RCl} \longrightarrow dl\text{-RCl} & k_{rac} \\ d\text{-RCl} \longrightarrow dl\text{-ROH} & k_t \end{array}\right\} k_\alpha \qquad (1)$$

The infinity readings were *ca.* zero rotation but difficult to read because of the yellow color which developed during the reaction. The data were treated using a first-order rate expression where α_0, α_t, and α_∞ are the polarimetric readings initially, at time t, and at t_∞, respectively.

$$k_\alpha = \frac{2.303}{t}\log\frac{\alpha_0 - \alpha_\infty}{\alpha_t - \alpha_\infty} \qquad (2)$$

In those runs with $CoCl_2$ the integrated first-order rate constants, k_α, were well behaved up to 60% reaction. These k values are summarized in Table I. The k_α values seem to be linearly depended on $[CoCl_2]$ in the concentration range studied, providing a second-order rate constant equal to $37.8 \pm 0.8 \times 10^{-4}$ sec^{-1}.

The rates of chlorine exchange between RCl and radiochlorine-labeled $CoCl_2$ were sampled up to 40–45% reaction using the sealed ampoule technique. In anhydrous acetone, the exchange proceeds to completion, where at 8 reaction half-lives the distribution of radiochloride between RCl and $CoCl_2$ is 98% of the calculated amount.

The exchange reactions showed good second-order kinetics. The integrated second-order rate constants were calculated using eq 3,[3c] where γ is the fraction of radioactivity measured in the organic layer at time t. The pseudo-first-order rate constants are given by the product of k_{2e} and the salt concentration (eq 4). The k_e values seem to be linearly related to the $CoCl_2$ concentration and are significantly lower than the corresponding k_α values. The second-order exchange rate constant has a value of $24.6 \pm 1.4 \times 10^{-4}$ M^{-1} sec^{-1}. These values are summarized in Table I.

$$k_{2e} = \frac{2.303}{t([RCl] + 2[CoCl_2])}\log\left[1 - \gamma\frac{[RCl] + 2[CoCl_2]}{[RCl]}\right] \qquad (3)$$

$$k_e = k_{2e}2[CoCl_2] \qquad (4)$$

Mercuric Chloride. The racemization of 1-phenylethyl chloride in anhydrous acetone containing $HgCl_2$ was followed as described above. These reactions are considerably slower than with $CoCl_2$ and the k_α values showed a slight downward drift during a run where the initial k values are decreased by *ca.* 5% at 30% reaction. This decrease is most likely due to the slow decomposition of 1-phenylethyl chloride under the reaction conditions to produce styrene and HCl, which renders $HgCl_2$ inactive. The amount of decomposition at 50% racemization is *ca.* 1.3% with 0.1 M $HgCl_2$. Thus, only the initial k values, *i.e.*, up to *ca.* 15% reaction, are listed in Table II for comparison with the other k values.

The k_{rac} values do not plot linearly with $[HgCl_2]$ but instead the slope increases with increasing $HgCl_2$ concentration as reported by Satchell.[4] These values are fit to within 3% by eq 5, which shows the sum of two kinetic terms, one first order in $HgCl_2$ and the other second order

in $HgCl_2$. This equation was obtained by a series of successive approximations. For the purpose of comparing our results with Satchell's, k_{rac} values for 1-phenylethyl chloride with $HgCl_2$ at 50.0° were calculated using the values at 25.0° published by Satchell.[4b] The calculations were made using ΔH^* values equal to 15.7 and 16.9 kcal for the second-order and third-order terms, respectively, obtained from the reaction of 1-phenylethyl chloride with $HgBr_2$. The resulting kinetic expression at 50° calculated from Satchell's values is given in eq 6, which provides k_{rac} values equal to 8.2×10^{-6} and 134×10^{-6} sec^{-1} at 0.01 and 0.05 M $HgCl_2$, respectively. These values agree well with our results and are listed in Table II.

$$k_{rac}(sec^{-1}) = 7.4 \times 10^{-4}[HgCl_2] + 78 \times 10^{-4}[HgCl_2]^2 \quad (5)$$

$$k_{rac}(sec^{-1}) = 7.6 \times 10^{-4}[HgCl_2] + 58 \times 10^{-4}[HgCl_2]^2 \quad (6)$$

$$k_e(sec^{-1}) = 4.9 \times 10^{-4}[HgCl_2] + 78 \times 10^{-4}[HgCl_2]^2 \quad (7)$$

The polarimetric rates measured with $HgCl_2$ in acetone containing 2.22 M H_2O were again treated using first-order kinetics. In this case, the k_α values show a very dramatic drift due to the solvolytic reaction. Thus only the initial k values (up to 10% reaction) are included in the summary in Table II. The effect of adding 2.22 M H_2O to the reaction solution is to increase k_α, while the nonlinear dependence on $[HgCl_2]$ still prevails.

The rates of radiochlorine exchange between RCl and $HgCl_2$*, followed as described above, were sampled up to 70 and 80% reaction. In anhydrous acetone, the exchange proceeds to near completion, where at 6 reaction half-lives the distribution of radiochlorine between RCl and $HgCl_2$ is 96.5% of the calculated amount. The integrated second-order rate constants calculated as above were constant within a run. The k_e values are significantly lower than the corresponding k_α values and the differences vary with the $HgCl_2$ concentration. As in the racemization reaction, the k_e values do not plot linearly with $[HgCl_2]$ but again deviate upward from linearity with increasing $HgCl_2$ concentration. These values can be fit to within 3% by the two-term expression given in eq 7.

The exchange rate constants for the reactions measured in the presence of 2.22 M H_2O were calculated using eq 8, where the value of $e^{-k_t t}$ at time t calculated using the measured k_t. Inspection of Table II brings out the fact that, in contrast to the reaction in anhydrous acetone, the k_e values are now linearly related to $[HgCl_2]$.

$$\frac{k_e}{2[HgCl_2]} = k_{2e} \frac{2.303}{([RCl] + 2[HgCl_2])t} \log\left[1 - \gamma \frac{[RCl] + 2[HgCl_2]}{[RCl]e^{-k_t t}}\right] \quad (8)$$

The rate of solvolysis of 1-phenylethyl chloride in acetone containing 2.22 M H_2O and $HgCl_2$ was followed by titrating the produced HCl with sodium methoxide to a Bromophenol Blue end point. The reaction followed good second-order kinetics and proceeded to 97% completion. The pseudo first-order k_t values given by the product of the second-order k and $[HgCl_2]$ are listed in Table II.

$$RCl + H_2O + HgCl_2 \longrightarrow ROH + H^+ + HgCl_3^- \quad k_t \quad (9)$$

Discussion

In considering the reactions of 1-phenylethyl chloride promoted by $CoCl_2$ and by $HgCl_2$ in acetone at 50° the reaction in the absence of salt is neglected, since even in CH_3NO_2 at 100° k_α is only 1.2×10^{-5} sec^{-1}.[7] The $CoCl_2$-promoted ionization reaction of 1-phenylethyl chloride in anhydrous acetone at 50.0° is reminiscent of the $HgCl_2$-promoted reactions of *p*-chlorobenzhydryl chloride in the same solvent.[3a] Thus $CoCl_2$ efficiently promotes the ionization reaction and is *ca.* 4–5 times a better catalyst than $HgCl_2$ at 0.01 M salt concentration in anhydrous acetone. The promoted reaction shows a linear dependence on $CoCl_2$ concentration where the racemization and exchange reactions differ in the ratio $k_{rac}/k_e = 1.54 \pm 0.09$. As in the case with $HgCl_2$, racemization and exchange in the promoted reaction proceed *via* ion pairs, $R^+//CoCl_3^-$, like I, which do not exchange the anion with the other $CoCl_2$ present in solution and which will equilibrate the two faces of the cation when and only when the three chlorine atoms on cobalt become equivalent. Therefore the probability of incorporating radiochlorine into the regenerated RCl is ⅔ as given by the constitution of the chlorine atoms on the anion.

Scheme I

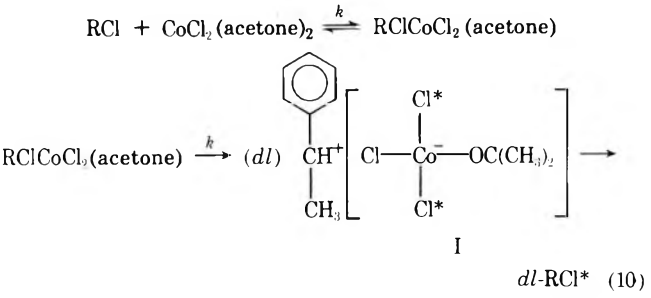


Table III
Comparison of Racemization and Exchange Rate Constants for 1-Phenylethyl Chloride in Acetone at 50.0°

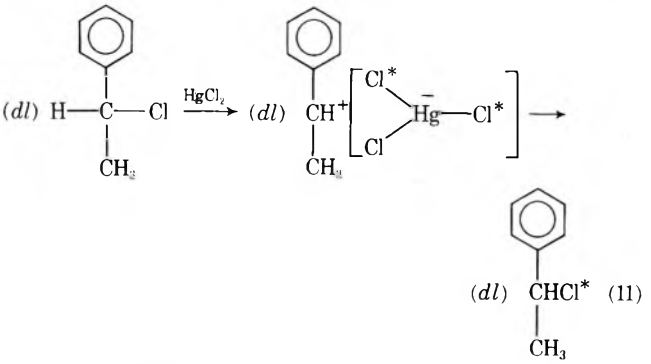
$[HgCl_2]$, M	k	$10^6 k$, sec^{-1} k_{rac}	k_e	k_{rac}/k_e	Per cent of reaction
0.01	Observed	8.23	5.60	1.47	
	Monomer	7.4	4.9	1.51	90
	Dimer	0.83	0.5	(1.2)	10
0.1	Observed	153	129	1.19	
	Monomer	74	49	1.51	48
	Dimer	79	80	0.99	52

The solution of $CoCl_2$ in anhydrous acetone is blue, suggesting the tetrahedral arrangement of two chlorine atoms and two acetone molecules around the cobalt atom. Thus, the overall reaction must involve a rapid and reversible displacement of acetone on cobalt by RCl followed by the rate-determining ionization of the RCl complex to give an intermediate like I which generates racemic RCl (Scheme I).

In the reactions with $HgCl_2$, both k_{rac} and k_e deviate upwardly from linearity with increasing $HgCl_2$ concentration. The k_α values are greater than the k_e values where the k_{rac}/k_e ratio decreases from 1.47 at 0.01 M $HgCl_2$ to 1.19 at 0.1 M $HgCl_2$. The ratio of 1.47 at the lower $HgCl_2$ concentration approximates the 3:2 ratio observed previously,[3a] suggesting a similarity in the nature of the ion pairs which give rise to racemization and exchange in the two systems. The ratio at the higher concentration is more difficult to interpret; however, if a kinetic dissection of the overall reaction is interpreted as the presence of two discrete reactions[5] which proceed *independently,* one being the reaction promoted by monomeric $HgCl_2$ (k_2) and the other a reaction involving two molecules of $HgCl_2$ (k_3), then the data will be easier to understand.

From such a dissection one calculates with the aid of eq 5 that at 0.1 M $HgCl_2$ the ionization of 1-phenylethyl chloride occurs *ca.* 48% with monomeric $HgCl_2$, where the k_{rac}/k_e ratio is 1.5 (Table III). Thus, racemization and exchange proceed *via* intermediates like I which do not dis-

sociate and do not exchange with the rest of the $HgCl_2$ present in solution.



(11)

The remaining 52% of the reaction is promoted by $HgCl_2$ involving two molecules where the k_{rac}/k_e ratio is 1. In this reaction the rates of racemization and exchange are equal. Efficient ion-pair dissociation in the reaction with the dimeric form of $HgCl_2$ will make the rates of racemization and exchange equal. Chemical capture of the ion pair II (Scheme II) by $HgCl_2$ will permit the chlorine atoms originally from RCl to become randomized with the total inorganic chloride pool (eq 12) before the ions recombine to regenerate racemic RCl. In line with this explanation is the expectation that an ion like $(HgCl_3HgCl_2)^-$ in the ion pair II will be more susceptible to dissociation and exchange than the anion in an ion pair like I. Therefore, at 0.1 *M* $HgCl_2$ the racemization in excess of exchange observed in the overall reaction appears to be wholly accountable by the reaction with monomeric $HgCl_2$.

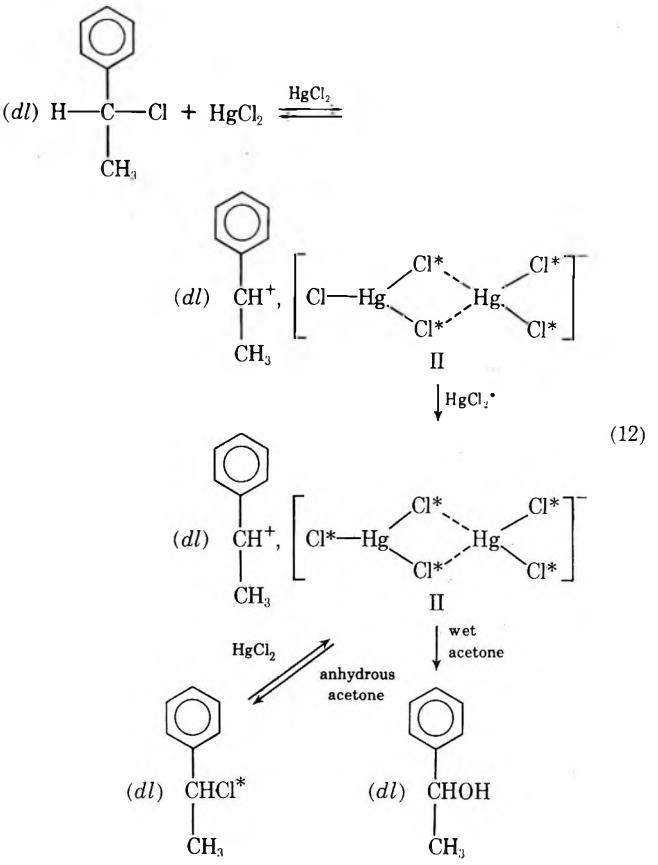
This kinetic behavior is in sharp contrast to that observed with the less endothermic benzhydryl chloride system, where k_α is linear in $[HgCl_2]$ up to 0.15 *M*. In the present case the termolecular term contributes 10% of the overall reaction already at 0.01 *M* $HgCl_2$.

This reaction was further studied in wet acetone, since the presence of a nucleophile such as water which can yield a chemical product will further test this theory on the relative susceptibilities of the two intermediates toward chemical capture. The presence of 2.22 *M* H_2O causes a small rate increase in the overall reaction. In considering our data no correction is made for the unpromoted reaction, since its contribution is small, where the value of k_t is *ca.* 1×10^{-6} sec^{-1}.[8,9] At 0.05 *M* $HgCl_2$, the k_t/k_α ratio indicates that *ca.* 35% of the reaction intermediates give rise to product (f = 0.35) and *ca.* 65% return to regenerate RCl. The intermediates that return to RCl must have the same constitution as I and must involve the reaction with monomeric $HgCl_2$, since k_{rac} and k_e are linear in $[HgCl_2]$ and the k_{rac}/k_e ratio is 3:2 (1.50 ± 0.04). See Table II.

While it is not clear how product is formed, one may expect by analogy with the benzhydryl system that those intermediates that dissociate will collapse to give product almost exclusively.[3a] Therefore, return to RCl from intermediates like II is effectively eliminated owing to efficient chemical capture of the intermediates by H_2O (eq 12). It seems consistent that the racemization process, loss of optical activity in *excess* of that which occurs *via* ion pair *dissociation* as measured either by exchange (anhydrous acetone) or solvolysis (wet acetone), involves the reaction with monomeric $HgCl_2$ to produce an ion pair like I. The role of the second molecule of $HgCl_2$ is depicted by Satchell as one of specific solvation rather than promotion of the ionization reaction by incipient dimer formation.[4]

Thus, while in the $HgCl_2$-promoted reactions of *p*-chlorobenzhydryl chloride, dissociation of the intermediates

Scheme II



(12)

was increased by solvent variation,[3a] with 1-phenylethyl chloride in anhydrous acetone, dissociation is increased by specific solvation of the $HgCl_3^-$ anion of the ion pair by a second molecule of $HgCl_2$.

While we do not intend to extend this study to higher $HgCl_2$ concentrations, it seems informative to discuss at this time the results of Read and Taylor.[5] These authors measured the rates of loss of optical activity and solvolysis of 1-phenylethyl chloride in acetone containing 2.78 *M* H_2O at 20°. Rate constants were calculated using their experimental data and are listed in Table II. The k_t values are more appropriately calculated using the second-order rate expression. Only the k_t values for the first 25–50% reaction are considered since at longer reaction times the k values drift down, probably owing to drastic changes in the reaction media arising from the relative low $H_2O/HgCl_2$ concentration ratio. Some of the drift may be due to common-ion rate depression.[10] The polarimetric runs were calculated using eq 2 and omitting the initial extrapolated polarimetic readings. In contrast to the k values calculated by the original authors, the run shows good pseudo-first-order k values with no apparent drift.

The results at these high $HgCl_2$ concentrations should be readily explicable based on the above discussion. Thus the reaction should proceed mostly *via* intermediates like II which are dissociated and primarily racemic. Accordingly, product formation at 0.3–1.2 *M* $HgCl_2$ is very efficient, f = 0.91–0.95, where the amount of ion pair return accompanying the reaction is minimal, $1 - f$ being *ca.* 0.07. In line with this we observe very little exchange accompanying the solvolysis reaction at 1.20 *M* $HgCl_2$ where k_e/k_t equals *ca.* 0.003. However, racemization is not complete in the intermediates, since the final ROH product is slightly inverted.[5] Therefore the results at these high $HgCl_2$ concentration are fit by a mechanism where racemization and hydrolysis occur *via* the same reaction pathway. This interpretation differs from the one originally

proposed by the authors where the mechanisms for racemization and hydrolysis were considered distinct.[5]

Ion-pair intermediates are also important in reactions promoted by $SnCl_4$. Thus, the $SnCl_4$-promoted racemization of optically active 1-phenylethyl chloride in CCl_4 containing excess styrene was reported by Heald and Williams.[11] Here, 1-phenylethyl chloride reacts with styrene to form styrene dimer *ca.* 36 times slower than it undergoes racemization, where the addition of styrene has no apparent effect on the rate of racemization. The authors described the reaction as proceeding by an ionization mechanism to produce a carbonium ion pair intermediate which regenerates racemic RCl more efficiently than it combines with styrene to form dimer. In this system, $1 - f$ is *ca.* 0.97.

$$(-)\text{-RCl} + SnCl_4 \rightleftharpoons (-)\text{-}R^+SnCl_5^- \xrightarrow[f]{\text{styrene}} \text{dimer}$$

$$\swarrow 1 - f$$

$$\text{(racemic) RCl} + SnCl_4$$

Experimental Section

Optically active 1-phenylethyl chloride was prepared from the resolved carbinol[12] using thionyl chloride.[13] The reaction mixture was dissolved in pentane and the pentane solution of RCl was washed carefully with aqueous $NaHCO_3$. The solution was dried over K_2CO_3 and the pentane was evaporated at reduced pressure. The alkyl chloride was used as such without further purification, chloride analysis 99.9% Cl, $[\alpha]_{589} - 8.8$.

Mercuric chloride was sublimed before use. Radiolabeled mercuric chloride was prepared using 0.25 *N* radiolabeled (^{36}Cl) hydrochloric acid as previously described.[3c] Reagent grade $CoCl_2 \cdot 6H_2O$ was dried over P_2O_5 in an Abderhalder drying apparatus at 110° (1 mm) before use. Radiolabeled cobalt(II) chloride was prepared by mixing 1 g of $CoCl_2$ with 0.1 ml of 0.25 *N* radiolabeled (^{36}Cl) hydrochloric acid in 10 ml of dry methanol. The methanol was next removed under reduced pressure and the recovered solid was dried at 110° (1 mm) for 2 days. The salt was neutral to Bromophenol Blue indicator in acetone. The activity of the sample was 2920 cpm/mg.

The solvents were prepared as previously described.[14]

The polarimetric rate measurements were made in a thermostated 1-dm all-glass cell using a Perkin-Elmer polarimeter, Model 141. The wavelengths used were 589 and 436 nm for runs with $HgCl_2$ and $CoCl_2$, respectively.

The exchange rate measurements were carried out using a sealed ampoule technique as previously described.[3c] The separation of organic chloride from inorganic chloride was afforded using pentane and water. Two-milliliter aliquots from each layer were delivered into 10 ml of Bray's solution[15] and the radioactivity level was measured using a Beckman LS100 Liquid Scintillation Counter.

The titrimetric rate measurements were carried out using a sealed-ampoule technique.[3c] Five-milliliter aliquots were titrated to the blue end point of Bromophenol Blue with 0.01095 *M* sodium methoxide in methanol solution.

Registry No.—$HgCl_2$, 7487-94-7; $CoCl_2$, 7646-79-9; 1-phenylethyl chloride, 72-65-1.

References and Notes

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Arene–Metal Complexes. VII. Stereoselective Catalytic Deuteration of *syn*-(Dibenzobicyclo[2.2.2]octatriene)tricarbonylchromium[1]

Walter S. Trahanovsky* and Charles Robert Baumann

Department of Chemistry, Iowa State University of Science and Technology, Ames, Iowa 50010

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The palladium on charcoal catalyzed deuteration of *syn*-(dibenzobicyclo[2.2.2]octatriene)tricarbonylchromium (1) in dioxane gave a high yield of *syn*-(dibenzobicyclo[2.2.2]octadiene)tricarbonylchromium which was predominantly a d_2 species with both of the deuteriums on the ethano bridge and anti to the tricarbonylchromium moiety. Deuteration of 1 and uncomplexed dibenzobicyclo[2.2.2]octatriene (2) was shown to go without rearrangement to the bicyclo[3.2.1]octane system or significant bridgehead hydrogen exchange. The predominantly anti addition of the deuteriums to 1 appears to be a result of the tricarbonylchromium moiety serving as a blocking group to shield one face of the carbon–carbon double bond.

Tricarbonylchromium groups complexed to benzene rings have been shown to exert electronic and conformational effects.[1a] In this report we describe a study of an addition reaction to a double bond of an arene–tricarbonylchromium complex that has one of its faces shielded by the metal moiety. The results of this study indicate that the metal moiety exerts a steric effect and serves as a blocking group and thus addition occurs predominantly to the unshielded face of the carbon–carbon double bond.

Results

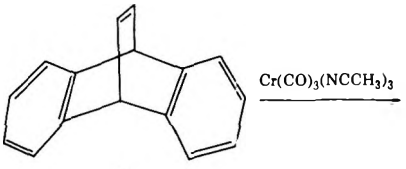
syn-(Dibenzobicyclo[2.2.2]octatriene)tricarbonylchromium (1) was prepared in moderate yield by refluxing the

Table I
Deuterium Content of Dibenzobicyclo[2.2.2]octadiene Obtained from Deuteration of 1 followed by Decomplexation of the Purified Product 3[a]

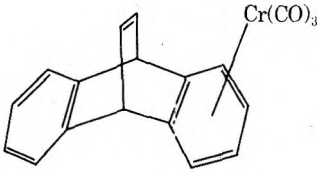
Run	Yield of deuterated species, % d_0	d_1	d_2	Deuterium incorporation, %
1	12.4	25.1	62.5	75.1
2	8.9	23.0	68.1	79.5
3	8.2	23.2	68.6	80.2

[a] Determined by mass spectroscopy with correction for normal isotopes.

free arene 2 with triacetonitriletricarbonylchromium in dioxane. Chemical analysis and the mass spectrum of 1

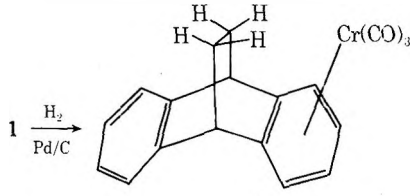


2



1

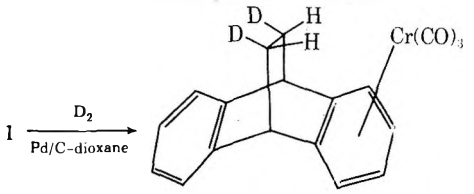
indicated that it contained only one tricarbonylchromium moiety. Oxidation of with ferric ion in 95% ethanol gave a high yield of 2, which shows that the arene did not rearrange upon complexation. The nmr spectrum of 1[2] confirms its constitution and the stereochemistry of 1 was indicated by the conversion of 1 to 3 by the addition of hydrogen to the etheno bridge. The nmr spectrum of 3[2]



3

shows that the signals for the two sets of ethano hydrogen atoms are separated by 0.5 ppm (at δ 2.2 and 1.7). In order to get a shift this large, the tricarbonylchromium moiety must be syn to the ethano bridge.[3,4] The lower field signal (δ 2.2) was assigned to the protons syn to the tricarbonylchromium group, since protons which are closer to the tricarbonylchromium group are generally shifted downfield.[3,4]

Catalytic hydrogenation of 1 in dioxane over palladium on charcoal (Pd/C) gave 87% of 3 and 13% of the uncomplexed dibenzobicyclo[2.2.2]octadiene (4). Yields were determined by nmr analysis using bibenzyl as an internal standard.



Catalytic deuteration of 1 under similar conditions followed by removal of decomplexed material by chromatography gave complex 3 which appeared, by nmr, to be largely dideuterated with both deuteriums on the ethano bridge anti to the metal moiety; the nmr spectrum of the product showed only small absorption at δ 1.7 (anti protons) and a board singlet at δ 2.2 (syn protons).[2]

Table II
Calculated and Measured R[a] Values from the Deuteration of 1

Run	R, calcd[b]	R, measured[c]
1	4.0	5.0
2	4.9	7.2
3	5.1	7.4

[a] Defined as the ratio of syn bridge protons to anti bridge protons of 3. [b] From mass spectral data. [c] By nmr.

Quantitative determination of the ratio of syn to anti addition of deuterium was difficult for two reasons. First, a small amount of impurities in the complexed product of deuteration made integration of the signal due to the anti protons impossible. Therefore, the chromium was oxidatively removed from deuterated 3 and the amount of bridge protons relative to bridgehead protons of 4 was determined by nmr. The amount of anti photons of deuterated 3 was obtained by measuring the amount of syn protons to bridgehead protons of deuterated 3 and substracting this number from the total bridge protons determined from the nmr spectrum of deuterated 4.

The second reason that it was difficult to determine the ratio of syn to anti addition was that the deuterated product was not entirely the d_2 species, since some protons were also added to 1. In Table I are presented the amounts of the d_0, d_1, and d_2 species determined from the mass spectra of three runs of decomplexed deuterated 3. No species greater than d_2 were observed. From the data in Table I it is seen that only 75–80% deuterium was added. Evidently this reflects a large isotope effect[5] on the catalytic addition of hydrogen and deuterium, since the deuterium gas used was relatively pure and there was no other definite source of hydrogen, although traces of water or some hydrogen–deuterium exchange with solvent molecules could have increased the amount of hydrogen available. If it is assumed that no syn addition occurs, then the ratio of syn to anti bridge protons, R, is given by eq 1. In Table II are presented for three runs the R values

$$\frac{\text{syn H}}{\text{anti H}} \equiv R = \frac{2(\%d_0 + \%d_1 + \%d_2)}{2(\%d_0) + 1(\%d_1)} \quad (1)$$

calculated from the mass spectral data and those determined from the nmr data. It is seen from these values that the observed values are actually higher than the calculated ones. Since the calculated values are maximum ones (because 100% anti addition was assumed), the larger measured values must reflect errors in the nmr measurements. The nmr measurements could easily be in error by 5% and if the integral of the signal for the syn protons is increased by 5% and that for anti protons is decreased by 5%, the R values for the three runs become 3.1, 3.8, and 4.9, respectively. These values are now below the calculated values but can be accounted for by only 1–8% syn addition.

In conclusion, then, we feel that our data clearly indicate that the addition of deuterium occurs mainly and possibly exclusively to the face of the carbon–carbon double bond which is anti to the tricarbonylchromium group.

For the sake of comparison, dibenzobicyclo[2.2.2]octatriene (2) was also deuterated under identical conditions. As shown in Table III, the distribution and per cent incorporation of deuterium compare favorably with the results obtained from the deuteration of complex 1. Small amounts of d_3 and d_4 species were observed from the deuteration of 2 but not from the deuteration of complex 1.

Table III
Deuterium Content of Dibenzobicyclo[2.2.2]octadiene Obtained from Deuteration of 2[a]

Run	Yield of deuterated species, % d_0	d_1	d_2	d_3	d_4	Deuterium incorporation, %
1	16.7	17.8	62.2	2.9	0.4	76.3
2	15.8	20.1	58.7	4.7	0.7	77.3

[a] See Table I, footnote *a*.

Table IV
Nmr Data of Deuterated Dibenzobicyclo[2.2.2]octadiene Obtained from Deuteration of 1 and 2

Run	Number of protons: Aromatic[a]	Bridgehead	Bridge
1[b]	8.00	1.96	2.54
2[b]	8.00	1.97	2.44
3[b]	8.00	2.01	2.39
1[c]	8.00	1.98	2.49
2[c]	8.00	1.91	2.54

[a] Integration of the aromatic region was set equal to 8.00 protons. [b] Obtained from deuteration of **1** followed by decomplexation of **3**. [c] Obtained from deuteration of **2**.

This suggests that a small amount of bridgehead exchange occurs with **2** but not with **1**.

The nmr data of deuterated **4** obtained from deuteration of **1**—decomplexation of **3**—and deuteration of **2** are given in Table IV. These data indicate that the two routes are identical. The average value for the bridgehead protons obtained from **2** are slightly lower, as they should be if bridgehead exchange occurred, but within the range given by the error associated with measurement of an nmr integral.

The inflated number of bridge protons for each run given in Table IV is consistent with deuterium incorporation as determined from the mass spectra.

Discussion

There are three main results from this deuteration study. First, catalytic addition of hydrogen to the dibenzobicyclo[2.2.2]octatriene ring system, whether complexed or uncomplexed, was unaccompanied by rearrangement to the bicyclo[3.2.1]octane system. Second, no significant amount of bridgehead hydrogen exchanged occurred during the deuteration of either the complexed or uncomplexed arene. Third, the tricarbonylchromium group effectively shielded one face of the carbon–carbon double bond and resulted primarily in addition of deuterium from the other face of the double bond (anti addition).

The propensity of dibenzo[2.2.2]octatriene for rearrangement accompanying ionic addition[6] as well as free-radical addition[7] to the double bond is well known. The lack of rearrangement during the catalytic reduction[8] indicates that nothing special occurs with this system and the normal Horiuti–Polanyi mechanism[10] can be invoked.

The lack of any significant amount of bridgehead hydrogen exchange is consistent with the mechanisms generally accepted for hydrogen–deuterium exchange reactions for olefins.[11-13] Catalytic deuteration of the bicyclo[2.2.1]heptene system has also been shown to go without exchange of bridgehead hydrogen atoms.[14]

A drawing of complex **1** was constructed from a Dreiding model of the uncomplexed arene **2** and the bond lengths and angles obtained from an X-ray diffraction study of (benzene)tricarbonylchromium.[15] Recently Mills reinterpreted the X-ray crystallographic data of several ortho-disubstituted complexed rings and concluded that the complexed rings are folded slightly (4° for six-membered rings) such that the two substituted ring carbon atoms are further away from the chromium than the other four ring atoms.[16] With or without the folding it is clear from our drawing that the tricarbonylchromium group shields one face of the carbon–carbon double bond; the distances between the midpoint of the etheno bridge and the carbonyl oxygen, the carbonyl carbon, and the chromium atoms are *ca.* 2.5, 2.5, and 3.5 Å, respectively (with the carbonyl group at its closest distance to the etheno bridge). The fact that the addition of the deuterium to complex **1** is predominantly anti indicates that the tricarbonylchromium moiety serves simply as a blocking group. Its presence prevents the catalyst from complexing with the syn face of the double bond.

Use of the tricarbonylchromium group as a blocking group could serve not only to force the stereoselectivity of a cis addition, but it is conceivable that it could force an addition reaction which is normally trans to become cis.

Experimental Section

Most equipment, materials, and methods have been previously described.[1a]

Dibenzobicyclo[2.2.2]octatriene (9,10-etheno-9,10-dihydroanthracene, 2) was prepared by the procedure of Cristol and Lim:[17] mp 118–120° (lit.[17] mp 119–120°); nmr ($CDCl_3$) δ 7.24 (m, 4), 6.98 (m, 2, -CH=CH-), 6.88 (m, 4), and 5.06 (d of d, 2).

Dibenzobicyclo[2.2.2]octadiene (9,10-ethano-9,10-dihydroanthracene, 4). A mixture of 0.49 mmol of **2** and 0.10 g of 10% palladium on charcoal in 20 ml of absolute ethanol was stirred under 1 atm of hydrogen until the hydrogen uptake ceased. A routine work-up gave a quantitative yield of white crystals, nmr ($CDCl_3$) δ 7.19 (m, 4), 7.04 (m, 4), 4.28 (poorly resolved quintet, 2), and 1.67 (t, 4), which agrees very well with the literature[18] nmr.

***syn*-(Dibenzobicyclo[2.2.2]octatriene)tricarbonylchromium (1).** A quantity of 4 g of **2** and triacetonitriletricarbonylchromium, prepared[19] from 2.1 g of hexacarbonylchromium, in 15 ml of dioxane (distilled from $LiAlH_4$) was heated to reflux for 14 min in a Strohmeier apparatus.[20] The reaction mixture was cooled to 25° and filtered through Celite. The filtrate was washed with three 200-ml portions of water, dried ($MgSO_4$), and concentrated. The residue was triturated with five 50-ml portions of pentane (to remove **2**), dissolved in 10 ml of boiling methylene chloride, and crystallized by adding pentane to the methylene chloride solution. A quantity of 1.5 g (44%) of yellow needle crystals was obtained which was recrystallized from methylene chloride–pentane: mp 184.5–185.5° (lit.[21] mp 175°, 186° dec); nmr[2] ($CDCl_3$) δ 7.23 (m, 2), 6.98 (m, 4), 5.67 (m, 2), 5.02 (m, 2), and 4.83 (t, 2).

Anal. Calcd for $C_{19}H_{12}O_3Cr$: C, 67.06; H, 3.53. Found: C, 66.89; H, 3.51.

Procedure for Catalytic Deuterations in Dioxane. Dioxane was purified[22] and stored under nitrogen.

Into a clean, dry hydrogenation flask, a 50-ml erlenmeyer flask with a 4-ml addition funnel and stopcock attached to its side was placed a magnetic stirring bar, 0.135 g of 10% palladium on charcoal (Matheson Coleman and Bell), and 6–7 ml of dioxane. The flask was attached to the hydrogen apparatus[23] and the system was flushed with deuterium gas (Matheson Coleman and Bell) for 25 min. The catalyst was reduced by stirring and then a solution of 0.265 mmol of the olefin in 2–3 ml of dioxane was added *via* the side arm. A little more dioxane was added to the flask until the final volume was 12–13 ml. The mixture was then stirred vigorously until the uptake of deuterium ceased.

Work-up for Measuring the Syn to Anti Addition of Deuterium to 1. The reaction mixture was filtered through Celite with gentle suction and the filter was then washed with dioxane. The solvent of the filtrate was removed on a rotary evaporator and the yellow solid was chromatographed on 26 g of silica gel using methylene chloride to transfer the solid to the column and pentane, and 10 and 50% methylene chloride–pentane mixtures as the eluents. An nmr spectrum of the yellow complex **3** was taken after the solvent was removed under vacuum. The complex was then transferred to a flask using methylene chloride, the solution was concentrated, and the residue was dissolved in 5 ml of 95% ethanol. To this solution was added 1.59 mmol of ferric chloride in 5 ml of ethanol. The solution was allowed to stand overnight and then a routine ether extraction gave **4** as a white solid, which was then analyzed by mass spectroscopy and nmr.

Work-up for Measuring the Absolute Yield of Products from 1. The reaction mixture was filtered and to the filtrate was added 0.124 mmol of bibenzyl[24] as an nmr standard. The solvent was carefully removed on a rotary evaporator.[25] The residue was completely dissolved in $CDCl_3$ and analyzed by nmr.

Work-up for Uncomplexed Materials. After filtration, a routine ether extraction was carried out and the residue was analyzed by mass spectroscopy and nmr.

Acknowledgment. We wish to thank Professor M. D. Rausch and Dr. G. A. Moser for making their results available to us prior to publication.

Registry No.—**1**, 51286-77-2; **2**, 2734-13-6; **3**, 51286-78-3; **3**-d_2, 51349-37-2; **4**, 5675-64-9; $Cr(CO)_3(NCCH_3)_3$, 22736-49-8.

Supplementary Material Available. The 100-MHz pmr spectra in $CDCl_3$ of **1**, **3**, and the tricarbonylchromium complexed products from the deuteration of **1** (mainly **3**-d_2 with the deuteriums on the ethano bridge anti to the tricarbonylchromium group) will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-1920.

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(24) When 1,1,2,2-tetrachloroethane was used as the standard, it caused decomposition of the complex.
(25) When the dioxane was removed by washing an ether solution of the complex several times with water followed by drying with $MgSO_4$, the complex unexplainably decomposed upon removal of the ether on the rotary evaporator.

Phase-Transfer Catalyzed Synthesis of Dimethylvinylidenecyclopropane Derivatives in Aqueous Medium[1]

Tadashi Sasaki,* Shoji Eguchi, and Tetsuo Ogawa

Institute of Applied Organic Chemistry, Faculty of Engineering, Nagoya University, Furo-cho, Chikusa-ku, Nagoya, 464, Japan

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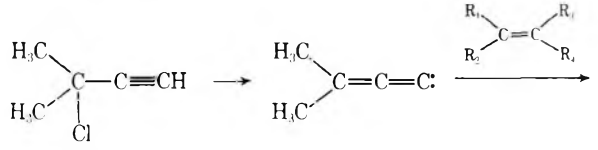
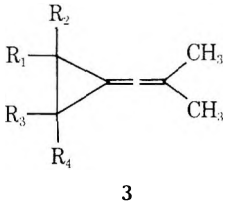
Phase-transfer catalyzed synthesis of dimethylvinylidenecyclopropane derivatives in aqueous medium from 3-chloro-3-methyl-1-butyne (**1**) and various olefins are described. Slow addition of **1** to a stirred mixture of 51% aqueous potassium hydroxide, benzene, and an appropriate substrate olefin (3-molar excess to **1**) in the presence of benzyltriethylammonium chloride as a catalyst afforded the corresponding dimethylvinylidenecyclopropane in moderate yields.

Since Hartzler's report on the generation of dimethylvinylidenecarbene (**2**) from 3-chloro-3-methyl-1-butyne (**1**) or 1-chloro-3-methyl-1,2-butadiene *via* base-catalyzed γ- or α-eliminations of hydrogen chloride, and on its reaction with some simple olefins (eq 1),[2-4] his procedure has been used widely for preparation of alkenylidenecyclopropane derivatives.[5] However, cyclopropanation of olefins with this carbene generally proceeds in low yield owing to the relatively low electrophilic reactivity of the carbene.[2,6] Furthermore, Hartzler's procedure requires rigorously anhydrous conditions for generation of the carbene **2**. This paper describes a convenient method for the generation of **2** in aqueous medium by the phase-transfer technique, and its wide applicability to the synthesis of various dimethylvinylidenecyclopropane derivatives.[7,8]



1 **2**



3 (1)

Results and Discussion

Reaction with Styrene under Various Conditions. In order to find the optimum conditions for the cyclopropanation of olefins with **2**, **1** was added to a stirred mixture of 51% aqueous potassium hydroxide[9] and styrene under several conditions (eq 2). The results are given in Table I. The best yield of the adduct 1-dimethylvinylidene [or -(2-methylpropenylidene)] -2-phenylcyclopropane (**4**)[2a] was

Table I
Yield Data of 4 under Various Conditions[a]

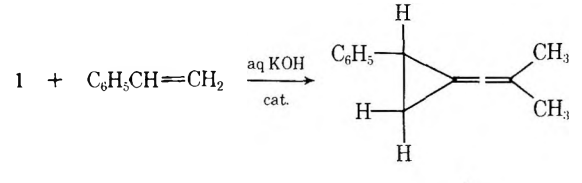
Run no.	Base	Catalyst	Solvent	Reaction temp, °C	Time,[b] hr	Stirring method	Yield, %[c]
1	51% aq KOH	$Me(CH_2)_{15}\overset{+}{N}Me_3Br^-$	*n*-Hexane	20–25	15	Magnetic	27.3
2	51% aq KOH	$C_6H_5CH_2\overset{+}{N}Et_3Cl^-$	*n*-Hexane	20–25	15	Magnetic	30.0
3	51% aq KOH	$C_6H_5CH_2\overset{+}{N}Et_3Cl^-$	Benzene	20–25	15	Magnetic	38.6
4	51% aq KOH	$C_6H_5CH_2\overset{+}{N}Et_3Cl^-$	Benzene	20–25	15	Mechanical	60.1
5	51% aq KOH	$C_6H_5CH_2\overset{+}{N}Et_3Cl^-$	Benzene	7–10	15	Mechanical	60.7
6	51% aq KOH	$C_6H_5CH_2\overset{+}{N}Et_3Cl^-$	Benzene	15–18	3	Mechanical	50.0
7	51% aq KOH	$C_6H_5CH_2\overset{+}{N}Et_3Cl^-$	Benzene	15–18	8	Mechanical	61.0
8	51% aq KOH	$C_6H_5CH_2\overset{+}{N}Et_3Cl^-$	Benzene	15–18	23	Mechanical	60.0
9	51% aq KOH	$C_6H_5CH_2\overset{+}{N}Et_3Cl$	Benzene	45	3	Mechanical	38.0
10	51% aq KOH	$C_6H_5CH_2\overset{+}{N}Et_3Cl^-$	Benzene	45	15	Mechanical	8.3
11	51% aq KOH	$C_6H_5CH_2\overset{+}{N}Et_3Cl^-$	Benzene	45	20	Mechanical	8.5
12	34% aq KOH	$C_6H_5CH_2\overset{+}{N}Et_3Cl^-$	Benzene	15–18	7	Mechanical	12.0
13	34% aq KOH	$C_6H_5CH_2\overset{+}{N}Et_3Cl^-$	Benzene	15–18	23	Mechanical	18.0
14	34% aq KOH	$C_6H_5CH_2\overset{+}{N}Et_3Cl^-$	Benzene	15–18	32	Mechanical	12.0
15	17% aq KOH	$C_6H_5CH_2\overset{+}{N}Et_3Cl^-$	Benzene	15–18	23	Mechanical	0
16	*t*-BuOK	None	*t*-BuOH	−10 to 0	3	Magnetic	35.0

[a] A 3.8-molar excess amount of styrene was used (see Experimental Section). [b] Addition time (*ca.* 2.5 hr) was involved. [c] Isolated yield. [d] A 48% yield was reported by Hartzler (ref 2a).

Table II
Dimethylvinylidenecyclopropane Derivatives from Various Olefins[a]

Olefin	Registry no.	Reaction temp, °C	Product	Yield, %[b]	Bp, °C (mm)	n_D (temp, °C)
α-Pinene	80-56-8	20–25	**3a**	20.0	62–65 (0.20)	1.5236 (25)
β-Pinene	127-91-3	20–25	**3b**	31.1	55–57 (0.20)	1.5247 (24)
Δ^3-Carene	13466-78-9	20–25	**3c**	20.0	58–60 (0.20)	1.5151 (23)
Camphene	79-92-5	20–25	**3d**	6.0	60–65 (0.27)	1.5227 (24)
1,5-Cyclooctadiene	111-78-4	20–25	**3e**	18.9	62–65 (0.26)	1.5424 (27)
Methallyl alcohol	513-42-8	20–25	**3f**	13.7	37–39 (0.20)	1.5096 (24)
Prenol acetate	1191-16-8	20–25	**3g**	14.5	54–56 (0.25)[c]	
Cinnamyl alcohol	104-54-1	20–25	**3h**	21.0	109–111 (0.23)	1.5805 (24)
2,5-Dimethyl-2,4-hexadiene	764-13-6	20–25	**3i**	28.5	40–44 (0.20)	1.5069 (22)
Isoprene	78-79-5	8–10	**3j** (+ **3j′**)[d]	26.0	68–72 (29)	1.5074 (24)
2,5-Dimethylhexa-1,5-dien-3-yne	3725-01-5	8–10	**3k**	38.1	55–57 (0.25)	1.5285 (23)
α-Methylstyrene	98-83-9	20–25	**3l**	51.5	61–65 (0.27)	1.5568 (30)
β-Methylstyrene	637-50-3	20–25	**3m**	35.7	60–64 (0.25)	1.5609 (24)
Indene	95-13-6	20–25	**3n**	15.9	75–77 (0.22),[e] mp 72–74°	

[a] The reaction was carried out under the conditions in run 4 in Table I. [b] Isolated yield. [c] Lit.[5a] bp 40° (0.02 mm). [d] 9:1 ratio. [e] Solidified distillate was recrystallized from ethanol.



(2)

4

obtained by slow addition of 1 (10 mmol) to a vigorously stirred mixture of 51% aqueous potassium hydroxide (50 ml), benzene (10 ml), and styrene (38.4 mmol) in the presence of a catalytic amount (150 mg) of benzyltriethylammonium chloride (BTA). The data in Table I shows that, as a phase-transfer catalyst, BTA was more effective than cetyltrimethylammonium bromide, and, as an organic solvent, benzene gave somewhat better results than *n*-hexane. Mechanical stirring was more effective than magnetic stirring. The reactions at 8–10 and at 20–25° gave similarly good results, but that at 45° gave a very low yield of **4**. This is due to some decompositions of the product **4** and to occurrence of some side reactions because several unidentified products were detectable on glc analysis. The decomposition of **4** was not serious at below 25° under the reaction conditions. Higher concentration of the base gave better results than lower ones.

Reaction of 2 with Various Olefins. Reactions of **2** with various olefinic substrates, including mono- and bicyclic olefins, olefins having alcoholic or ester functions, and conjugated olefins, were carried out under the conditions given at run 4 or 5 in Table I. These results are summarized in Table II and Chart I.

Chart I

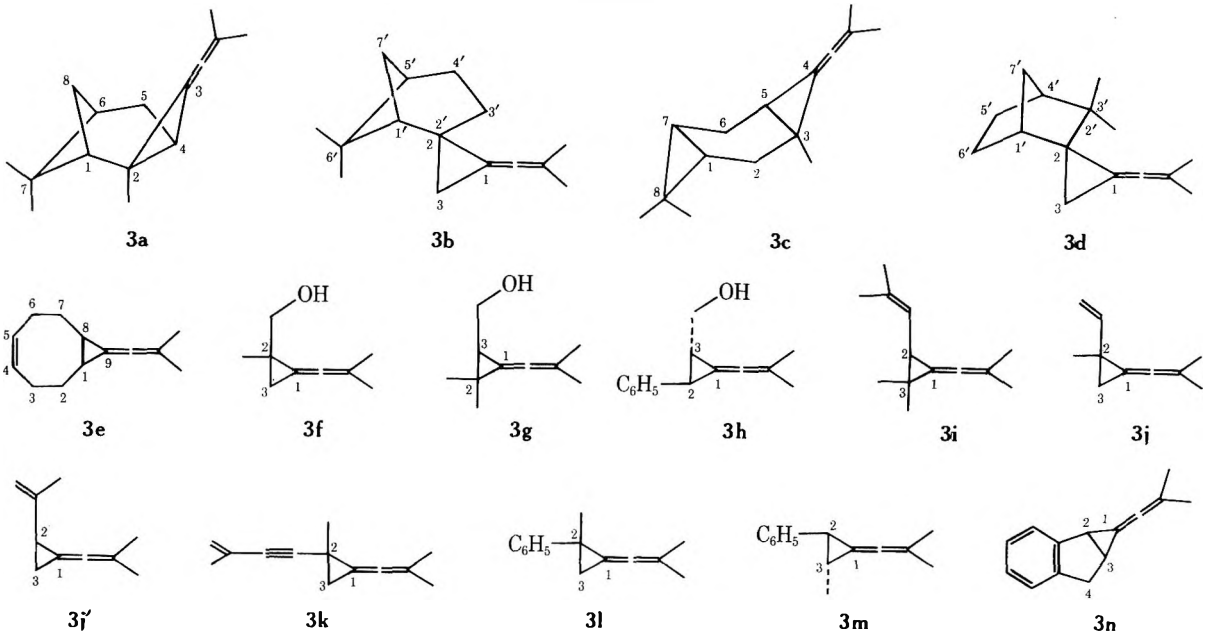


Table III
Spectral Data for Dimethylvinylidenecyclopropane Derivatives 3a–n[a,h]

Compd	Ir, cm^{-1} (neat)	Nmr chemical shift, δ (CCl_4)
3a	2010, 1450, 1370, 1030	1.75 (s, 6 H, vMe_2[b]), 1.30 (s, 6 H, C_7Me_2), 1.10 (s, 3 H, C_2Me), 1.07 (d, 1 H, J = 7 Hz, C_8H syn to C=C=C), 2.5–1.4 (m, 6 H, other H)
3b	2010, 1445, 1365, 1017	1.66 (s, 6 H, vMe_2), 1.30 (s, 2 H, C_3H_2), 1.8–1.4 (m, 2 H, $C_{1'}H$, $C_{3'\text{-endo}}H$), 1.17 (s, 3 H, $C_{6'\text{-endo}}Me$), 0.97 (s, 3 H, $C_{6'\text{-exo}}Me$), 2.4–1.7 (m, 6 H, other H)
3c	2000, 1442, 1372, 1020	1.65 (s, 6 H, vMe_2), 1.12 (s, 3 H, $C_{8\text{-endo}}Me$), 0.97 (s, 3 H, $C_{8\text{-exo}}Me$), 0.77 (s, 3 H, C_3Me), 0.40 (d, d, 1 H, J = 9.2 and 4.6 Hz, C_5H), 2.5–1.2 (m, 6 H, other H)
3d	2012, 1445, 1362, 1295, 1020	1.72 (s, 6 H, vMe_2), 0.87 (s, 6 H, C_3Me), 2.3–1.2 (m, 10 H, other H)
3e	2005, 1445	5.63–5.38 (m, 2 H, CH=CH), 1.68 (s, 6 H, vMe_2), 2.5–1.7 (m, 10 H, other H)
3f	3400, 2030, 1445, 1380, 1030	3.45 (s, 2 H, CH_2OH), 2.09 (bs,[c] 1 H, OH),[d] 1.71 (s, 6 H, vMe_2), 2.30 (s, 3 H, C_2Me), 1.5–1.12 (m, 2 H, C_3H_2)
3h	3320, 3060, 3030, 2010, 1600, 1500, 1450, 1100, 1035, 970, 750, 690	7.6–6.9 (m, 5 H, C_6H_5), 4.29 and 3.75 (each d, 2 H, J = 4.8 and 6.7 Hz, CH_2OH), 2.73 (d, 1 H, J = 4.5 Hz, C_2H) 2.4 (bs, 1 H, OH),[d] 2.35–1.9 (m, 1 H, C_3H), 1.79 (s, 6 H, vMe_2)[g]
3i	2003, 1658, 1448, 1376, 1145, 1065	4.85 (bd,[e] 1 H, J = 8.0 Hz, C=CH), 2.05 (d, 1 H, J = 8.0 Hz, C_2H), 1.64 (s, 12 H, vMe_2), C=CMe_2), 1.26 and 1.15 (each s, 6 H, C_3Me_2)
3j′	2020, 1635, 1450, 995, 895	3.9–4.8 (AB pattern, m, 3 H, $CH=CH_2$), 1.70 (s, 6 H, vMe_2), 1.45 (s, 2 H, C_3H_2), 1.31 (s, 3 H, C_2Me)
3k	3090, 2200, 2010, 1790, 1610, 1020, 890	5.07 (bs, 2 H, $C=CH_2$), 1.85–1.72 (m, 9 H, vMe_2, C=CMe), 1.66–1.37 (m, 2 H, C_3H_2), 1.40 (s, 3 H, C_2Me)
3l	3060, 3040, 2010, 1600, 1500, 1445, 1060, 1025, 760, 690	7.12 (s, 5 H, C_6H_5), 1.79 (s, 6 H, vMe_2), 1.65 (s, 3 H, C_2Me), 1.60 (s, 2 H, C_2H_2)
3m	3060, 3030, 2005, 1600, 1495, 1445, 1012, 750, 692	7.25–6.8 (m, 5 H, C_6H_5), 2.39 (d, 1 H, J = 4.5 Hz, C_2H), 1.75 (s, 6 H, vMe_2), 1.7–1.4 (m, 1 H, C_3H), 1.34 (d, 3 H, J = 6.0 Hz, C_3Me)
3n	3060, 3010, 2001, 1600, 1440, 1100, 775, 712	7.3–6.8 (m, 4 H, phenyl), 3.3–3.0 (m, 3 H, C_1H, C_4H_2), 2.7–2.4 (m, 1 H, C_3H), 1.68 and 1.55 (each s, 6 H, vMe_2)

[a] For **3g**, see ref 5a. [b] vMe_2 = C=C=CMe_3. [c] bs = broad s. [d] Disappeared on shaking with D_2O. [e] bd = broad d. [f] The signals due to isomeric **3j′** overlapped at δ 4.47 and 1.7–1.4. Glc analysis showed a 9:1 ratio of **3j**:**3j′**. [g] In $CDCl_3$. [h] Satisfactory elemental analytical data were reported for all compounds in the table.

Bicyclic monoterpene olefins such as α-pinene, β-pinene, and Δ^3-carene afforded the corresponding adducts **3a**, **3b**, and **3c**, respectively, in modest yields, but camphene gave only a very low yield of the adduct **3d**.[10] The structures of these adducts were characterized by analytical and spectral data (Table III).[11]

1,5-Cyclooctadiene afforded the adduct **3e** but norbornene as a strained olefin did not afford any isolable amount of the corresponding adduct.[12]

Olefinic alcohols such as methallyl alcohol and cinnamyl alcohol, and esters like prenol acetate, afforded the adducts **3f**, **3h**, and **3g**,[5a] respectively; the acetate group of prenol acetate was hydrolyzed simultaneously to afford **3g**, which is known to be obtained from **1** and prenol with *tert*-butoxide.[5a]

The reactions with conjugated olefins, especially those having phenyl substituents, afforded better yields of the adducts. Symmetrically substituted 2,6-dimethyl-2,4-hexadiene afforded the adduct **3i**. In the reaction with unsymmetrically substituted isoprene, a 9:1 mixture of isomeric adducts **3j** and **3j′** was obtained as demonstrated by glc and nmr analyses. Such a higher reactivity of the methyl-substituted double bond of isoprene is well known for dihalocarbenes and acyl- and carbethoxycarbenes.[13]

2,5-Dimethylhexa-1,5-dien-3-yne as an olefinic substrate conjugated with a triple bond afforded an adduct **3k** to

the end methylene group exclusively.[14] Diphenylacetylene as an acetylenic substrate did not afford any adduct, indicating considerably lower reactivity of **2** to the triple bond.

Styrene derivatives such as α-methyl- and β-methylstyrenes afforded the adducts **3l** and **3m** in moderate yields but indene as a cyclic substrate gave only a low yield of **3n**.[15]

Reactions with some other conjugated olefins such as cycloheptatriene and 4-vinylpyridine were also examined; however, no isolable amounts of the corresponding adducts were obtained.

Experimental Section[16]

Materials. 3-Chloro-3-methyl-1-butyne (**1**) was prepared by the reported method.[17] Prenol acetate (3-methylbut-2-enyl acetate) was prepared by the method of Halsall and Hands,[18] bp 55–56° (40 mm). All other olefinic substrates were commercially available and used after distillation.

General Procedure for Phase-Transfer Catalyzed Synthesis of Dimethylvinylidenecyclopropane Derivatives. In a 100-ml, three-necked flask fitted with a dropping funnel and a mechanical stirrer, a mixture of 51% (w/w) aqueous potassium hydroxide[9] (50 ml), benzene (4 ml), BTA (150 mg, 0.66 mmol), and an appropriate olefin (30 mmol) was vigorously stirred for 0.5 hr at *ca.* 25° under nitrogen. While stirring was continued, 3-chloro-3-methyl-1-butyne (**1**, 1.03 g, 10.0 mmol) in benzene (6 ml) was added slowly to the mixture over 2.5 hr. After the addition was completed, the mixture was stirred for a further 10–13 hr at 20–25°. The mixture was diluted with water (200 ml) and extracted with *n*-hexane or ether (4 × 30 ml). The combined extracts were dried (Na_2SO_4) and evaporated to afford crude adduct, which was purified by distillation under reduced pressure. The yields, boiling points, and n_D of the products **3a–n** are summarized in Table II. Spectral and analytical data are given in Table III.

Acknowledgment. The authors wish to thank Mr. Yoshihiko Tanaka, Nissin Chemical Industries, Ltd., for providing samples of **1** and some olefinic substrates and valuable suggestions.

Registry No.—**1**, 1111-97-3; **3a**, 51269-93-3; **3b**, 51269-94-4; **3c**, 51269-95-5; **3d**, 51269-96-6; **3e**, 51269-97-7; **3f**, 51269-98-8; **3g**, 32916-63-5; **3h**, 51269-99-9; **3i**, 51270-00-9; **3j**, 51270-01-0; **3j′**, 51270-02-1; **3k**, 51270-03-2; **3l**, 40922-91-6; **3m**, 33530-27-7; **3n**, 31462-23-4; **4**, 4544-23-4.

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Phosgenation of Methyl Anthranilate

Norton P. Peet* and Shyam Sunder

Dow Interdisciplinary Group, Chemical Biology Research, Dow Chemical Company, Midland, Michigan 48640

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The reaction of methyl anthranilate (**1a**) with phosgene in EtOAc produces 2-carbomethoxyanilinecarbonyl chloride (**2a**), 2-carbomethoxyphenyl isocyanate (**3a**), dimethyl 2,2′-[carbonylbis(imino)]benzoate (**4a**), methyl 2-[1,4-dihydro-2,4-dioxo-3(2*H*)-quinazolinyl]benzoate (**5a**), and isatoic anhydride (**6**), with distribution dependent upon reaction conditions. Product **2a**, **3a**, **4a**, or **6** can be obtained as the major product in excellent yield. Alternate syntheses of **5a** (and **4a**) are reported. In preparing **5a** from **4a** with polyphosphoric acid, conditions were developed which led to the exclusive formation of methyl 2-[(4-oxo-4*H*-3,1-benzoxazin-2-yl)amino]benzoate (**11**). The mechanism of isatoic anhydride formation is shown to involve the direct displacement of an ester alkyl group by chloride ion.

The reaction of methyl anthranilate (**1a**) with phosgene to produce 2-carbomethoxyphenyl isocyanate (**3a**) is well documented in the literature.[1] Although these preparations indicate the presence of at least one additional product,[2] no attempt was made to establish its identity. In a reinvestigation of the phosgenation of **1a** we have isolated and identified five products. The distribution of these products is altered rather markedly by changes in the reaction conditions.

When **1a** was treated with excess phosgene in EtOAc, the initial product was carbamoyl chloride **2a**. Carbamoyl chloride **2a** can be dehydrochlorinated to **3a** either thermally or by base treatment. When a benzene solution of carbamoyl chloride **2a** was treated with saturated K_2CO_3, distillation of the concentrated organic phase gave a good yield of isocyanate **3a**. Modest amounts of diester urea **4a**[3] and quinazolinedione **5a** were isolated from the distillation pot. Product **4a** could arise from the hydrolysis of some **2a** or **3a** to **1a** (during the base extraction) which could then react with either **2a** or **3a**. Product **5a** could have been formed from **4a** in the distillation pot by acid catalysis. Thermal elimination of HCl from **2a** also afforded **3a** in good yield, when a solution of **2a** in EtOAc was heated for 70 hr without interruption. See Scheme I.

Diester urea **4a** is a known compound[4] and its structure was readily established. This material could be prepared either by treating methyl anthranilate (**1a**) with isocyanate **3a**, or by treating **3a** with water using DME as a cosolvent.

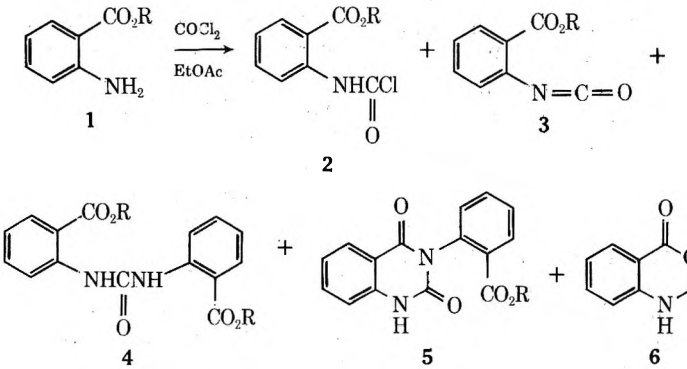
In devising an alternate route to quinazolinedione **5a**, for structural confirmation, we initially chose the route depicted in Scheme II. Several synthetic schemes for 3-substituted quinazolinediones are outlined in the literature.[5-8]

Perhaps the most obvious precursor of **5a** was the diester urea **4a**. *o*-Carboalkyoxyphenylureas have been converted, under acid-catalyzed conditions, to quinazoline-2,4-diones.[1b,9] Although we did pursue this route to **5a** (*vide infra*), it was not our first choice, since we felt that formation of the benz-3,1-oxazin-4-one ring system might be competitive.

Anthraniloylanthranilic acid (**7a**) was prepared[10] and esterified using 1-methyl-3-*p*-tolyltriazine (TMT),[11] since attempted esterification of **7a** with methanolic HCl led mainly to **7a** HCl. We found that, although ester **7b** would react with ethyl chloroformate in pyridine at reflux to give the corresponding carbamate, a nonbasic solvent with added triethylamine would not suffice. Cyclization of the carbamate to **5a** was effected with *p*-toluenesulfonic acid (HOTs) in toluene at reflux.

o-Aminobenzamides are important starting materials for the synthesis of quinazolin-4-ones and dihydroquinazo-

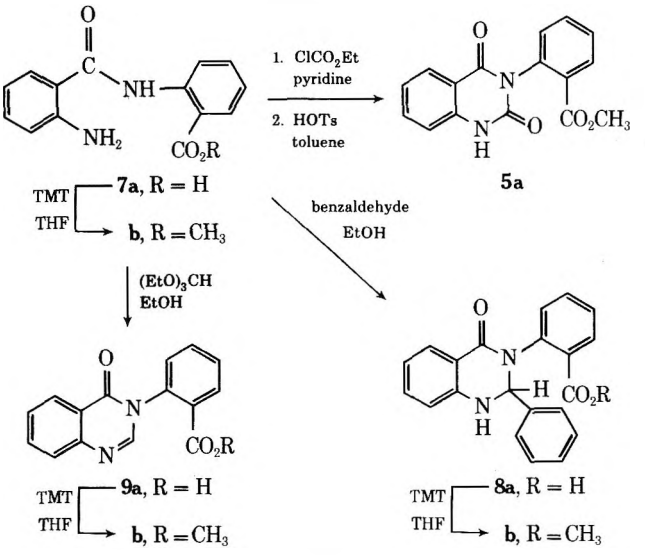
Scheme I



1 2 3 4 5 6

	Reaction conditions	Product yields, % 2	3	4	5	6	RCl
a series, R = CH_3	stir or heat briefly	100					
	heat briefly; wash with K_2CO_3		67	3.3	11		
	heat at reflux for 70 hr		70			18	
	heat for 2 hr; stir for 15 hr; heat for 2 hr		46			34	
	45–55° for 28 days		7			91	
	isolate **2**; thermolyze (neat) 100°		~20			73	?
b series, R = *n*-butyl	isolate **2**; thermolyze (neat) 100°		54			35	37

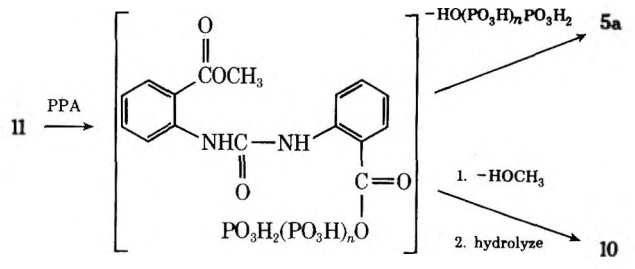
Scheme II



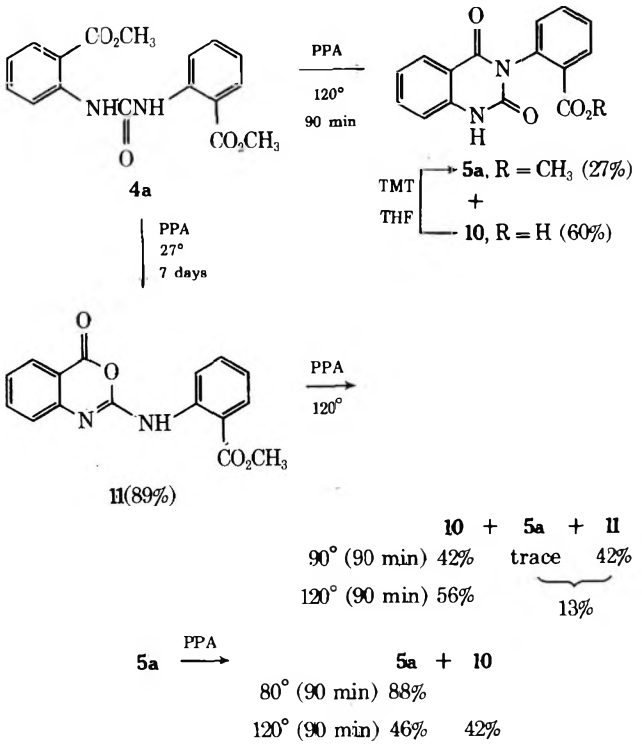
lin-4-ones. These two classes of heterocycles can be prepared by treating *o*-aminobenzamides with ortho esters[12] and aldehydes[13] or ketones,[14] respectively. Compounds **7a** and **7b** reacted readily with benzaldehyde and triethyl orthoformate to give cyclic products **8a,b** and **9a,b**, respectively, as shown in Scheme II. It should be recognized that isomeric with structures **8a** and **8b** are acyclic, Schiff base structures which are possible products of the condensation reactions. Some authors[13a] have failed to discount this possibility when making structural assignments. Our nmr data for compounds **8a** and **8b** clearly establish their structures. The methine protons for these compounds appear as sharp singlets[15] at δ 6.31 and 6.20, respectively. Aldimine protons would necessarily appear at lower field.[16]

In attempting to prepare quinazolinedione **5a** from diester urea **4a** with polyphosphoric acid (PPA), it became apparent that reaction temperature was a critical factor. When **4a** was stirred with PPA at room temperature for 7 days, benzoxazinone **11** was isolated in 89% yield. However, when **4a** was treated with PPA at 120° for 90 min, quinazolinediones **5a** and **10** were the products isolated in 27 and 60% yields, respectively. Intermediate reaction temperatures resulted in mixtures of **5a**, **10**, and **11**. These results indicate that **11** is the kinetically favored product while **5a** is favored thermodynamically.

In attempting to determine whether **11** was in intermediate in the conversion of **4a** to **5a** and to delineate the origin of **10**, benzoxazinone **11** was treated with PPA. After 90 min at 90°, equal amounts of **11** and **10** were isolated, while only the presence of **5a** in trace amounts was indicated by ir. Treatment of **11** with PPA for 90 min at 120° yielded acid **10** in 56% yield and a mixture of **5a** and **11** (indicated by ir) in 13% yield. Ester **5a** was shown to be stable in PPA at 80°, but at 120° 46% of **5a** was recovered and 42% of acid **10** was produced. These results (Scheme III) indicate that **11** is not necessarily an intermediate in the conversion of **4a** to **5a**. Although **10** can



Scheme III



	10	+ 5a	+ 11
90° (90 min)	42%	trace	42%
120° (90 min)	56%		13%

5a —PPA→

	5a	+ 10
80° (90 min)	88%	
120° (90 min)	46%	42%

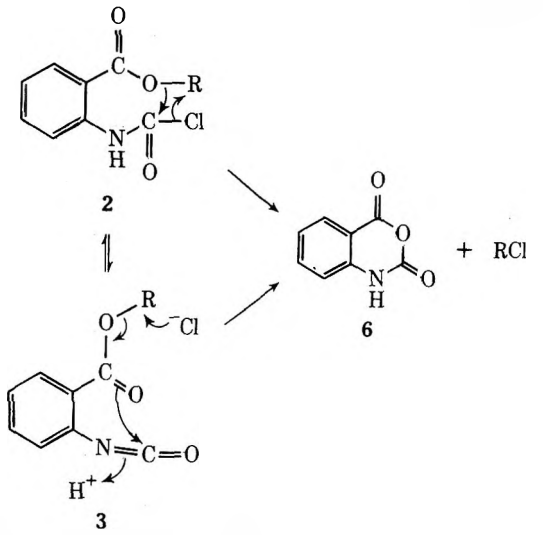
arise from **5a** as demonstrated, it might also be produced from an intermediate polyphosphoric ester originating from **11**. Cyclization of this intermediate could give both **5a** and **10**. Although none of the three possible tetracyclic products which might have arisen from **4a** and PPA by the loss of two molecules of methanol was observed, the possibility of their intermediacy (*i.e.*, in the conversion of either **11** or **5a** to **10**) cannot be excluded. One of these products has been isolated and characterized by Doleschall and Lempert[18] from the treatment of **10** with phosphoryl chloride.

Turning back to our consideration of the products obtained from the phosgenation of methyl anthranilate (**1a**), the product yet to be discussed is the most intriguing from a mechanistic standpoint. In Scheme I are shown the reactions in which isatoic anydride (**6**) was produced. Notably, when **1a** was treated with excess phosgene in EtOAc for 4 weeks, a 91% yield of **6** was obtained. These experiments indicated to us that the formation of **6** was favored either when **3a** was constrained in a chloride-rich environment for a long period of time or when **2a** was allowed to decompose at a solution temperature lower than required for its dehydrochlorination, or both.[19]

To explore the above possibilities, we isolated a sample of carbamoyl chloride **2a** and thermolyzed it (neat) at 100°. The result was a 73% yield of isatoic anhydride (**6**), with the remainder of material being mostly isocyanate **3a**. We next resubjected a sample of isocyanate **3a** to a solution of phosgene in EtOAc for 3 days at room temperature. The result was a 26% yield of **6**. In light of these results, the dual mechanistic pathway illustrated below seems reasonable.[20] However, since **2a** and **3a** are interconvertible, the possibility of **6** arising solely from **2a** or **3a** is not excluded. Imidate hydrohalides have been shown to decompose in chloroform and *tert*-butyl alcohol solutions at 60°, following first-order kinetics with respect to the disappearance of halide ion, to yield amides and haloalkanes.[21] *N*-Carboalkoxy-α-amino acid chlorides also decompose thermally to yield chloroalkanes and 2,5-oxazolidinediones.[22]

To test this mechanism, it was imperative to prove that

choloroalkane was being produced. Picking chlorobutane as our target chloroalkane for isolation, we synthesized and thermolyzed carbamoyl chloride **2b** (Scheme I). Although the ratio of isatoic anhydride (**6**) to isocyanate **3b** was different from the ratio of **6** to **3a** in the thermolysis of **2a**, **6** was isolated in 35% yield. To our satisfaction, a stoichiometric amount of chlorobutane was also isolated.



The work reported herein had its inception with the seemingly routine preparation of 2-carbomethoxyphenyl isocyanate (**3a**). The use of **3a** in the preparation of novel heterocyclic compounds will be the subject of future papers.

Experimental Section

Phosgenation of Methyl Anthranilate (1a) Followed by Treatment with K_2CO_3. A 200-g (1.32 mol) quantity of **1a** (Aldrich) in 400 ml of EtOAc was added, *via* syringe, over a period of 40 min to 400 ml of $COCl_2$ (Matheson) in 400 ml of EtOAc under a nitrogen atmosphere with ice-bath cooling and mechanical stirring. After 1 hr at reflux, the solution was concentrated, the resulting solid was dissolved in benzene, and the benzene solution was washed with saturated K_2CO_3, dried ($MgSO_4$), concentrated, and distilled to yield 156 g (67%) of **3a**, bp 99° (0.50 mm), mp 46–46.5° [lit.[1] bp 145–146° (10 mm)].

The distillation pot residue was lixiviated with benzene to remove, after concentration, 9.26 g of material which was recrystallized (heptane) to yield 7.24 g (3.3%) of dimethyl 2,2′-[carbonylbis(imino)]bisbenzoate (**4a**): mp 140–142° (lit.[4] mp 144°; ir (Nujol) 3270 (NH), 1695 (ester C=O), 1675 cm^{-1} (urea C=O); nmr ($CDCl_3$) δ 10.80 (s, 2, NH), 8.70–8.46 (m, 4, aromatic), 8.08–7.87 (m, 4, aromatic), 3.90 (s, 6, CH_3); mass spectrum (70 eV) *m/e* 177, 151.

Anal. Calcd for $C_{17}H_{16}N_2O_5$: C, 62.19; H, 4.91; N, 8.53. Found: C, 61.90; H, 4.91; N, 8.66.

The benzene-insoluble pot residue weighed 23.4 g and was recrystallized (EtOH) to yield 21.2 g (11%) of methyl 2-[1,4-dihydro-2,4-dioxo-3(2*H*)-quinazolinyl]benzoate (**5a**): mp 248–250° (lit.[18] mp 248–249°); ir (Nujol) 3280 (NH), 1720 (ester C=O), 1670 (amide C=O), 1645 cm^{-1} (urea C=O); nmr (DMSO) δ 8.20–7.01 (m, 9, aromatic and NH), 3.65 (s, 3, CH_3); mass spectrum (70 eV) *m/e* 296 (molecular ion).

Anal. Calcd for $C_{16}H_{12}N_2O_4$: C, 64.86; H, 4.08; N, 9.46. Found: C, 64.70; H, 4.38; N, 9.31.

Preparations of 2-Carbomethoxyphenyl Isocyanate (3a) and Isatoic Anhydride (6) from 1a. A 181-g (1.20 mol) quantity of **1a** was treated with 400 ml of $COCl_2$ as described above and the solution was heated at reflux for 70 hr. The cooled reaction mixture was filtered and the filtrate was concentrated, slurried with benzene, and again filtered. The combined precipitates yielded 34.6 g (18%) of **6**,[23] mp 243–247° dec (methyl ethyl ketone) (lit.[24] mp 240–243° dec). The filtrate was concentrated and distilled to yield 148 g (70%) of **3a**, bp 80° (0.05 mm).

A 181-g (1.20 mol) quantity of **1a** was treated with 400 ml of $COCl_2$ in the same manner, heated at reflux for 2 hr, stirred at room temperature for 15 hr, and heated at reflux for 2 hr. Work-up as above gave 67.1 g (34%) of **6** and 101 g (46%) of **3a**.

Preparation and Thermolysis of 2-Carbomethoxyanilinecarbonyl Chloride (2a). A 181-g (1.20 mol) quantity of **1a** was treated with 400 ml of $COCl_2$ as described above. A needle-like precipitate was present which dissolved with slight warming and formed again with cooling. Removal of an aliquot of the mixture and filtration separated **2a** as white needles, which were unstable in air: mp 80–82.5°; ir (Nujol) 3200 (NH), 1780 (carbamoyl C=O), 1675 cm^{-1} (ester C=O). Reaction of **2a** with excess morpholine afforded methyl 2-(3,3-oxydiethyleneuramido)benzoate,[23] mp 105–106° (hexane) (lit.[25] mp 110–112°). An ir of a concentrated aliquot of the reaction mixture showed it to be pure **2a**. A 15-ml aliquot of the solution was withdrawn and concentrated to leave 2.93 g (13.7 mmol) of **2a**, which was heated neat, under a nitrogen atmosphere, at 100° for 2.5 hr. The benzene-insoluble portion of the resulting mixture yielded 1.64 g (73%) of isatoic anhydride. The concentrated benzene filtrate yielded 550 mg of material which was shown (ir) to be mainly **3a**.

Re-treatment of 3a with Phosgene. A 15.0-g (89.6 mmol) quantity of **3a** was treated with 100 ml of $COCl_2$ as described above and stirred at room temperature for 3 days, and the mixture was heated at reflux for 22 hr. The mixture was concentrated to dryness and the semisolid was washed with benzene to leave 3.65 g (26%) of isatoic anhydride (**6**).

Preparation and Thermolysis of 2-(Carbo-*n*-butoxy)anilinecarbonyl Chloride (2b). A 29.0-g (15.0 mmol) quantity of *n*-butyl anthranilate[26] was treated with 50 ml of $COCl_2$ as described above to yield a clear solution. Evaporative crystallization of an aliquot yielded **2b** as white needles: mp 85–88°; ir (Nujol) 3200 (NH), 1780 (carbamoyl C=O), 1690 cm^{-1} (ester C=O). Reaction of **2b** with excess morpholine afforded *n*-butyl 2-(3,3-oxydiethyleneuramido)benzoate,[23] mp 54–59° (hexane) (lit.[25] mp 67–67.5°). A 50-ml aliquot of the solution was concentrated to yield 21.6 g (84.5 mmol) of pure **2b**, which was heated neat, under a nitrogen atmosphere, at 100° for 2 hr. The resulting mixture was slurried with pentane and filtered to yield 4.00 g of **6**. The filtrate was distilled (760 mm) in fractions, which were mixtures of pentane, chlorobutane, EtOAc, and EtOCOCl. Response factors for these components on a glpc system which separated them were determined as 3.58, 1.00, 1.05, and 1.07, respectively.[29] The yield of chlorobutane in the fractions was 2.88 g (37%). The material remaining in the distillation pot was again slurried with pentane and filtered to remove an additional 0.77 g of **6**. Total yield of **6** was 4.77 g (35%). The filtrate was concentrated to leave 10.1 g (54%) of *n*-butyl 2-isocyanatobenzoate (**3b**): bp 121° (0.6 mm); ir 2270 (NCO), 1710 cm^{-1} (C=O); nmr ($CDCl_3$) δ 8.33–7.12 (m, 4, aromatic), 4.45 (t, J = 6.5 Hz, 2, OCH_3), 2.10–1.78 (m, 7, $CH_2CH_2CH_3$).

Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.90; H, 5.73; N, 6.25.

Preparations of Dimethyl 2,2′-[Carbonylbis(imino)]bisbenzoate (4a). A 17.7-g (10.0 mmol) quantity of **3a** and 15.1 g (10.0 mmol) of **1a** in 60 ml of benzene were heated at reflux for 15 hr, and the solution was diluted with an equal volume of hexane. Cooling resulted in the formation of large, white prisms, which were collected by filtration to yield 27.9 g (85%) of **4a**, mp 142–145° (lit.[4] mp 144°). Diester urea **4a** could also be prepared in nearly quantitative yield by treating **4a** with a mixture of water and dimethoxyethane at room temperature.

Preparation of Methyl Anthraniloylanthranilate (7b). Anthranilic acid and **6** were condensed to give anthraniloylanthranilic acid (**7a**) in 62% yield as described in the literature.[10a] Since treatment of **7a** with methanolic HCl afforded mainly **7a** HCl in our hands, **7a** was esterified with 1-methyl-3-*p*-tolyltriazine (TMT, Eastman) to afford **7b**. Thus, 6.41 g (25.0 mmol) of **7a** and 4.03 g (27.0 mmol) of TMT in 50 ml of THF were allowed to react at room temperature for 3 hr. The reaction solution was concentrated, washed with ether–hexane, and recrystallized (EtOH) to give 4.30 g (64%) of **7b** as white needles: mp 109–111°; ir (Nujol) 3495 (NH), 1695 (ester C=O), 1660 cm^{-1} (amide C=O); nmr ($CDCl_3$) δ 11.87–11.70 (broad s, 1, NH), 9.00–6.56 (m, 10, aromatic and NH_2), 3.93 (s, 3, CH_3).

Anal. Calcd for $C_{15}H_{14}N_2O_3$: C, 66.65; H, 5.22; N, 10.37. Found: C, 66.60; H, 5.32; N, 10.41.

Preparation and Cyclization of Methyl 2-{[2-(Ethoxycarbonylamino)benzoyl]amino}benzoate. A 3.30-g (12.1 mmol) quantity of **7b** and 1.31 g (12.1 mmol) of EtOCOCl (Aldrich) in 50 ml of pyridine were heated at reflux for 4 hr. The dark solution was concentrated and the residue was taken up in CH_2Cl_2, washed with H_2O, dried (Na_2SO_4), and concentrated to leave 1.20 g (28%) of the carbamate: mp 154.5–155° (EtOH); ir (Nujol)

3270 (NH), 1730 (carbamate C=O), 1690 (ester C=O), 1650 cm^{-1} (amide C=O); nmr ($CDCl_3$) δ 9.00–6.83 (m, 8, aromatic), 4.21 (q, J = 7.2 Hz, 2, CH_2), 3.95 (s, 3, OCH_3), 1.32 (t, J = 7.2 Hz, 3, CH_2CH_3).

Anal. Calcd for $C_{18}H_{18}N_2O_5$: C, 63.15; H, 5.30; N, 8.18. Found: C, 63.30; H, 5.05; N, 8.50.

A 550-mg (16.0 mmol) quantity of the carbamate and 0.1 g of *p*-toluenesulfonic acid in 50 ml of benzene were heated at reflux for 15 hr. The solution was washed with H_2O, dried (Na_2SO_4), and concentrated to leave a mixture of **5a** and the carbamate, in a ratio of *ca.* 1:4, respectively. The recovered material was subjected to the same reaction conditions and work-up, substituting toluene for benzene, to give a mixture of **5a** and the carbamate, in a ratio of *ca.* 3:2, respectively. Fractional crystallization of the mixture from EtOH afforded 100 mg of the carbamate as a first crop and 150 mg of compound **5a**, mp 245–250°, as the second crop.

Preparation of 2-[1,4-Dihydro-4-oxo-2-phenyl-3(2*H*)-quinazolinyl]benzoic Acid (8a). A 12.8-g (50.0 mmol) quantity of amino acid **7a** and 5.41 g (51.0 mmol) of benzaldehyde in 100 ml of EtOH were heated at reflux for 4 hr. Cooling caused a precipitate to form which was collected to yield 15.1 g (86%) of **8a**: mp 171–173°; ir (Nujol) 3300–2400 (OH), 3280 (NH), 1690 (acid C=O), 1625 cm^{-1} (amide C=O); nmr ($CDCl_3$) δ 10.04 (s, 1, OH, D_2O exchangeable), 8.92–6.56 (m, 13, aromatic), 6.31 (s, 1, methine), 5.67–5.33 (broad s, 1, NH, D_2O exchangeable).

Anal. Calcd for $C_{21}H_{16}N_2O_3$: C, 73.24; H, 4.68; N, 8.14. Found: C, 73.64; H, 5.07.

Acid **8a** was converted into ester **8b** in 58% yield with TMT using the procedure described in the preparation of **7b**.

Preparation of Methyl 2-[1,4-Dihydro-4-oxo-2-phenyl-3(2*H*)-quinazolinyl]benzoate (8b). A 3.00-g (11.1 mmol) quantity of amino ester **7b** and 1.27 g (12.0 mmol) of benzaldehyde in 25 ml of EtOH were heated at reflux for 6 hr. The solution was concentrated and the resulting solid was recrystallized (EtOH) to give 2.40 g (63%) of **8b**: mp 169–171°; ir (Nujol) 3280 (NH), 1720 (ester C=O), 1635 cm^{-1} (amide C=O); nmr ($CDCl_3$) δ 8.06–6.36 (m, 8, aromatic), 6.20 (s, 1, methine), 5.18–4.80 (broad s, 1, NH, D_2O exchangeable), 3.73 (s, 3, CH_3).

Anal. Calcd for $C_{22}H_{18}N_2O_3$: C, 73.73; H, 5.06, N, 7.82. Found: C, 74.00; H, 5.09; N, 7.90.

Preparation of 2-[4-Oxo-3(4*H*)-quinazolinyl]benzoic Acid (9a). A 7.00-g (27.3 mmol) quantity of amino acid **7a** in 15 g of triethyl orthoformate (Aldrich) was heated at reflux for 20 hr. The mixture was cooled and filtered to remove 6.80 g (98%) of amino acid **9a**: mp 279–281° (lit.[30] mp 273–274°); ir (Nujol) 2700–2200 and 2000–1800 (protonated imine), 1690 cm^{-1} (C=O groups).

Anal. Calcd for $C_{15}H_{10}N_2O_3$: C, 67.66; H, 3.79; N, 10.52. Found: C, 67.90; H, 3.88; N, 10.39.

Acid **9a** was converted into ester **9b** in 92% yield with TMT using the procedure described in the preparation of **7b**.

Preparation of Methyl 2-[4-Oxo-3(4*H*)-quinazolinyl]benzoate (9b). A 3.00-g (11.7 mmol) quantity of amino ester **7b** in 7 ml of triethyl orthoformate was heated at reflux for 16 hr. The reaction solution was concentrated and recrystallized (EtOH) to yield 2.35 g (73%) of **9b**: mp 173–174° (lit.[30] mp 171–172°); ir (Nujol) 1720 (ester C=O), 1685 (amide C=O), 1615 cm^{-1} (C=N).

Anal. Calcd for $C_{16}H_{21}N_2O_3$: C, 68.56; H, 4.32; N, 10.00. Found: C, 68.30; H, 4.51; N, 10.21.

Preparation of 5a and 2-[1,4-Dihydro-2,4-dioxo-3(2*H*)-quinazolinyl]benzoic Acid (10) from 4a. A 5.00-g (15.2 mmol) quantity of diester urea **4a** was mixed with 50 g of polyphosphoric acid (PPA) and stirred at 110–120° for 90 min. The yellow reaction solution was poured into aqueous Na_2CO_3 and the mixture was extracted with CH_2Cl_2 (3 × 50 ml). The extracts were dried (Na_2SO_4) and concentrated to a small volume, and the crystalline solid which formed was collected to give 1.25 g (27%) of pure **5a**, mp 174–175°.

The aqueous phase was acidified (concentrated HCl) and the precipitated solid was removed by filtration to yield 2.60 g (60%) of **10**: mp 303–305° (EtOH) (lit.[31] mp 298–300°); ir (Nujol) 3400–2300 (OH), 1710 (acid C=O), 1675 (amide C=O), 1650 cm^{-1} (urea C=O).

Acid **10** was converted into ester **5a** in 95% yield with TMT using the procedure described in the preparation of **7b**.

Preparation of Methyl 2-[(4-Oxo-4*H*-3,1-benzoxazin-2-yl)amino]benzoate (11). A 5.00-g (15.2 mmol) quantity of diester urea **4a** was mixed with 50 g of PPA in a stoppered reaction vessel and stirred at room temperature for 7 days. The clear reaction solution was poured into aqueous Na_2CO_3 and the resulting mixture was extracted with CH_2Cl_2 (3 × 50 ml). The extracts were dried (Na_2SO_4) and concentrated to leave 4.00 g (89%) of pure **11**: mp 174–175° (EtOH); ir (Nujol) 3250–3000 (NH), 1765 (benzoxazinone C=O), 1695 (ester C=O), 1645 cm^{-1} (C=N); nmr ($CDCl_3$) δ 10.96 (broad s, 1, NH), 9.06–6.90 (m, 8, aromatic), 3.93 (s, 3, CH_3).

Anal. Calcd for $C_{16}H_{12}N_2O_4$: C, 64.86; H, 4.08; N, 9.46. Found: C, 65.20; H, 4.25; N, 9.45.

Reactions of 11 with PPA. A 2.00-g (6.75 mmol) quantity of benzoxazinone **11** was mixed with 35 g of PPA and heated at 90° for 90 min. Work-up of the clear solution as above afforded 850 g (42%) of recovered **11** from the CH_2Cl_2 extract and 800 mg (42%) of acid **10** from the acidified aqueous phase.

A 700-mg (2.36 mmol) quantity of **11** was mixed with 20 g of PPA and heated at 120° for 90 min. Work-up of the clear solution as above afforded 100 mg (13%) of a mixture of **11** and **5a** from the CH_2Cl_2 extract and 39.5 mg (56%) of acid **10** from the acidified aqueous phase.

Reactions of 5a with PPA. A 5.00-g (16.8 mmol) quantity of ester **5a** was mixed with 50 g of PPA and heated at 80° for 90 min. The clear solution was poured into aqueous Na_2CO_3 and the mixture was extracted with CH_2Cl_2 (3 × 50 ml). The extracts were dried (Na_2SO_4) and concentrated to leave 4.40 g (88%) of pure **5a**.

When a 5.00-g (16.8 mmol) quantity of ester **5a** was treated with 50 g of PPA at 120° for 90 min, work-up of the clear solution as above yielded 2.29 g (46%) of recovered **5a**. Acidification of the aqueous phase precipitated a white solid which was collected and dried to yield 1.99 g (42%) of acid **10**.

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Registry No.—**1a**, 134-20-3; **1b**, 7756-96-9; **2a**, 51310-17-9; **2b**, 51310-18-0; **3a**, 1793-07-3; **3b**, 51310-19-1; **4a**, 51364-45-5; **5a**, 13905-97-0; **6**, 188-48-9; **7a**, 612-34-0; **7b**, 49854-16-2; **8a**, 51310-20-4; **8b**, 51364-46-6; **9a**, 25380-15-8; **9b**, 51310-21-5; **10**, 1701-95-7; **11**, 51310-22-6; methyl 2-{[2-(ethoxycarbonylamino)benzoyl]amino}-benzoate, 51310-23-7.

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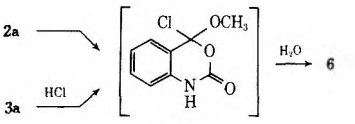
(19) Mechanisms which require water were necessarily excluded because of the anhydrous reaction conditions. Isatoic anhydride (**6**) was formed *in situ*, which eliminated the possibility of an intermediate such as i being converted to **6** on exposure to moisture during work-up.



i

(20) The 28-day reaction in Scheme I was monitored by ir. During the first half of the reaction, the concentration of **2a** was greater than that of **3a**, and the converse was true during the latter half. Therefore, it is conceivable that both **2a** and **3a** contributed to the formation of **6**.
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Carbon Magnetic Resonance Spectra of 2-Pyrones

W. V. Turner and W. H. Pirkle*

School of Chemical Sciences, University of Illinois, Urbana, Illinois 61801

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The cmr spectra of 21 2-pyrones or sulfur-containing analogs of 2-pyrones are assigned by selective proton decoupling, multiplicity, and uniformity of chemical shift or J_{CH} values. Cmr spectroscopy is a useful tool in establishing the structures of unknown 2-pyrones, complimenting pmr spectroscopy in this regard.

Substituted 2-pyrones occur commonly in nature, and this ring system has recently been found to have synthetic value and to undergo highly varied thermal and photochemical reactions. Our interest in 2-pyrones led to pmr studies[1] which we have now extended to cmr. Just as proton–proton coupling constants often allow unique assignment of 2-pyrone substitution patterns, carbon-13 chemical shifts and carbon-13 proton coupling constants prove to be especially informative, thus strongly complementing pmr as a tool for 2-pyrone characterization. Several sulfur-containing analogs of 2-pyrones have been included in this study for comparative purposes.

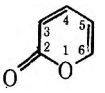
Experimental Section

Most of the 2-pyrones used in this study have been described previously. The thiones were prepared by action of P_2S_5 on the corresponding pyrones; thiapyran-2-ones were prepared by thermal isomerization of thiones.[2]

Cmr spectra were obtained with a Varian Associates Model XL-100-15 25.1-MHz spectrometer coupled with a Digilab NMR-3 Fourier transform system. The samples were quite concentrated (1.5–5.5 *M*) to minimize the time required to obtain selectively decoupled or undecoupled spectra. In several instances, solvents other than chloroform-*d* were used for increased solubility or for optimum separation of proton resonances for selective decoupling. Both 2-pyrone and 4,6-dimethyl-5-carbethoxy-2-pyrone were run almost neat (10% internal acetone-d_6 was used as a lock signal) to allow the recording of spectra in the continuous wave mode.

Results

Table I records chemical shifts for 2-pyrone ring carbons as parts per million downfield of TMS. The compounds in part A of the table are unsubstituted or monosubstituted pyrones (or sulfur analogs) for which each unsubstituted carbon resonance was identified by selective proton decoupling. Since the carbonyl carbon (C-2) chemical shift remains almost constant, the assignment of the substituted carbon is apparent.



2-pyrone

Like the corresponding proton resonances, the C-4 and C-6 resonances of 2-pyrone are downfield of those of C-3 and C-5. This order has also been observed in 2-pyridone.[3]

Single-bond carbon-13 proton coupling constants (J_{CH}, hertz) for most of the 2-pyrones appear in parentheses in Table I. They provide a means of identifying C-6 when it bears hydrogen. The ranges of values of J_{CH} for C-3 and C-5 are similar and larger than the usual values for C-4, although some overlapping occurs. The values for 2-pyrones may be compared with J_{CH} for 4-pyrone (200 Hz for C-2 and 169 Hz for C-3)[4] and furan (201 Hz for C-2 and 175 Hz for C-3).[5] A value of *ca.* 200 Hz is typical for J_{CH} of carbon atoms attached to oxygen in aromatic heterocycles.[6] J_{CH} values for sulfur analogs of 2-pyrones are similar to those of 2-pyrone, except that J_{CH} for C-6 of the thiapyran derivatives is *ca.* 180 Hz. (*Cf.* J_{CH} of 185 Hz for the α carbons of thiophene.[6]) Two exceptions to this pattern emerge from Table I. The unusually small J_{CH} of C-3 of 4-methylthiapyran-2-one and the unusually large J_{CH} for C-4 of coumalyl chloride are unexplained.

Significant longer range coupling is also observed, but this varies with the nature of the substituents. Thus, in 4-methyl-2-pyrone C-6 is coupled (J = 7 Hz) to some proton other than H-6, while in 4-methyl-6-chloro-2-pyrone the C-6 resonance is a singlet (J < 1 Hz). Because of

Table I
Chemical Shifts of Ring Carbons in 2-Pyrones and Some Sulfur Analogs

	Compd	Chemical shift (J_{CH}) C-2	C-3	C-4	C-5	C-6	CH_3	Registry no.
A.	2-Pyrone[a,l]	162.0	116.7 (170)	144.3 (163)	106.8 (173)	153.3 (200)		504-31-4
	4-Methyl-2-pyrone[b]	161.8	113.7 (169)	156.1	109.3 (169)	151.1 (199)	21.1	22682-12-8
	3-Hydroxy-2-pyrone[b]	161.8	142.7	115.2 (166)	107.3 (170)	142.3 (205)		496-64-0
	3-Methoxy-2-pyrone[b]	158.6	145.9	112.9	106.0	142.9	56.0	51270-28-1
	3-Acetoxy-2-pyrone[b,d]	157.6	137.3	131.2	105.4	149.1	20.2	51270-29-2
	Coumalyl chloride[b,e]	158.2	115.3 (175)	140.3 (170)	116.6	163.0 (203)		23090-18-8
	Thiapyran-2-one[c]	183.7	124.9 (169)	140.9 (163)	118.7 (169)	137.4 (180)		6788-51-8
	Pyran-2-thione[c]	196.9	131.8	134.4	109.6	155.6		23639-33-0
	4-Methylthiapyran-2-one[b]	184.3	123.8 (161)	153.4	122.2 (166)	136.0 (183)	24.1	51270-30-5
	4-Methylpyran-2-thione[b]	197.0	130.2 (172)	149.2	113.2 (170)	155.0 (202)	21.1	51270-31-6
B.	5-Methyl-2-pyrone[b]	161.2	115.7 (171)	146.5 (162)	114.7	148.0 (197)	14.4	51270-32-7
	6-Methyl-2-pyrone[b]	162.0	112.6 (171)	144.1 (162)	103.4 (171)	162.9	19.8	4394-76-7
	4-Chloro-6-methyl-2-pyrone[b,f]	160.9	110.8 (177)	151.8	106.1 (176)	162.9	19.8	17422-72-9
	4-Methyl-6-chloro-2-pyrone[b]	160.6	110.4 (171)	157.5	107.1 (176)	148.7	21.4	22682-15-1
	4-Methoxy-6-methyl-2-pyrone[b]	162.1	87.3 (172)	171.4	100.3 (168)	164.6	55.9 19.7	672-89-9
	4-Methoxy-6-(4-methoxystyryl-2-pyrone (yangonin)[b,g]	160.9	88.4	171.3	100.4	163.9		500-62-9
	4,6-Dimethyl-5-carbethoxy-2-pyrone[a,h]	159.6	111.9 (170)	154.4	112.9	165.1	21.0 (4) 19.6 (6)	3385-34-0
	4,6-Dimethyl-5-carbethoxypyran-2-thione[b,i]	195.7	128.6 (173)	146.8	116.6	168.4	20.5 19.9	51270-33-8
	Thiapyran-2-thione[b]	205.2	139.3 (169)	132.6 (163)	122.7 (169)	141.8 (180)		930-72-3
	Coumarin[b,j]	160.5	116.4 (172)	143.5 (164)	118.8	153.9		19-64-5
	Benzopyran-2-thione[k]	198.5	130.2 (176)	133.0 (164)	121.3	157.2		3986-98-9

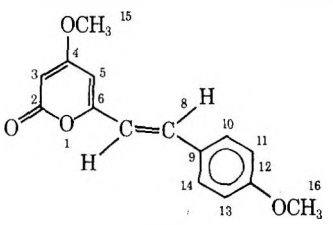
[a] As a 90% solution in acetone-d_6. [b] As $CDCl_3$ solution. [c] As solution in $CDCl_3$–CCl_4. [d] Acetate carbonyl at δ 167.8. [e] COCl at δ 162.7. [f] It is not obvious which of the resonances at δ 160.9 and 162.9 is C-2 and which C-6, or which of those at δ 106.1 and 110.8 is C-5 and which C-3. [g] In addition to the 2-pyrone ring carbons, we observed the following resonances: δ 55.4 and 55.8 (2 OCH_3), 114.5 (C-11 and C-13), 116.6 (C-7), 128.2 (C-9), 129.0 (C-10 and C-14), 135.4 (C-8), and 159.2 (C-12). The assignments agree well with those reported for *p*-methoxystyrene in K. S. Dhami and J. B. Stothers, *Can. J. Chem.*, **44**, 2855 (*1966*), and P. C. Lautebur, *Ann. N. Y. Acad. Sci.*, **70**, *841* (*1958*). [h] Carbonyl at δ 165.2. [i] Carbonyl at δ *164.6*. [j] Other resonances at δ 116.5, 124.4, 128.0, and 131.7. This has been reported before (ref 3, p 333) and is included for comparison. [k] Other resonances at δ 116.9, 126.3, 129.0, and 135.6; dilute in acetone. [l] A solvent effect is reflected in the chemical shifts of 2-pyrone carbons in dilute $CDCl_3$ solution: δ 117.0, 142.8, 106.0, and 152.0 for C-3, C-4, C-5, and C-6, respectively. C-2 was not observed.

uncertainties in the assignment of a number of the longer range couplings, these values have not been tabulated.

Assignments in part B of Table I are based on chemical shift data from part A, coupling constants, multiplicity in undecoupled spectra, and, where possible, selective decoupling.

The resonances of the methyl carbons attached to the ring in 4,6-dimethyl-5-carbethoxy-2-pyrone were identified by selective proton decoupling, the order of the carbon resonances being reversed from that of the corresponding protons. The original identification of the methyl proton resonances was based on the *ca.* 1 Hz coupling of 4-CH_3 to H-3, which is observed in a number of 4-methyl-2-pyrone derivatives.

The natural product yangonin[7,8] was prepared for this study. With 4-methoxy-6-methyl-2-pyrone and 4-methoxystyrene[10] as models, the interpretation of the spectrum is quite straightforward, although questions arise concerning C-2 and C-6.



yangonin

The greatest difficulty arose in interpreting the spectrum of 4-chloro-6-methyl-2-pyrone. Although it is clear from multiplicities which two resonances arise from C-3 and C-5, further assignment cannot be made *via* selective decoupling since the proton resonances have not been assigned. The order of proton and carbon resonances is, however, the same. The downfield carbon resonances arise from C-2 and C-6, leaving the resonance at δ 151.8 for C-4. This assignment means that the substitution of chlorine at C-4 results in a downfield shift of 7.5 ppm, while at C-6 it causes an upfield shift of 4.6 ppm.

Thiapyran-2-thione is not included in part A of Table I because the complexity of its proton spectrum precluded selective decoupling. The resonance at δ 205.2 represents C-2, and a tentative assignment of the other resonances follows from the assumption that the effects of the two sulfur substitutions are additive. Chemical shifts predicted in this way, based on 2-pyrone in $CDCl_3$ solution, are 140.0, 131.0, 121.5, and 139.7 ppm for C-3 and C-6, respectively; these are very close to the observed values. The observed J_{CH} values support the assignment.

Charge distribution in the 2-pyrone ring is indicated by the downfield shifts of C-4, C-6, H-4, and H-6 relative to C-3, C-5, H-3, and H-5 and also by the chemical shifts of methyl substituents. Thus, 4-methyl and 6-methyl carbons appear at 21 and 20 ppm downfield of TMS, respectively, but 5-methyl carbon appears at 14 ppm. Smaller differences also appear in pmr shifts of these methyl groups.

Localization of the double bonds of 2-pyrones is suggested by the observation that in the proton spectra of methyl pyrones H-3, but not H-5, is coupled to a 4-methyl group. In 2-pyrone cmr spectra, methyl substitution causes an upfield shift of the β carbon on the same double bond. However, both 4-methyl and 5-methyl substituents are observed to shift the remaining β carbon downfield. This effect is particularly noteworthy for 4-methoxy-6-methyl-2-pyrone, where the methoxy group causes an up-

field shift of C-3 of almost 30 ppm, but shifts C-5 upfield only 3 ppm. This effect has been discussed previously in the case of proton spectra.[11]

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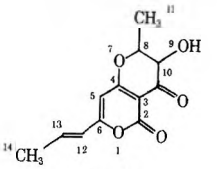

radicinin

spectra of our model compounds, we suggest that the resonances at 188, 172, 162, and 156 are more likely to be C-10, C-4, C-6, and C-2, respectively, than C-2, C-10, C-4, and C-6, respectively. This change does not, however, affect the conclusions drawn about location of acetate units in radicinin.
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Possible Bifunctional Catalysis by 2-Dimethylaminoethylamine in the Dealdolization of Diacetone Alcohol[1a]

Jack Hine* and William H. Sachs[1b]

Department of Chemistry, The Ohio State University, Columbus, Ohio 43210

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Catalysis of the dealdolization of diacetone alcohol by *n*-propylamine, 2-methoxyethylamine, 2-trimethylammonioethylamine, and 2-dimethylaminoethylamine has been studied in water at 35°. Combination of the resultant data with literature observations shows that catalytic efficiency increases with amine basicity when steric factors are kept reasonably constant. In a plot of log k *vs.* pK_a the points for most species of the type RCH_2NH_2 lie near a straight line of slope 0.44. The activity of $Me_2NHCH_2CH_2NH_2^+$, however, is about four times as great as would be expected from the data for the other amines. This increased catalytic activity may arise from bifunctional catalysis, in which the primary amino group from the catalyst transforms the carbonyl group of diacetone alcohol to an iminium ion and the tertiary amino group removes a proton from the hydroxy group. An analysis of the propagation of errors in the determination of rate constants for acids and bases from data obtained in buffer solutions is also given.

The dealdolization of hexose derivatives brought about by Class I aldolases is thought to involve iminium-ion formation between a carbonyl group of the substrate (*e.g.*, fructose 1,6-diphosphate) and a lysine residue of the enzyme, followed by base-promoted cleavage.[2,3] The nature of the second basic group may vary from enzyme to enzyme. In the case of at least one transaldolase there is evidence that it is the imidazole ring of a histidine residue.[4] A carboxylate anion group has been postulated to be the second basic group in 2-keto-3-deoxygluconate aldolase.[5]

Observations that simple primary[6-10] and secondary[6-8] amines and amino acids,[10,11] but not tertiary amines,[7] specifically catalyze the dealdolization of diacetone alcohol have contributed to an understanding of enzymatic dealdolizations. The present study was begun with the aim of learning how polar substituents affect the efficiency of primary amine catalysis of dealdolization and of using this knowledge to tell whether a diamine may act as a bifunctional catalyst for dealdolization. After the study was largely completed, an investigation of polar substituent effects on primary amine catalysis of dealdolization was published by Pollack and Cooper.[10]

Results

The dealdolization of diacetone alcohol is known to be catalyzed by hydroxide ions.[7,12] To learn the contribution of such catalysis to reactions carried out in the presence of amines we made kinetic studies using sodium hydroxide. The reaction in aqueous solution at 35° and ionic strength 0.10 was followed by spectrophotometric measurements at 264.5 nm, where the transformation of diacetone alcohol (λ_{max} 277 nm, $\epsilon_{264.5}$ 23.7 M^{-1} cm^{-1}) to acetone (λ_{max} 264.5 nm, $\epsilon_{264.5}$ 17.9 M^{-1} cm^{-1}) is accompanied by an increase in absorbance, largely because the concentration of carbonyl groups is doubled. The kinetics were complicated by the reversible dehydration of the diacetone alcohol to mesityl oxide (λ_{max} 243 nm, ϵ_{243} 11,400 M^{-1} cm^{-1}, $\epsilon_{264.5}$ 2640 M^{-1} cm^{-1}). This caused the absorbance at 264.5 nm to increase by an amount about 47% larger than the theoretical amount for the formation of acetone only, and it caused the increase in absorbance to be accompanied by a shift in the absorption maximum to shorter wavelengths. After about 9.5 half-lives the absorbance began to decrease and the absorption maximum to move back toward longer wavelengths. Comparison of the full-length spectrum of the reaction solution after 22 dealdolization half-lives with the spectrum of aqueous acetone solutions showed that the extra absorbance of the reaction solution arose from a material with an absorption maximum at about 243 nm. To allow for this complication the kinetics of the reaction of 0.01466 M diacetone alcohol in the presence of 0.0101 M sodium hydroxide were analyzed

in terms of eq 1, in which y_i is the absorbance at time t_i. The numbers in parentheses are the least-squares esti-

$$y_i = c_1 e^{-k_{obsd} t_i} + c_2 e^{-k'_{obsd} t_i} + c_3 \quad (1)$$

$c_1 = -0.2478\ (0.0002)$ $k_{obsd} = 1.986\ (0.004) \times 10^{-4}\ sec^{-1}$
$c_2 = 0.0827\ (0.0066)$ $k'_{obsd} = 1.665\ (0.17) \times 10^{-6}\ sec^{-1}$
$c_3 = 0.5139\ (0.0067)$

mates of the standard deviations of the respective parameters.

The reaction was assumed to have the mechanism shown in eq 2. Since only small amounts (<0.3%) of mesi-

$$\begin{array}{c} OH \\ | \\ Me_2CCH_2COMe \end{array} \xrightarrow{k_1} 2Me_2CO$$
$$k_{-2} \rightleftharpoons k_2 \quad (2)$$
$$Me_2C{=}CHCOMe$$

tyl oxide are ever formed and since the final disappearance of the mesityl oxide that is formed is a relatively slow process, it follows that $k_1 \gg k_2$ and k_{-2}. Under these circumstances it may be shown that the kinetics will follow eq 1 with $k_{obsd} = k_1$, $k'_{obsd} = k_{-2}$, and $k_2 = k_1(c_2 - \epsilon^m_{264.5}[M]_0/\epsilon^m_{264.5}[D]_0)$, where $[M]_0$ and $[D]_0$ are the initial concentrations of mesityl oxide and diacetone alcohol. The product $\epsilon^m_{264.5}[M]_0$ was between zero and 0.016, from which k_2 may be calculated to be in the range (3.4–4.2) $\times 10^{-7}\ sec^{-1}$.

Most of the runs carried out with sodium hydroxide were not followed for the long time required to get data from which c_2 and k'_{obsd} in eq 1 could be obtained. In these cases we used the single exponential relationship shown in eq 3, in which a_2 is a "pseudo-infinity" absorb-

$$y_i = a_1 e^{-k_1 t_i} + a_2 \quad (3)$$

ance approximately equal to $c_2 + c_3$ in eq 2. Each reaction was followed for 2–3 half-lives and a_1, a_2, and k_1 were determined by the method of least squares. The reliability of this method of determining k_1 is supported by the estimated standard deviations obtained (~1%) and by the fact that application of eq 3 to the first 3 half-lives of runs that had been carried well into the absorbance-decrease phase of the reaction gave the same k_1 values within 1% as were obtained by application of eq 1 to the entire set of data on the reaction. Values of $10^4 k_1$ (in sec^{-1}) of 1.950, 3.817, 5.735, and 7.662 were obtained at sodium hydroxide concentrations of 0.0102, 0.0202, 0.0301, and 0.0401, respectively. These give a second-order rate constant of $(1.91 \pm 0.02) \times 10^{-2}\ M^{-1}\ sec^{-1}$ for the hydroxide ion catalyzed reaction.

Before considering whether dealdolization in the presence of primary amines was complicated by simultaneous formation of mesityl oxide, we should consider another complication that arose in these reactions. The purified diacetone alcohol underwent slow dehydration upon storage at room temperature and the mesityl oxide content had reached about 0.2 mol % after 5 months, when the trouble was diagnosed. The increase in absorbance brought about by the dealdolization of such contaminated reactant was preceded by a much more rapid decrease in absorbance that was ≤10% as large as the later increase. Satisfactory first-order rate constants were obtained from eq 3 when the first 0.3–0.6 half-life (for dealdolization) was neglected and the reaction was then followed for a time 4–15 times as long as the neglected period. To assess the effect of mesityl oxide contamination on the validity of rate constants obtained in this way, we studied the decomposition of mesityl oxide in the presence of one of the primary amine catalysts, 2-dimethylaminoethylamine, at pH 9.9. Pollack and Strohbeen showed that the transformation of mesityl oxide to acetone in the presence of aqueous *n*-propylamine involves the relatively rapid reversible formation of a mesityl oxide–amine adduct, which then decomposes to acetone.[13] In the case of 2-dimethylaminoethylamine, we found the initial rapid formation of mesityl oxide–amine complex to correspond closely in rate to the initial decrease in absorbance observed in the cleavage of mesityl oxide contaminated diacetone alcohol. The rate of the subsequent decomposition of the mesityl oxide–amine complex was about as fast as the dealdolization of diacetone alcohol. For the most highly contaminated diacetone alcohol used the second phase of the mesityl oxide decomposition would change the absorbance by up to 30% as much as the dealdolization would. To estimate the effect of such contributions to the over-all change in absorbance on the calculated rate constants for dealdolization, we analyzed the kinetics in detail. If the only processes occurring are the dealdolization and the cleavage of mesityl oxide by the proposed two-step mechanism,[13] the absorbance should change in accord with eq 4, in which the c_1 term arises from the deal-

$$y_i = c_1 e^{-k_{obsd} t_i} + c_2 e^{-k'_{obsd} t_i} + c_3 e^{-k''_{obsd} t_i} + c_4 \quad (4)$$

dolization and the c_2 and c_3 terms from the mesityl oxide reaction. When the first few points, covering the rapid phase of the mesityl oxide reaction, are discarded, eq 4 reduces to eq 5, in which k_{obsd} and k'_{obsd} are of the same order of magnitude. The covariance of the parameters in such equations and the difficulty in obtaining their least-squares estimates unless k_{obsd} and k'_{obsd} are well separated is a notorious problem.[14a] For this reason it was not thought worthwhile to try to apply eq 5 to our data. In-

$$y_i = c_1 e^{-k_{obsd} t_i} + c_2 e^{-k'_{obsd} t_i} + c_4 \quad (5)$$

stead we made some calculations to estimate how much error we had introduced by using eq 3. This was done by using eq 4 to generate data, assigning a normal random deviate of 0.00015 (which is considerably better than the experimental data) to each value of y_i, and subjecting the resulting synthetic data to least-squares analysis. The relative magnitudes of k_{obsd}, k'_{obsd}, and k''_{obsd} were taken as 1:0.5:90, similar to those found experimentally in the case of catalysis by 2-dimethylaminoethylamine. Application of eq 3 to the synthetic data obtained between 0.16 and 1.9 half-lives for dealdolization gave values of k_1, which may be regarded as biased estimates of k_{obsd}, that deviated from k_{obsd} by amounts that were approximately linear in the assumed concentration of mesityl oxide in the diacetone alcohol. With the largest mesityl oxide concentration ever present in our diacetone alcohol the value of k_1 obtained was 5% larger than the value of k_{obsd} used to generate the data. Experimentally, when freshly purified diacetone alcohol was used in a repeat of the run carried out with 2-dimethylaminoethylamine the value of k_1 was 7.4% smaller than the value obtained with contaminated reactant. Therefore we concluded that the smaller amounts of mesityl oxide present in the previous studies of amine catalysis should have caused less than 10% uncertainty in the rate constants obtained.

In the case of all the runs carried out with *n*-propylamine and 2-methoxyethylamine the calculated infinite absorbance (a_2 in eq 3) was much closer to the value calculated assuming no mesityl oxide was being formed as a side reaction than had been the case in the hydroxide-catalyzed reaction. Therefore it was assumed that this side reaction was not occurring to a large enough extent to introduce significant error into the rate constants obtained, which are listed in Table I. There was also no significant

Table I
Kinetics of Dealdolization of Diacetone Alcohol in the Presence of Amine Catalysts at 35°[a]

Amine (registry no.)	$[Amine]_{total}$	$[B]/[BH^+]$[b]	pH	$10^6 k_1$, sec^{-1} Obsd	$10^6 k_1$, sec^{-1} Calcd
n-$PrNH_2$	0.0533	2.85	10.71	83.88	76.74
(107-10-8)	0.0520	1.92	10.53	65.00	61.71
	0.0524	1.65	10.48	58.62	57.98
	0.0510	1.34	10.39	52.62	50.63
	0.0534	1.25	10.35	48.23	50.06
	0.0539	1.09	10.29	45.10	46.83
	0.0491	0.77	10.16	35.62	35.39
	0.0529	0.78	10.15	35.08	37.65
NH_2	0.0536	5.77	9.94	17.92	17.20
|	0.0507	4.12	9.80	14.52	14.63
CH_2	0.0544	3.58	9.74	14.87	14.71
|	0.0503	2.63	9.61	12.00	12.36
CH_2	0.0537	2.39	9.57	12.64	12.49
|	0.0512	1.87	9.47	10.35	10.86
O	0.0544	1.75	9.43	10.97	10.99
|	0.0505	1.32	9.32	8.79	9.15
Me					
(109-85-3)					
NH_2	0.04215	19.48	10.29	28.78	26.94
|	0.04254	12.78	10.15	23.86	23.65
CH_2	0.04340	9.54	10.03	21.75	21.50
|	0.04100	8.96	10.01	20.14	20.20
CH_2	0.04163	7.99	9.94	19.39	19.33
|	0.04440	7.63	9.91	20.03	19.89
NMe_2	0.04361	6.71	9.85	17.77	18.57
(108-00-9)	0.04227	5.85	9.80	17.27	17.19
	0.04265	4.92	9.70	15.32	15.92
	0.04231	4.14	9.63	13.69	14.61
	0.04322	3.67	9.53	12.64	13.78
	0.04336	1.81	9.09	7.31	8.04
	0.04072	1.64	8.95	6.90	6.64
	0.04138	1.51	8.86	6.32	6.06
	0.04066	1.32	8.66	5.49	4.84
	0.04091	1.21	8.47	4.71	4.08
NH_2	0.0392[c]		9.08	2.07	2.21
|	0.0291[d]		9.07	1.85	1.79
CH_2	0.0218		9.06	1.65	1.48
|					
CH_2					
|					
$+NMe_3$					
(38170-37-5)					

[a] At ionic strength 0.10 unless otherwise noted. [b] Stoichiometric buffer ratio calculated from the amounts of amine, amine salt, acid, and/or base used. [c] Ionic strength 0.068. [d] Ionic strength 0.086.

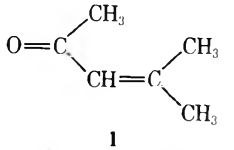
amount of mesityl oxide formed in the runs using 2-dimethylaminoethylamine above pH 8. Runs below pH 8 were discarded because of excessive mesityl oxide formation. The *N*-(2-aminoethyl)trimethylammonium cation is a relatively poor catalyst whose activity is obscured by mesityl oxide formation below pH 8 and by hydroxide ion catalysis above pH 10. As a compromise the rate was studied around pH 9.1, using a borate buffer to maintain the pH since this pH is outside the buffer range of the amine.

Discussion

The value 0.0191 M^{-1} sec^{-1} that we have obtained for k_{OH} agrees fairly well with the value 0.0204 M^{-1} sec^{-1} obtained at a hydroxide ion concentration and ionic strength of 0.010[15] and the value 0.0218 M^{-1} sec^{-1} obtained at a hydroxide ion concentration and ionic strength of 0.10,[16] both determined at 35.0° using a dilatometric method. Combination of our values of k_2 and k_{-2} (eq 2) gives an equilibrium constant of 4.5 ± 1 for the hydration of mesityl oxide to give diacetone alcohol in aqueous solution at 35°. Values of 13 and 16 may be calculated for the same reaction at 25° from data obtained in aqueous hydrochloric acid[17] and aqueous sodium hydroxide solutions,[18] respectively. The entropy of reaction is expected to be highly negative, since one molecule is being formed from two. The fact that the equilibrium is reasonably favorable shows that the reaction should be significantly exothermic. Hence the rapid decrease in equilibrium constant with increasing temperature is expected. This relatively favorable equilibrium in the hydration of mesityl oxide contrasts sharply with the analogous reaction of 10-methyl-$\Delta^{1,9}$-octalone-2, which can also be regarded as a reaction of the type

$$R_2C{=}CHCOR + H_2O \rightleftharpoons R_2\underset{\displaystyle OH}{\underset{|}{C}}CH_2COR$$

in which the R groups are all saturated hydrocarbon radicals, but in which the *dehydration* reaction is said to proceed essentially quantitatively in aqueous solution at 25°.[19] One probable reason for the difference in equilibrium constants for these two similar equilibria is that the hydration of mesityl oxide gives a species with greatly increased freedom of rotation around bonds whereas hydration of the cyclic unsaturated ketone does not. A second probable reason is that in the most favorable conformation for resonance interaction between the carbonyl group and the carbon-carbon double bond of mesityl oxide (1)



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there will be a destabilizing steric interaction between two methyl groups. No such interaction is present in the analogous conformation of 10-methyl-$\Delta^{1,9}$-octalone-2.

The observed first-order rate constants for dealdolization in the presence of 2-dimethylaminoethylamine buffers at various concentrations and various pH's were correlated in terms of eq 6, in which A represents the unprotonated and AH^+ the monoprotonated amine. In treating the data on the other amines the k_{AH} term was neglected. In this treatment k_{OH} was given the value obtained using sodium hydroxide as a catalyst. An alternative is to treat k_{OH} as a parameter of the regression analysis. In using either alternative one must choose between different formulae, which are mathematically equivalent but not statistically equivalent, for calculating the concentrations of the various species. Since this problem arises frequently in calculating rate constants from data on buffer solutions and in other cases, we have developed a propagation of errors analysis, which is given in the Appendix.

$$k_1 = k_{OH}[OH^-] + k_A[A] + k_{AH}[AH^+] \qquad (6)$$

In Table I are the values of k_1 calculated from the catalysis constants obtained, which are listed in Table II. Also listed are values for ethylamine[8] and *n*-propylamine[9,10] interpolated between data at higher and lower temperatures using the Arrhenius equation and values for six other amines[8,10] calculated from data at 25° (53.6° in the case of trifluoroethylamine)[10] assuming that their reactivities differ from that of *n*-propylamine only because of differences in the Arrhenius activation energy. To estimate the polar effect of substituents on the catalytic activity of these amines we have plotted log k against the pK_a of the conjugate acids of the amines,[20,21] as a measure of the polar character of the substituents. Since the pK_a of a singly charged cationic acid is relatively independent of the ionic strength, pK_a values at zero ionic strength have been used for the monoprotonated forms of electrically neutral amines. For the cationic and anionic amines the pK_a values refer to the ionic strengths (0.10 and 0.4, respectively) at which the kinetics were studied.

Table II
Catalysis Constants for the Dealdolizaton of Diacetone Alcohol in Water at 35°[a]

Catalyst	pK_a[b]	$10^6 k$,[c] M^{-1} sec^{-1}	Registry no.
$EtNH_2$	10.31	901[d]	75-04-7
n-$PrNH_2$	10.21	1330 ± 40 1070[d]	
i-$PrNH_2$	10.21	151[e]	75-31-0
$^-O_2CCH_2NH_2$	9.35[f]	252[e]	23297-34-9
$Me_2NCH_2CH_2NH_2$	9.34[g]	444 ± 8	
$HOCH_2CH_2NH_2$	9.21[h]	336[e]	
$MeOCH_2CH_2NH_2$	9.09	283 ± 3	
$PhCH_2NH_2$	9.00	354[e]	100-46-9
$H_2NCOCH_2NH_2$	7.69	111[e]	598-41-4
$Me_3NCH_2CH_2NH_2^+$	6.53[i]	41 ± 8	
$Me_2NCH_2CH_2NH_2 \cdot H^+$	6.23[i]	60 ± 8	51380-72-4
$CF_3CH_2NH_2$	5.52	7.8[j]	753-90-2

[a] From the present study unless otherwise noted. [b] For the monoprotonated form of the amine listed; at zero ionic strength for electrically neutral amines, at the ionic strength at which the kinetics were studied for charged amines. Values from ref 20 unless otherwise noted. [c] The ± figures are estimates of standard deviations. [d] Interpolated from data at higher and lower temperatures.[8-10] [e] Calculated from data at 25°.[8,10] [f] At ionic strength 0.4. [g] Determined in the present study. [h] From ref 21. [i] At ionic strength 0.1. [j] Calculated from data at 53.6°.[10]

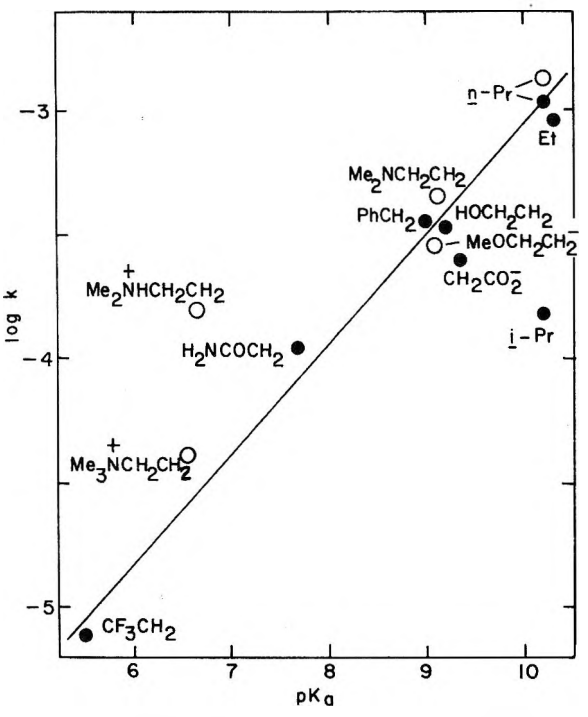
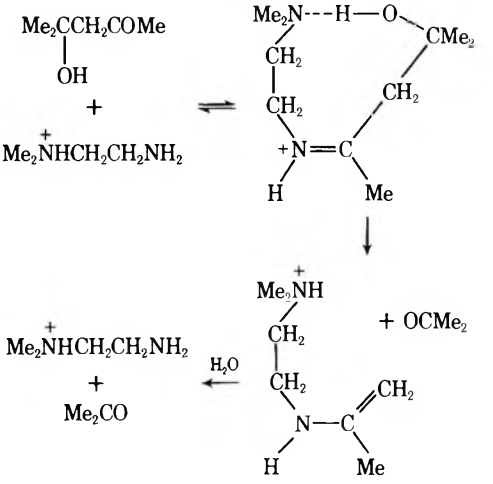


Figure 1. Plot of log k *vs.* pK_a for primary amines. Solid circles from work of other investigators. Point for each RNH_2 labeled with the appropriate R.

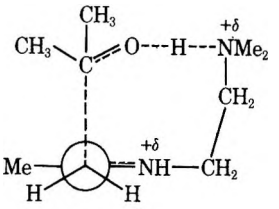
The value for glycine was extrapolated from the values of King[22] at ionic strengths 0.0, 0.1, and 0.3 using the Guggenheim equation[23] for activity coefficients. The values for the cationic amines were determined by potentiometric titrations in which the ionic strength passed through 0.1, with corrections to that ionic strength being made by use of the Davies equation.[24] All the pK_a values in Table II refer purely to the acidity of primary ammonium ions except those for 2-dimethylaminoethylamine and its conjugate acid. To put these constants on the same basis as the others they must be corrected (to 9.13 and 6.65, respectively) for the fact that monoprotonated 2-dimethylaminoethylamine is protonated at the primary amino group only to the extent of 62%.[25] The corrected

Scheme I



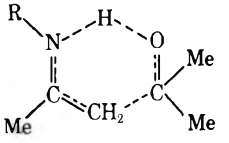
values are used in Figure 1. Inasmuch as dealdolization is not catalyzed by tertiary amines, the catalysis by monoprotonated 2-dimethylaminoethylamine must arise from the 38% of this material that is protonated at the tertiary amino group. Hence the catalysis constant listed for $Me_2NCH_2CH_2NH_2 \cdot H^+$ was divided by 0.38 to get the constant plotted for $Me_2NHCH_2CH_2NH_2^+$.

From the plot isopropylamine is seen to be a relatively poor catalyst for its basicity, a fact we attribute to steric hindrance. The line shown in the figure is the least-squares line through all the points for electrically neutral amines of the type RCH_2NH_2. The standard deviations of the nine points from this line is 0.09. The points for the *N*-(2-aminoethyl)trimethylammonium cation and the glycinate anion deviate by only 0.07 and 0.25, respectively, but the fact that they are on opposite sides of the line suggests that there may be a small tendency for cationic catalysts to be somewhat more reactive and anionic catalysts somewhat less reactive than similar electrically neutral catalysts.[26,27] The point for $Me_2NHCH_2CH_2NH_2^+$ lies 0.74 log unit above the line. The cationic nature of this catalyst may explain a small part of why this catalyst is 5.5 times as reactive as would be expected from the correlation of the activities of the other catalysts, but it does not plausibly explain it all. We believe that the deviation may well arise from bifunctional catalysis. Imine formation has been shown to be significantly faster than dealdolization for five primary amines ranging in basicity from *n*-propylamine to trifluoroethylamine.[10] Therefore, the rate-controlling step is the carbon–carbon bond cleavage step, and the ability of the protonated dimethylamino group to act as an internal acid catalyst in imine formation by $Me_2NHCH_2CH_2NH_2^+$ [28,29] cannot significantly increase the catalytic activity of this species in dealdolization. Instead, we suggest that the catalyst and diacetone alcohol react as shown in Scheme I to give an intermediate iminium ion in which the alcoholic hydroxy group is hydrogen bonded to the dimethylamino group from the catalyst. The nine-membered ring in the transition state of the rate-controlling step may be unnecessarily large. There is evidence that stereoelectronic constraints make eight members the favored ring size in the bifunctionally catalyzed dedeuteration of acetone-d_6 by ω-dimethylamino alkyl amines.[27,30] Because of the demands for coplanarity of six atoms in and attached to the double bond of the iminium ion and of a partly overlapping set of six atoms in the intermediate iminium ion and a preference for linearity in the hydrogen bond, the transition state in the 2-dimethylaminoethylamine-catalyzed reaction should have a structure like that shown in **2**, which is a Newman projec-



2

tion down the carbon–carbon bond that is changed from a single to a double bond in the rate-controlling step. Studies with molecular models suggest that transition states with rings as small as seven members can come close to meeting the stereoelectronic requirements. However, the six-membered ring in the cyclic transition state **3** com-



3

monly written for the rate-controlling step in the primary amine catalyzed dealdolization reaction[7,9,10] would suffer great strain in trying to achieve a conformation analogous to that in **2**. If this were not true, bifunctional catalysis by a species like 2-dimethylammonioethylamine would probably not be observable.

Experimental Section

Reagents. The diacetone alcohol (4-hydroxy-4-methyl-2-pentanone) used was fractionally distilled at 4-mm pressure. The absorbance of solutions of freshly distilled material in the range 220–270 nm showed that no more than 0.04% mesityl oxide was present. Although material stored at room temperature for 5 months had acquired 0.2% mesityl oxide, material kept in a freezer for 1 year had not deteriorated detectably. The electrically neutral amines used were fractionally distilled at atmospheric pressure, and stored under nitrogen. The (2-aminoethyl)trimethylammonium chloride hydrochloride prepared previously[29] was used.

Kinetics. To minimize loss of *n*-propylamine its standard solutions were prepared by additions to volumetric flasks already more than half full of aqueous solutions and standardized by adding excess acid and back titrating. Sodium chloride was present as needed to bring the ionic strength of kinetic solutions to 0.10. A Radiometer pH meter, Model 26, and G202B glass electrode were used to measure pH.

In a typical run 3.00 ml of buffer was pipetted into 1.0-cm uv cells and brought to 35.0 ± 0.2° in the sample chamber of a Cary 16 spectrophotometer. After 5.5 μl of diacetone alcohol had been added to each cell and the cells shaken and returned to the sample holders, the absorbance at 264.5 nm (slit width 0.4 mm) was monitored at preprogrammed time intervals.

pK Determinations. Standard solutions of 2-dimethylaminoethylamine and (2-aminoethyl)trimethylammonium chloride hydrochloride were titrated potentiometrically at 35° with hydrochloric acid and sodium hydroxide, respectively. After an aliquot of titrant was added the solutions were stirred for 1–2 min and then the pH was read without stirring. During the titration of 2-dimethylaminoethylamine the ionic strength varied from 0.097 to 0.12. Use of the Davies equation gave thermodynamic pK_a values for mono- and diprotonated amine of 9.34 and 6.00, respectively. For the 2-trimethylammonioethylammonium ion a thermodynamic pK_a of 6.30 was obtained from data at ionic strengths 0.14–0.064.

Analysis of Data. Absorbance–time data pairs were analyzed by least squares using eq 1 or 3 and a modified Gauss–Newton algorithm,[31] assigning all absorbance values equal weight. The computational algorithm, based in part on that of Deming,[32] for the least-squares treatment of pH–volume data pairs from titrations involved the regression analysis of an implicit function relating pH, volume, and the pK's and will be described in a future publication. The observed pH was taken as $-\log a_{H+}$. The pH–rate data were subject to standard linear regression analysis to obtain estimates of catalysis constants. The individual rate constants k_i, the dependent variables, were assigned unit weight except in the case of *n*-propylamine, where weighting proportional to $1/k_i^2$ was taken as a better measure of the reliability of the data. None of the second-order rate constants listed have been corrected for expansion of the solutions from room temperature to 35°.

Acknowledgment. We thank The Ohio State Instruction and Research Computer Center for the use of their facilities.

Appendix

Error Propagation Analysis. The following simple derivation of an expression for the effect of error in primary data on derived quantities leads to a general procedure and formulae. Given a set of functions,

$$\begin{aligned} x_1 &= f_1(\beta_1, \ldots, \beta_p) \\ x_2 &= f_2(\beta_1, \ldots, \beta_p) \\ &\vdots \\ x_n &= f_n(\beta_1, \ldots, \beta_p) \end{aligned} \tag{7}$$

the variances of $x_1, \ldots, x_n$ as a function of the variances of $\beta_1, \ldots, \beta_p$ may be computed from

$$\mathbf{M}_x = \mathbf{J}_\beta^f \mathbf{M}_\beta \mathbf{J}_\beta^{f\dagger} \tag{8}$$

where the diagonal elements of $\mathbf{M}_x$ are the variances of $x_1, \ldots, x_n$, and $\mathbf{M}_\beta$ is the variance covariance matrix for the parameters $\beta_1, \ldots, \beta_p$, for which a value is assumed. $\mathbf{J}_\beta^f$ is the Jacobian of the vector formed by the f_i

$$\mathbf{F} = \begin{bmatrix} f_1 \\ \vdots \\ f_n \end{bmatrix} \tag{9}$$

with respect to $\beta_1, \ldots, \beta_p$. This is the standard propagation of errors formula based on a Taylor series expansion of **F** truncated to the first order and is subject to assumptions discussed elsewhere.[14b]

The functions in eq 7 are explicit in $x_1, \ldots, x_n$, but this need not be the case. If one x_i were the pH, for example, no exact explicit formulation would be available.[33] Thus, more generally, one must deal with a series of functions nonlinear in the x_i.

$$\mathbf{G} = \begin{bmatrix} g_1 \\ \vdots \\ g_n \end{bmatrix} \quad \begin{aligned} g_1(x_1, \ldots, x_n, \beta_1, \ldots, \beta_p) &= 0 \\ &\vdots \\ g_n(x_1, \ldots, x_n, \beta_1, \ldots, \beta_p) &= 0 \end{aligned} \tag{10}$$

The vector $\mathbf{X} = x_1, \ldots, x_n$ is then solved for by an iterative procedure, *e.g.*, a Newton sequence.[34]

One may still make use of eq 8 to obtain the variances of **X**, however, by recourse to the implicit function theorem.[35] From this theorem one can construct $\mathbf{J}_\beta^f$ (although not **F**) by using the Jacobian of **G** with respect to **X**, $\mathbf{J}_x^g$, and with respect to β, $\mathbf{J}_\beta^g$, as shown below.

$$\mathbf{J}_\beta^f = -\mathbf{J}_x^{g^{-1}} \mathbf{J}_\beta^g \tag{11}$$

Thus

$$\mathbf{M}_x = \mathbf{J}_x^{g^{-1}} \mathbf{J}_\beta^g \mathbf{M}_\beta \mathbf{J}_\beta^{g\dagger} \mathbf{J}_x^{g^{-1}\dagger} \tag{12}$$

All matrix elements are evaluated at the solution, $\mathbf{X} = \mathbf{X}_0$, of the vector function g, *i.e.*

$$g(\mathbf{X}_0, \beta) = 0$$

Note that the elements of $\mathbf{J}_x^{g^{-1}}$ would be available as a by-product of a Newton sequence used in finding $\mathbf{X}_0$.

Equation 12 has been used to assess the effect of error in primary data on the derived concentrations entering eq 6 for each of several different sets of formulae. In this way it is possible to make a more objective decision concerning which set of formulae and associated primary data gives the least error in computing concentrations.

Registry No.—Diacetone alcohol, 123-42-2.

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Notes

Valence Isomers. Substituent Effects on the Equilibrium between 2*H*-Pyrans and Cis Dienones[1,2]

Thomas A. Gosink

Old Dominion University, Norfolk, Virginia 23508

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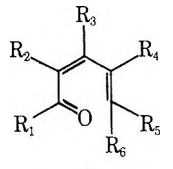
We have recently reported[3] that the system **1a** ⇌ **2a** exists almost completely as the cis dienone **1a**, and that **2a** has a fleeting, but spectroscopically demonstrable, existence in the synthesis of the system. We have also reported unequivocally that the bicyclic system **3** exists 95% as the 2*H*-pyran at ambient temperatures,[4,5] whereas systems related to **4** exclusively favor the cis dienone owing to the fact that the corresponding valence isomers of **4** would have two relatively unstable exocyclic double bonds.[6,7] Other substituent factors that shift the position of the equilibrium between the valence isomers to the 2*H*-pyran are two alkyl substituents on C-2 of the 2*H*-pyran[8-11] and substituents which extend the conjugation, *e.g.*, phenyl groups.[12]



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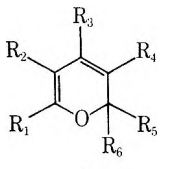

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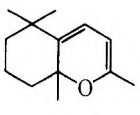
a, $R_1 = R_3 = R_5 = Me$; $R_2 = R_4 = R_6 = H$
b, $R_1 = R_5 = Et$; $R_3 = Me$; $R_2 = R_4 = R_6 = H$
c, $R_1 = R_5 = t\text{-Bu}$; $R_3 = Me$; $R_2 = R_4 = R_6 = H$
d, $R_1 = R_2 = R_4 = R_5 = Me$; $R_3 = Et$; $R_6 = H$



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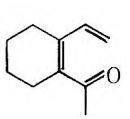

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The only case, here reported, which has been clearly observed to have a significant fraction of the 2*H*-pyran present in equilibrium with the cis dienone is the sterically hindered system **1d** ⇌ **2d**. The equilibrium **1d** ⇌ **2d** is clearly discernible by the lone proton substituent, which discloses that the system exists as 70–75% **2d** (quartet, J = 6.0 Hz, 0.7 H at δ 4.35) and 25–30% **1d** [quartet of quartets at higher resolutions, J(H, CH_3) = 7.00 and J(H,allyl CH_3) ≅ 1.0 Hz, 0.3 H at δ 5.25]. The methyl group R_5 at δ 1.2 also confirms the *ca.* 70% equilibrium concentration of **1d** by its coupling[13] with the lone proton (J = 6.0 Hz) and low integration curve (*ca.* 2 H).

The methyl portion of the ethyl group centered at δ 0.95 also lends support to the equilibrium mixture in that it appears as two nearly superimposed triplets in the ratio of about 3:1 (total 3 H). All of the other protons are in a very complex pattern between δ 1.5 and 2.4. No 4*H*-pyran was present in the spectral sample since it would be clearly discernible by its high methyl peak at δ 0.65 and the broad single hydrogen peak at δ 2.5.

The ketone **1d** exhibits an unusually high, weak carbonyl band at 5.83 μ, presumably because of lack of orbital overlap with the conjugated double bond system because of the extreme steric interactions within the molecule.

In compounds **1a–c** and **2a–c**, it is more difficult to elucidate the position of the equilibrium. In compounds **1a** $\rightleftharpoons$ **2a**, the transient presence of the 2*H*-pyran is clear,[3] the cis character has been established,[14] and the trace ($\leq$5%) presence of the 2*H*-pyran in the purified product is retained in the nmr spectrum. However, close examination of the nmr spectra of **1b** $\rightleftharpoons$ **2b** and **1c** $\rightleftharpoons$ **2c** suggests that in these cases the increase in the substituent bulk of R_1 and R_5 shifts the equilibrium so that as much as 20–25% of the 2*H*-pyran is present at ambient temperatures. In both the ethyl and *tert*-butyl cases (**b, c**) the protons R_2, R_4, and R_6 in the ketone form integrate for less than one proton each, and the small peaks in the δ 4–6 range, characteristic of those protons in the 2*H*-pyran form,[3] are slightly stronger than in the methyl case (**a**), accounting for about 0.8 protons over-all in each case.

In the ethyl case **b**, further support to the significant presence of the 2*H*-pyran is given by the fact that there is at shoulder on the spike at δ 2.08, due to the methyl groups R_3, and there is a significant multiplet pattern in the δ 1.4–2.08 region which would be due to the methylene group of R_5 in the 2*H*-pyran form.

The *tert*-butyl case **c** shows two principal peaks at δ 1.10 and 1.15, but they account for only 75% of the *tert*-butyl protons. A smaller pair of peaks at δ 1.08 accounts for the remaining *tert*-butyl protons.

Assessment of chemical and spectral data to establish the presence of valence isomers and the position of their dynamic equilibrium requires considerable care. No one method, save perhaps for nmr spectroscopy, is reliable for this assessment. For example, several systems have been clearly demonstrated spectroscopically to exist exclusively in the cis-dienone form;[6,7,15] yet the Diels–Alder adduct isolated was exclusively that of the 2*H*-pyran. The clear indication is that the 2*H*-pyran is the more active Diels–Alder diene and the techniques cannot be used as proof of the 2*H*-pyran as the major isomer present at ambient temperatures, as was done in one other report.[16]

Infrared spectroscopy is ambiguous, since both the conjugated carbonyl and the 2*H*-pyran are expected to have a band at or below 5.96 μ.[17] The cis dienones **1a–c** do indeed have strong bands near or just below 5.96 μ, but they are not the usual most intense bands in the spectra, presumably because of the rapid dynamic equilibrium process with the valence isomer. The 2*H*-pyran **3** has a strong distinct band at 6.06 μ with weak shoulders at higher wave numbers, whereas the predominantly 2*H*-pyran compound **1d** $\rightleftharpoons$ **2d** has a strong hand at 5.96 μ in addition to the weaker but distinct band at 5.84 μ.

Ultraviolet spectroscopy is also quite ambiguous, since most of the cases presented in the literature have calculated valves for both isomers which are quite close in value based on the empirical Woodward's rules which were developed from steroidal models. We have, through numerous literature examples, shown that the vinyl ether of the 2*H*-pyran should have a contribution of 10–15 nm to the λ_{max},[14] and not zero as presented in the rules.

In view of these spectral and chemical difficulties, it is recommended that some reports on 2*H*-pyrans and cis dienones be reevaluated.[11,16] Compounds **1a** and **2a** have been recently reported,[11] but with the conclusion based on ultraviolet spectroscopy that the final product is the trans dienone, as opposed to our reports that it is the cis product.[3,14] The difference in the experimental technique most probably accounts for the real differences in the spectral values reported. One case[11] was done under neutral and acid conditions, whereas the other experiments[3,14] were always kept neutral to basic.

Conclusions

Evidence presented in this paper indicates that for simple cis dienone 2*H*-pyran systems (1 $\rightleftharpoons$ 2) increasing the steric bulk of the alkyl substituents shifts the equilibrium from the cis dienone toward the 2*H*-pyran.

Great caution is advised in the interpretation of chemical and spectral data for cis dienones and 2*H*-pyrans. Several techniques should be employed along with nmr spectroscopy, which probably is the most reliable tool.

A report[11] that the dienone product is the trans isomer was probably due to the fact that it was an acid-catalyzed rearrangement.

Experimental Section

5-Methyl-*cis*-4-*trans*-6-nonadien-3-one (1b) and 2,6-diethyl-4-methyl-2*H*-pyran (2b) were prepared and purified as previously described.[18] Distillation to remove the minor, lower boiling 4*H*-pyran by-product afforded the mixture **1b** $\rightleftharpoons$ **2b**: bp 123° (50 mm); n^{20}D 1.4975; ir (neat) 5.84 (shoulder), 5.95, 6.13, and 6.32 μ; nmr (CCl_4) δ 1.0 (two nearly superimposed t, J = 7.0 Hz, 6 H), 1.78 (m, 2 H), 1.95 (d, J = 1 Hz, 3 H), 2.40 (m, 2 H), 5.88 (s, <1 H), 6.15 and 7.60 (AB part of an ABX pattern, J_{AB} = 16, J_{AX} = 1, and J_{BX} = 6 Hz, <2 H) plus smaller 2*H*-pyran (**3**) peaks at δ 4.4, 4.8, and 5.2 accounting for about 0.7 H.

2,2,5,8,8-Pentamethyl-*cis*-4-*trans*-6-nonadien-3-one (1c) and 2,6-(1,1-dimethylethyl)-4-methyl-2*H*-pyran (2c) were similarly prepared from the pyrylium salt.[19] Distillation at 126–128° (32 mm) produces the system **1c** $\rightleftharpoons$ **2c**: n^{20}D 1.4770; ir (neat) 5.99 (m), 6.14 (w), 6.35 μ (s); nmr (CCl_4) δ 1.0 (two s, 4 H), 1.10 and 1.15 (two s, 14 H), 2.0 (broad s, 3 H), 6.10 (d, J = 16 Hz, <1 H), 6.2 (s, <1 H under portion of d centered at 6.1), 7.58 (d, J = 16 Hz, <1 H). Smaller characteristic peaks assigned to the 2*H*-pyran 3 are discernible in the normal spectrum at δ 4.4, 4.8 and 5.2 totally accounting for <1 H.

Anal. Calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 81.16; H, 11.97. A 2,4-dinitrophenylhydrazone was obtained, mp 165–167°.

Anal. Calcd for $C_{20}H_{28}N_4O_4$: C, 61.84; H, 7.27. Found: C, 61.81; H, 7.48.

4-Ethyl-3,5-dimethyl-*cis*-3-*trans*-5-heptadien-2-one (1d) and 4-ethyl-2,3,5,6-tetramethyl-2*H*-pyran (2d) were also prepared from the pyrylium salt[20] using 3-ethyl-2-pentene.[21] Separation of **3d** $\rightleftharpoons$ **4d** from the 4*H*-pyran major product was achieved on a Nester-Faust adiabatic spinning band column with a 50:1 reflux ratio with a second similar distillation of the higher boiling material. The desired product boils at 90° (18 mm) or 128° (32 mm), n^{20}D 1.4794, and the 4*H*-pyran at 88° (18 mm). The product decomposes within a few weeks even when stored under nitrogen in the freezer. Refer to text for salient spectral data.

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.79; H, 10.81.

A compound, mp 144–146°, presumably the semicarbazone, was isolated.

Registry No.—1b, 38391-02-5; **1c,** 38391-05-8; **1c** 2,4-dinitrophenylhydrazone, 51310-42-0; **1d,** 51310-43-1; **1d** semicarbazone, 51310-44-2; **2b,** 51310-45-3; **2c,** 51310-46-4; **2d,** 51310-47-5; **3,** 5552-30-7.

Supplementary Material Available. Nmr spectra for isomers 1a–d and 2a–d will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-1942.

References and Notes

(1) Support from the Old Dominion University Research Foundation and from the Society of the Sigma Xi is gratefully acknowledged. A preliminary report of this work was presented: T. A. Gosink, Southeast-Southwest Regional Meeting of the American Chemical Society, New Orleans, La., Dec 1970, p 132. This report terminates the author's efforts in this field.

(2) See paragraph at end of paper regarding supplementary material.

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Reactions of Sulfur Dichloride with Active Methylene Compounds. A New Synthesis of 1,3-Dithietanes

S. K. Gupta

Process Research & Development Department, Pfizer Inc., Groton, Connecticut 06340

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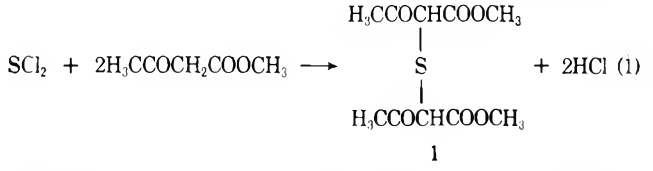
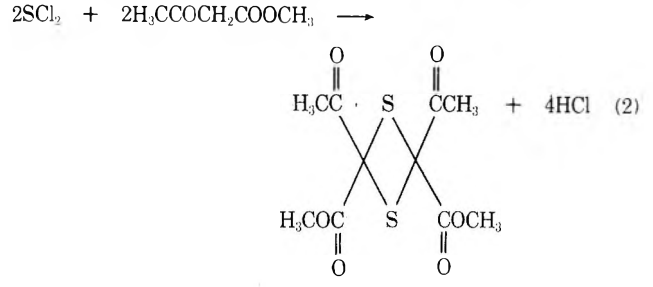
Sulfur dichloride (SCl_2) reacts with active methylene compounds under mild conditions to give sulfurated products in good yields. The course of product formation was dependent upon the reactivity of the active methylene moiety and the stoichiometry of the reaction. For example, sulfides **1** were produced with sulfur dichloride and a β-keto ester in a 1:2 ratio (eq 1). However, 1,3-dithietanes



(1)

1

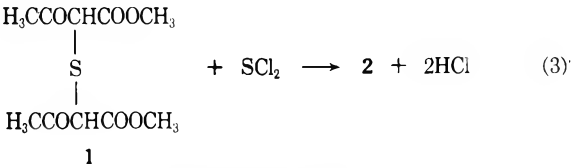
(**2**) were obtained when the stoichiometry of this reaction was changed according to eq 2. 1,3-Dithietanes (**2**) were



(2)

2

also synthesized by the reaction of sulfur dichloride with sulfides **1** (eq 3). Diethyl malonate, in sharp contrast to



(3)

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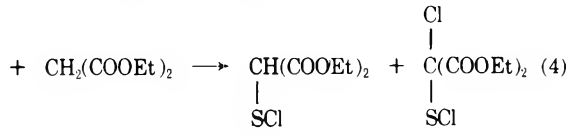
the results on the reaction of β-diketones and β-keto esters with SCl_2, reacted with sulfur dichloride according to eq 4. The representative examples of the reactions of sulfur

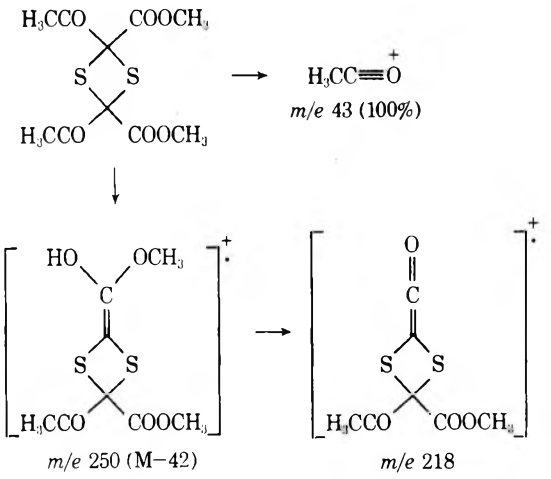


(4)

dichloride with active methylene compounds and the characterization data of the resultant products are summarized in Table I.[1]

A noteworthy feature of the reactions of sulfur dichloride reported here is the ready synthesis of 1,3-dithietanes (**2**) from β-diketones and β-keto esters. The structure of these 1,3-dithietanes is based on their nmr (absence of active methylene or methine hydrogens) and C, H, S analytical data. In addition to this, the mass spectral fragmentation pattern of **2** was similar to that expected for disubstituted β-keto esters (Scheme I),[2] and their desulfurization with Raney nickel regenerated the corresponding β-keto ester starting material.

Scheme I



m/e 43 (100%)

m/e 250 (M−42)

m/e 218

The sulfides **1** are capable of existence in meso or *dl*-pair configuration. The 1,3-dithietanes of type **2**, on the other hand, may involve cis–trans isomerism. Assignments in this regard have not been established and are beyond the scope of our current interests in this area.

Although the reactions of sulfenyl halides with various organic compounds are well known,[3] it is surprising that only few reactions of sulfur dichloride with organic compounds have so far been explored. These examples include the addition of SCl_2 to olefins,[3,4] dienes,[3,5] and carbon suboxide,[6] and the brief report on the reaction of SCl_2 with ethyl acetoacetate[7] and β-diethylaminoacrolein.[8] The present sequence of reactions thus opens a new area in organosulfur chemistry with many mechanistic and synthetic possibilities.

Experimental Section[9]

Reaction of Sulfur Dichloride with Active Methylene Compounds in a 1:2 Ratio. Bis(α-carbomethoxyacetonyl) Sulfide (1). A solution of 29.03 g (250 mmol) of methyl acetoacetate in 100 ml of ethyl acetate was cooled to 10° and then 14.4 g (125 mmol) of sulfur dichloride was added to it in 10 min with efficient stirring. The stirring was continued for an additional 1 hr at 25° and the

Table I
Reactions of Sulfur Dichloride with Active Methylene Compounds to Give Sulfurated Products[a]

Active methylene compound, reacted (registry no.)	SCl_2/ active methylene ratio	Product isolated (registry no.)	Yield,[b] %	Mp, °C	Nmr[c]	Mol wt[d]
$H_3CCOCH_2COOCH_3$ (105-45-3)	0.5	$H_3CCOCHCOOCH_3$ | S | $H_3CCOCHCOOCH_3$	65	141–143	2.41 (s, 3 H), 3.76 (s, 3 H), and 13.33 (s, 1 H)	262
	1	$H_3CCO-C(S)(S)-COOCH_3$ / $H_3CCO-C(S)(S)-COOCH_3$ (51270-70-3)	25	125–126	2.60 (s, 1) and 3.85 (s, 1)	292 (294)
$H_3CCOCHCOOCH_3$ | S | $H_3CCOCHCOOCH_3$ (51270-69-0)	1.1	$H_3CCO-C(S)(S)-COOCH_3$ / $H_3CCO-C(S)(S)-COOCH_3$	50	125–126	2.60 (s, 1) and 3.85 (s, 1)	292
H_3CCOCH_2COOEt (141-97-9)	0.5	$H_3CCOCHCOOEt$ | S | $H_3CCOCHCOOEt$ (51270-71-4)	70	123–124[e]	1.28 (t, 3 H, J = 6.5 Hz), 2.41 (s, 3 H), 4.24 (q, 2 H, J = 6.5 Hz), and 13.45 (s, 1 H)	290
$H_3CCOCH_2COCH_3$ (123-54-6)	0.5	$H_3CCOCHCOCH_3$ | S | $H_3CCOCHCOCH_3$ (31655-65-9)	70	104.5–105.5	2.35 (s, 6 H) and 16.9 (s, 1 H)	230
	1	$H_3CCO-C(S)(S)-COCH_3$ / $H_3CCO-C(S)(S)-COCH_3$ (51270-72-5)	30	165–166.5	2.4 (s)	262 (257)
$EtOCOCH_2COOEt$ (105-53-3)	2.5	$ClCH(COOEt)_2$ + (14064-10-9) SCl | $Cl-C(COOEt)_2$[f] (51270-73-6)		91–108[g] (0.3 mm)		

[a] Satisfactory analytical values (±0.3% for C, H, S) were reported for all compounds in table. Ed. [b] By isolation. [c] In $CDCl_3$ using TMS as internal standard at 0 ppm. [d] By mass spectrometry. The values in parentheses are by osmometry (benzene). [e] Lit.[8] mp 83–85.5°. [f] The mixture of products isolated by distillation was identified by glpc [$ClCH(COOEt)_2$] and mass spectrometry [$ClCSCl(COOEt)_2$]. [g] Boiling point of the mixture of two products.

reaction mixture was then cooled to 0°. The solid thus precipitated was filtered and washed with 10 ml of cold ethyl acetate to give 21.2 g (65%) of the desired product, mp 140–142°. Recrystallization from hot ethyl acetate provided the pure substance: mp 141–143°; mass spectrum (70 eV) m/e (rel intensity) 262 (0.08), 188 (0.1), 156 (0.09), 115 (0.09), 85 (0.11), 69 (0.07), 59 (0.08), 43 (100).

Reaction of Sulfur Dichloride with Active Methylene Compounds in a 1:1 Ratio. 2,4-Bis(acetyl)-2,4-bis(carbomethoxy)-1,3-dithietane (2). Methyl acetoacetate (29.03 g, 250 mmol) was dissolved in 50 ml of chloroform and then sulfur dichloride (28.8 g, 250 mmol) was added to it at 25° to 28° in 1.25 hr. The resulting yellow solution was stirred at 25° for 16 hr. The solvent was then removed under vacuum and the oil (43.6 g) crystallized upon cooling. The compound was triturated with diethyl ether (50 ml) and filtered. The solid thus obtained (15.6 g) was recrystallized from hot ethyl acetate to give the product as cubic crystals; yield 9.1 g (25%); mp 125–126°; mass spectrum (70 eV) m/e (rel intensity) 292 (0.001), 250 (0.04), 233 (0.2), 218 (0.31), 191 (0.22), 175 (0.05), 104 (0.07), 103 (0.07), 43 (100).

Reaction of Bis(α-carbomethoxyacetonyl) Sulfide (1) with Sulfur Dichloride. The sulfide 1 (2.62 g, 10 mmol) was dissolved in 10 ml of chloroform and then a solution of sulfur dichloride (1.1 g, 11 mmol) in chloroform (5 ml) was added to it at 10°. The resulting yellow solution was stirred for 16 hr at 25°. The solvent was then removed and the residue upon trituration with diethyl ether (10 ml) gave 2 as a crystalline product, yield 2.0 g. Recrystallization from ethyl acetate afforded 1.41 g (50%) of pure substance, mp 124–126°.

Reaction of Diethyl Malonate with Sulfur Dichloride. Diethyl malonate (40 g, 250 mmol) was added to sulfur dichloride (65.3 g, 625 mmol) at 10° in 0.5 hr. After the resulting yellow solution was stirred at 25° for 16 hr, the solvent was removed *in vacuo* to give an oil. The distillation provided 23.7 g of a yellow liquid, bp 91–108° (0.3 mm). Glpc analysis indicated it to be a mixture of two compounds (Table I).

Desulfurization of 2,4-Bis(acetyl)-2,4-bis(carbomethoxy)-1,3-dithietane (2) with Raney Nickel.[5] A mixture of 2 (2.92 g, 10 mmol) and 10 g of Raney nickel in 50 ml of ethanol was refluxed under nitrogen for 6 hr. Glpc analysis indicated the presence of methyl acetoacetate in the reaction mixture.

Acknowledgments. The author wishes to thank Dr. R. K. Blackwood for discussions and Mr. H. J. Slater for technical assistance.

Registry No.—Sulfur dichloride, 10545-99-0.

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(1) Unless specified otherwise, all compounds in Table I with yields given are new.
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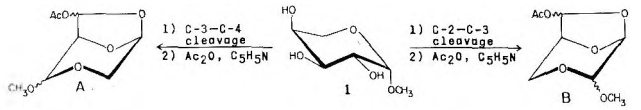
7(S)-Acetoxy-2(S)-methoxy-1(S)-3,6,8-trioxabicyclo-[3.2.1]octane.[1] Characterization of the Product from Periodic Acid Oxidation of Methyl β-L-Arabinopyranoside in Methyl Sulfoxide[3]

Jacques Gelas,[4] Derek Horton,* and Joseph D. Wander

Department of Chemistry, The Ohio State University, Columbus, Ohio 43210

Received December 19, 1973

It was shown by Yu and Bishop[2] that methyl β-L-arabinopyranoside (1) in methyl sulfoxide containing excess periodic acid consumes only one mole per mole of oxidant, presumably through C-3–C-4 glycol cleavage, as borohydride reduction and subsequent acid hydrolysis of the product gave a volatile compound chromatographically indistinguishable from ethylene glycol. The lack of further oxidation was attributed to rapid internal cyclization of the initial dialdehyde to afford a tricyclic product containing no group labile to the glycol-cleavage oxidant. Acetylation of the oxidized 1 gave a mixture from which was isolated a 38% yield of a crystalline monoacetate **2**, mp 89–90°, $[\alpha]^{22}D$ +44° (chloroform). Based on the presumption of C-3–C-4 cleavage in **1**, a structure of type A was assigned.[2] However, the modest yield of **2** leaves open the conceivable possibility that it could have arisen *via* C-2–C-3 cleavage in **1**, to generate an acetate having a structure of type B.

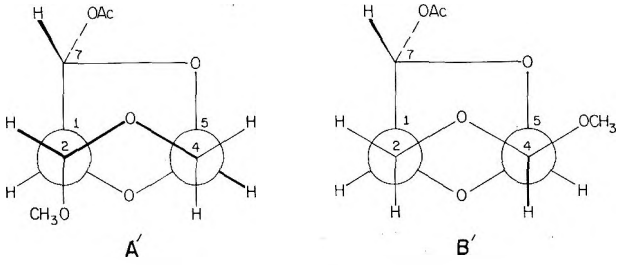


The present investigation was designed to place the structural characterization of compound **2** on a firm basis. Such products are useful matrices in which to examine, with dioxolane and 1,4-dioxane ring systems, the types of anomeric equilibria and polar anomeric effects that have already been studied extensively in this laboratory with respect to polysubstituted tetrahydropyran ring systems derived from sugars.[5] Related equilibria have also been investigated by one of us in racemic tricyclic analogs obtained from glycerol and dicarbonyl compounds.[6]

Mass spectral data for **2** include a weak (0.3% of the base peak) molecular ion (*m/e* 204) consistent with a formulation of $C_8H_{12}O_6$, relatively small fragments corresponding to the loss of $CH_3O\cdot$ at *m/e* 173 (0.3%) and of $CH_3CO_2\cdot$ at *m/e* 145 (4.7%), more prominent fragments at *m/e* 43 (100%), 103 (21%), and 145 (4.7%) characteristic of acetate groups, and a metastable-verified elimination of ketene at *m/e* 129–87 (m*, 58.8). These data accord with the formulation of a monomeric, monoacetylated, methyl acetal structure for **2**.

Also consistent with the formulation $CH_3O(C_5H_6O_3)O\text{-}COCH_3$ for compound **2** is the 22.3-MHz ^{13}C nmr spectrum in chloroform-*d*, which exhibits eight separate resonances assignable, respectively, to the acetate methyl group [δ^c (Me_4Si) +27.0], the *O*-methyl group (61.4), singly oxygenated methylene (69.1) and methine (85.8) carbon atoms, three doubly oxygenated carbon atoms (100.3, 101.5, and 109.0), and an acetate carbonyl carbon atom (176.7). Lacking appropriate reference compounds, specific assignments of the three acetal carbon atoms must be deferred. The shift of the methylene carbon atom corresponds fairly closely to the shifts (66.7–66.8) measured[7] for the resonance of the analogous methylene carbon atoms in some 4-alkoxy-5-methyl-3,6,8-trioxabicyclo[3.2.1]octanes in which the alkoxyl group has been shown[6] to adopt the axial disposition.

Four pairs of diastereoisomers could, in principle, exist for structure A, and a similar number for B. In actuality, however, a number of these possibilities may be excluded because the stereochemistry at the anomeric carbon atom of **1** and at the hydroxylated carbon atom that is *not* oxidized is retained in the final product; furthermore, the stereochemistry at the bridgehead acetal carbon atom is determined by the orientation of the unoxidized alcoholic center. These considerations decrease the possibilities to two pairs of compounds epimeric at C-7. In each pair the endo isomer would presumably experience sufficient destabilization due to repulsive interactions with O-3 to preclude the formation of this isomer. This conclusion is supported by the earlier observation that the resonance of H-7 in this molecule gives rise to a very narrow singlet, an observation consistent only with the location of this proton in the endo orientation[2] because of the ~90° dihedral relationship between the bond to the adjacent bridgehead proton (H-1) and the 7 endo bond.



Only two structural possibilities remain for **2**, namely, A′ and B′. Specific evidence permitting selection between these two structures is suggested in the 60-MHz ^1H nmr spectrum of **2** published by Yu and Bishop,[2] although the resolution in that spectrum is insufficient to permit extraction of the necessary coupling information. The ^1H nmr spectrum of **2** in chloroform-*d* was redetermined at 100 MHz with a sample that had been deoxygenated with a stream of nitrogen. Well-separated signals are observed for each of the six ring protons, permitting[8] extraction of a complete set of reliable, first-order coupling constants for this molecule. These values, which were measured from 100-Hz sweeps, were verified by double-irradiation experiments. As with other examples[9,10] of bicyclo[3.2.1]octane derivatives, long-range coupling interactions of the "W" and extended-"W" type[8] abound. See Table I.

A closely related compound, (racemic) 1,4,4-trimethyl-3,6,8-trioxabicyclo[3.2.1]octane (**3**), exhibits[10] two long-range couplings whose presence or absence can be used to

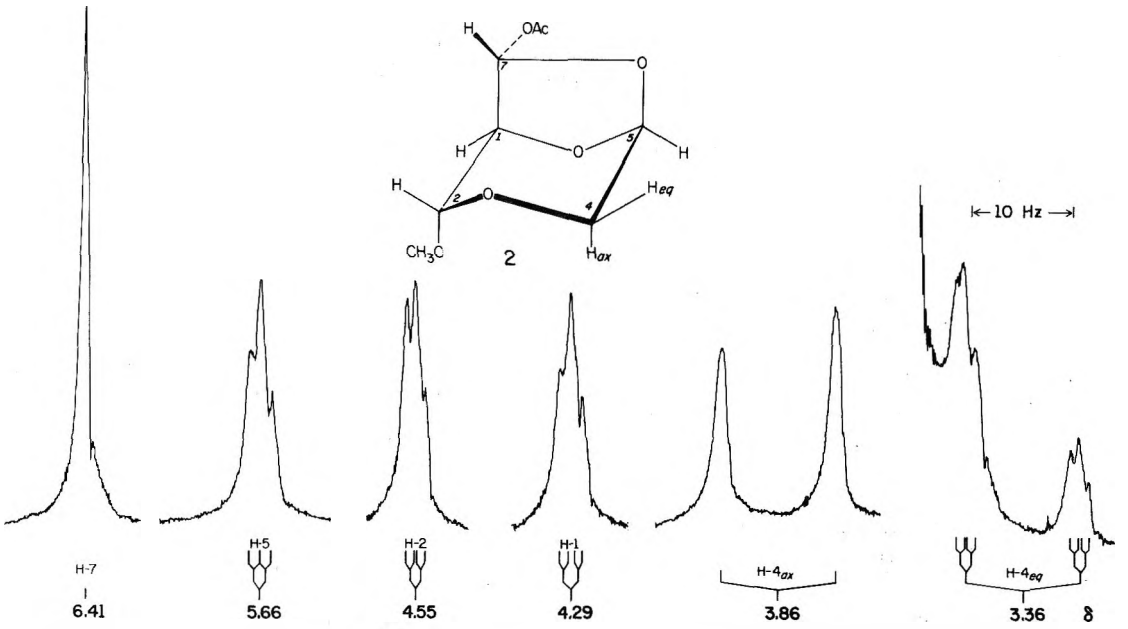
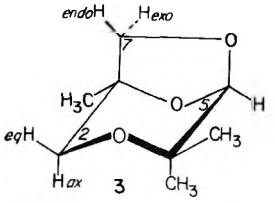


Figure 1. Expanded portions of the 100-MHz ^1H nmr spectrum of compound **2** in chloroform-*d*; the edge of the O-CH_3 resonance at δ 3.49 is visibly distorting the low-field portion of the H-4 eq signal.



$|^5J_{2eq,5}|$ 1.1 Hz
$|^4J_{2ax,7exo}|$ 1.4 Hz
$|^2J_{2ax,2eq}|$ 11.2 Hz

specify the location of the exocyclic substituents of **2**. The first of these, a four-bond interaction between H-2 ax and H-7 exo, is not observed for **2**, as the foregoing discussion of this proton requires. The other coupling, acting through five bonds between an equatorially disposed methylene proton and the remote bridgehead proton, provides a means for differentiating between A′ and B′ on the basis of the appearances of the signal for the proton geminal to the methoxyl group. In A′ this proton (H-2) would exhibit couplings to H-1, to H-5 (indicated by intensified bond lines), and possibly to H-4 eq, whereas the corresponding proton (H-4) in the isomeric representation B′ is axial and would, therefore, experience only a single coupling interaction, $^3J_{4,5}$. The observation that H-5 resonates as a slightly broadened doublet of doublets ($J_{2,5}$ = 1.1, $J_{4,5}$ = 1.1 Hz, see Figure 1) establishes that **2** has the structure A′ and validates the previous[2] tentative assignment.

There is evidence[6] for the operation of a strong anomeric effect[11] in 4-alkoxy-3,6,8-trioxabicyclo[3.2.1]octanes. Accordingly, it may be possible to account for the apparent singularity of **2**, as the only isolated product of this type formed from reaction of a methyl pentopyranoside with periodate in methyl sulfoxide, on the principle that analogous cyclization processes that would generate an equatorially disposed methoxyl group would be prohibitively disfavored. On the basis of this rationalization one would expect the analogous oxidation of methyl β-D-xylopyranoside to produce the 4 epimer of B′, as the appropriate C-2–C-3 cleavage is reported[2] to be favored.

Preparations of **2**, which had physical constants in acceptable agreement with literature[2] values, were made by Dr. R. H. Bell and by E. W. Rhode, III. Some preliminary ^1H nmr experiments were performed by Dr. J. H. Lauterbach. The ^{13}C Fourier transform nmr spectrum of **2** was recorded by Mr. J. M. Geckle with a Bruker HX-90 spectrometer; the spectrum was measured in a 10-mm tube at ~25° and is referenced to internal tetramethylsilane.

Table I
Chemical Shifts and Coupling Constants Measured for 7(*S*)-Acetoxy-2(*S*)-methoxy-1(*S*)-3,6,8-trioxabicyclo[3.2.1]octane (2) in Chloroform-*d* Solution at 100 MHz

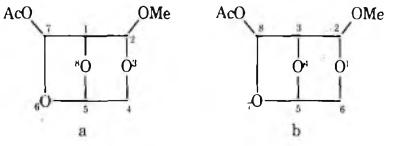
Chemical shifts	δ^a	Coupling constants	Hz
H-4 eq	3.36	$^3J_{1,2}$	0.8
H-4 ax	3.86	$^5J_{1,4eq}$	1.4
H-1	4.29	$^5J_{2,5}$	1.1
H-2	4.55	$^2J_{4eq,4ax}$	11.5
H-5	5.66	$^3J_{4eq,5}$	1.1
H-7	6.41	$^4J_{1,5}$	<0.5

[a] Expressed in parts per million downfield from internal Me_4Si.

Registry No.—**1**, 1825-00-9; **2**, 51271-13-7.

References and Notes

(1) The conventional numbering (a) for this ring system places the smallest numbers at the bridgehead positions along the longest ring leg; an earlier report[2] described an alternative notation (b) in which precedence was given to the heteroatoms of the 1,4-dioxane ring.



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Conformational Analysis. X. Chair–Twist Energy Difference in 1,3-Oxathianes[1a]

Kalevi Pihlaja*[1b,c] and Paavo Pasanen[1c]

Departments of Chemistry, University of Stirling, Stirling, FK9 4LA, Scotland, and University of Turku, 20500 Turku 50, Finland

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Several recent reports[2] have dealt with the chair–twist transformation of 1,3-dioxanes and a paper based on chemical equilibration and ^{1}H nmr spectroscopy has also been published on that of 1,3-dithianes.[3] The chair–twist enthalpy difference of the 1,3-oxathiane ring[4] has been estimated at 25 kJ mol^{-1} (6.0 kcal mol^{-1}) by comparison with the 1,3-dioxane and 1,3-dithiane values. A gas-phase value of 22.5 ± 4.0 kJ mol^{-1} (5.4 ± 1.0 kcal mol^{-1}) has very recently been obtained by use of appearance potentials of the $[M - CH_3]^+$ ions of *cis*- and *trans*-2,2,4,6-tetramethyl-1,3-oxathiane.[5]

The aim of our present study was to determine thermodynamic parameters for the chair–twist change of the 1,3-oxathiane ring by means of chemical equilibration. For this purpose, we selected the diastereoisomeric 2-*tert*-butyl-2,6-dimethyl-1,3-oxathianes, of which the *cis*-2,6-diMe isomer is likely to exist in a twist conformation to avoid the interactions present in a chair conformation, *viz.*, axial *tert*-butyl or syn-axial arrangement of 2 and 6 methyl groups.[2b,4,5]

Results

The equilibria were established at 280, 298, and 318°K. The respective equilibrium constants are shown in Table I together with $\Delta H°$ and $\Delta S°$ obtained from them by the method of least squares.

Table I
Equilibria between *r*-2-*tert*-Butyl-2,*trans*-6- and *r*-2-*tert*-Butyl-2,*cis*-6-dimethyl-1,3-oxathianes in 10% (v/v) CCl_4 Solutions

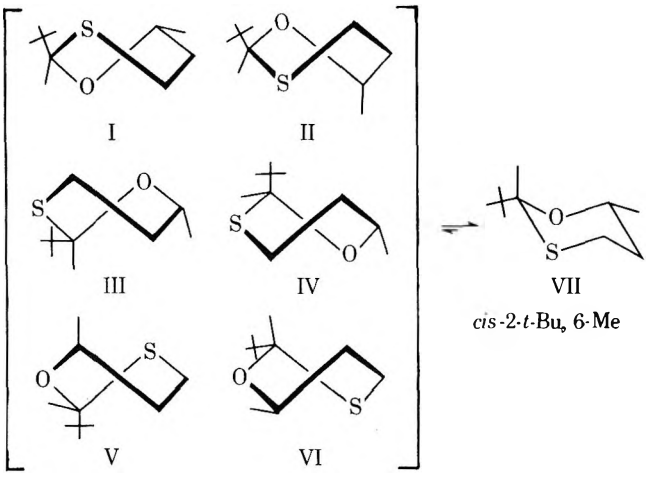
Temp, °K	K = [trans]/[cis][a]	$-\Delta G°$, kJ mol^{-1} (kcal mol^{-1})
280	81.18 ± 7.22[b]	10.241 ± 0.209[b] (2.448)
298	56.97 ± 2.78	10.021 ± 0.121 (2.395)
318	41.15 ± 0.96	9.833 ± 0.059 (2.350)
$-\Delta H°$	13.24 ± 0.14[c] kJ mol^{-1} (3.164 kcal mol^{-1})	
$-\Delta S°$	10.73 ± 0.48[c] J mol^{-1} °K^{-1} (2.564 cal mol^{-1} °K^{-1})	
$-\Delta G°$ (298)	10.04 kJ mol^{-1} (2.40 kcal mol^{-1})	

[a] Glpc area ratios; response ratio assumed to be unity. The values shown are the means of two or three parallel samples, which were analyzed 6–12 times. The systematic error introduced by assuming the response ratio to be unity is likely to be much less than the standard deviation of the measurements. [b] Standard deviations. [c] Statistical errors of the least-squares plot.

Discussion

r-2-*tert*-Butyl-2,*trans*-6-dimethyl-1,3-oxathiane has six conceivable twist conformations (I–VI) while the other isomer exists in a single chair conformation (VII) only, excluding enantiomeric forms (Scheme I).

Scheme I



Owing to the pseudo-axial *tert*-butyl groups the contributions of IV and V can be neglected. Inspection of molecular models[6] reveals that I and VI may not differ significantly in energy. Owing to the peculiar geometry of the ring[4] the pseudo-axial methyl group in VI leans appreciably outward. Consequently, the residual interactions due to the isoclinal[7] *tert*-butyl group in I and the "pseudo-axial" methyl group in VI are nearly equal and may not exceed 2 kJ mol^{-1} (0.5 kcal mol^{-1}).

As to the twist forms II and III, they also seem to be nearly equally stable.[6] II has an isoclinal *tert*-butyl group and a pseudo-axial methyl group at position 6, which interacts with the sulfur atom only. III has merely a pseudo-axial methyl group at position 2, which now, however, interacts with the "syn-axial" hydrogen atom at position 5. Both in II and III these nonbonded interactions are likely to be about 4 kJ mol^{-1} (1 kcal mol^{-1}).[3,4,8]

Table II
Chair–Twist Interconversion in Cyclohexane, 1,3-Dioxane, 1,3-Oxathiane, and 1,3-Dithiane

Compd	$\Delta G°_{CT}$, kJ mol^{-1} (kcal mol^{-1})	$\Delta H°_{CT}$, kJ mol^{-1} (kcal mol^{-1})	$\Delta S°_{CT}$, J mol^{-1} °K^{-1} (cal mol^{-1} °K^{-1})	Ref
Cyclohexane[a]	21.2 (5.1)	25.2 (6.0)	13.4 (3.2)	11
1,3-Dioxane[b,c]	33.5 (8.0)	35.8 (8.6)	$\lesssim$9.1 ($\lesssim$2.2)	11
1,3-Oxathiane[d]	23 ± 2 (5.5)	25.2 (6.0)	~9.1 (~2.2)	This work
1,3-Dithiane[e]	7.6 (1.8)	14.3 (3.4)	22.3 (5.3)	3
	11.0 (2.6)	16.7 (4.0)	19.0 (4.5)	11

[a] For the 1,3-di-*tert*-butyl isomer; N. L. Allinger and L. A. Freiberg, *J. Amer. Chem. Soc.*, **82**, 2393 (1960). [b] $\Delta H°_{CT}(g)$ = 35.6 ± 2.1 kJ mol^{-1} (8.5 ± 0.5 kcal mol^{-1}; ref 2e). [c] Values ranging from 26 to 30 kJ mol^{-1} (6.2–7.2 kcal mol^{-1}) have been proposed for $\Delta H°_{CT}$ on the basis of the dependence of geminal (C-2) and vicinal coupling constants on temperature in ref 2i. [d] $\Delta H°_{CT}(g)$ = 25.0 ± 4.0 kJ mol^{-1} (6.0 ± 1.0 kcal mol^{-1}) after a correction for the double-buttressing effect in 2,2,*cis*-4,6-tetramethyl-1,3-oxathiane (ref 5, see text also). [e] See discussion.

If we assume that the excess entropy of the *trans*-2-*t*-Bu-6-Me isomer is principally due to the mixing of the different twist conformations (I–III and VI), the contributions of the different twist forms may be estimated from the experimentally determined entropy difference (10.73 J mol^{-1} $°K^{-1}$ = 2.56 cal mol^{-1} $°K^{-1}$) and the equation

$$\frac{\Delta S^{\circ}_{\text{exptl}}}{R} = 2x \ln x + (1 - 2x) \ln (0.5 - x) \quad (1)$$

where x is the mole fraction of I and VI and $(0.5 - x)$ that of II and III. Then the proportions of I and VI will be about 36% and those of II and III about 14%. Thus the free-energy difference between I (or VI) and II (or III) is about 2.3 kJ mol^{-1} (0.55 kcal mol^{-1}).

The excess enthalpy of I and VI with respect to the unsubstituted twist conformations was assumed to amount to 2 kJ mol^{-1} (0.5 kcal mol^{-1}; see before) and hence that of II and III (if the twist forms do not differ in entropy) will be (2 + 2.3) = 4.3 kJ mol^{-1} (1.03 kcal mol^{-1}), also in close agreement with the preceding postulation.

Since

$$\Delta H = \Sigma x_i \Delta H_i$$

the total excess enthalpy of *r*-2-*tert*-butyl-2, *trans*-6-dimethyl-1,3-oxathiane will be $\Delta H°_{CT}$ +2.64 kJ mol^{-1} ($\Delta H°_{CT}$ +0.63 kcal mol^{-1}) over that of an unsubstituted chair form. The conformational enthalpy of an axial methyl group at position 2 in the 1,3-oxathiane ring has been determined (13.6 kJ mol^{-1} = 3.25 kcal mol^{-1}).[4a] Owing to the geminal substitution[2g,9] this interaction in *r*-2-*tert*-butyl-2,*cis*-6-dimethyl-1,3-oxathiane is likely to be slightly enhanced to, say, 14.6 kJ mol^{-1} (3.5 kcal mol^{-1}).

Now we are able to derive a value for $\Delta H°_{CT}$ from the experimental enthalpy difference (13.24 kJ mol^{-1} = 3.16 kcal mol^{-1}) between the epimeric 1,3-oxathianes (Table I), since $\Delta H°_{\text{exptl}}$ = [$\Delta H°_{CT}$ +2.64 (0.63)] − 14.6 (3.50) and $\Delta H°_{CT}$ = 13.24 (3.16) − 2.64 (0.63) + 14.6 (3.50) = 25.2 kJ mol^{-1} (6.0 kcal mol^{-1}). This estimate is not far from the gas-phase value, 22.5 kJ mol^{-1} (5.4 kcal mol^{-1}), based on appearance potential measurements.[5] Moreover, the latter value should in fact be revised upwards because of the double-buttressing effect in the reference chair form, 2,2,*cis*-4,6-dimethyl-1,3-oxathiane. In 2,2,*cis*-4,6-dimethyl-1,3-dioxane the magnitude of this effect is about 3.1 kJ mol^{-1} (0.74 kcal mol^{-1}).[2c,e,g] By comparing the corresponding interactions in 1,3-dioxanes[2b-e] and in 1,3-oxathianes[4,5] with each other the double-buttressing effect in 2,2,*cis*-4,6-dimethyl-1,3-oxathiane may be estimated at 2.5 kJ mol^{-1} (0.60 kcal mol^{-1}). Consequently, the corrected value of $\Delta H°_{CT}$ (g) is about 25 kJ mol^{-1} (6.0 kcal mol^{-1}).

1,3-Oxathiane itself has six possible twist conformations but only two possible chairs.[10] If all the twists are of the same energy, $\Delta S°_{CT}$ should be R ln 3 or 9.13 J mol^{-1} $°K^{-1}$ (2.18 cal mol^{-1} $°K^{-1}$) and, accordingly, $\Delta G°_{CT}$ = 22.5 kJ mol^{-1} (5.4 kcal mol^{-1}). If any of the twist forms predominates, then $\Delta S°_{CT}$ will be somewhat smaller and $\Delta G°_{CT}$ somewhat higher. Thus we can estimate $\Delta G°_{CT}$ to be 23 ± 2 kJ mol^{-1} (5.5 ± 0.5 kcal mol^{-1}) at 298°K.

It may be of some interest to compare chair–twist energy differences in cyclohexane, 1,3-dioxane, 1,3-oxathiane, and 1,3-dithiane, and this has been done in Table II. The parameters presented for the 1,3-dithiane ring in ref 3 are suitable for 2,5-disubstituted derivatives only.[3] Other 1,3-dithianes[11] have clearly greater $\Delta H°_{CT}$ (16–20 kJ mol^{-1} or 4–5 kcal mol^{-1}) and $\Delta G°_{CT}$ (10–14 kJ mol^{-1} or 2.4–3.4 kcal mol^{-1}).

Experimental Section

r-2-*tert*-Butyl-2,*cis*-6-dimethyl-1,3-oxathiane was prepared earlier.[12] The equilibration method and the analysis of the equilibrium mixtures have been described before.[4]

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Registry No.—*r*-2-*tert*-Butyl-2,*trans*-6-dimethyl-1,3-oxathiane, 51271-30-8; *r*-2-*tert*-butyl-2,*cis*-6-dimethyl-1,3-oxathiane, 51271-31-9.

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Rearrangements of α,β-Unsaturated α′-Halocyclobutanones

William T. Brady* and Arvind D. Patel

Department of Chemistry, North Texas State University, Denton, Texas 76203

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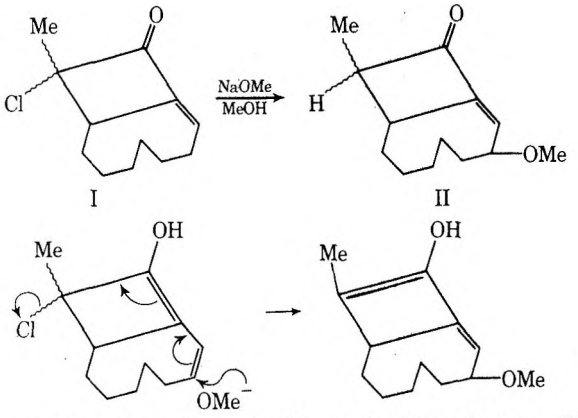
The base-catalyzed ring contraction of α-halocyclobutanones has been the subject of considerable study in recent years.[1] We have recently synthesized some α,β-unsaturated α′-halocyclobutanones[2] and now reveal the unexpected results obtained upon base treatment of such compounds.

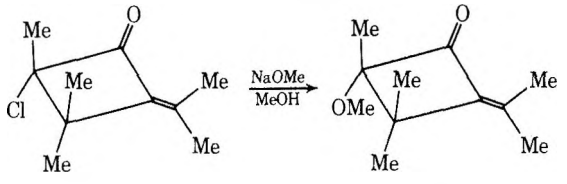
The treatment of 10-chloro-10-methylbicyclo[7.2.0]undec-1-en-11-one (I) with sodium methoxide in methanol resulted in allylic substitution rather than ring contraction to produce the 3-methoxy ketone II. The substitution



I II

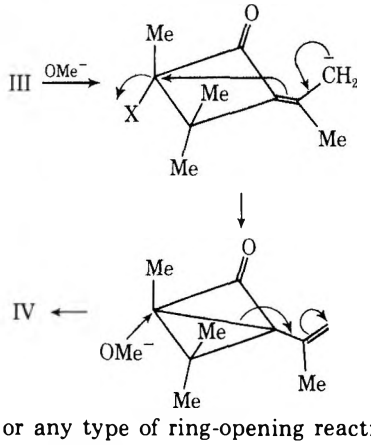
apparently occurs through the enol of the ketone. This substitution occurred readily at ambient temperature in an 80% yield.

Conversely, the treatment of 2-chloro-4-isopropylidene-2,3,3-trimethylcyclobutanone (III) with sodium methoxide in methanol under identical conditions resulted in a direct substitution product, the 2-methoxy ketone IV, in 80%



III IV

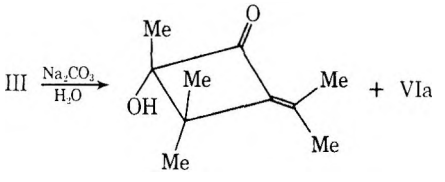
yield. Similarly, the methylbromo and ethylchloro compounds also give the direct substitution products. It seems unlikely that these substitution products are the result of a direct displacement because of the tertiary center. These products may result from an elimination proceeding through a bicyclobutanone intermediate which adds methoxide to furnish IV.[3] There is no evidence of ring



contraction or any type of ring-opening reaction in any of these systems described.

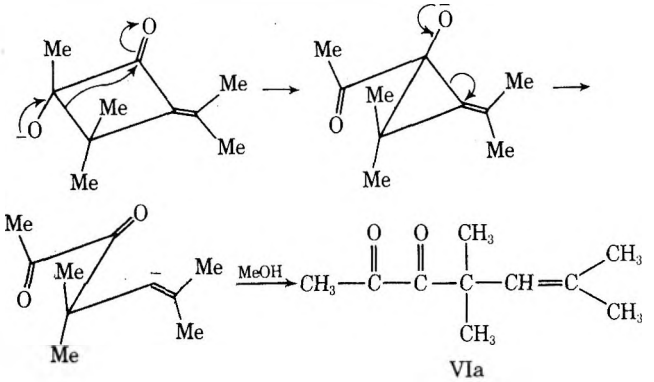
The different behavior of the two α,β-unsaturated α'-chlorocyclobutanones is intriquing. Perhaps the strain in the bicyclopropanone intermediate resulting from I is too severe for this pathway to be followed and the allylic substitution occurs instead.

Treatment of III with a 20% aqueous solution of sodium carbonate at reflux resulted in the expected hydroxy compound, V, and an unexpected product, VIa. The amount



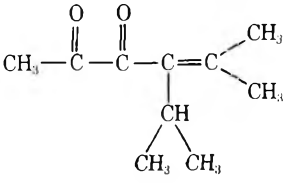
V

of VIa was dependent upon the reflux time and it soon became apparent that V was undergoing a ring-opening rearrangement reaction leading to VIa. The structure proposed for VIa is consistent with the elemental analysis, mass spectrum, infrared spectrum, and most significantly the nmr spectrum. This ring-opening reaction is believed to originate at the hydroxy group because the corresponding methoxy compound does not undergo this reaction. A mechanistic rationale is provided for the formation of this product.



VIa

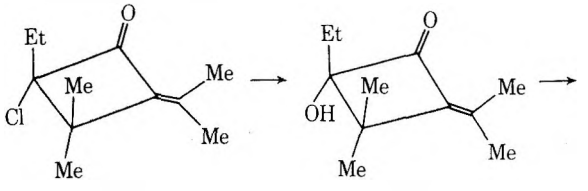
The ring-contraction step is probably concerted from the alkoxide ion because the intermediate allylic carbanion should undergo a rapid proton transfer to yield VIb.



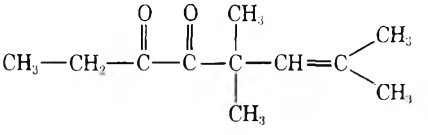
VIb

However, there was no evidence of an isopropyl group in the nmr spectrum, but a vinyl proton was apparent.

The hydrolysis of 2-chloro-2-ethyl-4-isopropylidene-3,3-dimethylcyclobutanone (VII) followed the same pathway, producing the hydroxy cyclobutanone VIII and the ring-opened dione IX.



VII VIII



IX

In conclusion, α,β-unsaturated α'-chlorocyclobutanones undergo substitution reactions rather than ring contraction upon treatment with base. The α,β-unsaturated α'-hydroxyl compounds undergo an interesting ring-opening reaction to a dione.

Experimental Section

The unsaturated cyclobutanones, I, III, and VII were prepared by the *in situ* cycloaddition of methylchloro- and ethylchloroketenes with tetramethylallene and 1,2-cyclononadiene as previously described by us.[2]

General Procedure for Methoxy Substitution. A 5.0-g portion of the α,β-unsaturated α'-halocyclobutanone was treated with an excess of sodium methoxide in 50 ml of methanol. An immediate precipitate of sodium chloride was observed at room temperature.

After the addition of 100 ml of water the reaction solution was extracted with chloroform. The chloroform extracts were dried and rotoevaporated. The residue was distilled under reduced pressure.

3-Methoxy-10-methylbicyclo[7.2.0]undec-1-en-11-one (II). The methoxy substitution product was distilled at 83–85° (0.005 mm): yield 80%; ir 1760 (C=O) and 1660 cm^{-1} (C=C); nmr δ 1.2 (d, 3 H), 1.5 (m, 11 H), 3.2 (s, 3 H), 3.4 (m, 1 H), and 5.6 (m, 2 H).

Anal. Calcd for $C_{13}H_{20}O_2$: C, 75.00; H, 9.62. Found: C, 74.68; H, 9.58.

4-Isopropylidene-2-methoxy-2,3,3-trimethylcyclobutanone (IV). This methoxy substitution product was isolated in 80% yield at 60° (0.5 mm): ir 1760 (C=O) and 1660 cm^{-1} (C=C); nmr δ 1.20 (s, 3 H), 1.22 (s, 3 H), 1.24 (s, 3 H), 1.8 (s, 3 H), 2.02 (s, 3 H), and 3.4 (s, 3 H).

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.53; H, 9.89. Found: C, 72.09; H, 10.00.

This methoxy substitution product was also obtained from the corresponding bromocyclobutanone.

Hydrolysis of 2-Chloro-4-isopropylidene-2,3,3-trimethylcyclobutanone (III). 2-Hydroxy-4-isopropylidene-2,3,3-trimethylcyclobutanone (V) and 4,4,6-Trimethyl-5-heptene-2,3-dione (VI). A 10-g portion of III was treated with 100 ml of 20% aqueous sodium carbonate at reflux with stirring for 20 hr. Upon cooling, the reaction mixture was extracted with chloroform and the extracts were dried over anhydrous calcium chloride. The solvent was removed by rotoevaporation and the residue was vacuum distilled. Two major fractions were obtained.

(1) The first fraction (VI) was a deep yellow colored liquid at 38–40° (0.8 mm): ir 1710 (C=O) and 1650 cm^{-1} (C=C); nmr δ 1.3 (s, 6 H), 1.5 (s, 3 H), 1.7 (s, 3 H), 2.24 (s, 3 H), and 5.3 (s, 1 H); mass spectrum parent peak at *m/e* 168 (theory 168) and major peaks at *m/e* 97 and 125 due to the loss of $CH_3C{=}O$ and $(H_3C(=O)C{=}O$ and another at *m/e* 55 which is due to $-CH{=}C(CH_3)_2$.

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.42; H, 9.52. Found: C, 71.59; H, 9.82.

(2) The second fraction (V) distilled at 85° (0.08 mm): ir 3400 (OH), 1740 (C=O), and 1660 cm^{-1} (C=C); nmr δ 1.3 (s, 6 H), 1.4 (s, 3 H), 1.9 (s, 3 H), 2.15 (s, 3 H), and 4.4 (s, 1 H).

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.42; H, 9.52. Found: C, 71.12; H, 9.38.

The total yield was 80% but the distribution of V and VIa was very dependent upon the reaction time. Under the conditions described, the distribution was a 20% yield of VIa and a 60% yield of V.

Hydrolysis of V. The hydroxy compound upon treatment with aqueous sodium carbonate as described above was converted to the yellow liquid, VIa.

Hydrolysis of 2-Chloro-2-ethyl-4-isopropylidene-3,3-dimethylcyclobutanone (VII). 2-Ethyl-2-hydroxy-4-isopropylidene-3,3-dimethylcyclobutanone (VIII) and 5,5,7-Trimethyl-6-octene-3,4-dione (IX). The same procedure was employed as described above. Two fractions were obtained as follows.

(1) The first fraction (IX) was a deep yellow colored liquid at 50° (0.15 mm): ir 1710 (C=O) and 1650 cm^{-1} (C=C); nmr δ 1.0 (t, 3 H), 1.3 (s, 6 H), 1.5 (s, 3 H), 1.7 (s, 3 H), 2.6 (q, 2 H), and 5.3 (s, 1 H); mass spectrum parent peak at *m/e* 182 (theory 182), with major peaks at *m/e* 97 and 125 due to loss of $CH_3CH_2C{=}O$ and $CH_3CH_2C(=O)C{=}O$ and also at *m/e* 55 and 57 due to $-CH{=}C(CH_3)_2$ and $CH_3CH_2C{=}O$.

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.5; H, 9.8. Found: C, 72.37; H, 9.92.

(2) The second fraction (VIII) was collected at 90–92° (0.08 mm): ir 3400 (OH), 1740 (C=O), and 1660 cm^{-1} (C=C); nmr δ 1.0 (t, 3 H), 1.28 (s, 3 H), 1.36 (s, 3 H), 1.6 (q, 2 H), 1.84 (s, 3 H), 2.05 (s, 3 H), and 4.15 (s, 1 H).

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.5; H, 9.8. Found: C, 72.23; H, 9.78.

Acknowledgments. The authors wish to express appreciation to the Robert A. Welch Foundation and the North Texas State University Faculty Research Fund for support of this investigation.

Registry No.—I, 42915-23-1; II, 51270-76-9; III, 42915-13-9; IV, 51270-77-0; V, 51270-78-1; VIa, 51270-79-2; VII, 42915-15-1; VIII, 51270-80-5; IX, 51270-81-6; 2-bromo-4-isopropylidene-2,3,3-trimethylcyclobutane, 42915-14-0.

References and Notes

(1) (a) J. M. Conia and J. R. Salaun, *Accounts Chem. Res.*, **5**, 33 (1972); (b) D. L. Garin and K. L. Cammack, *J. Chem. Soc., Chem. Commun.*, 333(1972); (c) W. T. Brady and J. P. Hieble, *J. Amer. Chem. Soc.*, **94**, 4278 (1972); (d) P. R. Brook and J. M. Harrison, *J. Chem. Soc., Chem. Commun.*, 997 (1972); (e) P. R. Brook, J. M. Harrison, and A. J. Duke, *Chem. Commun.*, 589 (1970).
(2) W. T. Brady, J. D. Stockton, and A. D. Patel, *J. Org. Chem.*, **39**, 236 (1974).
(3) The methoxide ion could attack the unsymmetrical bicyclobutanone at either bridgehead carbon, but attack at the one indicated produces a significantly more stable carbanion.

2,5-Dicarbomethoxy-3,4-diphenylcyclopentadienone. Synthesis and Reaction with Acetylenes

Dwain M. White

General Electric Research & Development Center, Schenectady, New York 12301

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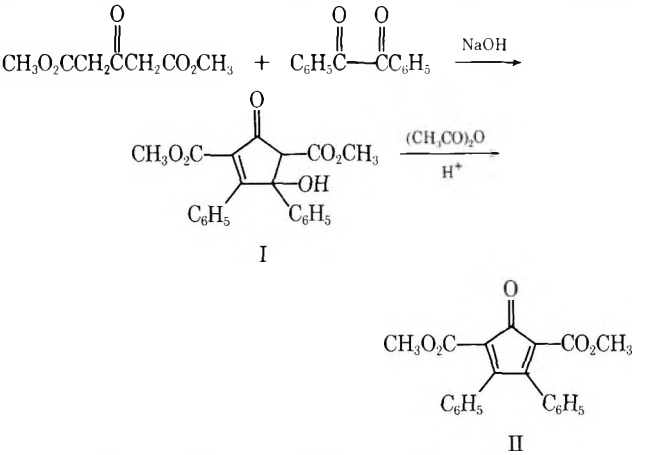
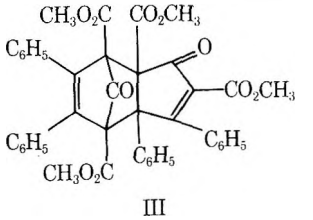
Diels-Alder additions of cyclopentadienones to acetylenes offer a convenient route to arenes.[1,2] If the cyclopentadienones contained functional groups which did not interfere with the addition reaction, useful functionality could be introduced into the products. We have found that 2,5-dicarbomethoxy-3,4-diphenylcyclopentadienone (II) does react with acetylenes to form the desired arene diesters. Compound II can be readily synthesized from available starting materials. It differs from most diphenylcyclopentadienones[1] in that at 25° it is predominantly monomeric in solution and only partially dimerized in the solid state. The synthesis and some properties of II are described below.

Base-catalyzed condensation of dimethyl acetonedicarboxylate with benzil produced the cyclopentenolone I, which appeared to be partially enolized in solution based on the nmr spectrum. Acid-catalyzed dehydration with acetic anhydride produced II, a bright-orange solid. Compound II is primarily a monomer, as shown by the strong methyl resonance in the ^1H nmr at δ 3.75. Four weak resonances of equal intensity at δ 3.38, 3.51, 3.81, and 3.83 correspond to the methyl resonances expected for III and indicate a molar ratio of II to III of *ca.* 30:1. The ^{13}C nmr



I

II



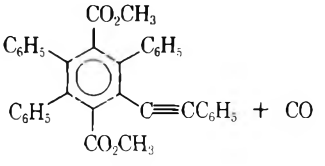
III

also indicated that II was the predominant species; the very weak resonances expected for III could not be discerned. In the solid state, a complex infrared absorption pattern indicated a variety of carbonyl groups. Medium and strong bands at 1703 and 1719 cm^{-1} could be ascribed to the ring carbonyl[1] and ester carbonyl,[3] respectively, in II, while absorptions at 1742, 1738, 1719, and 1675 cm^{-1} were within the expected ranges for the bridged carbonyl, saturated esters, unsaturated ester, and cyclopentenone, respectively, in III.

Most 3,4-diarylcyclopentadienones exist in the dimeric state at 25° if substituents in the 2 and 5 positions are small, whereas they are monomeric if the 2 and 5 substituents are bulky.[1] Apparently, the predominantly monomeric nature of II is due to the added resonance stabilization afforded by the ester groups and to the moderate extent of their steric bulk.

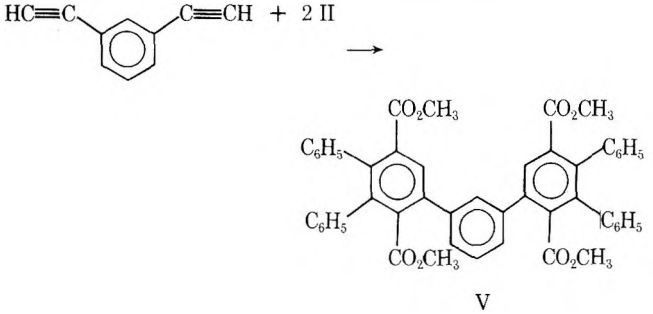
The intermediate reactivity toward dimerization is reflected in the reactivity of II with acetylenes. With diphenylbutadiyne the monoadduct IV was isolated in 70% yield. The reaction temperature of 180° was almost 50° lower than the temperature normally used for tetraphenylcyclopentadienone,[4] yet 50° above the temperature needed for 2,5-dimethyl-3,4-diphenylcyclopentadienone.[5]

II + $C_6H_5C{\equiv}CC{\equiv}C_6H_5$ ⟶



IV

The formation of a diadduct is illustrated by the addition to *m*-diethynylbenzene to furnish the tetraester V in 65% yield.



V

Experimental Section

All melting points were measured on a Leitz hot-stage microscope and are uncorrected: ^1H nmr spectra were measured in $CDCl_3$ *vs.* TMS; ^{13}C nmr spectra were measured in acetone-d_6 *vs.* TMS.

2,5-Dicarbomethoxy-4-hydroxy-3,4-diphenylcyclopenten-2-one (I). Benzil (21.0 g, 0.1 mol), dimethyl acetonedicarboxylate (Aldrich Chemical Co., 17.4 g, 0.1 mol), and potassium hydroxide (1.0 g) in 250 ml of ethanol under nitrogen were stirred for 20 hr at 25° and then poured into water. The crystals which formed were collected on a filter, washed with water, and dried: weight 26.0 g (71%); mp (recrystallized from benzene) 136–140°; nmr of I δ 3.80 and 3.81 (OCH_3's), 5.07 (OH), 7.33 (complex multiplet, aryl H's); the δ 5.07 peak and two peaks corresponding to partial enolization of the ring H at δ 3.23 (0.1 H) and 3.88 (0.9 H) disappeared when exchanged with D_2O.

Anal. Calcd for $C_{21}H_{18}O_6$: C, 68.8; H, 5.0. Found: 69.2; H, 4.9.

Compound I was also prepared in methanol; however, the yield was lower (66%) and the work-up initially led to oils.

2,5-Dicarboxymethyl-3,4-diphenylcyclopentadienone (II). Compound I (22 g, 0.06 mol) was added at 25° to 40 ml of acetic anhydride containing 3 drops of concentrated sulfuric acid. The mixture was heated with stirring until the solid dissolved and then allowed to stand for 0.5 hr without additional heating. The solution was added to 450 ml of water with stirring. When the crystals had settled they were filtered off, washed thoroughly with water, and dried at 50° (10 Torr). Orange crystals, weight 20 g (98%), were obtained: mp 162–167° (recrystallized from acetic acid, mp 162–164°); ^1H nmr δ 3.75 (OCH_3), 6.92–7.33 (complex multiplet, ArH's); very weak resonances of equal intensity from III were noted at δ 3.38, 3.51, 3.81, and 3.83; ^{13}C nmr δ 51.4 (CH_3), 118.6 (C-2), 126.7 (C-3), 126.8, 128.0, 129.2, and 130.0 (phenyl C's), 161.5 and 161.7 (carbonyls); ir (KBr) 1742 (s, shoulder), 1738 (s), 1719 (s), 1703 (m), 1675 cm^{-1} (w); uv (EtOH) λ_{max} 292 nm (ε 13,500), 360 (1220); mass spectrum *m/e* 348 (rel abundance 100).

Anal. Calcd for $C_{21}H_{18}O_5$: C, 72.4; H, 4.6. Found: C, 72.0; H, 4.5.

Dimethyl 2,3,5-Triphenyl-6-phenylethynylterephthalate (IV). A mixture of II (1.74 g, 0.005 mol) and diphenylbutadiyne (1.01 g, 0.005 mol) was heated with an oil bath at 180° for 2 hr. The melt was cooled to 80° and ethanol was added with stirring. The crystalline product was filtered off, washed with ethanol, dried, and then recrystallized from chloroform: yield 1.82 g (70%); mp 209–210°; nmr δ 3.20 (4-carbomethoxy), 3.63 (1-carbomethoxy), 7.17 (complex multiplet, 2,4 and 5 phenyl H's), 7.33 (phenylethynyl).

Anal. Calcd for $C_{34}H_{26}O_4$: C, 82.7; H, 5.0. Found: C, 82.5; H, 5.0.

2,2″,5,5″-Tetracarbomethoxy-3,3″,4,4″-tetraphenyl-*m*-terphenyl (V). *m*-Diethynylbenzene (0.63 g, 0.005 mol) was added dropwise to a solution of II (3.48 g, 0.01 mol) and 10 ml of Arochlor 1221 (chlorobiphenyl, Monsanto) at 200° over a 3-min period. After 10 min, gas evolution had ceased and the reaction mixture was cooled to 100°. Hexane was added to the viscous mixture. After cooling to 25°, crystals formed which were filtered off and washed with hexane: weight 2.5 g (65%); recrystallized from benzene–methanol (1:4), 2.0 g; mp 201–202°; nmr δ 3.27 and 3.50 (methyl H's), 7.00 (2,2″,5,5″-phenyl H's), 7.35 (3′ and 4′ H's), 7.48 (6′-H), 7.73 (6 and 6″ H's).

Anal. Calcd for $C_{50}H_{38}O_8$: C, 78.3; H, 5.0. Found: C, 78.0; H, 5.1.

Registry No.—I, 16691-78-4; II, 16691-79-5; III, 16691-80-8; IV, 51175-84-9; V, 51175-85-0; benzil, 134-81-6; dimethyl acetondicarboxylate, 1830-54-2; diphenylbutadiyne, 886-66-8; *m*-diethynylbenzene, 1785-61-1.

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(1) M. A. Ogliaruso, M. G. Romanelli, and E. I. Becker, *Chem. Rev.*, **65**, 261 (1965).
(2) W. Ried and D. Freitag, *Chem. Ber.*, **99**, 2675 (1966); W. Ried and K. Bonnighausen, *ibid.*, **93**, 1769 (1960).
(3) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," Wiley, New York, N. Y., 1958, pp 181–182.
(4) M. A. Ogliaruso and E. I. Becker, *J. Org. Chem.*, **30**, 3354 (1965).
(5) Heating the dimer of 2,5-dimethyl-3,4-diphenylcyclohexadienone with diphenylbutadiyne at 130° produced the monoadduct, 2,5-dimethyl-3,4,6-triphenyltolane, in 92% yield: D. M. White, unpublished results.

Reaction of Phosphorus Tribromide with a Conjugated Ketone. Locked Conformations in Acyclic Molecules

Eugene R. Kennedy and Roger S. Macomber*

Department of Chemistry, University of Cincinnati, Cincinnati, Ohio 45221

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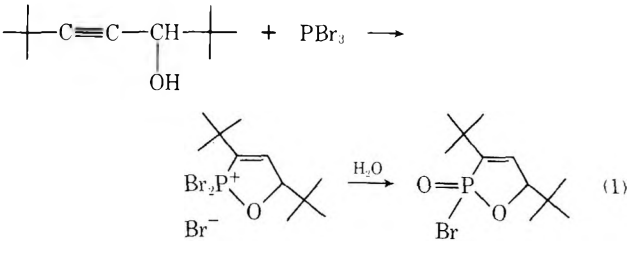
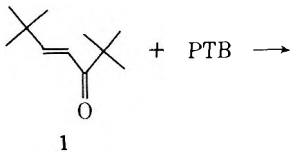
In connection with our recent findings[1] that certain propargyl alcohols react with phosphorus tribromide (PTB) to yield phosphorus–oxygen heterocycles and related compounds (eq 1), we attempted to enter isomeric manifolds

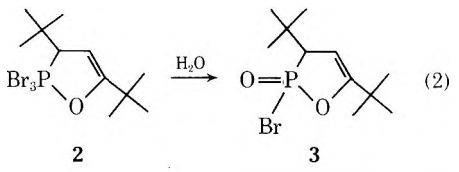


(1)

through the reaction of PTB with conjugated ketones (eq 2).

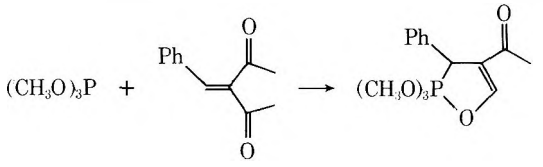


1



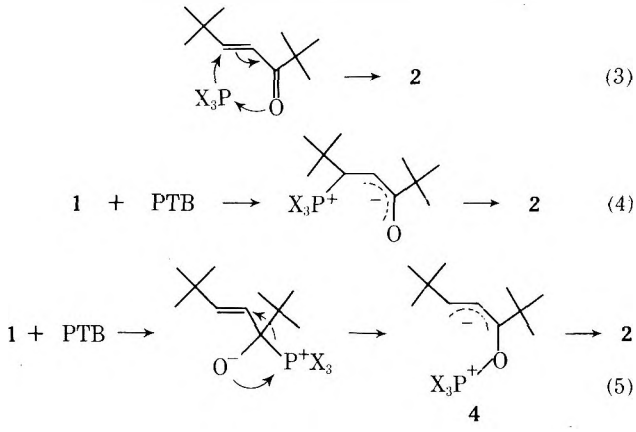
2 3 (2)

Reactions similar to eq 2 are not without precedent. Triethyl phosphite is known to react with 3-acetyl-4-phenyl-3-buten-2-one to yield an oxaphospholene.[2]



Similar reactions involving phosphorus trichloride (PTC) and related compounds have been sporadically reported over the last 55 years.[3] We have, however, been unable to locate reports of such reactions using PTB.

At least three mechanistic alternatives can be advanced for the cycloaddition of phosphorus(III) compounds to conjugated ketones: concerted (symmetry-allowed) 1,4-chelatropic addition (eq 3), preliminary nucleophilic attack by phosphorus at the β position of the enone, followed by cyclization (eq 4), or attack by phosphorus at the carbonyl carbon with subsequent rearrangement and ring closure (eq 5).[4] The relative favorability of each mechanism would depend on the steric requirements at the various sites of nucleophilic attack on the substrate, as well as on the nature of X, its steric bulk, and its nucleophilicity-increasing electronic effects. Because bromine is larger, slightly less electronegative, and a better leaving group (important during hydrolysis) than chlorine, it was of interest to determine if PTB functioned as well as PTC in such chelatropic reactions.



(3)

(4)

(5)

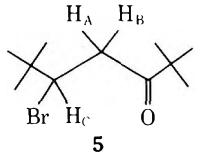
4

Table I
Best Fit Spectral Data for the ABC System of 5

ω, Hz[a]	$\lvert J\rvert$, Hz
H_A 162.9 ± 0.2	AB 17.7 ± 0.2
H_B 195.3 ± 0.2	AC 1.85 ± 0.23
H_C 262.9 ± 0.1	BC 9.96 ± 0.22

[a] Downfield from internal TMS at 60 MHz, carbon tetrachloride solution, ambient temperature.

When *trans*-2,2,6,6-tetramethyl-4-hepten-3-one (1) was allowed to react with a 15% excess of PTB in ether, a single crystalline product could be isolated after aqueous work-up. Its mass spectrum and elemental analysis (Experimental Section) indicated a molecular formula of $C_{11}H_{21}OBr$, resulting formally from the addition of HBr to . The isolated yield was 55%. The infrared spectrum of the product was unexceptional, save for an intense carbonyl absorption at 1715 cm^{-1}. Its pmr spectrum, however, was extremely interesting (Figure 1). In addition to two nine-proton *tert*-butyl singlets (δ 1.08 and 1.13), there appeared three four-line multiplets (one proton each) resembling the spectrum of an ABC (or ABM) system. Computer simulation of the observed spectrum (LAOCOON III) provided the exact parameters shown in Table I. The only structure consistent with the *chemical shifts* is 5-bromo-2,2,6,6-tetramethyl-3-heptanone (5), a new compound. However, this assignment requires that geminal protons H_A and H_B are anisochronous to the extent of 0.54 ppm, one of the largest geminal proton chemical shift nonequivalences to be observed in an acyclic system.[5,6] Certainly it is the chirally substituted C_5 which renders H_A and H_B diastereotopic; yet the magnitude of the effect suggests that other factors also contribute. An accurately scaled CPK space-filling molecular model of 5 provides an explanation. A representation of this is shown in C_4–C_5 Newman projection 6. One finds that the steric bulk of



5

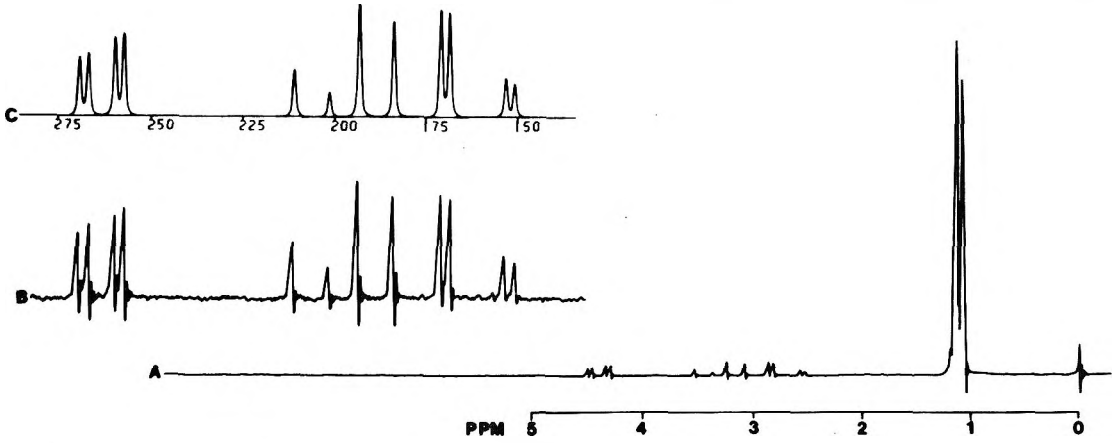
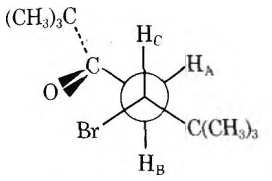


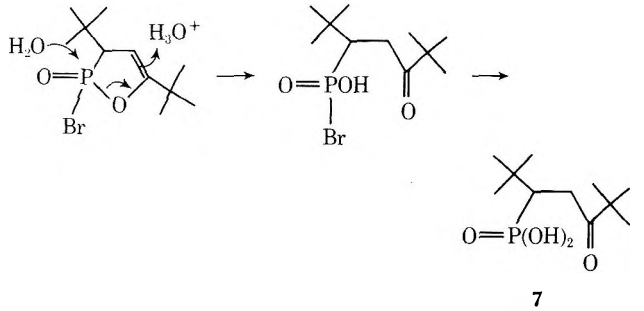
Figure 1. Pmr (60 MHz) spectrum of 5: (A) sweep width 500 Hz; (B) sweep width 250 Hz, increased amplitude, zero offset; (C) spectrum simulated with values in Table I.



6

the bromine atom and the front *tert*-butyl group prevent all but the most limited rotation around the C_4–C_5 single bond (and to lesser extents, the rotation around the C_3–C_4 and C_5–C_6 bonds). Further, the model suggests that the preferred conformation is almost perfectly staggered, and may be essentially static. Evidence to support this conclusion can be adduced from the magnitudes of J_{AC} and J_{BC} (1.85 and 9.96 Hz, respectively) as would be expected for fixed dihedral angles of *ca.* 59 and 180°,[7] which are not affected by rotational averaging. Moreover, the ordering of the coupling constants requires that the higher field geminal proton (H_A) must also be the one more isolated from the deshielding influence of the bromine atom, as shown in **6**. This might have been predicted for a proton essentially s-trans to the bromine. Analogous arguments, invoking single conformations in certain acyclic molecules, have been advanced to explain the unusually large geminal chemical shift nonequivalence and long-range coupling constants in compounds bearing several halogen atoms and methyl groups.[6]

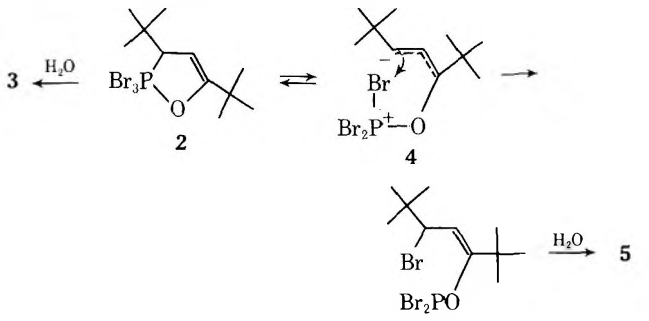
Compound **5** can arise in at least two ways. The most obvious is the Markovnikov addition of HBr, liberated from the partial hydrolysis of PTB, to **1**. Indeed, the reaction of **1** in ether with gaseous HBr provided **5** in virtually quantitative yield. However, even when carefully dried reagents and solvent were used, and aqueous work-up omitted, the pmr spectrum of the crude product showed that 40–75% (variations from different runs) of the material was **5**. The remainder of the crude product mixture was another compound which exhibited *tert*-butyl singlets at δ 1.13[8] and 1.20, as well as doublets of doublets at δ 2.75[8] (J_{HH} = 3.5, J_{PH} = 15.5 Hz) and 5.24 (J_{HH} = 3.5, J_{PH} = 38.7 Hz), exactly as would be expected[1,2] for heterocyclic structures such as **2** or **3**. Isolation by centrifugal removal of undissolved **5** provided an oil whose pmr spectrum matched the one above (integration ratio 9:9:1:1, respectively), while its ^{31}P nmr spectrum (δ −53.0, J_{PH_1} = 38.5 ± 0.5, J_{PH_2} = 15 ± 1 Hz) and ir and mass spectra (Experimental Section) provided compelling evidence for structure **3**. Not unexpectedly, **3** was fairly sensitive toward hydrolysis, and its yield was strongly affected by the nature of the work-up. Hydrolysis of **3** presumably involves ring opening to ketone **5** (*vide infra*) and/or acid **7**,



7

as shown by the slow increase in an infrared band at 1710 cm^{-1}. Such hydrolytic instability has been previously noted in the case of related chloro compounds,[9] whereas the heterocyclic double bond isomer shown in eq 1 is much more stable toward hydrolysis.[1] The ease of hydrolytic ring opening of **3** must derive from both the increased basicity of C_4 (owing to resonance with the oxygen lone pairs) and to the heat of formation of the carbon–oxygen double bond.

The isolation of **3** and inability to suppress formation of **5** suggest that both may arise from a common mechanistic path. The most economical interpretation of our results would simply involve the formation of **4** (eq 5), which could then be partitioned between **2** and enol phosphite **8** (expected to be even more hydrolytically reactive than **2** or **3**, since it is noncyclic).



2 4 8

Clearly, PTB is at least as effective as PTC in these oxaphospholene-forming reactions. Whether **2** arises exclusively from **4** (eq 5), or whether it is formed independently (eq 3 or 4) and serves as the *source* of **4**, is not yet clear. Reactions 4 and 5 both require nucleophilic attack at neopentyl-like centers, and this should be retarded for a nucleophile as large as PTB. Further work to clarify these points is underway.

Experimental Section

General. The instruments and methods used in this study were exactly similar to those previously described.[1] Microanalyses were performed by Chemalytics, Tempe, Ariz. PTB was distilled immediately before use, bp 169–169.5° (729 mm).

Reaction of 1 with HBr. Gaseous HBr was bubbled gently through a solution of 0.40 g (2.4 mmol) of **1**[10] in 20 ml of ether at 0° for 1 hr. The solvent was removed *via* rotary evaporation, leaving 0.61 (100% crude yield) of crystalline material: mp 73.0–74.5° after recrystallization from heptane and sublimation at 70° (1 mm); mass spectrum (70 eV) *m/e* 248 and 250 ($M\cdot^+$),[11] 169 (M − Br, 22%), and 57 [base peak, $(H_3C)_3C^+$]; ir (chloroform) 2970 (vs), 1715 (vs), 1480 (s), 1395 (m), 1370 (s), 1295 (m), 1240 (m), 1155 (m), 1088 (s), 1058 (m), 993 (m), 940 (m), 920 (m), 862 (m), 790 (vs), 653 cm^{-1} (m). The pmr spectrum is described in the text.

Anal. Calcd for $C_{11}H_{21}OBr$: C, 53.01; H, 8.50. Found: C, 52.90; H, 8.74.

Reaction of 1 with PTB. Dry argon was bubbled through a solution of 965 mg (3.57 mmol) of PTB in 50 ml of dry ether. Over a period of 15 min a solution of 563 mg (3.35 mmol) of **1** in 30 ml of ether was added dropwise. Stirring was continued at room temperature for 14 hr, with the argon flow rate maintained at *ca.* 2 ml/sec. A 1-ml aliquot was removed and evaporated, and the semisolid product was examined by pmr (ratio of **3**:**5** 1.0:1.0).[12] To the remaining solution was added 320 mg (4 mmol) of pyridine in 1 ml of water. The hydrolysis was exothermic, and the initially milky suspension clarified after stirring for 15 min. The aqueous phase was separated, and the ether phase was washed with 5 ml of water. The combined aqueous phases were extracted with 5 ml of ether, and then the combined ether solutions were dried over molecular sieve. Rotary evaporation left 968 mg (including aliquoted material) of a pale yellow semisolid, still exhibiting the 1:1 composition (106% crude yield). The most satisfactory separation[13] of **3** from **5** was accomplished by transfering the crude product mixture to a Craig tube and allowing it to sit at −20° overnight. The tube was centrifuged and the liquid portion was transferred to another Craig tube. The remaining solid was **5**, which could be purified as described above. Two more cycles of the cooling–centrifugation sequence provided **3** as a pale yellow oil containing *ca.* 5% of **5**. Distillation (60°, 0.1 mm) left the oil unchanged. The isolated yields were a function of the purity desired, and normally fell near 25% for 95% pure **3**, and 40% for >99% pure **5**; total isolation was 65% based on starting ketone.[14] Spectral data for **3** follow: mass spectrum (70 eV) *m/e* (rel abundance)[15]

297,* 295* (0.1, 0.1), 240,* 238* (10, 10), 225,* 223* (3, 3), 193, 191 (8, 8), 168 (17), 159* (7), 111* (100), 97* (5), 95* (4), 93* (9), 85 (25), 83 (18), 69 (8), 57 (38); ir (carbon tetrachloride) 2960 (s), 1665 (m), 1490 (w), 1480 (w), 1380 (w), 1272 (m), 1245 (s), 1065 (m), 860 (vs), 690 (m), 610 (w), 550 cm^{-1} (m). The ^1H and ^{31}P nmr spectral data for **3** are described in the text.

Acknowledgment. We appreciate the constructive criticisms offered by one of the referees. E. R. K. has been an NSF Trainee, 1970-present. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this work.

Registry No.—**1**, 20859-13-6; **3**, 51270-67-8; **5**, 51270-68-9; HBr, 10035-10-6; PTB, 7789-60-8.

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(6) To our knowledge, the only larger value was 0.6 ppm as exhibited by 1,3-dichloro-2,3-dimethylbutane: F. Schweinsberg and J. G. Traynham, *Tetrahedron Lett.*, 3809 (1970).
(7) M. Karplus, *J. Amer. Chem. Soc.*, **85**, 2870 (1963).
(8) Part of this absorption overlapped with peaks due to **5**. Locations of such lines were initially inferred from anomalous intensities.
(9) See, for example, J. B. Conant and A. A. Cook, *J. Amer. Chem. Soc.*, **42**, 830 (1920).
(10) W. Rundel, *Chem. Ber.*, **102**, 374 (1964); mp after sublimation (40°, 15 mm) 43–44°.
(11) $[M + H]^+$ peaks three times as intense as the parent ions were observed at *m/e* 249 and 251.
(12) Any variation in conditions (*e.g.*, omission of argon, more concentrated or moist solutions, etc.) which permits the buildup of HBr provided product mixtures richer in **5**, sometimes to the virtual exclusion of **3**. Another fascinating feature of this reaction, as well as those described earlier,[1] is the inability to suppress the hydrolysis of (presumed intermediate) **2** to **3**. Even under strictly anhydrous conditions without aqueous work-up, **3** was the sole heterocyclic product observed.
(13) Compounds **3** and **5** are similar enough in volatility that sublimation (0.60 mm and 40°) provides a mixture only slightly enriched in **5** (up to 65% from 50%). Nor were any chromatographic techniques, including tlc, elution, or glc, found that would allow **3** to survive.
(14) Although we have not been able to directly substantiate this by mass balance, it seems that, during the purification of **3**, the amount of **5** recovered at each stage exceeds the decrease of **5** observed in the oil. This would support the assertion that **3** can decompose to **5**, *via* an intermediate similar to **4**.
(15) Asterisks mark the peaks common to derivatives of the isomeric ring system shown in reaction 1. The appearance of weak $[M + H]^+$ ions, rather than M^+, seems to be a characteristic of these systems.[1] A single peak at *m/e* 281 (4), overlapping the $[M - CH_3]$ doublet, suggests the presence of a higher molecular weight impurity.

A General Indene Synthesis *via* Cyclization of Phenyl-Substituted Allylic Cations

Wayne G. Miller and Charles U. Pittman, Jr.*

Department of Chemistry, University of Alabama, University, Alabama 35486

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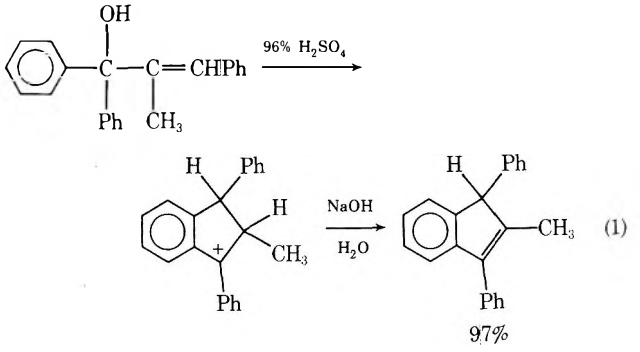
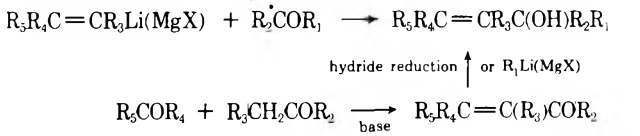
Indenes have been prepared by a number of cyclialkylation procedures, such as dehydration of phenyl-substituted diols and reaction of phenyl-substituted alkenes with phosphorus halides.[1-3] Recently, the reaction of *gem*-dihalocyclopropanes with benzene and aluminum chloride was used.[4] These procedures are of limited scope; so indenes have generally been prepared by treating Grignard or lithium reagents with an appropriate indanone followed by dehydration of the resulting indanol. The required indanones have usually been prepared by cyclization of β-phenyl-substituted carboxylic acids resulting from Reformatsky, Perkin, or Friedel-Crafts routes.[5,6] Overall, these routes consist of several steps with low overall yields and only moderate flexibility for the preparation of substituted derivatives.

Recently, we reported the generation of indanyl cations by dissolving phenyl-substituted allylic alcohols, of wide variety, into strongly acidic media (*i.e.*, FSO_3H, H_2SO_4, etc.).[7] Initially, acyclic allylic cations are formed. These then cyclize to give indanyl cations in the acidic media.[7] We have found that solutions of indanyl cations give good yields of the corresponding indenes when quenched into excess aqueous base. This fact, and the ease with which a variety of phenyl-substituted allylic alcohols can be prepared, make this indene synthesis a general and efficient procedure. A typical example is the cyclization of 1,1,3-triphenyl-2-methylpropenol to 1,3-diphenyl-2-methylindene in high yield (eq 1).



This method has several advantages over techniques employed previously. First, the overall yields are improved. Second, desired substitution at carbons 1, 2, and 3 is easily achieved in a few steps. For example, phenyl-substituted allylic alcohols in wide variety can be conveniently prepared by aldol condensation followed by treatment of the resulting α,β-unsaturated ketone with Grignard or lithium reagents. Alternatively, reaction of vinyl Grignard reagents with appropriate aldehydes or ketones give allylic alcohol precursors. These routes are outlined in Scheme I.

Scheme I



Another advantage of this method is that the indanyl cations can be directly observed by nmr spectroscopy, allowing one to monitor the cyclization. Also, some indanyl cations further rearrange in solution when the temperature is raised.[8] This allows two possible indenes to be generated from the same precursor alcohol simply by choosing the temperature the acid solution is permitted to reach before quenching (for examples see Scheme II).

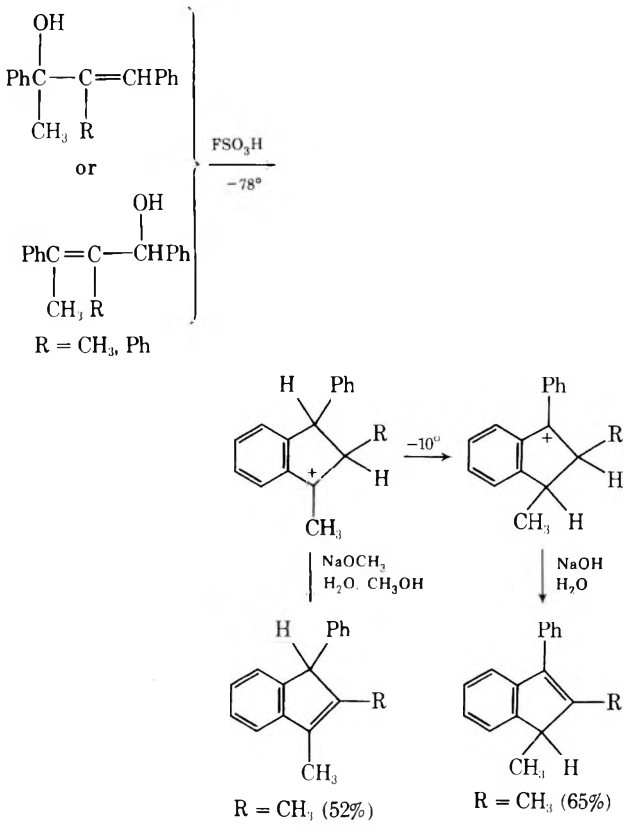
A few cases of indenes prepared by allylic cyclodehydration, presumably *via* transient indanyl cation intermediates, have appeared.[9,10] Bergman obtained an unspecified amount of 1,2-diphenylindene on treatment of 1,2,3-triphenylpropenol with dilute sulfuric acid followed by distillation.[9] Similarly, Koelsch converted 1,1,2,3,3-penta-

Table I
Synthesis of Indenes from Phenyl-Substituted Allylic Alcohols

Allylic alcohol	Registry no.	Indene product	Registry no.	Yield, %[a]
3-Methyl-2-phenyl-3-penten-2-ol	41231-83-8	1,2,3-Trimethylindene	4773-83-5	69
3,4-Dimethyl-2-phenyl-3-penten-2-ol	41231-84-9	1,2,3,3-Tetramethylindene	4705-87-7	58 (71)
2,4-Diphenyl-3-buten-2-ol	41231-78-1	1-Phenyl-3-methylindene	22360-62-9	72 (87)
2,3-Diphenyl-4-methyl-3-penten-2-ol	41231-85-0	2-Phenyl-1,3,3-trimethylindene	51310-24-8	74 (84)
1,1,3-Triphenyl-2-propenol	4663-36-9	1,3-Diphenylindene	4467-88-3	84
2,3,4-Triphenyl-3-buten-2-ol	41231-81-6	1,2-Diphenyl-3-methylindene	51310-25-9	84
2-Methyl-1,1,3-triphenyl-2-propenol	41231-87-2	1,3-Diphenyl-2-methylindene	51310-26-0	97

[a] Yields are given for reactions employing 96% H_2SO_4 with the exception that those in parentheses resulted from the use of 90% H_2SO_4.

Scheme II



phenylpropenol to 1,2,3,3-tetraphenylindene, also in unspecified yields.[10] Our procedure differs in that excess strong acid is used as the solvent. This medium effects nearly quantitative cyclodehydration of the alcohol (*via* the acyclic allylic cation) to a stable indanyl cation. By carefully quenching the cation solution into excess base by rapid dispersal techniques, second-order alkylation reactions, which prevail in less acid media,[11] are avoided. Generally, 90% H_2SO_4 gave better yields than 96% H_2SO_4. This is probably due both to the lowered sulfonating power of 90% H_2SO_4[12] and to its lower viscosity, which permits rapid stirring and dissolving of the alcohol without hot spots developing. Table I summarizes the synthetic results.

Experimental Section

Preparation of Phenyl-Substituted Allylic Alcohols. The syntheses of all alcohols listed in Scheme I or Table I were reported previously.[7]

Conversion of Allylic Alcohols to Indenes. All indenes in Table I were prepared as follows. One gram of phenyl-substituted allylic alcohol was dissolved in a few milliliters of carbon tetrachloride, the actual volume depending on the solubility of a given alcohol in carbon tetrachloride. These solutions were then added dropwise to 3 ml of 96% (or 90%) sulfuric acid at 0–5° with rapid stirring. When addition was complete stirring was stopped and the acid layer was allowed to settle to the bottom. The acid layer was removed and slowly added to an excess of cold, dilute (5–15%) sodium hydroxide. The residual base was then neutralized with 1:1 hydrochloric acid–water. The neutralized mixture was extracted twice with ether. The extract was dried (anhydrous sodium carbonate) and evaporated, and the residue was recrystallized or distilled, as necessary. Alternatively, the allylic alcohol was dissolved in SO_2 at −78° and this solution was added dropwise to FSO_3H at −78° with rapid stirring. The acid was warmed to the desired temperature and quenched.

1,2,3-Trimethylindene: bp 97–100° (10 mm) [lit.[13] bp 100–103° (11 mm)]; nmr (CCl_4) τ 8.89 (d, 3 H, J = 7.5 Hz, CH_3 at C-1), 8.20 (s, 3 H, CH_3 at C-2), 8.13 (s, 3 H, CH_3 at C-3), 7.07 (q, 1 H, J = 7.5 Hz, C-1 H), and 2.99 (m, 4 H, phenyl C-H).

1,2,3,3-Tetramethylindene: bp 47° (0.23 mm) [lit.[14] bp 113° (17 mm)]; nmr (CCl_4) τ 8.90 (s, 6 H, methyls at C-3), 8.24 (s, 3 H, CH_3 at C-2), 8.10 (s, 3 H, CH_3 at C-1), and 2.99 (m, 4 H, phenyl C-H).

1-Phenyl-3-methylindene: bp 116° (0.88 mm) [lit.[15] bp 87° (0.01 mm)]; nmr (CCl_4) τ 8.81 (d, 3 H, J = 7.5 Hz, CH_3 at C-3), 6.65 (q, 1 H, J = 7.5 Hz with additional 2-Hz coupling to C-2 H, C-1 H), 3.73 (d, 1 H, J = 2.0 Hz, C-2 H), and 2.74 (m, 9 H, phenyl C-H).

2-Phenyl-1,3,3-trimethylindene (recrystallized from EtOH): mp 82°; nmr (CCl_4) τ 8.69 (s, 6 H, CH_3 groups at C-3), 8.05 (s, 3 H, CH_3 at C-1), and 2.79 (m, 9 H, phenyl C-H). *Anal.* Calcd for $C_{18}H_{18}$: C, 92.26; H, 7.74. Found: C, 92.08; H, 7.85.

1,3-Diphenylindene (recrystallized from glacial acetic acid): mp 66–67° (lit.[16] mp 68–69°) and mp 84–85° when recrystallized from EtOH (lit.[16] mp 84–85°); nmr (CCl_4) τ 5.45 (d, 1 H, J = 2.0 Hz, C-1 H), 3.51 (d, 1 H, J = 2.0 Hz, C-2 H), and 2.66 (m, 14 H, phenyl C-H).

1,2-Diphenyl-3-methylindene (recrystallized from EtOH): mp 92–93°; nmr (CCl_4) τ 7.75 (d, 3 H, J = 2.0 Hz, CH_3 at C-3), 5.24 (q, 1 H, J = 2.0 Hz, C-3 H), and 2.97 (m, 14 H, phenyl C-H). *Anal.* Calcd for $C_{22}H_{18}$: C, 93.57; H, 6.43. Found: C, 93.70; H, 6.17.

1,3-Diphenyl-2-methylindene (recrystallized from EtOH): mp 109–110.5° (lit.[17] mp 108°); nmr (CCl_4) τ 8.14 (s, 3 H, CH_3 at C-2), 5.71 (s, 1 H, C-1 H), and 2.76 (m, 14 H, phenyl C-H).

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Improved Synthesis of 2-Methyl-6-methylene-2,7-octadien-4-ol, a Pheromone of *Ips paraconfusus*, and an Alternative Synthesis of the Intermediate, 2-Bromomethyl-1,3-butadiene

Robert G. Riley and Robert M. Silverstein*

Department of Chemistry, S. U. N. Y. College of Environmental Science and Forestry, Syracuse, New York 13210

John A. Katzenellenbogen and Ronald S. Lenox

Department of Chemistry, University of Illinois at Urbana-Champaign, Urbana, Illinois 61801

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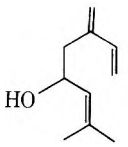
The objective of this study was to prepare 2-methyl-6-methylene-2,7-octadien-4-ol (**1**), a principal component of



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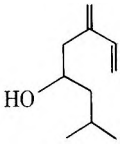


2

the aggregation pheromone of *Ips paraconfusus* Lanier (*confusus*), a bark beetle.[1]

Unsuccessful attempts have been made to synthesize **1** and **2** (2-methyl-6-methylene-7-octen-4-ol, another component of the pheromone of *Ips paraconfusus*) by coupling 3-methyl-2-butenal or isovaleraldehyde with either the Grignard reagent or the lithium salt of 2-bromomethyl-1,3-butadiene (**4a**). Both molecules were synthesized by a route involving the reaction of **4a** with the propane dithioketal anions of the respective aldehydes.[2] In both cases, the yield of alcohol was low. Vig, *et al.*,[3] has reported the synthesis of **2** in low yield and, most recently, Katzenellenbogen and Lenox[4] have synthesized **2** from the reaction of **4a** with zinc and isovaleraldehyde in THF in 52% yield. We wish to report the synthesis of **1** by the latter method.

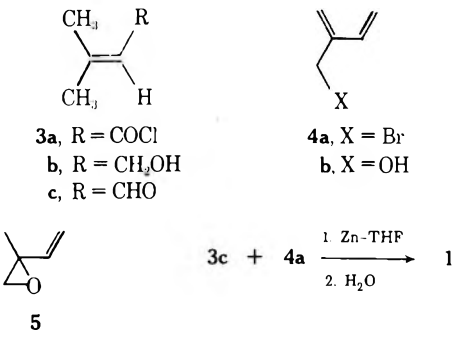
The precursor aldehyde, 3-methyl-2-butenal (**3c**), was synthesized by conversion of 3-methyl-2-butenoic acid to its acid chloride **3a** (98%), lithium aluminum hydride reduction of **3a** to 3-methyl-2-buten-1-ol (**3b**, 85%), and oxidation of **3b** with chromium trioxide–pyridine in methylene chloride to **3c** (48%).[5]

Attempted selective reduction of **3a** with $LiAlH(O\text{-}t\text{-}Bu)_3$ produced compound **3b** in low yield. Treatment of **3b** with CrO_3 on graphite[6] (Seloxcette) in pentane, hexane, or benzene gave a mixture of **3b**, **3c** (40% in the best experiment), and polymer.

2-Bromomethyl-1,3-butadiene (**4a**) was synthesized by the method of Krug and Yen[7] in 18% overall yield. Alternatively, compound **4a** can be synthesized by rearrangement of 3-methyl-3,4-oxido-1-butene (**5**, prepared from isoprene by the method of Reist, Junga, and Baker[8]) to 2-hydroxymethyl-1,3-butadiene (**4b**) with lithium diisopropylamide,[9] followed by bromination with phosphorus tribromide in ether. The convenience of this sequence compensates for its lower over-all yield (11%). Reaction of **3c** and **4a** with zinc in refluxing tetrahydrofuran followed by hydrolysis gave **1** in 65% yield after distillation (see Scheme I).

Caution! Distillation temperatures in excess of 100° should be avoided. Attempted distillation of **1** (>100°, 30 mm) produced *trans*-2-methyl-6-methylene-3,7-octadien-2-ol (ir and nmr identical with those reported by Silverstein, *et al.*[10]) and a mixture of tetraenes (dehydration products), *m/e* 136 (M^+), as major side products. Prolonged high temperature polymerizes the compound. Distillation conditions have been determined that give the alcohol in high purity (>95% by glc analysis).

Scheme I



Experimental Section

Reagents. 3-Methyl-2-butenoic acid (Aldrich) and 3-methylsulfolene (Chemicals Procurement Laboratories, Inc.) were used without further purification. Chromic anhydride was dried under vacuum over P_2O_5 and methylene chloride was purified by the method of Ratcliffe.[5] Pyridine was dried by distillation over barium oxide. The pyridine and THF were stored over 4A molecular sieves.

Methods. Nuclear magnetic resonance spectra were obtained with Varian A-60 and XL-100 spectrometers on $CDCl_3$ solutions (except where noted) with TMS as an internal standard. Infrared spectra were obtained with Perkin-Elmer Model 137 and 621 spectrophotometers, and mass spectra with a Hitachi RMU-6 spectrometer. The purities of some intermediates and the target molecule were determined with a Varian Model 1740 gas chromatograph fitted with flame ionization detectors and a splitter with a split ratio of 100:1. The following glc columns were used: column A, 4% Carbowax 20M on Chromosorb G 60/80 mesh (stainless steel), 5 ft × 0.125 in., He flow rate 30 cm³/min, column temperature 75°; column B, 5% Carbowax 20M on Chromosorb G 60/80 mesh (glass), 20 ft × 0.25 in., He flow rate 50 cm³/min, column temperatures 80 and 140°, injection temperatures 100 and 140° respectively; column C, 5% diethylene glycol succinate on chromosorb W 80/100 mesh (stainless steel). 15 ft × 0.125 in., N_2 flow rate 30 cm³/min, column temperature 150°. Carbon–hydrogen analyses were performed by Microanalysis Inc., Wilmington, Del. All boiling points are uncorrected.

3-Methyl-2-buten-1-ol (3b). To 50 g (0.5 mol) of 3-methyl-2-butenoic acid was added dropwise, over a period of 0.5 hr 89.25 g (0.74 mol) of thionyl chloride. Following addition, the stirred mixture was allowed to warm to room temperature over a period of 1 hr. The excess thionyl chloride was removed and the product was distilled, yield 55.8 g (94%) of **3a**: bp 43–44° (15 mm); nmr δ 6.10 (m, 1 H, olefinic), 2.14 (d, 3 H, J = 1 Hz, CH_3), 1.96 (d, 3 H, J = 1.5 Hz, CH_3). An ether solution of 27.44 g (0.231 mol) of **3a** was added dropwise over a period of 2 hr to a rapidly stirred solution of 8.76 g (0.231 mol) of $LiAlH_4$ in dry ether at 0°. Following addition, the mixture was warmed to room temperature and slowly hydrolyzed by dropwise addition of 8.8 ml of H_2O, 8.8 ml of 15% NaOH, and 27 ml of H_2O. The ether extract was filtered, dried (Na_2SO_4), and concentrated and the product was distilled, yield 16.94 g (85%) of **3b**, bp 50–52° (13 mm). Glc analysis of the product on column A showed the product to be >99% pure: ir (neat) 2.98 (OH), 5.95 mμ (C=C); nmr δ 5.45 (t, 1 H, olefinic), 4.13 (d, 2 H, CH_2), 1.95 (s, 1 H, OH), 1.75 (s, 3 H, CH_3), 1.68 (s, 3 H, CH_3).

Anal. Calcd for $C_5H_{10}O$: C, 69.72; H, 11.70. Found: C, 69.93; H, 11.72.

3-Methyl-2-butenal (3c). A methylene chloride solution of 10.0 g (0.116 mol) of **3b** was added dropwise, over a period of 15 min, to a stirred solution of 110.4 g (1.4 mol) of pyridine and 69.8 g (0.70 mol) of chromic anhydride in 1600 ml of methylene chloride at room temperature. Stirring was continued at room temperature for 2 hr, the mixture was filtered and concentrated, and ether was added to precipitate the salts. The salts were filtered and the process of salt removal was repeated. The solution was extracted twice with 100-ml portions of 5% HCl and then with 100 ml of brine. The ether extract was dried (Na_2SO_4) and concentrated, and the product was distilled, yield 4.7 g (48%) of **3c**, bp

133–135° (760 mm). Glc analysis of the product on column A showed the product to be >99% pure: ir (neat) 6.02 (conjugated C=O), 6.14 mμ (C=C); nmr δ 10.05 (d, 1 H, aldehydic proton), 5.92 (d, 1 H, olefinic), 2.17 (d, 3 H, J = 1 Hz, methyl), 1.98 (d, 3 H, J = 1 Hz, methyl).

2-Bromomethyl-1,3-butadiene (4a). This compound was prepared by the method of Krug and Yen[7] in 18% over-all yield. Glc analysis on column B showed the product to be 90% pure: ir (neat, glc pure) 6.28 (conjugated C=C), 11.05 mμ (olefinic C–H bend); nmr δ 6.42 (dd, 1 H, J = 17.5, 11.0 Hz, olefinic), 5.16–5.66 (m, 4 H, olefinic), 4.12 (s, 2 H, CH_2); mass spectrum m/e 146, 148 (M^+), 41, base peak ($C_3H_5^+$), 67 (M^+ − Br).

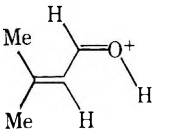
3-Methyl-3,4-oxido-1-butene (5). This epoxide was prepared according to a modification of the procedure of Reist, Junga, and Baker.[8] Isoprene (76.1 g, 1.12 mol) was emulsified by rapid stirring in 250 ml of water and the emulsion was cooled to 0°. N-Bromosuccinimide (200 g, 1.12 mol) was added slowly over a period of 0.5 hr and stirred for an additional 3 hr at 0°, and the organic phase was separated, combined with an ether extract of the aqueous phase, and dried ($MgSO_4$). Removal of solvent under reduced pressure gave a yellow oil containing crystals of succinimide which were removed by filtration; yield 160 g (87%) of a mixture of bromohydrins which was not further characterized.

The total bromohydrin product (160 g) was added over a 20-min period to 300 g of a rapidly stirred solution of 30% aqueous sodium hydroxide at 0°, and was stirred for an additional 2 hr at 0°. The organic phase was removed, combined with an ether extract of the aqueous layer, dried ($MgSO_4$), and fractionally distilled. A fraction (32.5 g, 34.5% overall yield) boiling at 78.0–82.1° (lit.[8] bp 79–82°) contained the desired epoxide **5**: nmr (CCl_4) δ 1.35 (s, 3 H), 2.58 (dd, J = 10.0, 6.0 Hz, 2 H), 4.98–5.80 (m, 3 H, olefinic).

2-Hydroxymethyl-1,3-butadiene (4b). Lithium diisopropylamide (18.0 g, 0.168 mol) was dissolved in 300 ml of anhydrous ether, and the epoxide **5** (11.0 g, 0.130 mol) was added over a 10-min period. After reflux had ceased, the solution was cooled to room temperature and poured into 200 ml of 2.0 M HCl. The organic layer was isolated, washed with 5% sodium bicarbonate, and dried ($MgSO_4$). Solvent was removed under vacuum to give 8.3 g (0.099 mol, 76% yield) of the desired alcohol **4b** as a brown oil. This material was used without purification, because its purification is difficult. However, distillation from 0.5 g of hydroquinone gave 3.3 g (0.039 mol, 30% yield) of **4b**, bp 69° (35 mm), as a clear liquid. Glc analysis on column C showed the product to be 99% pure, and its spectroscopic properties (nmr) were identical with those of a sample prepared from 2-bromomethyl-1,3-butadiene (**4a**) by the method of Thomas.[11]

2-Bromomethyl-1,3-butadiene (4a) from 2-Hydroxymethyl-1,3-butadiene (4b). The alcohol **4b** (2.0 g, 0.0238 mol) was dissolved in 50 ml of ether and cooled in an ice–salt bath. Phosphorus tribromide (2.16 g, 0.008 mol) was added dropwise over a 20-min period; the reaction mixture was then stirred in the absence of light at ice–salt temperatures for 30 min and then for 2 hr at 25°. The organic layer was extracted with 100 ml of 5% bicarbonate solution and dried ($MgSO_4$), and the solvent was removed to give 1.5 g (0.0102 mol, 43% yield) of the bromide **4a**. This material was 97% pure by glc analysis (column C) and had the same spectroscopic properties (nmr, ir) as the material prepared by the method of Krug and Yen[7] (see above).

2-Methyl-6-methylene-2,7-octadien-4-ol (1). To 30 ml of dry THF was added 2.43 g (0.037 mol) of zinc (99% pure, dried under vacuum over P_2O_5), 4.16 g (0.026 mol based on 90% purity by glc) of **4a**, and 2.36 g (0.028 mol) of **3c**. Compounds **4a** and **3c** had been dried overnight over molecular sieves. The mixture was refluxed with stirring for 4 hr (oil bath at 68°), cooled to room temperature, and hydrolyzed by addition to a stirred mixture of ether and water. The salts were filtered, and the ether layer was washed once with 25 ml of H_2O and transferred to a flask containing 4A molecular sieves. Salt was added to the combined water layers and this layer was extracted with 50 ml of ether. The ether extracts were combined, dried for 36 hr over 4A molecular sieves, and concentrated, and the remaining traces of solvent were removed in a micro distillation apparatus at room temperature by slowly reducing the pressure from 760 to 2 mm. The remaining oil was warmed to 30° and the pressure was reduced to 0.15 mm. The temperature of the oil bath was slowly increased. The product was collected in an ice-cooled trap, yield 2.57 g (65%) of **1**: bp 54–59° (0.15 mm); ir (CCl_4) 3605 (OH), 3085 (C=C), 901 cm^{-1} (olefinic C–H bend); nmr δ 6.41 (dd, 1 H, J = 18, 9 Hz, olefinic), 5.36–4.90 (m, 5 H, olefinic protons), 4.52 (m, 1 H, methine proton), 1.74 (d, 3 H, J = 1 Hz, CH_3), 1.69 (d, 3 H, J = 1 Hz, CH_3), 1.56 (s, 1 H, OH); mass spectrum m/e 152 (M^+), 85, base peak.



These spectra were identical with those of an authentic sample of **1** obtained from Chemical Samples Co. Glc analysis of a sample of distilled **1** on column B (column temperature 140°, injection temperature 140°) showed the sample to be >95% pure.

Acknowledgments. The Varian XL-100 nmr spectrometer was obtained through a National Science Foundation grant. We thank L. McCandless for the nmr spectra and H. Jennison for the mass spectra. Partial support of this work was furnished through NIH Grant GM 17061 and through Rockefeller Foundation Grant 73040.

Registry No.—**1**, 14434-41-4; **3a**, 3350-78-5; **3b**, 556-82-1; **3c**, 107-86-8; **4a**, 23691-13-6; **4b**, 13429-21-5; **5**, 1838-94-4; 3-methyl-2-butenoic acid, 541-47-9; isoprene, 78-79-5; N-bromosuccinimide, 128-08-5.

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A Practical Synthesis of α-Methylene-γ-butyrolactone

Paul A. Grieco* and Chester S. Pogonowski

Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

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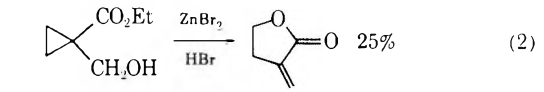
The unsubstituted α-methylene-γ-butyrolactone **1** was isolated by hydrolysis of a glycosidic substance occuring in *Erythronium americanum*.[1] More recently a fungitoxic substance identified as **1** has been isolated from tulips.[2] The structure of **1** has been confirmed by spectral data and synthesis. The primary interest in **1** stems from the presence of the α-methylene-γ-butyrolactone ring system in many natural products of biological interest[3] and the need for new efficient synthetic methods for the introduction of the α-methylene unit from lactone precursors.[4] Previous syntheses of **1** have involved as the key step (a) the reaction of a β,γ-acetylenic carbinol with nickel carbonyl (eq 1),[5] (b) the zinc bromide treatment of ethyl 1-hydroxymethylcyclopropanecarboxylate in hydrobromic acid (eq 2),[6] and (c) the reductive animation of an α-formyl lactone (eq 3).[4f]



(1)

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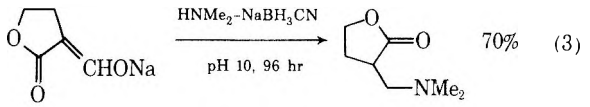
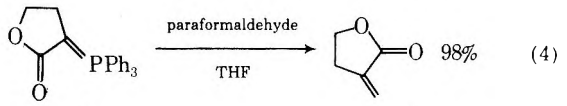
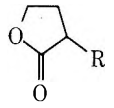




2 1

These approaches either suffer from low yields or require tedious, long chemical operations.[7] We wish to report a practical synthesis of α-methylene-γ-butyrolactone which employs as the key step a previously unreported method for the introduction of the α-methylene unit. We have observed that γ-butyrolactonylidene triphenylphosphorane (2) reacts with paraformaldehyde in refluxing anhydrous tetrahydrofuran, providing a near-quantitative yield of α-methylene-γ-butyrolactone (1) (eq 4).[8,9]

The required phosphorane 2 is readily available from the corresponding phosphonium bromide 3c in yields of 85–95% (crystalline) upon treatment of 3c with sodium carbonate in aqueous methanol.[10] The phosphonium salt 3c is obtained by treatment of α-bromo-γ-butyrolactone (3b) with triphenylphosphine in refluxing tetrahydrofuran.



3a, R = H
b, R = Br
c, R = $\overset{+}{P}Ph_3Br^-$

Yields for this reaction are 40–50% of crystalline material. Attempts to brominate[11] the lithium enolate[12] of 3a at low temperature have resulted in disappointingly low yields (20–30%) of 3b. However, the classical method of Price and Judge[13] provides reproducible yields (55%) of 3b which can be carried out on a very large scale.

The synthesis of 1 *via* readily available crystalline intermediates represents the most convenient route to 1 in comparison with previously reported syntheses. Furthermore, it permits large-scale production and facile isotopic labeling of the α-methylene unit for biochemical studies. We believe that the present method offers some obvious advantages over the existing methods for the preparation of α-methylene-γ-butyrolactone.

Experimental Section[14]

α-Methylene-γ-butyrolactone. A suspension of 3.46 g (0.01 mol) of α-(γ-butyrolactonylidene)triphenylphosphorane[10] and 0.6 g (0.02 mol) of paraformaldehyde in 150 ml of freshly distilled tetrahydrofuran under an atmosphere of nitrogen was heated at gentle reflux. After 2.5 hr, the contents of the flask were cooled to room temperature and the solvent was removed on a rotary evaporator, reducing the total volume of the reaction mixture by two-thirds. After addition of pentane, the contents of the flask were passed through a very short column of silica gel to remove triphenylphosphine oxide. After removal of the solvent *in vacuo*, there was obtained 974 mg of α-methylene-γ-butyrolactone (98% yield) which was pure by nmr analysis. Vacuum distillation afforded an analytical sample of 1: bp 60–53° (0.45 mm); ir ($CHCl_3$) 1765 (C=O) and 1670 cm^{-1} (=CH_2); nmr (CCl_4) 6.08 (t, J = 3 Hz, 1 H), 5.63 (t, J = 3 Hz, 1 H), 4.30 (t, J = 7 Hz, 2 H), 2.97 (m, 2 H); M^+ m/e 98. Ir and nmr spectra of 1 were identical with those previously reported for the natural product.[1,2] *Anal.* Calcd for $C_5H_6O_2$: C, 61.21; H, 6.17. Found: C, 61.09; H, 6.10.

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Registry No.—1, 547-65-9; 2, 34932-07-5.

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(10) S. Fliszar, R. F. Hudson, and G. Salvadori, *Helv. Chim. Acta*, **46**, 1580 (1963).
(11) We have observed the direct bromination of lactone enolates (*e.g.*, i and ii) (prepared from lithium diisopropylamide in tetrahydrofuran

i ii

at −78°) with bromine in 60–70% isolated yields: P. A. Grieco and J. J. Reap, unpublished results.
(12) We have demonstrated that lactone enolates undergo high-yield α-hydroxymethylation,[4a,b] α-carboxylation,[4c] α-phenylselenenylation,[4d] and α-phenylsulfenylation.[4e]
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New Routes for the Degradation of the Lanosterol Side Chain

Marcel Fetizon,* Frederic J. Kakis, and Valentine Ignatiadou-Ragoussis

Stereochemistry Laboratory, University of Paris, 11, 91415 Orsay, France[1]

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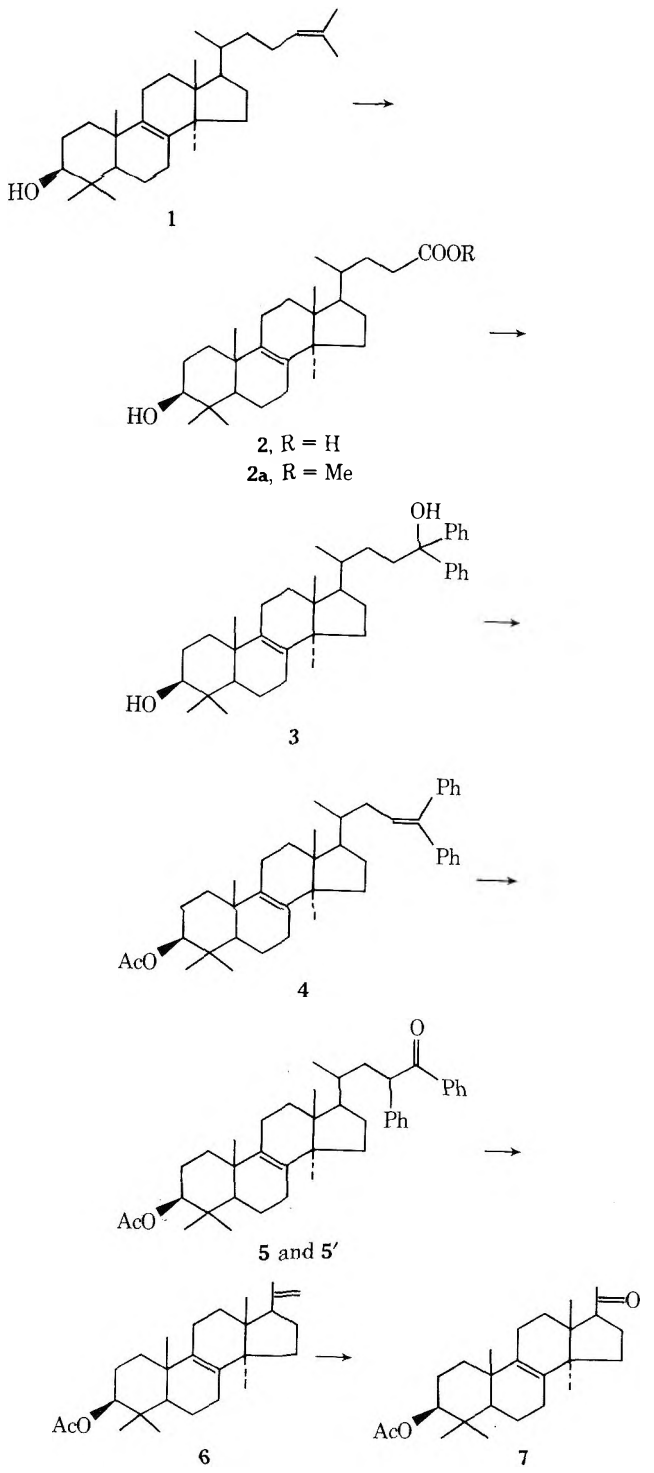
Recent reports[2,3a] describe the degradation of the lanosterol side chain with overall yields of approximately 4–10%. Other steroid side-chain degradations have also been reported,[4,5] but none of them seem to give particularly attractive yields. In view of this, we decided that it would be of considerable interest to apply a newly developed method of degradation[6] to these substrates, in the hope of improving the yields. This method, originally applied to the side-chain degradation of cholic acids,[6] utilizes as the key step a Norrish type II photoelimination reaction of a phenyl ketone which is easily obtained by means of an established rearrangement procedure.[7] Application of this photoelimination method[6] to lanosterol (Scheme I) resulted in a 23% overall yield.

Similarly, the modification of the original Briggs procedure[2] (Scheme II) gave a 15% overall yield, *i.e.*, approximately three times that obtained by the original method. Thus it appears that the photolysis of ketonic in-

Scheme I



termediates shows considerable promise as an alternative to currently used degradation schemes for the interconversion of natural products.

Experimental Section

General. Melting points were taken on a Kofler apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 257 spectrophotometer. Nmr spectra were determined on a Joel Model C60H spectrometer using tetramethylsilane as internal standard and are reported in parts per million. Optical rotations were measured with the aid of a Perkin-Elmer Model 141 polarimeter. Irradiations were performed with a Hanau TQ 150-W medium-pressure mercury lamp contained in a quartz immersion well. The 3130-Å line was isolated with 1-cm path of 0.002 *M* potassium chromate in a 5% aqueous solution of potassium carbonate. The required cooling was achieved by the circulation of this solution. For column chromatography Merck silica (0.063–0.2 mm) was always used. Microanalyses were performed by the microanalysis service of Centre national de la Recherche scientifique at the Gif sur Yvette laboratories in France.

Methyl 3β-Hydroxy-4,4,14α-trimethyl-5α-cholan-8-ene-24-methanoate (2a). A sample (4.7 g) of crude trisnorlanostenolic acid (**2**), obtained from the ozonolysis of commercial grade lanosterol[8] by the method of Curtis and Silbermann,[9,10] was esterified in the usual way by simple reflux with methanol (250 ml) and 12 N hydrochloric acid (10 ml). The crude ester was isolated by extraction with ether and purified by column chromatography over silica using a pentane–ether (2:1) mixture as the eluent. The product was further purified by recrystallizations from methanol. The pure (mp 154–156°) ester gave the following spectral data: ir (CS_2) 3630 and 1740 cm^{-1}; nmr ($CDCl_3$) δ 0.7 (3 H, singlet), 0.795 (3 H, singlet), 0.875 (6 H, singlet), 0.98 (6 H, singlet), 3.7 (3 H, singlet, $-COOCH_3$ protons).

3β,24-Dihydroxy-4,4,14α-trimethyl-24,24-diphenyl-5α-cholan-8-ene (3). This compound was prepared from a sample (7.2 g, 0.0167 mol) of pure (mp 154–156°) ester **2a** by the standard addition of phenylmagnesium bromide (25 g, 0.138 mol) in anhydrous tetrahydrofuran. The mixture was refluxed for 15 hr and then decomposed with a saturated solution of ammonium chloride. Ether extraction of the hydrolyzed mixture followed by drying and removal of the solvents afforded a crude, oily product mixture, which contained an excess of the usual Grignard coupling products. Crystallization of the diol **3** was achieved by treating the oil with hexane. Thus 6.8 of the diol **3** was obtained.

Column chromatography of the mother liquors over silica with pentane–ether (2:1) followed by recrystallization from methanol afforded another 2.2 g of the pure (mp 172–173°) diol **3**, bringing the total yield to 9 g (97%): ir (CS_2) 3610, 3090, 3060, 3030, and 700 cm^{-1}; nmr ($CDCl_3$) δ 0.57 (3 H, singlet), 0.77, 0.85, 0.92, 0.95 (15 H, singlet), 7.1–7.6 (10 H, multiplet, aromatic protons).

3β-Acetoxy-4,4,14α-trimethyl-24,24-diphenyl-5α-cholane-8,23-diene (4). The dehydration of the alcohol at C_{23} and the acetylation of the C_3 hydroxyl group were simultaneously achieved by refluxing a sample (9.2 g) of the diol **3** with a mixture of acetic anhydride–acetic acid (60 ml, 5:1) for a period of 5 hr. After the usual work-up and recrystallization of the crude product from acetone, 6.5 g of pure (mp 196–199°) diene **4** was obtained. Chromatography of the mother liquors over silica with pentane–ether (5:1) afforded another 2.4 g of pure product, bringing the total yield of the diene **4** to 8.9 g (93%): ir (CS_2) 3090, 3060, 3030, 1735, 1240, and 700 cm^{-1}; nmr ($CDCl_3$) δ 0.62 (3 H, singlet), 0.77, 0.85, 0.90, 0.95 (15 H, singlets), 2.0 (3 H, singlet, acetoxy protons), 4.47 (1 H, multiplet, 3α proton), 6.075 (1 H, triplet, ethylenic proton, J = 7.5 Hz), 6.95–7.5 (10 H, multiplet, aromatic protons).

Anal. Calcd for $C_{41}H_{54}O_2$: C, 85.07; H, 9.40; O, 5.53. Found: C, 84.83; H, 9.24; O, 5.59.

3β-Acetoxy-4,4,14α-trimethyl-23,24-diphenyl-5α-cholan-8-en-24-one (5 and 5′). The rearrangement of compound **4** above (1.156 g, 0.002 mol) to the mixture of ketones **5** and **5′** was achieved by the Kakis method,[7] except that a stoichiometric amount of bromine (5.5–6 ml of a 2% Br_2 solution in chloroform corresponding to *ca.* 0.32 g, 0.002 mol) had to be used to avoid the bromination of the $\Delta^{8,9}$ double bond.

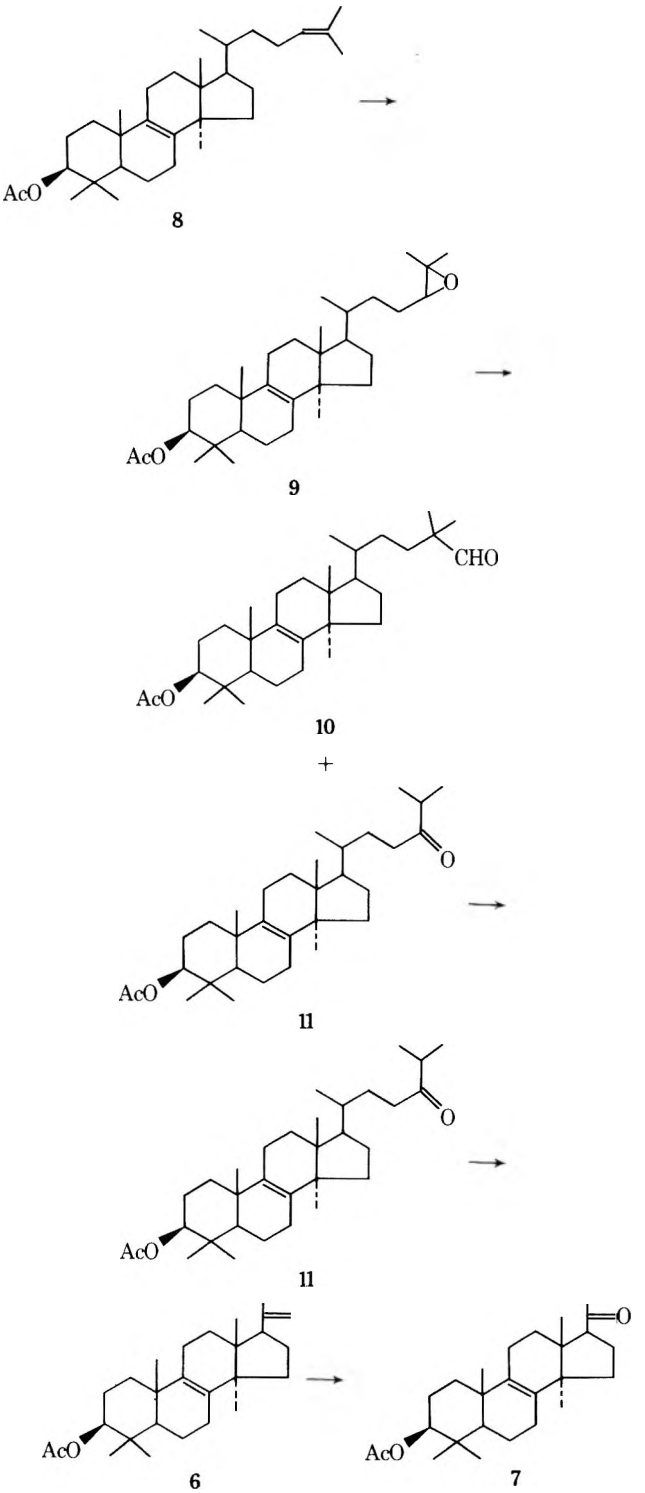
The crude mixture (1.4 g) of the diastereomeric ketones **5** and **5′** obtained from this rearrangement was purified by recrystallization from a mixture of ethanol and methylene chloride. Thus a pure sample (950 mg) of the ketones **5** and **5′** was obtained. By chromatographing the mother liquors another 70 mg of pure ketones were obtained, bringing the total yield of ketones to 1.020 g (87%): ir (CS_2) 3080, 3060, 3030, 1735, 1685, 1245, 910, 740, and 700 cm^{-1}.

Anal. Calcd for $C_{41}H_{54}O_3$: C, 82.78; H, 9.15; O, 8.07. Found: C, 82.54; H, 8.99; O, 8.17.

The separation of the two diastereomeric ketones **5** and **5′**, which was attempted on a small sample of the mixture, proved to be quite laborious. Separation was finally achieved by thin layer chromatography on fluorescent silica using several successive elutions with pentane–ether (10:1). Each isomer was subsequently recrystallized from a mixture of ethanol and methylene chloride.

The least polar isomer (**5**) gave needles (mp 187–189°), whereas the more polar isomer (**5′**) gave hexagonal plates (mp 229–232°). In addition the following physical data were obtained: compound **5**, $[\alpha]_D$ ($CHCl_3$) −36°; nmr ($CDCl_3$) δ 0.55 (3 H, singlet), 0.8 (9 H, singlet), 0.9 (6 H, singlet), 1.93 (3 H, singlet, acetoxy protons), 4.5 (2 H, multiplet, 3α and C_{23} protons), 6.9–8 (10 H, multiplet, aromatic protons); compound **5′**, $[\alpha]_D$ ($CHCl_3$) +108.5°; nmr ($CDCl_3$) δ 0.45 (3 H, singlet), 0.79 (9 H, singlet), 0.85 (6 H, singlet), 1.95 (3 H, singlet, acetoxy protons), 4.45 (2 H, multiplet, 3α

Scheme II



and C_{23} protons), 6.95–8.05 (10 H, multiplet, aromatic protons).

3β-Acetoxy-4,4,14α-trimethyl-5α-pregna-8,20-diene (6). A. From 5 and 5′. A sample (1 g) of the ketone mixture (5 and 5′) was dissolved in pure anhydrous benzene and irradiated for about 2 hr. Evaporation of the solvents afforded a yellow oil (1.09 g). The isolation of the diene 6 from the mixture of photolysis products was achieved by thin layer chromatography over fluorescent silica which contained 8% silver nitrate, using a mixture of pentane–ether (4:1) as the eluent. Thus a pure sample (0.3 g, 45%) of the diene 6 was obtained. Recrystallization from ethanol afforded an analytical sample: mp 168–170°; ir (CS_2) 3080, 1735, 1240, and 890 cm^{-1}; nmr ($CDCl_3$) δ 0.5 (3 H, singlet), 0.8, 0.85, 0.9 (12 H, singlets), 1.67 (C_{21} protons), 1.97 (3 H, singlet, acetoxy protons), 4.65 and 4.77 (3 H, two singlets and a multiplet, terminal methylene and 3α protons); $[\alpha]D$ ($CHCl_3$) +47.5°.

Anal. Calcd for $C_{27}H_{42}O_2$: C, 81.35; H, 10.62; O, 8.03. Found: C, 80.50; H, 10.41; O, 8.04.

B. From 11. A sample (500 mg) of the isopropyl ketone 11 was subjected to photoelimination by a procedure identical with that described for the irradiation of the mixture of phenyl ketones (5 and 5′). Complete disappearance of the ketone in this case required over 9 hr of irradiation. Following the same isolation and purification procedure used for the photolysis products of compounds 5 and 5′, a pure sample (215 mg, 52%) of compound 6 was obtained. The physical constants and spectra of this product were identical with those obtained for the product isolated from the photolysis of the phenyl ketones 5 and 5′ in part A above.

3β-Acetoxy-4,4,14α-trimethyl-5α-pregn-8-en-20-one (7). A sample of compound 6 (250 mg, 0.63 mmol) was dissolved in a mixture of pyridine (5 ml) and benzene (2 ml). The resulting solution was then treated with osmium tetroxide (160 mg, 0.63 mmol). The mixture became black-red. After the mixture was stirred for 1 hr at room temperature, a mixture of pyridine (2 ml), water (2 ml), and sodium bisulfite solution (2 ml) was added to the reaction flask. The stirring was continued for another hour, after which the mixture was diluted with water and extracted with methylene chloride. The organic phase was then washed successively with aqueous sulfuric acid (10%), a sodium bicarbonate solution (10%), and distilled water. Drying of the solvents, followed by evaporation, afforded 280 mg of crude 3β-acetoxy-4,4,14α-trimethyl-5α-pregn-8-ene-20,22-diol: ir (CS_2) 3630, 3580, 1735, and 1240 cm^{-1}. This intermediate, without purification, was dissolved in tetrahydrofuran and treated gradually with a mixture of H_5IO_6 (150 mg) in tetrahydrofuran. The reaction was instantaneous. Extraction of the reaction mixture followed by the usual work-up afforded a sample (265 mg) of product 7. Purification was achieved by thin layer chromatography over fluorescent silica with a pentane–ether (4:1) mixture as the eluent followed by recrystallization from methanol. Thus 165 mg of the pure (mp 167–169°) product 7 was obtained (66% yield based on compound 6): ir (CS_2) 1735, 1710, and 1240 cm^{-1}; nmr ($CDCl_3$) δ 0.57 (3 H, singlet), 0.85, 0.92, 0.96 (12 H, singlets), 2.03 (3 H, singlet, C_{21} protons), 2.1 (3 H, singlet, acetoxy protons). $[\alpha]D$ ($CHCl_3$), +115°; Mass spec. gave molecular ion peak at m/e 400.

3β-Acetoxylanosta-8,24-diene (8). Treatment of a commercial lanosterol sample[8] with acetic anhydride in pyridine led to a mixture of the corresponding acetates. Separation was achieved by column chromatography over silica impregnated with silver nitrate (10%), using a pentane–ether mixture (30:1) as the eluent. The weight ratio of column packing to mixture was 100:1. Thus a pure (mp 129–130°) sample of compound 8 was obtained (lit.[11] mp 127–128°).

3β-Acetoxylanost-8-en-24-one (11). This ketone was prepared from compound 8 by the same series of reactions used by Briggs.[2] The total yield of ketone 11 from compound 8 was 42%. All the physical constants and spectra were in agreement with the previously reported[2] values.

Acknowledgments. The participation of Dr. F. J. Kakis in this project was made possible through a grant by the Research Corporation. We are grateful for this assistance. We would also like to thank the Centre national de la Recherche scientifique for their generous support of this work.

Registry No.—1, 79-63-0; 2, 51348-64-2; 2a, 51348-65-3; 3, 51270-47-4; 4, 51270-48-5; 5, 51270-49-6; 5′, 51270-50-9; 6, 49810-38-0; 7, 27868-09-3; 11, 13553-26-9.

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Electrophilic Additions and Substitutions of *tert*-Butyl Hypochlorite Catalyzed by Boron Trifluoride[1]

Cheves Walling* and Roger T. Clark

Department of Chemistry, University of Utah, Salt Lake City, Utah 84112

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In nonpolar solvents with light or radical initiators, *tert*-butyl hypochlorite reacts with olefins to give allylic chlorides in good yield by a radical chain process.[2] On the other hand, Anbar and Ginsberg, in their comprehensive review,[3] report that, in polar solvents, addition occurs to yield β-chloro ethers *via* electrophilic addition where R′ is either *tert*-butyl or, in an alcohol solvent, the corresponding alcohol residue. Since we had need of such products for another study,[4] and since yields and procedures were ill-defined in the original papers cited by Anbar, we have reexamined this polar addition, and find that the success of the reaction depends markedly upon reaction conditions but proceeds particularly smoothly simply by adding the hypochlorite to cold olefin–alcohol mixture containing a few drops of boron trifluoride etherate. Yields are 50–90% and, of particular interest, β-chloro-*tert*-alkyl ethers can be produced which are difficulty accessible by other means. Typical results are shown in Table I, and we assume that reaction occurs *via* a typical "chloronium ion" intermediate which then reacts with solvent as the predominant nucleophile. Although the preparation appears general for simple olefins, it fails with negatively substituted olefins such as 1,1- and *cis*-1,2-dichloro- and trichloroethylene.

$$t\text{-BuOCl} + CH_2{=}CHR \rightarrow ClCH_2CH(OR')R$$

We were also unable to observe any cyclized product on attempting to prepare the hypochlorite from 4-penten-1-ol *in situ* and then carrying out the addition, although others have reported accomplishing the cyclization *via* a radical path.[5]

Anbar[3] also reports a few examples of acid-catalyzed electrophilic aromatic substitution by *tert*-butyl hypochlorite, and such reactions have occasionally been noted as complications in attempted radical chlorination of alkylbenzenes with strong electron-supplying groups and in the reactions of complex hypochlorites containing reactive aromatic nuclei.[4] We find that the *tert*-butyl hypochlorite–boron trifluoride technique leads to smooth chlorination of benzene, chlorobenzene, and toluene at room temperature, although the reaction fails with more negatively substituted aromatics. With toluene we obtain an isomer distribution of 70.2% ortho and 29.8% para and, in competition, toluene is 21 times as reactive as benzene. For Cl_2 in acetic acid the isomer distribution is reported as 59.8% ortho, 0.5% meta, and 39.7% para with toluene 344 times as reactive as benzene,[6] while with hypochlorous acid in water the isomer distribution is 74.6% ortho, 2.2% meta, and 23.2% para with a total reactivity 60 times that of benzene.[7] Our results are much closer to the latter, and indicate that the electrophilic species is indeed a *tert*-butyl hypochlorite–boron trifluoride complex, rather than traces of adventitious Cl_2 which might be formed during the reaction. With *tert*-butylbenzene we obtain a mixture of 53% ortho and 47% *p*-chloro substitution.

In summary, our results show that a variety of electrophilic addition and substitution reactions of *tert*-butyl hypochlorite (and presumably other alkyl hypochlorites) can be carried out in good yield under very mild conditions using small amounts of boron trifluoride catalyst. The reaction provides a simple, efficient synthesis of β-chloro ethers and a convenient laboratory alternative to gaseous Cl_2 for the chlorination of suitable aromatic nuclei.

Experimental Section

β-Chloro Ethers. The preparation of 2-chlorocyclohexyl isopropyl ether is typical. Anhydrous isopropyl alcohol (0.1 mol), cyclohexene (0.1 mol), and a few drops of boron trifluoride etherate were placed in a 25-ml flask cooled in ice water. *tert*-Butyl hypochlorite (0.03 mol) was added dropwise with stirring. Each drop apparently reacted immediately. The solvent was removed *in vacuo* and the product was distilled, yield 2.3 g (43.2%), bp 48° (0.1 mm). Analysis and nmr spectra were consistent with the assigned structure and vpc indicated a single isomer, assumed to have the trans structure. Other reactions were carried out similarly, using equimolar quantities of alcohol and olefin, except that addition to isobutylene was made at −78°. Yields were determined either by vpc or actual isolation as indicated in Table I.

Table I
Preparation of β-Chloro Ethers

Olefin	Registry no.	Product	Registry no.	Yield, % Vpc	Yield, % Isolated
Cyclohexene	110-83-8	*trans*-2-Chlorocyclohexyl *tert*-butyl ether	51286-79-4	49	49
Cyclohexene		*trans*-2-Chlorocyclohexyl isopropyl ether	51286-80-7	57	43
Cyclohexene		*trans*-2-Chlorocyclohexyl *n*-propyl ether	51286-81-8	96	66
Isobutylene	115-11-7	Chloro-*tert*-butyl *n*-propyl ether	51286-82-9	67	

Aromatic substitution reactions were carried out by adding hypochlorite at or below room temperature to an excess of the appropriate aromatic (or mixture) in the presence of a small amount of boron trifluoride etherate but no added solvent. The yellow color of the hypochlorite disappeared within 0.5 hr, and total yields (essentially quantitative) and product distributions were determined by vpc using known standards. The spread of analytical results indicated that the isomer distributions reported are reliable to ±1–2%.

Registry No.—*tert*-butyl hypochlorite, 507-40-4; boron trifluoride, 7637-07-2.

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Molecular Rearrangements in the Course of Ritter Reactions

Susan Edwards and Fritz-Hans Marquardt*[1]

Research Department, Pharmaceutical Division, CIBA-GEIGY Corporation, Summit, New Jersey 07901

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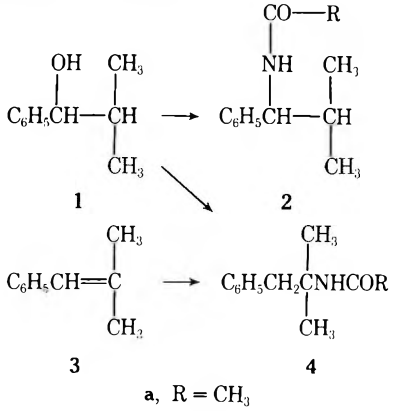
It is well known that the Ritter reaction occurs *via* ionic intermediates and that molecular rearrangements take place if the initial carbonium ion intermediate can isomerize to a more stable one.[2] Thus Boltze and Mühlenbein[3] reported that α-isopropylbenzyl alcohol (**1**) reacts with hydrogen cyanide or with nitriles under acidic conditions to yield amides of α,α-dimethylphenethylamine (**4**). On the other hand, this seems to contradict the report by Christol, *et al.*,[4] that Ritter reactions of **1** form amides of the unrearranged α-isopropylbenzylamine (**2**).



a, R = CH_3
b, R = C_6H_5

A check of the reaction conditions which were used by these two groups showed that a reasonable cause for this discrepancy could have been the different order of addition of reagents used, since this in turn could have easily changed the type of mechanistic factor which controlled the reactions. Thus, Boltze and Mühlenbein first mixed the carbinol and the acids, and only later added the nitrile, whereas Christol and coworkers first mixed the carbinol with the nitrile, and added the sulfuric acid last. In the first case, the initially formed carbonium ion may therefore have had ample time to rearrange into a more stable structure before the nitrile was added (*e.g.*, thermodynamic control of reaction), while in the second case the nitrile could trap the carbonium ions as they were being formed (*e.g.*, kinetic control). This would also explain Christol's additional observation that, while the Ritter reaction of **1** yielded **2**, the same reaction with the styrene derivative **3** only yielded **4**.

To check our rationalization, we only changed the order of addition of reagents when **1** was allowed to react with nitriles in a mixture of sulfuric and acetic acid under otherwise identical conditions. As was expected, **2** was obtained when sulfuric acid was the last reagent which was added, while **4** was obtained when the nitrile was added last.[5]

Experimental Section

Melting points were determined in capillaries and are uncorrected; nmr spectra were recorded on a Varian Associates A-60 spectrometer with TMS as internal standard.

α-Isopropylbenzyl Alcohol (1). To a refluxing suspension of 13 g (0.34 mol) of lithium aluminium hydride in 300 ml of tetrahydrofuran was added 100 g (0.675 mol) of isobutyrophenone (Aldrich) in 200 ml of tetrahydrofuran. After 2 hr of additional refluxing, the reaction mixture was cooled to room temperature and treated with 15 ml of water, 15 ml of 15% aqueous sodium hydroxide, and 39 ml of water. The suspension was filtered, the filter residue was washed thoroughly with 200 ml of tetrahydrofuran, and the solvent of the combined filtrates was evaporated under reduced pressure to yield 84.9 g of crude **1**, which was purified by fractionation over a Vigreux column and gave 73.9 g (0.526 mol, 78% of theory) of **1**, bp 77–78° (0.3 mm).

***N*-(α,α-Dimethylphenethyl)acetamide (4a).** To a solution of 6.0 g (0.04 mol) of compound **1** in 6.0 ml of glacial acetic acid and 3.3 ml of 95% sulfuric acid was added dropwise 1.9 g (0.046 mol) of acetonitrile at 70°, and the mixture was kept for an additional 1 hr at this same temperature. Then it was added to enough crushed ice to keep the resulting solution at room temperature, treated with 14 ml of 25% aqueous sodium hydroxide, returned just to acidic by addition of 15% aqueous sulfuric acid, and extracted in two steps with 150 ml of methylene chloride. The combined extracts were washed with 3 × 50 ml of water and dried over sodium sulfate and the solvent was evaporated under reduced pressure to yield 7.1 g of an oil, which crystallized in cyclohexane to give 2.7 g (0.014 mol, 35% of theory) of **4a**: mp 89–90° (lit.[3] mp 91–92°); nmr ($CDCl_3$) 2 CH_3 at 1.29 (s), CH_3 at 1.85 (s), CH_2 at 3.02 (s), C_6H_5 at 7.19 ppm (complex).

***N*-(α,α-Dimethylphenethyl)benzamide (4b).** By the method described for the preparation of **4a**, but using 3.3 g (0.032 mol) of benzonitrile instead of the acetonitrile, the crude product was 6.4 g of crystalline material which was purified by recrystallization in 95% ethanol: mp 109–110°; nmr ($CDCl_3$) 2 CH_3 at 1.43 (s), CH_2 at 3.14 (s), 10 aromatic at 7.1–7.8 ppm (complex).

Anal. Calcd for $C_{17}H_{19}NO$: C, 80.60; H, 7.56; N, 5.53. Found: C, 80.95; H, 7.33; N, 5.57.

***N*-(α-Isopropylbenzyl)acetamide (2a).** To a solution of 6.0 g (0.04 mol) of **1** and 1.9 g (0.046 mol) of acetonitrile in 6.0 ml of glacial acetic acid was added 3.3 ml of 95% sulfuric acid at 70°. After the previously described work-up, which yielded 6.6 g of crude product, a recrystallization in 2-propanol gave 2.6 g (0.0135 mol, 34% of theory) of **2a**: mp 114–116°; nmr ($CDCl_3$) CH_3 at 0.78 (d), CH_3 at 0.95 (d), CH_3 at 1.9 (s), CH at 1.9 (heptet), CH at 4.7 (broad triplet), C_6H_5 at 7.2 ppm (s).

Anal. Calcd for $C_{12}H_{17}NO$: C, 75.40; H, 8.96; N, 7.32. Found: C, 75.60; H, 8.56; N, 7.37.

***N*-(α-Isopropylbenzyl)benzamide (2b).** By the method described for the preparation of **2a**, but using 3.3 g (0.032 mol) of benzonitrile instead of acetonitrile, the crude product was 6.2 g of crystalline material, which was purified by recrystallization in ethanol: mp 139–140° (lit.[4] mp 141°); nmr ($CDCl_3$) CH_3 at 0.87 (d), CH_3 at 1.02 (d), CH at 2.23 (heptet), CH at 5.01 (broad triplet), 10 aromatic at 7.4–7.9 ppm (complex).

Acknowledgment. We wish to acknowledge the helpful discussions with Dr. J. L. Marsh and with Mr. L. Dorfman, whose staff we thank for microanalyses and spectra.

Registry No.—1, 611-69-8; **2a**, 33617-85-5; **2b**, 51310-27-1; **4a**, 5531-33-9; **4b**, 51310-28-2; isobutyrophenone, 611-70-1.

References and Notes

(1) To whom inquiries should be directed to Dyestuffs & Chemicals Division, CIBA-GEIGY Corp., P.O. Box 11422, Greensboro, N. C. 27409.
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N-Acyllactam Rearrangements. The Fate of the Carboxyl Carbon and the Synthesis of 2-*tert*-Butyl-1-pyrroline

Bradford P. Mundy,* Kenneth B. Lipkowitz, Marc Lee, and Brent R. Larsen

Department of Chemistry, Montana State University, Bozeman, Montana 59715

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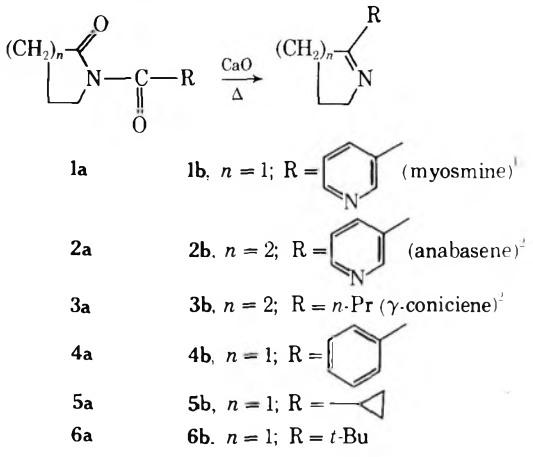
The rearrangement of *N*-acyllactams to 2-substituted cyclic imines has recently been investigated in our labora-

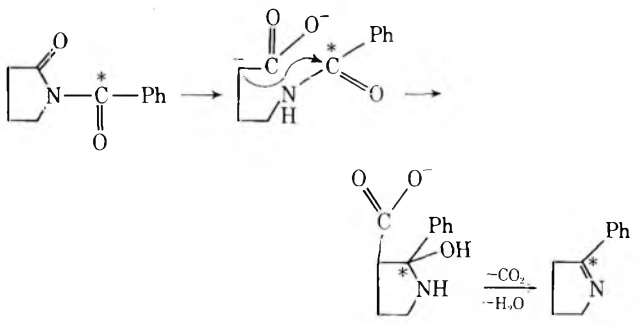
tory,[1,2] and has resulted in a simple entry into pyrroline and piperideine alkaloids, 1–3 (Scheme I). As a result of some exploratory research into the possible role of **1a** as an intermediate in nicotine biosynthesis,[3] we had occasion to consider the fate of the carboxyl carbon of the *N*-acyl moiety.

Scheme I
Synthesis of 2-Substituted Pyrrolines and Piperideine



To examine this point, and utilizing our experience with a readily available model, ^{14}C-carboxyl labeled benzoyl chloride was treated with 2-pyrrolidone to yield **4a** (specific activity 246 dpm/mmol). Dry distillation of an equal weight portion of **4a** and calcium oxide resulted in formation of **4b** (specific activity 233 dpm/mmol). Within the experimental error of our counting, one could suggest that all of the carbonyl carbon of the *N*-acyl group was maintained in the product. A partial mechanism consistent with this observation is delineated in Scheme II. Based on a consideration of this type, one might predict that the reaction would *not* be sensitive to the inherent electronic and steric effects of the R group. Two further entries suggest this to be true, **5** and **6** (Scheme I).

Scheme II
Proposed Mechanism for *N*-Acyllactam Rearrangement



N-Cyclopropanoyl-2-pyrrolidone (**5a**) was readily converted to 2-cyclopropyl-1-pyrroline (**5b**) without secondary reorganization of the cyclopropyl moiety. The propensity of this strained ring to suffer skeletal reorganization under many different reaction conditions is well documented.[4] For our last test of the nonparticipation of R during the reaction, we wished to examine a molecule which would be difficult to prepare by other methods. Since our previous synthetic efforts had shown us that the sequence worked equally well in the five- and six-ring series, our most important consideration focused on the nature of the R group. A literature search revealed a synthesis of 2-*tert*-butyl-1-piperideine starting from 2-*tert*-butyl-1-pyridine.[5] Since no corresponding pyrroline had ever been reported, and an obvious method was not apparent to incorporate the *tert*-butyl group into a pyrroline, this seemed a reasonable test molecule for our synthetic efforts. Dry distillation of *N*-pivaloyl-2-pyrrolidone (**6a**) in the presence of calcium oxide gave **6b**.

The ease of preparing *N*-acyllactams, coupled with the specificity of the rearrangement regardless of ring size and constitution of R, suggest this to be a general and useful methodology for 2-substituted cyclic imines.

Experimental Section

Nmr spectra were recorded on a Varian A-60 instrument, using TMS as an internal standard and deuteriochloroform as solvent. Boiling and melting points are uncorrected. Carbon-14 analyses were performed by liquid scintillation counting, using the channels ratio technique to determine efficiencies.

Synthesis of 2-Phenyl-1-pyrroline (4b). Benzoyl chloride (140 g), ^{14}C label at the carbonyl carbon, was converted to *N*-benzoyl-2-pyrrolidone by the method previously reported.[1] The product was repeatedly crystallized from hot ethanol (mp 91°) to constant specific activity of 246 dpm/mmol. This product was mixed with an equal weight of calcium oxide and the resulting mixture was heated with a free flame to give crude 2-phenyl-1-pyrroline.[1] A sample was purified by preparative glc [10 ft × 0.25 in. column, 10% Carbowax 20M on Chromosorb W, impregnated with 6% (w/w) sodium hydroxide]. A sample counted 233 dpm/mmol.

Synthesis of *N*-Cyclopropanoyl-2-pyrrolidone (5a). A solution of cyclopropanoyl chloride (5 g, 0.048 mol) and pyridine (10 g) was allowed to stir while 8.25 g of 2-pyrrolidone was slowly added. After stirring at room temperature for 8 hr, the reaction mixture was taken up in methylene chloride and washed with dilute hydrochloric acid until the washings were acidic. The methylene chloride solution was washed with saturated sodium bicarbonate, and the resulting neutralized solution was dried over anhydrous sodium sulfate and reduced in volume. The crude product was crystallized from chloroform–hexane to yield 6.9 g (94%) of **5a**: mp 62–63°; nmr δ 2.61 (t, 2), 1.97 (m, 2), 3.75 (t, 2), 3.17 (m, 1), 0.97 (m, 4).

Anal. Calcd for $C_8H_{11}NO_2$: C, 62.7; H, 7.2; N, 9.1. Found: C, 62.3; H, 7.1; N, 9.3.

Synthesis of 2-Cyclopropyl-1-pyrroline (5b). Calcium oxide (1.5 g) was intimately mixed with an equal weight of **5a** and the mixture was subjected to dry distillation with a free flame. Redistillation of the crude product yielded 0.78 g (73%) of **5b**: bp 45° (10 mm); picrate derivative mp 150–151°; nmr δ 3.75 (m, 2), 0.81 (d, 4), 1.5–2.6 (unresolved multiplet, 5).

Anal. (picrate) Calcd for $C_{13}H_{14}N_4O_7$: N, 16.5. Found: N, 16.5.

Preparation of 2-*tert*-Butyl-1-pyrroline (6b). A solution of 2-pyrrolidone (17 g) and pyridine (7.9 g) in 100 ml of benzene was stirred at room temperature while pivaloyl chloride (12 g) in 25 ml of benzene was slowly added. The reaction mixture was diluted with *ca.* 100 ml of methylene chloride and washed with dilute hydrochloric acid until the washings were acidic. The methylene chloride layer was separated and washed with saturated bicarbonate. This solution was dried over anhydrous sodium carbonate, filtered, and reduced in volume. Distillation (62–65°, 0.2 mm) gave 13.7 g (81% yield) of the desired *N*-acyllactam, which was taken immediately to the next step. An equal-weight mixture (6.72 g) of the above product and calcium oxide was heated with an open flame to yield the crude pyrroline. Distillation gave 2.0 g (40%) of **6b**: bp 110° (1.5 mm); nmr δ 1.15 (s, 9), 1.85 (m, 2), 2.5 (t, 2), 3.75 (t, 2).

Anal. Calcd for $C_8H_{15}N$: C, 76.8; H, 12.0; N, 11.2. Found: C, 76.8; H, 12.1; N, 10.9.

Acknowledgment. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research.

Registry No.—**4a**, 2399-66-8; **4b**, 700-91-4; **5a**, 51269-66-0; **5b**, 51269-67-1; **5b** picrate, 51269-68-2; **6a**, 51269-69-3; **6b**, 51269-70-6; cyclopropanoyl chloride, 4023-34-1; 2-pyrrolidone, 616-45-5; pivaloyl chloride, 3282-30-2.

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1a was added to the homogenate with the expectation that any naturally occurring 1a would mix with this and be reisolated. Careful purification of 1a after reisolation demonstrated *no* activity to be present. This work was presented at the Montana Academy of Sciences, Dillon, Mont., 1973.

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Facile Addition of Bromine to a Reissert Compound

T. George,* D. V. Mehta, and D. A. Dabholkar

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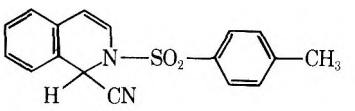
The chemistry of Reissert compounds has been reviewed in detail.[1] Dihydro Reissert compounds have been described by Shamma, *et al.*;[2] their nmr data have been studied by Bramley and Johnson.[3] This note describes the facile addition of bromine to Reissert compound 1 and the tentative stereochemistry of the vicinal dibromide 2 and its derivatives.

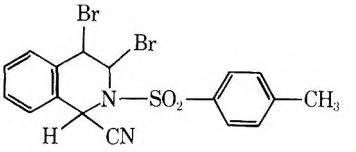
The bromination of isoquinoline is reported to give 4-bromoisoquinoline under drastic conditions.[4] A mechanism involving the addition of bromine followed by the elimination of hydrogen bromide has been postulated.[5] The dibromide has eluded isolation and characterisation. 1-Cyano-2-*p*-toluenesulfonyl-1,2-dihydroisoquinoline (1) was prepared according to the method described by Wefer, *et al.*[6] The bromination of 1 took place readily to give 1-cyano-3,4-*cis*-dibromo-2-*p*-toluenesulfonyl-1,2,3,4-tetrahydroisoquinoline (2), which could be isolated and characterized. The analytical values and the spectral data were in agreement with structure 2. Refluxing 2 with ethanol and 2-propanol gave 5 and 6, respectively. Treatment of 2 with aqueous sodium bicarbonate gave 4-bromo-1-cyano-3-hydroxy-1,2,3,4-tetrahydroisoquinoline (7). The above α-amino alcohol 7 would be expected to exist in equilibrium with the open-chain structure 8 in solution. However, poor solubility of the compound in solvents such as $CHCl_3$ and CCl_4 precluded such a study. The ir spectrum of 7 in Nujol showed bands at 3350 and 1700 cm^{-1}, showing evidence for the δ-amino aldehyde structure 8. In the nmr spectrum of the compound in CD_3SOCD_3 the signal corresponding to the aldehydic proton was not discernible, showing the absence of any significant amount of 8 in solution.

That the addition of bromine to 1 may take place in the cis fashion is shown by the magnitude of the coupling constant of C_3 and C_4 protons in 2 (J = 2.5 Hz). The above coupling constant is consistent also with a configuration in which the bromine atoms are trans and diaxial. However, it is highly unlikely that the bromine atoms would be axial. The magnitude of the coupling constants of C_3 and C_4 protons in 5, 6, and 7 remains of the same order as in 2, indicating a cis orientation of the hydrogen atoms. The facile formation of the above compounds can be visualised as the addition of elements of ethanol, 2-propanol, or water to the iminium species 3 or the enamine 4.

Treating 2 with 1 mol of morpholine in dioxane gave 4-bromo-1-cyano-2-*p*-toluenesulfonyl-1,2-dihydroisoquinoline (4), in which the C_1 proton occurs as a doublet (J = 0.5 Hz). This is in agreement with the observations of Chhabra, *et al.*,[7] on the long-range spin coupling in isoquinoline Reissert compounds. In the presence of morpholine, a facile trans-diaxial elimination of the elements of hydrogen bromide can be postulated for the formation of 4 from 2. However, the pathway involving the formation of iminium species 3 and loss of proton to give 4 cannot be ruled out under the above conditions. Confirmation of the product as 4 was obtained by establishing its identity with the product obtained by Reissert reaction on 4-bromoisoquinoline. Refluxing 2 with 3 mol of morpholine in dioxane caused elimination of *p*-toluenesulfonic acid along with hydrogen bromide to give 4-bromoisoquinaldonitrile (9). The latter compound has also been obtained by Wefer, *et al.*,[6] by use of sodium hydride in xylene.



1



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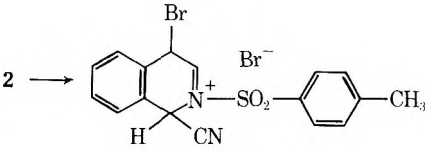

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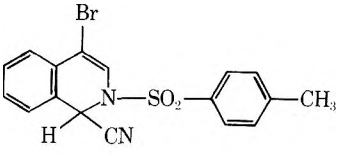

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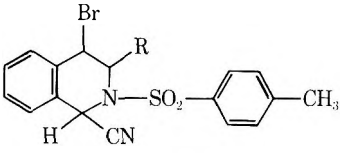
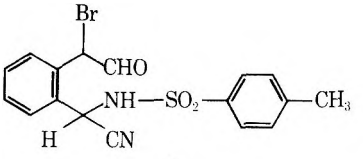


5, R = OC_2H_5
6, R = $OCH(CH_3)_2$
7, R = OH



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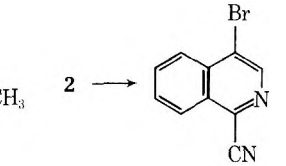

9

Experimental Section

Melting points are uncorrected. The ir spectra were examined as Nujol mulls on a Perkin-Elmer Model 421 spectrophotometer. The uv spectra in 95% ethanol were recorded on a Beckman Model DK-2A spectrophotometer and the nmr spectra were recorded on a Varian Associates A-60 spectrometer with TMS as internal standard.

1-Cyano-2-*p*-toluenesulfonyl-1,2-dihydroisoquinoline (1). The above compound was prepared in 52% yield according to the procedure of Wefer, *et al.*:[6] mp 101°: ir 1620 and 1170 cm^{-1}; uv max 227 nm (log ϵ 4.26) and 285 (3.93); nmr ($CDCl_3$) δ 2.31 (s, 3 H, $ArCH_3$), 6.11 (d, 1 H, J = 6 Hz, C_4 H), 6.18 (d, 1 H, J = 0.6 Hz, C_1 H), 6.80 (d, 1 H, J = 6 Hz, C_3 H), 6.95-7.90 (m, 8 H, aromatic).

3,4-*cis*-Dibromo-1-cyano-2-*p*-toluenesulfonyl-1,2,3,4-tetrahydroisoquinoline (2). To a solution of 12.41 g (0.04 mol) of 1 in 150 ml of chloroform was added gradually 7.04 g (0.044 mol) of bromine in 40 ml of chloroform at room temperature and the solution was stirred for 4 hr. Evaporation of the solvent gave a residue, which crystallized on trituration with ether. It was recrystallized

from methylene chloride–ether to give 6.5 g (34.5%) of yellow crystals: mp 118–118.5°; ir 1595 cm^{-1}; uv 228 nm (log ϵ 4.29); nmr δ 2.42 (s, 3 H, $ArCH_3$), 5.62 (d, 1 H, J = 2.5 Hz, C_4 H), 6.11 (s, 1 H, C_1 H), 6.88 (d, 1 H, J = 2.5 Hz, C_3 H), 7.3–7.55 (m, 6 H, aromatic), 7.9–8.05 (m, 2 H, aromatic). *Anal.* Calcd for $C_{17}H_{14}Br_2N_2O_2S$: C, 43.43; H, 3.00; Br, 34.00. Found: C, 43.72; H, 3.29; Br, 34.32.

4-Bromo-1-cyano-3-ethoxy-2-*p*-toluenesulfonyl-1,2,3,4-tetrahydroisoquinoline (5). A mixture of 2.0 g of **2** and 20 ml of absolute ethanol was stirred under reflux for 4 hr. The clear solution obtained was evaporated to dryness. Addition of ether and filtration yielded 1.1 g (59.4%) of colorless crystals of **5**: mp 163°, raised to 169° by recrystallisation from methylene chloride–hexane; ir 1600 cm^{-1}; uv 230 nm (log ϵ 4.32); nmr ($CDCl_3$) δ 1.20 (t, 3 H, CCH_3), 2.38 (s, 3 H, $ArCH_3$), 3.80 (q, 2 H, OCH_2), 5.28 (d, 1 H, J = 2.5 Hz, C_4 H), 5.70 (s, 1 H, C_1 H), 5.82 (d, 1 H, J = 2.5 Hz, C_3 H), 7.22–7.40 (m, 6 H, aromatic H), and 7.88–8.05 (m, 2 H, aromatic H).

Anal. Calcd for $C_{19}H_{19}BrN_2O_3S$: C, 52.42; H, 4.39; N, 6.44. Found: C, 52.20; H, 4.49; N, 6.72.

4-Bromo-1-cyano-3-isopropoxy-2-toluenesulfonyl-1,2,3,4-tetrahydroisoquinoline (6). A mixture of 3 g of **2** and 20 ml of 2-propanol was stirred under reflux for 4 hr. The clear solution was worked up under conditions described for **5** to give 2.2 g (76.8%) of colorless crystals of **6**: mp 162°, raised to 166° by recrystallisation from 2-propanol; ir and uv were similar to those of **5**; nmr ($CDCl_3$) δ 1.22 (t, 3 H, CCH_3), 2.40 (s, 3 H, $ArCH_3$), 4.12 (m, 1 H, OCH) 5.21 (d, 1 H, J = 2.5 Hz, C_4 H) 5.72 (s, 1 H, C_1 H) 5.90 (d, 11 H, J = 2.5 Hz, C_3 H), 7.22–7.40 (m, 6 H, aromatic H), and 7.88–8.05 (m, 2 H, aromatic H).

Anal. Calcd for $C_{20}H_{21}BrN_2O_3S$: C, 53.46; H, 4.71; N, 6.24. Found: C, 53.29; H, 4.91; N, 6.03.

4-Bromo-1-cyano-3-hydroxy-2-*p*-toluenesulfonyl-1,2,3,4-tetrahydroisoquinoline (7). To a solution of 2 g of **2** dissolved in 50 ml of chloroform was added 10 ml of a saturated aqueous solution of sodium bicarbonate and the solution was stirred overnight at room temperature. The chloroform layer was separated, dried over Na_2SO_4, and evaporated. After trituration with methylene chloride–ether the colorless crystals obtained were filtered to give 0.2 g (11.5%) of **7**: mp 177–178° (recrystallization from 2-propanol raised the melting point to 184°); ir (Nujol) 3350 and 1700 cm^{-1}; uv λ_{infl} 226 nm (log ϵ 4.32); nmr ($CDCl_3$, CD_3SOCD_3)[8] δ 2.35 (s, 3 H, $ArCH_3$), 5.25 (d, 1 H, J = 2.5 Hz, C_4 H), 5.85 (s, 1 H, C_1 H), 6.08 (d, 1 H, J = 2.5 Hz, C_3 H), 7.22–7.40 (m, 6 H, aromatic H), 7.75–8.00 (m, 2 H, aromatic H). *Anal.* Calcd for $C_{17}H_{15}BrN_2O_3S$: C, 50.14; H, 3.71; N, 6.88. Found: C, 50.14; H, 3.69; N, 7.15.

4-Bromo-1-cyano-2-*p*-toluenesulfonyl-1,2-dihydroisoquinoline (4). A. By Base Treatment of 2. A solution of 2.35 g (0.005 mol) of **2** in 30 ml of dioxane containing 0.44 g (0.005 mol) of morpholine was stirred for 6 hr at room temperature. The solution was evaporated to dryness under reduced pressure. Dilution with water and filtration gave 1.12 g (57.5%) of **4**: mp 161° (recrystallization from methylene chloride–ether raised the melting point to 164°); ir 1598 cm^{-1}; uv 232 nm (log ϵ 4.31) and 298 (3.99); nmr ($CDCl_3$) δ 2.35 (s, 3 H, $ArCH_3$), 6.15 (d, 1 H, J = 0.5 Hz, C_1 H), 7.15 (d, 1 H, J = 0.5 Hz, C_3 H), 7.22–7.45 (m, 6 H, aromatic H), 7.65–7.85 (m, 2 H, aromatic H). *Anal.* Calcd for $C_{17}H_{13}BrN_2O_2S$: C, 52.46; H, 3.37; N, 7.20. Found: C, 52.72; H, 3.70, N, 7.03.

B. By Reissert Reaction. To a suspension of 20.8 g (0.1 mol) of 4-bromoisoquinoline in methylene chloride (60 ml) containing 19.5 g (0.3 mol) of potassium cyanide in 48 ml of water was added gradually under vigorous stirring 57.0 g (0.3 mol) of *p*-toluenesulfonyl chloride in 40 ml of methylene chloride and stirring was continued for 6 hr. The methylene chloride layer was separated and washed with 10% aqueous hydrochloric acid, 5% aqueous sodium hydroxide, and finally water. It was dried over Na_2SO_4 and evaporated. On trituration of the residue with ether 22.5 g (57.85%) of **4** was obtained which was identical in all respects with the product obtained by procedure A.

1-Cyano-4-bromoisoquinoline (9). A solution of 2.35 g (0.005 mol) of **2** in 70 ml of dioxane containing 1.29 g (0.015 mol) of morpholine was refluxed for 4 hr. The solution was evaporated to dryness under reduced pressure. The residue was treated with sodium bicarbonate solution followed by water. Trituration with 2-propanol gave 0.92 g (78.9%) of **9**, mp 123°. Recrystallization from hexane afforded pure crystals of **9**: mp 125° (lit.[6] mp 122–123°); ir 1605 and 1550 cm^{-1}; uv 233 nm (log ϵ 4.62) and 339 (3.92). *Anal.* Calcd for $C_{10}H_5BrN_2$: C, 51.53; H, 2.16; N, 12.02. Found: C, 51.74; H, 2.27; N, 12.19.

Registry No.—**1**, 3340-68-9; **2**, 51270-04-3; **4**, 51270-05-4; **7**, 51270-06-5; **9**, 27224-09-5; bromine, 7726-95-6; 4-bromoisoquinoline, 1532-97-4; *p*-toluenesulfonyl chloride, 98-59-9; morpholine, 110-91-8.

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(6) J. M. Wefer, A. Catala, and F. D. Popp, *J. Org. Chem.*, **30**, 3075 (1965).
(7) S. R. Chhabra, J. R. Kershaw, and B. C. Uff, *Tetrahedron Lett.*, 3199 (1967).
(8) Drops of CD_3SOCD_3 were added to the compound suspended in $CDCl_3$ until a homogenous solution was formed.

Medium-Ring Systems.[1] IV. Synthesis of Spiro[2.*n*]alkan-5-ones. Neighboring Hydroxyl in a Hofmann Elimination

Jerry A. Hirsch,* Fredric J. Cross,[2] and William A. Meresak

Department of Chemistry, Seton Hall University, South Orange, New Jersey 07079

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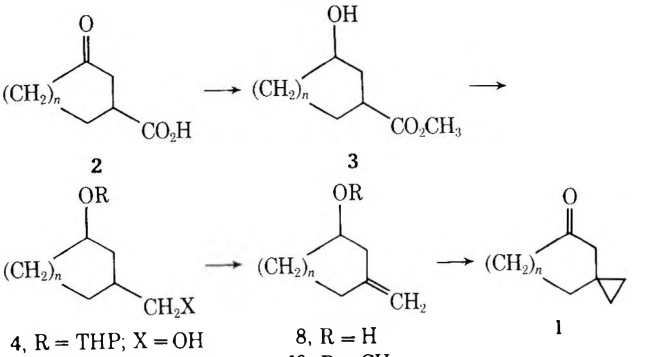
As a part of a study of the properties of medium-ring systems,[1] we have prepared spiro[2.7]decan-5-one (**1a**) and spiro[2.9]dodecan-5-one (**1b**) by the general route indicated in Scheme I. The appropriate 3-carboxycycloalkanones[1a] (**2**) were converted to the corresponding methyl 3-hydroxycycloalkanecarboxylates (**3**) by a reported procedure.[1b] The alcohol group was protected as the tetrahydropyranyl ether,[3] and the ester functionality was reduced to the alcohol level (**4**) with equimolar amounts of lithium aluminum hydride.[4] Attempts to directly dehydrate these alcohols using phosphorus oxychloride[5] or thionyl chloride[6] led to recovery of unreacted starting material.

Work[7] with cyclohexylmethanol and cyclooctylmethanol suggested that bromination with phosphorus tribromide in pyridine and benzene[8] followed by dehydrobromination with potassium *tert*-butoxide in dimethyl sulfoxide[9] might be the method of choice, but the bromination reaction

Scheme I



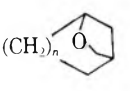
2 **3**

4, R = THP; X = OH
5, R = THP; X = OTs
6, R = H; X = $N(CH_3)_2$
7, R = H; X = $N^+(CH_3)_3{}^-OH$
11, R = CH_3; X = $N(CH_3)_2$

8, R = H
10, R = CH_3

1

a, n = 4
b, n = 6



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a, n = 4
b, n = 6

with alcohol **4a** produced a multicomponent mixture containing none of the desired bromide. Conversion of the alcohols **4** to the tosylate esters **5** proceeded in high yield, but elimination using refluxing pyridine[10] failed. However, the tosylates reacted cleanly with dimethylamine to produce the unprotected amino alcohols **6a** and **6b**, thereby setting the stage for elimination by the Cope or Hofmann procedures.[11] Quaternization with methyl iodide followed by conversion to the hydroxide over Rexyn 201 (OH)[12] provided the required quaternary ammonium hydroxide.

The Hofmann elimination of quaternary salt **7a** at 10 mm produced 56% of the desired alkenol (**8a**), 8% of bicyclic ether **9a**, and a small amount of methoxyalkene **10a**. Hofmann elimination of **7b** under analogous conditions produced 13% of the desired alkenol (**7b**), 33% of bicyclic ether **9b**, 3% of methoxyalkene **10b**, and a small amount of methoxyamine **11b**. While these Hofmann eliminations in compounds containing nearby hydroxy functions appear to be unprecedented, all of the products are reasonable based on the usual mechanistic picture for this reaction.

In each series, the alkenol **8** was treated with Simmons–Smith reagent,[13] and the resulting spiro alcohol was then oxidized with modified Collins reagent[14] to complete the synthetic route.

Experimental Section

Melting points and boiling points are uncorrected. Nmr spectra were recorded on a Varian A-60A instrument using 10% solutions in deuteriochloroform unless otherwise noted, and are reported in parts per million downfield from tetramethylsilane as an internal standard. Only distinct absorptions will be listed herein. Infrared spectra were determined with a Beckman IR-10 spectrophotometer on 5–7% solutions in chloroform unless otherwise specified. Only major absorptions are listed herein. Ultraviolet spectra were measured with a Cary 15 spectrophotometer. Elemental analyses were performed by Alfred Bernhardt Mikroanalytisches Laboratorium, Elbach, West Germany.

Tetrahydropyranyl Ether of Methyl 3-Hydroxycyclooctanecarboxylate. A solution of 28 ml of 2,3-dihydropyran (freshly distilled over NaOH pellets), 3.44 g (18.5 mmol) of methyl 3-hydroxycyclooctanecarboxylate (**3d**),[1b] and 2 drops of concentrated HCl was treated according to the procedure of Dauben and Bradlow,[3] yielding 4.10 g (82.5%) of a viscous, clear, and colorless oil: ir 1730 cm^{-1}; nmr δ 3.17–4.15 (m, 5), 4.65 (broad s, 1).

Anal. Calcd for $C_{15}H_{26}O_4$: C, 66.64; H, 9.69. Found: C, 66.69; H, 9.78.

Tetrahydropyranyl Ether of Methyl 3-Hydroxycyclodecanecarboxylate. This compound was prepared by the above procedure[3] from 1.96 g (9.15 mmol) of methyl 3-hydrocyclodecanecarboxylate (**3b**),[1b] 13 ml of 2,3-dihydropyran, and 2 drops of concentrated HCl. After distillation, a quantitative yield (2.75 g) of a viscous, clear, and colorless oil was obtained: bp 114–120° (0.2 mm); ir 1730 cm^{-1}; nmr δ 4.24–3.27 (m, 6), 4.69 (broad s, 1).

Anal. Calcd for $C_{17}H_{30}O_4$: C, 68.42; H, 10.13. Found: C, 68.29; H, 9.97.

1-Tetrahydropyranyl Ether of 1-Hydroxy-3-hydroxymethylcyclooctane (4a). A solution of 2.70 g (10.0 mmol) of the tetrahydropyranyl ether of methyl 3-hydroxycyclooctanecarboxylate in 8 ml of ethyl ether was added[4] to 0.38 g (10.0 mmol) of $LiAlH_4$, yielding 2.42 g (99.5%) of a clear and colorless oil: ir 3400 cm^{-1} (broad); nmr δ 2.55 (s, 1), 3.00–4.15 (m, 5), 4.61 (broad s, 1).

Anal. Calcd for $C_{14}H_{26}O_3$: C, 69.38; H, 10.81. Found: C, 69.20; H, 10.72.

1-Tetrahydropyranyl Ether of 1-Hydroxy-3-hydroxymethylcyclodecane (4b). This compound was prepared[4] from 185.15 g (623 mmol) of the tetrahydropyranyl ether of methyl 3-hydroxycyclodecanecarboxylate and 23.05 g (607 mmol) of $LiAlH_4$ to yield 156 g (93.5%) of a viscous, clear, and colorless oil: ir 3400 cm^{-1} (broad); nmr δ 2.78 (s, 1), 3.20–4.20 (m, 6), 4.70 (broad s, 1).

Anal. Calcd for $C_{16}H_{30}O_3$: C, 71.07; H, 11.18. Found: C, 70.98; H, 11.06.

1-Tetrahydropyranyl Ether of 1-Hydroxy-3-tosyloxymethylcyclooctane (5a). A solution of **4a** (84 g, 347 mmol) in 121 ml of pyridine at 0° was combined with 73.5 g (386 mmol) of *p*-toluenesulfonyl chloride[15] to give a heavy oil (133 g, 97% yield), nmr δ 2.60 (s, 3, $ArCH_3$), 3.70–4.20 (m, 5), 4.63 (m, 1), 7.56 (d of d, 4, ArH).

1-Tetrahydropyranyl Ether of 1-Hydroxy-3-tosyloxymethylcyclodecane (5b). This compound was prepared[15] from 73 g (302 mmol) of alcohol **4b** and 60 g (315 mmol) of *p*-toluenesulfonyl chloride. The resulting product was 115 g (96.5% yield) of the desired **5b**, nmr δ 2.43 (s, 3, $ArCH_3$), 3.70–4.30 (m, 5), 4.63 (m, 1), 7.61 (d of d, 4, ArH).

Anal. Calcd for $C_{23}H_{36}O_5S$: C, 65.06; H, 8.55. Found: C, 65.12; H, 8.54.

3-Hydroxy-1-dimethylaminomethylcyclooctane (6a). Tosylate **5a** was converted to **6a** in three batches which were combined. Wet dimethylamine was generated by adding 750 g (9.2 mol) of dimethylamine hydrochloride in 500 ml of water dropwise to 1500 g of a stirred 50% NaOH solution. The temperature in the generator rose to 37° by the end of the addition, after which time it was slowly heated to reflux. The wet dimethylamine was bubbled as generated into a flask containing 115 g of tosylate **5a** in 600 ml of dimethylformamide, during which time an exothermic process occurred (temperatures up to 55°). When bubbling ceased, the generator was disconnected and the reaction flask refluxed for 2 hr. Benzene (500 ml) was added, and the mixture was extracted with three 500-ml portions of 10% NaOH solution. The aqueous layers were back-extracted with 500 ml of benzene, and the combined benzene layers were dried (Na_2SO_4) and concentrated under reduced pressure.

A total of 356 g of **5a** treated in the above manner was combined and vacuum distilled. The main fraction (123 g, 61% yield) was a clear liquid, bp 132–148° (4–6 mm), corresponding to the desired hydroxy amine **6a**: ir 3400 cm^{-1} (broad); nmr δ 2.00 (broad, 2, CH_2N), 2.20 (s, 6, NCH_3), 3.50–4.15 (m, 2, CHOH); mass spectrum molecular ion *m/e* 185.

Anal. Calcd for $C_{11}H_{23}NO$: C, 71.30; H, 12.51; N, 7.56. Found: C, 71.27; H, 12.46; N, 7.71.

3-Hydroxy-1-dimethylaminomethylcyclodecane (6b). The above procedure was used to convert 115 g of tosylate **5b** to 37.9 g (65.5% yield) of the desired hydroxy amine **6b**: bp 124° (0.6 mm); ir 3400 cm^{-1} (broad); nmr δ 1.95–2.15 (broad, 3, CH_2N, OH), 2.23 (s, 6, NCH_3), 3.40–3.90 (m, 1, CHOH); mass spectrum molecular ion *m/e* 213.

Anal. Calcd for $C_{13}H_{27}NO$: C, 73.18; H, 12.76; N, 6.56. Found: C, 72.97; H, 12.70; N, 6.65.

Methiodide of Amine 6a. Amine **6a** (123 g, 665 mmol) was quaternized[11] with methyl iodide (492 g, 3.47 mol) to produce 186 g (85.3% yield) of the desired salt: mp 159–164° dec; nmr (D_2O) δ 3.16 (s, 9, NCH_3), 3.28–3.40 (m, 2, CH_2N), 3.73–4.13 (m, 1, CHOD); mass spectrum *m/e* 185, 142.

Anal. Calcd for $C_{12}H_{26}NOI$: C, 44.04; H, 8.00; N, 4.28. Found: C, 43.94; H, 8.05; N, 4.23.

Methiodide of Amine 6b. Amine **6b** (37.9 g, 178 mmol) was quaternized[11] with methyl iodide (75.7 g, 534 mmol) to yield 50.0 g (79.5% yield) of the desired methiodide: ir 3480 cm^{-1} (broad); nmr δ 3.48 (s, 9, NCH_3), 3.70–4.33 (broad, 2, CHOH); mass spectrum *m/e* 213, 142.

Anal. Calcd. for $C_{14}H_{30}NOI$: C, 47.33; H, 8.57; N, 3.94. Found: C, 47.15; H, 8.46; N, 4.05.

***N*-(3-Hydroxycyclooctylmethyl)trimethylammonium Hydroxide (7a).** The methiodide of amino alcohol **6a** (127 g, 388 mmol) was converted to the corresponding quaternary ammonium hydroxide (**7a**) in two batches, by a modification of the procedure of Coke and Mourning.[12] Prewashed Rexyn 201 (OH) (220 g) was added to a magnetically stirred solution of the salt in 500 ml of water. After 15 hr of stirring, the reaction mixture was filtered and the residue was washed twice with hot water. The filtrate and the washes were combined and concentrated under reduced pressure to 117 g of material containing an indeterminate amount of water.

***N*-(3-Hydroxycyclooctylmethyl)trimethylammonium Hydroxide (7b).** The above procedure was used to convert 50.0 g (141 mmol) of the methiodide of amine **6b** to the corresponding hydroxide **7b** using a threefold excess of Rexyn 201 (OH).

3-Methylenecyclooctanol (8a). A portion of quaternary hydroxide **7a** corresponding to 43 g of methiodide was heated under vacuum with stirring. Remaining water was removed at 25° (15 mm). At 40–45° (15 mm) vigorous bubbling ensued and trimethylamine was produced. The pressure was lowered to 7 mm and the heating was continued. At 75–80° (7 mm) crystalline material sublimed in the distillation head. Heating was discontinued so that this material could be removed as an ethereal solution. The ethereal solution as washed with water, dried ($MgSO_4$), and con-

centrated under reduced pressure. The resulting solid (1.6 g) contained two components, which were separated by column chromatography on neutral alumina. The faster moving material (1.18 g) appeared pure, but melted over a 6° range. A 140-mg portion was sublimed to give 55 mg of bicyclic ether **9a**: mp 54.5–56°; nmr δ 2.25–2.83 (m, 2), 3.60–4.50 (m, 3, CH_2OCH); mass spectrum molecular ion m/e 140.

Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 77.05; H, 11.59.

The distillation was resumed and a fraction was collected at 110–125° (8–9 mm), dissolved in ether, washed three times with water, dried (Na_2SO_4), and concentrated. The resulting material (11.5 g, 56% yield) was found to be the desired enol **8a** contaminated with a small amount of methoxyalkene **10a** (nmr δ 3.35, sharp singlet). Column chromatography on neutral alumina permitted the desired separation of pure 3-methylenecyclooctanol (**8a**): ir 3350, 3090, 1640 cm^{-1}; nmr δ 2.00 (s, 1, OH), 2.10–2.80 (m, 4, allylic), 3.86 (m, 1, CHO), 4.90 (m, 2, vinylic); mass spectrum molecular ion m/e 140.

Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 77.22; H, 11.43.

3-Methylenecyclodecanol (8b). Hofmann elimination of quaternary hydroxide **7b** was performed by the above procedure and was accompanied by serious foaming problems. After removal of water and trimethylamine, a 6.68-g fraction was obtained at 105–122° (4 mm), and another fraction (5.96 g) was obtained at 125–135° (4 mm). The first fraction consisted of approximately 85% bicyclic ether **9b** and about 15% methoxyalkene **10b**. Sequential column chromatography and preparative tlc permitted isolation of the methoxyalkene **10b** in about 90% purity: ir 1650, 3100 cm^{-1}; nmr δ 2.00–2.80 (m, 4, allylic), 3.30 (s, 3, OCH_3), 3.40–3.80 (m, 1, CHO), 4.88 (m, 2, vinylic).

The second fraction, approximately 50% of hydroxyalkene **8b**, 13% of methoxy amine **11b**, and 35% of bicyclic ether **9b**, was separated by column chromatography on neutral alumina. Approximately 600 mg of 3-methoxy-1-dimethylaminomethylcyclodecane (**11b**) was recovered and purified by vacuum distillation, nmr δ 2.07 (broad, 2, CH_2N), 2.20 (s, 6, NCH_3), 3.31 (s, 3, OCH_3), 3.40–3.80 (m, 1, CHO).

Anal. Calcd for $C_{14}H_{29}NO$: C, 73.95; H, 12.85. Found: C, 74.17; H, 12.83.

The desired 3-methylenecyclodecanol (**8b**, 1.78 g) was obtained in later chromatography fractions. A 380-mg sample was further purified by preparative tlc. Approximately one-third of the 300 mg of material recovered was vacuum distilled to give a clear liquid: ir 3200–3500 and 1650 cm^{-1}; nmr δ 1.66 (s, 1, OH), 2.10–2.75 (m, 4, allylic), 4.25 (m, 1, CHO), 4.95 (m, 2, vinylic); mass spectrum molecular ion m/e 168.

Anal. Calcd for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found: C, 78.42; H, 12.08.

Spiro[2.7]decan-5-ol. The Simmons–Smith procedure[13] was used for the cyclopropanation of 3-methylenecyclooctanol (**8a**). A 9.52-g (68 mmol) sample of slightly impure **8a** was treated twice with methylene iodide and Zn–Cu couple to produce 4.7 g of a liquid estimated to contain about 85% of the desired spiro alcohol (by nmr), nmr δ 0.10–0.70 (m, 4, cyclopropyl), 2.60 (s, 1, OH), 3.03–4.13 (broad m, 1, CHO).

Spiro[2.9]dodecan-5-ol. The Simmons–Smith procedure[13] was applied to 1.4 g (83.3 mmol) of 3-methylenecyclodecanol (**8b**) to give 500 mg of a crude oil which crystallized on standing. A 430-mg sample of this material was purified by preparative tlc followed by vacuum distillation to give pure spiro alcohol: mp 41–44°; nmr δ 0.10–0.46 (m, 4, cyclopropyl), 4.00 (m, 1, CHO).

Anal. Calcd for $C_{12}H_{22}O$: C, 79.06; H, 12.16. Found: C, 78.99; H, 12.10.

Spiro[2.7]decan-5-one (1a). The Collins oxidation as modified by Ratcliffe and Rodehorst[14] was used to oxidize 0.46 g (3 mmol) of spiro[2.7]decan-5-ol to the corresponding ketone. The resulting 0.39 g (85.5% yield) of product was distilled at 70–78° (0.9 mm): ir 1705 cm^{-1}; uv λ_{max} (EtOH) 280 nm (ϵ 44.5); nmr δ 0.29–0.70 (m, 4, cyclopropyl), 2.25 (s, 2, c-Pr($CH_2C{=}O$), 2.33–2.66 (m, 2, $CH_2C{=}O$); mass spectrum molecular ion m/e 152.

Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 78.74; H, 10.65.

Spiro[2.9]dodecan-5-one (1b). The Ratcliffe–Rodehorst procedure[14] was used to oxidize 80 mg (4.4 mmol) of spiro[2.9]dodecan-5-ol. A 73-mg sample of crude ketone was vacuum distilled to give 60 mg (75.8% yield) of pure ketone **1b**: ir 1700 cm^{-1}; uv λ_{max} (EtOH) 282 nm (ϵ 120); nmr δ 0.20–0.60 (m, 4, cyclopropyl), 2.33 (s, 2, c-Pr$CH_2C{=}O$), 2.50–2.80 (m, 2, $CH_2C{=}O$); mass spectrum molecular ion m/e 180.

Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 79.96; H, 11.26.

Registry No.—**1a**, 51364-58-0; **16**, 51364-59-1; **4a**, 51364-60-4; **4b**, 51364-61-5; **5a**, 51364-62-6; **5b**, 51364-63-7; **6a**, 51364-64-8; **6a** methiodide, 51364-65-9; **6b**, 51364-66-0; **6b** methiodide, 51364-67-1; **7a**, 51364-68-2; **7b**, 51364-69-3; **8a**, 51364-70-6; **8b**, 51364-71-7; **9a**, 18417-66-8; **9b**, 24995-59-3; **10b**, 51364-72-8; **11b**, 51364-73-9; methyl 3-hydroxycyclooctanecarboxylate tetrahydropyranyl ether, 51364-74-0; methyl 3-hydroxycyclodecanecarboxylate tetrahydropyranyl ether, 51364-75-1; spiro[2.7]decan-5-ol, 51364-76-2; spiro[2.9]dodecan-5-ol, 51364-77-3.

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Quantitative Conversion of Carboxylic Acids and Phenols to Esters and Ethers by Reaction of Their Salts with Alkyl Halides

James E. Shaw* and Dennis C. Kunerth

Department of Chemistry, Moorhead State College, Moorhead, Minnesota 56560

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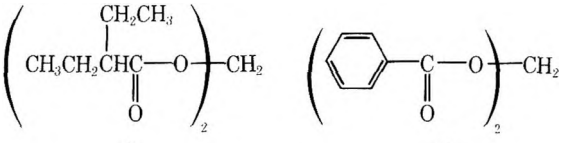
Recently we reported that carboxylic acids can be quantitatively converted to esters by reaction of their salts with alkyl bromides or iodides in hexamethylphosphoramide (HMPA) at room temperature.[1] We now wish to report results of further studies which extend the scope of this reaction. These include the rapid reaction of ethyl iodide with salts of hindered acids, the use of anhydrous potassium carbonate as base to prevent decarboxylation of certain acids, the use of geminal dihalides as the alkylating agent, and the quantitative O-alkylation of phenoxide ions.

Reaction of mesitoic acid and triethylacetic acid with sodium hydroxide (aqueous 25% NaOH) in HMPA followed by addition of ethyl iodide (4 equiv) gave the ethyl esters in quantitative yield. In each case the time required for alkylation was less than 5 min at room temperature. The short reaction time, simple procedure, and quantitative yield of this reaction make it a valuable method for preparing ethyl esters.[2] Other solvent systems such as dimethyl sulfoxide and dimethylformamide required the use of longer reaction times. Reaction of sodium triethylacetate with ethyl iodide at room temperature was only two-

thirds complete after 5 min in dimethyl sulfoxide and about one-third complete after 15 min in dimethylformamide.

Esterification of certain carboxylic acids required the use of anhydrous potassium carbonate as base, since sodium hydroxide caused some decarboxylation. When a solution of malonic acid, sodium hydroxide (aqueous 25% NaOH), and HMPA was stirred for 15 min at room temperature followed by addition of ethyl iodide and continued stirring overnight, only a 36% yield of diethyl malonate was produced. The sodium hydroxide caused some decarboxylation of malonic acid as evidenced by the precipitation of sodium carbonate from the solution. Some decarboxylation was also observed when triphenylacetic acid was treated with sodium hydroxide in HMPA. When a mixture of malonic acid, powdered anhydrous potassium carbonate, ethyl iodide, and dry HMPA was stirred for 24 hr at room temperature, a much higher yield (91%) of diethyl malonate was obtained. The same procedure used for triphenylacetic acid gave a 100% yield of ethyl triphenylacetate.[3]

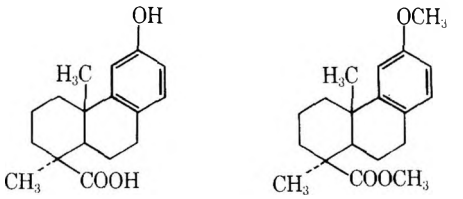
Reaction of the sodium salts of 2-ethylbutanoic acid and benzoic acid with dibromomethane in HMPA at room temperature gave 100 and 86% yields of diesters 1 and 2, respectively. Sodium benzoate required a longer reaction



1 2

time (48 hr) than sodium 2-ethylbutanoate (24 hr). This is probably because sodium benzoate, unlike sodium 2-ethylbutanoate, is not completely soluble in HMPA. Traditionally, diesters like 1 and 2 have been prepared by reaction of paraformaldehyde or polyoxymethylene with an acid anhydride in the presence of a mineral or Lewis acid.[4,5] Reaction of sodium carboxylates with dibromomethane provides a useful alternative to this procedure.[6] Sodium carboxylates failed to react with bromoform or carbon tetrabromide to give tri- or tetrasubstituted products even when higher temperatures were used.

Phenols were quantitatively converted to ethers by reaction of their sodium salts with alkyl iodides in HMPA at room temperature. Reaction of podocarpic acid (3) with sodium hydroxide and methyl iodide in HMPA gave a quantitative yield of the methyl ester and ether 4. The sodium salt of phenol reacted with isopropyl iodide in less than 2.5 hr to give a 100% yield of isopropyl phenyl ether. The reaction time was substantially less than that reported for the same reaction using tetrahydrofuran as solvent.[7] In the THF case a 22% yield of isopropyl phenyl ether was reported after 24 hr at 23° and at 80% yield after 24 hr at 80°. An attempt was made to prepare isopropyl cyclohexyl ether. However, when cyclohexanol, sodium hydride, isopropyl iodide, and HMPA were stirred at room temperature, much propene and only a trace of the desired ether were produced. This result is not surprising, since the alkoxide of cyclohexanol is a much stronger base than phenoxide.



3 4

Experimental Section[8]

Ethyl Mesitoate and Ethyl Triethylacetate. These esters were prepared by the procedure we previously reported for methyl mesitoate.[1] The yields of ethyl mesitoate and ethyl triethylacetate were determined by glpc[8] to be 99 and 96%, respectively.

Diethyl Malonate. To a solution of 1.04 g (10 mmol) of malonic acid in 25 ml of dry HMPA protected from moisture with a drying tube was added 3.45 g (25 mmol) of powdered anhydrous potassium carbonate and 4.9 ml (60 mmol) of ethyl iodide, and the mixture was stirred for 24 hr at room temperature (23–25°). The reaction mixture was then poured into 50 ml of water which was then extracted with two 40-ml portions of ether. The combined ether extract was washed with two 10-ml portions of water, dried with anhydrous sodium sulfate, and evaporated under reduced pressure to give 1.70 g of liquid. Analysis of the liquid by glpc[8] revealed that the actual yield of diethyl malonate was 91%. The infrared spectrum of the glpc-purified product was identical with that of an authentic sample.

Ethyl Triphenylacetate. To a mixture of 0.76 g (5.5 mmol) of powdered anhydrous potassium carbonate, 14 ml of dry HMPA, and 1.6 ml (20 mmol) of ethyl iodide protected from moisture with a drying tube was added 1.44 g (5.0 mmol) of triphenylacetic acid and the mixture was stirred for 24 hr at room temperature (23–25°). Work-up as described in the case of diethyl malonate gave 1.60 g (100%) of crystals, mp 116–118° (lit.[9] mp 116–117°, 120–121°). After recrystallization from ether the melting point was 117–119°. The infrared spectrum was identical with that of an authentic sample.

Reaction of 2-Ethylbutanoic Acid with Dibromomethane. To a solution of 2.32 g (20 mmol) of 2-ethylbutanoic acid in 50 ml of HMPA was added 4.8 g of an aqueous 25% sodium hydroxide solution (30 mmol of NaOH) and 5.6 ml (80 mmol) of dibromomethane. The solution was stirred for 24 hr at room temperature (23–25°). The solution was then poured into 100 ml of water which was then extracted with two 75-ml portions of ether. The combined ether extract was washed with two 25-ml portions of water, dried with anhydrous sodium sulfate, and evaporated under reduced pressure to give 2.84 g of liquid. Analysis of this liquid by glpc[8] revealed that it consisted only of diester 1 and some dibromomethane and that the actual yield of 1 was 100%. An analytical sample of 1 was obtained by glpc: $n^{26}D$ 1.4262; ir (neat) 1760 cm^{-1} (C=O); nmr (CCl_4) τ 4.28 (s, 2 H), 9.11 (t, 12 H, J = 7 Hz).

Anal. Calcd for $C_{13}H_{24}O_4$: C, 63.90; H, 9.90. Found: C, 63.85; H, 9.75.

Reaction of Benzoic Acid and Dibromomethane. To a solution of 2.44 g (20 mmol) of benzoic acid in 50 ml of HMPA was added 4.8 g of aqueous 25% sodium hydroxide solution (30 mmol of NaOH) and 5.6 ml (80 mmol) of dibromomethane. The mixture (sodium benzoate precipitated out initially) was stirred for 48 hr at room temperature. The solution was then poured into 100 ml of water which was then extracted with two 75-ml portions of ether. The combined ether extract was washed with two 25-ml portions of water, dried with anhydrous sodium sulfate, and evaporated under reduced pressure to give 2.50 g of a white solid, mp 85–88°. The 2.50-g sample was dissolved in about 50 ml of ether which was then washed with two 10-ml portions of 10% sodium hydroxide solution and two 10-ml portions of water. After drying over sodium sulfate, the ether solution was evaporated under reduced pressure to give 2.20 g (86%) of diester 2 as colorless crystals, mp 96.5–98.5° (lit.[5] mp 99°).

Methyl Ester and Ether of (+)-Podocarpic Acid. To a solution of 2.74 g (10 mmol) of (+)-podocarpic acid in 50 ml of HMPA was added 6.4 g of aqueous 25% sodium hydroxide solution (40 mmol of NaOH) and the solution was stirred for 0.5 hr at room temperature (23–25°). Then 5.0 ml (80 mmol) of methyl iodide was added and the solution was stirred for 7 hr at room temperature. The solution was then poured into 100 ml of 5% hydrochloric acid solution which was then extracted twice with 75-ml portions of ether. The combined ether extracts were washed with two 25-ml portions of water, dried over anhydrous sodium sulfate, and evaporated to give 3.04 g (100%) of 4 as yellow crystals, mp 128–129.5° (lit.[10] mp 128°). Recrystallization from ether gave white crystals but did not change the melting point.

Isopropyl Phenyl Ether. To a solution of 1.88 g (20 mmol) of phenol in 50 ml of HMPA was added 6.4 g of aqueous 25% sodium hydroxide solution (40 mmol of NaOH) and the solution was stirred for 5 min before the addition of 8.0 ml (80 mmol) of isopropyl iodide. After stirring for 2.5 hr at room temperature (23–25°), the reaction mixture was poured into 100 ml of 5% hydro-

chloric acid solution which was then extracted with two 75-ml portions of ether. The combined ether extract was washed with two 25-ml portions of water, dried with anhydrous sodium sulfate, and evaporated under reduced pressure to give 3.14 g of a liquid residue. Analysis of this liquid by glpc[8] revealed that it contained only isopropyl phenyl ether except for a little isopropyl iodide and that the yield of ether was 100%. Product purified by preparative glpc gave a refractive index of n^{25}D 1.4946 (lit.[11] n^{25}D 1.4944) and an infrared spectrum identical with that of an authentic sample.

Acknowledgment. We wish to thank the Research Corporation for financial support.

Registry No.—**1**, 51310-59-9; **2**, 5342-31-4; **3**, 5947-49-9; **4**, 1231-74-9; diethyl malonate, 105-53-3; malonic acid, 141-82-2; ethyl iodide, 75-03-6; ethyl triphenylacetate, 5467-22-1; triphenylacetic acid, 595-91-5; 2-ethylbutanoic acid, 88-09-5; dibromomethane, 74-95-3; benzoic acid, 65-85-0; methyl iodide, 74-88-4; isopropyl phenyl ether, 2741-16-4; phenol, 108-95-2; isopropyl iodide, 75-30-9.

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A New Method for Preparation of Alkyl and Aryl Isothiocyanates Using Amines, Butyllithium, and Carbon Disulfide

Shizuyoshi Sakai,* Toshiyuki Aizawa, and Tatsuo Fujinami

Department of Industrial Chemistry, Faculty of Engineering, Shizuoka University, Hamamatsu, 432 Japan

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Alkyl and aryl isothiocyanates are usually prepared in several steps from amines *via* dithiocarbamate derivatives.[1-4] We now describe a convenient alternative approach involving the amine, carbon disulfide, and butyllithium, which lead to isothiocyanates in good yields from alkyl- or arylamines which do not contain groups that react with butyllithium.

The amines are treated with an equimolar amount of butyllithium followed by carbon disulfide to give the lithium dithiocarbamate **1**. Treatment with additional butyllithium and carbon disulfide leads *via* the dilithio derivative **2** to the complex **3**. The formation of **3** is indicated by the absence of characteristic ir bands for carbon disulfide at 1520 and 2230 cm^{-1}. After the reaction mixture was for 2 hr at the temperature indicated in Table I, the inorganic lithium salt had precipitated, and the solution showed the ν_{NCS} band at about 2150 cm^{-1}. Isothiocyanate **4** was obtained in good yield by distillation of the reaction mixture, as shown in Table I.

$$\underset{\mathbf{1}}{RNHCS_2Li} \xrightarrow[-BuH]{BuLi} \underset{\mathbf{2}}{RN(Li)CS_2Li} \xrightarrow{CS_2} \underset{\mathbf{3}}{RN(CS_2Li)_2} \xrightarrow[-LiCS_3]{} \underset{\mathbf{4}}{RNCS}$$

Successive additions of butyllithium and carbon disulfide to form intermediate **3** are essential for the formation of isothiocyanate in good yield. For example, phenyl isothiocyanate was formed quantitatively in the reaction *via* the intermediate **3** (R = Ph) at 80°, while it was obtained only in 46 and 11% yields by thermal decompositions (150°) of lithium *N*-lithio-*N*-phenyldithiocarbamate, **2** (R = Ph), and of lithium *N*-phenyldithiocarbamate, **1** (R = Ph), respectively. When the reaction product formed by treatment of aniline with 2 equiv of butyllithium was allowed to react with 2 equiv of carbon disulfide for 4 hr at 70°, *N,N'*-diphenylthiourea was obtained in good yield, accompanied by the formation of a trace amount of phenyl isothiocyanate.

Experimental Section

All melting and boiling points were uncorrected. The ir and nmr spectra were determined with a JASCO Model IR-S spectrometer and a Hitachi Perkin-Elmer Model R-20 spectrometer, respectively. Solvents and amines were dried by common methods.

Standard Method for Preparation of Isothiocyanate. A. Butyl Isothiocyanate. Butylamine (4.39 g, 60 mmol) was dissolved in dry tetrahydrofuran (50 ml) under dry nitrogen in a flask equipped with a mechanical stirrer, a condenser, a dropping funnel, and a nitrogen inlet, and treated with butyllithium (66 mmol in 53 ml of petroleum ether) at 0°. After stirring for 30 min at room temperature, carbon disulfide (5.01 g, 66 mmol) in 5 ml of tetrahydrofuran was added dropwise at 0° to form the dithiocarbamate salt **1** (R = Bu). The solution of **1** thus prepared *in situ* was treated again with butyllithium (66 mmol) at 0° and was stirred for 30 min at room temperature, followed by the addition of carbon disulfide (66 mmol), to form the intermediate **3** (R = Bu). After the reaction mass was stirred for 30 min at room temperature, the inorganic lithium salt had precipitated and the characteristic band of isothiocyanate at 2170 cm^{-1} appeared in the ir spectrum of the reaction mixture. The mass was stirred for 2 hr at 60° and filtered to remove the salt. Tetrahydrofuran was evaporated *in vacuo* and butyl isothiocyanate was distilled: yield 5.5 g (80%); bp 47–48° (10 mm); ir ($CHCl_3$) ν_{NCS} 2170 cm^{-1}. The ir and nmr spectra were in good agreement with those of the authentic sample prepared by the published method.[1]

B. Other Isothiocyanates. The intermediates **3** were prepared *in situ* from the respective amines, analogously to the case of butylamine, and were heated for 2 hr at the temperature indicated in Table I. The isothiocyanates formed were isolated by distillation. Their yields and boiling points are summarized in Table I. Their ir and nmr spectra were the same as those of authentic samples prepared by the literature method.[1]

Among the isothiocyanates shown in Table I, α-naphthyl isothiocyanate was obtained by pyrolytic distillation of the reaction mixture.

Thermal Decomposition of Lithium *N*-Lithio-*N*-phenyldithiocarbamate, 2 (R = Ph). The solution of **2** (R = Ph) in tetrahydrofuran was prepared *in situ* analogously to the case of *N*-butyl dithiocarbamate, **2** (R = Bu), and was pyrolytically dis-

Table I
Yields of Isothiocyanates by the Reaction of the *N*-Lithio Carbamates 2 with Carbon Disulfide

Amine used (RNH_2)	Registry no.	Reaction temp, °C	RNCS formed		
			Bp, °C (mm)	Yield, %	Registry no.
$EtNH_2$	75-04-7	*a*	55 (50)	80	542-85-8
n-$PrNH_2$	107-10-8	*a*	50–55 (20)	85	628-30-8
n-$BuNH_2$	109-73-9	*a*	47–48 (10)	81	592-82-5
t-$BuNH_2$	75-64-9	*a*	50–53 (22)	75	590-42-1
Cyclohexyl-NH_2	108-91-8	*a*	109 (10)	74	1122-82-3
$PhCH_2NH_2$	100-46-9	70–80	105–110 (10)	55	622-78-6
$PhNH_2$	62-53-3	80	96–98 (15)	99	103-72-0
p-$CH_3C_6H_4NH_2$	106-49-0	80	77–78 (0.2)	99	622-59-3
α-Naphthyl-NH_2	134-32-7	*b*	109–112 (0.2)	71	551-06-4

[a] Room temperature. [b] Distilled with decomposition.

tilled *in vacuo* (15 mm) at 150° to afford phenyl isothiocyanate in 46% yield.

Thermal Decomposition of Lithium *N*-Phenyldithiocarbamate, 1 (R = Ph). The solution of 1 (R = Ph) in tetrahydrofuran was evaporated to dryness *in vacuo* (15 mm). The residue was pyrolyzed at 150° to afford the mixture of *N,N'*-diphenylthiourea (mp 154–155°, main product) and phenyl isothiocyanate. The latter compound was isolated by filtration of the mixture in 11% yield.

One-Step Thiocarbonylation Reaction of Aniline. Aniline (2.79 g, 30 mmol) was dissolved in dry tetrahydrofuran (30 ml) and treated with butyllithium (66 mmol) under dry nitrogen at room temperature. To the resulting solution was added carbon disulfide (5.02 g, 66 mmol) at 0°. The mixture was refluxed for 4 hr and evaporated to eliminate the solvent. The residue was distilled *in vacuo* (15 mm) to afford crude *N,N'*-diphenylthiourea, contaminated with a trace amount of phenyl isothiocyanate. The crude thiourea was recrystallized from ethanol to give pure *N,N'*-diphenylthiourea, yield 2.80 g (82%), mp 154–155° (lit.[5] mp 154°).

Registry No.—Butyllithium, 109-72-8; carbon disulfide, 75-15-0; *N,N'*-diphenylthiourea, 102-08-9.

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Synthesis of Racemic Globulol *via* Solvolysis–Cyclization of a 2,7-Cyclodecadien-1-ol Derivative

James A. Marshall* and James A. Ruth

Department of Chemistry, Northwestern University, Evanston, Illinois 60201

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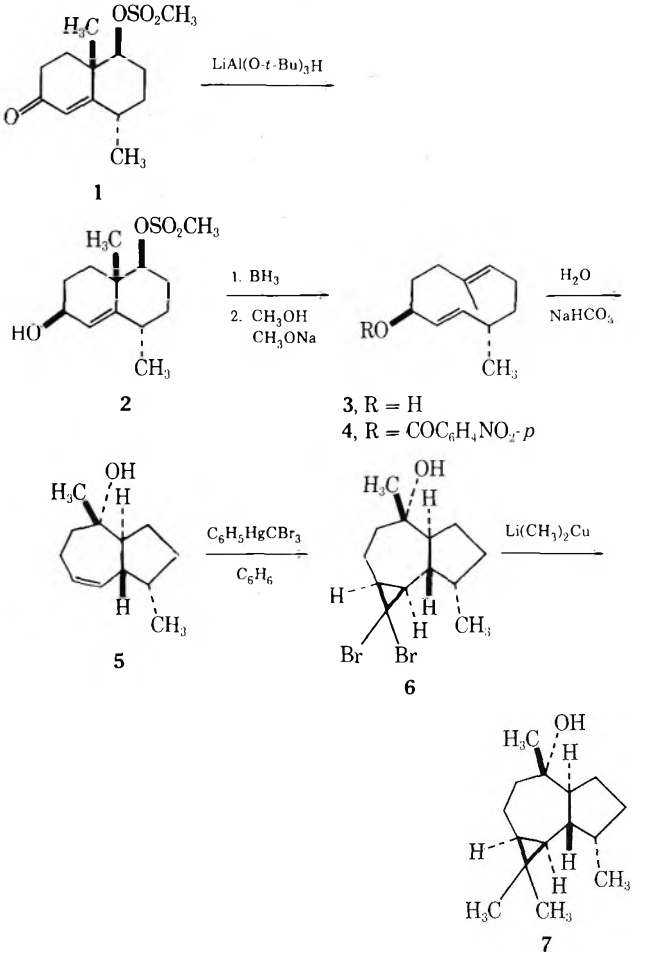
We have previously shown that 2,7-cyclodecadien-1-ol derivatives undergo facile and stereoselective solvolysis–cyclization to give hydroazulenes in high yield.[1] The cyclodecadienols, in turn, are conveniently prepared from 9-methyl-5(10)-octalin-1,6-dione.[2] In this report we describe an application of this approach to the synthesis of racemic globulol (7), a tricyclic hydroazulene sesquiterpene found in eucalyptus.[3]

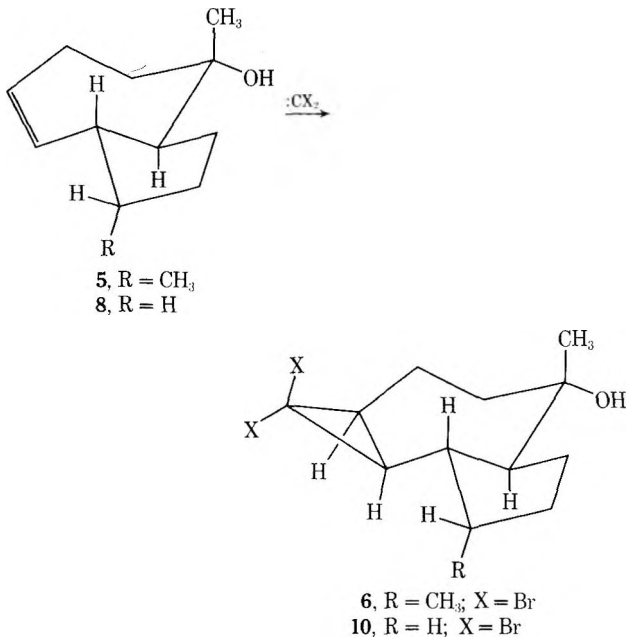
Our previous preparation of cyclodecadienol 3 involved treatment of the unsaturated keto methanesulfonate 1 with borane–tetrahydrofuran followed by methanolic sodium methoxide to effect the boronate fragmentation reaction.[1] Presumably carbonyl reduction precedes hydroboration, in which case the stereochemistry depicted in structure 3 would be expected.[4] This presumption was confirmed in the present study by first reducing enone 1 with lithium tri-*tert*-butoxyaluminum hydride and then subjecting the resulting equatorial alcohol 2 to hydroboration–fragmentation. The cyclodecadienol 3 thus secured gave the identical crystalline *p*-nitrobenzoate derivative 4 with that obtained in the combined reduction–hydroboration–fragmentation sequence.[5] Solvolysis of this *p*-nitrobenzoate in aqueous dioxane containing sodium bicarbonate as previously described yielded the hydroazulenol 5[1] (Chart I).

While simple hydroazulenes tend to show considerable conformational flexibility, thus rendering stereochemical predictions highly problematical, hydroazulene 5 projects a clear-cut picture upon examination of molecular models. The trans-fused cyclopentane ring tends to restrict cycloheptane pseudorotation and the double bond removes the most serious eclipsing interactions present in the idealized

Chart I



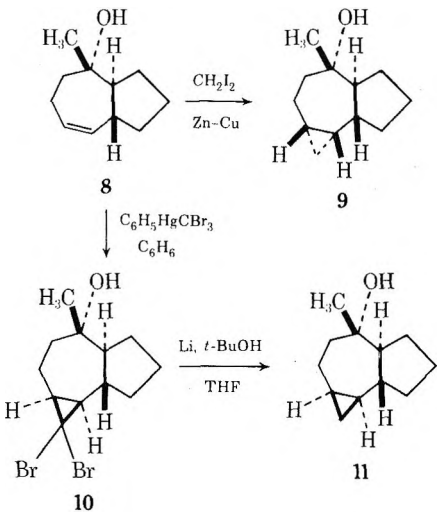
Scheme I



chair conformation.[6] This chair conformation (Scheme I) thus appears to be a highly preferred one for hydroazulene **5**. On this basis the prediction that carbenoid reagents should preferentially attack the top (convex) face of the double bond seemed quite reasonable. In that event adducts (Scheme I) with the assigned stereochemistry of the aromadendrane class of sesquiterpenes would be readily at hand.[7]

A test of this hypothesis (Chart II) was carried out on the more readily available demethyl analog 8[1] of hydroazulene **5**. Treatment of hydroazulene **8** with the Simmons–Smith reagent derived from methylene iodide afforded the adduct **9** in nearly quantitative yield.[8] Of the numerous methods tried, only that of Seyferth[9] gave a dibromocarbene adduct **10** of hydroazulene **8**. Other methods led to recovery of starting material.[10] Hydrogenolysis of the dibromide **10** afforded the cyclopropane derivative **11**, whose spectral and chromatographic properties indicated an isomeric relationship with the Simmons–Smith-derived cyclopropane **9**. The stereochemistry of cyclopropane **9** can be assigned on the basis of the hydroxyl directing effect of the Simmons–Smith reaction.[8] The carbene adduct **10** would therefore appear to possess the predicted stereochemistry.

Chart II



Addition of the Seyferth reagent to hydroazulene **5** afforded the unstable dibromocyclopropane **6**. Prolonged treatment of this material with lithium dimethylcuprate yielded the methylated derivative **7**, identified as racemic globulol by spectral and chromatographic comparison with natural globulol.[11]

Experimental Section[12]

c-1-Methanesulfonoxy-*t*-4,*r*-9-dimethyl-5(10)-octalin-*c*-6-ol (2). The method of Burgstahler[13] was used. A solution of 0.478 g (2.0 mmol) of the keto mesylate 1[1] in 15 ml of dry tetrahydrofuran was added to a cold (0°) solution of 1.85 g (8.0 mmol) of lithium tri-*tert*-butoxyaluminum hydride in 25 ml of tetrahydrofuran. The solution was stirred for 0.5 hr at 0° and for 1 hr at room temperature. At the end of this time the mixture was poured into 100 ml of water–ice slurry containing 3 ml of concentrated hydrochloric acid. The product was isolated with ether. Work-up afforded 0.48 g (100%) of a light yellow oil: λ_{max} (film) 3.0, 3.45, 3.53, 6.05, 6.9, 8.55, 9.55, and 11.0 mμ; δ_{TMS} ($CDCl_3$) 1.00 (d, $CHCH_3$, J = 6 Hz), 1.15 (s, CH_3), 3.0 (s, CH_3SO_2), 3.65 (m, CHOH), 4.25 (m, CHOMs), and 5.46 ppm (s, vinyl H).

The crude hydroxy mesylate **2** was subjected to fragmentation conditions described earlier for the enone 1.[1] The cyclodecadienol obtained in 37% yield had the same spectral properties as that obtained directly from enone fragmentation.

The *p*-nitrobenzoate **4**, mp 90–92°, obtained as described earlier[1] in 92% yield, was identical with that prepared from the enone **1**.

***t*-2,*c*-9-Dimethyl-6,6-dibromo-*r*-1H,*c*-5H,*c*-7H,*t*-8H-tricyclo-[6.3.0.0^{5,7}]undecan-*c*-2-ol (6).** A mixture of 0.180 g (1 mmol) of the hydroazulenol **5**[1] and 1.59 g (3 mmol) of phenyltribromomethylmercury in 25 ml of benzene was refluxed with stirring for 2 hr.[9] The reaction mixture was cooled to room temperature and filtered to remove the precipitated phenylmercuric bromide. Saturated ethanolic sodium borohydride solution was then added dropwise to the filtrate until the vigorous reaction subsided. The mixture was then poured into water, and the product was isolated with ether. The crude product was purified by column chromatography on 10 g of basic Woelm alumina (activity II–III). The benzene eluate afforded 0.17 g (50%) of a light yellow gum, which underwent extensive decomposition upon attempted short-path distillation [oven temperature 160°(0.1 mm)] or upon preparative thick layer chromatography on silica gel H: λ_{max} (film) 3.0, 3.45, 3.53, 5.85, 6.10, 6.90, 7.28, 8.10, 9.05, 9.70, 10.65, 11.05, 13.25, and 13.55 mμ; δ_{TMS} ($CDCl_3$) 1.02 (d, CH_3, J = 6 Hz) and 1.1 ppm (s, CH_3).

***dl*-Globulol (7).** A 0.180-g (0.515 mmol) sample of the dibromohydroazulenol **6** was added to 20 ml of a cold (−15°) solution of 3.5 mmol of lithium dimethylcuprate in ether.[14] The reaction mixture was stored at −15° for 120 hr. At the end of 24-, 48-, and 96-hr reaction times, the mixture was recharged with 20 ml of a fresh solution of 3.5 mmol of lithium dimethylcuprate in ether. After 120 hr the reaction mixture was poured into a slurry of concentrated ammonium hydroxide solution and ice. The product was isolated with ether. The work-up afforded 0.14 g (95%) of a light yellow oil which contained 60% globulol by glc analysis.

A gc–mass spectral comparison was made with the crude product and a sample of authentic globulol.[11] The mass spectra were identical.[15]

An analytical sample was secured by preparative glc on a 6 ft × 0.375 in. column packed with 4% DC-550 on Chromosorb G, followed by short-path distillation [oven temperature 70° (0.1 mm)]: λ_{max} (film) 3.0, 3.45, 3.55, 6.9, 7.3, 8.0, 9.25, 10.70, and 11.3 mμ; δ_{TMS} ($CDCl_3$) 0.98 (d, $CHCH_3$, J = 6 Hz), 0.98 (s, CH_3), 1.0 (s, CH_3) and 1.1 ppm (s, CH_3). Coinjection of this material with an authentic sample of natural globulol on a UCW-98 and DC-550 column gave a single peak. The infrared and nmr spectra were identical.

Anal. Calcd for $C_{15}H_{26}O$: C, 81.01; H, 11.78. Found: C, 81.05; H, 11.51.

***t*-2-Methyl-6,6-dibromo-*r*-1H,*c*-5H,*c*-7H,*t*-8H-tricyclo-[6.3.0.0^{5,7}]undecan-*c*-2-ol (10).** A mixture of 0.166 g (1 mmol) of the hydroazulenol **8**[1] and 1.59 g (3 mmol) of phenyltribromomethylmercury in 25 ml of benzene was refluxed for 2 hr.[9] After cooling to room temperature the mixture was treated with saturated ethanolic sodium borohydride dropwise until the vigorous reaction subsided. The reaction mixture was poured into water, and the product was isolated with ether. The crude product was purified by column chromatography on 10 g of Woelm

(activity II-III) basic alumina. The benzene eluate afforded 0.190 g (56%) of a light yellow oil.

The product underwent slight decomposition upon distillation [short path, oven temperature 140° (0.1 mm)] or upon preparative thick layer chromatography with silica gel H: λ_{max} (film) 3.0, 3.45, 3.55, 5.90, 6.10, 6.92, 7.30, 9.05, 10.60, 11.0, and 13.25 mμ; δ_{TMS} ($CDCl_3$) 1.08 ppm (s, CH_3). After standing for several weeks a sample solidified (mp 77–78°) but satisfactory analytical values could not be obtained.

***t*-2-Methyl-*r*-1H,*c*-5H,*c*-7H,*t*-8H-tricyclo[6.3.0.0^{5,7}]undecan-*c*-2-ol (11).** A mixture of 100 mg (0.55 mmol) of the dibromohydroazulenol **10**, 100 mg of lithium wire, and 3 ml of *tert*-butyl alcohol in 3 ml of tetrahydrofuran was stirred at room temperature for 2 days.[16] The mixture was cautiously quenched with 12 ml of water and the product was isolated with ether. Short-path distillation [oven temperature 70°(0.1 mm)] afforded 50 mg (50%) of a colorless oil, which gave a predominant peak on the gas chromatogram (UCW-98 column at 205°) with retention time of 3.2 min: λ_{max} (film) 3.0, 3.45, 6.9, 7.3, 9.0, 11.0, and 13.75 mμ; δ_{TMS} ($CDCl_3$) 0.68 (m, cyclopropyl H) and 1.10 ppm (s, CH_3).

Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 79.68; H, 11.19.

***t*-2-Methyl-*r*-1H,*t*-5H,*t*-7H,*t*-8H-tricyclo[6.3.0.0^{5,7}]undecan-*c*-7-ol (9).** A mixture of 0.332 g (2 mmol) of the hydroazulenol **8**,[1] 3.42 g (6.5 mmol) of methylene iodide, and 1.4 g (20 mmol) of zinc-copper couple in 20 ml of ether was stirred at room temperature for 3.5 days.[8] The mixture was filtered, and the ether was washed with 3% aqueous hydrochloric acid. Work-up of the ether solution and short-path distillation [oven temperature 70° (0.1 mm)] of the product afforded 0.350 g (97%) of a colorless oil which showed a predominant peak on the gas chromatogram (UCW-98 column at 205°) with retention time of 3.8 min: λ_{max} (film) 3.0, 3.45, 6.95, 7.35, 9.20, 9.82, 10.62, 11.05, and 13.75 mμ; δ_{TMS} ($CDCl_3$) 0.44 (m, cyclopropyl H) and 1.10 ppm (s, CH_3).

Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 79.95; H, 11.31.

A sample of this material solidified (mp 43–44°) upon short-path distillation.

Acknowledgment. We are grateful to the National Science Foundation and the National Institutes of Health for support of this work. A sample of authentic globulol was kindly provided by Professor George Büchi.

Registry No.—**1**, 51310-36-2; **2**, 51310-37-3; **4**, 51371-46-1; **5**, 51310-38-4; **6**, 51310-39-5; **7**, 51371-47-2; **8**, 30166-33-7; **9**, 51310-40-8; **10**, 51310-41-9; **11**, 51371-48-3.

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(12) The apparatus described by W. S. Johnson and W. P. Schneider ("Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 132) was used to maintain an argon atmosphere. The isolation procedure consisted of thorough extractions with the specified solvent, washing the combined extracts with saturated brine solution, and drying the extracts over anhydrous magnesium sulfate. The solvent was removed from the filtered extracts under reduced pressure on a rotary evaporator. Microanalyses were performed by Micro-Tech Laboratories, Inc., Skokie, Ill. Infrared spectra were obtained with a Perkin-Elmer 137 spectrophotometer. Infrared absorptions are reported in wavelengths (mμ) and are standardized with reference to the 6.24-mμ peak of polystyrene. Nuclear magnetic resonance spectra were recorded with a Varian T-60 spectrometer. Signals are reported as the chemical shift downfield from tetramethylsilane (TMS) in parts per million (ppm) of the applied field. The multiplicity of the peak is abbreviated: singlet, s; doublet, d; triplet, t; quartet, q; and multiplet, m. Coupling constants are reported in hertz (Hz). Melting points were determined on a calibrated Thomas capillary melting point apparatus. Melting points are not corrected.
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Preparation of Azetidine and Some *N*-Aroylazetidines[1]

Julian White* and George McGillivray

Department of Chemistry, University of South Africa, Pretoria, South Africa

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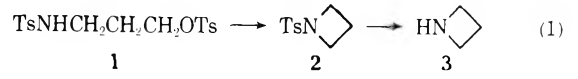
In the course of examination of selected amides of potential value in the Vilsmeier–Haack reaction it became evident that little information is available on otherwise unsubstituted *N*-aroylazetidines. Only a few of these compounds appear to have been reported.[2,3] Moreover, existing methods for the preparation[4–7] of azetidine itself are not only lacking in experimental simplicity but are unsuitable when it is desired to prepare small quantities only.

Investigation of certain of the reactions reported indicated that the sequence employed by Vaughan, *et al.* (eq 1) could, by the application of improved methods, be used



(1)

in small-scale operations to afford a somewhat better yield than previously reported.[5] Thus, the cumbersome cyclization of **1** by the action of ethoxide or *tert*-butoxide over 16 hr was found to be unnecessary, as the same result could be obtained by use of aqueous hydroxide over approximately 4 hr with much less effort.

For the reductive detosylation of **2**, sodium naphthalenide[8] in diglyme medium (which in the present context is far superior to dimethoxyethane or tetrahydrofuran) was found to be suitable. The benefit of this method lies not only in considerably improved yields but also in the greater simplicity of operation than that of Vaughan's method where reduction by sodium in amyl alcohol affords some 40% of product only after a somewhat tedious sequence of operations.

The present radical-anion reduction is quick and avoids complex work-up procedures, as the azetidine is obtained as an approximately 1 *M* solution in diglyme by simple distillation from the reaction mixture. The yield of azetidine is approximately 70% of theoretical.

The *N*-aroylazetidines listed in Table I were prepared in fair yield by the use of the azetidine–diglyme solution (to which was added an equimolecular quantity of triethylamine in order to conserve azetidine and simplify purification) and the appropriate aroyl chloride. The identity of each of these derivatives was established by the usual instrumental and analytical means.

Table I

ArCON⟨a, b⟩

Ar	Mp,[a] °C	Yield, %	$\nu_{C=O}$, cm^{-1} [b]	δ_{-CH_2-}	Registry no.[c]
Phenyl	61–62	54	1625	a 4.31 b 2.35	3420-62-0
4-Nitrophenyl	122–123	56	1620	a 4.36 b 2.45	51425-89-9
4-Chlorophenyl	107.0	45	1605	a 4.30 b 2.36	51425-90-2
4-Tolyl	86–86.5	68	1605	a 4.30 b 2.34	51425-91-3
3,5-Dinitrophenyl	155–156	48	1630	a 4.47 b 2.53	51425-92-4
2-Furyl	120–120.5	65	1620	a 4.42 b 2.40	51425-93-5

[a] Uncorrected, recrystallized from hexane or toluene–hexane. [b] Run as Nujol mulls. [c] Satisfactory analytical data (±0.3% for C, H, Cl, N) were reported for all new compounds listed.

Experimental Section

3-(4-Toluenesulfonamido)propyl-4-toluenesulfonate (1) was prepared by the method of Vaughan, *et al.*,[5] and used without further purification.

4-Toluenesulfonazetidide (2). To a suspension of 6.72 g (17.5 mmol) of 1 in 550 ml of water (the optimum volume for the high-dilution technique required) was added 176 ml of 0.1 *M* sodium hydroxide solution and the mixture was refluxed until most of the solid had dissolved (3–4 hr). The light pink solution was treated with charcoal and filtered while hot. On cooling, glittering white needles, 3.15 g (85% average), mp 123–124° (lit. mp 118–120°), were formed.

Azetidine (3). A solution of 16 g (125 mmol) of naphthalene in 100 ml of diglyme was magnetically stirred in a 500-ml flask fitted with a dropping funnel and a short fractionation column coupled to a condenser, receiver, and three small ice-cooled traps containing diglyme. The apparatus was flushed with dry argon, and *ca.* 10 g of sodium shot was added in one batch. After stirring for 30 min, a solution of 5.28 g (25 mmol) of 2 in 60 ml of warm diglyme was added over 40 min and stirring was continued for a further 30 min under a very slow stream of argon. This was followed by distillation (terminated when the boiling point of diglyme was reached) and the combined distillate (*ca.* 20 ml) and trap contents (*ca.* 10 ml) were assayed acidimetrically. Average yield was 70% of theoretical.

Registry No.—**1,** 51425-88-8; **2,** 7730-45-2; **3,** 503-29-7; benzoyl chloride, 98-88-4; 4-nitrobenzoyl chloride, 122-04-3; 4-chlorobenzoyl chloride, 122-01-0; 4-methylbenzoyl chloride, 874-60-2; 3,5-dinitrobenzoyl chloride, 99-33-2; 2-furancarbonyl chloride, 527-69-5.

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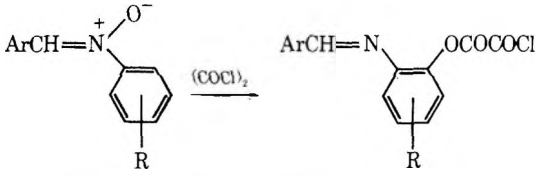
Communications

Reactions of *N*-Aryl Nitrogen Oxides. 2. The Reaction of *N*-Aryl Nitrones with Oxalyl Chloride

Summary: *N*-Aryl nitrones react rapidly with oxalyl chloride yielding imines in which the chloroglyoxalate group, -OCOCOCl, has been specifically introduced into the ortho position of the *N*-aryl ring.

Sir: Attention has been drawn to the need for the development of new ortho selective aromatic substitution reactions.[1] We have reported that phosgene or thionyl chloride react with *N*-aryl nitrones or amine oxides yielding the corresponding o-chloro imine hydrochlorides in high yield.[2,3]

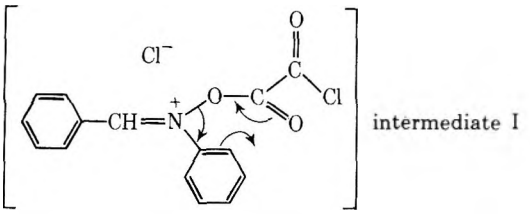
We now wish to report the positionally specific introduction of the chloroglyoxalate grouping into an aromatic ring, ortho to a nitrogen function, by the reaction of *N*-aryl nitrones with oxalyl chloride.



The reaction is performed by the addition of oxalyl chloride in 10% molar excess to a solution of the nitrone in dichloromethane or to a suspension of the nitrone in pentane, allowing the mixture to stand for 10 min. The latter method is particularly convenient since the product may be isolated simply by filtration. As the chloroglyoxalates are heat sensitive, purification is effected most efficiently by dissolving the product in a minimum amount of chloroform and reprecipitating it with pentane.

The chloroglyoxalates could be stored under nitrogen at the low temperature, but thermal decomposition and reactions with moisture and oxygen prevented adequate elemental analyses.[4] The products were characterized by spectra and by independent synthesis by the reaction of the appropriate *N*-(o-hydroxyphenyl) imine[5,6] with oxalyl chloride. Also, acid hydrolysis to the appropriately substituted 2-aminophenol and the appropriate aldehyde and quantitative ammonia hydrolysis to obtain the corresponding *N*-(*o*-hydroxyphenyl) imine. The mass spectra verified the proposed molecular weights and exhibited sequential fragmentation confirming the chloroglyoxalate linkage (Table I).

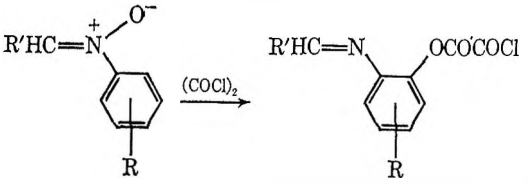
The mechanisms of the nitrone-oxalyl chloride reaction has not been established as yet, but, by analogy with other previously reported similar systems,[7] it most probably involves a cyclic six-centered transition state (intermediate I). Certainly the fact that only ortho ring substitution is observed would tend to indicate an intramolecular pathway.



Since *N*-aryl nitrones are readily available starting materials,[8] the reaction with oxalyl chloride apparently affords an excellent route to ortho oxygenated products. To our knowledge, this is the only general method for oxygenating an aromatic ring ortho to a nitrogen function in a rapid, high yield, and positionally specific manner. The only other reported methods involve reactions of *N,N*-dialkylaniline *N*-oxides with acetic anhydride[9] or benzenesulfonyl chloride.[10] These suffer from the disadvantages of either low yields (~20%) or poor positional selectivity (ortho:para ratio of <3) which necessitates isomer separation, sometimes quite tedious.

Since we have now shown that nitrones are viable substances for introducing either a chlorine atom[2,3] or an oxygen function into the ortho position of the benzene ring, we are currently investigating the feasibility of specifically substituting other functionalities ortho to the nitrogen.

Table I



Reactants[a]			Products[b]			
Compd	R	R′	Compd	Mp, °C	Yield, %	Ir frequencies
1	H	C_6H_5	**2**	183–186	78	1780, 1710, 1600[c]
3	H	4-$NO_2C_6H_4$	**4**	100 dec	72	1770, 1695, 1598[d]
5	H	4-$MeOC_6H_4$	**6**	147–149	76	1785, 1710, 1610[c]
7	4-Me	4-$MeOC_6H_4$	**8**	264–266	73	1785, 1715, 1612[c]
9	H	C_6H_5CH=CH	**10**	157–161	80	1792, 1721, 1620, 1605[c]

[a] References for the syntheses of these known nitrones are as follows: O. H. Wheeler and P. H. Gore, *J. Amer. Chem. Soc.*, **78**, 3363 (1956); G. E. Utzinger and F. A. Regenass, *Helv. Chim. Acta*, **37**, 1892 (1954); T. Kubota, M. Yamakawa, and Y. Mori, *Bull. Chem. Soc. Jap.*, **36**, 1552 (1963); J. H. Bowie, R. G. Cooks, and G. E. Lewis, *Aust. J. Chem.*, **20**, 1601 (1967). [b] All products were examined by mass spectrometry. Peaks corresponding to M^+, $(M - 35)^+$, $(M - 63)^+$, $(M - 72)^+$, and $(M - 91)^+$ were observed, corresponding to the parent ion, loss of ^-Cl, ^-COCl, $^-C_2O_3$, and ^-COCOCl. [c] $CHCl_3$ solution. [d] Nujol mull.

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Lanse, D. Felsen-Reingold, and R. Engel, manuscript submitted for publication in *J. Org. Chem.*
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(5) The o-hydroxy imines were obtained by direct condensation of 2-aminophenol with the appropriate aromatic aldehyde in benzene solution *via* Dean–Stark apparatus. All products exhibited the expected –OH and C=N bands in their spectra.
(6) Authentication of *N*-(o-hydroxyphenyl) imines was by independent preparation as described in ref 5 above and (1) comparison with *previous reports in the literature (listed below) and (2) complete* spectrometric analyses (ir, nmr, mass spectra). The previous reports of interest are (a) F. G. Singleton and C. B. Pollard, *J. Amer. Chem. Soc.*, **62**, 2288 (1940); (b) F. R. Bean, U. S. Patent 2,338,482 (Jan 4, 1944), U. S. Patent 2,394,587 (Feb 12, 1946); (c) T. J. Lane and A. J. Kandathil, *J. Amer. Chem. Soc.*, **83**, 3782 (1961); (d) K. K. Chatterjee, N. Farrier, and B. E. Douglas, *ibid.*, **85**, 2919 (1963); (e) N. K. S. Rao, K. R. Chandran, and U. P. Basu, *J. Indian Chem. Soc.*, **26**, 133 (1949); (f) T. G. Levi, *Gazz. Chim. Ital.*, **59**, 544 (1929); (g) R. Shimizn, *Am. Rept. Research Inst. Tuberc., Kanazawa Univ.*, **11** (2), 1 (1953).
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Department of Chemistry **Dennis Liotta**
Queens College of the **A. D. Baker**
City University of New York **Norman L. Goldman**
Flushing, New York 11367 **Robert Engel***

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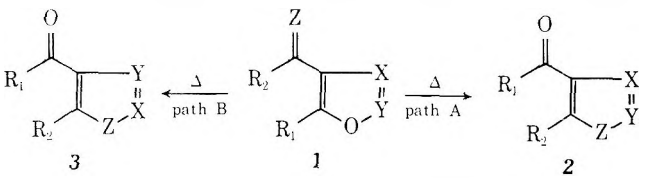
Thermal Valence Rearrangement of 4-Acylisoxazoles to 4-Acyloxazoles

Summary: A number of 3-phenyl-4-acyl-5-alkylisoxazoles have been found to undergo thermal rearrangement to 2-phenyl-4-acyl-5-alkyloxazoles; the formation of the rearranged oxazole requires bonding between the 3 carbon of the isoxazole ring with the oxygen atom of the acyl group; a mechanism involving the intermediacy of a 2*H*-azirine is suggested.

Sir: The photoisomerization of many different five-membered heterocyclic ring compounds has been shown to proceed by a path in which two of the ring atoms interchange their position under the influence of uv light.[1] The demonstration of a ring-contraction–ring-expansion process in these reactions was first documented by Ullman and Singh for the photorearrangement of 3,5-diarylisoxazoles to 2,5-diaryloxazoles.[2] An analogous pathway nicely rationalizes the major products produced in the photoisomerization of other five-membered heterocyclic rings.[3-7] There are also a number of reports in the literature which describe the thermally induced valence isomerizations of five-membered heterocyclic rings.[8-14] In each case previ-

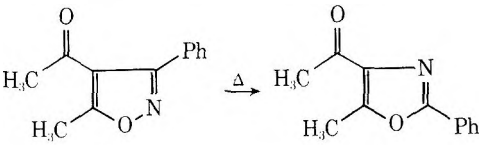


3 1 2

X = N, C; Z = N, O; Y = N, C

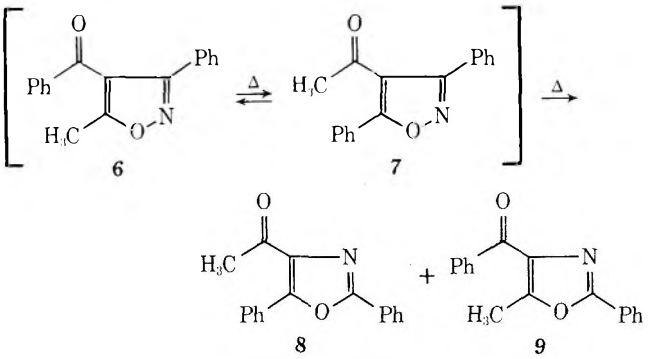
ously studied, the product obtained can only be rationalized by a sequence involving homolytic cleavage of the O–Y bond to produce a reactive acyclic intermediate which subsequently recloses to produce the rearranged heteroaromatic compound (*i.e.*, **1** → **2** *via* path A). In this communication we wish to describe the thermally induced rearrangement of several 4-acylisoxazoles which follow a ring-contraction–ring-expansion sequence (path B).

It is well known that, when two heteroatoms of higher electronegativity than carbon (*e.g.*, nitrogen, oxygen) are linked together through a single bond, the bond dissociation energy of such a linkage is considerably lower than that of a C–C single bond.[15,16] Taking this into consideration, we decided to examine the thermal behavior of 3-phenyl-4-acetyl-5-methylisoxazole (**4**).[17] Thermolysis of isoxazole **4** at 230° under a nitrogen atmosphere for 2 hr afforded 2-phenyl-4-acetyl-5-methyloxazole (**5**), mp 78–79°, in quantitative yield [nmr ($CDCl_3$) τ 7.50 (s, 3 H), 7.42 (s, 3 H)]. The structure of the rearranged product was unambiguously established by an independent synthesis.[18]



4 5

When 3-phenyl-4-benzoyl-5-methylisoxazole[17] (**6**) was subjected to similar thermolysis conditions, a mixture of three new compounds was produced. Analysis of the crude reaction mixture by nmr showed that it contained 3,5-diphenyl-4-acetylisoxazole (**7**, 8%), 2,5-diphenyl-4-acetyloxazole (**8**, 29%), and 2-phenyl-4-benzoyl-5-methyloxazole (**9**, 39%), as well as unreacted starting material (24%). Similarly, thermolysis of 3,5-diphenyl-4-acetylisoxazole (**7**) gave **6** (8%), **8** (30%), **9** (38%), and recovered starting



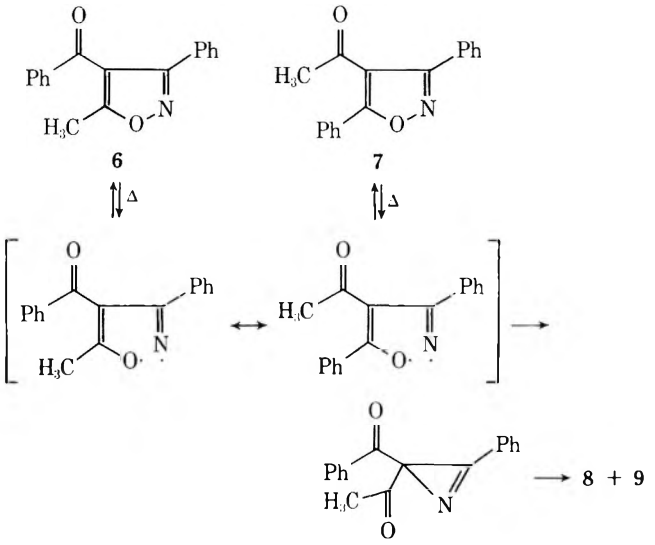
6 7 8 9

material (24%). Confirmation of the structure of isoxazole **7**, mp 93–94°, nmr ($CDCl_3$) τ 7.8 (s, 3 H), was obtained by comparison with an authentic sample prepared by treating 4-phenyl-3-butyn-2-one with benzonitrile oxide.[19] Structure **8** was established by comparison with an authentic sample.[18] Oxazole **9**,[19] mp 61–62°, nmr ($CDCl_3$) τ 7.32 (s, 3 H), was also independently synthesized by treating 5-methyl-2-phenyloxazole-4-carboxylic acid[18] with thionyl chloride in dimethylformamide to give the corresponding acid chloride, mp 131–133°, which in turn was treated with diphenylcadmium in benzene.

The thermal rearrangement of 4-carbonyl substituted oxazoles is a general reaction[8-12] which was first observed by Cornforth.[8] Consequently, it was of interest to determine whether oxazoles **8** and **9** were interconverted during the thermolysis conditions. Oxazole **8**, when subjected to thermolysis at 230° for 5 hr gave only a 5% yield of **9**. Similarly, **9** produced an insignificant (~4%) amount of **8** under identical reaction conditions. The lack of significant thermal interconversion of oxazoles **8** and **9** under the reaction conditions used rules out any regiospecific mechanism for the thermal rearrangement of **6** and/or **7**.

The formation of oxazole **8** from isoxazole **6** (or **9** from **7**) requires bonding, at some point in the reaction, between C-3 of the isoxazole ring and the oxygen of the benzoyl group. We believe that the experiments reported here require the intermediacy of a 2*H*-azirine (*i.e.*, **10**) to rationalize the transposition of the two ring atoms. The most reasonable pathway for the formation of **10** involves homo-

lytic cleavage of the relatively weak O–N bond of the isoxazole ring to form an acyclic intermediate which can either recyclize to generate rearranged isoxazole or close to



give a 3,3-diacyl-2-phenyl-2*H*-azirine (**10**) intermediate. The second step, **10** → **8** + **9**, most likely involves C–C bond rupture of the 2*H*-azirine ring followed by cyclization to the observed products.[20] Each step of the rearrangement is thermally induced, and the rates and products were not influenced by oxygen, radical inhibitors, or small amounts of acids and bases. It is interesting to note that 5-alkoxyisoxazoles have been reported to undergo a facile thermally induced skeletal rearrangement to alkyl 1-azirine-3-carboxylates.[21] This rearrangement provides good analogy for the first step of the proposed sequence. The literature also contains several references dealing with the thermal rearrangement of 4-isoxazolines.[22-26] Most of the rearrangements observed with these systems can also be attributed to a ring-contraction–ring-expansion sequence.

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Supplementary Material Available. Complete experimental data for this communication will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-1976.

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Department of Chemistry
State University of New York at Buffalo
Buffalo, New York 14214
Albert Padwa*
Edward Chen

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Sulfoxonium Salts as Reagents for the Oxidation of Primary and Secondary Alcohols to Carbonyl Compounds

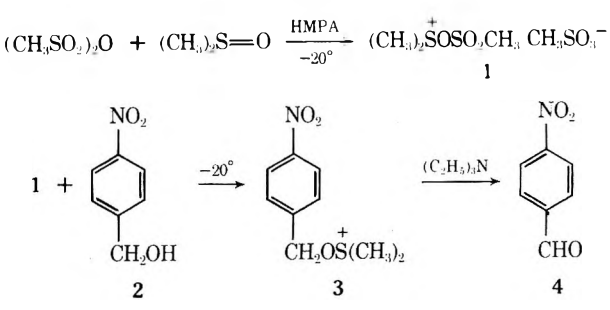
Summary: The generality of using sulfoxonium salts for oxidation of alcohols to carbonyl derivatives is illustrated.

Sir: We wish to report on a new method for the oxidation of alcohols to carbonyl derivatives which complements our previously described dimethyl sulfoxide–acetic anhydride procedure.[1] Since none of the previous methods based on dimethyl sulfoxide[2-4] give satisfactory results with all classes of compounds, our finding that reagents such as *p*-toluenesulfonyl chloride, *p*-toluenesulfonic anhydride, methanesulfonic anhydride, benzoyl chloride, and cyanuric chloride react with dimethyl sulfoxide (DMSO) at −20° to give sulfoxonium complexes useful in oxidizing alcohols to carbonyl derivatives opens up the possibility of choosing among these mild oxidative reagents to obtain good yields.

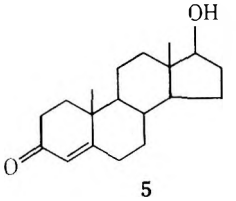
We have found that *p*-toluenesulfonyl chloride, *p*-toluenesulfonic anhydride, or methanesulfonic anhydride[5] with dimethyl sulfoxide in hexamethylphosphoramide (HMPA) at −20° oxidize secondary alcohols to ketones and primary alcohols to aldehydes in high yields. The overall mechanistic sequence is depicted in Scheme I for the oxidation of *p*-nitrobenzyl alcohol **2** to *p*-nitrobenzaldehyde **4**.

The following example demonstrates the simplicity and efficiency of the oxidative process and illustrates the typi-

Scheme I



cal ratio of reactants and solvents used. A solution of *p*-nitrobenzyl alcohol **2** (8 mmol) in 15 ml of HMPA and 6 ml of DMSO was cooled to −20° and methanesulfonic anhydride (16 mmol) added. After 3.5 hr at −20°,[6] triethylamine (32 mmol) was added and the mixture allowed to stand at room temperature for 10 min. Pouring into ice and water and filtration gave *p*-nitrobenzaldehyde (**4**) in 88% yield. Most of the exploratory work was carried out by oxidation of testosterone (**5**) to 4-androstene-3,17-dione (**6**). For example, methanesulfonic anhydride and DMSO in HMPA (−20°, 3 hr) gave **6** (99%), mp 168–170° (lit.[7] mp 170–171°). Thin layer chromatography (tlc) showed insignificant amounts of methylthiomethyl ether **7** which can be a troublesome impurity in DMSO oxidations.[1,3] With methanesulfonyl chloride the reaction was incomplete (5 hr) and tlc showed additional impurities. *p*-Toluenesulfonyl chloride–DMSO and **5** in HMPA (5 hr, −20°) gave **6** in high yield without significant amounts of by-product **7**; however, some of the excess *p*-toluenesulfonyl chloride necessary for efficient conversion of **5** to **6** remained in the product. Recrystallization gave **6** (77%), mp 170–171°. Both benzenesulfonyl chloride and toluenesulfonic anhydride oxidized **5** to **6** (~85% yields) while benzoyl chloride in DMSO and HMPA at −20° gave **6** in 75% yield. The solvents HMPA and dichloromethane are satisfactory but HMPA is superior because it gives cleaner products.



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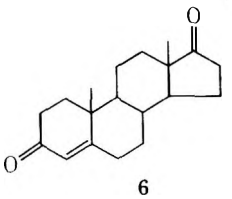

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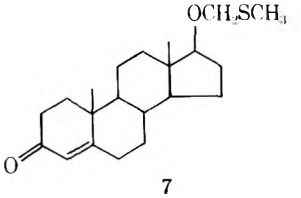

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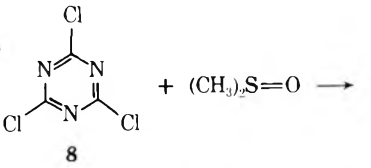
The generality of using sulfoxonium salts for oxidations of alcohols to carbonyl derivatives is illustrated by the use of cyanuric chloride and DMSO in HMPA. Cyanuric chloride (4 mmol) and testosterone **5** (4 mmol) in DMSO (3 ml) and HMPA (8 ml) (5 hr, −20°) gave, after addition of triethylamine (16 mmol), **6**, mp 167–169°, in 99% yield. Only a trace of by-product **7** was present as determined by tlc. Under similar conditions (5 hr, −20°)[8] *p*-nitrobenzyl alcohol **2** and cyanuric chloride gave a mixture (~1:1) of aldehyde **4** and *p*-nitrobenzyl chloride. Oxidations with cyanuric chloride **8** are visualized as occurring *via* intermediates **9**, **10**, and **11**. The intermediacy of ylides in conversions of sulfoxonium salts of type **10** has been established in previous studies[9] on oxidations with DMSO.

Oxidation of 1-adamantylmethanol with methanesulfonic anhydride and DMSO in HMPA (16 hr, −20°) gave 1-adamantylcarboxaldehyde (67%) while benzoin (5 hr, −20°) gave benzil in 99% yield. Yohimbine (**12**) with methanesulfonic anhydride in HMPA–CH_2Cl_2 gave **13**[10] (75%), mp 249–251° dec, while with cyanuric chloride **13** was obtained in 56% yield.[11]

The methanesulfonic anhydride and cyanuric chloride procedures have special merit since both are commercially available, polar solvents can be used, and the products from these reagents on aqueous work-up are water-soluble triethylamine salts. Cyanuric chloride is inexpensive and less toxic than *N,N*-dicyclohexylcarbodiimide and thus



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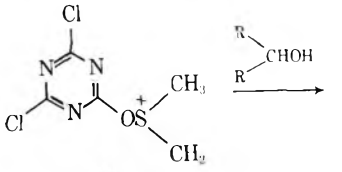

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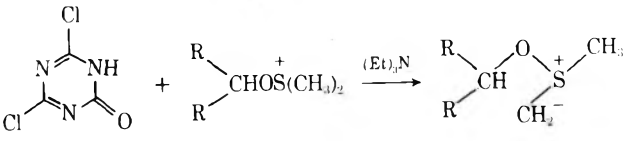
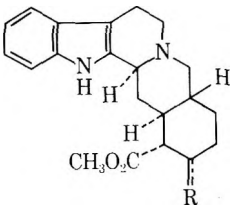


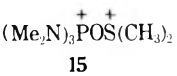
10 **11**



12, R = H, OH

13, R = O

14



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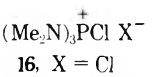

16, X = Cl

17, X = ClO_4

has advantages for large scale work. Methanesulfonic anhydride gives good yields of primary aldehydes, in contrast to acetic anhydride–DMSO where primary alcohols are not consistently oxidized in good yields.

Some consideration must be given to the possibility that intermediate **15** is involved in oxidations involving HMPA as solvent because *p*-toluenesulfonyl chloride and HMPA are reported[12] to give **14**. Reagents **16** and **17** have been reported[13] as useful in peptide synthesis and, if **15** is an intermediate in formation of alkoxysulfonium salts, some evidence on this point should be obtained by a study of the reaction of **16** and **17** with DMSO.[14] At present there is no necessity for invoking intermediate **15** since the oxidations reported also proceed in other solvents such as dichloromethane.

The use of compounds of type **16** and **17** for oxidations in DMSO, as well as a pmr study of the intermediates involved in the oxidations reported, is under investigation.

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Cardiovascular-Renal Disease Therapy Research Section Lederle Laboratories Division American Cyanamid Company Pearl River, New York 10965

J. Donald Albright

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Intramolecular Homoconjugate Addition. A Simple Entry to Functionalized Pyrrolizidines and Indolizidines

Summary: Intramolecular alkylation of amines by activated cyclopropanes, followed by lactam formation, gives functionalized bicyclic nitrogen heterocycles.

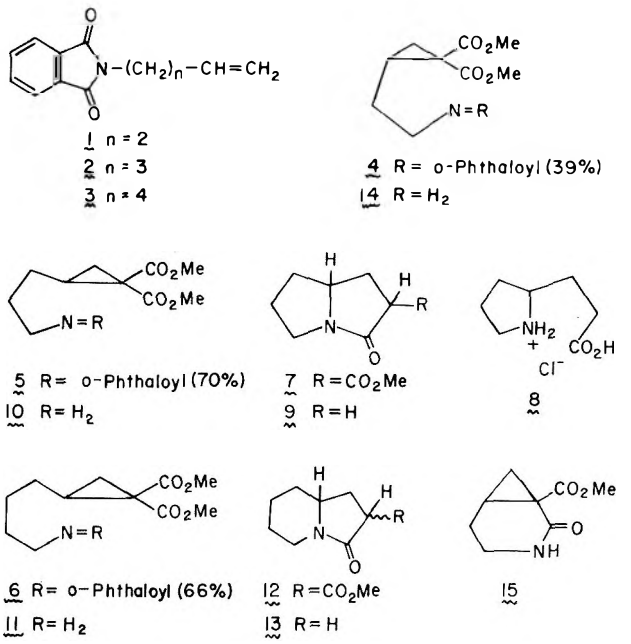
Sir: Recently we reported a new approach to the synthesis of functionalized carbocyclic ring system.[1] The method involves the generation of an anionic carbon center in juxtaposition with a cyclopropane ring which is so substituted as to render it vulnerable to nucleophilic attack. Below, we demonstrate the applicability of this concept to heterocyclic synthesis in the context of facile constructions of the pyrrolizidine[2] and indolizidine[2a] ring systems from readily available precursors.

The phthalimido olefins **1**,[3a] **2**,[3b] and **3**,[4a] mp 25.5–26.5°, were prepared by the alkylation of potassium phthalimide with 4-bromo-1-butene, 5-bromo-1-pentene, and 6-bromo-1-hexene, respectively. The cyclopropanes **4**,[4] mp 124–125°, **5**,[4] mp 84–85°, and **6**, mp[4] 91–92°, were prepared in the yields shown[5] by cyclopropanation of the corresponding olefins with dimethyl diazomalonate (*e.g.*, for the case of **4**, 0.107 mol of diazo compound added dropwise over 0.5 hr to a mixture of 0.094 mol of **1** and 130 mg of copper bronze which was heated at 140° under nitrogen).

Reaction of **5** with hydrazine (1.1 equiv of hydrazine to 1 equiv of **5** in methanol under reflux for 15 hr) gave the lactam ester **7**[4a] in quantitative recovery. Hydrolysis and decarboxylation of this compound (10% aqueous HCl, reflux 15 hr) is accompanied by ring opening. The pyrrolidine propionic acid salt, **8**, so produced,[6] was not purified. Esterification by MeOH–HCl produced the ester hydrochloride which was converted to the known[7] pyrrolizid-3-one (**9**) in 93% overall yield from **5**.

When the hydrazinolysis was conducted at room temperature, the intermediate amino diester **10** was isolated in 65% yield. Purification of **10**[4a] was rendered difficult by its tendency to undergo partial conversion to **7** on chromatography. Hence, for preparative purposes, direct conversion of **5** → **7** is the preferred method.

It appears reasonable to postulate that, in the pathway from **10** (or **5**) → **7**, internal alkylation of the amine by the activated cyclopropane occurs before lactamization. The reverse order of steps seems unlikely since it would require formation of a seven-membered lactam and, more seriously, necessitate an endocyclic[8] displacement during the alkylation step.



Preliminary experimentation revealed that the conditions required for conversion of amino diester **11**[4a] [obtained by room temperature hydrazinolysis (*cf.* above) of phthalimido diester **6**] to the epimeric indolizidine derivatives **12** are considerably more drastic than those required for the case of **10** → **7**. The considerably more facile formation of a pyrrolidine relative to a piperidine *via* intramolecular homoconjugate addition finds precedent in the carbocyclic series.[1] Hence, more vigorous hydrazinolysis conditions (1.1 equiv of hydrazine in MeOH at 115°, sealed tube, 15 hr) were employed for the conversion of **6** → **12**. The known epimeric mixture[9] thus obtained in crude form was carried through the same sequence of reactions as for the case of **7** to give 3-indolizidone **13**[7] in 82% overall from **6**. By the same reasoning set forth in the case of **10**, the most likely pathway from **11** → **12** involves intramolecular alkylation followed by lactamization.

The formation of **7** and **12** from **10** and **11**, respectively, corresponds to intramolecular homoconjugate addition *via* what has been termed the spiro mode.[1] As in the case of the carbocyclic series, no products corresponding to the alternative fused mode of attack are observed when the spiro mode[1] gives five- or six-membered primary ring products. In this connection it was of interest to examine the chemistry of amino diester **14** which might, in principle, have given, as primary products, an azetidine *via* the spiro mode or a pyrrolidine through the fused mode. Both processes have precedent,[1] though under drastic conditions, in the carbocyclic series.[1] In practice, depthaloylation of **4** *via* hydrazinolysis in methanol at room temperature gives upon work-up the desired **14**[4a] (63%). Upon standing in neat form, **14** cyclizes to give lactam ester **15** mp 133–136°.[4] No evidence for intramolecular homoconjugate addition was observed in this instance. However, these results do not constitute a valid test of the feasibility of the ring opening reactions, since lactamization prevents their occurence.[8]

Further studies of heterocyclic synthesis *via* activated cyclopropanes are in progress as are adaptations of this scheme to the synthesis of related alkaloids.[2a]

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Department of Chemistry **S. Danishefsky***
University of Pittsburgh **J. Dynak**
Pittsburgh, Pennsylvania 15260

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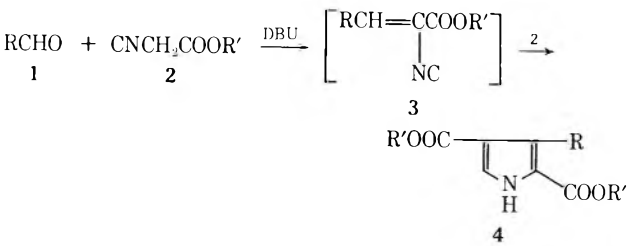
A Convenient Synthesis of 3-Substituted Pyrrole-2,4-dicarboxylic Acid Esters[1]

Summary: Pyrrole compounds **4** were synthesized by the reaction of isocyanoacetates with aldehydes in the presence of DBU in good yields.

Sir: In the course of our studies on the synthesis of amino acids and related compounds using isocyano compounds, we have investigated the reaction of isocyanoacetates **2** with aldehydes as a source of 3-substituted pyrrole-2,4-dicarboxylic acids. Schöllkopf, *et al.*, have detected diethyl 3-methylpyrrole-2,4-dicarboxylate from the reaction of acetaldehyde and ethyl isocyanoacetate in the presence of metallic base during the synthesis of ethyl α-formylaminoacrylate.[2]

We have carried out the condensation of alkyl isocyanoacetates with a variety of aliphatic and aromatic aldehydes in THF solution, using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a base (Table I). Spectral and analytical data confirm the pyrrole structures **4**. The reaction does not require anhydrous conditions.

The reaction presumably involves Michael addition of isocyanoacetate **2** to the α-isocyanoacrylate **3**; **4** (R = H; R′ = CH_3) was obtained in 60% yield from the condensation of **2** and methyl α-isocyanocinnamate.[3] However, the pyrrole was not obtained from the reaction of methyl α-formamidocinnamate with **2**.



Typical Procedure. To a mixture of methyl isocyanoacetate (1.98 g, 0.02 mol) and DBU (3.0 g, 0.02 mol) dissolved in THF (30 ml) was added dropwise benzaldehyde (1.06 g, 0.01 mol) in THF (10 ml) at 45–50° for a period of 15 min with stirring. After stirring for 5 hr at same temperature, the reaction mixture was neutralized with acetic acid and then the solvent was removed under reduced pressure. The resulting residue was extracted with ethyl acetate and the extract was washed with hydrochloric aicd and water, dried, and then evaporated *in vacuo*. The crystals (1.3 g) recrystallized from aqueous methanol showed mp 183–185°. The mass spectrum of this compound showed the M^+ at *m/e* 259 and the ir spectrum (nujol) showed an NH band at 3370 cm^{-1} and two ester C=O bands at 1735 and 1700 cm^{-1}, respectively. The nmr spectrum ($CDCl_3$) indicated the presence of two ester groups (CH_3) [δ 3.58 (s) and 3.51 (s)], NH [12.04 (br)], pyrrole C-5 H [7.52 (d)], and aromatic H [7.25 (s)].

Table I
Preparation of Pyrrole Derivative 4

R	R′	Conditions: Temp, °C	Conditions: Hr	Mp, °C[a,b]	Yield, %
H	CH_3	50–55	1	125–126	67
CH_3	$(CH_3)_2CH$	50–55	1	74–76	71
CH_3CH_2	CH_3CH_2	45–50	1	87–89[c]	63
Ph	CH_3	45–50	5	183–185	50
4-Methoxy Ph	CH_3	55–60	4	146–147	57
3,4,5-Trimethoxy Ph	CH_3	10–15	2	189–192	59
3-Pyridine	CH_3	50–55	3	212–213	60
3-Indole	CH_3	50–55	3	>250	58

[a] Recrystallization from aqueous ethanol or methanol. [b] Analyses agreed with the calculated values within ±0.3%. [c] Lit. mp 88.5–89°: R. Grigg, A. W. Johnson, and T. W. F. Wasley, *J. Chem. Soc.*, 359 (1963).

Acknowledgment. We wish to express our thanks to Drs. T. Takayanagi and I. Chibata for their encouragement in this study.

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Research Laboratory of Applied Biochemistry **Mamoru Suzuki**
Tanabe Seiyaku Co. Ltd. **Muneji Miyoshi**
962 Kashimo-cho **Kazuo Matsumoto***
Higashiydogawa-ku
Osaka, Japan

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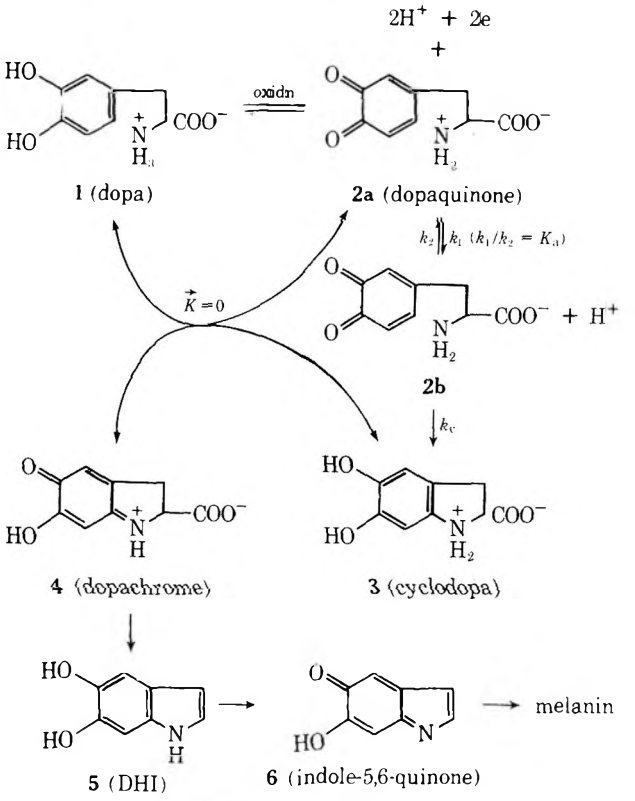
Melanin. I. Kinetics of the Oxidative Cyclization of Dopa to Dopachrome

Summary: Kinetics of the ring-closure of dopaquinone (**2**) to cyclodopa (**3**) have been studied *via* chronoamperometry of dopa (**1**) in the pH range of 5.0–6.0 and at temperatures of 15, 25, 30, and 37°; the rapidity of the cyclization process is attributed to a very favorable positive activation entropy; at pH 6.6 and above, cyclic voltammetry of dopa clearly demonstrates the formation of 5,6-dihydroxyindole (**5**).

Sir: Biogenesis of the important mammalian pigment melanin[1-4] from 3,4-dihydroxyphenylalanine (**1**, dopa) has long been considered to proceed *via* the series of fugitive intermediates illustrated in Scheme I, a pathway originally postulated by Raper[5] and not yet adequately characterized. Mason[6] has estimated the rate constant for decarboxylative rearrangement of dopachrome (**4**) to 5,6-dihy-

Scheme I



droxyindole (5) to be $\sim 5.8 \times 10^{-5}$ sec^{-1} at pH 5.1. More recently, Brun and Rosset[7] have shown by cyclic voltammetry that the redox system, 1 ⇌ 2, is essentially reversible in 1 *M* perchloric acid (E_0 = 0.81 V NHE). Furthermore, above pH 4 dopaquinone (2) cyclizes to cyclodopa (or leucodopachrome, 3), which is then oxidized by dopaquinone (2) to dopachrome (4) yielding a net conversion of 1 to 4 involving four electrons per molecule. This system comprises an ECC mechanism (*i.e.*, an electrochemical–chemical–chemical step sequence) analogous with the oxidative ring closure of adrenalin, whose kinetics have been determined by Adams[8] and coworkers using fast-sweep electroanalytical techniques. We are therefore prompted to report here a similar kinetic study of the dopa (1) → dopachrome (4) conversion at various pH values and several temperatures permitting calculation of the activation-thermodynamic parameters for the cyclization of dopaquinone (2) to cyclodopa (3).

Preliminary cyclic voltammetry experiments were run using a carbon-paste working electrode[9] on solutions of dopa (1) at 25°.[10] At pH 4.4 and a scan rate of 3.1 V/min dopa showed only a quasi-reversible oxidation-reduction couple with an anodic peak (+0.39 V) for oxidation of 1 and a more cathodic peak (+0.21 V) for reduction of dopaquinone (2). At pH 5.4 incursion of the ring closure of 2 to 3 introduced an additional set of peaks (oxidation, −0.05 V; reduction, −0.21 V) corresponding to the dopachrome (4)–cyclodopa (2) couple. At pH 7.4 the reduction wave for dopaquinone was entirely absent, resulting from rapid cyclization of 2 to 3, the dopachrome–cyclodopa couple was still evident, and a new oxidation peak (+0.05 V) had appeared. For the slow scan rate of 3.1 V/min, this new peak was readily observed at pH 6.6 and above and was in all cases identical with that of an authentic sample of 5,6-dihydroxyindole (5).[11]

Chronoamperometry experiments following the oxidation of dopa (1) were then run at various pH values and four temperatures (15, 25, 30, and 37°).[10] The current (i)–time (t) curves were then analyzed using a treatment similar to that of Adams[8] for comparable ECC reactions of adrenalin and based on the theoretical relationships developed by Hawley and Feldberg.[12] These latter authors have shown that for a reaction system comparable with that in Scheme I, the apparent number (n_{app}) of electrons transferred increases from an initial value of *two* for the simple redox system (1 ⇌ 2), prior to incursion of the ring closure (2b → 3), to a final value (n_f) of *four* for the overall reaction (1 → 4). Intermediate values of n_{app} at times (t) are related to the initial values (n_0) by eq 1 where C = [dopa], and the value $(it^{1/2}/C)_{kc=0}$ is either a value extrapolated to time zero or one-half the value at $t = \infty$. Because of uncertainty in the measurements at long times, we chose to determine the intercepts by computer extrapolation of $it^{1/2}/C$ at various times to t = 0. Minimally triplicate runs provided reproducible intercepts and derived rate data.

$$\frac{n_{app}}{n_0} = \frac{it^{1/2}/C}{(it^{1/2}/C)_{k_c=0}} \quad (1)$$

Calculated values of n_{app}/n_0 were converted to k_0t (where k_0 is the observed first-order rate constant for the overall reaction 1 → 4), using the potentiostatic working curve of Hawley and Feldberg[12] for K = 0 (equilibrium constant for the reaction 1 + 4 ⇌ 2a + 3; *cf.* Scheme I). Plots of k_0t *vs.* t were satisfactorily linear and their slopes afforded the observed rate constants (k_0) listed in Table I.

Analysis of the kinetics of Scheme I (2a → 4) using a steady-state approximation for intermediate 2b shows that $k_0 = k_1k_c/(k_2[H^+] + k_c)$ where k_c is the specific rate constant for ring closure (2b → 3) assuming first-order cyclization. At high $[H^+]$ where $k_2[H^+]$ is much greater than k_c the equation simplifies to eq 2 or 3 where K_a is the second ionization constant (for $-NH_3^+$) of the dopaquinone

$$k_0 = \frac{k_1k_c}{k_2[H^+]} = k_c\frac{K_a}{[H^+]} \quad (2)$$

$$\log k_0 = \text{pH} + \log K_ak_c \quad (3)$$

Table I
First-Order Rate Constants for Conversion of Dopaquinone (2a) to Dopachrome (4) at Various Temperatures[a]

pH	k_0 (sec^{-1}) at 15°	25°	30°	37°
5.00				0.064
5.40	0.014	0.039	0.073	0.13
5.83	0.032	0.099	0.16	0.50
6.00	0.053	0.15	0.24	

[a] The k_0 values represent the average of from three to six individual determinations. Reproducibility varied from 2 to 8% for temperatures of 15 to 30°. Values at 37° are less reliable since the runs at pH 5.83 were recorded on the oscilloscope.

Table II
First-Order Rate Constants for Cyclization of Dopaquinone (2b) to Cyclodopa (3) at Various Temperatures

pH	k_c (sec^{-1}) at 15°	25°	30°	37°
5.00				3.1×10^2
5.40	2.7×10^1	7.4×10^1	1.4×10^2	2.5×10^2
5.83	2.3×10^1	7.0×10^1	1.1×10^2	3.6×10^2
6.00	2.5×10^1	7.2×10^1	1.2×10^2	
Av	2.5×10^1	7.2×10^1	1.2×10^2	3.1×10^2
Av % Error	5.2	1.8	8.1	12

(**2a**). As a first approximation this K_a is taken to be equal to the second ionization constant (pK_a = 8.68) for dopa (**1**).[13] Plots of the pH–rate profile at the various temperatures all show approximately the theoretical slope = 1 expected from eq 3 in the pH range of 5.00–6.00. Using data only from this range, the slope of eq 2 yielded the values of k_c summarized in Table II.

An Arrhenius plot (correlation coefficient of 0.996) of the average k_c values from Table II yields an experimental activation energy of 20.0 kcal/mol for the cyclization of dopaquinone (**2b**) to cyclodopa (**3**). The activation thermodynamic parameters calculated at 25° are as follows: ΔH^* = 19.4 kcal/mol, ΔG^* = 14.9 kcal/mol, and ΔS^* = +15.1 eu. The rapidity of the ring closure may therefore be attributed to a very favorable probability factor as reflected by the large positive entropy of activation. This result is in accord with recent kinetic studies by Illuminati and coworkers,[14] who reported that ring-closure reactions of *o*-ω-bromoalkoxyphenoxides showed a gradual transition from negative to positive entropies of activation as the product ring size decreased from ten to six.

Finally it should be noted that the rate of cyclization of dopaquinone to cyclodopa at 25° is roughly 10^6 times as fast as the reported[6] rate of decarboxylative rearrangement of dopachrome to 5,6-DHI (**5**). Our cyclic voltammetry experiments suggest that this latter process is much more rapid at physiological pH; hence, additional studies of subsequent steps in Scheme I are currently in progress.

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Department of Chemistry **Thomas E. Young***
Lehigh University **John R. Griswold**[15]
Bethlehem, Pennsylvania 18015 **Matthew H. Hulbert**

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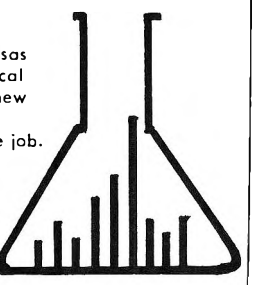

A major subsidiary of our Fortune 500 corporation, located in Kansas City, Kansas, is seeking a qualified individual to head-up its chemical laboratory. Broad duties will encompass directing R&D work of new applications of chemicals. Quality Control efforts, supervision of pesticide registrations and patent application work are part of the job.

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DMF ACETALS

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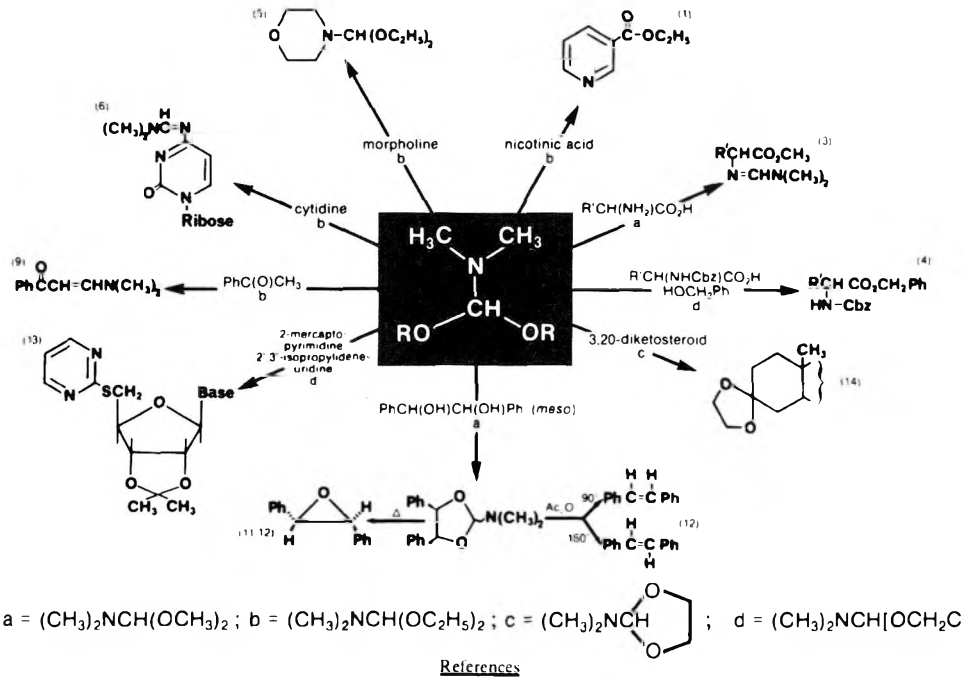
DMF acetals constitute a class of versatile synthetic and analytical reagents. With these acetals, carboxylic acids at room temperature give directly the corresponding esters;[1,2,3] amino acids form *N*-dimethylaminomethylene esters, suitable for glc analysis.[3] With **DMF dineopentyl acetal**, which is itself unreactive toward carboxylic acids but acts as a mediator, *N*-protected amino acids can be esterified with a wide variety of alcohols.[2,4] **DMF acetals** react with primary amino functions to yield *N*-dimethylaminomethylene derivatives.[5,6,7] The N^6-dimethylaminomethylene derivative of 9-β-D-arabinofuranosyladenine has anti-viral properties.[8] **DMF acetals** react with active methylene compounds such as acetophenone, ethyl cyanoacetate, 2-methylquinoline methiodide, etc.[5,9,10] Vicinal diols, *e.g.*, racemic and *meso*-diphenylethane-1,2-diol, cyclohexane-1,2-diol and 5α, 6β-dihydroxycholestane, are converted to epoxides and olefins.[11,12] The conversion of a nucleoside primary alcohol to a sulfide using **DMF dineopentyl acetal** has been reported. Raney nickel desulfurization gave the 5′-deoxy derivative.[13]

Many other reactions of **DMF acetals** are documented in our technical information bulletin which is available on request.



Reagents: a = $(CH_3)_2NCH(OCH_3)_2$; b = $(CH_3)_2NCH(OC_2H_5)_2$; c = $(CH_3)_2NCH$ (cyclic acetal) ; d = $(CH_3)_2NCH[OCH_2C(CH_3)_3]_2$

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17,854-3	*N,N*-Dimethylformamide dibutyl acetal	5g $7.25; 25g $24.00
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14,073-2	*N,N*-Dimethylformamide dimethyl acetal	12g† $10.20; 25g $15.30; 100g $40.25
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† Denotes tenth-molar unit

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