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THE JOURNAL OF Organic Chemistry®

VOLUME 38, NUMBER 3

FEBRUARY 9, 1973

Overcrowded Molecules. IV. Synthesis and Properties of Some Highly Strained 1-(2-Pyridyl)-9-oxa-9a-azoniabenzo[*b*]phenanthro[4,3-*d*]furans

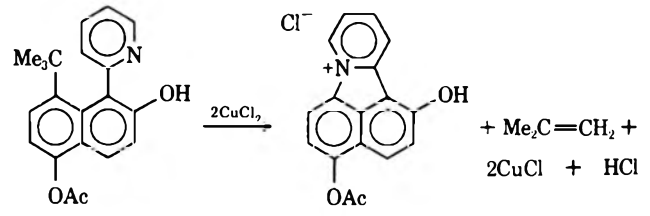
D. L. FIELDS,* T. H. REGAN, AND D. P. MAIER

Research Laboratories, Eastman Kodak Company, Rochester, New York 14650

Received September 5, 1972

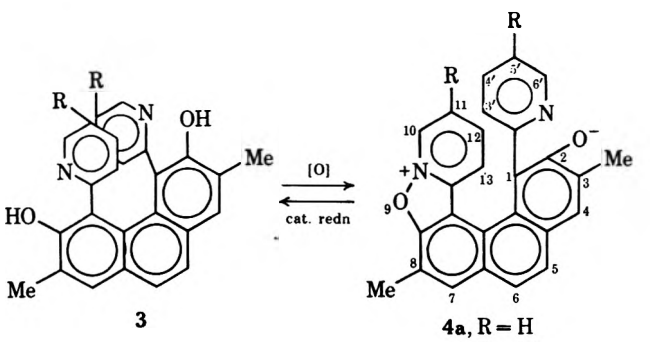
Oxidation of the overlapped pyridyl compounds **3** yields the even more highly overcrowded isoxazolium zwitterions, **4**, whose spectral properties indicate them to be intramolecular charge transfer complexes. Unusual, largely unexplained, chemical shifts and coupling constants occur in the nmr spectra of **4**. Reaction of **4** with several "hard" nucleophiles gives products resulting from addition at C-8a (BH_4^-, OH^-, OMe^-), or substitution at C-7 (CN^-) *via* an apparent 1,6 addition–elimination. In contrast, reaction of the closely related deoxy isoxazolium salt **8** with nucleophiles gives products resulting from the more common reduction (BH_4^-), or substitution (CN^-) of the pyridinium ring. The difference in reactivity is ascribed to the charge transfer character of the zwitterion.

The novel intramolecular cyclization reaction following oxidation of **1** with $CuCl_2$ was reported recently.[1]



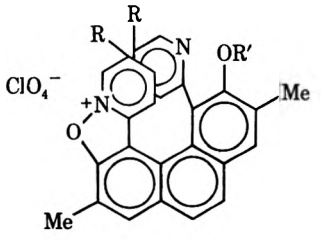
1 2

Since we had in hand other highly strained molecules with similar substituent placements (*e.g.*, **3**)[2] whose oxidation potentials[3] were even more favorable for reaction, we subjected **3a** and **3b** to the oxidizing conditions using *N*-chlorobenzotriazole in CH_2Cl_2. A red crystalline product was isolated in each case in 65–70% yield.[4] These compounds have been characterized as isoxazolium betaines **4a,b** based on spectral and chemical evidence, and their formation represents a new type of intramolecular oxidative cyclization reaction. A number of unusual chemical transformations are also recorded, related to the atypical behavior of **4a** toward a few selected nucleophilic reagents.



3 4a, R = H
b, R = Me

Isoxazolium Betaine (4a).—Elemental analysis and molecular weight determinations of **4a** (390 from mass spectrum, 387 ebullioscopic) established it to be monomeric with respect to **3a** with two less hydrogens in accord with a $C_{26}H_{18}N_2O_2$ formulation. Catalytic reduction (Pd/C) regenerated starting diol **3a**. Treatment of **4a** with dilute perchloric acid gave a yellow perchlorate salt, **5**, and with acetic anhydride–sulfuric acid followed by anion exchange, a monoacetyl perchlorate derivative, **6a**.



	R	R′
5	H	H
6a	H	Ac
6b	Me	Ac

The mass spectral fragmentation of **4a** was dominated by two ions, M^+ and $(M - \text{pyridyl})^+$, this un-

(1) (a) D. L. Fields and T. H. Regan, *J. Org. Chem.*, **36**, 2986 (1971); (b) see also G. Popp, *ibid.*, **37**, 3058 (1972).

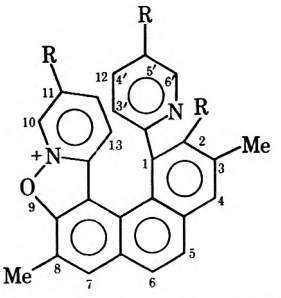
(2) D. L. Fields and T. H. Regan, *ibid.*, 2991 (1971).

(3) $E_{1/2}$ for **3a** = +0.75 V; $E_{1/2}$ for **1** = +1.00 V *vs.* sce in CH_3CN (TBAP as supporting electrolyte).

(4) $CuCl_2$ oxidation of **3a,b** followed by basification with 5% $NaHCO_3$ produced these same compounds, but this is not a preferred procedure, owing to difficulty in ridding the product of trace amounts of copper impurities.

TABLE I

NMR CHEMICAL SHIFTS[a] FOR 9-OXA-9a-AZONIABENZO[b]PHENANTHRO[4,3-d]FURANS

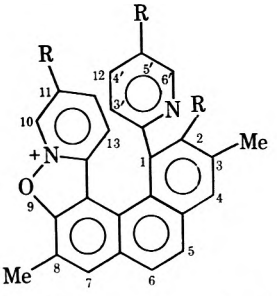


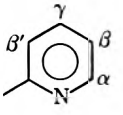
Compd	R-2	Me-3	H-4	H-5	H-6	H-7	H-8	H-9	R-11	H-12	H-13	H-3′	H-4′	R-5′	H-6′
4a[b]		2.30	7.39	6.76	7.30	6.60	1.99	8.43	6.71	7.60	10.12	6.93	7.50	7.14	8.50
[c]		2.30	7.42	6.92	7.38	6.87	2.02	8.36	6.85	7.66	10.00	6.90	7.67	7.24	8.47
4b[b]		2.32	7.44	6.81	7.37	6.60	2.02	8.22	2.24	7.50	10.17	6.84	7.48	2.21	8.30
5[d,e]		2.48	7.91	7.30	7.79	6.94	2.03	9.43	8.45	7.75	9.04	6.50	7.59	7.33	8.44
6a[e]	2.51	2.43	8.30	7.64	8.09	7.32	2.08	9.04	8.78	8.16	9.26	6.44	7.76	7.46	8.61
6b[e]	2.50	2.25	8.00	7.44	7.88	6.90	2.08	8.82	2.59	8.76	9.04	6.23	7.23	2.40	8.36
8[e]	8.65	2.52	8.06	7.56	7.99	7.16	2.06	9.22	8.68	8.06	9.04	6.59	7.71	7.44	8.65

[a] δ values in parts per million downfield from internal TMS. Obtained with a Bruker 90-MHz spectrometer using 1–4% solutions in DMSO-d_6 unless otherwise specified. [b] $CDCl_3$ solvent. [c] Spectrum recorded at 100°. [d] CD_3OD–CD_3CN solvent. [e] Counterion ClO_4^-.

TABLE II

NMR COUPLING CONSTANTS[a] FOR 9-OXA-9a-AZONIABENZO[b]PHENANTHRO[4,3-d]FURANS. COMPARISON WITH ANALOGOUS VALUES IN PYRIDINE[b]





	—$J_{\alpha,\beta}$ (5.5)—		——————$J_{\beta,\gamma}$ (7.5)——————				—$J_{\alpha,\gamma}$ (1.9)—		—$J_{\beta,\beta'}$ (1.6)—		—$J_{\alpha,\beta'}$ (0.9)—				
Compd	$J_{5',6'}$	$J_{10,11}$	$J_{3',4'}$	$J_{4',5'}$	$J_{11,12}$	$J_{12,13}$	$J_{4',6'}$	$J_{10,12}$	$J_{3',5'}$	$J_{11,13}$	$J_{3',6'}$	$J_{10,13}$	J_{7,CH_3}	J_{4,CH_2}	$J_{6,8}$
4a[c]	4.7	7.1	7.7	7.5	7.1	9.2	1.8	1.6	1.2	1.7	0.8	0.5	1.5	0.8	8.0
d, e	4.7	7.0	8	7.5	7.0	9.1	1.8	1.6	1.2	1.7	0.8	0.5	1.5	1.0	9.5
4b[c]			8.0			9.2							1.5	1.0	7.8
5[f,g]	4.8	8.5	7.8	7.8	7.2	6.7	1.8	1.6	1.2	1.5	1.0	0.6	1.5	1.0	8.0
6a[d,g]	4.7	8.2	7.6	7.6	7.4	6.5	2.0	1.5	1.2	1.5	1.0	0.5	1.5	0.5	8.3
6b[d,g]		8.2	7.8				1.8						1.5	0.5	8.5
8[d,g]	4.8	5.2	7.4	7.7			1.8		1.4	1.4		0.8	1.0	0.5	

[a] Hertz. [b] Reference 6. [c] $CDCl_3$ solvent. [d] DMSO-d_6 solvent. [e] Spectrum recorded at 100°. [f] CD_3OD–CD_3CN solvent. [g] Counterion ClO_4^-.

usual biphenyl-type cleavage being characteristic of the overlapped pyridine systems.[2] The nmr spectrum (see Tables I and II) showed that only the two exchangeable hydrogens were missing. The chemical shifts of the pyridinium hydrogens were puzzling at first; the low-field shifts expected on introduction of the positive charge were observed but not in the expected manner. The hydrogen α to the ring junction (*i.e.*, H-13) appears at very low field, but this hydrogen is β to the N^+ and, in general, should be least affected by the positive charge. However, removal of the negative charge on oxygen of C-2, either by protonation (**5**) or by forming the acetate ester **6a**, causes H-13 to shift to higher field, even though this shift is still at unusually low field. Molecular models show that the hydrogen in question (H-13) is very close to both the $-O^-$ and the N of the other pyridyl ring. Operation of a steric compression shift analogous to that observed by Anet[5] could account for the observed effect. This cannot be the entire explanation, however, since the unusual shifts in the pyridinium ring are accompanied by significant changes in the magnitude of several coupling constants. For example, $J_{12,13}$ (corresponding to $J_{\beta,\gamma}$ = 7.5 Hz in pyridine[6]) is ~9 Hz in the betaine, and falls to ~6.5 Hz in the protonated or acetylated compound. This probably reflects changes in the degree of bond localization in the pyridinium ring as a result of the high degree of strain, but we have been unable to rationalize all the changes in a coherent manner.

Unequivocal assignment of chemical shifts in **4a** could be made since **4b** and **6b** were synthesized with a

(5) S. Winstein, P. Carter, F. A. L. Anet, and A. J. R. Bourn, *J. Amer. Chem. Soc.*, **87**, 5247 (1965).

(6) R. F. M. White, "Physical Methods in Heterocyclic Chemistry," Academic Press, New York, N. Y., 1963, p 142.

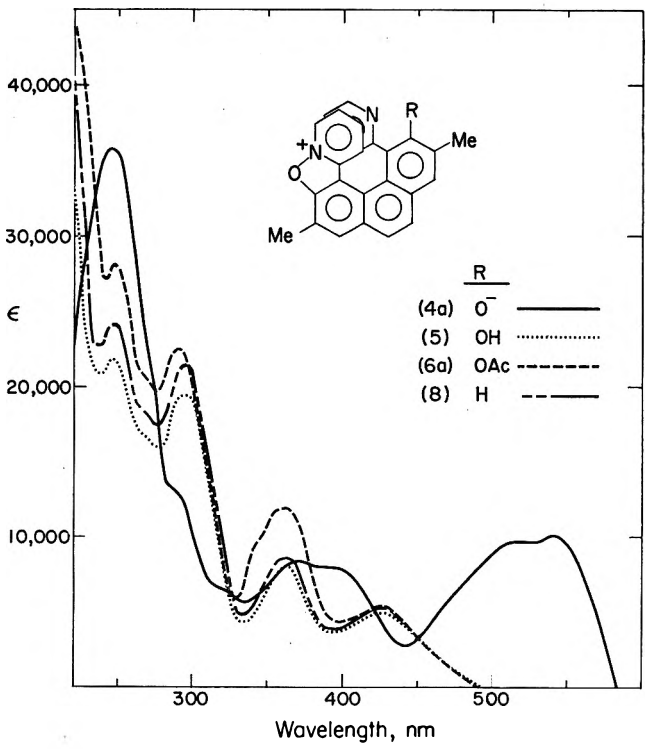
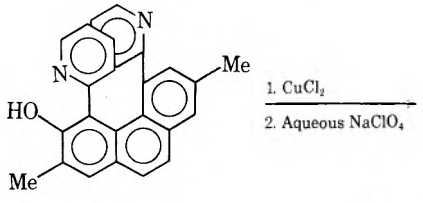


Figure 1.—Electronic spectra of isoxazolium salts **4a**, **5**, **6a**, and **8**. The counterion for **5**, **6a**, and **8** is ClO_4^-.

methyl substituent in each pyridine ring in a known position. Appropriate decoupling experiments served to confirm the assignments.

The electronic spectrum of **4a** (and **4b**) shows a significant long-wavelength shift for the betaine compared to the protonated and acetylated forms (Figure 1). This is interpreted in terms of an intramolecular charge transfer from $-O^-$ to the pyridinium ring, which could contribute to the chemical shift and coupling-constant changes as a result of changes of electron density distribution.

As this study progressed, another particularly useful and closely related isoxazolium salt became available, specifically, **8**. It was prepared by $CuCl_2$ oxidation of phenanthrol **7**, which in turn was obtained by a synthesis which will emerge later. The uv and nmr spectra of **8** bore the expected similarities to those of **5** and



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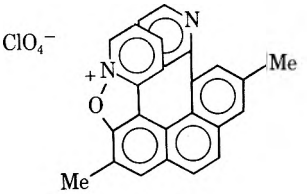


8

6a (see Figure 1 and Tables I and II), its elemental analysis was satisfactory, and the chemistry to be described below was interpretable in terms of the assigned structure.

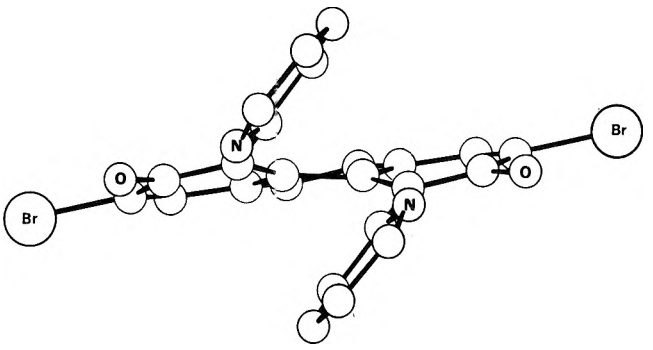


Figure 2.—View of a 4,5-bis(2-pyridyl)phenanthrene-3,6-diol derivative along the twofold symmetry axis.[7]

Reactions with Selected Nucleophiles.—An examination of space-filling models of isoxazolium salts **4** and **8** suggests that they are exceedingly sterically strained compounds, even more so than their phenanthrol precursors, **3** and **7**. It has previously been established by X-ray analysis[7] that the overcrowding found in the latter-type compounds produces a twisting of the phenanthrene skeleton out of its preferred planarity (see Figure 2), with the pyridines located on opposite sides and further rotated by ~40° from the phenanthrene mean plane. As such, the pyridines bear a stepped relationship, are nearly parallel, and are extraordinarily close, having a nonbonded contact of ~2.8 Å between C_2 and C_2' to a more normal 3.45 Å between C_6 and C_6'.

In the oxidative cyclization of these compounds to isoxazolium **4** and **8**, the ~2.6-Å N to O distance must be shortened to within bonding distance (~1.3–1.4 Å), and it would also appear desirable to rotate the pyridine involved in the isoxazolium ring more into the mean plane of the phenanthrene in order to achieve a reasonable degree of N–C bonding overlap and planarity of the atoms of the isoxazolium ring. However, this is not easily accomplished, since any rotation of one pyridine toward greater planarity with the phenanthrene will require displacement of the second pyridine further out of plane if the ~3-Å minimum separation between the pyridines is to be maintained. Therefore, regardless of how adequate bonding overlap is achieved, it seems likely that there will be more pronounced bond-angle deformations and constraint present in **4** than found in the already highly strained **3**, with concomitant higher ring-strain energy. One might expect the isoxazolium ring to reflect this additional strain by showing greater reactivity than is general for isoxazolium ring systems, and it should be quite responsive to interaction, directly or indirectly, with reagents capable of providing relief of this added ring strain.

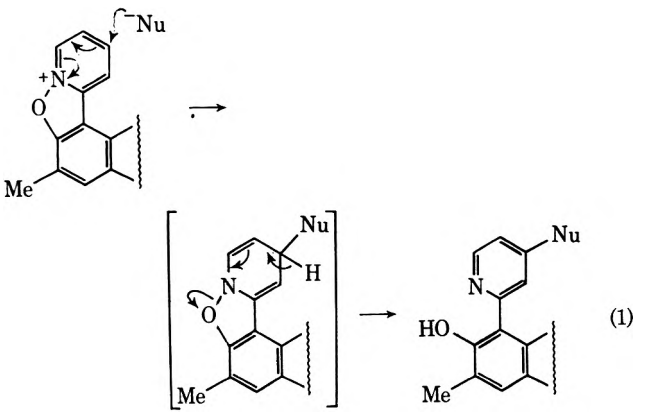
An obvious type of reaction that would achieve this end and one with considerable precedent[8] is a nucleophilic aromatic substitution at the 2 or 4 position of the pyridinium ring, as indicated in eq 1. Indeed, **8** experiences this mode of attack by such "hard" nucleophiles[9] as CN^-, BH_4^-, and probably OH^- and OMe^- as well. However, the closely related zwitterion

(7) D. L. Smith and E. K. Barrett, *Acta Crystallogr., Sect. B*, **27**, 419 (1971).

(8) See, for example, A. R. Katritzky and E. Lunt, *Tetrahedron*, **25**, 4291 (1969); R. Eisenthal and A. R. Katritzky, *ibid.*, **21**, 2205 (1965).

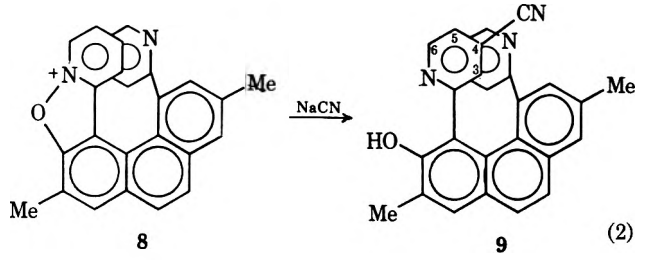
(9) R. G. Pearson, *J. Amer. Chem. Soc.*, **85**, 3533 (1963); R. G. Pearson and J. Songstad, *ibid.*, **89**, 1827 (1967).

4a differs dramatically from isoxazolium 8 in this respect and is obviously under the influence of strong directive factors not present in 8. This is illustrated by a comparison of product types from the reactions of 4a and 8 with cyanide ion.

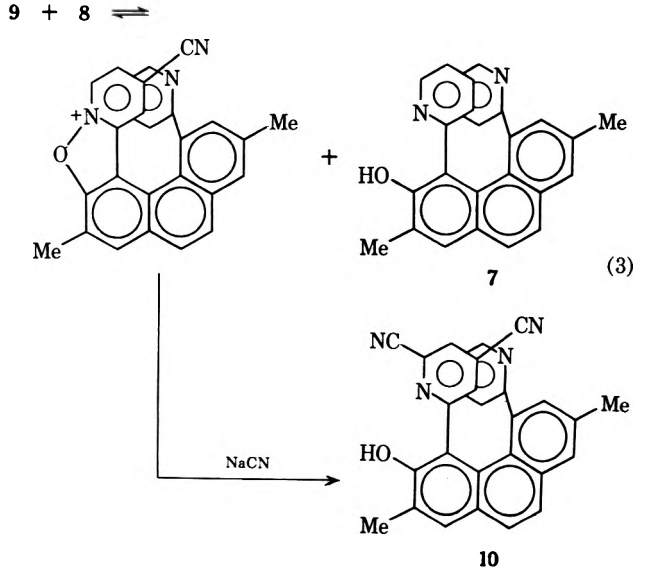


(1)

Treatment of 8 with excess sodium cyanide in DMSO for 5 min at room temperature provided, after work-up and chromatography, three recognizable phenanthrol products: a mono- and a dicyano derivative, 9 and 10, isolated in 30 and 12% yields, respectively, plus a 28% yield of 7. Cyanation of one of the pyridines was readily deduced for both 9 and 10 from mass spectroscopic and nmr evidence, wherein 9 displayed *m/e* 401 (9%, M^+), 322 (24%, M − Py), and 298 (100%, M − Py − CN) with a metastable transition 401 → 298, while 10 had *m/e* 462 (10%, M^+), 348 (6%, M − Py), and 298 (100%, M − Py − 2CN), with a metastable transition of 462 → 298. The position or positions of cyano substitution were assigned based on nmr evidence, the pyridine bearing the cyano group of 9 being observed as an AMX pattern [δ 6.88 (d of d, 1, *J* = 0.9, 1.6 Hz, H-3), 7.20 (d of d, 1, *J* = 1.6, 5.5 Hz, H-5), and 8.37 (d of d, 1, *J* = 0.9, 5.5 Hz, H-6)] and in 10, an AX pattern found at δ 7.08 (d, 1, *J* = 1.5 Hz, H-3) and 7.58 (d, 1, H-5). The formation of both reduction product 7 and dicyano derivative 10 in this reaction is unexpected, but can be rationalized on the basis that they are a resultant of a redox reaction as indicated in eq 3.

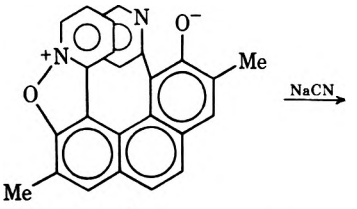


(2)

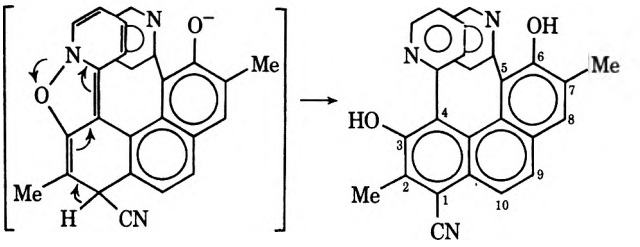


(3)

In contrast to these results, a single product, 1-cyano-2,7-dimethyl-4,5-bis(2-pyridyl)phenanthrene-3,6-diol (11), was obtained in virtually quantitative yield from the reaction of 4a with NaCN under reaction conditions comparable to those employed in the conversion of 8 to 7, 9, and 10. The very close similarity of the uv spectrum of 11 to that of 3a strongly suggested it to also be a 4,5-bis(2-pyridyl)phenanthrene-3,6-diol and its mass spectrum was also characteristic, having only two significant fragments, that of the parent ion (*m/e* 417, 27%) and M − pyridyl (*m/e* 341, 100%). The complete absence of a *m/e* 314, which would represent the loss of a cyanopyridyl group from the parent, as found in the fragmentation of 9, suggested that cyanation of the phenanthrene rather than the pyridine ring had occurred, and this was confirmed by nmr results which completely supported the 1-cyano derivative assignment. Two prominent features of the nmr spectrum are the absence of a signal from H-1 and 0.5-ppm shift downfield for H-10, consistent with the presence of the CN at C-1, peri to H-10.

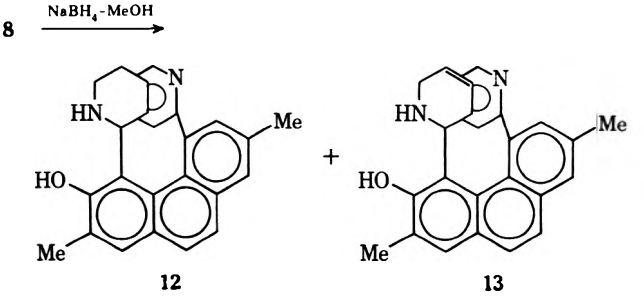


4a



11

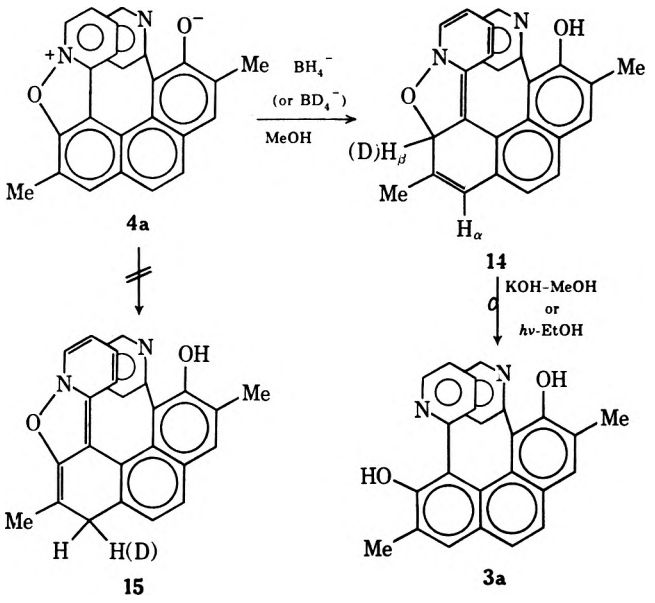
The difference in modes of reaction of 4a and 8 with $NaBH_4$ is equally striking. A complex mixture of products resulted from the reaction of 8 with excess methanolic $NaBH_4$ for 5 min at room temperature. The two major components were isolated by Florisil chromatography as a difficultly separable mixture and are assigned the hexa- and tetrahydropyridylphenanthrol structures 12 and 13, respectively, based on



spectral evidence presented in the Experimental Section.

On the other hand, treatment of **4a** with methanolic $NaBH_4$ under identical conditions resulted in the immediate discharge of its deep red color to a light orange followed by separation of a highly insoluble bright orange crystalline product, **14**, in essentially quantitative yield. This compound was not the known diol **3a**, which might be anticipated from our experience with the **4a**–cyanide reaction. However, it could be readily isomerized to **3a**, either by photolysis in ethanol or by heating at reflux temperature with methanolic KOH followed by neutralization.

Its mass spectrum has two dominant peaks, a parent *m/e* 392 (60%, M^+) and M − pyridyl *m/e* 314 (100%), establishing it to be isomeric with **3a**. The analogous product from a $NaBD_4$ reduction in CH_3OD has *m/e* 394 and 316, and that from $NaBD_4$ in CH_3OH has *m/e* 393 and 315, showing that one of the hydrogens (or deuteriums) provided by the reducing agent was incorporated into the product in a nonreadily exchangeable position.

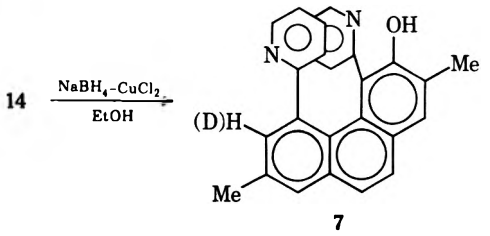


4a **14** **15** **3a**

Unfortunately, the very low solubility of **14** in all of the common nonacidic nmr solvents prevented its nmr examination *per se*. However, the nmr spectrum of a solution of it in CD_3OD acidified with DCl was obtained, and provided the desired information as to the site of BH_4^- (BD_4^-) attack, and a firm basis for its structure assignment as the 3-isoxazoline **14**.[10] Most noteworthy, double irradiation experiments showed one of the two methyls (at δ 2.05) now to be weakly coupled to *two* protons found at δ 5.93 (H_β) and 6.54 ppm (H_α), and they themselves coupled (J = 2.5 Hz) to each other. The absence of the upfield multiplet at δ 5.93 in the spectrum of the deuterio derivative identifies the signal as that associated with the hydrogen derived from the BH_4^- reagent. The 2.5-Hz spin coupling observed for these two protons is compatible with their having an allylic–axial relationship rather than the geminal one found in an alternative structural possibility, **15**.

(10) See I. Adachi and H. Kano, *Chem. Pharm. Bull.*, **17**, 2201 (1969), for an analogous example of reaction of Grignard reagents with a 5-unsubstituted isoxazolium salt to give 5-substituted 3-isoxazoline derivatives.

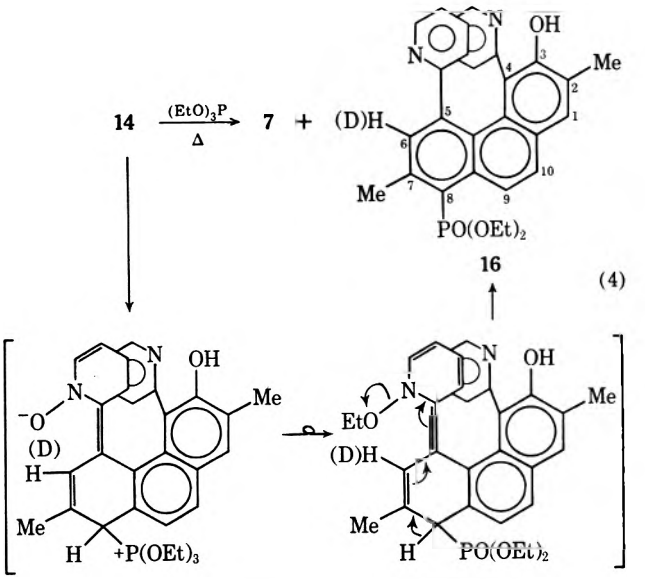
As additional support for the structural assignment, **14** was further reduced with resulting aromatization by $NaBH_4$–$CuCl_2$ in refluxing ethanol[11] to the aforementioned phenanthrol **7**. Its structure rests on correct elemental analysis, the usual spectral evidence (uv, ir, nmr, mass spectrometry), and its chemistry, which we have already mentioned.



7

An alternative approach to **7** which proved much less successful, but nonetheless interesting, was an attempted deoxygenation involving heating **14** with triethyl phosphite at reflux temperature (*ca.* 160°) until the starting material was consumed (2 hr, by tlc). At least four products were formed, two of which were isolated on a crystalline basis and identified. Phenanthrol **7** was one of these, but was obtained in only 4% yield. The other product, **16** (23%), also proved to be a 4,5-bis(2-pyridyl)phenanthren-3-ol, but was further substituted by a diethyl phosphonate group in the 8 position. The position of substitution of the phosphonate moiety was apparent from nmr spectral results, wherein half (H-9) of the AB pattern of H-9,10 was found at an unusually low-field position at 8.78 ppm, approximately 1.2 ppm lower field than that of H-9 of **7**, and is attributed to the deshielding influence of the peri phosphonate group.

A possible reaction path for the formation of this product is suggested in eq 4.



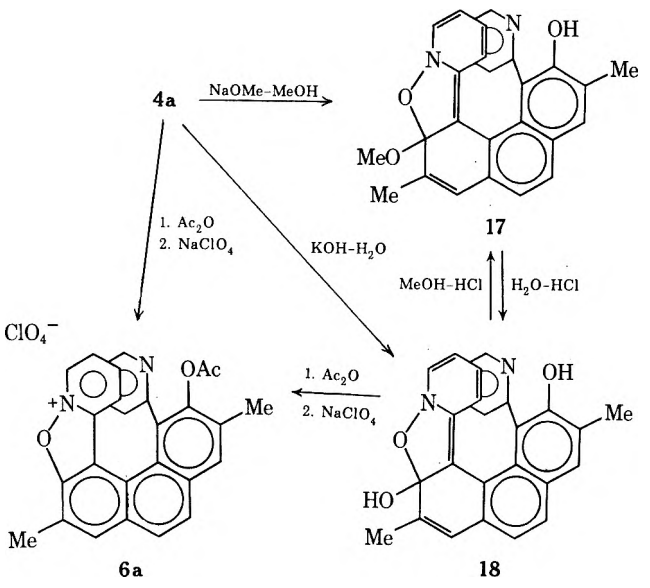
One final set of comparisons of reactivity behavior of **4a** and **8** has been determined using OH^- and OMe^- reagents. Isoxazolium **8** is transformed almost immediately into a dark, multicomponent mixture of products of undefined composition when treated with either aqueous NaOH or methanolic NaOMe at room

(11) See C. A. Brown, *J. Org. Chem.*, **35**, 1900 (1970); T. Satoh, S. Suzuki, T. Kikuchi, and T. Okada, *Chem. Ind.* (*London*), 1626 (1970).

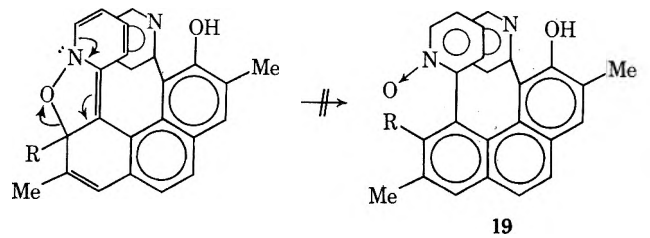
temperature. Isoxazolium **4a** also reacts with these reagents, but much more slowly over a 20–30-min period at 60° to yield after work-up in each case a single crystalline compound believed to be isoxazolines **17** and **18**, respectively.

Elemental analysis and mass spectral evidence establishes **17** to be a 1:1 adduct of **4a** with MeOH, and the marked resemblance of its uv spectrum to that of the BH_4^- product, **14**, suggests that they are closely related structurally. Particularly compelling spectral evidence is found in the high-resolution mass fragmentation of **17**, which displays a metastable transition for *m/e* 422 (M^+) → 363 ($M - CO_2CH_3$), indicative that one of the carbons of **17** attached to oxygen also bears the methoxyl group. The chemical interconversions of **4a**, **17**, and **18** outlined in Chart I lend further credence to the structural assignments.

CHART I



An interesting facet of the behavior of **14**, **17**, and **18** is that they show no tendency to undergo ring opening and aromatization to the *N*-oxide **19**. In such case, they could be classified as another type of isolable intermediate in an overall nucleophilic aromatic substitution reaction, somewhat akin to a neutral Meisenheimer complex. A rationale for this apparent lack of



a driving force toward rearomatization can be advanced based on steric arguments. Dreiding-model representations of **14**, **17**, and **18** show their benzisoxazoline moieties to be inclined somewhat away and reasonably separated from the neighboring pyridine, so that steric overcrowding is not a dominant structural concern. This suggests that they possess relatively negligible ring strain, epecially when compared to either *N*-oxide **19** or starting isoxazolium **4**, evidently to an extent that the gain in phenanthrene resonance energy derived from such an aromatization is not sufficient to compensate for the concomitant increase in steric strain.

At this point, it is a matter of conjecture as to why **4a** and **8** differ so in their reactions with these nucleophilic reagents. It certainly appears that the presence of an $-O^-$ at the seemingly remote 2 position of **8**, *i.e.*, **4**, inhibits the normal attack of the pyridinium ring by nucleophiles. The intramolecular charge-transfer properties of **4** may strongly contribute to a lessening of the electrophilic character of the pyridinium ring. Certainly the delocalization of electrons from the adjacent negatively charged oxygen into the pyridine positioned very close and directly behind the pyridinium ring should have a detrimental effect through electrostatic repulsive interactions on the approach of nucleophilic species.

Experimental Section[12]

Isoxazolium 4a, b.—A solution of 8.00 g (53 mmol) of *N*-chlorobenzotriazole[13] in 150 ml of methylene chloride was introduced into a mechanically stirred solution of 15.60 g (40 mmol) of 2,7-dimethyl-4,5-bis(2-pyridyl)phenanthrene-3,6-diol (**3a**)[2] in 150 ml of methylene chloride, and the mixture was stirred for 15 min at autogenous temperature. The resulting light red solution was extracted with 100 ml of 5% aqueous sodium bicarbonate solution, giving a deep red methylene chloride layer which was separated, dried over Na_2SO_4, and introduced onto the top of a Florisil column (5 × 85 cm). A yellow zone containing 0.89 g of starting **3a** was eluted with methylene chloride, followed by a deep red product zone which was eluted with methylene chloride–acetone (1:1, v/v). This was collected and concentrated to a red crystalline residue.

One recrystallization from CH_2Cl_2–Et_2O gave 10.40 g (71%) of **4a** as deep red plates, mp 242–243°.[14]

Anal. Calcd for $C_{26}H_{18}N_2O_2$ (**4a**): C, 80.0; H, 4.7; N, 7.2. Found: C, 80.1; H, 5.0; N, 7.2.

Zwitterion **4a** was converted to perchlorate **5**, mp 275° dec, by treatment with 10% perchloric acid.[14]

Anal. Calcd for $C_{26}H_{19}ClN_2O_6$: C, 63.6; H, 3.9; Cl, 7.2. Found: C, 63.3; H, 4.0; Cl, 7.1.

Isoxazolium **4b**, prepared by analogous oxidative procedure from **3b**,[2] had mp 254–256°.

Anal. Calcd for $C_{28}H_{22}N_2O_2$ (**4b**): C, 80.4; H, 5.3; N, 6.7. Found: C, 80.2; H, 5.2; N, 6.8.

A mixture of 200 mg of **4a**, 300 mg of 10% palladium/charcoal, and 200 ml of ethanol was hydrogenated at 60 psi (initial pressure) for 2 hr in a Parr shaker, giving (after standard work-up of the reaction mixture and Florisil chromatography) 120 mg (60%) of **1a** and 20 mg (10%) of a hexahydro derivative of **4a**: mass spectrum *m/e* 396 (M^+), 318 (M – pyridyl).

Acetate **6a** was prepared by dissolving **4a** (0.20 g, 0.51 mmol) in a mixture of acetic anhydride (20 g) and concentrated sulfuric acid (1.0 g). The solid produced by the addition of 75 ml of Et_2O was collected, dissolved in 20 ml of water, and treated with sodium perchlorate to give 0.24 g (84%) of **6a** as a yellow crystalline precipitate, mp 265–270° dec after one recrystallization from acetonitrile–ether.[14]

Anal. Calcd for $C_{28}H_{21}ClN_2O_7$: C, 63.0; H, 3.9; N, 5.2. Found: C, 63.0; H, 4.2; N, 5.4.

2,7-Dimethyl-4,5-bis(2-pyridyl)phenanthren-3-ol (7).—To a suspension of **14** (4.40 g, 11.2 mmol) and $NaBH_4$ (1.50 g) in 200 ml of refluxing ethanol was added dropwise, over a 4-min period, a solution of 350 mg of anhydrous cupric chloride in 15 ml of ethanol. The cupric chloride was immediately reduced to a

(12) Melting points (uncorrected) were determined on a Thomas-Hoover apparatus. Ultraviolet absorption spectra were recorded by a Cary Model 14 recording spectrophotometer. Nmr spectra were determined with a Bruker HX-90 spectrometer. Peak positions are reported in parts per million downfield from tetramethylsilane, followed by (in parentheses) multiplicity, relative area, and assignment. The mass spectra were determined on a Du Pont 21-110B mass spectrometer. Samples were analyzed *via* direct inlet at 70 eV.

(13) C. W. Rees and R. C. Storr, *J. Chem. Soc.*, 1474 (1969).

(14) For spectral data, see Tables I and II (nmr) and Figure 1 (uv).

black, insoluble substance, while starting **14** disappeared more slowly. After being heated at reflux for 15 min, the mixture was filtered, the filtrate was diluted with 600 ml of H_2O, and the resulting tan precipitate was collected and dried. The four major components of this mixture were easily separated by silica-gel column chromatography (3 × 50 cm column) into four product zones, the development of the chromatogram being followed visually using a 3660-Å light source.

In the order of elution there was isolated 100 mg (2%) of **1a** (nonfluorescent at 3660 Å), eluted with CH_2Cl_2; 510 mg (12%) of an isomerization product of **14** (bright yellow fluorescence at 3660 Å), eluted with CH_2Cl_2–EtOAc (20:1, v/v); 2.11 g (50%) of **7** (nonfluorescent at 3660 Å), CH_2Cl_2–EtOAc (10:1, v/v); and 350 mg (8%) of a tetrahydro derivative of **14** (blue fluorescence at 3660 Å, CH_2Cl_2–acetone (2:1, v/v).

Phenanthrol **7**, recrystallized from methylcyclohexane, had mp 256–257°; uv max (CH_3CN) 232 nm (log ϵ 4.67), 297 (4.39), 316 sh (4.33), 375 (3.48), 394 (3.54); mass spectrum (70 eV) *m/e* 376 (M^+), 298 (M − pyridyl); nmr ($CDCl_3$) δ 2.40 (d, 3, methyl), 2.50 (broadened s, 3, methyl) 6.57–7.67 (m, 11, aromatic), 8.00 (d of m, 1, pyridyl H-6), 8.21 (d of m, 1, pyridyl H-6), 13.17 (broadened s, 1, –OH).

Anal. Calcd for $C_{26}H_{20}N_2O$: C, 83.0; H, 5.3; N, 7.4. Found: C, 82.7; H, 5.3; N, 7.0.

The material eluted second is isomeric with **14**, and was purified by rechromatographing on silica gel. It was crystallized as stubby yellow needles from methylcyclohexane, mp 198–205° dec, mol wt 392 (mass spectrum).[15]

Anal. Calcd for $C_{26}H_{20}N_2O$: C, 78.7; H, 5.2; N, 7.1. Found: C, 78.8; H, 5.1; N, 7.3.

The tetrahydro derivative of **14** was recrystallized from methylcyclohexane: mp 243–250° dec; mass spectrum (70 eV) *m/e* (rel intensity) 396 (100) (M^+), 368 (18), 339 (37), 318 (15), 311 (62). Its structure has not been established nor was it further characterized.

The 6-deuterio derivative of **7** was obtained in analogous fashion starting with monodeuterated **14**, mass spectrum (70 eV) *m/e* 377 (M^+), 299 (M − pyridyl).

Isoxazolium 8.—The initially dark brown solution resulting from dissolving phenanthrol **7** (2.50 g, 6.7 mmol) and anhydrous $CuCl_2$ (2.50 g) in 150 ml of ethanol lightened to yellowish-green after heating at reflux for 5 min. The solution was filtered and diluted with ether to give 2.50 g of yellow crystals. These were collected, dissolved in 200 ml of methylene chloride, and passed through a silica gel column (3 × 50 cm), using CH_2Cl_2–methanol (5:1, v/v) as eluent. The yellow crystals obtained after concentrating the eluate were dissolved in aqueous methanol (1:1, v/v) and filtered, and the filtrate was treated with sodium perchlorate to give 1.80 g of **8**. Analytically pure **8** was obtained as yellow plates after one recrystallization from acetonitrile–ether, mp 275° dec.[14]

Anal. Calcd for $C_{26}H_{19}ClN_2O_6$: C, 65.8; H, 4.0; N, 5.9. Found: C, 65.8; H, 4.2; N, 5.9.

Phenanthrols 9 and 10.—A mixture of **8** (400 mg, 0.84 mmol) and sodium cyanide (400 mg) was dissolved in 10.0 g of dry DMSO. After standing for 5 min, the dark yellow solution was diluted with 5 ml of water, acidified with 5% HCl, and basified with 5% $NaHCO_3$ to yield a yellow multicomponent precipitate. The three major products were easily separated by silica gel chromatography using CH_2Cl_2–EtOAc (10:1, v/v) as eluent, and identified in order of elution. Phenanthrol **10** (40 mg, 12%) had mp >300° dec; uv max (CH_3CN) 227 nm (log ϵ 4.73), 236 sh (4.71), 290 (4.42), 314 sh (4.33), 400 sh (3.49); mass spectrum (70 eV) *m/e* (rel intensity) of major peaks 426 (10) (M^+), 348 (5) (M − pyridyl), 298 (100) (M − dicyanopyridyl); nmr ($CDCl_3$) δ 2.43 (d, 3, J = 1 Hz, Me) coupled to poorly resolved quartet at 7.70 (1, H-1), poorly resolved triplet at 2.53 (3, Me) coupled to multiplets at 7.22 (1, H-7) and 7.73 (1, H-8), AB quartet centered at 7.63 (2, J = 8 Hz, H-9,10), AX pattern at 7.08 (d, 1, J = 1.5 Hz, pyridyl H-3), and 7.58 (d, 1, J = 1.5 Hz, pyridyl H-5), typical 2-substituted pyridine pattern at 6.83 (H-3), 7.50 (H-4), 7.20 (H-5), 8.18 (H-6).

Anal. Calcd for $C_{28}H_{18}N_4O$: C, 78.9; H, 4.3; N, 13.1. Found: C, 79.3; H, 4.7; N, 13.1.

Phenanthrol **9** (100 mg, 30%) had mp 250–252°; uv max (CH_3CN) 233 nm (log ϵ 4.67), 289 (4.37), 318 (4.32), 395 (3.53); mass spectrum *m/e* (rel intensity) 401 (9) (M^+), 323 (24) (M − pyridyl), 298 (100) (M − cyanopyridyl); nmr ($CDCl_3$) AMX of cyanopyridyl at δ 6.88 (d of d, 1, J = 0.9, 1.6 Hz, H-3), 7.20 (d of d, 1, J = 1.6, 5.5 Hz, H-5), 8.37 (d of d, 1, J = 0.9, 5.5 Hz, H-6), AKMX of pyridyl at δ 6.88 (H-3), 7.40 (H-4), 7.06 (H-5), 8.07 (H-6), phenanthrene protons at δ 7.64 (H-1) coupled to Me at 2.42 (J = 1 Hz), 7.18 (H-6) and 7.68 (H-8) coupled to each other and to Me at 2.50 and AB pattern of H-9,10 at 7.53 and 7.63 (J = 8 Hz).

Anal. Calcd for $C_{27}H_{19}N_3O$: C, 80.8; H, 4.8; N, 10.5. Found: C, 80.6; H, 5.2; N, 10.4.

Phenanthrol **7** was also eluted, 90 mg (28%).

1-Cyano-2,7-dimethyl-4,5-bis(2-pyridyl)phenanthrene-3,6-diol (11).—A mixture of finely divided **4a** (100 mg, 0.26 mmol) and sodium cyanide (100 mg) was dissolved in 2.5 g of dry DMSO. After standing for 5 min, the dark yellow solution was diluted with 5 ml of water, acidified with 5% HCl, and basified with 5% $NaHCO_3$ to yield a yellow, crystalline precipitate consisting of a single product (tlc). One recrystallization from methylcyclohexane afforded 100 mg (94%) of analytically pure **11**: mp 281–283° dec; uv max (CH_3CN) 242 nm (log ϵ 4.72), 318 (4.46), 420 (3.64); nmr ($CDCl_3$) δ 2.40 (d, J = 0.5 Hz, 3, Me), 2.62 (s, 3, Me) 6.60 (m, 2, pyridyl H-3, H-3′), 6.94 (m, 2, pyridyl H-5, H-5′), 7.43 (pyridyl H-4, H-4′), 7.64 (d, 1, J = 8.5 Hz, H-9), 7.65 (q, 1, H-8), 7.94 (d, 1, J = 8.5 Hz, H-10), and 8.04 (m, 2, pyridyl, H-6, H-6′).

Anal. Calcd for $C_{27}H_{19}N_3O_2$: C, 77.7; H, 4.6; N, 10.1. Found: C, 77.9; H, 4.7; N, 10.3.

Borohydride Reduction of 8.—Isoxazolium **8** (300 mg) reacted immediately when treated with 500 mg of sodium borohydride in 15 ml of methanol to give a yellow solution. A multicomponent amorphous solid was precipitated from this solution by the addition of 450 ml of water. The two main constituents of this mixture were separated from the other products by silica gel chromatography (eluent CH_2Cl_2–EtOAc, 1:1 v/v), but even with repeated recrystallization we were unable to completely separate them from one another: mp 234–238°; mass spectrum (70 eV) *m/e* 382 (M^+ of **12**), 380 (M^+ of **13**), 326, 325, 304 (382 − pyridyl), 302 (380 − pyridyl), 298 (382 − hexahydropyridine and/or 380 − tetrahydropyridine), 286, 284, 282, 269; nmr ($CDCl_3$) δ 1.80 (t, 3, methyl), 2.48 (broadened s, 3, methyl), 2.61–4.10 (m, ~4), 4.96–6.27 (m, ~4), 6.40–7.76 (m, 8, aromatic), 8.56–8.70 (d of m, 1, pyridyl H-6). The position of the tetrahydropyridyl double bond of **13** is undefined.

Borohydride Reduction of 4a, *i.e.*, Isoxazoline 14.—To a stirred suspension of finely powdered **4a** (0.78 g, 2.0 mmol) in 25 ml of MeOH was added 0.26 g of $NaBH_4$, producing rapid dissolution of **4a** followed immediately by the separation of flocculent orange needles. The mixture was refrigerated for 1 hr at 5° and the crystals (0.75 g, 96%) were collected by filtration and washed with cold methanol: mp 160–171°, partially solidified and melted at 236°; uv max (MeOH) 258 nm sh (log ϵ 4.22), 279 (4.31), 317 sh (3.75), 383 (3.66), 487 (3.94); mass spectrum of major peaks (70 eV) *m/e* (rel intensity) 392 (64) (M^+), 314 (100) (M − pyridyl), 297 (58); partial nmr (CD_3OD + one drop of 5% DCl in D_2O) δ 2.04 (poorly resolved triplet, 3, Me), 5.93 (broad q, 1, H_β), 6.54 (broad q, 1, H_α). Double irradiation at δ 2.04 converts the 5.92 and 6.54 multiplets each to doublets (J = 2.5 Hz). Irradiation of either the 5.93 or 6.54 signal converts the other to a quartet and the methyl at δ 2.03 to a doublet (J = 1 Hz).

Anal. Calcd for $C_{26}H_{20}N_2O_2$: C, 79.6; H, 5.1; N, 7.1. Found: C, 79.7; H, 5.5; N, 6.9.

An analogous procedure using $NaBD_4$ gave the monodeuterio derivative, mass spectrum *m/e* (rel intensity) 393 (46), 315 (100), 298 (46).

Isomerizations of 14a to 3a. A. Photochemically.—A suspension of 100 mg of **14** in 250 ml of ethanol was irradiated over a 2-hr period using a Philips HPK 125-W source with Pyrex filter. Tlc analysis of the crystalline residue isolated after removal of solvent indicated the presence of only one product and it proved identical in every respect with authentic **3a**. A repeat of the above experiment, substituting THF for ethanol as solvent, produced no reaction after 24-hr irradiation.

B. By Base.—A mixture of 300 mg of **14** and 0.5 g of NaOMe in 15 ml of methanol was heated at reflux temperature for 3 hr, cooled, acidified with 5% HCl, and basified with 5% $NaHCO_3$, giving 280 mg of essentially pure **1a** as a yellow, crystalline precipitate.

Phosphonate 16.—A solution of **14** (500 mg, 1.27 mmol) in 10 g of triethyl phosphite was heated at reflux for 2 hr, during which

(15) This is an extraordinary rearrangement product of **14**, and is the subject of paper VI of this series to be submitted for publication.

time 14 was consumed (by tlc). The resulting purple solution was concentrated *in vacuo* to a syrup and the syrup was chromatographed on silica gel to yield in order of elution 20 mg (4%) of 7 (CH_2Cl_2–EtOAc, 2:1 v/v, as eluent), 150 mg (23%) of 16 (CH_2Cl_2–Me_2CO, 6:1 v/v, as eluent), and *ca.* 100 mg of purple syrup (Me_2CO eluent) which was discarded.

One recrystallization of 16 from methylcyclohexane provided yellow needles: mp 234–235°; mass spectrum (70 eV) *m/e* (rel intensity) 512 (20) (M^+), 434 (100) (M − pyridyl), 360 (30); nmr ($CDCl_3$) δ 1.40 (d of t, 6, phosphonate methyls), 2.42 (s, 3, 2-Me), 2.87 (d, 3, J = 2 Hz, 7-Me), 4.23 (m, 4, phosphonate $-CH_2-$), 6.56–7.53 (m, 8), 7.56 (d, 1, J = 9 Hz, H-10), 8.06 (d of m, 1, pyridyl H-6), 8.11 (d of m, 1, pyridyl H-6), 8.78 (d, 1, J = 9 Hz, H-9).

Anal. Calcd for $C_{30}H_{25}N_2O_4P$: C, 70.4; H, 5.7; N, 5.5. Found: C, 70.0; H, 6.1; N, 5.3.

By an analogous procedure, starting with 14 (deuterio), the 6-deuterio derivative was obtained, mass spectrum (70 eV) *m/e* (rel intensity) 513 (23) (M^+), 435 (100) (M − pyridyl), 361 (35).

Isoxazoline 17.—A mixture of 4a (800 mg, 2.0 mmol) and sodium methoxide (800 mg) in 50 ml of methanol was heated at reflux for 30 min, until the starting material had disappeared (tlc). The resulting orange solution was concentrated to dryness, and the residue was chromatographed on Florisil using CH_2Cl_2–Me_2CO–MeOH (5:5:1, v/v) as eluent. The single orange zone was eluted and concentrated to a syrup which crystallized. One recrystallization from CH_2Cl_2–ligroin (bp 35°) gave 530 mg (62%) of analytically pure 17 as reddish orange needles: mp 202–210° dec; uv max (MeOH) 264 nm (log ε 4.47), 355 (3.90), 480 (4.13); mass spectrum (70 eV) *m/e* (rel intensity) 422 (46%) (M^+), 407 (1) (M − Me), 391 (1) (M − OCH_3), 363 (1) (M − CO_2CH_3), 344 (100) (M − pyridyl), 335 (6), 284 (7), 270 (6), 256 (3), 254 (4), 242 (4), 241 (5), 167.5 (5), 78 (3), 59 (1); nmr ($CDCl_3$) δ 2.04 (d, 3, J = 2 Hz), 2.28 (d, 3, J = 1 Hz), 3.44 (s, 3), 6.56–7.73 (m, 9), 8.09 (d of m, 1), 8.42 (d of m, 1), 9.88 (d of m, 1).

Anal. Calcd for $C_{27}H_{22}N_2O_3$: C, 76.8; H, 5.2; N, 6.6. Found: C, 76.5; H, 5.3; N, 6.9.

Conversion of 17 to 18.—A solution of 120 mg of 17 in 12.5 ml of 2 *N* HCl was heated at reflux for 3 hr, concentrated to a syrup, and then redissolved in 10 ml of water. The yellow crystals which separated from solution over a 1-hr period proved identical with the hydrochloride of 18 in every respect.

Isoxazoline 18.—A suspension of 800 mg (2.0 mmol) of 4a in 20 ml of methanol and 40 ml of water containing 1.40 g of sodium hydroxide went into solution over a 30-min period at 60° to give an orange solution. The solution was filtered and slowly acidified with 5% HCl, producing an amphoteric, orange, crystalline precipitate. The solid was redissolved with the addition of another 2 ml of 5% HCl and the resulting yellow solution was refrigerated at 5° for 2 hr, during which time 0.84 g (96%) of light yellow crystals of 18, as the hydrochloride salt, separated. This sample initially dissolved readily in 15 ml of methanol, but within 5 min yielded a relatively insoluble yellow crystalline methanol solvate: mp 187–190° dec; uv max (CH_3OH) 261 nm (log ε 4.54), 360 (3.96), 418 (3.76), 480 (4.20); nmr (CD_3OD) δ 2.32 (d, J = 2 Hz, 3), 2.52 (d, J = 1 Hz, 3), 6.82–7.96 (m, 8), 8.30–8.62 (m, 2), 9.22 (d of m, 1), 9.41 (d of m, 1).

Anal. Calcd for $C_{26}H_{21}ClN_2O_3 \cdot CH_3OH$: C, 68.0; H, 5.2; N, 5.9; Cl, 7.5. Found: C, 67.6; H, 5.2; N, 5.8; Cl, 7.7.

Conversion of 18 to 17.—A sample (200 mg) of the above product (18) in 20 ml of 5% methanolic HCl was heated at reflux for 2 hr, cooled, and basified with 5% $NaHCO_3$, yielding an orange, crystalline precipitate. This product, after purification by Florisil chromatography and recrystallization from CH_2Cl_2–ligroin (bp 35°), proved to be identical in every respect with 17.

Conversion of 18 to 6a.—A mixture of 200 mg of 18 in 10 ml of acetic anhydride was refluxed for 2 min, concentrated to a syrup, and then dissolved in 5% $NaHCO_3$. Yellow crystals of 6a (180 mg) immediately separated upon the addition of aqueous $NaClO_4$ solution.

Registry No.—**4a**, 37387-76-1; **4b**, 37413-08-4; **5**, 37413-09-5; **6a**, 37420-75-0; **6b**, 37413-10-8; **7**, 37387-77-2; **8**, 37387-78-3; **9**, 37387-79-4; **10**, 37387-80-7; **11**, 37387-81-8; **12**, 37387-82-9; **13**, 37387-83-0; **14**, 37387-84-1; **16**, 37387-85-2; **17**, 37387-86-3; **18**, 37387-87-4.

Acknowledgment.—We wish to thank Dr. J. C. Chang for supplying the electrochemical data and Mr. Larry Costa for some of the uv data. We are also grateful for their helpful discussions regarding their interpretations of the data.

Lead Tetraacetate and Pyridine. New, Mild Conditions for a Hofmann-Like Rearrangement. A New Synthesis of 2-Oxazolidinones

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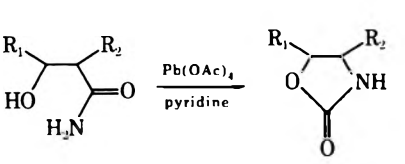
Lead tetraacetate in pyridine has been found to provide a new, mild procedure for effecting a rapid, high-yield, Hofmann-like rearrangement of β-hydroxy primary amides to 2-oxazolidinones. These products in turn give the corresponding β-hydroxy amines so that the reaction can also be used to transform primary amides to amines in high yield.

2-Oxazolidinones have been found useful as drugs and polymer monomers and as such they have attracted considerable attention.[2,3] Not unexpectedly, there are many methods available for their synthesis.[2-4] We would like to report that the reaction of β-hydroxy amides with lead tetraacetate in pyridine constitutes yet another synthetic route to these compounds (eq 1).



(1)

Lead tetraacetate is known to react with primary amides to give isocyanates in a Hofmann-like reaction.[5-7] Typically these reactions are run at 50–60°

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(2) J. W. Cornforth in "Heterocyclic Compounds," Vol. 5, R. C. Elderfield, Ed., Wiley, New York, N. Y., 1957, pp 396–402.

(3) M. E. Dyen and D. Swern, *Chem. Rev.*, **67**, 197 (1967).

(4) J. E. Herweh and W. J. Kauffman, *Tetrahedron Lett.*, 809 (1971).

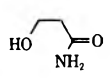
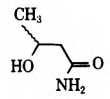
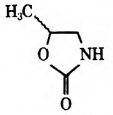
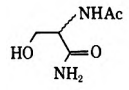
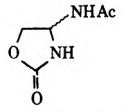
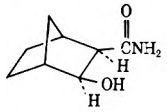
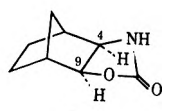
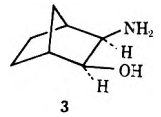
(5) J. B. Aylward, *Quart. Rev., Chem. Soc.*, **25**, 407 (1971).

(6) H. E. Baumgarten and A. Staklis, *J. Amer. Chem. Soc.*, **87**, 1141 (1965).

(7) B. Acott, A. L. J. Beckwith, A. Hassanali, and J. Redmond, *Tetrahedron Lett.*, 4039 (1965); B. Acott, A. L. J. Beckwith, and A. Hassanali, *Aust. J. Chem.*, **21**, 185, 197 (1968).

TABLE I

SYNTHESIS OF 2-OXAZOLIDINONES

Starting material	Product	Registry no.	Yield, %[a]	Mp, °C, of analytical sample[d]
		497-25-6	79	87.2–87.8
		36744-42-0	*b*	*b*
		36744-43-1	73	189.0–189.8
 1	 2	36826-32-1	95[c]	134.8–135.2
	 3	36744-44-2	72 (from 1)	91.0–92.0

[a] Yield after recrystallization or chromatography. [b] A crude yield of ~100% was realized (see footnote 11). The analytically pure product (78%) was obtained after acid–base extractions (see Experimental Section). [c] The ir of the unrecrystallized material was superimposable on the ir of the analytically pure sample. [d] Satisfactory analytical data (±0.29% for C, H, N) were reported for all compounds, Ed.

for 20 min to 2 hr in dimethylformamide,[5] benzene,[6,7] or alcoholic solvent.[7,8] The addition of some pyridine to the reaction was found to increase the rate of product formation.[7] We have found that, when an aliphatic β-hydroxy amide in pyridine is treated with solid lead tetraacetate, a fast (<10 min)[9] reaction occurs at room temperature to give the corresponding 2-oxazolidinone in crude yields of ≥95%.[11] No other organic product was detected by tlc. The yields of recrystallized 2-oxazolidinones (Table I) appear to be as good as or better than those obtained by the existing methods.[3]

The large number of methods available for the preparation of β-hydroxy amides (*e.g.*, *via* the Reformatsky reaction and β-lactones[12]) and their stability compared to some other 2-oxazolidinone precursors (*e.g.*, β-haloamines and isocyanates) are two advantages of this method of preparation. The speed of the reaction and its mild conditions should enable it to be used on β-hydroxy amides containing a wide variety of functional groups. The failure of this reaction with salicyl amide, however, is noteworthy.

From the above results, this procedure also appears to constitute a new, mild Hofmann-like reaction for the conversion of amides to amines with retention of configuration. In a preliminary run, the *cis,exo*-hydroxy amide (**1**) was converted to the *cis,exo*-amino alcohol (**3**) in 72% overall yield. The cis,exo stereochemistry of the amino alcohol **3** was inferred from the known stereochemistry of the hydroxy amide **1** and the observed coupling constant of 7 Hz for the C_4 and C_9 methine hydrogens of the 2-oxazolidinone **2**. This coupling is comparable to the observed $J_{2\text{-endo},3\text{-endo}}$ = 6–7 Hz[13,14] for a series of substituted 2-norbornenols.

While the intermediacy of a nitrene has not been conclusively disproved for the reaction of primary amides with lead tetraacetate, some results indicate that the reaction may proceed *via* a concerted oxidative rearrangement of a tetravalent lead–amide complex.[7] By analogy with the lead tetraacetate reaction of primary amides,[5-7] we assume that the synthesis of 2-oxazolidinones progresses *via* a similar complex and is immediately preceded by the formation of a β-hydroxy isocyanate. The lack of reactivity of two N-substituted hydroxy amides [*N*-(3-hydroxypropyl)benzamide and *N*-methyl-*dl*-3-hydroxybutyramide] in this reaction supports the intermediacy of an isocyanate. Finally, the large rate acceleration of this reaction in pyridine seems to implicate hydrogen abstraction from a tetravalent lead–amide complex as the rate-limiting step. While this oxidative cyclization reaction might provide a route to cyclic carbamates, and possibly cyclic ureas and thiol carbamates, of varying ring size, these possibilities have not been investigated.

(8) In this case the isocyanate was isolated as the carbamate, where the alkoxide of the latter was derived from the solvent alcohol.

(9) When lead tetraacetate[10] is added to dry pyridine in the absence of a β-hydroxy amide, a characteristic dark red color is immediately produced.[10] However, in the reactions described here, this red color does not start to appear, even though a slight excess of the lead tetraacetate is present, until the solution is allowed to stand at room temperature for several hours. Until this point is reached, the reaction solution is a clear yellow. The reactions described in the Experimental Section were shown by tlc to be complete in no more than 10 min. From the nature of the reaction, it would seem that the reaction is over as soon as all the lead tetraacetate has dissolved (~8 min). The dissolution of the solid is thus rate limiting.

(10) R. E. Partch, *Tetrahedron Lett.*, 3071 (1964).

(11) In all the cases examined (three of the four), the ir of the crude product was virtually identical with that of the analytically pure sample.

(12) See W. E. Barnett and J. C. McKenna, *Tetrahedron Lett.*, 2595 (1971), and references cited therein.

(13) J. I. Musher, *Mol. Phys.*, **6**, 93 (1963).

(14) R. R. Fraser and Y. S. Lin, *Can. J. Chem.*, **46**, 801 (1968).

Experimental Section[15]

No attempt has been made to maximize the yields of the reactions reported below.

β-Hydroxypropionamide.—Commercially available, crude β-hydroxypropionamide (K & K) was purified by extracting it with acetonitrile. Evaporation and two recrystallizations of the residue from warm acetonitrile gave reasonably pure material, mp 62.5–63.8° (lit. mp 65–66°). The ir and mass spectral data for this solid confirmed its structure.

2-Oxazolidinone.—About 5% excess of solid lead tetraacetate (3.40 g, 7.66 mmol) was added to a stirred solution of 0.65 g of β-hydroxypropionamide (7.30 mmol) in 36 ml of dry pyridine at room temperature. This addition is moderately exothermic. After the reaction mixture was stirred for approximately 1 hr (~8 min was required for dissolution of the lead tetraacetate), 4 drops of ethylene glycol was added to decompose any excess $Pb(OAc)_4$. The reaction solution was evaporated *in vacuo* and the residue was dissolved in methylene chloride. The precipitated $Pb(OAc)_2$ was filtered and the product was extracted from the filtrate with water. The aqueous solution was evaporated, the residue was dissolved in methylene chloride, the solid was filtered, and the filtrate was evaporated to give 0.88 g of crude 2-oxazolidinone. Chromatography on Florisil with ethyl acetate gave a 79% yield of product. Recrystallization from tetrahydrofuran afforded the analytical sample: mp 87.2–87.8°; ir (Nujol) ν_{NH} 3260, ν_{CO} 1720, 1245, 1080, 1020, 965, 918 cm^{-1}; mass spectrum *m/e* (rel intensity) 87 (100, P^+), 59 (28, P − CO), 42 (15, ketene); nmr (60 MHz, D_2O) δ 4.5 (m, 3 H, C_5 H, NH as HDO), 3.6 (m, 2 H, C_4 H).

***dl*-3-Hydroxybutyramide.**—To 20 ml (300 mmol) of concentrated ammonium hydroxide in ice was added 3.0 g (34.8 mol) of β-butyrolactone (Aldrich), also at 0°. After having warmed up to room temperature, the solution was treated with methanol and evaporated *in vacuo* to give a liquid. This liquid material was crystallized from hot ethyl acetate (with a hot filtration) to afford 2.89 g (80.5%) of needles, mp 82.9–84.0.[16] The ir and mass spectral data for this solid confirmed its structure.

***dl*-5-Methyl-2-oxazolidinone.**—The usual reaction conditions and work-up were employed. The methylene chloride filtrate was washed with a small volume of water and 1 *N* hydrochloric acid. Back-extraction with four portions of methylene chloride, followed by drying the combined organic fractions ($MgSO_4$) and evaporation *in vacuo*, yielded 105% of product, almost pure by tlc and ir. Attempts to obtain the analytical sample *via* chromatography or distillation, bp 82–85° (0.09 mm) [lit.[3] bp 111–113° (1 mm), 89–90° (0.04 mm)], resulted in loss of material and no purification. Simple acid–base extractions were found sufficient to give 78% of an analytically pure sample with some material still remaining in the aqueous layers.

The analytical sample had ir (neat) ν_{NH} 3300, ν_{CO} 1735, 1478, 1235, 1065, 967, and 770 cm^{-1}; mass spectrum *m/e* (rel intensity) 101 (86, P^+), 86 (9, P − CH_3), 73 (11, P − CO), 56 (37), 45 (100).

4-(*N*-Acetylamino)-2-oxazolidinone.[17]—The standard reaction conditions were used. The viscous residue obtained after evaporation of the solvent *in vacuo* was treated with acetone–methanol. The resulting solid was filtered, the filtrate was evaporated *in vacuo*, and the residue was treated with hot acetonitrile. The solid in the cooled solution was removed and the filtrate, after evaporation *in vacuo* and treatment with benzene–dichloromethane, yielded 100% of crude, solid product. After recrystallization from acetonitrile, a 73% yield of product was obtained (mp of first crop 180–181°). Recrystallization from ethanol was required to obtain the analytical sample: mp 189.0–198.8° (decomposition with evolution of gas); ir (Nujol) ν_{NH} 3300, 3110, $\nu_{amide\ I}$ 1730, $\nu_{amide\ II}$ 1655, 1550, 1227, 1135, 1105, 1025, 930, 705 cm^{-1}; mass spectrum *m/e* (rel intensity) 144 (8%, P^+), 114 (8, P − HCHO), 100 (21, P − CO_2), 86 (26), 60 (27), 43 (100).

***exo*-3-Carbamyl-*exo*-2-norborneol (1).**—Crude oxazinone[18] (mp 97–104°, 10.0 g, 35.4 mmol), prepared by the method of Smith, Speziale, and Fedder,[19] was slurried in 35 ml of acetone and added to a stirred solution at room tempersture of 50 ml of 0.5 *N* NaOH and 20 ml of acetone. The pH of the reaction solution was kept basic by the addition of 1 *N* NaOH. At the end of the addition 130 ml of water was added, the pH was adjusted to about 7.5 (total amount of base added was 35.4 mmol), and the solution was stirred for 30 min. The solution was flash evaporated to give a viscous oil, which was dissolved in 100 ml of acetonitrile. A white solid precipitated and was filtered and extracted with three 100-ml portions of acetonitrile. The combined filtrates were flash evaporated to give 4.64 g of product, mp 132.0–132.8°, after recrystallization from 20 ml of acetonitrile. A second crop, mp 129.8–131.5°, raised the yield to 5.07 g (92%). The analytical sample was obtained after a recrystallization from ethyl acetate with a hot filtration: mp 132.9–133.3°; ir (Nujol) $\nu_{NH,OH}$ 3350 and 3220, ν_{CO} 1650 and 1590 cm^{-1}; mass spectrum *m/e* (rel intensity) 155 (1, P^+), 127 (100, P − CO), 88 (63), 85 (90); nmr (100 MHz, DMSO-d_6) δ 7.15 and 6.80 (broad s, 2 H), 4.99 (d, J = 5 Hz, 1 H), 3.82 (d of d, J = 5, J' = 7 Hz, 1 H), 3.4–0.9 (m, 9–10 H).

Anal. Calcd for $C_8H_{13}NO_2$ (mol wt, 155.19): C, 61.91; H, 8.44; N, 9.03. Found: C, 61.84; H, 8.54; N, 9.11.

Norbornyl[2,3-*d*]2-oxazolidinone (2).—The usual reaction procedure and work-up gave a methylene chloride filtrate that was washed with water and 1 *N* HCl, dried over $MgSO_4$, and evaporated *in vacuo* to give a 95% yield of a tlc-pure, white powder, whose ir spectrum was identical with that of the analytical sample. One recrystallization of this powder from benzene gave the analytical sample: mp 134.8–135.2°; ir (Nujol) ν_{NH} 3220, ν_{CO} 1725 cm^{-1}; nmr (60 MHz, $CDCl_3$) δ 6.63 (broad s, 1 H, NH), 4.42 (d, J = 7 Hz, 1 H, C_9 H), 3.60 (d, J = 7 Hz, 1 H, C_4 H), 2.38 (broad s, 1 H, C_8 H), 2.17 (broad s, 1 H, C_5 H), 1.9–0.9 (m, 6 H); mass spectrum *m/e* (rel intensity) 153 (73, P^+), 87 (77), 67 (100).

***exo*-3-Amino-*exo*-2-norborneol (3).**—To 0.326 g (2.13 mmol) of crude, unrecrystallized norbornyl[2,3-*d*]2-oxazolidinone was added a solution of 0.34 g (8.51 mmol) of sodium hydroxide in 2.29 ml of water and 4.58 ml of absolute ethanol.[20] After 5 hr of refluxing, the reaction mixture was evaporated *in vacuo* and the residue was partitioned in methylene chloride–water. After two further extractions with methylene chloride, drying ($MgSO_4$), and evaporation *in vacuo*, 0.28 g (103%) of a white powder was obtained. Recrystallization from *n*-hexane gave, in two crops, 0.235 g (87% yield) of the amino alcohol, mp 90.0–90.8°. One final recrystallization from *n*-hexane gave the analytical sample: mp 91.0–92.0°; ir (Nujol) $\nu_{NH_2,OH}$ 3330, 3080, 2750 (broad), 1570, 1080, 813 cm^{-1}; mass spectrum *m/e* (rel intensity) 127 (51, P^+), 98 (82), 70 (59), 56 (100), 43 (67).

Registry No.—1, 36744-45-3; lead tetraacetate, 546-67-8; pyridine, 110-86-1.

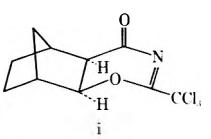
Acknowledgments.—The author wishes to thank Professor F. H. Westheimer for his help and encouragement, Professor James D. White and Dr. John M. McCall for their helpful discussions, Dr. James K. Whitesell for obtaining the 100-MHz nmr spectra, and Dennis K. Rohrbaugh for running all the mass spectra. He also wishes to acknowledge with gratitude Grant No. 30965X from the National Science Foundation to Professor F. H. Westheimer that made this work possible.

(15) Melting points were determined on a Thomas-Hoover capillary melting point apparatus and were not corrected. A Perkin-Elmer infrared spectrophotometer Model 137 was used to obtain the ir spectra. Nmr spectra were run using Varian T-60 and HA-100 spectrometers. Mass spectra were determined on an AEI MS-9 mass spectrometer. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn., and Scandinavian Microanalytical Laboratory, Denmark.

(16) The melting point given in "Dictionary of Organic Compounds," 4th ed, Oxford University Press, New York, N. Y., 1965, is 84–87°.

(17) The starting *N*-acetyl-*dl*-serine amide was obtained from Cyclo Chemical and used without further purification.

(18) The oxazinone i was always contaminated by varying amounts of



i

the amide trichloroacetate[19] resulting from the addition of 1 equiv of water. This material, however, does not complicate the reaction.

(19) L. R. Smith, A. J. Speziale, and J. E. Fedder, *J. Org. Chem.*, **34**, 633 (1969).

(20) C. D. Lunsford, R. P. Mays, J. A. Richman, Jr., and R. S. Murphy, *J. Amer. Chem. Soc.*, **82**, 1166 (1960).

The Course of the Alkyl Nitrate Nitration with Isopropylpyridines. Formation of 2,3-Bis(pyridyl)-2,3-dimethylbutanes[1]

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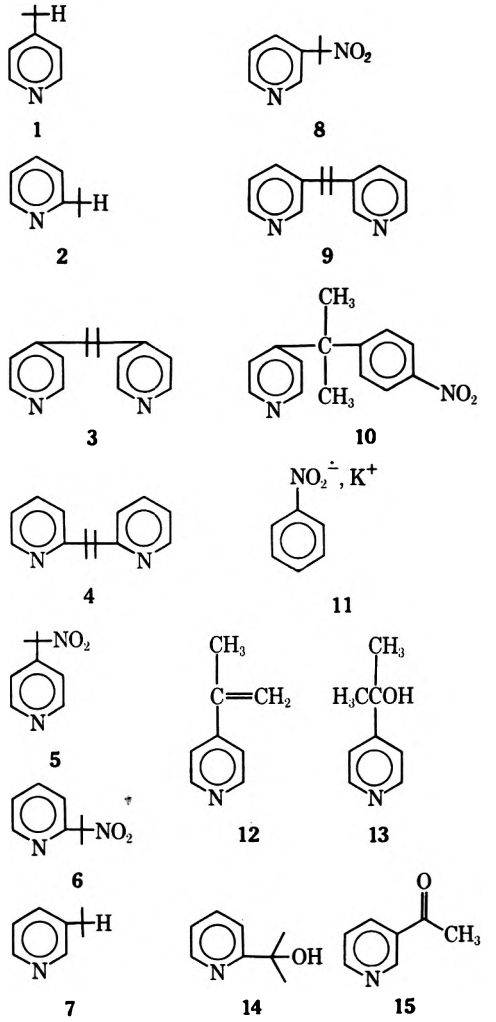
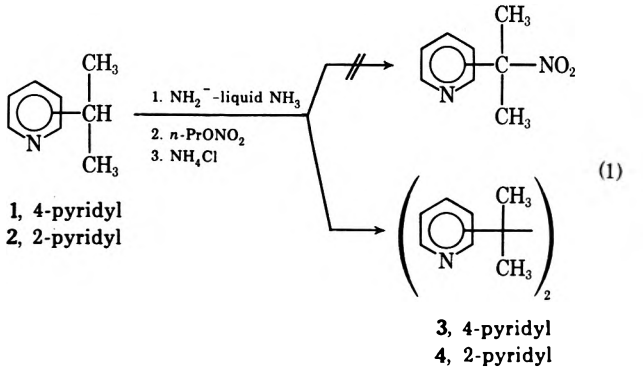
Received July 31, 1972

The alkyl nitrate nitration of 4-isopropylpyridine (1) and 2-isopropylpyridine (2) does not afford the tertiary 2-nitro-2-(4-pyridyl)propane (5) and 2-nitro-2-(2-pyridyl)propane (6) but instead leads to dimers, 2,3-bis(4-pyridyl)-2,3-dimethylbutane (3) and 2,3-bis(2-pyridyl)-2,3-dimethylbutane (4), respectively. On the other hand, 3-isopropylpyridine (7) is recovered unchanged. The tertiary nitro compounds 5, 6, and 2-nitro-2-(3-pyridyl)propane (8) prepared by an alternate route are converted, respectively, to dimers 3, 4, and 2,3-bis(3-pyridyl)-2,3-dimethylbutane (9) under the conditions of the alkyl nitration. Compounds 5 and 6 are considered intermediates in the dimerization reactions which very likely proceed by an electron-transfer process. The intermediacy of the nitro compounds is established by the fact that both 5 and dimer 3 are obtained when the anion of 1 is added to the nitrate ester in liquid ammonia (inverse addition).

Recently, we reported on the successful application of the alkyl nitrate nitration to the preparation of primary and secondary α-nitroalkyl heterocyclic compounds.[1] We are now reporting the results of the reaction with tertiary alkyl heterocyclics, which were found to take a different course.

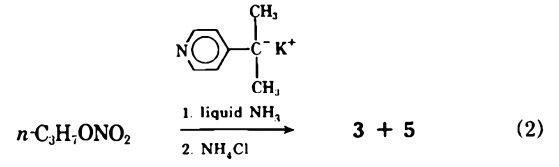


When 4-isopropylpyridine (1) was subjected to the alkyl nitrate nitration under the standard conditions (*vide infra*, Experimental Section) in the sodium amide–liquid ammonia system (A) or in the potassium amide–liquid ammonia system (B), 2,3-bis(4-pyridyl)-2,3-dimethylbutane (3) was obtained in 88% yield, instead of the expected tertiary nitro compound 2-nitro-2-(4-pyridyl)propane (5) (eq 1). Similarly, 2-isopropylpyridine (2) was converted to 2,3-bis(2-pyridyl)-2,3-dimethylbutane (4) in 90% yield in system B when the nitration time was 60 min. After the usual nitration time of 15 min, the yield was only 42%, and 47% of 2 was recovered. When the reaction was carried out in system A, no dimer was formed and compound 2 was recovered unchanged. Apparently, in sodium amide, compound 2 was converted to its anion at a much slower rate than the 4 isomer 1. Similar results have been observed in alkylations of these compounds.[2]



(1)

In a control test, it was established that the alkyl nitrate[3] was necessary for the dimerization to occur. Moreover, good evidence was obtained that the tertiary nitro compounds 2-nitro-2-(4-pyridyl)propane (5) and 2-nitro-2-(2-pyridyl)propane (6) were very likely intermediates in the formation of the dimers 3 and 4. For example, both 5 and 3 were obtained in yields of 60 and 32%, respectively, when, in an inverse addition, the anion of 1, generated in system B, was added to *n*-propyl nitrate in liquid ammonia (eq 2). In



(2)

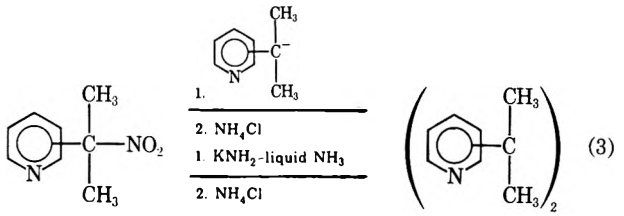
system B the tertiary nitro compounds 5 and 6 (*vide infra* for their preparation) were converted in yields

(1) Alkyl Nitrate Nitration of Active Methylene Compounds. X. For paper IX see H. Feuer and J. P. Lawrence, *J. Org. Chem.*, **37**, 3662 (1972).

(2) H. C. Brown and W. A. Murphy, *J. Amer. Chem. Soc.*, **73**, 3308 (1951).

(3) Dimer 3 was obtained in 50% yield when instead of *n*-propyl nitrate an alkyl nitrite, isoamyl nitrite, was employed.

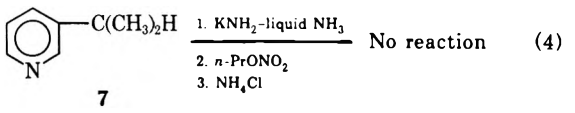
of 70% to dimers **3** and **4**, respectively (eq 3). Also, these dimers were formed when **5** and **6**, respectively, were added to equimolar amounts of the carbanions of **1** and **2**, generated in system A and B (eq 3).



5, 4-pyridyl
6, 2-pyridyl
7, 3-pyridyl

3, 4-pyridyl
4, 2-pyridyl
9, 3-pyridyl

The intermediacy of the tertiary nitroisopropylpyridines in the dimerization reaction was firmly established in experiments with 3-isopropylpyridine (**7**), which was recovered unchanged when subjected to the alkyl nitrate nitration in system B. No trace of the expected dimer or nitro compound was obtained (eq 4). The failure of **7** to undergo dimerization or



7

nitration cannot be attributed to lack of carbanion formation, for it has been shown to alkylate in system B to give 3-*tert*-butylpyridine.[2,4] Deuterium exchange reactions (see Experimental Section) have shown that **1**, **2**, and **7** incorporated 65, 9, and 4% deuterium, respectively. However, as indicated, **2** gave dimer **4** in 90% yield when the nitration time was extended from 15 to 60 min. On the other hand, no reaction occurred when **7** was subjected to a nitration time of 2 hr or when the nitrate ester was added slowly (4 hr). *n*-Propyl nitrate and **7** were recovered to the extent of 20 and 90%, respectively.

On the other hand, the reaction of 2-nitro-2-(3-pyridyl)propane (**8**), which was prepared by an alternate route (*vide infra*), with the carbanion of **7** generated in system B gave the dimer 2,3-bis(3-pyridyl)-2,3-dimethylbutane (**9**) in 84% yield (eq 3). Also **8** underwent dimerization directly in system B to give **9** in nearly quantitative yield (eq 3).

The structures of dimers **3**, **4**, and **9** were established by their infrared and nmr spectra, and also by their conversion to the corresponding dipicrates.

Discussion

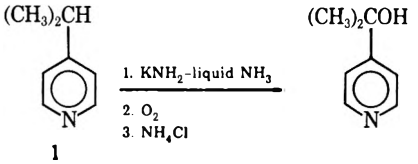
Regarding the formation of dimers **3**, **4**, and **9**, steric considerations would seem to eliminate the possibility of a direct displacement of the tertiary nitro group in **5**, **6**, and **8** by the tertiary carbanion of **1**, **2**, and **7**. It is proposed that these dimerizations occur by electron-transfer processes related to reactions reported by Kornblum in which the tertiary nitro group of α,p-dinitrocumene was readily replaced by a variety of anions.[5]

(4) Similarly, 3-methylpyridine does not undergo the alkyl nitrate nitration in systems A or B.[1]

(5) N. Kornblum, T. M. Davies, G. W. Earl, G. S. Greene, N. L. Holy, R. C. Kerber, J. W. Manthey, M. T. Musser, and D. H. Snow, *J. Amer. Chem. Soc.*, **89**, 5714 (1967).

Evidence that isopropylpyridines can participate in electron-transfer processes in the amide–liquid ammonia system was obtained in two experiments.

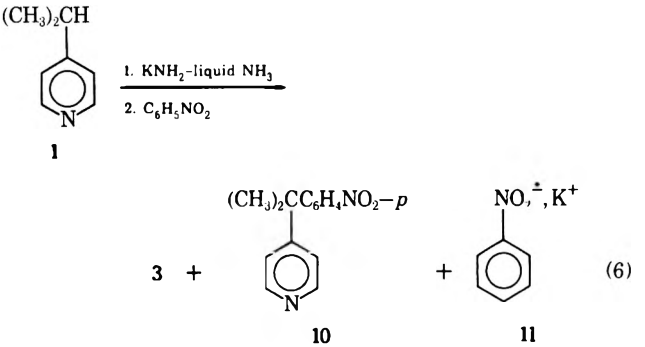
In system B, **1** was converted in the presence of oxygen to 2-(4-pyridyl)-2-propanol in 73% yield (eq 5).



1

A study of the oxygenation of carbanions has shown that the reaction involves a radical–radical anion mechanism, and Russell has reported that *p*-nitrocumene was converted to *p*-nitrocumyl alcohol in the presence of base and oxygen.[6]

The reaction of **1** with nitrobenzene in system B gave 53% of dimer **3** and 10% of 2-(4-nitrophenyl)-2-(4-pyridyl)propane[7] (**10**) (eq 6). There was also



1 **10** **11**

obtained a red-brown solid believed to be potassium nitrobenzenide[8] (**11**). On addition of water, it decomposed to nitrobenzene. Russell has discussed many examples of electron-transfer processes.[9] The formations of **3**, **10**, and **11** in liquid ammonia are also believed to be initiated by a one-electron transfer between the carbanion of **1** and the electron acceptor nitrobenzene.

By using the formation of dimer **3** as an example, the essential steps leading to dimerization are presented in Scheme I. The reaction is initiated by an electron transfer from the anion **1a** of **1** to compound **5** to form the radical anion A and isopropylpyridine radical B. A then collapses into nitrite ion and radical B (step 2), which then couples with **1a** to generate the radical anion C of dimer **3** (step 3). In the final step, the radical chain[10] is propagated by transfer of the odd electron from C to compound **5**, thereby forming **3** and regenerating A.[11]

The proposed scheme indicates that in the alkyl nitration of isopropylpyridines 0.5 equiv of the alkyl nitrate should be sufficient to obtain optimum yields

(6) G. A. Russell, E. H. Janzen, A. G. Bemis, E. J. Geels, A. J. Moye, S. Mak, and T. Strom, "Selective Oxidation Processes," Advances in Chemistry Series, No. 51, American Chemical Society, Washington, D. C., 1965, Chapter 10.

(7) The scope of this reaction is being investigated.

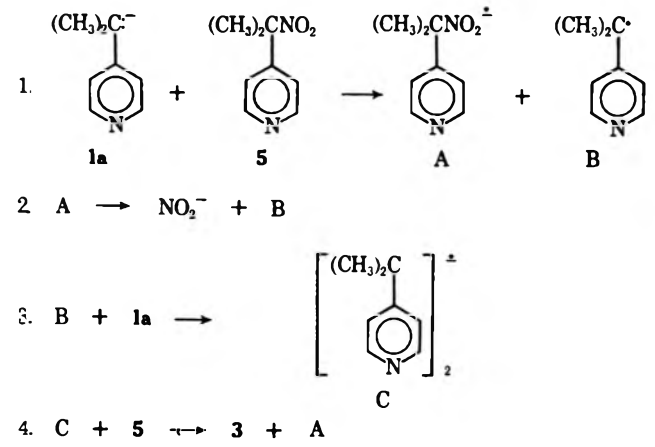
(8) G. A. Russell and A. G. Bemis, *Inorg. Chem.*, **6**, 403 (1967).

(9) G. A. Russell, E. G. Janzen, and E. T. Strom, *J. Amer. Chem. Soc.*, **86**, 1807 (1964).

(10) It is realized that dimer **3** could also form by the combination of radicals B. However, this process would be less favorable in the highly diluted solution in which the experiments were performed.

(11) A referee has pointed out that dimerization could occur by an anionic mechanism involving a front-side, four-centered mechanism; *e.g.*, attack of **1a** on **5** would give **3**.

Scheme I



of dimer, and also that acidification is unnecessary. The data presented in Table I bear this out.

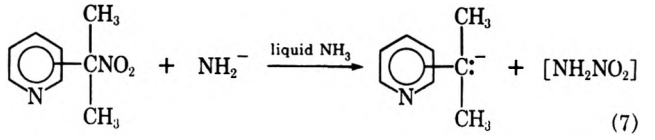
Table I

Alkyl Nitrate Nitration of 4-Isopropylpyridine[a] (1)

KNH_2, M	n-$PrONO_2$, M	NH_4Cl, M	Dimer 3, yield, %	Recovered 1, yield, %
2.0	2.5	2.0	71	
1.0	1.0	1.0	88	6
1.0	1.0		83	6
1.0	0.5		81	11

[a] In all experiments, 1 mol of 1 was used. The time for anion formation was 15 min and the total nitration time was 15 min.

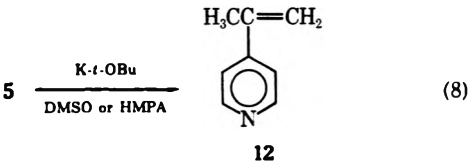
The direct formation of dimers from *tert*-nitroisopropylpyridines on treatment with amide in liquid ammonia requires an additional explanation. It is believed that the isopropylpyridine anion (the electron donor) is generated by displacement of the nitro group by amide ion (eq 7). An excess of base had to



(7)

be used to obtain maximum yields of dimer. For example, in the reaction of equimolar amounts of **5** and sodium amide, there was isolated in addition to 33% of dimer **3** and 42% of recovered **5**, **1** in 12% yield. Apparently, the carbanion of **1** was protonated at some stage of the reaction (perhaps by the nitramide) and the excess base is necessary to regenerate the carbanion.

It should be pointed out that the base–solvent system is rather critical for the success of the dimerization. The reaction of **5** with potassium methoxide in methanol at reflux temperature led only to recovered starting material. A reaction did occur when **5** was treated with potassium methoxide in DMSO at 75° and at ambient temperatures with potassium *tert*-butoxide in DMSO or HMPA. However, the product of these reactions was not the dimer **3** but the olefin 4-isopropenylpyridine (**12**) arising from the loss of nitrous acid (eq 8).



(8)

12

Synthesis of Nitroisopropylpyridines.—The synthesis of the nitroisopropylpyridines **5**, **6**, and **8** was achieved by direct nitration of the respective isopropylpyridines with 90% nitric acid. The results of various reaction conditions are presented in Table II. The data indicate that highest yields were obtained when reactions were carried out for 24 hr in sealed tubes at 100°. Under these reaction conditions there were also formed the tertiary alcohols 2-(4-pyridyl)-2-propanol (**13**) and 2-(2-pyridyl)-2-propanol (**14**) from the nitration of **1** and **2**, respectively, and 3-acetylpyridine (**15**) from the nitration of **7**. It is obvious that reactions should be carried out in an autoclave. However, only a Hastelloy steel autoclave was available (composition, 60% Ni, 20% Fe, and 20% Mo) which was attacked by the nitric acid. Large amounts of nickel hydroxide were formed and the material balance was low owing to considerable decomposition of the starting material (see Table II).

Table II

Nitration of Isopropylpyridines with 90% Nitric Acid[a]

Reaction conditions: Time, hr	Reaction conditions: Temp, °C	Nitro compounds, yield, %: 5	6	8	Tertiary alcohols, yield, %: 13	14	Ketone, yield, % 15
		Ambient Pressure					
26	100	56			2		
96	100		14			8	
48	100			15			17
		Sealed Tube					
24	100	70	55	35	5	30	31
24	75	32[b]	*c*		16		
24	50			*d*			
		Autoclave[e]					
24	100	58	17		7	12	

[a] The mole ratio of isopropylpyridine to nitric acid was 1:9. [b] About 42% of **1** was recovered. [c] No reaction occurred and 90% of **2** was recovered. [d] No reaction occurred and 98% of **7** was recovered. [e] Substantial amounts of $Ni(OH)_2$ were present. The material balance was low owing to considerable decomposition of the starting materials.

The structures of the nitroisopropylpyridines were established by their nmr spectra and also by their conversion into the respective picrates.

Experimental Section

Equipment.—All infrared spectra were taken with a Perkin-Elmer recording spectrophotometer, Models 21 and 421. Nuclear magnetic resonance spectra were determined on a Varian Model A-60 analytical nmr spectrometer using tetramethylsilane as an internal standard. Gas chromatographic analyses were performed on an Aerograph A-90S using either SF-96, SE-30, or DC-200 on Chromosorb P or Chromosorb W 4-ft columns. Solvents were evaporated on a Buchler flash evaporator.

Apparatus.—Reactions were performed in an oven-dried 500-ml four-necked flask equipped with a mechanical stirrer, Dry Ice condenser, thermometer, and pressure-equalizing addition funnel.

Materials.—*n*-Propyl nitrate of Eastman White Label grade, and nitric acid (90%), Baker Analyzed, were used as received. 4-Isopropylpyridine from Reilly Tar and Chemical Co. was dis-

tilled before use. 2- and 3-isopropylpyridines were prepared by the method of Brown and Murphy.[2]

2,3-Bis(4-pyridyl)-2,3-dimethylbutane (3). A. From 4-Isopropylpyridine (1).—To a freshly prepared solution of sodium amide (0.10 mol) in 300 ml of liquid ammonia was added 4-isopropylpyridine (12.0 g, 0.1 mol) at −35°. After the solution was stirred for 10 min, *n*-propyl nitrate (10.7 g, 0.10 mol) was added as rapidly as possible while the temperature was kept below −33°.[12] The mixture was then cooled to −50° and acidified with ammonium chloride (5.5 g, 0.11 mol), the ammonia was gradually replaced with absolute ether, and the reaction mixture was filtered after attaining room temperature (3–4 hr). The solid was stirred in 100 ml of methylene chloride and filtered. The combined ethereal and methylene chloride filtrates were concentrated *in vacuo* and the residue was recrystallized from 95% ethanol to give 10.5 g (88%) of 2,3-bis(4-pyridyl)-2,3-dimethylbutane (3): mp 205°; ir (KBr) 1600 cm^{-1} (C=N); nmr ($CDCl_3$) δ 8.5 (m, 4, N=CH), 7.0 (m, 4, N=CHCH), and 1.4 (s, 12, CH_3).

Anal. Calcd for $C_{16}H_{20}N_2$: C, 79.95; H, 8.39; N, 11.66. Found: C, 79.85; H, 8.32; N, 11.52.

The combined alcohol filtrates were concentrated *in vacuo* to give 0.77 g (6%) of 1. Its glpc retention time was identical with that of an authentic sample.

2,3-Bis(4-pyridyl)-2,3-dimethylbutane dipicrate was prepared in the usual manner,[13] mp 269° dec (95% EtOH).

Anal. Calcd for $C_{28}H_{26}N_8O_{14}$: C, 48.14; H, 3.72; N, 16.05. Found: C, 48.24; H, 3.95; N, 15.98.

B. From Compound 1 and 2-Nitro-2-(4-pyridyl)propane (5).—To a freshly prepared solution of sodium amide (0.057 mol) in 300 ml of liquid ammonia was added compound 1 (2.7 g, 0.023 mol). After the solution was stirred for 10 min at −33°, 2-nitro-2-(4-pyridyl)propane (5) (3.8 g, 0.023 mol) was added while the temperature was kept below −33°. Work-up of the reaction mixture as described in A except that 3.6 g (0.068 mol) of ammonium chloride was used gave 5.4 g (100%) of dimer 3, mp 205° (95% EtOH). A mixture melting point determination with a sample prepared in A gave no depression.

C. From Compound 5 and Sodium Amide.—To a freshly prepared solution of sodium amide (0.065 mol) in 40 ml of liquid ammonia was added 5 (4.3 g, 0.026 mol) while the temperature was kept below −33°. The solution was stirred for 15 min, cooled to −45°, acidified with ammonium chloride (4.2 g, 0.078 mol), and worked up as described in A to yield 4.5 g (73%) of dimer 3, mp 204° (95% EtOH).

2,3-Bis(2-pyridyl)-2,3-dimethylbutane (4). A. From 2-Isopropylpyridine (2).—The experimental procedure was similar to that described for the preparation of 3 from compound 1, except that potassium amide (0.102 mol), 2-isopropylpyridine (2) (6.2 g, 0.051 mol), propyl nitrate (13.1 g, 0.128 mol), and ammonium chloride (6.0 g, 0.17 mol) were employed: and that after addition of the nitrate the reaction was continued for 60 min prior to acidification.

Recrystallization from hexane afforded 5.5 g (90%) of 2,3-bis(2-pyridyl)-2,3-dimethylbutane[14] (4): mp 121°; ir (KBr) 1587 cm^{-1} (C=N); nmr ($CDCl_3$) δ 8.4 (m, 2, N=CH), 6.3–7.4 (m, 6, N=CCH=CHCH), and 1.4 (s, 12, CH_3).

Anal. Calcd for $C_{16}H_{20}N_2$: C, 79.95; H, 8.39; N, 11.66. Found: C, 79.69; H, 8.52; N, 11.80.

The combined hexane filtrates were concentrated *in vacuo* to give 0.2 g (2%) of 2. Its glpc retention time was identical with that of an authentic sample.

2,3-Bis(2-pyridyl)-2,3-dimethylbutane dipicrate was prepared in the usual manner,[13] mp 228° dec (95% EtOH).

Anal. Calcd for $C_{28}H_{26}N_8O_{14}$: C, 48.14; H, 3.72; N, 16.05. Found: C, 48.32; H, 3.56; N, 16.05.

B. From Compound 2 and 2-Nitro-2-(2-pyridyl)propane (6).—The experimental procedure was similar to that described for the preparation of 3 from compounds 1 and 5 except that potassium amide (0.057 mol), 2-isopropylpyridine (2.3 g, 0.023 mol), 2-nitro-2-(2-pyridyl)propane (3.8 g, 0.023 mol), and ammonium chloride (3.6 g, 0.068 mol) were employed and that after addition of the nitrate the reaction was continued for 60 min prior to acidification.

Recrystallization from hexane afforded 5.2 g (95%) of dimer 4, mp 120–121°. A mixture melting point determination with an authentic sample gave no depression.

C. From Compound 6 and Potassium Amide.—The experimental procedure was similar to that described for the preparation of 3 from compound 5 and sodium amide, except that 0.026 mol of potassium amide in 50 ml of liquid ammonia, 2.1 g (0.012 mol) of 2-nitro-2-(2-pyridyl)propane (6), and 1.9 g (0.035 mol) of ammonium chloride were employed and that after addition of the nitrate the reaction was continued for 60 min prior to acidification.

Recrystallization from hexane afforded 1.05 g (70%) of dimer 4, mp 121°.

2,3-Bis(3-pyridyl)-2,3-dimethylbutane (9). A. From 3-Isopropylpyridine (7) and 2-Nitro-2-(3-pyridyl)propane (8).—The experimental procedure was similar to that described for the preparation of dimer 4 from compounds 2 and 6 except that potassium amide (0.02 mol) in 50 ml of liquid ammonia, 3-isopropylpyridine (7) (1.21 g, 0.01 mol), and 2-nitro-2-(3-pyridyl)propane (8) (1.66 g, 0.01 mol) were used.

There was obtained 2.1 g (84%) of 2,3-bis(3-pyridyl)-2,3-dimethylbutane (9): mp 168° (C_6H_{14}); ir (KBr) 1585 cm^{-1} (C=N); nmr ($CDCl_3$) δ 1.38 (s, 12, CH_3), 7.2 (m, 4, aromatic H), and 8.4 (m, 4, aromatic H).

Anal. Calcd for $C_{16}H_{20}N_2$: C, 79.95; H, 8.38; N, 11.66. Found: C, 79.75; H, 8.39; N, 11.71.

2,3-Bis(3-pyridyl)-2,3-dimethylbutane dipicrate was prepared in the usual manner,[13] mp 260° dec (95% EtOH).

Anal. Calcd for $C_{28}H_{26}N_8O_{14}$: C, 48.14; H, 3.72; N, 16.05. Found: C, 47.93; H, 3.92; N, 16.33.

B. From Compound 8 and Potassium Amide.—The experimental procedure was similar to that described for the preparation of 3 from 5 and sodium amide. From 0.026 mol of potassium amide in 50 ml of liquid ammonia, 1.84 g (0.011 mol) of 2-nitro-2-(3-pyridyl)propane (8) and 1.6 g (0.03 mol) of ammonium chloride there was obtained 1.3 g (94%) of dimer 9, mp 168°. A mixture melting point determination with an authentic sample gave no depression.

Inverse Addition of 4-Isopropylpyridine Anion to *n*-Propyl Nitrate.—To a freshly prepared solution of potassium amide (0.05 mol) in 150 ml of liquid ammonia was added compound 1 (6.05 g, 0.05 mol) at −35°. After 15 min, the anion of 1 was added dropwise to a solution of *n*-propyl nitrate in 100 ml of ammonia at −40°. The reaction mixture was then stirred for 1 hr and acidified with ammonium chloride (2.65 g, 0.05 mol), and the ammonia was replaced by ether. Evaporation of the filtrate *in vacuo* left a suspension which was filtered to give 2.0 g (32%) of dimer 3, mp 204° (C_6H_{14}). The filtrate was distilled to yield 5.0 g (60%) of 2-nitro-2-(4-pyridyl)propane (5): bp 70° (0.07 mm); $n^{20}D$ 1.5231; ir (neat) 1550 cm^{-1} (NO_2). An authentic sample (*vide infra*) had the same physical constants.

Oxidation of 4-Isopropylpyridine (1) in Liquid Ammonia.—To a freshly prepared solution of potassium amide (0.06 mol) in 200 ml of liquid ammonia was added compound 1 (7.2 g, 0.059 mol) at −35°. After 15 min of anion formation, oxygen was introduced into the ammonia solution for a period of 1 hr. The solution was cooled to −50° and acidified with ammonium chloride (3.2 g, 0.06 mol), the ammonia was replaced by ether, and the reaction mixture was filtered after room temperature was attained. The ether filtrate was concentrated *in vacuo* to yield 5.9 g (73%) of 2-(4-pyridyl)-2-propanol (13), mp 131° (C_6H_{14}) (lit.[15] mp 132°). A mixture melting point with an authentic sample (*vide infra*) gave no depression.

Reaction of 4-Isopropylpyridine (1) with Nitrobenzene.—To a freshly prepared solution of potassium amide (0.05 mol) in 150 ml of liquid ammonia was added compound 1 (3.02 g, 0.025 mol). The solution was stirred for 15 min at −35°, and then nitrobenzene (3.1 g, 0.025 mol) was added. The reaction mixture was stirred for 8 hr at −35° and acidified with ammonium chloride (2.65 g, 0.05 mol), the ammonia was replaced by ether (3–4 hr), and the reaction mixture was filtered after room temperature was attained. The ethereal filtrate was extracted with 3 *N* HCl, basified with 3 *N* sodium hydroxide, and again extracted with ether. The combined ethereal extracts were dried ($MgSO_4$) and concentrated *in vacuo* to yield 3.0 g of material. Column chromatography on neutral alumina yielded three components. Fraction I (hexane) was 0.5 g (8%) of 4-isopropylpyridine (1). Fraction II (hexane–ether, 1:1) was

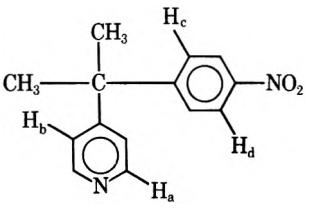
(12) *Caution!* The first few drops of alkyl nitrate should be added slowly because a considerable exotherm might develop.

(13) R. Shriner, R. Fuson, and D. Curtin, "The Systematic Identification of Organic Compounds," 4th ed, Wiley, New York, N. Y., 1957, p 229.

(14) G. Fraenkel and J. W. Cooper, *J. Amer. Chem. Soc.*, **93**, 7228 (1971), report mp 91° for this compound.

(15) C. R. Clemo and E. Hoggarth, *J. Chem. Soc.*, 41 (1941).

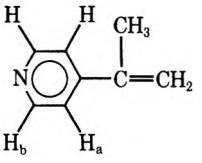
0.6 g (10%) of 2-(*p*-nitrophenyl)-2-(4-pyridyl)propane (**10**): mp 79–80° (C_6H_{14}); ir (KBr) 1595 (C=N), 1508 (NO_2), and 1340 cm^{-1} (NO_2); nmr ($CDCl_3$) δ 1.70 (s, 6, CH_3), 7.1 (m, 2, H_b), 7.3 (m, 2, H_c), 8.1 (m, 2, H_d), and 8.6 (m, 2, H_a).



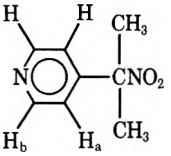
Anal. Calcd for $C_{14}H_{14}N_2O_2$: C, 69.42; H, 5.83; N, 11.57. Found: C, 69.16; H, 5.56; N, 11.73.

Fraction III (ether–acetone, 1:1) was 1.6 g (53%) of dimer **3**, mp 205°.

Reaction of 2-Nitro-2-(4-pyridyl)propane (5) with Potassium *tert*-Butoxide in DMSO.—To a dry 100-ml round-bottom flask flushed with nitrogen was added potassium *tert*-butoxide (2.8 g, 0.025 mol) and 50 ml of dry DMSO. The solution was degassed for 15 min and compound **5** (3.8 g, 0.0228 mol) was added by weight difference from a 5-ml syringe. After 4 hr at room temperature the reaction mixture was poured into water, extracted with 2 × 50 ml of ethyl ether, dried ($MgSO_4$), and concentrated *in vacuo* to yield 2.7 g (100%) of 4-isopropenylpyridine (**12**): $n^{20}D$ 1.5422; nmr ($CDCl_3$) δ 2.0 (s, 3, CH_3), 5.14 (s, 1, $=CH_2$), 5.50 (s, 1, $=CH_2$), 7.2 (m, 2, H_a), and 8.4 (m, 2, H_b).



2-Nitro-2-(4-pyridyl)propane (5).—The following experiment is typical of the procedure employed for the nitration of isopropylpyridines. 4-Isopropylpyridine (**1**) (12.0 g, 0.1 mol) and 90% nitric acid (35 ml) were heated at 100° in a sealed tube for 24 hr.[16] The solution was poured into 250 ml of water, basified with sodium hydroxide pellets, and extracted with ether. The combined ethereal extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Distillation of the residue and further purification of the distillate by chromatographing on alumina with ether as the eluent gave 11.6 g (70%) of 2-nitro-2-(4-pyridyl)propane (**5**): bp 70° (0.07 mm); $n^{20}D$ 1.5213; ir (neat) 1550 cm^{-1} (NO_2); nmr (CCl_4) δ 1.9 (s, 6, CH_3), 7.2 (m, 2, H_a), and 8.5 (m, 2, H_b).

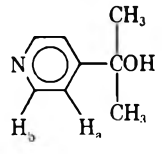


Anal. Calcd for $C_8H_{10}N_2O_2$: C, 57.83; H, 6.02; N, 16.87. Found: C, 58.04; H, 6.30; N, 17.16.

2-Nitro-2-(4-pyridyl)propane picrate was prepared in the usual manner,[13] mp 145–146° dec (95% EtOH).

Anal. Calcd for $C_{14}H_{13}N_5O_9$: C, 42.53; H, 3.29; N, 17.72. Found: C, 42.69; H, 3.51; N, 17.51.

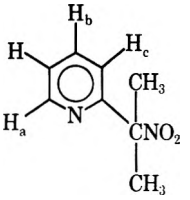
The aqueous solution was extracted with chloroform and dried ($MgSO_4$), and the combined extracts were concentrated *in vacuo* to give 0.7 g (5%) of 2-(4-pyridyl)-2-propanol (**13**): mp 130° (CCl_4) (lit.[15] mp 132°); nmr ($CDCl_3$) δ 1.6 (s, 6, CH_3), 4.8 (s, 1, OH), 7.4 (m, 2, H_a), and 8.4 (m, 2, H_b).



(16) *Caution!* The sealed tubes should be handled very carefully because of danger of explosion. Prior to opening, they should be cooled in liquid nitrogen.

Reactions which were carried out at ambient pressures in refluxing nitric acid were worked up by a similar procedure.

2-Nitro-2-(2-pyridyl)propane (6).—2-Isopropylpyridine (**2**) (12.1 g, 0.1 mol) gave 4.2 g (30%) of 2-(2-pyridyl)-2-propanol (**14**), bp 39–40° (0.04 mm), mp 49–50° (CCl_4) (lit.[17] mp 50–51°), and 9.2 g (55%) of 2-nitro-2-(2-pyridyl)propane (**6**): bp 54–55° (0.04 mm); $n^{20}D$ 1.5163; ir (neat) 1555 cm^{-1} (NO_2); nmr (CCl_4) δ 1.9 (s, 6, CH_3) 7.0–7.8 (m, 3, H_b + H_c), and 8.3–8.5 (m, 1, H_a).

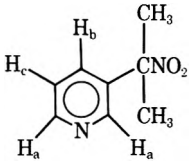


Anal. Calcd for $C_8H_{10}N_2O_2$: C, 57.83; H, 6.02; N, 16.87. Found: C, 57.70; H, 6.32; N, 17.16.

2-Nitro-2-(2-pyridyl)propane picrate was prepared in the usual manner,[13] mp 96–97° dec (95% EtOH).

Anal. Calcd for $C_{14}H_{13}N_5O_9$: C, 42.53; H, 3.29; N, 17.72. Found: C, 42.67; H, 3.57; N, 17.79.

2-Nitro-2-(3-pyridyl)propane (8).—The experimental procedure was similar to that described for the preparation of **5** except that 3-isopropylpyridine (**7**) (6.05 g, 0.05 mol) was used. After the ethereal extract was concentrated *in vacuo*, the residue was chromatographed on alumina. Elution with a 1:1 mixture of ether–hexane gave 2.8 g (35%) of 2-nitro-2-(3-pyridyl)propane (**8**): bp 89–90° (0.4 mm); $n^{20}D$ 1.5217; ir (neat) 1540 cm^{-1} (NO_2); nmr ($CDCl_3$) δ 2.0 (s, 6, CH_3), 7.2 (m, 1, H_c), 7.8 (m, 1, H_b), and 8.6 (m, 2, H_a).

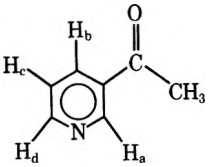


Anal. Calcd for $C_8H_{10}N_2O_2$: C, 57.83; H, 6.02; N, 16.87. Found: C, 57.90; H, 6.00; N, 16.91.

2-Nitro-2-(3-pyridyl)propane picrate was prepared in the usual manner,[13] mp 149–150° dec (95% EtOH).

Anal. Calcd for $C_{14}H_{13}N_5O_9$: C, 42.53; H, 3.29; N, 17.22. Found: C, 42.35; H, 3.46; N, 17.99.

Further elution of the column with ethyl ether gave 1.8 g (30%) of 3-acetylpyridine (**15**): nmr ($CDCl_3$) δ 2.64 (s, 3, CH_3), 7.3 (m, 1, H_c), 8.2 (m, 1, H_b), 8.7 (m, 1, H_d), and 9.1 (m, 1, H_a).



The nmr spectrum and glpc retention time were identical with those of an authentic sample.[18]

Deuteration of Isopropylpyridines.—The following experiment is typical of the procedure employed. To a freshly prepared solution of potassium amide (0.036 mol) in liquid ammonia (50 ml) was added **7** (2.18 g, 0.018 mol) at −35°. After 15 min, the ammonia was replaced by ether (30 min), and the reaction mixture was quenched with deuterium oxide (0.8 g, 0.04 mol) and filtered. The filtrates were concentrated *in vacuo* to yield 2.04 g of material. Nmr and mass spectra indicated about 4% deuterium incorporation at the tertiary carbon.

When the anion of **7** was quenched directly in the ammonia solution with deuterium oxide (tenfold excess), nmr and mass

(17) W. Sobecki, *Chem. Ber.*, **41**, 4103 (1908).

(18) An authentic sample of **15** was obtained from Aldrich Chemical Co.

spectra indicated about 4.5% incorporation of deuterium at the tertiary carbon.

Registry No.—**1**, 696-30-0; **2**, 644-98-4; **3**, 25128-23-8; **3** dipicrate, 25128-24-9; **4**, 25128-42-8; **4** dipicrate, 37387-92-1; **5**, 37387-93-2; **5** dipicrate, 37387-94-3; **6**, 37387-95-4; **6** picrate, 37387-96-5; **7**, 6304-18-3; **8**, 37387-98-7; **8** picrate, 37387-99-8; **9**, 37387-00-4; **9** dipicrate, 37388-01-5; **10**, 37388-02-6; **12**, 17755-30-5; **13**, 15031-78-4.

Acknowledgment.—We thank the Office of Naval Research and the Commercial Solvents Corporation for generous support. We are indebted to our colleague Professor Nathan Kornblum for helpful discussions.

Heteronuclear Stabilized Carbonium Ions. II. *N*-Aroyl- and Aryl-2-oxazolinium Cations. Intermediates in a New Class of Neighboring Group Reactions[1]

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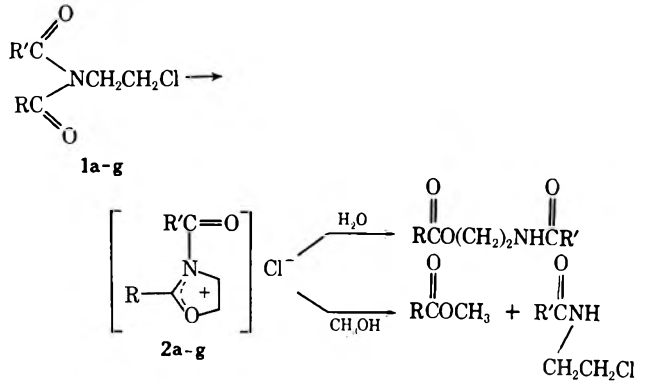
N-(2-Chloroethyl)-*N*-acyl/aroyl benzamides/acetamides were solvolyzed under several conditions: (a) in refluxing aqueous acetonitrile; (b) in aqueous acetonitrile with equimolar amounts of $AgNO_3$ (25°); and (c) in refluxing methanol. Hydrolyses produced the corresponding amido esters while methanolyses produced equimolar amounts of methyl esters and *N*-2-chloroethylamides. These solvolyses represent a new class of neighboring group reactions involving imide moiety participation, presumably *via* *N*-aroyl/acyl-2-oxazolinium cations. Several such cations were synthesized, isolated, and characterized. Evidence for the intervention of these cations in the solvolyses is presented. The preferred preparative route for the cations involved cyclization of appropriate *N*-(2-chloroethyl)imides with $AgBF_4$ or $AgSbF_6$. Selective participation of the better carbonium ion stabilizing carbonyl function was observed when cyclizing unsymmetrical imides. The ambident character of these cations was noted in that chloride ion attack occurred at the 5 position to produce *N*-(2-chloroethyl)imides; hydrolyses and methanolyses involved nucleophilic attack at the 2 position, producing, respectively, amido esters and equimolar amounts of methyl esters as well as 2-substituted 2-oxazolinium salts. Proposed solvolyses mechanisms are discussed.

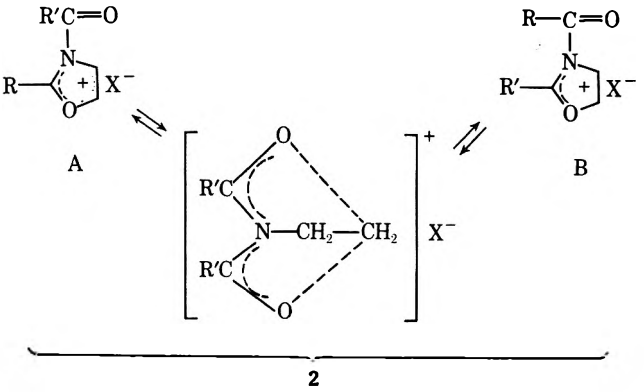
Participation of amide groups *via* 2-oxazolinium salts to produce various solvolysis products is well known. These reactions have been studied extensively by Winstein,[2] Heine,[3] and others.[4,5] In some instances these 2-oxazolinium salts[2,6] have actually been isolated and characterized. Although this area has received considerable attention, to our knowledge no report of imide group participation has yet appeared in the literature.

Recently, we noted that certain imides [*i.e.*, *N*-(2-chloroethyl)-*N*-acyl/aroyl benzamides/acetamides, **1a–g**], underwent facile solvolysis reactions in aqueous acetonitrile or in methanol as shown below.



These transformations represent a new class of neighboring group reactions in which *N*-aroyl/acyl-2-oxazolinium cations, **2a–g**, are postulated as transient intermediates.

Fry[7] first proposed these cations as intermediates in the ring opening of 2-oxazolines with acid chlorides. More recently, Nehring and Seeliger[8] proposed these cations as intermediates in the thermal equilibration of *N*-(2-chloroethyl)-*N*-benzoyl acetamide to mixtures of the symmetrical *N*-(2-chloroethyl)-*N*-(aroyl/acyl) benzamide and acetamide.



The unique structure of these cations offers the possibility of assessing various carbonyl participation aptitudes under equilibrating conditions as well as an opportunity to determine the effect of electronic and resonance properties of various R and R′ substituents on charge distribution in the oxazoline ring. As shown for the related 1,3-dioxolenium system,[9–11] the

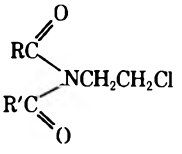
(1) Presented in part at the 158th National Meeting of the American Chemical Society, New York, N. Y., Sept 1969.
(2) S. Winstein, L. Goodman, and R. Boschan, *J. Amer. Chem. Soc.*, **72**, 2311 (1950).
(3) H. Heine, *ibid.*, **78**, 3708 (1956).
(4) B. Capon, *Quart. Rev., Chem. Soc.*, **18**, 45 (1964).
(5) S. Hünig, *Angew. Chem., Int. Ed. Engl.*, **3**, 548 (1964).
(6) M. E. Kreling and A. G. McKay, *Can. J. Chem.*, **37**, 504 (1959).
(7) E. M. Fry, *J. Org. Chem.*, **15**, 802 (1950).
(8) R. Nehring and W. Seeliger, *Justus Liebigs Ann. Chem.*, **709**, 113 (1967).
(9) H. Hart and D. A. Tomalia, *Tetrahedron Lett.*, **No. 29**, 3383 (1966).
(10) D. A. Tomalia and H. Hart, *ibid.*, **No. 29**, 3389 (1966).
(11) H. Hart and D. A. Tomalia, *ibid.*, 1347 (1967).

heterocyclic ring protons should serve as suitable electron density probes for assessing such charge delocalization by nmr spectroscopy.

The possibility of observing these phenomena in 3-acyl or aroyl-2-substituted 2-oxazolinium systems, as well as the need for demonstrating the intermediacy of these cations in *N*-(2-chloroethyl)imide solvolysis reactions, prompted the synthesis and an investigation of these cations.

Results and Discussion

Solvolysis Reactions of the Imides.—Seven imides, **1a–g**, were examined under three different solvolysis conditions: (A) in refluxing H_2O–CH_3CN (20:80, v/v); (B) in H_2O–CH_3CN (20:80) with equimolar $AgNO_3$ (25°); and (C) in refluxing methanol. Under conditions A and C a dramatic reduction in pH accompanied by the liberation of substantial amounts of chloride ion was observed upon heating. In the case of condition B a drop in pH with the concurrent formation of AgCl was noted.

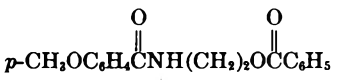


1a–g

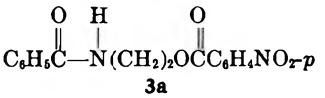
	R	R′
1a	C_6H_5	C_6H_5
1b	*p*-$CH_3OC_6H_4$	*p*-$CH_3OC_6H_4$
1c	CH_3	CH_3
1d	*p*-$NO_2C_6H_4$	*p*-$NO_2C_6H_4$
1e	*p*-$CH_3OC_6H_4$	C_6H_5
1f	C_6H_5	*p*-$NO_2C_6H_4$
1g	C_6H_5	CH_3

Essentially quantitative conversion to the corresponding amido esters was observed in refluxing aqueous acetonitrile (reaction times 2–27 hr) for the imides **1a**, **b**, and **d**. Imide **1c** appeared to hydrolyze anomalously to a mixture of acetic acid and 2-hydroxyethylamine·HCl rather than to *N*-(2-acetamido)ethyl acetate. However, further work showed that this expected amido ester hydrolyzes very rapidly to these products under condition A.

In the case of unsymmetrical imide **1e**, characteristic infrared absorption bands in the fingerprint region allowed an assessment of the relative amounts of the two possible amido esters that would be expected from this reaction. A predominance of 2-(*p*-anisamido)-ethyl benzoate (**3**), accompanied by smaller amounts of 2-(benzamido)ethyl *p*-anisate was observed. Hydrolysis of **1f** gave a mixture of the two possible esters, 2-(benzamido)ethyl *p*-nitrobenzoate (**3a**) and 2-(*p*-nitrobenzamido)ethyl benzoate (**3b**). The predominating



3



3a

3b

ester was not distinguishable by usual spectroscopic techniques. These reactions were also monitored by nmr spectroscopy. For example, imide **1a** exhibited an nmr spectrum (CD_3CN) which consisted of a complex multiplet at δ 7.66–7.05 ppm and two finely split triplets centered at δ 4.38 and 4.00 ppm (A_2B_2 type pattern). These protons were present in a ratio of 5:1:1, respectively. Hydrolysis was followed by observing the disappearance of the two upfield triplets accompanied by concurrent formation of two new multiplets centered at δ 4.46 and 3.76 ppm. Similarly, a new multiplet developed in the aromatic region at δ 8.25–7.67 ppm in addition to another multiplet at δ 7.67–7.08 ppm. The proton integration ratio was consistent with the proposed structure for the hydrolysis product.

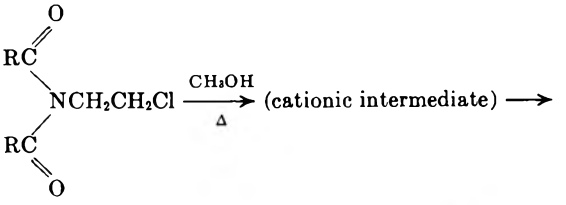
Attempts to hydrolyze analogous cyclic imides [*e.g.*, *N*-(2-chloroethyl)succinimide and *N*-(2-chloroethyl)-phthalimide] were unsuccessful. Even after reflux periods of 30–90 hr, complete recovery of starting materials was observed.

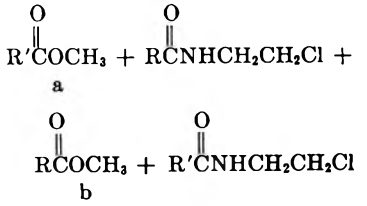
Treatment of imides **1a–d** under conditions B (*i.e.*, aqueous acetonitrile–$AgNO_3$) produced the same products as described above. Yields and products are described in the Experimental Section. In one instance, unsymmetrical imide **1e** was found by infrared analysis to have hydrolyzed under these conditions to a predominance of 2-(benzamido)ethyl *p*-anisate accompanied by 2-(*p*-anisamido)ethyl benzoate (**3**) as a minor product. This product distribution is the reverse of that obtained in the absence of the silver reagent (*cf.* condition A). Further comment on this aspect will be made later.

Methanolysis of **1a–d** under conditions C produced the corresponding methyl esters and *N*-(2-chloroethyl)-amides in fair to excellent yield. Unsymmetrical imides **1e–g** gave in each instance a four-component mixture of the corresponding methyl esters and *N*-(2-chloroethyl)amides as shown in Table I. According

Table I

Product Distribution from Methanolysis of Unsymmetrical Imides



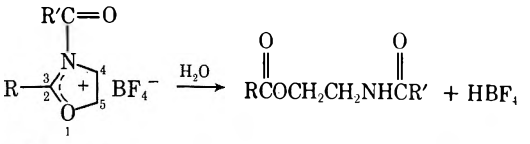


Imide	Mol % a	Mol % b
1e, R = C_6H_5; R′ = *p*-$CH_3OC_6H_4$	50	50
1f, R = C_6H_5; R′ = *p*-$NO_2C_6H_4$	57	43
1g, R = C_6H_5; R′ = CH_3	90	10

to glc analysis of the methyl esters, imides **1e** and **1f** solvolyzed in a nonselective manner, whereas **1g** led to

a predominance of methyl acetate accompanied by a minor amount of methyl benzoate.

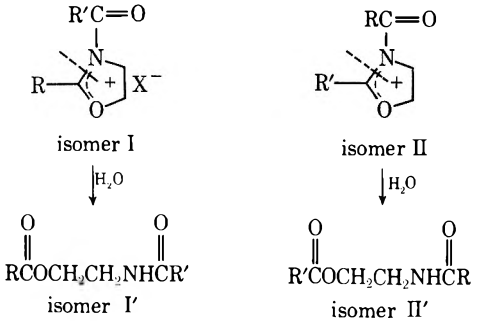
In order to test the intermediacy of oxazolinium cations **2** in these solvolyses, a number of these salts were synthesized, isolated, and solvolyzed as described later. When R = R′ (*i.e.*, **2a–c**), the same amido esters were obtained as were isolated from the hydrolysis of imides **1a–c**.



2a–c, e–g

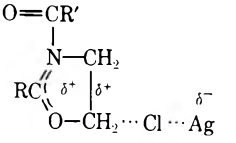
	R	R′
2a	C_6H_5	C_6H_5
2b	*p*-$CH_3OC_6H_4$	*p*-$CH_3OC_6H_4$
2c	CH_3	CH_3
2e	*p*-$CH_3OC_6H_4$	C_6H_5
2f	C_6H_5	*p*-$NO_2C_6H_4$
2g	CH_3	C_6H_5

This provides compelling evidence for the intermediacy of these salts. These products presumably arise *via* a selective cleavage between the 2 and 3 positions of the oxazolinium ring.[7,12,13] Because of the asymmetry of imides **1e–g**, isomeric cations I or II are possible intermediates depending on which amide carbonyl group participates in the displacement of the chloride ion. Based on work with authentic cations, hydrolysis of these cations would be expected to lead to the respective amido esters I′ and II′. Under con-

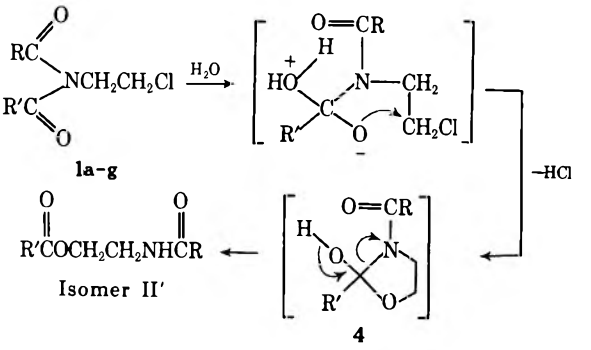


dition A, imide **1e** hydrolyzed preferentially to amido ester (isomer II′) according to infrared analysis. Hence it appears that cation **2e** (isomer II), where R′ = C_6H_5, R = *p*-$CH_3OC_6H_4$, is the primary cationic intermediate in this hydrolyis and presumably arose by participation of the benzamido group. Under condition B (*i.e.*, in the presence of $AgNO_3$), the predominance of amido ester I′ was noted, thus suggesting that participation of the *p*-anisamido group *via* cation **2e** (isomer I) prevailed under those conditions.

The latter selectivity can be readily rationalized in terms of the more nucleophilic carbonyl group (*i.e.*, R = *p*-anisamido) participating in the stabilization of the incipient carbonium ion generated by the silver reagent as shown below.

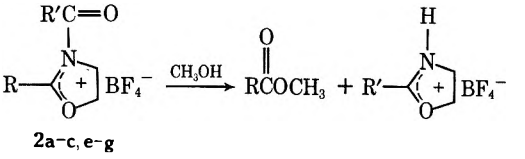


In the absence of a silver reagent, the preferential participation of the less nucleophilic carbonyl group (*i.e.*, R′ = benzamido) is more difficult to explain, unless one invokes a mechanism as shown below. In this



case the solvent attacks the more electron-deficient carbonyl group to produce the intermediate **4**. It should be noted that this intermediate is the same as that obtained in the first stage of the hydrolysis of cation **2e** (isomer II).

Additional evidence for the intermediacy of cations **2** was gained from methanolysis experiments. As described later, the cations solvolyzed very selectively to a stoichiometric mixture of the corresponding methyl benzoates and 2-oxazolinium salts. Although the methanolysis experiments with **1a–g** produced the corre-



2a–c, e–g

sponding methyl benzoates and *N*-(2-chloroethyl)-amides rather than the oxazolinium salt, it is well known that 2-substituted 2-oxazolinium hydrochlorides collapse readily to *N*-(2-chloroethyl)amides under the solvolysis conditions used.[14] In view of the fact that methanolysis of **1e**, **1f**, and **1g** yielded four-component mixtures of the corresponding methyl esters and *N*-(2-chloroethyl)amides (Table I) it seems apparent that both isomeric cations in each case (*i.e.*, isomers I and II) are intervening in these solvolysis reactions. Again the lack of selectivity observed for imides **1e** and **1f** may be explained by means of the proposed mechanism involving initial attack of the solvent on the carbonyl function followed by explusion of chloride ion. This mechanism, however, does not explain the selectivity observed in the methanolysis of **1g**, which is not well understood at this time.

Synthesis and Characterization of *N*-Aroyl- and *N*-Acyl-2-oxazolinium Cations.—Several approaches to the synthesis of these cations were attempted. They may be divided into two general methods. The first was to generate an oxocarbonium ion in the presence of an oxazoline with the expectation that carbonium ion capture would lead to formation of the desired 3-(aroyl or acyl)-2-(aryl or alkyl)-2-oxazolinium salts (see route A.) The second method was to cyclize appropriate *N*-(2-chloroethyl)-*N*-aroyl or -acyl benzamides with silver tetrafluoroborate or silver hexafluoroantimonate (route B).

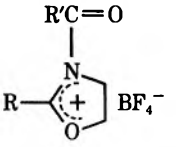
(12) Control experiments involving submission of these authentic amido esters, *p*-$CH_3OC_2H_4CONH(CH_2)_2OCOC_6H_5$, $C_6H_5CONH(CH_2)_2OCOC_6H_4$-$NO_2$-*p*, and *p*-$NO_2C_6H_4CONH(CH_2)_2$, to hydrolysis conditions showed no tendency to isomerization to the isomeric amido esters.

(13) P. Allen, Jr., and J. Ginos, *J. Org. Chem.*, **28**, 2759 (1963).

(14) A. A. Goldberg and W. Kelly, *J. Chem. Soc.*, 1919 (1948).

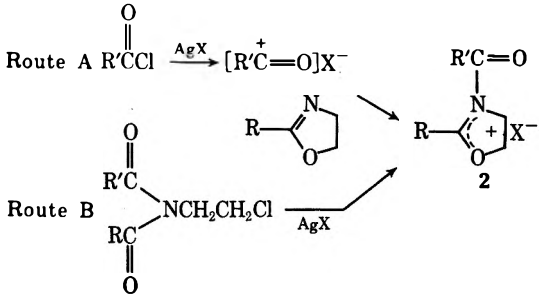
TABLE II

3-(AROYL/ACYL)-2-(ARYL/ALKYL)-2-OXAZOLINIUM SALTS

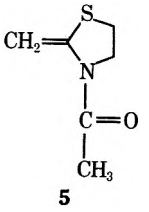


Cation	R′	R	Mp, °C	Route	Yield,[a] %	Analysis[h] C	H	N
2a	C_6H_5	C_6H_5	98–100[e]	B	91	56.7	4.16	4.13
						56.6	4.32	4.30
2a′	C_6H_5	C_6H_5	125–127[c]	A[b]	100	39.5	2.87	2.87
						39.7	2.78	2.90
2b	p-$CH_3OC_6H_4$	p-$CH_3OC_6H_4$	128.5–130[e]	B	75	54.2	4.51	3.51
						52.6	4.54	3.47
2c	CH_3	CH_3	88.5–90[c]	B	60	33.6	4.67	6.55
						33.7	4.95	6.62
2e	C_6H_5	p-$CH_3OC_6H_4$	140–144[f]	B	77	55.4	4.35	3.81
						55.1	4.44	3.85
2f	p-$O_2NC_6H_4$	C_6H_5	163–166[g]	B	60	50.0	3.39	7.30
						50.2	3.43	7.40
2g	C_6H_5	CH_3	140–142[d]	B	100	47.8	4.25	4.90
						47.7	4.35	4.90

[a] Crude yields. [b] Hexafluoroantimonate salt. [c] CH_2Cl_2–CH_3CN. [d] CH_3CN. [e] CH_2Cl_2. [f] CH_2Cl_2–Et_2O. [g] CH_3CN–Et_2O. [h] Top row, calculated; bottom row, found.



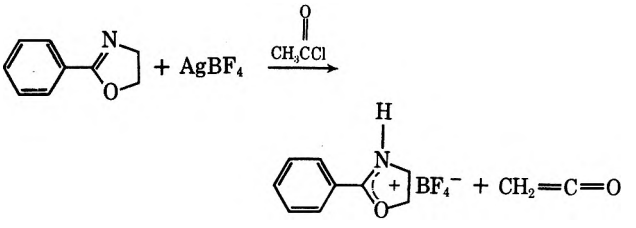
Successful syntheses of cations **2** by route A were dependent upon the nature of the R′ and R substituents of the acid chloride and oxazoline, respectively. Both substituents R′ and R had to be aryl in order to obtain **2** as the predominant product. Complex product mixtures resulted when the oxazoline substituent R was alkyl and the acid chloride substituent R′ was aryl. Perhaps the complexity of this reaction is related to the reaction of 2-methyl-2-thiazoline with acetyl chloride, wherein at least three products have been identified. The ketene *N*,*S*-acetal, **5**, was postulated as a key



5

intermediate in this acetylation.[15] Earlier work by Sheehan and coworkers[16] has also implicated such an intermediate in the reaction of 2-methyl-2-thiazoline with phthaloylglycyl chloride.

When the acid chloride substituent was alkyl (*i.e.*, R′ = CH_3) and the oxazoline substituent was aryl (*i.e.*, R = phenyl), route A produced ketene and the corresponding 2-aryl-2-oxazolinium salt. For example, when acetyl chloride was added to a mixture of 2-phenyl-2-oxazoline and silver tetrafluoroborate, nearly a quantitative yield of ketene and 2-phenyl-2-oxazolinium tetrafluoroborate was produced.



Adding aroyl chloride to a stoichiometric amount of 2-aryl-2-oxazoline and silver hexafluoroantimonate produced the desired 3-aroyl-2-aryl-2-oxazolinium salts **2** as the major products. The same reaction with silver tetrafluoroborate was not so clean. It is quite possible that the complexity of this reaction results from the known disproportionation of oxocarbonium tetrafluoroborates to acid fluorides and boron trifluoride.[17]

Route B proved to be the preferred method for preparing cations **2**. Both symmetrical and unsymmetrical *N*-2-chloroethyl precursors were prepared according to a modified method of Nehring and Seeliger.[8] Cyclizations of these imides proceeded readily with either silver tetrafluoroborate or hexafluoroantimonate.

The cations **2a–c, e–g**, were isolated as white, crystal-

Cation	R	R′
2e	C_6H_5	p-$CH_3OC_6H_4$
2f	p-$NO_2C_6H_4$	C_6H_5
2g	C_6H_5	CH_3

line products which were extremely reactive toward moisture and other nucleophiles (see Table II). Nuclear magnetic resonance, infrared, and elemental analyses were in agreement with the proposed cation structures. Characteristic reactions which also support the structure of these cations will be described

(15) L. V. Grobvosky, *Diss. Abstr.*, **28**, 3993B (1967).

(16) J. C. Sheehan, C. W. Beck, K. R. Henery-Logan, and J. J. Ryan, *J. Amer. Chem. Soc.*, **78**, 4478 (1956).

(17) G. E. Olah, S. J. Kuhn, W. S. Tolgyesi, and E. B. Baker, *ibid.*, **84**, 2733 (1962).

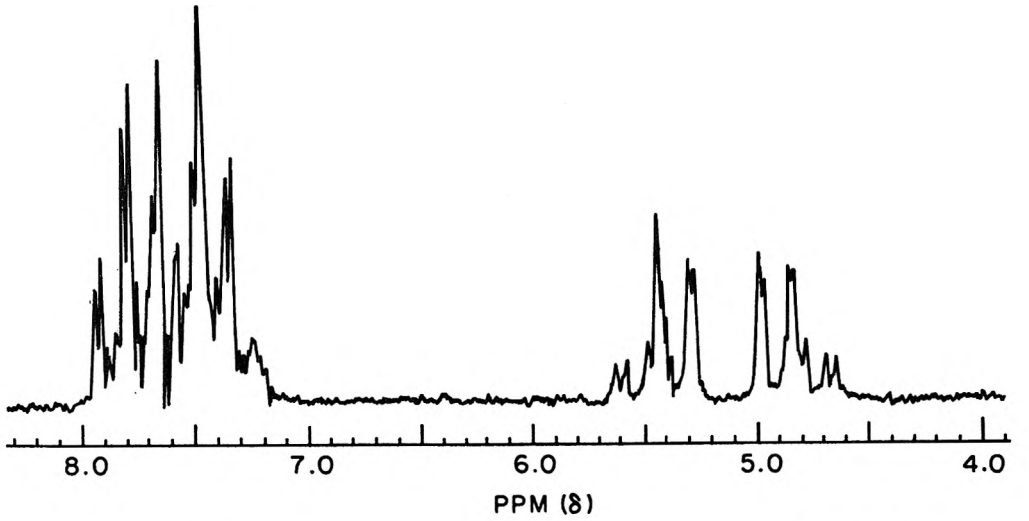


Figure 1.—Nuclear magnetic resonance spectrum of 3-benzoyl-2-phenyl-2-oxazolinium tetrafluoroborate (CD_3CN).

later. Infrared spectra of the cations 2 contained fairly intense absorption bands at 1725–1750 cm^{-1} for the carbonyl function and a similar type absorption at 1655–1710 cm^{-1} for the moiety

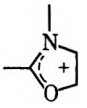
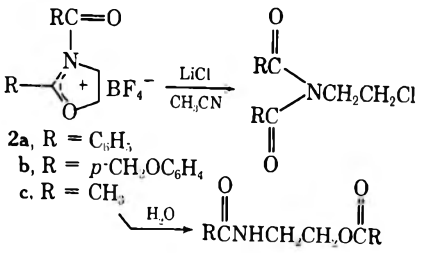


Figure 1 illustrates a typical nmr spectrum of one of these cations. A distinguishing feature of the nmr spectra was the deshielding of the oxazoline ring protons in the cations compared to the unquaternized oxazolines. Table III describes these data.

3-Acylated or aroylated oxazoline[7,18,19] and thiazoline salts[15] have been postulated as intermediates in the reactions of these heterocyclic rings with acid chlorides or acid anhydrides.

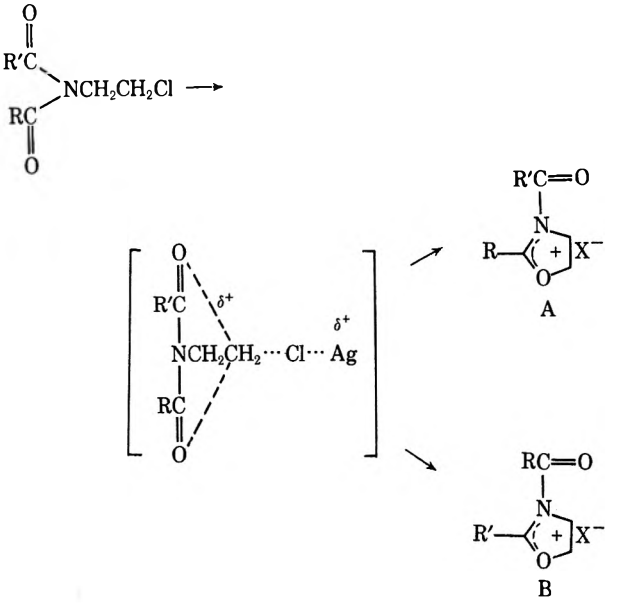
Fry[7] has shown that under anhydrous conditions 2-phenyl-2-oxazoline reacts with *p*-nitrobenzoyl chloride to yield *N*-(2-chloroethyl)-*N*-benzoyl-*p*-nitrobenzamide, whereas 2-(*p*-nitrobenzamido)ethyl benzoate is produced in the presence of water. Although no attempts to isolate these oxazoline salts have been reported thus far, an extensive but unsuccessful effort to trap the *N*-acetyl-2-methyl-2-thiazolinium salt has been described.[15]

The intermediacy of these salts in the reaction of acid chlorides with 2-oxazolines both under anhydrous conditions and in the presence of water is now well established. For example, 3-benzoyl-2-phenyl-2-oxazolinium tetrafluoroborate underwent immediate ring opening with LiCl in anhydrous acetonitrile to produce



N-(2-chloroethyl)-*N*-(benzoyl)benzamide. Likewise, the reaction of this cation with water resulted in a rapid, high-yield conversion to *N*-(2-benzamido)ethyl benzoate.

It was felt that the cyclizations of unsymmetrical *N*-(2-chloroethyl)-*N*-aroyl or -acyl benzamides would present a unique opportunity to determine neighboring group participation aptitudes of various carbonyl functions as they competed for the incipient carbonium ion that is generated by the silver reagent. In a limited series of *N*-(2-chloroethyl)-*N*-aroyl and -acyl benzamides which were examined, cyclization with silver tetrafluoroborate (CH_3CN solvent) led exclusively to the cation which contained the better carbonium ion stabilizing moiety in the 2 position (*i.e.*, structure B). The same reaction in CH_2Cl_2 gave a predominance of B accompanied by small amounts of A.



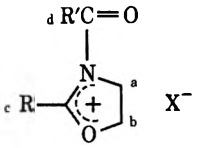
Evidence for the assignment of structure B to cations **2e** and **2f** was obtained by hydrolysis experiments. Fry[7] previously reported that the reaction of 2-phenyl-2-oxazoline with *p*-nitrobenzoyl chloride in the presence of water gave 2-(*p*-nitrobenzamido)ethyl benzoate. It was concluded that this compound resulted from

(18) P. G. Tryon, U. S. Patent 2,410,318 (1947).

(19) 3-Acylated 2-oxazolinium salts have been postulated as intermediates in the reaction of 2-(1-aziridinyl)-2-oxazolines with various acid chlorides [D. A. Tomalia, N. D. Ojha, and B. P. Thill, *J. Org. Chem.*, **34**, 1400 (1969)].

Table III

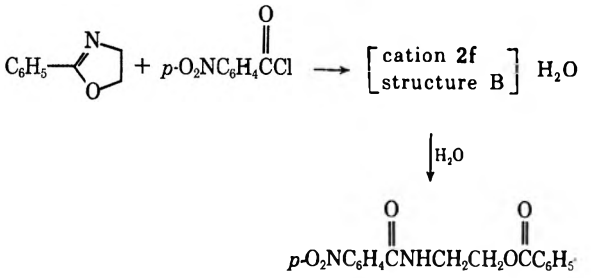
Nmr Chemical Shifts (δ)[a] of 3-(Aroyl/acyl)-2-(aryl/alkyl)-2-oxazolinium Salts



Cation	a	$\Delta\delta_a$[b]	b	$\Delta\delta_b$[b]	c	d
2a	4.83 (t)	0.85	5.46 (t)	1.07	7.21–7.99 (m)	
2b	4.71 (t)	0.75	5.28 (t)	0.90	6.97 (d), 7.76 (d), 7.91 (d)	
					p-CH_3O, 3.86 (s)	
2c	4.49 (t)	0.28	5.14 (t)	0.79	2.48 (s)	2.76 (s)
2e	4.74 (t)	0.76	5.30 (t)	0.91	6.94 (d), 7.77 (d)	
					(*p*-CH_3O), 3.87 (s)	
					7.33–8.09 (m)	
2f	4.88 (t)	0.91	5.51 (t)	1.12	7.38–8.20 (m)	
2g	4.51 (t)	0.53	5.21 (t)	0.82	2.56 (s)	7.58–8.03 (m)

[a] Chemical shifts were measured in CD_3CN with TMS as an internal standard: s = singlet, d = doublet, t = triplet, m = complex multiplet. [b] Difference in chemical shift between the cation and unquaternized 2-substituted 2-oxazolines (CD_3CN).

cleavage between the 2 and 3 position of the oxazoline ring. Fry postulated that cation **2f** with structure B

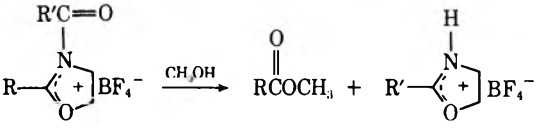


was the transient intermediate in this reaction. Adding our cation **2f** to water led to an immediate and quantitative conversion to 2-(*p*-nitrobenzamido)ethyl benzoate, which was shown by a mixture melting point to be identical with the product obtained by Fry. Assuming that our cation hydrolyzes by cleavage between the 2 and 3 position of the oxazoline ring, this demonstrates that cation **2f** has structure B. Hydrolysis of **2e** produced 2-(benzamido)ethyl *p*-anisate exclusively, thus leading to our assignment of structure B to this cation.

The structural assignment for cation **2g** is more tenuous in that the hydrolysis of this material does not lead to an amido ester as observed for all of the other cations, **2a,b,c,e,f**. However, based on analogy to the cations **2e** and **2f** wherein the better electron-donating substituent resided in the 2 position, we favor the assignment of structure B to cation **2g**. This assignment is supported by nmr in that the methyl signal in **2g** (2.56 ppm) is nearly the same ($\Delta\delta$ 0.08 ppm) as that for the 2-methyl substituent in cation **2c** (2.48 ppm). Comparing the methyl signal of cation **2g** to that of the 3-methyl substituent in **2c** (2.76 ppm), one finds a difference in chemical shift of 0.20 ppm (see Table IV).

Whereas amido esters were produced when R and R′ were both aryl or alkyl, cation **2g** hydrolyzed inexplicably to a mixture of acetic acid and the corresponding *N*-(2-hydroxyethyl)benzamide. An authentic sample of the anticipated amido ester [*i.e.*, *N*-(2-benzamido)ethyl acetate] was treated under the same conditions (*i.e.*, HBF_4) without any apparent hydrolysis, thus indicating that it is not the source of the products.

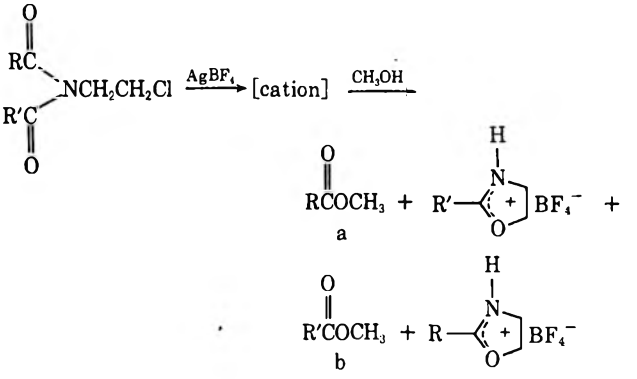
Allowing the cations to react with methanol resulted in a quantitative conversion to a mixture of the corresponding methyl ester and 2-substituted 2-oxazolinium salt. For example, cation **2a** (R = R′ = C_6H_5)



underwent methanolysis to a mixture of methyl benzoate and 2-phenyl-2-oxazolinium tetrafluoroborate. In the case of those cations resulting from unsymmetrical imide precursors (*i.e.*, **2e**, **2f**, and **2g**) both crude cations and purified cations were solvolyzed. Characterization of these products allowed us to determine the extent of selectivity of the cyclization process as well as the methanolysis. The purified cations were found to solvolyze selectively to methyl esters with the acyl or aroyl portion (R) being derived from the 2 substituent of the cation and oxazolinium salt substituent (R′) coming from the 3 substituent of the cation. Examination of the crude cations showed that selectivity still persisted, thus further corroborating the selectivity of the cyclization of the imides to the cations. Table IV shows the ratio of methyl esters arising from

Table IV

Product Distribution from Methanolysis of Crude Cations Derived from Unsymmetrical Imides

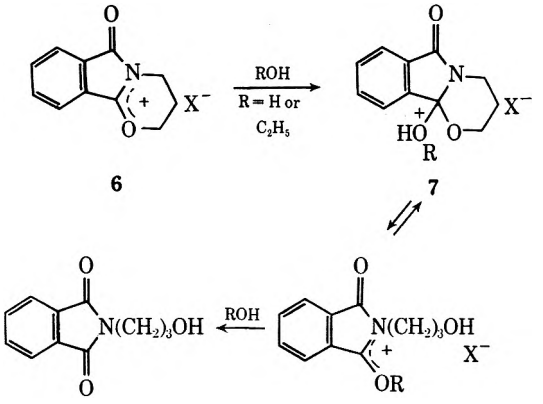


Imide	Mol % a	Mol % b
2e, R′ = C_6H_5; R = *p*-$CH_3OC_6H_4$	100	0
f, R′ = *p*-$NO_2C_6H_4$; R = C_6H_5	97	3
g, R′ = C_6H_5; R = CH_3	90	10

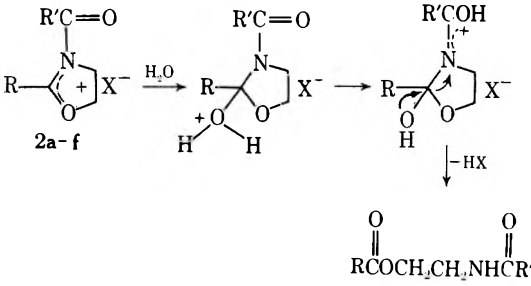
the methanolysis of unpurified cations as determined by glc analyses.

3-(Aroyl/acyl)-2-(aryl/alkyl)-2-oxazolinium salts are unquestionably ambident cations as defined by Hünig.[5] Depending upon the nature of the nucleophile, these cations are susceptible to attack at both the 2 and 5 positions. It is of interest to compare the reactivity of these cations to that of the structurally related *N,O*-trimethylenephthalimidium cation **6** reported recently by Hünig.[5]

Our cations appear to be very similar to Hünig's cation **6** in regard to preferred nucleophilic attack at



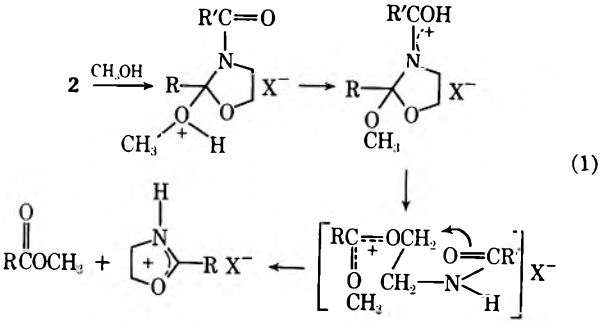
either the 2 or 5 position. Halide ion reactions are completely analogous in each series. Differences do arise in the prototropy in the incipient cations that form as a result of water or alcohol attack at the 2 position. For example, Hünig found that the incipient cation **7** resulting from the attack of water or ethanol at the 2 position of cation **6** cleaved between the 2 and 6 position to produce γ-hydroxypropylphthalimide in each case. Fry's work as well as this present investigation have shown that cations **2a–f** undergo hydrolyses which



result from cleavage between the 2 and 3 positions to produce amido esters. This mode of hydrolysis is analogous to the hydrolysis of 3-alkyl 2-substituted 2-oxazolinium salts, which has been described in detail by Allen and Ginos.[13] Cation **2g** is the only member of this series that hydrolyzes anomalously. The data are too meager to speculate on the mode of this transformation at this time.

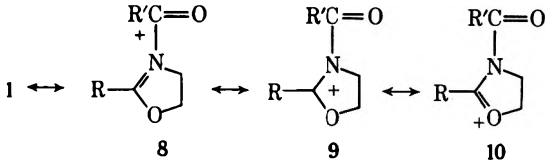
Methanolysis of **2** also appears to involve initial attack at the 2 position. Products arising from these reactions can be best rationalized in terms of a prototropy and cleavage between the 2 and 3 position as shown in eq 1.

All of the above reactions can be rationalized in terms of formal charge delocalization to various sites. Contributing structures to the resonance hybrid **1** can



(1)

be represented by ammonium ion (**8**), carbonium ion (**9**), or oxonium ion (**10**) type species. Reaction of



these cations with chloride ion can be visualized as a result of the oxonium ion character due to species **10**. Initial stages of the hydrolysis and methanolysis reactions presumably occur *via* the carbonium ion species **9**.

Experimental Section

General.—The *N*-acyl/aroyl-*N*-(2-chloroethyl)benzamides/acetamides were prepared according to the method of Nehring and Seeliger.[8] Special care had to be exercised in purifying these materials by distillation. Prolonged heating of the unsymmetrical intermediate resulted in scrambling of the acyl and aroyl groups.

In the solvolysis reactions of the imides, aqueous acetonitrile (20:80 v/v) was used for the hydrolyses while anhydrous methanol was used for the methanolyses.

Silver tetrafluoroborate and hexafluoroantimonate were obtained from Alfa Inorganic.

For preparation of the cations, it was essential to carefully dry all reagents to at least 10 ppm of water or less. All operations with the cations were performed under anhydrous conditions in a drybox.

Nuclear magnetic resonance (nmr) spectra were recorded on a Varian A-60 spectrometer. Chemical shifts are reported as parts per million relative to tetramethylsilane. Samples for infrared spectra were prepared as KBr pellets and scanned on a Perkin-Elmer 337 spectrometer. Melting points were determined in a capillary and are uncorrected unless otherwise noted. Vapor phase chromatography work was conducted on an F & M Model 500 unit.

Solvolysis Reactions of Imides. *N*-(2-Chloroethyl)-*N*-(benzoyl)benzamide (1a). Condition A.—A 2-g (0.007 mol) sample of **1a** was dissolved in 20 ml of aqueous acetonitrile. Upon warming, the homogeneous solution became very acidic within minutes (*i.e.*, pH <2). After refluxing for 21 hr and removing solvent, a sticky white solid residue was obtained, 1.4 g. Recrystallization from ethanol–water yielded a white powder which melted at 83–87° (lit.[14] mp 88–89°). Infrared and nmr spectra of this product were identical with those of genuine 2-(benzamido)-ethyl benzoate prepared according to Fry.[7] A mixture melting point with authentic **1a** was undepressed.

Condition B.—A mixture of **1a** (2.87 g, 0.01 mol) and silver nitrate (1.69 g, 0.01 mol) in 20 ml of aqueous acetonitrile was stirred for 28 hr at room temperature (25°). Silver chloride was filtered, 0.8 g (56%). Removal of solvent from the filtrate gave 1.9 g (70%) of an off-white solid which was identified as 2-(benzamido)ethyl benzoate by ir, nmr, and mixture melting point.

Condition C.—A 2.5-g sample of **1a** was dissolved in 30 ml of anhydrous methanol. Under anhydrous conditions this reaction mixture was refluxed for 14 hr. Nmr analysis of the crude reaction mixture at this point indicated that methanolysis was 54% complete. Removal of solvent gave a gummy white solid which had the odor of methyl benzoate. The presence of this

TABLE V
SOLVOLYSES OF IMIDES

Imide	Condition A R'CONHCH$_2$CH$_2$OCOR	Condition B R'CONHCH$_2$CH$_2$OCOR	Condition C
1b	R = R' = *p*-MeOC$_6$H$_4$ Mp 120–122° (EtOH–H$_2$O) [lit.[g] mp 127° (EtOH–Et$_2$O)]	R = R' = *p*-MeOC$_6$H$_4$ Mp 118–112°	*p*-MeOC$_6$H$_4$COOMe + *p*-MeOC$_6$H$_4$CONH(CH$_2$)$_2$Cl[a]
1c	HOCH$_2$CH$_2$NH$_2$·HCl contaminated with CH$_3$COOH and CH$_3$CONHCH$_2$CH$_2$OCOCH$_3$	R = R' = CH$_3$ (dark orange oil)	CH$_3$COOMe[b] + CH$_3$CONHCH$_2$CH$_2$Cl (dark orange oil)
1d	R = R' = *p*-NO$_2$C$_6$H$_4$ Mp 182–187° (CH$_3$COOH) (lit.[h] mp 188–189°)	Same as A	*p*-O$_2$NC$_6$H$_4$COOMe + *p*-O$_2$NC$_6$H$_4$CONH(CH$_2$)$_2$Cl
1e	Mixture of two possible esters[c] (see text)	Mixture of two possible esters[c] (see text)	*p*-CH$_3$OC$_6$H$_4$COOMe, C$_6$H$_5$COOMe, *p*-CH$_3$OC$_6$H$_4$CONH(CH$_2$)$_2$Cl, C$_6$H$_5$CONH(CH$_2$)$_2$Cl[d]
1f	Mixture of two possible esters	Same as A	C$_6$H$_5$COOMe, C$_6$H$_5$CONH(CH$_2$)$_2$Cl, *p*-O$_2$NC$_6$H$_4$COOMe, *p*-O$_2$NC$_6$H$_4$CONH(CH$_2$)$_2$Cl[e]
1g	Complex mixture	Same as A	CH$_3$COOMe, CH$_3$CONHCH$_2$CH$_2$Cl, C$_6$H$_5$COOMe, C$_6$H$_5$CONH(CH$_2$)$_2$Cl[f]

[a] Recrystallization from CCl_4 gives two components. Amide was identical with an authentic sample obtained from reaction of *p*-MeOC$_6$H$_4$COCl + aziridine. [b] Glc analysis: 10 ft silicone gum (410), He flow 50 ml/min; isothermal at 75° for 7 min and then 8°/min; 2.8 min = CH$_3$COOMe; 12–21 min = amide. [c] Each of the pure esters (prepared independently) was treated under these same hydrolysis conditions (20:80 aqueous acetonitrile at reflux). No interconversion was observed. [d] Presence of all four verified by glc analysis. See footnote *b*. Conditions: isothermal at 100° for 13 min followed by heating at 4°/min. [e] Glc analysis. See footnote *b*. Conditions: isothermal at 200°. [f] Glc analysis. See footnote *b*. Conditions: isothermal at 75° for 7 min followed by heating at 8°/min. [g] E. Bergman, *Recl. Trav. Chim. Pays-Bas*, **71**, 168 (1952). [h] S. Franket and M. Cornelius, *Ber.*, **51**, 1654 (1918).

ester was confirmed by ir and nmr spectral comparisons with authentic methyl benzoate. The white solid was identified as a mixture of *N*-2-chloroethyl benzamide and starting material. Recrystallization of this mixture from CCl_4 gave pure *N*-2-chloroethyl benzamide, which was identical in every respect with an authentic sample which had been prepared by the reaction of benzoyl chloride with aziridine.[20]

The solvolyses of the other imides are summarized in Table V.

Preparation of Authentic Amido Esters.—Authentic amido esters were either prepared according to the method of Fry[7] (*i.e.*, reaction of appropriate 2-substituted 2-oxazolines with carboxylic acids) or according to the references cited herein. The preparation of two new amido esters is described below.

N-(**2-Benzamidoethyl**) ***p*-Anisate.**—A mixture of *p*-anisic acid (1.52 g, 0.01 mol) and 2-phenyl-2-oxazoline (1.37 g, 0.0093 mol) was heated at 130° for 30 min. Upon cooling, the reaction mixture crystallized. This solid was ground up, washed with 10% sodium bicarbonate, and recrystallized from acetone. An analytical sample was obtained as a white powder, mp 126–129°.

Anal. Calcd for C$_{17}$H$_{17}$NO$_4$: C, 67.7; H, 5.63; N, 4.67. Found: C, 67.7; H, 5.72; N, 4.70.

N-(**2-*p*-Anisamidoethyl**) **Benzoate.**—A mixture of benzoic acid (0.405 g, 0.0033 mol) and 2-(*p*-methoxyphenyl)-2-oxazoline (0.55 g, 0.0031 mol) was heated for 45 min at 100°. The solid product obtained upon cooling to room temperature was ground and washed with 10% sodium bicarbonate. Recrystallization from ethanol gave a white powder, mp 108–112°.

Anal. Calcd for C$_{17}$H$_{17}$NO$_4$: C, 67.7; H, 5.63; N, 4.67. Found: C, 67.9; H, 5.71; N, 4.73.

Preparation of Cations. Route A. Reaction of 2-Phenyl-2-oxazoline and AgSbF$_6$ with Benzoyl Chloride.—To a stirred solution of dry 2-phenyl-2-oxazoline (3.55 g, 0.0242 mol) and silver hexafluoroantimonate (8.3 g, 0.0242 mol) in 60 ml of anhydrous nitromethane was added 3.42 g (0.0242 mol) of freshly distilled benzoyl chloride. The addition was made in four increments over a period of 1 hr. After the brown reaction mixture was allowed to stir for 23 hr, silver chloride was filtered and found to weigh 3.48 g (100% of theory). Removal of solvent from the filtrate gave a sticky, dark red residue which exhibited an nmr spectrum which was essentially identical with that obtained for cation **1a**. (See Table III for nmr data.) This crude product was purified by dissolving in equal volumes of methylene chloride and acetonitrile, cooling with Dry Ice, and then adding just enough diethyl ether to cause precipitation. The product was obtained as a white powder, mp 125–127°.

B. Reaction of 2-Phenyl-2-oxazoline and AgBF$_4$ with Acetyl Chloride.—A slurry of 2-phenyl-2-oxazoline (3.0 g, 0.021 mol) and silver tetrafluoroborate (4.0 g, 0.021 mol) in 20 ml of methylene chloride was stirred as acetyl chloride (1.61 g, 0.021 mol) was added dropwise. The mixture turned a milky white color and was accompanied by gas evolution. Bubbling the gas through methanol produced methyl acetate. The gas was identified as ketene. After the reaction mixture was stirred for 4 hr at room temperature, silver chloride was filtered and found to weigh 2.65 g (92% of theory). Removal of solvent from the filtrate yielded 4.33 g of a beige-colored powder which was identified as 2-phenyl-2-oxazolinium tetrafluoroborate, mp 116–118°.

Route B. Cyclization of *N*-Aroyl/Acyl-*N*-2-chloroethyl Benzamide or Acetamide with Silver Reagents.—Under anhydrous conditions, 0.02 mol of the appropriate *N*-aroyl/acyl-*N*-2-chloroethyl benzamide or acetamide in 40 ml of dry methylene chloride or acetonitrile was stirred as silver tetrafluoroborate or hexafluoroantimonate (0.02 mol) was added in one portion. The reaction mixture was stirred overnight, during which time a substantial amount of blue-gray precipitate was formed. Solvent was removed under vacuum, leaving essentially a quantitative yield of solid residue consisting of cation plus silver chloride. Product distribution between cation A and B was assessed by extracting this residue with acetonitrile and analyzing by nmr spectroscopy. Complete conversion to cation B always resulted when acetonitrile was used as the reaction solvent. When methylene chloride was used as the solvent for the preparation of cations **2g** or **2e**, cation B was the major product accompanied by small amounts of cation A. In one instance the crude reaction product, **2g**, was quenched in an excess of anhydrous methanol. The methanolysis products were analyzed by both nmr spectroscopy and glc. Methyl acetate was the major product accompanied by small amounts of methyl benzoate.

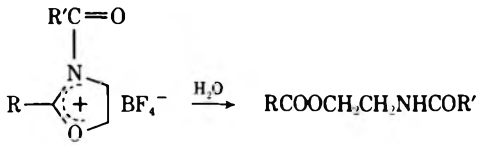
The cations were generally obtained in crude yields of 60–100%. Analytical samples of the cations were obtained by recrystallization from acetonitrile, CH_2Cl_2, or a combination of these solvents with diethyl ether (Dry Ice cooling). These data and physical properties of the cations are listed in Table II.

Hydrolysis of 3-Acetyl-2-methyl-2-oxazolinium Tetrafluoroborate (2c).—A sample of cation **2c** (220 mg) was added to 1 ml of D_2O, giving a homogeneous acidic solution. After standing overnight, the reaction mixture was scanned by nmr. The spectrum consisted of two singlets at 2.06 and 2.10 ppm, as well as two triplets centered at 3.36 and 3.70 ppm. These signals were identical with those recorded for authentic *N*-(2-acetamido)-ethyl acetate in D_2O.

Hydrolysis of 3-Benzoyl-2-methyl-2-oxazolinium Tetrafluoroborate (2g).—A sample of cation **2g** (0.35 g) was added to 2.5 ml of D_2O and allowed to stand overnight at room temperature. The reaction mixture was found to contain an equimolar amount of acetic acid and 2-hydroxyethyl benzamide by nmr analysis.

(20) H. Bestian, *Justus Liebigs Ann. Chem.*, **566**, 210 (1950).

TABLE VI



Cation	R	R'	Mp of ester, °C	Structure proof
2a	C_6H_5	C_6H_5	85–87	Identical with authentic ester (ir and nmr) (mp 88–89°)[a]
2b	p-$CH_3OC_6H_4$	p-$CH_3OC_2H_4$	121–122.5 (EtOH–H_2O)	Identical with authentic ester (ir + nmr); undepressed mixture melting point
2e	p-$CH_3OC_6H_4$	C_6H_5	127–129 (acetone)	Identical with authentic ester (ir and nmr) (mp 126–129°)[b]
2f	C_6H_5	p-$O_2NC_6H_4$	140–144 (abs EtOH)	Identical with authentic ester (ir and nmr);[b] undepressed mixture melting point

[a] Reference 14. [b] Reference 7.

Acetic acid exhibited a singlet at 2.15 ppm, whereas the amide displayed two triplets at 3.57 and 3.85 ppm as well as a complex multiplet at 7.46–7.90 ppm. The above signals were identical with those observed for authentic samples in each case. Authentic 2-hydroxyethyl benzamide was prepared by azeotropic (toluene) removal of water from a mixture of benzoic acid and 2-aminoethanol. Hydrolysis reactions of the other cations are shown in Table VI.

Methanolysis of 3-Acetyl-2-methyl-2-oxazolinium Tetrafluoroborate (2c).—Anhydrous methanol was added to a sample of cation **2c** in CD_3CN. The nmr spectrum of this mixture now contained two singlets at 3.62 and 2.00 ppm for methyl acetate. 2-Methyl-2-oxazolinium tetrafluoroborate was identified as the other component. The nmr of this material consisted of a slightly split singlet at 2.40 ppm and two triplets centered at 4.06 and 5.01 ppm. Removal of the solvent and other volatile material gave the crystalline oxazoline salt, mp 40–42°.

Methanolysis of 3-Benzoyl-2-methyl-2-oxazolinium Tetrafluoroborate (2g).—A sample of *N*-acetyl-*N*-(2-chloroethyl)-benzamide (3.1 g, 0.014 mol) in 50 ml of dry methylene chloride was treated with silver tetrafluoroborate (2.68 g, 0.014 mol) and then allowed to stir at room temperature for 24 hr. Solvent was removed under vacuum followed by the addition of anhydrous methanol (10 ml). The liquid phase was decanted and analyzed by glc. The major volatile product was methyl acetate (90 mol %) accompanied by small amounts (10 mol %) of methyl benzoate. The major nonvolatile component was identified by nmr as 2-phenyl-2-oxazolinium tetrafluoroborate.

When the cation **2g** was prepared in acetonitrile and then treated with methanol in the same manner, only methyl acetate was observed as the volatile component.

Methanolysis of 3-Benzoyl-2-(*p*-methoxyphenyl)-2-oxazolinium Tetrafluoroborate (2e).—To a purified sample of cation **2e** in CD_3CN was added anhydrous methanol. A slightly exothermic reaction was noted. The nmr spectrum of this mixture now contained a singlet at 3.83 ppm which was enhanced by the addition of methyl *p*-anisoate. In addition, two triplets at 4.26 and 5.18 ppm as well as a complex multiplet at 8.14 to 7.54 ppm were noted and are identical with those observed for authentic 2-phenyl-2-oxazolinium tetrafluoroborate.

A sample of the crude reaction product obtained by cyclization of *N*-benzoyl-*N*-(2-chloroethyl)-*p*-anisamide in CH_2Cl_2 was quenched in methanol. Analysis of the resulting solution by glc (silicone gum rubber, 410, 10-ft column) revealed the presence of only methyl *p*-anisoate.

Methanolysis of 3-(*p*-Nitrobenzoyl)-2-phenyl-2-oxazolinium Tetrafluoroborate (2f).—Anhydrous methanol was added to a purified sample of cation **2f** in CD_3CN. After several hours at room temperature, the sample was analyzed by nmr and found to contain methyl benzoate and 2-(*p*-nitrophenyl)-2-oxazolinium tetrafluoroborate in equimolar amounts. The salt was isolated as a tan, crystalline solid by removing all of the volatile components under vacuum. Recrystallization from methylene chloride and ether gave a tan powder melting at 143–146.5°. The nmr spectrum consisted of a quartet centered at 8.35 ppm and two triplets centered at 5.26 and 4.36 ppm (CD_3CN).

Anal. Calcd for $C_9H_8N_2O_3BF_4$: C, 38.6; H, 3.22; N, 9.95. Found: C, 38.5; H, 3.18; N, 10.1.

A sample of crude cation, **2f**, was treated in a similar manner with anhydrous methanol. Analysis of the reaction mixture by glc showed the presence of methyl benzoate and methyl *p*-nitrobenzoate in a ratio of 97:3 mol %, respectively.

Preparation of 2-Aryl- and Alkyl-2-oxazolinium Tetrafluoroborates.—While a solution of *N*-(2-chloroethyl)acetamide or benzamide[20] (0.0265 mol) in 40 ml of anhydrous acetonitrile was stirred, silver tetrafluoroborate (5.15 g, 0.0265 mol) was added in one portion. A white precipitate formed immediately. After the reaction mixture was stirred at room temperature for ~16 hr, silver chloride was removed by filtration. Evaporation of the solvent gave the corresponding oxazolinium tetrafluoroborate salts. Crude yields of the salts varied between 90 and 100%. Physical constants and recrystallization solvents are as described below.

2-Methyl-2-oxazolinium tetrafluoroborate was a white, hygroscopic solid, mp 40–42° from methylene chloride.

Anal. Calcd for $C_4H_8NOBF_4$: C, 27.9; H, 4.65; N, 8.15. Found: C, 27.8; H, 4.45; N, 7.90.

2-Phenyl-2-oxazolinium tetrafluoroborate was a white, crystalline material, mp 119.5–121° from methylene chloride.

Anal. Calcd for $C_9H_{10}NOBF_4$: N, 6.23. Found: N, 5.80.

2-(*p*-Methoxyphenyl)-2-oxazolinium tetrafluoroborate was a white solid, mp 178–180° from a mixture of acetonitrile and diethyl ether.

Anal. Calcd for $C_{10}H_{12}NO_2BF_4$: C, 45.3; H, 4.53; N, 5.28. Found: C, 45.3; H, 4.53; N, 5.30.

2-(*p*-Nitrophenyl)-2-oxazolinium tetrafluoroborate was a tan solid, mp 143–146.5° from methylene chloride–ether.

Anal. Calcd for $C_9H_9N_2O_3BF_4$: C, 38.6; H, 3.22; N, 9.95. Found: C, 38.5; H, 3.18; N, 10.1.

Reaction of Cation 2c with LiCl.—Anhydrous LiCl (0.09 g, 2.1 mmol) was added to a solution of **1c** (0.597 g, 2.1 mmol) in 40 ml of dry acetonitrile. An nmr spectrum of this reaction mixture was recorded within 5 min after combination of the reagents and found to be identical with the spectrum obtained for an authentic sample of *N*-2-chloroethyl-*N*-benzoyl benzamide prepared by the method of Nehring and Seeliger.[8]

Registry No.—**1a**, 17209-17-5; **1b**, 37056-12-5; **1c**, 17101-83-6; **1d**, 37056-14-7; **1e**, 37056-15-8; **1f**, 37056-16-9; **1g**, 17101-84-7; **2a**, 36994-88-4; **2a'**, 36994-89-5; **2b**, 36994-90-8; **2c**, 36994-91-9; **2e**, 36994-92-0; **2f**, 36994-93-1; **2g**, 36994-94-2; *N*-(2-benzamidoethyl) *p*-anisate, 37056-18-1; *N*-(2-*p*-anisamidoethyl) benzoate, 37056-19-2; *N*-(2-*p*-anisamidoethyl) *p*-anisate, 37056-20-5; 2-methyl-2-oxazolinium tetrafluoroborate, 37047-99-7; 2-phenyl-2-oxazolinium tetrafluoroborate, 37048-00-3; 2-(*p*-methoxyphenyl)-2-oxazolinium tetrafluoroborate, 37017-01-9; 2-(*p*-nitrophenyl)-2-oxazolinium tetrafluoroborate, 37048-01-4.

Acknowledgment.—The authors are grateful to Dr. B. P. Thill, Dr. W. L. Dilling, and Dr. R. J. Thomas for helpful discussions relating to this investigation. We also wish to thank Mr. J. Lalk for the synthesis of several amido esters.

Studies in Nonpyridinoid Aza-Aromatic Systems. V. The Methylation–Deprotonation Route to 4-Methyl-4*H*-cyclopenta[*b*]quinoline and Its 1,2-Dihydro Derivative[1]

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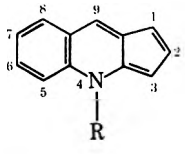
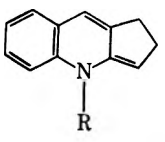
Received August 15, 1972

The synthesis of the fully conjugated, azulene-like heterocycle, 4-methyl-4*H*-cyclopenta[*b*]quinoline (**1c**), was attempted in two different approaches: (a) methylation of the tautomeric mixture of 1*H*-, 3*H*-, and 4*H*-cyclopenta[*b*]quinolines (**1a** and **3**), followed by deprotonation; and (b) dehydrogenation of 2,4-dihydro-4-methyl-1*H*-cyclopenta[*b*]quinoline (**2b**) by DDQ or by triphenylmethyl fluoroborate (**13**). The former route to **1c** was partially successful, but the methylation step involved N-protonation of **3**, C-methylation of **1a**, and probably some dimerization of **3** as side reactions. The latter approach from **2b** failed because **2b** formed an adduct with DDQ instead of simply dehydrogenating, and the **1c** formed from **2b** and **13** was further tritylated by **13**. As a model system for the C-methylation of **1a** observed in the former approach, the enamine system **2b** was found to undergo smooth C-methylation. The most reliable synthesis of **1c** involved the exclusive N-methylation of 3-acetoxy-2,3-dihydro-1*H*-cyclopenta[*b*]quinoline (**16**) with dimethyl sulfate, the dehydracetoxylation by brief heating with concentrated sulfuric acid, and the liberation of **1c** only in a strongly basic medium. In its visible and nmr spectra and in its behavior toward nucleophilic or electrophilic attack, **1c** shows itself to be a close electronic relative of azulene and the benzazulenes.

Although several syntheses of substituted cyclopenta[*b*]quinolines (benzo[*b*][1]pyrindines) have been reported,[3–5] only recently has the unsubstituted cyclopenta[*b*]quinoline nucleus been synthesized[6] and its tautomeric character fully described.[7,8] Of special interest was the detection of the 4*H* tautomer (**1a**, *ca.* 0.1%) in the cyclopenta[*b*]quinoline isolated. The fully conjugated, azulene-like character of **1a** was revealed in its deep violet color[6] and in the electrophilic attack that its lithium salt **1b** underwent at C_1 and C_3.[7] To obtain exclusively a derivative of the aromatic 4*H* tautomer, we next wished to synthesize 4-methyl-4*H*-cyclopenta[*b*]quinoline (**1c**). Two general approaches



1a, R = H
b, R = Li
c, R = CH_3



2a, R = Li
b, R = CH_3
c, R = H

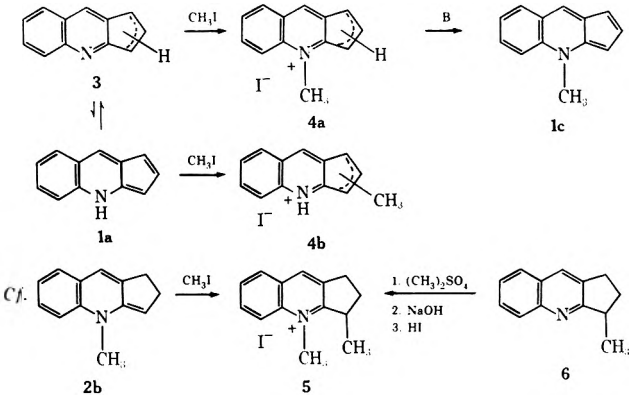
appeared feasible: (1) as with the related 1-pyrindine nucleus,[9] quaternization of cyclopenta[*b*]quinoline and deprotonation of the resulting salt or, alternatively, treatment of **1b** with methyl iodide; and (2) the dehydrogenation of 2,4-dihydro-4-methyl-1*H*-cyclopenta[*b*]quinoline (**2b**). This report describes the interesting chemistry encountered with each of these approaches and, in addition, presents a reliable route to **1c**.

Results

Methylation.—In contrast with the success claimed for the N-methylation of the sodium salt of 1*H*-1-pyrindine with methyl iodide, the lithium salt of benzo[*b*][1]pyrindine (**1b**) gave, as the only isolable products, a mixture of products mono- and dimethylated at C_1 and C_3.[7] Even the lithium salt of 2,3-dihydro-1*H*-cyclopenta[*b*]quinoline (**2a**) underwent methylation in almost a quantitative fashion at C_3. In neither case did the crude, undistilled product reveal any nmr signal ascribable to the NCH_3 of **1c** (3.97 ppm) or of **2b** (2.75 ppm), respectively. Hence, the deprotonation–methylation sequence was inapplicable.

The methylation–deprotonation sequence to **1c** (Scheme I) required the quaternization of cyclopenta[*b*]quinoline (**3**) with methyl iodide. Although the quaternization was conducted at room temperature, infrared and nmr spectral analysis of the isolated methiodide **4a** showed it to be contaminated with N-protonated and probably both C-methylated (**4b**) and dimeric side products. On the basis of previous

SCHEME I



(1) Part IV of this series: J. J. Eisch and G. Gupta, *Tetrahedron Lett.*, 3273 (1972).

(2) Inquiries should be addressed to this author at the Department of Chemistry, State University of New York at Binghamton, Binghamton, New York 13901.

(3) *Cf.* ref 6 for leading literature citations prior to 1970.

(4) L. E. Kholodov, I. F. Tishchenkova, and V. G. Yashunskii, *Tetrahedron Lett.*, 1535 (1970).

(5) V. N. Gogte, A. G. Namjoshi, and B. D. Tilak, *ibid.*, 4305 (1971).

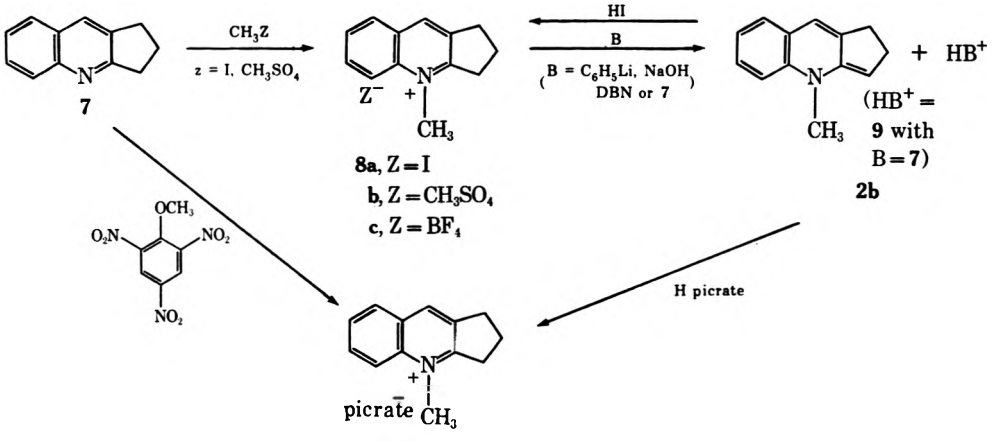
(6) J. J. Eisch and F. J. Gadek, *J. Org. Chem.*, **36**, 2065 (1971).

(7) J. J. Eisch and F. J. Gadek, *ibid.*, **36**, 3376 (1971).

(8) Contemporaneous with our report, I. F. Tishchenkova, L. E. Kholodov, and V. G. Yashunskii, *Khim. Geterotsikl. Soedin.*, **7**, 102 (1971) [*Chem. Abstr.*, **75**, 35668z (1971)] reported the synthesis of cyclopenta[*b*]quinoline involving the treatment of 3-bromo-2,3-dihydro-1*H*-cyclopenta[*b*]quinoline (*cf.* ref 6) dissolved in dimethylformamide with triethylamine. The oily product was neither distilled nor crystallized, but the nmr and uv spectral data seem to be in general agreement with our findings. However, their failure to observe a purple component in their product or to note the variable intensities of the 1-CH_2 and 3-CH_2 proton signals remains unexplained. In addition, the picrate of their product (mp 177–181°) melted much lower than the picrate of **3** (mp 217°).

(9) A. G. Anderson, Jr., and H. L. Ammon, *Tetrahedron*, **23**, 3601 (1967).

SCHEME II



nmr correlations for methyl derivatives of **3**, C-methylation is assumed to have occurred at C_3 (**4b**). The formation of **4b** can readily be explained by the presence of the 4*H* tautomer **1a** in **3**, for such an enamine would be expected to undergo C-methylation.[10] In support of this assumption, **2b**, the dihydro relative of **1c**, was found to undergo smooth C-methylation with methyl iodide. The resulting product **5** was prepared by an independent route from 2,3-dihydro-3-methyl-1*H*-cyclopenta[*b*]quinoline (**6**), in order to confirm its identity (Scheme I).

Assurance that quaternization of **3** did give largely the monomeric methiodide **4a**, rather than principally dimeric products as reported for the case of 1*H*-1-pyrindine,[9] was gained in two ways: (a) the nmr spectrum of **4** gave as its most intense singlet a sharp signal at 4.80 ppm (*cf.* ref 9 where the dimeric products displayed NCH_3 signals at 4.36 and 4.45 ppm); and (b) deprotonation yielded largely 4-methyl-4*H*-cyclopenta[*b*]quinoline (Scheme I, **4a** → **1c**) (*cf. infra*). However, because of the contaminants in **4a**, this method was not a completely satisfactory route to **1c**.

A satisfactory synthesis of **1c**, either by the methylation route or by the dehydrogenation route, demanded a suitable N-methylation procedure. In order to achieve N-methylation, exclusively and cleanly, it was necessary to start with a derivative of 2,3-dihydro-1*H*-cyclopenta[*b*]quinoline (**7**). Even in this approach, quaternization had to be conducted so as to avoid contamination with the acid salt of the amine (**9**, Scheme II). Purified methyl iodide in ether at 25° or dimethyl sulfate in benzene at 80° proved to be suitable.

The preparation of pure 2,4-dihydro-4-methyl-1*H*-cyclopenta[*b*]quinoline (**2b**) for dehydrogenation studies was achieved from **8a** or **8b**. Although the preparation of **2b** *in situ* has frequently been reported,[11] its isolation has not. In our hands, the usual method of deprotonating **8a** or **8b**, namely, treatment with aqueous sodium hydroxide, gave the lowest isolated yield of **2b**. The use of phenyllithium proved convenient for deprotonating large batches of **8a** in yields of *ca.* 50%. For small-scale preparations of highly pure **2b**, deprotonation with 1,5-diazabicyclo[4.3.0]-non-5-ene (DBN), conducted under anhydrous conditions, proved superior (Scheme II). The structure and purity of **2b** were ensured by spectral data and by its conversion with hydriodic acid into **8a** and with picric acid into **10**. Structure **10**, in turn, was made independently from **7** and 2,4,6-trinitroanisole.

Dehydrogenation.—Since 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) has been shown to effect the 1,2-dehydrogenation of certain cyclopenta[*b*]quinoline systems,[7] **2b** was treated with DDQ. However, a 1:1 adduct was formed initially whose high melting point (>300°) and insolubility is suggestive of a polymer.[12] No 2,3-dichloro-5,6-dicyanohydroquinone, indicative of dehydrogenation, was detectable by thin layer chromatography.

The removal of hydride ion from tertiary amines by triphenylmethyl fluoroborate[13] (**13**), followed by deprotonation, seemed to be an appealing way to dehydrogenate **2b** (Scheme III). The high yields of triphenylmethane (60–100%, depending upon the order of addition) confirmed that **2b** did undergo hydride loss on contact with **13**, but no pure product could be isolated by column chromatography (under N_2) of the resulting violet-colored oils (presumably **1c** and its dimer or tritylated products). When 1 equiv of **2b** was added to 2 equiv of triphenylmethyl fluoroborate (**13**) an air-sensitive purple solid was isolated that seemed to be a bistrityl derivative of 4-methyl-4*H*-cyclopenta[*b*]quinoline (possibly **12**). With a 1:1 reaction mixture of **2b** and **13**, the trityl groups were essentially accounted for by the 62% yield of triphenylmethane and 33% yield of **11**. One-half of the starting **2b** was accounted for as the fluoroboric acid salt (**8c**, 20%) and 3-trityl salt (**11**, 33%). Accordingly, 47% of **2b** furnished at least 62% of the hydride ion; this is consistent with the dimerization of **1c** and the further loss of one hydride per dimer (*ca.* 40% + 20%). Thus, although the dehydrogenation proceeded readily, this route to benzo[*b*][1]pyrindines seems to fail because of their acid sensitivity.

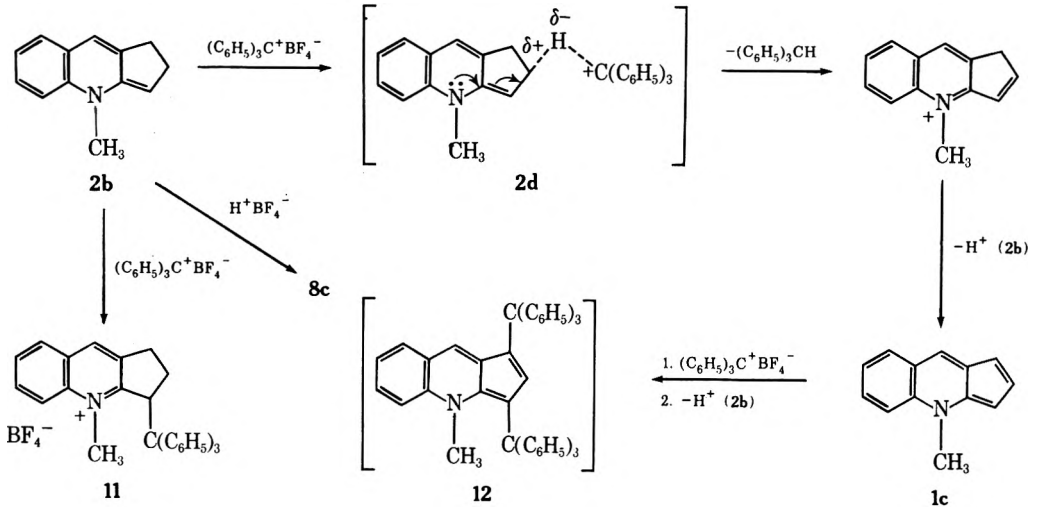
(10) G. H. Alt in "Enamines: Synthesis, Structure, and Reactions," A. G. Cook, Ed., Marcel Dekker, New York, N. Y., 1969, pp 116 ff.

(11) (a) W. Treibs, *Naturwissenschaften*, **49**, 37 (1962); (b) L. E. Kholodov, Z. F. Tishchenkova, I. V. Persianova, and V. G. Yashunskii, *Reakts. Sposobnost Org. Soedin.*, **6**, 1000 (1969); *Chem. Abstr.*, **72**, 121751r (1970); (c) I. F. Tishchenkova, L. E. Kholodov, and V. G. Yashunskii, *Khim.-Farm. Zh.*, **5**, 16 (1971); *Chem. Abstr.*, **74**, 125361c (1971); (d) I. F. Tishchenkova, L. E. Kholodov, and V. G. Yahsunskii, *Khim. Geterotsikl. Soedin.*, **7**, 87 (1971); *Chem. Abstr.*, **75**, 35656u (1971).

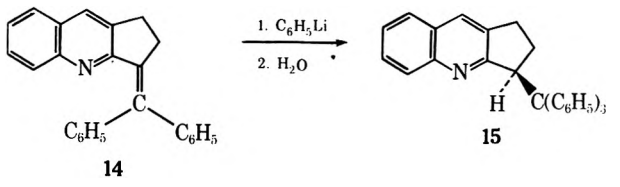
(12) S. Kanda and H. A. Pohl in "Organic Semiconducting Polymers," J. E. Katon, Ed., Marcel Dekker, New York, N. Y., 1969, p 118 ff.

(13) R. Damico and C. D. Broaddus, *J. Org. Chem.*, **31**, 1607 (1966).

SCHEME III



The remarkably easy electrophilic tritylation of **2b** by **13** to yield **11** posed the question of whether the trityl attachment was through methyl [$(C_6H_5)_3C-$] or, owing to better steric accessibility, through a para position [$-C_6H_4CH(C_6H_5)_2$]. The strong similarity between the nmr spectrum of **11** and that of the addition product (**15**) of phenyllithium to 2,3-dihydro-



3-diphenylmethylene-1*H*-cyclopenta[*b*]quinoline (**14**)[7] permits the conclusion that in **11** the trityl group is attached through methyl.[14]

The structure of model compound **15** can, in turn, be readily deduced from its mass spectrum: prominent peaks at *m*/*e* 243 and P − 243 show the clean fragmentation into trityl and quinindanyl moities. Such fragmentation rules out the possibility that **14** underwent phenylation at C_2 or C_9 with rearrangement.

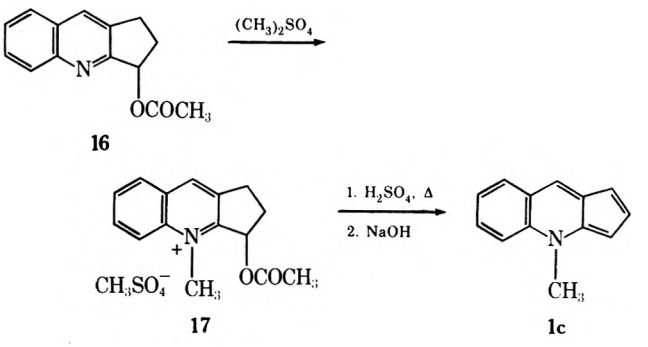
Attempts to dehydrogenate **2b**, by refluxing in xylene with 10% palladium on charcoal or by free-radical bromination at C_1 or C_2 with *N*-bromosuccinimide, failed. In the latter case, **2b** was transformed into a higher molecular weight green solid, similar to the acid-promoted product formed from **2b** upon storage (*cf.* Experimental Section).

Preparation of 4-Methyl-4*H*-cyclopenta[*b*]quinoline.—This synthesis succeeded by achieving exclusively N-methylation with a derivative of **7** suitable for the subsequent introduction of a double bond. Thus, 3-acetoxy-2,3-dihydro-1*H*-cyclopenta[*b*]quinoline (**16**) was quaternized with dimethyl sulfate and the resulting methosulfate **17** was heated briefly with concentrated sulfuric acid to eliminate acetic acid. Liberation of deep violet 4-methyl-4*H*-cyclopenta[*b*]-quinoline (**1c**) with base was conducted under an atmosphere of nitrogen (Scheme IV).

The mass and nmr spectral data on this violet solid give unequivocal proof of its identity as **1c**, free of any

(14) The detection of triphenylmethane in this reaction supports the occurrence of an autoxidation of **15** to form the 3-hydroxy derivative, which then suffers the loss of $(C_6H_5)_3CH$.

SCHEME IV



dimeric or C-methylated contaminants. Its visible spectral maximum at 525 nm (broad absorption between 495 and 555 nm in CCl_4) compares favorably with the absorptions ascribed to **1a** (470–540 nm in C_6H_6) and **1b** (468–530 nm in C_6H_6).[6]

Discussion

Our attempts to dehydrogenate 2,4-dihydro-4-methyl-1*H*-cyclopenta[*b*]quinoline (**2b**) should be compared with those found in two recent reports claiming the synthesis of 1,3-disubstituted 4-methyl-4*H*-cyclopenta[*b*]quinolines from derivatives of **2b** or **8a** and *p*-benzoquinones.[4,5] Benzo[*b*][1]pyrindine systems are postulated to be formed by dehydrogenation with either DDQ or chloranil and these nuclei then are assumed to be attacked by additional substituted benzoquinone to yield, with elimination of hydrogen chloride, 1,3-disubstituted derivatives of **1c**. The high decomposition ranges of our product from **2b** and DDQ and those reported for the above products (230–350°) suggests that such products may be charge-transfer polymers.[12] Mass spectral measurements of molecular weights are necessary to support the monomolecular nature claimed[4,5] for these solids.

Regardless of the molecular weight, however, there seems little doubt that **2b** can undergo dehydrogenation with benzoquinones or with triphenylmethyl fluoroborate (**13**). The nmr spectra of the 1,3-disubstituted 4-methyl-4*H*-cyclopenta[*b*]quinolines reported[4,5] display only aromatic and NCH_3 protons (solutions in DMSO, CF_3COOH, or $AsCl_3$). In our work, treatment of **2b** with **13** gave high yields of triphenylmeth-

ane. A recent mechanistic study points to a similarity in mechanism between the behavior of DDQ and that of **13**: the rapidity with which DDQ transforms tropylidene into the tropenium ion is ascribed to the hydridic transfer of the hydrogen to DDQ.[15] Thus, either in the attack of DDQ or **13** on **2b** the ease with which dehydrogenation occurs can be related to the ease with which hydride ion can be lost from C_2. The developing positive charge at C_2 can be stabilized by the nitrogen center (**2d** in Scheme III). The competing tritylations leading to **11** and presumably to **12** observed with **2b** and **13** are similar to the postulated electrophilic attack of DDQ or chloranil on C_1 or C_3 of benzo[*b*][1]pyrindines.[4,5]

The deprotonation–methylation approach to **1c**, apparently so successful for the synthesis of 1-methyl-1*H*-1-pyrindine from the sodium salt of 1-pyrindine and methyl iodide,[9] was not pursued, since the lithium salt **1b** gave only C-alkylation with methyl iodide. This sharp contrast between the behavior of the salts of pyrindine and benzopyrindine cannot readily be attributed just to the difference in metal ion. Perhaps in **1b** the peri interaction of the C_5 H with the methyl iodide hinders N-methylation. However, it should be observed that a wide variety of anions derived from 2-methylpyridines[16] and 1,2-dihydropyridines[17] undergo C-methylation preferentially.

The methylation–deprotonation route to **1c**, as applied to **3**, seems destined to unavoidable difficulties. Not only can the enamine **1a** compete with **3**, leading to C- and N-methylations, but the acidic methiodide **4a** can easily transfer a proton to unquaternized **3**, leading to salts of **3** and, eventually, dimers of **3**. These difficulties are obviated in the approach to **1c** from the 3-acetoxy derivative **16**. N-Methylation is performed with no such competitive processes and the acid-sensitive system in **1c** is generated only in a strongly basic medium.

In conclusion, the spectral properties of pure 4-methyl-4*H*-cyclopenta[*b*]quinoline (**1c**) provide decisive evidence for the azulene-like character of this heterocycle. The visible spectral absorptions of **1c** ($\lambda_{max}^{Et_2O}$ 525 nm) and of the lithium salt **1b** ($\lambda_{max}^{C_6H_6}$ 530 nm) compare favorably with that of 5,6-benzazulene ($\lambda_{max}^{c\text{-}C_6H_{12}}$ 557 nm).[6] A comparison of the nmr spectrum of **1c** with that of its 1,2-dihydro relative **2b** (in which the conjugation, and hence the ring current, is disrupted) shows the deshielding effect of complete conjugation: aromatic and vinyl protons absorb at 5.83–8.1 ppm in **1c** and at 4.15–7.1 ppm in **2b**, and the NCH_3 group occurs at 3.97 ppm in **1c** but at 2.75 ppm in **2b**. In addition, the ready electrophilic attack that **1b** (and probably also **1c**) undergoes at C_1 and C_3 and the nucleophilic attack that **1c** undergoes at C_9[1] also speak for the azulene-like, aromatic character of the benzo[*b*][1]pyrindine nucleus (**1a–c**).

Experimental Section[18]

2,3-Dihydro-4-methyl-1*H*-cyclopenta[*b*]quinolinium Iodide (8a).—Treatment of **7** in warm ethanolic or ethereal solution with 3 molar equiv of methyl iodide eventually led to the deposition of 98% of the yellowish-green needles of **8a**, mp 209–211° (lit. mp 207°). Recrystallization from 95% ethanol gave dark green needles, mp 212–214°. Extended extraction with hot benzene did not reveal by glpc that any free **7** was present. Spectral data follow: ir_{max}^{KBr} 4.0–4.25 and 5.0–5.3 (weak, $^+$NH), 6.15, 6.25, 8.2, 11.45, and 12.70 μ; nmr (CF_3COOH) 2.72 (q, 2 H), 3.74 (quintet, 4 H), 4.96 (s, <3 H), 8.2–8.7 (m, 4 H), and 9.1 ppm (s, 1 H). From this measurement it was estimated that 1–5% of the hydrogen iodide of **7** was admixed with **8a**. Purer samples resulted from quaternization at room temperature in ether.

2,4-Dihydro-4-methyl-1*H*-cyclopenta[*b*]quinoline (2b). Method A.—To a suspension of 72.8 g (234 mmol) of **8a** in 250 ml of dry benzene was added dropwise an ethereal solution of phenyllithium (246 mmol, 5% excess) at 0° over a period of 2.5 hr. The red-brown solution was then allowed to warm to room temperature with stirring over a 16-hr period. The hydrolysis of the reaction mixture was carried out with deoxygenated water at 0° and the separated organic layer was kept at all times under a nitrogen atmosphere. The organic extract was dried with powdered K_2CO_3 and the solvent was removed with a rotary film evaporator. Distillation under reduced pressure gave a main fraction of an orange-red oil consisting of principally **2b**, bp 133–135° (0.34 mm), for a yield of 46%. Upon standing under a nitrogen atmosphere this oil solidfied to a mass of stout yellow rods. Forerun and afterrun contained **2b**, contaminated with biphenyl and three other products.[19] The main fraction was analyzed by glpc on a 2-ft column (10% silicone gum rubber on firebrick, column temperature 175°, 60 ml/min He) and was shown to display peaks for **7** (192 sec) and **2b** (360 sec) in a 1:9 ratio. A further peak at a longer retention time (480 sec) appeared to be an oxidation product, since its area increased with time of storage and with conscious exposure of the sample to air. Also, oxidation caused the sharp diminution of the peak at 360 sec and the development of new peaks at 384 and 672 sec. However, the absolute amount of **7** in a distilled sample of anhydro base was undoubtedly only about a maximum of 5%, for the neat infrared spectrum did not show the characteristic, intense bands of **7** at 10.55, 11.05, and 12.9 μ, nor did the nmr spectrum display the prominent broad multiplet at 3.2 ppm, characteristic of the 1-CH_2 and 3-CH_2 groups. The presence of sharp singlets at 2.83 and 2.95 ppm, in addition to the principal NCH_3 singlet at 2.75 ppm due to **2b**, revealed the presence of NCH_3-containing components in a sample that had stood for 2 days under nitrogen. The relative intensities of 1.0 (2.95), 1.0 (2.83), and 2.8 (2.75), taken together with the glpc ratio of 1:9 for **7** and **2b**, leads to a minimum composition for this fraction of 55% **2b**, 5% **7**, and 40% of the components having the NCH_3 signals at 2.83 and 2.95 ppm. The latter peaks increased with time, so their origin was ascribed to dimerization or oxidation products of the anhydro hase (*cf. infra*). Samples for further reactions or for spectral measurements, accordingly, were freshly distilled under a nitrogen atmosphere just before use.

Spectral data follow: ir (neat) 2.9–3.1 (clear), 3.3–3.4, 6.1 (C=C str), 6.3, 6.7, 6.9, 7.5, 7.7, 7.8, 8.2, 8.8, 9.15, 9.6, 9.7, 10.8, 11.4, 11.55, and 13.5 (s); nmr (CCl_4) 2.48 (br s, 4 H), 2.75 (s, NCH_3), 4.15 (br s, C_3 H), 5.85 (br s, C_9 H) and 6.5–7.1 ppm (aromatic m). Signals attributable to further chemical reaction developed at 2.1–2.4, 2.83, 2.95, 3.6, and 5.0 ppm.

A solution of **2b** in dry, degassed methylene chloride was warmed with an excess of 45% aqueous hydriodic acid. Upon cooling the methiodide **8a** was formed and identified by melting point, mixture melting point, and infrared spectrum.

Admixture of ethanolic solutions of **2b** and of picric acid led to an immediate precipitation. Collection of the solid revealed a mixture of green and red needles which were mechanically separated. The green, rod-shaped crystals (**10**) melted at 138.0–139.5° after recrystallizations from ethanol and proved to be the methopicrate of **7**. Spectral data: ir_{max}^{KBr} 6.2, 6.45, 6.7, 6.8, 6.9, 7.05, 7.4–8.1, 8.7, 9.3, 11.05, 12.75, 12.95, 13.25, 13.45, 13.9, and 14.2 μ; nmr (CF_3COOH) 2.70 (c of quartet, 2-CH_2), 3.55 (c of quintet, 1-CH_2 and 3-CH_2), 4.6 (s, NCH_3), and 8.0–8.34 (m, 5 H).

Anal. Calcd for $C_{19}H_{16}N_4O_7$: C, 55.34; H, 3.91; N, 13.58. Found: C, 55.06; H, 4.02; N, 13.68.

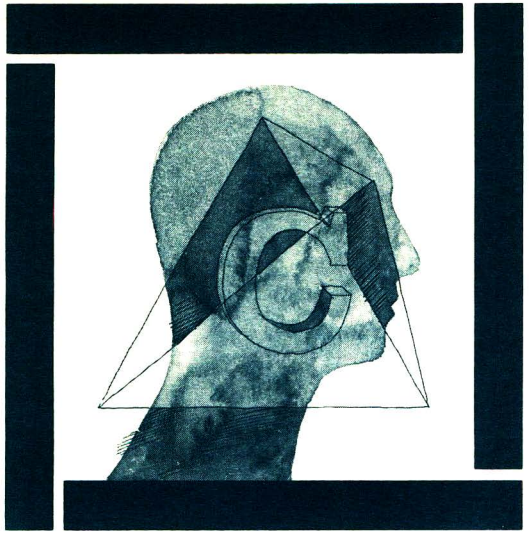
(15) P. Müller and J. Rocek, *J. Amer. Chem. Soc.*, **94**, 2716 (1972).

(16) K. Ziegler and H. Zeiser, *Justus Liebigs Ann. Chem.*, **485**, 174 (1931).

(17) C. S. Giam and J. L. Stout, *Chem. Commun.*, 478 (1970).

(18) Details of the general manipulative procedures and the instrumental methods are given in ref 6.

(19) The higher boiling fractions (150–200°, 0.34 mm) were dissolved in petroleum ether and concentrated to yield a colorless solid, mp 115°, whose infrared (13.5 and 14.4 μ, C_6H_5) and mass [261 (P), 245 (P − 16)] spectra are consistent with the addition of a phenyl group to **8a**.



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3-8

It is interesting to note that the separated dark red needles melted at 140.5–142.0° when recrystallized from ethanol and that a mixture melting point with the green methopicrate **10** was slightly depressed (134.5–135.5°). However, since the mass, ir, and nmr spectra were essentially identical, these differences may stem from polymorphism.

Method B.—A solution of 42.2 g (250 mmol) of **7** in 100 ml of dry toluene was heated to reflux under a nitrogen atmosphere and then a solution of 93.8 g (750 mmol) of freshly distilled dimethyl sulfate dissolved in 50 ml of toluene was introduced dropwise. The heat of reaction sustained the temperature. The solution was cooled and filtered with exclusion of moisture (if required to be hydrate-free) to give a quantitative yield of the methosulfate **8b**. A tlc examination of the almost colorless solid, even after digestion with hot toluene, still showed the presence of some **7**.

A solution of 7.4 g (25 mmol) of **8b** in 125 ml of degassed water was treated with 70 ml of a 10% aqueous potassium hydroxide solution at 0° and under nitrogen. A yellow-green precipitate formed promptly. The slurry was stirred for 1 hr at 25° and then filtered through a coarse glass frit under nitrogen. Repeated washing of the precipitate under nitrogen with degassed water seemed to cause solubilization of some **2b**. Drying overnight *in vacuo* yielded only 18% of the anhydro base **2b**. Its apparent content of **7** by glpc was about the same as that from method A and its ir spectrum was also in agreement with that recorded above. A melting point taken in a sealed tube was 54–57°.

Method C.—A suspension of **8a** (500 mg, 1.60 mmol) in 50 ml of anhydrous, purified tetrahydrofuran was treated with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN, 200 mg, 1.61 mmol, freshly distilled from calcium hydride) with vigorous stirring under an atmosphere of nitrogen for 2.5 hr. The cooled suspension was filtered through a glass frit under nitrogen and the filtrate was then subjected to reduced pressure evaporation to yield **2b** as a pale yellow solid, 257 mg, 87%. The nmr and infrared spectra were recorded immediately under a nitrogen atmosphere. The infrared spectrum was identical with those of **2b** prepared by methods A and B. The nmr spectrum (CCl_4) was free of any peaks attributable to impurities. The absence of the sharp singlets of equal intensity at 2.83 and 2.95 ppm, noted in the spectrum of **2b** made according to method A, is noteworthy. When the DBN was not dried just before use, these peaks also appeared in the **2b** isolated. Such peaks can be assigned to NCH_3 groups in a dimer of **2b**, apparently formed owing to a moisture-promoted reaction. The progress of such a reaction could be discerned by the eventual deposition of a green solid from a solution of **2b** in CCl_4. In contrast with freshly prepared **2b**, which gave a mass spectrum at 70 eV showing peaks at m/e 183 (P), 182 (P − 1), 168 (P − 15), and 167 (P − 16), this green solid gave weak peaks over m/e 500 and prominent peaks between m/e 330 and 370.

2,3-Dihydro-4-methyl-1*H*-cyclopenta[*b*]quinolinium Methopicrate (10).—Gentle heating of 1.0 g (5.9 mmol) of **7** with 1.46 g (6.0 mmol) of 2,4,6-trinitroanisole at 75° for 10 min yielded a dark green solid from which, by recrystallization from ethanol, 1.9 g (78%) of authentic, dark green needles of **10** was isolated, mp 138.0–139.5°.

Action of Triphenylmethyl Fluoroborate (13) on the Anhydro Base 2b.—A solution of freshly distilled **2b** (5.3 g, 29 mmol) in 100 ml of dry, degassed methylene chloride was treated dropwise with a solution of triphenylmethyl fluoroborate (**13**, 9.55 g, 29 mmol) in 125 ml of the same solvent over a period of 15 min at 0°. The dark solution was then stirred at room temperature for 10 hr, after which time tlc monitoring showed the consumption of **2b** and **13**. After evaporation of the solvent from the reaction mixture, the residue was extracted exhaustively with anhydrous ethyl ether to remove the triphenylmethane (4.4 g, 62% by melting point and ir).[20]

Fractional recrystallization of the residue from the previous extraction from acetone yielded two substances. (A) Colorless needles of 2,3-dihydro-4-methyl-3-triphenylmethyl-1*H*-cyclopenta[*b*]quinolinium fluoroborate (**11**) were obtained after several recrystallizations: mp 184.5–185.5°; 4.9 g (33% yield); ir_{max}^{KBr} 8.8–9.8 (BF_4^-), 13.0–13.4 and 14.3 μ [$(C_6H_5)_3C$]; nmr (CF_3CO_2H) 1.6 (m, 1 H), 2.7 (m, 3 H), 3.87 (s, 3 H), 5.58 (m, 1 H), 7.3 (s, 15 H), 8.05–8.2 (4 H), and 8.3 ppm (1 H). *Cf.* nmr spectral discussion under the section describing the action of phenyllithium on **14**.

Anal. Calcd for $C_{32}H_{28}BF_4N$: C, 74.86; H, 5.50. Found: C, 74.81; H, 5.83.

(B) Pale green needles of 2,3-dihydro-4-methyl-1*H*-cyclopenta[*b*]quinolinium fluoroborate (**8c**) were obtained after several recrystallizations, mp 170–171°, 1.6 g (20%). An authentic sample of **8c** was prepared by admixing aqueous solutions of **8a** (1.0 g, 3.3 mmol) and silver fluoroborate (0.9 g, 3 mmol). After collection of the silver iodide and concentration of the filtrate, colorless needles of **8c** were deposited, mp 171.5–172.0°.

Anal. Calcd for $C_{13}H_{14}BF_4N$: C, 57.60; H, 5.20. Found: C, 57.61; H, 5.50.

The dark mother liquor from these recrystallizations was evaporated under reduced pressure while under a nitrogen atmosphere. Addition of sodium hydroxide and extraction with benzene gave a deep purple organic layer. Passing gaseous hydrogen bromide into the dried benzene solution discharged the violet color and yielded a yellow-orange solution.

When a purple benzene solution was extracted with concentrated sulfuric acid, the purple color was discharged. However, dilution of the sulfuric acid layer with water did not regenerate the purple color. When the extraction of the purple benzene layer was repeated with 85% orthophosphoric acid, the color was again discharged but in this case dilution of the acid layer with water did restore the purple color. However, the purple-violet oils and solids obtained from such attempts at isolation could not be obtained pure.

Action of the Anhydro Base 2b on an Excess of Triphenylmethyl Fluoroborate (13).—To a solution of 5.88 g (17.9 mmol) of **13** in 125 ml of dry, degassed methylene chloride was added dropwise a solution of 1.56 g (8.5 mmol) of **2b** in 50 ml of the same solvent at 0°. After a 7-hr stirring period at room temperature a solution of 4.32 g (42.6 mmol) of dry, degassed triethylamine in 40 ml of methylene chloride was added to the dark mixture at 0°. The blue-purple mixture was concentrated *in vacuo* with warming to 55° and the residue, dissolved in methylene chloride, was chromatographed on an alumina–petroleum ether (bp 30–60°) column that was prepared and operated under a nitrogen atmosphere. Elution with petroleum ether yielded 2.63 g (60%) of triphenylmethane (melting point and ir spectrum). Use of petroleum ether–benzene yielded 0.50 g of a purple-violet solid, mp 160–170°, that by tlc was shown to contain some triphenylmethane. Spectral data follow: ir (mineral oil) 13.3, 13.5, and 14.35 μ [strong, $(C_6H_5)_3C$]; nmr ($CDCl_3$) 3.72 (s, NCH_3), 6.65 (s, 2 H, possibly C_2H and C_9H), 7.05–7.75 with spike at 7.75 ppm for $(C_7H_5)_3C$ (m, *ca.* 40 H). Although this compound could not be obtained analytically pure because of its air sensitivity, it seemed to be a 1,3-bistrityl derivative of 4-methyl-4*H*-cyclopenta[*b*]quinoline (**12**). It showed a behavior, on extraction of its benzene solution with acids, similar to that shown by the previous purple-colored products.

Successive elution with benzene, methylene chloride, and ether yielded 2.8 g of material composed of unknown solids, together with triphenylmethanol.

Action of 2,3-Dichloro-5,6-dicyanobenzoquinone on the Anhydro Base 2b.—A solution of 8.5 g (46 mmol) of **2b** in 50 ml of dry, degassed benzene was heated to reflux for 27 hr under nitrogen with a solution of 10.5 g (46 mmol) of DDQ in 500 ml of benzene. The cooled mixture was diluted with 500 ml of petroleum ether, in order to precipitate selectively any 2,3-dichloro-5,6-dicyanohydroquinone. However, the precipitated black solid was a quantitative yield of a 1:1 adduct of **2b** and DDQ: mp 192–202°, after one recrystallization from ethanol; mp >330°; ir (KBr) 2.80 (str OH), 4.40 (C≡N), and 6.3 μ (C=O).

Methylation of Anhydro Base 2b.—A solution of 250 mg (0.80 mmol) of freshly prepared **2b** in 40 ml of anhydrous tetrahydrofuran was heated at reflux under nitrogen for 24 hr with a threefold excess of methyl iodide. The dark green mixture was filtered to give 240 mg of product (92%). Recrystallization from methanol, after treatment with charcoal, afforded yellow crystals of **5**, mp 172–173°.

The identity of the product as the methiodide of 3-methyl-2,3-dihydro-1*H*-cyclopenta[*b*]quinoline (**5**) was established by preparing an authentic sample from the known 3-methyl derivative **6**. Although attempted quaternization with methyl iodide proceeded poorly, an indirect route proved successful. Thus, 200 mg (0.61 mmol) of **6** dissolved in benzene was heated with a

(20) In two runs where 1 equiv of **2b** was added dropwise to a solution of 1 equiv of **13**, yields of 95–100% of triphenylmethane were realized. However, again only intractable, violet-colored material resulted.

twofold excess of freshly purified dimethyl sulfate for 3 hr. The resulting mixture was treated with 10 *N* aqueous sodium hydroxide at 20°. The separated benzene layer was treated with 48% aqueous hydriodic acid. The precipitated yellow solid was collected and recrystallized from methanol, mp 172–173° (tends to darken above 60°). A mixture melting point with the methylation product of 2b was undepressed.

Action of Phenyllithium on 2,3-Dihydro-3-diphenylmethylene-1*H*-cyclopenta[*b*]quinoline (14).[21]—A solution of 6.60 g (20 mmol) of 14 in 40 ml of benzene was treated with 26 mmol of phenyllithium dissolved in 25 ml of ethyl ether. An immediate exothermic reaction accompanied the formation of a red-brown solution. After an 18-hr stirring period at 25° the solution was hydrolyzed and 2.6 g of an insoluble greenish precipitate was collected, mp 175–215°. The separated, dried, and evaporated organic layer was taken up in benzene and addition of ethanol then precipitated a yellow solid that was mostly 14.

The original crude product (mp 175–215°) was recrystallized from a benzene–petroleum ether pair to yield colorless crystals of 15, mp 221–222° dec, 28%. Recrystallization from acetone was necessary to avoid occluded benzene. Spectral data follow: ir$^{CS_2}_{max}$ 3.2, 13.3, and 14.3 μ (C_6H_5); nmr (CS_2) 1.5 (m, 1 H), 2.4 (m, 3 H), 5.13 (d of d, 1 H), and 6.9–7.6 ppm (m, 20 H); mass spectrum (70 eV) *m/e* 411 (P and base), 334 (P − 77), 243 [$(C_6H_5)_3C$], 168 ($C_{12}H_{10}N$), and 165 (9-fluorenyl). The proton at 1.5 ppm is ascribed to the 2-H trans to the 3-trityl group; the three-proton multiplet to the 2-H cis to the trityl group (causing deshielding) and to the two 1-H protons. The 3-H proton occurs at 5.13 ppm. The mass spectral peaks at *m/e* 334, 243, and 168 are of equal intensity and are the most prominent after the parent and base peak.

Anal. Calcd for $C_{31}H_{25}N$: C, 90.48; H, 6.12. Found: C, 90.41; H, 6.29.

The mother liquors from the separation of 15 and from the recovery of 14 were combined and freed of solvent. Column chromatography on neutral alumina and elution with petroleum ether yielded 100 mg of triphenylmethane, mp 91–92°, identified by mixture melting point and infrared criteria. An unidentified yellow solid, mp 225–240°, was also isolated.

4-Methyl-1*H*-cyclopenta[*b*]quinolinium Iodide (4).—A freshly distilled, 2.77-g sample of 1*H*- (and 3*H*- and 4*H*-) cyclopenta[*b*]-quinoline (3) (16.6 mmol) was treated at room temperature and under a nitrogen atmosphere with 5 ml of dry, degassed methyl iodide. The solution turned dark green and, upon standing overnight, a chartreuse-colored solid was deposited. This solid was collected, washed with petroleum ether, powdered, and then thoroughly dried in an Abderhalden pistol at 42° under reduced pressure for 60 hr, 4.7 g (92%), mp 221–236° (sealed tube). Although this methiodide was contaminated with N-protonated and probably both C-methylated and dimeric by-products, purification by washing had to suffice. No satisfactory recrystallization could be performed from acetonitrile, ethyl acetate, alcohols, or water, for decomposition ensued with the formation of purple solutions.

Anal. Calcd for $C_{13}H_{12}IN$: C, 50.50; H, 3.91. Found: C, 49.85; H, 4.16.

Spectral data follow: ir (mineral oil) 4.0–5.7 (HNR_3^+); nmr (CF_3COOH) 2.10 (s), 4.0–4.75 (br m), 4.80 (s), 8.2–8.8 (m), and 9.0–9.2 ppm (m). On the basis of the signal at 9.0–9.2 as one C_5H, the ratio of all vinylic H to all aliphatic H (4.0–4.8 ppm) is 7.0:8.0. Compound 4 would require a ratio of 7.0:5.0. It is concluded that the observed ratio signifies the formation of some dimer of 3 (*cf.* ref 8 and 9), causing loss of vinyl H and gain of aliphatic H. Comparison of signals at 2.10 (CCH_3) and 4.80 (NCH_3) ppm suggests a maximum of 15% C-methylation. Although methyl iodide also absorbs around 2.10 ppm, the thorough drying of 4 at 42° *in vacuo* assures its absence. Furthermore, repetition of the quaternization of 3 in benzene or in absolute ethanolic solution gave identical results.

4-Methyl-4*H*-cyclopenta[*b*]quinoline (1c). Method A.—Under a nitrogen atmosphere a yellow slurry of 380 mg (1.2 mmol) of 4 in 15 ml of degassed methylene chloride was slowly admixed with degassed, aqueous sodium carbonate solution at 0°. The blue-violet mixture was warmed to 25° with stirring. The organic layer was separated and the solvent was evaporated, all under a nitrogen atmosphere. The nmr spectrum of this product showed it to contain 4-methyl-4*H*-cyclopenta[*b*]quinoline (1c). Treatment with picric acid dissolved in ethanol gave a dark green picrate, mp 127–132°, whose nmr spectrum in CF_3COOH again displayed both *C*-methyl (2.10 ppm) and *N*-methyl (4.60 ppm) signals.

Method B.—A mixture of 400 mg (1.75 mmol) of 3-acetoxy-2,3-dihydro-1*H*-cyclopenta[*b*]quinoline (16) and 1 ml of freshly distilled dimethyl sulfate dissolved in 10 ml of benzene was stirred at 25° for 24 hr. Removal of the benzene and excess dimethyl sulfate under reduced pressure afforded an off-white methosulfate (17). (After this point all operations were conducted under nitrogen.) The solid was dissolved in 30 ml of concentrated sulfuric acid and the resulting solution was heated for 4 min in an oil bath maintained at 115–120°. The solution was poured over cracked ice. While the mixture was further chilled in an ice bath, 100 ml of ethyl ether was added and the system was made basic by the slow addition of 50% aqueous sodium hydroxide solution. After the ether layer was separated, the aqueous layer was extracted with three 100-ml portions of ether. All ether extracts were dried over anhydrous magnesium sulfate and the solvent was then removed to afford 1c as a violet solid, 175 mg (55%). Although solutions in degassed ether or CCl_4 were stable under nitrogen <0°. the violet color of 1c rapidly disappeared upon exposure to air and, in the solid state, 1c tended to form an insoluble, apparently polymeric (no mass spectral peaks at 25°) black solid.

Its spectral data are in complete accord with the assigned structure: (A) mass spectrum (70 eV) with the probe at 25° (mass, rel intensity, assignment) 181 (64, P), 167 (100, P − CH_2), 166 (56, P − CH_3), 146 (18, P − C_2H), 140 (22, P − CH_3 − C_2H), and 139 (18, P − CH_3 − C_2H_2); (B) nmr spectrum in CCl_4 (peak on δ scale with internal TMS): 3.97 (s, N − CH_3), 5.83 [br, C_1 H presumably split by C_2 H (*ca.* 4 Hz) and by C_3 H and C_9 H (~1 Hz)], 6.40 [d of d with higher intensity downfield (C_3 H, J_{23} = 5 Hz, J_{13} = 1.5 Hz)], 7.0–7.4 (two triplets of unequal splitting, C_2 H and C_9 H), 7.5–7.9 (m, 3 H), and 8.1 (br s, C_5-H); (C) visible spectrum in Et_2O, broad maximum between 495 and 555 nm [λ_{max} 525 nm (log ϵ *ca.* 2.5)]; and (D) infrared spectrum in CCl_4 2.5–3.4 (clear), principal band at 3.4–3.6, 6.3–6.6 (br str), 8.0, 9.2, 9.4, 9.9, and 11.6 μ).

Addition compounds were readily formed with *sym*-trinitrobenzene and with both picric acid and hydriodic acid. However, decomposition accompanied these reactions, since only dark green or black products of uncertain composition could be isolated. Moreover, the products from acid treatment of 1c, when treated with sodium carbonate solution, under a nitrogen atmosphere, did not regenerate the violet 4-methyl-4*H*-cyclopenta[*b*]quinoline (1c).

Registry No.—1c, 13038-93-2; 1c picrate, 37160-83-1; 2b, 31860-33-0; 4a, 26865-54-3; 8c, 37164-21-9; 10, 37160-86-4; 11, 37164-22-0; 12, 37160-87-5; 15, 37160-88-6; adduct (1:1) of 2b and DDQ, 37160-89-7.

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(21) This experiment was performed by Dr. Robert A. Harrell, Jr.

Intramolecular Cyclization of N-(ω-Aminoalkyl)-1,2-dihydroisoquinolines

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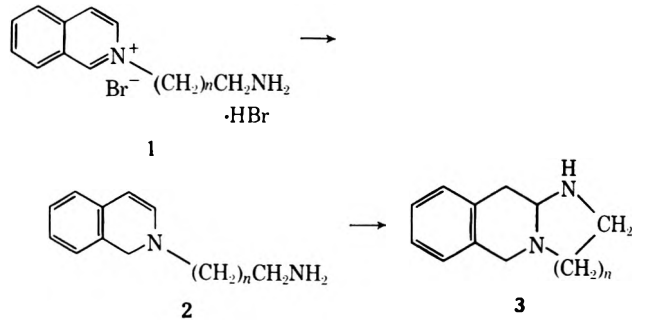
Reduction by $LiAlH_4$ of *N*-(2-aminoethyl)- and *N*-(3-aminopropyl)isoquinolinium salts leads directly to the tricyclic compounds, 1,2,3,4,5,10,10a-hexahydroimidazo[1,2-*b*]isoquinoline (**3**, $n = 1$) and 2,3,4,6,11,11a-hexahydro-1*H*-pyrimido[1,2-*b*]isoquinoline (**3**, $n = 2$). The latter compound is oxidized by mercuric acetate/EDTA to 1,3,4,11b-tetrahydro-2*H*-pyrimido[2,1-*a*]isoquinoline (**6**, R = H), identical with material obtained by treatment of *N*-(3-aminopropyl)isoquinolinium chloride hydrochloride with base, thus suggesting that the isoquinolinium salt is an intermediate in the oxidative transformation. An alternative unproven hypothesis proceeding *via* a macrocyclic intermediate **11** is discussed. This is given some credence by the reduction of the methiodide of **3** ($n = 2$), compound **13**, to 1,2,3,4,5,6,7,8-octahydro-2-methyl-2,6-benzodiazecine (**14**) and the failure of the *N*-methyl analog **9** to undergo the oxidative transformation in good yield, other oxidation products being formed concomitantly.

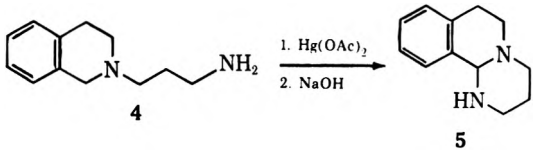
The intramolecular cyclization of 1,2-dihydroisoquinolines has been shown to be a very useful route to the Berberine alkaloids.[1]

More recently the chemistry of 1,2-dihydroisoquinolines has been the subject of extensive investigations by the groups of Dyke in England and Knabe in Germany.[2]

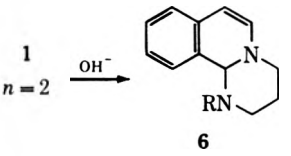
Based on the observations of these workers, it seemed possible that 1,2-dihydroisoquinolines would add other nucleophiles intramolecularly at position 3 and that this could be used to construct novel heterocyclic systems, which from our standpoint incorporated the pharmacologically significant phenethylamine moiety. To investigate this possibility, we chose to examine the reduction of a 2-(3-aminopropyl)isoquinolinium salt **1** ($n = 2$) to the 1,2-dihydroisoquinoline **2** ($n = 2$). Cyclization of **2** would yield a known member of the type of heterocycle we wished to investigate, *i.e.*, 1,3,4,6,11,11a-hexahydro-2*H*-pyrimido[1,2-*b*]isoquinoline **3** ($n = 2$).[3]



Rapid addition of the finely ground isoquinolinium salt **1** ($n = 2$), prepared in a manner analogous to that used for *N*-(3-dimethylaminopropyl)isoquinolinium chloride,[4] to a slurry of lithium aluminum hydride in ether, followed by rapid work-up, gave **3** ($n = 2$) directly in 53% yield. The spectra were in accord with the assigned structure and the material had a melting point (69–70°) close to that reported (70–72°).[3] As direct comparison, which would have removed any ambiguity about the direction of ring closure, could not be made,[5] the isomeric tricycle **5**, mp 83°, was prepared by the literature procedure.[6] This was not



identical with **3** ($n = 2$) based on comparison of nmr spectra. Furthermore, extraction of an aqueous solution of the isoquinolinium salt **1** ($n = 2$), which had been made thoroughly basic, gave compound **6** (R = H) in 95% yield.



Treatment of **6** (R = H) with lithium aluminum hydride in refluxing tetrahydrofuran overnight failed to reduce the double bond, which would have given **5**. Catalytic hydrogenation converted **6** (R = H) in 95% yield to *N*-(3-aminopropyl)-1,2,3,4-tetrahydroisoquinoline (**4**).[6] Cyclization of the amino group of the isoquinolinium salt **1** ($n = 2$) to position 1 of the isoquinoline as a prelude to reduction can therefore be excluded from consideration.

The reductive cyclization procedure also worked well on the isoquinolinium salt **1** ($n = 1$) to give an 83% yield of a crystalline product. From comparison of the nmr spectrum of this product **3** ($n = 1$) with that of compound **3** ($n = 2$) obtained previously, the new compound was clearly 1,2,3,5,10,10a-hexahydroimidazo[1,2-*b*]isoquinoline **3** ($n = 1$). It was, however, quite sensitive to autoxidation and discolored on standing in the air even in the solid state. Our investigations were therefore restricted to **3** ($n = 2$), which was more stable and, although previously synthesized,[3] had not been investigated. In view of the sensitivity to oxidation it was of interest to explore which pathway was pursued. Several oxidation conditions yielded intractable mixtures. One experiment using mercuric acetate-EDTA,[7] however, smoothly transformed **3** ($n = 2$) in 68% yield to a new com-

(1) A. R. Battersby, D. J. LeCount, S. Garratt, and R. I. Thrift, *Tetrahedron*, **14**, 46 (1961).

(2) S. F. Dyke, K. G. Kinsman, J. Knabe, and H. D. Holtje, *Tetrahedron*, **27**, 6181 (1971), and references cited therein.

(3) J. L. Neumeyer and K. K. Weinhardt, *Chem. Commun.*, 1423 (1968).

(4) A. P. Grey, W. L. Archer, D. C. Schlieper, E. E. Spinner, and C. J. Cavallito, *J. Amer. Chem. Soc.*, **77**, 3536 (1955).

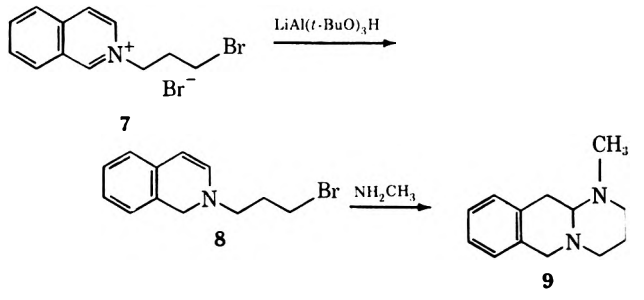
(5) Professor Neumeyer was unable to supply a sample or copies of the spectra.

(6) D. Beke and L. Toke, *Chem. Ber.*, **95**, 2122 (1962).

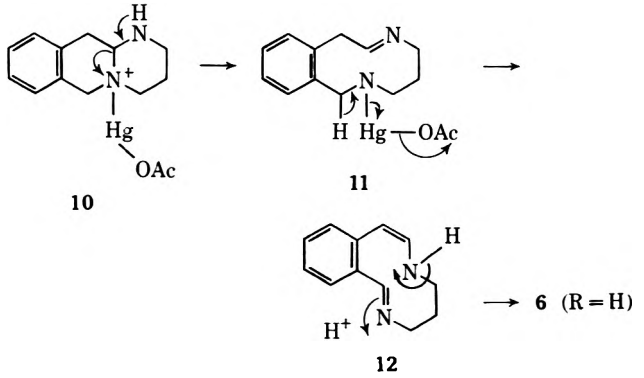
(7) J. Knabe and H. Roloff, *ibid.*, **97**, 3452 (1964).

pound, which was quickly identified *via* the cyclamate salt as the 1,3,4,11b-tetrahydro-2*H*-pyrimido[2,1-*a*]-isoquinoline **6** (R = H), obtained previously from treatment of the isoquinoline salt **1** (n = 2) with base. The mechanism of the formation of **6** (R = H) that we favor is therefore oxidation of **2** (n = 2), present in equilibrium with **3** (n = 2), to the isoquinolinium salt **1** (n = 2). This is cyclized to **6** (R = H) during the basification, which precedes extraction.

To increase the generality of the synthetic method an alternate route was devised so that other amino functions could be introduced. Lithium aluminum tri-*tert*-butoxyhydride reduction of *N*-(3-bromopropyl)-isoquinolinium bromide (**7**) yielded the 1,2-dihydroisoquinoline **8** as an oil, which decomposed on heating but was otherwise no less stable than the other intermediates. Reaction of this compound with ethanolic methylamine yielded the *N*-methyl analog of **3** (n = 2), compound **9**.

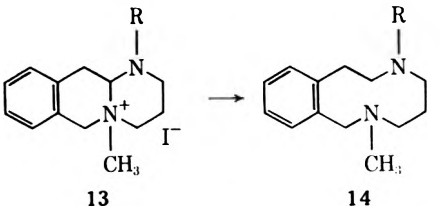


Compound **9**, 2,3,4,6,11,11a-hexahydro-1-methylpyrimido[1,2-*b*]isoquinoline, is a crystalline, readily characterizable compound. Application of the mercuric acetate oxidation conditions to **9** gave a complex product mixture, containing about 25% of an isocarbostyril (C=O in ir, low-field proton in nmr). The nmr spectrum resembled more that of the mixture of products obtained by extraction of a basified aqueous solution of 2-(3-dimethylaminopropyl)isoquinolinium chloride hydrochloride, which does not have the possibility to cyclize and perforce yields a pseudobase and products derived therefrom (*e.g.*, an isocarbostyril is also present). One interesting possibility[8] to account for the difference in the behavior of **9** and **3** (n = 2) would be that **3** (n = 2) has a pathway open to **6** (R = H) other than *via* the isoquinolinium salt.

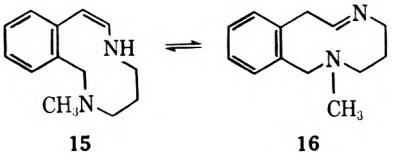


Attempts to provide substantiation for this hypothesis by demonstrating the stability of **6** (R = H) under reaction conditions gave inconclusive results. Nevertheless, some credence was provided by the observation that the methiodide of **3** (n = 2), compound **13** (R = H), on reduction with lithium aluminum hydride gave in 52% yield the macrocycle **14** (R = H) derived from an intermediate analogous to **11**.

Similarly **13** (R = CH_3) could be reduced to **14** (R = CH_3) by sodium borohydride. A related transformation was reported recently,[9] and a dimethoxybenzodiazecine related to **14** has been described by an alternative route.[10]



Further evidence for the propensity of the central bond to cleave in the methiodide **13** (R = H) was obtained by examination of the nmr spectrum in DMSO–D_2O and adding NaOD. On standing three peaks developed in the olefin region. This resembled an AB pattern with a further broad peak superimposed over one doublet of the AB at δ 5.98 and the other doublet at 5.18 (J = 6 Hz). This is what one might anticipate from some equilibrium between **15** and **16**.



Experimental Section[11]

***N*-(2-Aminoethyl)isoquinolinium Bromide Hydrobromide, 1** (n = 1).—Isoquinoline (50 g, 0.39 mol) was dissolved in isopropyl alcohol (800 ml), 2-bromoethylamine hydrobromide (80 g, 0.39 mol) was added, and the mixture was heated to reflux. After reflux overnight the precipitate was collected, washed, and dried to yield **1** (n = 1) (105 g, 80%): mp 281–283°; ν_{max} 1646 (m), 1100 (m), 834 cm^{-1} (m); λ_{max}^{MeOH} 232 mμ (ϵ 47,430), 278 (2980), 338 (4310).

Anal. Calcd for $C_{11}H_{14}Br_2N_2$: C, 39.55; H, 4.23; N, 8.39. Found: C, 39.67; H, 4.24; N, 8.22.

***N*-(3-Aminopropyl)isoquinolinium Bromide Hydrobromide, 1** (n = 2).—Isoquinoline (12.9 g, 0.1 mol) was dissolved in isopropyl alcohol (80 ml). 3-Bromopropylamine hydrobromide (21.9 g, 0.1 mol) was added and the mixture was refluxed. During 3 hr the insoluble hybrobromide dissolved; soon thereafter a solid precipitated from the refluxing solution. This was collected, washed, and dried to give **1** (n = 2) (26.5 g, 76%): mp 207–209°; ν_{max} 1644 (m), 828 (s), 762 cm^{-1} (s); λ_{max}^{MeOH} 233 mμ (ϵ 50,600), 278 (2950), 337 (4270).

Anal. Calcd for $C_{12}H_{16}Br_2N_2$: C, 41.41; H, 4.63; N, 8.05. Found: C, 41.37; H, 4.63; N, 7.88.

1,2,3,5,10,10a-Hexahydroimidazo[1,2-*b*]isoquinoline, 3 (n = 1).—The isoquinolium salt **1** (n = 1) (17.3 g, 0.051 mol) was ground to a dust and added rapidly to a well-stirred slurry of $LiAlH_4$ (5.6 g, 0.147 mol) in ether (200 ml). The mixture was stirred at room temperature for 25 min. The excess $LiAlH_4$ was decomposed with a saturated solution of potassium sodium tartrate. The salts were removed by filtration and washed with

(8) Suggested by Professor Peter Yates.

(9) M. Davis, P. Knowles, B. W. Sharp, R. J. A. Walsh, and K. R. H. Wooldridge, *J. Chem. Soc. C*, 2449 (1971).

(10) T. Yamazaki, *Yakugaku Zasshi*, **79**, 1014 (1959); *Chem. Abstr.*, **54**, 5680 (1960).

(11) Melting points were obtained in a Thomas-Hoover melting point apparatus and are uncorrected. Nmr spectra were obtained on a Varian A-60 instrument as $CDCl_3$ solutions and ir spectra as Nujol mulls, unless otherwise indicated. Mass spectra were obtained on a M.S.9 instrument, at 70 eV.

ether. The ethereal filtrate was washed, dried ($MgSO_4$), and removed to give **3** (n = 1) as a colorless, crystalline solid (7.4 g, 83%). This material could be recrystallized from ether, but showed a sensitivity to autoxidation. The analytical sample was obtained by sublimation (0.05 mm, 50°): mp 66–69°; ν_{max} 3222 (m), 1166 (m), 908 (m), 740 cm^{-1} (s); nmr δ 7.08 (br s, 4), 4.24 (d, 1, J = 6 Hz), 3.98 (d, 1, J = 6 Hz).

Anal. Calcd for $C_{11}H_{14}N_2$: C, 75.82; H, 8.10; N, 16.08. Found: C, 75.59; H, 8.04; N, 16.04.

1,3,4,6,11,11a-Hexahydro-2*H*-pyrimido[1,2-*b*]isoquinoline, 3 (n = 2).—The isoquinolinium salt **1** (n = 2) (60 g, 0.172 mol) was treated and worked up in an analogous manner as above with $LiAlH_4$ (9.8 g, 0.258 mol) in ether (1 l.). The ethereal filtrate yielded a colorless solid **3** (n = 2) (17.3 g, 53%), mp 68–70°, which could be recrystallized (water). An analytical sample was prepared by sublimation (0.05 mm, 50°), yielding material of mp 69–70° (lit.[3] mp 70–72°); ν_{max} 3275 (m), 1102 (m), 738 cm^{-1} (s); λ_{max}^{MeOH} benzenoid absorption; nmr δ 7.10 (s, 4), 3.84 (d, 1, J = 14 Hz).

Anal. Calcd for $C_{12}H_{16}N_2$: C, 76.55; H, 8.57; N, 14.88. Found: C, 76.87; H, 8.35; N, 14.74.

1,3,4,6,11,11a-Hexahydro-5-methyl-2*H*-pyrimido[1,2-*b*]isoquinolinium Iodide, 13 (**R** = H).—Compound **3** (n = 2) (2 g, 0.0106 mol) was dissolved in ice-cold CH_2Cl_2, which contained CH_3I (1.67 g, 0.0117 mol). After standing at 0° for 30 min, the solid was collected, washed (ether), and dried. The product was **13** (R = H) (1.4 g, 28%): mp 187–189°; ν_{max} 3270 (m), 1235 (m), 750 (s), 728 cm^{-1} (s); λ_{max}^{MeOH} benzenoid absorption; nmr[12] (D_2O) δ 7.34 (m, 4), 4.78 (q, 1), 4.58 (AB, 2, J = 16 Hz), 2.94 (s, 3), in DMSO/D_2O/NaOD, δ 5.98 (br s), 5.18 (d, J = 6 Hz).

Anal. Calcd for $C_{13}H_{19}N_2I$: C, 47.27; H, 5.75; N, 8.48. Found: C, 47.19; H, 5.67; N, 8.35.

***N*-(3-Aminopropyl)-1,2,3,4-tetrahydroisoquinoline (4).**—2-(3-Aminopropyl)isoquinolinium bromide hydrobromide, **1** (n = 2) (20.5 g, 0.059 mol), was dissolved in water (50 ml) and methanol (50 ml) was added. An aqueous solution of sodium borohydride (5 g in 60 ml) was added slowly to the well-stirred and cooled (ice bath) mixture. After addition, the mixture was stirred for 30 min, then made strongly basic (20% KOH) and continuously extracted with ether. The ether was dried ($MgSO_4$) and removed to give a colorless oil **4** (5.8 g, 52%), nmr δ 7.06 (s, 4), 3.60 (s, 2).

Solution in ethanolic HCl and precipitation by ether gave 6.8 g of HCl salt, mp 263–265° (lit.[6] mp 261°). Recrystallization from ethanol gave an analytical sample, mp 263–265°, ν_{max} 2670, 2560, 1602 (m), 1168 (m), 766 cm^{-1} (s).

Anal. Calcd for $C_{12}H_{18}N_2 \cdot 2HCl$: C, 54.80; H, 7.67; N, 10.65. Found: C, 54.61; H, 7.67; N, 10.43.

1,3,4,6,7,11b-Hexahydro-2*H*-pyrimido[2,1-*a*]isoquinoline (5).—*N*-(3-Aminopropyl)-1,2,3,4-tetrahydroisoquinoline (**4**, 2.83 g, 0.015 mol) was dissolved in 4% aqueous acetic acid (50 ml). Mercuric acetate (9.6 g, 0.03 mol) was added, and the mixture was warmed for 6 hr at 50° and then stirred overnight at room temperature. It was then filtered. The filtrate was basified (20% KOH) and extracted (ether). The ether extracts were washed (water), dried ($MgSO_4$), and removed to give a white solid, which was recrystallized from petroleum ether (bp 30–60°) to give **5** (760 mg, 27%): mp 74–76°; ν_{max} 3230 (m), 2800 (m), 2740 (m), 1294 (s), 1135 (s), 736 cm^{-1} (s); ν_{max}^{MeOH} benzenoid absorption; nmr δ 7.58 (m, 1), 7.08 (m, 3), 3.88 (s, 1).

Anal. Calcd for $C_{12}H_{16}N_2$: C, 76.55; H, 8.57; N, 14.88. Found: C, 76.66; H, 8.68; N, 15.03.

Compound **5** was identical (mixture melting point and spectra) with material prepared by the literature procedure.[6]

1,3,4,11b-Tetrahydro-2*H*-pyrimido[2,1-*a*]isoquinoline, 6 (**R** = H).—Compound **3** (n = 2) (10 g, 0.053 mol) was added to a well-stirred solution of mercuric acetate (16.9 g, 0.053 mol) and ethylenediaminetetraacetic acid disodium salt (19.8 g, 0.053 mol) in 2% aqueous acetic acid (100 ml) at room temperature under nitrogen. A gray precipitate separated rapidly from the initial solution. The mixture was stirred overnight at room temperature, and the precipitate was removed. The filtrate was made basic (20% KOH) and extracted (ether). The ethereal extracts were washed (water), dried ($MgSO_4$), and concentrated. The residue was an oil (6.8 g, 68%), which from the nmr spectrum was exclusively **6** (R = H). This was characterized as the biscyclamate salt: mp 154–155° (acetone); ν_{max} 3250 (m), 1224 (s), 1158 (s), 1028 cm^{-1} (s); λ_{max}^{MeOH} 231 mμ (ε 47,040), 277 (3010), 335 (4120); nmr (of free base) δ 7.02 (m, 4), 6.0 (d, 1, J = 7 Hz), 5.34 (d, 1, J = 7 Hz), 5.20 (s, 1).

Anal. Calcd for $C_{12}H_{14}N_2 \cdot 2C_6H_{13}NO_3S$: C, 52.93; H, 7.40; N, 10.29. Found: C, 53.29; H, 7.27; N, 10.15.

1,3,4,11b-Tetrahydro-2*H*-pyrimido[2,1-*a*]isoquinoline, 6 (**R** = H).—2-(3-Aminopropyl)isoquinolinium bromide hydrobromide (**1**, n = 2) (10 g, 0.028 mol) was dissolved in water (40 ml). The solution was covered with benzene (40 ml) and stirred; 20% aqueous KOH was added until the aqueous phase was strongly basic. The mixture was stirred at room temperature for 10 min. The benzene layer was separated, washed (water), dried ($MgSO_4$), and removed to yield an oil **6** (R = H) (5.1 g, 95%) identical by nmr spectroscopy with that obtained from the experiment above.

The oil was characterized as the biscyclamate salt, bp 154–156°. There was no depression in melting point on admixture with the biscyclamate from the experiment above. The two compounds were identical by ir spectroscopy.

***N*-(3-Bromopropyl)isoquinolinium Bromide (7).**—Isoquinoline (200 g, 1.55 mol) was dissolved in toluene (1 l.). 1,3-Dibromopropane (600 g, 2.96 mol) was added and the mixture was stirred at 60° for 21 hr. The resulting precipitate was collected well, washed with toluene, and dried to yield **7** (384 g, 75%): ν_{max} 1650 (m), 1194 (m), 854 cm^{-1} (m); λ_{max}^{MeOH} 232 mμ (ε 52,380), 277 (3050), 337 (4200).

Anal. Calcd for $C_{12}H_{13}Br_2N$: C, 43.53; H, 3.96; N, 4.23. Found: C, 43.92; H, 4.04; N, 4.16.

***N*-(3-Bromopropyl)-1,2-dihydroisoquinoline (8).**—*N*-(3-Bromopropyl)isoquinolinium bromide (90 g, 0.262 mol) was crushed to a fine dust and added to a well-stirred solution of lithium tri-*tert*-butoxyaluminum hydride (100 g, 0.394 mol) in dry tetrahydrofuran (500 ml) under nitrogen, in an ice bath. The mixture was stirred for 45 min, then concentrated to dryness *in vacuo*. The residue was shaken with an ether–water mixture and filtered through Celite, and the ethereal layer was separated. The ether was dried ($MgSO_4$) and removed to yield a pale yellow oil **8** (44.6 g, 68%); attempts at distillation gave decomposition. It was characterized by nmr: δ 6.90 (m, 4), 6.06 (d, 1, J = 7 Hz), 5.20 (d, 1, J = 7 Hz), 4.16 (s, 2), 3.36 (t, 2), 3.04 (t, 2), 1.96 (quintet, 2).

2,3,4,6,11,11a-Hexahydro-1-methylpyrimido[1,2-*b*]isoquinoline (9).—The above yellow oil **8** (44.6 g, 0.178 mol) was dissolved in ethanol (650 ml). Methylamine was slowly bubbled through the solution at room temperature overnight. The ethanol was removed. The residue was partitioned between ether and water. The aqueous solution was made basic (20% KOH). The ethereal layer was separated, washed (water), dried ($MgSO_4$), and removed. The residue was crystallized from petroleum ether to give **9** (25.34 g, 70%), mp 50–52°. Alternatively, the residue may be distilled to give a colorless main fraction, bp 94° (0.1 mm), which solidifies on standing: ν_{max} 2790 (m), 2750 (m), 1284 (m), 1138 (m), 744 (s); λ_{max}^{MeOH} benzenoid absorption; nmr δ 7.0 (m, 4), 3.80 (d, 1, J = 15 Hz), 3.28 (d, 1, J = 15 Hz), 2.26 (s, 3).

Anal. Calcd for $C_{13}H_{18}N_2$: C, 77.18; H, 8.97; N, 13.85. Found: C, 77.45; H, 8.96; N, 13.78.

1,2,3,4,5,6,7,8-Octahydro-2-methyl-2,6-benzodiazecine, 14 (**R** = H).—The methiodide **13** (R = H) (7.2 g, 0.0218 mol) was added to a suspension of $LiAlH_4$ (3 g) in ether (200 ml). The mixture was refluxed overnight, the excess $LiAlH_4$ was decomposed, and the mixture was filtered (Celite). The ethereal layer was separated, washed (water), dried ($MgSO_4$), and removed to yield an oil **14** (R = H) (2.4 g, 54%) which was by nmr spectroscopy essentially homogeneous. The oil was characterized as the biscyclamate: mp 113–116°; ν_{max} 3220 (m), 1588 (m), 1280 (m), 1220 (m), 1160 (m), 1032 cm^{-1} (s); λ_{max}^{MeOH} benzenoid absorption; nmr (free base) δ 7.12 (m, 4), 3.56 (s, 2), 2.96 (s, 4), 2.26 (s, 3).

Anal. Calcd for $C_{13}H_{20}N_2 \cdot 2C_6H_{13}NO_3S$: C, 53.43; H, 8.25; N, 9.97. Found: C, 53.41; H, 8.32; N, 9.85.

1,2,3,4,5,6,7,8-Octahydro-2,6-dimethyl-2,6-benzodiazecine, 14 (**R** = CH_3).—Compound **9** (6 g, 0.0297 mol) was dissolved in CH_2Cl_2 (60 ml) and cooled in an ice bath. Methyl iodide (4.3 g, 0.03 mol) in CH_2Cl_2 (10 ml) was added dropwise during 20 min. The mixture was stirred at room temperature for 2 hr. The CH_2Cl_2 was removed. The residue was dissolved in water and washed with ether. The aqueous part was then treated with excess aqueous sodium borohydride overnight. The mixture

(12) We wish to acknowledge the assistance of Dr. J. Karliner, CIBA-GEIGY Corp., Ardsley, who obtained these spectra on a Varian XL100 instrument.

was extracted (CH_2Cl_2, 3 × 60 ml) and the extract was concentrated. The residue was partitioned between 2 *N* HCl and ether. The 2 *N* HCl fraction was basified (20% KOH) and reextracted (ether). Removal of the ether gave an oil (3.34 g, 52%), which was essentially **14** (R = CH_3) from nmr spectroscopy. This was characterized as the biscyclamate: mp 126–128°; ν_{max} 3240 (m), 1584 (m), 1290 (s), 1270 (s) 1208 (s), 1170 (s), 1030 cm^{-1} (s); λ_{max}^{MeOH} benzenoid absorption; nmr (free base) δ 7.10 (q, 4), 3.64 (s, 2), 2.24 (s, 3), 2.04 (s, 3).

Anal. Calcd for $C_{14}H_{22}N_2 \cdot 2C_6H_{13}NO_3S$: C, 54.15; H, 8.39; N, 9.72. Found: C, 53.89; H, 8.66; N, 9.60.

Attempted Catalytic Reduction of 6 (R = H) to 5.—Compound **6** (R = H) (2.07 g, 0.011 mol) was hydrogenated (room temperature and pressure) in ethanol over PtO_2 (100 mg). Hydrogen was consumed (410 ml), the reaction mixture was filtered through Celite, and the ethanol was removed. The residue was an oil (0.02 g), identical (nmr, ir) with 2-(3-aminopropyl)-1,2,3,4-tetrahydroisoquinoline (**4**) prepared by $NaBH_4$ reduction of **1** (*n* = 2). The dihydrochloride melting point (263–265°) was identical with that of material above.

Attempted Reduction of 6 (R = H) to 5.—Compound **6** (R = H) (3.74 g, 0.02 mol) was dissolved in dry THF (30 ml) and added to a well-stirred slurry of $LiAlH_4$ (1.9 g) in THF (100 ml) under nitrogen. The mixture was refluxed overnight. The excess reagent was decomposed with saturated sodium potassium tartrate and the mixture was filtered through Celite. The filtrate was diluted with ether, well washed (saturated salt solution), dried ($MgSO_4$), and concentrated to yield an oil (3.31 g) identical (ir, nmr) with the starting material **6** (R = H).

Mercuric Acetate–EDTA Oxidation of Compound 9.—Compound **9** (700 mg, 0.0035 mol) was added to a solution of mercuric acetate (1.14 g, 0.0035 mol) and EDTA disodium salt (1.3 g, 0.0035 mol) in 2% aqueous acetic acid (50 ml). After 2 days at room temperature, the mixture was made basic (20% KOH) and extracted (ether). The ether was washed (saturated NaCl solution), dried ($MgSO_4$), and removed. The resulting oil (420 mg) was distilled in a hot box (0.05 mm). The distilled material (380 mg) was examined: ν_{max} 1650 cm^{-1} (m), 1620 (m); nmr δ 8.34 (d, ~0.25), 6.18 (d, ~0.5), 5.34 (d, ~0.5); mass spectrum *m/e* 216, 200, 187, 157, 129; 200 → 157 is loss of $\cdot CH_2{=}NCH_2$, linked by a metastable peak at 123.2; 157 → 129 is loss of C_2H_4 linked by a metastable peak at 106.0.

Registry No.—**1** (*n* = 1), 37384-28-4; **1** (*n* = 2), 37384-29-5; **3** (*n* = 1), 37394-04-0; **3** (*n* = 2), 21139-96-8; **4**, 5596-87-2; **5**, 37393-84-3; **6** (R = H, biscyclamate), 37393-83-2; **7**, 37413-11-9; **8**, 37393-85-4; **10**, 37393-86-5; **13** (R = H), 37393-87-6; **14** (R = H, biscyclamate), 37393-88-7; **14** (R = CH_3, biscyclamate), 37393-89-8.

Acknowledgment.—We wish to acknowledge the support and encouragement of Dr. George deStevens and helpful discussions of the spectral data with Mr. L. Dorfman, whose staff we thank for the microanalyses and spectra.

A Novel Approach to the Synthesis of Nitrogen Analogs of the Tetrahydrocannabinols

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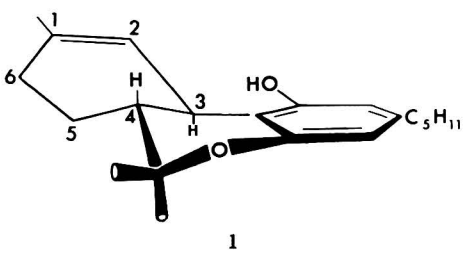
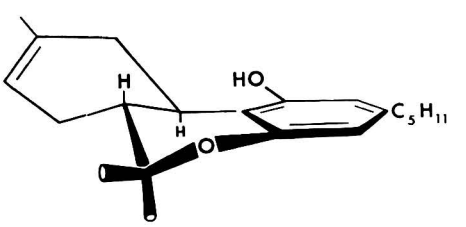
An approach to the synthesis of nitrogen analogs of the tetrahydrocannabinols which preserves the integrity of the trans ring fusion and a natural location of the double bond is reported in the present study. The condensation of *o*-anisylidenemethylamine (**10**) and glutaric anhydride yielded *trans*- and *cis*-1-methyl-5-carboxy-6-(*o*-methoxyphenyl)-2-piperidones (**11** and **12**). Subsequent O-demethylation and cyclodehydration of the trans diastereomer provided the tricyclic lactone **16**, which was converted into the corresponding *gem*-dimethyl alcohol **18**. Cyclodehydration of **18** gave the key tricyclic intermediate **23**, which was also obtained independently *via* the methyl ester **13** of **11**. Treatment of the trans ester **13** with CH_3MgBr yielded the tertiary alcohol **24**, which on treatment with BBr_3 gave the trans bromide **25**. Dehydrohalogenation of **25** provided a mixture of olefins **26** and **27**, which could be cyclized to the key intermediate **23** in CF_3COOH. Configurational and conformational assignments were made by nmr spectroscopy. Subsequent methylations and reductions of **23** provided the corresponding carbinolamines, enamines, and amines.

It has been shown that the biologically active constituents of *Cannabis* are Δ^1-*trans*-tetrahydrocannabinol (Δ^1-THC) **1**[2] and $\Delta^{1(6)}$-*trans*-tetrahydrocannabinol



1

($\Delta^{1(6)}$-THC) **2**.[3] The absolute configurations of Δ^1-THC and $\Delta^{1(6)}$-THC at C-3 and C-4 are R.[4]



2
(monoterpenoid numbering)

In view of the generally recognized psychotropic activity of the THC's,[5] a striking structural feature of these molecules is the absence of nitrogen. However, a number of THC nitrogen analogs have been reported. Thus far, the synthesis of most of these nitrogen analogs has been based on the early work of Adams and Todd and their collaborators,[6] who con-

(1) NDEA Predoctoral Fellow and American Foundation for Pharmaceutical Education Fellow.

(2) Y. Gaoni and R. Mechoulam, *J. Amer. Chem. Soc.*, **86**, 1646 (1964).

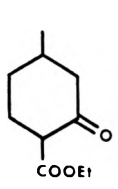
(3) R. L. Hively, W. A. Mosher, and F. W. Hoffmann, *ibid.*, **88**, 1832 (1966).

(4) R. Mechoulam and Y. Gaoni, *Tetrahedron Lett.*, 1109 (1967).

(5) L. E. Hollister, *Ann. N. Y. Acad. Sci.*, **191**, 132 (1971).

(6) R. Adams and B. R. Baker, *J. Amer. Chem. Soc.*, **62**, 2405 (1940); R. Ghosh, A. R. Todd, and S. Wilkinson, *J. Chem. Soc.*, 1121 (1940).

densed ethyl 5-methylcyclohexanone-2-carboxylate (**3**) with olivetol (**4**) in the presence of phosphorus oxychloride to give the benzopyrone **5**. Treatment of **5** with methylmagnesium iodide provided the unnatural and less physiologically active Δ^3-THC **6**. By con-



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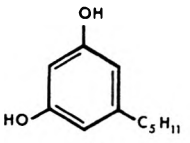

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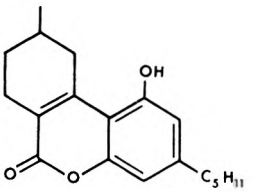

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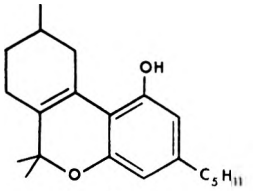
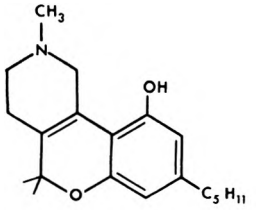


6

densation of appropriately substituted piperidones with olivetol under similar conditions followed by Grignard methylation, aza analogs **7**,[7] **8**,[8] and **9**[9a] have been prepared.[9b]



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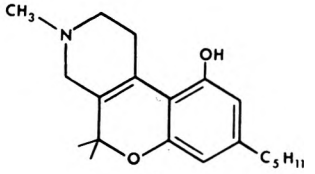

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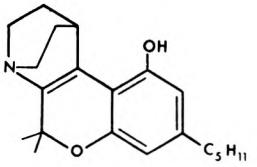
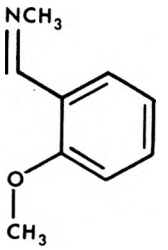


9

Anker and Cook synthesized compound **8** in 1946 and reported it to have no analgesic activity.[8] Razdan, *et al.*, repeated the synthesis of compound **8** and reported in 1968 that it is an active CNS agent similar to compound **7**,[10] reported by Pars, *et al.*[7] Both compounds were found to depress spontaneous activity and produce analgesia in mice.[11] The pharmacologic activity of these nitrogen analogs encouraged the synthesis of the quinuclidine derivative **9**, which was also reported to be an active CNS agent.[11]

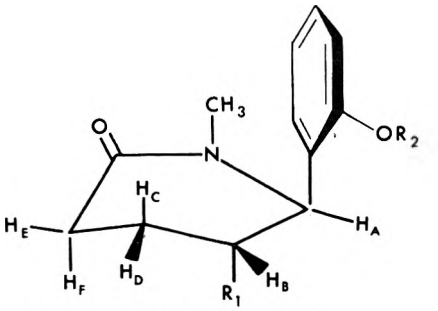
Since the unnatural Δ^3 isomer **6** is considerably less potent in animals[12] and in man[13] than the trans isomers **1** and **2**, it may be concluded that the stereochemistry of the terpene ring is an important factor in terms of any physiological response. Therefore, we have undertaken a new approach to the synthesis of nitrogen analogs of the THC's in which the integrity of the trans ring fusion and a natural location of the double bond are preserved. An additional factor which should be considered in the design of a synthetic route to these compounds is its potential versatility toward structural modification, since the preparation of a series of structurally related compounds should prove of value in the elucidation of parameters associated with the biological activity. With these considerations in mind, we chose *dl-trans*-1,5,5-trimethyl-2-oxo-1,2,3,4,4a,5,10b-heptahydro[1]benzopyrano[4,3-*b*]pyridine (**23**) as our first objective.

The condensation of *o*-anisylidenemethylamine (**10**)



10

and glutaric anhydride in refluxing xylene proceeded smoothly to yield a diastereomeric mixture of piperidones **11** and **12**, which could be separated by fractional crystallization. These trans and cis diastereomers were converted into their methyl esters **13** and **14** by treatment with diazomethane. By analogy with the condensation of Schiff bases and succinic anhydrides,[14,15] the major diastereomer would be expected to have the trans configuration while that of the minor diastereomer would be cis. In addition, the aromatic ring in both trans and cis diastereomers may be expected to occupy the axial conformation in



11, R_1 = COOH, R_2 = CH_3
13, R_1 = $COOCH_3$, R_2 = CH_3
15, R_1 = COOH, R_2 = H
18, R_1 = $C(CH_3)_2OH$, R_2 = H
24, R_1 = $C(CH_3)_2OH$, R_2 = CH_3
25, R_1 = $C(CH_3)_2Br$, R_2 = H
26, R_1 = $C(CH_3)=CH_2$, R_2 = H

view of the planar amide linkage containing two trigonal atoms and with reference to the work which has been done on A strain in cyclohexenes.[16] These expectations regarding the configurations and conformations of these compounds were verified by nmr as follows. The signal for the methoxycarbonyl pro-

(7) H. G. Pars, F. E. Granchelli, J. K. Keller, and R. K. Razdan, *J. Amer. Chem. Soc.*, **88**, 3664 (1966).

(8) R. M. Anker and A. H. Cook, *J. Chem. Soc.*, 58 (1946).

(9) (a) R. E. Lyle, R. K. Razdan, F. E. Granchelli, and H. G. Pars, U. S. Patent 3,493,579 (1970). (b) Benzodiazepine and benzopyranopyrimidine analogs of **6** have also been reported: W. Greb, D. Bieniek, and F. Korte, *Tetrahedron Lett.*, 545 (1972).

(10) R. K. Razdan, V. V. Kane, H. G. Pars, J. L. Kucera, D. H. Reid, L. S. Harris, W. L. Dewey, and J. F. Howes, Minutes, 30th Meeting Committee on Problems of Drug Dependence, NAS-NRC (1968).

(11) H. G. Pars and R. K. Razdan, *Ann. N. Y. Acad. Sci.*, **191**, 15 (1971).

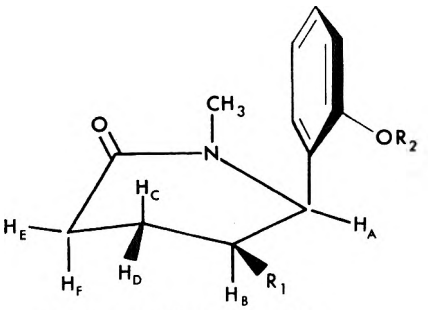
(12) R. Adams, *Bull. N. Y. Acad. Med.*, **18**, 715 (1942).

(13) L. E. Hollister, *Nature (London)*, **227**, 968 (1970).

(14) N. Castagnoli, Jr., *J. Org. Chem.*, **34**, 3187 (1969).

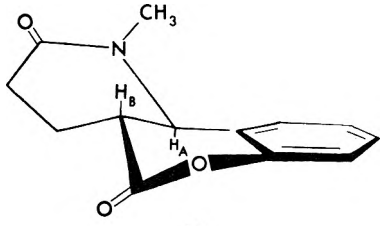
(15) M. Cushman and N. Castagnoli, Jr., *ibid.*, **36**, 3404 (1971).

(16) F. Johnson, *Chem. Rev.*, **68**, 375 (1968).



12, R_1 = COOH, R_2 = CH_3
14, R_1 = $COOCH_3$, R_2 = CH_3

tons of the methyl ester of the major trans diastereomer **13** appears at δ 3.75 ppm whereas the corresponding signal of the minor diastereomer **14** appears at δ 3.56 ppm. Inspection of Dreiding models reveals that the methoxycarbonyl protons of the equatorial ester group of **14** may experience the shielding effect of the aromatic π cloud whereas those of the axial ester group of **13** may not. Further support of these assignments is provided by the coupling constant of H_A in **11** (J = 2.5 Hz) in comparison with the coupling constant of H_A in **12** (J = 5 Hz). This is as expected since in comparable systems the coupling constants for diequatorial protons are invariably significantly smaller than those of axial–equatorial protons.[17] Finally, the trans lactone **16**, a key intermediate in our overall

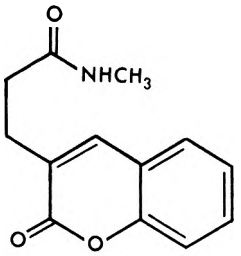


16

synthetic plan (see below), exists as a rigid diequatorial conformer. This conversion from the diaxial arrangement in the ring open system, *e.g.*, **11** to diequatorial **16** was accompanied by a change in coupling constant for H_A from 2.5 Hz for **11** to **13** Hz for **16**. It is firmly established that the nmr spectra of compounds containing six-membered rings show coupling constants for diaxial protons in the range of 8–13 Hz and diequatorial protons in the range 1–5 Hz.[17]

The relative amounts of **11** and **12** present in the crude reaction product could be estimated by integration of the O–CH_3 singlets in the nmr spectrum. Based on these values, the mixture contained 88% of the trans diastereomer and 12% of the cis. In order to determine the thermodynamic equilibrium for the methyl esters **13** and **14**, each diastereomer was heated in MeOH in the presence of an equivalent of CH_3O^-. The mixture obtained in this way starting from either pure trans or pure cis contained 92% of the trans isomer and 8% of the cis, determined by integration of methoxycarbonyl proton signals in nmr spectra. Comparable results were obtained by pyrolysis of the trans acid **11**.

The next step in our approach to the model aza analogs of THC involved formation of the tricyclic compound **16**. Attempted conversion[18] of the methyl ether **11** into **16** *via* the phenol intermediate **15** with HI in acetic acid gave unexpectedly the coumarin **17**.

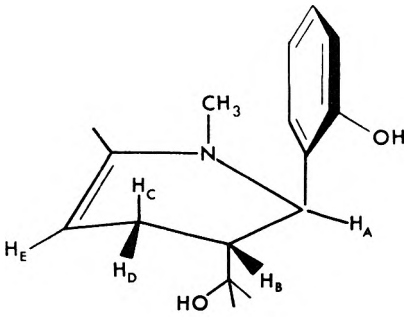


17

The ir spectrum of the solid reveals strong lactone and amide carbonyl bands as well as an N–H band at 3280 cm^{-1} which shifts to 2425 cm^{-1} after deuterium exchange with D_2O, consistent with the proposed secondary amide structure.[19] The nmr chemical shift value (δ 7.65 ppm) of the olefinic proton singlet agrees well with the δ 7.72 ppm value reported for the corresponding doublet in coumarin.[20] The remaining nmr signals as well as the mass spectral, uv, and microanalytical data also support this structure (see Experimental Section for details).

Synthesis of the desired tricyclic lactone **16** was finally accomplished by a two-step sequence. The methyl ether **11** was converted into the phenol **15** by treatment with boron tribromide in methylene dichloride.[21] The phenol underwent cyclodehydration smoothly to compound **16** in the presence of dicyclohexylcarbodiimide. Attempted thermal cyclization of phenol **15** to **16** gave instead the same coumarin **17** isolated by HI treatment of compound **11**. Since both **11** and **16** could not be converted into **17** by heating, it would appear that compound **15** is an obligatory intermediate in the formation of the coumarin.

Treatment of **16** with excess methylmagnesium bromide in tetrahydrofuran at 0° provided the lactam **18** as the sole isolable product. When the lactone **16** was treated with methylmagnesium bromide in refluxing xylene for 6 hr, glpc analysis showed the isolated product to be a 3:1 mixture of two components which could be separated by column chromatography on neutral alumina. Although the chemical ionization mass spectrum and elemental analysis of the major component could be interpreted in terms of the enamine **19**, the nmr spectrum could not be



19

(17) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, Elmsford, N. Y., 1969, p 288.

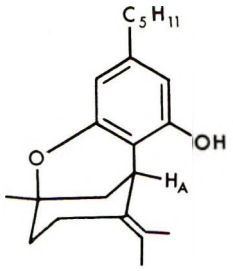
(18) R. Adams and R. B. Carlin, *J. Amer. Chem. Soc.*, **65**, 360 (1943).

(19) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed, Wiley, New York, N. Y., 1958, p 207.

(20) Varian High Resolution NMR Spectra Catalog, No. 225.

(21) J. F. W. McOmie, M. L. Watts, and D. E. West, *Tetrahedron*, **24**, 2289 (1968).

rationalized on the basis of this structure. In particular, the signal for the C–CH_3 α to nitrogen appeared at δ 1.26 ppm as a sharp singlet, which is at a higher field than expected for an olefinic methyl signal. Furthermore, the olefinic proton H_E of **19** should appear near δ 4.4 ppm.[22] The only signal in this area appeared as a singlet at δ 4.18 ppm which may be assigned to a benzylic proton. A review of the THC literature revealed that a compound originally thought to be $\Delta^{1(6)}$-3,4-*cis*-THC was reassigned structure **20** on the basis of its nmr spectrum.[23] Consideration of the arguments for this reassignment led to the realization that the corresponding structure **21** was consistent



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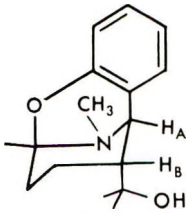
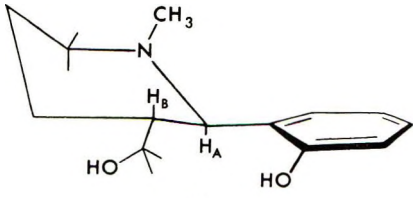


21

with our spectral data. The chemical shift value of the benzylic proton H_A of **21** of δ 4.18 compares favorably with the δ 4.19 reported for the allylic benzylic proton H_A of **20**. The δ 1.26 value for the *C*-methyl α to nitrogen in **21** also compares favorably with the δ 1.36 for the corresponding methyl group of **20**.

The second minor component of the reaction mixture proved to be the product resulting from the addition of four methyl groups to **16** yielding the diequatorially substituted ($J_{A,B}$ = 10.5 Hz) amine **22**. Mixtures of



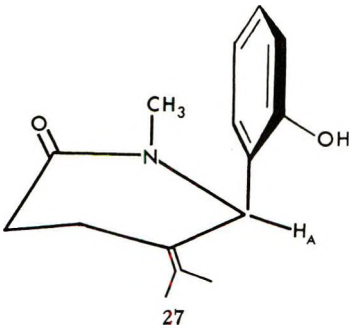
22

21 and **22** could be converted completely into **22** by repeated subjection of the mixture to the Grignard conditions in refluxing xylene.

The tricyclic amide **23** was obtained in 40% yield by cyclization of the tertiary alcohol **18** in CF_3COOH. As in the conversion of **15** into **16**, this reaction was accompanied by a conformational conversion from a diaxial to a rigid diequatorial ring system, as indicated by a change in the coupling constant $J_{A,B}$ from 2.5 to 9.5 Hz.

An alternative route to the tricyclic amide **23** was also established. Treatment of the trans ester **13** with methylmagnesium bromide in tetrahydrofuran provided the corresponding tertiary alcohol **24**, which was converted with boron tribromide into the trans bromide **25**. Dehydrohalogenation of this bromide **25** gave a mixture of the olefins **26** and **27**, which were shown by nmr to be present in a 19:1 ratio, respectively.

In addition to the above two olefins, concentration of the aqueous HBr solution of this reaction mixture gave a crystalline solid material which proved to be the amide hydrobromide **28**.[24] Comparison of the



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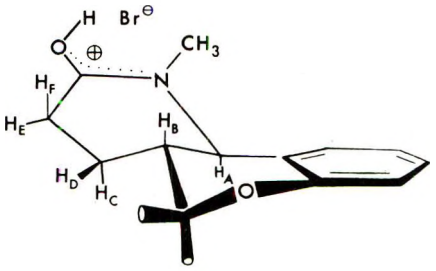
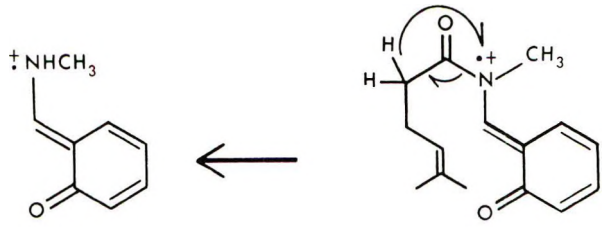


28

nmr spectrum in $CDCl_3$ of this material with that of the corresponding amide **23** reveals downfield shifts for the *N*-methyl group and all protons in the nitrogen-containing heterocyclic ring. Furthermore, the magnitude of this effect is greatest for the protons nearest the positive charge. Treatment of the nmr samples with a few drops of Py-d_5 or D_2O instantaneously generated the spectrum of the amide **23**. Except for the appearance of HBr, the electron impact mass spectrum of the hydrobromide **28** was identical with that of the amide **23**. The empirical formula of the base peak in both spectra was established as C_8H_9NO by high resolution, which is consistent with structure **29**. Radical



29 **23a**

ion **29** may be formed by ring opening of the pyran[25] followed by α cleavage of the amide **23a** with loss of a carbene.[26] The ir spectrum of hydrobromide **28** contained a broad absorption at 1650 cm^{-1}, near the $\nu_{C=O}$ (1660 cm^{-1}) of amide **23**. The amide **23** was obtained after extraction of $CHCl_3$ suspensions of **28** with water.

The 19:1 mixture of olefins **26** and **27** was treated with boiling CF_3COOH for 35 min and the nonphenolic material isolated in 70% yield. Integration of the NCH_3 groups at δ 3.15 and 3.35 ppm of the crude isolate indicated that the trans amide **23** and cis amide **30**

(22) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Amer. Chem. Soc.*, **85**, 207 (1963).

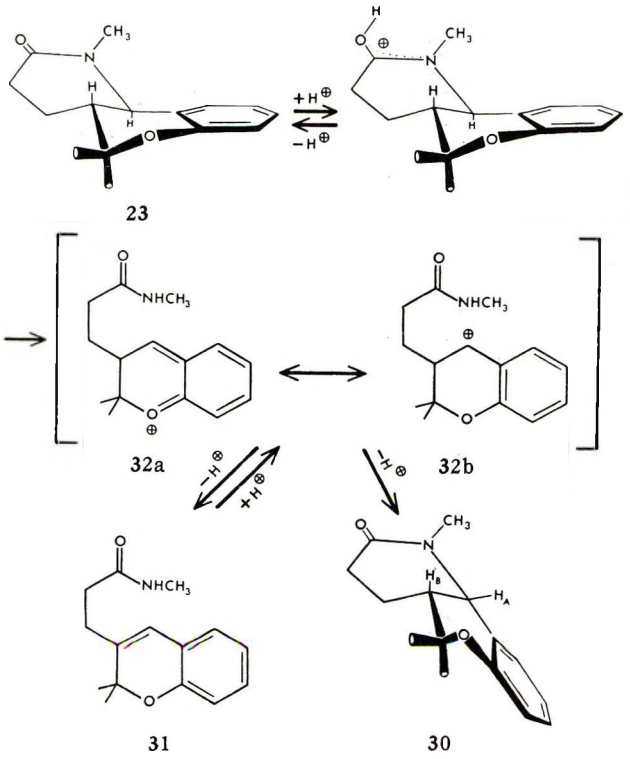
(23) Y. Gaoni and R. Mechoulam, *ibid.*, **88**, 5673 (1966).

(24) Houben-Weyl, "Die Methoden der organischen Chemie," 11/2, Georg Thieme, Leipzig, 1958, p 568.

(25) B. Wilhalm, A. F. Thomas, and F. Gautschi, *Tetrahedron*, **20**, 1185 (1964).

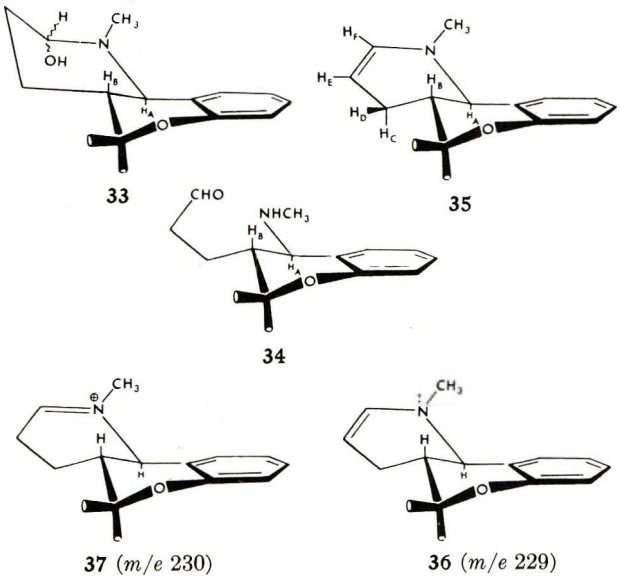
(26) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, San Francisco, Calif., 1967, pp 340–346.

were present in a 17:3 ratio, respectively. During separation of **23** and **30** by fractional crystallization, a trace impurity was detected by glpc on SE-30 which cocrystallized and cosublimed with the desired trans amide **23**. Column chromatography led to the separation of the trans and cis amides **23** and **30** from the impurity. As had been observed with the coumarin **17**, the *N*-methyl doublet (J = 5 Hz) in the nmr spectrum of the "impurity" collapsed to a singlet after addition of D_2O, suggesting the chromene **31**. Although the appearance of the signal for the four methylene protons as a sharp singlet was somewhat surprising, examples of other unsymmetrically 1,2-disubstituted ethylenes in which the four methylene protons appear as a singlet have been reported.[27] The ir characteristics of **31** were similar to those observed for the coumarin **17**. When the CF_3COOH reaction period was extended to 24 hr, the cis amide **30** ($J_{A,B}$ = 5 Hz) was the only isolable product, and none of **23** or **31** could be detected. Since the chromene **31** is a symmetrical molecule, our attention was directed to the possibility that it is an intermediate in the epimerization of **23** to **30**. Therefore a solution of **31** in CF_3COOH was heated at the boiling point and the reaction progress followed by nmr. Essentially complete conversion of the chromene **31** to the cis amide **30** was observed within 3 hr. Evidently the epimerization of **23** to **30** proceeds by cleavage of the benzylic carbon–nitrogen bond to form intermediate **32a** ↔ **32b**, which then deprotonates to generate the chromene



31 or cyclizes to the cis amide **30**. Similar results were also observed on treatment of the tertiary alcohol **18** with boiling CF_3COOH.

The carbinolamine **33** was isolated as a stable solid in 63% yield after reduction of the amide **23** with a large excess of lithium aluminum hydride in tetrahydrofuran. The corresponding amino aldehyde **34** and enamine **35** structures can be excluded due to the lack of any aldehyde or enamine double bond absorbance in the solid state ir spectrum. Broad multiplets were observed in the nmr spectrum for the methine and methylene protons. The nmr spectrum recorded 16 hr after dissolution of the carbinolamine **33** showed substantial conversion (>60%) into the enamine **35**. The signal for the benzylic proton H_A appeared as a distinct doublet ($J_{A,B}$ = 10 Hz) at δ 4.00 ppm. The signal for the olefinic proton H_F has been assigned to a doublet ($J_{E,F}$ = 7 Hz) at δ 6.19 ppm and the signal for the remaining proton H_E corresponds to a multiplet at δ 4.95 ppm.[28] This change in the nmr spectrum was paralleled by the appearance of the enamine double bond (1650 cm^{-1}) in the ir spectrum.[22,29,30] This



facile dehydration was also evident in the chemical ionization mass spectrum of the carbinolamine **33** which showed no ion at m/e 248 corresponding to protonated **33**, but did show the iminium ion **37** (m/e 230) as the base peak along with the enamine radical ion **36** (m/e 229, 47%).

Treatment of the trans amide **23** with an excess of methylmagnesium bromide in boiling tetrahydrofuran yielded the carbinolamine **38** as a stable solid in 86% yield. As with carbinolamine **33**, the corresponding amino aldehyde and enamine structures could be ruled out due to lack of any aldehyde or enamine double bond absorbance in the solid state ir spectrum. In contrast to carbinolamine **33**, the nmr and ir spectra recorded at 10-min intervals after dissolution of carbinolamine **38** indicated essentially complete conversion into the enamine **39** plus water within 1 hr. The olefinic proton in the nmr spectrum of the enamine **39** appeared as a multiplet at δ 4.87 ppm and the ir spectrum displayed an absorbance at 1650 cm^{-1}, corresponding to an enamine double bond.[22] The enamine **39** could be isolated and characterized as an oil after

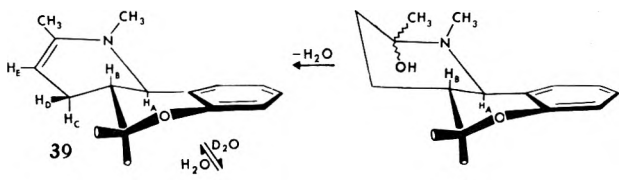
(27) Varian High Resolution NMR Spectra Catalog No. 106 and 129.

(28) H. Diekmann, G. Englert, and K. Wallenfels, *Tetrahedron*, **20**, 281 (1964).

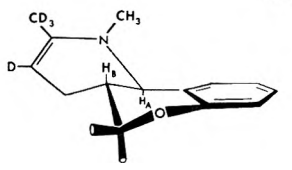
(29) N. J. Leonard and V. W. Gash, *J. Amer. Chem. Soc.*, **76**, 2781 (1954).

(30) N. J. Leonard, P. D. Thomas, and V. W. Gash, *ibid.*, **77**, 1552 (1955).

dehydration of the carbinolamine **38**. Unlike other members in this series, the signal for proton H_A appeared as a multiplet instead of the expected doublet, presumably due to virtual long-range coupling.[31] Addition of D_2O to $CDCl_3$ solutions of enamine **39** resulted in disappearance of the olefinic proton H_E and the olefinic methyl group in the nmr spectrum yielding the deuterated enamine **40**[32,33] ($t_{1/2}$ for exchange approximately 15 min). In order to establish that an exchange process had occurred rather than decomposition, the reversibility of the reaction was tested by back-exchange of deuterium in **40** with H_2O. Addition of H_2O to $CDCl_3$ solutions of **40** resulted in regeneration of the nmr spectrum of **39**.



39 38



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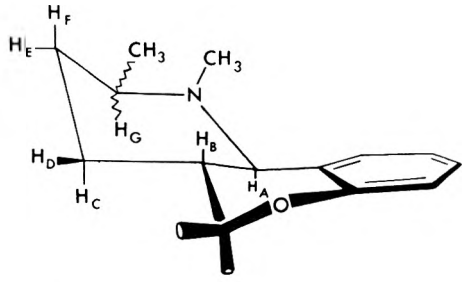
Proton H_A in the amine **41**, obtained by catalytic reduction of **38**, appeared as a doublet ($J_{A,B}$ = 11 Hz). The presence of a single diastercomer was indicated by the sharp melting point, the presence of single signals for the N-CH_3 and C-CH_3 groups in the nmr spectrum, and observation of a single peak on glpc. The relative configuration at C-2 was not assigned. Compound **42** was obtained by diborane reduction of amide **23**.



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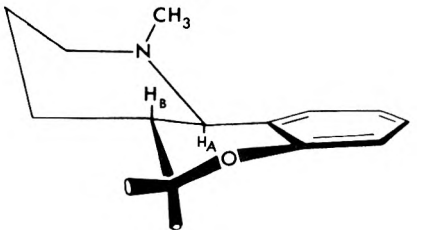

42

(31) R. M. Silverstein and G. C. Bassler, "Spectrometric Identification of Organic Compounds," 2nd ed, Wiley, New York, N. Y., 1968, pp 130, 131.

(32) W. H. Daly, J. G. Underwood, and S. C. Kuo, *Tetrahedron Lett.*, 4375 (1971).

(33) P. Beak and J. Bonham, *J. Amer. Chem. Soc.*, **87**, 3365 (1965).

Experimental Section[34]

***o*-Anisylidenemethylamine** (10).—*o*-Anisaldehyde (136.15 g, 1 mol) and methylamine (34.17 g, 1.1 mol) were stirred for 5 hr at room temp in 200 ml of C_6H_6 in the presence of molecular sieves (3A, 200 g). Following filtration and washing of the sieves with benzene, the solvent was removed and the residue distilled at 70° (0.2 mm) to give the Schiff base as a pale yellow oil (132.47 g, 89%): nmr δ 8.68 (q, J = 1.5 Hz, imino H), 7.92–6.91 (m, Ar), 3.77 (s, OCH_3), 3.48 (d, J = 1.5 Hz, NCH_3).

Anal. Calcd for $C_9H_{11}NO$: C, 72.46; H, 7.43; N, 9.39. Found: C, 72.22; H, 7.38; N, 9.41.

***trans*-1-Methyl-5-carboxy-6-(*o*-methoxyphenyl)-2-piperidone** (11).—*o*-Anisylidenemethylamine (74.60 g, 0.5 mol) and glutaric anhydride (57.05 g, 0.5 mol) were heated in refluxing xylene (100 ml) for 24 hr. Crystallization of a light yellow solid (109.92 g, 83%), mp 155–173°, was induced by scratching the hot solution. Analytically pure trans acid (71.68 g, 55%) was obtained from the diastereomeric mixture by fractional crystallization from 2-butanone (1 l.): mp 182–183; ir (KBr) 3400 (broad), 2900, 1715 (carboxylic acid $\nu_{C=O}$), 1605 (lactam $\nu_{C=O}$); nmr δ 11.99 (s, COOH, exchangeable with D_2O), 7.14 (m, Ar), 5.37 (d, J = 2.5 Hz, H_A), 3.86 (s, OCH_3), 3.02 (m, H_B), 2.89 (s, NCH_3), 2.65 (m, $H_{E,F}$) 2.01 (m, $H_{C,D}$).

Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.70; H, 6.47; N, 5.46.

***cis*-1-Methyl-5-carboxy-6-(*o*-methoxyphenyl)-2-piperidone** (12).—The filtrate left after separation of the above trans isomer was concentrated to a volume of 150 ml. After standing overnight, the white solid (7.03 g), mp 170–204°, was collected. The pure cis acid (12) (0.73 g, 0.6%) was obtained after three recrystallizations from EtOH: mp 215–216°; ir (KBr) 3385 (b, OH), 2890, 1710 (carboxylic acid $\nu_{C=O}$), 1595 (lactam $\nu_{C=O}$); nmr δ 10.27 (s, COOH, exchangeable with D_2O), 7.08 (Ar), 5.36 (d, J = 5 Hz, H_A), 3.62 (s, OCH_3), 3.24 (m, H_B), 2.81 (s, NCH_3), 2.19 (m, CH_2-CH_2).

Anal. Calcd for $C_{14}H_{17}NO$: C, 63.87; H, 6.51; N, 5.32. Found: C, 64.11; H, 6.53; N, 5.40.

***trans*-1-Methyl-5-methoxycarbonyl-6-(*o*-methoxyphenyl)-2-piperidone** (13).—An excess of CH_2N_2 in EtOH–Et_2O was added to the piperidone 11 (52.66 g, 0.2 mol). Evaporation of solvent from the resulting solution left the methyl ester as a glassy residue which crystallized from Et_2O–pentane (100:55 ml) as a colorless solid (45.52 g), mp 77–78°. An additional 4.06 g, mp 77–78°, was obtained after concentrating the filtrate to a volume of 50 ml to give a total yield of analytically pure solid of 49.58 g, 89%: mp 77–78°; ir (KBr) 2900, 1735 (ester $\nu_{C=O}$), 1640 (lactam $\nu_{C=O}$); nmr δ 7.14 (m, Ar), 5.28 (d, J = 3 Hz, H_A), 3.86 (s, OCH_3), 3.75 (s, $COOCH_3$), 2.99 (m, H_B), 2.84 (s, NCH_3), 2.51 (m, $H_{E,F}$), 2.00 (m, $H_{C,D}$).

Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 65.02; H, 6.89; N, 4.98.

***cis*-1-Methyl-5-methoxycarbonyl-6-(*o*-methoxyphenyl)-2-piperidone** (14).—Evaporation of solvent from the filtrate after crystallization of the trans acid 11 left a solid residue (38.24 g), mp 170–210°. An excess of CH_2N_2 in EtOH–Et_2O was added. Evaporation of solvent from the solution left a quantitative yield of diastereomeric esters 13 and 14 as an oil in a ratio of 3:1 (by nmr). The cis ester (0.13 g, 0.1%) was isolated by fractional crystallization once from Et_2O and twice from Me_2CO: mp 122–124°; ir (KBr) 2935, 1735 (ester $\nu_{C=O}$), 1650 (amide $\nu_{C=O}$); nmr δ 7.07 (m, Ar), 5.25 (d, J = 5 Hz, H_A), 3.78 (s, OCH_3), 3.56 (s, $COOCH_3$), 2.79 (s, NCH_3), 3.34–1.72 (m, $H_{B\rightarrow F}$).

(34) All reactions were performed under a nitrogen atmosphere, and solvents were evaporated on a rotary evaporator under vacuum. Melting points were taken on a Thomas-Hoover apparatus and are uncorrected. Nmr spectra were recorded on a JEOL JNM-4H-100 100-MHz instrument and, except where noted, in $CDCl_3$ solvent. Chemical shift values are reported in parts per million relative to TMS as internal standard. Ir spectra were recorded on a Perkin-Elmer Model 337 spectrophotometer. Glpc analyses were performed on Varian Aerograph Model 2100 gas chromatograph equipped with a flame ionization detector using a 1/8 in. × 6 ft column of 3% SE-30 on Chromosorb W, 100–120 mesh. The electron impact mass spectra were recorded on an AEI MS-12 instrument at 70 eV and the chemical ionization mass spectra were recorded on an AEI MS-901 spectrometer modified for chemical ionization. Details of the instrumental modification will be published elsewhere. Microanalyses were performed by the Microanalytical Laboratory, University of California, Berkeley. The uv spectrum was recorded on a Cary 15 spectrophotometer.

Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 65.16; H, 6.87; N, 5.08.

trans-1-Methyl-5-carboxy-6-(*o*-hydroxyphenyl)-2-piperidone (15).—A solution of BBr_3 (25 g, 100 mmol) in CH_2Cl_2 (200 ml) was added dropwise to a solution of the piperidone 11 (8.69 g, 33 mmol) in CH_2Cl_2 (225 ml) at room temperature. After stirring 48 hr H_2O (150 ml) and Et_2O (600 ml) were added. The two phases were stirred for 2.5 hr before the organic phase was separated. The aqueous phase was extracted with Et_2O (350 ml), and the combined organic phases were dried ($MgSO_4$) and concentrated to 25 ml (bath at room temperature) and the resulting suspension left at 1° overnight. A white solid (6.04 g, 73%), mp 197–199°, separated and was recrystallized twice from 50% aqueous EtOH to provide the analytical sample: mp 202–202.5°; ir (KBr) 3650-2500 (b, OH), 1735 (carboxylic acid $\nu_{C=O}$), 1580 (lactam $\nu_{C=O}$); nmr ($CDCl_3$–Py-d_5, 8:3) 10.01 ppm (s, COOH + OH, exchangeable with D_2O), 6.95 (m, Ar), 5.63 (d, J = 3 Hz, H_A), 3.28 (m, H_B), 2.95 (s, NCH_3), 2.65 (m, $H_{E,F}$), 2.10 (m, $H_{C,D}$).

Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.60; H, 6.17; N, 5.58.

trans-1-Methyl-2,5-dioxo-1,2,3,4,4a,5,10b-heptahydro[1]benzopyrano[4,3-*b*]pyridine (16).—A mixture of the piperidone 15 (20.00 g, 80.2 mmol) and *N*,*N*′-dicyclohexylcarbodiimide (16.54 g, 80.2 mmol) were heated in refluxing THF (175 ml) with stirring for 2 hr. The suspension was then stirred at room temperature for 21 hr. The *N*,*N*′-dicyclohexylurea was filtered off and the THF evaporated from the filtrate to give a quantitative yield (18.54 g) of the lactone, mp 149–152°. Crystallization from C_6H_6 gave the analytical sample: mp 150–152°; ir (KBr) 1765 (lactone $\nu_{C=O}$), 1645 (lactam $\nu_{C=O}$); nmr δ 7.26 (m, Ar), 4.57 (d, J = 13 Hz, H_A), 3.24 (s, NCH_3), 2.88–1.73 (m, $H_{B\rightarrow F}$).

Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.51; H, 5.97; N, 6.16.

3-(*N*-Methyl-β-propionamido)coumarin (17). A.—A mixture of Ac_2O (6 ml), 57% aqueous HI (6 ml), red phosphorus (1.00 g), and 11 (1.32 g, 5 mmol) was heated under reflux for 3.5 hr. After cooling to room temperature, the red phosphorus was removed by filtration and the filtrate in 5% aqueous $NaHCO_3$ (100 ml) was extracted with $CHCl_3$ (100 ml). The $CHCl_3$ layer was separated and washed with 5% aqueous $NaHCO_3$ (100 ml). Evaporation of the dried ($MgSO_4$) $CHCl_3$ solution left the coumarin (0.48 g, 41%) as a white powder, mp 155–156°, which was crystallized from EtOH to provide the analytical sample: mp 156–156.5°; ir (KBr) 3280 (ν_{N-H}, shifted to 2425 cm^{-1} after deuterium exchange), 2910, 1710 (lactone $\nu_{C=O}$), 1635 (amide $\nu_{C=O}$), 1605, 1570 (amide II band), ($CDCl_3$) 3450 (ν_{N-H}, shifted to 2555 cm^{-1} after deuterium exchange), 2930, 1715 (lactone $\nu_{C=O}$), 1665 (amide $\nu_{C=O}$), 1615, 1530 (amide II band); nmr δ 7.65 (s, C=CH), 7.15 (m, Ar), 6.58 (s, NH, exchangeable with D_2O, $t_{1/2}$ for exchange 10 min), 2.91 (t, J = 7 Hz, CH_2), 2.77 (d, N-CH_3, J = 5 Hz, collapsed to a singlet after deuterium exchange of N–H), 2.58 (t, J = 7 Hz, CH_2); electron impact mass spectrum m/e (rel intensity) 231 (25), 200 (32), 173 (100), 159 (18), 154 (19), 125 (30); high-resolution mass spectrum, calcd (for $C_{13}H_{13}NO_3$) m/e 231.0895, found 231.0896; uv max (C_2H_5OH) 307 nm (ϵ 6940) and 274 (11,300).

Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.37; H, 5.83; N, 5.89.

B.—*trans*-1-Methyl-5-carboxy-6-(*o*-hydroxyphenyl)-2-piperidone (15) (200.0 mg, 0.80 mmol) was heated neat at 204–206° for 0.5 hr. Trituration of the resulting oil with Me_2CO (1 ml) gave the coumarin in 80% crude yield. The analytical sample was recrystallized twice from 2-butanone and once from EtOH. The identity of the coumarin with that obtained above was established by superimposable nmr, ir, and mixture melting point behavior.

Epimerization Studies. A.—*trans*-1-Methyl-5-carboxy-6-(*o*-methoxyphenyl)-2-piperidone (11) (131.6 mg, 0.5 mmol) was heated neat at 204–206° for 0.5 hr. Treatment of the oily product (132.1 mg) with an excess of CH_2N_2 in EtOH–Et_2O followed by evaporation of solvent from the resulting solution provided a quantitative yield of the trans and cis esters 13 and 14, respectively, as an oil. The esters were identified as *trans*- and *cis*-1-methyl-5-methoxycarbonyl-6-(*o*-methoxyphenyl)-2-piperidone (13 and 14) by comparison of the nmr spectrum with those of the previously isolated esters. Integration of the methoxycarbonyl proton signals showed the ratio of trans/cis was 92:8.

B.—A solution of the piperidone 13 (27.7 mg, 0.1 mmol) and CH_3ONa (5.4 mg, 0.1 mmol) in dry MeOH (1 ml) was heated under reflux for 5 hr. The solution was cooled to room temperature and CH_2Cl_2 (10 ml) and H_2O (10 ml) were added. The separated CH_2Cl_2 layer was dried ($MgSO_4$) and the solvent evaporated, leaving a quantitative yield of esters as an oil. The esters were identified as *trans*- and *cis*-1-methyl-5-methoxycarbonyl-6-(*o*-methoxyphenyl)-2-piperidone (13 and 14, respectively) by comparison of the nmr spectrum with those of the previously isolated esters. Integration of the methoxycarbonyl proton signals showed that the ratio of trans/cis esters was 92:8.

C.—Exactly the same results were obtained when *cis*-1-methyl-5-methoxycarbonyl-6-(*o*-methoxyphenyl)-2-piperidone (14) was treated as in method B above (*i.e.*, the ratio of trans/cis esters was 92:8).

trans-1-Methyl-5-dimethylcarbinol-6-(*o*-hydroxyphenyl)-2-piperidone (18).—A solution of CH_3MgBr (2 ml of a 3 *M* solution in Et_2O, 6 mmol) was added dropwise to an ice-cold, stirred solution of the tricyclic intermediate 16 (231.3 mg, 1 mmol) in THF (5 ml). After stirring for 0.5 hr at 0°, saturated aqueous NH_4Cl (5 ml) was added dropwise, the organic phase separated and the aqueous phase washed with Et_2O (5 ml). The combined organic layers were dried ($MgSO_4$) and the solvent was evaporated. Crystallization of the glassy residue from EtOH–Et_2O (1 + 2 ml) gave a solid (139.1 mg, 53%), mp 180–182°, which was analytically pure after recrystallization from water: mp 182–183°; ir (KBr) 3475, 2930, 1600 (lactam $\nu_{C=O}$); nmr ($CDCl_3$–Py-d_5, 4:1) δ 6.94 (m, Ar), 5.08 (d, J = 2.5 Hz, H_A), 2.85 (s, NCH_3), 2.53 (m, $H_{E,F}$), 1.99 (m, $H_{B\rightarrow D}$), 1.36 (s, CH_3), 1.34 (s, CH_3).

Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04; N, 5.32. Found: C, 68.10; H, 8.08; N, 5.25.

trans-2-Methyl-5-dimethylcarbinol-2,6-*N*-methylimine-2,3,4,5-tetrahydrobenzoxocin (21).—A solution of CH_3MgBr (10 ml of a 3 *M* solution, 30 mmol) was added to a suspension of 16 (1.16 g, 5 mmol) in xylene (50 ml) and the resulting mixture stirred under reflux for 6 hr. The reaction mixture was cooled to room temperature and decomposed by addition of saturated aqueous NH_4Cl (50 ml). The organic phase was separated and dried ($MgSO_4$), and the solvent evaporated. Glpc analysis (190° column temp, N_2 flow rate 46 ml/min) of the residue showed one major component (retention time 3.0 min) and one minor component (retention time 4.3 min) present in a 7:3 ratio, respectively. Elution from a basic alumina column (36 × 2 cm, 100 g) with CH_2Cl_2 gave first compound 21 which was identified as the major component by glpc. Evaporation of solvent left 21 as an oil (0.34 g, 26%). The analytical sample was prepared by evaporative distillation at 98°/5 μ yielding a light yellow-colored oil: nmr δ 6.93 (m, Ar), 5.80 (b, OH), 4.18 (b s, H_A), 2.34 (s, NCH_3), 2.25–1.10 (m, $H_{B\rightarrow F}$), 1.46 (s, $C(CH_3)_2$), 1.26 (C-CH_3); chemical ionization mass spectrum (CH_4 ionizing gas, 1.2 mm, 200° source temp) m/e (rel intensity) 262 (MH^+, 100), 246 (14), 244 (14).

Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.88; H, 8.89; N, 5.54.

trans-1,2,2-Tridimethyl-5-dimethylcarbinol-6-(*o*-hydroxyphenyl)piperidine (22). A.—Continued elution of the above alumina column with CH_2Cl_2 provided fractions containing the minor component amine 22, which was obtained as an oil (0.04 g, 3%). Evaporative distillation at 120° (0.6 mm) gave the analytical sample: nmr δ 6.99 (m, Ar), 3.49 (d, J = 10.5 Hz, H_A), 2.05 (s, NCH_3), 2.40–1.30 (m, $H_{B\rightarrow F}$), 1.24 (s, CH_3), 1.15 (s, CH_3), 1.07 (s, CH_3), 1.05 (s, CH_3); chemical ionization mass spectrum (CH_4 ionizing gas, 1.2 mm, 200° source temp) m/e (rel intensity) 278 (MH^+, 100), 260 (48).

Anal. Calcd for $C_{17}H_{27}NO_2$: C, 73.61; H, 9.81; N, 5.05. Found: C, 74.10; H, 9.81; N, 4.85.

B.—A solution of CH_3MgBr (5 ml of a 3 *M* solution in Et_2O, 15 mmol) was added dropwise to a stirred, ice-cold solution of compound 16 (462.6 mg, 2 mmol) in xylene (10 ml) under nitrogen. The mixture was heated under reflux for 24 hr. The reaction mixture was then cooled on an ice bath before decomposition with saturated aqueous NH_4Cl (20 ml). The organic phase was separated and the aqueous phase washed with Et_2O (20 ml). Evaporation of solvent from the combined, dried ($MgSO_4$) organic layers left an amber oily residue (383.0 mg). Glpc analysis (190° column temp, N_2 flow rate 46 ml/min) of the residue showed the presence of compounds 21 (retention time 3.0 min) and 22 (retention time 4.3 min) in a 53:47 ratio, respectively. The oil was dissolved in xylene (10 ml) and was

treated again with CH_3MgBr (3 ml of a 3 *M* solution in Et_2O, 9 mmol). Following the same work-up procedure left an amber oily residue (354.2 mg) which on glpc was shown to consist of a 15:85 mixture of **21** and **22**. When repeated a third time, the methylation yielded an oily residue (262.5 mg) containing **21** and **22** as a 7:93 mixture. Compound **22** was separated from **21** on a basic alumina column (133 × 1 cm, 30 g), eluting with $CHCl_3$. Evaporative distillation of the residue obtained from fractions containing **22** at 120° (0.6 mm) yielded a light amber oil (132.1 mg, 24%) which was identical in all respects with the previously obtained pentamethyl compound.

trans-**1,5,5-Trimethyl-2-oxo-1,2,3,4,4a,5,10b-heptahydro[1]benzopyrano[4,3-*b*]pyridine (23).** A.—The piperidone **18** (7.90 g, 30 mmol) in CF_3COOH (75 ml) was heated at reflux for 45 min. The ratio of peak areas in the nmr spectrum of the resulting reaction mixture at δ 3.74 (NCH_3 of **30**) and at δ 3.52 (NCH_3 of **23**) was 6:94, respectively. The residue obtained after removing solvent was dissolved in Et_2O (150 ml) and the resulting solution washed with 5% aqueous NaOH (150 ml). The aqueous layer was back-extracted with Et_2O (150 ml). The combined organic phases were dried ($MgSO_4$) and the solvent was evaporated to give a solid residue (5.45 g). Glpc analysis (190° column temp, N_2 flow rate 35 ml/min) of the residue showed one major peak (retention time 4.8 min). The crude product was chromatographed with $CHCl_3$ on a column of silica gel (5.4 × 37 cm, Bio-Sil A, 200–325 mesh, 380 g). Evaporation of solvent from fractions containing the major component by glpc left a glass which crystallized from 50% aqueous MeOH (10 ml) as a colorless solid (2.94 g, 40%), mp 99–104°. Sublimation at 100° (10 μ) followed by recrystallization from Me_2CO provided the analytical sample: mp 102–104°; ir (KBr) 2955, 1670, and 1650 (lactam $\nu_{C=O}$); nmr δ 7.06 (m, Ar), 4.21 (d, J = 9.5 Hz, H_A), 3.15 (s, NCH_3), 2.46 (m, $H_{E,F}$), 1.74 (m, $H_{B\rightarrow D}$), 1.36 (s, $C(CH_3)_2$); electron impact mass spectrum *m/e* (rel intensity) 245 (86), 230 (39), 228 (14), 202 (18), 152 (29), 145 (11), 136 (68), 135 (100), 134 (61), 120 (14), 118 (14); high-resolution mass spectrum, calcd (for $C_{15}H_{19}NO_2$) *m/e* 245.1416, found 245.1427; calcd [for C_8H_9NO (**29**)] 135.0684, found 135.0684.

Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.57; H, 7.79; N, 5.82.

B.—A solution of the 19:1 mixture of *trans*-1-methyl-5-isopropenyl-6-(*o*-hydroxyphenyl)-2-piperidone (**26**) and 1-methyl-5-isopropylidene-6-(*o*-hydroxyphenyl)-2-piperidone (**27**) (15.45 g, 0.063 mol) in CF_3COOH (150 ml) was heated at reflux for 35 min. The ratio of peak areas in the nmr spectrum of the reaction mixture at δ 3.74 ppm (NCH_3 of **30**) and at δ 3.52 (NCH_3 of **23**) was 14:86, respectively. The residue obtained after removing CF_3COOH was dissolved in Et_2O (300 ml), and the Et_2O solution was washed with 5% aqueous NaOH (2 × 150 ml) and dried ($MgSO_4$). Glpc analysis (190° column temp, N_2 flow rate 35 ml/min) showed two peaks with retention times 4.8 (corresponding to **23** and **30**) and 5.8 min (corresponding to **31**) with the ratio of peak areas 92:8, respectively. Acidification of the aqueous layer with concentrated HCl to pH 4 caused precipitation of starting material (3.17 g, 20%), identified by mp 205–209° and by nmr. Evaporation of solvent from the Et_2O layer left a glass (10.85 g, 70%), which was chromatographed with $CHCl_3$ on a column of silica gel (5.4 × 86 cm, Bio-Sil A, 200–325 mesh, 880 g). Evaporation of solvent from fractions producing the major glpc peak with retention time 4.8 min left a solid residue (7.88 g) which when crystallized from 50% aqueous MeOH (16 ml) yielded pure **23** (5.41 g, 35%), mp 99–104°. Continued elution of the column (eluent vol 3.9–6.1 l.) yielded **2,2-dimethyl-3-(*N*-methyl-β-propionamido)chromene (31)** (0.48 g, 3%), mp 134–137°. The analytical sample was obtained by crystallization from 2-butanone: mp 144–144.5°; ir (KBr) 3260 (ν_{N-H}, shifts to 2400 cm^{-1} after deuterium exchange with D_2O), 2910, 1645 (amide $\nu_{C=O}$), 1575 (amide II band), ($CDCl_3$) 3450 (ν_{N-H}, shifts to 2565 after deuterium exchange with D_2O), 2960, 1660 (amide $\nu_{C=O}$), 1515 (amide II band); nmr δ 6.97 (m, Ar), 6.05 (b, NH, exchangeable with D_2O, $t_{1/2}$ for exchange about 10 min), 6.04 (s, vinyl proton), 2.82 (d, J = 5 Hz, collapsed to a singlet after D_2O addition), 2.44 (s, CH_2–CH_2), 1.42 (s, $C(CH_3)_2$).

Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.51; H, 7.76; H, 5.93.

C.—Water (20 ml) was added to a suspension of the hydrobromide **28** (1.24 g, 3.80 mmol) in $CHCl_3$ (40 ml). The $CHCl_3$ layer was separated and the aqueous layer extracted with $CHCl_3$ (20 ml). Evaporation of solvent from the combined, dried ($MgSO_4$) organic layers left a solid residue (0.70 g) which was recrystallized from 50% aqueous MeOH (2 ml) to yield **23** (0.51 g, 55%), mp 102–104°.

cis-**1,5,5-Trimethyl-2-oxo-1,2,3,4,4a,5,10b-heptahydro[1]benzopyrano[4,3-*b*]pyridine (30).** A.—A solution of a 19:1 mixture of *trans*-1-methyl-5-isopropenyl-6-(*o*-hydroxyphenyl)-2-piperidone (**26**) and 1-methyl-5-isopropylidene-6-(*o*-hydroxyphenyl)-2-piperidone (**27**) (490.6 mg, 2 mmol) in CF_3COOH (5 ml) was heated at reflux for 24 hr, under which conditions conversion into this cis cyclic product is complete. The solvent was evaporated and the purple, oily residue dissolved in Et_2O (20 ml). The solution was washed with 5% aqueous NaOH (20 ml) and dried ($MgSO_4$) and the solvent evaporated, leaving a solid residue (372.8 mg, 76%) mp 106–113°. The analytical sample was recrystallized three times from acetone: mp 115–116°; ir (KBr) 2925, 1650 (lactam $\nu_{C=O}$); nmr 6.97 (m, Ar), 4.63 (d, J = 5 Hz, H_A), 3.35 (s, NCH_3), 2.45–1.60 (m, $H_{B\rightarrow F}$), 1.41 (s, CH_3), 1.39 (s, CH_3).

Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.42; H, 7.99; N, 5.65.

B.—A solution of the chromene **31** (31.3 mg) in CF_3COOH (0.6 ml) was heated (bath 82°) for 4 hr. The nmr spectrum of the reaction mixture was identical with that of pure **30** in CF_3COOH: nmr (CF_3COOH) δ 7.16 (m, Ar), 5.12 (d, J = 5 Hz, H_A), 3.74 (s, NCH_3), 3.14–1.77 (m, $H_{B\rightarrow F}$), 1.54 (s, CH_3), 1.51 (s, CH_3).

trans-**1-Methyl-5-dimethylcarbinol-6-(*o*-methoxyphenyl)-2-piperidone (24).**—A solution of CH_3MgBr (1 mol of a 3 *M* solution in Et_2O) was added dropwise to a stirred solution of compound **13** (69.33 g, 0.25 mol) in THF (1300 ml) at 0°. The mixture was stirred at room temperature for 2 hr and then cooled to 0° before dropwise addition of saturated aqueous NH_4Cl (1 l.). The organic phase was separated and the aqueous phase extracted with Et_2O (600 ml). Evaporation of solvent from the combined, dried ($MgSO_4$) organic phases left a residue which was crystallized from acetone (100 ml) to give 40.35 g of product, mp 107–109°. Concentration of the mother liquors to 30 ml yielded additional product (6.70 g, total crude yield 68%), mp 107–109°. The analytical sample was obtained by crystallization from C_6H_6–pentane and from aqueous EtOH: mp 108–109°; ir (KBr) 3370, 2920, 1615 (lactam $\nu_{C=O}$); nmr δ 7.08 (m, Ar), 5.02 (d, J = 3 Hz, H_A), 3.86 (s, OCH_3), 2.78 (s, NCH_3), 2.49 (m, $H_{E,F}$), 2.17 (s, OH), 1.89 (m, $H_{B\rightarrow D}$), 1.36 (s, CH_3), 1.30 (s, CH_3).

Anal. Calcd for $C_{16}H_{23}NO_3$: C, 69.29; H, 8.36; N, 5.05. Found: C, 69.12; H, 8.29; N, 5.04.

trans-**1-Methyl-5-(2-bromoisopropyl)-6-(*o*-hydroxyphenyl)-2-piperidone (25).**—A solution of BBr_3 (97 g, 0.39 mol) in CH_2Cl_2 (388 ml) was added dropwise to a solution of the piperidone **24** (35.78 g, 0.129 mol) in CH_2Cl_2 (900 ml) at room temperature. The susepension was stirred at room temperature for 48 hr before dropwise addition of H_2O (600 ml). The resulting mixture was extracted twice with Et_2O (1800 and 600 ml). Evaporation of solvent from the combined, dried ($MgSO_4$) organic layers left **25** as a colorless solid (35.12 g, 84%), mp 129–132°. Recrystallization from aqueous EtOH and from 2-butanone provided the analytical sample: mp 134–135°; ir (KBr) 3400, 2950, 1600 (lactam $\nu_{C=O}$); nmr ($CDCl_3$–Py-d_5, 1:1) δ 6.95 (m, Ar), 5.06 (d, J = 4 Hz, H_A), 4.42 (b, OH), 2.81 (s, NCH_3), 2.58 (m, $H_{E,F}$), 2.28 (m, H_B), 2.07 (m, $H_{C,D}$); 1.84 (s, $C(CH_3)_2$). The Beilstein test for halogen was positive.

Anal. Calcd for $C_{15}H_{20}NO_2Br$: C, 55.22; H, 6.18; N, 4.29. Found: C, 55.32; H, 6.14; N, 4.51.

trans-**1-Methyl-5-isopropenyl-6-(*o*-hydroxyphenyl)-2-piperidone (26).**—Water (400 ml) was added to a hot solution of **25** (33.00 g, 0.101 mol) in EtOH (200 ml) and the mixture heated on a steam bath for 30 min. The suspension was stored at 1° to yield solid **26** (16.44 g, 66%), mp 205–210°. The analytically pure product was prepared by recrystallization from 2-butanone: mp 218–219°; ir (KBr) 3060, 2925, 1600 (lactam $\nu_{C=O}$); nmr ($CDCl_3$–Py-d_5, 3:1) δ 6.96 (m, Ar), 5.04 (d, J = 4.5 Hz, H_A), 4.88 (s, 1 olefinic proton) 4.78 (s, 1 olefinic proton), 4.15 (b, OH), 2.84 (s, NCH_3), 2.63 (m, $H_{B,E,F}$), 1.83 (m, $H_{C,D}$), 1.76 (s, CCH_3).

Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.17; H, 7.67; N, 5.84.

trans-**1-5,5-Trimethyl-2-oxo-1,2,3,4,4a,5,10b-heptahydro[1]benzopyrano[4,3-*b*]pyridine Hydrobromide (28).**—Evaporation of solvent from the filtrate after crystallization of **26** left a glass which crystallized on trituration with 2-butanone to give a colorless solid (4.15 g, 13%), mp 157–160°. The analytical sample of the amide hydrobromide **28** was prepared by dissolution in a minimum of $CHCl_3$ followed by precipitation with 2-buta-

none: mp 177–178° dec; ir (KBr) 2950, 2315 (broad band) 1650, 1580, 1480, 1455, 1380, 1345, 1300, 1255, 1110, 1028, 965, 870, 822, 750, 650, 590, 505; nmr δ 12.17 (s, OH), 7.08 (m, Ar), 4.73 (d, J = 9.5 Hz, H_A), 3.52 (m, $H_{E,F}$), 3.38 (s, NCH_3), 2.01 (m, $H_{B\rightarrow D}$), 1.39 (s, CCH_3), 1.36 (s, CCH_3); chemical ionization mass spectrum (isobutane ionizing gas, 0.5 mm, 200° source temp) m/e (rel intensity) 246 (100) 245 (6), 135 (4); electron impact mass spectrum m/e (rel intensity) 245 (61), 230 (28), 152 (22), 145 (14), 136 (58), 135 (100), 134 (47), 120 (17); 118 (14); 82 (28), 80 (28).

Anal. Calcd for $C_{15}H_{20}NO_2Br$: C, 55.22; H, 6.18; N, 4.29. Found: C, 55.18; H, 5.98; N, 4.09.

trans-1,5,5-Trimethyl-2-hydroxy-1,2,3,4,4*a*,5,10*b*-heptahydro[1]benzopyrano[4,3-*b*]pyridine (**33**).—A solution of compound **23** (2.45 g, 10 mmol) in THF (50 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (0.76 g, 20 mmol) in THF (50 ml) at 0°. The suspension was stirred at room temperature for 24 hr and the reaction mixture decomposed by addition of H_2O (0.8 ml), 15% aqueous NaOH (0.8 ml), and finally H_2O (2.4 ml). After stirring an additional 2 hr, the white solid was filtered and Et_2O (100 ml) added to the filtrate. Glpc analysis (150° column temperature, N_2 flow rate 35 ml/min) of the filtrate indicated one major product with retention time 5.9 min along with trace amounts (<1%) of a material with retention time 7.1 min corresponding to the retention time of pure **37** (see below). The organic solution was extracted with 5% HCl (50 ml) and, after cooling on an ice bath the extract was adjusted to pH 11 by addition of 15% aqueous NaOH to precipitate a colorless solid (1.55 g, 63%), mp 109–110° dec. The solid was washed with water (15 ml) and air-dried. A sample obtained by removing the solvent from an Et_2O solution of this product was analytically pure: mp 110–110.5° dec; ir (KBr) 3040, 2930, 1385, 1365 [δ $C(CH_3)_2$]; nmr (recorded immediately after dissolution of **33** in $CDCl_3$) δ 8.92 (b, 1 H, observed at −65° but not at 25°), 7.30 (m, Ar), 4.72 (b, 1 H), 4.03 (b, 1 H), 2.18 (s, NCH_3), 1.98 (b, 5 H), 1.42 (s, CCH_3), 1.17 (s, CCH_3); chemical ionization mass spectrum (isobutane ionizing gas, 1.0 mm, 220° source temperature) m/e (rel intensity) 230 ($MH^+ - H_2O$, 100), 229 (47), 228 (11), 173 (11), 161 (11); electron impact mass spectrum m/e (rel intensity) 230 (15), 229 (82), 228 (14), 214 (38), 173 (11), 161 (11), 186 (10), 183 (36), 120 (13), 159 (12), 157 (27), 146 (13), 145 (100), 136 (21), 115 (13).

Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 73.18; H, 8.44; N, 5.80.

trans-1,2,5,5-Tetramethyl-2-hydroxy-1,2,3,4,4a,5,10b-heptahydro[1]benzopyrano[4,3-*b*]pyridine (**38**).—A solution of CH_3MgBr (10 ml of a 3 M solution in Et_2O, 30 mmol) was added to a stirred solution of compound **23** (2.45 g, 10 mmol) in THF (25 ml). The mixture was heated at reflux for 73 hr. After cooling, saturated aqueous NH_4Cl (25 ml) was added. The organic phase was separated and the aqueous phase extracted with Et_2O (2 × 25 ml). Glpc analysis (190° column temp, N_2 flow rate 35 ml/min) of the combined organic phases showed only one peak with retention time 2.2 min. The combined organic phases were extracted with 5% aqueous HCl (50 ml), and the aqueous extract was cooled on an ice bath before the pH was adjusted to 12 by addition of 15% aqueous NaOH to yield a light yellow solid (2.25 g, 86%), mp 87–89° dec, which was washed with water (2 × 5 ml) and with Et_2O (5 ml) and dried over P_2O_5 at 25° (5 μ) for 2 hr: mp 87–89°; ir λ_{max}^{KBr} 3120 (broad), 2915, 1385, 1365 [δ $C(CH_3)_2$]; nmr (recorded 1 hr after dissolution of **38** during which time conversion of carbinolamine into enamine **39** was complete) δ 7.08 (m, Ar), 4.87 (m, H_E), 4.48 (b, H_2O), 3.90 (m, H_A), 2.14 (s, NCH_3), 1.92 (m, $H_{B\rightarrow D}$), 1.83 (d, J = 1 Hz, vinylic CCH_3), 1.41 (s, CCH_3), 1.12 (s, CCH_3); chemical ionization mass spectrum (isobutane ionizing gas, 2.0 mm, 220° source temp) m/e (rel intensity) 244 ($MH^+ - H_2O$, 100) 243 (59); electron impact mass spectrum m/e (rel intensity) 243 (92), 229 (19), 228 (100), 214 (25), 145 (87).

Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.68; H, 8.69; N, 5.43.

trans-1,2,5,5-Tetramethyl-1,4,4a,5,10b-pentahydro[1]benzopyrano[4,3-*b*]pyridine (**39**).—The carbinolamine **38** (261.4 mg, 1 mmol) was heated in an evaporative distillation apparatus at 80° (0.2 mm) in the dark. The enamine **39** (189.1 mg, 78%) condensed on the cold finger as an oil and was stored over $CaSO_4$ at 1° in the dark: ir ($CDCl_3$) 2970, 1650 (enamine C=C), 1390, 1375 [δ $C(CH_3)_2$]; nmr δ 7.08 (m, 4 Ar), 4.87 (m, H_E, exchangeable with D_2O), 3.90 (m, H_A), 2.14 (s, NCH_3), 1.92 (m, $H_{B\rightarrow D}$), 1.83 (d, J = 1 Hz, vinylic CCH_3, exchangeable with D_2O), 1.41 (s, CCH_3), 1.12 (s, CCH_3); chemical ionization mass spectrum (methane ionizing gas, 0.5 mm, 200° source temp) m/e (rel intensity) 244 (MH^+, 18), 243 (64), 228 (100); high-resolution mass spectrum, calcd 244.1701 (MH^+), found 244.1700.

Anal. Calcd for $C_{16}H_{21}NO$: C, 78.97; H, 8.70; N, 5.76. Found: C, 78.76; H, 8.53; N, 5.74.

trans-1,2,5,5-Tetramethyl-1,2,3,4,4a,5,10b-heptahydro[1]benzopyrano[4,3-*b*]pyridine (**41**).—A solution of the carbinolamine **38** (2.09 g, 8 mmol) in acetic acid (100 ml) was hydrogenated in the presence of 10% Pd/C (0.40 g) in a Parr hydrogenator (35 psi, 24 hr). The catalyst was filtered and solvent evaporated from the filtrate at 16° (0.2 mm). Aqueous NaOH (5%, 80 ml) and Et_2O (80 ml) were added to the oily residue. The organic layer was separated and the aqueous layer extracted with Et_2O (80 ml). The combined organic layers were dried (Na_2SO_4) and the solvent evaporated, leaving a light brown, solid residue (1.89 g, 96%), mp 87–90°. Glpc analysis (150° column temp, N_2 flow rate 37 ml/min) showed only one peak with retention time 4.4 min. The analytical sample was obtained by sublimation at 60° (0.2 mm), yielding a colorless solid: mp 91–92°; ir ($CDCl_3$) 2920, 1385, 1370 [δ $C(CH_3)_2$]; nmr δ 7.10 (4 Ar), 3.79 (d, J = 11 Hz, H_A), 3.12 (b, H_G), 1.97 (s, NCH_3), 1.90–1.25 (b, $H_{B\rightarrow F}$), 1.37 (s, C-5 CH_3), 1.18 (d, J = 7 Hz, C-2 CH_3), 1.13 (s, C-5 CH_3); chemical ionization mass spectrum (methane ionizing gas, 0.5 mm, 200° source temp) m/e (rel intensity) 246 (MH^+, 61), 245 (100), 230 (39); electron impact mass spectrum m/e (rel intensity) 245 (59), 231 (35), 230 (59), 173 (45), 162 (32), 148 (27), 145 (100), 134 (26); high-resolution mass spectrum, calcd 245.1779 (M^+), found 245.1774.

Anal. Calcd for $C_{16}H_{23}NO$: C, 78.32; H, 9.45; N, 5.71. Found: C, 78.09; H, 9.28; N, 5.63.

trans-1,5,5-Trimethyl-1,2,3,4,4a,5,10b-heptahydro[1]benzopyrano[4,3-*b*]pyridine (**42**).—A solution of compound **23** (735.9 mg, 3 mmol) in THF (6 ml) was added dropwise to an ice-cold solution of diborane in THF (6 ml of a 1 M solution, 6 mmol). The solution was heated at reflux for 2 hr and cooled and the reaction decomposed by the dropwise addition of 6 N aqueous HCl (6 ml). After stirring for 1 hr with evolution of H_2, NaOH (2 g, pellets) was added followed by H_2O (4 ml). The organic phase was separated and the aqueous phase extracted with Et_2O (3 × 10 ml). Glpc analysis (150° column temp, N_2 flow rate 35 ml/min) of the combined organic phases produced only one peak with retention time 7.1 min. Evaporation of solvent from the combined, dried ($MgSO_4$) organic phases left a clear, colorless, oily residue (459.8 mg, 66%). The analytical sample was prepared by evaporative distillation at 65° (10 μ): ir ($CDCl_3$) 2930, 1385, 1365, [δ $C(CH_3)_2$]; nmr δ 7.10 (m, Ar), 3.81 (d, J = 11 Hz, H_A), 3.08 (m, $H_{G,H}$), 2.18 (s, NCH_3) 1.80 (m, 3 H), 1.37 (s, CCH_3), 1.30 (m, 2 H), 1.13 (s, CCH_3); chemical ionization mass spectrum (isobutane ionizing gas, 0.5 mm, 220° source temp) m/e (rel intensity) 232 (MH^+, 100), 231 (23) 230 (9); electron impact mass spectrum 231 (100), 230 (31), 188 (19), 162 (62), 150 (21), 149 (62), 148 (87), 147 (19), 145 (44), 134 (32), 107 (21).

Anal. Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15; N, 6.05. Found: C, 77.95; H, 9.08; N, 5.97.

Registry No.—**10**, 1125-90-2; **11**, 37406-49-8; **12**, 37406-50-1; **13**, 37406-51-2; **14**, 37406-52-3; **15**, 37406-53-4; **16**, 37406-54-5; **17**, 37447-24-8; **18**, 37406-55-6; **21**, 37406-56-7; **22**, 37406-57-8; **23**, 37406-58-9; **24**, 37406-59-0; **25**, 37406-60-3; **26**, 37406-61-4; **28**, 37406-62-5; **30**, 37406-63-6; **31**, 37447-25-9; **33**, 37406-68-1; **38**, 37406-64-7; **39**, 37406-65-8; **41**, 37406-66-9; **42**, 37406-67-0.

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Cyclization Products Derived from o-Benzoyl Malonanilates[1]

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2′-Benzoyl-2-aminomalonanilates such as **6** were prepared *via* the corresponding carbobenzoxy derivatives **3** or by reduction of the 2-nitro- or 2-isonitrosomalonanilates **16** and **17**. Depending on the substitution pattern, these amines cyclized to the benzodiazepine-3-carboxylates **7** or to the 3-amino-4-hydroxytetrahydroquinoline-2-one-3-carboxylates **5**. The latter derivatives were rearranged to the benzodiazepines **7** as was the aziridine **13**, a possible intermediate in this ring expansion. Reaction of 2′-benzoyl-2-bromomalonanilates **19** with ammonia, instead of leading to the expected amines, yielded the 3,4-epoxycarbostyrils **23** and the 3-phenyloxindoles **22**.

The malonanilates **3** (Scheme I) were prepared by acylating the benzophenones **1** with the monoester of 2-(benzyloxycarbonylamino)malonic acid and phosphorus pentachloride in a two-phase system of methylene chloride and aqueous sodium carbonate. These compounds cyclized with good stereoselectivity to the tetrahydroquinolones **4**[1c] in the presence of triethylamine. Cleavage of the carbobenzoxy group with hydrogen bromide in glacial acetic acid led to the corresponding amines **5** with no change of stereochemistry as indicated by nmr spectroscopy. The configurations assigned to compounds **4** and **5** were based on the following experiments. Acid-catalyzed cyclization of **3d** yielded, in addition to **4d**, the oxazolo derivative **12**, which upon cleavage with hydrogen bromide led to **11**, the diastereoisomer of **5d**. Compound **11**, in turn, reacted smoothly and almost quantitatively with phosgene in pyridine to yield **12**, indicating the cis configuration for the participating hydroxy and amino groups. The reaction of the stereoisomer **5d** with phosgene, under similar conditions, gave a complex mixture, chromatography of which yielded 34% of the oxazolone **9**, the diastereoisomer of **12**, and 25% of compound **10**. The ethyl carbamate was formed during the quenching of the phosgene reaction with ethanol, the carbamoyl chloride corresponding to **10** being most likely the precursor. Further support for the assigned stereochemistry rests on the observation that compound **11**, but not the diastereoisomer **5d**, could be converted to the aziridine **13**. This follows if we assume that the aziridine had formed by a trans elimination[2] from the intermediate bromo amine, which would be expected to result from an SN2 reaction of the cis amino alcohol **11** only.

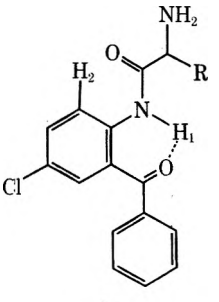
The diastereomeric amino alcohols **5d** and **11** were found to be thermally interconvertible. Refluxing either **5d** or **11** in toluene for 3 hr led to an equilibrium mixture containing the two isomers in a ratio of about 1:1. Treatment of these compounds with strong base, aqueous or anhydrous, yielded 3-aminocarbostyrils. Thus, compound **5d** was converted to the known 3-aminocarbostyril **8**.[3] Under acidic conditions, compounds **5** and **11** rearranged in high yields to the benzodiazepine-3-carboxylates **7**.[4]

This rearrangement was best effected by refluxing compounds **5** in an inert solvent such as toluene in the presence of a weak acid, *e.g.*, acetic acid. The stereoisomers **5d** and **11** showed no noticeable differences in their convertibility to the benzodiazepine **7d**. The aziridine **13** could also be transformed into the benzodiazepine **7d** under similar conditions. The acetyl derivative **14** was a by-product in this reaction, and for comparison it was prepared by acetylation of **13**. This finding suggests that the aziridine **13** is a likely intermediate in the conversion of **5** or **11** to the benzodiazepines. An alternate pathway would be ring opening of **5** or **11** to 2-aminomalonanilates such as **6** and recyclization to the seven-membered ring.

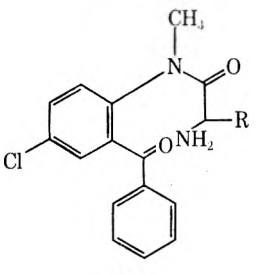
Removal of the protecting carbobenzoxy group from compounds **3** with hydrogen bromide in acetic acid led to the corresponding ammonium salts. The stability of the amines liberated from these salts was dependent on the substitution pattern. Three different cases designated A, B, and C in Scheme I were observed. In case A (R_1 = H; R_2 = Cl), the stable 2-aminomalonanilate **6** was obtained. It was cyclized to the benzodiazepine **7e** by heating in benzene in the presence of acetic acid. If both R_1 and R_2 were protons (case C) the main product was the tetrahydroquinolone **5a**, while, in case B (R_1 = CH_3; R_2 = H), the benzodiazepine **7c** was the major product.

While steric hindrance was most likely responsible for the lack of ring closure in case A, it is not obvious why a proton in place of a methyl group altered the course of cyclization. We suggest that it could be attributed to conformational differences due to hydrogen bonding. The existence of hydrogen bonding in acylated *o*-aminobenzophenones has been pointed out by Derieg and coworkers[5] on the basis of ir data and it is further supported by our nmr data.

Hydrogen bonding of the aniline proton to the car-



I



II

$H_1\delta$ ~11 ppm
$H_2\delta$ ~8.6 ppm

(1) (a) Address correspondence to Hoffmann-La Roche, Inc., Nutley, New Jersey 07110. (b) Presented in part at the Metrochem Meeting, San Juan, Puerto Rico, April 1971, and at the meeting of the Swiss Chemical Society, Lausanne, Switzerland, May 1971; *Chimia*, **25**, 247 (1971). (c) Related tetrahydroquinolones were described by C. Podseva, K. Vagi, and C. Solomon, *Can. J. Chem.*, **46**, 2263 (1968).

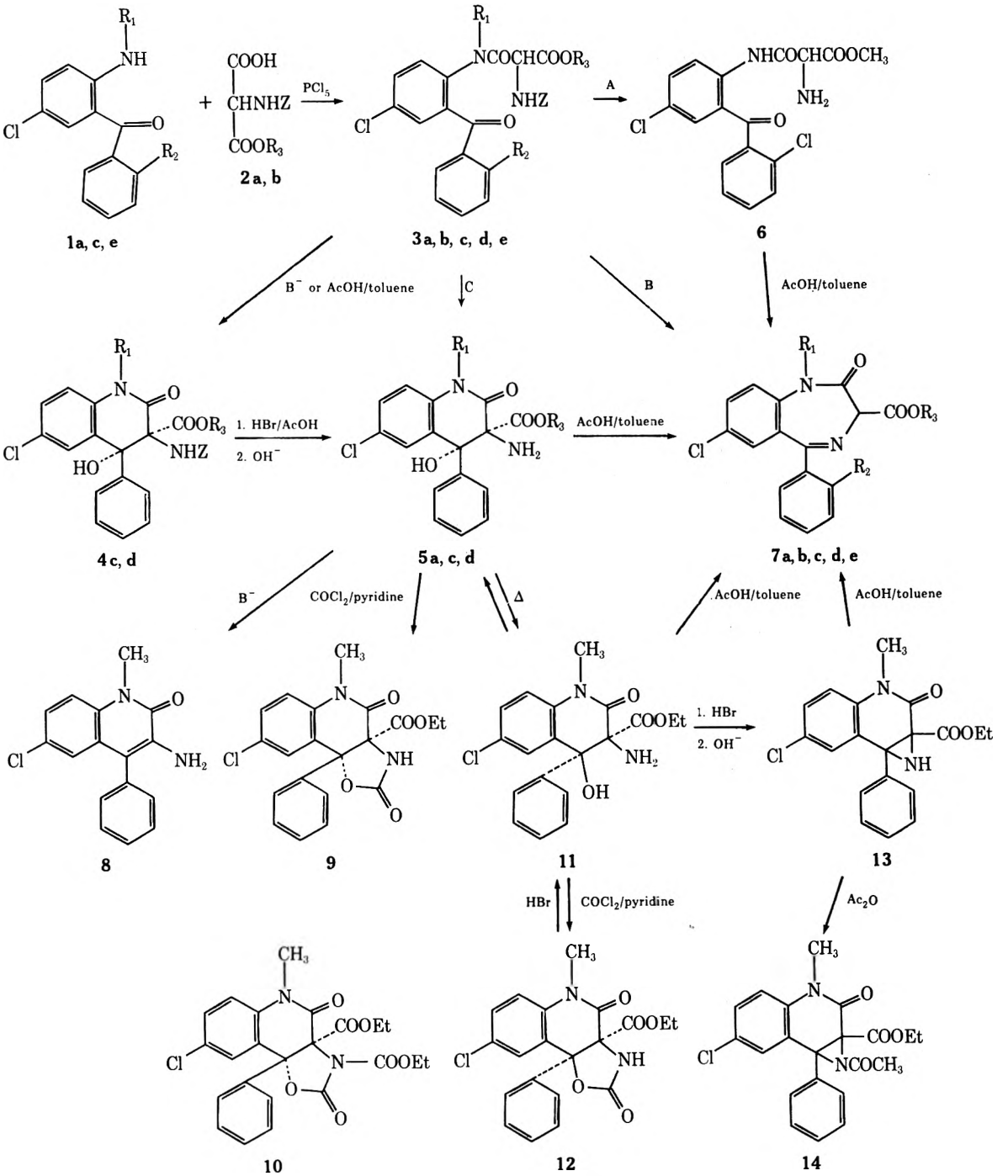
(2) A. Hassner and C. Heathercock, *Tetrahedron*, **20**, 1037 (1964).

(3) R. I. Fryer, B. Brust, and L. H. Sternbach, *J. Chem. Soc.*, 3097 (1964).

(4) (a) J. Schmitt, P. Comoy, M. Suquet, G. Callet, J. LeMeur, and T. Clim, *Chim. Ther.*, **4**, 239 (1969); (b) Etabs. Clin-Byla S. A., French Patent 978,360 (June 15, 1964).

(5) M. E. Derieg, R. M. Schweininger, and R. Ian Fryer, *J. Org. Chem.*, **34**, 179 (1969).

SCHEME I



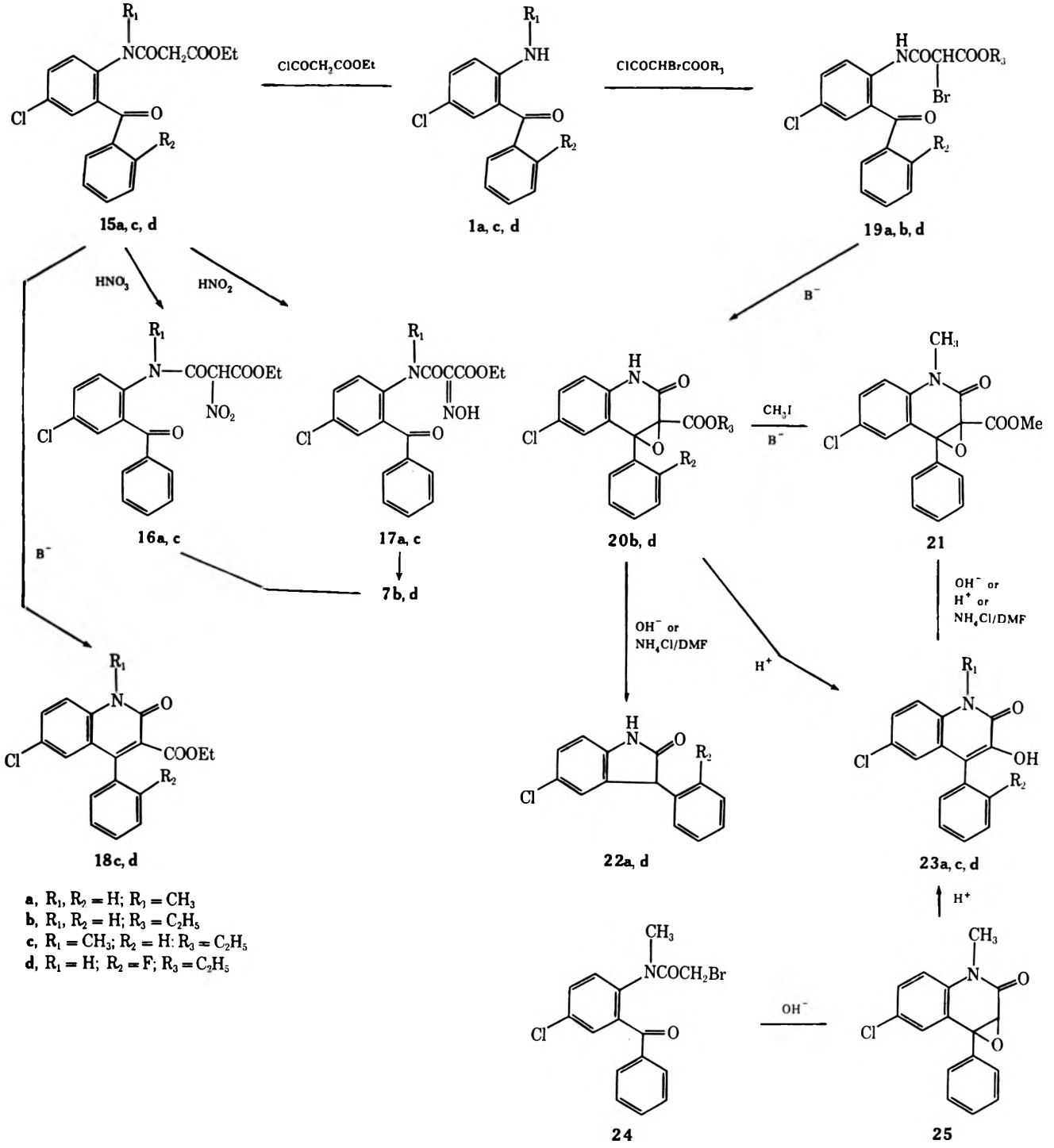
Z = $COOCH_2C_6H_5$
a, $R_1 = H$; $R_2 = H$; $R_3 = CH_3$
b, R_1, $R_2 = H$; $R_3 = C_2H_5$
c, $R_1 = CH_3$; $R_2 = H$; $R_3 = CH_3$
d, $R_1 = CH_3$; $R_2 = H$; $R_3 = C_2H_5$
e, $R_1 = H$; $R_2 = Cl$; $R_3 = CH_3$

bonyl oxygen of the benzophenone as illustrated in conformation I is responsible for its large chemical shift. The considerable deshielding of the proton ortho to the acylamino group also lends support for the dominance of conformation I. The N-methylated compounds represented by conformation II lack this deshielding of the ortho proton and often appear as a mixture of two rotamers in the nmr spectra.

Additional evidence for a stable conformation due to hydrogen bonding is the fact that the glycine derivative I (R = H) was obtained in crystalline form,[6] whereas the N-methylated derivative II (R = H) was never isolated; it cyclized spontaneously to the benzodiazepine. The same considerations may be valid for the 2-aminomalonanilates I and II (R = $COOR_3$), where formation of the six-membered ring dominates with compound I while the cyclization to

(6) A. Stempel and F. W. Landgraf, *J. Org. Chem.*, **27**, 4675 (1962).

Scheme II



a, $R_1, R_2 = H$; $R_3 = CH_3$
b, $R_1, R_2 = H$; $R_3 = C_2H_5$
c, $R_1 = CH_3$; $R_2 = H$; $R_3 = C_2H_5$
d, $R_1 = H$; $R_2 = F$; $R_3 = C_2H_5$

the seven-membered ring is favored with the N-methylated compound II.

1,4-Benzodiazepine-3-carboxylates were also accessible in good overall yield by the sequence of reactions depicted in Scheme II.

Acylation of the aminobenzophenones **1** with malonic ester acid chloride yielded compounds **15**. Alkaline conditions had to be avoided in order to prevent cyclization of the products to the quinolones **18**. The malonanilates were nitrated or nitrosated in acetic acid to give either the nitro derivatives **16** or the oximes **17**. The nitromalonates **16** proved to be rather strong acids which were extractable from ether with sodium bicarbonate solution. Both the nitro derivatives **16** and the oximes **17** were reduced with zinc in acetic acid. The amines obtained in this way were cyclized directly, without isolation, to the benzodiazepines **7** by refluxing in benzene and acetic acid.

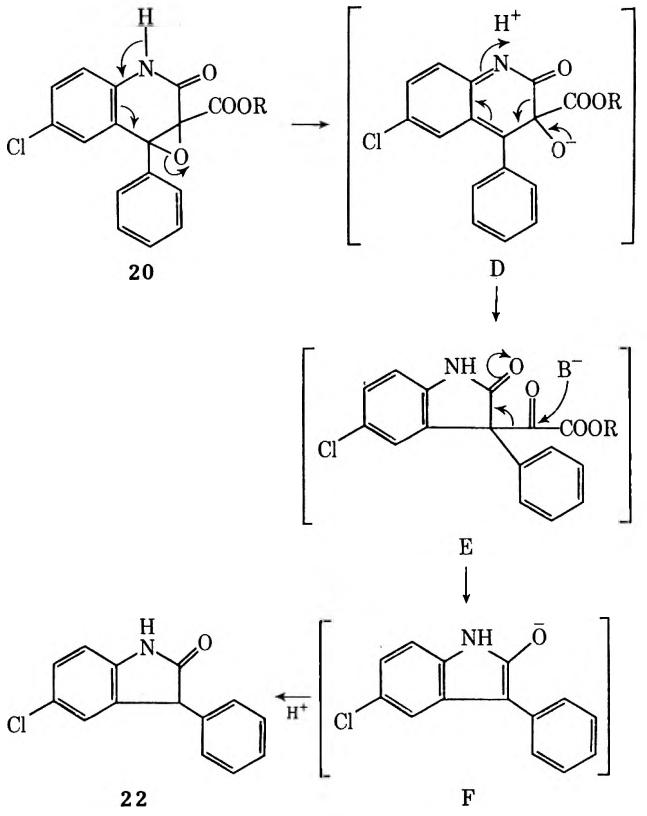
We also attempted the preparation of 1,4-benzodiazepine-3-carboxylates **7** by treating the bromides **19** with ammonia, a standard procedure for the synthesis of benzodiazepines. The bromomalonanilates **19** were obtained by acylation of the aminobenzophenones **1** with bromomalonic ester acid chloride. Displacement of the bromide with ammonia led, however, not to the desired amine, but to the epoxide **20** instead. Ammonia was apparently a strong enough base to generate the carbanion which attacked the

benzophenone carbonyl intramolecularly to form the epoxide *via* the intermediate bromohydrin.

In our search for a way to cleave the epoxide **20**, we heated it with ammonium chloride in dimethylformamide. Under these conditions, an almost quantitative conversion to the oxindole **22** was observed. The oxindole was also formed by treating the epoxide **20** with alkali. Strong acid, on the other hand, converted it to the carbostyril **23a**. When the N-methylated epoxide **21** was subjected to any of these conditions, no oxindole formation could be detected, and only the 3-hydroxycarbostyril **23c** was isolated. This same hydroxycarbostyril could be obtained *via* the epoxide **25** which was prepared in low yield from the bromoacetate **24**.

The interesting change in the path of epoxide cleavage due to the N-methyl group may be explained by the mechanism shown in Scheme III. Base is assumed to abstract the amide proton from compound **20**. Opening of the epoxide by the electron shifts as shown would lead to intermediate D. Reprotonation and ketol rearrangement would result in the ring-contracted β-dicarbonyl compound E. Decarbonylation of this intermediate leads to the enol form F, protonation of which yields the oxindole **22**. With the N-methylated compound **21**, the nucleophile cannot abstract a proton and must attack the carboxyl group. This will result in decarboxylation and conversion of the epoxide to the 3-hydroxycarbostyril **23c**.

SCHEME III



Experimental Section

Melting points were determined in a capillary melting point apparatus. The uv spectra were measured in 2-propanol on a Cary Model 14 spectrophotometer; nmr spectra were recorded with a Varian A-60 or Varian T-60 instrument. Ir spectra were determined on a Beckman IR-9 spectrometer. Silica gel Merck (70–325 mesh) was used for chromatography.

Methyl 2′-Benzoyl-2-(benzyloxycarbonylamino)-4′-chloromalonanilate (3a).—Phosphorus pentachloride (12.5 g, 0.06 mol) was added to a suspension of 16 g (0.06 mol) of methyl 2-(benzyloxycarbonylamino)malonate (**2a**)[7] in 100 ml of methylene chloride cooled to −20°. After the solution was stirred for 30 min at −20 to −10°, 9.3 g (0.04 mol) of 2-amino-5-chlorobenzophenone was added to the solution. The temperature was allowed to reach 5–10°, when 100 ml of 10% aqueous sodium carbonate was added. The two-phase system was stirred vigorously for 30 min. The methylene chloride layer was separated, washed with sodium carbonate solution, dried over sodium sulfate, and evaporated. Crystallization of the residue from methanol yielded 17.5 g (91%) of product, mp 108–111°. The analytical sample was recrystallized from ether–hexane: mp 110–112°; nmr ($CDCl_3$) δ 3.82 (s, 3, OCH_3), 5.08 (d, 1, J = 7 Hz, -CHNH), 5.11 (s, 2, OCH_2), 6.06 (broad d, 1, J = 7 Hz, CHNH), 7.15–8.0 (m, 12, aromatic H), 8.52 (d, 1, J = 9 Hz, C_6, H), 11.25 (broad s, 1, NHCO).

Anal. Calcd for $C_{25}H_{21}ClN_2O_6$: C, 62.44; H, 4.40; N, 5.82. Found: C, 62.42; H, 4.37; N, 5.92.

The following compounds were prepared in the same way. They were not isolated in crystalline form, but used directly in further reactions: ethyl 2′-benzyl-2-(benzyloxycarbonylamino)-4′-chloromalonanilate (**3b**), ethyl 2′-benzoyl-2-(benzyloxycarbonylamino)-4′-chloro-*N*-methylmalonanilate (**3d**), and methyl 2′-benzoyl-2-(benzyloxycarbonylamino)-4′-chloro-*N*-methyl-malonanilate (**3c**).

Methyl 2-(Benzyloxycarbonylamino)-4′-chloro-2′-(2-chlorobenzoyl)malonanilate (3e).—Methyl 2-(benzyloxycarbonylamino)malonate (**2a**) (16 g) was treated as described above with 12.6 g of phosphorus pentachloride and 10.6 g (0.04 mol) of 2-amino-2′,5-dichlorobenzophenone[8] to yield 13.5 g (65%) of product, crystallized from methanol: mp 115–118°; nmr ($CDCl_3$) δ 3.86 (s, 3, OCH_3), 5.15 (s, 2, OCH_2), 5.16 (d, 1, J = 7 Hz, CHNH), 6.11 (broad d, 1, J = 7 Hz, CHNH), 7.1–7.8 (m, 11, aromatic H), 8.66 (d, 1, J = 9 Hz, C_6, H), 12.0 (broad s, 1, NHCO).

Anal. Calcd for $C_{25}H_{20}Cl_2N_2O_6$: C, 58.25; H, 3.91; N, 5.44. Found: C, 58.20; H, 4.00; N, 5.50.

Methyl 3-(Benzyloxycarbonylamino)-6-chloro-4-hydroxy-1-methyl-4-phenyl-1,2,3,4-tetrahydroquinolin-2-one-3-carboxylate (4c).—5-Chloro-2-methylaminobenzophenone (9.5 g) was acylated as described above with 16 g of methyl 2-(benzyloxycarbonylamino)malonate and 12.6 g of phosphorus pentachloride to yield 23.8 g of methyl 2′-benzoyl-2-(benzyloxycarbonylamino)-4′-chloro-*N*-methylmalonanilate (**3c**) as a light yellow resin which resisted all attempts at crystallization. This material was dissolved in 300 ml of anhydrous methanol containing 1 ml of triethylamine. After the solution was allowed to stand overnight, the crystals which separated were collected and washed with methanol to leave 18.2 g (92%) of product: mp 177–180°; nmr ($CDCl_3$) δ 3.50 (s, 3, NCH_3), 3.60 (s, 3, OCH_3), 5.07 (s, 2, OCH_2), 6.53 (broad s, 1, OH or NHCO), 6.95 (d, 1, J = 9 Hz, C_8 H), 7.05–7.5 (m, 12, 2 C_6H_5, OH, or NHCO, C_7 H), 7.68 (d, 1, J = 2.5 Hz, C_5 H).

Anal. Calcd for $C_{26}H_{23}ClN_2O_6$: C, 63.10; H, 4.68; N, 5.66. Found: C, 63.10; H, 4.68; N, 5.62.

Ethyl 3-(Benzyloxycarbonylamino)-6-chloro-4-hydroxy-1-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydroquinoline-3-carboxylate (4d).

Method A. Base-Catalyzed Cyclization.—An ethanolic solution of crude ethyl 2′-benzoyl-2-(benzyloxycarbonylamino)-4′-chloro-*N*-methylmalonanilate (**3d**), prepared as was the corresponding methyl ester for **4c**, was treated with triethylamine. Crystallization from ethanol yielded the product, mp 165–168°.

Method B. Acid-Catalyzed Cyclization.—Crude ethyl 2′-benzoyl-2-(benzyloxycarbonylamino)-4′-chloro-*N*-methylmalonanilate (**3d**) (23 g) was refluxed for 3 days in a mixture of 200 ml of toluene and 100 ml of acetic acid. The solvents were evaporated under reduced pressure and the residue was partitioned between methylene chloride and 10% aqueous sodium carbonate solution. The organic phase was dried and evaporated. Chro-

(7) Mp 77–79°, prepared according to the procedure described by C. Ganser, *Bull. Soc. Chim. Fr.*, 1713 (1966), for the corresponding ethyl ester **2b**.

(8) L. H. Sternbach, E. Reeder, O. Keller, and W. Metlesics, *J. Org. Chem.*, **26**, 4488 (1961).

matography of the residue on 500 g of silica gel with methylene chloride yielded 13 g (56%) of product, mp 165–168°.

Anal. Calcd for $C_{27}H_{25}ClN_2O_6$: C, 63.72; H, 4.95; N, 6.96. Found: C, 63.56; H, 5.09; N, 7.12.

Methyl 3-Amino-6-chloro-4-hydroxy-2-oxo-4-phenyl-1,2,3,4-tetrahydroquinoline-3-carboxylate (5a).—A mixture of 4.8 g (0.01 mol) of methyl 2′-benzoyl-2-(benzyloxycarbonylamino)-4′-chloromalonanilate, 30 ml of methylene chloride, 30 ml of acetic acid, and 20 ml of acetic acid containing 30% hydrogen bromide was allowed to stand at room temperature for 20 hr. After evaporation under reduced pressure, the residue was dissolved in methylene chloride and the amorphous hydrobromide of methyl 2-amino-2′-benzoyl-4′-chloromalonanilate was precipitated with ether: nmr ($CDCl_3$) δ 3.80 (s, 3, OCH_3), 5.67 (s, 1, CH), 7.2–8.0 (m, 7, aromatic H), 8.33 (d, 1, J = 9 Hz, C_6, H), 8.65 (broad s, 3, NH_3^+), 11.15 (s, 1, NHCO).

The amorphous salt was partitioned between methylene chloride and 10% aqueous sodium carbonate solution. The organic layer was separated, dried, and evaporated. Crystallization of the residue from ether yielded 2.7 g (78%) of product, mp 168–170° after recrystallization from methylene chloride–ether: nmr ($CDCl_3$) δ 2.15 (very broad s, 2, NH_2), 3.55 (s, 3, OCH_3), 5.8 (broad s, 1, OH), 6.73 (d, 1, J = 9 Hz, C_8 H), 6.95 (d, 1, J = 2.5 Hz, C_5 H), 7.3 (q, 1, J_{AB} = 9, J_{AX} = 2.5 Hz, C_7 H), 7.36 (s, 5, C_6H_5), 9.1 (broad s, 1, NHCO).

Anal. Calcd for $C_{17}H_{15}ClN_2O_4$: C, 58.88; H, 4.36; N, 8.08. Found: C, 59.03; H, 4.39; N, 8.00.

Methyl 3-Amino-6-chloro-4-hydroxy-1-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydroquinoline-3-carboxylate (5c).—A mixture of 10 g of methyl 3-(benzyloxycarbonylamino)-6-chloro-4-hydroxy-1-methyl-4-phenyl-1,2,3,4-tetrahydroquinoline-2-one-3-carboxylate (**4c**), 50 ml of methylene chloride, 50 ml of acetic acid and 40 ml of acetic acid containing 30% hydrogen bromide was allowed to stand at room temperature for 16 hr. The solvents were removed under reduced pressure and the crystalline residue, after being slurried with ether, was collected to yield 8.5 g (96%) of hydrogen bromide salt, mp 143–148° dec. This salt was partitioned between methylene chloride and 10% aqueous sodium carbonate solution and the organic layer was dried and evaporated. The residue was crystallized from ether to yield 6.5 g (89%) of product: mp 125–128°; nmr ($CDCl_3$) δ 2.14 (broad s, 2, NH_2), 3.43 (s, 3, NCH_3), 3.62 (s, 3, OCH_3), 5.08 (s, 1, OH), 7.0 (d, 1 J = 9 Hz, C_8 H), 7.3 (s, 5, C_6H_5), 7.34 (q, 1, J_{AB} = 9, J_{AX} = 2.5 Hz, C_7 H), 7.62 (d, 1, J = 2.5 Hz, C_5 H).

Anal. Calcd for $C_{18}H_{17}ClN_2O_4$: C, 59.92; H, 4.75; N, 7.76. Found: C, 60.11; H, 4.74; N, 7.77.

Ethyl 3-Amino-6-chloro-4-hydroxy-1-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydroquinoline-3-carboxylate (5d).—Cleavage of ethyl 3-(benzyloxycarbonylamino)-6-chloro-4-hydroxy-1-methyl-4-phenyl-1,2,3,4-tetrahydroquinolin-2-one-3-carboxylate (**4d**) with hydrogen bromide as described in the previous experiment yielded the product in 70% yield: mp 98–100° crystallized from ether–hexane; nmr ($CDCl_3$) δ 1.0 (t, 3, J = 7 Hz, CH_3) 2.13 (broad s, 2, NH_2), 3.42 (s, 3, NCH_3), 4.05 (ABX_3 system, 16 lines in 100-MHz spectrum, 2, OCH_2CH_3), 5.10 (s, 1, OH), 6.96 (d, 1, J = 9 Hz, C_8 H), 7.3 (q, 1, J_{AB} = 9, J_{AX} = 2.5 Hz, C_7 H), 7.25 (s, 5, C_6H_5), 7.45 (d, 1, J = 2.5 Hz, C_5 H).

Anal. Calcd for $C_{19}H_{19}ClN_2O_4$: C, 60.88; H, 5.11; N, 7.48. Found: C, 61.30; H, 5.09; N, 7.37.

Ethyl 3-Amino-6-chloro-4-hydroxy-1-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydroquinoline-3-carboxylate (11). Method A. By Cleavage of Compound 12.—A solution of 3.6 g of ethyl 8-chloro-5-methyl-2,4-dioxo-9b-phenyl-2,3,5,9b-tetrahydrooxazolo[4,5-*c*]-quinoline-3a-carboxylate (**12**) in 140 ml of glacial acetic acid containing 30% hydrogen bromide and 35 ml of water was allowed to stand at room temperature for 3 days. The mixture was poured into ice and aqueous sodium carbonate solution and the base was extracted with ether. The extracts were washed with water, dried, and evaporated. Chromatography of the residue on silica gel using methylene chloride, followed by crystallization of the clean fractions from ether–petroleum ether (bp 30–60°), yielded 1.3 g (38%) of product: mp 110–112°; nmr ($CDCl_3$) δ 0.98 (t, 3, J = 7 Hz, CH_3), 2.37 (broad s, 2, NH_2), 3.52 (s, 3, NCH_3), 3.96 (q, 2, J = 7 Hz, OCH_2), 5.60 (broad s, 1, OH), 6.98 (d, 1, J = 2.5 Hz, C_5 H), 7.06 (d, 1, J = 9 Hz, C_8 H), 7.35 (s, 5, C_6H_5), 7.36 (q, 1, J_{AB} = 9, J_{AX} = 2.5 Hz, C_7 H).

Anal. Calcd for $C_{19}H_{19}ClN_2O_4$: C, 60.88; H, 5.11; N, 7.48. Found: C, 61.03; H, 5.13; N, 7.35.

Method B. By Thermal Isomerization of 5d.—A solution of 11.5 g of ethyl 3-amino-6-chloro-4-hydroxy-1-methyl-4-phenyl-1,2,3,4-tetrahydroquinolin-2-one-3-carboxylate (**5d**) in 200 ml of toluene was refluxed for 3 hr. The solvent was removed under reduced pressure and the residue was chromatographed over 300 g of silica gel using 5% ethyl acetate in methylene chloride. In addition to 5 g of starting material, 4 g (35%) of the isomeric product, mp 110–112°, was obtained.

Methyl 2-Amino-4′-chloro-2′-(2-chlorobenzoyl)malonanilate (6).—A mixture of 5.15 g of methyl 2-(benzyloxycarbonylamino)-4′-chloro-2′-(2-chlorobenzoyl)malonanilate (**3e**), 30 ml of methylene chloride, 30 ml of glacial acetic acid, and 20 ml of glacial acetic acid containing 30% hydrogen bromide was allowed to stand at room temperature for 4 hr. After evaporation of the solvents under reduced pressure, the residue was partitioned between water and ether. The water phase was washed with ether and was made alkaline with aqueous sodium carbonate solution. The precipitated base was extracted with methylene chloride. The dried extracts were evaporated and the residue was crystallized from ether to yield 2.75 g (72%) of product: mp 106–109°; ir (KBr) 3400, 3340, 3210 (CONH, NH_2), 1740 ($COOCH_3$), 1690 (NHCO), 1650 cm^{-1} (C=O); nmr ($CDCl_3$) δ 2.17 (broad s, 2, NH_2), 3.87 (s, 3, OCH_3), 4.47 (s, 1, CH), 7.2–7.8 (m, 6, aromatic H), 8.8 (d, 1, J = 9 Hz, C_6, H), 12.4 (broad s, 1, NHCO).

Anal. Calcd for $C_{17}H_{14}Cl_2N_2O_4$: C, 53.56; H, 3.70; N, 7.35. Found: C, 53.46; H, 3.79; N, 7.31.

Ethyl 8-Chloro-5-methyl-2,4-dioxo-9b-phenyl-2,3,4,9b-tetrahydrooxazolo[4,5-*c*]quinoline-3a-carboxylate (12). Method A.—Crude ethyl 2′-benzoyl-2-(benzoloxycarbonylamino)-4′-chloro-*N*-methylmalonanilate (**3d**) (23 g) was refluxed for 3 days in 200 ml of toluene and 100 ml of acetic acid. The solvents were evaporated under reduced pressure and the residue was partitioned between methylene chloride and 10% aqueous sodium carbonate solution. The organic phase was dried and evaporated. The residue was chromatographed over 500 g of silica gel using methylene chloride. After elution of 13 g of ethyl 3-(benzyloxycarbonylamino)-6-chloro-4-hydroxy-1-methyl-4-phenyl-1,2,3,4-tetrahydroquinolin-2-one-3-carboxylate (**4d**), 6.5 g of **12** was eluted and crystallized from ethanol: mp 218–220°; nmr ($CDCl_3$) δ 0.85 (t, 3, J = 7 Hz, CH_3), 3.53 (2, 3, NCH_3), 3.69 (m, 2, OCH_2), 6.6 (broad s, 1, NH), 7.13 (d, 1, J = 9 Hz, C_6 H), 7.20 (d, 1, J = 2.5 Hz, C_9 H), 7.2–7.6 (m, 6, rest of aromatic protons).

Anal. Calcd for $C_{20}H_{17}ClN_2O_5$: C, 59.93; H, 4.28; Cl, 8.84. Found: C, 59.97; H, 4.43; Cl, 8.68.

Method B.—Ethyl 3-amino-6-chloro-4-hydroxy-1-methyl-4-phenyl-1,2,3,4-tetrahydroquinolin-2-one-3-carboxylate (**11**) (0.5 g) was dissolved in 7 ml of pyridine, and 3 ml of a 20% solution of phosgene in chloroform was added with ice cooling. The mixture was allowed to stand at 0° for 2 hr and was then partitioned between methylene chloride and 2 *N* hydrochloric acid. The organic layer was dried, filtered, and evaporated. Crystallization of the residue from ethanol yielded 0.4 g (75%) of product, identical with the material obtained in A.

Ethyl 8-Chloro-5-methyl-2,4-dioxo-9b-phenyl-2,3,5,9b-tetrahydrooxazolo[4,5-*c*]quinoline-3a-carboxylate (9) and Diethyl 8-Chloro-5-methyl-2,4-dioxo-9b-phenyl-2,3,5,9b-tetrahydrooxazolo-[4,5-*c*]quinoline-3,3a-dicarboxylate (10).—A 27% solution of phosgene in chloroform (6 ml) was added to a solution of 3 g of ethyl 3-amino-6-chloro-4-hydroxy-1-methyl-4-phenyl-1,2,3,4-tetrahydroquinolin-2-one-3-carboxylate (**5d**) in 30 ml of anhydrous pyridine and 12 ml of chloroform. The mixture was stirred at 0° for 75 min, when ethanol was added and stirring was continued for an additional 15 min. The reaction mixture was partitioned between methylene chloride and 2 *N* hydrochloric acid. The organic layer was washed with 2 *N* hydrochloric acid and water, dried, and evaporated. The residue was chromatographed on 200 g of silica gel using 10% ethyl acetate in methylene chloride. Crystallization from ether yielded 1.1 g (34%) of **9**: mp 155–157°; nmr ($CDCl_3$) δ 0.96 (t, 3, J = 7 Hz, CH_3), 3.17 (s, 3, NCH_3), 4.00 (q, 2, J = 7 Hz, OCH_2), 6.72 (s, 1, NH), 6.95 (d, 1, J = 9 Hz, C_6 H), 7.1–7.6 (m, 6, aromatic H), 7.65 (d, 1, J = 2.5 Hz, C_9 H).

Anal. Calcd for $C_{20}H_{17}ClN_2O_5$: C, 59.93; H, 4.28; N, 6.99. Found: C, 59.70; H, 4.27; N, 6.80.

The second product which was eluted was crystallized from ether to yield 0.8 g (25%) of **10**, mp 206–208° dec.

Anal. Calcd for $C_{23}H_{21}ClN_2O_7$: C, 58.42; H, 4.48; N, 5.92. Found: C, 58.12; H, 4.44; N, 5.74.

Ethyl 6-Chloro-3-methyl-2-oxo-7b-phenyl-1,2,3,7b-tetrahydro-1a*H*-azirino[2,3-*c*]quinoline-1a-carboxylate (13).—A solution of 16 g of ethyl 3-amino-6-chloro-4-hydroxy-1-methyl-4-phenyl-1,2,3,4-tetrahydroquinolin-2-one-3-carboxylate (11) in 120 ml of glacial acetic acid containing 30% of hydrogen bromide was allowed to stand at room temperature for 24 hr. The solvent was evaporated under reduced pressure and the residue was partitioned between methylene chloride and ice-cold sodium carbonate solution. The methylene chloride layer was washed with water, dried, and evaporated. Crystallization of the residue from ether–petroleum ether yielded 11.2 g (73%) of product: mp 188–190°; nmr ($CDCl_3$) δ 0.92 (t, 3, J = 7 Hz, CH_3), 3.52 (s, 3, NCH_3), 3.97 (q, 2, J = 7 Hz, OCH_2), 6.96 (d, 1, J = 2.5 Hz, C_7 H), 7.03 (d, 1, J = 9 Hz, C_4 H), 7.2–7.9 (m, 6, aromatic H), NH very broad between 2 and 3 ppm.

Anal. Calcd for $C_{19}H_{17}ClN_2O_3$: C, 63.96; H, 4.80; N, 7.85. Found: C, 63.43; H, 4.69; N, 7.65.

Ethyl 1-Acetyl-6-chloro-3-methyl-2-oxo-7b-phenyl-1,2,3,7b-tetrahydro-1a*H*-azirino[2,3-*c*]quinoline-1a-carboxylate (14).—One drop of perchloric acid was added to a suspension of 0.1 g of ethyl 6-chloro-3-methyl-7b-phenyl-1,2,3,7b-tetrahydro-1a*H*-azirino[2,3-*c*]quinolin-2-one-1a-carboxylate in 1 ml of acetic anhydride. After stirring for 5 hr at room temperature the reaction mixture was partitioned between ice-cold 10% sodium carbonate solution and methylene chloride. The organic phase was washed, dried, and evaporated. Crystallization from ether yielded 60 mg (54%) of product, mp 228–230°.

Anal. Calcd for $C_{21}H_{19}ClN_2O_4$: C, 63.24; H, 4.80; N, 7.02; Cl, 8.89. Found: C, 63.26; H, 4.85; N, 7.01; Cl, 8.90.

3-Amino-6-chloro-1-methyl-4-phenylcarbostyril (8).[3]—Sodium methoxide (0.3 g, 5.5 mmol) was added to a solution of 1 g (3.7 mmol) of methyl 3-amino-6-chloro-4-hydroxy-1-methyl-4-phenyl-1,2,3,4-tetrahydroquinolin-2-one-3-carboxylate (**5c**) in 20 ml of methanol. The solution was allowed to stand at room temperature for 20 hr. It was then neutralized with acetic acid and partitioned between methylene chloride and aqueous sodium carbonate solution. The organic phase was separated, dried, and evaporated. Crystallization from ether yielded 0.65 g (85%) of product, mp 130–133°.

Methyl 7-Chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one-3-carboxylate (7a).[4]—A mixture of 1 g of methyl 3-amino-6-chloro-4-hydroxy-4-phenyl-1,2,3,4-tetrahydroquinolin-2-one-3-carboxylate (**5a**), 20 ml of benzene, and 2 ml of acetic acid was refluxed for 4 hr. The solvents were evaporated and the residue was crystallized from methylene chloride–methanol to yield 0.72 g (76%) of product, mp 217–219°.

Ethyl 7-Chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one-3-carboxylate (7b).[4] **Method A.**—Zinc dust (2 g) was added to a solution of 2 g of ethyl 2′-benzoyl-4′-chloromesoxalanilate-2-oxime (**17a**) in 40 ml of methylene chloride and, within 5 min, 4 ml of acetic acid was added dropwise with stirring. The mixture was stirred for 1 hr at room temperature and then filtered. The filtrate was evaporated, dissolved in 20 ml of benzene and 2 ml of acetic acid, and refluxed for 2 hr. The solution was extracted with 10% sodium carbonate solution, dried, and evaporated. Crystallization of the residue from ethanol yielded 1.1 g (60%) of product, mp 232–234°.

Method B.—Fuming nitric acid (98%) (30 ml) was added to a solution of 34.6 g of ethyl 2′-benzoyl 4′-chloromalonanilate (**15a**) in 250 ml of acetic acid. After sitting at room temperature for 2.5 hr, the mixture was diluted with 1 l. of water. The precipitated resin was collected, washed with water, and dissolved in ether. The ether phase was extracted several times with saturated sodium bicarbonate solution. The extracts were washed with ether and acidified with hydrochloric acid. The precipitated product was extracted with methylene chloride. The extracts were dried over sodium sulfate and evaporated to leave 26.5 g (68%) of ethyl 2′-benzoyl-4′-chloro-2-nitromalonanilate (**16a**) as a yellow resin. A solution of 2 g of this product in 50 ml of methylene chloride was treated with 2 ml of acetic acid and 2 g of zinc dust. After a vigorous reaction, the mixture was stirred for an additional 10 min and filtered. The filtrate was evaporated, dissolved in 70 ml benzene and 2 ml of acetic acid, and refluxed for 2 hr. The mixture was washed with saturated sodium bicarbonate solution, dried over sodium sulfate, and evaporated. Crystallization of the residue from ethanol yielded 0.8 g (45%) of product, mp 228–230°.

Methyl 7-Chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one-3-carboxylate (7c). Method A.—A mixture of 0.5 g of methyl 3-amino-6-chloro-4-hydroxy-1-methyl-4-phenyl-1,2,3,4-tetrahydroquinolin-2-one-3-carboxylate (**5c**), 20 ml of benzene, and 2 ml of acetic acid was refluxed for 3 hr. The residue, obtained upon evaporation to dryness, was recrystallized from methylene chloride–methanol to yield 0.43 g (91%) of product, mp 224–226°.

Anal. Calcd for $C_{18}H_{15}ClN_2O_3$: C, 63.07; H, 4.41; N, 8.17. Found: C, 63.25; H, 4.49; N, 8.05.

Method B.—Glacial acetic acid (40 ml) containing 30% of hydrogen bromide was added to a solution of 5 g of crude methyl 2′-benzoyl-2-(benzyloxycarbonylamino)-4′-chloro-*N*-methylmalonanilate (**3c**). After standing at room temperature for 4 hr, the solvent was removed under reduced pressure and the residue was partitioned between methylene chloride and 10% aqueous sodium carbonate solution. The organic layer was dried and evaporated. Crystallization of the residue from methylene chloride–methanol yielded 2.7 g (77%) of product, mp 224–226°.

Ethyl 7-Chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one-3-carboxylate (7d).[4] **Method A.**—A mixture of 3.74 g of ethyl 3-amino-6-chloro-4-hydroxy-1-methyl-4-phenyl-1,2,3,4-tetrahydroquinolin-2-one-3-carboxylate (**5d**), 50 ml of toluene, and 5 ml of acetic acid was refluxed for 2 hr. The usual work-up and crystallization from ethanol yielded 2.6 g (73%) of product **7d**, mp 196–199°.

Method B.—Ethyl 3-amino-6-chloro-4-hydroxy-1-methyl-4-phenyl-1,2,3,4-tetrahydroquinolin-2-one-3-carboxylate (11) (2 g) yielded, under the same conditions, 1.6 g (84%) of product **7d**.

Method C.—A mixture of 0.4 g of ethyl 6-chloro-3-methyl-7b-phenyl-1,2,3,7b-tetrahydro-1a*H*-azirino[2,3-*c*]quinazolin-2-one-1a-carboxylate (**13**), 20 ml of toluene, and 5 ml of acetic acid was refluxed for 5 hr. The residue obtained after the usual work-up was chromatographed over 20 g of silica gel using 10% ethyl acetate in methylene chloride. After elution of 0.1 g (22%) of ethyl 1-acetyl-6-chloro-3-methyl-7b-phenyl-1,2,3,7b-tetrahydro-1a*H*-azirino[2,3-*c*]quinolin-2-one-1a-carboxylate (**14**), 0.2 g (50%) of **7d**, mp 196–199°, was obtained.

Method D.—Zinc dust (2 g) was added to a solution of 2 g of ethyl 2′-benzoyl-4′-chloro-*N*-methylmesoxalanilate 2-oxime (**17c**) in 40 ml of methylene chloride, and 4 ml of acetic acid was added dropwise with stirring within 5 min. After the addition, stirring was continued for 20 min. The filtered reaction mixture was evaporated and the residue was refluxed for 2 hr in 20 ml of benzene and 2 ml of acetic acid. The solution was washed with 10% aqueous sodium carbonate, dried over sodium sulfate, and evaporated. Crystallization of the residue from ethanol–ether yielded 0.5 g (27%) of **7d**, mp 196–199°.

Method E.—Fuming nitric acid (98%) (30 ml) was added to a solution of 36 g of ethyl 2′-benzoyl-4′-chloro-*N*-methylmalonanilate (**15c**) in 250 ml of acetic acid. After standing for 2 hr at room temperature, the mixture was poured into 1 l. of water. The precipitated resin was collected, washed with water, and dissolved in benzene. The benzene solution was washed with water, dried, and evaporated to leave 34.5 g (85%) of crude ethyl 2′-benzoyl-4′-chloro-2-nitro-*N*-methylmalonanilate (**16c**), which was reduced as follows. To a solution of 2 g of the crude **16c** in 50 ml of methylene chloride and 2 ml of acetic acid, 2 g of zinc dust was added with stirring. After the exothermic reaction, stirring was continued for an additional 10 min. The residue obtained after filtration and evaporation of the reaction mixture was partitioned between benzene and 2 *N* hydrochloric acid. The benzene layer was extracted twice with 2 *N* hydrochloric acid. The extracts were combined, washed with ether, and made alkaline by addition of 10% aqueous sodium carbonate solution. The precipitated base was extracted with methylene chloride and the extracts were dried and evaporated. The residue was refluxed in 20 ml of benzene containing 2 ml of acetic acid for 2 hr. The cold mixture was washed with 10% aqueous sodium carbonate, dried, and evaporated. The residue was crystallized from ethanol to yield 0.5 g (48% overall) of **7d**, mp 196–199°.

Methyl 7-Chloro-5-(2-chlorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one-3-carboxylate (7e).—A mixture of 0.5 g of methyl 2-amino-2′-(2-chlorobenzoyl)-4′-chloromalonanilate (**6**), 20 ml of benzene, and 2 ml of acetic acid was refluxed for 3 hr. After evaporation, the residue was crystallized from methanol–ether to yield 0.33 g (70%) of product: mp 216–219°; nmr ($CDCl_3$) δ 3.94 (s, 3, OCH_3), 4.72 (s, 1, CH), 7.0–7.8 (m, 7, aromatic H), 9.55 (broad s, 1, NHCO).

Anal. Calcd for $C_{17}H_{12}Cl_2N_2O_3$: C, 56.22; H, 3.33; N, 7.71. Found: C, 56.02; H, 3.18; N, 7.73.

Ethyl 2'-Benzoyl-4'-chloromalonanilate (15a).—A solution of 23 g (0.1 mol) of 2-amino-5-chlorobenzophenone in 200 ml of methylene chloride was overlaid with 100 ml of saturated sodium bicarbonate solution. At 0–5°, 19.3 g (0.115 mol) of 2-carboethoxyacetyl chloride was added dropwise with vigorous stirring. After complete addition, stirring was continued for 10 min. The methylene chloride solution was separated, washed with bicarbonate solution, dried, and evaporated. The residue was crystallized from ether–hexane by cooling to −10° to yield 22 g (64%): mp 54–55°; nmr ($CDCl_3$) δ 1.30 (t, 3, J = 7 Hz, CH_2CH_3), 3.50 (s, 2, CH_2), 4.28 (q, 2, J = 7 Hz, OCH_2CH_3), 7.2–8.0 (m, 7, aromatic H), 8.55 (d, 1, J = 9 Hz, C_6 H), 11.04 (broad s, 1, NHCO); ir (KBr) 3260 (NH), 1720 (COOEt), 1690 (NHCO), and 1650 cm^{-1} (C=O).

Anal. Calcd for $C_{18}H_{16}ClNO_4$: C, 62.52; H, 4.66; N, 4.05. Found: C, 62.37; H, 4.62; N, 3.77.

Ethyl 2'-Benzoyl-4'-chloro-N-methylmalonanilate (15c).—2-Carboethoxyacetyl chloride (39.2 g, 0.235 mol) was added to a solution of 49.2 g (0.2 mol) of 5-chloro-2-methylaminobenzophenone in 400 ml of methylene chloride cooled to 0°. After 20 min, 400 ml of saturated sodium bicarbonate solution was added within 15 min at 0–5° with vigorous stirring. The organic layer was separated, dried, and evaporated. Crystallization of the residue from ether–hexane yielded 64.3 g (89.5%) of colorless crystals: mp 98–100°; ir (KBr) 1745 (COOEt), 1680 (NHCO), and 1660 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.22 (t, 3, J = 7 Hz, CH_2CH_3), 3.05 and 3.30 (s, 3, NCH_3), rotamers), 3.24 (s, 2, CH_2), 4.11 and 4.13 (q, 2, OCH_2CH_3, rotamers), 7.2–8.0 (m, 8, aromatic protons).

Anal. Calcd for $C_{19}H_{18}ClNO_4$: C, 63.43; H, 5.04; N, 3.89. Found: C, 63.18; H, 5.00; N, 3.84.

Ethyl 4'-chloro-2'-(2-fluorobenzoyl)malonanilate (15d) was obtained as above by treating 25 g (0.1 mol) of 2-amino-5-chloro-2'-fluorobenzophenone[9] with 18 g (1.2 mol) of 2-carboethoxyacetyl chloride. The product was crystallized from ether–hexane: mp 74–77°; ir ($CHCl_3$) 3300, 1745, 1700, 1655 cm^{-1}.

Anal. Calcd for $C_{18}H_{13}ClFNO_4$: C, 59.43; H, 4.16; N, 3.85. Found: C, 59.36; H, 4.02; N, 4.00.

Ethyl 6-Chloro-1,2-dihydro-4-(2-fluorophenyl)quinolin-2-one-3-carboxylate (18d).—Potassium *tert*-butoxide (1 g, 9 mmol) was added to a solution of 18.2 g (0.05 mol) of ethyl 4'-chloro-2'-(2-fluorobenzoyl)malonanilate in 200 ml of ethanol. After stirring at room temperature for 2 hr, the mixture was diluted with water. The precipitated product was filtered and recrystallized from ethanol–methylene chloride to yield 12.1 g (70%) of product: mp 245–247°; uv (2-PrOH) λ_{max} 237–238 mμ (ε 44,300), 271–272 (7120), sh 280 (6650), infl 333 (4700), 337–338 (6280), infl 360 (5350); ir ($CHCl_3$) 1735, 1660 cm^{-1}.

Anal. Calcd for $C_{18}H_{13}ClFNO_3$: C, 62.53; H, 3.79; N, 4.05. Found: C, 62.26; H, 3.83; N, 3.98.

Ethyl 6-Chloro-1,2-dihydro-1-methyl-4-phenylquinolin-2-one-3-carboxylate (18c).—By the same procedure a mixture of 18 g (0.05 mol) of ethyl 2'-benzoyl-4'-chloro-N-methylmalonanilate, 200 ml of ethanol, and 1 g of potassium *tert*-butoxide gave 15.3 g of 18c: mp 127–128°; nmr ($CDCl_3$) δ 0.97 (t, 3, J = 7 Hz, CH_3), 3.75 (s, 3, NCH_3), 4.05 (q, 2, J = 7 Hz, OCH_2), 7.1–7.7 (m, 8, aromatic H).

Anal. Calcd for $C_{19}H_{16}ClNO_3$: C, 66.77; H, 4.72; N, 4.10. Found: C, 66.60; H, 4.40; N, 4.03.

Ethyl 2'-Benzoyl-4'-chloromesoxalanilate 2-Oxime (17a).—A solution of 50 g of sodium nitrite in 100 ml of water was added dropwise to a solution of 34.6 g (0.1 mol) of ethyl 2'-benzoyl-4'-chloromalonanilate (15a) in 250 ml of acetic acid. The mixture was stirred for 90 min at room temperature. The precipitated crystals were separated, washed with water, and dried *in vacuo* to leave 33 g of product, mp 98–105°. The filtrate was diluted with water to yield a second crop, 3.5 g (total yield 97%).

The product was a mixture of two isomeric oximes which could be separated by chromatography on silica gel using 20% ethyl acetate in methylene chloride. The isomer eluted first crystallized from ethanol: mp 115–117°; ir (KBr) 3450, 3150, 1720, and 1650 cm^{-1}; nmr ($CDCl_3$) δ 1.35 (t, 3, J = 7 Hz, CH_3), 4.42 (q, 2, J = 7 Hz, OCH_2), 7.2–7.9 (m, 7, aromatic H), 8.64 (d, 1, J = 9 Hz, C_6 H), 10.4 (s, 1, OH), 11.55 (broad s, 1, NHCO).

Anal. Calcd for $C_{18}H_{13}ClN_2O_5$: C, 57.69; H, 4.03; N, 7.47; Cl, 9.46. Found: C, 57.68; H, 3.91; N, 7.51; Cl, 9.51.

The second isomer eluted had mp 131–132°; nmr ($CDCl_3$) δ 1.40 (t, 3, J = 7 Hz, CH_3), 4.46 (q, 2, J = 7 Hz, OCH_2), 7.4–8.0 (m, 7, aromatic H), 8.38 (d, 1, J = 9 Hz, C_6, H), 12.0 (broad s, NH or OH), 16.2 (broad s, 1, NH or OH).

Ethyl 2'-Benzoyl-4'-chloro-N-methylmesoxalanilate 2-Oxime (17c).—A solution of 25 g of sodium nitrite in 50 ml of water was added to a solution of 18 g (0.05 mol) of ethyl 2'-benzoyl-4'-chloro-N-methylmalonanilate (15c) in 125 ml of acetic acid. Concentrated sulfuric acid (10 ml) was added dropwise to the stirred solution and after stirring for 2 hr at room temperature, the product was precipitated by addition of water to yield 7 g (36%) of crystalline oxime, mp 196–198°. The analytical sample was recrystallized from benzene–ethyl acetate: mp 203–205°; mixture of two isomers in solution; nmr (DMSO) δ 1.12 and 1.15 (t, 3, CH_3), 3.14 and 3.20 (s, 3, NCH_3), 3.86 and 4.13 (q, 2, J = 7 Hz, OCH_2), 7.3–8.0 (m, 8, aromatic H), 12.9 (s, 1, OH).

Anal. Calcd for $C_{19}H_{17}ClN_2O_5$: C, 58.70; H, 4.41; N, 7.21; Cl, 9.12. Found: C, 58.33; H, 4.31; N, 7.09; Cl, 9.46.

Ethyl 2-Bromo-4'-chloro-2'-(2-fluorobenzoyl)malonanilate (19d).—2-Bromo-2-carboethoxyacetyl chloride[10] (25 g, 0.11 mol) was added to a solution of 25 g (0.1 mol) of 2-amino-5-chloro-2'-fluorobenzophenone in 200 ml of methylene chloride. After stirring at room temperature, the mixture was poured into 200 ml of saturated sodium bicarbonate solution. The methylene chloride layer was washed with water, dried, and evaporated. Crystallization of the residue from ethanol yielded 31 g (70%) of product: mp 81–83°; ir ($CHCl_3$) 3250, 1750, 1690, 1650 cm^{-1}.

Anal. Calcd for $C_{18}H_{14}BrClFNO_4$: C, 48.83; H, 3.19; N, 3.16. Found: C, 48.90; H, 3.19; N, 3.06.

Methyl 2'-Benzoyl-2-bromo-4'-chloromalonanilate (19a).—In the same way, reaction of 24 g (0.11 mol) of 2-bromo-2-carbomethoxyacetyl chloride with 23 g (0.1 mol) of 2-amino-5-chlorobenzophenone yielded 29 g (71%) of product, mp 92–93°, crystallized from methylene chloride–hexane: nmr ($CDCl_3$) δ 3.86 (s, 3, OCH_3), 4.90 (s, 1, CH), 7.3–8.0 (m, 7, aromatic H), 8.55 (d, 1, J = 9 Hz, C_6, H), 11.5 (broad s, 1, NHCO).

Anal. Calcd for $C_{17}H_{13}BrClNO_4$: N, 3.41; Br, 19.46; Cl, 8.63. Found: N, 3.57; Br, 19.83; Cl, 8.80.

Methyl 6-Chloro-3,4-epoxy-1,2,3,4-tetrahydro-4-phenylquinolin-2-one-3-carboxylate (20a).—A solution of 4.1 g of methyl 2'-benzoyl-2-bromo-4'-chloromalonanilate (19a) in 20 ml of methylene chloride was added to 20 ml of liquid ammonia. After the addition, the reaction mixture was allowed to warm gradually to room temperature, while being stirred for 1 hr. The methylene chloride solution was washed with water, dried, and evaporated. The residue was crystallized from methylene chloride–hexane to yield 3 g (91%): nmr δ 3.54 (s, 3, OCH_3), 7.04 (d, 1, J = 9 Hz, C_8 H), 7.07 (d, 1, J = 2.5 Hz, C_5 H), 7.2–7.9 (m, 6, aromatic H), 10.3 (broad s, 1 NH).

Anal. Calcd for $C_{17}H_{12}ClNO_4$: C, 61.92; H, 3.67; H, 4.25. Found: C, 62.07; H, 3.63; N, 4.25.

Ethyl 6-chloro-3,4-epoxy-4-phenyl-1,2,3,4-tetrahydroquinolin-2-one-3-carboxylate (20b) was obtained in the same manner by causing crude ethyl 2'-benzoyl-2-bromo-4'-chloromalonanilate (19b) to react with liquid ammonia: mp 192–193°; ir (KBr) 3210, 1770, 1750, and 1690 cm^{-1}.

Anal. Calcd for $C_{18}H_{14}ClNO_4$: C, 62.89; H, 4.11; N, 4.07. Found: C, 62.77; H, 4.00; N, 4.09.

Ethyl 6-Chloro-3,4-epoxy-4-(2-fluorophenyl)-2-oxo-1,2,3,4-tetrahydroquinoline-3-carboxylate (20d).—A solution (50 ml) of 2.3 g of sodium in 100 ml of ethanol was added to a solution of 22 g (0.05 mol) of ethyl 2-bromo-4'-chloro-2'-(2-fluorobenzoyl)-malonanilate (19d) in 200 ml of benzene. The mixture was stirred for 10 min, neutralized with acetic acid, and washed with water. The benzene layer was separated, dried, and evaporated. Crystallization of the residue from ether yielded 14 g (78%) of product: mp 223–226° after recrystallization from ethanol; ir ($CHCl_3$) 3375, 3250, 1750, and 1695 cm^{-1}.

Anal. Calcd for $C_{18}H_{13}ClFNO_4$: C, 59.76; H, 3.62; N, 3.87. Found: C, 59.80; H, 3.42; N, 3.88.

Methyl 6-Chloro-3,4-epoxy-1-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydroquinoline-3-carboxylate (21).—Potassium *tert*-butoxide (2.7 g, 0.024 mol) was added to a solution of 6.6 g (0.02 mol) of methyl 6-chloro-3,4-epoxy-4-phenyl-1,2,3,4-tetrahydroquinolin-2-one-3-carboxylate (20a) in 50 ml of dimethylformamide cooled to −10°. After stirring for 5 min, 3.4 g (0.024 mol) of methyl

(9) L. H. Sternbach, R. I. Fryer, W. Metlesics, G. Sach, and A. Stempel, *J. Org. Chem.*, **27**, 3781 (1962).

(10) H. Staudinger and H. Becker, *Ber.*, **50**, 1016 (1917).

iodide was added and the reaction mixture was allowed to reach room temperature. The product was precipitated by pouring into ice water. It was collected, washed with water, and dissolved in methylene chloride. The solution was dried and evaporated and the residue was crystallized from methanol to yield 5.5 g (80%) of **21**, mp 143–145°.

Anal. Calcd for $C_{18}H_{14}ClNO_4$: C, 62.89; H, 4.11; N, 4.07. Found: C, 63.10; H, 4.24; N, 3.77.

6-Chloro-3-hydroxy-4-phenylcarbostyril (23a).—Methyl 6-chloro-3,4-epoxy-4-phenyl-1,2,3,4-tetrahydroquinolin-2-one-3-carboxylate (**20a**) (3.3 g) was added with stirring to 30 ml of concentrated sulfuric acid. Evolution of carbon dioxide ceased within 15 min. The clear solution was poured into ice water and the precipitated product was collected, washed with water, and dissolved in methylene chloride. The solution was dried and evaporated. Crystallization of the residue from ethyl acetate–methanol yielded 2.05 g (75%) of **23a**: mp 255–258°; uv (2-PrOH) λ_{max} 231–232 mμ (ε 47,400), 287 (7750), infl 313 (7150), 325 (10,200), 338 (8100); ir (KBr) 3375 and 1640 cm^{-1}.

Anal. Calcd for $C_{15}H_{10}ClNO_2$: C, 66.31; H, 3.71; N, 5.16. Found: C, 66.54; H, 3.89; N, 5.02.

6-Chloro-4-(2-fluorophenyl)-3-hydroxycarbostyril (23d) was obtained in 93% yield by treating 12 g of ethyl 6-chloro-3,4-epoxy-4-(2-fluorophenyl)-1,2,3,4-tetrahydroquinolin-2-one-3-carboxylate (**20d**) with 50 ml of concentrated sulfuric acid as described in the previous example: mp 255–257°; ir ($CHCl_3$) 3400, 3150, 1660 cm^{-1}.

Anal. Calcd for $C_{15}H_9ClFNO_2$: C, 62.19; H, 3.13; N, 4.84. Found: C, 62.49; H, 2.96; N, 4.77.

6-Chloro-3-hydroxy-1-methyl-4-phenylcarbostyril (23c). Method A.—A mixture of 3.43 g (0.01 mol) of methyl 6-choro-3,4-epoxy-1-methyl-4-phenyl-1,2,3,4-tetrahydroquinolin-2-one-3-carboxylate (**21**), 1 g (0.018 mol) of ammonium chloride, and 30 ml of dimethylformamide was refluxed for 2 hr. The cooled mixture was poured into water. The precipitate was collected, washed with water, and dissolved in methylene chloride. The solution was dried and evaporated. The crystalline residue was slurried with methylene chloride–ether to yield 2.4 g (84%) of **23c**. The analytical sample was recrystallized from methylene chloride–ethyl acetate: mp 252–253; uv (2-PrOH) λ_{max} 232 mμ (ε 48,500), 290 (8300), sh 315 (7100), 321–322 (9700), 339 (7500); ir (KBr) 3250 and 1620 cm^{-1}.

Anal. Calcd for $C_{16}H_{12}ClNO_2$: C, 67.26; H, 4.23; N, 4.90. Found: C, 67.54; H, 4.24; N, 4.77.

The same compound was obtained by treating **21** with either concentrated sulfuric acid or aqueous alkali.

Method B.—6-Chloro-3,4-epoxy-1-methyl-4-phenyl-1,2,3,4-tetrahydroquinolin-2-one (**25**) (1 g) was added to 5 ml of concentrated sulfuric acid. After solution was complete, the reaction mixture was poured into ice water and the precipitate was extracted with methylene chloride. The dried extracts were evaporated and the residue was recrystallized from methylene chloride–ethyl acetate to yield 0.85 g (85%) of **23c**, mp 250–253°.

6-Chloro-3,4-epoxy-1-methyl-4-phenyl-1,2,3,4-tetrahydroquinolin-2-one (25).—A solution of 3 g (0.075 mol) of sodium hydroxide in 30 ml of water was added to a solution of 18.5 g (0.05 mol) of 2-bromo-2′-benzoyl-4′-chloro-*N*-methylacetanilide in 100 ml of dimethylformamide. The mixture, which was stirred at room temperature for 30 min. crystallized on seeding and cooling in ice water. Seeds were obtained by chromatography of crude material on silica gel using methylene chloride and crystallization of the clean fractions from methanol–ether. The separated crystals were collected, washed with methanol–water, and recrystallized twice from acetone–methanol to yield 5.1 g (35%) of **25**: mp 123–124°; ir (KBr) 1650 cm^{-1}; uv (2-PrOH) λ_{max} 266–267 mμ (ε 12,280), infl 300 (2900); nmr ($CDCl_3$) δ 3.41 (s, 3, CH_3), 3.75 (s, 1, CH), 6.8–7.6 (m, 8, aromatic H).

Anal. Calcd for $C_{16}H_{12}ClNO_2$: C, 67.26; H, 4.23; N, 4.90. Found: C, 67.30; H, 4.24; N, 4.98.

5-Chloro-3-phenyloxindole (22a).[11]—A mixture of 2 g (6 mmol) of methyl 6-chloro-3,4-epoxy-4-phenyl-1,2,3,4-tetrahydroquinolin-2-one-3-carboxylate (**20a**), 1 g (18 mmol) of ammonium chloride, and 20 ml of dimethylformamide was refluxed for 20 min. The product was precipitated by the addition of water to the cooled reaction mixture. It was collected, washed with water, and recrystallized from methanol–water to give 1.4 g (94%) of 5-chloro-3-phenyloxindole, mp 190–192°.

5-Chloro-3-(2-fluorophenyl)oxindole (22d).—A mixture of 1.8 g (5 mmol) of ethyl 6-chloro-3,4-epoxy-4-(2-fluorophenyl)-1,2,3,4-tetrahydroquinolin-2-one-3-carboxylate (**20d**), 1 g of ammonium chloride, and 30 ml of dimethylformamide was refluxed for 30 min. The product was crystallized by the addition of water to the cooled reaction mixture. It was collected, washed with water, and recrystallized from methanol to yield 1.17 g (90%) of **22d**: mp 188–190°; uv (2-PrOH) λ_{max} 255–256 mμ (ε 14,020), 293 (1640); ir ($CHCl_3$) 3450, 3200, and 1720 cm^{-1}; nmr ($CDCl_3$) δ 4.9 (s, 1, CH), 6.8 (d, 1, J = 9 Hz, C_7 H) 6.9–7.4 (m, 6, aromatic H), 9.3 (broad s, 1, NHCO).

Anal. Calcd for $C_{14}H_9ClFNO$: C, 64.27; H, 3.47; N, 5.35. Found: C, 64.38; H, 3.47; N, 5.34.

Registry No.—**3a**, 29177-48-8; **3e**, 37393-55-8; **4c**, 37393-91-2; **4d**, 37393-92-3; **5a**, 37393-93-4; **5c**, 37393-94-5; **5d**, 37393-95-6; **6**, 37393-56-9; **7a**, 5606-56-4; **7b**, 5606-55-3; **7c**, 29301-14-2; **7d**, 5606-57-5; **7e**, 37393-61-6; **8**, 5220-02-0; **9**, 37393-96-7; **10**, 37393-97-8; **11**, 37393-98-9; **12**, 37393-99-0; **13**, 37393-63-8; **14**, 37393-64-9; **15a**, 29177-68-2; **15c**, 29177-70-6; **15d**, 37393-67-2; *syn*-**17a**, 29230-24-5; *anti*-**17a**, 29312-54-7; *syn*-**17c**, 37394-02-8; *anti*-**17c**, 37394-03-9; **18c**, 37393-68-3; **18d**, 37393-69-4; **19a**, 37393-70-7; **19d**, 37393-71-8; **20a**, 37393-72-9; **20b**, 37393-73-0; **20d**, 37393-74-1; **21**, 37393-75-2; **22a**, 15815-97-1; **22d**, 37393-77-4; **23a**, 17259-81-3; **23c**, 37393-79-6; **23d**, 37393-80-9; **25**, 37393-81-0; methyl 2-amino-2′-benzoyl-4′-chloromalonanilate hydrobromide, 37393-82-1.

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(11) H. Kuch, G. Seidl, and K. Schmitt, *Arch. Pharm.*, **300**, 299 (1967).

A New Method for the Synthesis of Optically Active α-Amino Acids and Their N^{α} Derivatives *via* Acylamino Malonates

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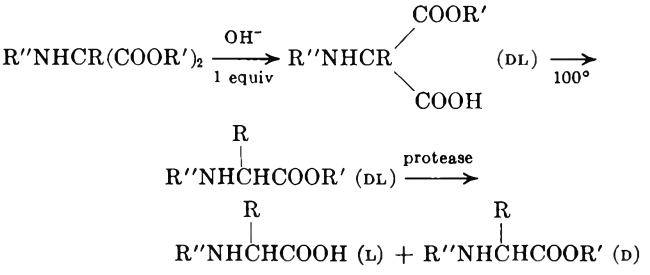
A diethyl 2-acyl(or 2-benzyloxycarbonyl)amino-2-alkyl(or 2-aralkyl)malonate is half-saponified in good yield to the DL monoester. The monoester is smoothly and quantitatively decarboxylated at 100° (*e.g.*, by refluxing in dioxane) to yield the DL-acylamino acid ethyl ester. This derivative is resolved directly by enzymic hydrolysis of the ester group (*e.g.*, chymotrypsin, subtilisin, etc.) to yield the L-acyl(or benzyloxycarbonyl)amino acid, which can be used directly for further peptide synthesis. In addition, the unchanged D derivative is obtained. Alternatively, the optically active amino acids can be recovered by total hydrolysis or by anhydrous cleavage, *e.g.*, by HBr, of their derivatives. The following compounds were synthesized by this method: *N*-acetyl-β-(*o*-methylphenyl)-L-alanine (**4**), *N*-acetyl-β-(*o*-methylphenyl)-D-alanine ethyl ester (**5**), *N*-acetyl-β-(2-naphthyl)-L-alanine (**7**), *N*-acetyl-β-(2-naphthyl)-D-alanine (**9**), *N*-acetyl-β-(2-naphthyl)-D-alanine ethyl ester (**8**), β-(6-quinolyl)-L-alanine (**13**), β-(6-quinolyl)-D-alanine dihydrochloride (**15**), *N*-acetyl-β-(6-quinolyl)-D-alanine ethyl ester (**14**), and *N*-benzyloxycarbonyl-L-phenylalanine (**20**). The preparation of dimethyl benzyloxycarbonylaminomalonate (**16**) is also described.

The malonic ester synthesis is frequently used for the preparation of α-amino acids. One of its advantages is that the intermediate substituted acylamino dialkyl malonates often crystallize well and are easily purified. Yields are generally good. Also, the necessary halogeno derivatives are in many cases easily accessible. To obtain optically active products, the racemic amino acid is usually first generated by simultaneous total hydrolysis and decarboxylation by heating in strong acid. After reacylation, the racemate is resolved enzymically by means of an acylase preparation. Resolution by means of chymotrypsin was reported after reacylation and recsterification.[2] Stereospecific enzymic synthesis (*e.g.*, of phenylhydrazides by means of papain) has also been employed.[3]

In the present paper we describe a much simpler method which converts the substituted malonic ester directly to an acylamino acid ester racemate under very mild conditions. The latter compound is then directly resolved taking advantage of the stereospecific esterase activity of proteolytic enzymes. The method is also applicable to the direct synthesis of benzyloxycarbonyl-L-amino acids (from benzyloxycarbonylaminomalonate) for use in peptide synthesis.

Results and Discussion

Diethyl acetamidomalonate and dimethyl benzyloxycarbonylaminomalonate (**16**) (prepared from commercial dimethyl aminomalonate) were used as starting materials and alkylated in the usual way with the appropriate halogen compounds. The intermediates were checked by tlc before proceeding. The N-substituted L-amino acid and D-amino acid ester were obtained by the reactions indicated in the following scheme.



Partial Hydrolysis of the Diester.—As can be seen from Figure 1, there is a very pronounced difference in the rate of saponification of the first ester group and the second. The reason for this is the electrostatic repulsion between the ionized monoester produced in the first stage of saponification and the hydroxyl ion catalyzing further saponification. Thus by controlling the reaction conditions the DL monoester can be obtained in satisfactory yield. Separation and purification of the monoester–monoacid from any residual diester is simple when there are no additional ionizable groups present; however, one may easily proceed to the decarboxylation step without purification at this stage as exemplified in the straightforward synthesis of the racemic amino acid esters **12** and **18**.

Decarboxylation of the Monoester.—Figure 2 shows the course of decarboxylation of monoethyl malonate derivative **2**, as followed by monitoring the evolution of carbon dioxide.[4] It is seen that at 100° (*e.g.*, in refluxing dioxane), without the addition of strong acid, the reaction was of first order with a half-time of about 10 min. That means that within 1 hr the reaction was practically quantitative. For complete decarboxylation of the benzyloxycarbonylaminomalonate **18** refluxing in dioxane for 24 hr was necessary. It is unknown whether this slower rate is a general behavior of benzyloxycarbonylaminomalonates. Purification is easily possible at this stage, since the product is either nonionizable altogether or at least considerably less acidic than the starting material.

Enzymic Resolution.—The decarboxylation product, being an ester of a DL-acylamino acid, serves directly as the substrate for a stereospecific esterase. A number of proteolytic enzymes available in a highly pure and stable form exhibit this type of activity. The amount of enzyme necessary for resolution at a reasonable rate is often very small. In the present study we used chymotrypsin and subtilisin.

The reaction can be followed by alkali uptake at constant pH (*e.g.*, using an automatic titration device) as shown in Figure 3. In the case of esters of low

(1) (a) Deceased November 1, 1972. (b) Recipient of a postdoctoral fellowship from the Swiss National Fund for the Advancement of Science.

(2) T. N. Pattabiraman and W. B. Lawson, *Biochem. J.*, **126**, 659 (1972).

(3) For a review see, *e.g.*, J. P. Greenstein and M. Winitz, "Chemistry of the Amino Acids," Vol. 1, Wiley, New York, N. Y., 1961, p 707.

(4) A. Patchornik and Y. Shalitin, *Anal. Chem.*, **33**, 1887 (1961).

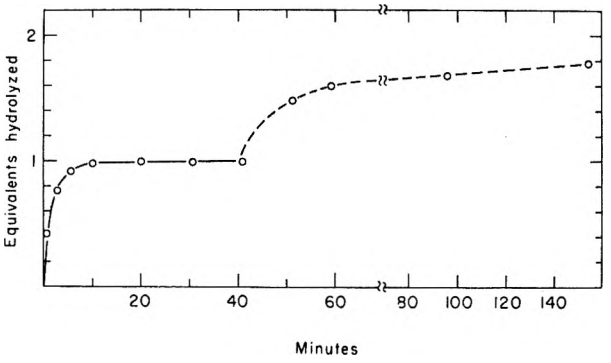


Figure 1.—The time course of partial hydrolysis of diethyl (*o*-methylbenzyl)acetamidomalonate (1) (128 mg) at room temperature in 0.75 ml of ethanol containing 0.3 ml of 3.9 *N* NaOH. Ordinate: equivalents hydrolyzed as determined in aliquots by titration with 0.01 *N* HCl of the excess base present. On heating to 80° (dotted line) the second ester group is seen to be hydrolyzed.

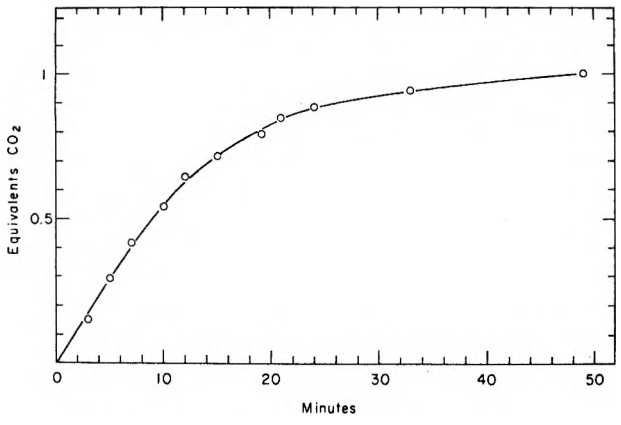


Figure 2.—The time course of decarboxylation of monoethyl (*o*-methylbenzyl)acetamidomalonate (2) (20 mg) in 2 ml of dioxane at 100°. CO_2 was trapped into benzylamine and titrated continuously with 0.11 *M* sodium methoxide.[4]

solubility one can work in suspension, in order to avoid the need for large volumes; thus the amount of enzyme required to achieve the optimal concentration is kept low. However, the suspension must be thin enough to allow proper stirring, mainly to prevent local accumulation of the alkali solution added to keep the pH constant. Alternatively, instead of using the pH-Stat, it may be possible to add enough buffer at the outset in order to prevent the pH from dropping too much during the hydrolysis.

The hydrolysis product (the L form of the acylamino acid) goes into solution at the pH values necessary for most enzymes, and the unhydrolyzed D form is removed at the end of the reaction by filtration, followed by extraction, or by extraction alone. If there is no protonatable group in the side chain, the L-acylamino acid is recovered from the aqueous solution after acidification. However, for instance, in the case of the quinoline derivatives, one either hydrolyzes directly to the free L-amino acid or alternatively isolates the L-acylamino acid as a salt, according to the need in further use of the products.

The advantages of the method described here are (a) hydrolysis and decarboxylation conditions are very mild; (b) one of the reaction intermediates is itself the substrate for enzymic resolution; (c) a variety of proteolytic enzymes can be employed for resolution

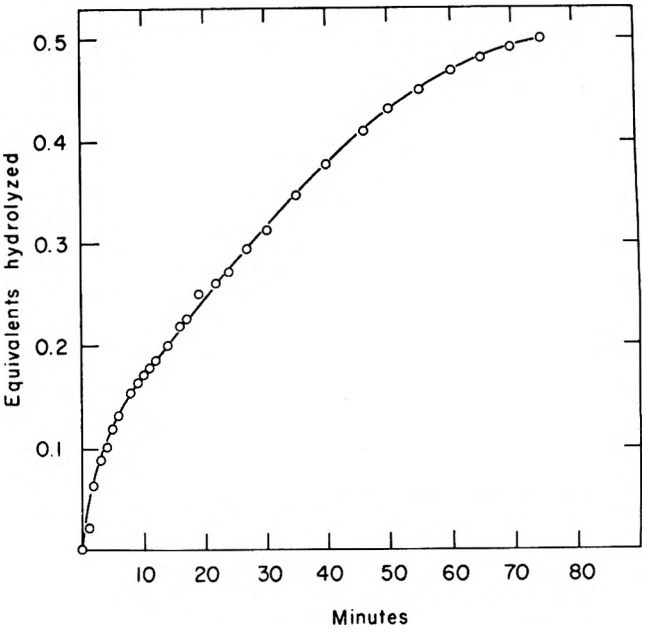


Figure 3.—Enzymic resolution of *N*-acetyl-β-(*o*-methylphenyl)-DL-alanine ethyl ester (3) with chymotrypsin. The course of the reaction was followed by measuring the alkali uptake in a pH-Stat assembly. For details see Experimental Section.

and these are available in a high state of purity and only minute amounts are necessary; (d) amino malonate can be N blocked by a variety of reagents before introducing the R group, a feature which should be of advantage in further peptide synthesis using the new N-blocked L-amino acid. Furthermore, it should be possible to introduce R groups carrying functions blocked by different moieties, thus facilitating differential deblocking in later synthetic steps.

Experimental Section

Melting points were determined in capillaries and are uncorrected.

Materials.—Diethyl acetamidomalonate and dimethyl aminomalonate hydrochloride were from Fluka AG (Buchs, Switzerland) and were used without further purification. α-Monobromoxylene, 2-methylnapthalene, and 6-methylquinoline were products of Eastman Kodak Company (Rochester, N. Y.); the latter two were distilled or recrystallized prior to use. α-Chymotrypsin was from Worthington Biochemical Corporation (Freehold, N. J.) and subtilisin Carlsberg from Novo Industri A/S (Copenhagen, Denmark). 2-Bromomethylnaphthalene was prepared according to Chapman, *et al.*[5]

Diethyl (*o*-Methylbenzyl)acetamidomalonate (1).—Diethyl acetamidomalonate (6.5 g, 30 mmol) was dissolved in a solution of sodium (0.72 g, 31.2 mmol) in 45 ml of dry ethanol. α-Bromoxylene (4.2 ml, 30.8 mmol) was added at room temperature and the reaction mixture was refluxed for 1 hr. The neutral, still boiling mixture was gradually mixed with 90 ml of hot water, slowly cooled to room temperature, and seeded. If still basic, the reaction mixture was neutralized with acetic acid prior to dilution with water. After 2 hr in an ice bath the crystalline precipitate was filtered off, washed with water, and dried, yield 8.05 g (84%), mp 83–84°. *Anal.* Calcd for $C_{17}H_{23}O_5N$ (321.4): C, 63.53; H, 7.21; N, 4.36. Found: C, 63.59; H, 7.13; N, 4.21.

Monoethyl (*o*-Methylbenzyl)acetamidomalonate (2).—To a clear solution of diester 1 (6.4 g, 20 mmol) in 37.5 ml of ethanol, 15 ml of 3.9 *N* NaOH was added. The reaction at room temperature was followed by titrating the excess base in aliquots withdrawn at different time intervals. After 40 min the reaction mixture was acidified with 6 *N* HCl to about pH 2. The ethanol

(5) N. B. Chapman and S. F. A. Williams, *J. Chem. Soc.*, 5044 (1952).

was evaporated and the remaining aqueous mixture was extracted with five 100-ml portions of ethyl acetate (to the first extraction some ethanol had to be added to obtain clear phases). The combined extracts were washed twice with saturated NaCl solution, dried (Na_2SO_4), and evaporated to dryness. The solid residue was triturated with a small amount of ethyl acetate (to remove some yellow impurities), suspended in petroleum ether (bp 30–60°), filtered after 12 hr at 4°, and dried, yield 5 g (86%), mp 126–128° dec, neut equiv calcd 293.3, found 284 (nonaqueous titration with sodium methoxide in dioxane). *Anal.* Calcd for $C_{15}H_{19}NO_5$ (293.3): C, 61.42; H, 6.53; N, 4.78. Found: C, 61.56; H, 6.42; N, 4.60.

N-Acetyl-β-(*o*-methylphenyl)-DL-alanine Ethyl Ester (3). Decarboxylation of Monoester.—Monoester **2** (4 g) was dissolved in 50 ml of absolute dioxane and refluxed for 45 min. By this time titratable acid had practically disappeared. The dioxane was evaporated and the oil obtained was dissolved in 30 ml of ethyl acetate, washed with $NaHCO_3$ solution and saturated NaCl solution, and dried (Na_2SO_4), and the solvent was evaporated. The oily residue crystallized on seeding and trituration with petroleum ether. The crystals were collected, washed with petroleum ether, and dried, yield 2.6 g (78%), mp 63–64°. *Anal.* Calcd for $C_{14}H_{19}O_3N$ (249.3): C, 67.44; H, 7.68; N, 5.62. Found: C, 67.65; H, 7.55; N, 5.63.

Enzymic Resolution of N-Acetyl-β-(*o*-methylphenyl)-DL-alanine Ethyl Ester (3). *N*-Acetyl-β-(*o*-methylphenyl)-L-alanine (4).—Ester **3** (18 g, 73 mmol) was suspended in 600 ml of 0.1 *N* KCl containing 400 mg of $NaHCO_3$ (as a buffer, to prevent pH jumping on addition of alkali, which can inactivate the enzyme). Solid α-chymotrypsin (40 mg) was added and the hydrolysis was run at 37° at pH 7–7.5. The reaction mixture was stirred efficiently by a magnetic stirrer and the pH was kept constant by means of a pH-Stat (2 *N* NaOH delivered from a buret equipped with a magnetic valve). After 120 min the unchanged ester of the D isomer **5** was filtered off and the clear filtrate was extracted with several portions of ethyl acetate. The aqueous solution was acidified with 6 *N* HCl (10 ml) and the free acid **4** was extracted into four portions of ethyl acetate which were combined, washed with saturated NaCl solution, dried (Na_2SO_4), and concentrated. The crystals formed were recrystallized from 60 ml of ethyl acetate, filtered, washed with petroleum ether, and dried, yield 6.2 g (78%), mp 156–157°, $[\alpha]^{25}D$ +40.6° (*c* 10, CH_3OH). *Anal.* Calcd for $C_{12}H_{15}O_3N$ (221.3): C, 65.14; H, 6.83; N, 6.33. Found: C, 65.01; H, 6.87; N, 6.20. (An additional 1.3 g, mp 150°, was precipitated from the mother liquor by petroleum ether, total yield 94%.)

N-Acetyl-β-(*o*-methylphenyl)-D-alanine Ethyl Ester (5).—The ester of the D isomer, collected by filtration and ethyl acetate extraction of the aqueous hydrolysis mixture as described above, was dissolved in ethyl acetate, washed twice with $NaHCO_3$ and once with saturated NaCl solution, and dried (Na_2SO_4), and the solution was evaporated to dryness. Reprecipitation from ethyl acetate (70 ml)–petroleum ether (300 ml) yielded 5.5 g (64%) of colorless needles, mp 77–78°, $[\alpha]^{25}D$ 4.84° (*c* 10, CH_3OH). *Anal.* Calcd for $C_{14}H_{19}O_3N$ (249.3): C, 67.44; H, 7.68; N, 5.62. Found: C, 67.58; H, 7.61; N, 5.74. The optical purity of this material was checked by gas–liquid chromatography.[6] No L isomer could be detected under conditions that would have revealed 1% contamination.

Diethyl (2-naphthylmethyl)acetamidomalonate (6) was prepared by treating 2-bromomethylnaphthalene with diethyl acetamidomalonate as described for **1**, yield *ca.* 75%, mp 109°. *Anal.* Calcd for $C_{20}H_{23}NO_5$ (357.4): C, 67.3; H, 6.45; N, 3.92. Found: C, 68.6; H, 6.42; N, 4.51.

The following compounds were prepared by partial alkaline hydrolysis, decarboxylation, and enzymic resolution with α-chymotrypsin of the malonate **6** as outlined above for derivatives **2** and **3**.

***N*-Acetyl-β-(2-naphthyl)-L-alanine (7)** had mp 178° (lit.[2] mp 181–182°), $[\alpha]^{24}D$ +41.4° (*c* 1.81, CH_3OH:DMF 1:2). *Anal.* Calcd for $C_{15}H_{15}NO_3$ (257.3): N, 5.44. Found: N, 5.20. Titration equiv: calcd 257.3; found 278 (nonaqueous titration with sodium methoxide in DMF).

***N*-Acetyl-β-(2-naphthyl)-D-alanine ethyl ester (8)** had mp 133–136°, $[\alpha]^{24}D$ −21.5° (*c* 2.11, CH_3OH:DMF 1:2). *Anal.* Calcd for $C_{17}H_{19}NO_3$ (285.3): C, 71.56; H, 6.71; N, 4.91. Found: C, 71.27; H, 6.57; N, 5.02.

***N*-Acetyl-β-(2-naphthyl)-D-alanine (9).**—Ester **8** (285 mg) was hydrolyzed at room temperature in 2 ml of ethanol containing 1.5 equiv of aqueous NaOH (6 *N*) for 2 hr. Following dilution with water the mixture was acidified with 6 *N* HCl to about pH 2 and the ethanol was evaporated. The crystalline product was collected and recrystallized from ethyl acetate, yield 60%, mp 170–171°, $[\alpha]^{24}D$ −40.8° (*c* 2.07, CH_3OH:DMF 1:2). *Anal.* Calcd for $C_{15}H_{15}NO_3$ (257.3): C, 70.07; H, 5.88; N, 5.44. Found: C, 69.80; H, 5.65; N, 5.42. Titration equiv: calcd 257; found 266 (nonaqueous titration with sodium methoxide in DMF).

6-Chloromethylquinoline[7] (10) was synthesized from 6-hydroxymethylquinoline[8] obtained from 6-methylquinoline *via* the 6-aldehyde.[9]

Diethyl (6-Quinolylmethyl)acetamidomalonate (11).—Chloride[10] **10** (7.65 g, 36 mmol) was added to diethyl acetamidomalonate (15.6 g, 72 mmol) dissolved in 60 ml (72 mmol) of 1.2 *M* ethanolic sodium ethoxide. The mixture was refluxed for 6 hr. After cooling the salt was filtered off, the filtrate was evaporated to dryness, the residue was taken up in 500 ml of ethyl acetate, and the organic layer was extracted with 3 × 150 ml of ethyl acetate, and the organic layer was extracted with 3 × 150 ml of ice-cold 4 *N* HCl. The combined extracts were carefully neutralized by the addition of 10 *N* NaOH with stirring and cooling to give a voluminous precipitate which was reextracted with 3 × 200 ml of ethyl acetate. After the organic extract was washed (H_2O), dried ($MgSO_4$), and evaporated, the residual solid was recrystallized from ethyl acetate–hexane, 8.7 g (67.5%), mp 150–151° (lit.[11] mp 156°). An additional 1.2 g (9.2%), mp 149–150°, was obtained from the concentrated mother liquor. *Anal.* Calcd for $C_{19}H_{22}N_2O_5$ (358.4): C, 63.67; H, 6.19; N, 7.82. Found: C, 63.82; H, 6.28; N, 7.81.

***N*-Acetyl-β-(6-quinolyl)-DL-alanine Ethyl Ester (12).**—Partial hydrolysis of diethyl malonate **11** (9.0 g, 25.1 mmol) in 200 ml of ethanol was accomplished by adding 6.5 ml (40 mmol) of 6.1 *N* NaOH and stirring for 1 hr at ambient temperature, after which period no more of the diester could be detected by tlc. The partly precipitated sodium salt of the monoacid–monoester was dissolved by adding 2 volumes of water, and the solution was neutralized with 3.6 ml (40 mmol) of 11.1 *N* HCl and evaporated to dryness. The solid residue, after drying over KOH *in vacuo*, was suspended in 200 ml of dioxane and refluxed for 90 min. Finely powdered NaCl (left from the partial hydrolysis) was removed by filtering the cold solution. Evaporation of the dioxane left an oily residue which solidified on scratching and was recrystallized from ethyl acetate–ether to yield 6.65 g (92.6%) of colorless racemic ester **12**, mp 130–131°. *Anal.* Calcd for $C_{16}H_{18}N_2O_3$ (286.4): C, 67.11; H, 6.34; N, 9.78. Found: C, 67.23; H, 6.25; N, 9.78.

Enzymic Resolution of *N*-Acetyl-β-(6-quinolyl)-DL-alanine Ethyl Ester. β-(6-Quinolyl)-L-alanine (13).—Powdered racemic ester **12** (4.0 g, 14 mmol) was suspended in 100 ml of 0.1 *M* KCl (10^{-4} *M* in KH_2PO_4 to prevent pH jumping on addition of alkali). After the pH was adjusted to 7.6 hydrolysis was initiated by adding 3.5 mg of subtilisin Carlsberg to the vigorously stirred mixture. The pH was kept constant by means of a pH stat (0.5 *N* NaOH as titrant). Alkali uptake (6.95 mmol) ceased after 130 min. The crystalline ester of the D isomer **14** was collected by filtration. The filtrate was concentrated to about 30 ml, extracted with 3 × 20 ml of $CHCl_3$, and evaporated to dryness. The residue (the acetyl L acid) was hydrolyzed by refluxing overnight in 40 ml of 6 *N* HCl.[12] The hydrochloric

(6) We are greatly indebted to Dr. B. Feibush, Department of Chemistry, Weizmann Institute of Science, for performing this analysis. The chromatographic system was a modification(U. Beitler and B. Feibush, unpublished work) of the method of E. Gil-Av, B. Feibush, and R. Charles-Sigler, *Tetrahedron Lett.*, 1009 (1966).

(7) C. E. Kaslow and J. M. Schlatter, *J. Amer. Chem. Soc.*, **77**, 1054 (1955).

(8) V. M. Rodionov and M. A. Berkenheim, *J. Gen. Chem. USSR*, **14**, 501 (1944); *Chem. Abstr.*, **39**, 4606 (1945).

(9) V. M. Rodionov and M. A. Berkenheim, *J. Gen. Chem. USSR*, **14**, 330 (1944); *Chem. Abstr.*, **39**, 4076 (1945).

(10) 6-Bromomethylquinoline[7] might also be an adequate starting material for this reaction. However, an attempt to obtain this compound by brominating 6-methylquinoline with *N*-bromosuccinimide failed.

(11) V. N. Konyukhov, L. N. P'yankova, and K. Yu. Bobarykina, *Khim. Geterotsikl. Soedin., Akad. Nauk Latv. SSR*, 140 (1965); *Chem. Abstr.*, **63**, 5733e (1965).

(12) Alternatively N^{α}-acetyl-β-(6-quinolyl)-L-alanine could be isolated as its potassium salt (KOH as titrant in the enzymic hydrolysis) as follows: the aqueous filtrate was evaporated to complete dryness, the residual salt was extracted with ethanol, the extract was filtered and concentrated, and the potassium salt was precipitated with ether.

acid was evaporated, the residue was redissolved in 20 ml water, and the free L acid was isolated by isoelectric precipitation at pH 7. Recrystallization from water gave 1.25 g (83%) of β-(6-quinolyl)-L-alanine (**13**), mp 250–255° dec (lit.[11] mp 246–247° for the racemic compound), $[\alpha]^{24}D$ +14.8 ± 1° (*c* 1.69, 5 *N* HCl). *Anal.* Calcd for $C_{12}H_{12}N_2O_2$ (216.24): C, 66.65; H, 5.59; N, 12.96. Found: C, 66.72; H, 5.53; N, 12.91.

***N*-Acetyl-β-(6-quinolyl)-D-alanine ethyl ester** (**14**), collected by filtration and chloroform extraction of the hydrolysis mixture as described above, was dried over NaOH *in vacuo*. Recrystallization from ethyl acetate–hexane yielded 1.84 g (92%) of colorless needles, mp 145–146°, $[\alpha]^{24}D$ +29.2 + 1° (*c* 4.47, CH_3OH). *Anal.* Calcd for $C_{16}H_{18}N_2O_3$ (286.4): C, 67.11; H, 6.34; N, 9.79. Found: C, 67.16; H, 6.34; N, 9.66.

β-(6-Quinolyl)-D-alanine Dihydrochloride (**15**).—Ethyl ester **14** (1.25 g) was hydrolyzed in 30 ml of 6 *N* HCl at reflux temperature overnight. Evaporation of the HCl and recrystallization of the product from methanol–2-propanol gave 1.18 g (93%) of the free D acid in the form of its dihydrochloride, mp 270–271° dec, $[\alpha]^{24}D$ −15.1 ± 1° (*c* 1.25, 5 *N* HCl). Titration equiv: calcd 96.4; found 98.4 (nonaqueous titration with sodium methoxide in DMF).

Dimethyl *N*-Benzyloxycarbonylaminomalonate (**16**).—To dimethyl aminomalonate hydrochloride (5.5 g, 30 mmol) in 60 ml of ice-cold water–dioxane (9:1, v/v) benzyl chloroformate (4.5 ml, 32 mmol) was added in small portions over a period of about 20 min. The reaction mixture was vigorously stirred and cooled in an ice bath while the pH was kept between 9 and 10 by dropwise addition of 4 *N* NaOH. When the uptake of alkali had ceased the mixture was adjusted to pH 7 with 1 *N* HCl and the precipitated product was collected by filtration and dried *in vacuo* over KOH. Recrystallization from ether–petroleum ether yielded 7.4 g (88%) of colorless prisms, mp 57–58°. *Anal.* Calcd for $C_{13}H_{15}NO_6$ (281.26): C, 55.51; H, 5.38; N, 4.98. Found: C, 55.70; H, 5.38; N, 4.74.

***N*-Benzyloxycarbonyl-DL-phenylalanine Methyl Ester** (**18**).—Benzyl chloride (1.09 ml, 9.45 mmol) was added with stirring into a solution of malonate **16** (2.65 g, 9.45 mmol) in 10 ml of 0.945 *M* ethanolic sodium ethoxide. The mixture was kept at reflux temperature for 3 hr, cooled, and filtered, the filtrate was evaporated, and the residue was taken up in 200 ml of ethyl acetate. The organic layer was washed with 5% $NaHCO_3$, 1 *N* HCl, and water, dried ($MgSO_4$), and evaporated to give a yellowish oil which was homogeneous in tlc; the oil was used without further purification for the subsequent steps.

For partial hydrolysis 2.6 g of the oil in 15 ml of ethanol containing 1.64 ml of 6.1 *N* NaOH was allowed to stand at room temperature for 45 min, 50 ml of water was added, the pH was adjusted to 6 with 1 *N* HCl, most of the ethanol was evaporated, and the aqueous solution was acidified with 1 *N* HCl (pH 2–3) and extracted with 2 × 100 ml of ethyl acetate. Washing (H_2O), drying ($MgSO_4$), and evaporating the ethyl acetate extract gave the monoacid–monoester **17** as a colorless oil, which was characterized as its dicyclohexylamine salt, mp 152° (from ethanol–ether). Titration equiv: calcd 538; found 535 (nonaqueous titration with $HClO_4$ in acetic acid). *Anal.* Calcd for $C_{31}H_{42}N_2O_6$ (538.69): C, 69.12; H, 7.86; N, 5.20. Found: C, 69.32; H, 7.66; N, 5.40.

Decarboxylation was accomplished by refluxing a solution of 2.1 g of the oily monoacid–monoester in 50 ml of dioxane for 20 hr. Evaporation of the solvent and crystallization from ether–petroleum ether gave 1.67 g (71% based on initial benzyloxycarbonylaminomalonate **16**) of **18**, mp 78–79°. *Anal.* Calcd for $C_{18}H_{19}NO_4$ (313.34): C, 68.99; H, 6.11; N, 4.47. Found: C, 69.24; H, 5.90; N, 4.36.

Enzymic Resolution of *N*-Benzyloxycarbonyl-DL-phenylanine Methyl Ester.—Ester **18** (450 mg, 1.56 mmol) suspended in 50 ml of 0.1 *M* KCl (10^{-5} *M* in KH_2PO_4) was hydrolyzed in the presence of 5 mg of chymotrypsin at 37° and pH 7.6 (pH stat, 0.1 *N* NaOH as titrant). The uptake of alkali (0.78 mmol) virtually stopped after 24 hr. The unchanged ester of the D isomer **19** was filtered off and the aqueous filtrate was extracted with 2 × 50 ml of ethyl acetate to gain some additional D isomer **19** by evaporation of the organic extract. Total yield of Z-D-Phe-OMe (**19**) after one recrystallization from ether–petroleum ether was 222 mg (90%), mp 80°, $[\alpha]^{24}D$ +1.6 ± 0.3° (*c* 2.5, CH_3OH). *Anal.* Calcd for $C_{18}H_{19}NO_4$ (313.34): C, 68.99; H, 6.11; N, 4.47. Found: C, 69.28; H, 6.32; N, 4.67.

The aqueous layer obtained above was acidified with dilute HCl and extracted with 2 × 50 ml of ethyl acetate. Washing (H_2O), drying ($MgSO_4$), and evaporating the organic extract gave Z-L-Phe (**20**) in a 72% yield (51% based on benzyloxycarbonylaminomalonate **16**) after one recrystallization from ethyl acetate–petroleum ether, mp 82–84° (lit.[13] mp 88–89°), $[\alpha]^{24}D$ +6 ± 1° (*c* 2.62, acetic acid) (lit.[13] $[\alpha]D$ +5.1°). Titration equiv: calcd 299; found 294 (nonaqueous titration with sodium methoxide in DMF). Removal of the carbobenzoxy group with HBr in acetic acid yielded L-Phe, $[\alpha^{24}D$ −36.2 ± 1.5° (c 2.09, H_2O) (lit.[13] $[\alpha]D$ −34.4°).

Registry No.—**1**, 5440-53-9; **2**, 37447-32-8; **3**, 37439-96-6; **4**, 37439-97-7; **5**, 37439-98-8; **6**, 37447-33-9; **7**, 37439-99-9; **8**, 37440-00-9; **9**, 37440-01-0; **10**, 2644-82-8; **11**, 2644-83-9; **12**, 37440-02-1; **13**, 37440-03-2; **14**, 37440-04-3; **15**, 37440-05-4; **16**, 37447-35-1; **17** dicyclohexylamine salt, 37447-36-2; **18**, 32563-40-9; **19**, 37440-07-6; **20**, 1161-13-3; diethyl acetamidomalonate, 1068-90-2; 2-bromo-*o*-xylene, 89-92-9; 2-bromomethylnaphthalene, 939-26-4; dimethylaminomalonate hydrochloride, 16115-80-3; benzyl chloroformate, 501-53-1.

(13) E. Grassmann and E. Wünsch, *Chem. Ber.*, **91**, 462 (1958).

The Synthesis and Characterization of Some Eight- and Ten-Membered Sulfur-Containing Heterocycles

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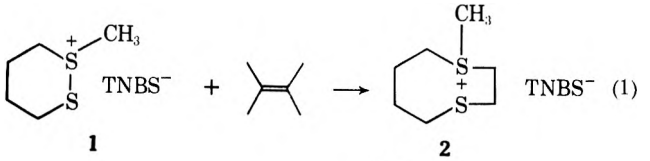
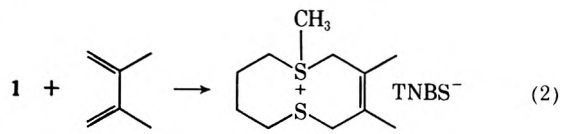
Eight- and ten-membered heterocycles containing two sulfur atoms were prepared by forming olefin and 1,3-diene adducts with 1-methyl-1-thionia-2-thiacyclohexane 2,4,6-trinitrobenzenesulfonate. The nmr spectra of the products suggested the absence of a transannular interaction leading to tetracovalent sulfur.

This research was pursued because of the unique method it provides for the synthesis of certain medium-sized heterocycles. Also, compounds similar to the products have been convenient for the investigation of transannular interactions.[1]

In a previous paper[2] we reported the successful synthesis of ethylene and 2,3-dimethyl-1,3-butadiene adducts of 1-methyl-1-thionia-2-thiacyclohexane 2,4,6-trinitrobenzenesulfonate (**1**). The eight- and ten-membered rings, 1-methyl-1-thionia-4-thiacyclooctane (**2**, eq 1) and 1,3,4-trimethyl-1-thionia-6-thia-



1 **2** (1)



3 (2)

3-cyclodecene (**3**, eq 2) cations, were prepared in good yields. ($TNBS^-$ = 2,4,6-trinitrobenzenesulfonate anion.)

We would now like to report the successful synthesis of a number of other olefin and diene adducts and interpret their nmr spectra as they relate to transannular interactions.

Results

The reaction of 1-methyl-1-thionia-2-thiacyclohexane cation (**1**) with olefins was investigated. Analytically pure products could be prepared from ethylene, propene, 1-pentene, *cis*- and *trans*-2-butene, and cyclohexene. Olefins which formed an adduct, as indicated by nmr spectra, but did not give products with a good elemental analysis were *cis*-stilbene, 2-methylpropene, and methylene cyclohexane. Olefins which did not react were *trans*-stilbene, *cis*- and *trans*-1,2-dichloroethylene, 2-methyl-2-butene, and tetramethylethylene.

The addition is sensitive to substituents on the olefin. In certain cases the reaction showed evidence of easy reversibility, so that unfavorable substituent interactions in the product and a transannular sulfur–sulfur interaction (at least in the transition state) would disfavor adduct formation. The unreactivity of vinyl chlorides suggests an electron density influence in the olefin, and the unreactivity of highly substituted olefins could be due to unfavorable steric factors in the forward direction of the addition process..

The 1,1-disubstituted olefins gave products of addition as revealed by their nmr spectra, but neither 2-methylpentene nor methylene cyclohexane gave a product with a satisfactory elemental analysis. Like the *cis*-stilbene adduct, the olefin seemed to be regenerated during recrystallization. Olefins which were trisubstituted showed no indication of a reaction. These results again point out the sensitivity of the reaction to steric factors.

The sensitivity of the reaction to electronic effects is revealed by the absence of reactivity of **1** with *cis*- and *trans*-dichloroethylene. The unreactivity was not unexpected because the addition reaction, even with more reactive olefins, was slow.

The scope of the reaction of **1** with 1,3-dienes was also investigated. Among several dienes tested only 2,3-dimethyl-1,3-butadiene, 1,2-dimethylenecyclohexane, and 2,3-diphenyl-1,3-butadiene gave products with good elemental analyses. Others that according to their nmr spectra had reacted but yielded impure products were 1,3-butadiene and 1,3-cyclohexadiene. Those which showed no indication of reaction were hexachlorocyclopentadiene and hexachloro-1,3-butadiene.

The success of the reaction of dienes was related to the nature of substitution at the "internal" sp^2 carbon atoms. Those that were unsubstituted at the 2,3 positions, namely butadiene and 1,3-cyclohexadiene, yielded no satisfactory product even though several different combinations of solvents and reaction times were tried.

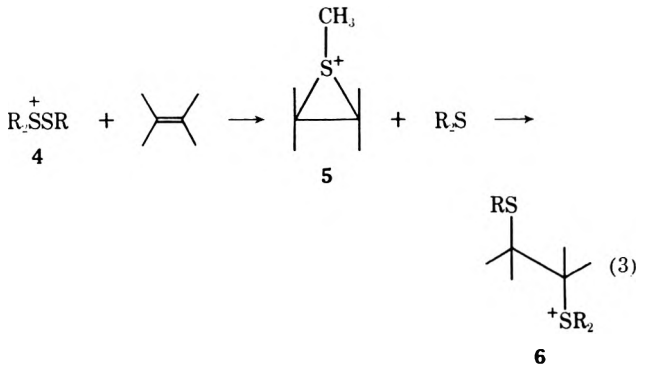
The same electronic limitations that applied to the olefins applied to the dienes. The dienes substituted with strongly electron-withdrawing chlorine were completely unreactive toward **1**.

Discussion of Possible Mechanisms.—The addition of dialkyl (alkylthio)sulfonium salts (**4**) (compounds analogous to **1**) to olefins has been thoroughly investigated and the stereochemistry of the products (**6**) has been demonstrated.[3] The mechanism proposed for this addition (eq 3) involved the initial formation of an

(1) S. M. Johnson, C. A. Maier, and I. C. Paul, *J. Chem. Soc. B*, 1603 (1970).

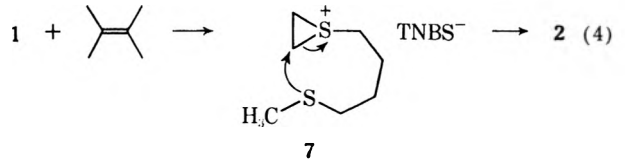
(2) N. E. Hester, G. K. Helmkamp, and G. L. Alford, *Int. J. Sulfur Chem., Part A*, **1**, 65 (1971).

(3) G. K. Helmkamp, B. A. Olsen, and J. R. Koskinen, *J. Org. Chem.*, **30**, 1623 (1965).

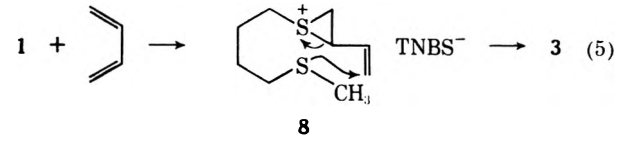


episulfonium ion intermediate (**5**) (where the anion in each case is 2,4,6-trinitrobenzenesulfonate) followed by back-side attack to give trans addition.

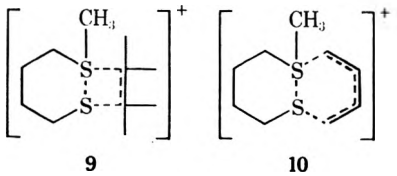
If this mechanism is operative for the addition of **1** to olefins, then a seven-membered transition state (**7**, eq 4) is required for the backside displacement,



which is highly unlikely to develop. Also, if an episulfonium ion intermediate (**8**) is formed when **1** reacts with a diene and if the ring closes by an SN2′ type mechanism, then a nine-membered transition state (**8**, eq 5) is required. This possibility would be even less favorable than in the olefin addition.



A mechanism which avoids the problems of the seven- and nine-membered transition states would be a concerted or nearly concerted addition. This manner of addition would give a four-membered transition state for the olefin addition (**9**) and a six-membered transition state for the addition of dienes (**10**). Although



a 2 + 2 addition normally is symmetry forbidden, the present system involves an unsymmetrical, highly polarized bond between atoms which can utilize d orbitals in the transition state. Given these arguments and the facts that the reactions proceed fairly rapidly without high-dilution techniques, a concerted or nearly concerted mechanism is highly probable.

One consequence of a concerted *vs.* episulfonium ion mechanism is that the stereochemistry of the products of the olefin adducts would be different. It was anticipated that the nmr spectra of some of the products would shed light on the stereochemistry, but the spectra were extremely complicated in the area of interest. An X-ray crystal structure determination of one of the 2-butene or cyclohexene adducts will shed the necessary light on the reaction mechanism.

Interpretation of Nmr Spectra as They Relate to Transannular Interactions between Sulfur Atoms.—In order to determine if a transannular interaction between the "thia" and "thionia" sulfurs was present, the chemical shift of the *S*-methyl protons was monitored. It was assumed that an upfield shift, similar to that observed by Owsley,[4,5] would be detected.

Owsley treated cyclooctene-*S*-methylepisulfonium 2,4,6-trinitrobenzenesulfonate with chloride ion, and the *S*-methyl peak shifted 36 cycles upfield.[3,4] It was expected that this 36-cycle shift would approximate that which would result from a transannular interaction.

The ethylene and 2,3-dimethyl-1,3-butadiene adducts were investigated in detail, since they provided the simplest spectra for the respective olefin and diene adducts. The *S*-methyl peaks were clean singlets.

In order to determine if an interaction was occurring, model compounds were prepared in which no sulfide ("thia") sulfur was available to interact with the sulfonium ("thionia") sulfur.

An approximate model for the ethylene adduct might be simply trimethylsulfonium 2,4,6-trinitrobenzenesulfonate. However, since the size of the alkyl chain would influence the chemical shift of an *S*-methyl peak, dimethylethylsulfonium 2,4,6-trinitrobenzenesulfonate also were prepared. The chemical shifts of all four compounds are summarized in Table I.

TABLE I

CHEMICAL SHIFTS OF THE *S*-METHYL PROTONS OF 1-METHYL-1-THIONIA-4-THIACYCLOOCTANE 2,4,6-TRINITROBENZENESULFONATE (2) AND MODEL SULFONIUM SALTS

Compd	Chemical shift, δ (cycles)
2	2.98 (179)
$(CH_3)_3S^+TNBS^-$ [a]	2.93 (176)
$CH_3CH_2\overset{+}{S}(CH_3)_2TNBS^-$	2.92 (175)
$(CH_3CH_2)_2\overset{+}{S}CH_3TNBS^-$	2.84 (170)

[a] TNBS = 2,4,6-Trinitrobenzenesulfonate anion.

Similarly, a model for the 2,3-dimethyl-1,3-butadiene adduct might be a trialkylsulfonium salt such as trimethylsulfonium 2,4,6-trinitrobenzenesulfonate. The possibility that the allylic double bond could influence the chemical shift of the *S*-methyl group also was considered; so dimethylallylsulfonium 2,4,6-trinitrobenzenesulfonate and diallymethylsulfonium 2,4,6-trinitrobenzenesulfonate were prepared. The chemical shifts of these compounds are summarized in Table II.

Table I reveals that the *S*-methyl protons of 1-methyl-1-thionia-4-thiacyclooctane 2,4,6-trinitrobenzenesulfonate (**2**) fall at 179 cycles, whereas the *S*-methyl protons of diethylmethylsulfonium 2,4,6-trinitrobenzenesulfonate, probably the best model, appear at 170 cycles. This would represent a downfield shift for 2 of 9 cycles. The shift is nowhere near the magnitude of the shift of 36 cycles observed by Owsley

(4) D. C. Owsley, G. K. Helmkamp, and M. F. Rettig, *J. Amer. Chem. Soc.*, **91**, 5239 (1969).

(5) D. C. Owsley, Ph.D. Dissertation, University of California, Riverside, Calif.

TABLE II

CHEMICAL SHIFTS OF THE *S*-METHYL PROTONS OF 1,3,4-TRIMETHYL-1-THIONIA-6-THIA-3-CYCLODECENE 2,4,6-TRINITROBENZENESULFONATE (3) AND MODEL SULFONIUM SALTS

Compd	Chemical shift, δ (cycles)
3	2.92 (175)
$(CH_3)_3S^+TNBS^-$ [a]	2.93 (176)
$(CH_3)_2SCH_2CH{=}CH_2\ TNBS^-$	2.85 (171)
$CH_3S(CH_2CH{=}CH_2)_2\ TNBS^-$	2.82 (169)

[a] TNBS = 2,4,6-Trinitrobenzenesulfonate anion.

and is in the opposite direction. The 9-cycle difference probably is due to the presence of the other sulfur in the ring, so that the shift most likely represents a "through space" interaction of the lone pair electrons on the sulfide sulfur rather than a bonding interaction.

Table II reveals that the *S*-methyl peak of 1,3,4-trimethyl-1-thionia-6-thia-3-cyclodecene 2,4,6-trinitrobenzenesulfonate (3) appears at 175 cycles and the *S*-methyl peak of dimethylallylsulfonium 2,4,6-trinitrobenzenesulfonate, probably the best model, apears at 171 cycles. Again the magnitude of the shift is small and in the wrong direction. This difference of only 4 cycles could be due to experimental error. However, since it is in the same direction as the 9-cycle difference mentioned above, it may also represent a through space effect of the lone pair electrons on the sulfide sulfur. In both of these systems then, the nmr evidence points very strongly toward the absence of any bonding interaction across the rings.

Experimental Section[6]

1,2-Dithiane.—The 1,2-dithiane[7] was used as the crude product isolated by evaporation of the CH_2Cl_2 extraction solvent. Alternatively the following combination of thiol preparation[8] and conversion to the 1,2-dithiane,[7] followed by direct alkylation as in procedure A, was effective. A mixture of 41 g (0.19 mol) of 1,4-dibromobutane, 29 g (0.38 mol) of thiourea, and 25 ml of water was refluxed with stirring for 3 hr. Then 30 g of NaOH in 300 ml of water was added and the solution was refluxed for an additional 3 hr. After the mixture was cooled (0°), 36.5 g (0.19 mol) of *p*-toluenesulfonyl chloride was added and the contents of the reaction flask were stirred for 1 hr. The resulting solution was extracted with four 50-ml portions of CH_2Cl_2. The combined organic extract was washed twice with water, dried over $MgSO_4$, and evaporated on a rotary evaporator to give crude 1,2-dithiane.

1-Methyl-1-thionia-2-thiacyclohexane 2,4,6-Trinitrobenzenesulfonate (1). Procedure A. Alkylation of 1,2-Dithiane with an Oxonium Salt.—Trimethyloxonium 2,4,6-trinitrobenzenesulfonate[9] (1.77 g, 0.0050 mol) was dissolved in a minimum amount of nitromethane, and 1.20 g (0.010 mol) of crude 1,2-dithiane in 10 ml of CH_2Cl_2 was added. The bright yellow solution was allowed to stand for 0.5 hr. Crystalline product was isolated by slowly adding dry Et_2O until all product precipitated, yield 87%. Three precipitations from CH_3NO_2–Et_2O gave mp 179–180° dec, nmr δ 8.48 (s, 3), 3.75–3.05 and 3.33 (m and s, respectively, 7), 2.43–1.92 (m, 4).

Anal. Calcd for $C_{11}H_{13}N_3O_9S_3$: C, 30.91; H, 3.07; N, 9.83. Found:[10] C, 31.07; H, 2.93; N, 10.11.

Procedure B. Alkylation of 1,2-Dithiane with Methyl Iodide in the Presence of Silver 2,4,6-Trinitrobenzenesulfonate.—The following mixture was refluxed overnight: 1.41 g (0.010 mol) of CH_3I in 5 ml of CH_2Cl_2; 5.2 g (0.010 mol) of the acetonitrile complex of silver 2,4,6-trinitrobenzenesulfonate[9] in 20 ml of CH_3NO_2; and 1.2 g (0.010 mol) of crude 1,2-dithiane[7] in 15 ml of CH_2Cl_2. After AgI was removed by filtration (Celite) the product was precipitated by adding the filtrate to 500 ml of dry Et_2O. The solid was redissolved in CH_3NO_2, warmed with decolorizing charcoal, filtered (Celite), and reprecipitated, yield 58%. Drying (15 hr, 0.1 mm, 40°) led to a melting point and nmr spectrum that were the same as those given above.

Reactions of 1-Methyl-1-thionia-2-thiacyclohexane 2,4,6-Trinitrobenzenesulfonate (1) with Alkenes. A. With Ethene.—A solution of 1 (0.43 g, 0.0010 mol) in 35 ml of CH_3NO_2–CH_2Cl_2 (2.5:1.0) was saturated with gaseous ethene twice a day for 4 days. The product was isolated by pouring the solution into 1 l. of vigorously stirred anhydrous Et_2O and collecting the precipitated: yield 78% after one reprecipitation from the same solvents; after three precipitations, mp 115–121° with effervescence; nmr δ 8.56 (s, 2), 2.98 (s, 3), 3.92–1.42 (a singlet at δ 2.98 superimposed on a series of multiplets, 15).

Anal. Calcd for $C_{13}H_{15}N_3O_9S_3$: C, 34.28; H, 3.76; N, 9.23. Found:[10] C, 34.31; H, 3.68; N, 9.27.

B. With Propene.—A 2-week reaction similar to that described above was carried out with propene, yield 85%. Three precipitations yielded the final product: mp 62–66° with effervescence; nmr δ 8.55 (s, 2), 3.83–1.67 (overlapping multiplets, 17).

Anal. Calcd for $C_{14}H_{19}N_3O_9S_3$: C, 35.81; H, 4.08; N, 8.95. Found:[10] C, 35.72; H, 4.03; N, 9.17.

C. With 1-Pentene.—A solution of about 0.03 mol of 1-pentene and 0.86 g (0.0020 mol) of 1 in 20 ml of CH_3NO_2 was allowed to stand for 5 days. An oily product was obtained by adding the solution to 1 l. of ether–petroleum ether (bp 30–60°) (9:1). Reprecipitation from the same solvent system yielded a pale yellow solid, yield 90%. Two additional precipitations yielded final product: mp 62–67° with effervescence; nmr δ 8.50 (s, 2), 2.42–0.58 (overlapping multiplets, 21).

Anal. Calcd for $C_{16}H_{23}N_3O_9S_3$: C, 38.62; H, 4.66; N, 8.45. Found:[10] C, 38.42; H, 4.62; N, 8.64.

D. With *cis*-2-Butene.—An excess of *cis*-2-butene was maintained as a separate layer in a reaction flask containing 0.86 g (0.0020 mol) of 1 in 15 ml of CH_3NO_2. After 5 days the precipitated product was collected and washed with a few milliliters of cold CH_3NO_2, yield 67%. The product was dried at reduced pressure: mp 161–163° dec; nmr δ 8.52 (s, 2), 3.90–0.97 (a singlet *S*-methyl peak at 2.86 superimposed on a series of multiplets, total area 19).

Anal. Calcd for $C_{15}H_{21}N_3O_9S_2$: C, 37.26; H, 4.38; N, 8.69. Found:[10] C, 37.15; H, 4.36; N, 8.46.

E. With *trans*-2-Butene.—The process described above was used with *trans*-2-butene: yield after 6 days 51%; mp 161–163° dec; nmr δ 8.52 (s, 2), 3.90–0.97 (a single *S*-methyl peak at 2.88 superimposed on a series of multiplets, total area 19).

Anal. Calcd for $C_{15}H_{21}N_3O_9S_3$: C, 37.26; H, 4.38; N, 8.69. Found:[10] C, 37.15; H, 4.36; N, 8.69.

F. With Cyclohexene.—The process described above was used with about 0.02 mol of cyclohexene: yield after 5 days 54%; slow decomposition above 93°; nmr δ 8.55 (s, 2), 3.78–0.95 (singlet *S*-methyl peak superimposed on a series of multiplets, total area 22 ± 1).

Anal. Calcd for $C_{17}H_{23}N_3O_9S_3$: C, 40.07; H, 4.55; N, 8.24. Found:[10] C, 40.10; H, 4.84; N, 8.60.

G. With *cis*-Stilbene, 2-Methylpropene, and Methylenecyclohexane.—Reactions run according to the method described for *cis*-2-butene, but with reaction times of up to 19 days, yielded products whose nmr spectra were consistent with those expected of the usual adducts. However, elemental analyses were never adequate, and often the attempted purification procedures resulted in partial reversal of the addition process.

H. With *trans*-Stilbene, *cis*-1,2-Dichloroethene, *trans*-1,2-Dichloroethene, 2-Methyl-2-butene, and Tetramethylethylene.—Reactions carried out under any of the conditions described above failed to yield any products. Starting materials were recovered.

(6) Reaction solvents were reagent grade and were dried over Molecular Sieve (Linde 4A) before use. Melting points are uncorrected. All nmr spectra were run using deuterionitromethane as solvent, and the residual absorbance due to undeuterated material was used as a standard (δ 4.28); spectra were recorded on a Varian A-60D spectrometer.

(7) L. Field and R. B. Barbee, *J. Org. Chem.*, **34**, 36 (1969).

(8) A. I. Vogel, "Practical Organic Chemistry," 3rd ed, Wiley, New York, N. Y., 1966.

(9) D. J. Pettitt and G. K. Helmkamp, *J. Org. Chem.*, **29**, 2702 (1964).

(10) Analysis by Galbraith Laboratories, Inc., Knoxville, Tenn.

Reactions of 1-Methyl-1-thionia-2-thiacyclohexane 2,4,6-Trinitrobenzenesulfonate (1) with 1,3-Dienes. A. With 2,3-Dimethyl-1,3-butadiene.—A mixture of 10 ml (about 0.09 mol) of 2,3-dimethyl-1,3-butadiene, 2.14 g (0.0050 mol) of 1, and 75 ml of acetone was brought to boiling and then was allowed to stand for 1.5 days. The precipitated product was recrystallized from acetone: yield 72%; mp 143–144° dec; nmr δ 8.50 (s, 2), 2.93 (s, 3), 1.88 (s, 6), 4.12–1.33 (series of multiplets including the listed superimposed singlets, total area 21).

Anal. Calcd for $C_{17}H_{23}N_3O_9S_3$: C, 40.07; H, 4.52; N, 8.25. Found:[10] C, 40.17; H, 4.66; N, 8.14.

B. With 1,2-Dimethylenecyclohexane.—A reaction similar to that described above was carried out with 0.86 g (0.0020 mol) of 1, about 0.02 mol of 1,2-dimethylenecyclohexane,[11] and 20 ml of acetone: yield 70%; mp 140–142° dec; nmr δ 8.52 (s, 2), 4.13–3.07 (m, 4), 2.93 (s, 3), 2.77–1.33 (a series of overlapping multiplets, 16).

Anal. Calcd for $C_{19}H_{25}N_3O_9S_3$: C, 42.60; H, 4.70; N, 7.84. Found:[10] C, 42.72; H, 4.72; N, 7.65.

C. With 2,3-Diphenyl-1,3-butadiene.—A mixture of 1.6 g (0.0080 mol) of 2,3-diphenyl-1,3-butadiene[12] and 0.86 g (0.0020 mol) of 1 was warmed until the diene started to melt, and then 15 ml of CH_3NO_2 was added. After 15 days the product was precipitated by addition of the solution to 500 ml of anhydrous Et_2O: yield 79%; mp >94° dec; nmr δ 8.55 (s, 2), 7.70–6.93 (m, 10), 3.68–1.10 (series of multiplets superimposed on singlets at 2.80 and 1.77, total area 12).

Anal. Calcd for $C_{27}N_{27}N_3O_9S_3$: C, 51.17; H, 4.30; N, 6.63. Found:[13] C, 50.70; H, 4.46; N, 6.76.

D. With 1,3-Butadiene and 1,3-Cyclohexadiene.—Reactions carried out by the above procedure yielded products with an appropriate nmr spectra, but purification procedures were inadequate for the production of analytically pure materials.

E. With Hexachlorocyclopentadiene and Hexachloro-1,3-butadiene.—These substractes failed to react with 1 under the conditions described above.

Dimethylethylsulfonium 2,4,6-Trinitrobenzenesulfonate.—An excess (0.76 g, 0.010 mol) of methyl ethyl sulfide in 20 ml of CH_3NO_2 was alkylated with 1.41 g (0.0040 mol) of trimethyloxonium 2,4,6-trinitrobenzenesulfonate.[9] The product was precipitated by the addition of anhydrous Et_2O (yield 90%) and recrystallized from CH_3NO_2: mp 196.5–197.5°; nmr δ 8.52 (s, 2), 3.33 (q, 2), 2.92 (s, 6), 1.45 (t, 3).

Anal. Calcd for $C_{10}H_{13}N_3O_9S_3$: C, 31.33; H, 3.42; N, 10.96. Found:[13] C, 31.66; H, 3.42; N, 10.50.

Diethylmethylsulfonium 2,4,6-Trinitrobenzenesulfonate.—An excess of diethyl sulfide (0.9 g, 0.01 mol) in 5 ml of CH_2Cl_2 was alkylated with 0.71 g (0.0050 mol) of methyl iodide. After a few minutes a solution of 2.60 g (0.0050 mol) of silver 2,4,6-trinitrobenzenesulfonate–acetonitrile complex in 15 ml of CH_3NO_2 was added. After 24 hr AgI was removed by filtration and the product was precipitated by adding anhydrous Et_2O to the filtrate, yield 78%. The product was recrystallized from CH_3NO_2: mp 173–174°; nmr δ 8.52 (s, 2), 3.33 (q, 4), 2.84 (s, 3), 1.44 (t, 6).

Anal. Calcd for $C_{11}H_{15}N_3O_9S_2$: C, 33.25; H, 3.42; N, 10.96. Found:[13] C, 33.67; H, 3.78; N, 11.16.

Diallylmethylsulfonium 2,4,6-Trinitrobenzenesulfonate.—The compound was prepared by the methyl iodide alkylation and anion metathesis described above, using 0.71 g (0.0050 mol) of diallyl sulfide: yield 81%; mp 120–121°; nmr δ 8.53 (s, 2), 6.52–5.02 (m, 6), 4.02 (d, 4), 2.80 (s, 3).

Anal.[14] Calcd for $C_{13}H_{15}N_3O_9S_2$: C, 37.05; H, 3.59; N, 9.97. Found: C, 36.91; H, 3.77; N, 9.73.

Dimethylallylsulfonium 2,4,6-Trinitrobenzenesulfonate.—The procedure described above was applied to methyl allyl sulfide: yield 91%; mp 173–174°; nmr δ 8.50 (s, 2), 5.93–5.36 (m, 3), 4.00 (d, 2), 2.85 (s, 6).

Anal.[14] Calcd for $C_{11}H_{13}N_3O_9S_2$: C, 33.42; H, 3.31; N, 10.63, Found: C, 33.14; H, 3.49; N, 10.31.

Registry No.—**1**, 33909-82-9; **2**, 33909-83-0; **3**, 33909-84-1; $C_{13}H_{15}N_3O_9S_3$, mp 115–121°, 37447-66-8; $C_{14}H_{19}N_3O_9S_3$, mp 62–66°, 37447-67-9; $C_{16}H_{23}N_3O_9S_3$, mp 62–67°, 37447-68-0; $C_{15}H_{21}N_3O_9S_3$, mp 161–163°, 37447-69-1; $C_{17}H_{23}N_3O_9S_3$, mp >93°, 37447-70-4; $C_{19}H_{25}N_3O_9S_3$, mp 140–42°, 37447-71-5; $C_{27}H_{27}N_3O_9S_3$, mp >94°, 37447-72-6; trimethyloxonium 2,4,6-trinitrobenzenesulfonate, 13700-00-0; 1,2-dithiane, 505-20-4; silver 2,4,6-trinitrobenzenesulfonate, 37447-76-0; ethene, 74-85-1; propene, 115-07-1; 1-pentene, 109-67-1; *cis*-2-butene, 590-18-1; *trans*-2-butene, 624-64-6; cyclohexene, 110-83-8; 2,3-dimethyl-1,3-butadiene, 513-81-5; 1,2-dimethylenecyclohexane, 2819-48-9; 2,3-diphenyl-1,3-butadiene, 2548-47-2; dimethylethylsulfonium 2,4,6-trinitrobenzenesulfonate, 37508-14-8; diethylmethylsulfonium 2,4,6-trinitrobenzenesulfonate, 37447-75-9; diallylmethylsulfonium 2,4,6-trinitrobenzenesulfonate, 37447-77-1; dimethylallylsulfonium 2,4,6-trinitrobenzenesulfonate, 37567-15-0.

(11) W. Bailey and H. Golden, *J. Amer. Chem. Soc.*, **75**, 4780 (1953).
(12) K. Alder and R. Hayden, *Justus Liebigs Ann. Chem.*, **570**, 212 (1946).
(13) Analysis by Geiger Laboratory, Ontario, Calif.
(14) Analysis by Elek Microanalytical Laboratories, Harbor City, Calif.

The Chemistry of *N*-Cyanodithioimidocarbonic Acid. II. Synthesis of 3-Halo-1,2,4-thiadiazoles[1,2]

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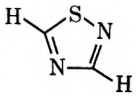
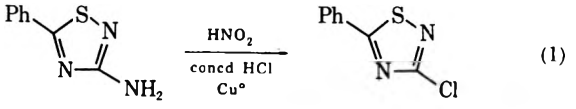
Reaction of dipotassium cyanodithioimidocarbonate ($NCN{=}CS_2K_2$) with 1 molar equiv of a variety of substituted alkyl halides has been shown to afford potassium 5-substituted cyanodithioimidocarbonate esters (monoesters). Halogenating agents (*e.g.*, Cl_2, SO_2Cl_2, Br_2, I_2) effected an oxidative cyclization of the monoesters to give a group of new 3-halo (chloro, bromo, iodo) 5-substituted thio-1,2,4-thiadiazoles. Oxidation of the external sulfur atom with 1 and 2 molar equiv of oxidizing agent yielded thiadiazole sulfoxides and sulfones, respectively. Attempted α-chlorination of a thiadiazole alkyl sulfide was unsuccessful. The 3-halo substituent proved inert to nucleophilic displacement. Discussion of infrared data on new compounds and mechanistic details of reactions are presented.

Because of the relative inaccessibility and sensitivity of the parent 1,2,4-thiadiazole molecule (**1**),[3] substi-



1

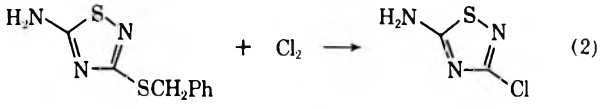
tuted 1,2,4-thiadiazoles have been constructed from appropriate acyclic parts and subsequently modified as desired by suitable transformations.[4] The history of 3-halo-1,2,4-thiadiazoles demonstrates the utility of such an approach. This class of compounds was first reported by Kurzer and Taylor[5] in 1960, who synthesized 3-chloro-5-aryl-1,2,4-thiadiazoles by a Sandmeyer–Gatterman type reaction (eq 1) and by Goer-



(1)

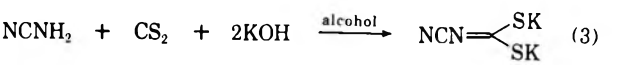
yield 40–54%

deler and coworkers,[6] who prepared 5-amino-3-chloro-1,2,4-thiadiazole by chlorolysis of a corresponding alkyl sulfide (eq 2).



(2)

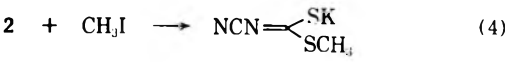
In 1967[1] we reported the first example of a direct route to 3-chloro-5-methylthio-1,2,4-thiadiazole starting from dipotassium cyanodithioimidocarbonate (**2**),[7,8] a compound readily obtained from cyanamide and carbon disulfide (eq 3). Alkylation of **2** with 1 molar equiv of



(3)

2

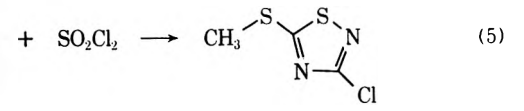
methyl iodide proceeds stepwise to give **3** in nearly quantitative yield (eq 4). When **3** is treated with sul-



(4)

3

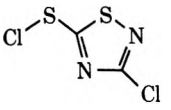
furyl chloride, an oxidative cyclization takes place to afford **4**, also in high yield (eq 5). More recently



(5)

4

Thaler and McDivitt[8] have provided convincing evidence that **2** undergoes a comparable cyclization to afford **5** in 80–100% yield. In the interval since our



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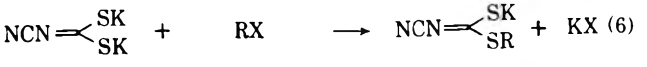
initial report we have investigated the scope of eq 4 and 5 and the chemical properties of the resultant 3-halo-1,2,4-thiadiazoles, and these results follow.

Results and Discussion

Monoesters of Dipotassium Cyanodithioimidocarbonate (2).—Monoalkylation of **2** was attempted with a sampling of primary, secondary, and tertiary halides in accord with eq 6. The products which were suc-



(6)

X = Cl, Br, I

cessfully obtained are those where R corresponds to substituents listed in Table I. Alkyl bromides and iodides were preferred in these reactions. In general, primary alkyl halides reacted smoothly with **2** in acetone–water at reduced temperature to afford the desired monoesters in yields of 30–95%. Limited success was obtained with secondary halides and we were un-

(1) For part I see R. J. Timmons and L. S. Wittenbrook, *J. Org. Chem.*, **32**, 1566 (1967).

(2) Presented in preliminary form at the 2nd Regional Meeting of the American Chemical Society, Columbus, Ohio, June 1970.

(3) First reported by J. Goerdeler, J. Ohm, and O. Tegtmeyer, *Chem. Ber.*, **89**, 1534 (1956); J. Goerdeler and O. Tegtmeyer, *Angew. Chem.*, **67**, 302 (1955).

(4) For a current review on the synthesis and chemistry of 1,2,4-thiadiazoles see F. Kurzer, *Advan. Heterocycl. Chem.*, **5**, 119 (1965).

(5) F. Kurzer and S. A. Taylor, *J. Chem. Soc.*, 3234 (1960).

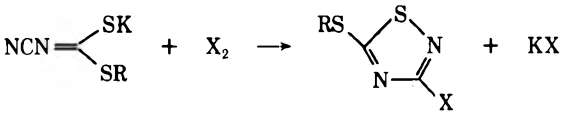
(6) J. Goerdeler and H. Rachwalsky, *Chem. Ber.*, **93**, 2190 (1960); see also J. Goerdeler and I. El Tom, *ibid.*, **98**, 1544 (1965).

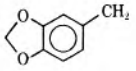
(7) Structure established by A. Hantzsch and M. Wolvekamp, *Justus Liebigs Ann. Chem.*, **331**, 265 (1904). Also accessible *via* calcium cyanamide and carbon disulfide, U. S. Patent 2,816,136.

(8) This versatile intermediate has only recently been given attention by other workers. See W. A. Thaler and J. R. McDivitt, *J. Org. Chem.*, **36**, 14 (1971), and references cited therein, for review. Also see K. A. Jensen and L. Henriksen, *Acta Chem. Scand.*, **22**, 1107 (1968).

TABLE I

3-HALO-1,2,4-THIADIAZOLE SULFIDES[a]



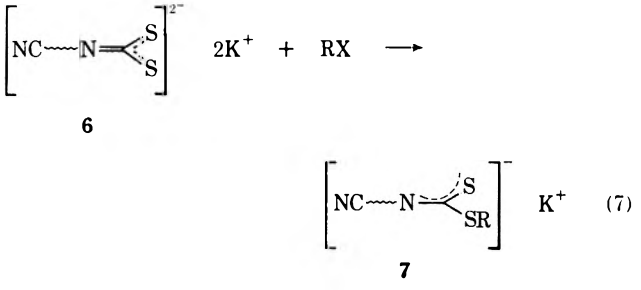
Compd	R	X	Yield, %[b]	Mp, °C	Bp, °C (mm)	Ir (ring), cm^{-1}
4	CH_3	Cl	70	54–55		1425, 1228
10	CH_3	Br	54	57–58		1404, 1202
11	CH_3	I	46	86.5–88.5		1381, 1175
12	CH_3CH_2	Cl	66		66 (0.25)	1429, 1215
13	$CH_3(CH_2)_2CH_2$	Cl	82		94–96 (0.45)	1420, 1212
14	$CH_3(CH_2)_4CH_2$	Cl	86		110–113 (0.24)	1429, 1220
15	$CH_3(CH_2)_8CH_2$	Cl	80		149–151 (0.20)	1425, 1214
16	$(CH_3)_2CH$	Cl	84		66–68 (0.15)	1422, 1214
17	$(CH_3)_2CH$	Br	67		66–67 (0.20)	1425, 1210
18	$(CH_3)_2CHCH_2$	Cl	83		82 (0.05)	1437, 1222
19	$(CH_3)(CH_3CH_2)CH$	Cl	43		64–65 (0.23)	1427, 1214
20	$C_6H_5CH_2$	Cl	85		144–147 (0.25)	1427, 1218
21	p-$NO_2C_6H_4CH_2$	Cl	59	94–97		1435, 1224
22	$C_6F_5CH_2$	Cl	72		109 (0.15)	1427, 1218
23		Cl	85	57–58		1431, 1232
24	$CH_2{=}CHCH_2$	Cl	22		81–85 (0.50)	1425, 1214
25	$CH_2{=}CClCH_2$	Cl	62		Oil[c]	1429, 1220
26	$CH_3CH_2OCH_2CH_2$	Cl	54		81–87 (0.06–0.07)	1441, 1227
27	$CH_3CH_2OCCH_2$ (O)	Cl	50		56 (0.3)[d]	1433, 1222
28	$NCCH_2$ (O)	Cl	40	89.5–91.5		1433, 1225
29	H_2NCCH_2 (O)	Cl	71	137–139		1435, 1215
30	$C_6H_5NHCCH_2$ (O)	Cl	50	105–106.5		1439, 1220

[a] Satisfactory analyses (±0.4% for C, H, N, or S) were reported for all new compounds listed in the table. [b] Crude yields. [c] Boiling point not determined. [d] Falling film distillation.

able to characterize a comparable ester from tertiary halides.[9]

Because of their hygroscopic nature, the monoesters were difficult to obtain in an analytically pure state.[10] Thus, in many cases spectral data and subsequent characterization of the cyclized products were relied upon for structure proofs. The infrared spectra were particularly instructive, since 2 exhibits a strong band at 1322 cm^{-1} (C=N stretch) which shifts to 1340–1380 cm^{-1} in the monoesters.[11]

The disposition of 2 to undergo stepwise alkylation[12]



may be represented by eq 7, wherein dianion 6 rapidly undergoes monoalkylation to give monoanion 7, which does not favorably compete with 6 for substrate giving rise to selective monoalkylation.[13]

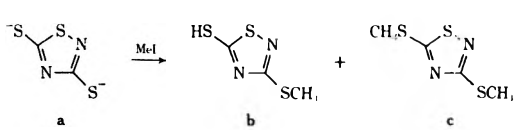
Acylation of 2 was not thoroughly studied, but reaction with 1 molar equiv of ethyl chloroformate in refluxing acetonitrile gave back 75% of 2 with no other characterizable product. A similar experiment with 2 molar equiv of ethyl chloroformate under more forcing conditions afforded two products assigned

(9) Varying yields of potassium thiocyanate were obtained in those experiments which failed to give the desired monoesters [*e.g.*, $(C_6H_5)_2CHCl$, $(CH_3)_3CBr$, $C_6H_{11}I$, 2,4-dinitrochlorobenzene, CF_3CH_2I]. A more thorough product study in these cases was not undertaken, but could prove helpful in determining the origin of the potassium thiocyanate.

(10) Synthetically this presented no problem because it was unnecessary to purify these prior to cyclization.

(11) Complete removal of charge by dialkylation results in a more noticeable shift to 1466–1490 cm^{-1}.[1]

(12) R. Seltzer, *J. Org. Chem.*, **34**, 2562 (1969), has reported that a somewhat related molecule, a, reacts with 1 molar equiv of methyl iodide to afford 28% b and 27% c after work-up, indicating sequential alkylation with the 3 position being the more reactive site.



(13) Other dianionic heteroatom systems that could conceivably exhibit similar properties are those, for example, of trithiocarbonic acid, thiourea, and dithiolmethylene malononitrile [$(NC)_2C{=}C(SH)_2$]. Apparently none of these have been looked at with sequential alkylation in mind.

structures **8** and **9**.[14,15] These products can be rationalized on the basis of S and N attack by **2** on substrate,

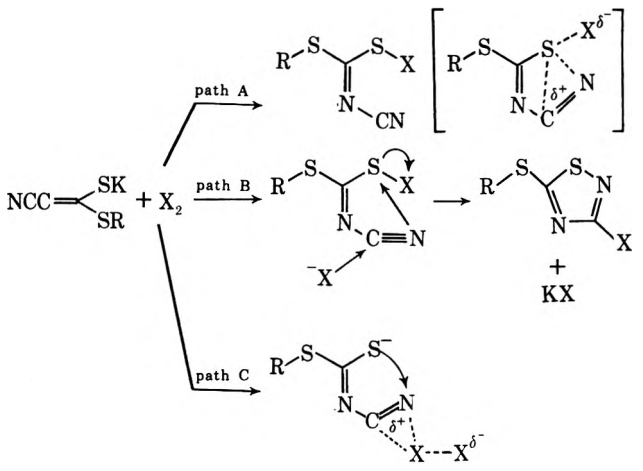
$(EtO_2C)_2S$	$(EtO_2C)_2NCN$
8 (major)	**9** (minor)

which is a predictable complication from soft–hard acid–base theory.[16] In this context, acylation of **3** also proved troublesome, although the desired S-acylated product was obtained with ethyl chloroformate.[1]

3-Halo-1,2,4-thiadiazole Sulfides.—Interaction of monoesters with chlorine, or more conveniently with sulfuryl chloride, at 0–5° resulted in an oxidative cyclization reaction furnishing the title compounds listed in Table I, where X = Cl. Similarly, treatment with bromine afforded **10** and **17**, and with iodine, **11**.[17] Chloroform, or alternatively methylene chloride, were the solvents of choice for these reactions. Rather surprisingly, water also served as solvent media for chlorine or bromine cyclizations.[18]

In the conversion of the monoesters to thiadiazole sulfides a diagnostic change was noted in the infrared spectra. To illustrate, monoesters exhibit a strong absorption at 1340–1380 cm^{-1} as described above. Cyclized products possess two strong bands ranging from 1381–1441 and 1175–1232 cm^{-1} which are assigned to ring vibrations.[19] As might be anticipated, substituents attached to the external sulfur atom do not appear to influence the position of these absorptions, but different halogen atoms at the 3 position (*i.e.*, **4**, **10** and **11**) produce a detectable red shift of both bands in the order Cl > Br > I. This phenomenon is associated with differences in atomic weight and electronic properties of the attached atoms.[20]

The mechanistic details surrounding formation of cyclized products from the monoesters have yet to be unraveled. Among the mechanisms considered, three are advanced as potential candidates.[21] In summary, path A requires formation of an intermediate sulfenyl halide, which then adds across the nitrile bond intramolecularly. In path B an intermediate sulfenyl halide is also assumed, but ring closure is assisted by halide ion attack on carbon followed by halogen displacement from sulfur with an incipient nitrogen anion in a concerted manner.[1] Electrophilic addition of elemental halogen to the nitrile bond with concomitant bond formation between sulfur and nitrogen as in path C would also lead to the observed thiadiazole. The common denominator implicit in these mechanisms is that, at some stage in the cyclization, the sp-hybridized nitrile bond is converted to sp^2, thereby enabling the heteroatoms to approach within bonding range.



As Thaler and McDivitt[8] have pointed out, sulfenyl halides do not commonly add to nitriles as required by path A. For intramolecular addition of sulfenyl halide to proceed in a manner normally associated with olefin addition,[22] a highly strained species would be required. This would appear to rule out a fast step following sulfenyl halide formation, but, if unassisted sulfenyl halide addition to nitrile is involved, the reaction is relatively fast because we have yet to isolate a sulfenyl halide precursor. Halide ion assisted ring closure (path B) appears more plausible because it avoids the strained species of path A. On the other hand, chloride ion attack in aqueous media seems unlikely, but the mechanism in water may differ in some respects from that in chloroform. Path C is attractive because of its simplicity and it circumvents the problems inherent in the two alternatives. The problem in this case is to rationalize why the nitrile band should effectively compete with a sulfur anion for oxidizing agent. In any event, experiments to rigorously establish the correct mechanism remain to be devised.

Reactions of 3-Halo-1,2,4-thiadiazole Sulfides.—Oxidation of a number of thiadiazole sulfides was carried out to yield sulfoxides and sulfones, listed in Tables II and III, respectively. Hydrogen peroxide in acetic anhydride–acetic acid solution was used effectively in preparing sulfones and a few sulfoxides. For sulfoxides and molecules containing more than one oxidizable group, *m*-chloroperbenzoic acid was the preferred oxidizing agent. All of the new sulfoxides and sulfones gave satisfactory analytical and spectral data. In addition to normal sulfoxide and sulfone bands, the infrared spectra of these derivatives also displayed the two bands attributed to thiadiazole ring vibrations, as indicated in Tables II and III. One notable feature of the thiadiazole ring absorptions in question is the rise in position of the higher frequency band relative to that of the sulfides, whereas the lower frequency band appears in about the same range.

A well-known reaction of sulfides which possess at least one hydrogen at an α-carbon atom is chlorination to give α-chloroalkyl sulfides.[23] An attempt to effect this exchange (eq 8) with 3-chloro-5-methylthio-1,2,4-

(14) Both **8** and **9** gave consistent analytical and spectral data and their physical properties compared reasonably well with literature values (see Experimental Section).

(15) R. Seltzer, *J. Org. Chem.*, **33**, 3896 (1968), reported a reaction of **2** with Ph_3SnCl which bears some resemblance to the production of **8**.

(16) (a) R. G. Pearson, *J. Amer. Chem. Soc.*, **85**, 3533 (1963); (b) R. G. Pearson and J. Songstad, *ibid.*, **89**, 1827 (1967).

(17) Kurzer and Taylor[5] obtained a 3-bromo derivative in low yield by modification of their procedure (eq 1). Thaler and McDivitt also reported a 3-bromo derivative.[8] To our knowledge, examples of 3-iodo thiadiazoles have not previously appeared in the literature.

(18) Compound **4** was first prepared from **3** and perchloromethyl mercaptan in water.[1]

(19) C. N. R. Cao and R. Venkatarazhavan, *Can. J. Chem.*, **42**, 43 (1964).

(20) See L. J. Bellamy, "Advances in Infrared Group Frequencies," Methuen, Great Britain, 1968, p 33.

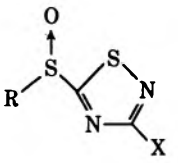
(21) See also ref 8 for discussion of mechanism.

(22) (a) N. Kharasch, "Organic Sulfur Compounds," Vol. I, Pergamon Press, Elmsford, N. Y., 1969, p 382; (b) D. R. Hogg, "Mechanisms of Reactions of Sulfur Compounds," Vol. V, Intra-Science Research Foundation, Santa Monica, Calif., 1970, p 87, and references cited therein.

(23) For review see L. A. Paquette, L. S. Wittenbrook, and K. Schreiber, *J. Org. Chem.*, **33**, 1080 (1968).

TABLE II

3-HALO-1,2,4-THIADIAZOLE SULFOXIDES[a]

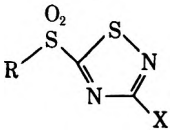


Compd	R	X	Yield, %[b]	Mp, °C	Bp, °C (mm)	Ir (ring), cm^{-1}
31	CH_3	Cl	72	99–99.5		1441, 1220
32	CH_3	Br	45	124–127		1431, 1198
33	CH_3CH_2	Cl	68		Oil[c]	1437, 1209
34	$(CH_3)_2CH$	Cl	65		Oil[c]	1439, 1214
35	$(CH_3)_2CH$	Br	82		Oil[c]	1440, 1200
36	$CH_3(CH_2)_2CH_2$	Cl	79		Oil[c]	1443, 1214
37	$CH_3(CH_2)_4CH_2$	Cl	85		Oil[c]	1441, 1214
38	$CH_3(CH_2)_8CH_2$	Cl	82		Oil[c]	1449, 1219
39	$C_6H_5CH_2$	Cl	50	92–95		1449, 1229

[a] Satisfactory analyses (±0.4% for C, H, N, or S) were reported for all new compounds listed in the table. [b] Crude yields. [c] Boiling point not determined (See Experimental Section).

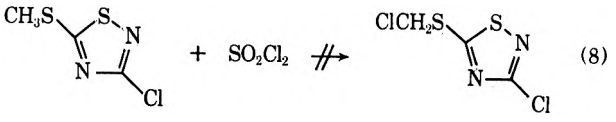
TABLE III

3-HALO-1,2,4-THIADIAZOLE SULFONES[a]



Compd	R	X	Yield, %[b]	Mp, °C	Bp, °C (mm)	Ir (ring), cm^{-1}
40	CH_3	Cl	38	82–83[c]		1447, 1232
41	CH_3	Br	59	69–71.5		1441, 1190, 1200 (sh)
42	$(CH_3)_2CH$	Cl	84	59–61		1435, 1227
43	$CH_3(CH_2)_2CH_2$	Cl	45		107 (0.55)	1441, 1217
44	$CH_3(CH_2)_4CH_2$	Cl	64		126–129 (0.20)	1447, 1220
45	$CH_3(CH_2)_8CH_2$	Cl	85	40.5–41		1437, 1206
46	$C_6H_5CH_2$	Cl	62	126.5–127		1441, 1215, 1224 (sh)
47	p-$O_2NC_6H_4CH_2$	Cl	56	137–138		1437, 1206
48	$CH_2{=}CHCH_2$	Cl	86	65–67		1433, 1224

[a] Satisfactory analyses (±0.4% for C, H, and S) were reported for all new compounds listed in the table. [b] Crude yields. [c] Reference 1.

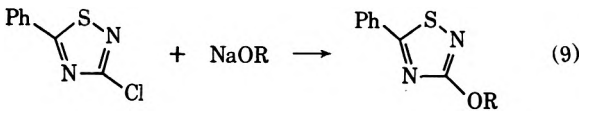


4

thiadiazole (4) under different conditions met with negative results.[24]

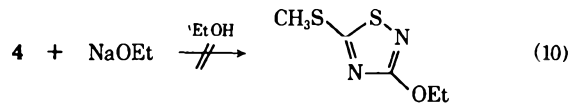
Why 4 should be so reluctant to undergo this reaction has yet to be determined.[25] Since none of the remaining compounds in Table I were subjected to similar reaction conditions, the generality of this phenomenon is an open question.

3-Halo-1,2,4-thiadiazoles are notoriously inert to nucleophilic displacement in contrast to halogen in the 5 position, which is relatively labile.[4] One of the few successful displacements has been reported by Kurzer and Taylor (eq 9).[5,26] In attempting to effect a similar



R = Me, benzyl

displacement on 4 with sodium ethoxide in absolute ethanol, none of the desired product was obtained (eq 10). Rather, after removal of a quantitative yield of



sodium chloride from the reaction mixture and further work-up, there was obtained a crude residue which exhibited prominent nitrile bands in the infrared spectrum suggesting ring opening with ejection of chloride ion. The nature of the ring-opened product(s) was not investigated further.

Experimental Section

Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. Boiling points are also uncorrected. Infrared spectra were determined with a Perkin-Elmer Model 621 grating spectrophotometer. Spectra of liquids were taken as films between NaCl or KCl and solids as KBr pellets. The nmr spectra were recorded on a Varian Model T-60 with TMS as internal standard.

Preparation of Dipotassium Cyanodithioimidocarbonate (2).—A solution of cyanamide, 53.0 g (1.25 mol), in 100 ml of 95% ethanol was treated with 105.0 g (1.38 mol) of carbon disulfide. The mixture was cooled to 0° in an ice-salt bath and potassium hydroxide, 140.5 g (2.50 mol), in 450 ml of 95% ethanol was added dropwise while stirring rapidly with a mechanical stirrer. The temperature of the reaction mixture was maintained at or below 10°. Upon completion of the addition (4 hr), the reaction mixture was allowed to stir overnight at ambient temperature. The insoluble solid was removed by filtration, washed with 95% ethanol, and dried *in vacuo* to give 211.0 g (86% of theoretical) of 2.

Example of Procedure for Preparing Monoesters. Potassium Allyl Cyanodithioimidocarbonate.—To a stirred solution of dipotassium cyanodithioimidocarbonate (2), 48.5 g (0.25 mol), in 210 ml of water and 185 ml of acetone previously cooled to 0° was added dropwise allyl bromide, 30.2 g (0.25 mol), in 90 ml of acetone. Upon completion of the addition the reaction mixture was allowed to warm to ambient temperature (approximately 21–24°) and stirred overnight. Shorter contact times down to 3 hr gave comparable results. Evaporation of the solvent on a rotary evaporator at reduced pressure (*in vacuo*) and elevated temperature afforded a solid residue which was slurried in 450 ml of acetone. The insoluble inorganic salt (in this case potassium bromide) was removed by filtration and the filtrate was evaporated *in vacuo* to furnish a solid residue. Treatment of this residue with 250 ml of ethyl acetate, in the same manner as described above for acetone, removed residual potassium bromide and any potassium thiocyanate that might have formed. Evaporation *in vacuo* of the ethyl acetate filtrate and further oven drying of the solid residue gave 47.3 g (97% of theoretical) of potassium allyl cyandithioimidocarbonate, mp 138–140°. The material prepared by this method gave the following elemental analysis.

Anal. Calcd for $C_5H_5KN_2S_2$: C, 30.59; H, 2.57; N, 14.27; K, 19.91. Found: C, 29.70; H, 2.45; N, 14.28; K, 20.30.

Recrystallization of the monoesters was not generally attempted prior to subsequent reactions, but ethyl acetate–chloroform or ethyl acetate–benzene were found to be suitable solvents for this purpose. As stated in the text, the monoesters are hygroscopic to varying degrees and, if retained for any period of time, should be stored under anhydrous conditions.

Reaction of 2 with 1 Molar Equiv of Ethyl Chloroformate.—To a stirred, refluxing solution of dipotassium cyanodithioimido-

(24) Chlorination of 4 with chlorine in acetic acid–water did lead to 3,5-dichloro-1,2,4-thiadiazole in 85–95% yield. These results and ramifications thereof will be made available elsewhere.

(25) We had suggested[2] that a complex between 4 and sulfuryl chloride might be the culprit in preventing this reaction from taking place. Later experiments failed to clearly substantiate this theory.

(26) See also J. Goerdeler and K. H. Heller, *Ber.*, **97**, 225 (1964).

carbonate (2), 1.0 g (5 mmol), in 80 ml of acetonitrile under a nitrogen atmosphere was added dropwise 0.6 g (5 mmol) of ethyl chloroformate in 20 ml of acetonitrile. Upon completion of the addition, the reaction mixture was refluxed for an additional 2 hr. Heat was removed and the reaction mixture was allowed to stand overnight at ambient temperature. The insoluble solid was filtered, washed with acetonitrile, and dried to give 750 mg of material identified as 2 by comparison of infrared spectra (75% recovery). Evaporation of the filtrate *in vacuo* gave approximately 150 mg of solid residue which was triturated with ethyl acetate, filtered, and dried. The infrared spectrum of this solid contained no carbonyl absorptions anticipated for a carboethoxy group, but did contain bands characteristic for 2.

Reaction of 2 with 2 Molar Equiv of Ethyl Chloroformate.—A heterogeneous mixture of 9.7 g (50 mmol) of dipotassium cyanodithioimidocarbonate (2, rendered as anhydrous as possible by drying over phosphorus pentoxide under high vacuum at elevated temperature) and ethyl chloroformate, 10.8 g (100 mmol), 100 ml of anhydrous acetonitrile was stirred and refluxed for 20 hr under a nitrogen atmosphere. The insoluble portion of the reaction mixture was filtered, washed with acetonitrile, and dried to give 8.4 g of pale yellow solid (A), mp >280°. An infrared spectrum of A was essentially devoid of any peaks, with the exception of a weak absorption at 2185 cm^{-1} (C≡N). When solid A was stirred in water, an insoluble brown solid (B) remained which upon work-up was found to weigh 1.0 g, mp >280°. Solid B gave an infrared spectrum that appeared polymer-like with broad absorptions at 3600–2600 and 1800–1100 cm^{-1} and one relatively sharp absorption at 2185 cm^{-1}. The soluble portion of A, approximately 7.4 g, was characterized as potassium chloride (theoretical, 7.5 g).

Evaporation *in vacuo* of the acetonitrile soluble portion (filtrate from above) afforded 8.9 g of a maroon oil (C). The infrared spectrum of this displayed prominent bands at 3000 (CH), 2270 (C≡N), 2198 (C≡N), 1970 (N=C=S), 1832–1720 (five peaks, C=O), 1235, 1100, and 1010 cm^{-1}. When C was stirred in anhydrous ethyl ether, a yellow solid (D) precipitated. Solid D was separated from the ether solution by filtration and was found to weigh 1.7 g (water insoluble). This was unstable and decomposed within minutes to a maroon-colored, viscous liquid. An infrared spectrum of D taken immediately after isolation resembled that of solid B with additional carbonyl bands around 1775 cm^{-1}. The ether soluble filtrate obtained after removal of solid C was evaporated *in vacuo* to give 7.3 g of yellow liquid (E). A tlc of the yellow liquid (silica gel, elution with ethyl acetate–acetonitrile, 4:1) showed two spots at R_f 0.33 and 0.55. Removal of solid D failed to noticeably alter the infrared spectrum of E as compared to C.

Fractional distillation of liquid E under reduce pressure gave 2.0 g (center cut; total of all cuts 3.5 g) of colorless liquid (F), bp 55–56° (0.2–0.3 mm), R_f 0.55. Liquid F was assigned structure 8, thiodiformic acid diethyl ester: bp 118° (22 mm),[27] ν_{max}^{film} 3000 (CH), 1785 (C=O), 1760 (C=O), 1720 (C=O), 1100, and 1010 cm^{-1}; nmr δ^{CDCl_3} 1.33 (t, 7, 3, $-OCH_2CH_3$), 4.32 (q, 7, 2, $-OCH_2CH_3$).

Anal. Calcd for $C_7H_{10}O_4S$: C, 40.44; H, 5.66; S, 17.99. Found: 40.30; H, 6.04; S, 17.66.

The pot residue which remained after removal of 8 was stirred in anhydrous ethyl ether to precipitate a small quantity of gummy yellow solid which was not investigated further. The ether portion was decanted and concentrated to lower volume on a steam bath. When cooled in a Dry Ice–acetone bath, a pale yellow solid (G) crystallized. This was filtered cold and immediately transferred to a sample bottle, where it melted at ambient temperature (crude weight 1.2 g; R_f 0.33). Recrystallization of G from ether at reduced temperature afforded pure G, mp 28–30°. Solid G was assigned structure 9, dicarboethoxy cyanamide: mp 32.8°;[28] ν_{max}^{film} 3000 (CH), 2275 (C≡N), 2199 (w, C≡N), 1830 (C=O), 1805 (C=O), 1770 (C=O), 1235, 1105, and 1000 cm^{-1}; nmr $\delta_{TMS}^{CDCl_3}$ 1.40 (t, 7, 3, $-OCH_2CH_3$), 4.39 (q, 7, 2, $-OCH_2CH_3$).

Anal. Calcd for $C_5H_{10}N_2O_4$: C, 45.16; H, 5.41; N, 15.05. Found: C, 44.60; H, 5.68; N, 14.80.

The data from this experiment suggests that S-acylation of 2 is not likely to be successful, partly because of competition between sulfur and nitrogen anions, but also because the resultant S-monoester can further collapse by elimination of cyanoisothiocyanate to give a more stable species.[29–31]

Example of Procedure for Preparing Thiadiazole Sulfides of Table I. 3-Chloro-5-benzylthio-1,2,4-thiadiazole (20).—To a stirred slurry of potassium benzyl cyanodithioimidocarbonate, 42.0 g (0.17 mol), in 225 ml of chloroform previously cooled to 0–5° was added dropwise sulfuryl chloride, 26.8 g (0.20 mol). Upon completion of the addition the reaction mixture was stirred at 0° for 1 hr and at reflux for 3.5 hr. Removal of the insoluble white solid by filtration and evaporation of the filtrate *in vacuo* at elevated temperature afforded 34.2 g (85% of theoretical) of crude 20. Fractional distillation of the crude product under reduced pressure furnished pure 3-chloro-5-benzylthio-1,2,4-thiadiazole, bp 144–147° (0.25 mm).

3-Chloro-5-(α-acetamidothio)-1,2,4-thiadiazole (29).—To a stirred slurry of potassium *S*-(α-acetamido)cyanodithioimidocarbonate, 2.1 g (10 mmol), in 10 ml of chloroform. Upon completion of the addition, the slurry was stirred for 24 hr at ambient temperature. Removal of the insoluble solid by filtration gave 2.4 g of crude product. Treatment of this with water to remove inorganic salt and subsequent filtration afforded 1.1 g of 29. An additional 0.4 g of 29 (total yield was 1.4 g or 71% of theoretical) was obtained by evaporation *in vacuo* of the filtrate from the reaction mixture. Recrystallization of the product from chloroform furnished pure 3-chloro-5-(α-acetamidothio)-1,2,4-thiadiazole, mp 137–139°.

Although oxidative cyclization of the monoesters was conveniently carried out with sulfuryl chloride as demonstrated in the preceding examples, elemental chlorine was also employed to give compounds in Table I where X = Cl with comparable results. Furthermore, an excess of chlorine is not detrimental to the reaction.

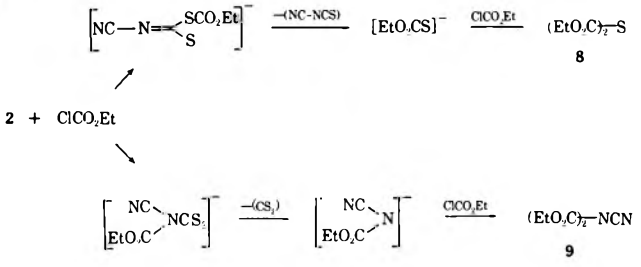
Contacting monoesters in chloroform or methylene chloride with bromine in the same manner as described above afforded the 3-bromo thiadiazoles listed in Table II. Treatment of 3 with iodine was not a clean reaction and a representative experiment is presented below. This was the only iodo derivative that was attempted.

3-Iodo-5-methylthio-1,2,4-thiadiazole (11).—To a stirred slurry of potassium methyl cyanodithioimidocarbonate (3), 3.4 g (20 mmol), in 50 ml of chloroform at ambient temperature was added dropwise 5.1 g (20 mmol) of iodine in 300 ml of chloroform. After completion of the addition, the reaction mixture was stirred overnight at ambient temperature. The reaction mixture was then transferred to a separatory funnel and washed successively with water, 10% aqueous sodium bisulfite solution, and again with water. The organic portion was dried over sodium sulfate, filtered, and evaporated *in vacuo* to afford 3.0 g of orange semisolid which exhibited characteristic thiadiazole bands in the infrared spectrum. Attempts to recrystallize the crude product were unsuccessful and it was necessary to chromatograph the material (80 g of Woelm alumina, activity I, elution with benzene followed by 3:1 benzene–chloroform). There was obtained 2.3 g of 11 as a colorless, crystalline solid (46% of theoretical), mp 86.5–88.5°, and 30 mg of yellow oil (eluted last). The yellow oil was not characterized, but spectral data was in line with a disulfide.

(27) *Beilstein*, **3**, 133.

(28) *Beilstein*, **3**, 82.

(29) A proposed sequence of events to explain formation of 8 and 9 is shown below. Evidence for the production of cyanoisothiocyanate obtains



from the broad band centered at 1975 cm^{-1} in the infrared spectra of fractions C and E.[30,31] The lack of good material balance in this experiment (17.3 g recovered from 20.5 g) could be partly accounted for by loss of carbon disulfide from the reaction mixture.

(30) The isothiocyanate band for EtO_2C–NCS has been reported to occur at 1960–1990 cm^{-1}: A. Takamizawa, *et al.*, *Bull. Chem. Soc. Jap.*, **36**, 1219 (1963).

(31) Cyanoisothiocyanate has been reported to be an unstable material (ref 7).

Water could also be employed as a solvent media in the cyclization reaction and an example procedure follows.

3-Bromo-5-methylthio-1,2,4-thiadiazole (10).—Bromine, 8.8 g (60 mmol), was added dropwise to a stirred solution of potassium methyl cyanodithioimidocarbonate (**3**), 8.5 g (50 mmol), in 100 ml of water previously cooled to 5°. The resultant slurry was stirred for 1 hr at 5° and 2.5 hr at ambient temperature. Sufficient sodium thiosulfate was added to destroy any excess bromine. Extraction of the solution with chloroform and routine work-up of the organic portion gave 5.7 g (54% of theoretical) of crude **10** as a pale yellow semisolid. Recrystallization from pentane furnished pure **10**, mp 57–58°.

In a like manner chlorine gas was introduced into an aqueous solution of **3** to afford a 60% yield of crude **4** (same work-up method as above).

Example of Procedures for Preparing Thiadiazole Sulfoxides and Sulfones of Tables II and III. 3-Chloro-5-methylsulfinyl-1,2,4-thiadiazole (31)..—To a stirred solution of 3-chloro-5-methylthio-1,2,4-thiadiazole, 16.6 g (0.1 mol), in 25 ml of acetic acid and 25 ml of acetic anhydride cooled to 0° was added dropwise 12.3 g (0.1 mol) of 30% hydrogen peroxide solution. The mixture was stirred at 0° for 1 hr and 2 days at ambient temperature. Any unreacted hydrogen peroxide was decomposed with a small amount of manganese dioxide. Filtration and evaporation of the filtrate under reduced pressure at 80° gave a semisolid residue which was treated with water followed by solid sodium bicarbonate. Extraction with chloroform and routine work-up of the organic portion afforded 13.0 g (72% of theoretical) of crude **31** as a white solid. Recrystallization of this from methanol afforded pure **31** as a white, crystalline solid, mp 99–99.5°.

Reaction of thiadiazole sulfides with 1 molar equiv of *m*-chloroperbenzoic acid in chloroform also afforded sulfoxides in a state of high purity with minimal difficulty. An example procedure is given below for sulfone **47** which is applicable to the sulfoxides with appropriate modification of stoichiometry. A major portion of the sulfoxides selected for this investigation were found to be oils that were difficult to distill without decomposition. However, the products were all obtained in state of purity sufficient enough to give acceptable analytical results.

3-Chloro-5-(4′-nitrobenzylsulfonyl)-1,2,4-thiadiazole (47).—A 30% hydrogen peroxide solution, 24.5 g (0.22 mol), was added dropwise to a stirred solution of 3-chloro-5-(4′-nitrobenzylthio)-1,2,4-thiadiazole, 24.4 g (0.08 mol), in 25 ml of glacial acetic acid and 25 ml of acetic anhydride previously cooled to 0°. Upon completion of the addition, the reaction mixture was stirred at 0° for 2 hr and 2 days at ambient temperature. A solid precipitated during this period. The reaction mixture was diluted with 20 ml of glacial acetic acid and cooled to 0°, and sufficient manganese dioxide was added to decompose excess hydrogen peroxide. The insoluble solid was separated by filtration, washed with glacial acetic acid, and dried under high vacuum. (Work-up procedure was altered accordingly when the product was soluble in acetic acid–acetic anhydride solution. For example, evaporation of the solution *in vacuo* gave the crude product in these cases.) Further purification of crude product was effected by taking the residue up in chloroform and washing with aqueous 5% sodium bicarbonate solution. The chloroform portion was then dried over sodium sulfate or magnesium sulfate, filtered, and evaporated *in vacuo* to give 15.1 g (56% yield) of **47**. Recrystallization of this material from methanol afforded pure **47**, mp 137–138°.

For thiadiazole sulfides which contained another oxidizable group, *m*-chloroperbenzoic acid gave cleaner product and better yields over hydrogen peroxide. The following example will illustrate the use of *m*-chloroperbenzoic acid.

3-Chloro-5-(allylsulfonyl)-1,2,4-thiadiazole (48).—To a stirred solution of 3-chloro-5-(allylthio)-1,2,4-thiadiazole, 14.1 g (0.07 mol), dissolved in 225 ml of chloroform previously cooled to 0° was added dropwise 25 g (0.21 mol) of 80–85% *m*-chloroperbenzoic acid also dissolved in chloroform. After the addition was complete, the reaction mixture was stirred for 1 hr at 0° and 3 hr at ambient temperature. Removal of the white, insoluble solid (*m*-chlorobenzoic acid) by filtration gave a chloroform solution which was repeatedly washed with aqueous 5% sodium bicarbonate solution (this treatment removed any chlorobenzoic acid still dissolved in the chloroform), dried over magnesium sulfate, filtered, and evaporated to afford 14.0 g (86% of theoretical) of **48** as a colorless oil. The oil crystallized on standing, however, and could be recrystallized from methanol to give pure **48**, mp 65–67°.

Attempted Preparation of α-Chloroalkyl Sulfides.—The following experiments describe attempts to chlorinate 3-chloro-5-methylthio-1,2,4-thiadiazole (**4**) with sulfuryl chloride. Evidence from the first experiment below directed attention to a possible complex between sulfuryl chloride and **4** which might be preventing the desired reaction. Although this is not an unreasonable concept, later experiments failed to confirm this possibility.

Reaction of 4 with Excess Sulfuryl Chloride.—A solution of **4**, 2.0 g (12 mmol), in 20 ml of sulfuryl chloride was heated (50°) and stirred for 24 hr. The excess sulfuryl chloride was removed at 40° *in vacuo* to give a yellow liquid residue which was further exposed to a high vacuum overnight. This treatment afforded 2.6 g of oil. An infrared spectrum of this oil was substantially featureless, but resembled that of sulfuric acid. When the oil was added to water, a solid separated. After work-up, there was obtained 1.5 g of solid material identified as **4** by comparison of infrared spectra. The aqueous phase was neutralized with sodium hydroxide solution and evaporated to dryness to give a white solid identified as mainly sodium sulfate, also by infrared comparison.

Since no precautions were taken to exclude water in the above experiment, it was repeated with appropriate modifications.

Reaction of 4 with Excess Sulfuryl Chloride (Anhydrous).—A 2.0-g (12 mmol) quantity of analytically pure **4** was heated at 50–55° in 20 ml of freshly distilled sulfuryl chloride under a blanket of nitrogen (drying tube exit) in the dark for 3 hr. Despite a very low positive nitrogen pressure and use of an efficient condenser, the volume of solution decreased during the heating period. Sulfur dioxide was detected (odor) in the effluent gases. The solution was cooled and excess sulfuryl chloride was removed *in vacuo* at 20° to give 2.4 g of yellow oil. An infrared spectrum of the oil compared with that of **4** in solution (CCl_4) with no peaks evident at 1410 and 1190 cm^{-1} (SO_2) expected for sulfuryl chloride. When the oil was poured over ice, an aqueous acidic solution developed and another oil separated. This was removed by extraction with ether and the organic layer was washed with water, dried over magnesium sulfate, filtered, and evaporated to afford 1.7 g (85% recovery) of tacky yellow solid which was characterized as **4**. A tlc (silica gel, elution with ether) of the crude **4** showed one spot at R_f 0.52 (uv) which compared with authentic **4**, but a noticeable spot remained at the origin.

Thus, by carefully excluding water from the reaction the result obtained in the previous experiment was not realized.

Reaction of 4 with 1 Molar Equiv of Sulfuryl Chloride.—To a stirred solution of analytically pure **4**, 2.5 g (15 mmol), in reagent grade carbon tetrachloride (15 ml) warmed to 35° under a nitrogen atmosphere was added dropwise 2.0 g (15 mmol) of freshly distilled sulfuryl chloride in 15 ml of carbon tetrachloride over a period of 15 min. The solution was brought to reflux and refluxed for 3 hr. The reaction mixture was cooled and volatile materials were removed *in vacuo* at 20° to give a white solid residue. This was found to weigh 2.45 g (98% recovery), mp 52–54°. An infrared spectrum of this material was superimposable upon that of authentic **4**.

The above experiment was typical of several experiments to chlorinate **4** under what might be termed "standard conditions" for preparing α-chloroalkyl sulfides. All of these ended with the same result as above.

Reaction of 3-Chloro-5-methylthio-1,2,4-thiadiazole (4) with Sodium Ethoxide.—To a stirred solution of sodium ethoxide in anhydrous ethanol (prepared from 1.8 g-atoms of sodium metal and 50 ml of ethanol) at 35° was added 3-chloro-5-methylthio-1,2,4-thiadiazole, 3.3 g (20 mmol), through a Gooch tube. Initially the thiadiazole dissolved, but a precipitate formed as the addition was continued. Upon completion of the addition the reaction mixture was stirred at ambient temperature for 5 hr. The white, insoluble solid was removed by filtration, washed with ether, and dried *in vacuo* to give 1.5 g of material, mp >280°, which was completely water soluble. This was readily determined to be primarily sodium chloride (1.2 g is theoretical if all of **4** is degraded), apparently contaminated with about 300 mg of organic salt which displayed nitrile bands at 2170 and 2185 cm^{-1} in the infrared spectrum (very weak spectrum because of sodium chloride dilution). Other absorptions occurred at 1620 and 1572 cm^{-1} indicative of C=O or C=N. Removal of solvent from the above filtrate afforded a residue which was taken up in water. Neutralization of this solution with 5 *N* hydrochloric acid separated a small quantity of oil. This was removed by extraction with ether and further treatment to give 200 mg of yellow semisolid residue (strong odor). The infrared of this material con-

tained bands at 2260 (C≡N) and 1775 cm^{-1} (C=O), but in general the peaks were quite broad. The neutralized, aqueous portion was evaporated *in vacuo* and the residue was dried to give 4.0 g of white solid, mp 60–65° (wet), 175° (bubbled), >300°. Although this residue was largely sodium chloride, an infrared spectrum again displayed a weak nitrile peak at 2175 cm^{-1}. None of the different fractions possessed peaks characteristic of a thiadiazole ring in the infrared spectra, but all displayed quartet–triplet combinations in the nmr indicative of ethoxy groups.

Registry No.—**2**, 13145-41-0; **4**, 10191-90-9; **8**, 36955-31-4; **9**, 19245-24-0; **10**, 36955-33-6; **11**, 36955-34-7; **12**, 36955-35-8; **13**, 36955-36-9; **14**, 36955-37-0; **15**, 36955-38-1; **16**, 36955-39-2; **17**, 36955-40-5; **18**, 36955-41-6; **19**, 36955-42-7; **20**, 36598-31-9; **21**, 36955-44-9; **22**, 36955-45-0; **23**, 36950-00-2; **24**, 36950-01-3; **25**, 36950-02-4; **26**, 36950-03-5; **27**, 36950-04-6; **28**, 36994-19-1; **29**, 36950-05-7; **30**, 36950-06-8; **31**, 36950-07-9; **32**, 36950-08-0; **33**, 36950-09-1; **34**, 36994-20-4; **35**, 36950-10-4; **36**, 36950-11-5; **37**, 36950-12-6; **38**, 36950-13-7; **39**, 36950-14-8; **40**, 10191-91-0; **41**, 36950-16-0; **42**, 36950-17-1; **43**, 36950-18-2; **44**, 36950-19-3; **45**, 36950-20-6; **46**, 36950-21-7; **47**, 36950-22-8; **48**, 36950-23-9; potassium allylcyanodithioimidocarbonate, 36598-32-0.

Intermediate Neglect of Differential Overlap Theoretical Studies.[1] 2-Substituted 1,3-Dioxolan-2-ylium Ions

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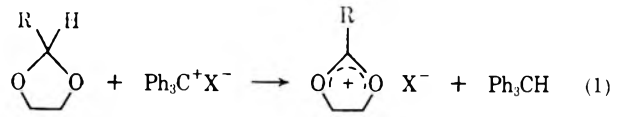
SCF–MO calculations in the INDO approximation have been performed on a series of 2-substituted 1,3-dioxolan-2-ylium cations where the 2 substituent was H (1), CH_3 (2), F (3), NH_2 (4), OH (5), and CN (6). In each of cations 1–6 a geometry search was performed to obtain the optimized geometry. The 2-cyano group was found to be a better electron donor than 2 hydrogen owing to back π_y donation to the C-2 carbon of the ring. A picture of both the π- and σ-electron distribution for this cation series was provided as a function of the 2 substituent. The NH_2 function was the best π donor followed by OH and F. However, fluorine is a better σ-electron-withdrawing function followed by OH and then NH_2, an order which parallels the electronegativity of the atom bond to C-2. This σ-withdrawal effect reduces the donor ability of fluorine to slightly less than that of a methyl function. The interrelation of σ- and π-electron framework over the ring oxygen atoms, C-2, and the 2 substituent is given. Rotational barriers are calculated. A comparison of the calculated positive charge densities on the ring methylene hydrogens is made with nmr chemical shifts for examples where spectra have been obtained.

Since the pioneering solvolytic studies of Winstein[2,3] and synthetic efforts of Meerwein,[4–6] a large body of chemistry has developed around the synthesis, reactions, structure, spectroscopy, and intermediacy (in organic reactions) of 1,3-dioxolan-2-ylium and related cations.[7] They have been isolated as stable salts[6,8–10] and shown to be stable in strong acids at high temperatures.[11] The great stability of 1,3-dioxolan-2-ylium ions is emphasized by their quantitative formation from 2-substituted 1,3-dioxolanes upon hydride abstraction by triphenylcarbonium ion salts[12] (see eq 1). Furthermore, the large rate accelerations



(1)

observed in the acetolysis of *trans*-2-acetoxycyclohexyl *p*-toluenesulfonate[13,14] and the high gas-phase stabilities of dioxonium ions relative to the methyl cation (*i.e.*, compare heats of formation: CH_3^+, 258; $(CH_3O)_2CH^+$, 101–113; $(CH_3O)_2CCH_3^+$, 146 kcal/mol)[15,16] demonstrate the inherent stability of these species. The heats of formation of a series of 2-substituted 1,3-dioxolan-2-ylium ions have been measured calorimetrically in strong acid solutions,[17,18] and a correlation between heats of formation and the nmr chemical shifts of the ring protons exists for a series of these ions with various 2-aryl substituents. Noteworthy was the fact that a 2-phenyl group destabilizes the cations, relative to a 2-methyl group. This is probably due to the relative effects of phenyl and methyl groups on the ester precursors used in the heat of formation measurements. Despite the enormous[7] number of studies on these cations, theoretical descriptions are noticeably lacking.

It is the purpose of this paper to present a SCF theoretical description in the INDO approximation[19,20] of 1,3-dioxolan-2-ylium ions, 1–6, where the substituent is varied to include H (1), CH_3 (2), F (3), NH_2 (4),

(1) Paper V. For papers I–IV in this series, see (a) L. D. Kispert, C. Engelman, C. Dyas, and C. U. Pittman, Jr., *J. Amer. Chem. Soc.*, **93**, 6948 (1971); (b) C. U. Pittman, Jr., C. Dyas, C. Engelman, and L. D. Kispert, *J. Chem. Soc., Faraday Trans. 2*, **68**, 345 (1972); (c) L. D. Kispert, C. U. Pittman, Jr., D. L. Allison, T. B. Patterson, Jr., C. W. Gilbert, C. F. Hains, and J. Prather, *J. Amer. Chem. Soc.*, **94**, 5979 (1972); (d) C. U. Pittman, Jr., L. D. Kispert, and T. B. Patterson, Jr., *J. Phys. Chem.*, in press.

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(3) S. Winstein and D. Seymour, *ibid.*, **68**, 119 (1946).

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(10) D. A. Tomalia and H. Hart, *ibid.*, 3389 (1966).

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(16) R. H. Martin, F. W. Lampe, and R. W. Taft, *ibid.*, **88**, 1353 (1966).

(17) J. W. Larsen and S. Ewing, *ibid.*, **93**, 5107 (1971).

(18) J. W. Larsen and S. Ewing, *Tetrahedron Lett.*, 539 (1970).

(19) J. A. Pople, D. L. Beveridge, and P. A. Bobosh, *J. Chem. Phys.*, **47**, 2026 (1967).

(20) J. A. Pople and D. L. Beveridge, "Approximate Molecular Orbital Theory," McGraw-Hill, New York, N. Y., 1970.

TABLE I

CALCULATED ROTATIONAL BARRIERS AND π-BOND ORDERS IN 2-SUBSTITUTED 1,3-DIOXOLAN-2-YLIUM IONS 1–6

Cation	X[a]	Rotational barrier[a] C_2^+–X, kcal mol^{-1}	π-Bond orders[a] in the C_2–X and C_2–O Bonds $\pi_y C_2^+$–X	$\pi_y C_2^+$–O	$\pi_z C_2^+$–X	$\pi_z C_2^+$–O
1	H			0.650		0.190
2	CH_3	0.013[b]	0.331	0.587[c]	0.194	0.174
3	F		0.414	0.586	0.197	0.199
4	NH_2	30.6	0.655	0.485	0.187	0.177
5	OH	8.5[d]	0.539	0.540	0.202	0.187
6	CN[e]		0.359	0.592	0.211	0.175

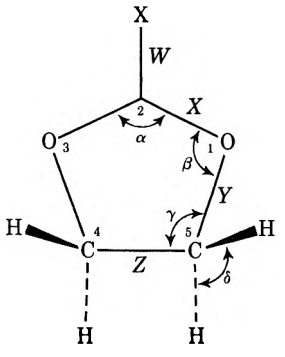
[a] X is the substituent at C-2 and the z direction is taken along the C_2–X and C_2–O bonds, respectively. [b] The most stable conformation is that with one of the methyl hydrogens in the plane of the ring. [c] Rotating the methyl group to the conformation containing one hydrogen perpendicular to the plane of the ring has a negligible influence on $\pi_y C_2^+$–O. [d] The most stable conformation is where the H–O bond is in the plane of the ring. [e] The values of the π-bond orders for the C≡N group itself are $\pi_y = 0.930$, $\pi_z = 0.975$.

OH (**5**), and CN(**6**). An analysis of the minimized geometries, charge distributions, π-bond orders, and rotational barriers with respect to the 2 substituent is given. Furthermore, the calculations provide some rationale for previous spectral observations.

Method.—The INDO program (CNINDO), QCPE No. 141, was obtained from the Quantum Chemistry Program Exchange, Indiana University, and was modified for use on a Univac 1108. The structures were generated using the Gordon–Pople model builder program QCPE No. 135, which determined the cartesian coordinates of the atoms when bond lengths and angles were supplied. The models were computed on an IBM 360/50. The numbering system is given in structure I.

For all structures, the y axis was defined perpendicular to the molecular plane (plane of the five-membered ring). Each cation, **1**–**6**, was studied by defining the geometry in the x and z axis in two ways. First, the z axis was defined along the bond from C-2 to the 2 substitutent. Secondly, the z axis was defined along the C-2 to ring oxygen bond. In this way, the polarization of the σ bonds between C_2O and C_2 to the 2 substituent could be conveniently expressed in HMO terms, as has been done in Tables I and II.

Calculations to define the minimized geometries were carried out in a stepwise fashion (refer to structure I for the following discussion). First a reasonable



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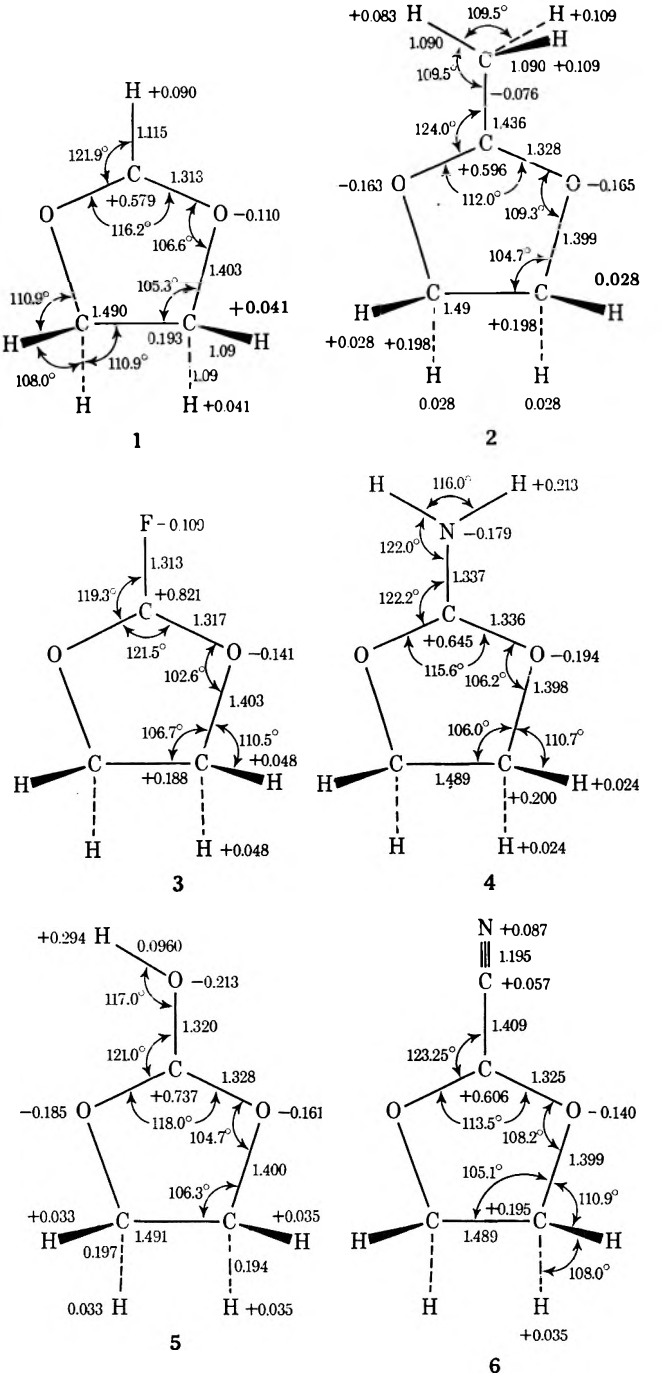
estimate was made of all bond lengths, and the length w was minimized for a set value of angles α, β, γ, and δ. Using this value of w the length x was minimized.

CHART I

INDO-OPTIMIZED GEOMETRIES AND TOTAL CHARGE DENSITIES OF 2-SUBSTITUTED 1,3-DIOXOLAN-2-YLIUM IONS 1–6[a]

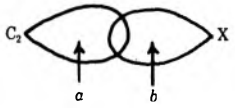
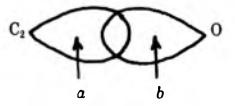
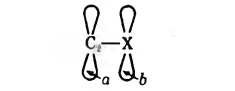
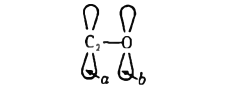


[a] The y coordinate is defined perpendicular to the molecular plane.

Next the angle α was systematically minimized (using values of w and x previously obtained), and this operation automatically defined angles β and γ given the high symmetry of the molecule. Using a minimized value of α, the lengths x, y, and z were minimized respectively (using the minimized value of each quantity in the determination of the next). The energy was far more sensitive to small bond length changes than to small changes in bond angle. After this procedure was completed, the entire process was repeated. This second iteration produced the geometry which was used, since a third iteration did not cause an appreciable variation in the optimized geometry.

Table II

Electronic Structure of 2-Substituted 1,3-Dioxolan-2-ylium Ions as a Function of the 2 Substituent (X) with the y Axis Defined Perpendicular to the Plane of the Ring

No.	Calcd quantity: Item		Cation X: 1, H	2, CH_3	3, F[a]	4, NH_2	5, OH	6, CN
1	α, deg		116.2	112.0	121.5	115.6	118.0	113.5
	σ-bond electron densities, q							
2		a	0.903	0.918	0.709	0.821	0.771	0.901
		b	0.910	0.973	1.423	1.116	1.292	0.878
	σ-bond electron densities, q							
3		a	0.824	0.838	0.783	0.811	0.797	0.830
		b	1.333	1.328	1.315	1.302	1.305	1.321
	π_y-bond, p_y-orbital electron densities, q							
4		a	0.629	0.626	0.637	0.695	0.655	0.655
		b		1.020	1.875	1.671	1.784	1.033
	π_y-bond, p_y-orbital electron densities, q							
5		a	0.629	0.626	0.637	0.696	0.655	0.655
		b	1.668	1.722	1.735	1.794	1.759	1.703

[a] The F_{p_x} orbital's electron density, q, is 1.967. [b] The electron distribution in the CN group is $q_{Cp_x} = 0.957$, $q_{Np_x} = 1.038$, $q_{Np_y} = 0.869$, and $q_{Np_z} = 1.295$.

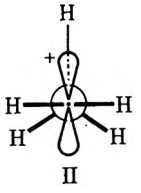
In this paper the term electron density is synonomous with q, while the total charge density is $n - q$ where n is the number of valence electrons.

Results and Discussion

Calculated Results.—The INDO-optimized geometries and total charge densities of 2-substituted 1,3-dioxolan-2-ylium ions **1**–**6** are summarized in Chart I. A summary of the calculated rotational barriers between C-2 and the C-2 substituent (hereafter designated X) is given in Table I along with both the C_2–X and C_2–O π_y and π_x bond orders. Table II summarizes the electron densities in both the σ and π orbitals of C-2 and the atoms directly bound to C-2 (X and the ring oxygens). Table II also shows the variation of the O–C_2–O angle (α in I) with X. From these results a clearer qualitative picture of the ground-state electronic structure of 2-substituted 1,3-dioxolan-2-ylium ions emerges.

In each of the cations, the preferred geometry at C-2 was planar (*i.e.*, sp^2). The calculated C_2–O_{ring} bond lengths varied from 1.313 (X = H) to 1.336 Å (X = NH_2), which correlates with the π_y bond orders discussed later). The O–$C_{4\text{ or }5}$ and C_4–C_5 bond lengths were practically invariant with changes in X, as were the C–C–O (x in I) angles. However, the C–O–C (β) and O–C_2–O (α) angles were quite sensitive to X. For example, the calculated values of α varied from 112.0° when X = CH_3 to 121.5° when X = F. However, no discernible correlation of the size of this angle with the electron-donating ability of X was apparent.

The rotational barriers about the C_2–X bond followed the expected order: NH_2 > OH > CH_3. The NH_2 plane and the O–H bond were found in the plane of the ring. Unexpectedly, one of the methyl C–H bonds was found in the plane of the ring in the most stable conformation of **2** in contrast to the ethyl cation,



II

where one C_2–H bond lies, preferentially, perpendicular to the $^+CH_2$ plane[21,22] (*i.e.*, conformer II). However, the small preference for this conformation (0.013 kcal/mol^{-1}) is too small to have confidence that this is the really preferred geometry.

The π_y bond orders between C-2 and X (Table I) decrease in the order NH_2 > OH > F > CN > CH_3 > H = O. For NH_2, OH, and F this order follows the trend based on the increasing electronegativity of the atom attached to C-2. The more electronegative that atom is, the more tightly will it hold its $2p_y$ electrons. The magnitude of the C_2–CN π_y bond order is only 0.359. This agrees with its calculated length (1.41 Å) which is fairly long for a C_{sp^2}–C_{sp} length in a cation.[23] Not only will bond lengths de-

(21) K. B. Wiberg, *J. Amer. Chem. Soc.*, **90**, 59 (1968); L. Radom, J. A. Pople, V. Buss, and P. v. R. Schleyer, *ibid.*, **92**, 6380 (1970).

(22) R. Sustmann, J. E. Williams, M. J. S. Dewar, L. C. Allen, and P. v. R. Schleyer, *ibid.*, **91**, 5350 (1969); L. J. Massa, S. Ehrenson, and M. Wolfsberg, *Int. J. Quantum Chem.*, **4**, 625 (1970).

(23) The C–C single bond length in acrylonitrile is 1.426 Å and the correlation of C–C bond lengths has been discussed in detail by B. P. Stoicheff, *Tetrahedron*, **17**, 135 (1962). The length of the C_{sp^2}–C_{sp} bond in the acetyl cation was found to be 1.378 Å by X-ray crystallography: F. P. Boer, *J. Amer. Chem. Soc.*, **90**, 6706 (1968).

crease at the cation center, but INDO calculations can underestimate such bond lengths.[24]

The electron densities (q) in the p_y orbital of X increase in the order CN < NH_2 < OH < F (Table II, quantity 4). This trend parallels the increasing electronegativity of the atom attached to C-2. For NH_2, OH, and F the greater the π_y bond order becomes, the lower the value of q_{p_y} becomes. Thus the π_y bond orders and the q_{p_y} values at X provide one view of the electron-donating ability of the substituent X.

The electron-donating ability of X is also qualitatively reflected in both the π and σ bonds between C-2 and the ring oxygens. For example, as X becomes a better electron donor toward C-2, one would expect that the demand, by C-2, for back π_y electron donation from the ring oxygens would diminish. This expectation is reflected in the C_2 ring oxygen π_y bond orders, which decrease as X is varied in the order H > CN > CH_3 ≥ F > OH > NH_2. This order suggests that NH_2 is the best electron donor *and that H, not CN, is the poorest.* The reason that CN is a better electron donator than H is revealed by examining both the σ and π framework. The σ bonds between C-2 and H (1) or CN (6) are not significantly polar (see Table II, quantity 2). Thus electron flow from H or CN to C-2 *via* the σ bond is minor.[25] However, a direct π_y interaction between C-2 and CN results in the π_y bond order of 0.359 which results from some net electron donation from CN to C-2.[26] Thus, on balance, a CN group attached directly to a charged carbon appears to be a better electron donor than hydrogen. This is further substantiated by comparing the total calculated charges at oxygen (−0.110 and −0.140 where X = H and CN, respectively). One would predict that the electron-donating ability of CN over H would even be larger comparing $^+CH_2CN$ *vs.* $^+CH_3$.[27]

Fluorine and methyl appear about equal in electron-donating ability using the C_2 ring oxygen π_y criteria. Again a dissection of the σ- and π-electron framework is instructive. Flourine is a better back π_y-electron donor. However, it simultaneously withdraws electron density from C-2 inductively *via* its C–F σ bond (*i.e.*, in Table II it can be seen that the C_2–F σ bond is highly polarized toward fluorine). The greater π_y back donation from F to C-2 slightly decreases the demand, at C-2, for π_y donation from the ring oxygens. However, the total electron density at oxygen is greater when X = CH_3 than when X = F (*i.e.*, the total charge density at the ring oxygens is −0.165 when X = CH_3 *vs.* −0.141 when X = F). This is probably due to the greater C_2–F σ polarization which, in turn, polarizes the C_2–O σ orbitals. This suggests that methyl is a slightly better overall electron donor than fluorine in 1,3-dioxolan-2-ylium ions.[28]

The polarization of the C_2–X σ bond followed the expected order based on electronegativity considerations: F > OH > NH_2 (see Table II, quantity 2). In fact, the magnitude of C–F σ-bond polarization in **3** appears comparable to that found in $^+CH_2F$,[1c,28] where no adjacent oxygen atoms are available for charge delocalization.

Other electronic effects of X show the need to simultaneously consider both the π- and σ-electron distribution. First, the total positive charge density at C-2 decreases as a function of X in the following order: F > OH > NH_2 > CN > CH_3 > H (see Figure 1). The most stabilizing substituents (*i.e.*, NH_2 and OH) do not result in the lowest positive charge density at C-2, and hydrogen gives the smallest C-2 charge density. This is a direct result of the σ-electron distribution. While both NH_2 and OH strongly back donate π_y electron density to C-2, they simultaneously withdraw C-2 electron density *via* the polarized C_2–X σ bond. Thus, the total positive charge density at C-2 increases as the number of directly bonded electronegative atoms increases. This, of course, is also true in the cation's precursor. Thus, the stability of the cation, relative to its precursor, might not be strongly influenced by this order.[7]

Comparison of Calculated Results with Experimentally Observed Properties.—Taft and Ramsey[29] calculated C⋯O π-bond orders in the range of 0.2 to 0.3 from infrared studies of $(CH_3O)_2C^+CH_3$ (C^+—O asym str, ν_{20} 1400 cm^{-1}) and $(CH_3O)_3C^+$ (1380 cm^{-1}) using $CH_3CO_2^-$ and CO_3^{2-} as models. The appropriateness of these models is a difficult question to answer definitely. From variable-temperature nmr studies[29] the energy of activation for $-OC^+$ bond rotation was found to be 11 ∓ 4 kcal mol^{-1} for $(CH_3O)_2C^+CH_3$ and a larger barrier was indicated for $(CH_3O)_2C^+H$. These values and trends are generally consistent with the INDO C_2–O π_y bond orders of 2 (0.587, X = CH_3) and 1 (0.650, X = H). Infrared studies of the C^+–O stretching region for 2,4,5,5-pentamethyl-1,3-dioxolan-2-ylium perchlorate[30] [1536 (s) and 1511 cm^{-1} (s)] as well as for 2-phenyl [1520 (s) and 1460 cm^{-1} (s)] and 2-*p*-anisyl [1460 (s) and 1435 cm^{-1} (s)] 1,3-dioxolan-2-ylium salts[31] are consistent with C^+–O π-bond orders of 0.4 or more.

Nmr spectroscopy has by far been the most important spectral method used to study 1,3-dioxolan-2-ylium cations and these studies have recently been reviewed in depth.[7] Hart and Tomalia[8-10] showed that the chemical shifts of the equivalent ring protons (sharp singlets at δ 5.59 to 4.98) for a series of 2-substituted aryl-1,3-dioxolan-2-ylium cations (IVa and b) gave a linear correlation with Hammett σ values (correlation coefficient of 0.966). A less satisfactory correlation was obtained using σ^+ values, suggesting that resonance interactions between electron-supplying substituents on the 2-phenyl ring and C-2 are not strong. In other words, resonance hybrid IVb is far more important than IVa. This agrees with the large calcu-

(24) J. A. Pople and M. S. Gordon, *J. Amer. Chem.*, **89**, 4253 (1967); and ref 1a.

(25) In the C_7–CN bond the normal polarization toward the nitrile carbon is counterbalanced by the electron demand of charged C-2.

(26) This results in a lowering of the π_y bond order in the CN bond to 0.930 *vs.* a π_x order of 0.975.

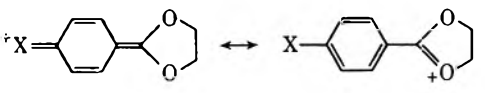
(27) From appearance potential studies the CN group has been shown to destabilize the methyl cation whereas all other functions examined, *including the NO_2 group*, stabilize methyl cations (see J. L. Franklin in "Carbonium Ions," Vol. I, G. A. Olah and P. v. R. Schleyer, Ed., Interscience, New York, N. Y., 1968, Chapter 2, pp 91–93). This is mildly suggestive that the appearance potential of CH_2CN^+ might not refer to the structure $N{\equiv}CCH_2^+$ or that this value needs to be reexamined.

(28) The ability of fluorine to back donate electron density to carbon in the fluoromethyl cation series increases as electron demand at the carbon increases. However, the total charge at fluorine in this series is approximately constant owing to an increased C→F σ polarization as the F→C π_y donation increased (see ref 1c).

(29) B. G. Ramsey and R. W. Taft, *J. Amer. Chem. Soc.*, **88**, 3059 (1966).

(30) J. A. Magnuson, C. A. Hirt, and P. J. Lauer, *Chem. Ind. (London)*, 691 (1965).

(31) J. F. King and A. D. Allbutt, *Can. J. Chem.*, **47**, 1455 (1969).



IVa IVb

lated π_y bond orders in the C_2–O bonds summarized in Table I.

It would have been extremely interesting to see if a linear correlation existed between the methylene proton nmr chemical shifts and the σ^+ (or σ) constants of H, CH_3, F, NH_2, OH, and CN in cations **1**–**6**. However, a thorough examination of the literature reveals that the nmr spectra of **1**, **3**, **4**, and **6** have never been recorded and no evidence for the preparation of **3**, **4**, or **6** has appeared.[32] However, the 2-diethylamino[9,10] and the 4,4-dimethyl[33] analogs of **4** and the 4,4-dimethyl[33] analog of **1** have been prepared, and these serve as models in order to compare the nmr δ values with the calculated total positive charge densities at the methylene protons. For those examples where these calculated charge densities could be compared to the measured chemical shifts, a linear correlation exists. As the positive charge on the methylene hydrogens increased, the δ values became increasingly deshielded. The only exception found was ion **5**, where X = OH. The point for **5** fell off the line on a plot of δ *vs.* the total charge density at the methylene protons. The measured value of δ for **5** was shielded about 34 Hz more than expected from the plot. This unexpected phenomenon has been noted twice before. Hart and Tomalia found that the methylene protons of **5** were more deshielded than those of **2** (X = CH_3) and several other 2-alkyl and 2-vinyl substituted cations as well.[9,10] Taft and Ramsey reported that the CH_3O protons, in the analogous acyclic series, were more deshielded in the trimethoxy cation than in the dimethoxymethyl cation. To quote Hart and Tomalia,[9] "a good explanation for these observations is not immediately obvious." However, given this linear correlation of δ *vs.* calculated charge density, one predicts that the methylene protons of **3** (X = F) should appear more deshielded than any other member of this series (δ 630–640 Hz downfield from TMS). The methylene protons of **6** (X = CN) should appear at δ 550–560 Hz.[34]

In conclusion, the INDO calculations have provided a conceptual view of the electron distribution (both π and σ) and the geometry of a series of 2-substituted 1,3-dioxolan-2-ylium ions. While the exact quantities of the calculated properties are subject to the usual criticisms,[19,20] the trends within the series should be realistic.

Registry No.—**1**, 37037-20-0; **2**, 18948-87-3; **3**, 37406-82-9; **4**, 37161-34-5; **5**, 18747-87-0; **6**, 37161-36-7.

(32) Cation **1** was prepared by treating 1,3-dioxolane with trityl tetrafluoroborate by Meerwein, *et al.*, but nmr spectra were not recorded; see H. Meerwein, V. Hederich, H. Morschel, and K. Wunderlich, *Justus Liebigs Ann. Chem.*, **635**, 1 (1960).

(33) C. U. Pittman, Jr., and S. P. McManus, *Tetrahedron Lett.*, 339 (1969).

(34) Experimental studies to test these predictions for **3** and **6** will be performed by S. P. McManus, C. U. Pittman, Jr., *et al.*

Dehydrocyanation of Dinitriles. Preparation of 1-Cyclobutenecarbonitrile by Direct Dehydrocyanation of 1,2-Cyclobutanedicarbonitrile

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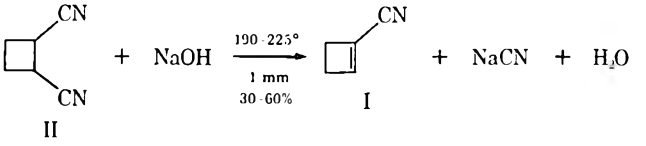
Contribution No. 1961 from the Central Research Department, E. I. du Pont de Nemours and Company, Wilmington, Delaware 19898

Received August 25, 1972

1-Cyclobutenecarbonitrile (I) was synthesized in high purity and good yield directly from 1,2-cyclobutanedicarbonitrile. The chemistry of I was investigated on a comparison basis with acrylonitrile. Dehydrocyanation with alkali appears to have general utility for double-bond formation.

1-Cyclobutenecarbonitrile (I) has been prepared by several routes,[1,2] but was not readily available in the required purity for our polymer studies.[3] An unusually facile, good-yield synthesis of high-purity I was devised from the readily available 1,2-cyclobutanedicarbonitrile (II) isomer mixture (acrylonitrile cyclodimer) by contacting the latter in the vapor phase at 190–225° with any of a number of granular bases (Table I). The crude product I contains only traces of starting material and thermal rearrangement product, 2-cyanobutadiene (III),[4] and needs only be purified by simple distillation for use as a high-grade monomer.



II I

This simple and direct synthetic process was almost overlooked because dehydrocyanations are not commonly employed in organic synthesis. Apparently, cyanide ion is not a particularly good "leaving group". Indeed, in seeking routes to I, we took a more classical approach and prepared *cis*- and *trans*-2-chlorocyclobutanecarbonitrile by a laborious literature procedure[5] in order to study their dehydrochlorination. The reaction of either isomer proceeds well at 110–115° to give I in good yield. Substantial improvements in the chloro-

(1) R. Tietz and W. G. Kenyon, U. S. Patent 3,468,861 (1969).

(2) D. M. Gale, *J. Org. Chem.*, **35**, 970 (1970).

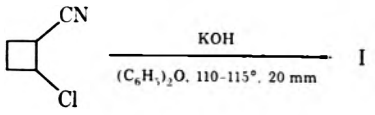
(3) Unpublished work.

(4) Kinetics of the rearrangement have been published: S. N. Sarner, D. M. Gale, H. K. Hall, Jr., and A. B. Richmond, *J. Phys. Chem.*, **76**, 2817 (1972). Some of the material presented here was issued in the form of a patent: D. M. Gale, U. S. Patent 3,657,313 (1972).

(5) W. A. Nevill, D. S. Frank, and R. D. Trepka, *J. Org. Chem.*, **27**, 422 (1962). These materials can also be prepared directly by cross-cycloaddition of vinyl chloride and acrylonitrile, but in low conversion: D. M. Gale, U. S. Patent 3,642,859 (1972).

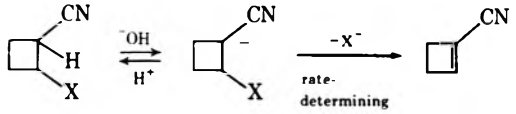
TABLE I
REACTION OF 1,2-CYCLOBUTANEDICARBONITRILE VAPOR WITH VARIOUS FORMS OF NaOH AT 200–225°

Base form	% Converted to I
Soda lime, 8 mesh	32
Soda lime, 20 mesh	42
Sodium hydroxide pellets	40
Ascarite (90% NaOH on asbestos)	59



nitrile synthesis were discovered, but even so the preparation of large quantities of I was time consuming.

Dehydrochlorination, then, proceeded to a similar conversion at a lower temperature than dehydrocyanation, implying a faster rate for the removal of HCl. A carbanion mechanism is called for in each case because each process works well with either *cis*- or *trans*-nitrile starting material.



X = CN or Cl
cis or trans isomer

The loss of X^-, therefore, can be assumed to be rate determining. This mechanism predicts that bases weaker than hydroxide will remove HCN at elevated temperatures as long as anion formation is feasible at that temperature. Furthermore, if the base is sufficiently weak not to react with HCN, a catalytic process should be possible; thus

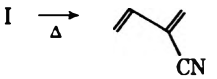
$$\text{II} + \xrightarrow[\Delta]{\text{basic catalyst}} \text{I} + \text{HCN}$$

To this end, we studied the reaction of II in the vapor phase with a number of MgO–ZnO catalysts (Table II).

TABLE II
REACTIONS OF II WITH VARIOUS BASIC CATALYSTS

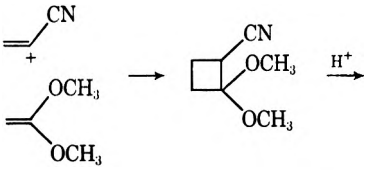
Catalyst	Temp, °C	Pressure, mm	Convn to I, %	Convn to III, %
ZnO:MgO (1:4)	298–303	0.6–0.9	23.7	4.9
ZnO:MgO (3:1)	300	0.5–2.0	12.5	3.3
ZnO:MgO (1:1)	300	0.5–2.0	16.7	3.0

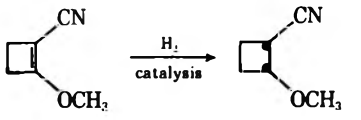
Although I is formed to some extent at 225°, best conversions were generally obtained at about 300°. The higher temperatures required may reflect greater difficulty in forming the anion or difficulty in freeing the base from HCN. Loss of CN^- is probably no longer rate determining. Because of the higher temperatures generally employed for the catalytic process, I was usually contaminated with III; the catalytic dehydrocyanation, therefore, was less desirable as a laboratory process than the stoichiometric dehydrocyanation. The conversion of I to III occurs readily with heat alone.[4] The formation of III from II over basic catalysts at 400° has been reported.[6] The true catalytic nature of the second II to I process was demonstrated by quantitative analysis of HCN corresponding to II converted with the 1:3 MgO–ZnO catalyst.



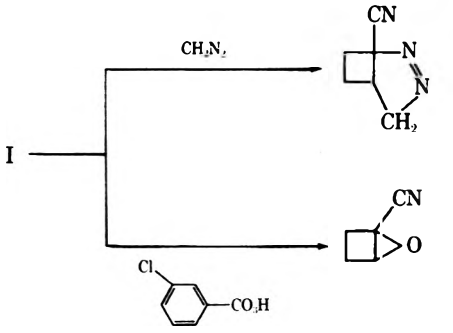
III

Chemistry of I.—It was of interest to briefly examine the chemistry of I because of its structural relationship to acrylonitrile (AN). Like AN, compound I underwent the Ritter reaction with *tert*-butyl alcohol, addition of methoxide ion, and addition of a mercaptal radical and bromine. In the case of methoxide addition, the trans isomer was favored over the cis by 8:1. Stereochemical assignments were made by stereospecific synthesis of *cis*-2-methoxycyclobutanecarbonitrile as well as by spectral evidence.





Compound I also underwent two reactions not known for AN.



Direct epoxidation was also demonstrated for methacrylonitrile; this suggests that the presence of an α hydrogen may explain the inability of AN to be directly epoxidized. The 1,3 cycloaddition of diazomethane probably to form an azo intermediate (characterization incomplete owing to the explosive nature of the material) perhaps occurs with AN, but again due to the presence of an α hydrogen the isolated product is 2-pyrazoline-3-carbonitrile.[7]

Dehydrocyanation *vs.* Dehydrochlorination in Other Systems.—In order to determine the possible general utility of dehydrocyanation, we studied the elimination of HX in several representative systems.

Dehydrochlorination, well known for its utility in double-bond formation, occurred in both reactions type A and B, although cyclobutanecarbonitrile (reaction B) was formed only in trace quantities (Table III). Dehydrocyanation, on the other hand, worked well with only reaction C, another example of utilizing a vicinal dinitrile starting material. These results sug-

(6) Grasselli, *et al.*, U. S. Patent 3,347,902 (1967).

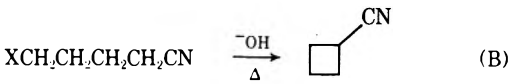
(7) Terent'ev and Gurvich, *Sb. Statei Obshch. Khim., Akad. Nauk SSSR*, 1, 404 (1953); see also "The Chemistry of Acrylonitrile," 2nd ed, American Cyanamid Co., New York, N. Y., 1959.

TABLE III
YIELD OF NITRILES FORMED BY DEHYDROCHLORINATION OR DEHYDROCYANATION WITH BASE

Process	Reaction conditions	Base employed	Yield of nitrile, %
A, X = Cl	115°, boiling toluene	85% KOH	40; recovered some starting material
A, X = CN	225°, 1 mm	Ascarite	None, recovered starting material
A, X = CN	225°, 250°, 300°, 1 mm	Soda lime	Trace
B, X = Cl	225°, 1 mm	Ascarite	Trace
B, X = CN	225°, 1 mm	Ascarite	None
C	250°, 1 mm	Ascarite	70; recovered some starting material

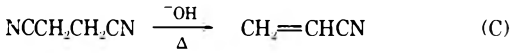
(A)

X = CN, Cl



(B)

X = CN, Cl



(C)

gest that dehydrocyanation might be general for vicinal double bond formation, and the method of choice only when warranted by starting material considerations.

Experimental Section

Cyclobutenecarbonitrile (I). A. By Dehydrocyanation of 1,2-Cyclobutanedicarbonitrile (II) with Ascarite.—A vertical quartz tube 50 cm long and 2.5 cm in diameter, packed 20 cm of its length with Ascarite, was heated with a 30-cm-long cylindrical furnace to 200° for 2 hr in an air stream until most of the water and absorbed gases were removed. The temperature was maintained at 225° and was recorded by a thermocouple well inserted at the top of the bed. The dinitrile II (10 g) was added in a melt dropwise over 2 hr and product I was collected in a series of traps cooled in solid carbon dioxide–acetone. The entire system was evacuated during the reaction at the best vacuum that could be maintained by an efficient oil pump (0.5–2 mm). A 59% conversion to I was obtained (determined by quantitative gc analysis on a silicone gum nitrile column at 150° or with a butanediol succinate column at 100°). An average contact time of II was about 0.41 sec. Trap-to-trap distillation of the contents (after separating the layers) of the traps gave 99.5% pure I (55% yield not corrected for II left in the tube).

Table I gives results with other bases treated as above. In each case, I was further purified by distillation in a low temperature (Dry Ice cooled) Vigreux column, bp 40° (20 mm). A free-radical inhibitor such as hydroquinone or phenothiazine was added to the pot to prevent polymerization.

Scale-up of the above procedure was accomplished by using a horizontally fixed 7.5-cm-diameter quartz tube (reactor) connected by an elbow joint to a vertical 2.5-cm quartz tube (vaporizer). Heating tapes were used to ensure the absence of cool spots between two split tube furnaces surrounding the tubes. Using predried 12-mesh soda lime (860 g), 133 g of II added over 24 hr at a reactor tube temperature of 194–197° (0.4–14 mm) led to 30.8 g of 95% pure I and 56 g of recovered II (33.5 g of II thus left in the reactor unaccounted for). Similarly, 860 g of Ascarite was used to form the reactor bed; 71 g of II was added at 197° (0.4–2.0 mm) over 13 hr, giving 24.2 g of crude I and 10 g of recovered II. Crude I (95 g) was collected from a number of these scale-up runs and distilled through a low-temperature still. Pure I (>99.5%) weighing 72.1 g was obtained. Isolated yields (corrected for recovered II) for both soda lime and "Ascarite" were therefore about 39%.

As noted in ref 1, pure I had a refractive index $n^{25}D$ of 1.456, a characteristic infrared absorption at 2240 cm^{-1} (CCl_4), and nmr (CCl_4) bands at τ 7.47, 7.40, 7.36 (total area 2), 7.34, 7.23, 7.17, 7.21 (total area 2), and 3.32, 3.30, and 3.29 (total area 1); our material also analyzed properly for C_5H_5N.

Anal. Calcd for C_5H_5N: C, 75.92; H, 6.37; N, 17.71. Found: C, 75.38; H, 6.42; N, 17.38.

B. By Dehydrochlorination of 2-Chlorocyclobutanecarbonitrile.[5]—A round-bottomed flask (three-necked and thermometer well) was fitted with a pressure-equalizing dropping funnel, powerful motor-driven stirrer, thermometer, and a gas exit connected *via* rubber tubing (sufficient in length to be clamped by a hemostat), to a series of traps (Dry Ice and liquid N_2) containing a trace of hydroquinone. The gas exit (frequently called "nitrogen inlet tube") and traps were washed with concentrated HCl and with acetone and thoroughly dried before use; the rubber connecting tubing was washed with 3 *N* HCl and acetone and dried. The system was dried under vacuum and charged with 6.0 g (0.11 mol) of 85% KOH pellets and 50 ml of diphenyl ether (nitrogen atmosphere). The dropping funnel was charged with 5.8 g (0.05 mol) of the chloronitriles (99% cis, 1% trans), and the system was evacuated to 20 mm. The pot was heated with stirring to 115° to "liquefy" the KOH and the chloronitrile was added dropwise at 110–115° over 30 min. Judicious application of heat from a mantel and cooling from a water bath, as well as occasional application of the hemostat clamp, were necessary to moderate the reaction and prevent flooding over into the product collection traps. When the addition was complete, the pressure was slowly reduced to 0.3 mm (occasional clamping required) to strip off the product. The pot temperature dropped but was maintained at 50° with a hot-water bath for 1 hr. The contents of the Dry Ice trap were distilled (at 0.3 mm) into an acid-washed trap (containing hydroquinone). Compound I (2.3 g, 58%) thus obtained as shown to be gc pure and had an infrared spectrum identical with that of an authentic sample. The *trans*-2-chloronitrile reacted similarly to give I in 60–70% yields.

Ritter Reaction of I with *tert*-Butyl Alcohol.—A 10.1-g sample of 98% H_2SO_4 was added over 10 min to 7.9 g (0.1 mol) of I (97% pure), 7.4 g (0.1 mol) of dry *tert*-butyl alcohol, and 50 ml of glacial acetic acid at 25–30° with stirring. About 5 min after the addition, the temperature rose to 42° and an H_2O bath was used to keep the temperature below 40° for 45 min. The reaction mixture was poured onto 200 g of ice and the white precipitate which formed was collected on a filter, washed with H_2O and pentane, and air dried, mp 125°. The nmr spectrum showed $C(CH_3)_3$ at τ 8.68, $-CH_2CH_2-$ and an A_2B_2 pattern at 7.4 and 7.6, NH at 7.14, and $-CH{=}CCO$ at 3.5 (triplet, J = 0.6 Hz) required by unsaturated amide structure. Ir showed NH stretch at 3300 cm^{-1} and no C≡N; yield 7.0 g (46%). Uv showed λ_{max}^{EtOH} 215 mμ (ε 1090).

Anal. Calcd for $C_9H_{15}NO$ (153.22): N, 9.15. Found: N, 8.85.

Reaction of I with *tert*-Butyl Mercaptan.—A solution of 7.9 g of CCB, 1.0 g of "Vazo" (azobisisobutyronitrile), and 20 ml of *tert*-butyl mercaptan were refluxed for 3 hr, let stand overnight, and distilled through a spinning band column, giving 7.3 g (43%) of thioether, bp 58–80° (0.6 mm). Nmr showed $-C(CH_3)_3$ absorption at τ 8.8, $-CH_2CH_2$ at 7.7, and two >CH– protons at 6.3. Ir showed CH at 3.39, 3.42, and 3.50 μ, C≡N at 4.49 μ, and $-ClCH_3$ at 7.20 and 7.34 μ. Raman showed bands at 600 (C–S) and 2400 cm^{-1} (C≡N). The mass spectrum showed a parent at *m/e* 169 and a base peak at *m/e* 57 for $-C(CH_3)_3$.

Anal. Calcd for $C_9H_{15}SN$ (169.29): C, 63.85; H, 8.93; N, 8.28; S, 18.94. Found: C, 63.77; H, 8.91; N, 8.46; S, 19.22.

2-Methoxycyclobutanecarbonitriles. A. From I with Sodium Methoxide.—A solution of 3.95 g (0.05 mol) of I in 7 ml of methanol was added to a stirred solution of 5.4 g (0.1 mol) of sodium methoxide in 25 ml of dry methanol over 0.5 hr. The reaction mixture was stirred overnight at room temperature, cooled in an ice bath, and diluted with 100 ml of H_2O; ether extraction followed by washing (H_2O) and drying of the ether extracts led on evaporation to an 8:1 trans to cis mixture of methoxynitriles. Spinning-band distillation afforded 2.9 g (51%) of purified product, bp 44–49° (3 mm). The stereochemical assignments were made by direct comparison with the cis isomer from the catalytic hydrogenation of 2-methoxycyclobutenecarbonitrile (see below). Nmr showed –CHO at τ 5.9, –CHCN at 7.0, $-OCH_3$ at 6.64, and $-Cl_2Cl_2$ at 7.9 for the trans

isomer. The ir spectrum showed CH at 3.33, 3.40, 3.47, and 3.53 μ, C≡N at 4.47 μ, and CO– at 8.84 μ.

Anal. Calcd for C_6H_9ON (111.14): C, 64.84; H, 8.16; N, 12.61. Found: C, 64.37; H, 8.07; N, 12.62.

B. **By Hydrogenation of 2-Methoxycyclobutenecarbonitrile.**—Four Carius types were each loaded with 0.4 g of phenothiazine, 37.5 ml of acrylonitrile, and 25 ml of ket deneimethyl acetal. The tubes were heated to 150° for 24 hr. The contents of the tubes were combined and distilled into a Dry Ice–acetone cooled trap at full vacuum using a heat gun. The volatiles were distilled through a 15-in. spinning-band column to give 58 g of 2,2-dimethoxycyclobutanecarbonitrile,[8] bp 68° (2.5 mm). The liquid could be induced to crystallize by scratching, mp 31–32°, ir 3.50, 4.45, 8–10 μ.

Anal. Calcd for $C_7H_{11}O_2N$: C, 59.55; H, 7.85; N, 9.92. Found: C, 59.63; H, 7.72; N, 10.31.

A 13.3-g sample of 2,2-dimethoxycyclobutanecarbonitrile was heated in the pot of a spinning band column with *ca.* 1 g of *p*-toluenesulfonic acid (not hydrate; dried over weekend at 300 mm and 80°) under vacuum (0.5 mm). Two fractions (40 and 70–100°) were collected as well as two traps (ice, Dry Ice). The low-boiling fraction and the traps were combined and redistilled to give 4.5 g (44%) of 2-methoxycyclobutenecarbonitrile (>99% pure),[8] bp 32–40° (0.3 mm). The nmr spectrum ($CDCl_3$) showed $-OCH_3$ absorption at τ 6.00 and an A_2B_2 pattern from the ring methylenes centered at 7.5. The ir spectrum showed a –CN band at 2225 and enol ether double bond at 1645 cm^{-1}. The uv spectrum showed $\lambda_{max}^{CH_3CN}$ 232 mμ (ϵ 10,000). The mass spectrum showed a base peak for the parent at *m/e* 109.

Anal. Calcd for C_6H_7NO (109.13): C, 66.03; H, 6.46; N, 12.84. Found: C, 65.33; H, 6.62; N, 12.60.

The same reaction could be accomplished by heating a mixture of 58 g of cyano ketal and 58 g of phosphorus pentoxide under full vacuum (*ca.* 0.3 mm) in a short-path still. The volatiles were distilled through a spinning-band column to give 17.8 g (40%) of product and 13.1 g (22%) of recovered starting material.

A 3.6-g sample of the cyclobutane (prepared by the P_2O_5 route), 0.5 g of 5% $Pd/CaCO_3$, and 50 ml of methanol were hydrogenated in a Parr apparatus until H_2 uptake was 105% of theory. Distillation of the crude product, obtained by removing catalyst and concentration, gave 3.8 g (quantitative) of *cis*-2-methoxycyclobutanecarbonitrile, bp 52–60° (1.25–1.5 mm). The nmr spectrum ($CDCl_3$) showed $-OCH_3$ at τ 6.67, >CHCN at 6.6, $>CHOCH_3$ at 6.1, and ring CH_2 at 7.8. The infrared spectrum showed strong –C≡N at 2250 and $-OCH_3$ at 2850 cm^{-1}. The mass spectrum showed a base peak at *m/e* 58, $CH_2{=}CH{-}(OCH_3)^+$, and a large fragment at *m/e* 83 P – (C_2H_4).

Anal. Calcd for C_6H_9NO (111.14): C, 64.84; H, 8.16; N, 12.61. Found: C, 64.29; H, 8.29; N, 12.23.

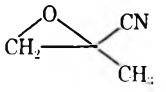
Reaction of I with Diazomethane.—*Caution!* A 7.9-g (0.1 mol) solution of I in ether was treated with excess dilute ethereal diazomethane. The disappearance of I was followed by gc. Very little I remained after about 8 hr. The ether solution was dried over $MgSO_4$ and the ether was evaporated. The oil obtained (10.7 g) had a nitrile band in the ir at 2250 cm^{-1}. The nmr spectrum showed an AB doublet of doublets at τ 5.16 and 5.25 (J = 14 Hz), the high-field proton split further (J = 1.5 Hz) by the methine proton ($\tau \approx 7.0$). Additional absorption (area 4) was found at τ 6.5–9.0 for the ethylene bridge. *The oil detonated on attempted distillation*, suggesting the azo structure.

1-Cyanobutenecarbonitrile Epoxide.—A suspension of 20 g of 85% *m*-chloroperbenzoic acid 7.9 g (0.1 mol) of I, and 100 ml of methylene chloride was stirred at room temperature for 3 months. The solution was filtered and washed with 5% $NaHCO_3$ solution (until basic), dilute $NaHSO_3$ (until no peroxide present), and then with brine and H_2O, then dried over $MgSO_4$. Concentration and distillation (spinning band) at 58° (12 mm) led to 0.95 g (10%) of cyano epoxide. The ir spectrum had –CN at 2250, bands at 1245, 1145, and 850 cm^{-1} for –OC–, and was blank in the 6-μ region. The nmr spectrum showed 1 H at τ 5.62 (epoxide H) split further and a very complex A_2B_2 pattern centered at 8.0 for $-CH_2CH_2-$. The mass spectrum showed a peak at *m/e* 95 for the parent ion, and peaks at *m/e* 94 (M – H) and 67 (M – C_2H_4).

Anal. Calcd for C_5H_5ON (95.11): C, 63.1; H, 5.30; N, 14.73. Found: C, 62.69; H, 5.36; N, 14.74.

The above procedure was improved to 30% yield by refluxing the reagents for 24 hr (60% converted), concentrating the $CHCl_3$ filtrate, and collecting the volatile from this filtrate into a Dry Ice trap by pumping under reduced pressure. The volatiles were then distilled directly, avoiding a wet work-up.

Methacrylonitrile Epoxide.—A solution of 30 g of *m*-chloroperbenzoic acid (85%), 100 ml of ethanol-free $CHCl_3$, and 7 g of methacrylonitrile was heated at reflux for 47 hr (precipitate formed). The solution was cooled, most of the solid was removed by filtration, and the filtrate was concentrated. The volatiles were distilled into a Dry Ice trap and redistilled through a small spinning band column. Two cuts, bp 46–48° (12 mm), were obtained (3.4 g) contaminated by chlorobenzene (gc yield 2.2 g, 26%). A sample was purified by preparative gc and showed the following nmr spectrum: AB quartet at τ 6.87, 7.11 (J = 11 Hz split further) for



and a singlet (split further) at τ 8.4 for the methyl group. The mass spectrum was consistent with a monomeric structure.

Anal. Calcd for C_4H_5NO (83.10): C, 57.81; H, 6.06; N, 16.84. Found: C, 57.84; H, 6.20; N, 17.04.

1,2-Dibromo-1-cyclobutanecarbonitrile.—To a magnetically stirred solution of 7.9 g (0.1 mol) of I (97% pure) in 50 ml of CCl_4 at room temperature was added over 2 hr a solution of 16 g (0.1 mol) of Br_2 in 100 ml of CCl_4. An induction period was noted with only little discharge of Br_2 color during the first 0.5 hr. The Br_2 color could be discharged completely, however, during the remaining 1.5 hr of addition. Only 95% of the Br_2 was added; no more color discharged. The CCl_4 was removed under reduced pressure and the liquid residue was distilled through a small spinning band still. The bromide, 20.0 g (84%), boiled at 63° (0.4 mm). Ir analysis showed strong C≡N absorption but no saturation. The nmr spectrum showed $-CH_2CH_2-$ at τ 6.6–7.6 and >CHBr at τ 5.15.

Anal. Calcd for $C_5H_5Br_2N$ (238.93): C, 25.14; H, 2.11; Br, 66.86; N, 5.86. Found: C, 25.74; H, 2.45; Br, 66.67; N, 5.72.

Registry No.—I, 23519-88-2; II, 3396-17-6; III, 5167-62-4; *cis*-2-chlorocyclobutanecarbonitrile, 36178-64-0; *trans*-2-chlorocyclobutanecarbonitrile, 36178-63-9; *tert*-butyl alcohol, 75-65-0; *tert*-butyl mercaptan, 75-66-1; sodium methoxide, 124-41-4; *cis*-2-methoxycyclobutanecarbonitrile, 37445-36-6; *trans*-2-methoxycyclobutanecarbonitrile, 37445-37-7; 2,2-dimethoxycyclobutanecarbonitrile, 37447-58-8; 2-methoxycyclobutenecarbonitrile, 37447-59-9; cyclobutene, 822-35-5; diazomethane, 334-88-3; 1-cyclobutenecarbonitrile epoxide, 37447-60-2; methacrylonitrile epoxide, 37447-61-3; 1,2-dibromo-1-cyclobutanecarbonitrile, 37447-62-4; *m*-chloroperbenzoic acid, 937-14-4.

(8) We are indebted to Dr. J. B. Sieja for the preparation of this material.

The Reaction of a Phosphorus Ylide with Aroyl Cyanides

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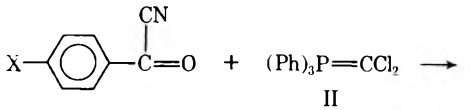
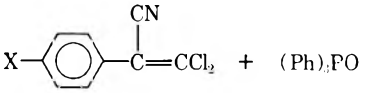
The reaction of aroyl cyanides with dichloromethylenetriphenylphosphorane, prepared *in situ* from carbon tetrachloride and triphenylphosphine, provides a convenient synthesis of 2-aryl-3,3-dichloroacrylonitriles. Aroyl cyanides studied in this reaction were benzoyl, 4-methylbenzoyl, 4-chlorobenzoyl, 4-methoxybenzoyl, and 4-nitrobenzoyl cyanide. Only 4-nitrobenzoyl cyanide failed to yield the desired product.

The Wittig reaction has provided an exceptionally versatile technique for the preparation of olefinic compounds. The literature bears proof of this with numerous examples of reactions of phosphorus ylides with aldehydes, ketones, acid chlorides, esters, anhydrides, and nitriles.[1] Except for our previous report,[2] there are no examples of the reaction phosphorus ylides with acyl cyanides. In particular, the reaction of dichloromethylenetriphenylphosphorane (II) with aroyl cyanides (I) offers a unique synthesis of 2-aryl-3,3-dichloroacrylonitriles (III). Previous methods of synthesis of β-halogenated acrylonitriles have not been particularly suitable for the preparation of α-alkyl or aryl derivatives, as most of these procedures start with the corresponding acrylamide or acrolein derivative, which are equally unavailable.[3]



II

Ia, X = H
b, X = CH_3
c, X = Cl
d, X = CH_3O
e, X = NO_2



III

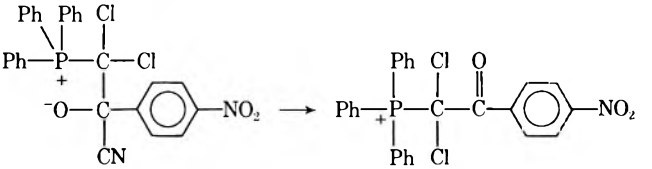
Dichloromethylenetriphenylphosphorane (II), synthesized by the reaction of carbon tetrachloride with triphenylphosphine[4] or by the decomposition of chloroform by potassium *tert*-butoxide in the presence of triphenylphosphine,[5] has been shown to react with representative aldehydes and ketones.[6] Except for a recent communication by Raulet and Levas,[7] the reactions of II have not been studied beyond the initial reports. In these most recent findings it was shown that II reacted preferentially with the ketone carbonyl of ethyl pyruvate to give ethyl 3,3-dichloro-2-methylacrylate.[7]

Results and Discussion

The 2-arylacrylonitriles (III) were obtained by mixing the aroyl cyanide (0.50 mol) and triphenylphosphine (1.0 mol) in a large excess of dry carbon tetrachloride under an inert atmosphere and then heating the mixture to reflux for 2–4 hr or stirring at room temperature for 48–72 hr. Work-up of the reaction mixture was initiated by the addition of ligroin to precipitate most of the triphenylphosphine oxide. The filtrate was concentrated and the residue was purified by distillation or recrystallized from a suitable solvent. Products IIIa, b, and d were obtained in 60–70% yield. Compound IIIc was obtained in only 20% yield; however, higher yields are undoubtedly possible.

Although most of the reaction mixtures darkened considerably as the reaction proceeded, the mixture of 4-nitrobenzoyl cyanide (Ie), carbon tetrachloride, and triphenylphosphine became black immediately at room temperature. Reaction conditions were varied in an attempt to obtain a product from this reaction; however, only tars resulted. It was apparent from several tests that a highly colored reaction was occurring between triphenylphosphine and Ie, even in the absence of carbon tetrachloride. In an attempt to avoid this side reaction a solution of triphenylphosphine and carbon tetrachloride was heated to 60° for 2 hr before Ie was added. This procedure also yielded only tarry by-products.

The failure of this reaction to yield the desired product is puzzling, since II has been shown to react smoothly with 4-nitrobenzaldehyde to give an 83% yield of 1,1-dichloro-2-(4-nitrophenyl)ethylene.[6] Two possible side reactions which may account for the absence of the desired product are a reduction of the nitro group by II[8] or by the loss of cyanide ion from the intermediate betaine to give an acylated phosphonium salt. This latter reaction path is not completely unexpected, since acyl chlorides are known to react with phosphorus ylides to form phosphonium salts similar to V.[9]



IV V

Several of the prominent bonds of the infrared spectra of the compounds prepared in this study are given in Table I, as this information does not appear in the literature. The most notable feature of the infrared spectra of the aroyl cyanides is the unexpected shift of the nitrile stretching frequency to the 2227–2218-cm^{-1} region typical of α,β-unsaturated alkyl or aryl nitriles. The intensity of the nitrile absorption was quite strong,

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(2) R. L. Soulen, D. B. Clifford, F. F. Crim, and J. A. Johnston, *J. Org. Chem.*, **36**, 3386 (1971).
(3) Reference 2 and references cited therein.
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(6) A. J. Speziale and A. W. Ratts, *ibid.*, **84**, 854 (1962).
(7) C. Raulet and E. Levas, *C. R. Acad. Sci., Ser. C*, **270**, 1467 (1970).
(8) J. P. A. Castrillon and H. Szmant, *J. Org. Chem.*, **30**, 1338 (1965).
(9) H. J. Bestmann and B. Arnason, *Chem. Ber.*, **95**, 1513 (1962).

TABLE I
INFRARED SPECTRA OF AROYL CYANIDES AND 3,3-DICHLORO-2-ARYLACRYLONITRILES

Compd	Frequency, cm^{-1} ν_{CN}	$\nu_{C=O}$	$\nu_{C=C}$	$\nu_{=CCl}$
Ia	2220	1680		
Ib	2225	1665		
Ic	2227	1680		
Id	2218	1675		
Ie	2225	1683		
IIIa	2227		1564	926
IIIb	2222		1609	926
IIIc	2220		1592	925
IIId	2217		1603	936

unlike most nitriles bearing oxygen on the α carbon.[10] The carbonyl absorption appeared as a strong band in the 1680-cm^{-1} region characteristic of an α,β-unsaturated ketone and 30–100 cm^{-1} below the region typical of aryl esters and aroyl halides.[10] The nitrile and geminal dichlorovinyl stretching frequency of the acrylonitriles III showed only slight influence from the para substituent, shifting some ± 6 cm^{-1} from the region 2222 and 932 cm^{-1}, respectively. By contrast, the olefinic stretching band appeared as a strong band between 1564 and 1609 cm^{-1}.

The reaction of ylide II with aliphatic acyl cyanides under the conditions used in this study gives very low yields of the desired coupled products. The appearance of resinous products and the odor of hydrogen cyanide tend to indicate that aldol type reactions are occurring owing to acidic conditions of the reaction media. Aldol condensations in the Wittig reaction of aliphatic aldehydes have been reported previously owing to the presence of strong base.[11] We are attempting to avoid this side reaction by adding reagents to maintain essentially neutral conditions during the course of the reaction.

Experimental Section

All melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Elemental analyses were performed by Huffman Laboratories, Wheatridge, Colo. A Beckman IR-8 was used to obtain the infrared spectra, which were calibrated at 2849.9 and 1601.0 cm^{-1} by a polystyrene film. All ylide reactions were carried out under a dry nitrogen atmosphere, until an infrared spectrum of an aliquot showed no carbonyl absorption.

Aroyl Cyanides.—The following aroyl cyanides were prepared by known literature procedures: benzoyl cyanide, bp 209–210° (lit.[12] bp 208–209°); 4-methylbenzoyl cyanide, mp 49–49.5° (lit.[13] mp 50–52°); 4-methoxybenzoyl cyanide, mp 58–60° (lit.[13] mp 58–59°); 4-chlorobenzoyl cyanide, mp 40–41.5° (lit.[14] mp 41–42.5°); 4-nitrobenzoyl cyanide, mp 115–117° (lit.[15] mp 116°). Of the various procedures reported for the preparation of aroyl cyanides, that given by Asinger, *et al.*,[13] affords the highest yields and is recommended. The addition of an inert solvent, such as *o*-xylene or *o*-dichlorobenzene, offers the advantage of moderating the reaction and permitted easy separation of the product from the cuprous salts. Subsequent removal of the solvent by distillation or recrystallization presented no difficulty.

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(15) A. Dornow and H. Grabhöfer, *Chem. Ber.*, **91**, 1824 (1958).

3,3-Dichloro-2-phenylacrylonitrile (IIIa).—Into a three-necked flask fitted with condenser, drying tube, thermometer, and nitrogen inlet was added 500 ml of dry carbon tetrachloride, 202 g (0.770 mol) of triphenylphosphine, and 50.5 g (0.385 mol) of Ia. The reaction mixture was stirred (magnetic stirrer) at room temperature for 65 hr and then 600 ml of ligroin (bp 63–75°) was added. A yellow precipitate of triphenylphosphine oxide was removed and the filtrate was concentrated under reduced pressure. Additional precipitate was removed and then the liquid residue was quickly distilled at 0.5 mm. The distillate was carefully refractionated, yielding 50.3 g (67%) of IIIa, bp 92–94° (0.4 mm). The previously reported[2] boiling point should read bp 101–104° (1.0 mm). The ir spectrum of IIIa was identical with that of the known compound.[2]

3,3-Dichloro-2-(4-methylphenyl)acrylonitrile (IIIb).—In a manner similar to that described above, 45 ml of dry CCl_4, 18.4 g (0.070 mol) of triphenylphosphine, and 5.0 g (0.0345 mol) of Ib were mixed and heated to reflux (60°) for 2.5 hr. After cooling to room temperature, 90 ml of ligroin was added and the precipitate of triphenylphosphine oxide was removed. The precipitate was washed with 100 ml of ether and the filtrate was concentrated under reduced pressure. The residue was added to the liquid residue obtained from the concentration of the CCl_4/ligroin filtrate and distilled through a short-path distillation apparatus, giving 5.0 g (68%) of a slightly yellow product, bp 150° (1.25 mm). A second distillation gave colorless IIIb, bp 98° (0.6 mm), $n^{25}D$ 1.5895.

Anal. Calcd for $C_{10}H_7Cl_2N$: C, 56.63; H, 3.33; N, 6.60; Cl, 33.44. Found: 56.86; H, 3.33; N, 6.51; Cl, 33.79.

3,3-Dichloro-2-(4-chlorophenyl)acrylonitrile (IIIc).—Dry CCl_4 (36 ml), 15.8 g (0.060 mol) of triphenylphosphine, and 5.0 g (0.030 mol) of Ic were mixed, giving an immediate yellow-colored solution. After stirring overnight at room temperature the mixture was heated to reflux for 4 hr, where the solution darkened rapidly. Ligroin (55 ml) was added on cooling to room temperature and a gummy solid was filtered off. The solid was washed with an additional 50 ml of hot ligroin and then the combined filtrates were treated with decolorizing charcoal and concentrated under vacuum. The yellow-orange residue was recrystallized from ligroin, decolorized again from methanol, and then recrystallized twice from anhydrous methanol to give 1.4 g (20%) of colorless crystals of IIIc, mp 84.5–85.0°.

Anal. Calcd for $C_9H_4Cl_3N$: C, 46.49; H, 1.73; Cl, 45.75; N, 6.02. Found: C, 46.56; H, 1.67; Cl, 45.95; N, 5.96.

3,3-Dichloro-2-(4-methoxyphenyl)acrylonitrile (IIId).—In a manner similar to that described for the preparation of IIIc, 32.6 g (0.124 mol) of triphenylphosphine, 10.0 g (0.062 mol) of Id, and 80 ml of CCl_4 gave 8.5 g (60%) of light yellowish-green platelets, mp 105–108°. Repeated recrystallization from methanol and ligroin sharpened the melting point to 107.5–108° but did not remove a light yellowish-green coloration.

Anal. Calcd for $C_{10}H_7Cl_2NO$: C, 52.66; H, 3.09; Cl, 31.09; N, 6.19. Found: C, 52.64; H, 3.00; Cl, 31.43; N, 6.14.

Attempted Preparation of 3,3-Dichloro-2-(4-nitrophenyl)acrylonitrile.—Three attempts were made to condense II with Ie. (1) The reagents were mixed and stirred overnight at room temperature, then warmed briefly. (2) Benzene was added to CCl_4 (2:1 ratio) to dissolve Ie and then triphenylphosphine was added. The dark mixtures was stirred at room temperature for 20 hr and then heated to reflux for 2 hr. (3) The CCl_4 and triphenylphosphine were heated to 60° for 2 hr and then Ie was added and heating was continued for 1 hr.

In each case the resulting black reaction mixture failed to show any typical $Cl_2C=$ absorption in the infrared. Work-up gave black residues from which only triphenylphosphine oxide could be isolated. Similar tarry residues were obtained when nitrobenzene or *p*-nitrobenzoyl chloride was used instead of *p*-nitrobenzoyl cyanide.

Registry No.—Ib, 14271-73-9; Ic, 13014-48-7; Id, 14271-83-1; IIIb, 37447-51-1; IIIc, 37447-52-2; IIId, 37447-53-3; triphenylphosphine, 603-35-0; dichloromethylenetriphenylphosphorane, 6779-08-4.

Acknowledgments.—We are indebted to Miss Rebecca Zuckero for her assistance in several of the experiments and to the Robert A. Welch Foundation (Grant AF-169) for their generous financial assistance.

The Reaction of Cyanide Ion with Carbonyl Compounds in Dipolar Aprotic Solvents[1]

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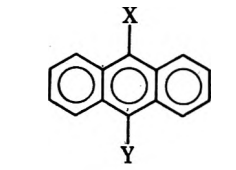
Dimethylformamide solutions of 9-benzoylanthracene and sodium cyanide at 80° give intensely blue solutions from which 9-cyanoanthracene, 9,10-dicyanoanthracene, 9,10-dihydroanthracene, anthracene, and benzoic acid can be isolated. Addition of the mild oxidizing agent sodium 9,10-anthraquinone-1-sulfonate to the blue solutions yields as major products only 9,10-dicyanoanthracene and benzoic acid. Similar treatment of 9-acetyl-, 9-benzoyl-, 9-chlorocarbonyl-, 9-formyl-, or 9-carbomethoxyanthracene also yields 9,10-dicyanoanthracene. 2,3,9,10-Tetracyanoanthracene is obtained from 9,10-dicyanoanthracene and cyanide ion in the presence of oxidizing agent.

The nucleophilic reactions of cyanide ion and of anions from active methylene compounds with certain aryl-substituted unsaturated hydrocarbons,[2] aromatic nitriles,[3] aromatic nitro compounds,[4,5] and aromatic heterocycles[3b] in dipolar aprotic solvents appear to proceed *via* carbanionic addition products, usually formed reversibly, which by further reaction with added oxidizing agents or protonating agents or by electron exchange reactions, in which the original aromatic compound may participate, lead to a variety of products. Some of the reactions promise to be of unique value in synthesis. The initiation of the reactions of aromatic compounds results from electron withdrawal by an activating group, nitro or nitrile, which facilitates the addition of the cyanide ion to the aromatic system. It would be expected that a carbonyl group attached to a suitable aromatic system would be less effective than a nitro or nitrile group in facilitating attack by the cyanide ion. The present work was undertaken to test the reactivity of some aromatic carbonyl compounds toward cyanide ion.

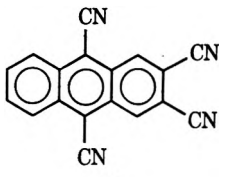
In the studies of the highly unsaturated hydrocarbons[2] and the nitriles[3] and nitro compounds[4] the development of color when the substance being tested was mixed with sodium cyanide in an aprotic solvent was taken as an indication of attack by cyanide ion with the formation of a carbanion. When simple aromatic carbonyl compounds, such as benzophenone, benzaldehyde, and ethyl benzoate, were tested in this way no significant color development was observed at ambient or slightly elevated temperatures, but, when the aromatic compound was one having a ketone, ester, acid chloride, or aldehyde function attached to the 9 position of the anthracene system, such a test solution developed a deep blue color, slowly at room temperature and rapidly at slightly elevated temperatures.

Examination of mixtures in which 9-benzoylanthracene **1a** and sodium cyanide were allowed to react in DMF revealed the presence of a number of products. By analogy with the reaction of the nitrile,[3] the carbanion **6** would be expected to form and to generate the keto nitrile **1d** even if no oxidizing agent were added. However, none of the keto nitrile was found, and a principal product isolated (23%, see Table I, expt A)

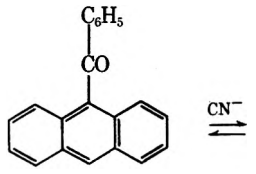


1a, X = C_6H_5CO; Y = H
b, X = CN; Y = H
c, X = Y = CN
d, X = C_6H_5CO; Y = CN
e, X = CH_3CO; Y = H
f, X = CHO; Y = H
g, X = ClCO; Y = H
h, X = CH_3OCO; Y = H

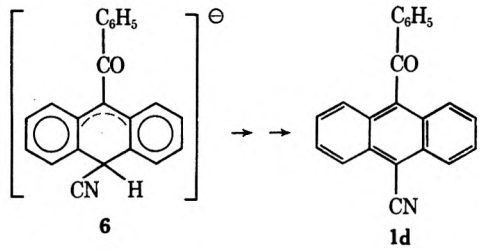
2, 9,10-dihydroanthracene
3, anthracene
4, benzoic acid



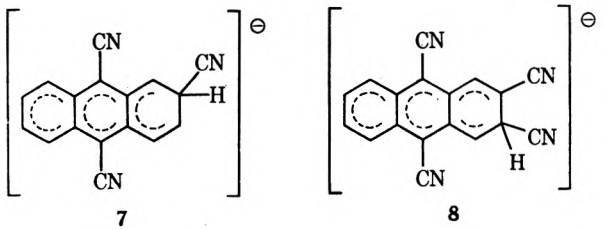
5



1a



6 **1d**



7 **8**

was the unexpected one, 9-cyanoanthracene; benzoic acid (29%) was also isolated in this experiment, as well as 9,10-dicyanoanthracene (15%), 9,10-dihydroanthracene (20%), and a trace of anthracene. In an experiment (C) in which the oxidizing agent sodium anthraquinone-α-sulfonate[2b] (α-SAS) was employed, some (10%) of the originally expected keto nitrile **1d** was isolated, along with a somewhat larger amount (13%) of the 9,10-dinitrile. When the keto nitrile **1d**

(1) Grateful acknowledgment is made to the U. S. Army Research Office (Grant No. DA-ARO(D)-G679 and G857) for the partial support of this work.

(2) (a) B. E. Galbraith and H. R. Snyder, *J. Org. Chem.*, **32**, 380 (1967); (b) K. E. Whitaker, B. E. Galbraith, and H. R. Snyder, *ibid.*, **34**, 1411 (1969).

(3) (a) K. E. Whitaker and H. R. Snyder, *ibid.*, **35**, 30 (1970); (b) R. B. Chapas, R. F. Nystrom, and H. R. Snyder, *ibid.*, **37**, 314 (1972).

(4) (a) R. G. Landolt and H. R. Snyder, *ibid.*, **33**, 403 (1968); (b) R. F. Aycock, Ph.D. Thesis, University of Illinois, Urbana, 1969; (c) B. Vickery, *Chem. Ind.* (London), 1523 (1967).

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TABLE I

INTERACTION OF SODIUM CYANIDE WITH SUBSTITUTED ANTHRACENES IN DIMETHYLFORMAMIDE

Expt	Substrate	Mole ratio of reactants[a]	Reaction time, hr	% recovered substrate	% 1b	% 1c	% 2	% 3	% 4	% 5	% other
A	1a	1:2.4:0	13.7	25	23	15	20	2	29	0	1 (1a + 3 complex)
B[b]	1a	1:2.5:0	8	30	9	12	6	0.7			5 (1a + 3 complex)
C	1a	1:2.4:3.1[c]	36	74	0	13	0	0	15	0.2	10 (1d)
D	1a	1:2.5:2.8[c]	11	87	0	6	0	0	Trace		
E[d]	1a	1:2:1.3[e]	8[f] + 11.5	21	0	27	0	0			
F	1a	1:2.5:1.3[e]	6[f] + 15	34	0	17	0	0	11	5	
G	1d	1:4.2:0	16	0	0	85	0	0	32	0	8 (impure 9-cyano-10-anthrone)
H	1d	1:3.2:1.5[c]	10.5	35	0	44	0	0	44	12	
I[b]	1d	1:3.3:1.4[c]	47	10	0	35	0	0	28	3	
J	1c	1:3.3:2.5[c]	27.7	82			0	0		18	
K	1c	1:9:5[c]	100	36			0	0		0	
L[g]	1e	1:2.5:1.6[e]	2.5[f] + 70			10					
M	1f	1:3.2:1.2[e]	4.5[f] + 16			28					
N[g]	1g	1:5:2[e]	0.1[f] + 35.5		0	10				2	17 (impure 9-cyano-10-anthroic acid)
O[d]	1h	1:2.4:1.3[c]	10.7	59		15					

[a] Substrate, NaCN, α-SAS. [b] Reaction mixture acidified with concentrated HCl. [c] Order of reagents added to reaction solvent: substrate, α-SAS, NaCN. [d] DMSO used as reaction solvent. [e] Order of reagents added to reaction solvent: substrate, NaCN, α-SAS. [f] Hours substrate and NaCN react before α-SAS addition. [g] Reaction product crystallized from hot DMF.

was separately prepared and submitted to the action of cyanide ion (expt G), it was converted in high yield (85%) into the 9,10-dinitrile. It is probable that **1d** occurs as an intermediate between the simple ketone and the dinitrile.

Another unexpected product from the reaction of 9-benzoylanthracene was a very slightly soluble substance having the composition of a tetracyanoanthracene. The similarity of the infrared spectrum of this substance to that of 2,3,9,10-tetramethylanthracene[6] suggests that it is the 2,3,9,10-tetracyano compound **5**. When the 9,10-dinitrile was treated with cyanide and the oxidizing agent (α-SAS) over a long period of time (expt J), substantially all of the dinitrile not recovered was converted into this same tetranitrile, obtained in about 18% yield.

Trisler and Frye[7] have found that the reaction of benzil with cyanide ion in DMSO proceeds by nucleophilic attack on the carbon atom of one of the active carbonyl groups, followed by a series of reactions which include isomerizations and addition to a second molecule of benzil, with the final ejection of cyanide ion and the formation of α,α′-stilbenediol dibenzoate in high yield; no substitution in the aromatic system was observed. It would not be surprising if 9-anthraldehyde (**1f**) would react preferentially at the carbonyl carbon atom, preventing attack of the aromatic system. However, when the reaction of the aldehyde (**1f**) was carried out in the presence of the oxidizing agent α-SAS, the dinitrile (**1c**) was isolated in a yield (28%) comparable to that obtained from the benzoyl compound (**1a**). Also, the methyl ketone (**1e**), the acid chloride (**1g**, which probably reacted as the acyl cyanide), and the methyl ester (**1h**) all produced some of the dinitrile (**1c**) in reactions in which the oxidizing agent α-SAS was present.

There seems little doubt that the reactions occurring when cyanide ion and 9-nitroanthracene,[4a] 9-cyanoanthracene,[3] or even acridine[3b] are brought together in DMF or DMSO proceed through an anionic intermediate, similar to a Jackson–Meisenheimer complex,[5] formed by attack of the cyanide ion upon the unsubstituted carbon of the central ring of the aromatic compound. The products obtained from 9-benzoylanthracene can be accounted for on the basis of a similar addition product **6**, but the addition proceeds less readily, because of the lesser electron withdrawal by the acyl group, and, at the higher temperatures required, further reactions, including oxidation–reductions, presumably proceeding *via* electron exchange reactions,[2b,8,9] and the participation of more active, newly introduced cyano groups lead to a greater variety of products. The isolation of some (10%) of the cyano ketone **1d** from a reaction conducted in the presence of the oxidizing agent α-SAS (expt C) and its further reaction to give 9,10-dicyanoanthracene **1c** in high (85%) yield are illustrative, and the latter process constitutes a new method of cleavage of activated aromatic ketones. The further reaction of 9,10-dicyanoanthracene to 2,3,9,10-tetracyanoanthracene **5** represents the first instance of attack by cyanide ion on a terminal ring of an activated anthracene compound. The tetracyano compound very probably is formed by way of the anion **7** which is oxidized to the tricyanoarene which reacts further *via* the addition product **8**.

Experimental Section[10]

Materials.—Unless otherwise specified, commercially available reagents were used without purification. Dimethylformamide, dimethyl sulfoxide, sodium cyanide, α-SAS, and laboratory nitrogen were dried as reported earlier.[3a] Brinkmann's No. 7734 silica gel was used for column chromatography. Thin layer chromatography analyses were carried out on sheets of Eastman chromagram 6060 silica gel with fluorescent indicator.

(6) Sadtler Standard Spectra Catalogue, Sadtler Research Laboratory, 1517 Vine Street, Philadelphia, Pa. 19102, Spectrum 19885.

(7) (a) J. C. Trisler and J. F. Frye, *J. Org. Chem.*, **30**, 306 (1965). (b) J. C. Trisler, C. S. Aaron, J. L. Frye, and J. Y. Park, *ibid.*, **33**, 1077 (1968).

(8) E. H. Jansen and J. W. Happ, *ibid.*, **35**, 96 (1970).

(9) G. A. Russell and W. C. Danen, *J. Amer. Chem. Soc.*, **90**, 347 (1968).

(10) Melting points are not corrected. Microanalyses were performed by Mr. J. Nemeth and his associates, mass spectra were obtained by Mr. J. Wrona with an Atlas CH4 spectrometer, and Mr. R. Thrift and his associates used a Perkin-Elmer 521 infrared spectrophotometer to obtain infrared spectra in potassium bromide disks. Ultraviolet spectra were run in absolute ethanol on a Perkin-Elmer 202 spectrophotometer.

9-Benzoylanthracene (1a).—The preparation of 9-benzoylanthracene from anthracene and benzoyl chloride with aluminum chloride catalyst in ethylene chloride solvent at 0° was carried out according to the method of Gore and Hoskins.[11] The ketone was twice chromatographed on alumina and twice crystallized from acetic acid to ensure complete removal of anthracene from the ketone,[12a] mp 147.5–149° (lit.[11,12b] mp 148°).

9-Benzoyl-10-cyanoanthracene (1d).—The method of Whitaker and Snyder[3a] was used to convert 9-benzoyl-10-bromoanthracene into 9-benzoyl-10-cyanoanthracene with anhydrous cuprous cyanide in DMSO. The product was obtained in 81% yield after elution from silica gel with cyclohexane–benzene (9:1) and crystallization of the fluorescent yellow solid from acetic acid, mp 188–189° (lit.[13] mp 184–185 and 187–188°). The cyano ketone showed medium–strong infrared absorption bands at 2220, 1670, 1450, 1230, 875, 775, 765, 715, 710, and 635 cm^{-1}.

9-Anthroyl Chloride (1g).—To 50 ml of dry benzene were added Aldrich's 9-anthroic acid (2.22 g, 0.01 mol) and 2 ml of thionyl chloride distilled from trimethyl phosphite. The solution was refluxed for 1 hr and stirred 10 hr at room temperature. The volatile components were removed by distillation (steam bath), leaving a yellow-brown solid which was twice dissolved in a minimum volume of hot pentane–benzene, filtered, and concentrated in a nitrogen stream. A dull yellow solid, mp 93.5–94.5°, was obtained when the process was repeated with a mixture of cyclohexane–benzene. The acyl chloride was used without further purification.

Methyl 9-Anthroate (1h).—A solution of diazomethane in ether prepared from Aldrich's Diazald[14] was added to 9-anthroic acid (0.408 g, 0.0018 mol), giving yellow methyl 9-anthroate: 0.412 g, 95%; mp 110–111° (lit.[15] mp 111–112°); strong infrared absorption bands at 1722, 1210, 1024, 897, 743, and 730 cm^{-1}.

General Reaction Procedure.—The general reaction procedure used was similar to that reported earlier from this laboratory.[3a] The addition order of reactants and reaction times are listed in the table. Reactions were carried out at 80° using 1–3 mmol of organic substrate.

Isolation and Identification of Reaction Products.—Separation of the reaction products was advantageously carried out by column chromatography using silica gel.

Nitriles 1b and 1c have been identified during earlier investigations in this laboratory.[3,4a] Dihydroanthracene and anthracene were identified in expt A and B by comparison with gas chromatography retention times of known compounds on a 5 ft × 1/4 in. column of 20% SE-30 on Chromosorb W at 235°.

The mixture of ketone 1a and its anthracene complex was treated with a few milliliters of hot acetic acid; the complex was insoluble and collected by gravity filtration, mp 187–192° (lit.[12] mp 158°). The infrared spectrum showed the following absorptions which were new or shifted from those observed in anthracene or ketone 1a: 2960, 1673, 1472, 1216, 1200, 1185, 822, 769, 695, 690, 670, 651, and 633 cm^{-1}. Strong absorptions of the parent hydrocarbon or ketone which no longer were apparent follow: anthracene, 1620, 1319, 958, 884, 739, 728, and 479 cm^{-1}; 9-benzoylanthracene, 898, 892, and 731 cm^{-1}. Mass spectrum (70 ev): *m/e* 460, 282, and 178.

In expt C, dinitrile 1c and keto nitrile 1d were not eluted cleanly by cyclohexane–benzene (1:1) from 10 g of silica gel. Fractional crystallization from chloroform ultimately yielded pure samples of each compound.

Benzoic acid was isolated from the filtrate in various experiments by addition of concentrated hydrochloric acid and extraction with methylene chloride. In turn, the methylene chloride solution was extracted with sodium hydroxide solution which was acidified to Congo Red paper and again extracted with methylene chloride, dried (Na_2SO_4), and evaporated to dryness, and the benzoic acid was crystallized from hot water.

Acidification of the aqueous filtrate in expt G caused precipitation of 15 mg of yellow solid. Its infrared spectrum indicated it was probably an impure sample of 9-cyano-10-anthrone.[4a]

9-Cyano-10-anthroic Acid.—In expt N, an additional fraction was eluted from the silica gel by absolute ethanol. The dark yellow solid was crystallized from aqueous acetic acid as a slightly impure sample of 9-cyano-10-anthroic acid, mp 224–226° with sublimation. Its infrared spectrum showed medium–strong absorptions at 3020, 2220, 1680, 1450, 1256, 770, and 725 cm^{-1}. Mass spectroscopy indicated that anthroic acid may be the contaminant.

Anal. Calcd for $C_{16}H_9NO_2$: C, 77.72; H, 3.67; N, 5.66; mol wt, 247.2. Found: C, 76.57; H, 4.02; N, 5.22; mol wt, 247 (mass spectrum).

Reaction of 9,10-Dicyanoanthracene. Preparation of 2,3,9,10-Tetracyanoanthracene (5).—A mixture of 9,10-dicyanoanthracene (0.295 g, 0.0013 mol) and α-SAS (1.035 g, 0.0033 mol) in 25 ml of DMF was degassed with nitrogen at 80° for 0.5 hr. Sodium cyanide (0.210 g, 0.0043 mol) was added and the solution turned dark blue in 10 min. After 4 hr the reaction mixture was quenched with a few milliliters of boiled water and poured into 300 ml of ice–water containing 12 g of ammonium chloride. The dark yellow precipitate (0.80 g) was collected and chromatographed on a short silica gel column. Elution with benzene gave 0.30 g of yellow-orange material, which was impregnated on a little silica gel which was added to the top of a silica gel column. Elution with benzene gave 0.24 g of unchanged 9,10-dicyanoanthracene (infrared spectrum) and 70 mg of an orange-brown solid which when dissolved in benzene gave a brilliant yellow-green fluorescent solution. The orange-brown solid was rechromatographed, yielding 67 mg (18%) of dark yellow solid to which was added 10 mg of the same material from another reaction. The combined solids were similarly chromatographed twice, yielding 67 mg of solid which was dissolved in 100 ml of hot ethyl acetate, filtered, and reduced in volume in a nitrogen stream. The amorphous dark yellow solid (35 mg, 9%) was essentially insoluble in the usual organic solvents. The infrared spectrum showed medium–strong absorptions at 3070, 2235, 2220, 1510, 1446, 1424, 1409, 1349, 1278, 1168, and 855 cm^{-1} and strong absorption at 772 cm^{-1}. The ultraviolet and visible spectra showed absorptions at λ_{max} 253 (sh), 272, 346, 364, 383, 414, and 442 nm; mass spectrum (70 ev) *m/e* (rel intensity) 278 (100), 251 (13), and 234 (9).

Anal. Calcd for $C_{18}H_6N_4$: C, 77.69; H, 2.17; N, 20.13; mol wt, 278. Found: C, 77.53; H, 2.12; N, 20.24; mol wt (mass spectrum), 278.

Registry No.—1a, 1564-53-0; 1c, 1217-45-4; 1d, 22970-75-8; 1e, 784-04-3; 1f, 642-31-9; 1g, 16331-52-5; 1h, 1504-39-8; 3, 120-12-7; 5, 37611-11-3; sodium cyanide, 143-33-9; benzoyl chloride, 98-88-4; 9-anthroic acid, 723-62-6; thionyl chloride, 7719-09-7; 9-cyano-10-anthroic acid, 37611-13-5.

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On the Mode of Reaction of Hydrogen Atoms with Organic Compounds in Aqueous Solutions[1]

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Yields of hydrogen from γ-irradiated aqueous solutions of organic compounds have been determined. From these yields the portion of H atoms reacting by H abstraction has been calculated. Using previous rate data the partial rate constants for the abstraction and for the other reactions which do not yield hydrogen have been derived. Correlation of structure and partial reactivities has led to some generalized patterns of reaction. Benzylic and allylic hydrogens were found to be respectively $\sim$3 and $\sim$5 times more reactive in abstraction reaction than those adjacent to methyl groups. An enol site adds hydrogen atoms with a partial rate constant of $1 \times 10^8\ M^{-1}$ sec^{-1} and a carbonyl group only $\sim 10^6\ M^{-1}\ sec^{-1}$ so that the reactivity of carbonyl compounds is largely dependent on their enol content. Partial rate constants have also been assigned to several other functional groups.

The hydrogen atom is one of the primary products of water radiolysis and is produced with a yield of G_H = 0.6 atoms/100 eV, along with the hydrated electron ($G_{e^-_{aq}}$ = 2.8) and the hydroxyl radical (G_{OH} = 2.8).[2] Molecular hydrogen and hydrogen peroxide are also formed. Since e^-_{aq} can be efficiently converted into H

$$e^-_{aq} + H_3O^+ \longrightarrow H + H_2O \qquad (1)$$

by reaction with acid, many studies on the hydrogen atom have been carried out in acid solutions, both for the sake of increasing the yield of H and for eliminating reactions of e^-_{aq} which might affect the product analyzed. A large number of papers have dealt with the reactivity of the H atom toward organic solutes and its mechanistic implications.[3] Many absolute rate constants have been determined by the *in situ* radiolysis steady-state esr method recently developed.[4] This method allows the determination of rate constants for the disappearance of H atoms upon reaction with solutes so that only the overall rates are measured with no indication of the mode of reaction. As a supplement to the previous determinations (summarized in ref 3) a set of experiments are presented here, which are devised to distinguish between the main different modes of H-atom reactions.

In these experiments the ratio between the partial rate of hydrogen abstraction and that of other reactions which do not yield H_2 is determined by measuring the yield of H_2 from irradiated solutions of various organic compounds. This yield, when corrected for the "molecular yield" of hydrogen G_{H_2} = 0.41 and compared with the total yield of H atoms $G(H) = G_H + G_{e^-_{aq}}$ under similar conditions, gives the portion of H which react by abstraction. The value of $G(H)$ is determined by the use of compounds known to react by hydrogen abstraction only, such as isopropyl alcohol or formic acid. The overall yield of hydrogen from acid solutions of these compounds at $10^{-2}\ M$ was found to be G = 3.96 and represents the sum of G_{H_2} = 0.41 and $G(H)$ = 3.55.[2]

Several series of compounds have been studied and the correlation between structure and mode of reaction is apparent in most cases.

Experimental Section

The organic compounds were of the purest grade commercially available (mostly from Baker, Aldrich, or Eastman) and were used without any further purification. Solutions containing 10^{-3}–$10^{-2}\ M$ of the organic compound and usually $10^{-1}\ M$ $HClO_4$ were degassed on a vacuum line by six freeze–pump–thaw cycles, irradiated in a gammacell 220, and analyzed for total gas formation by a McLeod gauge and for hydrogen content by mass spectrometry. All the details of the experiments are similar to those previously reported.[5] Yield *vs.* dose plots were examined for several cases and showed linearity up to doses three times higher than usually applied.

Results and Discussion

The hydrogen yields from irradiated acid solutions of the various organic compounds studied are given in Table I. The percentage of H atoms reacting by abstraction is given by $100 \times [G(H_2) - 0.41]/3.55$. From the overall rate constant for the reaction of H determined by the esr method, the specific rate constant for the abstraction reaction is derived (last column of Table I). The difference between the rate of abstraction and the overall rate is, of course, attributed to reactions which do not yield H_2, *i.e.*, addition to a double bond, aromatic ring, or other functional group or abstraction of a halogen atom.

It can be seen from Table I that isopropyl alcohol, formic, succinic, propionic, glycolic, and glyoxylic acids all react with H atoms practically *via* abstraction only. Most of the aromatic, olefinic, cyano, and bromo compounds undergo very little abstraction. Carbonyl and chloro compounds show various intermediate values depending on their structure.

Among the aromatic compounds examined benzoic acid, nitrobenzene, and acetophenone undergo little or no abstraction at all. The 3–4% abstraction calculated for phenol, phenylacetic acid, and benzaldehyde are not highly accurate, but suggest that abstraction from these compounds can take place with a rate constant of $\sim 5 \times 10^7\ M^{-1}\ sec^{-1}$. The 7% calculated for benzyl alcohol is more accurate and gives a value of 8×10^7 for the abstraction as compared to $1.1 \times 10^9\ M^{-1}\ sec^{-1}$ for the overall rate. Comparing the results for benzyl alcohol and benzaldehyde with the rate constants for hydrogen abstraction from ethanol ($2.6 \times 10^7\ M^{-1}\ sec^{-1}$) and acetaldehyde ($2.9 \times 10^7\ M^{-1}\ sec^{-1}$) one concludes that the aromatic ring

(1) Supported in part by the U. S. Atomic Energy Commission.

(2) See, *e.g.*, review by M. Anbar in "Fundamental Processes in Radiation Chemistry," P. Ausloos, Ed., Interscience, New York, N. Y., 1968, p. 651.

(3) See review by P. Neta, *Chem. Rev.*, **72**, 533 (1972).

(4) P. Neta, R. W. Fessenden, and R. H. Schuler, *J. Phys. Chem.*, **75**, 1654 (1971).

(5) P. Neta, G. R. Holdren, and R. H. Schuler, *ibid.*, **75**, 449 (1971).

TABLE I
HYDROGEN YIELDS FROM γ-IRRADIATED AQUEOUS SOLUTIONS OF ORGANIC COMPOUNDS AND PARTIAL REACTIVITIES WITH HYDROGEN ATOMS

Compd[a]	$G(H_2)$[b]	Percentage of H abstraction[c]	k_H (overall),[d] M^{-1} sec^{-1}	k_H (H abstraction), M^{-1} sec^{-1}
Isopropyl alcohol	3.96	(100)	6.5×10^7	6.5×10^7
Benzoic acid	0.44	<1	1.0×10^9[e]	$<10^7$
Nitrobenzene	0.41	~0	1.0×10^9[e]	$<10^7$
Acetophenone	0.45	~1	1.2×10^9	$\sim 1 \times 10^7$
Phenol	0.51	~3	1.4×10^9	$\sim 4 \times 10^7$
Phenylacetic acid	0.54	~4	6.0×10^8	$\sim 4 \times 10^7$
Benzaldehyde	0.54	~4	1.5×10^9	$\sim 6 \times 10^7$
Benzyl alcohol	0.66	7	1.1×10^9	8×10^7
Thiophenol	2.93	71	4.0×10^9	2.8×10^9
Allyl alcohol	0.49	~2	2.5×10^9[f]	$\sim 5 \times 10^7$
cis-4-Cyclohexene-1,2-dicarboxylic acid	0.69	8	1.0×10^9	8×10^7
1-Cyclopentenecarboxylic acid	0.74	9	1.5×10^9	1.4×10^8
Cyclopropanecarboxylic acid	0.69	8	5.3×10^6	4×10^4
Cyclobutanecarboxylic acid	2.93	71	1.3×10^7	9.2×10^6
Formic acid	3.96	(100)	4.5×10^5	4.5×10^5
Oxalic acid	0.39	0	4.1×10^5	$<10^4$
Malonic acid	3.06	75	4.2×10^6	3.1×10^5
Succinic acid	3.77	95	3.5×10^6	3.3×10^6
Propionic acid	3.81	96	6.4×10^6	6.1×10^6
Glycolic acid	3.81	96	1.8×10^7	1.7×10^7
Formaldehyde	3.36	83	5×10^6	4×10^6
Acetaldehyde	3.37	83	3.4×10^7	2.9×10^7
Glyoxal	3.25	80		
Glyoxylic acid	4.01	100	2.4×10^7	2.4×10^7
Acetone[g]	2.78	67[h]	2.8×10^6	1.9×10^6
Biacetyl	1.12	20	4.7×10^6	9.4×10^5
Acetylacetone[i]	0.51	~3	8.2×10^7	$\sim 2 \times 10^6$
2,3-Dihydroxyfumaric acid	0.97	16	9×10^7	1.4×10^6
Ascorbic acid	0.48	~2	1.1×10^8	$\sim 2 \times 10^6$
Ethyl acetoacetate[j]	1.18	22	1.3×10^7	2.9×10^6
Oxaloacetic acid	0.44	~1	2.1×10^7	$\sim 2 \times 10^5$
Barbituric acid	0.84	12	2.0×10^7	2.4×10^6
Ribose	3.34	83	5.5×10^7	4.6×10^7
Acetonitrile	0.67	7	1.5×10^6	1×10^5
Trimethylacetonitrile	0.60	5	1.5×10^7	7.5×10^5
Malononitrile	0.60	5		
Cyanoacetic acid	0.84	12	3.2×10^6	4×10^5
Aminoacetonitrile (pH 1)	0.45	~1	6.6×10^6	$\sim 6 \times 10^4$
Aminoacetonitrile (pH 7)	0.76	58[k]	5.6×10^7	3.2×10^7
Methyl chloride	1.71	37	7×10^4	3×10^4[l]
Methylene chloride	1.37	27	4×10^6	1.1×10^6
Chloroform	1.13	20	1.2×10^7	2.4×10^6
Carbon tetrachloride	0.40	~0	4.8×10^7	
Ethyl bromide	0.51	~3	1.7×10^8	$\sim 5 \times 10^6$
Cysteine	2.84	68	4×10^9	2.7×10^9
Thiodiglycolic acid	0.41	~0	2×10^9	$<10^7$
Dithiodiglycolic acid	0.40	~0	1×10^{10}	$<10^8$
Nitromethane	0.41[m]	~0	4.4×10^7	$<4 \times 10^5$
Histidine	0.51	~3	4.8×10^7	$\sim 1.5 \times 10^6$

[a] All compounds have been irradiated in aqueous solutions at 10^{-3}–10^{-2} M concentration and at pH 1 adjusted with perchloric acid. [b] Given in molecules/100 eV absorbed energy. Determined from total gas formation and mass-spectrometric analysis. The accuracy of $G(H_2)$ is $\sim \pm 0.03$. [c] Calculated by $[G(H_2) - G_{H_2}]/G(H)$ taking $G_{H_2} = 0.41$ and $G(H) = 3.55$ at pH 1. The sum of these two values, 3.96, is observed for isopropyl alcohol and formic acid, which are used as references. [d] Measured by the esr method except where noted. The esr measurements reported in ref 4, 6, and 7, and by P. Neta and R. H. Schuler, unpublished data. [e] Absolute rate determined by pulse radiolysis: P. Neta and L. M. Dorfman, *J. Phys. Chem.*, **73**, 413 (1969). [f] An average value between that reported by G. Scholes and M. Simic, *ibid.*, **68**, 1738 (1964), and that reported by W. A. Volkert and R. R. Kuntz, *ibid.*, **72**, 3394 (1968). [g] 2.5×10^{-4}% enol form. [h] 65% observed in ref 5. [i] 80% enol form. [j] 8% enol form. [k] Determined by reference to isopropyl alcohol solution at pH 7 from $[G(H_2) - 0.4]/0.60$. [l] An upper limit for the rate constant of methane has been determined as $<10^5$ M^{-1} sec^{-1}. This result and the trend that follows suggest that the upper limit for methane is probably an order of magnitude lower. [m] A yield of nitrogen of $G(N_2) \sim 0.5$ has also been observed and no mechanism for its formation is apparent.

enhances hydrogen abstraction from position α by a factor of 2–3 more than a methyl group.

In a recent correlation of the rate constants for reaction of H with aromatic compounds[6] with the substituent σ values it has been suggested that a considerable portion of H attacks the side chains of benzaldehyde and acetophenone. The present results rule out abstraction as a major contribution and assign this attack to addition to the carbonyl groups which must be activated by the ring.

The high percentage of H abstraction from thio-

(6) P. Neta and R. H. Schuler, *J. Amer. Chem. Soc.*, **94**, 1056 (1972).

phenol and its high overall rate constant are attributed to the SH group, which is known in aliphatic compounds to undergo H abstraction with a rate constant of $\sim 3 \times 10^9\ M^{-1}\ \text{sec}^{-1}$.[7] The rate of abstraction from thiophenol, $2.8 \times 10^9\ M^{-1}\ \text{sec}^{-1}$, is in line with those values (see also result for cysteine in Table I) and the remaining rate constant of $1.2 \times 10^9\ M^{-1}\ \text{sec}^{-1}$, attributed to addition to the aromatic ring, is also as expected by comparison to the other aromatic compounds.

Following the above finding that abstraction from a benzylic position is enhanced only by a factor of 2–3, it is interesting to examine the effect on abstraction from allylic positions. The result for allyl alcohol does not permit an accurate comparison, but those for 4-cyclohexene-1,2-dicarboxylic acid and 1-cyclopentenecarboxylic acid can be used to estimate the reactivity of the allylic positions. Comparing the rates of abstraction from these compounds with those from cyclohexane and cyclopentane[4] and taking into account the number of abstractable hydrogens in each case, it appears that the allylic position is activated by a factor of 3 in the case of the cyclohexenedicarboxylic acid and by a factor of 10 in the cyclopentenecarboxylic acid. Obviously these are rough estimates and they suggest that enhancement of abstraction from allylic position by a factor of ~ 5 can be reasonably expected in other compounds. It should be pointed out that a similar allylic enhancement by a factor of 5 has been recently estimated for the reaction of OH with cycloolefinic compounds.[8]

Cyclopropanecarboxylic acid undergoes ring opening upon addition of H and only 8% of abstraction has been observed. With cyclobutanecarboxylic acid abstraction accounts for 70% of the reaction. The overall rate constant for the latter compound is larger than that for the first by a factor of 2.5 but the partial rate constant for abstraction is larger by over two orders of magnitude.

Oxalic acid reacts with hydrogen atoms by addition to the carboxyl groups only and no abstraction is detected. The rate constant for this addition is only $4 \times 10^5\ M^{-1}\ \text{sec}^{-1}$. Oxalate ions have been found to react at least an order of magnitude more slowly,[9] apparently because COO^- groups have less of a double-bond character than COOH. Malonic acid also undergoes H addition to the COOH to some extent ($k \cong 1 \times 10^5\ M^{-1}\ \text{sec}^{-1}$) but the major reaction is abstraction from the CH_2. In succinic acid abstraction takes over completely, although an addition rate similar to that for malonic acid cannot be excluded because it would account for only 3% of the total rate.

Formaldehyde, acetaldehyde, glyoxal, and glyoxylic acid react with H atoms over 80% by abstraction. The rate constant for acetaldehyde, when compared to that for acetic acid, suggests that abstraction from the methyl group accounts for <10% of the total abstraction rate. The main reaction path in acetaldehyde, and in the other three compounds as well, is abstraction from the aldehyde group, either CHO or its hydrated form $CH(OH)_2$.

The mode of reaction with the remaining carbonyl compounds in Table I is affected by keto–enol tautomerization. Acetone undergoes H abstraction from CH_3 and H addition to CO with comparable rate constants as was previously observed.[5] The contribution of the enol form (2.5×10^{-4}%) is negligible. Biacetyl shows a slightly higher addition rate. However, acetylacetone, which is present in water 80% in the enol form, undergoes a negligible amount of abstraction and its rate constant for H addition is higher than that for biacetyl by a factor of 20. As compared with this high rate constant of $8.2 \times 10^7\ M^{-1}\ \text{sec}^{-1}$ the rate for abstraction from acetylacetone, although ~ 3% only, is of the same order of magnitude as abstraction from acetone and biacetyl. Similar partial rates are also observed for addition of H to dihydroxyfumaric and ascorbic acids. The results indicate that a C=C double bond bearing OH on the carbon reacts with a rate constant of $\sim 1 \times 10^8\ M^{-1}\ \text{sec}^{-1}$, considerably less than the rates for ethylene[4] or fumaric acid[7] ($\sim 10^9\ M^{-1}\ \text{sec}^{-1}$). In agreement with this generalization, ethyl acetoacetate with 8% enol in aqueous solution exhibits a rate constant for addition of $1 \times 10^7\ M^{-1}\ \text{sec}^{-1}$. The rate for addition to oxaloacetic acid is $2 \times 10^7\ M^{-1}\ \text{sec}^{-1}$, which suggests that this compound is present ~ 20% in the enol form. The result for barbituric acid can be explained similarly.

Cyano groups add H atoms with rate constants of 10^6–$10^7\ M^{-1}\ \text{sec}^{-1}$, as is seen in Table I for the nitriles examined. Aminoacetonitrile is a special case which has been examined both at pH 1 and pH 7 because the amino group in this compound has $pK_a = 5.3$. Protonation is expected to exert a large negative effect on the rate of H abstraction from the CH_2. In the acid form NH_3^+ strongly decreases the rate of abstraction to $<10^5\ M^{-1}\ \text{sec}^{-1}$ and practically all H atoms add to the cyano group. In neutral solution, however, a considerable amount of abstraction is observed and the partial rate for abstraction is almost three orders of magnitude higher than that for the acid form. From the overall rate constants in acid and neutral solutions and assuming that the rate of addition remains unchanged it has been recently concluded[9] that the neutral form of aminoacetonitrile would undergo 90% abstraction. The present results show, however, that abstraction accounts for 58% only and that the rate of H addition to the cyano group increases from 6.6×10^6 to $2.4 \times 10^7\ M^{-1}\ \text{sec}^{-1}$ in going from the NH_3^+ to NH_2. The result for trimethylacetonitrile shows that three methyl groups also cause a similar enhancement of addition.

Halogen compounds have been studied previously[10] and found to undergo H and Cl abstraction at comparable rates but Br abstraction at much higher rates. As a result practically no H abstraction is observed with bromo compounds, as in the case of ethyl bromide in Table I. Varying percentages of H abstraction have been observed[10] with the chloro compounds depending on the partial reactivities. The results in Table I show that increased chlorination of methane causes both H abstraction and Cl abstraction to have higher rate constants.

The yield of hydrogen from cysteine solutions (Table I) is slightly lower than previously reported.[11,12] All

(7) P. Neta and R. H. Schuler, *Radiat. Res.*, **47**, 612 (1971).
(8) T. Soylemez, Ph.D. Thesis, Carnegie-Mellon University, 1972.
(9) P. Neta and R. H. Schuler, *J. Phys. Chem.*, **76**, 2673 (1972).
(10) M. Anbar and P. Neta, *J. Chem. Soc.* A, 834 (1967).
(11) V. G. Wilkening, M. Lal, M. Arends, and D. A. Armstrong, *Can. J. Chem.*, **45**, 1209 (1967).
(12) A. Al-Thannon, R. M. Peterson, and C. N. Trumbore, *J. Phys. Chem.*, **72**, 2395 (1968).

results show that the main reaction is H abstraction from SH.[13] The partial rate for this abstraction is $2.7 \times 10^9\ M^{-1}\ \text{sec}^{-1}$, similar to that observed for thiophenol (Table I). Some abstraction of the SH group to form H_2S also takes place.[11-13] However, H abstraction from C–H bonds is negligible in cysteine. Other sulfur compounds which do not contain an SH group also react with hydrogen atoms very rapidly but in these cases no H_2 formation beyond the molecular yield is observed and the reaction must involve addition of H on the sulfur to rupture the C–S or S–S bonds as previously suggested.[7]

With nitromethane and histidine little abstraction is detected, confirming previous suggestions[4,7] based on the measured total rate constants.

In conclusion, measurement of hydrogen yields allows us to distinguish between the various modes of reaction of hydrogen atoms with organic compounds. Supplemented by rate-constant data it gives some insight into the structure of molecules. General patterns of reactivity have been summarized[3] and the present study gives additional information, mostly on the reactivities of benzylic and allylic hydrogens and of carbonyl compounds, and assigns a partial rate constant of $1 \times 10^8\ M^{-1}\ \text{sec}^{-1}$ for H addition to an enol site.

(13) G. Navon and G. Stein, *Israel J. Chem.*, **2**, 151 (1964).

Registry No.—Hydrogen, 12184-88-2.

Reactions of Polyarylated Carbinols. II.[1] Kinetic Study of a Suprafacial [1,5]-Sigmatropic Rearrangement[2]

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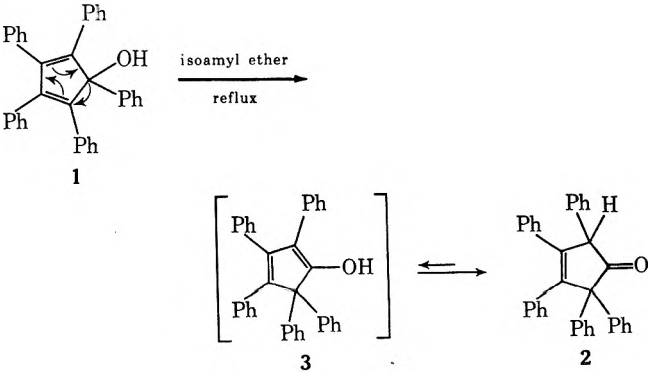
A kinetic study of the suprafacial [1,5]-sigmatropic phenyl rearrangement of 1,2,3,4,5-pentaphenyl-2,4-cyclopentadien-1-ol (1) to 2,2,3,4,5-pentaphenyl-3-cyclopenten-1-one (2) has been performed at 173° in isoamyl ether and at 173, 180, 190, and 200° in diphenyl ether. The rearrangement is observed to be first order throughout the temperature range investigated, and the rate constants (k) at the temperatures used were found to be 0.28, 0.40, 1.09, and $2.7 \times 10^{-2}\ \text{hr}^{-1}$, respectively. Calculation of the activation energy of this phenyl [1,5]-sigmatropic shift from the Arrhenius equation gave 36.1 ± 3.6 kcal/mol, while $\Delta S^{\ddagger}$ for this phenyl migration is −7 eu. These results are used to discuss both the mechanism of this rearrangement and the transition state for rearrangement in the pentaphenylcyclopentadienol system.

Since the initial work of Mironov[4] on methyl-substituted cyclopentadienes and on 5-deuteriocyclopentadiene several thermal sigmatropic reactions of cyclopentadiene systems have recently been discovered. McLean and Haynes[5] studied the [1,5]-hydrogen rearrangement of 1-methylcyclopentadiene and 1,2-dimethylcyclopentadiene, and Roth[6] has investigated the rearrangement of isotopically labelled 5*H*-perdeuteriocyclopentadiene, while Backes[7] has reported on [1,5]-ester migrations in the cyclopentadiene system. Work on the unsubstituted indene system has been performed by Roth,[6] Alder,[8] Berson,[9] and Isaacs,[10] while Koelsch and Johnson,[11] and more recently Miller,[12] have reported studied on substituted indene systems. More recently Wawzonek[13] has reported on the thermal sigmatropic rearrangement of 3a,7a-dihydro-3,3a,5,6-tetraphenylinden-1-one. Our recent report[1] that 1,2,3,4,5-pentaphenyl-2,4-cyclopentadien-1-ol (**1**) undergoes a thermally induced, symmetry allowed, suprafacial [1,5]-sigmatropic phenyl shift to produce 2,2,3,4,5-pentaphenyl-3-cyclopenten-1-one (**2**) has extended these initial observations concerning sigmatropic shifts in cyclopentadiene, indene, and indenone systems to the cyclopentadienol system.

In our initial publication[1] we postulated that the conversion of **1** to **2** proceeds through the keto–enol tautomerization of the dienol intermediate **3**. Since



the rearrangement of **1** to **2** proceeds so cleanly and because this is the first observation of a sigmatropic phenyl shift in a cyclopentadienol system, a kinetic study of this rearrangement was undertaken to establish that this is indeed a true sigmatropic rearrangement and to obtain some information about the activation energy and the entropy of activation for this rearrangement.

(1) For paper I in this series, see A. K. Youssef and M. A. Ogliaruso, *J. Org. Chem.*, **37**, 2601 (1972).

(2) Presented at the 164th National Meeting of the American Chemical Society, New York, N. Y., Aug 1972.

(3) Taken from the Ph.D. Thesis of A. K. Y. submitted to the faculty of the Department of Chemistry, VPI and SU, in partial fulfillment of the requirements for the Ph.D. degree, July 8, 1972.

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(12) L. L. Miller and R. F. Boyer, *ibid.*, **93**, 650 (1971).

(13) S. Wawzonek and B. H. Friedrich, *J. Org. Chem.*, **37**, 2520 (1972).

TABLE I

THE ISOMERIZATION REACTION OF 1,2,3,4,5-PENTAPHENYL-2,4-CYCLOPENTADIEN-1-OL AT DIFFERENT TEMPERATURES AND IN DIFFERENT SOLVENTS

Reaction time	% Ratio	
	Alcohol	Ketone
0.5[a,b,c]	89.5	10.5
1.0	85.0	15.0
2.0	70.9	29.1
2.5	65.5	34.5
3.0	60.8	39.2
3.5	55.9	40.1
4.0	49.5	50.5
4.5	46.7	53.3
5.0	44.0	56.0
5.5	39.5	60.5
6.0	36.0	64.0
6.5	33.0	67.0
7.0	30.8	69.2
8.2	24.0	76.0
9.0	22.5	77.5
10.0	17.5	82.5
11.0	15.4	84.6
11.5	14.0	86.0
15[d,e,f]	91.2	8.8
30	88.4	11.6
50	85.0	15.0
65	78.6	21.4
110	66.5	33.5
140	57.7	42.3
170	48.8	51.2
235	39.5	60.5
295	25.0	75.0
475	16.6	83.4
15[d,f,g]	91.1	8.9
30	82.3	17.7
45	73.3	26.7
60	63.0	37.0
90	48.1	51.8
120	34.5	65.5
180	17.0	83.0
240	7.7	92.3
10[d,f,h]	82.5	17.5
20	66.0	34.0
30	51.3	48.7
40	37.3	62.7
60	22.2	77.8
80	13.5	86.5
110	4.0	96.0
140	2.6	97.4

[a] Solvent is either isoamyl ether or diphenyl ether. [b] Temperature is 173°. [c] Time is in hours. [d] Solvent is diphenyl ether. [e] Temperature is 180°. [f] Time is in minutes. [g] Temperature is 190°. [h] Temperature is 200°.

Experimental Section

General.—Gas–liquid partition chromatography (glpc) was conducted using a Bendix Model 2600 gas chromatograph and a Bendix Model 1200 recorder. The glpc was equipped with a 3 ft × 0.25 in. column packed with 3% QF-1 on Chromosorb W (H. P., mesh 100/120) support. Operating conditions were as follows: temperature of inlet 210°, detector 255°, injector 255°, column 210°, and a He carrier gas flow rate of 80 ml/min. Analysis of each sample taken showed only three peaks, corresponding to the solvent, the remaining unreacted alcohol 1, and the ketone product 2. Retention time of the alcohol 1 was 6 min 15 sec; of the ketone, 13 min 45 sec. In order to study the kinetics at temperatures higher than 173° it was necessary to change the solvent from isoamyl ether to diphenyl ether (bp 259°), which was found to be satisfactory. To establish that changing to this solvent did not in any way affect the results, the kinetic study performed at 173° in isoamyl ether was again performed at 173° in diphenyl ether. The results obtained in both solvents at 173° were exactly the same. The solvents isoamyl ether and diphenyl ether were both purified by two distillations before use. The alcohol 1 was synthesized as previously described.[1] The temperature of the reaction mixture was maintained at the temperature reported ±1°, by means of a thermostatically controlled oil bath.

TABLE II

RATE CONSTANTS AND ACTIVATION PARAMETERS FOR THERMOLYSIS OF 1,2,3,4,5-PENTAPHENYL-2,4-CYCLOPENTADIEN-1-OL IN DIPHENYL ETHER

Temp, °C	$10^2 k$, hr^{-1}	$\Delta S^{\ddagger}$,[a] eu	E_a,[a] kcal/mol
173	0.28	−7.5	36.1
180	0.40		
190	1.09		
200	2.79		

[a] Calculated at 173°.

Kinetic Runs.—Into a 100-ml, two-necked, round-bottomed flask equipped with a reflux condenser, a serum cap, and a magnetic stirrer was placed 75 ml of the solvent (either isoamyl or diphenyl ether), which was then heated to the appropriate temperature (173° when isoamyl ether was used, and in separate kinetic runs 173, 180, 190, and 200° when diphenyl ether was used). At this point 2.0 g (0.0042 mol) of 1,2,3,4,5-pentaphenyl-2,4-cyclopentadien-1-ol (1) was added as a solid all at once. While the mixture was refluxing, samples of 5 ml each were taken at various times (Table I) by inserting a hypodermic syringe through the serum cap. The samples thus removed were placed in separate containers and cooled by means of an ice–water bath. After all the required samples were collected, glpc analysis was carried out using the instrument and conditions described above. For each kinetic run the peak areas of the two peaks corresponding to the alcohol 1 and the ketone 2 were determined by triangulation[14] and the per cent concentrations represented by these peak areas were then calculated (Table I) and the logarithm of the concentrations was determined. For each kinetic run the concentration of both the starting alcohol 1 and the product ketone 2 were separately plotted *vs.* time, and the logarithm of the concentration of the starting alcohol 1 *vs.* time was plotted.

Results

Plotting the logarithm of the concentration of the starting alcohol 1 only at the different temperatures *vs.* time afforded the curve shown in Figure 1. This curve illustrates that the slopes increase as the temperature is increased, which is in accord with increases in the rate of the reaction with increasing temperature. It can be readily seen from these plots in Figure 1 that at 200° the reaction goes to completion in less than 3 hr, whereas at 173° less than 90% of the starting alcohol 1 has reacted in 12 hr. Since a straight line is obtained at every temperature when the logarithm of the concentration of the starting alcohol 1 (the disappearance of alcohol 1 with time) is plotted *vs.* time, this indicates that the sigmatropic rearrangement of 1 is a first-order reaction throughout the temperature range investigated.

Using a least square program to calculate the slope of the curves in Figure 1, it was possible to calculate the rate constants (k) for each individual run, which are recorded in Table II. The activation energy of this sigmatropic rearrangement was then calculated by plotting log k *vs.* $1/T$ (°K), which gave an Arrhenius plot. Again using the least square program to calculate the slope of this plot afforded a value of 0.78863 × 10^4 for the slope. Using the standard Arrhenius

(14) As described in H. M. McNair and E. J. Bonelli, "Basic Gas Chromatography," Varian Associates, Palo Alto, Calif., 1969, p 154.

equation[15] gave an activation energy of 36.1 ± 3.6 kcal/mol for this rearrangement. Calculation of the entropy of activation[16] using this activation energy gave −7.5 cal deg^{-1} mol^{-1}.

Discussion

McLean and Haynes[5] have previously reported $\Delta S^{\pm} = -10$ eu for the [1,5]-hydrogen rearrangement of 1-methylcyclopentadiene and a $\Delta S^{\pm} = -4$ eu for the hydrogen migration process in 1,2-dimethylcyclopentadiene, while Roth[6] reported $\Delta S^{\pm} = -12$ eu for 5*H*-perdeuteriocyclopentadiene. Although phenyl migrations have not been studied kinetically in the cyclopentadiene system, there should be similar $\Delta S^{\pm}$ values observed for phenyl migrations in this system as have been observed for hydrogen migrations. Studies performed on hydrogen and phenyl migrations in substituted indene systems[12] have shown the need for justifying $\Delta S^{\pm}$ values obtained for phenyl migrations which differ drastically from the $\Delta S^{\pm}$ values obtained for hydrogen migrations in similar systems. In the cyclopentadienol system no kinetic studies have been performed on either hydrogen or phenyl migrations; however, it is expected that the values of $\Delta S^{\pm}$ observed in this system for hydrogen and/or phenyl migrations should correspond with the $\Delta S^{\pm}$ values reported in both the cyclopentadiene and indene systems for hydrogen and/or phenyl migrations. Thus the values of $\Delta S^{\pm} = -7.5$ eu reported here for [1,5]-phenyl migration in 1,2,3,4,5-pentaphenyl-2,4-cyclopentadien-1-ol seems well within the region of $\Delta S^{\pm}$ values expected for rearrangements of hydrogen or phenyl in five-membered ring diene systems.[17]

The results reported here in isoamyl and diphenyl ether combined with our initial results in DMSO reported earlier[1] indicate that the observed phenyl migration is not solvent dependent. In addition, since previously reported results[1] indicate that this rearrangement proceeds without any ionic or radical character, it appears that the transition state for this phenyl shift is similar to the proposed transition state for sigmatropic hydrogen migrations[17,18] and that the phenyl rearranges *via* a true sigmatropic mechanism in 1,2,3,4,5-pentaphenyl-2,4-cyclopentadien-1-ol.

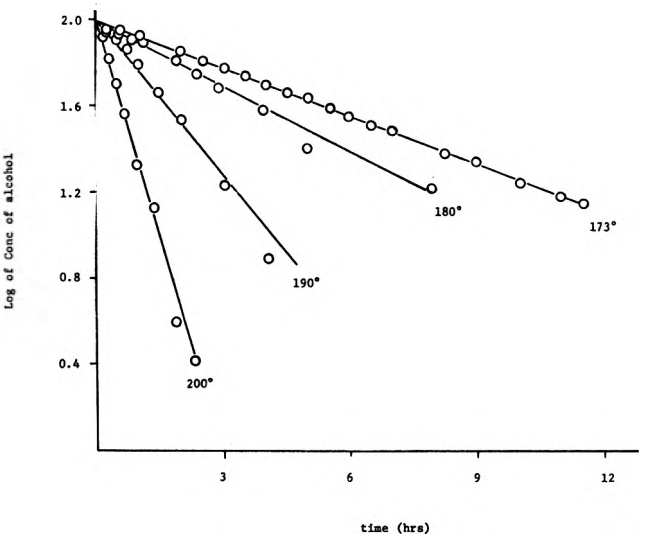

Figure 1.—Variation with time of the logarithm of the concentration of alcohol 1 at 173, 180, 190, and 200°.

Registry No.—1, 2137-74-8; 2, 34759-47-2.

Acknowledgments.—We wish to extend our sincere appreciation to Dr. Harold McNair for allowing us the use of his glpc equipment, and to Mr. Benjamin Esquivel-Hernandez for his technical assistance. We also wish to thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

(15) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," Wiley, New York, N. Y., 1965, p 23.

(16) J. H. Bunnett in "Technique of Organic Chemistry," Vol. VIII, Part I, S. L. Friess, E. S. Lewis, and A. Weissberger, Ed., Interscience, New York, N. Y., 1961, p 201.

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The Mechanism of the Base-Catalyzed Prototropic Propargylic Rearrangement in Vicinal Diamines[1]

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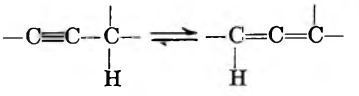
The relative rates of rearrangement of 3-hexyne with a strong base in various amines were ascertained, and vicinal diamines, particularly ethylenediamine (EDA), were found to be the most effective solvents. A concerted mechanism involving the EDA anion and the propargyl group in a nine-membered ring transition state is suggested. Since, in the presence of EDA-d_4, the rate of deuterium incorporation into the rearranged products parallels closely the rate of rearrangement, an intramolecular hydrogen transfer is not likely the preferred reaction path.

The base-catalyzed propargylic rearrangement is well known and documented.[2] Jacobs[3] equilibrated



the isomeric pentynes with alcoholic potassium hydroxide at 175°. The reaction mixture consisted of 1.3% 1-pentyne, 3.5% 1,2-pentadiene, and 95.2% 2-pentyne.

(1) Abstracted in part from the Ph.D. Thesis of Paul M. Barelski, Southern Illinois University, 1972.

(2) J. H. Wotiz in "Chemistry of Acetylenes," H. Viehe, Ed., Marcel Dekker, New York, N. Y., 1969, Chapter 7.

(3) T. L. Jacobs, R. Akawie, and R. G. Cooper, *J. Amer. Chem. Soc.*, **73**, 1273 (1951).

TABLE I
THE HALF-TIME OF REARRANGEMENT OF 3-HEXYNE AS A FUNCTION OF THE EDA-SODIUM AMIDE MIXING TIME

Mixing time, min	Half-time, min
0	12
5	11
15	9
30	0.5
60	0.5

Smadja[4] found equilibrium mixtures of heptynes and allenic heptadienes in alcoholic potassium hydroxide at 80–200°. However, the conjugated heptadienes were the major products when polar aprotic solvents (dimethyl sulfoxide, hexamethylphosphoric triamide, dimethylformamide, and dioxane) were used with potassium *tert*-butoxide.[4] The composition of the latter rearrangement mixtures represented the relative thermodynamic stabilities.

Wotiz[5] demonstrated that each of the isomeric normal C_6 acetylenes and allenes gave the same mixture when treated with sodium amide in ethylenediamine (EDA) at room temperature. The disproportionation time depended on the starting substrate and on the amounts of sodium amide used. Different quantities of sodium amide produced mixtures of different composition. No conjugated dienes, or other by-products, were observed.

Cram[6] proposed the "conducted tour" mechanism for the 1,3-intramolecular proton transfer in the isomerization of 1,3,3-triphenylpropyne to 1,3,3-triphenylallene. The intramolecularity ranged from 88% in dimethyl sulfoxide–methanol–triethylenediamine to 19% in methanol–potassium methoxide.

The purpose of the present investigation was to establish the mechanism of the base-catalyzed prototropic propargylic rearrangement of 3-hexyne in EDA.

Results and Discussion

Sodium amide or *n*-butyllithium (1.6 *M* in hexane) did not rearrange 3-hexyne within 72 hr at room temperature. Similarly, EDA alone did not rearrange 3-hexyne. However, the combination of such bases and EDA rapidly brought about rearrangement without by-products.

The relative rate of the 3-hexyne rearrangement was found to be a function of the time sodium amide and amine were allowed to interact prior to the addition of 3-hexyne. The rates were expressed as half-times, the time in which 50% of the starting 3-hexyne rearranged. Such values were secured by plotting experimental data, 3-hexyne (%) *vs.* reaction time (min). For EDA, the half-time decreased from 12 to 0.5 min (Table I) as the sodium amide and EDA interaction time increased. The lower limit was approached after 30 min of mixing time.

Recently it was found[7] that strong bases such as sodium amide or *n*-butyllithium react with EDA in the absence of air to yield the radical ion of pyrazine (I), which forms a gold-colored solution. However,

I

the presence of traces of air also produces an intense blue-colored product of unknown constitution.[7]

The rate of formation of the pyrazine radical ion and/or the blue-colored product seemed to parallel closely the enhancement in the rate of rearrangement of hexyne brought about by the product of the interaction of a strong base (*e.g.*, sodium amide) with EDA. The possibility that the propargylic rearrangement in EDA was brought about by I, and/or the blue-colored product, was eliminated when I and the blue compound, prepared directly from pyrazine,[8] failed to rearrange hexyne in EDA.

The rearrangement of hexyne was actually brought about by the salt of ethylenediamine (NaEDA), the first reaction product of sodium amide with EDA. This was demonstrated by measuring the rate of evolution of ammonia. Since sodium amide is only sparingly soluble in EDA, time was required before an effective concentration of NaEDA in EDA was formed.

$$H_2NCH_2CH_2NH_2 + NaNH_2 \longrightarrow Na^+EDA^- + NH_3$$

N-Lithoethylenediamine (LiEDA), which forms rapidly from *n*-butyllithium and EDA, was observed to rearrange hexyne as quickly as LiEDA prepared from lithium and EDA. However, the reaction product of sodium and EDA contained only small amounts of NaEDA and was not an effective rearrangement catalyst. This was in agreement with the earlier findings.[9]

In order to get an additional insight into the mechanism of the base-catalyzed rearrangement of 3-hexyne, the relative rates of rearrangement were also established in various amines and diamines (Table II). The "equilibrium" composition of the rearrangement products was always the same, irrespective of the amine used. With the molar ratio of 3-hexyne:sodium amide:amine of 18:1:18, the products consisted of 2-hexyne (80%), 3-hexyne (12%), 1-hexyne (4%), and 2,3-hexadiene (4%).

There was a definite rate enhancement in the presence of vicinal diamines of which EDA produced the fastest rearrangement. To show that this was due to more than the concentration factor involving twice as many amine groups and protons, the reaction with cyclohexylamine and 1,2-diaminocyclohexane was run with an equivalent amount of the amine function present. As the amount of cyclohexylamine was doubled, the half-time was almost halved. However, the half-time was still very high compared to the diamine (Table II). Similarly, 1-aminopropane gave no rearrangement after 100 hr, while 1,2- and 1,3-diaminopropane caused rearrangement of 3-hexyne with half-times of 3 and 15 min, respectively.

The half-times were found to increase with increased alkyl substitution on EDA. Steric crowding of the

(4) W. Smadja, *Ann. Chim. (Paris)*, **10**, 105 (1965).
(5) J. H. Wotiz, W. E. Billups, and D. T. Christian, *J. Org. Chem.*, **31**, 2069 (1966).
(6) D. J. Cram, F. Willey, H. P. Fischer, H. M. Relles, and D. A. Scott, *J. Amer. Chem. Soc.*, **88**, 2759 (1966); D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1965, Chapter V.
(7) J. H. Wotiz, R. D. Kloepfer, P. M. Barelski, C. C. Hinckley, and D. F. Koster, *J. Org. Chem.*, **37**, 1758 (1972).
(8) A. Carrington and J. dos Santos-Veiga, *Mol. Phys.*, **5**, 21 (1962).
(9) L. Reggel, S. Friedman, and I. Wender, *J. Org. Chem.*, **23**, 1136 (1958).

TABLE II
3-HEXYNE REARRANGEMENTS[d]

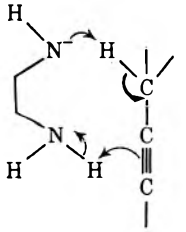
Amine	Base[a]	Half-time, min
Ethylenediamine	$NaNH_2$	0.5
Ethylenediamine	LiEDA	0.7
Ethylenediamine	Na and EDA reaction product	*c*
1-Aminopropane	$NaNH_2$	*c*
1,3-Diaminopropane	$NaNH_2$	15.0
1,6-Diaminohexane	$NaNH_2$	450.0
N,N'-Dimethylethylenediamine	$NaNH_2$	20.0
N,N-Dimethylethylenediamine	$NaNH_2$	12.0
N-Methylethylenediamine	$NaNH_2$	2.5
1-Methyl-1,2-diaminopropane	$NaNH_2$	44.0
1,2-Diaminocyclohexane, 36% *cis* and 64% *trans*	$NaNH_2$	9.3
Cyclohexylamine	$NaNH_2$	240.0
Cyclohexylamine	$NaNH_2$	145[b]
Trimethylethylenediamine	$NaNH_2$	540.0
Tetramethylethylenediamine	$NaNH_2$	2400.0
Aziridine	$NaNH_2$	4.5
Pyrrolidine	$NaNH_2$	63.0
Piperidine	$NaNH_2$	1500.0
Diethylamine	$NaNH_2$	*c*
Aniline	$NaNH_2$	*c*
Pyridine	$NaNH_2$	90.0
Tributylamine	$NaNH_2$	*c*

[a] $NaNH_2$ was stirred with the amine for 30 min before the addition of 3-hexyne. [b] Mole ratio: 3-hexyne, 18; $NaNH_2$, 1; amine, 36. [c] No arrangement after 100 hr. [d] Mole ratio: 3-hexyne, 18; base, 1; amine, 18.

active amine sites, as well as the decrease in the number of available protons, were likely reasons for the slower rearrangements in secondary and tertiary diamines. As the separation of the diamine function was increased, the half-times increased (Table II).

The reaction of sodium amide in diethyl- or diisopropylamine with 3-hexyne was too slow to observe even after 100 hr. In cyclic amines the half-time increased markedly as the ring size increased. Aniline and other aromatic amines failed as rearrangement solvents. The rate enhancement in pyridine over other tertiary amines may be due to its more effective solvating power.

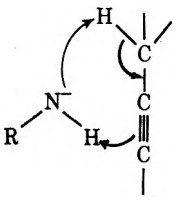
A mechanism is suggested that involves a concerted reaction with the diamine anion in a nine-membered ring transition state (II). Molecular models of II show



II

a favorable geometry. The linearity of the acetylene and allene preclude a ring size less than eight.[10]

A concerted mechanism with a monoamine anion involving a six-membered ring transition state (III) seems unlikely from examination of the models. However, this does not rule out a stepwise reaction of



III

base abstraction and proton recapture at the allenic position, or the conducted tour mechanism[6] by the base.

Valuable information concerning the mechanism of the proton transfer in the propargylic rearrangement was secured using deuterated EDA and *n*-butyllithium (BuLi). Starting with 3-hexyne these reagents produced rearranged products which contained deuterium. A mixture of EDA-d_4 (N–D) and 3-hexyne did not exchange deuterium and rearrangement was not noticed within 20 hr.

Since 1-hexyne does not appreciably rearrange within 12 hr[5] in the presence of EDA and strong base, it was treated with EDA-d_4 and BuLi to establish how much deuterium was exchanged without rearrangement. The terminal proton in 1-hexyne is relatively acidic and exchanges rapidly with solvent.[11] Mass spectroscopy was used in determining how many protons exchanged at the nonterminal position. The major peak of the 1-hexyne mass spectrum, recorded at 10 eV, was due to the hexynyl ion, $CH_3CH_2CH_2CH_2C{\equiv}C$, arising from the fragmentation of the terminal hydrogen (see also ref 12).

Table III shows that exchange occurred in the non-

TABLE III
PER CENT OF DEUTERIUM IN 1-HEXYNYL IONS FROM THE MASS SPECTRA OF THE REARRANGEMENT MIXTURES FROM THE REACTION OF 1-HEXYNE WITH BuLi AND EDA-d_4

Sample time	% d_0	% d_1	% d_2	% Total D
5 min	36.7	63.3	0	6.9
18 hr	27.9	72.1	0	8.1

terminal position when 1-hexyne reacted with BuLi and EDA-d_4 for 5 min. The per cent of deuterium was calculated from the mass spectra assuming that the labeled and unlabeled species fragmented identically, and correcting the parent peaks for the P + 1 and P − 1 peaks.[13]

The positions of exchange in 1-hexyne were determined from the HA-100 nmr spectra. The data in Table IV shows that the more acidic acetylenic and

TABLE IV
POSITION OF PROTON EXCHANGE IN 1-HEXYNE

Position	Number of protons	Number of protons exchanged[a]
Acetylenic	1.0	0.7
Propargylic	2.0	0.4
Methylenes	4.0	0
Methyl	3.0	0

[a] After reacting with BuLi-EDA-d_4 for 5 min.

(10) W. R. Moore and H. R. Ward, *J. Amer. Chem. Soc.*, **85**, 86 (1963).

(11) J. Dale in "Chemistry of Acetylenes," Marcel Dekker, New York, N. Y., 1969, Chapter 1.

(12) G. J. Zwolinski (Director), American Petroleum Institute Research Project 44, mass spectral data, 1969, serial numbers 1811–1813.

(13) K. Biemann, "Mass Spectrometry: Organic Chemical Applications," McGraw-Hill, New York, N. Y., 1962.

TABLE V

RESULTS FROM THE REARRANGEMENT REACTION OF 3-HEXYNE WITH EDA-d_4 AND BuLi

Sample time, min	Per cent of labeled species (mass spectrum) d_0	d_1	d_2	d_3	d_4	d_5	d_6	% D	Per cent of isomers (vpc) 2-Hexyne	2,3-Hexadiene	3-Hexyne
0.5	92.0	2.9	5.1					1.3	1.9	6.5	91.6
1	80.5	7.4	9.5	2.6				3.5	8.5	13.8	77.7
2	44.8	16.2	15.9	11.8	9.1	2.2		13.1	37.6	13.2	49.2
5	8.6	15.1	23.9	26.7	18.7	5.6	1.3	25.5	79.7	5.8	14.5

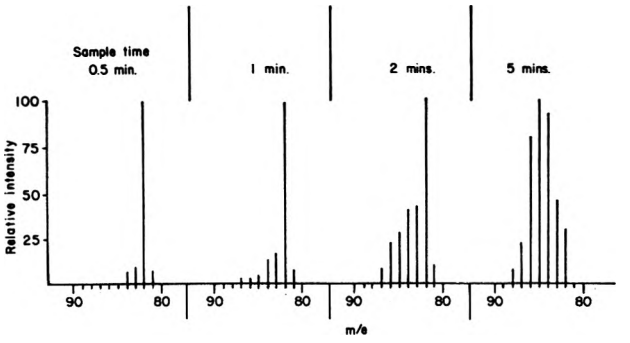


Figure 1.—Mass spectra from the reaction of 3-hexyne–EDA-d_4–BuLi.

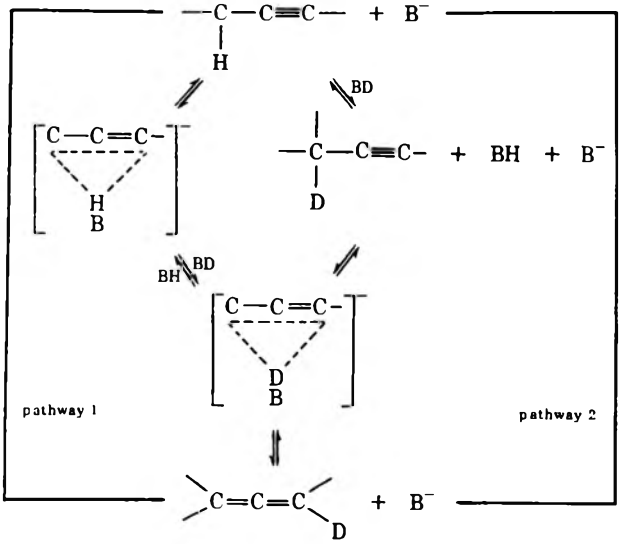
propargylic protons exchanged and 6.8% of deuterium (Table III) was incorporated at the propargylic positions. The lack of exchange in the methyl and methylene positions is in agreement with the findings of Shatenshtein,[14] who studied the exchange of hydrocarbons in deuterated potassium amide–amine systems.

In the rearrangement of 3-hexyne using BuLi and EDA-d_4, there was good correlation between the amount of rearrangement and the amount of deuterium incorporated into the rearranged mixture (Figure 1 and Table V). The amount of incorporated deuterium increased as the amount of 3-hexyne decreased. The per cent of d_0 species and the per cent of 3-hexyne may be within the limit of accuracy of the experiment.

It is likely that some deuterium exchange occurred independently of rearrangement in all the isomers, as shown with 1-hexyne. Thus, beside the pathway 1 in Scheme I, it is possible that some deuterium was incorporated through exchange followed by an intramolecular (conducted tour[6]) rearrangement, as in pathway 2.

SCHEME I

REARRANGEMENT AND DEUTERIUM INCORPORATION



On the basis of the relative amounts of deuterium incorporated in the 1-hexyne and 3-hexyne reactions (Tables III and IV), pathway 1 is more likely. Assuming the 6.9% deuterium incorporation in 1-hexyne without rearrangement to be general and applicable to 3-hexyne, there could be no more than twice that (13.8% deuterium) incorporated by exchange in 3-hexyne, which has twice as many propargylic protons. Table V shows that after 5 min 25.5% deuterium was incorporated during the 3-hexyne rearrangement.

The question of distinguishing between a concerted mechanism (II) and the intermolecular proton abstraction and proton (dueteron) recapture (pathway 1) cannot be answered at this time; most probably both occur in the EDA case.

Experimental Section

Vapor phase chromatograms were obtained using a Varian Aerograph Model 1860 chromatograph with a flame ionization detector, capillary splitter, and a Varian Aerograph Model 20 strip recorder with disc integrator.

All of the hexyne rearrangement mixtures were separated on a 200 ft × 0.01 in. (i.d.) stainless steel capillary column coated with (HHK) hexadecane, hexadecene, and k-cel (Perkin-Elmer).

The amines and diamines were analyzed on a 10 ft × 0.25 in. (o.d.) aluminum column packed with (DCKOH) 10% D.C. 710 silicone, 19% KOH on Chromosorb W.[15]

All mass spectra were obtained using a Consolidated Electrodynamics Corp. Model 21-104 mass spectrometer at both 10 and 70 eV. Nuclear magnetic resonance spectra were recorded on a HA-100 spectrometer.

Sodium amide (Robert's Chemicals, Inc.) was weighed into ampoules in the dry box (nitrogen atmosphere) and sealed.

n-Butyllithium (Foote Mineral Co.), 1.6 *M* in hydrocarbon solvent (hexane, pentane, benzene, and toluene), was always transferred in the drybox with a syringe.

Lithium wire and sodium (Matheson Coleman and Bell) were used as purchased, and were cut and weighed under benzene.

Ethylenediamine (Aldrich Chemical Co.), distilled (bp 116°) from sodium metal, was 99.9% pure (vpc).[7]

All of the other amines and diamines (Matheson Coleman and Bell or Aldrich Chemical Co.) were distilled from sodium prior to use.

Hexyne Rearrangements.—In the drybox, the amine was weighed into a 25-ml erlenmeyer flask containing a magnetic stirring bar. The base was added and the flask was capped with a rubber serum cap. Several of the vicinal primary or secondary diamines developed intensely colored solutions after a few minutes.[7] After this mixture stirred for 30 min outside the drybox, 3-hexyne was added with a syringe. The reaction was then stirred, sampled at intervals using a syringe to withdraw a portion through the rubber serum cap, and quenched with H_2O in an ice bath. The organic layer was separated, washed once each with 10% HCl and H_2O, and dried over sodium sulfate. In reactions run under vacuum samples of the volatile components were collected by vacuum transfer (precluding any 1-hexyne[5]). The mixtures were analyzed by vpc.

The purity of amide was determined by titration of the am-

(14) A. I. Shatenshtein, *Advan. Phys. Org. Chem.*, **1**, 178 (1963).

(15) E. D. Smith and R. D. Radford, *Anal. Chem.*, **33**, 1160 (1961).

monia liberated from the reaction with H_2O.[16] The amount of sodium amide, indicated in moles, was corrected for active amide present. The purity (55–64%) varied according to source and handling conditions. The equilibrium composition of the rearranged products was invariant to the amine or base used.

Reaction of Lithium and Sodium with EDA.—EDA (50 ml, 0.83 mol) and lithium wire (0.5 g, 0.07 mol) were allowed to react using the procedure described by Wender and coworkers.[9] The mixture immediately turned dark blue. It was refluxed and stirred for 30 min, after which the color discharged to cloudy white. On cooling, the condenser was replaced by a rubber stopper. Immediately, the solution turned light blue (different from the dissolved metal color) and on stirring, turned blue-purple.[7] Upon heating, the blue-purple color discharged and reappeared on cooling.

Sodium metal, when treated with EDA in a similar manner, gave a dark, viscous mixture. Numerous higher molecular weight amines were identified by vpc analysis.[7]

Preparation of Ethylenediamine-d_4 (94% N-D).—EDA (10 g, 0.17 mol) was stirred with D_2O (75 g, 3.7 mol) for 2 hr. The solution, cooled in a Dry Ice–acetone bath, was treated with sodium metal until the diamine layered out. The diamine (top layer) was separated in the same manner and was dried over sodium metal for 24 hr. Vacuum transfer gave 6.0 ml, nmr (CCl_4) δ 2.62 (s, 17, methylene), 0.99 (s, 1, NH).

Reaction of Sodium Amide with EDA.—EDA (78.3 mmol) was vacuum transferred into an evacuated flask containing sodium amide (5.7 mmol). The stirred mixture evolved ammonia (4.0 mmol), which was identified by ir and mass spectrometry. Quantitative data was obtained by using a volume calibrated vacuum manifold and a mercury manometer.

3-Hexyne and Pyrazine Radical Anion.[8]—The pyrazine radical anion was prepared by vacuum transferring 15 ml of 10^{-2} *M* pyrazine in THF to 0.015 mol of *n*-butyllithium.[7] 3-Hexyne was vacuum transferred and the mixture was stirred for 100 hr. No rearranged hexyne was found.

Reactions of Deuterated Ethylenediamine. A.—EDA-d_4 (2.0 ml, 28 mmol), BuLi (2.0 ml, 3.2 mmol), and 3-hexyne (2.0 ml, 18 mmol) were allowed to react. The reaction was sampled by vacuum transfer. The vpc and mass spectral results are found in Table V.

B.—EDA-d_4 (0.8 ml, 11 mmol), BuLi (1.0 ml, 1.6 mmol), and 1-hexyne (1.0 ml, 8.8 mmol) were mixed. A sample was vacuum transferred 5 min after thawing: nmr (CCl_4) δ 2.12 (m, 1.6, propargylic), 1.86 (t, 0.3, acetylenic), 1.47 (m, 4.0, methylene), 0.91 (m, 3.0, methyl); mass spectrum *m/e* (rel intensity) 81 (55.3), 82 (100), 83 (7.2). A second sample was taken after 18 hr, mass spectrum *m/e* (rel intensity) 81 (36.5), 82 (100), 83 (7.9). Neither sample showed any rearrangement (vpc).

C.—EDA-d_4 (0.5 ml, 7 mmol) and 3-hexyne (0.5 ml, 4 mmol) were stirred for 20 hr. The 3-hexyne did not rearrange (vpc) or incorporate any deuterium (mass spectrum).

Registry No.—3-Hexyne, 928-49-4; EDA, 107-15-3; 1-hexyne, 693-02-7; EDA-d_4, 37164-19-5; BuLi, 109-72-8.

(16) D. A. Skoog and D. M. West, "Analytical Chemistry," Holt, Rinehart, and Winston, New York, N. Y., 1965, p 308.

Electrophilic Bromination of Aromatic Conjugated Olefins. II. The Mechanism of the Dual-Path Additions in Stilbene Bromination. Evidence from Multiple Substituent Effects for Carbonium Ion Intermediates[1]

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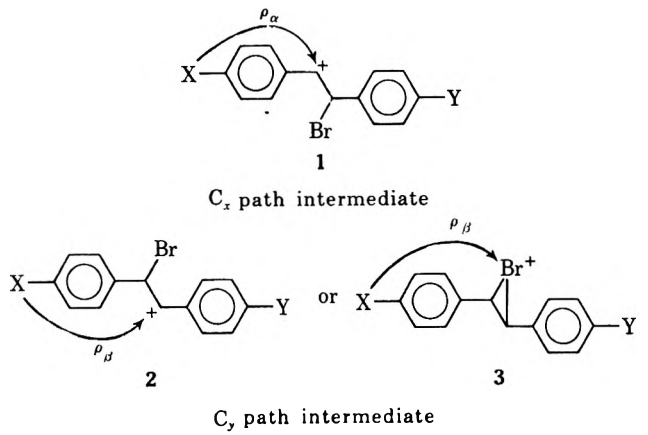
Kinetic data for the bromination of disubstituted stilbenes, $XC_6H_4C_xH{=}C_yHC_6H_4Y$, in methanol are interpreted in terms of the dual-path addition mechanism in which two pathways (with rate constants k_x and k_y, respectively), leading to discrete carbonium ions, C_x^+ and C_y^+, are involved. The nonlinear free energy relationship corresponding to this scheme is $\log (k/k_0) = \log [(k_x + k_y)/k_0] = \log [10^{\rho_\alpha \sigma_X^+ + \rho_\beta \sigma_Y} + 10^{\rho_\alpha \sigma_Y^+ + \rho_\beta \sigma_X}]$, where ρ_α and ρ_β are the reaction constants for aryl substituents α and β to the charged center, respectively. Values of ρ_α (−5.07) and ρ_β (−1.40) are obtained by simplification of the above equation using sets of compounds for which k_x or k_y can be neglected. These values are found to be applicable, in a reactivity range of six powers of ten, to compounds for which k_x and k_y are of comparable magnitude. However, substituent effects are only approximately additive; *i.e.*, substituents do not act wholly independently, and agreement between calculated and experimental reactivities is occasionally unsatisfactory. Nevertheless, it is possible to exclude any significant contribution from a bromonium ion pathway for this reaction. The bromination of the same stilbenes in carbon tetrachloride, where intermediates are bromonium-ion-like, reveals a dramatically different situation, there being an additive linear free-energy relationship, $\log (k/k_0) = \rho\Sigma\sigma$, which shows that in this solvent the structures of the transition states are symmetrical, whereas, in methanol, the transition states are carbonium-ion-like.

For electrophilic additions involving carbonium ion intermediates, a dual-path mechanism is postulated since the attacking electrophile can, in principle, choose for σ bonding either one of the two olefinic carbon atoms in the rate-determining step. The feasibility of this mechanism has been evaluated by studying the monosubstituted trans stilbenes, $XC_6H_4C_xH{=}C_yHC_6H_5$, whose bromination is assumed to lead to two discrete intermediates, the carbonium ions C_x^+ and C_y^+ (1 and 2; Y = H), by competitive pathways, referred to as the C_x and C_y paths. The kinetic data have been interpreted in terms of a nonlinear free-energy relationship derived from this mechanism by application of the Hammett equation to each pathway. Circumstantial evidence for the validity of this scheme is provided by the agreement between the regioselectivity of attack by methanol and the calculated relative importance of each pathway. However, the assumption regarding the structures of the intermediates cannot be verified beyond doubt. Only for the C_x path can it be stated with certainty that the intermediate is a carbonium ion; the effect of the substituent X in this path is expressed by ρ_α, whose value is closely related to those obtained for reactions with benzylic cationic intermediates. For the intermediate of the C_y path, the value of ρ_β requires only that the

(1) M. F. Ruasse and J. E. Dubois, *J. Org. Chem.*, **37**, 1770 (1972). Also regarded as Part XXXV of the series "Reactivity of Unsaturated Compounds: Bromination." Part XXXIV: J. E. Dubois, J. Guillo, and X. Q. Huynh, *J. Chim. Phys.*, in press.



charge be in the β position, so that the intermediate of this path could be the bromonium ion **3** or the carbonium ion **2**.

The bromination of the X,Y-disubstituted stilbenes, which we report now, was undertaken with two objectives in view: firstly, the generalization of the kinetic treatment of the dual-path additions to include polysubstituted compounds and, secondly, the determination of the real structure of the second intermediate. The distinction between the two possible structures can be tackled, in principle, by measurement of the effect of the substituent Y in the second aromatic ring. If the bromine atom bears the charge in the transition state, the effect of Y must equal the effect of the first substituent X in the C_y path. On the other hand, if the carbon atom bears the charge, the effect of Y must equal the effect of X in the C_x path.

However, nonadditivity of multiple substituent effects has been observed in electrophilic reactions, in the bromination of the 1,1-diarylethylenes in particular.[2a] It is possible that in stilbenes also the introduction of a second substituent modifies the effect of the first one, because of interactions between the charge and the substituents. The kinetic data for the bromination of disubstituted trans stilbenes must be examined with this problem in mind before we attempt to draw any conclusion regarding the structures of the intermediates.

Results and Discussion

The rate constants for the bromination of 21 trans-disubstituted stilbenes have been measured under the same conditions as those of the monosubstituted stilbenes,[1] *i.e.*, in methanol, 0.2 *M* NaBr added, at 25°, and are listed in Table I.

In this solvent, the brominating agents are molecular bromine and tribromide ion, the latter being formed in equilibrium by reaction of bromide ion with bromine. Strictly speaking, analysis of structural effects should be based on the elementary rate constant, k_{Br_2}, and not on the composite rate constant,[2b] k_{exp}. However, during the study of the bromination of the monosubstituted stilbenes, we established that there exists a linear relationship between the elementary rate constant and k_{exp}, $\log k_{exp} = 0.99 \log k_{Br_2} - 1.16$, in a reactivity range varying from 1 to 10^8 l. mol^{-1} min^{-1}. The disubstituted stilbenes investigated here are in this reactivity range. It can, therefore, be reasonably assumed that the same relationship is valid here and structural effects and ρ values can be discussed in terms of experimental rate constants alone. To analyze these rate constants, it is convenient to classify the compounds in subpopulations in which a substituent X is held constant and the other one, Y, varied. In Table II, the relative rates, $k_{X,Y}/k_{X,H}$, are given for the subpopulations where X is *p*-hydroxy, *p*-methoxy, *p*-methyl, *p*-chloro, and *p*-nitro. Inspection of Table II reveals that, when a strong electron-releasing group is attached to the first ring, the introduction of a second substituent alters the rate very slightly. However, if the first substituent is electron attracting, the rate is considerably affected by the second one. A horizontal comparison (Y constant,

(2) (a) E. D. Bergmann, A. F. Hegarty, and J. E. Dubois, *Chem. Commun.*, 1616 (1968); A. F. Hegarty, J. S. Lomas, V. W. Wright, E. D. Bergmann, and J. E. Dubois, *J. Org. Chem.*, **37**, 2218, 2222 (1972). (b) J. E. Dubois and X. Q. Huynh, *Bull. Soc. Chim., Fr.*, 1436 (1968); P. Alcais, J. J. Aaron, R. Uzan, F. Rothenberg, and J. E. Dubois, *ibid.*, 612 (1971).

TABLE I
EXPERIMENTAL RATE CONSTANTS OF STILBENE BROMINATION IN METHANOL

X	Y	k^a	Kinetic method[b]
p-OH	*p*-OH	3.40×10^6	A
p-OH	*p*-OMe	2.40×10^6	A
p-OH	*p*-Me	1.27×10^6	A
p-OH	*p*-Cl	3.37×10^5	B
p-OH	*p*-NO_2	8.40×10^4	B
p-OMe	*p*-OMe	2.20×10^5	C
p-OMe	*p*-Me	1.14×10^5	C
p-OMe	*m*-Me	9.53×10^4	C
p-OMe	*p*-Cl	4.50×10^4	D
p-OMe	*m*-Cl	3.39×10^4	D
p-OMe	*p*-NO_2	5.22×10^3	C
p-Me	*p*-Me	6.10×10^2	C
p-Me	*m*-Me	4.09×10^2	B
p-Me	*p*-Cl	1.04×10^2	D
p-Me	*m*-Cl	6.6×10	D
p-Me	*p*-NO_2	9.9	E
p-iPr	*p*-iPr	7.0×10^2	C
m-Me	*p*-NO_2	1.92	E
p-Cl	*p*-Cl	3.67	E
p-Cl	*m*-Cl	1.80	E
p-Br	*p*-Br	2.50	E

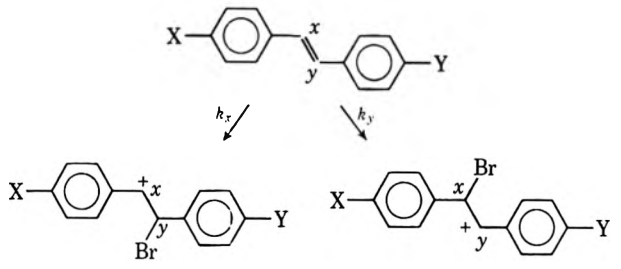
[a] k in l. mol^{-1} min^{-1} in methanol–0.2 *M* NaBr at 25°; average error 2.5%. [b] A, couloamperometry: J. E. Dubois, P. Alcais, and G. Barbier, *J. Electroanal. Chem.*, 8, 359 (1964). B, potentiometry: R. P. Bell and E. N. Ramsden, *J. Chem. Soc.*, 161 (1958). C, coulometric concentrostat: J. E. Dubois and G. Mouvier, *C. R. Acad. Sci.*, 255, 1104 (1962). D, spectrometry: J. E. Dubois and F. Garnier, *Spectrochim. Acta*, 28A, 2279 (1967). E, amperometric titrations: J. E. Dubois and E. Bienvenüe-Goetz, *Bull. Soc. Chim. Fr.*, 2086 (1968).

TABLE II
KINETIC EFFECTS, $k_{X,Y}/k_{X,H}$, OF THE VARIABLE SUBSTITUENT Y AS A FUNCTION OF THE CONSTANT SUBSTITUENT X IN THE BROMINATION OF THE X,Y-DISUBSTITUTED STILBENES

	X				
Y	*p*-OH	*p*-OMe	*p*-Me	*p*-Cl	*p*-NO_2
p-OH	4.00	30	4,230	43,000	80,000
p-OMe	2.80	2.80	380	5,800	5,000
p-Me	1.50	1.46	2.03	13.3	9.4
m-Me		1.22	1.37		1.80
H	1.00	1.00	1.00	1.00	1.00
p-Cl	0.39	0.58	0.35	0.47	
m-Cl		0.43	0.22	0.23	
p-NO_2	0.10	0.07	0.03		

X variable) also shows that the effect of an electron-releasing group depends essentially on the electronic character of the other substituent, while the effect of an electron-withdrawing one is only slightly influenced by the other. We shall now analyze the data in more detail in terms of the dual-path mechanism.

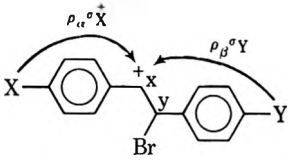
Extension of the Free-Energy Relationship for Dual-Path Additions to the Bromination of Disubstituted Stilbenes.—By analogy with the bromination of monosubstituted stilbenes[1] and if, as a first approximation, bromine participation is neglected, the mechanistic scheme for addition to a trans-disubstituted stilbene can be taken to involve two competitive pathways leading to two discrete intermediates, with rate constants k_x and k_y, respectively.



The measured rate constant is then the sum of the two partial rate constants

$$k_{exp} = k_x + k_y \quad (1)$$

Let us assume that each partial rate constant obeys the Hammett equation:[3] in the C_x intermediate, the effect of the substituent X, which is directly conjugated to the incipient carbonium center, is expressed by $\rho_\alpha\sigma_X^+$ and that of Y, transmitted by CHBr, is given by $\rho_\beta\sigma_Y$; ρ_α and ρ_β are the reaction constants for substituents in the aryl ring α and β with respect to the charge.[4] The σ^+ constant is used when the substituent is able to interact resonantly with the charged center and σ when it cannot do so.



To write the Hammett equation for the C_x path, it is necessary to assume the independence of the effect of X and Y. With this assumption,[5] we can write

$$\log (k_x/k_0) = \rho_\alpha\sigma_X^+ + \rho_\beta\sigma_Y \quad (2)$$

In the same way, for the C_y path

$$\log (k_y/k_0) = \rho_\alpha\sigma_Y^+ + \rho_\beta\sigma_X \quad (3)$$

Then the general free-energy relationship for electrophilic addition on trans-disubstituted stilbenes is

$$\log (k_{exp}/k_0) = \log [10^{\rho_\alpha\sigma_X^+ + \rho\beta\sigma_Y} + 10^{\rho_\alpha\sigma_Y^+ + \rho\beta\sigma_X}] \quad (4)$$

Reaction Constants, ρ_α and ρ_β.—From the rate constants of particular compounds for which the general free-energy relationship 4 could be simplified, two simple approaches, A and B, have been developed to obtain the values of the reaction constants, ρ_α and ρ_β.

(3) J. E. Leffler and E. Grunwald, "Rates and Equilibria in Organic Reactions," Wiley, New York, N. Y., 1963, p 171.

(4) The indexes x and y refer to the positions of the charge in α to the substituent X and Y, respectively. The indexes α and β refer to the position of the substituent α and β with respect to the charge.

(5) In this way, we postulate that the introduction of Y does not modify the effect of X, so that we can consider the kinetic effects of X and Y as additive. This assumption will be discussed in more detail later.

TABLE III

PARTICULAR REACTION CONSTANTS ρ_α^X AND ρ_β^X FOR A VARIABLE SUBSTITUENT Y AS A FUNCTION OF A CONSTANT SUBSTITUENT X

X	ρ_β^X[a]	ρ_α^X[a]	n[b]
p-OH	−1.25 ± 0.4	c	3
p-OMe	−1.52 ± 0.6	c	4
p-Me	−1.88 ± 0.3	c	3
H	−1.53 ± 0.2	−5.05 ± 0.7	5
p-Cl	c	−5.71 ± 0.4	3
m-Cl	c	−4.97 ± 0.7	3
p-NO_2	c	−5.25 ± 0.8	5

[a] For precisions, see footnote 7. [b] Number of compounds from which ρ_α^X and ρ_β^X have been determined. [c] The values of ρ_α^X and ρ_β^X corresponding to these substituents X cannot be calculated since their evaluation requires several substituents more electron-donating than p-hydroxy for $\rho_\alpha^{p\text{-OH}}$ or more withdrawing than p-nitro for $\rho_\beta^{p\text{-}NO_2}$.

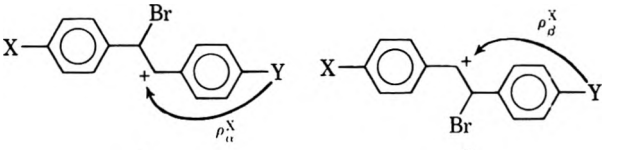
A. Reaction Constants ρ_α^X and ρ_β^X for Defined Subpopulations (X Constant, Y Variable).—In subpopulations so arranged that one substituent, X, is constant and only Y varies (Table III), are chosen the stilbenes for which it can be reasonably assumed from previous results[1] that only one pathway contributes. In these cases, the free-energy relationship 4 simplifies to

$$\log (k_{X,Y}/k_{X,H}) = \rho_\alpha^X\sigma_Y^+ \quad (5)$$

if the preferred pathway leads to the intermediate **4** and

$$\log (k_{X,Y}/k_{X,H}) = \rho_\beta^X\sigma_Y \quad (6)$$

if the intermediate is **5**.



4 **5**

The application of eq 5 and 6 to stilbenes[6] where X = p-OH, p-OMe, p-Me, p-Cl, m-Cl, and p-NO_2 leads to the ρ_α^X and ρ_β^X values collected[7] in Table III. No significant variation of these values as a function of X appears.

B. General Reaction Constants, ρ_α and ρ_β.—Since the values of ρ seem to be independent of the substituent, general values of ρ_α^X and ρ_β^X must be valid for all the stilbenes. Average values of ρ_α^X and ρ_β^X (−5.08 and −1.53) are first used to calculate the partial rate constants k_x and k_y for all the stilbenes. From this calculation, we find that, for the compounds

(6) For instance, we showed previously[1] that, for the p-methoxystilbene (X = p-OMe, Y = H), only the C_x path leading to **5** contributes. When Y is more electron attracting than H, there is all the more reason for only this path to contribute. Therefore, when X = p-OMe and Y = H, p-Cl, m-Cl and p-NO_2, the free-energy relationship is $\log k_{X,Y} = \rho_\beta^{p\text{-OMe}}\sigma_Y + \log k_{p\text{-MeO,H}}$. In the same way, $\rho_\alpha^{p\text{-}NO_2}$ is calculated from stilbenes where X = p-NO_2 and Y = p-OH, p-OMe, p-Me, m-Me and H by means of the equation $\log k_{X,Y} = \rho^{p\text{-}NO_2}\sigma_Y^+ + \log k_{p\text{-}NO_2,H}$.

(7) In preference to the correlation coefficients (ca. 0.99) and to the standard deviations (ca. 0.08), which are not very significant for calculations on rather few data, we give here the absolute errors on ρ for a confidence level of 95%.

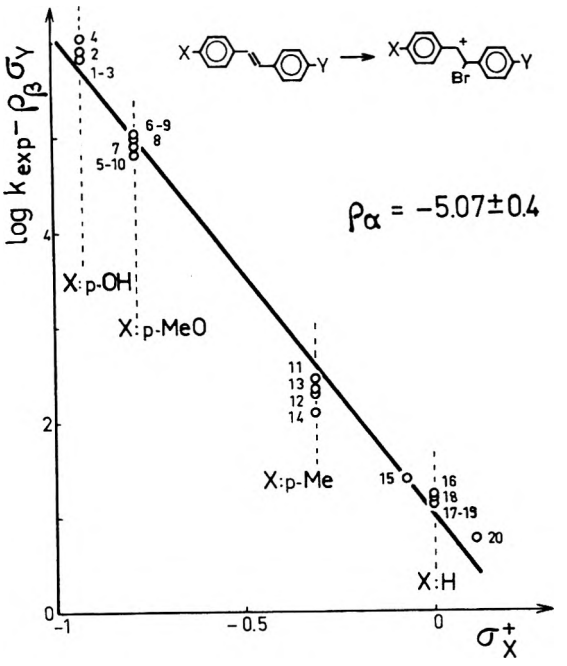


Figure 1.—Evaluation of ρ_α from disubstituted stilbenes whose bromination leads to a single intermediate (data of Table V); $\log k_{exp} - \rho_\beta\sigma_Y = \rho_\alpha\sigma_X^+$.

of Table IV, one of these rate constants is negligible[8] with respect to the other. We can, then, include in the subsequent calculations a number of additional compounds not used in the determination of the particular reaction constants. For the 20 mono- and disubstituted stilbenes where bromination occurs *via* a single pathway, the general relationship 4 simplifies to

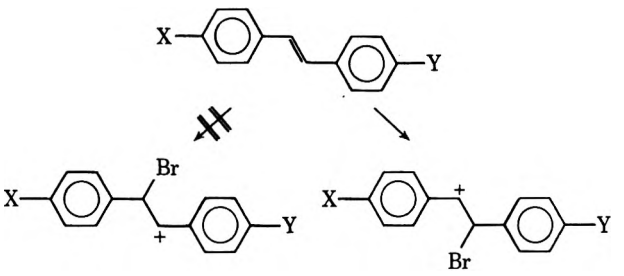
$$\log (k_{X,Y}/k_0) = \rho_\alpha\sigma_X^+ + \rho_\beta\sigma_Y \qquad (7)$$

if the substituent X is always chosen so as to be more electron donating than Y.

General values of ρ_α, ρ_β, and $\log k_0$ are thus obtained by multiple regression: $\rho_\alpha = -5.07 \pm 0.4$; $\rho_\beta = -1.41 \pm 0.4$; $\log k_0 = 1.04$ (correlation coefficient $R = 0.995$).

These values of ρ_α and ρ_β allow the calculation of k_x and k_y and therefore the overall rate constant for any stilbene. These overall rate constants for the stilbenes of Table V,[9a] compounds which have not been used in the calculation of general ρ_α and ρ_β values, are in good agreement with the experimental rate constants.[9b] This is the first evidence from kinetics in support of the initial assumption regarding the competition between two pathways for stilbene bromination in methanol.

TABLE IV
CALCULATED RATE CONSTANTS FOR METHANOLIC BROMINATION OF STILBENES BY ONE PATHWAY: $\log k/k_0 = \rho_\alpha\sigma_X^+ + \rho_\beta\sigma_Y$



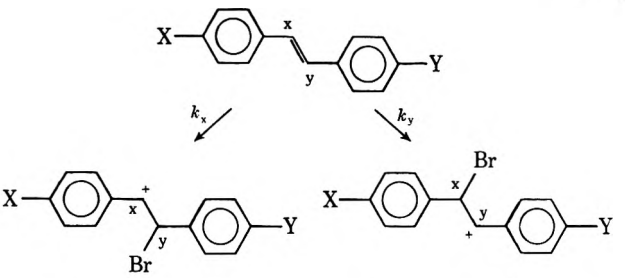
Registry no.[d]	No.	X	Y	Log k_{calcd}[a]	Log k_{exp}[b]	Δ[c]
18951-45-6	1	*p*-OH	*p*-Me	5.95 ± 0.6	6.10	−0.15
6554-98-9	2	*p*-OH	H	5.71 ± 0.4	5.93	−0.22
18951-46-7	3	*p*-OH	*p*-Cl	5.39 ± 0.4	5.53	−0.14
14064-83-6	4	*p*-OH	*p*-NO_2	4.61 ± 0.7	4.92	−0.31
37163-68-1	5	*p*-OMe	*p*-Me	5.24 ± 0.4	5.05	0.19
23940-93-4	6	*p*-OMe	*m*-Me	5.09 ± 0.3	4.98	0.11
1694-19-5	7	*p*-OMe	H	5.00 ± 0.3	4.89	0.11
18878-89-2	8	*p*-OMe	*p*-Cl	4.68 ± 0.3	4.65	0.03
37163-71-6	9	*p*-OMe	*m*-Cl	4.48 ± 0.4	4.53	−0.05
4648-33-3	10	*p*-OMe	*p*-NO_2	3.90 ± 0.6	3.72	0.18
1860-17-9	11	*p*-Me	H	2.61 ± 0.1	2.46	0.15
3041-83-6	12	*p*-Me	*p*-Cl	2.29 ± 0.2	2.02	0.27
37163-72-7	13	*p*-Me	*m*-Cl	2.09 ± 0.2	1.82	0.27
24325-70-0	14	*p*-Me	*p*-NO_2	1.50 ± 0.4	1.00	0.50
37163-74-9	15	*m*-Me	*p*-NO_2	0.29 ± 0.3	0.28	0.01
14064-43-8	16	H	*m*-Cl	0.52 ± 0.1	0.71	−0.19
891-70-3	17	H	*m*-CF_3	0.45 ± 0.1	0.53	−0.08
1149-56-0	18	H	*p*-CF_3	0.28 ± 0.2	0.40	−0.12
16194-20-8	19	H	*p*-NO_2	−0.06 ± 0.3	0.02	−0.08
25144-36-3	20	*p*-Cl	*m*-Cl	−0.06 ± 0.2	0.25	−0.31

[a] Log k_{calcd} calculated from eq 7. [b] k in l. mol^{-1} min^{-1} in methanol, 0.2 *M* NaBr at 25°. [c] Δ = log k_{calcd} − log k_{exp}. [d] Registry numbers apply to the *trans*-stilbenes.

TABLE V
CALCULATED PARTIAL AND OVERALL RATE CONSTANTS FOR BROMINATION OF STILBENES BY TWO COMPETITIVE PATHWAYS

$\log k/k_0 = \log [(k_x + k_y)/k_0] =$

$\log [10^{\rho_\alpha\sigma_X^+ + \rho_\beta\sigma_Y} + 10^{\rho_\alpha\sigma_Y^+ + \rho_\beta\sigma_X}]$



Registry no.[d]	No.	X	Y	Log k_x[a]	Log k_y[a]	Log k_{calcd}[b]	Δ[c]
15058-36-3	21	*p*-OH	*p*-OH	6.23	6.23	6.53	0.00
18951-44-5	22	*p*-OH	*p*-OMe	6.09	5.53	6.20	−0.18
15638-14-9	23	*p*-OMe	*p*-OMe	5.38	5.38	5.68	0.34
18869-29-9	24	*p*-Me	*p*-Me	2.85	2.85	3.15	0.37
37163-81-8	25	*p*-Me	*m*-Me	2.71	1.63	2.74	0.13
37163-82-9	26	*p*-*i*Pr	*p*-*i*Pr	2.67	2.67	2.97	0.13
14064-48-3	27	*m*-Me	H	1.39	1.14	1.58	−0.22
103-30-0	28	H	H	1.04	1.04	1.34	−0.16
1657-50-7	29	H	*p*-Cl	0.72	0.46	0.91	0.02
13041-70-8	30	H	*p*-Br	0.72	0.28	0.85	−0.06
1657-56-3	31	*p*-Cl	*p*-Cl	0.14	0.14	0.44	−0.12
18869-30-2	32	*p*-Br	*p*-Br	−0.04	−0.04	0.26	−0.14

[a] k_x and k_y calculated from eq 2 and 3. [b] $k_{calcd} = k_x + k_y$. [c] Δ = log k_{calcd} − log k_{exp}. [d] Registry numbers apply to the *trans*-stilbenes.

(8) For some compounds of Table IV, it can be remarked that the other path is not entirely negligible. For example, for the *p*-methylstilbene, the calculated reactivity, log k, of the C_x path is 2.60 whereas that of the C_y path is 1.24. The neglect of the C_y path leads therefore to an error on the overall reactivity of 1%, an error which is effectively negligible compared to the experimental errors (about 2%) and on the ρ values.

(9) (a) Seven stilbenes of this Table V are symmetrical compounds for which k_x equals k_y. Then for these, the general free energy relationship 4 simplifies to

$$\log (k/k_0) = \log (2k_x/k_0) = \rho_\alpha\sigma_X^+ + \rho_\beta\sigma_X + \log 2$$

This treatment for the symmetrical compounds provides the familiar value of ρ_α (−5.06 ± 0.5) but gives an abnormal and very imprecise ρ_β (−0.88 ± 1.5), although the coefficient correlation, 0.998, and the standard deviation, 0.004, are satisfactory. This result is probably due to the fact that $\rho_\alpha\sigma^+$ is very much greater than $\rho_\beta\sigma$ for electron-donating substituents, which predominate in this sample. (b) One of the referees suggested that the agreement between calculated and experimental reactivities might be the result of using a multiparameter calculation. The most striking argument in favor of our treatment is that the various methods of calculating the two ρ values lead to closely similar values. It might appear that simpler interpretations with fewer adjustable parameters could fit the data as well, but such interpretations are only valid for restricted sets of substituents chosen intuitively. To take into account all the data, this unifying treatment based on the dual-path mechanism is actually the most logical.

TABLE VI

VARIATION, ρ^X/ρ^H, OF THE REACTION CONSTANT AS A FUNCTION OF THE SUBSTITUENT X, IN REACTIONS OF X,Y-DISUBSTITUTED AROMATIC COMPOUNDS (X CONSTANT, Y VARIABLE)

X	Benzenes[a]	Benzhydryl chlorides[b]	1,1-Diarylethylenes[c]	Stilbenes[e] ρ_α	Stilbenes[e] ρ_β
p-NMe_2	0.19				
p-OH			(0.54)[d]		0.82
p-OMe	0.62	0.60	0.63		0.99
p-Me	0.92	0.85	0.80		1.23
H	1.00	1.00	1.00	1.00	1.00
p-Cl		1.01	1.04	1.13	
p-NO_2			(1.30)[d]	1.04	

[a] Electrophilic substitution by bromine in water: R. Uzan and J. E. Dubois, *Bull. Soc. Chim. Fr.*, 598 (1971); J. E. Dubois and J. J. Aaron, *J. Chim. Phys.*, 66, 1122 (1969); and ref 10 and 14. [b] Solvolysis of benzhydryl chlorides in ethanol: S. Nishida, *J. Org. Chem.*, 32, 2697 (1967); E. Berliner and M. Q. Malter, *ibid.*, 33, 2595 (1968). [c] Bromination of 1,1-diarylethylenes in methanol, ref 2. [d] Extrapolated value. [e] This work.

In Tables IV and V, differences >0.3 logarithmic units between calculated and experimental values can be observed for 4 of the 32 compounds investigated. In view of the imprecision of the calculated reactivities, these deviations may be taken as insignificant. Comparison of Figures 1 and 2 shows dramatically that ρ_β is subject to a much greater uncertainty than ρ_α: in the former case, $\log k_{exp} - \rho_\alpha\sigma_X^+$ for a constant Y depends markedly on the identity of X. This could indicate that the additivity assumption used in the general free-energy relationship 4 is not valid. A dependence on the constant substituent X of the reaction constant ρ for another variable substituent Y has been demonstrated in the bromination of 1,1-diarylethylenes[2] and benzenes.[10] It was proposed "that the presence of a substituent, particularly one capable of electron donation by resonance, in the aromatic ring so alters the charge distribution in the transition state that the second substituent in the other ring, then, interacts with a different charge." Examining in detail the two intermediates in the bromination of stilbenes,[11] we see that ρ_α^X, which measures the effect of the variable Y, can only be weakly affected by the remote X which is isolated from the charge by the bromomethylene group. On the other hand, ρ_β^X can be modified rather more by X interacting with the charge. However, since ρ_β is inherently small, the differences will also be small.

In Table VI, we show the variation, ρ^X/ρ^H, of the reaction constant for a variable substituent Y as a function of the constant substituent X for various reactions of disubstituted aromatic conjugated systems. Compared to the other reactions considered in Table VI, the variation of ρ_α for the stilbene bromination can be considered as insignificant, on account of the uncertainty involved in calculations on rather

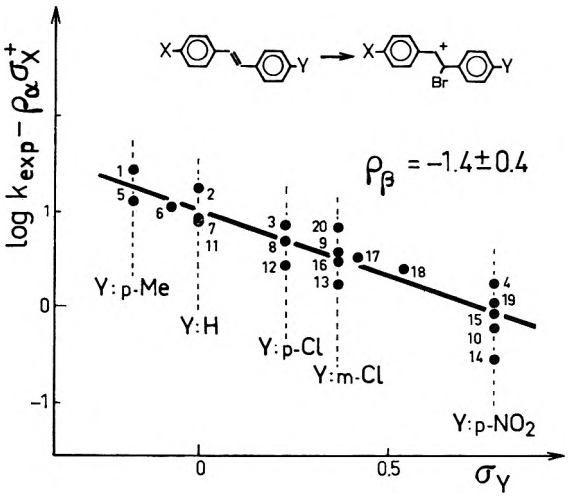


Figure 2.—Evaluation of ρ_β from disubstituted stilbenes whose bromination leads to a single intermediate (data of Table V); $\log k_{exp} - \rho_\alpha\sigma_X^+ = \rho_\beta\sigma_Y$. For a same Y, a considerable scatter is observed when X varies. In addition to a normal dispersion (as in Figure 1) due to the imprecise evaluations of ρ^X, this is to be related to a poor additivity of substituent effects for the reaction constant ρ_β; *i.e.*, ρ_β varies really as a function of X (Table III).

few points (Table III). In the same way, the variations of ρ_β, although somewhat larger than those of ρ_α, are too small and too imprecise[13] to allow us to infer the existence or the magnitude of any interaction between substituents. However, from Figure 2, the existence of a weak interaction modifying ρ_β might be inferred. Unfortunately, no quantitative estimation can be deduced, since deviations must be attributed in part to errors on ρ.

For stilbenes brominated *via* a single intermediate, another way of measuring the importance of substituent interaction is, in principle, possible. In this series, we had applied the free-energy relationship $\log (k_{X,Y}/k_0) = \rho_\alpha^H\sigma_X^+ + \rho_\beta^H\sigma_Y$. To take into account any nonadditivity of substituent effects, we should have to write $\log (k_{X,Y}/k_0) = \rho_\alpha^Y\sigma_X^+ + \rho_\beta^X\sigma_Y$. It has been shown[2] that the reaction constant ρ^H is modified by a substituent X in proportion to the value of its σ^+, so that $\rho^X = a\sigma_X^+ + \rho^H$. Therefore, this relationship becomes

$$\log (k_{X,Y}/k_0) = \rho_\alpha^H\sigma_X^+ + \rho_\beta^H\sigma_Y + a_\alpha\sigma_X^+\sigma_Y^+ + a_\beta\sigma_X^+\sigma_Y \quad (8)$$

Applying this equation to the stilbenes of Table IV, we find the familiar values for ρ_α^H and ρ_β^H (−5.05 and −1.42) and for the a_α and a_β coefficients, the small and highly uncertain values of −0.33 ± 3.2 and 0.29 ± 3.0, respectively. Therefore, no conclusion on additivity can be obtained from this treatment. The a coefficients, measuring the interaction causing the nonadditivity, are −6.2 for benzenes and −1.8 for 1,1-diarylethylenes. For stilbenes, estimated from the variations of ρ_β (Table III), this

(10) J. E. Dubois, J. J. Aaron, P. Alcais, J. P. Doucet, F. Rothenberg, and R. Uzan, *J. Amer. Chem. Soc.*, 94, 6823 (1972).

(11) Additivity of substituent effects assumes no variation of interaction between substituents in the transition state and also in the ground state. For stilbenes, it has been shown[12] from measurements of polar moments that the interaction moments, defined as $\mu_m = \mu_{XY}^{exp} - (\mu_X + \mu_Y)$, are weak and approximately independent of the nature of X and Y. Interaction in the ground state seems insensitive to the variation of the electronic character of the substituents. Therefore nonadditivity will be discussed only in terms of the structures of the transition states.

(12) K. B. Everard and L. E. Sutton, *J. Chem. Soc.*, 2826 (1951).

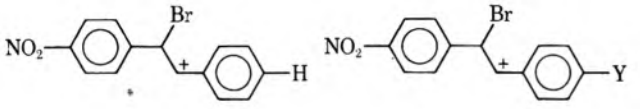
(13) The variation of ρ_β for the *p*-methyl substituent (Table VI) is particularly conspicuous. Obviously, its value is weak since its σ^+ is rather weak (−0.31). However, in 1,1-diarylethylenes, *p*-methyl diminishes the reaction constant by 20%, in benzenes it modifies it only slightly, and in stilbenes it seems to increase it. For 1,1-diarylethylenes[2] and stilbenes, the corresponding ρ values have been established only from a few compounds (4 and 3, respectively), whereas, for benzenes,[14] it was evaluated accurately over a large range of reactivity using numerous compounds. Therefore, the variation of ρ_β for the *p*-methylstilbenes would reflect only the uncertainty on μ.

(14) F. Rothenberg, P. Alcais, and J. E. Dubois, *Bull. Soc. Chim. Fr.*, 592 (1971).

coefficient could be of the order of −0.5. Therefore, if this interaction exists in stilbene bromination, it cannot be very important and the previous analysis of the kinetic data which neglects interaction can be considered adequate.

Carbonium or Bromonium Ion Intermediates in Stilbene Bromination.—The kinetic scheme involving two pathways is based on two assumptions: the first one supposes the additivity of the substituent effects (we have already discussed this hypothesis and concluded to its validity) and the second one excludes the participation of bromine in stabilizing the charge in the transition state. The agreement between the kinetic results and the reactivities calculated from this scheme tends to confirm the validity of the second assumption. In fact, a more detailed examination of the results is necessary to demonstrate the absence of bromonium ions in stilbene bromination in methanol.

From the analysis of the data for the monosubstituted stilbenes alone, it was not possible to determine the structure of the C_y path intermediate. For the strongly electron-attracting compounds (*p*-nitrostilbene, for instance), it was only established, from the value of ρ_β, that the charge of the transition state was on an atom β to the substituted ring, *i.e.*, on the β carbon or on the bromine atom. To distinguish between these two possibilities, it was proposed to measure the effect of a substituent on the second ring, since, if the charge is on the carbon atom β to the first substituent, the effect of the second must be expressed by ρ_α, whereas if the charge is on the bromine atom, the effect of this second substituent must be weaker.



In the analysis of the disubstituted stilbenes, it appears that, if the effect of one substituent is expressed by ρ_β, the effect of the other is always given by ρ_α and vice versa. These results are only consistent with a structure for the intermediate in which there is always one substituent directly conjugated to the charge; *i.e.*, this charge can only be on an olefinic carbon atom α to this substituent. Therefore, for the stilbenes investigated here, it can be affirmed that the bromine atom bears no significant charge.

This result is not unexpected for the stilbenes where one substituent at least is strongly electron donating, since the charge will be better stabilized by this electron-donating ring than by bromine, as is shown by the stereochemical results of Fahey[15] on the *trans*-β-methylstyrene and *trans*-anethole. However, bromine participation might be expected when both substituents are electron attractors, such as in the cases of the di-*p*,*p*′-chloro-, di-*p*,*p*′-bromo-, and di-*p*,*m*′-chlorostilbenes. These compounds do not deviate from the general correlation and we can deduce that bromine participation is unimportant also in these cases. In fact, the electron-attracting character of these substituents is rather weak, and it is possible that, when stronger electron attractors, such as in di-*p*,*p*′-nitrostilbene, are involved, bromine participation becomes important and, therefore, deviations from the correlation might be observed. Investigations on such compounds, which are in progress and which will be the subject of a forthcoming paper, are possible only if the kinetic parameters of the carbonium ion mechanism are known precisely.

(15) R. C. Fahey, *J. Amer. Chem. Soc.*, **88**, 4681, 1966.

TABLE VII

COMPARISON OF THE KINETIC SUBSTITUENT EFFECTS IN BROMINATION OF STILBENES IN CARBON TETRACHLORIDE AND IN METHANOL

X	Y	CCl_4, log k/k_0	MeOH, log k/k_0
p-OMe	H	3.72[a]	3.38[a]
p-Me	H	0.47	0.95
p-Cl	H	0.25	−0.62
p-NO_2	H	−0.21	−1.49
p-NO_2	*p*-OMe	2.01[a]	2.21[a]
p-NO_2	*p*-Me	0.00	−0.51
p-Me	*p*-Me	0.72	1.27

[a] For the *p*-methoxystilbenes, the similarity of the kinetic effect seems to show that the transition state structures are identical in both solvents: carbonium-like.[19]

Another argument against bromonium ion intermediates in methanol for the stilbenes so far examined can be found in a comparison of our data with the results of a recent kinetic investigation[16] on bromination of the same stilbenes in carbon tetrachloride.[17] There is no correlation of the form $\log k_{MeOH} = a \log k_{CCl_4} + b$, which would reveal an analogy between the two sets of data (Table VII) and therefore some similarity between the transition-state structures.

In carbon tetrachloride, the intermediate is bromonium-like[18] (10% only of syn adduct). Setting aside the *p*-methoxy compounds,[19] the relationship between the reactivities of mono- and disubstituted stilbenes in carbon tetrachloride and the sum of their σ constants is linear.

$$\log (k/k_0)_{CCl_4} = -0.65\ \Sigma\sigma \qquad (9)$$

A relationship in terms of $\Sigma\sigma^+$ is also linear, since σ and σ^+ are rather similar for the compounds included in this correlation. The inequality of the ρ values in methanol and in carbon tetrachloride indicates differences in the magnitude of the developing charge in the transition states. Comparison of the effects of X and Y, which are identical in carbon tetrachloride but different in methanol, underlines the fact that the charge distribution in the transition states are very different: bromonium-like in the first solvent, carbonium-like in the second. In fact, as shown here, the mechanisms of stilbene bromination in carbon tetrachloride and in methanol are very

(16) G. Heublein and E. Schutz, *Z. Chem.*, **9**, 147 (1969).

(17) In carbon tetrachloride, the bromination is a third-order reaction: first order in stilbene and second order in bromine. The first molecule of bromine forms with a molecule of stilbene a π-complex whose ionization is assisted by the second molecule of bromine.[22]

(18) (a) R. E. Buckles, J. L. Forrester, R. L. Burham, and T. W. McGee, *J. Org. Chem.*, **25**, 24 (1960); (b) G. Heublein, *J. Prakt. Chem.*, **31**, 84 (1966).

(19) Deviations in the linear relationship observed for the *p*-methoxystilbenes in carbon tetrachloride may be due to a decrease in bromine participation. From differences between the rate constants experimentally measured and calculated from eq 9, for the *p*-methoxystilbene ($1762 - 1.1\ M^{-2}\ sec^{-1}$) and for the *p*-methoxy-*p*′-nitro compound ($31.8 - 0.34\ M^{-2}\ sec^{-1}$), it can be assumed that in carbon tetrachloride the transition state is free from bromine bridging and resembles a carbonium ion. This result is confirmed by the stereochemical results of Fahey.[15] If a double bond is substituted by a *p*-anisyl group, the intermediate is preferentially a benzylic carbonium ion, even in apolar solvents.

different. In the apolar carbon tetrachloride,[20] the rate-determining step[22] is the bimolecular ionization of the CTC (charge transfer complex), with a symmetrical transition state leading to a bromonium intermediate. In polar solvents such as methanol, the reaction involves an unimolecular ionization[23] with a carbonium-ion-like transition state.

Conclusion

In short, the initial hypothesis of a dual-path mechanism for additions with carbonium ion intermediates is confirmed for stilbene bromination by the kinetic substituent effects, by the regiochemistry of the reaction, by the analogy with the kinetics of dehydration of 1,2-diarylethanols,[1] and by the differences between the results in methanol and in carbon tetrachloride.

Until now, the structure of the bromination intermediates has been determined by essentially stereochemical methods. In stereospecific brominations, it is evident that bromonium intermediates are involved. However, from reactions which are only *stereoselective*, no clear conclusion can be drawn regarding the magnitude of bromine participation, since stereoselectivity could be the result of several factors:[24] bromine bridging but also ion pairing or competition between rotation and nucleophilic attack. Our kinetic treatment based on the dual-path addition mechanism represents a new approach to the determination of the structure of intermediates in electrophilic addition. Now that the kinetic parameters for addition *via* carbonium intermediates are known, it should be possible to measure the extent of any bromine bridging, if it occurs, by observation of deviations from the general kinetic relationship.

Experimental Section

Synthesis of Stilbenes.—The disubstituted stilbenes are prepared by methods F, G, H, J, and K (Table VIII) described below.

Method F.—The demethylation by pyridine hydrochloride of di-*p,p'*-methoxystilbene leads to the di-*p,p'*-hydroxystilbene.[25]

Method G.—The condensation of the appropriately substituted benzaldehydes with the appropriate phenylacetic acid in the presence of piperidine leads to the substituted stilbenes.[26]

Method H.—The condensation of anisole and diethyl bromo acetal in acetic acid in the presence of hydrochloric acid[27] leads to the di-α,α'-*p*-anisyl-β-bromoethane. This compound, dehydrobrominated in pyridine, affords the di-*p,p'*-methoxystilbene in a yield of 55%.

Method J.—Substituted benzaldehydes are condensed with benzylmagnesium chlorides as described by House.[28] The resulting alcohols are dehydrated in cold benzene by phosphoric anhydride.

Method K.—To prepare symmetrical stilbenes, azines obtained from benzaldehydes and hydrazine are pyrolyzed by the method described by Buu-Hoi and Saint-Ruff.[29]

For the kinetic measurements, the stilbenes are purified by column chromatography on alumina or silica gel and further by recrystallizations from suitable solvents. The purity is checked by thin layer chromatography.

Among the stilbenes of Table VIII, the compounds listed in Table IX have not been described in the literature. All the ir spectra show the strong characteristic band at 960 cm^{-1}, due to the out-of-plane in-phase vibration of the olefinic hydrogen atoms.[30] In their nmr spectra, described and interpreted by Doucet, *et al.*,[31] the signals for the ethylenic protons are not readily distinguishable from the signals of the aromatic protons.

Kinetic Measurements.—Previous treatment of methanol and sodium bromide and the kinetic methods are already described in the references of Table I.

TABLE VIII

SYNTHESIS OF DISUBSTITUTED STILBENES

X	Y	Synthesis method	Mp, °C	Ref
p-OH	*p*-OH	F	278	25
p-OH	*p*-OMe	G	203-204	26
p-OH	*p*-Me	G	208-209	26
p-OH	*p*-Cl	G	186-187	26
p-OH	*p*-NO_2	G	204	26
p-OMe	*p*-OMe	H	214-215	25
p-OMe	*p*-Me	J	166-167	*a*
p-OMe	*m*-Me	J	98	*b*
p-OMe	*p*-Cl	J	196	*c*
p-OMe	*m*-Cl	J	96	*d*
p-OMe	*p*-NO_2	G	133-134	26
p-Me	*p*-Me	K	180	*e*
p-Me	*m*-Me	J	101-102	*b*
p-Me	*p*-Cl	J	203-204	*f*
p-Me	*m*-Cl	J	119	*b*
p-Me	*p*-NO_2	G	150	26
m-Me	*p*-NO_2	G	112-113	*b*
p-iPr	*p*-iPr	K	130-131	*b*
p-Cl	*p*-Cl	K	177-178	*g*
p-Cl	*m*-Cl	J	75	*b*
p-Br	*p*-Br	K	208-210	*g*

[a] D. Y. Curtin, A. Bradley, and Y. G. Hendrickson, *J. Amer. Chem. Soc.*, **78**, 4064 (1956). [b] New compound. [c] L. Horner, H. Hoffman, W. Klinl, H. Ertel, and V. G. Toscano, *Chem. Ber.*, **95**, 581 (1962). [d] S. S. Jenkins and E. M. Richardson, *J. Amer. Chem. Soc.*, **55**, 3874 (1933). [e] G. Drehafl and G. Plottner, *Chem. Ber.*, **91**, 1274 (1958). [f] W. J. Linn, *J. Amer. Chem. Soc.*, **87**, 3665 (1965). [g] J. A. Stanfield and L. B. Reynolds, *ibid.*, **74**, 2878 (1952).

TABLE IX

ELEMENTAL ANALYSIS OF NEW STILBENES

Stilbene X	Stilbene Y	Calcd, % C	H	X	N	Found, % C	H	X	N
p-OMe	*m*-Me	85.68	7.19			86.25	7.74		
p-Me	*m*-Me	92.26	7.74			92.50	7.23		
p-Me	*m*-Cl	78.76	5.68	15.52		78.56	5.60	15.62	
m-Me	*p*-NO_2	75.30	5.48		5.85	75.47	5.87		5.50
p-iPr	*p*-iPr	90.85	9.15			90.02	8.88		
p-Cl	*m*-Cl	67.46	4.01	28.51		67.14	4.68	28.21	

Acknowledgment.—We are grateful to Dr. J. S. Lomas for helpful discussion and criticism.

(20) Bromination of stilbenes in carbon tetrachloride is more closely related to epoxidation,[21] reaction in which the symmetry of the starting olefin is preserved in the transition state and even in the products, and linear relationships are obtained with $\Sigma\sigma^+$, including the *p*-methoxy- and the *p,p'*-dimethoxystilbenes.

(21) (a) B. M. Lynch and K. H. Pausacker, *J. Chem. Soc.*, 1525 (1955); (b) M. A. Hoefnagel, A. VanVeen, and B. M. Wepster, *Recl. Trav. Chim. Pays-Bas*, **88**, 569 (1969).

(22) G. Heublein and P. Umbreit, *Tetrahedron*, **24**, 4733 (1968).

(23) F. Garnier and J. E. Dubois, *Bull. Soc. Chim. Fr.*, 3797 (1969).

(24) J. A. Pincock and K. Yates, *Can. J. Chem.*, **48**, 2944 (1970).

(25) W. H. Laarhoven, R. J. F. Nivard, and E. Havinga, *Recl. Trav. Chim. Pays-Bas*, **80**, 775 (1961).

(26) H. Veschambre and A. Kergomard, *Bull. Soc. Chim. Fr.*, 336 (1966); 2846 (1967).

(27) R. Quelet, C. Broquet, and M. F. Ruasse-Touré, *C. R. Acad. Sci., Ser. C*, **254**, 1811, 1962.

(28) H. O. House, *J. Amer. Chem. Soc.*, **77**, 3070 (1955).

(29) N. P. Buu-Hoi and G. Saint-Ruff, *Bull. Soc. Chim. Fr.*, 955 (1967).

(30) S. F. D. Orr, *Spectrochim. Acta*, **8**, 218 (1956).

(31) J. P. Doucet, B. Ancian, and J. E. Dubois, *J. Chim. Phys.*, in press.

Intermediates in Nucleophilic Aromatic Substitution. VIII.[1] Temperature-Jump and Equilibrium Study of the Spiro Meisenheimer Complex of *N*-2-Hydroxyethyl-*N*-methyl-2,4-dinitroaniline

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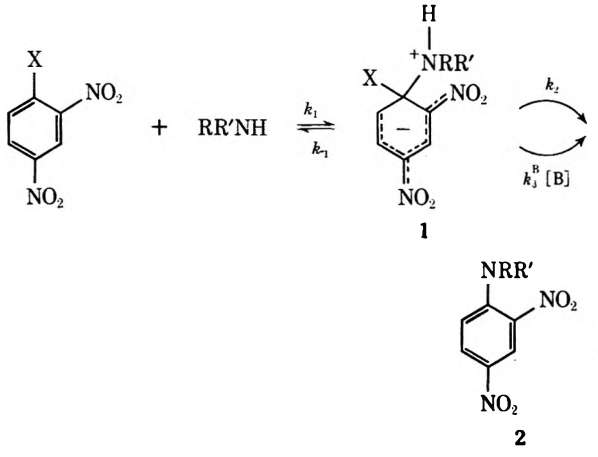
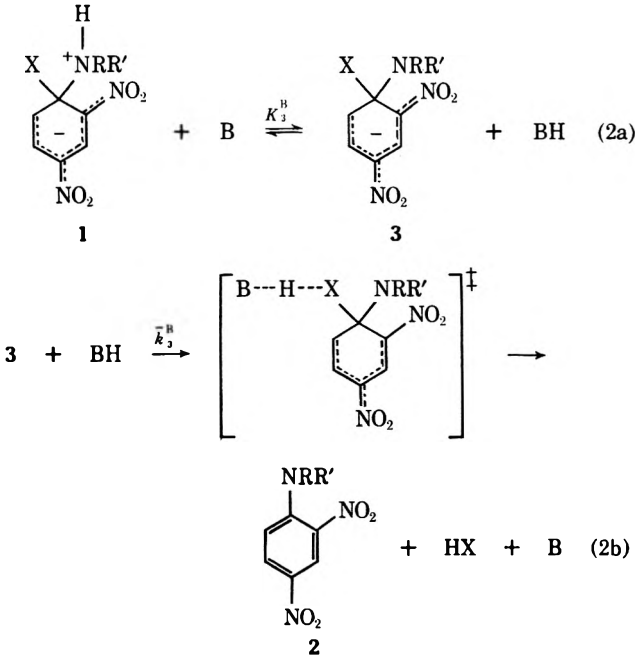
In the presence of strong base *N*-2-hydroxyethyl-*N*-methyl-2,4-dinitroaniline forms a spiro Meisenheimer complex in aqueous DMSO. In 2% DMSO (v/v) and 1 *M* KOH only 0.5% of the starting material is in the form of the complex but its stability increases in DMSO-rich solvents. In 85% DMSO (v/v) virtually all starting material is in the form of the complex at base concentrations ≥ 0.01 *M*. In solvents containing $\leq 65\%$ DMSO the rate of reversion of the complex to starting material could be measured. In 80 and 85% DMSO (v/v) the rate of its formation and the acid dissociation constant of the alcoholic proton in the starting material could be determined as well. The agreement between kinetic data and spectrophotometric equilibrium measurements was unsatisfactory when KOH was used as base and KCl as compensating electrolyte; it was excellent for the pair $(CH_3)_4NOH/(CH_3)_4NCl$. This suggests the presence of a differential salt effect in the former system and the absence of such an effect in the latter. The complex serves as a model for the anionic intermediate complex in nucleophilic aromatic substitutions by amine nucleophiles. Its rate of breakdown is central to an argument about the mechanism of the direct conversion of the zwitterionic intermediate complex into products.

Reactions of primary and secondary amines with activated aromatic substrates have played a central role in firmly establishing Bunnett's[3] intermediate complex mechanism for nucleophilic aromatic substitution reactions.[4] Equation 1 is representative and



shows the most frequently studied type of aromatic substrate. Owing to their greater complexity compared to substitutions by anionic nucleophiles, reactions of amines have also raised additional questions regarding the detailed mechanism of the conversion of the intermediate complex **1** into final products. The mechanism of the general base catalyzed step (k_3^B) has been controversial for several years,[4a] but that of eq 2 appears now firmly established mainly owing to the work of Orvik and Bunnett.[5] It involves a rapid acid–base equilibrium between the initially formed zwitterionic intermediate **1** and its conjugate



base **3** followed by a rate-limiting expulsion of the leaving group with general acid catalysis by BH.[6]

Until recently[4a] the mechanism of the direct conversion of the zwitterion **1** into products (k_2) has only received meager attention. It is sometimes referred to as "solvent assisted" or "solvent catalyzed"[4b] with the implication that the labile proton of the zwitterion is transferred to the solvent, presumably

(1) Part VII: C. F. Bernasconi, *J. Amer. Chem. Soc.*, **93**, 6975 (1971).

(2) Alfred P. Sloan Fellow, 1971–1975.

(3) J. F. Bunnett and R. E. Zahler, *Chem. Rev.*, **49**, 275 (1951).

(4) For recent reviews see (a) C. F. Bernasconi, *MTP Int. Rev. Sci., Org. Chem. Ser. One*, **3**, in press; (b) F. Pietra, *Quart. Rev., Chem. Soc.*, **23**, 504 (1969); (c) T. J. de Boer and I. P. Dirkx in "The Chemistry of the Nitro and Nitroso Groups," Part I, H. Feuer, Ed., Interscience, New York, N. Y., 1969, p 487; (d) J. Miller, "Aromatic Nucleophilic Substitution," Elsevier, New York, N. Y., 1968; (e) S. D. Ross, *Progr. Phys. Org. Chem.*, **1**, 31 (1963).

(5) J. A. Orvik and J. F. Bunnett, *J. Amer. Chem. Soc.*, **92**, 2417 (1970).

(6) Discussions concerning the mechanism of base catalysis[4a,b,5] might leave one with the impression that all base-catalyzed reactions follow the mechanism of eq 2. This is not the case. When BH is a weaker acid than XH there is no driving force for a general acid catalyzed leaving group expulsion; in such a case the k_3^B step does not involve general acid catalysis and the overall base catalysis (step k_3^B in eq 1) is specific rather than general (Libido rule[7]). Such must be the case with most leaving groups when B is the lyate ion, although it is difficult to prove directly. The absence of piperidine catalysis in the hydroxide ion catalyzed reactions of piperidine with 2,4-dinitrophenyl phenyl sulfide[8] and with 2,4-dinitrophenyl 4-nitrophenyl ether[9] in aqueous dioxane is probably a manifestation of this rule, since the pK_a of thiophenol is 6.52, of 4-nitrophenol 7.14 and of piperidinium ion 11.06. This interpretation of the lack of piperidine catalysis is, however, somewhat uncertain because the catalytic effect of the lyate ion is not very large so that catalysis by the weaker base might have been undetectable.

(7) W. P. Jencks, *J. Amer. Chem. Soc.*, **94**, 4731 (1972).

(8) (a) J. F. Bunnett and C. F. Bernasconi, *ibid.*, **87**, 5209 (1965); (b) C. F. Bernasconi, *J. Org. Chem.*, **32**, 2947 (1967).

(9) J. F. Bunnett and C. F. Bernasconi, *ibid.*, **35**, 70 (1970).

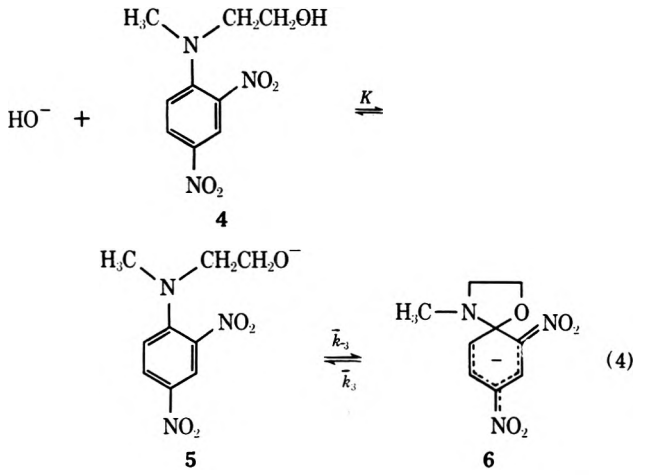
prior to the rate-determining leaving group expulsion. In keeping with the idea of the mechanism of general base catalysis, Orvik and Bunnett[5] considered the logical possibility that the k_2 mechanism might also consist of two steps including a lyonium ion catalyzed expulsion of X from **3**, *i.e.*, eq 2b, with BH being the lyonium ion.

Recently one of us[4a] presented evidence rendering such a mechanism very unlikely. The principal argument hinged upon an estimate of the rate ($\bar{k}_3$) at which **3** expels the leaving group in a protic solvent. Note that eq 3 is a special case of eq 2b where BH is the

$$3 \xrightarrow{\bar{k}_3} 2 + X^- \qquad (3)$$

solvent;[6] a logical symbol for the rate constant would be $\bar{k}_3^L$, where L stands for lyate ion. For simplicity we will use $\bar{k}_3$.

Thus an attempt to find a system where an intermediate like **3** would be stable enough to allow direct observation and a kinetic study of its decomposition seemed of special interest. We found that in the presence of base *N*-2-hydroxyethyl-*N*-methyl-2,4-dinitroaniline (**4**) is converted to a σ complex as shown in eq 4. We will demonstrate in the Discussion that



(4)

the rate coefficient for the transformation **6** → **5** can serve as an estimate of the lower limit to be expected for $\bar{k}_3$ in eq 3.

We now report a kinetic and equilibrium study of system **4** in aqueous DMSO of varying DMSO content. This study goes beyond the mere determination of $\bar{k}_3$, since the system is of interest in its own right.

Results

When base is added to an aqueous DMSO solution of **4** there is immediate formation of a red color which is very faint when the DMSO content is ≤20% (v/v) but intense in DMSO-rich mixtures. Figure 1 shows the characteristic Meisenheimer complex spectrum in 80% DMSO (v/v), λ_{max} 510 nm (ϵ_{510} 22,800). Conversion to the complex **6** is virtually quantitative in 80% DMSO (v/v) with 0.1 *M* $(CH_3)_4NOH$ or in 85% DMSO (v/v) with 0.01 *M* $(CH_3)_4NOH$.[10]

The pmr spectrum, with its characteristic AMX pattern for the ring protons and a complex ABCD pattern for the methylene protons, is similar to the spectrum reported for **7**.[11] The following chemical

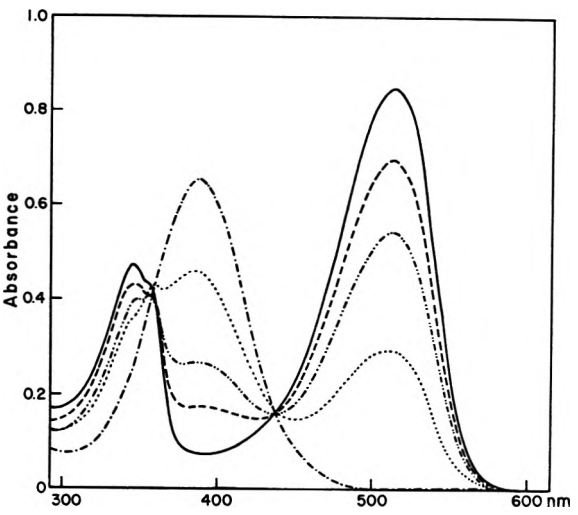
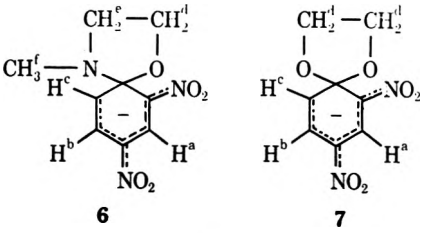


Figure 1.—Uv–visible spectra of **4** at various $(CH_3)_4NOH$ concentrations in 80% DMSO (v/v) (μ = 0.1 *M*; $[4]_0 = 3.79 \times 10^{-5}$ *M*): — · —, without base; · · · ·, 0.95×10^{-3} *M*; — · · —, 3.0×10^{-3} *M*; — —, 5.9×10^{-3} *M*; ——, 9.5×10^{-3} *M*.



shifts and coupling constants have been recorded in pure DMSO-d_6 in the presence of *t*-BuOK. The numbers in parentheses refer to **7**: τ_a 1.50 d[12] (1.48),[11a] τ_b 3.12 dd[12] (3.10),[11a] τ_c 4.87 d[12] (4.64),[11a] τ_d 6.03 m[12] (5.92),[11b] τ_e 6.92 m,[12] τ_f 7.63 s,[12] J_{ab} = 2.7 (3)[11a] Hz, J_{bc} = 10 (10)[11a] Hz.

Kinetics.—Chemical relaxation was studied by the temperature-jump method in DMSO–water mixtures at 25°. In any given solvent the ionic strength was kept constant by adding KCl when KOH was used as base, or $(CH_3)_4NCl$ when $(CH_3)_4NOH$ was used. Reaction system **4** is characterized by two relaxation times. One is associated with the rapid acid–base equilibrium **4** ⇌ **5** and is too short for the temperature-jump method. The much longer relaxation time associated with the equilibrium **5** ⇌ **6** is in an easily accessible time range. It is governed by eq 5. Equation **5** was derived according to standard procedures;[13] the concentrations refer to their values at equilibrium.

$$\frac{1}{\tau} = \bar{k}_{-3}\frac{K([HO^-]_e + [4]_e)}{1 + K([HO^-]_e + [4]_e)} + \bar{k}_3 \qquad (5)$$

2, 20, 50, and 65% DMSO (v/v).—Table I summarizes the data in these solvents. In all the runs the base was in large excess over **4**. For solvents ≤50% in DMSO the relaxation times are independent of base and substrate concentration within experimental error.

(10) The imperfect isosbestic point at 355–360 nm in Figure 1 is probably due to some hydrolysis of **4** to form the 2,4-dinitrophenolate ion, which has a strong absorption at these wavelengths; not, however, at 438 nm, the location of the other isosbestic point.

(11) (a) R. Foster, C. A. Fyfe, P. H. Emslie, and M. I. Foreman, *Tetrahedron*, **23**, 227 (1967); (b) E. J. Fendler, J. H. Fendler, W. E. Byrne, and C. E. Griffin, *J. Org. Chem.*, **33**, 4141 (1968).

(12) s = singlet, d = doublet, m = multiplet, dd = double doublet.

(13) M. Eigen and L. DeMaeyer in A. Weissberger, "Technique of Organic Chemistry," Vol. VIII, Part 2, Wiley-Interscience, New York, N. Y., 1963, p 895.

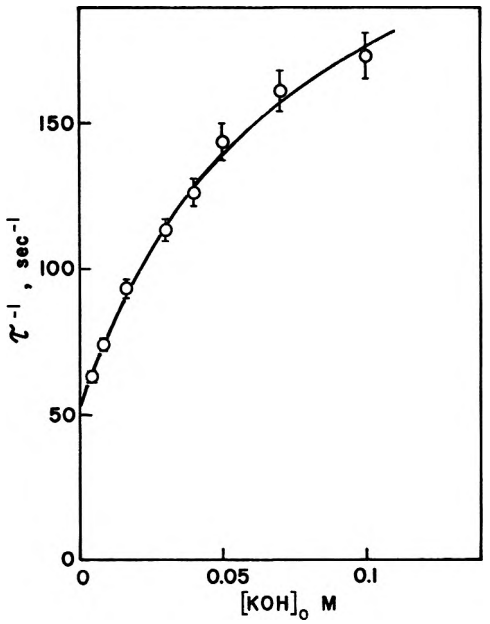


Figure 2.—Reaction in 80% DMSO (v/v), base KOH, μ = 0.1 M, τ^{-1} as a function of [KOH]$_0$, [4]$_0$ = 4–8 × 10^{-5} M.

TABLE I

RELAXATION TIMES IN 2, 20, 50, AND 65% DMSO (V/V) AT 25°

% DMSO (v/v)	[4]$_0$, M	[KOH]$_0$, M	μ,[a] M	τ^{-1}, sec^{-1}
2	~3 × 10^{-3} [b]	0.50	1.0	892 ± 90
2	~3 × 10^{-3} [b]	1.00	1.0	966 ± 50
20	2.0 × 10^{-3}	0.24	1.0	675 ± 40
20	2.0 × 10^{-3}	0.50	1.0	612 ± 30
20	2.0 × 10^{-3}	1.00	1.0	665 ± 30
20	2.0 × 10^{-3}	0.50	0.5	701 ± 35
50	2.0 × 10^{-3}	0.08	0.5	353 ± 20
50	2.0 × 10^{-3}	0.24	0.5	310 ± 20
50	2.0 × 10^{-3}	0.50	0.5	341 ± 20
50	2.0 × 10^{-4}	0.50	0.5	323 ± 15
65	3.1 × 10^{-4}	0.20	0.5	166 ± 7
65	2.0 × 10^{-4}	0.50	0.5	188 ± 8

[a] Compensating electrolyte KCl. [b] Saturated solution.

Independence of base concentration indicates that the first term in eq 5 is negligible and thus eq 6 holds. In

$$\frac{1}{\tau} = \bar{k}_3 \qquad (6)$$

other words, little complex **6** is present in equilibrium with **4** and **5** under these conditions; in fact, in the most aqueous solvents a high concentration of **4** is required in order to produce enough complex for spectral detection and monitoring chemical relaxation. Independence of substrate concentration excludes catalytic effects by **4**, **5**, or **6**; since such catalytic effects have been observed in related systems,[14] this is not a trivial point, particularly in view of the high substrate concentrations used.

Data in 20% DMSO (v/v) suggest a slight reduction in $\bar{k}_3$ with increasing ionic strength from 0.5 to 1.0 M.

In 65% DMSO (v/v) there is a slight dependence of τ^{-1} on base concentration which is just outside the experimental error.

80 and 85% DMSO (v/v).—In these solvents a significant fraction of the starting material is in the form of the complex and the concentration dependence of the relaxation time is strong. In 80% DMSO experiments with KOH as well as with $(CH_3)_4NOH$ were carried out. The latter base is more effective in converting **4** to **6**. In 85% DMSO only $(CH_3)_4NOH$ could be used for reasons of solubility.

(14) Unpublished results.

TABLE II

RELAXATION TIMES IN 80% DMSO WITH $(CH_3)_4NOH/(CH_3)_4NCl$ AT 25°

10^4[4]$_0$, M	10^4[HO$^-$]$_0$, M	τ^{-1},[a] sec^{-1}
2.30	1.92	28.5 ± 1.0
2.00	19.0	57.9 ± 1.8
0.80	47.0	71.1 ± 2.0
0.80	98.8	146 ± 5
0.80	190	246 ± 7
0.80	240	266 ± 8
0.80	330	341 ± 13
0.80	380	353 ± 14[b]
0.80	476	424 ± 16[b]
2.20	570	481 ± 20[b]
2.20	761	520 ± 25[b]
2.20	1000	597 ± 30[b]

[a] Determined at 510 or 530 nm. [b] Determined at 390 nm.

TABLE III

RELAXATION TIMES IN 85% DMSO WITH $(CH_3)_4NOH/(CH_3)_4NCl$ AT 25°

10^4[4]$_0$, M	10^4[4]$_e$,[a] M	10^4[HO$^-$]$_0$, M	10^4[HO$^-$]$_e$,[a] M	τ^{-1},[b] sec^{-1}
0.21	0.09	1.18	1.06	17.3 ± 0.6
0.33	0.12	1.57	1.36	18.5 ± 0.7
0.33	0.11	1.97	1.74	24.1 ± 0.8
0.21	0.05	2.99	2.83	25.0 ± 0.8
0.50	0.09	3.94	3.54	36.2 ± 1.0
0.66	0.07	7.85	7.26	63.5 ± 2.0
0.66	0.03	15.8	15.2	120 ± 4
0.66	0.01	39.4	38.8	295 ± 12
0.66	0.01	78.8	78.1	507 ± 25
4.64	0.02	192	187	940 ± 60[c]
9.28	0.05	192	183	976 ± 60[c]
6.60	0.03	285	278	1080 ± 70[c]

[a] Equilibrium concentrations; see text. [b] Determined at 510 or 525 nm. [c] Determined at 390 nm.

In 80% DMSO with KOH a large excess of base was used throughout, assuring pseudo-first-order conditions. Equation 5 simplifies to eq 7 where the concentrations are stoichiometric. Figure 2 shows a plot of τ^{-1} *vs.* [KOH]$_0$. From the intercept in Figure 2 one obtains $\bar{k}_3$. For the determination of $\bar{k}_{-3}$ and K eq 7 is rearranged and inverted to give eq 8. By

$$\frac{1}{\tau^{-1} - \bar{k}_3} = \frac{1}{\bar{k}_{-3}} + \frac{1}{\bar{k}_{-3}K[\mathrm{HO}^-]_0} \qquad (8)$$

plotting the left-hand side of eq 8 *vs.* [HO$^-$]$_0^{-1}$ ("inversion plot," not shown) one obtains a straight line with intercept $(\bar{k}_{-3})^{-1}$ and slope $(\bar{k}_{-3}K)^{-1}$; $\bar{k}_{-3}$ and K are in Table IV.

Data with $(CH_3)_4NOH$ as base are summarized in Table II and III. Note that at base concentrations ≥0.038 M in 80% DMSO and ≥0.0192 M in 85% DMSO relaxation was monitored at the wavelength of substrate absorption (~390 nm) with a concomitant use of a higher substrate concentration. This is because the equilibrium favors the complex to such an

TABLE IV

KINETIC AND EQUILIBRIUM PARAMETERS IN VARIOUS SOLVENT MIXTURES AT 25°

% DMSO (v/v)	$\bar{k}_3$, sec^{-1}	$\bar{k}_{-3}$, sec^{-1}	$\bar{K}_{-3}$ (kinetic)	$\bar{K}_{-3}$ (spec)	K (kinetic), M^{-1}	K (spec), M^{-1}	$K\bar{K}_{-3}$, (kinetic), M^{-1}	$K\bar{K}_{-3}$ (spec), M^{-1}
2	929 ± 40[a,b]							4.92 ± 0.15 × 10^{-3}[b]
20	650 ± 20[b,c]							7.60 ± 0.22 × 10^{-3}[b]
	(701 ± 30)[d]							
50	332 ± 15[d,e]							5.98 ± 0.18 × 10^{-2}
65	166 ± 8[d]			2.86 ± 0.15[d]		0.305 ± 0.015[d]		0.94 ± 0.05[d]
								(0.92 ± 0.05)[d,f]
80	53 ± 2[g]	238 ± 20[g]	4.5 ± 0.6[g]		12.7 ± 1.0[g]		57 ± 6[g]	295 ± 15[g]
80	26 ± 1[h]	1050 ± 50[h]	40.4 ± 4.0[h]		13.5 ± 1.0[h]		545 ± 70[h]	530 ± 25[h]
85	9 ± 1[h]	2000 ± 100[h]	222 ± 33[h]		43 ± 2[h]		9550 ± 1800[h]	

[a] Average of two runs at different [KOH]. [b] μ = 1 M, KOH/KCl. [c] Average of three runs with varying [KOH]. [d] μ = 0.5 M, KOH/KCl. [e] Average of four runs. [f] From initial slope in Figure 4. [g] μ = 0.1 M, KOH/KCl. [h] μ = 0.1 M, $(CH_3)_4NOH/(CH_3)_4NCl$.

extent as to render the relaxation amplitude very small at the wavelengths where the complex absorbs.[15]

In 80% DMSO pseudo-first-order conditions could be used at all but the two lowest base concentrations. At these lowest concentrations $[HO^-]_e$ and $[4]_e$ are unknown. However, here the equilibrium position strongly favors **4** over **6** and **5** and no significant error is introduced by setting $[HO^-]_e + [4] = [HO^-]_0 + [4]_0$.[17] A plot of τ^{-1} *vs.* $[HO^-]_0 + [4]_0$ (not shown) is similar to the one in Figure 2; from its intercept and from an inversion plot (not shown), including data points at base concentrations $\geq$0.019 M,[18] one obtains $\bar{k}_3$, $\bar{k}_{-3}$, and K as listed in Table IV.

In 85% DMSO the equilibrium favors **6** over **4** and **5**, even at relatively low base concentrations. This made it difficult to work under truly pseudo-first-order conditions; as can be seen in Table III, the excess of base over **4** is often less than tenfold. Therefore plotting τ^{-1} *vs.* $([HO^-]_e + [4]_e)$ according to eq 5 would be preferable to plotting τ^{-1} *vs.* $[HO^-]_0$ (eq 7). The equilibrium concentrations not being known, a plot of τ^{-1} *vs.* $[HO^-]_0$ was first made which yields a set of approximate values for $\bar{k}_3$, $\bar{k}_{-3}$, and K in the manner described for 80% DMSO. From these one can calculate "equilibrium concentrations" and use these in a new plot of τ^{-1}. In principle the procedure has to be repeated until convergence occurs. Since $[HO^-]_0$ is not much different from $[HO]_e + [4]_e$, the first plot is already a good approximation so that only one iteration was needed to obtain convergence. The first plot yields $\bar{k}_3 = 7 \pm 1$ sec^{-1}, $\bar{k}_{-3} = 2000 \pm 100$ sec^{-1}, $K = 42.7 \pm 2$ M^{-1}. The equilibrium concentrations based on these values are listed in Table III. From the new plot one obtains an intercept $\bar{k}_3 = 9 \pm 1$ sec^{-1}; from an inversion plot—note that $([HO^-]_e + [4]_e)$ replaces $[HO^-]_0$ in eq 8—including data at $[HO^-]_0 \geq 3.94 \times 10^{-4}$ M[18] (not shown) $\bar{k}_{-3} = 2000 \pm 100$ sec^{-1} and $K = 42.7 \pm 2$ M^{-1} are obtained. Thus only $\bar{k}_3$ changes slightly by the iteration procedure.

(15) Everything else being equal, the relaxation amplitude is always largest at the absorption wavelength of the disfavored species.[16]

(16) Reference 13, p 935.

(17) In fact, at the very lowest base concentration a more significant uncertainty arises from the possible presence of acidic impurities in the solvent, which may slightly reduce the base concentration in an uncontrolled way, as indicated by our equilibrium measurements described below.

(18) When points at lower base concentrations are included in the inversion plot, deviations from a straight line occur which may be due to uncertainties in the base concentrations[17] and to an increasing error in $\tau^{-1} - k_3$ (difference between two large numbers). The possibility of a differential salt effect will be analyzed in the Discussion.

Equilibrium Measurements.—Except for the solvents containing 80 and 85% DMSO, kinetic measurements provide only the rate coefficient $\bar{k}_3$. Spectrophotometric evaluation of the fraction of **4** converted to **6** gives access to some equilibrium parameters and thus complements the kinetic study. In 80% DMSO, equilibrium measurements are redundant with the equilibrium data derived from kinetics and thus provide a check for internal consistency. This is highly desirable in view of possible differential salt effects arising from the varying proportion of base and compensating electrolyte.

Light absorption was measured in solutions of **4** containing variable amounts of base, which was always present in large excess; the same ionic strength as for the kinetic runs was used throughout. Because of the mentioned slow hydrolysis, absorbance was determined as a function of time and extrapolated to time zero. Typically the extent of decomposition amounted to about 5% or less within 5 min after mixing, so that a linear extrapolation procedure could be used.

According to Beer's Law the absorption in cuvettes of 1-cm path length is given by eq 9. The measure-

$$A = \epsilon_4[4] + \epsilon_5[5] + \epsilon_6[6] \quad (9)$$

ments were carried out at 510 nm, which is the absorption maximum of **6** (ϵ_6 22,800 in 85% DMSO; see below). At this wavelength ϵ_4 and ϵ_5 are very small (ϵ_4 81 in 20% DMSO, ϵ_5 presumably very similar), which allows some simplifications in the use of eq 9.

The equilibrium concentration of **6** is given by eq 10. With regard to the system under investigation,

$$[6]_e = \frac{K\bar{K}_{-3}[HO^-]_0}{1 + (K + K\bar{K}_{-3})[HO^-]_0}[4]_0 \quad (10)$$

$$\bar{K}_{-3} = \frac{\bar{k}_{-3}}{\bar{k}_3} \quad (11)$$

two limiting situations are of interest. In the first the equilibrium positions strongly favors **4** over **5** and **6**, *i.e.*, $(K + K\bar{K}_{-3})[HO]_0 \ll 1$ and also $K[HO^-]_0 \ll 1$ so that eq 10 simplifies to eq 12. At the same time

$$[6]_e = K\bar{K}_{-3}[HO^-]_0[4]_0 \quad (12)$$

the relations $[4]_e \cong [4]_0$ and $[5]_e \ll [4]_0$ hold so that eq 9 becomes eq 13. Note that despite the much

$$\frac{A}{[4]_0} = \epsilon_4 + \epsilon_6 K\bar{K}_{-3}[HO]_0 \quad (13)$$

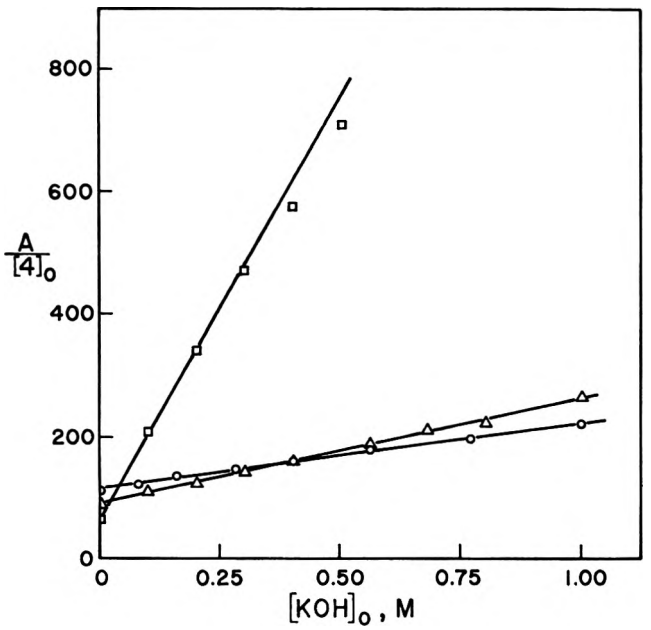


Figure 3.—$A/[4]_0$ (λ 510 nm) as a function of $[KOH]_0$ according to eq 13: ○, 2% DMSO (v/v), $[4]_0 = 1.87 \times 10^{-3}$ *M*; △, 20% DMSO (v/v), $[4]_0 = 8.6\text{–}9.1 \times 10^{-4}$ *M*; □, 50% DMSO (v/v), $[4]_0 = 9.1 \times 10^{-4}$ *M*.

smaller value of ϵ_4 compared to ϵ_6 the first term in eq 13 may not be negligible since $K\bar{K}_{-3}[HO^-]_0$ may be quite small.

In the second limiting situation complex **6** is present at equilibrium concentrations comparable to that of **4** so that the last term in eq 9 becomes predominant. Equation 9 then takes the form of eq 14.

$$A = \epsilon_6 \frac{K\bar{K}_{-3}[HO^-]_0}{1 + (K + K\bar{K}_{-3})[HO^-]_0}[4]_0 \qquad (14)$$

2, 20, and 50% DMSO (v/v).—The measurements in the three most aqueous solvents are summarized in Figure 3. In 2 and 20% DMSO the plot of $A/[4]_0$ *vs.* base concentration is linear up to the highest concentration used and conforms strictly to eq 13. Thus it is evident, in harmony with the kinetic results, that in these two solvents complex formation is strongly disfavored. In fact substrate concentrations in the order of 10^{-3} *M* had to be used in order to obtain workable absorptions. The possibility that Beer's Law might not hold at such high concentrations was a real one. However, it turned out that absorbance was linear with substrate concentration both in the presence and the absence of base throughout the range used in this study. This finding also excludes the presence of significant amounts of a Meisenheimer complex formed by a possible nucleophilic attack of **5** on **4**.

From the slopes in Figure 3 we calculated $K\bar{K}_{-3}$ as listed in Table IV. Since ϵ_6 cannot be determined in these solvents, the value in 85% DMSO was used instead. Inasmuch as ϵ_6 might be somewhat solvent dependent, $K\bar{K}_{-3}$ may be affected by a small systematic error.[19]

In 50% DMSO (v/v) the plot of $A/[4]_0$ *vs.* $[HO^-]_0$ is linear up to about 0.3 *M* with an indication of a slight downward curvature at higher concentrations. $K\bar{K}_{-3}$ was determined from the slope at $[HO^-]_0 \leq 0.3$ *M*.

(19) There is some indication from related systems[14] that ϵ_6 in aqueous solution might be about 20% lower than in a solvent high in DMSO.

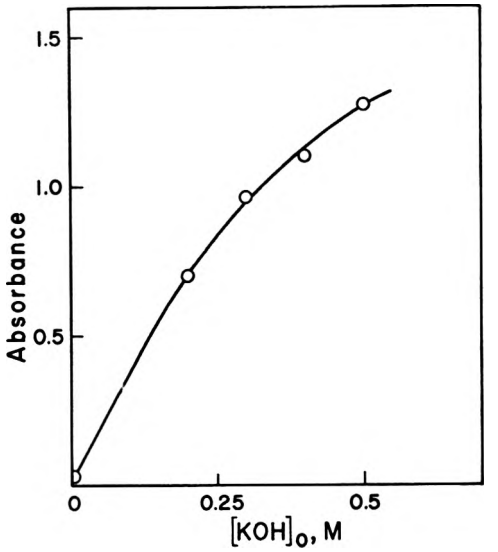


Figure 4.—Absorbance (λ 510 nm) as a function of $[KOH]_0$ in 65% DMSO (v/v), $[4]_0 = 1.97 \times 10^{-4}$ *M*. Intercept = 0.016 arising from residual absorption of **4**.

65, 80, and 85% DMSO (v/v).—As can be seen from Figures 4–6, the plots of *A vs.* $[HO^-]_0$ in 65 and 80% DMSO are distinctly curved, indicating that the term $(K + K\bar{K}_{-3})[HO]_0$ in the denominator of eq 14 becomes appreciable and eventually predominant at higher concentrations. This effect is most pronounced in 80% DMSO with $(CH_3)_4NOH$.

For evaluation we invert and rearrange eq 14 and obtain eq 15. A plot of the left-hand side of eq 15

$$\frac{\epsilon_6[4]_0}{A} = 1 + \frac{1}{\bar{K}_{-3}} + \frac{1}{K\bar{K}_{-3}[HO^-]_0} \qquad (15)$$

vs. $[HO^-]_0^{-1}$ (inversion plot) should yield a straight line with an intercept $(1 + 1/\bar{K}_{-3})^{-1}$. Unless $\bar{K}_{-3} \gg 1$, making the intercept indistinguishable from 1, both $\bar{K}_{-3}$ and K may be determined; otherwise only $K\bar{K}_{-3}$ can be obtained.

In 65% DMSO only points at $[KOH]_0 \geq 0.2$ *M* could be obtained because of precipitation of KCl. An inversion plot (not shown) allows the separate determination of $\bar{K}_{-3} = 2.86$ and $K = 0.305$ M^{-1}. $K\bar{K}_{-3} = 0.92$ M^{-1} determined from the initial slope in Figure 4 compares well with $K\bar{K}_{-3} = 0.94$ M^{-1} from the slope in the inversion plot and shows consistency of the data.

In 80% DMSO (v/v) the intercepts of both inversion plots (not shown) are indistinguishable from 1, which indicates $\bar{K}_{-3} \gg 1$; with KOH $K\bar{K}_{-3} = 295$ M^{-1}, with $(CH_3)_4NOH$ $K\bar{K}_{-3} = 530$ M^{-1}. A check for consistency with the initial slopes in Figures 5 and 6 is impractical because the lowest base concentrations are somewhat uncertain owing to minute acidic impurities in the solvent. Evidence for this is that *A* increases slightly more than linearly with $[HO^-]_0$ at the very lowest base concentrations.

In 85% DMSO (v/v) $K\bar{K}_{-3}$ is so large that a plot of *A vs.* $[HO^-]_0$ levels off at such low base concentrations that their determination is inaccurate owing to the mentioned acidic impurities. Therefore no attempt has been made to determine $K\bar{K}_{-3}$ spectrophotometrically in this solvent. The parameters ϵ_6 22,800 at λ_{max} 510 nm could conveniently be determined in this solvent.

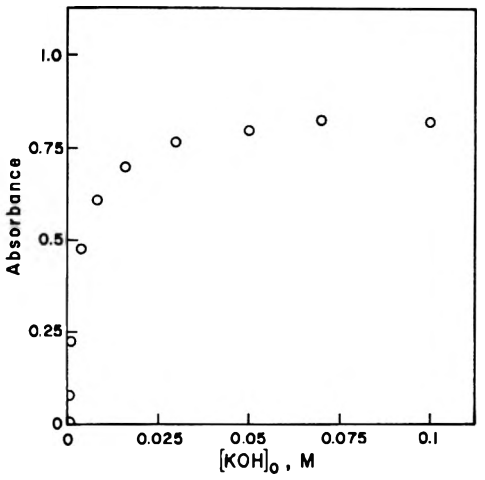


Figure 5.—Absorbance (λ 510 nm) as a function of $[KOH]_0$ in 80% DMSO (v/v), $[4]_0 = 3.79 \times 10^{-5}$ *M*.

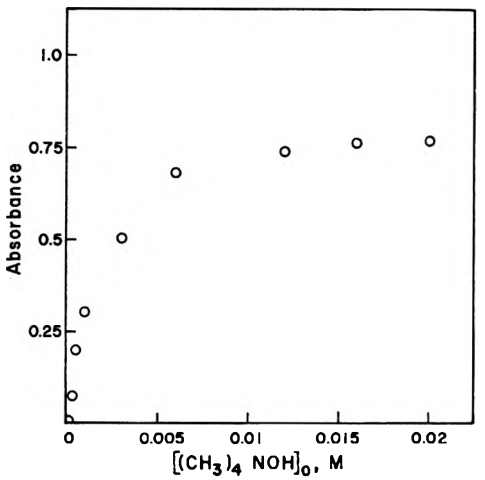


Figure 6.—Absorbance (λ 510 nm) as a function of $[(CH_3)_4NOH]_0$ in 80% DMSO (v/v), $[4]_0 = 3.79 \times 10^{-5}$ *M*.

Discussion

Solvent Effects.—Table IV summarizes all kinetic and equilibrium parameters. The stability of **6** relative to **4** depends on both the acidity of the 2-substituted 2-aminoethanol (K) and the complex formation constant ($\bar{K}_{-3}$) proper. Enriching the solvent with DMSO increases the product $K\bar{K}_{-3}$ about 10^5 fold from 2 to 80% DMSO and about 2×10^6 fold from 2 to 85% DMSO. Note that these comparisons are somewhat crude, since the conditions (ionic strength, base) in the various solvents are not all identical.

In media containing ≥65% DMSO (v/v) K and $\bar{K}_{-3}$ could be determined separately by kinetics and/or spectrophotometrically. Both constants increase with DMSO content from 65 to 85%. Based on numerous findings in related Meisenheimer complexes,[20] it is safe to conclude that K_{-3} increases with DMSO content over the entire solvent range. From the kinetic data it is apparent that both an increase in $\bar{K}_{-3}$ as well as a decrease in $\bar{k}_3$ is responsible for augmenting $\bar{K}_{-3}$, again as expected.[20] An increase in the nucleophilic reactivity of the oxy anion by desolvation in conjunction with a stabilization of the polarizable complex and of the transition state by the polarizable DMSO are commonly invoked to rationalize these effects.[20-22] It is noteworthy that a plot (not shown) of log $\bar{k}_3$ as a function of the mole fraction of DMSO is linear in solvents containing ≤65% DMSO. Although there may not be any theoretical significance, it can be useful for predictive purposes.

In interpreting the solvent dependence of K we have to consider two main factors. First, adding DMSO to an aqueous solution decreases the water activity both by dilution and *via* the ability of DMSO to form strong hydrogen bonds with water.[23] This effect, which becomes more pronounced at higher DMSO levels, is expected to increase K.

Second, the activity of both the hydroxide ion and of **5** increases as DMSO replaces water in the solvent.[21] If the activity of the former increases more than that of the latter, K is further augmented, whereas a stronger increase in the activity of **5** would have the opposite effect. A prediction seems rather difficult; all we can say is that between 65 and 85% DMSO the combined result of both effects is to increase K.

Salt Effects.—In order to minimize complications due to salt effects, all our data were collected at constant ionic strength. This does not, however, guarantee the absence of possible special salt effects at the relatively high salt and base concentrations used in this study. This may become a problem for data collected over an extended base concentration range when base and compensating salt exert different salt effects. Our data in 80% DMSO illustrate this point. With the pair KOH/KCl there is a more than fivefold discrepancy between $K\bar{K}_{-3}$ determined spectrophotometrically and from kinetics. Neither set of data taken separately would suggest any problem such as a nonlinear inversion plot except for the normal deviations at very low base concentrations. Nevertheless the discrepancy suggests the operation of a differential salt effect between KOH and KCl. The rationalization is as follows. A differential salt effect is likely to affect $\bar{k}_3$ and $\bar{k}_{-3}$ in opposite ways. The kinetic equilibrium constants are based on data treated according to eq 5, whereas the spectrophotometric constants are calculated from data *via* eq 10. Since these two equations are of quite different form, τ^{-1} and A are expected to respond differently to a differential salt effect and $K\bar{K}_{-3}$ determined by the two methods should be different.

On the other hand, the close agreement between the kinetic and spectrophotometric $K\bar{K}_{-3}$ for the pair $(CH_3)_4NOH/(CH_3)_4NCl$ can probably be taken as evidence that here the differential salt effect is negligible.

In 85% DMSO no such check is possible because spectrophotometric equilibrium determination is impractical. With the pair $(CH_3)_4NOH/(CH_3)_4NCl$ no significant differential salt effect is anticipated.

$\bar{k}_3$ and the Mechanism of Breakdown of the Intermediate Complex 1.—The value of $\bar{k}_3$, particularly in aqueous solution, is pertinent with regard to excluding the proposition[5] of a lyonium ion catalyzed leaving group departure from **3** as part of the mechanism of the nonbase-catalyzed conversion of **1** to **2** (k_2 step

(20) (a) M. R. Crampton, *Advan. Phys. Org. Chem.*, **3**, 211 (1969); (b) M. J. Strauss, *Chem. Rev.*, **70**, 667 (1970).

(21) (a) A. J. Parker, *Quart. Rev., Chem. Soc.*, **16**, 163 (1962); (b) A. J. Parker, *Chem. Rev.*, **69**, 1 (1969).

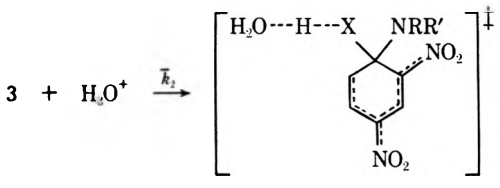
(22) J. W. Larsen, K. Amin, and J. H. Fendler, *J. Amer. Chem. Soc.*, **93**, 2910 (1971).

(23) C. H. Rochester, "Acidity Functions," Academic Press, New York, N. Y., 1970, p 256.

in eq 1). The argument has been briefly developed in a recent review;[4a] it is based upon an analysis of k_3^B/k_2 ratios and particularly k_3^{HO}/k_2 ratios in hydroxylic solvents. These ratios have been determined for a large number of reactions of the general type of eq 1 and have been recently summarized.[4a]

The mechanism suggested by Orvik and Bunnett[5] as a possibility for the k_2 step is represented in eq 16

$$1 + HO^- \overset{K_3^{HO}}{\rightleftharpoons} 3 + H_2O \quad (16a)[24]$$



$$2 + HX + H_2O \quad (16b)$$

for the specific case of an aqueous solution. The mechanism of the k_3^B step represented in eq 2 can be recast for catalysis by HO^- (k_3^{HO})[6] as follows.

$$1 + HO^- \overset{K_3^{HO}}{\rightleftharpoons} 3 + H_2O \quad (16a)[24]$$

$$3 \xrightarrow{k_3} 2 + X^- \quad (3)$$

In terms of these two mechanisms both k_3^{HO} and k_2 are composite quantities; they can be written as eq 17 and 18.

$$k_2 = \bar{k}_2 K_3^{HO} [HO^-][H_3O^+] = \bar{k}_2 K_3^{HO} K_w = 10^{-14}\, \bar{k}_2 K_3^{HO} \quad (17)$$

$$k_3^{HO} = \bar{k}_3 K_3^{HO} \quad (18)$$

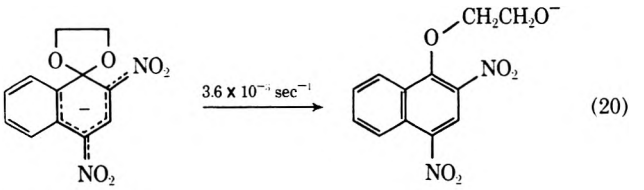
Combining eq 17 and 18 affords eq 19.

$$\frac{k_3^{HO}}{k_2} = 10^{14} \frac{\bar{k}_3}{\bar{k}_2} \quad (19)$$

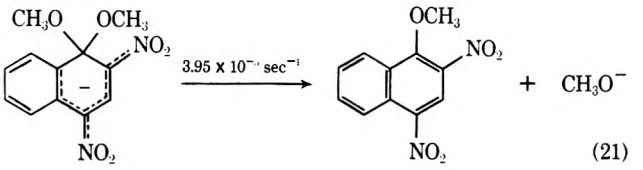
We can now estimate a lower limit for the ratio k_3^{HO}/k_2 to be expected on the basis of the mechanism of eq 16. For a leaving group with oxygen as first atom whose pK_a is equal to that of **4** (estimated at 14–15) we assume a $\bar{k}_3$ in the same order of magnitude as the one determined for **6** in 2% DMSO, *i.e.*, 10^3 sec^{-1}. A possible criticism of this assumption is that $\bar{k}_3$ of **6** might be significantly affected by the spiro configuration and thus be a poor model for the $\bar{k}_3$ step of **3**. A comparison between the rates of the two reactions 20[11b] and 21[25] in methanol at 25° shows in fact the leaving group expulsion to be slowed down compared to the noncyclic complex. The difference in rates is larger than the numbers suggest, since the pK_a of 2,4-dinitronaphthyl glycol ether may be 1 to 2 units lower than that of methanol.

In conclusion we can assume conservatively that the value of 10^3 sec^{-1} from **6** is a lower limit to be expected for the rate of leaving group departure from **3** in aqueous solution.

For $\bar{k}_2$ we assume the highest possible value, *i.e.*,



(20)



(21)

$\sim 10^{10}$ M^{-1} sec^{-1}, for a diffusion controlled process. Thus we obtain eq 22. Note this is a conservative

$$\frac{k_3^{HO}}{k_2} \geq 10^{14} \frac{10^3}{10^{10}} = 10^7 \quad (22)$$

estimate, since $\bar{k}_2$ is likely to be considerably slower than diffusion controlled. Furthermore $\bar{k}_3$ is certainly higher than 10^3 for less basic leaving groups. Thus the conclusion $k_3^{HO}/k_2 \gg 10^7$ is more realistic.

The 10^7 value is several orders of magnitude larger than experimental k_3^{HO}/k_2 ratios; these are typically in the range between 200 and 10^4 [4a] with the highest being $\sim 2 \times 10^5$ for the methoxy leaving group.[4a] We conclude that mechanism of eq 16 is untenable as a general proposition. A similar conclusion was reached previously[4a] based on a different model reaction; an alternative mechanism which involves intramolecular acid catalysis of leaving group departure by the ammonium proton in **1** was proposed.[4a]

Experimental Section

Materials.—*N*-2-Hydroxyethyl-*N*-methyl-2,4-dinitrophenylamine was prepared[26] by adding 7.56 g of *N*-methyl-2-aminoethanol to a solution of 10 g of 2,4-dinitrochlorobenzene in 150 ml of ethanol and refluxing for 2 hr. After distilling off the ethanol the remaining orange oil was extracted with four portions of 500 ml of ether, dried over $MgSO_4$, and filtered. After evaporation of the ether 11 g (92% yield) of pure oily product remained. Several attempts to induce crystallization failed.

Anal. Calcd for $C_9H_{11}N_3O_5$: C, 44.8; H, 4.61; N, 17.45. Found: C, 44.68; H, 4.51; N, 17.52.

DMSO (Baker Analyzed Reagent Grade) and KCl (Mallinckrodt) were used without further purification. KOH solutions were prepared from Titrisol (Merck). $(CH_3)_4NOH$ and $(CH_3)_4NCl$ (Aldrich) were recrystallized from ethanol. Reaction solutions in solvents containing ≤65% DMSO (v/v) were prepared by dispensing the appropriate amount of DMSO into a volumetric flask, then adding an aqueous solution of the other ingredients, and finally filling to the mark with water. The procedure was reversed for solutions containing 80 and 85% DMSO, *i.e.*, DMSO was added last to fill to the mark.

Rate and Equilibrium Measurements.—Kinetic determinations were made on a temperature-jump transient spectrophotometer of Messanlagen Studiengesellschaft Göttingen, Germany. The solutions equilibrated at 21° were subjected to temperature jumps of 4°. Relaxation was usually monitored between 510 and 530 nm, sometimes at 390 nm depending on the amplitude. Each relaxation time reported represents an average of 3 to 4 relaxation curves. Owing to hydrolysis, sometimes several solutions had to be prepared in order to collect all the data. Spectrophotometric equilibrium measurements were carried out in a thermostated Beckman DU spectrophotometer; the spectra in Figure 1 were taken on a Cary 14 spectrophotometer.

Registry No.—**4**, 37580-86-2; **6**, 37541-32-5; DMSO, 67-68-5.

(24) Note that depending on the pH, on the presence of other bases, and on the concentration and pK_a of the nucleophile, base catalysis of the proton abstraction from **1** to form **3** by these other bases may contribute or even be more important than hydroxide ion catalysis. Since this is a rapid equilibrium step this is of no consequence to the rate of the complete sequence 16a and 16b.

(25) J. H. Fendler, E. J. Fendler, W. E. Byrne, and C. E. Griffin, *J. Org. Chem.*, **33**, 977 (1968).

(26) We are indebted to Mr. T. E. Glass, who prepared this compound.

Acknowledgment. —We thank the National Science Foundation and the Alfred P. Sloan Foundation for their financial support. A Frederick Gardner Cottrell equipment grant is also gratefully acknowledged. We wish to thank Professor J. F. Bunnett for criticism of the manuscript.

Alkali Metal Reduction of Aromatic Nitro Compounds

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The reaction of nitrobenzene with lithium in tetrahydrofuran gave a mixture of products consisting of azobenzene, 2-anilinoazobenzene, 2,2′- and 2,4′-dianilinoazobenzenes, anilinodibenzopyridazine, and unidentified polymeric azo compounds. Similar products were obtained from the reaction of nitrosobenzene with lithium, whereas the reaction of azoxybenzene gave exclusively azobenzene. It has been suggested that radical anion intermediates are involved in these reactions. Substituted nitro compounds react in a manner analogous to that of nitrobenzene, whereas nitroanilines are unchanged under similar conditions. Compounds such as 4-bromoazoxybenzene and 2-chloronitrobenzene undergo both deoxygenation and dehalogenation reactions on treatment with lithium in THF. 2,2′-Dinitrobiphenyl, on the other hand, gave dibenzopyridazine and a trace of carbazole on treatment with lithium in ether solvents. Under similar conditions, however, 2,2′-dinitrodiphenyl ether did not give any cyclized product.

Aromatic nitro compounds, in general, are reduced in basic medium to the corresponding azoxy, azo, and hydrazo derivatives, whereas they are converted to the corresponding amines under strongly acidic conditions or under catalytic hydrogenation.[2]

The deoxygenation of nitro and nitroso compounds have been brought about by several reagents to give a variety of products depending on the reaction conditions and the nature of the reagents.[3] Aryl nitro compounds, for example, have been reduced to the corresponding azo derivatives in fairly good yields by metal hydrides[4-6] and thallium.[7]

The reaction of nitrobenzene with sodium in liquid ammonia is very complex and may warrant further investigation.[8] However, sodium amalgam has been reported to reduce aromatic nitro compounds to the corresponding azoxy and azo compounds.[2] Lukashevich[9] had observed the formation of mono- and disodium adducts of nitrobenzene, as well as nitrosobenzene in ether solvents. Addition of alkali metals to nitro compounds in aprotic solvents has been reported to give rise to radical anion intermediates and several groups of workers have examined the esr spectra of some of these intermediates.[10] We previously examined the electronic spectra of the radical anions of a few nitrobenzene derivatives and some of the intermediates formed on treatment with alkali metals.[11,12]

The radical anion of nitrobenzene has been reported to undergo oxidation to nitrobenzene in air[13] or disproportionation to nitrobenzene and phenylhydroxylamine in aqueous solution.[14] The chemistry of nitrobenzene radical anion and the products formed in these reactions, however, have not been investigated in detail. This article describes investigations of the reactions of some aromatic nitro compounds with alkali metals in ether solvents.

Results and Discussion

Reaction of Nitrobenzene with Lithium in Tetrahydrofuran.—Treatment of nitrobenzene with lithium in THF under nitrogen atmosphere gave a mixture of products consisting of azobenzene (**2**) (34%), 2-anilinoazobenzene (**3**) (12%), 2,2′-dianilinoazobenzene (**4**) (0.5%), 2,4′-dianilinoazobenzene (**5**) (0.5%), and a trace of anilinodibenzopyridazine (**6**) (Scheme I). In addition, an unidentified mixture of polymeric azo compounds was also isolated from this reaction. The identities of products **2**–**6** have been established on the basis of analytical results and independent syntheses, whereever possible.

The assignment of structure **3** was accomplished on the basis of its elemental analysis ($C_{18}H_{15}N_3$), mass spectrum (mol wt 273), and ir spectrum, which indicated a weak N–H band at 3340 cm^{-1} which was unaffected by dilution (intramolecular hydrogen bonding).[15] The assignment of **3** was confirmed by an independent synthesis from 2-aminodiphenylamine and nitrosobenzene.[16]

(1) To whom inquiries should be addressed.

(2) For some general references concerning the reduction of nitro compounds, see P. A. S. Smith, "Open Chain Nitrogen Compounds," Vol. 2, W. A. Benjamin, New York, N. Y., 1966, pp 422–430.

(3) For some of these deoxygenation reactions, see (a) J. I. G. Cadogan, *Quart. Rev., Chem. Soc.*, **22**, 222 (1968); J. H. Boyer in "The Chemistry of Nitro and Nitroso Groups," Vol. 1, H. Feuer, Ed., Interscience, New York, N. Y., 1969, p 260.

(4) R. F. Nystron and W. G. Brown, *J. Amer. Chem. Soc.*, **70**, 3738 (1948).

(5) H. Gilman and T. N. Goreau, *ibid.*, **73**, 2939 (1951).

(6) (a) M. G. Swanwick and W. A. Waters, *Chem. Commun.*, 63 (1970); (b) R. O. Hutchins, D. W. Lamson, L. Rwa, C. Milewski, and B. Maryanoff, *J. Org. Chem.*, **36**, 803 (1971).

(7) A. Mckillop, R. A. Raphael, and E. C. Taylor, *J. Org. Chem.*, **35**, 1670 (1970).

(8) G. W. Watt, *Chem. Rev.*, **46**, 317 (1950).

(9) (a) V. O. Lukashevich, *Justus Liebigs Ann. Chem.*, **521**, 198 (1936); *J. Gen. Chem. USSR*, **11**, 1007 (1947); *Chem. Abstr.*, **40**, 1150 (1946).

(10) For some of these studies, see (a) A. H. Maki and D. H. Geske, *J. Chem. Phys.*, **33**, 825 (1960); (b) R. L. Ward, *J. Amer. Chem. Soc.*, **83**, 1296 (1961); (c) T. A. Glaxton, W. M. Fox, and M. C. R. Symons, *Trans. Faraday Soc.*, **63**, 2570 (1967).

(11) V. Kalyanaraman, C. N. R. Rao, and M. V. George, *Tetrahedron Lett.*, 4889 (1969).

(12) C. N. R. Rao, V. Kalyanaraman, and M. V. George, *Appl. Spectrosc. Rev.*, **3**, 153 (1970).

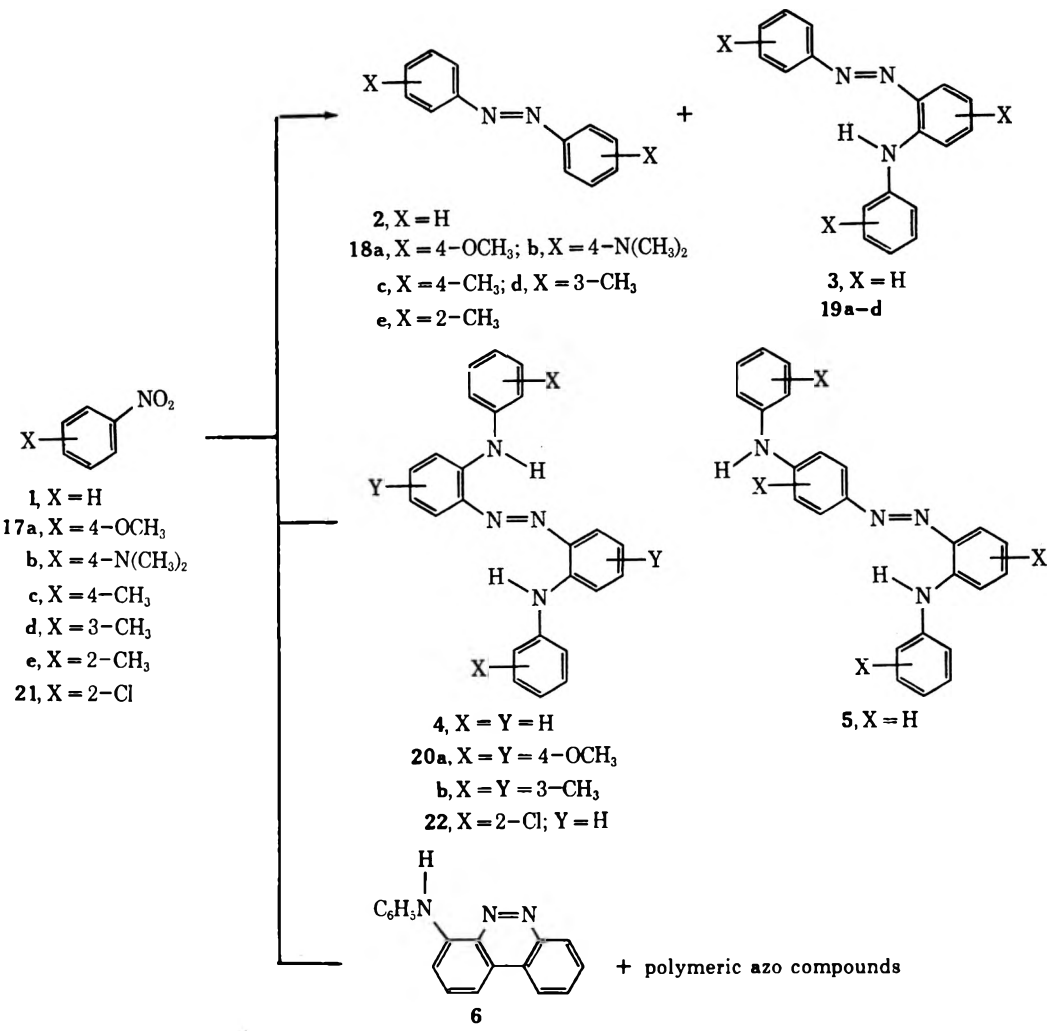
(13) G. A. Russell and A. G. Bemis, *Inorg. Chem.*, **6**, 403 (1967).

(14) B. Kastening, *Electrochim. Acta*, **9**, 241 (1964).

(15) For examples of similar intramolecular hydrogen bonding in ortho-substituted azobenzene, see (a) E. Sawicki and D. Gerber, *J. Org. Chem.*, **21**, 410 (1956); (b) L. Skulski, *Bull. Acad. Pol. Sci., Ser. Sci. Chim.*, **14**, 29 (1966); *Chem. Abstr.*, **64**, 19367 (1966).

(16) H. Zollinger, "Azo and Diazo Chemistry," Interscience, New York, N. Y., 1964.

SCHEME I



Compound **4**, mp 158° dec, obtained in the reduction of nitrobenzene analyzed for $C_{24}H_{20}N_4$ (mol wt 364, mass spectrometry). Allan and Swan[17] had reported the formation of a compound, mp 160°, identified as 2,2′-dianilinoazobenzene, in the reduction of 2-nitrodiphenylamine with zinc and sodium hydroxide. The uv spectral characteristics of this compound were in agreement with those of **4**, thereby suggesting the identity of **4** as 2,2′-dianilinoazobenzene. Further confirmation of the structure of **4** was derived from an independent synthesis involving the oxidation of 2-aminodiphenylamine using nickel peroxide[18,19] to afford a product identical with **4**.

Compound **5**, mp 120° dec, also analyzed for $C_{24}H_{20}N_4$ (mol wt, 364, mass spectrometry) and its ir spectrum was found to be similar to that of **4** except in the NH region. The presence of two NH stretching bands at 3400 and 3260 cm^{-1} is in agreement with the assigned structure. In the electronic spectrum of 2-anilinoazobenzene (**3**), the longest wavelength absorption maximum is observed at 457 nm. The corresponding para isomer, namely 4-anilinoazobenzene, is reported to have an absorption band at 420 nm.[20] In 2,2′-dianilinoazobenzene (**4**), the absorption maxima are observed at 288 nm (ε 32,300), 323 (10,500), and 504 (13,500). In compound **5**, the corresponding absorption maxima were observed at 290 nm (ε 32,400), 325 (15,300), and 472 (6900). Thus, the electronic spectrum of **5** is similar to that of **4**, except that the long-wavelength band has undergone a hypsochromic shift with a decrease in intensity. In addition, **5** and the 4,4′-dianilino derivative differ considerably in their melting points (120° *vs.* 238°,[21] respectively). An attempted synthesis of **5** employing the condensation of 2-aminodiphenylamine with 4-nitrosodiphenylamine, however, was not successful.

In addition to the azo- and anilinoazobenzenes obtained in the reduction of nitrobenzene, we have also isolated a small quantity of a light red compound tentatively assigned structure **6** on the basis of elemental analysis ($C_{18}H_{13}N_3$), mass spectrum (mol wt 271), and ir spectrum (–N=N– and intramolecular hydrogen bonding). In addition, the uv spectrum displayed maxima characteristic of dibenzopyridazine chromophore (λ_{max} 297, 338, 354, 364, 372, and 510 nm).

A probable route to the formation of azobenzene (**2**) in the reaction of nitrobenzene with lithium is shown in Scheme II. In this scheme we assume that the initially formed radical anion intermediate **8** is converted to nitrosobenzene (**7**) through the dianion intermediate **9**. Further reaction of lithium with nitro-

(17) L. T. Allan and G. A. Swan, *J. Chem. Soc.*, 3892 (1965).

(18) K. Nagakawa and T. Tsuji, *Chem. Pharm. Bull.*, **11**, 296 (1963); *Chem. Abstr.*, **59**, 3827 (1963).

(19) K. S. Balachandran and M. V. George, unpublished results.

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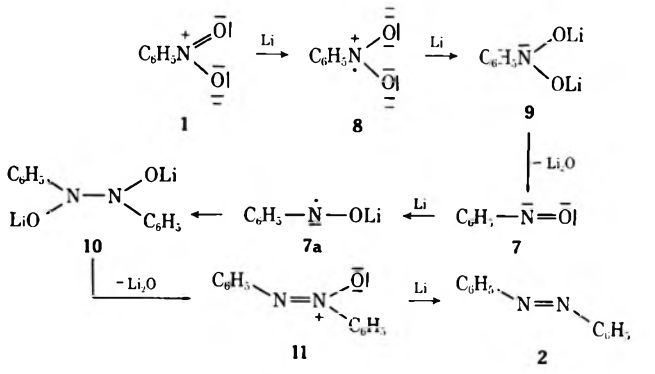
(21) M. Colonna and M. Angeletti, *Bull. Sci. Fac. Chim. Ind. Bologna*, **18**, 160 (1960); *Chem. Abstr.*, **55**, 23414 (1961).

SCHEME II



sobenzene should result in the formation of a new radical anion intermediate **7a**, which can be transformed to azoxybenzene (**11**) through the intermediate **10**. Azoxybenzene will undergo further deoxygenation in presence of lithium to azobenzene. It might be mentioned in this connection that azobenzene itself will undergo further addition in the presence of lithium to give a dianion derivative.[22] However, under the conditions of work-up, the hydroazobenzene that will be formed is rapidly oxidized back to azobenzene.

In order to test for the intermediacy of nitrosobenzene (**7**) and azoxybenzene (**11**), the reaction of both with lithium in THF was examined. Treatment of **7** with excess lithium in THF at room temperature gave a 53% yield of azobenzene. Under similar conditions, **11** afforded a nearly quantitative yield of azobenzene. Furthermore, a 3% yield of **11** was isolated from the reaction of nitrobenzene with lithium in ether at 0°. The changes observed in the time-dependent electronic spectra of nitrobenzene radical anion also support the intermediate formation of nitrosobenzene and azoxybenzene.[11,12] During the course of our studies, we had observed that 4 equiv of lithium metal is required for the complete reduction of every mole of nitrobenzene. However, stopping the reaction at intermediate stages led only to the partial conversion of nitrobenzene to azobenzene. This observation is in agreement with the fact that the intermediates such as nitrosobenzene and azoxybenzene are reduced under much lower potentials than nitrobenzene itself.[23]

The formation of 2-anilinoazobenzene (**3**), 2,2′-dianilinoazobenzene (**4**), and 2,4′-dianilinoazobenzene (**5**) may be explained in terms of the coupling of radical intermediates as shown in Scheme III. One of the probable modes for the formation of **3** is through a coupling of the radical anion of azobenzene (**12a**) with the addition product of lithium to nitrosobenzene to give the intermediate **13**, which can ultimately lead to **15**. Under the conditions of work-up, **15** will be converted to **3**. Similarly, the formation of both **4** and **5** may be rationalized through the reaction of the radical anion intermediate **16** as shown in Scheme III. From a study of the esr spectrum of the radical anion of azobenzene, it is known that the electron density is greater at the ortho position of the aromatic ring,[24] a fact which is in tune with our observation concerning the predominance of the ortho-substituted azobenzene derivatives. The exact mode of formation of the pyridazine derivative **6** in the reduction of nitrobenzene is not very clear. It is feasible that one of the radical anion intermediates such as **16** (Scheme III) may be undergoing oxidative cyclization leading to the formation of **6**.

Influence of the Solvent, Alkali Metal, and Temperature on the Reduction of Nitrobenzene.—With a view to improving the yield of azobenzene formed in the reaction of nitrobenzene with lithium, we have varied the solvents and alkali metals. The results of these studies are summarized in Table I. It has been observed that changing the solvent from tetrahydrofuran to 1,2-dimethoxyethane, dioxane, or diethyl ether had very little effect on the composition of the product mixture. The yield of azobenzene in these cases varied from 19 to 43%, increasing with solvents of increased dielectric constant and also with increasing temperatures. The yield of azobenzene was very poor (1–7%) when either sodium or potassium was used and this may be due to the relatively poor solubilities of the intermediates formed in these cases.

TABLE I

INFLUENCE OF SOLVENT, TEMPERATURE, AND ALKALI METAL ON THE YIELD OF AZOBENZENE IN THE REDUCTION OF NITROBENZENE

Solvent	Metal	Temp, °C	Time, hr	Azobezene yield, %
Diethyl ether	Lithium	0–5	24	8
Diethyl ether	Lithium	30	24	19
Tetrahydrofuran	Lithium	0	24	25
Tetrahydrofuran	Lithium	30	16	34
1,2-Dimethoxyethane	Lithium	30	24	43
Dioxane	Lithium	30	24	30
Tetrahydrofuran	Sodium	30	24	7
Tetrahydrofuran	Potassium	30	48	1

Reaction of Substituted Nitrobenzenes with Lithium in Tetrahydrofuran.—In continuation of our studies we have examined the reaction of a few substituted nitrobenzenes with lithium for evolving a convenient method for the preparation of azo compounds. Treatment of different monosubstituted nitro compounds with lithium in THF at room temperature gave rise to the corresponding azo compounds in varying yields. Table II summarizes the results of these studies.

Reaction of Aromatic Dinitro Compounds with Lithium.—In continuation of our studies we have examined the reactions of a few dinitro compounds with alkali metals, for evolving a convenient route to the synthesis of cyclic azo compounds. Treatment of 2,2′-dinitrobiphenyl (**23**) with lithium in tetrahydrofuran gave a 45% yield of dibenzopyridazine (**24**) and a trace of carbazole (**25**) (Scheme IV). A similar yield of **24** was obtained when the reaction of **23** was carried out with sodium in 1,2-dimethoxyethane. On the basis of analogy to the formation of azobenzene from nitrobenzene (Scheme II), one would assume that the reduction of **23** is proceeding through radical anion intermediates. The esr spectrum of a solution of **23** in THF after treatment with alkali metals such as

(22) For some of these addition reactions, see (a) J. W. B. Reesor and G. F. Wright, *J. Org. Chem.*, **22**, 375 (1957); (b) M. V. George, D. Wittenberg, and H. Gilman, *J. Amer. Chem. Soc.*, **81**, 361 (1959); (c) M. V. George, P. B. Talukdar, and H. Gilman, *J. Organometal. Chem.* **5**, 397 (1966); (d) S. S. Dua and M. V. George, *ibid.*, **9**, 413 (1967); (e) *ibid.*, **10**, 219 (1967).

(23) P. E. Iverson and H. Lund, *Tetrahedron Lett.*, 4027 (1967).

(24) R. K. Gupta, Ph.D. Thesis, Indian Institute of Technology, Kanpur, India, 1968.

SCHEME III

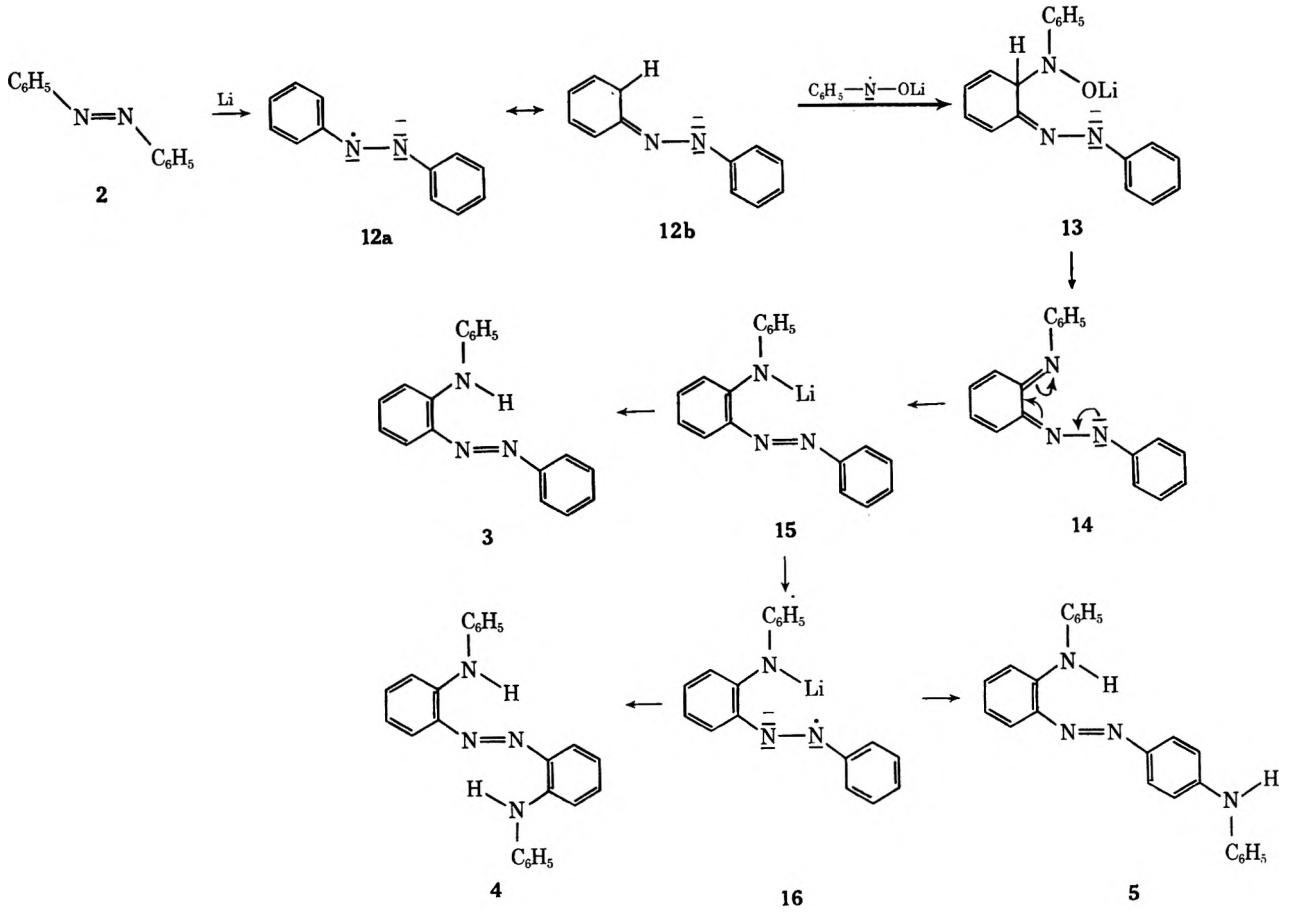


TABLE II

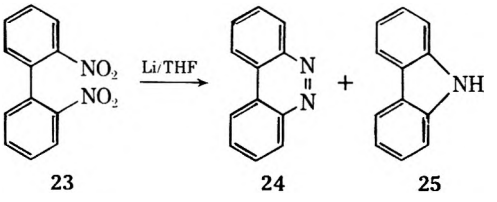
PRODUCTS OBTAINED FROM THE REACTION OF AROMATIC NITRO COMPOUNDS WITH LITHIUM IN THF

Nitro compd	Products (yield, %)
4-Nitroanisole (**17a**)	4,4′-Azoanisole (**18a**) (25); 2-(*p*-anisidino)-4,4′-azoanisole (**19a**) (18); 2,2′-bis(*p*-anisidino)-4,4′-azoanisole (**20a**) (1)
4-Nitro-*N*,*N*-dimethylaniline (**17b**)	4,4′-Bis(*N*,*N*-dimethylamino)azobenzene (**18b**) (18); 2-(*p*-*N*,*N*-dimethylamino)-4,4′-bis(*N*,*N*-dimethylamino)azobenzene (**19b**) (2)
4-Nitrotoluene (**17c**)	4,4′-Azotoluene (**18c**) (19); 2-(*p*-toluidino)-4,4′-azotoluene (**19c**) (0.6); 4,4′-azoxytoluene (0.5)
3-Nitrotoluene (**17d**)	3,3′-Azotoluene (**18d**) (31); 2-(*m*-toluidino)-5,5′-azotoluene (**19d**) (12); 2,2′-bis(*m*-toluidino)-5,5′-azotoluene (**20d**) (0.2)
2-Nitrotoluene (**17e**)	2,2′-Azotoluene (**18e**) (22)
2-Chloronitrobenzene (**21**)	2,2′-Bis(*o*-chloroanilino)azobenzene (**22**) (2)
2-Bromonitrobenzene	No definite product
4-Nitroaniline	Unchanged starting material
3-Nitroaniline	Unchanged starting material
4-Nitroacetanilide	Unchanged starting material

Li, Na, and K supports this view.[25] It might be pointed out in this connection that the esr spectrum of a solution of **23** on prolonged treatment with alkali metals corresponds to the spectrum of the radical anion of dibenzopyridazine (**24**).[25]

(25) J. Subramanian and P. T. Narasimhan, private communication.

SCHEME IV



In order to examine whether the reduction of 2,2′-dinitrodiphenyl ether (**26**) would give rise to the corresponding cyclic azo compound, dibenzo[1.4.5]oxadiazepine (**27**) we have studied the reaction of **26** with lithium in THF. It was observed that the initially formed radical anion intermediate does not undergo further reaction and the starting material was recovered unchanged in appreciable yields, on work-up. However, the reaction of **26** with sodium in tetrahydrofuran resulted in the cleavage of this molecule, and a small quantity of 2-nitrophenol (**28**) was isolated from this run. Similarly, the reaction of 1,8-dinitronaphthalene with lithium did not give rise to any of the cyclic products.

Reaction of Aromatic Nitroso and Azoxy Compounds with Lithium.—Treatment of nitrosobenzene with lithium in tetrahydrofuran gave a 53% yield of azobenzene and a 11% yield of 2-anilinoazobenzene (**3**). The formation of **3** in this reaction would be an indirect support to the reaction sequences shown in Scheme II. Similarly, a 28% yield of 4,4′-bis(*N*,*N*-dimethylamino)azobenzene was obtained from 4-nitroso-*N*,*N*-dimethylaniline. It might be mentioned

in this connection that Kauffman and Hage[26] were able to isolate a 48% yield of 4,4′-azoxytoluene in the reduction of 4-nitrosotoluene with sodium in ether solvents, whereas *N*-(*p*-tolyl)hydroxylamine was formed when excess sodium was employed. Also, it has been reported that phenyllithium reacts with aromatic nitro and nitroso compounds to give lithium derivatives of hydroxylamine, phenol, and diphenylamine.[27]

The reaction of azoxybenzene with lithium in THF gave a nearly quantitative yield of azobenzene. Similarly, 4,4′-azoxyanisole, on treatment with lithium was deoxygenated to the corresponding 4,4′-azoanisole in 99% yield. A similar observation was made by Kauffman and coworkers,[28] who were able to isolate a 80% yield of azobenzene from the reaction of azoxybenzene with alkali metals. In the reaction of *α*-4-bromoazoxybenzene with lithium, however, the product isolated was a 40% yield of azobenzene, suggesting thereby that a debromination step is also involved in this reaction.

Mass Spectral Fragmentation of Arylamino-Substituted Azobenzenes.—We have examined the mass spectral fragmentation pattern of a few arylaminoazobenzenes that were obtained during the course of the present studies. In this connection, the mass spectra of 2-anilinoazobenzene, 2,2′-dianilinoazobenzene, 2,4′-dianilinoazobenzene, and 2,2′-bis(*p*-anisidino)-4,4′-azoanisole were examined. The base peaks in all these compounds have been due to the molecular ions. Bowie and coworkers[29] have recently examined the mass spectra of several azobenzenes and have found that the base peak in these compounds has been due to biphenyl and biphenylene ions, arising through the loss of nitrogen. Similar loss of nitrogen has been observed in related systems.[30] However, we find that, in the arylaminoazobenzene examined by us, the loss of nitrogen is not very significant. The major fragmentation modes appeared to be the cleavage of the arylamino moiety and also of the loss of aryl groups, Without exception, all these compounds showed ions arising through skeletal rearrangements and many metastable peaks were also observed in the spectra.

Experimental Section

All melting points are uncorrected and were taken in a Thomas-Hoover melting point apparatus. Ir spectra were determined on either a Perkin-Elmer Model 137 or 521 infrared spectrometer. Electronic spectra were recorded in a Cary 14 spectrophotometer. Nmr spectra were recorded on a Varian HR-100 spectrometer using TMS as an internal standard. Mass spectra were recorded on a CEC 21-110 B mass spectrometer with 40 μA ionizing current and an ionizing voltage of 70 eV.

Starting Materials.—Solvents such as diethyl ether, 1,2-dimethoxyethane, tetrahydrofuran, and dioxane, used in the present studies, were purified by standard procedures and distilled over sodium. Reagent grade samples of nitrobenzene, 2-nitrotoluene, 3-nitrotoluene, 4-nitrotoluene, 4-nitroanisole, 2-chloronitrobenzene, 3-nitroaniline, 4-nitroaniline, 4-nitroacetanilide, 1,8-dinitronaphthalene, 4-nitrosodiphenylamine, azoxybenzene, 4,4′-azoxyanisole, and 2-aminodiphenylamine were purified either by distillation or recrystallization before use. 4-Nitro-*N*,*N*-dimethylaniline,[31] mp 163° (75% yield), 2,2′-dinitrobiphenyl,[32] mp 124° (50% yield), 2,2′-dinitrodiphenyl ether,[33] mp 111° (50% yield), nitrosobenzene,[34] mp 65–66° (40% yield), 4-nitroso-*N*,*N*-dimethylaniline,[35] mp 87° (80% yield), and 4-bromoazoxybenzene,[36] mp 73° (45% yield), were prepared by reported procedures.

General Procedure for the Reaction of Aromatic Nitro Compounds with Lithium.—In general, a mixture of the aromatic nitro compound with an excess of lithium metal (4–5 g-atoms) in a solvent such as tetrahydrofuran was shaken under an atmosphere of dry nitrogen.[37] In order to ensure a clean surface of the metal throughout, a few broken glass chips were added to the reaction mixture. On completion of the reaction, the excess of metal was removed by filtration under nitrogen and the solvent was stripped under vacuum. The residue was successively extracted with solvents such as benzene and acetone. Further separation and purification of the individual components were achieved through repeated chromatography over alumina.

Reaction of Nitrobenzene with Lithium.—A mixture of 2.5 g (20 mmol) of nitrobenzene and 0.7 g (0.1 g-atom) of lithium was shaken in tetrahydrofuran (60–75 ml) for about 16 hr. The reaction mixture became brown at first, and turned later to violet and finally deep brown. In several successive runs, a total of 22.1 g (0.18 mol) of nitrobenzene was treated with the requisite amount of lithium and the mixture of products thus obtained was extracted with hot benzene (2 l.) to give 17.2 g of a dark brown mass. This material was dissolved in benzene (50 ml) and chromatographed on alumina. Elution of the column with a mixture (3:1) of petroleum ether (bp 60–80°) and benzene gave 9.8 g of a red, viscous material. The residual material on the column was eluted out with hot ethanol and this eluate was mixed with the ethanol extract of the original reaction mixture (the residue left behind after extraction with benzene). Removal of the solvent gave 4.4 g of a violet-brown, viscous material which was worked up subsequently.

The red, viscous solid (9.8 g) obtained earlier was chromatographed thrice over alumina using petroleum ether to give 5.6 g (34%) of azobenzene (**2**), mp and mmp 68°. Further elution of the column with a mixture (5:1) of petroleum ether and benzene gave 1.9 g (12%) of 2-anilinoazobenzene (**3**), which melted over the range 50–54°. Repeated recrystallizations from methanol gave a pure product of **3** which melted at 56°.

Anal. Calcd for $C_{18}H_{15}N_3$: C, 79.12; H, 5.50; N, 15.39; mol wt, 273. Found: C, 79.31; H, 5.88; N, 15.50; mol wt (mass spectrometry), 273. Ir spectrum (KBr) ν_{max} 3340 (NH) and 1450 cm^{-1} (N=N); uv spectrum (cyclohexane) λ_{max} 288 nm (ε 30,200), 322 (22,500), and 457 (10,700).

The violet-brown mass (4.4 g) obtained from the ethanol extract was rechromatographed on alumina. Elution with a mixture (3:1) of petroleum ether and benzene gave 40 mg of azobenzene, mp and mmp 68°. Further elution with a mixture (2:1) of petroleum ether and benzene gave 0.2 g of a maroon-colored product, melting over the range 100–130° (darkens around 70°). The residue on the column was again extracted with ethanol to give 3.2 g of a dark-colored solid, which was subsequently worked up.

Further chromatography of the maroon-colored product (mp 100–130°) over alumina using petroleum ether gave 77 mg (0.5%) of 2,4′-dianilinoazobenzene (**5**), which melted at 120° dec after recrystallization from petroleum ether.

Anal. Calcd for $C_{24}H_{20}N_4$: C, 79.12; H, 5.50; N, 15.39; mol wt, 364. Found: C, 79.40; H, 6.08; N, 15.38; mol wt (mass spectrometry), 364. Ir spectrum (KBr) ν_{max} 3400 (NH),

(26) T. Kauffman and S. M. Hage, *Angew. Chem., Int. Ed. Engl.*, **2**, 156 (1963).

(27) P. Buck and G. Kobrich, *Tetrahedron Lett.*, 1563 (1967).

(28) T. Kauffman, S. M. Hage, and R. Buckelshauss, *Chem. Ber.*, **100**, 1235 (1967).

(29) J. H. Bowie, G. E. Lewis, and R. G. Cooks, *J. Chem. Soc. B*, 621 (1967).

(30) For some of the examples, see (a) N. S. Vulf'son, V. A. Puchkov, and Y. S. Nekrasov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, **8**, 1881 (1967); *Chem. Abstr.*, **68**, 68286 (1968); (b) E. V. Brown, *J. Heterocycl. Chem.*, **6**, 571 (1969); (c) J. H. Bowie, G. E. Lewis, and R. G. Cooks, *J. Chem. Soc. B*, 621 (1967); S. N. Bannore, J. L. Bose, K. G. Das, and V. N. Gogte, *Indian J. Chem.*, **7**, 654 (1969).

(31) T. W. C. Campbell, *J. Amer. Chem. Soc.*, **71**, 740 (1949).

(32) R. C. Fuson and E. A. Cleveland, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 339.

(33) J. J. Rendall, C. E. Lewis, and P. M. Slagen, *J. Org. Chem.*, **27**, 4098 (1962).

(34) G. H. Coleman, C. M. McCloskey, and F. A. Stuart, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 668.

(35) G. M. Bennett and E. V. Bell, "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1959, p 223.

(36) A. Angeli and B. Valon, *Atti Accad. Naz. Lincei*, **21**, 55 (1912); *Chem. Abstr.*, **6**, 1137 (1912).

(37) For purification of nitrogen, see L. J. Brady, *Ind. Eng. Chem., Anal. Ed.*, **20**, 1034 (1948).

3260 (NH), and 1490 cm^{-1} (N=N); uv spectrum (cyclohexane) λ_{max} 290 nm (ϵ 32,400), 325 (15,500), and 472 (6800).

Further elution of the chromatographic column using a mixture (4:1) of petroleum ether and acetone gave 85 mg (0.5%) of 2,2'-dianilinoazobenzene (**4**), mp 158° dec (lit.[17] mp 160°), after recrystallization from a mixture (1:1) of benzene and ethanol.

Anal. Calcd for $C_{24}H_{20}N_4$: C, 79.12; H, 5.50; N, 15.39; mol wt, 364. Found: C, 79.00; H, 5.68; N, 15.24; mol wt (mass spectrometry), 364. Ir spectrum (KBr) ν_{max} 3400–3250 (NH) and 1455 cm^{-1} (N=N); uv spectrum (cyclohexane) λ_{max} 288 nm (ϵ 32,300), 323 (10,500), and 500 (13,500).

The dark brown material obtained earlier was dissolved in about 35 ml of a mixture (1:1) of benzene and acetone and chromatographed over alumina. Elution of the column with a mixture (3:1) of petroleum ether and benzene gave 11 mg of a pink-colored compound melting at 135–137°. Recrystallization from petroleum ether gave 6 mg of a pure sample of anilinodibenzopyridazine (**6**), mp 138.5°.

Anal. Calcd for $C_{18}H_{13}N_3$: mol wt, 271. Found: mol wt (mass spectrometry), 271. Ir spectrum (CCl_4) ν_{max} 3280 (NH) and 1460 cm^{-1} (N=N); uv spectrum (cyclohexane) λ_{max} 241 nm (ϵ 38,300), 297 (42,600), 338 (2900), 354 (4300), 364 (3700), 372 (5400), and 510 (4500).

Further elution of the chromatographic column with a variety of solvents did not lead to the isolation of any definite product.

Influence of Solvent, Temperature, and the Alkali Metals on the Reaction of Nitrobenzene. A. Solvent.—In a typical run, 2.5 g (20 mmol) of nitrobenzene and 0.7 g (0.1 g-atom) of lithium were mixed together in 70 ml of tetrahydrofuran. On completion of the reaction, the mixture was worked up as described earlier and the yield of azobenzene was assessed. Similarly, the reaction was repeated in different solvents such as 1,2-dimethoxyethane, dioxane, and diethyl ether and Table I summarizes the results of these studies.

B. Temperature.—In a repeat run involving the reaction of nitrobenzene with lithium, the reaction was carried out around 0–5°, instead of at room temperature in ether medium. Work-up of the mixture in the usual manner gave a 8% yield of azobenzene and 60 mg (3%) of a product, identified as azoxybenzene, mp and mmp 36°. However, when the same reaction was carried out in tetrahydrofuran around 30°, a 25% yield of azobenzene was obtained after a reaction time of 24 hr (Table I).

C. Alkali Metals (Na and K).—Treatment of 2.5 g (20 mmol) of nitrobenzene with 2 g (0.09 g-atom) of sodium in 75 ml of tetrahydrofuran and work-up of the mixture in the usual manner gave 120 mg (7%) of azobenzene and 1 g (40%) of unchanged nitrobenzene, identified through its ir spectrum.

In a repeat run, 2.5 g (20 mmol) of nitrobenzene was treated with 3.5 g (0.09 g-atom) of potassium in 75 ml of tetrahydrofuran. Work-up of the mixture as in the earlier cases, after a 48-hr reaction time, gave 14 mg (2%) of azobenzene, mp and mmp 68°, and 1.6 g (65%) of unchanged nitrobenzene, identified through its ir spectrum.

Synthesis of 2-Anilinoazobenzene (3).—A mixture of 2-aminodiphenylamine (0.92 g, 5 mmol) and nitrosobenzene (0.53 g, 5 mmol) was dissolved in 10 ml of glacial acetic acid and was left at room temperature for 36 hr. The deep red reaction mixture was diluted with cold water and extracted with a mixture (1:1) of ether and benzene, after neutralization with potassium hydroxide. Removal of the solvent under vacuum gave a product which was chromatographed on alumina. Elution with a mixture (5:1) of petroleum ether and benzene gave 100 mg (7%) of **3**, which melted at 56° on recrystallization from methanol. Comparison of this compound with a sample of **3** obtained in the reaction of nitrobenzene with lithium revealed that they were identical. There was no depression in their melting points when they were mixed together and also their ir spectra were identical.

Synthesis of 2,2'-Dianilinoazobenzene (4).—A mixture of 0.92 g (5 mmol) of 2-aminodiphenylamine and 4.5 g of nickel peroxide in 100 ml of dry benzene was stirred at room temperature for 5 hr. Removal of the unchanged nickel peroxide and solvent under vacuum gave a product which was chromatographed on alumina. Elution with benzene gave 12 mg (0.5%) of **4**, which melted at 158° dec, on recrystallization from a mixture (1:1) of benzene and ethanol. There was no depression in the melting point of this material when mixed with a sample of **4** obtained in the reaction of nitrobenzene with lithium. The ir spectra of these two samples were also identical.

Attempted Synthesis of 2,4'-Dianilinoazobenzene (5).—A mixture of 4-nitrosodiphenylamine (1 g, 5 mmol), 2-aminodiphenylamine (0.92 g, 5 mmol), and glacial acetic acid (10 ml) was left at room temperature for 24 hr. Work-up of the mixture as in the case of **3** resulted in the recovery of a 20% yield (0.2 g) of unchanged 2-aminodiphenylamine, mp and mmp 80°, and a 60% yield (0.6 g) of 4-nitrosodiphenylamine, mp and mmp 144°.

Repetition of this experiment under different conditions, such as treatment of the reagents in pyridine, acetic acid, or aqueous sodium hydroxide, did not give rise to the desired product. In a separate run, when the reagents were heated in acetic acid in a sealed tube for 6 hr, only polymeric materials could be isolated.

Reaction of 4-Nitroanisole with Lithium.—Treatment of 4-nitroanisole (**17a**)) (9.2 g, 0.06 mol) with lithium (1.8 g, 0.26 g-atom) in tetrahydrofuran (120 ml) for a period of 18 hr gave a deep brown reaction mixture. Removal of the solvent under vacuum gave a mixture of products which was extracted with hot benzene, and the benzene-soluble product (7.2 g) was chromatographed on alumina. Elution with benzene gave 4.2 g of a red solid which, when fractionally crystallized from ethanol, yielded 1.8 g (25%) of 4,4'-azoanisole (**18a**), mp and mmp 161–162°. Removal of the solvent from the mother liquor gave a product which was rechromatographed on alumina. Elution with a mixture (2:1) of petroleum ether and benzene gave a yellow solid which, when fractionally crystallized from methanol, yielded 1.3 g (18%) of 2-(*p*-anisidino)-4,4'-azoanisole (**19a**), mp 108°.

Anal. Calcd for $C_{21}H_{21}N_3O_3$: C, 69.42; H, 5.80; N, 11.57; mol wt, 363. Found: C, 69.52; H, 5.80; N, 11.53; mol wt (mass spectrometry), 363. Ir spectrum (CCl_4) ν_{max} 3400 (NH), 3230 (NH), and 1470 cm^{-1} (N=N); uv spectrum (tetrahydrofuran) λ_{max} 288 nm (ϵ 17,000), 347 (18,000), and 451 (15,000); nmr spectrum (CCl_4) 3.69 (3 H, methoxy), 3.75 (3 H, methoxy), 3.79, (3 H, methoxy), 7.18 (11 H, multiplet, aromatic), and 10.5 ppm (1 H, NH).

Further elution of the column with a mixture (1:1) of petroleum ether and benzene gave 90 mg (1%) of 2,2'-bis(*p*-anisidino)-4,4'-azoanisole (**20a**), which melted over the range 163–165°, after recrystallization from a mixture (1:1) of benzene and ethanol.

Anal. Calcd for $C_{28}H_{28}N_4O_4$: C, 69.42; H, 5.80; N, 11.57; mol wt, 484. Found: C, 69.44; H, 5.30; N, 11.57; mol wt (mass spectrometry), 484. Ir spectrum (KBr) ν_{max} 3360 (NH), 3300 (NH), and 1495 cm^{-1} (N=N); uv spectrum (tetrahydrofuran) λ_{max} 298 nm (ϵ 33,900), 342 (14,500), 493 (23,400); nmr spectrum ($CDCl_3$) 3.96 (6 H, methoxy), 4.03 (6 H, methoxy), 7.38 (14 H, multiplet, aromatic), and 10 ppm (2 H, NH).

Reaction of 4-Nitro-*N*,*N*-dimethylaniline (17b) with Lithium.—Treatment of 8.3 g (0.05 mol) of **17b** with 1.8 g (0.25 g-atom) of lithium in tetrahydrofuran for 36 hr gave a dark red reaction mixture. Removal of the solvent under vacuum gave a mixture of products which was extracted with a hot mixture (1:1) of benzene and acetone and chromatographed over alumina. Elution of the column with benzene gave 1.2 g (18%) of 4,4'-bis(*N*,*N*-dimethylamino)azobenzene (**18b**), mp and mmp 272–274°.

Further elution of the column with benzene gave 87 mg (2%) of 2-(*p*-*N*,*N*-dimethylaminoanilino)-4,4'-bis(dimethylamino)azobenzene (**19b**), which melted at 243–244° after recrystallization from benzene.

Anal. Calcd for $C_{24}H_{30}N_6$: C, 71.64; H, 7.46; N, 20.89. Found: C, 71.70; H, 7.77; N, 21.06. Ir spectrum (KBr) ν_{max} 3322 (NH) and 1471 cm^{-1} (N=N); uv spectrum (tetrahydrofuran) λ_{max} 252 nm (ϵ 17,000), 320 (10,100), 448 (31,400), and 468 (33,300).

Reaction of 4-Nitrotoluene (17c) with Lithium.—A mixture of 11 g (0.08 mol) of **17c** and 2.5 g (0.36 g-atom) of lithium in 200 ml of tetrahydrofuran was allowed to stand at room temperature for 18 hr, with constant shaking. Removal of the unchanged metal and solvent under vacuum gave 7 g of a brown viscous solid which was chromatographed over alumina. Elution of the column with petroleum ether gave 1.6 g (19%) of 4,4'-azotoluene (**18c**), which melted at 146° (mixture melting point) after recrystallization from ethanol. Further elution of the column with a mixture (3:1) of petroleum ether and benzene afforded a red substance which was recrystallized from methanol to give 50 mg (0.6%) of 2-(*p*-toludino)-4,4'-azotoluene (**19c**), mp 112°.

Anal. Calcd for $C_{21}H_{21}N_3$: C, 80.00; H, 6.67; N, 13.34. Found: C, 80.30; H, 6.53; N, 13.77. Ir spectrum (CCl_4) ν_{max} 3400 (NH), 3230 (NH), and 1440 cm^{-1} (N=N); uv spectrum (tetrahydrofuran) λ_{max} 292 nm (ϵ 20,300), 353 (18,400), and 465 (11,100).

Subsequent elution of the column with the same solvent gave

46 mg (0.5%) of 4,4′-azoxytoluene, which melted at 68° after recrystallization from ethanol. There was no depression in the melting point of this compound when mixed with an authentic sample of 4,4′-azoxytoluene, prepared by a reported procedure.[38]

Reaction of 3-Nitrotoluene (17d) with Lithium.—Treatment of 11 g of 3-nitrotoluene (17d) with 2.5 g (0.36 g-atom) of lithium in 250 ml of tetrahydrofuran for 14 hr at room temperature and work-up in the usual manner gave a mixture of products which was chromatographed on alumina. Elution with petroleum ether gave 2.6 g (31%) of 3,3′-azotoluene (18d) which melted at 53° (mixture melting point) after recrystallization from petroleum ether (bp 40–60°).

Further elution of the column with a mixture (3:1) of petroleum ether and benzene gave 1 g (12%) of 2-(*m*-toludino)-5,5′-azotoluene (19d), which melted at 56–57° after distillation under high vacuum, followed by fractional crystallization from methanol.

Anal. Calcd for $C_{21}H_{21}N_3$: C, 80.00; H, 6.67; N, 13.30. Found: C, 80.23; H, 6.91; N, 12.80. Ir spectrum (CCl_4) ν_{max} 3390 (NH), 3220 (NH), and 1450 cm^{-1} (N=N); uv spectrum (cyclohexane) λ_{max} 293 nm (ϵ 21,100), 323 (14,000), and 482 (8400); nmr spectrum ($CDCl_3$) 2.38 (6 H, methyl), 2.46 (3 H, methyl), 7.45 (11 H, multiplet, aromatic), and 10.2 ppm (1 H, NH).

Further elution of the column with a mixture (2:1) of petroleum ether and benzene gave a red, viscous material which was repeatedly chromatographed to give 17 mg (0.2%) of 2,2′-bis(*m*-toludino)-5,5′-azotoluene (20d), showing a single spot to tlc.

Anal. Calcd for $C_{28}H_{28}N_4$: N, 13.30. Found: N, 12.80. Ir spectrum (CCl_4) ν_{max} 3333 (NH) and 1480 cm^{-1} (N=N); nmr spectrum ($CDCl_3$) 2.29, 2.43 (12 H, methyl), and 6.99 ppm (14 H, multiplet, aromatic).

Reaction of 2-Nitrotoluene with Lithium.—A mixture of 4.1 g (0.03 mol) of 2-nitrotoluene and 1.1 g (0.15 g-atom) of lithium in 60 ml of tetrahydrofuran was stirred for 20 hr around 0–5°. Removal of the solvent under vacuum gave 2.6 g of a red, viscous solid which was chromatographed on alumina. Elution of the column with petroleum ether gave 650 mg (22%) of 2,2′-azotoluene, mp and mmp 54–55° after recrystallization from petroleum ether.

Reaction of 2-Chloronitrobenzene with Lithium.—2-Chloronitrobenzene (15.8 g, 0.01 mol) was treated with lithium (4.2 g, 0.06 g-atom) in tetrahydrofuran (200 ml) for a period of 4 hr around 0–5°. The reaction mixture was worked up in the usual manner to give 8.5 g of a dark, viscous material which was repeatedly chromatographed on alumina to give 1.8 g of a reddish-brown product which was subsequently chromatographed on silica gel. Elution of the column with petroleum ether gave 200 mg of 2,2′-bis(*o*-chloroanilino)azobenzene (22), which melted at 164° after recrystallization from petroleum ether.

Anal. Calcd for $C_{24}H_{18}N_4Cl_2$: C, 66.51; H, 4.16; N, 12.93. Found: C, 66.67; H, 3.99; N, 12.76. Ir spectrum (CCl_4) ν_{max} 3311 (NH) and 1450 cm^{-1} (N=N); uv spectrum (cyclohexane) λ_{max} 288 nm (ϵ 40,800), 320 (27,200), and 504 (15,300); nmr spectrum ($CDCl_3$) 7.65 (16 H, multiplet, aromatic) and 10.2 ppm (2 H, NH).

Attempted Reaction of 4-Nitroaniline with Lithium.—Treatment of 4-nitroaniline (4.1 g, 30 mmol) with lithium (1.4 g, 0.02 g-atom) in tetrahydrofuran (100 ml) for 24 hr and work-up in the usual manner led to the recovery of 3.8 g (93%) of unchanged 4-nitroaniline, mp and mmp 147°.

Attempted Reaction of 3-Nitroaniline with Lithium.—3-Nitroaniline (2.1 g, 15 mmol) was treated with lithium (0.7 g, 0.1 g-atom) in tetrahydrofuran (40 ml) for 18 hr. Removal of the unchanged metal and the solvent led to the recovery of 1.8 g (90%) of the starting 3-nitroaniline, mp and mmp 114°.

Attempted Reaction of 4-Nitroacetanilide with Lithium.—Treatment of 4-nitroacetanilide (1.8 g, 10 mmol) with lithium (0.35 g, 0.05 g-atom) in tetrahydrofuran (60 ml) for 8 hr and work-up of the reaction mixture as before gave 1.7 g (95%) of unchanged 4-nitroacetanilide, mp and mmp 210°.

Reaction of 2,2′-Dinitrobiphenyl (23) with Alkali Metals. A. With Lithium.—A mixture of 3.7 g (15 mmol) of **23** and 1 g (0.14 g-atom) of lithium was stirred in tetrahydrofuran (125 ml) for 12 hr. Work-up of the reaction mixture in the usual manner gave a dark brown mixture, which was chromatographed on alumina. Elution of the column with benzene gave 1.2 g (45%) of dibenzopyridazine (24), which melted at 156° after recrystallization from benzene. There was no depression in the melting point of this sample on admixture with an authentic sample of **24** prepared from **23** by lithium aluminum hydride reduction.[39] Further elution of the column with a mixture (3:1) of chloroform and benzene gave 26 mg of carbazole **25**, mp and mmp 252° after recrystallization from benzene.

B. With Sodium.—In a repeat run, 1.2 g (5 mmol) of **23** was treated with sodium (1.2 g, 0.5 g-atom) in 1,2-dimethoxyethane (60 ml). Work-up of the reaction mixture as before gave 450 mg (50%) of **24**, mp and mmp 156°.

Reaction of 2,2′-Dinitrodiphenyl Ether (26) with Alkali Metals. A. With Lithium.—2,2′-Dinitrodiphenyl ether (3.3 g, 13 mmol) was treated with lithium (0.8 g, 0.11 g-atom) in tetrahydrofuran (60 ml) for 48 hr with occasional stirring. Removal of the unchanged metal and the solvent under vacuum gave a brown material, which on recrystallization from methanol gave 2.3 g (77%) of unchanged starting material, mp and mmp 111°.

B. With Sodium.—In a repeat run, 2.6 g (10 mmol) of **26** was treated with 2.1 g (0.9 g-atom) of sodium in tetrahydrofuran for 28 hr. Removal of the unchanged metal and solvent under vacuum gave a material which was steam distilled after acidification with hydrochloric acid to give 215 mg (15%) of 2-nitrophenol, mp and mmp 44°.

Reaction of 1,8-Dinitronaphthalene with Lithium.—1,8-Dinitronaphthalene (3.1 g, 15 mmol) was treated with lithium (1.1 g, 0.15 g-atom) for 8 hr. Most of the metal was consumed during the course of the reaction. Removal of the solvent under vacuum gave a dark-colored, polymeric material from which no definite product could be isolated.

Reaction of Nitrosobenzene with Lithium.—Lithium metal (0.4 g, 0.06 g-atom) was added to a solution of nitrosobenzene (2.1 g, 20 mmol) in tetrahydrofuran (60 ml) and the reaction mixture was kept at room temperature for 28 hr, with occasional stirring. The solution, which was initially green, became dark brown at the end of this period. Removal of the solvent under vacuum gave a product which was chromatographed over alumina. Elution with petroleum ether gave 965 mg (53%) of azobenzene, mp and mmp 68°.

Further elution of the column with a mixture (5:1) of petroleum ether and benzene gave 190 mg (11%) of 2-anilinoazobenzene, mp and mmp 56°.

Reaction of 4-Nitroso-*N*,*N*-dimethylaniline with Lithium.—A mixture of 3 g (20 mmol) of 4-nitroso-*N*,*N*-dimethylaniline and 0.3 g (0.04 g-atom) of lithium in 50 ml of tetrahydrofuran was kept at room temperature for 18 hr. Removal of the unchanged metal and solvent under vacuum gave a brown solid which was chromatographed over alumina. Elution with benzene gave 750 mg (28%) of 4,4′-bis(*N*,*N*-dimethylamino)azobenzene, mp and mmp 272–273°.

Reaction of Azoxybenzene with Lithium.—Azoxybenzene (1 g, 5 mmol) was stirred with lithium (0.1 g, 0.014 g-atom) in tetrahydrofuran (40 ml) for a period of 30 min. Removal of the solvent under vacuum gave a product which was repeatedly extracted with hot benzene. Removal of the solvent from the benzene extract gave 0.9 g (99%) of azobenzene, mp and mmp 68° after recrystallization from ethanol.

Reaction of 4,4′-Azoxyanisole with Lithium.—4,4′-Azoxyanisole (1.3 g, 5 mmol) was dissolved in 40 ml of tetrahydrofuran and shaken with lithium (0.1 g, 0.014 g-atom) for 30 min. Work-up of the material as in the earlier case gave 1.2 g (99%) of 4,4′-azoanisole, mp and mmp 162°.

Reaction of α-4-Bromoazoxybenzene with Lithium.—A mixture of α-4-bromoazoxybenzene (2.1 g, 8 mmol) and lithium (0.14 g, 0.02 g-atom) in 50 ml of tetrahydrofuran was kept at room temperature for 1 hr with constant stirring. Removal of the solvent under vacuum gave a product which was extracted with hot benzene and the benzene-soluble portion was subsequently chromatographed over alumina. Elution of the column with petroleum ether gave 550 mg (40%) of azobenzene, mp and mmp 68°. Further elution with benzene gave a small quantity of an unidentified mixture of products.

Registry No.—**1**, 89-95-3; **2**, 103-33-3; **3**, 37436-61-6; **4**, 2074-94-4; **5**, 37436-63-8; **6**, 37436-64-9; **7**, 586-96-9; **17a**, 100-17-4; **17b**, 100-23-2; **17c**, 99-99-0; **17d**,

(38) H. W. Galbraith, E. F. Degering, and E. F. Hitch, *J. Amer. Chem. Soc.*, **73**, 1323 (1953).

(39) N. L. Allinger and G. A. Youngdale, *ibid.*, **84**, 1020 (1962).

99-08-1; **17e**, 88-72-2; **18a**, 501-58-6; **18b**, 6257-64-3; **18c**, 501-60-0; **18d**, 588-04-5; **18e**, 584-90-7; **19a**, 37436-65-0; **19b**, 37436-66-1; **19c**, 37436-67-2; **19d**, 37436-68-3; **20a**, 37436-69-4; **20d**, 37436-70-7; **21**, 88-73-3; **22**, 37436-71-8; **23**, 2436-96-6; **24**, 230-17-1; **25**, 86-74-8; **26**, 2217-65-4; **28**, 88-75-5; 2-aminodiphenylamine, 534-85-0; 4-nitrosodiphenylamine, 156-10-5; 4-nitroaniline, 100-01-6; 3-nitroaniline, 99-09-2, 4-nitroacetanilide, 104-04-1; azoxybenzene, 495-48-7, 4,4′-azoxyanisole, 1562-94-3; 2,4-bromoazoxybenzene, 16109-68-5.

Acknowledgment.—The authors thank Professor C. N. R. Rao for helpful discussions. We are grateful to Dr. K. G. Das, National Chemical Laboratory, Poona, for his help in the recording of mass spectra, and Mr. A. H. Siddiqui (I. I. T., Kanpur) for microanalysis.

The Chemistry of Carbanions. XXII. C- *vs.* O-Acylation of Metal Enolates[1a]

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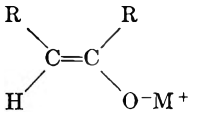
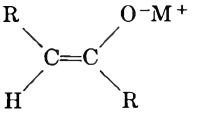
From a spectroscopic examination of metal enolates, the mercury(II) salts of ketones are found to exist as α-metalated ketones **2**, but salts with the metals lithium, sodium, zinc, and magnesium exist as enolate structures in which either contact ion pairs **4b** or solvent-separated ions **3** may be present. The existence of these metal enolates as solvent-separated ion pairs is favored (1) in a polar or a good solvating solvent, such as DME or DMF rather than ether; (2) by the presence of a metal cation such as lithium, sodium, or zinc rather than magnesium; and (3) by use of the trans (**1b**) rather than the cis (**1a**) stereoisomer of the enolate. In kinetically controlled reactions of metal enolates with acetylating agents, O-acylation is the favored reaction with α-metalated ketones **2** and with solvent-separated ion pairs **3**. The amount of of C-acylation is increased and may become the predominant reaction with metal enolates that exist as contact ion pairs **4b**. When the solvent and metal cation are kept constant, more C-acylation is obtained when acetyl chloride or acetyl bromide is used as the acylating agent rather than acetic anhydride or ketene.

Enolate anions **1** are members of a group of ambident nucleophiles that react wtih alkylating agents or acylating agents to form products with a new bond either at carbon or at oxygen.[2] When solutions of alkali metal enolates of monoketones in aprotic solvents are added slowly to an excess of reactive acylating agents such as $(CH_3CO)_2O$ or CH_3COCl, the major products of this kinetically controlled processes are usually the O-acetylated derivatives corresponding in structure and stereochemistry to the starting enolates.[2b,3] However, several groups have noted that, even with reaction procedures that result in kinetically controlled acylation, mixtures of C- and O-acylated products may result, especially when the metal cation is halomagnesium rather than lithium or sodium.[2b,3a,4] The proportion of C-acylation is also enhanced by the use of relatively nonpolar solvents,[2b,3a,4] by use of the metal enolate stereoisomer **1a** with the metal alkoxide and the β substituent trans[3a,b,4b] and by the use of acid chlorides rather than acid anhydrides as acylating agents.[4b]

Consideration of this information has led us to the

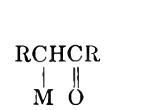


1a (cis enolate)

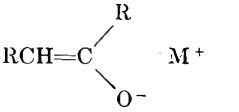


1b (trans enolate)

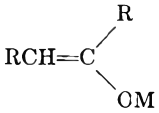
hypothesis that the reactions of ketone metal enolates can be explained by considering them to have one of three general structures: (1) structure **2** with a covalent carbon–metal bond; (2) solvent-separated ions **3**; or (3) either structure **4a** with a covalent metal–oxygen bond or the related contact ion pair **4b**. It is probable that many examples of the latter structures **4**



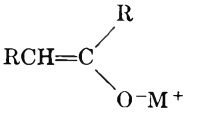
2 (covalent)



3 (solvent-separated ions)



4a (covalent)



4b (contact ion pair)

will exist in solution as molecular aggregates (dimers, trimers, tetramers), especially with nonpolar solvents and in cases with small R groups which do not sterically impede aggregation.[5]

In light of earlier discussions of ambident anions,[2] it would be expected that treatment with reactive acylating agents would lead to predominant O-acylation of enolates **2** and **3** and predominant C-acylation of enolates **4**. For this study we have prepared solutions of several metal enolates, determined the products

(1) (a) This research has been supported by Public Health Service Grant No. 7-RO1-CA-12634 from the National Cancer Institute. (b) A portion of this work was taken from the Ph.D. dissertation of Martin Gall, Massachusetts Institute of Technology, 1970.

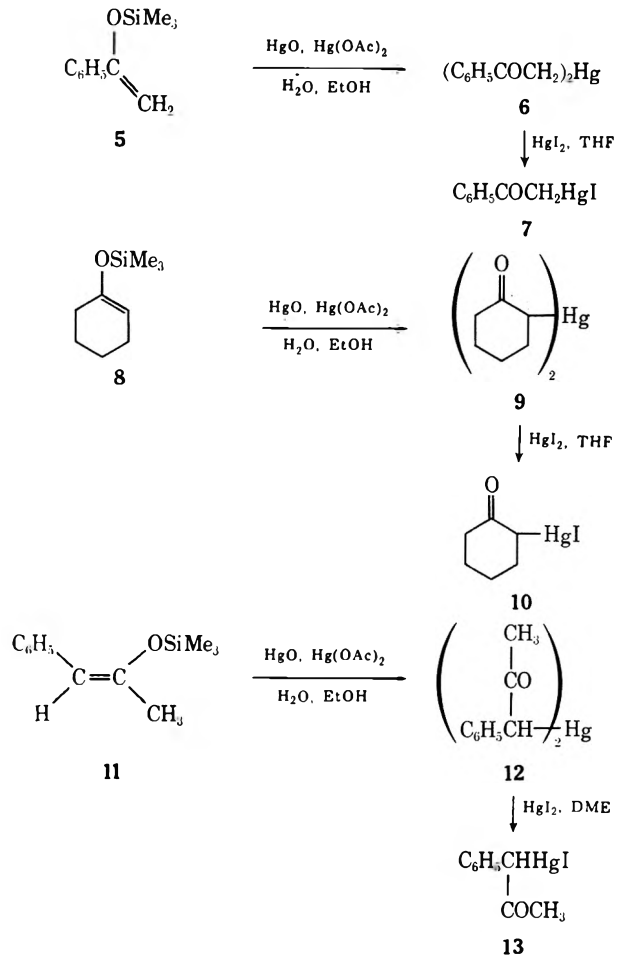
(2) For reviews, see (a) R. Gompper, *Angew. Chem., Int. Ed. Engl.*, **3**, 560 (1964); (b) H. O. House, "Modern Synthetic Reactions," 2nd ed, W. A. Benjamin, Menlo Park, Calif., 1972, pp 520–530, 762–765.

(3) (a) H. O. House, W. L. Respess, and G. M. Whitesides, *J. Org. Chem.*, **31**, 3128 (1966); (b) H. O. House, L. J. Czuba, M. Gall, and H. D. Olmstead, *ibid.*, **34**, 2324 (1969); (c) H. O. House, W. F. Fischer, Jr., M. Gall, T. E. McLaughlin, and N. P. Peet, *ibid.*, **36**, 3429 (1971); (d) W. M. Muir, P. D. Ritchie, and D. J. Lyman, *ibid.*, **31**, 3790 (1966); (e) K. Yoshida and Y. Yamashita, *Tetrahedron Lett.*, 693 (1966).

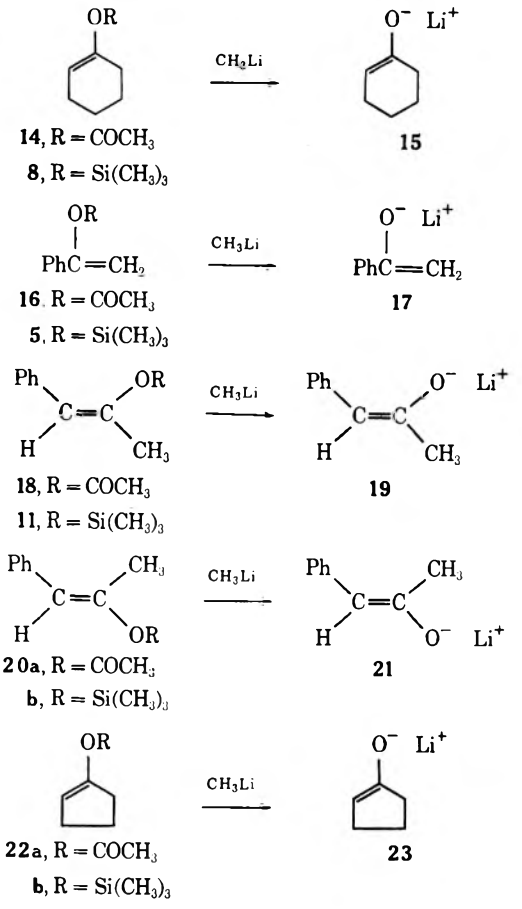
(4) (a) J. P. Ferris, C. E. Sullivan, and B. G. Wright, *J. Org. Chem.*, **29**, 87 (1964); J. P. Ferris, B. G. Wright, and C. C. Crawford, *ibid.*, **30**, 2367 (1965). (b) P. Angibeaud, and M.-J. Lagrange, *C. R. Acad. Sci., Ser. C*, **272**, 1506 (1971); L. Alais, P. Angibeaud, M.-J. Lagrange, and R. Michelot, *Bull. Soc. Chim. Fr.*, 2731 (1971). (c) For examples of the C-acylation of enol silyl ethers with acid chlorides, see S. Murai, Y. Kuroki, K. Hasegawa, and S. Tsutsumi, *Chem. Commun.*, **No. 16**, 946 (1972).

(5) For examples and discussion, see (a) H. D. Zook, T. J. Russo, E. F. Ferrand, and D. S. Stotz, *J. Org. Chem.*, **33**, 2222 (1968); (b) H. D. Zook, W. L. Kelley, and I. Y. Posey, *ibid.*, **33**, 3477 (1968); (c) A. G. Pinkus, J. G. Lindberg, and A. B. Wu, *Chem. Commun.*, 1350 (1969); 859 (1970); (d) H. O. House, M. Gall, and H. D. Olmstead, *J. Org. Chem.*, **36**, 2361 (1971).

Scheme I



Scheme II



formed upon acetylation, and examined the structures of certain metal enolates in solution by ir and nmr spectrometry.

Preparation and Properties of the Metal Enolate Solutions.—An earlier examination[6] of the ir (C=O at 1650 cm^{-1}) and nmr (δ_{CH_2} 2.80 with $J_{^{199}Hg-H}$ = 317 Hz and δ_{CH_3} 2.17 with $J_{^{199}Hg-H}$ = 14 Hz) spectra of α-chloromercuriacetone indicated that this metal enolate should be formulated as $ClHgCH_2COCH_3$, an enolate of the type **2** with a carbon–metal bond. To obtain additional α-mercuri ketones (Scheme I) we found the reaction of trimethylsilyl enol ethers with HgO and a catalytic amount of $Hg(OAc)_2$ in aqueous ethanol to be especially convenient.[7] Further reaction of the bisketomercurials **6**, **9**, and **12** with HgI afforded the relatively insoluble α-iodomercuri ketones **7**, **10**, and **13**. The ir, uv, and nmr spectra of these materials were compatible with the structures indicated and the nmr spectrum of each of the bisketomercurials exhibited satellite peaks corresponding to large $^{199}Hg-H$ coupling constants (172–200 Hz). Consequently, we conclude that each of these materials should be formulated as an enolate of type **2** with a covalent carbon–mercury bond.

(6) H. O. House and B. M. Trost, *J. Org. Chem.*, **30**, 1341, 2502 (1965).

(7) This method is a modification of an earlier synthetic method employing enol acetates or alkyl enol ethers: (a) A. N. Nesmeyanov, I. F. Lutsenko, and Z. M. Lumanova, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 601 (1949); *Chem. Abstr.*, **44**, 7225 (1950); (b) I. F. Lutsenko and R. M. Khomutov, *Dokl. Akad. Nauk SSSR*, **102**, 97 (1955); *Chem. Abstr.*, **50**, 4773 (1956); (c) A. N. Nesmeyanov, I. F. Lutsenko, and R. M. Khomutov, *Dokl. Akad. Nauk SSSR*, **88**, 837 (1953); *Chem. Abstr.*, **48**, 4434 (1954); (d) also see ref 3a.

The various lithium enolates indicated in Scheme II were prepared by previously described methods employing the reaction methyllithium with the appropriate enol acetates[6] or trimethylsilyl enol ethers.[3b,5d,8] The sodium enolates **25** and **26** of phenylacetone (**24**) were conveniently generated by reaction with sodium hydride in various solvents (Scheme III). In all cases this procedure afforded solutions containing primarily the more stable[3b] trans enolate **25** as a result of enolate equilibration during the relatively slow reaction of phenylacetone with the insoluble sodium hydride. A solution containing at least in part the zinc enolate **27a** in DME solution was obtained by treatment of the lithium enolate **19** (from the silyl ether **11**) with 0.5 molar equiv of anhydrous zinc chloride. A solution of the corresponding magnesium enolate **27b** in an Et_2O–PhH mixture was obtained by an analogous reaction of the lithium enolate **19** (from the silyl ether **11**) with 0.5 molar equiv of anhydrous magnesium bromide and a solution of the same enolate **27b** in Et_2O was obtained from the enol acetate **18** and dimethylmagnesium. Similarly, a solution of the magnesium enolate **28** was produced by reaction of the corresponding enol acetate **14** with dimethylmagnesium.

In the 6-μ region of the infrared, DME solutions of both the cis (**21**) and trans (**19**) lithium enolates do not exhibit a normal C=O stretching band but rather a pair of strong bands at 1560 and 1585 cm^{-1}; a DME solution of the trans sodium enolate **25** has analogous bands at 1550 and 1575 cm^{-1}. Furthermore, the subsequently discussed nmr spectra clearly indicate that

(8) G. Stork and P. F. Hudrlik, *J. Amer. Chem. Soc.*, **90**, 4462, 4464 (1968).

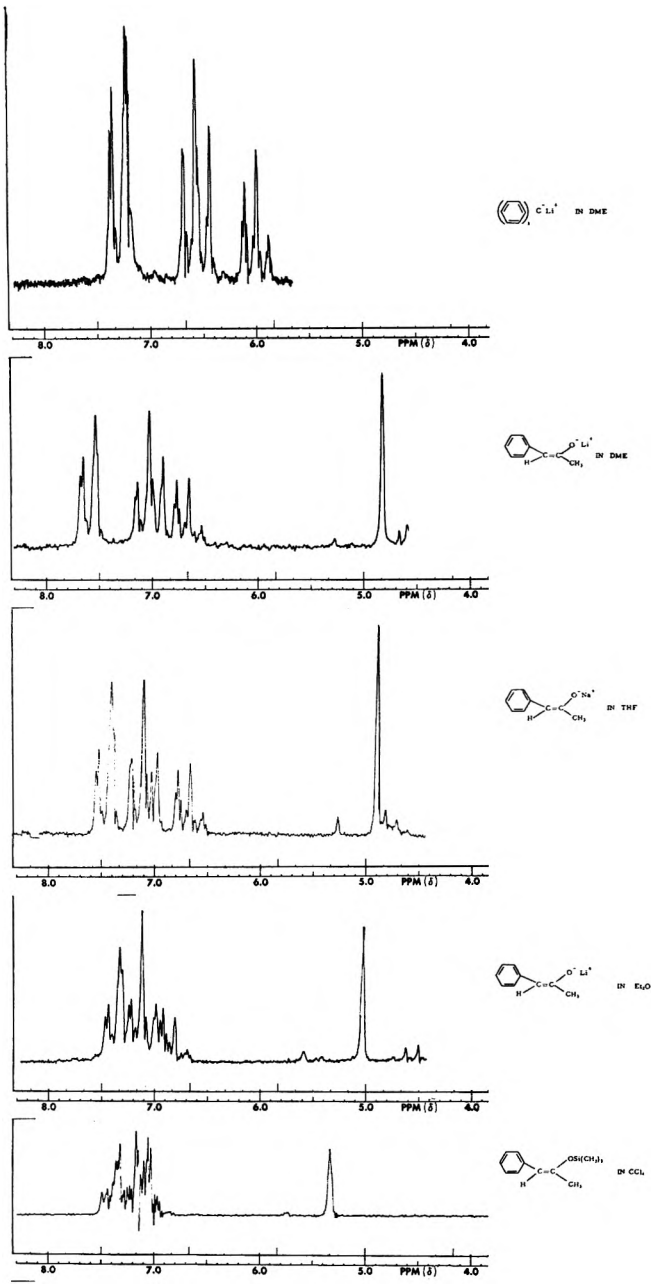


Figure 1.—Comparison of the nmr spectra of several trans enolates of phenylacetone with the spectra of the trans silyl ether 11 and triphenylmethyllithium.

these metal enolates have a vinyl CH bond. Thus, these enolates have structures of the type **3** or **4** and not **2**.

Although the nmr absorption of the various aliphatic metal enolates in ethereal solvents was obscured by solvent absorption, both the phenyl and vinyl CH absorption of the various phenylacetone enolates were at sufficiently low field to be examined. As noted earlier,[3b] the nmr spectra of the cis (**21** and **26**) and trans (**19** and **25**) phenylacetone enolates differ significantly and the composition of mixtures could be determined from the areas under the vinyl CH peaks. Representative spectra for the various phenylacetone enolates are presented in Figures 1 and 2. The sodium enolates prepared from phenylacetone (**24**) and excess sodium hydride in relatively polar solvents (THF, DME, DMF) contained primarily (92–>98%) of the trans enolate **25** as a result of equilibration during the relatively slow formation of the enolates **25** and **26**. In ether solution, this equilibration was slower and the initial enolate solution (see Figure 2) contained 76–78% of the trans isomer **25** and 22–24% of the cis isomer **26**. When an additional equivalent of the unionized ketone **24** was added to this solution to permit enolate equilibration by proton transfers,[6] the proportion of trans isomer **25** in Et_2O solution increased to about 90% during 18 hr. In the more polar solvents (DME and DMF) proton exchange between the ketone and the enolate was much more rapid and resulted in substantial line broadening of the enolate nmr signals when these solutions contained equimolar amounts of the ketone **24** and the enolate **25**.

SCHEME III

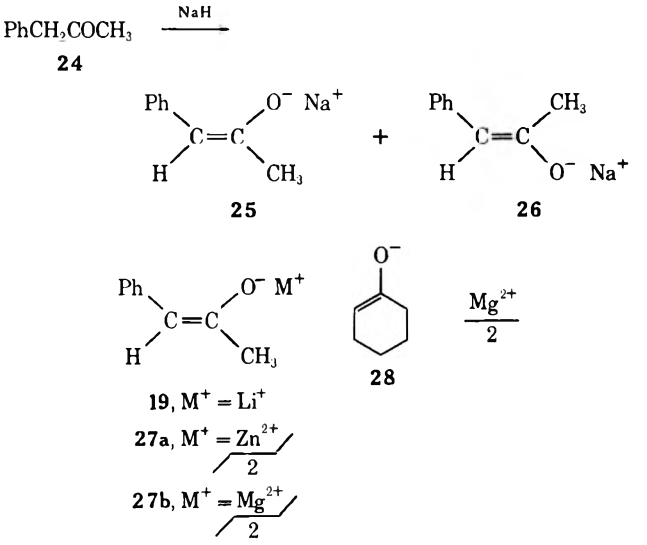
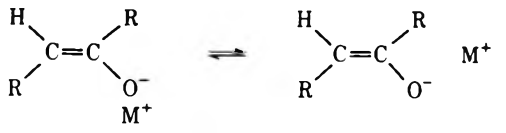


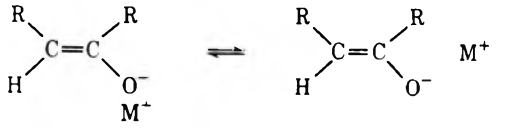
Figure 1 compares the nmr signals for triphenyllithium in DME solution (a solvent-separated ion pair[9]) and the trans trimethylsilyl enol ether **11** (a model for a covalent metal enolate **4a**) with the spectra of several representative metal trans enolates **19**, **25**, and **27** in various solvents. The nmr spectra of the sodium enolate **25** in either DMF or DME and the lithium enolate **19** in DME (shown in Figure 1) are practically identical and the phenyl absorption in these three spectra bears a striking resemblance to the phenyl absorption of triphenyllithium in DME. In THF solution the nmr spectra of the sodium (**25**) and lithium (**19**) enolates are practically the same with a phenyl absorption pattern intermediate between the patterns seen for the lithium enolate in DME and in Et_2O. The phenyl pattern in the nmr spectrum of an ether solution of the lithium enolate **19** resembles the pattern in the trans silyl ether **11**. The location of the vinyl CH signal exhibits a regular change, namely δ 4.83 for **19** in DME, 4.93 for **19** in THF, 5.02 for **19** in Et_2O, and 5.32 for the silyl ether **11**. This regular shift of the vinyl CH to lower field, like the progressive change in the phenyl pattern, is compatible with the presence of progressively less negative charge at the α carbon of the metal enolates as the solvent is changed from DME to THF to Et_2O. In spectra of the cis lithium enolate **21** and the related cis silyl ether **20b** (Figure 2) the vinyl CH is shifted downfield (δ 5.25 for **21** in DME, 5.57 for **21** in Et_2O, and 5.77 for **20b**) and little separation of the

(9) J. B. Grutzner, J. M. Lawlor, and L. M. Jackman, *J. Amer. Chem. Soc.*, **94**, 2306 (1972).

ortho, meta, and para phenyl protons is observed. These changes in nmr chemical shift values clearly arise in part from steric interference with a conformation in which the phenyl ring and the enolate C=C are coplanar so that little negative charge is delocalized into the phenyl ring. However, the change in position of the vinyl CH signal again suggests that the negative charge at the α carbon of the cis enolates is substantially greater in DME than in Et_2O solution. The subsequently discussed acetylation studies suggest that, in a given solvent, dissociation of the contact ion pairs is greater with the trans metal enolate **1b** than with the cis isomer **1a**. This apparent tendency of the trans



1b



1a

enolate **1b** to dissociate may be attributable to an unfavorable steric interaction between the solvated oxygen–metal ion pairs and the eclipsed α substituent in the trans enolate **1b** that is avoided in the cis enolate **1a** where the solvated oxygen–metal ion pair is relatively unhindered. An argument of this sort is based on the assumption that the solvated oxygen anion in a dissociated enolate has less steric bulk than a solvated (and possibly aggregated) oxygen–metal ion pair. The nmr spectrum of the zinc enolate **27a** (probably mixed with some lithium enolate **19**) in DME solution exhibits significant line broadening but the pattern of phenyl absorption and the position of the vinyl CH (δ 4.88) resemble the corresponding features in the spectrum of a DME solution of the lithium enolate **19**. The line broadening in the spectrum of an Et_2O solution of the magnesium enolate **27b** is sufficient to obscure the phenyl pattern. However, the low-field (δ 5.85) location of the vinyl CH absorption suggests that relatively little of the negative charge is located at the α-carbon atom of the enolate **27b**.

The above comparisons suggest that all of the trans enolate ions **19**, **25**, and **27a** in DME (or DMF) solution exist primarily as solvent-separated ions with an appreciable fraction of the negative charge in the phenyl ring and at the α-carbon atom. In Et_2O solution, the trans lithium (**19**) and sodium (**25**) enolates, and especially the cis lithium enolate (**21**) and the magnesium enolate **27b**, appear to be primarily contact ion pairs (or possibly covalent compounds).

Acetylation of the Metal Enolates.—The reactions of the various metal enolates with acetic anhydride and/or acetyl chloride (Scheme IV) were examined to determine the yield of O- and C-acetylated products. In an effort to obtain kinetically controlled mixtures of products the metal enolate solutions were added slowly with good mixing to a large excess of the acetylating agent. The reaction mixtures were quenched under conditions demonstrated not to remove either of the reaction products and the product mixtures were

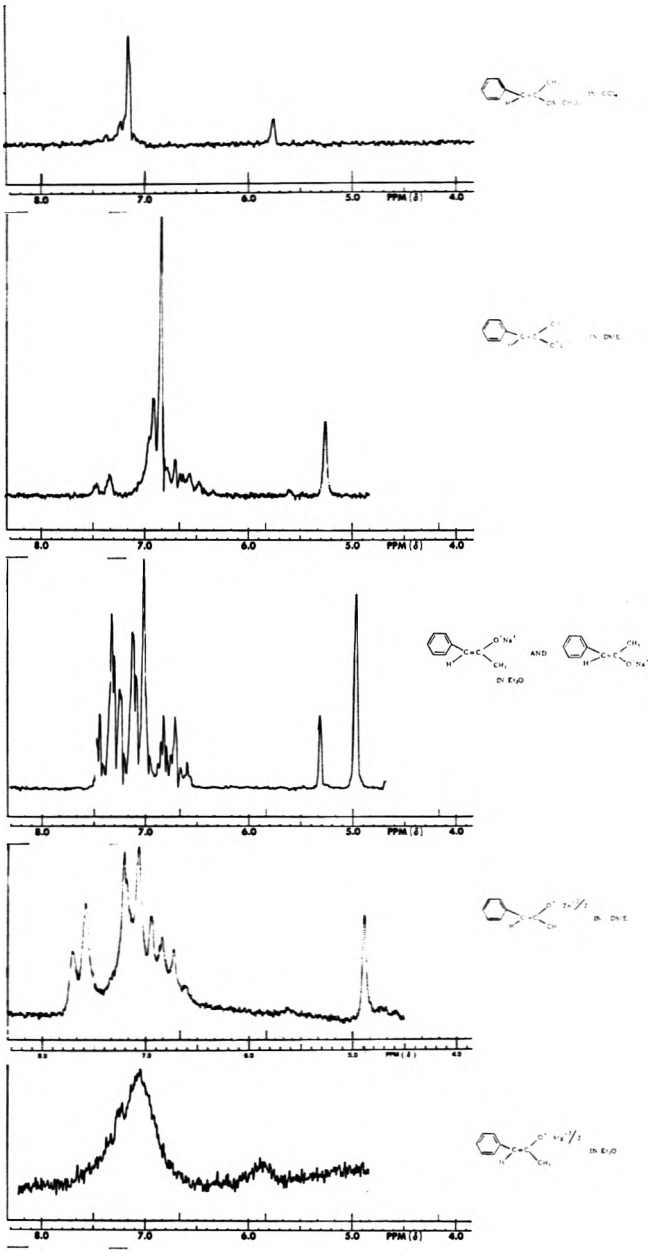
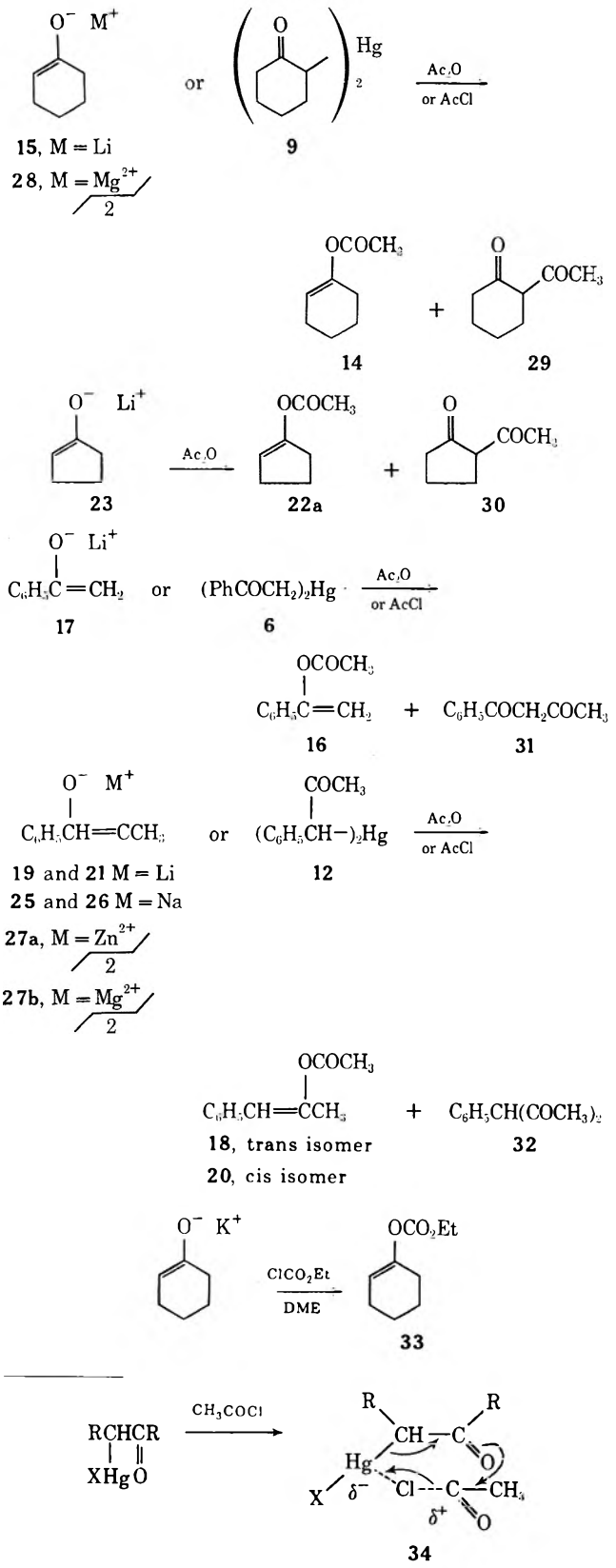


Figure 2.—Comparison of the nmr spectra of several cis and trans enolates of phenylacetone and the cis silyl ether **20b**.

mixed with internal standards and analyzed with calibrated glpc equipment to determine the yields of acetylated products. Table I summarizes both the results of the present studies and also several earlier studies performed in our laboratory. The bulk of the material not accounted for as O- or C-acetylated product in these experiments was the recovered unacetylated ketone formed by a competing protonation of the metal enolate during the quenching process.

Although the various α-mercuri ketones **6**, **9**, **12**, and **13** were relatively unreactive, they could be acetylated successfully with excess acetyl chloride. In every case the product was essentially only the O-acetylated material. The result can be interpreted[2] as either shielding of reaction at the α carbon by the α-mercuri substituent or as an intramolecular electrophilic catalysis by the α-mercuri substituent as implied in structure **34**. In any event the expectation that metal enolates of the type **2** should exhibit a preference for acylation at oxygen has clearly been realized.

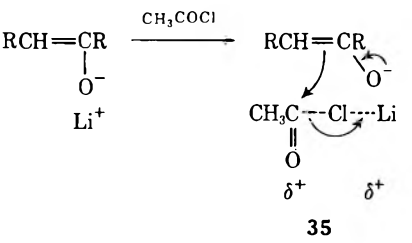
SCHEME IV



The reaction of the various trans metal enolates **1b** (see Table I, entries 3, 4, and 11) and also certain of the cis enolates **1a** (see Table I, entries 1, 8, 9, and 10) in DME solution with acetic anhydride gave mixtures of acylated products in which more than 80% of the product arose from O-acylation. However, in every case where cis (**1a**) and trans (**1b**) metal enolates were compared (Table I, entries 2 *vs.* 3, 4 *vs.* 5, and 10 *vs.* 11), more C-acylation was observed with the cis isomer **1a**, and in some cases (Table I, entries 2, 5, 6, and 7) involving relatively unhindered cis enolates, a substantial fraction of the product was formed by C-acylation even in DME solution. As the metal enolate solvent was changed from DME to Et_2O favoring the existence of the metal enolates as contact ion pairs rather than solvent-separated ions, the reaction with acetic anhydride resulted in a moderate increase in the proportion of C-acylation (see Table I, entries 1, 10, and 11). Interestingly, in a given solvent and with a given acylating agent, the change in metal cation from Li^+ to Na^+ to $Zn^{2+}/2$ had little effect on the position of acylation, a result in keeping with the earlier observation that the nmr spectra of the enolates **19**, **25**, and **27a** were all very similar in a common solvent. However, when the cation was changed from Li^+ to either $Mg^{2+}/2$ or $BrMg^+$, a substantial increase in C-acylation was observed (see Table I, entries 1, 7, and 11). The reported[4c] C-acylation of enol silyl ethers with acid chlorides illustrates the tendency of fully covalent enol derivatives to react practically exclusively at carbon.

As had been noted previously,[4b] changing the acylating agent from acetic anhydride to acetyl chloride (or acetyl bromide) resulted in a significant increase in the proportion of C-acylation. That this result should not be attributed to the initial formation of ketene from the acetyl halides was shown by appropriate acylation reactions with ketene that gave predominantly O-acylated products as had been noted earlier[3e] in reactions of dimethylketene with metal enolates. Reaction of the metal enolate **15** with ethyl acetate lead to predominant C-acylation in a Claisen reaction where equilibration among the acylated products is almost certainly occurring. Reaction of the cyclohexanone enolate with ethyl chloroformate formed the O-acylated derivative **33**, suggesting that this process is a kinetically controlled acylation.

From the foregoing data we conclude that solvent-separated metal enolates **3** do react with acylating agents predominantly at oxygen and that any change that tends to favor the existence of metal enolates as contact ion pairs **4b** will enhance the amount of C-acylation. Either of the two previously advanced explanations,[2a] steric shielding of the enolate oxygen by the metal cation or an intramolecular electrophilic catalysis of the type indicated in structure **35**, could ac-



count for this trend. However, the differing amount of C-acylation with acetic anhydride and acetyl chloride (or acetyl bromide) appears to be better explained by the intramolecular electrophilic catalysis scheme **35**, since the formation of lithium (or sodium) chloride (from acetyl chloride) should be more energetically favorable than the formation of lithium (or sodium) acetate.

Experimental Section[10]

Reagents and Starting Materials.—Previous papers have described the preparation and characterization of the trimethylsilyl enol ethers **5**,[3b] **8**,[3b] **11**,[3b] **20b**,[3b] and **22b**,[3b] and the enol acetates **14**,[11] **16**,[11] **18**,[3b] and **20a**.[3b] Ethereal solutions of halide-free methyllithium were obtained from Foote Mineral Co. and the methylmagnesium reagents were prepared as described previously;[3a] these solutions were standardized by the titration procedure of Watson and Eastham.[12] The ether and 1,2-dimethoxyethane were distilled from $LiAlH_4$ immediately before use. In all reactions involving methyllithium, a few milligrams of either 2,2′-bipyridyl or triphenylmethane was added as an indicator to establish when excess methyllithium was present.[12,13]

Following a previously described procedure,[5d] cyclopentanone was allowed to react with a CCl_4 solution of Ac_2O in the presence of a catalytic amount of aqueous 70% $HClO_4$. Distillation of the crude product separated a colorless liquid fraction (11% yield), bp 82–83° (90 mm), which contained (glpc, silicone fluid, no. 710, on Chromosorb P) primarily the enol acetate **22a** accompanied by small amounts of lower boiling materials. A pure sample was collected (glpc): $n^{24.5}$D 1.4492; ir (CCl_4) 1760 (enol ester C=O), 1665, and 1640 cm^{-1} (C=C); nmr (CCl_4) δ 5.3–5.5 (1 H m, vinyl CH), 2.05 (3 H s, $COCH_3$), and 1.7–2.6 (6 H m, aliphatic CH); mass spectrum *m/e* (rel intensity) 126 (35, M^+), 84 (100), 83 (94), 55 (34), and 43 (85).

Anal. Calcd for $C_7H_{10}O_2$: C, 66.64; H, 7.99. Found: C, 66.55; H, 7.87.

The preparation of an authentic sample of the diketone **32** was described in earlier work[3b] and a commercial sample of the diketone **31** was employed. 2-Acetylcyclohexanone (**29**), prepared by acetylation of a cyclohexanone enamine,[14] was obtained as a colorless liquid: bp 111° (22 mm), n^{26}D 1.5055 [lit.[14] bp 97–104° (12–14 mm)]; ir (CCl_4) 1700 and 1600 cm^{-1} (broad) (enolic β diketone); uv max (95% EtOH), 290 mμ (ε 9400); nmr (CCl_4) δ 2.05 (3 H s, $COCH_3$) and 1.5–2.5 (9 H m, aliphatic CH); mass spectrum *m/e* (rel intensity), 140 (17, M^+), 125 (30), 55 (24), 43 (100), and 41 (27). The BF_3-catalyzed acetylation of cyclopentanone with Ac_2O[15] yielded 2-acetylcyclopentanone (**30**) as a colorless liquid: bp 91–92° (18 mm) [lit.[15] bp 72–75° (8 mm)]; ir (CCl_4) 1750, 1720, 1670, and 1625 cm^{-1} (partially enolic β-diketone); uv max (95% EtOH), 284 mμ (ε 2630); nmr (CCl_4) δ 13.1 (*ca.* 0.7 H, enolic OH), 3.3 (*ca.* 0.3 H m, COCHCO), and 1.5–2.7 (9 H m, aliphatic CH); mass spectrum *m/e* (rel intensity), 126 (24, M^+), 111 (57), 83 (33), 71 (27), 70 (37), 55 (77), 43 (100), 42 (21), 41 (25), and 37 (43).

Preparation of the α-Mercuri Ketone Derivatives. A. The Acetophenone Derivatives 6 and 7.—To a mixture of 5.4 g (25 mmol) of HgO, 0.2 g (0.6 mmol) of $Hg(OAc)_2$, 1 ml of H_2O, and 5 ml of EtOH was added, dropwise with mixing, 9.6 g (50 mmol) of the trimethylsilyl enol ether **5**. During this period, an additional 25 ml of EtOH was added to keep the mixture fluid. After the addition was complete, mixing was continued for 20 min and then the reaction mixture was diluted with 150 ml of warm $CHCl_3$, dried, and filtered. The filtrate was concentrated to *ca.* 40 ml, diluted with isooctane, and cooled. The crude mercurial **6** was collected as 9.8 g (89%) of white solid, mp 163–168°. Recrystallization from a $CHCl_3$–isooctane mixture afforded the pure bisketomercurial **6** as white needles: mp 171–172.5° (lit.[7a,b] mp 168–170°); ir (CCl_4) 1640 cm^{-1} (C=O); uv max (CH_3CN), 244 mμ (ε 26,400) and 320 (1380); nmr ($CDCl_3$) δ 7.3–8.1 (10 H m, aryl CH) and 2.95 (2 H s, $HgCH_2CO$, with satellites corresponding to $J_{H-^{199}Hg}$ = 172.8 Hz).

When a slurry of 4.39 g (10.0 mmol) of the bisketomercurial **6** in 50 ml of tetrahydrofuran was treated with 4.54 g (10.0 mmol) of HgI_2, the materials dissolved to give a clear, colorless solution. After the solution had been concentrated, the residue was crystallized from a $CHCl_3$–isooctane mixture to separate 8.4 g (94%) of the α-iodomercuri ketone **7** as white needles: mp 168–173° (lit.[7a] mp 163–170°); ir (Nujol mull) 1630 cm^{-1} (C=O); uv max (CH_3CN) 250 mμ (ε 18,200) and 322 (667).

B. The Cyclohexanone Derivatives 9 and 10.—The same procedure was followed with 8.5 g (50 mmol) of the silyl enol ether **8**, 5.4 g (25 mmol) of HgO, 0.2 g (0.6 mmol) of $Hg(OAc)_2$, 1 ml of H_2O, and 5 ml of EtOH. The crude product was obtained as 6.5 g (66%) of white solid, mp 125–130° dec. Recrystallization from a benzene–pentane mixture afforded the bisketomercurial **9** as a white solid: mp 137–139° (lit.[7c] mp 120°); ir ($CHCl_3$) 1645 cm^{-1} (C=O); nmr ($CDCl_3$) δ 2.98 (2 H broad singlet, COCHHg, with satellites corresponding to $J_{H-^{199}Hg}$ = *ca.* 174 Hz) and 1.1–2.7 (16 H m, aliphatic CH).

Anal. Calcd for $C_{12}H_{18}HgO_2$: C, 36.50; H, 4.59. Found: C, 36.83; H, 4.34.

A solution of 4.55 g (10.0 mmol) of HgI_2 in 50 ml of tetrahydrofuran was treated with 3.95 g (10.0 mmol) of the bisketomercurial **9**. The resulting solution was diluted with $CHCl_3$ and hexane and then cooled to precipitate 6.0 g (71%) of crude iodomercury compound **10**. This material was recrystallized from a $CHCl_3$–isooctane mixture to separate 4.3 g (50%) of the α-iodomercuri ketone **10** as white prisms: mp 115–117°; ir ($CHCl_3$) 1670 cm^{-1} (C=O); nmr ($CDCl_3$) δ 3.65 (1 H broad singlet, COCHHgI) and 1.3–2.9 (8 H m, aliphatic CH).

Anal. Calcd for C_6H_9HgIO: C, 16.97; H, 2.13; I, 29.89; Hg, 47.24. Found: C, 16.74; H, 2.14; I, 30.15; Hg, 47.30.

C. The Phenylacetone Derivative 12.—The same procedure was applied to 10.3 g (50.0 mmol) of the silyl enol ether **11**, 5.4 g (25 mmol) of HgO, 0.2 g (0.6 mmol) of $Hg(OAc)_2$, 1 ml of H_2O, and 5 ml of EtOH. The crude product (7.7 g or 63%, mp 106–133° dec) was crystallized from chloroform to separate the bisketomercurial **12** as a mixture of diastereoisomers: mp 126–133 dec; ir ($CHCl_3$) 1670 cm^{-1} (C=O); nmr ($CDCl_3$, spectrum at 100 MHz) δ 6.9–7.5 (10 H m, aryl CH), 4.22 (2 H s, HgCHCO, $J_{H-^{199}Hg}$ = 200 Hz), and two partially resolved singlets centered at δ 2.11 (6 H, $COCH_3$ groups of diastereoisomers). The separation of these two singlets is 1.90 Hz in the 100-MHz spectrum and 1.11 Hz in a 50-MHz spectrum.

Anal. Calcd for $C_{18}H_{18}HgO_2$: C, 46.26; H, 3.88; Hg, 42.96. Found: C, 46.27; H, 3.76; Hg, 42.97.

The Acetylation of Metal Enolates. The lithium or magnesium enolates acetylated in this study were formed in THF, Et_2O, or DME solution from the corresponding enol acetates or trimethylsilyl enol ethers by methods outlined previously.[3a–c,5d,6] Aliquots of the metal enolate solution were added, dropwise and with vigorous stirring, to a fivefold or greater excess of freshly distilled Ac_2O, AcCl, or AcBr. For reactions with ketene, a solution of the metal enolate was added to a cold (0°), freshly prepared solution of excess ketene in DME or the ketene was bubbled through a cold (−20 to −30°) solution of the enolate in DME. After the resulting mixtures had been stirred at 25° for 10–15 min they were partitioned between pentane and saturated aqueous $NaHCO_3$. The pentane solutions were separated, dried, and concentrated to leave the crude reaction product. For reactions involving the keto mercurials 0.50 mmol of the solid α-mercuri ketone was added, with stirring, to a mixture of 4.0 ml of AcCl and 4.0 ml of 1,2-dimethoxyethane. The resulting mixture was stirred at 25° for 15–60 min, during which time the solid dissolved to give a clear solution. These solutions were subjected to the same isolation procedure described above. In each case the crude product was mixed with a known amount of an internal standard and then subjected to analysis on glpc equipment which had been calibrated with known mixtures of authentic samples.

Products were identified by collecting (glpc) samples from representative reactions and comparing the glpc retention times and ir spectra for collected and authentic samples. The products from acetylation of the phenylacetone enolates **19**, **21**, **25**, and **26** and the α-mercuri ketones **12** and **13** were analyzed by glpc. On one glpc column (silicone fluid, no. 710, on Chromosorb P) the product retention times were: phenylacetone (**24**), 24.5 min; 1,3,5-triisopropylbenzene (the internal standard), 34.0

(10) All melting points are corrected and all boiling points are uncorrected. Unless otherwise stated $MgSO_4$ was employed as a drying agent. The ir spectra were determined with a Perkin-Elmer Model 237 or Model 257 infrared recording spectrophotometer fitted with a grating. The uv spectra were determined with a Cary Model 14 or a Perkin-Elmer Model 202 recording spectrophotometer. The nmr spectra were determined at 60 MHz with a Varian Model A-60 or Model T-60 nmr spectrometer. The chemical shift values are expressed in δ values (parts per million) relative to a Me_4Si internal standard. The mass spectra were obtained with a Hitachi Perkin-Elmer or a Varian Model M-66 mass spectrometer. All reactions involving strong bases or reactive organometallic intermediates were performed under a nitrogen atmosphere.

(11) H. O. House, D. S. Crumrine, A. Y. Teranishi, and H. D. Olmstead, to be published.

(12) S. C. Watson and J. F. Eastham, *J. Organometal. Chem.*, **9**, 165 (1967).

(13) Triphenylmethane may be used as an indicator for organolithium reagents in DME or THF solution where the red triphenylmethyl anion is formed.

(14) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Amer. Chem. Soc.*, **85**, 207 (1963).

(15) R. M. Manyik, F. C. Frostick, Jr., J. J. Sanderson, and C. R. Hauser, *ibid.*, **75**, 5030 (1953).

TABLE I

THE ACETYLATION OF METAL ENOLATES

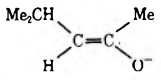
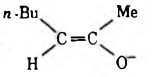
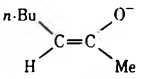
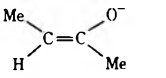
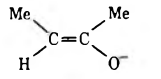
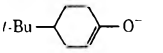
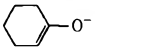
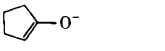
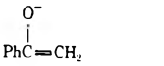
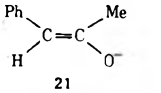
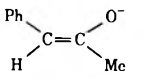
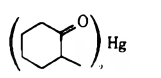
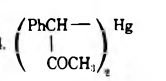
Enolate	Cation	Solvent	Acetylating agent	Product yields, % O-Acetyl derivative	Product yields, % C-Acetyl derivative	Ref
1. 	$Li^{+a,b}$	DME	Ac_2O	75	<1	3a
	$Li^{+b,c}$	Et_2O	Ac_2O	68	4	3a
	$BrMg^{+a,b}$	Et_2O	Ac_2O	37	34	3a
2. 	Li^{+b}	DME	Ac_2O	24	43	3b
	Li^{+d}	DME	Ac_2O	38	28	3b
3. 	Li^{+b}	DME	Ac_2O	72	7	3b
	Li^{+d}	DME	Ac_2O	75	4	3b
4. 	$Li^{+d,e}$	DME	Ac_2O	53	9	3b
5. 	$Li^{+d,f}$	DME	Ac_2O	21	32	3b
6. 	Li^{+d}	DME	Ac_2O	63	12	3b
7. 	Li^{+d}	DME	Ac_2O	49	16	
	Li^{+b}	DME	EtOAc	1	40	
15 or 28	$Mg^{+2}/2^{b,g}$	Et_2O	Ac_2O	25	43	
8. 	Li^{+d}	DME	Ac_2O	37	<1	
23						
9. 	Li^{+d}	DME	Ac_2O	59	<1	
17						
10. 	Li^{+d}	DME	Ac_2O	75	2	
	Li^{+h}	DME	Ac_2O	87	3	
21	Li^{+d}	Et_2O	Ac_2O	38	26	
11. 	Na^+	DME	Ac_2O	91–94	1	
	Na^+	DME	AcCl	50	14	
	Na^+	DME	Ketene	23–28	1–3	
19, 25, or 27	Na^+	THF	Ac_2O	92	<1	
	Na^{+i}	Et_2O	Ac_2O	73–79	7–9	
	Na^{+i}	Et_2O	AcCl	14–18	33	
	Na^{+i}	Et_2O	AcBr	12	46	
	Na^{+j}	Et_2O–hexane	Ac_2O	46–51	5–12	
	Li^{+d}	DME	Ac_2O	95–98	<1	
	Li^{+d}	DME	AcCl	24–47	16–22	
	Li^{+d}	THF	Ac_2O	61	<1	
	Li^{+d}	Et_2O	Ac_2O	68–76	5–9	
	Li^{+d}	Et_2O–PhH (1:3)	Ac_2O	54	12	
	Li^{+d} + 0.5 equiv $ZnCl_2$	Et_2O–DME (1:1)	Ac_2O	75	<1	
	$Mg^{+2}/2^{b,g}$	Et_2O	Ac_2O	41	43	
	Li^{+d} + 0.5 equiv $MgBr_2$	Et_2O–PhH (1:1)	Ac_2O	17	26	
12. $(PhCOCH_2-)_2Hg$		DME	AcCl	82	<1	
6						
13. 		DME	AcCl	88	<1	
9						
14. 		DME	AcCl	99	<1	
12						

Table I

(*Continued*)

Enolate	Cation	Solvent	Acetylating agent	Product yields, % O-Acetyl derivative	Product yields, % C-Aetyl derivative	Ref
15. PhCHHgI / COCH$_3$ (13)		DME	AcCl	100	<1	

[a] The enolate anion contained 81% of the indicated cis isomer and 19% of the trans stereoisomer. [b] The enolate was prepared from the corresponding enol acetate. [c] The enolate anion contained 75% of the indicated cis isomer and 25% of the trans stereoisomer. [d] The enolate was prepared from the corresponding trimethylsilyl enol ether. [e] The enolate anion contained 92% of the indicated trans isomer and 8% of the cis isomer. [f] The enolate anion contained 97% of the indicated cis isomer and 3% of the trans isomer. [g] The enolate was prepared by the reaction of the enol acetate with 2 equiv of ethereal dimethylmagnesium. [h] This enolate, prepared from the ketone **24** and $(i\text{-Pr})_2$NLi, contained 62–67% of the cis isomer **21** and 33–38% of the trans isomer **19**. [i] This enolate, prepared from the ketone **24** and NaH in Et_2O, contained 19–24% of the cis isomer **26** and 76–81% of the trans isomer **25**. [j] This enolate, prepared from 1 equiv of ketone **24**, 2 equiv of Et_2O, and excess NaH in hexane, contained 10–20% of the cis isomer **26** and 80–90% of the trans isomer **25**.

min; trans enol acetate **18**, 51.6 min; cis enol acetate **20a** and β-diketone **32** (not resolved), 56.4 min. On a second glpc column used (silicone gum, XE-60, on Chromosorb P), the retention times were: 1,3,5-triisopropylbenzene, 8.2 min; phenylacetone (**24**), 16.0 min; cis and trans enol acetates **18** and **20a** (not resolved), 24.4 min; β-diketone **32**, 27.6 min. On a third glpc column used (silicone QF_1 on Chromosorb P), the retention times were: 1,3,5-triisopropylbenzene, 4.0 min; phenylacetone (**24**), 6.1 min; cis and trans enol acetates **18** and **20a** (not resolved), 8.4 min; and β-diketone **32**, 9.5 min. The α-iodomercuri ketone **13** was generated *in situ* by adding 0.5 mmol of HgI_2 to a slurry of 0.5 mmol of the bisketomercurial **12** in 4.0 ml of DME. The resulting solution of the iodomercury compound **13** was then added to AcCl and subjected to the usual reaction and isolation procedures. For acetylations of the enolate **23**, the retention times (glpc, silicone fluid, no. 710, on Chromosorb P) of the possible products were: cyclopentanone, 4.8 min; enol acetate **22**, 10.0 min; *tert*-amylbenzene (internal standard), 19.1 min; β-diketone **30**, 27.6 min. For acetylations of the enolate **17** and the α-mercuri ketone **6**, the retention times (glpc, silicone fluid, No. 710, on Chromosorb P) of possible products were, acetophenone, 4.2 min; enol acetate **16**, 8.0 min; *n*-hexadecane (internal standard), 13.7 min; β-diketone **31**, 16.4 min. In the glpc (silicone fluid, no. 710, on Chromosorb P) used for the products from acetylation of the α-mercuri ketone **9**, the retention times were: cyclohexanone, 5.0 min; enol acetate **14**, 9.5 min; *n*-tridecane (internal standard), 14.6 min; β-diketone **29**, 27.8 min. For acetylation of the cyclohexanone enolates **15** and **28**, the product retention times [glpc, LAC-296 (diethylene glycol adipate) plus 3% (by weight) of H_3PO_4 suspended on Chromosorb W] were: cyclohexanone, 16.0 min; enol acetate **14**, 37.8 min; tetralin (internal standard), 46.2 min; β-diketone **29**, 85.0 min. For the reaction with EtOAc a solution of 1.4 mmol of the lithium enolate **15** in 3.5 ml of DME was added, dropwise and with stirring over 5 min, to 3.50 g (40 mmol) of EtOAc (freshly distilled from P_2O_5). After the resulting solution had been stirred for 30 min at 25° it was subjected to the usual isolation and analysis procedures.

Solutions of the sodium enolates **25** and **26** in various solvents were prepared by the dropwise addition of phenylacetone (**24**) to a suspension of excess NaH (dispersion washed with pentane before use) followed by a reaction period of 1–12 hr to ensure complete reaction. The resulting mixtures were allowed to settle and the supernatant solutions were removed; aliquots of these solutions were titrated with standard aqueous HCl for total base content and other aliquots were partitioned between pentane and aqueous NH_4Cl; the resulting pentane solutions were mixed with a known weight of internal standard and subjected to glpc analysis to determine the amount of phenylacetone (**24**) produced. Aliquots of these enolate solutions were also subjected to nmr analysis to determine the proportions of cis (**26**) and trans (**25**) isomers present. The procedures outlined above were employed for acetylation reactions and subsequent isolation and analysis.

In the reaction of phenylacetone with certain lots of NaH, either the alcohol **36a** (aqueous NH_4Cl quench) or the acetate **36b** (Ac_2O quench) was found as a by-product. Although the partial reduction of certain ketones with NaH has been reported,[16] we are inclined to attribute our reduction products, formed only with certain lots of NaH, to the presence of some metallic Na in some of the NaH samples. Another by-product found with enolate solutions prepared by the reaction of the ketone **24** with $(i\text{-Pr})_2$NLi was the amide **37**, formed during reaction of the enolate solution with Ac_2O. On one glpc column used (silicone fluid, DC-710, on Chromosorb P) the retention times of these components were: amide **37**, 14.9 min; alcohol **36a**,

$C_6H_5CH_2CHCH_3$ (OR; **36a**, R = H; **b**, R = $COCH_3$) $CH_3CON[CH(CH_3)_2]_2$ (**37**) $C_6H_5CH[C(CH_3)_2]_2$ (HO; **38**)

20.6 min; ketone **24**, 21.6 min; 1,3,5-triisopropylbenzene, 29.9 min; and acetate **36b**, 33.1 min. On a second glpc column used (silicone QF_1 on Chromosorb P) the retention times were: 1,3,5-triisopropylbenzene, 3.4 min; alcohol **36a**, 3.9 min; ketone **24**, 5.3 min; amide **37**, 5.6 min; and acetate **36b**, 5.7 min. Collected (glpc) samples of the components **36a** and **36b** were identified with subsequently described authentic samples by comparison of glpc retention times and ir spectra.

A commercial sample of the alcohol **36a**, bp 103.5–104° (13 mm), $n^{25}D$ 1.5169, was acetylated with refluxing Ac_2O to form in 98% yield the acetate **36b**: bp 57.5° (0.4 mm); $n^{25}D$ 1.4880 [lit.[17] bp 107–108° (13 mm), $n^{20}D$ 1.4876]; ir (CCl_4) 1740 cm^{-1} (ester C=O); uv (95% EtOH), series of weak maxima (ε 99–193) in the region 240–270 mμ; nmr (CCl_4) δ 7.0–7.4 (5 H m, aryl CH), 5.03 (1 H sextet, J = 6.5 Hz, CHO), 2.4–3.2 (2 H m, benzylic CH_2), 1.90 (3 H s, CH_3CO), and 1.17 (3 H d, J = 6.5 Hz, CH_3); mass spectrum m/e (rel intensity) 118 (98), 117 (24), 91 (66), 65 (24), and 43 (100). A collected (glpc) sample of the amide **37** was identified from its spectral properties: ir (CCl_4) 1650 cm^{-1} (amide C=O); nmr (CCl_4) δ 3.1–4.2 (2 H broad, CHN), 1.97 (3 H s, CH_3CO), and 1.27 (12 H d, J = 7 Hz, CH_3).

Although we were able to generate an ethereal solution of the magnesium enolate of phenylacetone by the addition of 880 mg (5.0 mmol) of the enol acetate **18** in 3 ml of Et_2O to 8.3 ml of a cold (0–5°) ethereal solution containing 5.3 mmol of Me_2Mg, an attempt to produce a comparable enolate solution by the addition of 5.00 g (28.4 mmol) of the enol acetate to 30 ml of an ethereal solution of MeMgI (from 11.9 g or 85 mmol of MeI and 2.02 g or 84 mg-atoms of Mg) was complicated by a side reaction. After the solution had been stirred at 25° for 6 hr, it was partitioned between dilute aqueous HCl and Et_2O and the organic layer was dried and concentrated, resulting in the separation of 1.38 g (24%) of the crude diol **38**, mp 95–100°. Recrystallization from Et_2O–hexane afforded the pure diol **38** as white crystals: mp 105–107°; ir ($CHCl_3$) 3590 and 3460 cm^{-1} (OH); nmr ($CDCl_3$) δ 7.0–7.7 (5 H m, aryl CH), 4.47 (2 H, s, OH), 2.96 (1 H s, benzylic CH), and two 6 H singlets at 1.41 and 1.19 [two $(CH_3)_2C$ groups].

(16) J. S. McConaghy and J. J. Bloomfield, *J. Org. Chem.*, **33**, 3425 (1968).

(17) W. J. Bailey and C. King, *ibid.*, **21**, 858 (1956).

Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.81; H, 9.76.

A magnesium enolate solution was also obtained from an ethereal solution of the lithium enolate **19**, formed by reaction of 738 mg (3.6 mmol) of the silyl ether **11** with 4.0 mmol of MeLi in 2.7 ml of Et_2O for 60 min. The resulting solution was treated with 0.8 ml of a solution containing 1.9 mmol of $MgBr_2$ in an Et_2O–PhH mixture (1:1, v/v).

A solution of the zinc enolate of phenylacetone was obtained from a solution of the lithium enolate **19** (from 1.650 g or 8.0 mmol of the silyl ether **11** and 8.25 mmol of MeLi) in 5.0 ml of DME. To the solution was added 6.0 ml of an Et_2O solution containing 4.25 mmol of anhydrous $ZnCl_2$. A white precipitate (primarily LiCl) separated from the DME–Et_2O solution on standing. Analyses of the precipitate and the supernatant liquid gave the following results: precipitate, 1.2 mmol of Cl^-, 1.4 mmol of Li^+, and 0.1 mmol of Zn^{2+}; solution, 4.2 mmol of Zn^{2+}, 6.8 mmol of Cl^-, and 8.0 mmol of Li^+. When a comparable solution was prepared and immediately concentrated under reduced pressure to remove the bulk of the Et_2O, no LiCl precipitated from the DME solution.

In a similar experiment the lithium enolate **19**, from 1.331 g (7.6 mmol) of the enol acetate **18** and 16.5 mmol of MeLi, in 6.0 ml of DME was treated with 11.0 ml of an Et_2O solution containing 8.05 mmol of anhydrous $ZnCl_2$. The precipitate contained 0.2 mmol of Zn^{2+}, 6.0 mmol of Cl^-, and 7.8 mmol of Li^+ and the solution contained 8.1 mmol of Zn^{2+}, 9.7 mmol of Cl^-, and 12.0 mmol of Li^+. Quenching an aliquot of the solution followed by glpc analysis indicated that 92% of the ketone **24** was in the solution.

Reaction of the Potassium Enolate of Cyclohexanone with Ethyl Chloroformate.[18]—A solution of triphenylmethylpotassium, prepared[19] from 7.82 g (0.20 g-atom) of potassium and 53.8 g (0.22 mol) of Ph_3CH in 120 ml of DME, was treated with 17.27 g (0.176 mol) of cyclohexanone. The resulting suspension of the potassium enolate was added, dropwise and with stirring, to a solution of 20.6 g (0.19 mol) of $ClCO_2Et$ in 50 ml of DME. The mixture was stirred at ambient temperature for 1 hr and then partitioned between Et_2O and H_2O. The organic phase was dried, concentrated, and distilled to separate early fractions, bp 50–78° (9 mm), containing (glpc, Carbowax 20 M on Chromosorb P) mixtures of cyclohexanone (12.6 min) and the enol carbonate **33** (41.8 min), and 11.3 g (39%) of a fraction, bp 79–81° (9 mm) [lit.[20] bp 108–110° (20 mm)], containing >96% of the enol carbonate **33**: ir (CCl_4) 1760 (enol ester C=O) and 1690 cm^{-1} (enol C=C); nmr (CCl_4) δ 5.3–5.6 (1 H m, vinyl CH), 4.22 (2 H q, J = 7.5 Hz, OCH_2), 1.5–2.5 (8 H m, aliphatic CH), and 1.33 (3 H t, J = 7.5 Hz, ethoxyl CH_3); mass spectrum M^+ at m/e 170 with abundant fragment peaks at m/e 98, 97, 83, 70, 55, and 41.

Registry No.—**6**, 37160-45-5; **9**, 37160-46-6; **10**, 37160-47-7; **12**, 37406-76-1; **13**, 37160-48-8; **15**, 21300-30-1; **17**, 35249-09-3; **19**, 37392-64-6; **21**, 37392-65-7; **22a**, 933-06-2; **23**, 37160-52-4; **25**, 37392-66-8; **27a**, 37413-04-0; **27b**, 37413-05-1; **28**, 37160-53-5; **36a**, 698-87-3; **38**, 37406-77-2.

(18) This experiment was performed in our laboratories by Dr. Jean Jacques Riehl.

(19) H. O. House and V. Kramar, *J. Org. Chem.*, **27**, 4146 (1962).

(20) A. Haller and E. Bauer, *Ann. Chim. (Paris)*, **10**, 294 (1924).

Cycloadditions of Benzyne with Cyclic Olefins. Competition between 2 + 4, Ene, and 2 + 2 Reaction Pathways[1]

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The course of benzyne reaction with six- to eight-membered ring polyenes is examined and the factors which control the relative partitioning between 2 + 4, 2 + 2, or ene cycloaddition are delineated. The relative amounts of products derived from 2 + 4 or ene reaction were observed to be sensitive to conformational features of the cyclic olefins. This behavior is consistent with the known concerted character of benzyne 2 + 4 cycloadditions. Arguments are advanced supporting concerted character for the ene addition.

As a synthetic reagent *o*-benzyne occupies a position of particular utility.[2] It behaves essentially as a reactive ethylenic chromophore and the observed stereochemistry of reaction products derived from $2_s + 2_s$ or $2_s + 4_s$ cycloadditions are consistent with predictions from orbital symmetry rules.[3] Therefore it is not surprising that approximate molecular orbital calculations predict a symmetric singlet *o*-benzyne ground state.

It should be mentioned that in contrast to most reactive olefins, benzyne participates readily in the ene cycloaddition reaction.[5] The outcome of benzyne cycloadditions can be controlled by a judicious choice of coreactants. A variety of enamines react with *o*-benzyne to give primarily 2 + 2 addition products (eq 1).[6] 2-Methylvinyl acetate or cyclohexene each give only ene reactions (eq 2),[7] and cyclopentadiene reacts entirely *via* 2 + 4 cycloaddition (eq 3).[8] However, there are many examples where products from all three reaction pathways can simultaneously be observed.[2] In view of the fact that much attention has been given to the reaction of benzyne *via* 2 + 2 and 2 + 4 cycloadditions,[3,7a,9] it is surprising to find that there is a paucity of discussion in the literature on the relative partitioning of benzyne between the three primary reaction paths.[10] We have previously noted

(1) (a) Support from the Committee on Research at UCSC and the Frederick G. Cottrell Fund of the Research Corp. is gratefully acknowledged. (b) For a preliminary report see ref 11.

(2) (a) R. W. Hoffman, "Dehydrobenzene and Cycloalkynes," Academic Press, New York, N. Y., 1967, Chapters 2 and 3; (b) T. L. Gilchrist and C. W. Rees, "Carbenes, Nitrenes, and Arynes," Appleton Century Crofts, New York, N. Y., 1969, Chapters 8 and 9.

(3) M. Jones, Jr., and R. H. Levin, *J. Amer. Chem. Soc.*, **91**, 6411 (1969).

(4) R. Hoffman, A. Imamura, and W. J. Hehre, *ibid.*, **90**, 1499 (1968); J. F. Olsen, *J. Mol. Struct.*, **8**, 307 (1971); R. W. Atkin and T. A. Claxton, *Trans. Faraday Soc.*, **66**, 257 (1970); D. L. Wilhite and J. L. Whitten, *J. Amer. Chem. Soc.*, **93**, 2858 (1971).

(5) The *ene* reaction has recently been reviewed: (a) H. M. R. Hoffman, *Angew. Chem., Int. Ed. Engl.*, **8**, 556 (1969); (b) E. C. Keung and H. Alper, *J. Chem. Educ.*, **49**, 97 (1972).

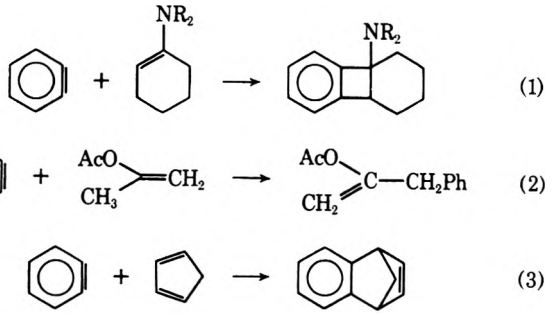
(6) D. J. Keyton, G. W. Griffin, M. E. Kuehne, and C. E. Bayha, *Tetrahedron Lett.*, 4163 (1969); M. E. Kuehne, *J. Amer. Chem. Soc.*, **84**, 837 (1962).

(7) (a) L. Friedman, R. J. Osiewicz, and P. W. Rabideau, *Tetrahedron Lett.*, 5735 (1968); (b) G. Ahlgren and B. Akermark, *ibid.*, 3047 (1970).

(8) G. Wittig and E. Knauss, *Chem. Ber.*, **91**, 895 (1958).

(9) (a) P. G. Gassman, H. P. Benecke, and T. J. Murphy, *Tetrahedron Lett.*, 1649 (1969); (b) P. G. Gassman and H. P. Benecke, *ibid.*, 1089 (1969); (c) H. H. Wasserman, A. J. Solodar, and L. S. Keller, *ibid.*, 5597 (1968).

(10) L. Friedman, J. G. Miller, and R. Osiewicz, Abstracts, 159th National meeting of the American Chemical Society, Houston, Texas, Feb. 22–27, 1970, 104-Petr; ref 2a, pp 197–199.



(1)

(2)

(3)

that the course of benzyne addition to cyclic olefins can be markedly influenced by traces of Ag^+.[11] It seemed to us that, before the mechanism of this effect could be fully understood, it would first be necessary to have a firm grasp upon the features which control the relative rates for the cycloaddition routes. We now report the results of our work on benzyne addition to cyclic olefins in which the factors controlling the relative rates of ene, 2 + 2, and 2 + 4 reactions for benzyne are identified.

Description of Coreactants.—Polyenes ranging in size from six- to eight-membered rings were chosen as coreactants for benzyne. These compounds were completely devoid of polar functionality and have known conformations over the di- or triene chromophore. The major parameters which vary over this compound series are the interplanar angle between the vinyl groups (angle θ, Figure 1) and the angle subtended between the plane of the vinyl, allylic CC–H bond and the plane of the double bond p orbitals (angle ϕ, Figure 1).

The 2 + 2 cycloaddition between benzyne and simple olefins is known to be stepwise.[3,9] It can be presumed that this reaction is initiated by attack of benzyne at the least hindered carbon from the direction of least steric hindrance. The degree of steric bulk changes very little within the set of six- to eight-membered ring olefins considered here. Thus, it seems reasonable to assume that the rate of 2 + 2 addition by benzyne will be approximately constant over the entire range of experiments described below.

The $2_s + 4_s$ cycloaddition between benzyne and 1,3-dienes is known to be concerted.[3] As a first assumption one would expect to find the net reaction for this type of cycloaddition to be sensitive to the extent of overlap in the transition state for the reacting π orbitals. Hence, the rate of 2 + 4 cycloaddition of benzyne to a diene should be chiefly dependent upon the diene interplanar angle (θ).

There does not seem to be agreement concerning the concerted or stepwise nature of the ene reaction. The reaction of an optically active olefin **6** with maleic anhydride has been shown to give optically active ene product **7**;[12] however, it has also been pointed out that it is not clear to what extent chirality is preserved during this reaction (eq 4).[5a] Others[13a] have suggested that the regiospecificity observed in the reactions of substituted olefins with benzyne is explained by a stepwise addition followed by hydrogen migration (eq 5).

(11) P. Crews, M. Loffgren, and D. J. Bertelli, *Tetrahedron Lett.*, 4697 (1971); see also ref 17 and 31.

(12) R. K. Hill and M. Rabinovitz, *J. Amer. Chem. Soc.*, **86**, 965 (1964).

(13) (a) I. Tabushi, K. Okazaki, and R. Oda, *Tetrahedron*, **25**, 4401 (1969). (b) See, for example, M. Pomarantz, R. N. Wilke, G. W. Gruber, and U. Roy, *J. Amer. Chem. Soc.*, **94**, 2752 (1972).

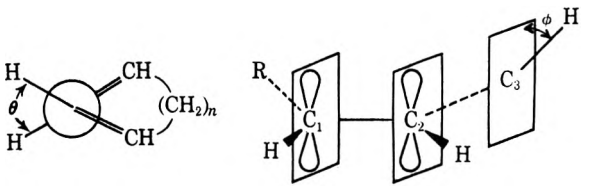
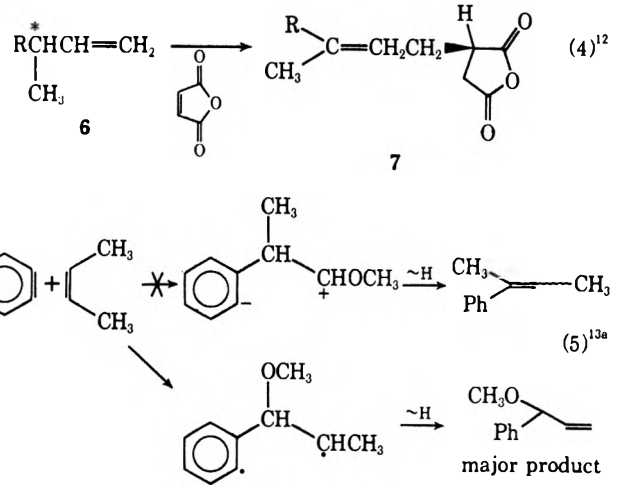


Figure 1.—Interplanar angle (θ) between 1,3 double bonds and angle ϕ between the plane of the C_2 p orbital and the plane containing C_2C_3–H.



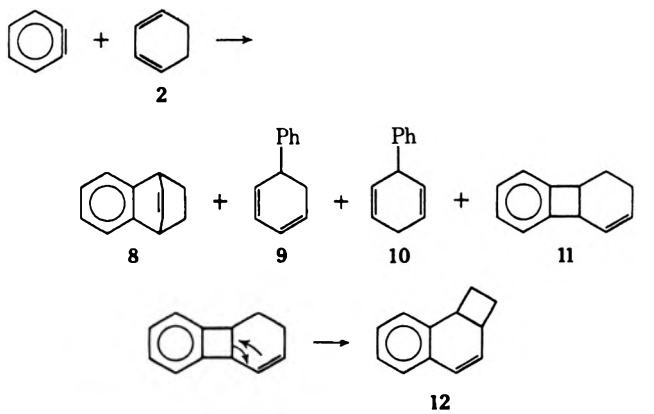
(4)[12]

(5)[13a]

Two contrasting situations can then be expected for the ene reaction. A stepwise ene reaction, occurring most probably by an intermediate in common with the 2 + 2 cycloaddition,[13b] should result in a minimal sensitivity of the reaction rate to cyclic olefin type. On the other hand, a concerted ene reaction should have a sizable rate variation with different angles of ϕ shown in Figure 1.

Results

The reaction between benzyne and cyclohexadiene has been reported by several authors.[14–16] Recently Braun reported the characterization of four hydrocarbon products, **8**, **9**, **10**, and **12**.[16] Benzobicyclo-



[2.2.2]octadiene (**8**) results from 2 + 4 reaction, and the two phenylcyclohexadienes, **9** and **10**, arise from ene reaction. Hydrocarbons **8**–**10** were reported earlier by Simmons[14] and Huisgen and Knorr,[15] but the unusual hydrocarbon **12** was not reported in these older papers.

(14) H. E. Simmons, *ibid.*, **83**, 1657 (1961).

(15) R. Huisgen and R. Knorr, *Tetrahedron Lett.*, 1017 (1963).

(16) A. M. Braun, *J. Org. Chem.*, **35**, 1208 (1970).

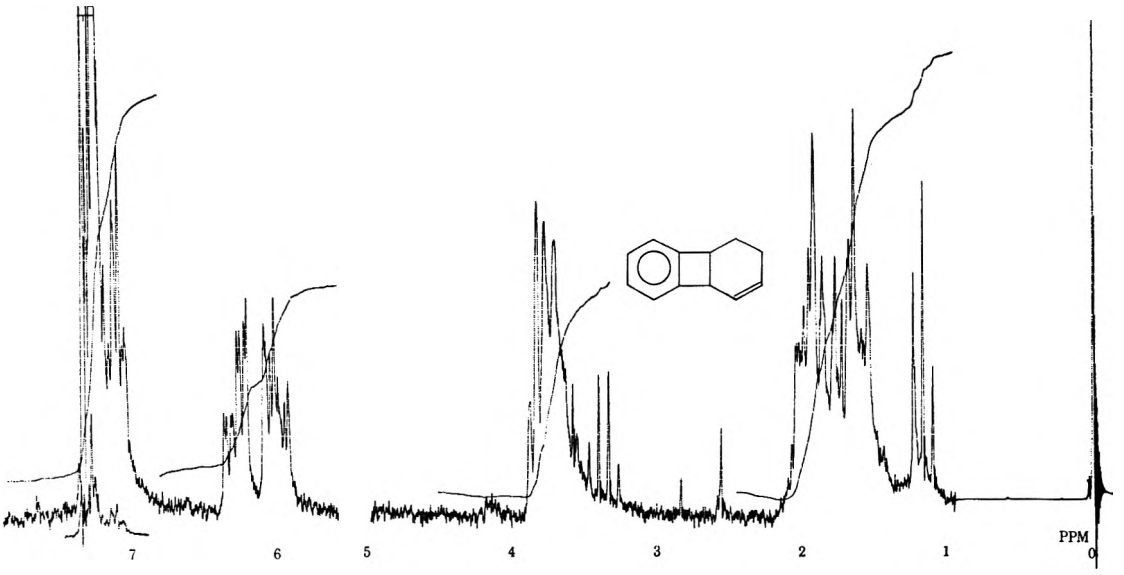
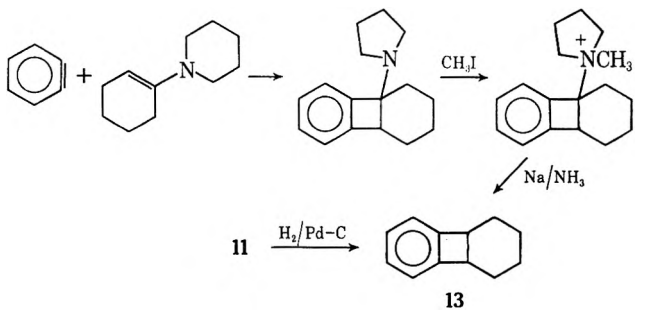


Figure 2.—Pmr spectrum of 11 at 100 MHz in $CDCl_3$ (see text for assignments); diethyl ether impurity.

SCHEME I



Braun suggested that 12 was formed by rearrangement of 11, and it was isolated in 3% overall yield.

We repeated this reaction using both *o*-benzendiazonium carboxylate[17] and 1,2,3-benzothiadiazole 1,1-dioxide[18] as benzyne sources, and found by pmr analyses of vpc collected samples the three hydrocarbon products **8**–**10** in agreement with earlier reports. However, in contrast to Braun's assignment, the fourth hydrocarbon required assignment as **11** (4.4% net yield). The pmr spectrum (Figure 2) displayed an unsymmetrical aromatic region (δ 7.07–7.40, A = 4), a vinyl absorption of two separate multiplets (centered at δ 6.30, A = 1; 6.00, A = 1), the methine H's as two sets of overlapping multiplets (centered at δ 3.97, A = 2), and a fairly complex alaphatic region (δ 1.70–2.40, A = 4). The ir spectrum confirmed the presence of unsaturation as the only functionality. The mass spectrum showed parent ion m/e 156 ($C_{12}H_{12}$) and principal fragments m/e 155, 141, 128, and 115. Our structural assignment of the 2 + 2 product as **11** was confirmed by hydrogenation of this material over Pd/C to yield hydrocarbon **13**. This latter compound was prepared by an alternate route, as outlined in Scheme I.[19]

Tricycloundeca-3,5-diene (**1**) was prepared by a route previously published by Wege and coworkers.[21,22]

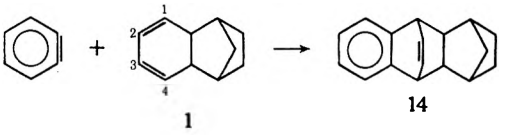
(17) L. Friedman, *J. Amer. Chem. Soc.*, **89**, 3071 (1967).

(18) G. Wittig and R. W. Hoffmann, *Chem. Ber.*, **95**, 2718 (1962).

(19) Apparently Braun's vpc conditions promoted a vinylcyclobutane-like rearrangement of **11** to **12**. Levin has also noted a similar occurrence for 2-vinylbenzocyclobutene derivatives.[20]

(20) R. Levin, Ph.D. Thesis, Princeton University, 1970.

Inspection of a Drieding model of this system shows that the bicyclic bridge constrains the diene group into a planar configuration.[23] Only one hydrocarbon product was observed from decomposition of *o*-benzendiazonium carboxylate in a slight excess of **1**. This product was assigned as **14** and was characterized by its



pmr spectra (Figure 3b); the general features of the aromatic, olefinic, and bridgehead regions were closely similar to the spectra obtained from 2 + 4 addition of benzyne to 1,3-cyclohexadiene (Figure 3a). The ir spectrum confirmed that **14** was a hydrocarbon and the mass spectrum gave m/e 222 ($C_{17}H_{18}$) as a parent ion with the following major fragments: m/e 179, 165, 152, 141, and 128.

In a preliminary account of this work we described the results of decomposition of *o*-benzenediazonium carboxylate with 1,3-cycloheptadiene and 1,3,5-cycloheptatriene, respectively.[11] The reaction with cycloheptadiene yielded two major hydrocarbon products, **15** and **16**, arising from 2 + 4 and 2 + 2 addition, along with a minute amount of material presumed to be an ene product on the basis of its relative vpc retention time (eq 6). In contrast, the cycloheptatriene reaction yielded no 2 + 4 product (**17**) but gave almost equivalent amounts of 2 + 2 and ene products **18** and **19** (eq 7).

The remaining cyclic olefin examined in the study was 1,3,5-cyclooctatetriene. This compound differs relative to the other olefins examined in that there is an equilibrium between a monocyclic and a bicyclic form

(21) We thank Professor W. G. Dauben for furnishing us with complete experimental details.

(22) R. McCulloch, A. R. Rye, and D. Wege, *Tetrahedron Lett.*, 5231 (1969).

(23) Analysis of the AA'BB' spectrum of the vinyl protons of **1** by computer simulation gave vicinal couplings of J_{12} = 9.69 and J_{23} = 5.47 Hz *vs.* 9.56 and 4.95 Hz computed for 1,3-cyclohexadiene (**2**) at 300 MHz; the increase in J_{23} is consistent with an increase in angle θ (Figure 1) from 0 to 17°. P. Crews, *J. Amer. Chem. Soc.*, in press.

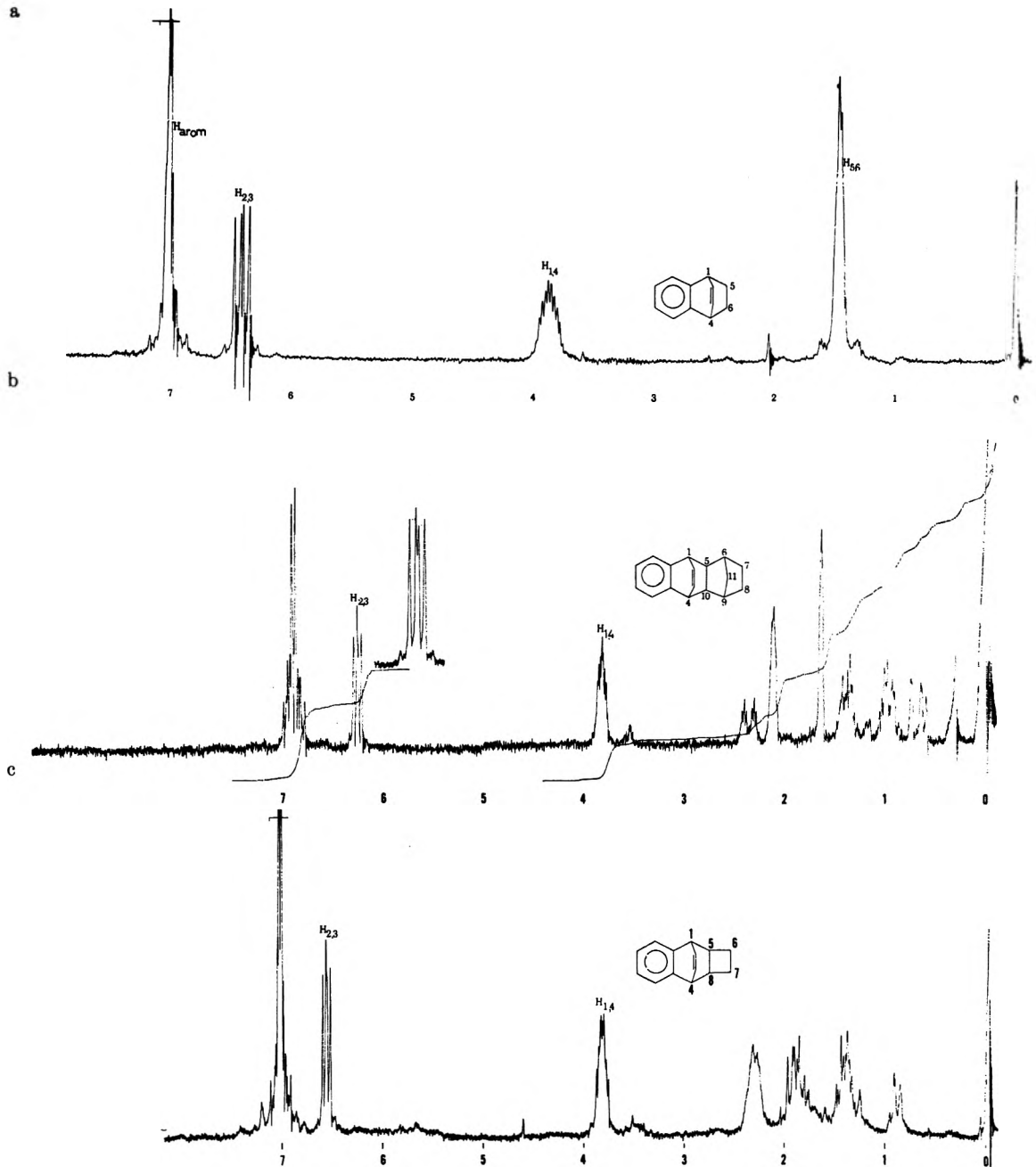


Figure 3.—60-MHz spectrum of **8** in CDCl with multiplet centers: H_{arom} = δ 7.0 (A = 4.0); $H_{2,3}$ = 6.4 (apparent J' s = 3.2, 4.2 Hz, A = 2.0); $H_{1,4}$ = 3.86 (A = 2.0); $H_{5,6}$ = 1.47 (A = 4.0). (b) 100-MHz spectrum of **14** in $CDCl_3$ with multiplet centers: H_{arom} = δ 6.9; $H_{2,3}$ = 6.25 (apparent J's = 3.2, 4.5 Hz); $H_{1,4}$ = 3.8; H_{11n} = 2.35 ($J_{11n-11x}$ = 10.0 Hz); $H_{6,9}$ = 2.1; $H_{5,10}$ = 1.65 ($W^{1/2}$ = 3 Hz); $H_{7,8}$ = two multiplets 1.4/1.0; H_{11x} 0.7 ($J_{11x-11n}$ = 10.0 Hz). Assignments of H_{11x}, H_{11n}, and $H_{5,10}$ are based upon similar arguments of R. McCulloch, A. R. Rye, and D. Wege [*Tetrahedron Lett.*, 5163 (1969)] and expected bottom-side attack by benzyne on **1** to give endo position for $H_{5,10}$. (c) 100-MHz spectrum of **20** in $CDCl_3$ with multiplet centers: H_{arom} = δ 7.0 (A = 4.0); $H_{2,3}$ = 6.55 (apparent J's = 3, 4 Hz, A = 1.9); $H_{1,4}$ = 3.8 (A = 1.9); $H_{5,8}$ = 2.3 (A = 2.1); H_6 and H_7, two multiplets 1.9/1.45 (A = 4.1).

(**5a** ⇌ **5b**) each of which is present in significant amounts.[24] Reaction of this isomeric mixture with benzyne gave only one hydrocarbon product, **20** (eq 8), which results from benzyne addition to **5b**. Structural assignment of this product was made on the basis of the mass spectrum: m/e 182 ($C_{14}H_{14}$) the parent ion and other major fragments, 178, 167, 165, 153, 152, 141, and 129. The ir spectrum confirmed the presence of an unsaturated hydrocarbon, and the pmr spectrum (Figure 3c) was very similar to that of analogous hydrocarbon products **8** and **14**.

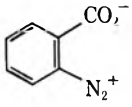
(24) R. Huisgen, G. Boche, A. Dahmen, and W. Hechtl, *Tetrahedron Lett.*, 5215 (1968). Cycloheptatriene does not contain spectroscopically detectable amounts of the norcaradiene valence tautamer: J. B. Lambert, L. J. Durham, P. Lepoutere, and J. D. Roberts, *J. Amer. Chem. Soc.*, **87**, 3896 (1965), and ref 26.

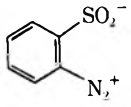
Discussion

A summary of the relative product distributions obtained from the various benzyne reactions is collected in Table I. Before considering the trends in the product ratios, some discussion of the conformation of the cyclic olefins is needed.

In a previous section we mentioned that tricyclic diene **1** appears to be entirely rigid from Dreiding models and can be assumed to have a planar diene chromophore.[23] Electron and X-ray diffraction work

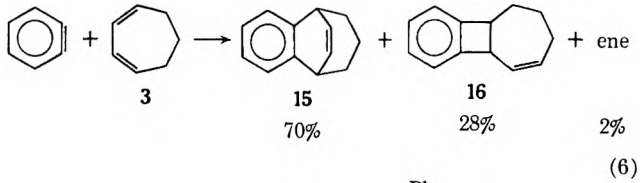
TABLE I
SUMMARY OF PRODUCT RATIOS FROM BENZYNE ADDITION TO CYCLIC OLEFINS


A

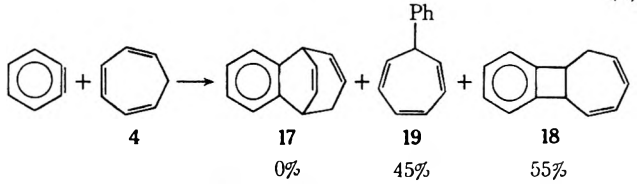

B

Benzyne precursor	Olefin	Net yield, %	% Product ratios 8	9	10	11
A[a]	2	36	48	18	21	13
B[b]		28	51	22	13	14
					14	
A	1				100	
			15		Ene	16
A	3	25	70		2	28
			17		19	18
A	4	46	0		45	55
					19	
A	5a ⇌ 5b (90%) (10%)	35			100	

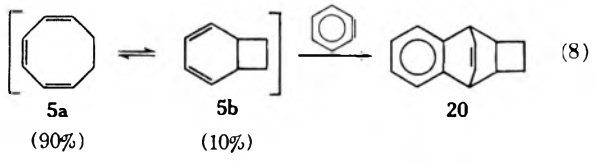
[a] Registry no.: 1608-42-0. [b] Registry no.: 37150-27-9.



(6)



(7)



(8)

has shown 1,3-cyclohexadiene[25] and 1,3,5-cycloheptatriene,[26] respectively, to have twist angles of 17 and 40° between the carbon–carbon double bonds. Recent pmr work from our laboratory indicates the corresponding twist angle for 1,3-cycloheptadiene as *ca.* 20–25°.[27] Although no exact structural data is available, cyclooctatriene in its monocyclic tub form (**5a**) can be assumed to have an interplanar angle of approximately 60° by virtue of its expected similarity to *cis,cis*-1,3-cyclooctadiene, which has been suggested to have an interplanar angle of ~60° from its molar Kerr constant[28] and from pmr data;[29] and cyclooctatetraene, which has been estimated[30] to have an angle of ~75° between the planes of the double bonds based upon X-ray data. The other structural parameter which

(25) H. Oberhammer and S. H. Bauer, *J. Amer. Chem. Soc.*, **91**, 10 (1969); S. S. Butcher, *J. Chem. Phys.*, **42**, 1830 (1965).
(26) M. Traetteberg, *J. Amer. Chem. Soc.*, **86**, 4265 (1964).
(27) P. Crews, *Chem. Commun.*, 583 (1971).
(28) C.-Y. Chen, R. J. W. LeFèvre, and K. M. S. Sundaram, *J. Chem. Soc.*, 553 (1965).
(29) H. Gunther, *Z. Naturforsch. B*, **24**, 680 (1969).
(30) M. A. Cooper, D. D. Elleman, C. D. Pearce, and S. L. Manatt, *J. Chem. Phys.*, **53**, 2343 (1970).

TABLE II
CONFORMATIONAL PARAMETERS FOR CYCLIC OLEFINS

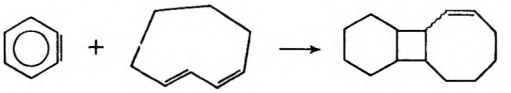
Olefin	Interplanar or dihedral angle, deg	Ref	ϕ,[a] deg
 1	0	*a*, 23	~30
 2	17	25	~5
 3	20–25	27	~37
 4	40	26	~33
 5a	~60	*b*	~42
 5b	0	*a*	~30

[a] Based upon inspection of Drieding models; see Figure 1 for description. [b] Based upon arguments in the text and ref 28–30.

varies with the cyclic olefin type is the angle ϕ, and this angle was estimated from examination of Drieding models (Table II).

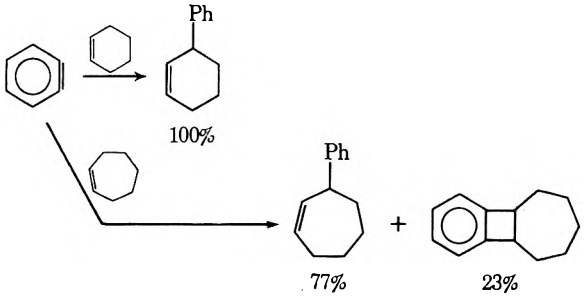
The planar tricycloundeca-2,5-diene (1) can be expected to have optimal geometry for 2 + 4 cycloaddition, and it is seen that *only* this type of addition product results with benzyne, and 2 + 2 reaction is entirely excluded. When the diene chromophore is skewed by an intermediate angle, 17 or ~23°, 2 + 4 reaction no longer predominates but is reduced to ~50% of the product mixture for cyclohexadiene (2 + 2 competes to the extent of 13%) and 70% of the product mixture for 1,3-cycloheptadiene (2 + 2 as 28%). When the skew angle is large, ~40° or greater, *no* 2 + 4 products are observable; for cycloheptatriene ~55% of the products arise by way of the 2 + 2 route; and for cyclooctatriene no products are derived from the predominating tub conformer; instead, exclusive 2 + 4 reaction occurs *via* the planar bicyclic form. Assuming that the rate of 2 + 2 reaction is constant (see earlier discussion), a simple change in the diene dehedral angle (d.a.) from 0 to 40° has changed the ratio of 2 + 4/2 + 2 cycloaddition from ∞ (d.a. 0°) to 3.7 and 2.5 (d.a. 17 and ~23°) to finally 0 (d.a. >40°). It is apparent that a qualitative correlation can be drawn between the relative rate of 2 + 4 reaction and the degree of overlap between the diene p orbitals (angle θ).

The above argument can also account for the results of cycloaddition of benzyne to *cis,trans*-1,3-cyclooctadiene studied by Gassmann,[9a] in which only reaction *via* 2 + 2 addition was observed (eq 9). Molecular models show that the cis,trans diene system is badly skewed (d.a. ~60°) with no possibility of alignment in a planar cis conformation.


(9)

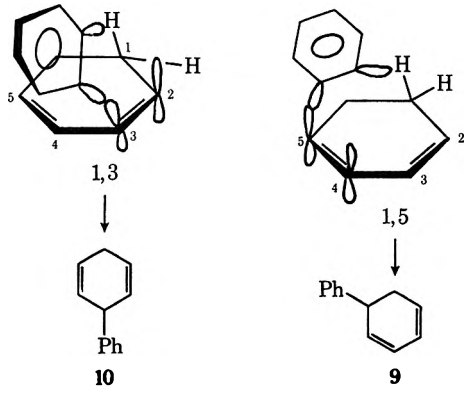
Having verified that the rate of concerted 2 + 4 benzyne reaction is sensitive primarily to the alignment of the reacting π orbitals, our preliminary assumption that a concerted ene reaction should show the same trend would seem to be strengthened. Hence, the relative ratio of ene/2 + 2 products was examined as a function of variations in angle ϕ (Figure 1). In the series cyclohexadiene, cycloheptatriene, cycloheptadiene, angle ϕ can be observed to increase from ~5°, to ~33°, and to ~37°; and the relative ratios of ene/2 + 2 products are, respectively, ~3, 0.8, and 0.07. Indeed it does seem that a simple qualitative correlation exists between ease of ene reaction and angle ϕ.

For simple olefins the same correlation is easily seen. Cyclohexene ($\phi \cong 4°$) is known to give only ene reaction,[6b] while cycloheptene ($\phi \cong 32°$) has been reported to give 77% ene and 23% 2 + 2 products.[31]



There is other circumstantial evidence in support of a concerted-like ene mechanism. Molecular models indicate that there are two approximately isoenergetic transition states leading to a concerted formation of ene products **9** and **10** from reaction of 1,3-cyclohexadiene with benzyne (in Scheme II transition states 1,3 and 1,5 are shown, and they appear to have approximately the same geometry). If a diradical mechanism, similar to that proposed by Tabushi,[13] were operating, one would expect at least *four* ene products from reaction of benzyne with cyclohexadiene. The fact that

SCHEME II

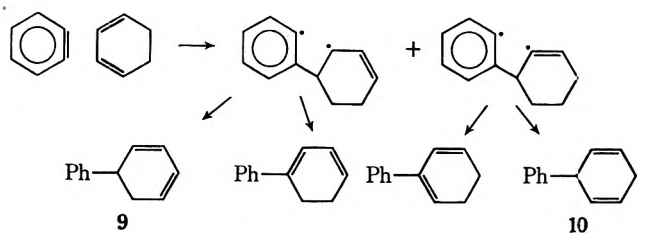


only two ene products are isolated would appear to be inconsistent with stepwise formation of intermediates, either radical or ionic (Scheme III).

Previous work has shown that extensive ene reaction occurs between benzyne and *trans*-1-alkoxypropene, and very little occurs with *cis*-1-alkoxypropene, while 2-alkoxypropenes give 100% ene reaction.[7a,9c] These data are consistent with a concerted ene mechanism in which there is a large steric inhibition to the requisite

(31) L. Lombardo and D. Wege, *Tetrahedron Lett.*, 3981 (1971).

SCHEME III



transition state when the alkoxy and allylic CH are cis, but none when the relative orientation is trans or geminal.

In summary,[32] the conformation of the olefin or polyolefin coreactant is of primary importance in influencing the facility of benzyne to undergo 2 + 4 or ene cycloadditions. Thus, benzyne will react with a planar 1,3-diene such as **1** principally by the 2 + 4 route, while ene reaction may predominate with substrates in which the olefinic p–π orbitals are nearly parallel to the allylic C–H bond, such as in cyclohexene. If, on the other hand, both of these conformational requirements are grossly violated, 2 + 2 cycloaddition is likely to predominate. An example of this latter situation can be seen in the exclusive formation of 2 + 2 products from the reaction of benzyne with *cis,trans*-1,3-cyclooctadiene.

Experimental Section

General.—The anthranilic acid was purified by recrystallization from water and allowed to dry before use. The *o*-aminobenzenesulfonic acid was used as received from Aldrich Chemical Co.

Pmr spectra were determined at 100 MHz on a Jeol JNM-PS-100 spectrometer, or at 60 MHz on a Varian 56/60 or a Jeol MH-60 spectrometer. Mass spectral measurements were run on a single-focusing Hatachi Perkin-Elmer RMU-6E instrument, and ir spectra were determined on a Perkin-Elmer 337 instrument.

Gas chromatographic conditions follow: A, 8 ft Carbowax (20%), 150°, 35 psi; B, 20 ft DEGS (30%), 140°, 35 psi; C, 8 ft Carbowax (20%), 126°, 50 psi. The quantitative yield determinations were obtained by vpc using 3-phenylcyclohexene as an internal standard. It was assumed that relative detector sensitivities were equivalent between the standard and hydrocarbon products.

Benzenediazonium 2-Carboxylate (BDC).—Owing to the explosive nature of this material, preparation and reaction were conducted in a special piece of glassware fashioned from a two-neck round-bottom flask to which was attached, at the opposite end, a fritted-disk Buchner funnel with a stopcock. A typical experiment involves generation of the benzenediazonium 2-carboxylate[34] with the flask tipped on its side; filtration of solvent washings was accomplished with the flask in an upright position; and the cycloaddition was conducted with the flask again tipped on its side.

BDC and Tricycloundeca-3,5-diene (1).—Benzenediazonium 2-carboxylate from anthranilic acid (2.2 g, 18.8 mmol) was decomposed with 1 (5.4 g, 36.7 mmol) in CH_2Cl_2 (100 ml) by heating in a bath at 50° for 4 hr. The dark, homogeneous solution was washed with water (2 × 100 ml) and saturated bicarbonate solution (2 × 100 ml). The organic material was dried over $MgSO_4$ and the solvent was evaporated. Pentane was added to the dark residue and the reddish solution was filtered

(32) Differences, which may be observed in reactions of the olefins studied here, between benzyne and other less reactive dienophiles could be principally a result of the fact that benzyne is a "hot" electrophilic species and the transition state occurs very early along the reaction coordinate. In addition, the orbital interactions of a diene with benzyne *vs.* ethylenic dienophiles are probably different, since approach of benzyne to the diene plane should be from a perpendicular direction as opposed to a parallel approach expected for ethylenic dienophiles.[33]

(33) For discussion of this latter point, see B. H. Klanderman and T. H. Criswell, *J. Org. Chem.*, **34**, 3426 (1969).

(34) L. Friedman and F. M. Logullo, *Org. Syn.*, **48**, 12 (1969).

to separate the insoluble material. The pentane was evaporated, leaving a red viscous oil. Vpc analysis, condition A, indicated only one product. Further purification by vacuum distillation gave recovered starting material, bp 33–38° (0.2 mm), and product, bp 85–95° (0.2 mm). This material was identified as **14** on the basis of spectral data (see text). The ir spectrum (in CCl_4) showed peaks at 3040 (m), 2950 (m), 2860 (m), and 1550 cm^{-1} (w).

BDC and 1,3-Cyclohexadiene.—The reaction and work-up of the reaction of benzyne derived from anthranilic acid (9.0 g, 65 mmol) with 1,3-cyclohexadiene (12.0 g, 150 mmol) was carried out by the above procedure. Chromatography of the residual oil, after pentane treatment, over neutral alumina (40 g) with hexane as eluent gave 3.7 g (36%) of hydrocarbon products. Vpc analysis, condition B, showed four products: **11** (36 min), **8** (42 min), **9** (46.5 min), **10** (51 min), in the relative amounts shown in Table I. The ir spectrum of **11** (in CCl_4) showed peaks at 2975 (m), 2925 (m), 2900 (m), 2860 (m), 1450 (w), and 1250 cm^{-1} (m).

BDC and 1,3-Cycloheptadiene.—The reaction and work-up of the reaction of benzyne derived from anthranilic acid (3.0 g, 22 mmol) with 1,3-cycloheptadiene (6.2 g, 66 mmol) was carried out by the above procedure. Vacuum distillation of the dark red oil which remained after pentane extraction gave 0.94 g (25%) of hydrocarbon products. Vpc analysis, condition C, showed three products: **15** (12.5 min), **16** (15.5 min), and an ene product (18 min) in the relative amounts shown in Table I. The products were separated by vpc collection and characterized from the data given in ref 11.

BDC and 1,3,5-Cycloheptatriene.—The reaction and work-up of the reaction of benzyne derived from anthranilic acid (3.0 g, 22 mmol) with 1,3,5-cycloheptatriene (6.0 g, 66 mmol) was carried out by the above procedure. After pentane treatment and chromatography on alumina (10 g) with hexane followed by dioxane–hexane (1:1) as eluent, vpc analysis showed two hydrocarbon products, **18** and **19** (relative yields in Table I), which were isolated by vpc collection and characterized by spectral data reported in ref 11.

BDC and 1,3,5-Cyclooctatriene.—The reaction and work-up of the reaction of benzyne derived from anthranilic acid (3.0 g, 22 mmol) with 1,3,5-cyclooctatriene (12.0 g, 66 mmol) was carried out by the above procedure. After pentane treatment, the residual oil was vacuum distilled to give two fractions: a low-boiling fraction, bp 24–30° (0.5 mm), identified as recovered cyclooctatriene (4.5 g), and a high-boiling fraction, 1.4 g, bp 80–90° (0.5 mm), shown by pmr analysis to be only one product, **20**. The product became crystalline at room temperature and was recrystallized from hexane, mp 69–70°. The ir spectrum in CCl_4 showed absorptions at 3050 (w), 2950 (m), 2875 (m), 1680 (m), 1600 (m), and 1500 cm^{-1} (m).

Benzothiadiazole and 1,3-Cyclohexadiene.—The procedure of Wittig and Hoffmann[18] for generating 1,2,3-benzothiadiazole 1,1-dioxide from *o*-aminobenzenesulfonic acid (1.44 g, 8 mmol) was followed. The benzothiadiazole was decomposed without purification with cyclohexadiene (1.9 g, 24 mmol) in CH_2Cl_2 (100 ml) at 55° for 4 hr. The work-up described above yielded 0.56 g of a yellow liquid, which was vpc-analyzed, condition B, without further purification. The net and relative hydrocarbon yields are given in Table I.

7,8-Benzobicyclo[4.2.0]octene (13). *N*-Methylpyrrolidinium-7,8-benzobicyclo[4.2.0]octene Iodide.—Methyl iodide (1.55 g, 10.9 mmol) was added to 1-pyrrolidino-7,8-benzobicyclo[4.2.0]-octene[6b] (1.82 g, 8.0 mmol) dissolved in absolute ethanol (25 ml), and the mixture was refluxed for 1.5 hr. At the end of this period the ethanol solution was cooled in an ice bath, but the solution remained completely homogeneous. Addition of ether (60 ml) to the cold solution resulted in the formation of an oil. The solvent was decanted, and the oil was washed with ether (2 × 50 ml). The residual solvent was evaporated to give a viscous oil (2.05 g) which was assumed to be the expected methyl iodide salt [pmr ($CDCl_3$) δ 1.0–4.2 (complicated series of multiplets), 7.1–7.9 (multiplet), and 8.1–8.4 (multiplet)].

7,8-Benzobicyclo[4.2.0]octene from Birch Reduction.—The ammonium salt obtained above (2.05 g, 5.75 mmol) along with absolute ethanol (0.26 g, 5.75 mmol) was dissolved in liquid ammonia (~50 ml). Sodium metal (0.26 g, 0.0115 g-atom) was added over a 5-min period with stirring. A blue color was formed, but it had entirely disappeared at the end of 0.5 hr and the stirring was discontinued. The ammonia was allowed to evaporate slowly. A 10% HCl solution was added to the residue and this mixture was extracted with ether. Evaporation of the ether yielded 0.37 g of a yellow-red oil; vpc analysis showed only a single peak. A pure sample was obtained by preparative vpc collection, and a pmr spectrum at 100 MHz of this material was in accord with structure **13** [δ 1.42–1.84 (multiplet), 3.49 (multiplet), 6.94–7.18 (symmetrical AA'BB' multiplet of 13 peaks), relative intensities 8:2:4].

Registry No.—**1**, 33482-87-0; **2**, 592-57-4; **3**, 4054-38-0; **4**, 544-25-2; **5a**, 1871-52-9; **5b**, 3725-28-8; **8**, 7322-46-5; **11**, 37150-32-6; **13**, 37150-33-7; **14**, 37150-34-8; **20**, 37150-35-9; benzyne, 462-80-6; *N*-methylpyrrolidinium-7,8-benzobicyclo[4.2.0]octene iodide, 37406-70-5.

Cycloadditions of Benzyne with Cyclic Olefins. Influence of Catalytic Silver[1]

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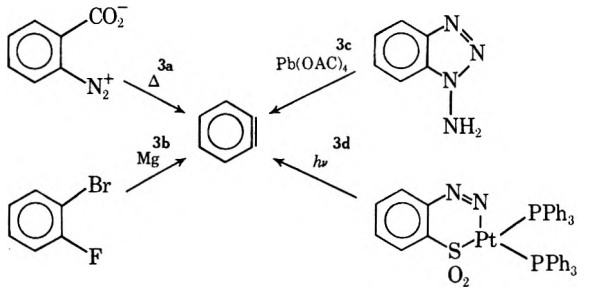
Received August 8, 1972

The effect of added Ag^+ upon the course of benzyne addition to cyclic and acyclic polyenes is examined. In the presence of catalytic amounts of Ag^+, benzyne reacts with cyclic six- and seven-membered di- and triolefins to give almost exclusive formation of 2 + 4 type products, but with acyclic systems little or no effect is observable on the product compositions. A mechanism is proposed to account for both the catalytic effect and the observed products as a function of olefin type.

There are a variety of methods described in the literature for the preparation of benzyne, and it has been shown that the character of benzyne obtained from rather diverse sources is identical.[2] A sampling of some of the different conditions that can be used to generate benzyne is shown below.[3]

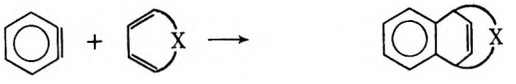


It seems intriguing that, in comparison to the above situation, minute amounts of silver salts[4] or trace metals of unknown origin[5] have been identified as being able to effect significant changes in the product distributions of benzyne additions to olefins. The source of this effect has been uniformly attributed to benzyne capture of Ag^+ giving a complex which is presumed to be far more electrophilic than uncomplexed benzyne.[4-7] If such a proposal is valid it would imply that catalytic effects of this type might be a useful, general feature of cycloaddition reactions.[8]

There is reason to believe that the origin of the Ag^+ catalytic effect might be different than previously proposed. The reaction of benzyne with excess benzene (9.8 mol) gives mainly a 2 + 4 product (benzobarrelene, 85%), but addition of Ag^+ ($\sim 10^{-5}$ mol) reduces the amount of 2 + 4 reaction (55%) while increasing the amounts of other products (benzocyclooctatetraene, 17%; biphenyl, 22%).[4] The previously proposed scheme involving the capture of Ag^+ by benzyne followed by reaction with benzene would imply that benzyne is able to survive more than 10^4 collisions with benzene before colliding with silver;[4] however, this would seem to be an unusual requirement, since benzyne is regarded as being a "hot" electrophile especially in comparison to reactive dienophiles such as maleic anhydride.[9] We feel that a somewhat different scheme provides a more attractive rationale for this effect. Moreover, our preliminary experiments involving benzyne addition to simple cyclic olefins with added Ag^+ indicated that the product types are different than would be predicted by extrapolation from the known benzyne–Ag^+ reactions with benzene and cyclooctatetraene.

Results

We have recently identified the primary influences on the relative partitioning of benzyne among three major paths: 2 + 4, 2 + 2, and ene cycloaddition.[10] Benzyne undergoes concerted 2 + 4 and ene reaction, but stepwise 2 + 2 cycloaddition, and none of these reaction types appear to share a common reaction surface. We have observed that reaction of 1,3-cyclohexadiene (1) with benzyne generated from either benzenediazonium 2-carboxylate (**6a**) or 1,2,3-benzothiadiazole 1,1-dioxide (**6b**) yields significant amounts of products from each of these types of reactions (products **7–10** Table I).[10] Addition of $AgBF_4$ (benzyne/$Ag^+ \approx 125$) shifts the product ratio greatly in favor of formation of the 2 + 4 product, **7**. A similar trend is observed when **6a** is decomposed in the presence of 1,3-cycloheptadiene (**2**) and 1,3,5-cycloheptatriene (**3**). In the absence of Ag^+ 1,3-cycloheptadiene yields 2 + 4 product **11** (70%) and 2 + 2 product **12** (28%), whereas cycloheptatriene gives no 2 + 4 product **13**, but 2 + 2 product **15** (55%) and ene product **14** (45%).[10] Repeating these reactions in the presence of Ag^+ causes an increase in the relative amounts of 2 + 4 products to 89% from cycloheptadiene and 100% from cycloheptatriene.



	% products	
X	No Ag^+	Ag^+
7 $(CH_2)_2$	48	97
11 $(CH_2)_3$	70	89
13 $CH_2CH{=}CH$	0	100

(1) (a) For a preliminary report see P. Crews, M. Loffgren, and D. J. Bertelli, *Tetrahedron Lett.*, 4697 (1971). (b) Support from the UCSC Committee on Research and from the Frederick G. Cottrell Fund of the Research Corp. is gratefully acknowledged.

(2) (a) R. Huisgen and R. Knorr, *Tetrahedron Lett.*, 1017 (1963); (b) B. H. Klanderman and T. R. Criswell, *J. Amer. Chem. Soc.*, **91**, 510 (1969).

(3) (a) L. Friedman and F. M. Logullo, *Org. Syn.*, **48**, 12 (1969); (b) G. Wittig and E. Benz, *Angew. Chem.*, **70**, 166 (1958); (c) C. D. Campbell and C. W. Rees, *Proc. Chem. Soc.*, 296 (1964); (d) T. L. Gilchrist, F. J. Graveling, and C. W. Rees, *Chem. Commun.*, 821 (1968).

(4) L. Friedman, *J. Amer. Chem. Soc.*, **89**, 3071 (1967).

(5) E. Vedejs and R. A. Shepard, *Tetrahedron Lett.*, 1863 (1970); E. Vedejs, *ibid.*, 2633 (1968).

(6) P. Warner, *ibid.*, 723 (1971).

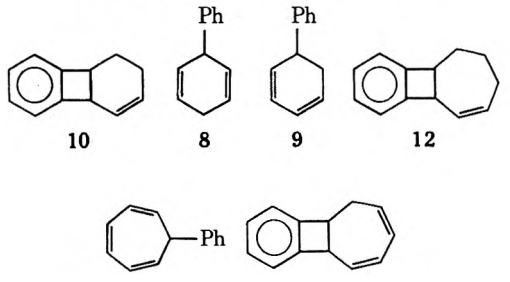
(7) L. A. Paquette, *Chem. Commun.*, 1076 (1971).

(8) In this regard it was reported in a recent theoretical study of electrophilic additions to olefins that Ag^+ complexation to an olefin should not cause enhanced electrophilic character as judged by the minimal perturbation calculated for the carbon framework of the π complex *vs.* free ethylene: R. D. Bach and H. F. Henneike, *J. Amer. Chem. Soc.*, **92**, 5589 (1970).

(9) (a) R. W. Hoffmann, "Dehydrobenzyne and Cycloalkynes," Academic Press, New York, N. Y., 1967, p 2; (b) B. H. Klanderman and T. R. Criswell, *J. Org. Chem.*, **34**, 3426 (1969).

(10) P. Crews and J. Beard, *J. Org. Chem.*, **38**, 522 (1973), and references cited therein.

TABLE I
REACTIONS OF BENZYNE WITH CYCLIC OLEFINS WITH AND WITHOUT Ag^+



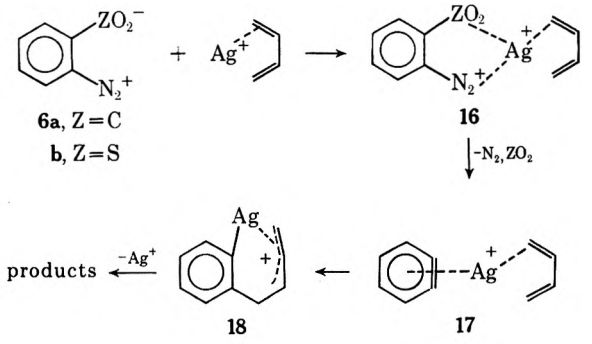
Benzyne precursor	Olefin	Benzyne[a]/silver	Net yield, %	Relative % products 7	8	9	10
6a	1,3-Cyclohexadiene	b	36	48	21	18	13
6a	1,3-Cyclohexadiene	125/1	6	79	8	7	6
6a	1,3-Cyclohexadiene	13/1	2	81	6	7	6
6b	1,3-Cyclohexadiene	b	28	51	13	22	14
6b	1,3-Cyclohexadiene	31/1	35	97	0	0	3
				11	Ene	12	
6a	1,3-Cycloheptadiene	b		70	2	28	
6a	1,3-Cycloheptadiene	16/1		89	1	10	
				13	14	15	
6a	1,3,5-Cycloheptatriene	b	36	0	45	55	
6a	1,3,5-Cycloheptatriene	16/1	20	100			

[a] Ratio based on amount of benzyne precursor used (*i.e.*, anthranilic acid). [b] No silver, results from preceding paper, ref 10.

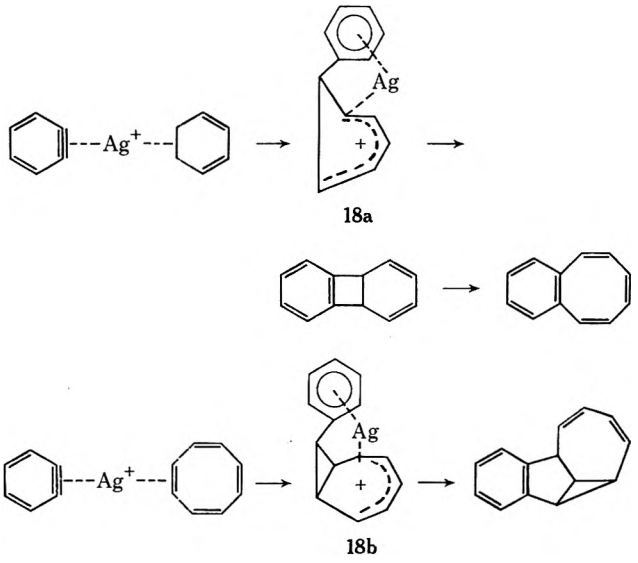
In the above reactions with added Ag^+ we observed the net hydrocarbon yields to be dependent upon the benzyne precursor and/or the amount of Ag^+ used. The net yields from reactions with **6a** are drastically reduced upon addition of Ag^+ (from cyclohexadiene with no silver, net yield 36%; benzyne/Ag^+ ≈ 125, net yield 6.5%), and, if the amount of Ag^+ added approaches the molar amount of benzyne precursor, no hydrocarbon products are obtained.[11] Alternatively, the reaction with **6b** is homogeneous and the net hydrocarbon yields from reactions with or without silver are almost identical (Table I). This can be taken as an indication that with added Ag^+ increased formation of 2 + 4 products occurs at the expense of ene and 2 + 2 reactions.

Discussion

Rather than assume capture of Ag^+ by benzyne we proposed the scheme below as a rationalization for the Ag^+ catalysis. The major points of this mechanism are a Ag^+–olefin complex which unites with the benzyne precursor **6** to give **16**, which decomposes to the benzyne–olefin complex **17**.[12] To account for the catalytic nature of the Ag^+ effect it must be assumed that the rate of decomposition of **16** and **17** is considerably faster for free **6a** or **6b**.[14] Finally, a stepwise electrophilic attack by the free double bond in the s-cis conformation leads to intermediate **18**, which is identical with that proposed earlier.[4,7]



In a previous publication Paquette pointed out that the seemingly divergent results of Ag^+-promoted benzyne reaction with benzene and cyclooctatetraene could be justified by assuming that intermediates **18a,b** collapse *via* partial bridging of silver to the electropositive terminus of the pentadienyl group followed by ejection of Ag^+ and C–C bond formation as shown below. We find that a similar argument can partially explain our observations with unsaturated six- and seven-membered ring systems. HMO calculations on pentadienyl cation[15] indicate the 1 and 3 positions to be almost equally as electron deficient. If, by analogy to the scheme above, the benzyne–Ag^+–cycloheptatriene complex were to decompose *via* intermediate **18c**, compound **15** would be the final product; however, none of this material is observed. The observed formation of **13** requires partial bonding of Ag^+ to C-3 of the pentadienyl system as in **18d**, followed by collapse to the product.



Extending this reasoning to the case of the 1,3-dienes, it is seen that two kinds of propenyl cation like intermediates are possible, **18e** or **18f**; the ultimate products of these species are different, but only intermediate **18f** can account for the observed increase in 2 + 4 type products, **7** or **11**.

(11) Infrared spectra of the product mixtures showed carbonyl absorption indicating lactone functionality (1770 cm^{-1}).

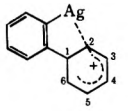
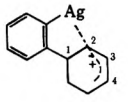
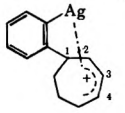
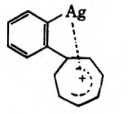
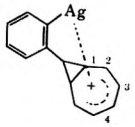
(12) The formation of a species such as **16** can be viewed as being similar to the intermediates that are isolated when **6a** or **6b** are decomposed in the presence of $(Ph_3)_4Pt$.[3d,13]

(13) C. D. Cook and G. S. Jauhal, *J. Amer. Chem. Soc.*, **90**, 1464 (1968).

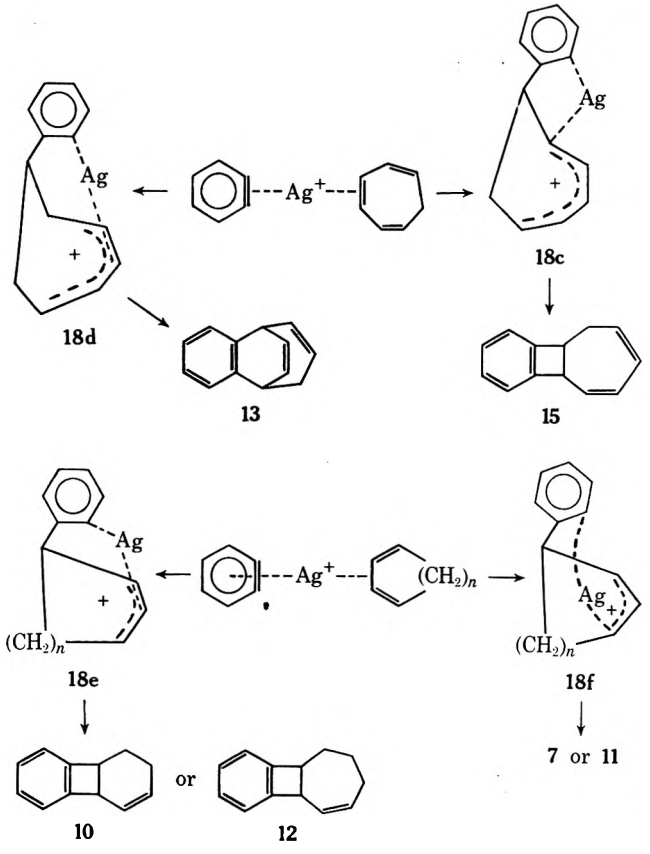
(14) The catalytic role of Ag^+ in the Arndt–Eistert synthesis might be regarded as a similar situation: J. March, "Advanced Organic Chemistry," McGraw-Hill, New York, N. Y., 1968, p 809.

(15) (a) For pentadienyl cation the following electron densities are calculated: C_1 = 0.666, C_2 = 1.000, C_3 = 0.664. For propenyl cation electron densities are C_1 = 0.500; C_2 = 1.000.[15b] (b) A. Streitweiser, "Molecular Orbital Theory for Organic Chemistry," Wiley, New York, N. Y., 1961.

TABLE II

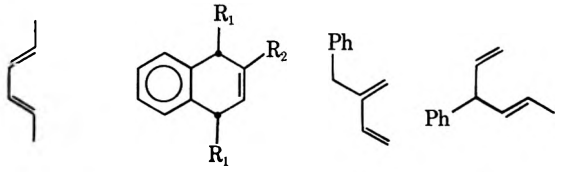
Polyene	Intermediate	C_b–C_N[a] $N = 2$	C_b–C_N[a] $N = 4$
		3.0	4.1
1		2.65	3.2
2		2.7	1.9
3		2.75	2.2
		2.5	2.6

[a] C_b–C_N distance is measured on a model of the intermediate between the benzene carbon σ bound to silver (C_b) and the carbon of the polyene ring (C_N).



We examined Drieding models of the σ-bonded silver intermediates, anticipating that this approach would offer some input to account for the different selectivity between intermediates observed above. In Table II are compiled the results of measurements of the distances between the benzene carbon σ bound to silver (C_b) and the polyene ring carbon (C_N). Inspection of this table reveals a striking pattern. A choice between the collapse of the two types of intermediates (*i.e.*, bond formation from C_b to either C_2 or C_4) to products seems to be dictated purely on the basis of ring closure by way of the shortest C_b–C_N bond distance. The one exception to this proposal is 1,3-cyclohexadiene, and in this case, since the two C_b–C_N bond distances are fairly close ($\Delta \approx 0.5$ Å), one might expect ring closure to occur *via* the six-membered intermediate derived from **18f** rather than through the more strained four-membered transition state from **18e**.

TABLE III
BENZYNE REACTIONS WITH ACYCLIC OLEFINS WITH AND WITHOUT Ag^+



5 **19a**, $R_1 = H$; $R_2 = CH_3$ **20** **21**
b, $R_1 = CH_3$; $R_2 = H$

Olefin	Benzyne[a]/ silver	Net yield, %	Relative % products 19a	20	Ref
Isoprene (4)	*b*		41	59[c]	This work
			45	55[d]	
Isoprene (4)	*b*	28	45	55	*e*
Isoprene (4)	46/1		48	52[c]	This work
			49	51[d]	
			19b	21	
5	*b*		90	10[c]	This work
5	*b*	74	85	6	16
5	61/1	3	85	4[c]	This work

[a] Ratio based upon the amount of **6a** used. [b] No silver. [c] Product analysis by vpc. [d] Product analysis by nmr. [e] G. Wittig and H. Dürr, *Justus Liebigs Ann. Chem.*, **672**, 55 (1964).

Two additional facts must be noted concerning the Ag^+-catalyzed benzyne addition to olefins. There is almost *no* change observable on the product distributions when acyclic systems are treated (Table III) with benzyne in the presence or absence of Ag^+. Secondly, the reaction of benzyne with 1,4-*trans*-dimethylbutadiene is observed to be stereospecific (>99%) with and without[16] Ag^+ catalysis. The data from cyclic systems indicates that the Ag^+ effect is not quenched as the diene s-cis chromophore becomes nonplanar,[17] but it would appear that this is not the case for acyclic dienes which have s-trans geometries. Based on the data of Muhs and Weiss, it would seem reasonable to assume that under our experimental conditions the complexing constants between Ag^+ and the cyclic or acyclic dienes are of the same order of magnitude.[18] Consequently, with acyclic dienes the formation of the benzyne–Ag^+–olefin complex **17** is to be expected. If this is a valid assumption, one possible rationalization for the absence of an Ag^+ catalytic effect upon product formation with acyclic dienes is that the σ-bound silver intermediate **18** is not formed (from 1- or 2-methylbutadienes), but instead intermediate **17** dissociates to

(16) M. Jones, Jr., and R. H. Levin, *J. Amer. Chem. Soc.*, **91**, 6411 (1969).

(17) Cyclopentatriene has a tub conformation with an angle of 40° between the planes of the double bonds: M. Traetteberg, *ibid.*, **86**, 4265 (1964).

(18) M. A. Muhs and F. T. Weiss, *ibid.*, **84**, 4697 (1962).

give free benzyne which reacts in a normal manner with the large pool of uncomplexed olefin.

Experimental Section

General.—The anthranilic acid was recrystallized from water and allowed to dry before use. The *o*-aminobenzenesulfonic acid was used as received from Aldrich Chemical Co.

Pmr spectra were determined on a JEOL JNM-PS-100 which had Pulse Fourier Transform accessories for proton observation or MH-60 or on a Varian A-56/60 spectrometer. Mass spectral measurements were run on a single-focusing Hitachi Perkin-Elmer RMU-6E instrument, and infrared spectra were run on a Perkin-Elmer 337 instrument.

Gas chromatography conditions follow: A, 20 ft DEGS (30%), 140°, 60 psi; B, 20 ft Carbowax (20%), 180°, 40 psi; C, 8 ft DEGS 140°, 60 psi; D, 8 ft Carbowax (20%), 150°, 35 psi; E, 12 ft Carbowax (20%), 140°, 40 psi. Quantitative yields were obtained by vpc with 3-phenylcyclohexene as a standard.

Benzenediazonium 2-Carboxylate (BDC).—Owing to the explosive nature of this material, preparation and reaction were conducted in a special flask described in ref 10.

BDC–1,3-Cyclohexadiene–Ag^+.—A silver–olefin complex of cyclohexadiene was prepared by adding $AgBF_4$ (0.11 g, 5.2 mmol) to cyclohexadiene (12.0 g, 150 mmol) followed by CH_2Cl_2 (50 ml). This mixture was allowed to stand for *ca.* 0.5 hr before use. Benzenediazonium 2-carboxylate from anthranilic acid (9.0 g, 65 mmol) in CH_2Cl_2 (100 ml) was decomposed with the silver–olefin solution by heating in a bath at 50° for 4 hr. At the end of this period the dark brown solution was filtered, washed with water (2 × 100 ml) and saturated bicarbonate (4 × 100 ml), and dried over $MgSO_4$. The solvent was evaporated, leaving a dark liquid; pentane (~50 ml) was added; and the orange solution was filtered to remove polymeric materials. Evaporation of the solvent gave a red liquid (0.88 g, 6% yield), and vpc analysis, condition A, showed four hydrocarbons (in the relative amounts in Table I) with identical retention times with those of an experiment without Ag^+.[10]

This same procedure was repeated exactly except that the amount of $AgBF_4$ (1.0 g, 5.2 mmol) was increased *ca.* tenfold. As before, four hydrocarbon products were observed (Table I), but the yield was greatly reduced (0.2 g, 2%).

Benzothiadiazole (6b)–1,3-Cyclohexadiene–Ag^+.—The procedure of Wittig and Hoffman[19] for generating **6b** from *o*-aminobenzenesulfonic acid (1.44 g, 8.7 mmol) was followed. **6b** in CH_2Cl_2 (100 ml) was decomposed without purification at 50° for 4 hr with a silver (0.055 g, 0.28 mmol)–cyclohexadiene (1.9 g, 24 mmol) solution prepared as above. The work-up as described above yielded, after chromatography on neutral alumina (hexane as eluent), a yellow liquid (0.56 g). Vpc analysis, condition A, showed two hydrocarbon products which were identified by retention times (compared to ref 10) and nmr spectra (Table I).

BDC–1,3-Cycloheptadiene–Ag^+.—The reaction and work-up of the reaction of benzyne derived from anthranilic acid (3.0 g, 22 mmol) with the silver ($AgBF_4$, 0.3 g, 1.4 mmol)–cycloheptadiene (6.2 g, 66 mmol) complex was carried out by the above procedure. A red liquid was obtained after chromatography on alumina (hexane as eluent). Vpc analysis, condition B, showed four products: 2 + 4 (40 min), 2 + 2 (43 min), ene product (47.5 min), and a final product which was not fully characterized (56 min). A small amount of this last material was vpc collected, and it proved to be a 1:1 adduct based upon the mass spectrum, *m/e* 170 (parent, $C_{13}H_{14}$) and additional fragments at *m/e* 142, 141, 128, 115, and 105. The ir showed only olefinic functionality. It is possible that this material was derived from the 2 + 2 product by a vinylcyclobutane rearrangement. For some similar cases see ref 10, footnotes 19 and 20.

BDC–1,3,5-Cycloheptatriene–Ag^+.—The reaction and work-up of the reaction of benzyne derived from anthranilic acid (3.0 g, 22 mmol) with the silver ($AgBF_4$, 0.3 g, 1.4 mmol)–cycloheptatriene (6.0 g, 65.7 mmol) complex were carried out by the above procedure. The work-up as described gave after chromatography on neutral alumina (hexane as eluent) a clear liquid (0.7 g, 21%). Vpc analysis, condition C, showed the material to have a different retention time from that of **14** or **15**. The product was characterized as **13** by spectral data in ref 1a.

BDC and Isoprene.—The reaction and work-up of the reaction of benzyne derived from anthranilic acid (3.0 g, 22 mmol) with isoprene (14.5 g, 66 mmol) was carried out by the above procedure. The work-up described above yielded a yellow liquid after pentane treatment. Product analysis: (a) nmr, **19a** (45%), **20** (55%); (b) vpc, condition D, **19a** (41%), **20** (59%).

BDC–Isoprene–$Ag.^+$—The reaction and work-up of the reaction of benzyne derived from anthranilic acid (3.0 g, 22 mmol) with the silver ($AgClO_4$, 0.1 g, 0.48 mmol)–isoprene (4.5 g, 66 mmol) complex was carried out by the above procedure. The reaction mixture was worked up as described above. Product analysis: (a) pmr, **19a** (49%), **20** (51%); (b) vpc, condition D, **19a** (48%), **20** (52%). A duplicate run with $AgClO_4$ (0.4 g, 1.9 mmol) gave identical results. Another set of duplicate runs with $AgBF_4$ (1.2 or 0.4 g) showed by pmr **19a** (~46%) and **20** (~54%).

BDC–*trans,trans*-1,4-Dimethylbutadiene–Ag^+.—The reaction and work-up of the reaction of benzyne derived from anthranilic acid (3.0 g, 22 mmol) with the silver ($AgBF_4$, 0.07 g, 0.36 mmol)–dimethylbutadiene (3.0 g, 37 mmol) complex was carried out by the above procedure. The reaction mixture was worked up as described above, and chromatography on alumina (hexane as eluent) yielded a light red liquid (0.43 g). Vpc analysis, condition E, indicated a net hydrocarbon yield of 3% with relative ratios being similar to the report by Jones and Levin (Table III, ref 16) for the same reaction without Ag^+. The 2 + 4 product was observed to be pure *cis*-dimethyldihydronaphthalene by pmr observation of the vinyl proton region in Fourier Transform mode (200 pulses) wherein less than 1% of the *trans*-dimethyldihydronaphthalene[20] could be easily seen.

Registry No.—**1**, 592-57-4; **2**, 4054-38-0; **3**, 544-25-2; **4**, 78-79-5; **5**, 5194-51-4; **6a**, 1608-42-0; **6b**, 37150-27-9; Ag^+, 14701-21-4; benzyne, 462-80-6.

(19) G. Wittig and R. W. Hoffman, *Chem. Ber.*, **95**, 2718 (1962).

(20) Prepared by procedure outlined in ref 16.

Chemical Evidence for Transition-State Geometry in Reaction of Monoolefins with Singlet Oxygen[1]

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To examine the possibility of stereoelectronic control in formation of the C–O bond in oxygenation of monoolefins with singlet oxygen, steroidal substrates were studied having allylic methyl groups in which optimum C–H orientation for a cyclic process is readily attainable. Hematoporphyrin-sensitized oxygenation of 3-methyl-5α-cholest-2-ene (**13**) in pyridine followed by reduction of the initially formed hydroperoxides afforded 3β-methyl-5α-cholest-1-en-3α-ol (**21**) and 3-methylene-5α-cholestan-2α-ol (**15a**) in the ratio 7:3. Under similar conditions, 2-methyl-5α-cholest-2-ene (**23**) gave 2-methylene-5α-cholestan-3α-ol (**24**), 2-methylene-5α-cholestan-3β-ol (**2a**), and 2-methyl-5α-cholest-1-en-3α-ol (**11**) in the ratio 57:13:30. The products were identified by comparison with authentic samples obtained from straightforward synthetic procedures. The results indicate that the formation of a quasiaxial C–O bond may be slightly favored over a quasiequatorial one, but the preference is not as strong as that observed for cleavage of a quasiaxial C–H bond over a quasiequatorial C–H in endocyclic cyclohexene systems. A transition state for the cyclic, product-forming step that resembles starting olefin more than it does the allylic hydroperoxide product is advanced to account for these results.

Reactions of singlet oxygen are of considerable synthetic, biological, and environmental importance.[2] For synthetic work the activated oxygen is conveniently produced in solution by photosensitization and among its reactions with unsaturated compounds the one that converts a monoolefin to an allylic hydroperoxide with a rearranged double bond has received extensive mechanistic attention.[3]

In conformationally fixed cyclohexene rings the allylic hydroperoxidation shows a strong preference for quasiaxial C–H bond cleavage and can be retarded by 1,3-diaxial type hindrance to the developing C–O bond. These results are understood in terms of the one-step ene mechanism between singlet oxygen and olefin and on geometric factors that could affect such a path.[4,5]

In the cases studied that gave information on stereochemistry, a cyclic process involving a quasiaxial C–H bond on a six-membered steroidal ring necessarily created a quasiaxial C–O bond. The question arises whether there is any inherent stereoelectronic factor favoring formation of a quasiaxial C–O bond. To separate this factor from those involving C–H bond cleavage, it was necessary to study substrates in which the allylic C–H bond available for reaction was not conformationally fixed.[6] Because certain methylated steroid olefins appeared to satisfy this requirement, we examined the photosensitized oxygenation of 3-methyl-5α-cholest-2-ene (partial structure **13**) and 2-methyl-5α-cholest-2-ene (**23**).

Preparation of Potential Reaction Products.—The starting methylcholest-2-enes **13** and **23** were prepared as described elsewhere.[7] Allylic alcohols and other products related to 2-methyl-5α-cholestane were prepared as follows (Chart I). 2-Hydroxymethylene-5α-cholestan-3-one (**1**)[8–10] was reduced with lithium aluminum hydride and gave 2-methylene-5α-cholestan-3β-ol (**2a**) together with a sharp-melting 1:1 complex of **2a** and **3**,[11] which was separated into its components by precipitation of the digitonide of **2a**. The structure and stereochemistry of **2a** were revealed by its ir and nmr spectra, by its quantitative precipitation with digitonin, and by the nmr spectra of the corresponding acetate (**2b**), benzoate (**2c**), and 3,5-dinitrobenzoate (**2d**) derivatives. Hydrogenation of **2a** in alkaline ethanol over a platinum catalyst afforded the 3β-hydroxy-2β-methyl compound **4a**. Oxidation of this alcohol gave 2β-methyl-5α-cholestan-3-one (**5**), which was in turn epimerized to the more stable 2α-methyl isomer **6**.[7b,12a]

Attempted hydrogenation of **2a** in ethyl acetate over palladium/charcoal led to quantitative isomerization to the 2β-methyl ketone **5**. Hydrogenation of **5** with platinum in alkaline ethanol afforded a mixture of the epimeric 2α-methyl-5α-cholestan-3-ols **7** and **8**,[7b,12a] indicating that isomerization to **6** had taken place prior to hydrogenation.

The epimeric 3-hydroxy-2-methyl-5α-cholest-1-enes **10** and **11** were prepared by aluminum isopropoxide

(1) (a) This work was supported by the National Institutes of Health (Grant GM 09693) and by a postdoctoral fellowship to J. B. D. from the National Cancer Institute. (b) For a preliminary communication of some of these results, see A. Nickon, V. T. Chuang, P. J. L. Daniels, R. W. Denny, J. B. DiGiorgio, J. Tsunetsugu, H. G. Vilhuber, and E. Werstiuk, *J. Amer. Chem. Soc.*, **94**, 5517 (1972).

(2) (a) C. S. Foote, *Science*, **162**, 963 (1968); (b) T Wilson and J. W. Hastings, "Photophysiology," Vol. V, A. C. Giese, Ed., Academic Press, New York, N. Y., 1970, p 49; (c) I. R. Politzer, G. W. Griffen, and J. L. Laseter, *Chem.-Biol. Interactions*, **3**, 73 (1971); (d) R. A. Ackerman, J. N. Pitts, Jr., and I. Rosenthal, *Amer. Chem. Soc., Div. Petrol. Chem., Prepr.*, **16**, A25 (1971); (e) R. W. Denny and A. Nickon, *Org. React.*, in press.

(3) For reviews see (a) K. Gollnick, *Advan. Photochem.*, **6**, 1 (1968); (b) C. S. Foote, *Accounts Chem. Res.*, **1**, 104 (1968); (c) D. R. Kearns, *Chem. Rev.*, **71**, 395 (1971); (d) ref 2e.

(4) (a) A. Nickon and J. F. Bagli, *J. Amer. Chem. Soc.*, **81**, 6330 (1959); (b) *ibid.*, **83**, 1498 (1961); (c) A. Nickon, N. Schwartz, J. B. DiGiorgio, and D. A. Widdowson, *J. Org. Chem.*, **30**, 1711 (1965); (d) A. Nickon and W. L. Mendelson, *Can. J. Chem.*, **43**, 1419 (1965); (e) A. Nickon and W. L. Mendelson, *J. Amer. Chem. Soc.*, **87**, 3921 (1965).

(5) (a) F. A. Litt and A. Nickon, *Advan. Chem. Ser.*, **77**, 118 (1968). (b) K. Gollnick, *ibid.*, 672 (1968). (c) Alternative mechanisms involving dioxetane or perepoxide intermediates have been proposed but subsequently have been modified or withdrawn. Papers dealing with those aspects are cited in ref 1b.

(6) For the behavior of methyl olefins in ring-flexible octalin systems see (a) J. A. Marshall and A. R. Hochstetler, *J. Org. Chem.*, **31**, 1020 (1966); (b) J. A. Marshall, N. Cohen, and A. R. Hochstetler, *J. Amer. Chem. Soc.*, **88**, 3408 (1966); (c) Y. Kithara, T. Kato, T. Suzuki, S. Kanno, and M. Tanemura, *Chem. Commun.*, 342 (1969).

(7) (a) D. H. R. Barton, A. da S. Campos-Neves, and R. C. Cookson, *J. Chem. Soc.*, 3500 (1956); (b) C. Djerassi, N. Finch, R. C. Cookson, and C. W. Bird, *J. Amer. Chem. Soc.*, **82**, 5488 (1960).

(8) (a) L. Ruzicka, V. Prelog, and J. Batterjay, *Helv. Chim. Acta*, **31**, 1296 (1948); (b) M. W. Goldberg and H. Kirchensteiner, *ibid.*, **26**, 288 (1943); (c) E. T. Stiller and O. Rosenheim, *J. Chem. Soc.*, 353 (1938); (d) J. L. Beton, T. G. Halsall, E. R. H. Jones, and P. C. Phillips, *ibid.*, 753 (1957).

(9) We confirmed the position of the hydroxymethylene group in **1** by oxidation[10] to the known 2,3-seco diacid.

(10) A. Aebi, D. H. R. Barton, A. W. Burgstahler, and A. S. Lindsey, *J. Chem. Soc.*, 4659 (1954).

(11) B. Fuchs and H. J. E. Loewenthal, *Tetrahedron*, **11**, 199 (1960).

(12) (a) Y. Mazur and F. Sondheimer, *J. Amer. Chem. Soc.*, **80**, 5220 (1958); (b) J. A. Mills, *J. Chem. Soc.*, 4976 (1952).

CHART I

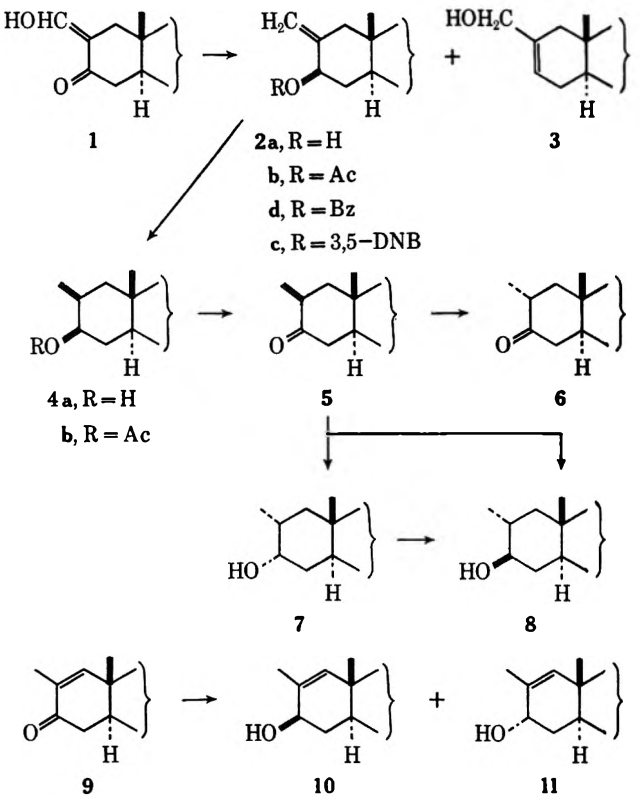
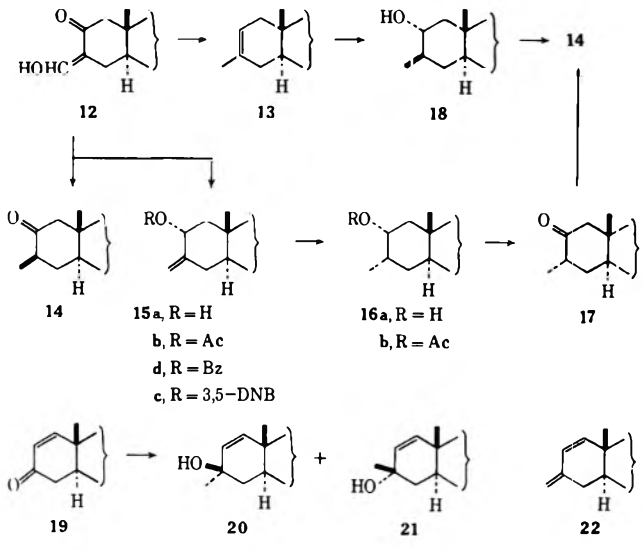


CHART II

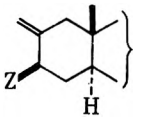


reduction of the known enone **9**.[7b,12a] The major product from our reduction was assigned the 3β-hydroxy structure **10** on the basis of nmr spectra and optical rotation considerations.[12b] Interestingly, when the isopropoxide reduction was run for longer periods, larger proportions of **10** were formed, indicating that equilibration favors **10**. This observation might be taken as further support for the quasiequatorial nature of the hydroxyl group; however, partial eclipsing by the vicinal methyl group could alter normal conformational preferences.

The preparation of allylic alcohols related to 3-methyl-5α-cholestane is shown in Chart II. Condensation of ethyl formate with 5α-cholestan-2-one afforded the hydroxymethylene derivative **12**, whose structure was proved by hydrogenation to a mixture of epimeric

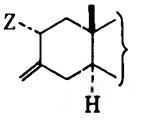
TABLE I

MOLECULAR ROTATIONS IN CHLOROFORM



2

Compd	Z	[φ][a]	Δ[φ]
	H	−19	
2a	OH	0	+19
2b	OAc	−80	−61
2c	OBz	−247	−228
2d	*O*-3,5-DNB[b]	−274	−255



15

	H	+96	
15a	OH	+112	+16
15b	OAc	−40	−136
15c	OBz[c]	−111	−207
15d	*O*-3,5-DNB	−155	−251

[a] [φ] = molecular rotation. [b] 3,5-DNB = 3,5-dinitrobenzoate. [c] Not obtained crystalline.

methyl ketones[13] followed by reduction with lithium aluminum hydride and dehydration to the known 3-methyl-5α-cholest-2-ene (**13**). Reduction of **12** with lithium aluminum hydride gave **15a** as well as a small amount of 3β-methyl-5α-cholestan-2-one (**14**).[14] Equatorial stereochemistry of the hydroxyl group in **15a** is supported as follows. Alcohol **15a** was readily converted into its esters **15b,c,d** and comparison of molecular rotation differences of these derivatives with the corresponding ones from the alcohol **2a** (Table I) shows striking similarities between the two series and indicates that the chirality of the two alcohols (**2a** and **15a**) is the same.[12b] Hydrogenation of the acetate **15b** in ethanol over platinum afforded a single compound **16b** in 80% yield. That **16b** possessed a 3α-methyl group was shown by lithium aluminum hydride reduction to the alcohol **16a** and oxidation to **17**,[14] which was separately isomerized to the more stable 3β-methyl ketone **14**. On the assumption that no epimerization of the acetate group occurs in the hydrogenation step steric considerations[15] are also consistent with the assigned stereochemistry of **15**. The C-3 methyl epimer **18** was prepared by hydroboration of **13**. Its structure follows from the known cis stereochemistry of such reactions[16] and by its oxidation to the ketone **14**.

The epimeric 3-hydroxy-3-methyl-5α-cholest-1-enes (**20** and **21**) were prepared by addition of methylmagnesium iodide to 5α-cholest-1-en-3-one (**19**). Assignment of stereochemistry to the hydroxyl groups in these compounds was based on their order of elution from alumina and on the considerable predominance of one isomer (**20**) in the reaction mixture, consistent

(13) H. J. Ringold, E. Batres, O. Halpern, and E. Necoechea, *J. Amer. Chem. Soc.*, **81**, 427 (1959).

(14) J. Hudec, Ph.D. Thesis, University of London, 1958.

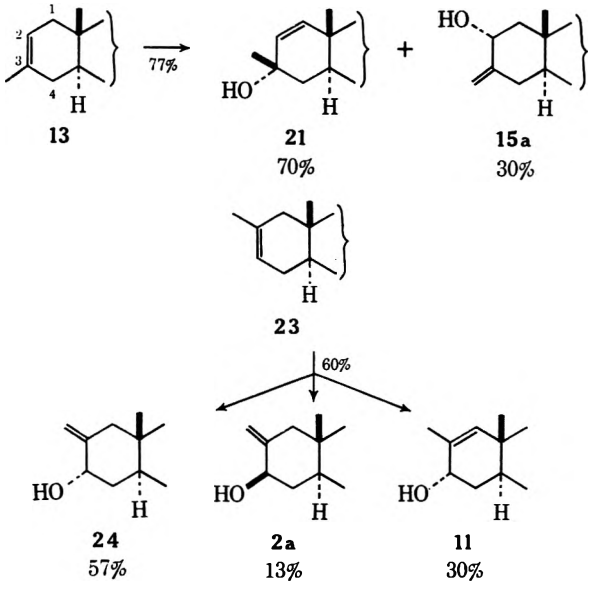
(15) As a model system the acetate **2b** was hydrogenated under the same conditions and afforded **4b** in 90% yield. Therefore, with **2b** and **15b** the hydrogen is delivered from the side opposite to that of the allylic substituent.

(16) H. C. Brown and G. Zweifel, *J. Amer. Chem. Soc.*, **83**, 2544 (1961).

with the expected preferential α attack of the Grignard reagent. When heated, both **20** and **21** were easily dehydrated to form a conjugated diene whose spectral data, hydrogenation behavior (see Experimental Section), and optical rotation indicated that it was largely **22**.[17]

Photooxygenations and Results.—Photooxygenations were conducted in pyridine solution with hematoporphyrin as sensitizer by methods described earlier.[4] The initially formed hydroperoxides were reduced directly to the corresponding alcohols with methanolic sodium iodide. The allylic alcohols were separated from small amounts of by-product by chromatography over alumina, and the mixtures were assayed by combinations of infrared and nmr spectroscopy and by optical rotations. The individual components of the mixtures were identified either spectroscopically or by isolation from the reaction mixtures. Chart III summarizes the results.

CHART III



Photooxygenation of 3-methyl-5α-cholest-2-ene (**13**) for 32 hr gave a mixture of allylic alcohols (77%) together with some ketonic material (6%). Assay of the alcohol mixture showed it to consist of **21** and **15a** in the ratio 7:3. Both alcohols were isolated and identified by comparison with our authentic samples. No evidence was found for the presence of 3-methylene-5α-cholestan-2β-ol (the epimer of of **15a**) in the reaction product. Similar photooxygenation of 2-methyl-5α-cholest-2-ene (**23**) for 19 hr afforded a mixture of allylic alcohols in *ca.* 60% yield as well as some ketonic (*ca.* 7%) and unidentified material (*ca.* 6%). The allylic alcohol mixture was composed of 2-methylene-5α-cholestan-3α-ol (**24**), **2a**, and **11** in the ratio 57:13:30, and chromatography of the mixture afforded pure samples of **24** and **2a**. The axial allylic alcohol **24** was identified by analytical and spectral data (infrared and nmr) and by its nonidentity with authentic **2a**.

(17) For properties of **22** and possible isomeric dienes see (a) H. Ziffer and C. H. Robinson, *Tetrahedron*, **24**, 5803 (1968); (b) F. Sondheimer and R. Mechoulam, *ibid.*, **79**, 5029 (1957); (c) O. C. Musgrave, *J. Chem. Soc.*, 3121 (1951); (d) N. F. Kucherova and M. I. Ushakov, *Zh. Obshch. Khim.*, **23**, 315 (1953); *Chem. Abstr.*, **48**, 2744*b* (1954).

Discussion

Previous work has shown that steric hindrance to C–O bond formation in the photosensitized oxygenation reaction is more important than hindrance to C–H bond cleavage,[4d] and additional support for that view has since appeared.[6a] For six-membered rings, there is a strong preference for quasiaxial (a′) hydrogen abstraction, since such hydrogens are better oriented for participation in a cyclic process than are quasiequatorial (e′) ones.[4] However, if the allylic hydrogen is located on a conformationally mobile methyl group, optimum geometric alignment of the C–H should be readily achievable, and therefore the behavior of methyl olefins permits evaluation of other factors in the cyclic process. The presumed ease with which a methyl group can orient a C–H bond optimally was invoked by Marshall and coworkers to explain the preferred formation of exocyclic olefins in photooxygenation of some 1,10-dimethyl-1(9)-octalins,[6a,b] and other workers have also observed preferences for methyl hydrogen involvement.[18] A distinctive feature in olefins **13** and **23** is that ring A can adopt only one half-chair conformation, and ambiguities that might arise from ring inversions are largely avoided.

In the case of **13** attack by activated oxygen from the β face of the steroid could in principle occur at three sites, *viz.*, (a) at C-3 with abstraction of the quasiequatorial (e′) β hydrogen at C-1; (b) at C-2 with abstraction of the quasiaxial β hydrogen at C-4; (c) at C-2 with abstraction of a hydrogen from the methyl group. That a did not occur was expected, because e′ hydrogens in half-chair rings cannot easily participate in the cyclic process. That b did not take place supports earlier findings[4c] that syn-axial interactions exerted by an angular methyl simultaneously on the developing C–O bond and on the allylic C–H bond can strongly retard oxygenation and reveals that, if there is any stereoelectronic factor favoring creation of a quasiaxial C–O bond, it is overshadowed here by the combination of these two adverse steric factors. That c did not occur is particularly significant, because it suggests that any stereoelectronic preference for axial C–O formation is even overridden by a single 1,3-diaxial interaction with the angular methyl group.

There are also three possibilities for α attack on olefin **13**. Only two of these were realized experimentally (*viz.* **21** and **15a** obtained in the ratio 7:3), and the absence of the third product is understandable because it requires the geometrically difficult abstraction of a quasiequatorial hydrogen from C-4. The preference for a product with an endocyclic rather than an exocyclic double bond is noteworthy but not surprising, since geometric and stereoelectronic factors act synergistically, and oxygen preferentially attacks the more substituted olefinic site.[19] More signifi-

(18) (a) G. O. Schenck, S. Schroeter, and G. Ohloff, *Chem. Ind.* (*London*), 459 (1962); (b) G. O. Schenck, H. Eggert, and W. Denk, *Justus Liebigs Ann. Chem.*, **584**, 177 (1953); (c) E. Klein and W. Rojahn, *Tetrahedron*, **21**, 2173 (1965).

(19) Other things equal, tertiary olefinic centers may be more susceptible to attack then secondary ones. For example, 2-methyl-2-butene gives approximately equal amounts of the two possible hydroperoxides despite a statistical factor that should favor oxygen attack at the less substituted carbon [(a) K. Gollnick and G. O. Schenck, *Pure Appl. Chem.*, **9**, 507 (1964); (b) ref 3, 6]. Statistical differences are virtually absent in **13** because all but the two types of attack observed are excluded on energetic grounds.

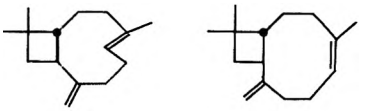
cantly, however, the exocyclic product has a quasi-equatorial OH (**15a**). Attack on the $CH_3C{=}C$ unit in the initial olefin from above and below the olefinic plane are *stereoelectronically* equivalent, and differences in allylic overlap (favoring axial C–O) develop only as the geometry approaches that of the final chair-like product.[20a] Therefore the degree of stereoelectronic control (*i.e.*, preference for axial C–O) reflects how far the transition-state geometry lies along the reaction coordinate. If orbital interaction between the new C–O bond and the π link were of paramount importance in a cyclic transition state that *resembles the allylic hydroperoxide*, the axial epimer of **15a** should have predominated over the equatorial epimer, in contrast to the experimental results. Evidently creation of an allylic axial C–O bond *per se* is not of paramount importance, and this finding implies a transition state that resembles starting olefin more than it does product.[20b] The oxygenation reaction contrasts with others where strong stereoelectronic preferences for axial have been observed in generation of allylic cyclohexenoid bonds, even in opposition to strong steric hindrance.[21]

Of the six possible oxygenation products from **23** (three from β attack and three from α attack) three were not expected on stereochemical and steric grounds. Thus β-oxygenation at C-2 was blocked by the angular methyl group (*cf.* behavior of **13**) and both α attack at C-2 and β attack at C-3 were precluded because these paths would involve quasiequatorial hydrogens. The remaining three possibilities fulfill the geometric requirements and lead to the observed products **24**, **2a**, and **11**. Product **2a** has an equatorial C–O bond and its formation supports the view that the cyclic transition state does not strongly prefer a geometry that stereoelectronically favors development of an axial C–O bond and further illustrates that an axial methyl group (at C-10) in a 1,4 relationship to an incipient C–O bond is not sterically prohibitive. The moderate predominance of the axial product **24** over **2a** could be due to an inherent steric preference for α attack along with a small stereoelectronic advantage.

The production of an appreciable proportion of **11** again shows that ring hydrogens can compete effectively with methyl hydrogens when geometric circumstances are favorable.

On the basis of our chemical evidence, we suggest that the geometry of the cyclic transition state in singlet oxygen reactions of monoolefins has more of the character of the starting olefin than of the final product, and that stereoelectronic preference for creation of an axial C–O bond is not an overriding factor. Although the chemical results say nothing about the extent of C–H bond breaking at the transition state, primary deuterium isotope effects have been found to be low ($k_H/k_D \sim 1.1$–2.4) and, along with the chemical evidence, point to a reactant-like transition state.[1b]

This picture of the transition state suggests that thermodynamic stability of the rearranged double bond should not provide a major driving force in the oxygenation. This expectation is borne out by the relative inertness of terminal open-chain olefins[21a,22] and of methylene cycloolefins such as methylenecyclopentane, methylenecyclohexane,[18c] 2-methylene-5α-cholestane, and 3-methylene-5α-cholestane (see Experimental Section). That double-bond stability plays but minor roles is also suggested by the only moderately faster rate of oxygenation (factor of *ca.* 5.8) of caryophyllene (**25**, strained trans endocyclic double bond) compared to its more stable isomer isocaryophyllene (**26**, cis double bond),[5a] although with these



25 26

isomers stereochemical and conformational differences preclude an unambiguous interpretation.[23]

A reactant-like transition state also clarifies why conformational ring inversion (which sometimes must accompany a double bond shift) does not block oxygenation,[4c,d] and why the susceptibility of the C–H to abstraction is not inherently related to whether it is primary, secondary, or tertiary.[3]

Experimental Section[24]

2-Hydroxymethylene-5α-cholestan-3-one (1) was prepared as described previously,[8a] mp 180.5–182°, $[\alpha]D$ +54° (*c* 1.14). Oxidation with alkaline hydrogen peroxide according to the method of Barton and coworkers[10] gave 2,3-seco-5α-cholestan-2,3-dioic acid, mp 195.5–196.5°, $[\alpha]D$ +30° (*c* 1.72) (reported[25] mp 196–197°, $[\alpha]D$ + 33°).

2-Methylene-5α-cholestan-3β-ol (**2a**).—2-Hydroxymethylene-5α-cholestan-3-one (1, 9.3 g) was reduced with lithium aluminum hydride (9.6 g) in refluxing ether (500 ml) for 1 week. Water and 15% sodium hydroxide solution[26] were added and the ethereal filtrate was separated, dried, and evaporated. Chromatography of the residue (7.9 g) over alumina (250 g) and crystallization from methanol afforded needles of 2-methylene-5α-cholestan-3β-ol (**2a**), mp 132.5–133° (5.1 g). Further crystallization from methanol gave the analytical sample: mp 134°; $[\alpha]D$ ±0° (*c* 2.37); ν 3610 (OH), 1653 (C=C), and 895 cm^{-1} (=CH_2).

(20) (a) We emphasize that these interpretations are based on normal half-chair → chair transformations. Presently there are no compelling reasons to invoke twist-boats. (b) The results of photosensitized oxygenations of monocyclic olefins such as carvomethene and limonene are understandable in these terms, although ring inversion involving more than one half-chair form limits the usefulness of those monocyclic systems for stereochemical conclusions. R. L. Kenney and G. S. Fisher, *J. Org. Chem.*, **28**, 3509 (1963); G. O. Schenck, K. Gollnick, G. Buchwald, S. Schroeter, and G. Ohloff, *Justus Liebigs Ann. Chem.*, **674**, 93 (1964); G. O. Schenck, O. A. Neumuller, G. Ohloff, and S. Schroeter, *ibid.*, **687**, 26 (1965).

(21) (a) G. Stork and S. D. Darling, *J. Amer. Chem. Soc.*, **82**, 1512 (1960); (b) G. Subrahmanyam, S. K. Malhotra, and H. J. Ringold, *ibid.*, **88**, 1332 (1966).

(22) K. R. Kopecky and H. J. Reich, *Can. J. Chem.*, **43**, 2265 (1965).

(23) (a) Photosensitized oxygenation of caryophyllene involves only the endocyclic olefinic link and gives mixtures of the expected products. Product identification was in progress in our laboratory but was discontinued when we learned that similar work had been carried out by K. H. Schulte Elte and G. Ohloff, *Helv. Chim. Acta*, **51**, 494 (1968). We are grateful to Dr. Ohloff for informing us of their work. (b) K. Gollnick and G. Schade, *Tetrahedron Lett.*, 689 (1968).

(24) Melting points are corrected and, unless stated otherwise, the following applies. Optical rotations were recorded at room temperature in chloroform solution with a sodium lamp light source. Ultraviolet spectra were taken in 95% ethanol and infrared spectra were recorded in chloroform. The light petroleum used (bp 40–60°) was distilled from potassium permanganate, the alumina for chromatography was obtained from Fisher Scientific Co. (Cat. No. A-540), and magnesium sulfate was the drying agent. Pyridine, acetic anhydride, and benzoyl chloride were distilled, and 3,5-dinitrobenzoyl chloride was crystallized from carbon tetrachloride. Sublimations were done at the high vacuum of an oil diffusion pump at temperatures 20–50° below the melting points of the compounds. Microanalyses were performed by Mr. Joseph Walter in this laboratory.

(25) B. Heath-Brown, I. M. Heilbron, and E. R. H. Jones, *J. Chem. Soc.*, 1482 (1940).

(26) V. M. Micovic and M. L. J. Mihailovic, *J. Org. Chem.*, **18**, 1190 (1953).

Anal. Calcd for $C_{28}H_{48}O$ (400.60): C, 83.93; H, 12.08. Found: C, 83.75; H, 12.18.

Concentration of the mother liquors afforded a 1:1 complex (1.4 g) of **2a** and **3** as plates, mp 155.5–156°, $[\alpha]D$ +28° (*c* 2.23). Separation of this complex by precipitation of **2a** with digitonin and regeneration afforded pure samples of **2a** and 2-hydroxymethyl-5α-cholest-2-ene (**3**): mp 141–141.5°; $[\alpha]D$ +61° (*c* 1.28); ν 3640 cm^{-1} (OH) (lit.[11] mp 140–142°; $[\alpha]D$ +63°). Acetylation of **3** afforded 2-acetoxymethyl-5α-cholest-2-ene, mp 80.5–81°, $[\alpha]D$ +54° (*c* 0.52) (lit.[11] mp 82–83°).

Derivatives of 2a.—Esterification of **2a** in the conventional manner in pyridine solution afforded 2-methylene-5α-cholestan-3β-yl acetate (**2b**), mp 106.5–107° (from methanol), $[\alpha]D$ −18° (*c* 2.41).

Anal. Calcd for $C_{30}H_{50}O_2$ (442.70): C, 81.39; H, 11.38. Found: C, 81.51; H, 11.42.

2-Methylene-5α-cholestan-3β-yl benzoate (**2c**) had mp 144.5–145° (from ether–methanol) and mp 143.5–144.5° after sublimation, $[\alpha]D$ −49° (*c* 2.06).

Anal. Calcd for $C_{35}H_{52}O_2$ (504.77): C, 83.28; H, 10.38. Found: C, 82.93; H, 10.48.

2-Methylene-5α-cholestan-3β-yl 3′,5′-dinitrobenzoate (**2d**) had mp 192.5–193° (from ether–methanol), $[\alpha]D$ −46° (*c* 1.88).

Anal. Calcd for $C_{35}H_{50}O_6N_2$ (594.78): C, 70.67; H, 8.47. Found: C, 70.81; H, 8.53.

Digitonide of 2a.—The alcohol **2a** formed an insoluble digitonide in 92% yield in ethanol.

3-Hydroxymethylene-5α-cholestan-2-one (**12**).—Hydroxymethylation of 5α-cholestan-2-one as described for 18a afforded an 89% yield of **12**, mp 127–128°. Crystallization from acetone gave yellow granules: mp 128–128.5°; $[\alpha]D$ +52° (*c* 2.40); ν 1645 (C=O) and 1590 cm^{-1} (C=C).

Anal. Calcd for $C_{28}H_{46}O_2$ (414.65): C, 81.10; H, 11.18. Found: C, 81.45; H, 11.28.

Conversion of 12 to 3-Methyl-5α-cholest-3-ene (**13**).—The hydroxymethylene ketone **12** (0.32 g) in methanol (50 ml) was hydrogenated for 24 hr over a 10% palladium on charcoal catalyst to give a solid saturated ketone (0.30 g) as evidenced by its infrared spectrum. Part of this ketone (0.120 g) was reduced with an excess of lithium aluminum hydride in refluxing ether for 4 hr, the excess of hydride was decomposed with acid, and the ether layer was separated, dried, and evaporated to an oily residue (infrared shows hydroxyl, but no carbonyl absorption). The oily residue (0.105 g) in pyridine (5 ml) was heated with phosphorus oxychloride (0.2 ml) on the steam bath for 1.5 hr, evaporated to dryness *in vacuo*, and dissolved in a mixture of ether and water. The ethereal layer was separated, dried, and evaporated and the residue in light petroleum was filtered through alumina and crystallized from ethyl acetate–methanol to give 3-methyl-5α-cholest-2-ene (**13**) (0.02 g), mp 80–81°, identical by melting point, mixture melting point, and infrared spectrum with an authentic sample.[7a] The mother liquors were evaporated and treated with acetic acid–perchloric acid on the steam bath for 1 hr and on work-up gave an additional 0.04 g of **13**.

3-Methyl-5α-cholest-2-ene (**13**).—This olefin was prepared by the method of Barton, *et al.*,[7a] mp 82–82.5°, $[\alpha]D$ +71 (*c* 3.90) [reported[7a] mp 82–83°, $[\alpha]D$ +74° (*c* 1.39)].

2-Methyl-5α-cholest-2-ene (**23**) prepared by a method previously described for **13** had mp 97.5–98°, $[\alpha]D$ +67° (*c* 3.09) [reported[11] mp 100–101°, $[\alpha]D$ +68° (*c* 1)].[11]

3-Methylene-5α-cholestan-2α-ol (**15a**).—The hydroxymethylene ketone **12** (7.2 g) was refluxed in ether (400 ml) with lithium aluminum hydride (7.7 g) for 1 week. The reaction mixture was worked up as for **2a** to give 6.45 g of a solid which was chromatographed over alumina (200 g). Elution with light petroleum–benzene (1:1–1:4) afforded **15a** (3.33 g), mp 107–111°. Recrystallization from methanol gave mp 113–114°; $[\alpha]D$ +28° (*c* 1.06); ν 3610 (OH), 1655 (C=C), and 895 cm^{-1} (=CH_2). The compound formed no precipitate with digitonin.

Anal. Calcd for $C_{28}H_{48}O$ (400.66): C, 83.93; H, 12.08. Found: C, 83.89; H, 12.08.

Elution of the column with light petroleum–benzene (2:1) afforded 3β-methyl-5α-cholestan-2-one (**14**) (0.70 g), crystallized from ether–methanol: mp 149–149.5°; $[\alpha]D$ +48° (*c* 1.54); ν (KBr) 1710 cm^{-1} (C=O). The reported values are mp 148–150°, $[\alpha]D$ +50°.[14]

Derivatives of 3-Methylene-5α-cholestan-2α-ol.—By conventional methods **15a** gave the following ester derivatives.

3-Methylene-5α-cholestan-2α-yl acetate (**15b**), crystallized from methanol, had mp 99.5–100.5°; $[\alpha]D$ −9° (*c* 2.04).

Anal. Calcd for $C_{30}H_{50}O_2$ (442.70): C, 81.39; H, 11.38. Found: C, 81.60; H, 11.49.

3-Methylene-5α-cholestan-2α-yl benzoate (**15c**) was oily: ν 1710 (C=O), 1655 (C=C), and 1275 cm^{-1} (C—O); $[\alpha]D$ −22° (*c* 2.88). Since the material was an oil, it may not be entirely pure.

3-Methylene-5α-cholestan-2α-yl 3′,5′-dinitrobenzoate (**15d**) from ether–methanol had mp 188–188.5°, $[\alpha]D$ −26° (*c* 1.90).

Anal. Calcd for $C_{35}H_{50}O_6N_2$ (594.78): C, 70.67; H, 8.47. Found: C, 70.75; H, 8.46.

2β-Methyl-5α-cholestan-3β-ol (**4a**).—Alcohol **2a** was recovered unchanged from attempted hydrogenation in ethanol containing a drop of 10% aqueous sodium hydroxide and a 10% palladium on carbon catalyst.

The alcohol (0.189 g) in ethanol (100 ml) containing 5 drops of 10% sodium hydroxide solution was hydrogenated over platinum oxide (0.018 g) for 24 hr. Evaporation and crystallization of the residue from methanol gave **4a**: mp 134–135°; $[\alpha]D$ +42° (*c* 2.12); ν 3750 (OH) and 1030 cm^{-1} (C—O) (lit.[7b] mp 121–124°, $[\alpha]D$ +27°).

Anal. Calcd for $C_{28}H_{50}O$ (402.68): C, 83.51; H, 12.52. Found: C, 83.60; H, 12.33.

With ethanolic digitonin **4a** gave an essentially quantitative precipitate of a digitonide. The alcohol gave the following derivatives by conventional methods.

2β-Methyl-5α-cholestan-3β-yl acetate (**4b**) had mp 109–109.5° (from ethanol), $[\alpha]D$ +37° (*c* 2.04).

Anal. Calcd for $C_{30}H_{52}O_2$ (444.72): C, 81.02; H, 11.79. Found: C, 80.59; H, 11.72.

2β-Methyl-5α-cholestan-3β-yl benzoate had mp 135.5–136° (from ethanol), $[\alpha]D$ +33° (*c* 2.41). Interestingly, the infrared spectrum showed two C=O bands (1712 and 1708 cm^{-1}).

Anal. Calcd for $C_{35}H_{54}O_2$ (506.78): C, 82.95; H, 10.74. Found: C, 83.18; H, 10.84.

2β-Methyl-5α-cholestan-3β-yl 3′,5′-dinitrobenzoate had mp 164.5–165° (from ethanol), $[\alpha]D$ +30° (*c* 1.51).

Anal. Calcd for $C_{35}H_{52}O_6N_2$ (596.78): C, 70.44; H, 8.78. Found: C, 70.40; H, 8.56.

2β-Methyl-5α-cholestan-3-one (**5**). **A. From Isomerization of 2a.**—Alcohol **2a** (0.20 g) in ethyl acetate (100 ml) was shaken for 12 hr in an atmosphere of hydrogen over a 10% palladium on carbon catalyst (0.04 g). Evaporation of the solvent and recrystallization of the residue from ether–methanol gave **5**: mp 98–99°; $[\alpha]D$ +122° (*c* 1.36); ν (KBr) 1715 cm^{-1} (C=O) (lit.[12] mp 96–97°, $[\alpha]D$ +86°).

Anal. Calcd for $C_{28}H_{48}O$ (400.66): C, 83.93; H, 12.08. Found: C, 84.22; H, 12.08.

B. By Oxidation of 4a.—Alcohol **4a** (0.020 g) in 6 drops of acetic acid was stirred with chromium trioxide (0.005 g) for 5 min at room temperature and then for 10 min at 60°. Dilution with water and extraction with ether afforded the ketone **5**, mp 96–97°, $[\alpha]D$ +111° (*c* 1.04). The infrared spectrum was identical with that of the product from method A.

Equilibration of 2-Methyl-5α-cholestan-3-one. A.—2β-Methyl-5α-cholestan-3-one (**5**) (0.0187 g, mp 98–99°, $[\alpha]D$ +122°) was refluxed overnight in 2 ml of chloroform saturated with hydrogen chloride. After evaporation, the residual solid had $[\alpha]D$ +39.8 ± 0.6° (*c* 2.72).

B.—2α-Methyl-5α-cholestan-3-one (**6**, 0.0228 g, mp 119–120.5°, $[\alpha]D$ +36°) was similarly treated and afforded material with $[\alpha]D$ +39.5 ± 0.7° (*c* 2.66). The infrared spectra of the materials from A and B were identical and the rotation corresponded to an equilibrium mixture containing 96% of **6**.

Hydrogenation of 2β-Methyl-5α-cholestan-3-one (**5**).—The ketone (0.016 g) in ethanol (5 ml) containing a trace of 10% aqueous sodium hydroxide solution was hydrogenated for 12 hr over platinum oxide (0.006 g). The product after evaporation of the solvent was recrystallized from ether–methanol to give 2α-methyl-5α-cholestan-3β-ol (**8**), 0.005 g, mp 137–138°, ν 3590 cm^{-1} (OH) (lit.[12] mp 139–140°).

The crude reduction product from a larger run (0.046 g) was treated with ethanolic digitonin solution. The precipitated digitonide was filtered off and the filtrate was evaporated to dryness. Ether extraction of the residue afforded 2α-methyl-5α-cholestan-3α-ol (**7**, 0.032 g, 69%). The digitonide was dissolved in pyridine and an excess of ether was added to precipitate the digitonin. Filtration and evaporation afforded 0.012 g (26%) of 2α-methyl-5α-cholestan-3β-ol (**8**).

2-Methyl-5α-cholest-1-en-3-one (**9**), prepared by the method of Djerassi, *et al.*,[7b] had mp 74–76° (lit. mp 75–76°).

Reduction of Enone 9. A. With Aluminum Isopropoxide.—The enone (0.285 g) in dry isopropyl alcohol was heated at 88° for 8 hr with freshly distilled aluminum isopropoxide (4.5 g). After an additional 8 hr at room temperature, the mixture was poured into water and 25 ml of 6 *N* sodium hydroxide was added to dissolve the aluminum salts. Ether extraction afforded a gum (0.281 g, ν 994 cm^{-1}) which was chromatographed over alumina (15 g). Elution with hexane–ether (49:1), gave unchanged enone (0.037 g), mp 74–77° after one crystallization from methanol. Further elution with the same solvent afforded 2-methyl-5α-cholest-1-en-3α-ol (**11**) as an oil (0.067 g). Rechromatography over alumina and extensive drying (10 days under vacuum at 40–50°) afforded a crystalline sample: mp 90–92° (did not clear); $[\alpha]D$ −4° (*c* 2.85); ν 3580 (OH) and 994 cm^{-1}; δ 5.72 (H at C-1), 3.87 (broad H at C-3), and 0.77 ppm (methyl at C-2).

Anal. Calcd for $C_{28}H_{48}O$ (400.66): C, 83.93; H, 12.08. Found: C, 83.51; H, 11.90.

Further elution of the column with hexane–ether (19:1) afforded 2-methyl-5α-cholest-1-en-3β-ol (**10**, 0.121 g) as plates from methanol: mp 122–123°; $[\alpha]D$ +28° (*c* 2.5); ν 3600 (OH) and 1011 cm^{-1} (C—O); δ 5.63 (H at C-1) and 4.08 ppm (broad, H at C-3).

Anal. Calcd for $C_{28}H_{48}O$ (400.66): C, 83.93; H, 12.08. Found: C, 83.94; H, 12.11.

The alcohol formed a precipitate with ethanolic digitonin solution.

B. With Sodium Borohydride.—Enone **9** (0.062 g) in methanol (20 ml) was reduced with sodium borohydride. The crude product contained less than 10% of **11** by infrared inspection at 994 cm^{-1}. Crystallization from methanol afforded **10**, mp 118–120°.

C. With Lithium Aluminum Hydride.—The enone (0.021 g) in dry ether (2 ml) was treated with lithium aluminum hydride (0.015 g) at room temperature. After 1 min the excess of hydride was destroyed with ethyl acetate and the product was isolated as a gum. Infrared inspection indicated the presence of less than 10% of alcohol **11**. Recrystallization afforded **10**, mp 120.5–122°.

Hydrogenation of 3-Methylene-5α-cholestan-2α-yl Acetate (15b).—The acetate (0.050 g) in ethanol (20 ml) was hydrogenated over platinum oxide (0.006 g) for 22 hr. Filtration, evaporation, and crystallization from ether–methanol gave 3α-methyl-5α-cholestan-2α-yl acetate (**16b**) (0.028 g): mp 108–110°, raised to 112.5–113° after two recrystallizations; $[\alpha]D$ +18° (*c* 1.48); ν (KBr) 1740 (C=O), 1243 (sp^2 C—O), and 1026 cm^{-1} (sp^3 C—O).

Anal. Calcd for $C_{30}H_{52}O_2$ (444.72): C, 81.02; H, 11.79. Found: C, 81.13; H, 11.59.

3α-Methyl-5α-cholestan-2α-ol (16a).—Acetate **16b** (0.053 g) in ether (10 ml) was treated with lithium aluminum hydride for 5 hr. After work-up[26] the residue was crystallized from acetone: 0.032 g; mp 100–100.5°; ν 3600 (OH) and 1031 cm^{-1} (C—O). Further recrystallization from acetone gave pure **16a**, mp 101.5–102°, $[\alpha]D$ +42° (*c* 1.47). Esterification in pyridine afforded the 3,5-dinitrobenzoate **16c**, mp 188–189° from ether–methanol, $[\alpha]D$ +20° (*c* 1.38).

Anal. Calcd for $C_{35}H_{52}O_6N_2$ (596.78): C, 70.44; H, 8.78. Found: C, 70.76; H, 8.98.

3β-Methyl-5α-cholestan-2α-ol (18) To a slurry of lithium aluminum hydride (0.64 g) in ether (25 ml) was slowly added a solution of the olefin **13** (2.00 g) in ether (80 ml) containing boron trifluoride etherate (3.00 g). The mixture was stirred at room temperature in a nitrogen atmosphere for 2 hr. Saturated aqueous sodium sulfate (15 ml) was added to destroy the excess of hydride, followed by solid sulfate to dry the ether phase. The solids were removed by filtration and the solution was evaporated to an oily residue, which was dissolved in tetrahydrofuran (10 ml) and treated successively with 15% aqueous sodium hydroxide (0.5 ml) and 30% hydrogen peroxide (0.5 ml). After several minutes on the steam bath, the solution was treated with water (15 ml) and the product was obtained by ether extraction (1.82 g). Chromatography over alumina and elution with benzene–ether (9:1) afforded the crude alcohol (0.85 g). Recrystallizations from ether–methanol gave pure **18**: mp 114.5–115°; $[\alpha]D$ + 18° (*c* 1.84); ν 3580 (OH) and 1024 cm^{-1} (C—O).

Anal. Calcd for $C_{28}H_{50}O$ (402.68): C, 83.51; H, 12.52. Found: C, 83.85; H, 12.19.

Acetylation gave an acetate, mp 106.5–107° from ether–methanol, $[\alpha]D$ −38° (*c* 0.75).

Anal. Calcd for $C_{30}H_{52}O_2$ (444.72): C, 81.02; H, 11.79. Found: C, 80.92; H, 11.69.

Esterification with 3,5-dinitrobenzoyl chloride gave a 3,5-dinitrobenzoate, mp 200–201° (from ether–methanol), $[\alpha]D$ −24° (*c* 1.18).

Anal. Calcd for $C_{35}H_{52}O_6N_2$ (596.78): C, 70.44; H, 8.78. Found: C, 70.47; H, 8.72.

3α-Methyl-5α-cholestan-2-one (17).—Chromium trioxide–acetic acid oxidation of alcohol **16a** (0.025 g) gave the crude ketone, 0.019 g, mp 115–118°. Two recrystallizations from methanol gave pure **17**, mp 124.5–125.5°, $[\alpha]D$ +76° (*c* 0.37). The reported values are mp 116–118°, $[\alpha]D$ +70° (*c* 0.40).[14]

Acid equilibration (sulfuric acid–ethanol) of ketone **17** (0.005 g) gave the epimeric ketone **14** (0.003 g), mp 144.5–146.5°, which showed no melting point depression on admixture with an authentic sample of **14**.

Oxidation of Alcohol 18.—Chromium trioxide–acetic acid oxidation of alcohol **18** (0.020 g) afforded a crude ketone (0.015 g), mp 142–143°. Recrystallization from ether–methanol gave **14** (0.010 g), mp 148.5–149.5°, $[\alpha]D$ +45° (*c* 1.06).

Addition of Methylmagnesium Iodide to Enone 19.—To a stirred solution of methylmagnesium iodide (from 0.189 g of magnesium) in tetrahydrofuran (25 ml) at 0–5° was slowly added a solution of enone **19** (2.35 g) in tetrahydrofuran (30 ml). The mixture was warmed to 35° for 13 hr, then cooled to −10° and treated with 50 ml of cold 10% ammonium chloride solution. Extraction with ether afforded a crystalline solid, 2.19 g, mp 145–148°. One crystallization from methanol gave 3α-methyl-5α-cholest-1-en-3β-ol (**20**): 1.08 g; mp 155.5–157.5°, raised to 157–158.5° by further crystallization; $[\alpha]D$ +32° (*c* 0.83); ν 3620 (OH), 1642 (C=C), 1022 (C—O), and 758 cm^{-1} (CH=CH–). The compound gave no precipitate with digitonin.

Anal. Calcd for $C_{28}H_{48}O$ (400.86): C, 83.93; H, 12.08. Found: C, 84.20; H, 11.74.

The mother liquors from the reaction were evaporated and the residue was chromatographed over alumina. Elution with hexane–ether (100:1–50:1) gave a crystalline solid (0.22 g) which was rechromatographed and recrystallized from acetone to give 3β-methyl-5α-cholest-1-en-3α-ol (**21**) as plates, mp 102–103°, $[\alpha]D$ +4° (*c* 0.25). The compound gave no precipitate with digitonin and was identical (melting point, mixture melting point, and infrared spectrum) with the material obtained from the photosensitized oxygenation of olefin **13**. Further elution with hexane–ether (97:3) afforded more of the 3β-hydroxy compound (0.54 g).

3-Methylene-5α-cholest-1-ene (22).—Sublimation of alcohol **21** at 60° under vacuum afforded crude diene **22**, mp 82–82.5°. The same compound was formed during attempted chromatography of **21** over basic alumina (Woelm, activity I) or on activated silica gel (W. R. Grace, desiccant grade). Sublimation of the epimeric alcohol **20** at 130–140° also afforded crude **22**. Crystallization from ethyl acetate–methanol gave the diene **22**: mp 84–84.5°; $[\alpha]D$ +62° (*c* 1.45); λ 236 nm (ϵ 14,150); ν (KBr) 1738, 869 (C=CH_2), and 1625, 1588 cm^{-1} (conjugated C=C). In view of the low molar absorptivity and the value of $[\alpha]D$, the sample probably contains an isomeric impurity, which may be the unreported 3-methyl-5α-cholesta-1,3-diene.

Anal. Calcd for $C_{28}H_{46}$ (382.68): C, 87.88; H, 12.12. Found: C, 88.00, 87.98; H, 12.09, 12.18.

Hydrogenation of Diene 22.—The diene (0.011 g) in ethyl acetate–acetic acid (1:1, 6 ml) was hydrogenated over platinum oxide (0.020 g). A total of 2.0 mol of hydrogen was taken up in 40 min and the product was isolated by filtration and evaporation of the solvent. Crystallization from ethyl acetate–methanol afforded 3β-methyl-5α-cholestane, identified by melting point (105–106°) and mixture melting point with an authentic sample.

Photosensitized Oxygenation of 2-Methyl-5α-cholest-2-ene (23).—Oxygenations were conducted according to the general methods described previously.[4] A pyridine solution (50 ml) of olefin **23** (0.80 g) was irradiated and oxygenated in the presence of hematoporphyrin (0.013 g) for 19 hr. The solution was diluted with ether, decolorized with Norit-A charcoal, and evaporated. The residue was taken up in methanol (40 ml), sodium iodide (4 g) was added, and the solution was allowed to stand overnight. After evaporation of the solvent the residue was taken up in ether, washed with 5% sodium thiosulfate solu-

tion and with water, and dried and evaporated to a gum, which was chromatographed over alumina (30 g). Elution with hexane gave unidentified oily material (0.049 g). Elution with hexane–ether (199:1, 99:1) gave oily ketonic material (ν 1720, 1680 cm^{-1}) and further hexane–ether (97:3, 20:1) elution gave a mixture of hydroxy compounds (0.488 g), $[\alpha]D$ +27° (*c* 5.45). Most of this mixture (0.434 g) was rechromatographed over alumina (20 g). Elution with hexane–ether (97:3) gave 13 fractions (0.342 g) composed of mixtures of 2-methylene-5α-cholestan-3α-ol (**24**) and alcohol **11** identified by infrared and nmr measurements. Recrystallization of this material from acetone afforded 2-methylene-5α-cholestan-3α-ol (**24**) (0.076 g): mp 116–120°, raised by further recrystallization to 127–128° (0.033 g); $[\alpha]D$ +35° (*c* 0.7); ν 3560 (OH), 1647 (C=C), 902, and 705 cm^{-1}; δ 4.90 and 4.75 (=CH_2), 4.23 (C-3 H), and 2.08 ppm (OH).

Anal. Calcd for $C_{28}H_{48}O$ (400.66): C, 83.93; H, 12.08. Found: C, 84.10; H, 12.01.

Further elution with hexane–ether (24:1 and 20:1) gave mixtures of alcohols **24**, **11**, and **2a**. These combined fractions were recrystallized from methanol and gave a sharp-melting compound, mp 150.5–151.5°, $[\alpha]D$ +11° (*c* 1.30). Infrared analysis indicated that this compound was a complex (*ca.* 1:1) of **24** and **2a**.

Anal. Calcd for $C_{28}H_{48}O$ (400.66): C, 83.93; H, 12.08. Found: C, 83.90; H, 12.12.

Final elution with hexane–ether (47:3 and 9:1) gave alcohol **2a** (0.015 g) identified by melting point (132–133°), mixture melting point, and infrared spectrum.

Assay of the alcohol mixtures by quantitative infrared, nmr, and optical rotation indicated that the alcohols **24**, **2a**, and **11** were formed in the ratio of 57:13:30, respectively. The corrected total yield was 60%.

Photosensitized Oxygenation of 3-Methyl-5α-cholest-2-ene (13).—A pyridine solution (180 ml) of olefin **13** (3.00 g) was irradiated and oxygenated in the presence of hematoporphyrin (0.050 g). After 32 hr, the starting olefin was completely consumed and the reaction mixture was worked up as in the preceding experiment to give a light brown gum (3.1 g), which was chromatographed over alumina (90 g).[27] Elution with hexane and hexane–ether (99:1 to 97:1) afforded several oily fractions (0.170 g). Further elution with hexane–ether (9:1 to 7:3) gave a mixture of alcohols **15a** and **21**, 2.40 g, $[\alpha]D$ +18.6° (*c* 4.806). Rechromatography of most (2.18 g) of this material over alumina followed by several crystallizations from acetone afforded **21**: mp 107–108°; $[\alpha]D$ +9° (*c* 3.34); ν 3571 (OH), 1642 (C=C), 1034 (C—O), 898, and 762 cm^{-1}. This sample was identical with authentic **21** (infrared, mixture melting point). For analysis the sample was dried *in vacuo* for 2 days at room temperature.

Anal. Calcd for $C_{28}H_{48}O$ (400.66): C, 83.93; H, 12.08. Found: C, 84.02; H, 11.72.

Assay of the alcohol mixture by quantitative infrared and comparison with synthetic mixtures established that **21** and **15a** were formed in the ratio of *ca.* 70:30, respectively, and in a corrected total yield of 77%.

Attempted Photosensitized Oxygenations of 2-Methylene- and 3-Methylene-5α-cholestane.—Pyridine solutions (40 ml) of each olefin (0.1 g) were separately irradiated and oxygenated in the presence of hematoporphyrin (0.008 g) with additional dye (0.004 g) being added after 75 hr. Infrared examination of aliquots showed no evidence of hydroperoxide formation and work-up at the end of 100 hr gave only the starting olefins.

Registry No.—**2a**, 22599-96-8; **2b**, 37392-80-6; **2c**, 22599-97-9; **2d**, 37392-82-8; **4a**, 20997-60-8; **4b**, 37163-88-5; **4** (R = COPh), 37163-89-6; **4** (R = 3′,5′-dinitrobenzoate), 37406-79-4; **5**, 14528-10-0; **6**, 2097-78-1; **10**, 22599-98-0; **11**, 22599-94-6; **12**, 37392-87-3; **15a**, 37392-88-4; **15b**, 37392-89-5; **15c**, 37392-90-8; **15d**, 37413-07-3; **16a**, 37392-91-9; **16b**, 37392-92-0; **16c**, 37392-93-1; **18**, 37392-94-2; **18** acetate, 37392-95-3; **18** 3,5-dinitrobenzoate, 37392-96-4; **20**, 37392-97-5; **21**, 37392-98-6; **22**, 21152-07-8; **24**, 22599-92-4.

(27) Chromatography over activated silica gel gave diene **22** along with unidentified material.

Syntheses in the Noradamantane Series

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Preparations of several derivatives of noradamantane, including 1- and 2-noradamantanols, 1-bromonoradamantane, and noradamantane-1-carboxylic acid, are described. The reaction of deltacyclane (tetracyclo[4.3.0.$0^{2,4}$.$0^{3,7}$]nonane) with sulfuric acid is shown to lead to either 1- or 2-noradamantanol or noradamantane, depending on conditions. Other compounds, such as *exo*-2-brendanol and oxaadamantane, are also found in the reaction mixtures. Reaction pathways leading to the various products are discussed.

Investigations of the chemistry of adamantane (**1**) have been abetted considerably by the ease and simplicity of direct functionalization of the parent hydrocarbon.[1] Ionic substitutions, *e.g.*, bromination[2] and Koch–Haaf carboxylation,[3] give bridgehead products cleanly.[1] Adamantanone and several disubstituted adamantanes can be obtained by sulfuric acid oxidation of **1** under a variety of conditions.[4] Even nonselective substitution reactions, such as free-radical halogenations,[1] can be synthetically useful because of the high symmetry of adamantane, which limits the number of monosubstituted isomers to two.

Noradamantane (**2**),[5] only a single methylene removed from adamantane (**1**), behaves quite differently. Ring contraction decreases bridgehead reactivity at

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(5) (a) B. R. Vogt and J. R. E. Hoover, *Tetrahedron Lett.*, 2841 (1967); (b) P. v. R. Schleyer and E. Wiskott, *ibid.*, 2845 (1967); (c) A. Nickon, G. D. Pandit, and R. O. Williams, *ibid.*, 2851 (1967).

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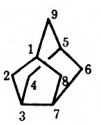
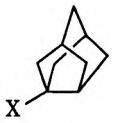


2



3, X = COOH
4, X = $COCH_3$
5, X = OH

both the 1 and 3 positions of 2 substantially,[6] and, as will be shown here, ionic substitutions of 2 are not useful synthetic methods. Furthermore, because of the lower symmetry, five monosubstituted noradamantane isomers are possible; photohalogenation of 2 gives complex mixtures.[7]

Most of the known noradamantane derivatives have been prepared by synthetic sequences starting from adamantane precursors.[1b,c] Vogt and Hoover[5a] obtained 3-noradamantanecarboxylic acid (3) by Favorskii ring contraction. An ingenious two-step oxidative cleavage–cyclization sequence makes 3-noradamantyl methyl ketone (4) readily available from 2-methyl-1-adamantanol.[8] Baeyer–Villiger oxidation of 4 gives 3-noradamantanol (5) *via* its acetate.[9,10]

Deltacyclene (tetracyclo[4.3.0.$0^{2,4}$.$0^{3,7}$]non-8-ene, 6)[11] or, more specifically its hydrogenation products, deltacyclane (7)[5c,12] and brexane (8),[5b,12] serve as alternative starting materials. With aluminum halide catalysts, 8 gives noradamantane (2).[5b] Deltacyclane (7) has been reported to react with sulfuric acid to yield the equatorial 2-noradamantanol (9).[5c] We have now found that this deltacyclane–sulfuric acid system, which is in fact quite complex, can also be used to prepare 1-noradamantanol (10) and even noradamantane itself in satisfactory yields by appropriate modification of the reaction conditions. As by-products, two alcohols, 2-exobrendanol (11)[12] and *epi*-2-noradamantanol (the epimer of 9),[5c] are formed in very small amounts. The major side-product (up to 10% yield), oxaadamantane (12),[13] was quite unexpected. In addition, if formic acid is added to the deltacyclane–sulfuric acid system, 1-noradamantanecarboxylic acid (13) can be obtained, but the yield is poor. (Attempts to prepare 13 *via* a Koch–Haaf reaction[3] directly on noradamantane (2) were unsuccessful.) Scheme I summarizes these reactions.

The procedure originally reported[5c] involved the addition of a dilute pentane solution of 7 to 96% sulfuric acid at about −3°, followed rapidly by a hydrolytic work-up to give 9 in 80% yield. We have now found that longer reaction times, increased initial concentration of deltacyclane, higher temperatures, or stronger acid favor the formation of tertiary alcohol 10 and diminish the proportion of 9. Table I illustrates the course of a reaction in which 7 was added to 96% H_2SO_4 kept at about −3°. Under these conditions 2-noradamantanol (9), probably present as its sulfate ester, rearranges moderately rapidly to the more stable 1-noradamantanol (10) or its sulfate. If deltacyclane is added at 25° to 99% sulfuric acid and the mixture is hydrolyzed after only 3 min, 1-noradamantanol (10) is the major component (80%) of the product. If an excess of pentane is used as a hydride transfer agent, up to 50% of noradamantane (2) can be isolated in pure form. Carbon monoxide (from the dehydration of formic acid) can also trap the 1-noradamantyl cation (16) to give 13, but this is less efficient.

Resistance to oxidation and the lack of CHOH pmr absorption reveal the tertiary nature of 1-noradamantanol (10). The spectral and physical properties of 10 (mp 224.5–225°, tosylate mp 65.8–66.4°) differ from those of 3-noradamantanol (mp 250–251°, tosylate mp 45–46.7°).[9] Phosphorus tribromide converted 10 to 1-bromonoradamantane (14), and the

SCHEME I

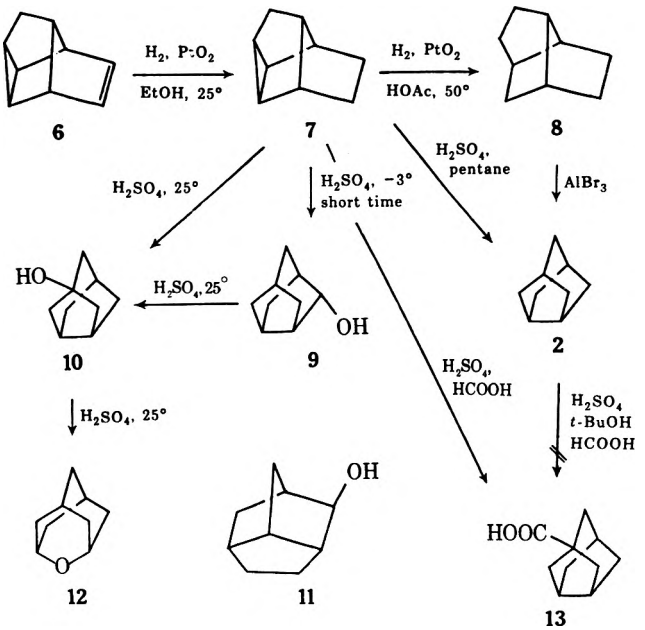


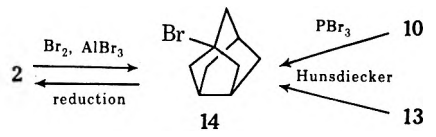
TABLE I

SULFURIC ACID TREATMENT OF DELTACYCLANE (7)[a]

		Noradamantanols,[b] relative %	
Aliquot	Time, min	9	10
1	0	87	13
2	1	77	23
3	5	64	36
4	11	49	51
5	20	35	65
6	40	23	77
7	60	21	79
8	90	16	84
9	600	12	88

[a] Deltacyclane (0.18 ml) added to 5 ml of 96% H_2SO_4 and kept at about −3°. [b] Relative percentages were determined by glpc. The two noradamantanols 9 and 10 constituted *ca.* 90% of the product extractable with ether. The other components and their ratios varied with time and included noradamantane (2), 2-*exo*-brendanol (11), 2-*epi*-noradamantanol (*epi*-9), and oxaadamantane (12), as well as some unreacted deltacyclane.

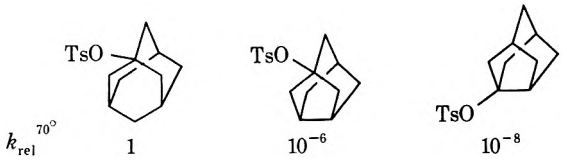
(6) R. C. Bingham and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **93**, 3189 (1971).
(7) J. S. Wishnok, unpublished observations.
(8) R. M. Black and G. B. Gill, *Chem. Commun.*, 972 (1970).
(9) E. M. Engler, unpublished observations, Princeton University. See ref 10.
(10) W. D. Graham and P. v. R. Schleyer, *Tetrahedron Lett.*, 1179 (1972).
(11) L. G. Cannell, *ibid.*, 5967 (1966); J. J. Mrowca and T. J. Katz, *J. Amer. Chem. Soc.*, **88**, 4012 (1966); T. J. Katz, J. C. Carnahan, Jr., and R. Boeke, *J. Org. Chem.*, **32**, 1301 (1967).
(12) A. Nickon, H. Kwasnik, T. Swartz, R. O. Williams, and J. B. Digiorgio, *J. Amer. Chem. Soc.*, **87**, 1613, 1615 (1965).
(13) (a) H. Stetter and P. Tacke, *Ber.*, **96**, 694 (1963); (b) M. Fisch, S. Smallcombe, J. C. Gramain, M. A. McKervey, and J. E. Anderson, *J. Org. Chem.*, **35**, 1886 (1970); (c) R. M. Black, G. B. Gill, and D. Hands, *Chem. Commun.*, 311 (1972).



same bromide was obtained by the Hunsdiecker reaction of 1-noradamantanecarboxylic acid (**13**) (mp 94–96°); the reported melting points for the isomer **3** are 106–107°[5a] and 107–108°[8]). Reduction of **14** with either sodium and *tert*-butyl alcohol in tetrahydrofuran or by tributyltin hydride gave noradamantane (**2**). These reactions constitute structure proofs for **10**, **13**, and **14**. Spectral evidence provided support.

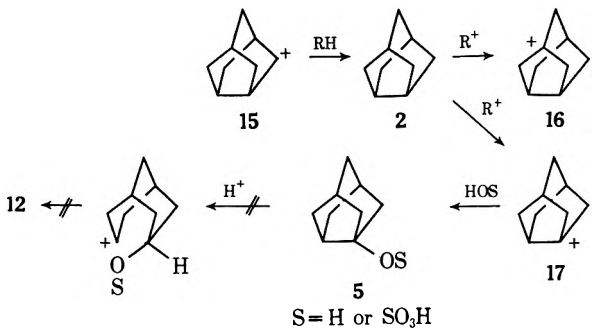
Direct ionic substitutions of noradamantane do not appear to be useful methods for the preparation of noradamantane derivatives. Sulfuric acid does not attack the hydrocarbon at room temperature, and only decomposition products result from the treatment of noradamantane with sulfuric acid at 80–90°. The failure of Koch–Haaf carboxylation of **2** has already been noted. Direct ionic bromination occurred only in the presence of the strong catalyst $AlBr_3$. At least three products were formed, and the major product, 1-noradamantyl bromide (**14**, less than 20% yield), required purification by preparative glpc. Noradamantane does not behave like adamantane.

This difference can be understood when one considers that the reactivity of both of the bridgehead positions of noradamantane are very much reduced relative to that of adamantane.[6] The acetolysis of 1-noradamantyl tosylate was studied here: k_1 (100.0°) = 8.14×10^{-6} sec^{-1}, k_1 (125.0°) = 8.5×10^{-5} sec^{-1}; $\Delta H^{\pm}$ = 27.0 kcal/mol, $\Delta S^{\pm}$ = 10 eu. Relative acetolysis rates at 70° are shown below, and provide quantitative comparison.[6,9,14]



The acid-catalyzed opening of the three-membered ring of deltacyclane (**7**) in carboxylic acid solution gives brexyl and brendyl products.[5c] In sulfuric acid, however, further rearrangement to the 2-noradamantyl cation (**15**) occurs. As in the adamantyl series,[15] the rearrangement of **15** to the 1-noradamantyl cation (**16**) is undoubtedly intramolecular and proceeds *via* noradamantane (**2**) which is always found as a by-product in these reactions. When an additional hydride source, such as pentane, is present, reduction becomes the predominant reaction course. Despite the modest yields, this is an attractive method for the preparation of noradamantane because of the experimental simplicity.[16]

The greater stability of the 1-noradamantyl (**16**) over the 3-noradamantyl cation (**17**), as revealed by the 100-fold difference in the tosylate solvolysis rates, helps explain why 1-noradamantyl and not 3-noradamantyl products are found in the reactions described. The interesting possibility also exists that 3-noradamantanol (**5**) or its sulfate ester is not stable in concentrated sulfuric acid, but suffers "wrong way" C_3–C_7 protolytic cleavage (*i.e.*, carbon protonation rather than oxygen protonation) with eventual production of oxaadamantane (**13**) as shown above. Recent experiments, however, indicate that 3-noradamantanol (**5**, S = H) is not converted readily to **12**, although partial conversion of **10** to **12** has been achieved in reaction in 96% H_2SO_4 at room temperature (Scheme I). The scope and mechanism of oxaadamantane formation are under investigation.



Experimental Section

Deltacyclane (7).—Twenty-five grams of tetracyclo[4.3.0.0^{2,4}.0^{3,7}]non-8-ene (**6**)[11] in 60 ml of 95% EtOH was hydrogenated at 25° in a Parr apparatus with PtO_2 catalyst. Initial H_2 pressure was 57 psi. The yield of deltacyclane[12] was quantitative.

1-Noradamantanol (10).—Deltacyclane (1.2 g) was added dropwise to a mixture of sulfuric acid (Baker analyzed, 97%, 36 ml) and fuming sulfuric acid (15% oleum, Baker Analar, 4 ml) at room temperature over a period of 1 min. The mixture was stirred at room temperature for 3 min and then poured over crushed ice (200 g). When the ice had melted, the solution was extracted with ether (2 × 50 ml) and the ether solution was washed with sodium bicarbonate and water. The acidic water phase together with the washings were refluxed and stirred for 4 hr to ensure hydrolysis of all sulfate esters. The mixture was reextracted with ether and the ether extracts were washed as before and dried over $MgSO_4$. Gas chromatographic analysis (SE-30) showed the presence of **10** (80%), **9** (~7%), oxaadamantane (**12**)[13] (~10%), and other minor components (~3%). The ether solution was evaporated carefully and the residue was sublimed to give 1.06 g of crude product, which was purified by chromatography on alumina (50 g of Woelm neutral; grade III made by addition of 5% w/w water). The elution was carried out with pentane and pentane–ether. Oxaadamantane was eluted with 5% ether, **9** was eluted with 15–20% ether, and **10** was eluted with 30% ether. Pure **10** was obtained after rechromatography on alumina, followed by two recrystallizations from pentane, and sublimation: mp (sealed capillary) 224.5–225°; ir (CCl_4) ν 3581, 1155, 1116, 1072, 1024 cm^{-1}; nmr ($CDCl_3$) δ 1.5 (6 H, s with shoulder), 1.76 (4 H, s, broad shoulder), 2.37 (3 H, broad peak, $W_{1/2}$ = 14 Hz, 2.9 (1 H, s).

Anal. Calcd for $C_9H_{14}O$ (138.20): C, 78.21; H, 10.21. Found: C, 78.50; H, 10.33.

1-Noradamantanol (**10**) could not be oxidized with chromic acid in pyridine, in acetic acid, or in acetone. This alcohol (10 mg) in ether (0.5 ml) was added to 96% H_2SO_4 (10 ml) and the pale yellow solution was stirred for 3 hr at room temperature. After pouring onto ice and conventional work-up, glpc analysis of the product mixture showed starting alcohol **10** and *ca.* 10% of a component with the same retention time as that of oxaadamantane (**12**).

1-Noradamantyl Tosylate.—Tosylation of **10** was achieved by the usual pyridine method.[17] Acetolysis rates were determined

(14) Solvolysis rates of 1-noradamantyl triflate: R. C. Bingham, W. F. Sliwinski, and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **92**, 3471 (1970).

(15) P. v. R. Schleyer, L. K. M. Lam, D. J. Raber, J. L. Fry, M. A. McKervey, J. R. Alford, B. D. Cuddy, V. G. Keizer, H. W. Geluck, and J. L. M. A. Schlatmann, *ibid.*, **92**, 5246 (1970). Also see P. Vogel, M. Saunders, W. Thielecke, and P. v. R. Schleyer, *Tetrahedron Lett.*, 1429 (1971).

(16) This method has also been found useful for the preparation of other cage hydrocarbons such as homoadamantane and substituted adamantanes: J. S. Wishnok, S. H. Liggero, and W. D. Graham, unpublished results, Princeton University. For a published example, see ref 10.

(17) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, p 1179f.

by standard techniques.[6] The analytical sample had mp 65.8–66.4°.

Anal. Calcd for $C_{16}H_{20}O_3S$ (292.397): C, 65.72; H, 6.89; S, 10.97. Found: C, 65.87; H, 6.90; S, 10.76.

Oxaadamantane (12).—The material isolated from the column chromatography described above had mp 231–232° after one sublimation and was more than 99% pure by glpc. An analytical sample, mp 232–233° (lit. mp 232.5°,[13a] 225–230°[13b]), was obtained by preparative glpc: ir (CCl_4) ν 1448, 1314, 1190, 1054, 1014, 893 cm^{-1}; nmr (CCl_4) broad maxima centered around δ 1.58, 1.74, 2.04, and a broad, symmetrical two-proton singlet at 4.0 due to the bridgehead CH's adjacent to oxygen.

Anal. Calcd for $C_9H_{14}O$ (138.20): C, 78.21; H, 10.21. Found: C, 77.94; H, 10.17; mass spectrum (molecular ion), *m/e* 138.

Reaction of Noradamantane with Sulfuric Acid.—Noradamantane (0.6 g) suspended in sulfuric acid (25 ml) was recovered unchanged after stirring for 9 hr at room temperature. In a separate experiment, 0.4 g of noradamantane and 9 ml of sulfuric acid were heated at 80–90° for 9 hr in a sealed tube. Following work-up (quenching with ice–water, extracting with ether, drying with $CaCl_2$, and evaporating the ether), only a few milligrams of material was recovered. Nmr and ir spectra showed this material to be mostly noradamantane, although there were some very weak absorptions in the infrared spectra corresponding to carbonyl groups (~1735 cm^{-1}). Reaction at 80–90° for shorter periods of time simply resulted in higher recoveries of noradamantane.

1-Bromonoradamantane (14). A. Direct Bromination.—A stirred mixture of noradamantane (1.5 g) and $AlBr_3$ (2.2 g) in CS_2 (20 ml) was cooled to 0°. Bromine (1.4 g) was added over a period of 45 min and the mixture was allowed to warm to room temperature and was stirred for 18 hr. At the end of this period considerable tar had formed on the walls of the flask. The CS_2 solution was decanted, washed with saturated $NaHCO_3$, and dried over $MgSO_4$. The solution was concentrated, and the major product was isolated by preparative gas chromatography (20 ft × 0.375 in., 30% SE-52 on 45/60 Chromosorb W). Yields of pure, waxy white **14** were less than 20%: mp 49–50° (sealed tube); *m/e* (molecular ion) 201 (with the characteristic bromine isotope distribution); nmr (CCl_4) δ 1.65 (4 H, s), 2.03, 2.18 (6 H, poorly resolved singlet), 2.41 (3 H, broad peak); ir (CS_2) ν_{max} 1311, 1271, 1138, 994, 870, 786, 686 cm^{-1}.

Anal. Calcd for $C_9H_{13}Br$ (201.19): C, 53.72; H, 6.51; Br, 39.76. Found: C, 53.73; H, 6.67; Br, 39.69.

Two other products (with retention times of 0.65 and 1.2 relative to **14** and relative concentrations of 3 and 8%, respectively) were also observed in this reaction mixture (glpc analysis on 5 ft × 0.25 in. 20% SE-30 on 60/80 Chromosorb W, 120°). These compounds have not been identified.

B. Action of PBr_3 on Tertiary Alcohol 10.—Alcohol **10** (1 g) was dissolved in benzene (4 ml) at room temperature, and a solution of distilled PBr_3 (0.7 ml) in benzene (1 ml) was added dropwise over a 5-min period. The pale yellow mixture was stirred at room temperature for 3 hr and then at 50° for 5.5 hr. The mixture was then poured into ice water, and the aqueous phase was extracted with pentane (3 × 10 ml). The combined organic layer and pentane extracts were washed with water, saturated $NaHCO_3$, and again with water, and then dried over $MgSO_4$. The solution was concentrated to a small volume, and the major product was isolated by preparative gas chromatography (20 ft × 0.375 in., 30% Carbowax 20M on 40/60 Chromosorb W). This compound (mp 49–50°, yield 36%) was identical in all respects (mass, ir, and nmr spectra) with compound **14** obtained by procedure A above.

Reduction of 14 to Noradamantane (2).—The bromo compound **14** (0.29 g) and *tert*-butyl alcohol (0.30 g) were dissolved in dry tetrahydrofuran (3 ml). Sodium (0.15 g) was added, and the mixture was stirred at room temperature for 3 hr. Additional *tert*-butyl alcohol (0.5 ml) was added to dissolve some remaining sodium, and the mixture was refluxed for 3 hr. Methanol was added, and the yellow reaction mixture was poured into 20 ml of ice water, which was extracted with pentane (3 × 15 ml). The pentane extracts were washed with water and dried over $MgSO_4$. Analysis by glpc (20 ft × 0.375 in., 30% SE-30 on 30/60 mesh Chromosorb W) showed only a single product which, after isolation by preparative gas chromotography, was identified as noradamantane (ir and nmr spectra identical with those of an authentic sample).[5]

The bromide **14** (*ca.* 0.01 g) was also converted smoothly to noradamantane by treatment with $(n\text{-Bu})_3SnH$ (*ca.* 0.20 g) for 5 hr at room temperature. During this period glpc analysis revealed a steady decrease in the starting material accompanied by the appearance and increase of the noradamantane peak.

Noradamantane (2).—Deltacyclane (10 g) in pentane (50 ml) was added to 60 ml of 96% sulfuric acid at room temperature, and the mixture was stirred mechanically at high speed for 2 hr. The layers were allowed to separate, and the pentane layer was taken up with a pipette and then evaporated, leaving 3.9 g of virtually pure **2**. An additional 50 ml of pentane was added to the acid layer and stirring was continued for several hours, after which the layers were separated again. This procedure was repeated several times over a 10-hr period, and led ultimately to a total yield of **2** of about 50%. A single sublimation gave material (mp 203–204°) that showed only one peak on flame-ionization gas chromatography and that was identical in all respects with noradamantane obtained *via* established methods.[5]

Noradamantane-1-carboxylic Acid (13).—Deltacyclane (0.5 g) was added dropwise to 96% sulfuric acid (200 ml), and the mixture was stirred at room temperature for 2.5 hr. The solution was cooled to 0°, ice-cold formic acid (75 ml) was added, and stirring was continued at 0° for 30 min. The reaction mixture was poured onto ice (300 g) and extracted with CCl_4 (3 × 20 ml). The combined extracts were washed with dilute NaOH and the combined basic solutions were neutralized with HCl to precipitate the organic acid. The precipitate was taken up in ether, and the aqueous solution was extracted with ether. The combined ether extracts were washed once with water and dried over $MgSO_4$. The ether was evaporated and the residue was sublimed to yield *ca.* 0.09 g of a white solid: mp 94–96°; *m/e* (molecular ion) 166; nmr (CCl_4) δ 1.6 (6 H, s), 1.82 (unresolved singlet), 12.2 (1 H, s). The signals at δ 1.82, 2.00, and 2.24 could not be integrated individually, but the total signal amounted to 4 H. The general appearance of this spectrum, except for the downfield acid proton, was very similar to that of **10** and was markedly different from that of 3-noradamantanecarboxylic acid[5a,b] (nmr spectrum kindly supplied by Dr. B. R. Vogt). The ir spectrum had prominent peaks at ν_{max} (CCl_4) 1700, 1415, 1280, and 1155 cm^{-1}.

Anal. Calcd for $C_{10}H_{14}O_2$ (166.21): C, 72.26; H, 8.49. Found: C, 72.2; H, 8.3.

A Hunsdiecker reaction[18] was carried out on this acid, and glpc analysis (Carbowax 20M and SE-30) revealed that the major product had retention times identical with those of **14**. Direct nmr analysis of the washed and dried $BrCCl_3$ solution from this reaction confirmed the identity of **14** as the major product.

Registry No.—**2**, 7075-86-7; **7**, 6567-11-9; **10**, 37392-59-9; **10** tosylate, 33305-61-2; **12**, 281-24-3; **13**, 37392-60-2; **14**, 37392-61-3.

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(18) J. A. Davis, J. Herynk, S. Carrol, J. Bunds, and D. Johnson, *J. Org. Chem.*, **30**, 415 (1965).

Synthesis and Reactions of 3- and 3,7-Substituted Bicyclo[3.3.1]nonanes[1]

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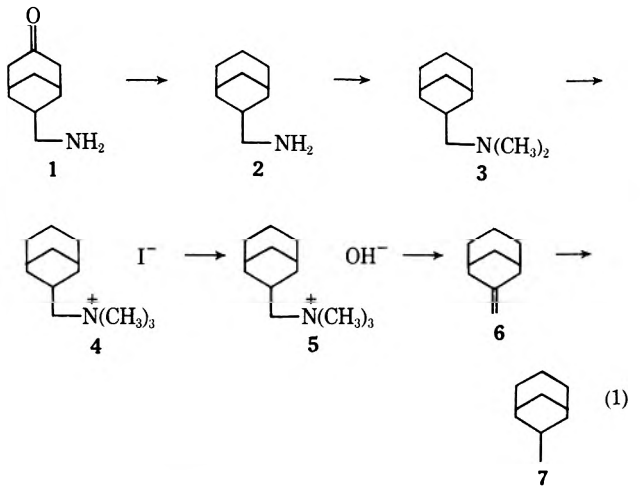
The readily available *endo*-7-aminomethylbicyclo[3.3.1]nonan-3-one serves as a convenient precursor for a variety of 3- and 3,7-substituted bicyclo[3.3.1]nonanes. The individual steps generally proceed in high yield. New compounds which are made available include *endo*-3-bicyclo[3.3.1]nonylmethylamine, *N*,*N*-dimethyl-7-methylene-*endo*-3-bicyclo[3.3.1]nonylamine, 7-methylenebicyclo[3.3.1]non-2-ene, and *endo*-3-bicyclo[3.3.1]-nonylcarbonitrile. 1-Methyl-2-oxaadamantane was also prepared. In addition, novel routes are provided for the indicated substances, 3-methylenebicyclo[3.3.1]nonane, *endo*-3-methylbicyclo[3.3.1]nonane, 3-methylbicyclo-[3.3.1]non-2-ene, and 3-bicyclo[3.3.1]nonylcarboxylic acid.

Various methods have been employed for the preparation of bicyclo[3.3.1]nonanes, in which acyclic or monocyclic materials serve as the immediate precursors.[2] Included in some of the newer approaches is the ring opening of suitably substituted adamantanes, which generally leads to 3,7-disubstituted derivatives.[2,3] Recently, in this category, 1-*N*,*N*-dichloroaminoadamantane was found[4] to provide *endo*-7-aminomethylbicyclo[3.3.1]nonan-3-one (**1**) in good yield from rearrangement by aluminum chloride with subsequent acid hydrolysis. The scope of this reaction has been investigated.[5,6] The present report is concerned with use of **1** as a versatile precursor for preparation of a variety of 3- and 3,7-substituted bicyclo[3.3.1]nonanes. New members of the series are made available, in addition to novel routes to previously reported compounds.

Results and Discussion

The first sequence of reactions involving the amino ketone is set forth in eq 1.



(1)

Wolff–Kishner reduction of **1** gave *endo*-3-bicyclo-[3.3.1]nonylmethylamine (**2**) in 99% yield. Since **2** is sensitive to carbon dioxide in air, characterization was accomplished mainly with the benzamide derivative; the nmr spectrum showed an indistinct triplet at δ 6.9 (1 H), attributed to NH (1 H) split by methylene protons, and another triplet at 3.3 (2 H) arising from CH_2N split by the bridgehead and NH protons. Compound **2** was converted to *N*,*N*-dimethyl-*endo*-3-bicyclo[3.3.1]nonylmethylamine (**3**) in 81% yield by formaldehyde in formic acid. Reaction with methyl iodide afforded the quaternary iodide **4** in 84% yield, which, in turn, gave rise to the quaternary hydroxide **5** on treatment with silver oxide. Hofmann elimination generated 3-methylenebicyclo[3.3.1]nonane[7] (**6**) (77% yield based on **4**). Exocyclic olefinic bands were present in the ir spectrum at 3100 and 875 cm^{-1}, in accord with the singlet at δ 4.6 (2 H) in the nmr spectrum. Hydrogenation of **6** with Pd/C gave 3-methylbicyclo[3.3.1]nonane (**7**) in 72% yield. Since **6** probably exists in the chair–chair conformation,[2] it is reasonable to assign the endo configuration to the major isomer on the basis of addition of hydrogen from the less hindered side. The minor component present is thought to be the exo isomer on the basis of a prior report[7] on hydrogenation of **16**. Our endo:exo ratio of 87:13 compares favorably with that, 86.5:13.5, reported for hydrogenation[7] of **16**.

Equation 2 summarizes the second sequence of reactions starting with **1**.

Exhaustive methylation was also performed with 4-azahomoadamantane (**8**) obtained from lithium aluminum hydride reduction[4] of **1**. The steps consisted of sequential formation of *N*-methyl-4-azahomoadamantane (**9**) in 83% yield, the iodide **10** in 98% yield, and then the hydroxide **11**. Decomposition of **11** gave *N*,*N*-dimethyl-7-methylene-*endo*-3-bicyclo[3.3.1]-nonylamine (**12**) in 64% yield (based on **10**). The structure of **12** was supported by the ir spectrum, indicating exocyclic olefinic CH at 3100 and 880 cm^{-1}, and the nmr spectrum, which also showed exocyclic olefin protons at δ 4.73 (s, 2 H). The tertiary proton CHN appeared at 3.0 (1 H). The direction of elimination is in accord with prior analogy.[8] The amino olefin **12** was subsequently converted to the iodide **13** (81% yield), and then to the hydroxide **14**. Pyrolysis of **14** provided 7-methylenebicyclo[3.3.1]non-2-ene (**15**) in 74% yield (based on **13**). Used in identification was the ir spectrum, displaying both exocyclic olefinic CH at 3100 and 878 cm^{-1} and endocyclic olefinic CH at 3050 and 720 cm^{-1}; alkene adsorption at 1645 cm^{-1} was also present. The nmr spectrum further

(1) VI. Adamantanes and Related Compounds. See ref 5 for the preceding paper in the series.

(2) G. L. Buchanan in "Topics in Carbocyclic Chemistry," Vol. 1, D. Lloyd, Ed., Plenum Press, New York, N. Y., 1969, Chapter 3.

(3) (a) R. M. Black and G. B. Gill, *Chem. Commun.*, 972 (1970); (b) W. H. W. Lunn, *J. Chem. Soc. C*, 2124 (1970); (c) H. Stetter and P. Tacke, *Chem. Ber.*, **96**, 694 (1963); (d) F. N. Stepanov and V. D. Sukhoverkhov, *Angew. Chem., Int. Ed. Engl.*, **6**, 864 (1967); (e) H. Hamill, A. Karim, and M. A. McKervey, *Tetrahedron*, **27**, 4317 (1971); (f) A. R. Gagneux and R. Meier, *Tetrahedron Lett.*, 1365 (1969).

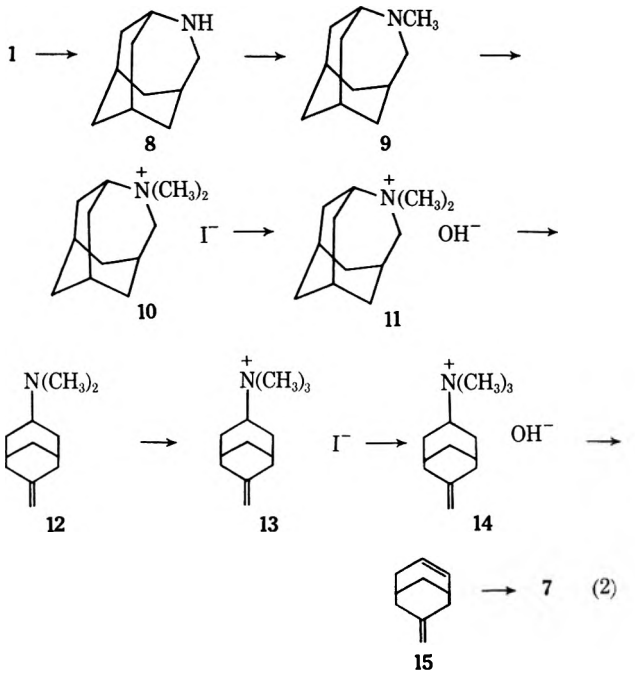
(4) P. Kovacic, J.-H. Liu, E. M. Levi, and P. D. Roskos, *J. Amer. Chem. Soc.*, **93**, 5801 (1971).

(5) S. J. Padegimas and P. Kovacic, *J. Org. Chem.*, **37**, 2672 (1972).

(6) T. Sasaki, S. Eguchi, T. Kiriyama, and H. Suzuki, *Syn. Commun.*, **1**, 267 (1971).

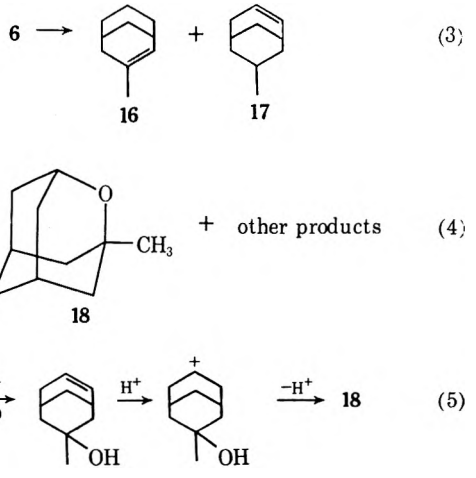
(7) R. A. Appleton and S. H. Graham, *Chem. Commun.*, 297 (1965).

(8) A. C. Cope and E. R. Trumbull, *Org. React.*, **11**, 317 (1960).

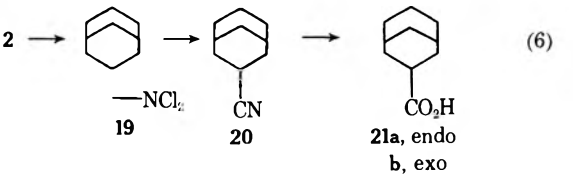


substantiated the presence of two types of olefinic protons. Catalytic hydogenation of **15** also gave **7**, consisting mainly of the endo isomer.

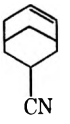
The behavior of the unsaturates **6** and **15** on exposure to 97% formic acid was examined. Appleton and Graham have reported[7] the isomerization of 3-methylenebicyclo[3.3.1]nonane (**6**) to **16** (93%) and **17** (7%) from contact with formic acid at room temperature for some months (eq 3). We observed a similar result, namely a ratio of 96:4, after 12 hr at 100°. **16** was characterized and **17** was assumed to be the minor product. In contrast, the diene **15** gave, on refluxing with formic acid, a complex mixture containing 1-methyl-2-oxaadamantane (**18**) as the principal component (eq 4). Compound **18** was identified[9] by elemental analysis and spectral data (ir, nmr, and mass). A number of mechanistic pathways can be visualized for formation of the oxa compound, one of which is set forth in eq 5.



Another series of reactions based on **2** is shown in eq 6. The first step entailed conversion to the *N,N*-dichloro derivative **19** in 67% yield by exposure to calcium hypochlorite. Various reagents, quinoline,



cesium fluoride, and potassium *tert*-butoxide, were examined for transformation of **19** to 3-bicyclo[3.3.1]-nonylcarbonitrile (**20**). The dehydrohalogenation was accomplished most effectively (65% yield) by quinoline. Only one nitrile product, presumably the endo isomer, was obtained under the various conditions, with no evidence for formation of the exo epimer. Structural confirmation for **20** was realized through synthesis by an alternate route. *endo*-3-Bicyclo[3.3.1]non-6-enecarbonitrile (**22**), prepared[10] from adamantanone



under conditions of the Schmidt reaction, was subjected to catalytic hydrogenation in the presence of Pd/C catalyst. After 2 hr, reduction of the alkene functionality was incomplete. Additional exposure to the same conditions gave **20** along with basic material which was not characterized.

Hydrolysis of the saturated nitrile **20** to the carboxylic acid function was explored under both acidic and basic conditions. With aqueous sulfuric acid at reflux for 6 hr, a 66:34 mixture of exo:endo acids was formed. In the presence of caustic (reflux for 8 hr in methyl Cellosolve), the exo:endo ratio was 90:10. Prolonged exposure of the epimeric mixture of acids to caustic brought about isomerization to the exo form almost exclusively. Both isomers are reported in the literature.[11] Equilibration of the ester derivatives by methoxide is known[11] to favor the exo isomer to the extent of about 99%.

Experimental Section

Materials and Analytical Procedures.—Methylene chloride was dried at reflux over calcium hydride and distilled. Methyl iodide (Matheson Coleman and Bell) was used as received. Ir spectra were obtained with a Beckman IR-8 spectrophotometer (calibrated with the 1601.8 cm^{-1} band of polystyrene). Varian T-60 and HA-100 instruments were used to obtain nmr data, which are reported in parts per million (δ) (in $CDCl_3$ unless otherwise indicated) relative to tetramethylsilane as internal standard. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn., Micro-Tech Laboratories, Skokie, Ill., and by Mr. A. Gasiecki. Glpc was conducted on a Varian Aerograph 1800 instrument with the indicated columns: (I) 3% silicone DC 550, 3% Carbowax 20M on Chromosorb P (30/60 mesh), 10 ft × 0.25 in., copper: (II) 15% Carbowax 20M on Chromosorb W (45/60 mesh), 10 ft × 0.25 in., copper. Melting points and boiling points are uncorrected.

endo-**7-Aminomethylbicyclo[3.3.1]nonan-3-one** (**1**).—A published procedure[4] was modified as indicated. The mixture obtained from addition of the acidic solution at about 10° to 1.4 l. of 50% sodium hydroxide was filtered and washed with water. The solid was extracted with warm (60–70°), 95% ethanol. After filtration, the residue, which contained inorganic solid, was extracted twice more with warm ethanol. The combined fil-

(9) The independent synthesis will be reported in a forthcoming publication.

(10) T. Sasaki, S. Eguchi, and T. Toru, *J. Org. Chem.*, **35**, 4109 (1970).

(11) R. A. Appleton, C. Egan, J. M. Evans, S. H. Graham, and J. R. Dixon, *J. Chem. Soc. C*, 1110 (1968).

trate (about 900 ml) was gradually cooled to 0°, then left at −20° overnight. The crystals were collected by filtration and dried to give about 40 g of 1, mp 161–162°. Concentration of the mother liquor provided another 3–5 g of product. Further purification should be carried out by sublimation (100°, 0.1 mm).

endo-**3-Bicyclo[3.3.1]nonylmethylamine** (**2**).—1 (16.7 g, 0.1 mol) and 64 g (2 mol) of 95% hydrazine were added to a mixture of 400 ml of diethylene glycol and 56 g of potassium hydroxide pellets.[12] While the mixture was slowly warmed to 143°, the caustic pellets gradually dissolved. After the mixture was refluxed at this temperature for 1 hr, the water and excess hydrazine were distilled until the pot temperature reached 190–200°. The viscous solution was refluxed for 3 hr, cooled to room temperature, and then poured into 500 ml of water. The aqueous solution was extracted portionwise with methylene chloride. The combined extract was washed several times with small portions of water and dried. Evaporation of solvent afforded 15.2 g (99% yield) of crude amine: bp 82–83.5° (1.3 mm); ir (neat) 3400, 2900, 2800, 1630, 1570, 1260, 1035, and 1020 cm^{-1}.

A literature procedure[13] provided 0.35 g of benzamide derivative, after crystallization from ethyl acetate, from 0.5 g of **2**. Two crystallizations from ethyl acetate–ether gave analytically pure material: mp 93.5–94.5°; ir ($CHCl_3$) 3500, 3010, 2930, 2860, 1650, 1560, 1520, 1470, and 1280 cm^{-1}; nmr ($CDCl_3$) δ 7.8 (m, 2 H), 7.45 (m, 3 H), 6.9 (indistinct t, 1 H), 3.3 (t, 2 H), 2.1–0.8 (m, 15 H).

Anal. Calcd for $C_{17}H_{23}NO$: C, 79.33; H, 9.00: N, 5.44. Found: C, 79.32; H, 8.96; N, 5.44.

The hydrochloride salt was obtained by passing HCl into an ethereal solution of **2**. A pure sample resulted after three crystallizations from ethanol–ether, mp >280° dec.

Anal. Calcd for $C_{10}H_{20}NCl$: C, 63.30; H, 10.62; N, 7.38; Cl, 18.68. Found: C, 63.54; H, 10.49; N, 7.11; Cl, 18.80.

N,N-**Dimethyl-*endo*-3-bicyclo[3.3.1]nonylmethylamine** (**3**).[14]—Formaldehyde (37%, 30 ml, 0.55 mol) was added to a mixture of 30 g (0.63 mol) of 97% formic acid and 15.2 g (0.1 mol) of **2**. On heating the mixture at 95° for 8 hr, gas evolution occurred. The dark solution was cooled, mixed with 60 ml of 4 *N* HCl, and then concentrated to a viscous liquid. After water (60 ml) was added, the solution was made basic with 50% NaOH at 0°. The ether extract was washed with water, dried, and freed of solvent. The residue weighed 14.7 g (81% yield): ir (neat) 2950, 2870, 2830, 2780, 1450, 1280, 1260, 1100, 1070, 1050, 1040, 1030, 1025, 850, 828, and 735 cm^{-1}; nmr δ 2.18 (s, 6 H), 2.15–0.70 (m, 17 H).

N,N,N-**Trimethyl-*endo*-3-bicyclo[3.3.1]nonylmethylammonium Iodide** (**4**).—Methyl iodide (20.4 g, 0.144 mol) was added to a mixture of 13 g (0.072 mol) of **3** in 75 ml of absolute ether. Salt immediately precipitated. After the mixture was allowed to stand overnight, the salt was filtered and dried, 19.5 g (84% yield) of **4**, mp 291–292° dec after three crystallizations from ethanol–ether.

Anal. Calcd for $C_{13}H_{26}NI$: C, 48.30; H, 8.10; N, 4.33; I, 39.26. Found: C, 48.18; H, 8.10; N, 4.22; I, 39.34.

N,N,N-**Trimethyl-*endo*-3-bicyclo[3.3.1]nonylmethylammonium Hydroxide** (**5**).—A mixture of 14.2 g (0.044 mol) of **4** and 60 ml of distilled water was cooled to 0°, whereupon precipitation occurred. After addition of 40 ml of ethanol, silver oxide (23 g, 0.1 mol) was added to the solution at 0°, and the mixture was stirred at this temperature for 5 hr. Following filtration, evaporation provided a viscous liquid, 8 g, after standing under high vacuum.

3-Methylenebicyclo[3.3.1]nonane (**6**).[7,15]—**5** (4 g) was placed in a 10-ml, round-bottom flask connected through a short-path distillation head to a 5-ml receiver cooled in an acetone–Dry Ice bath. Residual water was removed under high vacuum. Then degradation gradually took place at 95° during 1 hr. The ether extract of the olefin product was washed with water and dried. Removal of ether provided 2.3 g (77% yield overall from **4**) of **6**. The analytical sample was collected by glpc at 90° (column I): n^{20}D 1.4947; ir (neat) 3100, 3020, 2960, 2840, 1645, 1440, 1110, 905, 875, and 750 cm^{-1}; nmr δ 4.6 (s, 2 H), 2.50–0.90 (m, 14 H).

Anal. Calcd for $C_{10}H_{16}$: C, 88.16; H, 11.84. Found: C, 88.18; H, 11.76.

3-Methylbicyclo[3.3.1]nonane[7] (**7**) **from 6.**—**6** (1.6 g, 1.17 mmol) was hydrogenated overnight at room temperature in 50 ml of absolute ethanol with 0.5 g of 5% palladium on charcoal in a Parr apparatus. After filtration, removal of solvent afforded 1.3 g (72% yield) of **7**. The analytical sample was obtained as described for **6**: n^{20}D 1.4735; ir (neat) 3040, 2930, 1460, 1375, 1360, 1130, 1110, and 696 cm^{-1}; nmr δ 2.10–0.60 (m, sharp d at 1.80).

Anal. Calcd for $C_{10}H_{18}$: C, 86.87: H, 13.12. Found: C, 86.86; H, 12.97.

The crude product contained 13% of a second component.

N-**Methyl-4-azahomoadamantane** (**9**).—Methylation (adapted from **3**) of 16.1 g (0.106 mol) of **8**[4] gave 14.5 g (83% yield) of **9**: ir (neat) 2900, 2860, 2780, 1440, 1390, 1275, 1205, 1135, 1120, and 1035 cm^{-1}; nmr δ 2.98 (s, 1 H), 2.85 (d, 2 H), 2.50 (s, 3 H), 2.18–1.20 (m, 13 H). The hydrochloride was obtained as described for **2**·HCl.

Anal. Calcd for $C_{11}H_{20}NCl$: C, 65.49; H, 9.99; N, 6.94; Cl, 17.57. Found: C, 65.48; H, 10.00; N, 6.87; Cl, 17.75.

N,N-**Dimethyl-4-azoniatricyclo[4.3.1.1^{3,8}]undecane Iodide** (**10**).—**9** (14.5 g, 0.088 mol), on treatment (see **4**) with methyl iodide, gave 26.5 g (98% yield) of product, mp 311–312° dec.

N,N-**Dimethyl-4-azoniatricyclo[4.3.1.1^{3,8}]undecane Hydroxide** (**11**).—The hydroxide was obtained as a syrup (see **5**).

N,N-**Dimethyl-7-methylene-*endo*-3-bicyclo[3.3.1]nonylamine** (**12**).—Crude **11**, generated from 26.5 g of **10**, on pyrolysis (see **6**) provided 10 g (64% yield based on **10**) of product: ir (neat) 3100, 2940, 2830, 2780, 1645, 1450, 1380, 1365, 1300, 1260, 1175, 1145, 1100, 1080, 1030, and 880 cm^{-1}; nmr δ 4.73 (s, 2 H), 3.00 (s, 1 H), 2.40–0.80 (m, 18 H, sharp s at 2.20).

N,N,N-**Trimethyl-7-methylene-*endo*-3-bicyclo[3.3.1]nonylammonium Iodide** (**13**).—Compound **13** (12.3 g, 81% yield) was formed by treating 8.5 g (0.048 mol) of **12** with methyl iodide (see **4**), mp 287–288° dec (purified as for **4**).

Anal. Calcd for $C_{13}H_{24}NI$: C, 48.61; H, 7.53; N, 4.36; I, 39.50. Found: C, 48.88; H, 7.65; N, 4.51; I, 39.30.

N,N,N-**Trimethyl-7-methylene-*endo*-3-bicyclo[3.3.1]nonylammonium Hydroxide** (**14**).—The hydroxide was isolated as a syrup from 10.3 g (0.032 mol) of **13**.

7-Methylenebicyclo[3.3.1]non-2-ene (**15**).—The diolefin **15** was obtained by pyrolysis of **14** (see **6**): 3.2 g (74% yield based on **13**); n^{20}D 1.5037; ir (neat) 3100, 3050, 2900, 2850, 1645, 1430, 1045, 980, 910, 878, 726, and 705 cm^{-1}; nmr δ 5.62 (s, 2 H), 4.72 (s, 1 H), 4.52 (s, 1 H), 2.60–1.20 (m, 10 H).

Anal. Calcd for $C_{10}H_{14}$: C, 89.47; H, 10.53. Found: C, 89.40; H, 10.85.

endo-**3-Methylbicyclo[3.3.1]nonane**[7] (**7**) **from 15.**—Hydrogenation of **15** (as described for **7** from **6**) afforded **7** (83% yield), identical with material obtained from **6**. A minor component was present (13% of total).

3-Methylbicyclo[3.3.1]non-2-ene[7] (**16**).—A mixture of olefin **6** (0.25 g, 1.84 mmol) in a small amount of ether (used for transfer) and 2 ml of 97% formic acid was refluxed for 12 hr at 100°. After extraction with ether, the ether layer was washed in succession with water, 5% sodium carbonate, and water. Evaporation of ether from the dried solution gave 0.1 g (40% yield) of product. Glpc analysis (column I, isothermal at 90°, 60 ml/min) showed a ratio of 96:4 for **16** *vs.* the minor component. **16**: ir (neat) 3015, 2950, 2850, 1440, 915, 850, 818, and 725 cm^{-1}; nmr δ 5.4 (vague d, 1 H), 2.5–1.2 (m, 15 H).

1-Methyl-2-oxaadamantane (**18**).—A mixture of diolefin **15** (1 g, 7.5 mmol) in a small amount of ether (used for transfer) and 3 ml of 97% formic acid was refluxed for 10 hr at 100°. The color turned dark, and a light brown solid separated. Liquid was decanted from the solid, which was dissolved in ether, washed with water, dried, and freed of solvent, wt 0.2 g of gummy material. The original liquid was extracted with ether. The organic solution was washed in succession with water, 5% sodium hydroxide, and water. The combined aqueous fraction was extracted with ether which was combined with the main portion of the ether solution. After a water wash, removal of ether from the dried solution gave 0.7 g of residue which was analyzed by glpc (column II, 110° for 10 min, then to 180°, 100 ml/min). The seven-component mixture contained about 39% of **18** as the principal ingredient: ir (CCl_4) 2940, 2890, 1440, 1390, 1320, 1205, 1130, 1090, 1040, 1010, and 870 cm^{-1}; nmr (CCl_4) δ 4.05 (s, 1 H), 2.15–1.3 (m, 12 H), 1.10 (s, 3 H); mass spectrum *m/e*

(12) A. I. Vogel, "Practical Organic Chemistry," 3rd ed, Wiley, New York, N. Y., 1962, p 510.

(13) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 5th ed, Wiley, New York, N. Y., 1964, p 260.

(14) S. H. Pine and B. L. Sanchez, *J. Org. Chem.*, **36**, 829 (1971); R. N. Icke, B. W. Wisegarver, and G. A. Alles, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1967, p 723.

(15) A. C. Cope, N. A. LeBel, H.-H. Lee, and W. R. Moore, *J. Amer. Chem. Soc.*, **79**, 4720 (1957).

(rel intensity) 153 (8), 152 (58), 109 (10), 96 (10), 95 (100), 94 (85), 93 (9), 84 (23), 79 (21), 67 (13), 45 (24), 43 (14), and 41 (10).

Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 78.57; H, 10.77.

N,N-Dichloro-*endo*-3-bicyclo[3.3.1]nonylmethylamine (19).—An adaptation of a published procedure[16] was followed. A solution of 11.1 g (0.05 mol) of **2**, 45 ml of water, and 15 ml of concentrated HCl (warmed to effect solution) was added dropwise to a cooled (5–10°) mixture of 45 ml of water, 90 ml of methylene chloride, and 20.4 g (0.1 mol) of calcium hypochlorite (70% pure). The mixture was stirred for 15 min, after which the organic phase was separated, washed twice with water, and dried, yielding 11.5 g (67%) of product which titrated for 94% of the theoretical amount of positive chlorine. Sublimed product (100% of theory for positive chlorine) gave mp 37–39.5°.

endo-3-Bicyclo[3.3.1]nonylcarbonitrile (20). A. Quinoline Route.—According to a literature procedure,[17] a solution of 2 g (0.009 mol) of **19** (98% pure) and 15 ml of quinoline was heated with stirring under nitrogen at 160° for 18 hr. The reaction mixture was poured into 60 ml of cold 2 *N* HCl, and then extracted with ether. Solvent evaporation from the dried organic layer provided 1.3 g of a dark red-brown oil. Sublimation (35°, 0.01 mm) and crystallization from petroleum ether (bp 30–60°) yielded 0.9 g (65%) of **20**, mp 59–60°. The ir spectrum showed nitrile absorption at 2337 cm^{-1}.

B. CsF Route.—The method of Sharts[18] was used. A solution of 9.4 g (0.034 mol) of **19** (91% pure) and 12.7 g (0.084 mol) of cesium fluoride in 70 ml of acetonitrile was heated at 50° with stirring for 48 hr. After the solution was filtered, solvent removal yielded 7.6 g of dark brown, viscous liquid. Sublimation and crystallization from petroleum ether afforded **20** as a white, crystalline solid, 2.7 g (52% yield), mp 59–60°.

Anal. Calcd for $C_{10}H_{15}N$: C, 80.48; H, 10.13; N, 9.39. Found: C, 80.27; H, 10.34; N, 9.40.

C. *t*-BuOK Route.—A literature route[19] was modified. A solution of 2 g (7.9 mmol) of **19** (94% pure) dissolved in 20 ml of *tert*-butyl alcohol was added dropwise with stirring to 1.9 g (0.017 mol) of potassium *tert*-butoxide in 25 ml of *tert*-butyl alcohol. The reaction mixture was protected by a drying tube. The temperature rose to 60° and then dropped to 25° during the 3-hr reaction period. A white precipitate formed. After the *tert*-butyl alcohol was removed, the residue was treated with 25 ml of ether and 10 ml of water. The organic layer was separated and the aqueous phase was extracted with portions of ether. The combined organic phase was dried and freed of solvent. Sublimation and crystallization from petroleum ether yielded 0.4 g (33%) of **20**, mp 59–60°.

endo-3-Bicyclo[3.3.1]non-6-enecarbonitrile[10] (22).—To a stirred solution of 16 ml of acetic acid, 12 ml of methanesulfonic acid, and 4 g (0.027 mol) of adamantanone was added 2 g (0.031 mol) of NaN_3 portionwise over a period of 50 min. After being stirred for an additional 20 min, the mixture was poured over crushed ice, forming a precipitate which was washed with water and dried, 1.3 g (33% yield), mp 171–181° (lit.[20] mp 176.5–181.5°). The ir spectrum was essentially identical with that of authentic material.[21]

endo-3-Bicyclo[3.3.1]nonylcarbonitrile (20) from Hydrogenation[22] of *endo*-3-Bicyclo[3.3.1]non-6-enecarbonitrile (22).—**22** (1 g) was dissolved in 50 ml of ethanol and placed in a Parr apparatus along with 0.25 g of 10% Pd on carbon. After 2 hr of agitation at 42 psi, the catalyst was removed by filtration and the solvent was evaporated. The product was taken up in 20 ml of ether and extracted three times with 10-ml portions of cold 7.5% HCl. Solid from evaporation of the ether solution was sublimed, yielding 0.9 g of product. Ir analysis indicated that a minor amount of **22** was still present. Therefore, the product was hydrogenated for another 2 hr. The resulting neutral product (0.2 g, 15% yield), mp 60–61°, displayed an ir spectrum identical with that of the nitrile from **19**. Glpc analysis indicated a purity greater than 99%. Amine product, 0.7 g of the hydrochloride, from the second hydrogenation, was not characterized.

3-Bicyclo[3.3.1]nonylcarboxylic Acid (21a and 21b). A. By Acid Hydrolysis.[23]—A solution of 2 g (8.8 mmol) of **20**, 15 ml of water, and 12.5 ml of concentrated H_2SO_4 was refluxed for 6 hr. During this time, product which crystallized in the condenser was returned to the reaction flask. The mixture was diluted with 25 ml of cold water and filtered. The solid residue was dissolved in 15% NaOH and treated with activated charcoal. The acid was recovered by neutralization followed by sublimation (90°, 0.01 mm) and crystallization from petroleum ether, wt 2.1 g (92% yield), mp 112–113°. Differential scanning calorimetry gave a melting endotherm of 111°.

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.54; neut equiv, 168.2. Found: C, 71.23; H, 9.45; neut equiv, 168.7.

Preparation of the methyl esters[11] was accomplished by addition of ethereal diazomethane to a solution of 0.5 g (0.003 mol) of **21a** and **21b** (from acid hydrolysis) in 10 ml of anhydrous ether. Addition was continued until a slight yellow color remained for 5 min, indicating excess diazomethane. A blank containing only ether was used for comparison. Glpc of the methyl esters at 175° on 15% Carbowax 20M Chromosorb W indicated a composition of 66% exo and 34% endo.

B. By Basic Hydrolysis.[24]—A solution of 1.2 g (0.008 mol) of **20**, 10 ml of ethylene glycol monomethyl ether, and 2 g (0.036 mol) of KOH was refluxed under nitrogen for 8 hr. Progress of the reaction was followed by passing the evolved ammonia into a bromcresol green solution[25] (HCl). The reaction mixture was cooled, filtered, and neutralized with HCl. After filtration of the precipitate, sublimation and crystallization from petroleum ether yielded 0.9 g (65% yield) of the epimeric acids, mp 123–126°. Differential scanning calorimetry gave a melting endotherm of 127°, neut equiv 169.6 (calcd 168.2). Esterification was effected as described in the preceding section. Glpc analysis indicated a mixture of 90% exo and 10% endo.

***exo*-3-Bicyclo[3.3.1]nonylcarboxylic Acid (21b) by Isomerization.**—A solution of 200 mg (1.2 mmol) of a mixture of **21a** and **21b** (from basic hydrolysis of **20**), 0.33 g (0.006 mol) of KOH, and 5 ml of ethylene glycol monomethyl ether was refluxed (116°) under nitrogen for 24 hr. Work-up, as described for the basic hydrolysis of **20**, yielded 178 mg (89% yield) of **21b**, mp 130–131° [lit.[11] for **21b** (99% pure), mp 132–133.5°]. Differential scanning calorimetry gave a melting endotherm of 134°; ir (KBr) 3100–2500 (OH), 1675 (C=O), 1405, 1250, and 940 cm^{-1}; nmr δ 12.22 (s, 1, CO_2H), 3.02 (m, 1, $CHCO_2H$), 1.77 (m, 14, remaining protons).

Registry No.—**1**, 34650-78-7; **2**, 37445-20-8; **2** benzamide derivative, 37445-21-9; **2** HCl, 37445-22-0; **3**, 37445-23-1; **4**, 37445-24-2; **5**, 37445-25-3; **6**, 19437-17-3; **7**, 37439-64-8; **8**, 22776-74-5; **9**, 37439-66-0; **9** HCl, 37439-67-1; **10**, 37439-68-2; **11**, 37439-69-3; **12**, 37445-26-4; **13**, 37445-27-5; **14**, 37445-28-6; **15**, 37439-70-6; **16**, 2721-36-0; **18**, 6508-22-1; **19**, 37445-29-7; **20**, 37445-30-0; **21a**, 19489-18-0; **21b**, 19489-16-8; **22**, 26768-57-0.

Acknowledgment.—Support from the National Science Foundation and the Graduate School of the University of Wisconsin—Milwaukee is gratefully acknowledged. We thank Dr. Earl M. Levi and Dr. Peter Yates for assistance in obtaining the mass spectral data and Mr. A. Gasiecki for some of the microanalyses.

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A New Reaction Sequence Leading to the Formation of Unsaturated Carbenes[1]

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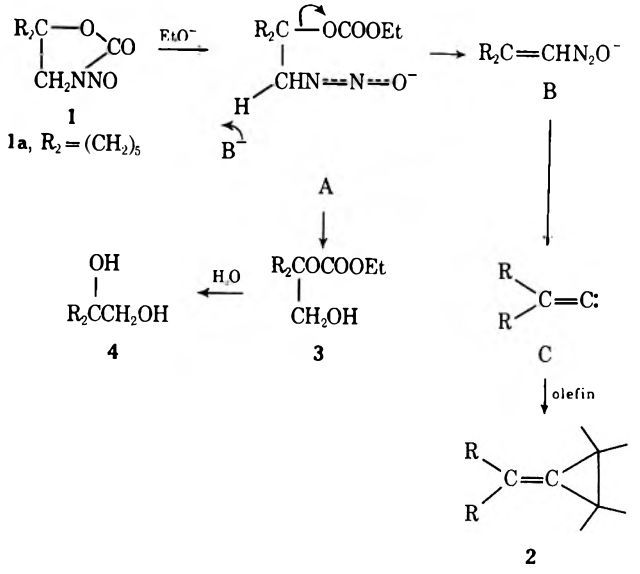
Treatment of a solution at −10 to −5° of 1-(*N*-nitrosoacetylamino)cyclohexanol in pentane containing an olefin and a tetraalkylammonium chloride with 50% sodium hydroxide initiates a series of reactions which results in the formation of cyclohexylidene carbene. The latter is trapped by olefins to yield unsaturated cyclopropane compounds in higher yields than were previously obtained by starting with *N*-nitrosooxazolidones under various conditions.

In earlier work, the formation of an unsaturated carbene was postulated to account for the formation of substituted methylenecyclopropanes (**2**) when *N*-nitrosooxazolidones (**1**) were treated with lithium ethoxide in cyclohexene.[2] A key step in the postulated mechanism is the elimination of the oxygenated carbonate function after abstraction of a proton from the carbon attached to nitrogen, as shown in the intermediate A formed by attack of a base on the carbonyl group of the substituted oxazolidone. Once the elimination has occurred the intermediate B is postulated to undergo further changes to yield the unsaturated carbene C.[2] On reaction of C with an olefin, the methylenecyclopropanes **2** result, as shown in Scheme I.

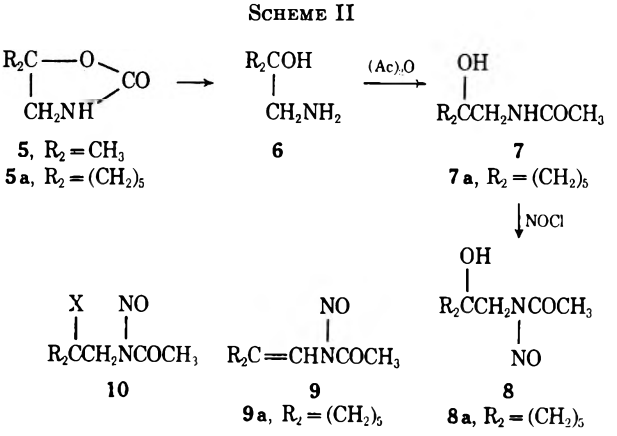
SCHEME I



In applying the above reaction, the yields of desired unsaturated cyclopropanes **2** are often below 40%. In many cases the formation of diols **4** accounts for about 40–60% of the starting materials **1**. The diols **4** are present in the reaction mixture mostly as esters of carbonic acid (**3**, cyclic or acyclic) and are isolated after alkaline hydrolysis. The diol derivatives result from loss of nitrogen from A before the elimination to B occurs. Another undesirable feature which arises on scaling up some reactions is the difficulty of controlling the exothermic reaction which sets in when base is added at room temperature[3] or above. In general the reactions do not occur in the 0–15° range.[3]

Accordingly, we sought to improve the synthetic scheme by modification of the starting materials **1** so that the elimination step as pictured for A → B would proceed more nearly to completion. We proposed to hydrolyze the oxazolidones **5** used to prepare **1** to the corresponding amino alcohols **6** which could be acetylated[4] on nitrogen to **7** and the latter nitrosated to yield *N*-nitrosoacetylamino alcohols **8**. With these new compounds in hand we hoped that conditions could be found which would permit dehydration to unsaturated *N*-nitrosoacetylamides **9** prior to treatment of the latter with base (thus ensuring elimination), or that the tertiary hydroxyl could be converted into a leaving group (X in **10**) so that the base-induced elimination would proceed more readily than in the previous examples.[2] The routes are outlined in Scheme II.

SCHEME II



The oxazolidones **5** are readily converted into the amino alcohols **6** by alkaline hydrolysis. Because of their tendency to react with carbon dioxide in the air, the amino alcohols **6** were immediately treated with 1 equiv of acetic anhydride to yield the desired acetylamino alcohols **7**, which were readily nitrosated to the nitrosoacetylamino alcohols **8**.

Attempts were made to dehydrate 1-(*N*-nitrosoacetylaminomethyl)cyclohexanol (**8a**) to the corresponding unsaturate **9** by treatment with concentrated sulfuric acid at 0° or with thionyl chloride at −5 to 0°. However, in each case only dark oils were obtained which gave no nitrogen when treated with base.

On treating a solution of **8a** and methanesulfonyl chloride in methylene chloride at 0–5° with triethylamine (or collidine)[5] vigorous evolution of nitrogen occurred. Hence we were unable to prepare the mesylate **10a**. If cyclohexene replaced methylene chloride

(1) This work was supported by Grant GP-12445X of the National Science Foundation.

(2) (a) M. S. Newman and T. B. Patrick, *J. Amer. Chem. Soc.*, **91**, 6461 (1970); (b) M. S. Newman and A. O. M. Okorodudu, *J. Org. Chem.*, **34**, 1220 (1969).

(3) Unpublished observations by several workers.

(4) In principle acyl groups other than acetyl could be used to advantage.

(5) Dr. Philip Hogan, Lewis College, Lockport, Ill., has informed me that he is studying the behavior of nitrosooxazolidones on treatment with amines. Hence we are not continuing this line of research here.

TABLE I

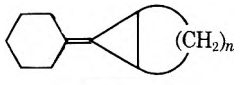
SYNTHESIS OF ALKYLIDENECYCLOPROPANES FROM 8a

Product[a]	Yield,[b] %	Bp, °C (mm)
11	78[c]	61–62
16‡	61[d]	73–74 (0.3)
17‡	60[d]	87–88 (0.2)
18, R = OC_6H_5‡	60[e]	107–108[f] (0.3)
19, R = OC_2H_5‡	83[e]	69–70 (2.5)
20, R = O-*t*-C_4H_9‡	60[d]	62–63 (0.5)

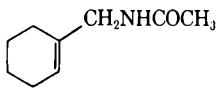
[a] All new compounds marked with ‡ gave ir, nmr, and mass spectra consistent with the assigned structures. [b] The yields represent material of >95% purity (by vpc) isolated by fractionation on a spinning band column. In all reactions there was isolated 9–10% of a mixture of about 8% of cyclohexylformaldehyde, 12% of cyclohexanone, and 80% of cycloheptanone as determined by vpc analysis. [c] Average of three runs. [d] One run. [e] Average of two runs. [f] Solidified on standing, mp 44–45°.

in a similar experiment at room temperature, 25–30% yields of bicyclo[4.1.0]hept-7-ylidenecyclohexane (**11**) were obtained.

Following the failure of these attempts to prepare **9a**, attempts were made to modify 1-(acetylaminomethyl)cyclohexanol (**7a**) prior to nitrosation. Treatment of **7a** with *p*-nitrobenzoyl or 3,5-dinitrobenzoyl chlorides in collidine or pyridine returned unchanged **7a**. On treatment of **7a** with concentrated sulfuric acid at 10° a 90% yield of 1-acetylaminomethylcyclohexene (**12**) was obtained. However, attempts to nitrosate **12** failed, as tarry materials were obtained.[6]



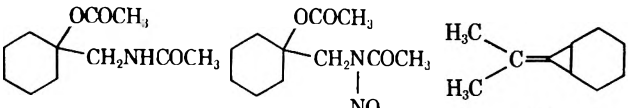
11, $n = 4$
16, $n = 5$
17, $n = 6$



12

Acetylation of **7a** to the *O,N*-diacetate **13** was accomplished by treatment with excess acetic anhydride at 100–104°. Nitrosation of **13** yielded the *N*-nitrosodiacetate **14**, which, in cyclohexene solution containing Aliquat-336,[7] afforded a 59% yield of **11** on treatment with sodium hydroxide. Thus, the desired goal of improving the yields of carbenic addition products seemed at hand. However, before doing intensive work with the diacetates, **8a** in cyclohexene was treated with sodium hydroxide.[7] To our surprise 75–80% yields (isolated) of **11** were obtained. Thus, having developed a potentially useful synthetic reaction, we have explored this method and report our results[8] herein.

The yields of products obtained by reaction of **8a** with cyclohexene, cycloheptene, cyclooctene, phenyl vinyl ether, ethyl vinyl ether, and *tert*-butyl vinyl ether, **11**, **16**, **17**, **18**, **19**, and **20**, respectively, are listed in Table I. The strained double bond exocyclic to the cyclopropane rings in **16–20** appears at about 5.58 μ, which is characteristic for such olefins.[9] In one experiment involving **8**, a 50% yield of 7-isopropylidenebicyclo[4.1.0]heptane (**15**) was obtained.



13 **14** **15**

We conclude from the above experiments that, if carbenic addition products are desired, it is preferable to use the new procedure involving nitrosoacetylamino alcohols **8** than nitrosooxazolidones **1**. However, when **8a** was treated with sodium ethoxide in ethanol, only a 50% yield of ethoxymethylenecyclohexene was obtained (together with 38% of cycloheptanone) whereas by starting with **1a** an 84% yield results.[2b] Thus, if vinyl ethers are the desired end products, the earlier reactions involving nitrosooxazolidones are preferable. It remains for further work to find out which procedure is better for the varied vinyl compounds preparable by the earlier methods.[10]

Experimental Section[11]

1-(Acetylaminomethyl)cyclohexanol (7a).[8]—A mixture of 15.5 g of **5a** and 50 ml of 50% potassium hydroxide was refluxed for 20 min. The cooled mixture was transferred under nitrogen to a small separatory funnel. The organic layer was diluted with 70 ml of methanol and treated dropwise with 10.2 g of pure acetic anhydride. After 30 min at reflux the volatile materials were removed on a rotary evaporator and the residue was recrystallized from benzene–petroleum ether (bp 60–110°) to yield 15.4 g (90%) of **7a**: mp 117–118°; ir 2.75 (OH), 2.95 (NH), 6.05 μ (C=O); nmr ($CDCl_3$ + 1 drop D_2O) δ 1.51 [s, 10 H, $-(CH_2)_5-$], 2.02 (s, 3 H, CH_3), 3.26 (s, 2 H, $-CH_2-$); *m/e* 171 (calcd 171).

1-Acetylamino-2-methyl-2-propanol (7).—The hydrolysis of 5,5-dimethyl-2-oxazolidone (**5**)[12] to 1-amino-2-methyl-2-propanol and acetylation of the latter to **7**, bp 116–117° (0.5 mm), proceeded in 82% overall yield as described for **7a**: ir 2.75 (OH), 2.94 (NH), 6.04 μ (C=O); nmr (CCl_4 + 1 drop D_2O) δ 1.17 [s, 6 H, $(CH_3)_2$], 2.00 (s, 3 H, CH_3), 3.28 (s, 2 H, $-CH_2-$); *m/e* 131 (calcd 131).

Anal. Calcd for $C_6H_{13}NO_2$: C, 55.0; H, 9.9; N, 10.7. Found: C, 55.1; H, 9.9; N, 10.5.

1-(*N*-Nitrosoacetylaminomethyl)cyclohexanol (8a).—A solution prepared at *room temperature* from 3.8 g of nitrosyl chloride in 25 ml of glacial acetic acid was added dropwise during 12–15 min to a solution of 4.0 g of **7a**, 5 g of freshly fused potassium acetate, and 0.5 g of phosphorus pentoxide in 25 ml of acetic acid *cooled so that the acetic acid is partly crystallized*. After 2 hr the mixture was allowed to come to room temperature and was then poured on ice. A cold methylene chloride extract was made rapidly and passed through a cone of magnesium sulfate. The solvent was removed at room temperature or below on a rotary evaporator to yield **8a** as a yellow oil which had no NH absorption in the ir spectrum and had the carbonyl band at 5.75 μ. Because of its instability a suitable elemental analysis was not obtained. This, and the nitroso compound obtained by a similar method from **7**, should be used rapidly or stored in the freezing compartment of a refrigerator (at best for only a few days).

1-Acetoxy-1-acetylaminomethylcyclohexane (13).—A solution of 2.0 g of **7a** in 10 ml of acetic anhydride and 2 ml of pyridine

(6) A similar failure to nitrosate $C_6H_5CH{=}CHNHCOOC_2H_5$, obtained by pyrolysis of cinnamoyl azide in ethanol, was met (unpublished observation by T. Patrick in our laboratories).

(7) Aliquat 336 is methyltricaprylammonium chloride. Our procedure is based on the principle outlined by C. M. Starks, *J. Amer. Chem. Soc.*, **93**, 195 (1971).

(8) For a preliminary communication, see M. S. Newman and Z. ud Din, *Syn. Commun.*, **1**, 247 (1971).

(9) H. E. Simmons, E. P. Blanchard, and H. D. Hartzler, *J. Org. Chem.*, **31**, 295 (1966).

(10) See, for example, M. S. Newman and C. D. Beard, *J. Org. Chem.*, **35**, 2412 (1970); *J. Amer. Chem. Soc.*, **92**, 4309 (1970), and references cited therein.

(11) All melting points and boiling points are uncorrected. The term "worked up as usual" means that an organic solvent layer of the reaction products was washed successively with dilute acid and/or alkali and saturated salt solution and was then filtered through a cone of anhydrous magnesium sulfate. The solvents were removed and the residue was distilled to yield the products. All compounds marked ‡ had ir, nmr, and mass spectra (parent peak) consistent with the assigned structures. Analyses were by Galbraith Laboratories, Knoxville, Tenn.

(12) M. S. Newman and T. B. Patrick, *J. Amer. Chem. Soc.*, **91**, 6461 (1969). See *ibid.*, **92**, 4312 (1970), for correction of nomenclature of unsaturated carbenes (footnote 2).

was held at 100–104° for 3 hr, cooled, and poured on ice. After the usual work-up ($CHCl_3$ solvent), distillation yielded 2.0 g (83%) of **13** as a colorless oil, bp 127–129° (0.3 mm).

Anal. Calcd for $C_{11}H_{19}NO_3$: C, 61.9; H, 8.9; N, 6.6. Found: C, 61.7; H, 8.8; N, 6.5.

Reactions of 8a with Cyclic Olefins.—In a typical reaction a stirred solution held at −10 to −5° of 4.5 g of **8a** in 25 ml each of pentane and cyclohexene containing 1 g of Aliquat-336[7] was treated dropwise with 50% sodium hydroxide. The theoretical amount of nitrogen was collected during 15 min. After the solution was warmed to 40° for 5 min the organic layer was worked up as usual. After solvent was removed the residue was chromatographed over Woelm neutral alumina to remove the Aliquat-336. Distillation afforded 3.1 g (80%) of **11**,[2b] bp 61–62° (0.3 mm). The reactions of **8a** with cycloheptene and cyclooctene were carried out essentially the same way to yield bicyclo[5.1.0]oct-8-ylidenecyclohexane ∓ (**16**), ir 5.58 μ, *m/e* 190 (calcd 190), and bicyclo[6.1.0]non-9-ylidenecyclohexane ∓ (**17**), ir, 5.58 μ, *m/e* 204 (calcd 204), respectively. The results are summarized in Table I.

Anal. Calcd for $C_{14}H_{22}$: C, 88.4; H, 11.6. Found: C, 88.3; H, 11.7. Calcd for $C_{15}H_{24}$: C, 88.2; H, 11.8. Found: C, 88.2; H, 11.8.

Reactions of 8a with Vinyl Ethers.[13]—The reactions of **8a** with ethyl vinyl ether and *tert*-butyl vinyl ether were carried out as described above for the reaction of **8a** with cyclic olefins except that the pentane was omitted. However, since on cooling a solution of **8a** in phenyl vinyl ether turbidity resulted, an equal volume of pentane was added.

(13) We acknowledge with thanks generous gifts of ethyl vinyl ether, *tert*-butyl vinyl ether, and phenyl vinyl ether from the General Aniline and Film Corp.

2-Ethoxycyclohexylidenecyclopropane (**19**).—In a typical reaction 50% sodium hydroxide was slowly added dropwise to a stirred solution of 4.6 g of **8a** in 60 ml of ethyl vinyl ether and 1 ml of Aliquat 336[7] at −10 to −5°. The slow addition requires about 15 min in order that the temperature be maintained below −5°. During this time about the theoretical amount of nitrogen was collected. After 10 ml of water was added the organic layer was worked up as usual. The organic product was dissolved in pentane and chromatographed over 40 g of Woelm neutral alumina to remove the Aliquat 336. Distillation through a 12-in. Nester-Faust spinning band column afforded **19** in 80% yield: ir 5.59 μ; nmr (CCl_4) δ 3.65 (m, 1 H, $-CHOC_2H_5$), 3.52 (q, J = 6.8 cps, 2 H, OCH_2CH_3), 2.26 (m, 4 H, allylic CH_2 in cyclohexyl ring), 1.58 (m, 6 H, nonallylic CH_2 in cyclohexyl ring), 1.15 (t, J = 6.8 cps, 3 H, CH_2CH_3), 1.05 (m, 2 H, CH_2 in cyclopropyl ring); *m/e* 166 (calcd 166).

Anal. Calcd for $C_{11}H_{18}O$: C, 79.5; H, 10.9. Found: C, 79.5; H, 10.7.

In a similar way 2-phenoxycyclohexylidenecyclopropane (**18**) and 2-*tert*-butoxycyclohexylidenecyclopropane (**20**) were isolated (see Table I). The nmr spectra of **18** and **20** were almost identical with that of **19** except for the number of methylene hydrogens in the bicyclic rings.

Anal. Calcd for $C_{15}H_{18}O$: C, 84.1; H, 8.5. Found: C, 83.9; H, 8.4. Calcd for $C_{13}H_{22}O$: C, 80.3; H, 11.3. Found: C, 80.1; H, 11.5.

Registry No.—**7** (R = Me), 37150-62-2; **7a**, 37150-63-3; **8a**, 37150-64-4; **11**, 19690-02-9; **13**, 37150-66-6; **16**, 37150-67-7; **17**, 37150-68-8; **18**, 37150-69-9; **19**, 37150-70-2; **20**, 37150-71-3.

Cyclooctatetraene Derivatives from Bromocyclooctatetraene[1]

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N,N-Dimethylaminocyclooctatetraene, cyclopropylcyclooctatetraene, and cyclooctatetraenenitrile have been prepared for the first time. *N,N*-Diethylaminocyclooctatetraene has also been prepared, but was found to rearrange to α-*N,N*-diethylaminostyrene. In addition, *p*-anisylcyclooctatetraene, cyclooctatetraenealdehyde, and vinylcyclooctatetraene have been prepared in greatly improved yields over previously described procedures.

Since the Reppe synthesis of cyclooctatetraene in 1948 from acetylene,[2] numerous substituted cyclooctatetraenes have been prepared,[3] but for the most part the yields of these preparations have been at best fair. Recent work, however, has provided several cyclooctatetraenes[4] in good yield from the reaction of bromocyclooctatetraene[5] with organocopper(I) lithium reagents.[6]

In our continuing study of derivatives of bis(cyclooctatetraene)uranium(IV),[7] the need arose for preparing various substituted cyclooctatetraenes. Because of the lack of good general synthetic procedures, it was necessary to develop alternate routes to such compounds. We report the preparation of several substituted cyclooctatetraenes that were previously difficult to prepare. In addition, the syntheses of three new derivatives of cyclooctatetraene are described.

During the 1950's, Cope reported that substituted COT's could be prepared from the reaction of organolithiums with cyclooctatetraene.[8] Yields from these reactions were generally low (less than 25%) and gave side products which were difficult to separate from the desired material. In an extension of Cope's work, Paquette found that *p*-anisylcyclooctatetraene could be prepared from cyclooctatetraene and *p*-anisyllithium, but only in 3% yield.[9] We have found that the reaction of bromocyclooctatetraene with a fourfold excess of lithium di-*p*-anisylcopper(I) at −50° gives *p*-anisylcyclooctatetraene cleanly in 80% yield.

Cope and Fenton in 1951 reported the isolation of vinylcyclooctatetraene from accumulated residues of cyclooctatetraene preparations.[10] The procedure was tedious and gave only miniscule amounts of the derivative. When excess lithium divinylcopper(I) is allowed to react with bromocyclooctatetraene, the same product is obtained in 88% yield. Similarly, it was found

(1) This research was supported in part by National Science Foundation Grant No. GP-31803X.

(2) W. Reppe, O. Schlichting, and H. Meister, *Justus Liebigs Ann. Chem.*, **560**, 93 (1948).

(3) G. Schroder, "Cyclooctatetraen," Verlag Chemie, Wienheim, Germany, 1965.

(4) J. Gasteiger, G. Gream, R. Huisgen, W. Konz, and U. Schnegg, *Chem. Ber.*, **104**, 2412 (1971).

(5) W. Konz, Ph.D. Thesis, University of Munich, 1970.

(6) G. Whitesides, W. Fischer, Jr., J. San Filippo, Jr., R. Bashe, and H. House, *J. Amer. Chem. Soc.*, **91**, 4871 (1969).

(7) A. Streitwieser and U. Müller-Westerhoff, *ibid.*, **90**, 7364 (1968); A. Streitwieser and C. Harmon, *Inorg. Chem.*, in press.

(8) A. Cope and M. Kinter, *J. Amer. Chem. Soc.*, **73**, 3424 (1951); A. Cope and H. van Orden, *ibid.*, **74**, 175 (1952).

(9) L. Paquette, J. Malpass, and T. Barton, *ibid.*, **91**, 4714 (1969).

(10) L. Craig and C. Larrabee, *ibid.*, **73**, 1191 (1951); A. Cope and S. Fenton, *ibid.*, **73**, 1195 (1951).

that lithium dicyclopropylcopper(I) can be prepared and apparently is a versatile cyclopropylating agent.[11] This reagent, when used in a fourfold excess with bromocyclooctatetraene at −50°, gives a 95% yield of cyclopropylcyclooctatetraene.

Elix, Sargent, and Sondheimer have demonstrated that the reaction of bromocyclooctatetraene with base produces a transient cyclooctatrienyne that may be trapped to give cyclooctatetraene derivatives.[12] Making use of the analogous reaction of amines with benzynes, we found that *N,N*-dimethylaminocyclooctatetraene is prepared in 79% yield from the reaction of potassium *tert*-butoxide with bromocyclooctatetraene in the presence of dimethylamine. As expected, this compound is extremely sensitive toward acids, giving cyclooctatrieneone. In addition, the amine is air sensitive and decomposes rapidly at room temperature. In the course of preparing the amine, the first derivative prepared was the *N,N*-diethylaminocyclooctatetraene. However, attempted distillation, even at 1 μ, results in rearrangement (at times violently) to α-*N,N*-diethylaminostyrene. In contrast, the dimethyl derivative is easily distilled without rearrangement as an orange oil by evaporative distillation at 1 μ.

Cyclooctatetraene does not normally undergo electrophilic reactions without rearrangement or polymerization.[13] Recently, however, it has been demonstrated that iron-coordinated cyclooctatetraene does survive Vilsmeier conditions to give a formylated cyclooctatetraene.[14] Although the free formylcyclooctatetraene can be generated by ceric oxidation, isolation procedures and the preparation of starting material are time-consuming. Since large quantities of the aldehyde were desired, an alternative approach to this derivative was sought. Collman has reported that carbonyl compounds may be prepared from the reaction of organolithiums with iron pentacarbonyl at low temperatures.[15] We find that the reaction of cyclooctatetraenyllithium with iron pentacarbonyl under similar conditions gives an unexpected product. Instead of cyclooctatetraenealdehyde, a modest yield of (formylcyclooctatetraene)iron tricarbonyl was obtained. This apparently anomalous result may be rationalized by the following mechanism: cyclooctatetraenyllithium adds to a carbonyl group of the iron pentacarbonyl, and the product decomposes on hydrolysis to give cyclooctatetraenealdehyde and iron tetracarbonyl, which, in turn, combine *via* complexing at the double bonds with concomitant loss of carbon monoxide. Although this method did provide the desired formyl derivative, oxidation was still required to obtain the free ligand. The synthesis of the aldehyde can be accomplished, however, by the more traditional approach of treating cyclooctatetraenyllithium with methyl formate at 0°. This method gives the aldehyde cleanly in 79% isolated yield.

Corey and Hegedus[16] have reported briefly that *trans*-β-bromostyrene is converted into *trans*-β-cyanostyrene by reaction with potassium hexacyanodinickelate(I)[17] in methanol.[16] Despite several attempts we have not been able to transform bromocyclooctatetraene into the corresponding nitrile by this method except in low yield (8%). The nitrile can be prepared by an alternate route, however, from the interaction of cyclooctatetraenyllithium with cyanogen at low temperature. Although the nitrile can be obtained by either procedure, both have obvious drawbacks. The first method requires large amounts of the nickel complex and gives low yields, and, in the latter route, the extreme toxicity of cyanogen and the considerable polymerization of the product during reaction leave room for improvement.

Experimental Section

^{1}H nmr spectra were taken with a Varian Associates T-60 instrument. Ir spectra were obtained with a Perkin-Elmer 137 instrument. Commercial *n*-butyllithium, 15% in hexane, was used in cyclooctatetraenyllithium preparations. All reactions were run under a dry nitrogen atmosphere. Satisfactory mass spectra for all compounds have been obtained. Analyses were performed by the Analytical Services Laboratory, University of California. Bromocyclooctatetraene was distilled from an apparatus in which the bath covered the side arm such that there is minimal reflux of material back into the pot. This distillation procedure gave consistently high yields and bromocyclooctatetraene of >98% purity.

***p*-Methoxyphenylcyclooctatetraene.**—A solution of 0.20 mol of *p*-anisyllithium in 200 ml of ether, prepared from the reaction of *p*-bromoanisole in ether with an excess of lithium metal (1% Na), was added dropwise to 39.0 g (0.10 mol) of CuI·PBu_3 in 150 ml of ether at −70°. After stirring for 0.5 hr, a solution of 4.6 g (0.025 mol) of bromocyclooctatetraene[4] in 50 ml of ether was added to the yellow complex over a period of 10 min. The mixture was stirred for an additional 5 hr at −40°, and allowed to warm to room temperature overnight. After hydrolysis and extraction with ether, the organic layer was extracted with 20% $AgNO_3$ (10 × 25 ml). Aqueous ammonia treatment freed the cyclooctatetraene derivative, which was taken up into ether and dried over $MgSO_4$. Solvent removal and subsequent chromatography over silica gel with pentane yielded 4.2 g (80%) of *p*-methoxyphenylcyclooctatetraene, nmr δ 3.6 (3 H, s), 5.8 (7 H, d), 6.8 (4 H, 2 d).

Anal. Calcd for $C_{15}H_{14}O$: C, 85.71; H, 6.66. Found: C, 85.60; H, 6.91.

Vinylcyclooctatetraene.—To 39 g (0.10 mol) of CuI·PBu_3 in 100 ml of ether at −70° was added a solution of 0.20 mol of vinyllithium (commercial 2 *M* solution of vinyllithium in THF, Research Organic Corp.) dropwise over 20 min. After the clear yellow solution was stirred for an additional 20 min at −70°, a solution of 4.6 g (0.025 mol) of bromocyclooctatetraene in 25 ml of ether was added over a period of 10 min. The mixture was warmed to −40° and stirred for 5 hr at that temperature, then allowed to warm up overnight. Upon hydrolysis (100 ml of water), the product was taken up in ether and the ether solution was washed with water and dried with $MgSO_4$. Distillation of the residue after solvent removal gave 2.86 g (88%) of vinylcyclooctatetraene, bp 90–93° (30 mm), nmr δ 6.3 (1 H, q), 5.7 (7 H, s), 4.9 (2 H, m). This sample has properties identical in all respects with those reported by Cope[7] for vinylcyclooctatetraene isolated from high-boiling residues of cyclooctatetraene preparations.

Anal. Calcd for $C_{10}H_{10}$: C, 92.30; H, 7.70. Found: C, 92.52; H, 7.37.

Cyclopropylcyclooctatetraene.—An ether solution (100 ml) containing 0.2 mol of cyclopropyllithium (prepared from cyclopropyl bromide in the presence of an excess of lithium metal) was added dropwise over 30 min to 39 g (0.10 mol) of CuI·PBu_3 in 100 ml of ether at −70°. After 20 min, 4.6 g (0.025 mol) of bromocyclooctatetraene in 25 ml of ether was added to the clear green solution. After stirring for 5 hr at −50°, the solution was warmed and hydrolyzed with 100 ml of water. The organic

(11) A detailed study of the reactivity of this complex will be reported in a separate communication.

(12) J. Elix and M. Sargent, *J. Amer. Chem. Soc.*, **91**, 4734 (1969); J. Elix, M. Sargent, and F. Sondheimer, *ibid.*, **92**, 962 (1970).

(13) A. Cope, T. Liss, and D. Smith, *ibid.*, **79**, 240 (1957).

(14) B. Johnson, J. Lewis, and G. Randall, *J. Chem. Soc. A*, 422 (1971).

(15) W. Siegl and J. Collman, *J. Amer. Chem. Soc.*, **94**, 2516 (1972).

(16) E. Corey and L. Hegedus, *ibid.*, **91**, 1234 (1969).

(17) W. Burgess and J Eastes, *Inorg. Syn.*, **5**, 197 (1957).

phase was separated and the aqueous layer was extracted with ether. The combined organic fractions were washed with water and dried over $MgSO_4$. Solvent removal followed by distillation gave 3.4 g (95%) of cyclopropylcyclooctatetraene, bp 40–43° (0.01 mm), nmr δ 5.8 (7 H, s), 1.6 (1 H, m), 0.7 (4 H, m).

Anal. Calcd for $C_{11}H_{12}$: C, 91.66; H, 8.34. Found: C, 91.33; H, 8.06.

N,N-**Diethylaminocyclooctatetraene.**—Over a period of 1 hr, 5.6 g (0.05 mol) of potassium *tert*-butoxide was added in small portions to a solution of 9.2 g (0.05 mol) of bromocyclooctatetraene in a mixture of 50 ml of diethylamine and 150 ml of ether at 0°. The suspension was stirred for 3 hr at 0°, and allowed to warm overnight to room temperature. Rapid vacuum filtration to remove precipitated potassium bromide followed by solvent removal gave an orange-brown residue. Attempted distillation, even at 1 μ, resulted in rearrangement to α-*N,N*-diethylaminostyrene. However, the nmr spectrum of the crude preparation is consistent with the *N,N*-diethylaminocyclooctatetraene structure: δ 5.9 (6 H, d, COT protons), 4.5 (1 H, d, enamine proton), 3.2 (4 H, q), 1.2 (6 H, t, ethyls).

N,N-**Dimethylaminocyclooctatetraene.**—Repetition of the above preparation, except that 200 ml of a saturated ether solution of dimethylamine was used, gave from 9.2 g of bromocyclooctatetraene 5.8 g (79%) of *N,N*-dimethylaminocyclooctatetraene by evaporative distillation (<30°) at 0.01 mm: nmr δ 5.8 (6 H, d), 4.4 (1 H, d), 2.6 (6 H, s). The analysis was poor but the assigned structure is supported by the nmr spectrum and by the mass spectral parent peak at *m/e* 147.

Anal. Calcd for $C_{10}H_{13}N$: C, 81.63; H, 8.84. Found: C, 81.11; H, 9.23.

Reaction of Cyclooctatetraenyllithium with Iron Pentacarbonyl.—A solution of 0.05 mol of cyclooctatetraenyllithium in 100 ml of ether at −70° was added dropwise to 19.5 g of iron pentacarbonyl in 100 ml of ether maintained at −70°. The deep red mixture was stirred for 3 hr at −70° and hydrolyzed with 15 ml of acetic acid. The solution was poured onto 250 ml of water and extracted with ether. The combined ether fractions were dried over $MgSO_4$ and the ether was removed under vacuum. The red residue was chromatographed over silica gel with a 5% methylene chloride–pentane mixture, giving 6.1 g (45%) of (formylcyclooctatetraene)iron tricarbonyl.

Cyclooctatetraenealdehyde.—To 100 ml of methyl formate at −30° was added a solution of 0.05 mol of cyclooctatetraenyllithium in 100 ml of ether over a period of 1 hr. The solution was stirred for 3 hr at 0° and hydrolyzed with 100 ml of water. The product was taken up in ether and dried with $MgSO_4$. Distillation of the orange residue after solvent removal gave 5.2 g (79%) of cyclooctatetraenealdehyde, bp 40–45° (0.5 mm), ir 1685 cm^{-1} (C=O).

Anal. Calcd for C_9H_8O: C, 81.81; H, 6.06. Found: C, 81.69; H, 5.98.

Cyclooctatetraenenitrile.—A mixture of 9.2 g of bromocyclooctatetraene, 7.8 g of potassium cyanide, and 22.2 g of $K_4Ni_2(CN)_6$ in 300 ml of absolute methanol was stirred for 8 hr at room temperature. The yellow suspension was poured into water and extracted with ether. The organic phase was washed with water and dried with $MgSO_4$. Solvent removal followed by chromatography of the residue with pentane over silica gel gave 0.52 g (8%) of cyclooctatetraenenitrile.

Cyclooctatetraenenitrile from Cyclooctatetraenyllithium.—Cyanogen was bubbled into 100 ml of ether until a saturated solution was obtained. This solution was cooled to −70°, and 0.05 mol of cyclooctatetraenyllithium in 100 ml of ether at −70° was added dropwise over a period of 20 min. The mixture was stirred for 2 hr at −70°, warmed to room temperature, and hydrolyzed with 200 ml of water. Upon standing overnight to decompose excess cyanogen, the organic phase was separated, washed with water, and dried. After the ether was removed, evaporative distillation of the residue at 1 mm (bath temperature, 40°) gave 1.6 g (25%) of cyanocyclooctatetraene. This sample was identical with the product obtained from $K_4Ni_2(CN)_6$, ir 2190 cm^{-1} (C=N). Yields up to 40% have been obtained by first converting cyclooctatetraenyllithium to the corresponding Grignard reagent by the addition of anhydrous magnesium bromide.

Anal. Calcd for C_9H_7N: C, 83.72; H, 5.43. Found: C, 83.67; H, 5.51.

Registry No.—Bromocyclooctatetraene, 7567-22-8; *p*-methoxyphenylcyclooctatetraene, 23697-18-9; vinylcyclooctatetraene, 37164-12-8; cyclopropylcyclooctatetraene, 37164-13-9; *N,N*-diethylaminocyclooctatetraene, 37164-14-0; *N,N*-dimethylaminocyclooctatetraene, 37164-15-1; cyclooctatetraenealdehyde, 30844-12-3; cyanocyclooctatetraene, 37164-17-3.

A New Synthesis of 2-Hydroxy-3-methylcyclopent-2-en-1-one. III[1]

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A new synthesis of 2-hydroxy-3-methylcyclopent-2-en-1-one (**7**) is described. The Mannich reaction of cyclopentane-1,2-dione (**3**) with morpholine and formalin gave a Mannich base **6**, which was hydrogenolized to afford **7**. However, the Mannich reactions of keto enamines **5a–c**, which are enamino derivatives of **3**, gave the Mannich bases **9a–c**, respectively, which were similarly hydrogenolized to afford 3,5-dimethyl-2-hydroxycyclopent-2-en-1-one (**10**).

2-Hydroxy-3-methylcyclopent-2-en-1-one (**7**) is a flavor constituent, for example, in coffee aroma[2] and maple flavor.[3] Erickson and Collins[4] have utilized **7** as an intermediate in a synthesis of dihydrojasmone, which is useful in perfumery.

Previous papers[1,5] described several routes to synthesize **7** from 2-carbethoxy-2-methylcyclopentanone.[6] In this paper, we wish to report a new synthesis of **7** from cyclopentanone (**1**).

Cyclopentanone (**1**) is monobrominated with dioxane dibromide in ether and 2-bromocyclopentanone (**2**) is oxidized by ferric chloride to afford cyclopentane-1,2-dione (**3**), which exists almost entirely in the enolic form.[7]

In an earlier paper,[1] we reported that the treatment of 2,5-dibromocyclopentanone (**4**) with excess morpholine in ether gives 2-morpholinocyclopent-2-en-1-one (**5a**) in good yield. Cyclopentane-1,2-dione (**3**) is also obtained by the hydrolysis of **5a** in 20% hydrochloric acid.

(1) For previous paper, see K. Sato, Y. Kojima, and H. Sato, *J. Org. Chem.*, **35**, 2374 (1970).

(2) M. A. Gianturco, A. S. Giammarino, and R. G. Pitcher, *Tetrahedron*, **19**, 2051 (1963).

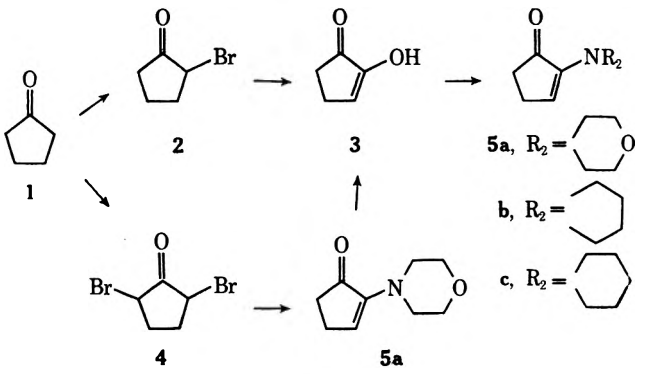
(3) V. J. Filipic, J. C. Underwood, and C. O. Willits, *J. Food Sci.*, **30**, 1008 (1965).

(4) J. L. E. Erickson and F. E. Collins, Jr., *J. Org. Chem.*, **30**, 1050 (1965).

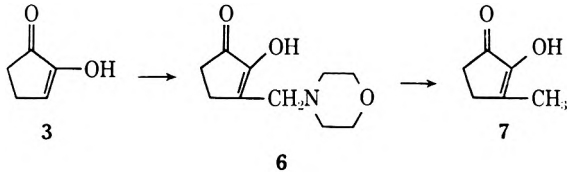
(5) K. Sato, S. Suzuki, and Y. Kojima, *ibid.*, **32**, 339 (1967).

(6) C. M. Leir has recently reported the synthesis of **7** from 2-carbomethoxy-2-methylcyclopentanone [*J. Org. Chem.*, **35**, 3203 (1970)].

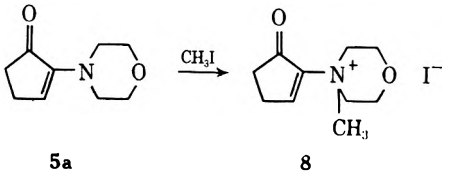
(7) C. W. N. Cumper, G. B. Leton, and A. I. Vogel, *J. Chem. Soc.*, 2067 (1965).



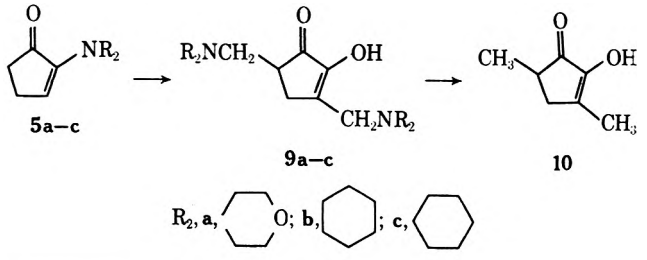
The Mannich reaction[8] of **3** with 1 equiv each of morpholine and formalin in dioxane afforded 2-hydroxy-3-morpholinomethylcyclopent-2-en-1-one (**6**). Since the Mannich base **6** precipitates very rapidly during the reaction, no more reaction occurs even with excess morpholine and formalin. The Mannich base **6** was treated with zinc powder in glacial acetic acid to afford **7** in 58% yield.



The direct methylation of **5a**, which might be a key intermediate in the above-described synthesis of **7**, was also examined. The reaction of **5a** with methyl iodide in acetonitrile gave no C-methylated compound, but did give N-methylated compound, *N*-methyl-*N*-(1-oxo-2-cyclopenten-2-yl)morpholinium iodide (**8**), almost quantitatively.



We studied the indirect methylation of keto enamine **5a**, using the Mannich reaction. The behavior of keto enamines in the Mannich reaction has not been investigated. The Mannich reaction of **5a** with morpholine and formalin in dioxane afforded 3,5-bismorpholinomethyl-2-hydroxycyclopent-2-en-1-one (**9a**). The product gave a positive ferric chloride reaction and had characteristic absorption at 3400 cm^{-1}. The structure of **9a** was assigned on the basis of its nmr, ir, and uv



(8) K. Tonari, I. Ichimoto, H. Ueda, and C. Tatsumi, *Nippon Noge Kagaku Kaishi*, **44**, 55 (1970), report the Mannich reaction of **7**.

TABLE I
THE MANNICH REACTION OF KETO ENAMINES 5a–c UNDER VARIOUS CONDITIONS

Keto enamine	Formalin, equiv	Amine	Equiv	Mannich base	Yield, %
5a	1.0	Morpholine	1.0	**9a**	32
	2.0		1.0		45
	2.0		2.0		73.5
	1.0		None		
	2.0		None		
5b	1.0	Pyrrolidine	1.0	**9b**	23.8
	2.0		1.0		41.6
	2.0		2.0		61.5
5c	2.0	Piperidine	1.0	**9c**	44.1
	2.0		2.0		61.2

spectra. This reaction was examined with various ratios of reagents, that are listed in Table I.

The formation of **9a** was not observed in the absence of morpholine and even with insufficient reagents no mono-Mannich derivative was obtained, while the best yields were obtained with 2 molar equiv each of morpholine and formalin. Moreover, the reaction of **5a** with morpholine and paraformaldehyde in various solvents, for example, ether, ethanol, THF, and dioxane, afforded **9a** in low yield.

Dione **3** reacted with the secondary amines, morpholine, pyrrolidine, and piperidine, to form enamine derivatives **5a–c**. Although 2,5-dibromocyclopentanone (**4**) and excess morpholine gave **5a**, as described above, **4** and the other secondary amines, pyrrolidine and piperidine, gave only trace amounts of the corresponding enamine derivatives (**5b** and **5c**), which were identified by vpc and ir with **5b** and **5c**, synthesized by the above-mentioned method. Then the Mannich reactions of **5b** and **5c** were examined. They also gave bis Mannich bases, **9b** and **9c**.

The hydrogenolysis of the Mannich bases **9a–c** afforded 3,5-dimethyl-2-hydroxycyclopent-2-en-1-one (**10**). The nmr spectrum of this product showed a doublet peak at δ 1.18 corresponding to the 5-methyl group and a singlet peak at δ 2.00 corresponding to the 3-methyl group.

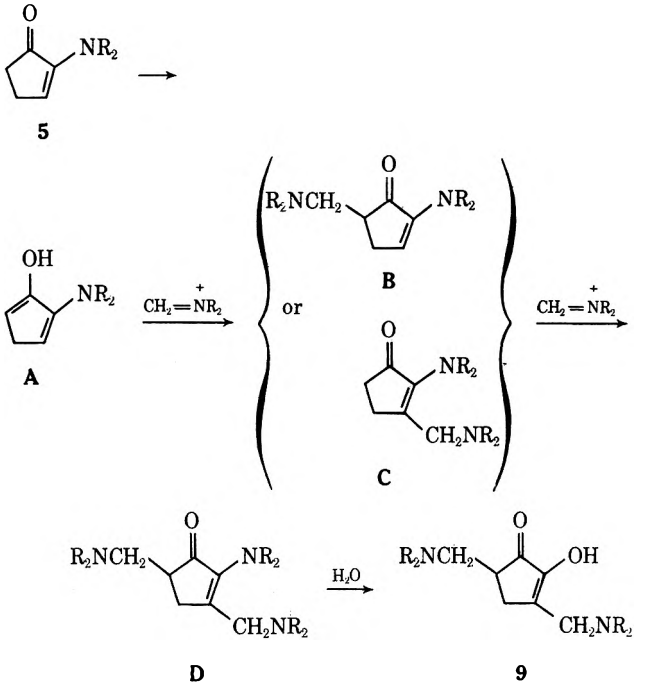
On the basis of these facts we deduced concerning the production of **9a–c** that the first aminomethylation occurs through the normal enolization mechanism. It is not easily explained whether the first aminomethylation occurs at the enol site or at the enamine site. The problem of determining which course, A → B → D or A → C → D, is actually being followed is under investigation. The second aminomethylation followed by hydrolysis during work-up would then lead to the Mannich base (Scheme I).

Experimental Section

General.—Boiling points and melting points are uncorrected. The infrared (ir) spectra were recorded on a Hitachi Model 215 spectrophotometer. The ultraviolet (uv) spectra were recorded on a Hitachi Model EPS-3T spectrophotometer. The nuclear magnetic resonance (nmr) spectra were obtained on a JEOL Model C-60 spectrometer (tetramethylsilane as internal standard). Vapor phase chromatographic (vpc) analysis was performed on a Shimadzu Model GC-1C instrument using a 3 mm × 260 cm column of 25% silicon DC-200 on Celite 545 with He as the carrier gas.

Cyclopentane-1,2-dione (3). A.—A mixture of 10 g (60 mmol) of **5a** and 100 ml of 20% HCl was stirred at room temper-

SCHEME I



ature for 3 hr. The solution was cooled, neutralized with concentrated NaOH solution, and extracted with ether. After evaporation, the residue afforded crystalline product, which was recrystallized from petroleum ether (bp 40–60°), affording 2.5 g (41% yield) of pure **3**: mp 54–55° (lit.[7] mp 50–52°, lit.[8] mp 55–56°).

B.—**3** was prepared by the procedure of Acheson[9] from 15.6 g (96 mmol) of 2-bromocyclopentanone (**2**) and 42 g (0.80 mol) of ferric chloride in water at 95–98° for 10 min. Distillation of the dried extract gave 5.6 g (59.8% yield) of **3**, bp 84–86° (8 mm) [lit.[8] bp 78–86° (8 mm)]. The distillate solidified spontaneously.

2-Morpholinocyclopent-2-en-1-one (5a). A.—To a stirred solution of 23.2 g (95 mmol) of **4** in 100 ml of dry ether and 20 ml of dry acetone was added dropwise 41.5 g (0.48 mol) of morpholine in 50 ml of dry ether at 0–5°. The precipitated morpholine hydrobromide was filtered, and solvents and the surplus morpholine were removed under reduced pressure. The residue was recrystallized from ethanol to afford 13.0 g (82% yield) of **5a**, mp 63–64° (lit.[1] mp 63°).

B.—A mixture of 2.0 g (20 mmol) of cyclopentane-1,2-dione (**3**), 2.1 g (25 mmol) of morpholine, and 40 ml of benzene was refluxed with removal of water for 1 hr. The benzene and the surplus morpholine were removed and the residue was cooled in a Dry Ice box. The precipitated solid was collected and recrystallized from isopropyl ether to afford 3.6 g (61.5% yield) of **5a**.

2-Pyrrolidinocyclopent-2-en-1-one (5b).—The preparation of **5b** was carried out according to procedure B described above. A mixture of 5.7 g (58 mmol) of **3**, 5.0 g (70 mmol) of pyrrolidine, and 60 ml of benzene was refluxed for 3.5 hr. After removal of benzene and the surplus pyrrolidine, distillation of the residue gave 6.2 g (72% yield) of **5b**: bp 81–84° (0.23 mm); $n^{20}D$ 1.5401; uv max (99% EtOH) 316 nm (ε 3400); ir (neat) 1680, 1600, 1380, 1300, 1150, 760 cm^{-1}; nmr (CCl_4) δ 5.55 (t, 1, J = 3 Hz), 3.20 (m, 4), 2.35 (m, 4), 1.80 (m, 4).

Anal. Calcd for $C_9H_{13}ON$: C, 71.49; H, 8.67; N, 9.26. Found: C, 71.05; H, 8.71; N, 9.31.

2-Piperidinocyclopent-2-en-1-one (5c).—The preparation of **5c** was carried out according to procedure B described above. **3** (2.5 g, 26 mmol) and 2.6 g (31 mmol) of piperidine gave 3.6 g (85.4% yield) of **5c**: bp 88–89° (0.25 mm); $n^{20}D$ 1.5296; uv max (99% EtOH) 288 nm (ε 3650); ir (neat) 1710, 1610, 1110, 1005, 780 cm^{-1}; nmr (CCl_4) δ 5.91 (t, 1, J = 3 Hz), 2.90 (m, 4), 2.33 (m, 4), 1.52 (m, 6).

Anal. Calcd for $C_{10}H_{15}ON$: C, 72.69; H, 9.15; N, 8.48. Found: C, 73.09; H, 8.86; N, 8.60.

2-Hydroxy-3-morpholinomethylcyclopent-2-en-1-one (6).—To 4.9 g (50 mmol) of **3** in 6 ml of dioxane and 4.3 g (50 mmol) of morpholine was added dropwise slowly at room temperature 4.0 g (50 mmol) of formalin. Soon the mixture crystallized, and the crystals were recrystallized from ethanol to afford 6.3 g (60% yield) of **6**: mp 141.5°; uv max (99% EtOH) 261 nm (ε 12,100); ir (KBr) 3400, 1690, 1650, 1110 cm^{-1}; nmr ($CDCl_3$) δ 7.84 (s, 1), 3.83 (m, 4), 3.45 (s, 2), 2.61 (m, 4), 2.42 (s, 4).

Anal. Calcd for $C_{10}H_{15}O_3N$: C, 60.90; H, 7.76; N, 7.10. Found: C, 61.03; H, 7.71; N, 6.67.

2-Hydroxy-3-methylcyclopent-2-en-1-one (7).—A mixture of 6.3 g (30 mmol) of **6**, 50 ml of glacial acetic acid, and 13 g (0.20 g-atom) of zinc powder was stirred at 80° for 5 hr. After zinc was filtered off and acetic acid was removed under reduced pressure, a small amount of water was added. The solution was extracted with chloroform. After drying, the chloroform was evaporated and the residue was recrystallized from water to afford 2.0 g (58% yield) of **7**: mp 102–103° (lit.[10] mp 102–104°).

***N*-Methyl-*N*-(1-oxo-2-cyclopenten-2-yl)morpholinium Iodide (8).**—To 0.8 g (4.8 mmol) of **5a** in 10 ml of acetonitrile was added 2.3 g (16 mmol) of methyl iodide, and the mixture was heated with stirring under reflux for 6 hr. The mixture was kept overnight at room temperature. The precipitated solid was recrystallized from ethanol to afford 1.4 g (93% yield) of **8**: mp 165°; ir (KBr) 1720, 1625, 1115 cm^{-1}; nmr (D_2O) δ 8.38 (t, 1, J = 1.5 Hz), 4.60–3.66 (m, 8), 3.55 (s, 3), 3.08–2.60 (m, 4).

Anal. Calcd for $C_{10}H_{16}O_2NI$: C, 38.85; H, 5.22. Found: C, 38.87; H, 5.20.

3,5-Bismorpholinomethyl-2-hydroxycyclopent-2-en-1-one (9a).—To 5.0 g (30 mmol) of **5a** in 10 ml of dioxane and 5.2 g (60 mmol) of morpholine was added dropwise slowly at room temperature 4.9 g (60 mmol) of formalin. The precipitated solid was recrystallized from isopropyl ether to afford 6.5 g (73.5% yield) of **9a**: mp 126–127°; uv max (99% EtOH) 266.5 nm (ε 5100); ir (KBr) 3400, 1695, 1115 cm^{-1}; nmr ($CDCl_3$) δ 7.45 (s, 1), 3.85 (m, 8), 3.50 (m, 4), 2.61 (m, 8), 2.46 (m, 3).

Anal. Calcd for $C_{15}H_{24}O_4N_2$: C, 60.79; H, 8.16; N, 9.45. Found: C, 60.73; H, 8.68; N, 9.56.

3,5-Bispyrrolidinomethyl-2-hydroxycyclopent-2-en-1-one (9b).—The preparation of **9b** was carried out according to the procedure described above. From 3 g (20 mmol) of **5b** in 15 ml of dioxane, 2.8 g (40 mmol) of pyrrolidine, and 3.2 g (40 mmol) of formalin, 3.1 g (61.5% yield) of **9b** was obtained after recrystallization from ethanol: mp 127–128°; uv max (99% EtOH) 263 nm (ε 6040); ir (KBr) 2950, 2770, 2550–2300, 1690, 1660, 1410, 1340 cm^{-1}; nmr ($CDCl_3$) δ 8.17 (s, 1), 3.43 (m, 1), 2.76–2.10 (m, 12), 1.93–1.46 (m, 10).

Anal. Calcd for $C_{15}H_{24}O_2N_2$: C, 68.15; H, 9.15; N, 10.60. Found: C, 68.27; H, 9.59; N, 10.28.

3,5-Bispiperidinomethyl-2-hydroxycyclopent-2-en-1-one (9c).—The preparation of **9c** was carried out according to the procedure described above. From 1.2 g (7.3 mmol) of **5c** in 10 ml of dioxane, 1.3 g (15 mmol) of piperidine, and 1.2 g (15 mmol) of formalin, 1.3 g (61.2% yield) of **9c** was obtained after recrystallization from isopropyl ether: mp 133–134°; uv max (99% EtOH) 262 nm (ε 5560); ir (KBr) 3500, 2900, 1690, 1650, 1340, 1100 cm^{-1}; nmr ($CDCl_3$) δ 6.10 (s, 1), 3.30 (m, 1), 2.80–2.00 (m, 12), 1.96–1.08 (m, 14).

Anal. Calcd for $C_{17}H_{28}O_2N_2$: C, 69.83; H, 9.65; N, 9.58. Found: C, 70.19; H, 10.05; N, 9.76.

3,5-Dimethyl-2-hydroxycyclopent-2-en-1-one (10). A.—A mixture of 6.0 g (20 mmol) of **9a**, 50 ml of glacial acetic acid, and 13 g (0.20 g-atom) of zinc powder was stirred at 80° for 5 hr. After zinc was filtered off, acetic acid was removed under reduced pressure, a small amount of water was added, and the solution was extracted with chloroform. After drying, the chloroform was evaporated to dryness and the residue was recrystallized from water to afford 0.8 g (32% yield) of **10**: mp 91–92°; uv max (99% EtOH) 261 nm (ε 12,100) [lit.[10] mp 91–91.5°; uv max (EtOH) 259 nm (ε 11,800)]; ir (KBr) 3250, 1690, 1640, 1130 cm^{-1}; nmr (CCl_4) δ 6.48 (s, 1), 2.97–1.85 (m, 3), 2.00 (s, 3), 1.18 (d, 3, J = 6 Hz).

Anal. Calcd for $C_7H_{10}O_2$: C, 66.65; H, 7.99. Found: C, 66.58; H, 8.25.

B.—Similarly, from 1.6 g (6.1 mmol) of **9b**, 20 ml of glacial acetic acid, and 4.0 g (0.061 g-atom) of zinc powder, 0.3 g (39.5% yield) of **10** was obtained.

C.—Similarly, from 1.5 g (5.1 mmol) of **9c**, 20 ml of glacial

(9) R. M. Acheson, *J. Chem. Soc.*, 4232 (1956).

(10) M. A. Gianturco and P. Friedel, *Tetrahedron*, **19**, 2039 (1963).

acetic acid, and 3.3 g (0.051 g-atom) of zinc powder, 0.25 g (38.5% yield) of **10** was obtained.

Acknowledgment.—The authors wish to thank Mr. T. Morofushi for his technical assistance.

Registry No.—**5a**, 24454-33-9; **5b**, 36287-24-8; **5c**, 37150-25-7; **6**, 37150-26-8; **7**, 80-71-7; **8**, 37160-44-4; **9a**, 37164-08-2; **9b**, 37164-09-3; **9c**, 37164-10-6; **10**, 21834-98-0.

Mono- and Di-2,2,2-trichloroethyl Acetals as Protecting Groups

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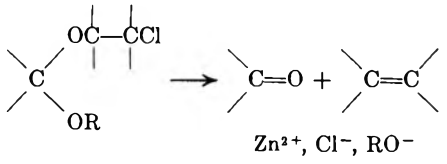
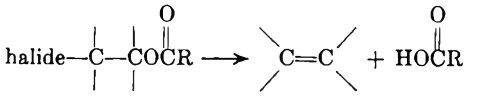
Mono- and di-2,2,2-trichloroethyl acetals have been selectively prepared in good yields by acid-catalyzed alcohol exchange with 2,2,2-trichloroethanol and dimethyl or diethyl acetals. A nonacidic and aprotic reductive cleavage using activated zinc dust in ethyl acetate or THF regenerates the carbonyl.

In connection with other synthetic work in these laboratories it was desirable to have available a protecting group for aldehydes that could be removed in a mild, selective, and nonacidic manner. The title compounds were therefore developed on the basis that the known reductive elimination of β-alkoxy halides[1] could, in the case of acetals, regenerate the carbonyl (eq 1). Reduction has previously been used



(1)

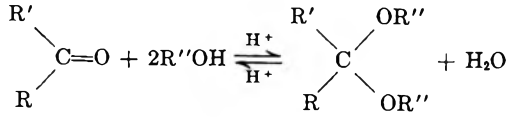
effectively in the removal of the 2-haloethyl carbonate (carbamate) protecting group from alcohols (amines), and the removal of the 2-haloethyl group from esters (eq 2).[2]



(2)

We would like to report the success of this overall design whereby a convenient, general synthesis of both the mono- and bis-2,2,2-trichloroethyl acetals has been developed and the optimum conditions for removal of the protecting group have been determined for a variety of systems.

Traditionally, an acetal is most expeditiously prepared from the aldehyde or ketone by treatment with the corresponding alcohols and a strong acid under conditions which would favor the equilibrium shown below (eq 3). Such methods as the use of excess al-

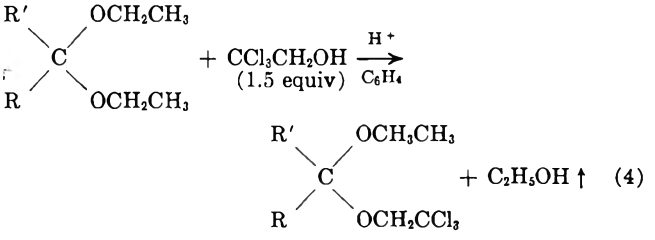


(3)

cohol, the use of a water scavenger such as triethyl orthoformate, or the azeotropic removal of water have all been employed.[3] These published techniques were found to be unsatisfactory with trichloroethanol, however, presumably due to the inductive ($-I$) effect of the trichloromethyl group which makes trichloroethanol less nucleophilic and less able to stabilize any intermediate carbonium ion. The use of tris-2,2,2-trichloroethyl orthoformate as a water scavenger was considered impractical due to its difficulty in preparation and its great stability to acid.[4]

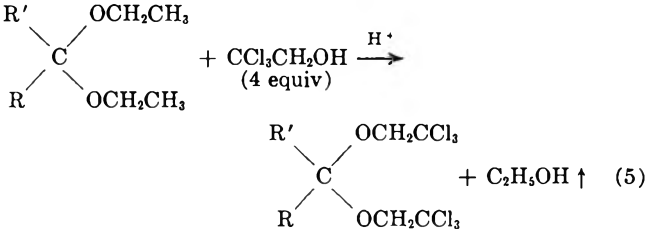
The method of choice for the preparation of trichloroethyl acetals proved to be a *p*-toluenesulfonic acid catalyzed alcohol exchange of a diethyl (or dimethyl) acetal with trichloroethanol in benzene or xylene. In this conversion, commerically available dimethyl or diethyl acetals were used whenever possible. However, in the majority of cases the free aldehyde or ketone was converted into the diethyl acetal with triethyl orthoformate and used without isolation in the subsequent alcohol exchange with trichloroethanol.

In the synthesis of the trichloroethyl acetals shown in Table I, advantage was taken both of the high boiling point of trichloroethanol, which allowed continuous removal of ethanol as an azeotrope, and of the acid stability of trichloroethyl ethers, which permitted the introduction of either one or two trichloroethoxy groups. For example, the use of 1.5 equiv of trichloroethanol in benzene gave the mixed acetal almost exclusively (eq 4), while the use of 4 equiv of trichloroethanol in



(4)

xylene gave good yields of the bistrichloroethyl acetals (eq 5).



(5)

A systematic search for the best experimental conditions for elimination soon focused on the use of ac-

(1) See, for example, O. Grummitt, *et al.*, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 748, and references cited therein.

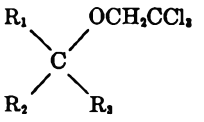
(2) E. Kasafirek, *Tetrahedron Lett.*, **20**, 2021 (1972); M. F. Semmelhack and G. E. Heinsohn, *J. Amer. Chem. Soc.*, **94**, 5139 (1972), and references therein.

(3) C. A. Buehler and D. E. Pearson, "Survey of Organic Synthesis," Wiley, New York, N. Y., 1970, Chapter 9.

(4) A. Kankaanpira and M. Lahti, *Suom. Kemistilehti B*, **42**, 406 (1969).

TABLE I

TRICHLOROETHYL ACETALS

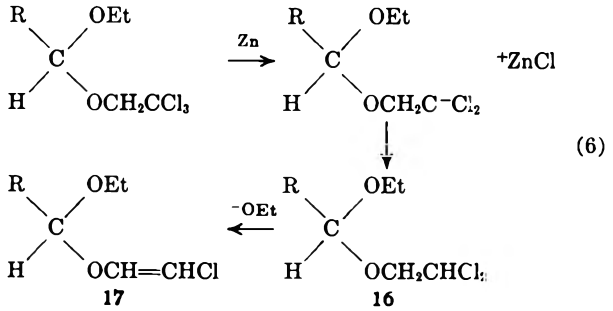


No.	R_1	R_2	R_3	Registry no.	Yield,[b] %	Method	Mp or bp (mm), °C	Nmr shift (τ),[g] $-OCH_2CCl_3$	Zinc elimination: Solvent	Zinc elimination: Reflux time, hr	Zinc elimination: Yield,[i] %	Acid hydrolysis[k]: Solvent[l]	Acid hydrolysis[k]: Time,[m] min
1	$PhCH_2-$	H	OCH_3	37150-37-1	60	A[c]	114 (0.6)	5.95 (AB)[h]	EA	7	40	THF	180
2	$CH_3(CH_2)_6-$	H	OC_2H_5	37150-38-2	81	A	88 (0.5)	5.88 (S)	EA	12	90	THF	5
3	$CH_3(CH_2)_6-$	H	OCH_2CCl_3	37150-39-3	72	A	120 (0.5)	5.78 (S)	EA	11	70	THF	n
4	$-(CH_2)_4-$		OC_2H_5	37150-40-6	72	B	77 (13)	6.03 (S)	THF	18	100	Dioxane	5
5	$-(CH_2)_4-$		OCH_2CCl_3	37150-41-7	52	A	70–72°[d]	7.52 (S)	THF	11	85	Dioxane	60
6	Ph–	H	OC_2H_5	37150-42-8	65	B	79 (0.4)	6.04 (AB)	THF	11	100	THF	5
7	Ph–	H	OCH_2CCl_3	37150-43-9	43	B	145 (0.2)	5.80 (S)	THF	11	100	THF	60
8	$[CH_3]_2C=CHCH_2CH_2$	CH_3	OC_2H_5	37150-44-0	50	B	100 (0.1)	6.00 (S)	THF	12	96	Dioxane	5
9		H	OC_2H_5	37150-45-1	78	B	95–100 (0.4)	5.95 (AB)	EA	4	83	THF	5
10	$PhC\equiv C-$	H	OCH_3	37150-46-2	50	B	141–145 (1.5)	5.71 (AB)	THF	5	40	Dioxane	120
11	Ph–	Ph	OCH_3	37150-47-3	84	A[c]	128–129[e]	6.10 (S)	EA	3	86	THF	10
12	n-C_3H_7-	n-C_3H_7	OCH_2CCl_3[a]	37406-78-3	76	B	99–100[f]	5.85 (S)	EA	3	100	Dioxane	70
13	$PhCH=CH-$	H	OC_2H_5	37150-48-4	50	B	138 (0.2)	5.88 (S)	EA	3	62	THF	5
14	$PhCH=CH-$	H	OCH_2CCl_3	37150-49-5	49	B	170 (0.1)	5.72 (S)	EA	4	73	THF	90
15	$CH_3C(OCH_3)HCH_2$	H	OCH_3	37150-50-8	53	A[c]	113 (10)	5.90 (S)	EA	12	j	Dioxane	25

[a] Monotrichloroethyl acetal could not be purified. [b] Yield after distillation. [c] Commercially available. [d] Recrystallized from hexane. [e] Recrystallized from acetone–water. [f] Recrystallized from acetone–water and sublimed [95° (0.2 mm)]. [g] Nmr taken in $CDCl_3$ or CCl_4. [h] In all cases where an AB pattern was displayed, $J/\Delta\nu$ 2–4. [i] Yield based on product judged better than 90% pure by nmr. [j] Aldehyde formation but with unidentified by-product. [k] Water–THF–p-toluenesulfonic acid. [l] Dioxane was used whenever necessary for nmr clarity. [m] Time required for better than 95% hydrolysis by nmr. [n] No reaction after 30 hr.

tivated zinc dust in ethyl acetate or tetrahydrofuran (THF). It can be seen from Table I that refluxing zinc in ethyl acetate works well for both the formation of aldehydes and ketones, while THF is best suited for those eliminations producing ketones. No decomposition was observed when solutions of the acetals in THF or ethyl acetate were refluxed in the absence of zinc. A comparison of activated zinc with a zinc-copper couple indicated that activated zinc was superior.

While the use of activated zinc in ethyl acetate or THF produced only aldehydes or ketones, several additional products were observed when other solvents were used. For example, acetic acid rapidly consumed the activated zinc with no recognizable carbonyl products produced. Moreover, the acetals **1**, **2**, and **10** when treated with zinc in ethanol gave only small amounts of reduction products **16** and **17** (eq 6).



(6)

The use of acetone as solvent gave improvements in yields of aldehydes from **1**, **2**, and **10**, but generated significant amounts of diacetone alcohol.

The stability of 2-chloroethyl ethers to acid has been previously observed.[4,5] Comparisons were therefore made between the rates of hydrolysis for trichloroethyl acetals and those for the corresponding diethyl or dimethyl acetals. When p-toluenesulfonic acid in THF–water was used all of the monotrichloroethyl acetals hydrolyzed noticeably although not appreciably slower than the coresponding diethyl or dimethyl systems. However, significant rate differences were observed for the bistrichloroethyl acetals such that the acid stability might be used as an additional option in synthetic design.

The procedure as outlined above offers a new method for the protection of aldehydes and ketones or, alternatively, for the hydrolysis of an ordinary acetal under nonaqueous conditions by alcohol exchange with trichloroethanol and subsequent zinc reduction.

Experimental Section

All boiling points and melting points are uncorrected. All of the trichloroethyl acetals are new compounds and gave satisfactory (±0.4%) analyses for carbon and hydrogen.

Materials.—The following items were obtained from Aldrich Chemical Co., Milwaukee, Wis., trichloroethanol (98%, distilled prior to use), triethyl orthoformate, p-toluenesulfonic acid monohydrate, phenylacetaldehyde dimethyl acetal, benzophenone dimethyl acetal, and 3-methoxybutyraldehyde dimethyl acetal. Aldehydes and ketones were obtained from a variety of sources and distilled prior to use. The zinc used was Mallinckrodt reagent grade. Both ethyl acetate and THF were the best commercial grades and were used as received.

Preparation of Diethyl Acetals.—The diethyl acetal was prepared by refluxing the aldehyde or ketone (0.1 mol) with triethyl orthoformate (16.3 g, 0.11 mol), absolute ethanol (13.8 g, 0.3 mol), and a trace of anhydrous ferric chloride in benzene (150 ml). An overnight reflux (drying tube) was sufficient for all those acetals prepared in this manner. The solution was then neutralized with sodium ethoxide, filtered, concentrated, and distilled. The freshly distilled diethyl acetal was then subjected to method A.

Preparation of Monotrichloroethyl Acetals. Method A.—A solution consisting of the diethyl or dimethyl acetal (0.1 mol) in benzene (150 ml) was heated on a steam bath in an apparatus set up for simultaneous liquid addition and distillation. Trichloroethanol (17.9–22.4 g, 0.12–0.15 mol) dissolved in benzene (30 ml) was added to the dropping funnel. Benzene was allowed to distil until a steady boiling point of about 81° was obtained. Approximately 3 ml of the trichloroethanol–benzene solution was then added, followed by the addition of p-toluenesulfonic acid

(5) T. Hara and J. Azizian, *Tetrahedron Lett.*, 4443 (1969).

monohydrate (25 mg). A drop of several degrees in the distillate temperature indicates removal of ethanol or methanol. Best results were obtained with a rapid distillation and a rate of addition of 1 drop/sec. Distillation was continued (additional benzene may be required) until the distillate temperature returned to 81°. Anhydrous sodium carbonate was then added, and the solution was filtered, concentrated, and distilled under vacuum through a 30-cm column packed with glass helices and heated with an electrical heating tape.

Method B.—The diethyl acetal was prepared as indicated above but was not neutralized with sodium ethoxide. Instead, the benzene was distilled off to remove ethyl formate and ethanol from the reaction mixture (more benzene may be required to bring the distillate temperature to 81°) and the crude residue was then subjected to method A.

Preparation of Bistrichloroethyl Acetals.—Either method A or B may be employed with the following modifications: (1) use 0.1 mol of the acetal and 0.4 mol (59.6 g) of trichloroethanol, (2) add the acetal in xylene to trichloroethanol in xylene, (3) distil until the boiling point of xylene is reached, then distil for one additional hour.

Zinc Elimination.—The trichloroethyl acetal (1.0 g) was refluxed in ethyl acetate or THF with zinc (2.0 g), previously activated by washing with 5% HCl, H_2O, ethanol, ether, and drying *in vacuo* over P_2O_5. The solution was then filtered, enriched with ether, washed with 1% HCl, 5% sodium bicarbonate, brine, dried (sodium sulfate), and evaporated to give the free aldehyde or ketone.

Acid Hydrolysis.—A solution consisting of the acetal (0.05 mol) THF or dioxane (9 ml) water (0.5 ml) and *p*-toluenesulfonic acid monohydrate (50 mg) was refluxed until the nmr of the reaction mixture indicated greater than 95% hydrolysis to the aldehyde or ketone.

Acknowledgment.—We gratefully acknowledge support of this work by the National Institutes of Health, Grant No. A1-10,597-01.

Glyoxal Derivatives. V. Reaction of Alcohols with Glyoxal[1]

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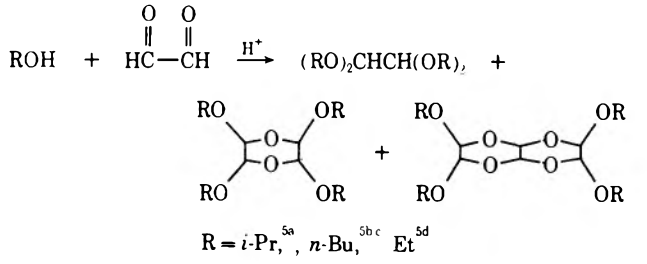
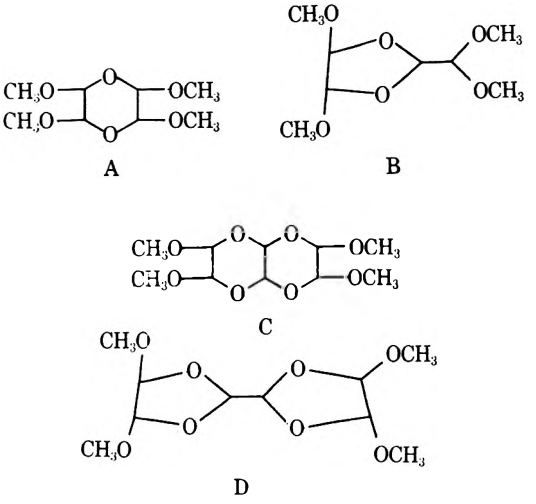
Received September 6, 1972

Aqueous glyoxal reacts with alcohols to give glycolates and acetal products consisting of 1,1′,2,2′-tetraalkoxyethanes, 1,3-dioxolanes, and 1,3-bisdioxolanes. It is shown that the dioxolanes are, in fact, the structures which have heretofore been misassigned as dioxane and naphthodioxanes. The relative abundance of any of the acetal products depends on the initial glyoxal concentration as well as the initial ratio of alcohol to glyoxal in the reaction mixture. It is also shown that dioxolane formation can be rationalized not only by the reaction of alcohol with dimeric and trimeric glyoxal, but also *via* the direct reaction of glyoxal with any of the already formed acetals.

The observation that glyoxal reacts readily with alcohols under acid conditions to give 1,1′,2,2′-tetraalkoxyethanes is well documented.[2-4] It has also been reported that higher molecular weight products are also afforded,[4,5] *i.e.*, the corresponding tetraalkoxydioxane and naphthodioxane derivatives.



More recently, we demonstrated[1] that one of the products derived from methyl alcohol and glyoxal was not the expected *p*-dioxane derivative A, but was rather the 1,3-dioxolane derivative B, and that the product derived from glyoxal trimer was not the naphthodioxane product, C, but was, in reality, the bis-1,3-dioxolane, D.



In this paper we shall present our findings on the general reaction of glyoxal with alcohols, as well as a partial insight into the equilibrium reactions of glyoxal with itself.

Results

We have found that, in general, the products of the reaction of glyoxal with alcohols include not only the bisacetals, but also glycolates, dioxolanes and bisdioxolanes (eq 1). The 1,3-dioxolane products were not isolated in addition to the previously presumed *p*-dioxane products, but, in fact, were the same compounds whose structures have been incorrectly assigned.[5]

Furthermore, the relative abundance of any of the acetal products (M, D, or T) depends on the initial

* Address correspondence to this author at GAF Corporation, 1361 Alps Road, Wayne, N. J. 07470.

(1) For previous paper, see J. M. Kliegman, E. B. Whipple, M. Ruta, and R. K. Barnes, *J. Org. Chem.*, **37**, 1276 (1972).

(2) C. B. Purves, U. S. Patent 2,194,405 (March 19, 1940).

(3) L. G. MacDowell and R. W. McNamee, British Patent 559,362 (Feb 16, 1944).

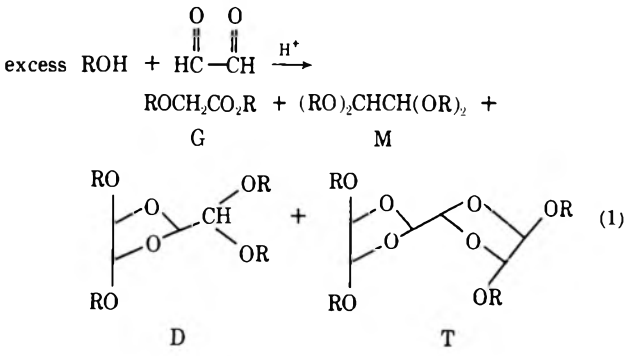
(4) Union Carbide Product Booklet, "General Chemistry of Glyoxal" F-41296, 1965.

(5) (a) O. C. Dermer and J. P. Yuk, *J. Amer. Chem. Soc.*, **77**, 1285 (1955); (b) B. DuVal, R. H. Hall, and B. K. Howe, *J. Appl. Chem.*, **2**, 546 (1952); (c) H. Fiesselmann and F. Horndler, *Chem. Ber.*, **87**, 906 (1954); (d) F. Chartrette, M. Chartrette, J. C. Duplan, and J. Delman, *Tetrahedron*, **27**, 5597 (1971).

TABLE I
PRODUCTS ISOLATED FROM ALCOHOL–GLYOXAL REACTIONS

Alcohol	ROH/glyoxal	% glyoxal	Yields,[a] % G	M	D	T	Residue
Hexanol	5:1	40	8 (1)	90 (2)			
2-Ethylhexanol	5:1	40		88 (3)			10
2-Pentanol	5:1	40	8 (4)	35 (5)	44 (6)		4
Cyclopentanol	5:1	40	8 (7)	73 (8)			10
2-Butanol	5:1	40	10 (9)	31 (10)	42 (11)		
Allyl alcohol	5:1	40	7 (12)	69 (13)	22 (14)		
Allyl alcohol	5:1	80	7	43	16		28 (15), mol wt 750
1-Butanol	5:1	40	10 (16)	80 (17)	8 (18)		
1-Butanol	4:1	80	10	63	16	5 (19)	
1-Butanol	2:1	40	9	10	52	23	
Ethanol	4:1	40	5 (28)	40 (20)	31 (21)		
Methanol	4:1	80	6 (22)	45 (23)	9 (24)		
Methanol	2:1	80	4	7	15	20 (25)	
2-Propanol	4:1	40		*b*	10 (26)	27 (27)	

[a] G is glycolate; M is monomer, based on glyoxal; D is dimer, based on glyoxal; T is trimer, based on glyoxal. [b] We were unable to isolate any monomer acetal. The only open product was a highly reactive material which appeared to be a linear dimer acetal in 15% yield.



glyoxal concentration as well as the ratio of alcohol to glyoxal utilized in the reaction.

In this study, we also show that the formation of acetal products based on dimeric and trimeric glyoxal can be rationalized not only by the reaction of dimeric and trimeric glyoxal with the alcohol, but also from the reaction of glyoxal directly with any of the already formed acetals.

Experimental Section[1,6]

In a typical experiment 5 mol of alcohol and 1 mol of glyoxal were mixed with 1–2 g of *p*-toluenesulfonic acid in a distillation flask. The mixture was brought to reflux and water removed azeotropically by the refluxing alcohol *via* a continuous Dean–Stark tube. In those cases where water solubility prevented separation of the water, another agent was used. Thus, for the reactions of ethanol, methanol, and isopropyl alcohol, the agents were carbon tetrachloride, chloroform, and benzene, respectively. In all cases, the pressure was regulated so that the kettle temperature did not rise above 120°. After water ceased to be generated, the reaction mixture was distilled through a Nester–Faust spinning-band column to give the observed products.

Table I lists the alcohols used in these reactions as well as the yields of glycolate, monomer, dimer, trimer, and residues. The terminology of monomer, dimer, etc., refers to the number of glyoxal residues in the molecule.

Table II lists the physical properties of the products given in Table I.

(6) Melting and boiling points are uncorrected. Infrared, nmr, and mass spectra were recorded on Perkin-Elmer, Varian A60A, and an AIC MS 9 spectrometers. Molecular weights were determined by Crobaugh Laboratories, Cleveland, Ohio. Elemental analysis were performed by the UCC staff.

TABLE II
PHYSICAL PROPERTIES OF PRODUCTS OBSERVED IN TABLE I[a]

Compound	Bp, °C (mm)	$n^{25}D$	Lit. values Bp, °C (mm)	Lit. values n_D
1	119 (3)	1.4321		
2	197 (2)	1.4366		
3	202–212 (3)	1.4455	215–25 (2)[g]	
4	100–110 (3)	1.4202		
5	137 (3)	1.4302		
6	173 (3)	1.4353		
7	101–106 (4)	1.4740		
8	170–180 (4)	Mp 34–37°		
9	90–98 (5)	1.4230	203–204 (743)	$n^{25}D$ 1.4150[b]
10	100–115 (5)	1.4263		
11	115–180 (5)	1.4314		
12	64–70 (3)	1.4475	95–97 (18)	$n^{20}D$ 1.4435[c]
13	92–95 (2)	1.4520	155–160 (25–30)[d]	
14	136–138 (2)	1.4600		
16	95 (10)	1.4234	113–115 (17.5)	$n^{25}D$ 1.4160[e]
17	130–140 (3)	1.4241	159–161 (10)[5c]	
18	160–170 (3)	1.4308	195–202 (10)[5c]	$n^{29}D$ 1.4315[5a]
19	185–205 (1–2)	1.4397		
20	84–85 (10)	1.4035	79 (10)[f]	$n^{20}D$ 1.4051
21	120–121 (4)	1.4238	135 (12)[5d]	
22	58–68 (110)	1.3968	57 (50)	$n^{25}D$ 1.3940[g]
23	83–85 (48)	1.4006	78–79 (50)	$n^{25}D$ 1.4010
24	98–99 (5)	1.4225	*h*	*h*
25	105–108 (5)	Mp 109–110°	*h*	*h*
26	108–110 (3)	1.4216	139 (8–9)	$n^{20}D$ 1.4242[5b]
27	153–155 (2)	Mp 49–58°	165–169 (8)	Mp 48–60[5b]

[a] Satisfactory analytical data (±0.4% for C, H, and ±6.0% for molecular weights (cryoscopic in benzene)) were reported for all new compounds in the table. [b] H. R. Henze and E. N. Kahlenberg, *J. Amer. Chem. Soc.*, **80**, 1664 (1958). [c] General Electric, U. S. Patent 240,659 (1944); *Chem. Abstr.*, **41**, 772 (1947). [d] P. Talet, U. S. Patent 3,197,447 (1965). [e] R. W. McNamee and L. G. McDowell, U. S. Patent 2,366,276 (1945). [f] H. A. Stansbury and D. T. Manning, U. S. Patent 3,130,234 (April 21, 1964). [g] H. Adkins, *et al.*, *J. Amer. Chem. Soc.*, **71**, 3629 (1949); D. J. Loder, U. S. Patent 2,302,618 (1943). [h] *Cf.* ref 1.

Structural Assignments

The structures of our products were deduced from their infrared spectra, molecular weight, elemental analysis, and nuclear magnetic resonance spectra. The glycolates were identified by a comparison of their infrared spectra with the infrared spectra of the known glycolates of 2-butanol, allyl alcohol, and 1-butanol. The unknown glycolates were identified from their infrared and mass spectra. Our analysis of the nuclear magnetic resonance spectra of the remaining acetals provides the bulk of the proof of structure of these

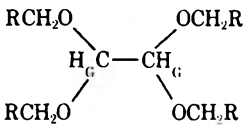
TABLE III
NMR SPECTRA OF ACETAL PRODUCTS[a]

Compd	ROH	Solvent	Acetal proton	R protons				Dioxolane protons		R protons			
				-C(H)O-	CH_2	CH	CH_3	$C_{4,5}$ H	$C_{2,\alpha}$ H	-C(H)O-	CH_2	CH	CH_3
2	Hexanol	Neat	4.27 (s)	3.55 (m)	1.38 (m)		0.95 (tr)						
3	2-Ethyl-hexanol	Neat	4.25 (s)	3.45 (m)	1.33 (m)	1.33 (m)	0.92 (m)						
5	2-Pentanol	Neat	4.17 (d, 2.0 Hz)	3.66 (m)	1.42 (m)		1.03 (d, 5.0 Hz) 0.90 (tr)						
8	Cyclopentanol	Neat	4.20 (s)	4.20	1.62								
		CS_2	4.17 (s)	4.17	1.60								
		Pyridine	4.45 (s)	4.30 (m)	1.68								
		CCl_4	4.20 (s)	4.20	1.62								
10	2-Butanol	Neat	4.28 (d, 1.0 Hz)	3.65 (q, 6.0 Hz)	1.40 (q, 6.0 Hz)		1.10 (d, 6.0 Hz) 0.90 (tr, 6.0 Hz)						
13	Allyl alcohol	Neat	4.42 (s)	4.20 (m)	5.33 (m) 5.08 (m)	5.83 (m)							
17	1-Butanol	Neat	4.18 (s)	3.50 (m)	1.47 (m)		0.73 (m)						
20	Ethanol	Neat	4.28 (s)	3.58 (q, d, 7.0 Hz, 2.0 Hz)			0.73 (m) 1.13 (tr, 7.0 Hz)						
6	2-Pentanol	Neat						4.92 (d)	4.90 (d, 5.0 Hz) 4.28 (d, 5.0 Hz)	3.67 (m)	1.40 (m)		1.15 (m) 0.90 (m)
11	2-Butanol	CCl_4						5.00 (d)	4.98 (d, 6.0 Hz) 4.28 (d, 6.0 Hz)	3.63 (m)	1.43 (q, 6.0 Hz)		1.12 (d, 6.0 Hz) 0.90 (tr, 7.0 Hz)
14	Allyl alcohol	Neat						5.10 (d)	5.00 (obscured) 4.38 (d, 6.0 Hz)	4.12 (m)	5.37 (m) 5.08 (m)	5.83 (m)	
18	1-Butanol	Neat						4.97 (d)	5.12 (d, 6.0 Hz) 4.30 (d, 6.0 Hz)	3.58 (m)	1.50 (m)		0.92 (tr, 6.0 Hz)
21	Ethanol	CCl_4						4.83 (d)	5.05 (d, 6.0 Hz) 4.12 (d, 6.0 Hz)	3.58 (m)			1.16 (tr, 7.0 Hz)
26	2-Propanol	Neat						4.95 (d)	4.95 (d, 6.0 Hz) 4.24 (d, 6.0 Hz)	3.82 (m)			1.09 (d, 4.0 Hz)
19	1-Butanol	CCl_4						5.0–5.1 (3 peaks)	3.65 (m)	1.50 (m)			0.92 (tr)
27	2-Propanol	Neat						4.94–4.98 (3 peaks)	3.90 (m)				1.15 (d, tr, 5.0 Hz 1.0 Hz)

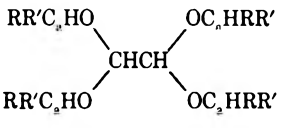
[a] All resonances are given in ppm from TMS with multiplicity and couplings in parentheses.

compounds. The results of these nmr analysis are given in Table III.

The monomeric acetal structures



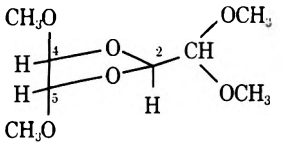
are distinguished by the appearance of the glyoxal aldehydic proton, H_G, as a single peak at 4.17–4.42 ppm. The two exceptions to this observation are with the 2-pentanol and 2-butanol compounds. In these cases, an asymmetric center is present at the carbon,



C_a connected to the acetal oxygen. This provides for at least two magnetically nonequivalent structures corresponding to the stereoisomeric enantiomers. Thus, the doublet shown is not really a doublet, but two singlets each from different stereoisomeric structures. The remainder of the spectrum corresponds normally to that expected for the alcohol portions of the molecule.

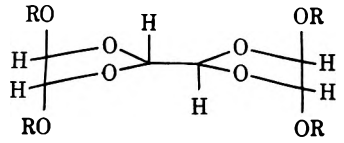
The acetal structures based on glyoxal dimer were deduced by a comparison of their nmr spectra with that

observed for the dimer acetal of glyoxal and methanol (compound **24**[1])



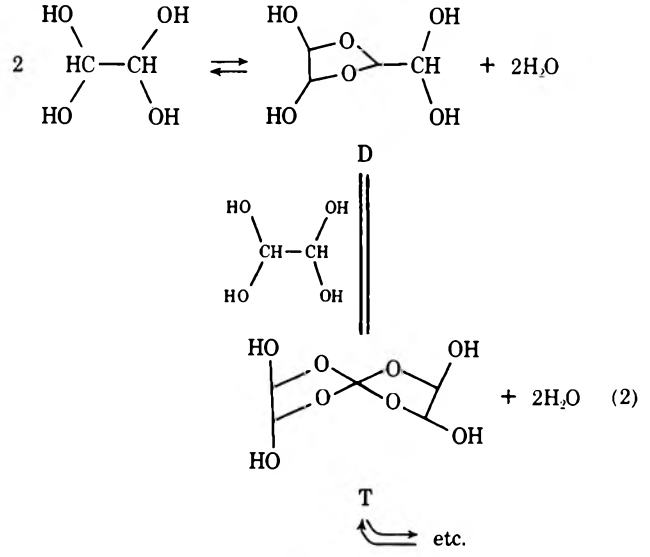
In that study, the dioxolane ring protons in the 4 and 5 positions appeared as two uncoupled peaks at 4.60 ppm, while the proton in the 2 position and the side-chain proton appeared as an AB pair with doublets at 4.78 and 3.82 ppm (J = 6–7 Hz), typical for vicinal, nonequivalent protons. The similarity between that spectrum and those observed in this case is striking. In the present dimer acetals, the adjacent dioxolane ring protons appear as two single peaks at 4.9–5.1 ppm. The AB pair derived from the 2 proton and side-chain proton are at 4.78 and 4.3 ppm (J = 6 Hz). The remaining portions of the spectra corresponding to the alcohol portion of the molecules were normal, and as expected.

The acetal structures based on glyoxal trimer, compounds **19** and **27**, were deduced by comparing their nmr spectra with that of the trimer isolated from the reaction of glyoxal with methanol **25**.[1] An extremely complicated group of peakes at 4.99–5.10 ppm corresponds to the dioxolane ring protons. The remaining



peaks correspond to the butyl and isopropyl group protons.

Mechanism.—Whipple has shown that the major portion of aqueous glyoxal dimers and trimers also are of the dioxolane type and they exist as an equilibrium between monomeric, dimeric, trimeric, etc., species[7] (eq 2). Equation 2 represents the major components of



40% aqueous glyoxal, with very small contributions from dioxane-type structures. This equilibrium is easily shifted by the removal of water. Thus, whereas in 40% solution the major form is the monomer, the dimer and trimer structures predominate in 80% glyoxal.

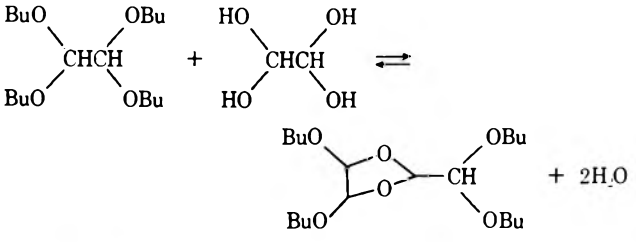
TABLE IV
PRODUCT DEPENDENCE ON GLYOXAL CONCENTRATION

Glyoxal concn, %	Alc/gly	Product yield, % G	M	D	T	Higher
40	BuOH 5:1	10	80	8		
80	BuOH 5:1	10	63	16	5	
40	BuOH 2:1	9	10	52	23	
40	Allyl 5:1	7	69	22		
80	Allyl 5:1	7	43	16		28 (mol wt 750)

The reaction of alcohols with aqueous glyoxal gives products whose structures are directly analogous with the above equilibrium of glyoxal in water. The differences in yields of monomeric and dimeric acetals, and the nonobservance of dimeric acetals with cyclopentanol, hexanol, and 2-ethylhexanol might be explained by the solubility of glyoxal monomer (tetrahydroxyethane) in the reacting alcohol. In those reactions which are two phase, one would expect the majority of the reactions to take place at the interface of the layers. If the complex equilibrium of glyoxal

SCHEME I

Pathway A



Pathway B

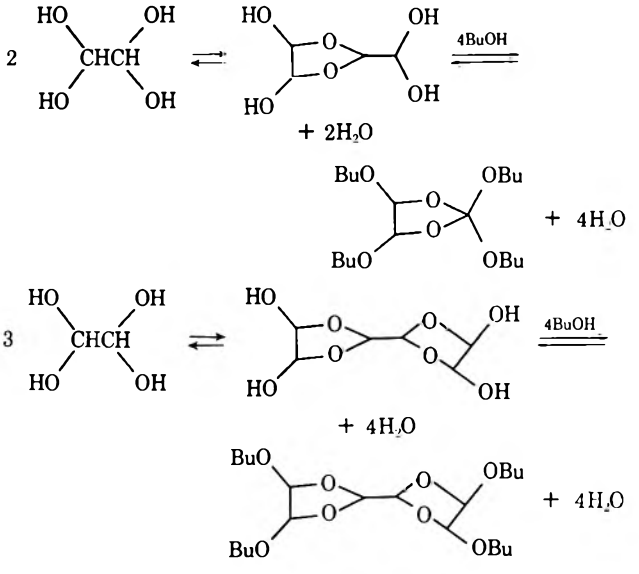


Table V
Reactions of 1,1′,2,2′-Tetrabutoxyethane[a]

Reactants	Products yield,[b] % Unreacted acetal	1,3-Dioxolane (dimer)	Bis-dioxolane (trimer)	Butanol
Water	38.8	37.0	5.4	26.4
Aqueous glyoxal	6.6	51.7	34.4	22.0

[a] The stoichiometry of the reaction with glyoxal was 1:1. The water reaction was run with the same water stoichiometry as was present in the reaction with glyoxal. [b] No free glyoxal was observed in these reaction mixtures.

in water, described by Whipple, is further complicated by an equilibrium between the water layer and water-insoluble alcohol, one might expect to see a wide range of yields of products. For example, if only tetrahydroxyethane goes into the hexanol layer the result would be (1) the formation of more acetal based on glyoxal monomer and (2) a decrease in the amount of dimer present in the aqueous phase. Another explanation might lie in the relative rates of acetal formation and exchange of the various species in the glyoxal solution.

Support for the above consideration of the complex equilibria of glyoxal in water comes from those experiments in which the concentration of glyoxal was varied as well as the molar ratio of alcohol to glyoxal (Table IV).

This table (IV) clearly shows that the change in equilibrium in going from 40 to 80% glyoxal provides higher yields of dimeric, trimeric, and even higher products. Even more striking is the reaction in which only half as much alcohol is present per mole of tetrahydroxyethane (hydrated glyoxal). It is in that case that we see the largest yield of dimer and trimer product.

The equilibrium reactions in Scheme I represent the two most probable mechanistic pathways to our observed products in which pathway B represents the glyoxal equilibria to products, and pathway A proposes the direct insertion reaction of glyoxal with acetals.

Support for the above pathways and equilibria was obtained by a study of the reactions of 1,1′,2,2′-tetrabutoxyethane with water and with aqueous glyoxal. The results of those reactions are given in Table V.

The reaction of 1,1′,2,2′-tetrabutoxyethane with water gives a 61% conversion of acetal whereas with glyoxal the conversion was 94%. In both cases the butanol yield indicates the same degree of hydrolysis reaction took place; so the only difference must be in the availability and concentration of glyoxal for direct insertion. This conclusion is augmented by the relatively unchanged yield of dimeric product and the six- to sevenfold increase in trimeric product.

We conclude from this study that this direct insertion reaction is a viable pathway and, indeed, plays a part in controlling the product mixture in the multiphase reactions described earlier.

The formation of glycolates in these reactions will not be discussed in this report, but will be taken up in a future publication.

Registry No.—**1**, 37160-54-6; **2**, 37160-55-7; **3**, 37160-56-8; **4**, 37160-57-9; **5**, 37160-58-0; **6**, 37160-59-1; **7**, 37160-60-4; **8**, 37406-80-7; **9**, 37160-61-5; **10**, 37160-62-6; **11**, 37160-63-7; **12**, 4704-23-8; **13**, 16646-44-9; **14**, 37160-66-0; **16**, 7397-62-8; **17**, 6284-81-7; **18**, 37160-68-2; **19**, 37160-69-3; **20**, 3975-14-2; **21**, 37160-71-7; **22**, 96-35-5; **23**, 2517-44-4; **24**, 33834-49-8; **25**, 33834-90-1; **26**, 37160-75-1; **27**, 37160-76-2; glyoxal, 107-22-2.

Acknowledgment.—We should like to thank Mr. B. E. Wilkes for the mass spectra and Mr. R. A. Thursack for helpful discussions of the nmr spectra.

Inductive Effect in Dithiocarbamate Decomposition Mechanism

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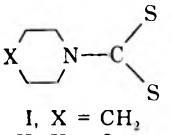
The acid-induced decomposition of $X(C_2H_4)_2NCS_2^-$ ions (X = CH_2, O, S, HN, CH_3N) was spectrophotometrically studied in pseudo-first-order conditions by varying ionic strength, dielectric constant, pH, and temperature. The reaction is first order with respect to the H^+ and dithiocarbamate ions. Activation parameters and activated complex radius values are also reported.

Some authors[1-6] have studied the dithiocarbamate ion decomposition mechanism using polarographic, potentiometric, or spectrophotometric techniques. Although some aspects of the problem have been clarified, we believe that this subject has not been completely dissected. In fact, ionic strength and the type of acid catalysis have never been considered, and the influence of dielectric constant variation has not been well defined. Moreover, increases of even 100-fold in decomposition rate constants have been explained by referring to steric and sometimes to electronic factors. In this paper we intend to carry out a more detailed treatment using a homogeneous series of ions, where it is possible to point out the inductive effects, such as shown below.



I, X = CH_2
II, X = O
III, X = S
IV, X = NH
V, X = CH_3N

(1) H. Bode, *Z. Anal. Chem.*, **142**, 414 (1952).
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(3) R. Zahradnik and P. Zuman, *Collect. Czech. Chem. Commun.*, **24**, 1132 (1959).
(4) D. M. Miller and R. A. Latimer, *Can. J. Chem.*, **40**, 246 (1962).
(5) S. J. Joris, K. I. Aspila, and C. L. Chakrabarti, *Anal. Chem.*, **41**, 1441 (1969).
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Results

Kinetics were studied by spectrophotometric measurements; the maxima wavelengths and ϵ values are reported in Table I. The maxima near 260 nm and

TABLE I
UV MAXIMA WAVELENGTHS, MOLAR ABSORBANCE VALUES IN ALKALINE AQUEOUS SOLUTION, AND ASSIGNMENTS

	$\pi \rightarrow \pi^*$		$n \rightarrow \sigma^*$		$n \rightarrow \pi^*$	
Compd	nm	ϵ	nm	ϵ	nm	ϵ
I	261	15,800 ± 200	280	15,800 ± 100	346	68
II	262	16,100 ± 200	286	16,800 ± 100	341	122
III	261	15,200 ± 80	286	17,050 ± 70	349	63
IV	269 sh	24,500 ± 300	283	22,400 ± 200	350	88
V	261	17,400 ± 400	285	17,000 ± 300	347	101

near 350 nm have been attributed by many authors[7-12] to the transition $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$, respectively, while the intense band around 280 nm, which is present in dithiocarbamate only, was tentatively assigned to an $n \rightarrow \sigma^*$ transition[13] on the basis of solvent effect and by comparison with the diselenocarbamic derivatives spectra.

The decomposition stoichiometry for I, II, and III, potentiometrically verified, is of the type shown in eq 1,

$$X(C_2H_4)_2NCS_2^- + 2H^+ \longrightarrow X(C_2H_4)_2NH_2^+ + CS_2 \quad (1)$$

whereas in the case of IV and V one H^+ ion more is consumed, including the X-substituent protonation.[14]

Each run was conducted under *pseudo-first-order* conditions, *i.e.*, at $[H^+]$ constant, with the use of the proper buffer solution (acetic acid–acetate). Therefore in every table the reported k values are first order with respect to the dithiocarbamate ion.

Working at 25° and with buffered ionic strength gave the result that in the explored range (pH 4.32–6.41) the reaction is of the first order with respect to H^+ ion (Table II).

Activation parameters were determined[15,16] (Table III) by varying the temperature (from 15 to 40°) and keeping pH (5.92) and ionic strength (1.00) values constant.

The influence of ionic strength, studied in the range 0.005–1.00, on the rate-constant value, determined at pH 5.00 and 25° (see Table IV), is, on the whole, moderate. Nevertheless, the shape of the graphs log k *vs.* $\mu^{1/2}$ (Figure 1) is noteworthy because a maximum is present for all compounds. This behavior was also confirmed for II and IV at pH 5.88.

With another set of measurements we found that the

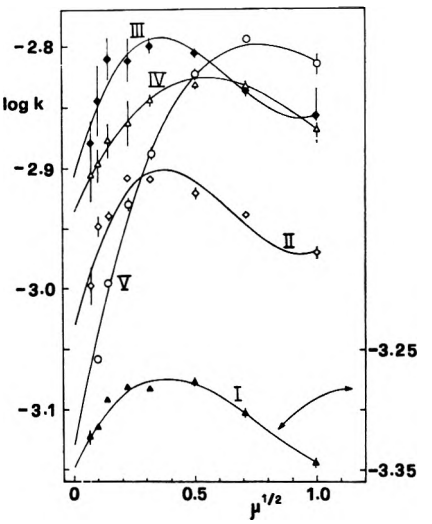

Figure 1.—Influence of ionic strength on the rate constant for the decomposition $X(C_2H_4)_2NCS_2^-$ ions, where X = (I) CH_2; (II) O; (III) S; (IV) NH; (V) CH_3N.

log k values are linear *vs.* $1/D$ (for water–methanol mixtures: MeOH wt % 0–76), keeping constant μ 0.1, T = 25°, and the molar ratio ($[A^-]/[HA]$ = 1.745) of the buffer solution (Table V).

In order to check whether the reaction is subject to general acid or specific hydrogen ion catalysis, some experiments were carried out in the presence of various buffer solutions (formic, acetic, and propionic acids and their sodium salts).

Results and Discussion

First we observe that (1) the reaction shows a total order of two [one with respect to H^+ and one with respect to dithiocarbamate (DTC^-) ions]; (2) the wavelengths of the maxima, characteristic of DTC^-, do not move during the whole decomposition; (3) the maxima of DTCH, which would fall at lower wavelengths, do not appear, up to pH $\geq$4.3; (4) the absorbance of the reaction products (Am, AmH^+, AmH_2^{2+}) was seen to be negligible in the experimental range (240–310 nm).

Therefore in the proposed reaction scheme (eq 2) we

$$DTC^- + H^+ \underset{k_2}{\overset{k_1}{\rightleftharpoons}} DTCH \xrightarrow{k_3} Am + CS_2 \xrightarrow{H^+} AmH^+ \xrightarrow[IV,V]{H^+} AmH_2^{2+} \quad (2)$$

suggest that the DTCH species should be considered in a steady-state condition. Hence the observed rate constant is defined by eq 3, which, assuming that $k_2 \gg$

$$k_{obsd} = \frac{k_3 k_1}{k_2 + k_3} \quad (3)$$

k_3, could be simplified as follows: $k_{obsd} = k_3/K_a$.

On the other hand, recent polarographic studies[5] have demonstrated that the first protonation of DTC^- species occurs on the sulfur atom.

Furthermore, this reaction is subject to general acid catalysis, as demonstrated by a set of runs with compound I in different acid–base couples. The catalytic constants, k_c, were estimated by plotting k against [HA] values while the Brønsted coefficient (α 0.75 ± 0.05) was obtained from the straight line log k_c *vs.* log K_{HA}.

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(14) Because of the high rate constant values we found it impossible to follow the reaction course by measurements of the H^+ uptake required to keep the pH constant.
(15) S. Glasstone, K. J. Laidler, and H. Eyring, "The Theory of Rate Processes," McGraw-Hill, New York, N. Y., 1941, p 199.
(16) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," Wiley, New York, N. Y., 1961, p 100.

Table II

Variation of First-Order Observed Rate Constants, $k \times 10^4$ sec^{-1} [a]

pH	I	II	III	IV	V
6.41	0.207 ± 0.001	0.500 ± 0.002	0.575 ± 0.000	0.672 ± 0.000	0.476 ± 0.000
5.85	0.744 ± 0.002	1.81 ± 0.03	2.19 ± 0.03	2.173 ± 0.0005	1.789 ± 0.004
5.36	2.246 ± 0.007	5.44 ± 0.08	7.01 ± 0.02	6.6 ± 0.3	5.64 ± 0.01
4.85	6.667 ± 0.002	16.9 ± 0.4	21.08 ± 0.04	18.5 ± 0.5	17.18 ± 0.05
4.32	23.18 ± 0.04	57.6 ± 1	71 ± 1	65 ± 3	56.7 ± 0.7
	0.97 ± 0.01	0.99 ± 0.01	1.00 ± 0.01	0.94 ± 0.01	1.00 ± 0.01

[a] Against pH at 25 ± 0.02° and μ 0.1 (acetic acid–acetate aqueous buffer solution). In the last line slope values of the equation $\log k = a - b$pH are reported. Each value is the average of two to four.

Table III

First-Order Observed Rate Constants, $k \times 10^4$ sec^{-1} [c]

Temp, °C	I	II	III	IV	V
15 ± 0.02	0.216 ± 0.0005	0.55 ± 0.01	0.686 ± 0.003	0.670 ± 0.000	0.899 ± 0.003
20	0.366 ± 0.002	0.93 ± 0.01	1.154 ± 0.002	1.106 ± 0.000	1.434 ± 0.005
25	0.629 ± 0.002	1.53 ± 0.05	1.922 ± 0.004	1.80 ± 0.04	2.351 ± 0.004
30	1.029 ± 0.0005	2.29 ± 0.05	2.90 ± 0.03	2.82 ± 0.04	3.48 ± 0.02
35	1.775 ± 0.0005	3.6 ± 0.1	4.88 ± 0.03	4.49 ± 0.05	5.42 ± 0.03
40	2.905 ± 0.006	5.5 ± 0.2	7.58 ± 0.09	7.1 ± 0.2	8.11 ± 0.03
E_a, kcal/mol	18.7 ± 0.2	16.4 ± 0.2	17.2 ± 0.2	16.9 ± 0.1	15.7 ± 0.2
$\Delta S^{\pm}$,[a] eu	−17.1 ± 0.6	−23.1 ± 0.9	−19.9 ± 0.7	−21.0 ± 0.3	−24.6 ± 0.6
$\Delta H^{\pm}$,[b] kcal/mol	18.1 ± 0.2	15.8 ± 0.2	16.6 ± 0.2	16.3 ± 0.1	15.1 ± 0.2

[a] S. Glasstone, K. J. Laidler, and H. Eyring, "The Theory of Rate Process," McGraw-Hill, New York, N. Y., 1941, p 199, eq 175. [b] A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," Wiley, New York, N. Y., 1958, p 100, eq 51. [c] Ionic strength μ 1.00; pH 5.92 ± 0.04 (acetic acid–acetate buffer); each value is the average of four runs.

Table IV

Variation of First-Order Observed Rate Constants, $k \times 10^4$ sec^{-1} [a]

μ	I	II	III	IV	V
1.000	4.55 ± 0.08	10.7 ± 0.1	13.9 ± 0.8	13.6 ± 0.2	15.4 ± 0.3
0.500	4.98 ± 0.03	11.3 ± 0.2	14.6 ± 0.2	14.7 ± 0.2	16.10 ± 0.06
0.250	5.28 ± 0.04	12.0 ± 0.2	15.7 ± 0.1	15.07 ± 0.01	14.7 ± 0.1
0.100	5.21 ± 0.02	12.35 ± 0.02	15.9 ± 0.2	14.34 ± 0.00	13.0 ± 0.1
0.050	5.22 ± 0.04	12.39 ± 0.00	15.5 ± 0.6	13.7 ± 0.6	11.8 ± 0.2
0.020	5.12 ± 0.02	11.5 ± 0.3	15.5 ± 0.6	13.3 ± 0.4	10.10 ± 0.05
0.010	4.83 ± 0.03	11.53 ± 0.00	14 ± 1	12.6 ± 0.4	8.8 ± 0.3
0.005	4.76 ± 0.05	10.0 ± 0.3	12.9 ± 0.9	12.4 ± 0.6	8.69 ± 0.01
k_0	4.49 ± 0.09	12.3 ± 0.5	12.4 ± 0.6	11.6 ± 0.2	7.6 ± 0.2

[a] Against ionic strength, pH 5.00 ± 0.02 (acetic acid–acetate buffer); temperature 25 ± 0.02°. Each value is the average of two to four runs. In the last line the values of k_0 obtained from the empirical equation $\log k = \log k_0 + a\mu^{1/2} + b\mu + c\mu^{3/2}$ are reported.

Table V

Variation of First-Order Observed Rate Constant, $k \times 10^4$ sec^{-1}

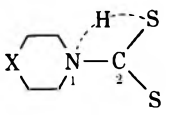
$1/D$	I	II	III	IV	V
2.266×10^{-2}	77 ± 5	50.3 ± 0.7	65 ± 0.2	39.6 ± 0.1	23.4 ± 0.8
2.032	51.8 ± 0.9	40 ± 3	54.8 ± 0.1	35.28 ± 0.00	17.5 ± 0.5
1.850	37.7 ± 0.7	35 ± 1	50 ± 2	30.04 ± 0.05	16.23 ± 0.5
1.704					16.0 ± 0.9
1.585	19.2 ± 0.3	26.0 ± 0.7	35.6 ± 0.4	23 ± 3	15.4 ± 0.4
1.486	14.1 ± 0.2				
1.402	10.4 ± 0.1	20.7 ± 0.8	28.2 ± 0.2	24 ± 3	16.7 ± 0.3
1.330	9.77 ± 0.2				
1.274	6.67 ± 0.00	16.86 ± 0.04	21.07 ± 0.04		8.74 ± 0.03
$r^{\pm}$ (Å)[a]	2.43	5.17	5.07	6.78	5.82

[a] C. H. Banford and C. F. H. Tipper, "Comprehensive Chemical Kinetics," Vol. II, "The Theory of Kinetics," Elsevier, Amsterdam, 1969. [b] Against dielectric constants (water–methanol mixtures) at 25 ± 0.02° and μ 0.01. The molar ratio in acetic acid–acetate buffer solution is $[A^-]/[HA] = 1:0.573$. Each value is the average of two runs.

The variation of the rate with the nature of X substituent is moderate. Nevertheless, standard deviation values show that the differences among rate constants for compounds I–V are significant. Furthermore, we point out that (1) in water solutions the reactivity sequence is $k_{III} > k_{IV} > k_{II} > k_V > k_I$ (see Table II, pH 4.32); (2) on going from water to methanol all the rate constants increase; (3) in pure methanol the reactivity order becomes $k_I > k_{III} > k_{II} > k_V > k_{IV}$ ($k \times 10^4$ sec^{-1}: I, 193; III, 113; II, 86; V, 74; IV, 34).

In order to explain these results it seemed reasonable to propose a transition state in which the acid H atom bridges between N and S atoms.

Assuming that the π system is the same for every molecule here studied, the most significant σ-charges



are those located on nitrogen (1) and carbon (2) atoms of the bond that will break in the event of decomposition. The charge on the C-2 atom has a positive sign both in DTC^- or DTCH and in the transition state model. Vice versa, the σ charge on the N-1 atom is negative in DTC^- and DTCH species and positive in the transition state.[17] Consequently the N-1–C-2 linkage is greatly weakened and the CS_2 molecule can leave. This fact points up the importance of the inductive effect which, obviously, may be transmitted both through the ring and through the solvent.[18]

If only inductive effects are considered, the behavior of compound I in water solutions seems surprising. In fact, the CH_2 substituent is the weakest electron withdrawing and, therefore, compound I should be the most reactive. On the contrary, it is not only the last of the series, but it also shows the maximum activation energy value. Thus, it is necessary to examine experimental results in water–methanol mixtures.

The relation between ln k and the dielectric constant inverse, $1/D$, is typical of opposite sign reactant ions. Within the approximation of the use of eq 4,[19] which

$$\ln k = \ln k_0 - \frac{Z_A Z_B e^2}{kTDr^{\pm}} \qquad (4)$$

fits well for two simple ion reactions, the activated complexes radii can be estimated. The $r^{\pm}$ values so obtained are reported in the last line of Table V.

Although steric hindrance is of the same order of magnitude for all the molecules considered here (for the S atom only a ring distortion may be considered), compound I exhibits an $r^{\pm}$ value less than a half lower than the remaining compounds.

As far as the $\Delta S^{\pm}$ values are concerned, we observe that I shows a probability factor of *ca.* 10^{-4}, that is, 10–100 times higher than II–V. These facts could be tentatively interpreted as due to the lack (for X = CH_2) of the X-substituent contribution to the degree of charge dispersion in the activated complex.

In fact, on passing from pure water to pure methanol the reactivity series changes and becomes almost coherent with the predicted order for an inductive effect −I. Particularly, the rate constant values increase about ten times for I, which becomes the most reactive, and about three times for the remaining compounds. This points out the importance of the role of solvation in the reaction mechanism. For all compounds a stronger solvation makes the transfer process of the proton from sulfur to the nitrogen atom more difficult. For compound I, in which the X substituent is the least solvated, the decrease of the D value produces a faster rate-constant increase.

As far as the influence of ionic strength is concerned, the shape of the curve log k *vs.* $\mu^{1/2}$ is not linear (Figure 1). Nevertheless, in the wide μ range (0–1.00) ordinate value variation is moderate, being about 0.13 for compounds I–IV and 0.23 for compound V. The presence of a maximum clearly indicates that more than one factor is acting simultaneously and this probably arises from the complexity of the mechanism (see eq 3). Disagreement with expected behavior for opposite sign ions reaction is more marked at lower ionic strength values. This phenomenon could be tentatively attributed to a different interaction between the solvent and the solute molecules having many different charged sites.

To point up the role of the leaving group, the study of the diselenocarbamate decomposition mechanism is now in progress.

Experimental Section

Preparation and Characterization of Compounds.—All compounds were prepared by adding 1.1 mol of CS_2 to an ethyl ether solution of 1 mol of amine vigorously stirred with a 30% aqueous solution of 1 mol of NaOH and cooled by an ice bath (in the case of piperazine derivative only 1 mol of CS_2 was used). The compounds were twice recrystallized from ethyl ether–aqueous acetone and dried *in vacuo* over $CaSO_4$.

They were tested alcalimetrically, obtaining (I) $C_6H_{10}NS_2Na \cdot 2H_2O$, mol wt found 223.2, calcd 219.3; (II) $C_5H_8NOS_2Na \cdot 3H_2O$, mol wt found 241.2, calcd 239.3; (III) $C_5H_8NS_3Na \cdot 3H_2O$, mol wt found 254.0, calcd 252.3; (IV) $C_5H_9N_2S_2Na \cdot 2H_2O$, mol wt found 217.1, calcd 220.3; (V) $C_6H_{11}N_2S_2Na \cdot 3H_2O$, mol wt found 250.8, calcd 252.3.

Spectrophotometric Measurements.—The uv-visible spectra were recorded in freshly prepared aqueous solutions being 0.1 N in NaOH, using a Perkin-Elmer Model 402 or a Beckman DK 2A spectrophotometer. The ir spectra were recorded in the range 250–4000 cm^{-1} as KBr discs with Perkin-Elmer Model 325 equipment.

pH Measurements.—pH values were detected by a DAT 2002 pH meter equipped with a Lauda K2RD thermostat and a glass electrode (reference Ag/AgCl). Accuracy was ±0.01 pH unit.

Kinetic Measurements.—These measurements were carried out with a Perkin-Elmer Model 402 spectrophotometer connected to a Lauda K2RD thermostat (±0.02°). The spectra were periodically recorded in the range 230–310 nm, reading the absorbance values at the maxima wavelength. Each run was carried out in *pseudo*-first order conditions, *i.e.*, at a constant pH value, by adding, all at once, the proper amount of solid compound to a prethermostated buffer solution, obtaining a solution of about 10^{-4} M. Under these conditions the reaction product's absorbances were seen to be negligible. The detailed conditions of each run set are reported in the table explications.

Processing the Data.—Kinetic experimental data were processed by an H. P. 9100 B calculator. Straight lines were calculated by the least squares method and curves were well averaged by our special program of multiple regression, by obtaining the parameters of the equation $y = a + bx + cx^2 + dx^3$. Quantochemical calculations were carried out by means of a 1130 IBM computer.

Registry No.—I, 18474-20-9; II, 36976-42-8; III, 36976-43-9; IV, 36976-44-0; V, 36976-45-1.

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(17) This fact has been confirmed by means of a simple quantum-chemical calculation carried out by using the Del Re method. See G. Del Re, *J. Chem. Soc.*, 4031 (1958); F. Momicchioli and G. Del Re, *J. Chem. Soc. B*, 674 (1969).

(18) Recently the influence of an unconjugated sterically remote substituent on the rate process has been indicated as a "polar effect," including inductive and field effects. See L. M. Stock, *Chem. Educ.*, **49**, 400 (1972).

(19) O. H. Bamford and C. H. F. Tipper, "The Theory of Kinetics," Vol. II, Elsevier, Amsterdam, 1969, p 321.

Rates and Isotope Effects in the Proton Transfer Reactions of Methyl 4-Nitrovalerate[1]

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The rates of proton transfer from methyl 4-nitrovalerate to pyridine and 2,4,6-trimethylpyridine have been measured by iodination and by racemization. The iodination rates closely resemble those for 2-nitropropane, except for a larger term for solvent catalysis. Rates from racemization and iodination are the same where both can be measured, but iodination becomes less useful as the rate drops, and is least valuable in the dilute solutions necessary for water solutions. The deuterium isotope effect for the racemization of methyl 4-nitrovalerate-*4-d* by 2,4,6-trimethylpyridine is in the excess of 20 at 30°.

The nitroalkanes have been popular substrates for the study of slow proton transfers to a variety of bases, because they are accessible, they have easily measurable acid dissociation constants, and they deviate about as far as any acids from the ideal Eigen behavior.[3] The hydrogen isotope effects have also been of interest from the beginning of such studies.[4] More recent studies have on the one hand borne on the variation of isotope effect with acid and base strength,[5,6] and with the contribution of tunneling to the isotope effect.[5,7,8]

The evidence for tunneling was based primarily on a very large deuterium[5,7] or tritium[8] isotope effect in the reaction of 2-nitropropane with 2,6-dimethyl- and 2,4,6-trimethylpyridine measured mostly by iodination methods. These large isotope effects are rather central to any arguments on the importance of tunneling in proton transfer reactions, although they are not the only evidence.[9] It appeared necessary to take criticisms of the results seriously and to attempt to get independent confirmation. A study of the isotope effect in the 2,6-dimethylpyridine–2-nitropropane reaction in aqueous ethanol[10] contradicts the results of ours in aqueous *tert*-butyl alcohol[7] and of Bell's in water. We have previously expressed an uncertainty about the significance of results in ethanolic solution and indeed abandoned our earlier groundwork in this solvent[11] because it is not inert to iodine, and therefore leads to a substantial blank reaction which is especially serious with the slower reactions, but we nevertheless felt that an independent demonstration would be valuable.

We here study methyl 4-nitrovalerate, which is accessible in optically active form[12] but is in most respects very similar to 2-nitropropane, and compare iodination rates with those of 2-nitropropane, to see how close the resemblance is, and compare iodination rates with racemization rates, to ascertain that the rate-determining step is indeed the same.

(1) In part from the 1972 Rice University Ph.D. Thesis of H. Wilson, Phillips Petroleum Fellow, 1970–1971, Welch Foundation Predoctoral Fellow, 1968, 1970.

(2) National Science Foundation Undergraduate Research Participant, 1970–1971.

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(12) W. Thielacker and C. Wendtland, *Justus Liebigs Ann. Chem.*, **570**, 33 (1950).

Results

The iodination of methyl 4-nitrovalerate, reaction 1, was followed spectrophotometrically at 30° in aqueous *tert*-butyl alcohol (54% *t*-BuOH by weight) and in water. The absorbance at 468 nm was not a linear function of time, as noted before,[7] because of the variable iodide ion concentration. Using suitable correction for varying extinction coefficients, plots of concentration of total iodine *vs.* time were linear. The pseudo-zero-order rate constants derived from these plots were proportional to ester concentrations and increased linearly with base concentration, showing a rate law of the form of eq 2, differing only by the detectable term in k_s from our earlier work.[7] The absence of a lyate ion term was demonstrated as before by the insensitivity of the rate to the presence of a small amount of perchloric acid. The results are shown in Table I, which also shows some rate of iodination of methyl 4-nitrovalerate-*4-d*.

$$B + CH_3CHNO_2CH_2CH_2CO_2CH_3 + I_2 \longrightarrow BH^+ + CH_3CINO_2CH_2CH_2CO_2CH_3 + I^- \quad (1)$$

$$-d(I_2)/dt = k_B(B)(\text{ester}) + k_s(\text{ester}) \quad (2)$$

Table I also includes rate constants for reaction of 2-nitropropane with the same bases at 25° where available. It is clear that the ester resembles the 2-nitropropane closely; most of the factor of about two discrepancy is attributable to the 5° temperature difference. The larger solvent term appears real, although the entry for 2,4,6-trimethylpyridine, larger than for pyridine itself, probably only reflects the fact that blank corrections with this base are so large that results are quite uncertain. We were unable in water to get an iodination rate of the deuterated compound because of excessive blank correction and other problems described in the Experimental Section. This difficulty is not due to worse behavior in the solvent water than in the *tert*-butyl alcohol solvent, but only due to the fact that measured zero-order rates are necessarily very slow because the concentration of ester is solubility limited, as is also that of collidine.

The k_s in *tert*-butyl alcohol was not found in the earlier work with 2-nitropropane;[7] in water a value of 4×10^{-9} sec^{-1} has been reported,[5] which is clearly smaller than the value of 4×10^{-7} in Table I. We suggest that the larger k_s term may arise from neigh-

TABLE I

IODINATION OF METHYL 4-NITROVALERATE AT 30°

Solvent	Base	Isotope	k_B, M^{-1} sec^{-1} [a]	k_s, sec^{-1} [a]	k_B^{2NP}, M^{-1} sec^{-1} [b]
54% *t*-BuOH–H_2O	Pyridine	H	$3.9 \pm 0.2 \times 10^{-6}$	1.4×10^{-7}	1.9×10^{-6}
54% *t*-BuOH–H_2O	Pyridine	D[c]	$4.3 \pm 0.1 \times 10^{-7}$ [c]	0.7×10^{-7} [c]	2.1×10^{-7} (k_D)
H_2O	Pyridine	H	$4.3 \pm 0.3 \times 10^{-5}$	3.9×10^{-7}	1.7×10^{-5}
H_2O	Pyridine	D[c]	$3.6 \pm 0.1 \times 10^{-6}$ [c,d]	2.0×10^{-7} [c,d]	1.7×10^{-6} (k_D)
H_2O	Collidine[e]	H	$1.9 \pm 0.2 \times 10^{-4}$ [e]	9.3×10^{-7} [e]	
H_2O	OAc^-	H	$1.3 \pm 0.1 \times 10^{-5}$	*f*	3×10^{-6}
54% *t*-BuOH–H_2O	OAc^-	H	$4.0 \pm 0.3 \times 10^{-5}$	*f*	

[a] The data were fitted to eq 2, with k_B the slope, together with the standard error, and k_s the intercept. Because extrapolation to k_s is fairly long and puts greatest emphasis on the slowest runs, where other errors become important, no estimates of error are given. [b] Rate constants for attack of the same base in the same solvent on 2-nitropropane at 25° from ref 5 and 7. [c] This sample contained 1.2% protium compound; the values of k_B are appropriately corrected. [d] All runs in water have substantial blank corrections and are therefore less accurate than the runs in *t*-BuOH, in spite of similar level of reproducibility. [e] Collidine is 2,4,6-trimethylpyridine; these data are of low precision, see text. [f] These data are not complete enough to warrant extrapolation to give k_s; k_B was calculated using k_s from the runs with pyridine.

TABLE II

RATES OF RACEMIZATION OF METHYL 4-NITROVALERATE AT 30°

Solvent	Base (M)[a]	Isotope	k_{obsd}, sec^{-1}	k_B, M^{-1} sec^{-1}	k_B (Iod)[b]
54% *t*-BuOH	Py (0.292)	H	1.3×10^{-6}	4.1×10^{-6}	3.9×10^{-6}
54% *t*-BuOH	Py (0.390)	H	1.5×10^{-6}	3.8×10^{-6}	
H_2O	Coll (0.0815)	H	1.48×10^{-5}	1.77×10^{-4}	1.9×10^{-4}
H_2O	Coll (0.0798)	H	1.57×10^{-5}	1.91×10^{-4}	
H_2O	Coll (0.0565)	D	8.2×10^{-7}	6.8×10^{-6}	
H_2O	Coll (0.0720)	D	9.4×10^{-7}	6.7×10^{-6}	
H_2O	Coll (0.0870)	D	1.01×10^{-6}	6.5×10^{-6}	

[a] Py = pyridine, Coll = 2,4,6-trimethylpyridine. [b] Values of k_B for iodination from Table I.

boring-group participation by the ester group analogous to that found in the carboxylate ion,[13] but we refrain from guessing whether solvent is involved essentially and in what position. The substantial uncertainty of k_s (see Table I, footnote *a*) makes extensive discussion unfruitful. Some efforts were made to measure k_s directly, but these were frustrated by the reversibility of reaction 1 in the absence of added base, which led to more complex kinetics and small iodine consumption.

The isotope effects with the base pyridine are not surprising; in *t*-BuOH (k_H/k_D = 9.1 for k_B) is, within experimental error, the same as that reported for 2-nitropropane (k_H/k_D = 8.9[7]), and in water (k_H/k_D = 11.8), considering the rather larger uncertainty, is also probably indistinguishable from the 2-nitropropane value (k_H/k_D = 10.3).[5] The isotope effect on k_s (k_H/k_D = 2.3 in *t*-BuOH, 2.0 in water) does appear smaller than that reported by Bell and Goodall[5] (k_H/k_D = 4 in water), possibly again reflecting a different mechanism for the k_s terms, but uncertain because of the k_s uncertainty.

It proved advisable to demonstrate that reaction 1 really represented the reaction. The methyl 4-iodo-4-nitrovalerate proved to be very sensitive, presumably because of the ready reversibility of reaction 1. However, spectrophotometric measurements (rough because of the volatility of bromine) showed that the rates of iodination and bromination were about the same, and bromination did produce a substance clearly identified as methyl 4-bromo-4-nitrovalerate.

Table II presents the racemization data under various conditions. The reactions are all very slow and it was impractical to extrapolate to zero base concentration. The racemization followed a first-order course with a pseudo-first-order constant k_{obsd} and was assumed to be first order in base. The deuterated compound showed the presence of protium compound by a faster initial rate; rates reported are for the later stages of the reaction.

The first four entries show that the polarimetric rates are reproducible within better than 10%, and are within this same precision the same as the rates measured by iodination. The last three entries show that the deuterium compound reacts far more slowly than the protium compound. The k_B values shown are calculated using k_s from the iodination rates, since the evaluation of k_s polarimetrically is unreliable. The isotope effect using these values then gives the average $k_B^H = 1.84 \times 10^{-4}$, $k_B^D = 6.7 \times 10^{-6}$, $k^H/k^D = 27$. The result is quite sensitive to the value of k_s chosen, especially for the deuterated compound, but the presence of a very large isotope effect in reasonable agreement with the earlier result is unequivocal; even if $k_s = 0$, the isotope effect, at 30°, based on the more concentrated solutions, is over 15.

We conclude that the earlier very large isotope effect in the hindered proton transfer is real; it is not an artifact of the iodination method used before.[5,7] The iodination method, however, does become less accurate as the reactions get slower and side reactions get faster, and is very close to its practical limit with some of the deuterated cases with the highly methylated pyridines, the earlier conditions.[7]

Experimental Section

Materials.—The *tert*-butyl alcohol used was of commercial grade and of good melting point. For reproducibility it was found preferable to prepare the solvent gravimetrically (54%

(13) H. Wilson and E. S. Lewis, *J. Amer. Chem. Soc.*, **94**, 2283 (1972).

tert-butyl alcohol by weight). All aqueous solutions were made up using glass distilled water.

Analytical grade pyridine was dried over molecular sieve and distilled through a Nester-Faust spinning band column. Purity was checked by an analysis on a Perkin-Elmer gas chromatograph using a 20-ft Carbowax column (<1% impurity).

1,3,5-Trimethylpyridine (commercial sample 99.9% purity claimed) was distilled after treatment with boron trifluoride etherate.

Methyl 4-nitrovalerate was prepared by a triethylamine-catalyzed Michael reaction of nitroethane and methyl acrylate according to published procedure.[14] The procedure used for preparation and analysis of the D ester was essentially that of Allen,[11] except that sodium carbonate was used as the base. Protio ester was combined with a large excess of D_2O (99.8%) and a small quantity of sodium carbonate to effect exchange. The mixture was heated at 45° for 24 hr, being stirred continuously. The organic layer was separated and fractionally distilled after each exchange. Four such exchanges were usually necessary. Yields were poor because of a competing reaction leading to the formation of levulinic acid. The extent of deuteration was readily estimated by nmr, approximately by disappearance of the 1 H sextet at τ 5.1–5.7, more accurately by the change of the 3 H doublet at τ 8.4–8.6 into a symmetric triplet.

Optically active ester was prepared by Fischer esterification of the optically active acid, which was prepared by published procedures.[7] Resolution of the deuterated acid (obtained by acid hydrolysis of the D ester) was found to be possible with only a small amount of exchange by the same method. Fischer esterification gave the optically active D ester.

All the materials had nmr spectra consistent with their assigned structures.

Rate Measurements.—All iodinations were carried out exactly according to the earlier procedure.[7]

Racemization data were obtained using a Bendix automatic polarimeter; a jacketed cell was thermostated at 30°.

Solutions for observation were made by mixing thermostated solutions of reagents, of known concentration, in a definite ratio. Prior to this the polarimeter had been zeroed with solvent in the cell. The cell was rinsed four or five times with the reaction mixture before being filled for measurement. The change of rotation with time was recorded automatically. Reactions were normally followed (where possible) over 3 half-lives.

With slower reactions ($t_{1/2}$ >1 week) an offset zero method was used to follow the change more accurately. The scale was chosen so that a change in rotation of 10 millidegrees would give readings across the full scale, *i.e.*, a full-scale deflection = 10 millidegrees, and the zero was set at the end of the chart instead of the middle. This increased sensitivity enabled measurements to be made a little more accurately, but prevented scale changes.

Product Studies.—Attempted iodination of methyl 4-nitrovalerate under the same conditions as those used in the kinetic studies were not fruitful because of equilibration. It was believed that bromination would overcome the problem of reversibility and that the position of bromination would be analogous to that of iodination, and rough rate measurements confirmed this.

Bromine was added, dropwise, to an alkaline solution of the ester until no additional bromine was consumed. The mixture was twice extracted with ether. After drying, the ether was removed and a gc analysis of the residue was made. This indicated the formation of a new higher boiling product which was purified by preparative gc on a 2.5 ft × 0.5 in. column (25% SE-30 on 60/80 mesh Chromosorb P) at 200°. It was identified as methyl 4-bromo-4-nitrovalerate by spectral methods: nmr, 3 H singlet τ 7.8, 3 H singlet 6.4, 4 H irregular multiplet 7.2–7.7; ir 1370, 1560 cm^{-1}, characteristic of the NO_2 group; mass spectrum showed the characteristic bromine doublets and the heaviest ion corresponded to loss of NO_2 only. The ester was independently synthesized by esterification of the corresponding acid[13] and was found to have the same spectral characteristics.

Registry No.—Methyl 4-nitrovalerate, 10312-37-5.

(14) J. Colonge and S. Pouchol, *Bull. Soc. Chim. Fr.*, 832 (1962).

Structural Directivity in the Diels–Alder Reaction. Dependence on Dienophile Cis–Trans Geometry

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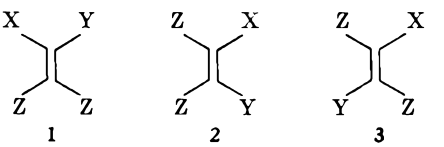
Citraconontrile and mesaconontrile were treated with six unsymmetrical dienes, and the structural isomer ratios were determined. Substantial differences between the ratios obtained from citraconontrile and mesaconontrile were observed in the reactions with 1,3-pentadiene and 3-phenyl-1,3-pentadiene. Determination of structural isomer ratios involved a one-step degradation of the dinitrile adducts to mixtures of substituted benzonitriles by treatment with potassium *tert*-butoxide and anthraquinone. This is a new reaction apparently involving the quinone dehydrogenation of carbanions.

The wealth of information available concerning structural directivity in the Diels–Alder reaction deals almost exclusively with orienting effects of diene and dienophile substituent groups as they vary in electronic character and size.[2] In general, any substituents X and Y located on the same olefinic carbon atom of the dienophile **1**, regardless of their electronic character, reinforce each other's structural directing influence in Diels–Alder reactions with unsymmetrical dienes. On the other hand, dienophiles **2** and **3**, with substituents X and Y located on opposite ends of the olefinic bond, whether they be cis or trans to each other in any particular compound, compete for structural directivity.



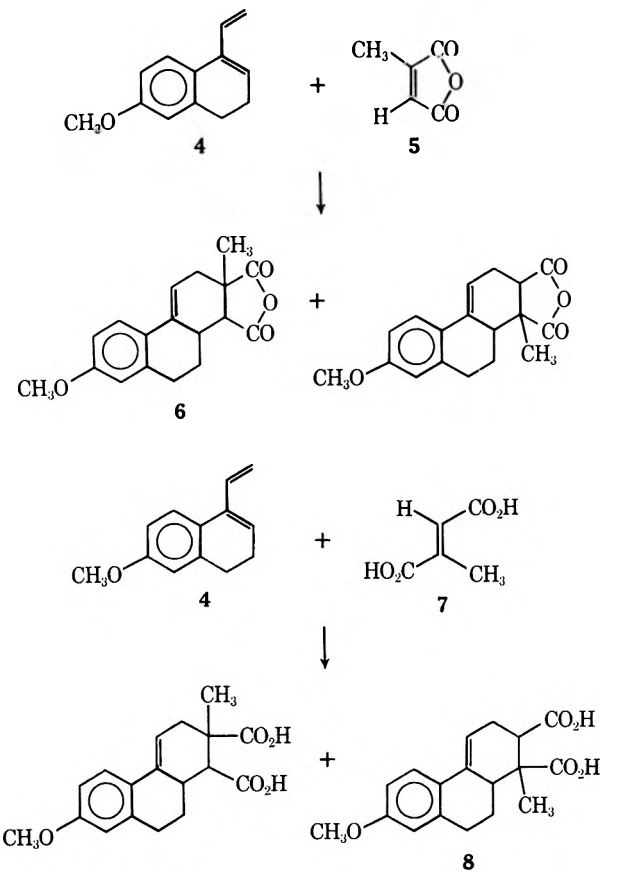
1 **2** **3**

The possibility that dienophile geometry may play a significant role in determining structural directivity is suggested by an example reported by Bachmann, who found that diene **4** reacted with citraconic anhydride (**5**) to give predominantly structural isomer **6**, while mesaconic acid (**7**) gave predominantly isomer **8**.[3] The opposing structural directing substituents are a methyl group and a hydrogen atom in both of these dienophiles. If one considers only the nature of these opposing groups, without regard to geometry or nature of the

(1) (a) To whom correspondence should be addressed: The University of Connecticut. (b) NASA Fellow, The University of Connecticut, 1966–1969.

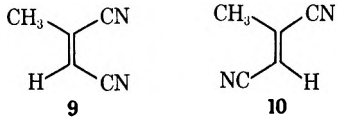
(2) (a) Y. A. Titov, *Usp. Khim.*, **31**, 529 (1962); *Russ. Chem. Rev.*, **31**, 267 (1962). (b) A. S. Onishchenko, "Diene Synthesis," Daniel Davey, New York, N. Y., 1964.

(3) (a) W. E. Bachmann and J. M. Chemerda, *J. Amer. Chem. Soc.*, **70**, 1468 (1948); (b) W. E. Bachmann and J. Controulis, *ibid.*, **73**, 2636 (1951).



symmetrically disposed dienophile substituents, one would expect that the same structural isomer would predominate in each case. It should be noted, however, that these two dienophiles differ in both geometry and in identity of the symmetrically located activating groups, both factors which must be considered in light of the experimental facts.

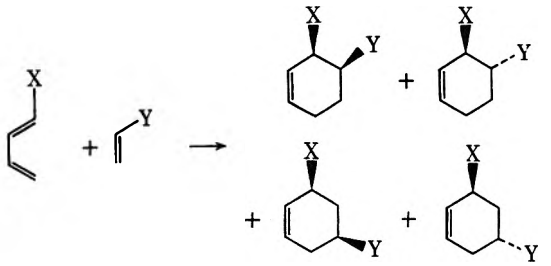
The purpose of this work was to investigate the possibility that the cis–trans geometry of dienophiles such as **2** and **3** has a significant influence on structural directing ability. A cis–trans isomeric pair of dienophiles, citraconontrile (**9**) and mesaconontrile (**10**),



which exhibits this behavior, was, in fact, found. That is, with certain dienes, the cis dienophile **9** gives structural isomer ratios significantly different from the ratios obtained by reaction of the trans dienophile **10** with the same dienes.

It was predicted that citraconontrile (**9**) and mesaconontrile (**10**) could be studied conveniently under identical reaction conditions, since the closely related dienophiles maleonitrile and fumaronitrile show nearly identical Diels–Alder reactivities.[4] It was found that citraconontrile actually reacts slightly faster than mesaconontrile in reactions using excess dienophile, and both dienophiles were shown to be thermally stable toward isomerization under the reaction conditions used. The chance that solvent polarity might influence the structural directivity was minimized by running the Diels–Alder reactions in a fourfold excess of diene, the diene thus serving as a solvent. Kinetic control of adduct isomer ratios at the reaction temperature of 100° is assumed, primarily on the basis of the absence of examples to the contrary for acyclic dienes. For example, some monocyclic adducts which have been thoroughly investigated in this regard do not undergo reverse Diels–Alder reaction, even at 350°.[5,6]

The major concern in carrying out this preliminary work was the development of a suitable method of analysis. Although direct glc analysis of Diels–Alder reaction mixtures containing four isomeric adducts (eq 1) has been accomplished in some cases,[6,7] several

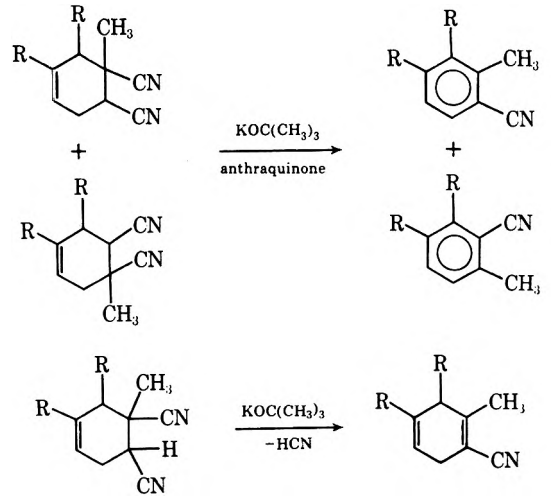


(1)

attempts to so separate the adducts obtained from **9** and **10** were unsuccessful.

In the past, researchers have generally resorted to degradative methods of analysis to obtain information on structural directivity. However, as Sauer has pointed out, most data obtained in this way is at best approximate and is useful only as an indication of the general direction of structural directivity.[8] However, in the present case it is not the absolute value of the isomer ratios that is important, but rather the comparison of ratios obtained *via* a single degradative procedure.

A one-step degradation was developed in which adduct mixtures were treated with potassium *tert*-butoxide and anthraquinone in benzene at room temperature, giving mixtures of the two possible isomeric benzonitriles (eq 2). The ratios of the benzonitriles were conveniently determined by integration of the methyl proton singlets in the nmr spectra[9] of the crude degradation product mixtures.



(2)

(3)

(4) (a) J. Sauer, D. Lang, and H. Wiest, *Chem. Ber.*, **97**, 3208 (1964); (b) J. Sauer, D. Lang, and H. Wiest, *Z. Naturforsch. B*, **17**, 206 (1962).

(5) H. E. Hennis, *J. Org. Chem.*, **28**, 2570 (1963).

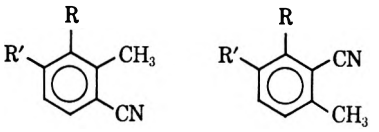
(6) T. Inukai and T. Kojima, *ibid.*, **32**, 869 (1967).

(7) O. Korver, T. L. Kwa, and C. Boelhouwer, *Tetrahedron*, **22**, 3305 (1966).

(8) J. Sauer, *Angew. Chem., Int. Ed. Engl.*, **6**, 16 (1967).

(9) (a) E. D. Becker, "High Resolution NMR, Theory and Chemical Applications," Academic Press, New York, N. Y., 1969, pp 236–240; (b) A. Mathias and D. Taylor, *Anal. Chim. Acta*, **35**, 376 (1966).

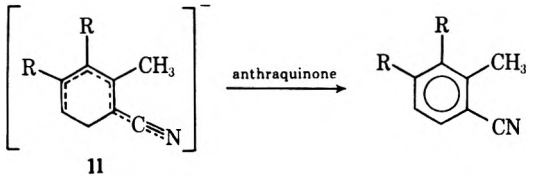
TABLE I
ISOMER RATIOS



Registry no.	Diene	R	R'	Citraconitrile Ratio	Citraconitrile Yield,[a] %	Mesaconitrile Ratio	Mesaconitrile Yield,[a] %
504-60-9	1,3-Pentadiene	CH_3	H	17:10	69	12:10	59
78-79-5	2-Methyl-1,3-butadiene	H	CH_3	1:1	75	1:1	69
1515-78-2	1-Phenyl-1,3-butadiene	C_6H_5	H	55:10	40	61:10	28
	2-Phenyl-1,3-butadiene	H	C_6H_5				
37580-41-9	3-Phenyl-1,3-pentadiene	CH_3	C_6H_5	21:10	74	10:10	74
37580-42-0	2-Methyl-1-phenyl-1,3-butadiene	C_6H_5	CH_3	36:10	77	33:10	68

[a] Overall yield of aromatized products based on dienophile as limiting reagent. Determined by use of methyl benzoate as a quantitative internal nmr standard.

The degradation is presumed to involve the initial loss of hydrogen cyanide from the adduct in a reverse Michael type elimination (eq 3). Potassium *tert*-butoxide alone in benzene, ether, or dimethyl sulfoxide causes elimination of hydrogen cyanide from the adducts, with formation of a mixture of products containing low yields of the substituted benzonitriles; autoxidation of the cyclohexadienide ion (**11**) ac-



11

counting for the limited aromatization which occurs in these cases.[10] Running the reaction in a pure oxygen atmosphere did not improve the yield of benzonitriles, however.

When anthraquinone is present in the strongly basic reaction mixture, pure benzonitriles can be isolated in about 90% yield. It has been previously suggested that phenanthrenequinone might find use in the dehydrogenation of preformed anions.[11] However, although a logical extension of quinone dehydrogenations, this is the first reported instance of the dehydrogenation of a carbanion (**11**) by a quinone. While most of the anthraquinone does not dissolve in the reaction mixture, 3 equiv of anthraquinone was required to obtain complete aromatization of the adducts. During the reaction a dark green solid was produced, which rapidly turned yellow on exposure to air. This material has not been characterized, but its properties resemble those of the known sodium salt of phenanthrene quinhydrone.[12]

The four isomeric adducts comprising each adduct mixture (eq 1) probably differ somewhat in the ease with which they lose HCN. The fact that no unreacted adducts are visible in the nmr spectrum of the reaction mixture after the degradation, coupled with the high yields obtained, led us to accept the use of this degradation in the analytical procedure.

The dienes shown in Table I were selected to provide examples with different degrees of structural directing ability. The structural isomer ratios obtained from the analysis are presented in Table I, and represent averages from duplicate determinations. Ratios from duplicate analyses differed by less than 2% of the larger number of the ratio in most cases, and by less than 5% in all cases. The yields determined by the use of methyl benzoate as an internal standard represent minimums, since controls run on known mixtures gave results 0–6% lower than actual. Control experiments using glc and nmr analysis showed that citraconitrile and mesaconitrile do not interconvert under the Diels–Alder reaction conditions used and, in the cases of 1-substituted dienes, only the trans isomers reacted with the dienophiles.

The reactions which show the largest dependence upon dienophile geometry are those of 1,3-pentadiene and 3-phenyl-1,3-pentadiene. Although the number of examples tested so far is not great enough to justify any generalizations, the characteristics that set these two dienes apart from the others should be noted. Both have terminal methyl substituents, which places the methyl group in proximity to the reactive site. The ratios obtained show that both are very weakly directing dienes, and 3-phenyl-1,3-pentadiene especially resembles the diene used by Bachmann.

Differences in structural directivity observed with the four remaining dienes were small or nonexistent. 2-Phenyl-1,3-butadiene polymerizes so rapidly that the yield of adducts produced was insufficient for analysis; and 1-phenyl-1,3-butadiene also polymerizes rapidly, reducing the yield of adducts and thus lowering the significance of the results. A decreased nmr signal to noise ratio and a relatively large difference in yield between the reactions of mesaconitrile and citraconitrile are factors which tend to decrease the reliability of the nmr detection method in general.

2-Methyl-1-phenyl-1,3-butadiene showed a small structural directivity dependence on dienophile geometry. This diene contains a terminal phenyl substituent and, according to the ratios listed in Table I, is more discriminating in its own structural directivity than the 1,3-pentadienes, which showed a greater sensitivity to dienophile geometry.

The degradation mixtures from the reactions of 2-methyl-1,3-butadiene could not be integrated effectively, since the maximum separation of methyl singlets was only 2 Hz. However, the methyl singlet peak heights for the two isomers were identical in the reaction mixtures from both dienophiles, indicating the ab-

(10) G. A. Russell, A. G. Bemis, E. J. Geels, E. G. Janzen, and A. J. Moye, *Advan. Chem. Ser.*, No. 75, 174 (1968).
(11) L. M. Jackson in "Advances in Organic Chemistry, Methods and Results," Vol. 2, Interscience, New York, N. Y., 1960, pp 331–345.
(12) S. Goldschmidt and F. Christmann, *Chem. Ber.*, **57**, 713 (1924).

sence of any detectable structural directivity dependence on dienophile geometry.

The results obtained from these few examples indicate a structural directivity dependence on dienophile geometry that may, in some cases, be of value in synthesis. It is clear, however, that a theoretical explanation of this phenomenon must be deferred until, as well as the structural isomer ratios, the stereoisomer ratios (eq 1) are determined. A mechanistic interpretation may require consideration of π-orbital overlap and steric interactions similar to those used in explaining the Alder endo rule.[13] However, any predictions based on the endo rule at this time would be premature, since very little data is available relative to acyclic dienes, and cyano activating groups show only weak endo-directing ability in reactions with cyclic dienes[14] and unusual directing effects with acyclic dienes.[15]

Experimental Section

All melting points and boiling points are uncorrected. Microanalyses are by Spang Microanalytical Laboratories, Ann Arbor, Mich. All infrared (ir) spectra were run neat or in potassium bromide pellets on a Perkin-Elmer Model 237B grating spectrometer. Analytical gas chromatography (glc) was done with a Varian Aerograph 90P3 gas chromatograph, using 5 ft × $^3/_{16}$ in. i.d. columns. Preparative gas chromatography (glc) was done with a Varian Aerograph Autoprep Model 705 gas chromatograph, using a 20 ft × $^5/_{16}$ in. i.d. column of 30% SE-30 on 60/80 mesh Chromosorb W. The nuclear magnetic resonance (nmr) spectra were run on a 60-MHz Varian A-60 spectrometer, with tetramethylsilane as the internal reference. The ultraviolet (uv) spectra were obtained with a Cary Model 14 recording spectrophotometer. Mass spectra were obtained with an AEI MS12 mass spectrometer. Preparative thin layer chromatography (tlc), unless otherwise indicated, was done with Brinkmann silica gel PF_{254} with 5% calcium sulfate.

Diels–Alder Reactions. General Procedure.—A mixture of 2.50–3.50 mmol of diene, 0.430–0.870 mmol of dienophile (citracononitrile[16] or mesacononitrile[17]), and 1–2 mg of hydroquinone was sealed in a glass tube and heated at 100° for 10 days. A reaction time in excess of 3 days at 100° was necessary to obtain complete reaction in all of the cases studied. Three tubes containing the diene and citracononitrile (9), three tubes containing the diene and mesacononitrile (10), and one tube containing the diene alone were immersed in the same oil heating-bath and heated at the same time. Examination of the heated diene sample by tlc and glc revealed extensive polymerization in each case.

Purification of Diels–Alder Reaction Mixtures.—The sealed reaction tube was opened and the contents were removed by adding dichloromethane to dissolve the mixture and pipetting the solution. A benzene–dichloromethane solution of the reaction mixture was applied to a 1 × 4 in. area near the bottom ("bottom" refers to one of the 5-in. sides) of a 5 × 8 in. ChromAR 1000 sheet (Mallinkrodt Chemical Co.). The sheet was developed 2–4 times with petroleum ether (bp 30–60°) until the excess diene and diene dimers had moved above a line 5.25 in. from the bottom of the sheet (observed under ultraviolet light). The sheet was then cut at 5.25 in. from the bottom, and the bottom portion was eluted with 50 ml of methanol by descending elution chromatography in an apparatus similar to that usually employed for descending paper chromatography. The methanol was removed from the adduct mixture with a rotary evaporator, the mixture was transferred in dichloromethane solution to a 30 × 100 mm vial, and the solvent was removed with a rotary evaporator.

Only polymeric material remained on the sheet, as evidenced by examination (tlc and ir spectrum) of additional material eluted from the sheet by subsequent elution with acetone and dichloromethane.

The ir spectrum of the material eluted with dichloromethane from the detached upper portion of the sheet showed no absorption in the C≡N stretching region of 2215–2260 cm^{-1}.

It may be concluded from the above results that the isolation of the adduct mixture was quantitative. Although the adduct mixture after this purification contained traces of colored impurities and a small amount of polymeric material, it was suitable for analysis by the procedure used in this work.

Degradation of Adduct Mixtures.—Three equivalents of powdered anthraquinone was added to the adduct mixture (0.430–0.870 mmol, theoretical yield from Diels–Alder reaction) in a 30 × 100 mm glass vial. The vial was then placed in a nitrogen-filled glove bag, where the degradation reaction was run. The adduct mixture was dissolved by stirring (magnetic stirrer) with 15 ml of dry benzene which had been saturated with anthraquinone. Then 0.50–0.60 g (4.4–5.3 mmol) of powdered potassium *tert*-butoxide was added to the rapidly stirred solution. The reaction mixture began to turn dark green immediately, and stirring was continued for 5 min. Then 3 ml of anhydrous ether was added, and stirring was continued for an additional 5 min. The reaction vial was then removed from the glove bag and pipetted directly into a spherical separatory funnel containing a rapidly stirred (magnetic stirrer) mixture of 40 ml of dichloromethane and 20 ml of 5% aqueous ammonium chloride solution. The green color of the reaction mixture disappeared within a few minutes after addition to the separatory funnel. The yellow dichloromethane layer was drawn off, and the clear aqueous solution was extracted with two additional 25-ml portions of dichloromethane. The solvent was removed from the combined dichloromethane extracts on a rotary evaporator. The residue was stirred well with 15 ml of ether, which was then filtered to remove the insoluble anthraquinone. The anthraquinone crystals and flask were thoroughly washed with three additional 15-ml portions of ether. The ether was removed on a rotary evaporator, and the residue was transferred in dichloromethane solution to a 15 × 120 mm test tube. The solvent was removed on a rotary evaporator. One drop of methyl benzoate (quantitative nmr standard) was added to the residue in the test tube and weighed. The reaction residue–methyl benzoate mixture was then mixed well with about 1 ml of chloroform-*d*, and the solution was filtered into an nmr tube.

Nmr Determination of Isomer Ratios.—Nmr spectra of samples prepared according to the procedure described under "Degradation of Adduct Mixtures" were obtained first at 500-Hz sweep width (downfield from internal tetramethylsilane) to determine relative positions of the methyl proton signals. The methyl protons of the substituted benzenecarbonitriles and methyl benzoate were integrated at 50-Hz sweep width and sweep time of 50 sec. The rf field was set low enough to eliminate saturation. Each sweep was started at a sweep offset of 190 Hz downfield from internal tetramethylsilane to integrate the methyl proton singlet of methyl benzoate (δ 3.92 ppm). Then, while the sweep continued, the offset was changed to 130–115 Hz downfield from internal tetramethylsilane for integration of the methyl proton singlets of the substituted benzenecarbonitriles (δ 2.63–2.04 ppm). Each sample was integrated five times and average values were determined. The results of these analyses are presented in Table I.

2,6-Dimethylbiphenyl-3-carbonitrile.—A mixture of 2.9 g (0.020 mol) of 2-methyl-1-phenyl-1,3-butadiene[18] and 3.7 g (0.040 mol) of citracononitrile was heated at 95° in a sealed glass tube for 8 days. The reaction mixture was chromatographed in benzene on 330 g of Florisil (column diameter 35 mm). The 24 100-ml fractions containing crystalline solid after removal of the benzene were combined and recrystallized three times from absolute ethanol to give 0.90 g (0.0038 mol, 19% yield) of colorless needles: mp 170–171°; ir (potassium bromide) 2250 and 2240 cm^{-1} (C≡N); nmr (chloroform-*d*) δ 7.48 (s, 5, C_6H_5), 5.85 (m, 1, C=CH), 3.35 (m, 1), 2.93 (m, 3), 1.63 (s, 3, CH_3), and 1.54 ppm (s, 3, CH_3).

(13) (a) R. Hoffmann and R. B. Woodward, *J. Amer. Chem. Soc.*, **87**, 4388 (1965); (b) K. Alder and G. Stein, *Angew. Chem.*, **50**, 510 (1937).

(14) (a) K. Alder, K. Heimbach, and R. Reubke, *Chem. Ber.*, **91**, 1516 (1958); (b) J. S. Meek and J. W. Ragsdale, *J. Amer. Chem. Soc.*, **70**, 2502 (1948); (c) M. Schwarz and M. Maienthal, *J. Org. Chem.*, **25**, 449 (1960).

(15) J. S. Meek, B. T. Poon, R. T. Merrow, and S. J. Cristol, *J. Amer. Chem. Soc.*, **74**, 2669 (1952).

(16) P. M. Brown, D. B. Spiers, and M. Walley, *J. Chem. Soc.*, 2882 (1957).

(17) L. van de Straete, *Bull. Sci. Acad. Roy. Belg.*, **21**, 226 (1935); *Chem. Abstr.*, **29**, 3985 (1935).

(18) K. Alder, J. Haydn, K. Heimbach, and K. Neufang, *Justus Liebigs Ann. Chem.*, **586**, 110 (1954).

Anal. Calcd for $C_{16}H_{16}N_2$: C, 81.32; H, 6.83. Found: C, 81.32; H, 6.82.

A 102-mg (0.432 mmol) sample of the above adduct was treated as described previously under "Degradation of Adduct Mixtures." The product was isolated by preparative tlc followed by sublimation at room temperature (0.3 mm), giving 68 mg (0.329 mmol, 76% yield) of colorless crystals: mp 63–64°; ir (potassium bromide) 2220 cm^{-1} (C≡N); nmr (chloroform-*d*) δ 7.65–7.05 (m, 7), 2.26 (s, 3, CH_3), and 2.11 ppm (s, 3, CH_3).

Anal. Calcd for $C_{15}H_{13}N$: C, 86.92; H, 6.32. Found: C, 86.93; H, 6.31.

Acidic hydrolysis of this material followed by decarboxylation with copper chromite in quinoline gave 2,6-dimethylbiphenyl.

3,6-Dimethylbiphenyl-2-carbonitrile.—A mixture of 2-methyl-1-phenyl-1,3-butadiene, 3.4 g (0.051 mol) of *trans*-2-butenenitrile, and 5 mg of hydroquinone was heated at 200° in a sealed tube for 3 days. The reaction mixture was dissolved in 200 ml of benzene, 20 g of 28–200 mesh silica gel was added, and the benzene was removed on a rotary evaporator. The silica gel was then thoroughly washed with methanol, which extracted the adduct mixture, leaving most of the polymeric material on the silica gel. The adduct mixture was separated from excess diene and diene dimers by preparative tlc, developed with petroleum ether.

The adduct mixture was aromatized by refluxing under nitrogen for 3 hr with 0.5 g of 5% palladium on charcoal. The mixture was taken up in acetone, filtered, and concentrated. The aromatic nitrile mixture was isolated as 1.2 g (0.0058 mol, 24% yield) of yellow oil by preparative tlc, developed with carbon tetrachloride.

A 60-mg sample of the above nitrile mixture was stirred with a mixture of 20 ml of 30% hydrogen peroxide, 20 ml of acetone, and 1 g of sodium carbonate for 2 days.[19] This effectively removed the undesired 2,6-dimethylbiphenyl-3-carbonitrile by converting it to the amide. The reaction mixture was extracted with two 40-ml portions of dichloromethane, the extract was concentrated, and the residue was purified by preparative tlc, developed with benzene. Further purification by sublimation at room temperature (0.3 mm) gave 47 mg (78% recovery) of colorless crystals: mp 45–46°; ir (neat) 2220 cm^{-1} (C≡N); nmr (carbon tetrachloride) δ 7.18 (m, 7), 2.45 (s, 3, CH_3), and 2.02 ppm (s, 3, CH_3).

Anal. Calcd for $C_{15}H_{13}N$: C, 86.92; H, 6.32. Found: C, 86.93; H, 6.55.

A sample of the above material gave 1,4-dimethylfluorenone when heated with polyphosphoric acid at 160°.

2,3-Dimethylbiphenyl-4-carbonitrile.—A mixture of 2.9 g (0.020 mol) of 3-phenyl-1,3-pentadiene[18] and 3.7 g (0.040 mol) of mesacononitrile was heated at 95° for 5 days. The reaction mixture was chromatographed on 150 g of Florisil (column diameter 34 mm). The excess diene and diene dimers were removed with petroleum ether eluent. The adduct mixture was then removed with benzene eluent. The adduct mixture was separated into its various isomers by preparative glc (column temperature 237°, nitrogen flow rate 180 ml/min). The third adduct to emerge from the gas chromatograph had mp 97–99°; ir (potassium bromide) 2240 cm^{-1} (C≡N); nmr (chloroform-*d*) δ 7.30 (m, 5, C_6H_5), 5.72 (m, 1, C=CH), 3.25 (m, 1), 3.06 (m, 1), 2.68 (m, 2), 1.55 (s, 3, CH_3), and 1.10 ppm (d, 3, J = 7 Hz, CH_3).

Anal. Calcd for $C_{16}H_{16}N_2$: C, 81.32; H, 6.83. Found: C, 81.24; H, 6.83.

A 143-mg (0.61 mmol) sample of the adduct was subjected to the reaction conditions described under "Degradation of Adduct Mixtures." The crude product was chromatographed by preparative tlc and further purified by sublimation at room temperature (0.3 mm), giving 86 mg (0.42 mmol, 69% yield) of white solid: mp 57.5–58.0°; ir (potassium bromide) 2220 cm^{-1} (C≡N); nmr (chloroform-*d*) δ 7.60–7.11 (m, 7), 2.57 (s, 3, CH_3), and 2.21 ppm (s, 3, CH_3).

Anal. Calcd for $C_{15}H_{13}N$: C, 86.92; H, 6.32. Found: C, 87.02; H, 6.32.

(19) (a) J. V. Murray and J. B. Cloke, *J. Amer. Chem. Soc.*, **56**, 2749 (1934); (b) K. B. Wiberg, *ibid.*, **75**, 3961 (1953).

Acidic hydrolysis of this material followed by decarboxylation with copper chromite in quinoline gave 2,3-dimethylbiphenyl.

2,4-Dimethylbiphenyl-3-carbonitrile.—A mixture of 3.4 g (0.024 mol) of 3-phenyl-1,3-pentadiene and 3.4 g (0.051 mol) of *trans*-2-butenenitrile was treated as described previously under "3,6-Dimethylbiphenyl-2-carbonitrile." The aromatized mixture was taken up in acetone and filtered, and the filtrate was concentrated. Preparative tlc of the residue, developed with carbon tetrachloride, gave a light yellow solid, which was recrystallized three times from absolute ethanol to give 0.90 g (0.0043 mol, 18% yield) of colorless crystals: mp 124.5–125.0°; ir (potassium bromide) 2220 cm^{-1} (C≡N); nmr (chloroform-*d*) δ 7.38 (m, 7), 2.61 (s, 3, CH_3), and 2.48 ppm (s, 3, CH_3).

Anal. Calcd for $C_{15}H_{13}N$: C, 86.92; H, 6.32. Found: C, 86.85; H, 6.29.

A sample of this material gave 2,4-dimethylbiphenyl when heated with polyphosphoric acid at 160°.[20]

3-Methylbiphenyl-2-carbonitrile.—A mixture of 0.908 g (6.98 mmol) of 1-phenyl-1,3-butadiene[21] and 0.980 g (14.6 mmol) of *trans*-butenenitrile was treated as described previously under "3,6-Dimethylbiphenyl-2-carbonitrile," giving 60 mg of a colorless oil: ir (neat) 2220 cm^{-1} (C≡N); nmr (chloroform-*d*) δ 7.70–7.23 (m, 8) and 2.63 ppm (s, 3, CH_3); mass spectrum (70 eV) *m/e* (rel intensity) 193 (100, M^+), 192 (60), 165 (28), 117 (38), 91 (35), and 28 (37).

A 25-mg (0.13 mmol) sample of the above material gave 1-methylfluorenone when heated with polyphosphoric acid at 160°.

2-Methylbiphenyl-3-carbonitrile.—A mixture of 0.70 g (7.6 mmol) of mesacononitrile, 1.38 g (10.6 mmol) of 1-phenyl-1,3-butadiene, and 2 mg of hydroquinone was heated at 100° for 10 days in a sealed glass tube, then purified as described previously under "Purification of Adduct Mixtures." The adduct mixture obtained was fractionally crystallized three times from 95% ethanol, giving 0.193 g (0.87 mmol, 11% yield) of colorless needles: mp 156–157°; ir (potassium bromide) 2240 cm^{-1} (C≡N); nmr (chloroform-*d*) δ 7.40 (m, 5, C_6H_5), 5.87 (m, 2, C=CH), 3.96 (m, 1), 3.42 (m, 1), 2.75–2.45 (m, 2), and 1.21 ppm (s, 3, CH_3).

Anal. Calcd for $C_{15}H_{14}N_2$: C, 81.05; H, 6.05. Found: C, 81.02; H, 6.36.

A 173-mg (0.780 mmol) sample of this adduct was treated as described previously under "Degradation of Adduct Mixtures." The crude product was chromatographed by preparative tlc, and developed with a mixture consisting of 60% petroleum ether and 40% benzene by volume. The yellow oil obtained was further purified by sublimation at room temperature (0.3 mm) to give 134 mg (0.695 mmol, 89% yield) of white crystals: mp 61.0–61.5°; ir (potassium bromide) 2240 cm^{-1} (C≡N); nmr (chloroform-*d*) δ 7.77–7.22 (m, 8) and 2.47 ppm (s, 3, CH_3).

Anal. Calcd for $C_{14}H_{11}N$: C, 87.01; H, 5.74. Found: C, 87.07; H, 5.71.

Acidic hydrolysis of this compound and subsequent decarboxylation with copper chromite and quinoline gave 2-methylbiphenyl.

Registry No.—**9**, 37580-43-1; **10**, 37580-44-2; $C_{16}H_{16}N_2$, mp 170–171°, 37580-45-3; $C_{16}H_{16}N_2$, mp 97–99°, 37580-46-4; $C_{15}H_{14}N_2$, mp 156–157°, 37580-47-5; 2,6-dimethylbiphenyl-3-carbonitrile, 37580-48-6; 3,6-dimethylbiphenyl-2-carbonitrile, 37580-49-7; *trans*-2-butenenitrile, 627-26-9; hydroquinone, 123-31-9; 2,3-dimethylbiphenyl-4-carbonitrile, 37580-50-0; 2,4-dimethylbiphenyl-3-carbonitrile, 37580-51-1; 3-methylbiphenyl-2-carbonitrile, 37580-52-2; 2-methylbiphenyl-3-carbonitrile, 37580-53-3.

(20) H. R. Snyder and C. T. Elson, *ibid.*, **76**, 3039 (1954).

(21) O. Grummitt and E. I. Becker in "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 771.

Favorskii Rearrangements. VII.[1] Formation of Amides from α-Halo α′-Aryl Ketones

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Reaction of *cis*-2-chloro-6-phenylcyclohexanone (1) with 0.05 *M* NaOMe in MeOH gave only *cis*- and *trans*-2-methoxy-6-phenylcyclohexanones. Observation of a small k^{Br}/k^{Cl} rate ratio (*ca.* 4) for this reaction showed that the deprotonation step was rate limiting. Even 2 *M* NaOMe failed to produce Favorskii ester from 1, whereas piperidine in MeOH gave the Favorskii amide in high yield. Piperidine was also effective in giving a Favorskii product from 1-bromo-1,3,3-triphenyl-2-propanone whereas NaOMe was not. With 1-chloro-2-phenyl-2-propanone (5) piperidine gave a high yield of Favorskii amide. In the presence of 0.17 *M* piperidine and 0.17 *M* NaOMe in MeOH 5 gave 60% of amide and 40% of ester. It is suggested that the superiority of piperidine to methoxide ion in promoting Favorskii rearrangements in these systems is caused by its ability to form a Favorskii amide from an intermediate other than a cyclopropanone; enamine 19 is suggested as a likely intermediate. 1-Bromo-1,3-diphenyl-2-propanone reacted with piperidine in 50% ether–chloroform to give 60% of amide; no amide was formed in MeOH.

Reactions of α-halo ketones with alkoxide bases proceed by two principal pathways: (1) attack at the carbonyl group leading to α-alkoxy oxiranes and (on work-up) to α-hydroxy ketones or α-hydroxy ketals, and (2) enolate ion formation leading to Favorskii rearrangement products and α-alkoxy ketones. Enolate ion formation is strongly promoted by the presence of a phenyl group at the α′-carbon atom. For example, $PhCH_2COCH_2Cl$ reacts with 0.05 *M* NaOMe in MeOH to give a quantitative yield of Favorskii ester,[3a] whereas the isomeric $PhCHClCOCH_3$ gives only 13% yield under these conditions.[3b] We have now examined the effect of substitution of a phenyl group into the α′ position of 2-chlorocyclohexanone by studying the behavior of *cis*-2-chloro-6-phenylcyclohexanone toward NaOMe in MeOH and toward piperidine in MeOH. The investigation with secondary amines was extended to certain other α′-phenyl-substituted α-halo ketones.

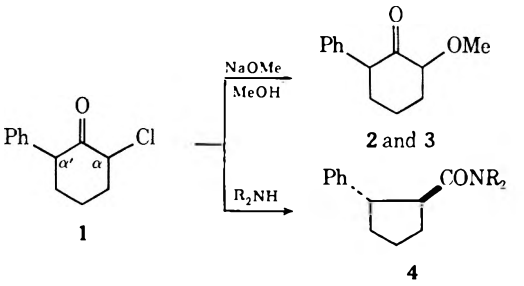
The reaction of secondary amines with α-halo ketones has generally been reported to give α-dialkylamino ketones as the primary product (SN2 reaction). In some instances small yields of Favorskii amides (20–30%) have been reported, however,[4] and two examples are known in which an amine derivative (an aminal) of a cyclopropanone was obtained in appreciable yield (37% from α-chlorocyclohexanone and 41% from α-chlorocycloheptanone).[5] In the present paper secondary amines have been found to produce Favorskii amides from several α′-phenyl α-halo ketones in high yields. The ability of piperidine to produce Favorskii products from two of these under conditions where methoxide ion is unable to do so is of synthetic and mechanistic significance.

Results

Reactions with Sodium Methoxide in Methanol.—Reaction of *cis*-2-chloro-6-phenylcyclohexanone (1) with 0.05 *M* NaOMe in MeOH gave a nearly quantitative conversion into a mixture of *cis*- and *trans*-2-methoxy-6-phenylcyclohexanones (2 and 3, respectively); little or no Favorskii ester (methyl 2-phenylcyclopentanecarboxylate) was formed. Increasing the sodium methoxide concentration to 2.5 *M* gave essentially the same result. Reactions with NaOMe in aprotic solvents (DME, DMSO, Et_2O) also failed to produce ester.

Rates of halide release at 0° in MeOH were determined under second-order conditions using varying concentrations at 1 (0.00106, 0.00108, 0.00121, and 0.00118 *M*) and of NaOMe (0.00951, 0.0698, 0.073, and 0.119 *M*). The average second-order rate constant was $9.0 \pm 2 \times 10^{-2}\ M^{-1}\ \text{sec}^{-1}$ ($r \cong 0.99$ for each run). The rate constant for the bromo analog of 1, determined in the same manner, was $3.67 \pm 0.23 \times 10^{-1}\ M^{-1}\ \text{sec}^{-1}$.

Reactions with Secondary Amines.—Reaction of chloride 1 with excess piperidine at 0° for 1 hr gave conversion in high yield into Favorskii amide (*trans*-2-phenylcyclopentanecarboxpiperidide, 4). Amides



were also produced in high yields using high concentrations of piperidine in methanol or 2.8 *M* dimethylamine in aqueous methanol. With low concentrations of piperidine in MeOH (0.10 to 0.33 *M*) mixtures of methoxy ketones (2 and 3) and amide 4 were obtained. For example, with 0.10 *M* piperidine in MeOH about 55% of methoxy ketones and 45% of amide were formed. Increasing the concentration of piperidine to 0.33 *M* increased the amount of amide, and an increase in amide relative to methoxy ketones was also observed on adding NaOMe (0.15 to 0.30 *M*).

(1) For part VI see F. G. Bordwell and R. G. Scamehorn, *J. Amer. Chem. Soc.*, **93**, 3410 (1971).

(2) National Institutes of Health Postdoctoral Fellow, 1969–1971. This investigation was supported by Public Health Service Research Grant No. CA-50610 from the National Cancer Institute.

(3) F. G. Bordwell, R. G. Scamehorn, and W. R. Springer, *J. Amer. Chem. Soc.*, **91**, 2087 (1969); (b) F. G. Bordwell and R. G. Scamehorn, *ibid.*, **90**, 6751 (1968).

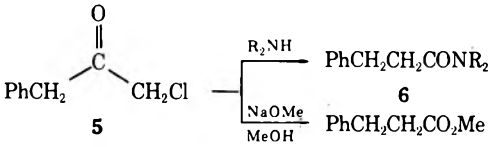
(4) A. S. Kende, *Org. React.*, **11**, 287 (1960); (b) E. L. May and E. Mosettig, *J. Amer. Chem. Soc.*, **70**, 1077 (1948); (c) R. M. Dodson, E. F. Morello, and W. G. Dauben, *ibid.*, **76**, 606 (1954); (d) J. Jullien and P. Fauche, *Bull. Soc. Chim. Fr.*, (5) **20**, 374 (1955); (e) C. L. Stevens, A. B. Ash, A. Thuillier, J. H. Amin, A. Balys, W. E. Dennis, J. P. Dickerson, R. P. Glinski, H. T. Hanson, M. J. Pillai, and J. W. Stoddard, *J. Org. Chem.*, **31**, 2593 (1966).

(5) J. Szmuszkovicz, E. Cerda, M. F. Grostic, and J. F. Zieserl, Jr., *Tetrahedron Lett.*, 3969 (1967); J. Szmuszkovicz, D. J. Duchamp, E. Cerda, and C. G. Chidester, *ibid.*, 1309 (1969).

Use of 0.33 *M* 2,2,6,6-tetramethylpiperidine in methanol gave only methoxy ketones (**2** and **3**) and no amide.

Rates of reaction of piperidine (0.990 *M*) with **1**, and its bromo analog, in MeOH at 0° were determined conductometrically; for **1**, $k = 1.85 \pm 0.03 \times 10^{-3}$ M^{-1} sec^{-1} (average of three runs with $r = 0.999$ or better) and, for the bromo analog, $k = 3.99 \pm 0.09 \times 10^{-3}$ M^{-1} sec^{-1} (average of three runs with $r = 0.999$ or better).

Reaction of 1-chloro-3-phenyl-2-propanone (**5**) with 1 *M* piperidine in methanol also gave Favorskii amide (**6**) as the principal product. With NaOMe present **5** gave both Favorskii amide (**6**) and Favorskii ester (**7**); for example, with **5** and 0.17 piperidine and 0.17 *M* NaOMe 60% of amide **6** and 40% of ester **7** were formed. With 0.17 *M* piperidine and 0.33 *M* NaOMe 40% of amide **6** and 55% of ester **7** were formed. Reaction of



action of 1-chloro-3-*p*-tolyl-2-propanone (**8**) with 2 *M* piperidine gave the corresponding amide (**9**) along with *ca.* 30% of 1-piperidino-3-*p*-tolyl-2-propanone, **10** (SN2 product). Using 1 *M* piperidine and 1 *M* NaOMe in MeOH gave amide **9** and the corresponding ester (**11**), but no **10**.

Reaction of 1-bromo-1,3-diphenyl-2-propanone (**12**) with 0.1 *M* piperidine in MeOH gave SN2 product, 1-piperidino-1,3-diphenyl-2-propanone, plus a small amount of methoxy ketone; no amide was formed. With 0.5 *M* piperidine in 50% (v/v) ether–chloroform 40% of the amino ketone and 60% of amide were obtained.

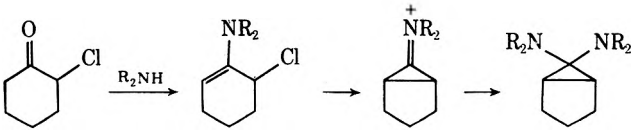
Reaction of 1-bromo-1,3,3-triphenyl-2-propanone (**13**) with neat piperidine or with 7 *M* piperidine in MeOH gave Favorskii amide as the principal product. With 1 *M* piperidine in MeOH only *ca.* 10% of amide was formed, together with *ca.* 35% of 1,3-diphenylindanone[1] and *ca.* 10% of 1-methoxy-1,1,3-triphenyl-2-propanone.[6] [1,3-Diphenylindanone did not react with (neat) piperidine to form the amide under the experimental conditions.]

Discussion

Formation of α-methoxy ketones **2** and **3** from the reaction of *cis*-2-chloro-6-phenylcyclohexanone (**1**) with low concentrations (0.05 *M*) of NaOMe in MeOH is expected by analogy with the behavior of 2-chlorocyclohexanone[7a] and of $PhCH_2COCHMeCl$ (**14**).[7b] The behavior of **1** differs, however, in that no Favorskii ester is produced even at high concentrations (2 *M*) of NaOMe. (With 2 *M* NaOMe 2-chlorocyclohexanone gives 49% of Favorskii ester and 47% of hydroxy ketal,[7a] and **14** gives 100% of Favorskii ester.[7b]) Substitution of a phenyl group into the α′ position of 2-chlorocyclohexanone greatly enhances the rate of enolate ion formation relative to attack at the carbonyl group in **1**; production of α-methoxy ketones (by methanolysis of the enol allylic chloride) and of Favorskii ester is thereby favored over hydroxy ketal formation.[3,4,7] The presence of an additional α′-alkyl (ring) substituent in **1**, as compared to **14**, would be expected to enhance the methanolysis rate,[8] which accounts for the formation of α-methoxy ketones in preference to Favorskii ester even in the presence of high concentrations of NaOMe.

The rate of chloride ion release from **1** with NaOMe in MeOH at 0° is *ca.* 22 times faster than from 2-chlorocyclohexanone. The rate acceleration can be attributed to the presence of the phenyl substituent in **1**, but the rates are not strictly comparable because preequilibrium carbanion–enolate ion formation is appreciable for 2-chlorocyclohexanone,[9] whereas for **1** the relatively small k^{Br}/k^{Cl} rate ratio (*ca.* 4; compare with 63 for $PhCH_2COCH_2X$) shows that proton removal is largely rate limiting. In this respect the behavior of **1** resembles that of **14** ($k^{Br}/k^{Cl} = 0.9$).[7b] The 73-fold slower rate for chloride ion release for **1** as compared to **14** is no doubt due primarily to retardation of the deprotonation rate caused by the presence of an additional α′-alkyl (ring) substituent in **1**.

The ability of secondary amines to produce high yields of Favorskii amide from **1** in light of the failure of even high concentrations of methoxide ion to produce Favorskii esters suggests that the amide is being formed by a route not available for ester formation. One possibility is reaction *via* an enamine allylic chloride in a route similar to that suggested by Szmuszkovicz and coworkers[6] for the conversion of 2-chlorocyclohexanone with piperidine into the aminal of the Favorskii cyclopropanone (**17**).



An alternative pathway for the formation of **17**, which does not appear to have been ruled out, is reaction of piperidine with an intermediate cyclopropanone. (Conversions of cyclopropanones into aminals are known to occur readily.[10]) The behavior of **1** toward piperidine (relative to methoxide ion) described above is accounted for much more readily by postulating an enamine intermediate, however, and the formation of Favorskii amides from 1-chloro-3-phenyl-2-propanone (**5**) and from 1-bromo-1,3,3-triphenyl-2-propanone (**13**) can also be accommodated best by this mechanism. There is persuasive evidence to favor an enamine intermediate over a cyclopropanone intermediate in the case of **5**. Here we have good reason to believe that the nearly quantitative yield of Favorskii ester formed from **5** and NaOMe–MeOH is derived from a cyclopropanone intermediate.[3] One would not expect piperidine to be able to compete with methoxide ion for this intermediate since the carbonyl group is ordinarily much

(6) The indanone and methoxy ketone are the principal products formed with sodium methoxide in methanol; see ref 1.

(7) (a) F. G. Bordwell and J. G. Strong, *J. Org. Chem.*, **38**, 579 (1973). (b) F. G. Bordwell and M. W. Carlson, *J. Amer. Chem. Soc.*, **92**, 3370 (1970).

(8) The ethanolysis rate of $Me_2C{=}CHCH_2Cl$ is *ca.* 65 times that of $MeCH{=}CHCH_2Cl$: C. A. Vernon, *J. Chem. Soc.*, 423, 4462 (1954).

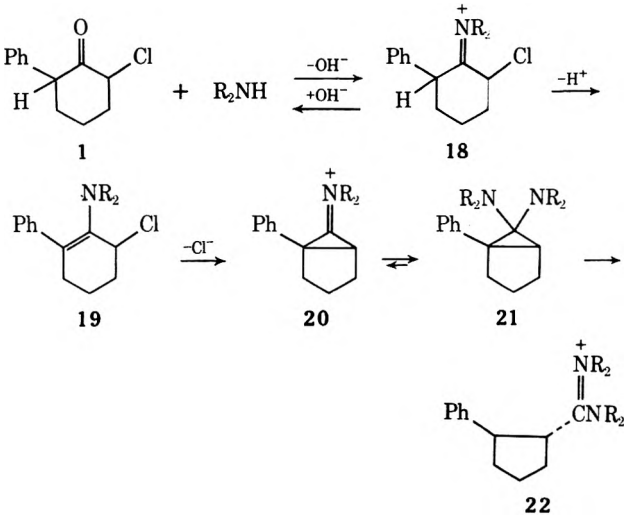
(9) F. G. Bordwell, R. R. Frame, R. G. Scamehorn, J. G. Strong, and S. Meyerson, *J. Amer. Chem. Soc.*, **89**, 6704 (1967).

(10) W. J. M. Van Tilborg, S. E. Schaafsma, H. Steinger, and T. J. de Boer, *Rec. Trav. Chem. Pays-Bas*, **86**, 417 (1967).

more receptive to attack by methoxide ion.[11] Formation of a *higher* yield of amide than ester from **5** on treatment with equivalent amounts of piperidine and methoxide ion is, therefore, inconsistent with the generation of both the amide and ester from a cyclopropanone intermediate. It seems more likely that the amide is derived from an enamine intermediate (comparable to **15**) and that the ester is derived from a cyclopropanone intermediate. If this explanation is correct, enamine formation must be a rapid reaction since the second-order rate constant for the reaction of **5** with methoxide ion is $2.6 \times 10^{-1}\ M^{-1}\ \text{sec}^{-1}$ at 0°.[3] Loss of bromide ion from **13** in the reaction with NaOMe–MeOH to form 1,3-diphenylindanone is *ca.* 10 times faster,[1] which may explain the inability of amide formation (presumably *via* the enamine) to compete with 1,3-diphenylindanone formation (presumably *via* a dipolar ion) except at high concentrations of amine. The rate of loss of halide ion from **1**, or its bromo analog, with NaOMe–MeOH is of the same order of magnitude as for **5** (see above). Enamine formation can be reasonably expected to compete favorably, therefore, with formation of the α-methoxy ketone from **1**, as observed.

Comparison of the behavior of **1** and 2-chlorocyclohexanone[6] toward piperidine shows that the presence of the phenyl group promotes enamine formation at the expense of the SN2 reaction, and causes formation of Favorskii amide in place of the aminal. The phenyl group no doubt promotes enamine formation by facilitating deprotonation of an intermediate, such as **18**. The effect of methoxide ion in increasing the yield of amide can be explained as facilitating this deprotonation.

The phenyl group would also be expected to promote cleavage of aminal **21** to amidinium ion **22**. The latter



would be hydrolyzed to amide on work-up or by the mole of water released in converting **1** into **19**.

Cleavage of the C–X bond is not involved in the rate-limiting step of enamine formation, judging from the small (~4) k^{Br}/k^{Cl} leaving group effect observed for the reaction of **1** and its bromo analog with 1 *M* piperidine in MeOH. According to the scheme shown, deprotonation of **18** will be rate limiting.[13] The smaller amount of amide *vs.* SN2 product formed from the *p*-methyl derivative of **5** can be accounted for by retardation of the deprotonation step in the reaction leading to amide. Work designed to gain additional information concerning the details of the mechanistic scheme shown for **1** is in progress.

Experimental Section

***cis*- and *trans*-2-Methoxy-6-phenylcyclohexanone (2 and 3).**—To 200 ml of 0.05 *N* sodium methoxide in methanol at 0° (prepared with 10 mmol of dry sodium methoxide, Matheson-equivalent weight 100 by titration) was added 0.97 g (0.0048 mol) of *cis*-2-chloro-6-phenylcyclohexanone (**1**), mp 122–123°.[14] The solution was stirred for 2 hr at 0° and then neutralized (phenolphthalein) with glacial acetic acid, concentrated under reduced pressure to 10% of its original volume, and shaken with water and ether. The organic phase was washed with brine and then water, dried, and concentrated to yield 0.90 g (99%) of a solid, mp 47–53°. Analysis of the crude material by nmr indicated that two methoxy ketones accounted for 70 and 30% of the product (by comparison of integrals of sharp singlets at δ 3.2–3.4 and a multiplet at 7.0–7.4 (see below)). Fractional crystallization from ether–hexane gave 0.356 g (36%, three crystallizations) of pure *cis*-2-methoxy-6-phenylcyclohexanone: mp 74–75°; nmr $\delta_{TMS}^{CCl_4}$ 1.4–2.3 (broad multiplet, 6, CH_2), 3.32 (s, 3, OCH_3), 3.40–4.0 (multiplet, 2, CH), 7.00–7.40 (multiplet, 5, Ph); ir λ_{max}^{KBr} 3.40, 5.81, 6.90. The structure was based on equilibration data (see below).

Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.49; H, 8.07.

Chromatography of combined mother liquors from the crystallizations described above yielded a second (trans) methoxy ketone from fractions eluted with 8% ether in hexane: $\delta_{TMS}^{CCl_4}$ 1.4–2.4 (m, CH_2, 6), 3.28 (s, 3, OCH_3), 3.40–4.00 (m, 2, CH), 7.0–7.4 (m, 5, Ph). The cis isomer was eluted with pure ether. Both the cis and trans isomers were subjected to equilibration conditions (0.1 *M* sodium methoxide in methanol. 0°, 44 hr or 0.5 *M* methoxide, 0°, 24 hr). The cis isomer predominated in each instance by a factor of *ca.* 4:1 (nmr analysis); unidentified products accounted for 3% of the total product.

Product Distribution Runs for Reactions of 2-Chloro-6-phenylcyclohexanone (1) with Metal Alkoxides in Methanol, *tert*-Butyl Alcohol, Dimethoxyethane, Dimethyl Sulfoxide, Ether, and Dichloromethane.—The solvent and base were combined and brought to the predetermined temperature. In the case of concentrated methoxide solutions, sodium or potassium was introduced to the alcohol solvent. The substrate was then introduced, and the solution was maintained at temperature for the prescribed time neutralized with glacial acetic acid, and shaken with ether and water. The organic phase was washed twice with water, combined, dried, and concentrated under reduced pressure and analyzed by nmr. Integration of the aromatic region (five protons) *vs.* peaks corresponding to the methoxy ketone products (*vide supra*) gave ratios of 2.3–3:1 of cis/trans. Other products included 2-hydroxy-6-phenylcyclohexanone[15] (42%) from reaction of **1** with 1.0 *M* potassium *tert*-butoxide in *tert*-butyl alcohol, and methyl 2-phenylcyclopentanecarboxylate (*ca.* 40%) from 4.8 *M* potassium methoxide in methanol. The ester was identified (nmr) by comparison with a sample prepared from the corresponding acid (see below).

Rates of Halide Ion of 2-Chloro-6-phenylcyclohexanone, 1, and 2-Bromo-6-phenylcyclohexanone.—The kinetic procedure followed a previously described method.[7a] Typically, 4.70 ml of 0.1085 *N* sodium methoxide in methanol cooled to 0° was rapidly added to 50.0 ml of 0.00118 *M* **1** kept at 0° under nitrogen in a single-neck pear-shaped flask. A 5-ml-capacity automatic

(11) For example, methoxide ion is 10^1 to 10^2 more effective in attacking the carbonyl group in aryl acetates than is piperidine.[12]

(12) W. P. Jencks and M. Gilchrist, *J. Amer. Chem. Soc.*, **90**, 2622 (1968).

(13) Another possible route to **19** would be attack of piperidine on the enolate chloride to give an adduct which forms **19** by loss of hydroxide ion. Deprotonation of **1** would then presumably be rate limiting. It seems doubtful, however, that addition of piperidine to the enolate chloride (or enol chloride) could be fast enough to make deprotonation rate limiting.

(14) G. Berti, F. Bottari, B. Macchia, and F. Macchia, *Tetrahedron*, **22**, 190 (1966).

(15) Identified by comparison of the nmr spectrum with that of an authentic sample prepared by the method of W. Treibs, M. Weissenfels, *Ber.*, **93**, 1374 (1960).

pipet (plunger type, Cole Parmer) was inserted and secured with a tightly fitting syringe cap. The flask was shaken and immersed above the pipet chamber in an Aminco Model 4-8600 constant temperature bath held at 0.0 ± 0.003°. Aliquots (4.0 ml) were drawn at various times and delivered into a quenching solution of 2 ml of acetone and 0.5 ml of 1 *M* nitric acid and titrated potentiometrically with 0.00283 *M* silver nitrate solution using a Sargent Model D titrator equipped with a constant rate buret and platinum electrodes. The second-order data were treated in the usual way and analyzed by a least-squares program.[16] Acceptable runs were followed to 3 half-lives, gave $r = 0.991$ or greater and standard deviations of 6% or less of the calculated rate constant. Rates (followed to 3 half-lives) were reproducible to within 15%.

Reactions of 1 with Secondary Amines.—Reaction of 1 with 1.0 *M* piperidine in methanol or neat piperidine gave conversion into amide 4 in high yield. Typically, 50 mg (0.00024 *M*) of 1 was added to a chilled mixture of 851 mg of piperidine in 10 ml of methanol. The solution was stirred and maintained at 0° for 3 hr and poured into water, rinsed with ether, and shaken. Excess piperidine was removed by washing several times with water. The organic phases were combined, dried, and concentrated to yield 52 mg (85%) solid, mp 83–85°, whose nmr spectrum showed no peaks corresponding to 2 or 3 or methyl 2-phenylcyclopentanecarboxylate. One crystallization from ether–hexane gave *trans*-2-phenylcyclopentanecarboxpiperidide (4): mp 87–88°; nmr δ 1.2–1.7 (m, 6), 1.8–2.3 (m, 6), 3.0–3.7 (m, 6), 7.15 (m, 5, Ph); λ_{max}^{KBr} 3.40, 3.50, 6.12, 6.95.

Anal. Calcd for $C_{17}H_{23}NO$: C, 79.33; H, 9, 01. Found: C, 79.55; H, 9.13.

The amide 4 produced was shown to possess the more stable trans configuration by an exchange–equilibration run similar to one reported for isomers of methyl 2-methyl-2-phenylcyclopentanecarboxylate.[7a] To 4 ml of methanol-*O*-*d* (Diaprep, 99% isotopic purity) was added 230 mg of freshly cut sodium and 100 mg of 4. The solution was refluxed under nitrogen for 100 hr and then 0.2 ml of deuterium oxide was added. The reaction was treated in the manner described above. The neutral and base fraction, 70 mg (70%), mp 80–82° (crude), possessed an nmr spectrum closely similar to that of the untreated pure amide, except that integration showed the loss of 0.8–1.5 of one proton in the region 3.0–3.7 ppm. No methyl ester was detected. The aqueous rinsings were acidified and reextracted to produce, after treatment, 30 mg of solid, mp 78–80° identified as *trans*-2-phenylcyclopentanecarboxylic acid[5d] (see below) whose nmr spectrum showed 0.8–1.2 of one proton loss in the methine region ($\delta_{TMS}^{CDCl_3}$ 3.0–3.6).

An authentic sample of *trans*-2-phenylcyclopentanecarboxylic acid was prepared from 4 with 48% aqueous hydrobromic acid refluxing for 10 hr.[5d] A sample of methyl 2-phenylcyclopentanecarboxylate was prepared from 100 mg of the acid, mp 82–84°.

Rates of Reaction of 2-Chloro-6-phenylcyclohexanone, 1, and 2-Bromo-6-phenylcyclohexanone with Piperidine in Methanol at 0°.—A 5.00-ml portion of a stock solution of 1.00 *M* piperidine in methanol was placed in a 6-ml conductometric cell and equilibrated 0.5 hr in an ice–water bath. Approximately 5 mg (0.023 mmol) of halo ketone dissolved in 0.200 ml of methanol was then added, and the mixture was shaken. The cell leads were attached to a Y.S.I. Model 31 conductivity bridge and readings were taken to 3 half-lives. Infinity readings were taken after 7 half-lives and the pseudo-first-order data were treated in the usual way. Correlation coefficients and standard deviations were obtained by a least-squares program,[16] and the second-order rate constants were corrected for dilution of base and solvent concentration at 0°.

Reactions of 1-Chloro-3-phenyl-2-propanone (5), 1-Chloro-3-*p*-tolyl-2-propanone (8), 1-Bromo-1,3-diphenyl-2-propanone (12), and 1-Bromo-1,3,3-triphenyl-2-propanone (13) with Piperidine under Various Conditions.—The reaction and analytical procedures used for reaction of the halo-2-propanone series was the same as that described for 1 above. For 5 and 13 the weighed yield after acidic work-up (see above) was at least 85% of theory. For 8 and 12 the crude products were obtained by pouring the reaction mixture into distilled water and washing five times. The organic phases were combined, dried, and concentrated as before and then analyzed. Procedures and analytical data for pure products are given below.

(16) Kindly supplied by W. J. Boyle, Jr.

3-Phenylpropionylpiperidide (6).—To 41 mg of 1-chloro-3-phenyl-2-propanone[3] was added 4.8 ml of methanol containing 278 mg (0.67 *M*) of piperidine at 0°. The reaction was maintained at 0° for 6 hr, neutralized, and extracted. The crude organic product 34 mg, contained 40% of starting material and 60% of 3-phenylpropionylpiperidide: $\delta_{TMS}^{CHCl_3}$ 1.4–1.7 (m, 6), 3.3–3.8 (m, 4), 2.5–3.1 (A_2B_2, 4), 7.2 (m, 5).

3-*p*-Tolylpropionylpiperidide (9), and 1-Piperidino-3-*p*-tolyl-2-propanone (10).—To 0.8 g of 2-*p*-tolyl-3-chloro-2-propanone[3] was added a solution of 8.5 g of piperidine and 40 ml of methanol. The mixture was kept at 0° for 18 hr, washed with dilute hydrochloric acid, and rinsed with ether. The organic phase was combined, dried, and concentrated to yield 666 mg of pale yellow oil, identified as 3-*p*-tolylpropionylpiperidide: $\delta_{TMS}^{CDCl_3}$ 1.4–1.7 (m, 6), 2.3 (s, 3), 2.5–3.1 (A_2B_2, 4), 3.2–3.7 (m, 4), 7.0 (s, 4); λ_{max}^{film} 3.40, 3.45, 6.05.

Anal. Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15, Found: C, 78.13; H, 9.28.

The amide product was hydrolyzed (water, methanol, and potassium hydroxide) to yield the known[17] 3-*p*-tolylpropionic acid, mp 115–116° (lit.[17] mp 116°). Analysis showed $\delta_{TMS}^{CDCl_3}$ 2.3 (s, 3), 2.5–3.0 (A_2B_2, 4), 7.0 (s, 4), 10.0 (s, 1).

The combined aqueous washings were neutralized with 10% aqueous potassium carbonate and reextracted, and the ether phase was washed five times with water. The organic layers were combined, dried, and concentrated to yield 300 mg of yellow oil identified as 1-piperidino-3-*p*-tolyl-2-propanone, 10: $\delta_{TMS}^{CDCl_3}$ 1.3–1.7 (m, 6), 2.1–2.5 (m, 4), 2.3 (s, 3), 3.1 (s, 2), 3.7 (s, 2), 7.1 (s, 4); λ_{max}^{film} 3.40, 5.80. An analytical sample was obtained from chromatography on silica gel (16% ether in hexane).

Anal. Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15. Found: C, 77.85; H, 9.36.

1-Piperidino-1,3-diphenyl-2-propanone and 2,3-Diphenylpropionylpiperidide.—To 0.4 g of 1-chloro-1,3-diphenyl-2-propanone[18] was added 1 ml of piperidine. The solution was kept for 15 min at 25° and then evaporated under reduced pressure. The residue was shaken with dilute hydrochloric acid and ether; the organic phase was washed five times with water, combined, dried, and concentrated to give 217 mg of a solid which was crystallized twice from ether–hexane. The crystalline product, mp 88–89°, was identified as 2,3-diphenylpropionylpiperidide: $\delta_{TMS}^{CDCl_3}$ 1.3–1.6 (m, 6), 2.8–4.2 (m, 7), 7.05 (s, 5), 7.10 (s, 5); λ_{max}^{KBr} 3.40, 3.50, 6.15.

Anal. Calcd for $C_{20}H_{23}NO$: C, 81.87; H, 7.90. Found: C, 81.72; H, 8.12.

The basic product obtained in the manner described above was 300 mg of pale yellow oil, identified as 1-piperidino-1,3-diphenyl-2-propanone: $\delta_{TMS}^{CDCl_3}$ 1.4–1.8 (m, 6), 2.2–2.5 (m, 4), 3.8 (AB, 2, $J = 14$ Hz), 4.0 (s, 1), 7.0–7.4 (m, 5), 7.3 (m, 5). An analytical sample was obtained by chromatography on silica gel (8% ether–hexane).

Anal. Calcd for $C_{20}H_{23}NO$: C, 81.87; H, 7.90. Found: C, 81.69; H, 8.09.

2,3,3-Triphenylpropionylpiperidide.—Freshly distilled piperidine (20 ml) was saturated with nitrogen for 20 min after which 600 mg of 1-bromo-1,3,3-triphenyl-2-propanone[1] was added. The solution was maintained under nitrogen for 30 min at 25° and then poured into excess aqueous hydrochloric acid and shaken with ether. The organic phase was washed twice with water, dried, and concentrated to give 635 mg of a red-brown solid which was crystallized from ether–chloroform. The crystalline product (mp 213–214°) was identified as 2,3,3-triphenylpropionylpiperidide: $\delta_{TMS}^{CDCl_3}$ 1.0–1.4 (m, 6), 3.2–3.6 (m, 4), 4.8 (AB, 2, $J = 12$ Hz), 7.0–7.4 (m, 15); λ_{max}^{KBr} 3.40, 6.15.

Anal. Calcd for $C_{26}H_{27}NO$: C, 84.51; H, 7.37. Found: C, 84.41; H, 7.35.

Registry No.—**1**, 6824-92-6; 1 bromo analog, 36702-36-0; **2**, 37108-06-8; **3**, 37108-07-9; **4** (NR_2 = piperidino), 37108-08-0; **5**, 937-38-2; **6** (NR_2 = piperidino), 21924-11-8; **8**, 24253-14-3; **9**, 37112-01-9; **10**, 37112-02-0; **12**, 29417-77-4; **13**, 33609-27-7; piperidine,

(17) K. Kindler and T. Li, *Chem. Ber.*, **74**, 321 (1941).

(18) A. W. Fort, *J. Amer. Chem. Soc.*, **84**, 2620 (1962). The bromo ketone which was used in the product studies was prepared by Dr. A. C. Knipe according to the method of Smith and Wilson: *J. Chem. Soc.*, 1342 (1955).

110-89-4; 3-*p*-tolylpropionic acid, 1505-50-6; 2,3-diphenylpropionylpiperidide, 37112-06-4; 1-piperidino-1,3-diphenyl-2-propanone, 37112-07-5; 2,3,3-triphenylpropionylpiperidide, 37112-08-6; *trans*-2-phenylcyclopentanecarboxylic acid, 37108-09-1; methyl *trans*-2-phenylcyclopentanecarboxylate, 37108-10-4.

Favorskii Rearrangements. VIII.[1] Effects of Methyl Substitution and a Test for Internal Return from Enolate Ions

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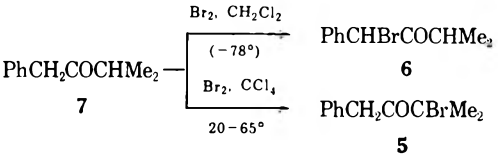
Tertiary bromide (or chloride) $C_6H_5CH_2COCMe_2X$ (**5**) reacted with 0.05 *M* NaOMe to give principally $C_6H_5CH_2COCMe_2OMe$ (**8**) plus a small yield of $C_6H_5CH_2CMe_2CO_2Me$ (**9**). With 1 *M* NaOMe the per cent of Favorskii ester (**9**) increased at the expense of α-methoxy ketone (**8**). The isomeric chloride $C_6H_5CHClCOCHMe_2$ (**6**) also gave **8** as the major product (plus minor amounts of **9**) with 0.05 *M* NaOMe, and again the formation of **9** was favored by increasing the methoxide concentration. On the other hand, bromide **6** gave principally $C_6H_5CHOHCOCHMe_2$ (presumably *via* an α-methoxyoxirane intermediate) and only small amounts of **8** and **9**. Rate studies showed that the rate of formation of **9** from chloride **6** and bromide **6** were identical, within experimental error. This contrasts with the results from the $C_6H_5CMeXCOCH_3$ system where $k^{Br}/k^{Cl} = 105$. Mechanistic interpretations are given. The rate of deuterium exchange for $C_6H_5CH_2COCHMe_2$ corresponded closely enough to the rate of halide loss from $C_6H_5CHXCOCHMe_2$ to show that little or no internal return occurs to the $C_6H_5CH_2(O^-)=CMe_2$ enolate ion during deuterium exchange in methanol.

In earlier papers we have shown that methyl substitution has a dramatic effect on the mode of reaction with bases of the isomeric aryl-α-chloro-2-propanones, $ArCH_2COCH_2Cl$ (**1**) and $ArCHClCOCH_3$ (**2**). Most 1-chloro-3-aryl-2-propanones (**1**) react with 0.05 *M* sodium methoxide in methanol at 0° to give quantitative yields of Favorskii esters, $ArCH_2CH_2CO_2Me$.[3] Methyl substitution α to the chlorine ($ArCH_2COCHMeCl$, **3**) changes the rate-limiting step of the Favorskii rearrangement and causes the formation of α-methoxy ketone by-products.[4] On the other hand, most 1-aryl-1-chloro-2-propanones (**2**) react with 0.05 *M* NaOMe in MeOH at 0° to give low yields of Favorskii esters (10–40%);[5] the major products are α-methoxyoxiranes, which are converted into α-hydroxy ketones during processing.[5] Here methyl substitution at the α′ position ($ArCHClCOCH_2Me$, **4**) eliminates the formation of α-methoxyoxiranes and leads to the formation of Favorskii esters and α-methoxy ketones, the relative amounts of which depend on the methoxide concentration. (With $PhCH_2COCHMeCl$ and 2 *M* NaOMe only ester is formed and with 0.0001 *M* NaOMe only α-methoxy ketone is formed.[4]) In order to continue the study of the effect of methyl substitution the reactions of the isomeric α-halo ketones $PhCH_2COCMe_2X$ (**5**) and $PhCHXCOCHMe_2$ (**6**) have now been examined. The reaction of **6** took on added interest with the observation that the rate of halide release from an analogous α-halo sulfone, $PhCHBrSO_2CHMe_2$, was over 500 times faster than the rate of base-catalyzed deuterium exchange of the tertiary hydrogen atom in the corresponding unhalogenated sulfone, $PhCH_2SO_2CHMe_2$, presumably because the internal return occurring in the exchange reaction was eliminated or decreased in the Ramberg–Bäcklund reaction.[6] Comparison of the rate of methoxide-induced chloride ion release from **6** with the rate of methoxide-catalyzed deuterium exchange for the corresponding ketone, $PhCH_2COCHMe_2$ (**7**), offered a way, then, to test for internal return from the enolate ion of **7**.

Results

Preparation of Bromo and Chloro Ketones 5 and 6.—Bromination of 3-methyl-1-phenyl-2-butanone (**7**) at



low temperature gave 1-bromo-3-methyl-1-phenyl-2-butanone (**6**, X = Br) contaminated with small amount of the isomeric bromo ketone **5**. At room temperature **5** was the principal product. The isomers were separated by chromatography.

Chlorination with sulfuryl chloride gave chlorides **5** and **6**, but conditions decidedly favoring one isomer over the other were not easily realized, and chromatographic separation was more difficult than with the bromides. Pure samples of chloride **6** were obtained by removal of the more reactive tertiary chloride **5** by treatment with methanolic sodium methoxide. A pure sample of chloride **5** was obtained from bromide **5** by treatment with LiCl in DMF.

Reactions of Halo Ketones 5 and 6 with Sodium Methoxide in Methanol.—Reactions of mixtures of either bromides **5** and **6** or chlorides **5** and **6** with 0.05 *M* NaOMe in MeOH showed that the tertiary α-halo ketones **5** reacted completely to give essentially all α-methoxy ketone (**8**) before an appreciable reaction of the secondary α-halo ketones **6** had occurred. Experiments with pure bromide **5** at higher methoxide concentrations gave some Favorskii ester **9** at the expense of α-methoxy ketone (**8**).

(1) For part VII see F. G. Bordwell and J. Almy, *J. Org. Chem.*, **38**, 571 (1973).

(2) National Institutes of Health Postdoctoral Fellow, 1969–1971. This investigation was supported by Public Health Service Research Grant No. CA-50610 from the National Cancer Institute.

(3) F. G. Bordwell, R. G. Scamehorn, and W. R. Springer, *J. Amer. Chem. Soc.*, **91**, 2087 (1969).

(4) F. G. Bordwell and M. W. Carlson, *ibid.*, **92**, 3370 (1970).

(5) F. G. Bordwell and R. G. Scamehorn, *ibid.*, **90**, 6751 (1968).

(6) F. G. Bordwell and M. D. Wolfinger, *ibid.*, **93**, 6303 (1971).

$$PhCH_2COCMe_2Br \quad (5)$$

0.05 M NaOMe: $PhCH_2COCMe_2OMe$ (8, 97%) + $PhCH_2CMe_2CO_2Me$ (9, 3%)

1 M NaOMe: $PhCH_2COCMe_2OMe$ (8, 60%) + $PhCH_2CMe_2CO_2Me$ (9, 35%)

Reaction of secondary chloride **6** with 0.05 M NaOMe gave α-methoxy ketone **8** as the major product (*ca.* 85%) accompanied by *ca.* 10% of Favorskii ester **9**. With 1 M NaOMe the percentage of **9** increased to *ca.* 45% at the expense of **8**.

$$PhCHClCOCHMe_2 \ (6) \xrightarrow{1\ M\ NaOMe} PhCH_2COCMe_2OMe\ (8, 55\%) + PhCH_2CMe_2CO_2Me\ (9, 45\%)$$

Reaction of bromide **6** with 1 M NaOMe in MeOH at 0° gave *ca.* 65% of α-methoxyoxirane **10** (judging from

$$PhCHBrCOCHMe_2 \ (6) \xrightarrow{1\ M\ NaOMe} \underset{\text{10 (65\%)}}{PhCH(O)CCHMe_2(OCH_3)} + 8\ (15\%) + 9\ (15\%)$$

the amount of α-hydroxy ketone **11** formed on processing), 15% of α-methoxy ketone **8**, and 15% of Favorskii ester **9**.

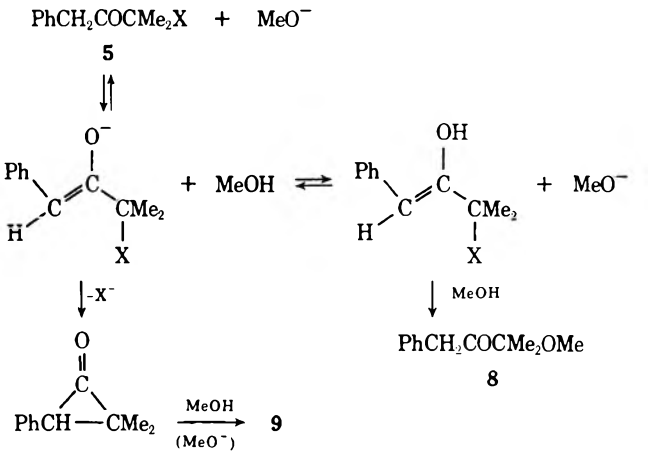
Kinetic Results.—From the rate of bromide ion release recorded over a period of 250 sec from a mixture of bromides **5** and **6** it is estimated that the rate constant for bromide **5** lies between 0.5 and 3 M^{-1} sec^{-1} at 0° in MeOH. (Less than 1% of reaction of **6** occurs during this time interval.)

Rates of chloride ion release were measured for chloride **6** at 0° under pseudo-first-order conditions using sodium methoxide concentrations of 0.0232 and 0.0518 M. The average of second-order rate constants for three runs was in each instance 2.29 ± 0.08 × 10^{-3} M^{-1} sec^{-1}. Identical runs with bromide **6** gave k_2 = 7.89 ± 0.3 × 10^{-3} M^{-1} sec^{-1} (average of three runs with 0.232 M NaOMe) and k_2 = 7.95 ± 0.3 × 10^{-3} M^{-1} sec^{-1} (average of three runs with 0.0518 M NaOMe). It is evident from these data that the kinetics are in each instance cleanly first order in methoxide. Correcting the rates by multiplying k_{obsd} times the per cent of Favorskii ester formed gave the k^{Br}/k^{Cl} ratio for the Favorskii reaction as 1.5.

Rates of base-catalyzed deuterium exchange for ketone **7** were determined with NaOMe–MeOD at 0, 25, and 37.5° by observing the disappearance of the α-tertiary proton by nmr. The second-order rate constants for five runs were 1.6 × 10^{-2} and 1.2 × 10^{-2} (at 37.5°); 4.8 × 10^{-3} (at 25°); 4.7 × 10^{-4} and 5.3 × 10^{-4} M^{-1} sec^{-1} (at 0°); E_a = 15 ± 1 kcal/mol (r = 0.998 for five points).

Discussion

The formation of 97% α-methoxy ketone from tertiary chloride **5** and 0.05 M NaOMe continues the trend observed for $PhCH_2COCHMeCl$ (**3**) relative to $PhCH_2COCH_2Cl$ (**1**), where 39% of α-methoxy ketone was formed from **3** at the expense of Favorksii ester (the exclusive product with **1**).[3,4] The additional methyl substituent in **5** (compare **3**) evidently causes a further acceleration of the rate of methanolysis of the enol allylic chloride causing the α-methoxy ketone (**8**) to be



the almost exclusive product at low (0.05 M) methoxide concentrations.

It is noteworthy that the formation of **8** was not accompanied by any of the isomeric methoxy ketone $PhCHOMeCOCHMe_2$, and that **8** was formed also from secondary bromide **6** and chloride **6**. This corresponds to the behavior of **3** and its isomer **4**.[4]

The shift in product toward Favorskii ester **9** at the expense of α-methoxy ketone **8** with increasing methoxide concentration is similar to the effect observed for **3**. It is believed to be caused by a shift in the enol ⇌ enolate equilibrium toward enolate ion with increasing methoxide concentration.[4]

The rate-limiting step changes from chloride ion release for **1** to proton abstraction for **3** because of the increased rate of ionization of chloride ion caused by the methyl substituent.[4] Ionization of chloride ion from the enol (or enolate ion) of **5** should be even faster than for **3**, and here too the rate of proton abstraction should be rate limiting. The rate estimated for bromide **5** is two to ten times slower than that for chloride **3**, which seems reasonable since the rate of abstraction of the benzylic proton in $PhCH_2COCXMe_2$ might be retarded to this extent by the presence of the extra methyl group (compare $PhCH_2COCHXMe$).

Rates for chlorides **2**, **4**, and **6** are summarized in Table I, along with those for $PhCMeXCOCH_3$ (**11**), an isomer of **4**.

For **2** and **11** the rate of ionization of the C–Cl bond enters into the rate-limiting step, as shown by the fact that extensive deuterium exchange has occurred in the resulting Favorskii ester (*e.g.*, a minimum of 84% prior to rearrangement for **11**[7]) and by large k^{Br}/k^{Cl} ratios (85 for **2** and 105 for **11**[7]). The approximately threefold slower rate for chloride **11** as compared to **2** is surprising, since methyl substitution should have a large accelerating effect on the rate of ionization of the chloride ion. [Note that $PhCH_2COCHClMe$ (**3**), an isomer of **11**, reacts at least 650 times as fast.] Apparently there are a number of retarding factors in the reaction of **11** which counteract the potential

(7) R. G. Scamehorn, Ph.D. Dissertation, Northwestern University, 1968.

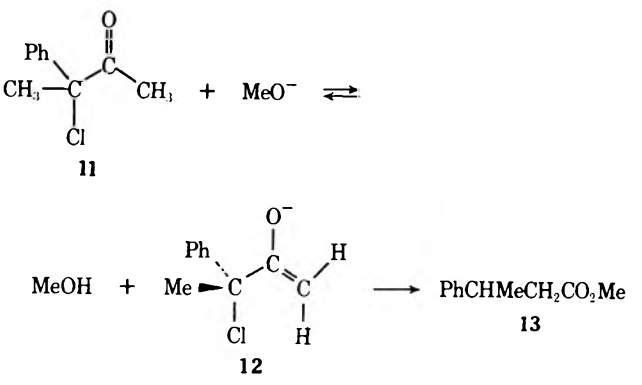
TABLE I
RATES OF FAVORSKII REARRANGEMENTS WITH 0.05 *M* SODIUM METHOXIDE IN METHANOL AT 0°

α-Chloro ketone	$10^3 k$,[a] M^{-1} sec^{-1}	Favorskii ester, %	Reference
$PhCHClCOCH_3$ (2)	0.40	13	5
$PhCHBrCOCH_3$ (2)	34	15	5
$PhCMeClCOCH_3$ (11)	0.124	49	7
$PhCMeBrCOCH_3$ (11)	13	56	7
$PhCHClCOCH_2Me$ (4)	80.5[b]	70	10
$PhCHClCOCHMe_2$ (6)	0.016[b]	7	c
$PhCHBrCOCHMe_2$ (6)	0.024[b]	3	c

[a] Corrected by multiplying k_{obsd} by the fractional yield of Favorskii ester. [b] Minimum value for halide release (deprotonation is rate limiting). [c] Present study.

accelerating effect of methyl. Retarding factors could include a shift in equilibrium between **11** and its enolate ion (**12**) favoring **11**, due to increased steric hindrance in **12** caused by the methyl substituent (compare **12** with the enolate ion from **2**), and steric retardation of ionization of halide ion from **12** caused perhaps by crowding in the transition state wherein the C–X bond is parallel to the p orbitals in **12**.

It is noteworthy that the yield of Favorskii ester **13**



from **11** is almost four times as great as that from **2**, even though the Favorskii rate for **11** is over three times *slower*. Evidently formation of the α-methoxyoxirane by-product is regarded even more by α-methyl substitution than is halide ion release. The latter effect has been demonstrated since $PhCOCHMeBr$ has been shown to form an α-methoxyoxirane in a reaction with NaOMe in MeOH at a rate nine times slower than that for $PhCOCH_2Br$.[8] For chlorides **4** and **6** α-methoxyoxirane formation is not able to compete with α-methoxy ketone and Favorskii ester formation. This is a consequence of the strong accelerating effect that methyl substitution has on the release of halide ion from the allylic enol and enolate chlorides derived from **4** and from **6**. For bromide **6**, however, α-methoxyoxirane once more becomes the major product. This is surprising since it indicates that the second methyl substituent in **6** has nowhere near the maximum α-Me effect on the methanolysis of the allylic enol and enolate bromides from **6**.[9] Once again a steric retardation of halide ion release is indicated (compare **12**).

Deuterium exchange experiments show that the rate of proton abstraction is rate limiting for **4**.[10] The fact that $k^{Br}/k^{Cl} \cong 1$ for **6** shows that proton abstraction is also rate limiting in this reaction. The 35-fold faster rate for **4** than for **6** then must represent the retarding effect of methyl substitution on the proton abstraction rate (*secondary vs. tertiary* hydorgen atom).[11]

Comparison of the rate of proton abstraction from **6** by NaOMe in MeOH with the rate of abstraction of the tertiary proton from the corresponding ketone **7** with NaOMe in MeOD shows that k_{obsd} for **6** is *ca.* 5 times faster at 0°. Taking into account the solvent effect[12] increases the difference to *ca.* tenfold. This is the order of magnitude expected for the inductive effect of Cl or Br.[13] We conclude that little or no internal return occurs from the enolate ion of **7** during methoxide-catalyzed deuterium exchange in methanol solution. In one sense this is not surprising since the close agreement between rates of deuterioxide-catalyzed racemization and deuterium exchange for PhCOCHMeEt in dioxane-D_2O[16] excludes internal return during deuterium exchange as being important in this system under these conditions. On the other hand, the remarkably slow rate of base-catalyzed exchange of the tertiary proton in $PhCOCHMe_2$ relative to $PhCOCH_2Me$ in DMF[11b] and the evidence for internal return to the carbanion derived from abstraction of the tertiary proton in $PhCH_2SO_2CHMe_2$[6] made it seem advisable to test for internal return to the $PhCH_2C(O^-)=CMe_2$ enolate ion. Our failure to observe internal return is in agreement with the earlier results with the $PhC(O^-)=CMeEt$ enolate ion[16] and once again emphasizes the striking difference between carbanions derived from ketones as compared to those derived from sulfones.[17]

Experimental Section

3-Methyl-1-phenyl-2-butanone.—Benzylmagnesium chloride prepared by the method of Benkeser and Johnston[18] from 8.7 g (0.36 g-atom) of magnesium turnings, 22.8 g (0.18 mol) of benzyl chloride, and 600 ml of dry ether was added over 1 hr to an efficiently stirred solution of 50 ml (0.48 mol) of isobutyryl chloride in 400 ml of ether maintained under nitrogen at −78°. The mixture was stirred for an additional 2 hr at −78° and then poured over sulfuric acid and ice. The organic phase was washed three times with water, dried, and concentrated under reduced pressure to yield 30 g of oil which was distilled under 0.5-mm pressure. The first fraction, 14 g, boiling below 35° was isobutyric acid; the second, 15 g, boiling between 35 and 70° was chromatographed on 150 g of 90–200 mesh silica gel (Baker). Fractions eluted with 1–4% ether in hexane (7.6 g, 26%) contained 65–95% of product and were rechromatographed. Fractions eluted

(8) V. S. Karavan and T. I. Temnikova, *Zh. Org. Khim.*, **2**, 1417 (1966).

(9) For solvolysis of an alkyl halide the maximum α-CH_3 effect is *ca.* 10^8; see J. F. Fry, J. M. Harris, R. C. Bingham, and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **92**, 2540 (1970).

(10) F. G. Bordwell and M. W. Carlson, *ibid.*, **92**, 3377 (1970).

(11) (a) R. P. Bell and H. C. Louguet-Higgins, *J. Chem. Soc.*, 636 (1946), found that the rate ratio of deprotonation by hydroxide ion in water for $(MeCH_2)_2C=O$ *vs.* $(Me_2CH)_2C=O$ was 18 to 1.0. (b) H. Shechter, M. J. Collis, R. Dessy, Y. Okuzumi, and A. Chen, *J. Amer. Chem. Soc.*, **84**, 2905 (1962), found that the rate ratio for deprotonation of $PhCOCH_2Me$ *vs.* $PhCOCHMe_2$ with Et_3N in D_2O–DMF was 700:1.0.

(12) Judging from deuterium exchanges of comparable rates for carbon acids $k^{MeOD}/k^{MeOH} \cong 2$; see S. Andreades, *ibid.*, **86**, 2003 (1964); W. T. Ford, E. W. Graham, and D. J. Cram, *ibid.*, **89**, 4604 (1967); J. N. Roitman and D. J. Cram, *ibid.*, **93**, 2225 (1971).

(13) A tenfold rate enchancement would require a ρ^* value of *ca.* 2.8; for acetate ion catalyzed bromination of ketones $\rho^* = 1.59$[14] and for methoxide ion catalyzed deuterium exchange of the α-hydrogen atoms in esters $\rho^* = 1.78$.[15]

(14) R. W. Taft, Jr., "Steric Effects in Organic Chemistry," M. Newman, Ed., Wiley, New York, N. Y., 1956, p 608.

(15) J. Hine, L. G. Mahone, and C. L. Liotta, *J. Amer. Chem. Soc.*, **79**, 5911 (1957).

(16) S. K. Hsu, C. K. Ingold, and C. L. Wilson, *J. Chem. Soc.*, 78 (1938).

(17) See D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1965, Chapters II and III, for a discussion.

(18) R. A. Benkeser and T. E. Johnston, *J. Amer. Chem. Soc.*, **88**, 2220 (1966).

TABLE II

PROPERTIES OF 1-PHENYL-2-BUTANONE DERIVATIVES AND METHYL 2,2-DIMETHYL-3-PHENYLPROPIONATE

Compound	Registry no.	δ CDCl3 TMS C(CH3)2	CH(CH3)2	CHPh	Ph	OCH3	Calcd, % C	Calcd, % H	Found, %[a] C	Found, %[a] H
$PhCH_2COCH(CH_3)_2$	2893-05-2	1.08[b]	2.68[b]	3.70						
$PhCHBrCOCH(CH_3)_2$	37112-23-5	1.05[c]	2.93[b]	5.57	7.27		54.79	5.43	54.69	5.45
$PhCHClCOCH(CH_3)_2$	37112-24-6	0.82[c]	2.75[b]	5.40	7.30		67.13	6.67	67.16	6.64
$PhCH(OH)COCH(CH_3)_2$	37112-25-7	0.90[d]	2.60[b]	5.15	7.30	4.30[e]				
$PhCH_2COC(CH_3)_2OCH_3$	37112-26-8	1.25		3.90	7.25	3.20	74.96	8.39	74.90	8.36
$PhCH_2COCBr(CH_3)_2$	29443-17-2	1.87		4.07	7.27		54.79	5.43	55.06	5.50
$PhCH_2COCCl(CH_3)_2$	37112-28-0	1.70		4.03	7.10					
$PhCH_2C(CH_3)_2CH_3$[e]	14248-22-7	1.12		2.80	7.15	3.60				

[a] Spectra were taken on a Varian T-60 spectrometer. Microanalyses were performed at Microtech Laboratories, Skokie, Ill. Samples were purified by evaporative distillation prior to analysis. [b] $J = 7$ Hz. [c] Doublet of doublets, $J = 7$ Hz; signal separation 3 Hz. [d] Doublet of doublets, $J = 7$ Hz; signal separation 18 Hz. [e] Signal for hydroxyl proton.

with 5–7% ether in hexane (4.1 g, 14%) contained pure 3-methyl-1-phenyl-2-butanone.[19]

3-Bromo-3-methyl-1-phenyl-2-butanone (5-Br).—To 700 mg (0.00432 mol) of 3-methyl-1-phenyl-2-butanone in 5 ml of carbon tetrachloride and 5 ml of ether was added 0.284 ml (0.80 g, 0.0050 mol) of bromine in 2 ml of carbon tetrachloride. The mixture was stirred and refluxed until the bromine color disappeared. The solution was dried with magnesium sulfate and saturated with anhydrous hydrogen bromide. The mixture was maintained for several hours at room temperature during which more HBr was added; the bromination and subsequent isomerization reaction was followed by examining filtered and evaporated aliquots by nmr. After 3 hr 71% of 3-bromo-3-methyl-1-phenyl-2-butanone and 10% of 1-bromo-3-methyl-1-phenyl-2-butanone were present. The total reaction mixture was filtered and evaporated to yield 746 mg of pale yellow oil, which was chromatographed on 20 g of silica gel. Fractions (20 ml) 12 and 13 (0.5% v/v) ether in hexane) yielded 60 and 35 mg of pure tertiary bromide. Intermediate fractions were combined and rechromatographed.

3-Chloro-3-methyl-1-phenyl-2-butanone (5-Cl).—To 35 mg (0.145 mmol) of 3-bromo-3-methyl-1-phenyl-2-butanone in 10 ml of dimethylformamide freshly distilled from lime was added 60 mg of fused lithium chloride. The mixture was stirred 8 hr at room temperature and poured into a separatory funnel containing carbon tetrachloride and water. The organic phase was washed five times with water, dried, and concentrated under reduced pressure to give 27 mg (95%) of 3-chloro-2-methyl-1-phenyl-2-butanone.

1-Chloro-3-methyl-1-phenyl-2-butanone (6-Cl).—To 857 mg (0.053 mol) of 3-methyl-1-phenyl-2-butanone in a 20 × 200 mm test tube was added 20 ml of dichloromethane. The solution was cooled to −20° with a Dry Ice–acetone–water slush and saturated with chlorine gas. A trace of anhydrous hydrogen chloride was added, and the tube was capped and maintained at −20° for 16 hr. Excess chlorine and hydrogen chloride were then removed under a stream of nitrogen, and the cold mixture was poured into aqueous saturated sodium bicarbonate. The organic layer was washed twice with water, dried, and concentrated to give 1.1 g of pale yellow oil which was chromatographed on 50 g of silica gel. Fractions eluted with 0.75% ether in hexane contained 0.907 mg (86%) of 1-chloro-3-methyl-1-phenyl-2-butanone.

1-Bromo-3-methyl-1-phenyl-2-butanone (6-Br).—Into a 20 × 200 mm test tube was placed 714 mg of 3-methyl-1-phenyl-2-butanone, 20 ml of dichloromethane, and 1 g of anhydrous magnesium sulfate. The test tube was cooled to −78°, and a solution of 0.25 ml of bromine in 5 ml of dichloromethane was added dropwise over 10 min. The mixture was saturated with anhydrous hydrogen bromide, capped, and kept at −78° for 24 hr, after which excess bromine and hydrogen bromide were removed in a stream of dry nitrogen. The pale yellow solution was poured into a separatory funnel, washed with saturated aqueous sodium bicarbonate solution, and then washed twice with water. The organic layer was dried with anhydrous magnesium sulfate; evaporation under partial pressure left 900 mg of a pale yellow oil whose analysis by nmr showed 67% 1-bromo-3-methyl-1-phenyl-2-butanone, 4% 3-bromo-3-methyl-1-phenyl-2-butanone, and 27% 3-methyl-1-phenyl-2-butanone. The products were partially separated by elution on 40 g of silica gel. Fractions eluted with 0.25% ether in hexane contained pure 1-bromo-3-methyl-1-phenyl-2-butanone. Fractions eluted with 0.50% or greater ether in hexane contained traces of isomeric bromo ketone and unbrominated ketone and were rechromatographed.

Product Distribution Runs.—The halo ketone (40–50 mg) was dissolved in a cooled solution of sodium methoxide–methanol of appropriate strength. The reactions were neutralized (phenolphthalein) with cold, dilute hydrochloric acid, concentrated below 25° when necessary, and shaken in ether–water mixtures. The organic phase was washed twice with water, dried, and concentrated under reduced pressure and analyzed by nmr. Product determinations were made by comparison of the integrals for one or more lines unique for a product (Table II) *vs.* that for the phenyl region. All weighed yields represent greater than 90% recovery. Pure products, isolated and analyzed, are described below.

3-Methoxy-3-methyl-1-phenyl-2-butanone and Methyl 2,2-Dimethyl-3-phenylpropionate.—To 3.16 g of 3-bromo-3-methyl-1-phenyl-2-butanone was added 100 ml of 2.0 *M* sodium methoxide in methanol at 0°. The mixture was maintained at 0° for 7 min and neutralized slowly while cooled with concentrated hydrochloric acid. The solution was concentrated to 10% of its volume and shaken with ether–water. The organic phase was washed twice with water, concentrated, and chromatographed on 120 g of silica gel. Fractions eluted with 1.5% ether in hexane contained 336 mg(13.5%) of pure methyl 2,2-dimethyl-3-phenylpropionate, a colorless oil. The methyl ester was hydrolyzed by boiling 1 hr with 12 ml of water, 12 ml of methanol, and 1 g of sodium hydroxide to the known[20] acid, mp 56–57° (ether–hexane).

Intermediate fractions (2% ether) contained ester and unidentified impurities. Fractions eluted with 2.5% ether in hexane contained 258 mg (10%) of 3-methoxy-3-methyl-1-phenyl-2-butanone, a colorless oil.

1-Hydroxy-3-methyl-1-phenyl-2-butanone.—Combined products (150 mg) of several product determination runs of 1-bromo-3-methyl-1-phenyl-2-butanone with base were chromatographed on 20 g of silica gel. Fractions eluted with 5% ether in hexane contained 45 mg of 1-hydroxy-3-methyl-1-phenyl-2-butanone. The semicarbazone derivative melted at 158–160° (lit.[21] mp 158–159°).

Kinetic Procedure. Rate of Halide Ion Release from 6 at 0°.—The rate of halide ion release was determined by analysis of aliquots withdrawn at timed intervals from a solution of halo ketone (0.001 *M*) and sodium methoxide (0.023 and 0.052 *M*) in methanol. The aliquots were quenched immediately in excess nitric acid and titrated potentiometrically using a Sargent Model D recording titrator equipped with a constant rate buret and platinum electrodes. The end point was determined from the first derivative of the titration curve.

Typically, 20.0 ml of 0.0251 *M* sodium methoxide in methanol and 80 ml of 0.0013 *M* ahlo ketone in MeOH (both equilibrated at 0° for 30 min) were combined rapidly, swirled, and maintained in an ice–water bath. Aliquots of 5.0 ml were withdrawn. The base concentration was corrected for cubic concentration upon cooling to 0°. The data were analyzed by the usual first-order

(19) This ketone was prepared in 66% yield from isobutyryl chloride and sodium phenyl(halomagnesio)acetate: D. Ivanoff and N. I. Nicoloff, *Bull. Soc. Chim. Fr.*, **4**, 1331 (1932).

(20) B. E. Hudson, Jr. and C. R. Hauser, *J. Amer. Chem. Soc.*, **62**, 2457 (1940), report mp 58°.

(21) M. Tiffeneau and J. Levy, *Bull. Soc. Chim. Fr.*, **37**, 1247 (1965). The hydroxy ketone was prepared from ethylmagnesium bromide and madelamide.

treatment (no aliquots were taken after 2 half-lives). Of the 15 kinetic points taken, one or two were rejected after a hand plot. Three infinity points were averaged. The correlation coefficient, slope, and least-squares standard deviation were calculated as before.[1]

Kinetics of Exchange of 3-Methyl-1-phenyl-2-butanone (7).—To a clean, dry 5-mm nmr tube was added approximately 30 mg of 3-methyl-1-phenyl-2-butanone and a measured amount of methanol-*O*-*d* (Diaprep, minimum 99% isotopic purity). The solution was analyzed at the appropriate temperature by a Varian A-60 nmr spectrometer equipped with a V-6040 variable temperature attachment. The probe was cooled with either an ice–water bath or Dry Ice–acetone bath, and temperature was checked periodically by lowering a calibrated thermometer into the probe to sample level. Temperature 25 and 0° were held to within 0.2° throughout all runs. After tuning, a full spectrum was taken and several additional scans were made on the dimethyl doublet 135 Hz upfield from the methyl resonance of the solvent. The tube was removed and the correct amount of 2.2 *M* sodium methoxide in methanol-*O*-*d* was added to achieve the desired base concentration and a total volume of 0.500 ml. The tube was capped, shaken, and replaced in the probe. After temperature equilibration, repetitive scans were taken on the upfield dimethyl signal. The instrument was periodically retuned and calibration samples (see below) were run.

Analysis of the scans of the dimethyl group for the amount of deuterium incorporation in the methine position was carried out by measuring line lengths of the two peaks of the doublet, together with that of the inner triplet (displayed as a broad singlet), correcting for the lack of base line separation for the doublet of the protio component, correcting for the relative widths of the individual peaks, and calibrating the corrected peak heights with three known standard mixtures (see below). These base line and line width corrections on the standard mixtures gave calibration curves which were nearly linear and had a slope of near unity. The mole fraction of unexchanged material before calibration is expressed as

$$[\mathrm{H}] = \frac{L_1 + L_2}{(L_1 + L_2)(1 - a) + L_3 b}$$

where L_1, L_2, L_3 refer to the line lengths of the low- and high-field lines of the doublet for the protio and inner triplet for the deuterio compounds, respectively, a is $L_3/L_1 + L_2$ prior to introduction of base, and b is $(2WH_3/L_3)/(WH_1/L_1 + WH_2/L_2)$. WH is the width at half-height measured for a given peak. Both a and b are constant throughout a run; b is calculated from data on lines 1 and 2 at $t = 0$ and line 3 at $t = \infty$. The infinity value of [H] was calculated from the equilibrium amounts of H in three positions in the ketone and one position in the solvent (1% H present originally). This treatment was adequate for all runs taken; the value $(L_1 + L_2)(1 - a) + L_3 b$ was uniform throughout a run indicating that the six-proton signal remained at a constant overall intensity despite changes in line shape. No runs was carried out to more than 2 half-lives beyond which L_1 and L_2 would be uncorrected for contributions from line 3.

Calibration samples were prepared by individually weighing pure protio and 97.5% isotopically pure trideuterio ketone (see below) into a single pan of a Cahn Model M-10 electrobalance. The mixtures were each dissolved in methanol and placed in separate nmr tubes. The mixtures contained 0.253, 0.397, and 0.672 of three atoms of deuterium after correction for the protio impurity in the deuterio component and the molecular weight difference between the components. A calibration curve was constructed for each run.

The calibrated mole fractions for protio ketone were used in the usual first-order treatment. A least-squares slope and standard deviations were obtained from a program[22] on a Wang 700 calculator.

The two runs each at 37.5 and 0° were at substantially different methoxide ion concentrations, showing that the reaction was first order in base.

3-Methyl-1-phenyl-1,1,3-trideuterio-2-butanone.—To 200 mg of partially deuterated 3-methyl-1-phenyl-2-butanone was added 1 ml of methanol-*O*-*d* and 0.02 ml of methanol-*O*-*d*–2.2 *M* sodium methoxide. The mixture was capped and left 10 hr at room temperature, then concentrated under reduced pressure. Fresh methanol-*O*-*d* was added, and the mixture was allowed to stand for an additional 10 hr. An equivalent amount of acetic acid-*O*-*d* was added, and the product was chromatographed after concentration under reduced pressure. Fractions eluted with 0.5–1.0% ether in hexane (120 mg, 60%) were analyzed by nmr in 0.022 *M* dichloromethane in carbon tetrachloride. Integration of the benzyl protons of the pure ketone *vs.* the dichloromethane showed 97.5% deuterium incorporation.

(22) This program was kindly supplied by Dr. T. G. Mecca.

Favorskii Rearrangements. IX. Stereochemistry of the Reaction with 2-Bromo-4-methyl-4-phenylcyclohexanone

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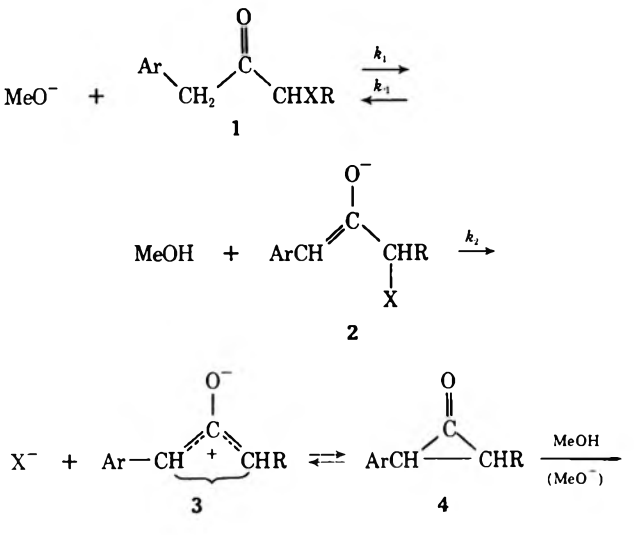
In the reaction of 2-chlorocyclohexanone or 2-bromo-5-methyl-5-phenylcyclohexanone (cis or trans) with NaOMe in MeOH the yield of Favorskii ester has been found to increase markedly at the expense of α-methoxyoxirane and α-methoxy ketone products on increasing the methoxide concentration. 2-Chloro- and 2-bromo-4-methyl-4-phenylcyclohexanones (**6**) are much less subject to this concentration effect, 40% yield of Favorskii ester being obtained even at low ($\sim 10^{-5}$ *M*) methoxide concentrations. The ratio of stereoisomeric esters formed from **6** was found to be *reversed* in going from low to high (2 *M*) methoxide concentrations. This result is rationalized in terms of equilibrating dipolar ion and cyclopropanone intermediates.

Previous papers in this series have provided evidence which points to the following mechanism for the Favorskii rearrangement, as applied to the $ArCH_2COCHXR$ (**1**) system with NaOMe in MeOH.[2]

The reversibility of the first step in the reaction sequence (*i.e.*, $k_{-1} \gg k_2$) was demonstrated for **1** with Ar = Ph and R = H by deuterium exchange and a large k^{Br}/k^{Cl} leaving group effect.[2c] (Similar evidence was also obtained for reversible carbanion formation in 2-halo-4,4-disubstituted cyclohexanones.[2a]) Ionization of the halogen from enolate ion **2** to form dipolar ion **3** was indicated by a large negative ρ (*ca.* −5) for this step with R = H, a sizable positive salt effect, and a strong rate acceleration by increasing the ionizing power of the solvent,[2b,c] Furthermore, a change in R from H to Me caused a marked rate acceleration, as expected in an ionization mechanism.[2d] In fact, the increase in k_2 was large enough to change the mecha-

(1) Abstracted in part from Ph.D. Dissertation of J. G. Strong, Northwestern University, 1968.

(2) (a) F. G. Bordwell, R. R. Frame, R. G. Scamehorn, J. G. Strong, and S. Meyerson, *J. Amer. Chem. Soc.*, **89**, 6704 (1967); (b) F. G. Bordwell and R. G. Scamehorn, *ibid.*, **90**, 6751 (1968); (c) F. G. Bordwell, R. G. Scamehorn, and W. R. Springer, *ibid.*, **91**, 2087 (1969); (d) F. G. Bordwell and M. W. Carlson, *ibid.*, **92**, 3370 (1970); (e) F. G. Bordwell and M. W. Carlson, *ibid.*, **92**, 3377 (1970); (f) F. G. Bordwell and R. G. Scamehorn, *ibid.*, **93**, 3410 (1971); (g) F. G. Bordwell and J. Almy, *J. Org. Chem.*, **38**, 575 (1973).



1

2

3 4

5

nism by making $k_2 \gg k_{-1}$, which was indicated by the absence of deuterium exchange, a k^{Br}/k^{Cl} rate ratio near 1.0 and a positive rather than a negative ρ in the $ArCH_2COCHXCH_3$ system.[2d] Evidence supporting the postulate of a dipolar ion intermediate was obtained from reactions of $Ph_2CClCOCH_3$ and $Ph_2CHCOCH_2Cl$. These isomers gave nearly quantitative yields of the same Favorskii ester with 0.05 M $NaOCH_3$, but with very dilute NaOMe ($\sim 10^{-5}$ M) 1-phenyl-2-indanone was formed in appreciable yields as a by-product.[2f] The formation of identical indanone/ester ratios (1.0:1.6) from the two substrates points to a common intermediate believed to be a dipolar ion, comparable in structure to **3**. This dipolar ion is presumably in equilibrium with the corresponding cyclopropanone.[3] The dipolar ion cyclizes (slowly) to the indanone, but at high methoxide ion concentrations the cyclopropanone reacts rapidly to form the ester to the exclusion of the indanone.[2f]

Additional evidence for a dipolar ion intermediate in Favorskii reactions can be deduced from the loss of stereospecificity of the reaction of 1-chloro-*cis*-1-acetyl-2-methylcyclohexane when carried out with NaOMe in MeOH in contrast to the stereospecificity observed with NaOMe in 1,2-dimethoxyethane.[5] On the other hand, it now appears that the formation of α-methoxy ketone by-products derived from reactions of α-halo ketones with NaOMe in MeOH *cannot* be used as evidence for the presence of dipolar ion intermediate as was formerly supposed.[6] These by-products arise instead from the methanolysis of enol allylic halide intermediates.[2e]

The present paper presents additional evidence for the above mechanistic scheme as deduced from a study of the stereochemistry of the reaction of 2-bromo-4-methyl-4-phenylcyclohexanone (**6**) and *cis*- and *trans*-2-bromo-5-methyl-5-phenylcyclohexanones (**7**) with NaOMe in MeOH.

(3) Recent calculations of R. Hoffmann, *J. Amer. Chem. Soc.*, **90**, 1475 (1968), indicate that the dipolar ion would be favored at equilibrium relative to either the cyclopropanone or allene oxide. [See, however, A. Liberles, A. Greenberg, and A. Lesk, *J. Amer. Chem. Soc.*, **94**, 8685 (1972).] In methanol solution the cyclopropanone would be expected to exist principally as its hemi methyl ketal.[4]

(4) N. J. Turro and W. B. Hammond, *ibid.*, **87**, 3258 (1965).

(5) H. O. House and W. F. Gilmore, *ibid.*, **83**, 3980 (1961).

(6) A. W. Fort, *ibid.*, **84**, 2620, 2625 (1962).

TABLE I

EFFECT OF SODIUM METHOXIDE CONCENTRATION ON PRODUCT DISTRIBUTION FROM 2-HALOCYCLOHEXANONES

α-Halocyclohexanone	[NaOMe], M	% ester	% hydroxy ketal	% ether
2-Chlorocyclohexanone	$\sim 10^{-5}$ [a]	3	62	28
	0.05	10		
	1.0	33		
	2.0	49	47	0
	3.5[b]	75[b]		
2-Bromo-4-methyl-4-phenylcyclohexanone (**6**)	$\sim 10^{-5}$ [a]	40	36	15
	2	55	37	0
2-Bromo-5-methyl-5-phenylcyclohexanone (**7**)	0.05	9		
	1.0	22–24		
	2.0	69		

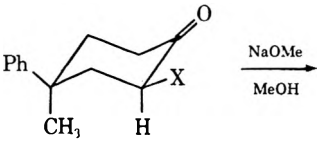
[a] Methoxide added slowly to α-halo ketone. [b] $C_6H_5CH_2ONa$ in $C_6H_5CH_2OH$; results of G. Stork and I. J. Borowitz, *J. Amer. Chem. Soc.*, **82**, 4307 (1960).

Results

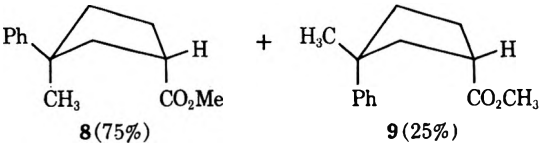
The striking variation in products frequently observed for the reaction of α-halo ketones with low *vs.* high concentrations of sodium methoxide[2b,d-g,6] prompted a study of this type with 2-chlorocyclohexanone, and with **6** and **7** (Table I).

The marked increase in yield of ester with increased [NaOMe] for 2-chlorocyclohexanone and for 2-bromo-5-methyl-5-phenylcyclohexanone (**7**) is similar to earlier observations. The increased yield can be attributed partly to a positive salt effect favoring ionization of halide ion from the enolate ion, which leads to an increased rate of ester formation. Earlier work has established the reality of such a salt effect and has indicated that the principal side reaction, *i.e.*, methoxyoxirane formation, is not subject to a comparable salt effect.[2b] As a consequence, with increased [NaOMe] the yield of ester increases at the expense of hydroxy methyl ketal (derived from the methoxyoxirane).[2b] The yield of ester also increases at the expense of ether (*i.e.*, methoxy ketone) formation, because at high methoxide concentrations the enol allylic halide, which is the precursor of the ether, is largely converted into enolate ion, which forms ester.[2e] Note that the behavior of 2-bromo-4-methyl-4-phenylcyclohexanone (**6**) differs in that ketal formation is not disfavored relative to ester formation at high methoxide concentrations (Table I).

The reaction of chloride **6** with 0.2 M NaOMe in MeOH gave a 53% yield of a mixture of two isomeric esters (**8** and **9**) in a 3:1 ratio. The esters were not isomerized under the reaction conditions, but prolonged (165 hr) reflux with 1 M NaOMe changed the ratio of **8**/**9** from 75:25 to 55:45.

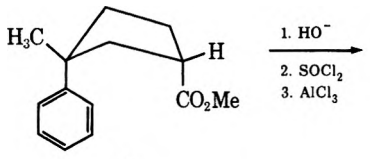


6 (X = Cl)

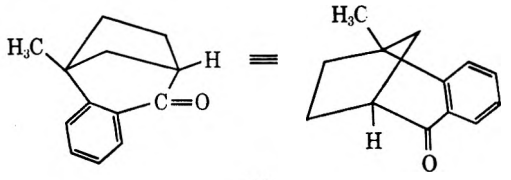


8 (75%) **9** (25%)

Structure assignments were made to **8** and **9** by conversion of the mixture of esters into a mixture of acid chlorides, **8b** and **9b** (*via* the acids **8a** and **9a**), which was treated with aluminum chloride to form 59% of bicyclic ketone **10** and 25% of a pure acid (recovered **8a**). Examination of molecular models shows that cyclization to form **10** can occur readily with **9b** in which the phenyl and carboxyl chloride groups are cis, but is impossible with **8b** where these groups are trans.



9

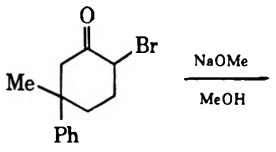


10

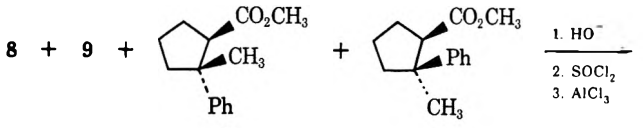
The yield of **10** was greater than that expected on the basis of the amount of ester **9** present in the mixture (vpc analysis), indicating that some of the acid chloride derived from **8** had epimerized during the reaction. This was confirmed by subjecting the recovered acid (**8a**) to the synthetic sequence; 25% of **10** was produced thereby and 45% of acid **8a** was recovered.

When the reaction of **6** (X = Br) was carried out at low methoxide concentrations, the same two esters were obtained (40% yield), but in an *inverse ratio* (**8/9** = 1:3). A similar ratio was obtained (in very low yield) by debromination of 2,6-dibromo-4-methyl-4-phenylcyclohexanone in methanol using a zinc–copper couple.

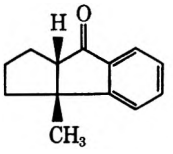
Reaction of *either cis-* or *trans*-2-bromo-5-methyl-5-phenylcyclohexanone (**7**) with NaOMe in MeOH gave a mixture of four products, esters **8** and **9** plus two new esters (**11** and **12**). The ester distribution (**8/9/11/12**) with 0.05 *M* NaOMe was 57:6:14:23, but with 2 *M* NaOMe this changed to 45:7:9:39. In other words, at higher methoxide concentrations the percentage of **12** appears to increase (and the percentage of **9** also appears to increase slightly) at the expense of **8** and **11**. The ester distribution of **8/9/11/12** obtained after equilibration was 26:24:28:22. Application to this mixture of the synthetic sequence leading to ring closure gave bicyclic ketone **10** and a new ketone **13**, the structure of which was assigned on the basis of its ir and nmr spectra. Ketone **13** must, for steric reasons, be derived from ester **12** in which the phenyl and methyl carboxylate groups are cis to one another.



7 (cis or trans)



11 **12**



13

+ **8a** + **11a** + **10**

suitable for epoxy ether formation.[2a] Such 1,3-diaxial effects are absent in **7** and 2-chlorocyclohexanone. The twofold slower rate of ester formation for **6** relative to 2-chlorocyclohexanone[2a] might be construed as evidence for a small 1,3-diaxial effect in loss of halide ion from the enolate ion (*i.e.*, ionization of axial halogen), but the rate difference could equally well result from a smaller concentration of enolate ion derived from **6**.

The evidence obtained does not indicate whether an equatorial or axial halogen is ejected during the reaction. In example **6** an intramolecular SN2-type displacement, such as Loftfield suggested,[7] would lead to inversion of configuration if the halogen is equatorial, and retention of configuration if it is axial. The major product from **6**, ester **8**, is the result of retention of configuration or presumed displacement of axial halogen. In example *cis*-**7** an intramolecular SN2-type displacement of axial halogen would be expected to afford ester **9**, whereas ester **8** is the major product. The formation of the same products from *cis-* and *trans*-**7** indicates that epimerization at the halogen-bearing carbon may occur. Thus to accommodate the SN2 mechanism example **6** would rearrange through an axial halogen to give a major product **8**, and examples *cis-* and *trans*-**7** would equilibrate and then rearrange through an equatorial halogen to give a major product **8**.

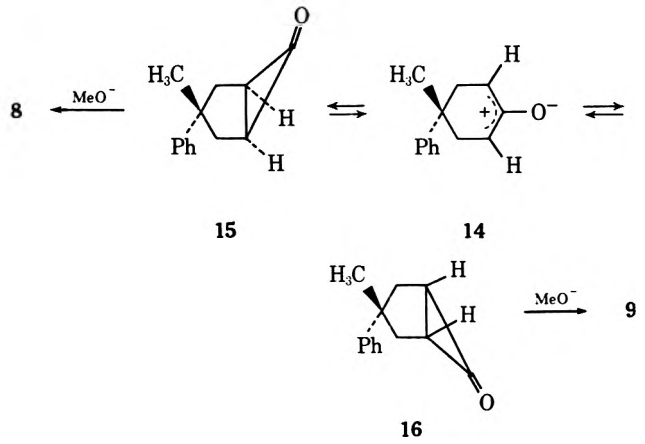
A more likely mechanism, however, is one where ionization from **6** occurs first to give a dipolar ion (**14**) which then undergoes a disrotatory ring closure in either of two ways to give cyclopropanones **15** and **16**. According to this mechanism the product stereochemistry is determined after release of the halide ion, which would account for the similar product distribution from **6** and *cis-* or *trans*-**7**.

At low methoxide concentrations the major product is ester **9**, which is derived from **16** (or its hemiketal[4]). In 2 *M* NaOMe the major product is, however, ester **8**. One possible rationalization of these results is that cyclopropanone **15** is formed more rapidly than **16** and that in the presence of high methoxide concentrations **15** and **16** both react very rapidly with methoxide ion, making the product composition controlled by the

Discussion

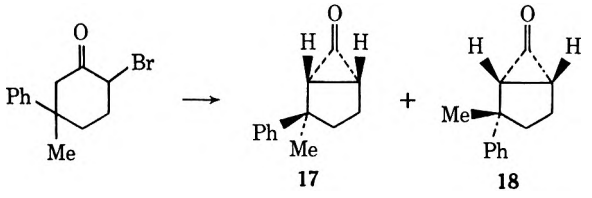
The difference in response of the 2-halo-4-methyl-4-phenyl- and 2-halo-5-methyl-5-phenylcyclohexanones (**6** and **7**, respectively) to variations in methoxide concentration is striking. With **6** formation of high yields of ester product even at low methoxide ion concentrations indicates the importance of the 1,3-diaxial effect in curbing side reactions, particularly in preventing the halogen atom from assuming the axial position most

(7) R. B. Loftfield, *J. Amer. Chem. Soc.*, **73**, 4707 (1951).



rate of their formation. At very low methoxide concentrations, on the other hand, there is time to establish the **15** ⇄ **16** equilibrium prior to ester formation; the product distribution under these conditions is controlled by this equilibrium position, as well as by the rate constants for the reactions of **15** and **16** (or their hemi methyl ketals) with methoxide ion. One would not expect, *a priori*, that **16** would be favored over **15** at equilibrium, but it might react fast enough with methoxide ion to make **9** the favored product. Since the reversal in product distribution from 3:1 to 1:3 corresponds to only a small difference in rates and/or equilibria (*ca.* 1.3 kcal/mol at 25°), it does not appear practical to speculate further on the reasons for this reversal at this time. The significant point is that the ratio *does change*, indicating that more than one intermediate is present and that they are being interconverted. This result is consistent with the mechanism outlined in the introduction wherein a dipolar ion is formed and is converted (reversibly at least under some conditions) into a cyclopropanone intermediate.

Formation of four esters from *cis*- or *trans*-**7** must be a consequence of the formation of two cyclopropanones, **17** and **18**, each of which can be cleaved by



methoxide–methanol to give two products. Cyclopropanone **17**, in which the phenyl and carbonyl groups are trans will give **8** and **11**, and cyclopropanone **18** will give **9** and **12**. Changing from 0.05 to 2 *M* NaOMe evidently increases the yield of **18** at the expense of **17**, since the proportions of **9** and **12** increase at the expense of **8** and **11**. This is the same trend as was noted in the reactions of **6**, and a similar explanation can be offered. It is not clear, however, why the ratios of **9**/**12** and **8**/**11** change with changing base concentration.

Equilibration of the ester mixture from **7** for 286 hr gave a slightly different ratio of **8**/**9** than was obtained from equilibration of the ester mixture derived from **6** for 165 hr. This no doubt reflects the difficulty of reaching equilibrium.

Experimental Section[8]

Favorskii Rearrangement of 2-Chloro-4-methyl-*cis*-4-phenylcyclohexanone (6, X = Cl).—A solution of 1.26 g (5.63 mmol) of **6** (X = Cl)[2a] in 37.5 ml of methanol was mixed with 50 ml of 0.193 *M* sodium methoxide in methanol at 0° and allowed to remain at that temperature for 20 hr (2 half-lives). The excess base was neutralized with 20 ml of 0.5 *M* nitric acid, and the products were extracted with ether (2 × 100 ml). The ether layer was washed with 5% bicarbonate (2 × 75 ml) and with saturated brine (2 × 75 ml), dried over magnesium sulfate, and concentrated. The residue was adsorbed onto a slurry-packed (4% ether in hexane) silica gel (200 g) column (45 × 3.3 cm) and eluted with 1000 ml each of 4, 5, and 7% ether in hexane. The 250-ml fractions 4, 5, 6, and 7 contained 0.65 g (2.97 mmol; 53%) of a mixture of methyl 3-methyl-3-phenylcyclopentane-1-carboxylates (**8** and **9**). Analysis by glpc using a 7-ft copper tube (0.25 in.) packed with 8% Carbowax 20 M on Gas Chromasorb W operated at 155° and 80 ml/min helium flow rate indicated a trans (**8**) to cis (**9**) isomer ratio of 3:1.

Examination by nmr revealed that the chemical shift (1.29 ppm) of the three 3-methyl hydrogens of **8** was downfield by 5 Hz from those of **9**. A ratio of the integrated intensities of each absorption confirmed the 3:1 ratio. Spectroscopic measurements were consistent with the assigned structure: λ_{max}^{film} 5.77 (s), 8.30, and 8.51 (s, doublet) μ: $\delta_{TMS}^{CCl_4}$ 7.25 (5 H), 3.59 (3 H), 3.10–2.65 (7 H), 1.29 and 1.20 (3 H, two singlets): mass spectrum *m/e* 218, molecular ion.

Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.93; H, 8.27.

Reaction of 2-Bromo-4-methyl-*cis*-4-phenylcyclohexanone (6, X = Br) by the Inverse Addition of Sodium Methoxide in Methanol.—A solution of 8.3 mmol (10% excess) of sodium methoxide in 100 ml of methanol was added over 5 hr to a stirred solution of 2.0 g (7.5 mmol) of **6** (X = Br)[2a] in 200 ml of methanol. The solution stood for 18 hr before a few drops of glacial acetic acid were added, and 200 ml of methanol was distilled through a Vigreux column. The concentrate was poured into 75 ml of saturated brine, and the products were extracted into pentane (4 × 100 ml). The extracts were combined, washed with saturated bicarbonate (2 × 50 ml) and with saturated brine, dried over magnesium sulfate, and concentrated. The residue was applied to a slurry-packed (3% ether in hexane) silica gel (70 g) column and eluted with 2 l. of 3% and 1 l. each of 10, 25, 50, and 100% ether in hexane. Fractions (250 ml) 3 and 4 contained 0.66 g (3.03 mmol; 40%) of a mixture of methyl 3-methyl-3-phenylcyclopentane-1-carboxylates. Analysis by glpc as above indicated a trans (**8**) to cis (**9**) isomer ratio of 1:3. Fractions 11 and 12 contained 0.25 g (1.15 mmol; 15%) of 2-methoxy-4-methyl-*cis*-4-phenylcyclohexanone. Rechromatography followed by bulb-to-bulb distillation, bp ~110° (0.2 mm), afforded an analytical sample: λ_{max}^{film} 5.75 (s), 8.4–9.3 (m, broad) μ; $\delta_{TMS}^{CCl_4}$ 7.8–7.4 (5 H), 3.5 (1 H, doublet of doublets, J_{ae} = 4.2 Hz, J_{aa} = 14.5 Hz), 3.46 (3 H, singlet), 3.1–1.7 (6 H, multiplet), 1.31 (3 H, singlet).

Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.21; H, 8.15.

Chromatography fractions 14–17 contained 0.68 g (2.72 mmol; 36%) of 2-hydroxy-4-methyl-4-phenylcyclohexanone dimethyl ketal: λ_{max}^{film} 2.84 (m), 8.5–9.7 (s) μ: $\delta_{TMS}^{CCl_4}$ 7.8–7.3 (5 H), 4.2–3.8 (1 H), 3.35 and 3.42 (6 H, two 3 H singlets), 2.4–1.5 (7 H), 1.26 (3 H, singlet).

A portion of the α-hydroxy ketal was dissolved in methanol and stirred with a few drops of concentrated hydrochloric acid for 30 min. The products were extracted into 50:50 mixture of ether and hexane, and the organic solution was water-washed, dried, and concentrated. The residue crystallized while standing for 2 days. Recrystallization from chloroform–methanol afforded an analytical sample: mp 293° dec; λ_{max}^{KBr} 2.89 (m), 8.90, 9.06, and 9.45 (s). This material was too insoluble to give a clear nmr spectrum, but no methoxy bands of a dilute chloroform solution of the above was observed. This compound is assigned

(8) Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Analyses were performed by Micro-Tech Laboratories, Skokie, Ill. Infrared spectra were taken on a Beckman IR-5 spectrophotometer. Nmr spectra were measured on a Varian A-60 using tetramethylsilane as an internal reference. Determinations of rearrangement product mixtures were carried out on an F & M Model 5752A gas chromatograph equipped with a thermoconductivity cell and a Disc Chart Integrator Model 227.

the structure of a dihemiketal resulting from the dimerization of 2-hydroxy-4-methyl-4-phenylcyclohexanone.

Anal. Calcd for $C_{26}H_{32}O_4$: C, 76.44; H, 7.90. Found: C, 76.28; H, 7.93.

Reaction of 2-Bromo-4-methyl-*cis*-4-phenylcyclohexanone (6, X = Br) with 2.0 *M* Sodium Methoxide in Methanol.—A 1.0 g (3.75 mmol) portion of 6 (X = Br)[2a] was added with stirring to a 0°, 100 ml solution of 2.0 *M* sodium methoxide in methanol. The solution was stirred at 0° for 40 min before 15 g (>0.2 mol) of glacial acetic acid was added. The resulting slurry was poured into 75 ml of saturated brine, and the products were extracted into pentane (5 × 75 ml). The extracts were combined, washed with saturated bicarbonate (2 × 50 ml) and with saturated brine (1 × 50 ml), dried over magnesium sulfate, and concentrated. The residue was applied to a slurry-packed (3% ether in hexane) silica gel (70 g) column and eluted as above. Isolated was 0.46 g (2.1 mmol; 56%) of a mixture of the esters **8** and **9** in a ratio of 3:1 as determined by glpc. Also eluted from the silica gel column was 0.35 g (1.4 mmol; 37%) of 2-hydroxy-4-methyl-4-phenylcyclohexanone dimethyl ketal identical with that above. There was no 2-methoxy-4-methyl-*cis*-4-phenylcyclohexanone detected.

Equilibration of Methyl 3-Methyl-3-phenylcyclopentane-1-carboxylates (8 and 9) by Sodium Methoxide in Methanol.—A solution of 2.0 g (9.16 mmol) of a mixture containing 70% of **8** and 30% of **9** in 40 ml of methanol was refluxed, moisture excluded, with 0.1 mol of sodium methoxide in 60 ml of methanol. Portions of 10 ml were withdrawn at 25-hr intervals: the esters were isolated; and the ratio of isomers was determined by nmr. After 165 hr there was no change in the isomer ratio. The remainder of the mixture was processed in the usual fashion; nmr and glpc analyses indicated the equilibrium mixture to be 55% of **8** and 45% of **9**.

Stereochemical Assignments for Methyl 3-Methyl-*trans*-3-phenylcyclopentane-1-carboxylate (8) and Methyl 3-Methyl-*cis*-3-phenylcyclopentane-1-carboxylate (9).—A mixture of 1.55 g (7.59 mmol) of the isomeric carboxylic acids (56% trans and 44% cis)[9] derived from the respective esters (**8** and **9**) by basic hydrolysis were converted into their acid chlorides by reaction with excess thionyl chloride. The acid chlorides were dissolved in 200 ml of dry carbon disulfide, and 2.48 g (17.8 mmol) of aluminum chloride was added portionwise over 30 min to the stirred, 0° solution. The mixture was stirred at 0° for 90 min and then at room temperature for 40 min. The contents were poured onto 200 ml of crushed ice, and the aqueous layer was extracted thoroughly with ether. The extracts were combined, concentrated to 100 ml, and extracted with 5% sodium bicarbonate (4 × 75 ml). The ether layer was dried over magnesium sulfate and concentrated. The neutral material was applied to a slurry-packed (5% ether in hexane) silica gel (200 g) column (48 × 3.5 cm) and eluted with 1000 ml each of 5, 6, 10, and 15% ether in hexane. Fractions (250 ml) 7, 8, and 9 contained 0.84 g (4.54 mmol) of 2,3-benzo-1-methylbicyclo-[3.2.1]oct-2-en-4-one (**10**). Evaporative distillation (bp ~95° at 0.05 mm) followed by crystallization from pentane afforded an analytical sample: mp 30.5–31.0°, λ_{max}^{film} 5.92 (s) μ: $\delta_{TMS}^{CCl_4}$ 8.15 and 8.05 (1 H, two triplets), 7.62–7.15 (3 H, multiplet), 3.08 (1 H, broad triplet), 2.38–1.38 (10 H, multiplet).

Anal. Calcd for $C_{13}H_{14}O$: C, 83.83; H, 7.58. Found: C, 84.00; H, 7.75.

The compound gave a colorless oxime, mp 138–139°.

Anal. Calcd for $C_{13}H_{15}NO$: C, 77.58; H, 7.51. Found: C, 77.55; H, 7.70.

The bicarbonate wash solutions were combined and neutralized with hydrochloric acid. The liberated carboxylic acid was extracted into ether, and the ether solution was dried and concentrated to yield 0.39 g (1.90 mmol) of 3-methyl-*trans*-3-phenylcyclopentane-1-carboxylic acid (**8a**). A small quantity of this acid was converted into its methyl ester with diazomethane, and the ester corresponded to **8** by infrared and nmr spectroscopy and by glpc retention time. The trans acid was purified by chromatography and recrystallized from ethanol–water, mp 42.5–44°.

Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.56; H, 7.88.

In order to confirm that the acid chloride derived from **8** has partially isomerized to that from **9** during reaction with aluminum chloride, the acid chloride from 0.4 g (2.0 mmol) of **8a** was dissolved in 70 ml of dry carbon disulfide and allowed to react with 0.86 g (6.2 mmol) of aluminum chloride as above. Isolation of the products gave 0.19 g (0.93 mmol) of the nonisomerized trans acid and 92 mg (0.50 mmol) of the tetralone **10**. This result indicates a 25% conversion of the trans into the cis acid chloride as compared with a 29% conversion in the first experiment.

***cis*-2,6-Dibromo-4-methyl-*cis*-4-phenylcyclohexanone.**—A solution of 16.6 g (0.104 mol) of bromine and 8.5 g (0.104 mol) of sodium acetate in 80 ml glacial acetic acid was added dropwise over 60 min to a stirred solution of 10.0 g (0.053 mol) of 4-methyl-4-phenylcyclohexanone[2a] in 100 ml acetic acid. Following the disappearance of bromine, the mixture was poured into 200 ml saturated brine, and the products were extracted with ether (3 × 100 ml). The ethereal solution was washed with 5% bicarbonate until all acetic acid was removed and with saturated brine, dried over magnesium sulfate, and concentrated. The remaining residue was applied to a slurry-packed (4% ether in hexane) silica gel (500 g) column (93 × 3 cm) and eluted with 1000 ml each of 4, 5, 6, and 8 ether in hexane. Fractions (500 ml) 5, 6, 7, and 8 contained, after recrystallization from benzene–hexane, 7.93 g (0.023 mmol; 44%) of *cis*-2,6-dibromo-4-methyl-*cis*-4-phenylcyclohexanone: mp 128–129°; λ_{max}^{KBr} 5.73 (s) μ; $\delta_{TMS}^{CDCl_3}$ 7.58 (5 H, broad), 4.68 (2 H, doublet of doublets, J_{ae} = 5 Hz, J_{aa} = 14.5 Hz), 3.31 and 2.37 (4 H, centers of multiplets), 1.29 (3 H, singlet).

Anal. Calcd for $C_{13}H_{14}OBr$: C, 45.12; H, 4.08. Found: C, 45.21; H, 4.07.

Reaction of *cis*-2,6-Dibromo-4-methyl-*cis*-4-phenylcyclohexanone with Zinc–Copper Couple in Methanol.—A suspension of zinc–copper couple prepared from 2.9 g (44 g-atoms) of powdered zinc and 2% cupric sulfate was added with 200 ml of methanol to 5.0 g (14.4 mmol) of dibromide in 200 ml of methanol. The mixture was stirred under reflux for 14 hr. The mixture was filtered through diatomaceous earth, and the filtrate plus washings were concentrated. The residue was dissolved in ether, and the ethereal layer was washed with 5% hydrochloric acid and with saturated brine, dried over magnesium sulfate, and concentrated. Chromatography on silica gel (150 g) gave by elution with 3% ether in hexane 66 mg (0.31 mmol; 2%) of the esters **8** and **9**. The ratio of isomers was determined by glpc to be 36% of **8** and 64% of **9**. Further elution (5% ether in hexane) of the column gave 0.24 g (1.27 mmol) of 4-methyl-4-phenylcyclohexanone, identified by comparison with an authentic sample.[2a] The other six products (by glpc) were unidentified.

Reaction of 2-Bromo-5-methyl-*cis*-5-phenylcyclohexanone (7a) with 5.0 × 10^{-2} *M* Sodium Methoxide in Methanol.—A 20-ml portion of 0.2 *M* sodium methoxide in methanol at 0° was added to 0.79 g (2.96 mmol) of **7a**[10] in 60 ml of methanol at 0°. The mixture was swirled and allowed to stand for 80 min (10 half-lives). A 4.0-ml solution of 0.25 *M* nitric acid was added, and the mixture was concentrated. The products were extracted into ether (2 × 75 ml), and the ether layer was washed with water (2 × 50 ml), with 5% sodium bicarbonate (1 × 50 ml), and with saturated brine (there were no carboxylic acids in the aqueous washings), dried over magnesium sulfate, and concentrated. The residue was chromatographed over 70 g of silica gel using 3% ether in hexane. The 250-ml fractions 2 and 3 contained 57 mg (0.26 mmol; 9%) of a mixture of carboxylic esters. Analysis by glpc using a 10-ft copper tube (0.25 in) packed with 10% Carbowax 20M on 60–80 Gas Chromasorb W operated at 175° and 35 ml/min helium flow rate revealed the isomer distribution in order of their elution as 23% of **12**, 14% of **11**, 57% of **8**, and 6% of **9**.

These esters were further purified by evaporative distillation (~80° at 0.1 mm) to yield an analytical sample.

Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.30; H, 8.44.

Reaction of 2-Bromo-5-methyl-*trans*-5-phenylcyclohexanone (7b) with 5.0 × 10^{-2} *M* Sodium Methoxide in Methanol.—The procedure for the reaction of 0.79 g (2.96 mmol) of **7b** (88% of **7b** and 12% of **7a**)[10] in 60 ml of methanol with 20 ml of 0.2 *M* sodium methoxide was the same as that described for **7a**. The reaction was terminated after 80 min (10 half-lives). The product isolated after chromatography weighed 51 mg (0.23 mmol, 9%) and was identical by glpc, infrared, and nmr to that

(9) By nmr analysis; the 3-methyl protons were found to be equally shielded by the carbomethoxy and carboxyl groups (δ 1.22 and 1.31 ppm).

(10) F. G. Bordwell, R. R. Frame, and J. G. Strong, *J. Org. Chem.*, **33**, 3385 (1968).

from **7a**. The distribution of isomers was 25% of **12**, 14% of **11**, 56% of **8**, and 5% of **9**.

Reaction of 2-Bromo-5-methyl-*cis*-5-phenylcyclohexanone (7a) with 1.0 *M* Sodium Methoxide in Methanol.—A 50-ml portion of 1.2 *M* sodium methoxide was cooled to 0° and added with stirring to 0.5 g (1.87 mmole) of **7a** in 10 ml of methanol. The reaction was maintained at 0° for 20 min before a solution of nitric acid (4.5 ml) in water was added. The products were extracted into ether, and the ether solution was washed with 5% bicarbonate (there were no carboxylic acids present) and with saturated brine, dried over magnesium sulfate, and concentrated. Elution of the residue over 70 g of silica gel with 3% ether in hexane gave 90 mg (0.41 mmol, 22%) of a mixture of carboxylic esters composed of (by glpc) 27% of **12**, 11% of **11**, 56% of **8**, and 6% of **9**.

Reaction of 2-Bromo-5-methyl-*trans*-5-phenylcyclohexanone (7b) with 1.0 *M* Sodium Methoxide in Methanol.—The same procedure as for the reaction of **7a** with 1.0 *M* sodium methoxide was employed for the reaction of 0.5 g (1.87 mmol) of 68% **7b** and 32% **7a** in 10 ml of methanol with 50 ml of 1.2 *M* sodium methoxide. Chromatography on silica gel yielded 110 mg (0.50 mmol, 24%) of Favorskii esters. Glpc analysis showed the product distribution as 26% of **12**, 11% of **11**, 56% of **8**, and 7% of **9**.

Reaction of 2-Bromo-5-methyl-*cis*-5-phenylcyclohexanone (7a) with 2.0 *M* Sodium Methoxide in Methanol.—A cooled, 50-ml solution of 2.4 *M* sodium methoxide in methanol was mixed at 0° with a 10 ml methanolic solution of 0.5 g (1.87 mmol) of **7a**. The remainder of the procedure followed that for the reaction of **7a** in 1.0 *M* sodium methoxide. The product esters weighed 0.28 g (1.28 mmol; 69%) and had an isomer distribution of 39% of **12**, 9% of **11**, 45% of **8**, and 7% of **9**.

Reaction of 2-Bromo-5-methyl-*trans*-5-phenylcyclohexanone (7b) with 2.0 *M* Sodium Methoxide in Methanol.—A solution of 0.5 g (1.87 mmol) of 68% **7b** and 32% **7a** in 10 ml of methanol was mixed at 0° with 50 ml of 2.4 *M* sodium methoxide in the manner as for **7a**. Termination and isolation as above gave 0.28 g (1.30 mmol; 69%) of Favorskii esters. Analysis by glpc revealed an isomer distribution of 39% of **12**, 9% of **11**, 45% of **8**, and 7% of **9**.

Equilibration of Methyl 2-Methyl-2-phenylcyclopentane-1-carboxylates (11 and 12) by Sodium Methoxide in Methanol.—A solution of 1.32 g (6.05 mmol) of a mixture containing 34% of **12**, 9% of **11**, 50% of **8**, and 7% of **9** in 40 ml of methanol was stirred at 0° for 1 hr with 0.1 mol of sodium methoxide. A 20-ml portion was withdrawn, the esters were isolated, and the distribution of isomers was determined by glpc. There had been no change in the isomer ratios, indicating that these products were stable under normal Favorskii conditions. The remaining solution was heated to reflux, and 10-ml portions were withdrawn after intervals of 154, 217, and 286 hr. After 286 hr, there was no change in the isomer ratios. The reaction mixture was processed in the usual fashion and a glpc analyses placed the equilibrium at 24% of **9**, 22% of **12**, 26% of **8**, and 28% of **11**.

Stereochemical Assignments for Methyl 2-Methyl-*cis*-2-phenylcyclopentane-1-carboxylate (12) and Methyl 2-Methyl-*trans*-2-phenylcyclopentane-1-carboxylate (11).—A mixture of 1.02 g (5.0 mmol) of the isomeric carboxylic acids derived from the respective esters (22% of **12**, 12% of **11**, 57% of **8**, and 9% of **9**) by basic hydrolysis were converted into their acid chlorides by reflux with excess thionyl chloride. The acid chlorides were dissolved in 110 ml of dry carbon disulfide, and the solution was cooled to −15°. Solid aluminum chloride (1.4 g, 10.5 mmol) was added over 15 min, and the mixture was stirred for 1 hr at −15° and at room temperature for 20 min. The mixture was poured onto 50 ml of ice, and the products were absorbed into ether (4 × 50 ml). The organic layers were combined, washed with dilute acid, and concentrated. The residue was dissolved in ether, and the solution was washed with 5% sodium bicarbonate (5 × 50 ml) and with saturated brine, dried over magnesium sulfate, and concentrated. The neutral material was adsorbed onto 70 g of silica gel and eluted with 1 l. of 2% and 4 l. of 4% ether in hexane. Fractions (250 ml) 8 and 9 contained 0.28 g (1.52 mmol) of 47% 2,3-benzo-1-methyl-*cis*-bicyclo[3.3.0]oct-2-en-4-one (**13**) and 53% 2,3-benzo-1-methylbicyclo[3.2.1]oct-2-en-4-one (**10**). These isomeric ketones were separated by collection of the eluted samples from a 10-ft 10% Carbowax 20M column operated at 160° with a helium flow rate of 35 ml/min. The tetralone (**10**) was identical with that previously isolated. The infrared and nmr spectra were consistent with the assigned structure for the *cis*-bicyclooctenone (**13**): λ_{max}^{film} 5.86 (s) μ: $\delta_{TMS}^{CCl_4}$ 8.15 and 8.05 (1 H, two triplets), 7.70–7.15 (3 H, multiplet), 2.60 (1 H, multiplet), 2.30–1.30 (10 H, multiplet).

Anal. Calcd for $C_{13}H_{14}O$: C, 83.83; H, 7.58. Found: C, 83.81; H, 7.60.

The solutions from the bicarbonate extractions were combined and neutralized with hydrochloric acid. The liberated acids were extracted into ether, and the ether solution was dried and concentrated to give 0.36 g (1.76 mmol). These acids were readily converted into their methyl esters with diazomethane, and the esters corresponded to **8** and **11** by infrared and nmr spectroscopy and by glpc retention time.

Yield of Methyl Cyclopentanecarboxylate (20) from 2-Chlorocyclohexanone (19) with Increasing Concentrations of Sodium Methoxide in Methanol. A.—A solution of 8.3 mmol (10% excess) of sodium methoxide in 100 ml of methanol was added over 6 hr to a stirred solution of 1.0 g (7.5 mmol) of distilled (bp 84–85°, 7.0 mm) 2-chlorocyclohexanone (**19**) in 200 ml of methanol. The solution was allowed to stand for 18 hr before a few drops of glacial acetic acid was added. Methanol (200 ml) was removed by distillation through a Vigreux column, and the concentrate was poured into 100 ml of saturated brine. The products were extracted into pentane (5 × 75 ml), and the extracts were combined, washed with saturated bicarbonate (3 × 50 ml) and with saturated brine (1 × 50 ml), dried over magnesium sulfate, and concentrated to ~2–3 ml by distillation of the pentane through a Vigreux column. The residue was diluted to 5.0 ml with chloroform in a volumetric flask. Measured volumes of the chloroform solution were injected into a 10-ft copper tube packed with 10% Carbowax 20M on Gas Chromasorb W operated at 120° with a helium flow rate of 35 ml/min. The yield of methyl cyclopentanecarboxylate (**20**), 3%, was calculated from the integrated peak area using a 0.214 *M* chloroform solution of prepared **20**[11] as a standard.

The other products could not be accurately analyzed by glpc because of their decomposition and interconversion during the analysis.

B.—A solution of 1.0 g (7.5 mmol) of **19** in 100 ml of methanol was added to a stirred solution of 15 mmol of sodium methoxide in 200 ml of methanol. The reaction was terminated after 12 hr by the addition of 0.48 g (8.0 mmol) of glacial acetic acid in 10 ml of methanol. The reaction mixture was processed, the products were isolated, and the yield of **20** (10%) was determined in the manner as above.

C.—A solution of 1.0 g (7.5 mmol) of **19** in 50 ml of methanol was added to a stirred solution of 0.1 mol of sodium methoxide in 50 ml of methanol. The cloudy suspension was stirred for 40 min before 6.0 g (0.1 mol) of glacial acetic acid was added. The mixture was poured into 100 ml of saturated brine, and the organic products were extracted into pentane (5 × 75 ml). The pentane extracts were processed and the yield of **20** (33%) was determined as above.

D.—A 100-ml portion of 2.0 *M* sodium methoxide in methanol was added to 1.0 g (7.50 mmol) of **19**, and the cloudy solution was stirred for 30 min. Glacial acetic acid (15 g, >0.2 mol) was added, and isolation as described in part C was followed. Analysis by glpc indicated a 49% yield of **20**.

Reaction of 2-Chlorocyclohexanone (19) by the Inverse Addition of Sodium Methoxide in Methanol.—A 100-ml solution of 0.413 *M* sodium methoxide in methanol was added over 6 hr to a stirred solution of 5.0 g (37.5 mmol) of **19** in 200 ml of methanol. The solution stood for 18 hr before excess glacial acetic acid was added. Methanol (250 ml) was removed by distillation through a Vigreux column and by distillation of 40 ml through a microware column packed with glass helices. The concentrate was applied to a slurry-packed (10% ether in hexane) silica gel (250 g) column and eluted with 1.0 l. each of 10, 15, and 25% ether in hexane with 2.0 l. of 50% ether in hexane and with 1.0 l. each of ether and chloroform. Fractions (250 ml) 14–19 contained 4.8 g of a mixture of 2-methoxycyclohexanone and 2-hydroxycyclohexanone dimethyl ketal. This mixture was rechromatographed as above, and fractions 14 and 15 contained 0.70 g (5.5 mmol; 15%) of 2-methoxycyclohexanone, identical with a prepared authentic sample,[12] and fractions 16–22 contained 3.74 g (23.3 mmol; 62%) of 2-hydroxycyclohexanone

(11) D. W. Goheen and W. R. Vaughan, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 594.

(12) H. Adkins, R. M. Elofson, A. G. Rossow, and C. C. Robinson, *J. Amer. Chem. Soc.*, **71**, 3622 (1949).

dimethyl ketal identical with that reported.[13] The α-hydroxy ketal gave a colorless 3,5-dinitrobenzoate, mp 97–98° (lit.[13] 97–98°).

Also when a small crystal of *p*-toluenesulfonic acid was added to 1.5 g (9.4 mmol) of the hydroxy ketal, and the mixture was allowed to remain at room temperature for 24 hr, a crystalline material weighing 1.1 g (4.1 mmol, 87%) was isolated and identified as dodecahydro-4a,9a-dimethoxydibenzo-*p*-dioxin, mp 167–168° (lit.[14] mp 165°).

Reaction of 2-Chlorocyclohexanone (19) with 2.0 *M* Sodium Methoxide in Methanol.—A 100-ml solution of 2.0 *M* sodium methoxide in methanol was added to 5.0 g (37.5 mmol) of **19**, and the cloudy mixture was stirred for 45 min. The mixture was cooled, and 15 g (>0.2 mol) of glacial acetic acid in 50 ml of methanol was added. Methanol (100 ml) was removed by distillation through a Vigreux column. The moist solid that remained was mixed with 200 ml of pentane, and the inorganic precipitate was removed by filtration. The filter cake was washed several times with pentane, and the filtrate was concentrated by the distillations of pentane through a Vigreux column and methanol (40 ml) through a microware column packed with glass helices. The residue was applied to a slurry-packed (10% ether in hexane) silica gel (250 g) column and eluted as in the above experiment. Fractions (250 ml) 12–16 contained 2.83 g (17.7 mmol; 47%) of 2-hydroxycyclohexanone dimethyl ketal identical with that described above. There was no 2-methoxycyclohexanone detected.

(13) C. L. Stevens and J. Tazuma, *J. Amer. Chem. Soc.*, **76**, 715 (1954).
(14) M. Bergman and M. Gierth, *Justus Liebigs Ann. Chem.*, **448**, 48 (1926); R. Criegee and W. Schnorrenberg, *ibid.*, **560**, 144 (1948).

Registry No.—**6** (X = Cl), 19054-51-4; **6** (X = Br), 19209-96-2; **7a**, 17245-79-3; **7b**, 17245-80-6; **8**, 37107-95-2; **8a**, 37107-96-3; **9**, 37107-97-4; **10**, 37107-98-5; **10** oxime, 37111-95-8; **11**, 37107-99-6; **12**, 37108-00-2; **13**, 37108-01-3; **17**, 37108-02-4; **19**, 822-87-7; 2-methoxy-4-methyl-*cis*-4-phenylcyclohexanone, 37108-03-5; 2-hydroxy-4-methyl-4-phenylcyclohexanone dimethyl ketal, 37111-97-0; 2-hydroxy-4-methyl-4-phenylcyclohexanone dimer, 37164-32-2.

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Ivalbatin, a New Xanthanolide from *Iva Dealbata*[1a]

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Ivalbatin, a new xanthanolide, has been isolated from *Iva dealbata* Gray and its gross structure established as **2**. The stereochemistry of ivalbin and ivalbatin is discussed and formulas **23** (stereochemistry at C-2 still uncertain) and **26** (stereochemistry at C-6 questionable) are derived.

In an earlier communication[2] we derived a gross structure for ivalbin (**1**), a crystalline xanthanolide from *Iva dealbata* Gray. In the present paper we report isolation and structure determination of a second new xanthanolide (**2**) from *Iva dealbata*, which we have named ivalbatin, and discuss the stereochemistry of ivalbin and ivalbatin. For the former, formula **23** is deduced, although the stereochemistry at C-2 remains uncertain, for the latter formula **26**, with the stereochemistry at C-6 still in doubt.

As ivalbatin was obtained as an unstable oil and polymerized rapidly, it was purified by immediate conversion into the crystalline acetate **3**, $C_{17}H_{22}O_5$. The yield of **3**, based on the crude chloroform extract, was 16.8%, twice the amount of ivalbin; hence, ivalbatin is the major sesquiterpene lactone of this species.

Ivalbatin had $[\alpha]^{24}D$ −84°, uv end absorption at 210 nm (ε 13,400) and ir bands at 3450 (OH), 1755 (γ-lactone), 1705 (ketone), and 1655 cm^{-1} (C=C). A comparison of the nmr spectra of **2** and **3** revealed only one significant change, signals at 3.65 (>CHOH) and 3.40 ppm (>CHOH) being replaced by signals at 4.80 (>CHOAc) and 2.11 ppm (>CHOCOCH$_3$), respectively. Hence formula $C_{15}H_{20}O_4$ containing a secondary alcohol group could be assigned to ivalbatin. Other functional groups of **3** were the following: conjugated lactone as evidenced by ir bands at 1755 and 1655 cm^{-1}, uv end absorption at 209 nm (ε 13,800), and an nmr signal

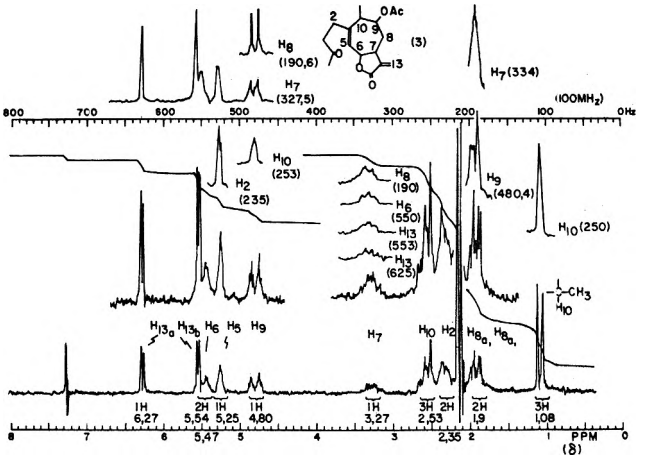


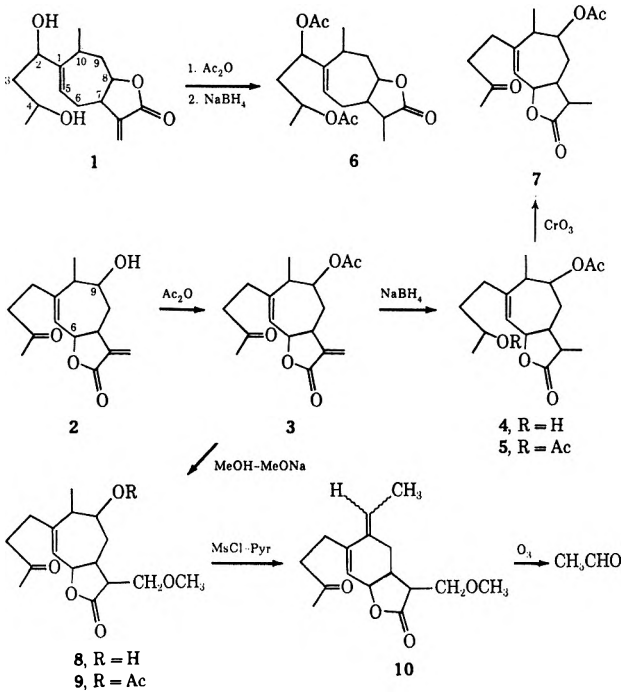
Figure 1.—Nmr spectrum and spin decoupling of acetylivalbatin (**3**).

characteristic of hydrogen under lactone at 5.47 ppm (Figure 1); methyl ketone (iodoform test, ir band at 1720 cm^{-1}, nmr signal at 2.17 ppm); secondary methyl (three-proton doublet at 1.08 ppm); trisubstituted double bond (one-proton broadened singlet at 5.25 ppm); and an exocyclic methylene group conjugated with the lactone group (two one-proton doublets at 5.54 and 6.27 ppm).

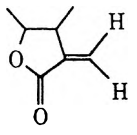
The presence of the exocyclic methylene group was confirmed by ozonolysis of **3** which yielded formaldehyde. Treatment of **3** with sodium borohydride gave an alcohol **4** which polymerized on standing and was converted into a diacetate **5** ($C_{19}H_{28}O_6$) (see Scheme I). The latter was not identical with diacetyldihydro-

(1) (a) Paper XIV: Constituents of *Iva* Species. For paper XIII, see G. D. Anderson, R. S. McEwen, and W. Herz, *Tetrahedron Lett.*, 4423 (1972). (b) Osaka University. (c) Florida State University. Work supported in part by a grant from the U. S. Public Health Service (CA-13121).
(2) W. Herz, H. Chikamatsu, N. Viswanathan, and V. Sudarsanam, *J. Org. Chem.*, **32**, 682 (1967).

SCHEME I



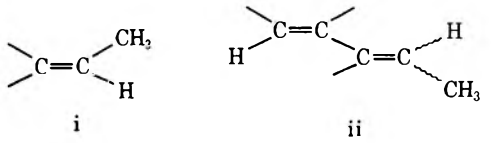
ivalbin (6). Oxidation of 4 with Jones reagent gave dihydroacetylivalbatin (7). That reduction of the exocyclic methylene group had taken place in 5 and 7 was indicated in the ir spectra by a shift of the γ-lactone band to higher wavenumber, in the uv spectra by a decrease in the end absorption, and in the nmr spectra by the disappearance of the two vinyl doublets and the appearance of a second methyl doublet. Further confirmation for the presence of partial structure A in ivalbatin was the formation of a noncrystalline



A

adduct 8, characterized as the crystalline acetate 9 (nmr spectrum in Figure 3),[3] on treatment of 3 with sodium methoxide–methanol under mild conditions.

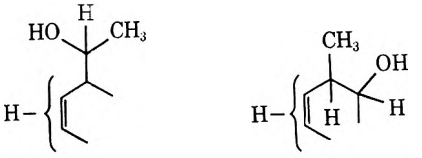
Dehydration of 8 with methanesulfonyl chloride–pyridine or treatment of 8 tosylate with lutidine gave a noncrystalline conjugated diene 10, $C_{16}H_{22}O_4$, λ_{max} 239 nm (ε 11,550), whose nmr spectrum (Figure 4)[3] no longer exhibited the signal of a secondary methyl group, but had a new vinyl methyl doublet at 1.75 ppm obviously coupled to a new vinyl quartet at 5.86 ppm. This was confirmed by spin decoupling (Figure 4); the presence of partial structure i deduced in this manner was confirmed by ozonolysis of 10 which liberated acetaldehyde. Since the conversion of 8 into 10 had also resulted in the transformation of the broadened vinyl proton singlet of 8 at 5.15 ppm to a distinct doublet at lower field (5.46 ppm), the existence of partial structure ii, where the methyl-substituted



i ii

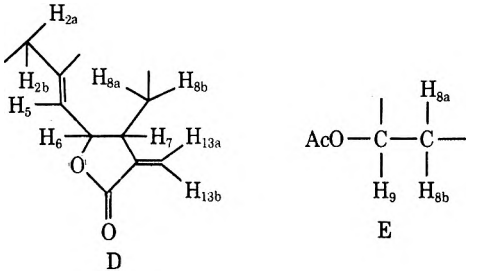
double bond is exocyclic (calcd λ_{max} 239 nm[4]), in 10 was assured.

Although the dehydration reaction leading to 10 could be interpreted in terms of partial structure B, spin-decoupling experiments on 3 (Figure 1) established the presence of C rather than B in 3 and therefore in 8. Thus, irradiation at 2.53 ppm (H-10) collapsed the methyl doublet at 1.08 ppm to a singlet and the doublet of triplets at 4.80 ppm (hydrogen under acetate, H-9) to a broad singlet, while irradiation at the frequency corresponding to H-9 did not affect the methyl doublet. Hence dehydration of 8 was accompanied by rearrangement of the carbon skeleton.



B C

Double resonance experiments on 3 (Figure 1) allowed expansion of A to partial structure D. Irradiation at the frequencies of the exocyclic methylene group (H-13a and H-13b) caused simplification of the multiplet at 3.27 ppm (H-7). Conversely, irradiation at the frequency of H-7 collapsed not only the doublets at 5.54 and 6.27 ppm (H-13a and H-13b), but affected also the signals of the lactone proton (H-6) and a methylene group (H-8a and H-8b), the double doublet at 5.47 ppm (H-6) collapsing to a doublet, and the multiplet at 1.8–2 ppm (H-8a and H-8b) to a singlet.



D E

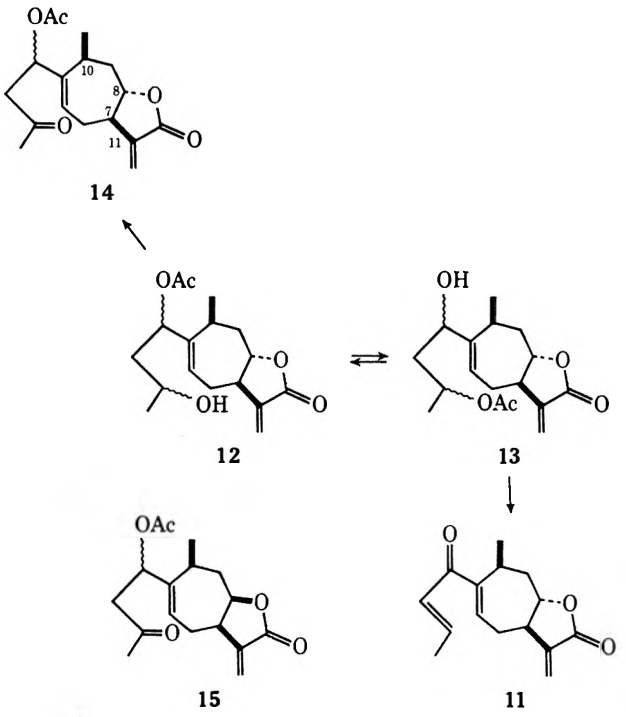
The chemical shift of the lactone proton in compounds of the ivalbatin series (5.50–5.32 ppm in 2, 3, 4, 5, 7, 8, and 9) which appears at considerably lower field than the lactone proton (H-8) in the ivalbin series (4.3–4.2 ppm) indicated that this proton was allylic and that the lactone ring was closed to C-6 rather than C-8 as in ivalbin. This conclusion was verified as follows. (1) In the nmr spectrum of the product obtained by catalytic hydrogenation of 9, the signal of H-6 is more complex and shifted to higher field (4.54 ppm). (2) Irradiation (Figure 1) at 2.35 ppm (H-2) collapsed the broad singlet of H-5 (5.25 ppm) to a doublet.[5] The J value (2.5 Hz) of this doublet was

(3) Nmr spectra and spin-decoupling data on compounds 9 (Figure 3) and 10 (Figure 4) will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 Sixteenth Street, N.W., Washington, D. C. 20036, by referring to code number JOC-73-585. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche.

(4) L. F. Fieser and M. Fieser, "Steroids," Reinhold, New York, N. Y., 1959, p 17.

(5) Allylic coupling between H-2 and H-5 was also demonstrated in the ivalbin series.[2]

SCHEME II



identical with one of the coupling constants of the lactone proton (H-6).

Partial structure D deduced in this manner was confirmed by spin-decoupling experiments carried out on **9** (Figure 3).

The presence of partial structure E in **3** was established by irradiation at the frequency of H-8a and H-8b (Figure 1). This caused simplification of the multiplet of H-7 and collapsed the doublet of triplets at 4.80 (H-9) to a doublet (J = 10 Hz); conversely, irradiation of the frequency of H-9 simplified the multiplet of H-8. Irradiation at the frequency of H-7 had no effect on H-9. Similar results were obtained by spin-decoupling experiments on **9** (Figure 3).

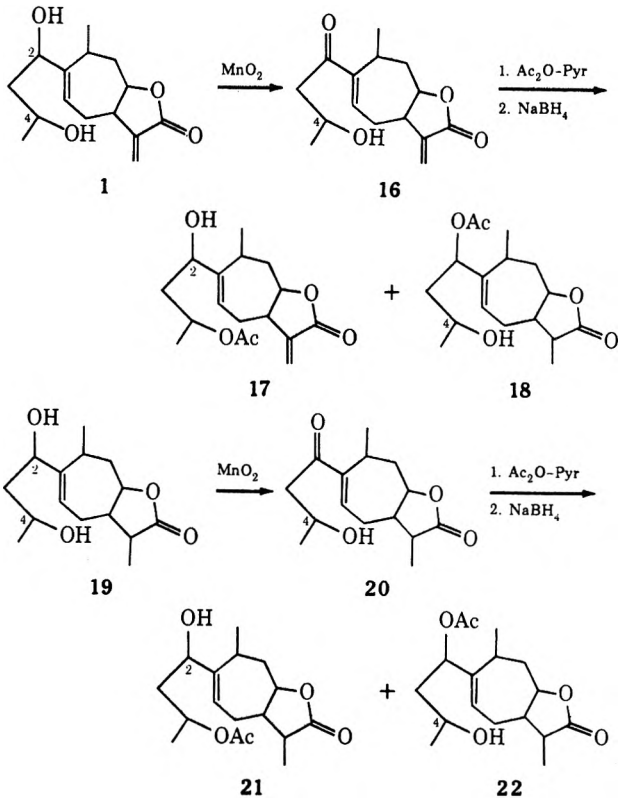
Combination of partial structures C, D, and E, which together account for 12 of the 15 carbon atoms of ivalbatin, with the methyl ketone function known to be present leads uniquely to formula **2** for ivalbatin, a ring-hydroxylated xanthanolide.

In the following we discuss the stereochemistry of ivalbin and ivalbatin. As regards the former, it has been correlated[6] through anhydrodehydroivalbin (**11**)[2] with xanthanol (**12**) and isoxanthanol (**13**) which in turn were correlated with xanthinin (**14**) as shown in Scheme II. Hence ivalbin has the same stereochemistry at C-7, C-8, and C-10 as xanthinin.

The absolute stereochemistry of xanthinin at C-10 has been established[6] by degradation to (−)-(*S*)-methylsuccinic acid. It has also been deduced[6] that xanthinin possesses a trans-fused γ-lactone ring because it differs from its stereoisomer xanthumin **15**. The latter also has a β-oriented C-10 methyl group and possesses a cis-fused γ-lactone ring.[7] Xanthumin has been correlated[8] with gafrinin for which a cis γ-lactone ring fusion has been deduced[9] independently

(6) T. E. Winters, T. A. Geissman, and D. Safir, *J. Org. Chem.*, **34**, 153 (1969).
(7) H. Minato and I. Horibe, *J. Chem. Soc.*, 7009 (1965).
(8) L. A. P. Anderson, W. T. de Kock, W. Nel, and K. G. R. Pachler, *Tetrahedron*, **24**, 1687 (1968).
(9) W. T. de Kock and K. G. R. Pachler, *ibid.*, **24**, 1701 (1968).

SCHEME III



by nmr analysis. If it be assumed that the absolute configuration of xanthinin and xanthumin at C-7 is the same as that of all other sesquiterpene lactones of established absolute configuration, *i.e.*, β, the absolute configuration of ivalbin at C-7, C-8, and C-10 is established as H-7 α, H-8 β, H-10 α.

The absolute configuration of ivalbin at C-2 and C-4 was investigated by means of Horeau's method[10] which has been found to be applicable to sesquiterpene lactones.[11] C-2 alcohols **17** and **21** and C-4 alcohols **16** and **20** were prepared from ivalbin (**1**) and dihydroivalbin (**19**), respectively (Scheme III). Acetylation of **17** and **21** gave ivalbin diacetate and dihydroivalbin diacetate, respectively, thus demonstrating that the configuration of **17** and **21** at C-2 was the same as that of ivalbin. Reaction of **16**, **17**, **20**, and **21** with excess (+)-α-phenylbutyric anhydride gave (−)-α-phenylbutyric acid in 21.0, 16.2, 15.0, and 10% optical yield, respectively. Hence the configuration at C-2 and C-4 should be *S*(2-OH α, 4-OH β).

Unfortunately, the nmr spectra of **17** and **21** showed that these substances were contaminated with C-4 alcohols **18** and **22**, respectively, as the result of partial migration of the acetyl group from C-4 to C-2 during the sodium borohydride reduction.[12] As a consequence the absolute configuration of ivalbin is as shown in **23** except for the situation at C-2 which requires further verification and is being investigated.

The absolute configuration of ivalbatin at C-9 was also deduced by application of Horeau's method. Reaction of ivalbatin and **8** with (±)-α-phenylbutyric anhydride gave (+)-α-phenylbutyric acid in 2.8 and 11.0% optical yield, respectively. The optical yield

(10) A. Horeau, *Tetrahedron Lett.*, 506 (1961); 965 (1962).
(11) W. Herz and H. B. Kagan, *J. Org. Chem.*, **32**, 216 (1967).
(12) A similar equilibrium was found to exist between **12** and **13**.[5]

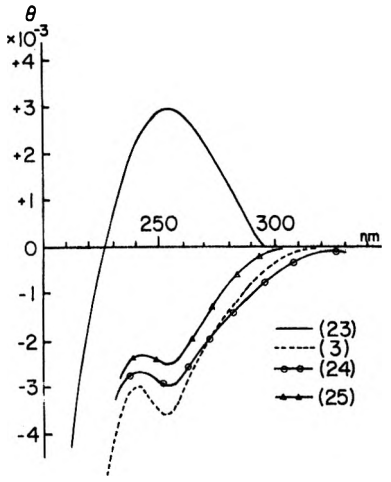


Figure 2.—CD curves of acetylivalbatin (3), ivalbin (23), parthemollin (24), and ivambrin (25).

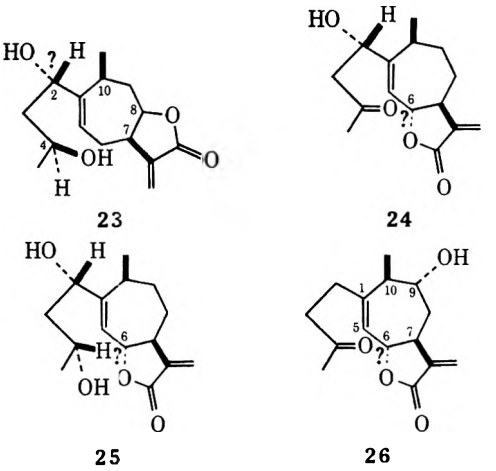
from 8 was sufficiently high to permit the conclusion that the configuration of ivalbatin at C-9 is R or OH α.

On biogenetic grounds it is plausible to assume that the C-10 methyl group of ivalbatin is β like that of ivalbin and all other xanthanolides and pseudoguaianolides isolated from related species. On this basis, H-9 and H-10 would be trans. The large value of $J_{H\text{-}9,H\text{-}10}$ (10 Hz) obtained from the spin-decoupling experiments on 3 and 9 is in accordance with this conclusion.

Just as in the case of parthemollin (24),[13] knowledge of the coupling constants involving H-5, H-6, and H-7 was not sufficient to decide unambiguously between cis and trans fusion of the lactone ring. The strong positive Cotton effects exhibited by ivalbin (23) (Figure 2) and its acetate (λ_{max} 257 nm, θ +2960 and λ_{max} 255 nm, θ +3090, respectively) are in agreement with the generalization[14] that, regardless of structural type, cis-fused α-methylene-γ-lactones closed to C-8 exhibit negative Cotton effects and that in trans-fused lactones closed to C-8 the Cotton effect is positive, whereas the reverse situation prevails in lactones closed to C-6.[15] On this basis, acetylivalbatin (3) which displays a strongly negative Cotton effect at 255 nm, and therefore invalbatin itself, would be trans-fused lactones and invalbatin would be 26.

However, applicability of the rule to ivalbatin is suspect due to our ambiguous results[13] with parthemollin (24) which exhibited a negative Cotton effect indicative of a trans-fused lactone ring, although application of the Hudson–Klyne rule suggested cis fusion.[16]

The CD curves of acetylivalbatin (3), parthemollin (24), and ivambrin (25)[18] are compared in Figure 2.



The similarity is striking, each displaying a hump near 242 nm. Subtraction of the curve of 25 from the curve of 24 gives a good minimum at 287 nm (θ −1730) which can be ascribed to the Cotton effect of the ketone group present in 24, but not in 25. This suggests that the curve of 24 is a composite of a relatively weak negative Cotton effect near 290 nm (ketone) superimposed on a stronger negative Cotton effect near 250 nm (n,π^* transition of conjugated lactone) which in turn is superimposed on strongly negative Cotton effects due to the π,π^* transitions. The very similar curve of 3, slightly modified by the presence of a much weaker ketone Cotton effect as expected,[15] indicates that the fusion of the lactone ring in ivalbatin and parthemollin is the same, although the configuration at C-6 remains in doubt.

Experimental Section[19]

Isolation of Ivalbatin.—*Iva dealbata* Gray was collected by Dr. Norlan C. Henderson on Aug 14 and 15, 1967, along Texas Ranch Road 2317 just south of the intersection with US 62-180 in Cornudas, Hudspeth County, Tex. In the usual manner[2] 160 lb of powdered plant (above-ground part) was extracted with chloroform to give 1500 g of crude gum.

In a typical run, 157 g of crude gum was extracted with 500 ml of hot chloroform–benzene (2:1). The soluble part was chromatographed over 1500 g of silicic acid (Mallinckrodt 100 mesh), 800-ml fractions being collected in the following order: 1–6 (chloroform–benzene, 2:1), 7–18 (chloroform), 19–21 (chloroform–methanol, 40:1), 22–29 (chloroform–methanol, 100:3.0). Fractions were monitored by tlc. Fractions 11–20 contained ivalbatin; fractions 21–26 contained semicrystalline material which yielded 13.65 g of crude ivalbin after filtration. The mother liquor (7 g) was combined with fractions 11–20 and taken up in ethyl acetate. The material soluble in ethyl acetate (59 g) was dissolved in 400 ml of benzene, rechromatographed over 220 g of neutral alumina (Woelm activity III), and eluted with benzene, 500-ml fractions being collected. Fractions 2 and 3 eluted 42 g of green gum (crude ivalbatin). Fraction 4–7 eluted 2 g of pale yellow gum which showed only one spot by tlc and was pure ivalbatin (2): $[\alpha]^{24}D$ −84.04° (c 2.586, chloroform); $n^{20}D$ 1.5263; uv spectrum (ethanol) 210 nm (end absorption) (ϵ 13,400); ir bands (liquid) at 3450 (OH), 1755 (γ-lactone), 1705 (C=O), and 1655 (C=C); nmr signals of 1.19 ($HCCH_3$, d, J = 7.5), 2.16 ($COCH_3$, s), 3.40 (OH, disappeared on addition of D_2O), 3.65 (HCOH, broad d, J = 10), 5.20 (C=CH, s), 5.50 (HCO, dd, J = 10 and 2.5), 5.63 and 6.24 (exocyclic methylene, d, J = 2.5); bp 150° (0.001 mm) (dec). As ivalbatin easily polymerized on standing without solvent, a

(13) W. Herz, S. V. Bhat, and A. L. Hall, *J. Org. Chem.*, **35**, 1110 (1970).

(14) W. Stöcklin, T. G. Waddell, and T. G. Geissman, *Tetrahedron*, **26**, 2397 (1970).

(15) The CD curves of xanthinin (14) and xanthumin (15) are composites of four contributions: double bond, π,π^* of lactone, n,π^* of conjugated lactones (maximum near 250 nm), and ketone. Comparison of the CD curve of 3 (Figure 2 of present paper) with the curves of 14 and 15 (Figure 3 of ref 14) suggests that the ketone chromophore of xanthinin and xanthumin is positive. The ketone Cotton effect of ivalbatin, whatever its sign, would be expected to be considerably weaker because of the absence of a substituent on C-2.

(16) Such difficulties seem to arise most commonly when the lactone ring is closed to an allylic position,[17] a situation which can easily affect the chirality of the unsaturated lactone chromophore.

(17) W. Herz and S. V. Bhat, *J. Org. Chem.*, **37**, 906 (1972).

(18) H. Yoshioka, A. Higo, T. J. Mabry, W. Herz, and G. D. Anderson, *Phytochemistry*, **10**, 401 (1971).

(19) Melting points are uncorrected. Nmr spectra were determined on a JNM-4H-100 spectrometer in $CDCl_3$ with TMS as internal standard. Coupling constants are expressed as hertz, s = singlet, d = doublet, t = triplet, q = quartet, sx = sextet, dd = double doublet, dt = doublet of triplet, and m = multiplet. Tlc was carried out with silica gel G as adsorbent.

satisfactory elemental analysis could not be obtained. It was stored in a refrigerator as a solution in benzene.

Acetylivalbatin (3).—A 44-g sample of ivalbatin (fractions 2–7 of the second chromatography on alumina described above) was acetylated with 80 ml of Ac_2O and 140 ml of pyridine to give 36 g of crude acetate after washing with cold ether. Recrystallization from ethanol afforded 26.4 g of pure acetate **3** (16.8% from the extract of plant): mp 127–128°; $[\alpha]^{20}D$ −136° (c 1.99, chloroform); uv spectrum 209 nm (end absorption) (ε 13,800) (ethanol); ir bands (chloroform) at 1755 (γ-lactone), 1730, 1240, and 1015 (acetate), 1720 (C=O), and 1655 (C=C); nmr signals at 1.08 ($HCCH_3$, d, J = 7.5), 2.11 ($OCOCH_3$, s), 2.17 ($COCH_3$, s), 4.80 (HCOAc, dt, J = 10 and 2.5), 5.25 (C=CH, s), 5.47 (HCO, dd, J = 10 and 2.5), 5.54 and 6.27 $C=CH_2$, each d, J = 2.5); CD (methanol) λ 320 (θ 0), 300 (θ −268), 255 (θ −3561), 242 (θ −2934), 202 (θ −49,060), and 198 mμ (θ −47,100).

Anal. Calcd for $C_{17}H_{22}O_5$: C, 66.65; H, 7.24. Found: C, 66.59; H, 7.10.

The 2,4-dinitrophenylhydrazone was recrystallized from ethanol, mp 140–141°.

Anal. Calcd for $C_{23}H_{26}O_8N_4$: C, 56.78; H, 5.39; N, 11.52. Found: C, 56.63; H, 5.40; N, 11.66.

Ozonolysis of 3.—A solution of 500 mg of **3** in 25 ml of chloroform was ozonized at 0° for 40 min. After evaporation of the solvent *in vacuo*, the ozonide was decomposed with water. The reaction mixture was steam-distilled into a chilled saturated aqueous solution of dimedone to afford the dimedone derivative of formaldehyde (110 mg, 23%), mp 188–189° (from methanol and water), undepressed on admixture with authentic material.

Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.83; H, 8.27. Found: C, 69.71; H, 8.28.

Reduction of 3 with Sodium Borohydride.—To a solution of 2.00 g of **3** in 20 ml of methanol was added with stirring 125 mg of $NaBH_4$ during 20 min at room temperature. Stirring was continued for 1.5 hr, the reaction mixture was acidified with 5 ml of 2 N H_2SO_4, diluted with 100 ml of water, and extracted with chloroform. The washed and dried extract was evaporated. The residual oil **4** (2.0 g) easily polymerized. It had ir bands (oil) at 3400 (OH), 1760 (γ-lactone), 1730, 1230, and 1020 (acetate and 1650 (C=C); nmr signals at 1.10 ($HCCH_3$, d, J = 7.5), 1.20 ($HCCH_3$, d, J = 7.5), 2.10 ($COCOCH_3$, s), 3.37 (COH, s), 3.80 (HCOH, sx, J = 6), 4.80 (HCOAc, dt, J = 10 and 2.5), 5.32 (HCO, m), and 5.40 (C=CH, broad s).

Acetate 5.—Acetylation of **4** with Ac_2O and pyridine immediately after evaporation of solvent gave crystalline acetate **5**: mp 129–131° (from ethanol and water); $[\alpha]^{22}D$ −54.1° (c 1.5, chloroform); uv spectrum (ethanol) 207 nm (end absorption) (ε 6800); ir bands (KBr) at 1760 (γ-lactone), 1725, 1230, and 1020 (acetate), and 1650 (C=C); nmr signals at 1.06 ($HCCH_3$, d, J = 7.5), 2.03 ($COCOCH_3$, s), 2.07 ($COCOCH_3$, s), 4.75 (HCOAc, dt, J = 10 and 2.5), 4.90 (HCOAc, sx, J = 7), and 5.38 (C=CH, and HCO, d, J = 2.5; 2 protons).

Anal. Calcd for $C_{19}H_{28}O_6$: C, 64.75; H, 8.01. Found: C, 64.58; H, 7.92.

Dihydroivalbatin Acetate (7).—To a solution of 1.86 g of alcohol **4** (obtained from 1.95 g of **3**) in 20 ml of acetone was added dropwise during 1 hr 2.1 ml of 8 N Jones reagent under cooling with an ice bath. After filtration, the filtrate was concentrated *in vacuo*, water was added, and the mixture was extracted with ether. The washed and dried extract was evaporated; the residue (1.56 g) crystallized on standing: mp 88–88.5° (from petroleum ether–ether); $[\alpha]^{22}D$ −108.5° (c 1.24, chloroform); uv spectrum 207 nm (end absorption) (ε 4400); ir bands (chloroform) at 1760 (γ-lactone), 1730, 1240, and 1015 (acetate), and 1650 (C=C); nmr signals at 1.10 ($HCCH_3$, m), 1.23 ($HCCH_3$, d, J = 7.5), 2.09 ($COCOCH_3$, s), 2.18 ($COCH_3$, s), 4.82 (HCOAc, m), 5.31 (C=CH, s), and 5.35 (HCO, overlap with vinyl proton).

Anal. Calcd for $C_{17}H_{24}O_5$: C, 66.21, H, 7.85. Found: C, 66.21; H, 7.89.

The 2,4-dinitrophenylhydrazone was recrystallized from ethanol–ethyl acetate.

Anal. Calcd for $C_{23}H_{28}O_8N_4$: C, 56.55; H, 5.78; N, 11.47. Found: C, 56.25; H, 5.84; N, 11.54.

Methanol Adduct 8.—To a solution of 500 mg of **3** in 25 ml of absolute methanol was added a solution of sodium methoxide–MeOH (prepared from 0.07 g of sodium and 5 ml of methanol). After 4 days in a refrigerator Dry Ice was added carefully, and the solvent was evaporated at room temperature *in vacuo*. The residue was dissolved in water, acidified with 2 N H_2SO_4, and extracted with chloroform. Evaporation of the washed and dried extract yielded a viscous oil (0.5 g): $n^{24}D$ 1.5107; $[\alpha]^{24}D$ −62.82° (c 0.5, chloroform); ir bands (chloroform) at 3450 (OH), 1750 (γ-lactone), 1705 (C=O), and 1645 (C=C); nmr signals at 1.13 ($HCCH_3$, d, J = 7.5), 2.11 ($CCOCH_3$, s), 2.28 (OH), 3.29 (OCH_3, s), 3.55 (HCOH, m), 3.59 (CH_2O, m), 5.15 (C=CH, s), and 5.34 (HCO, dd, J = 10 and 2.5).

The *p*-bromobenzoate was recrystallized from ethanol, mp 97° (from ethanol), $[\alpha]^{20}D$ −29.67° (c 0.728, chloroform).

Anal. Calcd for $C_{23}H_{27}O_3Br$: C, 57.63; H, 5.67; Br, 16.67. Found: C, 57.72; H, 5.87; Br, 16.79.

The acetate **9** was recrystallized from ethanol–water: mp 90–91°; $[\alpha]^{25}D$ −149.9° (c 0.926, chloroform); ir bands (KBr) at 1760 (γ-lactone), 1720, 1240, and 1025 (acetate), 1710 (C=O), and 1650 (C=C); nmr signals at 1.07 ($HCCH_3$, d, J = 7.5), 2.08 ($COCOCH_3$, s), 2.14 ($CCOCH_3$, s), 3.36 (OCH_3, s), 3.61 (CH_2OCH_3, octet, J = 5), 4.76 (HCOAc, dt, J = 10 and 3), 5.25 (C=CH, broad s), and 5.40 (HCO, dd, J = 8.5 and 3).

Anal. Calcd for $C_{18}H_{26}O_6$: C, 63.88; H, 7.74. Found: C, 63.93; H, 7.70.

The 2,4-dinitrophenylhydrazone was recrystallized from ethanol, mp 122–123°.

Anal. Calcd for $C_{24}H_{30}O_9N_4$: C, 55.59; H, 5.83; N, 10.81. Found: C, 55.67; H, 5.88; N, 10.80.

Catalytic Reduction of Acetate 9.—A solution of 750 mg of **9** in 50 ml of ethanol was reduced at atmosphere pressure with 210 mg of 10% Pd/C. Hydrogen uptake ceased after absorption of about 1 molar equiv of hydrogen. The gummy product was chromatographed over silicic acid to remove the less polar fraction (which showed no absorption in the lactone region of the ir spectrum) and afforded 110 mg of a mixture of diastereomeric (at C-1) dihydro derivatives of **9**. Vpc showed two partially resolved peaks at 2.5 and 2.7 min in the ratio of 1:2 (10% SE-30, 1 m, 250°). The ir spectrum (chloroform) exhibited bands at 1760 (γ-lactone), 1720, 1245, and 1015 (acetate), and 1715 (C=O). The nmr spectrum exhibited absorption for three protons at 0.85 ($HCCH_3$, d, J = 7.5) and 0.95 ($HCCH_3$, d, J = 7.5) in the ratio 2:1, 2.08 ($COCOCH_3$, s), 2.12 ($COCH_3$, s), 3.34 (OCH_3, s), 3.61 (CH_2O, m), 4.54 (HCO, m) and 4.84 (HCOAc, m). Although the material was homogeneous on tlc, a satisfactory elemental analysis could not be obtained.

Dehydration of 8. 1. With Methanesulfonyl Chloride and Pyridine.—A solution of 570 mg of **8** in 5 ml of pyridine and 1 ml of MsCl was heated at 70° for 2 hr. After addition of ice–water the reaction was extracted with chloroform. Evaporation of washed and dried extract afforded a red oil (420 mg) which was dissolved in benzene and purified by passing it through a column of 5 g of neutral alumina (activity III). Bulb-to-bulb distillation yielded 230 mg of diene **10**, bp 140–170° (0.01 mm).

2. *Via* the Tosylate.—To a solution of 980 mg of **8** (purified by chromatography over silicic acid) in 6 ml of pyridine was added 1 g of *p*-TsCl. After 2 days at room temperature and addition of ice–water, the mixture was extracted with chloroform. Evaporation of the washed and dried extract afforded 1.19 g of crude tosylate as a viscous oil which was dissolved in 20 ml of 2,6-lutidine and refluxed at 150° for 15 hr. The lutidine was evaporated *in vacuo*, water added to the residue, and the mixture extracted with chloroform. Evaporation of the washed and dried extract *in vacuo* afforded 530 mg of red oil which was dissolved in benzene and purified by chromatography over 10 g of alumina. Bulb-to-bulb distillation afforded 300 mg of diene **10**: bp 140–155° (0.01 mm); $n^{20}D$ 1.5192 (The material was homogeneous by vpc and tlc criteria. The mass spectrum showed a molecular ion peak at m/e 278; however, the carbon content of the elemental analysis was slightly outside theoretical limits); $[\alpha]^{18}D$ −3.57° (c 1.68, chloroform); ir bands (oil) at 1760 (γ-lactone, 1710 (C=O), 1635, and 1615 (C=C); uv spectrum (ethanol) 239 nm (ε 11,550); nmr signals at 1.75 (>C=CHCH$_3$, d, J = 7.5), 2.15 ($COCH_3$, s), 3.36 (OCH_3, s), 3.65 (CH_2O, d, J = 5), 5.03 (HCO, dd, J = 7.5 and 2.5), 5.46 (C=CH, d, J = 2.5), and 5.86 (>C=CHCH$_3$, q, J = 7.5).

Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04, H, 7.97. Found: C, 68.45; H, 7.91.

Ozonolysis of 10.—A solution of 850 mg of **10** in 20 ml of chloroform was ozonized at 0° for 1 hr. The solvent was evaporated *in vacuo* at room temperature. The residue was mixed with 50 ml of water and steam-distilled directly into a chilled 50% aqueous ethanolic solution of 1 g of dimedone. After standing, there precipitated 275 mg of the dimedone derivative

of acetaldehyde. Chromatography of a solution of the precipitate in benzene over 3 g of silica gel yielded 120 mg of adduct, mp 139–140° (from ethanol and water), which was identical with an authentic sample by mixture melting point, ir, and nmr spectrum.

Anal. Calcd for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55. Found: C, 70.50; H, 8.52.

Dehydroivalbin (16).—Oxidation of 2.08 g of ivalbin with MnO_2 and purification of the product by chromatography over silicic acid[2] gave 0.8 g of **16** as an oil, $n^{22}D$ 1.5244, $[\alpha]^{23}D$ −44.2° (*c* 1.11, chloroform).

Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 67.93; H, 7.73.

4-Acetylivalbin (17) and 2-Acetylivalbin (18).—A solution of 240 mg of dehydroivalbin acetate[2] in 5 ml of methanol was reduced with 20 mg of $NaBH_4$ at 0° for 20 min. The reaction mixture was acidified with 1 *N* H_2SO_4, diluted with water, and extracted with chloroform. The washed and dried extract was evaporated. When the residual oil was purified by chromatography over silicic acid, 160 mg of homogeneous material as determined by tlc was obtained as an oil: $n^{27}D$ 1.5045; $[\alpha]^{19}D$ −33.85° (*c* 0.774, chloroform). The nmr spectrum displayed absorptions totaling one proton at 3.84 (HC_4OH, m), and 4.13 HC_2OH, t, J = 7.5) in the ratio 1:2, totaling one proton at 4.93 (HC_4OAc, sx, J = 7.5) and 5.33 (HC_2OAc, t, J = 7.5) in the ratio 2:1, and totaling one proton at 5.7–6.0 (C=CH, m). On the basis of these data, the reduction product was a mixture of 4-acetylivalbin (**17**) and 2-acetylivalbin (**18**) in the ratio 2:1.

Anal. Calcd for $C_{17}H_{24}O_5$: C, 66.21; H, 7.85. Found: C, 65.91; H, 7.67.

Acetylation of the mixture of **17** and **18** with Ac_2O and pyridine afforded ivalbin diacetate, mp 106–107° (from ethanol and water), $[\alpha]^{26}D$ −47.1° (*c* 0.9, chloroform).

Anal. Calcd for $C_{19}H_{26}O_6$: C, 65.12; H, 7.48. Found: C, 64.93; H, 7.51.

Dehydrodihydroivalbin (20).—Oxidation of 2.4 g of dihydroivalbin with manganese dioxide and chromatography over silicic acid, as described previously,[2] gave 569 mg of **20** as an oil, $n^{24}D$ 1.5207, $[\alpha]^{23}D$ −26.56° (*c* 0.24, chloroform). The material was homogeneous by tlc criteria, but the carbon content was slightly low.

Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33. Found: C, 67.13; H, 8.33.

4-Acetyldihydroivalbin (21) and 2-Acetyldihydroivalbin (22).—A solution of 3.5 mg of dihydrodehydroivalbin acetate[2] in methanol was treated with 38 mg of $NaBH_4$ at 0°. The product was worked up in the same manner as in the reduction of dehydroivalbin acetate. Purification by chromatography over silicic acid gave 280 mg of a homogeneous material, as determined by tlc, as an oil, $n^{24}D$ 1.4967, $[\alpha]^{24}D$ −15.7° (c 0.668, chloroform). The carbon content was slightly below theoretical limits. The nmr spectrum displayed absorptions totaling one proton at 3.82 (HC_4OH, m) and 4.12 (HC_2OH, t, J = 7.5) in the ratio 1:2, totaling one proton at 4.97 (HC_4OAc, sx, J = 7.5) and 5.32 (HC_2OAc, t, J = 7.5) in the ratio 2:1, and totaling one proton at 4.72 and 4.92 (C=CH, each q, J = 5) in the ratio 2:1. On the basis of these data, the product was a mixture of **21** and **22** in the ratio 2:1.

Anal. Calcd for $C_{17}H_{26}O_5$: C, 65.78; H, 8.44. Found: C, 65.29; H, 8.43.

Acetylation of the mixture of **21** and **22** with Ac_2O and pyridine afforded dihydroivalbin diacetate, mp 88–89° (from ethanol and water), $[\alpha]^{23}D$ −33.8° (*c* 0.368, chloroform).

Anal. Calcd for $C_{19}H_{28}O_6$: C, 64.75; H, 8.01. Found: C, 64.79; H, 8.06.

Asymmetric Esterifications by the Horeau Method.—The purity of the α-phenylbutyric acid isolated from the esterification was checked by nmr spectroscopy. In all instances the esterification yield was estimated by nmr spectroscopy of the neutral extract and appeared to be practically quantitative.

A typical run for dehydroivalbin (**16**) follows. **16** (107.95 mg, 4.1×10^{-4} mol) was esterified with 365.4 mg (1.18×10^{-3} mol) of (±)-α-phenylbutyric anhydride in 4 ml of pyridine. The resultant mixture was worked up by the standard procedure.[20] The recovered α-phenylbutyric acid (yield 220.5 mg) showed $[\alpha]^{20}D$ −4.26° (*c* 4.41, benzene). A fully stereospecific esterification should give $[\alpha]^{20}D$ −20.25°. Therefore the optical yield was 21.04%.

The same procedure was applied to the other compounds.

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Registry No.—**2**, 37163-90-9; **3**, 37163-91-0; **3** DNP hydrazone, 37163-92-1; **4**, 37392-67-9; **5**, 37392-68-0; **7**, 37392-69-1; **7** DNP hydrazone, 37392-70-4; **8**, 37392-72-6; **8** *p*-bromobenzoate, 37392-71-5; **9**, 37392-73-7; **9** DNP hydrazone, 37413-06-2; **10**, 37392-74-8; **16**, 37163-93-2; **17**, 37163-94-3; **18**, 37163-95-4; **20**, 37392-75-9; **21**, 37392-76-0; **22**, 37392-77-1; ivalbin diacetate, 37163-96-5; dihydroivalbin diacetate, 7561-75-3.

Protection of Tyrosine in Solid-Phase Peptide Synthesis[1]

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N^{α}-*tert*-Butyloxycarbonyl-*O*-(*o*-bromobenzyloxycarbonyl)tyrosine has been synthesized and employed in the solid-phase peptide synthesis of the octapeptide Phe-Lys-Gln-Thr-Tyr-Ser-Lys-Phe, which occurs in the human growth hormone sequence. The new protecting group for tyrosine was found to be stable and gave no significant side product upon its removal in hydrogen fluoride.

In solid-phase peptide synthesis[2] benzyl protection of the phenolic hydroxyl group in tyrosine has generally been employed. This protection is known to be unsatisfactory since it is not only unstable under the acidic conditions required for the removal of N^{α}-Boc protection[3-5] but also yields a side product,[4,6] 3-benzyltyrosine,[4] when it is removed in hydrogen fluoride.[6] Modification of the tyrosine residue in HF has also been observed in solid-phase synthesis of tyrosine-containing peptides.[7]

We recently proposed use of the very stable Z(*o*-Br)[8] group for the protection of the side chain of lysine.[3] We have now successfully applied it for similar protection of tyrosine in the solid-phase synthesis of the octapeptide Phe-Lys-Gln-Thr-Tyr-Ser-Lys-Phe (1) corresponding to amino acid residues 138–145 in the human growth hormone molecule.[9,10] Evidence is presented that this protection is stable and gives no significant side product upon its removal in HF.

Quantitative data on the stabilities of protecting groups commonly used in solid-phase synthesis have been obtained on acetylated amides of amino acids with protected side-chain functions.[3] A comparable test was carried out with N^{α}-acetyl-*O*-Z(*o*-Br)tyrosinamide by treatment with 50% TFA in CH_2Cl_2 for 24 hr. As judged by tlc only 1% of the protection was lost as compared to standard benzyl protection where at least 50% is lost. The new protecting group was completely removed in HF in 10 min at 0° and only a single product was detected. Since the new protecting group forms a phenolic ester with tyrosine, the possibility of instability under basic conditions exists. Therefore, the acetylated amide was treated with 10% diisopropylethylamine in DMF for 24 hr; only about 5% of the protection was lost.

For use of the new protecting group in peptide synthesis N^{α}-Boc-O-Z(*o*-Br)Tyr was synthesized and isolated as its dicyclohexylamine salt. The compound was treated in HF and amino acid analysis showed a virtually quantitative yield (98%) of tyrosine. Octapeptide **1**, which has already been synthesized by solid-phase procedures,[5] was resynthesized with the following side-chain protecting groups: Z(*o*-Br) for Lys[3] and Tyr; Bzl for Ser and Thr.

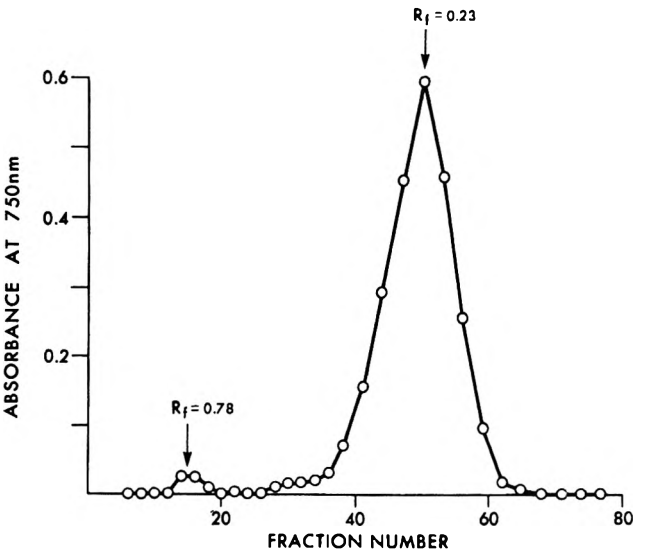

Figure 1.—Partition chromatography of octapeptide 1 on Sephadex G-25; absorbance by Folin–Lowry analysis.

The finished peptide was cleaved from the polymer and deprotected in HF[6,11] and purified as described previously.[5] The partition chromatography on Sephadex G-25 is shown in Figure 1. The R_f value of 0.23 is in close agreement with the value of 0.22 previously reported[5] for chromatography of **1** under these conditions. In the previous synthesis of **1**, either with Bzl protection of tyrosine or Bzl(*m*-Br) protection, significant amounts of side products were observed travelling faster than **1** in the partition chromatography.[12] In the present synthesis only a minute trace of peptide side product (R_f 0.78) could be detected. When peptide **1** from the partition chromatography was then subjected to chromatography on CM-cellulose[13] only one peak was obtained (Figure 2). The overall yield of highly purified octapeptide **1** was about 86% based on the starting Boc-Phe polymer, higher than the yields previously attained.

Experimental Section

Melting points were determined on a Fisher-Johns block and are uncorrected. Microanalyses were performed by the Microanalytical Laboratory, Department of Chemistry, University of

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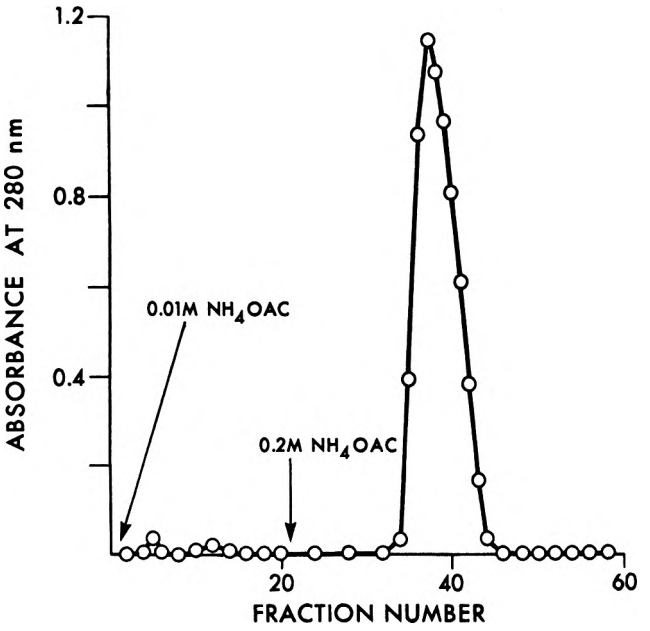

Figure 2.—CM-Cellulose chromatography of octapeptide 1.

California, Berkeley. Thin layer chromatography was run on silica gel in the following solvents: 1-butanol–acetic acid–water, 4:1:1 (BAW); 1-butanol–pyridine–acetic acid–water, 30:20:6:24 (BPAW). Thin layer data cited refer to single spot chromatograms unless otherwise noted.

***O*-(*o*-Bromobenzyloxycarbonyl)tyrosine.**—A solution of tyrosine (13.9 g, 77 mmol) in 78 ml of 2 *N* NaOH was mixed with a solution of $CuSO_4 \cdot 5H_2O$ (9.4 g) in 39 ml of water, heated to 60°, and then cooled to 24°. The pH was adjusted to about 5 with glacial HOAc; the solid was collected on a filter and washed with water and acetone. This solid was suspended in 1100 ml of 70% aqueous DMF, and *p*-nitrophenyl *o*-bromobenzyl carbonate[14] (41.5 g, 118 mmol) and $NaHCO_3$ (14.2 g) were added. The mixture was stirred for 20 hr and the product was collected on a filter and washed with 75% aqueous DMF, water, and acetone, yield 21.4 g of blue solid. This solid was stirred in 1 *N* HCl (300 ml) for 1 hr, filtered, and washed with 1 *N* HCl (250 ml), water, and acetone, yield 15.9 g (50%) of colorless solid. For analysis a sample was recrystallized from 50% HOAc: mp 203–208° dec; tlc (BAW) R_f 0.57 (ninhydrin and chlorine color developments); $[\alpha]^{24}D$ −4° (*c* 2, 80% HOAc).

Anal. Calcd for $C_{17}H_{16}NO_5Br \cdot H_2O$ (412.24): C, 49.53; H, 4.40; N, 3.40. Found: C, 49.49; H, 4.02; N, 3.82.

Dicyclohexylamine Salt of N^{α}-Boc-*O*-(*o*-bromobenzyloxycarbonyl)tyrosine.—The dimethyl sulfoxide method[15] was adapted for the preparation of the Boc derivative. Thus, *O*-Z(*o*-Br)-tyrosine (4.12 g, 10 mmol) was dissolved in dimethyl sulfoxide (50 ml) with 3.4 ml (20 mmol) of DIA, and Boc azide (2.8 ml, 20 mmol) was added. After 2 hr of stirring, an additional 1.7 ml of DIA was added. A solution was obtained from the initially gelatinous mixture and this was allowed to stand overnight. The following work-up was performed at 4°. Water (100 ml) was added to the solution, which was then washed with 100 ml of ether. The ether layer was back-extracted with 60 ml of 7% NaCl. The combined aqueous phases were mixed with 24 ml of saturated NaCl and extracted successively with 250-, 100-, and 100-ml portions of ethyl acetate. The combined ethyl acetate extracts were mixed with 150 ml of 12% NaCl and acidified to pH below 3 with 3 *N* HCl (5 ml). The ethyl acetate layer was washed with three 100-ml portions of 17% NaCl and then dried over anhydrous $MgSO_4$ at room temperature. Removal of drying agent and solvent gave 3.9 g of oil which was dissolved in ether (*ca.* 35 ml), cooled to 0°, mixed with dicyclohexylamine (1.6 ml), and diluted at 0° with petroleum ether (bp 30–60°) (30 ml). Crystallization at 4° gave 5.09 g (75% yield), mp 137–140°, $[\alpha]^{24}D$ +29.3° (*c* 2.04, absolute EtOH).

Anal. Calcd for $C_{34}H_{47}N_2O_7Br$ (675.67): C, 60.44; H, 7.01; N, 4.15. Found: C, 60.52; H, 7.08; N, 4.34.

For determination of optical purity a sample (407 mg) was treated in HF (15 ml) in the presence of anisole (1.5 ml) for 30 min at 0° and worked up as previously described.[5] Quantitative amino acid analysis for tyrosine gave a 98% yield. Determination of optical rotation gave $[\alpha]^{24}D$ −10.2° (c 2.13, 1 *N* HCl) based on the amount of tyrosine obtainable from the starting sample. The starting tyrosine gave $[\alpha]^{24}D$ −10.3° (*c* 2.07, 1 *N* HCl).

N^{α}-Acetyl-*O*-(*o*-bromobenzyloxycarbonyl)tyrosinamide.—This compound was prepared by procedures previously described,[3] mp 202–204°, tlc (BAW) R_f 0.80.

Anal. Calcd for $C_{19}H_{19}N_2O_5Br$ (435.28): C, 52.43; H, 4.40. Found: C, 52.36; H, 4.54.

Solid-Phase Peptide Synthesis Procedures.—For the esterification step[16] Boc-phenylalanine (1.33 g, 5.0 mmol) in 6.5 ml of methanol was mixed with 7.8 ml of 0.61 *N* tetramethylammonium hydroxide in methanol and evaporated *in vacuo*. The oil was reevaporated from dioxane and then methanol and dried *in vacuo* over P_2O_5 for 5 hr. The salt was treated with 2.52 g of chloromethylated polymer (0.57 mmol Cl/g) in DMF (25 ml) for 17 hr at 24°. The resin was filtered off and washed with DMF, DMF–H_2O (1:1), water, glacial HOAc, water, and EtOH, yield 3.03 g. A sample of the resin deprotected and neutralized gave an amine content[17] of 0.30 mmol/g. An aliquot (1.00 g) of Boc-Phe polymer was placed in a Beckman Model 990 peptide synthesizer and treated at 24° by the same schedule for synthesis as described previously.[5] Side-chain protecting groups were Bzl for Ser and Thr and Z(*o*-Br) for Lys and Tyr. Yield of protected peptide polymer was 1.54 g.

Phe-Lys-Gln-Thr-Tyr-Ser-Lys-Phe (1).—A portion (655 mg) of protected peptide resin was treated in HF and then submitted to gel filtration on Sephadex G-10 as described previously,[5] yield 157 mg. An aliquot (82 mg) of this material was submitted to partition chromatography[18] on a 2.21 × 59.6 cm Sephadex G-25 column in the solvent system 1-butanol–pyridine–0.1 *N* aqueous NH_4OH containing 0.1% HOAc (4:1:5) with collection of 5.9-ml fractions as shown in Figure 1. Isolation of material in fractions 38–60 gave 73 mg. This material was chromatographed on CM-cellulose[5] with collection of 10.2-ml fractions as shown in Figure 2. Isolation of material in fractions 35–43 gave 70 mg of octapeptide 1 (86% yield based on starting resin and assuming ϵ 1340 for tyrosine at 276 nm in 1 *N* HOAc): tlc (BPAW) R_f 0.30, identical with that of an authentic sample[5] of 1 (ninhydrin and Pauly reagents); $[\alpha]^{24}D$ −27° (*c* 0.5, 1 *N* HOAc) [lit.[5] $[\alpha]^{24}D$ −28° (*c* 0.5, 1 *N* HOAc)].

Paper electrophoresis in collidine acetate buffer (pH 6.9, 400 V, 4 hr) showed a single spot (ninhydrin and Pauly reagents) with R_f 0.55 relative to lysine, identical with that of an authentic sample[5] of 1. Amino acid analyses[19] of an acid hydrolysate and a leucine aminopeptidase digest (pH 8, 24 hr, 37°) gave $Lys_{1.9}$-$Thr_{1.6}Ser_{0.9}Glu_{1.0}Tyr_{1.0}Phe_{2.0}$ and $Lys_{1.9}(Thr + Gln + Ser)_{3.6}$-$Tyr_{1.0}Phe_{2.0}$, respectively.

Registry No.—1, 37440-42-9; *O*-(*o*-bromobenzyloxycarbonyl)tyrosine, 37440-25-8; tyrosine, 60-18-4; *p*-nitrophenyl *o*-bromobenzyl carbonate, 37440-43-0; dicyclohexylamine salt of N^{α}-Boc-*O*-(*o*-bromobenzyloxycarbonyl)tyrosine, 37440-44-1.

Acknowledgment.—We thank Mr. Richard L. Noble, Mr. W. F. Hain, and Mr. Kenway Hoey for their skilled technica lassistance.

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2,2'-Anhydropyrimidine Nucleosides. Novel Syntheses and Reactions

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A novel synthesis of 2,2'-anhydropyrimidine nucleosides is described. D-Arabinose and D-ribose react with cyanamide to yield the aminooxazoline derivatives **2** and **14**, respectively. The reactions of **2** with propiolonitrile, methyl propiolate, and dimethyl acetylenedicarboxylate yield the β-anhydronucleosides **4**, **8**, and **11**, respectively. Similarly, the reactions of **14** with the same acetylene derivatives yield the novel α-anhydronucleosides **16**, **18**, and **20**. The ring-opening reactions of certain of these anhydronucleosides with water and with other nucleophiles are described.

As a result of a series of investigations into the origins of nucleosides under primitive earth conditions, a new synthesis of certain pyrimidine anhydronucleosides was discovered. The preliminary results of these studies were described in the context of prebiological chemical evolution.[1]

We have continued with these studies and have developed suitable procedures for the preparation of both the α and β anomers of 2,2'-anhydrocytidine, 2,2'-anhydrouridine, and 2,2'-anhydroorotidine methyl ester. In the past some of these anhydronucleosides have only been available through tedious procedures that afford inadequate yields.[2,3] Recently, improved procedures have been described for the synthesis of the β anomers of 2,2'-anhydrocytidine[4] and 2,2'-anhydrouridine.[5]

We wish to describe simple, general procedures for the synthesis of anhydronucleosides and to emphasize the versatility of these compounds as intermediates in the synthesis of 2'-substituted 2'-deoxycytidines, α-ribosides, β-arabinosides, and other nucleoside analogs.

Experimental Section

General.—Melting points were taken in open capillaries in a Mel-Temp heating block and are uncorrected. Elemental microanalyses were performed by Midwest Microlab. Ultraviolet spectra were measured on a Unicam SP 800 recording spectrophotometer. Paper chromatography was performed by descending elution with the following solvent systems: A, *n*-butyl alcohol saturated with water; B, *n*-butyl alcohol–5 *N* acetic acid (2:1); and C, 95% ethanol–1 *M* ammonium acetate (pH 5.0) (7:3, with 0.001 *M* EDTA). Paper electrophoresis was carried out in Varsol-cooled tanks at 4000 V with the following buffer systems: D, 0.05 *N* formic acid buffered to pH 2.6 with ammonia; E, 0.05 *N* boric acid buffered to pH 8.5 with NaOH; and F, 0.03 *N* H_3PO_4 buffered to pH 7.1 with KOH. Whatman No. 3MM paper was used in every case.

2-Amino-β-D-arabinofurano[1',2':4,5]-2-oxazoline (2).—The synthesis and characterization of this compound was previously described.[1] Improved yields are obtained by the following modification. Concentrated ammonia solution (5.0 ml) and crystalline cyanamide (8.4 g, 0.20 mol) were added to a stirred slurry of D-arabinose (**1**, 15.0 g, 0.10 mol) in 50 ml of methanol. The mixture was stirred for 4 hr at 40–45° and then chilled in an ice bath. After filtering, washing with cold methanol, and air drying, the white powder weighed 14.1 g (81%) and melted at 175–176°. The pK_a in water was determined titrimetrically to be 6.52.

2-Amino-α-D-ribofurano[1',2':4,5]-2-oxazoline (14).—The synthesis and characterization of this compound has also been described.[1] The following method is more convenient for the synthesis of pure material, although the yield is lower. A slurry of D-ribose (**13**, 45.0 g, 0.30 mol) and cyanamide (25.0 g, 0.60 mol) in 50 ml of 1 *N* NH_4OH was swirled in a warm water bath until solution was essentially complete and the temperature was about 30°. After about 30 min at room temperature an exothermic crystallization commenced and was allowed to proceed for several minutes. The slurry of solids was heated in a 60° water bath for 30 min, then 100 ml of CH_3OH were added and the mixture was refrigerated overnight. The solids were filtered off, then washed with methanol and ether and finally dried under vacuum. The yield of free-flowing white powder was 34.2 g (65.5%), mp 197° dec. The pK_a value in water was determined titrimetrically to be 6.54.

Reaction of Cyanamide with Other Sugars.—The sugars (0.10 *M* each) were heated at 60° in aqueous solution containing NH_3 (0.10 *M*) and cyanamide (0.20 *M*). Aliquots were withdrawn periodically for analysis by chromatography in system A. Sugars were detected by development with aniline phthalate at 100°, and the oxazoline products were detected by the appearance of a characteristic blue color after spraying with dibromoquinone-*N*-chloroimide in ethanol at room temperature. The sugars used, and their half-lives in these reactions, were glycolaldehyde, glyceraldehyde, erythrose (1–2 min), ribose, arabinose (10–40 min), glucose, fructose, and lactose (3 hr). All of the products (presumably oxazoline derivatives) travelled with R_f values in the range 0.17–0.29 except for that from lactose, for which the R_f was 0.02 (system A).

2,2'-Anhydro-1-β-D-arabinofuranosylcytosine Salts (4a–c).—A suspension of **2** (6.96 g, 0.040 mol) in 20 ml of *N*,*N*-dimethylacetamide was stirred in a water bath at *ca.* 15° and propiolonitrile (2.50 ml, 0.040 mol) was added. After about 30 min the reaction was complete, giving a darkly colored but clear solution in which the major component is thought to be the cyanovinyl adduct **3**.[1] Solutions of **3** prepared in this way were found to survive unchanged after storage at room temperature for several weeks or heating at 60° for several hours. No attempts were made to isolate adduct **3**. In aqueous ammonia it is rapidly converted to β-arabinosylcytosine; in water the conversion is slower and 2,2'-anhydrocytidine is detectable as an intermediate.[1]

The acetate salt **4** was obtained by adding 4.6 ml of glacial acetic acid and 30 ml of water to the reaction mixture containing **3**. After 30 min at room temperature the solution was evaporated under high vacuum to a syrupy residue. The residue was dissolved in 100 ml of boiling methanol and diluted with 200 ml of warm ethyl acetate, whereupon crystallization soon occurred. The chilled mixture was filtered and the crystals were washed with ethyl acetate. In several preparations the yield of **4a** varied between 10.3 and 10.8 g (85–89%), and the product melted at 175–176°. Recrystallization from methanol–ethyl acetate yielded 9.4–10.0 g (78–83%): mp 178–179° (lit.[6] mp 190–192° dec, with sintering at 165–185°); uv (H_2O) λ_{max} 231.5, 262.5 nm (ε 9780, 10,800) [lit.[2] for the HCl salt (pH 1–7) λ_{max} 231, 262 nm (ε 9400, 10,600)].

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Anal. Calcd for $C_{11}H_{15}N_3O_6.0.5CH_3OH$: C, 45.84; H, 5.68; N, 13.94. Found: C, 45.70; H, 6.04; N, 14.17.

The hydrofluoride salt **4** was obtained by adding 2.8 ml of 48% HF solution and 30 ml of H_2O to the reaction mixture containing **3**. After 2 hr at room temperature 300 ml of cold dioxane was added to yield 7.85 g (80%) of crystalline **4b**: mp 186–188°; uv (H_2O) λ_{max} 232, 262 nm (ϵ 9760, 10,600); λ_{min} 244 nm (ϵ 7080).

Anal. Calcd for $C_9H_{12}N_3O_4F\cdot 0.5H_2O$: C, 42.55; H, 5.15; N, 16.51; F, 7.48. Found: C, 41.92; H, 5.24; N, 15.99; F, 8.79. The analytical values indicate the presence of additional fluorine and correspond most closely to the average composition $C_9H_{12}N_3O_4F\cdot 0.5H_2O\cdot 0.2HF$.

The phosphate salt **4c** was obtained by the addition of 1 molar equiv of H_3PO_4 to a solution of **4a** in water. After removal of water and acetic acid under high vacuum, a hygroscopic gum was obtained which was further dried by the repeated addition and evaporation of anhydrous ethanol, uv (H_2O) λ_{max} 232, 263 nm (ϵ 9600, 10,500), λ_{min} 244 nm (ϵ 7000).

Both **4b** and **4c** were chromatographically homogeneous (systems A and B) and travelled with the same R_f values as those of **4a**. Further purifications were not attempted.

2,2′-Anhydro-1-β-D-arabinofuranosyluracil (8) and 2-Imino-1-carbomethoxyvinyl-β-D-arabinofurano[1′,2′:4,5]oxazolidine (9).—A suspension of **2** (6.96 g, 0.040 mol) in 100 ml of absolute ethanol and methyl propiolate (10.1 ml, 0.12 mol) was heated under reflux with magnetic stirring for 1 hr. The suspension was chilled in an ice bath and filtered. The crystals of **8** were washed with cold ethanol and air dried. The product melts at 242–243° (lit.[5] mp 238–240°) and the yields in several preparations varied between 6.0 and 6.4 g (66–71%): uv (H_2O) λ_{max} 223, 250 nm (ϵ 8400, 8200); λ_{min} 235 nm (ϵ 6600) (lit.[3] λ_{max} 222, 250 nm; λ_{min} 239 nm).

The filtrate was evaporated to dryness and the residual syrup was dissolved in boiling acetonitrile. A small amount of **8** was filtered and the filtrate was refrigerated. The crystalline precipitate of the open-chain adduct **9** was filtered, washed with cold acetonitrile, and air dried. A yield of 1.85 g (18%) was obtained: mp 167–168°; uv (H_2O) pH 1, λ_{max} 248 nm (ϵ 17,500), λ_{min} 213 nm (ϵ 5000); pH 12, λ_{max} 264 nm (ϵ 18,000), λ_{min} 227 nm (ϵ 4300); nmr (DMSO-d_6, TMS internal standard) δ 7.64 (doublet, 1, α-vinyl H), 5.43 (doublet, 1, β-vinyl H, $J_{\alpha,\beta}$ = 3.6 Hz), 6.66 (singlet, 1, vinyl NH), 3.63 (singlet, 3, $-OCH_3$).

Isomerization of 9.—A 0.10 *M* solution of **9** in ethanol was heated at 100° for 1 hr in a tightly stoppered tube. The uv spectrum of a diluted aliquot showed that no change had taken place. Heating in the presence of charcoal, palladium black, or iodine also failed to produce any change in the spectrum, although with iodine there was a decrease in absorbance and a discharging of the violet color.

A 1.0×10^{-4} *M* solution of **9** in water was placed in a 10-mm quartz cell and irradiated with 2537-Å light (Rayonet photochemical reactor). The uv spectrum of the solution was scanned periodically. The spectrum changed rapidly to that of the anhydronucleoside **8**, and was followed by a slower decrease in absorbance due to photodestruction. The same photodestruction process was observed when a 1.0×10^{-4} *M* solution of **8** was irradiated under the same conditions.

2,2′-Anhydro-1-β-D-arabinofuranosylorotic Acid Methyl Ester (11).—A mixture of **2** (3.48 g, 0.020 mol) and dimethyl acetylenedicarboxylate (5.68 g 0.040 mol) in 50 ml of absolute ethanol was heated under reflux for 1 hr. The clear amber solution was chilled in an ice bath and the precipitate of cream-colored needles was filtered off, washed with ethanol, and air dried. The yield of solid was 3.95 g (69%), mp 228–230°. Recrystallization from hot water yielded 3.10 g (55%) of fine white needles: mp 233–233.3°; uv (H_2O) pH 1.5, λ_{max} 276 nm (ϵ 7100), λ_{min} 245 nm (ϵ 3400); pH 13, λ_{max} 267 nm (ϵ 7100), λ_{min} 246 nm (ϵ 5600).

Anal. Calcd for $C_{11}H_{12}N_2O_7$: C, 46.50; H, 4.26; N, 9.85. Found: C, 46.54; H, 4.30; N, 9.93.

Compound **11** was hydrolyzed in 0.1 *N* HCl at 100° for 3 days. Paper chromatography in several chromatographic systems including A–C confirmed the presence of orotic acid and arabinose as major products.

2,2′-Anhydro-1-α-D-ribofuranosylcytosine Hydrochloride (16).—A suspension of **14** (20.88 g, 0.12 mol) in 200 ml of *N*,*N*-dimethylacetamide was stirred magnetically in an ice bath, and propiolonitrile (7.50 ml, 0.12 mol) was added. After about 1 hr the ice bath was removed and the solution was stirred for 2 days at room temperature. The dark solution (still containing some undissolved solids) was stirred in an ice bath while 30 ml of glacial acetic acid and 100 ml of water were added. The solution was stirred at *ca.* 4° for 4 days and then evaporated to a thick syrup under high vacuum. The syrup was taken up in water and applied to a column of 400 g of Dowex 50 (H^+) ion exchange resin. The column was eluted with hydrochloric acid in a step-gradient (1 *M*, 2 *M*, 3 *M*) and the band of **16** was located in the 3 *M* HCl eluates by paper chromatography. The combined fractions were evaporated to dryness and the solid was recrystallized from ethanol–water, yielding 16.9 g (51%) of **16** as off-white crystals, mp 235° dec, uv (H_2O) λ_{max} 232 nm (ϵ 9700), 261 (10,800).

Anal. Calcd for $C_9H_{12}N_3O_4Cl\cdot {}^1/_2H_2O$: C, 39.93; H, 4.84; N, 15.52. Found: C, 39.82; H, 5.17; N, 14.97.

2,2′-Anhydro-1-α-D-ribofuranosyluracil (18).—The synthesis and characterization of this compound was described earlier.[1] The following is an improved procedure: **14** (61.7 g, 0.354 mol) and methyl propiolate (59.4 g, 0.708 mol) in 800 ml of water were heated under reflux for 30 min. The clear solution was evaporated to dryness and the residue was extracted with 400 ml of boiling methanol. The clear filtrate was refrigerated for 2 days and yielded 21.4 g (27%) of **18** as pale yellow crystals: mp 223–225°; uv (H_2O) λ_{max} 225, 250 nm (ϵ 8600, 8400); λ_{min} 235 nm (ϵ 7100).

2,2′-Anhydro-1-α-D-ribofuranosylorotic Acid Methyl Ester (20).—A suspension of **14** (25.0 g, 0.143 mol) in dimethyl acetylenedicarboxylate (40.6 g, 0.286 mol) and 300 ml of methanol was heated under reflux for 1 hr. Undissolved solids were removed by filtration and the clear, darkly colored filtrate was refrigerated. The crystals of **20** were filtered off and dried under high vacuum, yielding 21.6 g (52%), mp 230–232°, uv (H_2O) λ_{max} 267 nm (ϵ 6900), λ_{min} 245 nm (ϵ 3200).

Anal. Calcd for $C_{11}H_{12}N_2O_7$: C, 46.48; H, 4.25; N, 9.85. Found: C, 46.26; H, 4.16; N, 9.76.

Compound **20** was hydrolyzed in acid and analyzed in the same way as described for **11**. The presence of orotic acid and ribose as major products was confirmed.

1-β-D-Arabinofuranosylcytosine (5).—The synthesis of the cyanovinyl adduct **3** was carried out as described above for the synthesis of **4a**, but using 21.6 g of **2**, 9.8 ml of propiolonitrile, and 100 ml of *N*,*N*-dimethylacetamide. Water (50 ml) was added to the clear, dark solution, which was then heated at *ca.* 50° for 1 hr. The uv spectrum of a diluted aliquot indicated that the conversion to **5** was complete. The solution was evaporated under vacuum to a thick red oil, which was then taken up in 200 ml of hot 95% ethanol and refrigerated overnight. The crystalline product was filtered off, washed with ethanol and ether, and then air dried. The yield of **5** was 29.7 g (81%). This product was identical with authentic 1-β-D-arabinofuranosylcytosine (Upjohn Co.) in all respects (melting point, uv, ir, ORD, chromatography).

The synthesis of the HCl salt of **5** in a similar fashion was previously reported.[1] Yields of 82–84% were obtained. **5** is also obtained in high yield by the hydrolysis of **4** in warm aqueous ammonia, followed by evaporation of the solution to dryness and recrystallization of the residue from small volumes of hot water.

1-β-D-Arabinofuranosyluracil (10).—A solution of **8** (5.0 g, 0.022 mol) in 10 ml of 1 *N* HCl was heated at 100° for 40 min and then evaporated to dryness. The residue was taken up in water, adjusted to pH 9 with aqueous NH_3, and reevaporated to dryness. The residue was crystallized from a minimum volume of boiling water, and yielded 4.15 g (77%) of **10**, mp 215–216° (lit.[3] mp 220–221°). A second crop of 0.47 g was obtained by concentration of the filtrates (overall yield 86%): uv (H_2O) pH 2, λ_{max} 263 nm (ϵ 10500), λ_{min} 231 nm (ϵ 2300); pH 11, λ_{max} 262.5 nm (ϵ 8000), λ_{min} 242 nm (ϵ 5200) [lit.[3] (H_2O) λ_{max} 262.5–263.5 nm (ϵ 10,500), λ_{min} 230–231 nm (ϵ 2000)].

This material is chromatographically homogeneous in several systems, and travels with the same R_f as that of authentic 1-β-D-arabinofuranosyluracil.

1-α-D-Ribofuranosylcytosine (17).—The cyanovinyl adduct **15** was synthesized as previously described for the preparation of anhydronucleoside **16**, but using 15.1 g (0.086 mol) of **14** and 5.4 ml (0.086 mol) of propiolonitrile in 100 ml of *N*,*N*-dimethylacetamide. The dark solution (which contains undissolved solids) is presumed to contain the adduct **15** as a major component, in analogy to the synthesis of the β analog **3**. Water (100 ml) was added to the mixture and stirring was continued for 3 days at room temperature. Undissolved solids (2.85 g) were removed by filtration and the filtrate was evaporated to a dark syrup under high vacuum. The syrup was dissolved in 50 ml of

hot ethanol and then refrigerated. The dark-colored crystals which formed (12.3 g) were dissolved in 20 ml of hot water, and then treated with Norit A and filtered. The filtrate was diluted with 80 ml of hot isopropyl alcohol, and the clear supernatant was decanted from some dark gums and refrigerated. The crystals which formed were again recrystallized from water–isopropyl alcohol and yielded, after air drying, 7.50 g (35%) of **17** as granular crystals. The methods used in the identification of this compounds were previously discussed.[1]

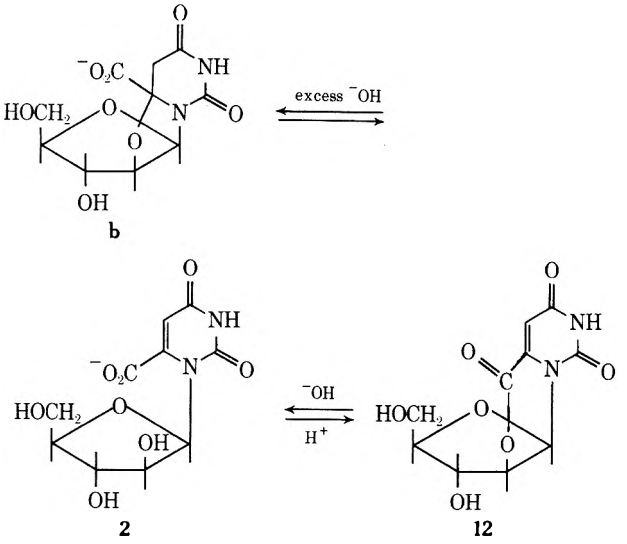
Compound **17** could also be prepared in high yield by the hydrolysis of **16** in aqueous ammonia, in the same way as described for the conversion of **4** to **5**.

1-α-D-Ribofuranosyluracil (19).—A solution of **18** (10.0 g, 0.044 mol) in 22 ml of 0.2 *N* HCl was heated under reflux for 2 hr, and the pale yellow solution was then evaporated to dryness under vacuum. The viscous residue was taken up in water and adjusted to a pH of 6 by the addition of Dowex 1X8 (OH^-) resin. The mixture was filtered and the resin was rinsed with water. The combined filtrates were freeze dried and yielded **19** as a hygroscopic white powder in essentially quantitative yield. The identification of this compound was previously described.[1]

1-β-D-Arabinofuranosylorotic Acid 2′,6-Lactone (12).—A suspension of 3.0 g of **11** in 50 ml of water was heated under reflux for 1 hr. Refrigeration of the clear solution at 4° produced a stiff gel which slowly crystallized. After 2 days the white precipitate of **12** was filtered off, washed with a little water, and dried under vacuum. The yield was 2.3 g (81%). An analytical sample was obtained by crystallization from boiling water: mp 248–250°; ir (KBr disc) 1735 cm^{-1} (lactone C=O); uv (H_2O) λ_{max} 290 nm (ε 7700), λ_{min} 245 nm (ε 2000).

Anal. Calcd for $C_{10}H_{10}N_2O_7$: C, 44.45; H, 3.73; N, 10.36. Found: C, 44.50; H, 3.92; N, 10.19.

On standing in water the uv spectrum of **12** slowly shifts to λ_{max} 273 nm (ε 8200), λ_{min} 236 nm (ε 2700), presumably the result of hydrolysis to 1-β-D-arabinofuranosylorotate. Upon acidification with HCl lactonization occurs and the original spectrum is regenerated. In strong alkali an additional reaction occurs which results in a partial loss of absorbance. We believe that this is due to the establishment of an equilibrium between 1-β-D-arabinofuranosylorotate and 2′,6-anhydro-1-β-D-arabinofuranosyl-5,6-dihydroorotate. Similar additions have been reported previously.[7]



1-α-D-Ribofuranosylorotic Acid 2′,6-Lactone (21).—This compound was prepared by the hydrolysis of ester **20**, in the same manner as described for the synthesis of the β analog **12** from **11**. White platelets, mp 268–269°, were obtained, uv (H_2O) λ_{max} 291 nm (ε 7600), λ_{min} 247 nm (ε 2200).

Anal. Calcd for $C_{10}H_{10}N_2O_7$: C, 44.45; H, 3.73; N, 10.36. Found: C, 43.13; H, 3.33; N, 9.95.

The aqueous solution chemistry of this compound is essentially the same as that described above for the β analog **12**.

2′(3′)-O-Acetylcytidine (6a).—A suspension of **4a** (1.0 g, 0.035 mol) in 35 ml of anhydrous *N*,*N*-dimethylformamide was heated in an oil bath at 100° for 2.5 hr. An aliquot of the clear brown solution was chromatographed in system A. The chromatogram showed a major spot of **6a** (*ca.* 60% yield, estimated by visual comparison of the spot intensity with those of standards of known concentration; R_f 0.29), smaller amounts of starting material **4a** (R_f 0.09), cytidine (R_f 0.14), 1-β-D-arabinofuranosylcytosine (**17**, R_f 0.18), and traces of other unidentified products. The solution was evaporated under vacuum to an oil, which was then applied to a 4 × 35 cm column of silica gel. The column was eluted with $CHCl_3$–CH_3OH (95:5) and the eluates were monitored by chromatography in system A. The fractions containing **6a** (contaminated by cytidine) were pooled and evaporated, yielding a yellow oil which could not be made to crystallize. An aliquot was further purified by tlc on silica gel plates with $CHCl_3$–CH_3OH (88:15), on which **6a** travelled with an R_f of 0.38. The band was eluted with methanol, and **6a** was crystallized after concentration: mp 118–122°; uv (H_2O) pH 2, λ_{max} 278.5 nm (ε 11,400), λ_{min} 252.5 nm (ε 1900); pH 10, λ_{max} 270 nm (ε 7700), λ_{min} 252.5 nm (ε 6300); nmr (D_2O, TMS internal standard) δ 2.19 (s, 3, acetyl CH_3). The uv spectrum, as well as the remaining features of the nmr spectrum, were consistent with the proposed structure.

Anal. Calcd for $C_{11}H_{15}N_3O_6$: C, 45.37; H, 5.42; N, 15.59. Found: C, 45.55; H, 5.38; N, 15.90.

The compound did not migrate in system E, which establishes that the acetyl group is on the 2′ and/or 3′ oxygen. Alkaline hydrolysis (1 *N* NH_4OH, 100°, 15 min) yielded cytidine quantitatively which was identified by the coincidence of its R_f with that of authentic cytidine in the chromatographic systems A and E.

2′-Fluoro-2′-deoxy-β-D-ribofuranosylcytosine (6b).—A suspension of **4b** (21.3 g, 0.086 mol) in 860 ml of anhydrous *N*,*N*-dimethylformamide was heated at 100° with magnetic stirring for 24 hr. An aliquot of the dark solution was chromatogrammed in system A, in which a major spot of R_f 0.18 corresponded to 1-β-D-arabinofuranosylcytosine (**5**) and two others corresponded to starting material **4b** (R_f 0.09) and cytidine (R_f 0.14). Product **6b** travelled with an R_f of 0.27 and its yield was estimated at 30% by the uv spectrum of the eluted spot. The reaction mixture was concentrated under high vacuum at 45° to a dark syrup which was then applied to a column of Dowex 1X8 (OH^-) ion exchange resin and eluted with methanol–water (25:75). The first major uv-absorbing band contained **6b**, and the combined fractions were concentrated under vacuum at room temperature until crystallization began. A yield of 4.26 g (16%, mp 161–163°) of **6b** was obtained after filtration and air drying. The elemental composition of this material was found to correspond approximately to that of a trihydrate.

Material dried at 60° under high vacuum for 2 days had the following properties: uv (H_2O) pH 1, λ_{max} 278, 212 nm (ε 12,900, 9900), λ_{min} 241 nm (ε 2300); pH 12, λ_{max} 272, 230 nm (ε 9100, 8300), λ_{min} 251 nm (ε 6400); mp 173° (with much prior shrinking; measured in a preheated block) [lit.[6] uv (H_2O) pH 1, λ_{max} 277, 211 nm (ε 12,910, 9550), λ_{min} 239 nm (ε 1840); pH 14, λ_{max} 271 nm (ε 9110), λ_{min} 248 nm (ε 5730); mp 171–173° with prior shrinking]; mass spectrum (70 eV), *m/e* 20 (HF^+). The mass spectrum of deoxycytidine does not show significant ion intensity at *m/e* 20.

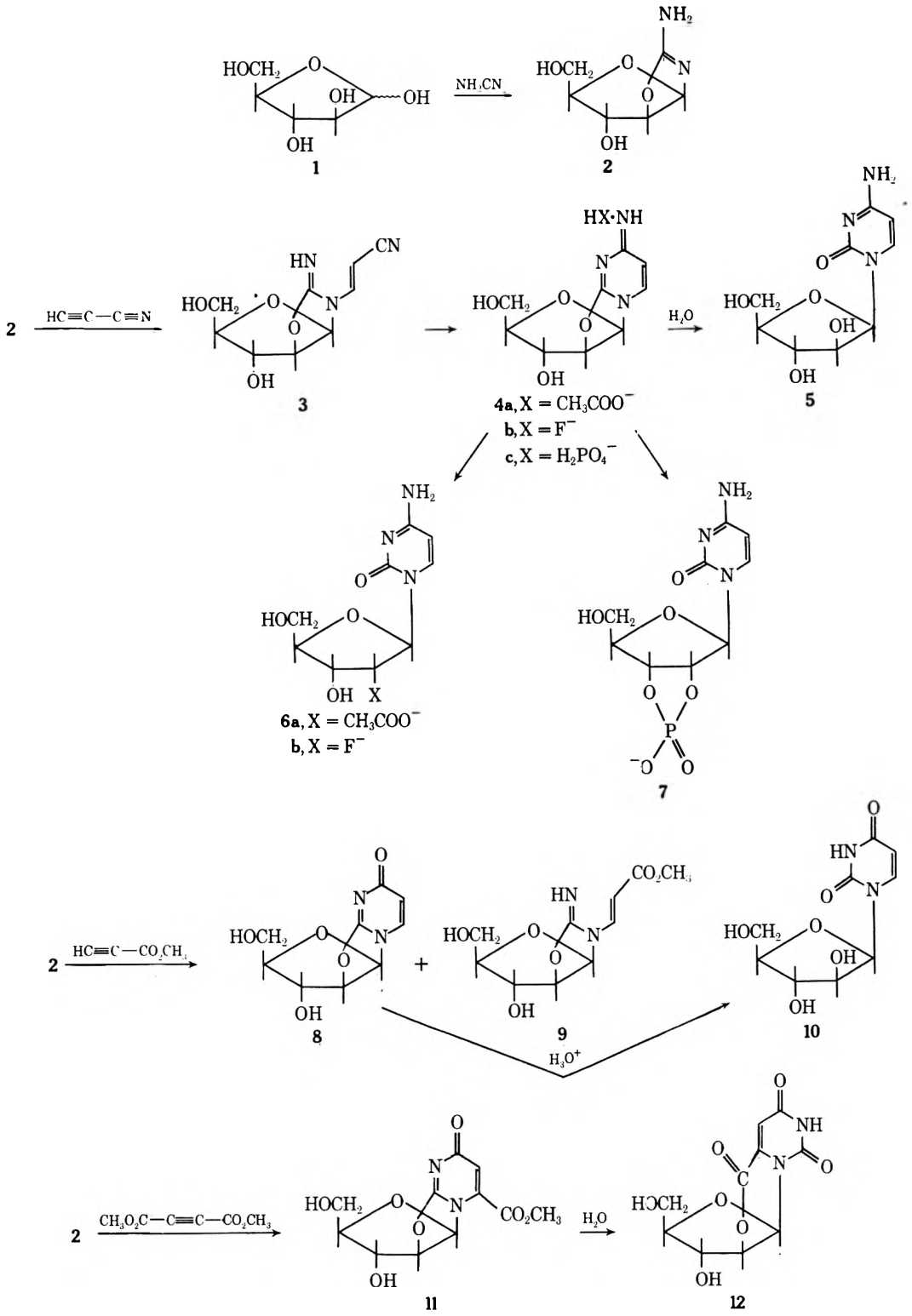
The synthesis of **6b** by this procedure generally ceases before all of **4b** is consumed, and further heating does not increase the yield. Anhydrous conditions appear to be necessary for optimum yields.

Preliminary attempts to synthesize **6b** by heating **4a** with HF in dioxane at 110° resulted only in recovery of **4a**.

Cytidine 2′,3′-Cyclic Phosphate (7).—A suspension of **4c** (14.6 mg, 0.045 mmol) in 0.45 ml of anhydrous hexamethylphosphoric triamide (HMPT) was heated at 100° for 21 hr. Aliquots of the resulting light brown solution were chromatogrammed in several systems (B–F) alongside authentic standards, and yields were estimated from the uv spectra of eluted spots. The major products present were cytidine 2′,3′-cyclic phosphate (**7**, 26%), unreacted starting material **4c** (44%), and 1-β-D-arabinofuranosylcytosine (**5**, 30%).

The following control reactions were carried out and analyzed in the same way. Cytidine and 1 molar equiv of H_3PO_4 produced a mixture of 5′- and 2′,3′-cyclic monophosphates in a combined yield of 5% or less. Cytidine 5′-monophosphoric acid was recovered unchanged and did not yield any 2′(3′)-monophosphate or 2′,3′-cyclic phosphate. Cytidine 2′(3′)-monophosphoric acid was converted in high yield (>50%) to the 2′,3′-cyclic phosphate.

(7) W. J. Wechter and R. C. Kelly, *Collect. Czech. Chem. Commun.*, **35**, 1991 (1970); B. A. Otter and J. J. Fox, *J. Amer. Chem. Soc.*, **89**, 3663 (1967).



Results

The condensations of D-arabinose (**1**) and of D-ribose (**13**) with cyanamide yield the novel aminooxazoline derivatives **2** and **14**, respectively. The compounds are obtained in the furanose ring forms, and the configuration of the heterocyclic ring in each case is uniquely specified by the orientation of the 2′-hydroxyl group, *i.e.*, β in **2** and α in **14**.

Preliminary results suggest that analogous aminooxazolines might be formed from a variety of other sugars. We have not yet confirmed this, however, by isolating and characterizing the products.

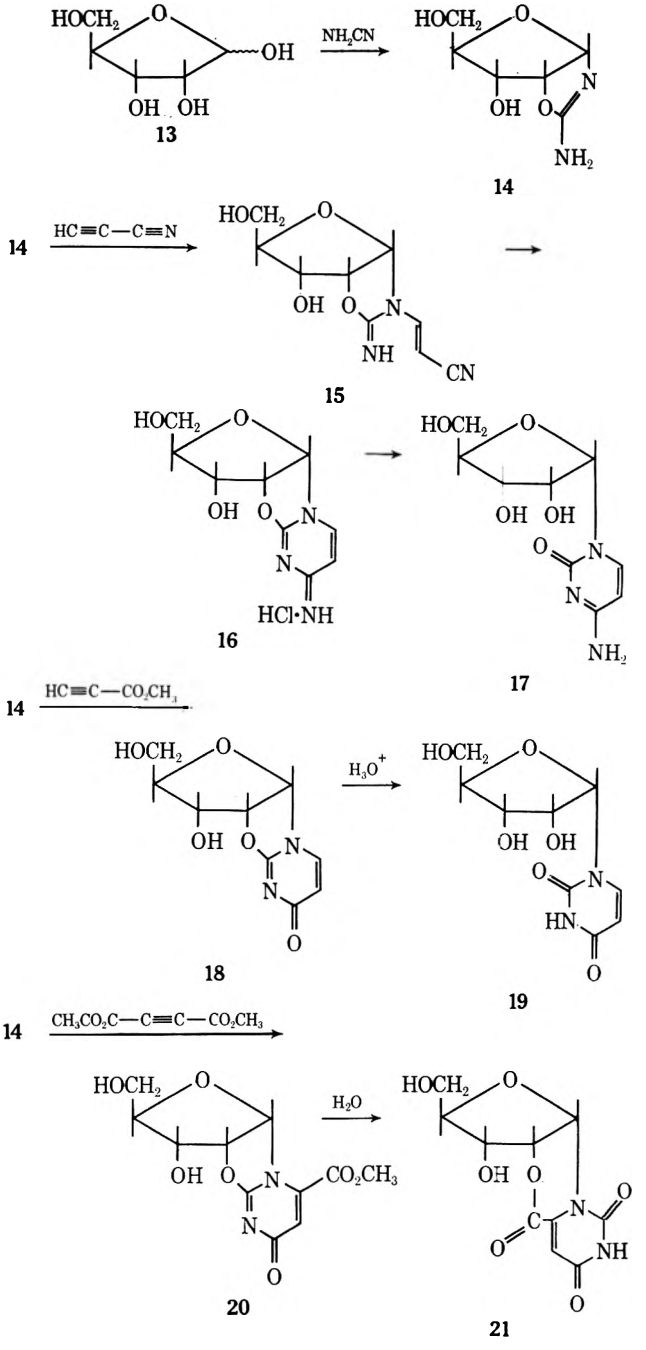
The aminooxazolines were found to react readily with a variety of electrophiles. Our results with propiolonitrile (cyanoacetylene), methyl propiolate, and dimethyl acetylenedicarboxylate are discussed here.

The arabinooxazoline **2** reacts rapidly with 1 molar equiv of propiolonitrile in *N*,*N*-dimethylacetamide at room temperature to yield a dark solution in which an open-chain cyanovinyl adduct **3** is thought to be the major component. This adduct is unchanged in the presence of anhydrous acids or by mild heating. However, in the presence of water or of aqueous acids it undergoes cyclization to 2,2′-anhydro-1-β-D-arbinofuranosylcytosine (**4**). We infer from this behavior

that **3** is possibly formed in a stable trans configuration, and that the function of water is to mediate an isomerization to the cis configuration, which then cyclizes spontaneously.

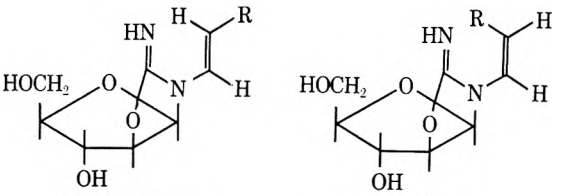
The pH of an aqueous solution of the free base **4** is sufficiently high to result in autohydrolysis, from which **5** is formed in quantitative yields.[2] In the presence of acids, however, **4** is stable. Both **4a** (acetate salt) and **5** may be isolated in yields of 80–90% based on **2**.

The reaction of the ribooxazoline **14** with propiolonitrile is presumed to occur predominantly *via* an analogous open-chain adduct **15**. However, the yield is



lower and tarry side products are also formed. 2,2′-Anhydro-1-α-D-ribofuranosylcytosine (hydrochloride salt, **16**) and 1-α-D-ribofuranosylcytosine (**17**) were isolated in yields of 51 and 35%, respectively.

The reaction of **2** with methyl propiolate in refluxing ethanol led to the formation of the *trans*-carbomethyoxyvinyl adduct **9** (18% yield) and of 2,2′-anhydro-1-β-D-arabinofuranosyluracil (**8**, 66–71% yield), the latter presumably resulting from the spontaneous cyclization of a *cis*-carbomethoxyvinyl adduct. The trans adduct **9** was thermally stable but could be photoisomerized to **8**, undoubtedly *via* the *cis*-carbomethoxyvinyl isomer.



R = C≡N or CO_2CH_3

The corresponding reaction of **14** with methyl propiolate in refluxing water gave 2,2′-anhydro-1-α-D-ribofuranosyluracil (**18**) in 27% yield. No attempt was made to isolate the corresponding *trans*-carbomethoxyvinyl adduct.

The aqueous hydrolyses of the β-anhydronucleosides **4** and **8** lead exclusively to the β-arabinosides **5** and **10**, respectively, as is already well known.[2,3] We find that the hydrolyses of the α-anhydronucleosides **16** and **18** also occur in high yield with retention of the 2′-oxygen configuration, yielding exclusively the α-ribosides **17** and **19**, respectively.

The reactions of **2** and **14** with dimethyl acetylenedicarboxylate in refluxing ethanol result in the formation of the methyl esters of the anhydroorotidine derivatives **11** (69% yield) and **20** (52% yield), respectively. In both cases conversion (to the corresponding lactones **12** and **21** could be achieved in boiling water.

Nucleophilic ring opening reactions (other than hydrolysis) of 2,2′-anhydro-1-β-D-arabinofuranosyluracil (**8**) and related anhydronucleosides have been described in the literature for a variety of nucleophiles. Anions such as I^-, Br^-, Cl^-, F^-,[8] N_3^-,[5] and thioacetate[9] have been reported to yield 2′-substituted 2′-deoxynucleosides in which the 2′ substituent was in the α configuration.

We decided to attempt the synthesis of certain 2′-substituted 2′-deoxycytidines by the application of related methods to the now easily available anhydrocytidine derivative **4**. In the past the preparation of such derivatives have generally involved a thiation–ammonation sequence applied to the corresponding uridine derivatives.[5,6]

When heated in dimethylformamide at 100°, the acetate salt **4** was converted to 2′(3′)-*O*-acetylcytidine (**6**) in *ca.* 60% yield. In a similar fashion the hydrofluoride salt **4b** was converted to the fluoronucleoside **6b** in 30% yield. Limiting factors in the synthesis of **6b** (and perhaps also of **6a**) appear to include a very facile hydrolysis of the starting anhydronucleoside as well as of the 2′-substituted product by small amounts of water, and the establishment of (or approach to) an equilibrium **4** ⇌ **6**. The conversion of **6b** to **4b** in dioxane at 100° has already been reported.[6]

When heated at 100° in HMPT, the phosphate salt **4c** was converted to a single phosphate ester, cytidine 2′,3′-cyclic monophosphoric acid (**7**), in 26% yield. Compound **7** was not an appreciable product from the

(8) J. F. Codington, I. L. Doerr, and J. J. Fox, *J. Org. Chem.*, **29**, 558 (1967).

(9) M. Imazawa and T. Veda, *Tetrahedron Lett.*, 4807 (1970).

reaction of cytidine 5′-monophosphoric acid, or of cytidine and orthophosphoric acid under the same conditions. On the other hand, cytidine 2′(3′)-monophosphoric acid was extensively cyclized to **7**. Therefore, we conclude that the predominant pathway in the conversion **6** → **7** proceeds *via* a direct ring opening of the anhydro link by orthophosphate to yield cytidine 2′-monophosphoric acid (**6c**) which then undergoes cyclization to **7**.

Discussion

The synthetic methods described in this paper provide easy routes to a variety of pyrimidine anhydronucleosides, many of which have not been previously described[10] or have been accessible only with difficulty. Because our method utilizes free sugars as starting materials, it is equally applicable, for example, to the synthesis of L nucleosides from the readily available L-arabinose.[11,12] A great variety of nucleosides could be generated by varying the sugars and electrophiles used in the standard synthesis.

(10) M. Ikehara, M. Kaneko, and Y. Nakahara, *Tetrahedron Lett.*, 4707 (1968).

Registry No.—**2**, 36994-58-8; **4a**, 10212-28-9; **4b**, 36963-54-9; **6a**, 36963-55-0; **6b**, 10212-20-1; **9**, 36963-57-2; **11**, 36963-58-3; **12**, 33886-19-0; **14**, 27963-97-9; **16**, 36963-61-8; **18**, 27964-04-1; **20**, 36959-85-0; **21**, 36959-86-1.

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(11) D. T. Gish, G. L. Neil, and W. J. Wechter, *J. Med. Chem.*, **14**, 882 (1971); R. L. Tolman and R. K. Robins, *ibid.*, **14**, 1112 (1971).
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Elimination Reactions on the Di- and Trimesylated Derivatives of N^3-Benzyluridine

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To investigate the base-catalyzed elimination reactions on multiply mesylated pyrimidine ribonucleosides, N^3-protected uridine derivatives, 3-benzyl-2′,3′-di-*O*-mesyluridine (**7**) and 3-benzyl-2′,3′,5′-tri-*O*-mesyluridine (**8**), were synthesized as model compounds, which would be less likely to undergo cyclonucleoside formation. Sodium benzoate catalyzed elimination reaction on **7** and **8** gave the 2′-uridinenes, **9** and **17**, with a mesyloxy group at $C_{2'}$, which were converted to the crystalline 2′-uridinenes, **10** and **11**. Treatment of **10** with potassium carbonate gave a new class of compound, *endo*-3-(3-benzyluracil-1-yl)-2-oxabicyclo[3.1.0]-4-oxocyclohexane (**13**). **8** with sodium acetate and sodium iodide gave 5′-substituted compounds, **18** and **19**, respectively. **8** with potassium carbonate gave 2′,3′-epoxy nucleoside (**20**) and **13**. This suggests the intervention of two synchronous reaction paths.

Although didehydronucleosides are potentially useful intermediates for the transformations of the sugar moieties of nucleosides, examples of their use in synthesis are limited.[1,2] This reflects the fact that this class of compounds are less accessible than the cyclonucleosides. In the pyrimidine series, 2′,3′-[3-6] and 3′,4′-unsaturated[7] nucleosides have been obtained by base-catalyzed elimination reactions. An elegant synthesis of 4′,5′-unsaturated uridine was also reported.[8] However, similar investigations on the introduction of 2′,3′-unsaturated bonds into the ribonucleosides are quite few.[4,9] This spurred us to examine the direction of base-catalyzed elimination reactions on N^3-protected uridine derivatives, where cyclonucleoside formation was considered less probable.

This paper deals with a simple revised method for selective N^3-benzylation of uridine and its derivatives, and the results of some elimination studies on their di- and tri-O-mesylated derivatives.

Preparation of the Starting Materials for the Elimination Reactions.—Benzylation of uridine and its derivatives was studied previously for the purpose of working out selective 2′-*O*-benzylation required for ribooligonucleotide synthesis.[10-12] In these cases, concomitant N^3-benzylation was also noted. For the present purpose, it was necessary to find better reaction conditions for the selective N^3-benzylation. Combination of benzyl chloride and potassium carbonate in a mixture of acetone and *N*,*N*-dimethylformamide (DMF) as a medium eventually proved to be satisfactory. Thus, 5′-*O*-trityluridine (**1**) (Scheme I) with a slight excess of benzyl chloride and potassium carbonate gave exclusively 3-benzyl-5′-*O*-trityluridine (**2**) after 3-hr reflux in a mixture containing equal amounts of acetone and DMF. The use of benzyl bromide revealed at least one more product in a lesser amount. Detritylation of **2** gave 3-benzyluridine (**3**)[11,12] in good yield. To establish structure **3**, 2′,3′-*O*-isopropylideneuridine (**4**) was benzylated to give 3-benzyl-2′,3′-*O*-isopropylideneuridine (**5**) as a homogeneous foam whose nmr spec-

(1) J. R. McCarthy, Jr, R. K. Robins, and M. J. Robins, *J. Amer. Chem. Soc.*, **90**, 4993 (1968).
(2) I. D. Jenkins, J. P. H. Verheyden, and J. G. Moffat, *ibid.*, **93**, 4323 (1971).
(3) J. P. Horwitz, J. Chua, M. Noel, and J. T. Donnatti, *J. Org. Chem.*, **32**, 817 (1967).
(4) J. P. Horwitz, J. Chua, M. A. Da Rooge, M. Noel, and I. L. Klundt, *ibid.*, **31**, 205 (1966).
(5) J. P. Horwitz, J. Chua, M. A. Da Rooge, and M. Noel, *Tetrahedron Lett.*, 2725 (1964).
(6) J. P. Horwitz, J. Chua, and M. Noel, *ibid.*, 1343 (1966).
(7) J. Zemlicka, R. Gasser, and J. P. Horwitz, *J. Amer. Chem. Soc.*, **92**, 4744 (1970).
(8) J. P. H. Verheyden and J. G. Moffatt, *ibid.*, **88**, 5684 (1966).
(9) W. H. Ruyle, T. Y. Shen, and A. A. Pachett, *J. Org. Chem.*, **30**, 4353 (1965).
(10) A. M. Michelson and A. R. Todd, *J. Chem. Soc.*, 3459 (1956).
(11) N. Imura, T. Tsuruo, and T. Ukita, *Chem. Pharm. Bull.*, **16**, 1105 (1968).
(12) H.-U. Blank and W. Pfleiderer, *Justus Liebigs Ann. Chem.*, **742**, 1 (1970).

trum was compatible with structure **5**. Treatment of **5** with 80% acetic acid yielded **3**. The reaction sequences **1** → **2** → **3** and **4** → **5** → **3** firmly established the position of benzylation in **2** and also in **5**. Uridine itself was analogously benzylated at N^3 in 72% yield. Imura and coworkers[11] also carried out the direct benzylation on uridine using benzyl bromide and sodium hydride in dimethyl sulfoxide, and obtained **3** in 30.5% and N^3,2′-*O*-dibenzyluridine in 33% yield. The 5′-*O*-trityl group in **2** is so labile to acid that attempted purification of **2** on silica gel resulted in complete conversion to **3**. Mesylation of **3** smoothly gave the 2′,3′,5′-tri-*O*-mesyl derivative **8**, thus giving further support to the assigned structures, since we have ample experience that the position N^3 of uridine cannot be mesylated at room temperature even with a large excess of mesyl chloride, if the work-up involves treatment with water. **2** was mesylated quantitatively to the 2′,3′-di-*O*-mesyl derivative **6**, which was converted to **7** in good yields.

The nmr spectra of these compounds showed neither NH signals nor the known characteristic splittings of H^5 signals due to the long-range interaction with the N^3 proton.[13]

Elimination Reactions on 3-Benzyl-2′,3′-di-*O*-mesyluridine (7) and 3-Benzyl-2′,3′,5′-tri-*O*-mesyluridine (8).—Reaction of **7** with excess sodium benzoate in DMF gave the starting material **7** (23.6%) and 1-(3′-deoxy-2′-*O*-mesyl-β-D-*glycero*-pent-2′-enofuranosyl)-3-benzyluracil (**9**) as a foam (37%) as shown in Scheme II. Its nmr spectrum exhibited a doublet of doublets at δ 6.7 with equal splittings (1.6 Hz) and a triplet at δ 5.95 (J = 1.6 Hz). The signal of $H_{4'}$ appeared at δ 5.25 (broad doublet, J = 3.3 Hz). The formation of another product in much smaller amount was indicated by thin layer chromatography, but repeated attempts to isolate it were unsuccessful. Mesylation of **9** gave crystalline 1-(3′-deoxy-2′,5′-di-*O*-mesyl-β-D-*glycero*-pent-2′-enofuranosyl)-3-benzyluracil (**10**), which was easily substituted with sodium iodide to yield 1-(3′,5′-dideoxy-5′-iodo-2′-*O*-mesyl-β-D-*glycero*-pent-2′-enofuranosyl)-3-benzyluracil (**11**). This series of compounds, **9**–**11**, showed characteristic similarities in their nmr spectra,[14] as an example of which the 100-MHz spectrum of compound **10** is given in Figure 1. The structure assigned to **10** (and therefore that of **9**, **11**, and **17**) is based upon the following considerations and its conversion to compound **13**. The introduction of one olefinic bond suggested as possible struc-

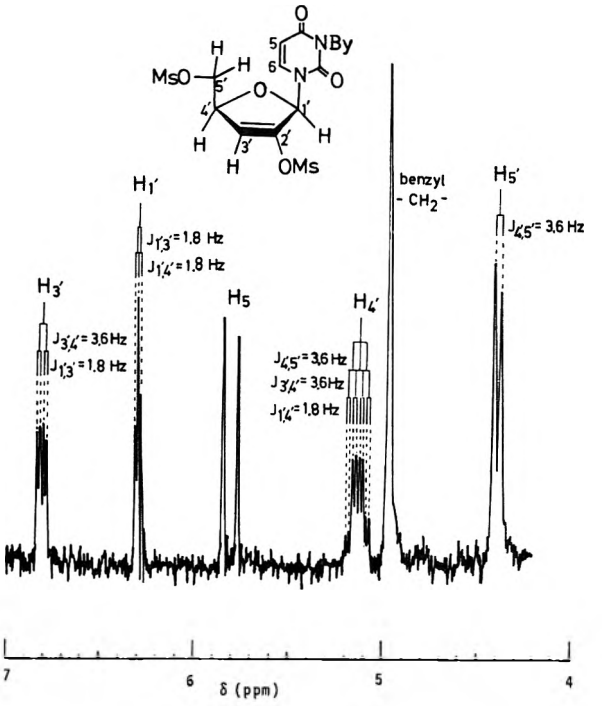
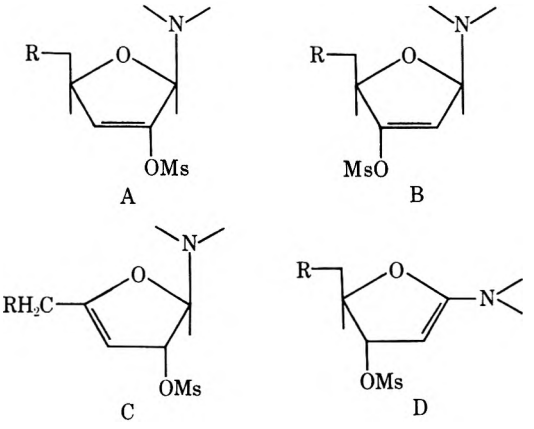


Figure 1.—Nuclear magnetic resonance spectrum of 1-(3′-deoxy-2′,5′-di-*O*-mesyl-β-D-*glycero*-pent-2′-enofuranosyl)-3-benzyluracil (**10**) in DMSO-d_6 at 100 MHz.

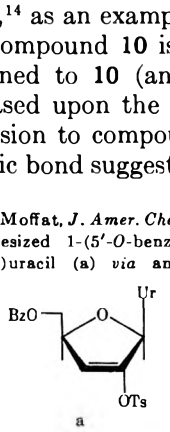


R = OMs, I, OH, and $PhCO_2$

tures A–D. The latter two, which might arise by a cis elimination of methanesulfonic acid, were ruled out because the presence of $H_{1'}$ and $H_{4'}$ is indicated in the nmr spectrum. The resonance of $H_{3'}$ and $H_{1'}$ of N^3-benzylated uridine derivatives usually lie in the range of 4.25–4.50 and 5.6–6.1 ppm, respectively, and are more or less comparable with those of uridine.[17] If a double bond is inserted between these protons, the observed signal centered at δ 5.12 can be reasonably assigned to $H_{4'}$. A chemical shift, δ 5.0, was reported for $H_{4'}$ in 2′,3′-dideoxycytidinene.[3] In the 60-MHz spectrum of **11** (see Experimental Section), the resonance of $H_{4'}$ appeared at δ 4.8–5.1 as a complex multiplet. Irradiation at δ 4.98 resulted in the collapse of the $C_{5'}$ protons (a pair of doublets at δ 3.28 and 3.38) into a singlet and of the other two protons (the doublet of doublets and the triplet at δ 6.76 and 6.22) into a similar doublet (J = 1.6 Hz). The final choice for structure A was given by a close inspection of the nmr spectra of **10** and its derivative **13** mentioned below. The quartet-like resonance of $H_{4'}$ at δ 5.12 is actually

(13) A. F. Cook and J. G. Moffat, *J. Amer. Chem. Soc.*, **89**, 2697 (1967).

(14) Recently we synthesized 1-(5′-*O*-benzoyl-3′-deoxy-2′-*O*-tosyl-β-D-*glycero*-pent-2′-enofuranosyl)uracil (**a**) *via* an unambiguous route. It



a

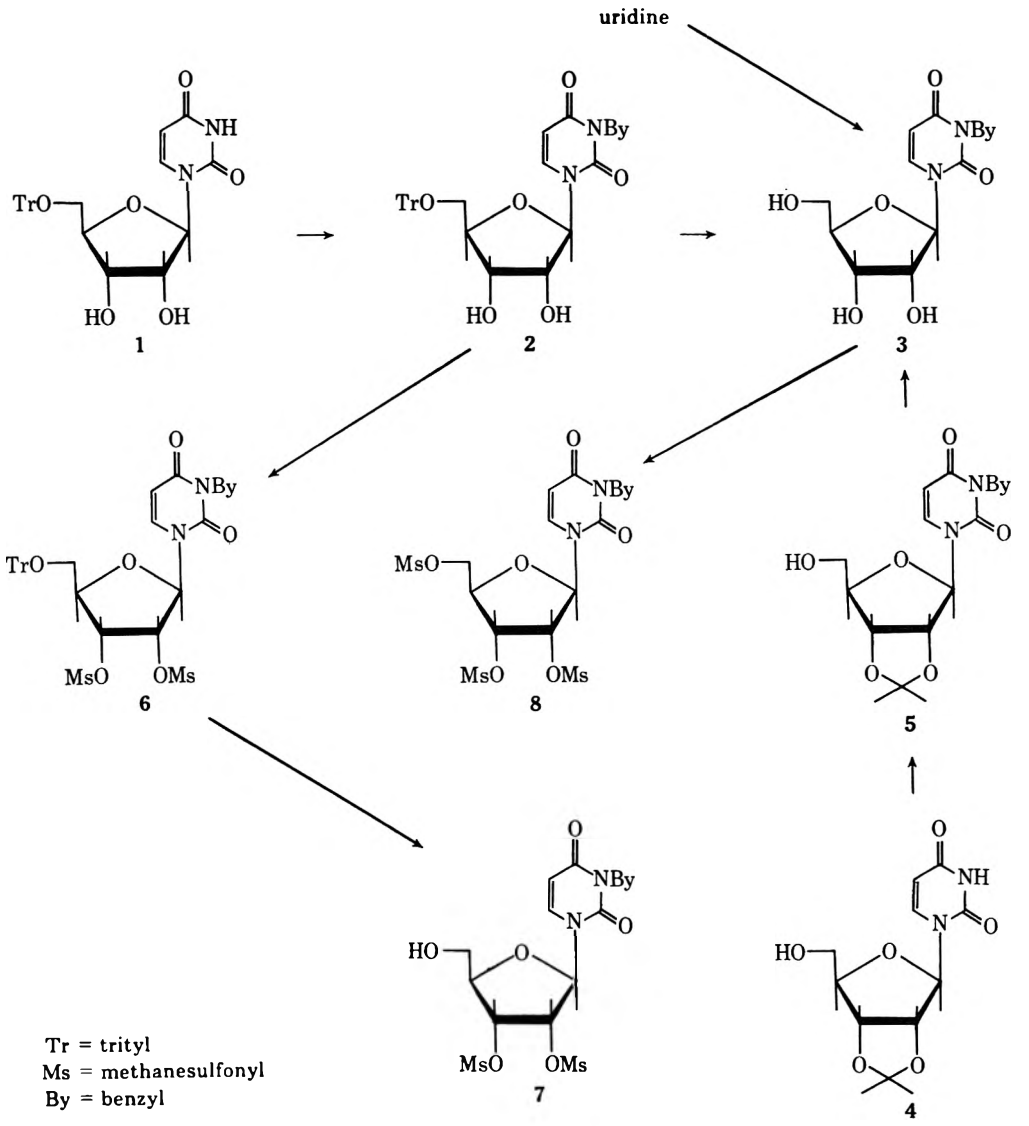
might be noted that the low field resonances (of $H_{1'}$ and $H_{3'}$) of compound **a**, 5-*O*-benzoyl-2-*O*-tosyl-2,3-dideoxy-β-D-*glycero*-pent-2-enofuranoside,[15] and 1-(2′,3′-dideoxy-2′-bromo-β-D-*glycero*-pent-2′-enofuranosyl)uracil[16] are strikingly similar in their splitting patterns; *i.e.*, a triplet and a doublet of doublets, in this order downward, were observed for the two low field furanose–ene protons. $H_{4'}$ in compound **a** gave a distinct octet with equal splittings of 1.6 Hz (to be described in a succeeding paper).

(15) J. Hildesheim, A. Gaudemer, and S. D. Gero, *Chem. Ind.* (*London*), 94 (1970).

(16) Y. Furukawa, Y. Yoshiko, K. Imai, and M. Horjo, *Chem. Pharm. Bull.*, **18**, 554 (1970).

(17) F. E. Hruska, *J. Amer. Chem. Soc.*, **93**, 1795 (1971).

SCHEME I



an octet with a relative intensity[14] of 1:1:3:3:3:3:1:1, and with equal splittings of 1.8 Hz, which, along with the triplet at δ 6.29 and the doublet of doublets at δ 6.8, can be theoretically expected, if we suppose structure A to be actual, in which the assignments of $H_{1'}$ and $H_{3'}$ and the coupling constants of the whole sugar protons are as shown in Figure 1. It is important to note that the signal of $H_{4'}$ contains two similar coupling constants of 3.6 Hz, one of which is due to the $H_{4'},H_{5'}$ interaction. The other should be assigned to a proton–proton interaction other than the 1′,4′ or allylic coupling on the basis of its magnitude. Hence, this splitting of 3.6 Hz must be assigned to a vicinal coupling with $H_{3'}$, which has a reasonable dihedral angle of ~60° with $H_{4'}$ as indicated by a molecular model. Thus, the assignments of $H_{1'}$ and $H_{2'}$ as shown are a logical result from the above arguments.[18,19] Attempts to convert **10** to **12** by partial hydrogenation were unsuccessful. When **10** was treated with potassium carbonate in hot DMF, a new crystalline compound, *endo*-3-(3-benzyluracil-1-yl)-2-oxabicyclo[3.1.0]-4-oxocyclohexane (**13**), was obtained as the major product. The structural assignment is based on its analysis, uv (λ_{max} 256 nm), ir (ν C=O 1733, 1709, and 1668 cm^{-1}), nmr, and mass spectrum. In the ir spectra of 2′- and 3′-ketouridine and their derivatives, characteristic absorptions of the furanose ketones were observed between 1750 and 1800 cm^{-1}.[3,20] The absorption of **13** at 1733 cm^{-1} suggested the presence of a conjugated carbonyl on the furanose ring. Interestingly, as Moffatt and coworkers experienced also,[13] this compound had a tendency for covalent hydration, which rendered its purification troublesome. Its nmr spectrum exhibited four one-proton multiplets at δ 1.35, 1.57, 2.20, and 4.75 as shown in Figure 2. The anomeric proton appeared at δ 5.55 as a sharp singlet, revealing its insulation from the other sugar protons.[21] The two-proton singlet at δ 4.9 is due to the benzyl methylene. In this case, a chemical shift at as high as 1.35 or 1.57

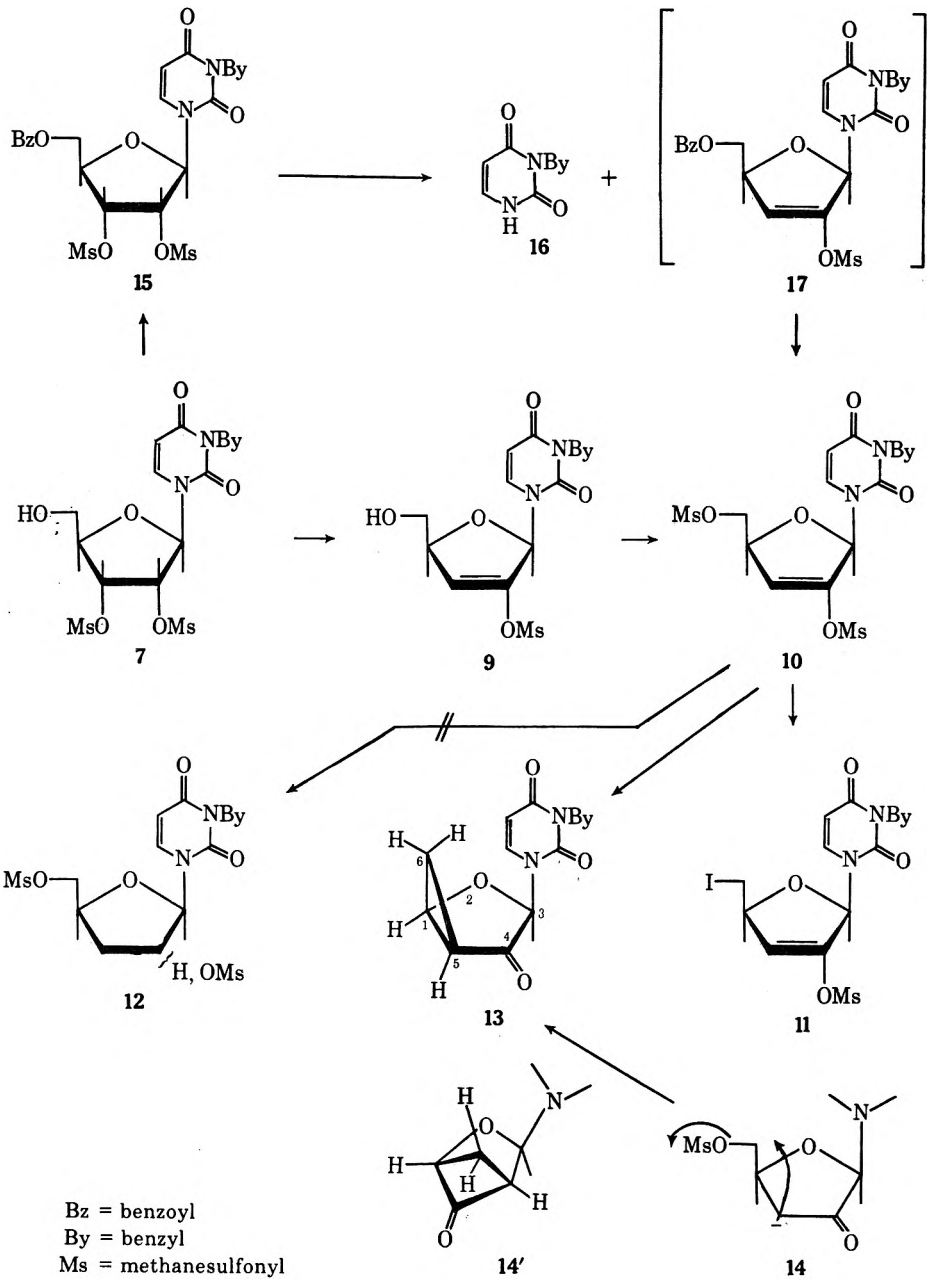
(18) The anomeric protons of some didehydronucleosides resonate at lower fields than the olefinic protons (see ref 1, 3, and 7). In our case, however, the strong deshielding effect by the mesyl group must be considered. For a deshielding effect by a mesyl in a saturated system, compare compounds **7**, **8**, and **5** in the Experimental Section.

(19) If structure B is to be assigned to **10**, the $H_{4'}$ signal should give a septet with a relative intensity of 1:1:3:3:3:1:1 and with equal splittings of 1.8 Hz, while the other protons, $H_{1'}$ and $H_{2'}$, should appear as the same doublet of doublets with a relative intensity 1:1:1:1 and equal splittings of 1.8 Hz.

(20) U. Brodbeck and J. G. Moffatt, *J. Org. Chem.*, **35**, 3552 (1970).

(21) The anomeric proton of 2′-ketouridine[13] and 2′-ketocytidine[20] resonates, respectively, at δ 5.42 and 5.48, each as a sharp singlet.

SCHEME II



ppm should be ascribed to a cyclopropane proton. The cyclopropane proton adjacent to the carbonyl in cyclopropyl methyl ketone resonates at δ 1.86[22] and that in methyl 2-bromocyclopropanecarboxylate at δ 2.07.[23] Hence, the sextet at δ 2.20 can be reasonably assigned to H_5. Thus, complete analyses for these complicated signals were achieved as shown, taking $J_{1,6A} = J_{1,5} = J_{5,6B} = 4.4$ Hz as a key coupling constant. Compound **13** is a new type of nucleoside derivative for which there is no literature analog to permit direct spectral comparison, and its material shortage impeded further chemical modification. The formation of **13** from **10** is also mechanistically justified by the intermediacy of the β-keto anion **14** formed after demesylation of **10**.[24] A ring expansion reaction *via* a similar intramolecular cyclopropane formation has been recorded.[25] A fused cyclobutanone structure **14'** can be excluded, since the β protons of cyclobutanone itself resonate at δ 1.96[26] and the anomeric proton should give a doublet ($J \cong 3$ Hz) as predicted by a molecular model study, on the basis of which the dihedral angle between the anomeric and its adjacent proton is expected to be approximately 60° in this rigid system. Furthermore, cyclobutanone absorbs at 1775 cm^{-1} in its ir spectrum.[27]

Some principal fragmentation patterns in the mass spectra of **10**, **11**, and **13** are given in Schemes III and IV. Molecular ions for **10** and **11** could not be measured because of their too high molecular weights.

(22) F. A. Bovey, "NMR Data Tables for Organic Compounds," Vol. 1, Interscience, New York, N. Y., 1967, p 97.

(23) See ref 22, p 93.

(24) We have demonstrated sodium benzoate catalyzed detosylation rather than desulfonyloxylation of compound **a** (to be described in a succeeding paper).

(25) H. W. Whitlock, Jr., and P. F. Schatz, *J. Amer. Chem. Soc.*, **93**, 3837 (1971).

(26) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, Oxford, 1969, p 198.

(27) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," Wiley, New York, N. Y., 1958, p 149.

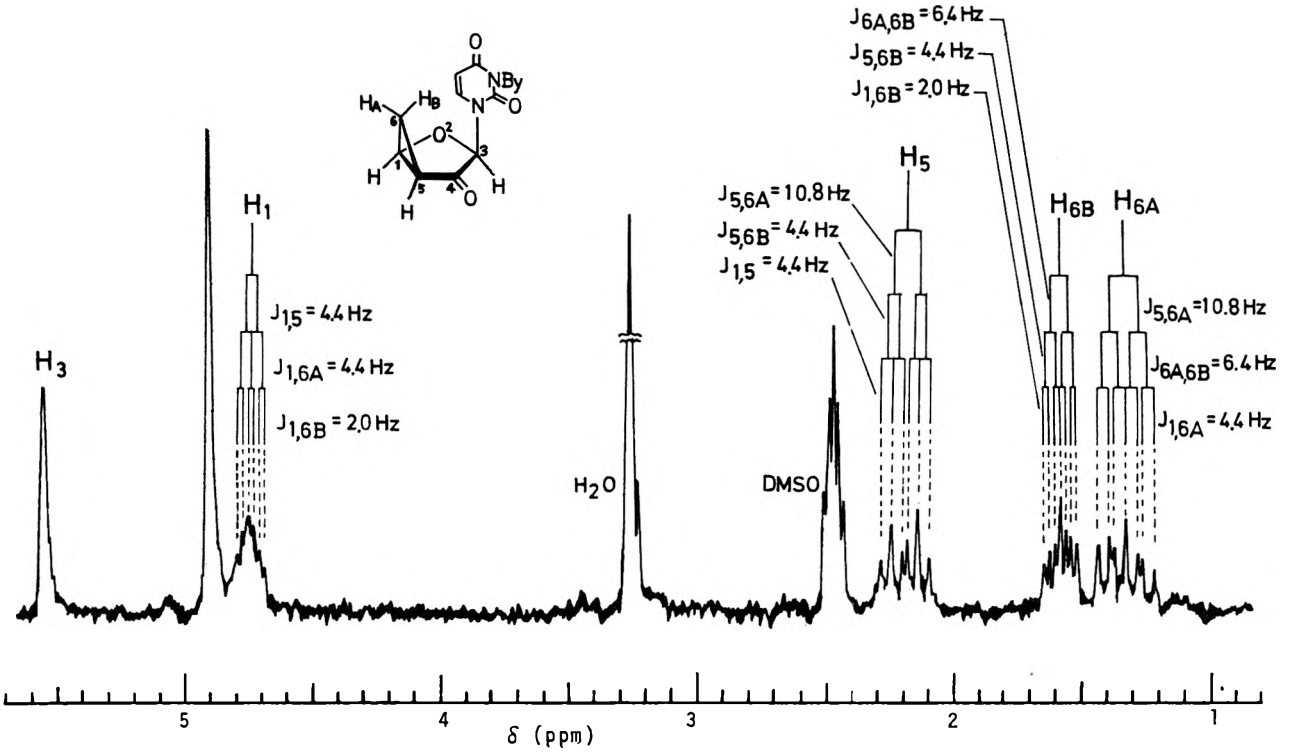
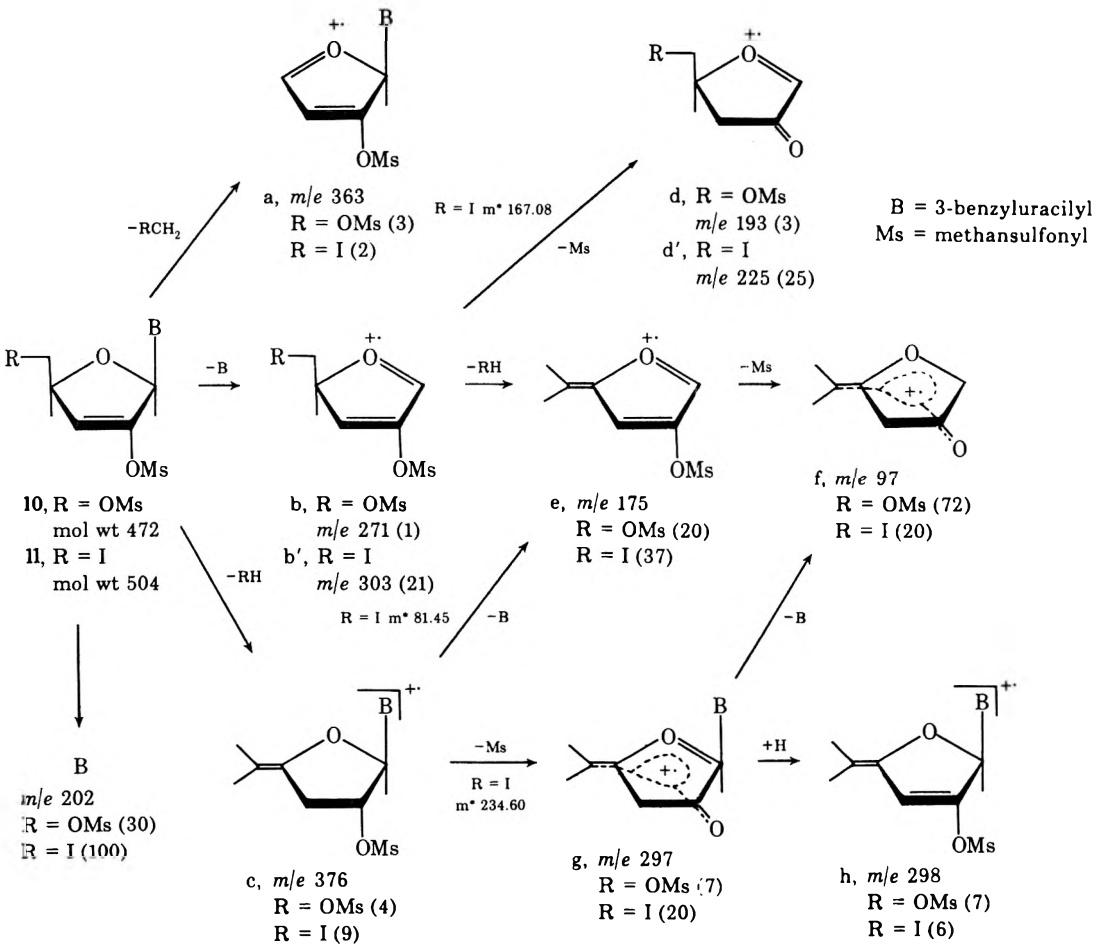


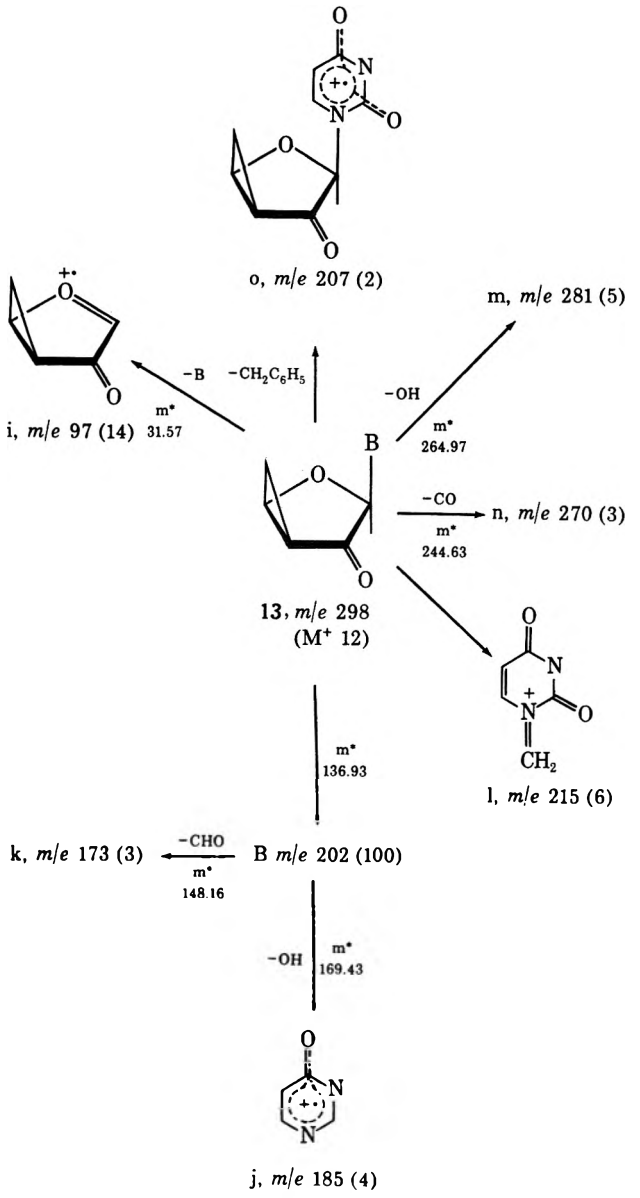
Figure 2.—Nuclear magnetic resonance of *endo*-3-(3-benzyluracil-1-yl)-2-oxabicyclo[3.1.0]-4-oxocyclohexane (**13**) in DMSO-d_6 at 100 MHz.

SCHEME III[a]



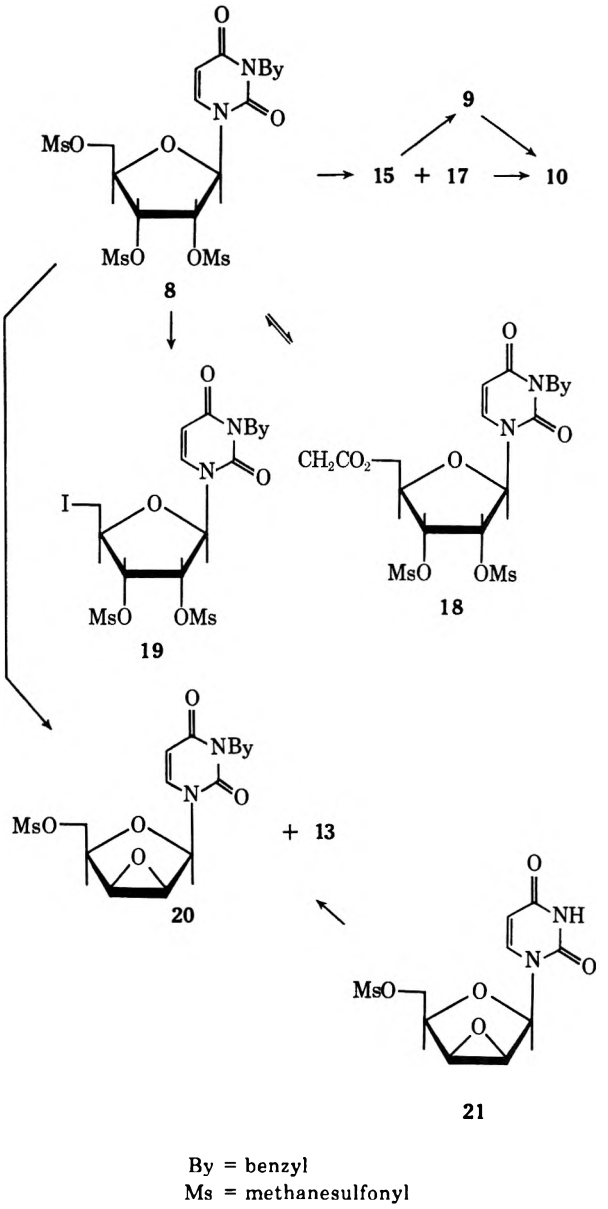
[a] Base peak for **10**: *m/e* 91 (benzyl or tropylium cation). Values in parentheses are relative intensities.

SCHEME IV



[a] Values in parentheses are relative intensities.

SCHEME V



By = benzyl
Ms = methanesulfonyl

Oxonium radicals like a, b, b′ (Scheme III) and i (Scheme IV) have enough precedents in the mass spectra of carbohydrates and nucleosides.[28,29] The 4′,5′-dehydro types of ions, c, e, f, g, and h, have also literature analogs.[30] Although metastable peaks appeared quite rarely in the case of **10** and **11**, the fragmentation sequences shown are reasonable. It seems interesting to note possible identity of ion f with ion i. The dehydronucleosides **10** and **11** seem to have a striking tendency of aromatization, thus limiting chances to cleave the bond between $C_{2'}$ and $C_{3'}$. Hence, as far as our qualitative analyses are concerned, decisive data were not obtained for a choice between A and B.

Since we noted that 3-benzyl-2′,3′-di-*O*-mesyl-5′-*O*-trityluridine (**6**) did not react with sodium benzoate under analogous conditions, presumably for steric reasons, a similar elimination reaction was carried out on 3-benzyl-5′-*O*-benzoyl-2′,3′-di-*O*-mesyluridine (**15**). Thin layer chromatography indicated that the reaction proceeded more or less similarly as in the case of **7**. The action of excess potassium carbonate or potassium *tert*-butoxide on **15** gave 3-benzyluracil (**16**) and 1-(3′-deoxy-5′-*O*-benzoyl-2′-*O*-mesyl-β-D-*glycero*-pent-2′-enofuranosyl)-3-benzyluracil (**17**) as major product, which was directly converted to **10** *via* debenzoylation and mesylation.

Similarly, 3-benzyl-2′,3′,5′-tri-*O*-mesyluridine (**8**) gave compounds **15** and **17** in 35 and 48% yield, respectively (Scheme V). The facile nucleophilic displacement of 5′-*O*-mesyl or tosyl groups is well documented,[31-33] and in this case **17** must have formed *via* **15**. With a view to converting **15** to highly crystalline **8**, **15** was treated with excess ammonia to give, unexpectedly, the noncrystalline compound **9** as major product, which was mesylated again to give **10**. Sim-

(28) S. J. Shaw, D. M. Desiderio, K. Tsuboyama, and J. A. McCloskey, *J. Amer. Chem. Soc.*, **92**, 2510 (1970).

(29) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Structure Elucidation of Natural Products by Mass Spectrometry," Vol. 2, Holden-Day, San Francisco, Calif., 1964, Chapter 27.

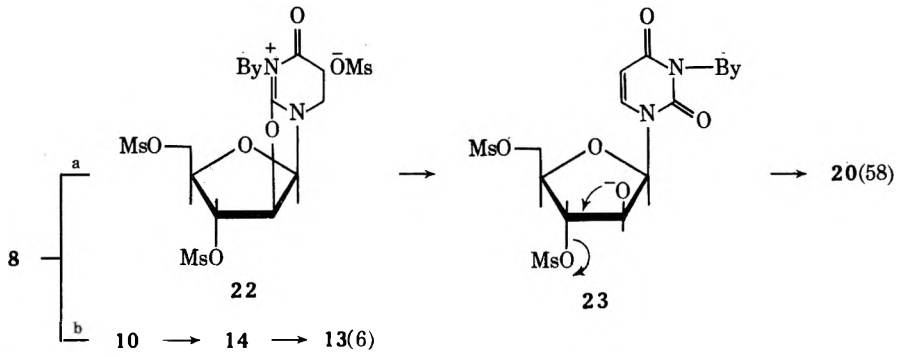
(30) A. M. Lawson, R. N. Stillwell, M. M. Tacker, K. Tsuboyama, and J. A. McCloskey, *J. Amer. Chem. Soc.*, **93**, 1014 (1971).

(31) J. F. Codington, R. Fecher, and J. J. Fox, *ibid.*, **82**, 2794 (1960).

(32) N. C. Yong and J. J. Fox, *ibid.*, **83**, 3060 (1961).

(33) E. Benz, N. F. Elmore, and L. Goldman, *J. Org. Chem.*, **30**, 3067 (1965).

SCHEME VI



ilar treatment of **17** also gave **10**. The action of sodium acetate on **8** yielded 3-benzyl-5′-*O*-acetyl-2′,3′-di-*O*-mesyluridine (**18**) as the sole product, which was reconverted to **8**. Substitution of **8** with sodium iodide also proceeded smoothly to give 3-benzyl-5′-deoxy-5′-iodo-2′,3′-di-*O*-mesyluridine (**19**) in good yield. Treatment of **8** with potassium carbonate gave no olefinic compounds. Instead, 1-(2′,3′-epoxy-5′-*O*-mesyl-β-D-lyxosyl)-3-benzyluracil (**20**) was obtained as major product with a small amount of **13** (Scheme VI). Characterization of **20** was difficult but was eventually carried out by simple benzylation of 1-(2′,3′-epoxy-5′-*O*-mesyl-β-D-lyxosyl)uracil.[34] As far as this particular experiment is concerned, two synchronous reaction paths are now obvious[35] (Scheme VI).

Discussion

The synthetic use of 2′,3′-unsaturated nucleosides has been limited to their use as precursors for 2′,3′-dideoxynucleosides.[3,6,16] The principal reason for this is probably the lack of factors for selective attack by chemical reagents at the double bond, whereas the 4′,5′ double bond would offer at least *regiospecificity* as exemplified by the specific introduction of a fluorine atom into the 4′ position of adenosine.[2] From this point of view, our experimental data described above are interesting since (1) the base-induced β elimination generally occurred specifically to leave a mesyl group at $C_{2'}$; (2) the strong electron-withdrawing mesyl group might regulate the attack, *e.g.*, of a dipolar addition reagent,[36] and (3) the mesyl group might be chemically modified without difficulty. Although we initially expected that the bulky aglycon moiety would exert a strong steric influence, it was rather surprising that the 2′ hydrogen was invariably more open to the attack of the basic reagents regardless of the size of the 5′-O substituent. Apparently, the same thing is true regardless of the kind and size of basic catalyst, since even ammonia must have attacked the 2′ hydrogen. This observation seems to suggest that the sugar moieties in the nucleoside derivatives exert a specific effect on the orientation of β elimination, an effect which might be clarified by accumulation of further data. A central problem in this work was the necessity for discriminating between two possible products of type A and B, which was solved in this particular case by the close analyses of the nmr spectra of **10** and **13**. Compound **13** offers a new possibility for the chemical modification of nucleosides. Although the N^3-benzyl group on the uracil skeleton is known to resist the usual catalytic hydrogenolysis,[11,37] the results obtained by us may be of some help after introduction of an appropriate protecting reagent.

(34) J. F. Codington, R. Fecher, and J. J. Fox, *J. Org. Chem.*, **27**, 163 (1962).

(35) The possible formation of the cyclonucleoside **22** was once suggested by a referee.

(36) As one referee suggested, a resonance effect stemming from electron-donating contribution of oxygen would be expected in $CH_3SO_2CH{=}CH{-}$. A steric effect might also be considered.

Experimental Section

All melting points are uncorrected. The electronic spectra were measured on a JASCO Model ORD/UV-5 spectrophotometer. The nmr spectra were recorded with a JNM C-60 HL ($CDCl_3$) and Varian HA-100 spectrometer (DMSO-d_6), TMS being used as an internal standard. In the case of the hydroxyl-containing compounds, measurements after D_2O exchanges were also carried out. The mass spectra were measured by a Hitachi RMU-D double-focusing spectrometer operating at an ionization potential of 75–80 eV. The solid samples were ionized by electron bombardment after sublimation directly into the electron beam at 200–250°. Wakogel B-5 silica gel, supplied by the Wako Pure Chemical Industries, was used for thin layer chromatography, while column chromatography was carried out using Mallinkrodt silicic acid (100 mesh) after washing with ethyl acetate.

3-Benzyl-5′-*O*-trityluridine (2).—To a solution of 5′-*O*-trityluridine (1) (2.12 g, 4 mmol) in a mixture of DMF (4 ml) and acetone (4 ml) were added benzyl chloride (0.58 ml, 5 mmol) and anhydrous potassium carbonate (0.78 g, 5.6 mmol). The mixture was gently refluxed for 3 hr, cooled to room temperature, and poured into ice–water (300 ml). The precipitating solid was filtered and dried (2.48 g). Thin layer chromatography at this stage showed one main product with trace amounts of the starting material and trityl carbinol. Preparative thin layer chromatography with the use of silica gel and a mixed solvent, chloroform–ethyl acetate (3:1, v/v), gave 1.96 g (86%) of **2** as a foam.

Anal. Calcd for $C_{35}H_{30}N_2O_6$: C, 72.90; H, 5.59; N, 4.86. Found: C, 73.13; H, 5.56; N, 4.72.

3-Benzyluridine (3). A.—The crude solid product **2** obtained by the same procedure as above was treated with 80% acetic acid at 90° for 1 hr. After the solvent was evaporated off, the residual paste was dissolved in benzene and again evaporated. The same procedure was followed a couple of times to give a pale yellow semisolid, which was triturated with ether (30 ml), and the ethereal solution was removed by decantation. This procedure was repeated five times. After standing overnight, the combined ethereal solutions gave a second crop, which was filtered, combined with the above obtained solid, and recrystallized from methanol to give **3** as colorless needles (1 g, 75%), mp 182° (lit.[11] mp 175.5–176.5°).

Anal. Calcd for $C_{16}H_{18}N_2O_6$: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.55; H, 5.54; N, 8.19.

B.—Uridine (977 mg, 4 mmol), benzyl chloride (0.7 ml, 6 mmol), and potassium carbonate (0.95 g, 6.8 mmol) were combined in a mixture of DMF (4 ml) and acetone (4 ml), and the mixture was heated to reflux for 4 hr. After acetone was evaporated off, the mixture was poured into ice–water (30 ml), and

(37) T. Kunieda and B. Witkop, *J. Amer. Chem. Soc.*, **93**, 3478 (1971).

the pasty precipitate was extracted with ethyl acetate (250 ml). The extract was recrystallized from methanol to give 0.96 g (72%) of colorless crystals, mp 181–182°. The identity of the product with a specimen prepared by the procedure a was confirmed by infrared spectroscopy and the mixture melting point determination.

C.—2′,3′-*O*-Isopropylideneuridine (**4**) (284.4 mg, 1 mmol), benzyl chloride (0.17 ml, 1.5 mmol), and potassium carbonate (240 mg, 1.7 mmol) were combined in a mixture of DMF (1 ml) and acetone (2 ml), and the mixture was heated to reflux for 2 hr. After the solvent was evaporated, the residual oil was triturated with water (5 ml) and the water was decanted off. The residue was taken into chloroform (100 ml), dried over sodium sulfate, evaporated to a paste, and applied on a silica gel column (30 × 1.5 cm). Elution with a mixed solvent, chloroform–ethyl acetate (3:1), gave **5** as a colorless, pure foam (0.28 g, 75%): nmr ($CDCl_3$) δ 1.35 (3 H, s, Me), 1.56 (3 H, s, Me), 2.86 (1 H, broad singlet, OH), 3.76 (2 H, m, 5′ CH_2), 4.25 (1 H, m, $H_{4'}$), 4.87 (2 H, broad singlet, $H_{2'}$ and $H_{3'}$), 5.03 (2 H, s, benzyl methylene), 5.59 (1 H, s, $H_{1'}$), 5.68 (1 H, d, $J_{5,6}$ = 8 Hz, H_5), 7.1–7.4 (5 H, m, Ph), 7.36 (1 H, d, $J_{5,6}$ = 8 Hz, H_6, partially merged with the phenyl signal). This sample was directly treated with 80% acetic acid at 95° for 2 hr. The reaction mixture was completely evaporated to a paste, which was recrystallized from methanol to give **3** (0.2 g).

3-Benzyl-2′,3′-di-*O*-mesyl-5′-*O*-trityluridine (**6**).—Compound **2** (1.835 g, 3.18 mmol) in dry pyridine (15 ml) was added with mesyl chloride (0.7 ml, 9 mmol), left at 0° for 8 hr, and then poured into ice–water (300 ml) to give a solid precipitate, which was filtered. The wet solid was dissolved in chloroform and dried with sodium sulfate. Evaporation of the solvent gave 2.24 g of a foam, which was purified by thin layer chromatography, using silica gel and a mixture, chloroform–ethyl acetate (3:1), to give a homogeneous foam (1.76 g, 85%). It is to be noted that the 5′-trityl group in the 3-benzyl compounds (**2** and **6**) is easily cleaved in attempts to separate by silica gel column using mixtures of chloroform and ethyl acetate as eluents.

Anal. Calcd for $C_{37}H_{36}O_{10}S_2N_2$: C, 60.65; H, 4.95; N, 3.82. Found: C, 60.68; H, 5.18; N, 3.75.

3-Benzyl-2′,3′-di-*O*-mesyluridine (**7**).—To an ice-cold stirred solution of **6** (1.5 g, 2.3 mmol) in chloroform (20 ml) was added HCl-saturated chloroform (5 ml) and the mixture was allowed to warm up to room temperature. After 1 hr of stirring at room temperature, the mixture was evaporated to a paste, which was taken into benzene and again evaporated. This procedure was followed several times. The paste was then digested with ether (10 ml) many times, until the ether washing gave no trityl-positive spot on tlc. Recrystallization of the semisolid residue from methanol gave **7** as colorless needles, mp 151–153° (0.72 g). A second crop (0.24 g) was obtained from the ether washings: total yield 85%; λ_{max}^{EtOH} 257 nm (ε 10,200); nmr (DMSO-d_6) δ 3.24 (3 H, s, Me), 3.28 (3 H, s, Me), 3.73 (2 H, broad singlet, 5′-CH_2), 4.28 (1 H, d, J = 3.4 Hz, $H_{4'}$), 4.98 (2 H, s, benzyl methylene), 5.38 (2 H, m, $H_{2'}$ $H_{3'}$), 5.85 (1 H, d, $J_{5,6}$ = 8 Hz, H_5), 6.10 (1 H, d, J = 4.6 Hz, $H_{1'}$), 7.24 (5H, s, Ph), 7.97 (1H, d, $J_{5,6}$ = 8 Hz, H_6).

3-Benzyl-2′,3′,5′-tri-*O*-mesyluridine (**8**).—To an ice-cold solution of **3** (1.03 g, 3.1 mmol) in anhydrous pyridine (15 ml) was added mesyl chloride (1.15 g, 10 mmol) and the mixture was left at 0° overnight. Then the reaction mixture was left at room temperature for 1 hr and poured into ice–water (300 ml). The solid precipitate was filtered, dissolved in chloroform, dried over sodium sulfate, and evaporated to a paste. Crystallization from a mixture of ethanol and ethyl acetate gave **8** as colorless, fine needles (1.58 g, 90%): mp 181–183°; λ_{max}^{EtOH} 257 nm (ε 9900): nmr (DMSO-d_6) δ 3.15 (3 H, s, Me), 3.25 (3 H, s, Me), 3.30 (3 H, d, Me), 4.50 (3 H, broad singlet, an overlap of the signals of $H_{4'}$ and 5′-CH_2), 4.99 (2 H, s, benzyl methylene), 5.35 (1 H, t, $J_{2',3'}$ = 6, $J_{3',4'}$ = 4.0 Hz, $H_{3'}$), 5.63 (1 H, q, $J_{2',3'}$ = 6, $J_{1',2'}$ = 4.5 Hz, $H_{2'}$), 5.83 (1 H, d, $J_{5,6}$ = 8 Hz, H_5), 6.06 (1 H, d, $J_{1',2'}$ = 4.5 Hz, $H_{1'}$), 7.24 (5 H, s, Ph), 7.75 (1 H, d, $J_{5,6}$ = 8 Hz, H_6).

1-(3′-Deoxy-2′-*O*-mesyl-β-D-*glycero*-pent-2′-enofuranosyl)-3-benzyluracil (**9**).—3-Benzyl-2′,3′-di-*O*-mesyluridine (**7**) (0.68 g, 1.38 mmol) and sodium benzoate (600 mg, 4.15 mmol) were combined in DMF (8 ml), and the mixture was heated at 110–120° for 1 hr. After cooling, the mixture was filtered *in vacuo* and the solid was washed with a small amount of ethanol. The filtrate was concentrated to half volume and poured into ice–water (100 ml). The pasty precipitate was filtered and the filtrate was extracted with ethyl acetate (2 × 50 ml). The ethyl acetate extracts were combined with the above obtained paste, dried over sodium sulfate, and evaporated to a paste. Tlc with the use of silica gel and 20% ethanol in benzene indicated a major product with a small amount of by-product, which ran on the tlc plate slightly faster than the former. The mixture was applied on a silica gel column (35 × 2 cm) and eluted with chloroform–ethyl acetate (2:1) to give the starting material (160 mg, 23.6%). Preparative thin layer chromatography was repeatedly carried out on the recovered product mixture, using silica gel plates and a solvent mixture, chloroform–ethyl acetate (3:1), to give **9** as a homogeneous foam (0.2 g, 37%): nmr ($CDCl_3$) δ 3.03 (3 H, s, Me), 3.78 (2 H, br t, 5′-CH_2), 5.04 (2 H, s, benzyl methylene), 5.25 (1 H, br d, $J_{3',4'}$ = 3.3 Hz, $H_{4'}$), 5.7 (1 H, d, $J_{5,6}$ = 8 Hz, H_5), 5.95 (1 H, t, J = 1.6 Hz, $H_{1'}$), 6.7 (1 H, dd, $J_{1',3'}$ = 1.6, $J_{3',4'}$ = 3.3 Hz, $H_{3'}$), 7.1–7.4 (5 H, m, Ph), 7.7 (1 H, $J_{5,6}$ = 8 Hz, H_6).

Anal. Calcd for $C_{17}H_{18}N_2O_7S$: C, 51.78; H, 4.61; N, 7.10. Found: C, 51.74; H, 4.84; N, 7.32.

1-(3′-Deoxy-2′,5′-di-*O*-mesyl-β-D-*glycero*-pent-2′-enofuranosyl)-3-benzyluracil (**10**).—To an ice-cold stirred solution of **9** (0.16 g, 0.4 mmol) in anhydrous pyridine (2 ml) was added mesyl chloride (0.1 ml), and the mixture was left at 0° overnight. The reaction mixture was then poured into ice–water (100 ml) and the separating oil was extracted with chloroform (3 × 50 ml). The chloroform solution was washed with water, dried over sodium sulfate, and evaporated to a paste, which gradually crystallized on standing at room temperature under the presence of ethanol. Repeated crystallization from a mixture of ethanol and acetone gave **10** as colorless, fluffy crystals: mp 167–169° (80 mg, 42.5%); λ_{max}^{EtOH} 257 nm (ε 8800); nmr (DMSO-d_6) δ 3.12 (3 H, s, 2′-mesyl) and 3.43 (3 H, s, 5′-mesyl). For the signals of the other sugar protons see Figure 1. Additional signals lie at 7.23 (5 H, s, Ph) and 7.56 ppm (1 H, d, $J_{5,6}$ = 8 Hz, H_6).

Anal. Calcd for $C_{18}H_{20}N_2O_9S_2$: C, 45.77; H, 4.23; N, 5.93. Found: C, 45.85; H, 4.32; N, 5.76.

1-(3′,5′-Dideoxy-5′-iodo-2′-*O*-mesyl-β-D-*glycero*-pent-2′-enofuranosyl)-3-benzyluracil (**11**).—A mixture of **10** (0.15 g) and sodium iodide (0.3 g) in dry acetone (5 ml) was refluxed for 4 hr. After the solvent was evaporated, the residue was taken into ethyl acetate (50 ml) and the brown solution was washed with water (5 ml). This was then decolorized by shaking with 5% sodium thiosulfate solution, washed once with water (5 ml), and dried with sodium sulfate. Evaporation of the solvent gave a paste, which was chromatographed on a silica gel column using chloroform–ethyl acetate (3:1) as eluent. The main fraction gradually crystallized on standing at room temperature. Recrystallization from a mixture of ethanol and acetone gave **11** as colorless granules: mp 157° (75 mg, 68%); nmr ($CDCl_3$) δ 3.28 (1 H, d, J = 3.38 Hz, $H_{5'a}$), 3.38 (1 H, d, J = 2.0 Hz, $H_{5'b}$), 5.1 (2 H, s, benzyl methylene), 4.8–5.1 (1 H, complex multiplet, $H_{4'}$), 5.26 (1 H, d, $J_{5,6}$ = 8 Hz, H_5), 6.22 (1 H, t, J = 1.6 Hz, $H_{1'}$), 6.76 (1 H, dd, J = 3.2 and 1.6 Hz, $H_{3'}$), 7.1–7.6 (6 H, m, Ph and H_6).

Anal. Calcd for $C_{17}H_{17}O_6N_2SI$: C, 40.49; H, 3.40; N, 5.56. Found: C, 40.78; H, 3.43; N, 5.64.

***endo*-3-(3-Benzyluracil-1-yl)-2-oxabicyclo[3.1.0]-4-oxocyclohexane** (**13**).—1-(3′-Deoxy-2′,5′-di-*O*-mesyl-β-D-*glycero*-pent-2′-enofuranosyl)-3-benzyluracil (**10**) (0.11 g, 0.233 mmol) and anhydrous potassium carbonate (0.1 g, 0.73 mmol) were combined in a mixture of DMF (1 ml) and acetonitrile (1 ml), and the mixture was gently refluxed for 3.5 hr. After cooling, the inorganic solid was filtered and washed with a small amount of acetone. The combined filtrate and washings were concentrated *in vacuo*, dissolved in ethyl acetate (50 ml), washed with water (10 ml), and dried with sodium sulfate. The ethyl acetate solution was concentrated to a gum and chromatographed on a silica gel column using chloroform–ethyl acetate (3:1) as eluent, to give a crystalline compound, which was recrystallized from a mixture of acetone and ether to afford **13** as colorless needles of mp 163–166° (after drying under high vacuum at 90° for 5 days), yield 28 mg (40%).

Anal. Calcd for $C_{16}H_{14}N_2O_4$: C, 64.62; H, 4.73; N, 9.39. Found: C, 64.95; H, 4.82; N, 9.18.

Reaction of Potassium Carbonate with 3-Benzyl-5′-*O*-benzoyl-2′,3′-di-*O*-mesyluridine (**15**).—To a stirred cold solution of **7** (0.8 g, 1.62 mmol) in anhydrous pyridine (5 ml) was added benzoyl chloride (280 mg). After standing at room temperature overnight, the reaction mixture was poured into ice–water (30 ml) and the sticky precipitate was filtered, dissolved in chloro-

form (100 ml), and washed with 5% sodium bicarbonate (10 ml) and water (10 ml). The chloroform solution was dried over sodium sulfate and evaporated *in vacuo* to a paste, which weighed 0.96 g (100%) after drying in a desiccator under high vacuum for 20 hr. Thin layer chromatography with an aliquot of the product evidenced the reaction to be complete. The whole product was dissolved in DMF (7 ml), added with anhydrous potassium carbonate (555 mg, 4 mmol), and the mixture was heated at 110° for 20 min under stirring. The brown reaction mixture was evaporated *in vacuo* to a gum, which was dissolved in ethyl acetate (100 ml), washed with water (30 ml), dried over sodium sulfate, and again evaporated to a gum. Thin layer chromatography with the use of silica gel plates and a mixture of chloroform and ethyl acetate (3:1) revealed a major product running the half length of the plates with a slightly slower moving minor product. Preparative thin layer chromatography gave colorless crystals (16) of mp 183–184° (from ethyl acetate) from the slower moving band (20 mg); λ_{max}^{EtOH} 257 nm (ϵ 7200); nmr (DMSO-d_6) δ 5.12 (2 H, s, benzyl methylene), 5.84 (1 H, d, $J_{5,6}$ = 8 Hz, H_5), 7.42 (5 H, s, Ph), 7.55 (1 H, d, $J_{5,6}$ = 8 Hz, H_6), 11.14 (1 H, br, s, NH).

Anal. Calcd for $C_{11}H_{10}N_2O_2$: C, 65.33; H, 4.98; N, 13.86. Found: C, 65.49; H, 4.75; N, 13.68.

The faster moving impure material was combined with the mother liquor separated from 16, and again submitted to preparative thin layer chromatography with the use of a mixture of chloroform and ethyl acetate (3:1). Complete purification was unsuccessful. The recovered total material (0.34 g of paste) was dissolved in a mixture of pyridine (2 ml) and concentrated ammonia (2 ml), and left at room temperature overnight. The mixture was evaporated to a paste, which was taken into ethyl acetate (50 ml) and washed with 5% sodium bicarbonate (10 ml) and water (10 ml). After drying over sodium sulfate, the ethyl acetate solution was evaporated *in vacuo* to a foam, which was treated with mesyl chloride (0.1 ml) in pyridine (3 ml) at 0° overnight. The reaction mixture was added with methanol (1 ml), left at room temperature for 30 min, and then evaporated *in vacuo* at a temperature below 45°. The residual paste was taken into ethyl acetate (50 ml), washed with water (10 ml), dried, and again evaporated to a gum, which gave 0.18 g of colorless crystals of mp 168° from a mixture of ethanol and ethyl acetate. Its identity with **10** was confirmed by infrared and ultraviolet spectral comparison.

Reaction of 3-Benzyl-2′,3′,5′-tri-*O*-mesyluridine (8) with Sodium Benzoate.—3-Benzyl-2′,3′,5′-tri-*O*-mesyluridine (**8**) (0.7 g, 1.22 mmol) and sodium benzoate (0.7 g, 4.88 mmol) were combined in DMF (10 ml) and the mixture was heated at 100–110° for 1 hr under stirring. After cooling, the mixture was poured into ice–water (300 ml) and the solid precipitate was filtered by suction. The semidry material was dissolved in chloroform (200 ml) and dried over sodium sulfate. Evaporation of the solvent gave a paste, an aliquot of which was examined by tlc to show two major spots of approximately equal intensities and two faster moving traces. The absence of the starting material was also indicated. The total paste was chromatographed on a silica gel column with the use of a mixed solvent, chloroform–ethyl acetate (5:1), to effect the separation of the major products as a slightly faster moving material A, foam, 0.23 g, and a slower running material B, foam, 0.255 g. Comparative thin layer chromatography suggested the identity of A with compound **17**. The total product A was dissolved in a mixture of pyridine (2 ml) and concentrated ammonia (2 ml), and the mixture was left at room temperature overnight. The reaction mixture was concentrated to a gum, which was taken into ethyl acetate (50 ml) and washed with 5% sodium bicarbonate (5 ml) and water (5 ml). The ethyl acetate solution was dried and evaporated to a paste, which was completely dried under high vacuum and treated with mesyl chloride (0.07 ml) in dry pyridine (1.5 ml) overnight. After the usual work-up, the crude mixture was applied on a silica gel column (30 × 1 cm) and eluted with chloroform–ethyl acetate (3:1) to give a colorless foam (30 mg) of unknown structure and then the major product as a paste. The latter was crystallized from a mixture of ethanol and acetone to give a wool of mp 169–170° (70 mg). Its identity with **10** was fully confirmed by infrared spectral comparison. The yield of material A (**17**), based on the constitution of **17**, was 48%. On the other hand, the product B was suggested to be identical with compound **15** by its nmr spectrum, which contained signals assignable to two phenyl groups and two mesyl groups (δ 3.05, 6 H, d). The yield of the practically pure product B (**15**) conformed to 35%. This was dissolved in a mixture of pyridine (2 ml) and concentrated ammonia (2 ml), and the mixture was left at room temperature for two days. After the usual work-up as described above, the obtained pasty material was treated with mesyl chloride (0.07 ml) in dry pyridine (1.5 ml) overnight. The reaction mixture was worked up essentially in a similar way to above. Thin layer chromatography indicated one main product with two other trace amounts of by-products. Crystallization from a mixture of ethanol and acetone gave **10** (80 mg).

3-Benzyl-5′-*O*-acetyl-2′,3′-di-*O*-mesyluridine (18).—Compound **8** (0.57 g, 1 mmol) and sodium acetate (0.41 g, 5 mmol) were combined in DMF (10 ml), and the mixture was heated at 100° for 1 hr under stirring. The brown reaction mixture was poured into ice–water (100 ml) and the precipitate was filtered, dissolved in chloroform (150 ml), washed with water (30 ml), and dried with sodium sulfate. After the solvent was evaporated, the residual paste was submitted to preparative thin layer chromatography with the use of silica gel and a mixture of chloroform and ethyl acetate (3:1). The major portion was again chromatographed on a silica gel plate using chloroform–ethyl acetate (4:1) to give 240 mg of **18** as a homogeneous foam: nmr ($CDCl_3$) δ 2.05 (3 H, s, acetyl), 3.10 (3 H, s, mesyl), 3.15 (3 H, s, mesyl), 4.40 (3 H, br s, an overlap of $H_{4'}$ and 5′-methylene signals), 5.05 (2 H, s, benzyl methylene), 5.32 (2 H, br d, $H_{2'}$ and $H_{3'}$), 5.73 (1 H, s, $H_{1'}$), 5.79 (1 H, d, $J_{5,6}$ = 8 Hz, H_5), and 7.2–7.5 (6 H, m, Ph and H_6). This sample was dissolved in a mixture of pyridine (1 ml) and concentrated ammonia (1 ml) and warmed at 50° for 3 hr. The mixture was concentrated and worked up as above to give 120 mg of an impure foam, which was dissolved in pyridine (2 ml) and treated with mesyl chloride (0.04 ml) at room temperature for 10 hr. After the usual work-up, 80 mg of crystals (**8**) were obtained.

3-Benzyl-5′-deoxy-5′-iodo-2′,3′-di-*O*-mesyluridine (19).—A mixture of **8** (0.2 g) and sodium iodide (0.4 g) in acetone (8 ml) was heated to reflux for 5 hr. The reaction mixture was evaporated to a gum, which was taken into chloroform (100 ml) and washed with dilute sodium thiosulfate solution and water. The separated organic layer was dried with sodium sulfate and evaporated to a paste, which was crystallized from a small amount of ethyl acetate or acetone to afford colorless granules, mp 143–146° (0.15 g, 70.5%).

Anal. Calcd for $C_{18}H_{21}O_9S_2N_2I$: C, 36.01; H, 3.53; N, 4.67. Found: C, 35.71; H, 3.46; N, 4.67.

Reaction of 3-Benzyl-2′,3′,5′-tri-*O*-mesyluridine (8) with Potassium Carbonate.—3-Benzyl-2′,3′,5′-tri-*O*-mesyluridine (**8**) (0.5 g, 0.89 mmol) and anhydrous potassium carbonate (400 mg, 2.9 mmol) were combined in DMF (4 ml) and the mixture was stirred at 115–120° for 20 min. The solvent was evaporated off and the tarry residue was extracted with chloroform (4 × 50 ml) under the presence of water (15 ml), when the tar remained undissolved between both layers. The separated organic layer was dried with sodium sulfate and again concentrated to a paste. Preparative thin layer chromatography with the use of silica gel and a mixed solvent, chloroform–ethyl acetate (3:1), gave colorless needles, mp 162–164°, from the slightly faster moving band, which was identified with **13** in all respects, yield 15 mg (6%). The pasty material recovered from the slower moving band was again submitted to preparative tlc to give 0.25 g of **20** as a homogeneous foam (0.25 g, 58%): λ_{max}^{EtOH} 258 nm (ϵ 9500); nmr ($CDCl_3$) δ 3.9 (2 H, q, J = 3.0 and 6.7 Hz, 5′-methylene), 4.35 (3 H, m, $H_{2'}$, $H_{3'}$, and $H_{4'}$), 5.1 (2 H, s, benzyl methylene), 5.8 (1 H, $J_{5,6}$ = 8 Hz, H_5), 6.2 (1 H, s, $H_{1'}$), 7.3 (5 H, br m, Ph), and 7.55 (1 H, $J_{5,6}$ = 8 Hz, H_6).

Anal. Calcd for $C_{17}H_{18}N_2O_7S$: C, 51.78; H, 4.61; N, 7.10. Found: C, 51.64; H, 4.71; N, 6.85.

This was characterized as 1-(2′,3′-epoxy-5′-*O*-mesyl-β-D-lyxosyl)-3-benzyluracil by spectral comparison with a specimen prepared below.

Synthesis of 1-(2′,3′-Epoxy-5′-*O*-mesyl-β-D-lyxosyl)-3-benzyluracil (20) from 1-(2′,3′-Epoxy-5′-*O*-mesyl-β-D-lyxosyl)uracil.—1-(2′,3′-Epoxy-5′-*O*-mesyl-β-D-lyxosyl)uracil (0.38 g, 1.24 mmol), benzyl chloride (0.17 ml, 1.44 mmol), and potassium carbonate (220 mg, 1.6 mmol) were combined in a mixture of DMF (1.2 ml) and acetone (1.2 ml), and the mixture was refluxed for 2 hr. Thin layer chromatography indicated the formation of only one product and the presence of the starting material. The solvent was removed by evaporation and the residue was extracted with ethyl acetate (2 × 30 ml) under the presence of water (10 ml). After the usual work-up, the pasty extract was applied on a silica gel column and eluted with a mixture, chloroform–ethyl acetate

(2:1), to give 0.35 g (72%) of a homogeneous foam. This was identified with compound 20 obtained above by nmr and uv spectroscopy.

Anal. Calcd for $C_{17}H_{18}N_2O_7S$: C, 51.78; H, 4.61; N, 7.10. Found: C, 51.77; H, 4.71; N, 6.78.

Registry No.—**1**, 6554-10-5; **2**, 37440-10-1; **3**, 14985-34-3; **4**, 362-43-6; **5**, 32464-90-7; **6**, 37440-11-2; **7**, 37440-12-3; **8**, 37440-13-4; **9**, 37440-14-5; **10**, 37445-38-8; **11**, 37567-14-9; **13**, 37445-39-9; **15**, 37445-43-5; **16**, 28734-85-2; **17**, 37445-44-6; **18**, 37445-40-2; **19**, 37445-41-3; **20**, 37445-42-4; **21**, 37445-45-7; uridine, 58-96-8.

Stobbe Condensations of Dimethyl 3,5-Bis(benzyloxy)homophthalate[1a]

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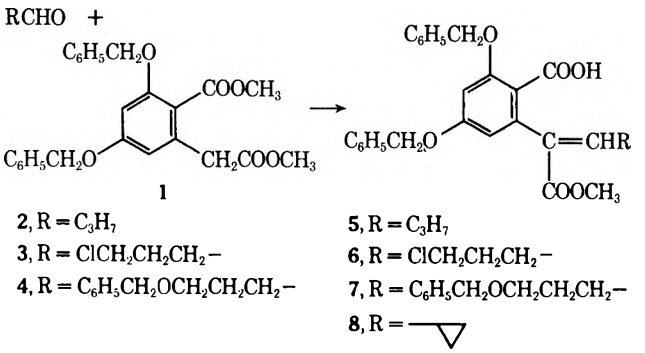
Dimethyl 3,5-bis(benzyloxy)homophthalate (1) reacts with aliphatic aldehydes under conditions of the Stobbe condensation to give preparative yields of Stobbe acid esters analogous to the Stobbe products of succinic esters. From butyraldehyde (2) and 4-benzyloxybutyraldehyde (4), respectively, are obtained 2,4-bis(benzyloxy)-6-(1-carbomethoxy-1-penten-1-yl)benzoic acid (5) and 6-(5-benzyloxy-1-carbomethoxy-1-penten-1-yl)-2,4-bis(benzyloxy)benzoic acid (7). In the case of 4-chlorobutyraldehyde (3), the Stobbe product (6) forms a cation (9) in the presence of base that undergoes intramolecular displacement of chlorine to give the cyclopropane derivative (8). In the condensation of 1 and 4 to give 7, a second product (12) is concurrently formed that is analogous to the paraconic esters formed in the Stobbe condensations of succinic esters. 3,4-Dihydroisocourmarins such as 12 have not been observed previously in Stobbe condensations of homophthalic esters. Ester acid (7) was readily saponified to diacid 13 and reduced to the β-resorcyclic acid derivative 14.

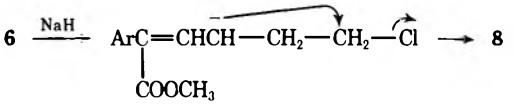
In the course of development of a synthetic route for (*R*,*S*)-zearalanone,[2] we have studied the reaction of dimethyl 3,5-bis(benzyloxy)homophthalate (1) with several aliphatic aldehydes under conditions of the Stobbe condensation.[3]

The original concept of the Stobbe reaction as a basic condensation of esters of succinic acid with aldehydes and ketones has been extended to homophthalic esters with a variety of aromatic aldehydes and ketones.[4] We find that this condensation proceeds smoothly with aliphatic aldehydes using sodium hydride as base,[5] to give preparative yields of the Stobbe half-esters. With butyraldehyde (2), for example, a quantitative yield of the Stobbe half-ester **5** was readily obtained.



2, R = C_3H_7
3, R = $ClCH_2CH_2CH_2-$
4, R = $C_6H_5CH_2OCH_2CH_2CH_2-$
5, R = C_3H_7
6, R = $ClCH_2CH_2CH_2-$
7, R = $C_6H_5CH_2OCH_2CH_2CH_2-$
8, R =

With 4-chlorobutyraldehyde (**3**), a secondary reaction also took place. In addition to normal Stobbe condensation (which would have given the half-ester **6**), cyclization occurred so that the only product isolated (in 63% yield) was the cyclopropane-containing half-ester **8**. The mechanism of formation of **8** probably involves the reaction of base with the first-formed Stobbe product **6** to give carbanion **9**, which



9

then cyclizes to **8** by intramolecular displacement of chlorine. Similar intermediates have been proposed before in the formation of cyclopropane derivatives, such as in the reaction of 4-chlorobutyronitrile and sodamide to give cyclopropanenitrile.[6] We believe that the formation of **8** represents the first observation of cyclization of a derivative of 6-halo-2-hexenoic acid to a cyclopropane.

The familiar, accepted mechanism for the Stobbe reaction proposed an intermediate paraconic ester.[3] In the use of succinic esters in the Stobbe reaction, paraconic esters have been identified and isolated on several occasions. A similar mechanism for the reaction of an aldehyde with methyl homophthalate would involve the steps shown in Scheme I. The 3,4-dihydroisocoumarin **10** is analogous to the paraconic esters formed during the Stobbe condensation of succinic esters, but until now **10** has not been isolated under Stobbe conditions. Instead, **11** is the isolated product. Under acidic conditions, however, **11** may be isomerized to **10**.[4b]

In the present work it was demonstrated that an analog of **10** was obtainable by reaction of **1** with 4-benzyloxybutyraldehyde (**4**) under Stobbe conditions. Two products were isolated, one of which is the expected half-ester **7**, and the other of which is the 3,4-dihydroisocoumarin **12**. The latter product was converted quantitatively into **7** by treatment with sodium

(1) (a) Part of this work was presented as a paper at the 157th National Meeting of the American Chemical Society, Minneapolis, Minn., April 1969, MEDI 28. (b) G. D. Searle International Co., P. O. Box 5486, Chicago, Ill. 60680.

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(5) G. H. Daub and W. S. Johnson, *J. Amer. Chem. Soc.*, **72**, 501 (1950).

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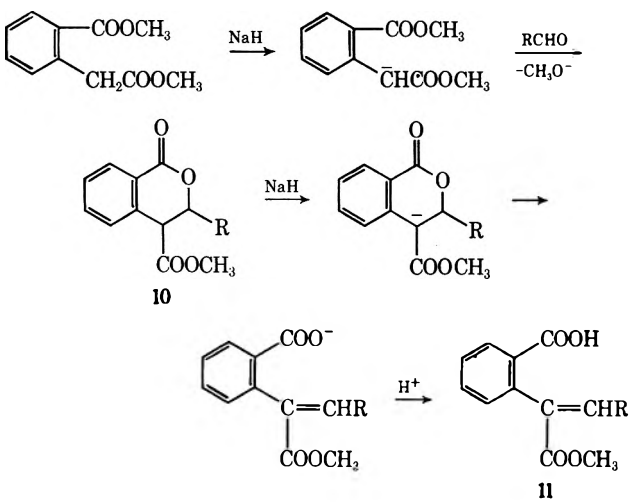
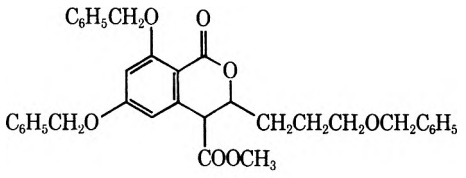
SCHEME I



methoxide in absolute methanol. Products **7** and **12** were separated chromatographically.



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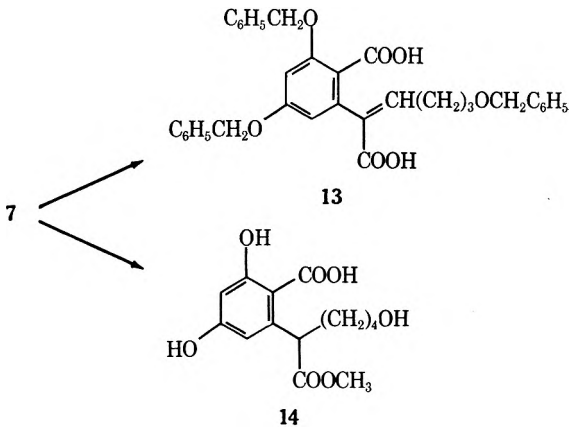
The infrared spectra of half-esters **5**, **7**, and **8** showed intense sharp bands at 1707 cm^{-1} from carbonyl absorptions of the α,β-unsaturated ester functions. The 3,4-dihydroisocoumarin **12** exhibited an equally intense sharp band at 1720 cm^{-1} for the lactone carbonyl, a value in good agreement with the values previously reported[4b] for other 3,4-dihydroisocoumarins prepared from Stobbe products. Crystalline half-esters **5** and **8** showed intense sharp bands at 1680 and 1688 cm^{-1}, respectively, for carboxyl carbonyl absorptions. Half-ester **7**, which was noncrystalline although analytically pure, showed only a poorly defined shoulder on the ester carbonyl band to indicate carboxyl.

Daub and Johnson, who developed the use of sodium hydride as a superior basic reagent for Stobbe condensations, reported that, although this reaction proceeded at a suitable rate to give a high yield of product from diethyl succinate, acetophenone, and this base, no appreciable reaction occurred comparably with benzophenone until a few drops of alcohol were added.[7] The reaction then proceeded suitably. As a general procedure, they recommended use of 0.25 mol of alcohol/mol of ketone (or aldehyde).[5] With respect to Stobbe condensations of homophthalic esters using sodium hydride, the literature is not consistent: Loewenthal and Pappo[4b] did not report use of alcohol in any of their successful Stobbe condensations, including one with benzophenone. Chatterjea, *et al.*,[4e] reported use of a catalytic amount of alcohol in one out of seven successful Stobbe condensations.

In our hands, using equimolar amounts of **1**, aldehyde, and sodium hydride in dry benzene at 25°, the Stobbe condensation proceeded satisfactorily to preparative yields *only* when alcohol was added. With **1** and **2**, for example, a quantitative yield of **5** was obtained if a 0.25 molar equiv of absolute ethanol was added initially; reduction to half this amount of alcohol gave only a 40% yield of Stobbe product **5**, accompanied by a 40% yield of a methyl hydrogen 3,5-bis(benzyloxy)homophthalate.

Similarly, condensation of **1** and **4** gave a quantitative total yield of **7** and **12** with use of 0.25 molar equiv of alcohol in a reaction time of 1 hr. Half this amount of alcohol, in the same time, gave only a 70% yield of Stobbe product together with a 30% recovery of **1**. When no alcohol was used, the yield fell to 66% in 1 hr of reaction time, and unchanged **1** was detected after 4 days.

Ester acid **7** was readily saponified to diacid **13**. Low pressure hydrogenolysis, catalyzed by palladium on charcoal, readily removed the three benzyl groups of **7** and reduced the ethylenic double bond, to give **14**.



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14

Experimental Section

Infrared spectra were obtained with a Perkin-Elmer 21 spectrophotometer. Nuclear magnetic resonance spectra were obtained on a Varian A-60A spectrometer. Melting points were taken in a Thomas-Hoover capillary melting point apparatus and are uncorrected.

Dimethyl 3,5-Bis(benzyloxy)homophthalate (1).—Dimethyl 3,5-dihydroxyhomophthalate[8] (1.2 g, 0.005 mol), benzyl chloride (2.35 ml, 0.02 mol), and anhydrous potassium carbonate[9] (2.0 g, 0.0146 mol) were mixed with 25 ml of dry methyl ethyl ketone. The mixture was refluxed for 72 hr, and then the solvent was removed under reduced pressure. The residue was treated with water, and the aqueous mixture was extracted with ether. From evaporation of the dried ether extract was obtained an oil that crystallized on trituration with methanol to yield 0.65 g (33%) of pure **1**, mp 85–86°.

Anal. Calcd for $C_{25}H_{24}O_6$: C, 71.33; H, 5.71. Found: C, 70.94; H, 5.96.

2,4-Bis(benzyloxy)-6-(1-carbomethoxy-1-penten-1-yl)benzoic Acid (5).—A solution of **1** (6.72 g, 0.016 mol), 53.3% sodium hydride (0.720 g, 0.016 mol), and anhydrous ethanol (12 drops) in 20 ml of dry benzene under nitrogen was added dropwise in 10 min to a solution of **2** (1.152 g, 0.016 mol) in 10 ml of dry benzene. After stirring overnight at room temperature, 50 ml of water was added. The aqueous phase was separated, washed with ether, and then acidified (dilute HCl) to precipitate a quantitative yield (7.5 g) of **5**, mp 130–132°.

Anal. Calcd for $C_{28}H_{28}O_6$: C, 73.02; H, 6.12. Found: C, 72.77; H, 6.47.

2,4-Bis(benzyloxy)-6-(1-carbomethoxy-2-cyclopropylvinyl)benzoic Acid (8).—Under conditions identical with those given for the preparation of **5**, except for the substitution of 1.70 g

(7) G. H. Daub and W. S. Johnson, *J. Amer. Chem. Soc.*, **70**, 418 (1948).

(8) D. S. Jerdan, *J. Chem. Soc.*, 808 (1899); H. Nogami, *J. Pharm. Soc. Jap.*, **61**, 24 (1941); A. Kamal, A. Robertson, and E. Tittensor, *J. Chem. Soc.*, 3375 (1950); W. R. Allison and G. T. Newbold, *ibid.*, 2512 (1960).

(9) With use of potassium carbonate sequihydrate, only dimethyl 4-benzyloxy-2-hydroxyhomophthalate can be obtained from this reaction.

(0.016 mol) of 3[10] for 2, 5.00 g (63%) of white 8, mp 178–179°, was obtained: nmr (DMSO-d_6) δ 0.5–1.0 (broad m, 5.5, cyclopropyl H's), 3.58 (s, 3, OCH_3), 5.15 (s, 4, 2 $OCH_2C_6H_5$), 6.24 (broad s, 1, >C=CH—), 6.45 (d, J = 2 cps, 1, aromatic H), 6.85 (d, J = 2 cps, 1, aromatic H), 7.45 (s, 10, 2 $OCH_2H_6H_5$).

Anal. Calcd for $C_{28}H_{26}O_6$: C, 73.35; H, 5.71. Found: C, 73.21; H, 5.80.

6-(5-Benzyloxy-1-carbomethoxy-1-penten-1-yl)-2,4-bis(benzyloxy)benzoic Acid (7) and 3-(3-Benzyloxypropyl)-4-carbomethoxy-6,8-bis(benzyloxy)-3,4-dihydroisocoumarin (12).—Under conditions identical with those given for the preparation of 5, except for the substitution of 2.85 g (0.016 mol) of 4[11] for 2, 9.00 g (quantitative yield) of a paste was obtained. This paste was a mixture of 7 and 12.

When 7 was desired, the paste was dissolved in 60 ml of anhydrous methanol, 0.865 g (0.016 mol) of sodium methoxide was added, and the resulting mixture was refluxed overnight. After cooling, it was acidified (dil HCl). Methanol was removed under reduced pressure, and the paste that remained was extracted with ether. The extract was dried ($MgSO_4$), and removal of ether gave 8.36 g (92.2%) of 7 as a paste: nmr ($CDCl_3$) δ 1.5–2.2 (broad m, 4, $-CHCH_2CH_2CH_2OCH_2C_6H_5$), 3.2–3.92 (m, 5, $-OCH_2$ and $-OCH_3$), 4.40 (s, 2, $-OCH_2C_6H_5$, aliphatic), 5.00–5.10 (d, 4, 2 $OCH_2C_6H_5$, aromatic), 6.40 (d, J = 2 cps, 1, aromatic H), 6.8–6.95 (m, 1, >C=CH—), 7.20–7.35 (d, 15, 3 $OCH_2C_6H_5$), 9.83 (broad s, 1, –COOH).

Anal. Calcd for $C_{35}H_{34}O_7$: C, 74.20; H, 6.00. Found: C, 73.97; H, 6.36.

When 12 was desired, the pasty mixture of 7 and 12 (9.00 g) was subjected to dry column chromatography on silica gel HF 254 using 2:3 acetone–cyclohexane mixture as the solvent. There was obtained 1.13 g (12.5%) of 12 which, after recrystallization from methanol, melted at 128–130°: nmr ($CDCl_3$) δ 1.7–2.00 (m, 4, $-CH_2CH_2CH_2O-$), 3.65 (s, 3, OCH_3), 3.40–3.80 (m, 3, C-4 H and $-CH_2CH_2CH_2O-$), 4.38 (broad s, 3, $-OCH_2-C_6H_5$ aliphatic and C-3 H), 5.02–5.18 (d, 4, 2 $OCH_2C_6H_5$ aromatic), 6.40 (d, J = 2 cps, 1, aromatic H), 6.60 (d, J = 2 cps, 1, aromatic H), 7.29–7.39 (d, 15, 3 $OCH_2C_6H_5$).

Anal. Calcd for $C_{35}H_{34}O_7$: C, 74.20; H, 6.00. Found: C, 74.54; H, 6.64.

The 3,4-dihydroisocoumarin (12) was converted into 7 in good yield by the method given above for the pasty mixture of 7 and 12.

α-(4-Benzyloxybutylidene)-3,5-bis(benzyloxy)homophthalic Acid (13).—Half-ester 7 was hydrolyzed by boiling in 10% alkali for 2 hr to give 10 as a paste in quantitative yield. This paste contained about 0.7 g-atom of sodium/mol of 13. To free the acid from its salt, the paste was dissolved in a minimal amount of ethanol, excess concentrated HCl was added, and the resulting solution was stirred overnight at 25°. Ethanol was removed under reduced pressure and water was added to the mixture. The product was extracted with ether. The ethereal extract was dried ($MgSO_4$), and ether was removed to give 13 as a paste. Final purification was accomplished by column chromatograph on Florisil (100–200 mesh) with chloroform: nmr ($CDCl_3$) δ 1.35–2.25 (broad m, 4, $=CHCH_2CH_2CH_2O-$), 3.25 (m, 2, $-CH_2OCH_2C_6H_5$), 4.25 (s, 2, $-OCH_2C_6H_5$, aliphatic), 4.80 (broad d, 4, 2 $OCH_2C_6H_5$, aromatic), 6.25 (broad s, 1, aromatic H), 6.35 (broad s, 1, aromatic H), 6.80 (m, 1, >C=CH—), 7.02 (s, 5, $-OCH_2C_6H_5$), 7.10 (s, 10, 2 $OCH_2C_6H_5$), 10.7 (broad s, 2, –COOH).

Anal. Calcd for $C_{34}H_{32}O_7$: neut equiv, 552. Found: neut equiv, 549.

6-(1-Carbomethoxy-5-hydroxypentyl)-β-resorcyclic Acid (14).—Half-ester 7 (6.00 g, 1.01 mol) was dissolved in 100 ml of absolute ethanol and hydrogenated (60 psi) over 5.0 g of 5% Pd/C catalyst for 6 hr. After removal of solvent and catalyst, 3.0 g (94%) of 14 was obtained as a paste.

Anal. Calcd for $C_{14}H_{18}O_7$: C, 56.37; H, 6.04. Found: C, 55.80; H, 6.32.

Registry No.—1, 37172-97-7; 5, 37172-98-8; 7, 37172-99-9; 8, 37172-00-5; 12, 37172-01-6; 13, 37172-02-7; 14, 37172-03-8.

Acknowledgment.—The authors express their appreciation to Mr. Carl Wassink for combustion analyses and infrared spectra.

(10) 4-Chlorobutyraldehyde (3) was prepared both by the three-step procedure of R. Paul, *Bull. Soc. Chim. Fr.*, 8, 911 (1941), from tetrahydrofurfuryl alcohol, and by a two-step process involving the conversion of butyric acid into 4-chlorobutyryl chloride followed by Rosenmund reduction of the latter to 3: R. B. Loftfield, *J. Amer. Chem. Soc.*, 73, 1365 (1951). In our hands, the latter process was the more convenient for laboratory-scale preparations.

(11) 4-Benzyloxybutyraldehyde was readily prepared from tetrahydrofurfuryl alcohol by its conversion into 1,2,5-pentanediol, acetalization of the vicinal hydroxyl groups, benzylation of the 5-hydroxy function, hydrolysis of the acetal, and oxidative cleavage with lead tetraacetate; see C. L. Wilson, *J. Chem. Soc.*, 48 (1945), and R. Paul and S. Tchelitcheff, *Bull. Soc. Chim. Fr.*, 15, 197 (1948).

Notes

Decarboxylation Studies on 3,5-Dihydroxyhomophthalic Acid Derivatives[1a]

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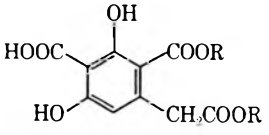
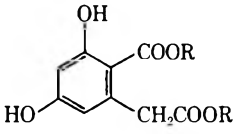
A synthetic pathway, developed for the preparation of (*R*,*S*)-zearalanone,[2] required removal of both the salicylic type and the α,β-unsaturated type of carboxyl group from polyfunctional derivatives of 3,5-dihydroxyhomophthalic acid.

Removal of the 4-carboxyl group of dialkyl 4-carboxy-3,5-dihydroxyhomophthalates has been reported on several occasions under various conditions. Poor yields generally have been experienced, which we have confirmed.

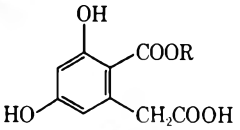
Treatment of dimethyl 4-carboxy-3,5-dihydroxyhomophthalate (**1**) with quinoline and copper powder consumed **1**, but did not yield the expected product **3**.[3] The action of hot 23% KOH on the diethyl ester **2** gave only a poor yield of crude half-ester **5**.[4] Poor



1, R = CH_3
2, R = C_2H_5



3, R = CH_3
4, R = C_2H_5



5

or unreproducible yields of **3** and **4** have been obtained by treatment of **1** and **2**, respectively, with hot quinoline and copper bronze.[5-7] Similarly, hot glycerol resulted in a poor, unreproducible yield of **3** from **1**.[5]

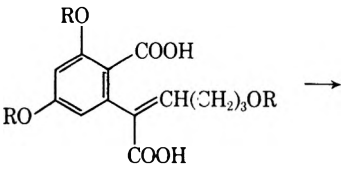
In contrast to these unproductive results, we found that an excellent, reproducible method for decarboxylation of **1** is to heat its solutions in dimethyl sulfoxide or dimethylformamide. No catalyst is necessary. Heating a solution of **1** in dimethyl sulfoxide[8] to 155° for 40–60 min consistently gave a 65–70% yield of **3**. A pure product could be obtained more readily in the same yield by refluxing a solution of **1** in dimethylformamide for 30 min.

Also, adaptation of a technique developed by Kaeding[9] for decarboxylation of salicyclic acids gave rise to a reproducible, preparative yield of diester **3** from 4-carboxy diester **1**. A mixture of **1** and magnesium benzoate in benzoic acid, when heated to 180° for 20 min, readily gave a 60% yield of recrystallized **3**. In this decarboxylation, **1** and magnesium benzoate were used in approximately 11:1 molar proportions. Doubling the relative amount of magnesium benzoate did not increase the yield. No **3** was obtained when benzoic acid was replaced with a less protic solvent, resorcinol.

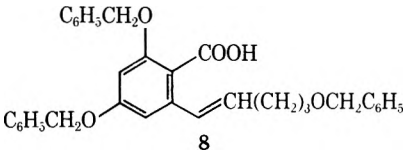
α-(4-Benzyloxybutylidene)-3,5-bis(benzyloxy)homophthalic acid (**6**), a Stobbe product,[10] proved more difficult to decarboxylate. Heating diacid **6** to 185° under nitrogen for 30 min gave a mixture of at least three unidentified products. A similar result was obtained at 185° in quinoline in the presence of copper powder.[3] Johnson and his coworkers developed a method for decarboxylation of Stobbe products from succinic esters, wherein the Stobbe product was refluxed with a 3:2:1 mixture of acetic acid, 48% hydrobromic acid, and water.[11] Under these conditions a 65% recovery of **6** was experienced after 2.5 hr of refluxing.

Aliphatic α,β-unsaturated acids, RCH=CHCOOH, have been decarboxylated to $RCH{=}CH_2$ in preparative yields by conversion to $RCHBrCH_2COONa$ and heating the latter to give the olefin.[12] This method was not applicable for **6**, however, since treatment with hydrogen bromide at 0° in chloroform chiefly promoted debenzylation to give benzyl bromide and debenzylated diacid **7**.

In contrast to the decarboxylation of **1** in dimethyl sulfoxide, we found that, in order to decarboxylate **6** into monoacid **8** in this solvent at 150°, it was necessary to use an acid salt of **6**. Pure **6** was unreactive under



6, R = $CH_2C_6H_5$
7, R = H



8

(1) (a) Part of this work was presented as a paper at the 157th National Meeting of the American Chemical Society, Minneapolis, Minn., April 1969, MEDI 28. (b) G. D. Searle International Co., P. O. Box 5486, Chicago, Ill. 60680.

(2) R. N. Hurd and D. H. Shah, *J. Med. Chem.*, in press.

(3) C. Walling and K. B. Wolfstirn, *J. Amer. Chem. Soc.*, **69**, 852 (1957).

(4) D. S. Jerdan, *J. Chem. Soc.*, 808 (1899), reported a 30% yield of **5** under the same conditions. For the correct structural assignments to Jerdan's products, see ref 5 and 6.

(5) A. Kamal, A. Robertson, and E. Tittensor, *J. Chem. Soc.*, 3375 (1950).

(6) H. Nogami, *J. Pharm. Soc. Jap.*, **61**, 24 (1941).

(7) W. R. Allison and G. T. Newbold, *J. Chem. Soc.*, 2512 (1960).

(8) Tetrahalophthalic acids have been decarboxylated in excellent yield by refluxing their solutions in dimethyl sulfoxide: C.-T. Chen, S.-J. Yan, and C.-H. Wang, *Chem. Ind. (London)*, 895 (1970).

(9) W. W. Kaeding, *J. Org. Chem.*, **29**, 2556 (1964).

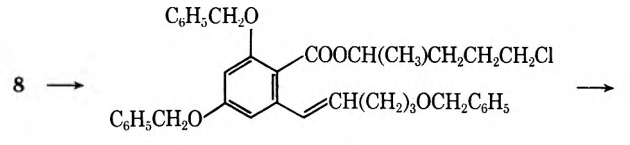
(10) R. N. Hurd and D. H. Shah, *J. Org. Chem.*, **38**, 607 (1973).

(11) W. S. Johnson, A. Goldman, and W. P. Schneider, *J. Amer. Chem. Soc.*, **67**, 1357 (1945).

(12) W. G. Young, R. T. Dillon, and H. J. Lucas, *ibid.*, **51**, 2528 (1929); S. Winstein, D. Pressman, and W. H. Young, *ibid.*, **61**, 1646 (1939).

these conditions. This acid salt,[10] which contained 0.7 g-atom of sodium per mole of **6**, underwent decarboxylation to give 80–90% yields of **8** consistently. As with **1**, we found that dimethyl sulfoxide could be replaced with dimethylformamide to give the same yield of **8**, but in a more readily purified state.

The structure shown for **8** was supported by conversion of acid **8** into ester **9** followed by debenzylation and reduction of the latter to the 6-substituted β-resorcylic ester **10**. Esterification of **8** was accomplished in 73%



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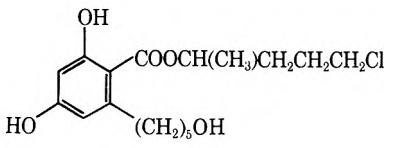

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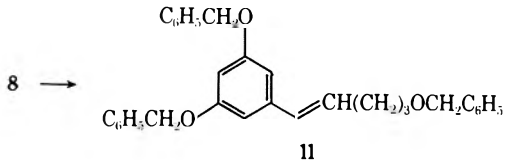
yield by intermediate formation of the acid chloride of **8**, and reaction of the acid chloride with 5-chloro-2-pentanol. Hydrogenation of **9** (Pd/C) gave **10** in 75% yield.

In contrast to the successful esterification of **8** to **9**, treatment of **8** with 5-chloro-2-pentanol in refluxing benzene, catalyzed by *p*-toluenesulfonic acid, led only to the decarboxylated resorcinol derivative **11**.



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Carboxylate anions have been shown to be intermediates in some, and proposed in many other, first- and second-order electrophilic thermal decarboxylations.[13] The fact that **6** is not decarboxylated in DMSO as **1** is, but requires conversion to an acid salt, appears to relate to the lower acidity of **6** compared to **1**. That **6** is weaker than **1** is evident by considering two models for **6** and **1**, namely, 2-methoxybenzoic acid, $pK_a = 4.09$, and atropic acid, $PhC(COOH)=CH_2$, $pK_a = 3.85$. The nonreaction of pure **6** in DMSO agrees with Chen, Yan, and Wang's observation[8] that relatively weak acids are not decarboxylated in this manner.

Experimental Section

Infrared spectra were obtained with a Perkin-Elmer 21 spectrophotometer. Nuclear magnetic resonance spectra were obtained on a Varian A-60A spectrometer. Melting points were taken in a Thomas-Hoover capillary melting point apparatus, and are uncorrected.

Dimethyl 3,5-Dihydroxyhomophthalate (3).—A solution of dimethyl 4-carboxy-3,5-dihydroxyhomophthalate (**1**)[2,14] (50.0 g, 0.12 mol) in 150 ml of DMF was refluxed under nitrogen for 30 min. On cooling, the mixture was diluted with 1 l. of water, and the whole was extracted seven times with 250-ml portions of ether. The combined ether extracts were washed thrice with 250-ml portions of water, then dried ($MgSO_4$). Removal of ether gave 29.0 g (70%) of crude **3** which was purified by chromatographic separation on 300 g of 100–200 mesh Florisil with chloroform. This treatment resulted in 17.0 g (40%) of **3**:[7] mp 144–145°; nmr (acetone-d_6) δ 3.66 (s, 3, $-OCH_3$), 3.87 (s, 5, benzylic CH_2 and $-OCH_3$), 6.38 (s, 2, 2 aromatic H), 9.3 (broad s, 1, –OH), 11.55 (s, 1, H-bonded –OH).

Anal. Calcd for $C_{11}H_{12}O_6$: C, 55.00; H, 5.00. Found: C, 54.92; H, 5.13.

From the aqueous wash of the above ether extracts, unreacted **1** (5.00 g) was recovered.

3 was also obtained by heating to 160° a solution of **1** (6.90 g) in 40 ml of dimethyl sulfoxide for 45–60 min until CO_2 evolution stopped. On cooling, the mixture was diluted with 400 ml of water, and the whole was extracted four times with 150-ml portions of ether. After the extracts were washed and dried, and the ether was removed, 3.8 g (64%) of crude **3** was obtained. This was recrystallized from benzene–hexane to give 1.2 g of **3**, mp 144–145°.

3 was also obtained by preparing a mixture of 2.0 g of **1**, 0.174 g of magnesium benzoate, and 10.0 g of benzoic acid. This mixture was heated to 180° for 20 min under nitrogen. After cooling, the mixture was dissolved in 20 ml of ether, and the ether solution was thrice extracted with 30-ml portions of 5% $NaHCO_3$ solution. The ether solution was dried, and ether was removed to give 2.0 g of viscous red oil. Some of this oil could be separated as crystals (0.6 g), mp 144–145°, by treatment with benzene–hexane followed by trituration with chloroform.

2,4-Bis(benzyloxy)-6-(5-benzyloxy-1-penten-1-yl)benzoic Acid (8).—A solution of the acid salt of α-(4-benzyloxybutylidene)-3,5-bis(benzyloxy)homophthalic acid (**6**)[10] (6.5 g) in 40 ml of DMSO was heated to 155° under nitrogen for 30 min. The reaction mixture was worked up in the same manner as isolation of **3** from its DMSO reaction mixture. The crude, oily **8** from the ether extract residues was purified by chromatographic separation on 170 g of Silicar-CC-7 with chloroform to give 4.75 g (80%) of **8**: nmr ($CDCl_3$) δ 1.5–2.5 (m, 4, $=CHCH_2CH_2CH_2O-$), 3.5 (t, 2, $-CH_2CH_2OCH_2C_6H_5$), 4.46 (s, 2, aliphatic $-OCH_2C_6H_5$), 4.96–5.00 (d, 4, 2 aromatic $-OCH_2C_6H_5$), 6.1–6.7 (m, 4, 2 aromatic H, and –CH=CH–), 7.2–7.32 (d, 15, 3 $-OCH_2C_6H_5$), 9.58 (broad s, 1, –COOH).

Anal. Calcd for $C_{33}H_{32}O_5$: C, 77.95; H, 6.30. Found: C, 78.28; H, 6.47.

8 was prepared also by refluxing a solution of the acid salt of **6**[10] (0.50 g) in 10 ml of DMF for 30 min under nitrogen. The mixture was worked up in the same manner as isolation of **3** from its DMF mixture, except that chromatographic purification was unnecessary. Ether extracts were evaporated to give 0.36 g (80%) of **8** with the same physical characteristics as above.

4-Chloro-1-methylbutyl 2,4-Bis(benzyloxy)-6-(5-benzyloxy-1-penten-1-yl)benzoate (9).—To a solution of **8** (2.03 g, 4 mmol) in 20 ml of dry benzene were added thionyl chloride (0.960 g, 8 mmol) and 12 drops of pyridine. The mixture was stirred overnight. Pyridine hydrochloride was filtered off. Volatiles were removed under vacuum to give a viscous red paste. To this paste was added 5-chloro-2-pentanol[15] (1.4 g, 10 mmol) in 20 ml of dry benzene. The mixture was stirred overnight, benzene was removed under vacuum, and the thick red liquid residue was chromatographed to give 1.75 g (73%) of **9** as a red paste: nmr ($CDCl_3$) δ 1.18–1.29 (d, 3, $>CHCH_3$), 1.50–2.50 (m, 8, $-CH_2-CH_2CH_2Cl$ and $-CH_2CH_2CH_2OCH_2C_6H_5$), 3.15–3.6 (m, 4, $-CH_2-OCH_2C_6H_5$ and $-CH_2Cl$), 4.45 (s, 2 aliphatic $-OCH_2C_6H_5$), 4.95 (d, 4, 2 aromatic $-OCH_2C_6H_5$), 6.00–6.35 (m, 2, –CH=CH–), 6.42 (J = 2 cps, 1, aromatic H), 6.62 (J = 2 cps, 1, aromatic H), 7.3 (d, 15, 3 $-OCH_2C_6H_5$).

Anal. Calcd for $C_{38}H_{41}ClO_5$: Cl, 5.80. Found: Cl, 5.71.

4-Chloro-1-methylbutyl 2,4-Dihydroxy-6-(5-hydroxypentyl)benzoate (10).—A mixture of **9** (11.8 g, 0.02 mol) and 6.0 g of 5% Pd/C catalyst in 200 ml of ethanol was reduced with hydrogen (1 atm, 25°). After the theoretical amount of hydrogen was taken up, the catalyst was removed, and the solution was concentrated under vacuum to give 6.0 g (90%) of **10**: nmr ($CDCl_3$) δ 1.3–1.4 (d, 3, $-OCHCH_3$), 1.43–2.00 (m, 10, $-CH_2CH_2CH_2Cl$ and $-CH_2CH_2CH_2CH_2CH_2OH$), 2.55–3.1 (m, 2, benzylic CH_2), 3.4–3.9 (m, 5, $-CH_2OH$ and $-CH_2Cl$), 5.2 (broad s, 1, –COO-

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(14) W. Theilacker and W. Schmid, *Justus Liebigs Ann. Chem.*, **570**, 15 (1950); E. Hardegger, W. Rieder, A. Walser, and F. Kugler, *Helv. Chim. Acta*, **49**, 1283 (1966).

(15) R. C. Elderfield, W. J. Gensler, F. Brody, J. D. Head, S. C. Dickerman, L. Wiederhold, III, C. B. Kremer, H. A. Hageman, F. J. Kreysa, J. M. Griffing, S. M. Kupchan, B. Newman, and J. T. Maynard, *J. Amer. Chem. Soc.*, **68**, 1579 (1946).

$CHCH_3$), 6.25 (s, 2, J = 2 cps, 2 aromatic H), 7.3 (s, 1, phenolic OH), 11.98 (s, 1, H-bonded phenolic OH).

Anal. Calcd for $C_{17}H_{25}ClO_5$: C, 59.21; H, 7.25; Cl, 10.30. Found: C, 59.01; H, 7.21; Cl, 9.79.

1-(5-Benzyloxy-1-penten-1-yl)-3,5-bis(benzyloxy)benzene (11).—A mixture of 8 (0.34 g, 0.67 mmol), 5-chloro-2-pentanol[16] (0.40 g, 3.27 mmol), and *p*-toluenesulfonic acid (0.05 g) in 75 ml of dry benzene was refluxed overnight, water being removed by a Dean-Stark receiver. On cooling, the mixture was washed with 15 ml of 5% $NaHCO_3$ and 15 ml of water, then dried ($MgSO_4$). Benzene was removed to leave a greenish liquid residue which was purified on a preparative tlc plate using chloroform to give 0.25 g (80%) of 11 as a paste. The ir spectrum of 11 showed no carbonyl absorption.

Anal. Calcd for $C_{32}H_{32}O_3$: C, 82.90; H, 6.94. Found: C, 82.40; H, 7.12.

Registry No.—**3**, 6110-30-1; **8**, 37173-19-6; **9**, 37173-20-9; **10**, 37173-21-0; **11**, 37173-22-1.

Acknowledgment.—The assistance of Mr. Carl Wassink and his staff in obtaining elemental analyses and ir spectra is gratefully acknowledged.

A Novel Furan Dimer

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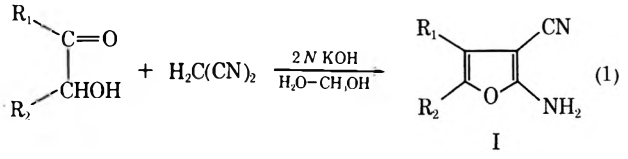
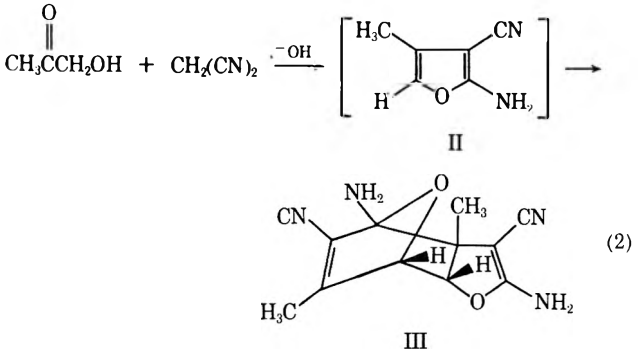
Gewald[1] has reported that the interaction of acyloins with malononitrile in aqueous base yields 2-amino-3-cyanofurans of type I (eq 1).[2] This scheme has subsequently been used to prepare a variety of such substances from readily available acyloins.



(1)

I

We would like to report that our experience with the synthesis of 2-amino-3-cyano-4-methylfuran (II), from hydroxy-2-propanone and malononitrile according to Gewald (eq 2), leads us to conclude that the product is not II but that it is 2,4-diamino-3,5-dicyano-3a,6-dimethyl-3a,4,7,7a-tetrahydro-*endo*-4,7-epoxybenzofuran (III), formed by way of a remarkable Diels–Alder cycloaddition of II with itself.



(2)

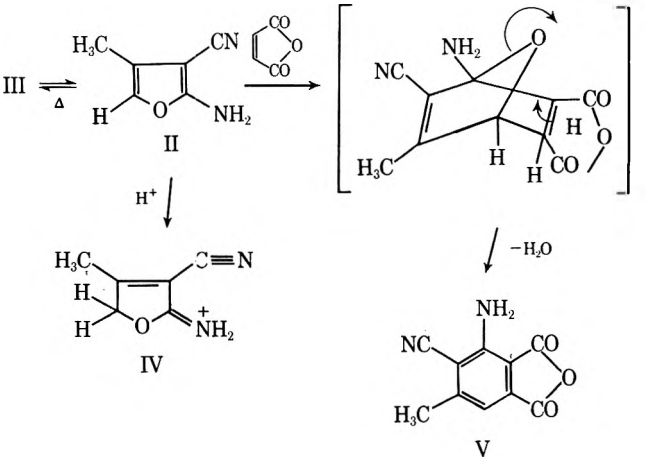
The nmr spectrum of III in pyridine-d_5 consisted of a singlet at 1.62 (3 H, 3a-CH_3), a singlet at 2.20 (3 H, 6-CH_3), an AB quartet centered at 4.37 (2 H, J = 8 Hz, $\Delta\gamma_{AB}$ = 21.6 Hz, 7-CH and 7a-CH), a broad singlet at 8.20 (2 H, 4-NH_2) and an identically broad singlet at 10.00 ppm (2 H, 2-NH_2) downfield from TMS. Upon ^{14}N double-irradiation both singlets underwent a considerable sharpening effect, and upon addition of D_2O the two broad downfield singlets collapsed immediately.

The mass spectrum (70 eV) of III using a direct-probe inlet and a relatively cold instrument (T 160°)[3] gave the following significant fragments: m/e (rel intensity) 244 (36, dimer molecular ion), 229 (100), 218 (21), 189 (14), 149 (20), 128 (23), 122 (52), and 93 (35). In addition, a well-resolved ir spectrum (KBr) revealed the presence of two closely spaced nitrile bands of equal intensity at 2200 and 2180 cm^{-1}.

The overall spectral evidence quite conclusively points to a dimer structure. More specifically, the two hydrogen AB pattern in the nmr indicates completely selective cycloaddition across the 4,5 double bond in the manner shown. The endo configuration is indicated by the coupling constant of 8 Hz for the AB hydrogens, which implies a dihedral angle near zero in a system such as III.[4]

Dimer III has been mentioned several times in the literature under the guise of the monomeric structure (II). Gewald[1] arrived at a clever synthesis of substituted 2-aminobenzonitriles by subjecting III and several other 2-amino-3-furonitriles to maleic anhydride in refluxing acetone, and Wie, Sunder, and Blanton[5] included III in a study of the enamine behavior of furan, pyrrole, and thiphene aminonitriles. They observed formation of IV upon treatment of III with trifluoroacetic acid. Brief mention is also made of III as structure II in Taylor and McKillop's recent monograph on *o*-aminonitriles.[6] The formation of IV and V indicate that III is quite capable of acting as a precursor for II (Scheme I).

SCHEME I



(1) K. Gewald, *Chem. Ber.*, **99**, 1002 (1966).

(2) Triethylamine in methanol gives comparable results.

(3) The mass spectrum using a Teflon slug showed only monomeric fragments.

(4) (a) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959); (b) F. A. L. Anet, *Can. J. Chem.*, **39**, 789 (1961); (c) K. Ramsey, D. Lini, R. Moriarty, H. Gospal, and H. G. Welsh, *J. Amer. Chem. Soc.*, **89**, 2401 (1967).

(5) C. T. Wie, S. Sunder, and C. D. Blanton, *Tetrahedron Lett.*, 4605 (1968).

(6) E. C. Taylor and A. McKillop, *Advan. Org. Chem.*, **7**, 126, 213 (1970).

To our knowledge, III represents the only reported example of a furan capable of dimerizing in a Diels–Alder fashion and the first member of the 4,7-epoxybenzofuran ring system.[7] We have subsequently examined several other analogs [I, $R_1 = R_2 = CH_3$; $R_1 = R_2 = Ph$; $R_1 = R_2 = (CH_2)_4$] and 2-amino-3-carboxamido-4-methylfuran but encountered no evidence of dimerization in these compounds.

Experimental Section

Compound III was prepared according to the method of Gewald.[1] The nmr spectrum was obtained on a Joel JNM-C60HL instrument. The ^{14}N hetero spin decoupling was performed with a Schomandl MS100M frequency synthesizer. The ir spectrum was recorded on a Perkin-Elmer Model 257 grating spectrophotometer and the low resolution mass spectrum on an Hitachi Perkin-Elmer RMU-6E single-focusing mass spectrometer.

Registry No.—III, 35895-53-5.

(7) The 4,7-epoxyisobenzofuran system is well known: A. M. Patterson, L. T. Capell, and D. F. Walker, "Ring Index," 2nd ed, No. 2245, 1960, p 291.

The Preparation of 5,7-Diamino-3*H*-imidazo[4,5-*b*]pyridine (2,6-Diamino-1-deazapurine)[1]

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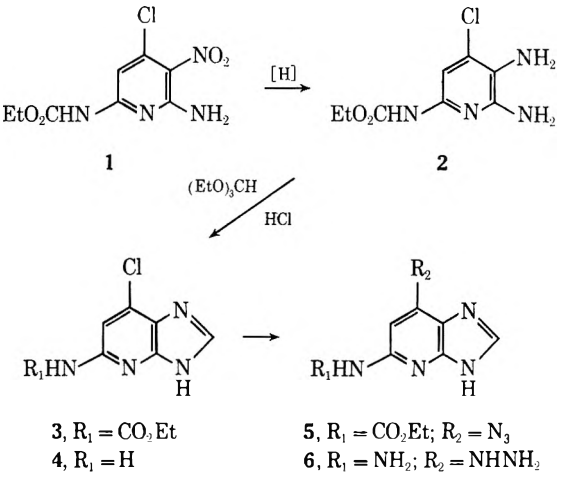
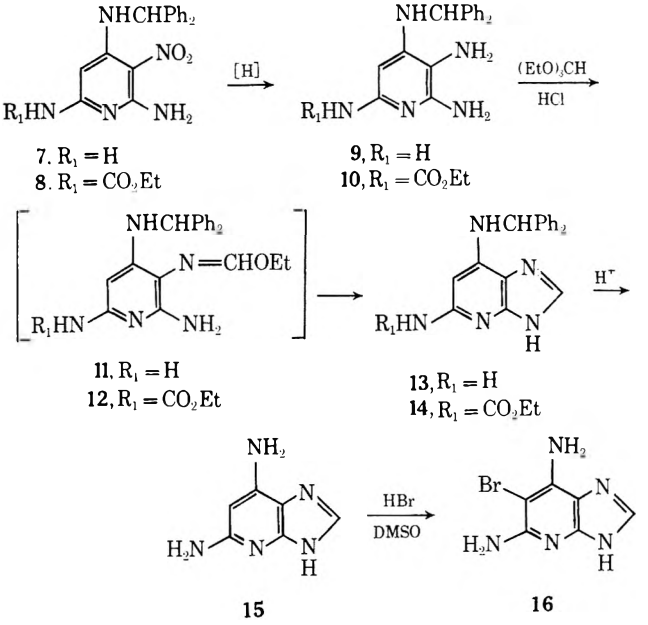
Recently the lack of reactivity of the chloro groups of both 5-amino-7-chloro- and 7-amino-5-chloro-3*H*-imidazo[4,5-*b*]pyridine (2-amino-6-chloro- and 6-amino-2-chloro-1-deazapurine) was reported.[2,3] We considered two approaches for the preparation of 5,7-diamino-3*H*-imidazo[4,5-*b*]pyridine (**15**). The first method involved the preparation of ethyl 7-chloro-3*H*-imidazo[4,5-*b*]pyridine-5-carbamate (**3**) in which the ethoxycarbonyl moiety was expected to decrease the electron-donating ability of the 5-amino group and increase the reactivity of the 7-chloro group. Hydrogenation of **1**[4] with Raney nickel gave **2**, which was cyclized with the ethyl orthoformate–concentrated HCl reagent[5] to give **3**. However, treatment of **3** with sodium azide to give **5** either in hot 1:1 EtOH–H_2O or hot 1:1 $EtOCH_2CH_2OH$–H_2O was unsuccessful. The stability of the chloro group was demonstrated by treatment of **3** with NaOMe in refluxing PrOH to give the known 5-amino-7-chloro compound **4**.[2,3] In contrast, hydrazinolysis of **3** HCl with anhydrous hydrazine at reflux resulted in displacement of both the chloro and (ethoxycarbonyl)amino groups to give the 5,7-dihydrazino compound **6**.[6] Under milder conditions reaction of **4** with hydrazine was reported to give the corresponding 5-amino-7-hydrazino derivative.[3]



Simultaneously with the above work, a route involving the cyclization of the 2,3,6-triamino-4-(diphenylmethyl)aminopyridines **9** and **10** was investigated. Hydrogenation of **7**[4] with Raney nickel at atmospheric pressure and room temperature gave **9**, isolated as a dihydrochloride. The cyclization of **9** with the ethyl orthoformate–concentrated HCl reagent at room temperature gave a mixture which was not purified but was shown to contain **13** as a major component (tlc). Hydrogenation of **8** with Raney nickel gave **10**, which was cyclized with ethyl orthoformate at room temperature to give **14**.[7] Presumably the cyclization of both **9** and **10** involves the ethoxymethylene-amino intermediates **11** and **12**, respectively.[8] Because of the greater nucleophilicity of the (diphenylmethyl)-amino group of **11** and **12** compared with that of the 2-amino group, cyclization to the nitrogen of the (diphenylmethyl)amino group should be favored. How-



(1) This investigation was supported by funds from the C. F. Kettering Foundation, and Chemotherapy, National Cancer Institute, National Institutes of Health, Contract No. NIH-71-2021.

(2) D. G. Markees and G. W. Kidder, *J. Amer. Chem. Soc.*, **78**, 4130 (1956).

(3) J. E. Schelling and C. A. Salemink, *Recl. Trav. Chim. Pays-Bas*, **91**, 650 (1972).

(4) R. D. Elliott, C. Temple, Jr., and J. A. Montgomery, *J. Org. Chem.*, **31**, 1890 (1966).

(5) C. Temple, Jr., C. L. Kussner, and J. A. Montgomery, *J. Med. Pharm. Chem.*, **5**, 866 (1962).

(6) C. W. Whitehead and J. J. Traverso, *J. Amer. Chem. Soc.*, **82**, 3971 (1960), report exchange aminations for purines and pyrimidines.

(7) C. Temple, Jr., B. H. Smith, and J. A. Montgomery, *J. Med. Chem.* in press.

(8) J. A. Montgomery and C. Temple, Jr., *J. Org. Chem.*, **25**, 395 (1960).

ever, the obtainment of **13** and **14** suggested that steric interaction between the (diphenylmethyl)amino and the ethoxymethylenamino groups blocked cyclization in this direction.[9] Cleavage of the urethane group of **14** with KOH–EtOH gave a pure sample of **13**.[7] Treatment of **13** with concentrated HCl at room temperature removed the diphenylmethyl group to give **15** 2HCl. The apparent pK_a value (determined potentiometrically) indicated that **15** (pK_a = 6.75) was more basic than 2,6-diaminopurine (pK_a = 5.09).[10] Also, removal of the diphenylmethyl group was effected with 30% HBr–HOAc to give a partial acetate salt of **15** 2HBr. The pmr spectrum in DMSO-d_6 showed that the two peaks for the ring CH protons of **15** decreased with time while the single-ring CH proton of a new compound increased. The latter resulted from oxidative bromination of **15**.[11] Confirmation was obtained by treatment of **15** 2HBr with DMSO to give the 6-bromo derivative **16** (M^+, 227, 229),[12] which also was obtained when the reaction was carried out in the presence of phenol. In addition, the pmr spectrum of **15** 2HBr in D_2O showed that the 6-CH proton underwent deuterium exchange.[13]

Experimental Section[14]

Ethyl 5,6-Diamino-4-chloro-2-pyridinecarbamate Hydrochloride (2).—A suspension of **1** (20.0 g)[4] in EtOH (1000 ml) was hydrogenated in the presence of Raney nickel (20 g, wet, washed with H_2O and EtOH) at atmospheric pressure and room temperature. The catalyst was removed by filtration (Celite), and the filtrate was evaporated to dryness *in vacuo*, yield 17.5 g (99%), mp 106–109°. A portion of this sample (2.5 g) was dissolved in Et_2O and acidified with ethanolic HCl to deposit the hydrochloride salt, yield 2.6 g (90% recovery), mp 196–197° dec.

Anal. Calcd for $C_8H_{11}ClN_4O_2 \cdot HCl$: C, 35.97; H, 4.53; Cl, 26.55; N, 20.98. Found: C, 36.36; H, 4.82; Cl, 26.10; N, 20.81.

Ethyl 7-Chloro-3*H*-imidazo[4,5-*b*]pyridine-5-carbamate (3).—Concentrated HCl (0.4 ml) was added to a solution of **2** HCl (1.00 g) in ethyl orthoformate (20 ml). After stirring at room temperature for 72 hr, the hydrochloride of **3** was collected by filtration and washed with Et_2O, yield 1.04 g (100%), mp >360°.

Anal. Calcd for $C_9H_9ClN_4O_2 \cdot HCl$: C, 39.00; H, 3.66; N, 20.22. Found: C, 39.46; H, 3.93; N, 20.16.

A portion of the above sample was suspended in H_2O and neutralized with aqueous NaOH. The solid was collected by filtration and recrystallized from a mixture of THF and petroleum ether (bp 85–105°), mp >350°.

Anal. Calcd for $C_9H_9ClN_4O_2$: C, 44.91; H, 3.77; Cl, 14.73; N, 23.28. Found: C, 45.20; H, 3.99; Cl, 14.46; N, 23.03.

5-Amino-7-chloro-3*H*-imidazo[4,5-*b*]pyridine (4).—A mixture of **3** HCl (1.0 g) and NaOMe (0.96 g) in EtOH (20 ml) protected with a drying tube was refluxed for 92 hr. Tlc of the reaction mixture indicated the presence of a considerable amount of **3**. The solvent was replaced with propanol, and the resulting mixture was refluxed for an additional 92 hr. Tlc of the reaction mixture showed the presence of only a trace amount of **3**. After the removal of the solvent, the resulting solid was heated in 1 *N* HCl (22 ml), the insoluble residue was removed by filtration, and the filtrate was adjusted to pH 5 (paper) with aqueous NaOH. The solution was chilled for 18 hr to deposit a partial hydrochloride of **4**, yield 0.28 g. The latter was treated with water (5 ml) containing $NaHCO_3$ (0.14 g) for 5 min. The insoluble residue was removed by filtration, and the filtrate was chilled to deposit **4**, which was dried *in vacuo* over P_2O_5 at 78°, yield 0.14 g (23%), mp 225–227°. The melting point of the hydrate was reported[2] as 229–231° after the loss of water >130°.

Anal. Calcd for $C_6H_5ClN_4$: C, 42.78; H, 2.99; N, 33.23. Found: C, 42.61; H, 3.03; N, 33.37.

5,7-Dihydrazino-3*H*-imidazo[4,5-*b*]pyridine (6).—A solution of **3**·HCl (5.0 g) in 95+% hydrazine (10 ml) was refluxed for 22 hr and evaporated to dryness *in vacuo*. The residue was suspended in H_2O, and the mixture was adjusted to pH 6 (paper) with glacial HOAc. The solid was collected by filtration, washed with H_2O, and dried *in vacuo* over P_2O_5 at 78°, yield 0.92 g (28%), mp 269° dec.

Anal. Calcd for $C_6H_9N_7$: C, 40.22; H, 5.06; N, 54.72. Found: C, 40.37; H, 5.38; N, 54.65.

2,3,6-Triamino-4-[(diphenylmethyl)amino]pyridine Dihydrochloride (9).—A suspension of **7** (1.0 g)[4] in EtOH (125 ml) was hydrogenated in the presence of Raney nickel (2 g, wet, washed with H_2O and EtOH) at atmospheric pressure and room temperature. The resulting yellow suspension was heated to 70° under N_2 and filtered hot into a flask containing concentrated HCl (1.0 ml). The filtrate was evaporated to dryness *in vacuo;* the resulting solid was dissolved in warm EtOH, reprecipitated by the addition of Et_2O, and dried *in vacuo* over P_2O_5 at 78°, yield 0.59 g (52%), mp ~215° dec. Tlc (1:1 $CHCl_3$–MeOH) showed two major spots, possibly a result of decomposition of the sample on the chromatogram.

Anal. Calcd for $C_{18}H_{19}N_5 \cdot 2HCl$: C, 57.14; H, 5.60; N, 18.51. Found: C, 56.98; H, 5.52; N, 18.25.

5,7-Diamino-3*H*-imidazo[4,5-*b*]pyridine (15). A.—A solution of **13** (4.93 g)[7] in 30% HBr in HOAc (50 ml) containing phenol (50 mg) was stirred at room temperature for 18 hr. The dihydrobromide partial acetate salt of **15** was collected by filtration, washed with Et_2O, and dried *in vacuo* over P_2O_5 at 56°, yield 3.68 g (71%), mp >300°. The presence of HOAc in this sample was confirmed by the pmr spectrum.

Anal. Calcd for $C_6H_7N_5 \cdot 2HBr \cdot 0.35CH_3CO_2H$: C, 24.23; H, 3.15; Br, 48.13; N, 21.09. Found: C, 23.85; H, 2.87; Br, 48.01; N, 20.78.

B.—A suspension of **13** HCl (1.0 g)[7] in concentrated HCl (20 ml) was stirred at room temperature for 18 hr. The dihydrochloride salt of **15** was collected by filtration, washed with Et_2O, and dried *in vacuo* over P_2O_5: yield 0.34 g (54%); mp >300°; pmr (DMSO-d_6) 5.88 (6 H), 8.55 (2 H), 10.22 (br, NH).

Anal. Calcd for $C_6H_7N_5 \cdot 2HCl$: C, 32.45; H, 4.09; Cl, 31.93; N, 31.54. Found: C, 32.61; H, 4.11; Cl, 32.05; N, 31.57.

Concentration of the filtrate from the first crop gave an additional 0.07 g of **15**·2HCl. The total yield was 0.41 g (65%).

5,7-Diamino-6-bromo-3*H*-imidazo[4,5-*b*]pyridine Hydrobromide (16).—A suspension of **15** 2HBr·0.35HOAc (200 mg) in DMSO (5 ml) was stirred at room temperature for 18 hr. The resulting solution was evaporated to dryness *in vacuo*. The residue was washed with $CHCl_3$, recrystallized from a mixture of ethanol–heptane, and dried *in vacuo* over P_2O_5 at 78°: yield 75 mg (39%); mp 260° dec; M^+ 227, 229. The presence of DMSO in this sample was confirmed by the pmr spectrum: pmr (DMSO-d_6) 7.65 (br, NH), 8.37 (2 H).

Anal. Calcd for $C_6H_6BrN_5 \cdot HBr \cdot 0.1Me_2SO$: C, 23.50; H, 2.41; Br, 50.44; N, 22.10. Found: C, 23.98; H, 2.55; Br, 50.34; N, 22.15.

Concentration of the recrystallization filtrate gave an additional 50 mg of **16**, mp 260° dec. The total yield was 65.5%.

Similar results were obtained when this reaction was carried out in the presence of phenol (50 mg).

Registry No.—**1**, 6506-86-1; **2**, 37437-06-2; **2** HCl, 37436-93-4; **3**, 37436-94-5; **3** HCl, 37436-95-6; **4**, 37436-96-7; **4** HCl, 37437-07-3; **6**, 37436-97-8; **7**, 6506-85-0; **9** 2HCl, 37436-98-9; **13**, 37436-99-0; **13**

(9) Unpublished results supported this conclusion. Nitrosation of **10** occurred between the 3-amino and 4-(diphenylmethyl)amino groups to give a *v*-triazolo[4,5-*c*]pyridine, presumably formed *via* a 3-diazopyridine intermediate.

(10) S. F. Mason, *J. Chem. Soc.*, 2071 (1954).

(11) W. D. Ranky and D. C. Nelson, "Organic Sulfur Compounds," N. Kharasch, Ed., Pergamon Press, New York, N. Y., 1961, I, Chapter 17, p 175, discuss oxidative brominations using mixtures of HBr and DMSO.

(12) J. A. Montgomery and N. F. Wood, *J. Org. Chem.*, **29**, 734 (1964), reported bromination of 5,7-diamino-3-methylpyrido[3,4-*b*]pyrazine in the pyridine ring.

(13) Complete experimental details for all new compounds will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 Sixteenth St., N.W., Washington, D. C. 20036, by referring to code number JOC-73-613. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche.

(14) Melting points were determined on a Mel-Temp apparatus, and thin layer chromatograms (silica gel H) were developed with mixtures of $CHCl_3$ and MeOH. Pmr spectra were determined with Varian A-60A and XL-100-15 spectrometers with TMS as an internal reference.

HCl, 37437-09-5; **14**, 37437-00-6; **15**, 37437-01-7; **15** 2HBr, 37437-02-8; **15** 2HCl, 37437-03-9; **16**, 37437-04-0; **16** HBr, 37439-95-5.

Acknowledgments.—The authors are indebted to Dr. W. C. Coburn, Jr., and members of the Molecular Spectroscopy Section of Southern Research Institute, who performed most of the microanalytical and spectral determinations.

An Empirical Correlation of Proton Magnetic Resonance Chemical Shifts for α Hydrogen to Lone-Pair Electrons

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Received September 31, 1972

We[1] earlier proposed an empirical rule to explain the upfield pmr shift of α H in neopentyl ethers and neopentylamines on the basis of (1) a restricted conformation at the C–X bond and (2) an empirical postulate that the α H was shifted downfield by 1.7 ppm when skew to an unshared electron pair on O or N, but was unshifted when trans. We now wish to report how remarkably well this latter simple postulate correlates the pmr chemical shifts for H α to unshared electron pairs in the first-, second-, and third-period elements in examples where conformation is not a complication, the methyl compounds.

The experimental values are listed in Table I, together with values calculated on the basis of the simple

TABLE I

PMR CHEMICAL SHIFTS FOR METHYL GROUPS ON SELECTED FIRST-, SECOND-, AND THIRD-PERIOD ELEMENTS, δ

IV	V	VI	VII
Me_3CCH_3	Me_2NCH_3	$MeOCH_3$	FCH_3
0.94	2.12 (2.07)[a]	3.24 (3.21)[b]	4.25 (4.34)[c]
Me_3SiCH_3	Me_2PCH_3	$MeSCH_3$	$ClCH_3$
0.00	0.94 (1.0)[a]	2.08 (2.0)[b]	3.05 (3.0)[c]
Me_3GeCH_3	Me_2AsCH_3	$MeSeCH_3$	$BrCH_3$
0.13[d]	0.88[e] (0.96)[a]	1.95[f] (1.80)[b]	2.68 (2.63)[c]

[a] The calculated value in parentheses is $\delta_{IV} + 2\Delta/3$; for first-period elements, $\Delta = 1.7$ ppm; for second, $\Delta = 1.5$ ppm; for third, $\Delta = 1.25$ ppm. [b] The calculated value is $\delta_{IV} + 4\Delta/3$. [c] The calculated value is $\delta_{IV} + 2\Delta$. [d] H. Schmidbaur, *Chem. Ber.*, **97**, 1639 (1964). [e] C. R. Russ, Ph.D. Dissertation, Department of Chemistry, University of Pennsylvania, 1965. [f] G. Klose, *Ann. Phys.*, **8**, 220 (1961).

postulate made earlier.[1] The only adjustment made in calculating the parenthetical values was to alter the $\Delta = 1.7$ ppm per skew unshared pair for first-period elements to $\Delta = 1.5$ ppm per skew unshared pair for the second-period elements and to $\Delta = 1.25$ ppm for the third-period elements.

For methyl fluoride (or chloride or bromide), each H must be flanked by two skew unshared pairs so the downfield shift will be 2Δ. Therefore the calculated $\delta_{CH_3F} = \delta_{Me_4C} + 2\Delta = 4.34$. For dimethyl ether (or sulfide or selenide) one hydrogen will be flanked by two skew unshared pairs, the other two by one each. The average downfield shift will then be $4\Delta/3$. Similarly for trimethylamine (or phosphine or arsine), two H will be flanked by a single skew unshared pair, the third by none, so the average downfield shift will be $2\Delta/3$.

Inspection of Table I reveals that all the calculated shifts, based on our empirical rule, agree with experiment within less than 0.1 ppm (except for Me_2Se, where the difference is 0.15 ppm). Since all these literature data are not in the same solvent, this may be one factor in the small discrepancies between experimental and calculated values for δ.

Since the form of the relationships in Table I is a simple linear correlation, these data could, of course, be fit to other factors, *e.g.*, the number of methyl groups attached to the heteroatom. There have, of course, been extensive efforts to correlate the chemical shifts with electronegativity.[2] The marked upfield shifts in neopentyl ether and amines[1] and other steric factors influencing the chemical shifts[2b] indicates that electronegativity is at least not the only factor affecting chemical shifts.

The complication of preferred conformation for primary alkyl groups, RCH_2, on O or N was discussed earlier.[1] An examination of ethyl halides suggests yet another possible factor which may influence the NMR shift of α H in primary and secondary alkyl groups. The normal downfield shift on substituting an H by CH_3 is about 0.3 ppm (see Table II). In

TABLE II

PMR CHEMICAL SHIFTS FOR METHYL, ETHYL, AND ISOPROPYL COMPOUNDS, δ

X	CH_3X	RCH_2X	R_2CHX
CH_3	0.9	1.2	1.5
OH	3.4	3.55 (3.70)[a]	3.85 (4.0)
OCOR	3.65	4.10 (3.95)	5.0 (4.25)
F	4.25	4.35 (4.55)	(4.85)
Cl	3.05	3.4 (3.35)	4.0 (3.65)
Br	2.7	3.3 (3.0)	4.1 (3.3)

[a] The parenthetical values are those calculated assuming that the downfield shift for introducing R in place of H in CH_3X would be the same as for $X = CH_3$.

ethyl fluoride and alcohol, the actual downfield shift is somewhat less; for chlorine and especially bromine and OCOR it is appreciably more. In the secondary alkyl derivatives, the enhanced downfield shift compared to calculated (see Table II) is much more marked, again increasing with the size of the group X. Simple scale molecular models, using standard bond angles, bond radii, and van der Waals radii, show that the van der Waals radii of β-H and F or O interpenetrate less than 0.2 Å, whereas the interpenetration is 0.45 Å for Cl and 0.5 Å for Br. A significant repulsive effect at the latter degree of interpenetration could be relieved by bending the C–C–X angle slightly outward.[3] A consequence of this would be to bring the α H closer

(1) C. C. Price, *Tetrahedron Lett.*, 4527 (1971).

(2) (a) B. P. Dailey and J. N. Shoolery, *J. Amer. Chem. Soc.*, **77**, 3977 (1955); (b) H. Spresecke and W. G. Schneider, *J. Chem. Phys.*, **35**, 722 (1961); (c) J. C. Müller, *Bull. Soc. Chim. Fr.*, 2022 (1964).

(3) Values reported for the C–C–X bond angles in ethyl halides are 109.5, 110.5, 110.5, and 112° for F, Cl, Br, and I, respectively (see "Tables of Interatomic Distances," L. E. Sutton, Ed., The Chemical Society, London, 1958 and 1965).

to the lone pair on X, which would then shift it further downfield. This steric hindrance in an isopropyl (or other secondary) compound would be much greater and would therefore produce the enhanced increment in downfield shift. An effect of the lone pair H distance on δ is also reflected in the decreasing value for Δ for the first, second, and third period elements, corresponding to an increasing C–X bond length and thus increasing α H to X distance.

The rather remarkable success of the empirical postulate of a constant chemical shift for α H by an adjacent skew unshared electron pair for cases where conformational changes are not a factor lends strong support to the utility of this postulate as one useful empirical means of estimating conformational relationships for such hydrogens.

Ionic Addition Mechanism Investigation. Determination of Deuterated Nortricyclyl Alcohol Stereochemistry

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Ionic additions to norbornadiene[1] and related solvolyses[2] have historically been scrutinized by stereochemical investigation of the olefinic product; this represented incomplete investigation of the various attendant ionic processes in that nortricyclyl (nonolefinic) product often was the *major* product. Complete analysis of labeled nortricyclyl derivatives in previous studies has been omitted because the nmr spectrum is such a complicated band of absorptions that even 220 MHz plus 100-MHz nmr spectra combined with spin-decoupling analyses have not permitted complete proton assignments.[3] This paper describes the successful application of shift reagents,[4] combined (in part) with spin-decoupling techniques, to the precise determination of the position of deuterium in so-labeled nortricyclyl alcohol samples. Thus the stereochemistry of the processes described above can be determined whenever significant amounts of nortricyclyl derivatives are obtained that can be converted into nortricyclyl alcohol without skeletal rearrangements.

The addition of acetic acid-*O*-d_1, using 0.018 *M* sulfuric acid catalyst, to norbornadiene (**1**) was carried out to afford the labeled products shown in Scheme I; nomenclature, analysis, and structure determination of the **2a**/**2b** (55:45 in this work) and the **2**/**3** (20:80 in this work) ratios have been described before.[1d-g] The **3a**/**3b** ratio is the focus of much of the remaining discussion. Mass spectroscopic analysis[1g] of the total

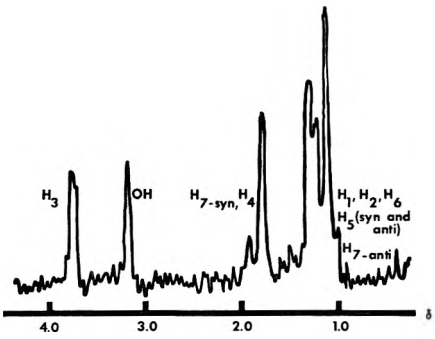
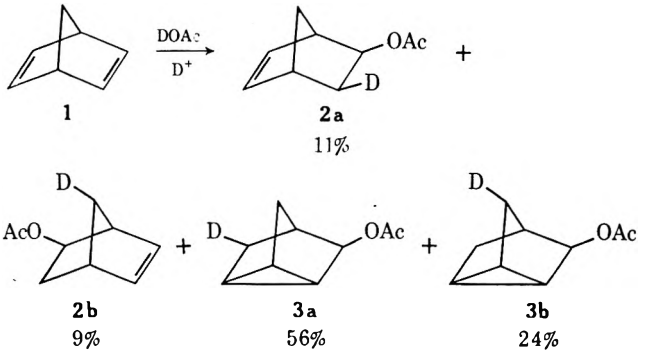


Figure 1.—60-MHz nmr spectrum of **4** in 0.5 ml of CCl_4.

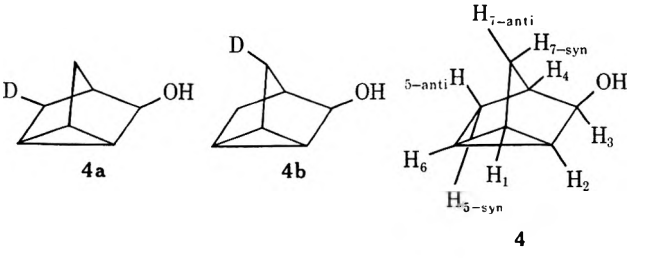
SCHEME I



OAc = acetoxy

deuterium content in the product **2a** plus **2b** acetates (77%) indicated that 77% of the sample was deuterated; this agreed within experimental error (*ca.* ±1%) with the deuterium content of the **3a**–**3b** sample measured mass spectroscopically, and both figures corresponded well to the total deuterium content in the product nortricyclyl acetate as determined by nmr (79%, see below). The data in Scheme I represent the spread of isomers within the *labeled* samples only (see below).

In view of the fact that alcohols respond more to shift reagents' effects than do acetates,[5] the **3a**/**3b** mixture was converted (Na/CH_3OH) into the corresponding **4a**/**4b** mixture. The nmr spectrum of Fig-



ure 1 allows assignment of only H_3 (α to OH[6]) and the $H_4/H_{7\text{-syn}}$ pair (β to OH[6]). The signal for H_2 is expected to be further upfield since it is a cyclopropyl proton[7] and is least proximate to the OH group of the three β protons. The remaining protons are assigned

(1) (a) S. Winstein and M. Shatavsky, *Chem. Ind. (London)*, 56 (1956); (b) S. J. Cristol, *et al.*, *J. Amer. Chem. Soc.*, **84**, 3918 (1962); (c) E. Vogelfanger, Ph.D. Thesis, UCLA, 1963; (d) S. J. Cristol, *et al.*, *J. Org. Chem.*, **31**, 2719 (1966); (e) *ibid.*, **31**, 2722 (1966); (f) *ibid.*, **31**, 2733 (1966); (g) *ibid.*, **31**, 2738 (1966); (h) T. C. Morrill and B. E. Greenwald, *ibid.*, **36**, 2769 (1971).

(2) S. J. Cristol, *et al.*, *J. Amer. Chem. Soc.*, **88**, 3087 (1966).

(3) G. Gray and W. Jackson, *ibid.*, **91**, 6205 (1969).

(4) R. Rondeau and R. Sievers, *ibid.*, **93**, 1522 (1971).

(5) J. K. M. Sanders and D. H. Williams, *ibid.*, **93**, 641 (1971).

(6) R. Silverstein and S. Bassler, "Spectrometric Identification of Organic Compounds," Wiley, New York, N. Y., 1967, p 137.

(7) L. M. Jackman and S. Sternhell, "Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, Elmsford, N. Y., 1969, p 98.

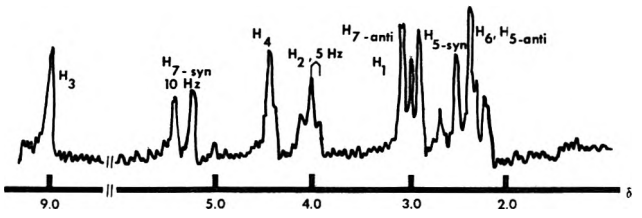


Figure 2.—60-MHz nmr spectrum of 70 mg of **4** in 0.5 ml CCl_4 containing 58 mg of $Eu(fod)_3$.

to the upfield band. Structure **4** is numbered by the method of Paasivirta.[8,9]

Treatment of the preceding **4** sample with $Eu(fod)_3$[4] resulted in the spectrum of Figure 2.[8] Only vicinal cyclopropyl (*ca.* 5 Hz) and geminal (*ca.* 10 Hz) coupling are considered significant herein.[8] Thus the δ 5.3 signal of Figure 2 is assumed to be $H_{7\text{-syn}}$ and $H_{7\text{-syn}}$ is geminally coupled to $H_{7\text{-anti}}$ which gives rise to outer pair of lines at *ca.* δ 2.8.[8] This is confirmed by the spin-decoupling experiment of Figure 3; irradiation at $H_{7\text{-syn}}$ collapses the doublet of $H_{7\text{-anti}}$ onto the center line of the H_1 triplet. All assignments in Figure 2 are consistent with very similar work on **4** using $Eu(DPM)_3$[9] which have been described in detail.[8,10]

When the (labeled) **4a**/**4b** alcohol mixture was subjected to shift reagent nmr analysis, Figure 4 was obtained. The intensity of the $H_{7\text{-anti}}$–H_4 signal decreases by 24% of one proton (referenced internally to, *e.g.*, H_4 as a one proton absorption). That this is due to deuterium incorporation at $H_{7\text{-anti}}$ is consistent with (a) the decrease in intensity being associated with the outer lines (compare Figure 4 to Figure 2), (b) the $H_{7\text{-syn}}$ signal (Figure 4) has lost much of its doublet character (loss of substantial geminal coupling constant magnitude), and (c) expectations consistent with addition mechanisms involving diene **1**.[1]

A decrease in intensity of the H_5 (syn and anti)–H_6 proton region is also noted in comparing Figures 4 and 2. The more downfield pair of lines has been assigned to $H_{5\text{-syn}}$.[8,10] That the decrease in intensity here is due to deuterium incorporation at $H_{5\text{-anti}}$ is substantiated by (1) a decrease in the H_6–$H_{5\text{-anti}}$ to $H_{5\text{-syn}}$ intensity from *ca* 2:1 to *ca.* 1.5:1 in going from Figure 2 to 4, (2) the substantial loss of geminal coupling in the same Figure sequence for $H_{5\text{-syn}}$, and (3) mechanistic expectations.[1] Thus of the total nortricyclyl acetates (as determined by alcohols), 55% are labeled as in **3a** and 24% as in **3b** with 21% unlabeled; *i.e.*, the **3a**/**3b** ratio is 70:30, and, since the percentage of product that is nortricyclyl skeleton is 80, 80% of 70 or 56% of all deuterated product is **3a** and (30)(80) = 24% is **3b** (see Scheme I).

A similar study utilizing $Pr(fod)_3$[4] was carried out; this study indicated a labeled **4** isomer partition of 55/29 but was less conclusive regarding the structural identity of the isomers than was the Eu study.

Observation of a nonunity **3a**/**3b** ratio precludes any discrete, symmetrical (or virtually symmetrical) cations, *e.g.*, **5** or **6**, as being the sole product determining

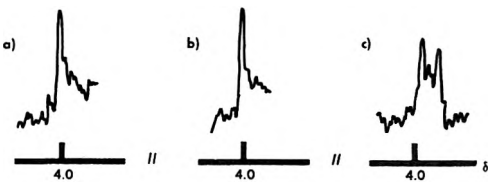


Figure 3.—Spin-decoupling study: 60-MHz nmr spectra of the δ 3.9 signal of **4** (δ 2.9 in Figure 2), signal (H_1 and $H_{7\text{-anti}}$) in 0.5 ml of CCl_4 containing 47 mg of $Eu(fod)_3$. (a) Irradiated at δ 7.0 ($H_{7\text{-syn}}$ signal); (b) repeat of a; (c) nonirradiated.

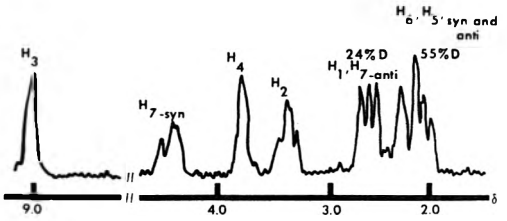
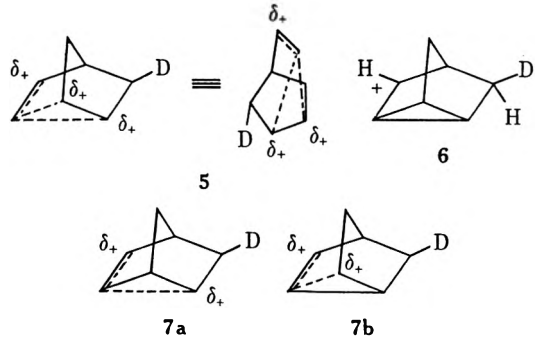


Figure 4.—Deuterium-labeled (see text) **4** (*ca.* 70 mg) plus 96 mg of $Eu(fod)_3$ in 0.5 ml of CCl_4.

intermediates. Proposing reaction pathways involving symmetrical cations and cis-concerted reactions[11] does not have direct application here. The results cannot be totally rationalized in terms of an equilibration between ions **7a** and **7b**; in either very rapid equilibration



or equilibration at a rate comparable to cation capture (steady state applied to **7b** in **1** → **7a** ⇄ **7b**, with **7a** giving **2a** and **3a** only and **7b** giving **2b** and **3b** only), the ratio of **2a**/**3a** would be predicted to be equal to the **2b**/**3b** ratio. This is expected since the rate of formation of **2a** from **7a** should be equal to the rate of formation of **2b** from **7b** by symmetry and the rate of formation of **3a** from **7a** should be equal to the rate of formation of **3b** from **7b**. Thus, the **2a**/**3a** and **2b**/**3b** ratios should also be identical (unity, if the **7a**,**7b** equilibrium is *rapidly* established) and governed by the rapid or moderate **7a**/**7b** partition. Concerted 1,5 addition must be discounted since this would be expected to give rise to labeled acetate **8** and there is no evidence for such a product.

The importance of ion pairing in acetic acid solvent cationic reactions is clear; the existence of two ion-pair intermediates has been required to explain acetolysis results.[12] An important ion pair might be expected to be represented by **9**. The proximity of the gegen ion is expected[12,13] to cause the product ratios (**2a**/**2b**, **3a**/**3b**) to be other than 50:50. Ion **9**, how-

(8) A very similar nmr spectrum for **4** in the presence of $Eu(DPM)_3$[5] has been reported;[5] their results and ours for $Eu(fod)_3$ (Figure 2) are essentially identical. In addition, the same work[9] yields the relative sensitivities of the protons in **4** to shift reagent as $H_3 > H_{7\text{-syn}} > H_2 \sim H_4 > H_{7\text{-anti}} \sim H_1 > H_6 \sim H_{5\text{-syn}} \sim H_{5\text{-anti}}$.

(9) J. Paasivirta, *Suom. Kemistilehti B*, **44**, 135 (1971).

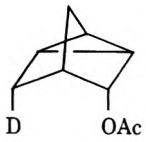
(10) J. Paasivirta, *ibid.*, **42**, 37 (1969).

(11) S. J. Cristol and J. M. Sullivan, *J. Amer. Chem. Soc.*, **93**, 1967 (1971).

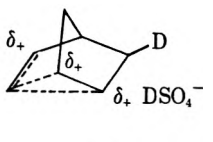
(12) E. L. Allred and S. Winstein, *ibid.*, **89**, 4012 (1967).

(13) J. R. Hazen, *Tetrahedron Lett.*, 1897 (1969).

ever, would be expected to cause the 2a/2b ratio to depart from 50:50 to a greater degree than would the 3a/3b ratio. Since this is not observed, ion pair 9 (or



8



9

the ion pairs corresponding to rapidly equilibrating 7a and 7b) cannot be the predominant product determining intermediate(s).

Since no single one of the preceding limiting cases applies, the reaction must involve a complex set of ionic intermediates with different, ion paired, unsymmetrical precursors to each of the 2a/2b and 3a/3b pairs. In addition, the precursor (or precursors) to the 3a/3b pair must cause less symmetrical product labeling than caused by the precursor(s) to 2a/2b.

Experimental Section

Nuclear magnetic resonance spectra were determined on a Hitachi Perkin-Elmer R-20 (60 MHz) spectrometer with tetramethylsilane as a reference standard (δ 0.00 ppm). Mass spectral analyses were determined on a CEC-104 mass spectrometer under conditions previously reported.[1g] Shift reagents were obtained commercially from Norell Chemical Co., Inc. The addition of labeled acetic acid to diene 1 was carried out, and the products (2a, 2b, 3) were analyzed using conditions previously reported.[1e]

Acknowledgments.—The authors gratefully acknowledge the Research Corporation for partial support of this work; one of us (T. C. M.) was the holder of an R. I. T. College of Science Dean's Fellowship during the course of this work. In addition, we are most indebted to Dr. Earl Krakower for the spin-decoupling experiments.

A Facile Rearrangement of a Carbohydrate Cyclic Carbonate

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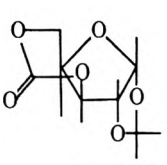
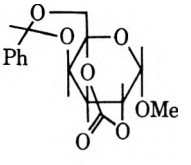
The Procter & Gamble Company, Miami Valley Laboratories, Cincinnati, Ohio 45239

Received August 3, 1972

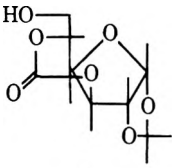
Five-membered ring carbonates are well known in the carbohydrate series and are readily prepared by treating sugars containing cis vicinal hydroxyl groups with difunctional carbonyl derivatives such as phosgene, diphenyl carbonate, and alkyl chloroformates.[1] In marked contrast to the large number of known sugar-derived ethylene carbonates, little has been reported on corresponding six-membered cyclic carbonates. In instances where alternate paths exist for five- and six-membered ring formation in the same molecule, the ethylene carbonate is formed exclusively; *e.g.*, with methyl α-D-galactopyranoside and benzyl chloroformate the only product obtained was methyl 2,6-di-*O*-benzyloxycarbonyl-α-D-galactoside-3,4-carbonate.[2] In the absence of cis vicinal hydroxyl groups an acyclic derivative usually results; *e.g.*, methyl α-D-glucopyranoside on similar treatment yields its tetra-*O*-benzyloxycarbonyl derivative.[2] Presumably the formation of a trimethylene carbonate is precluded because of additional bond strain required for forming a six-membered ring containing an sp^2 hybridized carbon atom.[3] The first six-membered ring carbonate known in the sugar series is 1,2-*O*-isopropylidene-α-D-xylofuranose-3,5-carbonate (1) prepared by Haworth, *et al.*, by treating



1



2



3

D-xylose with phosgene in acetone.[4] Compound 1 exhibited unusual reactivity for a sugar carbonate in that it underwent facile methanolysis at room temperature. The ease of ring opening suggested that cis-fused 1 might contain at least as much ring strain as the recently prepared trans-fused five-membered ring glucose carbonate 2.[5,6] In support of our supposition, methyl 2,3-di-*O*-methyl-α-D-glucopyranoside-4,6-carbonate was recently prepared and shown to undergo ring opening at twice the rate of 2.[7]

In accord with the seeming instability of six-membered ring sugar carbonates we were not able to prepare the desired 4,6-carbonate derivatives of methyl α-D-gluco- or galactopyranosides by direct reaction with phosgene in CH_2Cl_2–pyridine at −70°. In both cases only polymeric carbonates were obtained. The formation of polymer was surprising to us, since similar reaction conditions led to high yield of monomeric cyclic carbonates from 1,3-propanediol and both *cis*- and *trans*-2-hydroxymethylcyclohexanols. The possibility that a sugar 4,6-carbonate may have been first formed and then reacted intermolecularly to form polymer seemed unlikely because no reaction could be observed between methyl α-D-glucopyranoside and *cis*-2-hydroxymethylcyclohexanol carbonate in pyridine at 25° after 16 hr.

In view of the unusual behavior of the methyl glycosides toward phosgene, we decided to investigate the stability and fate of an intact, preformed six-membered carbonate ring in a sugar molecule also containing a free hydroxyl group. The compound chosen for study was 1,2-*O*-isopropylidene-α-D-glucofuranose-3,5-carbonate (3).

Results and Discussion

To achieve the synthesis of 3 we sought a function which could (1) be unequivocally attached to C-3 of a

(1) L. Hough, J. E. Priddle, and R. S. Theobald, *Advan. Carbohyd. Chem.*, **15**, 91 (1960).

(2) L. Hough and J. E. Priddle, *Chem. Ind. (London)*, 1600 (1959).

(3) H. C. Brown, J. H. Brewster, and H. Shechter, *J. Amer. Chem. Soc.*, **76**, 467 (1954).

(4) W. N. Haworth, C. R. Porter, and A. C. Waine, *Recl. Trav. Chim. Pays-Bas*, **57**, 541 (1938).

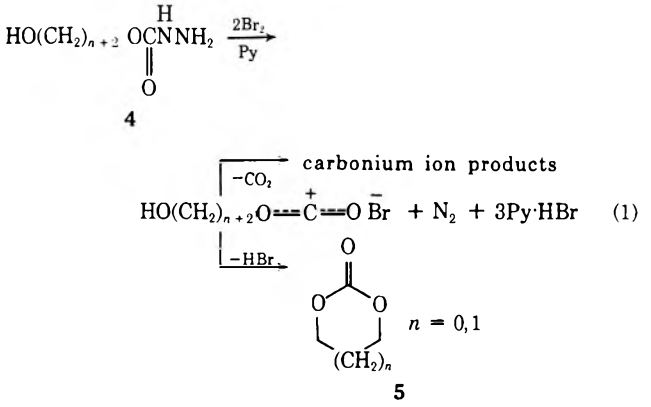
(5) W. M. Doane, B. S. Shasha, E. I. Stout, C. R. Russell, and C. E. Rist, *Carbohyd. Res.*, **4**, 445 (1967).

(6) W. M. Doane, B. S. Shasha, E. I. Stout, and C. R. Russell, *ibid.*, **11**, 321 (1969).

(7) D. Trimnell, W. M. Doane, C. R. Russell, and C. E. Rist, *ibid.*, **13**, 301 (1970).

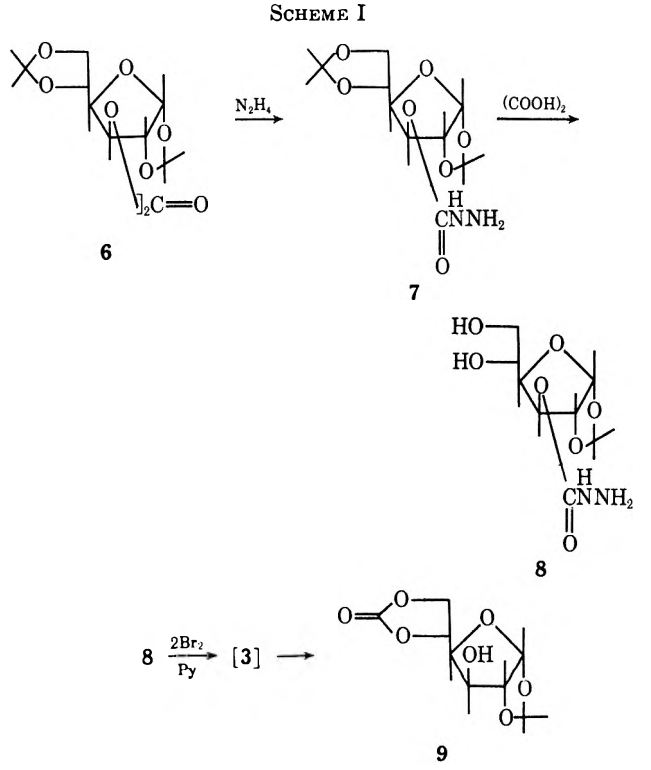
D-glucose derivative and (2) be triggered under mild conditions to effect rapid electrophilic attack and cyclization at C-5.[8]

In this connection we found that oxidation of ω-hydroxyalkyl carbazates **4** with bromine in pyridine at 0°[9] gave 49–66% yields of five- and six-membered ring carbonates **5** without concomitant polymer formation (eq 1). The principal side reaction encountered



was loss of carbon dioxide, presumably leading to ω-hydroxyalkyl bromides, pyridinium salts, or related carbonium ion derived products. Application of the carbazate oxidation in the carbohydrate series is shown in Scheme I. Reaction of the known 3,3′-diglucose

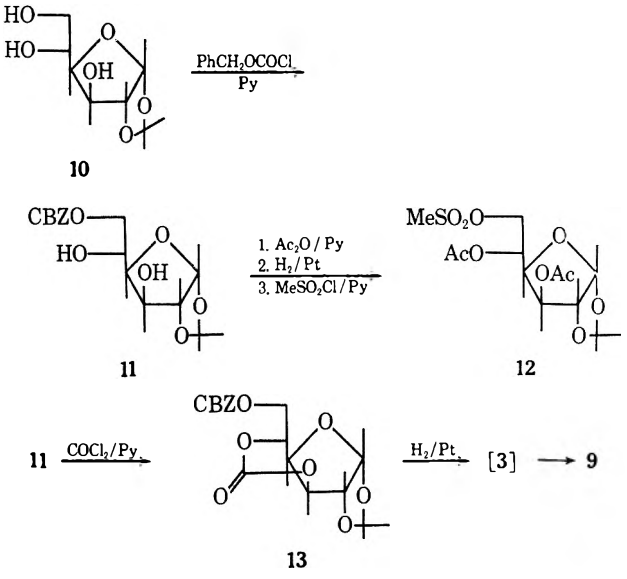
SCHEME I



carbonate **6** with hydrazine hydrate in THF at 25° gave **7** quantitatively. The carbazate structure was established by ir and nmr spectroscopy and by elemental analysis of its crystalline *p*-nitrobenzoyl derivative. Selective hydrolysis of **7** in 0.1 *N* oxalic acid at 50° gave diol **8** quantitatively after 6 hr. Treatment of an ice-cold pyridine solution of **8** with bromine (2 equiv) led to immediate gas evolution and separation of what appeared to be pyridine hydrobromide. Infrared analysis of the total crude organic product showed a single, strong carbonyl absorption at 5.63 μ.[10] This result seemed inconsistent with the expected product **3**, since trimethylene carbonate prepared by the method of Carothers and Van Natta[11] absorbed at 5.74 μ. Recrystallization gave pure 1,2-*O*-isopropylidene-α-D-glucofuranose-5,6-carbonate (**9**), mp 228.5–231°, whose ir spectrum was practically identical with that of the crude product. Thin layer chromatography (tlc) indicated two closely migrating materials in the crude product, of which the one with lower R_f corresponded to **9**.[12] Compound **9** was identified by comparison with a sample of the authentic material.[13] It seems likely that **9** was formed *via* rapid rearrangement of **3** or possibly *via* a seven-membered ring analog of **3** which would be obtained if cyclization occurred at C-6 instead of C-5.

In order to resolve the ambiguity of whether or not **3** was actually being formed and spontaneously reverting to **9** we prepared the 6-carbobenzyloxy (CBZ) derivative **13** in the hope that mild hydrogenolysis would yield **3**. The synthesis of **13** is shown in Scheme II. Treatment of 1,2-*O*-isopropylidene-α-D-glucofura-

SCHEME II



nose (**10**) with benzyl chloroformate in pyridine gave the 6-*O*-CBZ derivative **11** (63%). The structure of **11** was verified by diacetylation, hydrogenolysis, and methanesulfonation to yield the known substance **12** (52% overall). Reaction of **11** with phosgene in CH_2Cl_2/pyridine at −60° gave the cyclic carbonate **13** (85%). The structure of **13** was proven by ir, nmr, and mass spectrometry and by hydrolysis back to **11**. Also, a change in polarimetric behavior was noted in

(8) Analogous to stepwise $COCl_2$ carbonation, which presumably proceeds *via* a hydroxyalkyl chloroformate intermediate.

(9) Compare similar I_2 oxidations of acid hydrazides: Y. Wolman, P. M. Gallop, A. Patchornik, and A. Berger, *J. Amer. Chem. Soc.*, **84**, 1889 (1962).

(10) L. Hough *et al.*, *Chem. Ind. (London)*, 148 (1960).

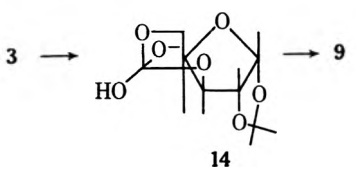
(11) W. H. Carothers and F. J. Van Natta, *J. Amer. Chem. Soc.*, **52**, 314 (1930).

(12) The fast-moving compound may have been the C-3 epimer of **9** formed as a result of inversion during oxidation.

(13) W. N. Haworth and C. R. Porter, *J. Chem. Soc.*, 2796 (1929).

going from **11** to **13** which paralleled the conversion of 1,2-*O*-isopropylidene-α-D-xylofuranose to **1**. Thus **11**, with $[\alpha]D$ −7.7° became more dextrorotatory, changing to $[\alpha]D$ +59.8° on cyclic ester formation. This is similar to the α-D-xylose derivatives, in which a change from −17.5 to +7.5° was noted.[4] Ester **13** was recrystallized unchanged from boiling ethanol but underwent 83% methanolysis of the carbonate ring on refluxing in methanol for 19 hr. Reaction of **13** with 0.1 *N* $Ba(OH)_2$ or NaOH was instantaneous at 25° but complex mixtures of products were formed. Hydrogenolysis of **13** in THF or ethanol over Adams catalyst at 25° yielded the ethylene carbonate **9** as the major product (~80%). No evidence was found for **3** by periodic tlc analysis during the course of hydrogenolysis. An attempt to trap **3** with phenyl isocyanate during hydrogenolysis was also unsuccessful. The hydrogen treatment appears to involve debenzylation followed by rapid CO_2 loss and rearrangement to the stable five-membered ring carbonate. No conclusive evidence was found for hydrogenation or hydrogenolysis products of **3**; however, several minor products were observed by tlc which, in view of their high polarity; may have been formates of **10**.

The rapid rearrangement of **3** apparently results from the possible close juxtaposition of the C-6 hydroxyl to the cyclic carbonate carbonyl. In the easily adopted boat form of **3** the oxygen–carbonyl carbon internuclear distance is *ca.* 2.2 Å. The propensity of **3** to rearrange is probably related to the facile base-catalyzed rearrangement of 1,2,3,4-tetra-*O*-acetyl-α-D-glucopyranose to the isomeric 1,2,3,6-*O*-acetyl derivative[14] and other similar rearrangements involving the participation of cyclic orthoester intermediates.[15] Based on this similarity we propose that **3** rearranges *via* the tricyclic intermediate **14**.



14

Experimental Section

Melting points were determined on a Mel-Temp apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 137 spectrophotometer. Nmr spectra were obtained with a Varian Associates T-60 spectrometer in $CDCl_3$ containing 0.2% tetramethylsilane (TMS) as internal reference. Chemical shifts are expressed in parts per million (δ) downfield from TMS. Multiplicity is indicated by letters, where s = singlet and d = doublet. Optical rotation data were obtained using a Durrum-Jasco ORD/CD spectropolarimeter. Mass spectra derived molecular weights were determined at 70 eV with an Atlas Model CH-4 spectrometer. Microanalyses were performed by the Spang Microanalytical Laboratory, Ann Arbor, Mich.

Bromine Oxidation of 3-Hydroxypropyl Carbazate.—To a stirred solution of bromine (16.0 g, 0.10 mol) in pyridine (150 ml) at 0–15° was added dropwise 6.7 g (0.05 mol) of 3-hydroxypropyl carbazate[16] in 50 ml of pyridine. A mild exothermic reaction ensued during the addition (20 min) with smooth evolution of N_2 and CO_2. After 15 min 2 g of $Na_2S_2O_3$ was added and pyridine was removed under vacuum. The residue was extracted with dry THF and the filtered THF solution was concentrated to give 2.5 g (49%) of trimethylene carbonate. The ir and nmr of the product were identical with those of the authentic material.[11] In a similar experiment designed to trap CO_2 by external N_2 entrainment through 5% $Ba(OH)_2$ a 28% yield of $BaCO_3$ was obtained. Similar oxidation of 2-hydroxyethyl carbazate[16] gave ethylene carbonate in 66% yield.

1,2-*O*-Isopropylidene-α-D-glucofuranose-3-carbazate (8).—A slurry of **6**[17] (0.530 g, 0.974 mmol) in EtOH (10 ml) was treated with 0.1 ml of 100% hydrazine hydrate and stirred at 25° for 4 hr. The clear solution was concentrated to dryness under vacuum and the residue was chromatographed over 50 g of silica gel (30–70 mesh). Elution with EtOAc first gave 0.262 g of crystalline 1,2:5,6-di-*O*-isopropylidene-α-D-glucopyranose identified by spectral comparison with authentic material. Further elution with EtOAc gave 0.317 g of **7** as a noncrystalline glass. The carbazate was homogeneous by tlc (silica gel, EtOAc development, H_2SO_4 charring): ir (liquid film) 2.99 (NH) and 5.76 μ (C=O); nmr[18] ($CDCl_3$) δ 1.35, 1.43, 1.53 (all s, 12, methyls), 4.58 (d, 1, J = 4 Hz, C-2 H), 5.20 (broad s, 1, C-3 H), and 5.87 ppm (d, 1, J = 4 Hz, C-1 H). Reaction of **7** with *p*-NO_2BzCl in pyridine gave the mono-*p*-nitrobenzoyl derivative, which after chromatography over silica gel eluting with benzene and 20% Et_2O/80% benzene had mp 87° dec.

Anal. Calcd for $C_{20}H_{23}N_3O_{10}$: C, 51.39; H, 5.39; N, 8.99. Found: C, 51.43; H, 5.37; N, 8.86.

For selective hydrolysis 0.818 g of freshly chromatographed **7** was dissolved in 20 ml of 0.1 *N* oxalic acid monohydrate in 1:1 THF–water and stirred at 50° for 6 hr. At this time tlc indicated complete disappearance of **7** and the formation of a single new material at lower R_f. After 0.2 g of $Ca(OH)_2$ was added the mixture was stirred for 5 min and filtered and the filtrate was concentrated under vacuum to give 0.615 g of nearly pure **8**: nmr ($CDCl_3$) δ 1.10, 1.30 (s, 6, methyls), 4.66 (d, 1, J = 4 Hz, C-2 H), and 5.93 ppm (d, 1.5, J = 4 Hz, C-1 H).

Bromine Oxidation of 8.—A solution of Br_2 (4.14 mmol) in 10 ml of ice-cold pyridine was treated dropwise with a solution of **8** (0.576 g, 2.07 mmol) in 5 ml of pyridine in an apparatus arranged for collection of evolved gases over water. In 15 min 33.4 ml of gas was collected at 23° (749 mm). The reaction mixture was concentrated under vacuum at 60° to remove pyridine and organic products were isolated by washing the residue with EtOAc. Evaporation of EtOAc gave 0.239 g of whitish solid whose tlc (EtOAc, silica gel) showed two closely moving spots (H_2SO_4) at R_f ~0.8. Recrystallization from EtOH gave colorless needles of **9**, mp 228.5–231° dec, identical by comparison of ir, nmr, and melting point with those of an authentic specimen.[19]

1,2-*O*-Isopropylidene-6-*O*-carbobenzyloxy-α-D-glucofuranose-3,5-carbonate (13).—To a stirred solution of monoacetone glucose[20] (5.00 g, 0.0227 mol) in 50 ml of dry pyridine was added 17.64 g (0.103 mol) of benzyl chloroformate dropwise over 15 min. The exothermic reaction was moderated at 27–35° with intermittent cooling during the addition. After *ca.* 1 hr pyridine was removed under vacuum and the residue was treated with water and extracted with ether three times. The ether was washed with 1 N HCl twice, saturated $NaHCO_3$ solution, and brine and finally dried over anhydrous $MgSO_4$. Concentration of the filtered ether solution gave a white solid which after benzene recrystallization gave 5.08 g (63%) of **11**: mp 118–120°; ir ($CHCl_3$) 5.72 μ (C=O); nmr ($CDCl_3$) δ 1.30, 1.47 (both s, 6, methyls), 4.51 (d, 1, J = 4 Hz, C-2 H), 5.21 (s, 2, benzylic CH_2), 5.93 (d, 1, J = 4 Hz, C-1 H), and 7.38 ppm (s, 5, benzene ring H); $[\alpha]^{30}D$ −7.7° (*c* 1, $CHCl_3$).

Anal. Calcd for $C_{17}H_{22}O_8$: C, 57.62; H, 6.26. Found: C, 57.69; H, 5.97.

Compound **11** (3.54 g, 0.010 mol) was dissolved in 50 ml of dry

(14) B. Helferich and W. Klein, *Justus Liebigs Ann. Chem.*, **450**, 219 (1926).

(15) R. M. Acheson, *Accounts Chem. Progr.*, **4**, 177 (1971); S. Hanessian and P. Dextraze, *Chem. Ind. (London)*, 958 (1971), and references cited therein.

(16) Norwich Pharmical Co., British Patent 944,594 (1963); *Chem. Abstr.*, **60**, 14510 (1964).

(17) L. v. Vargha, *Chem. Ber.*, **67B**, 1223 (1934).

(18) Spectral assignments of ring protons closely paralleled those made by A. Rosenthal and K. Shudo, *J. Org. Chem.*, **37**, 1608 (1972), for similar α-D-furanosides.

(19) Early workers (*cf.* ref 13) reported mp 223–224° dec for **9**, while Doane, *et al.*, *Carbohyd. Res.*, **8**, 346 (1967), reported 228–230°. Our material prepared by the method of ref 13 had mp 225–228° dec after several recrystallizations from EtOH.

(20) F. J. Bates and Associates, "Polarimetry, Saccharimetry and the Sugars," Circular of The National Bureau of Standards C440, U. S. Government Printing Office, Washington, D. C., 1942, p 483.

pyridine, diluted with CH_2Cl_2 (20 ml), and cooled to −60° in a Dry Ice–acetone bath. While stirring at −60° a mixture of 12.5% phosgene in benzene (9.1 ml, 0.010 mol) and CH_2Cl_2 (25 ml) was added dropwise over 16 min. After slow equilibration to 25° the reaction mixture was evaporated to dryness under vacuum and the residue was broken up with water, filtered, and dried to give 3.48 g of crude **13**. Recrystallization from EtOH gave 3.24 g (85%) of pure **13** as colorless, thin, lathe-like crystals: mp 145–146°; ir ($CHCl_3$) 5.69 μ (C=O); nmr ($CDCl_3$) δ 1.32, 1.48 (s, 6, methyls), 4.88 (d, 1, J = 4 Hz, C-2 H), 5.17 (s, 2, benzylic CH_2), 5.93 (d, 1, J = 4 Hz, C-1 H), and 7.39 ppm (s, 5, benzene ring H); $[\alpha]^{30}D$ +59.8 (*c* 1, $CHCl_3$); mass spectrum molecular ion *m/e* 380 (calcd mol wt, 380).

Anal. Calcd for $C_{18}H_{20}O_9$: C, 56.84; H, 5.30. Found: C, 56.83; H, 5.11.

Conversion of 11 to 12.—A solution of **11** (0.532 g) in pyridine (10 ml) was treated with Ac_2O (0.5 ml) and stirred for 1 hr at 25° and 1 hr at 100–120°. Removal of pyridine and Ac_2O under vacuum gave **11** diacetate quantitatively: nmr ($CDCl_3$) δ 1.30, 1.50 (s, 6, isopropylidene methyls), 1.97, 2.05 (s, 6, acetyl methyls), 5.17 (s, 2, benzylic CH_2), 5.36 (d, 1, J = 4 Hz, C-2 H), 5.90 (d, 1, J = 4 Hz, C-1 H), and 7.35 ppm (s, 5, benzene ring H). The crude diacetate was hydrogenolyzed with 10% Pd/C catalyst under 50 psig of H_2 for 4 hr at 25° after which time tlc analysis (Et_2O, silica gel) indicated complete removal of the CBZ group (R_f change of 0.90 to 0.55). Concentration of the filtered solution gave 0.462 g of yellow oil which was dissolved in pyridine (15 ml), cooled to 0°, and treated with 0.2 ml of methanesulfonyl chloride in $CHCl_3$ (6 ml). The mixture was kept at 4° for 16 hr, and concentrated to dryness under vacuum. After water was added the product was extracted with EtOAc, and the EtOAc solution was washed with 2% H_2SO_4, saturated $NaHCO_3$ solution, and water and dried over anhydrous $MgSO_4$. Concentration of the filtered EtOAc solution followed by recrystallization of the residue from MeOH gave 0.299 g (52% overall from **11**) of **12**: mp 141–143° (lit.[21] mp 143°); nmr ($CDCl_3$) δ 1.30, 1.52 (s, 6, isopropylidene methyls), 2.07 (s, 6, acetyl methyls), 3.03 (s, 3, methanesulfonyl methyl), 5.37 (d, 1, J = 4 Hz, C-2 H), 5.91 (d, 1, J = 4 Hz, C-1 H).

Anal. Calcd for $C_{14}H_{22}O_{10}S$: C, 43.97; H, 5.80; S, 8.38. Found: C, 43.81; H, 5.68; S, 8.13.

Acid-Catalyzed Hydrolysis of 13.—Pure **13** (0.328 g) was refluxed in 5 ml of 1:1 v/v HOAc–water for 50 min. Cooling to 4° followed by filtration gave 0.064 g of recovered **13**, mp 144–145.5°. The filtrate was concentrated to dryness under vacuum and the residue was crystallized from water to give 0.026 g of **11**. Recrystallization from benzene gave prisms, mp 118–119.5°. The balance of **13** apparently underwent more extensive hydrolysis to water-soluble products.

Hydrogenolysis of 13.—Compound **13** (0.180 g) in 25 ml of THF was treated with 0.050 g of PtO_2 and hydrogenated under 50 psig H_2 at 25° for 2 hr. Filtration of catalyst followed by removal of THF under vacuum gave 0.098 g (84%) of **9**, mp 207–209° dec, whose ir (KBr) was identical with the ir of authentic **9**. One recrystallization from EtOH gave colorless needles, mp 229–231.5° dec. Similar reduction (1 hr) with EtOH in place of THF gave 82% of **9**, mp 204–205° dec, which on recrystallization from EtOH had mp 227.5–230° dec.

Methanolysis of 13.—Compound **13** (0.105 g) was refluxed in dry methanol (5 ml) for 19 hr and subsequently solvent was removed under vacuum. Nmr ($CDCl_3$) showed a new singlet at δ 3.80 ppm corresponding to 2.5 H (methyl carbonates from ring opening). Tlc indicated complete disappearance of **13** and formation of three reaction products. No evidence was found for methanolysis of the CBZ group in that peaks corresponding to benzyl alcohol were not observed.

Registry No.—**7**, 37056-03-4; **7** mono-*p*-nitrobenzyl derivative, 37056-04-5; **8**, 37056-05-6; **9**, 2875-90-3; **11**, 37056-07-8; **11** diacetate, 37056-08-9; **12**, 37056-09-0; **13**, 37056-10-3.

Acknowledgments.—The author is indebted to Dr. Richard S. Treptow for optical rotation measurements and to Mr. John D. Wendel for his able technical assistance with synthetic aspects of the work.

(21) K. Freudenberg and K. v. Oertzen, *Justus Liebigs Ann. Chem.*, **574**, 37 (1951).

Use of L-1,4-Cyclohexadiene-1-alanine in Peptide Synthesis as a Phenylalanine Analog

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In constructing analogs of biologically active peptides with potential inhibitory activity, a residue to replace phenylalanine has been needed. For this purpose, L-1,4-cyclohexadiene-1-alanine (L-2,5-dihydrophenylalanine, L-DiHPhe, **1**), a new and effective antagonist of phenylalanine,[2-5] appeared to be a likely candidate. It is readily available by Birch reduction of commercial phenylalanine and it also occurs naturally in several bacterial sources.[6] The present note examines attempts to incorporate L-DiHPhe into peptides and into a variety of derivatives suitable for peptide synthesis. Dehydrogenation to the phenylalanine compound and spirolactonization were considered to be the major likely side reactions.[2] When this study was essentially complete, incorporation of D-1,4-cyclohexadienylglycine into semisynthetic penicillins and cephalosporins came to our attention.[7] This diene was N-protected as an enamine or *t*-BOC derivative, and coupling was effected by a mixed anhydride procedure. No information, however, was given concerning dehydrogenation.

It was recently established that dehydrogenation of L-DiHPhe in the solid state is associated with a hydrated form of the amino acid which is unstable if stored and if an attempt is made to desiccate it.[2,8] Precautions were thus taken to store the solid as a stable salt or in aqueous solution and to avoid subjecting it to a high vacuum;[8] acylations were done under nitrogen. To confirm structure and determine the content of the corresponding phenylalanine compound all products were examined carefully by nmr, column chromatography, or uv absorption.

L-1,4-Cyclohexadiene-1-alanine methyl ester hydrochloride (**2**) was obtained in high yield by application of the Brenner–Huber method[9] to DiHPhe hydrate and was purified by crystallization.[10] Nmr evidence

(1) Visiting Research Fellow, 1967–1969.

(2) M. L. Snow, C. Lauinger, and C. Ressler, *J. Org. Chem.*, **33**, 1774 (1968).

(3) B. A. Shoulders, R. M. Gipson, R. J. Jandacek, S. H. Simonsen, and W. Shive, *J. Amer. Chem. Soc.*, **90**, 2992 (1968).

(4) C. Ressler, D. S. Genghof, C. Lauinger, and M. L. Snow, *Fed. Proc.*, **27**, 764 (1968).

(5) D. S. Genghof, *Can. J. Microbiol.*, **16**, 545 (1970).

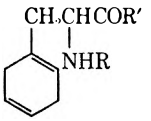
(6) Private communications: T. Yamashita, Fujisawa Pharmaceutical Co., Ltd., Osaka, Japan, 1968, and G. E. Mallett, Lilly Research Laboratories, 1968. See also T. Yamashita, N. Miyairi, K. Kunugita, K. Shimizu, and H. Sakai, *J. Antibiot.*, **23**, 537 (1970), and J. P. Scannell, D. L. Pruess, T. C. Demny, T. H. Williams and A. Stempel, Abstracts of Papers, 160th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1970.

(7) J. E. Dolfini, H. E. Applegate, G. Bach, H. Basch, J. Bernstein, J. Schwartz, and F. L. Weisenborn, *J. Med. Chem.*, **14**, 117 (1971).

(8) C. Ressler, *J. Org. Chem.*, **37**, 2933 (1972).

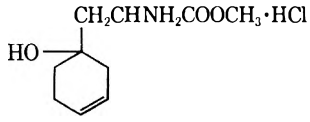
(9) M. Brenner and W. Huber, *Helv. Chim. Acta*, **36**, 1109 (1953).

(10) Compound **2** could also be prepared by starting from the Cu complex of L-DiHPhe. This was converted directly with $COCl_2$ to the *N*-carboanhydride by the general method of R. D. Hamilton and D. J. Lyman, *J. Org. Chem.*, **34**, 243 (1969). Without isolation the *N*-carboanhydride was then treated with MeOH–HCl.



	R	R′		R	R′
1	H	OH	6	Cbz	$OC_6H_4NO_2$
2	H·HCl	OMe	7	*t*-BOC	$OC_6H_4NO_2$
3	H	NH_2	8	Cbz	$NHCH_2COOBz$
4	Cbz	OH	9	*t*-BOC	$NHCH_2COOMe$
5	*t*-BOC	OH	10	*t*-BOC	$NHCH_2COOH$
			11	*t*-BOC	$NHCH_2CONH_2$

of three vinyl hydrogens supported its structure and excluded i, a possible product, under the acidic con-



i

ditions, of spirolactonization followed by methanolysis.[2] On storage, 2 tended to fall gradually in melting point and decompose with extensive dehydrogenation. However, freshly prepared 2 could be freed of HCl and treated with MeOH–NH_3 to give L-1,4-cyclohexadiene-1-alaninamide (3), which was isolated as the base in over 60% yield and which proved stable.

N-Benzyloxycarbonyl-L-1,4-cyclohexadiene-1-alanine (Cbz-L-DiHPhe, 4) was obtained from the crude reduction mixture of L-Phe, *i.e.*, without first isolating L-DiHPhe, by treating it with benzyloxycarbonyl chloride (CbzCl). After purification by crystallization, the overall yield from Phe was 41%, which approached the yield obtainable from isolated L-DiHPhe. Compound 4 was stable under prolonged storage in the cold. An attempt to similarly prepare *N*-*tert*-butyloxycarbonyl-L-1,4-cyclohexadiene-1-alanine (*t*-BOC-L-DiHPhe, 5) with *tert*-butyloxycarbonyl azide (*t*-BOC azide) was unsuccessful; the high concentration of salts in the crude reduction mixture of L-Phe seemed to retard acylation. L-DiHPhe was therefore first freed of salts by starting with the easily isolable copper complex and liberating L-DiHPhe from it with H_2S. This procedure was more convenient, especially on a large scale, than that described earlier,[2] involving Chelex resin in concentrated NH_3. Compound 5 is a low-melting solid (mp near 40°) that tended to decompose with dehydrogenation when stored at room temperature. Preferentially, it was used without isolation soon after it had been prepared or was isolated as the dicyclohexylammonium (DCHA) salt (5a), which was easily crystallized, was stable, and could be freed of DCHA before use.

Both 4 and 5, when treated with *N*,*N*′-dicyclohexylcarbodiimide (DCC) and *p*-nitrophenol, gave in good yield their *p*-nitrophenyl ester Cbz-L-DiHPheNPE (6) and *t*-BOC-L-DiHPheNPE (7), which proved stable. Compounds 6 and 7 coupled smoothly with glycine benzyl ester and glycine methyl ester, respectively, to yield *N*-benzyloxycarbonyl-1,4-cyclohexadiene-1-alanylglycine benzyl ester (Cbz-L-DiHPheGlyBz, 8) and *N*-*tert*-butyloxycarbonyl-1,4-cyclohexadiene-1-alanylglycine methyl ester (*t*-BOC-L-DiHPheGlyOCH$_3$, 9). These dipeptides were also prepared by a DCC coupling of 4 and 5 with the glycine esters. In each case, the *p*-nitrophenyl ester procedure gave a somewhat better yield and product.

Treatment of ester 9 in aqueous Me_2CO with 1 equiv of NaOH converted it in good yield to *N*-*tert*-butyloxycarbonyl-L-1,4-cyclohexadiene-1-alanylglycine (*t*-BOC-L-DiHPheGly, 10). Likewise, treatment of 9 with MeOH–NH_3 gave without difficulty *N*-*tert*-butyloxycarbonyl-L-1,4-cyclohexadiene-1-alanylglycinamide (*t*-BOC-L-DiHPheGlyNH_2, 11).

The foregoing experiments demonstrate the stability of L-1,4-cyclohexadiene-1-alanine to the conditions of peptide coupling by the carbodiimide and nitrophenyl ester procedures, to esterification under acidic conditions and to deesterification under alkaline conditions, to ester amidation, and to acylation by *tert*-butyloxycarbonyl azide. Carbobenzyloxylation led to 4–10% dehydrogenation, but the product, Cbz-L-DiHPhe, could be improved by recrystallization. L-DiHPhe-OCH$_3$·HCl and *t*-BOC-L-DiHPhe dehydrogenated gradually and extensively upon storage; these products, however, can be used soon after preparation. Thus, with appropriate care, L-1,4-cyclohexadiene-1-alanine can be used in peptide synthesis. *t*-BOC-L-DiHPhe-NPE so far appears to be the reagent of choice for introducing this amino acid into peptides.

Experimental Section

L-PheGly and L-PheNH_2 acetate were purchased from Mann Research Laboratories, New York, N.Y. Elemental analyses were carried out by Micro-Tech Laboratories, Skokie, Ill. Nmr spectra were obtained on a Varian T-60-C spectrometer by Sadtler Research Laboratories, Philadelphia, Pa. Melting points were taken in open capillaries on a Thomas-Hoover apparatus and are corrected.[2] Optical rotations were determined and automatic amino acid analyses[11] were carried out as described elsewhere.[2] Phe and DiHPhe were analyzed in system 2[2] and L-PheGly and L-DiHPheGly, in system 1,[2,12] in which they eluted 29 and 57 ml, respectively, after γ-aminobutyric acid. Ascending paper chromatography was done on Whatman No. 1 paper in *n*-BuOH–PYR–AcOH–H_2O (30:20:6:24).

Determination of Contamination of DiHPhe Derivatives by Phe Compounds.—Compounds 4 and 8 were deprotected with Na(NH_3) and 5 and 10 with trifluoroacetic acid (0.8 ml for 50 μmol, 15 min at 25°). The products were determined on the amino acid analyzer. Compounds 2, 3, 5, 5a, and 9–11 were each examined by uv absorption; compounds 6 and 7 were examined indirectly as 8 and 9. Occasionally, nmr spectra were obtained. In mixtures in CD_3OD, the $-C(CH_3)_3$ singlet of *t*-BOC-L-Phe, at δ 1.39, appeared separate from that of *t*-BOC-L-DiHPhe, at δ 1.45. Likewise, the $-C(CH_3)_3$ singlet of *t*-BOC-L-DiHPheGlyOCH$_3$ in acetone-d_6 was distinguishable from that of *t*-BOC-L-PheGlyOCH$_3$. Integration of the $-C(CH_3)_3$ protons gave the amount of Phe impurity, thus supplementing the use of the aromatic protons for this purpose.

L-1,4-Cyclohexadiene-1-alanine Methyl Ester Hydrochloride (2).—L-DiHPhe·0.75H_2O (2.6 g, 14.4 mmol) was added in portions over a 30-min period to a mixture of anhydrous MeOH (36 ml, 0.88 mol) and $SOCl_2$ (6 ml, 83 mmol) in a magnetically stirred bath at −10°. The mixture was allowed to come to room temperature, where it was kept for 18 hr. It was then concentrated to dryness. The oil was taken up in MeOH, which was then evaporated, and the process was repeated three times. The residue was crystallized from MeOH–Et_2O; the yield was 2.46 g (79%), mp 122–125°. Compound 2 was recrystallized (charcoal) three times from $CHCl_3$–Et_2O: mp 125–126°; $[\alpha]_D$ −30.4° (c 1, H_2O). It contained 2.8% Phe compound. 2 had R_f 0.85; L-Phe-OCH$_3$·HCl had R_f 0.79. Nmr for 2 in DMSO-d_6: δ 2.45–2.65 (allylic, 6 H), 3.7 (OCH_3, 3 H), 4.1 (α-CH, 1 H), 5.5–5.8 (vinyl, 3 H), 8.8 (NH_3^+, 2–3).

Anal. Calcd for $C_{10}H_{16}ClNO_2$: C, 55.2; H, 7.41; N, 6.44. Found: C, 55.7; H, 7.47; N, 6.62.

(11) D. H. Spackman, W. H. Stein, and S. Moore, *Anal. Chem.*, **30**, 1190 (1958).

(12) C. Ressler and D. V. Kashelikar, *J. Amer. Chem. Soc.*, **88**, 2025 (1966).

L-1,4-Cyclohexadiene-1-alaninamide (3).—A suspension of 2 (1 g, 4.6 mmol, 2.8% Phe compound) in 50 ml of EtOAc was freed of HCl with 1.3 ml of Et_3N, as described for 8. The oil was dissolved in 50 ml of dry MeOH and amidated for 3 days, essentially as described for 11. The product was concentrated to dryness, and the solid residue was crystallized from EtOAc, yielding 0.48 g (63%), mp 98–100°. The needles of 3 were redissolved in EtOAc at 55–60° (charcoal) and allowed to crystallize at room temperature: mp 103–104°; $[\alpha]^{27}D$ −21.6° (c 0.8, 1 N AcOH), with 2% Phe compound. 3 had R_f 0.7; L-PheNH$_2$ had R_f 0.68.

Anal. Calcd for $C_9H_{14}N_2O$: C, 65.0; H, 8.49; N, 16.9. Found: C, 64.7; H, 8.55; N, 16.8.

N-Benzyloxycarbonyl-L-1,4-cyclohexadiene-1-alanine (4).—L-Phe (10 g, 60.5 mmol) was reduced with Na–MeOH–NH_3.[2] The dry residue was suspended in 300 ml of H_2O, cooled in a water bath (15–20°), and placed under N_2. The solution was adjusted to pH 8.5 when most of the solid dissolved. A solution of CbzCl (12.3 g, 72 mmol) in 80 ml of Et_2O was added dropwise over a 70-min period, along with 69 ml of 2 N NaOH to maintain the pH. The mixture was stirred overnight.[13] The oily bottom phase was separated and diluted with 80 ml of H_2O. The solution was extracted with Et_2O, adjusted to pH 2 with 4 N HCl, and extracted with 120 ml of EtOAc. The extract was dried ($MgSO_4$) and concentrated to a syrup, which was taken up in CCl_4 and diluted with petroleum ether (bp 30–60°). Cooling this extract yielded 12.75 g of a white solid, mp 72–79°. Recrystallization of 6 g from CCl_4 (45–50° bath) yielded 3.48 g (41%), mp 77–81°. After three recrystallizations 4 melted at 82–83.5°: $[\alpha]^{20}_{546}$ −1.8°; $[\alpha]^{27}D$ +2.6° (c 1.1, MeOH). It contained 2.6% Phe compound and 3.3% Ene.

Anal. Calcd for $C_{17}H_{19}NO_4$: C, 67.8; H, 6.36; N, 4.65. Found: C, 68.0; H, 6.38; N, 4.68.

N-Benzyloxycarbonyl-L-1,4-cyclohexadiene-1-alanine p-Nitrophenyl Ester (6).—DCC (2.06 g, 10 mmol) dissolved in 10 ml of EtOAc was added to a solution of 4 (3 g, 10 mmol, 2.6% Phe) and p-nitrophenol (1.67 g, 12 mmol) in 50 ml of EtOAc, which had been placed in an ice bath. The mixture was stirred under N_2 for 30 min at 5° and then for 90 min at room temperature. AcOH (0.1 ml) was added, and after 5 min the urea was filtered off. The filtrate was concentrated to a pale yellow, crystalline residue, which was then recrystallized from 70 ml of hot EtOH containing 60 μl of AcOH, yielding 3.57 g (85%), mp 114–118.5°. This material was redissolved in EtOH and recrystallized: mp 118.5–120°; $[\alpha]^{25}D$ −33.2° (c 1, DMF), with 2.8% or less of the Phe derivative. Nmr for 6 in $CDCl_3$: δ 2.65–2.8 (allylic, 6 H), 4.6–5.0 (α-CH, 1 H), 5.3 ($C_6H_5CH_2O$, 2 H), 5.4–5.6 (NH, 1 H), 5.75–5.95 (vinyl 3 H), 7.35–7.57 (aromatic, 7 H); 8.4–8.57 (aromatic adjacent to $-NO_2$, 2 H).

Anal. Calcd for $C_{23}H_{22}N_2O_6$: C, 65.4; H, 5.25; N, 6.63. Found: C, 65.6; H, 5.29; N, 6.61.

N-Benzyloxycarbonyl-L-1,4-cyclohexadiene-1-alanylglycine Benzyl Ester (8a). Nitrophenyl Ester Coupling.—A suspension of GlyBz·HCl (1.53 g, 7.6 mmol) in 70 ml of EtOAc and 1.05 ml of Et_3N was stirred for 3.5 hr. The solid was filtered off and the filtrate was concentrated. The oil was taken up in 10 ml of EtOAc, 6 (2.2 g, 5.2 mmol) was added, and the solution was allowed to stand at 25° overnight. It was then shaken successively with 0.5 N NH_3, H_2O, 0.5 N HCl, and H_2O. The solution was dried ($MgSO_4$) and concentrated to a white solid, 2.28 g (98%), mp 112–116°. Compound 8a was recrystallized twice from EtOAc–petroleum ether: mp 118.5–119.5°; $[\alpha]^{26}_{546}$ −18.6° (c 1, MeOH); $[\alpha]^{27}D$ − 14.9° (c 1.25, MeOH). Crude and analytical materials contained 2.8 and 2.6% PheGly.

Anal. Calcd for $C_{26}H_{28}N_2O_5$: C, 69.6; H, 6.29; N, 6.25. Found: C, 69.7; H, 6.34; N, 6.15.

8b. Carbodiimide Coupling.—A suspension of GlyBz·HCl (0.20 g, 0.99) mmol) in 4 ml of THF was freed of HCl with 175 μl of Et_3N, as for 8a. The oil was taken up in 4 ml of THF, and to this was added 4 (0.25 g, 0.83 mmol) containing 6% Phe and 5.5% ene compounds. The solution was cooled in a bath at 5° under a stream of N_2. A solution of DCC (0.17 g, 0.83 mmol) in 1.5 ml of THF was then added. The mixture was stirred for 2 hr and then filtered. The solvent was removed, and the residue was taken up in EtOAc. The solution was shaken with 5% $NaHCO_3$, H_2O, 0.2 N AcOH, and H_2O. The extract was dried ($MgSO_4$) and concentrated, and the residue was crystallized from EtOAc–petroleum ether, yielding 0.24 g (65%), mp 115–117°, $[\alpha]^{26}_{546}$ −19.7° (c 1, MeOH), with 5.8% Phe compound. A mixture of 8b with 8a had mp 116–118°.

N-tert-Butyloxycarbonyl-L-1,4-cyclohexadiene-1-alanine Dicyclohexylammonium Salt (5a).—An aqueous solution (110 ml) of L-DiHPhe liberated by H_2S from the Cu complex (3.3 g, 16.7 mequiv) was stirred under a stream of N_2 as a solution of t-BOC azide (4.77 g) in 110 ml of dioxane and MgO (1.34 g) was added. Stirring was continued at room temperature and in an N_2 atmosphere for 50 hr. The mixture was filtered, and the filtrate, after being extracted twice with 150 ml of EtOAc, was cooled, adjusted to pH 7 with 20% citric acid, concentrated to 60 ml, and then adjusted to pH 3. The pasty mixture was extracted with 100 ml of EtOAc. The aqueous phase was saturated with NaCl and reextracted twice with 75 ml of EtOAc. The combined organic extract of 5 was washed with saturated NaCl and then dried ($MgSO_4$). It was concentrated to 15 ml and diluted with 75 ml of Et_2O. DCHA (6.05 g) diluted with several milliliters of Et_2O was then added. The crystals were collected after 1 hr in the cold, 5.53 g (72%), mp 208–209°. Recrystallization from approximately 100 ml of EtOH gave 4.63 g, mp 209–210°, with 1.7% Phe, 4.4% ene, and 93.9% DiHPhe compounds. For analysis, material was recrystallized three times from MeOH, mp 210–210.5° dec, $[\alpha]^{24}D$ +6.3° (c 1.2, MeOH), with 2.5% Phe compound.

Anal. Calcd for $C_{26}H_{44}N_2O_4$: C, 69.6; H, 9.89; N, 6.24. Found: C, 69.5; H, 9.97; N, 6.42.

N-tert-Butyloxycarbonyl-L-1,4-cyclohexadiene-1-alanine (5).—To a suspension of t-BOC-L-DiHPheDCHA (0.8 g, 1.78 mmol) in 25 ml of EtOAc at 5° were added 8 ml of 0.5 N H_2SO_4, and the mixture was shaken quickly. The organic phase was separated, washed twice with H_2O, and dried ($MgSO_4$). The extract was then concentrated almost to dryness, and 10 ml of petroleum ether (bp 37–51°) were added. The clear solution was set aside at −35°. The crystals of 5 were collected by filtration in the cold, mp 39–42°. These contained 1–3% Phe compound and were suitable for further work; yields ranged from 80 to 96%. Nmr for 5 in CD_3OD: δ 2.45 [$C(CH_3)_3$, 9 H], 2.28–2.67 (allylic, 6 H), 4.3 (α-CH, 1 H), 5.57–5.72 (vinyl, 3 H).

N-tert-Butyloxycarbonyl-L-1,4-cyclohexadiene-1-alanine p-Nitrophenyl Ester (7).—The concentrated extract of 5 before treatment with DCHA (see 5a) was taken to dryness, and the syrupy residue of 5 (2.77 g, 10.4 mmol) was converted to the p-nitrophenyl ester, as described for 6. Concentration of the reaction mixture left 7 as a residue, which solidified in the cold. This was triturated with petroleum ether and collected, wt 3.2 g (80%), mp 77–95°. Two recrystallizations from EtOH left 1.8 g (45% based on 5), mp 102–104°. For analysis, 7 was recrystallized three times from EtOH: mp 104–105°; $[\alpha]^{28}D$ −44.3° (c 1, MeOH), with 2.5% or less of the Phe compound; nmr ($CDCl_3$) δ 1.47 [$C(CH_3)_3$, 9 H], 2.51–2.71 (allylic, 6 H), 4.4–4.8 (α-CH, 1 H), 4.98–5.09 (NH, 1 H), 5.61–5.71 (vinyl, 3 H), 7.2–7.35 (aromatic, 2 H), 8.2–8.35 (aromatic adjacent to $-NO_2$, 2 H).

Anal. Calcd for $C_{20}H_{24}N_2O_6$: C, 61.8; H, 6.23; N, 7.21. Found: C, 61.8; H, 6.17; N, 7.07.

N-tert-Butyloxycarbonyl-L-1,4-cyclohexadiene-1-alanylglycine Methyl Ester (9a). Nitrophenyl Ester Method.—Distilled GlyOMe (0.356 g, 3.9 mmol) and 7 (0.712 g, 1.8 mmol) were coupled as described for 8a, except that CH_2Cl_2 (10 ml) was the solvent. Compound 9 was crystallized from EtOAc–petroleum ether and recrystallized from Et_2O–petroleum ether, yielding 0.43 g (69%), mp 85–87°, $[\alpha]^{24}D$ −18.7° (c 0.6 AcOH), with 2.5% Phe compound.

Anal. Calcd for $C_{17}H_{26}N_2O_5$: C, 60.3; H, 7.74; N, 8.28. Found: C, 60.8; H, 7.87; N, 8.25.

9b. Carbodiimide Method.—GlyOMe (0.47 g, 5.3 mmol) and 5 (1.1 g, 4.1 mmol, with 4.4% Phe compound) obtained from the DCHA salt were coupled in CH_2Cl_2 (25 ml) with DCC (0.9 g, 4.4 mmol) as described for 8b and isolated as described for 9a. The yield was 0.89 g, mp 73–76°. Recrystallization from Et_2O–petroleum ether followed by MeOH–H_2O left 0.64 g (46%) of material, mp 76–81°, containing 5.3% Phe compound.

N-tert-Butyloxycarbonyl-L-1,4-cyclohexadiene-1-alanylglycine (10).—To a solution of 9 (172 mg, 0.51 mmol, 5% Phe compound) in 1 ml of 66% Me_2CO was added dropwise 0.5 ml of 1 N NaOH. When base no longer was consumed, the solution was allowed to stand for 30 min; it was then adjusted to pH 7 with 5% citric acid and concentrated to a small volume. This was then extracted with wet EtOAc, cooled, acidified to pH 3, and again ex-

(13) This period can probably be shortened. Carbobenzyloxylation for 2 hr of L-DiHPhe liberated from the Cu complex with H_2S afforded 4 of similar purity in 57% yield (S. N. Banerjee, 1972, unpublished work).

tracted. The extract was washed with H_2O and dried ($MgSO_4$). On concentration, crystallization started and was complete after several hours in the cold; the yield was 118 mg (71%), mp 136.5–140.5°. For analysis, the material was recrystallized twice from EtOAc, mp 138.5–139.5°, $[\alpha]^{24}D$ −11.8° (*c* 0.7, MeOH), with 6% PheGly and 94% DiHPheGly derivatives.

Anal. Calcd for $C_{16}H_{24}N_2O_5$: C, 59.2; H, 7.46; N, 8.64. Found: C, 59.3; H, 7.41; N, 8.49.

N-tert-**Butyloxycarbonyl-L-1,4-cyclohexadiene-1-alanylglycinamide (11).**—Anhydrous MeOH (10 ml) was saturated with NH_3 distilled over Na. Ester 9 (275 mg, 0.81 mmol, with 5% Phe compound) was then added. The solution was allowed to stand at room temperature and, after 24 hr, was resaturated with NH_3. After 48 hr, the mixture was concentrated. The oily residue was taken up three times in MeOH and then twice in EtOAc, the solvent being evaporated off each time. Trituration with Et_2O gave a white solid, 230 mg (87%), mp 99–108°. Recrystallization from EtOAc–Et_2O left 166 mg (63%), mp 106–108°, $[\alpha]^{24}D$ +0.2° (*c* 0.9, MeOH), with 6% Phe compound.

Anal. Calcd for $C_{16}H_{25}N_3O_4$: C, 59.4; H, 7.79; N, 13.0. Found: C, 59.6; H, 7.85; N, 12.9.

Registry No.—**1**, 16055-12-2; **2**, 33423-61-9; **3**, 36959-88-3; **4**, 36959-89-4; **5**, 36959-90-7; **5a**, 36959-91-8; **6**, 36959-92-9; **7**, 36959-93-0; **8**, 36959-94-1; **9**, 36959-95-2; **10**, 36959-96-3; **11**, 36959-97-4.

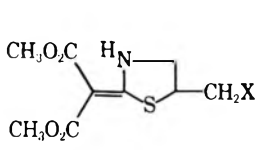
Acknowledgment.—This work was aided by Grant NS 04316 from the U. S. Public Health Service and by Muscular Dystrophy Associations of America. Preliminary experiments in acylating DL-1,4-cyclohexadiene-1-alanine were carried out by Dr. A. F. Wu.

Additions and Corrections

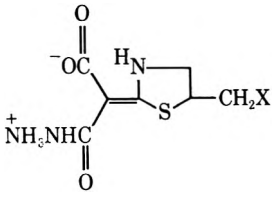
Vol. 37, 1972

George Just* and Phillip Rossy: The Action of Hydrazine and Its Derivatives on the Addition Products of Allyl Isothiocyanate and Dimethyl Malonate. A Correction.

Page 318. Column 2. The structures for Va–d and VIII should be given as



Va, X = Br
b, X = I
c, X = OH
d, X = ONO_2



VIII, X = I

Page 319. Column 1, paragraph 4, line 23. After "could be duplicated" the following sentences should be added. "However Worrall's assignment of the structure was wrong.[5] Compounds Va–d should be the thiazolidine and not the dihydrothiazine. Worrall suggested an intermediate dibromo compound. It has been shown[6] in analogous cases that the intermediate is a bromonium ion and the mechanism involves an ionic intermediate. The product of this type of cyclization usually has a five-membered and not a six-membered ring,[7] even if the carbonium ion leading to the six-membered ring is more favored.[6a,b] Reexamination of the nmr spectrum of Vd shows that there were two low-field protons at 4.7 ppm rather than one. Reduction of Vb with palladium on charcoal gives a compound which shows the presence of a methyl group (doublet at 1.4 ppm). Finally, treatment of Va with diethylamine or sodium hydroxide leads to a compound having a terminal methylene group (3030, 1645, and 870 cm^{-1} in ir spectrum). (Compound VIII has similarly been shown to have the five-membered structure.)"

(5) We wish to thank Dr. I. Monkovic and Dr. K. S. Dhami for having drawn our attention to this error, and for helpful discussions.

(6) (a) E. Demole and P. Enggist, *Helv. Chim. Acta*, **54**, 456 (1971); (b) O. Tanaka, *et al.*, *Tetrahedron Lett.*, 4235 (1968); (c) D. L. H. Williams, E. Bienvenue-Goetz, and J. E. Dubois, *J. Chem. Soc. B*, 517 (1969); (d) V. I. Staninets and E. A. Shilov, *Russ. Chem. Rev.*, **40**, (3), 272 (1971).

(7) H. S. Sachdev, K. S. Dhami, and M. S. Atwal, *Tetrahedron*, **14**, 304 (1961); (b) H. Singh, K. S. Bhandari, and K. S. Narang, *J. Indian Chem. Soc.*, **41**, 715 (1964); (c) T. Ajello and A. Miraglia, *Gazz. Chim. Ital.*, **78**, 921 (1948).

See Editorial, *J. Org. Chem.*, **38**, No. 19, 4A (1972)

The Disproportionation of Trityl Alkyl Ethers. The Synthesis of Aldehydes and Ketones in a Cationic Chain Reaction Involving Hydride Transfer

Summary: Trityl alkyl ethers undergo disproportionation in acetonitrile or methylene chloride, catalyzed by salts of the triphenylmethyl cation, to give aldehydes or ketones and triphenylmethane in good yields.

Sir: Alkyl ethers have been reported to be good hydride donors to carbenium ions.[1,2] Representative ethers have been oxidized to aldehydes or ketones by the triphenylmethyl cation with production of triphenylmethane.[3] These oxidations are, however, inefficient in that only one of the alkyl groups of dialkyl ethers undergoes oxidation, and have only recently received serious consideration in synthetic applications.[4] Ethers also undergo disproportionation to carbonyl compounds and hydrocarbons in related hydride transfer reactions.[1] However, in previous reports of ether disproportionation reactions, studied in strongly acidic media with ethers that form relatively stable carbenium ions, hydrogen transfer was described as occurring from an alcohol to a carbenium ion (Scheme I).[5] A similar

Scheme I

$$(R_2CH)_2O + H^+ \rightleftharpoons (R_2CH)_2OH^+ \quad (1)$$

$$(R_2CH)_2OH^+ \rightleftharpoons R_2CH^+ + R_2CHOH \quad (2)$$

$$R_2CH^+ + R_2CHOH \longrightarrow R_2CH_2 + R_2C{=}OH^+ \quad (3)$$

mechanism has been proposed for those reactions in which an alcohol serves simultaneously as a hydride donor and hydride acceptor.[6]

We have observed that trityl alkyl ethers undergo disproportionation to triphenylmethane and aldehydes or ketones when small amounts of the triphenylmethyl cation, as the PF_6^-, SbF_6^-, and AsF_6^- salts,[7] are employed (eq 4). In a typical experiment trityl benzyl

$$(C_6H_5)_3COCHR_2 \xrightarrow{(C_6H_5)_3C^+X^-} (C_6H_5)_3CH + R_2C{=}O \quad (4)$$

ether (5.0 mmol) was added as a solid to a stirred solution of triphenylmethyl hexafluorophosphate (0.50 mmol) in 10 ml of anhydrous acetonitrile. The progress of the reaction was followed by observing the increase in the benzaldehyde and triphenylmethane absorptions as well as the simultaneous decrease in the ether signals by pmr spectroscopy. After 4 hr at room temperature water was added, and the products were isolated and analyzed. In separate reactions with 0.50, 0.25, 0.10, and 0.05 equiv of triphenylmethyl hexafluorophosphate (based on trityl benzyl ether used) quantitative yields of benzaldehyde and triphenylmethane were obtained.[8] The same amount of trityl salt as that initially added could be recovered quantitatively, either as triphenylmethanol or trityl butyl ether (quenching with butanol). Both dipolar aprotic solvents, acetonitrile and nitromethane, and chlorinated hydrocarbon solvents, chloroform and methylene chloride, have been employed. The PF_6^- and SbF_6^- salts are soluble in the dipolar aprotic solvents, while trityl hexafluoroarsenate is conveniently soluble in the chlorinated hydrocarbon solvents; the trityl ethers are usually more soluble in chloroform and methylene chloride than in nitromethane or acetonitrile. Results from the disproportionation of several representative trityl ethers are given in Table I. Although no attempt was made to maximize product yields for each ether studied, the results obtained indicate that the disproportionation of trityl ethers may provide a general method for oxidation of alcohols[9] to aldehydes or ketones.[10]

Table I

Disproportionation of Trityl Alkyl Ethers in Anhydrous Solvents Using Various Salts of the Triphenylmethyl Cation[a]

$(C_6H_5)_3COCHR_2$, R_2CH	Equiv $(C_6H_5)_3C^+X^-$	Solvent	% yield[b] R_2CO
Benzyl	0.10[c]	CH_3CN	100
p-Chlorobenzyl	0.30	CH_2Cl_2	100
p-Methylbenzyl	0.10	CH_2Cl_2	100
p-Nitrobenzyl	1.00	CH_2Cl_2	100[d]
1-Phenylethyl	0.25	CH_2Cl_2	76[e]
Cyclohexyl	0.25	CH_2Cl_2	97
Octyl	0.25	CH_2Cl_2	56[f]

[a] Reactions were run at room temperature (25 ± 3°). Ether (5.0 mmol) was added to the trityl salt; unless noted otherwise, the hexafluoroarsenate salt was used. Reaction times were generally less than 4 hr. [b] Based on pmr spectroscopy and glpc analysis by reference to an internal standard. The yield of triphenylmethane was equal to that of the carbonyl compound. [c] The PF_6^- and SbF_6^- salts were used and gave identical results. [d] Required a reaction time of 90 hr in refluxing CH_2Cl_2. [e] 24% of the symmetrical 1-phenylethyl ether was also formed. [f] The yield of triphenylmethane was 82%.

(1) C. D. Nenitzescu in "Carbonium Ions," G. A. Olah and P. v. R. Schleyer Ed., Wiley-Interscience, New York, N. Y., 1970, Vol. 2, Chapter 13.

(2) N. C. Deno, H. J. Peterson, and G. S. Saines, *Chem. Rev.*, **60**, 7 (1960).

(3) P. D. Bartlett and J. D. McCollum, *J. Amer. Chem. Soc.*, **78**, 1441 (1956); N. C. Deno, G. Saines, and M. Spangler, *ibid.*, **84**, 3295 (1962).

(4) D. H. R. Barton, P. D. Magnus, G. Smith, G. Streckert, and D. Zurr, *J. Chem. Soc. C*, 542 (1972).

(5) (a) G. Baddeley and P. G. Nield, *J. Chem. Soc.*, 4684 (1954); (b) H. Burton and G. W. H. Chesseman, *ibid.*, 986 (1953); (c) A. Rieche and E. Schmitz, *Chem. Ber.*, **90**, 531 (1957); (d) F. G. Kny-Jones and A. M. Ward, *J. Chem. Soc.*, 535 (1930).

(6) M. P. Balfe, J. Kenyon, and E. M. Thain, *ibid.*, 790 (1952).

(7) These salts were obtained from the Ozark Mahoning Co. and were dried and purified, if necessary, to a minimum analysis of 99% trityl salt.

(8) Determined by pmr spectroscopy and glpc analysis through reference to an internal standard.

(9) Trityl ethers are conveniently prepared in high yields from trityl chloride and alcohols.

(10) Procedures for the preparation and disproportionation of trityl ethers will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 Sixteenth St., N.W., Washington, D. C. 20036, by referring to code number JOC-73-625. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche.

Since ether disproportionation should be characterized by first-order kinetics (rate = k_{obsd}[ether]), where the observed rate constant is dependent on the concentration of trityl salt ($k_{obsd} = k[(C_6H_5)_3C^+X^-]_0$), we undertook a kinetic study of the disproportionation of trityl benzyl ether. These results, given in Table II,

TABLE II

DISPROPORTIONATION OF TRITYL BENZYL ETHER IN METHYLENE CHLORIDE AT 23.5° IN THE PRESENCE OF TRIPHENYLMETHYL HEXAFLUOROARSENATE[a]

[Ether], *M*	[$(C_6H_5)_3C^+AsF_6^-$], *M*	$10^4 k_{obsd}$,[b] sec^{-1}	$10^3 k$,[c] $M^{-1} sec^{-1}$
0.371	0.0945	1.23	1.31
0.463	0.192	2.52	1.31
0.463	0.0960	1.16	1.22
0.467	0.0192	0.268	1.41

[a] Kinetic determinations were made by following the increase in benzaldehyde concentration and the decrease in ether concentration by pmr spectroscopy using an internal standard. Analyses were identical with those determined by glpc analysis. Temperature control was ±0.1°. [b] Good first-order plots were observed through more than one half-life. [c] Duplicate runs give the precision as $\pm 0.08 \times 10^{-3} M^{-1} sec^{-1}$.

demonstrate the expected rate law and show that the rate-limiting step is also the chain-propagating step (eq 5). The rate of appearance of benzaldehyde was

$$(C_6H_5)_3COCH_2C_6H_5 + (C_6H_5)_3C^+ \xrightarrow{k} (C_6H_5)_3C^+ + C_6H_5CHO + (C_6H_5)_3CH \quad (5)$$

observed to be equal to the rate of disappearance of ether, while the concentration of the triphenylmethyl cation remained constant. Although cationic chain reactions involving hydride transfer have been recognized in a number of reactions involving alkanes and alkyl cations,[1] the present study represents the first reported example of a similar chain-transfer reaction involving ethers.

Previous studies of ether disproportionation reactions have represented hydride transfer as occurring from an alcohol to an alkyl cation (Scheme I); our observations of hydride abstraction reactions with trityl ethers suggest that the accumulated data[5] can be equally well explained by a chain reaction involving hydride transfer from the ether. Under reaction conditions identical with those given in Table III, the rate of benzyl alcohol oxidation by an equivalent amount of triphenylmethyl hexafluoroarsenate is at least ten times as slow as that of the corresponding trityl ether.

We are continuing investigations concerning the synthetic utility of this oxidative method and examining the general characteristics of hydrogen abstraction reactions from trityl ethers and related systems.

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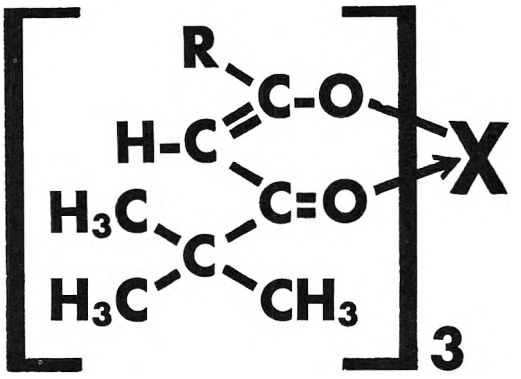

$R = C(CH_3)_3$
$X = Eu, Pr, Ho, Dy, Yb$

$R = n\text{-}C_3F_7$
$X = Eu, Pr$

Nmr is an extremely useful tool; however, in order to obtain maximum information from an nmr spectrum, the resonances of individual nuclei must be cleanly separated. In cases where resonances overlap or second-order spectra are obtained, expensive or time-consuming instrumental or chemical techniques are required.

Recently, rare-earth chelates have been shown to produce remarkable changes in chemical shifts of some nuclei (^{1}H, ^{31}P, ^{13}C) adjacent to an electronegative substituent of a particular molecule (substrate) simply by adding the chelate as a solid or solution to the nmr sample.[1,2] Unlike other paramagnetic shift reagents, the lanthanide chelates produce very little line broadening.[2] Furthermore, the experimentalist has a choice of shifting resonances either upfield or downfield since Resolve-Al*, Resolve-Al EuFOD* and Resolve-Al Yb* generally shift resonances to lower field and Resolve-Al Pr*, Resolve-Al PrFOD*, Resolve-Al Dy* and Resolve-Al Ho* to higher field.[2] At lanthanide: substrate ratios approaching one, readily obtained with Resolve-Al EuFOD* and Resolve-Al PrFOD*, large chemical shifts are observed for protons adjacent to strongly associating amino or hydroxyl groups. These chemical shifts could otherwise be obtained only with 500-1000 MHz spectrometers[2] which at present are not commercially available. These reagents also produce useable chemical shift changes for protons adjacent to oxime, aldehyde, ketone, ester, ether, sulfoxide, nitrile, phosphonate or phosphate substituents.[2] In addition, correlation of observed shifts with substrate-shift reagent geometry permits configurational assignments.[2]

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   R. von Ammon and R. D. Fischer, **Angew. Chem.,** Intern. Ed., **11,** 675 (1972).

15,697-3	Resolve-Al* [tris(2,2,6,6-tetramethyl-3,5-heptanedionato)europium]	1g-$11.50
16,088-1	Resolve-Al Pr* [tris(2,2,6,6-tetramethyl-3,5-heptanedionato)praseodymium]	1g-$11.50
16,093-8	Resolve-Al EuFOD* (Sievers' Reagent)	1g-$11.50
16,135-7	Resolve-Al PrFOD* (Rondeau's Reagent)	1g-$11.50
16,273-6	Resolve-Al Dy* [tris(2,2,6,6-tetramethyl-3,5-heptanedionato)dysprosium]	1g-$11.50
16,274-4	Resolve-Al Ho* [tris(2,2,6,6-tetramethyl-3,5-heptanedionato)holmium]	1g-$11.50
16,275-2	Resolve-Al Yb* [tris(2,2,6,6-tetramethyl-3,5-heptanedionato)ytterbium]	1g-$11.50

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