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NOTES

COMMUNICATIONS

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Photoisomerization of 2-Isocyano- and 2,x'-Diisocyanobiphenyls in Cyclohexane[1]

JOHANNES DE JONG AND JOSEPH H. BOYER*

Department of Chemistry, University of Illinois, Chicago Circle Campus, Chicago, Illinois 60680, and
Department of Organic Chemistry of the University, Zernikelaan, Groningen, The Netherlands

Irradiating cyclohexane solutions at 254 nm produced cyclohept[b]indole 2 from both 2-isocyanobiphenyl (1) and 2-isothiocyanatobiphenyl. Similar treatment produced 6- and 10-isocyanocyclohept[b]indole (6) (unisolated) and 10 from 2,2'-diisocyanobiphenyl (3); 7- and 9-isocyanocyclohept[b]indole (7 and 9) (not differentiated) from 2,3'-diisocyanobiphenyl (4); and 8-isocyanocyclohept[b]indole (8) from 2,4'-diisocyanobiphenyl (5). Cyclization of 6 accounted for properties expected of the aminoimino carbene 11 or its dimer 23. Prolonged irradiation changed 2 into unidentified material and isomerized 1 into phenanthridine (14) in trace amount. Each ring enlargement has been attributed to an intramolecular attack on the adjacent phenyl group by an electrophilic carbenoid isocyano carbon. Hydrolysis converted each isocyanide into the corresponding amino-cyclohept[b]indole.

An isomerization of 2-isocyanobiphenyl 1 into cyclohept[b]indole 2[2] has been extended to the 2,x'-diisocyanobiphenyls 3, 4, and 5 (Scheme I). This has initiated an investigation of substituent effects on the benzene ring undergoing expansion and also produced the isomeric isocyanocyclohept[b]indoles 6–10 as examples of hitherto unknown isocyanocycloheptatrienes. Each of the latter could undergo a resonance coupling between the isocyano and the seven-membered aromatic ring electrons; however, for a similar interaction between an isocyano group and the benzene ring to occur, it has been suggested that strong electron withdrawal from the isocyano group might be required.[3,4] Perhaps interaction was revealed by the ir absorption of p-nitrophenyl isocyanide (2116 cm^{-1} from a potassium bromide pellet);[5] unfortunately, efforts to obtain a dinitro derivative with a nitro group ortho to the isocyano group have failed.[6] Presumably electron withdrawal increases electrophilicity at the isocyano carbon through greater participation from the ordinarily less significant structures b and c (Scheme I). Structure a is generally predominant and accounts for reactivity in the ground state.[7] Structures e and f would bestow electrophilic properties upon the isocyano carbon of isocyanotropones and isocyanotroponimines; comparable structures are available to each isocyanide 6–10.

The possibility of ring-closure isomerization gave additional significance to 6 and 10 insofar as the amino-imino carbene 11 from 6 would share with diamino carbenes the controversial property of reversible dimeriza-

SCHEME I

3, o'-NC
4, m'-NC
5, p'-NC

6, 6-NC   9, 9-NC
7, 7-NC   10, 10-NC
8, 8-NC

Z = O, NR

11   12
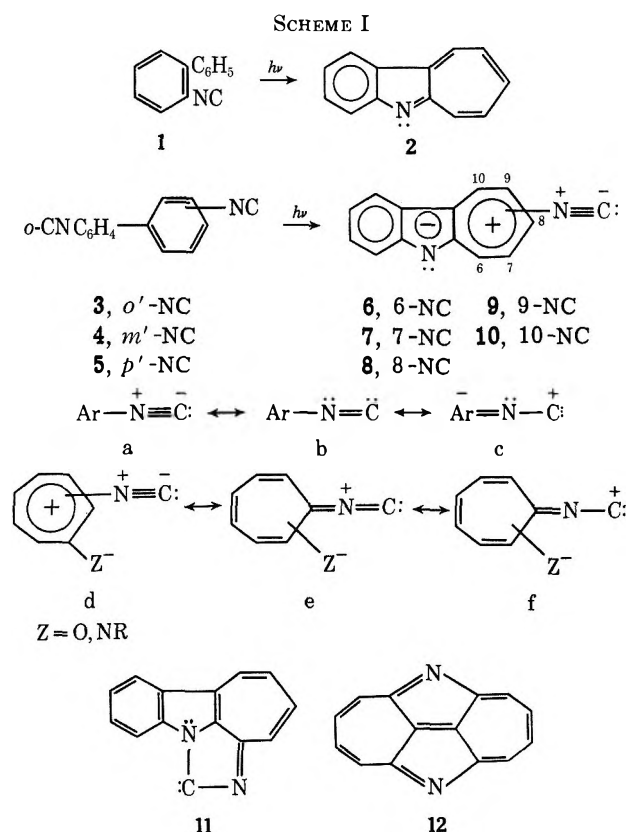
(1) Financial assistance was received from NASA Grant No. NGR 14 012 004.

(2) J. H. Boyer and J. de Jong, J. Amer. Chem. Soc., 91, 5929 (1969).

(3) L. L. Ferstandig, ibid., 84, 1323, 3553 (1962); P. v. R. Schleyer and A. Allerhand, ibid., 84, 1322 (1962); 85, 866 (1963).

(4) I. Ugi, "Isonitrile Chemistry," Academic Press, New York, N. Y., 1971, p 5.

(5) I. Ugi and R. Meyr, Chem. Ber., 93, 239 (1960).

(6) Reference 4, p 14. See also G. M. Dyson and T. Harrington, J. Chem. Soc., 191 (1940).

(7) Reference 4, pp 1–7.

tion,[8] and a ring closure from **10** with expansion of the benzene ring would afford the unknown 5,10-diazadipleiapentalene **12**, a bridged heteroannulene with $4n + 2 \pi$ peripheral electrons.

Results and Discussion

Isocyanides 1, 3, 4, and 5.—Each isocyanide was obtained by dehydration of the corresponding formamide with phosgene.[9] Incomplete dehydration gave 2-isocyano-2'-formamidobiphenyl and unresolved mixtures of each of 2,3'- and 2,4'-isocyanoformamides.

The minor variation in the NC stretching frequencies at 2127 cm^{-1} for **3–5** in chloroform and 2130 ± 3 cm^{-1} for nine derivatives of phenyl isocyanide in chloroform[10] agrees with reported values for aryl isocyanides in chloroform: phenyl, 2132[11] and 2136;[12] *p*-tolyl, 2136[12] and 2129.7;[13] *p*-chlorophenyl, 2136;[12] *p*-methoxyphenyl, 2140 cm^{-1}.[12] With this support for a minimal resonance between NC and C$_6$H$_5$ electrons, an NC stretching frequency at 2119 cm^{-1} for 2-isocyano-2'-formamidobiphenyl in chloroform appears exceptional. The effect of intramolecular hydrogen bonding needs to be investigated.[11,12]

Isomerization of *o*-Isocyanobiphenyl (1).—Irradiation of *o*-biphenylyl isothiocyanate led to the dissociation of sulfur, the generation of *o*-isocyanobiphenyl (**1**), and the discovery of the isomerization **1** → **2**.[2] The latter product was independently prepared by the dehydrogenation of 5,6,7,8,9,10-hexahydrocyclohept-[*b*]indole, obtained from the phenylhydrazone of cycloheptanone by the Fisher indole synthesis,[14] and by treating 6-amino-5,6,7,8,9,10-hexahydrocyclohept[*b*]-indole with palladium on charcoal or with chloranil (see Experimental Section).
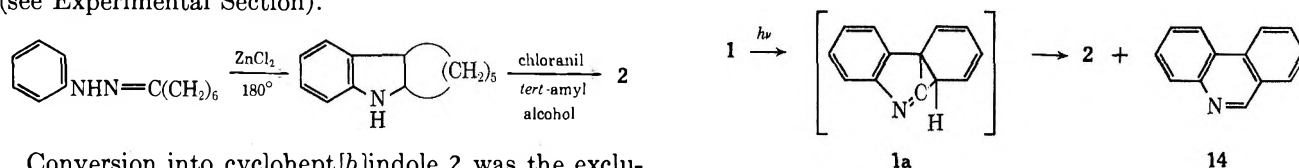
Conversion into cyclohept[*b*]indole **2** was the exclusive reaction during at least the first 5 min of irradiation of **1** in cyclohexane under either oxygen or nitrogen. After about 19 hr of irradiation, conversion under nitrogen gave cyclohept[*b*]indole **2** in 69% yield based on 76% recovery of isocyanide **1**.

A quantitative irreversible thermal isomerization of *o*-isocyanobiphenyl (**1**) in diphenyl ether at 250° into *o*-cyanobiphenyl occurred under conditions comparable

to the isomerization of other aryl isocyanides into cyanides and without an intramolecular reaction with the adjacent phenyl group.[15] Achieving the latter by photoexcitation apparently depended on a withdrawal of electron density from the isocyano carbon and its electrophilic attack on the adjacent phenyl group. A favorable geometry for attack at either of the two CC bonds adjacent to the pivotal bond places the rings nearly perpendicular to each other with the carbon atom of the *o*-isocyano group directly above one or the other of the pertinent CC bonds. The reaction was assumed to proceed from an excited singlet state, since it was not quenched by oxygen (*vide ante*).

The formation of a transient "intramolecular adduct" **1a** is proposed in analogy with norcaradiene, a postulated intermediate in the formation of cycloheptatriene from carbene and benzene.[16] Toluene, a minor product, represents formal carbene insertion into a CH bond; however, rearrangement of an intermediate adduct may be responsible, since thermal isomerization of 7,7-dicyanonorcaradiene gave both phenylmalononitrile and a cycloheptatriene.[17] The generation of phenanthridine **14** in trace amount after 57 hr of irradiating *o*-isocyanobiphenyl presents a similar uncertainty which has not been resolved.[18] It is not produced from **2**, since a slow transformation of the latter into unknown material was established by an independent experiment in which cyclohept[*b*]indole could no longer be detected after 19 hr of irradiation and neither phenanthridine **14**, acridine, nor other isomers were found.[19] Regeneration of the isocyanide **1** from **1a**, analogous to the photofragmentation of cyclopropanones,[20] has not been established.
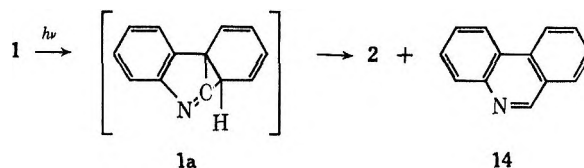
Isomerization of 2,*x*'-Diisocyanobiphenyl (3–5).—Localization of photoexcitation in **3–5** would be expected to increase, as rotation around the pivotal bond leads to orthogonal 2- and *x*'-isocyanobiphenyl rings. Enhanced electrophilicity at one or the other, but not both, isocyano groups would result from excitation in the appropriate plane. Just as electrophilic attack upon the adjacent phenyl group accounted for ring closure from **1**, a similar attack proposed for a 2-isocyano carbon leads to ring closure from **3–5**. The excited 3'- or 4'-isocyano group was nonproductive and apparently returned to its ground state without giving a chemical reaction, since a careful search revealed no evidence for the latter. Investigations on excited isocyano derivatives are continuing.

(8) D. Lemal in "The Chemistry of the Amino Group," S. Patai, Ed., Interscience, New York, N. Y., 1968, pp 701–749.

(9) I. Ugi, U. Fetzer, U. Eholzer, H. Knupfer, and K. Offermann, *Angew. Chem., Int. Ed. Engl.*, **4**, 472 (1965).

(10) We are indebted to Dr. V. T. Ramakrishnan for the ir spectra of these derivatives of phenyl isocyanide: 2-, 3-, and 4-methoxy; 3- and 4-nitro; 2,4-, 2,5-, and 3,4-dimethoxy; and 2-phenyl. Each spectrum was obtained from a chloroform solution and was calibrated against polystyrene.

(11) R. G. Gillis and J. L. Occolowitz, *Spectrochim. Acta*, **19**, 873 (1963), found that the frequency of the isocyanide fundamental stretching mode is greater and its intensity is slightly less in chloroform than in carbon tetrachloride, a behavior opposite to that of carbonyl groups in hydrogen bonding solvents.

(12) R. A. Cotton and F. Zingales, *J. Amer. Chem. Soc.*, **83**, 351 (1961), reported consistently high frequencies. Four aryl isocyanides showed higher frequencies in chloroform than in carbon tetrachloride, but methyl isocyanide showed a much lower frequency in chloroform (2142 cm^{-1}) than in carbon tetrachloride (2169 cm^{-1}).

(13) W. D. Horrocks, Jr., and R. H. Mann, *Specrochim. Acta*, **19**, 1375 (1963).

(14) W. Treibs, R. Steinert, and W. Kirchof, *Justus Liebigs Ann. Chem.*, **581**, 54 (1953).

(15) Unpublished results. See also ref 4, Chapter 3.

(16) W. Kirmse, "Carbene Chemistry," Academic Press, New York, N. Y., 1971, p 227.

(17) E. Ciganek, *J. Amer. Chem. Soc.*, **89**, 1458 (1967).

(18) J. de Jong and J. H. Boyer, *Chem. Cmmun.*, 961 (1971), describe a photoisomerization of **1** in methanol in which solvent participation gives phenanthridine in high yield. Similar participation is unavailable to cyclohexane and other aprotic solvents.

(19) M. Comtet and H. D. Mettee, *Mol. Photochim.*, **2**, 63 (1970), describe photoisomerization of azulene into naphthalene.

(20) Reference 16, pp 15 and 37.

Results obtained from irradiating **1**, **4**, and **5** each for 5 min were compared (Table I). From **1** each of

TABLE I

PHOTOISOMERIZATION OF ISOCYANOBIPHENYLS, *o*-CNC₆H₄C₆H₄R, INTO CYCLOHEPT[*b*]INDOLES. IRRADIATION OF 10 ML OF A 2.5 × 10⁻³ *M* SOLUTION IN CYCLOHEXANE UNDER ORDINARY ATMOSPHERE AT 254 NM FOR 5.0 MIN

				Cyclohept[*b*]indoles
				λ,		Yield^a
							mol		Φ ×
R	No.	No.	E^b	nm^c	ϵ^c	× 10⁴	%	10²
H	1	2	0.275	527.5^d	366^d	3.77	14.9	3.77
m'-CN	4	7 (9)	0.270	515.0	411	3.78	15.1	3.78
			0.390	600.0	296			
		7 (9)	0.270	515.0	268	1.75	7.0	1.75
			0.390	600.0	164			
p'-CN	5	8	0.460	525.0	326	6.90	27.6	6.90

^{a} The conversion of **1** → **2** was quantitative, since a 14.5 ± 0.4% decrease in the amount of **1** was determined by gc. ^{b} Absorbance. ^{c} Determined from benzene solutions. ^{d} A. G. Anderson, Jr., and J. Tazuma, *J. Amer. Chem. Soc.*, **74**, 3455 (1952), report absorption at 500 nm (log ϵ 2.61) for **2** in alcohol.

two equivalent paths in which bond cleavage occurred at one or the other of two ring CC bonds next to the pivotal bond produced **2** in 7.45% yield and 0.0188 quantum yield. Similarly, from **5** each of two equivalent paths produced **8** in 13.8% yield and 0.0345 quantum yield. Two nonequivalent paths from **4** produced **7** and **9** in total yield of 22.1% and 0.0553 quantum yield; however, one product, **7** or **9**, predominated with both a percentage yield of 15.1 and a quantum yield of 0.0378, describing the most efficient product formation. After irradiation for 45 min the total percentage yield of **7** and **9** was 30 ± 5 and after 90 min it was 45 ± 5 (determined spectroscopically by uv absorption data). After 90 min chromatography afforded the major product in 57.3% and the minor product in 16.4% yield after correcting for 45.0% recovery of starting material **4**.

Each indole, **2**, **7**, **8**, and **9**, showed absorption near 500 nm, as expected of an azulene chromophore.[21] The NC stretching frequency for **7** and **9** at 2119 cm⁻¹ and for **8** at 2114 cm⁻¹ (chloroform solutions) supported electron withdrawal by a resonance coupling with the seven-membered aromatic troponimine ring system (Scheme I). Further support was found in the extremely facile hydrolysis of **7**–**9** into the corresponding aminocyclohept[*b*]indoles **20**–**22**.

The nature of the assistance from the isocyano substituent in the ring undergoing attack is incompletely understood. An absence of ground-state resonance coupling of isocyano and phenyl electrons and a predicted retardation in ring closure to a derivative of **1a** by an inductive electron withdrawal by the isocyano substituent in **4** and **5** apparently eliminated assistance in the ring-closure step. On the other hand, ring expansion into a cyclohept[*b*]indole **7**–**9** could be assisted by the stabilization of product through a resonance coupling of electrons in the aromatic seven-membered ring with those in the isocyano substituent. A correlation between the substituent position and the extent of stabilization appears to place position 8 between **7** and **9**, one of which is more effective than the other. Fur-

ther investigations with a variety of electron-donating and withdrawing substituents are needed.

Irradiation of 2,2'-diisocyanobiphenyl (**3**) apparently produced 6- and 10-isocyanocyclohept[*b*]indoles. While further changes to undetected **6**, concerted with or subsequent to its formation, gave a new product **6a**, no evidence for the isomerization **10** → **12** was found. Separation of the product mixture on a silica gel column changed **6a** into an amine **15** (Scheme II), also produced by treating an ether solution of **6a** with 2 *N* hydrochloric acid. In a similar way the isocyanide **10** was transformed into an amine **16**, isomeric with **15**. The identification of **15** as 6-aminocyclohept[*b*]indole was established by its preparation from cyclohept[*b*]-indol-6(5*H*)-one (**17**) and ammonium acetate[22] and by the regeneration of the ketone **17** on treating the amine **15** with alcoholic alkali (Scheme II).

SCHEME II
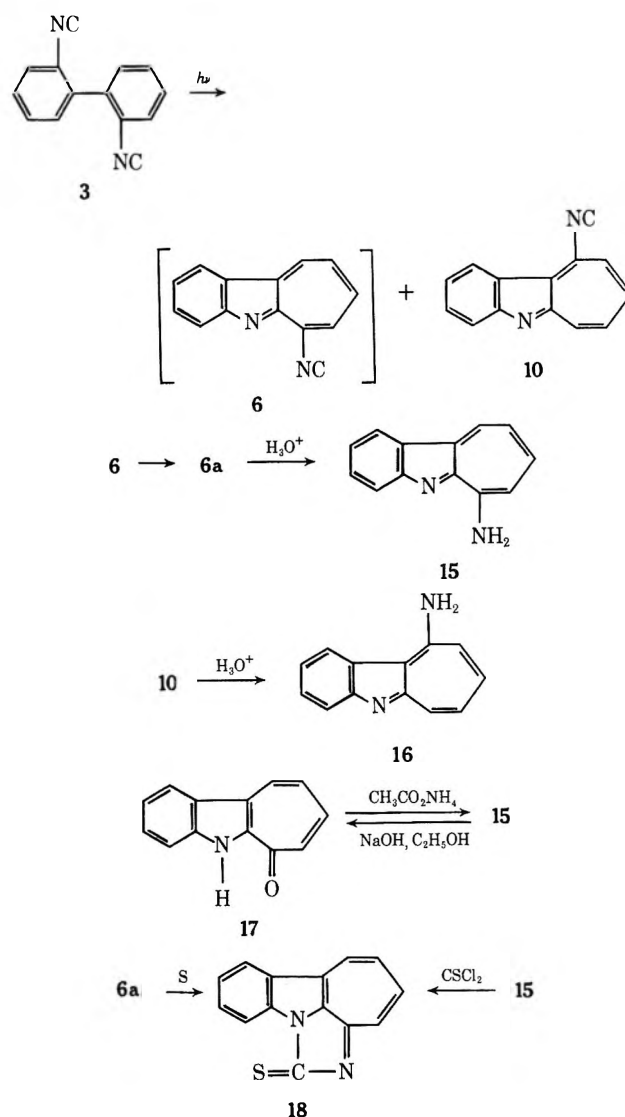
Sulfur, ethanol, aniline, and water each revealed the nucleophilicity of **6a**. At room temperature sulfur, added to the product mixture of **3**, **10**, and **6a**, slowly combined with **6a**. A 1:1 adduct was identical with a cyclic thiourea **18** also prepared by treating the amine

(21) A. G. Anderson, Jr., and J. Tazuma, *J. Amer. Chem. Soc.*, **74**, 3455 (1952), report absorption at 500 nm (log ϵ 2.61) for **2** in alcohol.

(22) T. Nozoe in "Non-Benzenoid Aromatic Compounds," D. Ginsburg, Ed., Interscience, New York, N. Y., 1959, p 339.

15 with thiophosgene (Scheme II), otherwise noteworthy for the lack of formation of the ring-opened isomer, 6-isothiocyanatocyclohept[b]indole. There was no reaction between sulfur and either of the isocyanides **3** and **10**.

Addition of a few drops of absolute ethanol to the product mixture **3**, **10**, and **6a** brought about an immediate color change from violet to yellow-red. A reaction with **6a** is assumed since the isocyanide **10** was detected after the addition of ethanol by absorption near 500 nm and was isolated chromatographically from silica. A slower reaction with aniline was found by uv monitoring to be complete after 60 hr. The usual chromatographic separation from silica gave the isocyanides **3** and **10**, formanilide, 6-aminocyclohept[b]-indole (**15**), and 6-anilinocyclohept[b]indole (a tentative assignment). The greater resistance of 10-isocyanocyclohept[b]indole (**10**) to aniline was established by an independent experiment. In the related facile hydrolysis of **6a**, 6-formamidocyclohept[b]indole (**19**) was formed. By acid or base hydrolysis and by thermal decarbonylation it was transformed into the amine **15**. Apparently formanilide resulted from an amide interchange between **19** and aniline.

+ $C_6H_5NH_2$ $\longrightarrow$ **15** + C_6H_5NHCHO

NHCHO
19
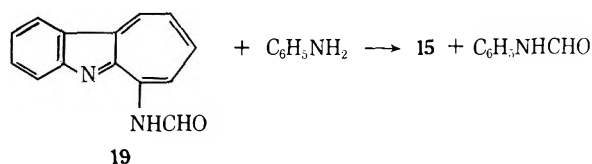
As expected 10-isocyanocyclohept[b]indole resembles its isomers **7–9** insofar as its NC stretching frequency at 2109 cm^{-1} (chloroform) supports resonance coupling of NC and the seven-membered aromatic ring electrons. The extent of the bathochromic shifts from reference values at 2130 ± 3 cm^{-1} alternates with the positions of the isocyano substituent so that the shifts for **7** and **9** are less than those for **8** and **10**. Presumably this is related to a charge alternation for the carbon atoms of the aromatic seven-membered ring.[23]

An alternation of color for the aminocyclohept[b]indoles gave blue to **20** and **22** and yellow-orange to **15**, **21**, and **16**.[24] The basicities of cyclohept[b]indole, $pK_a = 6.7$, and its 6-, 7-, 8-, 9-, and 10-amino derivatives, **15**, **20**, **21**, **22**, and **16**, respectively, $pK_a = 7.8-9.7$, are considerably higher than those of isomeric acridine, $pK_a = 5.6$, and its 6-, 7-, 8-, and 9-amino derivatives, $pK_a = 4.4-8.04$,[25] and phenanthridine, $pK_a = 3.30$, and its 6- and 9-amino derivatives, $pK_a = 6.88$,[26] 7.31.[25] These are expected results from an electron release required for aromaticity in the seven-membered ring.

20, 7(or 9) NH$_2$
21, 8 NH$_2$
22, 7(or 9) NH$_2$

While certain properties of **6a** are descriptive of 6-isocyanocyclohept[b]indole, both the ring-closure isomer, an aminoimino carbene **11**, and the dimer olefin **23** might accommodate better the enhanced nucleophilicity at the "isocyano" carbon and the absence of an NC stretching frequency in the region 2110–2140 cm^{-1}. Attributing nucleophilicity in the related structure to the diamino carbene monomer **24**, and later corrected to the tetraaminoethylene dimer **25**,[8] tends to suggest a similar property for **23**, but confirmation of the relationship between **6** and **23** needs further investigation.

$6 \longrightarrow 11 \longrightarrow$

23

$(R_2N)_2C$: $(R_2N)_2C=C(NR_2)_2$
24   **25**
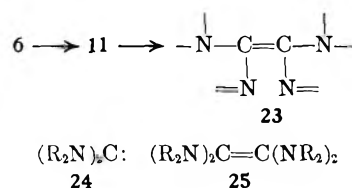
Experimental Section

Instruments included Cary 14 uv and Perkin-Elmer 237B grating ir spectrophotometers; Varian A-60 nmr and Perkin-Elmer 270 masss pectrometers; Barber-Coleman flame ionization gc Model 5320 equipped with an 8 × 0.25 in. steel coil packed with 5% Ge-Xe-60 Chromosorb G, 60–80 AW DMGS (Nuclear Chicago), operated with a column temperature of 210–220°, injection port about 250°, and detector about 280°, nitrogen carrier gas flow rate of 60–70 ml min^{-1}; and a Rayonet RPR 100 photochemical chamber reactor (Southern New England Ultraviolet Co.) equipped with 16 low-pressure mercury 254-nm lamps.

Before irradiation under nitrogen, solutions were degassed with a stream of nitrogen. Spectrograde cyclohexane was distilled from lithium aluminum hydride directly into the quartz reactor tube. J. T. Baker silica gel was used in column chromatography. Melting points and boiling points are uncorrected. Yields are based on recovered starting material. Elemental analyses were obtained from Micro-Tech Laboratories, Skokie, Ill.

Structure assignments for **2**, **14**, **15**, **17**, **18**, and each recovered starting material have been based on identical comparisons with corresponding authentic samples by examining two or more physical properties including ir, uv, nmr, tlc, nD, and mixture melting point. The molecular weight for o-isothiocyanato-biphenyl, **1–5**, **7–10**, and **14–22** was confirmed by the mass spectrum M$^+$ from m/e at 70 eV for each compound. The M$^+$ 194 for **21** was confirmed by m/e at 12 eV for **21**·HCl.

The NC stretching frequencies for eight isocyanides were measured in chloroform: **1**, 2130; **3**, 2128; **4**, 2127; **5**, 2126; **7**, 2119; **8**, 2114; **9**, 2119; and **10**, 2109 cm^{-1}.

By means of a Sargent-Welch pH meter, Model LS, pK_a values were determined from the titration curve at half-neutralization of about 20 mg of each base in 25 ml of 50% aqueous methanol by 0.05 N hydrochloric acid at 26–27° under nitrogen: **2**, 6.7; **15**, 7.8; **20** (or **22**), 9.2; **21**, 9.7; **20** (or **22**), 9.7; **15**, 9.3. The relatively low pK of 7.8 for **15** may be the result of intramolecular hydrogen bonding between the two amino nitrogen atoms.

Quantum Yields.—Samples (10 ml) of the standard actinometer solution of potassium ferrioxalate[27] were subjected to three freeze-thaw cycles (liquid nitrogen, vacuum line at 2 × 10^{-5} mm). They were then irradiated in small quartz tubes placed in a merry-go-round assembly in a Rayonet reactor equipped with 16 mercury low-pressure lamps emitting at 254 nm. After an irradiation time of 30.0 and 60.0 sec, conversions into ferrous ions of 1.25 × 10^{-3} and 2.50 × 10^{-3} M, respectively, were found. From the quantum yield (1.25) the calculation of the intensity of the absorbed light was found to be 2.0 × 10^{16} quanta sec^{-1} cc^{-1}. Each diisocyanobiphenyl in cyclohexane (10 ml, 2.5 × 10^{-3} M) was similarly irradiated for 5.0 min but in the presence of atmospheric oxygen. After evaporation of the

(23) A. Streitwieser, Jr., and J. I. Brauman, "Supplemental Table of Molecular Orbital Calculations," Pergamon Press, Oxford, 1965, p 305.

(24) M. Godfrey and J. N. Murrell, *Proc. Roy. Soc., Ser. A*, **278**, 64 (1964), have shown that color alteration in azulene derivatives is mainly the result of the inductive effect of the substituent.

(25) A. Albert, R. Goldacre, and J. Phillips, *J. Chem. Soc.*, 2240 (1948).

(26) V. de Gaouck and R. J. W. Le Fevre, *ibid.*, 1392 (1939).

(27) C. G. Hatchard and C. A. Parker, *Proc. Roy. Soc., Ser. A*, **235**, 518 (1956); C. A. Parker, *ibid.*, **220**, 104 (1953).

solvent the residue was dissolved in 5 ml of benzene and the yield of insertion products was determined spectrophotometrically. A yield of 14.9% of cyclohept[b]indole was calculated from λ_{max} 527.5 nm (ϵ 366), whereas a loss of 14.5 ± 0.4% of o-isocyanobiphenyl was calculated from integrated areas of several gas chromatograms compared with gas chromatograms from the standard solution. Results are found in Table I.

o-Isothiocyanatobiphenyl.—To a solution of 20.60 g (0.10 mol) of dicyclohexylcarbodiimide in 20 ml of pyridine and 40 ml of carbon disulfide cooled to −10°, a solution of 16.9 g (0.10 mol) of o-aminobiphenyl in 20 ml of pyridine was added dropwise with stirring, which was continued for 3 hr at −10 to 0° and for 18 hr at room temperature. A nearly quantitative yield of 1,3-dicyclohexylthiourea, mp 178–181°, was isolated after concentration and treatment with cold ether. Eluting the concentrated filtrate from silica with n-hexane followed by distillation gave o-isothiocyanatobiphenyl as a colorless, viscous liquid: yield 15.8 g (75.0%); bp 130–132° (0.25 mm); n^{26}D 1.6805; ir (neat) 2100 cm^{-1} (NCS); nmr (CDCl$_3$) δ 7.35 (m). Anal. Calcd for C$_{13}$H$_9$NS: C, 73.90; H, 4.29; N, 6.63; S, 15.18. Found: C, 74.25; H, 4.49; N, 6.75; S, 15.00.

Isocyanides.—Following general procedures,[9] formamides were dehydrated by phosphorus oxychloride or with phosgene into corresponding isocyanides. 2-Isocyanobiphenyl (1)[28] was obtained in 65% yield, bp 113–114° (1.5 mm), $n^{21.5}$D 1.6115. Anal. Calcd for C$_{31}$H$_9$N: C, 87.12; H, 5.06; N, 7 82. Found: C, 87.17; H, 5.32; N, 7.88.

2,2'-Diisocyanobiphenyl (3) was obtained in 29% yield, mp 110.5–112° (lit.[9] mp 101–104°). Anal. Calcd for C$_{14}$H$_8$N$_2$: C, 82.32; H, 3.95; N, 13.73. Found: C, 82.28; H, 3.95; N, 13.76.

The half-converted by-product, 2-isocyano-2'-formamidobiphenyl, obtained in 27% yield, recrystallized from ethanol as a colorless solid: mp 106–107.5°; ir (CHCl$_3$) 3378 (NH), 2119 (N≡C), 1695 cm^{-1} (C=O). Anal. Calcd for C$_{14}$H$_{10}$N$_2$O: C, 75.65; H, 4.54; N, 12.61; O, 7.19. Found: C, 75.39; H, 4.46; N, 12.61; O, 7.43.

2,3'-Diisocyanobiphenyl (4) was obtained in 54% yield, mp 145–146°. Anal. Calcd for C$_{14}$H$_8$N$_2$: C, 82.37; H, 3.95; N, 13.72. Found: C, 82.32; H, 4.09; N, 13.55.

2,4'-Diisocyanobiphenyl (5) was obtained in 39% yield, mp 94.5–95.5° (lit.[9] mp 97–98°).

Irradiation of o-Isothiocyanatobiphenyl.—A solution of 1.240 g (5.90 mmol) of o-isothiocyanatobiphenyl in 400 ml of cyclohexane was flushed with nitrogen for 3 hr and irradiated at 254 nm for 64 hr under a stream of nitrogen. Cyclohexane was removed and the residue, chromatographed on silica, gave 9 mg of sulfur, 24%, mp and mmp 117–119°, eluted with n-hexane; 1.030 g of starting material, 83.0%, eluted with n-hexane–benzene (10:1); 44.5 mg of o-isocyanobiphenyl (1), 25%, eluted with n-hexane–benzene (3:2); and 50 mg of cyclohept[b]indole 2, 28%, eluted with chloroform–ether (4:1), mp 134.5–136° (sealed tube) (lit.[14] mp 143°), methiodide mp 232°.[14] Anal. Calcd for C$_{13}$H$_9$N: C, 87.12; H, 5.06; N, 7.82. Found: C, 86.91; H, 5.16; N, 7.61. Unidentified fractions were obtained on eluting with n-hexane–benzene, benzene–chloroform, and chloroform–ether but neither carbazole (ring closure product from o-biphenylyl nitrene, if present) nor phenanthridin-6(5H)-one was detected.

Irradiation of o-Isocyanobiphenyl (1).—A solution of 540 mg (3.0 mmol) of o-isocyanobiphenyl in 400 ml of cyclohexane was irradiated under either oxygen or nitrogen at 254 nm. After about 3 hr the isomerization under nitrogen became slower, as a coating of unknown material had accumulated on the walls of the reaction flask. In contrast the flask containing the reaction under oxygen remained clear. Upon replacing the nitrogen atmosphere with oxygen in the fouled flask, continued irradiation slowly cleared away the heavy coating and after 6–7 hr the formation of 2 restarted. The formation of 2, monitored by absorption near 500 nm[21] for aliquots taken at intervals, reached a maximum after 19 hr of irradiation. At that time chromatographic separation of the mixture from silica gave starting material, eluted by n-hexane–benzene (3:2), 376 mg (69.5%) followed by elution of 2 with chloroform–ether (3:1), 103 mg (62.8%). Chromatography after 57 hr afforded 62.8% of starting material, less than 1% of phenanthridine 14, eluted with benzene–chloroform (1:3), and 42% of 2 eluted with chloroform. Examination of the crude reaction mixture after irradiation under oxygen (air)

did not reveal the formation of either o-isocyanatobiphenyl or phenanthridin-6(5H)-one. After 19 hr of irradiation under nitrogen, cyclohept[b]indole 2 was completely transformed into unknown material; however, phenanthridine 14 could not be detected.

Cyclohept[b]indole (2).—To a stirred refluxing solution of 5.0 g (27.0 mmol) of 5,6,7,8,9,10-hexahydrocyclohept[b]indole, mp 142–143.5°,[21] in 100 ml of tert-amyl alcohol, 15 g (61.0 mmol) of powdered chloranil, mp 290°, was added in small portions. Refluxing was continued for 6 hr. The cooled solution, diluted with ether, was extracted with 2 N sodium hydroxide and with 2 N hydrochloric acid. The yellow acidic aqueous layer was washed with ether and cyclohexane. Basifying, extracting with cyclohexane, drying (Na$_2$SO$_4$), concentrating, and recrystallizing afforded 55 mg (1.0%) of authentic cyclohept[b]indole 2. An attempted dehydrogenation of 6-amino-5,6,7,8,9,10-hexahydrocyclohept[b]indole (vide infra) with palladium on charcoal gave a trace of 2, but 6-aminocyclohept[b]indole 15 could not be found.
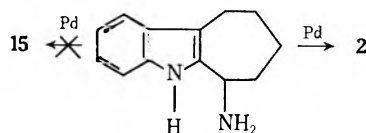
Irradiation of 2,2'-Diisocyanobiphenyl (3).—A solution of 250 mg (1.23 mmol) of 3 in 400 ml of cyclohexane was irradiated at 254 nm for 4 hr under nitrogen. Cyclohexane was removed. The residue separated from a column of silica gel to give the fractions (compound, milligrams, per cent yield, eluting solvent): 3, 44, 17.6, n-hexane–benzene (1:4); 19, as a red solid, 3, 1.2, benzene–chloroform (4:1); 10, 55, 26.7, benzene–chloroform (1:1); and 15, 84, 42.9, ether–ethanol (4:1). Recrystallization of the formamide 19 from n-hexane gave small, deep red needles: mp 115–140° dec; ir (CHCl$_3$) 3279 (m), (NH), 1704 cm^{-1} (C=O); nmr (CDCl$_3$) δ 9.87 (s, 1, NH), 9.00 (s, 1, O=CH), 9.30 (d, 1, J = 11 Hz), 8.85 (d, 1, J = 8 Hz), 8.6–7.3 (m, 6). It did not give a satisfactory elementary analysis. When heated at 145° for 10 min the formamide 19 lost carbon monoxide to give the corresponding amine 15. Shaking a solution of 19 in diethyl ether for 90 sec with aqueous 0.25 N sodium hydroxide also converted it into 15, but shaking a basic aqueous solution (pH 10) for 10 min had no effect.

From cyclohexane, 10-isocyanocyclohept[b]indole (10) recrystallized as long, violet needles: mp >300° (becoming black); nmr (CDCl$_3$) δ 8.95 (d, 1, J = 8 Hz), 8.63 (m, 1), 8.30–7.37 (m, 6). Anal. Calcd for C$_{14}$H$_8$N$_2$: C, 82.37; H, 3.95; N, 13.72. Found: C, 81.80; H, 3.97; N, 13.65.

Recrystallization of the fourth fraction from carbon tetrachloride gave 6-aminocyclohept[b]indole (15) as an orange solid: mp 179–180° (sealed tube) after sublimation at 160–180° (15 mm); nmr (CDCl$_3$) δ 8.60 (d, 1, J = 10 Hz), 8.27 (d, 1, J = 8 Hz), 8.01–6.93 (m, 6), 6.01 (s, 2, NH$_2$). Anal. Calcd for C$_{13}$H$_{10}$N$_2$: C, 80.37; H, 5.15; N, 14.43. Found: C, 80.48; H, 5.14; N, 14.59.

In another run after irradiation for 1 hr, the solvent was removed. Extraction of the product mixture with a minimum amount of dry ether separated the isocyanides 3 and 10 from 6a, a shiny black amorphous solid which resisted purification and did not show the strong isocyano ir absorption band in the region 2100–2150 cm^{-1}. An ether solution of the residue was extracted with 2 N hydrochloric acid. Starting material, 16.5%, was recovered from the ether layer. Ether extraction of the cooled aqueous layer, after neutralization with 2 N sodium hydroxide to pH 6–7, gave the amine 15, 46%. Further treatment of the aqueous layer with base and extraction with ether gave 10-aminocyclohept[b]indole (16), 28.4%, insoluble in n-hexane, cyclohexane, and benzene, slightly soluble in chloroform, and soluble in methanol and ethanol. It was not satisfactorily recrystallized and was apparently too basic for elution from silica gel by the usual solvents. It was eluted by mixtures of methanol and ether from basic aluminum oxide and isolated as a solid: mp >200°; nmr (DMSO-d$_6$) δ 8.97 (d, 1, J = 8 Hz), 8.83–7.37 (m, 7). A picrate derivative was prepared and recrystallized from 10% aqueous acetic acid and from ethanol as yellow needles, mp 229–230°. Anal. Calcd for C$_{19}$H$_{13}$N$_5$O$_7$: C, 53.91; H, 3.09; N, 16.55. Found: C, 53.61; H, 3.20; N, 16.23.

To the deep red-violet solution obtained after 4 hr of irradiation of 200 mg (1.0 mmol) of 3, 100 mg (3.1 mmol) of sulfur was added

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(28) Previously reported as a solid, mp 116–118°.[9]

and the solution was stirred for 60 hr under nitrogen as a red solid precipitated. Extraction of the product mixture in ether with an aqueous 2 N hydrochloric acid solution removed starting material and unreacted sulfur. The crude cyclic thiourea 18, 71 mg (30.7%), was obtained from the aqueous layer after neutralizing with aqueous sodium hydroxide to pH 5, extracting with ether, drying (Na$_2$SO$_4$), filtering, and removing ether. The material was purified by elution from basic aluminum oxide with benzene–chloroform (1:1) and recrystallization from carbon tetrachloride–ethanol (1:1) as orange-red needles: mp 208° dec; ir (CHCl$_3$) 1661, 1582 cm^{-1}; nmr (DMSO-d_6) δ 7.43–8.87 (m). *Anal.* Calcd for C$_{14}$H$_8$N$_2$S: C, 71.14; H, 3.41; N, 11.86. Found: C, 70.94; H, 3.54; N, 11.84.

Cyclic Thiourea 18 from 6-Aminocyclohept[*b*]indole (15).— To a solution of 50.0 mg (0.258 mmol) of 15 in 10 ml of anhydrous methylene chloride and 1 ml of triethylamine 3 drops of condensed thiophosgene was added. The mixture was heated at reflux for 0.5 hr, cooled in an ice bath, diluted with 50 ml of ether, and extracted with 2 N hydrochloric acid. After basifying with 2 N sodium hydroxide, extracting with ether, drying (Na$_2$SO$_4$), and removing the solvent, 16 mg of material was obtained and separated by preparative thin layer chromatography (Chromar Sheet 1000, Mallinckrodt). Elution with chloroform–ethanol (4:1) gave a solid identical with the thiourea 18, 9 mg (14.7%).

6-Amino-5,6,7,8,9,10-hexahydrocyclohept[*b*]indole.— As previously reported, 6-oxo-5,6,7,8,9,10-hexahydrocyclohept[*b*]-indole recrystallized from benzene as yellow plates: mp 149–151°;[29] ir (CHCl$_3$) 3436 (NH), 1626 cm^{-1} (C=O); nmr (CDCl$_3$) δ 9.46 (1, NH), 7.72–6.87 (m, 4, aromatic), 3.07 (m, 2, CH$_2$CO), 2.82 (m, 2, =CCH$_2$–), 1.96 [m, 4, (CH$_2$)$_2$]. The oxime derivative recrystallized from benzene–hexane and from carbon tetrachloride as colorless needles and prisms, mp 126.5–128.5°. *Anal.* Calcd for C$_{13}$H$_{14}$N$_2$O: C, 72.87; N, 6.59; N, 13.08. Found: C, 73.13; H6.64; N, 13.28.

A solution of 200 mg (0.935 mmol) of the oxime in 100 ml of dry ether was refluxed for 3 hr with 100 mg of lithium aluminum hydride. Inorganic hydroxides were precipitated by adding 3 drops of water, 9 drops of 2 N sodium hydroxide, and again 3 drops of water. The colorless ether filtrate was dried (Na$_2$SO$_4$) and the ether was removed. A sticky residue gave, upon trituration with carbon tetrachloride, 46 mg (25.7%) of 6-amino-5,6,7,8,9,10-hexahydrocyclohept[*b*]indole as colorless crystals, mp 111–112° after recrystallization from carbon tetrachloride, mass spectrum M$^+$, 70 eV, *m/c* 200. *Anal.* Calcd for C$_{13}$H$_{16}$N$_2$: C, 77.94; H, 8.06; N, 13.99; mol wt, 200.29. Found: C, 77.77; H, 8.02; N, 13.92.

Cyclohept[*b*]indol-6(5H)-one (17).— A mixture of 195 mg (1.0 mmol) of 6-keto-5,6,7,8,9,10-hexahydrocyclohept[*b*]indole[29] and 64 mg (2.0 mmol) of sulfur in a 3-ml tube provided with a condenser and gas outlet on top was immersed in a Wood's metal bath kept at 235°. Within 7 min 48.5 ml of gas was collected in a gas buret. After cooling, a black solid was triturated with 6 N hydrochloric acid. The acidic solution was filtered, cooled in ice, and neutralized with aqueous 6 N sodium hydroxide. A yellow precipitate was collected, dried, and sublimed at 220–230° (15 mm) to give 55 mg (28.0%) of 17 as bright yellow needles: mp 249.5–250.5°; ir (CHCl$_3$) 3413 (NH), 3175 (intramolecular H bonding), 1618 (C=O); nmr (DMSO-d_6) δ 12.7 (s, 1, NH), 8.38 (m, 2), 7.87–6.87 (m, 6). *Anal.* Calcd for C$_{13}$H$_9$NO: C, 79.97; H, 4.65; N, 7.18. Found: C, 79.93; H, 4.49; H, 7.28.

In an alternative preparation a solution of 60 mg (0.31 mmol) of 6-aminocyclohept[*b*]indole 15 and 170 mg of sodium hydroxide in 4 ml of ethanol–water (1:1) was heated under reflux for 15 hr. The solution was cooled and diluted to 25 ml with water and extracted with methylene chloride. The organic layer was dried (Na$_2$SO$_4$) and put on a silica column. Chloroform eluted 45 mg (74.5%) of 17.

6-Aminocyclohept[*b*]indole (15).— A mixture of 100 mg (0.5 mmol) of 17, 5 g of ammonium acetate, and 3 ml of acetic acid was refluxed for 10 hr. Dilution with water precipitated 75 mg (75%) of 17. The filtrate was basified, extracted with ether, dried (Na$_2$SO$_4$), and filtered. Removal of the solvent left about 5 mg of a red solid. Heating for 90 min at 85–90° in 2 N hydrochloric acid afforded a trace of 15 after the usual work-up.

Irradiation of 2,3′-Diisocyanobiphenyl (4).— A solution of 200 mg (1.0 mmol) of 4 in 400 ml of cyclohexane was irradiated for 1.5 hr under conditions similar to those described above. Analysis of the uv absorption for a sample taken after 45 min revealed a conversion into 7 and 9 of 30 ± 5% and after 90 min of 45 ± 5%. In the usual work-up 90 mg (45%) of starting material was eluted from silica with *n*-hexane–benzene (1:1). The isomers 7 and 9 were apparently separated by elution with benzene–chloroform (1:1). The one in lower yield, 18 mg (16.4%), eluted first and recrystallized from benzene as transparent violet plates, mp >280° (darkening above 210°). *Anal.* Calcd for C$_{14}$H$_8$N$_2$: C, 82.37; H, 3.95; N, 13.72. Found: C, 82.46; H, 4.06; N, 13.88. The major product, 63 mg (57.3%), recrystallized from cyclohexane as tiny, dark brown needles, mp >280°. *Anal.* Found: C, 82.07; H, 4.17; N, 13.58. An isomeric rather than an identical relationship between the minor product A (7 or 9) and the major product B (7 or 9) was best established by ir (CHCl$_3$) and supported by less decisive differences in the uv max (C$_6$H$_6$) and mass spectral [70 eV, *m/e* (rel intensity)] values, all obtained from analytically pure samples: A, ir 2119 (s), 1608 (s), 1595 (s), 1439 (m), 1404 (m), 1337 (m), and 915 cm^{-1} (s); uv 514 nm (ε 280), 412 (1900), 389 (4200), 373 (4600), 314 (33,000) and 302 (36,000); mass spectrum 205 (23), 204 (100), 203 (26), 178 (13), 177 (31), 176 (16), 102 (15), and 88.5 (18); B, ir 2119 (s), 1609 (s), 1484 (s), 1433 (s), 1410 (s), 1381 (s), 1368 (m), and 908 (s); uv 518 nm (ε 410), 410 (2400), 389 (4500), 362 (4700), 332 (16,600), and 322 (20,000); mass spectrum 205 (18), 204 (100), 203 (24), 178 (13), 177 (27), 176 (9), 102 (9), and 88.5 (7).

Each isomer 7 and 9 was hydrolyzed to the corresponding amine by shaking its methylene chloride solution with aqueous 2 N hydrochloric acid. The organic layer decolorized rapidly and the aqueous layer turned orange. Basifying with aqueous 2 N sodium hydroxide and shaking decolorized the aqueous layer and produced an intense blue color in the methylene chloride layer. Removing methylene chloride left the crude amine. Each amine 20 and 22 melted above 220° and was insoluble in *n*-hexane, benzene, and cyclohexane, slightly soluble in chloroform, and soluble in methylene chloride, methanol, or ethanol. Purification by recrystallization was unsatisfactory. Neither amine was eluted from silica gel with the usual organic solvents, but diethyl ether–methanol mixtures eluted each from basic aluminum oxide. The hydrochloride of the amine derived from the major product B crystallized as orange needles from aqueous 2 N hydrochloric acid and was recrystallized from methanol–aqueous 2 N hydrochloric acid (1:1), mp >280°. *Anal.* Calcd for C$_{13}$H$_{11}$N$_2$Cl·1.75H$_2$O: C, 59.54; H, 4.23; N, 10.68. Found: C, 59.54; H, 4.81; N, 10.66. *Anal.* Calcd for C$_{13}$H$_{11}$N$_2$Cl: C, 67.68; N, 4.81; N, 12.14. Found: C, 66.82; H, 4.72; N, 12.13 after drying to constant weight.

Irradiation of 2,4′-Diisocyanobiphenyl (5) in Cyclohexane.— A solution of 200.0 mg (1.0 mmol) of 5 in 400 ml of cyclohexane was irradiated for 1.5 hr. During the irradiation aliquots were taken after 45 and 90 min. The solvent in each aliquot was evaporated and the residue was dissolved in 5 ml of benzene. Absorption (benzene) at 525 nm (ε 326) revealed conversion into 8 of 62 and 73%, respectively. Irradiation was stopped after 90 min, and concentration of the solution gave 93 mg of 8 as black needles. After the concentrated filtrate was put on silica, elution with *n*-hexane–benzene (2:3) yielded 43 mg (21.5%) of 5. A dark band eluted with benzene–chloroform (1:1) to give a trace of a semisolid unidentified material, ir (CHCl$_3$) 2123 cm^{-1} (N≡C). A fraction of 8, 32 mg, was eluted with benzene–chloroform (1:1), bringing the yield of 8 to 125 mg (78%). An analytical sample of 8 was obtained upon recrystallizing from benzene as long, transparent, faintly violet plates which turned brown at 170° and gave no further change on heating to 320°, nmr (CDCl$_3$) δ 9.13–7.66 (m). *Anal.* Calcd for C$_{14}$H$_8$N$_2$: C, 82.37; H, 3.95; H, 13.72. Found: C, 82.52; H, 4.19; N, 13.88.

8-Aminocyclohept[*b*]indole.— A solution of 31.6 mg (0.15 mmol) of 8 in 50 ml of benzene was shaken in a separatory funnel with 50 ml of aqueous 2 N hydrochloric acid for 2 min. The deep violet color of 8 in benzene disappeared rapidly and the aqueous acid layer turned deep yellow. The layers were separated and the organic layer was again shaken with 20 ml of acid. The acid solution was basified and extracted with methylene chloride. The organic layer was dried (Na$_2$SO$_4$) and filtered. Concentrating the methylene chloride solution gave 29 mg (96.5%) of the amine as tiny yellow needles. It was eluted with methanol

(29) M. Mühlstädt and W. Treibs, *Justus Liebigs Ann. Chem.,* **608**, 38 (1957).

from basic aluminum oxide and after solvent concentration afforded yellow needles, mp 174° dec, nmr (DMSO-d_6) δ 8.96 (d, 1, J = 11 Hz), 8.66 (m, 2), 8.2 (d, 1, J = 8 Hz), 8.01–7.47 (m, 3), 7.27 (d, 1, J = 11 Hz), each peak a doublet with J = 2 Hz. The hydrochloride was prepared by shaking a benzene solution of 60 mg (0.29 mmol) of **8** with 50 ml of aqueous 2 N hydrochloric acid. The acidic solution was allowed to stand overnight and yielded 42 mg (54.5%) of the salt as tiny, bright yellow needles, mp >280°. *Anal.* Calcd for $C_{13}H_{11}N_2Cl$: C, 67.68; H, 4.81; N, 12.14. Found: C, 67.20; H, 4.73; N, 11.76 (12.03).

Stereochemistry of Nucleophilic Addition Reactions. The Addition of Thiophenol and of Hydrogen Chloride to 4-*tert*-Butyl-1-cyanocyclohexene

R. A. Abramovitch,* Milorad M. Rogić, Sandra S. Singer, and N. Venkateswaran

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

The addition of thiophenoxide ion to 4-*tert*-butyl-1-cyanocyclohexene (1) in ethanol gives the two products **2** and **3** containing an axial thiophenoxy group. In tetrahydrofuran, **14** is also formed. The stereochemistries of the products were established by a combination of nmr spectroscopy, chemical transformations, and equilibration experiments. An explanation is proposed for the observed steric course of the addition. r-1-*tert*-Butyl-*t*-3-phenylsulfonyl-*c*-4-phthalimidomethylcyclohexane was found to be somewhat more stable thermodynamically than the r-1,*c*-3,*c*-4 isomer (13). The data suggest that the r-1,*t*-3,*c*-4 isomer exists predominantly in the twist–boat conformation (12). Severe repulsive gauche interactions between the PhSO₂ and the phthalimidomethyl group are proposed to explain the observed order of stabilities. The addition of HCl to 1 gives only r-1-*tert*-butyl-*t*-3-chloro-*t*-4-cyanocyclohexane in which the chlorine is axial.

The stereochemistry of the Michael and Michael-type additions to activated olefins of rigid conformation has been the object of study in our laboratories. We have already established that, under conditions of kinetic control, the diethyl malonate anion in ethanol solution adds to 4-*tert*-butyl-1-cyanocyclohexene to give the addition product with the equatorial malonate and axial cyanide group as the main isomer, with the (e)-malonate (e)-nitrile as the minor product.[1] Under conditions of thermodynamic control, the latter was the main product. No axial malonate could be detected, though small amounts of the product of "abnormal" Michael addition, ethyl r-1-*tert*-butyl-*t*-3-carbethoxymethyl-*c*-4-cyano-*t*-4-cyclohexanecarboxylate were isolated, resulting from the rearrangement of the initially formed axial malonate anion intermediate. In a nonprotic solvent, the main product was that of "abnormal" addition.

To determine whether or not the behavior of the malonate anion was representative of the mode of addition of nucleophiles in general, we embarked on a study of the addition of thiols to activated olefins chosen such that the products would have an unambiguous stereochemistry and that product mixtures could be resolved readily, the stereochemistry of the isomers established, and the isomer ratios determined quantitatively with ease. The additions of nucleophiles have been shown to be of considerable biological importance and are thought to be involved in such diverse phenomena as the carcinogenicity of α,β-unsaturated lactones,[2] car-cinostatic activity of certain plant extracts,[3] stimulation of nerve endings,[4] isomerization of retinal in the visual process,[5] the action of oral contraceptives,[6] and the bacteriostatic activity of naphthoquinones.[7] It is obvious that a knowledge of the steric course of such additions could lead to the design of molecules which could better approach and fit into the active site of the biologically important molecules.

The addition of *p*-toluenethiol to 1-*p*-tolylsulfonylcyclohexene under mildly basic conditions gave mainly the thermodynamically less stable cis isomer, namely *cis*-2-*p*-tolylmercapto-1-*p*-tolylsulfonylcyclohexane.[8] Since chair–chair interconversion can occur in the final products, however, nothing can really be said definitely about the preferred mode of approach of the thiolate anion in this system under conditions of kinetic control. In contrast to the above reaction, addition of *p*-toluenethiolate to 1-*p*-tolylsulfonylcyclopentene gave the trans product, which was explained on the basis of steric interaction between the arylsulfonyl group and the arylmercapto group in the cyclopentyl intermediate anion.[9]

When thiophenoxide ion was added to 4-*tert*-butyl-1-cyanocyclohexene (1) in ethanol two products were formed which were resolved by gas chromatography

(1) R. A. Abramovitch and D. L. Struble, *Tetrahedron*, **24**, 357 (1968).
(2) J. B. Jones and J. M. Young, *Can. J. Chem.*, **46**, 1859 (1968); J. B. Jones and J. N. Baker, *ibid.*, **48**, 1574 (1970).

(3) S. M. Kupchan, *Trans. N. Y. Acad. Sci.*, **32**, 85 (1970); S. M. Kupchan, D. C. Fessler, M. A. Eakin, and T. J. Giacobbe, *Science*, **168**, 876 (1970); S. M. Kupchan, C. W. Siegal, M. J. Natz, J. A. Saenz Renaud, R. C. Haltiwanger, and R. F. Bryan, *J. Amer. Chem. Soc.*, **92**, 4476 (1970).
(4) R. F. Silver, K. A. Kerr, P. D. Frandsel, S. J. Kelly, and H. L. Holmes, *Can. J. Chem.*, **45**, 1001 (1967).
(5) F. M. Menger and J. H. Smith, *J. Amer. Chem. Soc.*, **91**, 4211 (1968).
(6) E. V. Jensen, quoted in *Chem. Eng. News*, **45**, 44 (March 27, 1967).
(7) R. F. Silver and H. L. Holmes, *Can. J. Chem.*, **46**, 1859 (1968).
(8) W. E. Truce and A. J. Levy, *J. Amer. Chem. Soc.*, **83**, 4641 (1961).
(9) W. E. Truce and A. J. Levy, *J. Org. Chem.*, **28**, 679 (1963).

and shown to be r-1-*tert*-butyl-*t*-3-thiophenoxy-*c*-4-cyanocyclohexane (2) and r-1-*tert*-butyl-*t*-3-thiophenoxy-*t*-4-cyanocyclohexane (3), the products of axial ad-

1

2   3
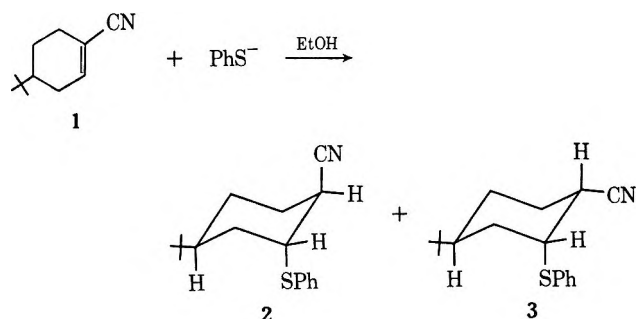
dition of thiophenol to the olefin. The ratio of 2:3 varied with time and could be conveniently followed by glc. Under conditions of kinetic control (boiling ethanol, 16 hr) the ratio of 2:3 was 1:52, but as the reaction time increased this ratio gradually changed until after 70 hr (thermodynamic control conditions, equilibration) it dropped to 1:1.97. Further heating did not lead to any change in the 2:3 ratio. This corresponds to $\Delta G^0{}_{78} = -0.47$ kcal/mol for the CN group, which agrees quite well with the reported value of -0.25 kcal/mol (at 66°).[10] Clearly, the two products formed are epimeric about the –HC$_4$CN group, with 2 presumably having the axial nitrile group.

The conformations of 2 and 3 followed readily from their nmr spectra. In the spectrum of 2 the C$_3$ (>CH-SPh) proton appeared as a narrow unresolved multiplet at δ 3.70, while the C$_4$ H also gave rise to an unresolved multiplet at 2.79, indicating the axial configuration of the substituents at C$_3$ and C$_4$ in this molecule. In 3, on the other hand, while the C$_3$ H is still equatorial (doublet at δ 3.59, $J_{ae} = 3$ Hz), the C$_4$ H is axial and gives rise to a doublet of triplets at higher field [δ 2.72 ($J_{aa} = 12$, $J_{ae} = 3$ Hz)] than the corresponding equatorial proton. Consequently, the thiophenoxy group is axial in both 2 and 3, and the nitrile group is equatorial in 3, confirming the equilibration result.

The axial configuration of the thiophenoxy group in 3 was also established by chemical means. An attempt to oxidize 3 to the corresponding cyano sulfone with 30% hydrogen peroxide in acetic acid gave, instead, the amide sulfone (4), which was resistant to acid hydrolysis with 6 N HCl. The nitrile group in 3 was reduced with lithium aluminum hydride to the primary amine (5) (nonepimerizable with base) which was protected as its phthalimide (6), and the sulfide oxidized to the sulfone (7). As expected from the fact that $\Delta G^0 = -2.6$ kcal/mol for PhSO$_2$–,[10] when 7 was heated with sodium ethoxide in ethanol it was converted in over 90% yield to the diequatorial conformer 8 (some cleavage of the phthalimido group occurred under these conditions but the phthalimidomethyl group was regenerated by heating the crude reaction mixture with phthalimide). The nmr spectra of 5, 6, and 7 (see below) confirmed that the transformations 3 → 7 had occurred with no inversions of configuration, so that the thiophenoxy group must have been axial in 3 (and hence in 4 as well since 3 and 4 are only epimeric about C$_4$). While 7 and 8 had almost identical ir spec-

3 —➤

5, Y = NH$_2$
6, Y = N(CO)$_2$C$_6$H$_4$ 7

OEt⁻

8

4
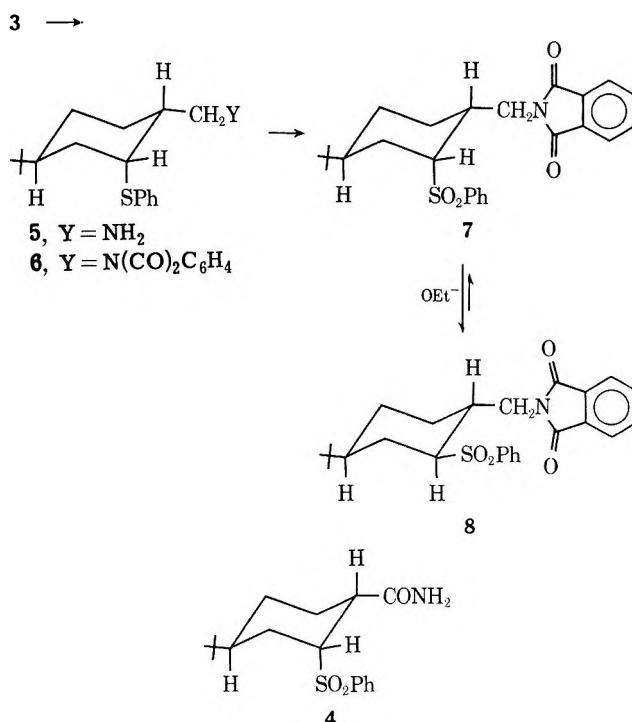
tra, their nmr spectra supported their epimeric nature about C$_3$, for 7 exhibited a narrow band at δ 3.37 due to the C$_3$ H, while the corresponding absorption in 8 was much broader (but still unresolved) and appeared at higher field, 3.08.

The same sequence of reactions was carried out with isomer 2 to yield the sulfone phthalimide presumed to have conformation 11. This, however, could not be equilibrated to 13 under the conditions used for the epimerization of 7 (nor did the C$_3$ proton undergo H–D exchange with EtOD and EtO⁻) and much more vigorous conditions were required, e.g., sodio ethylene glycolate in ethylene glycol at 130°, to effect this equilibration. The epimer ratio at equilibrium was thus found to be 60:40 11:13; i.e., the "axial" phenylsulfonyl configuration was preferred over the equatorial one! The nmr spectra of 9 and 10 (see below) confirmed that no inversion of configuration had taken place up to that point and, in view of the equilibration results, the possibility was considered that epimerization could have occurred in the oxidation step 10 → 11.[11]

This could be readily discounted when it was found that, when the addition of thiophenoxide ion to 1 was carried out in boiling tetrahydrofuran, a third isomer was isolated whose nmr confirmed it to be the product of equatorial addition of PhS⁻, followed by equatorial protonation to give r-1-*tert*-butyl-*c*-3-thiophenoxy-*c*-4-cyanocyclohexane (14). Thus the C$_3$ H appeared as a doublet of triplets at δ 2.95 ($J_{aa} = 15$, $J_{ae} = 4$ Hz) (axial proton), 0.7 ppm upfield from the C$_3$ H absorption in 2 and 3, and the C$_4$ H was a narrow unresolved multiplet at 2.76 (equatorial proton). The ratio of 2:3:14 formed in this reaction was 31:62:7 (85% overall yield). When the addition was carried out in boiling dimethylformamide solution, the ratio of 2:3:14 was 29:27:44 (69% overall yield), the higher reaction temperature apparently favoring the formation of more of the thermodynamically more stable isomer ($\Delta G^0{}_{25}$

(10) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience, New York, N. Y., 1965, p 436.

(11) J. A. Claisse, D. I. Davies, and C. K. Alden, *J. Chem. Soc. C*, 1498 (1966).

9, Y = NH₂
10, Y = N(CO)₂C₆H₄

11

12

14

15, Y = NH₂
16, Y = N(CO)₂C₆H₄

13
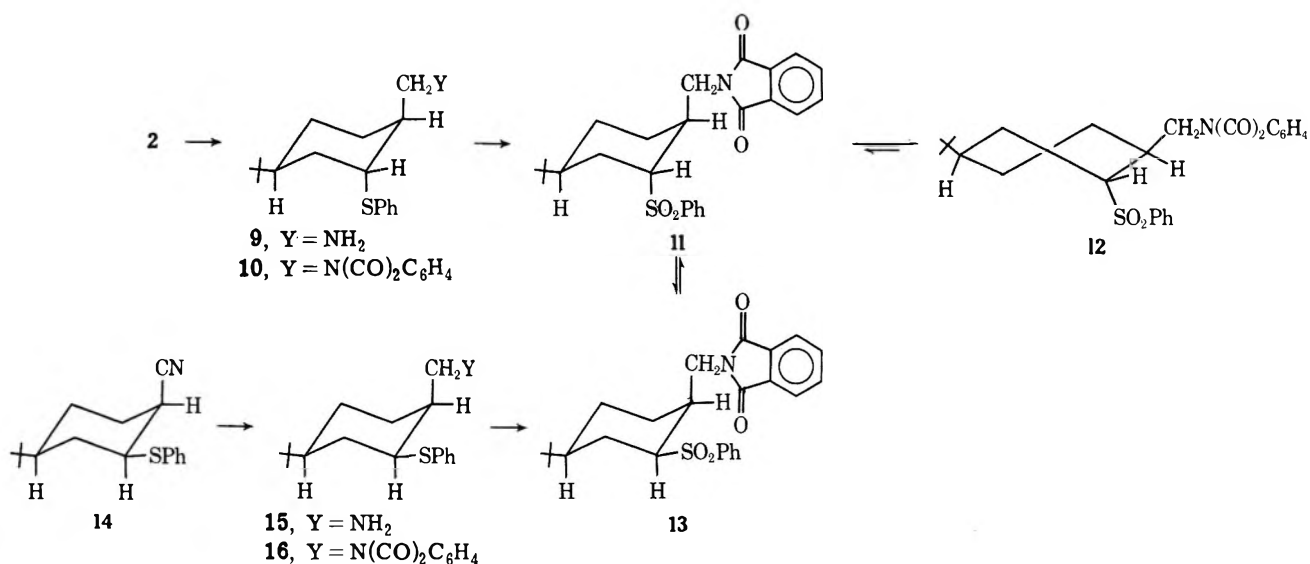
for PhS is −0.8 kcal/mol[10]), since the Michael-type addition is readily reversible (treatment of either **2** or **3** with OEt⁻ in EtOH causes appreciable reversal to **1** and thiophenol; if thiophenol was added to suppress the reversal then **2** and **3** could be equilibrated with base). **14** could be reduced to the primary amine **15** which was then protected as **16** and oxidized to give **13** so that all four possible sulfone phthalimides were now available. Equilibration of **13** with NaOCH₂CH₂OH in ethylene glycol at 130° gave the same equilibrium mixture of **11** and **13** as was obtained above from **11**, *i.e.*, with the "axial" isomer predominating.

The nmr spectra of the intermediates in these transformations were quite instructive. Thus, the equatorial C₃ H protons in **5**, **6**, **9**, and **10** all appeared as narrow unresolved singlets at δ 3.38–3.70, while the axial C₃ H proton in **15** gave a broad triplet (J_{aa} = 14, J_{ae} = 4 Hz) at 3.18. From this and other[12] work a number of compounds of the general type **17**, **18**, and **19** have become available. It was observed that, in

17, X = OH, Cl, NH₂, N(CO)₂C₆H₄

18, X = OH, Cl, NH₂, N(CO)₂C₆H₄

19, X = NH₂, N(CO)₂C₆H₄
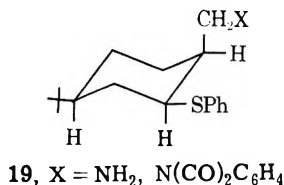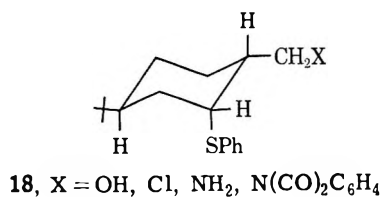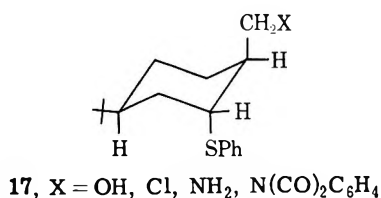
18 and **19**, the exocyclic methylene protons appear as the AB multiplet (eight lines) (J_{AB} = ±13.5–14.0 Hz)

(12) R. A. Abramovitch and S. S. Singer, unpublished results.

of an ABX system, owing to the anisotropic effect[13] of the vicinal thiophenoxy group on this methylene group which must not be able to undergo completely free rotation. On the other hand, the exocyclic methylene in compounds **17** exhibited a doublet (A₂X), the thiophenoxy group being too far from the methylene group to influence it (thereby also confirming the proposed stereochemistries). A first-order analysis of the ABX three spin system in **18** [X = N(CO)₂C₆H₄] (J_{AB} = 14 Hz) in CDCl₃ yielded the following values: J_{AX} = 10.5 Hz, J_{BX} = 4.5 Hz, and $\nu_A - \nu_B$ = 0.21 ppm. The coupling constants and chemical shifts were only slightly affected by the use of a higher dielectric constant solvent, *i.e.*, nitrobenzene: J_{AX} = 9.38 Hz, J_{BX} = 3.62 Hz, and $\nu_A - \nu_B$ = 0.22 ppm.

On the basis of these observations one could predict that, should they maintain their chair conformations, the exocyclic methylene group in sulfone phthalimides **7**, **8**, and **13** should give rise to *ABX* (*AMX*) multiplets while that in **11** should approximate an A_2X system. In actual practice, sulfone phthalimides **7**, **11**, and **13** exhibited *ABX* octets while **8** gave rise to an *AMX* pattern of lines. The fact that **11** does not give rise to the expected A₂X system suggested that the molecule might not exist in the chair form but in a twist–boat form, as does also the observation that it is thermodynamically somewhat more stable than **13**. Table I summarizes the nmr parameters for the four sulfone phthalimides.

To account for the fact that **7** is epimerized to **8** almost quantitatively under relatively mild conditions while **11** requires much more vigorous conditions to equilibrate to **13**, and also to explain the fact that **11** is somewhat thermodynamically more stable than **13**, we propose (i) that **11** actually prefers to exist in a twist–boat conformation and (ii) that there are severe repulsive gauche or torsional interactions between the bulky PhSO₂ and phthalimidomethyl groups in **7**, **8**, and **13**. The latter would be the same for all three if they existed in classical chair forms. This is unlikely to be the case since the *tert*-butyl-cyclohexane ring is appreciably flattened.[14] The influence of such gauche interactions

(13) J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution N.M.R. Spectroscopy," Vol. 2, Pergamon Press, Oxford, 1966, p 817.
(14) R. A. Wohl. *Chimia*, **18**, 219 (1964); F. Shah-Malak and J. H. P. Utley, *Chem. Commun.*, 69 (1967).

TABLE I

NMR PARAMETERS FOR C₃ H AND EXOCYCLIC METHYLENE GROUP IN SULFONE PHTHALIMIDES 7, 8, 11, AND 13 IN CDCl₃

Compd	C₃ H	δ (J in Hz) −CH₂X	First-order analysis of −CH₂X, J in Hz, ν − ν in ppm
7	3.67 (e)	3.83, 4.67 (J_{AB} = 13.5)	J_{AX} = 9.46, J_{BX} = 2.04, ν_A − ν_B = 0.32
8	3.03 (a)	3.83, 4.78 (J_{AM} = 13.5)	J_{AX} = 4.5, J_{MX} = 10.5, ν_A − ν_M = 0.94 (J_{AX} = 3.5, J = 10.5, ν_A − ν_M = 1.04)[a]
11	2.78 (br d, J = 6)	3.50 (J_{AB} = 14)	J_{AX} = 9.61, J_{BX} = 4.38, ν_A − ν_B = 0.25
13	3.12 (a) (d of t, J_{aa} = 14, J_{ae} = 5)	4.20	Not analyzed

[a] In nitrobenzene solution.

may be seen from a consideration of Newman projections of the conformations about the C₃–C₄ bond. Though it is appreciated that ring flattening of cyclohexanes involves an opening of the internal ring angles resulting in "pinching" of the external angles, it is felt that Newman projections can, with this understanding, lead to a clearer—though approximate—picture of the interactions involved. Ring flattening causes the C₃ and C₄ substituents to move closer together in 7, but further apart in 8. This, combined with the syn–axial

R_2 = phthaloyl
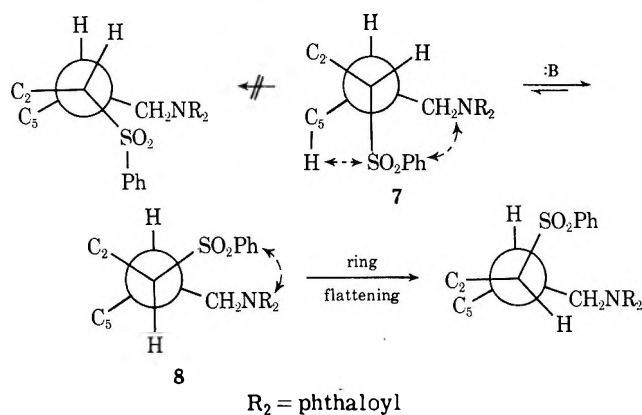
interactions of PhSO₂ in 7, explains the almost quantitative epimerization 7 → 8. With the r-1,c-3,c-4 sulfone phthalimide 13 ring flattening would again in-

crease the important axial–equatorial torsional interaction between the phenylsulfonyl and phthalimidomethyl groups so that flattening would be hindered. While no such large gauche interaction between these groups can be present in 11 in the chair form, the syn–axial interactions must be large and a minimum value
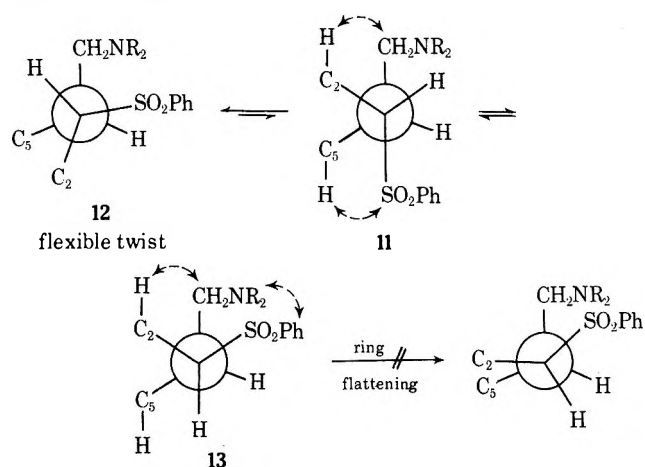
of 4.4 kcal/mol is estimated for the combined syn–axial interactions of the PhSO₂ and phthalimidomethyl groups. This should lead to the r-1,t-3,c-4 isomer existing predominantly in the twist–boat conformation (12), in which the three bulky groups would be pseudoequatorial, thus relieving the strain due to the diaxial functions in 11.[15] One sufficiently large axial group, as that in c-4-tert-butyl-1-phthalimidocyclohexane, is sufficient to cause the molecule to exist largely in the twist conformation.[16] The flexibility of 12 would permit the PhSO₂ and CH₂N(CO)₂C₆H₄ groups to move apart further than they would be in 13, so that, if the postulated gauche interaction is sufficiently large, 12 would be thermodynamically more stable than 13, as is observed. Other examples of the reversal of a group's usual preferred configuration due to vicinal interactions with another function are known.[17] While a flattened distorted chair form of 11 might also explain some of the observations, it appears to us to be more strained than 12, as well as not being able to account for the observed order of thermodynamic stabilities.

Support for the twist conformation comes from the nmr spectrum of the r-1,t-3,c-4 isomer. This conformation, but not the chair, would account readily for the fact that the exocyclic methylene group gives rise to an ABX spectrum rather than an A_2X one. Also the C₃ methine proton appears as a broad doublet (J = 6 Hz), which coupling constant is about twice that expected for an e,e coupling[18,19] but is reasonable for the coupling expected in a twist conformation such as 12,[16,20,21] though no data are available at this time which would permit an evaluation of the influence of the electronegativity of the PhSO₂ group on the vicinal coupling constants to be made.

As mentioned above, selective oxidation of 3 to the corresponding cyano sulfone could not be achieved with hydrogen peroxide, the oxidation going all the way to the amide sulfone 4. Oxidation to the desired sulfone nitrile could be effected with potassium permanganate. On the other hand, the r-1,c-3,c-4 nitrile sulfide (14) could be readily converted to the expected nitrile sulfone (20) with peracetic acid, but, unlike 2 and 3, could not be epimerized with base to give the diequatorial isomer 21.

(15) D. L. Robinson and D. W. Theobald, *Quart. Rev. Chem. Soc.*, **21**, 314 (1967).
(16) H. Booth and G. C. Gidley, *Tetrahedron Lett.*, 1449 (1964).
(17) D. J. Pasto and D. R. Rao, *J. Amer. Chem. Soc.*, **92**, 5151 (1970).
(18) Reference 10, p 152.
(19) E. L. Eliel, personal communication.
(20) E. Garbisch and D. Patterson, *J. Amer. Chem. Soc.*, **85**, 3228 (1963).
(21) E. L. Eliel, *Accounts Chem. Res.*, **3**, 1 (1970).

20

21

22
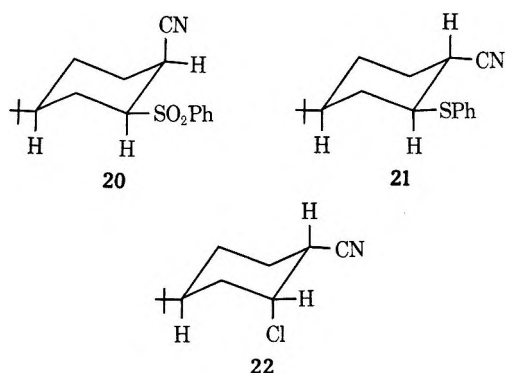
The addition of hydrogen chloride to **1** was also studied. Only one adduct was obtained, namely, *r*-1-*tert*-butyl-*t*-3-chloro-*t*-4-cyanocyclohexane (**22**), whose conformation was assigned on the basis of its nmr spectrum. The C_3 H proton appeared as a narrow unresolved band at δ 4.60 (equatorial proton, CR_2HCl), while the C_4 H gave rise to a doublet of triplets (axial proton, CR_2HCN) at 2.85 (J_{aa} = 7.5, J_{ae} = 2.5 Hz). This result is also in accord with the report[22] that the addition of HCl or DCl to 1-acetylcyclohexene gives the product of trans-diaxial addition only. The attempted addition of 48% HBr to **1** only led to the formation of 4-*tert*-butylcyclohexene-1-carboxamide.

The displacement of bromide by thiophenoxide ion from *cis*-4-*tert*-butyl-1-bromocyclohexane was shown to be an SN2 process, leading to a 1:1 mixture of *t*-4-*tert*-butyl-1-thiophenoxycyclohexane and 4-*tert*-butyl-1-cyclohexene.[23] When **22** was treated with thiophenoxide ion in a variety of solvents no direct displacement of the chlorine could be observed; instead elimination of the elements of hydrogen chloride occurred to give **1**. This is not unexpected in view of the fact that base-catalyzed trans-diaxial elimination of HCl from **22** should be a very facile process. In tetrahydrofuran solution, β elimination was followed by addition of thiophenol to the olefin to give a mixture of **2**, **3**, and **14**, as described earlier.

The present results show that, contrary to the behavior of the malonate anion which adds to **1** equatorially under conditions of kinetic control, both thiophenoxide and chloride ions prefer to add axially. The preferred equatorial approach of the bulky malonate was attributed[1] to large diaxial nonbonded interactions in the transition state for axial addition, which transition state was assumed to resemble the intermediate. With smaller nucleophiles such as PhS⁻ and Cl⁻ such 1,3-diaxial repulsions would be much less important and other factors obtaining in such additions would assume control of the guidance mechanism. In particular, axial approach to the nucleophile leads to almost continuous overlap between the developing σ bond and the conjugated system in the formation of the transition state A. For similar overlap to occur in the transition state B leading to equatorial addition the molecule would have to assume a boat-like conformation, so that this is avoided under conditions of kinetic control unless the 1,3-diaxial repulsions are large. Under conditions of thermodynamic control, some equatorial thiophenoxy adduct is formed.

(22) G. Armstrong, J. A. Blair, and J. Homer, *Chem. Commun.*, 103 (1968).
(23) E. L. Eliel and R. S. Ro, *J. Amer. Chem. Soc.*, **81**, 1949 (1959).

A

B

↓
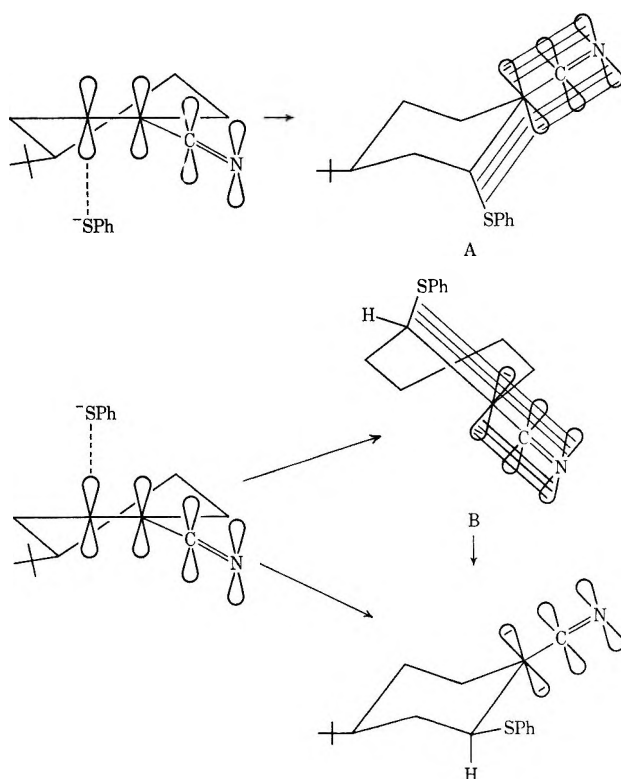
Mass Spectra of Isomeric *tert*-Butyl-4-cyano-3-thiophenoxycyclohexanes.—The three isomers, **2**, **3**, and **14**, gave similar fragmentation patterns (Table II). They all exhibited a parent ion at *m/e* 273, but

TABLE II

MASS SPECTRAL DATA FOR
r-1-*tert*-BUTYL-4-CYANO-3-THIOPHENOXYCYCLOHEXANES AT 70 EV

	Relative intensity		
m/e	**2**	**3**	**14**
274	4	2.5	10
273	17	9	44
217	2	2	7
216	8	6	29
164	2.5	2	11
148	4.5	3	6.5
121	6.5	4.5	10
111	9	9	9
110	100	100	100
109	9	9	15
108	11	7	26
107	4.5		
106	4		
57	63	50	75

it is noteworthy that **14**, which cannot undergo axial elimination of PhS· gives a much more intense M⁺ peak than do the other two. Other peaks are also more intense for **14**. Loss of *tert*-butyl occurs in all cases to give the *m/e* 216 ion and *tert*-Bu⁺ at *m/e* 57. Loss of PhS· occurs to a small extent leading to *m/e* 164, but the major fragmentation pathway involves the formation of the olefin and what is probably the charged thiophenol tautomer (*m/e* 110) as the base

m/e 110
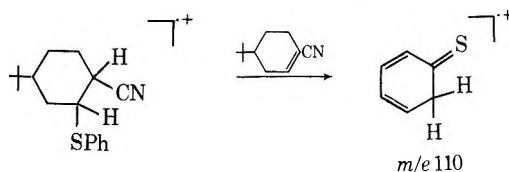
peak. This type of fragmentation has been found to occur in various alkylaryl thio ethers, *e.g.*, thioanisole.[24]

Experimental Section

Lithium thiophenolate was prepared by dissolving thiophenol (28 g, 0.27 mol) in toluene (25 ml), adding small pieces of lithium ribbon (1.7 g, 9.24 g-atoms) and boiling the mixture under reflux. It was then filtered; the solid was passed through a 35 mesh sieve to remove unreacted lithium and used without further purification.

Addition of Thiophenol to 4-*tert*-Butyl-1-cyanocyclohexene. A. In Ethanol.—Thiophenol (4.4 g, 0.04 mol) was added to a solution of sodium (0.07 g, 0.0033 g-atom) in anhydrous ethanol (50 ml) under nitrogen. To this solution was added 4-*tert*-butyl-1-cyanocyclohexene[1] (5 g, 0.032 mol) and the solution was boiled under reflux for 48 hr. At various intervals of time, aliquots were analyzed by glc using a 3 ft × 0.25 in 15% asphalt on Chromosorb W column and the ratio of **3**:**2** was determined: 16 hr, 52.5; 26 hr, 14.7; 48 hr, 11.0; 70 hr, 1.97; 90 hr, 1.97. The best yields (70–80%) of adducts were obtained after 48 hr. The solvent was evaporated, the mixture dissolved in chloroform and washed with 5% aqueous NaOH, and the solvent dried (MgSO₄) and evaporated. The residue was distilled at 170–180°(0.5 mm), and the distillate solidified partially on cooling. Crystallization from pentane gave r-1-*tert*-butyl-*t*-4-cyano-*t*-3-thiophenoxycyclohexane (**3**): mp 53.5–54°; ir (KBr) 3060, 3040, 2950, 2900, 2850, 2210 cm⁻¹ (C≡N); *m/e* 273 (9) (M⁺).

Anal. Calcd for C₁₇H₂₃NS: C, 74.67; H, 8.48. Found: C, 74.31; H, 8.18.

The residue from the recrystallization was subjected to preparative glc on a 5 ft × 0.25 in 20% Apiezon M on Chromosorb P column to give **2** as an oil which was purified by molecular distillation. This gave pure r-1-*tert*-butyl-*c*-4-cyano-*t*-3-thiophenoxycyclohexane (**2**): bp 125–130° (0.05 mm); ir (film) 3060, 2960, 2870, 2240 cm⁻¹; *m/e* 273 (17) (M⁺).

Anal. Calcd for C₁₇H₂₃NS: C, 74.67; H, 8.48. Found: C, 74.45; H, 8.60.

B. In Tetrahydrofuran.—4-*tert*-Butyl-1-cyanocyclohexene (1.1 g, 6.8 mmol), lithium thiophenolate (0.72 g, 6 mmol), and thiophenol (1 g, 9 mmol) were dissolved in dry tetrahydrofuran (10 ml), and the solution was boiled under reflux for 4 hr. It was then poured into water (10 ml); the aqueous layer was extracted with ether (3 × 20 ml) and combined with the organic layer. This was washed with 5% aqueous NaOH (3 × 20 ml) and brine (3 × 20 ml), dried (MgSO₄), and evaporated to give a yellow oil (1.60 g), glc analysis of which (20% SE-30 on Chromosorb W, 60–100 mesh; 6 ft × ³/₁₆ in.; 245°; 60 ml/min He carrier gas) indicated the presence of **2**, **3**, and **14** in the ratio of 31:62:7 and a small amount of starting olefin.

The oil was chromatographed on silica gel (100 g) and eluted with petroleum ether (bp 30–60°)–benzene (1:1 v/v). Isomer **2**, bp 125–130°(0.05 mm), was eluted first, followed by r-1-*tert*-butyl-*c*-4-cyano-*c*-3-thiophenoxycyclohexane: mp 93–94.5° (petroleum ether); ir (KBr) 3050, 3030, 2925, 2850, 2200 cm⁻¹; *m/e* 273 (39) (M⁺).

Anal. Calcd for C₁₇H₂₃NS: C, 74.67; H, 8.48. Found: C, 74.60; H, 8.59.

Further elution with the same solvent gave **3**, mp 53.5–54°.

C. In Dimethylformamide.—4-*tert*-Butyl-1-cyanocyclohexane (16.3 g, 0.1 mol), lithium thiophenolate (11.7 g, 0.1 mol), and thiophenol (33 ml, 0.3 mol) in dimethylformamide (150 ml) were boiled under reflux for 3.5 hr and worked up as described for the tetrahydrofuran reaction. Glc analysis showed the ratio of **2**:**3**:**14** to be 29:27:44. The products (18.7 g, 69%) were resolved preparatively by column chromatography on silica gel as above.

r-1-*tert*-Butyl-*t*-3-phenylsulfonyl-*t*-4-carboxamide (**4**).—To a solution of **3** (4 g) in glacial acetic acid (25 ml) was added 30% hydrogen peroxide (5.5 ml) followed by a few drops of concentrated H₂SO₄. The reaction mixture heated up considerably and was cooled in water. After being kept at room temperature for 0.5 hr the solution deposited crystals which were filtered, washed with water and recrystallized from methanol to give the carbox-

amide (4.2 g): mp 173–175°; ir (KBr) 3540, 3400, 3175 (NH₂), 1685 (CO), 1360, 1130 cm⁻¹ (SO₂).

Anal. Calcd for C₁₇H₂₅NO₃S: C, 63.21; H, 7.80; N, 4.34. Found: C, 63.48; H, 7.60; N, 4.31.

r-1-*tert*-Butyl-*t*-4-cyano-*t*-3-phenylsulfonylcyclohexane.—A solution of potassium permanganate (2.85 g) in water (50 ml) was slowly added with stirring to the thiophenoxy nitrile **3** (1.29 g) in glacial acetic acid (8 ml). The solution was stirred for 45 min and then treated with a saturated aqueous sodium bisulfite solution until the color was discharged. The solid was filtered and dissolved in benzene (100 ml); the benzene solution was washed with water and then brine and dried (MgSO₄). Evaporation of the solvent and recrystallization of the residue from petroleum ether (bp 60–80°)–benzene gave the nitrile sulfone (1.0 g, 70%): mp 145.5–147.5°; ir (KBr) 2250 (C≡N), 1290, 1135 cm⁻¹ (SO₂).

Anal. Calcd for C₁₇H₂₃NO₂S: C, 66.85; H, 7.59. Found: C, 66.83; H, 7.84.

r-1-*tert*-Butyl-*t*-4-phthalimidomethyl-*t*-3-thiophenoxycyclohexane (**6**).—**3** (4.37 g, 15.9 mmol) was added to a suspension of lithium aluminum hydride (1.15 g, 32.6 mol) in ether (50 ml) and the mixture heated under reflux for 13 hr. It was then cooled and decomposed with water and then filtered through Celite. The filtrate was dried (MgSO₄) and evaporated to dryness, and the residue, dissolved in benzene (50 ml), was treated with phthalic anhydride (2.47 g, 16.9 mmol) and triethylamine (0.5 ml) and boiled under reflux for 24 hr using a Dean-Stark water separator. The mixture was then washed with brine (20 ml), dried (MgSO₄), and evaporated, and the product recrystallized from alcohol to give the phthalimide **6** (4.8 g, 74%): mp 145–146°; ir (KBr) 1765, 1705 cm⁻¹.

Anal. Calcd for C₂₅H₂₉NO₂S: C, 73.67; H, 7.17; N, 3.43. Found: C, 73.72; H, 7.14; N, 3.77.

r-1-*tert*-Butyl-*t*-4-aminomethyl-*t*-3-thiophenoxycyclohexane (**5**).—A mixture of the above phthalimide (4.02 g) and hydrazine hydrate (2.1 ml) in ethanol (100 ml) was boiled under reflux for 6 hr. The ethanol was distilled off and benzene added simultaneously. 1,4-Phthalazdione was filtered; the filtrate was washed with water (60 ml) and brine (30 ml), dried (MgSO₄), and evaporated. The residue was distilled under vacuum to give the amine (2.96 g, 86%), bp 131–133° (0.02 mm).

Anal. Calcd for C₁₇H₂₇NS: C, 73.60; H, 9.81. Found: C, 73.81; H, 9.64.

r-1-*tert*-Butyl-*t*-3-phenylsulfonyl-*t*-4-phthalimidomethylcyclohexane (**7**).—A mixture of **5** (4.99 g), 30% aqueous hydrogen peroxide (10 ml), concentrated H₂SO₄ (0.1 ml), and glacial acetic acid (40 ml) was stirred at room temperature for 6 hr. The solid which separated was filtered, washed with water (40 ml), and recrystallized from ethanol to give sulfone phthalimide **7** (5.03 g, 98%): mp 193–194°; ir (KBr) 1285, 1130 cm⁻¹ (SO₂).

Anal. Calcd for C₂₅H₂₉NO₄S: C, 68.31; H, 6.65; N, 3.18. Found: C, 68.27; H, 6.42; H, 3.25.

r-1-*tert*-Butyl-*t*-4-aminomethyl-*t*-3-phenylsulfonylcyclohexane.—The above sulfone phthalimide (5.42 g) and hydrazine hydrate (5 ml) were boiled under reflux in ethanol (100 ml) for 15 hr. The ethanol was evaporated, the residue extracted with hot benzene (100 ml) and the benzene solution washed successively with water (3 × 30 ml) and brine (30 ml) and dried (MgSO₄). Removal of the solvent and recrystallization of the residue from cyclohexane afforded the amine (3 g, 78%): mp 115.5–117°; ir (KBr) 3380, 1290, 1125 cm⁻¹.

Anal. Calcd for C₁₇H₂₇NO₄S: C, 65.92; H, 8.79. Found: C, 65.94; H, 8.90.

r-1-*tert*-Butyl-*c*-4-phthalimidomethyl-*t*-3-thiophenoxycyclohexane (**10**).—A solution of lithium aluminum hydride (0.285 g) in dry ether (3 ml) was added dropwise under N₂ to r-1-*tert*-butyl-*c*-4-cyano-*t*-3-thiophenoxycyclohexane (**2**) (0.50 g) in dry ether (5 ml). The mixture was stirred and boiled under reflux for 15 hr, the excess hydride decomposed with ethanol, the mixture filtered through Celite and the filter cake washed with benzene (4 × 20 ml). The combined filtrates were dried (MgSO₄) and evaporated to give the amine as an oil (0.424 g): ir (KBr) 3350, 3280 (NH₂), 3065, 3055 (Ar H), 2960, 2860 cm⁻¹; nmr (CCl₄) δ 7.20 (m, 5 H, Ar H), 3.68 (br s, 1 H, C₃ H), 2.68 (br d, 2 H, CH₂NH₂), 0.90 (s, 9 H, *tert*-butyl). The pure amine had bp 155° (0.2 mm).

Anal. Calcd for C₁₇H₂₇NS: C, 73.60; H, 9.81. Found: C, 73.42; H, 9.71.

The crude amine (0.424 g) was dissolved in benzene (35 ml), and phthalic anhydride (0.42 g) and triethylamine (1 ml) were added. The mixture was boiled under reflux for 15 hr using a

(24) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, San Francisco, Calif., 1967, p 288.

Dean-Stark water separator. It was then washed with 1 N HCl (3 × 20 ml) and brine (3 × 20 ml), dried (MgSO₄), and evaporated. The residue was recrystallized from aqueous ethanol to give the phthalimide (0.205 g, 33%): mp 91.5–93.5°; ir (KBr) 1770, 1702 cm⁻¹; nmr (CCl₄) δ 7.80, 7.10 (m, 9 H, Ar H), 3.68 (br d, 2 H, CH₂NR₂), 3.38 (br s, 1 H, C₃ H), 0.90 (s, 9 H, *tert*-butyl); *m/e* 407 (9) (M⁺).

Anal. Calcd for C₂₅H₂₉NO₂S: C, 73.67; H, 7.17. Found: C, 73.14; H, 7.06.

r-1-*tert*-**Butyl**-*t*-3-**phenylsulfonyl**-*c*-4-**phthalimidomethylcyclohexane (11).**—The *r*-1,*t*-3,*c*-4-thiophenoxyphthalimide (1.05 g) in glacial acetic acid (25 ml) was oxidized at room temperature for 6 hr with 30% hydrogen peroxide (1.5 ml) and concentrated H₂SO₄ (2 drops). The product was recrystallized from aqueous ethanol to give the **sulfone** (0.97 g, 60%): mp 162.5–163.5°; ir (KBr) 1770, 1705 (C=O), 1300, 1140 cm⁻¹ (SO₂).

Anal. Calcd for C₂₅H₂₉NO₄S: C, 68.31; H, 6.65. Found: C, 67.97; H, 6.41.

r-1-*tert*-**Butyl**-*c*-4-**phthalimidomethyl**-*c*-3-**thiophenoxycyclohexane (16).**—*r*-*tert*-Butyl-*c*-4-cyano-*c*-3-thiophenoxycyclohexane (14, 1.38 g) was reduced with LiAlH₄ in the same manner as was 2 to give the amine 15 (1.29 g, 92%): ir (film) 3350, 3280 cm⁻¹ (NH₂); nmr (CCl₄) δ 7.20 (m, 5 H, Ar H), 3.20 (m, 4 H, CH₂NH₂, 2 H exchangeable with D₂O), 2.60 (t, *J*ₐₐ = 11 Hz, 1 H, C₃ H), 0.96 (s, 9 H, *tert*-butyl).

The crude amine (0.82 g) was treated with phthalic anhydride as before to give the phthalimide (0.883 g, 74%): mp 111–112° (aqueous EtOH); ir (KBr) 1770, 1710 cm⁻¹.

Anal. Calcd for C₂₅H₂₉NO₂S: C, 73.67; H, 7.17. Found: C, 73.84; H, 7.29.

r-1-*tert*-**Butyl**-*c*-3-**phenylsulfonyl**-*c*-4-**phthalimidomethylcyclohexane (13).**—Phthalimide 16 (1.3 g) was oxidized as usual with hydrogen peroxide to give the **sulfone** (1.04 g, 73%): mp 204.5–205°; ir (KBr) 1770, 1710 (C=O), 1305, 1145 cm⁻¹ (SO₂).

Anal. Calcd for C₂₅H₂₉NO₄S: C, 68.51; H, 6.65. Found: C, 68.50; H, 6.75.

r-1-*tert*-**Butyl**-*c*-4-**cyano**-*c*-3-**phenylsulfonylcyclohexane (20).**—The *r*-1,*c*-3,*c*-4 nitrile phenyl sulfide (14, 1.2 g) was oxidized with H₂O₂ in H₂SO₄ as usual to give the **nitrile sulfone** (0.654 g, 53%): mp 138.5–139.5°; ir (KBr) 2250 (C≡N), 1351, 1155 cm⁻¹ (SO₂); nmr (CDCl₃) δ 7.80, 7.50 (m, 5 H, Ar H), 3.22 (br s, 1 H, C₄ H), 2.96 (d of t, *J*ₐₐ = 13, *J*ₐₑ ≈ 4 Hz, 1 H, C₃ H), 0.82 (s, 9 H, *tert*-butyl).

Anal. Calcd for C₁₇H₂₃NO₂S: C, 66.64; H, 7.89. Found: C, 66.47; H, 7.84.

Base-Catalyzed Equilibration of the *r*-1,*t*-3,*t*-4 Sulfone Phthalimide (7).—A solution of sulfone phthalimide (7, 300 mg) in absolute ethanol containing sodium ethoxide (from 50 mg of Na) was boiled under reflux for 24 hr. The solvent was evaporated and the residue treated with phthalic anhydride (0.25 g) in acetic acid (15 ml) and boiled for 4 hr. The solvent was evaporated and the residue recrystallized from ethanol–pentane and then from ethanol to give a near-quantitative yield of the *r*-1-*tert*-butyl-*c*-3-phenylsulfonyl-*t*-4-phthalimidomethylcyclohexane (8), mp 142–143°, depressed on admixture with starting 7.

Anal. Calcd for C₂₅H₂₉NO₄S: C, 68.31; H, 6.65; H, 3.18. Found: C, 68.26; H, 6.47; H, 3.30.

Equilibration of *r*-1,*t*-3,*t*-4 Sulfone Amine.—The equilibration was carried out as for 7 above to give an oil which was converted into the phthalimide (8), mp 142–143°, undepressed on admixture with a sample obtained as above.

Equilibration of *r*-1,*t*-3,*c*-4 (12) and *r*-1,*c*-3,*c*-4 (13) Sulfone Phthalimides.—One of the sulfone phthalimides (0.20 g) was added to a solution of sodium (50 mg) in ethylene glycol (5 ml) and the solution heated at 130 ± 2° for varying lengths of time (24 to 192 hr). The solution was then poured into water (60 ml), sodium chloride (1 g) added, and the solution continuously extracted with CHCl₃ for 24 hr. The CHCl₃ was evaporated, the residue was dissolved in benzene (30 ml), phthalic anhydride (100 mg) and triethylamine (5 drops) were added, and the mixture was boiled under reflux using a Dean-Stark separator for 15 hr. It was then washed with 1 N HCl (2 × 15 ml) and brine (2 × 15 ml), dried (MgSO₄), and evaporated. The residue (100 mg) was dissolved in deuteriochloroform and analyzed by nmr. Relative amounts of the two sulfone phthalimides were determined by integration of the two *tert*-butyl peaks using a 50-Hz sweep width. The *tert*-butyl group of the *r*-1,*t*-3,*c*-4 isomer absorbed at δ 0.91, while that of the *r*-1,*c*-3,*c*-4 isomer absorbed at 0.93 and the lines were well resolved on the 100-MHz instrument. The isomers were isolated by preparative tlc (1-mm plates, 60% benzene, 39%

CHCl₃, 1% NH₃ eluent). Only two products were detected, namely, 12 and 13 (R*t* 0.50 and 0.44, respectively). Starting from either 12 or 13, the ratio found was 60:40 12:13. Equilibrium was attained after 24 hr, and further heating had little effect on the isomer ratio.

When 12 was boiled with MeONa in MeOH or EtONa in EtOH for prolonged periods of time the starting sulfone phthalimide was recovered quantitatively.

Attempted Equilibration of the *r*-1,*c*-3,*c*-4 Nitrile Sulfide (14).—The nitrile (14, 0.14 g) in absolute methanol (10 ml) was treated with NaOMe (54 mg) and the solution was boiled under reflux for 3 days and kept at room temperature for 10 days. Work-up followed by glc analysis indicated only the presence of starting material.

The nitrile (0.14 g), NaOMe (54 mg), and thiophenol (5 drops) in dimethylformamide (5 ml) were heated in a sealed tube at 110° for 15 days. Glc analysis showed that starting material was unchanged.

Addition of Hydrogen Chloride to 4-*tert*-Butyl-1-cyanocyclohexene.—4-*tert*-Butyl-1-cyanocyclohexene (2 g) was dissolved in dry ether (10 ml) and anhydrous HCl was bubbled through for 2 hr. The solution was kept at room temperature overnight, the solvent evaporated, and the residue dissolved in petroleum ether (bp 30–60°). *r*-1-*tert*-**Butyl**-*t*-3-**chloro**-*t*-4-**cyanocyclohexane** (0.69 g, 37%), mp 50–52°, separated: ir (KBr) 2970, 2900, 2870, 2230 (C≡N), 685 cm⁻¹ (CCl); nmr (CCl₄) δ 4.60 (br s, 1 H, C₃ H), 2.85 (d of t, *J*ₐₐ = 7.5, *J*ₐₑ = 2.5 Hz, C₄ H), 0.82 (s, 9 H, *tert*-butyl).

Anal. Calcd for C₁₁H₁₈ClN: C, 66.15; H, 9.08. Found: C, 66.20; H, 9.28.

Reaction of Chloro Nitrile 22 with Thiophenoxide Ion.—Thiophenol (1.10 ml) and the chloro nitrile (1 g) were added to a solution of sodium (0.23 g) in ethanol (20 ml), and the solution was then stirred at room temperature for 24 hr. Acidification with glacial acetic acid was followed by removal of thiophenol, extraction of the product, and glc analysis on a 20% SE-30 on Chromosorb W (60–100 mesh) 6 ft × ³/₁₆ in. column at 245°. 4-*t*-Butyl-1-cyanocyclohexene was detected together with traces of 2 and 3. Column chromatography on silica gel (50 g) and elution with benzene–petroleum ether (1:4 v/v) gave the olefin (0.30 g, 60%) and diphenyl disulfide (0.45 g).

Similar results were obtained when aqueous ethanol or DMSO were used as the solvents.

Attempted Hydrolysis of 3.—Thiophenoxy nitrile 3 (5 g) was boiled under reflux with 6 N HCl (50 ml) for 48 hr and for 6 days, but it was recovered unchanged in each case.

Attempted Deamination of *r*-1-*tert*-Butyl-*t*-3-phenylsulfonylcyclohexane-*t*-4-carboxylic Acid Amide (4).—Sodium nitrite (5 g) was added in small portions to a cold (0°) solution of the amide (3 g) in glacial acetic acid (50 ml). The mixture was allowed to come to room temperature, the acid was evaporated on a film evaporator to give an oil which was poured into water and extracted with ether, and the ether layer was washed with NaHCO₃ solution. The ether was dried (MgSO₄) and evaporated to yield the starting amide, mp 170–173°.

When the amide was heated with amyl nitrite only a dark tar could be isolated.

Attempted Addition of Hydrogen Bromide to 1.—The olefin (0.815 g) in glacial acetic acid (10 ml) was treated with 47% HBr (3 ml) and the solution stirred at room temperature overnight. It was poured into water (25 ml), basified, and extracted with ether (3 × 25 ml). The dried (MgSO₄) ether extracts were evaporated to give 4-*tert*-**butylcyclohexene**-1-**carboxamide** (0.5 g, 55%): mp 178–179°; ir (KBr) 3490, 3350, 3310, 1685, 1650 cm⁻¹; nmr (CDCl₃) δ 6.71 (br s, 1 H, vinyl H), 6.10 (br s, 2 H, CONH₂), 0.88 (s, 9 H, *tert*-butyl).

Anal. Calcd for C₁₁H₁₉NO: C, 72.88; H, 10.56. Found: C, 73.08; H, 10.70.

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3-phenylsulfonyl cyclohexane, 35925-50-9; 4-*tert*-butyl-cyclohexene-1-carboxamide, 35906-02-6.

The Direct Acylation of Pyridine 1-Oxides

R. A. ABRAMOVITCH,* R. T. COUTTS, AND ELIZABETH M. SMITH

*Department of Chemistry, University of Alabama, University, Alabama 35486,
and College of Pharmacy, University of Saskatchewan, Saskatoon, Saskatchewan, Canada*

The reaction of pyridine 1-oxides with BuLi at low temperature in nonprotic solvents gives the 2-lithiopyridine 1-oxides, which react with carbon dioxide to give acids and with esters to give ketones. Some interesting by-products are obtained when N,N-dimethylacetamide and benzonitrile are used as the electrophiles.

Though the direct introduction of an acyl group into the pyridine nucleus is possible *via* the Emmert reaction (a nucleophilic attack at the α positions[1]), the direct electrophilic acylation of pyridine derivatives has not been feasible until recently, since these π-deficient rings do not undergo the Friedel–Crafts reaction. In an earlier paper, we reported the base-catalyzed deprotonation of pyridine 1-oxides in nonprotic solvents and the trapping of the carbanion so formed with aldehydes and ketones to give 2- and 2,6-dialkylated pyridine 1-oxides.[2] We now report the reaction of these 1-oxido-2-pyridyllithium derivatives with carbon dioxide, esters, amides, and nitriles to give acids and ketones.[3]

The 2-pyridyl 1-oxide anions were generated by the addition of *n*-butyllithium to a solution of the *N*-oxide in ether or tetrahydrofuran at −65°, and trapped by the addition of the electrophile. The results of the carboxylation of the anions are summarized in Table I.

the nitro compound, followed by treatment with acetyl chloride. As before,[2] a 3-methyl substituent directs deprotonation preferentially para to itself. Only one example of 2,6 dilithiation was observed here, and that in the case of 4-picoline 1-oxide. Methyl groups at C_3 or C_4 are not affected. On the other hand, as observed previously in the alkylation reactions, a 2-methyl substituent does undergo some deprotonation as well. Thus, when 2-picoline 1-oxide (4) was lithiated and then treated with CO_2, both 6-methyl-2-picoline 1-oxide (5) and 2-picoline-6,α-dicarboxylic acid 1-oxide (6) were obtained.
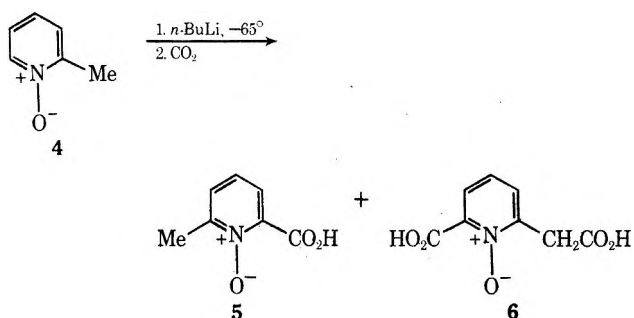
For possible comparison with **5** an attempt was made to synthesize authentic 2-pyridylacetic acid 1-oxide from **4** *via* the ethyl pyruvate as reported by Adams and Miyano[4] or by oxidation of ethyl 2-pyridylacetate with 30% H_2O_2 in glacial acetic acid. In both cases, picolinic acid 1-oxide was the final product obtained instead of the desired acetate.
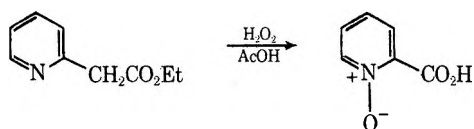
6-(1-Hydroxycyclohexyl)-3,4-dimethylpyridine 1-oxide (7) could only be metalated and carbonated in very low yield to give 8, the main product formed apparently being that of addition of butyllithium to the azomethine linkage (9).

Various carbonyl compounds were used to effect the acylation of the 2-lithio 1-oxides, and esters were found to give the best results, though yields of ketones were generally low. Reaction of 3,4-lutidine 1-oxide with *n*-butyllithium followed by ethyl acetate and work-

TABLE I

CARBOXYLATION OF 1-OXIDO-2-PYRIDYLLITHIUM
DERIVATIVES (1)

1	Product (%)	Registry no.
R = Cl; R′ = H	2 (49.0)	35895-54-6
R = Me; R′ = H	3 (48.0)	35895-55-7
R = Cl; R′ = Me	2 (23.8)	17117-05-4
R = R′ = Me	2 (17.9)	35895-57-9

Authentic 2 (R = Cl; R′ = Me) was synthesized by nitration of 5-methylpicolinic acid 1-oxide to yield

(1) R. A. Abramovitch and A. R. Vinutha, *J. Chem. Soc. C*, 2104 (1969).

(2) R. A. Abramovitch, E. M. Smith, E. E. Knaus, and M. Saha, *J. Org. Chem.*, **37**, 1690 (1972).

(3) Preliminary communication: R. A. Abramovitch, M. Saha, E. M. Smith, and R. T. Coutts, *J. Amer. Chem. Soc.*, **89**, 1537 (1967).

(4) R. Adams and S. Miyano, *ibid.*, **76**, 3168 (1954).

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8

9
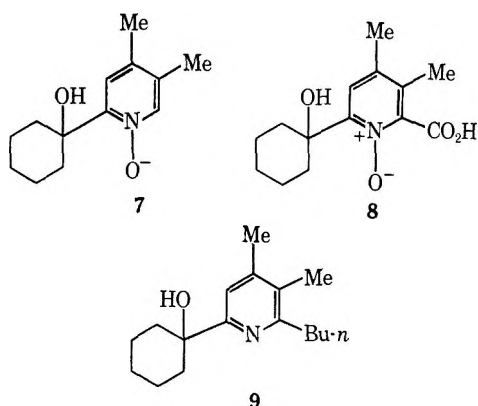
up of the reaction mixture by vacuum distillation gave a respectable yield (65%) of 2-acetyl-4,5-dimethylpyridine 1-oxide (**10**). On the other hand, if a similar reaction mixture was resolved by chromatography, **10** (19.6%) and 2-acetyl-3,4-dimethylpyridine 1-oxide (**11**) (6.3%) were obtained. Reaction of lithio-4-ethoxypyridine 1-oxide with ethyl butyrate gave a

10

11

12
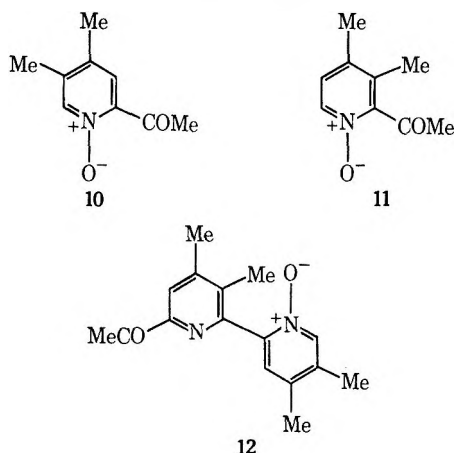
mixture of the 2-mono- and 2,6-dibutyryl derivatives. The use of *N*-acetylmorpholine as the carbonyl electrophile *in lieu* of ethyl acetate gave a much lower yield of **10** from **1** (R = R′ = Me). When *N,N*-dimethylacetamide was used none of the simple acylated product was obtained; instead the product formed was 6′-acetyl-3′,4,4′,5-tetramethyl-2,2′-dipyridyl 1-oxide (**12**). A similar result was obtained when the anion of **1** (R = Cl; R′ = Me) was treated with benzonitrile; the product isolated was 6′-benzoyl-4,4′-dichloro-3′,5-dimethyl-2,2′-dipyridyl 1-oxide (**13**). The structures of these dipyridyl mono-*N*-oxides were confirmed by high-resolution mass spectrometry and by nmr. **13** exhibited the isotopic cluster expected for 2Cl. Formation of these products involves initial reaction of the pyridyllithium derivative with the amide or nitrile function to give the expected intermediate (**14**) which undergoes subsequent *addition* of another pyridyllithium 1-oxide molecule at C₂ (addition ortho to the 3-methyl group is facile as expected[5a]) followed by elimination of LiOH (and hydrolysis on work-up) to give the product.

In a preliminary series of experiments to test the acylation procedure[5b] 2-pyridyllithium was treated with ethyl butyrate and with D-(−)-ethyl 2-methoxypropionate

(5) (a) R. A. Abramovitch and C. S. Giam, *Can. J. Chem.*, **42**, 1627 (1964); (b) R. H. Mizzoni in "Pyridine and Its Derivatives," Part 4, E. Klingsberg, Ed., Interscience, New York, N. Y., 1964, p 153.

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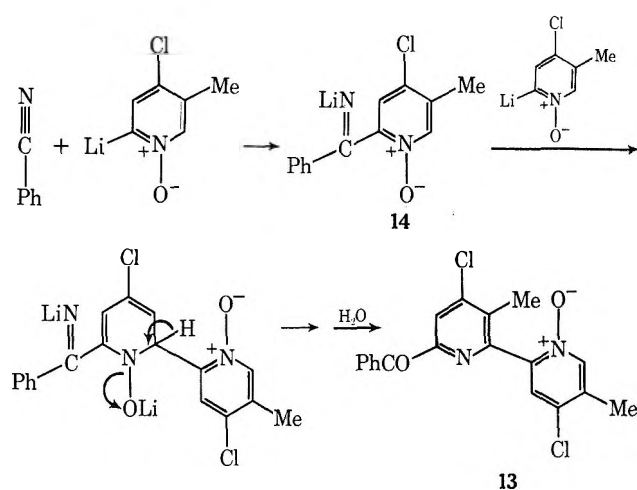
(kindly supplied by Professor G. Fodor), and gave 1-(2-pyridyl)-1-butanone (55%) and D-2-methoxy-1-(2-pyridyl)-1-propanone (56%), respectively.

Experimental Section

Melting points are uncorrected. In most cases only the main infrared bands are reported.

Reaction of Pyridyl 1-Oxide Carbanions with Carbonyl Compounds. General Procedure.—To a stirred solution (or suspension) of the substituted pyridine 1-oxide (0.007 mol) in anhydrous ether (or tetrahydrofuran) (40–60 ml) at −78° under a dry nitrogen atmosphere, *n*-butyllithium (0.96 g in hexane solution, 0.015 mol) was added dropwise. After the solution was stirred for 15 min, a solution of the carbonyl compound (0.015 mol) in ether (or tetrahydrofuran) (10 ml) was added dropwise to give a dark red to brown solution. The reaction mixture was stirred for 1–3 hr at −78°, and then warmed to room temperature. It was decomposed with water (10 ml) and the excess solvent was evaporated *in vacuo*. The products were isolated from the aqueous solution as described in individual cases.

Reaction of 4-Chloro-2-pyridyl 1-Oxide Carbanion with Carbon Dioxide.—*n*-Butyllithium (1.92 g in hexane, 0.03 mol) was added to a suspension of 4-chloropyridine 1-oxide (1.899 g, 0.014 mol) in anhydrous ether (50 ml) and the mixture was treated with gaseous carbon dioxide at −65° for 3 hr. The aqueous solution was carefully acidified with dilute hydrochloric acid to pH 2–3 to give a tan precipitate. The acidic solution was extracted with chloroform (4 × 75 ml) and the dried (MgSO₄) chloroform solution was evaporated *in vacuo* to give a brown oil. Trituration of the oil with acetone gave **4-chloropyridine-2-carboxylic acid 1-oxide** (1.25 g, 49.0%) (from acetone): mp 136° (lit.[6] mp 144°); ir (KBr) 1710 cm⁻¹ (s); nmr (DMSO-d₆) τ 1.70–2.20 (m, 2, C₃H, C₅H), 1.37 (d, 1, C₆H).

Anal. Calcd for C₆H₄ClNO₃: C, 41.52; H, 2.32; N, 8.07. Found: C, 41.35; H, 2.23; N, 7.73.

Reaction of 4-Methyl-2-pyridyl 1-Oxide Carbanion with Carbon Dioxide.—4-Methylpyridine 1-oxide (1.50 g, 0.0138 mol) in anhydrous tetrahydrofuran (60 ml) was treated with *n*-butyllithium (1.92 g in hexane, 0.03 mol) as usual, and then with gaseous carbon dioxide at −65° for 3 hr. The aqueous layer was carefully acidified to pH 2–3 with dilute HCl, the solution was extracted with CHCl₃ (4 × 75 ml), and the dried (MgSO₄) extract was evaporated *in vacuo* to give a brown oil which, on tritration with acetone, gave **4-methylpyridine-2,6-dicarboxylic acid 1-oxide** (1.30 g, 48.0%): mp 160° (from acetone); ir (KBr) 3080 (m), 1730 (s), 1485 (s), 1380 (m), 1230 (m), 1145 (w), 910 (m), 795 (m), 770 (m), and 600 cm⁻¹ (m); nmr (DMSO-d₆) τ 7.45 (s, 3, ArCH₃), 1.83 (s, 2, C₃H, C₅H), −1.17 (s, 2, OH, disappears on addition of D₂O).

Anal. Calcd for C₈H₇NO₅: C, 48.74; H, 3.58; N, 7.15. Found: C, 48.73; H, 3.71; N, 7.60.

4-Chloro-5-methylpyridine-2-carboxylic Acid 1-Oxide.—4-Chloro-3-methylpyridine 1-oxide (2.04 g, 0.014 mol) in anhydrous ether (50 ml) was treated with *n*-butyllithium (1.92 g in hexane,

(6) E. Profft and W. Steinke, *J. Prakt. Chem.*, **13**, 85 (1961); *Chem. Abstr.*, **56**, 10091a (1962).

0.03 mol) at −65° and then with gaseous carbon dioxide for 3 hr. Acidification of the aqueous solution to pH 2–3 with dilute HCl and extraction of the aqueous solution with CHCl₃ (4 × 75 ml) followed by evaporation of the dried (MgSO₄) chloroform solution gave a brown oil which, on tritration with acetone, gave the 2-carboxylic acid 1-oxide (0.56 g, 23.8%): mp 160° (from acetone); ir (KBr) 1700 (s), 1660 cm⁻¹ (s); nmr (CDCl₃) τ 7.60 (s, 3, ArCH₃), 1.83 (s, 1, C₃H), 1.17 (s, 1,C₆H).

Anal. Calcd for C₇H₆ClNO₃: C, 44.82; H, 3.22; N, 7.74. Found: C, 44.77; H, 3.31; N, 7.66.

5-Methylpyridine-2-Carboxylic Acid 1-Oxide.—5-Methyl-2-pyridylmethanol (5.0 g) (prepared from 2,5-dimethylpyridine 1-oxide and acetic anhydride[7]) was dissolved in concentrated nitric acid (30 ml) and fuming nitric acid (6 ml) and kept at room temperature for 72 hr. The reaction mixture was diluted with water, and the solution was made basic with solid sodium carbonate and then acidified to pH 4 with dilute hydrochloric acid. It was continuously extracted with CHCl₃ for 48 hr. Evaporation of the CHCl₃ solution gave 5-methylpyridine-2-carboxylic acid (3.41 g, 61.3%), mp 165° (from acetone) (lit.[8] mp 167–168°).

The acid (6.0 g) was oxidized in glacial acetic acid (150 ml) and 30% hydrogen peroxide (60 ml) at 80–90° for 18 hr to give 5-methylpyridine-2-carboxylic acid 1-oxide (5.20 g, 77.6%), mp 162–163° (lit.[9] mp 162–163°).

5-Methyl-4-nitropyridine-2-carboxylic Acid 1-Oxide.—Concentrated nitric acid (5 ml) was slowly added to a solution of 5-methylpyridine-2-carboxylic acid 1-oxide (1.0 g) in concentrated sulfuric acid (5 ml) at 10–15°. The reaction mixture was heated under reflux at 90–110° for 4 hr, and was then poured into ice water (20 ml). The solution was made basic with Na₂CO₃ and then acidified to pH 4–5 with dilute HCl to give 5-methyl-4-nitropyridine-2-carboxylic acid 1-oxide (0.35 g, 27.1%): mp 145° (from acetone); ir (KBr) 3140 (w), 3050 (m), 1703 (s), 1610 (s), 1525 (s), 1445 (s), 1350 (s), 1288 (s), 1276 (s), 1167 (m), 1110 (w), 1040 (m), 1010 (m), 956 (m), 878 (m), 862 (w), 788 (s), 758 (w), 696 (m), 660 (s), and 635 cm⁻¹ (m); nmr (DMSO-d₆) τ 7.07 (s, 3, ArCH₃), 1.06 (s, 1, C₃H), 0.72 (s, 1, C₆H); mass spectrum (no M⁺ at *m/e* 198) *m/e* (rel intensity) 154 (12.2) (M⁺ − CO₂), 138 (6.4), 108 (2.9), 92 (8.1), 65 (16.8), 39 (20.9).

Anal. Calcd for C₇H₆N₂O₅: C, 42.46; H, 3.26. Found: C, 42.75; H, 3.56.

Unreacted 5-methylpyridine-2-carboxylic acid 1-oxide (0.41 g) was isolated from the acidic solution.

Authentic 4-Chloro-5-methylpyridine-2-carboxylic Acid 1-Oxide.—4-Nitro-5-methylpyridine-2-carboxylic acid 1-oxide (0.100 g) and acetyl chloride (3 ml) were warmed briefly to give a yellow solid which was dissolved in chloroform (5 ml). The chloroform solution was filtered and evaporated *in vacuo* to give 4-chloro-5-methylpyridine-2-carboxylic acid 1-oxide (0.023 g, 26.4%), mp 155°, identical with the sample obtained from the pyridyl oxide carbanion.

4,5-Dimethylpyridine-2-carboxylic Acid 1-Oxide.—This was prepared from 3,4-dimethylpyridine 1-oxide (0.86 g, 0.007 mol) in anhydrous tetrahydrofuran (30 ml) and *n*-butyllithium (0.96 g, 0.015 mol), followed by gaseous carbon dioxide at −78° for 3 hr to give a brown oil. Trituration of the oil with acetone gave 4,5-dimethylpyridine-2-carboxylic acid 1-oxide (0.20 g, 17.9%): mp 180–181° (recrystallized from acetone); ir (KBr) 1700 (s), 1630 cm⁻¹ (s); nmr (DMSO-d₆) τ 7.85 (s, 6, 2ArCH₃), 2.07 (s, 1, C₃H), 1.58 (s, 1, C₆H).

Anal. Calcd for C₈H₉NO₃: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.81; H, 5.66; N, 8.38.

Reaction of 2-Methylpyridyl 1-Oxide Carbanions with Carbon Dioxide.—Using the method outlined previously, 2-methylpyridine 1-oxide (1.50 g, 0.014 mol) was treated with *n*-butyllithium (1.92 g in hexane, 0.03 mol) and the resulting solution was treated with gaseous carbon dioxide at −78° for 3 hr. The aqueous solution was acidified to pH 2–3 with dilute HCl. The acidic solution was extracted with CHCl₃ (4 × 75 ml) and the dried (MgSO₄) extract was evaporated *in vacuo* to give an orange oil which solidified to give 6-methylpyridine-2-carboxylic acid 1-oxide (0.28 g, 13.5%): mp 181–182° (lit.[10] mp 177°) (recrystallized from acetone); ir (KBr) 1675 cm⁻¹ (s); nmr (C₅D₅N) τ 7.64 (s, 3, ArCH₃), 2.82 (m, 3, C₃H, C₄H, C₅H).

Anal. Calcd for C₇H₇NO₃: C, 54.90; H, 4.60; N, 9.10. Found: C, 55.33; H, 4.66; N, 9.21.

After the aqueous solution was allowed to stand for 12 hr, 2-methylpyridine 1-oxide α,6-dicarboxylic acid (0.27 g, 10.1%), mp 177° (from acetone), separated: ir (KBr) 3200–3800 (m), 1705 (s), 1600 (m), 1495 (w), 1395 (s), 1310 (m), 1250 (m), 1195 (m), 1155 (m), 1070 (m), 915 (m), 835 (w), 810 (w), 755 (m), and 600 cm⁻¹ (m); nmr (DMSO-d₆) τ 5.92 (s, 2, ArCH₂CO₂H), 1.50–2.30 (m, 3, C₃H, C₄H, C₅H).

Anal. Calcd for C₈H₇NO₅: C, 48.74; H, 3.58. Found: C, 48.79; H, 3.76.

Oxidation of Ethyl 2-Pyridylacetate.—Ethyl 2-pyridylacetate (0.9 g) dissolved in glacial acetic acid (10 ml) and 30% hydrogen peroxide (1 ml) was heated under reflux at 70° for 10 hr. The colorless solution was basified with sodium carbonate, and the solution was acidified to pH 2 with 10% HCl and then extracted with CHCl₃, evaporation of which *in vacuo* gave pyridine-2-carboxylic acid 1-oxide (0.16 g, 21.4%), mp 160° (lit.[6] mp 162°).

6-(1-Hydroxycyclohexyl)-3,4-dimethylpyridine-2-carboxylic Acid 1-Oxide.—Prepared from 6-(1-hydroxycyclohexyl)-3,4-dimethylpyridine 1-oxide, butyllithium, and CO₂, the acid (7%) had mp 97°.

Anal. Calcd for C₁₄H₁₉NO₄: C, 63.38; H, 7.22. Found: C, 63.94; H, 7.39.

The main product appeared to be 2-*n*-butyl-6-(1-hydroxycyclohexyl)-3,4-dimethylpyridine: ir (KBr) 3600–3000 (m), 2930 (s), 2860 (m), 1600 (m), 1450 (m), 1400 (w), 1260 (m), 1168 (w), 1039 (m), 968 (m), 800 cm⁻¹ (w); mass spectrum *m/e* 261 (M⁺).

Reaction of 3,4-Dimethylpyridyl 1-Oxide Carbanion with Ethyl Acetate. A.—3,4-Dimethylpyridine 1-oxide (0.86 g, 0.007 mol) in tetrahydrofuran (60 ml) was treated with *n*-butyllithium [0.96 g in hexane (6 ml)] and the mixture was treated with ethyl acetate (1.23 g, 0.015 mol) for 1 hr. The aqueous solution was extracted with CHCl₃ (3 × 75 ml), and the dried (K₂CO₃) CHCl₃ extract was evaporated *in vacuo* to give a yellow oil (1.29 g), distillation of which at 108° (0.01 mm) gave a white solid (0.795 g) which was washed with ether to give 2-acetyl-4,5-dimethylpyridine 1-oxide (0.75 g, 65.1%): mp 61–62°; ir (KBr) 1685 (s), 1250 cm⁻¹ (s); nmr (CDCl₃) τ 7.80 (s, 6, 2ArCH₃), 7.28 (s, 3, COCH₃), 2.65 (s, 1, C₃H), 2.10 (s, 1, C₆H); mass spectrum *m/e* 165 (M⁺), 149 (M⁺ − O).

Anal. Calcd for C₉H₁₁NO₂: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.50; H, 6.92; N, 8.80.

B.—3,4-Dimethylpyridine 1-oxide (0.96 g, 0.0078 mol) dissolved in anhydrous tetrahydrofuran (60 ml) was treated with *n*-butyllithium (1.03 g in hexane, 0.016 mol) and the mixture was treated with ethyl acetate (1.50 g, 0.017 mol) at −78° for 1 hr. The aqueous solution was extracted with CHCl₃ (3 × 75 ml) and the dried (K₂CO₃) CHCl₃ extract was evaporated to give a yellow-orange oil (1.531 g) which was chromatographed on a silica gel column (18 g, 1 × 8 in.). Elution with benzene–ether (3:1 v/v, 300 ml) gave a noncrystalline material which was not further investigated. Elution with benzene–ether (1:1 v/v, 300 ml) gave 2-acetyl-4,5-dimethylpyridine 1-oxide (0.25 g, 19.6%), mp 61–62°. Elution with benzene–ether (1:3 v/v, 300 ml) gave 2-acetyl-3,4-dimethylpyridine 1-oxide (0.81 g, 6.3%): mp 109–110° (recrystallized from acetone–light petroleum); ir (KBr) 1700 (s), 1269 (s), 1243 cm⁻¹ (s); nmr (CDCl₃) τ 7.70 (m, 6, 2ArCH₃), 7.40 (s, 3, COCH₃), 2.94 (d, 1, C₅H), 2.10 (d, 1, C₆H); mass spectrum *m/e* 165 (M⁺), 149 (M⁺ − O).

Anal. Calcd for C₉H₁₁NO₂: C, 65.44; H, 6.71. Found: C, 65.31; H, 6.82.

Elution with ether–absolute ethanol (19:1 v/v, 200 ml) gave a yellow oil (0.06 g) which was not further investigated. Elution with ether–absolute ethanol (3:1 v/v, 300 ml) gave 3,4-dimethylpyridine 1-oxide (0.095 g).

Reaction of 3,4-Dimethylpyridyl 1-Oxide Carbanion with *N*,*N*-Dimethylacetamide.—3,4-Dimethylpyridine 1-oxide (0.86 g, 0.007 mol) in tetrahydrofuran (60 ml) was treated with *n*-butyllithium (0.96 g in hexane, 0.015 mol) and then with *N*,*N*-dimethylacetamide (1.22 g, 0.0145 mol) at −65° for 1 hr. The aqueous solution was extracted with CHCl₃ (3 × 75 ml) and the dried (K₂CO₃) extract was evaporated *in vacuo* to give a yellow oil (0.90 g) which was chromatographed on alumina (45 g, 2.5 × 18 cm). Elution with benzene–ether (1:3 v/v, 200 ml) and ether (100 ml) gave 6'-acetyl-3',4,4',5-tetramethyl-2,2'-dipyridyl 1-oxide (0.12 g, 12.9%): mp 217°; ir (KBr) 3070 (w), 3000–2920 (w), 1795 (s), 1580 (w), 1550 (w), 1505 (w), 1485 (w), 1465 (w), 1345 (w), 1315 (w), 1260 (m), 1230 (w), 1190 (w), 1160 (m),

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1095 (w), 1020 (w), 890 (w), 865 (w), 785 (w), 755 (w), and 740 cm^{-1} (w); nmr (CDCl$_3$) τ 7.55–7.80 (m, 12, 4ArCH$_3$), 7.36 (s, 3, ArCOCH$_3$), 2.80 (s, 1, C$_5$H), 2.13 (s, 1, C$_3$H), 1.88 (s, 1, C$_6$H); mass spectrum m/e (rel intensity) 270 (M$^+$) (35), 254 (M$^+$ − O) (33), 253 (M$^+$ − OH) (100).

Anal. Calcd for C$_{16}$H$_{18}$N$_2$O$_2$: C, 71.09; H, 6.71; N, 10.36. Found: C, 70.75; H, 6.65; N, 10.62.

Reaction of 3,4-Dimethylpyridyl 1-Oxide Carbanion with *N*-Acetylmorpholine.—3,4-Dimethylpyridine 1-oxide (0.86 g, 0.03 mol) in anhydrous tetrahydrofuran (100 ml) was treated with *n*-butyllithium (0.96 g in hexane, 0.015 mol), and the mixture was then treated with *N*-acetylmorpholine (1.85 g, 0.0145 mol) at −78° for 1 hr. The reaction mixture was decomposed with a saturated solution of ammonium chloride (75 ml). The organic layer was separated and evaporated to give an oil (1.50 g). A white solid was obtained from this oil and identified as 2-acetyl-4,5-dimethylpyridine 1-oxide (0.04 g, 2.8%).

Reaction of 4-Ethoxypyridine 1-Oxide Carbanion and Ethyl Butyrate.—4-Ethoxypyridine 1-oxide (1.00 g, 0.077 mol) suspended in tetrahydrofuran (40 ml) was treated with *n*-butyllithium (0.96 g in hexane, 0.015 mol) and then with ethyl butyrate (1.62 g, 0.015 mol), as outlined in the general procedure, to give an orange-red oil (1.76 g) which was column chromatographed on silica gel (15 g, 2.5 × 15 cm). Elution with light petroleum (bp 30–60°)–benzene (3:1 v/v, 300 ml) gave a noncrystalline material (0.023 g) which was not further investigated. Elution with light petroleum–benzene (1:3 v/v, 300 ml), benzene (300 ml), and benzene–ether (3:1 v/v, 300 ml) gave an oily solid (0.749 g) which, after recrystallization from light petroleum, gave **2,6-di-*n*-butyryl-4-ethoxypyridine 1-oxide** (0.33 g, 16.5%): mp 64–65°; ir (KBr), 1680 cm^{-1} (s); nmr (CDCl$_3$) τ 9.04 (t, 6, 2-CH$_2$CH$_2$CH$_3$), 8.60 (t, 3, –OCH$_2$CH$_3$), 8.15–8.40 (m, 4, 2CH$_2$-CH$_2$CH$_3$), 6.88 (t, 4, 2 –COCH$_2$), 5.94 (q, 2, –CH$_2$CH$_3$), 2.94 (s, 2, C$_3$H, C$_5$H).

Anal. Calcd for C$_{15}$H$_{21}$NO$_4$: C, 64.50; H, 7.58. Found: C, 64.59; H, 7.56.

Benzene–ether (1:3 v/v, 300 ml) and ether (300 ml) were used as eluents to give a noncrystalline material (0.054 g) which was not investigated further. Elution with ether–absolute ethanol (3:1 v/v, 300 ml) gave **2-butyryl-4-ethoxypyridine 1-oxide** (0.28 g, 18.5%) as an oil which decomposed on attempted purification: ir (film) 1710 (s), 1640 (s), 1460 (s), 1240 cm^{-1} (s); nmr (CDCl$_3$) τ 9.03 (t, 3, –CH$_2$CH$_2$CH$_3$), 8.58 (t, 3, –OCH$_2$-CH$_3$), 8.16–8.40 (q, 2, –CH$_2$CH$_2$CH$_3$), 6.82 (t, 2, –COCH$_2$-), 5.80–6.08 (q, 2, –OCH$_2$CH$_3$), 3.08–3.24 (q, 1, C$_5$H), 3.96 (d, 1, C$_3$H), 1.94 (d, 1, C$_6$H).

Reaction of 4-Chloro-3-methylpyridyl 1-Oxide Carbanion with Benzonitrile.—4-Chloro-3-methylpyridine 1-oxide (1.00 g, 0.007 mol) suspended in anhydrous ether (20 ml) was treated with *n*-butyllithium (0.96 g in hexane, 0.015 mol) and the mixture was treated with benzonitrile (1.00 g, 0.01 mol) at −78° for 3 hr.

The aqueous solution was extracted with chloroform (3 × 75 ml). Evaporation of the dried (K$_2$CO$_3$) chloroform solution gave a brown oil (0.75 g) which was chromatographed on an alumina column (40 g, 2.5 × 15 cm). Elution with benzene–absolute ethanol (19:1 v/v, 200 ml) gave **6′-benzoyl-4,4′-dichloro-3′,5-dimethyl-2,2′-dipyridyl 1-oxide** (0.15 g, 11.5%): mp 235° (recrystallized from acetone); ir (KBr) 3020 (m), 1656 (s), 1594 (m), 1547 (s), 1490 (m), 1445 (m), 1390 (m), 1381 (m), 1350 (w), 1310 (s), 1275 (w), 1255 (m), 1225 (m), 1178 (s), 1140 (m), 1080 (w), 1005 (m), 972 (m), 922 (m), 895 (m), 870 (w), 845 (m), 810 (m), 796 (m), 770 (m), 740 (s), 710 (s), 700 (s), and 690 cm^{-1} (s); nmr (C$_5$D$_5$N) τ 7.94 (s, 3, ArCH$_3$), 7.64 (s, 3, ArCH$_3$), 2.88 (s, 2, C$_5$′H, C$_3$H), 2.42–2.76 (m, 3, 3ArH), 1.85 (m, 3, C$_6$H, ArH).

Anal. Calcd for C$_{19}$H$_{14}$Cl$_2$N$_2$O$_2$: C, 61.14; H, 3.78; N, 7.51; mol wt (2 ^{35}Cl), 372.0432. Found: C, 61.03; H, 3.94; N, 7.63; mol wt, 372.0423 (mass spectrum).

D-2-Methoxy-1-(2-pyridyl)-1-propanone.—2-Bromopyridine (1.10 g, 0.007 mol) in anhydrous ether (40 ml) at −65° was treated with *n*-butyllithium (0.48 g in hexane) and then with a solution of D-(−)-ethyl 2-methoxypropionate (1.848 g, 0.014 mol) in anhydrous ether (10 ml) and worked up as usual to give an oil which, on distillation at 66° (0.05 mm), gave D-2-methoxy-1-(2-pyridyl)-1-propanone (0.64 g, 55.9%): mp 40–45°; ir (film) 1704 cm^{-1} (s); nmr (CDCl$_3$) τ 8.52 (d, J = 7 Hz, 3, CHCH$_3$), 6.57 (s, 3, –OCH$_3$), 4.62 (q, 1, CH), 1.77–2.60 (m, 3, C$_3$H, C$_4$H, C$_5$H), 1.27 (d, J = 5 Hz, 1, C$_6$H); mass spectrum m/e 165 (M$^+$).

Anal. Calcd for C$_9$H$_{11}$NO$_2$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.24; H, 6.70; N, 8.56.

Studies on the Reaction of Heterocyclic Compounds. VII.[1]
Oxidative Cyanation of Heteroaromatic *N*-Oxides[2]

YOSHIRO KOBAYASHI,* ITSUMARO KUMADAKI, AND HARUO SATO

Tokyo College of Pharmacy, Shinjuku-ku, Tokyo, Japan

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Most heteroaromatic *N*-oxides (*e.g.*, quinoline 1-oxide, isoquinoline 2-oxide, phenanthridine 5-oxide, acridine 9-oxide, 1,6-naphthyridine *N*-oxides, quinoxaline *N*-oxides, 1,6-phenanthroline *N*-oxides, and their substituted derivatives) were cyanated in their α position with potassium cyanide and potassium ferricyanide in protic solvents, especially in water. The merit of this reaction is that α-cyano heteroaromatic *N*-oxides are obtained from the *N*-oxides in one step. On the other hand, monocyclic heteroaromatic *N*-oxides (*e.g.*, pyridine 1-oxide, pyrazine 1-oxide, pyridazine 1-oxide, and pyrimidine 1-oxide) and α-substituted quinoline *N*-oxides did not react even at 130°. The reactivity of *N*-oxide for this reaction was estimated according to the reactivity index, "superdelocalizability," which was calculated from simple LCAO-MO.

Heteroaromatic *N*-oxides are very useful intermediates in the field of heterocyclic chemistry, since they are much more reactive to electrophilic and nucleophilic reagents than the free bases from which they are derived.[3] For example, pyridine 1-oxide is nitrated much more readily than pyridine, and quinoline 1-oxide is attacked by cyanide ion after quaternization with benzoyl chloride to give 2-cyanoquinoline. In other words, the *N*-oxide group increases or decreases electron density of carbon atoms in α and γ positions to it as shown in Scheme I.

SCHEME I
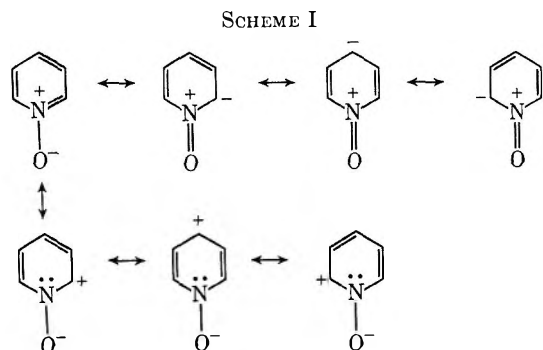
However, as in the case of quinoline 1-oxide, most nucleophilic reactions are followed by elimination of the *N*-oxide group, except in a few cases. This report will show new examples of nucleophilic reactions of heteroaromatic *N*-oxides without elimination of the *N*-oxide group, found in 1,6-naphthyridine *N*-oxides.[4]

As shown in our previous paper,[5] 1,6-naphthyridine 1,6-dioxide (1) reacted with aqueous potassium cyanide exothermally and decomposed to a tar, but treatment of this dioxide with methanolic potassium cyanide gave three compounds (3, 4, and 5) as shown in Scheme II.

This reaction seems to be initiated by the solvation at the *N*-oxide group and formation of an adduct, 2-cyano-1,2-dihydro-1,6-naphthyridine 1,6-dioxide (2). Therefore, we tried to oxidize this adduct and succeeded in obtaining α-cyano compound without elimination of

the *N*-oxide group. Further, we found that this reaction can be applied to other heterocyclic compounds.

Results

A solution of 1,6-naphthyridine 1,6-dioxide (1), dissolved in the aqueous solution of potassium cyanide and potassium ferricyanide at 0°, was stirred and the crystals that precipitated out were collected to afford 2,5-dicyano-1,6-naphthyridine 1,6-dioxide (6) in 17% yield. From the filtrate, 2-cyano- (7) and 5-cyano-1,6-naphthyridine 1,6-dioxide (8) were obtained in respective yields of 30 and 13%. In the same manner, 1,6-naphthyridine 1-oxide (9) treated at 20° afforded 2-cyano-1,6-naphthyridine 1-oxide (10) in a high yield of 57%. 1,6-Naphthyridine 6-oxide (11) gave 5-cyano-1,6-naphthyridine 6-oxide (12) by the same treatment at 25° in 26% yield (Scheme III).

The characteristic point of this cyanation was that the cyano group was introduced predominantly into the position α to the *N*-oxide group without elimination of the oxygen atom. This cyanation reaction gives α-cyanated heteroaromatic *N*-oxides in only one step from the parent *N*-oxides and may be called an "oxidative cyanation."

Application of this oxidative cyanation to many other heteroaromatic *N*-oxides was examined (Table I). Quinoline 1-oxide (13) and isoquinoline 2-oxide (14) underwent this oxidative cyanation at 75°, a much higher temperature than in the case of 1,6-naphthyridines, and afforded 2-cyanoquinoline 1-oxide (15) and 1-cyanoisoquinoline 2-oxide (16), respectively, both in 85% yield.

In contrast, pyridine 1-oxide (17) does not react even when the reaction temperature is raised to 130°. This reaction does not proceed with any diazine *N*-oxides [pyridazine 1-oxide (18), pyrazine 1-oxide (19), and pyrazine 1,4-dioxide (20)], but does so with diazanaphthalene *N*-oxides. As for other kinds of *N*-oxides, namely, benzoquinoline *N*-oxide, for example, acridine 9-oxide (21) and phenanthridine 5-oxide (22) gave 10-cyanoacridine 9-oxide (23) and 6-cyanophenanthridine 5-oxide (24) when treated at 70 and 50° in 35 and 58% yield, respectively, while benzo[*f*]quinoline 1-oxide (25) and benzo[*h*]quinoline 1-oxide (26) were recovered even when treated at 130°.

In these oxidative cyanation reactions, it is interesting that these *N*-oxides showed large difference in their reactivity. Acridine and phenanthridine *N*-oxides were more reactive than quinoline and isoquin-

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SCHEME II

SCHEME III
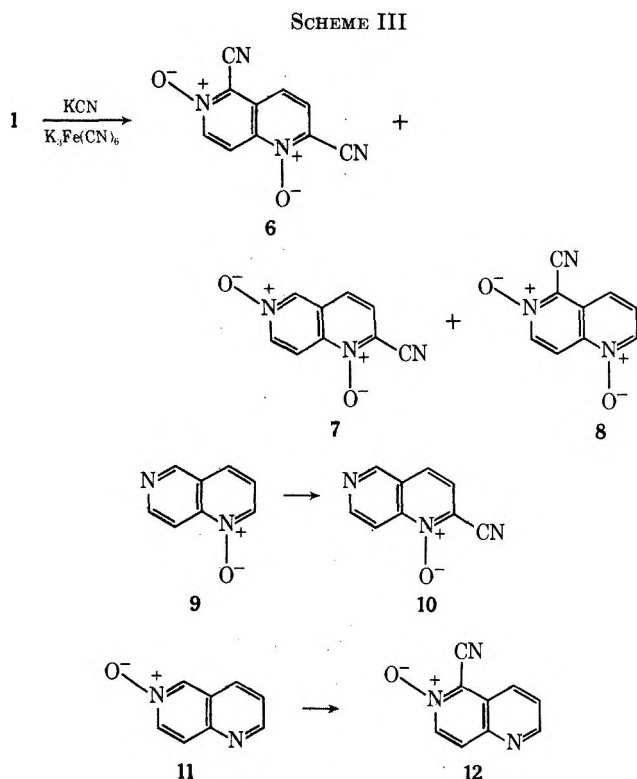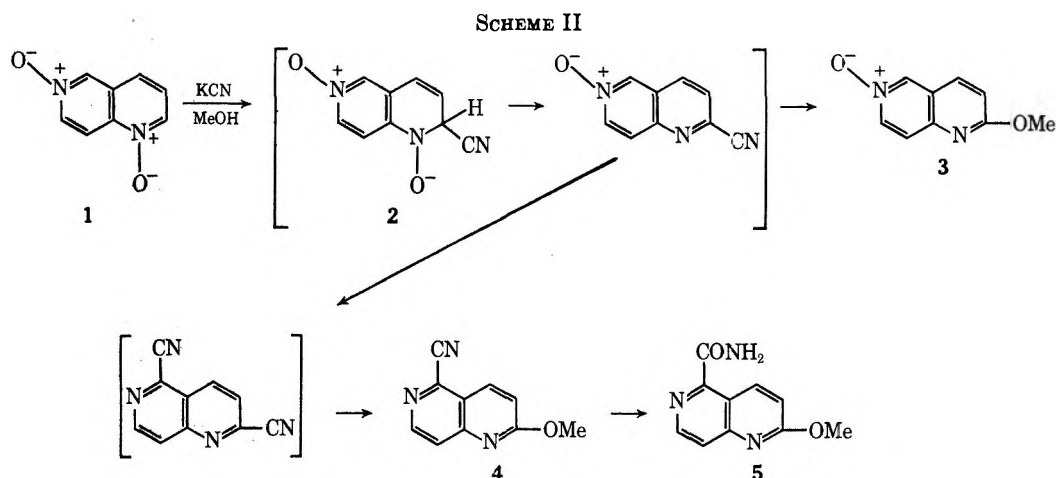
oline N-oxides, while pyridine 1-oxide and benzo[f]- and benzo[h]quinoline 1-oxides did not undergo this cyanation and the starting materials were recovered.

In this reaction mechanism, the rate-determining step was assumed to be the formation of a dihydro intermediate and, therefore, the reactivity of each N-oxide seemed to depend on the electrophilicity of the reaction site.

In order to elucidate the relationship between the reactivity of this oxidative cyanation and electrophilicity of N-oxides, the substituent effect was examined with a few derivatives of quinoline 1-oxides. Methoxyl was chosen as an electron-donating group and trifluoromethyl as an electron-attracting group. 3-(Trifluoromethyl)quinoline 1-oxide (**27**) and 4-(trifluoromethyl)-quinoline 1-oxide (**31**) gave their cyanated products (**28** and **32**) at a lower temperature than that in the case of quinoline 1-oxide; 4-methoxyquinoline 1-oxide (**29**) was treated at a higher temperature and gave 2-cyano compound (**30**) in poor yield. In this oxidative cyanation (trifluoromethyl)quinoline N-oxides were

more reactive than quinoline N-oxide. Therefore, the readiness of their oxidative cyanation depends on the electronic effect of the substituent, and the rate-determining step is the first step when cyanide ion attacks.

2-(Trifluoromethyl)qunioline 1-oxide (**33**) does not undergo this cyanation even at 130°. This experiment suggests that the reaction proceeds selectively at the α position and quinoline 1-oxide affords 2-cyanoquinoline 1-oxide exclusively. The only exception is acridine 9-oxide, which affords a γ-cyanated product. This formation of a γ-cyanated product depends on higher reactivity of the γ position in the acridine ring than that of quinoline 1-oxide. With 3-(trifluoromethyl)quinoline 1-oxide, the trifluoromethyl group accelerates the reactivity of the γ position and, therefore, a trace of 4-cyano-substituted product is obtained in addition to the 2-cyano derivative as the major product.

From the above experiment, it is certain that oxidative cyanation is specific to the α position of the N-oxide and that the success of the reaction depends on the electrophilicity of that position. Since the reaction takes place with potassium cyanide and potassium ferricyanide, the question of the solubility in water of the starting material becomes important; i.e., there are cases such as (trifluoromethyl)quinoline N-oxide where the α-cyano compound is not obtained in a good yield because of the low solubility in water, even though the reactivity of the α position is accelerated. In such a case mere raising of the reaction temperature would allow the hydroxide anion to attack the starting material or the cyanated compound, thereby preventing the selective attack of the cyanide ion from occurring; therefore, oxidative cyanation was attempted with diazanaphthalene N-oxides or diazaphenanthroline N-oxides, whose solubility in water is high and the electrophilicity of the α position is also high. As a result, 2-cyanoquinoxaline 1-oxide (**35**) was obtained from quinoxaline 1-oxide (**34**) and 2,3-dicyanoquinoxaline 1,4-dioxide (**37**) was obtained from quinoxaline 1,4-dioxide (**36**) at reaction temperatures below 0°.

However, in cases where the reactivity is as high as this, in accord with slight raising of the reaction temperature, the produced cyano compound is liable to be attacked by hydroxide anion and to decompose. Taking the above fact into consideration, this reaction was attempted with 1,6-phenanthroline 6-oxide[6]

(6) Y. Kobayashi, I. Kumadaki, and K. Morinaga, *Chem. Pharm. Bull.*, **17**, 1511 (1969).

TABLE I
REACTIONS OF HETEROAROMATIC N-OXIDES WITH $K_3Fe(CN)_6$ AND KCN[a]

Starting material	Reaction conditions Temp, °C	Solvent	Product	Yield, %	Mp,[b] °C	Ir (KBr), cm^{-1}	Nmr
1	0	H$_2$O	6	17.3	248 dec (M)	2240 (C≡N) 1320 (NO)	8.56 (s, 2, C$_7$ H, C$_8$ H) 8.27 (d, 1, J = 10 Hz, C$_4$ H) 7.85 (d, 1, J = 10 Hz, C$_3$ H)[d]
			7	30.2	260 dec (M)	2250 (C≡N) 1300 (NO)	9.08 (d, 1, J = 2.5 Hz, C$_5$ H) 8.33 (d, 1, J = 2.5 Hz, C$_7$ H, C$_8$ H) 8.03 (d, 1, J = 10 Hz, C$_4$ H) 7.74 (d, 1, J = 10 Hz, C$_3$ H)[d]
			8	13.5	257 dec (M)	2250 (C≡N) 1300 (NO)	8.68 (t, 1, J = 4 Hz, C$_4$ H) 8.58 (s, 2, C$_7$ H, C$_8$ H) 7.80 (d, 2, C$_2$ H, C$_3$ H)[d]
9	20	H$_2$O	10	57.7	235–236 dec (B)	2280 (C≡N) 1340 (NO)	9.40 (s, 1, C$_5$ H) 8.92 (d, 1, J = 7 Hz, C$_8$ H) 8.43 (d, 1, J = 7 Hz, C$_7$ H) 7.84 (d, 1, J = 9 Hz, C$_4$ H) 7.65 (d, 1, J = 9 Hz, C$_3$ H)[e]
11	25	H$_2$O	12	26.8	96.5 dec (B)	2290 (C≡N) 1320 (NO)	9.05 (d, 1, J = 5, 2.5 Hz, C$_2$ H) 8.57 (d, 1, J = 7.5 Hz, C$_7$ H) 8.27 (m, 2, C$_8$ H, C$_4$ H) 7.85 (dd, 1, J = 5 Hz, C$_2$ H)[e]
13	75	H$_2$O	15	85.0	171 (B)		
14	75	H$_2$O	16	85.0	207 (B)		
17	130	H$_2$O	c				
18	90	H$_2$O	c				
19	90	H$_2$O	c				
20	70	H$_2$O	c				
21	70	30% EtOH	23	35.4	225 dec (M)		
22	50	30% EtOH	24	57.5	216–217 (M)		
25	130	H$_2$O	c				
26	130	H$_2$O	c				
27	50	30% EtOH	28	53.3	212 (M)	2240 (C≡N) 1140–1190 (CF) 1340–1380 1260 (NO)	8.10–8.00 (m, 4, benzene ring) 8.80 (s, 1, C$_4$ H)[e]
29	90	H$_2$O	30	17.5	163 (M)	2280 (C≡N) 1220 (NO)	4.10 (s, 3, –OCH) 7.30 (s, 1, C$_3$ H) 8.80–7.50 (m, 4, benzene ring)[e]
31	35	20% EtOH	32	47.7	169 (M)	2260 (C≡N) 1350 (NO) 1240 (CF) 1130–1160	8.78 (m, 1, C$_3$ H) 8.20 (m, 1, C$_5$ H) 7.90–8.00 (m, 3, C$_6$ H, C$_7$ H, C$_8$ H)[e]
33	130	30% EtOH	c				
34	25	H$_2$O	35	30.0	135 (M)	2280 (C≡N) 1300 (NO)	8.87 (s, 1, C$_3$ H) 8.55 (dd, 1, C$_8$ H) 8.13 (dd, 1, J = 10, 2 Hz, C$_5$ H) 8.00–7.80 (m, 2, C$_6$ H, C$_7$ H)[e]
36	0	30% EtOH	37	15.3	228 dec (B)	2280 (C≡N) 1270 (NO)	10.58 (q, 2, C$_5$ H, C$_8$ H) 10.24 (q, 2, C$_6$ H, C$_7$ H)[d]
38	0	H$_2$O	39	82.5	218 (M)	2260 (C≡N) 1240 (NO)	9.10 (m, 2, C$_2$ H, C$_{10}$ H) 8.75 (m, 1, C$_7$ H) 8.30 (dd, 1, C$_4$ H) 7.80 (m, 2, C$_8$ H, C$_9$ H) 7.70 (dd, 1, C$_3$ H)[e]

[a] Satisfactory analyses ($\pm 0.35\%$ for C, H, N) were reported for **6, 7, 8, 10, 12, 35, 37,** and **39**: Ed. Exact mass spectral m/e values were reported for **28** and **32**. Compounds **15, 16, 23,** and **24** were identified with authentic samples by admixture and ir spectral comparison. [b] Recrystallization solvent: M, methanol; B, benzene. [c] Starting material was recovered. [d] Solvent (CD$_3$)$_2$SO. [e] Solvent CDCl$_3$.

(**38**), whose reactivity is fairly high and whose product is assumed to be stable; and 5-cyano 1,6-phenanthroline 6-oxide (**39**) was obtained in good yield as expected.

Discussion

The above experimental results show three characteristics of this cyanation. First, this cyanation does not proceed with either pyridine or diazine N-oxides. Second, many kinds of monoaza- or diazanaphthalene N-oxides reacted and afforded α-cyanated products predominantly and, in this case, an electron-donating group decreased the reactivity whereas an electron-attracting group increased it. Third, in the series of benzoquinoline oxides, some were more re-

TABLE II

SUPERDELOCALIZABILITY (Sr^N) VALUE OF
HETEROAROMATIC N-OXIDES

N-Oxide	Position	Sr^N	Exptl result
Pyridine 1-oxide (17)	2	1.518	
	4	1.435	
Pyridazine 1-oxide (18)	3	1.627	
	6	1.545	
Pyrazine 1-oxide (19)	2,6	1.617	
	3,5	1.504	
Pyrazine 1,4-dioxide (20)		3.746	
Quinoline 1-oxide (13)	2	1.956	+
	4	2.020	
Isoquinoline 2-oxide (14)	1	2.199	+
	4	1.894	
Phenanthridine 5-oxide (22)	6	2.705	+
Acridine 9-oxide (21)	10	3.350	+
(Acridine)	10	1.912	+
Benzo[f]quinoline 1-oxide (25)	2	1.747	
	4	1.756	
Benzo[h]quinoline 1-oxide (26)	2	1.774	
	4	1.790	
Quinoxaline 1-oxide	2	2.342	+
	3	1.439	
Quinoxaline 1,4-dioxide	2,4	5.197	+
1,6-Naphthyridine 1-oxide (9)	2	2.117	+
	4	2.149	
1,6-Naphthyridine 6-oxide (11)	5	2.388	+
1,6-Naphthyridine 1,6-dioxide (1)	2	3.366	+
	5	4.346	+
1,6-Phenanthroline 6-oxide	5	2.787	+

active than quinoline 1-oxide, but the others did not react even at 130°.

These experimental results cannot be explained merely by electronic interpretation and, therefore, we applied molecular orbital theory for the interpretation. The simple LCAO-MO was calculated for each unsubstituted heteroaromatic N-oxide, utilizing the parameter[7] of N-oxide in a protic solvent, and superdelocalizability[8] (Sr^N value, introduced by Fukui to compare the reactivity in aromatic substitution re-

(7) T. Kubota, *Bull. Chem. Soc. Jap.*, **80**, 578 (1959).
(8) K. Fukui, T. Konezawa, and C. Nagata, *ibid.*, **27**, 423 (1954).

actions) was applied to examine the difference of reactivities among N-oxides.

The calculated data are listed in Table II. The experimental results agreed with the calculated results. The oxidative cyanation occurred when the value of Sr^N is more than *ca.* 1.8. This calculated result can explain the above three characteristics. First, pyridine and diazine N-oxides have Sr^N values lower than *ca.* 1.8. Second, the values of reactivity of benzoquinoline oxides can be divided with *ca.* 1.8 as the boundary and the high reactivity of diazanaphthalene can, therefore, be interpreted quantitatively. Third, the selectivity of this cyanation was explained by comparing the Sr^N value of each position in N-oxides. Finally, we must note that the difference in the reactivities of the 2 and 4 positions in quinoline 1-oxide cannot clearly be interpreted by Sr^N. Sr^N is 2.020 in the 4 position and 1.950 in the 2 position, but that this reaction proceeded in the 2 position seems to be partly affected by steric factors.

Experimental Section

General Procedure of Oxidative Cyanation.—To a saturated solution of $K_3Fe(CN)_6$ (1.2 molar equiv) and KCN (3–5 molar equiv) in H_2O or $EtOH–H_2O$, an heteroaromatic N-oxide was added and stirred at the designated temperature for 3 hr. The precipitate was collected by filtration, washed with H_2O, dried, and recrystallized from an appropriate solvent and afforded the cyanated product. The filtrate obtained above was extracted with $CHCl_3$ and was purified by silica gel chromatography when necessary.

Photochemical Studies. XVIII.[1]
Light-Induced Ring Expansion of Pyridine *N*-Oxides

OLE BUCHARDT,* CHRISTIAN L. PEDERSEN, AND NIELS HARRIT

*Chemical Laboratory II, The H. C. Ørsted Institute, University of Copenhagen, Universitetsparken 5,
DK-2100 Copenhagen, Denmark*

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Irradiation of polyarylpyridine *N*-oxides results in ring expansion to 1,3-oxazepines in high yield and some deoxygenation to the parent amines. The 1,3-oxazepines were unambiguously identified by comparison with 2,4,5,7-tetraphenyl-6-(4-bromophenyl)-1,3-oxazepine, the structure of which has been determined by X-ray crystallography. Irradiation of 2,3,5,6-tetraphenylpyridine *N*-oxide in benzene and ethanol at three different wavelengths is described.

The photochemistry of heteroaromatic amine *N*-oxides in general[3] and pyridine *N*-oxides in particular has been the subject of a number of recent studies.[3−8] However, both for the *N*-oxides in general and for the pyridine *N*-oxides a number of important questions have not yet been answered in a satisfactory way; *e.g.*, the exact nature of the excited states leading to photoproducts, substituent, solvent and wavelength effects on the product distribution, etc. We wish here to report and discuss the light-induced ring expansion of pyridine *N*-oxides, including some results obtained by varying the solvent and the wavelength.

Light-induced ring expansion of a variety of heteroaromatic *N*-oxides has been described and the structures of the ring-expanded products have been unambiguously determined by X-ray crystallography. Thus quinoline *N*-oxides give benz[*d*][1,3]oxazepines,[9,10] isoquinoline *N*-oxides give benz[*f*][1,3]oxazepines,[2] and quinoxaline *N*-oxides give benz[*d*][1,3,6]oxadiazepine,[11] etc.

Aryl and cyano substituents on carbon atoms which become neighbors to the oxygen atom in the ring-expanded products have a strongly stabilizing effect on these.[3,9−11] Furthermore, when several routes of reaction are possible, the introduction of aryl groups tends to result in the predominance of one route. Consequently, we decided to examine aryl-substituted pyridine *N*-oxides.

Results

The classical method of obtaining pyridine *N*-oxides, *i.e.*, by oxidation of the parent amines with peroxy acids, turned out to be unpractical, and instead the substrates were prepared from the easily obtainable polyarylpyrylium salts and hydroxylamine.[12]

In a preliminary communication we reported that irradiation of 2,4,6-triphenylpyridine *N*-oxide gives a mixture of the parent amine, 2,4,6-triphenyl-3-hydroxy-

pyridine, 2-benzoyl-3,5-diphenylpyrrole, and a substance which was tentatively believed to be 2,4,6-triphenyl-1,3-oxazepine.[13,14] At that time the assumed 2,4,6-triphenyl-1,3-oxazepine could not be obtained in the pure state, but more recently it was found that on preparative layer chromatography (plc) on silica gel impregnated with silver nitrate it could be purified. Due to lack of stability during the purification, the yield was very small, and therefore work with 2,4,6-triarylpyridine *N*-oxides was discontinued.

However, irradiation of the tetra- and pentaarylpyridine *N*-oxides (**1a–f**) led to the formation in high yields
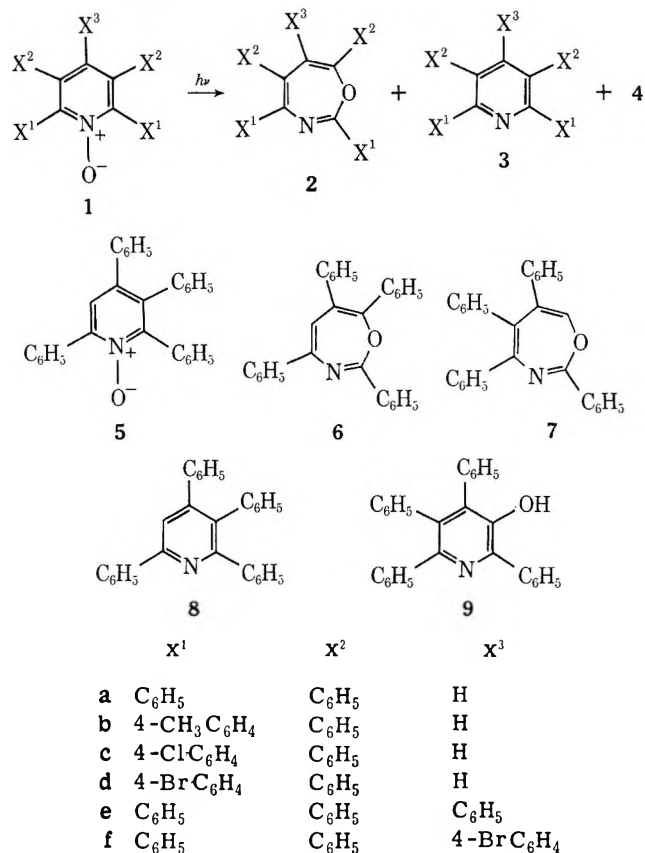
of the corresponding 1,3-oxazepines (**2a–f**) and minor amounts of the parent pyridines (**3a–f**). In the case of 2,3,5,6-tetraphenylpyridine *N*-oxide, minor amounts of

	X[1]	X[2]	X[3]
a	C_6H_5	C_6H_5	H
b	$4\text{-}CH_3C_6H_4$	C_6H_5	H
c	$4\text{-}ClC_6H_4$	C_6H_5	H
d	$4\text{-}BrC_6H_4$	C_6H_5	H
e	C_6H_5	C_6H_5	C_6H_5
f	C_6H_5	C_6H_5	$4\text{-}BrC_6H_4$

(1) For previous paper see ref 2.

(2) O. Simonsen, C. Lohse, and O. Buchardt, *Acta Chem. Scand.*, **24**, 268 (1970).

(3) For a recent review see G. G. Spence, E. C. Taylor, and O. Buchardt, *Chem. Rev.*, **70**, 231 (1970).

(4) J. Streith and C. Sigwalt, *Bull. Soc. Chim. Fr.*, 1157 (1970).

(5) M. Yamada and H. Arai, *Tetrahedron Lett.*, 2213, 2747 (1970).

(6) F. Bellamy, L. G. Ruiz Barragan, and J. Streith, *Chem. Commun.*, 456 (1971).

(7) C. Leibovici and J. Streith, *Tetrahedron Lett.*, 387 (1971).

(8) M. Ishikawa, C. Kaneko, I. Yokoe, and S. Yamada, *Tetrahedron*, **25**, 295 (1969).

(9) O. Buchardt, B. Jensen, and I. Kjøller Larsen, *Acta Chem. Scand.*, **21**, 1841 (1967).

(10) B. Jensen, *Acta Crystallogr., Sect. B*, in press.

(11) O. Buchardt and B. Jensen, *Acta Chem. Scand.*, **22**, 877 (1968).

(12) C. L. Pedersen, N. Harrit, and O. Buchardt, *ibid.*, **24**, 3435 (1970).

(13) P. L. Kumler and O. Buchardt, *Chem. Commun.*, 1321 (1968).

(14) Independently it was found that irradiation of 2,6-dicyanopyridine *N*-oxide resulted in the formation of 2,6-dicyanopyridine, 5-cyano-2-pyrrolecarbonyl cyanide, and a compound believed to be 2,4-dicyano-1,3-oxazepine. Similar results were obtained for 2,6-dicyano-4-methylpyridine *N*-oxide.[8]

SCHEME I
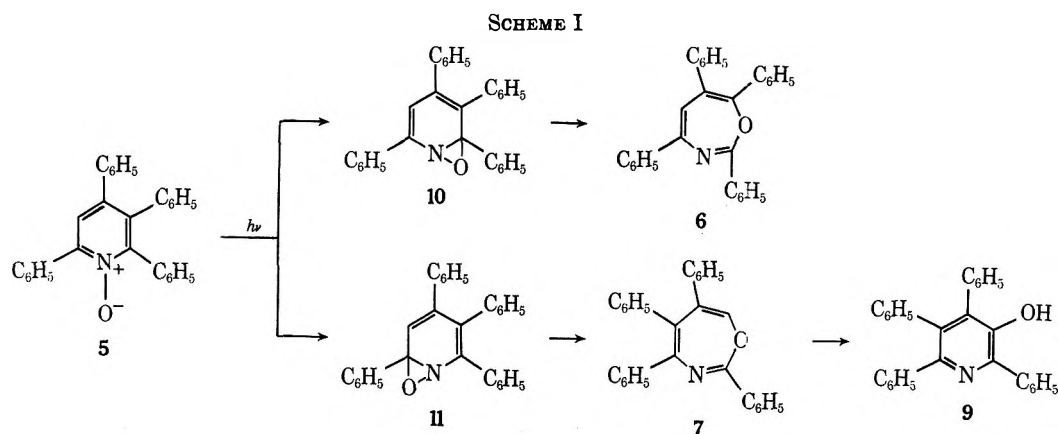
an as yet unidentified compound **4** were also isolated (Table I). To obtain further information about the

TABLE I

IRRADIATION OF PYRIDINE *N*-OXIDES

Substrate	Wavelength Å	Solvent	Product yields, %		
			2a	**3a**	**4**
	3500	Benzene	84–87	10–12	1–3
	3000	Benzene	78–83	14–15	2
	2537	Benzene	55–63	23–29	5–7
1a[a]	3500	Ethanol	75–76	13–19	3–4
	3000	Ethanol	77–83	13–14	4–5
	2537	Ethanol	71–75	17–20	4
	3500	Acetone	76–83	14–16	1–3
			2b	**3b**	
1b	3500	Benzene	78	19	
			2c	**3c**	
1c	3500	Benzene	87	9	
			2d	**3d**	
1d	3500	Benzene	83	17	
			2e	**3e**	
1e	3500	Benzene	80	17	
			2f	**3f**	
1f	3500	Benzene	76	20	

[a] These experiments have been repeated at least three times.

product distribution, 2,3,5,6-tetraphenylpyridine *N*-oxide (**1a**) was irradiated in various solvents with light of various wavelengths[15] (Table I).

Almost all the previously described experiments with pyridine *N*-oxides employed symmetrical substrates, whereby one complicating possibility of two pathways to products was eliminated. However, since the previous literature[4,16] indicates that one of the two possible pathways is favored (*vide supra*), it was deemed of interest to prepare and irradiate 2,3,4,6-tetraphenylpyridine *N*-oxide (**5**) (Scheme I). This resulted in the formation of a mixture of products which by plc was separated into a compound identified as 2,4,6,7-tetraphenyl-1,3-oxazepine (**6**), the parent amine (**8**), and a compound identified as 2,4,5,6-tetraphenyl-3-hydroxypyridine (**9**). When the crude reaction mixture was examined by nmr, no signals corresponding to compound **9** were observed. From the spectrum it was inferred that the mixture consisted of compound **8**, compound **6**, and 2,4,5,6-tetraphenyl-1,3-oxazepine (**7**), the two latter compounds being in the approximate ratio 2:3. We believe that
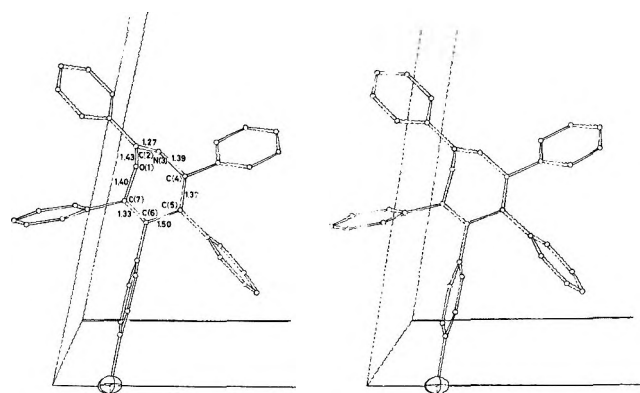
Figure 1.—A perspective view of 2,4,5,7-tetraphenyl-6-(4-bromophenyl)-1,3-oxazepine (IIf). The atomic numbering and the bond lengths of the oxazepine ring are given. The bromine atom is represented by its thermal ellipsoid while the rest of the atoms are represented by spheres of an arbitrary size.

compound **7** rearranges to compound **9** during the purification procedure.[17]

Finally we wish to mention some preliminary results which indicate a pronounced heavy-atom effect. If 2,3,5,6-tetraphenylpyridine *N*-oxide (**1a**) is irradiated in tetrachloromethane, in ethylene bromide, and in methyl iodide with 3500-Å light the ratio of **2a** to **3a** decreases markedly in this order.

Structure Determination.—The 1,3-oxazepines were identified by comparison with 2,4,5,7-tetraphenyl-6-(4-bromophenyl)-1,3-oxazepine (**2f**), which is the major photoproduct from 2,3,5,6-tetraphenyl-4-(4-bromophenyl)pyridine *N*-oxide (**1f**) (Table I). The structure of this oxazepine was unambiguously established by X-ray crystallography (Figure 1).[18] From Table II it will be seen that the ir spectra of the 1,3-oxazepines all show a characteristic absorption in the 1630-cm^{-1} region, while the uv spectra exhibit a characteristic absorption at *ca.* 380 nm, tailing into the visible region. Apparently the electron delocalization is of the same order of magnitude as that found in similar seven-membered ring compounds.[19]

2,4,6,7-Tetraphenyl-1,3-oxazepine (**6**) had the correct elemental analysis as well as the expected strong absorp-

(15) Rayonet reactor, type RPR-208 with RUL 3500-, 3000-, or 2537-lamps.

(16) See ref 3, p 243.

(17) 2-Cyanobenz[*c*][1,3]oxazepines rearrange extremely easily to the corresponding 3-hydroxyquinoline; *cf.* ref 3, p 247, and C. Kaneko and S. Yamada, *Chem. Pharm. Bull.*, **15**, 663 (1967).

(18) The detailed X-ray structure determination will be published independently by B. Jensen, *Acta Crystallogr., Sect. B*, in press. We wish to acknowledge the excellent collaboration of Dr. Jensen.

(19) A. R. Katritzky, "Physical Methods in Heterocyclic Chemistry," Vol. II, Academic Press, London, 1963, p 66.

TABLE II

CHARACTERISTIC SPECTROSCOPIC PROPERTIES OF 1,3-OXAZEPINES (2)[d]

Compd	Mp, °C	Ir,[a] cm^{-1}	Uv,[b] λ_{max}, nm (log ϵ)		Nmr,[c] Aromatic	Vinylic
2a	195–196	1640	270 (4.54)	375 (3.97)	1.8–3.0	3.62
2b	211–212	1630	275 (4.57)	378 (4.03)	1.8–3.2	3.58
2c	194–196	1630	271 (4.61)	380 (4.05)	1.7–3.0	3.58
2d	213–215	1620	279 (4.60)	380 (4.00)	1.9–2.9	3.60
2e	245–246	1630	268 (4.42)	350 (3.85)	2.0–3.3	
2f	240–241	1630	270 (4.50)	350 (3.91)	2.0–3.5	

[a] In KBr discs. [b] In 96% EtOH. [c] In CDCl₃ with TMS as internal reference; methyl resonances in 2b were 7.68 and 7.73. [d] Satisfactory analytical values (±0.3 for C, H, N) for all compounds were reported: Ed. Satisfactory analytical values for halogens for 2c, 2d, and 2f were reported: Ed.

tion band in the ir (see Experimental Section). The nmr spectrum consisted of a multiplet at τ 1.87–3.14 and a singlet due to the single vinyl proton at τ 3.36, in the intensity ratio 20:1. However, the assumed 2,4,5,6-tetraphenyl-1,3-oxazepine (7) is less rigorously identified. The evidence for its presence is found in the nmr spectrum of the crude photolysis product from 2,3,4,6-tetraphenylpyridine *N*-oxide (5). This spectrum contained no signals from 2,4,5,6-tetraphenyl-3-hydroxypyridine (9), but consisted of a multiplet due to the aromatic protons, a singlet at τ 3.36 (from compound 6), and a singlet at τ 3.68 (in the ratio 2:3); the latter singlet is assigned to the vinyl proton in compound 7. Furthermore, the rearrangement of compound 7 to give compound 9 is also in agreement with the proposed structure (*vide infra*). 2,4,5,6-Tetraphenyl-3-hydroxypyridine was identified on the basis of elemental analysis and spectroscopy (see Experimental Section). The pyridines 3a–f were identified by comparison with authentic samples (ir, melting point) prepared from pyrylium salts and aqueous ammonia.[20]

Discussion

The generation in high yields of stable 1,3-oxazepines requires a high degree of substitution with either aryl or cyano substituents, especially on carbons 2 and 7. Although this limits the types of 1,3-oxazepines which can be prepared by this method, it is nevertheless an excellent preparative method, leading to a hitherto unknown heterocyclic ring system. The X-ray data do not suggest any valence tautomerization to an oxaazanorcaradiene system.[18] An attempt to observe such a tautomerization by nmr spectroscopy at various temperatures was likewise unsuccessful.

Most evidence in the photochemistry of heteroaromatic amine *N*-oxides indicates that the deoxygenation mainly takes place from a triplet state, whereas the rearrangement mainly takes place from an excited singlet state.[4,6,21,22] Thus it has been found that triplet sensitization increases the extent of deoxygenation from 2-cyanopyridine *N*-oxide, whereas quenching with oxygen decreases the deoxygenation.[4,6]

When 2537-Å light is employed in benzene solution, energy transfer must take place *via* benzene. It is known that benzene can transfer singlet energy to

olefins,[23] and we assume similar transfer to the *N*-oxide to occur, as well as triplet energy transfer. This phenomenon will be studied further. Our preliminary results with heavy atom solvents also indicate that the deoxygenation takes place from a triplet state and the rearrangements from an excited singlet state. However, the observed fact that decreasing the oxygen concentration present during irradiation of quinoline *N*-oxides[24-26] and 1,4-diphenylphthalazine *N*-oxide[27] decreases the photochemical deoxygenation seems to be in conflict with such a general mechanism.

We have previously proposed a mechanism for the formation of 1,3-oxazepines and 3-hydroxypyridines from pyridine *N*-oxides.[3] Only one bit of information in the literature indicates that the oxygen atom in an unsymmetrically substituted pyridine *N*-oxide can move in two directions upon irradiation, *i.e.*, the formation of both 2-methyl-3-hydroxypyridine and 6-methyl-3-hydroxypyridine in the photolysis of 2-methylpyridine *N*-oxide.[4,28] The presently described results with 2,3,4,6-tetraphenylpyridine *N*-oxide clearly demonstrate this duality in mechanism.

Since the 1,3-oxazepines can be obtained in very high yields, they are apparently quite photostable. Irradiation of the pure compounds substantiated this observation. With 3000- or 3500-Å light virtually no photoreactions took place. However at 2537 Å some photoreactivity was observed. No formation of the unidentified compound 4 was observed either in the photolysis or the thermolysis of 2,4,5,7-tetraphenyl-1,3-oxazepine.[29]

Experimental Section

Melting points (uncorrected) were determined on a Büchi melting point apparatus. Elemental analyses were carried out in the microanalysis laboratory of this university. Ir spectra were recorded on a Perkin-Elmer Model 337 grating infrared spectrophotometer, uv spectra on a Perkin-Elmer Model 137 uv spectrophotometer, and nmr spectra on a Varian A-60A spectrometer.

Chemicals.—All solvents were dried before use. All starting materials were reagent grade.

(20) R. Lombard and J.-P. Stephan, *Bull. Soc. Chim. Fr.*, 1458 (1958).

(21) C. Lohse, *J. Chem. Soc. B*, in press.

(22) We have previously suggested that the increased deoxygenation of 2,4,6-triphenylpyridine *N*-oxide in the presence of benzophenone was due to triplet sensitization.[11] However, this is probably rather due to a light-induced chemical action of benzophenone and ethanol; *cf.* J. S. Splitter and M. Calvin, *Tetrahedron Lett.*, 3995 (1970).

(23) (a) J. G. Calvert and J. N. Pitts, "Photochemistry," Wiley, New York, N. Y., 1966, p 332 ff; (b) E. A. Andereesche, S. F. Kilin, I. Novotnyi, I. M. Rozinan, and F. Spurnyi, *Opt. Spectrosc.*, **24**, 117 (1965); (c) S. Sato, H. Kobayashi, and K. Fukano, *J. Chem. Soc. Jap., Ind. Chem. Sect.*, **72**, 209 (1969).

(24) M. Ishikawa, S. Yamada, H. Hotta, and C. Kaneko, *Chem. Pharm. Bull.*, **14**, 1102 (1966).

(25) O. Buchardt, C. Lohse, and P. L. Kumler, *Acta Chem. Scand.*, **23**, 159 (1969).

(26) C. Kaneko and S. Yamada, *Rep. Res. Inst. Dental Mater.*, Tokyo Medico-Dental Univ., **2**, 804 (1966).

(27) O. Buchardt, *Tetrahedron Lett.*, 1911 (1968).

(28) J. Streith, B. Danner, and C. Sigwalt, *Chem. Commun.*, 979 (1967).

(29) C. L. Pedersen and O. Buchardt, unpublished results.

Irradiations with an external light source were performed with a Rayonet reactor, type RPR-208, with RUL 3500-, 3000-, or 2537-Å lamps. The sample to be irradiated was stirred magnetically in a Pyrex flask (a quartz flask was used at 2537 Å). Irradiations with an internal light source were performed with a medium-pressure mercury arc, type Hanovia Q-700. The sample to be irradiated was placed in a water-cooled Pyrex container. All irradiations were performed at 25–35°.

Preparative layer chromatography was performed on 20 × 100 cm plates with a 2.5 mm thick layer of silica gel (Merck, PF$_{254-366}$). The plates were developed two times with a mixture of benzene and petroleum ether (bp 30–60°) (1:1). The fractions were scraped off the plates and isolated by extraction with chloroform in a Soxhlet apparatus.

Pyridine *N*-oxides were prepared according to the previously described method from the corresponding pyrylium salts.[12] 2,6-Di(4-methylphenyl)-3,5-diphenylpyridine *N*-oxide (**1b**) was prepared from 2,6-di(4-methylphenyl)-3,5-diphenylpyrylium bromide in 74% yield, mp 255–257°. *Anal.* Calcd for C$_{31}$H$_{25}$NO: C, 87.09; H, 5.89; N, 3.28. Found: C, 87.10; H, 5.95; N, 3.21. 2,6-Di(4-chlorophenyl)-3,5-diphenylpyridine *N*-oxide was prepared from 2,6-di(4-chlorophenyl)-3,5-diphenylpyrylium bromide in 76% yield, mp 249–251°. *Anal.* Calcd for C$_{29}$H$_{19}$Cl$_2$NO: C, 74.36; H, 4.09; N, 2.99; Cl, 15.14. Found: C, 74.25; H, 4.25; N, 2.97; Cl, 15.43. 2,6-Di(4-bromophenyl)-3,5-diphenylpyridine *N*-oxide was prepared from 2,6-di(4-bromophenyl)-3,5-diphenylpyrylium bromide in 95% yield, mp 248–249°. *Anal.* Calcd for C$_{29}$H$_{19}$Br$_2$NO: C, 62.50; H, 3.44; N, 2.51; Br, 28.68. Found: C, 62.35; H, 3.67; N, 2.50; Br, 28.72. 2,3,5,6-Tetraphenyl-4-(4-bromophenyl)pyridine *N*-oxide was prepared from 2,3,5,6-tetraphenyl-4-(4-bromophenyl)pyrylium bromide in 90% yield, mp 248–250°. *Anal.* Calcd for C$_{35}$H$_{24}$BrNO: C, 75.81; H, 4.37; N, 2.53; Br, 14.41. Found: C, 75.80; H, 4.47; N, 2.40; Br, 14.42. The above pyrylium salts were prepared by the previously described method.[30]

Pyridines were prepared from the corresponding pyrylium salts as previously described.[20] 2,6-Di(4-methylphenyl)-3,5-diphenylpyridine had mp 233–234°. *Anal.* Calcd for C$_{31}$H$_{25}$N: C, 90.47; H, 6.12; N, 3.40. Found: C, 90.13; H, 6.22; N, 3.34. 2,6-Di(4-chlorophenyl)-3,5-diphenylpyridine had mp 220–221°. *Anal.* Calcd for C$_{29}$H$_{19}$Cl$_2$N: C, 77.00; H, 4.23; N, 3.10; Cl, 15.67. Found: C, 77.10; H, 4.37; N, 2.98; Cl, 15.49. 2,6-Di(4-bromophenyl)-3,5-diphenylpyridine had mp 234–235°. *Anal.* Calcd for C$_{29}$H$_{19}$Br$_2$N: C, 64.34; H, 3.54; N, 2.59; Br, 29.53. Found: C, 64.30; H, 3.66; N, 2.50; Br, 29.37. 2,3,5,6-Tetraphenyl-4-(4-bromophenyl)pyridine had mp 224–226°. *Anal.* Calcd for C$_{35}$H$_{24}$BrN: C, 78.06; H, 4.50; N, 2.60; Br, 14.84. Found: C, 78.00; H, 4.56; N, 2.49; Br, 14.67.

Irradiation of Pyridine *N*-Oxides (**1a–f**, **5**).—All irradiations in benzene solution were performed analogously to the following procedure. 2,3,5,6-Tetraphenylpyridine *N*-oxide (1.000 g) was

dissolved in 400 ml of dry benzene and irradiated with an external light source for *ca.* 7 hr, the solvent was removed *in vacuo*, and the reaction mixture was separated by plc into 2,4,5,7-tetraphenyl-1,3-oxazepine (607 mg), 2,3,5,6-tetraphenylpyridine (84 mg), starting material (281 mg), and the unknown compound 4 (9 mg). This compound was difficult to separate from the pyridine. Its R_f value (eluent benzene–petroleum ether, 1:1) was marginally larger than the R_f of the pyridine. Irradiations in dry ethanol lasted for *ca.* 15 hr. In acetone 1.000 g of substrate was dissolved in 600 ml of acetone and irradiated for 12 hr. See Tables I and II.

The reaction mixture from the irradiation of 2,3,4,6-tetraphenylpyridine *N*-oxide (**5**) could be separated into 37% of 2,4,5,6-tetraphenyl-3-hydroxypyridine (**9**), 30% of 2,3,4,6-tetraphenylpyridine (**8**), and 30% of 2,4,6,7-tetraphenyl-1,3-oxazepine (**6**). However, from the tlc and nmr of the crude reaction mixture it could be seen that no compound 9 was present, but that the mixture consisted of compound 8 (tlc), compound 6 (nmr), and a compound believed to be 7 (nmr). Upon plc compound 7 disappeared and the hydroxypyridine 9 was isolated. 2,4,5,6-Tetraphenyl-3-hydroxypyridine had mp 210–211°. *Anal.* Calcd for C$_{29}$H$_{21}$NO: C, 87.19; H, 5.30; N, 3.51. Found: C, 87.30; H, 5.45; N, 3.55. Its ir spectrum showed a strong band at 3525 cm^{-1} (OH); its nmr (CDCl$_3$) showed a multiplet at τ 1.84–3.33 and a singlet at τ 4.88 (OH). This signal disappeared upon shaking with D$_2$O. 2,4,6,7-Tetraphenyl-1,3-oxazepine had mp 136–139°. *Anal.* Calcd for C$_{29}$H$_{21}$NO: C, 87.19; H, 5.30; N, 3.51. Found: C, 86.77; H, 5.60; N, 3.43. Its ir spectrum showed a strong absorption at 1615 cm^{-1}; its nmr (CDCl$_3$) showed a multiplet at τ 1.87–3.14 and a singlet due to the vinyl proton at τ 3.36, in the ratio 20:1.

Preparative Scale Synthesis of 2,4,5,7-Tetraphenyl-1,3-oxazepine (**2a**).—2,3,5,6-Tetraphenylpyridine *N*-oxide (2.00 g) was dissolved in dry benzene (280 ml) and irradiated with an internal light source until no more starting material could be detected by tlc. The solvent was removed and the residue was recrystallized from hexane to give 2,4,5,7-tetraphenyl-1,3-oxazepine (1.57 g, 79%).

Irradiation of 2,4,6-Triphenylpyridine *N*-Oxide.—This was undertaken as previously described.[13] Only by tlc on a mixture of silica gel and silver nitrate (98:2) could we separate the 2,4,6-triphenylpyridine and the 2,4,6-triphenyl-1,3-oxazepine. The silver nitrate, however, caused partial decomposition of the latter (*ca.* 50% per elution), which no attempt was made to overcome. The two separated products exhibited the spectral patterns (ir and nmr) attributed to them in the mixture.[13]

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Photolysis of Diazocarbonyl Compounds in Allylic Alcohols. New Preparation of Bicyclo[3.1.0]lactones and the Nature of the Reactive Intermediate

WATARU ANDO,* ISAMU IMAI, AND TOSHIHIKO MIGITA

Department of Chemistry, Gunma University, Kiryu, Gunma, Japan

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Carboalkoxycarbenes, generated photochemically from dimethyl diazomalonate or ethyl diazoacetate, react with allylic alcohols to form bicyclo[3.1.0]lactones and the insertion products of the carbene into the O–H bonds of allylic alcohols. Bicyclo[3.1.0]lactone is formed by the addition of the carbene to C=C double bond, followed by lactonization with elimination of methanol. Similar addition to the C=C bond and insertion into C—O bond by carboalkoxycarbenes were also observed in the reaction with allylic ethers. The product of insertion into C—O bond or O—H bond was not observed in the photosensitized reaction which is presumed to produce the triplet carbene. It is concluded that the singlet state of carboalkoxycarbene attacks the oxygen atom of the allylic alcohol or ether to give an intermediate oxygen ylide which rearranges to insertion product by 2,3-sigmatropic process or to O–H insertion product by hydrogen migration.

We recently reported a study of the reaction of carboalkoxycarbene with aliphatic sulfides[1–3] and allylic compounds containing sulfur, oxygen, and halides.[4–7] With an allylic compound such as allyl n-butyl sulfide the major processes were the insertion of the carboalkoxycarbene into the C—S bond, and addition of the carbene to the C=C bond. It was proposed that most of these reactions proceed through ylide formation by reaction of the singlet carbenes formed by the direct photolysis of diazocarbonyl compounds, and the insertion products were obtained *via* 2,3-sigmatropic allylic rearrangement of intermediate ylides.
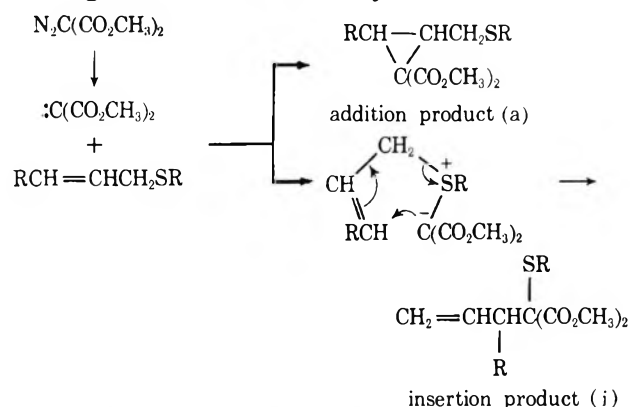
In the case of photosensitized decomposition of diazo compounds in allylic compounds, we found that such reaction with the C=C bond is prefered to the carbene insertion into the C—S, C—O, or C—Cl bond.

This study has now been extended to the direct and sensitized photolysis of diazocarbonyl compounds in allylic alcohols, and the results are compared with those obtained in allylic ethers.

Some of the reactions of the alcohols with diazoacetophenone[8] and ethyl diazoacetate[9] have been reported.

Padwa has reported that the initially formed singlet diazoacetophenone decomposes to a hydrogen-bonded singlet ketocarbene which undergoes Wolff rearrangement. As the strength of the hydrogen bond decreases, more intersystem crossing to the triplet occurs and larger amounts of acetophenone are formed. Similar results in the reaction of carbethoxycarbene have been obtained with 2-propanol, which gives a product of carbethoxymethylene insertion into the tertiary C—H bond, a polar addition product with the O—H bond, and a rearrangement product.

Results and Discussions

Irradiation of solutions of dimethyl diazomalonate in allylic alcohols was carried out in a Pyrex vessel with a high pressure mercury lamp. The reaction of allyl alcohol I with bis(carbomethoxy)carbene produced by direct photolysis of dimethyl diazomalonate afforded the two principal products (Ia and Ii) in 24.5 and 31.9%
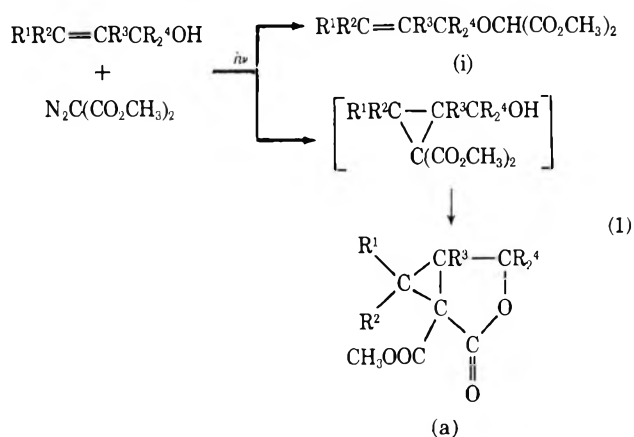
$$I, R^1 = R^2 = R^3 = R^4 = H$$
$$II, R^1 = CH_3; R^2 = R^3 = R^4 = H$$
$$III, R^1 = R^2 = R^4 = H; R^3 = CH_3$$
$$IV, R^1 = R^2 = CH_3; R^3 = R^4 = H$$
$$V, R^1 = R^2 = R^3 = H; R^4 = CH_3$$

yields, respectively (eq 1). The latter product may be rationalized by assuming a bis(carbomethoxy)carbene intermediate which inserts into the O—H bond to give Ii. The former product Ia was not expected; ir, nmr, and elemental analyses showed it to be the bicyclo[3.1.0]lactone. Its infrared spectrum showed bands indicative of an lactone and ester groups at 1800 and

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SCHEME I

$$N_2CHCO_2C_2H_5 \quad + \quad R^1R^2C{=}CR^3CR_2{}^4{-}OH \xrightarrow{h\nu}$$

C₂H₅OCH₂CO₂CR₂⁴CR³=CR²R¹

VI, Wolff rearrangement (WR)

R¹R²C=CR³CR₂⁴OCH₂CO₂C₂H₅

VII, O–H insertion

lactone VIII

carbinol IX

1735, no bands above 3000, but weak absorption at 3050 cm⁻¹, indicative of a methylene group of cyclopropane. No vinyl proton resonances were present in the nmr spectrum.

Photolysis of dimethyl diazomalonate in γ,γ-dimethylallyl alcohol gave O—H insertion product as the major product in 69.2%, and bicyclo[3.1.0]lactone as the minor product. Both products could be isolated by tlc; analytical glpc was used to determine their yields. Examination of the products by tlc suggested that the bicyclo[3.1.0]lactones were not formed under the glpc conditions.

TABLE I

PHOTOLYSIS OF DIMETHYL DIAZOMALONATE IN ALLYLIC ALCOHOLS

| Alcohol | Direct | | Ratio of i/a | Sensitized[a] lactone (a) |
	Lactone (a)	O–H (i)		
CH₂=CHCH₂OH (I)	24.5%	31.9%	1.3	38.7%
CH₃CH=CHCH₂OH (II)	14.9	33.2	2.2	19.7
CH₂=C(CH₃)CH₂OH (III)	34.1	21.2	0.6	39.4
(CH₃)₂C=CHCH₂OH (IV)	11.5	69.2	6.0	7.2
CH₂=CHC(CH₃)₂OH (V)	21.2	11.8	0.6	50.1

[a] No O–H insertion product was found in the sensitized reactions.

The formation of the bicyclo[3.1.0]lactones was of obvious interest. These products are presumably formed by lactonization with elimination of methanol from the initially formed cyclopropylcarbinols which arise by addition of the carbene to the C=C bond. In view of the reaction conditions, this lactonization is thought to occur by spontaneous intramolecular transesterification in the absence of particular acid or base catalyst. Such thermal transesterifications were found to occur also intermolecularly, as shown in the following Table II.

$$R^1CH_2CO_2R^2 \; + \; R^3OH \xrightarrow[5\,hr]{160°} R^1CH_2CO_2R^3 \; + \; CH_2(CO_2R^2)_2$$
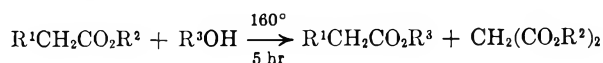
A B

TABLE II

TRANSESTERIFICATION BETWEEN ESTER AND ALCOHOL IN THE ABSENCE OF CATALYST

| Ester | | Alcohol, R³ | A, % | B, % |
R¹	R²			
CO₂CH₃	CH₃	CH₂=CHCH₂OH	52	25
CO₂CH₃	CH₃	CH₃CH₂CH₂OH	37	49
COCH₃	CH₃	CH₂=CHCH₂OH	70	0
COCH₃	CH₃	CH₃CH₂CH₂OH	70	0
H	C₂H₅	CH₂=CHCH₂OH	0	0

This reaction may be more useful for preparation of bicyclo[3.1.0]lactones than the method reported previously.[10]

The most marked change in going from the direct photolysis to the sensitized one is in the relative ratio of the products of insertion and addition. The direct photolysis of diazomalonate in allyl alcohol gave 31.9% of O–H insertion product and 24.5% of bicyclo[3.1.0]lactone. In contrast, the benzophenone-photosensitized decomposition of diazomalonate gave 38.7% of bicyclo[3.1.0]lactone, but no O–H insertion product. Table I contrasts the results of the sensitized and direct irradiation. Appropriate control experiments showed that under the reaction conditions the products were neither isomerized nor destroyed. Since the relative extinction coefficients of the diazo compound and the benzophenone in the >3000-Å region allow more than 98% of the light to be absorbed by the sensitizer, it is concluded that the direct photolysis does produce an intermediate which gives both O–H insertion and addition products, but sensitization of the decomposition with benzophenone produces dramatic changes in the mode of reaction.[4-7,11,12]

Photolysis of ethyl diazoacetate in allylic alcohols gave similar products VII and VIII together with *trans*-cyclopropylcarbinol IX and VI (Scheme I). *trans*-Cyclopropylcarbinol IX cannot be converted to bicyclo[3.1.0]lactone under the reaction conditions be-

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TABLE III

PHOTOLYSIS OF ETHYL DIAZOACETATE IN ALLYLIC ALCOHOLS

	Direct photolysis, %				Sensitized photolysis,[a] %	
Alcohols	WR	i	Lactone	Carbinol	Lactone	Carbinol
$CH_2=CHCH_2OH$	15.0	11.5	10.8	15.7	11.1	22.5
$CH_3CH=CHCH_2OH$	22.1	14.2	8.3	7.0	8.5	9.9
$CH_2=C(CH_3)CH_2OH$	24.0	12.0	7.0	12.8	11.9	17.1
$(CH_3)_2C=CHCH_2OH$	17.4	10.1	5.5	8.2	trace	15.4
$CH_2=CHC(CH_3)_2OH$	b	b	9.8	20.0	5.3	34.3

[a] "WR" and "i" products were not formed in the sensitized reactions. [b] "WR" and "i" products were not detected by gas chromatography.

cause of the distance between the ester and O–H groups. The formation of VI involves a migration of the ethoxy group and most probably proceeds through an isomeric ketene analogous to that formed in the Wolff rearrangement (WR). Various allylic alcohols were allowed to react with ethyl diazoacetate and the results are shown in Table III.

The sensitized photodecomposition of ethyl diazoacetate in allylic alcohols produced a species showing little tendency to undergo the Wolff rearrangement. The carboalkoxycarbene generated under these conditions was relatively unreactive toward the O—H bond and gave mainly the C=C addition product. As is shown in Tables I and III, the product distribution is drastically changed by introducing a photosensitizer, which suggests that the singlet carbene is the precursor of the O–H insertion and Wolff rearrangement products.

With regard to the mechanism of insertion of carbene into the O—H bond, the reactions of diazomalonate with allylic alcohols gave some significant results. Two mechanisms can be considered: (a) electrophilic

oxygen ylide intermediate   (i)

sertion to that of addition for allylic alcohols is in agreement with that of the products of O-allyl insertion to that of the addition for the corresponding allylic ethers (Table IV). Numerical coincidence was not observed

TABLE IV

YIELDS OF PRODUCTS FROM THE PHOTOLYSIS OF
DIMETHYL DIAZOMALONATE IN ALLYLIC ETHERS

Ether	i	a	Ratio of i/a
$CH_2=CHCH_2OCH_3$	31%	20%	1.6[a]
$CH_3CH=CHCH_2OCH_3$	37	17	2.2[a]
$CH_2=C(CH_3)CH_2OCH_3$	23	25	0.9
$(CH_3)_2C=CHCH_2OCH_3$	35	23	1.5
$CH_2=CHC(CH_3)_2OCH_3$	6.4	13	0.5

[a] See ref 7.

for the γ,γ-dimethylallyl compounds, but a qualitative tendency of preference for insertion was observed in the reaction of both allylic compounds. This means that the O–H insertions into allylic alcohols proceed *via* quite similar rate controlling processes to those of O-allyl insertion into allylic ethers, since the reactivities of the C=C bonds of allylic system would not be significantly influenced by the structural change in going from alcohol to the corresponding methyl ether. Thus it may be concluded that the O–H insertion takes place by mechanism a.

attack by carboalkoxycarbene at the oxygen atom of the alcohol to give an oxygen ylide, followed by the proton migration from oxygen to carbon, or (b) nucleophilic attack by the carbene at the proton of the alcohol. It is known that singlet carbenes are produced by direct photolysis of diazo compounds, and react with molecules bearing unshared electron pairs to give ylides. On the other hand, triplet carbenes produced by benzophenone-photosensitized photolysis do not lead to ylides. The fact that the O–H insertion was observed in the direct photolysis and not in the sensitized reaction suggests that the formation of these insertion products proceed through oxygen ylide intermediates derived by electrophilic attack of the carbenes on oxygen atoms of allylic alcohols. This is further supported by the fact that the relative reactivities of the O—H and C=C bonds toward the carbene correlated well with those of allylic ethers. Dimethyl diazomalonate was photolyzed with a high pressure mercury lamp in allylic methyl ethers. These reactions were found to give the "inverted insertion" product and the adduct of the carbene to the C=C bond. As shown in previous papers,[6,7] the "insertion" product can be considered to form through an intermediate oxygen ylide followed by 2,3-sigmatropic rearrangement. It can be seen that the ratio of the product (Table I) of O–H in-

Dependence of the product ratio cited above seems to show the following tendencies (see Tables I and IV). Methyl substituent on a terminal carbon atom retards the addition of the bis(carbomethoxy)carbene, while the substituent on the α, or central, position retards the O-ylide formation. This implies that, in reactions of bis(carbomethoxy)carbene, the tendency for addition *vs.* O-ylide formation is largely controlled by steric factors. As shown in Table III, however, these effects are slight in the reactions of carbethoxycarbene. In this case the addition products (lactone and carbinol) always predominate, regardless of the structure of allylic alcohols. It is understandable that steric control is less important in the reaction of carbethoxycarbene than in that of bis(carbomethoxy)carbene. Results shown in Table III also show that the precursor of Wolff rearrangement products is a singlet carbene, although the reason that α,α-dimethylallyl alcohol does

not give products of rearrangement and insertion is not yet clear.

In summary, allylic alcohols were found to react with a singlet carbene, mainly giving products of addition to C=C bonds and insertion into the O—H bonds, and with a triplet carbene to give only addition products. The most probable mechanism of the O–H insertion involves an *O*-ylide intermediate. Distribution of the products from the reaction of singlet bis(carbomethoxy)-carbene depends on the structure of the allylic alcohols, and seems to be controlled mainly by steric factors. It is noteworthy that the adducts of carboalkoxycarbenes with allyl alcohol lactonize spontaneously, giving bicyclo[3.1.0]lactones in high yields.

Experimental Section

General.—Infrared spectra were determined on a Japan Spectroscopic Co. LTD DS-21 instrument in chloroform, carbon tetrachloride, or neat. The nmr spectra were recorded on a Varian A-60D spectrometer using solutions in carbon tetrachloride with internal tetramethylsilane (TMS) as standard. Chemical shifts are reported in parts per million (ppm) downfield from TMS, with the parentheses designating the multiplicity of the signals: s, singlet; d, doublet; t, triplet; q, quartet; and m, multiplet. The number immediately following the parentheses indicates the number of protons causing the signal. Samples of diazo compound were added to clean 10×100 mm Pyrex tubes. The tubes were then corked (nondegassed) and placed in a water cooled bath for irradiation. The light source was a 400-W Rikosha high pressure mercury lamp having the maximum output at 3650–3660 Å with low intensities at 3126–2132 Å. Photolyses were carried to the disappearance of diazo band in infrared spectra. The solutions were analyzed on an Ohkura gas–liquid partition chromatography with a calibrated 5 ft × $^1/_4$ in. stainless steel column of 10% DC710 and 10% Carbowax 20M on C-22 firebrick. Hydrogen was used as the carrier gas. Peak areas were obtained by multiplying the height of the peak times the width at half-height. Absolute yields were then obtained relative to the area of the known amounts of internal standard.

Preparation of Starting Materials.—Dimethyl diazomalonate was prepared using the procedure in which a solution of dimethyl malonate and tosyl azide was treated with diethyl amine.[13] Ethyl diazoacetate[14] was prepared by treating ethyl glycinate hydrochloride with sodium nitrile, bp 36–36.5° (9 mm).

Research grade reagents of allyl alcohol, β-methylallyl alcohol, γ-methylallyl alcohol, and α,α-dimethylallyl alcohol (Tokyo Kasei) were used without further purification. γ,γ-Dimethylallyl alcohol was prepared by hydrolysis of γ,γ-dimethylallyl chloride with 10% NaOH,[15] bp 85–86° (89 mm), 32% yield. Allyl methyl ether, β-methylallyl methyl ether, γ-methylallyl methyl ether, and γ,γ-dimethylallyl methyl ether were prepared by converting the respective allylic chlorides with sodium metal in methanol.[16] α,α-Dimethylallyl methyl ether was prepared by converting the α,α-dimethylallyl alcohol with sodium in diethyl ether to the sodium allylalenoxide and then adding methyl iodide in excess and stirring at room temperature for 2 days, 32% yield, bp 66–69°.

Reaction of Dimethyl Diazomalonate with Allylic Alcohols. A. Allyl Alcohol (I).—A solution of 0.144 g (0.91 mmol) of dimethyl diazomalonate and 1.525 g (0.262 mol) of allyl alcohol was photolyzed for 15 hr. A large quantity of nitrogen gas was observed 1–2 min after the irradiation had begun. After the infrared spectrum of the reaction mixture showed no diazo band, the reaction mixtures were analyzed by glpc and showed two products Ii and Ia, yields given in Table I. Ii: nmr δ 3.75 (s, 6 H), 4.0–4.2 (m, 2 H), 4.48 (s, 1 H), 5.1–5.5 (m, 2 H), 5.5–5.9 (m, 1 H); ir 1750, 990, 930 cm⁻¹. *Anal.* Calcd for $C_8H_{12}O_5$: C, 51.06; H, 6.43; Found: C, 51.26; H, 6.79. Ia: nmr δ

1.2–1.5 (m, 1 H), 1.8–2.2 (m., 1 H), 2.5–2.9 (m, 1 H), 3.80 (s, 3 H), 4.10–4.4 (m, 2 H); ir 1800, 1735 cm⁻¹. *Anal.* Calcd for $C_7H_8O_4$: C, 53.84; H, 5.16. Found: C, 54.21; H, 5.40.

B. γ-Methylallyl Alcohol (II).—A similar procedure was followed in the reaction of 0.129 g (0.82 mmol) of diazomalonate in 0.71 g of γ-methylallyl alcohol for 20 hr. Glpc analysis showed that the products IIi and IIa were present in 33.2 and 14.9% yields. IIi: nmr δ 1.6–1.8 (m, 3 H), 3.75 (s, 6 H), 3.9–4.1 (m, 2 H), 4.35 (s, 1 H), 5.5–5.8 (m, 2 H); ir 1750 cm⁻¹. *Anal.* Calcd for $C_9H_{14}O_5$: C, 53.46; H, 6.98. Found: C, 53.65; H, 7.13. IIa: nmr δ 1.31 (d, 3 H), 1.4–1.8 (m, 1 H), 2.3–2.6 (m, 1 H), 3.80 (s, 3 H), 4.1–4.2 (m, 2 H); ir 1800, 1735 cm⁻¹. *Anal.* Calcd for $C_8H_{10}O_4$: C, 56.46; H, 5.92; Found: C, 56.14; H, 6.05.

C. β-Methylallyl Alcohol (III).—A solution of 1.15 mmol of dimethyl diazomalonate and 0.86 g of β-methylallyl alcohol were irradiated with a high pressure mercury lamp for 10 hr. Analysis by glpc showed two products IIIi and IIIa in 21 and 34% yields. Methanol was also found by glpc. IIIi: nmr δ 1.80 (s, 3 H), 3.78 (s, 6 H), 4.00 (s, 2 H), 4.36 (s, 1 H), 4.85 (s, 2 H); ir 1750 cm⁻¹. IIIa: nmr δ 1.37 (AB d, 1 H), 1.90 (AB d, 1 H), 1.42 (s, 3 H), 3.80 (s, 3 H), 4.10 (d, 2 H); ir 1800, 1735 cm⁻¹. *Anal.* Calcd for $C_8H_{10}O_4$: C, 56.46; H, 5.92. Found: C, 56.49; H, 6.28.

D. γ,γ-Dimethylallyl Alcohol (IV).—A similar reaction on the same scale was carried out. Glpc analysis of the reaction mixture showed the presence of IVi, IVa, and methanol. IVi: nmr δ 1.65–1.85 (m, 6 H), 3.75 (s, 6 H), 4.00–4.10 (m, 2 H), 4.36 (s, 1 H), 5.17–5.50 (m, 1 H); ir 1750 cm⁻¹. *Anal.* Calcd for $C_{10}H_{16}O_5$: C, 55.54; H, 7.46. Found: C, 55.31; H, 7.25. IVa: nmr δ 1.21 (s, 3 H), 1.23 (s, 3 H), 2.30–2.47 (m, 1 H), 3.75 (s, 3 H), 4.00–4.45 (m, 2 H); ir 1790, 1730. *Anal.* Calcd for $C_9H_{12}O_4$: C, 58.69; H, 6.57. Found: C, 58.39; H, 6.28.

E. α,α-Dimethylallyl Alcohol (V).—A 1-mmol-scale reaction was carried out using the same procedure. After the reaction was over, the reaction mixture was analyzed by glpc and Vi and Va were present in 11.8 and 21.1% yields, respectively. Vi: nmr δ 1.30 (s, 6 H), 3.73 (s, 6 H), 4.35 (s, 1 H), 4.93–5.35 (m, 2 H), 5.58–6.13 (m, 1 H); ir 1750, 930, 880 cm⁻¹. *Anal.* Calcd for $C_{10}H_{16}O_5$: C, 55.54; H, 7.46. Found: C, 55.21; H, 7.41. Va: nmr δ 1.35 (s, 3 H), 1.50 (s, 3 H), 1.70–2.00 (m, 1 H), 2.27–3.10 (m, 1 H), 3.80 (s, 3 H); ir 1790, 1735 cm⁻¹. *Anal.* Calcd for $C_9H_{12}O_4$: C, 58.69; H, 6.57. Found: C, 58.67; H, 6.84.

Photosensitized Reaction of Dimethyl Diazomalonate in Allylic Alcohols. A. Allyl Alcohol (I).—A solution of 0.41 g (2.2 mmol) of benzophenone and 0.136 g (0.86 mmol) of dimethyl diazomalonate in 1.4 g of allyl alcohol was irradiated in a Pyrex vessel at room temperature for 30 hr. The gas evolution had ceased and ir showed no diazo band at 2140 cm⁻¹. After irradiation, the solution was injected into the glpc and it was found that Ia was the only major product. Ii was not detected in glpc analysis. The yield is given in Table I.

B. γ-Methylallyl Alcohol (II), β-Methylallyl Alcohol (III), γ,γ-Dimethylallyl Alcohol (IV), and α,α-Dimethylallyl Alcohol (V).—The reactions were carried out in a similar manner on a 1-mmol scale. The glpc analyses gave only one major product, bicyclo[3.1.0]lactone, and the O–H insertion product was not detected. The bicyclolactones were identified on the basis of their retention time and infrared spectrum.

Photolysis of Ethyl Diazoacetate in Allylic Alcohols.—A photolysis of 0.97 mmol of ethyl diazoacetate in 1.3 g of allyl alcohol was carried out for 20 hr with a high pressure mercury lamp. Glpc analysis of the reaction mixture showed the presence of four major products, VI, VII, VIII, and IX, in 15, 11, 11, and 16% yields, respectively. On the other hand, sensitized photolysis of ethyl diazoacetate (1.13 mmol) in a solution of 3 mmol of benzophenone and 1.3 g of allyl alcohol was carried out for 25 hr. The glpc analysis of the reaction mixture showed the presence of only two products which correspond to VIII and IX in 11 and 23% yields, respectively.

Similarly, direct and sensitized photolyses were carried out for the other allylic alcohols, II, III, IV, and V, on the same scale. The glpc analysis of the reaction mixture in the direct photolysis showed the presence of four major products, Wolff rearrangement product, the O–H insertion product, bicyclo[3.1.0]lactone, and cyclopropylcarbinol, but analysis in the sensitized photolysis showed only the lactone and carbinol. The direct photolysis of ethyl diazoacetate in α,α-dimethylallyl alcohol gave only two products, the bicyclolactone and the carbinol in 10 and 20%

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TABLE V

ANALYTICAL DATA OF THE PRODUCTS OBTAINED FROM ALLYLIC ALCOHOLS AND DIAZOACETATE

Alcohol	Ir (>C=O), cm⁻¹ (registry no.)	Nmr, ppm downfield from internal TMS	Calcd, % C	H	Found, % C	H
		A. Wolff Rearrangement Product				
I	1740 (22874-92-6)	1.22 (t, 3 H), 3.56 (q, 2 H), 3.99 (s, 2 H), 4.60 (d, 2 H), 5.08–5.48 (m, 2 H), 5.63–6.02 (m, 1 H)	58.31	8.39	58.24	8.45
II	1740 (35620-08-7)	1.20 (t, 3 H), 1.70 (d, 3 H), 3.53 (q, 2 H), 3.95 (s, 2 H), 4.41–4.62 (m, 2 H), 5.50–5.77 (m, 2 H)	60.74	8.92	60.70	8.73
III	1740 (35620-09-8)	1.20 (t, 3 H), 1.78 (s, 3 H), 3.57 (q, 2 H), 4.00 (s, 2 H), 4.52 (s, 2 H), 4.80–5.04 (m, 2 H)	60.74	8.92	60.44	8.69
IV	1740 (35620-10-1)	1.20 (t, 3 H), 1.72 (s, 6 H), 3.50 (q, 2 H), 3.91 (s, 2 H), 4.41–4.65 (m, 2 H), 5.10–5.40 (m, 1 H)	62.76	9.36	62.38	9.11
		B. O–H Insertion Product				
I	1750 (15224-07-4)	1.27 (t, 3 H), 3.93 (s, 2 H), 3.90–4.23 (m, 4 H), 5.00–5.40 (m, 2 H), 5.55–5.95 (m, 1 H)	58.31	8.39	58.29	8.32
II	1750 (35620-12-3)	1.30 (t, 3 H), 1.75 (s, 3 H), 3.90 (s + d, 4 H), 4.15 (q, 2 H), 5.50–5.77 (m, 2 H)	60.74	8.92	60.55	8.96
III	1750 (22874-89-1)	1.30 (t, 3 H), 1.78 (s, 3 H), 3.93 (s, 4 H, =CCH₂O + OCH₂CO₂), 4.17 (q, 2 H), 4.80–5.04 (m, 1 H)	60.74	8.92	60.67	8.67
IV	1750 (35620-14-5)	1.28 (t, 3 H), 1.70 (s, 6 H), 3.90 (s, 2 H), 3.77–4.28 (m, 4 H), 5.10–5.45 (m, 1 H)	62.76	9.36	62.48	9.21
		C. Bicyclo[3.1.0]lactone				
I	1785, 1730	0.73–1.00 (m, 1 H), 1.15–1.48 (m, 1 H), 1.83–2.40 (m, 2 H), 4.20 (d, 2 H)	Known compound[a]			
II	1780, 1745	1.05–1.55 (m, 1 H), 1.38 (d, 3 H), 1.65–2.30 (m, 2 H), 4.10–4.85 (m, 2 H)	Known compound[b]			
III	1785, 1730 (35589-61-8)	0.90–1.07 (m, 1 H), 1.02–1.30 (m, 1 H), 1.41 (s, 3 H), 1.63–2.11 (m, 1 H), 4.08 (d, 2 H)	64.27	7.19	64.22	7.09
IV	1780, 1740 (16860-52-9)	1.20 (s, 6 H), 1.63–2.11 (m, 2 H), 3.93–4.50 (m, 2 H)	66.64	7.99	66.45	7.87
V	1780 (15143-62-1)	0.60–1.30 (m, 2 H), 1.20 (s, 3 H), 1.30 (s, 3 H), 1.60–2.00 (m, 2 H)	66.64	7.99	66.48	7.91
	(–OH)	D. Cyclopropylcarbinol				
I	3420, 1730 (15224-11-0)	0.70–1.78 (m, 4 H), 1.28 (t, 3 H), 3.10 (s, 1 H), 3.33–3.62 (m, 2 H), 4.10 (q, 2 H)	58.31	8.39	58.42	8.44
II	3440, 1730 (35621-62-6)	1.10–1.65 (m, 6 H), 1.27 (t, 3 H), 2.80 (s, 1 H), 3.35–3.60 (m, 2 H), 4.10 (q, 2 H)	60.74	8.92	60.42	8.75
III	3420, 1730 (35621-63-7)	0.80–1.75 (m, 3 H), 1.20 (s, 3 H), 1.25 (t, 3 H), 2.93 (s, 1 H), 3.38 (d, 2 H), 4.10 (q, 2 H)	60.74	8.92	60.56	8.69
IV	3420, 1730 (35621-64-8)	0.78–1.71 (br m + s, 11 H), 3.20–3.71 (m, 3 H), 4.10 (q, 2 H)	62.76	9.36	62.41	9.33
V	3420, 1730 (35621-65-9)	0.81–1.76 (m + br s, 14 H), 4.10 (q, 2 H)	62.76	9.36	62.74	9.29

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yields, respectively. The Wolff rearrangement and the O–H insertion products were not isolated by glpc.

The spectral properties of resulting products are shown in Table V.

Photolysis of Dimethyl Diazomalonate in Allylic Ethers.—In 1 ml of γ,γ-dimethylallyl methyl ether was dissolved 0.38 mmol of dimethyl diazomalonate. The solution was then irradiated for 20 hr using the high pressure mercury lamp as described before. From the analysis by glpc, the two main products were found; one of them was identified as the product of insertion of the carbene into C—O bond involving the allylic rearrangement and the other as a product of addition of the carbene to C=C bond. The structures were assigned by comparison of the ir and nmr spectra with those of authentic samples.

A similar reaction on the same scale was carried out in allyl methyl ether, γ-methylallyl methyl ether, β-methylallyl methyl ether, and α,α-dimethylallyl methyl ether. The reaction mixture was examined by glpc. Two principal products were present in each case. These are found to be "insertion" and addition products from the comparison of the ir and nmr spectra with authentic samples.

Preparation and Properties of Some Isomeric
v-Triazolopyridines. 1- and 3-Deaza-8-azapurines[1]

Carroll Temple, Jr.,* B. H. Smith, and J. A. Montgomery

Kettering-Meyer Laboratory, Southern Research Institute, Birmingham, Alabama 35205

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The preparation of both 1- and 3-deaza-8-azapurine (v-triazolopyridines) analogs of adenine, purine-6(1H)-thione, 6-(methylthio)purine, and hypoxanthine are reported. The Dimroth rearrangement of the 7-amino-3H-v-triazolo[4,5-b]pyridine (2)-4-amino-1H-v-triazolo[4,5-c]pyridine (5) system and the rearrangement of two v-triazolopyridinethione–amino[1,2,3]thiadiazolopyridine systems are described.

When the work herein reported was started, the synthesis of both 1- and 3-deaza-8-azapurines (v-triazolopyridines), analogs of 6-substituted purines, had not been reported. Recently a number of derivatives of these ring systems were prepared.[2] In this paper we report the preparation of the analogs of adenine, 6(1H)-purinethione, 6-(methylthio)purine, and hypoxanthine by more direct procedures. Also the reversible v-triazolopyridinethione–amino[1,2,3]thiadiazolopyridine rearrangement and the existence in the amino-v-triazolopyridines of a new type of Dimroth rearrangement are described.

The conversion of 4-amino-2-chloropyridine[3] to 4-amino-2-chloro-3-nitropyridine[3,4] and reduction of the latter with Raney nickel[5] gave 3,4-diamino-2-chloropyridine, which was nitrosated by the reported method to give 4.[4] Similarly the nitrosation of 2,3-diamino-4-chloropyridine[6] gave 1.[2]

The displacement of the chloro group of 1 to give 2 with ethanolic ammonia at 145° for 20 hr was reported to result in total decomposition.[2] We found that treatment of 1 with ethanolic ammonia at 150° for 19 hr gave a 55% yield of 2 and a 7% yield of about a 1:1 mixture of 2 and the rearrangement product 5.

The latter was identified by tlc and by comparison of its pmr spectrum with that of an authentic sample of 5 (see below). Presumably this rearrangement involves diazo-type intermediates like 3a–b, similar to the intermediates recently proposed for a new kind of Dimroth rearrangement observed in an 8-azapurine system.[7] Under essentially the same conditions treatment of 4 with ethanolic ammonia gave a 71% yield of 5 and a 22% yield of about a 1:1 mixture of 2 and 5 (tlc, pmr). Also treatment of pure 5 with ethanolic ammonia at 150° (65 hr) gave a mixture of 2 and 5 (tlc). The amount of 2 obtained in the mixtures suggested that the thermodynamic stability of 2 is greater than 5 in the presence of ammonia. In contrast the nitrosation of 2,3,4-triaminopyridine gave a mixture of 2 and 5 with that of 5 predominating.[2] The thermal rearrangement of 5 to 2 was unsuccessful as shown by heating a solution of 5 in either ethanol (150°, 65 hr) or tetramethylene sulfone (165°, 5 hr), heating solid 5 (200°, 18 hr) *in vacuo*, and refluxing a solution of 5 in 3,4-lutidine (18 hr). Although an 8-azapurine was rearranged in hot dimethylacetamide,[7] refluxing a solution of 5 in this solvent gave a mixture containing a minor amount of 5 and mainly an N-acetyl compound. The latter is presumably the corresponding 4-acetamido derivative of 5 based on elemental analyses, the presence of CH_3CO and broad NH (δ 2.2, 8–13) absorption in the pmr spectrum, and treatment of the mixture with dilute NaOH to again give 5 (tlc, pmr). The above results imply that the interconvertibility of 2 and 5 is catalyzed by ammonia.

Treatment of 4 with hydrated NaSH in propanol gave an 84% yield of the thione 10. In contrast to the report that reaction of 4 with thiourea in ethanol for 1 hr gave 10 directly,[2] we found that treatment of 4 with thiourea in propanol for 3.5 hr gave an 18% yield of the propylthio compound 8 and a 30% yield of the thiadiazolopyridine rearrangement product 12. Presumably 8 results from addition of propanol to the intermediate 2-thiopseudourea 6 to give 7 followed by an O → S propyl group migration with concomitant elimination of urea.[8] The structure of 8 was confirmed by comparison of its spectral properties with those of 9, prepared by methylation of 10 with MeI. The thiadiazolopyridine 12 must result from an intermediate in which the v-triazole ring is opened, and this intermediate might be formed from 6, 7, or 10. Support for a diazo-type intermediate like 11 was shown by refluxing a solution of 10 in propanol (18 hr) to give

(1) This investigation was supported by funds from the C. F. Kettering Foundation, and Chemotherapy, National Cancer Institute, National Institutes of Health, Contract NIH-71-2021.

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SCHEME I
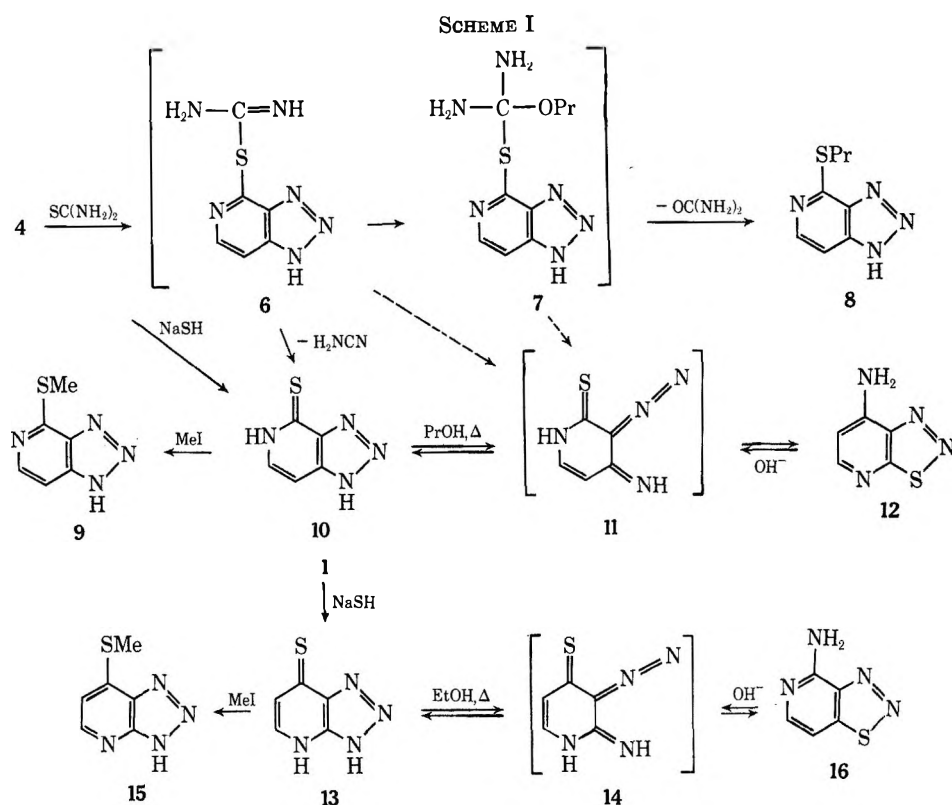
a mixture of **10** and **12** (tlc). The rearrangement of **10** to **12** and not **5** to **2** in alcohol suggested that triazole ring opening is controlled at least in part by the electron-withdrawing inductive effect of the substituent in the pyridine ring (–HNCS– or –NCSH > –NCNH₂–). The rearrangement of a thiadiazolopyrimidine to a 8-azapurinethione[9] and of related thiazolopyrimidines to purinethiones[10] with base has been demonstrated, and the conversion of **12** to **10** was also effected under these conditions. Presumably, opening of the thiadiazolo ring of **12** with base gave the electron-donating anion of the pyridinethione intermediate **11**, which favored triazole ring formation. Reaction of **1** with hydrated NaSH gave a 75% yield of **13**. This material was alkylated with MeI to give **15** and refluxed in propanol (141 hr) to give a 72% yield of **16** presumably formed *via* **14**. The anomalous low decomposition point (∼176°) of **13** was attributed to rearrangement of **13** to **16** by heat (tlc). Treatment of **16** with aqueous NaOH in ethanol reversed the rearrangement to give **13**. (See Scheme I.)

Treatment of **4** with anhydrous formic acid at reflux for 4 hr gave a 91% yield of **20**. Apparently this reaction involves the attack of the formyloxy anion on the protonated chloro compound **17** to give **18**, which undergoes hydrolysis to give **20**. In contrast treatment of **1** with formic acid gave a low yield of **22**, presumably formed from **19**. Another sample obtained from this reaction was shown by its pmr spectrum to contain a minor amount of **22** and mainly two unidentified compounds. Elemental analyses and the pmr spectrum suggested that these compounds are N-formylated derivatives of **1** and **22**. Practically com-

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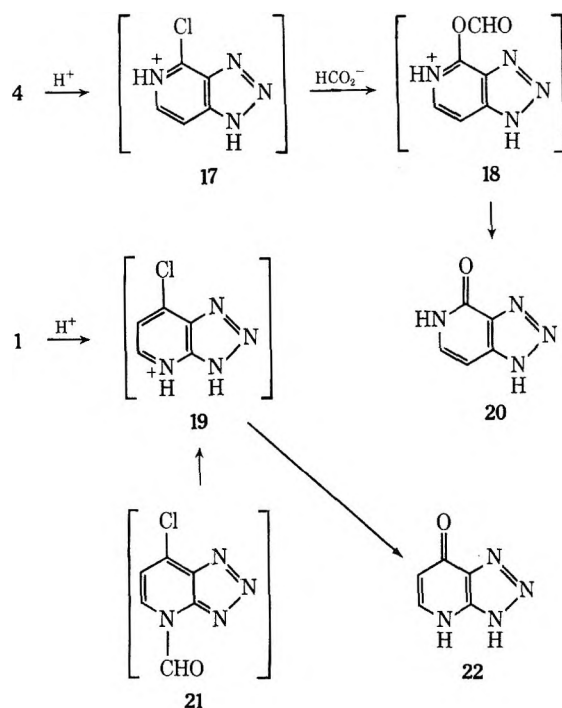
plete conversion to **22** was effected by heating the mixture with formic acid (42 hr). These results suggest that the slow rate of formation of **22**, when compared with that of **20**, is because of N-formylation of **1** to give presumably **21**, which undergoes deformylation to give **19** before conversion to **22**. In contrast to the conversion of **13** into **16** refluxing a solution of **22** in propanol (140 hr) gave no detectable rearrangement to 4-amino[1,2,3]oxodiazolo[4,5-*c*]pyridine.

The ultraviolet, infrared, and pmr spectral properties of these compounds are listed in Table I.

TABLE I

Compd	Uv absorption[a] spectra at pH 7, λ_{max}, nm ($\epsilon \times 10^{-3}$)	Ir absorption[b] spectra in KBr, selected bands, cm⁻¹	Pmr spectral assignments,[c] chemical shift, δ (rel area)
1	285 (10.6)	1575	7.66 (1, 6 H), 8.66 d (1, 5 H, J_{56} = 5.0 Hz), ~10–12(1, NH)
4	257 sh (3.76), 263 (4.30), 286 (6.20)	1610, 1580	7.87 d (1, 7 H), 8.31 d (1, 6 H, J_{67} = 5.8 Hz)[d]
2	214 (15.1), 265 (9.15), 302 (14.8), 330 sh (1.24)	1620, 1515	6.39 d (1, 6 H), 7.50 (2, NH₂), 8.01 d (1, 5 H, J_{56} = 5.8 Hz), 10.9 br (NH)
5	286 (6.68), 326 (1.81)[e]	1690, 1650, 1625	6.89 d (1, 7 H), 7.36 br, 7.58 d (4, NH, 6 H, J_{67} = 6.0 Hz)
8	262 (3.27), 305 (10.7)	1600, 1575	1.03 t (3, CH₃), 1.78 m (2, CH₂), 3.39 t (2, CH₂), 7.53 d (1, 7 H), 8.33 d (1, 6 H, J_{67} = 6.0 Hz), ~13–16 (NH)
9	261 (3.12), 303 (10.7)[f]	1600, 1575	2.70 (3, CH₃), 7.53 d (1, 7 H), 8.35 (1, 6 H, J_{67} = 5.8 Hz), ~10–13 (NH)
15	212 (15.9), 286 (13.6), 302 (13.6)[f]	1595, 1570	2.71 (CH₃),[g] 7.27 d (1, 6 H), 8.52 d (1, 5 H, J_{56} = 4.8 Hz), ~12–16 (NH)
10	253 (5.20), 334 (16.8)	1585, 1530	7.18 d (1, 7 H), 7.52 t (1, 6 H, J_{56} = 6.0 Hz, J_{67} = 7.0 Hz), 13.2 br, ~15–18 (NH)
13	230 (10.9), 278 sh (4.73), 281 (6.42), 292 sh (5.69), 354 (17.8)[f]	1610, 1590	7.11 d (1, 6 H), 7.83 d (1, 5 H, J_{56} = 6.2 Hz), ~13–16(2, NH)
12	233 (13.1), 243 (13.2), 269 (4.46), 342 (5.47)	3365, 3320, 1655	6.73 d (1, 6 H), 7.76 (2, NH₂), 8.27 d (1, 5 H, J_{56} = 5.2 Hz)
16	249 (5.92), 284 (4.38), 338 (4.44)[e]	3375, 3300, 1640	7.37 d (1, 7 H), 7.62 (2, NH₂), 8.71 d (1, 6 H, J_{67} = 5.2 Hz)
20	263 (6.62), 273 (6.80)	1660, 1610, 1570	6.64 d (1, 7 H), 7.31 d (1, 6 H, J_{67} = 7.0 Hz), ~10.4 br, 14–17 (1, 1, NH)
22	209 (15.7), 258 (8.50), 296 (14.7), 304 (11.9)[f]	1620, 1525	6.14 d (1, 6 H), 7.91 d (1, 5 H, J_{56} = 6.8 Hz), ~12.3 br (2, NH)

[a] Cary Model 17 spectrophotometer. [b] Perkin-Elmer Model 521 and 621 spectrophotometers. [c] Pmr spectra of samples were determined in DMSO-d_6 solutions (4–10% w/v) with Varian A-60A and XL-100-15 spectrometers with TMS as an internal reference; peak positions quoted in the case of multiplets are measured from the approximate center, and the relative peak areas are given to the nearest whole number. [d] Position of the NH peaks was not determined. [e] Solvent contains 0.8% DMSO 9.2% MeOH, and 90% pH 7 buffer. [f] Solvent contains 10% 0.1 N NaOH and 90% pH 7 buffer. [g] This peak overlapped the DMSO-d_5 multiple.

Experimental Section[11]

7-Chloro-1H-v-triazolo[4,5-b]pyridine (1)[2] was prepared by a procedure similar to that reported from 2,3-diamino 4-chloropyridine (3.4 g)[6] and solid sodium nitrite (1.8 g) in 0.4 N HCl, yield 2.3 g (63%). A sample was recrystallized from aqueous EtOH and dried in vacuo over P₂O₅ at 78° for analyses, mp >300°.

Anal. Calcd for C₅H₃ClN₄: C, 38.87; H, 1.95; Cl, 22.93; N, 36.24. Found: C, 38.68; H, 1.84; Cl, 23.18; N, 36.07.

7-Amino-3H-v-triazolo[4,5-b]pyridine (2).—A suspension of 1 (0.50 g) in 12% w/w ethanolic ammonia (20 ml) was heated in a Parr bomb for 19 hr at 150°. The reaction mixture was evaporated to dryness, and the resulting residue was dissolved in 0.4 N NaOH. Acidification (pH 5, paper) of this solution with HOAc deposited the product, which was dried in vacuo over P₂O₅ at 110°, yield 0.24 g (55%), mp 250° dec (lit.[2] mp 270° with sublimation).

Anal. Calcd for C₅H₅N₅: C, 44.45; H, 3.73; N, 51.83. Found: C, 44.20; H, 3.66; N, 51.60.

The filtrate from above was evaporated to dryness, and the residue was washed with H₂O to give a solid, yield 0.03 g (7%). This sample was identified as an approximately 1:1 mixture of 2 and 5 by tlc and by its pmr spectrum.

4-Chloro-1H-v-triazolo[4,5-c]pyridine (4).[4]—Solid sodium nitrite (4.8 g) was added with stirring to a cooled solution (10°) of 3,4-diamino-2-chloropyridine (9.0 g)[4,5] in 0.4 N HCl (350 ml). After the solution was stirred at ice bath and room temperatures for 1 hr each, the tan solid was collected by filtration and dried in vacuo over P₂O₅, yield 8.8 g (91%). A sample was recrystallized from EtOH for analyses, mp >325°.

Anal. Calcd for C₅H₃ClN₄: C, 38.87; H, 1.95; N, 36.24. Found: C, 39.02; H, 1.96; N, 36.42.

4-Amino-1H-v-triazolo[4,5-c]pyridine (5).[2]—A suspension of 4 (1.5 g) in 12% w/w ethanolic ammonia (60 ml) was heated in a Parr bomb for 19 hr at 150–152°. The reaction mixture was evaporated to dryness, and the resulting solid was suspended with stirring in H₂O (15 ml) containing 1 N NaOH (10 ml). After 15 min the product was collected by filtration, yield 0.93 g (71%). A sample was precipitated from a NaOH solution with HOAc and dried in vacuo over P₂O₅ at 78° for analyses, mp >325°.

Anal. Calcd for C₅H₅N₅: C, 44.45; H, 3.73; N, 51.83. Found: C, 44.34; H, 3.75; N, 51.73.

The basic wash from above was acidified with HOAc to deposit a solid, yield 0.29 g (22%). This sample was shown to be an approximately 1:1 mixture of 2 and 5 by tlc and by its pmr spectrum.

7-(Propylthio)-1H-v-triazolo[4,5-c]pyridine (8) and 7-Amino-[1,2,3]thiadiazolo[5,4-b]pyridine (12).—A solution of 4 (5.0 g) and thiourea (2.7 g) in PrOH (150 ml) was refluxed for 3.5 hr and evaporated to dryness in vacuo. The residue was stirred in 1 N NaOH (50 ml) for 15 min, and 12 was collected by filtration, washed with H₂O, and dried in vacuo over P₂O₅, yield 1.5 g (30%), mp 190–191° dec.

Anal. Calcd for C₅H₄N₄S: C, 39.46; H, 2.65; N, 36.82. Found: C, 39.60; H, 2.72; N, 36.58.

Tlc indicated that a mixture of 10 and 12 resulted from refluxing a suspension of 10 in PrOH for 18 hr.

The combined filtrate and wash from above was acidified to pH 6 (paper) with dilute HCl to deposit 8, yield 1.1 g (18%), mp 158–160°.

Anal. Calcd for C₈H₁₀N₄S: C, 49.46; H, 5.19; N, 28.84. Found: C, 49.32; H, 5.16; N, 28.31.

4-(Methylthio)-1H-v-triazolo[4,5-c]pyridine (9).—A solution of 10 (2.40 g) in DMF (50 ml) containing anhydrous K₂CO₃ (2.18 g) and CH₃I (2.24 g) was stirred at room temperature for 18 hr and evaporated to dryness in vacuo. The residue was dissolved in H₂O (70 ml), and the solution was acidified to pH 5 (paper) with dilute HCl. After being chilled for 20 hr the product was collected by filtration and dried in vacuo over P₂O₅ at 78°, yield 0.72 g (27%), mp 170°.

Anal. Calcd for C₆H₆N₄S: C, 43.35; H, 3.64; N, 33.71; S, 19.29. Found: C, 43.52; H, 3.54; N, 33.62; S, 19.28.

Tlc indicated that the aqueous filtrate was a complex mixture of 9 and four other components.

1,5-Dihydro-4H-v-triazolo[4,5-c]pyridine-4-thione (10). A.—A suspension of 4 (4.0 g) and hydrated NaSH (20 g) in PrOH was refluxed for 20 hr. After filtration the filtrate was evaporated to dryness, and the resulting solid was dissolved in H₂O (100 ml). This solution was acidified with HOAc to deposit 10, which was collected by filtration, washed with C₆H₆, and dried in vacuo over P₂O₅ at 110°, yield 3.3 g (84%), mp ~234° dec (lit.[2] dec > 230°).

Anal. Calcd for C₅H₄N₄S: C, 39.46; H, 2.65; N, 36.82. Found: C, 39.22; H, 2.57; N, 36.98.

B.—A solution of 12 (0.20 g) in EtOH (25 ml) and 1 N NaOH (3 ml) was refluxed for 2 hr and evaporated to dryness. The resi-

due was dissolved in H_2O and acidified with dilute HCl to deposit 10, which was identified by tlc with an authentic sample, yield 0.14 g (70%), mp ~227 dec.

1,4-Dihydro-7H-v-triazolo[4,5-b]pyridine-7-thione (13). A.— Treatment of 1 (2.7 g) and hydrated NaSH (13 g) under conditions similar to that described above for the preparation of 10 gave 13, yield 2.0 g (75%), mp 176–177° dec with sublimation (lit.[2] dec > 200°).

Anal. Calcd for $C_5H_4N_4S$: C, 39.46; H, 2.65; N, 36.82. Found: C, 39.41; H, 2.56; N, 36.60.

B.—A solution of 16 (0.10 g) in EtOH (12 ml) and 1 N NaOH (3 ml) was refluxed for 16 hr and acidified to pH 1 (paper) with concentrated HCl to deposit 13, yield 0.04 g, mp 176–177° dec with sublimation.

7-(Methylthio)-1H-v-triazolo[4,5-b]pyridine (15) was prepared by a procedure similar to that of 9 from 13 (0.89 g), anhydrous K_2CO_3 (0.81 g), and CH_3I (0.83 g) in DMF (18 ml), yield 0.50 g (51%), mp 208–209°.

Anal. Calcd for $C_8H_6N_4S$: C, 43.35; H, 3.64; N, 33.71; S, 19.29. Found: C, 43.42; H, 3.54; N, 33.88; S, 19.15.

4-Amino[1,2,3]thiadiazolo[4,5-c]pyridine (16). A.—A suspension of 13 (1.55 g) in EtOH (160 ml) was refluxed for 141 hr and evaporated to dryness *in vacuo*. The residue was extracted with hot CH_3CN (250 ml), and the extract was evaporated to dryness. Recrystallization of the resulting solid from EtOAc–petroleum ether (bp 80–105°) gave the product, which was dried *in vacuo* over P_2O_5 at 78°, yield 1.11 g (72%), mp 185–187°.

Anal. Calcd for $C_5H_4N_4S$: C, 39.46; H, 2.65; N, 36.82; S, 21.07. Found: C, 39.67; H, 2.65; N, 36.62; S, 20.85.

B.—A sample of 13 was heated to 190° in a capillary tube. Tlc indicated that the resulting dark, gummy residue and white sublimate contained only 16.

1,5-Dihydro-4H-v-triazolo[4,5-c]pyridin-4-one (20).—A solution of 4 (2.0 g) in formic acid (40 ml) was refluxed for 4 hr and evaporated to dryness *in vacuo*. The residue was dissolved in dilute aqueous NaOH, and after filtration the filtrate was acidified with concentrated HCl to deposit 20, which was dried *in vacuo* over P_2O_5 at 78°, yield 1.6 g (91%). A sample was recrystallized from H_2O for analyses, mp >360°.

Anal. Calcd for $C_5H_4N_4O$: C, 44.12; H, 2.96; N, 41.16. Found: C, 43.92; H, 2.83; N, 40.99.

1,4-Dihydro-7H-v-triazolo[4,5-b]pyridin-7-one (22).—A solution of 1 (2.0 g) in formic acid (40 ml) was refluxed for 4 hr and evaporated to dryness; the resulting residue was dissolved in dilute NaOH. After filtration the filtrate was neutralized with dilute HCl to deposit a solid, which was again reprecipitated from a NaOH solution with dilute HCl, yield 1.0 g. This material was dissolved in hot H_2O (400 ml), and the solution was cooled for about 60 hr to deposit a tan precipitate, yield 0.30 g. Elemental analysis of this solid showed the presence of chlorine, and the pmr spectrum indicated that the sample contained a minor amount of 22 and mainly two unidentified components, presumably N-formylated intermediates. A sample (0.13 g) was refluxed in formic acid for 42 hr, and the resulting solid was recrystallized from H_2O to give a trace amount of the unidentified component and 22 (see below), yield 0.08 g, mp 290° dec.

The aqueous filtrate from the mixture of components described above was concentrated to a low volume to deposit pure 22, which was dried *in vacuo* over P_2O_5 at 78°, yield 0.51 g (29%), mp 290° dec.

Anal. Calcd for $C_5H_4N_4O$: C, 44.12; H, 2.96; N, 41.16. Found: C, 43.96; H, 3.11; N, 40.94.

Synthesis and Infrared Spectra of Nitrogen-15 Labeled 3-Methyl-2-benzothiazolinone Hydrazones and Related Compounds

RICHARD A. BARTSCH,*[1,2] SIEGFRIED HÜNIG, AND HELMUT QUAST

Institute of Organic Chemistry, University of Würzburg, 87 Würzburg, West Germany

The syntheses of 3-methyl-2-benzothiazolinone hydrazone-*1*-^{15}N (1a) and -*2*-^{15}N (1b), 2-imino-^{15}N-3-methylbenzothiazoline (2a), N-(3-methyl-2-benzothiazolinylidene)benzamide-^{15}N (6a), 3-methyl-2-(nitrosimino-*imino*-^{15}N)benzothiazoline (7a), and 3-methyl-2-(nitrosimino-*nitroso*-^{15}N)benzothiazoline (7b) are reported. Infrared spectral studies of 1a, 1b, 2a, 6a, 7a, and 7b and the corresponding unlabeled compounds allow for the assignment of several absorption bands.

Mechanistic studies of the oxidation of 3-methyl-2-benzothiazolinone hydrazone (1) with potassium ferricyanide[3] required the preparation of 3-methyl-2-benzothiazolinone hydrazone-*1*-^{15}N (1a) and -*2*-^{15}N

(1b). We wish to report viable synthetic routes to 1a and 1b which employ $Na^{15}NO_2$ and $^{15}NH_4NO_3$ as the sources of the isotopic nitrogen label.

Results and Discussion

Stepwise introduction of the two hydrazone nitrogen atoms was deemed necessary in view of the isotopic scrambling that would attend reactions in which both nitrogen atoms become incorporated in one step.[4]

3-Methyl-2-benzothiazolinone Hydrazone-*1*-^{15}N.—It appeared that an attractive method for introduction of labeled nitrogen into the imino nitrogen position of 1a might include the reaction of $^{15}NH_3$ with an appropriate benzothiazolium salt to form 2-imino-^{15}N-3-methyl-
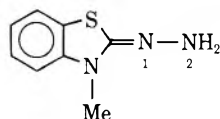
1a, 1-^{15}N
b, 2-^{15}N
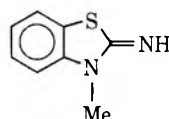
2a, 1-^{15}N

(1) NATO Postdoctoral Fellow, 1967–1968.
(2) Address correspondence to Department of Chemistry, Washington State University, Pullman, Wash. 99163.
(3) R. A. Bartsch, S. Hünig, and H. Quast, *J. Amer. Chem. Soc.*, **92**, 6007 (1970).
(4) R. Riemschneider, *Monatsh. Chem.*, **89**, 683 (1958).

Table I

Reaction of 2-X-3-Methylbenzothiazolium Fluoroborate with Ammonium Nitrate and Sodium Methoxide in Methanol

Run	X	NH₄NO₃, mmol	MeONa, mmol	Solvent	Reaction time, days	Yield of imine 1, %[a,b]
1	SMe	1.05	1.0	MeOH	0.1	0[c]
2	SMe	1.03	2.0	MeOH	2	22[d]
3	SMe	1.05	2.0	MeOH	5	57–68
4	SMe	1.01	2.0	MeOH–MeCN	5.5	15
5	SMe	1.03	3.0	MeOH	1	0
6	SMe	1.00	4.0	MeOH	6	0
7	Cl	1.00	2.0	MeOH–MeCN	3	0[c]
8	OEt	1.01	2.0	MeOH–MeCN	5	0

[a] Isolated as the benzoylated derivative, N-(3-methyl-2-benzothiazolinylidene)benzamide. [b] Yield based upon ammonium nitrate. [c] Apparent formation of 3-methyl-2-benzothiazolinone monoazamonomethinecyanine fluoroborate by reaction of 2 with 3: H. Quast and S. Hunig, *Justus Liebigs Ann. Chem.*, 711, 157 (1968). [d] Incomplete reaction.

benzothiazoline (2a), since this step has been employed in the preparation of similar imino compounds.[5]

With the goal of establishing appropriate conditions for the reaction of 2-substituted 3-methylbenzothiazolium salts with ammonia, which was to be generated *in situ* from ammonium nitrate and sodium methoxide, the experiments summarized in Table I were performed. The course of the reactions was followed with ultraviolet spectroscopy by observing the appearance of absorption at λ_{max} 292 nm for the imine 2. Reaction of 3-methyl-2-methylmercaptobenzothiazolium fluoroborate with 1 equiv of ammonium nitrate and 2 equiv of sodium methoxide in methanol gave reasonable yields of 2-imino-3-methylbenzothiazoline (2). Other ratios of sodium methoxide to ammonium nitrate and other 2-substituted 3-methylbenzothiazolium fluoroborates failed to produce 2. In runs 2–4, the ultraviolet spectrum of the reaction solution exhibited a maximum at 301 nm soon after mixing of the reagents. During the span of several days, the absorption at 301 nm decreased and was replaced by an absorption with λ_{max} 292 nm for the imine 2. A mechanism which is consistent with the observed stoichiometry and the spectral changes[6-8] is presented in Scheme I.
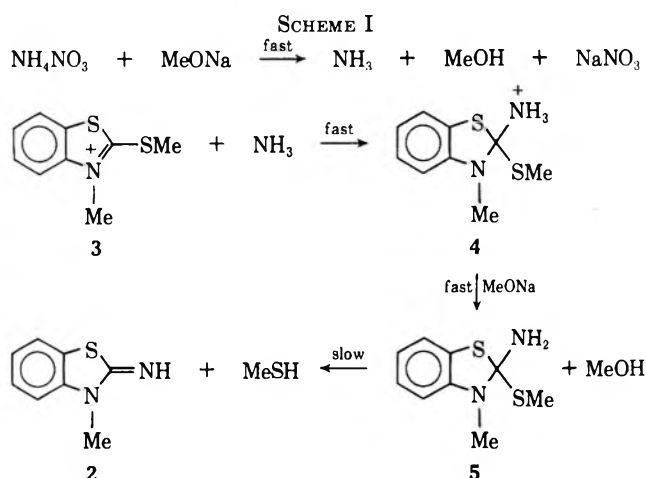
Scheme I

The synthetic route to 3-methyl-2-benzothiazolinone hydrazone-1-^{15}N is outlined in Scheme II. The reported yields are yields for each step. Conversion of

(5) H. Quast and S. Hünig, *Chem. Ber.*, 101, 435 (1968).

(6) The ultraviolet spectra of 3-methylbenzothiazolium iodide in ethanol exhibits λ_{max} at 276 nm.[7]

(7) J. Metzger, H. Larivé, R. Dennilauler, R. Baralle, and C. Gaurat, *Bull. Soc. Chim. Fr.*, 2868 (1964).

(8) The ultraviolet spectrum of 2-ethoxy-3-methylbenzothiazoline in ethanol exhibits λ_{max} at 308 nm.[7]

Scheme II
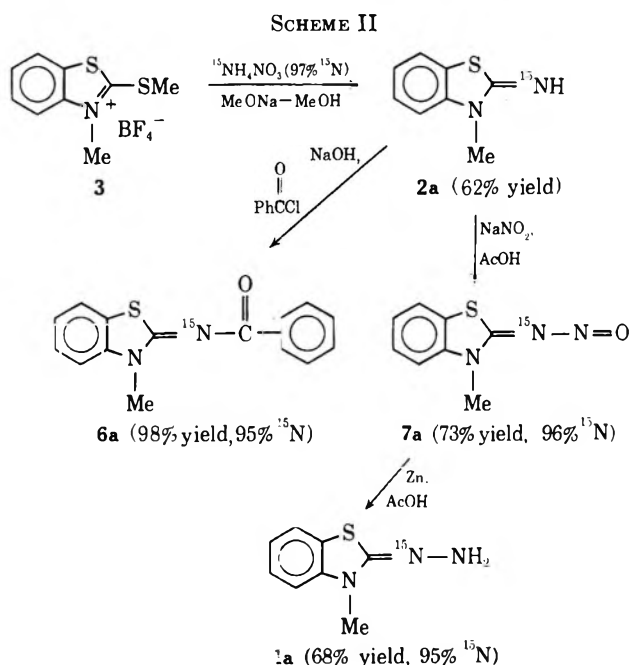
the imine 2a into the hydrazone 1a was accomplished by modification of the procedure of Besthorn.[9] The ^{15}N content of 1a, 6a, and 7a, as determined by mass spectrometry, demonstrates complete incorporation of the isotopic nitrogen label.

3-Methyl-2-benzothiazolinone Hydrazone-2-[15]N.— The synthesis of hydrazone 1b from 2-imino-3-methylbenzothiazoline is depicted in Scheme III. The

Scheme III
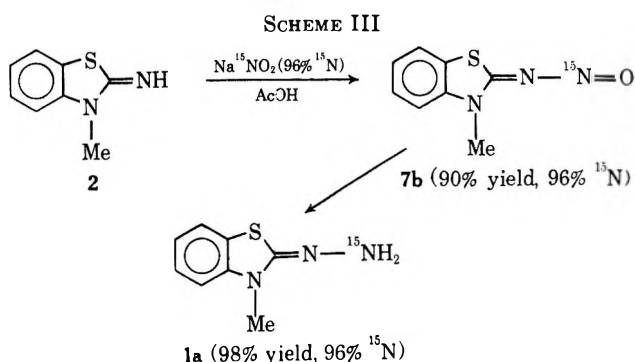
procedure of Besthorn for this conversion[9] was modified to achieve the highest yield of 7b from reaction of limited labeled ammonium nitrite. Again complete incorporation of the ^{15}N label was observed.

(9) E. Besthorn, *Chem. Ber.*, 43, 1519 (1910).

Infrared Spectral Investigations.—The availability of ^{15}N labeled derivatives of 1, 2, 6, and 7 encouraged careful study of the infrared spectra of corresponding labeled and unlabeled compounds.[10] The results of this investigation, which are presented in Tables II–V,

TABLE II

INFRARED ABSORPTION BAND SHIFTS^{a,b} FOR
2-IMINO-3-METHYLBENZOTHIAZOLINE (2) AND
2-IMINO-^{15}N-3-METHYLBENZOTHIAZOLINE (2a) IN THE REGIONS
3200–3400 AND 800–1700 CM^{-1}

Absorption maxima, cm^{-1}		Strength of ab-	$\Delta\nu(2-2a)$,	
2	2a	sorption^c	cm^{-1}	Assignment
3344	3338	w	6	NH stretch
1610	1602.5	s	7.5	C=N stretch
1590	1586	s	4	NH bend
1584	1579.5	s	4.5	NH bend

^{a} Measured in CH$_2$Cl$_2$ solution. ^{b} Shifts of 2 cm^{-1} or less are not reported. ^{c} w, weak; s, strong.

For 2-imino-3-methylbenzothiazoline (2), characteristic ketimine absorptions in the regions 3200–3260 (NH stretch) and 1600–1650 cm^{-1} (C=N stretch) might be anticipated.[11,12] For 2, the absorptions at 3344 (NH stretch) and 1610 cm^{-1} (C=N stretch) shift by 6 and 7.5 cm^{-1}, respectively, when a ^{15}N-labeled imino nitrogen is incorporated (Table II). For the gas-phase spectrum of ethyleneimine, the N–H stretch at 3346 cm^{-1} is displaced by 9 cm^{-1} in ^{15}N-ethyleneimine.[13] The bands at 1590 and 1584 cm^{-1}, which both shift by 4 cm^{-1} in 2a, are in the region (1500–1590 cm^{-1}) of N–H bending vibrations for imines.[14]

The absorption bands of 3-methyl-2-benzothiazolinone hydrazone 1 at 3358 and 1645 cm^{-1} may be assigned to N–H stretch and C=N stretch, respectively, on the basis of the frequency shifts observed for 1a and 1b (Table III). Although both symmetrical and asymmetrical N–H stretching vibrations might be anticipated, hydrazones only exhibit one absorption in the

TABLE III

INFRARED ABSORPTION BAND SHIFTS^{a,b} FOR 3-METHYL-2-BENZOTHIAZOLINONE HYDRAZONE (1)
3-METHYL-2-BENZOTHIAZOLINONE HYDRAZONE-1-^{15}N (1a) AND 3-METHYL-2-BENZOTHIAZOLINONE HYDRAZONE-2-^{15}N (1b)
IN THE REGIONS 3100–3550 AND 800–1700 CM^{-1}

Absorption maxima, cm^{-1}			Strength of	$\Delta\nu(1-1a)$,	$\Delta\nu(1-1b)$,	
1	1a	1b	absorption^c	cm^{-1}	cm^{-1}	Assignment
3358	3358	3348	vw	0	10	NH stretch
1645	1631	1646	s	14	-1	C=N stretch
1568	1565	1567	m	3	1	
1082.5	1077.5	1077	w	5	5.5	NN stretch
1021	1018	1020	w	3	1	

^{a} Measured in CH$_2$Cl$_2$ solution. ^{b} Shifts of 2 cm^{-1} or less are not reported. ^{c} vw, very weak; w, weak; m, medium; s, strong.

TABLE IV

INFRARED ABSORPTION BAND SHIFTS^{a,b} FOR 3-METHYL-2-NITROSIMINOBENZOTHIAZOLINE (7),
3-METHYL-2-(NITROSIMINO-$imino$-^{15}N)BENZOTHIAZOLINE (7a), AND 3-METHYL-2-(NITROSIMINO-$nitroso$-^{15}N)BENZOTHIAZOLINE (7b)
IN THE REGION 800–1700 CM^{-1}

Absorption maxima, cm^{-1}			Strength of	$\Delta\nu(7-7a)$,	$\Delta\nu(7-7b)$,	
7	7a	7b	absorption^c	cm^{-1}	cm^{-1}	Assignment
1556, 1548	1554	1548	w, b			
1436	1436	1429	s	0	7	N=O stretch
1405	1403	1396	s	2	6	N=O stretch
1063.5	1059	1060	m	4.5	3.5	NN stretch
1020.5	1015	1018	m	4.5	2.5	NN stretch
861.5	857.5	857	s	4	4.5	

^{a} Measured in CH$_2$Cl$_2$. ^{b} Shifts of 2 cm^{-1} or less are not reported. ^{c} w, weak; m, medium; s, strong; b, broad.

TABLE V

INFRARED ABSORPTION BAND SHIFTS^{a,b} FOR
N-(3-METHYL-2-BENZOTHIAZOLINYLIDENE)BENZAMIDE (6)
AND N-(3-METHYL-2-BENZOTHIAZOLINYLIDENE)BENZAMIDE-^{15}N
(6a) IN THE REGION 800–1700 CM^{-1}

Absorption maxima, cm^{-1}		Strength of ab-	$\Delta\nu(6-6a)$,	
6	6a	sorption^c	cm^{-1}	Assignment
1510	1505	s	5	C=N stretch
1456.5	1462	s	-3.5	
1367	1350	s	17	OC—N stretch
905	900	m	5	

^{a} Measured in CH$_2$Cl$_2$. ^{b} Shifts of 2 cm^{-1} or less are not reported. ^{c} m, medium; s, strong.

region.[15] The shifts noted in the absorption band at 1082.5 cm^{-1} of 1 for both 1a and 1b suggest that this band is an N–N stretching vibration. The N–N stretching mode of nitrosoamines occurs in this region.[16]

In the monomeric state, nitrosoamines exhibit infrared absorptions in the regions 1430–1530 (N=O stretch) and 925–1150 cm^{-1} (N–N stretch).[16] The infrared spectra of 2-nitrosoimino-3-methylbenzothiazoline (7) and its ^{15}N-labeled drivative (7a and 7b) (Table IV) indicate the presence of the two geometrical isomeric forms 8 and 9 for 7. The presence of two iso-

further support the specificity of the synthetic routes to 1a and 1b and allow for the identification of several absorption bands in the complex spectra of 1, 2, 6, and 7.

(10) For a recent summary of infrared spectra of ^{15}N-labeled compounds see S. Pinchas and I. Laulicht, "Infrared Spectra of Labelled Compounds," Academic Press, New York, N. Y., 1971, pp 216–237.

(11) P. L. Pickard and G. W. Polly, *J. Amer. Chem. Soc.*, **76**, 5169 (1954).

(12) C. J. Thoman and I. M. Hunsberger, *J. Org. Chem.*, **33**, 2852 (1968).

(13) R. W. Mitchell, J. C. Burr, Jr., and J. A. Merritt, *Spectrochim. Acta*, **23A**, 195 (1967).

(14) R. T. Conley, "Infrared Spectroscopy," Allyn and Bacon, Boston, Mass., 1966, p 135.

(15) L. A. Jones, J. C. Holmes, and R. B. Seligman, *Anal. Chem.*, **28**, 191 (1956).

(16) C. N. R. Rao and K. R. Bhaskar in "The Chemistry of the Nitro and Nitroso Group," Part 1, H. Feuer, Ed., Interscience, New York, N. Y., 1969, pp 144–147.

8   9

mers is inferred from the similar frequency shifts in the absorptions at 1436 and 1405 cm^{-1} (N=O stretch) when the nitroso nitrogen is labeled with ^{15}N and at 1063.5 and 1020.5 cm^{-1} (N–N stretch) when either the imino or the nitroso nitrogen of **7** is labeled. In the spectrum of N-methyl-p-nitrophenylnitrosoamine, single absorptions at 1466 (N=O stretch) and 942 cm^{-1} (N–N stretch) have been identified by ^{15}N labeling.[17] Evidence for geometrical isomerism of imino compounds[18] and alkoxydiazenium salts[19] has been obtained by pmr spectroscopy. However, the pmr spectrum of **7** in deuteriochloroform shows only a singlet for the 3-methyl group. The presence of only a single absorption indicates either that the distance between the anisotropic nitrosimino function and the N-methyl group is too great or that **8** and **9** are in rapid equilibrium relative to the pmr time scale so that an averaged signal is obtained. No infrared absorption which could be attributed to a C=N stretching vibration was evident in the spectrum of **7**.

On the basis of the observed shifts in the spectrum of N-(3-methyl-2-benzothiazolinylidene)benzamide (**6**), when the imino nitrogen is labeled with ^{15}N, the 1510- and 1367-cm^{-1} bands are assigned to C=N stretching and OC–N stretching modes, respectively. The OC–N stretching band of dimethylformamide is displaced from 1383 to 1370 cm^{-1} in ^{15}N-dimethylformamide.[20]

Experimental Section

General.—Melting points are uncorrected. Infrared spectra were measured in methylene chloride solution (0.12–0.17 g/ml) with a Beckman IR-12 infrared spectrophotometer. Mass spectrometric analysis was performed using low ionization voltages (8–18 eV).

2-Imino-^{15}N-3-methylbenzothiazoline (2a).—To 0.34 g (4.2 mmol, 97% ^{15}N, Isocommerz, Berlin, DDR) of ^{15}NH$_4$NO$_3$ dissolved in 40 ml of MeOH was added 8.0 ml of 1.04 M MeONa–

MeOH. During 2 hr, a solution of 1.13 g (4.0 mmol) of 2-methylmercapto-3-methylbenzothiazolium fluoroborate[4] (**3**) in 160 ml of MeOH was added. After 5 days the reaction solution was evaporated *in vacuo*. Recrystallization of the residue from cyclohexane gave 0.38 g (56%) of crude **2a**, mp 105–115° (reported[9] mp 123°), which was used without further purification.

N-(3-Methyl-2-benzothiazolinylidene)benzamide-^{15}N (6a).—As in the synthesis of **2a**, 0.085 g (1.05 mmol) of ^{15}NH$_4$NO$_3$ in 10 ml of MeOH, 2.0 ml of 1.04 M MeONa–MeOH, and 0.28 g (1.00 mmol) of **3** were combined. After 4 days, the reaction solution was evaporated *in vacuo*. To the residue was added 50 ml of H$_2$O, 2 g of NaOH, and 0.5 ml of benzoyl chloride. After vigorous shaking, the mixture was placed in a refrigerator overnight. The precipitate was filtered, washed with H$_2$O and dissolved in hot AcOH, and slowly reprecipitated with H$_2$O. Filtration, washing with H$_2$O, and drying the resulting **6a** *in vacuo* yielded 0.18 g (62%), mp 149–150° (reported[21] mp 155°).

3-Methyl-2-(nitrosimino-*imino*-^{15}N)benzothiazoline (7a).—During 15 min, a solution of 0.17 g (2.5 mmol) of NaNO$_2$ in 1.5 ml of H$_2$O was added dropwise to a stirred solution of 0.24 g (1.5 mmol) of **2a** in 2 ml of AcOH at room temperature. After 1.5 hr, 20 ml of H$_2$O was added and the mixture was stirred for several hours. The orange precipitate was filtered, washed with H$_2$O, and dried *in vacuo*, producing 0.20 g (73%) of **7a**, mp 149° dec (reported[9] mp 147° dec).

3-Methyl-2-benzothiazolinone Hydrazone-*1*-^{15}N (1a).—To a stirred mixture of 0.18 g (0.93 mmol) of **7a** and 5 ml of 90% AcOH cooled to 0° was added 0.41 g (6.2 mg-atoms) of zinc dust in small portions during 1 hr. After an additional 1 hr, the excess zinc dust was removed by filtration. The filtrate was cooled to 0° and the hydrazone **1a** was precipitated by addition of concentrated NH$_4$OH. The precipitate was filtered and dried *in vacuo*, yielding 0.11 g (68%) of crude **1a**, with mp 133–135°. Three recrystallizations from benzene gave **1a**, mp 142–143° (reported[9] mp 143°).

3-Methyl-2(nitrosimino-*nitroso*-^{15}N)benzothiazoline (7b).—Using the procedure described for **7a**, 0.36 g (5.2 mmol) of Na^{15}NO$_2$ (96% ^{15}N, Isocommerz, Berlin, DDR) in 5 ml of H$_2$O and 1.08 g (6.6 mmol) of **1** in 4 ml of AcOH were combined. The orange **7b** weighed 0.90 g (90%) and had mp 147.5° dec (reported[9] mp 147° dec).

3-Methyl-2-benzothiazolinone Hydrazone-*2*^{15}N (1b).—The synthetic method reported for **1a** was used to treat 0.48 g (2.5 mmol) of **7b** in 15 ml of 90% AcOH with 1.22 g (18.7 mg-atoms) of zinc dust. The crude **1b** (0.36 g, 80% yield) had mp 140–141° (reported[9] mp 143°).

(17) R. Kuebler, and W. Luettke, *Ber. Bunsenges. Phys. Chem.* **67**, 2 (1963).

(18) M. Raban and E. Carlson, *J. Amer. Chem. Soc.*, **93**, 685 (1971), and references cited therein.

(19) S. Hünig, G. Büttner, J. Cramer, L. Geldern, H. Hansen, and E. Lücke, *Chem. Ber.*, **102**, 2093 (1969).

(20) E. W. Randall, C. M. S. Yoder, and J. J. Zucherman, *Inorg. Chem.* **5**, 2240 (1966).

(21) S. Hünig, and H. Quast, *Justus Liebigs Ann. Chem.*, **711**, 139 (1968).

Some Aspects of the Selective Acetylation of Methylhydrazine. 1-Acetyl-1-methyl- and 1-Acetyl-2-methylhydrazine

F. E. CONDON

Department of Chemistry, The City College of the City University of New York, New York, New York   10031

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The selective acetylation of methylhydrazine—with acetic anhydride to give chiefly 1-acetyl-1-methylhydrazine (1) and with ethyl acetate to give chiefly 1-acetyl-2-methylhydrazine (2)—was studied, with nmr spectroscopy as the method of analysis. The ratio, 1/2, was found to be ~0.30 with ethyl acetate as acetylating agent, ~38 with acetic anhydride in pyridine or triethylamine as solvent, and >100 with acetic anhydride in acetic acid. The ratios result from kinetic control. The equilibrium ratio, 1/2, was found to be 0.39 at 27° and 0.49 at 87°, from which ΔH^0 = 785 ± 40 cal/mol and ΔS^0 = 0.75 ± 0.6 cal/deg mol for the process 2 → 1. The isomerization is ~$^1/_6$ as fast as the acetylation of methylhydrazine with ethyl acetate at 80-90°. Isomer 2 is ~1.5 times as rapidly acetylated as 1 with acetic anhydride to give 1,2-diacetyl-1-methylhydrazine, and, judging from the compositions of reaction mixtures, 1 and 2 appeared to be <$^1/_{50}$ as reactive as methylhydrazine toward ethyl acetate and ~$^1/_5$ as reactive toward acetic anhydride. The acetylation of methylhydrazine with ethyl acetate is acid catalyzed, with ethanol, water, and acetic acid being increasingly effective in that order. The results are rationalized in terms of a difference in mechanisms, with the anhydride reacting by nucleophilic displacement of the BAc2 type and the ester by an addition–elimination mechanism. The isomers 1 (mp 16°) and 2 (mp 42°) were isolated and characterized.

Hinman and Fulton[1a] have shown and Theuer and Moore confirmed[1b] that the acylation of methylhydrazine with acid anhydrides produces chiefly 1-acyl-1-methylhydrazines, while acylation with esters gives chiefly 1-acyl-2-methylhydrazines. The phenomenon cannot be reconciled with the reactivity–selectivity principle—the less reactive a reagent, the more selective it is between a pair of substrates or sites within a given substrate.[2] Given that an anhydride shows preference for the methylated nitrogen of methylhydrazine, the principle would lead one to expect an even greater preference for that same nitrogen to be shown by the less active esters, or, given that an ester shows preference for the nonmethylated nitrogen, one would expect the anhydrides to show a lesser preference for that nitrogen or, at most, no selectivity at all between the two nitrogens. The complementary specificities exhibited by the two classes of reagents toward methylhydrazine is uncommon in its clarity and in the simplicity of the substances involved and resembles that found in biological systems.

In this paper are presented some results of further study of the selective acylation of methylhydrazine in which ethyl acetate and acetic anhydride were the acylating agents and nmr spectroscopy was used extensively in examination and analysis of reaction mixtures. This work had two objectives: (i) to acquire some understanding of the phenomenon of selective acylation; and (ii) to use the selective acylation as a means of preparing the two isomers, 1-acetyl-1-methylhydrazine (1) and 1-acetyl-2-methylhydrazine (2) in a high enough state of purity for use as intermediates in syntheses of 1-ethyl-2-methylhydrazine as shown in eq 1 and 2. These isomers had not yet been isolated and characterized.[3]

Isomer 1 was isolated in high yield and purity and was then shown to be a useful intermediate for synthesis of not only 1-ethyl-2-methylhydrazine but also many

$$MeNHNH_2 \xrightarrow{Ac_2O} MeNAcNH_2 \xrightarrow{CH_3CHO}$$
$$1$$
$$MeNAcN{=}CHCH_3 \xrightarrow{NaBH_4} MeNAcNHCH_2CH_3 \xrightarrow{H_2O,\ HCl}$$
$$MeNHNHEt \cdot 2HCl \quad (1)$$

$$MeNHNH_2 \xrightarrow{EtOAc} MeNHNHAc \xrightarrow{LiAlH_4} MeNHNHEt \quad (2)$$
$$2$$

$$1 \xrightarrow{R_1R_2CO} MeNAcN{=}CR_1R_2 \xrightarrow{NaBH_4}$$
$$MeNAcNHCHR_1R_2 \xrightarrow{H_2O,\ etc.} MeNHNHCHR_1R_2 \quad (3)$$
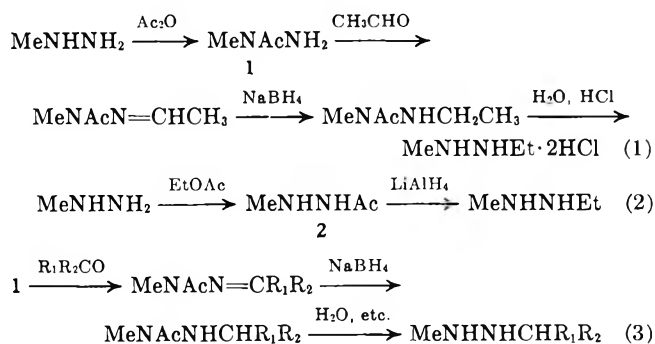
other 1-alkyl-2-methylhydrazines as shown in eq 3. Isomer 2 was also isolated and characterized, but it was almost wholly converted to methylhydrazine by reaction with lithium aluminum hydride, ~10% being reduced in accordance with eq 2. That work is described in another paper, this one being limited to the acetylation reaction, the first step in eq 1 and 2.

Results

Acetylation of Methylhydrazine.—In Table I are presented results of acetylation of methylhydrazine with ethyl acetate and with acetic anhydride under various conditions. Product compositions are based on analysis of fractions from distillation, by means of nmr spectroscopy. The isomers, 1 and 2, were easily distinguished by means of their N-methyl peaks, which came at ~3.2 ppm downfield for 1 and at 2.56 ppm for 2. A diacetylmethylhydrazine, presumably 1,2-diacetyl-1-methylhydrazine,[4] which was not reported by Hinman and Fulton,[1a] was always found as a residue from distillation of the acetylation products under reduced pressure. Its boiling point was so much higher than those of the monoacetyl derivatives that a fairly sharp separation was possible by distillation. Small amounts of it were detectable by nmr in the last volatile fraction and could be accounted for by use of its singlets at 2.01, 2.04, and 3.07 ppm.

Table I is concerned with the influences of choice of acetylating agent (ethyl acetate or acetic anhydride) and, in the case of acetic anhydride, of solvent and method of work-up on two observables: the selectivity

(1) (a) R. L. Hinman and D. Fulton, *J. Amer. Chem. Soc.*, **80**, 1895 (1958); (b) W. J. Theuer and J. A. Moore, *J. Org. Chem.*, **29**, 3734 (1964).

(2) (a) L. M. Stock and H. C. Brown, *J. Amer. Chem. Soc.*, **81**, 3323 (1959), and references cited therein; (b) F. E. Condon and H. Meislich, "Introduction to Organic Chemistry," Holt, Rinehart and Winston, Inc., New York, N. Y., 1960, pp 51–52.

(3) *Chemical Abstracts* through 1970 was searched under the heading, "Hydrazine, acetyl-methyl."

(4) A. Michaelis and E. Hadanck, *Ber.*, **41**, 3285 (1908).

TABLE I
INFLUENCES OF SOLVENT AND ACETYLATING AGENT ON RESULTS OF ACETYLATION OF METHYLHYDRAZINE

Run no.	1	2	3	4	5	6	7	8	9	10
Scale, mol of MeNHNH2	1.025	1.11	0.99	0.49	1.00	0.695	1.00	4.00	2.42	1.00
Solvent		——EtOAc[a]–H2O——			HOAc		——Pyridine——			Et3N[b]
Solvent, mol[c]	1.19/0.1	1.35/0.06	1.26/0.05	1.27/0.06	1.01	1.23	1.33	1.20	1.20	1.20
Ac2O, mol[c]					1.00	1.00	1.00	1.00	1.00	1.00
Temperature, °C	80–90[d]	78–87[e]	80–90[f]	80–90[f]	10–15	10–20	30–40	10–15	15–20	15–20
Extractive[g,h]					py	Ether	Ether	py	py	ch
Product, mol[c,i]										
MeNHNH2	0.115	0.020	0.180	0.163	0.109	0.104	0.070	0.0650	0.014	0.013
MeNAcNH2, 1	0.176	0.213	0.170	0.517[j]	0.529	0.430	0.255	0.6550	0.814	0.677
MeNHNHAc, 2	0.620	0.656	0.592	0.736	0.005	0.011	0.0055	0.0156	0.027	0.020
MeNAcNHAc	0.023	0.042	0.018	0.020	0.164	0.115	0.066	0.065[k]	0.049	0.022
Loss	0.066	0.069	0.040	0.074	0.193	0.340	0.6035	0.1994	0.096	0.268
MeNAcNH2/MeNHNHAc	0.28	0.32[l]	0.29		~100	39	46	42	30	34
k/k'[m]	51	62	46		4.9	5 1	4.8	(18.5)[n]	(58)[n]	~100

[a] Solvent and acetylating agent. [b] Heterogeneous reaction mixture. [c] Basis: 1 mol of methylhydrazine. [d] 50 hr of refluxing. [e] 141 hr of refluxing, followed by 6 months at room temperature. [f] 68 hr of refluxing. [g] For the solid NaOAc·3H2O produced by neutralization of by-product HOAc with 50% NaOH. [h] py, pyridine; ch, chloroform. [i] Based on nmr analysis of fractions from distillation. [j] In this run, 0.51 mol of MeNAcNH2 (per mole of MeNHNH2) was introduced at the start to determine the extent of its isomerization under acetylating conditions. [k] Approximate value equated to recovered MeNHNH2. [l] There may have been some rearrangement of MeNHNHAc to MeNAcNH2 as the reaction mixture stood for 6 months at room temperature before work-up. [m] Indicated ratio of specific rates of acetylation of methylhydrazine and acetylmethylhydrazine. [n] Unreliable because of loss of methylhydrazine during work-up.

between the two positions in methylhydrazine, as measured by the isomer ratio, MeNAcNH2/MeNHNHAc, and the selectivity between methylhydrazine and acetylmethylhydrazine, as measured by the ratio of specific rate constants, k/k', presented in the last row of the table. For the latter, the system is regarded as an instance of competing consecutive second-order reactions, as in eq 4, where AcX stands for the acetylating

$$\text{MeNHNH}_2 \xrightarrow{\text{AcX}}_{k} \begin{bmatrix} \text{MeNAcNH}_2 \\ \text{MeNHNHAc} \end{bmatrix} \xrightarrow{\text{AcX}}_{k'} \text{MeNAcNHAc} \quad (4)$$
$$\text{A} \qquad\qquad\quad \text{B} \qquad\qquad \text{C}$$
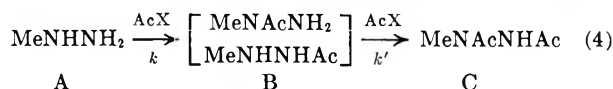
agent and k and k' are second-order rate constants. The ratio, k/k', was computed from the data by use of eq 5,[5] in which A and B stand for the mole fractions of

$$\frac{k'}{k} \log A = \log\left(A + B - \frac{k'}{k}B\right) \quad (5)$$

methylhydrazine and acetylmethylhydrazine, respectively, in a particular product.[6]

In runs 1–3, with ethyl acetate as acetylating agent, fairly consistent values for the two aforementioned ratios were obtained. The isomer ratio, 1/2, averaged 0.30 ± 0.02 in the three runs, and this result is similar to the findings of Hinman and Fulton with *methyl* acetate.[1a] An average of 53 ± 6 was obtained for the ratio of k/k'.

In runs with acetic anhydride as acylating agent, it was found that the products underwent marked changes in composition if left overnight at room temperature or if distilled without prior removal of the acetic acid by-product, apparently as a result of catalysis by the

acid. In runs 6–10, in which pyridine or triethylamine was used as a solvent, the acetic acid was neutralized with concentrated sodium hydroxide, and ether, pyridine, or chloroform was used as an extractive for the solid sodium acetate trihydrate produced. Fairly consistent values for the isomer ratio, 1/2, in the range of 30–46, were obtained. In run 5, in which acetylation was carried out in acetic acid as solvent, the acetic acid was neutralized with sodium hydroxide and the extractive was pyridine, an isomer ratio of >100 was obtained. In other runs not shown, in which reaction mixtures were distilled without treatment with sodium hydroxide, or in which neutralization of the acetic acid was incomplete, much lower values of the isomer ratio were obtained as a result of isomerization of 1 to 2 during work-up. Such results could not be used, of course, as a measure of the selectivity of acetic anhydride toward the two nitrogens of methylhydrazine. From the data shown the selectivity appears to be 38 ± 5 in favor of the methylated nitrogen in the presence of pyridine or triethylamine and >100 when the acetylation is done in excess acetic acid.

For the selectivity of acetic anhydride for methylhydrazine over acetylmethylhydrazine, k/k', the most reliable value seems to be 5.0 ± 0.2, regardless of whether the acetylation is carried out in pyridine or acetic acid (runs 5–7). In triethylamine, however, the selectivity was much higher, approaching 100. Here the reaction mixture consisted of two phases, and there may have been a favorable partitioning of the components between the two phases.

Further theoretical discussion of the anomalous results with acetic acid and triethylamine seems premature at this time. The data are sparse and in need of verification and amplification.

From a practical point of view, however, acetylation of methylhydrazine with acetic anhydride provided isomer 1 of 99% purity in 46% yield (acetylation in acetic acid, run 5) or of 96% purity in 76% yield (ace-

(5) F. E. Condon, *J. Amer. Chem. Soc.*, **70**, 2053 (1948).

(6) (a) Although the amount of methylhydrazine used in the several runs varied from 0.49 mol (run 4) to 4 mol (run 8), product compositions have been reduced to a common charge of 1.00 mol for presentation in Table I, to facilitate comparison of the several results. (b) For the purpose of eq 5, each product composition was necessarily converted to a "no-loss" basis by dividing the number of moles of each component by the total number of moles of methylhydrazine and its derivatives found in that product.

TABLE II

COMPETITIVE ACETYLATION OF 1-ACETYL-1-METHYLHYDRAZINE AND 1-ACETYL-2-METHYLHYDRAZINE

Ac_2O, portions added	0	1	2	3	4	5	6
Nmr peak areas[a]							
$MeNAcNH_2$ + MeNAcNHAc	57.0 $(n_1{}^0)$	60.0	63.5	69.2	76.6	78.0	80.8
MeNHNHAc, n_2	43.0 $(n_2{}^0)$	40.0	36.5	30.8	23.4	22.0	19.2
MeNHNHAc, decrease		3.0	6.5	12.2	19.6	21.0	23.8
Total $-COCH_3$	106.0	117.5	132.2	156.5	184.0	188.4	196.0
Total $-COCH_3$, increase		11.5	26.2	50.5	78.0	82.4	90.0
$-COCH_3$ increase, less HOAc		5.7	13.1	25.2	39.0	41.2	45.0
$-COCH_3$ above, less decrease in MeNHNHAc		2.7	6.6	13.0	19.4	20.2	21.2
Net $MeNAcNH_2$, n_1	57.0 $(n_1{}^0)$	54.3	50.4	44.0	37.6	36.8	35.8
$n_2/n_2{}^0$		0.930	0.848	0.716	0.544	0.511	0.446
$n_1/n_1{}^0$		0.953	0.884	0.772	0.660	0.645	0.628
$-\text{Log } n_2/n_2{}^0$ ($\log_2$)		0.0315	0.0715	0.145	0.265	0.292	0.351
$-\text{Log } n_1/n_1{}^0$ ($\log_1$)		0.0210	0.0535	0.112	0.181	0.190	0.202
k_2/k_1 ($\log_2/\log_1$)		1.50	1.34	1.30	1.46	1.54	1.74

Average 1.48 ± 0.11

[a] Basis: $MeNAcNH_2$ + MeNAcNHAc + MeNHNHAc = 100.

tylation in pyridine, run 9).[7]   Furthermore, it seems likely the yields could be improved by a more thorough extraction of the solid sodium acetate trihydrate than was achieved in the runs described in the table.

Isomer **2** of 96% purity was obtained in 28% yield by crystallization from the product of acetylation with ethyl acetate. The melting points of **1** and **2** were 16° and 42°, respectively, which are in accord with a generalization made by Hinman and Fulton.[1a]

Competitive Acetylation of 1 and 2.—It was of interest to determine the relative reactivities of **1** and **2** toward acetic anhydride, as it was possible that the high isomer ratio, 1/2, obtained with this reagent was a consequence of strongly selective further acetylation of **2** to 1,2-diacetyl-1-methylhydrazine. A mixture of the two isomers was therefore treated in an nmr sample tube with successive small portions of acetic anhydride, and changes in the composition of the mixture were determined by means of nmr. Data and results are presented in Table II, and further procedural details are given in the Experimental Section.

The ratio of reactivities, k_2/k_1, was calculated as a ratio of logarithms as shown in Table II, in accordance with the theory for competing reactions, first order in acetylating agent and first order in acetylmethylhydrazine.[5] The nearly constant value for the ratio throughout the course of the experiment indicates that **2** is only ~1.5 times as rapidly acetylated as **1**, and this cannot be an important cause of the high ratio of 1/2 in the products of acetylation with acetic anhydride. It is noteworthy, however, that in its reaction with the mixture of acetylmethylhydrazines, as in its reaction with methylhydrazine, acetic anhydride prefers the methylated (more nucleophilic) nitrogen.

Acid Catalysis.—In monitoring by nmr the reaction between methylhydrazine and ethyl acetate, an initial slow period was observed, which was suggestive of acid catalysis by the ethanol produced as a by-product. The acid catalysis was confirmed strikingly in parallel runs made in nmr sample tubes heated in an oil bath, in which the rates with added ethanol, with water, and with acetic acid were compared with the rate with no

additive. The results are presented in Figure 1. Ethanol, water, and acetic acid were increasingly effective in that order, which is the order of increasing acidity.

Tests for Thermodynamic Control.—The possibility was considered that the difference in the results with anhydrides and esters is a consequence of kinetic vis-à-vis thermodynamic control. The reaction with an anhydride is very fast at ambient temperatures and gives a ratio, 1/2, that is much different from the isomerization equilibrium ratio (see below). The result is very likely one of kinetic control. The reaction with an ester, however, requires prolonged heating at the boiling point of the mixture, and it seemed possible that under these conditions a first-formed 1-acyl-1-methylhydrazine might undergo rearrangement to a more stable 1-acyl-2-methylhydrazine to give a result thermodynamically controlled.

To test for thermodynamic control, the stability of **1** under acetylating conditions leading mainly to **2** (boiling ethanol–ethyl acetate, 87°) was determined. No rearrangement of **1** to **2** was observed after 71 hr of heating with ethyl acetate. Upon addition of ethanol, then water, and then acetic acid to the same mixture, each addition being followed by periods of heating and examination by nmr spectroscopy, a very slow acid-catalyzed rearrangement, accompanied by a similar amount of acetylation (by acetic acid) to 1,2-diacetyl-1-methylhydrazine, was observed. The data are not presented in detail because of a more cogent experiment, presented as run 4 in Table I.

In run 4, Table I, methylhydrazine was acetylated with ethyl acetate in the presence of much added **1**. The results should be compared with those of run 3, made under essentially the same conditions, but without added **1**. In both runs, ~80% (0.8 mol) of the methylhydrazine was acetylated. In run 4, however, there was almost no *net* production of **1**, whereas comparison with run 3 indicates ~0.2 mol must have been produced. About 0.2 mol of **1**, 40% of that originally present, must have isomerized to **2**.

The reactions may be treated as first order, since the ethyl acetate was present in excess. Applying the first-order rate law to the data in the preceding paragraph leads to the conclusion that the specific rate of

(7) These practical yields are a little lower than what is indicated by the data in Table I because the data in the table include the **1** and **2** contained in other fractions from the distillation.
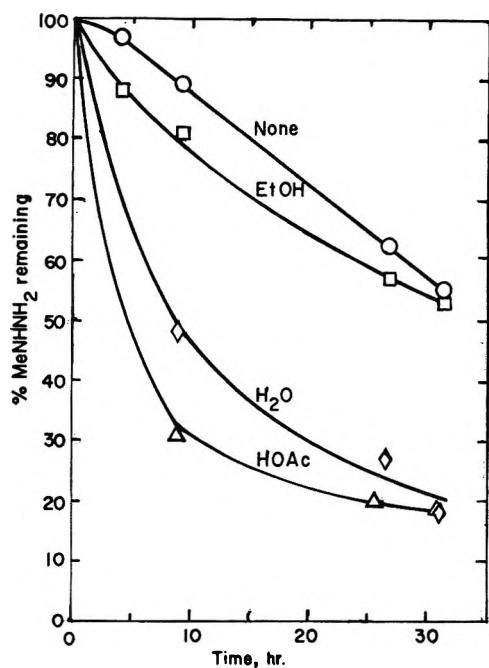
Figure 1.—Brønsted acid catalysis of the acetylation of methylhydrazine with ethyl acetate at 82°.
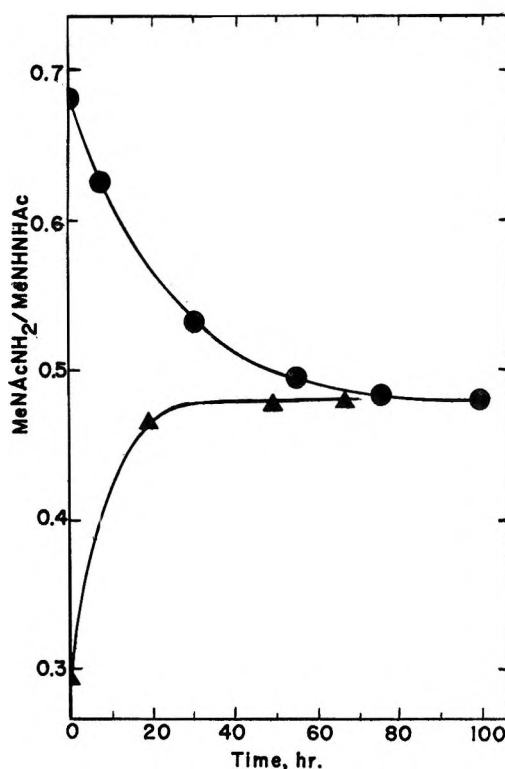
isomerization of **1** to **2** is about $^1/_3$ the specific rate of acetylation of methylhydrazine with ethyl acetate. Below it is shown that the equilibrium ratio, **1/2**, at 87° is 0.49, which is larger than the ratio, 0.30, obtained from the reaction with ethyl acetate, If anything, therefore, the acetylation with ethyl acetate must be accompanied by isomerization of **2** to **1**, rather than the reverse. From the equilibrium ratio it is clear that the rate of isomerization of **2** to **1** is $\sim^1/_2$ the rate of isomerization of **1** to **2**, or $\sim^1/_6$ the rate of acetylation of methylhydrazine with ethyl acetate. The latter reaction is therefore predominantly a kinetically controlled process.[8]

Equilibrium between 1 and 2.—For the analysis in the foregoing section, it was necessary to know the equilibrium ratio, **1/2**. This was determined at two temperatures, 27 and 87°, to permit calculation of the thermodynamic functions, ΔH^0 and ΔS^0. Mixtures of the two isomers with 10–20 mol % of acetic acid in nmr sample tubes were kept at the appropriate temperature and examined by nmr from time to time, until the ratio of **1/2**, became constant. The isomerization was accompanied by a relatively rapid disproportionation of 10–20% of the material to methylhydrazine (present in part as the acetate) and 1,2-diacetyl-1-methylhydrazine, and by some further acetylation to 1,2-diacetyl-1-methylhydrazine, Typical data are presented in Figure 2, and the results in Table III.

Discussion

The failure of esters and anhydrides to obey the reactivity-selectivity principle in their reactions with methylhydrazine may be a consequence of a difference in mechanism. A nucleophilic displacement of the $B_{AC}2$ type would be expected to occur with anhy-

(8) Further evidence is available from monitoring the reaction by nmr. The ratio, **1/2**, is seen to be ~0.3 right from the start. Both **1** and **2** are primary products, therefore.

Figure 2.—Equilibration of 1-acetyl-1- and 1-acetyl-2-methylhydrazine with acetic acid in ethanol at 87°.

TABLE III

THE EQUILIBRIUM, $MeNHNHAc$ (2) $\rightleftharpoons$ $MeNAcNH_2$ (1)

Temp, °C	27	87
K, 1/2	0.39 ± 0.02	0.49 ± 0.01
ΔG^0, cal/mol (liquid)	560 ± 30	512 ± 15
ΔH^0, cal/mol	785 ± 40	
ΔS^0, cal/deg mol	0.75 ± 0.6	

drides,[9] while an addition–elimination mechanism, like that proposed for ester and amide hydrolyses,[10] would be expected with esters. Application of these ideas to be present study may be made clear by reference to eq 6 and 7 and Figures 3 and 4.

Both reactions may be initiated by nucleophilic attack by either nitrogen on the carbon of the carbonyl group to give the dipolar ions IA and IB (from acetic anhydride) or IIA-1 and IIB-1 (from ethyl acetate). The reaction with acetic anhydride is very fast, even at subambient temperatures, and is also sensibly exergonic, as cooling with ice is necessary to control the temperature. A reasonable estimate for its activation free energy, ΔG^*, would be not much more than 15 kcal/mol, and a reasonable estimate for ΔH and ΔG would be -15 kcal/mol. From the product ratio, 1/2, of 38, a difference in activation free energies, $\Delta\Delta G^*$, of 2.2 kcal at 27° can be calculated ($2.303RT$ log 38). The dipolar ions IA and IB shed an acetate ion readily and go on by way of proton transfers to form products having a free-energy difference of 560 cal at 27°. These energy relationships are depicted in Figure 3.

The fact that the less stable product is formed the

(9) (a) V. Gold, *Trans. Faraday Soc.*, **44**, 506 (1948); (b) E. Berliner and L. H. Altschul, *J. Amer. Chem. Soc.*, **74**, 4110 (1952); (c) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p 754.

(10) (a) M. L. Bender, *J. Amer. Chem. Soc.*, **73**, 1626 (1950); (b) M. L. Bender and R. D. Ginger, *ibid.*, **77**, 348 (1955).

MeNHNH$_2$ + Ac$_2$O $\longrightarrow$

$$\left\{ \begin{array}{l} \text{IA} \\ \\ \text{IB} \end{array} \right.$$

IA: $\underset{\text{H}_2\text{N}}{\overset{\text{Me}}{\diagdown}}\overset{+}{\text{N}}\text{HC}\underset{\text{CH}_3}{\overset{\text{OAc}}{\diagup}}\text{O}^- \longrightarrow \longrightarrow \text{MeNAcNH}_2 + \text{HOAc}$

IB: $\underset{}{\overset{\text{Me}}{\diagdown}}\overset{+}{\text{N}}\text{HNH}_2\text{C}\underset{\text{CH}_3}{\overset{\text{OAc}}{\diagup}}\text{O}^- \longrightarrow \longrightarrow \text{MeNHNHAc} + \text{HOAc}$

(6)

MeNHNH$_2$ + EtOAc $\longrightarrow$

IIA-1: $\underset{\text{H}_2\text{N}}{\overset{\text{Me}}{\diagdown}}\overset{+}{\text{N}}\text{HC}\underset{\text{CH}_3}{\overset{\text{OEt}}{\diagup}}\text{O}^-$ $\longrightarrow$ IIA-2: $\underset{\text{H}_2\text{N}}{\overset{\text{Me}}{\diagdown}}\text{N}-\text{C}\underset{\text{CH}_3}{\overset{\text{OEt}}{\diagup}}\text{OH}$ $\longrightarrow$ IIA-3: $\underset{\text{H}_2\text{N}}{\overset{\text{Me}}{\diagdown}}\text{N}-\text{C}\underset{\text{CH}_3}{\overset{\overset{+}{\text{HOEt}}}{\diagup}}\text{O}^-$ $\longrightarrow$ 1 + EtOH

IIB-1: $\underset{}{\overset{\text{Me}}{\diagdown}}\overset{+}{\text{N}}\text{HNH}_2\text{C}\underset{\text{CH}_3}{\overset{\text{OEt}}{\diagup}}\text{O}^-$ $\longrightarrow$ IIB-2: $\underset{}{\overset{\text{Me}}{\diagdown}}\text{NHNHC}\underset{\text{CH}_3}{\overset{\text{OEt}}{\diagup}}\text{OH}$ $\longrightarrow$ IIB-3: $\underset{}{\overset{\text{Me}}{\diagdown}}\text{NHNHC}\underset{\text{CH}_3}{\overset{\overset{+}{\text{HOEt}}}{\diagup}}\text{O}^-$ $\longrightarrow$ 2 + EtOH

(7)
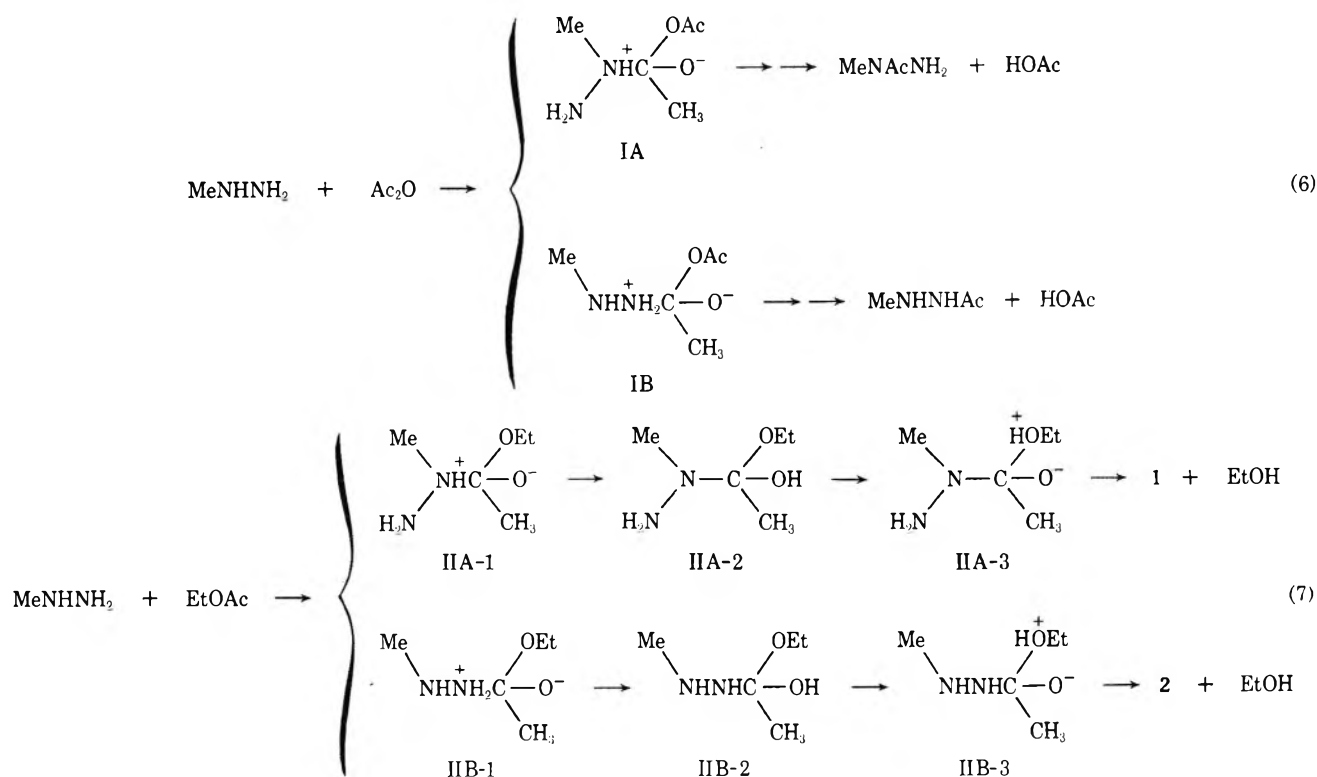
most rapidly is a consequence of the greater nucleophilicity of the methylated nitrogen, which is observed also in the reactions of alkylhydrazines with alkyl halides.[11] The dipolar ions IA and IB differ essentially only in having a methyl replacing hydrogen on a positively charged nitrogen. From earlier work,[12] the inductive effect of a methyl replacing hydrogen in stabilizing an ammonium ion can be calculated. It is a factor of 46, or 2.3 kcal at 27°, *almost precisely the same as is indicated by the results here with acetic anhydride!*

The reaction with ethyl acetate, by comparison, is slow, even at elevated temperatures (87°) and is not sensibly exergonic. In no case was the reaction observed to go to completion, even in a reaction mixture that stood at room temperature for 6 months (run 2). A nearly isergonic reaction is indicated, and a reasonable estimate for the activation free energy would be not much less than 25 kcal/mol.

The activation energy barriers leading to IIA-1 and IIB-1 may not be much different from those leading to IA and IB. In both cases, A and B differ essentially in having a methyl replacing hydrogen on a positively charged nitrogen, and the same stabilizing inductive effect would be expected. The dipolar ions, IIA-1 and IIB-1, do not readily shed an ethoxide ion, however, but find it easier to revert to starting materials by shedding the weaker base, methylhydrazine. They may, however, be converted by tautomerization into the addition products, IIA-2 and IIB-2, and thence into the new dipolar ions, IIA-3 and IIB-3, which can readily shed an alcohol molecule to give the final products.

The dipolar ions, IIA-3 and IIB-3, with protonated

ether-type oxygen, must certainly be higher in energy than the dipolar ions, IIA-1 and IIB-1, with protonated amine-type nitrogen. An energy difference of 13 kcal/mol, which corresponds to a ΔpK of $\sim$8 at 87°, is not unreasonable. The nonpolar intermediates, IIA-2 and IIB-2, must be lower in energy than either of the dipolar forms but, to remain undetected, must be much richer in energy (10 kcal?) than the starting materials. These energy relationships are depicted in Figure 4.

The ester reaction, then, involves a relatively rapid establishment of equilibrium between the starting materials and the intermediate addition products, IIA-2 and IIB-2, followed by slow conversion of these to the products at equal rates. The product ratio is determined by the relative stabilities of the intermediates, which are similar to, but not identical with, the products. The product ratio, 0.3, ignoring possible isomerization of 2 to 1 during acetylation, corresponds to an energy difference of 860 cal at 87°. It is probable that steric factors determine the relative stabilities, for 1 and IIA-2, with two bulky substituents on the same nitrogen, are more crowded molecules than 2 and IIB-2.

The acid catalysis observed with the ester reaction is presumably a consequence of an acid's aiding in protonation to form the intermediates, IIA-3 and IIB-3. It should be obvious, furthermore, that the reaction could be discussed in terms of intermediates differing by a proton from those used here. They would simply have to be drawn on another energy profile, similar to the one used here.

An intermediate like IIA-3 and IIB-3 has been implicated in the aminolysis of esters in aqueous solution,[13] and seems particularly likely in the case of methyl formate at low pH.[14] These and other extensive studies of the kinetics of aminolysis in aqueous solution[15] are

(11) (a) M. J. Gregory and T. C. Bruice, *J. Amer. Chem. Soc.*, **89**, 4400 (1967); (b) R. A. Hasty and S. L. Sutter, *J. Phys. Chem.*, **73**, 3154 (1969); (c) H. H. Sisler, G. M. Omietamski, and B. Rudner, *Chem. Rev.*, **57**, 1021 (1957), and references therein.

(12) F. E. Condon, *J. Amer. Chem. Soc.*, **87**, 4485 (1965). In the absence of hydration, $\Delta pK_2 = 3.38\Delta\sigma^*$ for ammonium ions, and $\Delta\sigma^* = 0.49$ for methyl and hydrogen.

(13) W. P. Jencks and M. Gilchrist, *J. Amer. Chem. Soc.*, **90**, 2622 (1968).

(14) G. M. Blackburn and W. P. Jencks, *ibid.*, **90**, 2638 (1968).

(15) T. C. Bruice, A. Donzel, R. W. Huffman, and A. R. Butler, *ibid.*, **89**, 2106 (1967), and references therein.
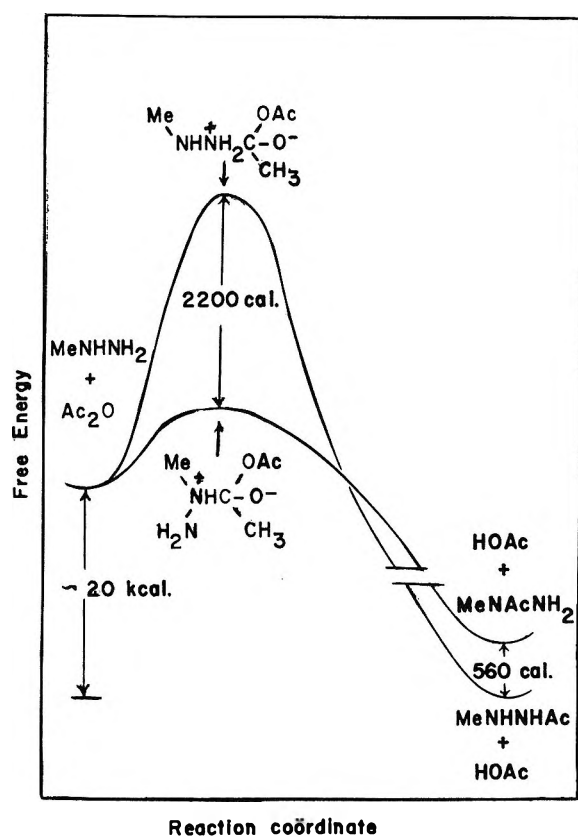
Figure 3.—Potential energy profile for acetylation of methylhydrazine with acetic anhydride at 27°.
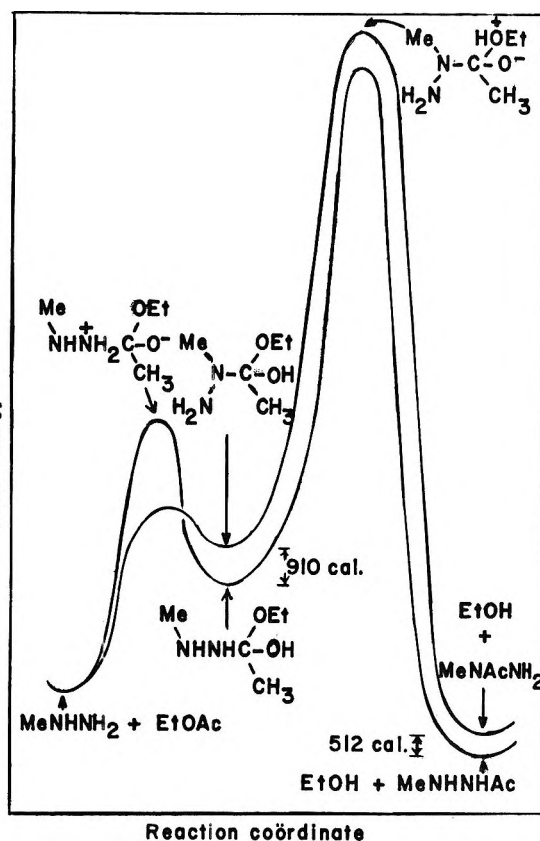
Figure 4.—Potential energy profile for acetylation of methylhydrazine with ethyl acetate at 87°.

not of much help, however, in understanding the phenomena described here. The failure to detect acid catalysis of the hydrazinolysis of phenyl acetate in aqueous solution,[15] for example, may be due to overriding catalysis by the water present. The conditions used here resemble more those of ammonolysis of esters in liquid ammonia, where acid catalysis by ammonium salts has been observed,[16] and in butylamine, where catalysis by water has been demonstrated.[17]

If the mechanisms with the two types of acetylating agents are different, their failure to conform to the reactivity–selectivity principle is not surprising, since this principle should be applied only to reagents that react by essentially the same mechanism.[2] The result with anhydrides, then, is a consequence of the greater nucleophilicity of the methylated nitrogen, while an explanation of the results with esters must be sought in the reasons, possibly steric,[1a] for differences in the stabilities of two alternative metastable intermediate addition products.

Experimental Section

Materials and Instruments. Methylhydrazine was obtained from Matheson Coleman and Bell, Inc., E. Rutherford, N. J. With 0.1 N HCl it gave a titer indicating 100% purity. It was used without prior treatment.

Nmr spectra were obtained on a Varian A-60 instrument. Melting points were taken with a Hoover-Thomas capillary melting point apparatus and are uncorrected.

Acetylation of Methylhydrazine with Ethyl Acetate.—Run 1, Table I, is described in detail. A mixture of 47.2 g (1.025 mol) of methylhydrazine, 107.4 g (1.22 mol) ethyl acetate, and 1.9 g (0.1 mol) water as catalyst was heated under reflux with protec-

tion from atmospheric moisture for a total of 50 hr in the course of 11 days. Heating periods alternated with periods during which the reaction mixture stood at room temperature, and the mixture was sampled almost daily by nmr spectroscopy. Near the end of the heating period, the temperature of the boiling mixture was 89°, and the nmr spectrum indicated that ∼80% of the methylhydrazine had reacted.

The reaction mixture, now 147 g because of a 9.5-g loss due to evaporation, sampling for nmr analysis, and handling, was distilled under reduced pressure[18] and yielded fraction 1, boiling to 83° (60 Torr), 69.0 g; fraction 2, boiling to 140° (12 Torr), 71.5 g; residue, 3.0 g; loss on distillation, 3.5 g. Analysis by nmr spectroscopy showed that fraction 1 consisted of ethyl acetate (24.1 g), ethanol (37.6 g), methylhydrazine (5.4 g), and water (1.9 g). fraction 2 consisted of 1-acetyl-1-methylhydrazine (15.8 g) and 1-acetyl-2-methylhydrazine (55.7 g). The residue was 1,2-diacetylmethylhydrazine. The nmr spectrum (CHCl₃ with internal TMS) showed singlets at 2.01, 2.04, and 3.07 ppm (CHCl₃, 60% by wt, singlet at 463.4. Hz).

Run 2, Table I, was done similarly except that the heating period was uninterrupted, and the reaction mixture stood for 6 months at room temperature before being distilled.

Isolation of 1-Acetyl-2-methylhydrazine.—Fraction 2, above, was cooled in an ice bath, and the crystalline product so formed was collected by filtration with suction: yield 25 g; white needles; mp 38–42°; bp (observed during distillation above) ∼110–111° (12 Torr). The nmr spectrum, in CCl₄ with TMS, consisted of two somewhat broadened singlets at δ 1.93 and 2.56 ppm. The nmr spectrum indicated 4% isomer 1.

Anal.[19] Calcd for C₃H₈N₂O: C, 40.90; H, 9.15. Found: C, 40.90; H, 9.07.

A second crop of less pure material was obtained by rechilling the filtrate in ice and refiltering, and a third crop of 3 g was obtained by cooling the filtrate from the second crop in a freezer at

(16) L. F. Audrieth and J. Kleinberg, *J. Org. Chem.*, **3**, 312 (1938).

(17) P. K. Glasoe, L. D. Scott, and L. F. Audrieth, *J. Amer. Chem. Soc.*, **63**, 2965 (1941).

(18) To minimize losses, a simple Claisen flask was used, with a receiver consisting of a simple distilling flask attached to the side arm by means of a rubber stopper, and an extremely fine capillary bleed was used as an aid to smooth ebullition. *Cf.* R. Adams and J. R. Johnson, "Laboratory Experiments in Organic Chemistry," Macmillan, New York, N. Y., 1949, p 365.

(19) All analyses were performed by Schwartzkopf Microanalytical Laboratory, Woodside, N. Y.

−10°. Total yield of solid product was 36 g (40%). The compound yellowed on standing, as was observed by Hinman and Fulton with other 1-acyl-2-methylhydrazines.[1,20]

Acetylations with Acetic Anhydride.—The most consistent results were obtained by use of mechanical stirring and the procedure now to be described, which was used in runs 5, 8, 9, and 10. A 1-l. or (in run 8) 2-l. three-necked flask was fitted with a sealed motor-driven stirrer, a thermometer, and, in the other side neck, a 125- or (in run 8) 250-ml pressure-equilizing dropping funnel. The stem of the dropping funnel was extended into the liquid (later charged to the flask) by attachment (by means of a short length of Tygon tubing) of a glass tube constricted at the lower end to ∼1 mm (Pasteur pipet).

The solvent and then the methylhydrazine were placed in the flask. When acetic acid was the solvent, the methylhydrazine was introduced with cooling beneath the surface of the acid by means of the modified dropping funnel already described. The contents of the flask were cooled to 10°, and the acetic anhydride was introduced in a thin stream beneath the surface of the liquid with stirring and cooling at such a rate as to maintain the temperature within desired limits (1–9 hr).[22] In runs with acetic acid as solvent, pyridine (1.2 mol/mol of MeNHNH₂) was introduced at this point in the same manner as the acetic anhydride.

The glass tubing extension to the dropping funnel was removed, and 50% sodium hydroxide (1.05 mol/mol of HOAc)[23] was added in the course of ∼1 hr with stirring and cooling so as to maintain the temperature below 25°. The mixture was then stored at least overnite in a freezer at −10° to complete crystallization of the sodium acetate trihydrate.

The solid was filtered with suction. A Dry Ice cooled trap was interposed between the aspirator and filter flask to prevent loss.[24] The solid was transferred to a beaker and mixed throughly with solvent for extraction (ether, pyridine, or chloroform, 50 ml/mol of MeNHNH₂ charged; see Table I). The mixture was filtered with suction into a clean, dry flask. The extraction was repeated twice. The combined extracts, kept separate from the primary filtrate, were distilled at 30–40°, ether being distilled at atmospheric pressure, chloroform at 140 Torr, and pyridine at 20–30 Torr. A Dry Ice trap was used to prevent loss.[18]

The primary filtrate was added to the residue from distillation of the extracts, and distillation was continued under reduced pressure. After removal of pyridine (in run 10, triethylamine and chloroform), some water, and unchanged methylhydrazine, a small intermediate fraction was collected, boiling to ∼100° (25 Torr). At this point, the residue in the flask usually became thick with solid (sodium acetate?), which interfered with further distillation. It was cooled, therefore, mixed with a little ether or, better, chloroform, and filtered with suction through a small fritted-glass funnel. Distillation was then continued with an oil pump at 1–2 Torr. A fraction consisting almost wholly of 1 and 2, with ∼2% 1,2-diacetylmethylhydrazine, was collected in the range of 80–130° (2 Torr). The residue was weighed and then dissolved in chloroform or water for analysis by nmr spectroscopy. All the fractions, including those collected in the Dry Ice trap, were weighed and analyzed by means of nmr spectroscopy.

In early modifications of the above-described procedure, used in the other runs in Table I, the acetylation was carried out in an erlenmeyer flask open to the atmosphere; the acetic anhydride was introduced by hand by means of a Pasteur pipet; and mixing was by hand swirling of the flask.

Isolation of 1-Acetyl-1-methylhydrazine.—The acetylmethylhydrazine fraction from run 6, amounting to 24.5 g, was found by nmr spectroscopy to be ∼96% 1 and ∼2% each of 2 and diacetylmethylhydrazine. Redistillation under reduced pressure

(20) The yellowing was thought to be due to air oxidation to acetylazomethane, CH₃CON=NCH₃, but an attempted oxidation of **2** with mercuric oxide according to published procedures[21] was accompanied by gas (N₂?) evolution and failed to give any acetylazomethane.

(21) R. Renaud and L. C. Leitch, *Can. J. Chem.*, **32**, 545 (1954).

(22) In runs with pyridine as solvent, the nmr spectrum of the mixture at this stage shows that **1** and **2** are present in a ratio of 40:1. If the mixture is allowed to stand overnight at room temperature, however, the ratio decreases to ∼10:1. Similarly, if the reaction mixture is distilled under reduced pressure (∼25 Torr) at this stage, the ratio of 1/2 in the distillate is generally found to be somewhat less than 10, apparently because of acetic acid catalyzed rearrangement of **1** to **2**.

(23) A slight excess of sodium hydroxide is used to ensure complete neutralization of the acetic acid, but a large excess is avoided, as it causes saponification later during distillation of the product.

(24) If the objective were simply the preparation and isolation of **1**, the trap could be omitted.

gave 23 g (0.26 mol, 39%) of 98% pure 1, bp 103° (8 Torr), mp 16°. The nmr spectrum, in CCl₄ with internal TMS, consisted of two sets of singlets, indicative of the syn–anti isomerism characteristic of amides. An inner set, with δ 2.16 and 3.15 ppm, was ∼2.5–3.0 times as intense as the outer set, with δ 2.06 and 3.23 ppm, D^{25} 1.0678 g/cm³.

Anal. Calcd for C₃H₈N₂O: C, 40.90; H, 9.15. Found: C, 40.72; H, 8.88.

Work-Up of Synthetic Mixtures.—The method of work-up and analysis of the products of acetylation with acetic anhydride entailed extensive handling and was accompanied by some loss, apparently because of retention of material by the sodium acetate trihydrate. Two synthetic mixtures of known composition were worked up and analyzed by the same method, therefore, to determine whether the loss was strongly selective of any of the components. Results are presented in Table IV. In addition to the

TABLE IV

RESULTS OF WORK-UP OF SYNTHETIC MIXTURES

Mixture	1	2
Extractive	Pyridine	Chloroform
Component, mol charged (found)		
MeNHNH₂	0.236 (0.182)	0.137 (0.111)
MeNAcNH₂	0.203 (0.210)	0.166 (0.133)
MeNHNHAc	0.268 (0.250)	0.207 (0.145)
MeNAcNHAc	0.210 (0.122)	0.182 (0.126)
Loss, mol	(0.153)	(0.177)

components listed there, mixture 1 contained at the start acetic acid and pyridine in proportions similar to those present at the conclusion of the acetylation runs, 6–9, Table I. Mixture 2 was made to contain acetic acid and triethylamine, as in run 10. Each mixture was treated with 50% sodium hydroxide sufficient to neutralize the acetic acid and was then worked up and analyzed as described above.

On the whole, the results in Table IV show that the losses were not strongly selective of any one component, the relatively low recoveries of methylhydrazine and diacetylmethylhydrazine from mixture 1 being regarded as artifacts of that experiment. They provide an indication of the limits of uncertainty of the results in Table I, but to use them as the basis of an "adjustment" of the earlier data does not seem justified.

Competitive Acetylation of 1 and 2.—A nearly equimolar mixture of the isomers was prepared in an nmr sample tube and the nmr spectrum and integrator curves were run. A small amount of acetic anhydride was introduced beneath the surface of the mixture by means of an elongated Pasteur pipet, care being taken to distribute the anhydride throughout the mixture during its addition, so as to avoid an effect of localized depletion of one of the isomers through reaction with the anhydride. The nmr spectrum and integrator curves were run again. Additions of acetic anhydride and spectral determinations were continued until a total of six portions of the anhydride had been added and almost half of the acetylmethylhydrazines had been consumed.

Data and results are presented in Table II. The MeNAcNH₂ and MeNAcNHAc were measured together by means of their N-CH₃ signals in the region of δ 3.0–3.3 ppm from TMS. The MeNHNHAc, n_2, was measured by its isolated N-CH₃ signal at 2.56 ppm. In addition, the total of the acetyl group signals (including that due to acetic acid) was measured in the region of 1.8–2.2 ppm. The integrator data were reduced to a common basis of 100 for the total of the N-CH₃ signals. The decrease in the relative number of moles of MeNHNHAc was then clearly apparent. The increase in the total acetyl was divided by two to correct for the acetic acid contribution. From this quotient was subtracted a contribution due to MeNAcNHAc produced from MeNHNHAc, equal to the decrease in MeNHNHAc. The remainder was regarded as a contribution due to MeNAcNHAc produced from MeNAcNH₂ and provided the means of calculating the remaining MeNAcNH₂, n_1.

Acid Catalysis.—Four identical nmr sample tubes were charged as follows: (1) EtOAc + MeNHNH₂, (2) EtOAc + EtOH + MeNHNH₂, (3) EtOAc + H₂O + MeNHNH₂, and (4) EtOAc + HOAc + MeNHNH₂. The nmr spectra and integrator curves were obtained before and after addition of the MeNHNH₂, and again after about 4, 9, 26, and 31 hr of heating in an oil bath at

82°. The following signals were variously used for analysis of the mixtures (δ, parts per million, from TMS external standard): CH_2CH_3 triplets, 1.0-1.5; $MeNHNHCOCH_3$, 1.93; $EtOCOCH_3$, 2.00; total $COCH_3$, 1.8-2.3; $CH_3NHNHAc$, 2.56; CH_3NHNH_2, 2.56 in neutral medium, 2.59 with water present, and 2.83 with HOAc present; $CH_3NAcNHAc + CH_3NAcNH_2$, 3.0-3.3; CH_3CH_2OH quartet, 3.4-3.9; CH_3CH_2OAc quartet, 3.9-4.4; and NH and OH, further downfield. The initial compositions (molar ratios, averages based on nmr analyses) were as follows: (1) $MeNHNH_2/EtOAc$, 1.0/1.3; (2) $MeNHNH_2/EtOAc/EtOH$, 1.0/1.3/0.5; (3) $MeNHNH_2/EtOAc/H_2O$, 1.0/1.4/0.7; and (4) $MeNHNH_2/EtOAc/HOAc$, 1.0/0.85/0.6. The percentages of methylhydrazine reacted at various times are shown in Figure 1.

Equilibrations of 1 and 2.—About 0.4-ml samples of mixtures of the two isomers were placed in nmr sample tubes and a few drops of glacial acetic acid were added. In some runs at 87°, ethanol was added to approximate the conditions of acetylation of methylhydrazine with ethyl acetate. The air was displaced by nitrogen, the tubes were tightly capped, and the contents were mixed by thorough shaking. The tubes were either kept at room temperature (27°) or in a constant-temperature bath at 87°, comprised of ~400 ml of water contained in a 500-ml erlenmeyer flask resting on a thermostated hot plate and loosely stoppered to retard evaporation of the water.

They were examined from time to time by nmr. The amounts of acetic acid and alcohol were estimated from the nmr spectra. The acetic acid was 10-20 mol % and the alcohol 80 mol % of the total hydrazine content. In one sample at room temperature, the ratio, 1/2, changed from 16 to 0.37 in the course of 154 days, while in another the ratio went from 0.32 to 0.41 in the same period, to give an average equilibrium ratio of 0.39 ± 0.02. Runs at 87° required ~100 hr for equilibration and gave an average equilibrium ratio of 0.49 ± 0.01, with or without alcohol. (See Figure 2.)

Synthesis of 1-Alkyl-2-methylhydrazines by Way of Hydrazones of 1-Acetyl-1-methylhydrazine

F. E. CONDON

Department of Chemistry, The City College of the City University of New York, New York, New York 10031

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1-Acetyl-1-methylhydrazine was converted to acetylmethylhydrazones by reaction with the aldehydes and ketones: formaldehyde, acetaldehyde, propionaldehyde, butyraldehyde, isobutyraldehyde, benzaldehyde, acetone, and 2-butanone. Boiling points, densities, and nmr spectra of these hydrazones are reported. By reduction with sodium borohydride in ethanol, followed by hydrolysis with dilute hydrochloric acid, each hydrazone, except benzaldehyde acetylmethylhydrazone, was converted to the corresponding 1-alkyl-2-methylhydrazine. Boiling points and nmr spectra of the following are reported: 1-ethyl-2-methyl-, 1-methyl-2-propyl-, 1-isopropyl-2-methyl-, 1-butyl-2-methyl-, 1-isobutyl-2-methyl-, and 1-sec-butyl-2-methylhydrazine and 1-acetyl-1-methyl-2-ethylhydrazine.

It has been shown that the acetylation of methylhydrazine with acetic anhydride can be controlled so as to give chiefly 1-acetyl-1-methylhydrazine (1), accompanied by small amounts of its isomer, 1-acetyl-2-methylhydrazine (2), and 1,2-diacetyl-1-methylhydrazine; and 1 of 96% purity was obtained in 76% yield.[1] In this paper is described the use of 1 for the synthesis of some 1-alkyl-2-methylhydrazines as shown in eq 1.

$$MeNAcNH_2 + R_1R_2C{=}O \xrightarrow{NaBH_4} MeNAcN{=}CR_1R_2 \longrightarrow$$
$$1$$
$$MeNAcNHCHR_1R_2 \xrightarrow[\text{2. NaOH}]{\text{1. } H_2O,\ HCl} MeNHNHCHR_1R_2 \quad (1)$$
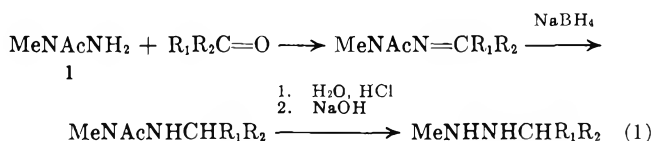
The hydrazines obtained in good yield were 1,2-dimethyl-,[2] 1-ethyl-2-methyl-,[3] 1-isopropyl-2-methyl-,[3,4] 1-methyl-2-propyl-,[4b] 1-butyl-2-methyl-,[5] 1-isobutyl-2-methyl-, and 1-sec-butyl-2-methylhydrazine. The method failed in the case of 1-benzyl-2-methylhydrazine.[5a,6] Those for which references are given had been synthesized before by one method or another. The route from 1, eq 1, provides an alternative method which seems preferable in many cases.

Each of the 1-alkyl-2-methylhydrazines made here might have been made by lithium aluminum hydride reduction of an appropriate formylhydrazone, $HCO{-}NHN{=}CR_1R_2$, for example.[4b] Lithium aluminum hydride reduction of hydrazides, however, is frequently accompanied by cleavage at the acyl-nitrogen bond.[7] In the present case, this would have led to 1-alkyl-2-methylhydrazine accompanied by a monoalkylhydrazine having nearly the same boiling point. This possibility may account for the failure of the earlier workers to obtain good analytical results for dialkylhydrazines made that way and for the low yields of azoalkanes obtained from them by mercuric oxide oxidation. The new route described here is free of this complication and gave dialkylhydrazines for which acceptable analyses were obtained.

Experimental Section

Materials and Instruments.—These were as described in previous publications from this laboratory.[1,8] Liquid densities were obtained with a U-shaped pyknometer having a volume of ~3.3 cm³.

Preparation of Acetylmethylhydrazones. A. From Aldehydes.—Forty-six grams (0.50 mol) of 96% 1-acetyl-1-methylhydrazine[1] (containing 2% each of 2 and 1,2-diacetyl-1-methylhydrazine) was placed in a 250-ml erlenmeyer flask cooled in an ice bath, and 0.55 mol of freshly distilled aldehyde was introduced beneath the surface by means of a Pasteur pipet with swirling and cooling so as to maintain the temperature below 25°. Formaldehyde was used as a 37% aqueous solution, and acetaldehyde as a 58% aqueous solution. In these two cases, 15 g of sodium

(1) F. E. Condon, *J. Org. Chem.*, **37**, 3608 (1972).

(2) 1,2-Dimethylhydrazine dihydrochloride is available commercially from Aldrich Chemical Co., Milwaukee, Wis.

(3) N. V. Khromov-Borisov and T. N. Kononova, *Probl. Poluch. Poluprod. Prom. Org. Sin., Akad. Nauk SSSR, Otd. Obshch. Tekh. Khim.*, 10 (1967); *Chem. Abstr.*, **68**, 4721 (1968).

(4) (a) H. C. Ramsperger, *J. Amer. Chem. Soc.*, **51**, 918 (1929); (b) L. Spialter, D. H. O'Brien, G. L. Untereiner, and W. A. Rush, *J. Org. Chem.*, **30**, 3278 (1965).

(5) (a) G. H. Coleman, H. Gilman, C. E. Adams, and P. E. Pratt, *ibid.*, **3**, 99 (1938); (b) E. Schmitz, *Angew. Chem.*, **73**, 23 (1961).

(6) J. Thiele, *Ann.*, **376**, 239 (1910).

(7) R. L. Hinman, *J. Amer. Chem. Soc.*, **78**, 1645 (1956).

(8) F. E. Condon and D. Fǎrcasiu, *ibid.*, **92**, 6625 (1970).

TABLE I

ACETYLMETHYLHYDRAZONES, $MeNAcN=CR_1R_2{}^a$

R_1 R_2 (Registry no.)	Bp,[b] °C (Torr)	Density, 25°, g/cm³	Nmr spectrum (in CCl₄ with TMS), δ, ppm
H H (35906-04-8)	78 (30)	1.0197	6.66 and 6.34 (d, 2, $J = 11$ Hz, $N=CH_2$), 3.13 (s, 3, CH_3N), 2.22 (s, 3, CH_3CO)
H Me[c] (35906-05-9)	88 (18)	0.9803	6.96 (q, 1, $J = 5$ Hz, $N=CH$), 3.10 (s, 3, CH_3N), 2.19 (s, 3, CH_3CO), 1.99 (d, 3, $J = 5$ Hz, $=CHCH_3$)
H Et (35906-06-0)	106 (25)	0.9608	7.00 (t, 1, $J = 5$ Hz, $N=CH$), 3.11 (s, 3, CH_3N), 2.33 (m, 2, CH_2), 2.19 (s, 3, CH_3CO), 1.12 (t, 3, $J = 7$ Hz, CH_2CH_3)
H Pr[d] (35907-07-1)	83 (1.5)	0.9443	6.98 (t, 1, $J = 5$ Hz, $N=CH$), 3.12 (s, 3, CH_3N), 2.2 (m, 2, $=CHCH_2CH_2$), 2.18 (s, 3, CH_3CO), 1.6 (m, 2, $CH_2CH_2CH_3$), 0.98 (t, 3, $J = 7$ Hz, CH_2CH_3)
H i-Pr (35906-08-2)	74 (1.7)	0.9348	6.93 (d, 1, $J = 5$ Hz, $N=CH$), 3.11 (s, 3, CH_3N), 2.5 [m, 1, $CH(CH_3)_2$], 2.19 (s, 3, CH_3CO), 1.12 [d, 6, $J = 7$ Hz, $CH(CH_3)_2$]
H Ph (21075-81-0)	120 (2.8)	e	7.1–7.8 (m, 6, $C_6H_5CH=N$), 3.40 (s, 3, CH_3N), 2.33 (s, 3, CH_3CO)
Me Me (35906-10-6)	117 (25)	f	3.01 (s, 3, CH_3N), 2.08 (s, 3, CH_3CO), 1.93 [s, 3, $=C(CH_3)_2$], 1.97 [s, 3, $=C(CH_3)_2$]
Me Et[g] (35906-11-7)	128 (30)	0.9575	2.97[h] (s, 3, CH_3N), 2.37 (q, 2, $J = 7$ Hz, CH_2CH_3), 2.03 and 1.90[i] (s, 3, CH_3CO), 1.83 (s, 3, $=CEtCH_3$), 1.13 (t, 3, $J = 7$ Hz, CH_2CH_3)

[a] *Anal.*[11] All C values were ±0.32 and H ±0.10 of theoretical, except as noted. [b] Midpoint of narrow range. [c] *Anal.* Calcd for $C_5H_{10}N_2O$: C, 52.62; H, 8.83. Found: C, 53.16; H, 8.86. [d] *Anal.* Calcd for $C_7H_{14}N_2O$: C, 59.12; H, 9.93. Found: C, 59.13; H, 10.28. [e] Solid, mp 80° (benzene–petroleum ether). [f] Not determined. [g] *Anal.* Calcd for $C_7H_{14}N_2O$: C, 59.12; H, 9.93; N, 19.70. Found: C, 57.58, 57.80; H, 9.98, 9.73; N, 19.73. [h] With small branches at 3.05 and 3.15 attributable to syn–anti isomerism. [i] Main branch; branching attributable to syn–anti isomerism.

hydroxide was added to the reaction mixture, and the hydrazone was extracted into ether prior to purification by distillation under reduced pressure. In other cases, the reaction mixture was simply distilled under reduced pressure. After a wet forerun, obtained by distillation with the aspirator, the product was collected over a narrow range, as shown in Table I. Additional product was obtained by redistillation of the forerun. Yields were quantitative, except in the case of formaldehyde (67%) and acetaldehyde (87%).

B. From Ketones.—Acetone and 2-butanone reacted only slowly with 1. Benzene (150 ml) was added, therefore, and the mixture was heated under reflux with a Dean-Stark trap[9] being used for removal of water. After 2 hr 90% of the theoretical amount of water had collected. Most of the benzene was removed by distillation at atmospheric pressure. The residue was distilled under reduced pressure for recovery of the product. Yields were quantitative.

The products are described in Table I.

1-Alkyl-2-methylhydrazines.—The acetylmethylhydrazone (0.50 ml) was mixed with 200 ml of 95% ethanol in a 500-ml erlenmeyer flask, and 2 g (0.55 mol) of sodium borohydride was added in small portions with swirling. The flask was capped with a one-holed rubber stopper fitted with an inverted Pasteur pipet and was heated in a hot water both at 80° for 10 hr.[10] The mixture was allowed to cool and was filtered with suction. The solid (Borax?) was extracted with three 10-ml portions of absolute ethanol and removed by filtration with suction each time. The filtrates were combined in a 500-ml erlenmeyer flask, cooled in an ice bath, and acidified by slow addition of 250 ml of 4 M HCl. The mixture was distilled to remove alcohol and until the vapor temperature reached 101°. The residue was allowed to cool to room temperature. It was then filtered with suction from a small amount of crystalline solid, presumably boric acid. To the resulting filtrate, contained in a 500-ml erlenmeyer flask cooled in an ice bath, 100 g of solid sodium hydroxide was added in small portions with continuous swirling to ensure complete dissolution. As the large amount of solid sodium chloride that formed made impractical the use of a separatory funnel, the mixture was poured into a 250-ml erlenmeyer flask and allowed to settle. The upper layer of crude hydrazine was drawn off with a pipet and placed in a 125-ml flask with solid sodium hydroxide for additional drying. The aqueous layer, containing much suspended sodium chloride, was returned to the 500-ml

erlenmeyer flask, mixed thoroughly with 20 ml of ether, and then returned to the 250-ml flask. The ether layer was drawn off with a pipet and mixed with the crude hydrazine in the 125-ml flask. In this flask, an aqueous concentrated sodium hydroxide solution formed slowly beneath the hydrazine, and, from time to time, this was withdrawn with the pipet and returned to the aqueous layer in one of the larger flasks. After the extraction with ether already described, the aqueous layer was filtered with suction. The solid was washed well with two 20-ml portions of ether, each portion being used also to extract the aqueous filtrate and then combined with the hydrazine already isolated. After removal of as much as possible of the concentrated aqueous sodium hydroxide that had formed beneath the ether–hydrazine mixture, the mixture was left to dry overnight with sodium hydroxide.

The crude hydrazine–ether mixture was decanted carefully from the sodium hydroxide into a 125-ml Claisen flask, and ~0.5 g of calcium hydride was added. After reaction subsided, the hydrazine was distilled under reduced pressure. After removal of the ether and a small forerun, the bulk of the remaining material was collected as a single fraction and redistilled from fresh calcium hydride so as to obtain the products described in Table II.

A modification of the foregoing procedure was also used with 1,2-dimethyl-, 1-ethyl-2-methyl-, and 1-methyl-2-propylhydrazine, which form crystalline dihydrochlorides. Instead of being dried with solid sodium hydroxide, the crude hydrazine and ether extracts were injected carefully beneath the surface of 165 ml of 12 M HCl by means of a Pasteur pipet, with cooling by means of an ice bath. The crude dihydrochloride was purified by recrystallization from 6 M HCl, and also by precipitation with ether from a solution in absolute ethanol.[3,4]

Isolation of 1-Acetyl-1-methyl-2-ethylhydrazine.—In general, the acetylhydrazine resulting from sodium borohydride reduction of a hydrazone was hydrolyzed as described above without being isolated. That isolation was possible, however, was shown with the reduction product of acetaldehyde acetylmethylhydrazone. The procedure above was followed, and a 10-ml portion of the alcoholic filtrate, prior to addition of hydrochloric acid, was distilled under reduced pressure. The material that distilled up to 95° (14 Torr) was twice redistilled with rejection of small foreruns and residues. There was obtained 2 g of colorless liquid boiling at 90–95° (14 Torr). The nmr spectrum indicated the syn–anti isomerism characteristic of amides: the N-CH₃ group gave signals at δ 2.97 and 3.12 ppm (in CCl₄ with internal TMS), and the COCH₃ group gave two signals at δ 2.02 and 2.20 ppm; the upfield signal was the stronger in each case. A 2 H multiplet centered at ~2.8 ppm and a 3 H triplet centered at 1.03 ppm ($J = 7$ Hz) completed the spectrum.

(9) E. W. Dean and D. D. Stark, *Ind. Eng. Chem.*, **12**, 486 (1920).

(10) Reactions were monitored by means of nmr spectroscopy, and heating was continued until the spectrum remained unchanged by 2 hr of heating. Runs with smaller amounts of sodium borohydride (0.25 mol/mol of hydrazone is theoretical) did not go to completion.

TABLE II

1-ALKYL-2-METHYLHYDRAZINES, MeNHNHCHR₁R₂^a

R₁ R₂ (Registry no.)	Yield,^{b} %	Bp,^{c} °C (Torr)	Nmr spectrum (in CCl₄ with TMS),^{d} δ, ppm
H H^e (540-73-8)	82^f	81 (755)	2.70 (s, 2, NH), 2.48 (s, 6, CH₃NH)
H Me^e (18247-19-3) (18247-20-6)^h	65^g	93 (758)	2.90 (s, 2, NH), 2.74 (q, 2, J = 7 Hz, CH₂NH), 1.02 (t, 3, J = 7 Hz, CH₂CH₃)
H Et (3711-30-6)	42	65 (110)	2.87 (s, 2, NH), 2.65 (t, 2, J = 7 Hz, CH₂NH), 1.4 (m, 2, CH₂CH₃), 1.07 (t, 3, J = 7 Hz, CH₂CH₃)
H Pr (35906-16-2)	60	80 (80)	2.89 (s, 2, NH), 2.69 (t, 2, J = 7 Hz, NHCH₂), 1.4 (m, 4, CH₂CH₂CH₃), 0.93 (t, 3, J = 6 Hz, CH₂CH₃)
H i-Pr (35906-17-3)	56	84 (140)	3.06 (s, 2, NHO), 2.52 (d, 2, J = 7 Hz, NHCH₂), 1.7 [m, 1, CH(CH₃)₂], 0.90 [d, 6, J = 6 Hz, CH(CH₃)₂]
Me Me (1615-82-3)	38^i	69 (140)	3.10 (s, 2, NH), 2.92 [m, 1, NHCH(CH₃)₂], 0.97 [d, 6, J = 6 Hz, CH(CH₃)₂]
Me Et^j (35906-19-5)	61	83 (140)	2.81 (s, 2, NH), 2.63 (m, 1, CHEtMe), 1.28 (m, 2, CHMe-CH₂CH₃), 0.97 (t, 3, CH₂CH₃), 0.95 (d, 3, J = 6 Hz, CHEt-CH₃)

^{a} *Anal.* All C values were ±0.24 and H ±0.28 of theoretical, except as noted. ^{b} From MeNAcN=CR₁R₂. ^{c} Midpoint of narrow range. ^{d} All compounds gave a 3 H singlet for NHCH₃ at δ 2.48 ± 0.01 ppm. ^{e} Known compounds were not analyzed or were identified as the known dihydrochloride. ^{f} As the dihydrochloride. ^{g} As the dihydrochloride, mp 141–143° in an open capillary and 163–167° in a sealed capillary (lit.³ mp 139–140°). ^{h} Dihydrochloride. ^{i} Autoxidizes rapidly to MeN=NPr-i. ^{j} *Anal.* Calcd for C₅H₁₄N₂: C, 58.80; H, 13.80. Found: C, 58.16; H, 13.56.

Anal.[11] Calcd for C₅H₁₂N₂O: C, 51.73; H, 10.41; Found: C, 51.95; H, 10.22.

Attempted Catalytic Hydrogenation of Hydrazones.—Several attempts were made to reduce some of the hydrazones in Table I by catalytic hydrogenation at 5–6 atm in 1 *M* solution in absolute alcohol. The catalysts used were 10% palladium on charcoal, platinum oxide, 5% rhodium on alumina, and freshly prepared Raney nickel (W-2). The catalysts were effective for the hydrogenation of cinnamic acid to hydrocinnamic acid, but no hydrogen absorption took place with the hydrazones.

Lithium Aluminum Hydride Reduction of 2.—This was investigated as a route to 1 ethyl-2-methylhydrazine. A 1-l. three-necked flask was fitted with a motor-driven Teflon stirrer, dropping funnel, and reflux condenser protected from atmospheric moisture. Provision was made for escape of vapors from the top of the condenser into a hood. The flask was charged with 100 g (130 ml, 0.50 mol) of a 19% solution of lithium aluminum hydride in ether[12] and cooled thoroughly in an ice bath. A solution of 36 g (0.41 mol) of 2, melting point about 40°,¹ in 150 ml of ether was added dropwise with stirring in the course of 2 hr. The mixture was heated at reflux for 2 hr and then cooled again in an ice bath. About 150 ml of 50% aqueous potassium hydroxide was added very slowly with stirring and cooling. The mixture was then distilled from the same flask, with stirring, until a vapor temperature of 105° was reached. The entire distillate, consisting of two layers, was added slowly to 150 ml of concentrated hydrochloric acid with stirring and cooling in an ice bath. The ice-cold mixture was filtered with suction and gave 34 g of moist solid melting at 100–110° with decomposition. Examination by nmr spectroscopy in D₂O as solvent indicated this solid was about 90% methylhydrazine sesquihydrochloride

(11) All analyses were by Schwartzkopf Microanalytical Laboratory, Woodside, N. Y.

(12) Obtained from Foote Mineral Co., Exton, Pa.

sesquihydrate (lit.¹³ mp 118°) and only ~10% 1-ethyl-2-methylhydrazine dihydrochloride. No effort was made to isolate the latter from it.

The filtrate was allowed to evaporate at room temperature to a volume of 50 ml and was then chilled thoroughly in ice. Filtration then yielded 1.3 g of solid which was purified by dissolving it in 10 ml of 95% ethanol, with slight heating, and reprecipitation by addition of 50 ml of ether.³ There was obtained 0.9 g (1.5%) of solid melting at 152–153° in an open capillary and 160–164° in a sealed capillary. The reported melting point of 1-ethyl-2-methylhydrazine dihydrochloride is 139–140°.³ The nmr spectrum, in D₂O with TMS external, indicated this was ~95% 1-ethyl-2-methylhydrazine dihydrochloride [δ 1.3 (t, 3, J = 7 Hz), 3.8 (q, 2, J = 7 Hz), and 2.9 ppm (s, 3)] and 5% methylhydrazine sesquihydrochloride sesquihydrate [δ 3.0 ppm (s)].

Registry No.—2, 29817-35-4; 1-acetyl-2-methyl-2-ethylhydrazine, 35906-20-8.

(13) D. L. Hammick and D. J. Voaden, *J. Chem. Soc.*, 3308 (1961).

Facile Introduction of Ester Groups into the Pyrrole Nucleus
via Trichloroacetylation and Alcoholysis[1]

JOHN W. HARBUCK AND HENRY RAPOPORT*

Department of Chemistry, University of California, Berkeley, California 94720

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The trichloroacetylation of alkylpyrroles, α-ethoxycarbonylpyrroles, and dipyrrylmethanes is described, using trichloroacetyl chloride and appropriate bases as acid scavengers. Treatment of trichloroacetylpyrroles with alcohols and mild base converts them directly into pyrrole esters of primary alcohols; secondary and tertiary alcohols do not give synthetically useful yields. Trifluoroacetylpyrroles are not directly converted to esters.

Pyrrole esters are most generally prepared by ring synthesis, a method usually giving good yields but limited to certain substitution patterns and to esters which will survive the condensation conditions. Pyrrole acids are readily prepared *via* sulfuryl chloride oxidation of nuclear methyl groups; however, esterification with reagents other than diazomethane frequently proves troublesome.

Potentially, the most versatile method would be the direct introduction of the ester functionality into a preexisting pyrrole ring. Existing methods, however, suffer from several drawbacks: poor yields are often obtained, a multiplicity of products is common, and reaction conditions may be inimical to other ring substituents. For example, methyl chloroformate, when treated with pyrrylmagnesium bromide or with pyrryllithium, gives small amounts of the desired methyl pyrrole-2-carboxylate and generally more of the 1 ester and 1,2 diester.[2] An unambiguous and better procedure involves the alkaline silver oxide oxidation of 2-formylpyrrole to the carboxylic acid.[2] This route also requires subsequent esterification; however, it can be avoided by conversion of the aldehyde to oxime, dehydration to nitrile, and acid-catalyzed alcoholysis to ester.[3] Recently a Friedel–Crafts type trichloroacetylation of pyrroles followed by hydrolysis of the trichloroacetyl group to carboxyl by treatment with sodium hydroxide has been reported.[4a] Similarly, the synthesis in high yield of pyrrole-2-carboxylic acid has been effected through the trifluoroacetyl moiety.[4b] However, the conversion of these pyrrole acids to esters again requires esterification which may prove limiting.

We hoped to develop a method that could introduce a wide variety of esters unambiguously and under mild conditions into pyrroles having varying substitution patterns. Functionalization of dipyrrylmethanes was likewise of interest, and here in particular the possible conditions are severely limited. The usual procedures mentioned above, involving metallopyrryl reagents or oxidation, cannot be used with dipyrrylmethanes because of the multiplicity of products from the former and the sensitivity of the methylene bridge to the latter. Furthermore, since rearrangement of dipyr-

rylmethanes may readily occur in acid,[5] neutral or mildly alkaline conditions were necessary.

Results

Trichloroacetylation.—We decided to explore the possibilities of using the trichloroacetyl (TCA) group, but, to avoid the Friedel–Crafts acylation with trichloroacetyl chloride (TCAC) and the concomitant strong acid conditions, we attempted a Vilsmeier acylation with *N,N*-diethyltrichloroacetamide. Since 2-chloroacetylpyrrole had been obtained in this manner from pyrrole and *N,N*-diethylchloroacetamide,[6] a precedent existed. Although we successfully repeated the synthesis of 2-chloroacetylpyrrole, Vilsmeier acylation afforded no 2-dichloroacetylpyrrole or 2-trichloroacetylpyrrole (2-TCA-pyrrole).

We were thus faced with the necessity of carrying out the trichloroacetylation with TCAC and, in contrast to the previous use of this reagent,[3] scavenging the acid produced with a suitable base, sufficiently strong to neutralize all the acid, but unreactive to TCAC. Such conditions were obtained by adding a solution of pyrrole and 2,6-lutidine in chloroform to a refluxing chloroform solution of TCAC. An 80% yield of pure 2-TCA-pyrrole resulted and, although some 1-TCA-pyrrole was observed, it was less than 10% of the product and was easily separated by silica gel chromatography.

This procedure now was applied to 2,4-dimethylpyrrole as a model that would more closely reflect the reactivity of the dipyrrylmethanes that we anticipated using. The yields of 2-TCA-3,5-dimethylpyrrole were poor, <20%, and proportionately greater fractions of the 1-TCA-2,4-dimethylpyrrole were formed. Other hindered amines [1,8-bis(dimethylamino)naphthalene, 1,2,2,6,6-pentamethylpiperidine] were also unsuitable. A highly convenient procedure was developed using potassium carbonate as an insoluble phase with TCAC in chloroform to which 2,4-dimethylpyrrole was added at room temperature. This method gave a 75% yield of 2-TCA-3,5-dimethylpyrrole and also was applicable to pyrrole.

These conditions were now examined for the trichloroacetylation of dipyrrylmethanes. Since we wished to test not only whether acylation would take place, but also whether potassium carbonate would inhibit acid-induced scrambling, a suitably unsymmetrical methane was needed. This was available

(1) This research was supported in part by Grant AI-04888 from the National Institutes of Health, U. S. Public Health Service.

(2) P. Hodge and R. W. Richards, *J. Chem. Soc.*, 2543 (1963), and references cited therein.

(3) H. Nakano, S. Umio, K. Kariyone, K. Tanaka, T. Kishimoto, H. Noguchi, I. Ueda, H. Nakamura, and Y. Morimoto, *Tetrahedron Lett.*, 737 (1966).

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(5) (a) H. Fischer and H. J. Riedl, *J. Physiol. Chem.*, **207**, 193 (1932); (b) D. Mauzerall, *J. Amer. Chem. Soc.*, **82**, 2605 (1960); (c) A. H. Jackson, G. W. Kenner, and G. S. Sach, *J. Chem. Soc. C*, 2045 (1967).

(6) A. Ermili, A. J. Castro, and P. A. Westfall, *J. Org. Chem.*, **30**, 339 (1965).

TABLE I
CONVERSION OF TCA-PYRROLES TO PYRROLE ESTERS

Expt	Compd	Alcohol	Base	Temp, °C	Time	Yield, %[a]	
						Uv	Isolated
1	2-TCA-pyrrole	CH_3OH	CH_3O^-	25	1 min	100	88
2	2-TCA-pyrrole	CH_3OH	TEA[b]	65	20 min	100	
3	2-TCA-pyrrole	CH_3OH	TEA	25	70 hr	93	
4	2-TCA-pyrrole	C_2H_5OH	TEA	75	20 hr	97	
5	2-TCA-pyrrole	$CH_2=CHCH_2OH$	TEA	60	38 hr	97	77
6	2-TCA-pyrrole	$CH_2=CHCH_2OH$	K_2CO_3	60	1 hr	100	66
7	2-TCA-pyrrole	$(CH_3)_2C=CHCH_2OH$	TEA	60	62 hr	96	72
8	2-TCA-pyrrole	$C_6H_5CH_2OH$	TEA	60	38 hr	98	92
9	2-TCA-pyrrole	$(CH_3)_2CHOH$	$(CH_3)_2CHO^-$	80	2.5 hr		15
10	c	CH_3OH	TEA	65	3 min	100	25
11	d	$C_6H_5CH_2OH$	K_2CO_3	60	15 min	100	81
12	3,5-Dimethyl-2-TCA-pyrrole	Cl_3CCH_2OH	K_2CO_3	60	4.2 hr	100	74
13	3,5-Dimethyl-2-TCA-pyrrole	$ClCH_2CH_2OH$	K_2CO_3	60	3 hr	100	66

[a] Based on ratio of starting material and product absorbances. [b] Triethylamine. [c] Ethyl 3-methyl-4-isopropyl-5-trichloroacetyl-2-pyrrolecarboxylate. [d] Compound 9.

in the form of **2**, obtained from **1**,[7] with a substituent pattern typical of methanes useful in porphyrin syntheses. When dipyrrylmethane **2** was added to TCAC–potassium carbonate in chloroform as above, a single pure (tlc) compound was obtained which showed the expected nmr and uv spectral characteristics and the proper mass spectrum for structure **3**. Nonetheless, this did not completely rule out the presence of the rearranged methanes **4** and **5**, since **3**, **4**, and **5** all have as molecular ion m/e 490. However, the M+, M + 2, and M + 4 peaks of the product were in the proper ratio required for three chlorines, and high-resolution mass spectroscopy shows that the m/e 490 peak is only the desired methane **3**.
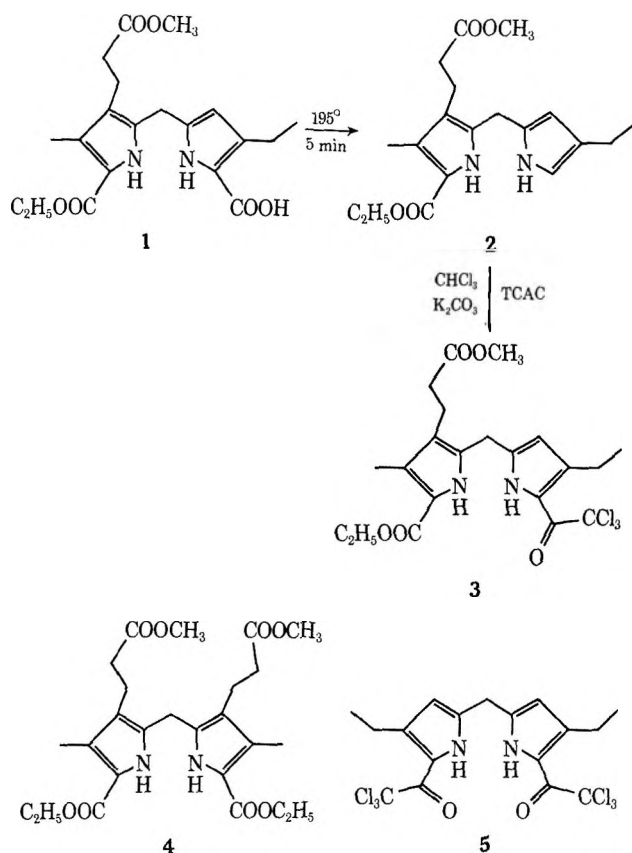
Since rearrangement had not occurred under the conditions of trichloroacetylation, we now applied this procedure to another dipyrrylmethane of interest as a porphyrin intermediate. Methane **6**[7] was hydrogenolyzed, decarboxylated, and trichloroacetylated. The trichloroacetylation was carried out with a threefold excess of TCAC and a 15-fold excess of carbonate. The product was obtained crude in quantitative yield and in 70% yield as pure material after crystallization.

To extend the generality of the reaction we examined an example of trichloroacetylation of an α-free α'-ethoxycarbonylpyrrole, since successful trichloroacetylation has been reported[3] only for β-carboethoxy pyrroles. When ethyl 3-methyl-4-ethyl-2-pyrrolecarboxylate was heated with a fivefold excess of TCAC in dry diglyme, the uv soon indicated complete reaction and after chromatography a 75% yield of pure trichloroacetylated product **9** was obtained as a light yellow oil.

1

195°
5 min

2

$CHCl_3$ / K_2CO_3 | TCAC

3

4

5

6

1. H_2, Pd/C
2. 195°, 5 min

Cl_3CCOCl
$CHCl_3$
K_2CO_3

7

8

TCAC
diglyme
100°

9
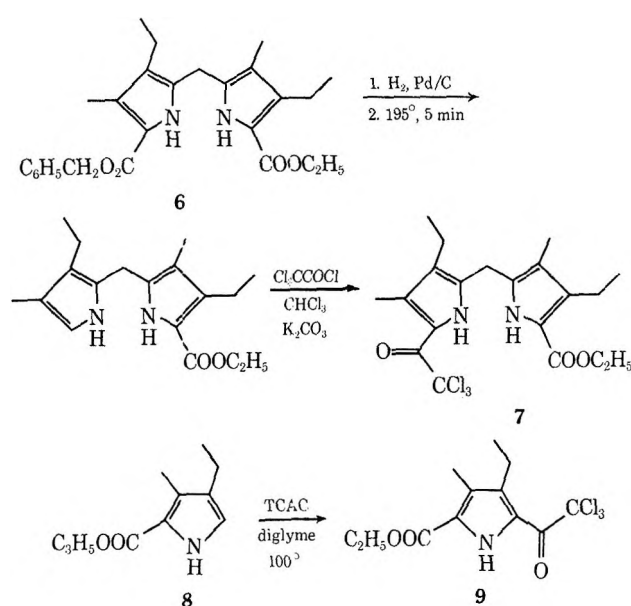
Alcoholysis of Trichloroacetylpyrroles.—Trichloroacetylpyrroles have been successfully converted to the corresponding pyrrole acids by heating in aqueous sodium hydroxide.[3] This reaction undoubtedly involves hydroxide ion attack at the carbon of the tri-

(7) Prepared by D. Bergstrom, Ph.D. Thesis, University of California, Berkeley, 1970.

chloroacetyl carbonyl followed by trichloromethyl anion elimination. If this mode of reaction could be extended to alcohols it would lead directly to pyrrole esters, which are much more useful synthetic intermediates than the acids. The first choice was to attempt preparation of methyl esters, and we found that methanol and methoxide at room temperature affected instantaneous and quantitative conversion of 2-TCA-pyrrole to 2-methoxycarbonylpyrrole. Triethylamine (TEA) and refluxing methanol also affected the conversion rapidly, the half-life being less than 5 min.

Table I indicates the conversions that have been carried out. The reaction is greatly influenced by the steric factors in the alcohol as well as the base, as methanol reacts extremely rapidly in this haloform-type reaction, but other alcohols behave much more sluggishly. Isopropyl alcohol reacts only poorly with TEA as base; with alkoxide the reaction proceeds fairly rapidly, but is accompanied by much darkening and formation of side products. *tert*-Butyl alcohol reacted not at all even with the most effective alkoxide catalyst.

The reactions utilizing potassium carbonate as base point out again the value of this heterogeneous system. The rate of ester formation is much greater than with TEA, no darkening of the reaction occurs, the base is easily removed, and the conditions are still much milder than with alkoxide catalyst. Of particular interest are entries 10 and 11, where the advantage of the mild base is well demonstrated. The diesters were obtained with no contamination of the preexisting ethyl esters whatsoever. These reactions were all conducted on a small scale and were admirably suited for uv monitoring, the absorption maximum shifting cleanly from 312 to around 265 nm for the monosubstituted and from 317 to around 282 nm for the fully substituted pyrroles.

Another possible utilization of the difunctionality is the selective conversion of trichloroacetyl to carboxyl. This conversion has been accomplished by heating in sodium hydroxide, which does not hydrolyze β-ethoxycarbonyl groups.[3] However, since α-ethoxycarbonyl groups are much more susceptible to alkaline hydrolysis,[8] we preferred to operate at lower pH. When ethyl 3-methyl-4-ethyl-5-trichloroacetyl-2-pyrrolecarboxylate (9) was heated in aqueous potassium carbonate for less than 2 min the trichloroacetyl group was converted to carboxyl with no loss of ethyl ester. Potassium bicarbonate took 45 min but the results were similar; isolated yields in the two cases were 91 and 87%, respectively. These two reagents also convert 2-TCA-pyrrole to 2-pyrrolecarboxylic acid, but not quite so rapidly. With potassium carbonate the reaction was complete in 25 min using the concentrations of the above experiment.

A recent publication[4] described the improved synthesis of trifluoroacetylpyrroles using trifluoroacetic anhydride with dimethylaniline as an acid scavenger. Attempted extension of the alcoholysis reaction to TFA pyrroles was unsuccessful. Although these compounds could be converted to the corresponding acid with hydroxide, alcoholysis under a variety of con-

ditions gave at best less than 20% yield of the desired ester.

Thus trichloroacetylation of pyrroles, in the presence of an acid scavenger where necessary, and subsequent treatment with an alcohol and mild base, is a convenient method for directly introducing an ester group into the pyrrole nucleus. The trichloroacetylation reaction gives good yields when the pyrrole ring is unsubstituted, alkyl substituted, or α- or β-ethoxycarbonyl substituted. Alcoholysis to ester, which proceeds in synthetically useful yields with primary alcohols, takes place readily in the presence of a tertiary amine or potassium carbonate, and other ester groups in the molecule are unaffected. Also, pyrrole acids may be prepared from TCA-pyrroles in the presence of other nuclear ester groups without affecting these preexisting esters using carbonate reagents.

Experimental Section[9]

2-Trichloroacetylpyrrole.—To a refluxing solution of 14 ml of chloroform and 3.24 ml (5.38 g, 29.5 mmol) of trichloroacetyl chloride was added over 60 min a solution of 1.85 ml (1.80 g, 26.8 mmol) of pyrrole and 3.43 ml (3.15 g, 29.5 mmol) of 2,6-lutidine in 14 ml of chloroform. Refluxing was continued for 15 min, the solvent was evaporated, ether was added, and the mixture was filtered. The light-yellow filtrate was washed twice with 3 N HCl and thrice with water, dried, and evaporated, giving a crude yield of 5.69 g (100%). Chromatography on silica gel, elution with chloroform, and recrystallization from hexane gave pure trichloroacetylpyrrole: yield 4.54 g (80%); mp 73.5–74° (lit.[3] mp 70°); uv 312 nm (ϵ 13,400); nmr (CCl$_4$) δ 6.27 (m, 1), 7.12 (m, 1), 7.31 (m, 1), 10.4 (br s, 1); mass spectrum m/e (rel intensity) 215 (4), 213 (13), 211 (M$^+$, 15), 150 (7), 149 (4), 148 (11), 95 (6), 94 (100), 66 (17).

3,5-Dimethyl-2-trichloroacetylpyrrole.—To 8.55 g (62 mmol) of anhydrous potassium carbonate, 20 ml of chloroform, and 1.71 ml (15.5 mmol) of TCAC was added over 65 min a solution of 1.81 g (12.4 mmol) of 2,4-dimethylpyrrole in 10 ml of chloroform. After completion of the addition, the mixture was filtered, the solid was washed with chloroform, the combined washings and filtrate were washed once with saturated NaHCO$_3$ solution, once with water, and thrice with brine, and the solution was evaporated, leaving a residue of 2.94 g (99%). Chromatography on silica gel, elution with chloroform, and recrystallization from hexane gave 2.23 g (75%) of 3,5-dimethyl-2-trichloroacetylpyrrole: mp 107–108° (lit.[3] mp 106–107°); uv 324 nm (ϵ 15,600); nmr δ 2.32 (s, 3), 2.41 (s, 3), 5.92 (m, 1), 8.8 (br s, 1); mass spectrum m/e (rel intensity) 243 (5), 241 (15), 239 (M$^+$, 16), 178 (7), 176 (10), 123 (8), 122 (100), 94 (4), 67 (7).

1-Trichloroacetyl-2,4-dimethylpyrrole was isolated as the first fraction on chromatography of the trichloroacetylation mixture: nmr δ 2.00 (s, 3), 2.45 (s, 3), 5.85 (m, 1), 7.27 (m, 1); mass spectrum m/e (rel intensity) 241 (6), 239 (M$^+$, 8), 206 (6), 205 (5), 204 (9), 122 (7), 95 (5), 94 (100), 67 (9).

Ethyl 3-Methyl-4-ethyl-5-trichloroacetyl-2-pyrrolecarboxylate (9).—A solution of 1.15 g (6.4 mmol) of ethyl 3-methyl-4-ethyl-2-pyrrolecarboxylate (8), 9.0 ml of diglyme, and 3.49 ml (31.7 mmol) of TCAC was stirred at 100° for 19 hr. The reaction mixture was then poured into ice water and diluted with ether, and the layers were separated. The ether was washed twice with water, twice with bicarbonate, and twice with brine, dried (MgSO$_4$), and evaporated. Chromatography of the residue on silica gel, eluting with chloroform, gave 1.55 g (75%) of a pale yellow oil: uv 317 and 236 nm; nmr δ 1.13 (t, 3), 1.40 (t, 3), 2.34 (s, 3), 2.82 (q, 2), 4.38 (q, 2), 9.7 (br s, 1); mass spectrum m/e (rel intensity) 329 (3), 327 (10), 325 (M$^+$, 10), 290 (6), 209 (14), 208 (100), 163 (10), 162 (85).

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(8) A. H. Corwin and J. L. Straughn, *J. Amer. Chem. Soc.*, **70**, 1416 (1948).

Anal. Calcd. for $C_{12}H_4NO_3Cl_3$: C, 44.2; H, 4.3. Found: C, 43.8; H, 4.3.

4-Methyl-3'-ethyl-3-(β-methoxycarbonylethyl)-5-ethoxycarbonyl-5'-trichloroacetyl-2,2'-dipyrrylmethane (3).—The corresponding methane-5'-carboxylic acid 1 (27 mg, 0.069 mmol)[7] was heated at 195° for 5 min to effect decarboxylation and the decarboxylated methane 2, dissolved in 2.0 ml of chloroform, was added to 127 mg (0.92 mmol) of potassium carbonate and 2.0 ml of chloroform containing 12.3 μl (0.112 mmol) of TCAC. The mixture in the flask was stirred at room temperature as the solution of 2 was added over 70 min. During and after the addition, another 30 μl (0.29 mmol) of TCAC was added and the mixture was heated at reflux for 30 min, during which time no change was observed in uv peak ratios. The reaction mixture was filtered, the filtrate was washed once with saturated bicarbonate, twice with brine, dried, and evaporated, and the residue was chromatographed on silica gel, eluting with chloroform. A 12-mg (35%) fraction contained the pure product, dipyrrylmethane 3: uv 326 and 278 nm; nmr δ 1.20 (t, 3), 1.32 (t, 3), 2.26 (s, 3), 2.6 (m, 6), 3.62 (s, 3), 4.03 (s, 2), 4.22 (q, 2), 6.05 (d, 1), 9.1 (br s); mass spectrum m/e (rel intensity) 494 (1), 492 (2), 490 (M+, 2), 456 (37), 454 (44), 421 (33), 420 (52), 384 (30), 383 (48), 372 (41), 345 (37), 299 (100). High resolution mass spectrum calcd for $C_{21}H_{25}N_2O_5Cl_3$: 490.0829. Found: 490.0835.

3,4'-Dimethyl-3',4-diethyl-5-ethoxycarbonyl-5'-trichloroacetyl-2,2'-dipyrrylmethane (7).—Hydrogenolysis of the 5'-o-chlorobenzyloxycarbonyl compound 6[7] gave the 5'-carboxy compound, and 254 mg (0.73 mmol) of this acid was decarboxylated by heating for 3 min at 198°. The resulting oil was dissolved in 3.0 ml of chloroform and added to 1.45 g (11.0 mmol) of potassium carbonate, 5.0 ml of chloroform, and 242 μl (2.20 mmol) of TCAC with vigorous stirring over 50 min. Stirring was continued for another 15 min, and then the mixture was poured into saturated NaHCO₃ solution and diluted with chloroform, and the layers were separated. The organic phase was washed twice with brine, dried (MgSO₄), and evaporated, giving 325 mg (99%) of a reddish-brown solid which was recrystallized from hexane: yield 231 mg (70%) of needles; mp 151–153°; uv 335 nm (ε 17,100), 279 (20,500); nmr δ 1.07 (t, 3), 1.11 (t, 3), 1.28 (t, 3), 1.95 (s, 3), 2.34 (s, 3), 2.46 (q, 2), 2.70 (q, 2), 3.98 (s, 2), 4.18 (q, 2), 9.03 (br s, 1), 10.00 (br s, 1); mass spectrum m/e (rel intensity) 450 (4), 448 (10), 446 (M+, 11), 414 (8), 412 (12), 330 (26), 329 (100), 274 (11), 273 (49).

Anal. Calcd for $C_{20}H_{25}N_2O_3Cl_3$: C, 53.6; H, 5.6; N, 6.3. Found: C, 53.7; H, 5.5; N, 6.5.

Methyl 2-Pyrrolecarboxylate.—2-TCA-pyrrole (101 mg, 0.48 mmol) was added to a solution of 26 mg (1.1 mg-atoms) of sodium in 11 ml of methanol. Reaction was immediate and the solution was evaporated to dryness, the residue was partitioned between ether and water, and the ether was washed three times with water, dried and evaporated, leaving 52 mg (88%) of crystals which were recrystallized from hexane: mp 69–70° (lit.[10] mp 72–73°); uv 265 nm (ε 15,400); nmr δ 3.80 (s, 3), 6.22 (m, 1), 6.95 (m, 2), 10.1 (br s, 1); mass spectrum m/e (rel intensity) 126 (7), 125 (M+, 100), 95 (7), 94 (98), 94 (30), 66 (17), 65 (9), 39 (23), 38 (7).

Allyl 2-Pyrrolecarboxylate.—2-TCA-pyrrole (424 mg, 2.00 mmol) was dissolved in 0.68 ml (0.58 g, 10.0 mmol) of allyl alcohol, 0.35 ml (0.25 g, 2.5 mmol) of triethylamine was added, and the solution was heated at 60° for 38 hr. The solvent was evaporated, the residue was partitioned between ether and water, the aqueous layer was twice extracted with ether, and the combined ether layers were washed with three portions of water, dried (MgSO₄), and evaporated, giving 288 mg (95%) of brown oil. This was distilled (10 mm, 90°) onto a cold finger to give 231 mg (77%) of the allyl ester: uv 265, 229 nm; nmr δ 4.73 (d, 2), 5.2 (m, 2), 5.8 (m, 1), 6.20 (m, 1), 6.87 (m, 2); mass spectrum m/e (rel intensity) 151 (M+, 42), 106 (6), 95 (11), 94 (100), 93 (18), 86 (23), 77 (8), 76 (15), 41 (15), 39 (15).

Anal. Calcd for $C_8H_9NO_2$: C, 63.6; H, 6.0; N, 9.3. Found C, 63.3; H, 6.1; N, 9.1.

γ,γ-Dimethylallyl 2-Pyrrolecarboxylate was prepared from 2-TCA-pyrrole, dimethylallyl alcohol, and triethylamine, as described for the allyl ester, by heating for 62 hr. Distillation (10 mm, 90°) onto a cold finger gave a 72% yield of the β,β-dimethylallyl ester: uv 265 and 229 nm; nmr (CCl₄) δ 1.75 (s, 6), 4.68 (d, 2), 5.36 (m, 1), 6.07 (m, 1), 6.78 (m, 2), 10.3 (br s, 1);

mass spectrum m/e (rel intensity) 180 (12), 179 (M+, 90), 150 (11), 112 (21), 111 (100), 94 (71), 93 (86), 69 (58), 68 (18), 67 (24), 66 (23).

Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.0; H, 7.3. Found: C, 66.6; H, 7.2.

Benzyl 2-pyrrolecarboxylate was prepared from 2-TCA-pyrrole and benzyl alcohol using the triethylamine procedure above and heating for 38 hr. The benzyl ester was obtained in 92% yield on crystallization from hexane: mp 54–55°; uv 267 nm (ε 18,000), 236 (4900), nmr δ 5.27 (s, 2), 6.21 (m, 1), 6.89 (m, 2), 7.32 (s, 5), 9.7 (br s, 1); mass spectrum m/e (rel intensity) 202 (15), 201 (M+, 100), 94 (29), 92 (9), 91 (91).

Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.6; H, 5.5. Found: C 71.6; H, 5.4.

Isopropyl 2-Pyrrolecarboxylate.—Sodium (123 mg, 5.35 mg-atoms) was dissolved in 30 ml (200 mmol) of isopropyl alcohol and heated to 70°, and 1.0 g (4.7 mmol) of 2-TCA-pyrrole was added. The temperature was raised to 80° for 2.5 hr, the solvent was evaporated, the residue was partitioned between ether and water, and the ether layer was washed thrice with water, dried (MgSO₄), and evaporated. Silica gel–chloroform chromatography of the residue and sublimation gave 109 mg (15%) of the isopropyl ester: mp 32–34°; uv 265 nm (ε 16,800), 235 (4800); nmr δ 1.32 (d, 6, J = 9 Hz), 5.18 (m, 1), 6.20 (m, 1), 6.88 (m, 2); mass spectrum m/e (rel intensity) 153 (M+, 30), 111 (50), 94 (45), 93 (100), 67 (8), 66 (19), 65 (9).

Anal. Calcd for $C_8H_{11}NO_2$: C, 62.7; H, 7.2. Found: C, 62.6; H, 7.2.

2-Ethoxycarbonyl-5-methoxycarbonyl-3-methyl-4-propylpyrrole was prepared from ethyl 3-methyl-4-propyl-5-trichloroacetyl-2-pyrrolecarboxylate and methanol using the triethylamine procedure above and heating at 90° for 20 min. Crystallization from hexane gave a 25% yield of the 5-methoxycarbonyl compound: mp 41–42°; uv 282 nm; nmr δ 0.91 (t, 3), 1.36 (t, 3), 2.07 (s, 3), 2.72 (t, 2), 3.85 (s, 3), 4.35 (q, 2); mass spectrum m/e (rel intensity) 254 (9), 253 (M+, 57), 225 (18), 224 (100), 222 (6), 208 (7), 192 (8), 179 (11), 178 (85), 176 (16), 174 (16), 174 (7), 148 (9), 146 (9).

Anal. Calcd for $C_{13}H_{19}NO_4$: C, 61.6; H, 7.6; N, 5.5. Found: C, 61.4; H, 7.6; N, 5.5.

2-Benzyloxycarbonyl-5-ethoxycarbonyl-3-ethyl-4-methylpyrrole.—Ethyl 3-methyl-4-ethyl-5-trichloroacetyl-2-pyrrolecarboxylate (9), 425 mg (1.30 mmol), 0.70 g (6.5 mmol) of benzyl alcohol, and 225 mg (1.62 mmol) of potassium carbonate were heated at 60° for 15 min. The reaction mixture was diluted with ether and filtered, and the filtrate was washed twice with salt solution, dried (MgSO₄), and evaporated. The residue was chromatographed on silica gel, eluting with benzene, to yield 330 mg (81%) of the benzyl ester: mp 47–50°; uv 283 nm (ε 22,800), 221 (17,800), 218 (18,000); nmr δ 1.08 (t, 3), 1.28 (t, 3), 2.24 (s, 3), 2.72 (q, 2), 4.26 (q, 2), 5.27 (s, 2), 7.31 (s, 5), 9.81 (br s, 1); mass spectrum m/e (rel intensity) 316 (15), 315 (M+, 63), 270 (13), 269 (8), 226 (6), 225 (16), 224 (100), 208 (26), 206 (13), 178 (16), 162 (22), 160 (15), 149 (21), 111 (15), 97 (16), 95 (14), 91 (88).

Anal. Calcd for $C_{18}H_{21}NO_4$: C, 68.6; H, 6.7; N, 4.4. Found: C, 68.6; H, 6.6; N, 4.3.

β,β,β-Trichloroethyl 3,5-dimethyl-2-pyrrolecarboxylate was prepared from 3,5-dimethyl-2-trichloroacetylpyrrole and β,β,β-trichloroethanol using the potassium carbonate procedure described above. Crystallization from petroleum ether (bp 30–60°) gave the β,β,β-trichloroethyl ester in 74% yield: mp 126–128°; uv 281 nm (ε 22,900), 249 (4900); nmr (CCl₄) δ 8.8 (br s, 1), 5.70 (d, 1, J = 3 Hz), 4.84 (s, 2), 1.97 (s, 3), 1.93 (s, 3); mass spectrum m/e (rel intensity) 275 (4), 273 (30), 271 (100), 269 (99), 238 (2), 236 (12), 234 (19), 138 (19), 122 (93), 121 (95), 94 (7), 93 (8).

Anal. Calcd for $C_9H_{10}Cl_3NO_2$: C, 40.0; H, 3.7; N, 5.2. Found: C, 40.3; H, 3.9; N, 5.3.

β-Chloroethyl 3,5-dimethyl-2-pyrrolecarboxylate was prepared by the potassium carbonate procedure, using excess 2-chloroethanol, at 60° for 2 hr. The mixture was cooled, diluted with ether, and filtered, and the filtrate was washed twice with brine, dried (MgSO₄), and evaporated. Crystallization of the residue from hexane gave pure ester in 66% yield: mp 79–82°; uv 278 nm (ε 20,500), 248 (4800); nmr δ 2.23 (s, 3), 2.30 (s, 3), 3.70 (t, 2), 4.47 (t, 2), 5.78 (d, 1), 9.4 (br s, 1); mass spectrum m/e (rel intensity) 203 (15), 201 (M+, 48), 166 (12), 139 (45), 138 (34), 123 (12), 122 (100), 121 (98), 120 (46), 95 (23), 94 (51), 93 (59), 92 (28), 67 (67), 66 (77), 65 (59), 64 (10), 63 (22).

(10) H. Fischer and H. Orth, "Die Chemie des Pyrrols," Vol. 1, Akad. Verlags., Leipzig, 1934, p 237.

Anal. Calcd for $C_3H_{12}ClNO_2$: C, 53.6; H, 6.0; N, 7.0. Found: C, 53.4; H, 5.9; N, 7.0.

5-Ethoxycarbonyl-3-ethyl-4-methyl-2-pyrrolecarboxylic Acid.— The corresponding 5-trichloroacetylpyrrole 9 (233 mg, 0.71 mmol) was heated at 100° with 1.97 g (14.3 mmol) of potassium carbonate in 3 ml of water for 5 min. Cooling and acidification to pH 5.5 gave 145 mg (91%) of the acid, mp 214–217° (lit.[10] mp 211°).

In the same manner, but heating with a potassium bicarbonate solution for 45 min, an 87% yield of the acid was obtained: uv 283 and 217 nm; nmr δ 1.03 (t 3), 1.30 (t, 3), 2.20 (s, 3), 2.68 (q, 2), 4.23 (q, 2), 8.8 (br s, 1), 11.23 (br s, 1).

A Direct Synthesis of 2-Acylindoles

CHARLES D. JONES* AND TULIO SUÁREZ

The Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana 46206

o-Aminocarbonyl compounds have been found to undergo direct and facile conversion to 2-acylindoles upon heating with α-halo ketones in dimethylformamide. A variety of o-aminoacetophenones and o-aminobenzophenones gave the corresponding 2-acyl-3-methyl- and 2-acyl-3-phenylindoles, respectively. Although o-aminobenzaldehyde did not undergo this reaction, use of the derived ethylene acetal permitted preparation of the 3-unsubstituted 2-acylindole in moderate yield. The overall indole formation is presumed to proceed *via* N-alkylation, followed by intramolecular aldol condensation and dehydration. Chemical evidence in support of this hypothesis is presented.

Although the direct assemblage of 2-acylindoles, depicted by the transformation of 1 → 2, represents an
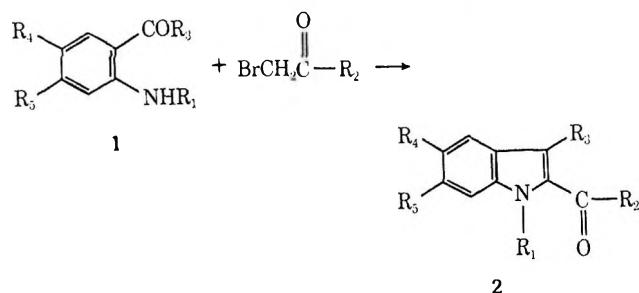
attractive route to the indole nucleus, this conversion has not been exploited to any great degree.[1] Our need for 2-acylindoles for use in a related problem prompted us to examine this reaction in some detail. In this paper we wish to report a convenient method for the transformation of o-amino ketones into 2-acylindoles under mild reaction conditions and in good yield.

In a preliminary experiment, equivalent quantities (0.5 mmol) of o-aminobenzophenone and phenacyl bromide dissolved in DMF-d_7 were heated together at 80° for 12 hr. Periodic observation of the nmr spectrum of the mixture revealed a loss of the halo ketone methylene singlet at δ 4.94. A broad one-proton signal appeared at δ 11.90, attributable to the NH proton of 2-benzoyl-3-phenylindole (2a). When the reaction was repeated on a preparative scale, crystalline 2a was obtained in 73% yield (Table I), and its structure was fully characterized spectroscopically.

Further efforts to evaluate the scope of the reaction first concerned the effect of substituents in the o-amino ketone moiety. Under the same reaction conditions, the appropriate o-aminobenzophenones formed 5-chloro- (2b), 6-chloro- (2c), and 5,6-dimethoxyindole

(2d) in good yields, thereby demonstrating the tolerance of the reaction for diverse aromatic substituents. Furthermore, the indole formation proceeded equally well with N-alkyl-o-amino ketones, as shown by the formation of 1-methyl-2-benzoyl-3-phenylindole (2e), also in good yield.

Particular attention was warranted concerning the variation of R_3 substituents since 2-acylindoles lacking substituents at the 3 position are often difficult to prepare by available means. The reaction of o-aminoacetophenone and phenacyl bromide yielded under the usual conditions 2-benzoyl-3-methylindole (2f). However, when treated similarly, o-aminobenzaldehyde gave an intractable tar to the virtual exclusion of indole formation. Nevertheless, by modifying reactants and reaction conditions, it was possible to prepare the 3-unsubstituted derivative. To this end, acetal 3 was alkylated with phenacyl bromide in the presence of 1 equiv of NaHCO$_3$. Subsequent acidification and heating cleaved the presumed intermediate acetal (4) and also effected condensation to 2-benzoylindole (2g).
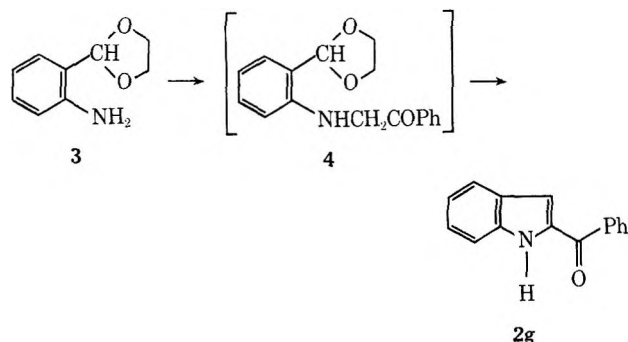
Chemical evidence that reactions of this type proceed *via* the expected N-alkylation, followed by condensation, was obtained in the preparation of 2f. In this example, cyclization of intermediate 6 to the indole is the rate-limiting step. Thus, heating the reactants

(1) To our knowledge, only α-bromo diketones have been converted to indoles by this reaction; see G. Kempter and E. Schiewald, *J. Prakt. Chem.*, 28, 169 (1965), and R. I. Fryer, J. V. Earley, and L. H. Sternbach, *J. Org. Chem.*, 32, 3798 (1967).

TABLE I

2-ACYLINDOLES[a]

Compd	R_1	R_2	R_3	R_4	R_5	Recrystn solvent	Mp, °C	% yield
2a	H	Ph	Ph	H	H	MeOH	203–204 (lit.[b] 203.5–5.0)	73
2b	H	Ph	Ph	Cl	H	MeOH	194–195	75
2c	H	Ph	Ph	H	Cl	MeOH	198–199	70
2d	H	Ph	Ph	OCH₃	OCH₃	MeOH	211–212	50
2e	CH₃	Ph	Ph	H	H	Hexane	87–88	71
2f	H	Ph	CH₃	H	H	MeOH	138–139 (lit.[c] 140)	69
2g	H	Ph	H	H	H	MeOH	147–148 (lit.[d] 146–148)	60
2h	H	CH₃	Ph	H	H	MeOH	150–151 (lit.[e] 151)	69

[a] Satisfactory analytical values (±0.4 % for C, H, N) were reported for compounds 2b–e: Ed. [b] D. Y. Curtin, M. L. Poutsma, *J. Amer. Chem. Soc.*, **84**, 4887 (1962). [c] V. I. Shvedov, V. V. Alekseev and A. N. Grinev, *Khim-Farm. Zh.*, **2**, 8 (1968); *Chem. Abstr.*, **70**, 11469f (1969). [d] R. J. Sundberg, *J. Org. Chem.*, **30**, 3604 (1965). [e] Reference 2.

for a relatively short period yielded the uncyclized intermediate 6. With further heating, 6 converted easily into the expected indole 2f.

5   6   2f
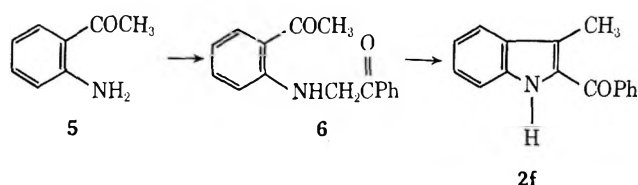
Modifications of R_2 are important since the removal of the 2-acyl group would provide a synthesis of the parent indoles. The successful reaction of bromoacetone with *o*-aminobenzophenone to provide the 2-acetyl derivative 2h proves that the alkylation–cyclization sequence applies to both alkyl- and aryl bromomethyl ketones. The deacetylation of 2h to the parent 3-phenylindole has already been reported.[2]

In conclusion, the alkylation–condensation sequence between *o*-amino ketones and α-bromo ketones provides ready access to a wide variety of 2-acylindoles. Removal of the 2-acetyl group gives rise to the parent indoles themselves. We are continuing our efforts regarding the more easily removable functions at the 2 position and the application of this method to the synthesis of indoles of biological significance.

Experimental Section

All melting points were taken in a Mel-Temp capillary melting point block and are uncorrected. Nmr spectra were recorded on a Varian T-60 spectrometer in CDCl₃ or DMF-d_7 using TMS as internal reference. Except for compound 2g, the following general procedure was used for all of the 2-acylindoles in Table I. Satisfactory analytical data has been obtained for all new compounds.

General Procedure.—The *o*-amino ketone (0.02 mol) and the appropriate α-halo ketone (0.02 mol) were dissolved in 50 ml of anhydrous DMF, and the solution was heated in an oil bath (80–90°) for 16 hr. The reaction mixture was then poured over ice (1500 ml), and the crystalline 2-acylindole was isolated by filtration.

(2) R. H. F. Manske, W. H. Perkin, Jr., and R. Robinson, *J. Chem. Soc.*, 1 (1927).

In those cases (2e, 2a, and 2h) where an oil was obtained, the product was extracted into ether (200 ml), and the ether layer was routinely washed with 48% HBr (10 ml), 5% NaHCO₃ (2 × 50 ml), and, finally, H₂O (50 ml). Drying the ether solution over MgSO₄, followed by evaporation, resulted in each instance in a yellow oil which was separated from polymeric material by column chromatography (1.5 in. × 8 in. silica gel using ether as the eluent). Trituration of the resultant products with MeOH or hexane gave the crystalline 2-acylindole. Analytical samples were prepared by recrystallization from MeOH or by vacuum sublimation.

Preparation of 3-Unsubstituted Derivatives.—Amino acetal 3[3] (5.0 g, 0.03 mol) was alkylated when stirred in DMF (100 ml) at room temperature for 14 hr with phenacyl bromide (6.05 g, 0.03 mol) in the presence of NaHCO₃ (3 g, 0.035 mol). Then 0.5 cc of 48% HBr was added, and the mixture was heated at 80–90° for 24 hr. The reaction mixture was then poured over ice and worked up as described above to provide 4.0 g (60%) of 2-benzoylindole (2g). This material was characterized by its melting point as well as its nmr, ir, and uv spectra, each of which closely matched the corresponding values reported for 2-benzoylindole prepared by a different route.[4]

Isolation of Uncyclized Intermediate 6.—A solution of *o*-aminoacetophenone (5.0 g, 0.037 mol) and phenacyl bromide (7.35 g, 0.037 mol) in DMF (100 cc) was heated at 80–90° for 2 hr. The hot mixture was treated with water until slightly cloudy and then allowed to cool slowly. Precipitated yellow crystals were collected, washed with cold MeOH, and then recrystallized from the same solvent to provide 4.5 g (48%) of 6: mp 131–132° nmr δ (CDCl₃) 2.54 (s, 3 H, COCH₃), 4.60 (d, 2 H, J = 4 Hz, COCH₂N), 6.45–6.75 (m, 2 H, Ar H), 7.10–8.10 (m, 7 H, Ar H), 10.40 (m, 1 H, NH); mass spectrum M⁺ 253. *Anal.* Calcd for C₁₆H₁₅NO₂: C, 75.87; H, 5.97; N, 5.53; O, 12.63. Found: C, 75.78; H, 6.04; N, 5.57; O, 12.62.

Further heating of 6 (2 g) at 80–90° in 20 ml of DMF containing 0.5 cc of HBr for 16 hr gave the expected 2-benzoyl-3-methylindole (2f), mp 138–139°.

Registry No.—2a, 36004-54-3; 2b, 36004-55-4; 2c, 36004-56-5; 2d, 36004-57-6; 2e, 36004-58-7; 2f, 1025-97-4; 2g, 1022-86-2; 2h, 36015-23-3; 3, 26908-34-9; 6, 36004-62-3.

(3) This amino acetal was prepared by reduction of *o*-nitrobenzaldehyde ethylene acetal over Raney nickel in ethanol solution at 60° for 45 min. Although this compound decomposes on standing overnight at 25°, a freshly prepared sample gave the following spectra data: nmr δ (CDCl₃) 4.02 (s, 4 H, OCH₂CH₂O), 3.80–4.40 (broad, 2 H, NH₂), 5.77 (s, 1 H, ArCH<), 6.42–7.38 (m, 4 H, Ar H).

(4) Reference *d* in Table I.

The Preparation of 2-Substituted Indole Sulfonamides and Subsequent Conversion to Indole-2-carboxylic Acids, Indole-2-carbonitriles, and 2-Acylindoles

CHARLES D. JONES

The Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana 46206

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A convenient and general synthesis of indole-2-carboxylic acids, indole-2-carbonitriles, and 2-acylindoles is described. Sulfonamides of *o*-aminocarbonyl compounds (1) are N-alkylated by active halides to provide compounds of type 2. On base-catalyzed aldol condensation of 2, and subsequent dehydration, crystalline 2-substituted indole sulfonamides (3) are obtained. Hydrolysis of 3 removes the tosyl moiety to yield the corresponding 2-acylindoles and indole-2-carbonitriles. The synthesis of indole-2-carboxylic acids from 2-carbomethoxy-indole sulfonamides was also achieved in a similar manner.

In an accompanying paper,[1] a method was described for the preparation of 2-acylindoles by the direct condensation of *o*-amino ketones with *α*-halo ketones. As an extension of this investigation, we wish to discuss the use of an analogous alkylation–condensation route to 2-acylindoles which we have applied successfully to the preparation of synthetically more useful derivatives (*i.e.*, indole-2-carboxylic acids and indole-2-carbonitriles).

Although *o*-amino ketones and aldehydes do not yield indolic products on direct reaction with methyl bromoacetate or bromoacetonitrile under conditions analogous to those described earlier[1] (DMF, 80–90°), we have found that the corresponding *N*-sulfonyl derivatives can be converted into the desired indoles in excellent yield (Chart I). In this method sulfonamides

CHART I

1, prepared by sulfonylation of *o*-amino ketones or by Rosenmund reduction of *N*-sulfonylanthranilic acid halides, are alkylated by active halides to provide 2 (Table I). On base-catalyzed aldol condensation of 2 and subsequent dehydration of the intermediate carbinol(s), crystalline 2-substituted indole sulfonamides (3) are obtained in excellent yield. This indole-forming reaction is generally applicable to the R and Z substituents listed in Table II.

Hydrolysis of the resultant 2-substituted indole sulfonamides (3) with aqueous NaOH removes the

tosyl moiety and provides the 2-substituted indole (4) in nearly quantitative yield (Table III). If a 2-carboxylic ester group is initially present in 3, saponification also occurs under conditions of excess base to provide the corresponding indole-2-carboxylic acid (5), also in excellent yield (Table III).

In summary, N-alkylation of *o*-amino ketone sulfonamides by active halo compounds, followed by cyclization and hydrolysis of the resultant indole sulfonamides, provides a convenient route to 2-acylindoles, indole-2-carbonitriles,[2] and indole-2-carboxylic acids. The indole-forming reactions proceed readily under quite mild conditions and the overall sequence permits isolation of the various intermediates enroute to the final products. Since decarboxylation of indole-2-carboxylic acids proceeds in virtually quantitative yield on simple heating, the parent indoles are also easily accessible *via* this sequence.
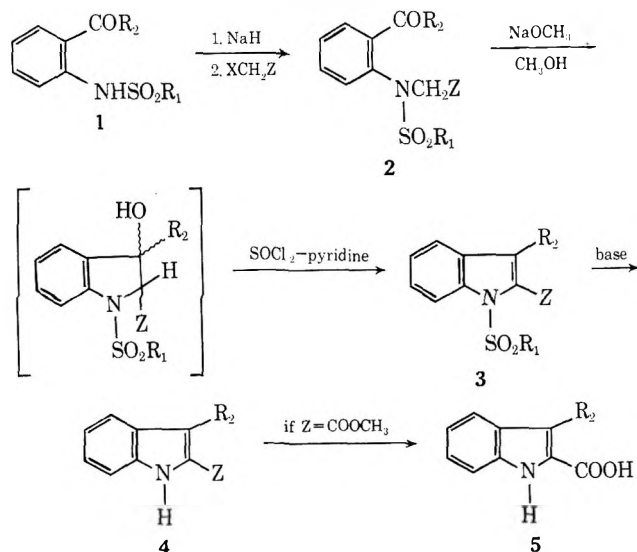
Experimental Section

Melting points were determined on a Mel-Temp apparatus and are uncorrected. Nmr spectra were recorded on a Varian T-60 spectrometer in CDCl$_3$ or DMSO-d_6 using TMS as internal reference. Mass spectra were taken on a CEC 21-110 spectrometer. All compounds included in this report gave correct molecular ions and satisfactory analytical and spectral data.

General Procedure for Alkylation of *N*-Sulfonyl-*o*-amino-carbonyl Compounds by Methyl Bromoacetate, Phenacyl Bromides, and Chloroacetonitrile.—The appropriate sulfonamide 1 (0.25 mol) was suspended in anhydrous DMF (100 cc) at 0°. With stirring, NaH (6.0 g, 0.25 mol) was added in small portions and the mixture was kept at 0° for an additional 30 min. The resulting yellow amide anion solution was added dropwise over a 30-min period to a stirred solution of the appropriate halide (0.25 mol) in 20 cc of DMF. (In the alkylation of *N*-*p*-toluene-sulfonyl-*o*-aminobenzaldehyde and *N*-*p*-toluenesulfonyl-*o*-amino-acetophenone, a 5-fold excess of methyl bromoacetate was advantageous.) After the solution was stirred for 1 hr at room temperature, the DMF was evaporated, and H$_2$O was added. The precipitated product (2a–i) (Table I) was collected on a filter and recrystallized from MeOH or MeOH–H$_2$O.

Cyclization of 2a–i. General Procedure for Preparation of 2-Substituted Indole Sulfonamides.—To the alkylated sulfon-anilide 2a–h (0.025 mol) suspended in MeOH (400 ml) was added NaOMe (0.025 mol). (In the case of 2i, 0.025 mol of potassium *t*-butoxide in 300 ml of *t*-BuOH was used in lieu of NaOMe–MeOH.) After the suspension was stirred for 2 hr, the solvent was evaporated on a rotary, and the residue was dissolved in a mixture of H$_2$O (300 ml) and CHCl$_3$ (200 ml). The chloroform layer was washed with H$_2$O (50 ml), dried over MgSO$_4$, and evaporated to dryness.

(1) C. D. Jones and T. Suárez, *J. Org. Chem.*, **37**, 3622 (1972).

(2) While this manuscript was in preparation an example of synthesis of an indole-2-carbonitrile by a similar sequence appeared in the literature; see M. Oklobdzija, M. Japelj, and T. Fajdiga, *J. Heterocycl. Chem.*, **9**, 161 (1972).

Table I[a]

Compd	R₁	Z	R₂	Recrystn solvent	Mp, °C	% yield
2a	C₆H₄-p-CH₃	COOCH₃	H	MeOH–H₂O	115–116	85
2b	C₆H₄-p-CH₃	COOCH₃	CH₃	MeOH	90–91	90
2c	C₆H₄-p-CH₃	COOCH₃	Ph	MeOH	126–127	86
2d	C₆H₄-p-CH₃	COCH₃	Ph	MeOH	109–110	82
2e	C₆H₄-p-CH₃	COPh	Ph	MeOH	159–160	96
2f	C₆H₄-p-CH₃	COC₆H₄-p-OCH₃	Ph	CHCl₃–MeOH	199–200	90
2g	CH₃	COC₆H₄-p-Cl	Ph	MeOH	157–158	75
2h	CH₃	COC₆H₄-p-CH₃	Ph	MeOH	135–136	88
2i	C₆H₄-p-CH₃	CN	Ph	MeOH	95–96	91

[a] Satisfactory analytical values (±0.4) for C, H, N, and O were reported for all compounds in this table and in Tables II and III: Ed.

Table II

Compd	R₁	Z	R₂	Recrystn solvent	Mp, °C	% yield
3a	C₆H₄-p-CH₃	COOCH₃	H	MeOH	83–84	95
3b	C₆H₄-p-CH₃	COOCH₃	CH₃	MeOH	114–115	89
3c	C₆H₄-p-CH₃	COOCH₃	Ph	MeOH	93–94	92
3d	C₆H₄-p-CH₃	COCH₃	Ph	MeOH	75–77	80
3e	C₆H₄-p-CH₃	COPh	Ph	Acetone	192–193	89
3f	C₆H₄-p-CH₃	COC₆H₄-p-OCH₃	Ph	MeOH	156–157	76
3g	CH₃	COC₆H₄-p-Cl	Ph	MeOH	149–150	64
3h	CH₃	COC₆H₄-p-CH₃	Ph	MeOH	164–165	63
3i	C₆H₄-p-CH₃	CN	Ph	Acetone–H₂O	147–148	31

Table III

Compd	R	Z	Recrystn solvent	Mp, °C	% yield
4d	Ph	COCH₃	MeOH	151–152 (lit.[a] 151)	92
4e	Ph	COPh	MeOH	203–204 (lit.[b] 203.4–5.0)	98
4f	Ph	COC₆H₄-p-OCH₃	MeOH	155–156	94
4g	Ph	COC₆H₄-p-Cl	MeOH	179–180	79
4h	Ph	COC₆H₄-p-CH₃	MeOH	148–149	84
4i	Ph	CN	MeOH–H₂O	145–146	99
5a	H		Et₂O–hexane	205 (lit.[c] 205)	90
5b	CN₃		Benzene–hexane	164–165 (lit.[d] 166)	85
5c	Ph		MeOH	186–187 (lit.[e] 186)	96

[a] R. H. F. Manske, W. H. Perkin, Jr., and R. Robinson, *J. Chem. Soc.*, 1 (1927). [b] D. Y. Curtin and M. L. Poutsma, *J. Amer. Chem. Soc.*, **84**, 4887 (1962). [c] S. Gabriel, W. Gerhard, and R. Wolter, *Ber.*, **56**, 1024 (1923). [d] W. B. Whalley, *J. Chem. Soc.*, 1651 (1954). [e] A. R. Kidwai and N. H. Khan, *C. R. Acad. Sci.*, **256**, 3709 (1963).

The residue was dissolved in benzene (100 ml), and pyridine (0.05 mol) was added. After the mixture was chilled to 5°, SOCl₂ (0.025 mol) was added dropwise, and the mixture was stirred at room temperature for 1 hr. Ice and water were then added; the benzene layer was separated, washed with 5% NaHCO₃ (50 cc) and with H₂O (50 cc), and dried over MgSO₄. Evaporation of the benzene, trituration with MeOH, and recrystallization from the appropriate solvent provided the N-sulfonylindole (3a–i) in good yield (Table II).

Hydrolysis of 2-Substituted Indole Sulfonamides.—The appropriate indole sulfonamide (3a–i, 5 mmol) was dissolved in 50 ml of MeOH containing 10 ml of 2 N aqueous NaOH and refluxed on a steam bath until tlc revealed no remaining starting material. (In the case of 3a, cleavage was accomplished using 1 M NaOCH₃ in refluxing MeOH with gradual introduction of moisture.) The MeOH was then evaporated, and H₂O was added. In those cases (3d–i) in which a neutral product was obtained, it was collected by filtration and purified by recrystallization from MeOH or MeOH–H₂O to provide pure 4-i (Table III).

When the hydrolysis product was an H₂O-soluble carboxylate salt, as in the cases 3a–c, the alkaline solution was washed with ether (50 cc), and the aqueous layer was then acidified. The precipitated indole-2-carboxylic acid was collected by filtration or extracted into ethyl acetate. Recrystallization of the crude product from the solvent indicated in Table III gave rise to 5a–c in excellent yield.

The Synthesis of 6-Substituted Thieno[3,2-*b*]pyrroles. Analogs of Tryptophan, Tryptamine, and Indoleacetic Acid[1,2]

A. J. HUMPHRIES, RONALD L. KEENER,[3] KUNIHIKO YANO,
F. S. SKELTON, EDWARD FREITER, AND H. R. SNYDER*

School of Chemical Sciences, University of Illinois at Urbana-Champaign, Roger Adams Laboratory, Urbana, Illinois 61801

The conversions of 6-piperidinomethylthieno[3,2-*b*]pyrrole to the thieno[3,2-*b*]pyrrole analogs of tryptophan, tryptamine, indoleacetic acid, indoleacetic acid methyl ester, the ethyl ester of *N*-acetyltryptophan, and *N*-acetyltryptophan are reported. The thieno[3,2-*b*]pyrrole compounds are much less stable than the corresponding indole derivatives.

In a preceding paper[4] we reported practical syntheses of 6-piperidinomethylthieno[3,2-*b*]pyrrole (1a) and 6-dimethylaminomethylthieno[3,2-*b*]pyrrole (1b), substances which, by analogy with the similar indole compounds, e.g., gramine,[5] were expected to serve conveniently in the synthesis of many 6-substituted thieno-[3,2-*b*]pyrroles analogous to naturally occurring indole compounds but having the benzene ring of the indole system replaced by a thiophene unit. The synthesis of the analog 7 of the amino acid tryptophan was of particular interest because of the possibility that the greater chemical reactivity of the thienopyrrole nucleus, as compared to the indole nucleus, might greatly alter the biochemical function of a peptide containing a unit of the new amino acid in a position normally occupied by a tryptophan residue.

In the present work the tertiary amine 1a and its methiodide were found to have the expected activity as alkylating agents. Thus, good yields of the nitrile 2, the alkylated amidomalonates 3a and 3c, and the cyano ester 3d were readily obtained from the methiodide of 1a. Reaction of the amine 1a with diethyl acetamidomalonate gave 3a in lower yield. Reduction of the nitrile 2 with lithium aluminum hydride gave the amine 4. Alkaline hydrolysis of the nitrile 2 produced the acid 5a, but attempts to obtain it in the pure crystalline state were unsuccessful; however, the pure methyl ester 5b was readily isolated after methylation of the crude acid with diazomethane.

In the hydrolysis and decarboxylation of the malonic acid derivatives 3a and 3c the intermediates proved to be very much more unstable than anticipated. In general, the compounds were highly sensitive to acid, heat, and air, and some of them to light, especially if traces of acid were present. In acidic media, except under strict pH control, those thienopyrroles lacking a stabilizing 5-carboethoxy group rapidly formed complex dark-colored mixtures, usually initially purple. However, it has been possible to isolate the amido ester 6a by half-saponification of 3a, followed by thermal decarboxylation of the acid ester 3b.

The amidomalonate 3a underwent saponification and decarboxylation on heating in aqueous ethanolic so-

dium hydroxide. The small amount of the corresponding malonic acid, concurrently formed with the amido acid 6b, was decarboxylated when the reaction

1a, R₂ = (CH₂)₅
b, R = R = CH₃

2

3a, Z = CO₂C₂H₅; R = C₂H₅; R¹ = CH₃
b, Z = CO₂H; R = C₂H₅; R¹ = CH₃
c, Z = CO₂C₂H₅; R = C₂H₅; R¹ = H
d, Z = CN; R = C₂H₅; R¹ = CH₃

4

5a, R = H
b, R = CH₃

6a, R = C₂H₅; R¹ = CH₃
b, R = H; R¹ = CH₃
c, R = H; R¹ = H

7

8
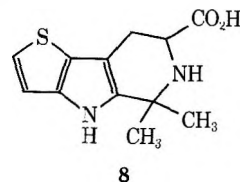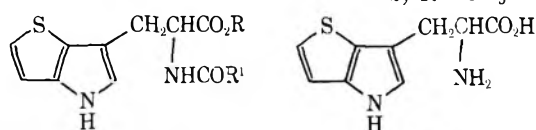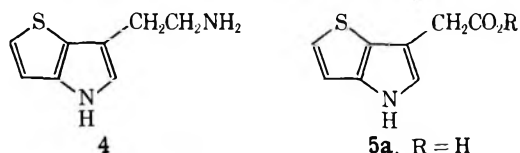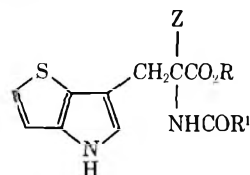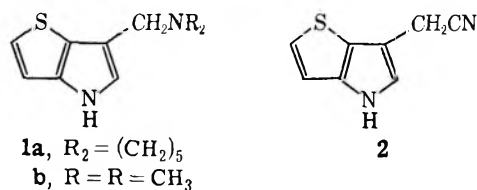
mixture was boiled after the pH was adjusted to and maintained at 6. The isolation of the amido acid 6b was accomplished by an extractive–azeotropic distillation with nitromethane, which conveniently freed it from reaction solvents and sodium chloride. No 6b was detected on attempted hydrolysis of the amido ester 6a or the cyano ester 3d.

The amino acid 7 has been obtained by hydrolysis and decarboxylation of the formamidomalonate 3c followed by deformylation without isolation of inter-

(1) Supported in part by a research grant (CA-8663) from the National Cancer Institute, U. S. Public Health Service.

(2) Abstracted in part from a thesis submitted by R. L. Keener to the Graduate College of the University of Illinois in partial fulfillment of the requirements for the degree of Doctor of Philosophy, 1967.

(3) (a) National Science Foundation Summer Fellow, 1964; (b) Phillips Petroleum Company Fellow, 1964–1966.

(4) R. L. Keener, F. S. Skelton, and H. R. Snyder, *J. Org. Chem.*, **33**, 1355 (1968).

(5) E. E. Howe, A. J. Zambito, H. R. Snyder, and M. Tishler, *J. Amer. Chem. Soc.*, **67**, 38 (1945).

mediates. One of the problems in the isolation of the amino acid 7 lay in the complete removal of sodium chloride from the very soluble crude reaction product. The purification of 7 was finally achieved by the aid of a series of Amberlite and DEAE–cellulose columns; the experimental procedures developed may prove useful in the conversion of other amidomalonates to amino acids.

The failure to obtain the amino acid 7 from the amido acid 6b led to a large number of attempts, all unsuccessful, to circumvent the final hydrolytic deacylation by utilizing intermediates derived from various carbobenzyloxy-protected amidomalonates, nitromalonic ester, and chloroacetamidomalonic ester,[6] which might permit the introduction of the free α-amino group in a nonhydrolytic step, *e.g.*, reduction or reaction with thiourea.[6] In a search for a nonhydrolytic deacylation which might be applied to 6b, it was found that, in the presence of small amounts of its dihydrochloride, hydrazine is effective in the conversion of several amido acids to the amino acids (see Experimental Section). When 6b was subjected to the action of hydrazine the reaction mixture developed much less color than had been observed in the hydrolysis attempts. However, some destruction of the thienopyrrole nucleus was indicated by the formation of hydrogen sulfide, especially when the mixture was heated. Furthermore, when the reaction mixture was poured into acetone to consume the excess hydrazine and precipitate the amino acid, under conditions that were quite satisfactory in the conversion of *N*-acetyltryptophan to tryptophan, the solid obtained proved to be a mixture of the amino acid 7 and a compound for which the mass spectrum [molecular ion at m/e 250.0772 ($C_{12}H_{14}N_2SO_2$) and chief fragment ions at m/e 235.0536 (loss of CH_3) and 189.0481 (loss of CH_3 and HCO_2H)] and the nmr spectrum in DMSO-d_6 (two singlet nonequivalent methyl groups and only an AB pattern for the thiophene protons) strongly suggest the tricyclic structure 8.

A key intermediate in the earlier described synthesis of the tertiary amines 1a and 1b is 5-carboethoxythieno[3,2-b]pyrrole (9), obtained in about 50% yield by the reductive cyclization of ethyl 3-nitro-2-thienylpyruvate with stannous chloride and hydrochloric acid. A major by-product (*ca.* 25% yield) was a dimer of 9 which could be largely converted to 9 by treatment with acid and for which the structure 10 was tentatively suggested.[4] In the present work the dimer was aromatized by the action of chloranil in boiling xylene. The nmr spectrum of the product confirms the previous formulation 10 of the dimer.
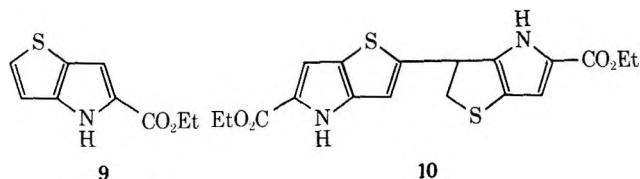
The dimerization of 9 and the reaction of 7 with acetone under very mild conditions indicate that unsubstituted 5 and 2 positions in thieno[3,2-b]pyrroles are much more reactive than corresponding positions in

indoles. The tendency of many of the reactions mentioned above to give very complex mixtures, especially if exposed to strong acid, air, and light, may result from attack at these sites by electrophilic species supplied either inter- or intramolecularly or by free-radical species generated in the reaction mixtures, yielding intermediates comparable to 8 and 10 and capable of generating various further products by elimination, oxidation, condensation, etc. It is hoped that further study will elucidate some of these reactions.

Experimental Section

6-Piperidinomethylthieno[3,2-b]pyrrole Methiodide.—Excess methyl iodie (9.2 ml) was added dropwise and under anhydrous conditions to a stirred solution of 6-piperidinomethylthieno[3,2-b]pyrrole[4] (1a, 3.83 g, 17.4 mmol) in anhydrous ether (80 ml). The mixture was left stirring overnight and then cooled to 0° for 1 hr. The methiodide of 1a was collected, washed with ether, and dried. The yield was 4.04 g (62.5%), mp 166–167°.

Anal. Calcd for $C_{13}H_{19}N_2SI$: C, 43.13; H, 5.29; N, 7.74. Found: C, 43.05; H, 5.42; N, 7.62.

A further crop was obtained on concentrating the mother liquors (total yield 90–99%).

6-Cyanomethylthieno[3,2-b]pyrrole (2).—A stirred mixture of the methiodide of 1a (250 mg, 0.69 mmol) and potassium cyanide (200 mg, 3.07 mmol) in water (12 ml) was refluxed for 1.5 hr. The nitrile 2 was extracted into ether (100 ml) and dried (MgSO₄). Evaporation of the ether *in vacuo* afforded 75 mg (67%) of 2 as a pale yellow oil, ir (CHCl₃) 3500 (NH), 2250 cm⁻¹ (CN).

Methyl 6-Thieno[3,2-b]pyrrolylacetate (5b).—A solution of crude 2 (450 mg) in 10% alcoholic sodium hydroxide (60 ml) was refluxed for 12 hr. The cooled reaction mixture was made slightly acidic (pH 5) by the addition of dilute hydrochloric acid. The liberated 6-thieno[3,2-b]pyrrolylacetic acid (5a) was extracted into ether (150 ml) and washed with water (25 ml), and the dried (Na₂SO₄) solution[9] was concentrated *in vacuo* to approximately 50 ml and then treated dropwise with a slight excess of diazomethane in ether. The solution was left at room temperature for 30 min. Excess diazomethane was removed by gently warming the solution on a steam bath and the remaining solution was evaporated under reduced pressure. The residual oil was distilled *in vacuo* to afford 350 mg (65%) of 5b as a pale yellow oil: bp 120° (0.1 mm); $n^{25}D$ 1.5876; ir (CHCl₃) 1750 cm⁻¹ (ester); nmr (CCl₄) δ 3.46 (s, 2 H, CH₂), 3.55 (s, 3 H, CH₃), 6.40 (s, 1 H, H-5), 6.55 (d, 1 H, $J_{2,3}$ = 5.0 Hz, H-3), 6.85 (d, 1 H, $J_{2,3}$ = 5.0 Hz, H-2). The absorptions due to H-2 and H-5 were further split by $J_{2,5}$ = 1.3 Hz.

Anal. Calcd for $C_9H_9NO_2S$: C, 55.42; H, 4.64; N, 7.17. Found: C, 55.67; H, 4.91; N, 7.23.

6-(2-Aminoethyl)thieno[3,2-b]pyrrole (4).—A solution of crude 2 (500 mg) in anhydrous ether (25 ml) was added dropwise to a

9   10

(6) M. Masaki, T. Kitihara, H. Kurita, and M. Ohta, *J. Amer. Chem. Soc.*, **90**, 4508 (1968).

stirred dispersion of excess lithium aluminum hydride (120 mg) in anhydrous ether (25 ml). The mixture was stirred for 15 min at room temperature and then the excess hydride was destroyed by the cautious addition of water. The ethereal layer was separated and the aqueous layer was shaken with chloroform (100 ml). The combined organic extracts were dried (MgSO$_4$) and then evaporated to leave a pale yellow oil. Distillation in a microsublimation apparatus gave 300 mg (59%) of the amine **4** as pale yellow prisms: mp 84–86°; nmr (acetone-d_6) δ 2.86 (t, 2 H, J = 7 Hz, CH$_2$CH$_2$), 3.27 (s, 2 H, NH$_2$), 3.52 (t, 2 H, J = 7 Hz, CH$_2$CH$_2$), 6.82 (s, 1 H, H-5), 6.90 (d, 1 H, $J_{2,3}$ = 5.0 Hz, H-3), 7.06 (d, 1 H, $J_{2,3}$ = 5.0 Hz, H-2). The absorptions due to H-2 and H-5 were further split by $J_{2,5}$ = 1.3 Hz.

Anal. Calcd for C$_8$H$_{10}$N$_2$S: C, 57.87; H, 6.02; N, 16.86. Found: C, 57.94; H, 5.97; N, 16.57.

Ethyl 2-Acetamido-2-carboethoxy-3-(6-thieno[3,2-*b*]pyrrolyl)-propionate (3a). Method 1.—The solution formed by reaction of sodium (149.5 mg, 6.5 mmol) with dry ethanol (10 ml) was added under anhydrous conditions and a nitrogen atmosphere to a stirred solution of diethyl acetamidomalonate[10] (1.41 g, 6.5 mmol) in dry ethanol (5 ml). The methiodide of **1a** (2.354 g, 6.5 mmol) was added in small portions over a 10-min period, and the resulting heterogeneous mixture was left stirring for 3.5 hr at room temperature. The solid was collected, washed with cold dry ethanol, and dried to give 1.734 g (76%) of **3a**, mp 198.5–200.5°. A further 215 mg of **3a** was obtained by concentrating the filtrate and adding water (total yield 86%). One recrystallization from ethanol produced the analytical sample: mp 199–200°; ir (KBr) 1645 (amide), 1730, with a shoulder at 1750 cm^{-1} (ester carbonyl); nmr (DMSO-d_6) δ 1.16 (t, 6 H, J = 7 Hz, OCH$_2$CH$_3$), 2.00 (s, 3 H, CH$_3$), 3.50 (s, 2 H, CH$_2$), 4.18 (q, 4 H, J = 7 Hz, OCH$_2$CH$_3$), 6.76 (s, 1 H, H-5), 6.93 (d, 1 H, $J_{2,3}$ = 5.0 Hz, H-3), 7.14 (d, 1 H, $J_{2,3}$ = 5.0 Hz, H-2), 8.00 (s, 1 H, NH), 10.97 (s, 1 H, NH). The absorptions due to H-2 and H-5 were further split by $J_{2,5}$ = 1.3 Hz.

Anal. Calcd for C$_{16}$H$_{20}$N$_2$O$_5$S: C, 54.59; H, 5.73; N, 7.96. Found: C, 54.59; H, 5.68; N, 7.74.

Method 2.—A mixture of **1a** (315 mg, 1.43 mmol), diethyl acetamidomalonate[10] (311 mg, 1.43 mmol), and powdered sodium hydroxide (17 mg) in toluene (3 ml) was refluxed for 53 hr under nitrogen. On cooling overnight the solution deposited **3a** (275 mg). A 23-mg recovery of **1a** was obtained from the filtrate. The yield of **3a** after allowing for recovered **1a** was 59%. Recrystallization from ethanol gave 194 mg (48%) of **3a**.

Anal. Calcd for C$_{16}$H$_{20}$N$_2$O$_2$S: C, 54.59; H, 5.73; N, 7.96. Found: C, 54.83; H, 5.79; N, 7.65.

Ethyl 2-Acetamido-2-cyano-3-(6-thieno[3,2-*b*]pyrrolyl)propionate (3d).—This was prepared from ethyl acetamidocyanoacetate and the methiodide of **1a** by the procedure given for **3a** (method 1). The yield (first crop) was 40%; mp 192–193° (from ethanol); ir (KBr) 1660 (amide), 1740 (ester), 2240 cm^{-1} (CN); nmr (DMSO-d_6) δ 1.00 (t, 3 H, J = 7 Hz, OCH$_2$CH$_3$), 1.98 (s, 3 H, CH$_3$), 3.46 (s, 2 H, CH$_2$), 4.07 (q, 2 H, J = 7 Hz, CH$_2$CH$_3$), 6.97 (d, 1 H, $J_{2,3}$ = 5.0 Hz, H-3), 7.05 (s, 1, H, H-5), 7.17 (d, 1 H, $J_{2,3}$ = 5.0 Hz, H-2), 9.20 (s, 1 H, NH), 11.15 (s, 1 H, NH). The absorptions due to H-2 and H-5 were further split by $J_{2,5}$ = 1.3 Hz.

Anal. Calcd for C$_{14}$H$_{15}$N$_3$O$_3$S: C, 55.13; H, 4.96; N, 13.78. Found C, 55.20; H, 4.97; N, 13.46.

Ethyl 2-Acetamido-2-carboxy-3-(6-thieno[3,2-*b*]pyrrolyl)propionate (3b).—A mixture of **3a** (2.456 g, 7.0 mmol), 1 *N* sodium hydroxide (7.2 ml), water (18 ml), and ethanol (50 ml) was stirred under nitrogen for 4.5 hr at room temperature. The mixture was diluted with 1 *N* sodium hydroxide (0.3 ml) and ethanol (15 ml) and stirred for 11 hr. The resulting solution was concentrated to *ca.* 10 ml under reduced pressure with very little heat. Unreacted **3a** (310 mg) was collected after the solution had cooled to 0°. The filtrate was diluted to about 25 ml with water, cooled to 0°, and carefully acidified with 1 *N* hydrochloric acid (8 ml). The copious white precipitate which formed was left at 0° for 24 hr. The half-ester **3b** was collected and washed well with ice-cold water. Decomposition of **3b** was minimized by adding the wash water before the last trace of acidic solution was filtered. The white, granular, slightly hygroscopic solid was dried to give 1.42 g (72% based on reacted **3a**) of analytically pure **3b**: mp 103–107°; ir (KBr) 1610–1650 (amide, carboxylic acid), 1720–1730 cm^{-1} (ester).

Anal. Calcd for C$_{14}$H$_{16}$N$_2$O$_5$S: C, 51.90; H, 4.98; N, 8.65. Found: C, 52.15; H, 4.98; N, 8.80.

Ethyl 2-Acetamido-3-(6-thieno[3,2-*b*]pyrrolyl)propionate (6a).—A thin film of **3b** (1.26 g, 3.9 mmol) was deposited on the walls of a 100-ml round-bottom flask by evaporating a solution of **3b** in ethanol to dryness on a rotary evaporator. The flask was filled with nitrogen and heated for 1 hr at 110–115° in an oil bath. Water (30 ml) was added and the aqueous mixture was refluxed for 4 hr until the evolution of carbon dioxide had ceased. The crude product was extracted into ethyl acetate. Evaporation of the extracts under reduced pressure left a viscous yellow oil which slowly solidified to give 0.994 g of a highly hygroscopic solid. The solid was purified by column chromatography (silica gel, ethyl acetate) to give 0.602 g (55%) of **6a** as an amber, highly hygroscopic solid: ir (KBr) 1625–1645 (amide), 1705–1715 cm^{-1} (ester); nmr (CDCl$_3$) δ 1.23 (t, 3 H, J = 7 Hz, OCH$_2$CH$_3$), 1.98 (s, 3 H, CH$_3$), 3.16 (d, 2 H, J = 5.0 Hz, CH$_2$CH), 4.17 (q, 2 H, J = 7 Hz, OCH$_2$CH$_3$), 4.88 (broad m, 1 H, CH$_2$CHNH), 6.25 (d, 1 H, J = 7 Hz, NHCH), 6.73 (s, 1 H, H-5), 6.87 (d, 1 H, $J_{2,3}$ = 5.4 Hz, H-3), 7.04 (d, 1 H, $J_{2,3}$ = 5.4 Hz, H-2), 8.87 (s, 1 H, H-4). The absorptions due to H-2 and H-5 were further split by $J_{2,5}$ = 1.2 Hz.

Anal. Calcd for C$_{13}$H$_{16}$N$_2$O$_3$S: C, 56.76; H, 5.76; N, 10.01. Found: C, 56.03; H, 5.89; N, 9.95.

2-Acetamido-3-(6-thieno[3,2-*b*]pyrrolyl)propionic Acid (6b).—A stirred mixture of **3a** (1.775 g, 5 mmol), ethanol (50 ml), 1 *N* sodium hydroxide (7.50 ml), and water (42.5 ml) was refluxed under nitrogen with minimum exposure to light. A slow flow of nitrogen was passed through the apparatus and into a trap containing a saturated aqueous solution of barium hydroxide. The trap was periodically changed in order to follow the progress of the decarboxylation. The mixture became homogeneous almost immediately and carbon dioxide evolution started within 1 hr. The solution was refluxed until carbon dioxide evolution had ceased (approximately 14 hr). The cooled reaction solution was adjusted to pH 6 by the careful addition of 1 *N* hydrochloric acid. Boiling was continued and carbon dioxide was rapidly evolved. The pH was 8 after 1 hr. Hydrochloric acid was again added until the pH was 6, and this procedure was repeated until carbon dioxide evolution had ceased and the pH of the resultant solution remained constant. The cooled solution was treated with charcoal and then acidified, with stirring, to pH 3 by the addition of 1 *N* hydrochloric acid (5.40 ml). Nitromethane (1 l.) was added, and with efficient stirring the two-phase system was heated in a distillation apparatus. The ethanol and water were distilled along with the nitromethane and gradually a homogeneous solution was formed. Toward the end of the distillation a suspension of sodium chloride appeared. The distillation was continued until the refractive index of the distillate was identical with that of nitromethane. The heterogeneous mixture was filtered through a fluted filter paper and the colorless filtrate was concentrated to *ca.* 150 ml under reduced pressure, when **6b** usually started to separate. The mixture was left at $-15°$ overnight. The white crystals were collected and redissolved in a minimum volume of acetone (*ca.* 40 ml).[11] High-boiling petroleum ether was added to the cloud point (*ca.* 30 ml). Gentle warming on a steam bath gave a homogeneous solution, which was cooled to room temperature and then to $-15°$. The extremely hygroscopic white crystals of **6b** that were deposited amounted to 0.556 g (43.6%): mp 191–194°; mass spectrum m/e 252.0569 (C$_{11}$H$_{12}$N$_2$O$_3$S), 193 (M − CH$_3$CONH$_2$), 136.0220 (C$_7$H$_6$NS); ir (Nujol mull) 1700 (carboxylic acid), 1592, 1545 (amide), 1460, 1377, 1225, 825 cm^{-1}; ir (DMSO) 1720 (carboxylic acid), 1662, 1545 (amide), 1222, 830 cm^{-1}; nmr (DMSO-d_6) δ 1.87 (s, 3 H, CH$_3$), 3.00 (d, 2 H, J = *ca.* 8 Hz, CH$_2$CH), 4.50 (m, 1 H, CH$_2$-CHNH), 7.09 (m, 3 H, 6-substituted thieno[3,2-*b*]pyrrole), 8.06 (d, 1 H, J = *ca.* 8 Hz, NHCH), 10.78 (broad s, 1 H, H-4).

Anal. Calcd for C$_{11}$H$_{12}$N$_2$O$_3$S: C, 52.37; H, 4.79; N, 11.10. Found: C, 52.65; H, 5.03; N, 11.01.

A second crop of 138 mg (10.9%) of **6b** was obtained by concentrating the mother liquors.

The amido acid **6b** was soluble in DMSO, DMF, ethanol, nitromethane, and *n*-butyl alcohol. It was very soluble in acetone or THF only when a trace of water was present.

Ethyl 2-Formamido-2-carboethoxy-3-(6-thieno[3,2-*b*]pyrrolyl)-propionate (3c).—Sodium hydride (110.4 mg, 2.76 mmol)[12] was

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(10) Dow Chemical Co.

(11) If this solution was colored, it was treated with charcoal.

(12) As a 60.2% dispersion in mineral oil (Metal Hydrides Inc., Beverly, Mass.).

added to a stirred solution of diethyl formamidomalonate[13] (0.560 g, 2.76 mmol) in dry THF (50 ml) maintained under anhydrous conditions. The methiodide of 1a (1.05 g, 2.9 mmol) was added in small portions and stirring was continued overnight at room temperature. The mixture was evaporated under reduced pressure. The crude product was taken up in chloroform, washed three times with water, and dried (Na₂SO₄). The chloroform was removed and the residual oil was purified by column chromatography (silica gel, ethyl acetate) and gave 0.700 g (76% based on malonate ester) of 3c: mp 173–174°; a mass spectrum showed the molecular ion at m/e 338; nmr (acetone-d_6) δ 1.28 (t, 6 H, J = 7 Hz, OCH₂CH₃), 3.72 (s, 2 H, CH₂), 4.3 (q, 4 H, J = 7 Hz, OCH₂CH₃), 6.91 (s, 1 H, H-5), 6.97 (d, 1 H, $J_{2,3}$ = 5.2 Hz, H-3), 7.14 (d, 1 H, $J_{2,3}$ = 5.2 Hz, H-2), 7.80 (broad s, 1 H, NH), 8.28 (s, 1 H, CHO). On expansion of the aromatic portion, the absorptions due to H-5 and H-2 were found to be further split by $J_{2,5}$ = 1.25 Hz.[14]

Anal. Calcd for C₁₅H₁₈N₂SO₅: C, 53.25; H, 5.36; N, 8.28. Found: C, 53.44; H, 5.32; N, 8.39.

A similar yield of 3c (75%) was obtained when the alkylation was carried out in anhydrous ethanol rather than in THF.

2-Amino-3-(6-thieno[3,2-b]pyrrolyl)propionic Acid (7).—A stirred mixture of 3c (1.13 g, 3.34 mmol), ethanol (28 ml), 1 N sodium hydroxide (5 ml), and distilled water (24 ml) was gently refluxed under nitrogen with the minimum exposure to light. Nitrogen was passed slowly through the system and the exiting gases were passed through a trap containing a saturated aqueous solution of barium hydroxide. The trap was periodically changed in order that the progress of the decarboxylation might be followed. The mixture became homogeneous almost immediately and carbon dioxide evolution started within 1 hr. The pale yellow solution was refluxed for 26 hr, until carbon dioxide evolution had ceased. The pale brown solution was cooled to room temperature, 1 N hydrochloric acid (5 ml) was carefully added to bring the pH to a value between 2.5 and 3, and gentle refluxing was continued. Refluxing was stopped after 6 hr, when carbon dioxide evolution had ceased. The brown aqueous ethanolic solution was cooled and diluted with water (75 ml) and was then concentrated by heating the solution under s stream of nitrogen at atmospheric pressure until the volume was *ca.* 60 ml. The resulting aqueous solution was refluxed for 19 hr under nitrogen with the minimum exposure to light. A tlc of the reaction solution (methanol, silica gel) then showed the predominance of one component which had an R_f value practically identical with that of tryptophan and which gave a positive ninhydrin color. The dark brown reaction solution was cooled, becoming slightly cloudy. It was diluted with water (10 ml) and passed, at the rate of approximately 1 drop/sec, through Amberlite IR-4B (OH⁻ form, 100 ml of 20–50 mesh) made up into a column of length 18 cm and 2.9-cm internal diameter. The column was then washed with degassed distilled water and the eluate was collected in a vessel through which a slow stream of nitrogen was flowing. The product was in the first 750–850 ml. The solution was concentrated to *ca.* 10–15 ml under reduced pressure at near room temperature. A column of well-washed DEAE–cellulose[15] was made up measuring about 40 cm in length and 3.75 cm in internal diameter. A pressure head of degassed, distilled water was connected at the top of the column and the height was adjusted until the rate of flow was 30–66 ml/hr and then *ca.* 2–3 l. of water was passed through the column. The pressure head was disconnected and the water which remained above the DEAE-cellulose was drained until *ca.* 1–2 cm of water covered the surface. The dark-colored concentrate from the Amberlite IR-4B (OH⁻ form) column was placed at the top of the column and was then allowed to be absorbed by the DEAE-cellulose by apply-

ing a slightly positive nitrogen pressure such that the rate of flow was about the same as that above. The pressure head was reconnected and the column was eluted with degassed, distilled water. Fractions were collected and tested for chloride ion (silver nitrate) and for amino acid (ninhydrin). The first 256 ml was negative to both tests. Sodium chloride was contained in the next 182 ml of pale yellow eluate. The following 316 ml was again negative to both tests. The amino acid 7 was contained in the next 1124 ml. Further elution gave only a fraction negative to both tests. Dark decomposition products from the reaction were held at the top of the column. The fraction containing 7 was concentrated to *ca.* 5 ml under reduced pressure at about room temperature. Ethanol and then benzene were added and the remaining water was removed as the azeotrope under reduced pressure. The remaining ethanolic solution was about 20 ml in volume, and a small amount of dark solid was deposited when the solution was left overnight at room temperature. The dark yellow filtrate was diluted with ethanol, concentrated to 10–15 ml, and left at −15° for 5 days. Impure 7 separated and was collected, washed with cold dry ethanol followed by ether, and dried. A further yield of 7 was obtained on adding ether to the filtrate. The combined crops were rechromatographed on DEAE–cellulose. Work-up, as above, gave a concentrated ethanolic solution (10–15 ml) which deposited 7 (186.5 mg) on being left at −15° for several days. A further 212.5 mg of slightly less pure 7 was obtained on adding ether to the filtrate. The total yield, based on 3c, was 56.9%. Recrystallization from ethanol gave a solid which decomposed between 240 and 245°: m/e 210.0463 (C₉H₁₀N₂O₂S), 136.0221 (C₇H₆NS); ir (KBr) 3425 (NH), 3300–2500 (broad), 1625, 1590 (amino acid), 1525, 1500 cm⁻¹; nmr (D₂O) δ 7.027 (s, 1 H, H-5), 7.050 (d, 1 H, $J_{2,3}$ = 5.2 Hz, H-3), 7.204 (d, 1 H, $J_{2,3}$ = 5.2 Hz, H-2). The absorptions due to H-2 and H-5 were further split by $J_{2,5}$ = 1.3 Hz. In addition, there was an ABX system with the X portion consisting of an apparent doublet of doublets with J_{app} = 5.1 Hz, centered at 4.004 and integrating for 1 H (CH₂-CH), and with the AB portion consisting of a multiplet centered at 3.245 and integrating for 2 H (CH₂CH).

Anal. Calcd for C₉H₁₀N₂O₂S: C, 51.41; H, 4.79; N, 13.32; S, 15.25. Found: C, 51.39; H, 4.82; N, 13.08; S, 14.99.

Hydrazinolysis by Hydrazine Hydrate Containing a Catalytic Quantity of Hydrazine Dihydrochloride.—A 69% yield of pure tryptophan resulted when a mixture of *N*-acetyltryptophan and hydrazine hydrate containing a trace of the dihydrochloride was boiled for 1 hr and then added to acetone. A 90% yield of pure glycine was obtained by reaction of the reagent with *N*-acetylglycine at room temperature for 58 hr and isolation as above.

Dehydrogenation of the Dimer 10.—A mixture of the dimer[4] 10 (300 mg, 1 mmol) and chloranil (300 mg, 1.2 mmol) in xylene (15 ml) was refluxed for 4 hr. A first crop of the dehydrogenated dimer was collected from the cooled solution. The filtrate was mixed with an equal volume of ether and washed with 1 N sodium hydroxide. The organic layer was dried (MgSO₄) and concentrated to *ca.* 5 ml. On cooling, a second crop of product was precipitated from the solution. The two crops were combined and washed with hot methylcyclohexane. Crystallization from aqueous methanol gave 180 mg (60%) of product: mp 205°; mixture melting point with 10 showed a depression; nmr (DMSO-d_6) showed aromatic absorptions at δ 7.12, 7.23, 7.64 and 7.73.

Anal. Calcd for C₁₈H₁₆N₂O₄S₂: C, 55.67; H, 4.13; N, 7.22. Found: C, 55.56; H, 4.11; N, 6.81.

Registry No.—1a methiodide, 36004-16-7; 3a, 36004-17-8; 3b, 36004-18-9; 3c, 36004-19-0; 3d, 36004-20-3; 4, 36004-21-4; 5b, 36004-22-5; 6a, 36004-23-6; 6b, 36004-24-7; 7, 36004-25-8; 10 dehydrogenation product, 36004-26-9; tryptophan, 73-22-3; tryptamine 61-54-1; indoleacetic acid, 87-51-4.

(13) Aldrich Chemical Co., Inc., Milwaukee, Wis.

(14) R. J. Tuite, H. R. Snyder, A. L. Porte, and H. S. Gutowsky, *J. Phys. Chem.*, **65**, 187 (1961).

(15) Sigma Chemical Co., St. Louis, Mo.

Dichloromaleimide Chemistry.[1] II. A Thionyl Chloride–Pyridine Method for the Conversion of Maleimides to Dichloromaleimides

HOWARD M. RELLES

General Electric Research and Development Center, Schenectady, New York 12301

Maleimides are converted to dichloromaleimides by treatment with pyridine and thionyl chloride. The yields are high and no other products appear to be produced. Intermediates are present during the overall conversions and, by appropriate choice of conditions, these were isolated and/or identified. The mechanism of these reactions was investigated and is discussed herein.

Dichloromaleimides have been prepared by the reaction of dichloromaleic anhydride with primary amines. The yields are relatively high if care is taken to avoid the formation[2] of a secondary product, 1.

(1)
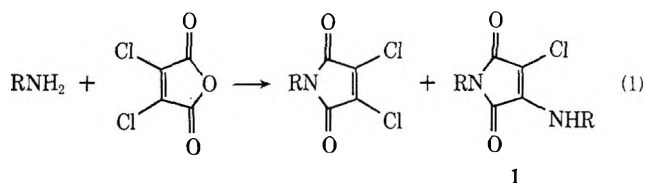
We have recently uncovered an alternate route to dichloromaleimides which involves treatment of maleimides with thionyl chloride and pyridine (eq 2 and 3).

(2)

a, R = C₆H₅
b, R = CH₃
c, R = H

(3)

a, R′ =

b, R′ =

c, R′ =
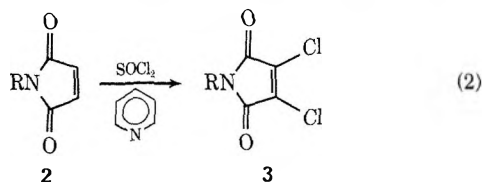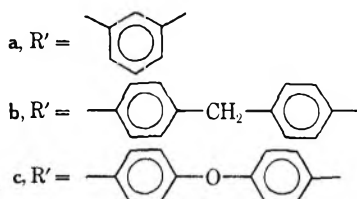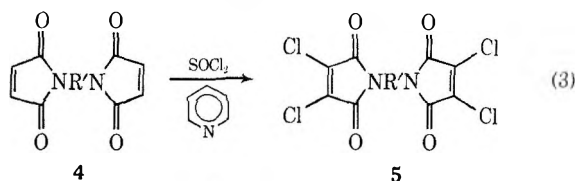
Similar treatment of maleic anhydride gave dichloromaleic anhydride in very high yield. These results are summarized in Table I.
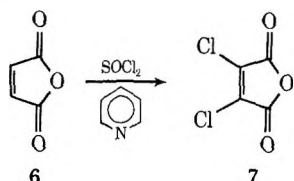
The overall course of these reactions was quite surprising since, at first glance, it appeared to be straightforward replacement of hydrogen by chlorine under

TABLE I
CONVERSION OF MALEIMIDES TO DICHLOROMALEIMIDES IN
THIONYL CHLORIDE

Starting material	Moles of pyridine	Product	Crude yield, %		Isolated yield, %[a]
			Nmr	Vpc	
2a	2	3a	100	99	76
2b	2	3b	87		20
2c	2	3c	b		25
4a	4	5a	100		50
4b	4	5b	100		65
4c	4	5c	100		60
6	2	7	100		80

[a] After recrystallization. [b] Not determined with certainty.

conditions which are conducive to "normal ionic" reactions, that is, reactions in which hydrogen and chlorine would be expected to ionize in opposite senses. It therefore seemed appropriate to undertake an investigation of the mechanism of these conversions. In general, it was most convenient to employ *N*-phenylmaleimide (2a) for this purpose, but some evidence was also obtained from other maleimide systems which, in all cases, appeared to substantiate the findings from the former system.

It was established at the outset that (a) 2a does not react with thionyl chloride alone, (b) pyridine, under *our* reaction conditions, does not react with thionyl chloride,[3] and (c) 2a does not react with pyridine in nonpolar (methylene chloride) or polar (dimethyl sulfoxide) solvents at temperatures and concentrations where reactions occurred readily in thionyl chloride solutions.

When a solution of 2a in thionyl chloride was treated with two equivalents of pyridine and the slightly exothermic reaction maintained at 20–30° for 30 min, the solution was found to contain ⅓, ⅔, and ⁴⁄₃ mol equiv of 2a, 8, and pyridine hydrochloride, 9, respectively (eq 4). The relative amounts of these three substances

(4)
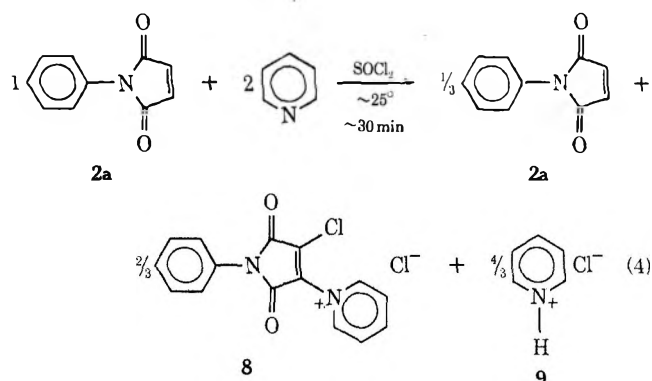
(1) Organic Chemistry in Thionyl Chloride. I.
(2) A Salmony and H. Simonis, *Ber.*, **38**, 2594 (1905).
(3) A slow reaction has been reported to occur over more extended times to afford 4-(pyridyl)pyridinium chloride: R. F. Evans, H. C. Brown, and H. C. van der Plas, *Org. Syn.*, **43**, 97 (1963).

were determined by integration of the vinyl singlet of **2a**, the α-pyridinium multiplet of **8**, and the NH singlet of **9** (see Figure 1C; downfield acidic proton peak not shown in 1C or 1D). Isolation of each was then achieved after removal of the excess thionyl chloride. Compound **8** was separated and displayed an nmr spectrum in methanol in complete agreement with the assigned structure (see Experimental Section). It was then converted to its tetrafluoroborate salt in 94% overall yield, *i.e.*, 94% of two-thirds mol equiv (the amount determined to be present by nmr). The remaining **2a** was isolated and identified by nmr and vapor-phase chromatography (vpc); the only other component detected was a trace of **3a**. Pyridine hydrochloride was also separated and identified by its nmr spectrum.

Similarly, the reactions of **2b**, **4a**, **4b**, and **4c** were carried out initially at ~25° and, in each case, nmr results indicated *ca.* $^1/_3$: $^2/_3$: $^4/_3$ relative mol equiv of unreacted olefinic groups,[4] pyridinium salt groups **10**,[4] and pyr-

10
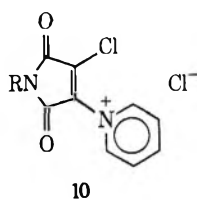
idine hydrochloride **9**, respectively. The results are summarized in Table II and indicate that three molecules of pyridine were consumed in converting each maleimide double bond to products, one giving rise to **8** (or **10**) and two others leading to **9**. Thus, since only 2 mol equiv of pyridine were present initially, only two-thirds of the maleimide double bonds reacted under these conditions.

When the reaction of **2a** with 2 equiv of pyridine was allowed to proceed at 25° for 15.5 hr, a significant amount of further reaction was noted (see Table II and compare with the 3-hr results). At that point in time, addition of another 0.55 mol equiv of pyridine caused a reduction in the amount of **2a**, a corresponding increase in **8**, a corresponding double increase in **9**, but no appreciable change in **3a**[5] (see Table II). This result again indicates that, in the initial reaction of **2a**, three molecules of pyridine were consumed.

Further substantiation of the stoichiometry of these initial reactions was obtained when **2a** was treated with 3 mol equiv of pyridine at 25° in thionyl chloride. After 3 hr, examination of the nmr spectrum of the reaction mixture indicated that the mole ratio of **2a**:**8**:**9** was 0.02:0.98:2.00. Again, **8** was isolated from this reaction mixture and its structure was established by nmr, infrared, and mass spectrometry and by its facile hydrolysis to **11**, presumably *via* the path described in

(4) For the bisimide cases (**4a–c**), mixtures of **4**, **i**, and **ii** would be expected to be present.

i   ii
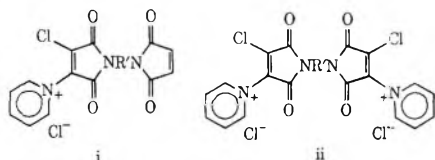
(5) The fact that **3a** definitely did not diminish is critical to later discussions (*vide infra*).
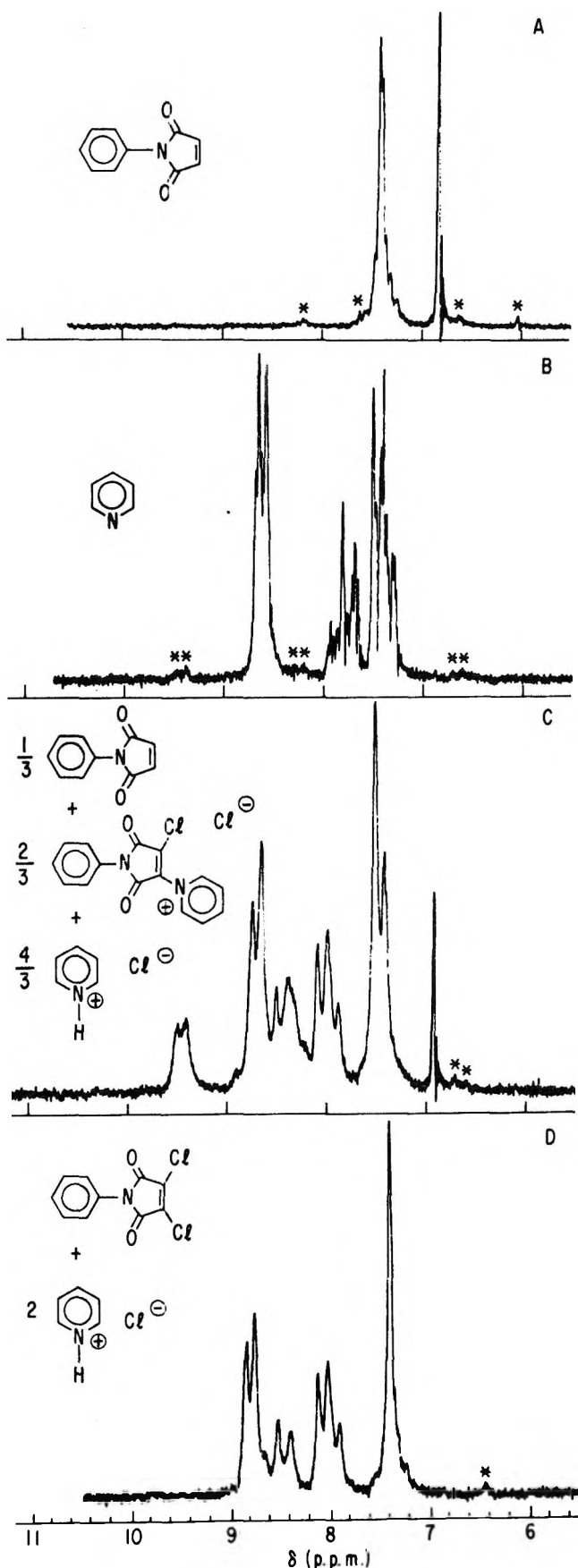
Figure 1.—Nmr spectra in thionyl chloride solution (external tetramethylsilane as reference). An asterisk denotes a spinning side band. (A) *N*-phenylmaleimide (**2a**); (B) pyridine; (C) reaction mixture after 1 hr at ambient temperatures (**2a**, **8**, and **9**); (D) reaction mixture after 1 hr at reflux (**3a** and **9** only).

TABLE II

NMR RESULTS OF REACTIONS AT 25° IN THE PRESENCE OF 2 MOL EQUIV^a OF PYRIDINE PER MALEIMIDE DOUBLE BOND

Starting material	Reaction time, hr	Chemical Shift, δ^b			Relative moles of groups^c			
		Vinyl protons (s)	α-Pyridinium protons of 8 or 10 (m)	NH Protons of 9^d (s)	Vinyl	8 or 10	9	Dichlorovinyl^e
2a	0.5	6.82	9.35–9.64	16.9	0.31	0.68	1.39	0.01
2a	2.0	6.82	9.41–9.68	17.1	0.33	0.66	1.47	0.01
2a	3.0	6.83	9.38–9.61	16.9	0.29	0.67	1.45	0.04
2b	1.0	6.62	9.18–9.43	16.8	0.35	0.65	1.37	0.00
4a	1.0	6.82	9.30–9.55	16.8	0.31	0.69	1.38	0.00
4b	16.0^f	6.72	9.25–9.50	16.7	0.25^f	0.64^f	1.50^f	0.11^f
4c	1.0	6.75	9.32–9.52	16.9	0.30	0.70	1.42	0.00
2a	15.5	6.80	9.31–9.54	17.0	0.26	0.52	1.53	0.22
2a	18.5^g				0.05	0.71	1.87	0.24

^{a} Complete details in Experimental Section (NOTE: 2.1 mol equiv of pyridine were usually used since enough HCl was always present in the SOCl$_2$ to neutralize ~0.1 mol equiv.) ^{b} Ppm downfield from external tetramethylsilane. ^{c} Values may have ±4% error. ^{d} The very large chemical shifts observed for the NH protons of 9 are probably due to NH···Cl hydrogen bonding; see H. M. Relles, *J. Org. Chem.*, **35**, 4280 (1970). ^{e} α,β-Dichloromaleimide groups determined by difference (see Experimental Section). ^{f} Differences largely due to further reaction during this 16-hr period (*vide infra*). ^{g} This represents analysis of a reaction mixture which, after 15.5 hr, had an additional 0.55 mol equiv of pyridine added to it.

Scheme I.^{6} Compound 11 was isolated and identified through its infrared and mass spectra.

When the reaction of 2a with 1 mol equiv of pyridine and excess thionyl chloride was carried out in methylene chloride at 25° for 15 hr, there was obtained only a mixture of 2a, 9, and 3a in the ratio of 0.5:1.0:0.5, respectively. It was thus apparent that either (a) 8 was not an intermediate in this case, or (b) it had been present and was converted to 3a and pyridine by the mechanism shown in eq 5. Clearly, if this latter al-

SCHEME I
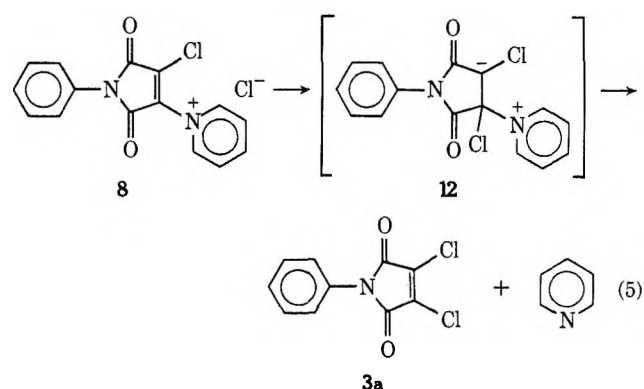
ternative had prevailed, the regenerated pyridine was then available to cause additional conversion of 2a to 3a *via* 8 and 12. It is perhaps not unreasonable to expect that methylene chloride, being considerably less polar than thionyl chloride, would induce stronger ion-pair formation, thereby increasing the localized concentrations of the reactant ions and increasing the rate of conversion of 8 to 3a.^{7}

On heating the reaction mixtures initially obtained from 2a, 2b, 4a, 4b, or 4c (in which 2 mol equiv of pyridine in thionyl chloride solution was used) at reflux for short periods, it was observed by nmr that the resulting solutions contained only 3a, 3b, 5a, 5b or 5c, respectively, along with 2 mol equiv of 9 per mol equiv of maleimide group. Each of the dichloromaleimide products was then isolated in good yield (see Table I).

It was also found that by refluxing 1 mol of 2a with

(6) For the presentation of a strictly analogous methanolysis in a series of 12 similar compounds, see M. J. Karten, S. L. Shapiro, E. S. Isaacs, and L. Freedman, *J. Org. Chem.*, **30**, 2657 (1965).

(7) Viewed in the extreme, perhaps an excellent way for chloride ion to become solvated in such a poorly solvating medium is by forming 12 (or possibly iii, which, of course, would not lead to products).
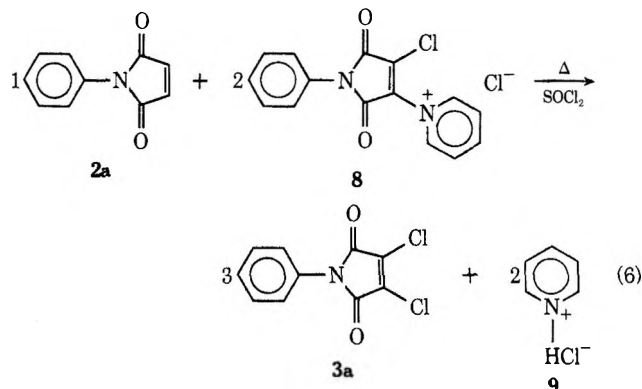
2 mol of previously isolated 8 in thionyl chloride, a 3:2 mixture of 3a and 9, respectively (eq 6), was obtained.

These results argue strongly that **8** was converted thermally to **3a** (*via* **12**) and that the pyridine thus generated caused more **2a** to react to give more **3a** (*via* **8** and **12**). These observations also account for the fact that one maleimide group only requires two pyridine molecules to be converted to a dichloromaleimide group in the *overall* reaction sequence; this is summarized in Scheme II.

Scheme II

2a (1 mol) + pyridine (2 mol)

$\downarrow$ SOCl₂, 25°

products of eq 4

$\downarrow$ SOCl₂, Δ

3a (1 mol) + **9** (2 mol)
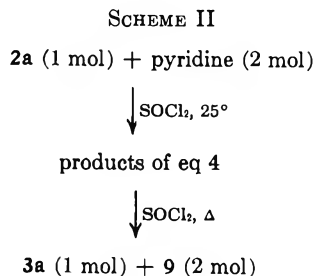
Having established the stoichiometry of both the facile ambient- and reflux-temperature reactions and a probable mechanism to explain the latter, it was of interest to attempt to learn something about the mechanism of the former.

Control experiments (see Experimental Section) indicated that **3a** was not a precursor for **8** *during the reaction* because (a) the ambient-temperature reaction leading from **2a** to **8** was much faster than pyridine was found capable of reacting with **3a** to give **8** under the same reaction conditions, and (b) pyridine was found to be *unable to completely convert* **3a** to **8** under the reaction conditions (while *initially none* of **3a** was observed during the conversion of **2a** to **8**). This fact (b) is in agreement with the equilibrium shown in eq 7 ($K \cong 3$). Interestingly, extended periods in the ambient-temperature reaction (equation 4) did lead to the formation of some **3a** (see Table II, **2a** at 15.5 hr and also note that the **4b** reaction after 16 hr showed evidence for dichloromaleimide groups), a fact also in agreement with the equilibrium (eq 7)
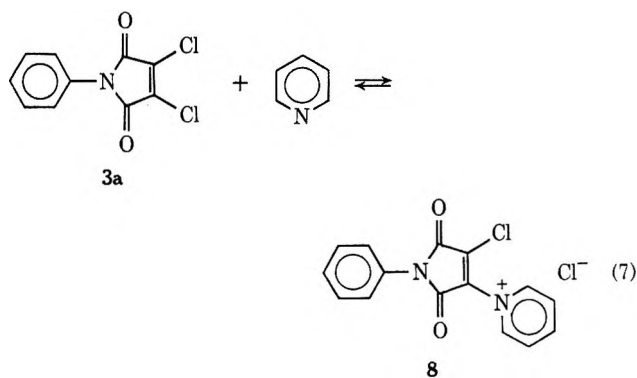
being approached more slowly from the right than from the left. By heating the reaction mixture, equilibration became more rapid, pyridine was regenerated, and it then reacted further with **2a**. Ultimately, all of the pyridine was neutralized by the HCl produced and was then no longer able to take part in the equilibration. Hence, only **3a** and **9** remained after the heating period.

No other intermediates were ever observed during the reactions using vpc or nmr techniques, although

any reasonable mechanism requires that they be invoked. Presumably, if they were present, they were consumed much faster than they were produced.

One mechanism which is consistent with observations on the formation of **8** from **2a** is depicted below (Scheme III). This should apply equally well to the other maleimides examined.

Scheme III
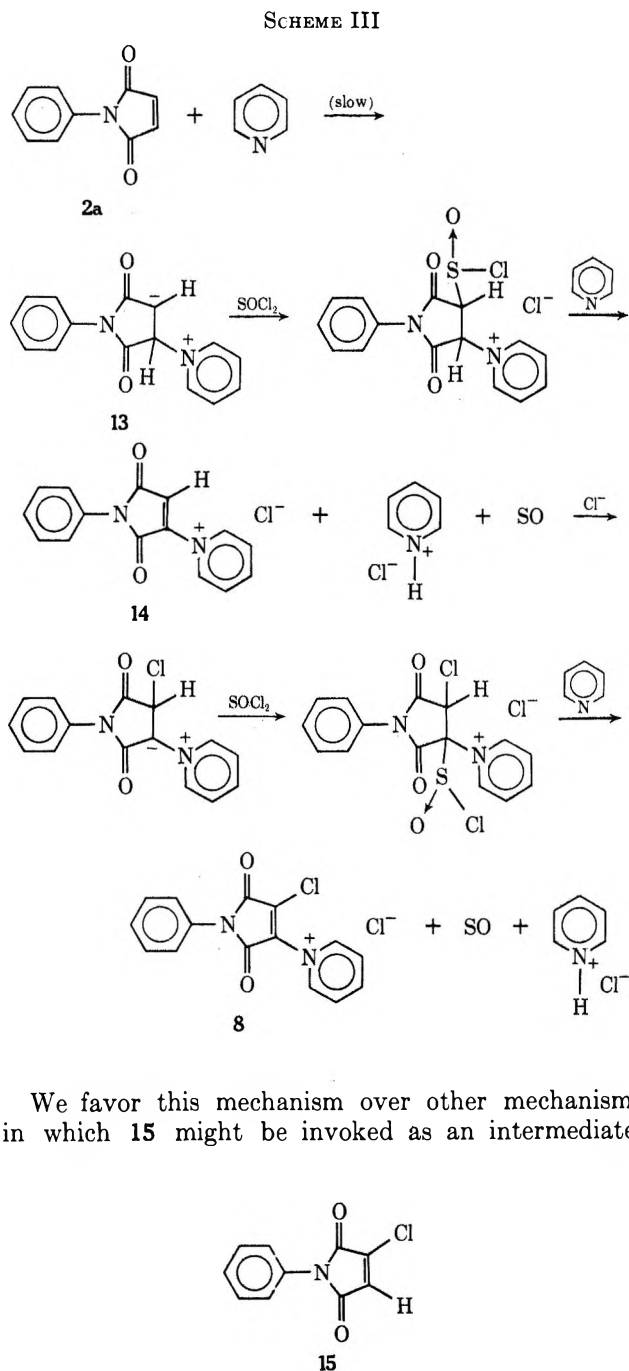
We favor this mechanism over other mechanisms in which **15** might be invoked as an intermediate.

In view of the sluggishness of attack of pyridine on **3a**, one would predict a rate of attack of pyridine on **15** to be at least slow enough to allow **15** to be observed in the system when all of the pyridine had been consumed. However, *none was observed*. On the other hand, **14** (Scheme III) should be much more reactive than **2a**, **15**, or **3a** toward a nucleophile (Cl⁻) and, indeed, might not be expected to be observed. The formation of sulfur monoxide has been observed or

invoked in several previous instances.[3,8,9] However, our efforts to trap this very unstable molecule with isoprene[10] were completely unsuccessful since the isoprene reacted rapidly with 2a under the usual reaction conditions (thionyl chloride solution), or slightly modified reaction conditions (methylene chloride solution), to give the expected Diels–Alder adduct along with other unidentified products;[11] none of 16 was produced, however.

16
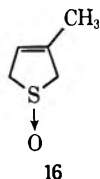
Some nmr evidence was obtained for the intermediacy of 17 in the conversion of 6 to 7; 17 was much more reactive than 8 (or 10) and underwent facile conversion to products (eq 8) at ambient temperatures.

17

7
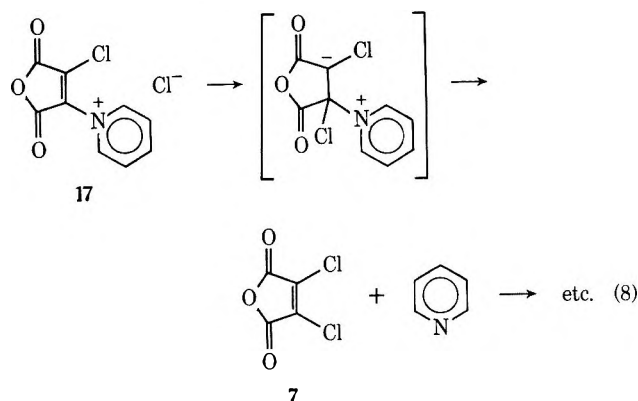
In light of the above discussion, it is possible that the reported conversion[12] of acetylenedicarboxylic acid to 7 could occur by (1) HCl addition to the triple bond, (2) ring closure to monochloromaleic anhydride, and (3) reaction with pyridine–thionyl chloride to give 7 via 17.

Experimental Section

Nmr spectra were recorded with a Varian Associates T-60 spectrometer (abbreviations: m = multiplet, s = single peak, d = doublet). Infrared spectra were taken (KBr pellets) on a Perkin-Elmer 521 grating infrared spectrophotometer.

Mass spectra were recorded on a C. E. C. 21-104 analytical mass spectrometer. Vapor-phase chromatographic (vpc) analyses were done with a silicone rubber (SE-30) column. Melting points were taken with a Mel-Temp apparatus and are uncorrected.

The pyridine used was Eastman "Karl Fischer" reagent grade; the thionyl chloride was obtained from Matheson Coleman and Bell. The maleimides (2a and 4a–c) were prepared from the appropriate amines and maleic anhydride by a standard literature technique;[13] 2b and 2c were obtained from the Aldrich Chemical Co.

(8) L. F. Fieser and Y. Okumura, *J. Org. Chem.*, **27**, 2247 (1962).

(9) (a) Y. Okumura, *ibid.*, **28**, 1075 (1963); (b) G. Büchi and G. Lukas, *J. Amer. Chem. Soc.*, **86**, 5654 (1964); (c) R. M. Dodson and R. F. Sauers, *Chem. Commun.*, 1189 (1967); (d) R. M. Dodson, and J. P. Nelson, *ibid.*, 1159 (1969); (e) Y. L. Chow, J. N. S. Tam, J. E. Blier, and H. H. Szmant, *ibid.*, 1604 (1970), and references cited therein.

(10) D. Lemal (private communication) and others,[9c-e] have been able to trap SO with dienes and trienes as cyclic sulfoxides.

(11) H. M. Relles, unpublished results.

(12) R. N. McDonald and R. A. Krueger, *J. Org. Chem.*, **28**, 2542 (1963).

(13) M. K. Hargreaves, J. G. Pritchard, and H. R. Dave, *Chem. Rev.*, **70**, 439 (1970).

Conversion of N-Phenylmaleimide (2a) to N-Phenyldichloromaleimide (3a) Using 2 Equiv of Pyridine in Thionyl Chloride. **A. Synthetic Procedure.**—To a solution of 1.73 g (0.0100 mol) of 2a in 20 ml of thionyl chloride was added 1.66 g (0.0210 mol) of pyridine while the system stirred in a cold-water bath. Stirring was continued at ~20° for 15 min and then the slightly turbid solution was heated for 1 hr at reflux.

All of the excess thionyl chloride was then removed *in vacuo* and the residue was taken up in 100 ml of chloroform. The chloroform solution was extracted with dilute HCl (to remove the pyridine hydrochloride), dried, filtered, and freed of solvent giving 2.78 g of a solid residue which, by quantitative vapor phase chromatography (vpc), was found to contain 2.40 g (0.0099 mol) of 3a (99% yield).

The crude product was recrystallized from chloroform to give 1.85 g of 3a (76% isolated yield), mp 204–205° (lit.[14] mp 203°). The infrared spectrum of this material was exactly the same as that for 3a obtained from aniline and dichloromaleic anhydride[11] and from the methylene chloride–thionyl chloride reaction described herein. The mass spectrum of 3a showed the expected two-chlorine molecular-ion cluster at *m/e* 241–245.

E. Procedures for Mechanistic Information.—(1) To a solution of 1.73 g (0.0100 mol) of 2a in 20 ml of thionyl chloride was added 1.58 g (0.0200 mol) of pyridine while stirring in a water bath to maintain the system at *ca.* 25°. Samples of the homogeneous solution were removed at various times and the progress of the reaction was monitored by nmr spectroscopy. The results are listed in Table II in the discussion section. The amount of 2a was determined from the integral of vinyl proton peak at δ 6.82. The amount of 8 was determined from the integral of the α-pyridinium proton multiplet between δ 9.35–9.64. The amount of 3a was determined from the N-phenyl integral after subtracting out that required by 2a and 8. The amount of 9 was determined from the integral of the NH singlet at δ 16.9. The α, β, and γ protons of 9 and the β and γ protons of the pyridinium ring of 8 were found as overlapping multiplets between δ 7.72 and 8.97. The experimental error was ±4%.

After the system had remained at 25° for 15.5 hr, an additional 0.0055 mol of pyridine was added and further reaction which occurred was determined (nmr) after 3 hr (see Table II).

(2) Exactly 1.73 g (0.01 mol) of 2a was dissolved in 20 ml of thionyl chloride. The solution was stirred in a water bath at 20–25° in dry air and 1.66 g (0.0210 mol) of pyridine was added at once. After 2 hr, the nmr spectrum of a sample was obtained (see Table II) and the sample was then returned to the reaction mixture.

All of the excess thionyl chloride was then removed *in vacuo* at ~25° during 45 min. Addition of 100 ml of chloroform to the residue caused complete solution followed rapidly by the precipitation of a solid. Filtration gave (after vacuum drying) 2.45 g of slightly impure 8 which showed the expected nmr spectrum in CH₃OH: N-phenyl, s, δ 7.24, 5 H; β-pyridinium, m, δ 7.97–8.33, 2 H; γ-pyridinium, m, δ 8.53–8.93, 1 H; α-pyridinium, m, δ 8.93–9.18, 2 H. While this spectrum was being recorded, no changes were detected, but, after 13 hr, it had changed appreciably.[6]

A solution of 2.00 g of this salt (8) in 25 ml of methanol was prepared and filtered to remove ~0.01 g of insoluble material. After 3 min, this clear yellow solution was added to a solution of 1.10 g (0.01 mol) of sodium tetrafluoroborate in 40 ml of methanol. A large amount of solid separated quickly. After another 7 min, this solid was filtered, washed with some methanol, and vacuum dried for 8 hr at 60°. The resulting pale yellow solid, mp ~240° dec, was the tetrafluoroborate salt of 8 (obtained 1.86 g of 8 BF₄ from 2.00 g of impure 8 Cl; this would correspond to 2.28 g, 0.0062 mol, of 8 BF₄ from 2.45 g of impure 8 Cl, or 94% yield, based on nmr analysis of the mixture just before work-up). This material displayed an infrared spectrum (carbonyl at 1730 cm⁻¹, etc.) which was identical with that of 8 Cl (*vide infra*) except for the presence of an additional band at 1050 cm⁻¹ due to the tetrafluoroborate anion.

Due to its nonvolatility, a sample of 8 BF₄ had to be heated to ~230° in an attempt to obtain a mass spectrum. At this temperature, the spectrum showed the following (*m/e*, relative intensities, and probable rationale given): 79, 100.0, pyridine⁺; 119, 57.2, (C₆H₅N═C═O)⁺; 225, 27.2, N-phenylchlorofluoromaleimide⁺ (arising *via* a decomposition; appropriate

(14) R. Anschütz and C. Beavis, *Justus Liebigs Ann. Chem.*, **263**, 159 (1891).

one-chlorine cluster); 241, 33.6, *N*-phenyldichloromaleimide+ (arising *via* a decomposition; appropriate two-chlorine cluster); 162, 17.9, $C_6H_5N^+\equiv CC\equiv CCl^{15}$ (appropriate one-chlorine cluster); and 146, 13.6, $C_6H_5N^+\equiv CC\equiv CF$.

Anal. Calcd for $C_{15}H_{10}BClF_4N_2O_2$: C, 48.3; H, 2.7; N, 7.5; Found: C, 47.9; H, 2.8; N, 7.6.

All of the solvent was evaporated from the initial chloroform filtrate. The solid residue was taken up in 10 ml of deuterio-chloroform and analyzed by nmr. This analysis indicated that pyridine hydrochloride (9) and *N*-phenylmaleimide (2a) were present in a molar ratio of 0.0151:0.0034, in agreement with the nmr evidence before work-up. The CDCl₃ solution, after extraction with D₂O/DCl, showed (nmr) that only the *N*-phenyl-maleimide (2a) remained; all of the pyridine hydrochloride (9) was now present (nmr) in the D₂O phase. Further analysis of the CDCl₃ phase by vpc (6-ft 10% SE-30 column, 160°) showed that it contained only two volatile materials, *N*-phenylmaleimide (2a) and *N*-phenyldichloromaleimide (3a) in the molar ratio of 30:1 (again in agreement with the nmr spectrum before work-up).

(3) A solution of 1.73 g (0.01 mol) of 2a in 20 ml of thionyl chloride was stirred at ~25° and 1.66 g (0.0210 mol) of pyridine was added at once. The reaction caused the solution temperature to increase to 45° during 6 min and then drop back slowly to 26° during the next 47 min. After a total of 60 min since the pyridine was added, the nmr spectrum of a sample showed that the mixture contained 0.0034 mol of 2a, 0.0065 mol of 8, 0.0001 mol of 3a, and 0.0147 mol of 9 (spectral data the same as given in expt 1 above).

The nmr sample was returned and the homogeneous system was then heated at reflux for 1 hr. On cooling back to ~25°, much solid platelets crystallized out. The addition of 20 ml of methylene chloride or deuteriochloroform at this point caused all of the solid to redissolve. The nmr spectrum of this solution now showed (a) none of 2a, (b) none of 8, (c) 0.0100 mol of 3a (aryl, m, centered at δ 7.55), (d) 0.0204 mol of 9 (NH, s, δ 17.7; α protons, m, δ 8.92–9.17; γ protons, m, δ 8.52–8.92; β protons, m, δ 7.98–8.39), and no other materials.

Conversion of *N*-Phenylmaleimide (2a) to *N*-Phenyldichloro-maleimide (3a) Using 1 Equiv of Pyridine and Excess Thionyl Chloride in Methylene Chloride.—A solution of 17.30 g (0.100 mol) of *N*-phenylmaleimide, 100 ml of methylene chloride, and 20.0 ml of thionyl chloride was stirred at room temperature while 7.90 g (0.100 mol) of pyridine in 100 ml of methylene chloride was added slowly during 12 min. During 1 hr the temperature of the solution rose to *ca.* 31° and then slowly began to fall back to room temperature. A small amount of solid separated. After the system had been stirred for 15 hr, the nmr spectrum of a sample was consistent with a mixture of ~0.1 mol of 9 (β protons m, δ 7.85–8.17, 2 H; γ protons m, δ 8.32–8.68, 1 H; α protons, m, δ 8.77–8.99, 2 H; NH s, δ 17.8, 1 H), *ca.* 0.05 mol of 3a (aromatic part of the multiplet, δ 7.18–7.68, centered at δ 7.42), and ~0.05 mol of 2a (aromatic part of the multiplet centered at δ 7.42, olefinic s, 6.87, 1 H).

HCl (100 ml, 1 *N*) was then added (CAUTION!) to destroy the excess thionyl chloride and the layers were separated. The methylene chloride layer was extracted with another 100 ml of 1 *N* HCl, then with 100 ml of H₂O, dried, and freed of solvent *in vacuo* to give a yellow solid. This solid was found by vpc (6 ft 10% SE-30 column, 200°) to contain nearly equal amounts of 2a and 3a (and *no other* volatile products). Fractional crystallization from chloroform afforded 7.25 g of 3a (30%, isolated yield), mp 201–202° (lit.[14] mp 203°). The mass spectrum showed a molecular-ion cluster with the expected relative intensities at *m/e* 241, 243, 245. The nmr spectrum showed only aryl protons; the ir spectrum showed a strong double carbonyl absorption (1718 and 1732 cm⁻¹).

Anal. Calcd for $C_{10}H_5Cl_2NO_2$: C, 49.62; H, 2.08; N, 5.79. Found: C, 49.7; H, 1.99; N, 5.96.

Reaction of 2a with 3 Equiv of Pyridine in Thionyl Chloride. Deliberate Synthesis of 8 from 2a.—A solution of 1.73 g (0.0100 mol) of 2a was dissolved in 20 ml of thionyl chloride and 2.45 g (0.0310 mol) of pyridine was added during 2 min while the temperature of the system was maintained at ~25° with external cooling. After the system had been stirred at this temperature for 3 hr, a sample was removed and found (by nmr) to contain only 0.0002 mol of 2a (vinyl, s, δ 6.80), 0.0098 mol of 8 (α-pyridinium protons m, δ 9.39–9.65), and 0.0200 mol of pyridine hydrochloride (NH, s, δ 16.8).

(15) H. M. Relles and R. W. Schluenz, *J. Org. Chem.*, **37**, 1742 (1972).

All of the excess thionyl chloride was then removed *in vacuo* at 30–35° during 1 hr. Chloroform (100 ml) was added to dissolve the residue; much solid then deposited rapidly from this solution. This solid was filtered, washed with a little chloroform, and air dried to give 3.44 g of 8; melting point with decomposition begins at 125°. Elemental analysis indicated this material contained 1 mol of HCl.

Anal. for 8·HCl: Calcd for $C_{15}H_{11}Cl_3N_2O_2$: C, 50.35; H, 3.08; N, 7.83; Cl, 29.8. Found: C, 50.1; H, 2.9; N, 7.7; Cl, 29.6.

The nmr spectrum of this material could be recorded in acetone-d_6-D₂O solution before any significant amount had been converted to 11 (*vide infra*). It shows *N*-phenyl (m, δ 6.85–7.36), 5 H), β-pyridinium (m, δ 8.00–8.43, 2 H), γ-pyridinium (m, δ 8.43–8.89, 1 H), and α-pyridinium protons (m, δ 8.89–9.24, 2 H) in accord with the assigned structure of 8. (After 5 min changes in all of these nmr multiplets began to appear; after 30 min much solid had separated from the solution.) The infrared spectrum showed a strong, sharp carbonyl absorption at 1730 cm⁻¹. The mass spectrum had a weak molecular ion at *m/e* 285 corresponding to the cation portion of the salt 8 and other prominent peaks at 241 (91, two-chlorine cluster, 3a+), 79 (100, pyridine+), and 36 (25, one-chlorine cluster, HCl) resulting from decomposition in the heated source.

Exactly 0.100 g of the above sample of 8 was dissolved in 2 ml of 70% aqueous acetone. After a short time, solid began to precipitate. After this system was kept at 25° overnight, the solid was filtered, washed with some water, and dried *in vacuo* at 40° to give 0.040 g of 11, mp 266–268°. This material showed absorptions in the infrared spectrum at 1755 (m), 1705 (s), and 1655 (vs) cm⁻¹ [lit.[7] a series of 12 compounds of this type showed corresponding bands at *ca.* 1754 (m), 1695 (s), and 1640 (vs) cm⁻¹]. Its mass spectrum was in complete accord with structure 11: *m/e* 266 (81, molecular ion), 238 [34, (M − CO)+], 194 [36, (M − CO − CO₂)+], 119 (100, $C_6H_5N=C=O^+$), 91 (99, $C_6H_5N^+$), and 79 (94, pyridine+).

Reaction of 2a with 8 in Thionyl Chloride.—A sample of 8 (*vide supra*), 1.64 g (0.0051 mol), and 0.43 g (0.0025 mol) of 2a were refluxed with 15 ml of thionyl chloride for 4 hr. The nmr spectrum of a sample of the resulting solution (homogeneous above ~40°, much solid precipitates at 25°) showed the presence of 0.0002 mol of 2a (vinyl, s, δ 6.80), 0.0074 mol of 3a (aryl, m, δ 7.17–7.65 with main peak at δ 7.40), and 0.0050 mol of 9 (NH, s, δ 17.1, 1 H; β protons, m, δ 7.78–8.12, 2 H; γ protons, m, δ 8.32–8.65, 1 H; α protons, m, δ 8.65–8.88, 2 H).

All of the excess thionyl chloride was removed *in vacuo* and the residue was taken up in 150 ml of chloroform, extracted with 1 *N* HCl to remove the pyridine hydrochloride, dried, and freed of solvent *in vacuo*. Vpc showed that much 3a was present. The crude product, 1.71 g, was triturated with a little methanol to remove residual 2a. This treatment gave 1.61 g (0.0068 mol, 90% yield) of 3a, mp 203.5–205° (lit.[14] mp 203°), the infrared spectrum of which was superimposable on that of an authentic sample of 3a.

Reaction of 3a with 1 Equiv of Pyridine in Thionyl Chloride.—A solution of 2.42 g (0.0100 mol) of 3a was stirred at 25° with 20 ml of thionyl chloride (most soluble) and 0.87 g (0.0110 mol) of pyridine was added (homogeneous solution after ~0.5 hr). Samples were taken at various times and analyzed for the amounts of 8, 3a, and pyridine by nmr spectroscopy. The α-pyridinium proton multiplet of 8 was characteristically downfield (δ 9.14–9.42) from all the rest of the absorptions (δ 7.07–8.73) so that a careful integration was possible. The results are listed in Table III.

TABLE III

Reaction time, hr	Moles[a] of 8	Moles[b] of 3a	Moles[b] of pyridine
0		0.0100	0.0110
1.5	0.0044	0.0056	0.0066
3.5	0.0065	0.0035	0.0045
7	0.0076	0.0024	0.0034
17.5	0.0073	0.0027	0.0037

[a] Determined from integral of α-pyridinium multiplet at δ 9.14–9.42. [b] Determined by difference.

Reaction of 3a with 1 Equiv of Pyridine in Thionyl Chloride in the Presence of 2 Equiv of Pyridine Hydrochloride.—A thionyl chloride solution containing 0.0100 mol of 3a (most soluble) and

0.0200 mol of pyridine hydrochloride was prepared by allowing 1.73 g (0.0100 mol) of 2a to react with 1.58 g (0.0200 mol) of pyridine in 20 ml of thionyl chloride for 15 min at 25° and then for 1 hr at 80°.

On cooling back to 25°, 0.79 g (0.0100 mol) of pyridine was added, the system was stirred continuously (homogeneous after *ca.* 0.5 hr), and samples were taken at various times and analyzed by nmr spectroscpy for 8, 3a, pyridine, and 9. The results are listed in Table IV.

TABLE IV

Reaction time,[a] hr	Moles[b] of 8	Moles[c] of 3a	Moles[c] of pyridine	Moles[d] of pyridine HCl
0		0.0100	0.0100	0.0200
0.5	0.0030	0.0070	0.0070	0.0200
1.5	0.0039	0.0061	0.0061	0.0200
13	0.0060	0.0031	0.0031	0.0200

[a] Since second portion of pyridine was added. [b] Determined from integral of α-pyridinium proton multiplet (δ 9.40–9.67). [c] Determined by difference. [d] Determined from NH integral (δ 17.2).

Competitive Reactions of 2a and 3a with 2 Equiv of Pyridine in Thionyl Chloride.—Exactly 1.73 g (0.0100 mol) of 2a and 1.21 g (0.0050 mol) of 3a were dissolved (completely soluble) in 20 ml of thionyl chloride. Then, 1.60 g (0.0202 mol) of pyridine was added and stirring was maintained at 25°. Samples were removed at various times and analyzed by nmr. The results are listed in Table V.

TABLE V

Reaction time, hr	Moles[a] of 2a	Moles[b] of 8	Moles[c] of 3a	Moles[d] of pyridine HCl
0	0.0100		0.0050	
0.75	0.0040	0.0069	0.0041	0.0125
1.5	0.0038	0.0071	0.0041	0.0126

[a] Determined from vinyl integral. [b] Determined from integral of α-pyridinium multiplet. [c] Determined by difference. [d] Determined from NH integral.

Conversion of *m*-Phenylenediaminebismaleimide (4a) to *m*-Phenylenediaminebisdichloromaleimide (5a).—A solution of 1.34 g (0.0050 mol) of 4a in 20 ml of thionyl chloride was stirred in a cold-water bath as 1.66 g (0.0210 mol) of pyridine was added. This system was stirred at 20–25° for 1 hr, its nmr spectrum was recorded (see Table II), and it was then refluxed for 1 hr and cooled. The nmr spectrum of a sample showed that 0.0050 mol of 5a (aryl, m. δ 7.20–7.47) and 0.0210 mol of 9 (NH, s, δ 16.7, 1 H; β protons, m, δ 7.74–8.09, 2 H; γ protons, m, δ 8.23–8.57, 1 H; α protons, m, δ 8.57–8.82, 2 H) were the only materials present. Removal of the excess thionyl chloride followed by a chloroform–water work-up and recrystallization from benzene–cyclohexane gave 1.01 g (50% isolated yield) of 5a, mp 172.5–174°. The infrared spectrum of this material was superimposable on that of a sample of 5a which was prepared from *m*-phenylenediamine and 2 mol of dichloromaleic anhydride in acetic acid; both showed strong carbonyl absorption at 1729 cm⁻¹. (This latter sample of 5a had mp 172.5–173.1°.) The mass spectrum of 5a, in accord with the assigned structure, showed a four-chlorine cluster for the molecular ion at *m/e* 404–412.

Anal. Calcd for $C_{14}H_4Cl_4N_2O_4$: C, 41.41; H, 0.99. Found: C, 41.4; H, 1.1.

Conversion of 4,4'-Diaminodiphenylmethanebismaleimide (4b) to 4,4'-Diaminodiphenylmethanebisdichloromaleimide (5b).—Exactly 1.66 g (0.0210 mol) of pyridine was added to a solution of 1.79 g (0.0050 mol) of 4b in 20 ml of thionyl chloride with cooling in a cold-water bath. The resulting solution was stirred at 25° for 16 hr; the nmr spectrum is summarized in Table II. After refluxing for 1 hr, the nmr spectrum indicated the presence of 0.0050 mol of 5b (aryl, broad singlet, δ 7.18, 8 H; methylene, s, δ 3.87, 2 H) and 0.0210 mol of 9 (same data as given above in preparation of 5a). After the excess thionyl chloride was removed *in vacuo*, the solid residue was triturated with methanol and then recrystallized from chloroform–methanol. The isolated yield of 5b was 1.61 g (65%), mp 225–226°. The infrared

spectrum of this material was superimposable on that of a sample of 5b prepared from 4,4'-diaminodiphenylmethane and 2 mol of dichloromaleic anhydride in acetic acid, both showing strong carbonyl absorption at 1734 cm⁻¹. (This latter sample of 5b had mp 226–227.5°.) The mass spectrum of 5b showed the expected four-chlorine molecular-ion cluster at *m/e* 494–502.

Anal. Calcd for $C_{21}H_{10}Cl_4N_2O_4$: C, 50.84; H, 2.03; N, 5.65; Cl, 28.59. Found: C, 51.03; H, 2.10; N, 5.62; Cl, 28.7.

Conversion of 4,4'-Diaminodiphenyl Ether Bismaleimide (4c) to 4,4'-Diaminodiphenyl Ether Bisdichloromaleimide (5c).—This was carried out as described for 4b to 5b above. The nmr data after 1 hr of reaction are summarized in Table II. After recrystallization, there was obtained a 60% yield of 5c, mp 260–261.5°. The infrared spectrum of this material was identical with that of 5c obtained from 4,4'-diaminodiphenyl ether and dichloromaleic anhydride; both showed strong carbonyl absorption at 1733 cm⁻¹. (The latter sample of 5c had mp 260.5–261.5°.) The mass spectrum of 5c showed the expected four-chlorine molecular-ion cluster at *m/e* 496–504.

Anal. Calcd for $C_{20}H_8Cl_4N_2O_5$: C, 48.2; H, 1.6; N, 5.6; Cl, 28.5. Found: C, 48.5; H, 1.6; N, 5.9; Cl, 28.7.

Conversion of *N*-Methylmaleimide (2b) to *N*-Methyldichloromaleimide (3b).—A solution of 1.11 g (0.0100 mol) of 2b in 20 ml of thionyl chloride was stirred in a cold-water bath and 1.66 g (0.0210 mol) of pyridine was added. The system was stirred at ~25° for 1 hr. Its nmr spectrum is partially summarized in Table II. In addition it contains the following: 10, N–CH₃, s, δ 3.05; 2b, N–CH₃, s, δ 2.62. The solution was refluxed for 1 hr and its nmr spectrum then indicated the presence of 0.0087 mol of 3b (N–CH₃, s, δ 2.95) and 0.0185 mol of 9 (same data as given above in the preparation of 5a). Some impurities were apparent in the N–CH₃ region. Removal *in vacuo* of all of the excess thionyl chloride and trituration of the residue with 50% aqueous ethanol gave 0.79 g of 3b. This was subsequently recrystallized from 50% aqueous ethanol to give 0.36 g (20% isolated yield) of 3b, mp 81.5–82.5° (lit.[16] mp 85°). In accord with the structure of 3b, its infrared spectrum contained a very strong carbonyl band at 1720 cm⁻¹ (lit.[17] 1720 cm⁻¹), a medium intensity band at 1792 cm⁻¹ (lit.[17] 1793 cm⁻¹), and a C=C band at 1621 cm⁻¹ (lit.[17] 1620 cm⁻¹). The mass spectrum, as expected, showed a molecular-ion cluster at *m/e* 179 (intensity 100.0), 181 (63.5), and 183 (12.0).

Conversion of Maleimide (2c) to Dichloromaleimide (3c).—While a solution of 1.94 g (0.0200 mol) of 2c in 40 ml of thionyl chloride was stirred in a cold-water bath, 3.24 g (0.0410 mol) of pyridine was added. Stirring was continued at *ca.* 20° for 15 min and then at reflux for 1 hr. The nmr spectrum of the resulting system showed that 9 (NH, very broad peak, δ 16.6; α, β, and γ protons same as reported above in preparation of 5a) and probably 3c (NH, broad peak, δ 11.0) were present in the molar ratio of 0.0410:0.0131, respectively. No peak remained for the vinyl protons of 2c (see control expt F).

All of the excess thionyl chloride was removed *in vacuo* and, following the subsequent chloroform–water work-up and a chloroform recrystallization, 0.81 g (25% isolated yield) of 3c was obtained, mp 174–175.5° (lit.[18] mp 174–175°). The infrared spectrum of this product showed very strong bands for N—H at 3215 cm⁻¹ and for C=O at 1735 cm⁻¹ (lit.[17] 1738 cm⁻¹), a medium intensity C=O band at 1784 cm⁻¹ (lit.[17] 1785 cm⁻¹), and a C=C band at 1610 cm⁻¹ (lit.[17] 1610 cm⁻¹). As expected for the structure of 3c, the mass spectrum contained a molecular-ion cluster at *m/e* 165 (intensity 100.0), 167 (62.1), and 169 (12.1).

Conversion of Maleic Anhydride (6) to Dichloromaleic Anhydride (7).—A solution of 9.81 g (0.100 mol) of maleic anhydride in 100 ml of thionyl chloride (SOCl₂) was stirred in an ice bath in dry air while 16.22 g (0.205 mol) of pyridine was added dropwise during 12 min. Nmr evidence was obtained for the presence of 17 (α-pyridinium protons, m, δ 9.48–9.72) in spectra recorded *rapidly* at 25–35°. After only 30 min, all of 17 had been destroyed and only 7 and 9 were present. Following the addition, the system was heated to ~75° during 10 min and then cooled. The thionyl chloride was removed *in vacuo* and the solid residue triturated with benzene and filtered. Removal of solvent from the benzene filtrate gave 16.48 g (99% yield) of slightly impure dichloromaleic anhydride (mp 111–116°).

(16) H. Scharf, F. Korte, H. Seidler, and R. Dittmar, *Ber.*, **98**, 764 (1965).
(17) H. Schmelzer, E. Degener, and H. Holtschmidt, *Tetrahedron Lett.*, 2801 (1967).
(18) V. I. Shevchenko and V. P. Kukhar, *Zh. Obshch. Khim.*, **36**, 735 (1966).

The product was sublimed and then Soxhlet extracted with hexane to give 13.34 g (80%) of pure dichloromaleic anhydride, mp 118–120° (lit.[19] 119°). It was further identified unequivocally by mass spectrometry: molecular-ion two-chlorine cluster at m/e 166–170 and appropriate peaks and chlorine clusters for $M - CO_2$, $M - CO_2 - CO$, $M - CO_2 - Cl$, C_2Cl, C_3O, CCl, and C_2.

Control Experiments. A.—No reaction could be detected (nmr) between 2a (1.73 g) (vinyl, s, δ 6.83, 2 H; aromatic, m, centered at δ 7.40, 5 H) and thionyl chloride (4 ml) in methylene chloride (20 ml) during 16 hr at 25°.

B.—No reaction could be detected by nmr spectroscopy between 2a (1.73 g) (vinyl, s, δ 6.75, 2 H; aromatic, m, centered at δ 7.33, 5 H) and thionyl chloride (20 ml) (homogeneous solution) during 19 hr at 25° or 3 hr at reflux (~80°).

C.—No reaction could be detected (nmr) between pyridine (0.87 g) (β protons, m, δ 7.27–7.62, 2 H; γ protons, m, δ 7.62–8.06, 1 H; α protons, m, δ 8.55–8.80, 2 H) and thionyl chloride (20 ml) during 17.5 hr at 25°.[8]

(19) T. Zincke and O. Fuchs, *Justus Liebigs Ann. Chem.*, **267**, 20 (1891).

D.—No reaction could be detected (nmr) between pyridine (0.79 g) (α protons, m, δ 8.17–8.44, 2 H) and 2a (1.73 g) (vinyl, s, δ 6.90, 2 H) in anhydrous dimethyl sulfoxide (20 ml) during 17 hr at 25°.

E.—No reaction could be detected (nmr) between thionyl chloride and 2b, 4a, 4b, 4c, or 6 during several hours at 25–35°.

F.—The nmr spectrum of 2c in thionyl chloride (vinyl, d, J = 1.2 Hz, 2 H, coupling with NH; NH, very broad peak, δ 7.90, 1 H) remained unchanged during several hours at 25–35°.

Dichloromaleimide Chemistry. III. The Reaction of N-Aryldichloromaleimide with Phenols. The Preparation and Mass Spectral Rearrangements of N-Aryl-3-aryloxy-4-chloromaleimides and N-Aryl-3,4-bis(aryloxy)maleimides

HOWARD M. RELLES* AND ROBERT W. SCHLUENZ

General Electric Research and Development Center, Schenectady, New York 12301

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N-Aryldichloromaleimides have been found to react with substituted phenols under basic conditions to give aryloxychloro and/or bisaryloxy substituted maleimides, depending on the base/solvent system employed. A hindered phenol (2,6-dimethylphenol) was observed to undergo some carbon alkylation in its reaction with N-phenyldichloromaleimide. The mechanisms of these reactions (and some side reactions) are discussed, as are the ¹³C nmr and mass spectra of many of the products.

A few examples of the displacement of chloride by nucleophiles in N-substituted dichloromaleimides have appeared in the literature in recent years. In the reaction with primary amines,[1] displacement of one chlorine occurred together with transimidation. In all other cases, a chlorine was displaced by a group (–CN,[2] –SO₂R,[2] –SR,[3] and –NR₃⁺[4]) which subsequently facilitated the displacement of the second chlorine, presumably through its ability to stabilize an α-carbanionic center.[5] The reactions of phenols with N-substituted dichloromaleimides have not been reported previously.[6] In this paper we discuss these reactions

in detail as well as the mass spectra of the products produced therein.

Results and Discussion

When N-aryldichloromaleimides 1a–h were treated with phenols in the presence of base, a facile reaction ensued which led first to N-aryl-3-aryloxy-4-chloromaleimides (2) and then to N-aryl-3,4-bis(aryloxy)-maleimides (3). In certain base/solvent systems this condensation could be carried out to give only 2 with total exclusion of further reaction. For example, when a methylene chloride solution of N-phenyl-3,4-dichloromaleimide 1d (1 mol), 4-methylphenol (4 mol), and triethylamine (3 mol) was stirred at *ca.* 25° for 2 hr, the only product formed in >99% yield was N-phenyl-3-(4-methylphenoxy)-4-chloromaleimide 2dj; no detectable amount of N-phenyl-3,4-bis(4-methylphenoxy)maleimide 3dj was formed. Similarly, a 1:1 mixture of 1d and 4-methylphenol in methylene chloride in the presence of an excess of potassium carbonate gave only 2dj.

Most of the N-aryl-3-aryloxy-4-chloromaleimides (2) (see the first column of Table II) were prepared under similar reaction conditions (see Experimental Section) and were not contaminated with any other products. A few (2bk, 2dp, 2gj, and 2hp) were prepared using K_2CO_3 or Na_2CO_3 in N,N-dimethylformamide (DMF); side reactions (*vide infra*) were minimized by appropriately limiting the reaction times in these

(1) R. Oda, Y. Hayashi, and T. Takai, *Tetrahedron*, **24**, 4051 (1968).

(2) E. L. Martin, C. L. Dickinson, and J. R. Roland, *J. Org. Chem.*, **26**, 2032 (1961).

(3) (a) K. Fickentscher, *Tetrahedron Lett.*, 4273 (1969); (b) P. Dimroth and F. Reicheneder, *Angew. Chem., Int. Ed. Engl.*, **8**, 751 (1969).

(4) M. J. Karten, S. L. Shapiro, E. S. Isaacs, and L. Freedman, *J. Org. Chem.*, **30**, 2657 (1965).

(5) For example, a probable structure for one intermediate in the reactions of Karten, *et al.*,[4] is i.

(6) Brief mention, with no experimental details, was made[2] of a reaction which takes place between phenols, N-phenyldichloromaleimide, and presumably sodium cyanide.

SCHEME I

a, X = *p*-OCH₃
b, X = *p*-OC₆H₅
c, X = *p*-CH₃
d, X = H
e, X = *p*-Cl
f, X = *m*-Cl
g, X = *p*-CN
h, X = 2,6-di-CH₃

i, Y = *p*-OCH₃
j, Y = *p*-CH₃
k, Y = H
l, Y = *p*-Cl
m, Y = *m*-Br
n, Y = *p*-CN
p, Y = 2,6-di-CH₃

cases. *N*-Methyl-3-(4-methylphenoxy)-4-chloromaleimide **4** was obtained with K₂CO₃ in methylene chloride from *N*-methyl-3,4-dichloromaleimide and 4-methylphenol.
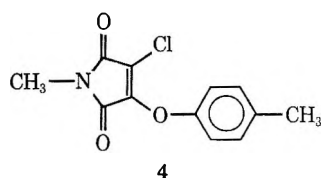
Although **2dp** was readily prepared with Na₂CO₃ in DMF, the use of K₂CO₃ in CH₂Cl₂ solution led to a mixture of **2dp** and **5**. Apparently, with the hindered 2,6-dimethylphenol, some competititive para-carbon alkylation occurred, presumably leading to **7** *via* **6** (Scheme I) and thereafter to **5** with a second molecule of **1d**. The failure to observe any of **7** is perhaps not surprising since its increased acidity would allow it to react much more rapidly with the base (and then with **1d**) than 2,6-dimethylphenol and thus prevent its buildup over the course of this particularly slow overall reaction (∼11 days at 25°).

Under strongly basic conditions, both chlorines of **1** could be displaced quantitatively. Thus, **3aj**, **3dj**, and **3hj** were the only products obtained from the rapid reactions of **1a**, **1d**, and **1h**, respectively, with 2 equiv of sodium 4-methylphenoxide in DMSO or DMSO–chlorobenzene. **3dk** was similarly obtained from **1d** and 2 equiv of sodium phenoxide.

The facility with which aryl oxide displaced one chlorine from **1** relative to that for the chlorine of **2** is undoubtedly due to a combination of factors. Comparing the two presumed intermediates (**8** and **9**) in

these cases, it is clear that steric requirements for the formation of **9** would be much greater than that for **8**. Similarly, inductive effects for chlorine and phenoxy (Cl, σ*⁷ 1.05; C₆H₅O, 0.85) would be expected to result in an increase in the stability of the carbanionic center in **8** compared with that in **9**, but stronger evidence bearing on this matter was obtained from the infrared and ¹³C nmr spectra of **2**. The infrared spectrum of all structures **2** displayed two strong carbonyl absorptions: one at 1720–1731 cm⁻¹ for the carbonyl group adjacent to the aryloxy group and one at 1648–1654 cm⁻¹ for the carbonyl group conjugated with the aryloxy-ether oxygen. Such conjugation, as depicted in the hybrid contributors **10** and **11**, would be expected to lead to increased electron density at the chlorine-bearing carbon, thereby decreasing the tendency for a nucleophile, such as an aryloxide ion, to attack at that position. Likewise, ¹³C nmr spectra of **2aj**, **2dj**, **2dk**,

(7) R. W. Taft, Jr., "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, p 595.

TABLE I

^{13}C NMR SPECTRA^a AND PROBABLE ASSIGNMENTS^b
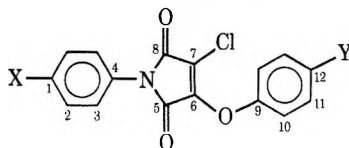
Compd	X	Y	1	2	3	4	5 and 8	6	7	9	10	11	12	In X	In Y
2aj	CH₃O-	CH₃	159.0	114.3	128.5	123.5	162.8, 164.3	148.3	109.5	151.5	118.7	130.1	135.0	55.4	20.3
2dj	H	CH₃	128.1	129.0	126.9	131.1	162.5, 164.1	148.4	109.6	151.5	118.8	130.1	135.0		20.3
2dk	H	H	128.2	129.0	126.9	131.0	162.5, 163.9	148.1	110.6	153.7	118.8	129.8	125.7		
2ej	-Cl	CH₃	129.9	(129.1 or 128.5)		132.7	162.3, 163.8	148.5	109.8	151.5	118.7	130.1	135.1		20.3
2gj	-CN	CH₃	10.4	133.2	126.8	c	162.0, 163.6	148.6	110.1	151.5	118.8	130.2	135.2	118.3	20.4

^{a} Determined in DMSO-d_6. The chemical shifts given are in parts per million downfield from internal TMS. ^{b} Personal communication: G. L. Nelson, G. C. Levy, and J. D. Cargioli, *J. Amer. Chem. Soc.*, **94**, 3089 (1972). ^{c} Probably obscured by the peak for carbon atom 12 at 135.2 ppm; the chemical shifts of each carbon atom 4 in this table are very nearly the same as those for the same carbon atom in the corresponding N-aryldichloromaleimides: 1a, 124.0; 1d, 131.7; 1e, 134.0; 1g, 136.3 ppm in DMSO-d_6 (see ref 8).

2ej, and **2gj** (see Table I) further suggest the importance of the resonance hybrid contributor **10**. The chemical
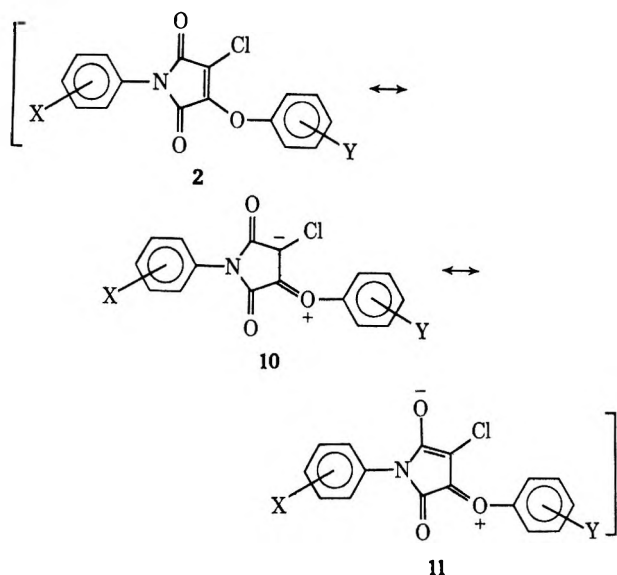
shift of the chlorine-bearing carbon in these structures (in DMSO-d_6) occurs at 109.5–110.6 ppm while those in the corresponding dichloromaleimide structures **1a**, **1d**, **1e**, and **1g** occur at 133.1–134.2 ppm.[8,9]

The reaction of **2fi** with 4-chlorophenoxide led to a mixture of **3fi**, **15**, and **3fl**. These results can be interpreted to indicate that the rate of attack on the chlorine-bearing carbon was slow compared to that on the aryloxy-bearing carbon to give an intermediate **13** (Scheme II) even though the formation of such an intermediate would be accompanied by strong steric interactions. Dissociation of **13** back to starting materials or to **2fl** and **14** would provide all the necessary reactants to give the final product mixture.

Although the reactions discussed thus far were relatively straightforward, resulting either in displacement of exactly one chlorine (weakly basic conditions such as K_2CO_3/CH_2Cl_2) or exactly two chlorines (strongly basic conditions such as NaOAr/DMSO), reaction conditions were also investigated which led to facile displacement of one chlorine followed by a

much slower displacement of the second. (In fact, **2bk**, **2dp**, **2gj**, and **2hp** were prepared by such a method under controlled conditions; see Experimental Section.) Under these conditions, a side reaction, namely imide-ring hydrolysis, became competitive with the slow rate of displacement of the second chlorine. For example, in the reaction of calcium oxide with **1d** and 2 equiv of 4-methylphenol in DMF, rapid formation of **2dj** was followed by hydrolysis of **2dj**, formation of some **3dj**, and hydrolysis of **3dj**. The thermal behavior (during vapor phase chromatographic analysis) of these hydrolysis products was of interest since it allowed a complete analysis of the changing complex reaction mixture. At ~350° (injection port temperature), the amic acids lost aniline to give anhydrides **16**[10a] and **17**[10b] (isolated and identified by nmr and/or mass spectra) while the silylated amic acids lost presumably trimethylsilanol [or bis(trimethylsilyl) ether] to give **2dj** and **3dj**. Control experiments[11] showed that **1d**, **2dj**, and **3dj** were each stable in DMF solution in the presence of CaO, Ca(OH)₂, and CaO/Ca(OH)₂/CaCl₂. In the presence of the mixture of calcium salts *and* 4-methylphenol, **2dj** underwent hydrolysis to amic acid(s) (which gave **16** thermally, vpc) as well as slow conversion to **3dj** followed by hydrolysis of the latter to an amic acid (which gave **17** thermally, vpc). Similarly, the calcium salt mixture *and* 4-methylphenol caused **3dj** to undergo hydrolysis to an amic acid (which gave **17** thermally, vpc). Perhaps a *soluble* calcium hydroxide, such as Ca(OH)(OC₆H₅CH₃), is implicated by these experiments. These results are summarized in Scheme III. Similar hydrolysis and thermal behavior was observed for other reactions with other inorganic bases in DMF (see Experimental Section).

Mass Spectra.—We have recently reported[8] our observations on the mass spectral rearrangement and cleavage of N-aryldichloromaleimides, **1**. We now wish to disclose the mass spectral behavior of the two new related classes of N-aryl-disubstituted maleimides, **2** and **3**; the salient features of the spectra are listed in Tables II and III, respectively.

(8) H. M. Relles and R. W. Schluenz, *J. Org. Chem.*, **37**, 1742 (1972).

(9) Similar differences have been reported in the ^{13}C nmr spectra of vinyl ethers and their corresponding olefins: K. Hatada, K. Nagata, and H. Yuki, *Bull. Chem. Soc. Jap.*, **43**, 3195 (1970).

(10) (a) This anhydride was also isolated by preparative vpc (and identified by its mass spectrum) during a preparation of **2gj** with Na₂CO₃ in DMF.[11] In this case, 4-cyanoaniline was the other thermally produced product (vpc). (b) This anhydride was also isolated by preparative vpc (and identified by its mass spectrum) during a preparation of **2hj** and **3hj** with Na₂CO₃ in DMF.[11] Here, 2,6-dimethylaniline was also produced.

(11) H. M. Relles, unpublished results.

SCHEME II

2fi

↕ (fast)

13

↕ (fast)

2fl

2fi + 12 + 2fl + 14

↓ (slow)

3fi

+

15

+

3fl

These spectra contrast in several ways with those reported[8] for **1**. All three structural types showed prominent cleavage giving rise to (ArNCO)⁺ ions (see **1'**, **2'**, and **3'**), but only in the case of **1** did the other

1'   2'   3'
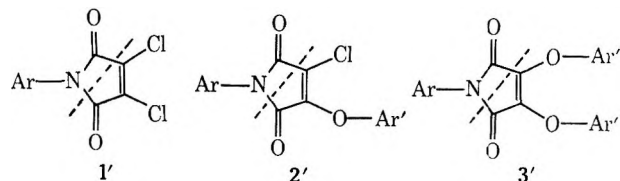
portion of the molecule (produced by this cleavage) also appear as a prominent ion, $(C_3Cl_2O)^+$; in none of the compounds **2** or **3** were there any peaks corresponding to $(C_3ClO_2Ar')^+$ or $(C_3O_3Ar'_2)^+$, respectively.

Other gross differences occurred because of the variety of rearrangement paths available to **2** and **3** (as a result of the presence of –OAr' groups) which were not available in **1**. Of interest in the case of **2** were the rearrangement-cleavage ions $(M - C_3ClO_2)^+$ and $(M - C_4ClO_3)^+$. The fact that the portion lost from the former (C_3ClO_2) also occurred as a major ion in all of the spectra (and in many cases as the base peak) may be of significance for a mechanistic rationale of these rearrangement processes. One such possible rationale is illustrated in Scheme IV. The mechanism depicted also explains the prominent rearrangement-cleavage ions $(M - C_3O_3Ar')^+$, $(C_3-O_3Ar')^+$, and $(M - C_4O_4Ar')^+$ of structure **3** if each chlorine is replaced in this scheme with an OAr' group.

Experimental Section

All ¹H nmr spectra were recorded with a Varian Associates T-60 nmr spectrometer using tetramethylsilane as an external standard and deuteriochloroform as solvent, unless noted otherwise. All ¹³C nmr spectra were recorded with a Varian Associates XL-100-15 nmr spectrometer using complete ¹H decoupling at 100 MHz with simultaneous ¹³C observation at 25.2 MHz. Chemical shifts were measured from internal tetramethylsilane or calibrated to this standard using known chemical shifts of solvent peaks. Mass spectra were determined on a C. E. C. 21-104 analytical mass spectrometer at 70 eV. Infrared spectra were taken as KBr pellets unless noted otherwise. Vapor-phase chromatography (vpc) was carried out on a Hewlett-Packard 5750 with 6 ft 10% SE-30 silicone gum rubber columns and temperature programming from 200–290° at 10°/min; injection port temperature was 350°. All of the dichloromaleimides used herein were prepared from the appropriate amine and dichloromaleic anhydride in refluxing glacial acetic acid.[8] The synthesis of one not reported previously is given below. Anhydrous DMSO and DMF were obtained by distillation from CaH₂, at reduced pressure and atmospheric pressure, respectively.

Preparation of N-(2,6-Dimethylphenyl)dichloromaleimide, 1h. —A solution of 24.2 g (0.20 mol) of 2,6-dimethylaniline in 150 ml of acetic acid was added slowly (30 min) to 50.1 g (0.30 mol) of dichloromaleic anhydride in 300 ml of acetic acid. Much precipitate formed during this addition which was presumably the amide acid.[12] The system was refluxed for 1 hr and cooled, and the solid product which had crystallized was filtered. A second batch of solid product was obtained by adding 300 ml of water to the above filtrate. The total product was recrystallized from hexane giving 46.1 g (85%) of 1h: mp 140.5–141.5°; mass spectrum m/e [rel intensity, assignment]; 269 [100, M⁺], 190 [50, (M − CO₂ − Cl)⁺],[8] 147 [9.0, (M − C₃Cl₂O)⁺],[8] 146 [16.5, M − C₃Cl₂O − H)⁺], 122 [3.5, (C₃Cl₂O)⁺].[8]

Anal. Calcd for C₁₂H₉Cl₂NO₂: Cl, 26.3. Found: Cl, 26.2.

N-(4-Methoxyphenyl)-3-(4-methylphenoxy)-4-chloromaleimide, 2aj.—A solution of 27.21 g (0.10 mol) of *N*-(4-methoxyphenyl)-3,4-dichloromaleimide, 1a, and 10.81 g (0.10 mol) of 4-methylphenol in 250 ml of methylene chloride was stirred for 3 days at ∼25° with 69.1 g (0.50 mol) of anhydrous K₂CO₃. The system was added with caution (CO₂ evolution) to excess 1 N HCl and an additional 250 ml of CH₂Cl₂. The resulting organic phase was extracted with water, dried (MgSO₄), and freed of solvent *in vacuo*. Recrystallization of the product (cyclohexane) gave 28.9 g (84%) of 2aj: mp 155.0–155.5°; ¹H nmr spectrum δ 6.67–7.28 (m, 8, aromatic), 3.70 (s, 3, CH₃O), and 2.30 (s, 3, CH₃Ar); ir 1648 and 1720 cm⁻¹ (two C=O). The ¹³C nmr spectrum and mass spectrum were also in accord with the product and are given in Tables I and II, respectively.

Anal. Calcd for C₁₈H₁₄ClNO₄: C, 63.0; H, 4.11; N, 4.08. Found: C, 63.7; H, 4.0; N, 4.0.

N-(4-Methoxyphenyl)-3,4-bis(4-methylphenoxy)maleimide, 3aj.—Exactly 1.60 g of 50.0% aqueous sodium hydroxide (0.020 mol of NaOH) was added to 2.16 g (0.020 mol) of 4-methylphenol

(12) In many similar preparations of other *N*-aryldichloromaleimides, this initially formed solid dissolved when the system was heated and another solid crystallized from solution at reflux which eventually proved to be the imide product.

SCHEME III
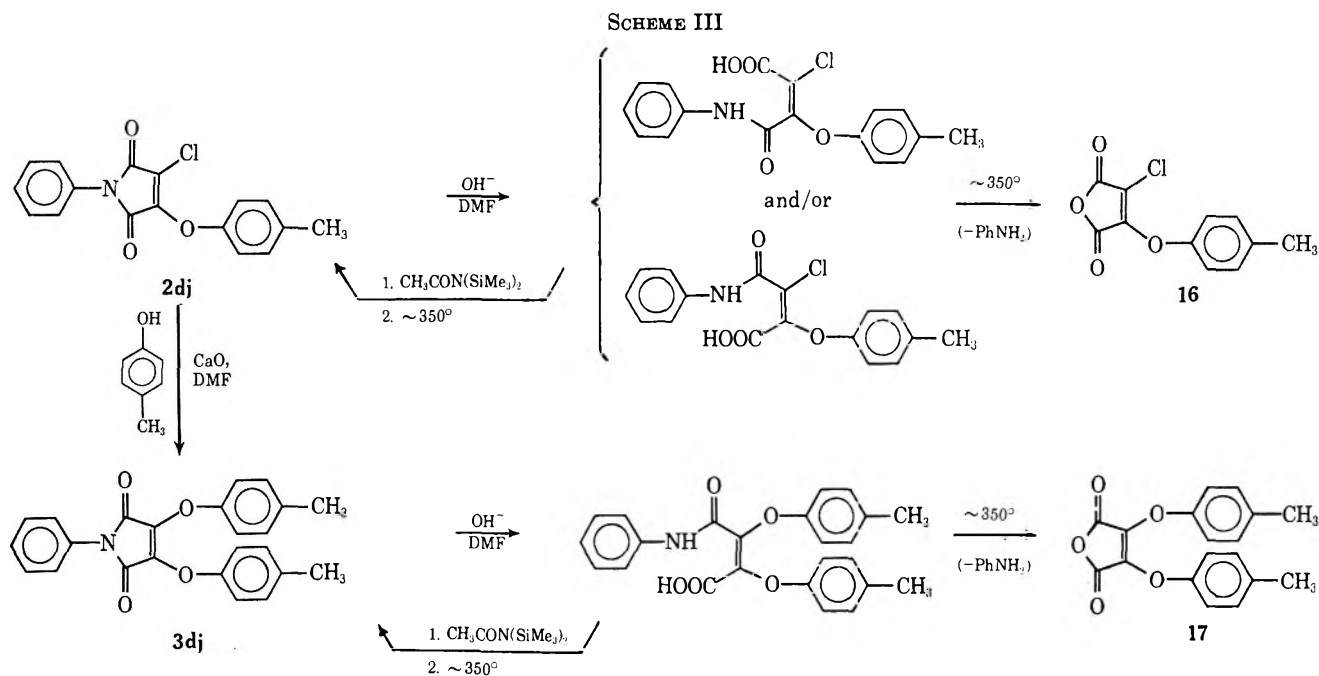
TABLE II

MASS SPECTRA[a] OF *N*-ARYL-3-ARYLOXY-4-CHLOROMALEIMIDES, 2
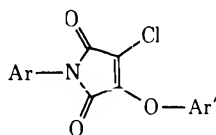
Compd	M$^+$	(M − C$_3$ClO$_2$)$^+$	(M − OAr′)$^+$	(M − C$_4$ClO$_3$)$^+$	(ArNCCl)$^+$	(ArNCO)$^+$	(OAr′)$^+$	(C$_3$ClO$_2$)$^+$
2aj	343 (100)	240 (41)	236 (21)	212 (62)	168 (19)	149 (21)	107 (20)	103 (43)
2bk	391 (100)	288 (18)	298 (3)	260 (38)	230 (7)	211 (23)	93 (2)	103 (36)
2cj	327 (100)	244 (87)	220 (50)	196 (75)	152 (40)	133 (29)	107 (45)	103 (124)
2di	329 (100)	226 (92)	206 (25)	198 (42)	138 (46)	119 (25)	123 (105)	103 (101)
2dj	313 (100)	210 (88)	206 (26)	182 (41)	138 (22)	119 (23)	107 (10)	103 (52)
2dk	299 (100)	196 (120)	206 (20)	168 (55)	138 (18)	119 (22)	93 (7)	103 (52)
2dl	333 (100)^c	230 (107)^b	206 (63)	202 (42)^b	138 (48)	119 (44)	127 (9)^b	103 (143)
2dm	377 (100)^d	274 (129)^e	206 (51)	246 (7)^e	138 (51)	119 (83)	171 (1)^e	103 (170)
2dn	324 (100)	221 (170)	206 (23)	193 (87)	138 (33)	119 (77)	118 (2)	103 (176)
2dp	327 (100)	224 (14)	206 (16)	196 (4)	138 (23)	119 (38)	121 (13)	103 (98)
2ej	347 (100)^c	224 (76)^b	240 (19)^c	216 (49)^b	172 (23)^c	153 (23)^b	107 (22)	103 (154)
2fi	363 (100)^c	260 (8)^b	240 (10)^c	232 (24)^b	172 (25)^c	153 (17)^b	123 (163)	103 (168)
2fk	333 (100)^c	230 (142)^b	240 (17)^c	202 (34)^b	172 (20)^c	153 (39)^b	93 (7)	103 (172)
2fl	367 (100)^f	264 (100)^c	240 (57)^c	236 (28)^c	172 (47)^c	153 (51)^b	127 (24)^b	103 (321)
2fm	411 (100)^g	308 (119)^d	240 (39)^c		172 (44)^c	153 (101)^b		103 (395)
2gj	338 (100)	235 (75)	231 (7)	207 (56)	163 (9)	144 (8)	107 (9)	103 (101)
2hj	341 (100)	238 (15)	234 (58)	210 (15)	166 (22)	147 (8)	107 (15)	103 (54)
2hp	355 (100)	252 (1)	234 (22)		166 (13)	147 (12)	121 (151)	103 (86)

[a] *m/e* (and relative intensity) given. Unless otherwise indicated, the (M)$^+$, (M − OAr)$^+$, (ArNCCl)$^+$, and (C$_3$ClO$_2$)$^+$ ions occurred as one-chlorine clusters. Many peaks were present with *m/e* less than 93 but were omitted from this tabulation. Some significant peaks, other than those tabulated, were also observed: 2aj, 134 (36); 2bk, 167 (31); 2cj, 119 (25), 132 (45), 181 (28); 2di, 228 (25); 2dj, 167 (15); 2dl, 111 (118),^{b} 123 (33),^{b} 139 (37),^{b} 167 (57), 178 (16);^{b} 2dm, 155 (92),^{e} 167 (158), 178 (29),^{b} 183 (22);^{e} 2dn, 102 (174), 114 (38), 130 (37); 2dp, 292 (91); 2ej, 119 (36), 125 (30), 181 (42); 2fi, 226 (69);^{b} 2fk, 167 (51); 2fl, 111 (283),^{b} 123 (59),^{b} 125 (37),^{b} 139 (57),^{b} 201 (81);^{b} 2fm, 155 (201),^{e} 201 (168);^{b} 2gj, 119 (16), 192 (18), 210 (22);^{b} 2hj, 221 (39); 2hp, 208 (43),^{b} 320 (122). ^{b} One-chlorine cluster. ^{c} Two-chlorine cluster. ^{d} One-chlorine, one-bromine cluster. ^{e} One-bromine cluster. ^{f} Three-chlorine cluster. ^{g} Two-chlorine, one-bromine cluster.

in 40 ml of chlorobenzene being stirred in a nitrogen atmosphere. Water was completely removed by azeotropic distillation and subsequent passage of the refluxing liquid through a calcium hydride bed. The system was then cooled to ~25°.

To the resulting suspension of 0.020 mol of sodium 4-methylphenoxide was added 2.72 g (0.010 mol) of *N*-(4-methoxyphenyl)-3,4-dichloromaleimide, 1a, 20 ml of anhydrous chlorobenzene, and 6 ml of anhydrous dimethyl sulfoxide (DMSO). The solution rapidly became homogeneous and, after it was stirred at ~25° for 1.5 hr, it was added to 100 ml of chloroform and extracted several times with 1 *N* HCl (to remove the DMSO), dried

(MgSO$_4$), and freed of solvent *in vacuo*. The solid residue, which also contained a small amount of chlorobenzene, was recrystallized from hexane. There was obtained 3.60 g (87%) of 3aj: mp 166–167°; ^{1}H nmr spectrum δ 6.53–7.26 (m, 12, aromatic), 3.68 (s, 3, OCH$_3$), and 2.20 (s, 6, CH$_3$Ar); ir strong C=O with fine structure maxima at 1690, 1710, and 1720 cm^{-1} (*no peak* at all near 1650 cm^{-1}); for mass spectrum see Table III.

N-(4-Phenoxyphenyl)-3-phenoxy-4-chloromaleimide, 2bk.—
N,*N*-Dimethylformamide (DMF, 50 ml) was added to 3.34 g (0.010 mol) of *N*-(4-phenoxyphenyl)-3,4-dichloromaleimide, 1b, and 0.94 g (0.010 mol) of phenol. To the resulting solution was

TABLE III

MASS SPECTRA[a] OF N-ARYL-3,4-DIARYLOXYMALEIMIDES, 3
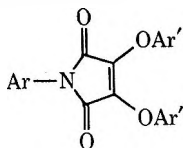
Compd	M⁺	$(M - C_3O_2Ar')^+$	$(M - OAr')^+$	$(M - C_4O_4Ar')^+$	$(ArNCO)^+$	$(OAr')^+$	$(C_3C_3Ar')^+$
3aj	415 (100)	240 (29)	308 (1)	212 (59)	149 (57)	107 (147)	175 (35)
3dj	385 (100)	210 (27)	278 (3)	182 (19)	119 (66)	107 (58)	175 (30)
3dk	357 (100)	196 (41)	264 (2)	168 (22)	119 (15)	93 (43)	161 (19)
3hj	413 (100)	238 (21)	306 (14)	210 (4)	147 (24)	107 (102)	175 (67)

[a] m/e (and relative intensity) are given. Some significant peaks, other than those tabulated, were also observed: **3aj**, 252 (39), 224 (28), 134 (73), 119 (140); **3dj**, 222 (28); **3dk**, 331 (49), 239 (36), 238 (50), 208 (32); 105 (53); **3hj**, 278 (21), 262 (19), 221 (24), 132 (26), 119 (215).

SCHEME IV
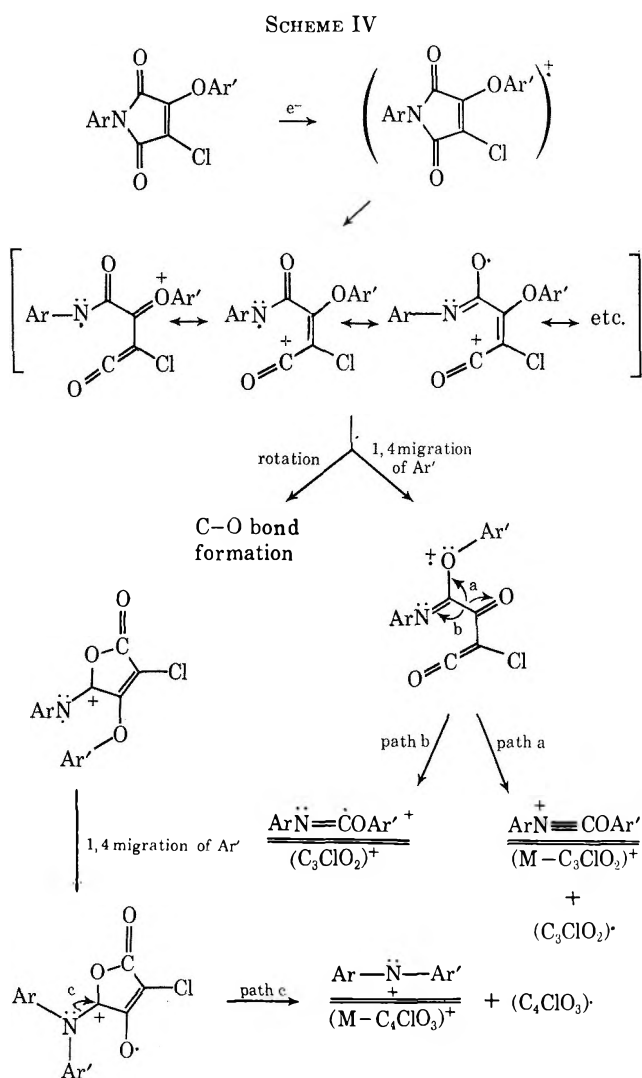
added 6.91 g (0.05 mol) of anhydrous K_2CO_3 and stirring was maintained for 3 hr at ~25°. Chloroform was added, the excess K_2CO_3 was filtered off, and the filtrate was extracted with 1 N HCl (to remove DMF) and dried over $MgSO_4$. Solvent removal and recrystallization of the product from carbon tetrachloride gave 2.5 g (64%) of **2bk**, mp 146–148°. Another recrystallization from chloroform afforded an analytical sample: mp 148.5–149°; ir 1649 and 1722 cm⁻¹ (two C=O); for mass spectrum see Table II.

Anal. Calcd for $C_{22}H_{14}ClNO_4$: C, 67.5; H, 3.6; N, 3.6; Cl, 9.1. Found: C, 67.3; H, 3.6; N, 3.5; Cl, 9.1.

N-(4-Methylphenyl)-3-(4-methylphenoxy)-4-chloromaleimide, **2cj**.—A solution of 5.12 g (0.020 mol) of *N*-(4-methylphenyl)-3,4-dichloromaleimide, **1c**, and 2.16 g (0.020 mol) of 4-methylphenol in 50 ml of methylene chloride was stirred with 13.8 g (0.10 mol)

of anhydrous K_2CO_3 in dry air, at ~25°, for 7 days. The reaction mixture was cautiously (CO_2 evolution) added to a stirred mixture of 250 ml of chloroform and 250 ml of 1 N HCl. The layers were separated; the organic layer was extracted with water, dried ($MgSO_4$), and freed of solvent *in vacuo* to give 6.40 g of a solid product. Recrystallization from ethanol afforded 5.78 g (88%) of **2cj**: mp 166–167°; ¹H nmr spectrum δ 2.33 (slightly broadened singlet, 6, two CH₃'s), 6.90–7.40 (m, 8, aromatic); ir 1650 and 1723 cm⁻¹ (two C=O); for mass spectrum see Table II.

N-Phenyl-3-(4-methoxyphenoxy)-4-chloromaleimide, **2di**.—A solution of 4.84 g (0.020 mol) of *N*-phenyl-3,4-dichloromaleimide, **1d**, and 2.48 g (0.020 mol) of 4-methoxyphenol in 50 ml of methylene chloride was stirred at ~25° for 20 hr with 13.8 g (0.10 mol) of anhydrous K_2CO_3. Work-up and recrystallization, as described above for **2cj**, afforded 5.79 g (88%) of **2di**: mp 130.5–131.5°; ¹H nmr spectrum δ 3.66 (s, 3, OCH₃), 6.54–7.36 (m, 9, aromatic); ir 1653 and 1726 cm⁻¹ (two C=O); for mass spectrum see Table II.

N-Phenyl-3-(4-methylphenoxy)-4-chloromaleimide, **2dj**.—Exactly 24.21 g (0.100 mol) of *N*-phenyl-3,4-dichloromaleimide, **1d**, and 10.81 g (0.100 mol) of 4-methylphenol were stirred in 250 ml of methylene chloride with 69.1 g (0.50 mol) of anhydrous K_2CO_3 at ~25° for 3 days. [After only 2 days, vapor phase chromatographic (vpc) analysis showed that all of the starting materials were absent and only **2dj** was present.] The system was then carefully added to 1 l. of 1 N HCl and 750 ml of methylene chloride. The organic phase was separated, extracted with water, dried, and freed of solvent in vacuo. The pale yellow solid (29.8 g) obtained was recrystallized from hexane to give 25.3 g (81%) of pure **2dj**: mp 102–103°; ¹H nmr spectrum (CH_2Cl_2) δ 6.8–7.5 (m, 9, aromatic), 2.27 (s, 3, CH₃); ir ($HCCl_3$) 1653 and 1730 cm⁻¹ (two C=O); for ¹³C nmr spectrum and mass spectrum see Tables I and II, respectively.

Anal. Calcd for $C_{17}H_{12}ClNO_3$: C, 65.0; H, 3.9; Cl, 11.3. Found: C, 64.7; H, 3.9; Cl, 11.4.

N-Phenyl-3-phenoxy-4-chloromaleimide, **2dk**.—This material was prepared from **1d** and phenol by the method used for **2cj** except that the reaction time was only 20 hr. Recrystallization, as in the case of **2cj**, afforded 4.52 g (76%) of **2dk**: mp 132.5–133.5°; ir 1653 and 1725 cm⁻¹ (two C=O); for ¹³C nmr spectrum and mass spectrum see Tables I and II, respectively.

Anal. Calcd for $C_{16}H_{10}ClNO_3$: Cl, 11.8. Found: Cl, 11.8.

N-Phenyl-3-(4-chlorophenoxy)-4-chloromaleimide, **2dl**.—This material was prepared from **1d** and 4-chlorophenol and recrystallized by the method described for **2cj** except that the reaction time was 20 hr. The yield was 5.86 g (88%): mp 139–141°; ir 1643 and 1728 cm⁻¹ (two C=O); for mass spectrum see Table II.

Anal. Calcd for $C_{16}H_9Cl_2NO_3$: Cl, 21.2. Found: Cl, 21.5.

N-Phenyl-3-(3-bromophenoxy)-4-chloromaleimide, **2dm**.—Preparation of this material from **1d** and 3-bromophenol and recrystallization were carried out using the method described for **2cj** except that the reaction time was 20 hr. There was obtained 5.50 g (73%) of **2dm**: mp 115–116.5°; ir 1657 and 1727 cm⁻¹ (two C=O); for mass spectrum see Table II.

Anal. Calcd for $C_{16}H_9BrClNO_3$: C, 50.7; H, 2.4; N, 3.7. Found: C, 50.4; H, 2.6; N, 3.9.

N-Phenyl-3-(4-cyanophenoxy)-4-chloromaleimide, **2dn**.—This material was prepared from **1d** and 4-cyanophenol and recrystallized as described for **2cj** except that the reaction was carried out

for 11 days. (After 6 days, vpc analysis showed that the reaction was not yet complete.) The amount of **2dn** obtained was 5.54 g (86%): mp 161–163°; ir 1652 and 1730 cm^{-1} (two C=O), 2235 cm^{-1} (C≡N); for mass spectrum see Table II.

Anal. Calcd for C$_{17}$H$_9$ClN$_2$O$_3$: Cl, 10.9. Found: Cl, 10.9.

N-**Phenyl-3,4-bis(4-methylphenoxy)maleimide, 3dj.**—To an anhydrous solution of 0.0212 mol of sodium 4-methylphenoxide in 40 ml of DMSO and 20 ml of chlorobenzene, prepared in a manner analogous to that used during the preparation of **3aj**, was added 2.567 g (0.0106 mol) of *N*-phenyl-3,4-dichloromaleimide, **1d**. Vpc analysis showed that the reaction was complete in less than 20 min; only **3dj** was present; **1d** and **2dj** were absent. Chloroform was added and the mixture was extracted with 1 *N* HCl until no more DMSO remained (according to nmr analysis), dried, and freed of solvent *in vacuo*. The product thus obtained (8.1 g) was essentially pure **3dj**: ^{1}H nmr spectrum δ 6.5–7.5 (m, 13, aromatic), 2.22 (s, 6, CH$_3$). Recrystallization from cyclohexane afforded an analytical sample: mp 171–172°; ir strong C=O with fine structure maxima at 1686 and 1723 cm^{-1} (no bands were present in the 1650-cm^{-1} region); for mass spectrum see Table III.

Anal. Calcd for C$_{24}$H$_{19}$NO$_4$: C, 74.8; H, 4.9; N, 3.6. Found: C, 75.2; H, 5.0; N, 3.9.

N-**Phenyl-3,4-bis(phenoxy)maleimide, 3dk.**—While a solution of 2.42 g (0.0100 mol) of **1d** in 25 ml of anhydrous DMSO was being stirred in a nitrogen glove box, 2.32 g (0.0200 mol) of anhydrous sodium phenoxide was added in small portions so as to maintain the reaction temperature below 50° (25 min). A chloroform/water work-up afforded 3.5 g of a yellow solid which, after recrystallization from cyclohexane/benzene, gave 2.70 g (76%) of **3dk**: mp 165.5–166°; ir 1700 and 1728 cm^{-1} (C=O); for mass spectrum see Table III. The ^{13}C nmr spectrum (acetone-*d*$_6$) was in accord with the assigned structure (C$_n$ designations from **18**
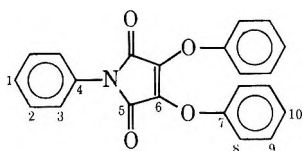
18

and chemical shift in parts per million): C$_1$, 128.4; C$_2$, 129.6; C$_3$, 127.3; C$_4$, 132.4; C$_5$, 164.8; C$_6$, 134.6; C$_7$, 156.1; C$_8$, 118.0; C$_9$, 130.2; C$_{10}$, 125.1.

Anal. Calcd for C$_{22}$H$_{15}$NO$_4$: C, 73.9; H, 4.2; N, 3.9. Found: C, 74.2; H, 4.4; N, 4.2.

N-**(4-Chlorophenyl)-3-(4-methylphenoxy)-4-chloromaleimide, 2ej.**—A solution of 1.66 g (0.0060 mol) of *N*-(4-chlorophenyl)-3,4-dichloromaleimide, **1e**, and 0.65 g (0.0060 mol) of 4-methylphenol in 15 ml of methylene chloride was stirred at ~25° for 47 hr with 4.15 g (0.030 mol) of anhydrous K$_2$CO$_3$. Work-up and recrystallization were carried out, as described for **2cj**, to give 1.68 g (81%) of **2ej**: mp 156.5–157.5°; ir 1648 and 1727 cm^{-1} (two C=O); ^{1}H nmr spectrum δ 6.90–7.60 (m, 8, aromatic), 2.40 (s, 3, CH$_3$); for mass spectrum see Table II; for ^{13}C nmr spectrum see Table I.

N-**(3-Chlorophenyl)-3-(4-methoxyphenoxy)-4-chloromaleimide, 2fi.**—The preparation of this material from **1f** and 4-methoxyphenol and its purification were carried out as described for **2cj** except that the reaction was run on a 0.030 mol scale for 41 hr. The yield of **2fi** was 9.8 g (90%): mp 119–120°; ir 1648 and 1727 cm^{-1} (two C=O); for mass spectrum see Table II; ^{1}H nmr spectrum δ 6.6–7.4 (m, 8, aromatic), 3.70 (s, 3, OCH$_3$).

N-**(3-Chlorophenyl)-3-phenoxy-4-chloromaleimide, 2fk.**—This material was prepared from **1f** and phenol and recrystallized by the method described for **2cj** except that the scale was 0.015 mol and the reaction time was 25 hr. The yield of **2fk** was 3.36 g (67%): mp 98–99°; ir 1651 and 1730 cm^{-1} (two C=O); for mass spectrum see Table II.

Anal. Calcd for C$_{16}$H$_9$Cl$_2$NO$_3$: Cl, 21.2. Found: Cl, 21.6.

N-**(3-Chlorophenyl)-3-(4-chlorophenoxy)-4-chloromaleimide, 2fl.**—Using the method described for the preparation and purification of **2cj**, **2fl** was prepared in a 0.0154 mol scale reaction (reaction time of 22 hr) from **1f** and 4-chlorophenol. The yield of **2fl** was 3.73 g (66%): mp 124.5–125.5°; ir 1648 and 1731 cm^{-1} (two C=O); for mass spectrum see Table II.

Anal. Calcd for C$_{16}$H$_8$Cl$_3$NO$_3$: Cl, 28.8. Found: Cl, 28.8.

N-**(3-Chlorophenyl)-3-(3-bromophenoxy)-4-chloromaleimide, 2fm.**—This material was prepared from **1f** and 3-bromophenol and recrystallized as described for **2cj** except that the reaction time was 25 hr and the scale was 0.015 mol. The yield of **2fm** was 4.61 g (74%): mp 116.5–118.5°; ir 1654 and 1723 cm^{-1} (two C=O); for mass spectrum see Table II.

Anal. Calcd for C$_{16}$H$_8$BrCl$_2$NO$_3$: C, 46.5; H, 1.93; N, 3.4. Found: C, 46.2; H, 2.04; N, 3.6.

N-**(4-Cyanophenyl)-3-(4-methylphenoxy)-4-chloromaleimide, 2gj.**—A solution of 0.450 g (0.0017 mol) of *N*-(4-cyanophenyl)-3,4-dichloromaleimide, **1g**, and 0.184 g (0.0017 mol) of 4-methylphenol in 4.5 ml of anhydrous *N*,*N*-dimethylformamide (DMF) was stirred with 0.180 g (0.0017 mol) of anhydrous, powdered Na$_2$CO$_3$ at ~25° for 100 min. The entire system was added to 10 ml of chloroform and 10 ml of 1 *N* HCl and, after the layers were shaken, the aqueous layer was discarded. The chloroform layer was extracted four more times with 15-ml portions of 1 *N* HCl, dried (MgSO$_4$), and freed of solvent *in vacuo*. The solid product (0.58 g), after recrystallization from EtOH, gave 0.36 g (63%) of **2gj**: mp 190–191.5°; ir 1648 and 1728 cm^{-1} (two C=O), 2235 cm^{-1} (C≡N); ^{1}H nmr spectrum (DMSO-*d*$_6$) δ 7.2–8.2 (m, 8, aromatic), 2.32 (s, 3, CH$_3$); for mass spectrum see Table II; for ^{13}C nmr spectrum see Table I.

N-**(2,6-Dimethylphenyl)-3-(4-methylphenoxy)-4-chloromaleimide, 2hj.**—This material was prepared from **1h** and 4-methylphenol and purified by the method described for the preparation of **2cj** except that the reaction time was only 47 hr. The yield of **2hj** was 5.89 g (86%): mp 151.5–152.5°; ir 1653 and 1723 cm^{-1} (two C=O); ^{1}H nmr spectrum δ 6.95–7.33 (m, 7, aromatic), 2.17 (s, 6, CH$_3$'s on the *N*-aryl ring), 2.36 (s, 3, CH$_3$ on the *O*-aryl ring); for mass spectrum see Table II.

N-**(2,6-Dimethylphenyl)-3-(2,6-dimethylphenoxy)-4-chloromaleimide, 2hp.**—Exactly 5.40 g (0.020 mol) of *N*-(2,6-dimethylphenyl)-3,4-dichloromaleimide, **1h**, and 2.44 g (0.020 mol) of 2,6-dimethylphenol in 50 ml of anhydrous DMF were stirred at ~25° for 5 hr with 10.6 g (0.10 mol) of anhydrous, powdered Na$_2$CO$_3$. Work-up, similar to that used in the preparation of **2gj**, gave 6.56 g of crude product which, after recrystallization from EtOH, gave 5.39 g (76%) of **2hp**: mp 157.5–158.5°; ir 1650 and 1725 cm^{-1} (two C=O); ^{1}H nmr spectrum δ 7.00–7.35 (m, 6, aromatic), 2.18 (s, 6, CH$_3$'s on the *N*-aryl ring), 2.32 (s, 6, CH$_3$'s on the *O*-aryl ring); for mass spectrum see Table II.

N-**(2,6-Dimethylphenyl)-3,4-bis(4-methylphenoxy)maleimide, 3hj.**—Exactly 0.01801 mol of anhydrous sodium 4-methylphenoxide was prepared, as described in the preparation of **3aj**, in 35 ml of DMSO and 35 ml of chlorobenzene. To this solution under nitrogen was added 2.43 g (0.00900 mol) of **1h** and, after 1.5 hr, work-up was affected as described for **3aj**. Recrystallization from hexane afforded 2.24 g (60%) of **3hj**: mp 128–129.5°; ir 1690 and 1720 cm^{-1} (C=O); ^{1}H nmr spectrum δ 6.5–7.1 (m, 11, aromatic), and two very nearly coincident singlets, for the *N*-aryl ring methyls and the *O*-aryl ring methyls, both at 2.17 δ (total 12 H); for mass spectrum see Table III.

N-**Methyl-3-(4-methylphenoxy)-4-chloromaleimide, 4.**—This material was prepared from *N*-methyl-3,4-dichloromaleimide and 4-methylphenol by the method used for the synthesis of **2cj** except that the reaction time was only 47 hr. After recrystallization, there was obtained 3.93 g (78%) of **4**: mp 111–112°; ir 1652 and 1723 cm^{-1} (two C=O); ^{1}H nmr spectrum δ 6.90–7.35 (m, 4, aromatic), 3.04 (s, 3, N–CH$_3$), 2.36 (s, 3, CH$_3$Ar); mass spectrum *m/e* [rel intensity, probable assignment given] 251 [100, one-chlorine molecular ion cluster], 148 [3, (M – C$_3$ClO$_2$)$^+$], 147 [10, (M – C$_3$ClO$_2$ – H)$^+$], 144 [17, (M – OAr)$^+$ one-chlorine cluster], 120 [5, (M – C$_4$ClO$_3$)$^+$], 119 [20, (M – C$_4$ClO$_3$ – H)$^+$], 107 [12, OAr$^+$] 103 [101, (C$_3$ClO$_2$)$^+$ one-chlorine cluster].

The Reaction of 1d with 2,6-Dimethylphenol. A. Preparation of *N*-Phenyl-3-(2,6-dimethylphenoxy)-4-chloromaleimide, 2dp.—To a solution of 4.84 g (0.02 mol) of **1d** and 2.44 g (0.02 mol) of 2,6-dimethylphenol in 50 ml of anhydrous DMF was added 10.6 g (0.1 mol) of anhydrous Na$_2$CO$_3$. The system was stirred at ~25° for 5 hr, combined with 50 ml of chloroform, and then extracted with six 100-ml portions of 1 *N* HCl. The crude product was isolated by drying the chloroform solution with MgSO$_4$ and removing the solvent *in vacuo*. (It was completely soluble in ethanol, a fact which indicates the total absence of **5**; see expt B below.) Recrystallization from 75 ml of cyclohexane gave 3.6 g of **2dp**: mp 88–89°; ^{1}H nmr spectrum δ 2.33 (s, 6, CH$_3$), 7.25–7.59 (m, 8, aromatic); ir 1649 and 1728 cm^{-1} (two C=O); for mass spectrum see Table II.

Anal. Calcd for $C_{18}H_{14}ClNO_3$: Cl, 10.84. Found: Cl, 11.2.

B. Preparation of N-Phenyl-3-(2,6-dimethylphenoxy)-4-chloromaleimide, 2dp, and N-Phenyl-3-{2,6-dimethyl-4-[3-(N-phenyl-4-chloro)maleimido]phenoxy}-4-chloromaleimide, 5.—A solution of 4.84 g (0.02 mol) of 1d and 2.44 g (0.02 mol) of 2,6-dimethylphenol in 50 ml of methylene chloride was stirred at ~25° with 13.8 g (0.10 mol) anhydrous K_2CO_3. After 6 days, vpc analysis showed that much of the starting materials remained and that only one volatile product, $R_t = 9.7$ min, had been produced. After 11 days, only a trace of 1d was left, although a significant amount of 2,6-dimethylphenol remained; the material with $R_t = 9.7$ min was still the only volatile product observed. The system was then worked up as described for 2cj and 7.19 g of crude product was obtained. This material was dissolved in 250 ml of EtOH and 100 ml of $HCCl_3$, concentrated to 200 ml by distillation, and then allowed to cool slowly to ca. 25°. The yellow crystalline material, which had separated, was filtered and dried. In this way, 1.31 g of a material, mp 208–211°, was obtained which subsequently proved to be 5:[13] ir 1656, 1708, and 1722 cm⁻¹ (C=O) (no –OH band); ¹H nmr spectrum δ 2.29 (slightly broadened singlet, 6, CH_3), 7.2–7.9 (m, 12, aromatic); mass spectrum *m/e* [rel intensity, assignment] 532 [100, two-chlorine molecular-ion cluster], 497 [55, $(M - Cl)^+$ one-chlorine cluster], 429 [5, $(M - C_3ClO_2)^+$ one-chlorine cluster], 413 [15, $(M - C_6H_5NCO)^+$ two-chlorine cluster], 378 [17, $(M - C_6H_5NCO-Cl)^+$ one-chlorine cluster], 326 [9, OAr^+ one-chlorine cluster], 310 [29, Ar^+ (from OAr portion) one-chlorine cluster], 206 [34, $(M - OAr)^+$ one-chlorine cluster], 119 [37, $(C_6H_5NCO)^+$], 103 [66, $(C_3ClO_2)^+$ one-chlorine cluster].

Anal. Calcd for $C_{28}H_{18}Cl_2N_2O_5$: Cl, 13.4. Found: Cl, 13.9.

Concentration of the above filtrate to 80 ml gave a second crop of 0.12 g of 5; the total yield of 5 was 1.43 g (27%, based on 1d).

Solvent removal from the second crop of 5 gave a viscous oil which could not be crystallized. Vpc and nmr analysis indicated that it was approximately a 1:4 mixture of 2,6-dimethylphenol and 2dp. Indeed, a pure sample of the latter ($R_t = 9.7$ min) was isolated by preparative vpc and displayed the same mass spectrum as found previously for 2dp (Table II).

Attempted Preparation of N-(3-Chlorophenyl)-3-(4-chlorophenoxy)-4-(4-methoxyphenyl)maleimide, 15.—To a suspension of 0.0150 mol of anhydrous sodium 4-chlorophenoxide in 40 ml of chlorobenzene, prepared in a manner analogous to that described above for the preparation of sodium 4-methylphenoxide, was added 5.46 g (0.0150 mol) of 2fi and 10 ml of anhydrous DMSO in a nitrogen atmosphere. The system rapidly became homogeneous. After the solution stirred for 1 hr at ~25°, it was worked up as described in the preparation of 3aj. A total of 5.16 g of material (mp 94–100°) crystallized from the hexane–chlorobenzene solution. Thin layer chromatography (on silica, with benzene as solvent) indicated that this material contained at least three components. Several attempts at purification by recrystallization failed; each time there was obtained a broad melting mixture which showed an appropriate methoxy singlet (δ 3.72) and aromatic multiplet (δ 6.5–7.5) in the ¹H nmr spectrum in various ratios, all within ±15% of that expected for 15. The three components of these mixtures were found by mass spectrometry to be 3fi, 15, and 3fl; they displayed the appropriate one-, two-, and three-chlorine molecular-ion clusters, respectively (Table IV).

Other Reactions between 1d and 4-Methylphenol. I. Triethylamine in Methylene Chloride.[14]—A solution of 0.24 g (0.0010 mol) of 1d and 0.43 g (0.0040 mol) of 4-methylphenol in 10 ml of methylene chloride was stirred at ca. 25° and 0.30 g (0.0030 mol) of triethylamine was added. Samples of the solution were taken at various times and analyzed by vpc (reaction time and mole ratio of 1d:2dj given): 45 min, 2:98; 110 min, 0.3:99.7; no impurities were detected. A sample of the product was collected by preparative vpc and gave the same mass spectrum as found previously for 2dj (Table II). The reaction mixture was extracted with 1 N HCl, 10% aqueous NaOH, and water,

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(13) This material could not be eluted at 290° from the vpc columns used herein.

(14) Mole ratios given in this experiment were determined from vpc peak areas and so must be regarded in a qualitative and not quantitative sense (error ±10%). Although retention times for the material involved were quite reproducible and, therefore, useful for identification, in many cases samples of the components were collected by preparative vpc and identified further by their mass spectra.

TABLE IV

PARTIAL MASS SPECTRUM[a] OF A MIXTURE OF 3fl, 15, AND 3fl

| *m/e* | Obsd rel intensity | Calcd rel intensities | | | |
		3fi[b]	15[c]	3fl[d]	Total[e]
451	100.0	100.0			100.0
452	27.6	27.7			27.7
453	34.8	36.9			36.9
454	12.9	9.5			9.5
455	211.0	1.6	209.4		211.0
456	59.1	0.2	55.5		55.7
457	145.4		143.2		143.2
458	37.5		36.6		36.6
459	50.4		27.4	23.0	50.4
460	12.9		6.5	5.8	12.3
461	22.4		1.0	22.9	23.9
462	5.7		0.1	5.7	5.8
463	7.2			7.9	7.9
464	1.5			1.9	1.9
465	0.8			1.0	1.0
466	0.2			0.2	0.2

[a] No peaks at all above 466 or between 450 and 444; no significant peaks between 443 and 321. [b] Calculated for $C_{24}H_{18}ClNO_6$ by setting the intensity of the 451 peak equal to 100.0. [c] Calculated for $C_{23}H_{15}Cl_2NO_5$ by setting the intensity of the 455 peak equal to 209.4 (the difference between the observed intensity and that calculated for this peak in the molecular-ion cluster of 3fi). [d] Calculated for $C_{22}H_{12}Cl_3NO_4$ by setting the intensity of the 459 peak equal to 23.0 (the difference between the observed intensity and that calculated for this peak in the molecular-ion cluster of 15). [e] Agrees within experimental error with the observed relative intensities.

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dried with $MgSO_4$, and freed of solvent *in vacuo.* The "crude" product (0.2 g) displayed ¹H nmr and infrared spectra which were superimposable on those obtained previously for 2dj.

II. Pyridine in Methylene Chloride.[14]—Using pyridine (0.0030 mol) in place of triethylamine in expt I gave the same results, but at a much slower rate according to vpc analysis (reaction time and mole ratio of 1d:2dj given): 30 min, 56:44; 60 min, 35:65.

III. Calcium Oxide in DMF.[14] A.—A solution of 0.24 g (0.0010 mol) of 1d and 0.054 g (0.00050 mol) of 4-methylphenol in 2.50 ml of anhydrous DMF was stirred at ca. 25° with 0.56 g (0.010 mol) of anhydrous, powdered CaO. Samples (0.25 ml) of the slurry were removed at various times and added to 5 ml of chloroform and 5 ml of 1 N HCl with vigorous stirring. The chloroform layer was separated, dried, and then analyzed by vpc (reaction time and mole ratio of 1d:2dj given): 20 min, 96:4; 45 min, 90:10; 110 min, 72:28; 24 hr, 48:52 (theory for this experiment, 50:50). No other products were detected.

B.—A solution of 0.24 g (0.0010 mol) of 1d and 0.216 g (0.0020 mol) of 4-methylphenol in 2.50 ml of anhydrous DMF was stirred at ca. 25° with 0.56 g (0.01 mol) of CaO. Approximately 0.25-ml aliquots were removed at various times and each was then treated and analyzed by vpc as described above (expt III, A). In this way, 16 and 17 were detected, isolated, and identified. A portion of each aliquot was further treated with bis(trimethylsilyl)acetamide and then analyzed again by vpc. The results are listed in Table V.

Structures 16 and 17 are in complete accord with their mass spectra (Tables VI and VII, respectively). ¹H nmr spectrum of 16 showed δ 7.2 (m, 4, aromatic), 2.3 (s, 3, CH_3).

C.—Reactions using 0.0010 or 0.0040 mol of 4-methylphenol gave results similar to those reported above (expt III, B).

IV. Potassium Carbonate in DMF.[14]—A solution of 0.968 g (0.0040 mol) of 1d and 0.432 g (0.0040 mol) of 4-methylphenol in DMF (10.00 ml = total volume) was stirred at ~25° with 5.52 g (0.040 mol) of anhydrous K_2CO_3. As described above, the reaction was followed by vpc (reaction time and relative molar amounts of 16:1d:2dj, respectively, given): 20 min, 0:24:76; 155 min, 0:0:100; 17.5 hr, 5:0:95. No other materials were detected.

V. Sodium Carbonate in DMF.[14]—This reaction was carried out as described in IV except that the base was 4.24 g (0.040 mol) of anhydrous Na_2CO_3: 20 min, 0:2:98; 155 min, 0:0:100; 17.5 hr, 3:0:97. No other materials were observed.

Table V

Approximate Mole Ratios of Compounds Determined
by Vpc on Each Aliquot[a]

Reaction time, min	Compounds[b]				
	16	**1d**	**17**	**2dj**	**3dj**
20	0 (0)	79 (82)	0 (0)	21 (18)	0 (0)
45	2 (0)	8 (4)	0 (0)	89 (95)	1 (1)
75[c]	59[d] (0)	0 (0)	9[d] (0)	16[d] (68)[d]	16 (23)[d]
110[c]	61 (0)	0 (0)	24 (0)	9 (68)	4 (20)
24[c]	61 (0)	0 (0)	30 (0)	5 (70)	1 (19)

[a] Values in parentheses are from the vpc of the aliquots after
silylation with bis(trimethylsilyl)acetamide. [b] **2dj** and **3dj** were
identified by comparing retention times with those of authentic
materials and by isolating them by preparative vpc and com-
paring their mass spectra with those of the authentic materials.
16 and **17** were identified by similar isolation and examination
of nmr and/or mass spectra (see Tables VI and VII, respectively);
the observed retention times on the silicone column used were in
agreement with the observed molecular weights (mass spectra)
of **16** and **17**. Retention times (minutes) follow: **16**, 2.05; **1d**,
2.40; **17**, 6.30; **2dj**, 7.60; **3dj**, 12.40. [c] Unknown minor im-
purities were also present. [d] These were the samples collected
and identified by their mass spectra.

Table VI

Mass Spectrum of 16

m/e	Rel intensity		Probable assignment
	Found	Calcd	
91	230.5		C_7H_7
103	274.0		One-chlorine cluster for C_3ClO_2;
105	82.7		rearrangement ion[a]
107	36.2		C_7H_7O
119	98.6		C_7H_7OC
134	46.3		C_7H_6OCO; rearrangement ion[a] −H
135	18.9		C_7H_7OCO; rearrangement ion[a]
147	24.7		C_7H_7OCCO; $M - C_2ClO_2$
210	21.6		One-chlorine cluster for $M -$
212	7.1		CO
238	100.0	100.0	Molecular-ion cluster:
239	13.0	12.6	$C_{11}H_7ClO_4$
240	33.3	33.5	
241	4.3	4.2	

[a] See discussion section for corresponding rearrangement ions
in structurally similar imides **2** and **3**.

VI. Sodium Bicarbonate in DMF.[14]—This reaction was
carried out as described in IV except that the base was 3.36 g

Table VII

Mass Spectrum of 17

m/e	Rel intensity		Probable assignment for ion
	Found	Calcd	
91	160.0		C_7H_7
107	104.0		C_7H_7O
119	54.0		C_7H_7OC
135	21.6		C_7H_7OCO; rearrangement ion[a]
147	18.8		C_7H_7OCCO
175	37.2		$C_7H_7OC_3O_2$; rearrangement ion[a]
310	100.0	100.0	Molecular-ion cluster:
311	20.9	20.5	$C_{18}H_{14}O_5$
312	3.1	3.0	
313	0.5	0.3	

[a] See footnote a, Table VI.

(0.040 mol) of anhydrous NaHCO₃: 20 min, 0:99:1; 155 min,
0:55:45; 17.5 hr, 0:0:100. Carbon dioxide evolution was
observed during this reaction. No other products were observed
and, in particular, none of 16 was detected (vpc).

VII. Zinc Oxide in DMF.—This reaction was conducted as
described in IV except that the base used was 3.34 g (0.040 mol)
of anhydrous ZnO: 17.5 hr, 0:98:2 (very slow reaction).

VIII. Calcium Oxide in DMSO.—This experiment was per-
formed as described in IV except that the solvent was anhydrous
DMSO and the base was 2.24 g (0.040 mol) of anhydrous CaO:
20 min, 0:99:1; 155 min, 0:78:22; 31 hr, 0:0:100.

IX. Potassium Carbonate in DMSO.—This experiment was
performed as described in IV except that the solvent was anhy-
drous DMSO: 20 min, 0:5:95; 155 min, 13:0:87.

X. Sodium Carbonate in DMSO.—This experiment was
conducted as described in IV except that the solvent was anhy-
drous DMSO and the base was 4.24 g (0.040 mol) of anhydrous
Na₂CO₃: 20 min, 1:0:99; 155 min, 8:0:92.

Nucleophilic Substitutions Initiated by Electrochemical Oxidation. II. Substitution of a *tert*-Butyl Group in 2,4,6-Tri-*tert*-butylphenol by Pyridine

GERHARD POPP* AND NANCY C. REITZ

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

The electrochemical oxidation at controlled potential of 2,4,6-tri-*tert*-butylphenol (2) in the presence of pyridine affords 1-(3,5-di-*tert*-butyl-2-hydroxyphenyl)pyridinium perchlorate (8) and 1-(1,3,5-tri-*tert*-butyl-4-oxocyclo-hexa-2,5-dien-1-yl)pyridinium perchlorate (9) in a molar ratio of 2:1. Treatment of 8 with 0.1 *N* aqueous base leads to the formation of a novel dark blue phenol betaine (10). The solvatochromic and thermochromic long-wavelength absorption of 10 is shown to be due to an intramolecular charge-transfer band.

Recently we reported the intramolecular displacement of a *tert*-butyl group by pyridine in derivatives of 8-*tert*-butyl-1-(2-pyridyl)-2-naphthols. The mechanism of this reaction was proposed[1] to be an ECE sequence wherein the nucleophile pyridine attacks carbon atom 8 of the naphthalene moiety after the loss of two electrons and one proton from the starting molecule.

The resulting cationic species eliminated the *tert*-butyl group slowly to form a naphthol perchlorate, which, upon treatment with aqueous base, is converted into a naphthol betaine (1).[1,2]

1
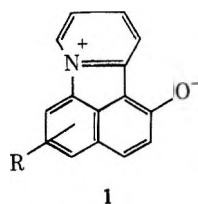
We now report the preparation of a phenol betaine through *intermolecular* nucleophilic displacement of a *tert*-butyl group on 2,4,6-tri-*tert*-butylphenol (2) by pyridine. The electrochemical oxidation of 2,4,6-tri-*tert*-butylphenol in acetonitrile was recently reported to proceed with the exchange of 2 faradays of current per mole of starting material when the base α-lutidine was present in solution. In the presence of the nucleophiles, water, methanol, and acetate ion, the corresponding cyclohexadienone derivatives were isolated in high yields.[3,4] In an earlier note[5] the preparation of 3-methyl-5,7-di-*tert*-butyl-1,2-benzisoxazole (3) through electrochemical oxidation of 2, 4,6-tri-*tert*-butylphenol in acetonitrile was described.

3
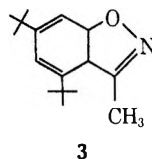
Acetonitrile was considered to react as a nucleophile in the course of this reaction with the intermediate 2,4,6-tri-*tert*-butylphenoxylium ion (4).

Pyridine appeared to be a promising nucleophile in these reactions for the electrochemical preparation of substituted arenol betaines.

(1) G. Popp, *J. Org. Chem.*, **37**, 3058 (1972).
(2) D. L. Fields and T. H. Regan, *J. Org. Chem.*, **36**, 2986 (1971).
(3) V. D. Parker and A. Ronlán, *J. Electroanal. Chem.*, **30**, 502 (1971).
(4) A. Ronlán and V. D. Parker, *J. Chem. Soc. C*, 3214 (1971).
(5) A. B. Suttie, *Tetrahedron Lett.*, 953 (1969).

4
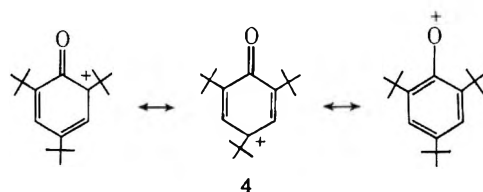
Cyclic voltammetric scans of 2,4,6-tri-*tert*-butyl-phenol (2) in an anhydrous acetonitrile–tetrabutylam-monium perchlorate medium show one irreversible response at +1.46 V. No cathodic response can be detected for 2 if the scan is started at 0.0 V. However, if the scan is begun at a potential corresponding to the diffusion plateau of the oxidation response, a reductive response is observed at −0.10 V. This response can be attributed to the reduction of protons which have been generated through oxidation of 2. Voltammetric scans of 2 in a 1:1 acetonitrile–pyridine mixture using a graphite anode show an irreversible response at +1.26 V, and a broad irreversible response at −1.20 V when the scan is started at a potential corresponding to the diffusion plateau of the oxidation response. Comparison of the peak current of the cyclic voltammetric response of 2 with 9,10-diphenylanthra-cene showed that at a scan rate of 0.1 V/sec the oxidation response of 2 corresponds to the exchange of approximately two electrons per molecule of starting material. However, coulometric oxidation at a potential corresponding to the diffusion plateau of the oxidation response of 2 proceeded in general with the exchange of approximately four electrons per molecule of substrate. The addition of a base like pyridine or α-lutidine led to a two-electron process for the oxidation response of 2 in these media.

Macroelectrolyses have been performed on a gram scale at potentials corresponding to the diffusion plateau of the oxidation response of 2. The oxidations were continued until the current had decayed to approximately 5% of its original value.

When the oxidation of 2 was performed in an anhydrous acetonitrile–sodium perchlorate medium at room temperature, 2,6-di-*tert*-butyl-*p*-benzoquinone (5) and *tert*-butylacetamide (6) were isolated from the reaction mixture in approximately 80 and 39% yield, respectively. Approximately 4–5 faradays were exchanged per mole of starting material. It was found that the nature of the isolated products depended on the acetonitrile used. In cases where acetonitrile from Burdick and Jackson was used as a solvent, 2-methyl-5,7-di-*tert*-butylbenzoxazole (7) was isolated in approximately 2% yield from the reaction mixture

as its perchlorate salt, in addition to **5** and **6** (Scheme I). The oxidation proceeded in these cases with the exchange of approximately 2–3 faradays per mole of **2**.

Thus far we have not been able to determine the reasons for the formation of the benzoxazole **7** in acetonitrile from Burdick and Jackson. Although it contained approximately the same amounts of water by Karl Fischer titration) and acid impurities as acetonitrile from Burdick and Jackson, acetonitrile, X-488 from Eastman Organic Chemicals, in no case competed effectively with traces of water to form the benzoxazole, even when solvent and supporting electrolyte were dried carefully before use and the reaction was carried out in an atmosphere of dry nitrogen.

Cyclic voltammetric studies together with coulometric experiments and product characterization of macroelectrolyses have shown that **2** in aprotic solvents is oxidized in a two-electron process to a cationic species that can react with nucleophiles present in solution.[3–5] With water as nucleophile, 2,4,6-tri-*tert*-butyl-4-hydroxycyclohexadienone is formed, which decomposes in the presence of acids to give the corresponding 2,6-di-*tert*-butylhydroquinone. This, in turn, is further oxidized to 2,6-di-*tert*-butyl-*p*-benzoquinone. The leaving group of the acid-catalyzed decomposition of the cyclohexadienone derivative is *tert*-butyl cation, which reacts under these conditions with acetonitrile and water in a Ritter reaction[6] to give *tert*-butylacetamide (**6**). The electrochemical oxidation of 8-*tert*-butyl-1-(2-pyridyl)naphthalenes in the presence of pyridine has shown earlier[1] that vinylogs of *tert*-butylcyclohexadienones are also stable only in basic media. Since carbon atoms 2, 4, and 6 of compound **2** are sterically hindered toward attack by a nucleophile, the choice of base becomes decisive for the course of the reaction. Ronlán and Parker[3,4] have shown that sterically hindered bases like α-lutidine act strictly as proton acceptors, whereas nucleophiles like water, methanol, or acetate ion attack preferentially carbon atom 4 of compound **2**. Although HMO calculations have predicted[4] an even distribution of the positive charge of the phenoxylium ion between carbon atoms 2, 4, and 6, so far there has been no case reported where product arises from attack by the nucleophile in the 2 position. We have observed that pyridine as nucleophile attacks the phenoxylium ion intermediate in the 2 and 4 position to give **8** and **9** in approximately the same product distribution, as predicted by the theory.[4]

(6) L. Eberson and K. Nyberg, *Acta Chem. Scand.*, **18**, 1567 (1964).

The oxidation of **2** in a 1:1 mixture of acetonitrile (Eastman Organic Chemicals X-488)–pyridine on a graphite electrode at 5–10° yielded initially a mixture of 1-(3,5-di-*tert*-butyl-2-hydroxyphenyl)pyridinium perchlorate (**8**) and 1-(1,3,5-tri-*tert*-butyl-4-oxocyclohexa-2,5-dien-1-yl)pyridinium perchlorate (**9**) in 44 and 23% yield, respectively (Scheme II). In addition, a brown
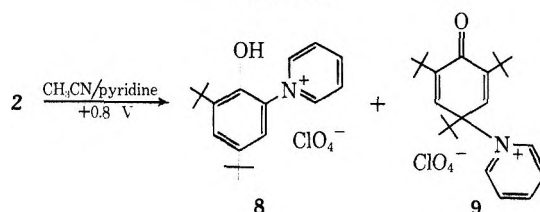
tarry material was isolated from the product mixtures. However, attempts to elucidate the chemical nature of this material were frustrated by its resistance toward further purification. No indication was found for the formation of compounds **5** and **6**. Since the unprotonated form of **8**, the zwitterion **10**, is oxidized further at a potential of +0.46 V, we feel that the tarry material may arise from further oxidation of **10** which had been incompletely protonated during the reaction.

The detailed mechanism of the overall reaction involves the generation of a phenoxylium ion through the loss of two electrons and one proton from **2**. The question whether deprotonation occurs after the loss of the first (ECE mechanism) or second electron (EEC mechanism) has been discussed in great detail by others[3,4] and our data at present also do not allow differentiation between the two mechanisms. In general, proton transfer reactions are held to be very rapid, and therefore an ECE step appears plausible. However, several cases have been reported where proton transfer from a cationic species appeared to be slow on the time scale of voltammetric experiments.[7–9] We are currently studying the voltammetric oxidation of 5-hydroxy-8-*tert*-butylanthracene, the cation radical of which also deprotonates only slowly.

Compound **8** can be converted easily to the red phenol betaine **10** on treatment with 0.1 N aqueous sodium hydroxide (Scheme III). Under these conditions compound **9** remains unchanged.
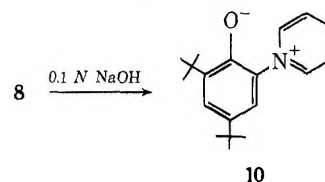
The structures of compounds **8, 9,** and **10** have been confirmed by elemental analysis, ^{1}H nuclear magnetic resonance spectra, mass spectra, and infrared spectra.

Phenol betaine **10** is a new member of a class of compounds which has been investigated earlier by

(7) A. M. F. Marcus and M. D. Hawley, *Biochem. Biophys. Acta*, **201**, 1 (1970).

(8) A. Ronlán and V. D. Parker, *Chem. Commun.*, 1567 (1970).

(9) V. D. Parker, *J. Amer. Chem. Soc.*, **91**, 5380 (1969).

Dilthey and Dierichs,[10] Schneider, *et al.*,[11] and in great detail by Dimroth, *et al.*[12] Similarly to Dimroth's experience with phenol betaines, **10** always contained water and it can be obtained in the form of dark blue, water-free crystals only in a high-vacuum system. As soon as the compound is exposed to air the color changes from dark blue to red. Elemental analysis shows that the blue form of **10** is water-free, whereas the red species is a monohydrate. Like other phenol betaines,[13] **10** exhibits remarkable solvatochromic and thermochromic properties.

Spectroscopic analysis of **10** in solvents of different polarities, according to Kosower's[14] and Dimroth's[13,15] proposals, shows that the long-wavelength absorption is due to an intramolecular charge-transfer band. The temperature sensitivity[16] of this charge-transfer band of **10** in diethyl ether has been determined to be $d\bar{\nu}_{max}/d(1/T) = 8.62 \times 10^{-3} cm^{-1} {}^\circ K$.

To our knowledge, phenol betaines so far have been prepared only through reaction of pyrylium salts with aminophenols.[11-13] Since this method excludes the preparation of phenol betaines with an unsubstituted pyridine moiety, it appears that the chemical and electrochemical methods complement each other ideally. Further work on the scope and limitation of these electrochemical reactions is in progress and will be reported elsewhere.

Experimental Section

Apparatus.—Cyclic voltammetric experiments were performed in a conventional three-electrode cell with an Electrochemistry System Model 170 from the Princeton Applied Research Corp. All potentials are referred to an aqueous saturated sodium chloride calomel reference electrode (ssce). If not mentioned otherwise, all voltammetric scan rates refer to 0.1 V/sec.

Controlled-potential coulometry and preparative oxidations were carried out in conventional two-compartment cells at platinum working electrodes. The potentiostat was either the Model 170 from Princeton Applied Research Corp. or a Model AS100 from Tacussel Electronique.

[1]H nuclear magnetic resonance spectroscopy was performed with a Varian A-60 instrument, mass spectroscopy was performed with the Hitachi RMS-4 spectrometer, and uv-visible and ir spectra were obtained with the Cary Model 14 and Perkin-Elmer Model 137 instruments, respectively.

Materials.—2,4,6-Tri-*tert*-butylphenol (TTBP) (Aldrich T4940-9) was purified by recrystallization from hot isopropyl alcohol, mp 129-130°. Acetonitrile (Eastman Organic Chemicals X-488 and Burdick and Jackson) and pyridine (Eastman Organic Chemicals ACS) were dried over 4-Å molecular sieves. Sodium perchlorate (G. F. Smith) and tetrabutylammonium perchlorate (Eastman Organic Chemicals) were used as obtained.

Controlled Potential Oxidation of 2,4,6-TTBP in Acetonitrile-Pyridine.—A 50% acetonitrile-pyridine solution (150 ml) of sodium perchlorate (0.5 *M*) and 2,4,6-TTBP (3.13 g, 1.19 × 10⁻² mol) was oxidized at 10° at a graphite wool electrode (6 × 6 × 0.6 cm) fitted over a platinum screen maintained at a potential of 0.80 V. The catholyte solution consisted of sodium perchlorate (0.5 *M*) in 50% pyridine-acetonitrile. After 1.3 hr, 2.52 × 10⁻² faradays (2.1 electrons/molecule) had been passed.

After most of the liquid had evaporated from the reaction mixture, addition of water slowly precipitated a white solid, mp

193-195°. Nmr analysis of this solid (2.9 g) showed it to consist of a 60:40 mixture of **8** and **9**. This solid was extracted into ether-water. The portion that did not dissolve in either was filtered and recrystallized from hot chloroform to yield white needles of **9**. The water layers from this extraction were combined and the water was evaporated, leaving the white solid **7**, which was not purified further. The aqueous filtrate from the reaction mixture was extracted first with ether and then with dichloromethane. The dichloromethane extracts were rinsed with water and evaporated under high vacuum. A mixture (0.256 g) of **8** and **10** precipitated upon the addition of a small volume of water. The overall yields of **8** and **9** were 44 and 23%, respectively.

Compound **8** had ^{1}H nmr spectrum (60 MHz, deuterioacetonitrile) δ 1.33 (9 H, s, *tert*-butyl protons), 1.45 (9 H, s, *tert*-butyl protons), 7.32 (1 H, d, aromatic proton), 7.61 (1 H, d, aromatic proton), 7.9-8.9 (5 H, pyridine protons); ir (KBr pellet) 3400 (broad, s), 2940 (m), 1620 (s), 1450 (m), 1100 (broad, s), 880 (w), 779 (w), 670 cm⁻¹ (m).

Anal. Calcd for C₁₉H₂₆ClNO₅: C, 59.5; H, 6.8; N, 3.6; Cl, 9.3. Found: C, 58.7; H, 6.2; N, 3.6; Cl, 9.3.

Compound **9** had ^{1}H nmr spectrum (60 MHz, acetonitrile) δ 1.11 (9 H, s, protons of *tert*-butyl group on C-4), 1.32 (18 H, s, *tert*-butyl protons), 7.30 (2 H, s, ring proton), 7.0-8.0 (5 H, pyridinium protons); ir 5400 (broad, w), 2930 (m), 1650 (m), 1625 (w), 1600 (w), 1450 (m), 1350 (m), 1090 (broad, s), 684 cm⁻¹ (w).

Anal. Calcd for C₂₃H₃₄ClNO₅: C, 62.8; H, 7.7; N, 3.2; Cl, 8.3. Found: C, 62.9; H, 7.8; N, 3.1; Cl, 8.3.

Based on these spectral and analytical data, compounds **8** and **9** were assigned the following structure, respectively, 1-(3,5-di-*tert*-butyl-2-hydroxyphenyl)pyridinium perchlorate and 1-(1,3,5-tri-*tert*-butyl-4-oxocyclohexa-2,5-dien-1-yl)pyridinium perchlorate.

Phenol Betaine 10.—The addition of aqueous sodium hydroxide (0.1 *N*) to an aqueous solution of **5** (0.115 g, 0.30 mmol) resulted in the formation of red needles of **7** (0.060 g, 0.20 mmol, 65%) in the monohydrate form. Under high vacuum, the orange-red color changes to dark blue: mass spectrum *m/e* 283 (M⁺), 268, 252, 241, 240, 80; ir (KBr pellet) 3500 (broad, m), 2990 (s), 1620 (w), 1460 (s), 1440 (s), 1420 (s), 1395 (m), 1340 (m), 1310 (s), 1260 (m), 825 (m), 782 (m), 735 cm⁻¹ (m); ^{1}H nmr (60 mHz, deuterioacetonitrile) δ 1.26 (9 H, s, *tert*-butyl protons), 1.37 (9 H, s, *tert*-butyl protons), 7.02 (1 H, d, ring proton), 7.23 (1 H, d, aromatic proton), 7.75-9.00 (5 H, pyridine protons); uv and visible max. (acetonitrile) 532 mμ (ε 3.7 × 10³), 303 (7.8 × 10³), 254 (1.5 × 10⁴).

Anal. Calcd for C₁₉H₂₅NO (7): C, 80.5; H, 8.8; N, 4.9. Found: C, 80.3; H, 9.0; N, 4.9.

Controlled Potential Oxidation of 2,4,6-TTBP in Acetonitrile.—2,4,6-TTBP (1.0 g, 3.85 × 10⁻³ mol), dissolved in an acetonitrile (Eastman Organic Chemicals X-488) solution of sodium perchlorate (0.5 *M*) was oxidized at 1.60 V on a platinum screen. After 0.50 hr, the current had decayed to 2% of the original value and 2.07 × 10⁻² faradays (5.4 electrons/molecule) had been consumed.

Upon evaporation of the acetonitrile, a yellow solid residue remained and was shaken in water. A pale yellow solid (0.681 g, 3.1 × 10⁻³ *M*, 80%) was filtered and recrystallized from ethanol-water as yellow needles, mp 65.5-66.0° (lit.[17] mp 67.5-68.5°) and identified as 2,6-di-*tert*-butyl-1,4-benzoquinone (**5**). The aqueous filtrate was extracted with dichloromethane. After drying and evaporation of this solvent, a solid (0.171 g, 1.62 × 10⁻³ mol, 39%) was isolated. Recrystallization from hexane afforded white needles, mp 95.0-95.5° (lit.[18] mp 98°), which were identified as *tert*-butylacetamide (**6**).

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Electrophilic Aromatic Triphenylmethylation. Self-Consistent Field–Molecular Orbital Calculations on Aniline, *N*-Methylaniline, *N*,*N*-Dimethylaniline, and Ortho-Substituted Anilines

MANFRED K. EBERHARDT*

Puerto Rico Nuclear Center,[1] Caparra Heights Station, San Juan, Puerto Rico   00935

GABRIEL CHUCHANI

Centro de Química, Instituto Venezolano de Investigaciones Científicas (I.V.I.C.), Apartado 1827, Caracas, Venezuela

SCF–MO calculations were carried out on aniline, *N*-methylaniline, *N*,*N*-dimethylaniline, 2-methyl-*N*,*N*-dimethylaniline, 2,6-dimethyl-*N*,*N*-dimethylaniline, and 2,6-dimethylaniline, using the CNDO/2 approximation. The results on triphenylmethylation have established the sequence $(CH_3)_2N > CH_3NH > NH_2$ in activating power. The calculations show a decrease in the HOMO energy levels in this sequence. This result indicates a considerable amount of charge transfer in the transition state in agreement with the idea of a late transition state. The results show further that the tritylation does not proceed *via* direct attack at the para position. Nitrogen inversion barriers were calculated, but were found to be too high (aniline, 6.4 kcal, experimentally estimated, 2 kcal). The frontier electron theory correctly predicts the reactivity of ortho-substituted aniline and *N*,*N*-dimethylaniline in electrophilic aromatic substitution. Experiments on the tritylation of 2,6-dimethylaniline and 2,6-dimethyl-*N*,*N*-dimethylaniline are reported.

Electrophilic aromatic substitution has been studied extensively both from an experimental and theoretical point of view.[2] One of the most selective electrophiles is the triphenylmethyl carbonium ion, which is known to react at the para position of anilines, alkoxybenzenes, and phenols, but does not react with alkylbenzenes, halobenzenes, and nitrobenzene.[3] Results of Kese and Chuchani[4] on the tritylation of anilines involving competition of the anilines for a trityl ion have shown the sequence $(CH_3)_2N > CH_3NH > NH_2$ in activating power. The purpose of this work was to see whether CNDO/2 calculations would predict correctly the above sequence of reactivity. In addition these calculations may allow us to draw certain conclusions concerning the detailed mechanism of the reaction and the nature of the transition state. The first problem in carrying out these calculations is to find out the favored structure of the anilines. We have therefore calculated the nitrogen inversion barriers for aniline, *N*-methylaniline, and *N*,*N*-dimethylaniline. Few semiempirical SCF–MO calculations of inversion barriers have been reported, mostly using the MINDO method.[5,6] The MINDO treatment gave good agreement with experimental values. It was therefore of interest to establish the usefulness of the CNDO/2 method for this type of calculation.

Results

The results of CNDO/2 calculations[7] on aniline, *N*-methylaniline, and *N*,*N*-dimethylaniline assuming dif-ferent pyramidal structures are shown in Tables I–III. Symmetric structures were assumed. The following bond distances[3] were used: $C_{ar}-C_{ar}$, 1.392 Å; $C_{ar}-H$, 1.085 Å; $C_{ar}-N$, 1.431 Å; N–H, 1.04 Å; N–CH₃, 1.45 Å; $C_{ali}-H$, 1.09 Å. Different angles were used for the –N< groups as shown in Tables I–III. For the calculations of the ortho-substituted anilines the following bond distances were used: $C_{ar}-N$, 1.426 Å; $C_{ar}-CH_3$, 1.52 Å. All other distances were as stated above. The orientation of the methyl groups at the nitrogen were chosen so that all C–H bonds were staggered. The methyl groups at the aromatic ring were assumed to be symmetrical with respect to the plane perpendicular to the ring (as shown in Figure 1).

Discussion

Several theoretical approaches to the problem of electrophilic aromatic substitution have been proposed.[2] There are basically three different methods: the "static approach," the "localization approach," and the "delocalization approach." The static approach considers the π-electron distribution in the isolated molecule, whereas the localization approach considers the energy of the localized σ complex or Wheland intermediate.[9] The interesting idea of early and late transition states, which combines these two approaches was proposed by Brown.[10] In an early transition state the aromatic is disturbed little by the electrophile and the π-electron densities in the aromatic will predict the reactivity, while a late transition state will resemble the products and the stability of the Wheland intermediates will be a measure of reactivity. The third approach is the delocalization approach. Among this category the most successful theory has been the "frontier electron theory" developed by Fukui and coworkers.[11] This theory is closely related to Mulliken's theory of charge

(1) Puerto Rico Nuclear Center is operated by the University of Puerto Rico for the U. S. Atomic Energy Commission under Contract AT-(40-1)-1833.

(2) (a) For a recent review, see G. A. Olah, *Accounts Chem. Res.*, **4**, 240 (1971); (b) for a review of theory, see A. Streitwieser, "Molecular Orbital Theory for Organic Chemists," Wiley, New York, N. Y., 1957, p 307 ff. (c) K. Fujui, *Topics Current Chem.*, **15**, 1 (1970).

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TABLE I

CNDO/2 CALCULATIONS ON ANILINE

Pyramidal angle, deg	109.5	110.0	110.5	111.0	113.0	120.0
Total energy, au	−59.557601	−59.55762	−59.55759	−59.55752	−59.55669	−59.54685
HOMO energy, au	−0.4433	−0.4426	−0.4419	−0.4411	−0.4378	−0.4231
Max HOMO coefficient (p_z) at						
N	−0.4728	−0.4780	−0.4832	−0.4884	0.5106	−0.6037
2	0.3304	0.3306	0.3308	0.3310	−0.3320	0.3395
3	−0.1854	−0.1844	−0.1834	−0.1825	0.1784	−0.1629
4	−0.4811	−0.4801	−0.4791	−0.4781	0.4743	−0.4632
p_z-π density at						
N	1.5883	1.6005	1.6125	1.6247	1.6772	1.9160
2	1.0596	1.0601	1.0606	1.0612	1.0638	1.0789
3	0.9759	0.9757	0.9755	0.9753	0.9744	0.9694
4	1.0390	1.0394	1.0398	1.0402	1.0422	1.0533

TABLE II

CNDO/2 CALCULATIONS ON *N*-METHYLANILINE

Pyramidal angle, deg	109.5	110.0	110.5	111.0	112.0	113.0	120.0
Total energy, au	−68.25315	−68.25331	−68.25345	−68.25350	−68.25345	−68.25314	−68.24437
HOMO energy, au	−0.4382	−0.4372	−0.4352	−0.4341	−0.4320	−0.4297	−0.4107
Max. HOMO coefficient (p_z) at							
N	0.5095	0.5156	0.5249	−0.5311	0.5432	−0.5560	0.6532
2	−0.3036	−0.3032	−0.3034	0.3031	−0.3027	0.3026	−0.3086
3	0.1797	0.1786	0.1744	−0.1731	0.1707	−0.1680	0.1483
4	0.4463	0.4444	0.4389	−0.4371	0.4336	−0.4302	0.4123
5	0.1573	0.1555	0.1501	−0.1484	0.1453	−0.1421	0.1225
6	−0.3213	−0.3212	−0.3221	0.3221	−0.3219	0.3219	−0.3258
p_z-π density at							
N	1.5622	1.5741	1.5849	1.5973	1.6218	1.6486	1.8809
2	1.0577	1.0581	1.0578	1.0583	1.0593	1.0606	1.0741
3	0.9761	0.9759	0.9769	0.9767	0.9764	0.9760	0.9715
4	1.0370	1.0374	1.0396	1.0399	1.0407	1.0416	1.0519
5	0.9764	0.9762	0.9770	0.9769	0.9766	0.9762	0.9719
6	1.0582	1.0586	1.0578	1.0582	1.0592	1.3603	1.0735

TABLE III

CNDO/2 CALCULATIONS ON *N*,*N*-DIMETHYLANILINE

Pyramidal angle, deg	109.5	111.0	112.0	113.0	114.0	120.0
Total energy, au	−76.94918	−76.94977	−76.94987	−76.94968	−76.94930	−76.94118
HOMO energy, au	−0.4304	−0.4261	−0.4232	−0.4201	−0.4170	−3.4003
Max. HOMO coefficient (p_z) at						
N	0.5511	0.5706	0.5830	0.5958	0.6080	0.6790
2	−0.2976	−0.2945	−0.2930	−0.2918	−0.2910	−0.2928
3	0.1481	0.1417	0.1377	0.1337	0.1301	0.1166
4	0.4099	0.3998	0.3939	0.3884	0.3836	0.3706
p_z-π density at						
N	1.5512	1.5848	1.6078	1.6328	1.6576	1.8468
2	1.0561	1.0571	1.0579	1.0588	1.0599	1.0708
3	0.9779	0.9775	0.9773	0.9770	0.9767	0.9718
4	1.0387	1.0396	1.0402	1.0410	1.0419	1.0471

transfer.[12] To calculate reaction rates exactly one should calculate the whole energy surface for the reacting system and in this way determine the energy of the transition state. Since at the present time this type of calculation is impossible for large systems we have to limit ourselves to interpreting reaction rates in terms of the electronic structure of the reacting molecules. The transition state is treated as a perturbation of the ground state. The theoretical quantity which is used as a measure of the relative rate at different positions in a molecule or in different molecules is the reactivity index.

(12) R. S. Mulliken, *J. Amer. Chem. Soc.*, **74**, 811 (1952); *Revl. Trav. Chim. Pays-Bas*, **75**, 845 (1956).

One reactivity index which was derived by Fukui, *et al.*,[2,11] through application of perturbation theory to the Schroedinger equation is the superdelocalizability defined for reaction with an electrophilic reagent as shown in eq 1 where $c_r^{(i)}$ is the coefficient of the ith MO

$$S_r^{(E)} = 2 \sum_i^{occ} \frac{c_r^{(i)2}}{\alpha - \epsilon_i} (-\beta) \tag{1}$$

at position r, α is the LUMO (lowest unoccupied molecular orbital) energy level of the electrophile, and ϵ_i is the energy level of the ith MO. α and ϵ_i are expressed in eq 1 in units of β, the resonance integral.

On the basis of the principle of narrowing of the interfrontier level separation and the growing of the frontier electron density along the reaction path Fukui[2,11] has pointed out that the frontier term is the dominant term in eq 1. Thus $S_r^{(E)}$ can be approximated by the frontier term only, where c_r^{HO} and ϵ_{HO} are the coefficient

$$S_r^{(E)} = 2 \frac{c_r^{(HO)^2}}{\alpha - \epsilon_{HO}} (-\beta) \qquad (2)$$

in the HOMO (highest occupied molecular orbital) and the energy level of the HOMO respectively. If we are interested only in intramolecular reactivity a comparison of reactivity can be made by the numerator of eq 2 only. $2C_r^{(HO)^2}$ is known as the frontier electron density. Comparing the reactivity of different molecules with the same electrophile we see from eq 2 that $S_r^{(E)}$ increases with increasing HOMO coefficient and with increasing (i.e., less negative) HOMO energy. The results (Table I–III) show that the maximum HOMO ecoefficients are at the nitrogen and para positions. The absolute magnitude of the HOMO coefficient at the nitrogen increases from aniline to N,N-dimethylaniline, and the HOMO energy level becomes less negative in this series. The reactivity index $S_r^{(E)}$ therefore is increasing in agreement with the experimentally observed reactivities. Tables I–III show the results on aniline, N-methylaniline and N,N-dimethylaniline assuming a number of different pyramidal structures. With increasing substitution at the nitrogen the pyramid gets flattened and the inversion barrier is decreasing. This is due to nonbonded repulsions which are stronger in the pyradmidal than in the planar state. From microwave spectroscopy data Lister and Tyler[8] estimated the inversion barrier of aniline to be about 2 kcal/mole. The CNDO/2 calculations give 6.4 kcal/mol, a considerably higher value. However the CNDO/2 method correctly predicts the decrease in inversion barrier with increasing N substitution. Since conjugation of the amino group with the ring is more favorable in the planar state the π-electron density in the ring is expected to increase from aniline to N,N-dimethylaniline, which is indeed borne out by the calculations. The $p_z-\pi$
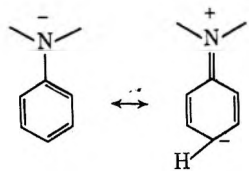
density is greater in the ortho than in the para position. π-Electron density obviously does not correlate well with the experimental results on tritylation which gives exclusively para substitution. This is not surprising since only in reactions with very reactive electrophiles where we have an early transition state can we expect a correlation with π-electron density. With decreasing reactivity of the electrophile a greater degree of charge transfer has to take place in the transition state for reaction to take place. Triphenylmethyl carbonium ion is certainly a weak electrophile and will form a late transition state. The large amount of charge transfer in the transition state for tritylation is quite evident from the high solute selectivity. Trityl does react with anilines, but does not react with toluene, chlorobenzene, or nitrobenzene (HOMO energy levels
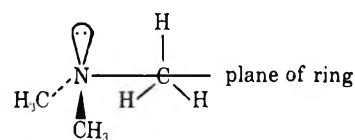
Figure 1.—In calculations on toluene we have found that the orientation of the methyl group affects the HOMO energy level, the π- and total electron densities to an insignificant extent.

of -0.4730, -0.4677, and 0.4741 au, respectively).[13] These latter compounds have considerably lower lying HOMO energy levels than the anilines.

As we have pointed cut above intramolecular reactivity should be proportional to the frontier electron density or simply the absolute value of the HOMO coefficient. With the exception of aniline where the HOMO coefficients at the nitrogen and para position are about equal, the maximum HOMO coefficients are at the nitrogen. It is well known that N-tritylaniline will rearrange in acid media to p-tritylaniline. In experiments of cross-migration from N-tritylaniline to phenol or N,N-dimethylaniline in acid media, Chuchani and Rodríguez-Uzcanga[14] found evidence for inter and intramolecular rearrangement (Scheme I).

SCHEME I
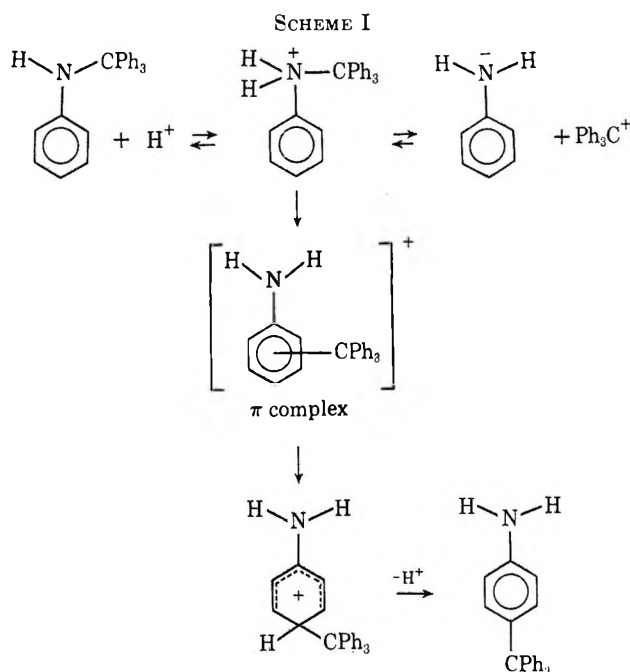
Cross-migration between N-tritylaniline and N,N-dimethylaniline gave p-tritylaniline and p-trityl-N,N-dimethylaniline in a ratio of about 1:2, whereas direct tritylation of a mixture of aniline and N,N-dimethylaniline by trityl perchlorate gave exclusively p-trityl-N,N-dimethylaniline. The rearrangement most likely will involve π complexes. The intermolecular migration requires that the N-tritylaniline in acid media splits into trityl ion and aniline. On the basis of the experimental evidence and the results of the CNDO/2 calculations we propose the mechanism shown in Scheme II for tritylation. The long range interaction between the trityl ion and the aromatic amine is

(13) M. K. Eberhardt and M. Yoshida, unpublished results.
(14) G. Chuchani and V. Rodríguez-Uzcanga, *Tetrahedron*, **22**, 2665 (1966).

SCHEME II

charge transfer type
transition state

I II

σ complex
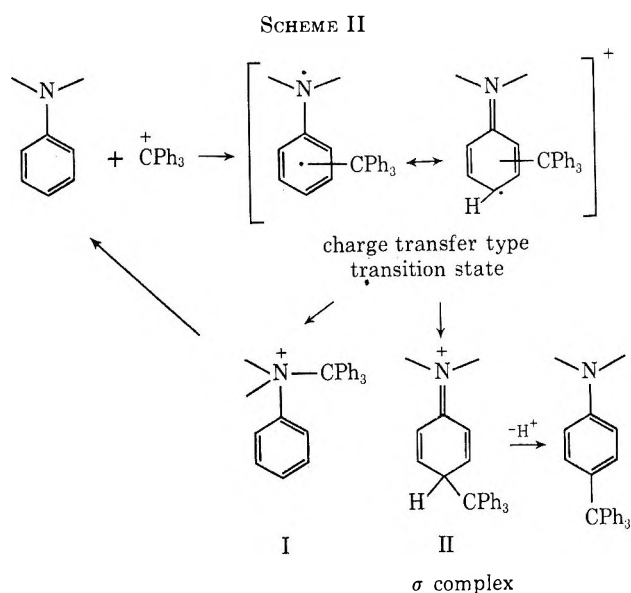
governed by the total electron density, which is always highest at the nitrogen. As the trityl ion approaches its empty orbital begins to overlap with the HOMO of the aromatic. This overlap is proportional to the absolute magnitude of the HOMO coefficient. The highest HOMO coefficients are usually p_z orbitals, unless otherwise indicated in the tables. This means that the most favorable approach of the trityl ion is from the top of the plane of the aromatic ring. For σ-bond formation to occur charge transfer has to take place in the transition state. The ease of formation of the charge transfer type transition state is governed by the HOMO-LUMO overlap and the energy level of the HOMO, *i.e.*, the reactivity index $S_r^{(E)}$. $S_r^{(E)}$ increases in the series: $NH_2 < NHCH_3 < N(CH_3)_2$. The charge transfer type transition state can lead to σ-bond formation either at the nitrogen (I) or at the para position (II). These two positions have the highest spin density in the radical cation of the anilines. Only intermediate II will give a stable final product, whereas I will dissociate to starting components. With increasing alkyl substitution at the nitrogen the formation of II might be favored over I due to steric hindrance.

Since we are dealing with a late transition state the stability of the Wheland intermediates should also correlate with the inter- and intramolecular reactivity. Based on the charge distribution of benzenium ion Olah[2] has pointed out that a substituent will exert a more powerful effect on the stability of the benzenium ion when it is para to the attacking electrophile than when it is ortho. This will lead to high para/
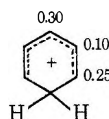
ortho ratios as in indeed observed in high selectivity reactions (trityl ion presenting the extreme case of exclusively para substitution). Since in the series NH_2, $NHCH_3$, and $N(CH_3)_2$ we have increasing electron-donating power (Tables I–III) we expect the stability of the σ complexes to increase. The superdelocalizability predicts the relative rates of a series

of compounds, whereas the Wheland intermediate reflects the stability of the final products. The experimental reactivity sequence $NH_2 < NHCH_3 < N(CH_3)_2$ has been established using the nonkinetic competition method. Our calculations indicate the same reactivity sequence whether we have a kinetically or a thermodynamically controlled process. In the tritylation of some alkoxybenzenes rate constants have been determined[15] and were found to correlate with the superdelocalizability as well as the stability of the σ complexes.[16]

To lend further support to our interpretation of the relative reactivities based on the frontier electron theory, we have carried out some calculations on 2,6-dimethylaniline (I) and 2,6-dimethyl-*N,N*-dimethylaniline (II) (Charts I and II). We find that the amino

CHART I

← plane of ring →

Maximum (p_z) HOMO Coefficients

HOMO energy, au −0.4266   −0.4567
E_{total}, au −76.9637   −76.9594

ΔE = 2.67 kcal

CHART II

← plane of ring →

Maximum HOMO Coefficients

HOMO
energy, au −0.3692   −0.4282
E_{total}, au −93.8785   −94.3044

ΔE = 265 kcal
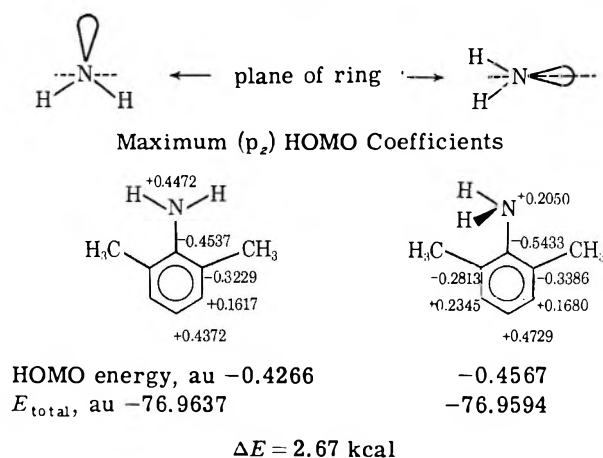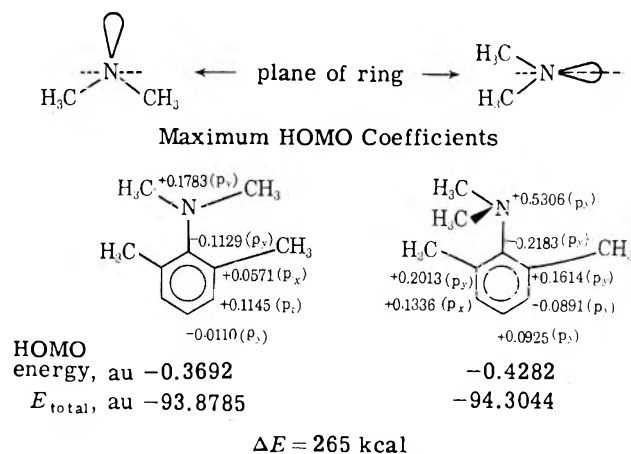
p_z HOMO Coefficients
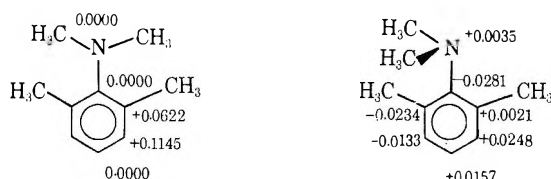
group in I has a low barrier of rotation, whereas the *N,N*-dimethylamino group in II cannot rotate freely, but it twisted 90° out of the plane of the ring. On the

(15) G. Chuchani, H. Díaz, and J. Zabicky, *J. Org. Chem.*, **31**, 1573 (1966).

(16) M. K. Eberhardt and G. Chuchani, *ibid.*, **37**, 3654 (1972).

basis of the very small HOMO coefficients of II we expect a very low reactivity for this compound. Experimentally it was indeed found to be completely unreactive toward the trityl ion. The HOMO coefficients of I and aniline are not very different, but the HOMO energy level of I is considerably higher than in aniline (-0.4266 *vs.* -0.4420 au) which should make the former more reactive. This was again confirmed by experiment.

A decrease in reactivity upon ortho substitution was also observed by Brown, Widiger, and Letang.[17] These authors measured the rate of deuterium exchange of a variety of ortho-substituted N,N-dimethylanilines, and they found a considerable decrease in rate upon ortho substitution in agreement with the decrease of the HOMO coefficients. Friedlander[18] found that $2,6,N,N$-tetramethylaniline does not couple with diazotized amines.

Experimental Section

Triphenylmethanol (Matheson Coleman and Bell) was purified by recrystallizations from glacial acetic acid. Aniline (Matheson Coleman and Bell), N,N'-dimethylaniline (Matheson Coleman and Bell), and 2,6-dimethylaniline (Aldrich) were purified by distillations under vacuum. Triphenylmethyl perchlorate was prepared as previously described.[15] Synthesis of other compounds are described below. Ir spectra were determined with a Perkin-Elmer Model 337 spectrometer. Nmr spectra were determined with a Varian A-60 instrument. For mass spectra a Hitachi Perkin-Elmer RMU-6H was used. Melting points were taken with a Fisher-Johns apparatus.

4-Amino-3,5-dimethyltetraphenylmethane. Method A.— Triphenylmethanol (0.10 mol), 2,6-dimethylaniline (0.015 mol), glacial acetic acid (50 ml), and concentrated hydrochloric acid (4.0 ml) were refluxed for 1 week. The reaction mixture was diluted with water, then treated with 20% solution of sodium hydroxide, and the filtered solid was warmed in a solution of potassium hydroxide in ethanol. The product was recrystallized from ethanol (yield 66%) and had mp 185° (lit.[19] mp 177°).

Method B.—2,6-Dimethylaniline (0.015 mol) was added to triphenylmethyl perchlorate (0.010 mol) and heated to 75–80° for 6 hr under nitrogen. The solid mass was dissolved in acetone, diluted with water, and treated with 10% solution of sodium hydroxide. The product, warmed with a solution of potassium hydroxide in ethanol, filtered off, and recrystallized from ethanol (yield 73%), had mp 183–184°, not depressed on a mixture with the product obtained by method A. The ir, nmr, and mass spectra of the products obtained by both methods were identical: ν_{max} (KBr) 3425 and 3380 cm^{-1} (HNH); δ (CDCl$_3$) 2.1 (s, CH$_3$), 3.4 (s, NH$_2$), and 7.2 ppm (m, aromatic); M$^+$ m/e 363. *Anal.* Calcd for C$_{27}$H$_{25}$N: C, 89.2; H, 6.9; N, 3.9. Found: C, 88.7; H, 7.1; N, 3.6.

2,6-Dimethyl-N,N'-dimethylaniline.—This compound was prepared according to the method described by Bamberger and

Rudolf.[20] The product was distilled at 89.5–90.9° (20 mm) [lit.[20] 76.8–77.2° (11 mm): ν_{max} (pure) 1140 cm^{-1} [=CN-(CH$_3$)$_2$]; δ (CDCl$_3$) 2.3 (s, CH$_3$), 2.8 (s, CH$_3$), and 7.0 ppm (m, aromatic). *Anal.* Calcd for C$_{10}$H$_{15}$N: C, 80.5; H, 10.1; N, 9.4. Found: C, 79.7; H, 9.6; N, 9.6.

The tritylation of 2,6 dimethyl-N,N-dimethylaniline does not give the corresponding tetraphenylmethane derivative. Method A yields triphenylmethane (69%), mp 92–93° (lit.[3] mp 93–94°), and 9-phenylfluorene (14%), mp 144–145° (lit.[21] mp 145.5°). These compounds were separated by neutral alumina column chromatography (Woelm, grade I) and identified by mixture melting point and ir spectral comparison with an authentic sample. In method B, the reagent triphenylmethyl perchlorate is recovered quantitatively as triphenylmethanol.

I. Competitive Tritylation of Aniline and 2,6-Dimethylaniline. **Method A.**—Aniline (0.05 mol), 2,6-dimethylaniline (0.05 mol), and triphenylmethyl perchlorate (0.005 mol) were heated at 75–80° for 18 hr under nitrogen and protected from light. The reaction mixture was dissolved in acetone and diluted with water and concentrated hydrochloric acid added until no further precipitate formed. The solid is warmed in potassium hydroxide-ethanol solution for 10 min, diluted with water, dried, and dissolved in small amount of chloroform, and the compounds were separated by column chromatography. The column was packed with acid alumina (40 g, Woelm, grade I) and eluted with petroleum ether and then with a mixture of benzene–chloroform (2:1 by volume). Products and yields follow: triphenylmethane, 8.1%; 4 amino-3,5-dimethyltetraphenylmethane, 57.2%; and 4-aminotetraphenylmethane, 13.6% [mp 254–256° (lit.[3] mp 256–257°)]. Each compound obtained was checked by mixture melting point and ir and nmr spectral comparison with the corresponding authentic sample.

Method B.—A mixture of aniline (0.10 mol), 2,6-dimethylaniline (0.10 mol), triphenylmethanol (0.01 mol), glacial acetic acid (100 ml), and concentrated hydrochloric acid (8 ml) was refluxed for 1 week. The reaction mixture was diluted with water and treated with 20% sodium hydroxide solution, and the filtered solid was warmed in potassium–ethanol solution for 15 min. The products are separated as indicated in method A. Products and yields follow: 4-amino-3,5-dimethyltetraphenylmethane, 66.4%, and 4-acetamido-3,5-dimethyltetraphenylmethane, 24.9% (mp 284–285°). The identification of these compounds were accomplished by mixture melting point and ir, nmr, and mass spectral comparison with authentic samples. The structural proof of the 4-acetamido-3,5-dimethyltetraphenylmethane was made by the common method of acetylation[22] of the 4-amino-3,5 dimethyltetraphenylmethane.

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Electrophilic Aromatic Triphenylmethylation.   Self-Consistent Field–Molecular Orbital Calculations on Phenol, Alkoxybenzenes, and Ortho Alkoxyphenols

MANFRED K. EBERHARDT*

Puerto Rico Nuclear Center,[1] Caparra Heights Station, San Juan, Puerto Rico   00935

GABRIEL CHUCHANI

Chemistry Center, Instituto Venezolano de Investigaciones Científicas (I.V.I.C.), Apartado 1827, Caracas, Venezuela

SCF–MO calculations were carried out on phenol, phenolate, anisole, phenetole, isopropoxybenzene, 2,6-dimethylanisole, and ortho alkoxyphenols using the CNDO/2 approximation.   Experimental results on triphenylmethylation have established the sequence anisole < phenol < phenetole < isopropoxybenzene of increasing reactivity.   The results of the calculations are in agreement with the generally accepted inductive release sequence: i-Pr > Et > Me > H.   The calculations indicate that the trityl ion does not attack directly at the para position, but that the reaction proceeds *via* a charge-transfer-type transition state.   2,6-Dimethylanisole where the methoxy group is twisted 90° out of the plane could not be tritylated.   This result is in agreement with the decrease in overlap between the empty orbital of the trityl ion and the HOMO of the 2,6-dimethylanisole as compared to anisole.   The results on phenol and ortho alkoxyphenols suggest the importance of hydrogen-bond formation in the tritylation of these compounds.

In the previous paper[2] we have reported SCF–MO calculations on a series of anilines.   The results of these calculations showed a quantitative correlation between the HOMO coefficients, the HOMO energy levels, and the relative reactivity of these compounds toward the trityl carbonium ion.   The success of these calculations encouraged us to carry out further CNDO/2 calculations on a series of compounds for which rate data for tritylation were already available.[3]   Rate studies on phenol and a series of its alkyl ethers have been reported by Chuchani, Díaz, and Zabicky,[3a] and on ortho alkoxyphenols by Barroeta, Chuchani, and Zabicky.[3b]   We wish now to report CNDO/2 calculations on these compounds.

Results and Discussion

The CNDO/2 calculations[4] were carried out using the following bond distances and angles: C_{ar}–C_{ar}, 1.40 Å; C_{ar}–H, 1.085 Å; C_{ali}–C_{ali}, 1.54 Å; C_{ar}–O, 1.36 Å; O–CH_3, 1.35 Å; C_{ali}–H, 1.09 Å; O–H, 0.958 Å; C_{ar}–O–H, angle and tetrahedral angles, 109.5°; all other angles, 120°.

The results on phenol and alkoxybenzenes are summarized in Chart I.   In all these calculations a planar geometry was assumed.   For isopropoxybenzene structure i was found to be most stable.

i

In our previous work[2] on anilines we have found that the frontier orbital theory[5] gave a good description of

the experimental results.   One of the reactivity indices proposed by Fukui[5] is the superdelocalizability (eq 1)

$$S_r^{(E)} = 2 \sum_i^{occ} \frac{c_r^{(i)2}}{\alpha - \epsilon_i}(-\beta) \qquad (1)$$

where $c_r^{(i)}$ is the coefficient of the ith MO at atom r, α is the LUMO (lowest unoccupied molecular orbital) energy level of the attacking electrophile, ϵ_i is the energy of the ith MO.   The superdelocalizability is expressed in units of β, the resonance integral.   Fukui[5] has shown that the dominant term in the sum of eq 1 is the frontier term, eq 2.   Equation 2 shows that the

$$S_r^{(E)} = 2 \frac{c_r^{(HO)2}}{\alpha - \epsilon_{HO}}(-\beta) \qquad (2)$$

relative reactivity of a series of compounds depends on the HOMO coefficient $c_r^{(HO)}$ and the HOMO energy level ϵ_{HO}.

Through the work of Chuchani, *et al.*,[3] the following reactivity sequence was established: anisole < phenol < phenetole < isopropoxybenzene.   Unlike the reactivity sequence in the aniline series,[2] which was determined by the nonkinetic competition method, the reactivity of the alkoxybenzenes and phenol was determined by direct measurement of second-order rates.   The results of our calculations show that the biggest HOMO coefficients (which are all p_z coefficients) are at the oxygen and at the para position.   The HOMO coefficient at the para position decreases in the series OH > OCH_3 > OC_2H_5 > $OCH(CH_3)_2$.   A direct attack at the para position therefore appears to be unlikely since it would lead to a reactivity sequence contrary to the experimental results.   However the HOMO coefficient at the oxygen increases in the above series and so does the HOMO energy level (*i.e.*, becomes less negative).   This corresponds to an increase in $S_r^{(E)}$.   The importance of the HOMO energy level is evident from the high solute selectivity of the trityl ion.   Trityl does react with aniline (HOMO level: −0.4424 au),[2] *N*-methylaniline (−0.4373),[2] *N,N*-dimethylaniline (−0.4296),[2] anisole (−0.4477), phenetole (−0.4455), isopropoxybenzene (−0.4353), and phenol (−0.4556), but does not react with toluene (−0.4730),[2] chlorobenzene (−0.4677)[2] or nitrobenzene (−0.4741).[2]

(1) The Puerto Rico Nuclear Center is operated by the University of Puerto Rico for the U. S. Atomic Energy Commission under Contract AT-(40-1)-1833.

(2) M. K. Eberhardt and G. Chuchani, *J. Org. Chem.*, **37**, 3649 (1972).

(3) (a) G. Chuchani, H. Díaz, and J. Zabicky, *ibid.*, **31**, 1573 (1966); (b) N. Barroeta, G. Chuchani, and J. Zabicky, *ibid.*, **31**, 2330 (1966).

(4) The program was obtained from the Quantum Chemistry Program Exchange, Bloomington, Ind.   The method is described by J. A. Pople and D. L. Beveridge in "Approximate Molecular Orbital Theory," McGraw Hill, New York, N. Y., 1970.

(5) For a recent review, see F. Fukui in *Topics Current Chem.*, **15**, 1 (1970).

Chart I
CNDO/2 Calculations on Phenol, Phenolate, and Alkoxybenzenes
p_z HOMO Coefficients and HOMO Energy Levels

p_z–π Densities

Total Electron Densities
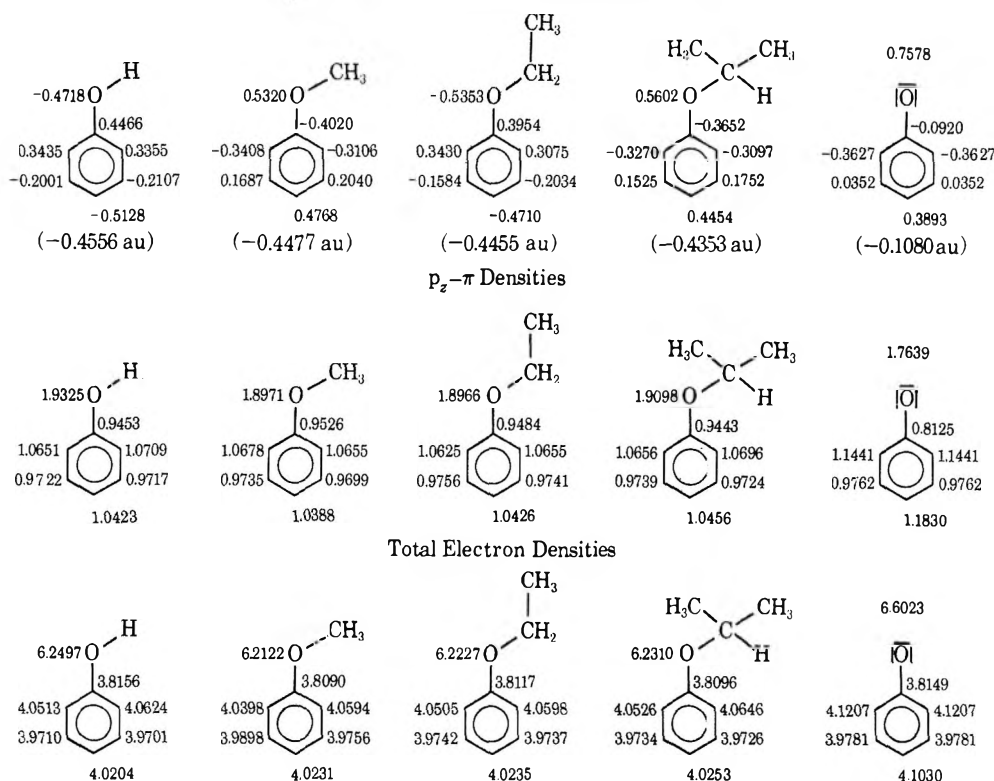
In addition to HOMO coefficients Chart I shows p_z–π densities and total electron densities. The p_z–π densities cannot explain the exclusive attack at the para position, since the ortho positions have a higher p_z–π density. As discussed previously[2] the increase in para p_z–π density in the series anisole < ethoxybenzene < isoproxybenzene means increasing stability of the σ complex. One may be inclined to attribute the exclusive para substitution to steric hindrance in the ortho position. This however cannot be the only reason especially in the case of phenol since m-aminophenol was found to react para to the amino and ortho to the hydroxyl group.[6]

The total electron densities show that the highest net negative charge is at the oxygen atoms. At large distances the trityl ion will be attracted to the point of highest net negative charge. As the trityl ion approaches its empty orbital (LUMO) begins to overlap with the HOMO of the aromatic forming a charge-transfer-type transition state, which then forms a σ bond either at the oxygen or at the para position. The alkoxybenzene radical ion has the highest spin density at the oxygen and at the para position (Chart II).

Chart II
p_z Spin Densities of Alkoxybenzene Radical Ions
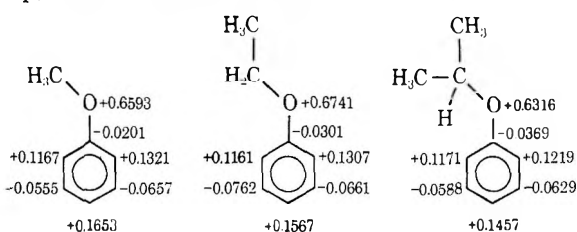
(6) G. Chuchani and J. Zabicky, *J. Chem. Soc. C*, 297 (1966).

Only a σ bond formation at the para position leads to a stable final product (Scheme I).

Scheme I

charge transfer type
transition state

According to the generally accepted inductive release sequence, i-Pr > Et > Me > H, and to our calculations, phenol should react slower than any of the alkoxybenzenes; however, experimentally it was found that phenol falls between anisole and phenetole in reactivity.[3a] The phenolate ion with a very high HOMO coefficient at the oxygen and a very high lying HOMO energy level should react faster than any of the alkoxybenzenes. This disagreement suggests, as argumented with supporting evidence in previous work,[3] hydrogen-bond formation between the phenol molecules and the solvent. This hydrogen-bond formation may sufficiently increase the HOMO coefficients at the oxygen to render phenol more reactive

TABLE I
EFFECT OF ROTATION
Phenol

Angle of OH bond with plane of ring, deg	0	30	60	90
Total energy, au	−65.5523	−65.5509	−65.5487	−65.5479
HOMO energy level, au	−0.4556	−0.4582	−0.4653	−0.4706
Max HOMO coefficient at oxygen (p_z)	−0.4718	−0.4362	−0.3496	0.2938
Max HOMO coefficient at para position (p_z)	−0.5128	−0.5112	−0.5141	0.5294

Anisole

Angle of OCH₃ group with plane of ring, deg	0	30	60	90
Total energy, au	−74.2178	−74.2165	−74.2162	−74.2162
HOMO energy level, au	−0.4477	−0.4490	−0.4572	−0.4677
Max HOMO coefficient at oxygen (p_z)	0.5320	−0.4928	0.3909	0.3413
Max HOMO coefficient at para position (p_z)	0.4768	−0.4617	0.4486	0.5203

Ethoxybenzene

Angle of OC₂H₅ group with plane of ring, deg	0	30	60	90
Total energy, au	−82.9286	−82.9268	−82.9266	−82.9265
HOMO energy level, au	−0.4455	−0.4465	−0.4555	−0.4650
Max HOMO coefficient at oxygen (p_z)	−0.5353	−0.4992	−0.4044	−0.3520
Max HOMO coefficient at para position (p_z)	−0.4710	−0.4589	−0.4614	−0.5174

than anisole. Further evidence for hydrogen-bond formation will be presented below.

Table I shows the effect of rotation of the alkoxy groups on the HOMO coefficients. While the HOMO coefficients at the para position stay almost constant the coefficients at the oxygen change much more drastically. It was therefore of interest to study the tritylation of an alkoxybenzene in which the alkoxy group is twisted out of the plane of the ring. The tritylation of 2,6-dimethylanisole was tried by two common methods but failed. The calculations are shown in Chart III. If we compare the HOMO coefficients of

CHART III
CNDO/2 CALCULATIONS ON 2,6-DIMETHYLANISOLE[a]
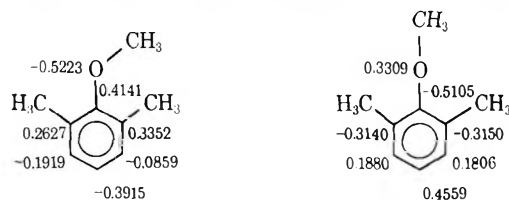
HOMO energy level, −0.4226 au HOMO energy level, −0.4507 au

E_{total} = −91.5985 au E_{total} = −91.6300 au

[a] Maximum (p_z) HOMO coefficients, HOMO energy levels, and total energies of 2,6-dimethylanisole with OCH₃ group in the plane of the ring (left) and twisted by 90° (right).

anisole with the twisted form of 2,6-dimethylanisole we realize again that direct attack at the para position could not explain this difference in reactivity. In the twisted 2,6-dimethylanisole we find a much smaller HOMO coefficient at the oxygen than in anisole. The decreased overlap at the oxygen must be responsible for the failure to react. Even if a charge-transfer-type transition state would be formed σ-bond formation appears unlikely owing to the very small spin densities in the para position of the twisted 2,6-dimethylanisole radical ion (see Chart IV).

Evidence for the importance of hydrogen bonding in the tritylation of phenols can also be deduced from the tritylation of ortho alkoxyphenols. On the basis of the experimentally established reactivity sequence one would expect that *o*-ethoxyphenol and *o*-isopro-

CHART IV
SPIN DENSITIES IN 2,6-DIMETHYLANISOLE RADICAL ION

p_z spin densities   *maximum* (p_y) spin densities
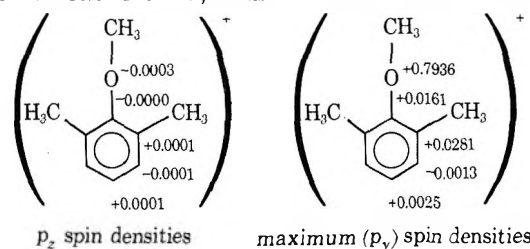
poxyphenol react para to the alkoxy group. All ortho alkoxyphenols react para to the OH group.[3b]

Calculations were carried out on the nonhydrogenbonded ortho alkoxyphenols (Chart V) and the hy-

CHART V
CNDO/2 CALCULATIONS ON
NONHYDROGEN-BONDED ALKOXYPHENOLS
Maximum (p_z) HOMO Coefficients

HOMO	+0.3705	−0.3674	+0.3680
energy, au	−0.4260	−0.4220	−0.4151
E_{total}, au	−92.6861	−101.3764	−110.0521

p_z −π Densities

Total Electron Densities
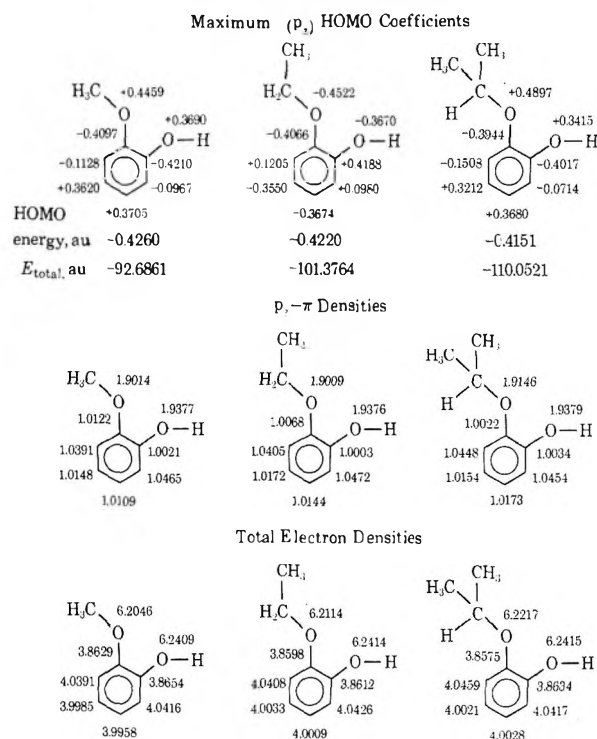
drogen-bonded structures (Chart VI). In all cases the HOMO (highest occupied molecular orbital) was

CHART VI

CNDO/2 CALCULATIONS ON HYDROGEN-BONDED ALKOXYPHENOLS

Maximum (p_z) HOMO Coefficients

H₃C −0.4338
O H −0.3773
+0.4119 O
+0.0992 +0.4243
−0.3709 +0.1065
HOMO −0.3654
energy, au −0.4273
E_{total}, au −92.6881

CH₃
H₂C −0.4353
O H −0.3750
+0.4100 O
+0.1016 +0.4233
−0.3686 +0.1055
−0.3654
−0.4250
−101.3785

CH₃
H₃C C +0.4728
H −0.4005 H +0.3505
O
−0.1337 −0.4067
+0.3358 −0.0780
+0.3680
−0.4185
−110.0542

$p_z-\pi$ Densities

CH₃
H₃C 1.9034
O H 1.9375
1.0180 O
1.0378 1.0010
1.0153 1.0411
1.0108

CH₃
H₃C 1.9036
O H 1.9377
1.0151 O
1.0386 1.0016
1.0155 1.0412
1.0121

CH₃
H₃C C 1.9171
H O H 1.9380
1.0106 O
1.0430 1.0044
1.0138 1.0394
1.0149

Total Electron Densities

H₃C 6.2130
O H 6.2457
3.8765 O
4.0372 3.8646
3.9990 4.0313
3.9965

CH₃
H₃C 6.2213
O H 6.2462
3.8788 O
4.0379 3.8652
3.9991 4.0314
3.9973

CH₃
H₃C C 6.2315
H O H 6.2466
3.8766 O
4.0431 3.8670
3.9981 4.0303
3.9991

a pure $p_z-\pi$ orbital. In addition to the HOMO coefficients the charts list the $p_z-\pi$ densities and the total electron densities. We have shown previously for the case of anilines[2] and alkoxybenzenes that σ-bond formation takes place at the ring position which has the highest spin density in the radical ion. As has been shown for alkoxybenzenes and anilines[2] the highest spin density in the radical ion is always at the position of the maximum HOMO coefficient in the neutral molecule. Chart V shows that the maximum HOMO coefficient at the nonsubstituted ring carbons is at the position para to the alkoxy group and substitution would be expected at that position contrary to experimental results.

The calculation of the hydrogen-bonded structures (Chart VI), however, show that the maximum HOMO coefficient at the unsubstituted ring carbons is now para to the OH group for guaiacol and *o*-ethoxyphenol. This means that hydrogen bonding increases the directive power of the OH group. For *o*-isopropoxyphenol the reaction would still be expected to take place para to the isopropoxy group, but we can see

that compared to the nonhydrogen-bonded structure the HOMO coefficient at the position para to the OH group has increased. A stronger hydrogen bond may give the desired result. An increase in the strength of the hydrogen bond from guaiacol to isopropoxyphenol is to be expected because of the increasing total electron density at the oxygen of the alkoxy group. The distance O—H···OR in the structures of Chart VI is 2.26 Å. We have found that by shortening this distance to 1.60 Å we can indeed obtain the maximum HOMO coefficient para to the OH group. However, owing to the required distortion of the C_{ar}-O-H angle the total energy also increases considerably. Hydrogen-bond formation with the solvent does not require any such deformation of the C_{ar}-O-H angle.

Experimental Section

Triphenylmethanol (Matheson Coleman and Bell), anisole (Fisher), and 2,6-dimethylanisole (Aldrich) were purified by crystallization or distillations under vacuum. Triphenylmethyl perchlorate was prepared as described before.[3a] Ir spectra were determined with a Perkin-Elmer 337. For nmr spectra a Varian A-60 was used. Mass spectra were determined in a Hitachi Perkin-Elmer RMU-6H instrument. Melting points were taken with a Fisher-Johns apparatus.

Attempts to tritylate 2,6-dimethylanisole with triphenylmethyl perchlorate alone and with triphenylmethanol in an acetic acid–hydrochloric acid mixture resulted in no reaction.

Competition of Anisole and 2,6-Dimethylanisole. Method A.—Anisole (0.05 mol), 2,6-dimethylanisole (0.05 mol), and triphenylmethyl perchlorate (0.005 mol) were heated at 80–85° for 19 hr under nitrogen and in absence of light. The reaction mixture was dissolved in acetone, diluted with water, extracted with ether, and dried. The ether and anisoles were distilled and the residue was dissolved in small amounts of chloroform. The compounds were separated with a neutral alumina column chromatography (30 g, Woelm, grade I) and eluted with petroleum ether and then with a benzene–chloroform mixture (2:1 by volume). The only product obtained was 4-methoxytetraphenylmethane, 81.4% [mp 194° (lit.[7] mp 194–195°)]. This product was identified by mixture melting point and ir, nmr, and mass spectral comparison with an authentic sample.

Method B.—A mixture of anisole (0.10 mol), 2,6-dimethylanisole (0.10 mol), triphenylmethanol (0.01 mol), glacial acetic acid (100 ml), and hydrochloric acid (8 ml) was refluxed for 1 week, diluted with water, extracted with ether, and dried. The ether and excess of anisole were distilled and residue was treated as described in method A. Products and yields follow: recovered triphenylmethanol, 87.2%, and 4-methoxytetraphenylmethane, 11.4%.

Registry No.—Phenol, 108-95-2; phenolate, 3229-70-7; anisole, 100-66-3; phenetole, 103-73-1; isopropoxybenzene, 2741-16-4; 2,6-dimethylanisole, 1004-66-6; guaiacol, 90-05-1; *o*-ethoxyphenol, 94-71-3; *o*-isopropoxyphenol, 4812-20-8.

(7) C. A. MacKenzie and G. Chuchani, *J. Org. Chem.*, **20**, 336 (1955).

Condensation Cyclization Reactions of Electron-Deficient Aromatics. IV. Tricyclic Nitropropene Nitronates from the Reaction of Phloroglucinol and Cycloalkanones with *sym*-Trinitrobenzene

MICHAEL J. STRAUSS* AND STEPHAN P. B. TAYLOR

Department of Chemistry, University of Vermont, Burlington, Vermont 05401

H. SHINDO

JEOL Inc., Cranford, New Jersey 07016

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Interesting similarities have been shown between the reactions of *sym*-trinitrobenzene with cycloalkanones and with phloroglucinol. Previously unsuspected common intermediates have been shown to intervene. The structurally similar products in each case are tricyclic nitropropene nitronates. Protonation of these yields the corresponding nitronic acids in certain instances.

The reaction of simple acyclic ketones with electron-deficient aromatics in the presence of secondary amines has been shown to yield an interesting new type of bicyclic anion, 1.[1,2] Acidification of such species (X = NO$_2$) many times gives a polymeric material, making it difficult to characterize the previously unreported nitropropene nitronic acids which might be expected to result. Because acidification of an alkaline mixture of phloroglucinol and *sym*-trinitrobenzene (TNB) was reported to yield a neutral compound, 2,

1

2
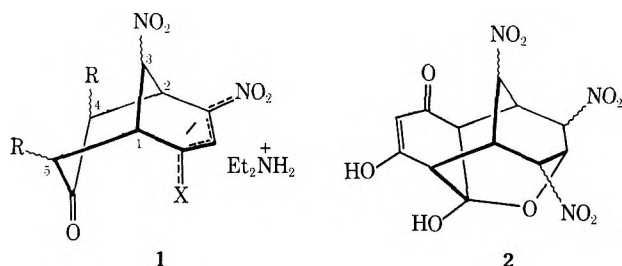
which closely resembles the type of compound which might be expected from the acidification of 1 (X = NO$_2$),[3,4] and because phloroglucinol can formally be considered a cyclic triketone which could condense with TNB in a manner analogous to simple ketones,[1,2] it was of interest to study the reaction of monocyclic ketones with TNB. The symmetry of the anticipated products, 3 or 4, was expected to simplify pmr structural analysis

3a, *n* = 2
 b, *n* = 3
 c, *n* = 4

4
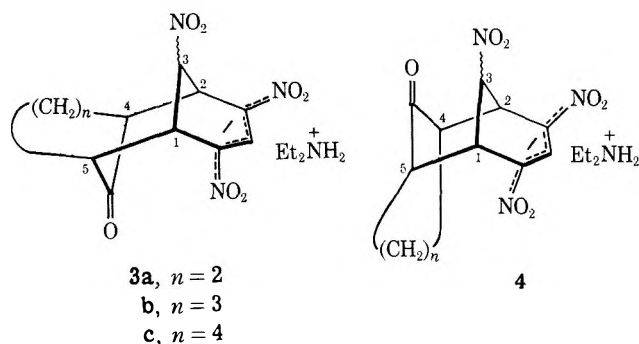
(previously made difficult by possible configurational isomerism at C-4 and C-5 of 1), and we supposed that the rigid tricyclic structure of 3, if formed, might be

favorable for intramolecular cyclization to a structure analogous to 2. In addition, it was of interest to reinvestigate the reaction of phloroglucinol and TNB to see whether the anionic precursor to 2 could be isolated.

We report here some interesting and previously unsuspected similarities between the phloroglucinol and simple cyclic ketone reactions, as well as a structural and chemical characterization of the tricyclic nitropropene nitronates 3b, 3c, and 9, as well as the protonated forms (nitronic acids) of 3b and 9. These latter nitronic acids are the first examples of protonated nitropropene nitronates in the bicyclic series[1,2] to be characterized, and their properties relative to the nitronic acids, 6, formed from protonation of 2,4,6-

5

6
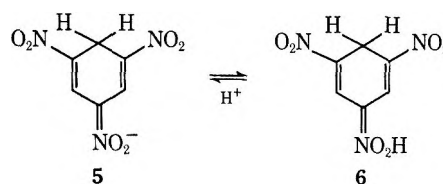
trinitrocyclohexadienate σ complexes, 5, are of considerable interest.[5]

Addition of excess diethylamine to a solution of TNB in an excess of cyclohexanone results in an exothermic reaction which yields an intensely colored solution. The visible spectrum of this mixture exhibits the double maxima characteristic of anionic σ complexes, 5.[6] The double maxima rapidly disappears as a single new maximum develops at 500 nm, characteristic of the nitropropene nitronate function of 1 (X = NO$_2$). Isosbestic points are observed at 470 and 570 nm. On standing for 24 hr at ambient temperature, crystals of product precipitate from solution. Recrystallization (see Experimental Section) yields bright red crystals, mp 225°, which analyze correctly for a 1:1:1 adduct of amine, TNB, and cyclohexanone. The 100-MHz pmr spectrum and ir spectrum of this product, when compared with pmr and ir spectra of bicyclic anions formed from acyclic ketones and TNB,[1,2,6] provide substantial evidence for structure 3b. An alternate structure, 4, in which the C-6 keto bridge is *cis* to the C-3 CHNO$_2$ bridge, is ruled out by the $J_{1,5}$ ($J_{2,4}$) coupling constant of 2.5 cps. The H-1–H-5

(1) M. J. Strauss and H. Schran, *J. Org. Chem.*, **36**, 856 (1971).
(2) M. J. Strauss, T. C. Jensen, H. Schran, and K. O'Conner, *ibid.*, **35**, 383 (1970).
(3) T. Severin, *Chem. Ber.*, **90**, 2898 (1957).
(4) T. Severin and M. Bohn, *ibid.*, **100**, 211 (1967).

(5) C. Moberg and O. Wennerstrom, *Acta Chem. Scand.*, **25**, 2355 (1971); L. B. Clapp, H. Lacey, G. G. Beckwith, R. M. Srivastava, and N. Muhammed, *J. Org. Chem.*, **33**, 4262 (1968).
(6) M. J. Strauss, *Chem. Rev.*, **70**, 667 (1970).

(H-2–H-4) dihedral angle in **3b** results in the observed value of 2.5 cps, whereas that in a structure like **4** would be about 8 cps. This result is not entirely unexpected, since **4** ($n = 3$) should be less thermodynamically stable. The relative thermodynamic stability of **3** and **4** would influence the type of product isolated only if equilibration is complete, however.

The configuration of C-3 in **3b** cannot be unambiguously established. We have provided some evidence that H-3 in **1** (X = NO$_2$; R = H) is directed toward the keto bridge.[7] In a series of anions like **1**,[1,2,7] the chemical shift of H-3 is always between δ 5.0 and 5.9, whereas in **3b** it is 6.2. The direction of this shift is not directly explicable.

The structure of **3b**, coupled with the previously proposed mechanism of secondary amine–acyclic ketone condensations with TNB[1] and the spectral changes occurring in the TNB–diethylamine–cyclohexanone reaction mixture (see Experimental Section), allow us to propose a reasonable mechanistic route to the tricyclic product through the enamine σ complex **7b**. This latter type of complex likely forms from *in situ* generated enamine and TNB. Our recently reported kinetic study of a related sequence involving tertiary amines supports the intermediacy of tricyclic structures like **8**.[7]

7a, $n = 2$
b, $n = 3$
c, $n = 4$

8a, $n = 2$
b, $n = 3$
c, $n = 4$
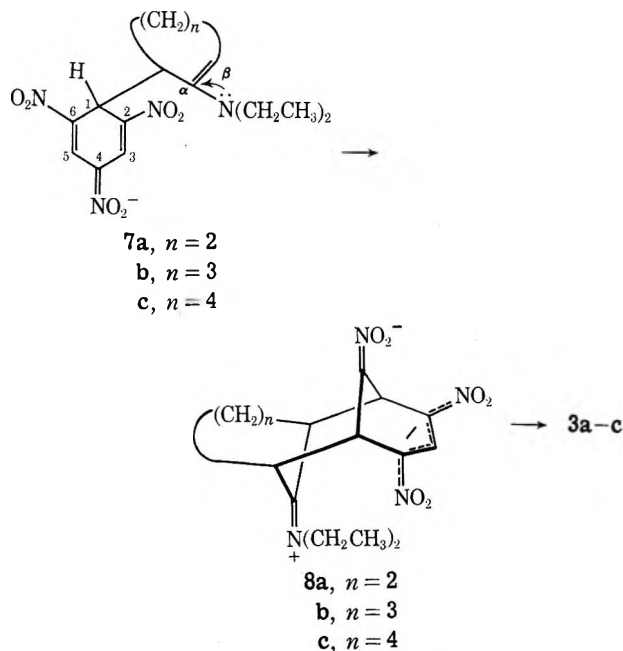
The reaction of cycloheptanone with TNB and diethylamine yielded the tricyclic anion **3c**. The reaction proceeded less rapidly than with cyclohexanone, and purification of the product by column chromatography was necessary. The pmr spectrum was essentially identical with that of **3b**, except for the added upfield methylene absorptions. The stereochemistry of the bridge cannot unambiguously be established, as the H-1 and H-5 (H-2 and H-4) protons are not well resolved and the $J_{1,5}$ ($J_{2,4}$) coupling constant could not be determined.

When an analogous reaction was attempted with cyclopentanone, the corresponding tricyclic anion **3a** could not be isolated. Although a small absorption at

500 nm (characteristic of the nitropropene nitronate function in **1**) was apparent in the visible spectrum of the reaction mixture, its rate of development was several orders of magnitude less than that which developed during formation of **3b**. Tlc of the cyclopentanone reaction mixture provided evidence for several products. These exhibited double maxima in their visible spectra, and are probably anionic σ complexes formed by attack of *in situ* generated enamine, cyclopentanoate anion, and diethylamine on TNB. It seems apparent that cyclization of **7a** is unfavorable relative to cyclization of **7b**, and that the reaction terminates at the σ complex stage. Drieding models clearly show that the distance between C-3 (C-5) and C-β in **7a** is almost 50% greater than in **7b**, when both intermediates are in the most favorable conformation for intramolecular cyclization. This results primarily from the rigidity of the cyclopentene ring in **7a**.

It is interesting to note that Severin has reported the tetracyclic structure **2**, which closely resembles **3**, as resulting from acidification of an alkaline solution of phloroglucinol and TNB.[4] Since tautomeric ketonic structures can be written for phloroglucinol, the possibility for a mechanistic route to the anionic precursor of **2** proceeding through anionic σ complex intermediates seems likely. We have reacted equivalent amounts of phloroglucinol and TNB in DMSO solution with excess diethylamine. The same visible spectral behavior of the reaction mixture is observed as in the reactions leading to **3b** and **3c**, except that the changes occur at a much more rapid rate. After several minutes, the spectrum of the reaction mixture consists of a single maximum at 500 nm, characteristic of the nitropropene nitronate function. A red powder can be obtained upon work-up of the reaction mixture (Experimental Section). This material contains a minimum of five compounds (tlc). Attempts at isolating pure products by chromatographic methods were unsuccessful. A similar diversity of products has been shown to arise from the reaction of diethylamine, acetone, and TNB.[8] The reaction was then carried out with triethylamine, since we supposed that the acidity of phloroglucinol would be sufficient so that a carbanionic mechanism for nitronate formation could occur. It is known that for nonacidic ketones, *i.e.*, acetone, diethylketone, and cyclohexanone, secondary amines must be employed to effect condensation–cyclization reactions with electron-deficient aromatics through enamine and immonium intermediates.[9,10] For more acidic ketones, *i.e.*, acetylacetone or dibenzyl ketone, tertiary amines will effect such reactions through carbanionic rather than enamine intermediates. The reaction of phloroglucinol, triethylamine, and TNB gave good yields of a single product which analyzed correctly for a 1:2:1 adduct of phloroglucinol, amine, and TNB. The pmr spectrum of this adduct is in accord with structure **9**. The $J_{1,5}$ coupling constant is less than 3 cps. Structure **10** should be much less stable due to repulsion of the two charge-delocalized functions. Structure **9** could quite possibly be a precursor to the tetracyclic structure **2**, isolated by Severin upon treating a mixture of TNB, potassium

(7) M. J. Strauss and H. Schran, *Tetrahedron Lett.*, 2349 (1971).

(8) R. Foster and C. A. Fyfe, *Tetrahedron*, **22**, 1831 (1966).

(9) M. J. Strauss and H. Schran, *J. Amer. Chem. Soc.*, **91**, 3974 (1969).

(10) M. J. Strauss and H. Schran, *J. Org. Chem.*, **36**, 856 (1971).

9

10
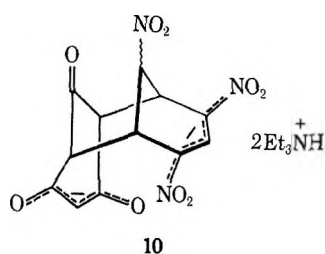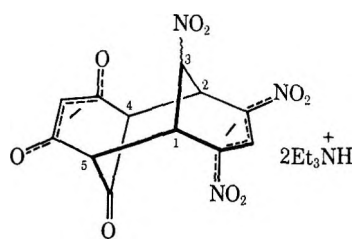
hydroxide, and phloroglucinol with 60% sulfuric acid.[4] Formation of the tetraanion 11 as an unstable inter-

$$9 \xrightarrow{OH^-} \quad \xrightarrow{H^+} 2$$

11
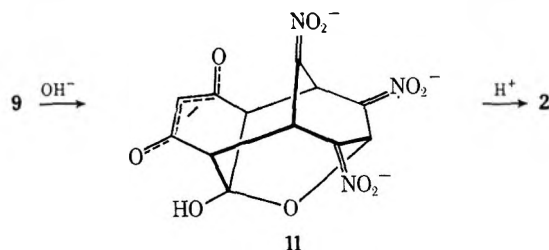
mediate preceding protonation is quite reasonable, since the structurally similar and isolable tetraanion 12

12
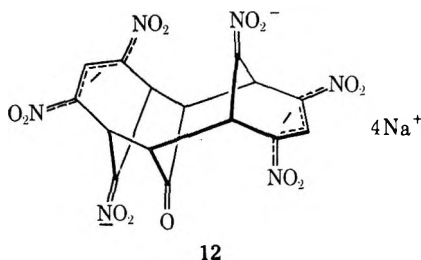
has previously been characterized.[11] All our attempts to isolate 2 by basification followed by acidification of 9 were unsuccessful. A variety of different procedures were attempted (see Experimental Section).

Although we have previously had some difficulty in isolating the nitronic acids of the bicyclic nitropropene anions 1, we thought it essential to do so in the case of the structurally symmetric 3b in order to compare the pmr spectral properties of the anion with those of the acid and 2. After many failures we found that, by very carefully acidifying a methanol solution of 3b with concentrated HCl at 15°, crystals of the nitronic acid 13 were formed after 24 hr. These analyzed

13

(11) K. Kohasi, Y. Ohkura, and T. Momose, *Chem. Pharm. Bull.*, **19**, 213 (1971).
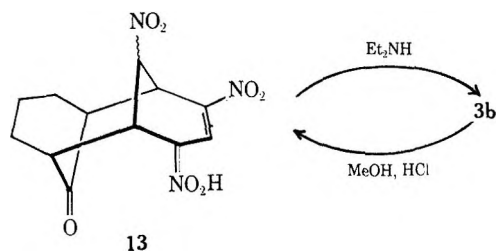
correctly for the expected acid and were readily converted back to the crystalline salt 3b by treatment with diethylamine. The pmr spectrum of 13 and 3b are quite similar, except for a few significant changes. Since the olefinic proton is a sharp singlet in 13, protonation must have occurred on nitronate oxygen. There are no absorptions for the triethylammonium cation. The strong carbonyl band at 1710 cm^{-1} in the infrared spectrum of 13 appears at the same frequency as that in 3b, clearly showing that cyclization to a structure analogous to 2 has not occurred.

By a similar acidification of 9 with methanolic HCl solution (anhydrous), yellow crystals of an acidic compound were obtained. These were extremely hygroscopic and unstable, and a satisfactory pmr spectrum and elemental analysis could not be obtained. The material could be the hydroxy endone nitronic acid of 9, or the corresponding methyl enolate or nitronate. Upon standing in the atmosphere the surface of these crystals turn orange, and in aqueous solution a strong absorption at 500 nm rapidly develops, characteristic of the nitropropene nitronate function of 9. Interestingly, treatment of the crystals with triethylamine yields a red powder, which after recrystallization is identical in all respects with the original salt 9.

Experimental Section

All melting points are uncorrected. Ir and uv spectra were recorded with Perkin-Elmer Model 21 and Model 402 spectrophotometers, respectively. Pmr spectra were recorded with JEOL MH-100 and PS-100 spectrometers, and chemical shifts are reported with respect to internal tetramethylsilane. Elemental analyses were performed by G. I. Robertson Laboratory, Florham Park, N. J.

Reaction of Cyclohexanone, Diethylamine, and TNB.— *sym*-TNB (2.0 g, 0.094 mol) was dissolved in a minimum amount of cyclohexanone at 40°. Diethylamine (2 ml) was then added, and the resulting exothermic reaction was moderated in a water bath at 15° (caution should be exercised with large-scale preparations). After standing for 24 hr, crystalline product is sometimes deposited from the reaction solution. If no crystals are deposited the reaction mixture can be washed with anhydrous diethyl ether until the oily residue is transformed to a red powder. Recrystallization from a 1:2 methanol-ether mixture yields red crystals of 3b (*ca.* 30% yield), mp 225–226°. These analyzed correctly for a 1:1:1 adduct.

Anal. Calcd for $C_{16}H_{24}N_4O_7$: C, 50.11; H, 6.30; N, 14.61. Found: C, 50.27; H, 6.42; N, 14.80.

A methanolic solution of 3b shows intense absorption at 510 nm, characteristic of the nitropropene nitronate function.

Since 3b is the first tricyclic nitropropene nitronate isolated, and since its symmetry allows a detailed interpretation of the pmr spectrum, a complete analysis of the latter is included here (DMSO-d_6).

3b
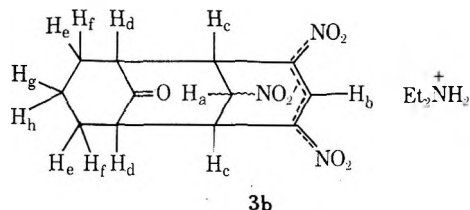
Proton	Chemical shifts (δ) and splittings
H$_a$	1 H (t, J = 2.5 cps) 6.30; irrad H$_c$ (s)
H$_b$	1 H (s) 8.21
H$_c$	2 H (m) 4.30; irrad H$_d$ or H$_a$ (d, J = 2.5 cps)
H$_d$	2 H (m) 2.58; irrad H$_c$ (sharp m)
H$_e$, H$_f$	4 H (m) 2.2
H$_g$, H$_h$	1 H (m) 1.8; 1 H (m) 1.35
Cation	6 H (t) 1.1; 4 H (q) 3.0; 2 H (br) 6.6

The ir spectrum of **3b** (KBr) shows absorptions at 2860, 1730, 1550, 1460, 1378, 1265, 880, 778, and 753 cm^{-1}.

Protonation of 3b.—A saturated solution of **3b** in methanol at 25° was prepared under dry nitrogen and cooled to 10°. Concentrated HCl was then added until the orange color of **3b** disappeared. Cooling the resulting yellow solution for 24 hr at 10° resulted in the formation of yellow needles of the nitronic acid **13** (*ca.* 40%), mp 165°.

Anal. Calcd for $C_{12}H_{13}N_3O_7$: C, 46.35; H, 4.22; N, 13.50. Found: C, 46.10; H, 4.27; N, 13.42.

Addition of diethylamine to **13** yields a red powder, which when recrystallized from methanol–ether solution gave red crystals of **3b**, mp 226°, with spectral properties identical with those of the originally prepared salt. In all hydrolytic solvents, **13** dissociates to yield solutions having an intense absorption at 510 nm.

The pmr spectrum of **13** (acetone-d_6) is quite similar to that of **3b**, except for the absence of the cationic absorptions in the latter: δ7.86 (CH=CNO$_2$H, s), 6.42 (CHNO$_2$, t), 4.55 (NO$_2$H, s, exchange rapid with H$_2$O present in small quantities), 4.40 (2 H, bridgehead α to NO$_2$, m), 2.71 (2 H, bridgehead α to carbonyl, m), 2.41 (4 H, methylene, m), and 1.70 (2 H, methylene, m). The ir (KBr) of **13** shows absorptions at 1725, 1647, 1610, 1558, 1525, 1315, 1070, 905, and 778 cm^{-1}.

Reaction of Cycloheptanone, Diethylamine, and TNB.—sym-TNB (1.0 g, 0.047 mol) was dissolved in a minimum amount of cycloheptanone at 40°. Diethylamine (2 ml) was then added. After standing at room temperature for 3 weeks the total reaction mixture was chromatographed on a neutral silica gel column (15 × 0.75 in.) with THF containing 0.1% diethylamine. Various eluent fractions were evaporated down and the resulting oils were chromatographed by tlc (silica gel). Those fractions containing a single component (major product) were combined, and the resulting material was recrystallized from a 1:3 methanol–ether solution to give bright red crystals of **3c**, mp 215°. This product had an intense visible absorption at 510 nm in methanol solution, and analyzed correctly for the expected 1:1:1 adduct. The carbon analysis was not within the standard limit of ±0.3%, as the material was difficult to dry.

Anal. Calcd for $C_{17}H_{26}N_4O_7$: C, 51.25; H, 6.58; N, 14.06. Found: C, 50.69; H, 6.81; N, 13.81.

The nmr spectrum (DMSO-d_6) of **3c** was quite similar to that of **3b**, except for additional upfield methylene absorptions: δ 8.18 (O$_2$NC=CHC=NO$_2$, s), 5.8 (CHNO$_2$, t), 4.02 (2 H, bridgehead α to NO$_2$, m), 2.72 (2 H, bridgehead α to carbonyl, m), 2.0–1.5 (8 H, methylenes, br), 1.15 (6 H, CH$_3$CH$_2$NH$_2$$^+$, t), and 2.9 (4 H, CH$_3CH_2NH_2$$^+$, q).

The ir spectrum of **3c** (KBr) shows absorptions at 1718, 1630, 1560, 1425, 1377, 1260, 887, 726, and 745 cm^{-1}.

Reaction of Cyclopentanone, Diethylamine, and TNB.— Attempts to prepare the bicyclic adduct **3a** by methods similar to those described for **3b** and **3c** were unsuccessful. Tlc of the reaction mixture after 2 hr or after 2 weeks showed more than four major products.

Reaction of Phloroglucinol, Diethylamine, and TNB.—Although the visible spectrum of a mixture of phloroglucinol, TNB, and diethylamine does show evidence for initial formation of a σ complex, followed by cyclization to the bicyclic nitropropene nitronate, no crystalline product could be obtained from this reaction. The *in situ* generated enamine of diethylamine and phloroglucinol must be of considerably different reactivity from those of simple cyclic ketones, since a variety of products is observed to form (tlc).

Reaction of Phloroglucinol, Triethylamine, and TNB.—sym-TNB (1.0 g, 0.047 mol) and phloroglucinol·2H$_2$O (1.0 g, 0.061 mol) were dissolved in a mixture of 4 ml of THF and 1 ml of DMF. To this mixture 3 ml of triethylamine were slowly added and the mixture was cooled to 10–15°. After 1 hr, the reaction mixture was triturated with four 50-ml portions of anhydrous ether. After the ether was decanted, the remaining insoluble oil was recrystallized from a 1:3 methanol–ether solution to yield orange crystals (*ca.* 50%), mp 123–124°, which analyze correctly for **9**.

Anal. Calcd for $C_{24}H_{39}N_5O_9$: C, 53.20; H, 7.25; N, 12.98. Found: C, 53.11; H, 7.62; N, 12.91.

The pmr spectrum of **9** (DMSO-d_6) shows absorptions at δ 8.1 (O$_2$NC=CHC=NO$_2$, s), 5.9 [2 H, (CH$_3$CH$_2$)$_3$N$^+$H, br], 5.6 (CHNO$_2$, t), 5.0 (O—C=CHC=O, s), 4.17 (2 H, bridgehead α to NO$_2$, m), 3.08 [12 H, (CH$_3$CH$_2$)$_3$N$^+$H, q], 2.93 (2 H, bridgehead α to carbonyl, d), and 1.15 [18 H, (CH$_3$CH$_2$)$_3$N$^+$H, t]. The ir spectrum of **9** (KBr) shows absorptions at 1720, 1550, 1520, 1235, and 1225 cm^{-1}. The electronic spectrum shows two intense peaks of equal intensity at 510 and 272 nm (MeOH). The latter absorption undoubtedly arises from the hydroxy enolate anion function in **9**, as it is not observed in **3b** or **3c**.

Alkyl Nitrate Nitration of Active Methylene Compounds.   IX.
The Nitration of Alkyl Substituted Heterocyclic Compounds[1]

H. FEUER* AND J. P. LAWRENCE

Department of Chemistry, Purdue University, Lafayette, Indiana 47907

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π-Deficient heterocyclic compounds such as 2-picoline (1) and 4-methylpyrimidine (2) and π-excessive heterocyclics such as 2-methylbenzoxazole (3) and 2-methylbenzothiazole (4) are readily converted to the corresponding α-nitroalkyl heterocyclics on treatment with an alkali metal amide and an alkyl nitrate in liquid ammonia. With 2,4-lutidine (5), 2,3-lutidine (6), and s-collidine (7) exclusive mononitration is observed, the reactivity of the methyl groups being in the order of 4 > 2 > 3.   Spectral data of the α-nitroalkyl heterocyclics indicate that the primary nitro compounds are in equilibrium with their dipolar structures.   The pK_a values of the three isomeric nitromethylpyridines have been determined and the order of acidities is 3 > 4 > 2.

In continuation of our studies of the alkyl nitration we are now reporting on its application to the synthesis of α-nitroalkyl heterocyclics.[2]

Previously, the only available methods for preparing these compounds involved several steps, and in general the overall yields were quite low.[3-7]

Both sodium and potassium amides were found to be effective as bases in the nitration reaction. By employing 4-picoline (8) as a model compound, it was found that, in the sodium amide–liquid ammonia system (A), a 1.0:2.5:3.1 molar ratio of 8 to sodium amide to *n*-propyl nitrate afforded optimum yields. In the potassium amide–liquid ammonia system (B) employing 2-picoline (1), a molar ratio of 1.0:2.0:2.5 of 1 to potassium amide to nitrate ester gave the highest yield.

The generality of the reaction was established by its successful application to alkyl derivatives of π-deficient and π-excessive heterocyclics as well as to 2-methylthiazoline, a nonaromatic heterocyclic compound. As can be seen from the results which are summarized in Table I, systems A and B were not equally effective in providing optimum yields. For example, the nitration of lepidine (9) in systems A and B afforded 4-nitromethylquinoline (10) in 58 and 93% yields, respectively (eq 1). On the other hand,

$$(1)$$
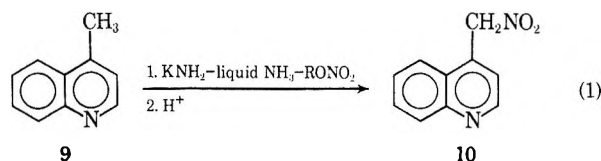
in the nitration of 1-(4-pyridyl)-3-phenylpropane (11), the yield of 3-phenyl-1-(-4-pyridyl)nitropropane was 90% in system A and only 74% in system B (eq 2).

It is noteworthy that the nitrations of 5-ethyl-2-methylpyridine and of quinaldine (13) were only successful in system B. Moreover, as shown in Table

$$(2)$$
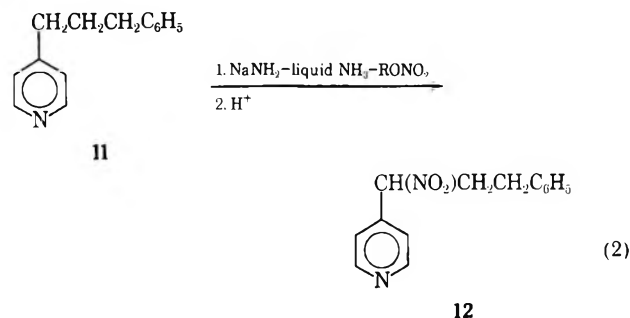
II, more concentrated reaction mixtures had to be employed to obtain potassium quinaldylnitronate (13a) in reasonable yield from 13. As indicated in Table I, the nitration of 13 in system A led only to 1-(2-quinolyl)-2-butanol. It is very likely that the alcohol formed from the base-catalyzed reaction of 13 and propanal. The latter originated by attack of base (NH_2^-) on propyl nitrate *via* α-hydrogen abstraction.

The nitrations of heterocyclics having more than one methyl group afforded only mononitration products (Table I) even though an excess of base and nitrate ester were employed. Also, further nitration was unsuccessful and resulted only in recovery of 14, when compound 14 was treated with 3.5 mol of amide and propyl nitrate. 2,4-Lutidine (5), 2,3-lutidine (6), 2,6-lutidine, and s-collidine (7) were converted to 2-methyl-4-nitromethylpyridine (14), 3-methyl-2-nitromethylpyridine (15), 6-methyl-2-nitromethylpyridine, and 2,6-dimethyl-4-nitromethylpyridine (16), respectively. The higher reactivities of the methyl groups in the 4 and 2 positions in compounds 5 and 6, respectively, have also been demonstrated in side-chain alkylation[8] and oximation[9] reactions.

The structure of compound 14 was confirmed by reduction to the known 4-aminomethyl-2-methylpyridine[10] (17) (eq 3) and by its nmr spectrum which
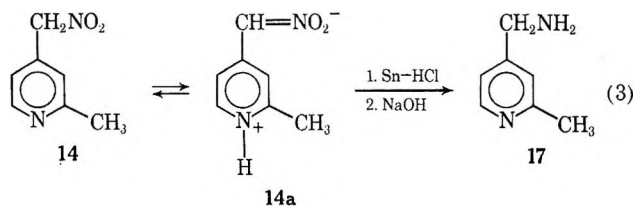
(1) For previous publications see (a) H. Feuer and R. P. Monter, *J. Org. Chem.*, **34**, 991 (1969); (b) H. Feuer and M. Auerbach, *ibid.*, **35**, 2551 (1970).

(2) A preliminary announcement of this work has appeared: H. Feuer and J. P. Lawrence, *J. Amer. Chem. Soc.*, **91**, 1856 (1969).

(3) L. Zalukaev and E. Vanag, *Zh. Obshch. Khim.*, **26**, 2639 (1956); *J. Gen. Chem. USSR*, **26**, 2943 (1956).

(4) P. E. Fanta, R. A. Stein, and R. M. W. Rickett, *J. Amer. Chem. Soc.*, **80**, 4577 (1958).

(5) L. Zalukaev and E. Vanag, *Zh. Obshch. Khim.*, **29**, 1639 (1959); *J. Gen. Chem. USSR*, **29**, 1614 (1959).

(6) W. Ried and A. Sinharay, *Chem. Ber.*, **96**, 3306 (1963).

(7) L. Zalukaev and D. G. Vnenkovskaya, *Khim. Geterotsikl. Soedin.*, **3**, 515 (1967); *Chem. Abstr.*, **68**, 87112 (1968).

$$(3)$$

(8) H. Lochte and T. H. Cheavens, *J. Amer. Chem. Soc.*, **79**, 1667 (1957).

(9) S. E. Forman, *J. Org. Chem.*, **29**, 3323 (1964).

(10) E. Ochiai and T. Suzuki, *Pharm. Bull.*, **2**, 147 (1954); *Chem. Abstr.*, **50**, 1015 (1956).

TABLE I

PRODUCTS FROM REACTIONS OF SUBSTITUTED HETEROCYCLICS
WITH ALKYL NITRATE IN LIQUID AMMONIA

Product[a,b]	System A,[c] yield, %[d]	System B,[e] yield, %[d]
2-Nitromethylpyridine	58	48[f]
3-Nitromethylpyridine	0[g]	0[h]
4-Nitromethylpyridine	66[f]	33
2-Methyl-4-nitromethylpyridine	69	53
6-Methyl-2-nitromethylpyridine	68	65
3-Methyl-2-nitromethylpyridine	32[i]	
5-Ethyl-2-nitromethylpyridine	0[j]	42[k]
2,6-Dimethyl-4-nitromethylpyridine	76	55
1-(4-Pyridyl)nitroethane	l	l
1-(4-Pyridyl)-3-phenylnitropropane	90	74
2-Nitromethylpyridine N-oxide	m	n
4-Nitromethylpyridine N-oxide	o	o
2-Nitromethylquinoline	0[p]	33[f]
4-Nitromethylquinoline	58	93
4-Nitromethylpyrimidine		71
1-Nitromethylisoquinoline	54	50
2-Nitromethylbenzoxazole	62	
2-Nitromethylbenzothiazole	66	
2-Nitromethylquinoxaline	55	58
4-Nitromethylcinnoline		88
2-Nitromethylthiazoline	43	

a Unless otherwise stated, the nitrations were carried out in *ca.* 0.5 *M* solutions of potassium amide or sodium amide in liquid ammonia and the nitro compounds were obtained directly after aqueous acidification of their crude nitronate salts with acetic acid. *b* Yields are based on starting material. *c* Sodium amide–liquid ammonia system. *d* In most cases unreacted starting material was recovered (see Experimental Section). *e* Potassium amide–liquid ammonia system. *f* Obtained after acidification of an aqueous solution of the pure salt of the nitro compound. *g* 3-Picoline was recovered in 91% yield. *h* 3-Picoline was recovered in 88% yield. *i* In another experiment 3-methyl-2-nitromethylpyridine was obtained in 52% yield when isolated as the picrate salt. *j* 5-Ethyl-2-methylpyridine was recovered in 87% yield. *k* The nitration was carried out in a 1.19 *M* solution of potassium amide in liquid ammonia. When a 0.55 *M* solution was used the yield was only 30%. *l* A mixture consisting of 1-(4-pyridyl)nitroethane and 4-acetylpyridine was obtained. *m* The product was isolated in 71% yield as the dibromo derivative, 2-(dibromonitromethyl)pyridine N-oxide. *n* Crude 2-nitromethylpyridine N-oxide was obtained in 54% yield after acidification of the crude salt with 5% hydrochloric acid. *o* The product was isolated in about 58% yield as the dibromo derivative, 4-(dibromonitromethyl)pyridine N-oxide. *p* The only product isolated was 26% of 1-(2-quinolyl)-2-butanol.

TABLE II

EFFECT OF POTASSIUM AMIDE CONCENTRATION
ON THE NITRATION OF QUINALDINE[a]

KNH₂, M	13a,[b] yield, %	Recovered 13, yield, %
0.35	0	88
0.59	42	42
1.58	43	43
2.84	50	37

a The molar ratio of 13 to KNH₂ to propyl nitrate was maintained in the ratio of 1.0:2.0:2.5. *b* Potassium quinaldylnitronate.

indicated that **14** was in equilibrium with its dipolar structure **14a**. The signal for the vinyl proton in **14a** fell at the same position (6.9 ppm) as that for the vinyl proton in sodium 4-picolylnitronate (**18**).

The structure of compound **15** was indicated by the 396-mμ absorption band in its ultraviolet spectrum. 3-Nitromethylpyridine (**19**) was found to absorb at 310 mμ (*vide infra*).

The structure of compound **16** was established by the fact that its dibromo derivative, 4-dibromonitro-methyl-2,6-dimethylpyridine (**20**), showed in the nmr spectrum only one signal at 2.6 ppm for the two methyl groups. Compound **20** was prepared by treating the potassium salt of **16** with potassium hypobromite (eq 4).

(4)
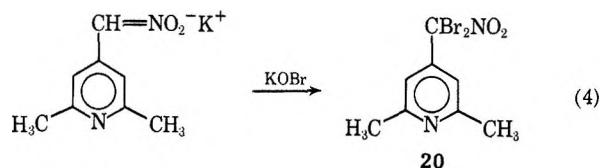
Nitrations of 2-picoline N-oxide and 4-picoline N-oxide led to the corresponding nitro salts which, however, could not be purified. A stronger acid than acetic acid, 5% hydrochloric acid was required to obtain the free nitro compounds from their salts. In this manner, 2-nitromethylpyridine N-oxide (**21**) was obtained in 54% yield, but it could not be purified.[11] On treatment with benzoyl chloride compound **21** was converted to the benzoyl derivative of 2-pyridylhydroxamyl chloride N-oxide (**23**) in 92% yield (eq 5). Sim-

(5)
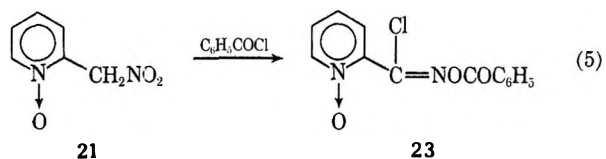
ilar conversions of α-nitroalkyl heterocyclics have been reported by Zalukaev.[12]

Although the salts of the nitromethylpyridine N-oxides **21** and **22** could not be purified, they were converted on bromination in good yields to the stable dibromo derivatives, 2-(dibromonitromethyl)pyridine N-oxide and 4-(dibromonitromethyl)pyridine N-oxide, respectively.

Attempts to prepare 3-nitromethylpyridine (**19**) directly from 3-methylpyridine were unsuccessful and led only to recovered starting material, but it could be prepared by the nitration of ethyl 3-pyridylacetate (**24**) which afforded a mixture of compound **19** and ethyl α-nitro-3-pyridylacetate (**25**). The mixture was converted completely to **19** on treatment with base followed by acidification (eq 6).

(6)
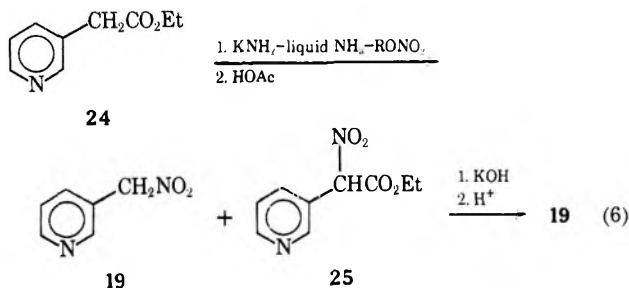
The nitration of 4-ethylpyridine (**26**) led to a mixture of 1-(4-pyridyl)nitroethane (**27**) and 4-acetylpyridine

(11) 4-Nitromethylpyridine N-oxide (**22**) which was obtained by acidifying the corresponding sodium or potassium salts could not be purified and decomposed on standing.

(12) L. Zalukaev and E. Vanag, *J. Gen. Chem. USSR*, **28**, 474 (1958); **30**, 529 (1960).

(28) after acidification of the crude nitro salt (29) (eq 7). Attempts to separate the mixture by distilla-

(7)
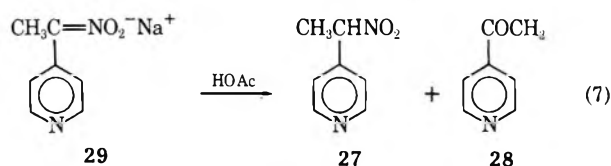
tion, column chromatography, or extraction of the nitro compound by base were unsuccessful. However, compound 27 was prepared in quantitative yield by reduction of 1-bromo-1-nitro-1-(4-pyridyl)ethane (30) with sodium borohydride. Compound 30 was prepared in 39% yield (based on 26) by bromination of crude salt 29 (eq 8). Ketone 28 was not formed dur-

(8)
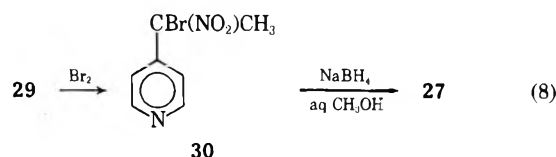
ing the nitration because analytically pure 27 was found to convert slowly to 28 on standing.[13]

The structures of the α-nitroalkyl heterocyclics were confirmed by ultraviolet, infrared, and nmr spectral data, and by conversion to derivatives such as picrate salts and halonitro compounds.

The halogen derivatives were prepared in good yield by treating aqueous solutions of the crude nitro salts with potassium hypobromite or hypochlorite. In the case of primary nitro compounds both acidic hydrogens were replaced by halogen. For example, bromination of the crude sodium salt of 14 afforded a 50% yield of 4-(dibromonitromethyl)-2-methyl-pyridine (31). It was readily converted to the monobromo compound, 4-(bromonitromethyl)-2-methyl-pyridine (32) in 83% yield on treatment with liquid ammonia at $-33°$ (eq 9).[14]

(9)

Spectra of α-Nitroalkyl Heterocyclics.—The ultraviolet spectra of all of the primary α-nitroalkyl heterocyclics revealed that these compounds are in equilibrium with their dipolar structures. The case of 4-nitromethylpyridine (33) is discussed somewhat in detail

because its infrared and nmr spectra also confirmed the presence of the dipolar structure 33a.

In the ultraviolet spectrum of 33, there appear, in addition to the maxima at 233 and 258 mμ characteristic of the pyridine ring, absorption bands at 332 and 404 mμ. The former is attributed to the presence of the nitronate function in structure 33a because it

is also present in the spectrum of sodium 4-picolylnitronate (18). The band at 404 mμ which is absent in the spectrum of salt 18 might be attributed to the contribution of the higher energy structure 33b.

In the infrared spectrum, structure 33a is confirmed by a broad band at 3640–2200 cm^{-1} characteristic of the immonium group[15] and by a peak at 1502 cm^{-1} attributed to the carbon–nitrogen double-bond frequency of the nitronate group. It is shifted 77–103 cm^{-1} to lower frequencies from the normal stretching vibration of alkanenitronates[16] owing to the conjugation with the pyridine ring. In the salt 18, the peak appears at 1527 cm^{-1}.

The presence of structures 33 and 33a is also clearly demonstrated in the nmr spectrum which shows signals of both the methylene protons in 33 at 5.9 ppm and the vinyl proton in 33a at 7.0 ppm.

The presence of the dipolar tautomers of 2-nitromethylpyridine (34) and 3-nitromethylpyridine (19) are clearly indicated in their ultraviolet spectra by the absorption maxima at 325 and 398 mμ in 34 and at 310 mμ as a shoulder in 19. The absorption bands at 325 and 310 mμ are also present in the spectra of the potassium salts of 34 and 19, respectively.

The positions of the equilibria between the dipolar and neutral tautomers as calculated from the nmr data are given in Table III. They indicate that the contribution of the dipolar structures in the three isomeric nitromethylpyridines is in the order of 4 > 2 > 3. In the nitromethylquinolines the dipolar contribution is greater in the 2 isomer than in the 4 isomer. The reason for this, as suggested by molecular models might be due to steric interference to planarity in the 4 isomer between the nitro group and the peri hydrogen in the dipolar and quinoid contributions.

It should be emphasized that the ultraviolet, infrared, and nmr spectra of secondary α-nitroalkyl heterocyclics do not show the presence of dipolar structures.

Acidities of the Isomeric Nitromethylpyridines.— The pK_a values of the three isomeric nitromethylpyri-

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(13) The transformation of a secondary nitro compound to a ketone was also found to occur with analytically pure diphenylnitromethane. It was converted on standing to benzophenone (unpublished results from the Ph.D. thesis of Dr. H. Friedman). It is very likely that a Nef-type reaction is involved in these transformations.

(14) Zalukaev reported that 2-(dibromonitromethyl)quinoline was converted to 2-(bromonitromethyl)quinoline on treatment with ethanolic ammonia at room temperature.[12]

(15) R. T. Conley, "Infrared Spectroscopy," Allyn and Bacon, Boston, Mass., 1966, p 136.

(16) H. Feuer, C. Savides, and C. N. R. Rao, *Spectrochim. Acta*, 19, 431 (1963).

TABLE III

CALCULATED EQUILIBRIA BETWEEN THE TAUTOMERS OF
NITROMETHYL HETEROCYCLICS FROM THEIR NMR SPECTRA
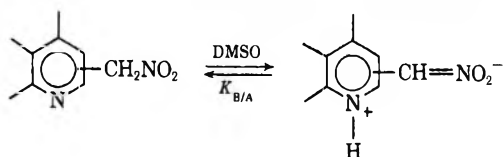
Compd[a,b]	$K_{B/A}$
2-Nitromethylpyridine[c]	0.09
3-Nitromethylpyridine[c]	0.02
4-Nitromethylpyridine	0.50
2-Methyl-4-nitromethylpyridine	0.46
2,6-Dimethyl-4-nitromethylpyridine	0.67
2-Nitromethylquinoline	1.63
4-Nitromethylquinoline[c]	0.50
1-Nitromethylisoquinoline	3.56
4-Nitromethylpyrimidine	0.50
4-Nitromethylcinnoline	10.70
2-Nitrobenzothiazole	5.70

[a] Nmr data are detailed in the Experimental Section. [b] Unless otherwise stated the spectra were determined in dimethyl sulfoxide on a Varian A-60 spectrometer. [c] Spectra were determined on a Varian XL-100.

dines were determined by titrating aqueous solutions of their pure salts with dilute hydrochloric acid and by plotting the pH *vs.* the volume of titrant added. Two pK_a values were obtained because both the nitronate function and ring nitrogen are protonated in this process (eq 10). The salts employed in this study were
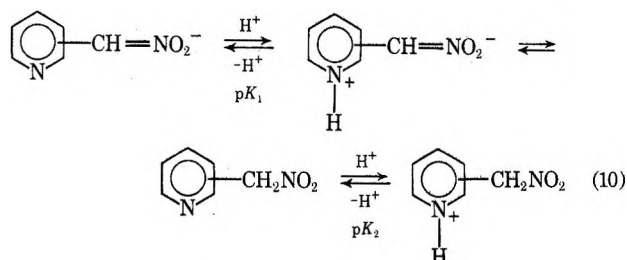
potassium 2-picolylnitronate (**35**), potassium 3-picolylnitronate (**36**), and **18**. The results which are summarized in Table IV, show that the order of acidity in the nitromethylpyridine series is 3 > 4 > 2. This order parallels that reported for the three isomeric hydroxypyridines.[17] The higher acidity of 3-hydroxypyridine has been explained by the lack of resonance stabilization of the dipolar structure. A similar rationale can be advanced to explain the higher acidity of 3-nitromethylpyridine (**19**).
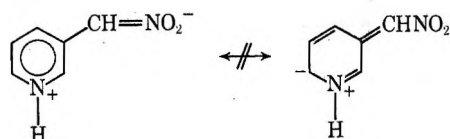
19

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. Ultraviolet spectra were obtained with

TABLE IV

pK_a VALUES OF THE ISOMERIC NITROMETHYLPYRIDINES AT 25°

Nitromethyl- pyridine	pK_1	pK_2
2	7.21	3.92
3	5.55 (5.75)[a]	3.50
4	6.60	3.35

[a] This value was obtained by titrating an aqueous solution of 3-nitromethylpyridine with dilute aqueous potassium hydroxide.

a Bausch and Lomb Spectronic 505 UV spectrometer. Gas chromatographic analyses were performed on an Aerograph A-90-s using a 4 ft SF-96 on Chromosorb P or Chromosorb W column. Solvents were evaporated on a Buchler flash evaporator.

Apparatus.—Nitrations were performed in a thoroughly dried 500-ml 4-necked flask equipped with a mechanical stirrer, Dry Ice condenser, thermometer, and pressure equalizing additional funnel.

Materials.—Ethyl nitrate and propyl nitrate of Eastman White Label grade were used as received. 4-Methylpyrimidine[18] and 4-methylcinnoline[19] were prepared by methods described in the literature. 1-Methylisoquinoline was prepared by catalytic dehydrogenation of 1-methyl-3,4-dihydroisoquinoline[20] with palladium on carbon in refluxing decalin. The remaining alkyl substituted heterocyclics were obtained from commercial sources and were distilled prior to use.

2-Nitromethylpyridine (34).—The following experiment is typical of the procedure employed in the sodium amide–liquid ammonia system (A). To a freshly prepared solution of sodium amide (0.23 mol) in 300 ml of liquid ammonia was added 8.4 g (0.09 mol) of 2-picoline (1) rapidly at −33°. After stirring for 10 min, 29.6 g (0.28 mol) of *n*-propyl nitrate was added as rapidly as possible while the temperature was kept below −33°.[21] The mixture was stirred an additional 5 min, the ammonia gradually replaced with absolute ether, and the reaction mixture filtered after room temperature was reached (3–5 hr).

The crude sodium 2-picolylnitronate[22] was dried *in vacuo*, dissolved in 20 ml of water, and acidified with 11.0 g of glacial acetic acid at room temperature. Extracting the solution with chloroform, drying (Na₂SO₄), concentrating the extract *in vacuo*, and distilling the residue afforded 7.3 g (58%) of 2-nitromethylpyridine: bp 70° (0.2 mm); n^{20}D 1.5519; uv max (95% C₂H₅OH) 253 mμ (sh), 259 (log ε 3.46), 265 (sh), 325 (3.23), and 398 (2.40); ir (neat) 1568 cm⁻¹ (NO₂); nmr (DMSO-d_6) δ 8.5 (m, 0.9, H$_a$), 7.95 (m, 0.09, H$_b$), 7.4 (m, 3, N=CHCH=CHCH), 6.91 (s, 0.09, CH) and 5.5 (s, 2, CH₂).
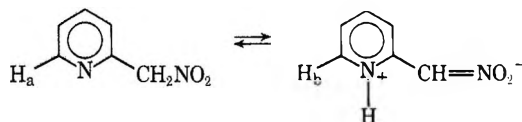
Anal. Calcd for C₆H₆N₂O₂: C, 52.17; H, 4.38; N, 20.28. Found: C, 51.84; H, 4.41; N, 19.97.

The ethereal filtrate was concentrated *in vacuo* and the residue treated with excess ethanolic picric acid solution. The precipitate was recrystallized from 95% ethanol to yield 2.6 g (9%) of 2-picolinium picrate: mp 167° (lit.[23] mp 165°).

2-Nitromethylpyridinium picrate was prepared in the usual manner:[24] mp 152° (95% ethanol) (lit.[25] mp 152–153°).

4-Nitromethylpyridine (33).—The experimental procedure was similar to that described for the preparation of **34**, except that 0.205 mol of sodium amide, 7.6 g (0.082 mol) of 4-picoline, and 26.9 g (0.256 mol) of *n*-propyl nitrate were employed.

Recrystallization of the crude salt from 95% ethanol afforded 12.1 g (92%) of sodium 4-picolylnitronate[22] (**18**): mp 255–257°;

(17) A. Albert and J. N. Phillips, *J. Chem. Soc.*, 1294 (1956).

(18) V. E. Smith and B. E. Christensen, *J. Org. Chem.*, **20**, 829 (1955).

(19) T. L. Jacobs, S. Winstein, R. B. Henderson, and E. C. Spaeth, *J. Amer. Chem. Soc.*, **69**, 1310 (1946).

(20) W. M. Whaley and W. H. Hartung, *J. Org. Chem.*, **14**, 650 (1949)

(21) CAUTION! The first few drops of alkyl nitrate should be added slowly because a considerable exotherm develops.

(22) CAUTION! The dry nitro salts exhibit a high heat of hydration and may decompose violently on exposure to the atmosphere.

(23) A. Ladenburg, *Justus Liebigs Ann. Chem.*, **247**, 1 (1888).

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

(25) L. Zalukaev and E. Vanag, *J. Gen. Chem. USSR*, **27**, 3314 (1957).

uv max (95% C_2H_5OH) 332 mμ (log ϵ 4.13); ir (KBr) 1527 cm^{-1} (C=NO$_2^-$); nmr (D$_2$O) δ 8.3 (m, 2, N=CH), 7.6 (m, 2, N=CHCH), and 7.0 (s, 1, CH).

Anal. Calcd for $C_6H_5N_2NaO_2$: C, 45.00; H, 3.12; N, 17.50; Na, 14.37. Found: C, 44.99; H, 3.22; N, 17.36; Na, 14.32.

A solution of 5.0 g (0.031 mol) 18 in 25 ml of water was acidified at 0–5° with 3.8 g of glacial acetic acid. Filtering, drying *in vacuo*, and recrystallizing the precipitate from warm ($\sim$50°) 95% ethanol afforded 3.1 g (72%) of 4-nitromethylpyridine (**33**): mp 97° dec; uv max (95% C_2H_5OH) 233 mμ (log ϵ 3.28), 258 (3.23), 332 (3.47), and 4.0 (3.20); ir (KBr) 3640–2200 (=N$^+$H) and 1502 cm^{-1} (C=NO$_2^-$); nmr (DMSO-d_6) δ 8.9 (m, 1.33, H$_a$), 8.0 (m, 0.67, H$_b$), 7.6 (m, 2, H$_c$), 7.0 (s, 0.33, CH), and 5.9 (s, 1.33, CH$_2$).
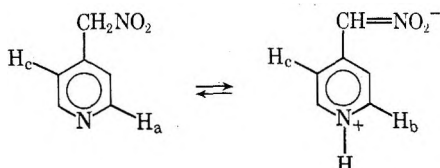
Anal. Calcd for $C_6H_6N_2O_2$: C, 52.17; H, 4.38; N, 20.28. Found: C, 52.16; H, 4.43; N, 19.99.

2-Methyl-4-nitromethylpyridine (14).—From 0.21 mol of sodium amide, 9.1 g (0.08 mol) of 2,4-lutidine (**5**) and 28.0 g (0.27 mol) of *n*-propyl nitrate there was obtained 22.4 g of crude salt, dried *in vacuo*.[22] A 17.4-g portion was dissolved in 25 ml of water and acidified with 8.0 g of glacial acetic acid at 0–5°. Filtering, drying *in vacuo*, and recrystallizing the precipitate from warm ($\sim$50°) acetone–water (1:1) gave 6.9 g (69%) of 2-methyl-4-nitromethylpyridine: mp 120°; uv max (95% C_2H_5OH) 241 mμ (log ϵ 3.18), 262 (3.28), 331 (3.48), and 394 (3.44); ir (KBr) 3640–2191 (=N$^+$H) and 1497 cm^{-1} (C=NO$_2^-$); nmr (DMSO-d_6) δ 8.6 (m, 0.68, H$_a$), 7.9 (m, 0.32, H$_b$), 7.4 (m, 2, H$_c$ + H$_d$), 6.9 (s, 0.32, CH), 5.8 (s, 1.37, CH$_2$), 2.5 (s, 2.06, H$_e$), and 2.4 (s, 0.94, H$_f$).
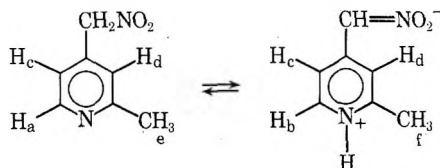
Anal. Calcd for $C_7H_8N_2O_2$: C, 55.25; H, 5.30; N, 18.41. Found: C, 55.40; H, 5.49; N, 18.17.

The ethereal filtrate was concentrated *in vacuo* and the residue treated with excess picric acid solution to yield 2.9 g (11%) of 2,4-lutidinium picrate: mp 180° (lit.[23] mp 179°).

Reduction of 2-Methyl-4-nitromethylpyridine (14).—Granulated tin (12.0 g) was added in two portions over a 10-min period to a solution of 4.0 g (0.03 mol) 14 in 200 ml of 6 *N* hydrochloric acid. After refluxing for 2 hr, the colorless solution was cooled and made basic to litmus with 6 *N* sodium hydroxide. The filtrate was extracted with ether and dried (Na$_2$SO$_4$), and the ethereal extract concentrated *in vacuo* to give a colorless oil which was divided into two portions.

Treating one portion with ethanolic picric acid gave 4-aminomethyl-2-picolinium picrate: mp 198° dec (95% EtOH) (lit.[10] mp 195–196°).

The second portion was taken up in absolute ether and saturated with hydrogen chloride to give 4-aminomethyl-2-picolinium chloride: mp 272° (MeOH) (lit.[10] mp 274°).

6-Methyl-2-nitromethylpyridine (37).—The general procedure was followed except that the acidified solution was extracted with chloroform, dried (MgSO$_4$), and concentrated *in vacuo*. The residue was eluted with benzene on an aluminum oxide (alumina, acid washed) column. 2,6-Lutidine (10.0 g, 0.094 mol) gave 9.7 g (68%) of 6-methyl-2-nitromethylpyridine: n^{20}D 1.5487; uv max (95% C_2H_5OH) 258 mμ (sh), 263 (log ϵ 3.49), 270 (sh), 310 (2.67), and 396 (2.83); ir (neat) 1553 cm^{-1} (NO$_2$); nmr (CCl$_4$) δ 7.2–7.9 (m, 3, ring H), 5.6 (s, 2, CH$_2$), and 2.6 (s, 3, CH$_3$).

Anal. Calcd for $C_7H_8N_2O_2$: C, 55.25; H, 5.30; N, 18.41. Found: C, 55.04; H, 5.54; N, 18.48.

6-Methyl-2-nitromethylpyridinium picrate was prepared in the usual manner:[24] mp 122–124° dec (95% ethanol).

Anal. Calcd for $C_{13}H_{11}N_5O_9$: C, 40.94; H, 2.89; N, 18.37. Found: C, 41.03; H, 3.00; N, 18.08.

3-Methyl-2-nitromethylpyridine (15).—The work-up procedure was similar to that described for the preparation of **37**. 2,3-Lutidine (9.9 g, 0.092 mol) gave 4.5 g (32%) of 3-methyl-2-nitromethylpyridine: mp 79°; uv max (95% C_2H_5OH) 256 mμ (sh), 263 (log ϵ 4.01), 279 (sh), 302 (3.32), and 396 (3.87); ir (KBr) 1551 cm^{-1} (NO$_2$); nmr (CDCl$_3$) δ 8.7 (m, 2, N=CHCH=CH), 7.6 (m, 1, N=CHCH), 5.7 (s, 2, CH$_2$), and 2.5 (s, 3, CH$_3$).

Anal. Calcd for $C_7H_8N_2O_2$: C, 55.25; H, 5.30; N, 18.41. Found: C, 54.99; H, 5.08; N, 18.55.

3-Methyl-2-nitromethylpyridinium picrate was prepared in the usual manner:[24] mp 157° (95% ethanol).

Anal. Calcd for $C_{13}H_{11}N_5O_9$: C, 40.94; H, 2.97; N, 18.37. Found: C, 40.92; H, 3.08; N, 18.10.

2,6-Dimethyl-4-nitromethylpyridine (16) (76%): mp 129° dec (H$_2$O); uv max (95% C_2H_5OH) 258 mμ (sh), 266 (log ϵ 3.49), 279 (sh), and 401 (3.92); ir (KBr) 3640–2078 (=N$^+$H) and 1475 cm^{-1} (C=NO$_2^-$); nmr (DMSO-d_6) δ 7.4 (s, 2, H$_a$ + H$_b$), 6.9 (s, 0.4, CH), 5.9 (s, 1.2, CH$_2$), 2.5 (s, 3.6, H$_c$), and 2.4 (s, 2.4, H$_d$).
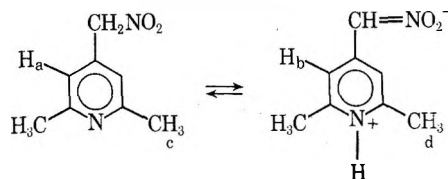
Anal. Calcd for $C_8H_{10}N_2O_2$: C, 57.83; H, 6.02; N, 16.87. Found: C, 58.07; H, 6.28; N, 17.13.

1-(4-Pyridyl)-3-phenylnitropropane (12) (90%): mp 58° (EtOH); uv max (95% C_2H_5OH) 260 mμ (log ϵ 3.22); ir (KBr) 1551 cm^{-1} (NO$_2$); nmr (CDCl$_3$) δ 8.9 (m, 2, N=CH), 7.4 (m, 7, N=CHCH + C$_6$H$_5$), 5.5 (m, 1, CH), and 2.8 [m, 4, (CH$_2$)$_2$].

Anal. Calcd for $C_{14}H_{14}N_2O_2$: C, 69.40; H, 5.83; N, 11.56. Found: C, 69.47; H, 5.89; N, 11.33.

1-Nitromethylisoquinoline (54%): mp 167° dec (95% EtOH); uv max (95% C_2H_5OH) 230 mμ (log ϵ 4.20), 253 (3.57), 262 (3.59), 305 (3.85), 380 (sh), 410 (4.28), and 432 (4.34); ir (KBr) 1538 cm^{-1} (NO$_2$); nmr[26] (DMSO-d_6) δ 14.0 (s, NH), 6.8–8.5 (m, ring H), 7.2 (s, CH), nad 6.4 (s, CH$_2$).
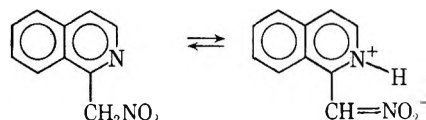
Anal. Calcd for $C_{10}H_8N_2O_2$: C, 63.82; H, 4.26; N, 14.89. Found: C, 63.82; H, 4.14; N, 15.10.

2-Nitromethylbenzoxazole (3) (62%): mp 76° (lit.[6] mp 78°) (EtOH); uv max (95% C_2H_5OH) 236 mμ (log ϵ 3.79). 265 (3.39), 272 (3.43), 280 (3.29), and 348 (3.45); ir (KBr) 1558 cm^{-1} (NO$_2$); nmr (CDCl$_3$) δ 7.2–7.9 (m, 4, ring H) and 5.8 (s, 2, CH$_2$).

2-Nitromethylbenzothiazole (4).—The general procedure was followed except crude 4 was purified by dissolving it in 200 ml of 5% aqueous sodium bicarbonate, precipitating with glacial acetic acid and recrystallizing from warm ($\sim$50°) 95% ethanol. 2-Methylbenzothiazole (10.6 g, 0.071 mol) gave 9.1 g (66%) 2-nitromethylbenzothiazole: mp 144° dec (lit.[6] mp 125–126° dec); uv max (95% C_2H_5OH) 383 mμ (log ϵ 4.21); ir (KBr) 3599–2162 (=N$^+$H) and 1473 cm^{-1} (C=NO$_2^-$); nmr[26] (DMSO-d_6) δ 9.1 (s, NH), 7.0–8.2 (m, ring H + CH), and 6.3 (s, CH$_2$).
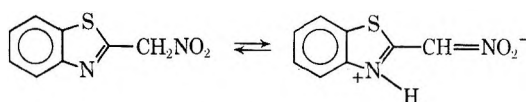
Anal. Calcd for $C_8H_6N_2O_2S$: C, 49.48; H, 3.02; N, 14.43, S, 16.49. Found: C, 49.20; H, 2.89; N, 14.15; S, 16.30.

2-Nitromethylthiazoline (43%): mp 128–130° dec; ir (KBr)

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(26) The relative proton values could not be determined because the signals for the aromatic and vinyl protons fell in the same range.

3636–2439 (=N⁺H) and 1575 cm⁻¹ (C=NO₂⁻); nmr (DMSO-d_6) δ 9.1 (s, 0.42, NH),[27] 7.0 (s, 1, H$_a$), and 3.1–4.1 (m, 4, CH₂).
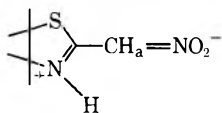
Anal. Calcd for C₄H₆N₂O₂S: C, 32.88; H, 4.11; N, 19.18; S, 21.92. Found: C, 33.48; H, 4.40; N, 18.56; S, 22.21.

Attempts to further purify the crude product by recrystallization or sublimation resulted in decomposition.

4-Nitromethylquinoline (10).—The following experiment is typical of the procedure employed in the potassium amide–liquid ammonia system (B). To a freshly prepared solution of potassium amide (0.13 mol) in 300 ml of liquid ammonia was added rapidly 9.3 g (0.06 mol) of lepidine (9) at −33°. After the mixture stirred for 3 min, 17.2 g (0.16 mol) of n-propyl nitrate was added as rapidly as possible while the temperature was kept below −33°.[21] The mixture was stirred an additional 5 min, the ammonia gradually replaced with absolute ether, and the reaction mixture was filtered after room temperature was reached (3–4 hr).

The crude salt[22] was dried *in vacuo*, dissolved in 100 ml of water, and acidified with 7.9 g of glacial acetic acid at room temperature. The precipitate was filtered, dried *in vacuo*, and recrystallized from warm (~50°) 95% ethanol to yield 11.3 g (93%) of 4-nitromethylquinoline: mp 136° dec; uv max (95% C₂H₅OH) 304 mμ (log ε 3.50), 317 (3.51), 370 (3.42), 440 (sh), and 456 (3.44); ir (KBr) 3640–2213 (=N⁺H) and 1470 cm⁻¹ (C=NO₂⁻); nmr (100 MHz) (DMSO-d_6) δ 9.06 (d, 0.66, H$_a$), 8.47 (d, 0.34, H$_b$), 8.35–7.45 (m, 5.7, NH + CH + ring H), and 6.42 (s, 1.32, CH₂).
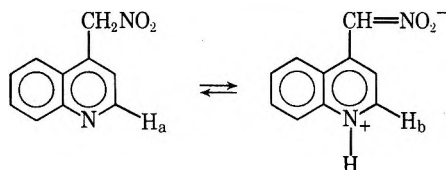
Anal. Calcd for C₁₀H₈N₂O₂: C, 63.82; H, 4.26; N, 14.89. Found: C, 63.67; H, 4.73; N, 14.54.

5-Ethyl-2-nitromethylpyridine.—The experimental procedure was similar to that described for the preparation of 10, except that 0.179 mol of potassium amide in 150 ml of liquid ammonia, 10.8 g (0.089 mol) of 5-ethyl-2-methylpyridine, and 23.5 g (0.224 mol) of n-propyl nitrate were employed. Work-up as described in the preparation of compound 37 gave 6.2 g (42%) of 5-ethyl-2-nitromethylpyridine: n^{20}D 1.5378; uv max (95% C₂H₅OH) 259 mμ (sh), 264 (log ε 3.28), 270 (3.27), 322 (2.67), and 400 (2.84); ir (neat) 1555 cm⁻¹ (NO₂); nmr (CCl₄) δ 8.6 (m, 1, N=CH), 7.4–7.9 (m, 2, CH=CH), 5.6 (s, 2, CH₂NO₂), 2.7 (q, 2, CH₂), and 1.3 (t, 3, CH₃).

Anal. Calcd for C₈H₁₀N₂O₂: C, 57.83; H, 6.02; N, 16.87. Found: C, 57.58; H, 5.86; N, 16.64.

5-Ethyl-2-nitromethylpyridinium picrate was prepared in the usual manner:[24] mp 115°.

Anal. Calcd for C₁₄H₁₃N₅O₉: C, 42.53; H, 3.29; N, 17.72. Found: C, 42.76; H, 3.57; N, 17.68.

2-Nitromethylpyridine N-Oxide (21).—The experimental procedure was similar to that described for the preparation of compound 10 except that the crude dry salt[22] was dissolved in 20 ml of water and carefully acidified with 5% hydrochloric acid at 0–5° to pH 2. The precipitate was filtered, washed with a little cold water, and recrystallized repeatedly from 95% ethanol to give 2.4 g (54%) of analytically impure 2-nitromethylpyridine N-oxide: mp 120° dec; ir (KBr) 3636–1681 (OH), 1546 (C=NO₂⁻), and 1220–1205 cm⁻¹ (N–O); nmr (DMSO-d_6) δ 11.4 (s, 1, OH), 8.0–8.4 (m, 1, H$_a$), and 7.2–8.0 (m, 4, H$_b$ + H$_c$ + H$_d$ + CH).
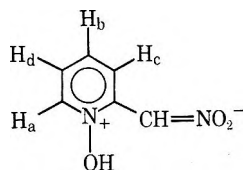
2-Nitromethylquinoline.—The experimental procedure was similar to that described for the preparation of compound 10 except that 0.284 mol of potassium amide in 100 ml of ammonia, 20.3 g (0.142 mol) of quinaldine (13), and 37.4 g (0.356 mol) of n-propyl nitrate were employed.

The crude salt was recrystallized from 95% ethanol to give 16.0 g (50%) of **potassium 2-quinaldylnitronate:**[22] mp 290° dec; uv max (95% C₂H₅OH) 283 mμ (sh), 290 (log ε 4.02), 323 (4.09), and 337 (4.09); ir (KBr) 1531 cm⁻¹ (C=NO₂⁻); nmr (D₂O) δ 6.9–8.4 (m, 6, ring H) and 6.9 (s, 1, CH).

Anal. Calcd for C₁₀H₇KN₂O₂: C, 53.10; H, 3.10; K, 17.30; N, 12.39. Found: C, 53.01; H, 3.23; K, 17.04; N, 12.54.

Concentrating the ethereal filtrate *in vacuo* afforded 7.4 g (37%) of unreacted 13. Potassium 2-quinaldylnitronate (16.0 g, 0.07 mol) gave (67%) of **2-nitromethylquinoline:** mp 122° (95% EtOH) (lit.[3] mp 121–122°); uv max (95% C₂H₅OH) 302 mμ (log ε 3.67), 395 (sh), 416 (4.27), and 439 (4.37); ir (KBr) 1538 cm⁻¹ (NO₂); nmr (DMSO-d_6) δ 13.2 (s, 0.38, NH), 6.8–8.4 (m, 6, ring H), 7.0 (s, 0.62, CH), and 5.9 (s, 0.76, CH₂).
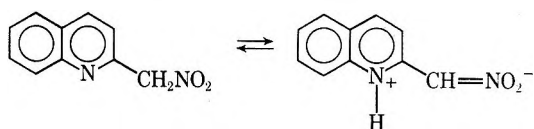
4-Nitromethylpyrimidine (71%): mp 125° dec (CH₃OH); uv max (95% C₂H₅OH) 244 mμ (log ε 3.45), 362 (3.58), and 402 (sh); ir (KBr) 1575 cm⁻¹ (NO₂); nmr (DMSO-d_6) δ 9.1 (m, 0.78, H$_a$), 8.8 (m, 0.78, H$_b$), 8.4 (s, 0.33, H$_c$), 7.8 (m, 0.33, H$_d$), 7.6 (m, 0.78, H$_e$), 7.2 (m, 0.33, H$_f$), 6.8 (s, 0.33, CH), and 5.9 (s, 1.33, CH₂).
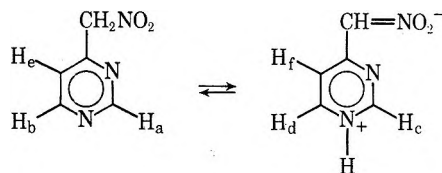
Anal. Calcd for C₅H₅N₃O₂: C, 43.17; H, 3.59; N, 30.22. Found: C, 43.38; H, 3.70; N, 30.10.

4-Nitromethylquinoxaline. (58%): mp 121° (purified by sublimation at 100°, 0.03 mm) (lit.[4] mp 122–123°); uv max (95% C₂H₅OH) 235 mμ (log ε 4.27), 302 (sh), 317 (3.77), 407 (3.62), 435 (sh), and 462 (sh); ir (KBr) 1537 cm⁻¹ (NO₂); nmr (DMSO-d_6) δ 9.0 (s, 1, N=CH), 7.7–8.3 (m, 4, C₆H₄), and 5.8 (s, 2, CH₂).

4-Nitromethylcinnoline (88%): mp 152° dec (95% EtOH); uv max (95% C₂H₅OH) 260 mμ (log ε 3.69), 282 (sh), 322 (3.27), 430 (sh), 450 (4.13), and 479 (4.17); ir (KBr) 1515 cm⁻¹ (C=NO₂⁻); nmr (DMSO-d_6) δ 13.6 (s, 0.52, NH),[27] 9.3 (s, 1, H$_a$), 7.1–8.0 (m, 4, C₆H₄), 7.4 (s, 0.91, CH), and 6.4 (s, 0.17, CH₂).
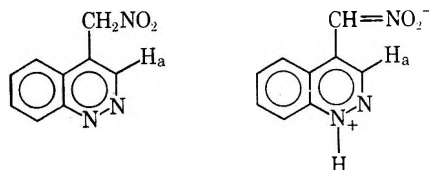
Anal. Calcd for C₉H₇N₃O₂: C, 57.14; H, 3.65; N, 22.22. Found: C, 57.24; H, 3.85; N, 22.19.

Potassium 2-picolylnitronate (35) (67%): mp 294–296° dec (95% EtOH); uv max (95% C₂H₅OH) 327 mμ (log ε 3.77); ir (KBr) 1538 cm⁻¹ (C=NO₂⁻); nmr (D₂O) δ 8.4 (m, 2, N=CHCH =CHCH), 7.8 (m, 1, N=CHCH=CH), 7.2 (m, 1, N=CHCH), and 7.2 (s, 1, CH).

Anal. Calcd for C₆H₅KN₂O₂: C, 40.91; H, 2.84; K, 22.21; N, 15.91. Found: C, 40.87; H, 2.93; K, 21.94; N, 16.10.

3-Nitromethylpyridine (19).—To a freshly prepared solution of potassium amide (0.085 mol) in 300 ml of liquid ammonia was added rapidly at −33° 12.7 g (0.077 mol) of ethyl 3-pyridylacetate (24). After the mixture stirred for 3 min, 10.5 g (0.115 mol) of ethyl nitrate was added as rapidly as possible while the temperature was kept below −33°. The mixture was stirred an additional hour, the ammonia gradually replaced with absolute ether, and after attaining room temperature (3–4 hr) the reaction mixture was filtered. The solid as dissolved in 100 ml of water and acidified with glacial acetic acid to pH 5. The solution was ex-

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(27) This value was determined by comparing the integrated area with that for H$_a$ considered to be 1.0. The low integration is probably due to the broadness of the signal.

tracted with chloroform and dried (MgSO₄), and the extract concentrated *in vacuo* to yield 9.6 g of a pale yellow oil. An nmr spectrum of this material indicated that it was a mixture consisting of 65% **19** and 35% ethyl α-nitro-3-pyridylacetate (**25**): nmr (CDCl₃) δ 8.6 (m, 2, N=CH), 7.8 (m, 1, N=CHCH=CH), 7.3 (m, 1, N=CHCH₁), 6.3 (s, 0.32, CH), 5.5 (s, 1.28, CH₂NO₂), 4.2 (q, 0.67, CH₂), and 1.2 (t, 1.07, CH₃).

The mixture was dissolved in 25 ml of 40% aqueous sodium hydroxide (the temperature rose to 60°), 20 ml of water was added, and the solution heated to 80°. After cooling to 10–15°, the mixture was diluted with a little water, acidified to pH 4–5 with aqueous oxalic acid, and sodium oxalate removed by filtration. The filtrate was extracted with chloroform, dried (MgSO₄), and concentrated *in vacuo*. Eluting the residue with chloroform on an aluminum oxide (alumina, acid washed) column gave 7.0 g (66%) of pure **3** nitromethylpyridine: n^{20}D 1.5338; uv max (95% C₂H₅OH) 310 mμ (log ε 2.66); ir (neat) 1563 cm⁻¹ (NO₂); nmr (DMSO-d_6) δ 8.3 (m, 2, N=CH), 7.5 (m, 1, N=CHCH=CH), 7.0 (m, 1, N=CHCH), and 5.4 (s, 2, CH₂).

Anal. Calcd for C₆H₆N₂O₂: C, 52.17; H, 4.38; N, 20.28. Found: C, 52.18; H, 4.58; N, 20.40.

3-Nitromethylpyridinium picrate was prepared in the usual manner:[24] mp 150–151° (95% EtOH).

Anal. Calcd for C₁₂H₉N₅O₉: C, 39.24; H, 2.47; N, 19.07. Found: C, 39.35; H, 2.41; N, 19.37.

1-(4-Pyridyl)nitroethane (27).—To a solution of 1.5 g (39.0 mmol) sodium borohydride in 20 ml of 75% aqueous methanol (by volume) was added 2.0 g (8.7 mmol) of 1-bromo-1-(4-pyridyl)-nitroethane (**30**) (*vide infra* for preparation) at such a rate as to maintain a gentle reflux. After the addition was completed the reaction mixture was cooled to room temperature, diluted with 50 ml of water, and acidified to pH 1–2 with 30% sulfuric acid. The solution was then concentrated to 50 ml *in vacuo* and the residue neutralized with 5% aqueous sodium bicarbonate. The solution was extracted with methylene chloride and dried (MgSO₄), and the extract concentrated *in vacuo* to yield 1.3 g (100%) of 1-(4-pyridyl)nitroethane: n^{25}D 1.5255; uv max (95% C₂H₅OH) 258 mμ (log ε 3.25); ir (neat) 1555 cm⁻¹ (NO₂); nmr (CCl₄) δ 8.6 (m, 2, N=CH), 7.4 (m, 2, N=CHCH), 5.7 (q, 1, CH), and 1.8 (d, 3, CH₃).

Anal. Calcd for C₇H₈N₂O₂: C, 55.25; H, 5.30; N, 18.41. Found: C, 55.35; H, 5.26; N, 18.61.

4-(1-Nitroethyl)pyridinium picrate was prepared in the usual manner:[24] mp 118–120° dec (95% EtOH).

*Anal.* Calcd for C₁₃H₁₁N₅O₉: C, 40.94; H, 2.89; N, 18.37. Found: C, 41.11; H, 3.06; N, 18.27.

2-(Dibromonitromethyl)pyridine.—The following experiment is typical of the procedure employed for the bromination of the salts of α-nitroalkyl heterocyclics. Crude sodium 2-picolylnitronate obtained from the nitration of 7.8 g (0.08 mol) 2-picoline (**1**) was dissolved in 100 ml of water and added in one portion to 0.17 mol of aqueous potassium hypobromite (prepared from 26.9 g of bromine and 22.2 g of 85% assay potassium hydroxide in 100 ml of water) at 0–5°. The solution was extracted with chloroform and dried (Na₂SO₄). The extract was concentrated *in vacuo* and the residue recrystallized from ether–petroleum ether (bp 30–60°) (1:1) to yield 14.2 g (57%) of 2-(dibromonitromethyl)-pyridine: mp 43° (lit.[7] mp 42–43°); ir (KBr) 1575 cm⁻¹ (NO₂); nmr (CCl₄) δ 8.5 (m, 1, N=CH), 7.9 (m, 2, N=CHCH=CHCH), and 7.3 (m, 1, N=CHCH).

4-(Dibromonitromethyl)pyridine (61%): mp 94–97° (95% EtOH); ir (KBr) 1587 cm⁻¹ (NO₂); nmr (CDCl₃) δ 8.8 (m, 2, N=CH) and 7.6 (m, 2, N=CHCH).

Anal. Calcd for C₆H₄Br₂N₂O₂: C, 24.32; H, 1.35; Br, 54.05; N, 9.46. Found: C, 24.59; H, 1.58; Br, 54.15; N, 9.49.

4-(Dibromonitromethyl-2-methylpyridine (**31**) (50%): mp 107° (95% EtOH); ir (KBr) 1575 cm⁻¹ (NO₂); nmr (CDCl₃) δ 8.6 (m, 1, H$_a$), 7.4 (m, 2, H$_b$ + H$_c$), and 2.7 (s, 3, CH₃).
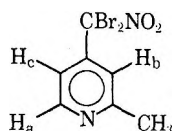
Anal. Calcd for C₇H₆Br₂N₂O₂: C, 27.10; H, 1.94; Br, 51.45; N, 9.03. Found: C, 27.30; H, 2.09; Br, 51.59; N, 8.98.

2-(Dibromonitromethyl)-6-methylpyridine (54%): mp 56–57° (95% EtOH); ir (KBr) 1580 cm⁻¹ (NO₂); nmr (CDCl₃) δ 7.9 (m, 2, H$_a$ + H$_b$), 7.3 (m, 1, H$_c$), and 2.5 (s, 3, CH₃).
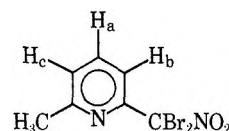
Anal. Calcd for C₇H₆Br₂N₂O₂: C, 27.10; H, 1.94; Br, 51.45; N, 9.03. Found: C, 26.90; H, 2.07; Br, 51.59; N, 8.75.

2-(Dibromonitromethyl)-3-methylpyridine (49%): mp 97° (95% EtOH); ir (KBr) 1590 cm⁻¹ (NO₂); nmr (CDCl₃) δ 8.5 (m, 1, N=CH), 7.3–7.9 (m, 3, N=CHCH=CHCH), and 2.6 (s, 3, CH₃).

Anal. Calcd for C₇H₆Br₂N₂O₂: C, 27.10; H, 1.94; Br, 51.45; N, 9.03. Found: C, 26.82; H, 1.70; Br, 51.70; N, 8.77.

4-(Dibromonitromethyl)-2,6-dimethylpyridine (**20**) (41%): mp 90–94° (chloroform–hexane, 1:1); ir (KBr) 1575 cm⁻¹ (NO₂); nmr (CDCl₃) δ 7.4 (s, 2, ring H) and 2.6 (s, 6, CH₃).

Anal. Calcd for C₈H₈Br₂N₂O₂: C, 29.63; H, 2.47; Br, 49.39; N, 8.64. Found: C, 29.74; H, 2.58; Br, 49.20; N, 8.48.

1-Bromo-1-(4-pyridyl)nitroethane (**30**) (39%): bp 80–82° (0.13 mm); n^{20}D 1.5693; ir (neat) 1575 cm⁻¹ (NO₂); nmr (CCl₄) δ 8.7 (m, 2, N=CH), 7.5 (m, 2, N=CHCH), and 2.6 (s, 3, CH₃).

Anal. Calcd for C₇H₇BrN₂O₂: C, 36.36; H, 3.03; Br, 34.63; N, 12.12. Found: C, 36.40; H, 3.07; Br, 34.52; N, 12.25.

1-Bromo-1-(4-pyridyl)-3-phenylnitropropane (62%): mp 64–66° (95% EtOH); ir (KBr) 1567 cm⁻¹ (NO₂); nmr (CDCl₃) δ 8.9 (m, 2, N=CH), 7.6 (m, 2, N=CHCH), 7.4 (m, 5, C₆H₅), and 2.7–3.3 (m, 4, CH₂CH₂).

Anal. Calcd for C₁₄H₁₃BrN₂O₂: C, 52.34; H, 4.36; Br, 24.92; N, 8.97. Found: C, 52.19; H, 4.28; Br, 25.03; N, 8.69.

2-(Dibromonitromethyl)pyridine N-oxide (71%): mp 181–183° dec (acetone–95% ethanol, 2:1); ir (KBr) 1575 cm⁻¹ (NO₂); nmr (DMSO-d_6) δ 8.3 (m, 2, N=CHCH=CHCH) and 7.4 (m, 2, N=CHCH=CH).

Anal. Calcd for C₆H₄Br₂N₂O₃: C, 23.08; H, 1.28; Br, 51.28; N, 8.97. Found: C, 23.35; H, 1.46; Br, 51.00; N, 8.75.

4-(Dibromonitromethyl)pyridine N-oxide (59%): mp 103–104° dec (chloroform); ir (Nujol) 1577 cm⁻¹ (NO₂); nmr (CDCl₃) δ 8.2 (m, 2, N=CH) and 7.7 (m, 2, N=CHCH).

Anal. Calcd for C₆H₄Br₂N₂O₃: C, 23.08; H, 1.28; Br, 51.28; N, 8.97. Found: C, 23.09; H, 1.21; Br, 51.35; N, 9.18.

4-(Dibromonitromethyl)quinoline (75%): mp 159° (95% ethanol); ir (KBr) 1575 cm⁻¹ (NO₂); nmr (CDCl₃) δ 9.2 and 7.7–8.4 (m, aromatic H).

Anal. Calcd for C₁₀H₆Br₂N₂O₂: C, 34.68; H, 1.73; Br, 46.24; N, 8.09. Found: C, 34.65; H, 1.79; Br, 46.03; N, 7.80.

2-(Dibromonitromethyl)benzoxazole (53%): mp 79° (95% ethanol); ir (KBr) 1553 cm⁻¹ (NO₂); nmr (CDCl₃) δ 7.2–8.0 (m, C₆H₄).

Anal. Calcd for C₈H₄Br₂N₂O₃: C, 28.57; H, 1.19; Br, 47.62; N, 8.33. Found: C, 28.79; H, 1.42; Br, 47.52; N, 8.36.

2-(Dibromonitromethyl)benzothiazole (61%): mp 70° (95% ethanol); ir (KBr) 1575 cm⁻¹ (NO₂); nmr (CDCl₃) δ 7.3–8.2 (m, C₆H₄).

Anal. Calcd for C₈H₄Br₂N₂O₂S: C, 27.27; H, 1.14; Br, 45.45; N, 7.97; S, 9.23. Found: C, 27.24; H, 1.20; Br, 45.42; N, 7.97; S, 9.22.

2-(Dibromonitromethyl)quinoxaline (55%): mp 88° (95% ethanol); ir (KBr) 1587 cm⁻¹ (NO₂); nmr (CDCl₃) δ 9.4 (s, 1, N=CH) and 7.7–8.3 (m, 4, C₆H₄).

Anal. Calcd for C₉H₅Br₂N₃O₂: C, 31.12; H, 1.44; Br, 46.11; N, 12.10. Found: C, 31.32; H, 1.48; Br, 46.38; N, 11.84.

3-(Dibromonitromethyl)pyridine.—The following experiment is typical of the procedure employed for the bromination of α-nitroalkyl heterocyclics. Pure 3-nitromethylpyridine (1.4 g, 0.01 mol) was dissolved in 10 ml of 10% aqueous sodium hydroxide and added in one portion to an aqueous solution of 0.05 mol

potassium hypobromite at 0–5°. The precipitate was filtered and recrystallized from ethanol–water (1:1) to give 3.0 g (100%) of 3-(dibromonitromethyl)pyridine: mp 74–75°; ir (KBr) 1570 cm⁻¹ (NO₂); nmr (CDCl₃) δ 9.1 (m, 1, H$_a$), 8.7 (m, 1, H$_b$), 8.1 (m, 1, H$_c$), and 7.4 (m, 1, H$_d$).
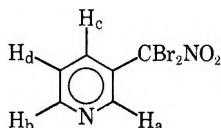
Anal. Calcd for C₆H₄Br₂N₂O₂: C, 24.32; H, 1.35; Br, 54.05; N, 9.46. Found: C, 24.28; H, 1.54; Br, 54.30; N, 9.46.

4-(Dibromonitromethyl)pyrimidine (85%): mp 73–74° (ethanol–water, 1:1); ir (KBr) 1572 cm⁻¹ (NO₂); nmr (CDCl₃) δ 9.1 (s, 1, N=CHN), 8.9 (d, 1, N=CH), and 7.9 (d, 1, N=CH-CH).

Anal. Calcd for C₅H₃Br₂N₃O₂: C, 20.20; H, 1.01; Br, 53.87; N, 14.14. Found: C, 20.28; H, 0.86; Br, 54.12; N, 14.17.

1-(Dibromonitromethyl)isoquinoline (100%): mp 135–136° (95% ethanol); ir (KBr) 1587 cm⁻¹ (NO₂); nmr (CDCl₃) δ 7.5–8.0 and 8.3–8.6 (m, ring H).

Anal. Calcd for C₁₀H₆Br₂N₂O₂: C, 34.68; H, 1.73; Br, 46.24; N, 8.09. Found: C, 34.71; H, 1.71; Br, 46.23; N, 8.00.

4-(Dibromonitromethyl)cinnoline (98%): mp 134° dec (95% ethanol); ir (KBr) 1587 cm⁻¹ (NO₂); nmr (CDCl₃) δ 9.8 (s, 1, N=CH), 8.6–8.9, and 7.8–8.0 (m, 4, C₆H₄).

Anal. Calcd for C₉H₅Br₂N₃O₂: C, 31.12; H, 1.44; Br, 46.11; N, 12.10. Found: C, 31.22; H, 1.65; Br, 46.06; N, 11.82.

2-(Dichloronitromethyl)pyridine.—A solution of 5.4 g (0.03 mol) of pure potassium 2-picolylnitronate (35) in 50 ml of water was added in one portion to 51 ml of aqueous potasssium hypochlorite[28] (prepared from 125 g of 70% calcium hypochlorite (HTH), 87.5 g of potassium carbonate, and 25 g of 85% assay potassium hydroxide) at room temperature. The mixture was extracted with ether and dried (Na₂SO₄), and the extract concentrated *in vacuo*. Distillation of the residue afforded 3.0 g (48%) of 2-(dichloronitromethyl)pyridine: bp 62° (0.05 mm); n^{20}D 1.5519; ir (neat) 1587 cm⁻¹ (NO₂); nmr (CCl₄) δ 8.6 (m, 1, N=CH), 8.0 (m, 2, N=CHCH=CHCH), and 7.4 (m, 1, N=CHCH=CH).

Anal. Calcd for C₆H₄Cl₂N₂O₂: C, 34.80; H, 1.93; Cl, 34.27; N, 13.53. Found: C, 34.93; H, 2.15; Cl, 34.48; N, 13.58.

1-Chloro-1-(4-pyridyl)nitroethane.—Crude potassium 1-(4-pyridyl)ethanenitronate prepared from 17.8 g (0.17 mol) of 4-ethylpyridine was dissolved in 300 ml of water and the solution saturated with chlorine at −10°. The solution was basified with 10% sodium hydroxide solution and extracted with chloroform. The extract was dried (MgSO₄) and concentrated *in vacuo*. The residue was distilled to give 19.5 g (63%) of 1-chloro-1-(4-pyridyl)-nitroethane: bp 65–67° (10⁻³ mm); n^{20}D 1.5393; ir (neat) 1575 cm⁻¹ (NO₂); nmr (CCl₄) δ 8.7 (m, 2, N=CH), 7.5 (m, 2, N=CHCH), and 2.5 (s, 3, CH₃).

Anal. Calcd for C₇H₇ClN₂O₂: C, 45.16; H, 3.76; Cl, 19.06; N, 15.05. Found: C, 45.39; H, 3.79; Cl, 19.08; N, 15.23.

Potassium 3-Picolylnitronate (36).—A solution of 2.3 g (0.017 mol) of pure 3-nitromethylpyridine in 10 ml of absolute ethanol was added in one portion to a solution of 0.018 mol of potassium ethoxide in 50 ml of absolute ethanol. The solution was poured into 200 ml of absolute ether and the precipitate filtered to give 2.6 g (89%) of potassium 3-picolylnitronate: mp 235° dec (isopropyl alcohol); uv max (95% C₂H₅OH) 315 mμ (log ε 4.36); ir (KBr) 1543 cm⁻¹ (C=NO₂⁻); nmr (D₂O) δ 8.6 (m, 1, H$_a$), 8.2 (m, 2, H$_b$ + H$_c$), 7.3 (m, 1, H$_d$), and 7.0 (s, 1, CH).
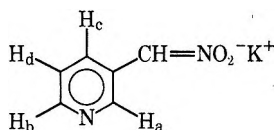
Anal. Calcd for C₆H₅KN₂O₂: C, 40.91; H, 2.84; K, 22.21; N, 15.91. Found: C, 40.64; H, 3.11; K, 22.02; N, 15.77.

4-(Bromonitromethyl)-2-methylpyridine (32).—4-(Dibromonitromethyl)-2-methylpyridine (31) (5.0 g, 0.016 mol) was dissolved in 300 ml of liquid ammonia at −33°. After 10 min the ammonia was gradually replaced with absolute ether and the mixture filtered after room temperature was attained. Then the solid was dissolved in 50 ml of water and acidified with 1.0 g of glacial acetic acid at room temperature. Filtering the precipitate afforded 3.1 g (83%) of 4-(bromonitromethyl)-2-methylpyridine: mp 116–117° dec (95% ethanol); uv max (95% C₂H₅OH) 271 mμ (log ε 3.44) and 419 (3.18); ir (KBr) 3636–1818 (=N⁺H) and 1481 cm⁻¹ (C=NO₂⁻); nmr (DMSO-d_6) δ 8.6 (s, 1, NH), 7.8 (m, 1, H$_a$), 7.5 (m, 2, H$_b$ + H$_c$), and 2.5 (s, 3, CH₃).
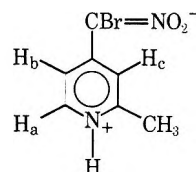
Anal. Calcd for C₇H₇BrN₂O₂: C, 36.36; H, 3.03; Br, 34.63; N, 12.12. Found: C, 36.60; H, 3.08; Br, 34.80; N, 11.89.

2-Pyridylhydroxamyl Chloride N-Oxide (23).—Crude 2-nitromethylpyridine N-oxide (21) (1.1 g, 0.007 mol) was covered with 7.5 ml of benzoyl chloride and the mixture warmed gently on a steam bath. The white precipitate was slurried in ether, filtered and washed with water to yield 1.8 g (92%) of 2-pyridylhydroxamyl chloride N-oxide: mp 187–188° (95% ethanol); ir (KBr) 1764 cm⁻¹ (C=O); nmr (CDCl₃) δ 8.0–8.4 and 7.2–7.7 (m, ring H).

Anal. Calcd for C₁₃H₉ClN₂O₃: C, 56.52; H, 3.26; Cl, 12.84; N, 10.14. Found: C, 56.43; H, 3.53; Cl, 13.05; N, 9.92.

Determination of Acidity Constants.—Samples (0.1 g) of nitronate salt were dissolved in 20 ml of carbon dioxide free water and titrated under nitrogen with 0.04 M hydrochloric acid. The pK_a values were determined by plotting the volume of titrant against the pH which was read directly from a Beckman Zeromatic pH meter. The pK_a values are tabulated in Table IV.

Registry No.—4, 22918-12-3; 10, 22918-11-2; 12, 22918-10-1; 14, 22918-07-6; 15, 35624-30-7; 15 picrate, 35624-31-8; 16, 22918-09-8; 18, 35624-32-9; 19, 35589-59-4; 19 picrate, 35589-60-7; 20, 35624-33-0; 21, 35624-34-1; 23, 35624-35-2; 25, 35624-36-3; 27, 35624-37-4; 27 picrate, 35624-38-5; 30, 35624-39-6; 32, 35624-40-9; 33, 22918-06-5; 34, 3243-07-0; 35, 35624-43-2; 36, 35624-44-3; 37, 22918-08-7; 37 picrate, 35624-46-5; 1-nitromethylisoquinoline, 35624-47-6; 2-nitromethyl-thiazoline, 35624-48-7; 5-ethyl-2-nitromethylpyridine, 24998-78-5; 5-ethyl-2-nitromethylpyridinium picrate, 35624-50-1; potassium 2-quinaldylnitronate, 35624-51-2; 4-nitromethylpyrimidine, 35624-52-3; 4-nitromethylquinoxaline, 35624-53-4; 4-nitromethylcinnoline, 35624-54-5; 4-(dibromonitromethyl)pyridine, 35624-55-6; 2-(dibromonitromethyl)-6-methylpyridine, 35624-56-7; 2-(dibromonitromethyl)-3-methylpyridine, 35624-43-2; 1-bromo-1-(4-pyridyl)-3-phenylnitropropane, 35624-58-9; 2-(dibromonitromethyl)pyridine N-oxide, 22918-13-4; 4-(dibromonitromethyl)pyridine N-oxide, 35624-60-3; 4-(dibromonitromethyl)quinoline, 35619-67-1; 2-(dibromonitromethyl)benzoxazole, 35619-68-2; 2-(dibromonitromethyl)benzothiazole, 35619-69-3; 2-(dibromonitromethyl)quinoxaline, 35619-70-6; 3-(dibromonitromethyl)pyridine, 35619-71-7; 4-(dibromonitromethyl)pyrimidine, 35619-72-8; 1-

(28) A. I. Vogel, "A Textbook of Practical Organic Chemistry," 3rd ed, Wiley, New York, N. Y., 1962, p 461.

(dibromonitromethylisoquinoline, 35619-73-9; 4-(dibromonitromethyl)cinnoline, 35619-74-0; 2-(dichloronitromethyl)pyridine, 35619-75-1; 1-chloro-1-(4-pyridyl)nitroethane, 35619-76-2; 4-(bromonitromethyl)-2-methylpyridine, 35619-77-3.

The Free-Radical Addition of *tert*-Butyl Hypochlorite to Some Bridged Polycyclic Olefins

PETER K. FREEMAN* AND R. S. RAGHAVAN

Department of Chemistry, Oregon State University, Corvallis, Oregon 97331

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Irradiation of *tert*-butyl hypochlorite and *endo*-tricyclo[3.2.1.0²,⁴]oct-6-ene in carbon tetrachloride at 40° produces a 59% yield of *exo*-6-*tert*-butoxy-*endo*-7-chloro-*endo*-tricyclo[3.2.1.0²,⁴]octane and *exo*-6-*tert*-butoxy-*exo*-7-chloro-*endo*-tricyclo[3.2.1.0²,⁴]octane in a ratio of 43:57, while similar treatment of *tert*-butyl hypochlorite and *exo*-tricyclo[3.2.1.0²,⁴]oct-6-ene results in a 56% yield of trans adduct, *exo*-6-*tert*-butoxy-*endo*-7-chloro-*exo*-tricyclo[3.2.1.0²,⁴]octane, and cis adduct, *exo*-6-*tert*-butoxy-*exo*-7-chloro-*exo*-tricyclo[3.2.1.0²,⁴]octane, in a ratio of 78:22. Similar photolytic treatment of *tert*-butyl hypochlorite and deltacyclene generates *exo*-8-*tert*-butoxy-*endo*-9-chlorodeltacyclane and *exo*-8-*tert*-butoxy-*exo*-9-chlorodeltacyclane in a ratio of 85:15 in an overall yield of 37%. The stereochemistry of the chain transfer step of the intermediate *tert*-butoxycycloalkyl radicals and the lack of cyclopropylethyl radical rearrangement are rationalized as a result of predominant 1,2 addition taking place by way of classical *tert*-butoxycycloalkyl intermediates.

Recently we have reported that radical chlorination of *exo*-tricyclo[3.2.1.0²,⁴]octane with *tert*-butyl hypochlorite results in abstraction of hydrogen from C-6 and C-1 to generate *exo*- and *endo*-6-chloro-*exo*-tricyclo[3.2.1.0²,⁴]octane (2) and 1-chloro-*exo*-tricyclo[3.2.1.0²,⁴]octane (3), while, in contrast, radical chlorination of *endo*-tricyclooctane 4 results in 93% or greater
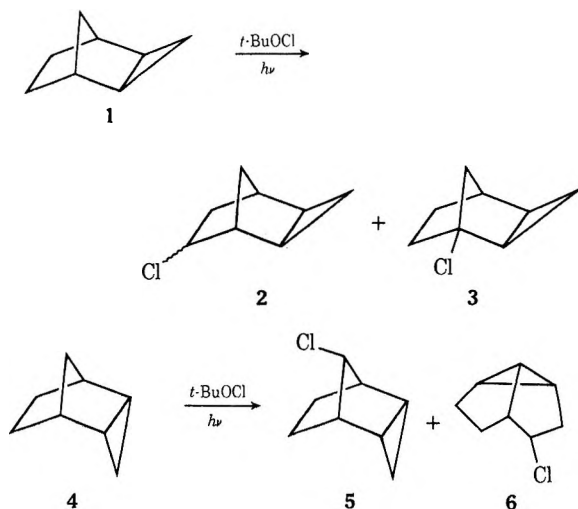
abstraction of hydrogen at C-8, leading to *anti*-8-chlorotricyclooctane 5 and *endo*-2-chlorotricyclo[3.3.0.0⁴,⁶]octane (6).[1]

Since several unique aspects of *tert*-butoxy abstraction in these tricyclooctane ring systems have been at least partially revealed, it appeared to be of some interest to pursue a complementary line of research to gain additional insight into the nature of related radical intermediates. Tobler and coworkers[2] have shown that the radical reaction of *tert*-butyl hypochlorite with norbornene results in both addition and sub-

stitution, addition predominating. Therefore, we chose to investigate the analogous reaction of *tert*-butyl hypochlorite with *exo*-tricyclo[3.2.1.0²,⁴]oct-6-ene (7), *endo*-tricyclo[3.2.1.0²,⁴]oct-6-ene (8), and deltacyclene (9). Abstraction reactions are of interest in each case, since there is the potential for anchimeric assistance to abstraction of the bishomocyclopropenyl (abstraction at a in 7 and 8) and trishomocyclopropenyl type (abstraction at b in 8), while abstraction at c in 9 could produce an interesting degenerate 5-deltacyclenyl radical. Addition of *tert*-butoxy to the double bond of 7 or 9 would generate a radical intermediate analo-

gous to the major intermediate in the abstraction reaction of 1, while addition to *endo*-tricyclooctene 8 would yield a radical we have been unable to characterize in the radical chlorination of 4, due to the predominance of C-8 abstraction.
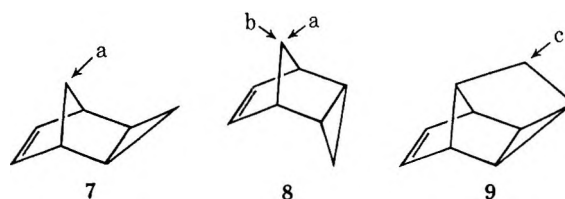
Results

When *endo*-tricyclooctene 8 was irradiated with *tert*-butyl hypochlorite using a 2:1 molar ratio of olefin to *tert*-butyl hypochlorite in carbon tetrachloride solution at 40°, the products on vpc analysis were found to consist of two components in a ratio of 43:57 in the order of increasing retention times, in an overall yield of 59%. The retention times of the two components were much longer than expected for monochlorides, suggesting the possibility that free-radical adducts had been formed. Since the monochloride region in the chromatogram was conspicuously free of peaks, hydrogen abstraction did not compete with addition.

(1) P. K. Freeman, R. S. Raghavan, and G. L. Fenwick, *J. Amer. Chem. Soc.*, **94**, 5101 (1972).

(2) E. Tobler, D. E. Battin, and D. J. Foster, *J. Org. Chem.*, **29**, 2834 (1964).

The ir spectrum of the 43% component shows weak bands at 3096 and 3040 cm^{-1} (cyclopropane methylene), while the nmr spectrum (100 MHz, CCl$_4$) exhibits resonance signals at τ 6.24 (doublet of a triplet, J = 3.4, 0.7 Hz, HCCl), 6.58 (broad, poorly resolved multiplet, $W_{1/2}$ = 5 Hz, HCO-*t*-Bu), 7.5 (envelope, 1 H), 7.9 (envelope, 1 H), 8.0 (broad singlet, 2 H), 8.28 (a pair of overlapping triplets, J = 7, 3 Hz, 1 H), 8.55–8.75 (multiplet, 2 H), 8.82 (singlet, 9 H), and 9.03 (multiplet, 1 H). The spectrum is consistent with the structure of the trans adduct, *exo*-6-*tert*-butoxy-*endo*-7-chloro-*endo*-tricyclo[3.2.1.0^{2,4}]octane (**10**).

The ir spectrum of the 57% component exhibits peaks characteristic of cyclopropane methylene at 3080 and 3032 cm^{-1}, while in the nmr spectrum (100 MHz, CCl$_4$) signals at τ 6.36 (doublet of a doublet, J = 5.6, 1.7 Hz, HCCl), 6.68 (doublet of a doublet, J = 5.6, 1.7 Hz, HCO-*t*-Bu), 7.68 (envelope, 1 H), 7.73 (A component of an AB pattern, J = 9.5 Hz, 1 H), 7.92 (envelope, 1 H), 8.15 (multiplet of the B doublet of the AB pattern, J = 9.5 Hz, 1 H), 8.60–8.80 (multiplet, 2 H), 8.82 (singlet, 9 H), and 9.0–9.35 (complex multiplet, 2 H) are observed. The spectrum is consistent with the structure of the cis adduct, *exo*-6-*tert*-butoxy-*exo*-7-chloro-*endo*-tricyclo[3.2.1.0^{2,4}]octane (**11**).

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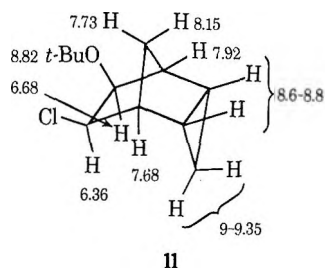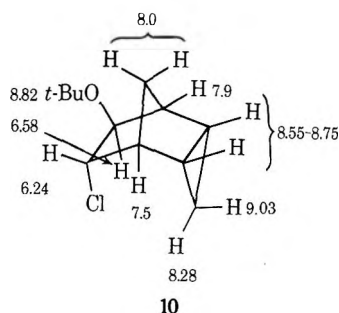
A convenient verification of these structural assignments was possible through tri-*n*-butyltin hydride reduction[3] of the two adducts. Radical reduction of both of the adducts followed by vpc analysis showed that the same exclusive product, *exo*-6-*tert*-butoxy-*endo*-tricyclo[3.2.1.0^{2,4}]octane (**12**), resulted from both in yields of 75% from the trans adduct and 97% from the cis adduct. The ir spectrum of the product from both the adducts showed absorptions at 3064 and 3016 cm^{-1} while the nmr spectrum (100 MHz, CCl$_4$) exhibited signals at τ 6.74 (doublet of a doublet, J = 6.4, 3.0 Hz, HCO-*t*-Bu), 7.8 (unresolved multiplet, 1 H, the bridgehead proton β to *tert*-butoxy), 8.0 (unresolved multiplet, 1 H, the other bridgehead proton), 8.2 (broad singlet, 2 H, the C-8 protons), 8.6–8.85 (complex multiplets, 4 H, the protons on C-7, C-2, and C-4), 8.9 (singlet, 9 H, the *tert*-butoxy protons),

(3) H. G. Kuivila, *Accounts Chem. Res.*, **1**, 299 (1968).

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12   **10**
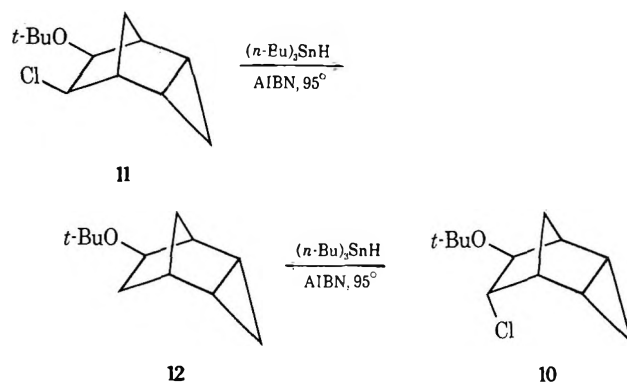
and 9.1–9.45 (complex multiplets, 2 H, the C-3 protons). The spectrum showed a striking similarity to that of *exo*-3-hydroxy-*endo*-tricyclo[3.2.1.0^{2,4}]octane.

The irradiation of a solution of *exo*-tricyclooctene **7** and *tert*-butylhypochlorite in carbon tetrachloride at 40° resulted in the formation of two adducts in 56% yield in the ratio 78:22 in the order of increasing retention times. These two components were identified as the trans and the cis adducts on the basis of their spectral data. The ir spectrum of the trans adduct showed bands attributable to a cyclopropane ring (3088 and 3032 cm^{-1}), while the nmr spectrum (100 MHz, CCl$_4$) exhibited resonance signals at τ 6.23 (doublet of a doublet, J = 2.9, 2.0 Hz, HCCl), 6.61 (triplet, J = 2.0 Hz, HCO-*t*-Bu), 7.63 (unresolved multiplet, 1 H, the bridgehead proton β to chlorine), 7.94 (singlet, 1 H, the bridgehead proton β to *tert*-butoxy), 8.5–8.9 (multiplets with a large singlet at 8.86, 11 H, the anti C-8 proton, the C-2 proton, and O-*t*-Bu), 9.08 (a poorly resolved multiplet of a doublet of an AB pattern, J = 12 Hz, the syn C-8 proton), 9.2–9.5 (multiplets, the C-4 and the syn C-3 protons), and 9.65–9.92 (a quartet, J = 7 Hz, the anti C-3 proton) (structure **13**). The ir

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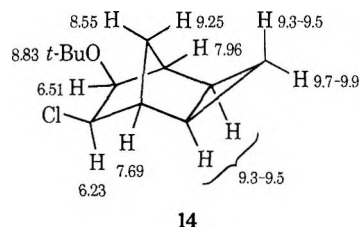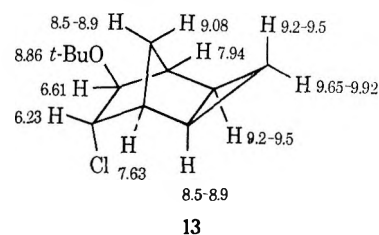
spectrum of the cis adduct showed characteristic bands at 3092 and 3032 cm^{-1} (cyclopropane methylene stretching), while the nmr spectrum (100 MHz, CCl$_4$) showed resonance signals at τ 6.23 (doublet of a doublet, J = 6.0, 2.3 Hz, HCCl), 6.51 (doublet of a doublet, J = 6, 1.9 Hz, HCO-*t*-Bu), 7.69 (singlet, 1 H, the bridgehead proton β to chlorine), 7.96 (singlet, 1 H, the bridgehead proton β to *tert*-butoxy), 8.55 (a doublet of an AB pattern, J = 11 Hz, the anti C-8 proton), 8.83 (a large singlet, 9 H, the *tert*-butoxy protons), 9.25 (an unresolved multiplet of a doublet of an AB pattern, J = 11 Hz, the syn C-8 proton), 9.3–9.5

(multiplet, 3 H, the C-2, C-4, and the syn C-3 protons), and 9.7–9.9 (multiplet, the anti C-3 proton) (structure 14). In addition vpc analysis indicated that no monochlorides were formed (<1%).

Both the trans and the cis adducts on reduction with tri-*n*-butyltin hydride at 95° (AIBN initiation) gave exclusively *exo*-6-*tert*-butoxy-*exo*-tricyclo[3.2.1.0²,⁴]octane (15). The ir spectrum of the tricyclic *tert*-butyl
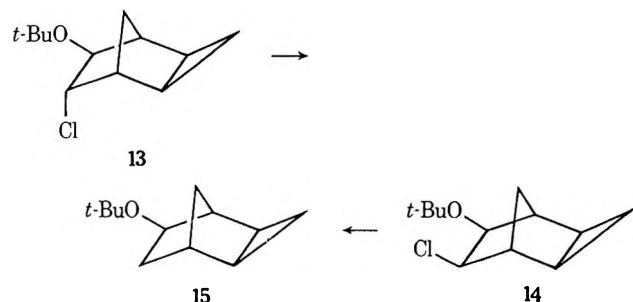
ether shows bands at 3092 and 3016 cm⁻¹, while the nmr spectrum (100 MHz, CCl₄) exhibits resonance signals at τ 6.54 (doublet of a doublet of a doublet, $J = 7.0, 3, 1$ Hz, HCO-*t*-Bu), 7.87 (poorly resolved multiplet, 1 H, the C-1 proton), 7.95 (singlet, 1 H, the bridgehead proton β to *tert*-butoxy), 8.35 (a doublet of an AB pattern split additionally by 2 H, $J = 12.5, 7.0, 2.2$ Hz, the endo C-7 proton), 8.75 (a doublet of an AB pattern split into a pair of triplets, $J = 12.5, 3$ Hz, the exo C-7 proton), 8.86 (singlet, 9 H, O-*t*-Bu), 8.96 (doublet of an AB pattern, $J = 12$ Hz, the anti C-8 proton), 9.28 (a doublet of an AB pattern, $J = 12$ Hz, with additional splitting by *ca.* 1 Hz, the syn C-8 proton), 9.35–9.6 (multiplet, 3 H, the C-2 and C-4 protons and the syn C-3 proton), and 9.85–10.09 (multiplet, 1 H, the anti C-3 proton). The spectrum shows a remarkable resemblance to that of *exo*-6-hydroxy-*exo*-tricyclo[3.2.1.0²,⁴]octane.

A similar picture emerged from the irradiation of a solution of deltacyclene (9) with *tert*-butyl hypochlorite under conditions identical with those employed for the exo and endo tricyclooctene. The product fraction was found by vpc analysis to consist of two components, the trans and the cis adducts in the ratio 85:15, in a yield of 37%. No significant amounts of monochlorides (>2% could have been detected) were observable. The ir spectrum of the trans adduct shows the presence of a cyclopropane ring (a weak band at 3056 cm⁻¹) and a nortricyclene ring (a strong band at 800 cm⁻¹), while the nmr spectrum (100 MHz, CCl₄) exhibits signals at τ 6.07 (doublet of a doublet, $J = 4.0, 2.0$ Hz, HCCl), 6.24 (poorly resolved doublet, $J = 2$ Hz, HCO-*t*-Bu), 7.8 (unresolved multiplet, the bridgehead proton β to chlorine), 7.88 (unresolved multiplet, the bridgehead proton β to *tert*-butoxy), 8.15 (unresolved triplet, the C-6 proton), 8.42 (singlet, 2 H, the C-5 protons), 8.74 (singlet, 2 H, the C-2 and C-3 protons), 8.82 (singlet, 9 H, *tert*-butoxy protons), 9–9.15 (a multiplet, the C-4 proton), consistent with 22 (endo Cl). The cis adduct was contaminated to the extent of 32% by an unidentified, inseparable material. The ir spectrum shows bands at 3056 (cyclopropane) and 800 cm⁻¹ (nortricyclene ring), and the nmr spectrum (100 MHz, CCl₄) exhibits signals at τ 5.9 (doublet, $J = 6$ Hz) and 6.15 (doublet, $J = 6$ Hz).

Both the adducts on reduction with tri-*n*-butyltin hydride at 95° gave the same product, *exo*-8-*tert*-butoxydeltacyclane (22, Cl = H). The cis adduct, in addition to this ether, gave 32% of an unidentified product, probably due to its contaminant. The ir spectrum of 22 (Cl = H) shows the presence of a cyclopropane ring (3056 cm⁻¹) and a nortricyclene skeleton (798 cm⁻¹), while the nmr spectrum (100 MHz, CCl₄) contains resonance signals at τ 6.2 (doublet with additional poorly resolved splitting, $J = 6.6$ Hz, HCO-*t*-Bu), 8.0–8.25 (a series of poorly resolved multiplets, 4 H, the bridgehead C-1 and C-7 protons, the endo proton on C-9, and the C-6 proton), 8.46 (sharp singlet with poorly resolved adjacent multiplet, 3 H, the C-5 and exo C-9 protons), 8.85 (a large singlet with a poorly resolved multiplet buried under it, 10 H, O-*t*-Bu and the C-4 proton), and 9.25 (multiplet, 2 H, the C-2, C-3 cyclopropyl protons). The spectrum shows marked similarity to that of *exo*-8-hydroxydeltacyclane.

Discussion

In each case, irradiation of solutions of *tert*-butyl hypochlorite and polycyclic alkene in carbon tetrachloride result exclusively in 1,2 addition of the elements of *tert*-butyl hypochlorite. It seems reasonably certain, therefore, that the addition proceeds by a radical process, analogous to that suggested by Tobler for the addition of *tert*-butyl hypochlorite to norbornene,² since extensive rearrangement has been observed upon generation of the 6-*endo*-tricyclo[3.2.1.0²,⁴]octyl,⁴ 6-*exo*-tricyclo[3.2.1.0²,⁴]octyl,⁴,⁵ and 8-deltacyclyl⁶ carbonium ions.⁷ Since, as noted above, it was not possible to characterize the 6-*endo*-tricyclo[3.2.1.0²,⁴]octyl radical in our investigation of abstraction reactions of 4, the radical 16 generated by *tert*-
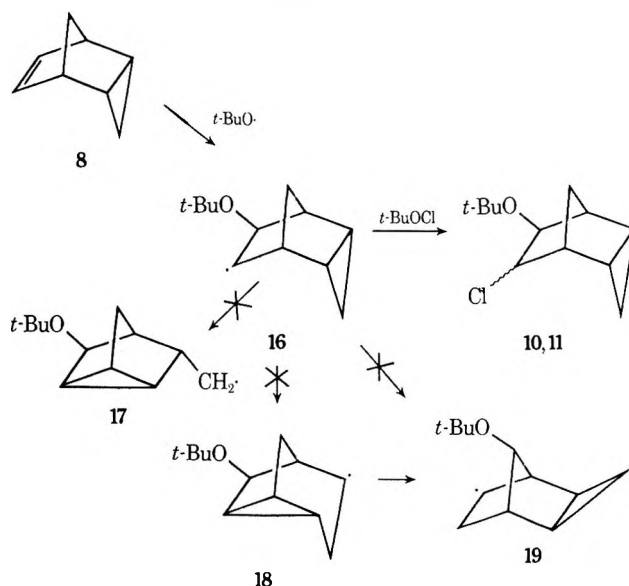
(4) G. D. Sargent, M. J. Harrison, and G. Khoury, *J. Amer. Chem. Soc.*, **91**, 4937 (1969); K. B. Wiberg and G. R. Wenzinger, *J. Org. Chem.*, **30**, 2278 (1965).

(5) J. A. Berson, R. G. Bergman, G. M. Clarke, and D. Wege, *J. Amer. Chem. Soc.*, **90**, 3236 (1968); R. R. Sauers, J. A. Beisler, and H. Feilich, *J. Org. Chem.*, **32**, 569 (1967); A. K. Colter and R. C. Musso, *ibid.*, **30**, 2462 (1965); R. R. Sauers and J. A. Beisler, *Tetrahedron Lett.*, 2181 (1964).

(6) P. K. Freeman, D. M. Balls, and J. N. Blazevich, *J. Amer. Chem. Soc.*, **92**, 2051 (1970).

(7) The evidence for a radical process is qualitative only and rests principally on the lack of skeletal rearrangements and lack of stereospecificity found in the addition processes. No quantum yields were determined.

butoxy addition is of considerable interest. The observation of a cyclopropylethyl radical rearrangement in the chlorination of *endo*-tricyclooctane **4** suggests, *a priori*, that one might expect interaction and/or rearrangement involving either the C-2–C-3 or C-2–C-4 cyclopropane bonds. Rearrangement using the C-2–C-3 bond would produce the nortricyclylmethyl radical **17**, while rearrangement *via* fission of the C-2–C-4 bond would result in the tricyclo[3.2.1.0^{2,7}]octyl radical **18** and/or the 6-*exo*-tricyclo[3.2.1.0]octyl radical **19** (equivalent to a Wagner–Meerwein rearrangement). Since the chlorides related to these radicals are clearly not formed, as evidenced by the nmr spectra of the addition products, the results are explained by chlorine atom transfer to the radical center at C-6 to produce cis,exo (**11**) and trans (**10**) adducts in a ratio of 57:43. A comparison with the 3-*tert*-butoxy-2-norbornyl radical, which undergoes chain transfer to generate a 1:4 ratio of cis and trans addition products,[2] suggests that the addition of the endo-fused cyclopropane ring provides steric shielding for endo approach, which balances the steric shielding of the exo *tert*-butoxy group. The fact that no monochlorides were formed demonstrates that hydrogen abstraction, even with trishomocyclopropenyl assistance, cannot compete with radical addition to a strained double bond.

Radical addition of *tert*-butyl hypochlorite to *exo*-tricyclooctene **7** proceeds *via* *tert*-butoxytricyclooctyl radical **20** with chlorine atom transfer to C-6, yielding
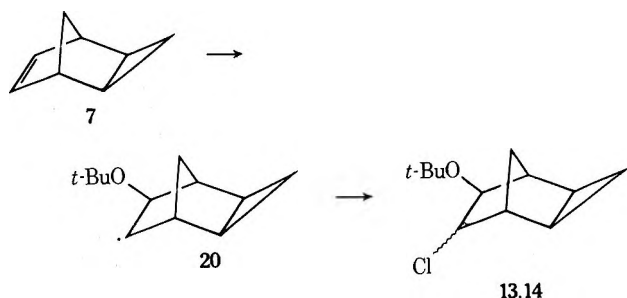
cis,exo (**14**) and trans (**13**) addition products in a ratio of 22:78. Rearrangements involving the C-2–C-3 and C-2–C-4 cyclopropane bonds can be ruled out by consideration of the spectral data of the addition products. The ratio of exo to endo attack of *tert*-butyl hypochlorite on *exo*-tricyclooctyl radical **20** is quite similar to that of the 3-*tert*-butoxy-2-norbornyl radical, as expected.

Radical addition of *tert*-butyl hypochlorite to deltacyclene (**9**) was considered in order to obtain additional evidence which would provide either reinforcement for, or an interesting contrast to, the data on addition to *exo*- and *endo*-tricyclooctene. In the case of addition to deltacyclene, a cyclopropylethyl radical rearrangement involving the C-3–C-4 cyclopropane bond is more likely than in addition to **7**, since it involves a rearrangement of a secondary radical to a secondary radical, in contrast to the secondary to primary process anticipated for **20**. Such a process would be analogous to that observed in the case of the 8-deltacyclyl carbonium ion[6] and would generate the 5-*tert*-butoxy-8-deltacyclyl radical (**23**). Reduction of the monochloride(s) **25** formed from **23** with tri-*n*-butyltin hydride would have produced 5-*tert*-butoxydeltacyclane

(**25**, Cl = H). That this route was not utilized, at least to an extent of 95% or greater (the uncertainty being due to the unknown contaminant present to an extent of 5%), was established by nmr spectral comparison of product *tert*-butyl ether with an authentic sample of 5-*tert*-butoxydeltacyclane.[8]

A cyclopropylethyl rearrangement involving the C-2–C-3 bond would result in radical **24**, with chain transfer producing chlorides **26**. Since the *tert*-butyl hypochlorite adducts labeled as trans and cis above exhibit splitting in the nmr for hydrogen α to chlorine (trans adduct, doublet of a doublet, $J = 4.0, 2.0$ Hz; cis adduct, doublet, $J = 6$ Hz), it is clear that neither is the expected major rearranged epimer (**26**, exo Cl), for **26** (exo Cl) should exhibit an unsplit HCCl in the nmr.[9] The hydrogen α to chlorine in the endo epimer **26** (endo Cl) would be expected to be split (HCCl in **26**, endo Cl, O-*t*-Bu = 0 appears as a doublet of a doublet, $J = 8, 2$ Hz),[9] so that **26** (endo Cl) might be considered as a structural possibility. This appears highly unlikely, however, since we have demonstrated above that an endo fused cyclopropane ring provides steric shielding of the endo face of radical **16**, and thus the ratio of exo to endo chain transfer for radical **24** should be enhanced (>7:1)[10] over that expected for norbornyl and one would not expect to observe **26** (endo Cl) if **26** (exo Cl) is not observed. Moreover, tri-*n*-butyltin hydride reduction of both major *tert*-butyl hypochlorite adducts to the same *tert*-butyl ether strongly suggests that the adducts are epimers. Thus, addition proceeds *via* **21** to exo,endo epimers **22**.

In summary, we find that the irradiation of *tert*-butyl hypochlorite in the presence of *endo*-tricyclooctene **8**, *exo*-tricyclooctene **7**, and deltacyclene (**9**) results in radical addition of *tert*-butoxy, which produces a classical radical, which, in turn, undergoes chain transfer to form *tert*-butyl hypochlorite adduct, a step which appears to be simply controlled by steric factors. There is no evidence for participation of the cyclopropane bonds in cyclopropylethyl rearrangements, and the radical addition to the strained alkene double bond, in each case, is rapid enough to mask all hydrogen abstraction reactions, anchimerically assisted or not.

Experimental Section

(8) We express our appreciation to Professor P. v. R. Schleyer for providing us with nmr spectral data for 5-*tert*-butoxydeltacyclane.

(9) Related derivatives, **26** (exo Cl, *t*-BuO = =O), **26** (Cl = exo OAc, *t*-BuO = =O), and **26** (Cl = exo OAc, *t*-BuO = H) show a singlet for the corresponding proton α to Cl in the first case and α to OAc in the latter two cases; in contrast the epimeric hydrogen appears as a doublet of a doublet: B. K. Stevenson and D. H. Jones, unpublished observations.

(10) P. D. Bartlett, G. N. Fickes, F. C. Haupt, and R. Helgeson, *Accounts Chem. Res.*, **3**, 177 (1970).
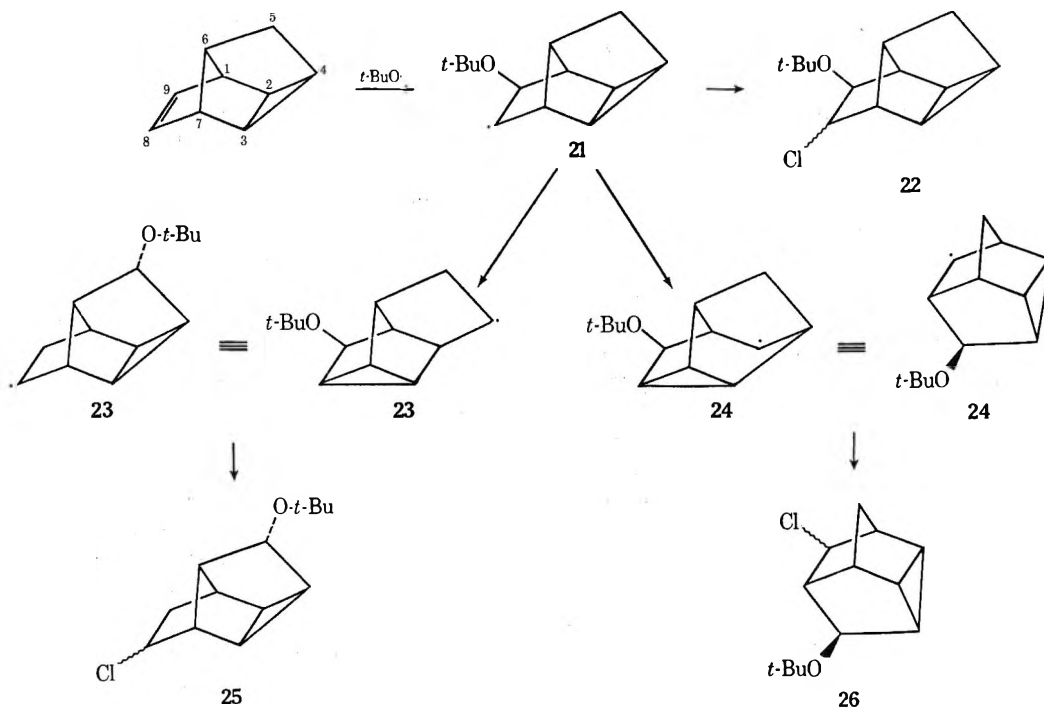
minimum column containing 15% QF-1 on Anakrom 70-80 ABS; (2) 28 ft × 0.25 in. aluminum column containing 9% FFAP on Anakrom 70–80 ABS.

Reaction of *exo*-Tricyclo[3.2.1.0²,⁴]oct-6-ene with *tert*-Butyl Hypochlorite.—The title olefin (1.40 g, 13.2 mmol) was dissolved in 4 ml of carbon tetrachloride in a flask provided with a reflux condenser, a drying tube, and a magnetic stirrer. The flask was covered with aluminum foil to avoid exposure to light. After addition of *tert*-butyl hypochlorite (0.71 g, 6.5 mmol), the foil was removed and the flask was placed in a 40 ± 2° bath and irradiated for 20 min with a 300-W Sylvania light bulb from a distance of 1 in. After partial removal of volatile components at reduced pressure (20 mm), the mixture (1.37 g) was analyzed by vpc (column 1, 140°, 40 ml/min). The product mixture contained two components in the ratio of 78:22 (in the order of increasing retention times) in a yield of 56%.

The 78% component was identified as *exo*-6-*tert*-butoxy-*endo*-7-chloro-*exo*-tricyclo[3.2.1.0²,⁴]octane (trans adduct) on the basis of its spectral data: ir (neat) 3088 and 3032 (w, cyclopropane C–H stretching), 1190 (s), 1116 (s), 1064 (s), 1030 (s) (C–O stretching region), 806 (s) and 755 cm⁻¹ (m) (C–Cl stretching region); nmr (100 MHz, CCl₄) τ 6.22 (poorly resolved doublet of doublet, J = 2.9, 2.0 Hz, HCCl), 6.61 (triplet, J = 2.0 Hz, HCO-*t*-Bu), 7.63 (unresolved multiplet, bridgehead proton β to chlorine), 7.94 (singlet, the bridgehead proton β to *tert*-butoxy), 8.5–8.9 (multiplets with a large singlet at 8.86, 11 H, the anti C-8 proton, the *tert*-butoxy protons, and the C-4 proton), 9.08 (a poorly resolved multiplet of a doublet of an AB pattern, J = 12 Hz, the syn C-8 proton), 9.2–9.5 (multiplets, the C-2 proton and the syn C-4 proton), and 9.65–9.92 (a quartet, J = 7 Hz, the anti C-3 proton).

Anal. Calcd for C₁₂H₁₉OCl: C, 67.13; H, 8.92. Found: C, 67.29; H, 9.07.

The 22% component was identified as *exo*-6-*tert*-butoxy-*exo*-7-chloro-*exo*-tricyclo[3.2.1.0²,⁴]octane (cis adduct) on the basis of its spectral data: ir (neat) 3092 (w) and 3032 (s), both assignable to cyclopropane C–H stretching, 1195 (s), 1110 (s), 1090 (s), 1080 (s), 1030 (s) (C–O stretching, region), 745 (s), 712 cm⁻¹ (s) (C–Cl stretching region); nmr (100 MHz, CCl₄), τ 6.23 (doublet of a doublet, J = 6.0, 2.3 Hz, HCCl), 6.51 (doublet of a doublet, J = 6, 1.9 Hz, 1 H, HCO-*t*-Bu), 7.69 (singlet, 1 H, the bridgehead proton β to chlorine), 7.96 (singlet, 1 H, the bridgehead proton β to *tert*-butoxy), 8.55 (a doublet of an AB pattern, J = 11 Hz, the anti C-8 proton), 8.83 (a large singlet, 9 H, the *tert*-butoxy protons), 9.25 (an unresolved multiplet of a doublet of an AB pattern, J = 11 Hz, the syn C-8 proton), 9.3–9.5 (multiplet, 3 H, the C-2, C-4, and syn C-3 protons), and 9.7–9.9 (multiplet, the anti C-3 proton).

Anal. Calcd for C₁₂H₁₉OCl: C, 67.13; H, 8.92. Found: C, 67.05; H, 8.72.

Reduction of the Trans Adduct, *exo*-6-*tert*-Butoxy-*endo*-7-chloro-*exo*-tricyclo[3.2.1.0²,⁴]octane, with Tri-*n*-butyltin Hydride.—A sample of the trans adduct (0.12 g, 0.56 mmol) was combined with tri-*n*-butyltin hydride (0.17 g, 0.58 mmol) and a crystal of AIBN in a small tube, and the tube was sealed and placed in a 95° bath. After 12 hr the tube was cooled and opened and the contents were analyzed by vpc (column 2, 155°, 40 ml/min). There was only one product, estimated to be formed in a yield of ca. 90%. The product was identified as *exo*-6-*tert*-butoxy-*exo*-tricyclo[3.2.1.0²,⁴]octane on the basis of its spectral data and the similarity of its nmr spectrum to that of *exo*-6-hydroxy-*exo*-tricyclo[3.2.1.0²,⁴]octane: ir (neat) 3092 (w), 3016 (m) (cyclopropane C–H stretching), 1195 (s), 1185 (s), 1155 (s), 1088 (s), 1060 (s), 1025 cm⁻¹ (s) (C–O stretching region); nmr (100 MHz, CCl₄) τ 6.54 (doublet of a doublet of a doublet, J = 7.0, 3, 1 Hz, HCO-*t*-Bu), 7.87 (poorly resolved multiplet, the bridgehead proton β to *tert*-butoxy), 7.95 (singlet, 1 H, the other bridgehead proton), 8.35 (a doublet of an AB pattern split additionally by 2 H, J = 12.5, 7.0, 2.2 Hz, the endo C-7 proton), 8.75 (a doublet of an AB pattern split into a pair of triplets, J = 12.5, 3 Hz, the exo C-7 proton), 8.86 (singlet, 9 H, the *tert*-butoxy protons), 8.96 (a doublet of an AB pattern, J = 12 Hz, the anti C-8 proton), 9.28 (a doublet of an AB pattern, J = 12 Hz, with additional splitting by 3 H, J = 1 Hz, the syn C-8 proton), 9.35–9.6 (multiplet, the C-2, C-4, and syn C-3 protons), and 9.85–10.09 (multiplet, 1 H, the anti C-3 protons).

Anal. Calcd for C₁₂H₂₀O: C, 79.91; H, 11.19. Found: C, 79.93; H, 11.15.

Reduction of the Cis Adduct, *exo*-6-*tert*-Butoxy-*exo*-7-chloro-*exo*-tricyclo[3.2.1.0²,⁴]octane, with Tri-*n*-butyltin Hydride.—The cis adduct (0.044 g, 0.21 mmol) was reduced with tri-*n*-butyltin hydride (0.0575 g, 0.198 mmol) with AIBN initiation under conditions identical with those employed for the trans adduct. Vpc analysis (column 2, 155°, 40 ml/min) showed only one product, in a yield of ca. 64%, which had retention time and ir spectrum identical with those of the product obtained from the trans adduct.

Reaction of *endo*-Tricyclo[3.2.1.0²,⁴]oct-6-ene with *tert*-Butyl Hypochlorite.—The endo olefin (3.13 g, 29.5 mmol) in 6 ml of carbon tetrachloride was irradiated with *tert*-butyl hypochlorite (1.57 g, 14.5 mmol) for 20 min at 40 ± 2° with a 300-W Sylvania light bulb as in the case of the exo olefin. After partial removal of solvent at reduced pressure, the mixture was analyzed by vpc (column 1, 140°, 40 ml/min). Two adducts were observed in the ratio 43:57 in the order of increasing retention times, formed in a yield of 59%. There was no peak in the monochloride region.

The 43% component was identified as *exo*-6-*tert*-butoxy-*endo*-7-chloro-*endo*-tricyclo[3.2.1.0²,⁴]octane (trans adduct) on the basis of its spectral data: ir (neat) 3096 (w), 3040 (w) (cyclo-

propane C–H stretching), 1190 (s), 1125 (s), 1096 (s), 1065 (s), 1040 (s) (C–O stretching region), 783 (m), 770 (m), 748 (m) and 736 cm^{-1} (m); nmr (100 MHz, CCl$_4$) τ 6.24 (doublet of a triplet, J = 3.4, 0.7 Hz, HCCl), 6.58 (broad, poorly resolved multiplet, $W_{1/2}$ = 5 Hz, HCO-t-Bu), 7.5 (envelope, 1 H, the bridgehead proton β to chlorine), 7.9 (envelope, 1 H, the bridgehead proton β to $tert$-butoxy), 8.0 (a broad singlet, 2 H, the C-8 protons), 8.28 (a pair of overlapping triplets, J = 7, 3 Hz, the syn C-3 proton), 8.55–8.75 (multiplet, the C-2 and C-4 protons), 8.82 (singlet, 9 H, the $tert$-butoxy protons), and 9.03 (multiplet, the anti C-3 proton).

Anal. Calcd for C$_{12}$H$_{19}$OCl: C, 67.13; H, 8.92. Found: C, 67.10; 8.89.

The 57% component was identified as *exo*-6-*tert*-butoxy-*exo*-7-chloro-*endo*-tricyclo[3.2.1.0^{2,4}]octane on a consideration of its spectral data: ir (neat) 3080 (shoulder), 3032 (shoulder) (cyclopropane C–H stretching), 1190 (s), 1114 (s), 1104 (s), 1042 (s) (C–O stretching region), 780 (s), 770 (s), 757 (m), 750 (s), 718 cm^{-1} (s) (C–Cl stretching region); nmr (100 MHz, CCl$_4$) τ 6.36 (doublet of a doublet, J = 5.6, 1.7 Hz, HCCl), 6.68 (doublet of a doublet, J = 5.6, 1.7 Hz, HCO-t-Bu), 7.68 (envelope, the bridgehead proton β to chlorine), 7.73 (a component of an AB pattern, J = 9.5 Hz, the anti C-8 proton), 7.92 (envelope, 1 H, the bridgehead proton β to $tert$-butoxy), 8.15 (multiplet of the B doublet of the AB pattern, J = 9.5 Hz, the syn C-8 proton), 8.60–8.80 (multiplet, the C-2 and C-4 protons), 8.82 (singlet, 9 H, the $tert$-butoxy protons), and 9.0–9.35 (complex multiplet, the C-3 protons).

Anal. Calcd for C$_{12}$H$_{19}$OCl: C, 67.13; H, 8.92. Found: C, 67.11; H, 8.90.

Reduction of the Trans Adduct, *exo*-6-*tert*-Butoxy-*endo*-7-chloro-*endo*-tricyclo[3.2.1.0^{2,4}]octane, with Tri-n-butyltin Hydride.—The trans adduct (0.081 g, 0.38 mmol) was treated with tri-n-butyltin hydride (0.114 g, 0.392 mmol) and cyclohexane (60 μl) in a small tube. Approximately 5 μl was removed for later analysis. A crystal of AIBN was added and the tube was sealed and placed in a 95° bath for 12 hr. Vpc analysis (column 2, 155°, 40 ml/min) showed only one product, formed in a yield of 75% (vs. cyclohexane internal standard). The product was identified as *exo*-6-*tert*-butoxy-*endo*-tricyclo-[3.2.1.0^{2,4}]octane on the basis of its spectral data and on the basis of the similarity of its nmr spectrum to that of *exo*-6-hydroxy-*endo*-tricyclo[3.2.1.0^{2,4}]octene: ir (neat) 3064 (w), 3016 (shoulder) (cyclopropane C–H stretching), 1194 (s), 1086 (s), and 1030 cm^{-1} (s) (C–O stretching region); nmr (100 MHz, CCl$_4$) τ 6.74 (doublet of doublets, J = 6.4, 3.0 Hz, finer splitting of each of the lines to about 0.5 Hz was also observable, HCO-t-Bu), 7.8 (unresolved multiplet, bridgehead proton β to $tert$-butoxy), 8.0 (unresolved multiplet, 1 H, the other bridgehead proton), 8.2 (broad singlet, 2 H, the C-8 protons), 8.6–8.85 (complex multiplets, 4 H, protons on C-7, C-2, and C-4), 8.9 (singlet, 9 H, $tert$-butoxy protons), 9.1–9.45 (complex multiplets, 2 H, protons on C-3).

Anal. Calcd for C$_{12}$H$_{20}$O: C, 79.91; H, 11.19. Found: C, 79.80; H, 11.00.

Reduction of the Cis Adduct, *exo*-6-*tert*-Butoxy-*exo*-7-chloro-*endo*-tricyclo[3.2.1.0^{2,4}]octane, with Tri-n-butyltin Hydride.—A sample of the cis adduct (0.15 g, 0.71 mmol) was reduced with tri-n-butyltin hydride (0.21 g, 0.73 mmol), cyclohexane (130 μl), and a crystal of AIBN under conditions identical with those used for the trans isomer. Vpc analysis (column 2, 155°, 40 ml/min) showed only one product in a yield of ca. 97% (vs. cyclohexane internal standard). The sole product was identical with the one obtained from the trans adduct as observed by comparison of vpc retention times and ir spectra.

Reaction of Deltacyclene with *tert*-Butyl Hypochlorite.—The reaction of deltacyclene[11] (4.00 g, 34 mmol) in carbon tetrachloride (11 ml) with *tert*-butyl hypochlorite (1.84 g, 17 mmol) was performed exactly as above for the other olefins. Vpc analysis of the products (column 1, 155°, 45 ml/min), after partial removal of solvent at reduced pressure (20 mm), showed four peaks in the ratio 12.5:4.5:66:17 in the order of increasing retention times. The 12.5% component showed a multiplicity of signals, including aromatic proton signals, in the nmr and

possibly arose from indene, a contaminant in deltacyclene. The 4.5% component on further vpc analysis was found to be a mixture of four components none of which showed the correct molecular weight for the monochloride or the *tert*-butyl hypochlorite addition product on mass spectra analysis.

The 66 and 17% components were identified as the trans and cis adducts on the basis of their spectral data and on the basis of their reduction to *exo*-8-*tert*-butoxydeltacyclane. The trans adduct (66% component) had the following spectral characteristics: ir (neat) 3056 (w) (cyclopropane C–H stretching), 1185 (s), 1152 (m), 1060 (s), 1021 (s) (C–O stretching region), 800 (s) (nortricyclene), 790 (s), 775 (m), 733 cm^{-1} (m) (C–Cl stretching region); nmr (100 MHz, CCl$_4$) τ 6.07 (doublet of a doublet, J = 4.0, 2.0 Hz, HCCl), 6.24 (poorly resolved doublet, J = 2 Hz, HCO-t-Bu), 7.8 (unresolved multiplet, bridgehead proton β to chlorine), 7.88 (unresolved multiplet, bridgehead proton β to $tert$-butoxy), 8.15 (unresolved triplet, C-6 proton), 8.42 (singlet, 2 H, C-5 protons), 8.74 (singlet, 2 H, C-2 and C-3 protons), 8.82 (singlet, 9 H, $tert$-butoxy protons), 9–9.15 (multiplet, the C-4 proton).

Anal. Calcd for C$_{13}$H$_{19}$OCl: C, 68.85; H, 8.45. Found: C, 68.58; H, 8.23.

The cis adduct (17% component) was contaminated to the extent of about 32% by an unidentified material: ir (neat) 3056 (w) (cyclopropane C–H stretching), 1185 (m), 1086 (s) (C–O stretching region), 800 (s) (nortricyclene ring), 765 (w), 715 cm^{-1} (w) (C–Cl stretching region); nmr (100 Mz, CCl$_4$) τ 5.9 (doublet, J = 6.0 Hz) and 6.15 (doublet, J = 6 Hz).

Anal. Calcd for C$_{13}$H$_{19}$OCl: C, 68.85; H, 8.45. Found: C, 68.50; H, 8.23.

Reduction of the Trans Adduct, *exo*-8-*tert*-Butoxy-*endo*-9-chlorodeltacyclane, with Tri-n-butyltin Hydride.—A sample of the trans adduct (0.1780 g, 0.786 mmol) was treated with tri-n-butyltin hydride (0.25 g, 0.85 mmol) and cyclohexane (100 μl) in a small tube. Approximately 4 μl was removed for later analysis. A crystal of AIBN was added and the tube was sealed and placed in a 95° bath for 10 hr. After cooling to room temperature, the tube was opened and the contents were analyzed by vpc (column 2, 155°, 40 ml/min). There was only one product (ca. 81% yield vs. cyclohexane internal standard) which was identified as *exo*-8-*tert*-butoxydeltacyclane on the basis of its spectral data and the similarity of its nmr spectrum to that of *exo*-8-hydroxydeltacyclane: ir (neat) 3056 (w) (cyclopropane C–H stretching), 1190 (s), 1178 (s), 1136 (m), 1070 (s), 1040 cm^{-1} (s) (all C–O stretching region); nmr (100 MHz, CCl$_4$) τ 6.2 (poorly resolved multiplet of a doublet, J = 6.6 Hz, HCO-t-Bu), 8–8.25 (a series of poorly resolved multiplets, 4 H, bridgehead protons on C-1 and C-7, endo proton on C-9 and the proton on C-6), 8.46 (singlet with adjacent multiplet, 3 H, C-5 and exo C-9 protons), 8.85 (large singlet with a poorly resolved multiplet buried under it, 10 H, $tert$-butoxy and the C-4 protons), and 9.25 (multiplet, 2 H, the C-2 and C-3 cyclopropyl protons).

Anal. Calcd for C$_{13}$H$_{20}$O: C, 81.17; H, 10.49. Found: C, 81.30; H, 10.62.

Reduction of the Cis-Adduct, *exo*-8-*tert*-Butoxy-*exo*-9-chlorodeltacyclane, with Tri-n-butyltin Hydride.—The cis adduct (0.0490 g, 0.22 mmol) was reduced with tri-n-butyltin hydride (0.0680 g, 0.23 mmol), cyclohexane (ca. 40 μl), and a crystal of AIBN at 95° for 10 hr. Vpc analysis (column 2, 155°, 40 ml/min) showed two products in the ratio of 68:32 in a yield of ca. 67%. The 68% component was identical (retention time and ir) with the sole product obtained on reduction of the trans adduct. The 32% component could not be isolated in sufficient quantities to enable its characterization.

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Vinylalkylidenecyclopropanes from *gem*-Dichlorocyclopropanes by HCl Eliminations

W. E. BILLUPS,*[1] T. C. SHIELDS, W. Y. CHOW, AND N. C. DENO

Department of Chemistry, Rice University, Houston, Texas 77001, and
Department of Chemistry, The Pennsylvania State University, University Park, Pennsylvania 16802

Vinylalkylidenecyclopropanes are produced by treating *gem*-dichlorocyclopropanes with potassium *tert*-butoxide in dimethyl sulfoxide (DMSO). Highly strained cyclopropenes and alkylidenecyclopropenes are probable intermediates. Prolonged exposure of vinylethylidenecyclopropane to the strongly basic medium resulted in further rearrangement to give *cis*- and *trans*-1,2-divinylcyclopropane. The cis isomer undergoes a spontaneous Cope rearrangement and bond migration to form 1,3-cycloheptadiene.

Alkali-induced elimination reactions of halo- and dihalocyclopropanes offer simple routes to certain cyclopropenes.[2] More typically, isomerization products[3] or nucleophilic addition adducts[4] are observed, particularly if the base is a strong nucleophile or the cyclopropene is highly strained. This suggested that appropriately substituted dihalocyclopropanes would be suitable precursors for previously unknown vinylalkylidenecyclopropanes. This paper presents more complete data for several systems which demonstrate the generality of this reaction.[5]

The simplest example is the formation of vinyl-methylenecyclopropane (2) from 1,1-dichloro-2-ethyl-3-methylcyclopropane (1).[5] The reaction proceeds effi-

ciently using potassium *tert*-butoxide in dimethyl sulfoxide (DMSO).

The conversion of **1** to **2** is interpreted as proceeding by the two closely related paths shown in eq 1, which avoid high-energy intermediate cyclopropenyl anions.[6] These paths rationalize the absence of 1-ethynyl-2-methylcyclopropane, which might have arisen if there had been consecutive HCl eliminations toward the ethyl substituent. Both paths proceed through relatively stable allylic anions except for the initial HCl elimination. As anticipated, attempts to detect intermediate methylenecyclopropenes between **1** and **2** were unsuccessful.

1,1-Dichloro-2,3-diethylcyclopropane (**3**) allows isomerization of the initial product, vinylethylidenecyclopropene (**4**), to divinylcyclopropanes. However, it was

(1)

(2)
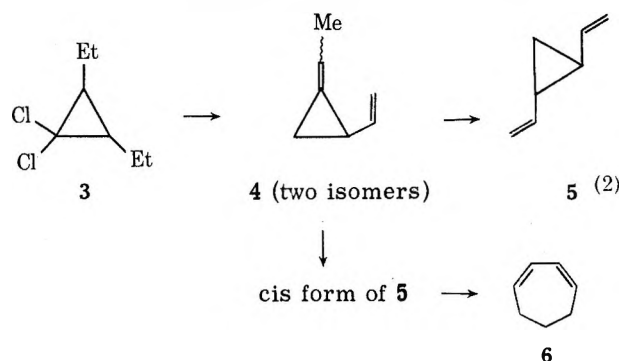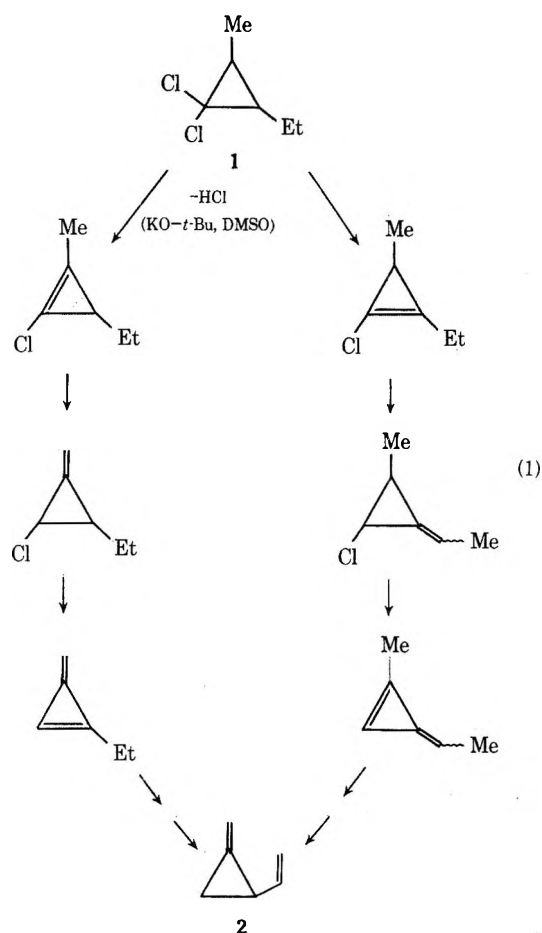
possible to isolate **4** (syn–anti mixture) in 80–90% yield after 30 min at 25°. After 2.3 hr, the yields were 34% **4**, 5% **5**, and 14% **6**. These results are all in accord with reports that *trans*-1,2-divinylcyclopropane (**5**) is stable at 25° while *cis*-**5** spontaneously undergoes a Cope rearrangement at −40°.[7] The immediate product of the Cope rearrangement would be 1,4-cycloheptadiene, but this would isomerize to the 1,3 isomer (**6**) under basic conditions, as was observed. Dichloride **7** gave

(1) Address inquiries to W. E. B., Department of Chemistry, Rice University, Houston, Texas 77001.

(2) S. W. Tobey and R. West, *Tetrahedron Lett.*, 1180 (1963); P. D. Gardner, B. A. Loving, and T. C. Shields, *Chem. Commun.*, 556 (1967).

(3) J. A. Carbon, W. B. Martin, and L. R. Swett, *J. Amer. Chem. Soc.*, **80**, 1002 (1958); C. L. Osborn, T. C. Shields, B. A. Shoulders, J. F. Krause, H. V. Cortez, and P. D. Gardner, *ibid.*, **87**, 3158 (1965).
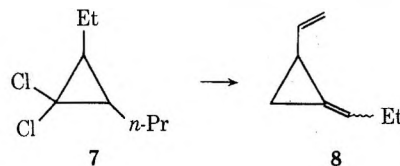
(4) K. B. Wiberg, R. K. Barnes, and J. Albin, *ibid.*, **79**, 4994 (1957); T. C. Shields, B. A. Shoulders, J. F. Krause, C. L. Osborn, and P. D. Gardner, *ibid.*, **87**, 3026 (1965).

(5) For preliminary results see T. C. Shields, W. E. Billups, and A. R. Lepley, *ibid.*, **90**, 4749 (1968); T. C. Shields and W. E. Billups, *Chem. Ind. (London)*, 619 (1969).

(6) R. Breslow, "Organic Reaction Mechanisms," W. A. Benjamin, New York, N. Y., 1966, p 26.

(7) E. Vogel, K. H. Ott, and K. Gajek, *Justus Liebigs Ann. Chem.*, **644**, 172 (1961); E. Vogel and R. Erb, *Angew. Chem., Int. Ed. Engl.*, **1**, 53 (1962); W. v. E. Doering and W. R. Roth, *ibid.*, **2**, 115 (1963).

a single major product identified as vinylpropylidene-cyclopropane (**8**).

1,1-Dichloro-2,2-dimethyl-3-propylcyclopropane (**9**) forces both HCl eliminations to take place in the same

9 → **10**
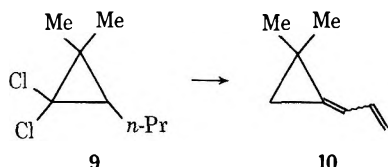
direction. The product was now a diene (**10**), 1-allylidene-2,2-dimethylcyclopropane (syn–anti mixture), and was isolated in 60% yield.

1,1-Dichloro-2-methyl-3-propylcyclopropane (**11**) introduces the opportunity for producing a conjugated

11 **12**
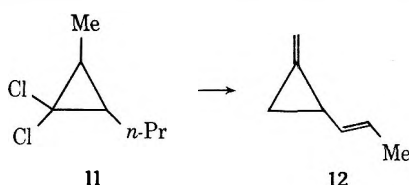
diene. However, 1-methylene-2-propenylcyclopropane (**12**) was produced in strict analogy to the formation of **1**.

1,1-Dichloro-2,2-dimethyl-3-ethylcyclopropane (**13**) introduces a constraint in that products of the type

13 →

$(Me)_2C=CHC\equiv CMe$ +

14 **15**
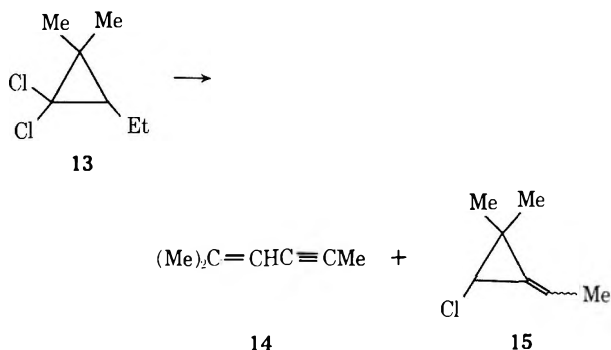
formed previously are not possible. The formation of 2,2-dimethylethynylcyclopropane was still avoided. Instead a complex mixture of products whose composition was dependent upon reaction time was produced; however, at an early stage of the reaction 2-methyl-2-hexen-4-yne (**14**) was shown to be the major product. A second product, provisionally identified as 1-chloro-2,2-dimethyl-3-ethylidenecyclopropane (**15**), was also detected.

1,1-Dichloro-2-ethyl-3-isopropylcyclopropane (**16**)

16 → **17** + **18**

19 **20**
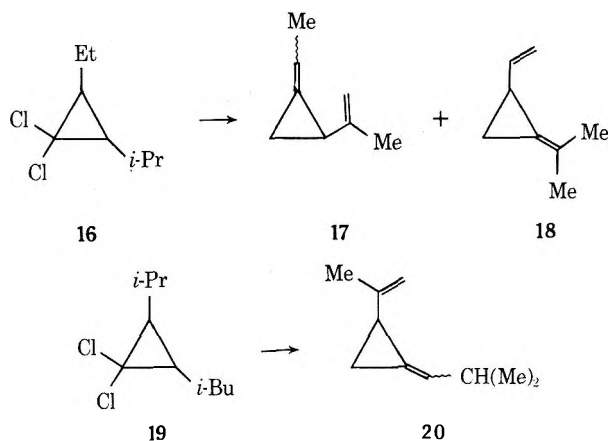
and 1,1-dichloro-2-isobutyl-3-isopropylcyclopropane (**19**) are representative of more highly branched dichlorocyclopropanes. The former gave a mixture of **17** and **18** (3.5:1), whereas **19** gave **20** (>95%).

The elimination–isomerization reaction sequence also occurs readily when dichlorocarbene adducts of some cyclic olefins are treated with KO-*t*-Bu–DMSO. Thus, 13,13-dichlorobicyclo[10.1.0]tridecane (**21**) gave **22** in 94% yield.

21 **22**
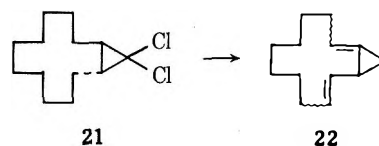
Experimental Section

General.—Nmr spectra were obtained at 60 Mc with TMS internal standard, and signal positions are reported in δ units. Infrared spectra were recorded using Beckman IR-5-A and IR-8 spectrometers. Ultraviolet spectra were obtained in cyclohexane solvent with a Cary Model 14 spectrophotometer.

Materials.—Dimethyl sulfoxide (Crown Zellerbach or Aldrich) was dried over calcium hydride. 2-Pentene (Phillips Petroleum Co.) and other olefins (Chemical Samples Co.) were used without further purification. Potassium *tert*-butoxide was K and K, Alfa Inorganics, or MSA Corp. material. Dichlorocyclopropanes were prepared by the method of Skell and Garner.[8]

Vinylmethylenecyclopropane (2).—The preparation of this compound from **1** is representative of the other preparations outlined. Potassium *tert*-butoxide (84 g, 0.75 mol) was added to 400 ml of dimethyl sulfoxide in a creased flask fitted with stirrer and condenser. 1,1-Dichloro-2-ethyl-3-methylcyclopropane (**1**) (38 g, 0.25 mol) was added dropwise at 25° under nitrogen (external cooling). After 2 hr, product was isolated in 62% yield (determined by gc) by addition to ice–water, pentane extraction, drying, and removal of pentane at 25°. The thermal instability of **2** necessitated purification by preparative glpc (10 ft × 0.5 in. column, Varian FFAP packing operated at 45°). Both injection port and detector were kept below 100° to minimize rearrangement to 3-methylenecyclopentene.[5]

Anal. Calcd for C_6H_8: C, 89.9; H, 10.1; mol wt, 80. Found: C, 89.6; H, 10.3; mol wt, 80 (mass spectrum, **2** probably isomerized in the heated inlet).

Spectra follow: ir (film) 5.71, 5.80, 6.12, 7.11, 8.41, 8.90, 9.22, 9.75, 10.15, 10.6, 11.2 (broad), 11.6, and 12.06 μ; nmr (CCl_4) δ 1.0 (m) and 1.46 (m, 1 H each, cyclopropyl-CH_2-), 2.0 (m, 1 H, cyclopropyl), 5.45 (m, $=CH_2$), and 4.7–5.8 (m, vinyl).

Vinylethylidenecyclopropane (4).—Addition of 1,1-dichloro-2,3-diethylcyclopropane (**3**) to KO-*t*-Bu–DMSO produced a mixture of *syn*- and *anti*-**4** (~1:1)[9] in 80–90% yield after 30 min at 25°. After 2.3 hr **4**, **5**, and **6** were produced in yields of 34, 5, and 14%. The products were isolated by preparative glpc using columns packed with Varian FFAP or propylene carbonate[9] packing.

Identification of **4** rested on its spectra: ir (film) 6.12 (C=C) and 11.2 μ (methylenecyclopropane); nmr (CCl_4) δ 1.76 (m, 3 H, methyl), 0.65–2.20 (m, 3 H, cyclopropyl), 4.60–5.4 (m, 3 H, vinyl), and 5.70 (m, 1 H, olefinic). The nmr spectra of *syn*- and *anti*-**4** were virtually indistinguishable. The mass spectrum had a parent peak of 94, as calculated.

The ir and nmr spectra of **5** coincide with those of an authentic sample.[10] The nmr spectrum of **6** [δ 1.92 (m, 4 H, allylic), 2.31 (m, 4 H, -CH_2CH_2-), and 5.69 (m, 4 H, vinyl H)], is identical with that reported previously.[11]

Vinylpropylidenecyclopropane (8).—Treatment of 1,1-dichloro-2-ethyl-3-propylcyclopropane (**7**) with KO-*t*-Bu in DMSO for 30 min produced **8** in 70–80% yield: nmr multiplets at δ 1.02, 1.42, 2.12 (9 H), 4.65–5.6 (3 H, vinyl), and 5.7 (1 H, olefinic).

(8) P. S. Skell and A. Y. Garner, *J. Amer. Chem. Soc.*, **78**, 3409 (1956).

(9) Syn and anti isomers separated on a 7-ft propylene carbonate column operated at room temperature. We thank Mr. Steven Vanderpool for assistance with this separation.

(10) We thank Professor E. Vogel for providing these spectra.

(11) R. Burton L. Pratt, and G. Wilkinson, *J. Chem. Soc.*, 594 (1961).

1-Allylidene-2,2-dimethylcyclopropane (**10**).—This product formed in 60% yield from 1,1-dichloro-2,2-dimethyl-3-propylcyclopropane (**9**) after treatment with 3 equiv of base for 75 min at 25°; it was isolated by flash distillation.

Anal. Calcd for C_8H_{12}: C, 88.2; H, 11.2; mol wt, 108. Found: C, 88.5; H, 11.5, mol wt, 108 (mass spectrum).

Spectra follow: ir (film) 5.55, 6.19, 6.95 (broad), 7.27, 8.03, 8.89, 10.1 (very broad), and 11.15 μ (broad); nmr δ 0.98 (m, 2 H, cyclopropyl), 1.19 (s) and 1.23 (s, 6 H total, methyls), 4.85–5.5 (m, 2 H, =CH$_2$), and 6.0–6.8 (m, 2 H, –CH=CH–); λ_{max} 230 nm (ε 21,900). The nmr bands at δ 1.19 and 1.23 are interpreted as due to the *gem*-dimethyl on the syn and anti isomers. The area ratio of the δ 1.23 to 1.19 band was 1.2:1. It is not known which band corresponds to which isomer.

1-Methylene-2-propenylcyclopropane (**12**).—1,1-Dichloro-2-methyl-3-propylcyclopropane (**11**) afforded a major product in 40–50% yield when treated with a threefold excess of the base for 25 min at 25°. **12** was purified by preparative glpc, and showed strong infrared absorption at 10.22 μ, characteristic of methylenecyclopropanes. The nmr spectrum showed one proton signal at δ 0.98, 1.5, 2.2 (cyclopropyl), a methyl doublet at 1.74 (*J* = 6.5 cps), and an olefinic pattern extending from 4.6 to 5.7.

2-Methyl-2-hexen-4-yne (**8**).—1,1-Dichloro-2,2-dimethyl-3-propylcyclopropane (**7**) produced two products when treated with base for 25 min. The major product (57%) was isolated by preparative glpc and identified as **8** by its nmr spectrum:[12] signals at δ 1.92 (s, 3 H, –C≡CCH$_3$), 1.7 (m, 6 H, isopropylidene), and 5.48 (m, 1 H, olefinic). A second product, obtained in impure form, is provisionally identified as 1-chloro-2,2-di-

(12) I. A. Favorskaya, E. M. Auvinene, and Y. P. Artsybasheva, *Zh. Obshch. Khim.*, **28**, 1785 (1958); *Chem. Abstr.*, **52**, 1097i (1958).

methyl-3-ethylidenecyclopropane on the basis of an nmr singlet at δ 3.28 (–CHCl–) and by analogy to the formation of 1-chloro-2,2-dimethyl-3-methylenecyclopropane from 1,1-dichloro-2,2,3-trimethylcyclopropane.[13]

1-Ethylidene-2-isopropenylcyclopropane (**17**) **and 1-Isopropylidene-2-vinylcyclopropane** (**18**).—1,1-Dichloro-2-ethyl-3-isopropylcyclopropane (**16**) produced **17** (56%) and **18** (16%) when treated with base: nmr (**17**) δ 1.2 (cyclopropyl), 1.6 (3 H isopropenyl methyl), 1.8 (3 H, ethylidene methyl) overlapping a multiplet extending to 2.3 (cyclopropyl) 4.65 (2 H, methylene), and 5.5 (q, 1 H, olefinic); nmr (**18**) δ 0.6–2.3 (3 H, cyclopropyl), 1.78 (6 H, isopropylidene), 4.5–5.7 (3 H, vinyl).

1-Isobutylidene-2-isopropenylcyclopropane (**20**) was produced in 48% yield from 1,1-dichloro-2-isobutenyl-3-isopropylcyclopropane: nmr δ 1.05 (6 H, isopropyl methyls), 0.8–2.2 (3 H, cyclopropyl), 1.58 (3 H, isopropenyl methyl), 2.5 (1 H, isopropyl), 4.65 (2 H, methylene), and 5.72 (1 H, olefinic).

Bicyclo[10.1.0]trideca-1,10-diene (**22**).—Addition of 13,13-dichlorobicyclo[10.1.0]tridecane (**21**) to KO-*t*-Bu–DMSO provided **22** in 94% yield: nmr δ ~1.1, 1.4, 1.15 (~17 H), 4.74–6.1 (3 H); ir (film) prominent absorptions at 6.17, 6.87, 7.0, 7.6, 10.2, and 13.9 μ.

(13) T. C. Shields and W. E. Billups, *Chem. Ind. (London)*, 1999 (1967).

The Vinyl Anion. II

JOHN F. ARNETT[1] AND H. M. WALBORSKY*

Department of Chemistry, Florida State University, Tallahassee, Florida 32306

Received May 2, 1972

The exchange and racemization reactions of 2,2,4,6,6-pentamethylcyclohexylideneacetophenone (**1**) with sodium methoxide in methanol have been investigated. The ketone **1** exhibits only a moderate degree of retention of optical activity (30% at 50°), k_e/k_r = 1.43. This contrasts with the high degree of retention (>99% at 50°) observed with the corresponding 2,2,4,6,6-pentamethylcyclohexylideneacetonitrile (**2**). On the basis of primary hydrogen–deuterium and deuterium–tritium isotope effects, it is suggested that in both the base-catalyzed exchange and racemization reactions of **1** the rate-determining step is proton abstraction. Both (−)-**1** and its precursor (−)-2,2,4,6,6-pentamethylcyclohexylideneacetic acid [(−)-**3**] have been tentatively assigned the *R* configuration on the basis of their Cotton effects.

Recently this laboratory reported that the vinyl anion obtained by reaction of 2,2,4,6,6-pentamethylcyclohexylideneacetonitrile (**2**) with sodium methoxide in methanol was capable of maintaining its configuration (>99% retention at 50°). Moreover, based on the small kinetic isotope effect for the hydrogen isotope exchange reactions of **2**, it was proposed that proton abstraction was *not rate determining* in either the exchange or racemization reactions.[2]

These observations paralleled analogous data obtained in the investigation of the configurational stability of the cyclopropyl anion similarly derived from 1-cyano-2,2-diphenylcyclopropane (**4**) which indicated >99% retention at 50–75°.[3] In contrast to the behavior exhibited by the anion derived from **2** and **4**, however, the cyclopropyl anion generated from 1-benzoyl-2,2-diphenylcyclopropane (**5**) by base-catalyzed proton abstraction showed only moderate re-

2   4   5
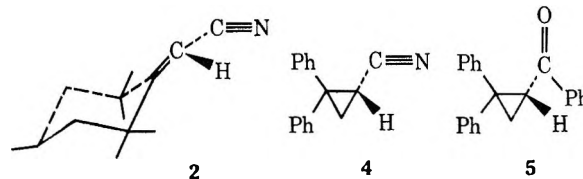
tention of optical activity (~27% retention at 75°). Further, the normal kinetic isotope effects observed in the isotope exchange reactions of **5** suggested that proton abstraction was rate limiting in both the exchange and racemization reactions.[4] This article presents our data on the rates of the sodium methoxide catalyzed exchange and racemization reactions of 2,2,4,-6,6-pentamethylcyclohexylideneacetophenone (**1**).

Results and Discussion

Synthesis.—The synthesis of racemic 2,2,4,6,6-pentamethylcyclohexylideneacetophenone is outlined in

(1) National Science Foundation Predoctoral Fellow, 1970–1971; National Aeronautics and Space Administration Trainee, 1967–1970.

(2) H. M. Walborsky and L. M. Turner, *J. Amer. Chem. Soc.*, **94**, 2273 (1972).

(3) H. M. Walborsky and J. M. Motes, *ibid.*, **92**, 2445 (1970).

(4) J. M. Motes and H. M. Walborsky, *ibid.*, **92**, 3697 (1970).

Scheme I. The pentamethyl ketone 6 was obtained by a sodium hydride–methyl iodide alkylation of the commercially available 4-methylcyclohexanone (7).[5] Directed aldol condensation[6] of 6 with lithiated α-methylbenzylidene cyclohexylamine to yield the hydroxy imine 8 followed by dehydration with thionyl chloride–dimethylformamide gave the α,β-unsaturated imine 9. Conversion of 9 to the desired acetophenone, 1, was accomplished by refluxing with aqueous oxalic acid.
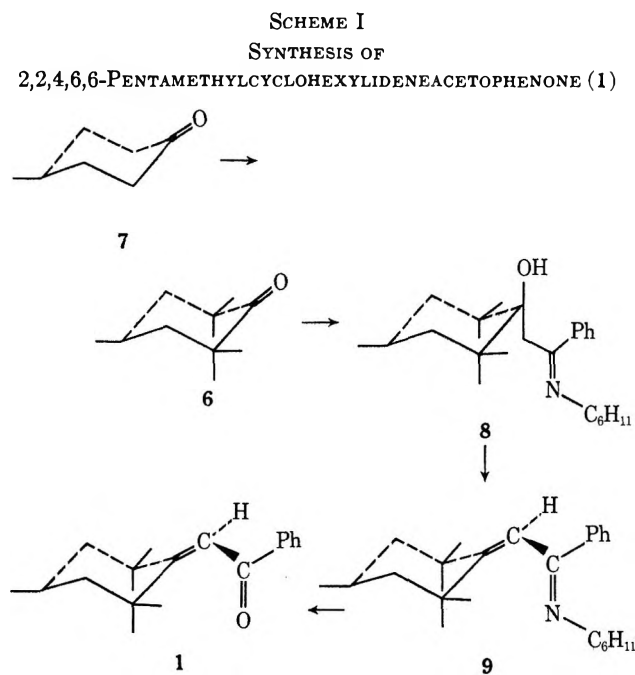
The optically active ketone, (−)-1, was obtained by treating (−)-2,2,4,6,6-pentamethylcyclohexylideneacetic acid with commercially available phenyllithium. The racemic acid was synthesized as in Scheme II.[7] Directed aldol condensation[6] of penta-

SCHEME I
SYNTHESIS OF
2,2,4,6,6-PENTAMETHYLCYCLOHEXYLIDENEACETOPHENONE (1)
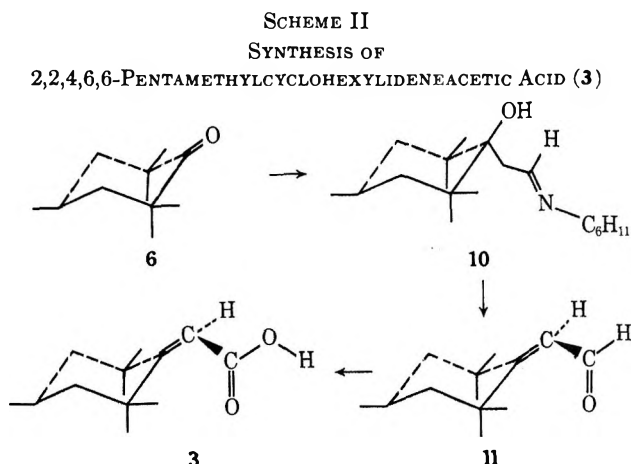
methyl ketone 6 with lithiated ethylidenecyclohexylamine followed by steam distillation of the re-

SCHEME II
SYNTHESIS OF
2,2,4,6,6-PENTAMETHYLCYCLOHEXYLIDENEACETIC ACID (3)

sulting hydroxy imine 10 from aqueous oxalic acid yielded the α,β-unsaturated aldehyde 11.[2] Oxidation of 11 with silver oxide[8] gave racemic 1, which was resolved through its brucine salt.[2]

(−)-1 has tentatively been assigned the R configuration on the basis of a comparison of the Cotton effects of its acid precursor (−)-3, and (−)-(R)-4-methylcyclohexylideneacetic acid,[9] (−)-12 (Table I). The

TABLE I
ORD–CD DATA FOR
(−)-2,2,4,6,6-PENTAMETHYLCYCLOHEXYLIDENEACETIC ACID
AND (−)-4-METHYLCYCLOHEXYLIDENEACETIC ACID

Compd		Data
(−)-1	ORD	$[\alpha]_{220}^{25}$ −218.2 (c 1.34, MeOH)
	CD	$\Delta\epsilon_{243}^{25}$ + 3.12, $\Delta\epsilon_{208}^{25}$ −6.98 (c 1.34, MeOH)
(−)-(R)-12	ORD	Negative plain rotatory dispersion curve (MeOH)
	CD	$\Delta\epsilon_{280}^{25}$ +0.0103, $\Delta\epsilon_{226}^{25}$ −3.08 (EtOH)

absolute configuration of (−)-12 has been previously established by Gerlach[9] by means of a chemical correlation.

The increased signal intensity observed for (−)-1 relative to (−)-12 is thought to be caused by increased steric distortion of the symmetry of the π-electron cloud upon introduction of additional methyl substituents into the cyclohexyl ring.[10]

The deuterated (1-d) and tritiated ketones (1-t) were synthesized by successive treatment of the protio ketone with sodium methoxide in methanol-d (-t), respectively.

Exchange and Racemization Rates.—The kinetic methods used are described in the Experimental Section. The second-order rate constants (Table II) were

TABLE II
SECOND-ORDER RATE CONSTANTS FOR THE EXCHANGE AND RACEMIZATION REACTIONS OF
2,2,4,6,6-PENTAMETHYLCYCLOHEXYLIDENEACETOPHENONE[a]

Reaction	Solvent	Temp, °C	k_2,[b] l. mol^{-1} sec^{-1}
H → D	MeOD	50.00 ± 0.01	8.80 ± 0.01 × 10^{-4}
D → H	MeOH	50.00 ± 0.01	6.75 ± 0.04 × 10^{-5}
T → H	MeOH	50.00 ± 0.01	3.55 ± 0.01 × 10^{-5}
H → D	MeOD	10.20 ± 0.10	1.21 ± 0.02 × 10^{-6}
D → H	MeOH	10.20 ± 0.10	7.93 ± 0.02 × 10^{-7}
T → H	MeOH	10.20 ± 0.10	3.42 ± 0.01 × 10^{-7}
Racemization	MeOD	50.00 ± 0.01	6.15 ± 0.01 × 10^{-4}
Racemization	MeOH	50.00 ± 0.01	2.90 ± 0.01 × 10^{-4}

[a] 1.0 M NaOCH₃; 0.05 M ketone. [b] Average rate constant ± standard deviation.

determined by dividing the pseudo-first-order rate constants by the base concentration. The first-order rate plots yielded straight lines in all cases studied.

(5) A. Haller, *C. R. Acad. Sci.*, **157**, 737 (1921).
(6) G. Wittig and H. Reiff, *Angew. Chem., Int. Ed. Engl.*, **7**, 7 (1968).
(7) See ref 2 for an alternative synthesis.
(8) A. Calieze and H. Schinz, *Helv. Chim. Acta*, **32**, 2556 (1949).
(9) The ORD–CD data for (−)-(R)-4-methylcyclohexylideneacetic acid were kindly supplied by Professor H. Gerlach, Erdg. Technische Hochscule, Zurich, Switzerland; see also H. Gerlach, *ibid.*, **49**, 6718 (1966).
(10) G. Snatzke, *Angew. Chem., Int. Ed. Engl.*, **7**, 14 (1968).

Exchange Reactions.—A general mechanism for the exchange reactions of a carbon acid may be written as that in eq 1.[2-4]

$$RH + B^- \underset{k_{-1}H}{\overset{k_1H}{\rightleftharpoons}} R^- \cdots HB \overset{k_2}{\underset{k_{-2}}{\rightleftharpoons}}$$

$$R^- \cdots DB \underset{k_{-1}D}{\overset{k_1D}{\rightleftharpoons}} RD + B^- \quad (1)$$
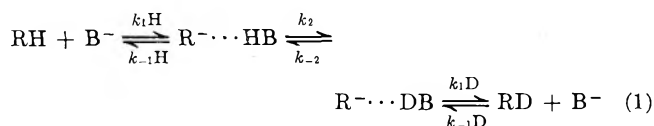
The rate law for the formation of the exchanged (deuterated) carbon acid is then given, under the experimental conditions of this work, by

$$k_{exptl} = \frac{k_1 k_2}{k_{-1} + k_2} \quad (2)$$

For those reactions predominated by internal return, i.e., $k_{-1} \gg k_2$, this expression simplifies to

$$k_{exptl} = Kk_2 \quad (3)$$

where K is the equilibrium proton abstraction–recapture equilibrium constant. On the other hand, if proton abstraction is rate limiting, i.e., $k_2 \gg k_{-1}$, eq 2 reduces to

$$k_{exptl} = k_1 \quad (4)$$

Mechanisms typified by rate expressions eq 2 and 3 may be differentiated from that typified by eq 4 by the magnitude of primary kinetic isotope effects. Rate-limiting proton transfer will exhibit a normal primary isotope effect, while internal return and mixed or competitive mechanisms (i.e., $k_1 \sim k_2$) will exhibit small kinetic effects in the absence of media and steric effects.[11] The experimentally observed kinetic isotope effects, uncorrected for solvent effects, are presented in Table III for the exchange reactions of 2,2-4,6,6-pentamethylcyclohexylideneacetophenone (1).

TABLE III
UNCORRECTED ISOTOPE EFFECTS[a]

Temp, °C	k_H^{MeOD}/k_D^{MeOH}	k_D^{MeOH}/k_T^{MeOH}
50.00 ± 0.01	13.0 ± 0.1	1.90 ± 0.08
10.20 ± 0.10	15.2 ± 0.2	2.32 ± 0.02

[a] 1.0 M NaOCH$_3$; 0.05 M ketone.

Theoretically, T, D, and H isotope effects are interrelated by

$$\left(\frac{k_H}{k_D}\right) = \left(\frac{k_D}{k_T}\right)^x \quad (5)$$

where $x = 2.26$ or 2.344.[12] Applying eq 5 to the data in Table III, we calculate from the T and D exchange data that at 50° $k_A/k_D = 4.3$–4.5. These values contrast with the experimentally determined ratio $k_H^{MeOD}/k_D^{MeOH} = 13.0$, suggesting the presence of a solvent isotope effect $k^{MeOD}/k^{MeOH} = 3.0$–2.9. This

hypothesis is supported by the presence of an experimentally observed isotope effect in the racemization reactions $k_{rac}^{MeOD}/k_{rac}^{MeOH} = 2.12$. Moreover, solvent isotope effects of similar magnitude have been reported previously for this solvent system.[12b,13] These solvent isotope effects may be attributed to the weakening of the solvent–methoxide hydrogen bond and the increasing vibrational frequency of the oxygen–hydrogen (deuterium) bond as reaction progresses.[14] This view is supported by the recent work of Gold and Grist.[15]

The calculated k_H/k_D values are presented in Table IV. All of these values lie in the normal high range

TABLE IV
CALCULATED ISOTOPE EFFECTS[a]

Temp, °C	$(k_D/k_T)^{2.26}$	$(k_D/k_T)^{2.344}$
50.00 ± 0.01	4.3	4.5
10.20 ± 0.10	6.7	7.2

[a] 1.0 M NaOCH$_3$; 0.05 M ketone.

indicative of substantial proton transfer at the transition state. Further, the magnitude of the primary isotope effect increases with decreasing temperatures, as would be expected for rate-limiting proton abstraction.[11]

A mechanism consistent with rate-determining proton transfer is presented in Scheme III and is analogous to the scheme proposed for the cyclopropyl ketone 2.[4] The first step involves the removal of the acidic proton by the active base, methoxide ion hydrogen bonded to one or more methanol molecules to form a hydrogen-bonded carbanion (k_1). Once the hydrogen-bonded carbanion is formed, the solvent exchange reactions (k_2 or k_3, k_4) occur in competition with the back reaction (k_{-1}) with the observed primary kinetic isotope effect requiring that $k_{-1} < k_2$ (k_3, k_4).

Racemization Reaction.—The data in Table I show that the reaction of $(-)$-1 with sodium methoxide occurs with only a moderate degree (30%) of retention of optical activity, $k_e/k_r = 1.43$. This degree of retention of optical activity corresponds to 65% retention of configuration and 35% inversion. A possible reaction scheme is illustrated in Scheme IV, where S–OH signifies an aggregate of hydrogen-bonded solvent molecules. The retention of optical activity is attributed to an internal return mechanistic component with racemization most probably occurring through the delocalized, planar carbanion.

As in the work with the vinyl nitrile, the observed k_e/k_r ratio is not consistent with an addition–elimination mechanism such as that illustrated in Scheme V. In the absence of isotope effects the exchange rate for such a mechanism at the most would be only half as fast as the rate of racemization. Moreover, the

(11) For an excellent review of isotope effects see (a) W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill, New York, N. Y., 1969, Chapter 4, and references cited therein; (b) L. Melander, "Isotope Effects on Reaction Rates," Ronald Press, New York, N. Y., 1960. See also F. G. Bordwell and W. J. Boyle, *J. Amer. Chem. Soc.*, **93**, 512 (1971), and references cited therein.

(12) (a) C. G. Swain, E. C. Stivers, J. F. Reuwer, Jr., and L. J. Schaad, *ibid.*, **80**, 5885 (1958); (b) A. Streitwieser, Jr., W. B. Holyhead, A. H. Pudjaatmaka, P. H. Owens, T. L. Kruger, P. A. Rubenstein, R. A. MacQuarrie, M. L. Brokaw, W. K. C. Chu, and H. M. Niemeyer, *ibid.*, **93**, 5088 (1971).

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SCHEME III

EXCHANGE MECHANISM FOR 2,2,4,6,6-PENTAMETHYLCYCLOHEXYLIDENEACETOPHENONE (1)
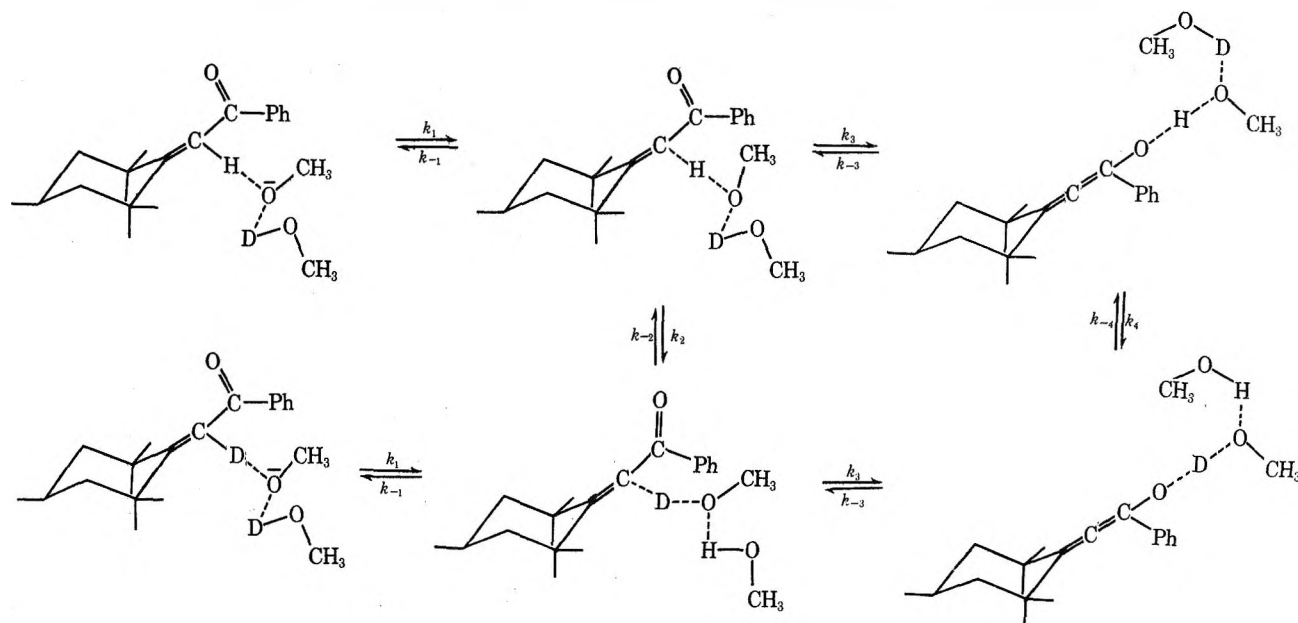
SCHEME IV

RACEMIZATION MECHANISM FOR 2,2,4,6,6-PENTAMETHYLCYCLOHEXYLIDENEACETOPHENONE (1)
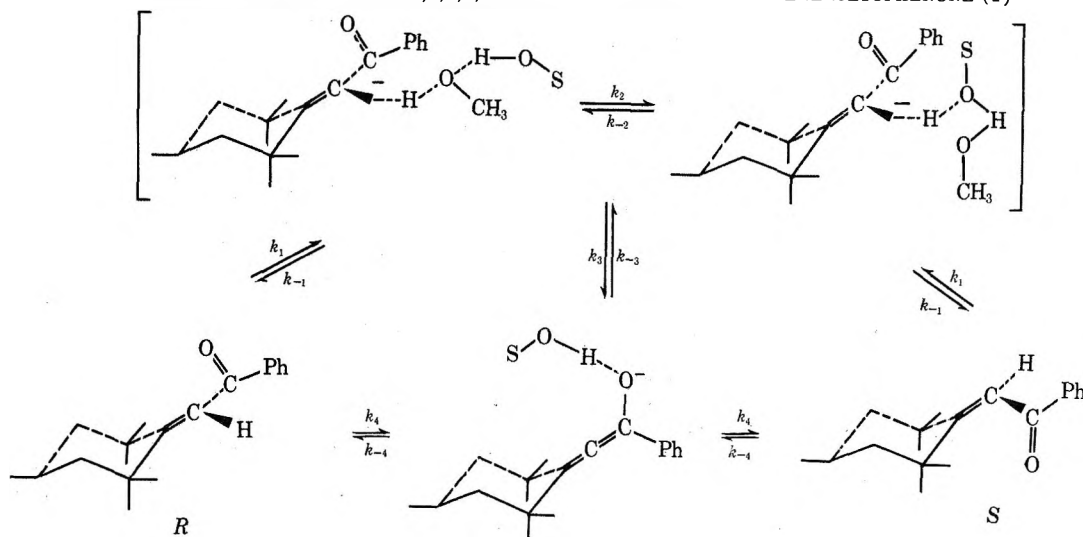
steric hindrance at the β carbon of the double bond minimizes the probability of addition.[16]

Comparison of Nitrile and Ketone.—Both the racemization and exchange data for the ketone 1 contrast sharply with that for the analogous nitrile 2. The cause of this divergent behavior most likely lies in the differing acidities of the two compounds and the relative stabilities of the delocalized carbanions. Carbon acids stabilized by the carbonyl group are usually several pK_a units more acidic and have smaller recombination rates than those stabilized by cyano groups.[17] Moreover, the increased delocalization possible in the benzoyl ketone due to the phenyl ring shifts the equilibrium between the nonplanar localized and planar delocalized carbanion toward the planar anion relative

to the equilibrium position in the nitrile system. The result is an increase in the rate of exchange ($k_{H \to D}^{ketone}$ $\cong 100 k_{H \to D}^{nitrile}$) and a shift in the stereochemical course of the reaction.

Direct comparison of the stereochemical stability of the cyclopropyl and vinyl ketones 1 and 5 is not possible because exchange and racemization data were not obtained under identical conditions. The close parallel between the behavior of the ketone and nitrile compounds in each of the two systems, however, makes an indirect comparison possible. In both the cyclopropyl and vinyl systems[2] the exchange reaction for the ketones proceeds with carbon–hydrogen bond breaking being rate determining. Further, in both systems the nitrile retains its configuration while under the same conditions the ketones undergo considerable racemization.[2-4]

Direct comparison of the exchange–racemization data for the nitriles shows that the cyclopropyl nitrile,

(16) For a discussion of the problem of the addition–elimination mechanism in evaluation of the stereochemical stability of the vinyl anion, see ref 2.

(17) (a) R. G. Pearson and R. L. Dillon, *J. Amer. Chem. Soc.*, **75**, 2439 (1955); L. A. Cohn and W. M. Jones, *ibid.*, **85**, 337, 3402 (1963).

SCHEME V

ADDITION–ELIMINATION MECHANISM FOR

2,2,4,4,4-PENTAMETHYLCYCLOHEXYLIDENEACETOPHENONE (1)
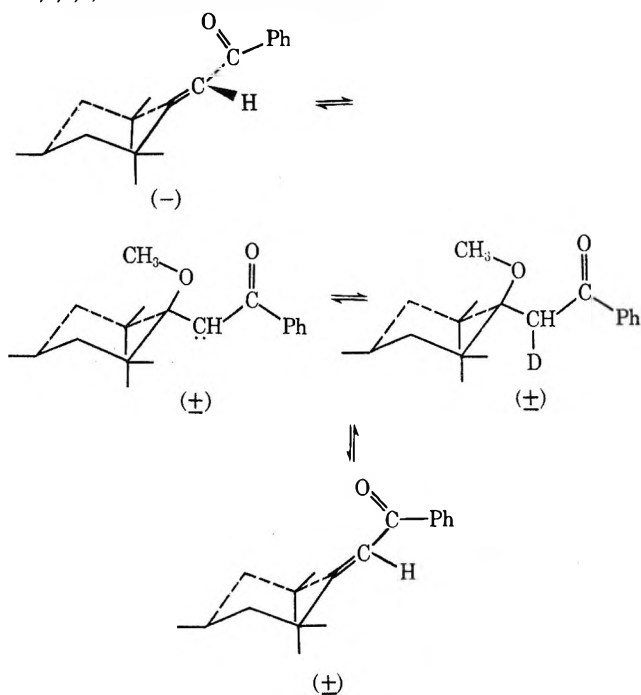
because of ring strain, is configurationally more stable than the analogous vinyl compound.[2] The close parallel in the internal behavior of the systems argues that the cyclopropyl ketone will likewise exhibit greater configurational stability than the analogous vinyl compound under identical conditions.

Experimental Section

Melting points were measured with a Mel-Temp apparatus and both melting and boiling points are uncorrected. Infrared spectra were determined using a Perkin-Elmer Model 257 spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Varian A-60 or Bruker 90-MHz spectrophotometer; chemical shifts are reported in parts per million downfield from tetramethylsilane and coupling constants are in hertz. Low-resolution mass spectra were obtained on a Nuclide electron impact mass spectrometer, and high-resolution mass spectra were obtained on an Associated Electronics Industries MS902 instrument. All mass spectra gave parent ions consistent with the expected molecular weight. Tritium counts were obtained with a Packard Tricarb liquid scintillation counter. Optical rotatory and circular dichroism spectra were recorded with a JASCO-5 and optical rotations at 5461 Å with a Bendix-Ericson Model 143A polarimeter. Microanalyses were performed by the Beller Laboratories, Gottingen, Germany.

Solvents.—Methyl alcohol-*t* (9800 cpm/mg) was prepared by the method of Streitwieser.[18] Methyl alcohol-*d* (>99.9% isotopically pure) was purchased from Diaprep. The deuterated and tritiated methanol were dried by distillation from a small amount of sodium, and reagent grade methanol was dried by distillation from magnesuim.

Stock base solutions of 1.0 N sodium methoxide in methanol (-*d*,-*t*) were prepared by adding a weighed amount of clean sodium metal to the anhydrous alcohol at −78° under an argon atmosphere. After all the sodium metal had reacted, the solution was allowed to warm to room temperature and transferred to a volumetric flask, which was diluted to the mark with anhydrous methanol. The stock solution was standardized with hydrochloric acid.

Exchange Method.—The stock solutions were prepared in volumetric flasks by adding the stock base solutions to a weighed

(18) A. Streitwieser, Jr., L. Verbit, and P. Stang, *J. Org. Chem.*, **29**, 3706 (1964).

amount of the vinyl compound. These solutions were shaken until all of the vinyl compound was dissolved. Portions (5 ml) were removed with a syringe and transferred to Pyrex screw cap vials with Teflon liners which were then placed in a constant-temperature bath at the appropriate temperature. Each tube was removed after a predetermined time and quenched in a Dry Ice–acetone bath before opening. The samples were acidified with dilute hydrochloric acid and extracted with pentane. The pentane extracts were combined and washed with 5% sodium bicarbonate solution and three portions of water. The pentane solution was dried over sodium sulfate and evaporated.

Quantitative Nuclear Magnetic Resonance Analysis.—For the hydrogen and deuterium exchange samples, the residue obtained above was dissolved in Spectrograde carbon tetrachloride containing tetramethylsilane as an internal standard and submitted to nmr analysis. The analysis was performed by integrating the phenyl and vinyl regions five times and averaging the areas obtained to determine the relative per cent deuterium in the sample. Excellent first-order rate plots were obtained and the first-order rate constants were determined by a least-squares fit of the experimental data. Second-order rate constants were calculated by dividing the first-order rate constants by the base concentration.

Radioactive Counting.—The relative tritium concentrations of kinetic samples were determined by scintillation counting. The unknown ketone was carefully weighed into a counting vial and 15.0 ml of the scintillation fluid [50 mg of 1,4-2-(5-phenyloxazoyl)-benzene and 4 g of 2,5-diphenyloxazole per liter of toluene] was added. The vial was capped, shaken to ensure solution, and placed in the scintillation counter. Two 2-min counts were taken after thermal equilibration of the sample. After adjustments were made for background radiation and quenching, the activity of the sample was determined.

Racemization Kinetics.—The rate of racemization of the ketone was determined directly on the reaction mixture by following the change in ellipticity of the sample with time using the JASCO-5. A 1.003-mm thermostated cell was used and the ellipticity was observed at 340 μ. The rate constants for the racemization and exchange reactions are listed in Table II.

2,2,4,6,6-Pentamethylcyclohexanone (6).—To a stirred suspension of 126 g of sodium hydride dispersion (57% in mineral oil) in 900 ml of dry dimethoxyethane (DME) at 0° under nitrogen was added a solution of 67.2 g (0.600 mol) of 4-methylcyclohexanone in 50 ml of dry DME. After 30 min, 250 ml of a solution of 426 g (3.00 mol) of methyl iodide in 750 ml of dry DME was added dropwise over a period of 12 hr. The reaction mixture was allowed to stir overnight at 0° and the addition sequence was repeated until all the methyl iodide solution had been added. The reaction mixture was then allowed to come to room temperature and stirred for an additional 24 hr. Water was added dropwise until hydrogen gas evolution ceased and the reaction mixture was poured onto ice, diluted with water, and extracted with five 200-ml portions of pentane. The combined pentane extracts were washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate. Removal of the solvent under reduced pressure followed by distillation through a spinning band column gave 85.5 g (0.510 mol, 85.0%) of 2,2,4,6,6-pentamethyl-cyclohexanone: bp 68° (13 mm), 194–195° (760 mm) [lit.[1,8] bp 68° (13 mm)], ir (neat) 1700 (C=O), 1385 and 1370 cm⁻¹ (*gem*-dimethyl).

N-α-Methylbenzylidenecyclohexylamine.—*N*-α-Methylbenzylidenecyclohexylamine was prepared following the procedure of Tiollais.[19]

N-Cyclohexyl α-(1-Hydroxy-2,2,4,6,6-pentamethylcyclohexyl)-acetophenone Imine (8).—To a stirred solution of 10.1 g (0.100 mol) of diisopropylamine in 50 ml of anhydrous ether at −10° under nitrogen was slowly added 55 ml of 2 *M* methyllithium in ether (Foote Chemical Co.). After the mixture was stirred for 15 min at −10° a solution of 20.1 g (0.100 mol) of *N*-α-methyl-benzylidenecyclohexylamine in 20 ml of anhydrous ether was added and the reaction mixture was stirred for 10 min at 0°. The temperature was lowered to −70° and 16.8 g (0.100 mol) of 2,2,4,6,6-pentamethylcyclohexanone in 50 ml of dry ether was added dropwise. When the addition was completed, the reaction mixture was allowed to come to room temperature and was stirred for 1 hr. The reaction mixture was poured onto ice and extracted with three 50-ml portions of ether. The extracts were combined, washed with saturated sodium chloride solution, and

(19) R. Tiollais, *Bull. Soc. Chim. Fr.*, **14**, 708 (1947).

dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and the crude product was recrystallized from low-boiling petroleum ether to yield 22.1 g (0.600 mol, 60.0%) of hydroxy imine **8**: mp 73.0–75.0; ir (CCl₄) 3200 (OH), 1650 (C=N), 1395 and 1382 (*gem*-dimethyl), 1240 cm⁻¹ (CO); nmr (CCl₄) δ 7.3–7.1 (m, 5 H), 2.6 (s, 2 H), 1.8–0.8 (m, 31 H).

Anal. Calcd for C₂₅H₃₉NO: C, 81.31; H, 10.57; N, 3.79. Found: C, 81.20; H, 10.54; N, 3.70.

N-Cyclohexyl α-(2,2,4,6,6-Pentamethylcyclohexylidene)acetophenone Imine (**9**).—To a solution of 2 ml of *N,N*-dimethylformamide in 10 ml of thionyl chloride at 0°, under nitrogen, was added 1.00 g (2.72 mmol) of **8**. After the reaction mixture was stirred for 1 hr at room temperature, it was poured onto ice and diluted with water. Solid sodium carbonate was added until carbon dioxide was no longer evolved and the reaction mixture was extracted with three 10-ml portions of pentane. The extracts were combined, shaken with water and 10% sodium bicarbonate solution, and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the crude product was recrystallized from *N,N*-dimethylformamide to give 0.700 g (2.00 mmol, 73.5%) of **9**: mp 81.0–81.5°; ir (CCl₄) 3045 (OH), 1680 (C=N), 1625 (C=C), 1382, and 1370 cm⁻¹ (*gem*-dimethyl); nmr (CCl₄) δ 8.0–7.0 (m, 4 H), 5.9 (s, 1 H), 2.3–0.7 (m, 31 H).

Anal. Calcd for C₂₅H₃₇N: C, 85.41; H, 10.61; N, 3.98. Found: C, 85.41; H, 10.71; H, 3.91.

2,2,4,6,6-Pentamethylcyclohexylideneacetophenone (**1**).—A mixture of 36.9 g (100 mmol) of **9** and 25.2 g (200 mmol) of oxalic acid dihydrate in 200 ml of water was refluxed for 36 hr. The reaction mixture was cooled and extracted with three 50-ml portions of pentane. The pentane extracts were combined, washed with 10% sodium carbonate solution and saturated sodium chloride solution, and then dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and the crude product was distilled to give 32.4 g (120 mmol, 60.0%) of 2,2,4,6,6-pentamethylcyclohexylideneacetophenone: bp 120° (0.025 mm); ir (neat) 1670 (C=O), 1620 (C=C), 1385 and 1370 cm⁻¹ (*gem*-dimethyl); nmr (CCl₄) δ 8.0–7.2 (m, 4 H), 5.35 (s, 1 H), 1.8–0.7 (m, 20 H).

Anal. Calcd for C₁₉H₂₆O: C, 84.39; H, 9.69. Found: C, 84.51; H, 9.80.

Ethylidenecyclohexylamine.—Ethylidenecyclohexylamine was prepared following the procedure of Tiollais.¹⁹

2,2,4,6,6-Pentamethylcyclohexylideneacetaldehyde (**11**).—To a stirred solution of 1.01 g (0.100 mol) of diisopropylamine in 50 ml of anhydrous ether at −10°, under nitrogen, was slowly added 50 ml of 2.0 *M* methyllithium in ether (Foote Chemical Co.). After the mixture was stirred for 15 min at −10° a solution of 12.5 g (0.100 mol) of ethylidenecyclohexylamine, bp 47.5–48.5°, in 20 ml of ether was added and the reaction mixture was stirred for 10 min at 0°. The temperature was lowered to −70° and 16.8 g (0.100 mol) of 2,2,4,6,6-pentamethylcyclohexanone in 50 ml of anhydrous ether was added dropwise. When the addition was completed, the solution was allowed to come to room temperature and stirred for 1 hr. The reaction mixture was poured onto ice and extracted with three 50-ml portions of pentane. The extracts were combined, shaken with saturated sodium chloride solution, and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to yield 28.5 g (92.0 mmol, 92.0%) of crude adduct: ir (neat) 3300 (OH), 1710 (C=N), 1380 and 1375 (*gem*-dimethyl), 1200 cm⁻¹ (CO); nmr (CCl₄) δ 8.2 (t, 1 H), 4.9 (s, 1 H), 2.5 (d, 2 H), 2.2–0.8 (m, 31 H). The crude hydroxy imine adduct was hydrolyzed upon steam distillation from oxalic acid to yield 18.1 g (90.0 mmol, 90.0%) of 2,2,4,6,6-pentamethylcyclohexylideneacetaldehyde: ir (neat) 1670 (C=O), 1595 (C=C), 1385 and 1370 (*gem*-dimethyl), 1225 cm⁻¹ (CO); nmr (CCl₄) δ 6.07 (d, 1 H, *J* = 8.0 Hz), 2.1–0.8 (m, 20 H). Ir and nmr are identical with those reported in the literature.²

2,2,4,6,6 Pentamethylcyclohexylideneacetic Acid (**3**).—To a solution of 15.5 g (80.0 mmol) of 2,2,4,6,6 pentamethylcyclohexylideneacetaldehyde in 36.0 ml of ethanol was added a solution of 28.0 g (0.170 mol) of silver nitrate dissolved in the mini-

mum amount of water. The mixture was cooled with stirring to −10° and a solution of 16.8 g (0.300 mol) of potassium hydroxide in 280 ml of water was added at a rate such that the temperature was maintained between 0 and 10°. The reaction mixture was then *vigorously* stirred at room temperature for 2 weeks and decanted, and the precipitate was washed with hot water. The decanted solution and washings were combined and extracted with three 50-ml portions of ether. The ether extracts were combined, washed with saturated sodium chloride solution, and dried over anhydrous sodium sulfate. Evaporation of the solvent under reduced pressure gave 6.00 g (31.0 mmol) of unreacted aldehyde. Acidification of the aqueous solution obtained above, followed by extraction with three 50-ml portions of pentane, drying over sodium sulfate, evaporation of solvent, and recrystallization of the crude product from methanol–water gave 6.50 g (31.0 mmol, 39.0%) of 2,2,4,6,6-pentamethylcyclohexylideneacetic acid: mp 91–93° (lit.³ mp 91–93°); ir (neat) (CCl₄) 3500 (OH), 1690 (C=O), 1620 (C=C), 1382 and 1368 cm⁻¹ (*gem*-dimethyl); nmr (CCl₄) δ 12.0 (s, 1 H), 5.77 (s, 1 H), 2.0–0.8 (m, 20 H). Ir and nmr were identical with those reported in the literature.²

(−)-2,2,4,6,6-Pentamethylcyclohexylideneacetophenone.—To a solution of 20.0 g (95.0 mmol) of (−)-2,2,4,6,6-pentamethylcyclohexylideneacetic acid in anhydrous ethyl ether, [α]²⁴₅₄₆₁ −60.3 ± 0.3 (*c* 5.0, CHCl₃), at ambient temperature was added over a 30-min period 13.6 ml of 2.2 *M* phenyllithium in benzene–ether (Foote Chemical Co.). Stirring was continued for 1 hr, after which the reaction mixture was hydrolyzed by pouring it into an ice-cold saturated ammonium chloride solution which was extracted with three 10-ml portions of ether. The extracts were combined, shaken with water and saturated sodium chloride solution, and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was distilled to yield 1.89 g (6.80 mmol, 70.0%) of (−)-2,2,4,6,6-pentamethylcyclohexylideneacetophenone, [α]²⁴₅₄₆₁ −47.0 ± 0.3 (*c* 5.0, CHCl₃). Boiling points, ir, nmr, and mass spectra were identical with those of the racemic ketone.

Anal. Calcd for C₁₉H₂₆O: C, 84.39; H, 9.69. Found: C, 84.53; H, 9.68.

α-Deuterio-2,2,4,6,6-Pentamethylcyclohexylideneacetophenone (**1**-*d*).—A 1.0 *N* solution of sodium methoxide in methanol-*d* (10 ml) was added *via* syringe to a culture tube containing 1.00 g (3.70 mmol) of 2,2,4,6,6-pentamethylcyclohexylideneacetophenone. The tube was flushed with nitrogen, fitted with a Teflon-lined cap, and placed in an oil bath at 90° for 24 hr. The tube was removed from the bath and cooled to 0°, 1 ml of deuterium oxide was added, and the resulting solution was extracted with three 5-ml portions of pentane. The pentane extracts were combined, shaken with saturated sodium chloride solution, and dried over anhydrous sodium sulfate. The pentane was removed under reduced pressure and the residue was distilled to give 0.750 g (2.80 mmol, 75.0%) of α-deuterio-2,2,4,6,6-pentamethylcyclohexylideneacetophenone, which was shown by nmr analysis to have 99% deuterium in the α position: bp 120° (0.025 mm); ir (neat) 1670 (C=O), 1605 (C=C), 1385 and 1370 cm⁻¹ (*gem*-dimethyl); nmr (CCl₄) δ 8.0–7.2 (m, 4 H), 1.8–0.7 (m, 20 H).

α-Tritio-2,2,4,6,6-pentamethylcyclohexylideneacetophenone (**1**-*t*).—α-Tritio-2,2,4,6,6-pentamethylcyclohexylideneacetophenone was prepared in a manner exactly analogous to the preparation of the α-deuterio-2,2,4,6,6-pentamethylcyclohexylideneacetophenone above, yield 75%, 271 cpm/mg.

Application of the Hammett Equation to Nonaromatic Unsaturated Systems. XII.   Reactivity and Physical Properties of the Ethynyl Proton

MARVIN CHARTON

Department of Chemistry, Pratt Institute, Brooklyn, New York   11205

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Data for rates of hydrogen–deuterium and hydrogen–tritium exchange in substituted acetylenes, equilibrium constants for complex formation between substituted acetylenes and diethyl acetamide, CH stretching frequencies in the infrared spectra of substituted acetylenes, and chemical shifts of substituted acetylenes were correlated with the extended Hammett equation, $Q_X = \alpha\sigma_{I,X} + \beta\sigma_{R,X} + h$. Of the 16 sets correlated with the extended Hammett equation, 14 gave statistically significant results. The correlations clearly demonstrated that the resonance effect is in all cases an important and, in some, the predominant component of the electrical effect.

We have for some time been interested in the application of linear free energy relationships to structure-reactivity problems, involving nonaromatic unsaturated systems.[1-14] In this work we extend our investigations to substituent effects upon the reactivity and physical properties of the ethynyl proton.   There have been several attempts to correlate data for rates of hydrogen–deuterium exchange[15,16] and hydrogen-tritium exchange[17] of $XC{\equiv}CH$ with the Taft equation.   Values of k_0 for complex formation between $XC{\equiv}CH$ and N,N-diethylacetamide are said to be linear in the Taft σ^* constants,[18]   We have reported the application of the Hammett equation to ionization constants of substituted propiolic acids, rates of alkaline hydrolysis of substituted ethyl propiolates, and dipole moments of substituted acetylenes and acetylene derivatives using the σ_p constants.   No previous attempts to apply the extended Hammett equation (eq 1) to data for compounds of the

$$Q_X = \alpha\sigma_{I,X} + \beta\sigma_{R,X} + h \qquad (1)$$

type $XC{\equiv}CH$ are extant in the literature.   To remedy this deficiency we have correlated rates of hydrogen–deuterium and hydrogen–tritium exchange, equilibrium constants for complex formation, C–H stretching frequencies, and nmr chemical shifts for ethynyl protons with eq 1.   The data used are set forth in Table I.   The σ_I constants required are generally

taken from our compilation.[19]   The σ_R constants were obtained from eq 2 using the σ_p values reported by

$$\sigma_R = \sigma_p - \sigma_I \qquad (2)$$

McDaniel and Brown[20] whenever possible.   Substituent constants were also obtained from previous papers in this series.[1-14]   Substituent constants taken from other sources are reported in Table II.   Correlations were carried out by multiple linear regression analysis.[21]

Another function of this investigation is the determination of the composition of the electrical effect of substituents upon the reactivity of the ethynyl proton.   In this system, resonance interaction between substituent and reaction site is not possible.   Superficially, the system might be expected to show a substituent effect composition analogous to that of the σ_p constants which were defined from the system 4-X-$C_6H_6CH_2Y$ where the substituent is also incapable of resonance interaction with the reaction site, Y.

Results

The results of the correlations are presented in Table III.   Of the four sets of rates of hydrogen–deuterium or hydrogen–tritium exchange one gave excellent, one gave good, and one gave fair correlation.   The other set did not give a significant correlation.   Of the three sets of equilibrium constants for hydrogen-bonded complex formation with dimethylacetamide, one gave very good, one gave good, and one gave fair correlation.   Of the five sets of infrared C–H stretching frequencies, three gave excellent, one gave very good, and one gave good correlation.   Of the four sets of nmr chemical shifts two gave good and one gave fair correlation.   The other set did not give a significant correlation.   Set 16 was correlated with the inclusion (set 16A) and exclusion (set 16B) of the values for the formyl, phenyl, and vinyl substituents.   A slight improvement was noted for set 16B over 16A.   Thus, overall, of the 16 sets correlated with eq 1, 14 gave significant results.

For purposes of comparison, a set of data consisting of partial rate factors for hydrogen–deuterium exchange at the para position of substituted benzenes

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<div align="center">

TABLE I

DATA USED IN CORRELATIONS

</div>

1. Rates of hydrogen–deuterium exchange for substituted acetylenes in 90% (v/v) acetone–water at 21°[a]

   t-BuS, 910; MeO, 63; t-Bu, 2.1; C_2H_3S, 4000

2. Rates of hydrogen–deuterium exchange for substituted acetylenes in 88.5% (v/v) methanol–water at 21°[a]

   t-BuS, 64; MeO, 15; t-Bu, 0.8; C_2H_3S, 430; C_2H_3O, 60

3. Rates of hydrogen–deuterium exchange for substituted acetylenes in dimethylformamide, 5 M in D_2O containing triethylamine, at 40°[b]

   Ph, 6.6; H, 4.8; Bu, 0.38; MeO, 130; Ph_3Si, 450

4. Rates of hydrogen–tritium exchange for substituted acetylenes in 1:4 (v/v) methanol–water at 25°[c]

   $BrCH_2$, 430; $ClCH_2$, 490; ICH_2, 265; Ph, 250; Me_3Si, 66; $PhCH_2$, 25; i-Pr, 12.3; Bu, 9.7; $BuCH_2CH_2$, 9.4; t-Bu, 8.9; t-$BuCH_2$, 7.0

5. Equilibrium constants for complex formation of substituted acetylenes with diethylacetamide in squalane at 28°[d]

   $BuCH_2$, 0.60; t-Bu, 0.60; Me_3Si, 0.65; $ClCH_2$, 1.54; $BrCH_2$, 1.50

6. Equilibrium constants for complex formation of substituted acetylenes with diethylacetamide in squalane at 0°[d]

   t-Bu, 0.96; Me_3Si, 1.12; $ClCH_2$, 2.78; $BrCH_2$, 2.74

7. Equilibrium constants for complex formation of substituted acetylenes with diethylacetamide in squalane at 25°[d]

   t-Bu, 0.58; Me_3Si, 0.66; $ClCH_2$, 1.73; $BrCH_2$, 1.67; $BuCH_2$, 0.60

8. CH stretching frequencies for substituted acetylenes in hexane[e]

   $ClCH_2$, 3318; 4-$MeOC_6H_4$, 3323; Ph, 3323; 4-$O_2NC_6H_4$, 3319; Bz, 3306; EtO_2C, 3310; EtO, 3339; $BrCH_2$, 3316; $BuCH_2CH_2$, 3319

9. CH stretching frequencies of substituted acetylenes in diethyl ether[e]

   $ClCH_2$, 3317; Ph, 3320; Bz, 3304; EtO_2C, 3309; $BrCH_2$, 3315; $BuCH_2CH_2$, 3317

10. CH associated stretching frequencies of substituted acetylenes in diethyl ether[e]

    $ClCH_2$, 3250; Ph, 3250; Bz, 3219; EtO_2C, 3320; $BrCH_2$, 3250; $BuCH_2CH_2$, 3267

11. CH stretching frequency differences of substituted acetylenes in dimethylacetamide[f]

    Bu, 74; Ph, 91; $ClCH_2$, 94; MeO, 81; EtO_2C, 123; $BrCH_2$, 94; $BuCH_2$, 74; $BuCH_2CH_2$, 72

12. CH stretching frequencies of substituted acetylenes in dimethylacetamide[f]

    Bu, 3314; Ph, 3314; $ClCH_2$, 3314; MeO, 3328; EtO_2C, 3306; $BrCH_2$, 3313; $BuCH_2$, 3314; $BuCH_2CH_2$, 3314; CN, 3304

13. Proton chemical shifts of substituted acetylenes[a]

    Me, −1.76; Pr, −1.79; Bu, −1.73; CHO, −1.89; CH_2OH, −2.33; CH_2I, −2.19; CH_2Br, −2.33; CH_2Cl, −2.40; C_2H_3, −2.92; Ph, −2.93; EtS, −2.64; EtO, −1.33

14. Proton chemical shifts of substituted acetylenes (vapor phase)[g]

    H, 1.50; Me, 1.56; Et, 1.59; HC_2, 1.48; Pr, 1.72; t-Bu, 1.75; CHO, 2.75; Ac, 3.00

15. Proton chemical shifts of substituted acetylenes in CCl_4[g]

    Me, 1.76; Et, 1.78; HC_2, 2.01; Pr, 1.75; t-Bu, 1.87; CHO, 3.28; Ac, 3.03

16. Proton chemical shifts of substituted acetylenes in CCl_4[h]

    H, 8.20; Pr, 8.21; Bu, 8.27; $BuCH_2$, 8.25; $ClCH_2$, 7.60; $BrCH_2$, 7.67; ICH_2, 7.81; $HOCH_2$, 7.67; $MeOCH_2$, 7.63; $PhOCH_2$, 7.99; CHO, 8.11; Ph, 7.07; C_2H_3, 7.08; $HOCH_2CH_2$, 8.08

21. Partial rate factors for hydrogen–deuterium exchange with KNH_2 in NH_3 (1)[i]

    F, 100; CF_3, 10,000; PhO, 4; Ph, 2.9; Me_2N, 0.07; H, 1; Me, 0.4; MeO, 0.5

[a] W. Drenth and A. Loewenstein, *Recl. Trav. Chim. Pays-Bas,* **81,** 635 (1962). [b] R. E. Dessy, Y. Okuzumi, and A. Chen, *J. Amer. Chem. Soc.,* **84,** 2899 (1962); [c] C. Eaborn, G. A. Skinner, and D. R. M. Walton, *J. Chem. Soc. B,* 989 (1966). [d] R. Queignec and B. Wojtkowiak, *Bull. Soc. Chim. Fr.,* 860 (1970). [e] J. C. Brand, G. Eglinton, and J. F. Morman, *J. Chem. Soc.,* 2526 (1960). [f] R. West and C. S. Kraihanzel, *J. Amer. Chem. Soc.,* **83,** 765 (1961). [g] P. Jouve, Thesis, Faculte des Science de l'Université de Paris, Paris, 1966, p 23. [h] M. M. Kreevoy, H. B. Charman, and D. R. Vinard, *J. Amer. Chem. Soc.,* **83,** 1978 (1961). [i] A. I. Shatenshtein, *Tetrahedron,* **18,** 95 (1962).

<div align="center">

TABLE II

SUBSTITUENT CONSTANTS

</div>

X	σ_I	Ref	σ_R	Ref
t-BuS	0.23	a	−0.21	b
C_2H_3S	0.27	a	−0.15	b
C_2H_3O	0.35	a	−0.50	b
Ph_3Si	−0.07	c	0.17	c
t-$BuCH_2$	−0.02	a	−0.15	a
$BuCH_2CH_2$	−0.04	a	−0.11	a
4-$MeOC_6H_4$	0.09	d	−0.18	e
4-$O_2NC_6H_4$	0.22	d	0.01	e
HC_2	0.35	f	−0.09	f
CH_2CH_2OH	0.00	g	−0.10	a
$PhOCH_2$	0.13	a	−0.06	a

[a] Estimated as described in M. Charton, Abstracts, 148th National Meeting of the American Chemical Society, Chicago, Ill., Aug 30–Sept 4, 1964, p 56-V. [b] Calculated from the σ_p value estimated by the method of M. Charton, *J. Org. Chem.,* **28,** 3121 (1963). [c] Calculated from σ_m and σ_p values reported by R. A. Benkeser, C. E. DeBoer, R. E. Robinson, and D. M. Sauve, *J. Amer. Chem. Soc.,* **78,** 682 (1956). [d] Calculated from the pK_a for 4-$XC_6H_4CH_2CO_2H$. [e] Calculated from σ_p values reported by E. Berliner and L. H. Liu, *J. Amer. Chem. Soc.,* **75,** 2417 (1953). [f] M. Charton in "The Chemistry of the Alkenes," Vol. 2, J. Zabicky, Ed., Wiley-Interscience, London, 1970, p 511. [g] Calculated from the pK_a of $HOCH_2CH_2CH_2CO_2H$.

(set 21) was correlated with eq 1. Excellent results were obtained for this correlation.

Discussion

Substituent Effects on the Acidity of the Ethynyl Proton.—The two factors which characterize the nature of a substituent effect are its composition and its magnitude. The composition of the electrical effect may be described in terms of the quantity P_R, where[22]

$$P_R = \frac{100\beta}{\alpha + \beta} \tag{3}$$

Table IV lists P_R values for the sets studied here.

The values of P_R obtained for the hydrogen–deuterium exchange (sets 1 and 2) show clearly the presence of a significant resonance effect. This conclusion is supported by the results obtained for the hydrogen–tritium exchange, for which a very much greater value of P_R is obtained. We have previously noted that the composition of the substituent effect upon the ethynyl proton might be expected to be compar-

(22) M. Charton, Abstracts, 157th National Meeting of the American Chemical Society, Minneapolis, Minn., April 13–18, 1969, p 17-P.

TABLE III
RESULTS OF CORRELATIONS

Set	α	β	h	R^a	F^b	r^c	$s_{est}{}^d$	s^d	s^d	$s_h{}^d$	n^e
1	6.86	4.41	2.37	0.9991	286.8[k]	0.434	0.0755	0.0301[k]	0.267[k]	0.0747[k]	4
2	7.74	3.46	0.909	0.990	51.88[j]	0.595	0.197	0.762[h]	0.637[k]	0.183[k]	5
3	12.3	7.26	1.22	0.694	0.930[m]	0.910[l]	1.13	10.5[o]	5.36[o]	0.569[n]	5
4	5.59	6.55	2.08	0.969	62.75[j]	0.011	0.204	0.613[l]	1.05[l]	0.113[l]	11
5	1.53	0.828	-0.0362	0.993	72.94[j]	0.114	0.0354	0.129[h]	0.237[l]	0.0203[o]	5
6	1.63	0.891	0.211	0.999	217.9[k]	0.240	0.0205	0.0783[k]	0.155[n]	0.0119[k]	4
7	1.73	0.995	-0.0130	0.995	100.0[h]	0.114	0.0343	0.125[h]	0.230[k]	0.0197[p]	5
8	-0.791	-47.8	3315	0.989	89.08[j]	0.156	1.92	6.11[q]	3.63[j]	1.41[j]	7
9	11.8	-60.8	33.11	0.970	23.91[j]	0.870[e]	1.88	12.5[o]	14.5[k]	2.32[j]	6
10	-74.3	-78.6	3255	0.981	37.77[h]	0.870[l]	4.82	32.1[n]	37.1[n]	5.96[j]	6
11	-4.27	-34.7	3311	0.981	77.05[j]	0.283	1.49	2.67[n]	3.06[j]	0.776[j]	9
12	97.1	50.4	82.9	0.991	135.0[j]	0.009	2.70	7.05[j]	5.69[j]	1.42[j]	8
13	-0.355	-1.31	-2.30	0.367	0.702[m]	0.127	0.514	1.21[p]	1.11[o]	0.240[j]	12
14	0.328	4.08	2.02	0.883	8.874[j]	0.635	0.334	0.836[p]	1.37[k]	0.166[h]	8
15	1.02	3.48	2.22	0.929	12.56[j]	0.676	0.297	0.798[o]	1.28[l]	0.171[l]	7
16A	-3.79	5.30	8.47	0.712	5.669[k]	0.702[h]	0.307	1.19[h]	1.77[i]	0.207[j]	14
16B	-2.51	-0.137	8.08	0.797	6.942[k]	0.477	0.184	0.776[i]	1.85[q]	0.169[j]	11
21	6.20	3.01	0.270	0.951	23.59[g]	0.140	0.599	1.09[h]	0.655[h]	0.361[o]	8

[a] Multiple correlation coefficient. [b] F test for significance of regression. [c] Partial correlation coefficient of σ_I on σ_R. [d] Standard errors of the estimate, α, β, and h. [e] Number of points in set. [f] 99.9% confidence level (CL). [g] 99.5% CL. [h] 99.0% CL. [i] 98.0% CL. [j] 97.5% CL. [k] 95.0% CL. [l] 90.0% CL. [m] 90% CL. [n] 80.0% CL. [o] 50.0% CL. [p] 20% CL. [q] 20% CL.

TABLE IV
VALUES OF P_R

Set	P_R	Set	P_R	Set	P_R
1	39	7	36	12	34
2	31	8	b	13	a
3	a	9	b	14	b
4	54	10	c	15	b
5	35	11	b	16	d
6	d			21	33

[a] Correlation was not significant for this set. [b] α was not significant for this set. [c] α and β were not significant for this set. [d] β was not significant for this set.

able to that of the $\sigma_p{}^\circ$ constants, for which P_R is 40. This does indeed seem to be the case. It is of interest to compare the values of P_R obtained for rates of hydrogen–deuterium exchange on substituted acetylenes with rates of hydrogen–deuterium exchange on other systems. Of particular interest is exchange at the ortho and para positions of substituted benzenes. Data are available for the rates of hydrogen–deuterium exchange of substituted benzenes in liquid ammonia. The solvent is not the same as that used for the substituted acetylenes and this may very well affect the P_R value for exchange at the ortho position. The composition of the electrical effect for exchange at the para position should be independent of solvent, however. That this is the case may readily be seen from the following argument. Data for a wide variety of para-substituted benzene set types have been correlated in various solvents by the σ_p constants. For a substituent constant σ_X, we may write

$$P_R = \frac{100\delta}{\lambda + \delta} \tag{4}$$

where

$$\sigma_X = \lambda \sigma_{I,X} + \delta \sigma_{R,Y} \tag{5}$$

For σ_p, the value of P_R observed is 50. Since data in various solvents are all correlated by the σ_p constants with P_R of 50, obviously the composition of the electrical effect is independent of solvent. This does not mean that α and β for para-substituted benzenes are

independent of solvent, but simply that they vary in such a way that their ratio, and therefore P_R, is a constant.

The value of P_R obtained for the ortho position is 5.7.[23] Clearly, the localized effect is by far the predominant factor. This is in sharp contrast to the behavior of the substituted acetylenes. It is presumably due to the different geometries of the two systems. In the exchange at the ortho position, the reaction site is almost in contact with the substituent, whereas in the substituted acetylenes, two carbon atoms intervene between the reaction site and the substituent. The value of P_R obtained for the rates of hydrogen–deuterium exchange in the para position of substituted benzenes is 33, in excellent agreement with the values obtained for the substituted acetylenes. This value was calculated from a correlation of partial rate factors for hydrogen–deuterium exchange of substituted benzenes with eq 1 (set 21, Tables I and III).

The magnitude of the electrical effect is measured by the magnitude of α. The value of α may be calculated from the field effect by the equation

$$\alpha_G = \frac{\cos\theta_G r^2{}_{G^\circ} \alpha_{G^\circ}}{\cos\theta_{G^\circ} r^2{}_G} \tag{6}$$

where θ and r are defined below. G refers to the skeletal group to which the substituent X and reaction site Y are bonded and G° refers to the reference skeletal group (the phenylene group).
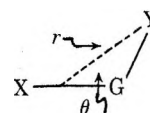
The value of α calculated from α_{G° for set 21 is 14.2 (in liquid ammonia). The values obtained for 90% (v/v) acetone–water at 21° (set 1) and 88.5% (v/v) methanol–water at 21° (set 2) are 6.86 and 7.74, respectively. The difference in α values can be ascribed to the differences in medium and in temperature. The value of α obtained for hydrogen–tritium exchange in

(23) M. Charton, *Progr. Phys. Org. Chem.*, **8**, 235 (1971).

methanol–water at 25° (set 4) is 5.59, in fairly good agreement with the value of α for hydrogen–deuterium exchange in methanol–water at 21° of 7.74.

Another measure of the acidity of the ethynyl proton is provided by the data for complex formation of substituted acetylenes with diethylacetamide. The values of P_R obtained for these data (sets 5 and 7) are 35 and 36, respectively, in excellent agreement with the values of P_R obtained for hydrogen–deuterium exchange of substituted acetylenes. The magnitude of the localized effect in these sets is much smaller than that observed for hydrogen–deuterium or hydrogen–tritium exchange; the values are 1.53, 1.63, and 1.73. Obviously the complex formation is much less sensitive to substituent effects. The same effect is observed in a comparison of the magnitude of α for complex formation of 2-substituted pyridines with phenols with α for ionization of 2-substituted pyridinium ions (1.43 and 11.4, respectively).

Infrared C–H Stretching Frequencies.—The resonance effect is predominant in the majority of the sets of infrared C–H stretching frequencies, although the C–H stretching frequencies of substituted acetylenes in dimethylacetamide (set 12) show a P_R value of 34, in good agreement with those observed for hydrogen–deuterium exchange and for complex formation with diethylacetamide. There is no explanation known to us for the predominance of the resonance effect in sets 8, 9, and 11. Comparable studies of C–H stretching frequencies as a function of substituent variation do not seem to be extant for substituted benzenes or ethylenes. It should be noted that C–H stretching frequencies involve very small changes. In any case,

the importance of the resonance effect in these data is obvious.

Nmr Proton Chemical Shifts.—We have previously observed that proton chemical shifts of cis and trans protons in substituted ethylenes are successfully correlated by eq 1. It therefore seemed of interest to study the proton chemical shifts of substituted acetylenes. Although significant correlations were obtained for three of the four sets studied (sets 14, 15, and 16B), the results are not particularly good. Excluding set 16B, in which the substituents are all of the type –CH₂X, and therefore there is no dependence on the resonance effect, the results are in good agreement with the majority of the sets of infrared frequencies studied and in accord with the values of P_R observed for proton chemical shifts of cis and trans protons in substituted ethylenes.[13] As regards the magnitude of the resonance effect, it is larger for proton chemical shifts in substituted acetylenes (β 4.08 and 3.48 for sets 14 and 15, respectively) than it is for either trans protons (β 2.11) or cis protons (β 2.20) in substituted ethylenes.[13] As the correlation of proton chemical shifts for substituted acetylenes failed with the most extensive set of substituents studied (set 13), the conclusion we have arrived at can only be regarded as qualitative.

Conclusion

Overall, the results obtained clearly show that resonance effects are important in determining the reactivity and physical properties of the ethynyl proton. They also demonstrate the applicability of eq 1 to data for substituted acetylenes.

A Synthesis of 2,3-Dihydro-1*H*-cyclopenta[*a*]chrysene[1]

AUGUSTINE SILVEIRA, JR.

Chemistry Department, State University of New York, College at Oswego, Oswego, New York 13126

EARL J. MCWHORTER*

Chemistry Department, University of Massachusetts, Amherst, Massachusetts 01002

2,3-Dihydro-1*H*-cyclopenta[*a*]chrysene (13) has been synthesized from 9,10-dihydrophenanthrene by a ten-step reaction sequence. The peripheral benzo ring atoms arise from succinic acid by a Haworth-type reaction sequence and the cyclopenteno atoms from carboethoxyethanoyl chloride by a Friedel–Crafts condensation, leading after several steps (7–9) to the key intermediate, 2-(3-carboxypropyl)-7-(2-carboxyethyl)phenanthrene (10), which was cyclized to give a mixture of products. The major constituent, established as the pentacyclic diketone, 2,3,8,9,10,11-hexahydro-1*H*-cyclopenta[*a*]chrysene-1,11-dione (11) by spectroscopic evidence, was converted to the final product (13) by reduction and dehydrogenation. Several examples of Friedel–Crafts acylation with carboethoxyethanoyl chloride are described.

In 1943 Ruzicka and coworkers[2] dehydrogenated quinovic acid and isolated among other products two aromatic hydrocarbons which were assumed to be alkylcyclopentenochrysenes. Since quinovic acid is now known to be an ursane rather than a lupane type triterpene,[3] these aromatic hydrocarbons probably have a picene rather than a cyclopentenochrysene ring

system. Nevertheless it seems possible that aromatic hydrocarbons with a cyclopentenochrysene ring system could be formed, at least in small amounts, during dehydrogenation of authentic lupane type triterpenes, just as cyclopentenophenanthrene derivatives are formed by dehydrogenation of steroids. However, as yet there are no authentic reports of isolation of such substances.

Similarly, several picene type hydrocarbons, apparently formed from triterpenes during the carbonization process, have been isolated by Šorm and coworkers[4]

(1) (a) Presented in part at the 154th National Meeting of the American Chemical Society, Chicago, Ill., Sept 11–15, 1967.   (b) Taken in part from the Ph.D. Dissertation of A. Silveira, Jr., University of Massachusetts, Amherst, Mass., 1962.

(2) L. Ruzicka, A. Grov, and G. Anner, *Helv. Chim. Acta*, **26**, 254 (1943).

(3) For a listing of the various types of triterpenes see T. G. Halsall and R. T. Aplin, *Fortschr. Chem. Org. Naturstoffe*, **22**, 153 (1964).

(4) V. Jarolim, K. Hejno, F. Hemmert, and F. Šorm, *Collect. Czech. Chem. Commun.*, **30**, 873 (1965).

from Bohemian brown coal. Since the lupane type triterpene, betulin, is also a constituent of this coal,[5] one might reasonably expect the presence of some cyclopentenochrysene derivatives, even though to date none has been reported. In anticipation of isolation of systems of this type we have developed a synthesis of 2,3-dihydro-1*H*-cyclopenta[a]chyrsene (13) that should be applicable to the synthesis of various alkyl-substituted derivatives.

Our synthesis of 13 is based on a route to alkylpicenes described by Phillips and coworkers[6] in which the picene nucleus is built up from a phenanthrene system by Haworth-type reaction sequences which generate the two terminal benzo rings of the molecule. By appropriate modification alkyl groups may be attached to the terminal rings. Similarly, in our synthesis of 13 the three central rings are derived from phenanthrene, the terminal benzo ring from succinic acid, and the cyclopenteno ring from malonic acid. The most unique feature of the synthesis is the use of the monoester acid chloride of malonic acid as an acylating agent in a Friedel–Crafts reaction to introduce the three-carbon unit that becomes the cyclopenteno ring.

The synthesis starts with succinoylation of 9,10-dihydrophenanthrene (1) as previously described.[7] The resulting keto acid 5 was converted to methyl 4-(9,10-dihydro-2-phenanthryl)butanoate (6) by Wolff–Kishner reduction and esterification.[6a] An alternative

route of catalytic hydrogenation of the methyl ester of 5 worked satisfactorily, but offered no advantage over the published one.[6a]

The next step, the introduction of the three-carbon unit that becomes the cyclopenteno ring, was accomplished by a Friedel–Crafts condensation of 6 with carboethoxyethanoyl chloride (2). The use of 2 as an acylating agent in Friedel–Crafts reactions was reported by Marguery[8] in 1905. He describes the formation of β-keto esters by reaction of 2 with benzene, toluene, and *p*-xylene; however, no yields are given. Since then, the reaction has found no application except for one report of its condensation with ferrocene.[9] To check the feasibility of the reaction, 2 was condensed with benzene and gave a 64% yield of ethyl benzoylacetate. Reaction of 2 with 9,10-dihydrophenanthrene (1) gave a 73% yield of ethyl 3-oxo-3-(9,10-dihydro-2-phenanthryl)propanoate (3). The same compound was prepared from the known compound 2-acetyl-9,10-dihydrophenanthrene (4) by base-catalyzed carboethoxylation with diethyl carbonate, thereby establishing the point of attachment of the side chain in 3 as the expected 2 position. On the basis of this result as well as the other known acylations of 9,10-dihydrophenanthrene and its derivatives,[6,7,10] all of which upon Friedel–Crafts acylation react at the 2 (or 7) position, we assume that the reaction of 6 and 2 occurs similarly, giving 2-(2-carboethoxy-1-oxoethyl)-7-(3-carbomethoxypropyl)-9,10-dihydrophenanthrene (7).

Catalytic reduction of the keto group in 7 gave 8, which was dehydrogenated to 9 and then converted to the diacid 2-(3-carboxypropyl)-7-(2-carboxyethyl)-phenanthrene (10). Polyphosphoric acid cyclization of
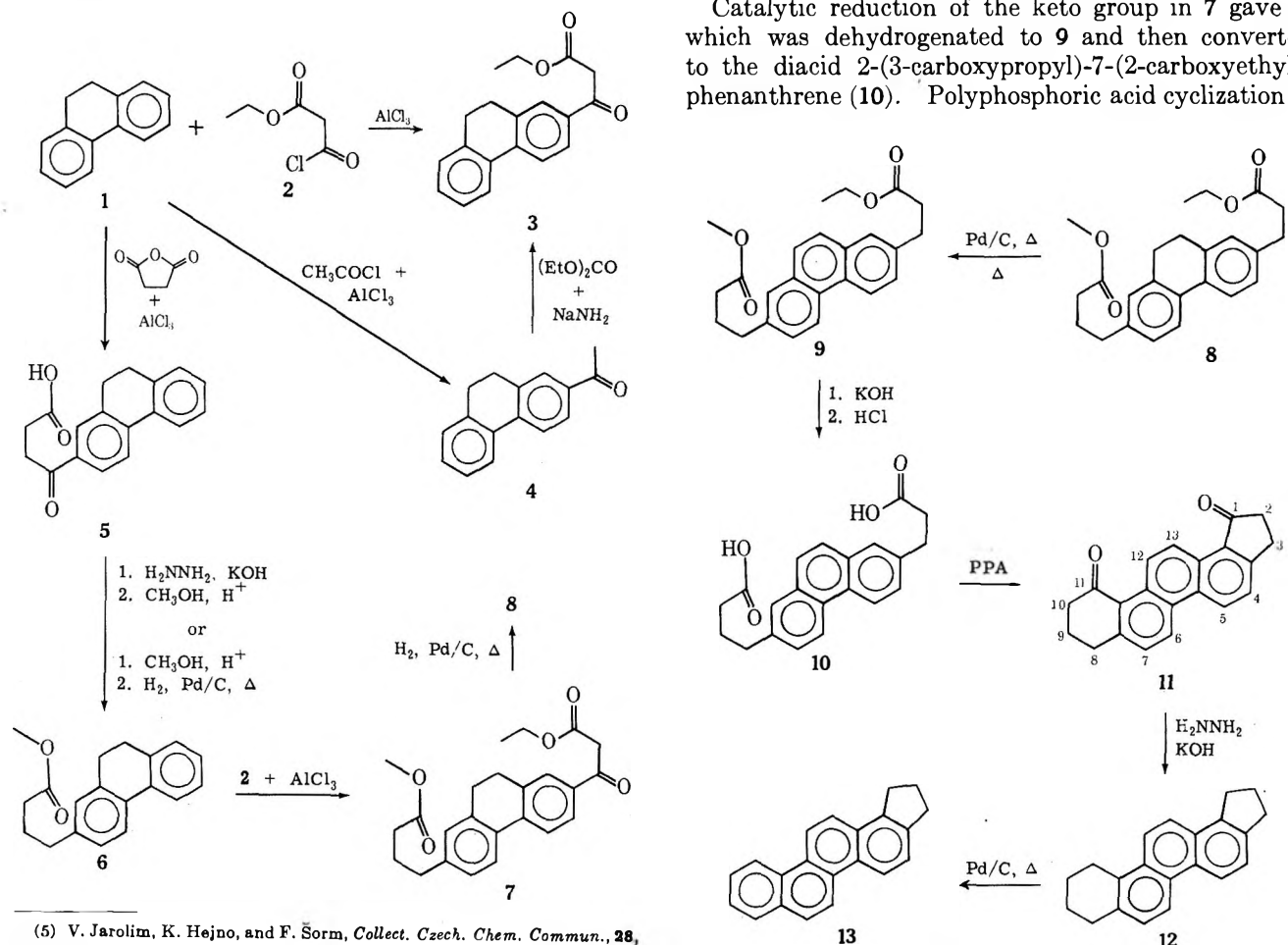
(5) V. Jarolim, K. Hejno, and F. Šorm, *Collect. Czech. Chem. Commun.*, **28**, 2318 (1963).

(6) (a) D. D. Phillips, *J. Amer. Chem. Soc.*, **75**, 3223 (1953); (b) D. D. Phillips and E. J. McWhorter, *ibid.*, **77**, 3856 (1955); (c) D. D. Phillips and D. E. Tuites, *ibid.*, **78**, 5438 (1956).

(7) D. D. Phillips and E. J. McWhorter, *ibid.*, **76**, 4948 (1954).

(8) F. Marguery, *Bull. Soc. Chim. Fr.*, **33**, 548 (1905).

(9) K. L. Rinehart, Jr., R. J. Curby, Jr., and P. E. Sokol, *J. Amer. Chem. Soc.*, **79**, 3421 (1957).

(10) W. Carruthers and D. A. Watkins, *J. Chem. Soc.*, 724 (1964).

10 gave a diketone mixture from which the major component was isolated by column chromatography. Although in principle four isomers would be formed, on the basis of known examples of cyclizations of this type[6,7,10] in which the side chains invariably cyclize predominantly to the 1 and 8 positions of the phenanthrene ring, the major product should be the desired isomer, 2,3,8,9,10,11-hexahydro-1H-cyclopenta[a]chrysene-1,11-dione (**11**). The subsequent conversion of the major product **11** to a compound with a chrysene-like uv spectrum confirms the cyclization of the four-carbon side chain of **10** to C$_1$ of the phenanthrene nucleus. The nmr and ir data proved that the three-carbon side chain cyclized to give **11** rather than **14**. The nmr spectrum shows doublets at δ 8.74
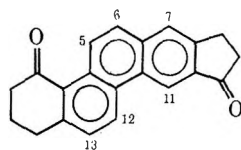
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(1 H, $J = 8.1$ Hz) and 8.66 (1 H, $J = 8.1$ Hz) for the two peri hydrogens at positions 5 and 6 of **11** corresponding to the expected values near δ 8.7.[11a] These doublets require hydrogens ortho to both the C-5 H and C-6 H, thus eliminating structure **14** in which one of the peri hydrogens would appear as a singlet. Also the spectrum shows two doublets between δ 9.0 and 9.5 corresponding to the C-12 H and C-13 H of **11**. These observed downfield shifts of the C-12 and C-13 H peri to the keto function agree with values reported for similar compounds.[11b] If the compound had structure **14**, one should observe three peaks (C-5 H doublet and C-11 H singlet) in the region of δ 9.0–9.5. The integral of the other aromatic hydrogens near δ 7.5 corresponds to two protons (C-4 and C-7 H). Compound **14** would have shown three protons in this region (C-6 H, C-7 H, C-13 H). The structural assignment of **11** was substantiated by its ir spectrum, which in the region of aromatic C–H out-of-plane deformation showed absorption at 844, 813, and 803 cm⁻¹ but no peaks in the 900–860-cm⁻¹ region indicating no isolated aromatic C–H bonds,[12] as would be present if cyclization of **10** had occurred at other than the 1 and 8 positions.

Compound **11** was converted to the corresponding hydrocarbon **12** by a Wolff–Kishner reduction. Although **12** was not isolated in pure condition, its ir spectrum with peaks at 828 and 800 and a shoulder at 837 cm⁻¹ again is consistent with the ring system of 2,3,8,9,10,11-hexahydro-1H-cyclopenta[a]chrysene. A similar structure (**15**) described by Carruthers and
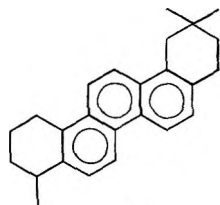
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Watkins[10] showed but a single peak at 810 cm⁻¹. The fact that our system has five rather than six carbons in one of the peripheral rings may account for the extra peaks we observe.

Dehydrogenation of **12** gave the final product, 2,3-dihydro-1H-cyclopenta[a]chrysene (**13**). The uv spectrum of the compound unequivocally establishes the aromatic portion of the system as a chrysene rather than a benzanthracene unit.[13] The uv spectrum of **13** together with the nmr and ir data of the precursor diketone, **11**, fully establishes the structure of **13**. Again the ir spectrum shows peaks in the out-of-plane aromatic C–H region characteristic of sets of ortho hydrogens rather than isolated aromatic hydrogens.

The synthetic route for preparation of **13** outlined above can be applied to the preparation of alkyl-substituted cyclopentenochrysenes by introduction of alkyl groups at the ketonic functions of **5** and **11** and by substitution of the acidic hydrogen of **7**. These extensions of the synthesis as well as investigations of further applications of **2** as a Friedel–Crafts acylating agent are anticipated.

Experimental Section

Methyl 4-(9,10-Dihydro-2-phenanthryl)butanoate (6).—Absolute MeOH (60 ml) and 10% Pd/C catalyst (1.0 g) were added to an electrically heated hydrogenation flask[14] containing 8.0 g (25 mmol) of methyl 4-oxo-4-(9,10-dihydro-2-phenanthryl)butanoate prepared from the acid **5** as described by Fieser and Johnson.[15] The mixture was shaken in a Parr hydrogenation apparatus at 48 psi for 12 hr at 60°. The catalyst was filtered off, the solvent was removed, and the residue was distilled, giving 5.68 g (72%) of the ester **6**, bp 230–236° (5 mm), n^{27}D 1.5955.

Carboethoxyethanoyl Chloride (2).—Carboethoxyethanoyl chloride was prepared by the method of Breslow, Baumgarten, and Hauser.[16]

Ethyl Benzoylacetate.[8,17]—Benzene (2.58 g, 33 mmol) and carboethoxyethanoyl chloride (5.0 g, 33 mmol) dissolved in 50 ml of freshly distilled ethylene chloride were added to a 500-ml, three-necked, round-bottom flask, equipped with stirrer, addition tube for solids,[18] and reflux condenser with drying tube. To the stirred, ice-cooled solution anhydrous AlCl₃ (21.1 g, 158 mmol) was added over a period of 45 min. The reaction mixture was maintained at 0° for 30 min and then allowed to warm to room temperature. After 3 hr a mixture of ice and 3 N HCl was added to the reaction mixture, and the organic layer was separated, washed three times with water, and dried (MgSO₄). Removal of solvent and distillation gave 4.1 g (65%) of ethyl benzoylacetate, bp 142–146° (6 mm) [lit.[19] bp 132–137° (4 mm), 165–169° (20 mm)].

Ethyl 3-Oxo-3-(9,10-dihydro-2-phenanthryl)propanoate (3). Method A. Acylation with Carboethoxyethanoyl Chloride.—

(11) R. H. Martin, N. Defay, and F. Geerts-Evrard, *Tetrahedron*, **20**, 1505 (1964); *e.g.*, (a) Figures 3 and 5, compounds XXVIII and XXX; (b) Figures 2–5, compounds XX, XXI, XXVII, and XXVIII.

(12) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," Wiley, New York, N. Y., 1958, p 79.

(13) M. F. Ansell, G. T. Brooks, and B. A. Knights, *J. Chem. Soc.*, 212 (1961). The uv spectrum of 1,2-dimethylchrysene is given and is very similar to that of compound **13**.

(14) R. Adams and V. Voorhees, *Org. Syn.*, **1**, 61 (1941).

(15) L. F. Fieser and W. S. Johnson, *J. Amer. Chem. Soc.*, **61**, 1647 (1939).

(16) D. Breslow, E. Baumgarten, and C. Hauser, *ibid.*, **66**, 1286 (1944).

(17) A preliminary investigation of this reaction was made by J. P. Bourgault in an undergraduate senior research project.

(18) L. F. Fieser, "Experiments in Organic Chemistry," 3rd ed, Revised, D. C. Heath, Boston, Mass., 1957, p 265.

(19) R. L. Shriner, A. G. Schmidt, and L. J. Roll, *Org. Syn.*, **2**, 266 (1943).

Anhydrous AlCl₃ (27.8 g, 209 mmol) was added over a period of 30 min to a solution of 15.0 g (83.4 mmol) of 9,10-dihydrophenanthrene (1) and 14.7 g (98 mmol) of carboethoxyethanoyl chloride (2) in 250 ml of freshly distilled ethylene chloride cooled to 0°. The green-black reaction mixture was stirred at 0° for 3 hr and at room temperature for 6 hr and then poured with vigorous stirring into a mixture of ice and 6 *N* HCl. The organic layer was washed three times with water, dried (MgSO₄), and concentrated under reduced pressure in a rotary evaporator, giving 17.9 g (73%) of crude 3. Further purification by chromatography on neutral alumina using benzene–chloroform (9:1) as eluent gave an analytical sample of 3 as a pale yellow oil: n^{28}D 1.6186; uv max 252 nm (log ε 4.42), 265 (4.36), 302 (4.39); ir 735, 769, 1605, 1681, 1736, 2907 cm⁻¹.

Anal. Calcd for C₁₉H₁₈O₃: C, 77.53; H, 6.16. Found: C, 77.64; H, 5.96.

3. Method B. Acetylation and Carboethoxylation.—To 30 ml of tetrahydrofuran, dried and distilled over LiAlH₄, was added 3.90 g (100 mmol) of NaNH₂ (Farchan Research Laboratories, Cleveland, Ohio) and while cooling in an ice bath 11.1 g (50 mmol) of 2-acetyl-9,10-dihydrophenanthrene²⁰(4) in 175 ml of anhydrous tetrahydrofuran was added over a 15-min period. To this stirred mixture diethyl carbonate (11.8 g, 0.10 mmol) was added dropwise over a period of 20 min. The reaction mixture was stirred at 0° for 30 min and at 55–60° for 2 hr and then poured into a slush of ice and acetic acid. The mixture was extracted with ether, the organic layer was washed with NaHCO₃ solution and three times with water and dried (CaSO₄), and the solvent was removed, leaving 10.5 g (71%) of a yellow-orange oil, n^{33}D 1.6180, which has ir and uv spectra identical with those of 3 prepared by method A.

2-(2-Carboethoxy-1-oxoethyl)-7-(3-carbomethoxypropyl)-9,10-dihydrophenanthrene (7).—Anhydrous AlCl₃ (88.0 g, 600 mmol) was added at ice temperature over a period of 1 hr to a solution containing 48.0 g (171 mmol) of methyl 4-(9,10-dihydro-2-phenanthryl)butanoate (6) and 30.2 g (200 mmol) of carboethoxyethanoyl chloride (2) in 500 ml of purified ethylene chloride. The green-brown complex was stirred for 3 hr at 0° and for 8 hr at room temperature. The reaction mixture was poured with vigorous stirring into a mixture of 6 *N* HCl and ice. The organic layer was separated, washed three times with water, and dried (MgSO₄). The solvent was removed on a rotary evaporator, leaving 49.9 g (74%) of crude product which was used in the next step without further purification. In other runs yields ranged from 80 to 88%. For analytical purposes a sample of the oil was chromatographed on alumina with petroleum ether (bp 30–60°)–benzene as eluent, giving 7 as a pale yellow oil: n^{28}D 1.5784; uv max 253 nm (log ε 4.49), 275 (4.34), 315 (4.36); ir 743, 820, 893, 1605, 1681, 1739, 2898 cm⁻¹.

Anal. Calcd for C₂₄H₂₆O₅: C, 73.07; H, 6.64. Found: C, 73.26; H, 6.43.

2-(3-Carbomethoxypropyl)-7-(2-carboethoxyethyl)-9,10-dihydrophenanthrene (8).—To an electrically heated hydrogenation flask was added 1.5 g of 10% Pd/C catalyst and 15 g (39.4 mmol) of crude ester 7 dissolved in 50 ml of anhydrous ethyl acetate. The solution was heated at about 72° and shaken for 22 hr under a pressure of 60 psi of H₂. The solution was cooled, the catalyst was filtered off, and the solvent was removed, leaving 12.3 g (85%) of a yellow oil. This oil was filtered through an alumina column using benzene–ligroin (50:50) as an eluent. The residue left on evaporation of solvent was used directly in the next reaction. For analytical purposes a small amount of the oil was chromatographed on alumina, giving ester 8 as a pale yellow oil: n^{24}D 1.5570; uv max 269 nm (log ε 4.31); ir 741, 823, 881, 1736, 2898 cm⁻¹.

Anal. Calcd for C₂₄H₂₈O₄: C, 75.76; H, 7.42. Found: C, 75.62; H, 7.39.

2-(3-Carbomethoxypropyl)-7-(2-carboethoxyethyl)phenanthrene (9).—To 15.46 g (40.7 mmol) of ester 8 was added 0.7 g of Pd/C catalyst. The reactants were intimately mixed by heating in a water bath using a rotary evaporator and heated under N₂ on an oil bath at 270° for 6 hr, the melt was dissolved in benzene, the catalyst was filtered off, and the solution was run through an alumina column. Evaporation of solvent gave 11.6 g (75.5%) of oily product. Further chromatography on alumina using benzene–ligroin as eluent gave an analytical sample of the ester 9 as a pale yellow oil: n^{27}D 1.5821; uv max 253 nm (log ε 4.93), 277 (4.40), 296 (4.11); ir 717, 746, 813, 833, 889, 1623, 1739, 2898 cm⁻¹.

(20) A. Burger and E. Mosettig, *J. Amer. Chem. Soc.*, **58**, 1857 (1936).

Anal. Calcd for C₂₄H₂₆O₄: C, 76.16; H, 6.93. Found: C, 76.32; H, 7.18.

2-(3-Carboxy-1-propyl)-7-(2-carboxyethyl)phenanthrene (10).—To a solution containing 4.2 g of 85% KOH dissolved in 50 ml of MeOH was added 11.6 g (61.4 mmol) of ester 9 dissolved in 80 ml of MeOH. After refluxing on a steam bath for 6 hr the solvent was removed and 125 ml of water was added to give a clear orange solution. After three extractions with ether the water layer was briefly heated on a steam bath, then chilled in ice and slowly poured into an ice–6 *N* HCl slush. The precipitated acid 10 was filtered and dried to give 9.18 g (88.5%) of gray powder, mp 209–211°. Recrystallization from acetic acid gave white, powdery crystals, mp 213–216°. After a further recrystallization from CH₃OH and five recrystallizations from acetic acid an analytical sample was obtained: mp 217–219°; uv max 256 nm (log ε 4.96), 278 (4.27), 297 (3.89); ir 714, 816, 897, 1698, 2898 (broad), 3390 cm⁻¹.

Anal. Calcd for C₂₁H₂₀O₄: C, 74.98; H, 5.99. Found: C, 74.68; H, 6.35.

2,3,8,9,10,11-Hexahydro-1*H*-cyclopenta[a]chrysene-1,11-dione (11).—Polyphosphoric acid (60 g) was added with stirring to 1.5 g (4.4 mmol) of acid 10, mp 213–216°. The temperature rose slightly and the mixture became yellow-orange in color. The flask was gradually heated to 60° in an oil bath and held at this temperature for 48 hr. The color gradually changed from yellow-orange to red. The reaction mixture was poured into a water–ice slurry with vigorous stirring, giving a dark red solid which was collected and washed with water, then dissolved in CHCl₃. The solution was extracted four times with NaHCO₃ solution and four times with water and dried (MgSO₄). Acidification of the NaHCO₃ extract gave no precipitate. Evaporation of the solvent left a red solid which was dissolved in a 9:1 benzene–chloroform mixture and chromatographed on 50 g of neutral alumina. Elution with 9:1 and 8:2 benzene–chloroform solutions gave 0.11 g of solid, mp 189–193°. Later fractions obtained by elution with 6:4 and 4:6 benzene–chloroform solutions had mp 212–215° and totaled 0.70 g (52%). Further purification of the higher melting material by filtration of a CHCl₃ solution of it through alumina, evaporation of solvent, and recrystallization first from acetic acid, then three times from acetone, and finally from MeOH produced pale yellow flakes of 11: mp 221–223°; uv max 261 nm (log ε 4.80), 320 (4.32); ir 803, 813, 844, 1664, 1692, 2898 cm⁻¹; nmr δ 9.43 (d, 1 H, *J* = 9.6 Hz, C-12 H), 9.23 (d, 1 H, *J* = 9.6 Hz, C-13 H), 8.74 (d, 1 H, *J* = 8.1 Hz, C-6 H), 8.66 (d, 1 H, *J* = 8.1 Hz, C-5 H), 7.59 (d, 1 H, *J* = 8.1 Hz, C-4 H), 7.45 (d, 1 H, *J* = 8.1 Hz, C-7 H), 3.1 (m, 4 H, ArCH₂), 2.7 (m, 4 H, COCH₂), 2.2 (m, 2 H, CH₂CH₂CH₂). (The assignment of C-6 H, C-5 H, C-4 H, and C-7 H is not entirely certain; it might be C-5 H, C-6 H, C-7 H, and C-4 H in order of increasing field strength.)

Anal. Calcd for C₂₁H₁₆O₂: C, 83.97; H, 5.37. Found: C, 84.03; H, 5.47.

In subsequent runs the main fraction from chromatography melted at 211–214° and 214–217°, respectively, in two separate runs. Recrystallization from MeOH gave product of mp 218–221°. The corresponding minor fraction, mp 186–205° and 187–203°, respectively, apparently was a mixture. The ratio of main product to minor fraction was about 6:1.

2,3-Dihydro-1*H*-cyclopenta[a]chrysene (13).—Compound 11 (400 mg, 1.33 mmol), mp 214–217°, was dissolved in 15 ml of diethylene glycol; 0.5 ml of 85% hydrazine was added; and the mixture was refluxed for 3 hr. The red solution was cooled to 90° and 0.51 g (9.1 mmol) of KOH dissolved in 6 ml of diethylene glycol was added. After refluxing for 1.5 hr (175°) the condenser was removed and the temperature was allowed to rise to 195°, when refluxing was continued for 4 hr longer. Addition of an ice–water mixture to the cooled contents of the flask gave a dark red precipitate, which after washing with water and drying produced 0.35 g (96%) of a gray powder, mp 185–190°. Recrystallization, first from 95% EtOH, then from ligroin gave pale yellow, powdery crystals: mp 197–199° uv max 264 nm (log ε 4.97), 285 (4.32), 295 (4.27), 308 (4.38); ir 800, 828, 837 (sh), 2898 cm⁻¹. This material, 12, was used without further purification in the subsequent dehydrogenation. Crude 12 (100 mg, 0.36 mmol), mp 197–199, was intimately mixed with 30 mg of 10% Pd/C in a test tube and heated under N₂ in a bath initially at 220°. The bath was gradually raised to 270° and held at that temperature for 1 hr. During this time white, mica-like flakes formed on the sides of the tube. These were separated and dissolved in EtOH, and the solution was filtered through alumina. Recrystallization from EtOH gave 6 mg of 13: mp 260–261°; uv max 263 nm (log

ε 4.83), 272 (5.21), 297 (4.27), 308 (4.28), 324 (4.22), 347 (3.49), 364 (3.29) ir 743, 778, 801, 860 (w), 1255 (w), 2898 cm⁻¹.

Anal. Calcd for $C_{21}H_{16}$: C, 93.99; H, 6.01. Found: C, 94.11; H, 6.13.

The remainder of the product was recovered directly from the reaction mixture by vacuum sublimation, giving 42 mg (42%) of 13 as a white powder, mp 256–261°.

Studies of the Synthesis of Cephalotaxine. I

L. J. DOLBY,* S. J. NELSON, AND D. SENKOVICH

Department of Chemistry, University of Oregon, Eugene, Oregon 97403

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An attempted synthesis of cephalotaxine is described. The key intermediate, 8,9-methylenedioxy-1,2,3,6-tetrahydro-5H-pyrrolo[2,1-b][3]benzazepine (1) was obtained by a six-step sequence from N,N-dimethylpiperonylamide and pyrrole. Annelation of 1 with ethyl γ-bromoacetoacetate afforded a rearrangement product, 11,12-methylenedioxy-2-oxo-3-carboethoxy-2,3,3a,4,5,6,8,9-octahydro-1H-benzo[a]cyclopenta[i]quinolizine (10), rather than the expected product 8 bearing the cephalotaxine skeleton. Hydrolysis of 10 yielded 11,12-methylenedioxy-2-oxo-2,3,3a,4,5,6,8,8-octahydro-1H-benzo[a]cyclopenta[i]quinolizine (11), which was reduced to yield 11,12-methylenedioxy-2,3,3a,4,5,6,8,9-octahydro-1H-benzo[a]cyclopenta[i]quinolizine which was identical with authentic material.

Cephalotaxine and several closely related compounds have been isolated from several species of the *Cephalotaxacea* family.[1] The structure of cephalotaxine was deduced from its spectroscopic properties[2] and an X-ray crystallographic study.[3] In particular, the harringtonines which are naturally occurring esters of cephalotaxine have shown promising antileukemic activity.[4] Neither the acid portion of the harringtonines nor cephalotaxine show antileukemic activity alone. However, cephalotaxine presents the more difficult synthetic problem.
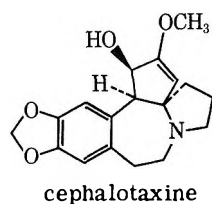
cephalotaxine

An attractive approach to the synthesis of cephalotaxine involves the annelation of the tricyclic enamine 1, which was obtained by the sequence outlined in Scheme I.

1
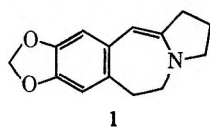
The sequence leading to the enamine 1 proceeds smoothly and none of the steps is exceptional. The Vilsmeier–Haack condensation[5] between N,N-dimethylpiperonylamide and pyrrole affords the 2-acylpyrrole

SCHEME I
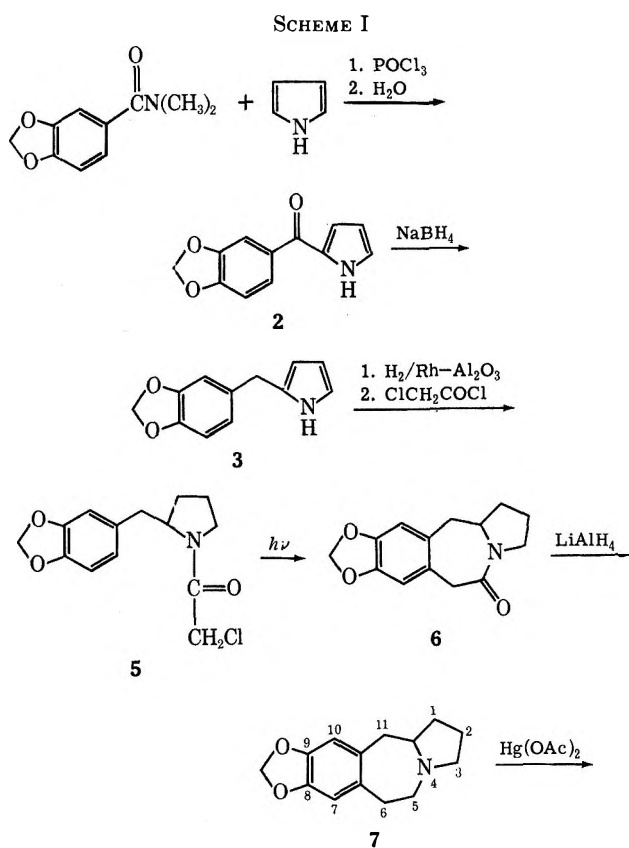
2 in 80% yield. Removal of the ketonic oxygen by treatment with sodium borohydride gives the benzylpyrrole 3 in 60% yield. Hydrogenation of the pyrrole ring and acetylation with chloroacetyl chloride give good yields of the chloroacetamide 5. Photolytic cyclization of the chloroamide affords the benzazepine derivative 6 in 25% yield.[6] The structure of this material is supported by its spectroscopic properties.

(1) W. W. Paudler, G. I. Kerley, and J. McKay, *J. Org. Chem.*, **28**, 2194 (1963).

(2) R. G. Powell, D. Weisleder, C. R. Smith, Jr., and I. A. Wolff, *Tetrahedron Lett.*, 4081 (1969).

(3) D. J. Abraham, R. D. Rosenstein, and E. L. McGandy, *ibid.*, 4085 (1969).

(4) R. G. Powell, D. Weisleder, C. R. Smith, Jr., and W. K. Rohwedder, *ibid.*, 815 (1970).

(5) G. H. Cooper, *J. Org. Chem.*, **36**, 2897 (1971).

(6) O. Yonemitsu, Y. Okuno, Y. Kanaoka, and B. Witkop, *J. Amer. Chem. Soc.*, **92**, 5686 (1970).

The infrared spectrum shows carbonyl absorption at 1640 cm^{-1}, whereas the proton magnetic resonance spectrum exhibits two singlets, one proton each, at δ 6.25 and 6.60 ascribed to the remaining hydrogens on the aromatic ring. The methylenedioxy graoup appears as a singlet at δ 5.87. Decoupling experiments were useful in analyzing the remainder of the spectrum; the benzylic protons at C-11 appear as a broad doublet at 2.97 ppm, the benzylic protons at C-6 are found as an AB quartet at 3.45 and 3.98 ppm, the methine proton adjacent to nitrogen is found as a multiplet at 4.10 ppm, and the methylene protons adjacent to nitrogen are found at 3.55 ppm. The remaining protons of the pyrrolidine ring absorb as a complex multiplet at 1.52–2.22 ppm.

Lithium aluminum hydride reduction of the lactam affords the tricyclic base **7** in 65% yield. Oxidation of **7** with mercuric acetate in dilute acetic acid gave the enamine **1** on isolation.[7] Use of a chelating ion exchange resin to remove the excess mercuric acetate proved superior to precipitation of mercuric sulfide by treatment with hydrogen sulfide. The enamine was isolated by basifying the eluates from the ion exchange resin and extracting with methylene chloride. The enamine **1** proved to be unstable and very unpleasant to handle. However, the mass spectrum showed the expected parent ion and the pmr spectrum showed the single vinyl proton at C-11 as a broad singlet at 4.90 ppm. Four triplets of two protons each are assigned to the methylene groups of carbons 1, 3, 5, and 6. The C-2 protons appear as a multiplet at 1.60–2.2 ppm. The ultraviolet spectrum of **1** shows a single broad and intense maximum at 322 nm in alkaline solution, whereas in dilute acid three maxima are observed: absorptions of about equal intensity at 235 and 291 nm characteristic of the methylenedioxyphenyl chromophore are shown along with a weaker absorption at 321 nm.

The desired annelation of enamine **1** to produce the cephalotaxine skeleton is outlined in Scheme II.

SCHEME II
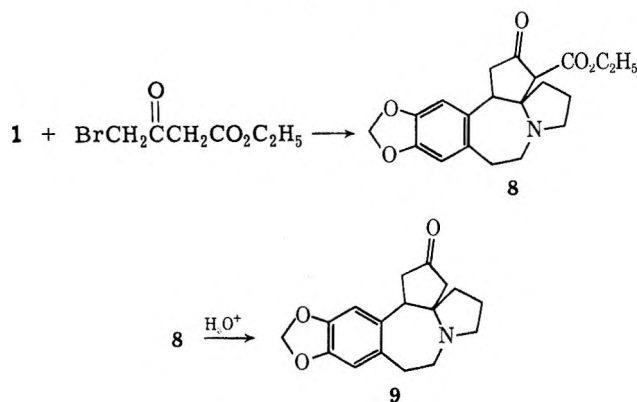
In fact, treatment of the enamine **1** with ethyl γ-bromoacetoacetate in acetonitrile did produce a tetracyclic β-keto ester of the expected molecular formula. The infrared spectrum of this material showed absorptions at 1755 and 1720 cm^{-1}, indicating formation of a 2-carboethoxycyclopentanone. Treatment of this

material with dilute acid effected removal of the carboethoxy group to give a tetracyclic cyclopentanone, as indicated by its infrared absorption at 1745 cm^{-1}. However, careful inspection of the mass spectra and the proton magnetic resonance spectra of these two materials indicated that they have structures **10** and **11**, respectively.
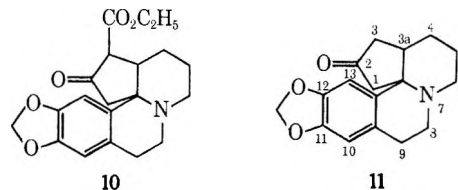
Treatment of the cyclopentanone **11** with deuterium oxide–dioxane in the presence of potassium carbonate produced a tetradeuterio compound which did not exhibit a signal in its pmr spectrum in the region δ 3.5–3.8 as expected for the benzylic methine proton of structure **9**.[2] Moreover, by comparing the spectra of the deuterated and undeuterated materials, and AB quartet (J_{AB} = 17.0 Hz) could be discerned, which is assigned to the protons adjacent to the carbonyl group at C-1. The same AB quartet appears in the spectrum of the β-keto ester **10** along with a one-proton doublet at δ 3.80, which is ascribed to the proton attached to the carbon bearing the carboethoxy group. These observations are consistent with structures **10** and **11** but rule out structures **8** and **9**. The fragmentation mass spectrum pattern of the ketone **11** shows the most prominent peaks arising from loss of C_2H_3O and C_3H_5O from the parent ion, a pattern which is difficult to rationalize on the basis of structure **9**.

Firm chemical evidence for the structure **11** was obtained by removal of the ketonic oxygen to give the parent base, which has been prepared independently by Taylor and Robinson.[8] Treatment of **11** with 1,3-propanedithiol gave the thioketal, which was reduced with Raney nickel to the parent tetracyclic base. The material thus obtained was identical with an authentic sample prepared by Taylor and Robinson and kindly furnished to us by Dr. Neville Finch of the CIBA-GEIGY Corp.

We would propose that β-keto ester **10** is formed by rearrangement of the desired isomer **8** as outlined in Scheme III.

The mechanistic details of the formation of **10** are obscure, but the rearrangement is undoubtedly initiated by elimination of **8**, probably *via* the enol, to give tricyclic intermediate **12** containing a ten-membered ring. Double bond isomerization would be expected to be facile in such a system and would lead to intermediates **13** and/or **14**, both of which could cyclize to the observed product.

Since the formation of **10** is initiated by elimination from a β-keto ester system, changes which inhibit the elimination might be expected to lead to the desired product. Accordingly, enamine **1** was alkylated with bromoacetone in the hope that cyclopentanone **9** would be formed directly and survive the reaction conditions. The condensation of enamine **1** and bromo-

(7) N. J. Leonard, A. S. Hay, R. W. Fulmer, and V. W. Gash, *J. Amer. Chem. Soc.*, **77**, 439 (1955).

(8) W. I. Taylor and M. M. Robinson, U. S. Patent 3,210,357 (1966); *Chem. Abstr.*, **65**, 2234e (1966).

acetone instead gave the simple alkylation product **15**, which was subsequently cyclized.

15
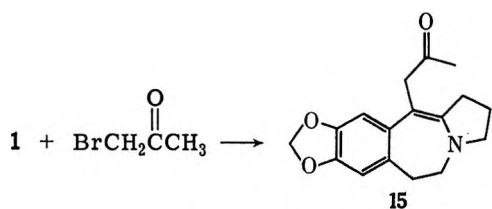
Acetic acid–sodium acetate solutions did not effect the cyclization of **15**. At room temperature no reaction was observed, and on warming some new products were formed but they did not possess a cyclopentanone ring. It appears that the enamine double bond moves into conjugation with the carbonyl group in acetic acid–sodium acetate solution, but the products were not characterized. Trifluoroacetic acid–methylene chloride solutions also failed to effect cyclization, but treatment with pyrrolidine and *p*-toluenesulfonic acid under enamine-forming conditions did effect cyclization with the formation of a cyclopentanone. Isolation of the cyclopentanone revealed that ketone **11** was the product once again. We would propose that ketone **11** is obtained from this reaction *via* its isomer **9** by a sequence similar to that outlined in Scheme III. In view of the difficulty encountered in cyclizing the enamino ketone **15**, it appears that the desired cyclopentanone **9** will not be isolated although it is formed as an intermediate. Moreover, this type of rearrangement is disastrous to the final stages of the synthesis, in which we planned to make the enol ether of ketone **9** as the next step, since enol ether forming conditions would surely cause rearrangement.

Experimental Section[9]

N,N-Dimethylpiperonylamide.—Piperonylic acid (63.8 g, 0.384 mol) was added in portions with stirring to thionyl chloride (270 ml) over 20 min. The slurry was heated under reflux for 1 hr, during which time the acid gradually dissolved. Excess thionyl chloride was removed under reduced pressure and the residue was evaporated with dry benzene. The crude acid chloride was added to 40% aqueous dimethylamine in portions with stirring and cooling over 15 min. The mixture was stirred for 2 hr at room temperature and then made strongly alkaline with 4 *N* sodium hydroxide and saturated with sodium chloride. The aqueous solution was extracted with methylene chloride, and the organic phases were filtered through paper and concentrated under reduced pressure to give the crude amide (57.1 g, 77%) as a dark oil. Distillation gave the amide as a hygroscopic, viscous liquid (53 g, 71%): bp 122–125° (0.01 mm); ir $\nu_{max}^{CCl_4}$ 2980, 1620, 1498, 1455, 1392, 1340, 1250, 1145, 1100, 1058, 1045, 932, 875, and 818 cm⁻¹; pmr (CCl₄) δ 2.90 (s, 6),

(9) All melting points and boiling points are uncorrected. Infrared spectra were measured with Beckman IR-5A or IR-7 infrared spectrophotometers. Proton magnetic resonance spectra were determined at either 60 or 100 MHz with Varian Models A-60 and HA-100 pmr spectrometers. The chemical shift values are expressed in δ values (parts per million) relative to tetramethylsilane internal standard. In the presentation of the pmr spectra the following notations are used: b, broad; u, unsymmetrical; s, singlet; d, doublet; t, triplet; q, quartet; p, pentuplet; and m, multiplet. Ultraviolet spectra were determined on a Cary Model 15 recording spectrophotometer. The mass spectra were obtained with a Consolidated Electrodynamics Corp. Model 21-110 double-focus mass spectrometer equipped with a direct inlet system. Thin layer chromatographic analyses were carried out on silica gel plates. A 3% ceric sulfate–10% sulfuric acid solution or a 5% phosphomolybdic acid solution was used to visualize the spots. Combustion analyses were performed either by Chemalytics, Inc., Tempe, Ariz., or by Dr. Susan Rottschaefer, Department of Chemistry, University of Oregon, Eugene, Oregon. Unless otherwise specified, all organic solutions were dried with anhydrous magnesium sulfate.

Scheme III

12   **13**

14   **10**
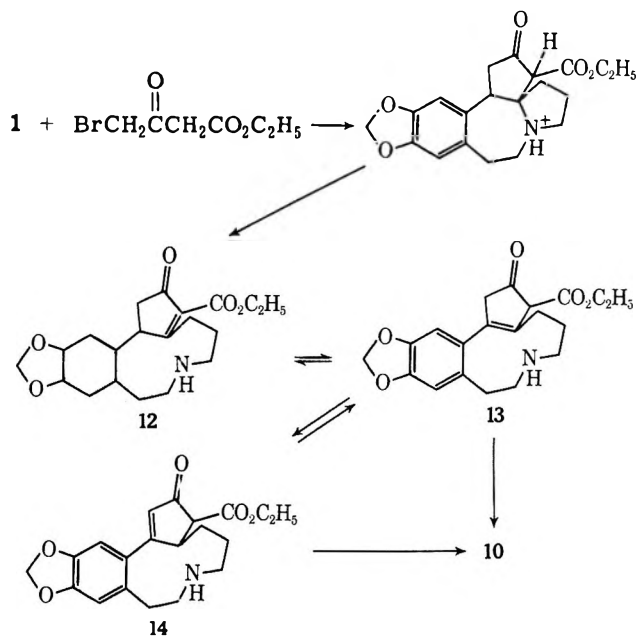
5.91 (s, 2), and 6.62–6.9 (m, 3). A satisfactory combustion analysis was not obtained.

2-(3,4-Methylenedioxybenzoyl)pyrrole (2).—To a cooled solution of *N,N*-dimethylpiperonylamide (58.5 g, 0.303 mol) in ethylene dichloride (60 ml) was added dropwise over 15 min freshly distilled phosphorus oxychloride (46.5 g, 0.303 mol) with stirring. The mixture was stirred in the cold for 10 min and then at room temperature for 1.5 hr. Additional ethylene dichloride was added (60 ml) followed by addition of a solution of freshly distilled pyrrole (20.3 g, 0.303 mol) in ethylene dichloride (60 ml) over 10 min. The mixture was stirred at room temperature for 10 min and then brought to reflux for 1 hr. The dark red mixture was cooled and sodium acetate trihydrate (300 g) in water (600 ml) was added, slowly at first, then as rapidly as possible with vigorous stirring. The mixture was brought to reflux for 15 min, after which the phases were separated while still warm. The aqueous phase was extracted with chloroform and the combined organic solutions were washed with brine, dried, and concentrated under reduced pressure. The dark solid residue was washed with a small amount of cold methanol, then ether, and dried to give the acylpyrrole (51.7 g, 80%) as a yellow solid. An analytical sample, recrystallized twice from ethanol and then ethyl acetate–hexane, had mp 146–147°; ir $\nu_{max}^{CHCl_3}$ 3460, 1625, 1595, 1442, 1405, 1328, 1255, 1100, and 1045 cm⁻¹; pmr (CDCl₃) δ 6.05 (s, 2), 6.30 (q, 1, $J_{4-3} = 6.0$, $J_{4-2} = 1.7$ Hz), 6.90 (m, 2), 7.13 (m, 1), 7.39 (ud, 1, $J = 1.5$ Hz), and 7.53 (q, 1, $J_{2-3} = 8.0$, $J_{2-4} = 1.7$ Hz).

Anal. Calcd for C₁₂H₉NO₃: C, 66.97; H, 4.22; N, 6.51. Found: C, 66.80; H, 4.13; N, 6.45.

2-(3,4-Methylenedioxybenzyl)pyrrole (3).—A mixture of the acylpyrrole **2** (37.8 g, 0.175 mol), sodium borohydride (19 g, 0.50 mol), and dioxane (500 ml) was refluxed under nitrogen for 4 hr. The solution was concentrated under reduced pressure, diluted with water (500 ml), and extracted with ether–methylene chloride (2:1, 300 ml). The organic solution was washed with water, dried, and concentrated under reduced pressure to leave a dark viscous oil. Distillation under reduced pressure gave the benzylpyrrole **3** as a colorless liquid (20.8 g, 59%), bp 125–130° (0.03 mm). An analytical sample was obtained by preparative vpc, 20% SE-30 on Chromosorb W, 5 ft × 0.375 in. column at 209°. The infrared spectrum showed $\nu_{max}^{CCl_4}$ 3455, 2845, 2770, 1500, 1490, 1445, 1245, 1042, and 710 cm⁻¹; pmr δ (CDCl₃) 3.77 (s, 2), 5.70 (s, 2), 5.80 (bs, 1), 5.93 (q, 1, $J_{4-2} = 7.2$, $J_{4-3} = 2.6$ Hz), 6.35 (m, 1), and 6.52 (m, 3).

Anal. Calcd for C₁₂H₁₁NO₂: C, 71.63; H, 5.51; N, 6.96. Found: C, 71.28; H, 5.45; N, 6.95.

2-(3,4-Methylenedioxybenzyl)pyrrolidine (4).—A solution of the benzylpyrrole **3** (28.9 g, 0.144 mol) in glacial acetic acid (100 ml) was hydrogenated at an initial pressure of 50 psi in a Parr apparatus over 5% rhodium on alumina (3 g) for 8 hr. The catalyst was filtered and the filtrate was diluted to 500 ml with

water. The aqueous solution was extracted with ether and then made strongly alkaline with 50% sodium hydroxide and extracted with methylene chloride. The organic solution was dried and concentrated under reduced pressure and the dark oil was distilled under reduced pressure to give the benzylpyrrolidine 4 (18.3 g, 75%) as a hygroscopic, colorless liquid: bp 125–130° (0.01 mm); ir $\nu_{max}^{CHCl_3}$ 3200–3400 (b), 1505, 1492, 1445, 1205, 1045, 942, and 865 cm^{-1}; pmr (CCl$_4$) δ 1.1–1.9 (m, 4), 2.52 (d, 2, J = 7.0 Hz), 2.62–3.75 (m, 3 H), 5.80 (s, 2), and 6.45–6.70 (m, 3). A hydrochloride salt was prepared by the addition of saturated ethanolic hydrogen chloride to an ether solution of the pyrrolidine 4. Recrystallization from ethyl acetate–ethanol provided an analytical sample, mp 164–165°.

Anal. Calcd for C$_{12}$H$_{16}$ClNO$_2$: C, 59.63; H, 6.67; N, 5.79. Found: C, 59.51; H, 6.66; N, 5.79.

N-Chloroacetyl-2-(3,4-methylenedioxybenzyl)pyrrolidine (5). —A solution of chloroacetyl chloride (21.2 g, 0.189 mol) in dry methylene chloride (50 ml) was added with vigorous stirring to an ice-cold mixture of the benzylpyrrolidine 4, methylene chloride (200 ml), water (200 ml), and K$_2$CO$_3$ (35 g, 0.25 mol), over 20 min. Vigorous stirring was continued for 2 hr, during which time the mixture was allowed to warm to room temperature. The phases were separated and the aqueous phase was extracted with methylene chloride. The combined organic solutions were washed with bicarbonate solution, filtered, and concentrated under reduced pressure. Trituration of the oily residue with ether gave the chloroacetamide 5 (29.0 g, 82%) as a cream-colored powder. Recrystallization from ether gave colorless blocks: mp 81–2°, ir $\nu_{max}^{CHCl_3}$ 1650, 1505, 1490, 1230, 1045, and 930 cm^{-1}; pmr (CCl$_4$) δ 1.65–2.08 (m, 4), 2.48 (q, J_{AB} = 12.5, J_{AX} = 9.0 Hz), 3.35–3.75 (m, 2), 3.90 (s, 2), 4.15 (bs, 1), 5.78 (s, 2), and 6.45–6.75 (m, 3).

Anal. Calcd for C$_{14}$H$_{16}$ClNO$_3$: C, 59.68; H, 5.72; N, 4.97. Found: C, 59.51; H, 5.73; N, 4.83.

5-Oxo-8,9-methylenedioxy-1,2,3,6,11,11a-hexahydro-5*H*-pyrrolo[2,1-*b*] [3]benzazepine (6).—A 0.04 *M* solution of the chloroacetamide 5 (14 g, 49 mmol) in 40% aqueous ethanol was purged with nitrogen for 30 min. The solution was irradiated with a Hanovia 450-(high-pressure mercury lamp in a quartz immersion well with a Corex filter for 44 hr. After 24 hr the immersion well was cleaned to remove a gummy deposit. The clear yellow solution was concentrated under reduced pressure to remove the ethanol and the turbid concentrate was extracted with methylene chloride. The organic solution was filtered through paper and concentrated under reduced pressure to leave a dark oil (6.05 g). The combined material from two identical experiments was filtered through 300 g of Florisil eluting with chloroform to give 12.1 g of pale yellow oil. Trituration of the oil with ether and standing overnight in the cold gave the amide 6 (6.9 g, 27%) as a colorless powder. Recrystallization from benzene–hexane gave colorless blocks: mp 153–155°; ir $\nu_{max}^{CHCl_3}$ 1640, 1508, 1485, 1230, 1042, and 930 cm^{-1}; pmr (CDCl$_3$) δ 1.52–2.22 (m, 4), 2.97 (ud, 2), 3.45 (d, 1, J = 14 Hz), 3.55 (m, 2), 3.98 (d, 1, J = 14 Hz), 4.10 (m, 1), 5.87 (s, 2), 6.52 (s, 1), and 6.60 (s, 1).

Anal. Calcd for C$_{14}$H$_{15}$NO$_3$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.62, H, 6.18; N, 5.60.

8,9-Methylenedioxy-1,2,3,6,11,11a-hexahydro-5*H*-pyrrolo-[2,1-*b*] [3]benzazepine (7).—A solution of the amide 6 (6.88 g, 28.0 mmol) in dry tetrahydrofuran (75 ml) was added rapidly to a slurry of lithium aluminum hydride (3.6 g, 95 mmol) in tetrahydrofuran (110 ml) and the mixture was brought to reflux for 12 hr. The mixture was cooled and water (3.6 ml) was carefully added followed by 4 *N* sodium hydroxide (3.6 ml) and an additional amount of water (10 ml). The salts were filtered and washed with tetrahydrofuran and the combined filtrates were concentrated under reduced pressure. The residue was hydrogenated over Adams catalyst (0.5 g) in 100 ml of 0.5 *N* hydrochloric acid at 50 psi for 14 hr to reduce any enamine which had formed. The catalyst was filtered and the filtrate was made strongly alkaline with solid potassium carbonate followed by 50% sodium hydroxide. The aqueous mixture was extracted with methylene chloride, which was concentrated to leave a pale yellow oil (4.5 g). Bulb-to-bulb distillation (125°, 0.07 mm) provided a colorless, hygroscopic oil (4.22 g, 65%) which on standing solidified. The infrared spectrum showed absorption at $\nu_{max}^{CHCl_3}$ 1500, 1485, 1260, 1209, 1165, 1040, 938, and 858 cm^{-1}; pmr (CDCl$_3$) δ 1.40–3.35 (m, 13), 5.82 (s, 2), and 6.58 (bs, 2). A hydrochloride salt was prepared for analysis by passing dry hydrogen chloride into an ether solution of the amine. Recrystallization from ethanol gave colorless needles, mp 265–266° dec.

Anal. Calcd for C$_{14}$H$_{18}$NO$_2$Cl: C, 62.80; H, 6.78; Ni, 5.23. Found: C, 62.45; H, 6.82; N, 5.02.

8,9-Methylenedioxy-1,2,3,6-tetrahydro-5*H*-pyrrolo[2,1*b*] [3]-benzazepine (1).—A solution of the amine 7 (513 mg, 2.24 mmol) in 2% acetic acid (3 ml) was stirred under nitrogen at 80° (oil bath) for 100 min, during which time a precipitate of mercurous acetate had formed and the solution had darkened. The precipitated salts were filtered and the filtrate was passed through Dowex chelating resin A-1 (40 ml wet volume) eluting with 0.2 *N* hydrochloric acid. The eluents were made strongly basic with 50% sodium hydroxide and extracted with methylene chloride. The organic solution was filtered and concentrated to leave the enamine 1 (301 mg, 59%) as a dark oil. Tlc (5% triethylamine in benzene) indicated that the material was homogeneous. A portion was filtered through a small amount of alumina (Woelm neutral) to give a pale yellow oil which on standing partially crystallized. Solutions of the purified material rapidly turned dark even when protected by nitrogen atmosphere.[10] The infrared spectrum showed absorptions at $\nu_{max}^{CHCl_3}$ 1640, 1605, 1500, 1580, 1230, 1045, and 795 cm^{-1}; pmr (CDCl$_3$) δ 1.60–2.02 (m, 2), 2.65 (t, 2, J = 8.0 Hz), 2.90 (ut, 2, J = 4.5 Hz), 3.25 (t, 2, J = 8.0 Hz), 3.42 (ut, 2, J = 4.5 Hz), 4.90 (bs, 1), 5.75 (s, 2), 6.42 (bs, 2); uv $\lambda_{max}^{EtOH-OH^-}$ 322 nm; $\lambda_{max}^{EtOH,\ H^+}$ 322, 291, and 235 nm; mass spectrum m/e 229.110 (calcd for C$_{14}$H$_{16}$NO$_2$, 229.110).

11,12-Methylenedioxy-2-oxo-3-carboethoxy-2,3,3a,4,5,6,8,9-octahydro-1*H*-benzo[*a*]cyclopenta[*i*]quinolizine (10).—A mixture of enamine 1 (57.6 mg, 0.250 mmol) and ethyl γ-bromoacetoacetate was refluxed in acetonitrile (2 ml) for 17 hr. Ether (10 ml) was added and the precipitated salt was washed by decantation with two small portions of ether. The material was taken up in water and the aqueous solution was made alkaline with potassium carbonate (pH 10) and extracted with methylene chloride. The organic solution was filtered and concentrated under reduced pressure to leave the keto ester 10 as a yellow, gummy solid (45.6 mg, 51%). Recrystallization from ethyl acetate gave the analytical sample as colorless needles: mp 171–173°; ir $\nu_{max}^{CHCl_3}$ 1755, 1720, 1505, 1485, 1370, 1145, 1045, 945, and 860 cm^{-1}; pmr (CDCl$_3$) δ 1.30 (t, 3, J = 7 Hz), 1.45–2.05 (m, 4), 2.30 (d, 1, J = 18 Hz), 2.92 (d, 1, J = 18 Hz), 2.20–3.62 (m, 6), 3.80 (d, 1, J = 11 Hz), 4.22 (p, 2), 5.85 (s, 2), 6.50 (s, 1), and 6.82 (s, 1); uv λ_{max}^{EtOH} 292 nm (ε 6050), 234 (5880); $\lambda_{max}^{EtOH-OH^-}$ 288 nm (ε 22,200); mass spectrum m/e 357 (M$^+$), 314, 228 (100), and 156.

11,12-Methylenedioxy-2-oxo-2,3,3a,4,5,6,8,9-octahydro-1*H*-benzo[*a*]cyclopenta[*i*]quinolizine (11). A. By Hydrolysis of 10. —A solution of the keto ester 10 (21.8 mg, 0.061 mmol) in 5% sulfuric acid (3 ml) was heated under gentle reflux for 14 hr. The mixture was cooled, made alkaline with 50% sodium hydroxide, and extracted with methylene chloride. The organic solution was filtered and concentrated under reduced pressure to leave a crystalline residue (15.6 mg, 90%). Sublimation (130–150°, 0.01 mm) and recrystallization from ethyl acetate–hexane gave colorless needles, mp 173–174°. The infrared spectrum showed $\nu_{max}^{CHCl_3}$ 1745, 1505, 1485, 1255, 1045, 945, and 865 cm^{-1}; pmr (CDCl$_3$) δ 1.20–1.95 (m, 4), 2.22 (d, 1, J = 18.0 Hz), 2.24–3.85 (d, 1, J = 18.0 Hz), 5.88 (s, 2), 6.52 (s, 1), and 6.79 (s, 1); mass spectrum m/e 285 (M$^+$), 242 (100), and 228.

Anal. Calcd for C$_{17}$H$_{19}$NO$_3$: C, 71.56; H, 6.71; N, 4.91. Found, C, 71.56; H, 6.82; N, 4.80.

B. By Annelation of Enamine 1 with Bromoacetone.—A solution of enamine 1 (350 mg) and bromoacetone (260 mg) was heated for 10 hr under reflux in *ca.* 15 ml of acetonitrile. The mixture was diluted with 5% sulfuric acid and extracted with ether. The aqueous solution was basified and extracted with methylene chloride to yield 170 mg (40%) of enamino ketone 15. The material showed carbonyl absorption at 1700 cm^{-1} but no absorption at 1745 cm^{-1} in its infrared spectrum. Treatment of 15 with 1 *M* sodium acetate in acetic acid at room temperature effected no change, but warming on the steam bath for 8 hr produced a mixture showing new carbonyl absorption at 1690 cm^{-1} and peaks at 1635 and 1620 cm^{-1} but no maxima in the 1745-cm^{-1} region. Treatment of 15 with 2% trifluoroacetic acid in methylene chloride had effected no change after 32 hr at room temperature. A solution of 15 (150 mg), *p*-toluenesulfonic acid

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(10) After this paper had been submitted, Professor Steven Weinreb of Fordham University kindly informed us of the synthesis of crystalline enamine 1 in his laboratory. The ir and pmr spectra of our preparation were identical with those of a sample provided by Dr. Weinreb. He noted that contact with chlorinated solvents as we used in our work greatly accelerates the decomposition of the enamine.

(103 mg), and pyrrolidine (110 mg) was heated under reflux in a Soxhlet extraction apparatus containing molecular sieves (5A) for 2 days. The cooled reaction mixture was stirred for 20 min in 5% sulfuric acid, after which the layers were separated and the benzene layer was extracted twice with 20-ml portions of 5% sulfuric acid. The sulfuric acid solution was basified and extracted with methylene chloride. The methylene chloride was evaporated and the residue was subjected to preparative tlc (silica gel, 10% methanol–chloroform) to yield 28 mg (19%) of ketone 11 identical in all respects with the material obtained above. The other materials from preparative tlc showed no maxima at 1745 cm^{-1} in their infrared spectra.

Deuterium Exchange of Ketone 11.—A solution of the tetracyclic ketone 11 (12.0 mg, 0.045 mmol) in 1:1 deuterium oxide–dioxane (0.5 ml) containing a small amount of anhydrous potassium carbonate was heated at 80° (oil bath) for 5 hr. Additional deuterium oxide was added (0.25 ml) and the solution was allowed to stand at room temperature for 24 hr. The solution was extracted with dry methylene chloride and the organic phase was washed with a small volume of deuterium oxide. The organic solution was concentrated under reduced pressure and the residue was dried under high vacuum for 15 hr to give the deuterated ketone (11.6 mg, 95%) as a colorless, crystalline solid. The pmr spectrum showed a disappearance of the AB quartet assigned to the methylene protons of C-1 in the protio compound. The mass spectrum showed m/e 289, 244, and 228.

11,12-Methylenedioxy-2,3,3a,4,5,6,8,9-octahydro-1H-benzo-[a]cyclopenta[i]quinolizine.—A solution of ketone 11 (18 mg), 1,3-propanedithiol (180 mg), and p-toluenesulfonic acid hydrate (25 mg) in benzene (15 ml) was placed in a Soxhlet extractor containing molecular sieve (5A) and heated under reflux for 4.5 hr. The reaction mixture was extracted with 5% sulfuric acid and the aqueous extracts were basified and extracted with methylene chloride to yield the crude thioketal, which showed no carbonyl absorption in its infrared spectrum. The crude thioketal was dissolved in 10 ml of 95% ethanol and heated under reflux overnight with ca. 100 mg of Raney nickel. The reaction mixture was filtered, concentrated, and subjected to preparative tlc (5% methanol–chloroform on silica gel) to afford 10 mg of the title compound. The mass spectrum of this material was identical with that of an authentic sample[8] obtained from the hydrochloride in the usual manner. The picrates[8] of the two samples were identical by melting point behavior and their pmr spectra were identical.

The Direct Utilization of Unsaturated Sugars in Nucleoside Syntheses. The Synthesis, Configuration, and Conformation of Certain Hex-1-enitol-3-yl-, Hex-2-enopyranosyl-, and Hexopyranosylpurines. The Preparation of 9-(1,5-Anhydro-2,3-dideoxy-D-*arabino*-hex-1-enitol-3-yl)adenine and 9-(2,3-Dideoxy-β-D-*erythro*-hex-2-enopyranosyl)adenine from D-Glucal[1]

Eldon E. Leutzinger,[2] Takashi Meguro, and Leroy B. Townsend

Department of Chemistry and Department of Biopharmaceutical Sciences, University of Utah, Salt Lake City, Utah 84112

Dennis A. Shuman,* Martin P. Schweizer, Charles M. Stewart, and Roland K. Robins

ICN Nucleic Acid Research Institute, Irvine, California 92664

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The acid-catalyzed fusion of 3,4,6-tri-O-acetyl-D-glucal (I) and 2-acetamido-6-chloropurine has furnished the α and β anomers of 2-acetamido-6-chloro-9-(4,6-di-O-acetyl-2,3-dideoxy-D-*erythro*-hex-2-enopyranosyl)-9H-purine (III) and 2-acetamido-6-chloro-9-(1,5-anhydro-2,3-dideoxy-D-*arabino*-hex-1-enitol-3-yl)-9H-purine (IX). A facile conversion of III to 2-amino-9-(2,3-dideoxy-D-*erythro*-hex-2-enopyranosyl)-9H-purine-6-thiol (VI) and 9-(2,3-dideoxy-D-*erythro*-hex-2-enopyranosyl)guanine (VII) was effected by the appropriate functional group transformation. Cis dihydroxylation of VII furnished the 2',3'-dihydroxyhexopyranoside, which hydrolyzed to give D-mannose, D-allose, and guanine and firmly established the position of the endocyclic double bond of III as C-2'–C-3'. The direct fusion of I with either 6-chloro-2-methylthiopurine or 6-benzamidopurine furnished a mixture of the corresponding diastereoisomeric 9-(1,5-anhydro-2,3-dideoxy-D-*erythro*-hex-1-enitol-3-yl)-9H-purines and 9-(2,3-dideoxy-D-*erythro*-2-enopyranosyl)-9H-purines. The conformation and anomeric configuration of these nucleosides was assigned with the aid of pmr spectroscopy. 9-(2,3-Dideoxy-β-D-*erythro*-hexopyranosyl)adenine (XXIII) and 9-(1,5-anhydro-2,3-dideoxy-D-*arabino*-hexitol-3-yl)adenine (XXII) were obtained by hydrogenation of XIX and XX, respectively. Compound XXIII has a 2',3'-dideoxypyranosyl structure similar to that found in amicetin.

The direct utilization of glycals in the "acid-catalyzed" fusion reaction has been the subject of preliminary reports from our laboratories[3,4,5] as a new and general synthetic approach to the preparation of 2',3'-unsaturated pyranosyl nucleosides structurally related to Blasticidin S.[6] The structural elucidation[7,8] of Blasticidin S has established this nucleoside antibiotic to be a pyranosyl derivative of cytosine possessing an endocyclic double bond in the 2,3 position of the carbohydrate moiety. Blasticidin S has been shown to inhibit several transplantable animal tumors[9] and to inhibit protein synthesis.[10]

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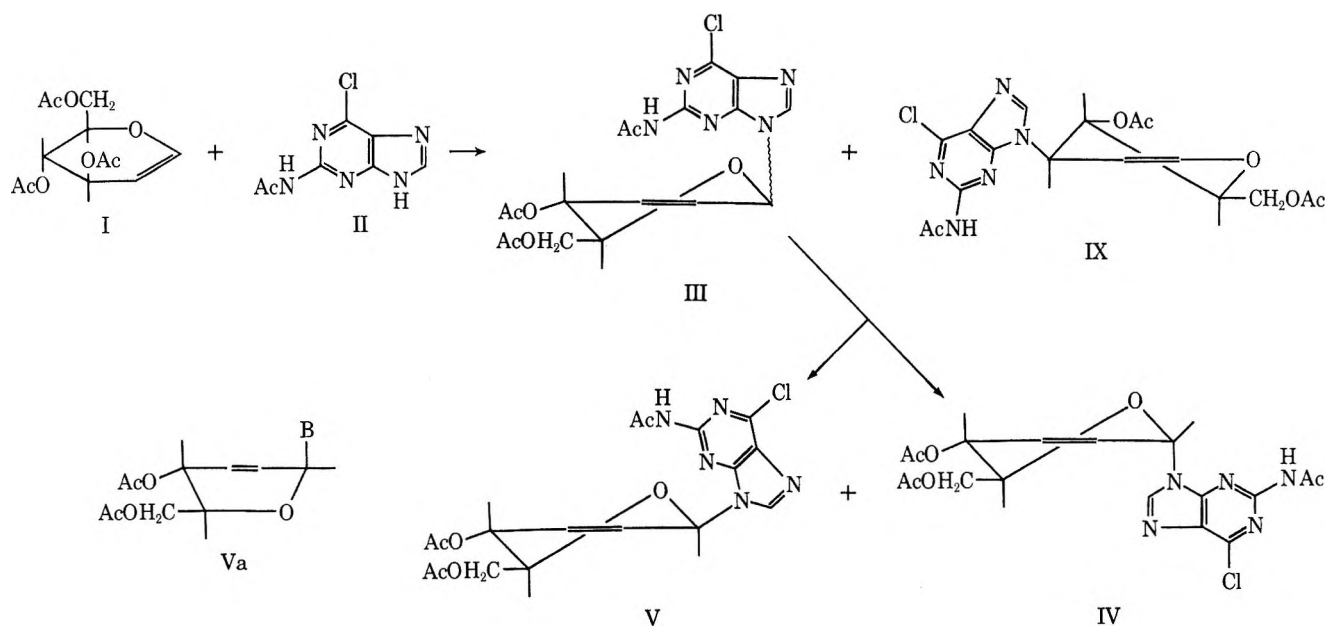
Another nucleoside antibiotic, amicetin,[11,12] has been shown to possess a 2,3-dideoxypyranose moiety attached directly to the heterocyclic base, cytosine. Since amicetin has likewise shown biological activity as a selective inhibitor of protein synthesis,[12] it seemed worthwhile to investigate the synthesis of similar 2′,3′-unsaturated and 2′,3′-dideoxypyranosyl nucleosides of purine bases. The use of D-glucal for syntheses of nucleosides of this type was first reported by Bowles and Robins[3] in 1964. It was discovered during the course of these studies that fusion of the requisite purine base with D-glucal gave in addition to the desired 2′,3′-unsaturated nucleoside also a 1′,2′-unsaturated pyranosyl nucleoside with purine attachment at position 3 of the pyranose ring. A preliminary report of this interesting observation has been reported from our laboratory.[5] Since our first report,[5] Ferrier, *et al.*,[13] and Kondo, *et al.*,[14] have recently noted the isolation of the 3′-deoxyglycal nucleosides of 2,6-dichloropurine and uracil. The present work describes the char-acterization of the various nucleoside products obtained from our studies in this area. In particular, 3,4,6-tri-*O*-acetyl-D-glucal and 6-benzamidopurine gave an excellent yield (total 76%) of the four isomeric nucleosides, XVIII, XIX, XX, and XXI. The 9-(1,5-anhydro-2,3-dideoxy-D-*arabino*- (or *ribo*-) hex-1-enitol-3-yl)-9*H*-purines represent a type of nucleoside which should be resistant to enzymatic degradation and chem-ical hydrolysis. It should be noted that the presence of a double bond at the 2′,3′ position such as in Blas-ticidin S or in 9-(2,3-dideoxy-β-D-*erythro*-hex-2-enopy-ranosyl)adenine (XIX) and similarly at the 1′,2′ po-sition as in 9-(1,5-anhydro-2,3-dideoxy-D-*arabino*-hex-1-enitol-3-yl)adenine (XX), gives the pyranose ring rigidity and conformation not totally unlike the fur-anose ring of the naturally occurring nucleosides. The importance of this observation will be determined by further research in various biological systems.

A mixture of 3,4,6-tri-*O*-acetyl-D-glucal (I) and 2-acetamido-6-chloropurine (II) was fused in the pres-ence of a catalytic amount of *p*-toluenesulfonic acid at 120° for 2 hr under vacuum. Preparative thick layer chromatography separated the nucleosidic mixture into two nucleoside types, III and IX. Nucleoside III was assigned the structure 2-acetamido-6-chloro-9-(4,6-di-*O*-acetyl-2,3-dideoxy-D-*erythro*-hex-2-enopyranosyl)-9*H*-purine.

The absorption peaks in the δ 6.1–6.3 region of the pmr spectrum of III were assigned to H-2′ and H-3′ of a 2′,-3′-unsaturated pyranosyl nucleoside derivative by com-parison with similar absorption patterns observed pre-viously[3,15,16] for certain 2,3-dideoxy-D-*erythro*-hex-2-enosides. The signals at δ 2.05–2.15 were assigned to the acetyl groups at C-4′ and C-6′ of the carbohydrate. The presence of only two acetyl groups for the carbo-hydrate moiety of III indicated that loss of one acetoxy group[17] from 3,4,6-tri-*O*-acetyl-D-glucal (I) had oc-curred and was accompanied by a rearrangement of the 1,2 endocyclic double bond to the 2,3 position during nucleoside formation. This type of rearrange-ment with glycals has also been observed in the reac-tions of certain phenols[16,19] with 3,4,6-tri-*O*-acetyl-D-glucal to furnish the corresponding 4,6-di-*O*-acetyl-2,3-dideoxy-D-*erythro*-hex-2-enopyranosides.

That nucleoside III was in fact an anomeric mixture was obtained from the pmr spectrum in deuteriochloro-form, which showed two sets of resonances for the –NH of the 2-acetamido group, the H-8 proton and the vinyl protons. The separation and anomeric assign-ment is presented later.

Treatment of the anomeric mixture III with a meth-anolic solution of sodium hydrosulfide resulted in a facile nucleophilic displacement of the 6-chloro group with a concomitant removal of the acetyl blocking groups to furnish a 41% yield of 2-amino-9-(2,3-di-deoxy-D-*erythro*-hex-2-enopyranosyl)-9*H*-purine-6-thiol (VI). A comparison of the ultraviolet absorption

(11) For a review of the chemistry and biochemistry of amicetin, see R. J. Suhadolnik, "Nucleoside Antibiotics," Wiley-Interscience, New York, N. Y., 1970, p 203.

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(17) Presumed to be the C-3′ acetoxy group.[18]

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spectrum of VI with the uv spectra of 1-methyl-,[20] 3-methyl-,[21] 7-methyl-,[22] and 9-methyl-2-amino-6-thiopurine[23] established N-9 as the site of glycosylation for VI, and consequently for III and IX.

VI

VII → VIII → guanine + D-mannose + D-allose
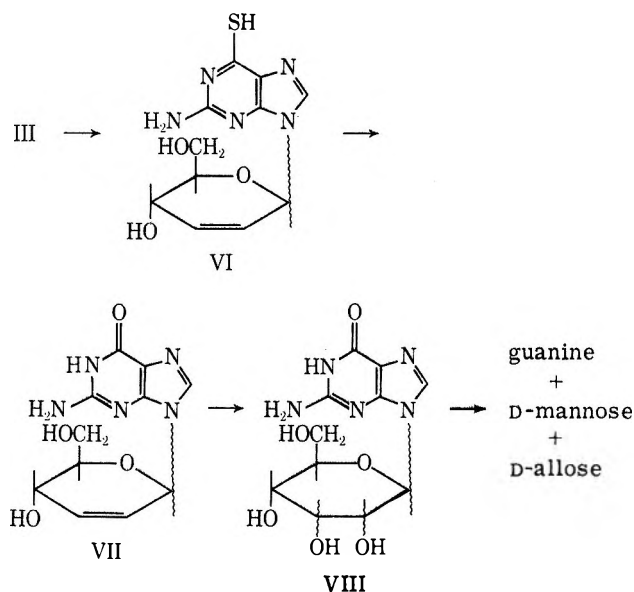
Treatment of VI with hydrogen peroxide in a 20% aqueous ammonia solution effected a smooth conversion of the sulfur atom at position six to an oxygen atom and afforded a 78% yield of 9-(2,3-dideoxy-D-*erythro*-hex-2-enopyranosyl)guanine (VII). The pmr spectrum of VII revealed a retention of the absorption peaks assigned to the olefinic protons (H-2' and H-3', δ 6.0–6.35, multiplet) and established that the oxidation step had occurred without effect at the 2',3' endocyclic double bond.

The endocyclic double bond of the carbohydrate moiety for the above nucleosides was tentatively assigned to the 2',3' positions; however, this double bond could theoretically be located in one of several possible positions, 1',2' (A), 2',3' (B), and 3',4' (C). Structure

R = H, Ac
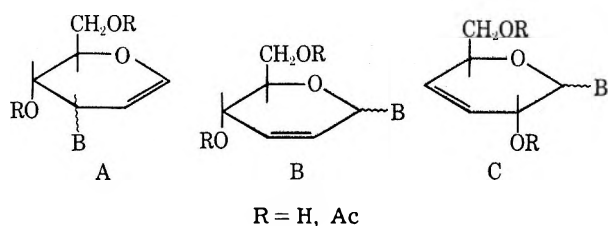
A was eliminated on the basis of the significant differences observed in the pattern of absorption peaks assigned to the carbohydrate moiety in the pmr spectra of I and III. Elimination of structure C was possible on the basis of the following study. Treatment of 9-(2,3-dideoxy-D-*erythro*-hex-2-enopyranosyl)guanine (VII) with 30% hydrogen peroxide containing a catalytic amount of osmium tetroxide furnished a cis glycol derivative which was subsequently assigned structure VIII. The stereospecific mode of addition

for osmium tetroxide should furnish a nucleoside with the carbohydrate moiety in the manno and/or allo configuration. The hydrogen peroxide–osmium tetroxide reagent has been reported[24] to effect a facile conversion of an ethyl 2,3-dideoxy-D-*erythro*-hex-2-enopyranoside to the corresponding cis glycol. Acidic hydrolysis of VIII furnished a mixture of D-mannose, D-allose, and guanine as judged by paper chromatography against authentic samples of D-mannose, D-allose,[25] and guanine. The presence of D-mannose and D-allose in the hydrolysate of VIII indicated that VIII must be a mixture of 9-(D-*manno*-hexopyranosyl)-guanine and 9-(D-*allo*-hexopyranosyl)guanine. These results firmly established the 2',3' position as the site of the endocyclic double bond in VII, and consequently in VI, III, IV, and V.

The nucleoside designated as III was successfully separated into two components (IV and V) by thick layer chromatography. Pmr techniques were employed to characterize IV and V (Table I). The signals at δ 5.44 in the 100-MHz pmr spectrum for IV and at δ 5.50 in the 100-MHz pmr spectrum for V were assigned to H-4'. These assignments for H-4' were made on the basis of the similar chemical shifts observed for the signal at δ 5.42 for III (which was established as H-4' by decoupling from H-5'). The AB patterns for the protons in the δ 6.15–6.34 region for IV and in the δ 6.04–6.26 region for V were assigned to the C-2' and C-3' protons. The fine splitting seen in these patterns can be attributed to the additional coupling of the C-2' and the C-3' protons with H-1' and H-4'. On the basis of these assignments, the downfield signals at δ 6.48 for IV and δ 6.60 for V were assigned to the anomeric protons.

Ferrier[13] has determined the anomeric configuration at C-1' of the corresponding 2,6-dichloro derivatives by analysis of the various coupling constants. The magnitudes of these couplings for the two anomers were quite similar except for $J_{1'-2'}$. The results of our analysis of anomers IV and V in CDCl₃ are generally in accord with those of Ferrier,[13] though we consider other conformational possibilities.

The $J_{1'-2'}$ coupling for anomer IV was 2.8 Hz compared with 1.8 Hz for anomer V. Large $J_{4'-5'}$ values were found, 8.7 and 8.4 Hz, respectively, suggesting the half-chair *H1* conformation for the carbohydrate moiety. However, the alternate half-boat[26,27] conformation (Va) will also fit the $J_{4'-5'}$ data and cannot be readily eliminated, since the anomeric configuration is not known. In the discussion below regarding the adenine analogs XVIII and XIX, the conformation and the α,β anomeric configuration dilemma were solved by synthesizing the N³ → C-6' cyclonucleoside of the β anomer XIX. The spectra of XVIII and XIX with respect to the deblocked carbohydrate were essentially comparable to those of IV and V, and it is not expected that the conformation would change from *H1* for the adenine compounds to alternate half-boat for the 2-acetamido-6-chloro derivatives. On the basis of

(20) C. W. Noell, D. W. Smith, and R. K. Robins, *J. Med. Pharm. Chem.*, **5**, 996 (1962).

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(25) The authors wish to thank Dr. Bernice Kohn and Dr. Leon Lerner for a gift of D-allose.

(26) K. A. Watanabe, R. S. Goody, and J. J. Fox, *Tetrahedron*, **26**, 3883 (1970).

(27) We acknowledge one of the referees for this suggestion.

TABLE I

Compd	H-8	H-2	H-1'	H-2'	H-3'	H-4'	H-5'	H-6',6''
IV[a]	8.18		6.48	6.15	6.34	5.44	~3.94	~4.16
V[a]	8.12		6.60	6.04	6.26	5.50	~4.2	~4.24
XVIII[b]	8.61	8.61	6.82	6.44	6.67	4.45	3.91	3.91
XIX[b]	8.50	8.57	6.83	6.32	6.56	4.54	4.05	4.05
IX[c]	8.18		6.89	5.00	5.50			
XI[c]	8.50		6.63	4.80	5.20	4.28		
XII[c]	8.33		6.75	4.88	5.23	4.00		
XX[b]	8.49	8.49	6.94	5.10	5.47	4.62	4.27	4.12
XXI[b]	8.48	8.60	7.15	5.27	5.65	4.43	4.43	4.10

[a] Spectra were determined in $CDCl_3$ with TMS as internal standard at 100 MHz on a Varian XL-100 spectrometer. [b] Spectra were determined in DMSO-d_6/D_2O with TMS as external standard at 90 MHz on a Bruker HFX-90 spectrometer. [c] Spectra were determined in DMSO-d_6/D_2O with TMS as internal standard at 60 MHz on a Jeolco C60H spectrometer.

these considerations, IV and V were assigned the α and β configurations, and *H1* conformations, respectively.

The formation of 9-(1,5-anhydro-2,3-dideoxy-D-*erythro*-hex-1-enitol-3-yl)-9*H*-purines has been previously reported from the fusion of 3,4,6-tri-*O*-acetyl-D-glucal with purines.[5,13,14] The pmr spectra of the only other nucleoside IX isolated from the fusion of the D-glucal (I) with 2-acetamido-6-chloropurine (II) was similar to that of 6-chloro-9-(4,6-di-*O*-acetyl-1,5-anhydro-2,3-dideoxy-D-*arabino*-hex-1-enitol-3-yl)-2-methylthio-9*H*-purine (XIII) and revealed a pair of doublets at δ 6.89 and a pair of overlapping doublets at δ 5.00, which are characteristic of a hex-1-enitol derivative, and which were assigned to H-1' and H-2', respectively. The doublet at δ 5.50 in the pmr spectrum of IX was assigned to H-3' and the large coupling constant ($J_{3'-4'}$ = 7.5 Hz) suggested that the 2-acetamido-6-chloropurinyl substituent was in approximately the same orientation as the 6-chloro-2-methylthiopurinyl substituent in XIII. Thus, based on the similarities between the pmr spectra of XIII and IX and the large $J_{3'-4'}$ observed, the nucleoside IX was tentatively assigned the structure 2-acetamido-6-chloro-9-(4,6-di-*O*-acetyl-1,5-anhydro-2,3-dideoxy-D-*arabino*-hex-1-enitol-3-yl)-9*H*-purine.

The direct isolation and characterization of a minor nucleoside from certain transfer RNAs as a 2-methylthiopurine nucleoside derivative[28,29] has created interest in the synthesis of other 2-methylthiopurine nucleosides. The fusion of 3,4,6-tri-*O*-acetyl-D-glucal and 2-methylthio-6-chloropurine as reported in a preliminary communication[5] gave the three nucleosides XI, XII, and XV after treatment with methanolic ammonia followed by fractional crystallization.

The assignment of the position of the endocyclic double bond in XI and XII was previously firmly established by a comparison of the pmr spectra of XI and XII with that of 3,4,6-tri-*O*-acetyl-D-glycal (I) (in particular, $J_{1'-2'} \cong 6$ Hz was indicative of a vinyl ether[30]) and by the utilization of the double resonance technique at 100 MHz.[5] Acetylation of XI and XII to XIII and XIV caused a significant downfield shift of the C-4' proton which was in agreement with the assignment of purinyl substitution at C-3'.[5] The configuration at C-3' of XI and XII has now been deter-

mined by pmr studies in analogy to those reported by Ferrier[13] for the 3'-substituted 2,6-dichloro derivatives. Large $J_{4'-5'}$ (9.0 Hz) and $J_{3'-4'}$ (8.0 Hz) couplings suggest essentially diaxial orientations for H-3', H-4', and H-5', which is consistent with the *H1* conformation and pseudoequatorial orientation of the substituent at C-3'. Thus XI is 9-(1,5-anhydro-2,3-dideoxy-D-*arabino*-hex-1-enitol-3-yl)-6-chloro-2-methylthio-9*H*-purine and XII is the corresponding ribo derivative.

The other nucleosides XV showed absorption peaks in the δ 5.9-6.3 region, which was characteristic for H-2' and H-3' of a 2',3'-unsaturated pyranosyl derivative. On the basis of the similarities in the pmr spectra in the region attributed to the carbohydrate moiety of XV and III, this nucleoside was assigned the structure 6-chloro-9-(2,3-dideoxy-D-*erythro*-hex-2-enopyranosyl)-2-methylthio-9*H*-purine.

Treatment of XV with methanolic ammonia in a sealed vessel at room temperature for 4 days furnished a 40% yield of 6-amino-9-(2,3-dideoxy-D-*erythro*-hex-2-enopyranosyl)-2-methylthio-9*H*-purine (XVI). The subsequent desulfurization of XVI with Raney nickel furnished 9-(2,3-dideoxy-D-*erythro*-hex-2-enopyranosyl)-adenine (XVII), mp 241-242°. A pmr spectrum of XVII revealed an absorption pattern in the δ 5.8-6.2 region attributed to H-2' and H-3' of a 2',3'-unsaturated pyranosyl derivative and indicated a retention of the endocyclic double bond. The synthesis of 9-(2,3-dideoxy-D-*erythro*-hex-2-enopyranosyl)adenine, mp 241-242°, has been previously prepared by a different procedure, although no attempt was made to establish the anomeric configuration of the product.[31] In fact, this structural assignment has been recently questioned.[13]

In view of the claimed antitumor activity of the latter product,[32] a detailed investigation and synthesis of the four possible isomeric adenine nucleosides XVIII, XIX, XX, and XXI was undertaken. The fusion of 2,4,6-tri-*O*-acetyl-D-glucal (I) with 6-benzamidopurine in the presence of *p*-toluenesulfonic acid catalyst at 165° for 3 hr gave a 76% yield of nucleosidic material. Deacylation of the crude nucleoside mixture with methanolic ammonia was followed by separation of the nucleosides by column chromatography and fractional crystallization to give the isomeric nucleosides XVIII, XIX, XX, and XXI. A

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XI, R = H
XIII, R = Ac

XII, R = H
XIV, R = Ac

XV

XVII ← XVI
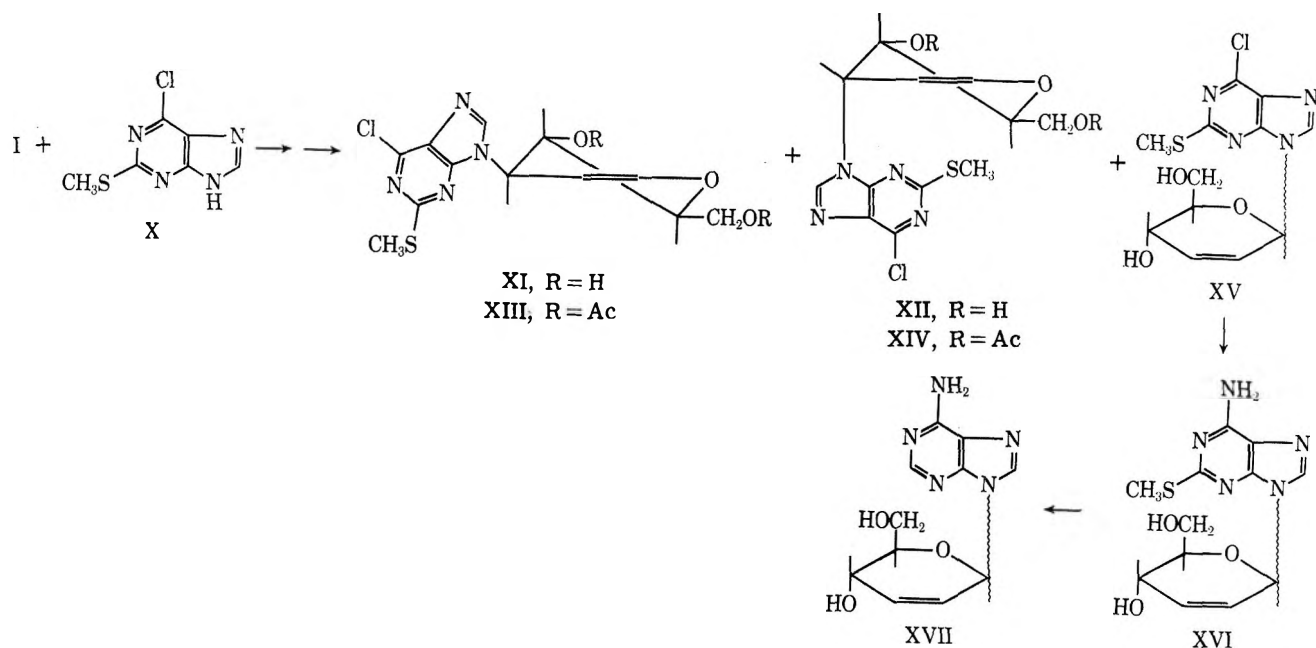
comparison of the ultraviolet absorption spectra of these nucleosides with the ultraviolet spectra of the possible N-methyladenines[22,33,34] established N-9 as the site of glycosylation.

The α and β anomers of 9-(2,3-dideoxy-D-*erythro*-hex-2-enopyranosyl)adenine were identified readily due to the presence of the typical AB spin patterns for H-2' and H-3', with ~10 Hz coupling. Large $J_{4'-5'}$ couplings of 8–9 Hz for each isomer suggested diaxial arrangements of H-4' and H-5', consistent not only with *H1*, but also with the alternate half-boat.[26] A large $J_{1'-2}$ of 2.9 Hz was observed for XVIII, whereas for XIX the coupling was about 1.5 Hz.[35] Examination of models revealed that an α anomer in the *H1* conformation and a β anomer in the alternate half-boat (Va) were both consistent with diaxial H-4' and H-5' and equatorial-vinylic H-1' and H-2', the latter arrangement leading to an expected vicinal $J_{1'-2'}$ of about 3 Hz (in an axial-vinylic case the $J_{1'-2'}$ would be about 1.5 Hz).[30]

At this point it was not possible to proceed with an assignment based upon pmr, since both conformation and anomeric configuration were unknown. Thus, a chemical assignment was attempted. Further study of Drieding's models showed that in the case of the β anomer it might be possible to form a $N^3 \rightarrow C\text{-}6'$ cyclonucleoside; however, $N^3 \rightarrow C\text{-}6'$-cyclonucleoside formation from the α anomer would be difficult, if not impossible, no matter what the carbohydrate conformation because of distance considerations. Accordingly, the 6'-O-tosyl derivatives of both XVIII and XIX were synthesized by treatment with p-toluenesulfonyl chloride in pyridine–chloroform. Selective tosylation at the 6' position was shown in the pmr spectra in DMSO-d_6 by the absence of the 6'-OH (triplet signal δ 5.09 ppm from TMS-capillary). Upon heating, the tosylated XIX reacted to form the $N^3 \rightarrow$

C-6' cyclonucleoside as determined by thin layer chromatography[36] and uv[37] (λ_{max}^{pH1} 271 nm) which established XIX as the β anomer. The conformation could then be assigned as *H1*, since the β anomer XIX exhibited a small $J_{1'-2'}$ and XVIII, the α anomer, exhibited a 2.9 Hz coupling. It is of interest to note that this assignment of C-1 configuration is consistent with other reported pmr data on anomeric pairs of 2',3'-unsaturated glycosides and nucleosides where the H-1' signal for the α anomer resonates at higher field than the β anomer.[13,27,38–40]

Compound XX was assigned the structure 9-(1,5-anhydro-2,3-dideoxy-D-*arabino*-hex-1-enitol-3-yl)adenine and compound XXI the structure 9-(1,5-anhydro-2,3-dideoxy-D-*ribo*-hex-1-enitol-3-yl)adenine based on the similarities in the pmr spectra of these compounds with 9-(1,5-anhydro-2,3-dideoxy-D-*arabino*-hex-1-enitol-3-yl)-6-chloro-2-methylthio-9H-purine (XI) and 9-(1,5-anhydro-2,3-dideoxy-D-*ribo*-hex-1-enitol-3-yl)-6-chloro-2-methylthio-9H-purine (XII), respectively.

Chemical shift data for the various nucleosides are presented in Table I. In the case of XIX and XXI, the H-8 proton was assigned by incorporation of deuterium at C-8.[41]

Reduction of the endocyclic double bond of 9-(2,3-dideoxy-β-D-*erythro*-hex-2-enopyranosyl)adenine (XIX) with hydrogen in the presence of palladium/charcoal catalyst gave 9-(2,3-dideoxy-β-D-*erythro*-hexopyranosyl)-adenine (XXIII) in a 60% yield. The synthesis of compound XXIII is of interest since it represents a route to 2',3'-dideoxypyranosylpurines related to the nucleoside antibiotic, amicetin.[11,12] Hydrogenation of 9-(1,5-anhydro-2,3-dideoxy-D-*arabino*-hex-1-enitol-3-yl)adenine (XX) and 9-(2,3-dideoxy-α-D-

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(35) Because of solubility considerations, DMSO-d_6 was used as solvent. Somewhat poorer resolution is observed in this solvent than is seen in CDCl₃ for the acyl derivatives.

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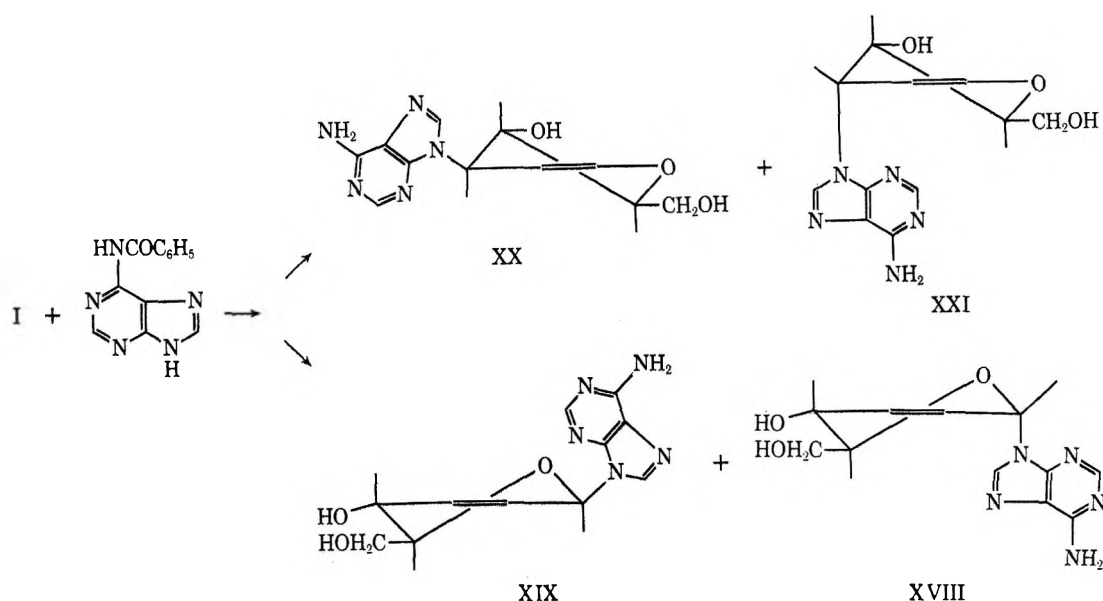
erythro-hex-2-enopyranosyl)adenine (XVIII) gave 9-(1,5-anhydro-2,3-dideoxy-D-*arabino*-hexitol-3-yl)ade-

nine (XXII) and 9-(2,3-dideoxy-α-D-*erythro*-hexopyranosyl)adenine (XXIV), respectively. The structure of the hydrogenated compounds XXIII, XXII, and XXIV was confirmed by ultraviolet and pmr spectra, elemental analysis and by a negative color test for carbohydrate unsaturation with Hanes–Isherwood reagent.[42]
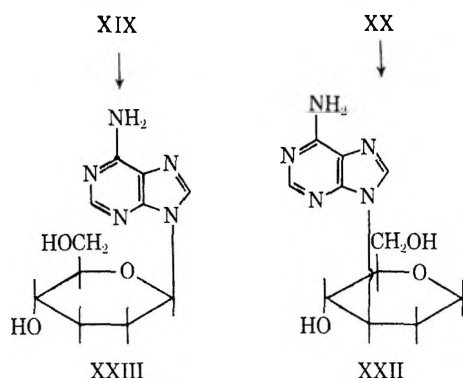
Experimental Section

Pmr spectra at 60 MHz were obtained on a C6OH Jeolco instrument using TMS as an internal standard. A Varian HA-100 and a Bruker HFX were used to obtain pmr spectra at 100 and 90 MHz, respectively. Chemical shifts were measured to within an accuracy of ±0.01 ppm. Coupling constants were measured to within an accuracy of ±0.1 Hz. Ultraviolet spectra were obtained on a DK-2 absorption spectrometer. Melting points were observed on a Thomas–Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were performed by Heterocyclic Chemical Corp., Harrisonville, Mo.

2-Acetamido-6-chloropurine.—Chlorine gas was passed into 150 ml of cold (−5°) absolute ethanol for 5 min. The flow of chlorine was decreased to a moderate rate and to this cold solution was added 2-acetamido-6-benzylthiopurine[43] (6.0 g, 21 mmol) over a period of 1 hr. During this addition, the 2-acetamido-6-benzylthiopurine slowly dissolved and a white solid gradually separated from solution. The flow of chlorine was continued for an additional 10 min, then discontinued, and the mixture was allowed to stand at −5° with stirring for 1 hr. The solid was then collected by filtration, washed with cold absolute

ethanol (200 ml), and slurried in 600 ml of anhydrous ether and the solid was collected by filtration. The solid was washed with an additional 600 ml of anhydrous ether and air dried to furnish 3.5 g of 2-acetamido-6-chloropurine. Recrystallization from a dimethylacetamide–water mixture (1:10, v/v) gave 2.0 g (47%) of pure 2-acetamido-6-chloropurine (II), mp >300° dec, which was found to be identical in all respects with an authentic sample of 2-acetamido-6-chloropurine:[44] uv $\lambda_{max}^{pH\ 1}$ 249 nm (ϵ 11,000), 285 (10,600); $\lambda_{max}^{pH\ 11}$ 236 nm (ϵ 26,200), 284 (9930); $\lambda_{max}^{H_2O}$ 253.5 nm (ϵ 10,150), 284.5 (10,800).

2-Acetamido-6-chloro-9-(4,6-di-*O*-acetyl-2,3-dideoxy-D-*erythro*-hex-2-enopyranosyl)-9*H*-purine (III).—A finely powdered mixture of 2-acetamido-6-chloropurine (II) (0.8 g, 4 mmol) and 3,4,6-tri-*O*-acetyl-D-glucal (I) (3.2 g, 0.012 mol) was heated to an inside temperature of 120° in an oil bath. To this hot mixture was added 50 mg of *p*-toluenesulfonic acid with thorough stirring, and heating was then continued at an inside temperature of 140° under aspirator vacuum for 2 hr. The dark melt was dissolved in warm ethyl acetate (300 ml) and the insoluble material was removed by filtration. The filtrate was cooled to 0° and washed with cold saturated sodium bicarbonate solution (3 × 75 ml) and cold water (3 × 75 ml), and the solution was then dried over anhydrous sodium sulfate. The sodium sulfate was removed by filtration and the filtrate was concentrated under high vacuum and at room temperature to 5 ml. This solution was applied to four preparative thick layer chromatography plates (7.75 × 15.75 in., 2 mm thickness of absorbent) of SilicAR 7GF (Mallinckrodt Chemical Co.). The plates were developed the full length (14 in., measured from the base line) with a *n*-heptane–tetrahydrofuran–acetone (7:3:1, v/v/v) solvent system and then air dried. The plates were developed in this solvent system three additional times, which resulted in the separation of two major bands [detected by a short-wave (254 nm) ultraviolet light]. The slower moving ultraviolet-absorbing band was removed and extracted with 400 ml of warm absolute ethyl alcohol. The ethyl alcohol was evaporated under high vacuum and at room temperature to afford a residue which was dissolved in 10 ml of bromoethane. This was allowed to stand at −20° for 2 days to afford 90 mg of III: mp 125–127°; uv $\lambda_{max}^{pH\ 1}$ 227 nm (ϵ 27,300), 257.5 (13,000), 283 (12,400); $\lambda_{max}^{pH\ 11}$ 229 nm (ϵ 22,900), 257 (12,000), 283.5 (11,900); λ_{max}^{EtOH} 228.5 nm (ϵ 27,700), 257.5 (12,000), 286.5 (11,500).

Anal. Calcd for $C_{17}H_{18}ClN_5O_6$: C, 48.17; H, 4.25; N, 16.53. Found: C, 48.03; H, 4.20; N, 16.45.

2-Amino-9-(2,3-dideoxy-D-*erythro*-hex-2-enopyranosyl)-9*H*-purine-6-thiol (VI).—Metallic sodium (4.7 g) was dissolved in 100 ml of absolute methanol, and the solution was cooled to 0° and then saturated with H₂S gas. To 40 ml of this solution (2 *N* NaSH) was added 420 mg (0.991 mmol) of 2-acetamido-6-chloro-9-(4,6-di-*O*-acetyl-2,3-dideoxy-D-*erythro*-hex-2-enopyranosyl)-9*H*-purine (III). This solution was heated at reflux temperature for 3 hr and cooled to 0°, and the pH was adjusted to 7.0 by the slow addition of glacial acetic acid. Excess H₂S and

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(44) R. H. Iwamoto, E. M. Acton, and L. Goodman, *ibid.*, **6**, 684 (1963).

solvent were removed under aspirator vacuum at room temperature. The residue was extracted with anhydrous acetone (2 × 200 ml), insoluble material was removed by filtration, and the filtrate was evaporated under high vacuum at room temperature to afford a white solid. This solid was then slurried in 10 ml of cold methyl alcohol. The solid was collected by filtration, washed with cold methyl alcohol (2 × 2 ml), and air dried to yield 120 mg (41%) of product. Recrystallization from absolute methyl alcohol gave 60 mg of an analytical sample of 2-amino-9-(2,3-dideoxy-D-*erythro*-hex-2-enopyranosyl)-9*H*-purine-6-thiol (VI): mp 187–188°; uv $\lambda_{max}^{pH\ 1}$ 345 nm (ϵ 12,000), 361.5 (4600); $\lambda_{max}^{pH\ 11}$ 251.5 nm (ϵ 7500), 318 (11,000).

Anal. Calcd for $C_{11}H_{13}N_5O_3S$: C, 44.75; H, 4.41; N, 23.73. Found: C, 44.81; H, 4.45; N, 23.64.

9-(2,3-Dideoxy-D-*erythro*-hex-2-enopyranosyl)guanine (VII).— To 80 ml of 20% ammonia solution was added 340 mg (1.20 mmol) of 2-amino-9-(2,3-dideoxy-D-*erythro*-hex-2-enopyranosyl)-9*H*-purine-6-thiol (VI). To this solution was added 4% hydrogen peroxide (12 ml) and the solution was stirred at room temperature for 15 min. The excess hydrogen peroxide was destroyed by the addition of small amounts of platinum black and then evaporated to a residue under water aspirator vacuum with a water bath at 50°. The residue was extracted with hot absolute ethyl alcohol (2 × 200 ml) and filtered through a 4-mm-thick Celite pad. The Celite pad was washed with hot absolute ethyl alcohol (50 ml) and the combined filtrates were evaporated to a residue under high vacuum at room temperature. This residue was slurried in 20 ml of acetone and the solid was collected by filtration to yield 270 mg (84%) of product. Recrystallization from 10 ml of water gave an analytical sample of 9-(2,3-dideoxy-D-*erythro*-hex-2-enopyranosyl)guanine (VII): mp >220° dec; uv $\lambda_{max}^{pH\ 1}$ 253 nm (ϵ 11,500), 275 (8200); $\lambda_{max}^{pH\ 11}$ 262 nm (ϵ 12,000).

Anal. Calcd for $C_{11}H_{13}N_5O_4 \cdot 1.50H_2O$: C, 43.13; H, 5.26; N, 22.86. Found: C, 42.75; H, 5.19; N, 22.58.

The pmr spectrum of VII revealed an absorption peak at δ 4.0 which integrated for three protons and was assigned to the 1.5 mol of water.

9-(D-*manno*,D-*allo*-Hexopyranosyl)guanine (VIII).—9-(2,3-Dideoxy-D-*erythro*-hex-2-enopyranosyl)guanine (VII) (50 mg, 0.16 mmol) was dissolved in a 1:1 mixture of water and *tert*-butyl alcohol (10 ml) and to this solution was added 0.5 mg (0.002 mmol) of osmium tetroxide and 1 ml of 30% hydrogen peroxide. The solution was allowed to stand at room temperature for 2 days, after which the excess hydrogen peroxide was decomposed by the addition of a small amount of platinum black. The mixture was filtered through a 4-mm-thick Celite bed, the Celite bed was washed with 20 ml of hot water, and the combined filtrates were evaporated to a residue under high vacuum at room temperature. The residue was recrystallized from water (3 ml) to furnish 6 mg of VIII: mp >160° dec; uv $\lambda_{max}^{pH\ 1}$ 253 nm (ϵ 10,000), 275 (7000); $\lambda_{max}^{pH\ 11}$ 263 nm (ϵ 10,000).

Anal. Calcd for $C_{11}H_{15}N_5O_6$: C, 42.17; H, 4.79; N, 22.36. Found: C, 42.21; H, 4.83; N, 22.50.

Hydrolysis of 9-(D-*manno*,D-*allo*-Hexopyranosyl)guanine (VIII). —9-(D-*manno*,D-*allo*-Hexopyranosyl)guanine (VIII) (50 mg, 0.16 mmol) was dissolved in 5 ml of water. To this solution was added 10 g of Amberlite IR-120 resin (H+ form) and the mixture was allowed to stand at room temperature for 24 hr. The resin was then removed by filtration and washed with 50 ml of water at room temperature. The filtrates were combined and concentrated to 1 ml under high vacuum at room temperature. An ultraviolet absorption spectrum and a positive Fehling's test indicated that hydrolysis had occurred. The hydrolysate was applied to Whatman No. 1 chromatography paper, and the paper was developed by the descending technique with a cyclohexane–pyridine–water (40:23:19.5, v/v/v) solvent system,[45] air dried, and then sprayed with a silver nitrate spray reagent.[46] A final spray with ethanolic sodium hydroxide solution revealed two components (detected as black spots) present in the hydrolysate. These two components were identified as D-mannose and D-allose by comparison of the $R_{galactose}$ values (1.45 and 1.25, respectively) with those observed for authentic D-mannose (1.45) and D-allose (1.25).[25]

2-Acetamido-6-chloro-9-(4,6-di-*O*-acetyl-2,3-dideoxy-α- and -β-D-*erythro*-hex-2-enopyranosyl)-9*H*-purine (IV and V).—2-Acetamido-6-chloro-9-(4,6-di-*O*-acetyl-2,3-dideoxy-D-*erythro*-hex-2-

enopyranosyl-9*H*-purine (III) (0.5 g) was dissolved in 10 ml of ethyl acetate and applied to three preparative layer plates (7.75 × 15.75 in., 2 mm thickness) of SilicAR 7GF (Mallinckrodt Chemical Co.). The plates were developed the full length (14 in. measured from the base line) in an isopropyl ether–*n*-propyl alcohol–acetone solvent system (8:1:1, v/v/v) and air dried. The same plates were developed two more times with the same solvent system, which resulted in the separation of two distinct ultraviolet-absorbing bands. The bands were removed and individually extracted with 500 ml of warm ethyl acetate. The slower moving component was crystallized from bromoethane to give 170 mg of pure 2-acetamido-6-chloro-9-(4,6-di-*O*-acetyl-2,3-dideoxy-β-D-*erythro*-hex-2-enopyranosyl)-9*H*-purine (V), mp 149–159°, $[\alpha]^{26}$D +80.6° (c 0.5, CHCl₃).

Anal. Calcd for $C_{17}H_{19}ClN_5O_6$: C, 48.17; H, 4.25; N, 16.53. Found: C, 48.30; H, 4.34; N, 16.83.

The faster moving component was dissolved in 5 ml of methylene chloride and the solution was added dropwise with stirring to *n*-pentane (2 ml of CH₂Cl₂ solution per 100 ml of *n*-pentane). The solid which precipitated was collected by filtration to yield 60 mg of pure 2-acetamido-6-chloro-9-(4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranosyl)-9*H*-purine (IV), mp 78–80°, $[\alpha]$D −16.4° (c 0.5, CHCl₃).

Anal. Found: C, 48.17; H, 4.41; N, 16.11.

2-Acetamido-6-chloro-9-(4,6-di-*O*-acetyl-1,5-anhydro-2,3-dideoxy-D-*arabino*-hex-1-enitol-3-yl)purine (IX).—The faster moving ultraviolet-absorbing band from the preparative plate used in the preparation and chromatography of III was extracted with 400 ml of warm ethyl alcohol. The ethyl alcohol was evaporated under high vacuum and at room temperature to furnish a syrup. This syrup was dissolved in 400 ml of hot *n*-heptane and the resulting solution was allowed to cool at room temperature for 2 days in a closed vessel. The crystalline solid which had separated was collected by filtration to yield 120 mg of an analytically pure sample of IX: mp 104–105°; uv $\lambda_{max}^{pH\ 1}$ 229 nm (ϵ 25,500), 260 (9700), 285 (11,100); $\lambda_{max}^{pH\ 11}$ 231 nm (ϵ 24,000), 260 (9700), 285 (11,100); λ_{max}^{MeOH} 230 nm (ϵ 26,100), 257 (9500), 288 (11,100).

Anal. Calcd for $C_{17}H_{18}ClN_5O_6$: C, 48.17; H, 4.25; N, 16.53. Found: C, 48.21 H, 4.40; N, 16.15.

9-(1,5-Anhydro-2,3-dideoxy-D-*arabino*-hex-1-enitol-3-yl)-6-chloro-2-methylthio-9*H*-purine (XI) and 9-(1,5-Anhydro-2,3-dideoxy-D-*ribo*-hex-1-enitol-3-yl)-6-chloro-2-methylthio-9*H*-purine (XII).—A finely powdered mixture of 6-chloro-2-methylthiopurine[47] (X) (10 g, 50 mmol) and 3,4,6-tri-*O*-acetyl-D-glucal (I) (20 g, 73 mmol) was heated to an inside temperature of 120° in an oil bath. To the hot mixture was added, with thorough mixing, 50 mg of *p*-toluenesulfonic acid and heating was continued at 120° (inside temperature) under aspirator vacuum for 2.5 hr. The dark melt was dissolved in warm ethyl acetate (900 ml), the insoluble material was removed by filtration, and the filtrate was cooled to 0°. The filtrate was washed with cold saturated sodium bicarbonate solution (3 × 200 ml) and cold water (3 × 200 ml) and then dried over anhydrous sodium sulfate. The sodium sulfate was removed by filtration and the filtrate was concentrated to 500 ml. Silica gel (J. T. Baker powder, 40 g), Celite (Johns Manville, 20 g) and 0.05% by weight of phosphor (Du Pont # 609) was added to the ethyl acetate solution and the resulting mixture was evaporated under high vacuum and at room temperature to a dry powder. This powder was placed on top of a preformed nylon dry column (1.75 × 13 in.) of Baker silica gel powder containing 0.05% by weight of phosphor. The column was eluted with 2 l. of a *n*-pentane–ethyl acetate (9:1, v/v) solvent system and the eluent was discarded. The nucleoside band near the top of the column (dark band under ultraviolet light, 254 nm) was excised and triturated with 1 l. of warm absolute ethyl alcohol, and the silica gel was removed by filtration. The filtrate was concentrated to a stiff foam under high vacuum at 60°. This foam was dissolved at room temperature in absolute methyl alcohol (250 ml) and then cooled to −20°. The cold solution was saturated with ammonia and then allowed to stand at −20° for 12 hr. Excess ammonia and solvent was removed at room temperature under aspirator vacuum to afford a syrup. The syrup was dissolved at room temperature in absolute methanol (500 ml) and the resulting solution was allowed to stand at room temperature for 2 days. The crystalline solid which had separated was collected by filtration to furnish 1.77 g of XI, mp 196–198°. Recrystallization from absolute methanol furnished 1.24 g of XI: mp 214–215°; uv $\lambda_{max}^{pH\ 1}$ 236 nm (ϵ 11,000), 260

(45) H. Ruckert, E. Pfeil, and C. Sharf, *Chem. Ber.*, **90**, 2558 (1965).

(46) L. Hough and J. K. N. Jones in "Methods in Carbohydrate Chemistry," Vol. 1, Academic Press, New York, N. Y., 1962, p 21; L. Hough, *Nature (London)*, **165**, 400 (1950).

(47) C. Wayne Noell and R. K. Robins, *J. Org. Chem.*, **24**, 320 (1959).

(7200), 305 (5300); $\lambda_{max}^{pH\ 11}$ 238.5 nm (ϵ 12,800), 260 (7900), 305 (6200); $\lambda_{max}^{H_2O}$ 236 nm (ϵ 14,100), 260 (8500), 305 (6900).

Anal. Calcd for $C_{12}H_{13}ClN_4O_3S$: C, 43.84; H, 3.98; N, 17.04. Found: C, 43.96; H, 4.12; N, 16.98.

The filtrate from above was concentrated to 100 ml and allowed to stand at room temperature for 72 hr. The crystals which had formed were collected by filtration to yield 1.36 g of XV, mp 170–174°.

The above filtrate was then concentrated to 50 ml. After 1 week in a closed vessel at room temperature there was obtained 1.81 g of XII, mp 149–157°. Recrystallization from absolute methanol furnished 827 mg of an analytically pure sample of XII: mp 177–178°; uv $\lambda_{max}^{pH\ 1}$ 237.5 nm (ϵ 18,000), 261 (10,200), 306 (7700); $\lambda_{max}^{pH\ 11}$ 236 nm (ϵ 29,200), 261 (11,300), 305 (8200); $\lambda_{max}^{H_2O}$ 237.5 nm (ϵ 18,000), 261 (9500), 305 (8200).

Anal. Calcd for $C_{12}H_{13}ClN_4O_3S$: C, 43.84; H, 4.00; N, 17.20.

6-Chloro-9-(4,6-di-*O*-acetyl-1,5-anhydro-2,3-dideoxy-D-*arabino*-hex-1-enitol-3-yl)-2-methylthio-9*H*-purine (XIII) and 6-Chloro-9-(4,6-di-*O*-acetyl-1,5-anhydro-2,3-dideoxy-D-*ribo*-hex-1-enitol-3-yl)-2-methylthio-9*H*-purine (XIV).—To 25 ml of acetic anhydride and pyridine (1:4, v/v) was added 230 mg (0.70 mmol) of XI and the mixture was allowed to stand at room temperature for 12 hr with frequent shaking. The resulting solution was poured into 150 ml of crushed ice and stirred thoroughly for 15 min. This mixture was extracted with CHCl$_3$ (2 × 100 ml), the chloroform fractions were combined and washed with cold (0°) 1 *N* HCl solution (3 × 200 ml) and cold (0°) saturated sodium bicarbonate solution (3 × 200 ml), and the chloroform solution was then dried over anhydrous sodium sulfate. The sodium sulfate was removed by filtration and the chloroform filtrate was concentrated to 10 ml volume and applied to the top of a dry-packed column of Baker silica gel powder (12 × 0.5 in.). The column was eluted with ethyl acetate (500 ml) and the eluent was evaporated under high vacuum and at room temperature to afford a stiff syrup. This syrup was dissolved in 2 ml of anhydrous ether and allowed to stand at −10° for 24 hr. The crystals which had separated were collected by filtration to yield 40 mg of analytically pure XIII: mp 117–118°; uv $\lambda_{max}^{pH\ 1}$ 237 nm (ϵ 18,100), 260 (10,600), 305 (8400); $\lambda_{max}^{pH\ 11}$ 238 nm (ϵ 16,700), 260 (10,600), 304 (8800); λ_{max}^{EtOH} 237.5 nm (ϵ 20,400), 260 (11,900), 305 (9800).

Anal. Calcd for $C_{16}H_{17}ClN_4O_5S$: C, 46.54; H, 4.12; N, 13.58. Found: C, 46.47; H, 4.18; N, 13.43.

The same procedure as above was followed except that 260 mg (0.791 mmol) of XII was used instead of 250 mg. The dry column was eluted with ethyl acetate (700 ml) and the eluent was concentrated to a 5-ml volume. This solution was applied to two preparative layer SilicAR 7GF chromatography plates (7.75 × 15.75 in., 2 mm thickness). The plates were developed the full length (14 in., measured from the base line) in an ether–petroleum ether (bp 60–90°) (9:1, v/v) solvent system. The band was removed and extracted with 200 ml of warm absolute ethanol. The ethanol solution was evaporated under high vacuum and at room temperature to a syrup. This syrup was dissolved in 5 ml of water–methanol (9:1, v/v) and the resulting solution was lyophylized to yield 40 mg of analytically pure XIV: mp 72–73°; uv $\lambda_{max}^{pH\ 1}$ 236.5 nm (ϵ 18,200), 261 (9800), 305 (7800); $\lambda_{max}^{pH\ 11}$ 238 nm (ϵ 16,300), 261 (9600), 305 (7800); λ_{max}^{EtOH} 237 nm (ϵ 19,100), 261 (10,000), 306 (8700).

Anal. Calcd for $C_{16}H_{17}ClN_4O_5S \cdot H_2O$: C, 44.60; H, 4.41; N, 13.01. Found: C, 44.98; H, 4.24; N, 12.97.

A pmr spectrum of XIV in DMSO-d_6 showed a water peak at δ 4.0 which integrated for two protons or one molecule of water.

6-Chloro-9-(2,3-dideoxy-D-*erythro*-hex-2-enopyranosyl)-2-methylthio-9*H*-purine (XV).—The filtrate from the acid-catalyzed fusion of 3,4,6-tri-*O*-acetyl-D-glucal with 6-chloro-2-methylthiopurine was reported to furnish a crude nucleoside with mp 170–174°. Recrystallization of this product from absolute methanol gave 1.03 g of analytically pure 6-chloro-9-(2,3-dideoxy-D-*erythro*-hex-2-enopyranosyl)-2-methylthio-9*H*-purine (XV): mp 184–185°; uv $\lambda_{max}^{pH\ 1}$ 260 nm (ϵ 11,800), 305 (7200); $\lambda_{max}^{pH\ 11}$ 234 nm (ϵ 19,100), 263.5 (11,500), 305 (7600); $\lambda_{max}^{H_2O}$ 233 nm (ϵ 18,400), 263 (11,800), 305 (7800).

Anal. Calcd for $C_{12}H_{13}ClN_4O_2S$: C, 43.84; H, 3.98; N, 17.04. Found: C, 43.75; H, 4.15; N, 17.34.

6-Amino-9-(2,3-dideoxy-D-*erythro*-hex-2-enopyranosyl)-2-methylthio-9*H*-purine (XVI).—To 40 ml of methanolic ammonia was added 200 mg (0.608 mmol) of 6-chloro-9-(2,3-dideoxy-D-*erythro*-hex-2-enopyranosyl)-2-methylthio-9*H*-purine (XV). This

mixture was sealed in a pressure bottle and allowed to stand at room temperature for 3 days. Excess ammonia and solvent were removed under aspirator vacuum and the residue was then triturated with four portions of 150 ml each of anhydrous ether.

The remaining solid was slurried in 10 ml of hot absolute ethyl alcohol and cooled to room temperature, and the solid was collected by filtration to yield 116 mg (62%) of product, mp 196–198°. Recrystallization from 5 ml of ethyl alcohol–water (9:1, v/v) furnished 49 mg of pure 6-amino-9-(2,3-dideoxy-D-*erythro*-hex-2-enopyranosyl)-2-methylthio-9*H*-purine (XVI): mp 236–237°; uv $\lambda_{max}^{pH\ 1}$ 269 nm (ϵ 13,000); $\lambda_{max}^{pH\ 11}$ 235 nm (ϵ 17,300), 275 (13,000); $\lambda_{max}^{H_2O}$ 260 nm (ϵ 17,600).

Anal. Calcd for $C_{12}H_{15}N_5O_2S$: C, 46.60; H, 4.85; N, 22.65. Found: C, 46.69; H, 4.87; N, 22.68.

9-(2,3-Dideoxy-D-*erythro*-hex-2-enopyranosyl)adenine (XVII).—6-Amino-9-(2,3-dideoxy-D-*erythro*-hex-2-enopyranosyl)-2-methylthio-9*H*-purine (XVI) (80 mg, 0.26 mmol) was dissolved in 80 ml of water, 400 mg of W-4 Raney nickel[48] was added, and the mixture was heated at reflux temperature for 3 hr. An additional 400 mg of Raney nickel was then added and the mixture was allowed to stand at room temperature for 16 hr. The Raney nickel was removed by filtration through a 3-mm-thick Celite bed, the Celite bed was washed with 50 ml of hot water, and the combined filtrates were evaporated to dryness under high vacuum and room temperature. Ultraviolet spectral analysis revealed that the 2-methylthio group had been removed. Crystallization from water furnished 12 mg of an analytically pure sample of 9-(2,3-dideoxy-D-*erythro*-hex-2-enopyranosyl)adenine (XVII): mp 241–242°; uv $\lambda_{max}^{pH\ 1}$ 257 nm (ϵ 14,700); $\lambda_{max}^{pH\ 11}$ 260 nm (ϵ 15,600); $\lambda_{max}^{H_2O}$ 259.5 nm (ϵ 15,300).

Anal. Calcd for $C_{11}H_{13}N_5O_3$: C, 50.19; H, 4.95; N, 26.62. Found: C, 49.99; H, 4.90; N, 26.78.

9-(2,3-Dideoxy-β-D-*erythro*-hex-2-enopyranosyl)adenine (XIX) and 9-(2,3-Dideoxy-α-D-*erythro*-hex-2-enopyranosyl)adenine (XVIII).—A finely powdered mixture of 6-benzamidopurine[49] (20.0 g, 84 mmol) and I (46.5 g, 0.171 mol) was heated in an oil bath (165°) until a melt was formed. To the melt was added *p*-toluenesulfonic acid monohydrate (100 mg) and the heating was continued under aspirator vacuum for 3 hr. The melt was poured into 500 ml of ethyl acetate and washed twice with water. The ethyl acetate layer was dried over magnesium sulfate, filtered, concentrated to a small volume, and applied to a silicic acid column (J. T. Baker, No. 3405; 18 × 2.5 in.). The column was washed with petroleum ether (bp 30–60°)–chloroform (1:4, v/v) to remove glucal and then chloroform to remove nucleosidic material (64 mmol). The nucleosidic material was dissolved in 750 ml of methanol saturated with ammonia at 0° and set at room temperature for 3 days. Concentration of the methanolic solution gave 7.9 g of crystalline material, mp 212–214°. A 500-mg portion of this was preabsorbed on 15 g of Mallinckrodt SilicAR CC7 (200–325 mesh) and applied to a SilicAR CC7 column (15 × 1.25 in., packed in chloroform). The column was successively washed with 2 l. of methanol–dichloromethane (5:95, v/v) and 2 l. of methanol–dichloromethane (6:94, v/v), followed by methanol–dichloromethane (7:93, v/v). The first main fraction was evaporated and the residue was crystallized from ethanol to give a mixture of XX and XXI (0.14 g). The second main fraction after evaporation and crystallization from ethanol gave 0.16 g of pure XVIII: mp 243–245° dec; uv $\lambda_{max}^{pH\ 1}$ 257 nm (ϵ 15,500); $\lambda_{max}^{pH\ 11}$ 260 nm (ϵ 16,200); λ_{max}^{EtOH} 260 nm (ϵ 16,000).

Anal. Calcd for $C_{11}H_{13}N_5O_3$: C, 50.19; H, 4.94; N, 26.62. Found: C, 50.19; H, 4.93; N, 26.80.

The filtrate which was obtained from the filtration of the nucleosidic material, mp 212–214°, in the above preparation was concentrated and applied to a silicic acid column (J. T. Baker No. 3405; 10 × 2.5 in.). Elution of the column with methanol–chloroform (8:92, v/v) removed 7 g of nucleosidic material. Fractional crystallization of the nucleosidic material from ethanol concentrated XIX in the filtrates. The filtrate was evaporated and the residue (5.8 g) was dissolved in water and applied to a Dowex AG 1X8 200–400 mesh column (OH form; 20 × 5.5 in.). Elution with 50% aqueous methanol gave, after evaporation and crystallization of the appropriate fractions, 1.4 g of XIX: mp 195–196.5° (resolidifies, mp 210–215°); uv $\lambda_{max}^{pH\ 1}$ 257 nm (ϵ 15,000); $\lambda_{max}^{pH\ 11}$ 259 nm (ϵ 16,000); λ_{max}^{EtOH} 259 nm (ϵ 15,600).

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(48) Purchased from W. R. Grace and Co.

(49) A. Kossel, *Z. Physiol. Chem.*, **12**, 241 (1888).

Anal. Found: C, 49.98; H, 4.97; N, 26.56.

9-(1,5-Anhydro-2,3-dideoxy-D-*arabino*-hex-1-enitol-3-yl)adenine (XX) and 9-(1,5-Anhydro-2,3-dideoxy-D-*ribo*-hex-1-enitol-3-yl)-adenine (XXI).—A mixture of XX and XXI (1.6 g) obtained as described in the preparation of XVIII was applied to a Dowex AG 1X8 200–400 mesh column (OH form; 19 × 5.5 in.). Elution of the column with 50% aqueous methanol gave after concentration and crystallization from ethanol 0.67 g of XXI, mp 219–220, uv $\lambda_{max}^{pH\,1}$ 258 nm (ϵ 15,200), $\lambda_{max}^{pH\,11}$ 260 nm (ϵ 15,600), λ_{max}^{EtOH} 260 nm (ϵ 15,400), and 0.69 g of XX, mp 198–201°, uv $\lambda_{max}^{pH\,1}$ 258 nm (ϵ 15,200), $\lambda_{max}^{pH\,11}$ 260 nm (ϵ 15,600), λ_{max}^{EtOH} 260 nm (ϵ 15,400).

Anal. Found for XXI: C, 50.20; H, 5.00; N, 26.49. Found for XX: C, 49.95; H, 5.03; N, 26.63.

9-(2,3-Dideoxy-α-D-*erythro*-hexopyranosyl)adenosine (XXIV).—9-(2,3-Dideoxy-α-D-*erythro*-hex-2-enopyranosyl)adenine (XVIII) (200 mg, 0.8 mmol) was dissolved in 50 ml of water. To this solution was added 100 mg of 10% Pd/C and the mixture was then shaken with hydrogen at 45 psi and room temperature for 8 hr. The Pd/C was removed by filtration through a Celite bed, the Celite bed was washed with 50 ml of hot water, and the combined filtrates were evaporated *in vacuo* to a residue. The residue was crystallized from ethanol–water to give 100 mg of XXIV: mp 236–237°; uv $\lambda_{max}^{pH\,1}$ 257 nm (ϵ 14,300); $\lambda_{max}^{pH\,11}$ 260 nm (ϵ 14,900); $\lambda_{max}^{H_2O}$ 260 nm (ϵ 15,700).

Anal. Calcd for $C_{11}H_{15}N_5O_3$: C, 49.80; H, 5.69; N, 26.40. Found: C, 49.62; H, 5.61; N, 26.56.

9-(2,3-Dideoxy-β-D-*erythro*-hexopyranosyl)adenine (XXIII).—Hydrogenation of 9-(2,3-dideoxy-β-D-*erythro*-hex-2-enopyranosyl)adenine (XIX) (100 mg, 0.4 mmol) for 6 hr as in the procedure for XXIV gave after crystallization from ethanol 60 mg of

XXIII: mp 218.5–219.5° dec; uv $\lambda_{max}^{pH\,1}$ 256 nm (ϵ 11,800); $\lambda_{max}^{pH\,11}$ 258 nm (ϵ 12,300); $\lambda_{max}^{H_2O}$ 258 nm (ϵ 12,200).

Anal. Calcd for $C_{11}H_{15}N_5O_3$: C, 49.80; H, 5.69; N, 26.40. Found: C, 49.77; H, 5.49; N, 26.55.

9-(1,5-Anhydro-2,3-dideoxy-D-*arabino*-hexitol-3-yl)adenine (XXII).—Hydrogenation of 9-(1,5-anhydro-2,3-dideoxy-D-*arabino*-hex-1-enitol-3-yl)adenine (XX) (200 mg, 0.8 mmol) as in the procedure for XIV gave after crystallization from ethanol 120 mg of XXII: mp 233–235°; uv $\lambda_{max}^{pH\,1}$ 257 nm (ϵ 14,400); $\lambda_{max}^{pH\,11}$ 260 nm (ϵ 14,700); $\lambda_{max}^{H_2O}$ 260 nm (ϵ 14,700).

Anal. Calcd for $C_{11}H_{15}N_5O_3 \cdot {}^{1}/_{4}H_2O$: C, 48.17; H, 5.88; N, 25.53. Found: C, 48.15; N, 5.60; N, 25.73.

The Absolute Configuration of Methyl 3-O-Acetyl-2,3-dihydroxy-2-methylpropanoate by Nuclear Magnetic Resonance and Chemical Determination

FRED L. SHORE[1] AND GEORGE U. YUEN*

Department of Chemistry, Arizona State University, Tempe, Arizona 85281

The chemical transformation of (S)-(+)-atrolactic acid to methyl 3-O-acetyl-(R)-2,3-dihydroxy-2-methylpropanoate (1), $[\alpha]^{23}D$ −9.5°, gives an absolute configuration in agreement with the prediction from solvate models and the sense of nonequivalence apparent in the nmr spectra of 1 in the solvent (R)-1-(1'-naphthyl)ethylamine.

A study of the Grignard reaction with optically active carbonyl compounds, being carried out in this laboratory, yields products of unknown stereochemistry, whose absolute configuration can be determined most conveniently by degradation to an enantiomer of α-methylglyceric acid. The resolution of α-methylglyceric acid (2,3-dihydroxy-2-methylpropanoic acid) was attempted without success by Glattfield and Sherman.[2] Preparation and assignment of the absolute configuration of methyl 3-O-acetyl-2,3-dihydroxy-2-methylpropanoate (1) (Table I) is described herein. Two methods of assignment were used: chemical transformation of (S)-(+)-atrolactic acid of known absolute configuration[3] to methyl 3-O-acetyl-(R)-2,3-dihydroxy-2-methylpropanoate, *via* reactions remote from the asymmetric center; and establishment of a consistent pattern between the sense of nonequivalence apparent in the nmr spectra of methyl 3-O-acetyl-(R)-2,3-dihydroxy-2-methylpropanoate and its enantiomer in the solvent (R)-1-(1'-naphthyl)ethylamine with predictions based on solvate models.

Atrolactic acid was prepared by the method of Eliel
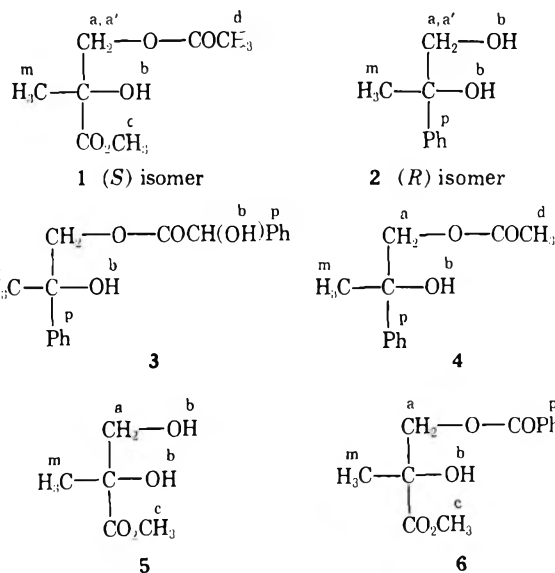
and Freeman[4] and partially resolved as the quinine salt using the procedure of McKenzie and Clough.[5] The partially resolved (S)-atrolactic acid was then reduced by lithium aluminum hydride to (S)-(+)-

(1) Taken from the Ph.D. Dissertation of Fred L. Shore.

(2) J. W. E. Glattfeld and L. P. Sherman, *J. Amer. Chem. Soc.*, **47**, 1742 (1925).

(3) J. H. Brewster, *ibid.*, **78**, 4061 (1956).

(4) E. L. Eliel and J. P. Freeman, *Org. Syn.*, **33**, 7 (1953).

(5) A. McKenzie and G. W. Clough, *J. Chem. Soc.*, **97**, 1016 (1910).

TABLE I
NUCLEAR MAGNETIC RESONANCE SPECTRA[a] OF DERIVATIVES OF 1,2-PROPANEDIOL

Compd	H_p	H_m	H_a	$H_{a'}$	H_b	H_c	H_d	Coupling constants $J_{a,a'}$, Hz
Methyl 3-O-acetyl-2,3-dihydroxy-2-methylpropanoate (1)		1.40	4.32	4.09	3.65	3.79	2.03	11.2
2-Phenyl-1,2-propanediol (2)	7.45	1.42	3.75	3.49	3.10			11.0
1-O-((2'R)-Mandeloyl)-(2S)-2-phenyl-1,2-propanediol (3)	7.23	1.36	4.24		2.69 5.07			
1-O-Acetyl-2-phenyl-1,2-propanediol (4)	7.5	1.59	4.31		2.65		2.07	
2,3-Dihydroxy-2-methylpropanoate (5)		1.36	3.80	3.56	2.96	3.81		11.7
Methyl 2-O-benzoyl-2,3-dihydroxy-2-methylpropanoate (6)	7.6	1.48	4.42		3.63	3.79		
4 in (R)-1-(1'-naphthyl)ethylamine and CFCl₃	7.41	1.46	4.23				1.76 (S), 1.74 (R)	
1 in (R)-1-(1'-naphthyl)ethylamine and CFCl₃		1.34	4.20			3.50	1.79 (R), 1.78 (S)	
75% op[c] (R)-4 in (R)-1-(1'-naphthyl)ethylamine and CFCl₃, 100 MHz[b]	7.39	1.46	4.19				1.81 (S), 1.79 (R)	
77.1% op[c] (R)-1 in (R)-1-(1'-naphthyl)ethylamine and CFCl₃, 100 MHz[b]		1.32	4.21			3.48	1.80 (R), 1.79 (S)	

[a] At 60 MHz in CDCl₃ at 30° unless indicated.   [b] Chemical shifts are concentration and temperature dependent.   [c] Optically pure.

2-phenyl-1,2-propanediol (2), whose optical purity was 77.1% by comparison with the rotation reported by Eliel and Freeman for the optically pure compound.[6]

(S)-(+)-2-Phenyl-1,2-propanediol was also obtained from α-methylstyrene. α-Methylstyrene was converted to α-methylstyrene oxide via the bromohydrin as described by Eliel and Rerick.[7] (R)-Mandelic acid opening of α-methylstyrene oxide gave the expected mixture of diastereomers from which 1-O-((2'R)-mandeloyl)-(2S)-2-phenyl-1,2-propanediol (3) was separated by fractional crystallization. The assignment of the mandeloyl group to the terminal position of this half-ester was based on the nmr spectral chemical shift of the methylene protons (δ 4.24) vs. the chemical shift of the methylene protons of 2-phenyl-1,2-propanediol (average δ 3.50) and on the mass spectral base peak at m/e 121 derived from α cleavage of the bond between the carbons containing oxygen in the substituted glycol. The mandelate half-ester was treated with a catalytic amount of sodium in an excess of methanol to give, after chromatography, (S)-2-phenyl-1,2-propanediol of 97.5% optical purity. By this procedure, the (R)-2-phenyl-1,2-propanediol of 75.1% optical purity was obtained by using (S)- instead of (R)-mandelic acid to effect epoxide ring opening.

Acetylation of DL-2-phenyl-1,2-propanediol with acetic anhydride in pyridine gave the primary acetate (by nmr and mass spectrum), 1-O-acetyl-DL-2-phenyl-1,2-propanediol (4). This reaction was repeated with the two samples of (S)-2-phenyl-1,2-propanediol (2) of 77.1 and 97.5% optical purity to give the respective crude acetates, which were ozonized in acetic acid. The crude acids were esterified with diazomethane and, after chromatographic purification, the rotations of the respective samples of crystalline methyl 3-O-acetyl-(R)-2,3-dihydroxy-2-methylpropanoate were determined. From these experimental rotations and the optical purities determined for the samples of 2 and assumed identical for the samples of the product 1, optically pure methyl 3-O-acetyl-(R)-2,3-dihydroxy-

2-methylpropanoate (1) is calculated to have $[\alpha]^{23}$D −9.5°.

An independent synthesis of methyl 3-O-acetyl-DL-2,3-dihydroxy-2-methylpropanoate from methyl methacrylate confirmed the identity of this derivative of α-methylglyceric acid. Methyl methacrylate was hydroxylated with osmium tetroxide plus anhydrous hydrogen peroxide in tert-butyl alcohol to yield 2,3-dihydroxy-2-methylpropanoate (5). Treatment of this ester with acetic anhydride in pyridine gave methyl 3-O-acetyl-DL-2,3-dihydroxy-2-methylpropanoate having identical melting point and ir spectra with those of the optically inactive 1 obtained from the ozonolysis followed by esterification of 2.

Pirkle and Beare[8] have shown that (R)-1-(1'-naphthyl)ethylamine is an excellent optically active solvent for many chiral alcohols, pertinently methyl esters of α-hydroxy acids. The protons of the ester methyl group were observed to have a sense of nonequivalence. However, methyl 2,3-dihydroxy-2-methylpropanoate (5) as well as all derivatives of this compound studied (1 and 6) did not show an observable sense of nonequivalence for the ester methyl protons. The solvent–solute models proposed by Pirkle and Beare[9a] need to be modified in order to explain the spectra of these compounds.

Methyl 2-O-acetyl-2,3-dihydroxy-2-methylpropanoate has a hydrogen attached to oxygen available for hydrogen bonding to the nitrogen of the (R)-1-(1'-naphthyl)ethylamine, but there are two carbonyl groups available for dipolar attraction with the naphthyl ring of the amine. The nmr spectra show that only the methyl protons of the acetyl group have a sense of nonequivalence, indicating that the carbonyl group of the acetyl is more strongly attracted to the naphthyl ring than the carbomethoxy portion of the molecule. The acetyl protons of the (R)- and (S)-1-O-acetyl-2-phenyl-1,2-propanediol enantiomers show a greater sense of nonequivalence (Δδ 0.9 Hz) in the nmr spectra in (R)-1-(1'-napththyl)ethylamine as

(6) E. L. Eliel and J. P. Freeman, *J. Amer. Chem. Soc.*, **74**, 923 (1952).

(7) E. L. Eliel and M. N. Rerick, *ibid.*, **82**, 1362 (1960).

(8) W. H. Pirkle and S. D. Beare, *Tetrahedron Lett.*, 2579 (1968).

(9) (a) W. H. Pirkle and S. D. Beare, *J. Amer. Chem. Soc.*, **91**, 5150 (1969); (b) T. Ledaal, *Tetrahedron Lett.*, 1683 (1968).

compared to the acetyl protons of (R)- and (S)-1 (Δδ 0.6 Hz). This difference reflects the greater size of the phenyl group as compared to the carbomethoxy group.

7a   **7b**
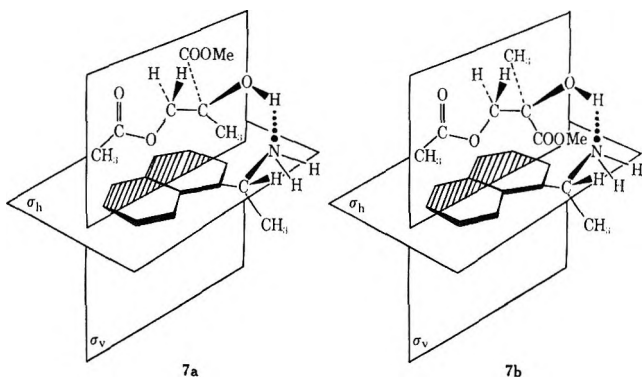
Two diastereomerically related solvate models (7a and 7b) are the most probable for the two enantiomers of 1 (7a = S, 7b = R) in (R)-1-(1'-naphthyl)ethylamine. In structures 7a and 7b, the naphthyl ring is in the σ_h plane, whereas the acetoxy group and carbons C-2 and C-3 of the methyl dihydroxypropanoate molecule are in the σ_v plane. The C=O σ-bond axis of the acetyl group is aligned perpendicular to the σ_h plane with the carbon atom nearer the naphthyl ring, as described by Pirkle and Beare[9a] and by Ledaal.[9b] Although the C=O orientation is fixed, sufficient flexibility exists for the remainder of the chain to freely assume one of several other possible conformations rather than be in the eclipsed one as shown in structures 7a and 7b. An examination of the diastereomeric solvate models leads to the prediction that the model with the methyl group pointing down toward the ring (7a) would allow a closer approach (stronger attraction) of the carbonyl group to the naphthyl ring than the model which shows the carbomethoxy group down (7b). These models lead to the prediction that the protons of the acetyl group of methyl 3-O-acetyl-(S)-2,3-dihydroxy-2-methylpropanoate in (R)-1-(1'-naphthyl)ethylamine (7a) would be more shielded (closer to the shielding portion of the aromatic ring) than the acetyl protons of the R enantiomer (7b). This prediction is in agreement with the nmr spectra of optically active 1 in (R)-1-(1'-naphthyl)ethylamine. In the 100-MHz nmr spectra of 77% optically pure (R)-1 in (R)-1-(1'-naphthyl)ethylamine, the relative peak ratio for the acetyl proton of the R and S enantiomers was 878:122, respectively, from which an optical purity value of 75.6% was obtained.

Replacement of the carbomethoxy groups by phenyl groups in structures 7a and 7b provide the most probable solvate models for the R and S enantiomers of 4, respectively. Again, the acetyl protons of the enantiomer with the methyl group down (as in 7a), being more shielded by the naphthyl ring, should resonate at higher field than the enantiomer with the phenyl group down. This was found to be the case. The nmr spectrum of (R,S)-4 in (R)-1-(1'-naphthyl)ethylamine at 50 sweepwidth on a 60-MHz instrument showed two distinct peaks of equal heights, one for each group of acetyl protons of the enantiomers. By adding a small amount of (R)-4 to this R,S sample, the higher field peak height increased in the nmr spectrum. The 100-

MHz nmr spectrum of 75% optically pure (R)-4 showed peak heights ratio of 105:895 for the S and R enantiomers, respectively, from which an optical purity value of 79.0% was obtained. The deviation of these results from the polarimetric values are slightly greater than the errors reported by Pirkle and Beare[9a] for the nmr determination of the optical purity of amino acids. In part, the error is due to the rather small chemical shift difference ($\geq$1 Hz) between the acetyl protons of the enantiomers such that as the abundance of one becomes predominant and the lesser component appears as a shoulder on the larger peak, which is sometimes difficult to measure.

Experimental Section[10]

Atrolactic Acid.—This compound was synthesized from acetophenone through the cyanohydrin by the method of Eliel and Freeman.[4] The instructions were followed with a lower yield obtained. Atrolactic acid is listed in the Aldrich Chemical Co. catalog but is apparently not currently commercially available.

Resolution of Atrolactic Acid.—The racemic atrolactic acid was resolved by fractional crystallization of its quinine salt, following the method of McKenzie and Clough.[5]

Reduction of (S)-Atrolactic Acid with Lithium Aluminum Hydride.—This reaction was performed by the method of Eliel and Freeman.[6] The product was not crystallized but chromatographed on 80 g of SilicAR CC-7;[11] the eluent was collected in 80-ml fractions. Fractions 1–8 were chloroform and 9–14 were 1:9 acetone:chloroform. Fractions 8–12 were shown to be the diol by thin layer chromatography with 1:1 chloroform–acetone and were combined and distilled at 0.40 Torr and an oil bath temperature of 120°. A 2.30-g sample of (S)-atrolactic acid gave 1.40 g of (S)-2-phenyl-1,2-propanediol, [α]^{23}D 6.89° (c 7.15, Et₂O). Comparison with the value obtained by Eliel and Freeman[6] of 8.94 ± 0.08° gives an optical purity of 77.1%. Also, the optical rotation of the diol was determined in ethanol, [α]^{23}D 7.28° (c 8.08, EtOH), from which the optically pure compound in this solvent was calculated to be [α]^{23}D 9.42°.

Anal. Calcd for C₉H₁₂O₂: C, 71.02; H, 7.95. Found: C, 70.89; H, 8.04.

α-Methylstyrene Oxide.—The method of Eliel and Rerick,[7] from α-methylstyrene via the bromohydrin, was followed to give the same yield of α-methylstyrene oxide, bp 54–57° (1.8 Torr) [lit. bp 62° (2.3 Torr)]. Caution! This product is a lachrymator. Gas chromatography at 100° showed only a trace of contaminates.

1-O-((2'R)-Mandeloyl)-(2S)-2-phenyl-1,2-propanediol.—A 15-g sample of (R)-mandelic acid was dissolved in 500 ml of chloroform. α-Methylstyrene oxide (13.5 g) was added and the solution was heated under reflux for 61 hr. The cooled solution was washed with an equal volume of 1 M aqueous potassium bicarbonate. After removal of the solvents in vacuo the resulting oil was crystallized from acetone–hexane. These crystals were recrystallized twice from ethanol–water to yield 3.06 g (10.7%) of white crystals, mp 101–102°. By substituting (S)-mandelic acid in this procedure, 1-O-((2'S)-mandeloyl)-(2R)-2-phenyl-1,2-propanediol was produced in comparable yields, [α]^{23}D 70.5° (c 6.54, EtOH), 75% optical purity.

(10) All melting points were taken on a Fisher-Johns melting point apparatus and are uncorrected. Boiling points are also uncorrected. Elemental analyses were performed by Midwest Microlabs, Inc., Indianapolis, Ind. All nmr spectra were obtained by Katie Reimer with a Varian A-60 instrument or by Dave O'Keeffe with a JEOL JNM-4H-100. The rotations were measured in a 2-dm capillary cell in a Rudolph 80 polarimeter. All gas chromatograms were obtained with an Aerograph Model A-350-B dual column thermal conductivity instrument with helium as the carrier gas and using an 8 ft × 0.25 in. o.d. copper column containing 5% XE-60 on less than 80 mesh ABS (Analab Inc., Hamden, Conn.). Thin layer chromatography was conducted on 1 × 3 in. glass plates covered with a layer of silicic acid, HF₂₅₄ (Merck, Darmstadt, Germany), using the solvent system specified. Iodine vapor or uv light was used to detect compounds in the developed chromatograms. Ozone was produced by an OREC model 03C6 ozonizer. The mass spectra were obtained on an Atlas CH-4B at 70 eV by Richard Scott or Gene Kelley.

(11) Silicic acid, Mallinckrodt Chemical Works.

Anal. Calcd for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.40; H, 6.52.

(S)-2-Phenyl-1,2-propanediol from 1-O-((2'R)-Mandeloyl)-(2S)-2-phenyl-1,2-propanediol.—A 2.81-g sample of the ester was dissolved in 200 ml of anhydrous methanol. A few milligrams of sodium metal was added and the reaction was monitored by thin layer chromatography using 1:1 chloroform–acetone as the eluent. The starting material has an R_f of 0.45 compared with the products methyl mandelate, 0.57, and 2-phenyl-1,2-propanediol, 0.25. The reaction appeared complete after 1.5 hr but was allowed to remain at room temperature for 21.5 hr. After the reaction mixture was poured through 20 ml of methanol-washed Dowex 50 W-X8, the solution was evaporated and the resultant oil was chromatographed on 140 g of SilicAR CC-7. The first 19 fractions were 80 ml of chloroform each and later fractions 80 ml each of 1:9 acetone:chloroform. Fractions 21–24 contained the 2-phenyl-1,2-propanediol, 1.16 g (77.8%). After removal of the solvent the oil was distilled at 0.4 Torr and an oil bath temperature of 120°, $[\alpha]^{23}D$ 9.18° (c 8.13, EtOH). By comparison with the rotation calculated for the optically pure diol of 9.42, an optical purity of 97.5% is calculated for this sample. (2R)-2-Phenyl-1,2-propanediol of 75% optical purity, $[\alpha]^{23}D$ −7.05° (c 7.28, EtOH), was obtained by this procedure from 1-O-((2'S)-mandeloyl)-(2R)-2-phenyl-1,2-propanediol (Table II).

TABLE II

MASS SPECTRA OF
1-O-((2'S)-MANDELOYL)-(2R)-2-PHENYL-1,2-PROPANEDIOL

m/e	% of base peak	m/e	% of base peak
43	77	118	64
77	52	121	100
79	53	122	65
91	54	134	45
105	67	166	41
107	70	286 (M)	12

Anal. Calcd for $C_9H_{12}O_2$: C, 71.02; H, 7.95. Found: C, 70.96; H, 7.98.

2-Phenyl-1,2-propanediol from α-Methylstyrene.—The method of Milas and Sussman[12] was used. α-Methylstyrene (59 g, 0.5 mol) was dissolved in 272 ml of the anhydrous hydrogen peroxide–*tert*-butyl alcohol solution. After the addition of 20 mg of osmium tetroxide (caution, toxic) the solution was cooled in an ice bath for 1 hr. The color of the solution changes from yellow to orange to black. After 11 hr at room temperature, the solution tested negative to potassium iodide starch paper, the solvents were removed *in vacuo*, and the oil was distilled to yield 22.4 g (29.3%) of 2-phenyl-1,2-propanediol, bp 104–107° (0.45 Torr).

Methyl 2,3-Dihydroxy-2-methylpropanoate.—This compound was prepared by the same method as 2-phenyl-1,2-propanediol: a 20-g (0.2 mol) sample of methyl methacrylate in 100 ml of the hydrogen peroxide–*tert*-butyl alcohol solution plus 4.9 mg of osmium tetroxide, 19 hr total reaction time. Distillation gave 6.18 g (23.1%) of methyl 2,3-dihydroxy-2-methylpropanoate, bp 82–84° (0.65 Torr). A 2.0-g sample was chromatographed on 100 g of SilicAR CC-4 with acetone, 75-ml fractions. Fraction 3 was evaporated and distilled at 0.65 Torr (oil bath temperature 95°) to give 1.6 g of an oil. Crystallization of this oil from ether–hexane was unsuccessful and the vacuum distillation was repeated to give 1.5 g of methyl 2,3-dihydroxy-2-methylpropanoate. *Anal.* Calcd for $C_5H_{10}O_4$: C, 44.77; H, 7.52. Found: C, 44.86; H, 7.56.

Methyl 3-O-Acetyl-2,3-dihydroxy-2-methylpropanoate from Methyl Methacrylate.—Osmium tetroxide hydroxylation of 10 g (0.1 mol) of methyl methacrylate with 50 ml of the hydrogen peroxide–*tert*-butyl alcohol solution plus 10 mg of osmium tetroxide was allowed to proceed for 24 hr. From this solution, after solvent removal, was obtained 6.77 g (38.5%) of a black tar. This tar was dissolved in 30 ml of anhydrous pyridine and cooled to 0°, and 30 ml of acetic anhydride was added. After 17 hr at room temperature the flask was cooled to 0° and 10 ml of water was added. The solvents were removed *in vacuo* and attempted crystallization from ether–hexane (after the solution was treated

with Norite) was unsuccessful. The oil was chromatographed on 300 g of SilicAR CC-7 and eluted with 200-ml fractions of 6:4 chloroforom–Skellysolve B (fractions 1–11) and 7:3 chloroform–Skellysolve B (fractions 12–21). Gas chromatography at 190° showed that fractions 18–20 were methyl 3-O-acetyl-2,3-dihydroxy-2-methylpropanoate (2.13 g, 12.1% overall). Fraction 18 gave crystals (mp 48.5–49.5°) from ether–hexane.

Anal. Calcd for $C_7H_{12}O_5$: C, 47.72; H, 6.87. Found: C, 47.69; H, 6.95.

Methyl 3-O-Benzoyl-2,3-dihydroxy-2-methylpropanoate from Methyl Methacrylate.—By a procedure similar to that described for its acetate derivative, a 7.7-g sample of methyl methacrylate, 39 ml of hydrogen peroxide–*tert*-butyl alcohol solution, and 5 mg of osmium tetroxide were allowed to react for 26 hr. Solvent removal *in vacuo* yielded 5.4 g (38.9%) of crude 2,3-dihydroxy-2-methylpropanoate, which was dissolved in 25 ml of pyridine and cooled to 0°. To this cold solution, benzoyl chloride (5 ml) was added dropwise with swirling. The reaction mixture was allowed to warm to room temperature. After 10 hr a few drops of water and 75 ml of chloroform were added. The solution was washed in succession with 50-ml portion of water, once; 1 N aqueous hydrochloric acid, six times; 1 M aqueous potassium-bicarbonate, four times; and finally water, four times. Removal of the solvent *in vacuo* gave 8.71 g of crude product, which was chromatographed on 200 g of SilicAR CC-7. Elution was started with 7:3 chloroform–Skellysolve B (fractions 1–17), then 8:2 chloroform–Skellysolve B (fractions 18–24), and fractions 25–27 were chloroform. Fractions 1–22 were 80 ml and fractions 23–27 were 200 ml. Gas chromatography at 210° showed that fractions 21–24 were the product (2.14 g, 11.7% overall). Fractions 21–24 were combined and crystallized three times from ether–Skellysolve B to yield 0.66 g of methyl 3-O-benzoyl-2,3-dihydroxy-2-methylpropanoate, mp 66–67°.

Anal. Calcd for $C_{12}H_{14}O_5$: C, 60.50; H, 5.92. Found: C, 60.76; H, 6.10.

1-O-Acetyl-2-phenyl-1,2-propanediol.—A 2.0-g sample of 2-phenyl-1,2-propanediol was dissolved in 20 ml of anhydrous pyridine and cooled to 0°. Acetic anhydride (20 ml) was added. The solution was allowed to warm to room temperature and after 12 hr the solvents were removed *in vacuo*. The resulting yellow oil was chromatographed on 95 g of SilicAR CC-7. Fractions 1–3 were eluted by 80-ml portions of 6:4 chloroform–Skellysolve B. Fractions 4 and 5 were eluted by 100-ml portions of 7:3 chloroform–Skellysolve B, and fractions 6–11 were eluted by 80 ml of 8:2 chloroform–Skellysolve B. Thin layer chromatography with chloroform showed one spot (R_f 0.24) for fractions 7–11. Fractions 7–11 were concentrated *in vacuo* to yield 1.69 g of oil. This oil was distilled at 1.1 Torr with a pot temperature of 158° to yield 1.6 g (69.4%) of 1-O-acetyl-2-phenyl-1,2-propanediol. By this procedure both 1-O-acetyl-(2R)-2-phenyl-1,2-propanediol, $[\alpha]^{23}D$ 13.48 (c 8.17, EtOH), optical purity 75%, and 1-O-acetyl-(2S)-2-phenyl-1,2-propanediol, $[\alpha]^{23}D$ −13.54 (c 9.45, EtOH), optical purity 75%, were prepared.

Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.26. Found: C, 67.80; H, 7.37.

Nmr Spectra of Compounds in (R)-1-(1'-Naphthyl)ethylamine.—Following Pirkle and Beare[9a] the nmr spectra were obtained on samples with a mole ratio (R)-1-(1'-naphthyl)ethylamine:ester:fluorotrichloromethane of 2:1:3. These samples were prepared directly in the nmr sample tubes because of possible solubility differences of the enantiometers in the amine and because of the rapid reaction of the amine with carbon dioxide in the air to form an insoluble salt.

Methyl 3-O-Acetyl-(R)-2,3-dihydroxy-2-methylpropanoate from (S)-2-Phenyl-1,2-propanediol.—Samples of (S)-2-phenyl-1,2-propanediol from lithium aluminum hydride reduction of (S)-atrolactic acid (I) and from methanolysis of 1-O-((2'R)-mandeloyl-(2S)-2-phenyl-1,2-propanediol (II) were carried through the same procedure to yield samples I and II of methyl (2R)-2,3-dihydroxypropanoate. The (S)-2-phenyl-1,2-propanediol (I, 0.81 g; II, 0.87 g) was dissolved in 10 ml of anhydrous pyridine and cooled to 0°. After addition of 10 ml of acetic anhydride the solution was allowed to warm to room temperature. After 17 hr, the solvents were removed at 25° (1 Torr) to yield the crude acetate. This yellow oil was dissolved in 20 ml of glacial acetic acid and ozonized with a stream of approximately 1% ozone in oxygen at a rate of 1.8 l./min (I for 2.75 hr, II for 2.5 hr). Following ozonolysis the solution was diluted with 40 ml of 2% aqueous hydrogen peroxide and heated for 30 min on the steam bath. These solutions were concentrated to ~10 ml at 25° (1

(12) N. A. Milas and S. Sussman, *J. Amer. Chem. Soc.*, **58**, 1302 (1936).

Torr) and then further concentrated with an air stream overnight.

The oil was dissolved in a little methanol, and ethereal diazomethane (less than 1 g, from Diazald, following the procedure of de Boer)[13] was added until the yellow color remained. After 1 hr at room temperature the solvents were removed *in vacuo*. The crude products were chromatographed on 75 g of SilicAR CC-7 with 7:3 chloroforom–Skellysolve B by the procedure described for the preparation of this compound from methyl methacrylate. Gas chromatography at 190° led to a combination of identical fractions. Crystallization from ether–hexane gave the following physical constants for the two samples of 3-O-acetyl-(R)-2,3-dihydroxy-2-methylpropanoate. Sample I (derived from (S)-atrolactic acid) weighed 0.49 g (52.3%), mp 31–34°. The rota-

(13) (a) T. J. deBoer and H. J. Backer, *Recl. Trav. Chim. Pays-Bas*, **73**, 229 (1954); (b) Technical Information Sheet, D2800-0, Aldrich Chemical Co., Jan 1967.

tion of sample I (optical purity 77.1%) was determined, $[\alpha]^{23}D$ −7.33° (c 6.09, EtOH), from which the rotation of an optically pure sample in ethanol is calculated to be −9.52°.

Anal. Calcd for $C_7H_{12}O_5$: C, 47.72; H, 6.87. Found: C, 48.00; H, 7.01.

Sample II (derived from α-methylstyrene) weighed 0.62 g (61.5%), mp 35–36°C, $[\alpha]^{23}D$ −9.18° (c 5.07, EtOH). Assuming that sample II is 97.5% optically pure, the rotation for a pure sample should be −9.42°.

Anal. Calcd for $C_7H_{12}O_5$: C, 47.72; H, 6.87. Found: C, 47.49; H, 6.74.

Registry No.—1, 35638-89-2; (R)-1, 35638-90-5; 2, 4217-66-7; (R)-2, 35638-92-7; (S)-2, 2406-22-6; (R,S)-3, 35638-93-8; (S,R)-3, 35638-94-9; (R)-4, 35638-95-0; (S)-4, 35638-96-1; 5, 19860-56-1; 6, 35638-98-3.

Mesomorphic Properties of Some Ring-Methylated Phenyl Benzoyloxybenzoates

WILLIAM R. YOUNG,* IVAN HALLER, AND DENNIS C. GREEN

IBM Watson Research Center, P. O. Box 218, Yorktown Heights, N. Y. 10598

To delineate the role of laterally placed methyl groups upon mesomorphic character, a series of esters of the general formula 1 was prepared, where R and S were ethoxyl and butyl, respectively, and A, B, Y, and Z were the nine independent combinations of methyl and hydrogen. Every derivative exhibited a nematic phase, and the nematic–isotropic transition temperatures decreased as the number of appended methyl groups increased. An investigation of the nematic–isotropic transition by means of differential scanning calorimetry revealed that methylation of the central ring increased the intermolecular interactions and order in the nematic phase, relative to the isotropic phase, while no such effect was apparent upon methylation of the terminal ring. This result demonstrates that the concept of increased intermolecular separation, resulting from laterally placed substituents, is not always sufficient to account for a decrease in nematic–isotropic transition temperatures.

As part of our efforts to obtain stable, low-melting nematic liquids with long mesomorphic ranges and to delineate the effects of symmetry and molecular structure upon mesomorphic properties,[1–3] an investigation was undertaken to uncover the liquid crystalline character of a series of esters derived from phenyl 4-benzoyloxybenzoate.[4] Previous work on more symmetrical esters, *viz.*, the 1,4-phenylene bis(4-*n*-alkoxybenzoates)[5–9] and di-4-*n*-alkoxyphenyl terephthalates,[7] have demonstrated that these esters can exhibit very long nematic ranges (~100°). In addition, Arora, *et al.*, by affixing a methyl group to the central ring of one of their phenylene bisbenzoates, have prepared a material, the lowest melting substance in either series, with a nematic range of 72–156°.[8]

For this investigation, compounds of the general formula 1 were prepared, where R and S were selected to be ethoxyl and *n*-butyl, respectively, in analogy with the low melting points and high nematic CMD values (clearing point/melting point differences[2]) for Schiff

1
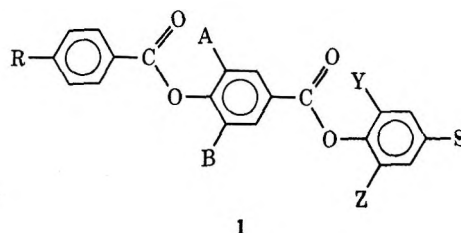
bases,[10–12] acetylenes,[13] and chlorostilbenes.[1,2] With the aim of understanding the role of laterally placed methyl groups upon mesomorphic properties, nine compounds were prepared corresponding to all independent combinations of methyl and hydrogen in positions A, B, Y, and Z. Two compounds in which R and S were interchanged were also prepared. The pertinent phase transition temperatures of the compounds were determined, and, in addition, the enthalpies and entropies of the mesomorphic transitions were measured by differential scanning calorimetry. The results are presented in the next section.

Results and Discussion

Synthesis.—The esters prepared in this investigation and their physical properties are listed in Tables IA and IB. The sequence of reactions employed in their

(1) W. R. Young, A. Aviram, and R. J. Cox, *Angew. Chem., Int. Ed. Engl.*, **10**, 410 (1971).

(2) W. R. Young, A. Aviram, and R. J. Cox, *J. Amer. Chem. Soc.*, **94**, 3976 (1972).

(3) W. R. Young, I. Haller, and A. Aviram, *Mol. Cryst. Liquid Cryst.*, **15**, 311 (1972).

(4) Nematic esters of this class have been previously reported. See D. Vorlaender, *Z. Phys. Chem. (Leipzig)*, **105**, 211 (1923).

(5) M. J. S. Dewar and J. P. Schroeder, *J. Org. Chem.*, **30**, 2296 (1965).

(6) M. J. S. Dewar and R. S. Goldberg, *J. Amer. Chem. Soc.*, **92**, 1582 (1970).

(7) M. J. S. Dewar and R. S. Goldberg, *J. Org. Chem.*, **35**, 2811 (1970).

(8) S. L. Arora, J. L. Fergason, and T. R. Taylor, *ibid.*, **35**, 4055 (1970).

(9) S. A. Haut, D. C. Schroeder, and J. P. Schroeder, Abstracts of Papers, 162nd National Meeting of the American Chemical Society, Washington, D. C., 1971, Abstract PHYS 146.

(10) H. Kelker, B. Scheurle, R. Hatz, and W. Bartsch, *Angew. Chem., Int. Ed. Engl.*, **9**, 962 (1970).

(11) D. L. Fishel and Y. Y. Hsu, *Chem. Commun.*, **1971**, 1557.

(12) H. J. Dietrich and E. L. Steiger, *Mol. Cryst. Liquid Cryst.*, **16**, 263 (1972).

(13) J. Malthete, M. Leclercq, J. Gabard, J. Billard, and J. Jacques, *C. R. Acad. Sci.*, **273C**, 265 (1971).

TABLE I

PHYSICAL PROPERTIES OF SOME MESOMORPHIC DERIVATIVES OF PHENYL 4-BENZOYLOXYBENZOATE

No.	A	B	Y	Z	Transition[a]	Temp, °C	ΔH, kcal/mol	ΔS, eu
1a	H	H	H	H	C → N	124	9.15	23.0
					N → I	231	0.39	0.77
1b	H	H	CH₃	H	C → N	113	8.36	21.7
					N → I	188	0.25	0.55
1c	CH₃	H	H	H	C → N	91	7.32	20.1
					N → I	179	0.39	0.87
1d	H	H	CH₃	CH₃	C → N	143	8.82	21.2
					N → I	145	0.29	0.69
1e	CH₃	H	CH₃	H	C → I	160	10.97	25.3
					N → I[b]	143	0.36	0.88
1f	CH₃	CH₃	H	H	C → N	122	9.83	24.9
					N → I	129	0.51	1.26
1g	CH₃	H	CH₃	CH₃	C → I	195	c	c
					N → I[b]	104	d	d
1h	CH₃	CH₃	CH₃	H	C → I	138	10.41	25.9
					N → I[b]	103	0.50	1.32
1i	CH₃	CH₃	CH₃	CH₃	C → I	137	c	c
					N → I[b]	79	d	d
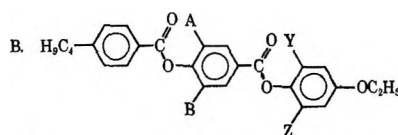
No.	A	B	Y	Z	Transition[a]	Temp, °C	ΔH, kcal/mol	ΔS, eu
1j	H	H	H	H	C → N	138	7.63	18.6
					N → I	225	0.30	0.61
1k	CH₃	H	H	H	C → N	96	6.28	17.0
					N → I	176	0.40	0.90

[a] C, crystalline; N, nematic; I, isotropic. [b] Monotropic transition. [c] Not measured. [d] Rapid crystallization of supercooled liquid precluded measurement.

preparation is outlined in Scheme I, and the reaction pathways leading to the several key intermediate substances are depicted in Scheme II.

For the most part, the syntheses were based on well-known procedures and were routine. It is noteworthy, however, that esterifications employing a hindered 2,6-dimethylphenol derivative, such as 4c and 7c, required prolonged heating at reflux (3-4 days) in pyridine-toluene to effect complete reaction. Also, during the isolation of the benzoyloxybenzoic acids, 5, a period of reflux in aqueous dioxane was sometimes required in order to hydrolyze the undesired carboxylic anhydride by-products.

The esters 1a-1k, which were previously unreported, exhibited satisfactory elemental analyses[14] and consistent spectral properties. In every instance, intense vibrational absorption occurred in the infrared region at 1735 cm⁻¹ (carbonyl stretching) and at 1505 and 1606 cm⁻¹ (phenyl ring vibrations). In addition, at least five intense vibrational bands were detected in the C-O stretching region (1000-1300 cm⁻¹) for each ester. In the nmr spectra taken in deuteriochloroform, sharp singlets for the absorption of the methyl group on the central aromatic ring (A and/or B of structure 1) appeared at 2.3 ppm downfield from TMS, while the ab-

sorption for methyl groups on the terminal ring (Y and/or Z) appeared as a sharp singlet at about 2.2 ppm.

The esters are colorless materials and, in comparison with the nematic Schiff bases, azobenzenes, azoxybenzenes, nitrones, and stilbenes, are highly transparent in the ultraviolet region.[2,15] For example, in ethanol solution ester 1f exhibited a λ_max at 262 nm (ε 34,000) while ester 1a exhibited λ_max at 267 (28,800); neither substance absorbed above 340 nm.

Melting Point Trends.—The melting points for esters 1a-1i are listed in Table IA. They do not vary in any regular fashion as additional lateral methyl groups are affixed to the aromatic rings. Also, the desired low-melting ester, with a long nematic range including room temperature, was not approached; the lowest melting substance of the group exhibited a crystal-nematic transition of 91°.

The lack of a clear-cut trend in melting point as molecular structure is regularly varied is a common occurrence. Similar results have been reported and discussed several times for many series of mesomorphic compounds[15,16] and nonmesomorphic materials.[16] It is important to realize, however, that the addition of several methyl groups to the molecule can grossly affect

(14) The elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

(15) W. R. Young, I. Haller, and A. Aviram, *IBM J. Res. Develop.*, 15, 41 (1971); *Mol. Cryst. Liquid Cryst.*, 13, 357 (1971).

(16) G. W. Gray, "Molecular Structure and the Properties of Liquid Crystals," Academic Press, New York, N. Y., 1962.

SCHEME I

R, S = C₂H₅O, n-C₄H₉; A, B, Y, Z = CH₃ or H

SCHEME II

(a)

(b)

(c)

4b, B = H
c, B = CH₃

(d)

9a, Z = H
b, Z = CH₃

7b, Z = H
c, Z = CH₃
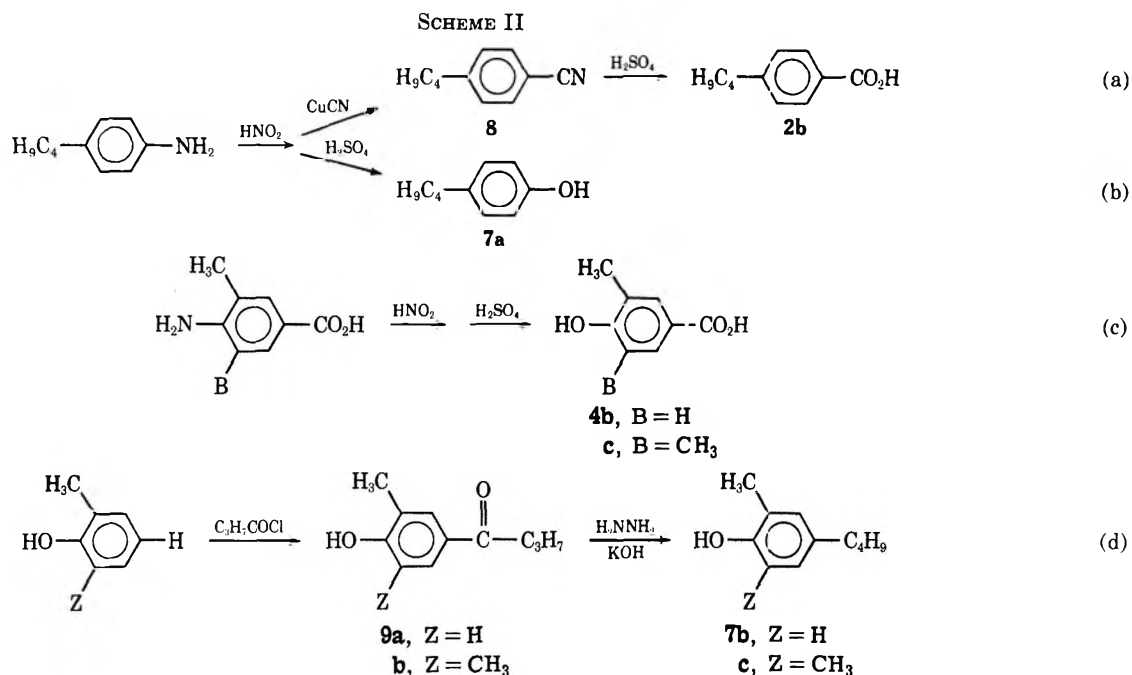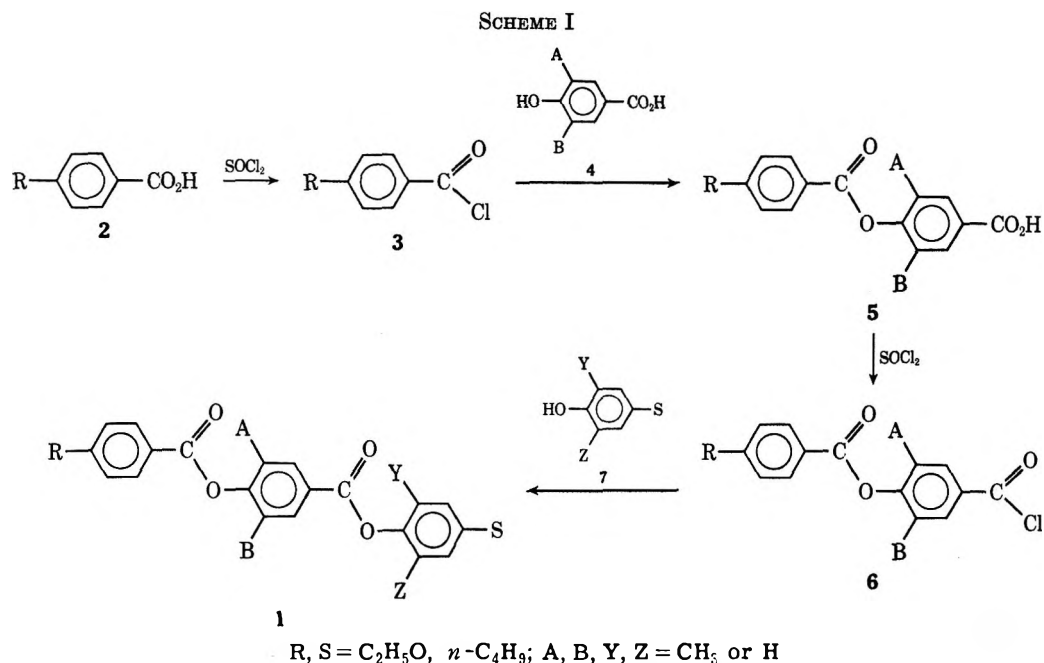
the molecular shape, and, as a direct consequence, the intermolecular interactions in the crystalline state. Hence the large variation in melting point with methyl substitution is not unreasonable.

It is interesting to compare the effect of a single aromatic methyl substituent upon melting point for a few different mesomorphic materials.[17-19] The results, shown in Table II, indicate that the addition of a lone methyl group tends to lower the melting point of a nematogenic compound, when placed ortho to the linkage group. Although the magnitude of this effect varies greatly with molecular features, o-methyl substitution appears to offer promise as a method of lowering C → N transition temperatures.[20]

Nematic-Isotropic Transition Temperatures.—The data in Table IA indicate that the nematic-isotropic transition temperatures decrease systematically as the number of aromatic methyl group appendages increases. Analogous results in polysubstituted nematogenic materials have been previously reported.[16,17,21] This result is usually explained in terms of increased molecular broadening with increased methyl substitution, such that intermolecular interactions that are responsible for mesomorphism are decreased as the intermolecular separation increases. As will be discussed in the section on calorimetry, this explanation is too simple and can only accommodate part of the experimental findings.

In considering positional effects of methyl substitution, the following observations can be made. The nematic-isotropic transition temperature, T_{NI}, is lowered by about the same amount when a *single*

(17) R. J. Cox, *Mol. Cryst. Liquid Cryst.*, in press.
(18) W. Leister, Dissertation, Universitaet Halle, Germany, 1920.
(19) J. v. d. Veen and A. H. Grobben, *Mol. Cryst. Liquid Cryst.*, **15**, 239 (1971).
(20) See ref 19 for several additional examples.
(21) C. Wiegand, *Z. Naturforsch. B*, **6**, 240 (1951).

TABLE II

TRANSITION TEMPERATURES OF SOME NEMATOGENIC COMPOUNDS

Compound	Transition	Temp, °C A = H	A = CH₃	Difference
	C → N N → I	124 231	91 179	33 52
	C → N[a] N → I	124 213	88 172	36 41
	C → I[b] N → I	209 189	110 105	99 84
	C → N[c] N → I	203 >330	143 272	60 >58
	C → N[d] N → I	112 134	89[e] 66	23 68

[a] Reference 8. [b] Reference 17. [c] Reference 18. [d] Reference 19. [e] C → I transition.

methyl group is placed in either of positions A or Y. Placing *two* methyl groups on the *same* ring results in approximately twice the lowering of T_{NI} *vs.* that obtained by substitution with a single methyl group. However, when two methyls are affixed to *different* rings, the depression of T_{NI} is somewhat lower. Finally, when the molecule contains three or four methyl groups, the transition temperature drops more slowly with each additional methyl, owing in part, perhaps, to the fact that molecule was already broadened by two or more methyl groups and the addition of further methyls cannot have as much of an effect.

A comparison of the effect of methyl substitution upon the nematic–isotropic transition temperatures of nematogenic materials is presented in Table II. There appears to be little regularity in the magnitude of the effect of *o*-methyl groups upon nematic clearing points as the linkage group and molecular length/breadth ratio vary, although in every case the clearing point is lowered by about 40 to 80°. It is hoped, however, that the data in Table II may prove useful in making crude estimations of the clearing point for a methylated derivative once the nor-methyl compound has been prepared. Such predictions should be limited to pairs of compounds that belong to one of the classes in Table II, with structural changes limited to wing group variations. Although preliminary work in our laboratory and some results reported elsewhere[19] support this conjectural concept, additional experimental corroboration is required.

Reversal of the wing groups in esters such as **1a** and **1c** should have a minimal effect upon molecular geometry, although it would alter the electronic distribution somewhat due to a loss of direct mesomeric interaction between the ethoxyl and carbonyl groups in these materials. The resulting compounds, **1j** and **1k** (Table IB), however, exhibit transition temperatures that are very similar to those of **1a** and **1c**. These facts underscore[3] the dominant role played by the central

part of the molecule in affecting transition temperatures.

Entropies and Enthalpies of the Nematic–Isotropic Transition.—Two facts stand out on inspection of the calorimetric data of Tables IA and IB. (1) Substitution of the central ring by one, and even more so by two methyl groups results in a significant increase in the entropy of the nematic–isotropic phase transition. Central ring substitution affects the heat of transition in the same direction, but to a smaller extent. (2) Substitution on the end ring has no comparable effect.

These data are pertinent to the reduction in the transition temperature upon methyl substitution on the central ring. The transition temperature is determined by the heat and the entropy of the transition, two more fundamental quantities that are representative of the change in the interaction energy and in the order when the transition takes place. The decrease

$$T_{NI} = \Delta H_{NI}/\Delta S_{NI}$$

in T_{NI} upon methyl substitution is usually ascribed to a reduction in the energy of intermolecular interactions in the nematic phase, *i.e.*, a lower value for ΔH_{NI}. In particular, this result has been attributed to either increased intermolecular separation due to lateral substitution[16] or to decreased molecular polarizability resulting from a steric loss of conjugation.[8] While in some instances the experimentally measured ΔH_{NI} is smaller for methyl-substituted derivatives than for the parent compound,[22,23] in accord with previous postulates, this trend cannot be universally true. Methyl substitution in the A and B positions of the compounds reported here *increases* ΔH_{NI}; hence the decrease in transition temperature is due to an even larger increase in ΔS_{NI}.

(22) W. R. Young, I. Haller, and A. Aviram, submitted for publication.
(23) G. W. Gray and K. J. Harrison, Faraday Symposium on Liquid Crystalline Properties, Dec 1971.

There is insufficient evidence to provide a definitive explanation as to why methyl substitution on the central ring should result in the unusually large increase in ΔS_{NI}. There are a large number of degrees of freedom, both internal and external, that contribute to the entropy, and subtle changes in the restrictions that these experience in the two phases may result in a nonsystematic variation of ΔS_{NI} with substitution. For example, the barriers to internal rotation about the ester linkages are undoubtedly influenced by the steric repulsions of both the methyl groups and the neighboring molecules. Any nonsystematic change in ΔS_{NI} with substitution could be rationalized on this basis.

If it is assumed that the observed systematic changes in ΔS_{NI} are dominated by external, *i.e.*, intermolecular, degrees of freedom, the data imply that at the clearing point there is a larger change in positional correlation of molecules methylated at the central ring than of molecules methylated at the end ring. That is to say, methylation of the center of the molecule increases the coupling between orientational and translational degrees of freedom. The possibility of enhanced positional correlation, or short-range order, in the nematic phase, relative to the isotropic phase, due to a central bulge in the repulsion envelope of the molecules, is consistent with the large value of ΔS_{NI} for compounds **1f** and **1h**. It is also compatible with X-ray observations of the nematic phase of a diester, which was broadened by chlorination, rather than methylation, of the central ring.[24] Also, enhanced short-range order in the nematic phase has been suggested by other investigators.[25-27]

Experimental Section

All of the new compounds exhibited satisfactory spectral properties and elemental analyses.[14] Infrared spectra were recorded on a Perkin-Elmer 137B Infracord spectrometer. Nmr spectra were obtained on a Jeolco Minimar 60 spectrometer. Ultraviolet spectra were taken on a Cary 14 spectrophotometer.

4-Substituted Benzoic Acids (2).—4-Ethoxybenzoic acid (**2a**) was obtained commercially (Aldrich Chemical Co.). 4-*n*-Butylbenzoic acid (**2b**), mp 102°, T_{NI} 112° (lit.[28] mp 99.5°, T_{NI} 113°), was prepared by hydrolysis[29] of 4-*n*-butylbenzonitrile (**8**), bp 122° (6 mm), obtained from 4-*n*-butylaniline (Aldrich) by the method of Clarke and Read.[30]

4-Substituted Benzoyl Chlorides (3).—4-Ethoxybenzoyl and 4-*n*-butylbenzoyl chlorides were prepared by refluxing the corresponding acids in thionyl chloride and isolating the products by distillation.

4-Hydroxybenzoic Acids (4).—4-Hydroxybenzoic acid was obtained from Aldrich Chemical Co. 4-Hydroxy-3-methylbenzoic acid (**4b**), mp 172° (lit.[31] 174-175°), and 4-hydroxy-3,5-dimethylbenzoic acid (**4c**), mp 216-217° (lit.[32] 218°), were prepared from 4-amino-3-methylbenzoic acid (Aldrich) and 4-amino-3,5-dimethylbenzoic acid (Aldrich), respectively, by means of diazotization and sulfuric acid hydrolysis.

4-(4′-Substituted benzoyloxy)benzoic Acids (5).—The key intermediate acids of type **5** prepared in this investigation are listed in Table III. They were prepared by reaction of the appro-

priate acid chloride (**3**) with the appropriate hydroxybenzoic acid (**4**) under reflux in toluene–pyridine solvent for 12–16 hr. After removal of the solvents in the rotary evaporator, the residue was dissolved in ether and washed with dilute HCl and water. Evaporation of the ether yielded an oily or gummy residue which generally contained the desired product plus some anhydride by-product. The residue was allowed to reflux in aqueous dioxane for 4 hr to hydrolyze any anhydride which was present. The dioxane was removed by azeotropic distillation, and the product was isolated by filtration of the hot, aqueous mixture. Recrystallization from a suitable solvent afforded the desired white, crystalline products in 50–80% yield.

4-(4′-Substituted benzoyloxy)benzoyl Chlorides (6).—These acid chlorides were prepared by allowing the corresponding acids (**5**) to reflux in an excess of thionyl chloride and removing the volatile materials by vacuum distillation. The residual products were employed for esterification reactions without additional purification.

4-Substituted Phenols (7 and 9).—4-*n*-Butylphenol (**7a**), mp 22° (lit.[33] 22°), was prepared from 4-*n*-butylaniline by diazotization and sulfuric acid hydrolysis.

4-Hydroxy-3-methylbutyrophenone (**9a**), mp 130–133° (lit.[34] 132–133°), and 4-hydroxy-3,5-dimethylbutyrophenone (**9b**), mp 123–125° (lit.[35] 124–125°), were prepared by the standard Friedel–Crafts acylation of 2-cresol and 2,6-dimethylphenol, respectively, with butyryl chloride in nitrobenzene with aluminum chloride.

4-*n*-Butyl-2-methylphenol (**7b**), bp 130–132° (16 mm) [lit.[34] 127–129° (15 mm)], and 4-*n*-butyl-2,6-dimethylphenol (**7c**), bp 107° (2.5 mm) [lit.[35] 138–146° (20 mm)], were prepared from the corresponding butyrophenones **9a** and **9b** by means of the Huang-Minlon modification of the Wolff–Kishner reduction.[36]

Substituted Phenyl Benzoyloxybenzoates (1).—The esters listed in Table I were all prepared by the following general procedure. An appropriate phenol (**7**) was dissolved in pyridine. An equivalent amount of an acid chloride (**6**) was dissolved in toluene and added to the pyridine solution. Following an overnight reflux period, the solvents were removed and the residue was taken up in ether. Following washes with water, 10% HCl, 10% NaOH, and water, the ether layer was dried and evaporated. The residual product was chromatographed through a column of silica gel with chloroform. The product was then repeatedly crystallized from alcohol or methylcyclohexane and, in some cases, sublimed under high vacuum. The yields of the purified, white products ranged from 20 to 50%.

Microscopy and Calorimetry.—The mesophases were identified and the transition temperatures were determined as described previously.[3] The heats of transition were determined as before,[1] with the exception that the peak areas were determined by means of an on-line IBM 1800 computer. The base-line sections (two for each transition) required for integration were computed by

TABLE III
TRANSITION TEMPERATURES OF SOME SUBSTITUTED BENZOYLOXYBENZOIC ACIDS

No.	R	A	B	Temp, °C[a] C → N	N → I
5a	C_2H_5O	H	H	198	>300
5b	C_2H_5O	CH₃	H	230	233
5c	C_2H_5O	CH₃	CH₃	272[b]	
5d	*n*-C₄H₉	H	H	182	250
5e	*n*-C₄H₉	CH₃	H	173	214

[a] These intermediates were not purified so rigorously as the final esters. [b] C → I transition temperature.

(24) A. de Vries, *Mol. Cryst. Liquid Cryst.*, **10**, 219 (1970).

(25) Reference 16, p 85.

(26) L. Pohl and R. Steinstraesser, *Z. Naturforsch. B*, **26**, 26 (1971).

(27) H. Gruler, personal communication.

(28) C. Weygand and R. Gabler, *Z. Physik. Chem., Abt. B*, **46**, 270, 272 (1940).

(29) H. T. Clarke and E. R. Taylor, "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1943, p 588.

(30) H. T. Clarke and R. R. Read, "Organic Syntheses," Collect. Vol. I, Wiley, New York, N. Y., 1941, p 514.

(31) I. Remsen and J. Kuhara, *Amer. Chem. J.*, **3**, 428 (1881).

(32) O. Jacobsen, *Chem. Ber.*, **12**, 606 (1879).

(33) G. Sandulesco and A. Girard, *Bull. Soc. Chem. Fr.*, **47**, 1300 (1930).

(34) C. E. Coulthard, J. Marshall, and F. Pyman, *J. Chem. Soc.*, **1930**, 291.

(35) K. v. Auwers and E. Janssen, *Justus Liebigs Ann. Chem.*, **483**, 44 (1930).

(36) Huang-Minlon, *J. Amer. Chem. Soc.*, **68**, 2487 (1946).

least-squares fits from visually determined start and end points, and are extrapolated to the center of the peak.

2,3-Di(2-pyridyl)-2,3-butanediol. A Crystal and Molecular Structure Study of the Meso Form with Ancillary Proton Magnetic Resonance Data

J. N. Brown, R. M. Jenevein, J. H. Stocker,[*1] and L. M. Trefonas[*1]

Department of Chemistry, Louisiana State University in New Orleans, New Orleans, Louisiana 70122

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The crystal and molecular structure of 2,3-di(2-pyridyl)-2,3-butanediol ($C_{14}H_{16}N_2O_2$) has been determined by a single-crystal, X-ray diffraction study. The compound crystallizes with four molecules in a monoclinic cell ($P2_1/c$) of dimensions $a = 9.293$, $b = 11.885$, $c = 13.615 \pm 0.001$ Å, and $\beta = 123.98 \pm 0.01°$. The structure was solved by direct methods and the 1097 statistically significant reflections were refined to a final value of $R = 0.05$. Estimated standard deviations were less than 0.008 Å for bond distances and 0.5° for bond angles for those bonds not involving hydrogen atoms. The configuration was established as the meso compound, and, furthermore, the conformation was shown to be that involving hydrogen bridging between each of the pyridyl nitrogens and the more distant oxygen forming additional six-membered rings. Although not required by crystallographic symmetry, the molecule possesses a center of symmetry well within the estimated standard deviation. Pmr data for an additional ten compounds with analogous five-, six-, and seven-membered hydrogen-bonded ring possibilities are given and evaluated, and effectively underscore the uniqueness of the title compound. A comparison of the pmr data with a limited set of corresponding infrared data casts doubt on the reliability of the predictions from the infrared data regarding intramolecular hydrogen bonding.

Unequivocal assignment of the stereochemical identities of the two diastereomeric pinacols (I) resulting

I (meso, *dl* forms)
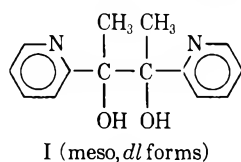
from the electropinacolization of 2-acetylpyridine was necessary as part of a continuing study[2] of the stereochemical consequences of this type of electrochemical bimolecular reduction. Such assignments may be made by the tedious and often unsuccessful procedures of absolute synthesis or enantiomeric resolution. More equivocal but often adequate approaches include differences in gross crystal structure, melting point comparisons, and infrared and pmr analysis of the hydroxyl group, particularly where several of these methods reinforce each other. In the present case, these convenient techniques were precluded; the two diastereomers have identical melting points, no free hydroxyl stretching bands in the infrared, and essentially identical hydroxylic proton resonances buried in the aromatic area.[3] A tentative assignment was made, however, on the basis of the degree of shielding encountered

by the methyl groups as based on the apparent most favorable conformations for the several different forms possible for each diastereomer as determined from molecular models.[2] To establish this assignment unequivocally, an X-ray crystallographic study was undertaken on the diastereomer that had tentatively been assigned the meso form. Additional pmr studies of related compounds were also undertaken to consider the relative degrees of hydrogen bonding encountered in such compounds. The data are brought together and evaluated in this report.

Crystallographic Studies

Obtaining crystals of suitable quality for an X-ray structure study proved to be exceedingly difficult and time consuming. First, the compound crystallized in more than one space group, depending on solvent and experimental conditions; *i.e.*, monoclinic crystals in space group $P2_1$ (or $P2_1/m$) were obtained from hot carbon tetrachloride, while crystals in space group $P2_1/c$ were obtained from warm hexane solutions. Second, all of the crystals exhibited extreme layering perpendicular to the *b* axis. Intensity differences of 5:1 (or greater) in a φ scan at $\chi = 90°$ on a General Electric XRD-5 diffractometer were obtained repeatedly. Finally, a crystal of dimensions $0.10 \times 0.15 \times 0.23$ mm was recrystallized from one of the hexane solutions and exhibited an intensity ratio of 1.13:1.00. Extinctions [$k = 2n + 1$ for the ($0k0$) reflections and $l = 2n + 1$ for the ($h0l$) reflections] uniquely characterized the space group as $P2_1/c$.

Lattice constants were determined by a least-squares fit of 16 carefully measured 2θ values (1° take-off angle

(1) (a) Address pmr inquiries to J. H. S., crystallographic inquiries to L. M. T. (b) Tables of structure factor data and refined coordinates and temperature factors 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-72-3712. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche.

(2) J. H. Stocker and R. M. Jenevein, *J. Org. Chem.*, **34**, 2807 (1969).

(3) For a more detailed discussion of these several approaches, with suitable references, see ref 2.

and 0.05° slit) at $2\theta > 66°$ where the Cu Kα_1 and Cu Kα_2 doublet is resolvable. The resultant lattice constants and their estimated standard deviations are $a = 9.293 \pm 0.001$ Å; $b = 11.885 \pm 0.001$ Å; $c = 13.615 \pm 0.001$ Å; $\beta = 123.98 \pm 0.01°$.

The experimental density of 1.29 ± 0.01 g/cm³ agrees with the calculated density of 1.29 g/cm³ assuming four molecules per unit cell.

Three-dimensional intensity data were collected on a General Electric XRD-490 fully automated diffractometer by the stationary-counter, stationary-crystal method using balanced nickel and cobalt filters and Cu Kα radiation. A total of 2135 independent reflections were measured to a 2θ maximum of 140° ($d = 0.82$ Å). Of these, 1097 reflections (51%) were considered statistically acceptable by the criterion $[I_{Ni} - 2\sigma(I_{Ni})] - [I_{Co} + 2\sigma(I_{Co})] > 100$ counts (10-sec counting times; σ based on counting statistics).

The data were corrected for $\alpha_1-\alpha_2$ splitting[4] as a function of 2θ and for absorption as a function of φ (linear $\mu = 7.2$ cm^{-1} and a maximum difference of 13% in the φ scan at $\chi = 90°$). An irregular crystal decay of 17% was observed during data collection and corrected by multiplicative factors as a function of time. Lorentz-polarization corrections were made and the intensities were reduced to structure amplitudes in the usual manner.

Structure Determination

The structure was solved by direct methods. After conversion to normalized structure magnitudes ($|E|$'s) and appropriate scaling using a k curve,[5] 279 reflections with $|E|$ values greater than 1.5 were obtained. Using only three-dimensional data, an origin and four other $|E|$'s were chosen from among the 15 largest $|E|$ values. The phases of these additional four were permuted, resulting in 16 combinations. Five of the 16 combinations resulted in the phasing of approximately 190 reflections each and these five also had consistency indices[6] significantly greater than the other 11. Of these five, only one had the combination (200) = − and (400) = + (both of which have large $|E|$'s, which would be anticipated if the molecule did not utilize the inversion center of the unit cell). An $|E|$ map was calculated for this case and 16 peaks were found, consistent with our expectations on chemical grounds. Five cycles of block-diagonal, least-squares isotropic refinement using $\sigma^{1/2}$ weights and approximating all of the peaks as carbon atoms resulted in a value of the reliability index, $R = 0.31.$[7] A new electron-density map phased by these 16 atoms clearly indicated the remaining two peaks anticipated. The relative heights of two of the peaks, combined with their small temperature factors in the least-squares refinement, made the assignment of the oxygen atoms on crystallographic
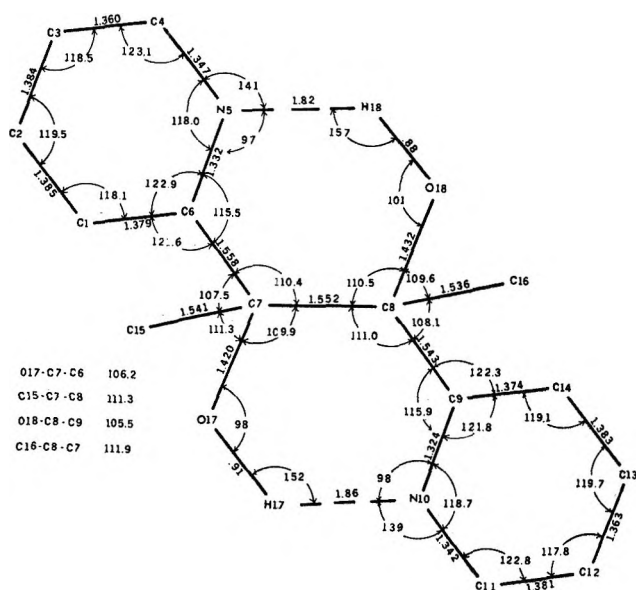
Figure 1.—Schematic drawing of the molecule showing bond distances and bond angles. Proposed intramolecular hydrogen bonding scheme indicated on the drawing.

grounds relatively simple. Since this was not the case for the nitrogens, all other atoms were left as carbons. Additional isotropic least-squares refinement resulted in a value of $R = 0.14$. At this stage, the temperature factors clearly indicated the nitrogens and thus all of the atoms were assigned appropriate scattering factors. After conversion to anisotropic temperature factors, refinement was continued for ten more cycles, resulting in a value of $R = 0.09$.

The hydrogen atoms were located from a difference electron-density map and proved to be the only peaks with an electron density greater than 0.2 e/Å³ (the hydrogen positions had peak heights ranging from 0.6 to 0.9 e/Å³). A final series of similar least-squares was carried out varying the coordinates of all atoms (including the hydrogens). The anisotropic temperature factors of the nonhydrogens were also varied, but the isotropic temperature factors of the hydrogens were held fixed at a value of 4.0 Å². The refinement converged to a final value of $R = 0.05_2$ with the shifts of all of the parameters varied being significantly less than one-tenth of the estimated standard deviation of the respective parameter.

Crystallographic Results

Table I[1b] lists the final coordinates and temperature factors for the nonhydrogen atoms together with their estimated standard deviations (ESD's). Table II[1b] lists the analogous data for the refined hydrogen coordinates with the exception that the hydrogen positions were refined with fixed isotropic temperature factors of 4.0 A². Figure 1 is a schematic drawing of the molecule with bond angles and bond distances indicated on the drawing. ESD values for bond distances and bond angles (for the nonhydrogen bonds) are less than 0.008 Å and 0.5°, respectively. For those bond distances and bond angles involving hydrogen, the ESD's were significantly higher at values less than 0.04 Å and 3.0°, respectively. The refined hydrogen distances are available[1b] in tabular form.

(4) A. Tulinsky, C. Worthington, and E. Pignataro, *Acta Crystallogr.*, **12**, 623 (1959).

(5) J. Karle, H. Hauptman, and C. L. Christ, *ibid.*, **11**, 757 (1958).

(6) The consistency index was defined as $C = \Sigma_h(T_t - T_a)/\Sigma_h(T_t + T_a)$, where T_t = sum of triple products contributing towards the accepted phases and T_a = sum of triple products contributing against the accepted phases.

(7) The conventional reliability index $R = \Sigma w||kF|_0 - F_c||/\Sigma w|F_0|$ is cited throughout the paper. Scattering factors for carbon, nitrogen, and oxygen are taken from the paper by D. Cromer and J. Waber, *Acta Crystallogr.*, **18**, 104 (1965), while that for hydrogen is from "International Tables for X-Ray Crystallography," Vol. III, Kynoch Press, Birmingham, England, 1968.
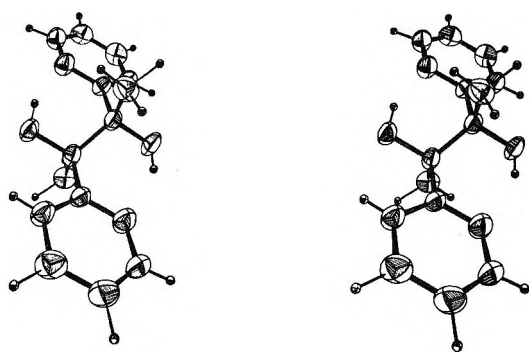
Figure 2.—ORTEP stereodrawing of the molecule.

The *meso*-pinacol may be considered to consist of two α-methyl-2-pyridylcarbinol groups bonded through the C7–C8 bond and held essentially rigid in the indicated conformation (Figure 1) by the hydrogen bridging between each of the pyridyl nitrogens and the more distant oxygen. The compound does not utilize the crystallographic center of symmetry in space group $P2_1/c$, hence affording two independent measurements of each parameter. However, within the ESD values observed in the parameters, the molecule does, in fact, possess a center of symmetry. All bond distances (including the N to O distances) are centrosymmetrically disposed within 2 ESD's and all bond angles within 3 ESD's. It is thus reasonable to compare parameters averaged over all of the molecule with analogous values found in the literature.

Within the pyridyl ring itself, the C–N distances average to $1.33_6 \pm 0.01_2$ Å, a value in agreement with the analogous value reported by Bak, *et al.*,[8] for pyridine (1.34 Å), and by Seff and Trueblood[9] for a substituted pyridine (1.34_6 Å). Similarly the C–C distances in this study average to $1.37_6 \pm 0.00_8$ Å compared to 1.39^8 and 1.38^9 in the aforementioned studies. A close parallel also exists between the pyridyl angles reported here and those reported by Trueblood:[9] *i.e.*, CNC = 118.3° (*vs.* 117.0°), CCC = 118.8° (*vs.* 118.7°), and NCC = 122.7° (*vs.* 123.5°).

A least-squares fit to the best planes indicates that each pyridyl ring (atoms 1–6 and 9–14) is planar within 0.005 Å. If one includes the immediately adjacent carbon in each case (C7 to pyridyl ring C1–C6 and C8 to pyridyl ring C9–C14), each seven-atom structure is still planar within 0.012 Å. The meso compound then consists of these two centrosymmetrically related planes bonded together at C7–C8 with an overall deviation from total plarity of 2.6°. The hydroxylic oxygens of each segment are in sufficiently close proximity to the nitrogen atom of the *other* segment to permit hydrogen bonding resulting in two additional six-membered rings which effectively fix the meso compound in the structure indicated in the ORTEP stereodrawing (Figure 2). The N to O distances of 2.66 and 2.70 Å lead to hydrogen-bonding distances of 1.82 and 1.86 Å with NHO angles of 152 and 157°, respectively.

In addition to the intramolecular hydrogen bonding already discussed, there exist a limited number of inter-

molecular close contacts. These lie in the range of 3.40–3.48 Å and consequently represent, at best, very weak interactions. Figure 3 shows the contents of the unit cell projected down the *b* axis and indicates these contacts. One of the pyridyl carbons (C2) has two close contacts (with an O18 at 3.43 Å and a C11 at 3.48 Å). The chemically related carbon in the other pyridyl ring (C13) has two analogous close contacts (with an O17 at 3.48 Å and a C4 at 3.40 Å).

Experimental Section

meso- and *dl*-acetophenone pinacols were synthesized as previously reported,[10] mp 121° (meso), 125° (*dl*). The two diastereomeric pinacols of 2-acetylpyridine have also been reported and were correspondingly prepared.[2] Hydropyridoin was purchased from the Aldrich Chemical Co. The 2-pyridoin and the several 2-pyridylalkanols were purchased from the J. T. Baker Co. The α-methyl-2-pyridylcarbinol [1-(2-pyridyl)ethanol] was synthesized by the routine NaBH₄ reduction of 2-acetylpyridine.

2,3-Di(2-pyridyl)-2-butanol was prepared by a modification of the published preparation for 1,2-di(2-pyridyl)ethane.[11] To a stirred ether solution of phenyllithium prepared from 14.8 ml of bromobenzene and 2.0 g of Li wire was added 15.7 g of ethylpyridine in 10 ml of anhydrous ether and the mixture was refluxed for 1 hr. After the reaction mixture was cooled to −10°, a solution of 13.4 g of 2-acetylpyridine in 10 ml of anhydrous ether was added dropwise with stirring and the stirring was continued for 1 hr at −10°. Water (50 ml) was added, and, after agitation, the reaction was transferred to a separatory funnel. The organic layer was extracted successively with 50 and 50 ml of H₂O, 18 and 10 ml of concentrated HCl. The collected aqueous extractions were neutralized with sodium bicarbonate and multiply extracted with ether. The ether extracts were dried and evaporated to yield 16.9 g of a dark oil. A fraction of this was distilled at reduced pressure, bp 125–130° (1 mm), to yield a colorless liquid that solidified on standing, mp 97°, uv 262 nm (ε 9000).

Nmr spectra were determined on an A-60 (Varian) instrument in deuterochloroform solution.

Nmr Studies

Conformational analysis of simple diastereomeric alkyl phenyl pinacols indicates that intramolecular hydrogen bonding should occur more favorably in the *dl* diastereomer, *e.g.*, for the acetophenone pinacols A and B, considering only those major conformations allowing such bonding

A, meso
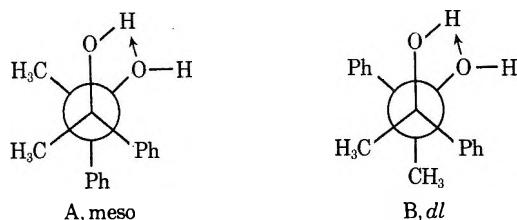
one of two conformational forms; maximum nonbonded interactions

B, *dl*

one of two conformation forms; minimum nonbonded interactions

This is reflected in the greater degree of hydrogen bonding displayed by the *dl* form in the infrared,[12] and the greater downfield shift of the hydroxylic protons of this diastereomer. This latter phenomenon has been observed for a number of related pinacols[13] and has

(8) B. Bak, L. Hansen-Nygaard, and J. Rastrup-Andersen, *J. Mol. Spectrosc.*, **2**, 361 (1958).

(9) K. Seff and K. N. Trueblood, *Acta Crystallogr., Sect. B*, **24**, 1406 (1968).

(10) J. H. Stocker and R. M. Jenevein, *J. Org. Chem.*, **33**, 294 (1968).

(11) C. S. Marvel, A. T. Tweedie, and J. Economy, *ibid.*, **21**, 1420 (1956).

(12) W. A. Mosher and N. D. Heindel, *ibid.*, **28**, 2154 (1963); L. P. Kuhn, *J. Amer. Chem. Soc.*, **80**, 5950 (1958).

(13) J. H. Stocker, D. H. Kern, and R. M. Jenevein, *J. Org. Chem.*, **33**, 412 (1968); A. D. Thomsen and H. Lund, *Acta Chem. Scand.*, **23**, 3582 (1970).

been utilized previously for stereochemical assignment.[14]

The 2-acetylpyridine pinacols present an unique case in which consideration of hydrogen bonding possibilities includes not only forms analogous to A and B (structure C) but, among others,[15] *two* additional five-membered ring forms (D, meso and *dl*) and two further
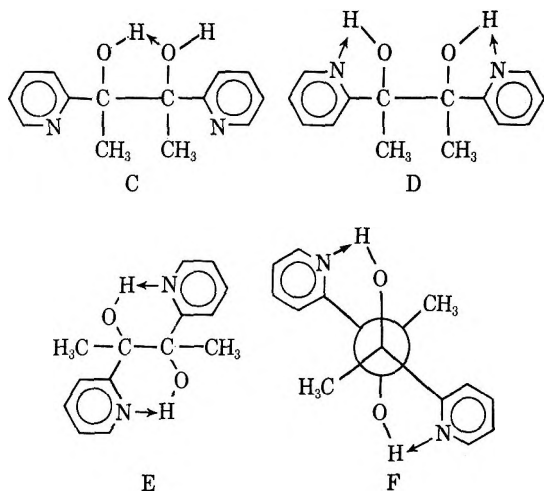
six-membered ring forms (E, meso and *dl*). Structure F provides a conformational analysis of hydrogen bridging in the meso form according to E (as well as the conclusions from the subsequent crystallographic study).

There is, of course, nothing to preclude one diastereomer from adopting preferentially a ring structure different from the other diastereomer.

Pmr data for 11 compounds appear in Table III. These compounds, all but two 2-pyridyl derivatives, were selected to permit hydrogen-bonding comparisons that involved five-, six-, and seven-membered rings, primary, secondary and tertiary carbinols, pinacols, and an enediol. The data may be summarized briefly as follows.

(1) The concentration independence of the hydroxylic proton resonance for the meso and *dl* forms underscores the intramolecular nature of the hydrogen bonding.

(2) The simplest pyridine glycol (hydropyridoin, no. 6) shows the effects of intramolecular bonding but in somewhat lesser degree than the title compound (3) (contrast δ 5.58 with 7.25).

(3) The maximum deshielding observed for hydroxylic protons involves a tertiary carbinol adjacent to a tertiary carbon atom, with both five- and six-membered ring possibilities (3, 4, 5) (excepting compound 7, *vide infra*).

(4) The simple carbinols (8–11) do not display the strong hydrogen bonded effects shown by the title compound and its diastereomer. The resonance position of the hydroxylic proton in these simple carbinols is strongly concentration dependent, suggesting that hydrogen bonding at higher concentrations is maximally intermolecular. The most dilute solutions

(14) J. H. Stocker, *J. Amer. Chem. Soc.*, **88**, 2878 (1966).

(15) For example, hydrogen bonding of the nonbridging hydroxylic proton in the pyridine analogs of A and B with a ring nitrogen may be considered less important.
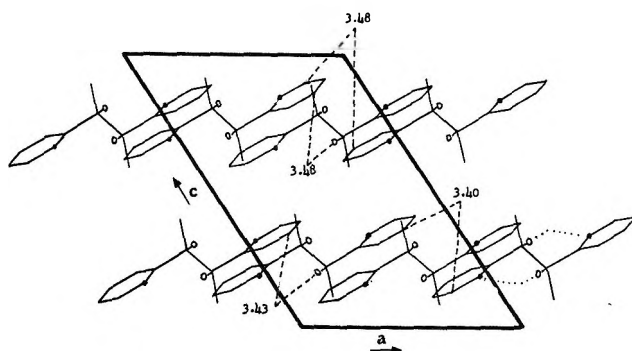
Figure 3.—Drawing of the unit cell projected down the *b* axis. Closest contacts (less than 3.50 Å) indicated.

have values comparable to the acetophenone pinacols 1 and 2.

(5) Only one compound, "pyridoin"[16] (7), showed a hydroxylic proton resonance more downfield than the title compound.

Additional General Comments

While the specific intent of the research reported here was to establish the diastereomeric identities of compound I, the data derived, taken in conjunction with selected pmr, crystallographic, and infrared information about hydrogen bonding in the same or related compounds from the literature, permit some additional comments placing the diastereomers of compound I in a larger framework, and allow some useful contrasts and comparisons.

Range of Pmr Values. —An impressively large range of intramolecularly bonded hydrogen values have been observed.

Fields and Regan[17] studied compound III, sterically a very crowded molecule, and reported that it displayed a hydroxylic proton resonance at δ 12.5–13.0 (broad singlet, concentration independent).

Vogt and Werth[18] reported the crystallographic structure of IV and suggested that there was a considerable resonance contribution by the quinoid-type structure indicated.

Compounds II, III, and IV may reasonably be considered to represent examples of extreme intramolec-

(16) "Pyridoin" has been clearly established [see C. A. Buehler, *Chem. Rev.*, **64**, 7 (1964)] as being 1,2-di(2-pyridyl)-1,2-ethenediol by infrared studies. Pmr data for this compound apparently have not been reported. The trans, double six-membered ring structure has been proposed (see above reference) as being the most reasonable hydrogen-bonded form, without additional data or consideration of alternate five-membered ring structures.
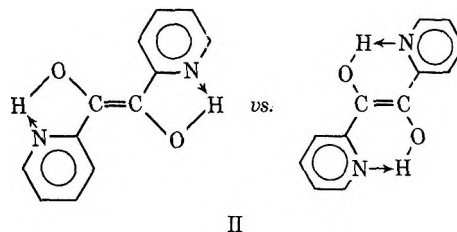
II

The name "pyridoin" appears to persist and is used routinely in the chemical catalogs.

(17) D. L. Fields and T. H. Regan, *J. Org. Chem.*, **36**, 2991 (1971).

(18) L. H. Vogt, Jr., and J. G. Werth, *J. Amer. Chem. Soc.*, **93**, 5402 (1971).

TABLE III

PMR SPECTRA OF VARIOUS CARBINOLS AND GLYCOLS[a]

Registry no.	No.	Compd[b]	Concn[c]	Aromatic	Alkyl[d] α	β	γ	Hydroxy
4217-65-6	1	meso-PhC(CH₃)(OH)C(CH₃)(OH)Ph	3.3	7.25 (s)		1.59 (s)		2.28
			1.67	7.25		1.59		2.25
			0.83	7.24		1.60		2.25
22985-90-6	2	dl-1	3.3	7.25 (s)		1.50 (s)		2.60
			1.67	7.25		1.51		2.55
			0.83	7.24		1.51		2.54
20445-38-9	3	meso-PyC(CH₃)(OH)C(CH₃)(OH)Py	3.3	7.05–8.60 (m)		1.27		7.25
			1.67	7.05–8.60		1.27		7.25
			0.83	7.05–8.60		1.27		7.25
20445-39-0	4	dl-3	3.3	6.75–8.25		1.68		6.98
			1.67	6.75–8.24		1.68		6.97
			0.83	6.75–8.24		1.68		6.98
35657-31-9	5	PyC(CH₃)(OH)CH(CH₃)Py	13.3	6.90–8.70 (m)	1.35 (s)	3.68 (q)	1.00 (d)	6.30
			6.7	6.90–8.70	1.35	3.58	1.00	6.16
			3.3	6.90–8.70	1.35	3.57	1.00	6.03
1141-05-5	6	PyCH(OH)CH(OH)Py	6.7	7.00–8.70 (m)	4.96 (s)			5.59
			3.3	7.00–8.70	4.95			5.58
			1.67	7.00–8.70	4.94			5.58
			0.83	7.00–8.70	4.94			(5.58)
1141-06-6	7	PyCOCH(OH)Py	3.3	7.00–8.60 (m)				12.8
			1.67	7.00–8.60				12.8
586-98-1	8	PyCH₂OH	13.3	7.00–8.60 (m)	4.76 (s)			5.20
			6.7	7.00–8.60	4.76			4.55
			3.3	7.00–8.60	4.78			4.03
			1.67	7.00–8.60	4.77			3.12
			0.83	7.00–8.60	4.77			2.30
103-74-2	9	PyCH₂CH₂OH	13.3	6.95–8.60 (m)	3.02 (t)	4.01 (t)		4.63
			6.7	6.95–8.60	3.03	4.03		4.27
			1.67	6.95–8.60	3.02	4.03		3.44
			0.83	6.95–8.60	3.02	4.03		3.07
2589-68-9	10	PyCH₂CH₂CH₂OH	13.3	6.95–8.60 (m)	2.96 (t)	2.00 (m)	3.72 (t)	4.98
			6.7	6.95–8.60	2.96	2.00	3.71	4.59
			1.67	6.95–8.60	2.96	1.98	3.70	3.27
			0.83	6.95–8.60	2.96	1.98	3.70	2.85
18728-61-5	11	PyCH(OH)CH₃	13.3	6.90–8.70 (m)	4.93 (q)	1.50 (d)		4.54
			6.7	6.90–8.70	4.93	1.52		4.06
			1.67	6.90–8.70	4.91	1.51		3.15
			0.83	6.90–8.70	4.91	1.51		2.80

[a] In CDCl₃; all chemicals shifts (δ) are given with respect to TMS. [b] Ph = phenyl, Py = 2-pyridyl. [c] w/w, as per cent. [d] α, β, and γ are with respect to the hydroxylic carbon.

R₁R₂ = H, alkyl

III

IV

N–H, 1.69 Å   N–O (closest), 2.568 Å

O–H, 0.69 Å   NHO, 150.9°
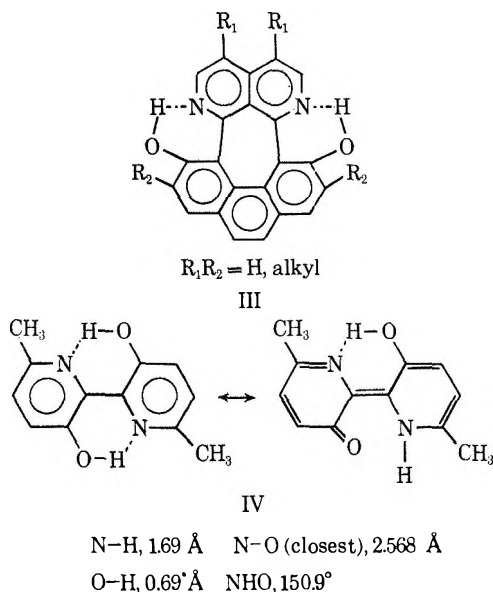
ular hydrogen bonding for the type of system under consideration here. Two of the three compounds (II and III) display essentially identical hydroxylic proton

resonance values (12.8 vs. 12.5–13.0). All three compounds permit a partial formulation as V. Such enolic

V   VI
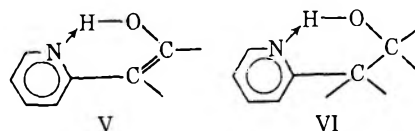
structures have notably more deshielded hydroxylic protons and the pmr values are not unprecedented.

Compound I, as well as VII, VIII, and IX (compounds 8, 9, and 10, Table III) may be partially formulated as VI or an analog and cannot display the enolic

VII   VIII   XI

OH (concd), δ 5.20	4.63	4.98
OH (dilute), δ 2.30	3.07	2.85
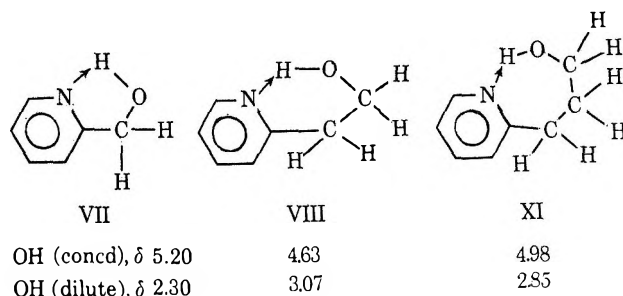
formulation V. It will be noted in the present studies that the hydroxylic proton resonance values of such compounds vary from the most deshielded, I, concentration independent at δ 7.25, to dilute solution values of 2.30 for VII, 2.85 for IX, and 3.07 for VIII (the most comparable to VI), *an overall range of almost five δ units.* The total range of contrast between V and VI is almost ten such units.

Crystallographic Comparisons.—Contrasting the crystallographic data for the title compound (I, average values, N–H 1.84 Å, N–O 2.68 Å, and NHO 155°) with that published for IV (see under structure) it will be noted that the enolic structure type V has the shorter distances, correlating with the tighter hydrogen bonding as reflected in the more deshielded proton. If the observed differences in NHO angles of 4° is significant, the more tightly bound structure IV has the more acute angle, in contrast to the presumed maximum favorability of linear overlap.[19]

In comparing such crystallographic data for solids with pmr solution data, separating the contributions of intramolecular, intermolecular, and π-type hydrogen bonding is always difficult, since the observed pmr resonances reflect a total of such contributions. It may be pointed out that crystal studies should reflect an irreducible minimum of such *intra*molecular bonding; *i.e.*, if essentially complete intramolecular hydrogen bonding prevails in the presence of closely packed molecules, no less than this should be found in solution, assuming negligible solvent interactions. It is then pertinent to underscore the fact that, in both of the molecules for which crystallographic data are considered here, the minimum *inter*molecular potential hydrogen bonding contact is greater than 3.4 Å, well beyond the accepted distance. The point being made is that the solution pmr values do, in fact, reflect an effective measure of such intramolecular hydrogen bonding.

Pmr and Infrared Contrasts.—The available data do not lead to the same conclusions. This point is emphasized for the following reasons. Much of the assessment of such hydrogen bonding is customarily by infrared techniques.[12] In tightly *intra*molecularly bonded species, no free O–H stretching is observed in the infrared, and diagnostic values of $\Delta\bar{\nu}$, the frequency difference between the free and bonded forms, cannot be determined. Pmr approaches should be of particular value in such cases. Further, the use of $\Delta\bar{\nu}$ as a measure of the strength or distance of hydrogen bonding has been seriously challenged.[20]

Since infrared data have been published for three compounds considered in this present report, a formal comparison between the two techniques is possible. Kuhn,[19] *et al.*, interpreted infrared data for VII, VIII, and IX as reflecting "strong intramolecular hydrogen bonds." Based on $\Delta\bar{\nu}$ values for very dilute solutions, the order of strength of bonding was found to be IX (seven-membered ring) > VIII (six-membered ring) > VII (five-membered ring), with the last being somewhat more strongly bonded than anticipated. The use of Dreiding model comparisons of static conformations, leading to maximum intramolecular hydrogen

bonding for each of these molecules, led to the conclusion that IX, with its seven-membered ring, in accord with the infrared data, should display the most favorable intramolecular hydrogen bonding. Assuming in the present study that the extreme concentration dependence of the hydroxylic proton resonances for these compounds reflects appropriate interplays of inter- and intramolecular bonding, the corresponding ratings for those concentrations involving appreciably intermolecularly bonded species would be VII > IX > VIII. The reverse order is suggested for the most dilute solutions, VIII > IX > VII, *i.e.*, the six-membered ring would appear to be the most favored arrangement, *in contrast to* the infrared data. Perhaps, more to the point, these values in very dilute solution would *not* appear to reflect *strong intra*molecular hydrogen bonding forces, whether considered simply as distinctly "upfield" values or when contrasted to the resonances observed for compound I. The use of model analogies for what is clearly a very dynamic situation is undoubtedly misleading. *Most important, however, is that the infrared and pmr data do not lead to the same conclusions.*

Meilahn and Munk[21] have commented briefly and succinctly on the differences in pmr and infrared approaches to conformational evaluation. In a pair of papers[21,22] dealing with the conformational equilibria of diastereomeric 1,2-amino- and substituted amino alcohols, their results underscore the importance of intramolecular hydrogen bonding. Of particular pertinence here is that for such bonding (NHO) giving rise to a five-membered ring, hydroxylic proton resonances for 15% CDCl$_3$ solutions appeared between *ca.* δ 3.3 and 5, essentially analogous for the corresponding concentrations to those observed in the present study for compounds VII–X. These values and the general discussion above serve to further emphasize the unique degree of intramolecular hydrogen bonding reflected in the δ 7.25 value for compound I.

The presence of the methyl group in X, as contrasted to its absence in VII, would appear to decrease the

X
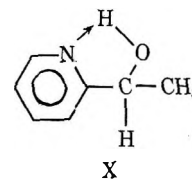
OH (concd), δ 4.54
OH (dilute), δ 2.80

total hydrogen bonding, presumably by steric interference with intermolecular activity, while increasing the intramolecular bonding as demonstrated by the downfield shift in dilute solution. This parallels the influence of the two methyl groups in I when compared to simple hydropyridoin (compound 6, Table I).

(19) L. P. Kuhn, R. A. Wires, W. Ruoff, and H. Kwart, *J. Amer. Chem. Soc.*, **91**, 4790 (1969).

(20) *E.g.*, see E. L. Eliel and H. D. Banks, *ibid.*, **94**, 171 (1971), for a brief but useful summary of this problem: ". . . attempted correlations of $\Delta\bar{\nu}$ with molecular geometry have tended to be empirical."

(21) M. K. Meilahn and M. E. Munk, *J. Org. Chem.*, **34**, 1440 (1969).

(22) M. E. Munk and M. K. Meilahn, *ibid.*, **33**, 3480 (1968).

The Stereochemistry of the Conjugate Addition of Derivatives of endo-2-Norbornylcopper(I) to Mesityl Oxide[1a]

GEORGE M. WHITESIDES* AND PHILIP E. KENDALL[1b]

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

Received June 6, 1972

Reaction between mesityl oxide and the ate complex formed by mixing endo-2-norbornyl(tri-*n*-butylphosphine)copper(I) (endo-2) and *tert*-butyllithium yields the conjugate adduct, 4-methyl-4-(endo-2-norbornyl)pentan-2-one (3), with high stereoselectivity; no detectable 4-methyl-4-(exo-2-norbornyl)pentan-2-one (4) is formed. This stereochemical outcome excludes a free norbornyl radical as an intermediate in this particular conjugate addition reaction. Similar stereochemical results are obtained using either the analogous trimethyl phosphite complex or the ate complex formed by mixing endo-2 with methyllithium; the same mechanistic conclusion can be drawn concerning these reactions. The copper-catalyzed conjugate addition of endo-2-norbornylmagnesium bromide (endo-1) to mesityl oxide yields an 81:19 ratio of endo and exo conjugate adducts; the conjugate addition of 2 itself occurs with extensive loss of stereochemistry. Mechanistic interpretation of these latter reactions is complicated both by the formation of conjugate adduct in relatively low yields, and by the two possibilities that epimerization of the copper reagents competes with their conjugate additions and that the endo and exo organometallic reagents differ in their reactivity in these additions. A comparison of the combined yields of 3 and 4 obtained on reaction of mesityl oxide with 1 in a copper-catalyzed reaction, with 2, and with a number of ate complexes containing 2 and primary, secondary, tertiary, and aromatic lithium reagents indicates that the mixed ate complex of 2 and *tert*-butyllithium is uniquely active in the transfer of the 2-norbornyl group in the conjugate addition.

Both the copper-catalyzed conjugate addition of organomagnesium and -lithium reagents to α,β-unsaturated ketones and the rapid stoichiometric conjugate addition of lithium dialkylcuprates to these substances are well established and synthetically important reactions.[2] However, the mechanism by which the copper ion encourages addition of the anionic organic moiety to the β-carbon atom of the unsaturated ketone moiety at the expense of addition to the carbonyl group is not understood.[3] Several experimental generalizations known or believed to be true for it follow.

(a) Copper(I) is the valence state that is active in the conjugate addition; further, the copper(I) is apparently not oxidized or reduced irreversibly during the course of the reaction.[4]

(b) Copper(I) alkyls add to a number of types of carbon–carbon multiple bonds in the absence of a conjugating carbonyl moiety; in particular, lithium dialkylcuprates add smoothly to α,β-unsaturated epoxides[6] and ethynylcarbinyl acetates,[7] and organocopper-(I) compounds themselves add to terminal acetylenes[8] and nitroaromatics.[9] Thus, the presence of a conjugat-

ing carbonyl group is not necessary for the addition of an organic moiety bonded to copper to a carbon–carbon multiple bond.

(c) Conjugate addition can occur successfully to α,β-unsaturated ketones confined to a transoid configuration; a cyclic transition state for the addition, involving a cisoid conformation for the ketone, is thus not required.[3,10,11]

Four basic classes of mechanisms have been proposed to account for the influence of copper on reactions of organometallic reagents with α,β-unsaturated ketones. First, the reaction has been suggested to involve as its basic step the nucleophilic addition of an anionic alkyl group to the carbon–carbon double bond. In this mechanism (represented schematically by eq 1), the copper atom might serve either to orient
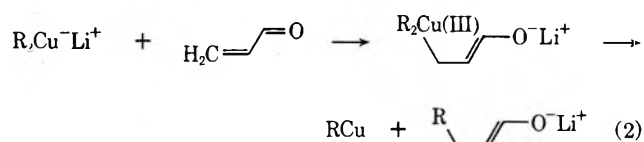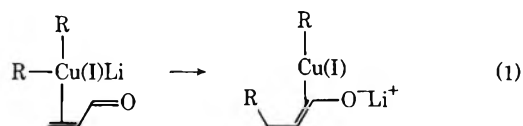
the alkyl group in a position favorable for attack on the β-carbon atom of the enone moiety by coordination with the double bond, or to activate this bond for

(1) (a) Supported by the National Science Foundation, Grants GP-28586X and GP-14247, and by the International Copper Research Association; (b) National Science Foundation Trainee, 1970–1971.

(2) For reviews and references, see (a) H. O. House, W. L. Respess, and G. M. Whitesides, *J. Org. Chem.*, **31**, 3128 (1966); (b) H. O. House and W. F. Fischer, Jr., *ibid.*, **33**, 949 (1968).

(3) The catalytic activity of copper in organic reactions has been reviewed: R. G. R. Bacon and H. A. O. Hill, *Quart. Rev., Chem. Soc.*, **19**, 95 (1965); O. A. Chaltykian, "Copper-Catalytic Reactions," A. E. Stubbs, Translator, Consultants Bureau, New York, N. Y., 1966.

(4) Alkylcopper(I) compounds frequently precipitate on reaction of the corresponding lithium dialkylcuprates with α,β-unsaturated ketones.[2b,5]

(5) H. O. House and W. F. Fischer, Jr., *J. Org. Chem.*, **34**, 3615 (1969).

(6) R. W. Herr and C. R. Johnson, *J. Amer. Chem. Soc.*, **92**, 4979 (1970); R. J. Anderson, *ibid.*, **92**, 4978 (1970).

(7) P. Rona and P. Crabbé, *ibid.*, **91**, 3289 (1969).

(8) J. F. Normant and M. Bourgain, *Tetrahedron Lett.*, 2583 (1971).

(9) M. Nilsson, C. Ullenius, and O. Wennerström, *ibid.*, 2713 (1971).

(10) H. O. House, R. A. Latham, and C. D. Slater, *J. Org. Chem.*, **31**, 2667 (1966).

(11) C. P. Casey and R. A. Boggs, *Tetrahedron Lett.*, 2455 (1971).

addition.[12] Second, the copper atom might take part directly in the reaction by an oxidative addition process yielding an intermediate copper(III) species, followed by reductive elimination of the conjugate adduct from this intermediate (eq 2).[13,14] Third, conjugate addition might take place through a free radical chain process (eq 3–5). In this reaction se-

$$R_2CuLi \xrightarrow{\text{initiation}} R\cdot \qquad (3)$$

$$R\cdot + H_2C{=}\!\!\!\diagup{=}O \longrightarrow R\diagdown\!\!\!\diagup{-}O\cdot \qquad (4)$$

$$R\diagdown\!\!\!\diagup{-}O\cdot + R_2CuLi \longrightarrow$$

$$R\diagdown\!\!\!\diagup{-}OLi + RCu + R\cdot \quad (5)$$

quence, the copper(I) would serve as the metallic center in a radical displacement reaction (eq 5).[17] The conjugate addition of trialkylboranes to α,β-unsaturated ketones is reported to be a free-radical process, presumably taking place by a sequence of reactions analogous to those represented by eq 3–5, and provides precedent for the involvement of free radicals in conjugate additions.[18] Finally, conjugate addition has been suggested to involve electron transfer in an important step (eq 6).[2,19] The catalytic activity of cop-

$$R_2Cu(I)Li + H_2C{=}\!\!\!\diagup{=}O \longrightarrow \left[R_2Cu(II)Li \cdot H_2C{-}\!\!\!\diagup{-}\overset{O^-}{} \right]$$

$$\downarrow$$

$$RCu(I) + R\diagdown\!\!\!\diagup{-}OLi$$

$$(6)$$

per(I) in a reaction of this type would be due to the accessibility of the copper(II) valence state, and the resulting ease of one-electron oxidation of organocopper(I) compounds. Lithium dialkylcuprates do in general react readily with oxidizing agents. However, the principal organic products from these reactions are the corresponding alkyl dimers,[15,20] and oxidative dimerization of alkyl groups derived from the organometallic component of a conjugate addition reaction mixture is not a common side reaction.

The work reported in this paper was designed to detect free alkyl radicals that might be present as intermediates in representative conjugate addition reactions, viz., the reactions of lithium dialkylcuprates derived from *endo*-2-norbornylcopper(I) with mesityl oxide (2-methylpent-2-en-4-one). The intermediacy of free 2-norbornyl radicals (eq 3–5) in these reactions would be expected to result in the formation of conjugate adduct containing norbornyl groups epimerized at C-2;[21] nucleophilic addition of the norbornyl moiety to the carbon–carbon double bond (eq 1) or an oxidative addition–reductive elimination path (eq 2) would be expected to take place with retention of stereochemistry at C-2, by analogy with the stereochemical outcome of reactions of 2-norbornylcuprates with alkyl halides and tosylates.[15,20] The stereochemical course of an electron-transfer mechanism not involving free alkyl radicals (eq 6) is difficult to predict, but might also involve retention of configuration at C-2.
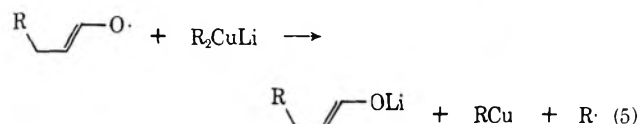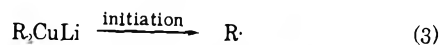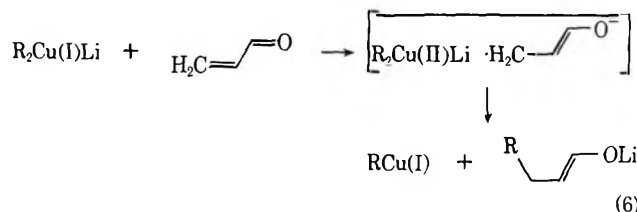
Results

endo-2-Norbornylmagnesium bromide (*endo*-1) was obtained from a mixture of endo and exo epimers by preferential destruction of the exo epimer using the procedure of Jensen and Nakamaye;[22] its conversion into *endo*-2-norbornyl(tri-*n*-butylphosphine)copper(I) (*endo*-2) was accomplished by reaction with bromo-(tri-*n*-butylphosphine)copper(I) in ether at −78°.[20] The diastereomeric purity of the resulting 2 was determined by glpc analysis of the mixture of *endo*- and *exo*-2-methylnorbornane formed on nitrobenzene oxidation of the solution obtained by addition of methyllithium to 2. This oxidative coupling has been demonstrated previously to take place stereospecifically with retention of configuration.[20]

Reactions of a number of organometallic derivatives of the 2-norbornyl moiety with mesityl oxide were surveyed to find conditions that would give high conversions to the 2-norbornyl conjugate adduct. For convenience, these reactions were carried out using the epimeric mixture of alkyl metal compounds obtained from the equilibrium mixture of *exo*- and *endo*-2-norbornylmagnesium bromides (~35 exo:65 endo),[19] and,

(12) The structures of the ate complexes formed between organocopper(I) compounds and organolithium reagents have not been established. For simplicity, we will refer to these materials as "lithium dialkylcuprates," and represent them by formulas of the type R_2CuLi or $R_2Cu^-Li^+$, with no conviction that these descriptions of the structures of the copper ate complexes necessarily bear any relationship to those actually existing.

(13) The activation of carbon–carbon double bonds toward nucleophilic attack by coordination with transition metals is illustrated, *inter alia*, by the Wacker process and many reactions of the type i → ii.

$$N{:}\diagup\!\!\!\Vert{-}M \longrightarrow N{-}\!\!\!\diagup{-}M$$

$$\text{i} \qquad\qquad \text{ii}$$

See, for examples, J. Halpern, *Advan. Chem. Ser.*, **70**, 1 (1968); P. M. Henry, *ibid.*, **70**, 126 (1968); M. M. Jones, "Ligand Reactivity and Catalysis," Academic Press, New York, N. Y., 1968, pp 84–85; P. M. Maitlis, "The Organic Chemistry of Palladium," Academic Press, New York, N. Y., 1971; A. Panunzi, A. De Renzi, and G. Paiaro, *J. Amer. Chem. Soc.*, **92**, 3488 (1970); G. N. Schrauzer, J. H. Weber, and T. M. Beckham, *ibid.*, **92**, 7078 (1970).

(14) Oxidative addition of carbon-containing residues to copper(I) has been discussed previously in connection with the reactions of lithium dialkylcuprates with organic halides,[15,16] and α,β-unsaturated epoxides.[6] However, no firm experimental evidence bearing on the importance of this process in organocopper(I) chemistry is presently available.

(15) G. M. Whitesides, W. F. Fischer, Jr., J. San Filippo, Jr., R. W. Bashe, and H. O. House, *J. Amer. Chem. Soc.*, **91**, 4871 (1969), and references cited therein.

(16) J. R. Collman, *Accounts Chem. Res.*, **1**, 136 (1968).

(17) A rapidly increasing body of evidence indicates that radical displacements at metallic centers may be very rapid processes: P. J. Krusic and J. K. Kochi, *J. Amer. Chem. Soc.*, **91**, 3942 (1969); A. G. Davies and B. P. Roberts, *J. Organometal. Chem.*, **19**, P17 (1969); K. U. Ingold and B. P. Roberts, "Free Radical Substitution Reactions," Wiley, New York, N. Y., 1971; and references in each.

(18) H. C. Brown, *et al.*, *J. Amer. Chem. Soc.*, **92**, 710 (1970); H. C. Brown and G. W. Kabalka, *ibid.*, **92**, 712, 714 (1970).

(19) (a) I. N. Rozhkov and S. M. Makin, *Zh. Obshch. Khim.*, **34**, 59 (1964); *Chem. Abstr.*, **60**, 10576 (1964); (b) H. O. House and M. J. Umen, *J. Amer. Chem. Soc.*, **94**, 5495 (1972).

(20) G. M. Whitesides, J. San Filippo, Jr., C. P. Casey, and E. J. Panek, *J. Amer. Chem. Soc.*, **89**, 5302 (1967). These oxidative dimerizations apparently do not involve free alkyl radicals as intermediates; *cf.* G. M. Whitesides, J. San Filippo, Jr., E. R. Stedronsky, and C. P. Casey, *ibid.*, **91**, 6542 (1969).

(21) For previous studies in which a reaction involving an intermediate free 2-norbornyl radical has been characterized by loss of stereochemistry at C-2, see P. J. Kropp, *ibid.*, **91**, 5783 (1969); A. Fang, Ph.D. Thesis, Massachusetts Institute of Technology, Cambridge, Mass., 1966; P. D. Bartlett, G. N. Fickes, F. C. Haupt, and R. Helgeson, *Accounts Chem. Res.*, **3**, 177 (1970); D. I. Davies and S. J. Cristol, *Advan. Free Radical Chem.*, **1**, 155 (1965); G. M. Whitesides and J. San Filippo, Jr., *J. Amer. Chem. Soc.*, **92**, 6611 (1970).

(22) F. R. Jensen and K. L. Nakamaye, *ibid.*, **88**, 3437 (1966).

in several instances, no effort was made to analyze the resulting mixtures of the adducts 4-methyl-4-(*endo*-2-norbornyl)pentan-2-one (**3**) and 4-methyl-4-(*exo*-2-norbornyl)pentan-2-one (**4**) for epimeric compositions. Instead, product mixtures were analyzed for the combined yield of **3** and **4**. Results of these experiments
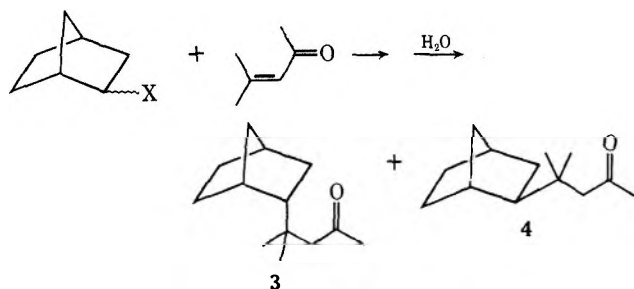
are listed in Table I. In this table, the entries in the column headed "X" are not intended to imply the ex-

TABLE I

COMBINED YIELD OF THE EPIMERIC
4-METHYL-4-(2-NORBORNYL)PENTAN-2-ONES **3** AND **4** FROM
CONJUGATE ADDITION OF ORGANOMETALLIC DERIVATIVES
NORBORNANE-2-X TO MESITYL OXIDE[a]

X	Yield **3** + **4**, %[b]
MgBr	0
MgBr + 5 mol % ICuPBu₃	18
MgBr + 12 mol % BrAgPBu₃	3
MgBr + 5 mol % (Ph₃P)₂Ni(CH₂=CH₂)	0
MgBr + 5 mol % (Ph₃P)₂NiBr₂	0
MgBr + 4 mol % (Ph₃P)₂Pt(CH₂=CH₂)	0
MgBr + 5 mol % (Ph₃P)₂PtCl₂	0
MgBr + 5 mol % K₂PtCl₄	0
MgBr + 5 mol % ClAuPEt₃	0
Cu(I)PBu₃	16
Cu(I)PBu₃ + C₆F₅Li	0
Cu(I)PBu₃ + *n*-C₄H₉Li	2
Cu(I)PBu₃ + *n*-C₄H₉Li·TMEDA	18
Cu(I)PBu₃ + *n*-C₄H₉Li	0[c]
Cu(I)PBu₃ + *s*-C₄H₉Li	4
Cu(I)PBu₃ + (C₆H₅)₃CLi	4
Cu(I)PBu₃ + *c*-C₆H₉Li	5
Cu(I)PBu₃ + C₆H₅Li	5
Cu(I)PBu₃ + C₆H₅(CH₃)₂CH₂Li	6
Cu(I)PBu₃ + CH₃Li	8[d]
Cu(I)PBu₃ + 3 *t*-C₄H₉Li	35[e]
Cu(I)PBu₃ + 5 *t*-C₄H₉Li	59[f]
Cu(I)PBu₃ + *t*-C₄H₉Li	66

[a] Reactions were carried out between 1 mmol of norbornylmetal compound and 1 mmol of mesityl oxide in 20 ml of ether at 0° for 0.5–2.0 hr, unless otherwise noted. Solutions contained 1 mmol of magnesium bromide. [b] Reproducibility in yields was ~±2%. [c] The solvent in this reaction was 50:50 ether–pyridine. [d] A 90% yield of 4,4-dimethylpentan-2-one was obtained in this reaction. [e] Ca. 4 mmol of mesityl oxide was used. [f] Ca. 6 mmol of mesityl oxide was used.

istence of discrete, characterized ate complexes having compositions related in some simple way to the quantities of reagents present; the entries refer simply to the components that have been added to the solution. Thus, "Cu(I)PBu₃ + C₆H₅Li" indicates a solution prepared by adding 1 equiv of phenyllithium to a solution of 2-norbornyl(tri-*n*-butylphosphine)copper(I); the name "lithium norbornylphenylcuprate" is used only

for convenience in referring to this solution. Although both chemical and spectroscopic evidence suggests that solutions prepared in this manner do in fact contain organometallic clusters having more than one type of organic moiety on the cluster, such clusters have not been characterized.[23]

One feature of the data of Table I may have pertinence to the synthetic application of organocopper reagents in conjugate addition that extends beyond the immediate stereochemical object of this work. The high yield of **3** + **4** obtained on reaction of lithium norbornyl-*tert*-butylcuprates with mesityl oxide suggests that "mixed" copper ate complexes may have useful practical application in their own right: this yield is sufficiently higher than that obtained in the other experiments summarized in Table I that it would clearly be the method of choice in a preparative procedure.[24]

The origin of the marked superiority of the mixed ate complex, lithium *tert*-butyl-2-norbornyl(tri-*n*-butylphosphine)cuprate, in transferring the norbornyl group in conjugate addition reactions is not clear. The product distribution observed in reaction of lithium methyl-2-norbornylcuprate with mesityl oxide indicates, in this instance, that the conversion of the α,β-unsaturated ketone to its conjugate adducts containing either methyl or norbornyl moieties proceeds in very high yield (Table I), and that the important factor in determining the composite yield of **3** + **4** is apparently the relative facility with which the norbornyl and methyl moieties transfer from the metal cluster to the α,β-unsaturated ketone (eq 7). However, the limited
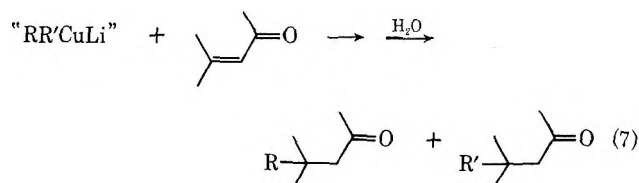
data available in Table I are not sufficient to establish whether steric bulk, alkyl group basicity, or aggregate structure determine this facility of transfer.

Taking the data of Table I as a guide in selecting reaction systems for examination, the stereochemistry of the conjugate addition of several metal derivatives of the *endo*-2-norbornyl moiety to mesityl oxide was determined. In order to prove the stereochemistry of the products, and to obtain materials for glpc calibration, an authentic sample of **4** was prepared following the reaction sequence outlined in Scheme I;[25] an anal-

(23) J. San Filippo, Jr., Ph.D. Thesis, Massachusetts Institute of Technology, Cambridge, Mass., 1970. For structural analogies in related organometallic series, see also T. L. Brown, *Advan. Organometal. Chem.*, **3**, 365 (1966); J. P. Oliver, *ibid.*, **8**, 167 (1970); T. L. Brown, *Accounts Chem. Res.*, **1**, 23 (1968); M. Y. Darensbourg, B. Y. Kimura, G. E. Hartwell, and T. L. Brown, *J. Amer. Chem. Soc.*, **92**, 1236 (1970).

(24) We presume that lithium dinorbornylcuprate would compete in yield in these conjugate addition reactions with lithium norbornyl-*tert*-butylcuprate. However, in this system, as in many of synthetic interest, the Grignard reagent of one component can be obtained more easily and in higher purity than can the corresponding alkyllithium compound. Thus the copper ate complex obtained by mixing 1 equiv of the Grignard reagent of a component of interest and 1 equiv of *tert*-butyllithium may provide a practical alternative to the ate complex obtained from the lithium reagent of this component.

(25) Diastereomerically pure *endo*- and *exo*-norbornane-2-carboxylic acids were obtained from a mixture of *endo*- and *exo*-norborn-5-ene-2-carboxylic acids by the procedure of J. A. Berson and D. A. Ben-Efraim, *J. Amer. Chem. Soc.*, **81**, 4083 (1959), and references cited therein.

SCHEME I

SYNTHESIS OF *exo*-2-NORBORNYL-4-METHYPENTAN-2-ONE (4)

gents examined appears to have greater reactivity toward α,β-unsaturated ketones than the endo epimer, and that epimerization at C-2 competes in certain instances with conjugate addition. Nonetheless, the stereochemistry of several of the conjugate additions is readily interpreted.

The reactions listed in Table II can be classified into two groups on the basis of their stereoselectivity. The first, including the reactions of the phosphine and phosphite complexes of lithium *tert*-butyl-*endo*-norbornylcuprate with mesityl oxide, clearly is characterized by retention of configuration at C-2 of the norbornyl group during the step that results in carbon–carbon bond formation in the conjugate addition. The corresponding reaction of lithium methyl-*endo*-2-norbornylcuprate should probably also be included in this group. The second, including the reaction between mesityl oxide and *endo*-2-norbornyl (tri-*n*-butylphosphine)copper and possibly also the copper-catalyzed conjugate addition of *endo*-2-norbornylmagnesium bromide to this ketone, takes place with significant loss of stereochemistry.

Control experiments carried out in the first group of reactions, using cuprate solutions containing approximately 65:35 mixtures of *endo*- and *exo*-2-norbornyl moieties (Table II), establish that the high stereoselectivity observed in these reactions is not an artifact resulting either from the differences in reactivity of *endo*- and *exo*-2-norbornyl diastereomers in the conjugate addition or from isomerization of the conjugate adduct, once formed. The origin of the loss in stereochemistry observed in the second group of reactions is more difficult to identify. Attempts to determine the stereochemical stability of *endo*-2-norbornyl(tri-*n*-butylphosphine)copper(I) (2) under the conditions of the conjugate addition did not yield easily interpreted results.[27] Thus, a solution of 2 (99.5% endo) was allowed to react with 0.5 equiv of mesityl oxide for 15 min at 0°. Analysis of the stereochemistry of the remaining 2 by conversion to 2-methylnorbornane[20] demonstrated that it was composed of a 94:6 mixture of endo and exo diastereomers. This result could be interpreted to indicate either that epimerization of 2 is relatively slow under the conditions of the conjugate addition, or that epimerization is rapid, but that the *exo*-2 reacts preferentially with the mesityl oxide as it is formed. However, although reaction of a 74:26 mixture of *endo*- and *exo*-2 with limiting amounts of mesityl oxide under similar reaction conditions demonstrated enhanced reactivity for the exo epimer, the difference in reactivity between epimers appears insufficient to account for all of the loss of stereochemistry observed on reaction of *endo*-2 with mesityl oxide (see Experimental Section). Thus it appears that some epimerization may actually take place during the conjugate addition of 2 to mesityl oxide. However, the yields of 3 and 4 obtained in this reaction were sufficiently small that this result unfortunately cannot be considered to be of great mechanistic significance (Table I).

In an effort to test the proposal of a free-radical mechanism for the conjugate addition of trialkylboranes to

ogous procedure starting with the *endo*-2-norbornyl carboxylic acid yielded a 70:30 mixture of 3 and 4.[26]

Table II summarizes data pertinent to the stereochemistry at C-2 of the norbornyl group of a number of

TABLE II

STEREOCHEMISTRY OF CONJUGATE ADDITION OF THE
ORGANOMETALLIC DERIVATIVES NORBORNANE-2-X
TO MESITYL OXIDE[a]

X	*endo*-X:*exo*-X	3 (endo):4 (exo)
MgBr + 5 mol % ICuPBu₃	65:35[b]	62:38
	99:1[c]	81:19
CuPBu₃	65:35[b]	17:83
	99:1[c]	47:53
CuPBu₃ + CH₃Li	65:35[b]	1:99
	99:1[c]	94:6
CuPBu₃ + (CH₃)₃CLi	65:35[b]	40:60
	99:1[c]	99:1[c,d]
CuP(OCH₃)₃ + (CH₃)₃CLi	99:1[c,e]	99:1[c]

[a] Reactions were carried out at 0° in diethyl ether. [b] This ratio was not measured for each experiment. These samples were derived from 2-norbornylmagnesium bromide that had been allowed to reach epimeric equilibrium, and the 65:35 ratio is the value characteristic of this equilibrium. [c] This ratio is a minimum value. [d] In a separate experiment Mg²⁺ was precipitated with dioxane after addition of *tert*-butyllithium, and its concentration was reduced to 5% that of the Cu⁺; however, ~6% epimerization was observed in the mixture of 3 and 4 obtained in this reaction, presumably due in major part to epimerization occurring during manipulation of the solution. The yield of 3 and 4 in this reaction was 57%. [e] The yield of 3 in this reaction was 40%.

derivatives of 2 on conjugate addition to mesityl oxide. Discussion of these data is complicated by the facts that the exo epimer of each of the organometallic rea-

(26) The conversion of the α,β-unsaturated ester 5 to 4 by reaction with lithium dimethylcuprate is carried out under conditions in which the organometallic compound is decomposing thermally, and presumably proceeds by initial conversion of 5 to iii, followed by rapid subsequent conjugate addition of remaining lithium dimethylcuprate to iii.

$$(CH_3)_2CuLi \xrightarrow{\Delta} CH_3Li + \text{''}CH_3\text{''} + Cu(0)$$

(27) The epimerization of 2-norbornyl(tri-*n*-butylphosphine)copper(I) is known to be faster than its thermal decomposition; however, quantitative rate data are available for neither of these reactions: *cf.* C. P. Casey, Ph.D. Thesis, Massachusetts Institute of Technology, Cambridge, Mass., 1968.

α,β-unsaturated ketones, we attempted to add tri-*exo*-2-norbornylborane to mesityl oxide using reaction conditions described by Brown (see Experimental Section).[18] Essentially no conjugate addition was obobserved under these and a variety of other conditions, and the experiments were abandoned.

Conclusions

The conjugate addition of norbornyl groups to mesityl oxide from a mixture of 2 and *tert*-butyllithium takes place in good yield with essentially complete retention of stereochemistry at the 2 position of the norbornyl moiety. This observation, taken together with the loss of stereochemistry at this position characteristic of reactions involving free 2-norbornyl radicals,[21] excludes the mechanism of eq 3–5 for this conjugate addition. The stereochemistry of the remaining systems summarized in Table II is less clear-cut; however, the predominant retention of stereochemistry observed in the stoichiometric reaction between mesityl oxide and lithium methyl-*endo*-2-norbornylcuprate and in its copper-catalyzed reaction with 1 suggest that the same mechanistic conclusions can be applied to these reactions. No mechanistically significant interpretation concerning the stereochemistry of the addition of 2 to mesityl oxide can be drawn at present, for reasons discussed above. Using a different stereochemical test, Casey and Boggs[11] have concluded that free vinylic radicals are not involved in the conjugate addition of lithium dipropenylcuprate to cyclohexenone.[28]

House and Umen have successfully correlated the susceptibility of a number of α,β-unsaturated ketones toward conjugate addition with their one-electron reduction potentials.[19b] Further, products easily rationalized on the basis of α,β-unsaturated ketone radical anions have been detected in certain conjugate addition reactions.[29] These observations are consistent with the hypothesis that electron transfer from the copper ate complex to the α,β-unsaturated ketone is an important part of conjugate addition (eq 6). However, neither observation necessarily establishes that free-radical anions derived from the α,β-unsaturated ketones are necessarily intermediates in the conjugate addition, since the reduction potentials may correlate with other properties of the ketones [*e.g.*, susceptibility to attack by the cuprates or ability to complex with Cu(I)], and the anion radical-derived products[29] may originate in reactions unrelated to the conjugate addition. Thus, although the data presented in this paper exclude free 2-norbornyl radicals in the conjugate addition of derivatives of 2 to mesityl oxide (and presumably exclude free radicals in other related reactions by analogy[11]), it is not yet possible to differentiate rigorously between mechanisms for conjugate addition involving electron transfer to the enone moiety (eq 6) and those requiring nucleophilic attack of an alkyl anion or metallate anion on it (eq 12).[30]

Experimental Section[31]

5-Norbornene-2-carboxylic acid (371 g), bp 131–134° (11 Torr) [lit.[30] bp 132–134° (22 Torr)], was obtained from cyclopentadiene and acrylic acid in 87% yield following the procedure of Diels and Alder.[34]

endo-**Norborn-5-ene-2-carboxylic Acid.**—Norborn-5-ene-2-carboxylic acid (278 g, 2.01 mol) was dissolved in a solution of 25% sodium hydroxide (80.0 g, 2.00 mol) and the solution was cooled to 0°. Sodium bicarbonate (50 g, 0.6 mol) was added, followed by a solution of iodine (570 g, 2.20 mol) dissolved in 450 ml of a saturated aqueous solution of potassium iodide. The reaction mixture was stirred for 2 hr, and the organic layer was extracted into diethyl ether. The ether phase was separated, washed with a saturated solution of sodium thiosulfate until clear, washed with water, and dried (MgSO$_4$). Ether was removed on a rotary evaporator to yield 415 g of crude iodolactone. Recrystallization of this material from a mixture of ethyl acetate and *n*-pentane (1:5) gave 316 g (63%) of pure iodolactone, mp 57.0–57.5° (lit.[35] mp 58.5°).

This iodolactone (456 g, 1.80 mol) was dissolved in 800 ml of glacial acetic acid, and the resulting solution was cooled to 15°. Zinc dust (245 g, 3.74 g-atoms) was added to the mixture over a 20-min interval. An additional 250 ml of glacial acid was added, and the reaction mixture was stirred for an additional 2 hr at 15°. The reaction mixture was warmed to 25° for 2 hr, and the remaining solids were then removed by filtration. The reaction solution was diluted with 1 l. of water and extracted with five 200-ml portions of diethyl ether. Distillation of the ether phase yielded *endo*-norborn-5-ene-2-carboxylic acid (134 g, 54%), bp 127° (12 Torr) [lit.[25] bp 134° (16 Torr)].

endo-**2-Norbornanecarboxylic Acid.**—*endo*-Norborn-5-ene-2-carboxylic acid (95 g, 0.688 mol) was dissolved in *ca.* 100 ml of ethyl acetate, mixed with 3 wt % palladium on charcoal (10%), and charged into a Parr hydrogenation apparatus. The solution was shaken under a hydrogen atmosphere until no further hydrogen uptake was observed, and was then pressurized to 40 psi and shaken for an additional 1 hr. The catalyst was removed by filtration, and solvent was removed under vacuum to yield crude *endo*-2-norbornanecarboxylic acid. Nmr spectroscopic analysis of the resulting crude acid indicated that the starting material had been completely consumed. The acid could be recrystallized from *n*-pentane to yield pure *endo*-2-norbornanecarboxylic acid,

based on its ability to coordinate with double bonds, it is curious that derivatives of a number of other transition metals, some of which are known to coordinate with double bonds more strongly than copper, show little or no catalytic activity in conjugate addition (Table I). However, many of these salts either form organometallic derivatives or are reduced in solutions containing organolithium reagents; thus, the apparent lack of catalytic activity of these ions may simply reflect their conversion to noncoordinating substances under the reaction conditions.

(31) All melting points and boiling points are uncorrected. Infrared spectra were determined with a Perkin-Elmer Model 237 grating spectrophotometer. Nmr spectra were determined with a Varian T-60 nmr spectrometer. Mass spectra were determined on a Hitachi Perkin-Elmer RMU-6 mass spectrometer. Analytical analyses were performed by Midwest Microlabs, Ltd., Indianapolis, Ind. Samples for elemental and spectral analyses were purified on a Hewlett-Packard Model 700 thermal conductivity gas chromatograph. Analytical glpc analyses were performed on F & M Model 810 flame ionization instruments. Absolute yields of products were calculated from peak areas using internal standard techniques, with response factors obtained from authentic samples. Diethyl ether and tetrahydrofuran were distilled from lithium aluminum hydride before use. Olefins were removed from hydrocarbon solvents by treatment with sulfuric acid, and the olefin-free hydrocarbons were purified by distillation from a suspension of sodium benzophenone ketyl before use. Dimethoxyethane was distilled from a solution of sodium benzophenone dianion before use. Methyl-, cyclopentyl-, *n*-butyl-, and *tert*-butyllithium reagents were supplied by Foote Mineral Corp. *sec*-Butyllithium was supplied by Alpha Inorganics, Inc. Grignard reagent solutions were analyzed following the procedure of Eastham,[31] and lithium reagents were analyzed by the Gilman double titration method.[32] All reactions involving organometallic reagents were carried out under prepurified nitrogen, using standard inert atmosphere techniques.[33]

(32) S. C. Watson and J. F. Eastham, *J. Organometal. Chem.*, **9**, 165 (1967); H. Gilman, F. K. Cartledge, and S.-Y. Sim, *ibid.*, **1**, 8 (1963); G. M. Whitesides, C. P. Casey, and J. K. Krieger, *J. Amer. Chem. Soc.*, **93**, 1379 (1971).

(33) D. F. Shriver, "The Manipulation of Air-Sensitive Compounds," McGraw-Hill, New York, N. Y., 1969, Chapter 7.

(34) O. Diels and K. Alder, *Justus Liebigs Ann. Chem.*, **460**, 117 (1928).

(35) C. D. VerNooy and C. S. Rondestvedt, *J. Amer. Chem. Soc.*, **77**, 3583 (1955).

(28) Similar stereochemical results have been obtained by F. Naf and P. Degen, *Helv. Chim. Acta*, **54**, 1939 (1971); F. Naf, P. Degen, and G. Ohloff, *ibid.*, **55**, 82 (1972).

(29) J. A. Marshall and R. A. Ruden, *Tetrahedron Lett.*, 2875 (1971); J. Hooz and R. B. Layton, *Can. J. Chem.*, **48**, 1626 (1970).

(30) For pertinent proposals concerning the mechanism by which copper acts as a catalyst in decarboxylation of aromatic acids, see T. Cohen and R. A. Schambach, *J. Amer. Chem. Soc.*, **92**, 3189 (1970); A. Cairncross, J. R. Roland, R. M. Henderson, and W. A. Sheppard, *ibid.*, **92**, 3187 (1970). If the catalytic activity of copper(I) in conjugate addition reactions is

mp 63.5–65.5° (lit.[25] mp 64–66°). The major part of the acid was not recrystallized, but was stored at −25° until use.

Methyl Norborn-5-ene-2-carboxylate.—Norborn-5-ene-2-carboxylic acid (370 g, 2.68 mol, a mixture of epimers) was added to 1300 g of absolute methanol containing 7 ml of concentrated sulfuric acid, and the resulting solution was refluxed for 5 hr. The solution was diluted with 1 l. of water, and the aqueous phase was extracted with four 200-ml portions of diethyl ether. The combined ether extracts were washed with 50 ml of a saturated aqueous solution of sodium bicarbonate and two 50-ml portions of water, and dried (MgSO₄). Distillation gave methyl norborn-5-ene-2-carboxylate (300 g, 73%): bp 70° (8 Torr) [lit.[36] bp 63.5° (5 Torr)]; nmr (CCl₄) δ 5.8–6.3 (2, m), 3.65 (1.1, s), 3.58 (1.9, s), 1.0–3.4 (7, various multiplets).

Epimerization of Methyl Norborn-5-ene-2-carboxylate.—Methyl norborn-5-ene-2-carboxylate (330 g, 2.31 mol, predominantly the endo epimer) was added to a solution of sodium methoxide (185 g, 3.43 mol) in ca. 800 ml of methanol, and the mixture was refluxed for ca. 50 hr, at which time it appeared to have partially polymerized to a thick gel. Solvent was removed by distillation, and 500 ml of water was added to the resulting solids. Distillation of residual methanol, with periodic addition of water, was carried out until the boiling point of the distillate reached 95°. The distillation residue was then cooled, its acidity was adjusted to pH 3 with hydrochloric acid, and it was extracted with three 50-ml portions of diethyl ether. The combined ether portions were washed with 100 ml of water, dried (MgSO₄), and distilled to give 159 g of norborn-5-ene-2-carboxylic acid. The acid was shown to contain ca. 60% of the exo epimer by nmr spectroscopy. An additional 100 g of methyl norborn-5-ene-2-carboxylate, shown to be ca. 70% exo epimer by nmr spectroscopy, was recovered from the initial water and methanol distillate.

***exo*-2-Norbornylcarboxylic Acid.**—Norborn-5-ene-2-carboxylic acid (obtained from epimerization of methyl norborn-5-ene-2-carboxylate, ca. 60% exo, 157 g, 1.10 mol) was dissolved in 1 equiv of 30% aqueous sodium hydroxide solution. Sodium bicarbonate (5.0 g, 0.04 mol) was added, followed by a solution of iodine (132 g, 0.52 mol) in ca. 500 ml of a saturated solution of aqueous potassium iodide.[37] The mixture was shaken for 15 min, and the resulting heterogeneous mixture was extracted with four 250-ml portions of diethyl ether. The combined ether fractions were worked up as described above to obtain the iodolactone. The aqueous phase was treated with sodium thiosulfate until colorless, made acidic (pH 3) with hydrochloric acid, and extracted with three 250-ml portions of diethyl ether. The combined ether extracts were washed with 100 ml of water, dried (MgSO₄), and distilled, yielding norborn-5-ene-*exo*-2-carboxylic acid (88 g, ca. 96%), bp 85° (0.05 Torr) [lit.[25] bp 134° (16 Torr)]. The distilled acid was washed with 5 ml of a saturated solution of sodium thiosulfate and with 5 ml of water, and dried (MgSO₄). Recrystallization from *n*-hexane gave pure norborn-5-ene-*exo*-2-carboxylic acid, mp 43.0–44.5° (lit.[25] mp 44.0–45.0°). Norborn-5-ene-*exo*-2-carboxylic acid (12.2 g, 0.0885 mol) was dissolved in 10 ml of ethyl acetate, and the solution was mixed with palladium on charcoal (10%, 0.5 g, 4 wt %). The mixture was charged into a Parr hydrogenation apparatus, and was hydrogenated at 40 psi until no pressure drop was observed for 1.5 hr. The resulting solution was filtered to remove the catalyst, and solvent was removed using a rotary evaporator to give crude *exo*-2-norbornylcarboxylic acid (12.2 g, 99%). Recrystallization from *n*-hexane gave pure *exo*-2-norbornylcarboxylic acid: mp 57–58° (lit.[25] mp 57–58.5°); nmr (CCl₄) δ 12.2 (s, 1), 2.57 (m, 1), 2.29 (m, 2), 1.20–2.00 (m, 8).

***endo*-2-Norbornyl Methyl Ketone.**—*endo*-2-Norbornylcarboxylic acid (17.1 g, 0.124 mol) was dissolved in 150 ml of dimethoxyethane, and the solution was transferred to a three-necked 500-ml flask fitted with a reflux condenser and mechanical stirrer. Methyllithium (1.68 N, 148 ml, 0.248 mol) was added dropwise through a cannula at a rate that maintained the solution at gentle reflux. The mixture was refluxed with external heating for 18 hr after the addition was completed, and was then transferred cautiously into 500 ml of a stirred solution of saturated aqueous ammonium chloride. The water and ether layers were separated, and the aqueous phase was extracted with three 100-ml portions of diethyl ether. The combined organic fractions were washed with

25 ml of water and dried (Na₂SO₄). Distillation gave *endo*-2-norbornyl methyl ketone (10.1 g, 60%), bp 53° (2.5 Torr) [lit.[38] bp 91° (30 Torr)]. Glpc analysis showed the ketone to be ca. 90% pure, and samples were collected by glpc for spectral and elemental analyses. Pure samples had nmr (CCl₄) δ 2.65–2.97 (m, 2), 2.23 (m, 1), 2.03 (s, 3), 1.10–1.70 (m, 8); ir (CCl₄) 2940, 2860, 1705, 1450, 1350, 1305, 1190, 1176, 1166, 1110, 947 cm⁻¹; mass spectrum *m/e* (rel intensity): 138 (5), 120 (8), 105 (8), 95 (53), 80 (51), 71 (74), 67 (57), 43 (100).

Anal. Calcd for C₉H₁₄O: C, 78.21; H, 10.21. Found: C, 78.50; H, 10.46.

***exo*-2-Norbornyl Methyl Ketone.**—*exo*-2-Norbornylcarboxylic acid (12.0 g, 85.7 mmol) was dissolved in 20 ml of DME and dried over molecular sieves for 1C hr. The solution of the acid was transferred to a three-necked, 1-l., round-bottomed flask fitted with a dropping funnel, condenser, and mechanical stirrer, and was diluted with an additional 80 ml of DME. Methyllithium (1.68 N, 102 ml, 171 mmol) was transferred into the addition funnel, and added to the acid solution at a rate sufficient to maintain gentle reflux. The reaction mixture was heated to reflux for 15 hr after addition had been completed, and was then transferred rapidly through a cannula into 300 ml of a stirred saturated aqueous solution of ammonium chloride. The resulting aqueous and organic phases were separated, and the aqueous phase was extracted with two 100-ml portions of diethyl ether. The combined ether fractions were washed with 25 ml of water and dried (Na₂SO₄). Distillation gave *exo*-2-norbornyl methyl ketone (7.0 g, 59%), bp 56° (3.0 mm) [lit.[38] bp 91° (30 mm)]. Samples were collected by glpc for analyses: nmr (CCl₄) δ 2.25–2.39 (m, 3), 2.08 (s, 3), 1.03–1.90 (m, 8); ir (CCl₄) 2940, 2860, 1710, 1450, 1355, 1310, 1175, 1060 cm⁻¹; mass spectrum *m/e* (rel intensity) 138 (4), 95 (100), 80 (13), 71 (33), 67 (55), 43 (84).

Anal. Calcd for C₉H₁₄O: C, 78.21; H, 10.21. Found, C, 78.12; H, 10.35.

Ethyl 3-(*exo*-2-Norbornyl)but-2-enoate (5).—Triethyl phosphonoacetate[39] (5.55 g, 25.0 mmol) was added slowly to a slurry of sodium hydride (0.600 g, 25.0 mmol) in 50 ml of DME, and the mixture was heated to 50° until the sodium hydride had reacted. *exo*-2-Norbornyl methyl ketone (3.5 g, 25.3 mmol) was added to the solution, and the reaction mixture was stirred at 55° for 16 hr. The reaction mixture was poured into 300 ml of water, and the resulting aqueous phase was extracted with two 50-ml portions of diethyl ether. The combined ether fractions were washed with 20 ml of water, dried (Na₂SO₄), and distilled to yield ethyl 3-(*exo*-2-norbornyl)but-2-enoate (3.0 g, 57%): bp 70° (0.06 Torr); nmr (CCl₄) δ 5.51 (m, 1), 4.04 (q, 2), 1.98–2.35 (m, 3), 2.08 (d, 3), 1.25 (t, 3), 1.02–1.80 (m, 8); ir (CCl₄) 2935, 2860, 1720, 1645, 1450, 1370, 1325, 1265, 1170, 1150, 1050 cm⁻¹.

Ethyl 3-(*endo*-2-Norbornyl)but-2-enoate.—Triethyl phosphonoacetate (10.6 g, 47.1 mmol) was added dropwise to a stirred slurry of sodium hydride (1.10 g, 45.8 mmol) in 100 ml of DME at 25°. The mixture was heated to 60° for 3 hr, and the remaining sodium hydride was allowed to settle. The supernatant solution was transferred to a clean, dry 250-ml round-bottomed flask, and was cooled to 10° in a water bath. *endo*-2-Norbornyl methyl ketone (6.50 g, 47.1 mmol) was added, and the resulting solution was stirred for 14 days at 10°. (A higher reaction temperature resulted in unacceptable epimerization of the starting ketone.) The reaction mixture was poured into 500 ml of water, and the resulting aqueous phase was extracted with two 100-ml portions of diethyl ether. The combined ether fractions were washed with 10 ml of water, dried (Na₂SO₄), and distilled to give ethyl 3-(*endo*-2-norbornyl)but-2-enoate (3.6 g, 27%), bp 85° (0.3 mm). Nmr spectroscopy indicated that the material was ca. 85% endo epimer and 15% exo epimer. Samples for analyses were collected by glpc: nmr (CCl₄) δ 5.63 (m, 1), 4.06 (q, 2), 2.22–2.67 (m, 3), 2.20 (d, 3), 1.25 (t, 3), 1.20–1.40 (m, 8); ir (CCl₄) 2945, 2860, 1710, 1638, 1450, 1360, 1310, 1260, 1210, 1145, 1070, 1035 cm⁻¹; mass spectrum *m/e* (rel intensity) 208 (15), 193 (6), 163 (14), 145 (23), 95 (44), 79 (46), 67 (92), 59 (80), 43 (68), 41 (100).

Anal. Calcd for C₁₃H₂₀O₂: C, 74.96; H, 9.68. Found: C, 74.68; H, 9.66.

4-Methyl-4-(*endo*-2-norbornyl)pentan-2-one (3).—Methyllithium (1.68 N, 35.4 ml, 60.0 mmol) was added to cuprous iodide

(36) J. D. Roberts, *et al., J. Amer. Chem. Soc.*, **72**, 3116 (1950).

(37) It is important to have only a slight excess of iodine, relative to the amount of endo epimer believed to be present, in order to avoid reactions involving the exo epimer.

(38) J. G. Dinwiddie, Jr., and S. P. McManus, *J. Org. Chem.*, **30**, 766 (1965).

(39) Triethyl phosphonoacetate was obtained commercially from Aldrich Chemical Co., and was used without further purification.

(6.05 g, 30.3 mmol) at $-30°$ in a 100-ml round-bottomed flask, and the mixture was warmed to room temperature after the cuprous iodide had dissolved. Ethyl 3-(endo-2-norbornyl)but-2-enoate (ca. 85% endo, 0.9174 g, 4.58 mmol) was added slowly, and the reaction was stirred for 36 hr at 25°. The reaction was quenched in 500 ml of a saturated aqueous solution of ammonium chloride, and the aqueous and ether phases were separated. The aqueous phase was extracted with three 50-ml portions of diethyl ether, and the combined ether fractions were washed with 20 ml of water, dried (Na_2SO_4), and distilled to give a mixture of 4 and 3 (0.405 g, ca. 45%), bp 60° (0.05 mm). The nmr spectrum indicated that the material was ca. 70% endo epimer and 30% exo epimer, and this conclusion was verified by glpc analysis. Samples of 3 were purified by glpc for analyses: nmr (CCl_4) δ 2.28 (s, 2), 2.22 (m, 2), 2.03 (s, 3), 1.08–2.00 (m, 9), 1.04 (s, 3), 0.98 (s, 3); ir (CCl_4) 2940, 2860, 1715, 1460, 1380, 1350, 1300, 1200, 1150 cm^{-1}; mass spectrum m/e (rel intensity) 194 (1), 136 (21), 107 (20), 95 (35), 67 (26), 43 (100).

Anal. Calcd for $C_{13}H_{22}O$: C, 80.46; H, 11.33. Found: C, 80.44; H, 11.18.

4-Methyl-4-(exo-2-norbornyl)pentan-2-one (4).—Methyllithium (1.68 N, 47.7 ml, 80.6 mmol) was added to cuprous iodide (9.01 g, 47.3 mmol) at 0° in a 100-ml flask fitted with a magnetic stirring bar, and the mixture was stirred at 0° until solution of this cuprous iodide was completed. The resulting lithium dimethylcuprate was warmed to 25°, and ethyl 3-(exo-2-norbornyl)but-2-enoate (ca. 2.0 g, 9.7 mmol) was added by syringe. The solution was stirred for 24 hr at 25°, and was then poured into 300 ml of a saturated aqueous solution of ammonium chloride. The aqueous and ether phases were separated, and the aqueous phase was extracted with two 50-ml portions of diethyl ether. The combined ether fractions were washed with 20 ml of water, dried ($MgSO_4$), and distilled to give 4-(exo-2-norbornyl)-4-methyl-2-pentanone (0.90 g, ca. 50%), bp 60° (0.05 Torr). Samples were collected by glpc for analyses: nmr (CCl_4) δ 2.21 (s, 2), 2.08 (m, 2), 2.06 (s, 3), 1.00–1.52 (m, 9), 0.93 (s, 3), 0.87 (s, 3); ir (CCl_4) 2950, 2870, 1715, 1460, 1380, 1360, 1350, 1295, 1205, 1140, 1020 cm^{-1}; mass spectrum m/e (rel intensity) 136 (18), 121 (5), 107 (16), 95 (49), 67 (28), 43 (100).

Anal. Calcd for $C_{13}H_{22}O$: C, 80.46; H, 11.33. Found: C, 80.62; H, 11.14.

endo-2-Norbornylmagnesium bromide (endo-1) was prepared following the description of Jensen and Nakamaye.[22] An equilibrium mixture of diastereomers of 2-norbornylmagnesium bromide (20 ml, 1.175 N, 23.5 mmol) was cooled to $-70°$ in a 40-ml centrifuge tube capped with a No-air stopper and containing a magnetic stirring bar. The tube containing the Grignard reagent solution was removed from the cold bath and was stirred vigorously as a solution of benzophenone in ether (7.40 ml, 1.91 N, 14.1 mmol) was injected into it using a syringe. The reaction mixture was stirred at ambient temperature for ca. 1 min, the tube was transferred to a centrifuge, and the precipitated solids were compacted by centrifugation. The clear, deep red solution of endo-2-norbornylmagnesium bromide was transferred to a clean, dry centrifuge tube by cannula, cooled to $-78°$, and titrated.[31] The Grignard reagent solution was stored at $-78°$ until used. Analysis of the diastereomeric composition of the solution by conversion first to 2 and then to 2-methylnorbornane (*vide infra*) indicated that it contained >99.5% endo diastereomer.

Copper-Catalyzed Conjugate Addition of 1 to Mesityl Oxide.—Bromo(tri-n-butylphosphine)copper(I) (0.0186 g, 0.0538 mmol) and n-heptadecane (0.0770 g, 0.321 mmol, an internal glpc standard) were weighed into a 40-ml centrifuge tube and dissolved in 20 ml of diethyl ether. The solution was cooled to $-78°$, and 2-norbornylmagnesium bromide (1.175 N, 0.853 ml, 1.00 mmol) was added by syringe. The resulting solution was warmed to 0°, and mesityl oxide (0.098 g, 1.00 mmol) was added by syringe. The reaction was stirred for 2 hr at 0°, and then poured into 100 ml of a saturated aqueous solution of ammonium chloride. The aqueous and ether layers were separated, and the aqueous phase was extracted with two 20-ml portions of diethyl ether. The combined ether fractions were washed with 10 ml of water and dried ($MgSO_4$). Analyses for total yields of 3 and 4 were carried out on a 6 ft × 0.125 in. 10% UC-W98 on Chromosorb P column at 140°. For analyses of relative yields of 3 and 4, the unresolved peak corresponding to these materials was collected from an 8 ft × 0.25 in. UC-W98 column at 180° and reanalyzed on a 48 ft × 0.125 in. 1% SE-30 column. Results of these experiments are summarized in Tables I and II.

Conjugate Addition of 2-Norbornyl(tri-n-butylphosphine)-copper(I) (2) to Mesityl Oxide.—Bromo(tri-n-butylphosphine)-copper(I) (0.345 g, 1.00 mmol), tri-n-butylphosphine (0.404 g, 2.00 mmol), and n-heptadecane (0.0859 g, 0.358 mmol) were weighed into a 40-ml centrifuge tube capped with a No-air stopper, and dissolved in 20 ml of diethyl ether. The solution was cooled to $-78°$, and 2-norbornylmagnesium bromide (1.175 N, 0.853 ml, 1.00 mmol) was added by syringe. The resulting solution was warmed to 0°, and mesityl oxide (0.098 g, 1.00 mmol) was added by syringe. The reaction was stirred for 2 hr at 0° and then poured into 100 ml of a saturated aqueous solution of ammonium chloride. The aqueous and ether layers were separated, and the aqueous phase was extracted with two 20-ml portions of diethyl ether. The combined ether fractions were washed with 10 ml of water and dried ($MgSO_4$). Analyses were carried out as described previously.

Conjugate Addition of Lithium Alkyl(2-norbornyl)cuprates to Mesityl Oxide.—Iodo(tri-n-butylphosphine)copper(I) (0.396 g, 1.01 mmol) and n-heptadecane (0.0816 g, 0.340 mmol) were weighed into a 40-ml centrifuge tube capped with a No-air stopper and dissolved in 20 ml of diethyl ether. The solution was cooled to $-78°$, and 2-norbornylmagnesium bromide (1.175 N, 0.853 ml, 1.00 mmol) was added. The solution was mixed, and the appropriate alkyllithium reagent (1.05 mmol) was added by syringe. The resulting solution was warmed to 0° with stirring, and mesityl oxide (0.103 g, 1.05 mmol) was added by syringe. The reaction mixture was stirred at 0° for 2 hr and then poured into 100 ml of a saturated aqueous solution of ammonium chloride. The aqueous and ether layers were separated, and the aqueous phase was extracted with two 20-ml portions of diethyl ether. The combined ether fractions were washed with 10 ml of water and dried ($MgSO_4$). Analyses were carried out as described above.

Attempted conjugate additions of tri-exo-2-norbornylborane to mesityl oxide, carried out using ca. 8 mmol of borane, 10–20 mmol of mesityl oxide, and 10–20 mmol of water, with oxygen or irradiation (3000- and 3500-Å lamps in a Rayonet photochemical reactor) for initiation failed over reaction times of up to 48 hr.

Bis(triphenylphosphine)(ethylene)platinum(0) (72.0 mg, 50%), mp 121–124° (lit.[36] mp 122–125°), was obtained from ethylene and bis(triphenylphosphine)platinum(II) oxide following the procedure of Cook.[40]

Bis(triphenylphosphine)(ethylene)nickel(0) (2.34 g, 73%) was obtained from bis(acetylacetonato)nickel(II), ethylene, and triphenylphosphine following the procedure of Wilke.[41]

Attempts of catalyze the conjugate addition of 1 to mesityl oxide using catalysts other than copper were carried out using the same procedure as described above; the results of these experiments are summarized in Table I.

Bromobis(trimethyl phosphite)copper(I).—Trimethyl phosphite (46.7 g, 0.376 mol) was mixed with a slurry of cuprous bromide (27.0 g, 0.187 mol) in 200 ml of diethyl ether. The ether solution was refluxed for 30 min and filtered while hot. The resulting solution was cooled to 0°, at which temperature bromobis(trimethyl phosphite)copper(I) precipitated. The crude complex was recrystallized from 400 ml of diethyl ether to give 49.7 g (68%) of bromobis(trimethyl phosphite)copper(I), mp 61.0–62.5°, nmr (CCl_4) δ 3.68 (d, $J = 10.6$ Hz).

Anal. Calcd for $C_6H_{18}BrCuO_6P_2$: C, 18.40; H, 4.63; Br, 20.40. Found: C, 18.98; H, 4.86; Br, 19.68.

Analysis of the Diastereomeric Composition of Mixtures of endo- and exo-2.—Samples of 2 in an ethereal solvent containing ca. 0.25 mmol of organocopper reagent were transferred through a cannula into a clean 40-ml centrifuge tube held immersed in a Dry Ice–acetone bath. Methyllithium (ca. 5 equiv, in ether) and nitrobenzene (ca. 1 ml) were added in succession to the tube by syringe. The oxidation reaction appeared to be complete on mixing. Samples of the reaction mixture were injected directly onto an 8 ft × 0.25 in. 20% UC-W98 on Chromosorb P column at 110°, and the unresolved peaks due to the diastereomeric 2-methylnorbornanes were collected. This mixture of diastereomers was diluted in ca. 250 μl of solvent, and analyzed for diastereomeric composition by glpc on a 48 ft × 0.25 in. 1% SE-30 column at 65°. Under these conditions, the endo-2-methylnorbornane has the longer retention time.

Epimerization of endo-2-Norbornyl(tri-n-butylphosphine)copper(I) (2).—A solution of endo-2 was prepared and shown to con-

(40) C. D. Cook and G. S. Jauhal, *J. Amer. Chem. Soc.*, **90**, 1464 (1968).

(41) G. Wilke and G. Herrmann, *Angew. Chem.*, **74**, 693 (1962).

tain >99.5% endo diastereomer. Equal portions of this solution were transferred into two 40-ml centrifuge tubes containing magnetic stirring bars immersed in a Dry Ice–acetone bath. The tubes were warmed to 0° with stirring. Mesityl oxide (0.5 equiv) was added to one tube. Aliquots from both solutions were taken periodically by transferring into 40-ml centrifuge tubes held at Dry Ice temperatures. These aliquots were analyzed for the diastereomeric content of the remaining **2**. Immediately after warming to 0°, the diastereomeric purity of the **2** in the solution not containing mesityl oxide was 98.5%; after standing for 5 min at 0°, it was 97.1%. The sample containing mesityl oxide contained **2** that was 98.6% endo immediately after warming to 0°, 99.5% after 1 min at 0°, and 93.7% after 15 min.

Competition of a Mixture of *endo*- and *exo*-2 for Limiting Quantities of Mesityl Oxide.—An epimeric mixture of **2** was prepared at −78° and was shown to be 74% endo and 26% exo. Aliquots calculated to contain 1.19 mmol of **2** were transferred to 40-ml centrifuge tubes and warmed to 0°. Calculated amounts of mesityl oxide were added, and the reaction mixtures were stirred at 0° for *ca.* 2 min. The reaction mixtures were then cooled to −78°, and the remaining **2** was analyzed for epimeric composition

by treatment with methyllithium and oxidation with nitrobenzene. The conjugate additions of **2** and of lithium methyl-2-norbornylcuprate to mesityl oxide at −78° are very slow. The results of these experiments are as follows: for 0.250 equiv of mesityl oxide/equiv of **2**, the epimeric composition of the **2** remaining after quenching was 67.8% endo; for 0.336 equiv, 69.6% endo; for 0.505 equiv, 74.8% endo; for 0.675 equiv, 77.6% endo.

The Reaction of Steroidal 3-Keto-19-carboxylic Acids and 19-Nor Steroidal Dienones in Solutions of Iodine in Pyridine[1]

FRANCISCO S. ALVAREZ* AND ALEXANDER N. WATT

Institute of Organic Chemistry, Syntex Research, Palo Alto, California 94304

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The treatment of 3,17-dioxoestr-4-en-19-oic acid (**1**) with iodine in pyridine yielded estra-4,9-diene-3,17-dione (**6**). This compound reacted further with iodine to give 3-hydroxyestra-1,3,5(10),9(11)-tetraen-17-one (**7**). The reaction of estra-4,6-diene-3,17-dione (**11**) under the same conditions afforded 3-hydroxyestra-1,3,5(10),6-tetraen-17-one (**12**). When 3,17-dioxoandrosta-4,6-dien-19-oic acid (**10**), 3,17-dioxo-5α-androstan-19-oic acid (**16**), and 3,17-dioxo-5β-androstan-19-oic acid (**16a**) were treated with iodine in pyridine, they yielded, respectively, the lactones **15**, **17**, and **17a**. Pyridine–iodine appears to be a new reagent capable of yielding γ-lactones and unsaturated phenols from suitable γ-keto carboxylic acids and conjugated dienones. A deviation from the helicity rule of the homoannular diene **13a** is reported.

In 1960 Hagimara, *et al.*,[2] reported that treatment of androst-4-ene-3,17-dion-19-oic acid (**1**) in hot pyridine solution afforded estr-5(10)-ene-3,17-dione (**2**) in almost quantitative yield. Subsequently, Perelman, *et al.*,[3] reported the synthesis of estra-4,9-diene-3,17-dione (**6**) in unspecified yield by the reaction of estr-5(10)-ene-3,17-dione (**2**) with bromine in pyridine solution. These authors reported that pyridine is unique in transforming the resulting 5,10-dibromo · intermediate into the dienone **6** instead of phenolic products, obtained when the reaction is carried out in other solvents.

The possibility of obtaining the dienone **6** in a single reaction by decarboxylation of the acid **1** in pyridine solution in the presence of halogen was considered. This type of decarboxylation should produce the intermediate enol **4** *via* the anion **3**, which in principle may be "trapped" by an electrophilic reagent, such as positive halogen.[4]

With this aim, the following transformations were

carried out. Reaction of androst-4-ene-3,17-dion-19-oic acid (**1**) in pyridine solution with 1 mol of iodine at 60–65° led to an immediate evolution of carbon dioxide and formation of a heavy crystalline precipitate of pyridine hydriodide. After isolation of the products, an oil with strong ultraviolet absorption at 302 mμ, characteristic of a $\Delta^{4,9}$-3-ketone chromophore,[3] was obtained. Purification of the reaction mixture by elution chromatography on activated alumina yielded 59% of estra-4,9-diene-3,17-dione (**6**).

Under the conditions of the experiment, the C-10 iodo derivative **5** (X = I) (probably with the 10β configuration) proved to be unstable, decomposing rapidly with elimination of 1 mol of hydrogen iodide to produce the dienone **6**. In the more polar fractions, a mixture of ring A phenolic steroids with ultraviolet absorption at 264 mμ was obtained, suggesting the presence of an estra-1,3,5,9(11)-tetraene chromophore. Apparently estra-4,9-diene-3,17-dione (**6**) undergoes further attack by iodine, the intermediate iodo compound being transformed into 3-hydroxyestra-1,3,5,9-(11)-tetraen-17-one (**7**) by elimination and rearrangement. To support this proposal, the following experiments were carried out. Treatment of the dienone **6** with 1 mol of iodine in pyridine solution at reflux for 6 hr yielded 48% of 3-hydroxyestra-1,3,5,9(11)-tetraen-17-one (**7**). Treatment of the acid **1** with 2 mol of iodine in refluxing pyridine afforded the $\Delta^{9(11)}$ compound **7** in 30% yield. This appears to be the first example of

(1) This paper represents Contribution No. 389 from Syntex Research, Institute of Organic Chemistry, Palo Alto, Calif.

(2) H. Hagimara, S. Noguchi, and M. Nishikama, *Chem. Pharm. Bull.*, **8**, 84 (1960).

(3) M. Perelman, E. Farkas, E. S. Fornefeld, R. S. Kraay, and R. T. Rapala, *J. Amer. Chem. Soc.*, **82**, 2402 (1960).

(4) K. S. Pedersen, *ibid.*, **51**, 2098 (1929); **58**, 250 (1936); F. S. Fawcet, *Chem. Rev.*, **47**, 219 (1950). For a similar type of trapping of carbanion intermediates derived from carboxylic acids having strong electron-attracting groups, see K. S. Pedersen, *J. Phys. Chem.*, **38**, 559 (1934).

1 → 2

3   4

5

7   6
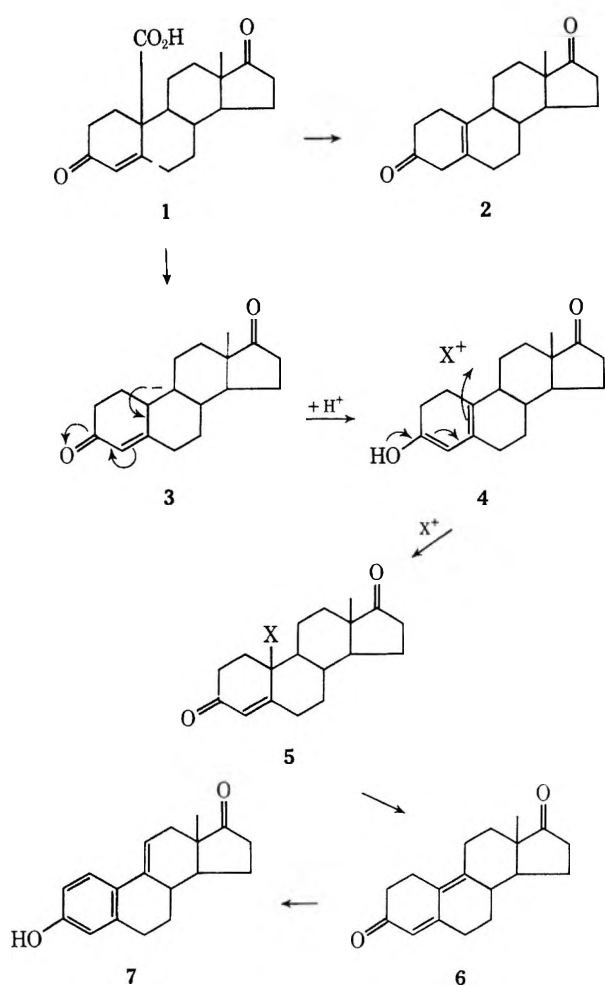
a one-step transformation of a C-19 steroid into an estra-1,3,5,9-(11)-tetraene derivative.[5]

Because of alternate possibilities of enolization of the dienone 6, it is uncertain whether electrophilic attack by iodine takes place at C-2 or C-11. In either case, subsequent elimination and rearrangement can yield the $\Delta^{9(11)}$ derivative 7.

19-Hydroxyandrost-4-ene-3,17-dione[6] (8) was dehydrogenated with chloranil in refluxing *tert*-butyl alcohol to yield 19-hydroxyandrosta-4,6-diene-3,17-dione (9) in 50% yield. Oxidation of this material in acetone–dichloromethane solution with Jones reagent yielded 3,17-dioxoestra-4,6-dien-19-oic acid[7] (10) in good yield. Decarboxylation of this material in refluxing methanol containing hydrochloric acid afforded estra-4,6-diene-3,17-dione (11).

When estra-4,6-diene-3,17-dione (11) was treated with iodine in pyridine as described before, estra-1,3,5(10),6-tetraen-17-one (12) was obtained in moderate yield.

(5) (a) The transformation of steroidal $\Delta^{1,4,9(11)}$-3 ketones into estra-1,3,5(10),9(11)-3-ol derivatives has been described; *cf.* K. Tsuda, E. Ohki, and S. Nozoe, *J. Org. Chem.*, **28**, 783, 786, 789, 795 (1963). However, the $\Delta^{9(11)}$ double bond was already present in the starting material. (b) Farkas and Owen have reported the transformation of 9α,10α-oxidoestr-4-en-17β-ol-3-one into estra-1,3,5(10),9(11)-tetraene-3,17β-diol under acidic conditions; *cf.* E. Farkas and J. M. Owen, *J. Med. Chem.*, **9**, 510 (1966).

(6) A. Bowers, R. Villotti, J. A. Edwards, E. Denot, and O. Halpern, *J. Amer. Chem. Soc.*, **84**, 3204 (1962).

(7) When this work was completed, a paper appeared in the literature describing the transformation of 19-hydroxyandrosta-4,6-diene-3,17-dione (9) into estra-5(10),6-diene-3,17-dione (13) and estra-4,6-diene-3,17-dione (11) by procedures similar to the ones described here; *cf.* J. Kalvoda and G. Anner, *Helv. Chim. Acta*, **50**, 269 (1967).

11, R = R' = O

11a, R = OH/H >; R' = H/HO > and H/HO >

9   8

10

13, R = R' = O

13a, R = H/HO >; R' = H/HO >
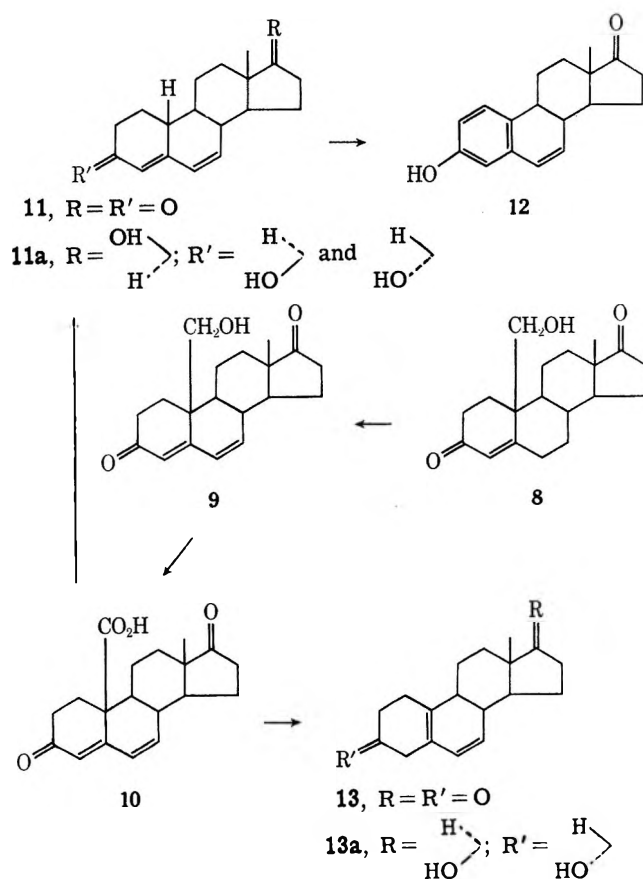
Treatment of androsta-4,6-diene-3,17-dion-19-oic acid (10) in pyridine solution at 60–65° yielded 60% of crude estra-5(10),6-diene-3,17-dione[7] (13). Thin layer chromatography showed that the product was contaminated with about 5% of estra-4,6-diene-3,17-dione (11). Reduction of 13 with lithium tri-*tert*-butoxyaluminum hydride and purification by preparative tlc yielded 3α,17β-dihydroxyestra-5(10),6-diene (13a). The ultraviolet absorption at 264 mμ (ε 4274) is compatible with the homoannular diene chromophore.[8] The nmr spectrum shows two resonances for chemically equivalent protons as a singlet at 5.63 ppm in support of structure 13a.

Examination of Dreiding models for the homoannular diene 13a shows a positive helix formed by the C_{10}–C_5–C_6–C_7 carbon chain, and consequently a positive Cotton effect was expected for this system.[9] Experimentally, the Cotton effect was found to be negative.[10] In order to determine if contamination of the homoannular diene 13a with the diene 11a is responsible for this unexpected result, the latter compound was prepared by reduction of the dienone 11 with lithium tri-*tert*-butoxyaluminum hydride. However, its Cotton effect was also negative, although of a much smaller magnitude (see Experimental Section) than that observed for 13a. The variance of the helicity rule with experimental observation has already been reported by Beechmann and Mathieson.[10]

Having established that the carboxylic acid 10 is capable of being transformed into the nonconjugated

(8) L. Dorfman, *Chem. Rev.*, **53**, 47 (1953).

(9) P. Crabbé, "Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry," Holden-Day, San Francisco, Calif., 1965, Chapter 10.

(10) A. F. Beechmann and A. Mc. L. Mathieson, *Tetrahedron Lett.*, 3139 (1966). These authors determined the absolute chilarity of gliotoxin by X-ray analysis and found that a "left-handed twist" is associated with a strong positive Cotton effect.

ketone **13**, the following experiments were carried out in order to "trap" the intermediate trienol **14**, as in the preceding transformations.

14   **15**

16, 5α-H
16a, 5β-H

17, 5α-H; R = R' = O
17a, 5β-H; R = R' = O

17b, 5α-H; R = (CH₃O / CH₃O); R' = O

17c, 5β-H; R = (CH₃O / CH₃O); R' = O

17d, 5α-H; R = O; R' = (H / HO)

17e, 5β-H; R = O; R' = (H / HO)

17f, 5β-H; R = (CH₃O / CH₃O); R' = (H / HO)

18, 5α-H; R = H
18b, 5α-H; R = Ac
18c, 5β-H; R = H
18d, 5β-H; R = Ac
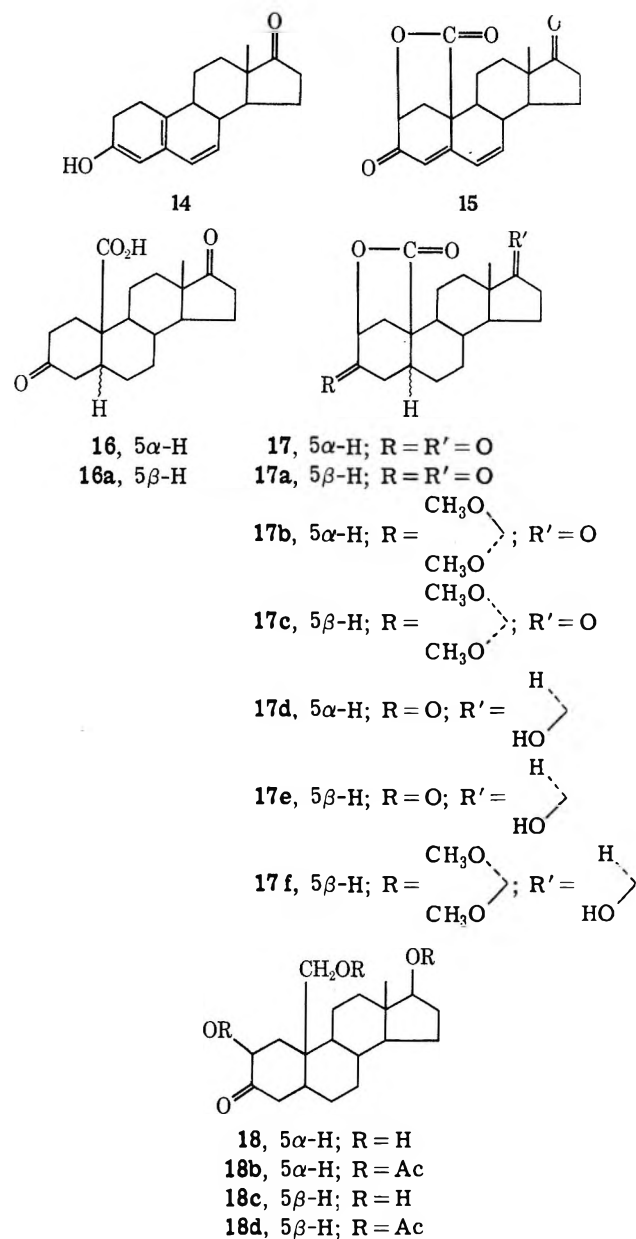
When 3,17-dioxoandrosta-4,6-dien-19-oic acid (**10**) was treated at room temperature with 1 mol of iodine in pyridine, a complex mixture was obtained. Resolution of this mixture by chromatography on silica gel yielded ring A phenolic steroids and estra-4,6-diene-3,17-dione (**11**) in addition to the major compound isolated in 60% yield. The presence of a carbonyl band at 1775 cm⁻¹ in the infrared spectra of the latter product suggested the presence of a γ-lactone, *e.g.*, **15**. The nmr spectrum shows a narrow multiplet at 6.5–6.6 ppm characteristic of an equatorial proton attached to a carbon bearing oxygen. This is consistent with a lactone structure and suggests intramolecular attack by the carboxylate anion, most probably at C-2. A reasonable path may involve initial formation of a C-19 hypoiodite function, followed by hydrogen abstraction and ring closure. However, the possibility of iodination at C-2, followed by ring closure, is not excluded.

Two physical characteristics of **15** are worth noting.

A. The observed 9-mμ bathochromic shift in the ultraviolet absorption spectra shown by **15**, as compared with the precursor Δ⁴,⁶-3-keto 19-oic acid (**10**), suggests the existence of electronic interaction between the lactone and the Δ⁴,⁶-3-keto group.

B. The 7.8-Hz paramagnetic shift experienced by the C-18 protons of **15**, as compared to **10**, shows a deshielding effect of the carbonyl dipole of the lactone on these protons. Examination of Prentice Hall molecular orbital models shows that the C-18 methyl protons in structure **15** lie close to the plane of the C-19 trigonal carbon atom. Under these circumstances a deshielding effect should be expected.[11]

It is noteworthy that no evidence of a lactonization process was encountered on careful examination of the reaction mixture obtained from the treatment of androst-4-en-3,17-dion-19-oic acid (**1**) with iodine in pyridine solution. Even when this reaction was allowed to proceed at room temperature, only products derived from decarboxylation were present.

A more favorable situation for lactone formation would be expected with a 3-keto saturated C-19 carboxylic acid such as 5α- and 5β-androsta-3,17-dion-19-oic acids, since, with these compounds, the competitive decarboxylation process should be fully prevented, considering the mild reaction conditions used. In fact, when 5α-androsta-3,17-dion-19-oic acid[12] (**16**) was treated in pyridine solution with 1 mol of iodine at 60–65° for 2 hr, it was transformed in high yield into 3,17-dioxo-2β-hydroxy-5α-androstan-19-oic acid 2,19-lactone (**17**). This compound was previously prepared in low yield in a multistep process by Kwok and Wolff[13] *via* photolysis of the nitrite ester of 5α-androstane-2β,3α,17β-triol-3,17-diacetate.

When 3,17-dioxo-2β-hydroxyandrosta-4,6-dien-19-oic acid 2,19-lactone (**15**) was treated in ethanol solution with 5% Pd/C at a hydrogen pressure of 50 psi, it was transformed into **17**, identical in all respects with 3,17-dioxo-2β-hydroxy-5α-androstan-19-oic acid 2,19-lactone described above. This result yields conclusive evidence that structure **15** is correct for the lactone obtained from androsta-4,6-diene-3,17-dion-19-oic acid (**10**).

Similarly, reaction of 5β-androstane-3,17-dion-19-oic acid[12] (**16a**) with the iodine–pyridine reagent at 95–100° for 2 hr (no reaction occurred at 60–65°) gives a new lactone characterized as **17a**.

Examination of the Prentice Hall flexible molecular orbital models for the saturated 5β-19-oic acid **16a** shows that it can be closed to the lactone **17a**, provided that ring A and ring B are transformed into a boat conformation (see Scheme I). Under these circumstances the molecule is reasonably strain free, although the hydrogen atoms at C-1α–C-4α, C-1β–C-11β, and C-6α–C-9α are in an eclipsed conformation. This unusual structure containing three cis-fused rings[14] was confirmed as follows.

(11) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, London, 1959, pp 122–124.

(12) L. H. Knox, E. Blossey, H. Carpio, L. Cervantes, P. Crabbé, E. Verlarde, and J. A. Edwards, *J. Org. Chem.,* **30,** 2198 (1965)

(13) R. Kwok and M. Wolff, *ibid.,* **28,** 422 (1963).

(14) *Cf.* J. S. McKechnie and I. C. Paul, *J. Amer. Chem. Soc.,* **90,** 2144 (1968) for a structure containing three five-membered cis-fused rings.
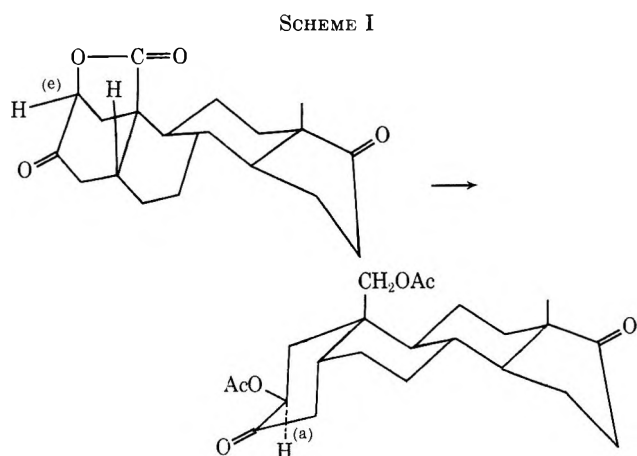
SCHEME I

Examination of the nmr spectrum of **17a** shows a narrow multiplet at 4.05–4.25 ppm, indicating an equatorial hydrogen attached to a carbon-bearing oxygen. Conversion of **17a** into the triacetate **18d** allows ring A to flip from boat to chair (Scheme I), producing a C-2 axial proton. The resonance of this proton should appear as an ABX system, as found[15] in the case of 2α-acetoxycholestanone.

When the lactone **17a** was treated with anhydrous methanol in the presence of perchloric acid, it was transformed smoothly into the C-3 methyl ketal **17c** which, on reduction with lithium aluminum hydride followed by acid hydrolysis, yielded 2β,17β-19-trihydroxy-5β-androstan-3-one (**18c**). This compound was transformed into its triacetate **18d** by acetic anhydride in pyridine.

The nmr spectrum of this triacetate shows the C-2 axial proton as a quartet at 5.14, 5.2, 5.27, and 5.34 ppm with coupling constants $J_{1\alpha,2\alpha}$ and $J_{1\beta,2\alpha}$ of 6.5 and 13.5 Hz. These results are in full agreement with the corresponding resonances in 2α-acetoxycholestanone and in agreement with the structure **17a**.
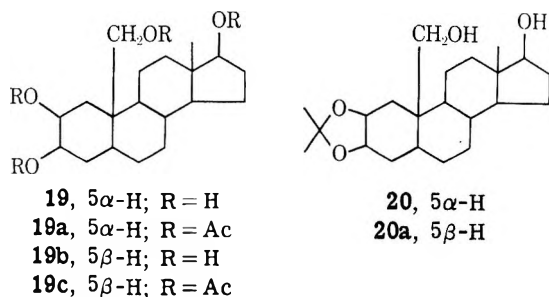
Reduction of lactones **17** and **17a** with lithium aluminum hydride yielded the 2β,3β,17β,19-tetrols **19** and **19b**, which were transformed into the corresponding

19, 5α-H; R = H	**20,** 5α-H
19a, 5α-H; R = Ac	**20a,** 5β-H
19b, 5β-H; R = H	
19c, 5β-H; R = Ac	

tetraacetates **19a** and **19c** in the usual manner. Treatment of the tetrols **19** and **19b** with acetone in the presence of p-toluenesulfonic acid afforded the acetonides **20** and **20a**, providing additional support for the vicinal oxygenation pattern at C-2 and C-3 in the lactones **17** and **17a**.

Lactones **17** and **17a** were transformed into the corresponding C-3 methyl ketals **17b** and **17c** by treatment with anhydrous methanol in the presence of strong

(15) K. L. Williamson and W. S. Johnson, *J. Amer. Chem. Soc.*, **83**, 4623 (1961).

acid. These ketals were reduced with sodium borohydride to yield the corresponding 17β alcohols, which, on acid hydrolysis, afforded the 3-keto 17β-hydroxy lactones **17d** and **17e**. Examination of the ORD curves for these lactones shows the correct Cotton effects for steroidal C-3 ketones epimeric at C-5[16] (see Experimental Section).

Experimental Section[17]

Estra-4,9-diene-3,17-dione (6).—A solution of 248.1 g of iodine in pyridine (previously distilled over potassium hydroxide) was prepared. To this solution, 294 g of androst-4-ene-3,17-dion-19-oic acid (**1**) was added, and the mixture was heated with stirring to 80° for 20 min. The mixture was cooled to room temperature and poured into a solution of 3 l. of concentrated hydrochloric acid in 30 l. of water. The resulting mixture was extracted three times with 2-l. portions of methylene chloride; the extracts were washed with water until neutral and concentrated to 1 l. at atmospheric pressure. The resulting extract was filtered through a column of 3 kg of washed alumina. The column was eluted with methylene chloride until no more product could be eluted. The eluates were concentrated to dryness under reduced pressure and the residue was crystallized from ethyl acetate–hexane to yield 150.7 g (59.5%) of **6**: mp 119–121°; $[\alpha]_D$ −134°; λ_{max}^{MeOH} 302 mμ (ε 19,400). A pure specimen was obtained after several crystallizations from ethyl acetate–hexane and showed mp 128–130° (reported[3] mp 130–131°).

3-Hydroxyestra-1,3,5,9(11)-tetraen-17-one (7). A.—A solution of 150 g of estra-4,9-diene-3,17-dione (**6**) in 1.5 l. of pyridine containing 150 g of iodine was refluxed for 6 hr. The mixture was cooled to room temperature and poured into 15 l. of water. The mixture was extracted three times with 2 l. of methylene chloride each time. The combined extracts were washed with excess 10% aqueous hydrochloric acid and then with water until neutral. The solution was dried with anhydrous sodium sulfate and the solvent was eliminated under reduced pressure. The residue was crystallized from methylene chloride–ether to yield 71 g of 3-hydroxyestra-1,3,5,9(11)-tetraen-17-one: mp 243–246°; $[\alpha]_D$ 265°; λ_{max}^{MeOH} 264 mμ (ε 18,120) [reported[6] mp 256–258°; λ_{max}^{MeOH} 262.5 mμ (ε 18,000)].

B.—Similarly, when 50 g of androst-4-en-3,17-dion-19-oic acid in 1000 ml of pyridine containing 100 g of iodine was refluxed for 6 hr and worked up as described above, 15.2 g of 3-hydroxyestra-1,3,5,9(11)-tetraen-17-one, mp 250–251°, was isolated. The material was shown to be identical with the material prepared previously.

19-Hydroxyandrosta-4,6-diene-3,17-dione (9).—A solution of 260 g of 19-hydroxyandrost-4-ene-3,17-dione[7] (**8**) in 2500 ml of *tert*-butyl alcohol was treated with 265 g of chloranil under reflux for 2 hr. The reaction mixture was cooled to room temperature and the precipitate of tetrachlorohydroquinone formed during the reaction was collected by filtration. The filtrate was concentrated under vacuum to dryness, and benzene was added at the end of the evaporation to help the elimination of the residual *tert*-butyl alcohol. The crystalline residue so obtained was taken up in 5 l. of dichloromethane and refluxed for 1 hr. The residual tetrachlorohydroquinone was filtered off and the filtrates were washed two times with 2.5 l. of 5% aqueous sodium hydroxide each time, then with water until neutral. The dichloromethane layer was dried with anhydrous sodium sulfate and decolorized with charcoal. The solution was concentrated to a small volume

(16) C. Djerassi, "Optical Rotatory Dispersion: Applications to Organic Chemistry," McGraw-Hill, New York, N. Y., 1960.

(17) Melting points are corrected. Optical rotations were measured in chloroform solution unless stated otherwise using an O. C. Rudolph and Sons Model 80 polarimeter. Ultraviolet spectra were measured in methanol using a Cary Model 14 spectrometer. Infrared spectra were measured using a Perkin-Elmer Model 137 spectrophotometer. Nmr spectra were recorded on Varian HA-100 and A-60 spectrometers using deuteriochloroform or DMSO-d_6 as solvent. Chemical shifts are recorded in parts per million. We wish to thank Mrs. J. Nelson for these measurements and Miss Irma Delfin for her able technical assistance. Optical rotatory dispersion (ORD) curves were measured in dioxane or methanol on a Jasco ORD/UV-5 spectrometer. Sufficient values are quoted to allow a rough curve to be plotted. Analytical tlc plates with a thickness of 0.25 mm silica gel GF$_{254}$ (E. Merk, A. G. Darmstadt) and preparative tlc plates with a thickness of 0.25 mm silica gel GF$_{254}$ were used.

and the material was crystallized by addition of methanol to yield 130 g of title compound. This material was crystallized once more from dichloromethane, affording 104 g of pure compound, mp 195–196°. The analytical sample was obtained after several crystallizations from dichloromethane: mp 197–198°; [α]D 128°; λ_{max}^{MeOH} 284 mμ (ε 26,650) [reported[7] mp 196–199°; [α]D 135.6°; λ_{max} 283 mμ (ε 25,400)]. *Anal.* Calcd for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05; O, 15.98. Found: C, 75.63; H, 7.97; O, 16.04.

3,17-Dioxoestra-4,6-dien-19-oic acid (10)[18] had mp 133–135° dec; [α]D 128°; λ_{max}^{MeOH} 287 mμ (ε 22,300) [reported[7] mp 134–135°; [α]D 125°; λ_{max} 287 mμ (ε 22,800)]. *Anal.* Calcd for $C_{19}H_{24}O_4$: C, 72.12; H, 7.65; O, 20.23. Found: C, 71.96; H, 7.81; O, 20.04.

Estra-4,6-diene-3,17-dione (11)[18] had mp 180–182°; [α]D 61°; λ_{max}^{MeOH} 282 mμ (ε 26,250) [reported[7] mp 181.5–182.5°; [α]D 58.3°; λ_{max} 282 mμ (ε 26,600)]. *Anal.* Calcd for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20; O, 11.84. Found: C, 80.01; H, 8.31; O, 12.01.

3α,17β-Dihydroxyestra-5(10),6-diene (13a).—A solution of 1 g of androst-4,6-diene-3,17-dion-19-oic acid (10) in 5 ml of pyridine was heated on the steam bath for 10 min. Evolution of carbon dioxide started almost at once. The reaction mixture was poured into 75 ml of water saturated with sodium chloride, and the solid material that precipitated was collected by filtration and washed with water. This compound was dried under vacuum over calcium chloride to yield 0.510 g of the crude homoannular dienone 13. Examination of this material on tlc in a 1:1 hexane–ethyl acetate system showed it to be contaminated with about 5% of the conjugated dienone 11. A solution of this compound in 5 ml of anhydrous tetrahydrofuran was treated with 2 g of lithium tri-*tert*-butoxyaluminum hydride at room temperature for 2 hr, then poured into 150 ml of 5% aqueous acetic acid. The mixture was extracted with ether; the combined extract was washed with water, dried over anhydrous sodium sulfate, and filtered. The solvent was evaporated under reduced pressure. The material thus obtained was dissolved in 75 ml of dichloromethane and filtered through 5 g of acid-washed alumina, eluting with the same solvent. The crystalline fractions were combined and purified on a preparative tlc plate to yield, after crystallization from acetone–hexane, 17.8 mg of pure title compound: mp 165–167°; ORD [Φ]₆₀₀ −272°, [Φ]₃₅₀ −1850°, [Φ]₂₉₃ −9900°, [Φ]₂₇₂ ±0°, [Φ]₂₄₀ 13,800°, [Φ]₂₁₁ 6260°; λ_{max} 265 mμ (ε 4274); ν_{max} 3410 (s), 726 cm⁻¹ (m); nmr (DMSO-d_6) 0.64 (18-H), 3.34–3.83 (3β- and 17α-H), 4.5 (2 OH), singlet at 5.63 ppm (6-H and 7-H). *Anal.* Calcd for $C_{18}H_{26}O_2$: C, 78.79; H, 9.55. Found: C, 78.84; H, 9.37.

3ξ,17β-Dihydroestra-4,6-diene (11a).—Similarly, 11a was prepared from 11: mp 190–195°; ORD [Φ]₆₀₀ −130.5°, [Φ]₃₅₀ −721°, [Φ]₂₆₀ −2740°, [Φ]₂₅₆ −2500°, [Φ]₂₅₉ −3290°, [Φ]₂₅₃ ±0°, [Φ]₂₅₀ 1690°, [Φ]₂₄₀ ±0°; nmr (DMSO-d_6) 0.67 (18-H), 3.17–3.67 (17α-H), 3.84–4.42 (3-H), 4.5, 4.6, 4.68 (2 OH), 5.4 (4-H), 5.48, 5.67, 5.87, and 6.05 ppm (6-H and 7-H). *Anal.* Calcd for $C_{18}H_{26}O_2$: C, 78.79; H, 9.55. Found: C, 78.54; H, 9.73.

3-Hydroxyestra-1,3,5(10),6-tetraen-17-one (12).—A solution of 1 g of estra-4,6-diene-3,17-dione (11) in 10 ml of pyridine was treated with 2.2 g of iodine under reflux for 6 hr. The reaction mixture was cooled to room temperature and then poured into 150 ml of water. The solid that precipitated was collected by filtration, washed with water, and air dried to give 0.54 g of crude 12. A pure specimen was obtained after several crystallizations from methanol: mp 258°; [α]D −115° (dioxane); λ_{max}^{MeOH} 264 mμ (ε 8560) and 304 (2620); nmr 0.93 (18-H), quartet at 5.83, 6.03, 6.33, and 6.5 (C-6, C-7 olefinic protons), and 9.07 ppm (phenolic OH). The infrared spectrum of this material was superimposable with the one of an authentic sample [reported[19] mp 261–263°; [α]D −127° (dioxane); λ_{max} 262 mμ (ε 8900) and 304 (2750)].

2β-Hydroxy-3,17-dioxoandrosta-4,6-dien-19-oic Acid 2,19-Lactone (15).—A solution of 15.83 g of iodine in 84.6 ml of pyridine was prepared. To this solution, 28.2 g of 3,17-dioxoandrosta-4,6-dien-19-oic acid (10) was added, and the mixture was stirred at room temperature for 72 hr. The precipitate of pyridine hydroiodide was collected by filtration and washed with methylene chloride. The filtrates were concentrated to dryness under reduced pressure and the residue was dissolved in methylene

chloride. An insoluble residue of pyridine hydriodide was filtered off. The filtrates were passed through a column of 400 g of silica gel. The fractions eluted with a mixture of 2% ether–98% methylene chloride were combined and concentrated to dryness. The residue was crystallized from acetone–hexane to yield 16.8 g (59.7%) of 15: mp 256–258°; [α]D −104°; λ_{max}^{MeOH} 294 mμ (ε 19,600). The analytical sample was prepared by crystallization from methylene chloride–ether twice: mp 268–270°; [α]D −108°; λ_{max}^{MeOH} 294 mμ (ε 20,600), ν_{max}^{KBr} 1775, 1740, 1695, 1615 cm⁻¹; nmr 1.06 (18-H), 5.59 (4-H), 6.47–6.56 (6-H and 7-H), 6.50–6.60 ppm (2α-H); molecular ion *m/e* 312. *Anal.* Calcd for $C_{19}H_{20}O_4$: C, 73.06; H, 6.45; O, 20.49. Found: C, 73.25; H, 6.66; O, 20.60.

3,17-Dioxo-2β-hydroxy-5α-androstan-19-oic Acid 2,19-Lactone (17). A.—A suspension of 100 mg of lactone 15 in 2 ml of absolute ethanol plus 30 mg of 5% Pd/C was shaken in a hydrogen atmosphere under a pressure of 50 psi for 2 hr. The mixture was filtered and the filtrate was concentrated under vacuum. The residue was dissolved in methylene chloride and extracted in turn with 3% sodium bicarbonate and water until neutral. The organic solution was dried with anhydrous sodium sulfate and filtered through a column of 3 g of silica gel. The fractions eluted with 3% ether–97% methylene chloride yielded a crystalline material homogeneous on tlc analysis: mp 202–204°; [α]D 200°; ν_{max} 1740, 1775 cm⁻¹. The infrared spectrum of this material was superimposable with that of the material obtained by lactonization with iodine in pyridine of the 3,17-dioxo-5α-androstan-19-oic acid (16) as described below. No depression was observed on mixture melting point determination with this same sample.

B.—A solution of 83.5 g of iodine in 285 ml of pyridine was prepared. To this solution, 95 g of 3,17-dioxo-5α-androstan-19-oic acid (16) was added and the mixture was heated to 60–70° for 2 hr. A precipitate of pyridine hydriodide was formed during the reaction. The mixture was cooled to room temperature and diluted with methylene chloride. This solution was washed with 5% aqueous sodium thiosulfate solution, 5% aqueous sodium bicarbonate solution, water, dilute hydrochloric acid, and finally water until neutral. The organic layer was dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. The crystalline residue was crystallized from acetone–hexane to yield 63 g in the first crop, mp 195–198°, and 23.5 g in the second crop, mp 193–196° (total 96%). The analytical sample obtained after three crystallizations from acetone–hexane showed mp 202–203.5°; [α]D 200°;[20] ORD [Φ]₂₈₀ −10,650°, [Φ]₂₃₈ −4310°, [Φ]₂₁₂ −10,590°; ν_{max} 1775, 1740 cm⁻¹; nmr 0.97 (18-H), 4.48–4.59 ppm (2α-H). *Anal.* Calcd for $C_{19}H_{24}O_4$: C, 72.12; H, 7.65; O, 20.23. Found: C, 72.09; H, 7.75; O, 20.13.

3,17-Dioxo-2β-hydroxy-5β-androstan-19-oic Acid 2,19-Lactone (17a).—A solution of 65 g of iodine in 140 ml of pyridine was prepared. To this solution 46.3 g of 3,17-dioxo-5β-androstan-19-oic acid (16a) was added, and the mixture was heated on the steam bath for 2 hr. The reaction mixture was worked up as described above. Crystallization of the crude material from acetone yielded 27.1 g (59%) of 17a, mp 221.5–223.5°. A pure specimen was obtained after two crystallizations from acetone: mp 223.5–224.5°; [α]D 89°; ORD [Φ]₆₀₀ 0°, [Φ]₃₄ 570°, [Φ]₃₂₀ 6320°, [Φ]₃₀₀ 0°, [Φ]₂₇₆ −6990°, [Φ]₂₄₄ −5110°, [Φ]₂₂₂ −9070°; ν_{max} 1770, 1735 cm⁻¹; nmr 0.95 (18-H), 4.00–4.40 ppm (2α-H). *Anal.* Calcd for $C_{19}H_{24}O_4$: C, 72.12; H, 7.65; O, 20.23. Found: C, 72.16; H, 7.52; O, 20.12.

2β,3β,17β,19-Tetrahydroxy-5β-androstane (19b).—Reduction of 17a with lithium aluminum hydride in the usual manner[21] yielded 19b: mp 228–229°; [α]D 0° (dioxane); ν_{max} 3400 cm⁻¹; nmr poor resolution (see below for the tetraacetate). *Anal.* Calcd for $C_{19}H_{32}O_4$: C, 70.33; H, 9.94; O, 20.73. Found: C, 69.69; H, 9.55; O, 20.53.

The acetonide 20a was prepared from 19b in the usual manner:[22] mp 175.5–177.8°; [α]D 82°; ν_{max} 3450, 1155, 1135, 1080 (shoulder), 1075 cm⁻¹ (strong); nmr 0.72 (18-H), 1.33 and 1.52

(18) Prepared as described by Kalvoda, *et al.*; *cf.* ref 7.

(19) St. Kaufmann, J. Pataki, G. Rosenkranz, J. Romo, and C. Djerassi, *J. Amer. Chem. Soc.*, **72**, 4531 (1950).

(20) The physical constants reported[13] for the 5α-lactones **17** and **17b** are in good agreement with those observed by us, with the exception of the [α]D values, which are almost twice those reported. We can offer no sure explanation for this difference.

(21) See, for example, H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, New York, N. Y., 1965, Chapter 2.

(22) See, for example, C. Djerassi in "Steroid Reactions," Holden-Day, San Francisco, Calif., 1963, p 67.

(acetonide H), 1.54–1.72, and 3.00–3.25 (2 OAc), 4.3–4.41 (2α-H + 3α-H), 3.61 (17α-H), quartet 3.43, 3.54, 3.70, and 3.8 ppm (C-19 H). *Anal.* Calcd for $C_{22}H_{36}O_4$: C, 72.49; H, 9.96; O, 17.56. Found: C, 72.44; H, 9.81; O, 17.45.

The tetraacetate **19c** was prepared in the usual manner:[23] mp 182–183°; $[\alpha]D$ −2°; ν_{max} 1730, 1235 cm⁻¹; nmr 1.75 (18-H), 1.97 (acetate H), 2.00 (acetate H), 2.07 (2 acetate H), quartet centered on 4.19 (19-H), quartet centered on 4.55 (17α-H), multiplet spread over 4.70–4.95 (2α-H), narrow multiplet centered on 5.28 ppm (3α-H). *Anal.* Calcd for $C_{27}H_{40}O_8$: C, 65.83; H, 8.19; O, 25.99. Found: C, 65.91; H, 8.17; O, 26.02.

2β,3β,17β,19-Tetrahydroxy-5α-androstane (19).—Lithium aluminum hydride reduction of **17** in the usual manner[21] yielded **19**: mp 234°; $[\alpha]D$ 20° (dioxane). *Anal.* Calcd for $C_{19}H_{32}O_4 \cdot CH_3$-$COCH_3$: C, 69.07; H, 10.01; O, 20.91. Found: C, 68.84; H, 10.00; O, 21.32.

The acetonide **20** was prepared from **19** in the usual manner:[22] mp 183–184°; $[\alpha]D$ 34°; ν_{max} 3445, 1148, 1125, 1080 (shoulder), 1050 cm⁻¹ (strong); nmr 0.75 (18-H), 1.33 and 1.51 (acetonide H), multiplet centered at 2.73 (1β-H), 3.38 (methanol H), 3.7 (broad) (19-H), 4.2 (narrow multiplet) (2α-H), 3.74–4.4 ppm (broad multiplet) (3α-H). *Anal.* Calcd for $C_{22}H_{36}O_4 \cdot CH_3OH$: C, 69.66; H, 10.17; O, 20.17. Found: C, 70.20; H, 10.32; O, 19.94.

The tetraacetate **19a** was prepared as described above: mp 175.5–176.5°; $[\alpha]D$ 20°; ν_{max} 1735, 1280 cm⁻¹; nmr 0.74 (18-H), 1.97 (2 acetate H), 2.01 (2 acetate H), quartet centered at 2.61 (1β-H), quartet centered at 4.33 (19-H), quartet centered at 4.54 (17α-H), broad multiplet spread over 4.70–4.95 (3α-H), narrow multiplet centered at 5.24 ppm (2α-H). *Anal.* Calcd for $C_{27}H_{40}O_8$: C, 65.83; H, 8.19; O, 25.99. Found: C, 65.78; H, 8.10; O, 26.07.

2β-Hydroxy-3,3-dimethoxy-17-oxo-5β-androstan-19-oic acid 2,-19-lactone (17c) was prepared in the usual manner:[13] mp 159.5–160°; $[\alpha]D$ 137°; ν_{max} 1935, 1775, 1040 (shoulder), 1060, 1107, 1120 cm⁻¹. *Anal.* Calcd for $C_{21}H_{30}O_5$: C, 69.58; H, 8.53; O, 22.07. Found: C, 69.68; H, 8.32; O, 22.20.

2β,17β,19-Trihydroxy-5β-androstan-3-one (18c) was prepared from **17c** by lithium aluminum hydride reduction in the usual manner:[21] mp 234.5–237°; $[\alpha]D$ 16°; ORD $[\Phi]_{600}$ 92°, $[\Phi]_{589}$ 92°, $[\Phi]_{334}$ 0°, $[\Phi]_{304}$ −690°, $[\Phi]_{298}$ −690°, $[\Phi]_{288}$ 0°, $[\Phi]_{260}$ 2300°, $[\Phi]_{230}$ 2600°, $[\Phi]_{210}$ 4540° (in methanol); ν_{max} 3525, 3400, 1735 cm⁻¹; nmr (DMSO-d_6) 0.67 (18-H), multiplet spread over 4.05–4.25 (2α-H). *Anal.* Calcd for $C_{19}H_{30}O_4$: C, 70.77; H, 9.38; O, 19.85. Found: C, 71.25; H, 9.51; O, 19.22.

The triacetate **18d** was prepared from **18c** in the usual manner:[23] mp 168–170°; $[\alpha]D$ +4°; ORD $[\Phi]_{600}$ 18°, $[\Phi]_{589}$ 18°, $[\Phi]_{420}$ −73°, $[\Phi]_{330}$ −405°, $[\Phi]_{304}$ −1505°, $[\Phi]_{299}$ 0°, $[\Phi]_{270}$ 2165°, $[\Phi]_{260}$ 2310°, $[\Phi]_{248}$ 2260°, $[\Phi]_{232}$ 2905°; ν_{max} 1735, 1225 cm⁻¹;

(23) See, for example, J. March, "Advanced Organic Chemistry," Mc-Graw-Hill, New York, N. Y., 1968, p 320.

nmr 0.82 (18-H), 2.03, 2.05, 2.14 (3 AcO), quartet centered at 4.25 (19-H), multiplet spread over 4.55–4.74 (17α-H), quartet 5.14, 5.2, 5.27, 5.34 ppm (2α-H) ($J_{1\beta,2\alpha}$ = 13.5, $J_{1\alpha,2\alpha}$ = 6.5, $J_{1\beta,2\alpha}$ + $J_{1\alpha,2\alpha}$ = 20 Hz). *Anal.* Calcd for $C_{25}H_{36}O_7$: C, 67.24; H, 7.68; O, 25.08. Found: C, 67.49; H, 8.06; O, 24.28.

3,3-Dimethoxy-2β,17β-dihydroxy-5β-androstan-19-oic Acid 2,19-Lactone (17f).—Reduction of **17c** with lithium tri-*tert*-butoxyaluminum hydride as usual[21] gave **17f**: mp 165–166°; $[\alpha]D$ −46°; ν_{max} 3450, 1775, 1130, 1060, 1023 cm⁻¹. *Anal.* Calcd for $C_{21}H_{32}O_5$: C, 69.20; H, 8.85; O, 21.95. Found: C, 68.60; H, 9.04; O, 22.48.

2β,17β-Dihydroxy-3-oxo-5β-androstan-19-oic Acid 2,19-Lactone (17e).—A solution of 150 mg of ketal **17f** in 3 ml of methanol and 1 ml of water was treated with 1 ml of concentrated hydrochloric acid. The mixture was heated on the steam bath until most of the methanol had evaporated. The product crystallized as long needles and was collected by filtration. The pure specimen was prepared by crystallization from acetone–hexane: mp 194–195°; $[\alpha]D$ −48°; ORD $[\Phi]_{600}$ −242°, $[\Phi]_{560}$ −341°, $[\Phi]_{370}$ −712°, $[\Phi]_{338}$ −1697°, $[\Phi]_{307}$ 725°, $[\Phi]_{260}$ −1515°, $[\Phi]_{234}$ −1775°, $[\Phi]_{209}$ −11,580° (in dioxane); ν_{max} 3500, 1750 cm⁻¹; nmr 0.83 (18-H), multiplet spread over 1.3–1.6 (17β-OH), multiplet spread over 3.5–3.7 (17α-H), and 4.45 and 4.51 ppm (2α-H). *Anal.* Calcd for $C_{19}H_{26}O_4$: C, 71.67; H, 8.23; O, 20.10. Found: C, 71.31; H, 8.95; O, 20.75.

3,3-Dimethoxy-2β-hydroxy-17-oxo-5α-androstan-19-oic acid 2,19-lactone (17b) was prepared from **17** as usual:[13] mp 208–209°; $[\alpha]D$ 118°; ν_{max} 1125, 1082, 1058, 1048, 1780, 1740 cm⁻¹; nmr 0.95 (18-H), 3.22 and 3.24 (2 MeO), 4.34–4.60 ppm (2α-H) (reported[13,20] mp 210–212°; $[\alpha]D$ 55°). *Anal.* Calcd for $C_{21}H_{30}O_5$: C, 69.45; H, 8.34; O, 22.07. Found: C, 69.47; H, 8.38; O, 22.01.

2β,17β-Dihydroxy-3-oxo-5α-androstan-19-oic Acid 2,19-Lactone (17d).—Reduction of **17b** with sodium borohydride as usual[21] followed by acid hydrolyses as described before yielded **17d**: mp 182–182.5°; $[\alpha]D$ 133.5°; ORD $[\Phi]_{600}$ −131°, $[\Phi]_{400}$ −412°, $[\Phi]_{350}$ 1385°, $[\Phi]_{330}$ 3455°, $[\Phi]_{300}$ 0°, $[\Phi]_{280}$ −4912°, $[\Phi]_{250}$ −3004° (in dioxane); ν_{max} 3420, 1775, 1730 cm⁻¹; nmr 0.85 (18-H), quartet centered at 3.0 (1β-H), multiplet spread over 3.5–3.8 (17α-H) and doublet at 4.23 and 4.3 ppm (2α-H) (reported[13] mp 182.5–183.5°; $[\alpha]D$ 145°). *Anal.* Calcd for $C_{19}H_{26}O_4$: C, 71.67; H, 8.23; O, 20.10. Found: C, 70.89; H, 8.23; O, 20.02.

The Thermal Transformation of Two Tetrahydroacridandionecarboxylic Acids

R. J. Highet*

Laboratory of Chemistry, National Heart and Lung Institute, Bethesda, Maryland 20014

J. F. Biellmann

Institut de Chimie, University Louis Pasteur, 67 Strasbourg, France[1]

On melting, the tetrahydroacridandionecarboxylic acid **7** is converted into a complex series of products, **8** through **16**. It is shown that the primary products are the decarboxylation product **8** and the keto alcohol **10**, which interact by a novel intermolecular hydride transfer to produce the diketone **9** and the monoketone **12**; the keto olefin **11** arises from acid-catalyzed dehydration of **10**. The analogous acid **22** undergoes similar transformations.

Earlier studies have reported the thermal transformation of a series of 1,4-dihydropyridine-4-carboxylic acids, bearing such 3,5 substituents as carbethoxy (**1a**), cyano (**1b**), and acetyl (**1c**).[2] In particular, the diester **1a** has been shown to be converted by heating into the pyridine **2** and the pyrroles **3**, **4**, and **5**.[2b] Reasonable
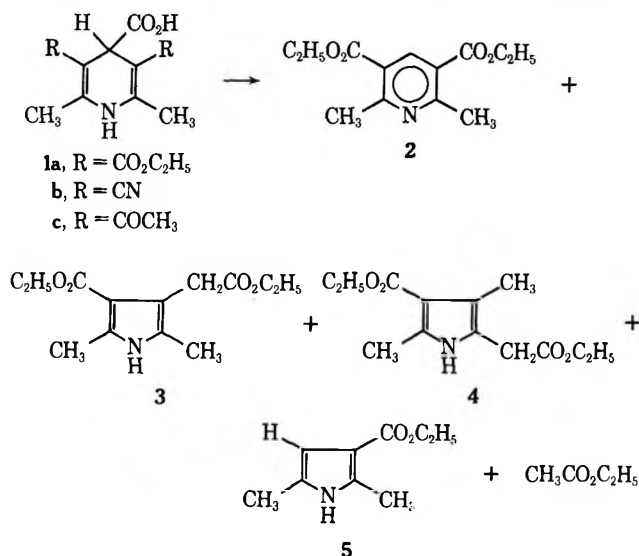
mechanisms could be proposed for the formation of **2**, **3**, and **4** which were consistent with observations in related series, but the mode of the fragmentation which led to the pyrrole **5** and ethyl acetate remained obscure. The study of a tricyclic system in which the fragmentation products must remain part of a single molecule seemed a promising approach to these problems, and is described here. In the event, the reactions led to very different results.

The diketoacridancarboxylic acid **7** promised a suitable entry for this study, and proved to be readily available from the dimedone derivative of glyoxylic acid, **6**, *via* a Hantzsch condensation in ethanolic ammonia. The product has an ultraviolet absorption maximum characteristic of the desired structure.[2,3]

A pure sample of the acid **7** was stable when heated under nitrogen at 240°, the temperature which effected
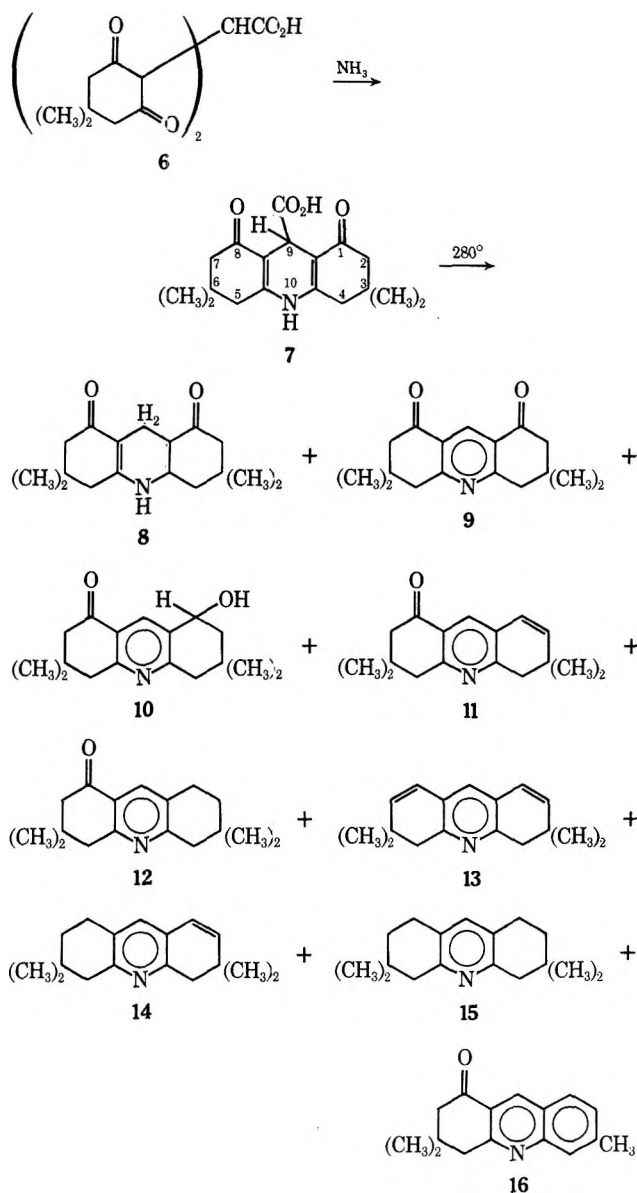
(1) Laboratoire associe au CNRS.

(2) (a) J. F. Biellmann and H. J. Callot, *Chem. Commun.*, 140 (1969); (b) J. F. Biellmann and H. J. Callot, *Tetrahedron*, **26**, 4799, 4809 (1970); (c) J. F. Biellmann, H. J. Callot, and M. P. Goeldner, *Chem. Commun.*, 141 (1969); (d) J. F. Biellmann, H. J. Callot, and M. P. Goeldner, *Tetrahedron*, **26**, 4655 (1970); (e) J. F. Biellmann, R. J. Highet, and M. P. Goeldner, *Chem. Commun.*, 295 (1970); (f) J. F. Biellmann and M. P. Goeldner, *Tetrahedron*, **27**, 1789 (1971).

(3) P. J. Brignell, U. Eisner, and P. G. Farrell, *J. Chem. Soc. B*, 1083 (1966).

the decomposition of the monocyclic compounds **1a–c**; however, melting and ebulition occurred at 280°, transforming **7** into a mixture separable by chromatography on silicic acid. The most polar material was recognized as the product of simple decarboxylation **8**, for it retained the absorption at 388 nm, and proved to be identical with the known condensation product from the dimedone derivative of formaldehyde.[4]

(4) G. Y. Vanag and E. I. Stankevich, *Zh. Obshch. Khim.*, **30**, 3287 (1960).

TABLE I
NMR CHARACTERISTICS[a]

| | | | | | Proton position (in ppm, J in Hz) | | | | | |
Compd	Solvent[b]	1	2	3:C(CH$_3$)$_2$	4	5	6:C(CH$_3$)$_2$	7	9	Other
7	D		2.36 2.40[c]	1.03:1.05	2.17 2.20	2.17 2.20	1.03:1.05	2.36 2.40	4.50	CO$_2$H, 9.36 (br)
7 (CO$_2$CH$_3$)	D		2.32 2.39	0.98:1.02	2.14:2.17 	2.14 2.17	0.98:1.02	2.32 2.39	4.56	OCH$_3$, 3.44
8	D		2.28	1.01	2.20	2.20	1.01	2.28	3.10	NH, 8.80 (br)
9	C		2.57	1.12	3.05	3.05	1.12	2.57	8.80	
10	C	4.90 (X)	1.60 (A) 2.10 (B)	0.98 1.14	2.78	2.97	1.10	2.52	8.48	
		$J_{AX} = 10.0$, $J_{AB} =$ -12.0, $J_{BX} = 7.0$								
10 (OCOCH$_3$ for OH) {H-1, 2.08} {H-1, 1.65}	C	6.04	2.08 1.65	0.98 1.07	2.76	2.95	1.05	2.48	8.13	OCOCH$_3$, 2.10
			$J = 6.5$ (H, d, 6.04), $J = 6.0$ (d), $J =$ 14.0								
11	C	6.35	5.88	1.08	2.98	2.90	1.08	2.50	7.85	
			$J = 10$								
12	C	2.84	1.60	1.03	2.72	2.96	1.12	2.50	7.97	
			$J = 6.0$								
16	C	7.82	7.36	2.54	7.84	3.15	1.10	2.60	8.77	
		$J_{12} = 8.5$, $J_{24} =$ 1.5									
17	C	4.62 (X)	1.63 (A) 2.10 (B)	1.00 1.15	2.78	2.98	1.11	2.53	8.35	OH, $\sim$2.3 OCH$_2$CH$_2$OH, 3.8 (m)
		$J_{AX} = 9.0$, $J_{AB} =$ -13.5, $J_{BX} = 6.0$									
22	C		2.36 2.38	1.10	2.30	2.30	1.10	2.36 2.38	4.88	OAc, 2.17
23	F		2.62 (m)[d]	2.02 (m)[e]	2.38 (m)[d]	2.38 (m)[d]	2.02 (m)[e]	2.62 (m)[e]	4.77	NH, 9.70

[a] Peaks not shown with coupling constants were observed as singlets. Integrated areas corresponded to the required number of protons. In 9, the peak at 2.57 is tentatively assigned to H-2 and H-7 because its position is less changed by structural modification than that at 3.05; assignments in the remaining compounds are made to correspond. [b] C, CDCl$_3$; D, (CD$_3$)$_2$SO; M, CD$_3$OD; F, (CD$_3$)$_2$NCO). [c] Outer limbs of anticipated AB quartet are obscured by neighboring peaks. [d] These assignments could be interchanged. [e] CH.

A product of intermediate polarity and melting point was recognized as the diketone 9 by its ir spectrum, absorption at 290 nm, and a peak in the nmr spectrum at low field, δ 8.98 ppm (Table I). It proved to be identical with known material prepared by the nitrous acid oxidation of 8.[4] A material of similar polarity and uv absorption and mp 150° displayed a carbinol proton at δ 4.90 ppm and an aromatic proton at δ 8.48 ppm, appropriate to the keto alcohol 10; it was readily converted to the known diketone by manganese dioxide oxidation.

The least polar components of the reaction mixture were isolated as a mixture, from which a pure component of mp 97° could be obtained by crystallization. Ultraviolet absorption at 320 nm and, in the nmr spectrum, an AB system of δ 6.28, 5.82 ppm (J = 10 Hz), implied an olefin conjugated with the aromatic ring, as in 11. To demonstrate the structure, the same material was prepared by elimination of acetic acid at 260° from the acetyl derivative of 10. The filtrates from the crystallization of the nonpolar column fractions were rechromatographed on thick layer, to provide a material of mp 95°, displaying a pair of triplets at δ 1.56 and 2.84 ppm. That this was the monoketone 12 could be shown by preparation of the same material by hydrogenation of the olefin, 11.

Mass Spectral Characteristics.—The fragmentations observed in the mass spectra of these compounds followed familiar courses and provided useful structural

information for trace products which could be studied only by the gas–liquid chromatography–mass spectra (glc–ms) pairing. The predominant process was the loss of 56 mu (Table II), corresponding to elimination of isobutene from the side rings by the familiar reverse Diels–Alder process.[5] This process produces the base peak of both the diketone 9 and the monoketone 12. Since the loss occurs twice in the fragmentation of 12 (m/e 257 to 201 and 201 to 145) it is clear that both the unsubstituted alicyclic system and that bearing the keto group undergo this process. Losses of methyl and of carbonyl radicals provide less abundant fragments.

6

m/e 215
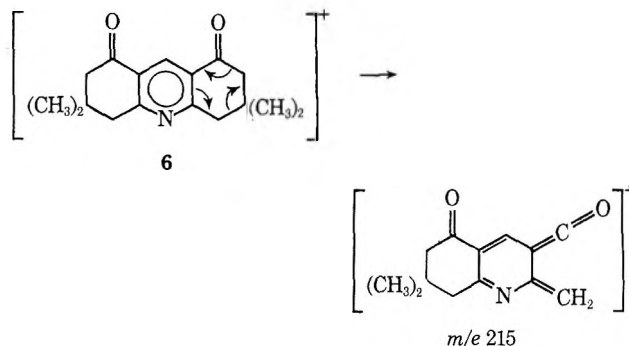
The spectrum of the acid 7 shows no molecular ion peak, the heaviest ion observed resulting from the loss of car-

(5) K. Biemann, "Mass Spectrometry," McGraw-Hill, New York, N. Y., 1962, p 105.

TABLE II
MASS SPECTRAL DATA

Compd	m/e (rel intensity)
7	Calcd 317; 274 (18), 273 (87), 272 (100), 271 (30), 258 (11), 256 (19), 243 (17), 215 (92), 203 (19), 45 (55); m* 151.0 (273 to 203)
8	Calcd 273; 274 (8), 273 (80), 272 (60), 271 (55), 270 (15), 258 (18), 256 (22), 243 (15), 216 (17), 215 (100), 203 (40), 189 (20); m* 151.0 (273–203)
9	Calcd 271; 272 (8), 271 (38), 257 (3), 256 (15), 243 (16), 216 (16), 215 (100), 159 (5), 131 (11); m* 171.0 (271–215), 138 (215–172)
10	Calcd 273; 274 (21), 273 (100), 272 (29), 271 (20), 259 (7), 258 (28), 256 (12), 255 (26), 240 (29), 217 (43), 215 (52), 190 (36), 189 (45), 161 (47), 83 (11); m* 226.0 (255–240), 119.5 (217–161), 132.5 (273–190)
11	Calcd 255; 256 (10), 255 (47), 254 (3), 241 (18), 240 (100), 158 (20), 156 (22), 83 (59); m* 226.0 (255–240), 132.0 (189–158)
12	Calcd 257; 258 (17), 257 (88), 256 (4), 242 (46), 229 (20), 202 (28), 201 (100), 173 (6), 158 (20), 145 (30); m* 204.0 (257–229), 149.0 (201–173), 124.5 (201–158), 104.7 (201–145)
13	Calcd for $C_{17}H_{21}N$, 239; 240 (8), 239 (38), 225 (19), 224 (100), 209 (6), 208 (16), 195 (5), 194 (16), 182 (20) 85 (38), 83 (60); m* 210.0 (239–224)
14	Calcd for $C_{17}H_{23}N$, 241; 242 (7), 241 (37), 227 (20), 226 (100), 85 (60), 83 (100); m* 212 (241–226)
15	Calcd for $C_{17}H_{25}N$, 243; 244 (19), 243 (93), 228 (34), 188 (36), 187 (100), 131 (21), 85 (60), 83 (100)
16	Calcd for $C_{16}H_{17}NO$, 239; 240 (18), 239 (89), 224 (22), 211 (38), 183 (100)
17	Calcd for 317; 318 (2), 317 (11), 273 (17), 272 (95), 258 (10), 257 (63), 256 (100), 255 (11), 240 (16), 215 (5), 214 (9); m* 233.8 (317–272)
22	Calcd 359; 274 (6), 273 (35), 272 (65), 271 (46), 256 (26), 243 (34), 216 (20), 215 (100), 177 (7), 159 (9); m* 214.5 (243–228), 171.0 (271–215)

bon dioxide; the spectrum thus produced closely resembles that of the decarboxylation product 8. Both show a major fragmentation route *via* loss of a molecule of hydrogen to a fragment isomeric or identical with the molecular ion of the diketone 9; peaks important in the spectrum of 9 also occur in those of 7 and 8. A competing process involves the loss of isopentene from the intact ion of 8 (m/e 273 to 203). Surprisingly, the molecular ion of the keto alcohol 10 provides the base peak, the sequential loss of two isobutene moieties, supported by metastable peaks, leading to major fragment ions. Peaks resulting from the loss of methyl, carbonyl, and water moieties are present but less abundant. In the spectrum of the olefin 11, the ion resulting from the loss of the methyl radical is stabilized by allyl resonance, and forms the base peak, twice as intense as the

6

m/e 240

molecular ion. That the aromatic rings of these compounds remained intact was demonstrated by the spectra of the 9-deuterio derivatives, described below.[6] Thus the mass spectra provide an indication of the functional groups, the methyl substituents, and the styrene system of these series.

Minor Products. — Examination of the total reaction mixture from the pyrolysis by gas–liquid chromatography confirmed that the materials isolated by chromatography on silicic acid formed the major reaction products, and revealed the presence of several trace products. The mass spectra of these materials could be obtained from glc–ms pairing and provided reasonable hypotheses for their structures. Thus, the material of least retention time showed a molecular ion of m/e 239 with prominent loss of 15 mu to give the base peak at m/e 224; the spectrum is devoid of prominent peaks arising from the loss of hydroxyl, carbonyl, or isobutenyl fragments. The diolefin 13 possesses an appropriate molecular weight, and accords well to the observed fragmentations.

The material next eluted from the column showed a molecular ion at m/e 241, again with a prominent loss of methyl to m/e 226, and sequential loss of 56 mu. Structure 14, possessing a monostyrene system and saturated alicyclic system, satisfies these observations. The third material eluted (molecular ion at m/e 243) showed only minor loss of methyl, but loss of two isobutene moieties, and is presumably the symmetrical structure 15.

A fourth minor product showed a molecular ion at m/e 239, with the loss of butene providing the base peak, while the loss of carbonyl and methyl fragments produced less abundant ions. Characterization of the material was facilitated by the observation that the same material was formed during the preparation of the olefin 11 by pyrolysis of the acetyl derivative of 10. Chromatography provided material which could be shown by glc to be only slightly contaminated with 11. The nmr spectrum of this material showed, in addition to the singlet at low field, an aromatic AA′B system with δ 7.82, 7.82, and 7.36 ppm and coupling constants of $J_{AB} = 8.5$, $J_{A'B} = 1.5$, and $J_{AA'} = 0$ Hz. Accurate mass measurement showed the molecular formula to be $C_{16}H_{17}NO$.[7] These observations suggested the structure 16, which is supported by the ultraviolet spectrum, which resembled that of 3-acetylquinoline.

Reaction Course and Mechanism. — Thus nine products were recognized from the decomposition on melting of 7. Casual inspection of the accumulation of structures suggested that 8 must arise from simple decarboxylation of the acid 7,[8] while the olefinic group of 11 could be produced by dehydration of the alcohol 10. Experiment confirmed this suspicion that 8 and 10 are primary products. When 7 is refluxed under nitrogen in triglyme, 10 is formed in good yield, and may be

(6) Although this observation is quite obvious in the mass spectra of the monodeuterated derivatives of compounds 9–12, the spectrum of 8 is at first confusing, as important peaks arise from the loss of H or D from C-9. A less equivocal observation is that the base peak occurs as a doublet at m/e 216 and 215, consistent with the fragmentation postulated above through the dehydrogenation product, 9.

(7) We are indebted to Dr. David Rosenthal of Research Triangle Institute for the element map of this material. The formulae arising from accurate measurement of the fragment ions support the modes of fragmentation suggested above.

(8) *Cf.* B. R. Brown, *Quart. Rev., Chem. Soc.,* **5**, 131 (1951).
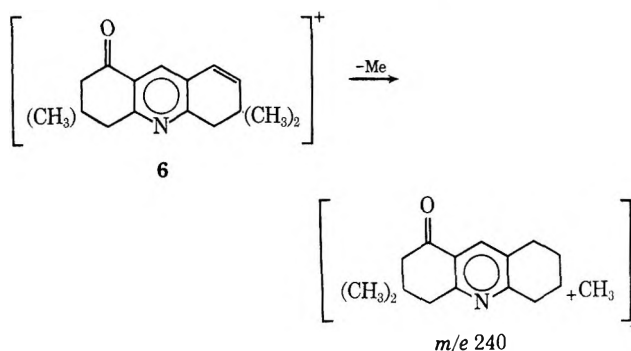
crystallized directly from the reaction products. A smaller quantity of **8** is produced concomitantly.

Although **10** might arise from the disproportionation of the isomeric **8**, in fact **8** is stable under conditions of the pyrolysis, and in the presence of dilute acetic acid. To gain further insight into the course of the reaction, the reactions of 9-deuterio-**7** were studied. Deuterioglyoxylic acid was prepared by the reduction of sodium oxalate by sodium amalgam in deuterium oxide[9] and led through the Hantzsch process as before. Refluxing 9-deuterio-**7** in triglyme provided 9-deuterio-**10**, essentially uncontaminated by the normal product.

This observation eliminates intermediates in the formation of **10** in which a double bond has shifted into conjugation with the carboxylic group, or in which the aromatic system is formed prior to decarboxylation. In view of the stability of the decarboxylation product **8**, the formation of **10** must involve concomittant reduction of the keto group and decarboxylation, as represented by the following mechanism.
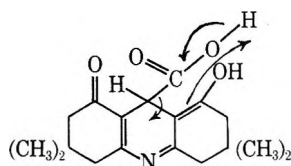

The postulate that the keto olefin **11** arose from the keto alcohol **10** by dehydration could now be tested. Scrupulously purified, **10** proved to be stable at 280°. However, the presence of a carboxylic acid in the melt suggested that the dehydration might occur by acid catalysis. Indeed **11** was produced on heating **10** in 0.7 *N* acetic acid-triglyme.

The acid lability of **10** was further exemplified by an unexpected observation. Refluxing the carboxylic acid **7** in ethylene glycol produced a product readily recognized by composition and spectral characteristics as **17**, the ether of ethylene glycol and the alcohol **10**. Although mechanisms for its direct formation from **7** could be envisaged, it could be demonstrated that heating the keto alcohol **10** in ethylene glycol 0.7 *N* in acetic acid caused the formation of **17**, perhaps *via* the benzylic carbonium ion.
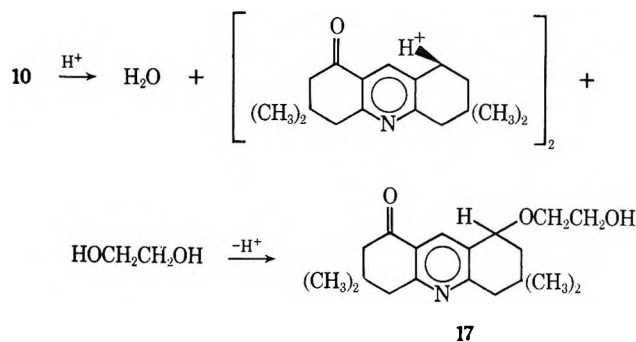

The keto alcohol **10** and the decarboxylation product **8** were individually stable at 280°; however, a mixture of **10** and **8** heated under nitrogen at 284° produced largely the diketone **9** and the monoketone **12**. In view of the lability to acid of the keto alcohol **10**, it is

(9) A. Murray, C. W. Bills, and A. R. Ronzio, *J. Amer. Chem. Soc.*, **74**, 2405 (1952).

convenient to represent this interaction by such a process as
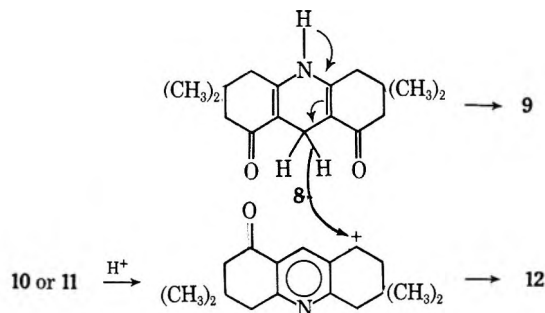
To test the hypothesis, dideuterio-**8** was prepared by leading dideuterioformaldehyde through the dimedone condensation and Hantzsch reaction. A mixture of this material and normal **10** was heated at 280° with the following results. The sample of the diketone **9** produced bore a deuterium atom at the 9 position, as anticipated from its formation from **8**; most of the monoketone **12** formed was monodeuterated at C-1. A smaller portion was dideuterated, evidently 1,9-dideuterio-**12**, for the aromatic peak in the nmr was diminished in intensity. This portion may arise by disproportionation between **9** and **10**.

Other processes than those discussed here may be occurring in the melt. It could be shown, for instance, that the carboxylic acid **7** was converted cleanly to the diketone **9** by heating in the presence of dilute mineral
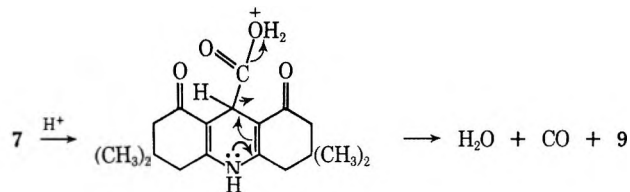
acid. The procedure is evidently a decarbonylation favored by the formation of the aromatic system.[10]

Further indication of the complexity of the processes occurring could be seen in the pyrolysis of 9-deuterio-**7**. Mass spectra of the products formed showed clearly that they were primarily monodeuterio derivatives. However, an nmr spectrum of the benzene soluble products showed that an appreciable portion of **9**, **10**, and **12** possess aromatic protons. This is anticipated for **9**, and the protons of **10** and **12** may arise from minor reactions such as intermolecular hydride transfer reactions, not elucidated here.

Comparison of 1 and 7.—Thus, it is abundantly clear that the behavior of the acridan systems discussed here is quite different from that observed in the earlier studies of **1a-c**. The behavior of **1c** provides a particularly striking contrast of chemical properties. The two acids, **1c** and **7**, possess identical functional groups identically situated around the 1,4-dihydropyridine system. Their electronic characteristics are shown by their very similar spectra to be essentially identical, but, on melting, **1c** is converted into the lactone **19**, with the expulsion of an acetyl group, *via* an intermediate

(10) Acid-catalyzed decarbonylation has previously been observed when the carbonium ion produced is stabilized by suitable substitution. *Cf.* J. Meinwald, H. C. Hwang, D. Christmar, and A. P. Wolf, *ibid.*, **82**, 483 (1960), and A. H. Blatt, "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1943, p 5.

thought to be the anhydride **18**. In accord with this supposition, the mixed anhydride **20** can be prepared
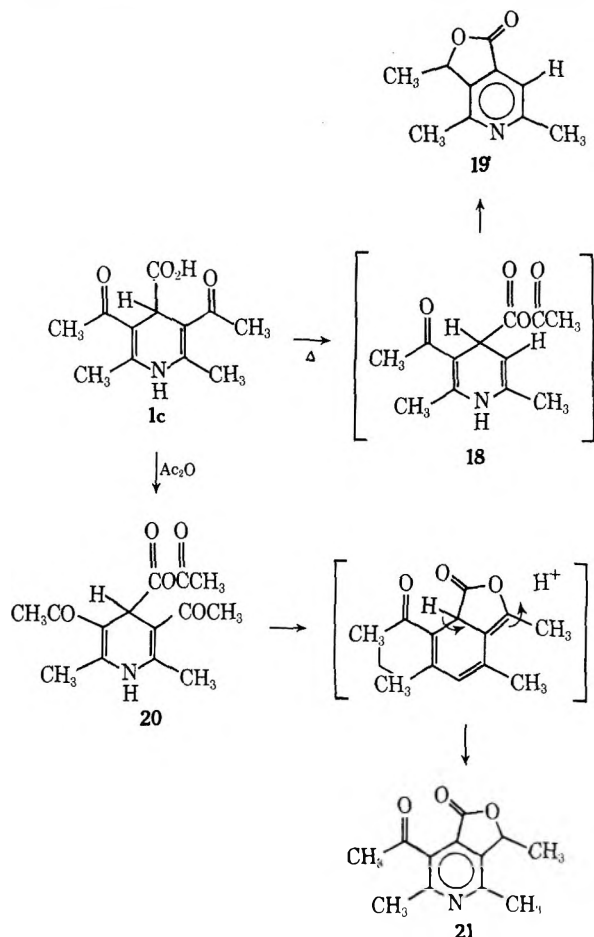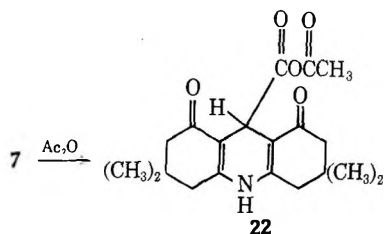

from **1c**, and is readily transformed to the keto lactone **21**.

To extend the comparison, the mixed anhydride **22** was prepared from **7** by stirring with acetic anhydride. It is perfectly stable at moderate temperatures, and, on melting, is converted to the diketone **9**, apparently with the expulsion of acetic acid and carbon monoxide.

It seemed worthwhile to eliminate the possibility that the *gem*-dimethyl groups of **7** were responsible for the different reaction course. Accordingly, a preliminary examination of the behavior of **23** was carried out. Dihydroresorcinol was led through the same reaction sequence as that leading to **7** to provide **23**, which was
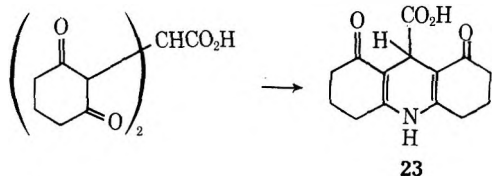
subjected to pyrolysis. The mass spectra of the products showed fragmentation corresponding closely to

those of the earlier products, and the characteristic nmr peaks appeared at very similar chemical shifts. It is clear that the reaction followed a very similar course, and the difference in behavior in **7** and **1c** must be found in the effect of the tricyclic character of **7** upon the reaction mechanism. It must be presumed that tetracyclic systems corresponding to those leading to **18** and **21** are sufficiently strained in the reactions of **7** to prevent the reaction taking the same course as **1c** and its anhydride.

Experimental Section[11]

3,4,6,7-Tetrahydro-3,3,6,6-tetramethylacridan-1,8(2H,5H)-dione-9-carboxylic Acid (7).—The dimedone adduct of glyoxylic acid,[12] 5 g, was treated with 50 ml of ethanol which had been saturated with ammonia at 4°. The suspension was sealed in a glass tube, and heated cautiously with shaking until dissolution was complete. The solution was now heated overnight in a steam bath, gradually depositing yellow crystals. It was chilled, opened, and filtered. The product was washed with scanty portions of chilled ethanol, dissolved in ~50 ml of water, and added to excess chilled 1 *N* hydrochloric acid with stirring, precipitating a light yellow powder. This was filtered, dried by pressing on porous pot, and crystallized from ~70 ml of ethanol. The product was 1.4 g of handsome yellow crystals: mp 280° dec; uv max 247 nm (ϵ 23,500), 373 (7600); ir (Nujol film) 3200–2500 (br), 1720, 1640, 1570 cm^{-1}. *Anal.* Calcd for $C_{18}H_{23}O_4N$: C, 68.12; H, 7.31; N, 4.40. Found: C, 68.01; H, 7.42; N, 4.51.

Pyrolysis of 7.—A 1.2-g sample of **7** was heated under N$_2$ at 280° for 15 min until ebullition ceased. A 93-mg sample of the crude product, which amounted to 1.0 g, was removed and the remainder was chromatographed on 30 g of silicic acid. Elution by 20% ethyl ether in petroleum ether removed 143 mg of a mixture of **11** and **12**; 33% ether eluted 180 mg of **9**; 50% ether eluted 530 mg of **10**; methanol eluted 100 mg (10%) of **8**. The following yields were based on glc analysis on 3% OV-1 on Gas-Chrom P at 180° (retention times): **13**, trace (3.3 min); **14**, trace (3.7 min); **15**, trace (4.2 min); **11**, 17% (6.1 min); **12**, 15% (7.1 min); **16**, trace (9.7 min); **9**, 20% (12.1 min); **10**, 28% (13.9 min); **8** not observed.

3,4,5,6-Tetrahydro-3,3,6,6-tetramethyl-1(2H)-acridinone (11).—Recrystallization of the first fraction eluted from the column from hexane provided 49 mg of **11**: mp 97°; uv max 234 nm (ϵ 27,000), 271 (12,100), 279 sh (10,100), 320 (3560), (OH$^-$) no change, (H$^+$) 242 sh (12,100), 279 (9700), 330 (4200); ir (CHCl$_3$) 1680, 1592, 1320 cm^{-1}. *Anal.* Calcd for $C_{17}H_{21}NO$: C, 79.96; H, 8.29. Found: C, 79.81; H, 8.55.

3,4,5,6,7,8-Hexahydro-3,3,6,6-tetramethyl-1(2H)-acridinone (12).—Filtrates from the above procedure were chromatographed on a 2-mm-thick plate of silicic acid developed three times with 20% ether in hexane. Elution of the lower portion of the band provided material substantially free of **11**; recrystallization from hexane provided material of mp 95–96°, identical with material prepared as follows.

A 21-mg sample of **11** was stirred in ethanol with 5 mg of 10% Pd/C under hydrogen; the solution absorbed 2.0 ml in 15 min. Filtration and evaporation of the solvent provided 21 mg of compound **12**: uv max 213 nm (ϵ 14,800), 241 (8300), 293 (6500),

(11) Melting points were observed on a microscope hot stage. Uv spectra were obtained in absolute ethanol solution on recording spectropolarimeters; those designated "(OH$^-$)" were recorded after adding 1 drop of 1 *N* sodium hydroxide to the ethanolic solution; those designated "(H$^+$)" were obtained after adding 1 drop of 1 *N* hydrochloric acid to the ethanolic solution. Ir spectra were obtained on chloroform solution unless otherwise described. Nmr spectra were obtained on a Varian A-60 or HA-100 spectrometer using tetramethylsilane (δ 0.0) as an internal standard. Mass spectra were obtained on an LKB 9000 mass spectrometer at 70 eV; those of trace products were obtained as the material was eluted from an OV-1 (1%) column heated from 150 to 230° at 5°/min. The identities of materials from alternative preparations were established by nmr spectra and, in the case of **7** and **8**, by thin layer chromatography on silicic acid, eluting by 5% methanol in chloroform; in the case of **9–12**, by gas chromatography on a column of 3% OV-1 Gas-Chrom P at 180°.

(12) D. Vorländer, *Z. Anal. Chem.*, **77**, 244 (1929).

301 sh (6300), (H⁺) 235 sh (6170), 292 (9400) [*cf.* 3-acetyl-pyridine: 228 (8500), 267 (2900), (H⁺) 224 (5700), 267 (3900)[13]]. *Anal.* Calcd for $C_{17}H_{23}NO$: C, 79.33; H, 9.01. Found: C, 79.41; H, 9.06.

3,4,6,7-Tetrahydro-3,3,6,6-tetramethyl-1,8(2H,5H)-acridinedione (9).—Recrystallization of column fractions from ethyl acetate provided material of mp 147° (lit.[4] 146); uv max 248 nm (ε 10,650), 289 (6200), 299 (5720), (OH⁻) no change, (H⁺) 245 (10,300), 289 (8100), 298 (7500); ir (CHCl₃) 1690, 1580. *Anal.* Calcd for $C_{17}H_{21}NO_2$: C, 75.24; H, 7.80; N, 5.16. Found: 75.21; H, 8.01; N, 5.25.

1,2,3,4,6,7-Hexahydro-3,3,6,6-tetramethyl-8(5H)-acridinon-1-ol (10).—Repeated recrystallization of column eluates provided material of mp 153–153.5°; uv max 242 nm (ε 8900), 291 (7200), 296 sh (7100), (OH⁻) no change, (H⁺) 235 (6100), 291 (9700); ir (CHCl₃) 3580, 3400 (br), 1678, 1590, 1560 cm⁻¹. *Anal.* Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.64; H, 8.67; 8.43; N, 5.31.

Oxidation.—A solution of 30 mg of the above keto alcohol (10) was stirred 24 hr with 300 mg of Merck manganese dioxide; the suspension was filtered and concentrated to dryness. The product (24 mg) was identical in infrared spectrum and tlc with the diketone 9.

This compound (10) was more conveniently prepared by the following procedure. A 0.25-g sample of 7 was refluxed under nitrogen for 90 min in 1 ml of triglyme, which was diluted with benzene and filtered to yield a small quantity of 8. The solution was washed three times with water and concentrated to dryness. The residue was crystallized from benzene–hexane, to provide 112 mg (52%) of mp 145–150°.

1,2,3,4,6,7-Hexahydro-3,3,6,6-tetramethyl-8(5H)-acridinon-1-yl Acetate (10, OCOCH₃ instead of OH).—An 83-mg sample of the pure alcohol was dissolved in 1 ml of cold acetic anhydride–pyridine (1:1) and allowed to stand in a freezer overnight. The solution was diluted with benzene and stirred with 10 ml of 1 *N* potassium bicarbonate for 3 hr, then extracted twice with chloroform; the extract was washed with water and concentrated to dryness. The residue, 95 mg, mp 100–103°, was recrystallized from ether to provide material of mp 103–103.5°; ir (CHCl₃) 1735, 1692, 1602 cm⁻¹. *Anal.* Calcd for $C_{19}H_{25}NO_3$: C, 72.35; H, 7.99; N, 4.44; Found: C, 72.60; H, 7.96; N, 4.62.

3,4,6,7-Tetrahydro-3,3,6,6-tetramethyl-1,8(2H,5H)-acridandione (8).[4]—A 2.0-g sample of formaldehyde dimedone[14] was heated with 20 ml of concentrated ammonium hydroxide for 24 hr. The solution was chilled and the precipitate filtered, to provide 1.45 g of 8: mp >310° dec; uv max 248 nm (ε 16,600), 263 sh (7500), 388 (6400); ir (Nujol) 1590 cm⁻¹.

Preparation of 11 by Dehydroacetoxylation.—The acetate of 10 prepared as described above from 106 mg of 10 was distilled at 120° (0.1 mm), then sealed in a test tube under nitrogen and heated 25 min at 260°. Chromatography over 10 g of silicic acid, eluting with 10% ether–hexane, produced 28 mg of pure olefin 11, identical by glc and nmr with material obtained from the pyrolysis of 7.

Continued elution provided 11 mg of **6,7-dihydro-3,6,6-trimethyl-8(5H)-acridinone (16)** as a glass: uv max 215 nm (ε 17,700), 253 (36,400), 312 (9000), (H⁺) 212 (19,300), 257 (30,200), 336 (9700) [*cf.* 3-acetylquinoline: 243 (50,000), 287 (8000), 322 (1000)[15]]. On addition of NaBH₄ the solution of 16 showed uv max 210 (62,000), 236 (36,000), 239 (36,400), 298 (6200), 305 (6100), 311 (7400), 317 (6200), 350 (3800) [*cf.* quinoline: 235 (35,500), 278 (3500) 300 (2600), 314 (3030)[16]]; ir (CHCl₃) 1680, 1628, 1590, 1495, 880 cm⁻¹; mass spectrum[7] *m/e* 239.131 (calcd for $C_{16}H_{17}NO$, 239.131), 224.107 ($C_{15}H_{14}NO$, 224.105), 216.137 ($C_{15}H_{17}N$, 211.136), 183.067 ($C_{13}H_9NO$, 183.068), 155.072 ($C_{11}H_7N$, 155.073).

Bis(1,3-dioxocyclohexyl-2)acetic Acid.—A 17-g portion of dihydroresorcinol and 6.5 g of glyoxylic acid were dissolved by warming in 50 ml of water and treated with 10 drops of concentrated HCl. On cooling, a white precipitate formed, which, when separated by filtration and washed, amounted to 16.0 g, mp 88–90°. *Anal.* Calcd for $C_{14}H_{16}O_6$: C, 59.99; H, 5.75. Found: C, 60.33; H, 6.08.

(13) M. L. Swain, A. Eisner, C. F. Woodward, and B. A. Brice, *J. Amer. Chem. Soc.*, **71**, 1341 (1949).

(14) D. Vorlander and F. Kalkow, *Justus Liebigs Ann. Chem.*, **309**, 356 (1899).

(15) K. Eiter and E. Mrazek, *Monatsh. Chem.*, **83**, 1491 (1952).

(16) The suffix "a" denotes structures modified by the substitution of CH₂ for C(CH₃)₂.

3,4,6,7-Tetrahydro-1,8(2H,5H)-acridandione-9-carboxylic Acid (23).—A 2.0-g portion of the above adduct was heated in 10 ml of concentrated ammonia for 16 hr, then acidified with HCl. The suspension was filtered and the precipitate was washed with water and dried, to provide 1.7 g, >250° dec pt. This was crystallized by dissolution in 350 ml of ethanol and concentrated to 75 ml, yielding, on scratching and chilling, 1.1 g of fine yellow crystals mp >250°. In a preliminary run, crystallization was allowed to proceed slowly, producing a mixture of crystalline forms, prisms, and needles. Solid-phase ir spectra of these different forms were very similar, but not identical and uv spectra had identical λ_{max}, but ε values were not closely reproducible: uv max 369 nm (ε 6600), (OH⁻) 249 (45,600), 379 (6250); ir (Nujol) 3250–2000, 1700, 1610, 1565. *Anal.* Calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36. Found: C, 64.31; H, 6.06, 5.92; N, 5.53, 5.49.

A sample of this material was heated under nitrogen at 284° for 5 min. It was chromatographed on a silicic acid plate by repeated development with chloroform, providing sufficient separation of the products to allow the recognition of their salient spectrometric characteristics. An nmr spectrum of the benzene-soluble portion of the product showed the approximate composition 9a,[16] 20%, 10a, 35%, 11a, 20%, 12a, 25%. 9a: nmr 880 ppm (s); mass spectrum 216 (9), 215 (60), 214 (10), 188 (6), 187 (100). 10a: nmr 8.35 (s), 4.85 (br); mass spectrum 218 (13), 217 (92), 216 (60), 215 (29), 200 (15), 199 (38), 189 (54), 188 (33), 187 (46), m* 165 (217 → 189). 11a: nmr 7.83 (s), 6.4 (m) 6.17 (m); mass spectrum 200 (29), 199 (100), 198 (36), 197 (35), 184 (33), 171 (40), 169 (35). 12a: nmr 8.0 (s); mass spectrum 202 (12), 201 (70), 200 (24), 173 (100), 145 (29), m* 122.0 (173 → 145).

1-(2-Hydroxyethoxy)-1,2,3,4,6,7-hexahydro-3,3,6,6-tetramethyl-8(5H)-acridinone (17).—7 (0.25 g) and 1 ml of ethylene glycol were refluxed under N₂ for 2 hr, cooled, and diluted with chloroform to precipitate 24 mg of 8. The filtrates were chromatographed on a thick layer of silicic acid with 1:1 hexane–ether. Extraction of the band 0.1 cm from the base line provided 120 mg of 17. Recrystallization from benzene–hexane provided material of mp 137–139°; uv max 239 nm (ε 9500), 293 (6700). *Anal.* Calcd for $C_{19}H_{27}O_3N$: C, 71.89; H, 8.57; Found: C, 71.90; H, 8.48.

Acid Treatment of 7.—An 102-mg sample of 7 was heated with 0.25 ml of 0.1 *N* sulfuric acid in triglyme in a sealed tube under nitrogen at 225° for 40 min. The solution was cooled, diluted with water, and filtered. The precipitate was washed repeatedly with water, and dried to provide 70 mg of 9, mp 149–151°.

9-Deuterio Derivative of 7.—A solution of 670 mg of sodium oxalate in 20 ml of deuterium oxide was adjusted to pD 1 with concentrated deuteriosulfuric acid, and a total of 75 g of 1% sodium amalgam was added in five portions over a period of 1 hr together with the further addition of deuteriosulfuric acid as required to maintain the pD at ~1. To this solution was added 1.0 g of dimedone reagent. On standing overnight the solution precipitated 0.9 g of the adduct which was crystallized from aqueous ethanol.

A 0.416-g sample of this material was treated as above with ethanolic ammonia to produce material identical with previous preparations of 7 but lacking an nmr peak at δ 4.50 ppm.

Pyrolysis of this material was carried out as before. The product was taken up in benzene and filtered. The precipitate was chromatographed on thin layer, developing with 5% methanol in chloroform to provide a sample of 8b:[17] *m/e* 275 (35), 274 (100), 273 (60), 272 (30), 259 (27), 216 (39), 215 (23), 204 (49), m* 152 (274 → 204). The benzene solution was examined by glc–ms to provide the following spectra: 9b, 272 (35), 257 (15), 244 (17), 216 (100), 215 (26); 10b, 275 (25), 274 (100), 273 (32), 259 (33), 256 (20), 241 (20), 218 (53), 191 (45), 190 (65), 189 (12); 11b, 256 (42), 241 (100), 240 (12), 83 (70); 12b, 258 (100), 257 (20), 243 (43), 202 (89), 201 (24).

Mixed Anhydride of 7 and Acetic Acid (22).—A 5.0-g sample of recrystallized 7 was stirred in the dark with 25 ml of acetic anhydride for 4 days. The suspension was diluted with ether and filtered to provide 5.3 g of the mixed anhydride, mp 184–187°. Crystallization from chloroform–ethanol provided material of mp 183–184°; uv max 363 nm (ε 6900); ir 3240, 3070, 1810, 1730, 1640, 1610, 1562. *Anal.* Calcd for $C_{20}H_{25}O_5N$: C, 66.83; H, 7.01; N, 3.90. Found: C, 66.44; H, 7.48; N, 3.79.

(17) The suffix "b" denotes structures modified by substitution of D for H at C-9.

Acid Dehydration of 10.—A 10-mg sample of 10 was heated with 0.2 ml of 4 *M* acetic acid in triglyme. The solution was diluted with benzene and washed repeatedly with water. The organic layers were concentrated to dryness under reduced pressure to yield an 11-mg residue, which was shown by glc and nmr to be a mixture of 10 and 11, approximately 1:1, slightly contaminated by triglyme.

Conversion of 9-Deuterio-7 to 9-Deuterio-10.—An 11-mg sample of 9-deuterio-7 was heated under nitrogen with 0.1 ml of triglyme at 240° for 30 min. The solution was diluted with benzene and hexane and chilled. The precipitate amounted to 3.3 mg. The filtrates were washed repeatedly with water and concentrated to dryness under reduced pressure. The residue was crystallized from benzene to provide 4.3 mg of 9-deuterio-10, mp 148–151°. The nmr spectrum was identical to that of 10, but lacked the aromatic proton absorption. Collection of 420 spectra and integration by cut and weigh showed that ~5% of this possessed an aromatic proton, δ 8.5 ppm; mass spectrum *m/e* 276 (3), 275 (22), 274 (100), 273 (32), 272 (19), 259 (30), 256 (22), 241 (19), 218 (48), 216 (38), 162 (60).

Interaction of 8 and 10.—A mixture of 73 mg of 8 and 76 mg of 10 was heated under nitrogen at 280° for 5 min. The product was taken up in benzene and filtered to recover 45 mg of 8. The benzene solution was concentrated to dryness to leave 103 mg. Analysis by nmr and glc showed the following composition: 9, 29%; 10, 54%; 12, 12%. When heating was continued 70 min, recovery of 8 amounted to 17%; the composition of the benzene soluble portion was 9, 46%; 10, 15%; 11, 6%; 12, 34%.

Interaction of 9,9-Deuterio-8 and 10.—A sample of dideuterioparaformaldehyde (0.32 g) was converted to the dimedone derivative[14] (2.5 g), of which 0.5 g was heated with 5 ml of ammonia in a steam bath overnight to provide 0.38 g of dideuterio-8.

This material was recrystallized from ethanol. A recrystallized sample (20 mg) was mixed with an equal weight of 10 and heated in a sealed tube under nitrogen at 284° for 75 min. The material was suspended in benzene, filtered, and the filtrate concentrated to dryness (32 mg). Glc showed 9, 43%; 10, 13%; 11, 17%; 12, 28%. Mass spectra: 9-deuterio-9, *m/e* 273 (8), 272 (31), 271 (5), 216 (100), 215 (12); 10, identical with that of pure material; 11, identical with pure material, except for *m/e* 256 (19) and 241 (38); 1-deuterio-12 and 1,9-dideuterio-12, 260 (24), 259 (72), 258 (72), 244 (45), 243 (45), 204 (42), 203 (100), 202 (95).

This material was chromatographed on a thick plate eluting by 1:1 hexane–ether. The slowest moving band provided 10, with nmr identical with that of known material; the next band provided 9-deuterio-9 with nmr identical with known material, but lacking the aromatic proton; the fastest moving band provided a 1:1 mixture of 11 and 9-deuterio-12 with the nmr δ 7.88 ppm (relative strength 0.6), 7.76 (0.9), 6.25 (d, 1.0), and 5.75 (d, 1.0). Intensities were determined by cut and weigh of the spectrum obtained by accumulating 225 spectra.

Interaction of 8 and 11.—A mixture of 1.2 mg of 11 and 1.5 mg of 8 was heated under nitrogen at 280° for 18 min. Glc analysis of the volatile components of the mixture showed 9:11:12 in the approximate ratio 8:4:3.

Asymmetric Induction in the Thermal Reactions of Allylic Alcohols with N,N-Dimethylacetamide Dimethyl Acetal and Triethyl Orthoacetate[1]

Richard K. Hill,* Raghovan Soman, and Seiji Sawada

Department of Chemistry, University of Georgia, Athens, Georgia 30601

Optically active *trans*-3-penten-2-ol was used as the substrate for Claisen-type reactions with N,N-dimethylacetamide dimethyl acetal and triethyl orthoacetate. The products, the N,N-dimethyl amide and ethyl ester, respectively, of 3-methyl-4-hexenoic acid, were formed in greater than 90% optical purity and with inversion of configuration. The magnitude of asymmetric induction observed makes these reactions particularly useful for the stereospecific introduction of a carbon–carbon bond at an asymmetric center.

Stimulated by recent practical modifications,[2] the Claisen rearrangement of allyl vinyl ethers (eq 1) has
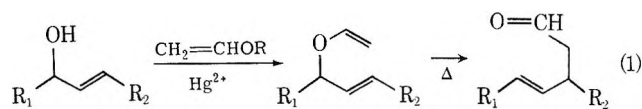
seen increasing use in synthesis. A characteristic feature of the reaction, responsible in large measure for its success, is the high degree of stereospecificity which extends to the creation of asymmetric centers in high optical yield as well as to the production of predominantly trans double bonds.[3]

Of a number of variants of the Claisen rearrangement, two have proven particularly valuable for practical synthetic application in attaching a two-carbon chain because, in contrast to the original procedure, they can be carried out directly on an allylic alcohol without the need to isolate a vinyl ether intermediate. They are (a) the reaction of an allylic alcohol with N,N-dimethylacetamide dimethyl acetal (I) or its equivalent, 1-methoxy-1-dimethylaminoethylene (II), a reaction discovered by Meerwein[4] and systematized by Eschenmoser and coworkers[5] and which provides a one-step route to unsaturated amides (eq 2); and (b) the acid-catalyzed thermal reaction of allylic alcohols with triethyl orthoacetate (III), recently reported by

(1) This research was supported by grants from the National Science Foundation (GP-9094 and GP-28056X), to whom the authors express their appreciation.

(2) (a) A. F. Thomas and M. Ozainne, *J. Chem. Soc. C*, 220 (1970), and references cited therein; (b) W. S. Johnson, T. J. Brocksom, P. Loew, D. H. Rich, L. Werthemann, R. A. Arnold, T. T. Li, and D. J. Faulkner, *J. Amer. Chem. Soc.*, **92**, 4463 (1970); (c) G. Büchi and J. E. Powell, Jr., *ibid.*, **89**, 4559 (1967); **92**, 3126 (1970).

(3) (a) J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions," Prentice-Hall, Englewood Cliffs, N. J., 1971, p 375, and references cited therein; (b) A. Jefferson and F. Scheinmann, *Quart. Rev., Chem. Soc.*, **22**, 391 (1968), and references cited therein.

(4) H. Meerwein, W. Florian, N. Schön, and G. Stopp, *Justus Liebigs Ann. Chem.*, **641**, 1 (1961).

(5) A. E. Wick, D. Felix, K. Steen, and A. Eschenmoser, *Helv. Chim. Acta*, **47**, 2425 (1964); D. Felix, K. Gschwend-Steen, A. E. Wick, and A. Eschenmoser, *ibid.*, **52**, 1030 (1969).
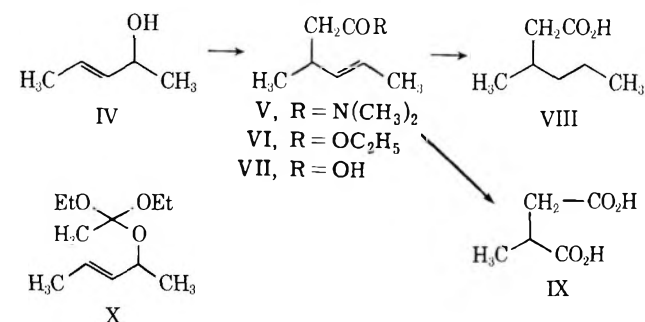
Johnson and coworkers,[6] which leads directly to the corresponding ethyl ester (eq 3).
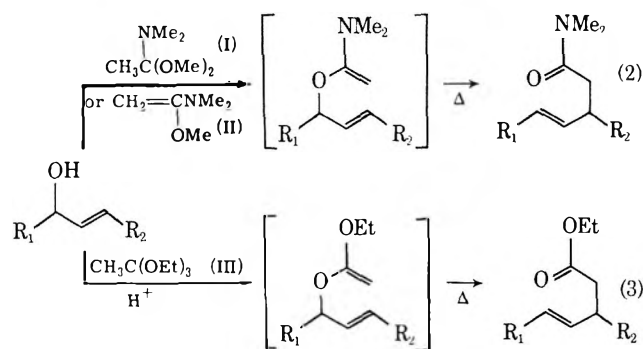
Both of these variations allow the easy, high-yield addition of an acetic acid unit to the γ carbon of an allylic alcohol, and both have already found extensive application in the synthesis of natural products.[7]

It has been reported[6,7] that both reactions lead almost exclusively to products in which the new double bond is trans, and we were led to investigate whether this striking geometrical specificity was paralleled by comparable optical stereospecificity. We now report that both rearrangements, when applied to an optically active alcohol, proceed in optical yields greater than 90%, and consequently provide valuable methods of forming new carbon–carbon bonds at an asymmetric center with high stereospecificity.

Treatment of *trans*-3-penten-2-ol (IV) with a mixture of I and II in refluxing xylene for 17 hr afforded an amide in 80% yield. The nmr spectrum (see Experimental Section) confirmed its structure as N,N,3-trimethyl-4-hexenamide (V). Similarly, heating IV with 7 equiv of triethyl orthoacetate containing a trace of propionic acid at 180° for 22 hr while ethanol was removed through a long Vigreux column yielded, on fractionation, ester VI in 68% yield. Alkaline hydrolysis of V or VI gave 3-methyl-4-hexenoic acid (VII). Compounds V, VI, and VII all appeared as single peaks on glc analysis and, from the strong infrared absorption at 950–970 cm^{-1}, are apparently >98% trans isomers. Hydrogenation of VII gave the known 3-methyl-

hexanoic acid (VIII), while ozonolysis furnished methylsuccinic acid (IX).

When optically active *trans*-3-penten-2-ol was used in these reactions, both the amide V and ester VI formed were optically active. Alcohol IV, $[\alpha]^{25}$D −13.2°, afforded amide V, $[\alpha]$D −15.7°, while dextrorotatory IV, $[\alpha]^{25}$D +8.52°, yielded levorotatory VI, hydrolyzed to acid VII, $[\alpha]^{25}$D −13.6°.

To assess the direction and magnitude of asymmetric induction, it was necessary to determine the absolute configuration and optical purity of acid VII. The racemic acid was partially resolved with quinine, giving a salt of mp 138–139°, $[\alpha]^{25}$D −82.1° (CHCl₃), after three recrystallizations from chloroform–acetone. Regeneration of the acid with dilute HCl gave material with $[\alpha]^{25}$D +33.8°. Ozonolysis of this dextrorotatory acid yielded methylsuccinic acid of $[\alpha]^{25}$D −14.1°. Since the maximum rotation reported[8] for methylsuccinic acid is 16.5°, the ozonolysis product and its precursor are 85.4% optically pure, and the maximum rotation of VII is calculated to be 39.6°. Moreover, since levorotatory methylsuccinic acid has been conclusively established[9] as the R enantiomer, dextrorotatory VII is the R enantiomer.

These conclusions about maximum rotation and absolute configuration of VII were independently checked by hydrogenating a sample of VII, $[\alpha]^{25}$D +22.5°, to 3-methylhexanoic acid (VIII), $[\alpha]^{24}$D +1.63°. Based on the maximum reported rotation[10] of VIII of 2.5° and its reported configuration as L-(−), the maximum rotation of VII is calculated to be 34.5° and its configuration R-(+), in agreement with the conclusions derived from ozonolysis.

The absolute configuration of the starting allylic alcohol, (S)-(−)-*trans*-3-penten-2-ol, has been determined both by ozonolysis[11] to the levorotatory zinc salt of (S)-(+)-lactic acid and by hydrogenation[11,12] to (S)-(+)-2-pentanol. As Goering and Kimoto[13] have emphasized, the optical purity is best based on the phthalate, with a maximum rotation of 38° (CHCl₃) established by isotope dilution,[14] since the rotation of the allylic alcohol itself is not accurately reproducible. Using these values, the optical purities calculated for the starting alcohol and rearrangement products are shown in Table I.

Both reactions produce rearrangement products of inverted configuration and in optical yields of 90% or greater.[15] Inversion of configuration is the conse-

(6) W. S. Johnson, L. Werthemann, W. R. Bartlett, T. J. Brocksom, T. T. Li, D. J. Faulkner, and M. R. Petersen, *J. Amer. Chem. Soc.*, **92**, 741 (1970).

(7) H. Muxfeldt, R. S. Schneider, and J. B. Mooberry, *J. Amer. Chem. Soc.*, **88**, 3670 (1966); D. F. Morrow, T. P. Culbertson, and R. M. Hofer, *J. Org. Chem.*, **32**, 361 (1967); W. Sucrow, *Angew. Chem.*, **80**, 626 (1968); W. Sucrow, *Tetrahedron Lett.*, 4725 (1970); F. E. Ziegler and J. G. Sweeny, *ibid.*, 1097 (1969); F. E. Ziegler and G. B. Bennett, *J. Amer. Chem. Soc.*, **93**, 5930 (1971); I. J. Bolton, R. G. Harrison, and B. Lythgoe, *Chem. Commun.*, 1512 (1970); R. G. Harrison and B. Lythgoe, *ibid.*, 1513 (1970); D. H. Miles and W. S. Johnson, Abstracts of Papers, 23rd Southeastern Regional Meeting of the American Chemical Society, Nashville, Tenn., Nov 4–5, 1971, p 43.

(8) A. Fredga, *Ark. Kemi, Mineral. Geol.*, **15B**, No. 23, 1 (1942), reported $[\alpha]^{20}$D +16.5° (c 4.352, ethanol). R. Adams and D. Fles, *J. Amer. Chem. Soc.*, **81**, 4946 (1959), reported $[\alpha]^{25}$D +15.9° (c 1.36, ethanol) for optically pure methylsuccinic acid.

(9) J. A. Mills and W. Klyne in "Progress in Stereochemistry," Vol. 1, W. Klyne, Ed., Academic Press, New York, N. Y., 1954, pp 188, 202, 203.

(10) I. A. Holliday and N. Polgar, *J. Chem. Soc.*, 2934 (1957).

(11) P. A. Levene and H. L. Haller, *J. Biol. Chem.*, **81**, 703 (1929).

(12) H. W. J. Hills, J. Kenyon, and H. Phillips, *J. Chem. Soc.*, 576 (1936).

(13) H. L. Goering and W. I. Kimoto, *J. Amer. Chem. Soc.*, **87**, 1748 (1965).

(14) H. L. Goering, M. M. Pombo, and K. D. McMichael, *ibid.*, **85**, 965 (1963).
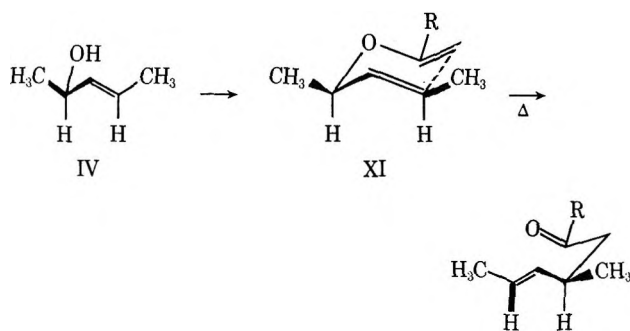
(15) Some uncertainty results in calculating optical yields since different values for the maximum rotation of the starting alcohol IV are obtained depending on whether the phthalate or saturated alcohol is used as the standard, different values for the maximum rotation of the acid VII are obtained depending on whether the ozonolysis product or hydrogenation product is used as the standard, and different maximum rotations have been reported for methylsuccinic acid. In each case we have chosen the more conservative value, so that our yields of 90% are a minimum and may be as much as 5–6% higher.

TABLE I

Starting alcohol			Rotation of product			
Rotation of phthalate	Rotation of alcohol	Optical purity, %	V	VII	Optical purity,d %	Optical yield, %
+37.3°	−13.2°	63.2a	+15.7°	+22.5°	56.9	90.0
(c 5.2, ether)	(c 2.5, CHCl₃)		(c 3.1, CHCl₃)	(c 1.6, CHCl₃)		
	−7.35°	35.2b	+9.90°	+12.6°	31.9	90.6
	(c 1.6, CHCl₃)		(c 4.7, CHCl₃)	(c 0.77, CHCl₃)		
−14.5°	+8.52°	38.2c		−13.6°	34.4	90.1
(c 1.24, CHCl₃)	(c 7, CHCl₃)			(c 28, CHCl₃)		

a Based on phthalate calculated to have maximum rotation of 59.0° in ether. *b* Based on above optical rotation of alcohol. *c* Based on maximum rotation[14] of phthalate of 38° in chloroform. *d* Based on maximum rotation of VII of 39.6° (see text).

quence of reaction *via* a transition state conformation (XI), resembling chair cyclohexane with all substit-

uents equatorial, characteristic of Claisen and Cope rearrangements in unconstrained molecules;[3,16] the generation of a trans double bond in the product is, of course, a simultaneous consequence of this transition-state geometry.[3] The magnitude of the asymmetric induction, which parallels (as it should) the geometric stereospecificity, is higher in these two reactions than in most simple Claisen rearrangements, and approaches that observed[16a] in the Cope rearrangement of 3-methyl-3-phenyl-1,5-heptadiene. It has already been pointed out[6,17] that the high stereoselectivity in the formation of trans double bonds can be attributed to nonbonded interactions between the group R in XI and other substituents in the transition states leading to cis product, and this also accounts for the high optical specificity in the generation of a new asymmetric center.

The unusual magnitude of asymmetric induction in these modifications of the Claisen rearrangement makes them particularly suitable for stereospecific synthesis. Beginning with optically active allylic alcohols, compounds readily available by resolution or by asymmetric reduction,[18] it is possible to form a new carbon–carbon bond at an asymmetric center in almost quantitative optical yield and in a predictable absolute orientation. Even the simple examples reported here illustrate the power of this approach: an earlier attempt to prepare 3-methyl-4-hexenoic acid by malonic ester synthesis with optically active 2-chloro-3-pentene led to totally racemized product,[19] in contrast to the 90% optical yields reported here.

Experimental Section

Melting points were determined on a Thomas-Hoover oil immersion apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 237B spectrophotometer. Nuclear magnetic resonance spectra were obtained on a Varian HA-100 spectrometer by Mr. Courtney Pape; chemical shifts are recorded as δ units, using tetramethylsilane as an internal reference. Elemental analyses were performed by Galbraith Microanalytical Laboratories, Knoxville, Tenn.

3-Penten-2-ol.—Racemic 3-penten-2-ol, bp 45–47° (25 mm), was prepared in 60% yield by the reaction[20] of methylmagnesium iodide with crotonaldehyde, and converted to the phthalate, mp 90–91°. Resolution was effected[12] through the brucine salt, which was recrystallized four times from chloroform-acetone. The phthalate was regenerated by stirring the brucine salt in ice-cold 3 *M* hydrochloric acid, extracting with ether, concentrating the dried extracts, and recrystallizing the residue from ether-pentane. The product of a typical resolution had mp 83–84°, $[\alpha]^{25}D$ +39.2° (c 5.6, ether), +38.9° (c 6.6, ethanol), +25.2° (c 2.6, CHCl₃).[21] Optically active alcohol was obtained by lithium aluminum hydride reduction of the phthalate as recommended by Goering.[14] In a typical run, phthalate of $[\alpha]^{25}D$ +37.3° (c 5.2, ether) was reduced to alcohol with $[\alpha]D$ −13.2° (c 1.78, CHCl₃), −7.23° (c 4.3, ether), bp 45° (30 mm).

Hydrogenation of 3-Penten-2-ol.—An ether solution of 2.8 g of 3-penten-2-ol, $[\alpha]^{25}D$ +8.35° (c 2.5, CHCl₃), was hydrogenated over Adams catalyst (220 mg) at atmospheric pressure. After the catalyst was filtered, distillation gave 2.2 g of 2-pentanol, bp 47° (25 mm), $[\alpha]^{25}D$ −6 37° (c 2.3, CHCl₃), −5.32° (neat, 1 dm). The product was homogeneous by vpc and had an infrared spectrum identical with that of authentic material.

In another run, 3-penten-2-ol, $[\alpha]^{25}D$ −13.2° (c 2.5, CHCl₃), was reduced to 2-pentanol, $[\alpha]^{25}D$ +10.7° (c 1.8, CHCl₃).

Based on the maximum reported[22] rotation of 2-pentanol of 13.9° (neat), 2-pentanol with $[\alpha]^{25}D$ −5.32° (neat) is 38.3% optically pure. The maximum rotation calculated for 3-penten-2-ol from this experiment is 21.8°.

Reaction with N,N-Dimethylacetamide Dimethyl Acetal. A. —A solution of 4.3 g of *trans*-3-penten-2-ol and 13 g of a mixture[6,23] of N,N-dimethylacetamide dimethyl acetal and 1-methoxy-1-dimethylaminoethylene in 70 ml of dry xylene was refluxed for 17 hr and then fractionated. Amide V was collected at 110–150° (20 mm): yield 6.1 g (80%); ir (neat) 1655, 1260, 1120, 950 cm⁻¹; nmr (CDCl₃) δ 0.98 (3 H, d, J = 6 Hz), 1.58 (3 H, d, J = 5.5 Hz), 2.21 (2 H, m), 2.63 (1 H, m), 2.83 (3 H, s), 2.97 (3 H, s), 5.40 (2 H, m).

Anal. Calcd for C₉H₁₇NO: C, 69.63; H, 11.04; N, 9.02. Found: C, 69.76, 69.83; H, 10.98, 11.03; N, 9.06, 8.90.

B.—*trans*-3-Penten-2-ol, $[\alpha]^{25}D$ −13.2° (c 2.5, CHCl₃), 0.43 g, when treated under the same conditions with 2.0 g of a mixture of I and II in 20 ml of xylene, gave V, $[\alpha]^{25}D$ +15.7° (c 3.1, CHCl₃).

C.—*trans*-3-Penten-2-ol, $[\alpha]^{25}D$ −7.35° (c 1.6, CHCl₃), treated as in B, gave V, $[\alpha]^{25}D$ +9.90° (c 4.7, CHCl₃).

Hydrolysis of Amide V. A.—Amide V, 550 mg, $[\alpha]D$ +15.7°,

(16) (a) R. K. Hill and N. W. Gilman, *Chem. Commun.*, 619 (1967); (b) R. K. Hill and N. W. Gilman, *Tetrahedron Lett.*, 1421 (1967).

(17) C. L. Perrin and D. J. Faulkner, *Tetrahedron Lett.*, 2783 (1969).

(18) See ref 3a, Chapter 5, for an excellent survey.

(19) E. Bergmann, *Helv. Chim. Acta*, **20**, 590 (1937).

(20) E. R. Coburn, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 696.

(21) In contrast to the report[13,14] that the phthalate has essentially the same rotation in ether as in chloroform, we consistently observed the magnitude of the rotation in ether tc be 1.5 that of the rotation in chloroform.

(22) D. H. Brauns, *J. Res. Nat. Bur. Stand.*, **31**, 83 (1943).

(23) H. Bredereck, F. Effenberger, and G. Simchen, *Angew. Chem.*, **73**, 493 (1961); *Chem. Ber.*, **96**, 1350 (1963).

was heated in a solution of 4 g of sodium hydroxide in 30 ml of water at 100–110° for 8 hr. After cooling, the solution was washed with ether, acidified with hydrochloric acid, and extracted with ether. The ether extracts were washed with water, dried, and distilled to yield 3-methyl-4-hexenoic acid[24] (VII): bp 160° (bath) (25 mm); yield 330 mg (73%); $[\alpha]^{25}D$ +22.5° (c 1.6, CHCl$_3$). The infrared spectrum was identical with that of the acid from hydrolysis of ester VI.

B.—Hydrolysis of a sample of V, 120 mg, $[\alpha]^{25}D$ +9.9°, under similar conditions gave acid VII: bp 140° (bath) (18 mm) $[\alpha]^{25}D$ +12.6° (c 0.77, CHCl$_3$); yield 90 mg (90%); nmr δ 1.03 (3 H, d, J = 6.5 Hz), 1.62 (3 H, d, J = 5 Hz), 2.29 (2 H, m), 2.60 (1 H, m), 5.41 (2 H, m), 11.2 (1 H, s).

Reaction with Ethyl Orthoacetate.—A mixture of 17 g of racemic *trans*-3-penten-2-ol, 225 g of ethyl orthoacetate, and 1.0 g of propionic acid was refluxed vigorously (bath temperature 180°) for 22 hr, then fractionally distilled. The product VI (21 g, 68%) was collected at 85–90° (20 mm); vpc analysis (on 20% SDC 710, at 150°, flow rate 40 ml/min) showed a single peak. The compound was identified as VI by chemical and spectroscopic evidence: ir (neat) 1735, 1180, 3040, 970 cm^{-1}; nmr (CCl$_4$) δ 1.03 (3 H, d, J = 6 Hz), 1.25 (3 H, t, J = 7 Hz) 1.65 (3 H, d, J = 5 Hz), 2.26 (2 H, d), 2.55 (1 H, m), 4.17 (2 H, q, J = 7 Hz), 5.48 (2 H, m).

Anal. Calcd for C$_9$H$_{16}$O$_2$: C, 69.19; H, 10.32. Found: C, 69.25; H, 10.47.

In a similar run under milder conditions, the reagents were heated at 140° (bath temperature) for 18 hr while ethanol was continuously removed by fractionation through a long Vigreux column. The product collected at 87–95° (40 mm) showed two main peaks on vpc analysis. Pure samples of the two major components were collected by preparative vpc. The more volatile was identical with VI, while the second was assigned the structure X: ir 3040, 1230, 1192, 1160, 1060, 970 cm^{-1}; nmr δ 1.18 (6 H, t, J = 7 Hz), 1.23 (3 H, d, J = 7 Hz), 1.45 (3 H, s), 1.68 (3 H, d, J = 5 Hz), 3.6 (4 H, q, J = 7 Hz), 4.4 (1 H, m), 6.62 (2 H, m).

Anal. Calcd for C$_{11}$H$_{22}$O$_3$: C, 65.31; H, 10.96. Found: C, 65.10; H, 11.12.

Hydrolysis.—A solution of 21 g of VI in 90 ml of ethanol was treated with 30 g of sodium hydroxide in 90 ml of water and refluxed for 30 min. After acidification the mixture was extracted with ether. Distillation of the dried extracts furnished 13.5 g (80%) of 3-methyl-4-hexenoic acid (VII), bp 129° (15 mm). The infrared spectrum was identical with that of the acid obtained by hydrolysis of amide V.

Anal. Calcd for C$_7$H$_{12}$O$_2$: C, 65.59; H, 9.44. Found: C, 65.38; H, 9.31.

Reaction of (+)-IV with Ethyl Orthoacetate.—A mixture of *trans*-3-penten-2-ol, $[\alpha]^{25}D$ +8.52° (c 7, CHCl$_3$), prepared by hydrolysis of acid phthalate of $[\alpha]^{25}D$ −14.5° (c 1.24, CHCl$_3$), together with 26 g of ethyl orthoacetate and 0.5 g of propionic acid was heated at 145° for 40 hr. Because of difficulty in cleanly separating the product from excess orthoacetate by dis-

(24) A. W. Burgstahler, *J. Amer. Chem. Soc.*, **82**, 4681 (1960).

tillation, the reaction mixture was heated with 5 ml of 10 M NaOH and 20 ml of methanol for 2 hr, then distributed between water and ether. The alkaline layer was acidified with hydrochloric acid and extracted with ether several times. The combined extracts were washed with saturated ammonium chloride solution, dried, and distilled, affording 1.75 g (60%) of acid VII, bp 127–130° (37 mm), $[\alpha]^{25}D$ −13.6° (c 28, CHCl$_3$). The ir and nmr spectra were identical with those of racemic material.

Resolution of 3-Methyl-4-hexenoic Acid. A. With Brucine. A mixture of 6.4 g of the racemic acid and 23.3 g of brucine tetrahydrate was dissolved in 80 ml of hot 9:1 acetone–methanol and allowed to crystallize. The first crop, yield 6.31 g, mp 89–92°, $[\alpha]^{24}D$ −50.7° (c 2.5, CHCl$_3$), was recrystallized three more times from the same solvent pair to give 3.0 g of salt with mp 93–94°, $[\alpha]^{24}D$ −48.9° (c 4.1, CHCl$_3$).

The acid was regenerated by dissolving the salt in dilute hydrochloric acid and extracting with ether. Distillation gave 0.55 g, bp 160° (bath) (2.5 mm), $[\alpha]^{25}$ D −13.6° (c 1.9, CHCl$_3$).

B. With Quinine.—A warm solution of 5.12 g of the racemic acid and 12.97 g of anhydrous quinine in 50 ml of 1:2 chloroform–acetone was diluted with 100 ml of ether and allowed to crystallize. The first crop, yield 6.98 g, mp 131–133°, $[\alpha]^{24}D$ −100.7° (c 1.05, CHCl$_3$), was recrystallized three more times from chloroform–acetone to afford salt with mp 138–139°, $[\alpha]^{24}D$ −82.1° (c 1.9, CHCl$_3$).

Regeneration of the acid was again effected by dissolving the salt in dilute hydrochloric acid and extracting with ether. Distillation gave 0.63 g of acid, bp 100–105° (bath) (0.3 mm), $[\alpha]^{25}D$ 33.8°, $[\alpha]^{25}_{578}$ +35.1°, $[\alpha]^{25}_{546}$ +40.2°, $[\alpha]^{25}_{436}$ +71.3° (c 1.89, CHCl$_3$).

Ozonolysis of 3-Methyl-4-hexenoic Acid.—A stream of ozonized oxygen (3% in ozone) was bubbled through a solution of 220 mg of 3-methyl-4-hexenoic acid, $[\alpha]^{25}D$ +33.8° (c 1.89, CHCl$_3$), in 25 ml of ethyl acetate at −75° for 4 min, until the solution became blue. The solvent was removed at reduced pressure at room temperature and the residue was treated with a mixture of 10 ml of 10% aqueous sodium carbonate and 6 ml of 30% hydrogen peroxide at 70–80° for 3 hr. After cooling, the solution was acidified with concentrated hydrochloric acid, saturated with sodium chloride, and extracted with ether. Removal of the solvent left a crystalline residue (128 mg) of methylsuccinic acid, mp 108–110°, $[\alpha]^{25}D$ −14.1° (c 1.27, ethanol).

Hydrogenation of 3-Methyl-4-hexenoic Acid.—A solution of 70 mg of 3-methyl-4-hexenoic acid, $[\alpha]^{25}D$ +22.5° (c 1.6, CHCl$_3$), in 35 ml of ethanol was hydrogenated at atmospheric pressure over platinum black for 12 hr. After filtration of the catalyst, the filtrate was concentrated and distilled to afford 60 mg of 3-methylhexanoic acid, bp 150° (bath) (25 mm), $[\alpha]^{25}D$ +1.63° (c 0.67, benzene).

Registry No.—I, 18871-66-4; III, 78-39-7; (+)-IV, 35666-69-4; (−)-IV, 926-58-9; (+)-V, 35666-71-8; (±)-VI, 35666-72-9; (±)-VII, 35666-73-0; (+)-VII, 35666-74-1; (−)-VII, 35666-75-2; (−)-VII brucine salt, 35666-76-3; (+)-VII quinine salt, 35737-20-3; (+)-VIII, 35666-77-4; (±)-X, 35666-78-5.

Notes

Basic Hydrogen Peroxide Cleavage of a Bicyclic Ketone. A New Procedure for a Prostaglandin Intermediate

NED M. WEINSHENKER* AND REBECCA STEPHENSON

Alza Research, Palo Alto, California 94304

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In work on improving the efficiency and simplicity of prostaglandin synthesis *via* the Corey method,[1] we questioned the need for isolating and then hydrolyzing the intermediate bicyclic lactone **2** in order to obtain hydroxy acid **3** for optical resolution.
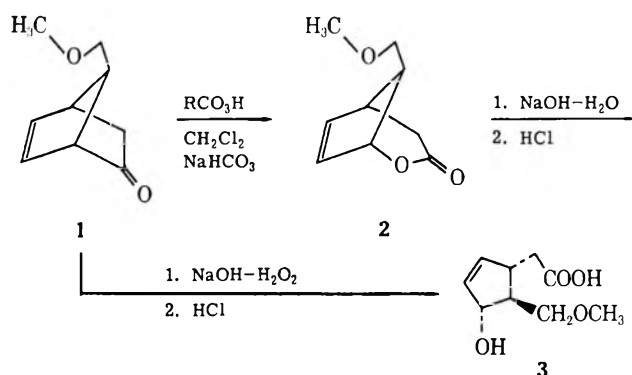
Treatment of the ketone **1** ($\sim$85% pure) with 1.20 equiv of sodium hydroxide and 1.5 equiv of 30% hydrogen peroxide proceeded rapidly and exothermically to yield the desired product. This material could be isolated (quantitative) and resolved *via* *d*-ephedrine. Purification of this salt removed by-products formed from the oxidation of undesired isomers of the starting ketone. In addition, if *racemic* lactone **4** were desired,
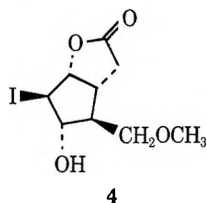
direct iodolactonization of the resulting basic solution should be feasible according to the existing procedure.[2] This procedure greatly reduces the time and cost of reagents involved and is readily adaptable to scaling up.[3] Although this reaction is reported[4] to give poor to fair yields with unstrained ketones, it should work reasonably well with other strained bicyclic ketones.

(1) E. J. Corey, T. K. Schaaf, W. Huber, V. Koelliker, and N. M. Weinshenker, *J. Amer. Chem. Soc.*, **92**, 397 (1970).

(2) E. J. Corey, N. M. Weinshenker, T. K. Schaaf, and W. Huber, *ibid.*, **91**, 5675 (1969).

(3) The sequence has been carried out without difficulty on a 500-g scale.

(4) Several examples of basic hydrogen peroxide cleavage of ketones are given in J. G. Wallace, "Hydrogen Peroxide in Organic Chemistry," E. I. du Pont de Nemours and Co., Wilmington, Del., pp 35–37.

Experimental Section

($\pm$)-3α-Carboxymethyl-4β-methoxymethyl-5α-hydroxycyclopentene (3).—The ketone 1 (45.1 g, 0.296 mol, 85% pure by vpc analysis) was dissolved in 125 ml of ether and mixed with a solution of 14.1 g (0.353 mol) of sodium hydroxide in 120 ml of water. The two-phase system was cooled (ice bath) and rapidly stirred while 53 ml of 30% hydrogen peroxide solution was added over a period of 40 min. The internal reaction temperature was maintained at 10–25°. After the addition, vpc analysis indicated that the ether phase was devoid of starting ketone. The aqueous phase was separated, washed with 100 ml of ether, and then neutralized (pH 6–7) with concentrated hydrochloric acid. Solid sodium sulfite was added cautiously to destroy excess hydrogen peroxide. The ethyl acetate (100 ml) was added, the mixture was cooled in ice–water, and concentrated hydrochloric acid was added to pH 3–4. The aqueous phase was separated and extracted with ethyl acetate (4 $\times$ 50 ml and 2 $\times$ 100 ml). The combined organic phases were combined, dried (MgSO$_4$), and concentrated to yield 42.0 g (78%) of the hydroxy acid as a colorless, viscous oil. Further acidification of the aqueous phase (with cooling) to pH 1.5–2 and extraction with ethyl acetate yielded an additional 13.0 g of **3**, total yield 55.0 g (99%); tlc analysis (silica gel; benzene:dioxane:HOAc, 20:20:1) indicated material identical with hydroxy acid prepared by the published procedure.[1]

Resolution[5] of the Hydroxy Acid 3.—The hydroxy acid (55.0 g) was dissolved in 655 ml of ethyl acetate and thoroughly mixed with 49.8 g of *d*-(+)-ephedrine (Fluka) dissolved in 1455 ml of benzene. The first crop of crystals ($\sim$35 g) was redissolved in 1400 ml of 30% ethyl acetate–benzene and yielded 27.3 g of resolved salt, $[\alpha]^{25}$D 37.5° (c 1.0780, MeOH) [lit.[1] $[\alpha]^{23}$D 37.2° (c 1.0, MeOH)]. The overall yield (61.5%) takes into consideration the actual amount of desired ketone in the starting material.

Registry No.—3, 35672-36-7; hydrogen peroxide, 7722-84-1.

(5) The solvent system for resolution of the hydroxy acid has been modified from the original procedure[2] and allows for a severalfold decrease in the volume of solvent with no compromise in optical purity or number of crystallizations. The solvent system was developed by Dr. Niels Andersen.

Disaccharide Nucleosides of Benzimidazole

DAVALURI R. RAO AND LEON M. LERNER*

Department of Biochemistry, State University of New York, Downstate Medical Center, Brooklyn, New York 11203
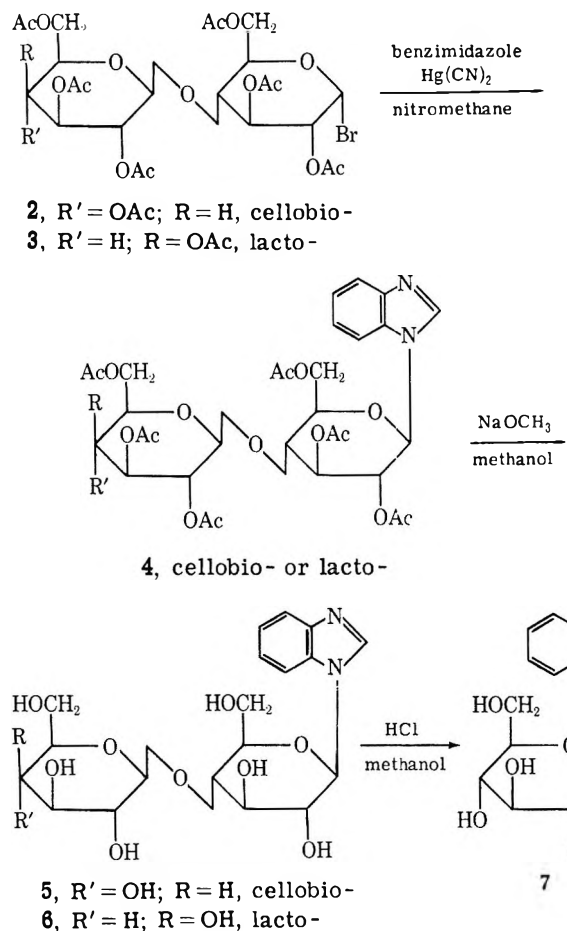
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This laboratory has been engaged in exploring methods of synthesis of disaccharide nucleosides, and reports concerning the synthesis of 9-β-melibiosyladenine[1] and 9-(2-deoxycellobiosyl)adenine[2] have appeared. The method of preparation of these compounds was based upon the coupling procedure devised by Davoll and Lowy,[3] in which a blocked glycosyl halide was condensed with the mercuric chloride salt of a purine base in a neutral solvent such as xylene or toluene. Similar techniques were used by Wol-

(1) L. M. Lerner, *J. Org. Chem.*, **32**, 3663 (1967).

(2) L. M. Lerner, *J. Med. Chem.*, **11**, 912 (1968).

(3) J. Davoll and B. A. Lowy, *J. Amer. Chem. Soc.*, **73**, 1650 (1951).

Scheme I

2, R′ = OAc; R = H, cellobio-
3, R′ = H; R = OAc, lacto-

4, cellobio- or lacto-

5, R′ = OH; R = H, cellobio-
6, R′ = H; R = OH, lacto-

7

from and coworkers,[4] who prepared purine nucleosides derived from maltose, cellobiose, and lactose. In more recent work,[5] applications to nucleoside synthesis have been made of a procedure for glycoside synthesis first reported by Helferich and coworkers[6] in which glycosyl halides were treated with alcohols in nitromethane using mercuric cyanide as an acid acceptor. Thus, the disaccharide nucleoside, 2,6,8-trichloro-9-(hepta-O-acetyl-β-D-gentiobiosyl)purine (**1**), was prepared in 45% yield under quite similar conditions using hot nitroethane as the solvent and anhydrous calcium sulfate (Drierite) as an internal desiccant.[5] This same article also reported a good yield of 1-β-D-glucopyranosylbenzimidazole when the coupling reaction was performed in refluxing nitromethane. We now wish to report on what appears to be the first preparation of disaccharide nucleosides of benzimidazole.[7]

Taking note of the fact that Yamaoka, *et al.*,[5] had failed in their attempt to prepare **1** by using a heavy metal salt of the purine and of the failure of other coupling procedures tried in this laboratory to give significant yields of disaccharide nucleosides when attempted with a variety of nitrogen bases, the mercuric cyanide–nitromethane procedure[5,6] was applied toward

the synthesis of 1-β-cellobiosylbenzimidazole (**5**) and 1-β-lactosylbenzimidazole (**6**) and successfully carried out (Scheme I). Hepta-O-acetyl-α-cellobiosyl bromide[8] (**2**) and hepta-O-acetyl-α-lactosyl bromide[9] (**3**) were each treated with benzimidazole in refluxing nitromethane. After work-up and deacetylation in methanolic sodium methoxide, the nucleosides were isolated free of sugar by-products and unreacted disaccharides by preparation of their crystalline picrates. Removal of the picrate ion with an anion exchange resin[10] followed by cellulose column chromatography gave **5** and **6**.

Proof of structure of these new compounds was based upon (1) elementary analyses, (2) ultraviolet spectra, which were similar to those reported earlier for benzimidazole nucleosides,[11] and (3) degradation of **5** and **6** to 9-β-D-glucopyranosylbenzimidazole (**7**), which was crystallized as the picrate.[12] The latter procedure was conducted in a manner similar to that which was applied to the structure proof of some pyrimidine disaccharide nucleosides,[13] namely by cleavage of the O-glycosidic bond of the disaccharide in a mixture of hydrogen chloride in methanol. This procedure, therefore, demonstrated that the configuration at the N-glucosyl bond was β.

Experimental Section[14]

1-β-Cellobiosylbenzimidazole (5).—A suspension of benzimidazole (1.2 g, 10 mmol) and mercuric cyanide (5 g) in 800 ml of nitromethane was dried by distillation of 150 ml of the solvent. The mixture was allowed to cool slightly and 5 g of molecular sieves 3A and 14.8 g (21 mmol) of hepta-O-acetylcellobiosyl bromide[8] (**2**) in 50 ml of dry nitromethane were added. The reaction mixture was heated at reflux for 18 hr (*hood!*) and filtered while hot, and the solvent was evaporated. The residue was extracted with hot chloroform (300 ml) and this extract, after cooling, was washed three times with 150-ml portions of 30% aqueous potassium iodide and once with water and dried over anhydrous magnesium sulfate. Evaporation of the solvent gave a foam containing the blocked nucleoside **4**, which was deacetylated by heating at reflux in methanolic sodium methoxide (*ca.* pH 11 with moist pH paper) for 45 min. The methanol was removed by evaporation, the residue was dissolved in 200 ml of water, and the pH was adjusted to 7 with a Dowex-50 (H+) resin. The aqueous solution was washed well with chloroform and evaporated to a residue which was dissolved in a minimum amount of methanol and treated with 50 ml of 10% methanolic picric acid. After being chilled in the refrigerator for several days, a crystalline picrate was obtained which was recrystallized from water to afford 1.6 g (26%). An analytical sample was obtained by recrystallization from water, mp 150–151°.

Anal. Calcd for $C_{25}H_{29}N_5O_{17}$: C, 44.72; H, 4.35; N, 10.43. Found: C, 44.59; H, 4.34; N, 10.23.

The main portion of the picrate (1.35 g) was dissolved in 200 ml of warm water and treated with Bio-Rad AG1-X8 ($CO_3{}^{2-}$) anion exchange resin until the solution became colorless.[10] After an additional 1 hr of stirring, the resin was removed by filtration and the water was evaporated to give a foam which was chromatographed on a column (48 × 4.5 cm) of Whatman cellulose powder with 86:14 n-butyl alcohol–water. Fractions containing

(4) M. L. Wolfrom, P. McWain, and A. Thompson, *J. Amer. Chem. Soc.*, **82**, 4353 (1960); M. L. Wolfrom, P. McWain, F. Shafizadeh, and A. Thompson, *ibid.*, **81**, 6080 (1959).

(5) N. Yamaoka, K. Aso, and K. Matsuda, *J. Org. Chem.*, **30**, 149 (1965).

(6) B. Helferich and K. Weis, *Chem. Ber.*, **89**, 314 (1956); B. Helferich and R. Steinpreis, *ibid.*, **91**, 1794 (1958).

(7) For an excellent review of the subject of benzimidazole nucleosides, see L. B. Townsend and G. R. Revankav, *Chem. Rev.*, **70**, 389 (1970).

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(9) E. Fischer and H. Fischer, *Ber.*, **43**, 2521 (1910).

(10) B. R. Baker and K. Hewson, *J. Org. Chem.*, **22**, 959 (1957).

(11) G. R. Revankar and L. B. Townsend, *J. Heterocycl. Chem.*, **5**, 477 (1968); J. Davoll and G. B. Brown, *J. Amer. Chem. Soc.*, **73**, 5781 (1951).

(12) A. W. Johnson, G. W. Miller, J. A. Mills, and A. R. Todd, *J. Chem. Soc.*, 3061 (1953).

(13) C. L. Stevens and P. Blumbergs, *J. Org. Chem.*, **30**, 2723 (1965).

(14) Melting points were determined on a Kofler micro hot stage and are corrected values. Elementary analyses were performed by the Baron Consulting Co., Orange, Conn. Evaporations were carried out under reduced pressure on a rotary evaporator at a bath temperature of 40–45°.

10 ml each were collected and the major component was found in tubes 49–102. The fractions were combined, the solvents were evaporated, and the product was crystallized from aqueous ethanol to afford 0.8 g (86%) of colorless needles: mp 186–188°; $[\alpha]^{25}$D 13.5° (c 0.4, 0.1 N HCl); uv max (0.01 N HCl) 253 mμ (ϵ 5300), 262 (5610), 268 (6580), and 274 (5560).

Anal. Calcd for $C_{19}H_{26}O_{10}N_2 \cdot H_2O$: C, 49.56; H, 6.13; N, 6.09. Found: C, 49.14; H, 6.24; N, 6.12.

1-β-Lactosylbenzimidazole (6).—The preparation of 6 followed the exact same procedure given above for the preparation of 5. A picrate was obtained from cold methanol, the analytical sample of which had mp 219–222°.

Anal. Calcd for $C_{25}H_{29}N_5O_{17}$: C, 44.72; H, 4.35; N, 10.43. Found: C, 44.93; H, 4.59; N, 10.29.

Regeneration of the free nucleoside with an anion exchange resin as described above and chromatography on a cellulose column gave 6, which resisted crystallization for many months. Therefore, it was lyophilized and dried further in a drying pistol (P_2O_5) under high vacuum at 40° for 48 hr and at 110° for 24 hr to afford 0.46 g of a fluffy, white powder which liquified slowly at temperatures above 170° to a viscous syrup: $[\alpha]^{25}$D 4° (c 1.3, H_2O); uv max (0.01 N HCl) 253 mμ (ϵ 5095), 262 (5390), 268 (6230), and 275 (5325).

Anal. Calcd for $C_{19}H_{26}N_2O_{10} \cdot H_2O$: C, 49.56; H, 6.13; N, 6.09. Found: C, 49.77; H, 5.80; N, 6.00.

Picrate of 1-β-D-Glucopyranosylbenzimidazole (7). From 5.— A sample (0.2 g) of 5 was dissolved in 50 ml of methanol and the solution was saturated with dry hydrogen chloride gas at 0°, then kept at room temperature for 2 days in a pressure bottle. The solution was evaporated to dryness, the residue was dissolved in methanol, and the pH (moist pH paper) was adjusted to neutrality with a few drops of ammonium hydroxide. To this solution was added 1 ml of 10% methanolic picric acid and the flask was chilled in the refrigerator for several days. The crystals (mp 142–152°) were filtered off and recrystallized from water to give yellow needles, mp 146–149°, $[\alpha]^{25}$D $-19.4°$ (c 1, pyridine) [lit.[12] mp 145–148°, $[\alpha]^{15}$D $-18°$ (c 2, pyridine)].

From 6.—Application of the same procedure as above to 6 resulted in a product (mp 128–138°) which required two recrystallizations from water to give yellow needles whose melting point was not depressed upon admixture with the picrate of 7.

Registry No.—5, 35672-33-4; 5 picrate, 35672-34-5; 6, 35672-35-6; 6 picrate, 35737-07-6.

A Convenient Deuterium Exchange Technique

JAMES M. WATSON, ALAN R. TANNER, AND
ROYSTON M. ROBERTS*

*Department of Chemistry, The University of Texas at Austin,
Austin, Texas 78712*

During the course of our investigations of the enolene rearrangement,[1-3] a convenient and mild deuterium exchange technique was developed which we believe to be superior to presently used procedures. Our technique capitalizes on the elegant procedure of Pasto and Meyer,[4] which makes ethanol-O-d_1 easily and economically available as a source of exchangeable deuterium and incorporates a novel method of isolating the desired deuterated product from the reaction mixture.

The compound to be deuterated is dissolved in an appropriate excess of ethanol-O-d_1 and a catalytic amount of sodium metal is added. The resulting

solution is stirred at room temperature overnight, the ethanol is removed *in vacuo*, and a second portion of ethanol-O-d_1 is added. After exchange with two or three portions of ethanol-O-d_1 has been carried out in this way, an amount of acetyl chloride just sufficient to destroy the sodium ethoxide present is added. The resulting ethyl acetate is removed along with ethanol-O-d_1 by flash distillation, and the remaining material is distilled to effect isolation of the desired deuterated product.

This method has been shown to be generally applicable to ketones which boil considerably higher than ethanol and ethyl acetate and it should also be suitable for the deuteration of other compounds which possess acidic hydrogens. Among the compounds which were successfully deuterated in the α position by this technique are 4-pentenophenone; 4'-R-4-pentenophenone where R = CH_3, CH_3O, Cl; 2-R-4-pentenophenone where R = CH_3, CH_2CH_3, $(CH_2)_2CH_3$, $CH(CH_3)_2$, $C(CH_3)_3$, and C_6H_5; 2-allyl-1-indanone; 2-allyl-1-tetralone; 3-methyl-4-pentenophenone; 2,3-dimethyl-4-pentenophenone; 2-ethyl-3-methyl-4-pentenophenone; 3-methyl-2-m-propyl-4-pentenophenone; and 2-α-methylallyl-1-tetralone.

In all cases encountered in our work, the reaction substrate was soluble in ethanol; however, in instances where the material to be deuterated is not ethanol soluble, an inert cosolvent such as dioxane may be added to maintain homogeneity.

Experimental Section

The following examples are representative of the technique.

4-Pentenophenone-2-d_2.—4-Pentenophenone[2] (8.0 g, 0.05 mol) was stirred with 59 ml (1.0 mol) of ethanol-O-d_1 and *ca.* 0.2 g of sodium metal for 24 hr, after which time the ethanol-O-d_1 was removed by the application of aspirator vacuum and a second 59-ml portion of ethanol-O-d_1 was added. After 24 hr this process was again repeated and, after the final period of stirring, the solution was neutralized by the addition of *ca.* 1 ml of acetyl chloride. The resulting mixture was concentrated and distilled *in vacuo* to obtain product, bp 58–65° (0.05 mm), n^{25}D 1.5282. The yield was 6.5 g. The nmr spectrum (CCl_4) was consistent with the structure of 4-pentenophenone-2-d_2: δ 2.45 (d, $-CH_2-$, 2 H), 5.0 (m, $=CH_2$, 2 H), 5.9 (m, $-CH=$, 1 H), 7.4 and 7.9 ppm (2 m, H_{arom}, 5 H). The ir spectrum contained strong absorptions at 1690, 975, and 910 cm^{-1}.

Anal. Calcd for $C_{11}H_{10}D_2O$: C, 81.44; H + D, 8.69. Found: C, 81.27; H + D, 8.70.

4'-Chloro-4-pentenophenone-2-d_2.—The deutration procedure used was identical with that employed with 4-pentenophenone: 5.0 g (0.026 mol) of 4'-chloro-4-pentenophenone[5] was used and, after work-up, vacuum distillation gave water-clear distillate, bp 80–85° (0.06 mm). This product was further purified by column chromatography on silica gel [petroleum ether (bp 60–80°)–benzene] followed by micro vacuum distillation. The product thus obtained was pure to glpc analysis and the nmr spectrum (neat) was consistent with the structure of 4'-chloro-4-pentenophenone wherein the α position was 96.5% deuterated: δ 2.1 (d, $-CH_2-$, 2 H), 2.5 (m, $-CH_2-$, 0.07 H), 4.7 (m, $=CH_2$, 2 H), 5.5 (m, $-CH=$, 1 H), 6.9 (d, H_{arom}, 2 H), and 7.4 ppm (d, H_{arom}, 2 H). The ir spectrum contained strong absorptions at 1680, 1000, and 915 cm^{-1}.

Anal. Calcd for $C_{11}H_9D_2OCl$: C, 67.17; H + D, 6.66. Found: C, 67.31; H + 6.64.

2-Methyl-4-pentenophenone-2-d.—The deuteration applied to 2-methyl-4-pentenophenone[6] was identical with that employed with 4-pentenophenone with the exception that reflux was

(1) R. M. Roberts and R. G. Landolt, *J. Amer. Chem. Soc.*, **87**, 2281 (1965).

(2) R. M. Roberts, R. G. Landolt, R. N. Greene, and E. W. Heyer, *ibid.*, **89**, 1404 (1967).

(3) R. M. Roberts and J. M. Watson, *J. Org. Chem.*, **34**, 4191 (1969).

(4) D. J. Pasto and G. R. Meyer, *ibid.*, **33**, 1257 (1968).

(5) J. M. Watson, Ph.D. Dissertation, University of Texas at Austin, 1969.

(6) A. R. Tanner, Ph.D. Dissertation, University of Texas at Austin, 1969.

maintained. After work-up, simple distillation gave product, bp 62–72° (0.07 mm), which was pure to glpc. The nmr spectrum (neat) was consistent with the structure of 2-methyl-4-penteno-phenone wherein the α position was completely deuterated: δ 1.2 (s, –CH$_3$, 3 H), 2.4 (m, –CH$_2$–, 2 H), 5.0 (m, =CH$_2$, 2 H), 5.7 (m, –CH=, 1 H), 7.4 and 7.9 ppm (2 m, H$_{arom}$, 5 H). The ir spectrum contained strong absorptions at 1690, 990, 920, and 700 cm^{-1}.

Registry No.—4-Pentenophinone-*2-d$_2$*, 35666-59-2; 4′-chloro-4-pentenophenone-*2-d$_2$*, 35666-62-7; 2-methyl-4-pentenophenone-*2-d*, 35666-63-8.

The Reaction of Atomic Nitrogen with Propene

J. J. HAVEL*[1] AND P. S. SKELL

*Department of Chemistry,
The Pennsylvania State University,
University Park, Pennsylvania 16802*

The reaction of atomic nitrogen with propene was first reported by Winkler and Trick.[2] Later work on this reaction in the gas[3-6] and solution[7] phases has shown widely differing results. We report here the solution phase reaction of propene with atomic nitrogen. The atomic nitrogen of this study was generated by a microwave discharge through molecular nitrogen. This is a conventional source of nitrogen atoms.

The major nitrogen-containing product of the reaction of atomic nitrogen with all hydrocarbons is HCN. Lichtin[6] has reported that the nitrogenous products from the propene reaction ($[C_3H_6]/[N]$ = 2.7) in the gas phase are HCN (30% yield), acetonitrile (10% yield), and acrylonitrile (2% yield).

Lichtin, Shinozaki, and Shaw[3] have also used carbon-14 labeling to follow the fate of each of the three carbons in propene (labeled $^1CH_2={}^2CH—{}^3CH_2$). Hydrogen cyanide arises slightly more extensively from C-3 than from C-1 or C-2. The acetonitrile contains one carbon from C-2 and another carbon from either C-1 or C-3. This result indicates that acetonitrile is formed from an intermediate in which C-1 and C-3 are equivalent.

Oka, Suda, and Sato[7] have studied the γ-radiolysis of liquid nitrogen containing a small amount of propene. Under these conditions, the only nitrogenous product was acetonitrile (12% yield). They propose that ground state (^4S) atomic nitrogen is the precursor of the acetonitrile. This result is in contrast to that previously reported for atomic nitrogen reactions with hydrocarbons, where HCN is the major product.

Oka, Suda, and Sato have also investigated the reaction of a 1:1 mixture of propene-d_0 and propene-d_6 and the reaction of CD$_3$CH=CHD. The acetonitrile from the propene-d_0–propene-d_6 mixture was mainly d_0 and

d_3, while the acetonitrile from CD$_3$CH=CHD was mainly d_3. They conclude that the key intermediate in acetonitrile formation is made by nitrogen atom addition to C-2 to make a primary radical. This radical makes acetonitrile by simultaneously cleaving away the hydrogen atom on C-2 and the CH$_2$ group.

$$CD_3CH=CHD + N \longrightarrow CD_3—\overset{:\dot{N}\cdot}{\underset{\overset{|}{H}}{C}}—\dot{C}HD \longrightarrow$$

$$CD_3C{\equiv}N + \cdot CH_2D$$
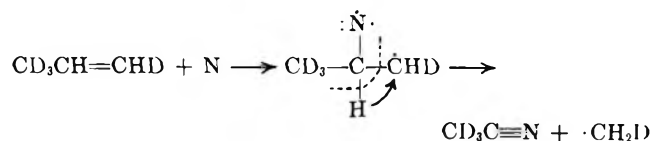
In their pathway, acetonitrile is formed from C-2 and C-3; C-1 and C-3 never become equivalent as in the gas phase study of Lichtin.

We have examined the liquid phase reaction of propene with atomic nitrogen at −160°. The nitrogenous products from this reaction are HCN (55.4% yield), acetonitrile (4.9%), and acrylonitrile (0.17%). The mechanism of formation of acetonitrile and acrylonitrile was studied by reaction of 2-deuteriopropene and 3-deuteriopropene. Hydrogen cyanide from these reactions was not analyzed for deuterium content, because the proton of HCN readily exchanges with protons adsorbed on glass.

Acetonitrile from the reaction of 3-deuteriopropene was 55% undeuterated and 45% monodeuterated by mass spectrometric analysis at 15 eV. The acetonitrile formed from 2-deuteriopropene was 61% undeuterated and 39% monodeuterated. These results are consistent with an intermediate for acetonitrile formation in which C-1 and C-3 become equivalent by a 1,2-hydrogen (or deuterium) shift from C-2 to C-1. It is proposed that the intermediate preceding nitrile formation from atomic nitrogen–alkene reactions is the imino radical. Independently generated imino radicals are reported to β cleave to product nitriles and other radicals (Scheme I).[8]

SCHEME I

$$H_2C=CHCH_2D + N \longrightarrow$$
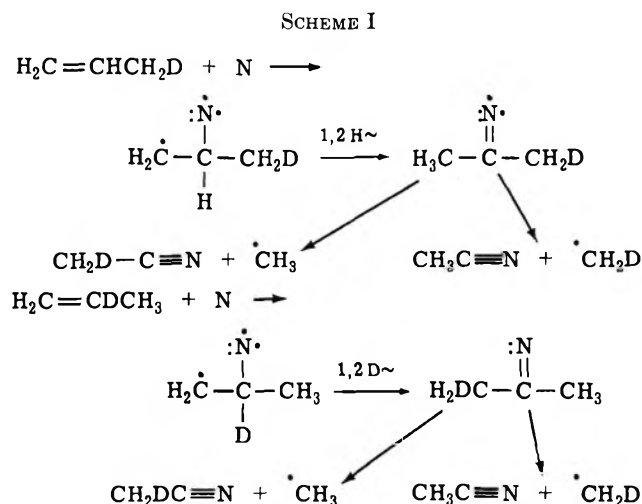
These results cannot be explained by the mechanism of Sato, Oka, and Suda,[7] which postulates a nearly simultaneous cleavage of the carbon–hydrogen bond on C-2 and the C-1 to C-2 bond.

Hydrogen cyanide, the major product of the propene–atomic nitrogen reaction, may be formed by the pre-

(1) National Science Foundation Fellow, 1968–1972. Address correspondence to the Department of Chemistry, Rice University, Houston, Texas 77001.

(2) C. A. Winkler and G. S. Trick, *Can. J. Chem.*, **30**, 915 (1952).

(3) Y. Shinozaki, R. Shaw, and N. N. Lichtin, *J. Amer. Chem. Soc.*, **86**, 341 (1964).

(4) P. T. Hinde, Y. Titani, and N. N. Lichtin, *ibid.*, **89**, 1411 (1967).

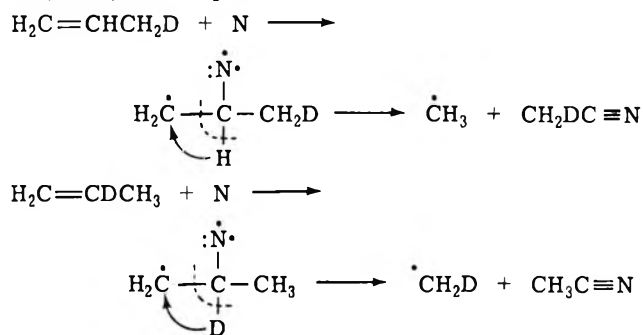(5) Y. Titani and N. N. Lichtin, *J. Phys. Chem.*, **72**, 526 (1968).

(6) N. N. Lichtin, "The Chemistry of Ionization and Excitation," G. R. A. Johnson and G. Scholes, Ed., Taylor and Francis, London, 1967, p 181.

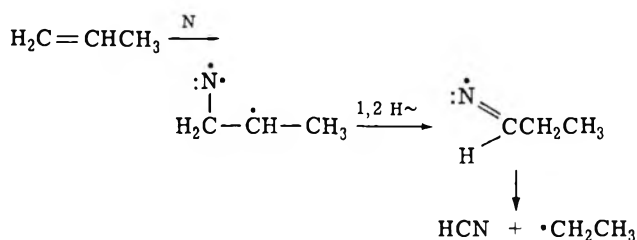(7) T. Oka, Y. Suda, and S. Sato, *Bull. Chem. Soc. Jap.*, **42**, 3083 (1969).

(8) M. L. Poutsma and P. A. Ibarbia, *J. Org. Chem.*, **34**, 2848 (1969).
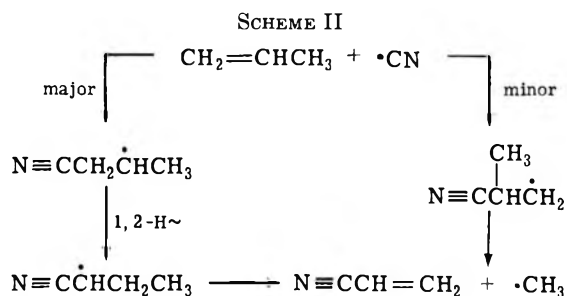
Oka, Suda, Sato Proposal

$$H_2C=CHCH_2D + N \longrightarrow$$

$$H_2\overset{\cdot\cdot}{C} \overset{:\overset{\cdot}{N}\cdot}{\underset{\underset{H}{\cdot\cdot}}{\vert}} CH_2D \longrightarrow \overset{\cdot}{C}H_3 + CH_2DC \equiv N$$

$$H_2C=CDCH_3 + N \longrightarrow$$

$$H_2\overset{\cdot\cdot}{C} \overset{:\overset{\cdot}{N}\cdot}{\underset{\underset{D}{\cdot\cdot}}{\vert}} CH_3 \longrightarrow \overset{\cdot}{C}H_2D + CH_3C \equiv N$$

ferred addition of nitrogen atoms to the terminal olefinic carbon of propene.

$$H_2C=CHCH_3 \xrightarrow{N}$$

$$H_2\overset{:\overset{\cdot}{N}\cdot}{\underset{\vert}{C}}-\overset{\cdot}{C}H-CH_3 \xrightarrow{1,2\ H\sim} \overset{:\overset{\cdot\cdot}{N}}{\underset{H}{\parallel}}CCH_2CH_3$$

$$\downarrow$$

$$HCN + \cdot CH_2CH_3$$

The deuterium content of the acrylonitrile formed from propene was also studied. The acrylonitrile from 3-deuteriopropene was 97% undeuterated and 3% monodeuterated by mass spectrometric analysis at 14 eV. That formed from 2-deuteriopropene was 9% undeuterated and 91% monodeuterated. These results indicate selective elimination of the methyl group of propene. They can be explained by a mechanism involving cyanogen radicals, which are present in hydrocarbon–atomic nitrogen reactions to a small extent.[9]

Addition of cyanogen radicals to propene can occur in two ways (Scheme II). The major pathway includes

SCHEME II

$$\text{major} \begin{array}{c} \\ \end{array} CH_2=CHCH_3 + \cdot CN \begin{array}{c} \\ \end{array} \text{minor}$$

$$N\equiv CCH_2\overset{\cdot}{C}HCH_3 \qquad\qquad N\equiv C\overset{\overset{\displaystyle CH_3}{\vert}}{C}H\overset{\cdot}{C}H_2$$

$$\downarrow 1,2\text{-}H\sim \qquad\qquad\qquad\qquad \downarrow$$

$$N\equiv C\overset{\cdot}{C}HCH_2CH_3 \longrightarrow N\equiv CCH=CH_2 + \cdot CH_3$$

a 1,2-hydrogen rearrangement, which is uncommon in low temperature condensed phase chemistry. It is possible that this major pathway does not lead to acrylonitrile, but to other products by addition of another molecule of propene (C_4 nitriles were not found). However, the minor pathway is a reasonable one to account for this product.

The reaction of atomic nitrogen with liquid propene closely parallels the gas phase reaction. There is little resemblance between these reactions and the reactions of the reactive species produced by the γ-radiolysis of propene in liquid nitrogen. The active species in the latter reactions cannot be ground state atomic nitrogen.

(9) A. N. Wright and C. A. Winkler, "Active Nitrogen," Academic Press, New York, N. Y., 1968.

Experimental Section

"Active" nitrogen, which is mainly ground state (quartet) atomic nitrogen, was generated by a 2450-Mc microwave discharge through molecular nitrogen. The molecular nitrogen (prepurified grade) was first passed over copper turnings at 500° to remove all but a few ppm of oxygen. Reaction with propene was accomplished by bubbling the atomic nitrogen stream through liquid olefin. Most reaction takes place in the condensed phase, since reaction flames[9] are not seen before the nitrogen reaches substrate, and the yellow nitrogen afterglow does not persist after contact with the substrate. The molar ratio of propene to atomic nitrogen was 120:1. The flow rate of atomic nitrogen (43.8 μmol/min) was determined by a calorimetric method[10] and by the nitric oxide titration method.[11]

2-Deuteriopropene and 3-deuteriopropene were made by D_2O hydrolysis of the corresponding Grignard reagents. Propene was purified by trap-to-trap distillation through a $-131°$ trap. The isotopic purity of the deuterated propenes was determined by mass spectrometry at 11.2 eV. The infrared spectrum of 3-deuteriopropene showed a carbon–deuterium stretch at 2160 cm^{-1}; the carbon–deuterium stretch in 2-deuteriopropene was at 2225 cm^{-1}.

Nitrilic products from the atomic nitrogen reactions were separated from excess propene by trap-to-trap distillation and were analyzed by gas chromatography on a dinonylphthalate column and by comparison of the infrared and mass spectra to those of known samples.

(10) J. J. Havel and P. S. Skell, *J. Amer. Chem. Soc.*, **94**, 1792 (1972).

(11) P. Harteck, G. Mannella, and R. R. Reeves, *J. Chem. Phys.*, **29**, 608 (1958).

Benzyl Alcohol as Hydrogen Donor in Selective Transfer Hydrogenation of Unsaturated Steroids

R. Vitali, G. Caccia, and R. Gardi*

Warner-Vister Steroid Research Institute, Casatenovo (Como), Italy

In a previous paper[1] we suggested transfer hydrogenation as the first step of the reaction of an α,β-unsaturated ketone with benzyl alcohol under conditions of homogeneous basic catalysis. This prompted us to investigate benzyl alcohol as donor in hydrogen transfer also under conditions of heterogeneous catalysis.[2] To our knowledge, these properties were still unexplored, although some alcohols had been occasionally used to reduce various acceptors in the presence of nickel or palladium.[3]

The present report deals with experiments performed on representative unsaturated steroids as acceptors in order to investigate the scope and limitations of this reaction.

The results obtained by heating solutions of the steroid in benzyl alcohol or other carbinol in the presence of Pd catalyst are summarized in Table I. Benzyl alcohol

(1) R. Vitali, G. Caccia, and P. P. Castelli, *Ann. Chim. (Rome)*, **62**, 315 (1972).

(2) *Cf.* E. A. Braude and R. P. Linstead, *J. Chem. Soc.*, 3544 (1954).

(3) E. C. Kleiderer and E. C. Kornfeld, *J. Org. Chem.*, **13**, 455 (1948). For other references see E. A. Braude, R. P. Linstead, and P. D. W. Mitchel, *J. Chem. Soc.*, 3578 (1954).

Acceptor	Donor	Product	Conversion, %
17β-Hydroxy-5α-androst-1-en-3-one (I)	Benzyl alcohol	17β-Hydroxy-5α-androstan-3-one	100
17β-Hydroxy-5α-androst-1-en-3-one (I)	Cyclohexanol	17β-Hydroxy-5α-androstan-3-one	5
17β-Hydroxy-5α-androst-1-en-3-one (I)	3-Pentanol	17β-Hydroxy-5α-androstan-3-one	5
17β-Hydroxy-5α-androst-1-en-3-one (I)	1-Butanol	No reduction	
17β-Hydroxy-5α-androst-1-en-3-one (I)	Allyl alcohol	No reduction	
17β-Hydroxy-4-androsten-3-one (II)	Benzyl alcohol	17β-Hydroxy-5α-androstan-3-one and	5
		17β-Hydroxy-5β-androstan-3-one	20
17α-Pregn-5-en-20-yne-3β,17-diol (III)	Benzyl alcohol	17α-Pregn-5-ene-3β,17-diol	100
3β-Hydroxy-5,16-pregnadien-20-one (IV)	Benzyl alcohol	3β-Hydroxypregn-5-en-20-one	100
3β-Hydroxy-16-methyl-5,16-pregnadien-20-one (V)	Benzyl alcohol	No reduction	
17β-Hydroxy-1,4-androstadien-3-one (VI)	Benzyl alcohol	17β-Hydroxy-5α-androstan-3-one,	3
		17β-Hydroxy-5β-androstan-3-one,	25
		and 17β-Hydroxy-4-androsten-3-one	72
17β-Hydroxy-4,6-androstadien-3-one (VII)	Benzyl alcohol	17β-Hydroxy-5α-androstan-3-one,	3
		17β-Hydroxy-5β-androstan-3-one,	15
		and 17β-Hydroxy-4-androsten-3-one	82

proved to be by far more effective as hydrogen donor than any other alcohol assayed. Thus, Δ^1-5α-3-ketone I was quantitatively hydrogenated in 3 hr at 80°, while cyclohexanol and 3-pentanol gave rise to only 5% reduction at 100°. Unchanged starting compound was recovered after a similar treatment with 1-butanol and allyl alcohol.

On the contrary, only 25% of the trisubstituted double bond in testosterone (II) was hydrogenated even with benzyl alcohol at 100°. Also the 5,6 double bond survived these reaction conditions. Thus, III and IV were quantitatively converted into 17α-pregn-5-ene-3β,17-diol and 3β-hydroxy-5-pregnen-20-one, respectively, by selective hydrogenation. The role of steric hindrance was further shown by the behavior of tetrasubstituted 16,17-ene in 3β-hydroxy-16-methyl-5,16-pregnadien-20-one (V), which, unlike IV, was recovered unchanged after similar processing.

The promising selectivity of the procedure is further emphasized by the results obtained on $\Delta^{1,4}$-3-ketone VI and $\Delta^{4,6}$-3-ketone VII, both converted in high yield (70–80%) into Δ^4-3-ketone II. Such separation in reactivity of double bonds in $\Delta^{1,4}$-3-ketones toward heterogeneous catalytic hydrogenation is almost unprecedented and strikingly parallels that observed in homogeneous hydrogenations catalyzed by tris(triphenylphosphine)-chlororhodium.[4,5] However, reduction of Δ^4-3-ketone by benzyl alcohol gave rise to isomeric mixtures mainly compounded by 5β epimer, while homogeneous catalytic hydrogenation has been reported to afford exclusively the 5α epimer.[5,6]

Experimental Section

Uv spectra were determined in 95% EtOH with an Optica CF₄ spectrometer; ir spectra were measured in a Nujol mull on a Perkin-Elmer 457 instrument. Tlc was run with 9:1 benzene–acetone on 250-μ-thick layers of silica gel (Carlo Erba, Milan, Italy), containing 1% fluorescence indicator (S5 grün/1, Leuchstoffwerk Gmbh and Co., Heidelberg, West Germany). After a preliminary examination under short-wave uv light (254 mμ), spots were visualized by spraying with 1:1 H₂SO₄–EtOH and heating at 110° for 10 min. Identification of products relied on tlc behavior, mixture melting point, optical rotation, and super-

imposable uv and ir spectra. Reduction percentages were calculated by uv analysis and semiquantitative tlc.

General Hydrogenation Procedure.—To a solution of the unsaturated steroid (1 g) in the appropriate carbinol (30 ml), 10% Pd on carbon (0.4 g) was added and the resulting suspension was kept under stirring for 3 hr at 80–100°. After removal of the catalyst by filtration and elimination of the alcohol under reduced pressure, the reaction product was isolated in the conventional manner. Recoveries ranged from 90 to 100%.

Registry No.—Benzyl alcohol, 100-51-6.

Evidence for a Cationic Imine Intermediate in N,N-Disubstituted α-Aminonitrile Formation[1]

JAMES W. STANLEY,[2] JAMES G. BEASLEY, AND IAN W. MATHISON*

Department of Medicinal Chemistry, College of Pharmacy, University of Tennessee Medical Units, Memphis, Tennessee 38103

α-Aminonitriles are important intermediates in the synthesis of amino acids[3] and sterically hindered amines.[4–7] They may be prepared in one step by treatment of an aldehyde or ketone with NaCN and NH₄Cl (Strecker synthesis). Salts or primary and secondary amines may be used instead of NH₄⁺ to obtain N-substituted and N,N-disubstituted α-aminonitriles (I).[8]

Alternatively, they may be prepared by treating

(1) This investigation was supported by grants from Marion Laboratories, Inc., Kansas City, Mo.; A. H. Robins Co., Richmond, Va.; and the National Science Foundation, Grant B007383.

(2) American Foundation for Pharmaceutical Education Fellow, 1970–1972. The work in this paper constitutes a segment of the thesis to be submitted by James W. Stanley to the Graduate School—Medical Sciences of the University of Tennessee in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(3) "Organic Syntheses," Wiley, New York, N. Y.: Collect. Vol. I, pp 21, 355; Collect. Vol. III, pp 66, 84, 88, 275; Collect. Vol. IV, pp 25, 43, 274.

(4) J. Sansoulet and C. Tackx, *C. R. Acad. Sci.*, **250**, 4370 (1960).

(5) W. H. Taylor and C. R. Hauser, *J. Amer. Chem. Soc.*, **82**, 1960 (1960).

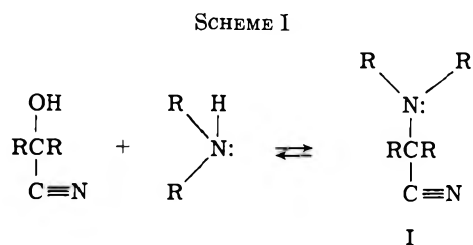(6) M. Velghe, *Bull. Sci. Acad. Roy. Belg.*, II, 301 (1925).

(7) P. Bruylants, *ibid.*, II, 261 (1925).

(8) D. B. Luten, *J. Org. Chem.*, **3**, 588 (1938).

(4) See C. Djerassi and J. Gutzwiller, *J. Amer. Chem. Soc.*, **88**, 4537 (1966), and ref 8–11 therein.

(5) A. J. Birch and K. A. M. Walker, *J. Chem. Soc. C*, 1894 (1966).

(6) W. Voelter and C. Djerassi, *Chem. Ber.*, **101**, 58 (1968).

SCHEME I

the cyanohydrin with the appropriate amine (Scheme I).[9]

Ogata and Kawasaki recently presented evidence of a Schiff base intermediate in the reaction of ring-substituted anilines or primary alkylamines with benzaldehyde.[10] These results supported an earlier report by Stewart and Li[11] that direct displacement of the hydroxyl group of the cyanohydrin was unlikely in the presence of amines.

A possible intermediate in the formation of α-aminonitriles from secondary amines is the cationic imine ($>C=N<$)$^+$(II) (Scheme II).

SCHEME II
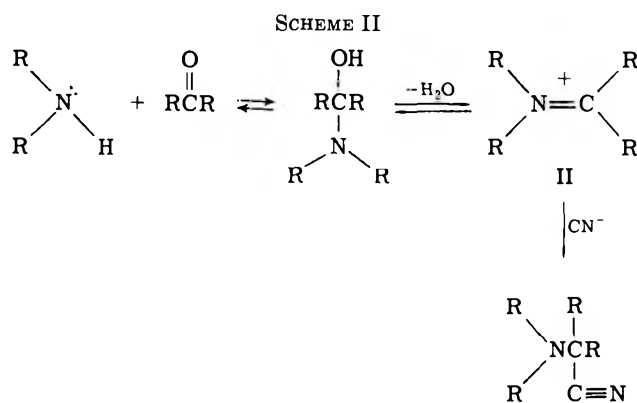
This species is highly reactive to nucleophiles such as the cyanide ion.[12] Accordingly, we selected reactants and conditions that would demonstrate graded differences in their ability to form the proposed cationic imine intermediate II; in particular, we studied acetone and its cyanohydrin with some representative amines, piperidine, morpholine, pyrrolidine, diethylamine, and dimethylamine. A comparison of these amines is particularly pertinent, since their ability to demonstrate exocyclic double bond character is markedly different.[13] Pyrrolidine, morpholine, and piperidine are known to react with aldehydes and ketones to give products that proceed through cationic imine intermediates.[14,15] The order of reactivity is pyrrolidine > morpholine > piperidine, pyrrolidine being by far the most reactive.[16] For example, while pyrrolidine perchlorate will react with anhydrous acetone to yield *N*-isopropylidene pyrrolidinium perchlorate almost quantitatively[17] (Scheme III), the

SCHEME III[17]
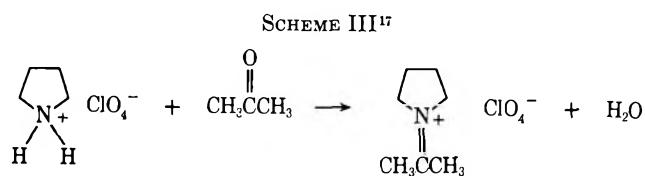
piperidine perchlorate salt will not react under similar conditions.[18] This reactivity difference is well known in enamine chemistry where piperidine does not form enamines to the same extent as other amines.[19] This difference in reactivity is attributed to the relative stability of exocyclic double bonds in five- and six-membered rings.[20–22] This application of Brown's generalization for cationic imines is not without precedent. Gurowitz and Joseph[23] have correlated the extent of exocyclic double bond character with vinyl proton absorption in the nmr spectra of some analogous enamines (Chart I). The pyrrolidine enamines dem-

CHART I[a]
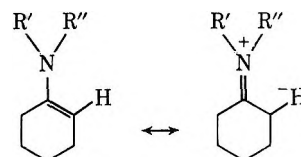
[a] Strong overlap of the lone pair on nitrogen with the double bond leads to delocalization as shown above. This causes an upfield shift of the proton on the carbon bearing the charge (from ref 13).

onstrate considerable exocyclic double bond character, whereas the morpholine and piperidine derivatives show much less. Thus one would expect reactivity of N,N-disubstituted aminonitrile formation to parallel the established order of double bond character if the formation of a cationic imine is the rate-determining intermediate.

Results and Discussion

The observed order of reactivity was indeed pyrrolidine > morpholine > piperidine, correlating with the extent of exocyclic double bond character (see Table I). The *magnitude* of the reactivity differences supports the proposed rate-determining step as being the formation of a cationic imine. While this is in agreement with Brown's generalization, it was felt that the differences in reactivity were greater than could be explained simply by the nature of the ring interactions resulting from exocyclic double bonds.[24] Some observations from alkene chemistry are pertinent in this respect. In methylenecyclohexane the ethylenic hydrogen atom syn to the 2-equatorial proton is slightly

(9) R. A. Jacobson, *J. Amer. Chem. Soc.*, **67**, 1996 (1945); **68**, 2628 (1946).

(10) Y. Ogata and A. Kawasaki, *J. Chem. Soc. B*, 325 (1971).

(11) T. D. Stewart and C. Li, *J. Amer. Chem. Soc.*, **60**, 2782 (1938).

(12) N. J. Leonard and A. S. Hays, *ibid.*, **78**, 1984 (1956).

(13) W. D. Gurowitz and A. Joseph, *Tetrahedron Lett.*, **No. 49**, 4433 (1965).

(14) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Vol. I, Wiley, New York, N. Y., 1967, p 972.

(15) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Vol. II, Wiley, New York, N. Y., 1969, p 354.

(16) G. Stork, A. Brizzolna, H. Landesman, J. Szmuskovicz, and R. Terrell, *J. Amer. Chem. Soc.*, **85**, 207 (1963).

(17) N. J. Leonard and J. V. Paukstelis, *J. Org. Chem.*, **28**, 302 (1963).

(18) The procedures outlined in ref 17 were used unsuccessfully in the attempted preparation of the *N*-isopropylidene piperidinium perchlorate, although the pyrrolidine derivative was easily obtained by simply adding the perchlorate salt of the amine to anhydrous acetone and swirling.

(19) J. Szmuskovicz, "Advances in Organic Chemistry: Methods and Results," Vol. 4, Interscience, New York, N. Y., 1963, p 10.

(20) H. C. Brown, *et al.*, *J. Amer. Chem. Soc.*, **76**, 467 (1954).

(21) H. C. Brown, *et al.*, *ibid.*, **73**, 212 (1951).

(22) H. C. Brown, *J. Org. Chem.*, **22**, 439 (1957).

(23) W. D. Gurowitz and M. A. Joseph, *ibid.*, **32**, 3289 (1967).

(24) R. B. Turner and R. H. Garner, *J. Amer. Chem. Soc.*, **80**, 1424 (1958).

Table I

Preparation of N,N-Disubstituted α-Aminonitriles

Compd	Amine	Time, hr	Yield,[a] %	Bp, °C (mm)	Formula	C, %	H, %	N, %
1		b	100	32–34[c] (0.6–0.8)	$C_8H_{14}N_2$	C 69.52 F 69.22	C 10.21 P 10.25	C 20.27 F 20.48
2		<1[d]	98	52–54[e] (20)	$C_6H_{12}N_2$	C 64.24 F 64.02	C 10.78 F 10.52	C 24.72 F 24.94
3		24	93	69–70[f] (1.5)	$C_8H_{14}N_2O$	C 62.31 F 62.05	C 9.15 F 9.33	C 18.16 F 17.94
4		24	70	46–48[g] (0.6–0.8)	$C_9H_{16}N_2$	C 71.01 F 71.02	C 10.59 F 10.64	C 18.40 F 18.23
5		24	59	71–74[h] (20)	$C_8H_{16}N_2$	C 68.52 F 68.40	C 11.50 F 11.30	C 19.98 F 19.70

[a] Yields reported are those of distilled product. [b] Reacts violently to give, in a matter of seconds, quantitative yields. [c] Lit. bp 75° (12 mm), 88.7%: R. B. Moffett, *J. Org. Chem.*, **14**, 862 (1949). [d] Reacts exothermically to give product in minutes. [e] Lit.[7] bp 50° (20 mm), 87.6%. [f] Lit. bp 123–125° (21 mm): R. A. Henry and W. M. Dehn, *J. Amer. Chem. Soc.*, **72**, 2804 (1950). [g] Lit.[4,7] mp 44–46°; bp 93–94° (14 mm), 70.7%. [h] Lit.[7] bp 66–68° (14 mm), 58.6%.

closer than the usually accepted van der Waals H–H distance (2.5 Å).[25,26] However, the interaction is only a slight repulsion of about 0.2–0.4 kcal/mol. On the other hand, in the case where the hydrogens are replaced by methyl groups (*i.e.*, isopropylidenecyclohexane) there is a larger steric interaction and here the energy of nonbonded interactions between the methyl groups and the 2-equatorial H atoms may be close to twice that of *cis*-2-butene or 2.6 kcal/mol.[27] (Conformational inversion has no meaning here since it leads to the same molecule.) This observation is particularly relevant since one would expect similar steric requirements for formation of a formal $(>C=N<)^+$ species. Thus, this factor alone could account for approximately a 100-fold difference in reactivity between piperidine and pyrrolidine,[28] since the latter shows little steric interactions of this type, as evidenced from inspection of Dreiding models. It is important to note that both factors, ring interactions and nonbonded steric interactions, tend to destabilize the piperidine intermediate.

Pyrrolidine, however, appears to be uniquely capable of satisfying the strict steric requirements, thus making additional factors, such as hyperconjugation[29,30] and optimal hybridization of the nitrogen atom, possible contributors to the stability of this intermediate. The combination of these factors may account for the large reactivity differences. The relative contribution of these factors would be of interest and in this regard the results with dimethylamine and diethylamine are useful. Dimethylamine, although less reactive than pyrrolidine, is considerably more reactive than the remaining amines. Ring interactions seem to retard piperidine reactivity relative to di-

methylamine while diethylamine appears to be less reactive than dimethylamine because of fairly severe nonbonded steric interactions.

The intermediate reactivity of morpholine may be attributed to a dual role by the oxygen in the ring, reducing the number and degree of unfavorable conformational interactions in relation to piperidine as well as stabilizing the positive charge generated by the cationic imine intermediate.

Thus while in fundamental agreement with previous findings on the intermediate involved in α-aminonitrile formation with primary amines, the reaction with secondary amines and ketones includes an important steric parameter, that being the ability to form a cationic imine.

Experimental Section

All compounds reported demonstrated characteristic spectra of α-aminonitriles, ir (CHCl₃) 2220 (C≡N, weak), nmr (CDCl₃) δ 1.50 (s, 6 H, –CH₃), as well as satisfactory analytical data (±0.3% for C, H, N) performed by Galbraith Laboratories, Knoxville, Tenn.

General Procedure.—The formation of the α-aminonitriles was conducted in the same manner for all compounds. The appropriate amine (0.230 mol) was mixed with 20 ml of acetone in a 100-ml round-bottom flask and stirred with a magnetic stirrer. After approximately 2 min acetone cyanohydrin (0.230 mol) was added and the flask was tightly stoppered and allowed to stir for the period indicated in Table I. Work-up involved removal of solvent under vacuum followed by immediate vacuum distillation to yield the product, which in all cases was a colorless oil. The yields obtained are outlined in Table I.

Starting Materials.—Acetone, A. R. (Mallinckrodt), was purified according to Vogel.[31] Acetone cyanohydrin (Aldrich Chemical Co.) was distilled before use to yield a clear, colorless liquid, bp 80–82° (15 mm). The anhydrous amines (Eastman) were dried over KOH and distilled before use.

(25) L. S. Bartell, *J. Chem. Phys.*, **32**, 827 (1960).
(26) R. Bucourt and D. Hainaut, *Bull. Soc. Chim. Fr.*, 501 (1966).
(27) F. Johnson, *Chem. Rev.*, **68**, 375 (1968).
(28) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, N. Y., 1962, p 207.
(29) A. Streitwieser, *J. Amer. Chem. Soc.*, **77**, 6713 (1955).
(30) V. J. Shiner, *ibid.*, **78**, 2654 (1956).

(31) A. I. Vogel, "A Textbook of Practical Organic Chemistry," Longmans, Green and Co., New York, N. Y., 1956, p 171.

Reaction of Phenylethynylmagnesium Bromide or Styrylmagnesium Bromide with Thionyl Chloride, a Novel Coupling Reaction

Akira Uchida,* Tokuaki Nakazawa, Isao Kondo,
Nobuhiro Iwata, and Sumio Matsuda

*Department of Petroleum Chemistry, Faculty of Engineering,
Osaka University, Yamadakami, Suita, 565, Japan*

Although the formation of sulfoxides and sulfides by the reaction of alkylmagnesium halide or arylmagnesium halide with thionyl chloride has already been reported,[1,2] the reaction of acetylenic or olefinic Grignard reagents with thionyl chloride is unknown. In the course of our study of the syntheses of as yet unknown bis ethynyl sulfoxides or bis ethenyl sulfoxides, the reaction of phenylethynylmagnesium bromide or styrylmagnesium bromide with thionyl chloride was attempted.

When a mixture of freshly distilled thionyl chloride and 2 molar equiv of phenylethynylmagnesium bromide or styrylmagnesium bromide in tetrahydrofuran (THF) was stirred at 0° for 3.5 hr, and the product was submitted to chromatographic separation, a crystalline compound and a tarry residue were obtained. On the basis of the elementary analyses and spectroscopic data, the crystalline product was identified as 1,4-diphenylbuta-1,3-diyne or 1,4-diphenylbuta-1,3-diene. The Beilstein tests and sodium fusion tests of the tarry residue indicated the presence of halogen and sulfur, but no sulfur compounds could be isolated.

Though several coupling reactions of acetylenic compounds, such as Glaser coupling,[3] Grignard coupling,[4,5] Reformatsky reaction,[6] and Chodwiecz–Cadiot coupling,[7] are known, the coupling reaction of acetylenic or vinylic compounds *via* Grignard reagents and thionyl chloride is as yet unknown.

The reaction of phenylethynylmagnesium bromide or styrylmagnesium bromide with thionyl chloride was attempted under various reaction conditions and the yields of coupling products are summarized in Table I. In expt 1–5 and 11–15, the molar ratio of Grignard reagents and thionyl chloride was varied. In the

TABLE I
Reaction of Phenylethynylmagnesium Bromide or Styrylmagnesium Bromide with Thionyl Chloride

Expt	Temp, °C	Molar ratio, $SOCl_2/RMgBr$	Solvent	Yield of coupling product,[a] %
		$C_6H_5C{\equiv}CMgBr$		
1	0	0	THF	0
2	0	0.25	THF	34
3	0	0.50	THF	38
4	0	1.0	THF	61
5	0	1.5	THF	58
6	−40	1.0	THF	57
7	30	1.0	THF	55
8	0	1.0	DEE[b]	33
9	0	1.0	DBE[c]	17
10	0	1.0	DGM[d]	43
		$C_6H_5CH{=}CHMgBr$		
11	0	0	THF	28
12	0	0.25	THF	35
13	0	0.50	THF	68
14	0	1.0	THF	89
15	0	1.5	THF	81
16	−40	1.0	THF	70
17	30	1.0	THF	88

[a] Based on the initial amounts of Grignard reagents in the reaction systems. [b] Diethyl ether. [c] Di-*n*-butyl ether. [d] Diethylene glycol dimethyl ether.

absence of thionyl chloride, phenylethynylmagnesium bromide gave no coupling product, and phenylacetylene was recovered quantitatively. Yet in the case of styrylmagnesium bromide, 1,4-diphenylbuta-1,3-diene was obtained in 28% yield even in the absence of thionyl chloride. This indicates the occurrence of a Wurtz type reaction during the preparation of styrylmagnesium bromide. The yields of coupling products increased with the increase of the molar ratio of reagents. Though the stoichiometric ratio of reagents for the formation of sulfoxides was 0.5, the maximum yields of coupling products were obtained at a molar ratio of 1.0. From these observations it seems reasonable to assume that thionyl chloride plays some important role in this coupling reaction.

In expt 4, 6, 7, 14, 16, and 17, the reaction temperature was varied. It is surprising that the yields of coupling products at −40° were comparatively high, and that the reaction temperature did not markedly influence the yields of coupling products.

In expt 4 and 8–10, the solvent was varied. Because of difficulty in the preparation of styrylmagnesium bromide in ethers other than THF, only the reaction of phenylethynylmagnesium bromide was investigated. The type of solvent markedly influenced the yield of diphenylbutadiyne. The maximum yield was obtained in THF, and the minimum yield in diethyl ether. The basicity of the solvent is known to influence the stability of some charged transition states and Schlenk equilibrium of Grignard reagents.[8] However, the Schlenk equilibrium of acetylenic Grignard reagents is unknown, and it is not possible to decide the precise effect of basicity of the solvent without more detailed experiments.

In Table II are shown the results of the reactions of

(1) (a) B. Oddo, *Gazz. Chim. Ital.*, **41**, 1, 11 (1911); *Chem. Abstr.*, **5**, 2635 (1911). (b) N. P. Volynskii, G. D. Gal'pern, and V. V. Smolyaninov, *Neftekhimiya*, **4** (3), 371 (1964); *Chem. Abstr.*, **61**, 8245 (1964). (c) N. P. Volinskii, G. D. Gal'pern, and V. V. Smolyaninov, *Khim. Seraorg. Soedin. Soderzh. Neftyakh Nefteprod.*, **6**, 216 (1964); *Chem. Abstr.*, **61** 6965 (1964). (d) W. Strecker, *Ber.*, **43**, 1131 (1910); *Chem. Abstr.*, **4**, 2467 (1910). (e) C. Courtot, *Chim. Ind. (Paris)*, **45**, 80 (1941); *Chem. Zentralbl.*, I, 194 (1942); *Chem. Abstr.*, **37**, 2366 (1943). (f) N. P. Volynskii, G. D. Gal'pern, and V. V. Smolyaninov, *Neftekhimiya*, 1, 473 (1961); *Chem. Abstr.*, **57**, 16510 (1961). (g) V. Grignard and L. Zorn, *C. R. Acad. Sci.*, **150**, 1177 (1909); *Chem. Abstr.*, **4**, 2098 (1910).

(2) (a) M. S. Kharasch and O. Reiumth, "Grignard Reaction of Non-Metallic Substances," Prentice-Hall, Englewood Cliffs, N. J., 1954, pp 1285–1294. (b) M. M. Szmant and W. Emerson, *J. Amer. Chem. Soc.*, **78**, 454 (1956).

(3) W. J. Glasler, *Chem. Rev.*, **57**, 215 (1957).

(4) (a) V. Grignard and Tchéoufaki. *C. R. Acad. Sci.*, **188**, 357 (1929). (b) V. Grignard and Perrichon, *Ann. Chim. (Paris)*, **5**, 13 (1926).

(5) (a) H. K. Black and B. C. L. Weedon, *J. Chem. Soc.*, 1785 (1953). (b) H. K. Black, P. M. S. Horn, and B. C. L. Weedon, *ibid.*, 1704 (1954). (c) L. Skattebøl, *Tetrahedron*, **21**, 1387 (1965).

(6) W. P. Norris and W. G. Finnigan, *J. Org. Chem.*, **31**, 3282 (1966).

(7) W. Chodkiewicz, *Ann. Chim. (Paris)*, **2**, 819 (1957); *C. R. Acad. Sci.*, **295**, 322 (1957).

(8) (a) E. C. Ashby, *Quart. Rev., Chem. Soc.*, **21**, 259 (1967). (b) F. W. Waker and E. C. Ashby, *J. Amer. Chem. Soc.*, **91**, 3845 (1969). (c) G. E. Parris and E. C. Ashby, *ibid.*, **93**, 1206 (1971).

Table II

Reaction of Acetylenic Grignard Reagents
with Thionyl Chloride[a]

RMgBr, R =	Yield of coupling products,[b] %
p-CH₃C₆H₄C≡C-	75
p-C₂H₅C₆H₄C≡C-	80
p-i-C₃H₇C₆H₄C≡C-	85
p-BrC₆H₄C≡C-	33
n-C₄H₉C≡C-	c

[a] Solvent, THF; molar ratio, 1.0; temperature, 0°. [b] Based on the initial amounts of Grignard reagents in the reaction systems. [c] Coupling product was not isolated, but detected by tlc.

para-substituted diphenylethynylmagnesium bromide and 1-hexynylmagnesium bromide. The introduction of electron-releasing groups in the para position of the phenyl group increased the yields of coupling products, and thus the electron density of the triple bond must be important at some stage in this reaction. When a similar reaction of 1-hexynylmagnesium bromide was attempted, each attempt to isolate dodeca-5,7-diyne failed, but its presence as a major component of the reaction product was confirmed by thin layer chromatography (tlc) on silica gel and activated alumina.

A mechanistic study of this coupling reaction is now in progress.

Experimental Section

Melting points were not corrected.

THF, diethyl ether, di-n-butyl ether, and diethylene glycol dimethyl ether were refluxed in the presence of sodium and then fractionated. Ethyl bromide was dried over anhydrous sodium carbonate prior to distillation. Thionyl chloride was distilled, and magnesium was used as received. Phenyl-, p-tolyl-, p-ethylphenyl-, p-isopropylphenyl-, and p-bromophenylacetylene were prepared according to the method of Campbell, et al.[9]

The nmr spectra were recorded on a JNM-3H-60 (60 MHz) nmr spectrometer; chemical shifts (τ) are reported in parts per million relative to tetramethylsilane (s, singlet; d, doublet; t, triplet; q, quartet; se, septuplet; m, multiplet). Mass spectra and ir spectra were measured with a Hitachi RMN-6E-type mass spectrometer and EPI-G2-type grating infrared spectrometers.

Acetylenic Grignard reagents were prepared by the reaction of acetylenic compounds with ethylmagnesium bromide in various solvents, and styrylmagnesium bromide was prepared by the reaction of trans-β-bromostyrene with magnesium in THF.

A solution of 0.083 mol of Grignard reagent in 120 ml of the selected solvent was prepared under nitrogen in a 500-ml round-bottomed flask fitted with a reflux condenser, dropping funnel, gas-inlet tube, and magnetic stirrer. The flask was immersed in a Dry Ice–acetone bath or a water bath to keep the reaction temperature at −40, 0, or 30°. A solution of a predetermined amount of thionyl chloride in 80 ml of solvent was added over a period of 3 hr to the stirred solution of the Grignard reagent. An exothermic reaction took place. After the reaction mixture was stirred for an additional 0.5 hr, the solvent was removed in vacuo. The residue was washed with saturated aqueous ammonium chloride solution and water and then extracted with ether. The ethereal extract was dried over anhydrous magnesium sulfate. The black-brown tar which was left after removal of the ether was separated into benzene eluate and ethanol eluate by column

chromatography on activated alumina. Benzene was removed from the benzene eluate and needle crystals were obtained. Recrystallization of these crystals afforded the following coupling products.

1,4-Diphenylbuta-1,3-diyne (from phenylethynylmagnesium bromide) had mp 87–89° (ethanol–water); ir (KBr disk) 2140 cm⁻¹ (C≡C); nmr (CCl₄) τ 2.63 (aryl H). Anal. Calcd for C₁₆H₁₀: C, 95.02; H, 4.98; mol wt, 202.24. Found: C, 95.17; H, 4.73. The mass spectrum showed m/e (rel intensity) 202 (100), 101 (7).

1,4-Di-p-tolylbuta-1,3-diyne (from p-tolylethynylmagnesium bromide) had mp 183° (ether); ir (KBr disk) 2130 cm⁻¹ (C≡C); nmr (CDCl₃) τ 7.70 (s, 6 H, CH₃), 2.18 (m, 8 H, aryl H). Anal. Calcd for C₁₈H₁₄: C, 93.87; H, 6.13; mol wt, 230.29. Found: C, 93.74; H, 5.99. The mass spectrum showed m/e (rel intensity) 230 (100), 215 (13), 115 (9).

1,4-Di-p-ethylphenylbuta-1,3-diyne (from p-ethylphenylethynylmagnesium bromide) had mp 98–99° (ethanol); ir (KBr disk) 2140 cm⁻¹ (C≡C); nmr (CCl₄) τ 8.74 (t, 6 H, CH₃, J = 7.0 Hz), 7.37 (q, 4 H, CH₂, J = 7.0 Hz), 2.77 (m, 8 H, aryl H). Anal. Calcd for C₂₀H₁₈: C, 92.98; H, 7.02; mol wt, 258.34. Found: C, 93.01; H, 7.03. The mass spectrum showed m/e (rel intensity) 258 (100), 243 (67), 229 (28), 129 (8).

1,4-Di-p-isopropylphenylbuta-1,3-diyne (from p-isopropylphenylethynylmagnesium bromide) had mp 131–132° (ethanol); ir (KBr disk) 2140 cm⁻¹ (C≡C); nmr (CCl₄) τ 8.75 (d, 12 H, CH₃, J = 7.0 Hz), 7.17 (se, 2 H, CH, J = 7.0 Hz), 2.77 (q, 8 H, aryl H). Anal. Calcd for C₂₂H₂₂: C, 92.26; H, 7.75; mol wt, 286.40. Found: C, 92.22; H, 7.44. The mass spectrum showed m/e (rel intensity) 286 (100), 256 (12), 143 (6), 128 (27).

1,4-Di-p-bromophenylbuta-1,3-diyne (from p-bromophenylethynylmagnesium bromide) had mp 260° (benzene); ir (KBr disk) 2150 cm⁻¹ (C≡C); very insoluble in common organic solvents. Anal. Calcd for C₁₆H₈Br₂: C, 53.39; H, 2.24; mol wt, 360.05. Found: C, 53.37; H, 2.18. The mass spectrum showed m/e (rel intensity) 362 (52), 360 (100), 358 (52), 200 (30).

trans,trans-1,4-Diphenylbuta-1,3-diene (from *trans*-styrylmagnesium bromide) had mp 152–153° (ether); ir (KBr disk) 994, 986 cm⁻¹ (trans CH=CH); nmr (CCl₄) τ 2.72 (m, 4 H, CH=CH), 3.27 (m, 10 H, aryl H). Anal. Calcd for C₁₆H₁₄: C, 93.16; H, 6.58; mol wt, 206.29. Found: C, 93.10; H, 6.58. The mass spectrum showed m/e (rel intensity) 206 (100), 191 (38), 128 (33).

After ethanol was removed from ethanol eluates, black-brown colored tarry materials were obtained. Beilstein tests and sodium fusion tests indicated the existence of halogen and sulfur in these substances. However, each attempt to separate compounds containing sulfur by distillation or recrystallization failed.

When the reaction of 1-hexynylmagnesium bromide with thionyl chloride was attempted under the condition described previously, separation of reaction products by distillation or recrystallization was impossible. However, dodeca-5,7-diyne was detected in the reaction product by tlc on silica gel and activated alumina. Two spots appeared on the plates after development with benzene. The larger spot (Rf 0.60 on silica gel and 0.78 on activated alumina) corresponded to an authentic sample of dodeca-5,7-diyne prepared by the method described by Cameron, et al.[10]

Registry No.—Phenylethynylmagnesium bromide, 6738-06-3; *trans*-styrylmagnesium bromide, 35672-47-0; thionyl chloride, 7719-09-7; 1,4-diphenyl-1,3-butadiyne, 886-66-8; 1,4-di-p-tolylbuta-1,3-diyne, 22666-07-5; 1,4-di-p-ethylphenylbuta-1,3-diyne, 35672-48-1; 1,4-di-p-isopropylphenylbuta-1,3-diyne, 35672-49-2; 1,4-di-p-bromophenylbuta-1,3-diyne, 959-88-6; *trans,trans*-1,4-diphenylbuta-1,3-diene, 538-81-8.

(9) K. N. Campbell and B. K. Campbell, *Org. Syn.*, **4**, 117 (1963).

(10) M. D. Cameron and G. E. Bennett, *J. Org. Chem.*, **22**, 557 (1957).

Communications

The Influence of Substituents on the Photochemical Behavior of Cross-Conjugated Cyclohexadienones. A Facile Total Synthesis of (−)-Cyclocolorenone[1]

Summary: (−)-Cyclocolorenone has been totally synthesized using photochemical rearrangement of an appropriately substituted cross-conjugated cyclohexadienone to produce the tricyclic ring skeleton of the natural product.

Sir: Büchi, Kauffman, and Loewenthal[2] have reported the synthesis of 1-epicyclocolorene (1) from santonin. This work also established the stereochemistry of cyclocolorenone (2). However, the synthetic sequence involved closure of the three-membered ring by reaction of the bromo enone 3 under basic
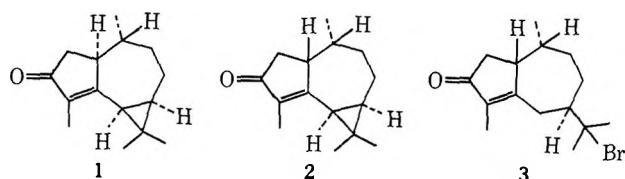
conditions which caused epimerization at C-1. Thus the more thermodynamically stable tricyclic enone 1 was the only product isolated.

The photochemical rearrangement of the tricyclic cross-conjugated cyclohexadienone 4a[3,4] appeared to be an attractive route to cyclocolorenone itself. By analogy with the behavior of related 4-methyl-substituted systems,[2,3,5] this compound was expected to give the tricyclic hydroxy ketone 5 on irradiation in aqueous acetic acid.[6] However, Streith and Blind[3] have reported that 4a is unreactive toward uv light in this solvent and similar results have been obtained by Kropp and Krauss[4] using benzene or ether as the solvent.[7] We have confirmed these results and have found that, although rearrangement of 4a can be induced using benzophenone as a photosensitizer, the process is accompanied by opening of the cyclopropane

(1) This investigation was supported by Public Health Service Research Grants No. Gm 15044 from the National Institute of General Medicine and No. CA 12193 from the National Cancer Institute.

(2) G. Büchi, J. M. Kauffman, and H. J. E. Loewenthal, *J. Amer. Chem. Soc.*, **88**, 3403 (1966).

(3) J. Streith and A. Blind, *Bull. Soc. Chem. Fr.*, 2133 (1968).

(4) P. J. Kropp and H. J. Krauss, *J. Org. Chem.*, **32**, 4118 (1967).

(5) (a) D. H. R. Barton, P. De Mayo, and M. Shafiq, *J. Chem. Soc.*, 929 (1957); (b) D. Caine and J. B. Dawson, *J. Org. Chem.*, **29**, 3108 (1964); (c) P. J. Kropp, *ibid.*, **29**, 3110 (1964); (d) E. Piers and K. F. Cheng, *Can. J. Chem.*, **45**, 1591 (1967); (e) E. Piers and K. F. Cheng, *Chem. Commun.*, 562 (1969); (f) E. Piers and K. F. Cheng, *Can. J. Chem.*, **48**, 2234 (1970).

(6) Streith and Blind[3] have reported the synthesis of 5 via a procedure involving irradiation of dehydro-(−)-7-epi-α-cyperone in aqueous acetic acid to give a 5/7-fused hydroxy ketone followed by closure of the three-membered ring.

(7) The steroidal dienone, *O*-acetyl-1-dehydro-6α,7α-methylenetestosterone, related to 4 has also been shown to be stable toward uv irradiation: J. Pfister, H. Wehrli, and K. Schaffner, *Helv. Chem. Acta*, **50**, 166 (1967).

ring.[8] Thus the photochemical conversion of 4a into a precursor of 2 does not appear to be possible.

Another possible route to a precursor of 2 appeared to involve photochemical rearrangement of the 2-carboxy derivative of 4a, *i.e.*, 4b. As we reported earlier,[9] the bicyclic dienone 6, having an electron-withdrawing carboxyl group at C-2, is photochemically converted into 5/7-fused products in a variety of solvents. For example, irradiation of 6 in dioxane gave the decarboxylated dienone 7 in 67% yield. Thus it was felt that
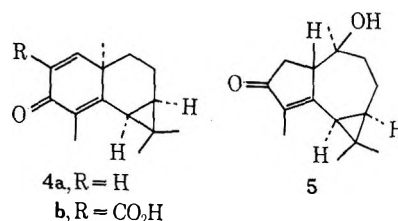
4b might undergo a similar photochemical reaction to give the tricyclic dienone 8 which would be expected
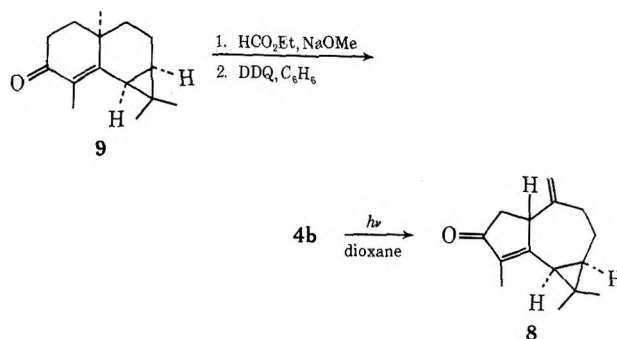
to be convertible into 2 by selective hydrogenation of the exocyclic double bond.

The dienone acid 4b was prepared by a procedure similar to that described for the synthesis of 6.[9] Reaction of (−)-maalione (9)[10] with ethyl formate and sodium methoxide in benzene gave the 2-hydroxymethylene derivative which was oxidized to the corresponding 2-formyl dienone with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in benzene and further to 4b with Jones reagent.[11,12] The product showed mp 100–102°; $\lambda_{max}^{95\% EtOH}$ 220 nm (ε 10,300), 297 (4,500); ir $\nu_{max}^{CHCl_3}$ 2715 (carboxyl OH), 1730 (conjugated carboxyl

(8) The results of irradiation of 4a using benzophenone as a photosensitizer will be discussed later in a full paper.

(9) D. Caine, J. F. DeBardeleben, Jr., and J. B. Dawson, *Tetrahedron Lett.*, 3627 (1966).

(10) R. B. Bates, G. Büchi, T. Matsuura, and R. R. Shaffer, *J. Amer. Chem. Soc.*, **82**, 2327 (1960).

(11) K. Bowden, J. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

(12) Correct elemental analyses and mass spectral data have been obtained on all new compounds.

C=O), 1645 (conjugated C=O), 1580 cm^{-1} (conjugated C=C); nmr $\delta_{TMS}^{CDCl_3}$ 0.84 (s, 3 H, CH$_3$), 1.27 (s, 3 H, CH$_3$), 1.38 (s, 3 H, CH$_3$), 1.97 (d, J = 1 Hz, 3 H, vinyl CH$_3$), 1.00–2.20 (broad absorption, 6 H), 8.16 ppm (s, 1 H, vinyl H); [α]^{25} D −51° (c 0.226, CHCl$_3$). On irradiation for 5 hr in dry dioxane at room temperature using a 450-W Hanovia high pressure mercury lamp fitted with a Pyrex probe and rapid chromatography of the photolysis mixture on silica gel, the tricylic dienone **8** was isolated in ∼60% yield as a white crystalline solid: mp 57–58°; $\lambda_{max}^{95\% EtOH}$ 262 nm (ϵ 7500); ir $\nu_{max}^{CHCl_3}$ 1695 (conjugated cyclopentenone), 1630 (conjugated C=C), 885 cm^{-1} $\left(=C<{H \atop H}\right)$; nmr $\delta_{TMS}^{CDCl_3}$ 1.00 (s, 3 H, CH$_3$), 1.26 (s, 3 H, CH$_3$), 1.70 (d, J = 2 Hz, 3 H, vinyl CH$_3$), 2.55 (d, J = 5 Hz, 2 H, C-2 CH$_2$), 3.40 (br t, 1 H, C-1 H), 0.80–2.80 (broad absorption, 6 H), 4.84 (br s, 1 H, vinyl H), 4.96 ppm (t, J = 1.5 Hz, vinyl H); [α]^{25} D −417° (c 0.134, CHCl$_3$).

Examination of a molecular model of **8** having the B ring in the most stable comformation revealed that the β face of the molecule should be the less hindered, and selective introduction of the C-10 hydrogen cis to the C-1 hydrogen was expected to occur on catalytic hydrogenation. Thus, when **8** was dissolved in ethyl acetate and shaken with hydrogen for 40 min in the presence of 5% palladium on charcoal, saturation of the exocyclic double bond took place in essentially quantitative yield. Glc analysis (SE-30 column) of the product revealed the presence of >90% of one major dihydro product. Distillation of this material gave a colorless oil [bp 110–115° (bath temperature) at 0.05 mm] at which was essentially one component by glc and exhibited identical ir and nmr spectra with those of an authentic sample of (−)-cyclocolorenone.[13] Other physical properties of the material were also in agreement with those reported[2,14] for the natural product.

A complete explanation for the photolability of the dienone acid **4b** compared with that of the unsubstituted compound **4a** is not possible at this time. The carboxyl substituent may influence the energy and electronic distribution of the photoexcited species sufficiently to allow the formation of a zwitterionic cyclopropyl intermediate analogous to that suggested to be involved in the rearrangement of the dienone acid **6**.[9] Such a species could then collapse to a β-keto acid which could undergo decarboxylation to give **8**. However, it is possible that a somewhat different reaction pathway may intervene in this case. Irrespective of the exact details of the process, the high degree of stereospecificity normally involved in photochemical rearrangements of simpler cross-conjugated dienones appears also to obtain in this case. Further studies on the photochemistry of other dienones related to **4** are in progress.

(13) We are grateful to Professors G. Büchi and R. E. Corbett for providing us with copies of spectra of authentic samples of cyclocolorenone.

(14) R. E. Corbett and R. N. Speden, *J. Chem. Soc.*, 3710 (1958).

SCHOOL OF CHEMISTRY   DRURY CAINE*
GEORGIA INSTITUTE OF TECHNOLOGY   PAUL F. INGWALSON
ATLANTA, GEORGIA   30332

Additions and Corrections

Vol. 34, 1969

Wendell L. Dilling, Charles E. Reineke, and Raymond A. Plepys: Pentacyclodecane Chemistry. V. The Synthesis and Acetolysis of *syn*- and *anti*-Pentacyclo[5.3.0.0²,⁵.0³,⁹.0⁴,⁸]dec-6-yl *p*-Toluenesulfonate. Evidence Concerning the Intermediacy of Bridges Carbonium Ions.

Page 2605. Column 1. Under figures, "OPCL₄" should read OPCl₄.

Page 2607. Table II, third column, second entry. "1.10 ± 0.02 ± 10⁻⁴" should read 1.10 ± 0.02 × 10⁻⁴.

Page 2613. Column 2, line 26. "thered unction" should read the reduction.

Page 2614. Column 1, equation. "k_t" should read kt.

Vol. 35, 1970

Wendell L. Dilling and Raymond A. Plepys: Metal Hydride Reductions of *endo*-Tricyclo[5.2.1.0²,⁶]deca-4,8-dien-3-one (*endo*-Dicyclopentadienone).

Page 2972. Column 2, first equation. "LiAlH₄" should read LiAlD₄.

Page 2975. Column 2, line 13. "−1.66" should read −1.56.

Denis M. Bailey and Robert E. Johnson: Reduction of Cyclic Anhydrides with NaBH₄. Versatile Lactone Synthesis.

Page 3575. Column 4, Table I. The method for glutaric anhydride should be B-2.

Page 3575. Last line. In reference to the Vaughan, *et al.*, work (ref 3) "camphoric anhydride" should read 2-methylnor-bornane-*endo*-2,3-dicarboxylic anhydride and "α-campholide" should read camphenolide.

Samuel P. McManus, John T. Carroll, and Charles U. Pittman, Jr.: Acid-Catalyzed Cyclization Reactions. IX. The Formation of Oxazolinium and Thiazolinium Cations from *N*-Allyl and Substituted *N*-Allylamides, -urethans, -ureas, and -thioureas.

Page 3769. Scheme II. In legend, "p-r, X = T" should read p-r, X = S. Structure **3** should appear as follows.

3
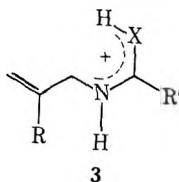
Vol. 36, 1971

C. A. Kingsbury* and R. A. Auerbach: Conformations of Certain Acyclic Sulfoxide Alcohols.

Page 1739. A communication from M. Nishio has led us to believe that our failure to observe nonequivalent hydrogens in the nmr spectrum of phenyl benzyl sulfoxide dissolved in trifluoro-acetic acid was in error. Repetition of the experiment indeed did indicate nonequivalent hydrogens, as originally reported by Nishio.

Page 1742. Compounds 10 and 11 were inverted. Compound 10 melts at 106°, and compound 11 melts at 129°.

Peter Blumbergs,* Chandrakant B. Thanawalla, Arthur B. Ash, Claire N. Lieske, and George M. Steinberg: Synthesis and Stereochemistry of *syn*- and *anti-p*-Nitrophenyl Phenacyl Methylphosphonate Oxime.

Page 2025. Column 2, line 37. The sentence starting with "Less reproducible . . ." has a portion omitted and should read Less reproducible was the thermal isomerization of 2 to 1 by heating a deuteriochloroform solution of it at 50–55° for 40 min, and isomerization in deuteriochloroform at ambient temperature catalyzed by DCl-D₂O.

Tadashi Sasaki,* Shoji Eguchi, and Takeshi Toru: Synthesis of Adamantane Derivatives. XV. No Ring-Fission Aptitude of the Homoadamantan-4-one System in the Schmidt and Beckmann Rearrangements.

Page 2455. Formulas 5 and 6 in Scheme II should be as follows.

5   **6**
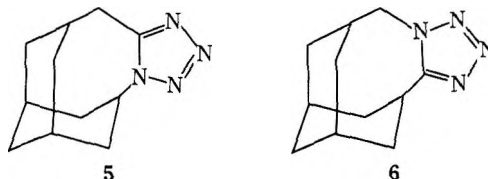
Juane J. Silber and Henry J. Shine:* Ion Radicals. XXII. Reaction of Thianthrenium Perchlorate ($C_{12}H_8S_2$·⁺ClO_4^-) with Aromatics.

Page 2924. Column 2, Table II. Heading for column 5 should read $10k_{app}{}^a$.

Page 2925. Column 1, Table IV. Heading for column 3 should read $10k'_{app}$, M^{-1} sec⁻¹ ᵇ.

J. M. Bobbitt,* H. Yagi, S. Shibuya, and J. T. Stock: Electrochemistry of Natural Products. II. Electrolytic Oxidation of Some Simple 1,2,3,4-Tetrahydroisoquinoline Phenols.

Page 3010. Column 2, line 43. "21" should read 20.

J. F. Wojcik* and I. J. Ostrich: Ionization Scheme for the *N,N*-Di(carboxymethyl)anilines.

Page 3052. Table II. Column 1 of data should read as follows.

$$-1.3 \pm 0.2$$
$$-0.3 + 0.2$$
$$-0.4 \pm 0.2$$
$$0.2 + 0.2$$
$$0.5 + 0.2$$

John C. Stowell: *tert*-Alkylnitroso Compounds. Synthesis and Dimerization Equilibria.

Page 3055. We wish to call attention to a paper by J. E. Baldwin, A. K. Qvereshi, and B. Sklarz, *J. Chem. Soc. C*, 1073 (1969), in which the direct oxidation of 2,4,4-trimethyl-2-pentyl-amine to the nitroso compound is described.

Jay K. Kochi* and C. L. Jenkins: II. Kinetics of Ligand Transfer Oxidation of Alkyl Radicals. Evidence for Carbonium Ion Intermediates.

Page 3103. The formula for allylcarbinyl chloride was incorrectly given as allyl chloride throughout the paper.

B. D. Mookherjee,* R. W. Trenkle, and R. R. Patel: Synthesis of Racemic Muscone and Cyclopentadecanone (Exaltone) from 1,9-Cyclohexadecadiene.

Page 3266. The name "Exaltone" used in this publication and in related publication on page 4124 is a trade-mark registered in the name of Firmenich & Cie, and should be spelled with a capital E.

Harry Rubinstein,* James E. Skarbek, and Henry Feuer: Reactions of 3-Carboxyacryloylhydrazine and the Formation of Maleimides, Isomaleimides, and Pyridazinones.
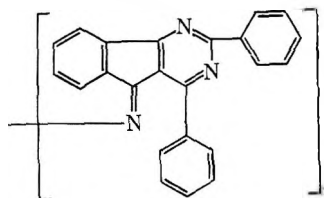
Page 3372. Formula 1 should be
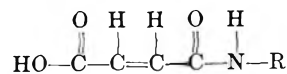
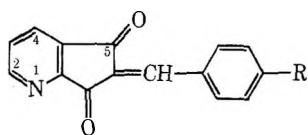

Page 3372. Formula 4 should be
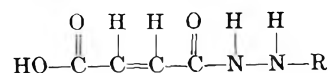
W. A. Mosher* and J. L. Brenner: The Synthesis of 2,4-Diaryl-5*H*-indeno- and 2,4-Diaryl-5*H*-pyridocyclopenta[1,2-*d*]-pyrimidin-5-ones.

Page 3383. The formula of compounds 7 should be as follows.

The formula of compounds 9a–e should be as follows.

Howard E. Smith* and Ann A. Hicks: Optically Active Amines. XII. Synthesis and Spectral Properties of Some Optically Active α-Oximino Ketones and α-Amino Ketone Hydrochlorides. Dimerization of α-Amino Ketones.

Page 3667. Column 1, line 2. "0.507 g (5.07 mmol)" should read 0.155 g (0.507 mmol).

B. D. Mookherjee,* R. R. Patel, and W. O. Ledig: Synthesis of *dl*-Muscone from Exaltone (Cyclopentadecanone).

Page 4124. The name "Exaltone" (a trade-mark) should be capitalized.

Vol. 37, 1972

J. W. Huffman* and M. L. Mole: A Stereoselective Non-annelation Synthesis of Eudalene Sesquiterpenes.

Page 14. In the structure for 10 and 11 R and R′ should be transposed.

Graham F. Whitfield,* Rodney Johnson, and Daniel Swern: Clarification of the Acid-Catalyzed Reaction of Glyoxal with Carbamate Esters.

Page 95. An important reference [P. M. Quan, *J. Org. Chem.*, **33**, 3937 (1968)] was overlooked in which the structure of the glyoxal–ethyl carbamate reaction product was clarified.

Clayton H. Heathcock,* Rodney A. Badger, and Ronald H. Starkey: Photochemistry of 1,6-Cyclodecadienes. I. 1-Methyl-(*E*,*E*)-1,6-cyclodecadiene.

Page 231. Name in title should be Ronald H. Starkey.

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 follows.
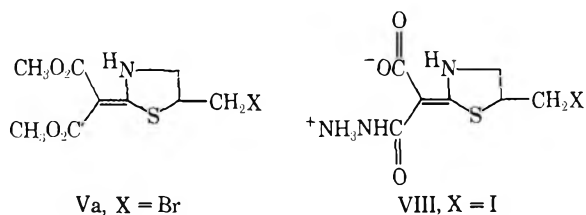
Va, X = Br
b, X = I
c, X = OH
d, X = ONO₂

VIII, X = I

Thomas J. Barton,* Michael D. Martz, and Rodney G. Zika: Facile Bridge Expulsion of Sulfur Heterocycles. The 7-Thiabicyclo[2.2.1]hepta-2,5-diene and 7-Thiabicyclo[4.1.0]hepta-2,4-diene Systems in Thiepin Synthesis.

Page 554. Column 2. Insert the following at the end of the paper.

Zvi Rappoport* and Aharon Gal: Vinylic Cations from Solvolysis. X. SN1 and Nucleophilic Addition–Elimination Routes for 9-(α-Haloarylidene)fluorenes.

Page 1179. Table IV, column 3, lines 5 and 6. "13.5^b and 0.29^b" should be 5.45^b and 0.12^b.

Page 1181. Last line. Rreference 41 should be

(41) R. C. Williams and J. M. Taylor, *J. Chem. Educ.*, **47**, 129 (1970).

W. G. Dauben* and T. J. Dietsche: Stereospecific Introduction of Functionalized Angular Methyl Groups *via* the Claisen Rearrangement. The Octalin and Hydrindenyl Ring Systems.

Page 1216. Column 2. "Thermolysis of 13." Line 6 and part of 7 should read (s, angular methyl α-methyl ketone) and 0.90 (s, angular methyl, β-methyl ketone).

Philip E. Pfeffer,* Edward Kinsel, and Leonard S. Silbert: α-Anions of Carboxylic Acids. V. A Simple High Yield Presentation of α-Alkylhydracrylic Acids and α-Alkylacrylic Acids.

Page 1256. In the second line of the title, "Presentation" should read Preparation.

Albert W. Burgstahler, Donald E. Walker, Jr., John P. Kuebrich, and Richard L. Schowen:* A Convenient Synthesis of Benzaldehyde-*formyl-d* from Benzil.

Page 1272. To the references cited in footnote 3 should be added the report of the versatile lithium aldimine route to 1-deuterio aldehydes by H. M. Walborsky and G. E. Niznik [*J. Amer. Chem. Soc.*, **91**, 7778 (1969)] and A. F. Thomas's monograph "Deuterium Labeling in Organic Chemistry," Appleton-Century-Crofts, New York, N. Y., 1971.

R. C. Nickolson and Marcel Gut:* Stereospecific Synthesis of (20*S*,22*R*)-17α,20,22-Trihydroxycholesterol and (20*S*,22*S*)-17α,-20,22-Trihydroxycholesterol.

Pages 2119, 2120, 2122, 2125, and 2126. "*sec*-Butyllithium" should read isobutyllithium on page 2119, line 8, page 2120, Scheme II, page 2122, column 1, lines 25 and 33, page 2125, column 2, line 62, and page 2126, column 1, lines 2 and 61. "*sec*-Butyl bromide" should read isobutyl bromide on page 2125, column 2, lines 64 and 70, and page 2126, column 1, line 6. Delete footnote 27 on page 2125.

R. A. Abramovitch,* S. R. Challand, and E. F. V. Scriven: Intermolecular Aromatic Substitution by Aryl Nitrenes.

Page 2710. Insert the following at the end of the paper.

Robert A. Ellison,* Warren D. Woessner, and Craig C. Williams: New Synthetic Methods from Dithianes. A Convenient Oxidation of Aldehydes to Acids and Esters.

Page 2759. Column 2. In line 12 replace "methyl iodide" with *n*-butyl iodide.

Gary N. Taylor: A Convenient Synthesis of Barrelene.

Page 2904. In column 1, paragraph 2, line 2, and Experimental Section, lines 3, 16, and 19, "1-" should read 2-.