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MAY 19, 1972

Studies of Benzonorbornene and Derivatives. VI. Peroxide-Induced Decarbonylation of *syn*- and *anti*-Benzonorbornene-7-carboxaldehydes[1,2]

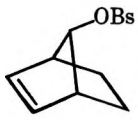
JAMES W. WILT* AND EDMUNDAS VASILIAUSKAS[3]

Department of Chemistry, Loyola University of Chicago, Chicago, Illinois 60626

Received November 12, 1971

The synthesis of the title aldehydes has been achieved. As a sidelight to the synthesis, a convenient new preparation of benzonorbornen-7-one was developed. The peroxide-induced decarbonylation of the title aldehydes proceeded faster with the anti epimer. Benzonorbornene was the principal product along with uncharacterized resinous material. The faster reaction of the anti epimer was most probably a reflection of its greater chain-transfer ability and *not* a consequence of any pronounced participation in decarbonylation by the π electrons of the aromatic ring. Chain-transfer reactions with chlorine donors served to demonstrate these reaction features. Discussion of the nmr spectra of the aldehydes is also presented.

The ability of the norbornene double bond to participate in the solvolysis of *anti*-7-norbornenyl substrates such as **1** is amply documented.[4] A similar rate effect



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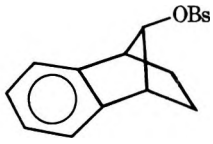

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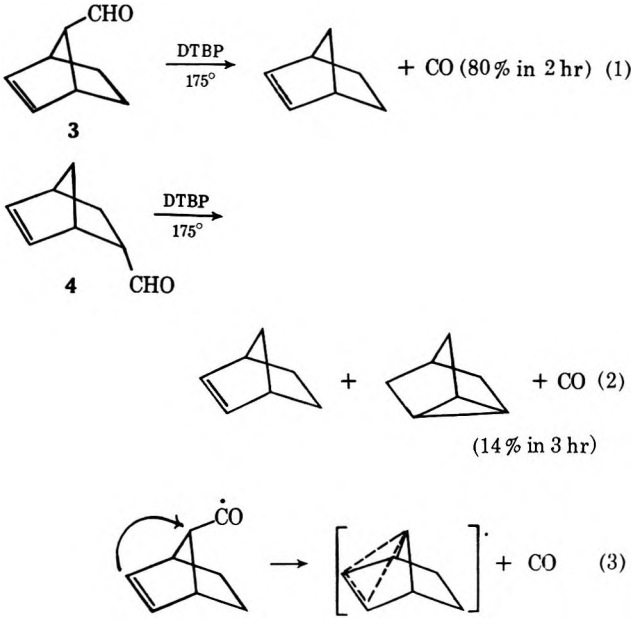
exists for the benzonorbornenyl analog **2**, though π participation by the aromatic ring is here somewhat less dramatic.[4]

In earlier work it was found that a *radical* reaction involving the 7 position in norbornene likewise seemed to be influenced by the double bond.[5] Aldehyde **3** lost carbon monoxide much more readily than its isomer **4** (eq 1 and 2). It was suggested that **3** utilized π participation in the loss of carbon monoxide leading to a symmetrical, delocalized radical species (eq 3). Since that time several claims and counterclaims concerning nonclassicality in 7-norbornenyl and related radicals have appeared.[6]

The reactions in eq 1 and 2 were disadvantaged because a side reaction leading to polymer cut the yield of monomeric hydrocarbon badly (2.3% from **3**, 8.6% from **4**). It was therefore of interest to prepare the benzo analog of **3**, benzonorbornene-*anti*-7-carboxaldehyde (**5**), and to study its decarbonylation, particularly with regard to its syn epimer **6**. Polymerization would no longer be a problem and the benzo analog otherwise should mirror **3** to an extent comparable to the ionic situation with **1** and **2** mentioned above. So perhaps a more meaningful search for π participation in the formation of a 7-norbornenyl type radical could be made by such a study.



Synthesis of Aldehydes.—The synthesis of aldehydes **5** and **6** employed a Wittig reaction between ketone **7**

(1) Paper V: J. W. Wilt and E. Vasiliauskas, *J. Org. Chem.*, **35**, 2410 (1970).

(2) Taken from a portion of the dissertation of E. V., Loyola University of Chicago, 1970. Some of this material was presented at the Third Great Lakes Regional Meeting of the American Chemical Society, DeKalb, Ill., June 5–6, 1969, Abstracts of Papers, p 58.

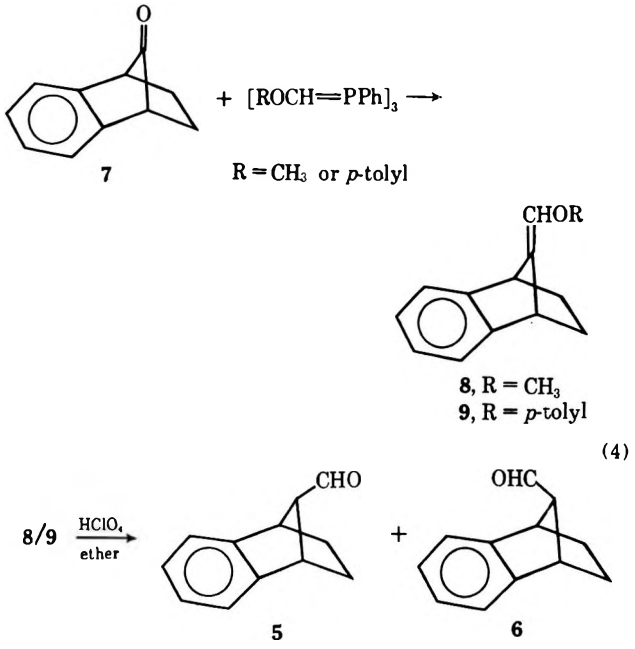
(3) NDEA Fellow, 1966–1969.

(4) *Cf.* H. Tanida, *Accounts Chem. Res.*, **1**, 239 (1968).

(5) J. W. Wilt and A. A. Levin, *J. Org. Chem.*, **27**, 2319 (1962).

(6) Some claims, strong and otherwise: J. W. Wilt, G. Gutman, W. J. Ranus, Jr., and A. R. Zigman, *ibid.*, **32**, 893 (1967); J. Warkentin and E. Sanford, *J. Amer. Chem. Soc.*, **90**, 1667 (1968); H. O. Ohorodnyk and D. P. Santry, *ibid.*, **91**, 4711 (1969). The counterclaims: S. J. Cristol and A. L. Noreen, *ibid.*, **91**, 3969 (1969); P. Bakuzis, J. K. Kochi, and P. J. Krusic, *ibid.*, **92**, 1434 (1970).

and the ylide from either methoxymethylene-[7] or *p*-tolyloxymethylene-[8] triphenylphosphorane, formed *in situ* from the appropriate phosphonium salt (eq 4).[9]

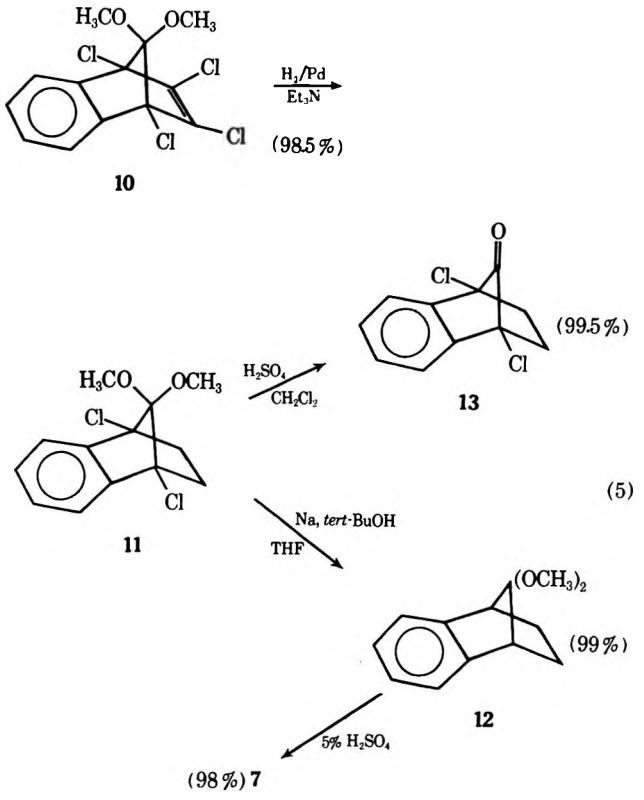


Benzonorbornen-7-one (**7**) is known,[10] but during this work a convenient new synthesis was developed.[11] The sequence (eq 5) commenced with **10**[1] and proceeded *via* two reduction processes[12] to **11**[13] and **12**, respectively. Ketals **11** and **12** readily afforded ketones **7** and **13** upon hydrolysis. Full details are given in the Experimental Section.

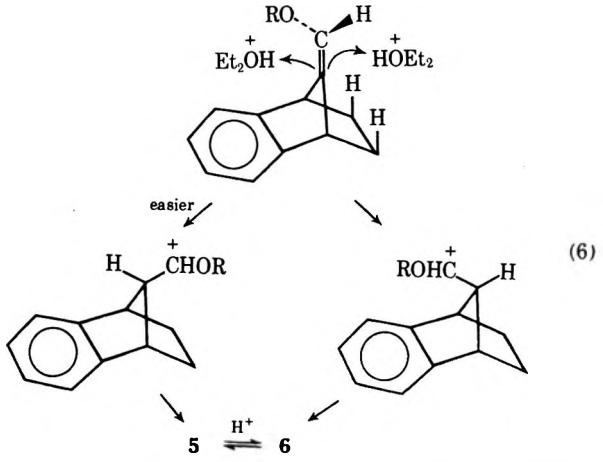
The Wittig reaction in eq 4 proceeded better with dimsyl sodium[14] as the ylide-generating base. For example, enol ether **8** (R = CH_3) was produced in 55% yield in this way as compared to 20% when *n*-butyllithium was used. Acidic hydrolysis of enol ether **8** or **9** was best achieved with ethereal perchloric acid.[7] Somewhat better yields in these two steps were achieved with R = CH_3 (55 and 84%) rather than with R = *p*-tolyl (49 and 61%).

The acidic hydrolysis of either enol ether **8** or **9** led to the same product, a mixture of aldehydes **5** (69.8%) and **6** (30.2%). Extensive efforts by gas–liquid partition chromatography failed to separate the epimers, although partial resolution was achieved. Careful distillation also changed the composition somewhat, but again the epimers were inseparable under any conditions tried.

The preferential formation of **5** rather than **6** upon



hydrolysis of the enol ethers may reflect a kinetic favorability for protonation of the enolic double bond from the syn side (leading to anti aldehyde). Anti protonation would possibly be hindered by the exo ring H's (eq 6). Of course thermodynamic control of the



product *via* epimerization through the enol of **5** and **6** is also conceivable. However, *nucleophilic* attack on ketone **7**[9a,15] and 7-norbornenone[16] favors syn approach kinetically, and later observations (*vide infra*) imply that the syn aldehyde **6** would be preferred over the anti epimer **5** if an equilibrium were established between them.[17] In any case no hydrolytic conditions

(7) S. G. Levine, *J. Amer. Chem. Soc.*, **80**, 6150 (1958).

(8) G. Wittig, W. Böll, and K. Krück, *Chem. Ber.*, **95**, 2514 (1962).

(9) For other Wittig reactions of **7**, *cf.* (a) H. Tanida, Y. Hata, S. Ikegami, and N. Ishitobi, *J. Amer. Chem. Soc.*, **89**, 2928 (1967); (b) R. Muneyuki and H. Tanida, *ibid.*, **90**, 656 (1968).

(10) (a) P. D. Bartlett and W. P. Giddings, *ibid.*, **82**, 1240 (1960). (b) For a recent ozonation procedure to **7**, *cf.* R. Muneyuki and H. Tanida, *J. Org. Chem.*, **31**, 1988 (1966).

(11) Independently, a similar route was recently reported by P. F. Ranken and M. A. Battiste, *ibid.*, **36**, 1996 (1971). We thank Dr. Battiste for a preprint of their work. No detailed discussion of the sequence in 5 is given here because the sequence mirrors others which have been used and discussed for the nonbenzo analog.[12]

(12) *Cf.* (a) K. V. Sherer, *Tetrahedron Lett.*, 5685 (1966); (b) P. G. Gassman and P. G. Pape, *ibid.*, 9 (1963); *J. Org. Chem.*, **29**, 160 (1964).

(13) Some additional chemistry of ketal **11** and the ketone **13** obtained from it by hydrolysis will be reported in a subsequent paper of this series.

(14) E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **84**, 866 (1962).

(15) K. Tori, K. Aono, Y. Hata, R. Muneyuki, T. Tauji, and H. Tanida, *Tetrahedron Lett.*, 9 (1966).

(16) J. Warkentin, *Can. J. Chem.*, **48**, 1391 (1970). Calculations indicate that the methano bridge in 7-norbornenone is bent back toward the saturated ethano arm, favoring syn attack on the carbonyl group. *Cf.* S. Yankelevitch and B. Fuchs, *Tetrahedron Lett.*, 4945 (1967).

(17) The situation is confused, however. Muneyuki and Tanida[9b] reported that catalytic hydrogenation of ethyl benzonorbornenylidene-7-acetate over platinum oxide (usually kinetic control) gave mainly (87%) reduction from the anti side whereas use of palladium on charcoal (usually thermodynamic control) gave predominantly (60%) syn reduced product. These are opposite to expectation and perhaps reflect the different type process (heterogeneous) involved.

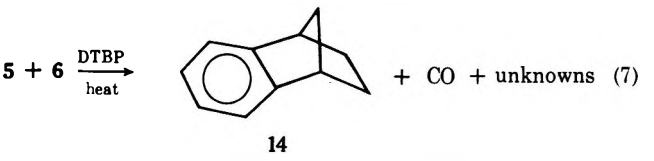
were found that favored **6** over **5** from either enol ether.

Structural Assignments.—The assignment of structure to these aldehydes rests on the nmr position of the aldehydic proton doublet in each case. In **6**, this proton is positioned in the deshielding zone above the plane of the aromatic ring[18] and the doublet resonance was at δ 9.22. In **5**, contrariwise, the aldehydic doublet resonance was at δ 9.57. Integration of these signals then allowed a ready determination of the composition of any mixture isolated by preparative glpc or distillation. An interesting additional difference between **5** and **6** was the spin–spin coupling constant (J value) for the doublet, 0.5 Hz for **5** *vs.* 3.5 Hz for **6**. Neither value changed (<0.3 Hz) upon variable-temperature nmr studies over the range 25–150°; so the J value difference presumably is not due to conformational preferences in the aldehydes. Possibly other molecular features, such as the bridge angle at C-7 and/or the effective electronegativity of the carbonyl group, differ in the epimers and cause the disparate J values.[19] Further study, including low-temperature nmr studies, are in progress on this point.

The resonance position of the 7 proton in **5** and **6** deserves comment. In a number of 7-substituted benzobornenes, the syn 7 proton is shielded by the aromatic ring and its resonance position is upfield relative to that for the anti 7 proton in the epimer.[20] The reverse is true for norbornene and benzonorbornene themselves[15,21] and for the aldehydes **5** and **6**. The assignment in the latter compounds seems secure nonetheless because the syn 7 proton in **5** is a multiplet (δ 2.55) evidencing coupling with the bridgehead and endo ring protons as well as the aldehydic proton. In **6**, the anti 7 proton is a doublet tripleted (δ 2.42) as would be expected for larger coupling to the aldehydic proton (J = 3.5 Hz) and weaker coupling ($J \sim 1.5$ Hz) to the bridgehead protons. It has been claimed[22] that the *lower* field resonance for syn 7 protons in norbornene is general, with a reversal expected when anisotropic functions complicate matters. Presumably the aldehyde function in **5** and **6** is not such a complicating function. The entire rationale for bridge proton resonance positions in 7-substituted norbornenes obviously needs development.

Decarbonylation and Related Studies on Aldehydes 5 and 6.—Liquid-phase decarbonylation of a neat aldehyde mixture (**5**:**6** = 69.8:30.2) in the customary fashion[23] using 10–30 mol % di-*tert*-butyl peroxide at 180° for 3 hr yielded benzonorbornene (**14**, 60.6%), carbon monoxide (85%), ill-defined higher molecular weight material (~20%), and recoverable initial aldehydes (~15%), as shown in eq 7.

The unusual feature of the process was that the recovered aldehyde mixture was now richer in the syn epimer



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(**5**:**6** = 37.7:62.3), *indicating preferential loss of the anti aldehyde* **5**![24] This was confirmed by the results in Table I obtained from a different initial aldehyde mixture.

TABLE I

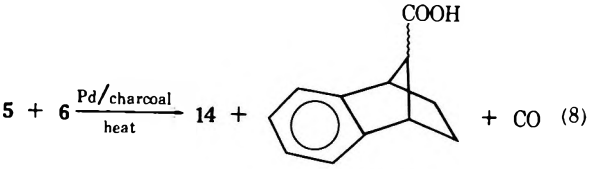
RATIO OF ALDEHYDES 5 AND 6 RECOVERED AFTER PARTIAL DECARBONYLATION

Reaction time, min[a]	5:6 Ratios[b]
0	73.6:26.4
95	60.4:39.6
141	54.0:46.0

[a] At 180°. [b] Determined by nmr analysis of the recovered aldehydic mixture isolated *via* glpc at the indicated time.

A similar reaction without peroxide gave only a 1.3% yield of **14**; so a radical chain process seems implicated in the formation of the products in eq 7.

In contrast to the peroxide-induced process, decarbonylation of aldehydes **5** and **6** with palladium on charcoal[25] at 194° led cleanly to **14** (97.5%). Only small amounts of unchanged aldehydes and their corresponding acids **15** were otherwise detected (eq 8). This



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result reemphasizes the utility of this method as a *preparative* decarbonylation technique (considerably superior to the peroxide method).

The faster decarbonylation observed under peroxidic conditions with the anti aldehyde **5** could be the result of π participation as in (eq 3). On the other hand, its faster decarbonylation could be due to easier chain transfer with **5** than with **6** (eq 9).

To evaluate these possibilities, the aldehyde mixture was treated with benzoyl peroxide and carbon tetrachloride under reflux at ~77° or with di-*tert*-butyl peroxide (DTBP) and benzotrichloride at 180°.[26] The resulting mixture was then treated with methanol and the products were isolated by gas chromatography (eq 10). The data from this study are given in Table II.

The assignment of structure to the esters **16** and **17** was again by nmr evidence. The syn epimer **17** exhibited the methyl singlet resonance at δ 3.38, upfield as expected[18] from the methyl resonance of **16** at δ 3.63. Integration of these singlets then allowed a determination of the ester ratio.

The formation of esters **16** and **17** with no apparent **14** indicates that the acyl radicals from the aldehydes were effectively trapped by the chlorine donors used as

(18) L. M. Jackson, "Applications of Nuclear Magnetic Resonance in Organic Chemistry," Macmillan, New York, N. Y., 1959, p 125. See also D. J. Pasto and C. R. Johnson, "Organic Structure Determination," Prentice-Hall, Englewood Cliffs, N. J., 1969, p 172.

(19) M. Karplus, *J. Amer. Chem. Soc.*, **85**, 2870 (1963).

(20) J. W. Wilt and P. J. Chenier, *J. Org. Chem.*, **35**, 1562 (1970), and references cited therein.

(21) B. Franzus, W. C. Baird, Jr., N. F. Chamberlain, T. Hines, and E. I. Snyder, *J. Amer. Chem. Soc.*, **90**, 3721 (1968).

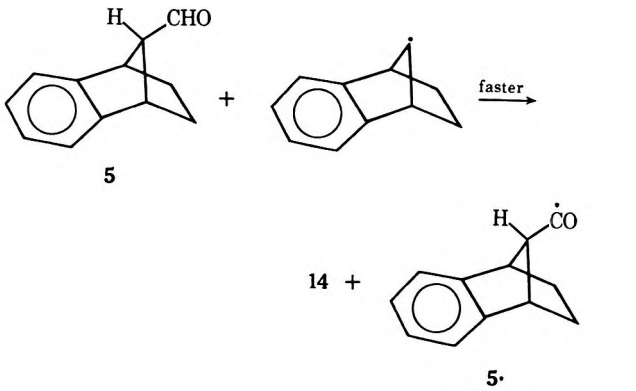
(22) A. P. Marchand and J. E. Rose, *ibid.*, **90**, 3724 (1968). These authors also note that the *coupling* of bridge protons in norbornenes is better evidence for their stereochemistry than is their *chemical shift*.

(23) *Cf.* J. W. Wilt, L. L. Maravetz, and J. F. Zawadzki, *J. Org. Chem.*, **31**, 3018 (1966), and references to earlier studies cited therein.

(24) The **5**:**6** ratio is of course time dependent (see Table I). However, in this typical example **5** was some fourfold faster in the process than **6**.

(25) J. W. Wilt and V. P. Abegg, *J. Org. Chem.*, **33**, 923 (1968).

(26) This technique was used some time ago by S. Winstein and F. H. Seubold, Jr., *J. Amer. Chem. Soc.*, **69**, 2916 (1947), and more recently by D. E. Applequist and L. Kaplan, *ibid.*, **87**, 2194 (1965).



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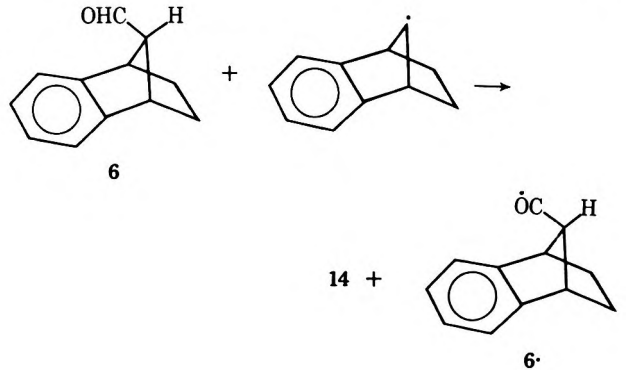

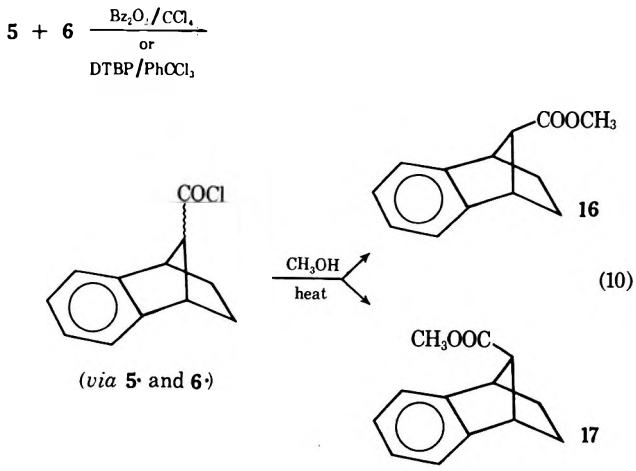

TABLE II

TRAPPING STUDIES ON ACYL RADICALS 5· AND 6·

5:6	Yield of esters 16 + 17, %	16:17
77.2:22.8[a]	93.5	76.0:24.0[c]
65.1:34.9[b]	68.9	65.3:34.7[c]

[a] Initial ratio of aldehydes 0.3 *M* in CCl_4 heated under reflux for 0.5 hr. Benzoyl peroxide was used as the initiator. [b] Initial ratio of aldehydes 0.68 *M* in benzotrichloride held at 180° for 4 hr. DTBP was used as the initiator. [c] By nmr analysis of material isolated *via* glpc.

solvents. The virtual identity of the initial aldehydes and final ester anti:syn ratios at two widely different temperatures and with two solvents of somewhat different chain-transfer ability[27] strongly indicates that π participation analogous to eq 3 was *not* a detectable cause of the faster decarbonylation of **5**.[28] Rather, better chain transfer with the anti aldehyde probably occasioned the different decarbonylation rates as shown earlier in Table I. Such a difference in chain-transfer ability between aldehydes has been suggested before[29] and in the present case may be related to the different steric environment of the aldehydic hydrogens in **5** *vis-à-vis* **6**. Available data does not allow, however, a definitive conclusion in this regard.

Attempts to epimerize the ester mixture **16** + **17** were only partly successful. Heating a mixture of esters with sodium methoxide in methanol for various times led to enrichment of the syn epimer **17**. However, recovery of the ester mixture was not quantitative after each heating period and the anti:syn ratio did not level off; so the meaning of the syn enrichment is not immediately clear. If the enrichment is due to a thermodynamic preference for the syn epimer, it lends credence to the aforementioned kinetic preference for the anti aldehyde formed upon hydrolysis of the enol ethers.

In summary, the peroxide-induced decarbonylation of the epimeric benzonorbornene-7-carboxaldehydes proceeded faster with the anti compound. Evidence from chain-transfer experiments indicated that this favorability was not due to any pronounced preferential decarbonylation of the acyl radical derived from the anti aldehyde. More probably the favorability may be ascribed to differences in the chain-transfer abilities of the epimeric aldehydes. No evidence supporting our earlier suggestion of possible π electron assistance in such systems was found.

Experimental Section

Melting points were taken on a calibrated Fisher-Johns block. Boiling points are uncorrected. Infrared spectra (λ) were determined on a Beckman IR-5A instrument. Only prominent or structurally significant absorptions are listed (in microns). Nuclear magnetic resonance spectra were taken on a Varian A-60A spectrometer. Values are given in parts per million (δ) downfield from internal TMS. The usual splitting abbreviations are used. Integrations of signals agreed with the structural assignments. Gas–liquid partition chromatography (glpc) was done on a Varian Aerograph A-90P chromatograph with helium gas as carrier. Peaks were disc-integrated. Microanalyses were performed by Micro-Tech Laboratories, Skokie, Ill.

1,4-Dichloro-7,7-dimethoxybenzonorbornene (11).—1,2,3,4-Tetrachloro-7,7-dimethoxybenzonorbornadiene (**10**,[1] 5.0 g, 14.7 mmol) was hydrogenated at 25° over palladium on carbon (5%, 1.0 g) in 95% ethanol (200 ml) containing excess triethylamine (70 ml).[12a] After 1.5 hr the filtered solution was evaporated to dryness. Water and ether (150 ml of each) were added and the mixture was shaken. The ether phase was separated and combined with ether washes of the aqueous phase. After a wash with potassium carbonate solution (10%), the combined ether solution was dried ($MgSO_4$) and evaporated. The residual oil was distilled to afford colorless **11**: yield 3.95 g (98.5%); bp 117–118° (0.55 mm); $n^{27}D$ 1.5488; d^{29}_4 1.2843; λ (neat) 6.84, 8.90–9.03 μ (OCH_3); nmr (CCl_4) δ 7.46 (s, ArH), 3.74 (s, anti OCH_3), 3.40 (s, syn OCH_3), 2.55 (dd, exo ring H's, $J_{exo,endo}$ = 11 Hz, J_{vic} = 4.5 Hz), 1.58 (dd, endo ring H's). The analytical sample was collected by glpc at 170° using a column of 20% Reoplex 400 on 30/60 mesh Gas-Chrom (column R).

Anal. Calcd for $C_{13}H_{14}O_2Cl_2$: C, 57.16; H, 5.16. Found: C, 57.41; H, 5.22.

(27) R. A. Gregg and F. R. Mayo, *J. Amer. Chem. Soc.*, **75**, 3530 (1953), report the following chain transfer constants at 60° in styrene polymerization: CCl_4, 0.920 × 10^{-2}; $C_6H_5CCl_3$, 0.575 × 10^{-2}.

(28) It remains a possibility, nonetheless. The acyl radicals may simply undergo chain transfer with the chlorine donor solvent faster than they lose carbon monoxide, even though this latter process may still be potentially faster in the anti epimer **5**. If so, however, we feel that the difference between **5** and **6** in this regard cannot be very large or significant.

(29) J. W. Wilt and H. Philip, *J. Org. Chem.*, **25**, 891 (1960).

7,7-Dimethoxybenzonorbornene (12).—To a vigorously stirred solution of ketal 11 (10.0 g, 36.7 mmol) in dry *tert*-butyl alcohol (50 ml) and tetrahydrofuran (210 ml) under nitrogen was added finely chopped sodium metal (27 g, 1.17 g-atoms).[12b] The mixture was refluxed for 18 hr. Methanol was next slowly added to destroy the excess sodium. The solution was poured into cold water (1.5 l.) and extracted with ether (3 × 500 ml). The ether extracts were combined, washed with water, and dried ($MgSO_4$). Removal of solvent left quite pure 12 as an oil that slowly solidified. Distillation in a short-path apparatus, bp *ca.* 90° (0.05 mm), gave colorless product: yield 7.40 g (99%); mp 49–50°; λ (neat) 6.83, 8.84, 9.08–9.38 μ (OCH_3); nmr (CCl_4) δ 7.11 (s, ArH), 3.25 (s, anti OCH_3), 3.21 (m, bridgehead H's), 3.02 (s, syn OCH_3), 2.07 (m, exo ring H's), 1.07 (m, endo ring H's). The analytical sample was collected by glpc at 175° using column R.

Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.60; H, 7.94.

1,4-Dichlorobenzonorbornen-7-one (13).—A mixture of ketal 11 (4.97 g, 18 mmol), methylene chloride (100 ml), and concentrated sulfuric acid (40 ml) was stirred at 25° for 24 hr. The methylene chloride phase was separated and combined with methylene chloride washes of the sulfuric acid phase. The combined organic material was washed to neutrality, dried ($MgSO_4$), and evaporated. The yellow oily residue was dissolved in pentane and precipitated by chilling to −50°. Ketone 13 formed white needles upon recrystallization from pentane: yield 3.97 g (99.5%); mp 69–69.5°; λ (KBr) 5.51 μ (CO); nmr (CCl_4) δ 7.79 (s, ArH), 2.85–1.85 (sym m, ring H's).

Anal. Calcd for $C_{11}H_8OCl_2$: C, 58.18; H, 3.55. Found: C, 57.88; H, 3.44.

The yellow **2,4-dinitrophenylhydrazone** derivative was best prepared with the phosphoric acid–ethanol solution of the reagent,[30] mp 220.5–221.5° dec.

Anal. Calcd for $C_{17}H_{12}O_4N_4Cl_2$: N, 13.76. Found: N, 13.82.

Benzonorbornen-7-one (7).—The ketone was prepared as reported by Oppenauer oxidation of *anti*-7-benzonorbornenol.[10a] Small-scale preparation was also effected by oxidation of this alcohol with chromium trioxide in pyridine. A convenient alternative method involved hydrolysis of ketal 12 (5 g, 24.5 mmol) with dilute sulfuric acid (5%, 250 ml) for 20 hr at 50°. The ketone was isolated by extraction with ether (2 × 125 ml). The water-washed extract was dried ($MgSO_4$) and distilled to afford pale yellow 7 (3.90 g, 98%, spectra agreed with those reported[10a,11]).

7-Methoxymethylenebenzonorbornene (8).—Dimsyl sodium (33 mmol) was prepared in dry dimethyl sulfoxide (15 ml) as reported.[31] To this at 20° under nitrogen was added methoxymethyltriphenylphosphonium chloride[32] (11.25 g, 33 mmol, mp 199–202° dec) dissolved in warm dimethyl sulfoxide (45 ml). The dark red solution of the phosphorane was stirred at 25° for 10 min and then ketone 7 (5.20 g, 33 mmol) was added slowly with external cooling to maintain the temperature at 30–35°. The reaction mixture was stirred at 35° for 30 min and at 55° for 16 hr. The cooled solution was added to water (150 ml) and extracted with pentane (3 × 200 ml). The combined pentane extracts were washed well with water and brine, dried ($MgSO_4$), and evaporated. The residual oil was chromatographed through alumina (100 g) and then distilled to yield 8 as a colorless oil: yield 3.35 g (54.8%); bp 81–85° (0.08 mm); λ (neat) 5.81, 8.21, 8.56–8.72, 8.97 μ (C=$COCH_3$); nmr (CCl_4) δ 7.22 (m, ArH), 5.67 (s, vinyl H), 4.09 (m) and 3.52 (m, bridgehead H's), 3.49 (s, OCH_3), 1.95 (m, exo ring H's), 1.25 (m, endo ring H's). The analytical sample was collected by glpc at 178° using column R.

Anal. Calcd for $C_{13}H_{14}O$: C, 83.83; H, 7.58. Found: C, 83.64; H, 7.53.

A similar reaction (24-mmol scale) of 7 and the phosphorane using *n*-butyllithium (46 mmol) in ether as base gave only a 20.3% yield of 8.

7-*p*-Tolyloxymethylenebenzonorbornene (9).—Dimsyl sodium (21 mmol) in dry dimethyl sulfoxide (60 ml) was used to convert *p*-tolyloxymethyltriphenylphosphonium chloride[8] (8.8 g, 21 mmol, mp 195–198°) to the phosphorane as described above for 8. Reaction with ketone 7 (3.39 g, 21 mmol) again as described above, led to enol ether 9, best isolated by glpc (20% SE-30 on 30/60 mesh Gas-Chrom column at 233°) as a pale yellow oil: yield 2.77 g (49.4%); $n^{29}D$ 1.5985; λ (neat) 5.81, 8.00, 8.18, 8.99 μ (C=COR); nmr (CCl_4) δ 6.77–7.34 (m, ArH), 6.12 (s, vinyl H), 4.15 (m) and 3.64 (m, bridgehead H's), 2.29 (s, $ArCH_3$), 2.04 (m, exo ring H's), 1.32 (m, endo ring H's).

Anal. Calcd for $C_{19}H_{18}O$: C, 86.99; H, 6.92. Found: C, 87.50; H, 6.75.

***anti*- (5) and *syn*-Benzonorbornene-7-carboxaldehyde** (6).—Perchloric acid (17 ml of 70% reagent grade material) was added dropwise to ether (70 ml) with good stirring. Enol ether 8 (4.10 g, 22 mmol) was added and the solution was heated under reflux for 2 hr. Water (100 ml) and ether (100 ml) were then added to the cooled solution. The material was vigorously shaken and the ether layer was separated. The aqueous phase was extracted with several more portions of ether. The ether layer and combined extracts were washed several more times alternately with water and sodium bicarbonate solution and then dried ($MgSO_4$). Distillation produced aldehydes 5 and 6 as a colorless oil: yield 3.23 g (84.4%); bp 88–93° (0.8 mm); λ (neat) 3.60, 3.72, 5.85 μ (–CHO); nmr (CCl_4) δ 9.57 (d, –CHO of 5, $J \cong 0.5$ Hz), 9.22 (d, –CHO of 6, J = 3.5 Hz), 7.07 (m, ArH), 3.55 (m, bridgehead H's), 2.55 (m, 7-H of 5), 2.42 (partially obscured doublet of triplets, 7-H of 6), 1.95 (m, exo ring H's), 1.18 (endo ring H's).

Anal. Calcd for $C_{12}H_{12}O$: C, 83.69; H, 7.02. Found: C, 83.70; H, 7.09.

The J values for the aldehydic protons were unchanged over the temperature range 25–148°. The doublet of triplets for the 7-H of 6 has J values of 3.5 and *ca.* 1.5 Hz.

The **2,4-dinitrophenylhydrazone** upon precipitation had mp 180–190° dec. Repeated recrystallization from ethanol–ethyl acetate apparently fractionated the mixture to give an analytical sample, mp 206–209° dec, although which epimeric derivative was obtained is unknown.

Anal. Calcd for $C_{18}H_{16}O_4N_4$: N, 15.90. Found: N, 15.82.

Analogous hydrolysis treatment of enol ether 9 gave a 67.3% yield of 5 and 6. Analysis of the aldehyde mixture from either enol ether by integration of the nmr signal at δ 9.57 and 9.22 gave a ratio 5:6 of 2.3:1. Separation of the mixture at 180–200° was unsuccessful on the following glpc columns: Reoplex 400, Flexol 8N8, SE-30, neopentyl glycol succinate, Carbowax 20M, and Apiezon L. Partial resolution was achieved at 185° with an Apiezon N column.

The aldehydes were substantially oxidized to acids at 25° upon exposure to air as a thin film for 3 days. The unoxidized aldehydes were decanted from the crystalline acid(s). From an initial mixture of 5:6 of 68.3:31.7 the recovered aldehydes were almost unchanged in proportion by nmr analysis (5:6, 69.3:30.7). The crystalline material was taken up in dilute sodium hydroxide (10%), washed with ether, and then precipitated by the addition of dilute hydrochloric acid. The crude product, mp 147–151°, was recrystallized several times from hexane to give white crystals of **benzonorbornene-*anti*-7-carboxylic acid**: mp 153–154°; λ (Nujol mull) 5.92 μ (COOH); nmr (CCl_4) δ 10.58 (s, COOH), 7.14 (s, ArH), 3.65 (m, bridgehead H's), 2.85 (close pentuplet, (7-H), 2.17 (m, exo ring H's), 1.25 (m, endo ring H's).

Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.74; H, 6.58.

The anti nature of the acid is a provisional assignment based upon the pentuplet nature of the syn 7 proton. This is the expected splitting for this proton because of probable coupling with the bridgehead and endo ring protons. Presumably the syn acid was fractionated away upon the recrystallizations.

Peroxide-Induced Decarbonylation of Aldehydes 5 and 6.—A known mixture of aldehydes was mixed with freshly distilled di-*tert*-butyl peroxide (10 mol %) and heated in a gas-collecting system under helium. Two additional increments of peroxide (10 mol % each) were added to the mixture by syringe through a septum cap at ~1-hr intervals when gas evolution slackened. Several reactions were conducted at 180 ± 1° and for 3–4 hr. The collected gas was analyzed for carbon monoxide *via* glpc on a molecular sieves 13X column at 25°, using calibration data from injected authentic carbon monoxide. The brown oil remaining after reaction was also analyzed *via* glpc. Benzonorbornene (14) and unreacted aldehydes 5 and 6 were the only volatile products. Distillation of the reaction material again gave only these products along with a resinous residue. A typical reaction on 0.3858 g (2.2 mmol) of aldehydes (5:6, 69.8:30.2) gave carbon

(30) L. F. Fieser, "Organic Experiments," 2nd ed, Raytheon Education Co., Lexington, Mass., 1968, p 98.

(31) R. Greenwald, M. Chaykovsky, and E. J. Corey, *J. Org. Chem.*, **28**, 1128 (1963).

(32) G. Wittig and M. Schlosser, *Chem. Ber.*, **94**, 1373 (1961).

monoxide (42.7 ml at STP, 85%), benzonorbornene (14, 0.1958 g, 1.4 mmol, 60.6%), unreacted aldehydes (~15%, 5:6, 37.7:62.3), and uncharacterized distillation residue (~20%).

Other reactions were sampled by syringe through the septum at various intervals and the aldehyde composition was ascertained by nmr analysis (see Table I).

A reaction carried out as above but without the di-*tert*-butyl peroxide afforded 14 in small amount (1.3%). The aldehydic mixture was essentially unchanged otherwise.

Palladium-Promoted Decarbonylation of Aldehydes 5 and 6.—Aldehydes 5 and 6 (0.4935 g, 2.9 mmol) and palladium on charcoal (5%, 0.495 g) were heated at 194 ± 1° for 3.5 hr, at which time the evolution of carbon monoxide effectively ceased. Analysis of an aliquot of the residual oil by glpc indicated the presence of 14 (97.5%) and unreacted aldehydes. Microdistillation of the remainder afforded 14, with a distillation residue comprised mainly of acids 15. Benzonorbornene was *isolated* by distillation in 91.5% yield.

Reaction of Aldehydes with Carbon Tetrachloride and Benzotrichloride.—An aldehydic mixture (5:6, 77.2:22.8, 0.5226 g, 3.0 mmol), together with recrystallized benzoyl peroxide (0.07 g, 0.3 mmol) and purified carbon tetrachloride (10 ml), were heated at reflux under nitrogen. After 30 min another 0.07 g of peroxide was added and heating was continued for another 30 min. Dry methanol (6 ml) was then added to the cooled solution and the material was again heated at reflux for 20 min. Water was added to the cooled solution and the carbon tetrachloride phase was separated. The material was washed with sodium bicarbonate solution (saturated, 10 ml) and water until it was neutral. The dried solution ($MgSO_4$) was distilled free of solvent and chloroform [δ 7.42 (s)] formed in the reaction. The oil remaining was separated by glpc on column R at 190° into methyl benzoate (from the peroxide) and **methyl benzonorbornene-*anti*- and -*syn*-7-carboxylates** (16 and 17, respectively, 0.57 g, 93.5%). The ratio of 16:17 was 76.0:24.0 by nmr analysis. The esters were obtained as a colorless oil: λ (neat) 5.78 μ (C=O); nmr (CCl_4) δ 7.09 (s, ArH), 3.64 (s, OCH_3 of anti ester 16), 3.56 (m, bridgehead H's), 3.38 (s, OCH_3 of syn ester 17), 2.68 (m, 7-H), 2.05 (m, exo ring H's), 0.95 (m, endo ring H's).

Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.07; H, 7.13.

The esters were separable on a 0.25 in. × 6 ft Apiezon N column (20% on 30/60 mesh Gas-Chrom) at 180°.

Reaction of the aldehydes (5:6, 65.1:1.34.9, 0.5841 g, 3.4 mmol), di-*tert*-butyl peroxide (0.05 g, 0.3 mmol), and freshly distilled benzotrichloride (5 ml) was carried out under helium at 180 ± 1° for 4 hr. Additional peroxide (0.05-g increments) was added at 75-, 83-, 64-, and 65-min intervals. The reaction was treated with methanol and processed as described above. The products observed were some **tolane tetrachloride** (from the solvent, mp and lit.[33] mp 160–161°), esters 16 and 17 (68.9%, 16:17, 65.3:34.7) and unidentified products (~25%) possessing carbonyl and monosubstituted aromatic functions (λ 5.75–5.78, 13.4, and 14.4 μ).

Attempted Epimerization of Esters 16 and 17.—Sodium methoxide (4.0 mmol) was freshly prepared in methanol (3 ml). Esters 16 and 17 (80:20, 0.83 g, 4 mmol) were added in methanol (2 ml) and the solution was heated under reflux for various times. The cooled solution was diluted with water and quickly extracted with ether. The ether extracts were washed, dried ($MgSO_4$), and evaporated. The remaining oil was then analyzed by nmr to obtain the ratio of esters (OCH_3 resonances). After each determination the esters were heated for an additional period and processed again. The data are given in Table III.

TABLE III

EPIMERIZATION OF ESTERS 16 AND 17

Reaction time,[a] hr	16:17 Ratio	Recovery, %
0	80:20	
0.5	79:21	91.7
3.5	71.5:28.5	88.2
9.5	67.3:32.7	79.2
26.8	55.4:44.6	79.4
89.0	33.4:66.6	62.0
210[b]	22.2:77.8	65.4

[a] Under reflux in methanol. [b] Too little material available after this time for further study.

Registry No.—**5**, 34225-91-7; **6**, 34225-92-8; **6** DNP, 34201-91-7; **8**, 34201-92-8; **9**, 34201-93-9; **11**, 34201-94-0; **12**, 29370-70-5; **13**, 34201-96-2; **13** DNP, 34201-97-3; **16**, 34225-93-9; **17**, 34225-94-0; benzonorbornene-*anti*-7-carboxylic acid, 34225-95-1.

(33) D. C. Sayles and M. S. Kharasch, *J. Org. Chem.*, **26**, 4210 (1961).

Competition between Anchimerically Assisted and Anchimerically Unassisted Routes in Solvolyses of Fused Norbornyl Derivatives[1,2]

ROBERT K. HOWE*

Research and Development Department, Agricultural Division, Monsanto Company, St. Louis, Missouri 63166

PETER CARTER AND S. WINSTEIN[3]

Department of Chemistry, University of California at Los Angeles, Los Angeles, California 90024

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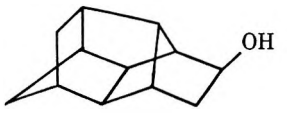
The products of acetolysis at 50° of VI-OBs are 65.3% VI-OAc, 27.3% VII-OAc, and 7.4% twisted monoene. VII-OBs produces 96.3% VI-OAc, 3.1% VII-OAc, and 0.6% twisted monoene. VIII-OBs produces 90.7% VIII-OAc, 2.6% IX-OAc, 6.7% twisted monoene, and 0.006% V-OAc. IX-OBs produces 99.22% VIII-OAc, 0.25% IX-OAc, and 0.53% twisted monoene. The very reactive X-OBs (k = 0.104 sec^{-1} at 27°) forms 14.5% bird-cage hydrocarbon, 0.06% twisted monoene, 25.3% V-OBs, 15.0% V-OAc, 14% VI-OBs, 19% VI-OAc, 5.4% VIII-OBs, 3% VIII-OAc, and 3.8% XII-OAc in acetic acid at 27°. The results suggest that endo acetates VII-OAc and IX-OAc produced in acetolysis of VI-OBs and VIII-OBs, respectively, are formed by anchimerically unassisted solvolysis in competition with anchimerically assisted solvolysis. The olefin appears to arise from concerted (probably cis) elimination from covalent VI-OBs and VIII-OBs. Formation of olefin and endo acetate in acetolysis of VII-OBs and of IX-OBs evidently results, in each case, from the small amount of exo brosylate produced from the endo brosylate *via* ion pair return.

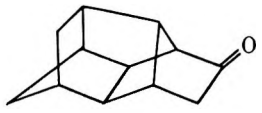
In continuance of studies[4] of the solvolysis of the *p*-bromobenzenesulfonates VI-OBs and VIII-OBs, we have found that endo products are formed from these exo brosylates and also from the endo brosylates VII-OBs and IX-OBs. The present work provides further examples[5] of the competition between anchimerically assisted and anchimerically unassisted routes in solvolyses of norbornyl derivatives and provides insight into the mechanism of olefin formation from norbornyl brosylates.

Results

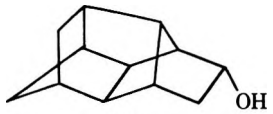
VI-OH, VI-OBs, VIII-OH, and VIII-OBs were known previously.[4] The structure of the previously reported[4] alcohol of mp 71.5–72.6° has been revised to that of VII-OH indicated below. Oxidation of both VI-OH and VII-OH gave the same ketone (VI-ketone), and lithium aluminum hydride reduction of VI-ketone gave a 31:69 mixture of VI-OH and VII-OH. Oxidation of VIII-OH and lithium aluminum hydride reduction of the resultant VIII-ketone gave a 9:91 mixture of VIII-OH and IX-OH, from which pure IX-OH was isolated.



VI-OH



VI-ketone



VII-OH

The brosylates were solvolyzed at 50° at 0.010 *M* concentration in acetic acid that contained 0.020 *M* sodium acetate for 20 half-lives for the product analyses, which were performed by gas chromatography (gc). The product mixture from VI-OBs was found to consist of 65.3 ± 1.5% VI-OAc, 27.3 ± 1.5% VII-OAc, and 7.4 ± 0.5% twisted monoene,[4] with <0.03% XII-OAc (none detected). This analysis by gc is in agreement with the infrared analysis reported previously,[4] taking into consideration the corrected structural assignment for VII-OH and VII-OAc. VII-OBs gave 96.3% VI-OAc, 3.1 ± 0.3% VII-OAc, and 0.6 ± 0.2% twisted monoene, with <0.03% XII-OAc; acetolysis of VII-OBs under similar conditions but with incorporation of 0.02 *M* tetrabutylammonium *p*-bromobenzenesulfonate gave the same product mixture. Pure VIII-OBs yielded 90.7% VIII-OAc, 2.6% IX-OAc, 6.7% twisted monoene, and 0.006% half-cage V-OAc. Pure IX-OBs produced 99.22% VIII-OAc, 0.25 ± 0.10% IX-OAc, and 0.53% twisted monoene.

The acetolysis rate data are summarized in Table I.

TABLE I
FIRST-ORDER RATE CONSTANTS, ACETOLYSIS AT 25°

ROBs	$10^6 k$, sec^{-1}
VI-OBs[a]	39.1
VII-OBs[a]	57.0
VIII-OBs[a]	8.54
IX-OBs	2.30

[a] Reference 4.

Our previous attempts to prepare X-OBs had resulted in isolation of V-OBs, identified by melting point, elemental analysis, and first-order acetolysis rate constant.[6] In the present work the extremely reactive X-OBs was prepared by a low-temperature method. This brosylate produces 14.5% bird-cage hydrocarbon,[4] 0.06% twisted monoene, 25.3% V-OBs, 15.0% V-OAc, 14% VI-OBs, 19% VI-OAc, 5.4% VIII-OBs, 3% VIII-OAc, and 3.8% XII-OAc in acetic acid at 27° with a first-order rate constant of 0.104 sec^{-1}.

(1) An extension of the compound designations used previously[4] is employed herein for ease of cross reference between past, present, and future papers in this series.

(2) Taken in part from the Ph.D. thesis of Robert K. Howe, UCLA, March 1965.

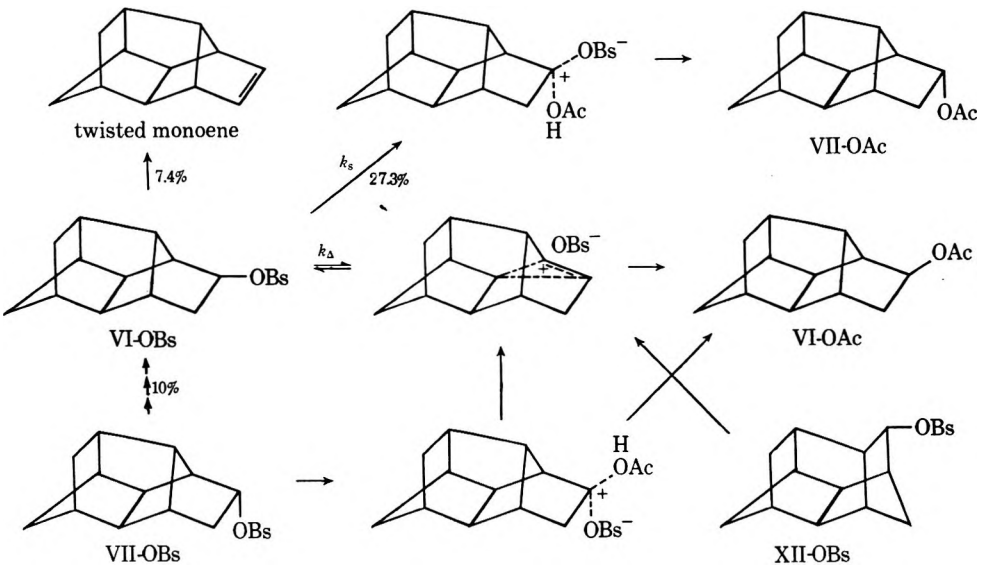
(3) Deceased Nov. 23, 1969.

(4) L. deVries and S. Winstein, *J. Amer. Chem. Soc.*, **82**, 5363 (1960).

(5) Other recent examples: (a) H. Tanida, H. Ishitobi, T. Irie, and T. Tsushima, *ibid.*, **91**, 4512 (1969); (b) H. Tanida, T. Irie, and T. Tsushima, *ibid.*, **92**, 3404 (1970); (c) R. Muneyuki and T. Yano, *ibid.*, **92**, 746 (1970); (d) G. W. Oxer and D. Wege, *Tetrahedron Lett.*, 457 (1971).

(6) P. Bruck, D. Thompson, and S. Winstein, *Chem. Ind. (London)*, 590 (1960).

SCHEME I



Discussion

Several years ago[7,8] we had discussed the competition between k_Δ (anchimerically assisted) and k_s (anchimerically unassisted) routes in ionization of *exo*-norbornyl brosylate. Anchimerically assisted ionization predominates with the exo brosylate, and the products arise very predominantly *via* the nonclassical ion.[7,8] In 75% aqueous acetone, the resultant alcohol is >99.98% exo.[8] We discussed[8,9] solvolysis of *endo*-norbornyl brosylate on the basis of anchimerically unassisted ionization (with, however, any nucleophilic solvent assistance that may be present[10]) to a classical carbonium ion species. A major fraction of the classical ions underwent leakage to the nonclassical ions, while the remaining fraction collapsed directly to inverted *exo* product (7% in acetic acid). If the stability of the norbornyl nonclassical ion could be lowered sufficiently so as to approach that of the classical ion, then solvolysis of the exo brosylate could produce detectable proportions of endo products. Such is the case in the work presented here.[5]

The acetolysis titrimetric rate ratio at 25° of VI-OBs and VII-OBs is 0.69:1. This rate ratio indicates either that the nonclassical and classical ions in this system are of comparable energy or that the nonclassical ion is not involved in VI-OBs acetolysis. The titrimetric rate constant, k_t, of VI-OBs acetolysis appears to be considerably smaller, however, than k_Δ, the rate constant for anchimerically assisted ionization, for there appears to be very pronounced ion pair return in VI-OBs acetolysis. XII-OBs has been found[2,11] to rearrange *ca.* 98% to VI-OBs through the same ion pair produced in VI-OBs acetolysis. The ratio of the rearrangement rate constant to the solvolysis rate constant of XII-OBs is greater than 64:1. This provides a rough measure for the partitioning of the carbonium ion from VI-OBs between ion pair return and collapse to product. The k_Δ for VI-OBs acetolysis thus may be 65 times greater than the titrimetric rate constant; this would indicate the exo/endo ionization rate ratio to be of the order of 45:1. The *ca.* 65% retention of configuration, in contrast to predominant inversion in classical solvolysis of secondary substrates,[12] and the exo/endo ionization rate ratio suggest that VI-OBs acetolysis involves a nonclassical ion. The rate constant for formation of VI-OAc *via* the anchimerically assisted pathway is the product of k_Δ and F, where $F = 1/65$, the fraction of nonclassical ion pairs that produces VI-OAc. Since $k_\Delta F$ is of the magnitude of the rate constant k_s (estimated from the VII-OBs rate) expected for anchimerically unassisted solvolysis, product formation occurs quite significantly from both the anchimerically assisted and anchimerically unassisted routes of solvolysis. The k_s route results in predominant inversion[12] and produces 27.3% endo acetate in VI-OBs acetolysis *via* the classical carbonium ion (Scheme I). Attack on the VI-OBs nonclassical cation to form XII-OAc is not observed. Evidently, the greater strain in the XII system[2,11] is manifested in the transition state leading to it and also, to a lesser degree, in the VI-OBs nonclassical ion. This strain results in less stabilization than usual for a norbornyl nonclassical ion.

Acetolysis of half-cage V-OBs results in ion pair return to VIII-OBs *via* the VIII-OBs nonclassical ion.[4] Thus, ion pair return in VIII-OBs acetolysis must make the titrimetic rate constant a low measure of k_Δ for VIII-OBs. The available data do not permit an estimate of the extent of ion pair return in this case. In VIII-OBs acetolysis, as in VI-OBs acetolysis, classical solvolysis with inversion[12] *via* the classical carbonium ion (Scheme II) is competitive with product formation from the nonclassical ion; 2.6% endo product is produced by the classical path. Only *ca.* 0.006% V-OAc is formed in VIII-OBs acetolysis. There is severe non-

(7) S. Winstein and D. Trifan, *J. Amer. Chem. Soc.*, **74**, 1154 (1952).

(8) S. Winstein, E. Clippinger, R. Howe, and E. Vogelfanger, *ibid.*, **87**, 376 (1965).

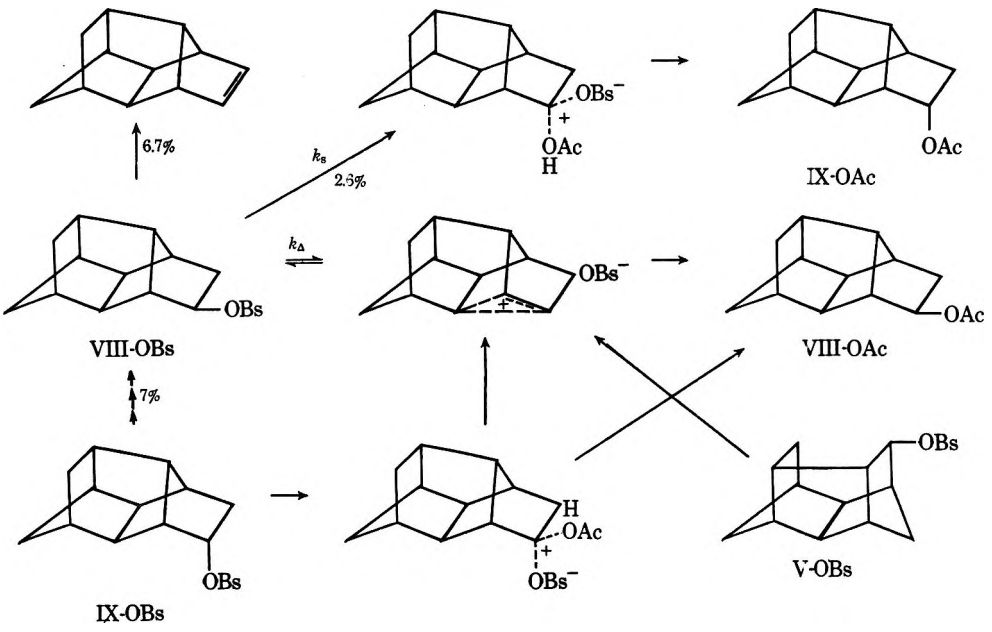
(9) S. Winstein and D. Trifan, *ibid.*, **74**, 1147 (1952).

(10) Our previously stated thought [S. Winstein, E. Grunwald, and H. W. Jones, *ibid.*, **73**, 2700 (1951)] that solvolysis of certain secondary aliphatic systems "may approach the *Lim.* category in acetic acid and more closely in formic acid" implies some residual nucleophilic solvent assistance to ionization in acetic acid. The extent of residual solvent assistance, of course, can vary considerably with the secondary substrate.

(11) Robert K. Howe and S. Winstein, to be published.

(12) (a) A. Streitwieser and T. D. Walsh, *Tetrahedron Lett.*, 27 (1963); (b) M. C. Whiting, *Chem. Brit.*, **2**, 482 (1966); (c) N. C. G. Campbell, D. M. Muir, R. R. Hill, J. H. Parish, R. M. Southam, and M. C. Whiting, *J. Chem. Soc. B*, 355 (1968).

SCHEME II

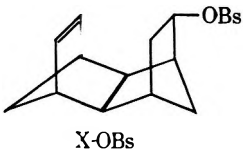


bonded repulsion between the opposed transannular hydrogen atoms of V-OAc.[13]

The large selectivity of attack by solvent on the VIII-OBs nonclassical cation is a result of some of this strain being present in the transition state leading to V-OAc.

Acetolysis of the extremely reactive X-OBs has revealed the nature of olefin formation from VI-OBs and VIII-OBs. X-OBs acetolyzed at 27° to a first infinity of 53.5% acid production with a first-order rate constant of 0.104 sec^{-1}. Analysis at this stage of acetolysis revealed the product mixture to contain 0.06% twisted monoene, 14% VI-OBs, 19% VI-OAc, 5.4% VIII-OBs, and 3% VIII-OAc, among other products. The 0.06% twisted monoene is a maximum value; some or all of this could have arisen from VI-OBs or VIII-OBs in the alumina chromatography used to isolate the hydrocarbon products. The carbonium ion that forms VI-OAc therefore produces at most 0.3% twisted monoene. Since VI-OBs acetolysis produces 7.4% twisted monoene, at least 96% of the elimination from VI-OBs appears to be concerted and not from the fully developed carbonium ion. Similarly, the elimination from VIII-OBs probably arises largely, if not completely, by concerted elimination from covalent brosylate. The concerted elimination most likely is cis.[14]

The ratio of twisted olefin to VII-OAc is the same (within experimental error) in acetolysis of VI-OBs and VII-OBs. This may be fortuitous; however, it is also consistent with formation of *ca.* 10% VI-OBs in VII-



X-OBs

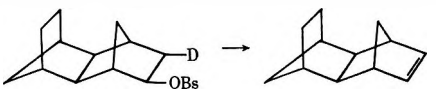
OBs acetolysis. This amount of VI-OBs would produce *ca.* 3% VII-OAc and *ca.* 0.7% twisted monoene, as is observed. This interpretation would indicate that there is very little direct elimination from VII-OBs.[14]

Information on the mechanism of formation of VI-OBs in VII-OBs acetolysis was sought by means of an acetolysis experiment with added brosylate anion. In the acetolysis of 0.010 *M* VII-OBs in the presence of 0.02 *M* sodium acetate, the average concentration of sodium brosylate, produced by neutralization of the liberated brosylic acid by the sodium acetate, is 0.005 *M*. The addition of 0.02 *M* tetrabutylammonium brosylate would result in an average brosylate salt concentration of 0.025 *M*, five times that without added brosylate salt. If VI-OBs were formed in VII-OBs acetolysis by brosylate anion attack on covalent VII-OBs or on a VII-OBs ion pair, five times the 3.1% VII-OAc would be expected. In fact, addition of 0.02 *M* tetrabutylammonium brosylate was shown to have no effect on the amount of VII-OAc produced in VII-OBs acetolysis.

Another pathway for formation of VI-OBs from VII-OBs exists. This involves rearrangement within intimate ion pairs as illustrated in Scheme I.[15] Similarly, formation of 7% VIII-OBs from IX-OBs *via* the illustrated path (Scheme II) would result in formation of 0.5% twisted monoene and 0.2% IX-OAc in IX-OBs

(13) D. Kivelson, S. Winstein, P. Bruck, and R. L. Hansen, *J. Amer. Chem. Soc.*, **83**, 2938 (1961).

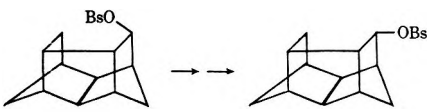
(14) In pyridine at 100°, IV-OBs[4] forms 75% endo-exo monoene, and IV-D-OBs forms 55% monoene with a k_H/k_D isotope effect of 2.85 for elimination (97.5% cis) and 1.10 for ionization; III-OBs,[4] the corresponding endo brosylate, forms less than 1% monoene directly. In acetic acid at 100°, IV-D-OBs produces 0.95% monoene with a k_H/k_D isotope effect of 2.8,



IV-OBs, X = H
IV-D-OBs, X = D

consistent with a concerted cis elimination in this solvent (P. Carter, unpublished results).

(15) Such endo-OBs to exo-OBs isomerization through intimate ion pairs has been observed directly by nmr and kinetic measurements in the partial isomerization of endo V-N-OBs in acetic acid to the much less reactive exo V-OBs. In this case, 24% of V-OBs is formed from V-N-OBs at 25° (R. Howe and P. Carter, unpublished results).



V-N-OBs V-OBs

acetolysis, as is observed. The small amount of endo brosylate to exo brosylate isomerization in these cases is not directly detectable because of the pertinent exo/endo rate ratios. The exact extent of leakage between the k_s and k_Δ routes in VII-OBs and IX-OBs acetolyses are not apparent; minimum values of 10% in VII-OBs acetolysis and 7% in IX-OBs acetolysis are indicated.

Tanida and coworkers[5a,b] have found endo acetate and olefin formation in acetolysis of both *exo*- and *endo*-6,7-dinitrobenzonorbornen-2-yl brosylates and have stated[5b] that "the minor formation of endo acetates (products of retention) and olefins (products of elimination) from [the nitro- and dinitrobenzonorbornen-*endo*-2-yl brosylates] should be considered as *via* cationic intermediates." We note upon examination of the data of Tanida, *et al.*,[5a,b] that the ratios of the percentages of olefin to endo acetate formed in acetolysis at 180° of 6,7-dinitrobenzonorbornen-*exo*-2-yl brosylate (ratio 21:35) and of the endo brosylate (ratio 2.2:3.0) are the same within experimental error. Thus, formation of *ca.* 9% of exo brosylate *via* ion pair return in acetolysis of the endo brosylate would account for the formation of *ca.* 2% of olefin by a concerted cis elimination and *ca.* 3% of endo acetate by classical solvolysis.

Experimental Section

Melting points are corrected. Standard acetolysis procedures were employed.[16]

Decahydro-2,4,7-metheno-1*H*-cyclopenta[*a*]pentalen-6-one (VI-Ketone).—A mixture of 1.0 g of VI-OH, mp 76–77° (lit.[4] mp 76.2–77.6°), in 50 ml of ether and 10 g of chromium trioxide in 50 ml of water was stirred vigorously for 4 hr. Then 50 ml of pentane was added, and the organic layer was washed with water until it was colorless. Distillation of the solution at 0.05 mm gave 0.7 g of oil that slowly solidified to a white solid, mp 32–34°.

Anal. Calcd for $C_{12}H_{14}O$: C, 82.71; H, 8.10. Found: C, 82.68; H, 8.13.

Similar oxidation of 100 mg of VII-OH, mp 71–72° (lit.[4] mp 71.5–72.6°), left from the original work,[4] gave 50 mg of solid ketone, mp 32–34°, mmp 32–34°. The ir spectra of both samples of ketone were identical.

Decahydro-2,4,7-metheno-1*H*-cyclopenta[*a*]pentalen-*exo*-6-yl *p*-Bromobenzenesulfonate (VI-OBs).—VI-OBs, mp 100–101° (lit.[4] mp 97–98°), was prepared from VI-OH, mp 76–77° (lit.[4] mp 76.2–77.6°), that was 100% pure (analysis by gc of alcohol and derived acetate).

Decahydro-2,4,7-metheno-1*H*-cyclopenta[*a*]pentalen-*endo*-6-yl *p*-Bromobenzenesulfonate (VII-OBs).—VII-OBs, mp 104–106° (lit.[4] mp 105–106°), was prepared from VII-OH, mp 72–73° (lit.[4] mp 71.5–72.6°), that was 100% pure (analysis by gc of alcohol and derived acetate).

Decahydro-2,4,7-metheno-1*H*-cyclopenta[*a*]pentalen-*exo*-5-yl *p*-Bromobenzenesulfonate (VIII-OBs).—VIII-OBs, mp 91–92° (lit.[4] mp 91–92°), was prepared from VIII-OH, mp 48–50° (lit.[4] mp 49.5–51.5°), that was 100% pure (gc analysis).

Decahydro-2,4,7-metheno-1*H*-cyclopenta[*a*]pentalen-5-one (VIII-Ketone).—Oxidation of 230 mg of VIII-OH from the original work[4] gave 200 mg of colorless liquid that contained less than 0.1% residual alcohol (gc analysis).

Anal. Calcd for $C_{12}H_{14}O$: C, 82.71; H, 8.10. Found: C, 82.66; H, 8.25.

Decahydro-2,4,7-metheno-1*H*-cyclopenta[*a*]pentalen-*endo*-5-ol (IX-OH).—Reduction of the ketone from VIII-OH with excess lithium aluminum hydride in ether gave a solid alcohol mixture that consisted of 8.8% VIII-OH and 91.2% IX-OH (gc analysis). Chromatography of 0.24 g of alcohol mixture on a 2 × 52 cm column of activity 2.5 alumina with 10% ether in hexane gave 0.16 g of pure IX-OH (gc analysis indicated <0.5% VIII-OH present) as an oil. Crystallization of the oil from pentane at −10° gave solid IX-OH, mp 66.0–67.5°.

Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.73; H, 8.95.

IX-OBs had mp 104–106°.

Anal. Calcd for $C_{18}H_{19}SO_3Br$: C, 54.68; H, 4.84. Found: C, 54.69; H, 4.82.

VI-OBs Acetolysis Products.—A 50-ml solution (0.0101 *M* VI-OBs) prepared from 0.2004 g of VI-OBs and acetic acid (0.0200 *M* sodium acetate) was held at 50° for 4.16 hr (20 half-lives). The solution was cooled, diluted with 50 ml of pentane, and extracted with 100 ml of water. The water layer was extracted with 30 ml of pentane. The pentane layers were combined, extracted with three 25-ml portions of saturated sodium bicarbonate solution and 50 ml of water, dried (Na_2SO_4), and concentrated to 2 ml with use of a $^3/_8$ × 14 in. column packed with glass helices. Gc analysis on a $^1/_4$ in. × 4 m column packed with 5% DOW X2405 on Chromosorb W, 80–100 mesh, at 155° and 30-psi helium pressure, indicated the product mixture to consist of 65.3 ± 1.5% VI-OAc (retention time 65 min), 27.3 ± 1.5% VII-OAc (retention time 59 min), and 7.4 ± 0.5% twisted monoene (retention time 5.6 min).

The product mixture was treated with excess lithium aluminum hydride in ether. The resultant products were examined on a $^1/_4$ in. × 2 m column of 10% UCON 50-HB 2000 on Chromosorb W, 60–80 mesh, at 180° and 30-psi helium pressure. There was <0.03% XII-OH and <0.03% V-OH (none detected). Under these analytical conditions, 0.03% XII-OH in VI-OH could be reproducibly detected.

VII-OBs Acetolysis Products.—A 25-ml solution (0.0102 *M* VII-OBs) was prepared from 0.1007 g of pure VII-OBs and acetic acid (0.0200 *M* sodium acetate) and was held at 50° for 3.82 hr (20 half-lives). The solution was worked up and analyzed as in the VI-OBs product study. There was 96.3% VI-OAc, 3.1 ± 0.3% VII-OAc, and 0.6 ± 0.2% twisted monoene. Gc analysis of the derived alcohol fraction revealed that <0.03% XII-OH and <0.03% V-OH were present (none detected).

A similar experiment in which 0.02 *M* tetrabutylammonium brosylate was incorporated gave an identical product mixture.

VIII-OBs Acetolysis Products.—A 25-ml solution (0.0100 *M* VIII-OBs) prepared from 98.6 mg of VIII-OBs and acetic acid that contained 0.0200 *M* sodium acetate was held at 50° for 14.46 hr (20 half-lives). After work-up, gc analysis on an NMPN column revealed the product mixture to consist of 93.3% acetates and 6.7% twisted monoene (2,3,3a,4,6a,7,7a-octahydro-2,4,7-metheno-1*H*-cyclopenta[*a*]pentalene), with <0.07% bird-cage hydrocarbon (decahydro-1,5,2,4-ethanediylidenecyclopenta-[*cd*]pentalene; none detected).

The product mixture was treated with 0.2 g of lithium aluminum hydride in 15 ml of ether. After the usual work-up, the alcohol fraction was analyzed by gc on a $^1/_8$ in. × 20 ft column packed with 2% UCON 50-HB 2000 on Chromosorb W, 80–100 mesh, at 150° and 50 psi of nitrogen, and was found to consist of 97.2% VIII-OH (retention time 49 min) and 2.8% IX-OH (retention time 52 min). There was <0.03% XII-OH (none detected); there was a peak with the same retention time as V-OH with 0.006% of the area of the VIII-OH peak.

IX-OBs Acetolysis Products.—A 5-ml solution (0.00988 *M* IX-OBs) prepared from IX-OBs and acetic acid (0.0200 *M* sodium acetate) was held at 50° for 50 hr (*ca.* 20 half-lives). After work-up, gc analysis on a $^1/_4$ in. × 2 m column packed with 25% NMPN revealed that the product mixture contained 99.47% acetates and 0.53% twisted monoene, with <0.05% bird-cage hydrocarbon (none detected).

The acetates were converted to alcohols with excess lithium aluminum hydride in ether. Gc analysis for IX-OH as in the VIII-OBs product study showed the alcohol fraction to consist of 99.75% VIII-OH and 0.25 ± 0.10% IX-OH.

1,2,3,4,4a,5,8,8a-Octahydro-*endo*,*endo*-1,4:5,8-dimethanonaphthalen-*exo*-2-ol (X-OH).—Hydroboration–oxidation[17] of purified isodrin in THF gave hexachloro-X-OH, mp 220–224° (lit.[18] mp 222° dec), in 74% yield. To a solution of 25 g (0.0653 mol) of the chlorinated alcohol and 158 g (2.13 mol) of *tert*-butyl alcohol in 400 ml of THF (distilled from $LiAlH_4$) under nitrogen in a 5-l. flask was added 30 g (4.3 g-atoms) of lithium wire cut

(16) (a) S. Winstein, C. Hansen, and E. Grunwald, *J. Amer. Chem. Soc.*, **70**, 812 (1948); (b) S. Winstein, E. Grunwald, and L. L. Ingraham, *ibid.*, **70**, 821 (1948).

(17) (a) H. C. Brown and G. Zweifel, *ibid.*, **83**, 2544 (1961); (b) H. C. Brown, *Tetrahedron*, **12**, 117 (1961).

(18) S. B. Soloway, A. M. Damiana, J. W. Sims, H. Bluestone, and R. E. Lidov, *J. Amer. Chem. Soc.*, **82**, 5377 (1960).

into 0.5-in. lengths so as to allow the freshly cut pieces to fall directly into the flask. The mixture was stirred vigorously. An exothermic reaction ensued with considerable foaming, and the solvent began to boil violently. Ice bath cooling was employed only as long as necessary to keep the reaction under control. The mixture was stirred until the spontaneous reflux subsided, then was heated at reflux for another 30 min, and then was poured while hot through a wire screen (to remove residual lithium). The solution was cooled, diluted with ice water, and extracted with ether. The organic solution was concentrated under aspirator vacuum and steam bath heat. Two crystallizations of the residue from hexane gave 5.0 g of pure (nmr analysis, quantitative hydrogenation assay) X-OH, mp 103.0–103.6° (lit.[19] mp 98–100°, lit.[20] mp 102.5–103.5°). **X-OAc**, mp 42.5–43.5°, was prepared by treatment of X-OH with acetic anhydride in pyridine at 5° for 3 days.

Anal. Calcd for $C_{11}H_{18}O_2$: C, 77.02; H, 8.33. Found: C, 77.15; H, 8.61.

X-OBs.—To a frozen solution of 1.00 g (5.68 mmol) of X-OH in 10 ml of pyridine was added 1.66 g (6.50 mmol) of powdered brosyl chloride, and the flask was tightly stoppered. The pyridine was allowed to melt, and solution of the brosyl chloride was effected with swirling; the temperature of the mixture was kept well below 0° with intermittent cooling in Dry Ice–acetone. After complete solution was attained, the reaction mixture was placed in a dewar flask filled with Dry Ice. The dewar flask was lightly stoppered. After 36 hr, the frozen reaction mixture was allowed to melt and was added to 750 ml of pentane. The mixture was swirled vigorously for 3 min and filtered. The filtrate was rapidly concentrated adiabatically under vacuum. The residual pyridine was removed under vacuum while the flask was maintained in an ice bath. The white solid brosylate was dissolved in 210 ml of methylcyclohexane at room temperature, the mixture was filtered, and the filtrate was cooled in Dry Ice–acetone for crystallization. The resultant solid was collected by filtration and was washed well with pentane. There was obtained 0.90 g of X-OBs that had no odor (neither brosylic acid nor brosyl chloride was present). The X-OBs was used immediately as it is extremely unstable (a small sample developed the odor of brosylic acid within 5 min at room temperature). This sample of X-OBs contained less than 1% X-OH, as evidenced by there being less than 1% X-OH in the alcohols derived from the acetolysis products.

X-OBs Acetolysis Rate.—X-OBs was prepared in the usual way; because of its extreme reactivity, the brosylate was not dried well after the pentane wash performed after collection by filtration. A 24.8-mg quantity of the brosylate was rapidly weighed out and was added to 5 ml of acetic acid that contained 6 drops of indicator solution and 1.000 ml of a titrant solution that consisted of 0.02000 *M* sodium acetate in acetic acid. The acetic acid was at room temperature, 27 ± 1°. Complete solution was attained in *ca.* 15 sec. The indicator changed color 12 sec after the addition of the brosylate. The solution was titrated at various time intervals, and was held at 75° for 75 min for the final infinity determination (see Table II).

A plot of log T_∞ − log (T_∞ − T) *vs.* time was made, and extrapolation of the straight line portion after 200 sec gave an intersection of 0.332 on the log axis at zero time; this value corresponds to a first infinity titer of 1.51 ml. This titer, 53.5% of the final infinity titer, was taken as the first infinity for calculation of the X-OBs total rate constant from zero time to 35 sec.

X-OBs Acetolysis Products after 100% Acid Production.—X-OBs was prepared by the low-temperature method from 0.50 g of X-OH and 0.83 g of brosyl chloride in 5 ml of pyridine. Immediately after isolation, the 0.40 g of X-OBs was added to 100 ml of acetic acid (that contained 0.020 *M* sodium acetate) at room temperature; the resultant solution was 0.0101 *M* in X-OBs. After 100 sec, the solution was placed in a 50° bath and held there for 15 hr (21 half-lives of VIII-OBs). The solution was cooled and worked up as usual. Gc analysis on an NMPN column showed the product mixture to consist of 24.1% bird-cage hydrocarbon, 1.7% twisted monoene, and 74.2% acetates.

(19) P. Bruck, D. Thompson, and S. Winstein, *Chem. Ind.* (*London*), 405 (1960).

(20) R. B. Woodward, T. Fukunaga, and R. C. Kelly, *J. Amer. Chem. Soc.*, **86**, 3162 (1964).

TABLE II

X-OBs RATE AT 27 ± 1°

Time, sec	Titer, ml	10^4k,[a] sec^{-1}
0	sample added	
12	1.000	
35	1.47	1040.0
55	1.51	
85	1.53	
205	1.57	2.62
395	1.61	2.06
840	1.77	2.74
1125	1.81	2.36
1380	1.86	2.27
1580	1.91	2.32
1920	1.97	2.25
∞	2.825[b]	

[a] See text for method of calculation of the first rate constant, k = 0.104 sec^{-1}. The subsequent rate constants are based on integration from 85 sec; average k = (2.37 ± 0.17) × 10^{-4} sec^{-1}. [b] 90.2% of theory.

A small portion of the product mixture was treated with excess lithium aluminum hydride in ether. Gc analysis on a UCON 50-HB 2000 column showed the alcohol fraction to consist of 62.4% VI-OH plus VII-OH plus VIII-OH, 5.48% XII-OH, and 32.1% V-OH. There was <1% X-OH and <0.2% of the endo epimer of X-OH.

The remainder of the acetolysis product mixture was analyzed by nmr in carbon tetrachloride solution. Integration over the α-proton region revealed the acetate portion to consist of 32.1% V-OAc, 41.6% VI-OAc, 5.8% VII-OAc, and 20.5% VIII-OAC plus XII-OAc.

From the combined gc and nmr data, the total acetolysis product composition from X-OBs is calculated to be 24.1% bird-cage hydrocarbon, 1.7% twisted monoene, 23.8% V-OAc, 30.9% VI-OAc, 4.3% VII-OAc, 11.1% VIII-OAc, and 4.1% XII-OAc.

X-OBs Acetolysis Products after 95% Reaction (Solvolysis Plus Rearrangement).—Immediately after it was prepared, 0.873 g of X-OBs was added to 100 ml of acetic acid (0.050 *M* sodium acetate) at 28°. The mixture was vigorously swirled, and the brosylate dissolved in *ca.* 15 sec. After an additional 15 sec the solution was poured into 500 ml of pentane. The pentane was rapidly extracted with 200 ml of water, three 150-ml portions of saturated sodium bicarbonate solution, and 200 ml of water. The pentane layer was dried (Na_2SO_4), and a small portion of it was passed through a short column of alumina to remove the brosylates and acetates. The column was washed with pentane, and the combined eluents were concentrated to 2 ml and analyzed by gc on an NMPN column. The hydrocarbon product consisted of 99.6% bird-cage hydrocarbon and 0.4% twisted monoene.

The remainder of the pentane solution containing all the acetolysis products was concentrated adiabatically under vacuum with a rotary evaporator. The residue was examined immediately in carbon tetrachloride solution by nmr. Integration over the aromatic proton region and over the α-proton region revealed that the substitution products (brosylates and acetates) consisted of 31.2% V-OBs, 18.4% V-OAc, 23.9% VI-OBs plus VIII-OBs, and 26.5% VI-OAc plus VIII-OAc plus XII-OAc. A series of simultaneous equations was set up from these data and from the product composition data for acetolysis of VI-OBs, VIII-OBs, X-OBs after 100% acid production, and V-OBs (38% bird-cage hydrocarbon, 1.3% twisted monoene, 34.8% V-OAc, 9.8% VI-OAc, 2.1% VII-OAc, 12.8% VIII-OAc, 1.2% XII-OAc; revised analyses by gc and nmr methods). Solution of the equations gave the direct products from X-OBs acetolysis: 14.5% bird-cage hydrocarbon, 0.06% twisted monoene, 25.3% V-OBs. 15.0% V-OAc, 14% VI-OBs, 19% VI-OAc, 5.4% VIII-OBs, 3% VIII-OAc, and 3.8% XII-OAc.

Registry No.—VI-ketone, 34220-07-0; VIII-ketone, 34220-08-1; IX-OH, 34226-03-4; IX-OBs, 34226-04-5; X-OAc, 34226-05-6; X-OBs, 34226-06-7.

1,2 Migrations in Alkyl Radicals[1]

S. N. LEWIS,*[2] J. J. MILLER, AND S. WINSTEIN[3]

Department of Chemistry, University of California at Los Angeles, Los Angeles, California 90024, and the Rohm and Haas Company, Spring House, Pennsylvania 19477

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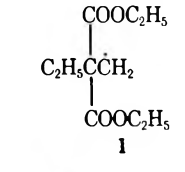
The behavior of three β-substituted alkyl radicals, geometrically and energetically capable of "bridging," has been examined in environments conducive to their rearrangement. Although the β-carbethoxyalkyl radical generated by the decarbonylation of β,β-dicarbethoxyvaleraldehyde produced only unrearranged products, compelling evidence is presented for the 1,2 migration of an acetoxy group during the free-radical initiated addition of butyraldehyde to α,α-dimethylallyl acetate. In contrast, β-thiophenoxyalkyl radicals, similarly generated during addition of both butyraldehyde and thiophenol to α,α-dimethylallyl phenyl sulfide, displayed an overwhelming preference for elimination of the thiophenoxy group.

Since the first reported instances[4,5] of phenyl migration in the "neophyl" radical, there have been numerous attempts to extend this apparent analogy of Wagner–Meerwein carbonium ion rearrangements.[6] Nonetheless, no *bona fide* examples of hydrogen or alkyl migration have surfaced, hardly surprising in view of the vastly different energetic requirements imposed by the odd electron on a transition state or intermediate involved in the actual shift of a migrating group. Indeed it has been suggested that 1,2-alkyl or hydrogen migration in ground-state free radicals is forbidden by orbital symmetry restrictions.[7]

The aromatic nucleus clearly is satisfying some requirement for migration, presumably formation of a bridged species, that hydrogen or alkyl groups cannot. Significantly, the only credible reports of 1,2 migration of substituents other than aryl involve those groups (Cl,[6] Br,[6] SR,[6b] $OCOCH_3$[8,9]) which are also capable of accommodating, both geometrically and orbitally, the odd electron of the adjacent radical center in some kind of bridged intermediate or transition state.

In this paper we wish to report the behavior of three β-substituted alkyl radicals which, by virtue of either valence shell expansion[10] (**5**) or π electron delocalization (**4** and **6**), are theoretically capable of rearrangement *via* bridged species. The β-carbethoxyalkyl radical (**1**) was generated by the decarbonylation of the homologous aldehyde, an elegant method pioneered by Winstein and Seubold[5] for the generation of the "neophyl" radical from β-phenylisovaleraldehyde, and especially effective when the migrating group is resistant to competitive loss by reverse Michael reaction. Alternatively, addition of free radicals (R·) to allylically substituted terminal olefins, a procedure successfully exploited by Weinstock and Lewis[11] for the study of β-phenylbutyl radicals, was selected for the generation of the β-thiophenoxyalkyl (**2**) and β-acetoxyalkyl (**3**) radicals so as to avoid the reported[8,12] nonradical elimination of the corresponding aldehydes. In order to afford the greatest opportunity for observing rearranged products, the concentration and reactivity of the chain-transfer agent RH was manipulated in accord with the ground rules[13] established by comprehensive investigation of phenyl migration in alkyl radicals.[6a]



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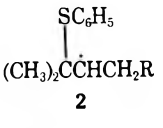

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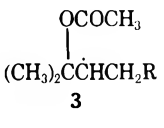

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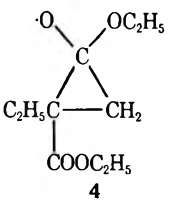

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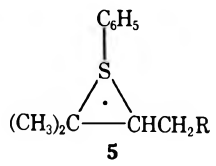

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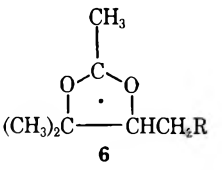
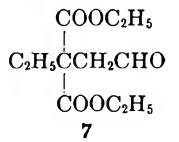


6

Results and Discussion

β-Carbethoxyalkyl Radical.—β,β-Dicarbethoxyvaleraldehyde (**7**) smoothly decarbonylated at 130° in the presence of di-*tert*-butyl peroxide (DTBP) to give a >97% theoretical yield of carbon monoxide and a 92% yield of a single product which was characterized as the unrearranged diester **8** by hydrolysis to the known methylethylmalonic acid and its subsequent decarboxylation. Similar decarbonylation of a 1 *M* so-



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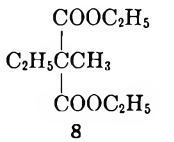

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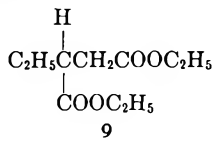


9

lution of the aldehyde in diphenyl ether gave >95% carbon monoxide evolution and a 92% yield of the unrearranged diester. Again, no rearranged diester **9** was detected, suggesting that, even in the presence of a sub-

(1) Abstracted in part from the Ph.D. thesis of Sheldon N. Lewis, submitted to the University of California at Los Angeles in Aug 1959.

(2) Eastman Kodak Company Fellow, 1958–1959; Rohm and Haas Co.

(3) Deceased, Nov 23, 1969.

(4) W. H. Urry and M. S. Kharasch, *J. Amer. Chem. Soc.*, **66**, 1438 (1944).

(5) S. Winstein and F. H. Seubold, *ibid.*, **69**, 2916 (1947).

(6) For a comprehensive review of free-radical rearrangements, see (a) C. Walling in "Molecular Rearrangements," P. de Mayo, Ed., Part I, Wiley-Interscience, New York, N. Y., 1963, pp 407–450; (b) R. Kh. Freidlina in "Advances in Free Radical Chemistry," G. H. Williams, Ed., Vol. I, Logos Press, London, 1965, pp 211–278.

(7) M. J. Perkins in "Organic Reaction Mechanisms," B. Capon and C. W. Reese, Ed., Wiley-Interscience, London, 1969, p 293.

(8) D. D. Tanner and F. C. P. Law, *J. Amer. Chem. Soc.* **91**, 7535 (1969).

(9) J. M. Surzur and P. Teissier, *C. R. Acad. Sci.*, **264**, 1981 (1967).

(10) H. H. Jaffe, *J. Phys. Chem.*, **58**, 185 (1954), has reported evidence of sulfur valence shell expansion in radical reactions.

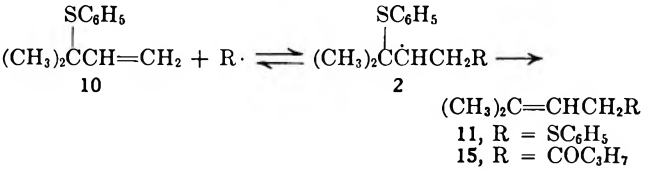
(11) J. Weinstock and S. N. Lewis, *J. Amer. Chem. Soc.*, **79**, 6243 (1957).

(12) S. J. Lapporte, Ph.D. Thesis, UCLA, 1956.

(13) These studies show that, irrespective of bridged intermediacy, product formation results from the reaction of the *classical* unrearranged and rearranged radicals with the chain-transfer agent RH. Thus the lifetime of the unrearranged radical is dictated by the reactivity and concentration of RH and its opportunity for migration is determined not only by the rate (k_1) at which the bridged species is formed but also by the rate (k_2[RH]) at which the unrearranged radical competitively collapses to unrearranged product. Even when migration is feasible, formation of rearranged product *via* the rearranged radical may be precluded if the ratio of k_2[RH]/k_1 is sufficiently large. While increased stability of the rearranged radical need not provide the "driving force" for migration, it does provide the incentive for the bridged species to open to the rearranged rather than the unrearranged radical.

stantially reduced concentration of aldehyde, the unrearranged radical had either insufficient inclination or time to assume the bridged conformation preparatory to migration.

β-Thiophenoxyalkyl Radical.—Pure samples of α,α- (**10**) and γ,γ- (**11**) dimethylallyl phenyl sulfides, prepared by the acid-catalyzed addition of thiophenol to isoprene, were characterized by oxidative ozonolysis to α-phenylsulfonylisobutyric acid and phenylsulfonylacetic acid, respectively. The *tert*-butyl hydroperoxide (TBHP)[14] initiated reaction of the terminally unsaturated isomer **10** with *n*-butyraldehyde, despite no evidence of butyraldehyde decarbonylation, gave only a trace of a ketonic product which boiled in a range considerably lower than that expected for a keto sulfide adduct. Only its primary allylic isomer **11** was pro-



duced and recovered in high yield with *ca.* 50% of unreacted **10**. Although it was thermally stable, partial isomerization of **10** could be accomplished just by heating at 75° in the presence of a trace of TBHP. Isomerization, dramatically increased by a trace thiophenol, was complete in 30 min at 75° and, in excess thiophenol, afforded considerable primary isomer even at room temperature in the absence of TBHP. Its free-radical character was supported by acceleration with TBHP, suppression with 1,3,5-trinitrobenzene, and an insensitivity to pyridine.

Significantly, no adduct formation accompanied isomerization even in excess thiophenol at 75°, despite the fact that these adducts, obtained independently[16] (Scheme I), were completely stable under the reaction conditions. Clearly, if free-radical addition proceeded through the expected radical intermediate (**2**), loss of the tertiary thiophenoxy group must have occurred at a rate substantially faster than chain transfer, even in the presence of the highly reactive thiophenol (see ref 26). This behavior is quite consistent with the established reversibility of thiol additions to olefins[17] and also is in accord with the isomerization of α-methylallyl methyl sulfide reported by Huyser and Kellogg.[18] The intermediate **2** (R = SC_6H_5) reversibly formed by the addition of a thiophenoxy radical now, unaware of its ancestry, has a choice of β-thiophenoxy groups to expel. Although simple bond dissociation energy considerations suggest a preference for loss at the tertiary alkyl position, the primary sulfide **11** would accumulate in

(14) An attractive low-temperature initiator (*ca.* 80°) mainly because of its ease of removal by distillation and the innocuous nature of its decomposition products. Its role is obscure, however, since its first-order rate of homolysis at 80° is insufficiently fast to provide radical fragments at these temperatures.[15] It usually does function nonetheless, undoubtedly as a consequence of second-order-induced decomposition (*e.g.*, with RSH) or first-order homolysis of subsequent reaction products [*e.g.*, RCH(OH)OO-*tert*-C_4H_9 from reaction with aldehydes].

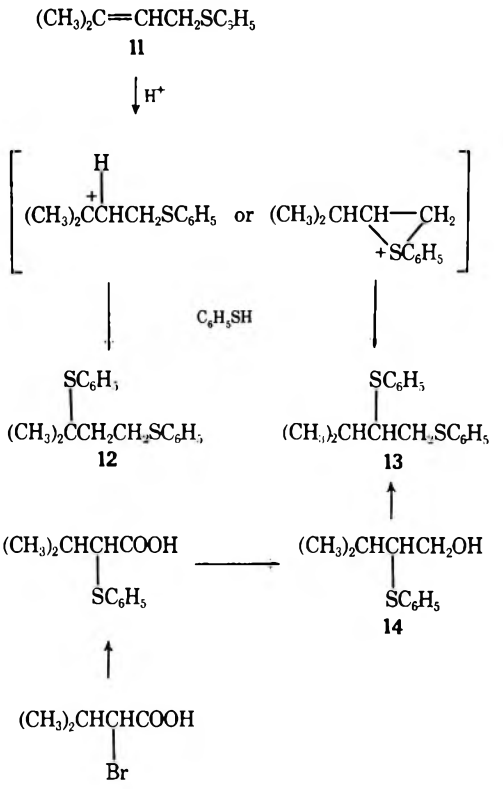
(15) C. Walling, "Free Radicals in Solution," Wiley, New York, N. Y., 1957, pp 403, 404.

(16) The validity of Scheme I as an unambiguous synthesis of **12** *via* orthodox protonation of **11** suffers from the possibility of anomalous protonation induced by thiophenoxy participation to give **13** instead. The unequivocal preparation of **13**, however, established its dissimilarity to **12**.

(17) C. Walling and W. Helmreich, *J. Amer. Chem. Soc.*, **81**, 1144 (1959).

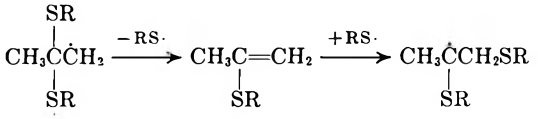
(18) E. S. Huyser and R. M. Kellogg, *ibid.*, **87**, 2867 (1965).

SCHEME I

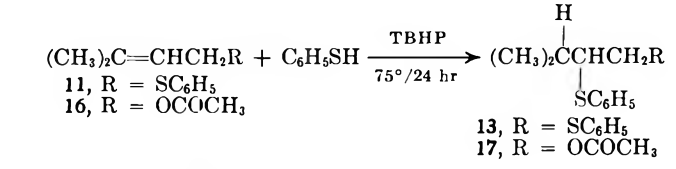


any case since its formation is essentially irreversible under these conditions. Its isolation as the major product, even from the attempted addition of butyraldehyde in the absence of thiophenol, simply attests to the greater efficiency of the thiophenoxy radical in continuing the chain process. After the first few additions of a butyryl radical, the expelled thiophenoxy radical preferentially adds to the olefinic unsaturation of **10** rather than chain transfer with butyraldehyde, and only a small quantity of the unsaturated ketone **15** (R = COC_3H_7) is produced.

The overwhelming preference of the intermediate radical (**2**) for elimination over admittedly rapid chain transfer certainly compromises its opportunity for rearrangement, casting serious doubt on the validity of reports of 1,2-thiophenoxy migration during the reaction of acetone mercaptols with peroxides.[6b] The products observed are probably more appropriately explained by an elimination–addition sequence.



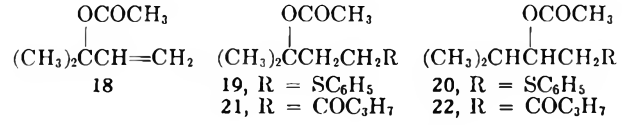
Conceivably, subsequent reaction of thiophenol and **11** to give the expected adduct **13** could have created the misleading impression of thiophenoxy migration



during isomerization of **10**; none of this adduct was detectable under these conditions, however. In fact, the reaction of **11** with thiophenol was very slow, providing, after 24 hr at 75°, a high recovery of reactants and only

a few per cent of a material which, although analyzing correctly for a 1:1 adduct, appeared to be a mixture of isomers. In sharp contrast, the addition of thiophenol to γ,γ-dimethylallyl acetate (**16**) under similar conditions gave >40% of an adduct identical in all respects with **17** prepared independently by the acetylation of **14**.[19]

β-Acetoxyalkyl Radical.—The TBHP-initiated reaction of α,α-dimethylallyl acetate (**18**) with thiophenol produced essentially equivalent quantities of acetic



18 **19**, R = SC_6H_5; **21**, R = COC_3H_7 **20**, R = SC_6H_5; **22**, R = COC_3H_7

acid and γ,γ-dimethylallyl phenyl sulfide (**11**) as well as a single adduct by vpc which was completely stable under the reaction conditions and identical in all respects with an authentic sample of the unrearranged adduct (**19**) prepared independently by acetylation of the tertiary alcohol obtained from the reaction of methyl β-thiophenoxy propionate with methylmagnesium iodide. The negative trend in adduct formation with increasing dilution of the reactants (Table I)

TABLE I

EFFECT OF CHLOROBENZENE DILUTION ON THE REACTION PRODUCTS OF α,α-DIMETHYLALLYL ACETATE, THIOPHENOL, AND TBHP[a]

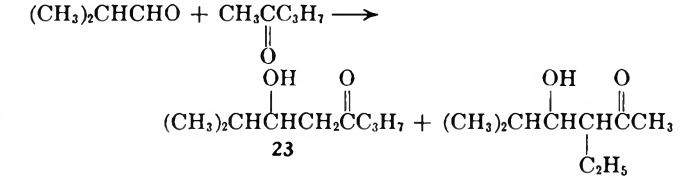
C_6H_5Cl	**11**/CH_3COOH[b]	**19**[c]
0.00	0.53	0.45
1.00	0.58	0.40
2.00	0.68	0.30
4.50	0.74	0.23
7.50	0.79	0.16
10.00	0.80	0.13

[a] Values refer to moles of chlorobenzene and product/mole of acetate employed, after 24 hr at 75°. [b] Titrimetric estimates of acetic acid; distilled recovery of **11** generally >90% of acetic acid titer. [c] Estimated by saponification.

is suggestive of a competitive acetoxy radical elimination from **3** (R = SC_6H_5) in a manner analogous to thiophenoxy loss from **2** (R = SC_6H_5). The stoichiometric isolation of acetic acid, however, is inconsistent with the well-documented rapid decomposition of acetate radicals (CO_2 + $\cdot CH_3$), which is extensive even in the presence of highly efficient radical scavengers.[20] Furthermore, simple thermodynamic calculations[21] lend little encouragement to acetoxy radical loss, indicating that it should occur at a rate 10^{11} slower than thiophenoxy radical loss.

Although the free-radical nature of product formation was implied by the stability of the reactants in the absence of TBHP, the presence of 0.25 mol % pyridine appeared to enhance adduct yield while completely suppressing the production of acetic acid and primary allylic sulfide, thus suggesting strong acid involvement in their formation. Indeed, quantities of thiophenol, TBHP, and chlorobenzene representative of those employed in a typical reaction of **18**, after 24 hr at 75° in sealed ampules, revealed, on aqueous extraction, the presence of 0.25–0.35 mol % of a strong acid by potentiometric titration.[25] When solutions of **18** in thiophenol (no TBHP), either neat or diluted with chlorobenzene were, in turn, spiked with comparable amounts of *p*-toluenesulfonic acid, essentially quantitative conversion to acetic acid and γ,γ-dimethylallyl phenyl sulfide (**11**) was observed after 24 hr at 75°, leaving little doubt that these products derive from the strong acid-catalyzed solvolysis of the allylic acetate in competition with normal radical addition. Accordingly, when the TBHP initiator was replaced by AIBN, only the normal unrearranged adduct **19** was produced, and no acetic acid and primary allylic sulfide were detected by vpc. Chlorobenzene dilution served only to reduce the conversion and consequently the yield of the unrearranged adduct consistent with the trend observed in Table I. Significantly, no rearranged product (**20**) was noted even at the lowest thiophenol concentration examined (1.3 *M*).

Replacement of the thiophenol with butyraldehyde, a much less reactive chain transfer agent,[26] also elicited no migration of the intermediate radical **3** (R = COC_3H_7). The TBHP- or AIBN-initiated reaction of α,α-dimethylallyl acetate (**18**) with pure *n*-butyraldehyde (two and tenfold excesses) gave only a single adduct (vpc) which was characterized as the unrearranged keto acetate **21** by virtue of its elemental analysis, infrared spectrum, and especially its nmr spectrum, which displayed a high-field methyl triplet for the terminal methyl centered at 0.95 ppm, a strong singlet for the *gem*-dimethyl system at 1.5 ppm, and the acetyl methyl at 2.0 ppm. Careful vapor phase chromatography of the reaction mixture indicated the absence of the product of 1,2-acetoxy migration (**22**), obtained independently by acetylation of the major product (**23**)



of the condensation of isobutyraldehyde and 2-pentanone and characterized by elemental analysis and infrared, mass, and nmr spectra; especially definitive in the nmr was the multiplet at 5.2 ppm due to the single methinyl hydrogen on the carbon adjacent to the

(19) The relatively slow rate of normal addition of thiophenol to **11** suggests that the adduct isolated is at least in part 1,4-dithiophenoxy-3-methylbutane, formed *via* an allylic isomerization [$(CH_3)_2C{=}CHCH_2SC_6H_5 \rightarrow CH_2{=}C(CH_3)CH_2CH_2SC_6H_5$] prior to thiophenol addition in accord with the reported isolation of 1,4-dithiophenoxybutane from the radical-initiated addition of thiophenol to *trans*-crotyl phenyl sulfide (S. J. Cristol, private communication).

(20) J. C. Martin, J. W. Taylor, and E. H. Drew, *J. Amer. Chem. Soc.*, **89**, 129 (1967).

(21) $k_{SC_6H_5}/k_{OCOCH_3} = \exp(E_{OCOCH_3} - E_{SC_6H_5})/RT \cong \exp[D(CH_3\text{–}OCOCH_3) - D(CH_3\text{–}SC_6H_5)]/RT \cong \exp(77.7 - 60.0)/0.69 \cong 1.4 \times 10^{11}$. $D(CH_3\text{–}SC_6H_5)$ has been estimated at 60.0 kcal by M. H. Back and A. H. Sehon, *Can. J. Chem.*, **38**, 1076 (1960), and $D(CH_3\text{–}OCOCH_3)$ was calculated as 77.7 kcal from published thermodynamic data: $\Delta Hf°_{\cdot OCOCH_3}$ (−49.0 kcal),[22] $-\Delta Hf°_{\cdot CH_3}$ (+32.1 kcal),[23] $-\Delta Hf°_{CH_3OCOCH_3}$ (+80.6).[24]

(22) L. Jaffe, E. J. Prosen, and M. Swarc, *J. Chem. Phys.*, **27**, 416 (1957).

(23) J. S. Roberts and H. A. Skinner, *Trans. Faraday Soc.*, **45**, 339 (1949).

(24) Obtained from heats of combustion of reported in International Critical Tables of the National Research Council, Vol. V, McGraw-Hill, New York, N. Y., 1926, p 167.

(25) Most likely benzenesulfinic or benzenesulfonic acid, resulting from the oxidation of thiophenol by TBHP—an unwanted bonus of this unorthodox initiator in this instance (see ref 14).

(26) 100% phenyl migration was observed (ref 11) during the addition of *n*-butyraldehyde to 3,3-diphenyl-1-butene. In contrast, migration was completely suppressed by generation of the β,β-diphenylbutyl radical in the presence of thiols.

acetoxy group. Thus the rearranged keto acetate (22) was readily separable from its unrearranged isomer (21) by vpc and easily distinguishable in mixtures by nmr.

When the butyraldehyde concentration was reduced, 1,2-acetoxy migration was observed. In an AIBN-initiated reaction of α,α-dimethylallyl acetate (18) with butyraldehyde diluted tenfold (on moles of acetate) with chlorobenzene, rearranged adduct (22) (1:5, rearranged/unrearranged) was clearly visible both in the vpc and nmr spectrum of the reaction mixture. Its identity was confirmed by the elemental analysis, nmr, and mass spectra of a pure sample isolated by preparative vpc. Further increasing the chlorobenzene dilution by another factor of five (50-fold) resulted in a depressed yield of products but again clearly indicated the presence of a substantially increased proportion of the rearranged adduct (1:1.6). Both the unrearranged and rearranged keto acetates were stable under the reaction conditions.

The effect of butyraldehyde concentration on the extent of migration is summarized in Table II. It is

Table II

Effect of Butyraldehyde Concentration on 1,2-Acetoxy Migration during the Addition of Butyraldehyde to α,α-Dimethylallyl Acetate

$[C_3H_7CHO]$, M	Rearranged (22)/ Unrearranged (21)
9.5[a]	0.00
6.2[b]	0.00
1.5[c]	0.20
0.4[c]	0.63

[a] Neat aldehyde/acetate (10:1); TBHP initiation. [b] Neat aldehyde/acetate (2:1); AIBN initiation. [c] Aldehyde/acetate (2:1) diluted with chlorobenzene; AIBN initiation.

especially interesting to note that a ratio of rearranged/unrearranged product similar to that observed by Tanner and Law[8] during the decarbonylation of β-acetoxyisovaleraldehyde was obtained at *ca.* twice the aldehyde concentration. This reduced influence of the chain transfer agent is likely a reflection of a greater rate constant for the chain transfer of the more reactive primary radical generated by decarbonylation and further attests to the role of the ratio $(k_2[RH]/k_1)$ in determining the extent of migration of classical unrearranged radicals (see ref 13).

There appears to be little question that acetoxy migration during the addition of butyraldehyde to α,α-dimethylallyl acetate must proceed by way of the bridged species 6. Alternative explanations involving an elimination–addition sequence,[6a] even when refined by invoking cage recombination[8] of the dissociated fragments 24 to circumvent the rapid decomposition of

$$(CH_3)_2C{=}CHCH_2R$$
$$\cdot OCOCH_3$$
24

the acetoxy radical, are not consistent with the absence of rearranged or unsaturated products from the addition of thiophenol to the allylic acetate. Certainly the nature of R in 3 would not be expected to significantly influence the essentially irreversible formation of 11, and cage recombination, by definition, should be relatively insensitive to the media (thiophenol $\sim$ butyraldehyde). Once generated, 24 must then collapse to either rearranged or unsaturated products.

The success of π delocalization in serving as a vehicle for acetoxy and not carbethoxy migration may be a reflection of the geometry of their respective bridged structures [five-membered ring (6) favored over three-membered ring (4)]. More likely, however, it is a manifestation of a greater preference for bond formation at the electron-rich oxygen of the acetoxy carbonyl group to give the relatively stable carbon radical 6 rather than the high-energy oxygen radical required by bond formation at the carbon of the carbethoxy carbonyl group (4); of course, bond formation at the carbonyl oxygen in the latter case is geometrically unfavorable.

Experimental Section

Melting and boiling points are uncorrected. Infrared spectra were determined on Perkin-Elmer Model 21 and 257 grating spectrometers, mass spectra on a Hitachi RMU-6 double-focusing instrument, and nmr spectra on a Varian T-60 spectrometer using tetramethylsilane as an internal standard.

Diethyl Acetal of β,β-Dicarbethoxy-*n*-valeraldehyde.—To a stirred, refluxing solution of 10.85 g (0.473 g-atom) of sodium in 300 ml of dry ethanol, 89.0 g (0.473 mol) of diethyl ethyl malonate was added, followed by 90 min of reflux. Diethyl bromoacetal, 75.0 ml (0.043 mol), prepared according to the method of McElvain,[27] was added over 12 hr; another 10 ml of the bromoacetal was added after 12 hr and reflux was maintained for a total of 142 hr. Conventional work-up and distillation through a 21-in. Helix-packed column afforded 51.2 g (36%) of the acetal as a colorless liquid, bp 109.0–109.5° (0.5 mm), $n^{25}D$ 1.4304.

Anal. Calcd for $C_{15}H_{28}O_6$: C, 59.19; H, 9.27. Found: C, 59.37; H, 9.18.

β,β-Dicarbethoxy-*n*-valeraldehyde (7).—A vigorously stirred suspension of 13.5 g of the acetal and 40 ml of 50% aqueous citric acid was heated under a 6-in. Vigreux column equipped with a variable take-off head for a total contact time of 50 min; 5.2 ml of ethanol was removed at a head temperature of 77–80°. The colorless residue was diluted with water, extracted with ether, and worked up conventionally. Concentration and distillation in a nitrogen atmosphere through a 6-in. Vigreux column gave 5.30 g of the aldehyde as a colorless liquid, bp 98.0–99.0° (1.5 mm), $n^{25}D$ 1.4350, semicarbazone mp (water) 124.0–124.5°.

Anal. Calcd for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88. Found: C, 57.16; H, 7.60.

Decarbonylation of β,β-Dicarbethoxy-*n*-valeraldehyde.—The decarbonylation apparatus consisted of a 250-ml flask equipped with a variable reflux distillation head vented *via* an air-cooled safety trap to a water-filled inverted 1-l. calibrated burette; a receiver was fitted onto the stillhead to collect low-boiling material.

Immediately upon distilling the aldehyde into the 250-ml decarbonylation flask, optionally diluted with diphenyl ether, the system was flushed with nitrogen, stirred magnetically, and allowed to equilibrate (10 min) in an oil bath thermostated at 130 ± 1°. Di-*tert*-butyl peroxide, 0.32 g (10 mol %), was quickly injected into the flask and gas evolution began almost immediately. From 5.01 g (0.0218 mol) of the aldehyde a corrected volume of 473 ml (97% of theory) of carbon monoxide was collected over a 6-hr period. Conventional work-up and distillation of the residue through a 6-in. Vigreux apparatus provided the following fractions: (1) 3.85 g, bp 77.0–79.0° (5.0 mm), $n^{25}D$ 1.4167; and (2) 0.20 g, bp 70–90° (5.0–2.5 mm), $n^{25}D$ 1.4150; and 0.28 g of a residue, $n^{25}D$ 1.4470, shown by ir to be starting aldehyde. Fractions 1 and 2 had identical ir spectra and exhibited only a single peak on vapor phase chromatography indicating a 92% recovery of pure unrearranged product 8. Fraction 1 was submitted for analysis and quantitatively hydrolyzed in aqueous NaOH to a white crystalline solid, mp 124.5–125.2° (chloroform–Skelly B) (lit.[28] for methyl ethyl malonic acid, mp 121–122°).

Anal. Calcd for $C_{10}H_{18}O_4$: C, 59.38; H, 8.97. Found: C, 59.67; H, 8.90.

(27) S. M. McElvain and D. Kunigar, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1943, p 123.

(28) I. Vogel, *J. Chem. Soc.*, 1438 (1929).

Decomposition of 0.37 g of this diacid in a microstill at 170–180° (25 mm) gave 0.129 g of a colorless distillate, n^{25}D 1.4068, neut equiv 102 (lit.[29a] for α-methylbutyric acid, n^{20}D 1.4051, neut equiv 102), *p*-phenylphenacyl ester mp 69–70° (ethanol–water) (lit.[29b] mp 71°).

Decarbonylation of 5.10 g (0.22 mol) of the aldehyde in 17.8 ml (0.11 mol) of diphenyl ether, similarly conducted, evolved a corrected volume of 471 ml (95% of theory) of carbon monoxide over a 9-hr period. Distillation followed by infrared and vpc analysis again confirmed the presence of only the unrearranged ester in 92% yield.

α,α- (10) and γ,γ- (11) Dimethylallyl Phenyl Sulfides.—To a solution of 62.4 ml (0.60 mol) of thiophenol, 100 ml (1.0 mol) of isoprene, and 10 ml of dry ether cooled in an ice bath, 20 ml (0.37 mol) of concentrated sulfuric acid was added dropwise with vigorous stirring over a 15-min period. After stirring for another 15 min, 43 g (0.4 mol) of powdered anhydrous sodium carbonate was added followed by 300 ml of ice water. The organic layer was then combined with two ether extracts of the aqueous phase and washed repeatedly with 10% aqueous sodium carbonate and finally with water before drying over magnesium sulfate. Concentration and distillation of the light yellow liquid residue through a 2-ft Podbielniak column afforded 5.5 g of α,α-dimethylallyl phenyl sulfide as a colorless liquid: bp 51.0° (0.5 mm); n^{25}D 1.5447; ir (pertinent absorptions) 1630, 1583 (w), 1412, 908 cm^{-1}.

Anal. Calcd for $C_{11}H_{14}S$: C, 74.13; H, 7.92. Found: C, 74.33; H, 7.87.

Continued distillation provided the isomeric γ,γ-dimethylallyl phenyl sulfide as a colorless liquid: bp 69.0–70.0° (0.5 mm); n^{25}D 1.5635; ir (pertinent absorptions) 1664, 1583 (s), 837 cm^{-1} [lit.[30] for γ,γ-dimethylallyl phenyl sulfide, bp 124–126° (14 mm), n^{25}D 1.5644].

The structure of the low-boiling isomer was confirmed by exposure of 1.0 g to a stream of 3% ozone in 15 ml of acetic anhydride–glacial acetic acid (1:1 v/v) at 0–5°, followed by oxidation with 5 ml of 30% hydrogen peroxide at room temperature. Conventional work-up gave 1.0 g of white needles, neut equiv 224, mp 142–143° (benzene), which was undepressed on admixture with an authentic sample of α-phenylsulfonylisobutyric acid. Similar treatment of the high-boiling isomer (1.0 g) gave 0.33 g of white flakes, mp 110–111° (benzene) (lit.[31] for phenylsulfonylacetic acid, mp 111.5–112.5°), and acetone, isolated as its 2,4-DNPH, mp 124–125° (lit.[29b] mp 126°).

α-Phenylsulfonylisobutyric Acid.—A solution in 50 ml of water of 8.60 g (0.13 mol) of potassium hydroxide, 6.2 ml (0.060 mol) of thiophenol, and 10.0 g (0.060 mol) of α-bromoisobutyric acid, mp 40–42°, prepared according to the procedure of Marvel,[32] was stirred for 1 hr at 0°, heated on the steam bath for 4 hr, and allowed to stand overnight. Conventional work-up and distillation of the liquid residue in a 6-in. Vigreux apparatus afforded 3.30 g of a pale yellow oil, bp 125.0–126.0° (0.8 mm), which solidified completely on standing, mp 68–69° (benzene). Exposure of this solid to a glacial acetic acid solution of 30% hydrogen peroxide for 16 hr gave, after decomposition of excess peroxide with manganese dioxide and acidification with concentrated HCl, white needles, mp 142–143° (benzene).

Anal. Calcd for $C_{10}H_{12}O_4S$: C, 52.63; H, 5.30; neut equiv, 228. Found: C, 52.87; H, 5.00; neut equiv, 228.

1,3-Dithiophenoxy-3-methylbutane (12).—To a vigorously stirred solution of 14.6 g (0.082 mol) of γ,γ-dimethylallyl phenyl sulfide and 10.7 g (0.090 mol) of thiophenol in 50 ml of glacial acetic acid cooled in an ice bath, 4.5 ml of concentrated sulfuric acid was slowly added. The ice bath was removed after 10 min and stirring was continued for 27 hr at room temperature. The resulting two-phase solution was poured over crushed ice, diluted with water, and extracted with carbon tetrachloride. Conventional work-up followed by distillation through a 6-in. Vigreux column afforded a 42% recovery of the primary allylic sulfide and 8.8 g of its thiphenol adduct as a very pale yellow liquid, bp 159.0–160.0° (0.7 mm), n^{25}D 1.6041.

Anal. Calcd for $C_{17}H_{20}S_2$: C, 70.81; H, 6.99. Found: C, 70.85; H, 6.96.

A solution of 0.50 g of this material in 15 ml of glacial acetic acid and 5 ml of 30% hydrogen peroxide gave, after 2 hr on a steam bath, the disulfone as long white needles, mp 118.4–119.4° (EtOH–H_2O).

Anal. Calcd for $C_{17}H_{20}S_2O_4$: C, 57.95; H, 5.72. Found: C, 57.72; H, 5.72.

2-Thiophenoxy-3-methylbutanol (14).—The crude α-thiophenoxyisovaleric acid (20.1 g), obtained from the reaction[32] in water of thiophenol (12.2 g, 0.11 mol), sodium hydroxide (10.0 g, 0.25 mol), and isovaleric acid (20 g, 0.11 mol), was dissolved in 100 ml of dry ether and slowly added to a vigorously stirred solution of 7.2 g of lithium aluminum hydride in 400 ml of absolute ether cooled in an ice bath. After 15 min the ice bath was removed and the reaction mixture was refluxed on the steam bath overnight. After cooling, 14.4 ml of water and 11.5 ml of 10% aqueous sodium hydroxide were added successively with vigorous stirring and the suspension was filtered. Concentration left 13.8 g of a colorless liquid which on distillation in the 6-in. Vigreux apparatus afforded 8.0 g of the thiophenoxy alcohol as a colorless liquid, bp 93.0–93.5° (0.5 mm), n^{25}D 1.5542. Oxidation with excess 30% hydrogen peroxide in acetic acid followed by reaction with 3,5-dinitrobenzoyl chloride provided the 3,5-dinitrobenzoate of 2-phenylsulfonyl-3-methylbutanol as colorless plates from ethanol, mp 120.0–121.0°.

Anal. Calcd for $C_{18}H_{18}O_8N_2S$: C, 51.19; H, 4.30. Found: C, 50.98; H, 4.17.

1,2-Dithiophenoxy-3-methylbutane (13).—To 1.00 g of 2-thiophenoxyisoamyl alcohol in a test tube was slowly added 3.0 ml of thionyl chloride with cooling. After the initial vigorous reaction and copious evolution of gas subsided, the solution was heated in an oil bath at 65° for 10 min and then excess thionyl chloride was removed to give 1.1 g of a pale yellow liquid residue which was then taken up in 5 ml of methanol and refluxed for 2 hr with a solution of 0.61 g of thiophenol and 3 ml of methanol containing 5.00 ml of 1.11 *N* sodium methoxide in methanol. Dilution with water and extraction with pentane gave 1.29 g of the crude 1,2-dithiophenoxy-3-methylbutane as a colorless liquid residue. A solution of 0.50 g of this residue in 15 ml of glacial acetic acid was oxidized with 5 ml of 30% hydrogen peroxide to afford a colorless oil which crystallized to white plates, mp 87.6–89.2° (benzene–hexane); admixture with the disulfone of 1,3-dithiophenoxy-3-methylbutane gave mp 77–107°.

Anal. Calcd for $C_{17}H_{20}S_2O_4$: C, 57.95; H, 5.72. Found: C, 58.08; H, 5.62.

***tert*-Butyl Hydroperoxide Initiated Reaction of α,α-Dimethylallyl Phenyl Sulfide with *n*-Butyraldehyde.**—A solution of 5.00 g (0.028 mol) of the sulfide and 10.0 g (0.140 mol) of freshly distilled *n*-butyraldehyde was stirred in an oil bath for 15 min at 80° while the system was flushed with nitrogen. The nitrogen flow was terminated, 0.25 g (0.003 mol) of *tert*-butyl hydroperoxide was injected, and the reaction mixture was allowed to remain at 80° for 9 hr; a negligible quantity of gas was evolved. Distillation through a 6-in. Vigreux provided the following fractions: (1) 0.85 g, bp 55–70° (750 mm), n^{25}D 1.3790; (2) 3.42 g, bp 70–71° (750 mm), n^{25}D 1.3770; (3) 3.99 g, bp 73–43° (150 mm), n^{25}D 1.3772; (4) 1.15 g, bp 48–53° (0.3 mm), n^{25}D 1.4902; (5) 2.41 g, bp 53–67° (0.3 mm), n^{25}D 1.5320; (6) 1.29 g, bp 67–80° (0.3 mm), n^{25}D 1.5530; and 0.068 g of an amber liquid kettle residue. Fractions 1–3 were essentially butyraldehyde; fractions 4–6 as well as the residue consisted mainly of isomeric mixtures of α,α- and γ,γ-dimethylallyl phenyl sulfides in varying proportions as indicated by ir. The spectrum of fraction 4 also suggested the presence of ketonic material.

***tert*-Butyl Hydroperoxide Initiated Reaction of α,α-Dimethylallyl Phenyl Sulfide with Thiophenol.**—A solution of 3.00 g (0.017 mol) of the tertiary sulfide, 3.70 g (0.034 mol) of thiophenol, and 0.15 g (0.002 mol) of *tert*-butyl hydroperoxide was stirred at 75° for 2 hr. Distillation through a 6-in. Vigreux apparatus revealed a small amount of uncollected volatile material, presumably hydroperoxide and hydroperoxide decomposition products, and provided the following fractions: (1) 3.42 g, bp 59–39° (10–1 mm), n^{25}D 1.5850; (2) 0.46 g, bp 60–64° (0.5 mm), n^{25}D 1.5535; (3) 1.91 g, bp 64–65° (0.5 mm), n^{25}D 1.5629; and 0.61 g of an amber residue which solidified on standing and gave fine white needles, mp 60–61° (MeOH), identified as diphenyl disulfide. Fractions 2 and 3 were identified by ir as γ,γ-dimethylallyl phenyl sulfide.

(29) (a) H. Gilman and R. H. Kirby, "Organic Syntheses," Collect. Vol. I, Wiley, New York, N. Y., 1932, p 353; (b) S. M. McElvain, "The Characterization of Organic Compounds," Macmillan, New York, N. Y., 1953.

(30) P. B. de LaMare and C. A. Vernon, *J. Chem. Soc.*, 3555 (1953).

(31) A. C. Cope, D. E. Morrison, and L. Field, *J. Amer. Chem. Soc.*, **72**, 59 (1950).

(32) C. S. Marvel, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1943, p 523.

tert-Butyl Hydroperoxide Initiated Reaction of γ,γ-Dimethylallyl Phenyl Sulfide with Thiophenol.—A solution of 5.00 g (0.028 mol) of the sulfide, 6.15 g (0.056 mol) of thiophenol, and 0.50 g (0.006 mol) of *tert*-butyl hydroperoxide was heated at 75° for 24 hr in a sealed ampule. Distillation provided the following fractions: (1) 5.19 g, bp 52–25° (10–0.6 mm), n^{25}D 1.5857; and (2) 4.31 g, bp 70–72° (0.7 mm), n^{25}D 1.5629 (corresponding to an 85 and 87% recovery of thiophenol and the primary allylic sulfide, respectively). The amber residue (1.31 g) which solidified on cooling was chromatographed on a 5 × 1.25 in. column of Alcoa alumina. Elution with 500 ml of pentane provided 0.88 g of diphenyl disulfide, mp 60–61° (ethanol). A yellow liquid, 0.20 g, was then eluted with 250 ml of 50:50 pentane–ether. Distillation in a microstill at a bath temperature of 205° (0.5 mm) provided a small amount of 1:1 adduct, n^{25}D 1.6051.

Anal. Calcd for $C_{17}H_{20}S_2$: C, 70.81; H, 6.99. Found: C, 70.64; H, 6.81.

Another solution of 3.00 g (0.017 mol) of the primary allylic sulfide, 7.4 g (0.068 mol) of thiophenol, and 0.50 g of *tert*-butyl hydroperoxide was heated at 75° for 48 hr in a sealed ampule. Concentration and chromatography of the residue (1.48 g) in similar fashion provided 0.29 g of 1:1 adduct. Oxidation with excess 30% H_2O_2 in glacial acetic acid gave a gummy white solid which defied numerous attempts at crystallization, even when seeded with crystals of authentic disulfones of 1,2- (13) and 1,3-dithiophenoxy-3-methylbutane (12).

α,α- (18) and γ,γ- (16) Dimethylallyl Acetates.—These acetates were prepared according to the procedure of Young and Webb[33] from 236 ml (2.5 mol) of freshly distilled acetic anhydride and 172 g (2.0 mol) of α,α-dimethylallyl alcohol, bp 96.5°, n^{25}D 1.4140, prepared by hydrolysis of a mixture of dimethylallyl chloride isomers obtained from the hydrochlorination of isoprene by the method of Goodman.[34] Distillation through a 21-in. helix-packed column afforded 54.3 g of the pure (vpc) tertiary allylic acetate, bp 49.0–50.0° (40 mm), n^{25}D 1.4098; continued distillation gave the primary isomer, γ,γ-dimethylallyl acetate, bp 75.0–76.0° (45 mm), n^{25}D 1.4287.

2-Acetoxy-2-methyl-4-thiophenoxybutane (19).—An ethereal solution of 15.0 g (0.077 mol) of methyl β-thiophenoxypropionate, bp 91.5–92° (0.6 mm), n^{25}D 1.5480, prepared from β-thiophenoxypropionic acid which was obtained by reaction of thiophenol with β-chloropropionic acid, was added with stirring to a solution of 0.23 mol of methylmagnesium iodide. The mixture was refluxed for 1 hr, poured into 100 ml of saturated aqueous ammonium chloride, extracted with ether, washed with water, and dried over magnesium sulfate. Concentration left 10.8 g of liquid which was diluted with an equal volume of acetic anhydride and stirred for 4 hr at 80° and 30 min at 105° in the presence of a small crystal of zinc chloride. Work-up and distillation afforded the colorless acetate, bp 99.5° (0.5 mm), n^{25}D 1.5307.

Anal. Calcd for $C_{13}H_{18}O_2S$: C, 65.63; H, 7.61. Found: C, 65.49; H, 7.51.

Hydrolysis of this ester with methanolic sodium hydroxide followed by oxidation with hydrogen peroxide in acetic acid and the reaction with 3,5-dinitrobenzoyl chloride provided the 3,5-dinitrobenzoate of 2-methyl-4-phenylsulfonylbutan-2-ol as fine white needles, mp 147.5–148.2° (EtOH).

Anal. Calcd for $C_{18}H_{18}N_2O_8S$: C, 51.19; H, 4.30. Found: C, 50.97; H, 4.28.

tert-Butyl Hydroperoxide Initiated Reaction of α,α-Dimethylallyl Acetate with Thiophenol.—A solution of 5.00 g (0.039 mol) of the tertiary allylic acetate, 8.60 g (0.078 mol) of thiophenol, and 0.35 g (0.0039 mol) of *tert*-butyl hydroperoxide was heated at 75° for 20 hr. Distillation of the reaction product through a 6-in. Vigreux column afforded a small amount of uncollected volatile material and the following fractions: (1) 1.02 g, bp 41° (41 mm), n^{25}D 1.3780; (2) 2.88 g, bp 49–42° (10–1 mm), n^{25}D 1.5753; (3) 2.55 g, bp 72–74° (1–0.8 mm), n^{25}D 1.5629; (4) 0.77 g, bp 75–110° (0.8 mm), n^{25}D 1.5529; (5) 3.46 g, bp 110–111° (0.8 mm), n^{25}D 1.5390; and 2.0 g of diphenyl disulfide residue, mp 60–61° (EtOH). Fraction 1 consisted mainly of acetic acid (87% by titration), confirmed by conversion to its *p*-phenylphenacyl ester, mp 112–112.5° (EtOH) (lit.[30] mp 111°). Fractions 3 and 5 were identified as γ,γ-dimethylallyl phenyl sulfide and 2-acetoxy-2-methyl-4-thiophenoxybutane, respectively, by comparison of ir spectra with those of authentic specimens. The spectrum of fraction 4 was consistent with that of a binary mixture. The identity of fraction 5 was established by quantitative saponification with ethanolic potassium hydroxide (sapon equiv 238), followed by oxidation with 30% hydrogen peroxide in acetic acid, and conversion to a 3,5-dinitrobenzoate ester, mp 148.2–148.8° (MeOH), which was identical with the 3,5-dinitrobenzoate of 2-methyl-4-phenylsulfonylbutan-2-ol.

The influence of chlorobenzene dilution on the product distribution of this reaction was determined in the following manner: 2.00 g (0.0156 mol) of α,α-dimethylallyl acetate, 3.44 g (0.0312 mol) of thiophenol, 0.28 g (0.003 mol) of *tert*-butyl hydroperoxide, and an appropriate quantity of chlorobenzene (1:1 to 10:1 molar ratio to acetate) were placed in sealed tubes and immersed in an oil bath thermostated at 75° for 24 hr. The contents were then washed into a distilling flask with enough chlorobenzene to bring the total chlorobenzene content to 20 ml. This solution was then distilled at reduced pressure through a 6-in. Vigreux column and 10 ml of distillate, free of thiophenol, was collected [bath temperature <75° (60–70 mm)] and acetic acid content was determined by titration with methanolic sodium methoxide. The residual chlorobenzene and thiophenol were removed by continued distillation at increasingly diminished pressure until thiophenol ceased to distil [bath temperature 75° (0.5 mm)]. The bath temperature was raised to 100° and the distillation was terminated at a head temperature of 50° (0.5 mm). Infrared spectra of the residues indicated essentially binary mixtures of γ,γ-dimethylallyl phenyl sulfide and 2-acetoxy-2-methyl-4-thiophenoxybutane in varying proportions contaminated by small quantities of diphenyl disulfide. Adduct content was determined by quantitative saponification with methanolic sodium hydroxide. Results are summarized in Table I.

Azoisobutyronitrile-Initiated Reaction of α,α-Dimethylallyl Acetate with Thiophenol.—A solution of 5.2 g (0.04 mol) of the acetate, 9.0 g (0.08 mol) of thiophenol, and 0.33 g (0.002 mol) of azoisobutyronitrile (DuPont) was heated at 75° for 5 hr. Another 0.33 g of AIBN was charged and the solution was maintained at 75° for a total of 28 hr, at which time vpc on a 4-ft 20% Se-30 Chromosorb W column at 120° with a 60-ml/min helium flow indicated 80% consumption of the tertiary allylic acetate. The vpc displayed two minor unidentified peaks and peaks for α,α-dimethylallyl acetate, thiophenol, tetramethylsuccinonitrile (a decomposition product of AIBN), and diphenyl disulfide as well as a single major product peak at the retention time of the unrearranged 1:1 adduct; no acetic acid or γ,γ-dimethylallyl phenyl sulfide was evident. Removal of excess acetate and thiophenol and distillation of the residue in a 6-in. Vigreux column provided the following fractions: (1) 3.6 g, bp 30–75° (0.4 mm), containing mostly allylic acetate and thiophenol; (2) 0.7 g, bp 75–90° (0.04 mm); and (3) 6.3 g, bp 90–93° (0.04 mm), consisting mainly of the 1:1 adduct (60% yield) contaminated with about 10% diphenyl disulfide. The nmr of fraction 3 corroborated the presence of 2-acetoxy-2-methyl-4-thiophenoxybutane (19) as the major component, displaying phenyl absorption centered at 7.17 ppm, the acetyl methyl at 2.0 ppm, and the *gem*-dimethyls at 1.5 ppm; the methylene protons are centered at 2.05 and 2.97 ppm in the proper ratios.

A solution of 5.2 g (0.04 mol) of α,α-dimethylallyl acetate and 9.0 g (0.08 mol) of thiophenol in 45 ml (0.4 mol) of chlorobenzene was stirred at 75° for 28 hr and catalyzed with a total of 0.66 g (0.004 mol) of AIBN in two portions in the manner described above. Vapor phase chromatography showed only 16% consumption of the allylic acetate with production of a similar product distribution as that observed above but in much lower yield; again only the normal 1:1 adduct 19 was observed.

tert-Butyl Hydroperoxide Initiated Reaction of γ,γ-Dimethylallyl Acetate with Thiophenol.—A solution of 5.00 g (0.039 mol) of the acetate, 8.60 g (0.078 mol) of thiophenol, and 0.70 g (0.008 mol) of *tert*-butyl hydroperoxide was heated for 24 hr at 75° in a sealed ampule. Volatiles were removed to a bath temperature of 110° (0.06 mm). The infrared spectrum of the light yellow kettle residue (6.11 g) was essentially identical with that of an authentic sample of 2-thiophenoxy-3-methylbutyl acetate (17). Saponification (indicating 41% yield of adduct), followed by oxidation with hydrogen peroxide in acetic acid, and finally reaction with 3,5-dinitrobenzoyl chloride, gave the 3,5-dinitrobenzoate of 2-phenylsulfonyl-3-methylbutanol, mp 121.0–121.4°, undepressed on admixture with authentic material.

2-Methyl-3-hydroxy-5-octanone (23).—A solution of 86 g (1

(33) W. G. Young and I. D. Webb, *J. Amer. Chem. Soc.* **73**, 780 (1951).
(34) L. Goodman, Ph.D. Thesis, UCLA, 1950.

mol) of 2-pentanone and 17 ml of 1 *N* alcoholic potassium hydroxide was stirred in an ice bath and 23 g (0.32 mol) of isobutyraldehyde was added over a 2-hr period according to the procedure of Powell and Hagemann.[35] Neutralization with 2.5 g of tartaric acid, filtration, and concentration gave 41.6 g of a liquid which by vpc showed only a trace of isobutyraldehyde and three products in a ratio of 7.3:2:9.7. Distillation through a spinning band column provided ten fractions, the first three of which (combined weight 8.2 g) were discarded. The remaining fractions (combined weight 22.5 g), boiling range 55–58° (0.015 mm), were shown by vpc and nmr to be binary solutions of 2-methyl-3-hydroxy-5-octanone (**23**) and its lower boiling isomer, 2-methyl-3-hydroxy-4-ethyl-5-hexanone, in proportions varying from 54:46 to 97:3; the higher boiling isomer was produced in the largest amounts. The final fraction [97% pure 2-methyl-3-hydroxy-5-octanone, bp 58° (0.015 mm)] was submitted for elemental analysis. Its nmr spectrum was consistent with the structural assignment, displaying a multiplet at 3.8 ppm for the methinyl proton adjacent to the hydroxyl function. The significant acetyl methyl proton of the contaminating low boiler, seen to decrease as boiling point increased, was virtually absent; strong hydroxyl and carbonyl absorptions were evident in the infrared at 3460 and 1712 cm^{-1}, respectively.

Anal. Calcd for $C_9H_{18}O_2$: C, 68.31; H, 11.46. Found: C, 68.47; H, 11.62.

2-Methyl-3-acetoxy-5-octanone (22).—To a refluxing solution of 5.9 g (0.074 mol) of pyridine and 9.0 g (0.057 mol) of a 82:18 isomeric mixture of 2-methyl-3-hydroxy-5-octanone and 2-methyl-3-hydroxy-4-ethyl-5-hexanone in 25 ml of dry benzene was added 7.0 g (0.0685 mol) of acetic anhydride over a 15-min period. The mixture was refluxed for 1.5 hr and allowed to cool and stand overnight; vpc revealed two products in the expected 4:1 ratio, confirming that acetylation was accomplished with essentially no change in isomer distribution. Distillation in a spinning band column provided five fractions with a combined weight of 12.6 g, boiling range 60–79° (0.75 mm), containing 30–90% of the higher boiling component. A pure sample of the high-boiling material [2.0 g, bp 78–79° (0.75 mm)] was collected by preparative vpc; the nmr spectrum displayed the *C*-methyl protons split and centered at 0.9 ppm and the acetyl methyl protons at 2.05 ppm, consistent with assignment as 2-methyl-3-acetoxy-5-octanone. The most definitive portion of the spectrum is the multiplet due to the single methinyl hydrogen on carbon adjacent to the acetoxy group at 5.2 ppm. A mass spectrum indicated that the most predominant cleavage is loss of acetic acid to give the conjugated olefin to which can be assigned the major ions observed in the spectrum, *m/e* 140, 97, 71, 43; *m/e* 97 is the most abundant. Although the neat keto acetate tended to lose acetic acid *via* reverse Michael reaction on prolonged standing, it was completely stable under the conditions employed for the butyraldehyde-α,α-dimethylallyl acetate reactions. Neither loss of keto acetate nor appearance of its ketonene decomposition product was evident in the vpc.

***tert*-Butyl Hydroperoxide Initiated Reaction of α,α-Dimethylallyl Acetate with *n*-Butyraldehyde.**—A solution of 5.2 g (0.04 mol) of the acetate, 28.8 g (0.4 mol) of *n*-butyraldehyde, and 1.14 g (0.009 mol) of *tert*-butyl hydroperoxide was maintained at 78° for 32 hr, at which time vpc indicated an 80% conversion of the allylic acetate. Concentration gave 5.1 g of a residue which on distillation through a 6-in. Vigreux column provided (1) 1.0 g, bp 90–93° (0.5 mm); (2) 1.5 g, bp 93–95° (0.5 mm); (3) 1.6 g, bp 90–92° (0.45 mm); and (4) 0.6 g, bp 95–97° (0.45 mm). Vpc on a 6-ft 10% Carbowax 20M Anakrome Q column operated isothermally at 165° with a 60-ml/min helium flow of these fractions showed them to contain, respectively, 57, 75, 85, and 91% of the unrearranged 1:1 adduct (22% yield) with a retention time of 12.25 min in addition to a substantial amount of material with high retention time. No product was observed at the retention time (10.15 min) expected for the rearranged 1:1 adduct, 2-methyl-3-acetoxy-5-octanone. A sample of the major product in fraction 4 was isolated by preparative vpc as a colorless liquid, bp 58° (0.05 mm).

Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07. Found: C, 65.83; H, 10.11.

The nmr of fraction 4 was consistent with its 2-methyl-2-acetoxy-5-octanone (**21**) assignment, displaying a high-field methyl triplet for the terminal methyl centered at 0.95 ppm, a strong singlet for the *gem*-dimethyl system at 1.50 ppm, and the acetyl methyl at 2.0 ppm. A split carbonyl absorption in the infrared at 1715 and 1732 cm^{-1} supported the presence of ketone and ester groups, respectively.

Azoisobutyronitrile-Initiated Reaction of α,α-Dimethylallyl Acetate with *n*-Butyraldehyde.—A solution of 5.2 g (0.04 mol) of the acetate, 5.75 g (0.08 mol) of *n*-butyraldehyde, and 0.33 g (0.002 mol) of azoisobutyronitrile was heated at reflux (90°) for 4 hr, another 0.33 g of azoisobutyronitrile was charged, and the reaction mixture was maintained at 90° for a total of 28 hr. Vpc analysis showed the unrearranged 1:1 adduct as the major product with no trace of the rearranged isomer. Distillation provided (1) 1.6 g, bp 28–55° (2.0 mm); (2) 2.5 g, bp 55–60° (2.0 mm); (3) 0.5 g, bp 60–65° (2.0–0.06 mm); and (4) 3.0 g, bp 65° (0.06 mm). All cuts were impure; however, fraction 4 was estimated (vpc) to contain 89% of 2-methyl-2-acetoxy-5-octanone. A pure sample of the major product isolated from fraction 4 by vpc possessed an nmr superimposable with that of the product of the *tert*-butyl hydroperoxide initiated reaction.

Azoisobutyronitrile-Initiated Reaction of α,α-Dimethylallyl Acetate with *n*-Butyraldehyde in Chlorobenzene.—A solution of 15.6 g (0.12 mol) of the acetate, 17.4 g (0.24 mol) of *n*-butyraldehyde, and 1.0 g (0.006 mol) of AIBN in 135 g (1.2 mol) of freshly distilled chlorobenzene was heated at 75° for 24 hr, another 1.0 g of AIBN was charged, and the solution was maintained at 75° for another 24 hr. Vpc analysis indicated a 50% conversion of the allylic acetate and the presence of unrearranged 1:1 adduct 2-methyl-2-acetoxy-5-octanone as the major product along with minor quantities of butyric acid and tetramethylsuccinonitrile. The rearranged 1:1 adduct, 2-methyl-3-acetoxy-5-octanone (1:5, rearranged to unrearranged), was clearly evident at a retention time of 10.15 min. Distillation of the crude mixture gave the following fractions: (1) 0.4 g, bp 25–35° (0.25 mm); (2) 0.08 g, bp 35–60° (0.25 mm); (3) 1.0 g, bp 60–61° (0.25 mm); (4) 0.08 g, bp 61–65° (0.25 mm); and (5) 0.5 g, bp 65–68° (0.25 mm). Vpc analysis indicated that fractions 2 and 3 contained, respectively, 1:2 and 1:4 ratios of rearranged to unrearranged adduct contaminated in each case with a trace of the succinonitrile. Fraction 4 appeared to be a 1:4 mixture, while fraction 5 contained a 1:7 ratio plus a small amount of higher boilers. The nmr of fractions 3 and 4 were almost identical and were consistent with a composite spectrum of the pure 2-acetoxy and 3-acetoxy isomers in the indicated ratio. Absorption for the proton α to the 3-acetoxy group is apparent at 5.12 ppm and the *gem*-dimethyls α to the 2-acetoxy group are apparent at 1.5 ppm. Pure samples of the unrearranged and rearranged adducts were separated by vpc and collected. Mass spectral analysis of the pure cuts indicated that material with a 12.25-min retention time was identical in cracking pattern with the product obtained from the neat reactions of α,α-dimethylallyl acetate and butyraldehyde and the cut with the 10.15-min retention time was identical with an authentic sample of 2-methyl-3-acetoxy-5-octanone. A sample of fraction 4 was submitted for analysis.

Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07. Found: C, 65.63; H, 10.23.

A repeat of this reaction employing like amounts of reactants but 575 g (6.0 mol) of chlorobenzene (50-fold dilution) resulted in a much lower conversion of allylic acetate and yield of products. The presence of rearranged and unrearranged 1:1 adducts, however, was clearly evident in the vpc. A substantial increase in the ratio of rearranged to unrearranged adduct was noted (1:1.6).

Registry No.—**1**, 34195-74-9; **2** (R = SPh), 34195-75-0; **3** (R = SPh), 34195-76-1; **3** (R = O=CC_3H_7), 34195-77-2; **7**, 3576-07-6; **7** diethyl acetal, 3494-86-8; **8**, 2049-70-9; **10**, 34043-60-2; **11**, 10276-04-7; **12**, 34224-38-9; **12** disulfone, 34224-39-0; **13**, 34224-40-3; **14**, 34220-15-0; **16**, 1191-16-8; **18**, 24509-88-4; **19**, 34220-19-4; **21**, 34220-20-7; **22**, 34220-21-8; **23**, 34220-22-9; butyraldehyde, 123-72-8; thiophenol, 108-98-5; α-phenylsulfonylisobutyric acid, 34220-23-0; α-phenyl sulfide isobutyric acid, 5219-64-7; 3,5-DNB of 2-phenylsulfonyl-3-methylbutanol, 34220-16-1; 1:1 adduct of 2-methyl-2-butene and diphenyl disulfide, 34220-25-2; 3,5-DNB of 2-methyl-4-phenylsulfonylbutan-2-ol, 34202-01-2.

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Acknowledgments.—We are indebted to the National Science Foundation, the Petroleum Research Fund, and the Rohm and Haas Company for financial support of this work. We are especially grateful to Mr. James Laudadio for invaluable technical assistance.

Structure and Isomerization Phenomena of Olefin Radical Ions. The 1,2-Bis(*N*-methyl-4-pyridyl)ethylene Tetrafluoroborate Radical Cation

JOHN W. HAPP, JOHN A. FERGUSON, AND DAVID G. WHITTEN*[1]

Department of Chemistry, University of North Carolina, Chapel Hill, North Carolina 27514

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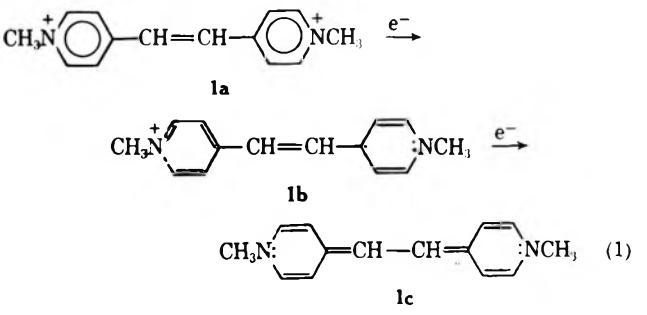
Preparation and structural studies of the radical cation of 1,2-bis(*N*-methyl-4-pyridyl)ethylene tetrafluoroborate by one-electron reduction of the parent diquaternary salt are reported. Both cis and trans isomers of the parent diquaternary are readily reduced to the radical cation by electrolytic reduction at −0.60 V (*vs.* SSCE), by reduction with zinc, or by photolysis in the presence of amines or ethers. The radical is quite stable and structurally similar to the stable methyl viologen radical cation. Cyclic voltammetry experiments indicate that reduction to the radical and neutral species are both reversible; disproportionation of the radical is evidently unimportant. A planar trans structure is indicated for the single form of the radical cation by results of esr and chemical quenching studies. Conversion of cis to trans is very rapid with the lifetime of the cis form evidently being less than 10 μsec at room temperature.

In previous papers[2-5] we have reported on the photochemical isomerization of electron-deficient olefin in various types of molecular complexes. Although in certain cases[3,4] photoisomerization has been found to proceed *via* excited states of the olefin, in other instances[2,4,5] there is strong evidence that electron transfer to the olefin within the excited complex occurs to form a transient radical ion which is the active species in isomerization. Although it has been established that radical anions of stilbene and related olefins can undergo facile geometric isomerization, there has been some uncertainty regarding the structures of these species and the mechanisms and rates for the isomerization. There is good evidence[6] that dianions of stilbene prefer a twisted conformation. The same twisted geometry has been proposed[7,8] for the electronically similar "phantom" excited singlet and triplet states of stilbene on the basis of experimental evidence as well as theoretical considerations. Because of similarities in their electronic structures, the dianion and triplet state of stilbene are predicted by molecular orbital theory to have similar geometric structures.[6] For stilbene radical anion, there is evidence that cis and trans isomers can exist. A difference of 0.03 V has been observed between the half-wave reduction potentials of *cis*- and *trans*-stilbene. In dimethylformamide (DMF), the lifetime of the cis anion is estimated to be in excess of 1 min at room temperature.[9] Furthermore, when *cis*- or *trans*-stilbene is reduced electrolytically in the presence of carbon dioxide in DMF, DL- and *meso*-diphenylsuccinic acid are isolated. Stereochemical analysis of the products indicates that *trans*-stilbene forms a larger proportion of DL acid in relation to meso acid than that formed from *cis*-stilbene.[9] These results are consistent with carboxylation of separate cis and trans radical anions.

Electron spin resonance (esr) experiments[10] have given additional information regarding cis–trans isomerism of stilbene radical anion. The same esr spectrum with roughly uniform line widths is obtained with either *cis*- or *trans*-stilbene over a wide range of temperatures. These results are interpreted in terms of a moderately rapid interconversion of cis–trans isomers which may well occur before esr spectra can be recorded. An interesting result of this work is the finding that rotation about the exocyclic bond joining the ethylenic carbon to the phenyl ring is rather slow and results in an unsymmetrical spin distribution in the phenyl rings. Thus, the bond has a considerable amount of double bond character as predicted by Huckel molecular orbital calculations. Similar hindered rotation is observed for the radical anions of *trans*-1,2-bis(4-pyridyl)ethylene, *trans*-azobenzene, and tolan.[10] Like the stilbene radical anion, only one radical species is observed for each of the above anions.

In the present paper we report an investigation of the structure and isomerization of the radical cation **1b** which is formed by one-electron reduction of 1,2-bis(*N*-methyl-4-pyridyl)ethylene tetrafluoroborate (**1a**) (eq 1). Recently we have found that **1a** undergoes very



(1)

inefficient cis–trans isomerization upon direct or sensitized irradiation in inert solvents such as acetonitrile.[5,11] However, we find that formation of **1b** by one-electron reduction occurs on irradiation of **1a** in the presence of

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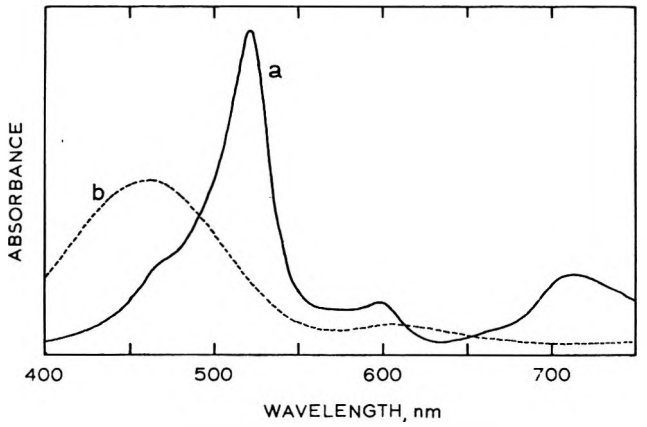
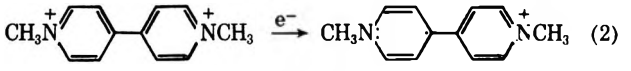


Figure 1.—(a) Visible absorption spectrum of 1,2-bis(*N*-methyl-4-pyridyl)ethylene tetrafluoroborate radical cation (**1b**) produced by electrolytic reduction of *trans*-**1a** in acetonitrile at −0.49 V *vs.* SSCE. (b) The spectrum of the neutral, doubly reduced form, **1c**.

certain electron donors.[5] **1b** can also be formed by electrolytic reduction of **1a** at a very low potential (−0.45 V *vs.* Ag/AgCl electrode in acetonitrile for the dimethiodide salt)[12] or *via* electron transfer between the doubly reduced species and **1a**.[13] Results from INDO and CNDO[14] molecular orbital calculations on **1a** and **1b**[15] suggest that the lowest antibonding π orbital has small coefficients on the ethylenic carbons. A lack of antibonding character in the ethylenic double bond could account for the reluctance of **1a** to undergo cis–trans isomerization from the excited singlet state. Similarly we anticipated that diminished antibonding character at the olefinic carbons might hinder isomerization in **1b** and permit the observation of cis and trans forms of the radical.

Radical **1b** is structurally similar to the stable methyl viologen radical cation (**2b**) produced by one-electron reduction of paraquat (**2a**). Paraquat has been used



(2)

2a **2b**

successfully as a redox indicator in chemical[16] and biological[17] electron-transfer systems, and has found wide commercial use as a herbicide.[18]

Our approach to the analysis of the structure of radical cation **1b** has included studies of its chemical and spectral properties and determination of the geometrical structure of the radical.

Results and Discussion

Methods of Production.—Electrolytic reduction of *trans*-**1a** in acetonitrile at −0.60 V *vs.* a standard saturated sodium chloride calomel electrode (SSCE) produces a red solution whose visible spectrum is shown in Figure 1a. At the same potential, the esr spectrum shown in Figure 2a is recorded, which we assign to radical **1b**. Upon reduction at the second half-wave potential, the solution turns yellow and gives the visible spectrum shown in Figure 1b which we assign to the neutral, doubly reduced form, **1c**.

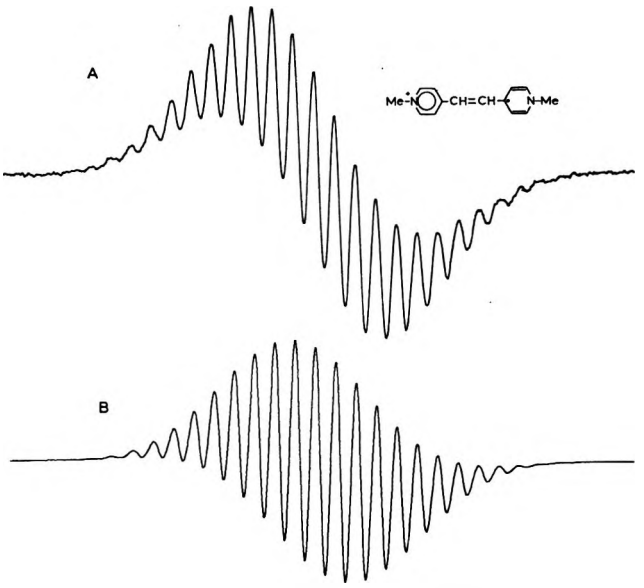


Figure 2.—(a) Esr spectrum of 1,2-bis(*N*-methyl-4-pyridyl)-ethylene tetrafluoroborate radical cation produced by electrolytic reduction of *trans*-**1a** in acetonitrile. (b) Computer-simulated spectrum using the coupling constants listed in Table I.

Reduction of *trans*-**1a** with powdered zinc or a distilled zinc mirror under nitrogen in acetonitrile initially produces the same visible spectrum shown in Figure 1a and the same esr spectrum shown in Figure 2a. Prolonged reduction on a zinc mirror in degassed solution produces the visible spectrum shown in Figure 1b.

In our earlier studies[5] of the photochemistry of **1a**, we observed formation of radical **1b** during the photolysis of **1a** in ethyl ether and in pyridine at 3130 Å. Although the radical lifetime in 1:1 ether–acetonitrile is fairly short (approximately 4 min as determined by visible spectra), the lifetime in 1:1 pyridine–acetonitrile is quite long (2 days). As we suggested earlier,[5] it may be possible that photochemical formation of radical **1b** involves electron transfer from ether or pyridine to an excited olefin singlet, or possibly electron transfer accompanying decay of an exciplex formed between **1a** and ether or pyridine. A similar photoreduction by electron transfer from ethanol or other alcohols to paraquat (**2a**) to produce the methyl viologen radical cation (**2b**) has been observed.[19,20]

In contrast to ethyl ether and pyridine, more reactive electron donors such as 2,6-lutidine, piperidine, *n*-butylamine, and di- and triethylamine react with the ground state of **1a** in acetonitrile under nitrogen to produce esr-detectable quantities of radical **1b**. Visible spectra of these solutions appear similar to that shown in Figure 1a. However, additional absorption appears between 350 and 400 nm which appears to be due to complex formation. The concentration of the radical cation is not sufficient to account for all of the starting

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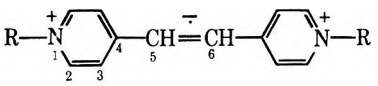
TABLE I
OBSERVED AND CALCULATED HYPERFINE COUPLING CONSTANTS



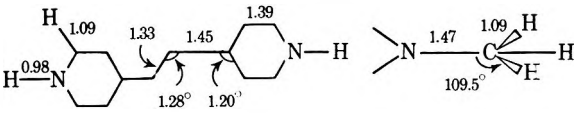
	Experimental[a]			Theoretical[b]		
			trans		cis,	twisted,
	R = CH_3	R = CH_2CH_3	R = H	R = CH_3	R = H	R = H
A_1^N	3.1	3.3	3.8	4.1	3.5	3.3
A_2^H	1.6	1.3	−1.8, −2.0	−1.6, −1.7	−2.1, −2.4	0.0, 0.2
A_3^H	<0.5	<0.5	−0.1, −0.2	−0.3, −0.4	0.2, 0.4	−1.6, −1.9
A_5^H	1.6	2.0	−1.3	−1.3	4.7	15.3
A_{NH}^H			−5.2		−4.9	−4.2
$A_{NCH_3}^H$	3.1			4.0, 5.2		
$A_{NCH_2Me}^H$		3.3				

[a] Hyperfine coupling constants extracted from spectra obtained experimentally. [b] Coupling constants predicted from INDO molecular orbital calculations; see text.

olefin. Therefore, the radicals have likely escaped from a nonparamagnetic (ground state) donor–acceptor complex in a manner analogous to radical formation from amine complexes of tetracyanoethylene.[21] In a typical experiment, 0.002 *M* **1a** and 0.2 *M* *n*-butylamine in acetonitrile produce a radical concentration of **1b** which is 16% that of starting olefin **1a** as determined by comparison of spins with a paramagnetic standard. A mixture of 0.001 *M* 1,2-bis(4-pyridyl)ethylene diethiodide and 0.2 *M* *n*-butylamine in acetonitrile produces a concentration of the *N*-ethyl substituted radical cation that is 56% that of starting olefin.

Analysis of Esr Spectra.—Hyperfine coupling constants from analysis of esr spectra obtained in this study are shown in Table I. Coupling constants from this Table were used to simulate the computer spectrum shown in Figure 2b. Methyl hydrogen coupling constants were assigned with the aid of *N*-deuteromethyl and *N*-ethyl substitution. Figure 3 shows the esr spectrum observed from zinc reduction of 1,2-bis(*N*-ethyl-4-pyridyl)ethylene iodide in acetonitrile; below it is the computer-simulated spectrum based on coupling constants in Table I. The ratio of methylene to methyl hydrogen coupling constants in Table I ($A_{CH_2Me}^H/A_{CH_3}^H = 1.06$) is very similar to the ratio of the methylene to methyl coupling constants for benzyl and methyl viologen ($A_{CH_2Ph}^H/A_{CH_3}^H = 1.04$).[19] Based on the known ratio, $A^H/A^D = 6.5$,[22] the predicted spectral length of the *N*-deuteriomethyl substituted radical **1b** is 28 G. The experimentally observed spectrum has a length of 29 G. For methyl viologen the ratio of nitrogen to methyl hydrogen coupling constants is 1.06,[19] while for radical **1b** the ratio is near unity.

Other coupling constants were assigned on the basis of molecular orbital calculations using the INDO method. In using this method, reasonably good agreement has been previously obtained[23-25] between experimental and calculated hyperfine coupling constants for a large number of free radicals. One of the major approximations of INDO calculations involves the choice of appropriate geometries. As is the usual case, the precise geometry of the radical in question is unknown. In theory, the appropriate geometry could be obtained by adjusting the internal coordinates so as to minimize the molecular energy. Bond angles and lengths were varied to ascertain trends in molecular energies and coupling constants. Standard bond lengths and bond angles[26-28] for the trans geometry of the radical are shown below.



For the cis geometry, coordinates for the trans isomer were rotated 180° about the ethylenic double bond. Coordinates for the pyridyl rings were then rotated 34° about the C_4–C_5 bond axis in propeller fashion.[29] A twisted geometry was achieved by rotating coordinates for the trans isomer 90° about the ethylenic double bond. The energy of the twisted form was further minimized by changing exocyclic bond lengths to C_4–C_5 = 1.45 Å and C_5–C_6 = 1.33 Å.

Coupling constants predicted by INDO calculations for *trans*-**1b** (Table I) agree fairly well with those observed experimentally. The calculated methyl hydrogen coupling constants are expectedly in error since a rigid geometry was assumed for the methyl groups. Nevertheless, substituting a *N*-methyl group for a *N*-hydrogen is predicted to have only a small effect on the spin distribution of the trans radical. Except for differences in coupling constants for the ethylenic hydrogens, coupling constants predicted for the trans, cis, and twisted conformations of the radical show only small variations.

Isomerization of the Radical.—Both cis and trans isomers of **1a** can be prepared and are stable at room temperature. To determine whether cis and trans forms of radical **1b** could be detected, both isomers of **1a** were reduced by several methods under various conditions. Cyclic voltammetric measurements (at 200 mV/sec sweep rates) on solutions of *cis*-**1a** in acetonitrile at a platinum bead electrode yielded the

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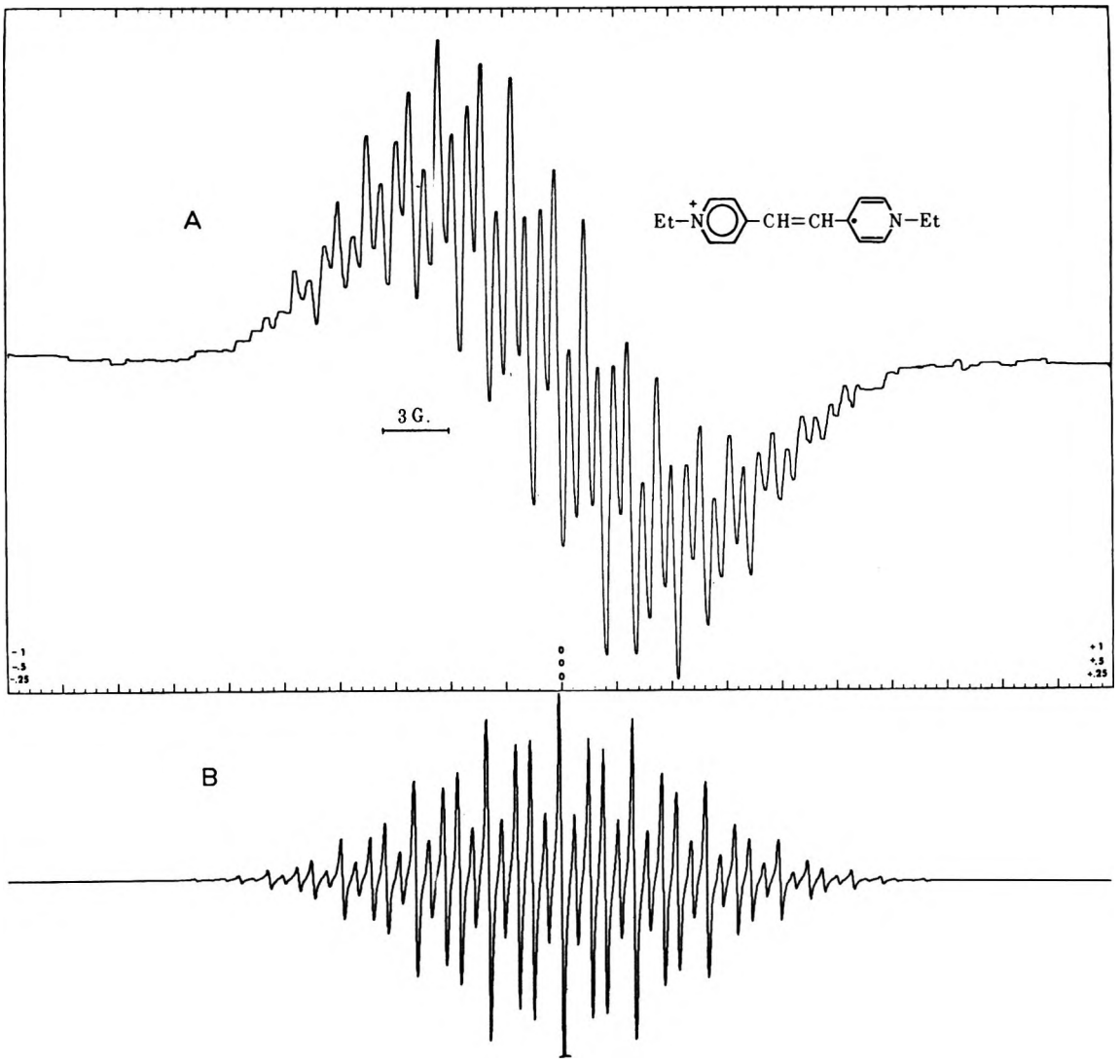

Figure 3.—(a) Esr spectrum of 1,2-bis(*N*-ethyl-4-pyridyl)ethylene iodide radical cation produced by zinc reduction of 1,2-bis(*N*-ethyl-4-pyridyl)ethylene iodide in acetonitrile. (b) Computer-simulated spectrum using the coupling constants listed in Table I.

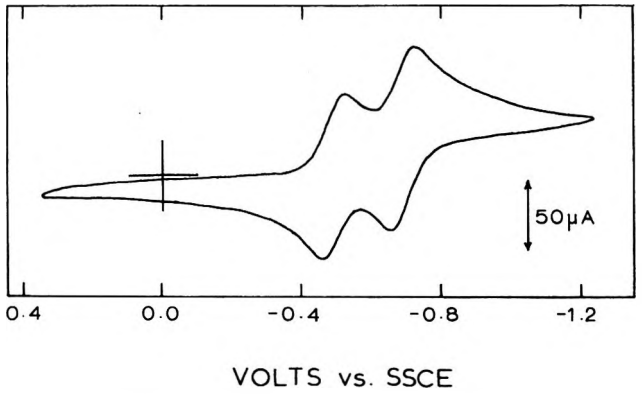

Figure 4.—Cyclic voltammogram of *trans*-1,2-bis(*N*-methyl-4-pyridyl)ethylene tetrafluoroborate in acetonitrile containing 0.1 *M* TBAH. Rate of scan was 200 mV/sec using a platinum bead electrode and a SSCE cell as reference.

same cyclic voltammogram as that obtained for the trans isomer (Figure 4). Peaks corresponding to two one-electron reversible reductions were identical within the accuracy of measurement for both isomers. Within the time scale of the cyclic experiments no disproportionation or other side reactions could be detected. Reduction potentials for *cis*- and *trans*-**1b** were also determined by single sweep voltammetry under conditions that would yield more precise results than those from cyclic measurements. For the cis and trans isomers, reduction potentials were −0.488 and −0.492 V (±0.003 V at 28 ± 0.5° *vs.* SSCE), respectively. Radical formation is accompanied by isomerization. An exhaustive electrolysis of *cis*-**1a** to **1b** at −0.60 V *vs.* SSCE at a platinum electrode followed by a reoxidation at 0.00 *vs.* SSCE resulted in complete cis to trans isomerization of **1a**. In fact, when only small portions of *cis*-**1a** were reduced to **1b**, total cis to trans isomerization of the solution occurred in less than 1 hr.

Esr spectra from zinc or electrolytic reduction of either *cis*- or *trans*-**1a** at room temperature were identical with that in Figure 2. At −60°, spectra obtained for the electrolytic reduction of *trans*-**1a** in butyronitrile under vacuum showed essentially the same linewidth broadening as that observed at room temperature. Electrochemical reduction of *cis*-**1a** at −0.60 V *vs.* SSCE under vacuum in butyronitrile at −30° produced spectra that were essentially the same as those produced from *trans*-**1a** at low temperatures. The spectra showed slight differences in peak intensities during the initial period of radical production, which could have resulted from nonhomogeneous solution currents. However, after several minutes, electrolytic reduction of *cis*-**1a** produced spectra that were identical with

those from *trans*-**1a**. Line widths from spectra produced by electrolytic reduction of *cis*-**1a** showed very little temperature dependence and were the same as those produced from reduction of *trans*-**1a**.

As previously mentioned, photolysis of *trans*-**1a** in 1:1 ether–acetonitrile solutions produced visible spectra which are the same as those produced by either chemical or electrochemical reductions of *cis*- or *trans*-**1a**. Experiments were performed to determine whether new visible absorption could be detected on a microsecond time scale when *cis*-**1a** was irradiated by flash photolysis. Acetonitrile solutions of *cis*-**1a** were mixed with ether *via* a break-seal joint just prior to flashing, and solutions were flashed no more than twice within 10 min of mixing. Flash photolysis at approximately 325 nm produced no new transient absorption in the region of 400–630 nm having a lifetime of 10 μsec or longer.

Flash photolysis at 500–600 nm of an acetonitrile solution of **1b** produced by electrochemical reduction also failed to show changes in absorption in the regions of 400–490 and 610–630 nm having a duration of 10 μsec or longer.

One possibility suggested by these results from the esr and flash photolysis experiments is that the energy barrier to rotation about the ethylenic double bond of radical **1b** is too small to permit easy detection of unique cis and trans isomers. Theoretical predictions of the energy change as a function of rotation about the ethylenic double bond were obtained from INDO calculations. Results from these calculations for **1a** and **1b** are shown in Figure 5. The energy change between *trans*-**1a** and *trans*-**1b** is theoretically proportional to the reduction potential of *trans*-**1a**. Since voltammetric measurements yielded the same reduction potential for *cis*-**1a** as for *trans*-**1a**, the enthalpy change between *cis*- and *trans*-**1a** should be very similar to that between *cis*- and *trans*-**1b**. The voltammetric measurements are thus in accord with the relative enthalpy changes predicted by INDO calculations. The actual magnitude of the cis–trans enthalpy change is considerably overestimated by the INDO calculations, since the cis–trans enthalpy change for stilbene has been estimated experimentally to be about 3–4 kcal/mol.[30] Also, the energy maxima at 90° for the twisted forms of **1a** and **1b** are likely to be overestimated owing to the restricted choice of molecular coordinates. For stilbene, the energy of activation for conversion of cis to trans forms is found by experiment to be approximately 37 kcal/mol.[31] Although the calculations have their limitations in predicting actual energies, it is evident that the relative energy of activation for cis–trans isomerization for radical **1b** is predicted to be considerably less than that for **1a**.

The above experiments suggest strongly that the single radical observed in this study is *trans*-**1b**. The observed and calculated hyperfine coupling constants (Table I) also support a planar trans or cis form for **1b** but argue against a twisted structure. Computer-simulated esr spectra for planar cis and trans radical cations (compared in Figure 6) appear different enough so that a long-lived *cis*-**1b** could be detected under the

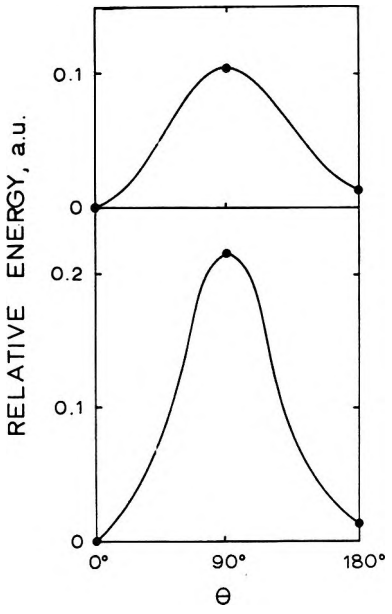

Figure 5.—Energies predicted by INDO molecular orbital calculations as a function of rotational angle about the ethylene bond: upper trace, radical cation **1b**; lower trace, starting dication **1a**.

experimental conditions. Therefore it seems safe to conclude that the only radical surviving long enough to detect in these experiments is *trans*-**1b**. It is perhaps a little surprising that *cis*-**1b** does not survive long enough to be detected in flash photolysis experiments or in the low-temperature reduction of *cis*-**1a**. Although the barriers to the radical estimated by INDO calculations are considerably lower than those for the unreduced olefin, reaction with free energies of activation in the range 14–16 kcal/mol (reasonable estimates based on predicted relative barriers for **1a** and **1b** and assuming that the barrier for **1a** is ~37 kcal/mol)[31] should be detectable under the flash photolysis conditions employed. However, a free energy of activation barrier as low as 12 kcal/mol would be nearly impossible to detect; so fast rotation can not be excluded as the mechanism for isomerization.

Although disproportionation of the cis cation to **1a** and **1b** with subsequent generation of *trans*-**1b** (eq 3, 4)

$$2\ cis\text{-}\mathbf{1b} \underset{}{\overset{k_{eq}}{\rightleftharpoons}} \mathbf{1c} + cis\text{-}\mathbf{1a} \qquad (3)$$

$$cis\text{-}\mathbf{1a} + \mathbf{1c} \xrightarrow{k_r} cis\text{-}\mathbf{1b} + trans\text{-}\mathbf{1b} \qquad (4)$$

can certainly occur, it is unlikely that this provides the dominant route for isomerization at the concentrations employed in the flash experiments. The calculated rate expression for reaction from eq 3 and 4 is eq 5.

$$\frac{d\,[trans\text{-}\mathbf{1b}]}{dt} = k_r K_{eq}\,[cis\text{-}\mathbf{1b}]^2 = k_d\,[cis\text{-}\mathbf{1b}]^2 \qquad (5)$$

Assuming $k_r = k_{diff} = 10^{10}\ M^{-1}\ sec^{-1}$ [32] in acetonitrile and $K_{eq} = 2.5 \times 10^{-4}$ [12] and that all of the *cis*-**1a** is converted to *cis*-**1b** on flashing we estimate that even at the highest concentrations employed (0.001 *M*) no more than 5% isomerization by the above-outlined disproportionation path could occur. If less *cis*-**1b** is produced or if $k_r < k_{diff}$ the reacted fraction would be much lower. The equal wave heights of the cyclic

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(31) T. W. J. Taylor and A. R. Murray, *J. Chem. Soc.*, 2078 (1938).

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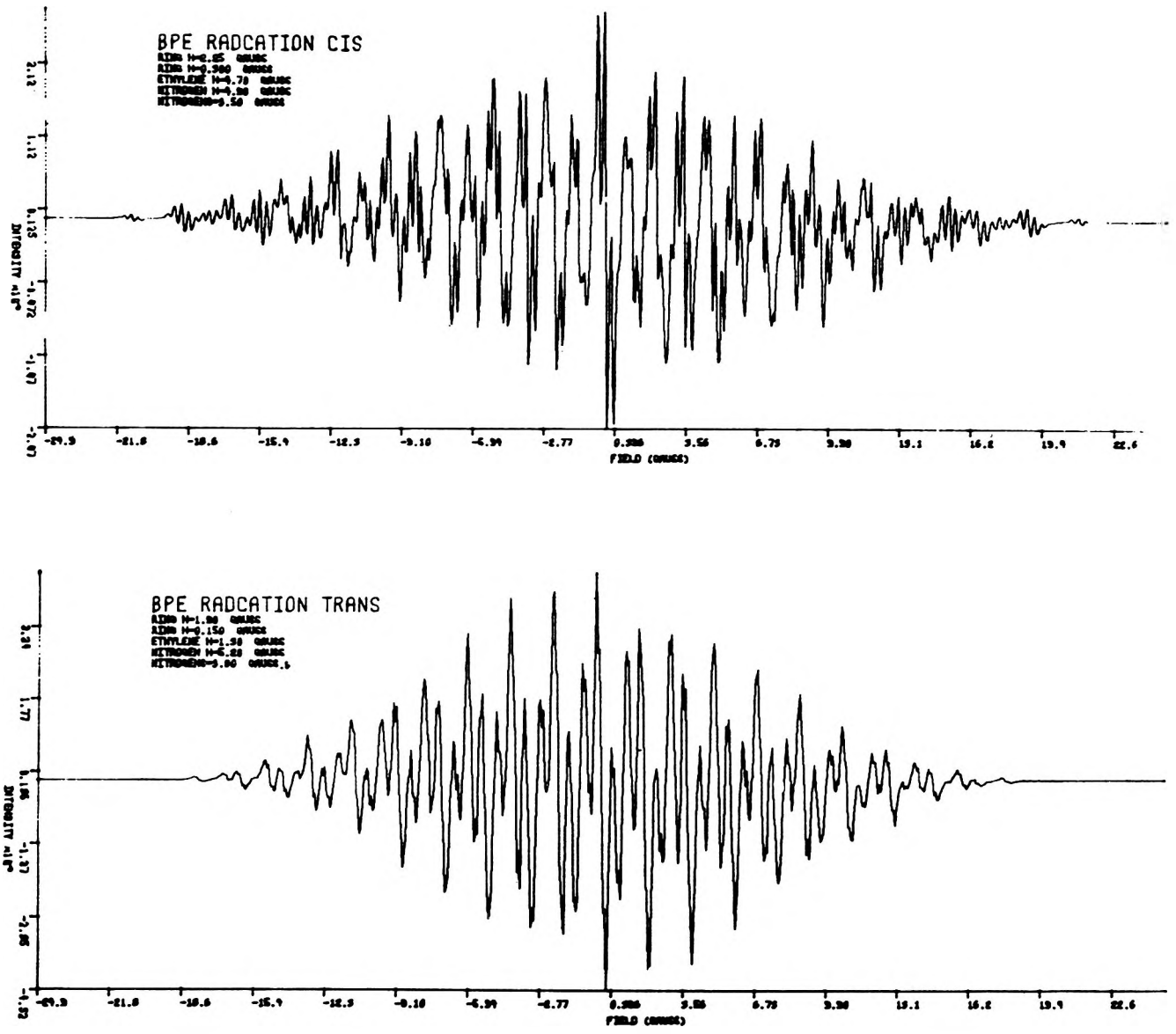

Figure 6.—Computer-simulated (using data in Table I) esr spectra for cis and trans olefin radical cations.

voltammograms (Figure 4) also rule out the occurrence of substantial disproportionation.

The presence of what is evidently such a low barrier to rotation in radical cation **1b** presents a striking contrast to the relatively large barriers indicated for other substituted ethylenic cation radicals.[33,34] However, as indicated earlier, the present system is really a reduced ethylene while the earlier cation radicals are oxidized ethylenes, so that perhaps the behavior of **1b** is best compared to that of radical anions.

It is frequently tempting to draw correlations between the behavior of excited states and one-electron reduced species. However, on a quantitative basis these comparisons are often less than satisfactory. In the present case radical **1b** apparently isomerizes *via* rotation much more readily than does the stilbene radical anion; in contrast, excited states of **1a** have some preference for planar cis and trans forms while stilbene excited states readily attain a twisted geometry. The observed rapid rate of isomerization of **1b** indicates that isomerization *via* formation of transient radical ions *via* electron transfer within excited molecular complexes is a viable mechanism for photoisomerization. Such a mechanism could conceivably be important in photobiological processes related to vision.

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Experimental Section

Materials.—The preparation and purification of *cis*- and *trans*-1,2-bis(*N*-methyl-4-pyridyl)ethylene tetrafluoborate (**1a**) has been described in a previous publication.[5] The diethyl iodide salt of 1,2-bis(4-pyridyl)ethylene was prepared and purified by the same general procedure.[5] Butyronitrile was distilled from potassium permanganate and anhydrous sodium carbonate, and then dried by distillation from P_2O_5. Other solvents were of spectral quality and were distilled before use. The supporting electrolyte, tetra-*n*-butylammonium hexafluorophosphate (TBAH), was prepared by the general procedure of Lange and Muller[35] and Ferguson,[36,37] recrystallized three times from ethanol–water, and dried at 100° under vacuum for 10 hr. The paramagnetic standard, diphenylpicrylhydrazyl, was purchased from Aldrich Chemical Co., and was used without further purification.

Methods.—Visible spectra were recorded on either a Cary Model 14 or Unicam SP800B spectrophotometer. A Varian E-3 spectrometer, equipped with X-band frequencies and an E-3

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(36) J. A. Ferguson, Ph.D. Thesis, University of North Carolina, Chapel Hill, N. C., 1971.
(37) J. A. Ferguson and T. J. Meyer, *Inorg. Chem.*, **11**, 1024 (1971).

variable-temperature accessory, was used to record esr spectra. Computer-simulated spectra were obtained using a computer program written by Griffin.[38] Esr spectra recorded at room temperature were produced from solutions electrolyzed in a Varian E-3 electrochemical cell under oxygen-free nitrogen. At low temperatures, radicals were electrolytically generated in an esr vacuum cell designed by Holz[39] and modified by Rieke and Rich.[40] The cell was degassed by five freeze–pump–thaw cycles before sealing and could maintain a vacuum of at least 10^{-3} Torr for the duration of the experiment. A silver bead reference electrode was used in the cell.

Standard three-electrode operational amplifier circuitry was used. All electrical measurements are *vs.* the saturated sodium chloride colomel reference electrode (SSCE) and are uncorrected for junction potentials. The cell design and instrumentation have been described previously.[37] In a typical experiment, solutions containing 1×10^{-3} *M* 1a and 0.1 *M* TBAH were studied electrochemically at a platinum electrode in any oxygen-free nitrogen atmosphere.

The apparatus for flash spectroscopic studies has been described[2] previously. Samples for flash photolysis were 1×10^{-4} *M* and were degassed by five freeze–pump–thaw cycles.

Zinc reductions were carried out under vacuum by exposing a 1×10^{-3} *M* solution of 1a to a freshly distilled zinc mirror.

Registry No.—*trans*-1b (tetrafluoroborate), 34247-36-4; 1,2-bis(4-pyridyl)ethylene diethyl iodide radical cation, 34195-73-8.

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The Mechanism of Nucleophilic Substitution of *N*-Methyl-4-Substituted Pyridinium Salts[1]

MARION H. O'LEARY* AND ROBERT W. STACH

Department of Chemistry, University of Wisconsin, Madison, Wisconsin 53706

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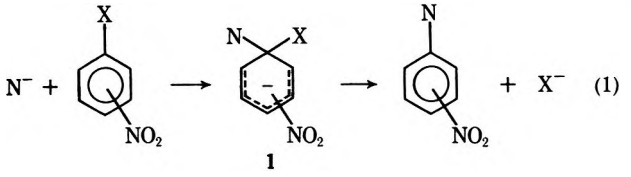
Rates and activation parameters have been determined for the reaction of sodium hydroxide in aqueous solution with *N*-methyl-4-halopyridinium salts and *N*-methyl-4-methoxypyridinium fluoroborate. The results obtained indicate that the mechanism is similar to the mechanism of nucleophilic displacement which occurs with halogenated nitrobenzenes.

Nucleophilic aromatic substitution of halogenated nitrobenzenes is a well-understood process.[2-9] The reaction occurs by a two-step mechanism (eq 1) and is



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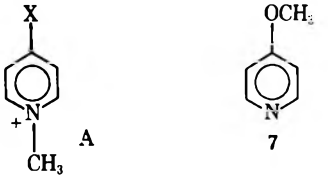
significantly different from nucleophilic substitution at saturated centers in a number of respects. (1) The transition state is characterized by little or no carbon–halogen bond breaking. (2) The reactivity of various halogens is related to their inductive effects, rather than to their bond strengths. (3) The reaction proceeds *via* a Meisenheimer complex intermediate (1).[10]

Nucleophilic displacements in heteroaromatic systems have been studied much less thoroughly than those in the benzene system. *N*-alkyl pyridinium salts undergo nucleophilic displacement much more readily than do the corresponding *N*-oxides, which in turn react more readily than do the corresponding unsubstituted compounds.[11] Meisenheimer-type complexes have been isolated from the reactions of a number of pyridine compounds.[12] However, it is not clear to what extent the mechanism in the pyridine series is like that of the benzene series.

The purpose of the present study was to obtain kinetic data for nucleophilic displacement reactions of compounds 2–7 in order to make comparisons with the



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2, X = F; A = I^-
3, X = Cl; A = I^-
4, X = Br; A = BF_4^-
5, X = I; A = BF_4^-
6, X = OCH_3; A = BF_4^-

corresponding nitro and dinitrobenzene compounds. From these data we hope to determine the extent to which the reaction mechanism in the pyridine series is similar to that in the benzene series.

Results

Rates of reaction of compounds 2–6 with hydroxide ion in aqueous solution at several temperatures are summarized in Table I. All measurements were carried out spectrophotometrically under pseudo-first-

(1) This research was supported by Grant NS 07657 from the National Institutes of Health.
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Table I

Rates of Reaction of 4-Substituted N-Methylpyridinium Salts with Sodium Hydroxide in Water

Compd	Temp, °C	k, M^{-1} sec^{-1} ($\times 10^4$)[a]
2	40.2	77,400
	30.0	36,100
	20.5	18,100
	15.2	11,500
3	40.0	376
	30.0	150
	20.1	60.2
	10.0	19.8
4	39.0	284
	30.0	131
	20.1	48.6
	10.0	16.2
5	45.9	217
	37.6	100
	30.0	52.9
	18.0	16.4
6	40.7	57.0
	30.0	20.0
	20.0	7.59
	10.0	2.34

[a] Rate constants are the average of three runs at constant ionic strength.

order conditions at ionic strength 0.1. The concentration of pyridinium salt was about 10^{-5} M. Each reported rate constant is a composite of three measurements made over a twofold range of hydroxide concentrations. The kinetic data were fitted to the usual first-order rate law using the nonlinear least-squares program of Taylor and Williams.[13] All reactions followed good second-order kinetics, first order in hydroxide and first order in pyridine.

The rate of hydrolysis of **6** is very sensitive to ionic strength. Increasing the ionic strength from 0.076 to 0.15 resulted in a decrease in the observed second-order rate constant from 7.82 M^{-1} sec^{-1} to 7.23 M^{-1} sec^{-1}. For this reason all kinetic measurements were made at constant ionic strength.

Beak, Bonham, and Lee[14] have shown that under certain conditions **6** is susceptible to nucleophilic attack on a methyl group, forming either 4-methoxypyridine or *N*-methyl-4-pyridone. We thus deemed it essential to determine whether reaction of this compound with hydroxide occurs on the ring or on the methyl group. The hydrolysis was carried out at 70° for 4 hr in aqueous 0.1 M sodium hydroxide containing 23 atom % ^{18}O. The product *N*-methyl-4-pyridone was isolated and analyzed by mass spectrometry. It contained 23 atom % ^{18}O. Thus displacement occurs primarily on the ring, although we cannot exclude the possibility of a small amount of displacement on the methyl group.

The rate constants in Table I were used to calculate the activation parameters shown in Table II. In all cases an excellent fit to the usual equation was obtained by the method of least squares.[15]

Several attempts were made to measure the rate of reaction of 4-methoxypyridine (**7**) with hydroxide ion in water. However, no reaction was observed in 43 days at 25°. Assuming that we might have missed 1% reaction, an upper limit of 1.2×10^{-8} M^{-1} sec^{-1} can be placed on the rate constant.

Table II

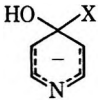
Activation Parameters for 4-Substituted N-Methylpyridinium Salts[a]

Compd	ΔH^*, kcal/mol	ΔS^*, cal/deg mol
2	13.0	−13.0
3	16.6	−12.1
4	16.8	−11.8
5	16.4	−15.0
6	17.7	−12.6

[a] Calculated using a standard least-squares method from rate constants at four different temperatures.

Discussion

4-Methoxypyridine and 4-chloropyridine are extremely unreactive toward nucleophilic displacement. The aza function in **8**, the anticipated intermediate,



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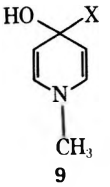
is ineffective in supporting a negative charge, and reaction occurs only very slowly. On the other hand, 4-substituted *N*-methylpyridines are quite reactive, being similar in reactivity to substituted 2,4-dinitrobenzenes, and more than a millionfold more reactive than 4-substituted pyridines. The intermediate which is presumably formed in this case, **9**, is sufficiently stable



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that numerous examples of this structure are known.[16] The high sensitivity of the hydrolysis reaction to ionic strength is consistent with the occurrence of intermediate **9**, although a similar dependence on ionic strength would be expected if **9** were a transition state, rather than an intermediate.

The variation in hydrolysis rate of 4-substituted *N*-methylpyridinium salts with the nature of the leaving group is similar to that encountered in the benzene series[17-19]—the fluoro compound is the most reactive by more than two orders of magnitude, and methoxide is about as good a leaving group as iodide. However, the rate variation is quite unlike that encountered in concerted displacements. The similarity between the pyridine series and the benzene series is striking. In Figure 1 are plotted rate constants for the reaction of the various pyridine compound with hydroxide *vs.* the rate constants for the reaction of the corresponding dinitrobenzene compounds with methoxide. The ex-

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cellent straight line which is obtained is further evidence that aromatic nucleophilic substitution in N-substituted pyridines occurs by a mechanism very similar to that of the substituted nitrobenzenes.

The entropies of activation for compounds 2–6 show no significant trend. Only the iodo compound differs appreciably from the others. The larger $\Delta S^{\pm}$ in this case is presumably a result of van der Waals repulsion between the bulky iodine and the nucleophile. Significantly, the entropies of activation are more than 15 eu more positive than those observed in the benzene series, presumably because the transition state in the pyridine series is much less polar than the ground state, and is therefore less solvated. Except for the iodo compound, the rates of reaction of the substituted pyridines with hydroxide closely parallel the activation enthalpies.

We conclude that the mechanism of nucleophilic displacement in 4-substituted *N*-methylpyridinium salts is strikingly similar to the mechanism of nucleophilic displacement of halonitrobenzenes.

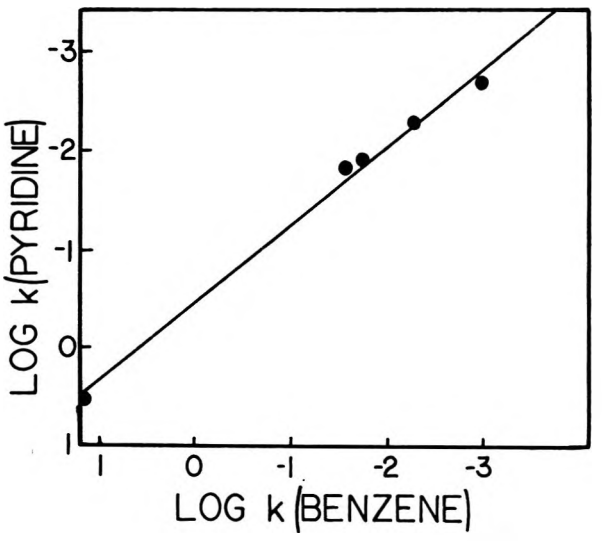

Figure 1.—Rates of reaction of 4-substituted *N*-methylpyridinium salts with hydroxide in water at 30° *vs.* rates of reactions of 1-substituted 2,4-dinitrobenzenes with methoxide in methanol at 25° (data from ref 17–19).

Experimental Section

All melting points are uncorrected. All compounds gave satisfactory elemental analyses and had nmr, ir, and uv spectra consistent with the assigned structures.

Materials.—4-Methoxypyridine and 4-chloro-*N*-methylpyridinium iodide were prepared by standard methods.[20,21]

4-Methoxy-*N*-methylpyridinium tetrafluoroborate was prepared in a manner similar to that of Beak and Bonham.[22] 4-Methoxypyridine (7.9 g) was dissolved in 150 ml of ethylene chloride, and 12.3 g of $AgNO_3$ and 40 ml of CH_3I were added. The mixture was stirred at room temperature overnight. The yellow product was recrystallized from methanol–acetone–ether, yield 10.9 g (60%), mp 141.5–142.5°. *Anal.* Calcd: C, 33.45; H, 4.01; N, 5.58; I, 50.54. Found: C, 33.50; H, 4.01; N, 5.70; I, 50.83. The tetrafluoroborate salt was prepared by mixing equimolar amounts of 4-methoxy-*N*-methylpyridinium iodide and $AgBF_4$ in CH_3OH; the white solid obtained was recrystallized from acetone–ether, mp 56–57° (lit. mp 56–58). *Anal.* Calcd: C, 39.85; H, 4.78; N, 6.64. Found: C, 39.90; H, 4.77; N, 6.80.

4-Bromo-*N*-methylpyridinium tetrafluoroborate was prepared by a method similar to that used by Berson, *et al.*[23] 4-Bromopyridine (prepared by neutralizing 10 g of the hydrochloride with Na_2CO_3 in ether with 1% H_2O and drying with $MgSO_4$) was treated with CH_3I (24 ml) in the presence of $AgBF_4$ (10 g) at 0° for 18 hr in the dark. The product was precipitated with ether and recrystallized twice from methanol–ether, yield 6.5 g (63.2%), mp 110.5–111.5°. *Anal.* Calcd: C, 27.73; H, 2.72; N, 5.39; Br, 30.75. Found: C, 27.61; H, 2.70; N, 5.41; Br, 30.57.

4-Fluoro-*N*-methylpyridinium iodide was prepared by a method similar to that used by Finger.[24] 4-Chloro-*N*-methylpyridinium iodide (2.56 g) was treated with dry KF (2 g) in DMF at 55° for 14 hr. The product was precipitated by addition of ether and recrystallized from DMF–ether and then from methanol–acetone–ether, yield 2.3 g (96.2%), mp 181–182°. *Anal.* Calcd: C, 30.15; H, 2.95; N, 5.86. Found: C, 29.99; H, 2.91; N, 5.79.

4-Iodo-*N*-methylpyridinium tetrafluoroborate was prepared by a method similar to that used by Finger.[24] 4-Bromo-*N*-methylpyridinium tetrafluoroborate (2.0 g) was treated with dry NaI (14 g) in dimethyl sulfoxide at 130° for 3 hr. The product, 4-iodo-*N*-methylpyridinium iodide, was precipitated by addition of ether. The tetrafluoroborate salt was prepared by treatment of the iodide with 1 equiv of $AgBF_4$ in aqueous solution. After removal of water, the product was recrystallized from acetone–ether, yielding 1.87 g (70%), mp 151.5–153.5°. *Anal.* Calcd: C, 23.49; H, 2.30; N, 4.56. Found: C, 23.71; H, 2.34; N, 4.53.

All other materials were reagent grade. Water was deionized and then twice distilled in an aged all-glass apparatus.

Kinetics.—Kinetic measurements were made by observing the increase in absoprtion at 259–265 nm of *N*-methyl-4-pyridone on a Gilford Model 222 recording spectrophotometer. For the 20 and 10° runs of 6, and for the 10° runs of 3 and 4, the kinetics were followed by taking aliquots from a 100-ml volumetric flask containing the standard hydroxide solution and approximately 10^{-5} *M* of the appropriate pyridinium salt, and quenching with 1 ml of 2 *M* acetic acid. Kinetics at all other temperatures were conducted in a Teflon stoppered 3-ml uv cell. Infinity points were taken after 10 half-lives. $NaClO_4$ was used to maintain constant ionic strength. The temperature control was ±0.05°. The uv spectrum of the product was always identical with that of *N*-methyl-4-pyridone.

Isotopic Experiments.—4-Methoxy-*N*-methylpyridinium tetrafluoroborate was treated with potassium hydroxide in water containing 23 atom % ^{18}O at 70° for 4 hr. Water was removed by lyophilization, a small amount of 0.1 *M* HCl was added, and the product was dissolved in $CHCl_3$. The mass spectrum taken after evaporation of the solvent was identical with that of *N*-methyl-4-pyridone except for the presence of a peak at *m/e* 111 corresponding to *N*-methyl-4-pyridone-^{18}O and a small amount of *N*-methyl-4-pyridone-d_2.

Registry No.—2, 34236-36-7; 3, 15592-05-9; 4, 34268-13-8; 5, 34268-14-9; 6, 2701-45-3; sodium hydroxide, 1310-73-2; 4-methoxy-*N*-methylpyridinium iodide, 21823-37-0.

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Mechanism of Bimolecular Nucleophilic Substitution in β-Halo Ketones and Related Compounds

EDWARD N. TRACHTENBERG* AND THOMAS J. WHALL[1]

Jeppson Laboratory, Clark University, Worcester, Massachusetts 01610

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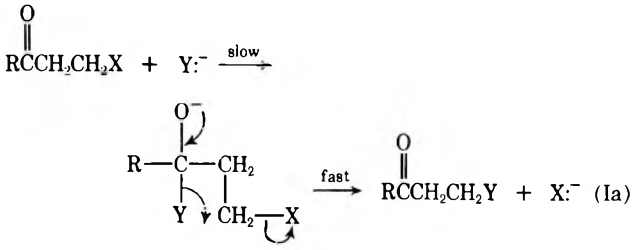
The rates of reaction of 4-chloro-3,3-difluorobutanone-2 (1) and of 1-chloro-2,2-difluoropropane (2) toward sodium iodide in anhydrous acetone have been measured and compared to literature values for 4-chlorobutanone-2 (3) and *n*-propyl chloride (4). The relative rates, calculated for 75°, for 1:2:3:4 are $0.10:6.3 \times 10^{-5}:6.4:1.00$. The much higher reactivity of 1 compared to 2 is due to a 10 kcal/mol more favorable $\Delta H^{\ddagger}$ counteracted by an unfavorable $\Delta S^{\ddagger}$. These results serve to eliminate a number of mechanistic hypotheses including one involving dehydrochlorination of the β-halo ketone followed by Michael addition of the elements of hydriodic acid. In agreement with this finding, α,α-dideuterio-β-chloropropiophenone undergoes bimolecular nucleophilic displacement without deuterium–hydrogen exchange, but ω-trimethylammoniumpropiophenone iodide exchanges one α hydrogen when treated with thiophenol-d_1 in methanol-d_1, indicating that it follows the elimination–addition pathway.

In the same papers on the reactivity of organic chlorides toward iodide ion in acetone in which he reported on the exceptional reactivity of phenacyl chloride, Conant also showed that β-chloropropiophenone exhibits enhanced reactivity.[2] More recent work has served to correct the rate constant assigned to the reference compound, *n*-butyl chloride,[3] but this does not alter the fact that β-halo ketones, although considerably less activated toward nucleophilic displacement than are the α-halo ketones, show significantly heightened reactivity comparable to that of allyl chloride. No satisfactory explanation for this marked reactivity has been advanced. It is clear that the activation provided by the carbonyl is not merely due to its inductive electron withdrawal. Hughes had suggested as an explanation for the exceptional reactivity of α-halo ketones the facilitation of approach of a negatively charged nucleophile toward a carbon made more positive by the strong inductive withdrawal of the adjacent carbonyl.[4] However, studies of 1,2-dihalides,[5] β-halo ethers,[6] and β-halo thioethers[3] all showed that inductive electron withdrawal leads to rate retardation. On theoretical grounds, one would not expect β-halo ketones to undergo SN1 reaction, since the halide is frequently on a primary carbon, the reactions are often run in relatively nonpolar media, and the presence of the carbonyl function β to the reaction site should increase the energy required for carbonium ion formation leading to depressed, rather than enhanced, reactivity compared to that of simple alkyl halides. In agreement with these expectations, displacements in β-halo ketones show second-order kinetics, first order in organic substrate and first order in nucleophile.[2,3] Also untenable on theoretical grounds is the proposal by Sneen and Larsen that there is a single mechanism of unimolecular and bimolecular nucleophilic substitution in which all displacements at a saturated carbon are described as occurring *via* a reversibly formed ion pair.[7] The central feature of this hypothetical, unifying mechanism requires the intermediacy of a configurationally stable ion pair, whose formation is rate determining at the first-order end of the mechanistic spectrum and whose destruction by nucleophilic attack is rate-determining at the second-order extreme. "Borderline" behavior is presumed to result when the rates of formation and destruction of the intermediate are competitive. Although ion pairs may play important roles in certain solvolyses, they would appear to be highly unlikely intermediates in the case of α- and β-halo ketones. As pointed out above, many of these systems involve primary halides and, since the reactions are clearly second order, the Sneen–Larsen mechanism requires that the generation of ion pairs involving primary carbonium ions further destabilized by the electron-withdrawing effect of an α- or β-carbonyl be rapid and that bimolecular attack on such destabilized ion pairs be rate determining.

There are a number of mechanistic hypotheses which are consistent with the known experimental facts and which could provide an explanation for the enhanced rate of nucleophilic displacement in β-halo ketones.



The fact that alkyl halides β substituted with electron-withdrawing halo, alkoxyl, or mercaptyl groups show depressed reactivity toward nucleophiles whereas β-halocarbonyl compounds are highly reactive suggests that it is the electrophilic character of the carbonyl group, rather than its inductive electron withdrawal, which increases reactivity. A mechanism analogous to Ia was suggested by Baker[8] to explain the enhanced reactivity of α-halo ketones. It is untenable in that case because it is inconsistent with the observation that bromide is displaced much more rapidly than chloride,[9] which suggests that carbon–halogen bond breaking is involved in the rate-determining process. However,

(1) Taken from the Ph.D. dissertation of T. J. W., Clark University, 1970.

(2) (a) J. B. Conant and W. R. Kirner, *J. Amer. Chem. Soc.* **46**, 232 (1924); (b) J. B. Conant and R. E. Hussey, *ibid.*, **47**, 476 (1925); (c) J. B. Conant, W. R. Kirner, and R. E. Hussey, *ibid.*, **47**, 488 (1925).

(3) F. G. Bordwell and W. T. Brannen, Jr., *ibid.*, **86**, 4645 (1964).

(4) (a) E. D. Hughes, *Trans. Faraday Soc.*, **37** (2), 603 (1941); (b) E. D. Hughes, *Quart. Rev., Chem. Soc.*, **5**, 245 (1951).

(5) J. Hine and W. H. Brader, *J. Amer. Chem. Soc.*, **75**, 3964 (1953).

(6) F. B. Tutwiler and R. L. McKee, *ibid.*, **76**, 6342 (1954).

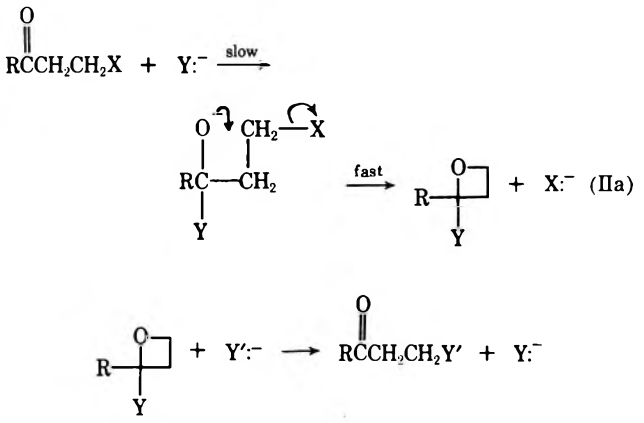
(7) (a) R. A. Sneen and J. W. Larsen, *ibid.*, **91**, 362 (1969); (b) R. A. Sneen and J. W. Larsen, *ibid.*, **91**, 6031 (1969).

(8) J. W. Baker, *Trans. Faraday Soc.*, **37**, 632 (1941).

(9) (a) H. T. Clarke, *J. Chem. Soc.*, **97**, 416 (1910); (b) R. G. Pearson, S. H. Langer, F. V. Williams, and W. J. McGuire, *J. Amer. Chem. Soc.*, **74**, 5130 (1952).

no such evidence exists with respect to β-halo ketones, and their enhanced reactivity could stem from the fact that in this mechanism the nucleophile adds to a polarized π-electron system rather than being required to break a σ bond in the rate-determining process.

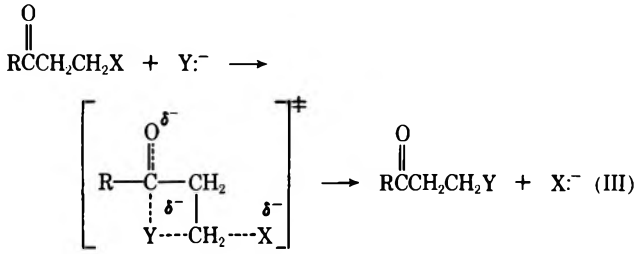
A variant of mechanism Ia in which the first step is rapid and reversible and the second rate determining (mechanism Ib) would also be in agreement with the observed second-order kinetics. It could explain the enhanced reactivity as resulting from more effective juxtaposition of the nucleophile back side to the β-carbon–halogen bond through its initial complexation to the carbonyl. If this is so, the rate enhancement should be manifested in the entropy of activation. Indeed, this would have to override a highly unfavorable enthalpy of activation term arising from several factors. The nucleophile should lose some of its activity because it is already complexed to the carbonyl, the carbon–halogen bond should for inductive effect reasons be less labile than in simple alkyl halides, and the necessity for closure to a sterically strained four-membered ring should all serve to increase the enthalpy of activation of the rate-determining step.



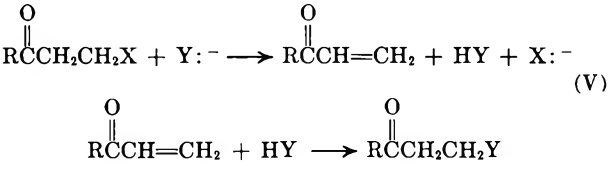
The proposal above (mechanism IIa) has the same rate-determining step as mechanism Ia but differs in that the nucleophilic species which is eventually incorporated in the product need not be the same as that which adds to carbonyl in the first step. Making use of this distinction, Pearson[9b] has shown it to be inoperative in the case of α-halo ketones, but it offers a feasible explanation for β-halo ketone reactivity, identical to that discussed for mechanism Ia.

Again in complete analogy to the relation between mechanisms Ia and Ib, there is that variant of mechanism IIa in which the second step is rate determining and which leads to the prediction that rate enhancement is due to a dominant favorable entropy of activation (mechanism IIb).

The proposal below (mechanism III) is in analogy to the mechanism proposed by Bartlett and Trachtenberg to explain the exceptional reactivity of α-halo ketones in nucleophilic displacement reactions.[10] In this mechanism, bond making is proposed to lead over bond breaking with the extra electron density of the nucleophile being accommodated on carbonyl carbon or alternatively with the carbonyl carbon acting as a Lewis acid to facilitate release of the β-halide.



Another possibility is that the enhanced reactivity stems from the dipole moment of the carbonyl helping the approach of the nucleophile (mechanism IV). This had been suggested by Pearson[9b] as an explanation for α-halo ketone reactivity, but it has been disputed by Bartlett and Trachtenberg[10] and by Sisti and Lowell.[11]



The above elimination–addition (mechanism V) has been proposed as the major pathway for reaction with nucleophiles of Mannich bases and Mannich–Robinson intermediates, *i.e.*, the cases where X is dialkylamine and trialkylammonium, respectively.[12] In general support of this suggestion is the observation that ω-dimethylaminoisobutyrophenone undergoes racemization during substitution reactions under conditions where the α carbon is not racemized through enolization.[13] Winstein's observation that tosylates undergo considerable elimination when treated with halide ion in acetone,[14] essentially Conant's conditions,[2] also lends support to this possibility. The fact that α,α-dialkylated Mannich bases do not undergo alkylation with active methylene compounds had been offered as evidence in favor of the elimination–addition mechanism. However, the fallacy in this argument has been pointed out.[15] Such compounds are for steric and/or electronic reasons incapable of reacting rapidly by any of the mechanisms under consideration.

With the exception of mechanism V, which would not even be possible in the case of chloromethyl ketones, the other working hypotheses are based on analogies to mechanisms proposed to explain α-halo ketone reactivity. However, Bordwell and Brannen have suggested that the "mild activating effect of the β-C_6H_5CO group . . . would appear to be different in type from that of the α-C_6H_5CO group . . ."[3] This would imply that α- and β-halo ketones do not react by analogous mechanisms. Their suggestion is based on admittedly small effects, but they do assert that electron-withdrawing groups cause rate retardation in ω-chloropropiophenone but rate acceleration in ω-chloroacetophenone. The effect in the latter is probably correct, since Baker's data[8] on the reaction of ω-bromoacetophenone with pyridine in dry acetone leads to a Hammett ρ of +0.56 ± 0.09, although Bordwell and Brannen's data sur-

(10) P. D. Bartlett and E. N. Trachtenberg, *J. Amer. Chem. Soc.*, **80**, 5808 (1958).

(11) A. J. Sisti and S. Lowell, *Can. J. Chem.*, **42**, 1896 (1964).

(12) (a) E. D. du Feu, F. J. McQuillin, and R. Robinson, *J. Chem. Soc.*, 53 (1937); (b) F. F. Blicke in "Organic Reactions," Vol. I, Wiley, New York, N. Y., 1942, pp 320, 321; (c) H. Hellmann and G. Opitz, "Alpha-Aminoalkylierung," Verlag Chemie, Weinheim/Bergstr., Germany, 1963, p 12.

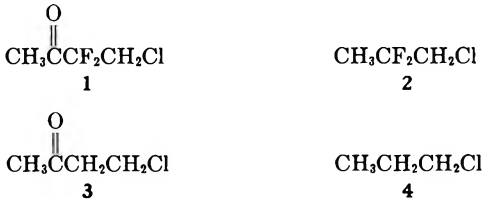
(13) A. F. Casey and J. L. Myers, *J. Chem. Soc.*, 4639 (1964).

(14) (a) A. J. Parker, M. Ruane, G. Beale, and S. Winstein, *Tetrahedron Lett.*, 2113 (1969), and references cited therein; (b) S. Winstein, D. Darwish, and N. J. Holness, *J. Amer. Chem. Soc.*, **78**, 2915 (1956).

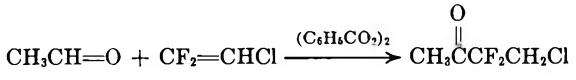
(15) H. R. Snyder and J. H. Brewster, *J. Amer. Chem. Soc.*, **71**, 1061 (1949).

prisingly show that the *p*-methoxy group also slightly enhances the rate of reaction of ω-chloroacetophenone with potassium iodide in acetone. Their results on the ω-chloropropiophenone system are dubious. Despite the fact that they studied only para substituents and should, therefore, have avoided random entropy of activation effects, their data indicate otherwise. Rather than showing a negative ρ, a least-squares plot of their data against Hammett σ constants yields a ρ value of $+0.39 \pm 0.52$, an obviously meaningless result.

In order to elucidate the mechanism of nucleophilic substitution in β-halo ketones, the rates of reaction with iodide ion in acetone of 4-chloro-3,3-difluorobutanone-2 (**1**) and of 1-chloro-2,2-difluoropropane (**2**) were measured and compared to previously determined values for their respective unfluorinated analogs, 4-chlorobutanone-2 (**3**)[3] and *n*-propyl chloride (**4**).[2]

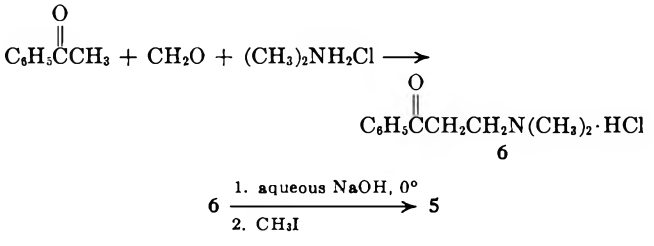


Compound **1** was synthesized by the free radical induced addition of acetaldehyde to 2-chloro-1,1-difluoroethylene.



Compound **2** was commercially available, and its chemical and physical properties agree with literature values.

Also studied was the reaction of β-trimethylammoniumpropiophenone iodide (**5**) with thiophenol-d_1 in methanol-d_1. Thiophenol reacts with **5** at a conveniently measurable rate whereas iodide ion does not. Furthermore, thiophenol combines the property of being a very good nucleophile without being very basic.[16] It thus makes less likely the elimination of trimethylamine from **5** to generate acrylophenone. Compound **5** was synthesized in straightforward manner by methylation of ω-dimethylaminopropiophenone (**6**), itself formed by a Mannich reaction.



Results and Conclusions

The reaction of 4-chloro-3,3-difluorobutanone-2 (**1**) with sodium iodide in anhydrous acetone proceeded cleanly to yield 4-iodo-3,3-difluorobutanone-2 (**7**). The structure of **1** followed from its method of synthesis, elemental analysis, high carbonyl stretching frequency (1750 cm^{-1}) commonly observed for α-fluorinated ketones,[17] and proton nmr spectrum. Although the synthesis involving free-radical addition of acetaldehyde to 1,1-difluoro-2-chloroethylene can go in the opposite sense to yield 3-chloro-4,4-difluorobutanone-2, such product would have given a more complex nmr than the one observed. The nmr of **1** showed a triplet at δ 3.85 due to the β CH_2 coupled to the α,α-difluoro group. The signal from the methyl group at δ 2.40 was also split into a triplet (J = 2 Hz) due to long range spin–spin interaction with the α,α-difluoro group.[18] The structure of **7** followed from its elemental analysis and the fact that its carbonyl stretching frequency and proton nmr splitting patterns were similar to those of **1**.

The conversion of 1-chloro-2,2-difluoropropane to 1-iodo-2,2-difluoropropane also proceeded smoothly. The assigned structures followed from their elemental analyses and ir and proton nmr spectra.

A summary of the kinetic results obtained for the reaction of 4-chloro-3,3-difluorobutanone-2 (**1**) and 1-chloro-2,2-difluoropropane (**2**) with sodium iodide in anhydrous acetone is contained in Table I.

The activation parameters are in Table II and rates relative to the unfluorinated analogs, 4-chlorobutanone-2 (**3**) and *n*-propyl chloride (**4**), are in Table III.

TABLE I

Compd	Temp, °C	Number of runs	$k \times 10^5$, l. mol^{-1} sec^{-1}
1	148.90	19	190.0 ± 4.5
1	158.90	23	313.3 ± 5.0
2	148.90	29	1.555 ± 0.033
2	158.90	24	3.400 ± 0.078

TABLE II

Compd	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, cal/deg mol
1	17.3 ± 0.3	−30.7 ± 1.0
2	27.5 ± 0.6	−16.0 ± 2.0

TABLE III

Compd	Relative rates of reaction with NaI in acetone at 75°
1	1.024×10^{-1}
2	6.29×10^{-5}
3	6.36[a]
4	1.00[b]

[a] Calculated from data in ref 3. [b] Calculated from data in ref 2.

The fact that **3** is some 60-fold more reactive than **1** serves to rule out mechanisms Ia and IIa, both of which require rate-determining addition of the nucleophile to the carbonyl carbon and both of which, therefore, predict higher reactivity for **1** whose carbonyl is made more electrophilic by the two α-fluorines. Also ruled out are mechanisms Ib and IIb, since, as pointed out before, they predict that the rate-enhancing effect of the carbonyl should be due to a highly favorable $\Delta S^{\ddagger}$ dominating over an unfavorable $\Delta H^{\ddagger}$. The data in Table II show that just the opposite is true.

The experimental results can be accommodated by mechanism III, which requires in its four-membered

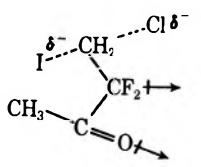
(16) U. Belluco, L. Cattalini, F. Basolo, R. G. Pearson, and A. Turco, *J. Amer. Chem. Soc.*, **87**, 241 (1965).

(17) J. K. Brown and K. J. Morgan in "Advances in Fluorine Chemistry," Vol. 4, Butterworths, Washington, D. C., 1965, p 284, and references cited therein.

(18) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1955, p 86.

ring transition state that nucleophilic addition to the carbonyl and bond breaking of the β-carbon–halogen bond both occur within the rate-determining process. Previous work has shown that β-fluorinated alkyl halides and tosylates react with iodide ion in acetone at a rate some four powers of ten slower than for the corresponding unfluorinated analog.[19] The results here reported for **2** and **4** support this. By contrast, fluorination of the analogous position in a β-halo ketone only leads to a 60-fold rate retardation or, to put it another way, the presence of the carbonyl leads to a compensating accelerating factor of between 10^2 and 10^3. This is readily explicable if carbonyl addition by the nucleophile is required. Evidence of the enhanced electrophilic character of a carbonyl group when α fluorinated comes from studies of hydration of aldehydes and ketones,[20] carboxylic acid acidity,[21] and the extent of addition of alkoxide to esters.[22] The fact that **1** has a $\Delta H^{\pm}$ about 10 kcal more favorable than **2** but that much of this advantage is lost through an unfavorable $\Delta S^{\pm}$ difference of about 15 eu is in striking similarity to the results found in support of mechanism III in the case of the α-halo ketones.[10]

Mechanism IV attributes carbonyl activation to a favorable dipole interaction with the attacking nucleophile. According to this mechanism, the transition state for reaction of **1** should be represented by **8** or **9** or by some intermediate conformation. The presence of the fluorines in **8** is clearly unfavorable compared to



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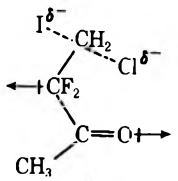

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the analogous transition state from **3**, since one is forced to align the CF_2 and the C=O dipoles. This destabilizing influence should more than outweigh the extra benefit afforded the approach of the nucleophile. In **9**, the bad alignment of dipoles is avoided but then the approach of the nucleophile is hindered by the CF_2 dipole. One, therefore, predicts and finds that **1** is slower than **3**. A difficulty with this hypothesis shows up when one examines the conformation of the transition states for **2** and **4**. The dipole of the CF_2 group in **2** should be at least comparable to that of the carbonyl and **2** can assume a conformation favorable for the approach of the nucleophile without alignment of its dipole with that of an adjacent carbonyl. Notwithstanding this favorable situation, **2** is over 10^4 slower than **4** whereas the factor is only 60 for **1** *vs.* **3**. A further difficulty with mechanism IV is that it fails to provide an explanation for the observed difference in $\Delta S^{\pm}$ between **1** and **2**.

Finally, the fact that **1** is 1600 times faster than **2** whereas **3** is only six times faster than **4** clearly disposes of mechanism V. This follows from the fact that the carbonyl activating influence is much larger in the fluorinated substrate and yet it is unable to undergo the elimination step required by mechanism V.

Further evidence against mechanism V was obtained when α,α-dideuterio-β-chloropropiophenone (**10**) was treated with iodide ion in *tert*-butyl alcohol–acetone to yield α,α-dideuterio-β-iodopropiophenone (**11**). No hydrogen–deuterium exchange at the α position was observed. Compound **10** was synthesized by acid-catalyzed deuterium–hydrogen exchange on β-chloropropiophenone, itself made by Friedel–Crafts acylation of benzene with β-chloropropionyl chloride. The nmr spectrum of **10** established that the position α to the carbonyl was fully deuterated. There was a broadened singlet at δ 3.90 due to the chloromethylene group.[23] Because the coupling constant between deuterium atoms and protons on adjacent carbons is very small (0–2 Hz),[24] the observed singlet was to be expected only if deuterium exchange α to the carbonyl was complete. Had it only been partial, a more complex proton nmr spectrum such as that for β-chloropropiophenone with a triplet at δ 3.90 (CH_2Cl) and a triplet at δ 3.50 (CH_2CO) would have been observed. The absence of deuterium–hydrogen exchange during reaction of **10** with iodide ion in a protonic solvent followed from the fact that **11** also gave a singlet at δ 3.45 due to the CH_2I rather than the more complex pattern expected from coupling with any available protons on an adjacent carbon. Thus β-chloropropiophenone, although fully capable of dehydrohalogenating, does not do so under these conditions for nucleophilic displacement. However, ω-trimethylammoniumpropiophenone iodide (**5**) does eliminate when treated with thiophenol-d_1 in methanol-d_1. Both **5** and ω-dimethylaminopropiophenone hydrochloride (**6**) failed to react with iodide ion to give ω-iodopropiophenone even when refluxed in acetonitrile or methanol for extended periods. Nor did **6** react in refluxing acetone, a solvent in which **5** was not soluble enough to test reactivity. The only products formed other than by replacing the ionic chlorides in **5** and **6** by iodide were acrylophenone and ω-methoxypropiophenone, and these only formed in very low yield (≤8%). On the other hand, **5** reacted quantitatively with thiophenol in methanol to give β-phenylthiopropiophenone (**12**). When this reaction was investigated with thiophenol-d_1 in methanol-d_1, the product **12** was found by mass spectroscopic analysis to be 94% monodeuterated at the α carbon. Thus in the case of this Mannich–Robinson intermediate, the elimination–addition pathway is favored. It is not clear whether this shift in mechanism is brought about because of enhanced acidity of the α hydrogens in the Mannich–Robinson intermediate or because the steric requirements of the trialkylamine group destabilize the transition state for displacement more seriously than for elimination.

Experimental Section

Infrared spectra were taken on samples in potassium bromide, Nujol, or carbon tetrachloride, or neat as film on sodium chloride plates with a Perkin-Elmer Model 137 double-beam spectrophotometer.

(19) E. T. McBee, R. D. Battershell, and H. P. Braendlin, *J. Amer. Chem. Soc.*, **84**, 3157 (1962), and references cited therein.

(20) H. P. Braendlin and E. T. McBee in "Advances in Fluorine Chemistry," Vol. 4, Butterworths, Washington, D. C., 1965, pp 1–18, and references cited therein.

(21) J. E. Dippy, *Chem. Rev.*, **25**, 151 (1939).

(22) M. L. Bender, *J. Amer. Chem. Soc.*, **75**, 5986 (1953).

(23) R. N. Bible, "Interpretation of NMR Spectra," Plenum Press, New York, N. Y., 1965, p 16, and references cited therein.

(24) Reference 23, p 61.

Nuclear magnetic resonance spectra were measured on a Jeolco JNM-C-60H spectrometer on samples dissolved in deuteriochloroform containing tetramethylsilane (TMS) as internal standard and are reported in δ units in parts per million from TMS.

Refractive indices were measured with a Bausch and Lomb Abbe 3-L refractometer. Melting points were determined in soft glass capillaries on a Thomas-Hoover apparatus and are corrected. Microanalyses were performed by M-H-W Laboratories, Garden City, Mich., or Spang Microanalytical Laboratory, Ann Arbor, Mich.

Thin layer chromatography was done with silica gel H (Brinkmann) or "Silac AR" 7G (Mallinckrodt) as the solid support and iodine vapor development. Glpc analyses and separations were performed on a Wilkens Aerograph Model A-700 Autoprep equipped with a thermal conductivity detector unit with helium gas as carrier. The column was $^3/_8$ in. $\times$ 10 ft stainless steel containing 20% silicone (Fluoro) QF-1 (Varian Aerograph) coated on 60/80 mesh, acid washed and DMCS (dimethyldichlorosilane) treated Chromosorb W (diatomaceous earth, manufactured by Johns-Manville).

4-Chloro-3,3-difluorobutanone-2 (1).—The free radical addition of acetaldehyde to 2-chloro-1,1-difluoroethylene was carried out according to a modification of the procedure of Muramatsu and Inukai.[25] To a Carius tube cooled in an ethylene glycol monoethyl ether–Dry Ice bath were added 18.5 g (0.189 mol) of Pierce 2-chloro-1,1-difluoroethylene, 14.0 g (0.318 mol) of freshly distilled acetaldehyde, and 3.0 g (0.012 mol) of recrystallized dibenzoyl peroxide. The tube was sealed and the mixture was agitated at 105–110° for 21 hr. The tube was then cooled to Dry Ice temperature and opened, and unreacted starting material was distilled off under reduced pressure. The residue was taken up in 100 ml of ether and washed with 5% sodium bicarbonate. The ethereal solution was then rotary evaporated and the residue was distilled at atmospheric pressure to yield 4.83 g (18%) of 1, bp 101–102°. Final purification was effected by glpc (75°, retention time 3.3 min): ir, strong carbonyl stretch at 1748 cm^{-1}; nmr δ 3.85 (t, 2, J = 13 Hz, CF_2CH_2Cl) and 2.40 (t, 3, J = 2 Hz, CH_3COCF_2). The 2,4-dinitrophenylhydrazone (95% ethanol) melts at 130–131°.

Anal. Calcd for $C_{10}H_9ClF_2N_4O_4$ (322.69): C, 37.22; H, 2.82. Found: C, 37.40; H, 2.93.

1-Chloro-2,2-difluoropropane (2).—A sample of K and K Laboratories 1-chloro-2,2-difluoropropane was used without further purification: atmospheric bp 55.1° (lit.[26] bp 55.0–55.2°); n^{20}D 1.3520 (lit.[26] n^{20}D 1.3520); nmr δ 3.60 (t, 2, J = 12 Hz, CF_2CH_2Cl) and 1.70 (t, 3, J = 20 Hz, CH_3CF_2). It gave only a single peak on glpc at three different column temperatures (35, 50, 100°) and showed the expected ir spectrum.

Reaction of 4-Chloro-3,3-difluorobutanone-2 (1) with Sodium Iodide in Anhydrous Acetone.—A sample of 0.3453 g (2.423 mmol) of 1 was treated with 1.8854 g (12.569 mmol) of Fisher reagent grade sodium iodide in 5 ml of anhydrous acetone for 3 days at 100° in a sealed combustion tube. The tube was then cooled in Dry Ice and opened. The contents were concentrated under reduced pressure and the organic material in the residue was extracted with anhydrous ether and chloroform. The combined extracts were rotary evaporated and glpc analyzed (75°) to show two peaks. The first (retention time 3.3 min) was unreacted 1 as shown by peak enhancement and the second (retention time 8.4 min) was 4-iodo-3,3-difluorobutanone-2 (7): ir, strong carbonyl stretch at 1748 cm^{-1}; nmr δ 3.50 (t, 2, J = 15 Hz, CF_2CH_2I) and 2.30 (t, 3, J = 2 Hz, CH_3COCF_2). Its 2,4-dinitrophenylhydrazone (95% ethanol) melts at 128–130°.

Anal. Calcd for $C_{10}H_9IF_2N_4O_4$ (414.02): C, 28.99; H, 2.17. Found: C, 28.63; H, 2.26.

Reaction of 1-Chloro-2,2 difluoropropane (2) with Sodium Iodide in Anhydrous Acetone.—A sample of 0.57 g (5.0 mmol) of 2 was treated with 0.3773 g (2.515 mmol) of Fisher reagent grade sodium iodide in 50 ml of anhydrous acetone for 8 days at 160° in a sealed combustion tube. The work-up procedure was essentially identical with that used for reaction of 1 (*vide supra*). Glpc analysis (70°) showed two peaks. The first (retention time 1.4 min) was unreacted 2 as shown by peak enhancement and the second (retention time 2.4 min) was 1-iodo-2,2-difluoropropane. It showed the expected ir and its nmr exhibited absorptions at δ 3.50 (t, 2, J = 14 Hz, CF_2CH_2I) and 1.80 (t, 3, J = 16 Hz, CH_3CF_2).

Anal. Calcd for $C_3H_5F_2I$ (205.96): C, 17.47; H, 2.43. Found: C, 17.30; H, 2.39.

β-Trimethylammoniumpropiophenone Iodide (5).—β-Dimethylaminopropiophenone hydrochloride was prepared in 68% yield by the method of Maxwell.[27] A sample of 64.2 g (0.300 mol) of this compound, mp 153–154° (lit.[27] mp 152–153°), was treated with an ice-cold solution of 15 g (0.375 mol) of sodium hydroxide in 500 ml of water. The solution was ether extracted and the extract was repeatedly washed with water, dried ($MgSO_4$), filtered, and rotary evaporated to yield 49.6 g (93.3%) of β-dimethylaminopropiophenone as a clear, colorless oil, bp 106–108° (10 mm) [lit.[28] bp 106–109° (10 mm)]. Upon standing at 10° for 3 days, this oil crystallized to yield 39.7 g (80%) of β-dimethylaminopropiophenone, mp 29–31° (lit.[29] mp 30–32°), which showed the expected ir and nmr spectra. To a solution of 10.25 g (0.058 mol) of β-dimethylaminopropiophenone in 100 ml of ice-cold 3:1 (v:v) ether–benzene was added 8.45 g (0.060 mol) of methyl iodide. On standing overnight at 10°, product crystallized. It was filtered and recrystallized from methanol to yield 13.9 g (87%) of 5, mp 262.5–264° (sealed capillary) (lit.[30] mp 261–264° dec).

Reaction of β-Trimethylammoniumpropiophenone Iodide (5) with Sodium Iodide.—A solution of 0.4812 g (1.507 mmol) of 5 and 2.1285 g (14.20 mmol) of sodium iodide in 80 ml of methanol was refluxed for 11 days. The solvent was distilled off under reduced pressure and the solid residue was triturated with ether. The only ether-soluble product, obtained by concentration of the ether solution, was β-methoxypropiophenone (0.0164 g, 6.7%). It had the expected ir spectrum and its 2,4-dinitrophenylhydrazone had mp 175–176° (lit.[31] mp 175.5–176.5°).

A solution of 0.2983 g (0.934 mmol) of 5 and 1.5989 g (10.66 mmol) of sodium iodide in 80 ml of acetonitrile was refluxed for 26 days. The solvent was distilled off under reduced pressure and the solid residue was triturated with ether. The ethereal solution was concentrated to yield 0.0094 g (7.63%) of acrylophenone. The ir spectrum of the product was identical with that of authentic sample prepared by dehydrochlorinating β-chloropropiophenone with potassium acetate.

Reaction of β-Dimethylaminopropiophenone Hydrochloride with Sodium or Potassium Iodide.—A solution of 1.63 g (7.63 mmol) of β-dimethylaminopropiophenone hydrochloride and 4.48 g (27.0 mmol) of potassium iodide in 100 ml of methanol was refluxed for 6 days. The solvent was distilled off under reduced pressure and the solid residue was triturated with ether. The only ether-soluble product, obtained by concentration of the ether solution, was β-methoxypropiophenone (0.069 g, 5.5%), identical in all respects with the product obtained from similar treatment of 5.

To a solution of 5.44 g (0.0255 mol) of β-dimethylaminopropiophenone hydrochloride in 160 ml of hot acetonitrile was added 9.60 g (0.064 mol) of sodium iodide in 160 ml of hot acetonitrile. After being refluxed for 15 days, the mixture was filtered to remove 1.437 g (96.4%) of sodium chloride which had precipitated almost immediately. Concentration of the filtrate yielded a water-soluble, white powder which was triturated with ether. The ethereal extracts were rotary evaporated to yield 0.1004 g (3.0%) of acrylophenone, identical in all respects with the material formed by similar treatment of 5.

The white, water-soluble, ether-insoluble product formed both in methanol and in acetonitrile (and also produced under similar treatment in acetone) proved to be β-dimethylaminopropiophenone hydriodide, mp 203–205°. It had the expected ir spectrum.

Anal. Calcd for $C_{11}H_{16}ONI$ (305.25): C, 43.28; H, 5.28. Found: C, 42.98; H, 5.23.

Reaction of β-Trimethylammoniumpropiophenone Iodide (5) with Thiophenol in Methanol.—An anhydrous solution of 0.123 g (0.386 mmol) of 5 in 30 ml of methanol was prepared by gentle warming and magnetic stirring under a nitrogen atmosphere. After solution had been effected, a solution of 0.0844 g (0.766

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mmol) of Eastman thiophenol in 5 ml of methanol was added and the resulting solution was refluxed for 1.5 hr. The methanol was distilled off under reduced pressure and the solid residue was triturated with ether. The ethereal solution was then concentrated to a white residue which on recrystallization from methanol yielded 0.0802 g (85.8%) of β-phenylthiopropiophenone (12), mp 74–75° (lit.[32] mp 75°). Compound 12 showed the expected ir and its 2,4-dinitrophenylhydrazone, prepared by standard techniques and recrystallized from 95% ethanol, had mp 147–148° (lit.[32] mp 147.5°).

Exactly the same results were obtained when the reaction was run in the dark or in the presence of hydroquinone.

Reaction of β-Trimethylammoniumpropiophenone Iodide (5) with Thiophenol-d_1 in Methanol-d_1.—By exactly the same procedure used for nondeuterated substrates (*vide supra*), 0.0612 g (0.191 mmol) of **5** was treated with 0.0425 g (0.382 mmol) of Stohler thiophenol-d_1 (98% D) in 17.5 ml of Stohler methanol-d_1. The product (0.0396 g, 85.2%) was α-deuterio-β-phenylthiopropiophenone, mp 74–75°. It was shown to be 94% monodeuterated by mass spectroscopic analysis.[33]

α,α-Dideuterio-β-chloropropiophenone (10).—β-Chloropropiophenone (6) was synthesized in 61% yield by the method of Conant.[2a] It melted at 49–50° (lit.[2a] mp 49–50°), had the expected ir spectrum, and its nmr showed peaks at δ 7.20–8.18 (AA'BB'C, 5, C_6H_5), 3.9 (t, 2, CH_2Cl), and 3.5 (t, 2, CH_2CO). In a variation of the method of Karabatsos[34] in which acid, rather than base, catalysis was employed, **6** was α,α-dideuterated. To a solution of 0.60 g (3.56 mmol) of **6** in 10 ml of anhydrous ether contained in a pressure bottle was added 10 ml of Bio-Rad 38% deuterium chloride in deuterium oxide. The bottle was sealed and shaken in a Parr apparatus for 22 hr. The organic layer was separated, dried ($MgSO_4$), and concentrated. The entire procedure was then repeated a second time and the resulting solid residue was twice recrystallized from anhydrous ether to yield 0.54 g (89%) of **10**, mp 49–50°, nmr δ 7.2–8.1 (AA'BB'C, 5, C_6H_5) and 3.9 (s, 2, CH_2Cl).

Reaction of β-Chloropropiophenone (6) with Sodium Iodide in Anhydrous Acetone.—To a solution of 1.078 g (7.187 mmol) of sodium iodide in 15 ml of anhydrous acetone was added a solution of 0.145 g (0.862 mmol) of **6** in 10 ml of anhydrous acetone. The solution was refluxed for 4 hr and concentrated under reduced pressure to a solid residue which was triturated with ether. The ethereal solution was then concentrated and the residue was recrystallized from petroleum ether (bp 30–60°) to yield 0.1953 g (0.753 mmol, 87%) of β-iodopropiophenone, mp 61.5–63° (lit.[35] mp 61–62°), ir as expected, nmr δ 7.2–8.1 (AA'BB'C, 5, C_6H_5) and 3.5 (A_2B_2, 4, CH_2CH_2).

Reaction of α,α-Dideuterio-β-chloropropiophenone (10) with Sodium Iodide in Anhydrous Acetone Containing *tert*-Butyl Alcohol.—A solution of 0.107 g (0.63 mmol) of **10** and 0.908 g (6.05 mmol) of sodium iodide in 16.5 ml of anhydrous acetone and 3.5 ml of *tert*-butyl alcohol was refluxed for 60 hr and then worked up as indicated above for the undeuterated substrate **6** to yield 0.124 g of a white, crystalline product, mp 43–50°. The nmr spectrum showed peaks at δ 7.2–8.1 (AA'BB'C, 10, C_6H_5), 3.9 (broadened s, 2, CH_2Cl), and 3.45 (broadened s, 2, CH_2I). This spectrum corresponds to an equimolar mixture of **10** and α,α-dideuterio-β-iodopropiophenone (**11**). A similar mixture of the undeuterated analogs **6** and β-iodopropiophenone showed nmr peaks at δ 7.2–8.2 (AA'BB'C, 10, C_6H_5) and 3.4–4.1 (two overlapping A_2B_2, 8, CH_2CH_2Cl and CH_2CH_2I).

Kinetic Measurements. Reagents.—Reagent-grade Fisher chloroform, Du Pont reagent grade hydrochloric acid, and Fisher Certified Reagent grade potassium iodide, sodium iodide, and potassium iodate were employed. The latter three salts were dried for 24 hr at 110° and cooled in a desiccator. Fisher Certified Reagent grade acetone was purified by refluxing each liter with 25 g of potassium permanganate until the color disappeared, filtering the precipitated manganese dioxide, drying the filtrate over phosphorus pentoxide, and then distilling from the latter.

Thermal Control.—By a combination of a continuous heat supply (a 250-W blade heater) and an intermittent heat supply (a coil of nichrome wire) controlled by a mercury thermoregulator, temperature was maintained to ±0.03°. Temperature was determined on a Beckmann thermometer calibrated against a National Bureau of Standards thermometer.

Procedure.—The pure organic substrates (**1** or **2**) were placed in tared, thin-walled soft glass ampoules prepared from soft glass disposable pipets and then weighed and sealed. The ampoule, 5 ml of a standard solution of sodium iodide in dry acetone, and a piece of 2 × 0.7 cm glass rod were placed in a clean combustion tube, 1.2 × 30 cm. The tube was protected from the atmosphere by a calcium chloride drying tube, cooled in a freezing mixture of Dry Ice in ethylene glycol monoethyl ether, and quickly sealed in such a manner that the free space above the liquid was approximately equal to the volume of the liquid. The tubes, which were placed in a vertical position in the constant-temperature bath and thermally equilibrated for at least 30 min, were quickly withdrawn, shaken vigorously ($t = 0$) to break the ampoule and initiate reaction, and then returned to the bath. This operation required less than 15 sec. After measured time intervals, tubes were withdrawn and quenched in an ethylene glycol monoethyl ether–Dry Ice bath. After 5 min, the tubes were opened and wiped clean, and the contents and distilled water washings were poured into a 250-ml glass-stoppered bottle containing 5 ml of chloroform, 20 ml of concentrated hydrochloric acid, and 20 g of ice. The amount of unreacted iodide ion was then determined by the standard Andrews titration procedure[36] with a standard solution of potassium iodate according to the equation

$$2KI + KIO_3 + 6HCl \longrightarrow 3KCl + 3ICl + 3H_2O$$

The iodate solution was added rapidly with swirling. This caused an iodine color to develop, which color began to lighten at the equivalence point. At this point, 30 g more of ice was added and the titration was continued with ever-decreasing increments of iodate, with vigorous shaking between each addition, until the end point was approached. The end point was taken as the point at which the chloroform layer became colorless.

This titration is sensitive to acid concentration, and optimum conditions were previously determined by titration of solutions with known concentrations of iodide. Thus, in the later points of the kinetic runs, it was found necessary to employ lesser amounts of hydrochloric acid. It was also found desirable to work rapidly and to keep the solutions cold during the titration by addition of ice. If one uses too low an acid concentration or permits the solutions to warm up, the iodine chloride is hydrolyzed. Too high an acid concentration results in indistinct end points, which come far before the equivalence point. By observing the above precautions, the values obtained titrametrically for standard solutions were found to agree with gravimetrically determined values.

At each temperature, 19 or more points were taken to determine each rate constant. Different ratios of organic substrate to sodium iodide were used. The second-order rate constants were calculated by the method of least squares from the usual second-order rate equation

$$k = \frac{2.303}{t(a - b)} \log \frac{b(a - x)}{a(b - x)}$$

where $a = [RCl]$, $b = [NaI]$, and x = amount of I^- reacting in time t. The standard deviations were determined by the method of least squares. The reactions generally were followed beyond 70% completion. The sodium iodide concentration was in the 2×10^{-2} molar range and the organic substrate in the range of 2×10^{-2} to 12×10^{-2} M. Blanks were run in all cases to check the initial iodide titer, and these were found to agree with the amounts determined by weight to within three parts per thousand.

Registry No.—**1**, 34236-28-7; **1** 2,4-DNP, 34236-29-8; **2**, 420-99-5; **5**, 5724-15-2; **7**, 34236-32-3; **7** 2,4-DNP, 34236-33-4; **10**, 34236-34-5; 1-iodo-2,2-difluoropropane, 34280-36-9; β-dimethylaminopropiophenone HI, 34236-46-9.

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The Chemistry of Blocked Isocyanates. I. Kinetics and Mechanism of the Reaction of Macromolecular Benzophenone Oxime Carbamates with Dibutylamine

AARON W. LEVINE* AND JOHN FECH, JR.

RCA Corporation, David Sarnoff Research Center, Princeton, New Jersey 08540

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Dibutylamine reacts with benzophenone oxime carbamates to give the corresponding dibutylureas. This reaction, with a polymeric bis(oxime carbamate) derived from a toluene-2,4-diisocyanate–polypropylene oxide adduct, was studied in toluene solution using kinetic techniques. The reaction exhibited first-order kinetics and had entropy of activation of −1.86 eu and enthalpy of activation of 24.8 kcal/mol, and the rate was insensitive to added tertiary amine. The reaction was favored by electron-releasing substituents on the oxime moiety with $\rho = -0.45$. An intramolecular, cyclic transition state is postulated for the rate-determining dissociation step.

Blocked polyurethanes are those polymers whose reactive isocyanate groups have been treated (eq 1)

$$RN{=}C{=}O + BH \rightleftarrows RNHCOB \quad (1)$$

with a thermally removable active hydrogen compound, BH. The term "unblocking" may refer to dissociation of the unstable adduct or to the reaction of a blocked polyurethane with some monomeric or polymeric coreactant. In this paper, unblocking will be used to indicate the latter (eq 2), whereas the reverse reaction in eq 1 will be referred to as dissociation.

$$RNHCOB + B'H \longrightarrow RNHCOB' + BH \quad (2)$$

The thermal dissociation and unblocking of isocyanate adducts have been studied by several workers. Interchange of the ester portion of a carbamate with an alcohol higher boiling than that from which the carbamate was derived is well known. Ben-Ishai and Katchalski[1] and Gaylord and Sroog[2] further extended the scope of this reaction, the latter authors using lower boiling alcohols and acid catalysis. The mechanism of this transesterification may involve dissociation as a first step. There is some evidence[3] which implies such an equilibrium, although much of the data of Gaylord and Sroog[2] as well as more recent evidence[4] are not adequately explained by this hypothesis, and a duality of mechanism has been proposed.[2]

The thermal dissociation of urethanes and ureas in the presence of coreactants was the subject of extensive investigations of Mukaiyama and collaborators.[5,6] They have established that isocyanates are intermediates in the reactions of urethanes under a variety of conditions. A general base catalyzed double-proton transfer was proposed on the basis of kinetics data. Additional studies of thermal reactions of monomeric and polymeric urethanes in the presence of coreactants or catalysts have been made by several workers and have been reviewed.[7]

Dyer and coworkers[8,9] have studied the thermal degradation of carbamates in the absence of coreactants. Dissociation *via* a cyclic intramolecular transition state appears to be the first step in a series of reactions which provides numerous products.

Investigations more closely related to the use of blocked polyurethanes have centered around determination of minimum unblocking temperatures.[7,10] At least one coreactant was present in all such studies.

There have apparently been no kinetic experiments related to unblocking in which the blocking agent was an oxime, although at least one commercial product is based on such a structure. We undertook to study the unblocking of oxime carbamates in the hope that a low-temperature unblocking polyurethane coating system could be developed. This paper reports the results of investigation of the kinetics of unblocking of aromatic ketoximes based on benzophenone from an isocyanate terminated polyether.

Experimental Section

Melting points are uncorrected. Infrared spectra (ir) were determined on a Perkin-Elmer Model 457 spectrophotometer. Nuclear magnetic resonance (nmr) spectra were run on a Joelco Minimar at ambient temperature in deuteriochloroform solution. Tetramethylsilane was used as internal standard. Benzophenone, substituted ketones, hydroxylamine hydrochloride, and toluene-2,4-diisocyanate (TDI) were used as purchased from Eastman Organic Chemicals. Solvents were reagent or electronic grade and were dried over activated 4A molecular sieve. Poly(propylene oxide) was supplied by Wyandotte Chemicals Corp. (Pluracol 1040).

Synthesis of Oximes.—A stirred solution of ketone, hydroxylamine hydrochloride, and pyridine (1 equiv each) in anhydrous ethanol was heated to reflux and the temperature was held for 2 hr. The cooled solutions were concentrated under reduced pressure and the product was precipitated by adding it to faintly alkaline (NH_3) water, collected on a Büchner funnel, washed, and dried. The oximes were recrystallized from methanol to constant melting behavior. In the case of oximes of substituted benzophenones, two distinct melting ranges were observed, corresponding to the syn and anti isomers. Table I lists the properties of the oximes including the approximate syn:anti ratio determined by nmr.

Preparation of Blocked Urethane Prepolymers (Polymers 1–4).—Poly(propylene oxide) of average mol wt 1040 was added dropwise and with stirring to a toluene solution of TDI so as to give a prepolymer solution with nonvolatiles' content of 75%. A dry nitrogen atmosphere was maintained and ice–water cooling was used to keep the temperature below 50°. After addition, the reaction mixture was held until the isocyanate content was

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TABLE I

SYNTHESIS OF BENZOPHENONE OXIMES BY THE PYRIDINE METHOD

Para substituent	% yield, pure	Isomer	Mp, °C Found[a]	Mp, °C Lit.[b]	Estimated syn:anti[a] (by nmr)
H	95		143.5–144.5	144	
OCH_3	79	Syn	116–120	115–116	50:50
		Anti	137–142	137–138	
Cl	36	Syn	94	95	5:95
		Anti	156–159	155–156	
NO_2	51	Syn	115–116	115	40:60
		Anti	136–143	158	

[a] Syn and anti with reference to the substituted aromatic ring; two distinct melting ranges were observed. [b] Values were taken from Beilstein.

constant, as determined by the dibutylamine procedure.[11] When a constant per cent NCO, equal to that predicted for reaction of one-half of the TDI originally present, was obtained, the solution was diluted with toluene and the calculated amount of solid oxime was added. The mixture was held at 50° until a solution was obtained and no isocyanate could be detected. The final solution had a nonvolatiles' content of 75%.

A check on the extent of blocking was made by heating a sample of blocked polymer containing a known excess of dibutylamine, added as a standardized toluene solution, under reflux for 15 min. After cooling and dilution with 2-propanol, the remaining amine was titrated with HCl to a bromcresol green end point and the equivalent weight of the blocked polymer solution was determined. The polymers prepared are shown in Figure 1.

Preparation of the Bis(dibutylurea) of TDI-Terminated Poly(propylene oxide) (Polymer 5).—To a solution of isocyanate-terminated polyether prepared as discussed above was added an amount of dibutylamine equal to the concentration of free NCO. The resulting solution was stirred until no NCO could be detected by the dibutylamine procedure.[11]

Kinetic Measurements.—Solutions of dibutylamine in 100 ml of toluene and blocked prepolymer in 250 ml of the same solvent were simultaneously equilibrated in a Lab-Line constant-temperature water bath. Temperature was controlled to ±0.05° using a mercury-contact thermoregulator. A slick of mineral oil was floated over the bath water to limit evaporation and increase precision of the control. An ASTM standardized thermometer was used to measure temperature.

After a 30-min equilibration period, the polymer solution was diluted with the amine solution with vigorous mixing and a timer was started. Initial reactant concentrations ranged from 0.0242 to 0.242 *N*.

At measured time intervals 10-ml aliquots of reaction mixture were withdrawn and quenched in 100 ml of 2-propanol. The quenched solutions were titrated with 0.1 *N* aqueous HCl to the yellow bromocresol green end point. The volume of HCl used in the titration (in milliliters) was thus equal to 100 times the molar concentration of dibutylamine in the reaction mixture at the time of sampling.

First-order rate constants were taken as the least-squares slopes of plots of $\ln([\text{dibutylamine}]_{\text{time } t} - [\text{dibutylamine}]_{\text{time } \infty})$ *vs.* time. The infinity value of concentration was measured after the expiration of 10 half-lives. Least-squares analysis was performed by computer. Half-lives were also obtained from hand-drawn first-order plots. Attempts to fit the data to higher order kinetic plots did not provide straight lines. The minimum acceptable correlation coefficient for a single run was 0.997 with most having 0.999. Agreement between repeat runs was usually better than 2%. A number of control experiments were carried out in conjunction with the kinetics determinations. (1) It was determined that the reaction product of the urethane prepolymer with dibutylamine was inert both to dibutylamine at the reaction temperature and to 2-propanol at ambient temperature. (2) The rate of reaction of dibutylamine with blocked polymer at ambient temperature was more than two orders of magnitude slower than the rate at 60°. (3) The continued unblocking of quenched reaction solutions at room temperature was more than two orders of magnitude slower than the rate of reaction at 60° before quenching. Additionally, the quenched rate was less than half the unquenched rate at ambient temperature.

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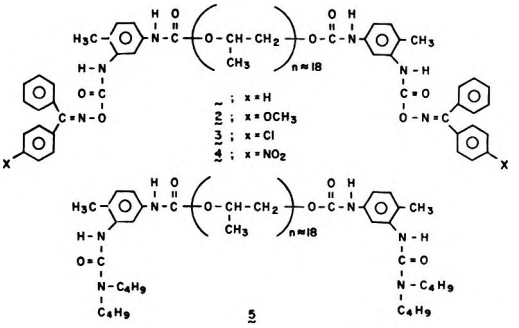


Figure 1.—Polymers synthesized for this investigation.

Product Isolation and Identification.—To a 50-ml one-neck flask were added 45.05 g of a 75% solution of polymer 1 in toluene (33.79 g of polymer, 0.038 equiv) and 4.95 g (0.0384 equiv) of distilled dibutylamine. The solution was stirred magnetically and heated under reflux for 20 min. After cooling, 1 g of reaction mixture was chromatographed on an 8 × 300 mm column of alumina (Fisher 80–200 mesh). The column was eluted with acetone (16 ml) and then ether (6 ml) and 2-ml fractions were collected and concentrated. Fractions 1–3 contained polymer while 5–11 gave a white solid upon concentration. The combined solids were recrystallized from ether to give 75.3 mg (50% based on blocked polymer) of white crystals, mp 142–144°, identified as benzophenone oxime by peak matching of its ir spectrum with that of an authentic sample.

The remaining reaction mixture was allowed to stand at ambient temperature for 3 days after which time white solid had separated. The supernatant liquid was decanted and concentrated, and the concentrate was dissolved in $CHCl_3$. The ir spectrum of the $CHCl_3$ solution was equivalent to that of a solution of polymer 5 in the same solvent.

Results and Discussion

The blocked polymers used in this study are shown in Figure 1. Polymer 1 was subjected to some exploratory unblocking reactions,[12] which served as controls and to assign reaction stoichiometry. These experiments demonstrated that the reaction products were stable in the presence of dibutylamine, that the stoichiometry was 1 equiv of dibutylamine consumed/equiv of carbamate reacted, and that there was no competition for free isocyanate between dibutylamine and other N–H functions (urethane and urea) present. It was thus indicated that the rate of disappearance of amine would be an effective probe in determining reaction kinetics.

The reaction of polymers 1, 2, 3, and 4 with dibutylamine in toluene was followed by titrating quenched aliquots of reaction mixtures with aqueous HCl. The values of concentration of dibutylamine remaining were plotted in the usual manner for first-order reactions. A typical plot is shown in Figure 2, and Table II lists rate constants under various conditions. The fit of data to a first-order rate law is consistent with 1:1 stoichiometry provided that either the dibutylamine or the polymer is not kinetically active. Since it is impossible for the kinetics to be observed if the

(12) The details of these experiments, including method, results, and discussion as well as the graphical solution to the Eyring equation will appear immediately following this article in the microfilm edition of this volume of the journal. Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 Sixteenth Street, N.W., Washington, D. C. 20036, by referring to code number JOC-72-1500. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche.

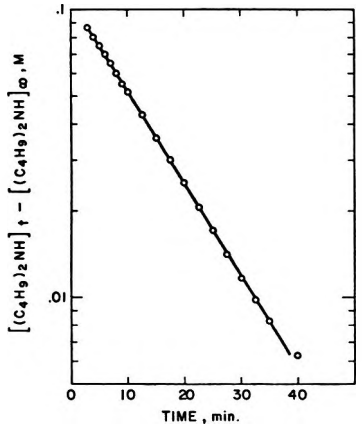


Figure 2.—Reaction of 1 with dibutylamine in toluene at 80.0° and 1:1 equivalent ratio.

TABLE II
FIRST-ORDER RATE CONSTANTS FOR REACTION OF POLYMERS WITH DIBUTYLAMINE

Polymer	Equiv ratio[a]	Temp, °C, ±0.1	10^4k,[b,c] sec^{-1}
1	1:1	70	4.42 ± 0.07
1	2:1	70	4.16 ± 0.10
1	5:1	70	4.28 ± 0.004
1	10:1	70	4.49 ± 0.07
1	1:1	60	1.46 ± 0.04
1	1:1	80	12.96 ± 0.04
2	1:1	70	5.33 ± 0.03
3	1:1	70	3.67 ± 0.01
3	5:1	70	3.97[d]
4	1:1	70	1.84 ± 0.003
1	0.5:1	80	11.7[d,e]
1	0.5:1	70	4.15 ± 0.02[e]
1	0.5:1	70	4.37[d-f]

[a] Dibutylamine:blocked isocyanate. [b] Average of at least two experiments with different initial concentrations. [c] Limits are ± average deviation of the mean. [d] Single experiment. [e] Using the special plot. See text. [f] Contained a molar amount of triethylamine equal to that of the dibutylamine.

polymer does not enter into the rate-determining step and since the rate constants are unaffected by both initial reactant concentration and ratio of amine to blocked isocyanate, the conclusion must be that the dibutylamine reacts with an intermediate generated by a unimolecular reaction of the blocked polymer. Such a reaction would be dissociation to the oxime and isocyanate-terminated prepolymer.

The rate constants for reaction of 1 with dibutylamine at three temperatures were used to solve the Eyring equation.[12] Assuming the transmission coefficient to be unity, the value of enthalpy of activation ($\Delta H^{\pm}$) was found to be 24.8 ± 0.5 kcal mol^{-1}. The entropy of activation ($\Delta S^{\pm}$) was −1.86 ± 0.8 cal deg^{-1} mol^{-1}. The near-zero value of $\Delta S^{\pm}$ is consistent with a rate-determining unimolecular decomposition analogous to values found for unimolecular ester hydrolyses.[13]

Based on the foregoing data, a pathway for the unblocking reaction may be presented as shown in eq 3a and 3b. The blocked polymer dissociates to

$$\text{RNHCOOX} \underset{}{\overset{k_1}{\rightleftharpoons}} \text{RN=C=O} + \text{HOX} \qquad (3a)$$

$$\text{RN=C=O} + (C_4H_9)_2NH \xrightarrow{k_2} \text{RNHCON}(C_4H_9)_2 \qquad (3b)$$

(13) L. L. Schaleger and F. A. Long, *Advan. Phys. Org. Chem.*, **1**, 1 (1963).

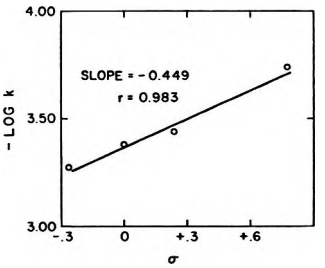


Figure 3.—Reaction of 1, 2, 3, and 4 with dibutylamine in toluene at 70 and 1:1 equivalent ratio. Plot of log k *vs.* the Hammett σ constant.

give an isocyanate and the blocking oxime, HOX. That this reaction is reversible seems quite reasonable when the blocking reaction and the high $\Delta H^{\pm}$ are considered. In a subsequent, fast reaction, dibutylamine adds to the isocyanate giving a urea. Provided that k_2 is larger than k_1, the dissociation will be rate determining and the reaction will be first order. Since dibutylamine is known[14] to be very reactive toward isocyanates, the $k_2 > k_1$ condition is easily met in this case. We have observed qualitatively that unblocking of 1 in the presence of 1-butanol is much slower than in the presence of dibutylamine. Since alcohols react more slowly with isocyanates than do amines,[15] it is possible that $k_1 \geq k_2$ in the 1-butanol case. Under such circumstances, the reaction in eq 3 would follow second-order (or possibly higher) kinetics. This would result in an observed decrease in rate since the fractional change in concentration with time would no longer be time independent.

The pathway shown in eq 3 is the same as that proposed by previous workers for reaction of phenol blocked isocyanates with amines and carboxylic acids. However, there is a major difference in this case. Previously it has been found[7,16] that electron-withdrawing substituents on the blocking agent facilitate the unblocking reaction. Considering polymers 2, 3, and 4 in our case it can be seen that the reverse is true. From a plot of the appropriate rate constants in Table II according to the Hammett equation,[17] a ρ value of −0.45 was obtained as shown in Figure 3. This indicates that the reaction is slightly favored by electron-releasing substituents. The implication of these data is that, while the overall pathway of unblocking of oxime carbamates is similar to that for carbamates derived from phenols, the mechanism of the rate-determining dissociation is different. It should be noted that we performed no isomer separation on the substituted benzophenone oximes. The fact that smooth first-order kinetic behavior was found for polymers 2, 3, and 4 tends to confirm the report that both isomers of substituted benzophenone oximes give the same derivative when treated with phenyl isocyanate.[18]

An interesting test for overall reaction pathway was available for this reaction. We found that straightforward kinetics were demonstrated by all reactions where the number of equivalents of dibutylamine present was either equal to or greater than the number

(14) E. Dyer, H. A. Taylor, S. J. Mason, and J. Samson, *J. Amer. Chem. Soc.*, **71**, 4106 (1949).
(15) F. Hostettler and E. F. Cox, *Ind. Eng. Chem.*, **52**, 609 (1960).
(16) G. R. Griffin and L. J. Willwerth, *Ind. Eng. Chem., Prod. Res. Develop.*, **1**, 265 (1962).
(17) H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953).
(18) O. L. Brady and R. P. Mehta, *J. Chem. Soc.*, **125**, 2297 (1924).

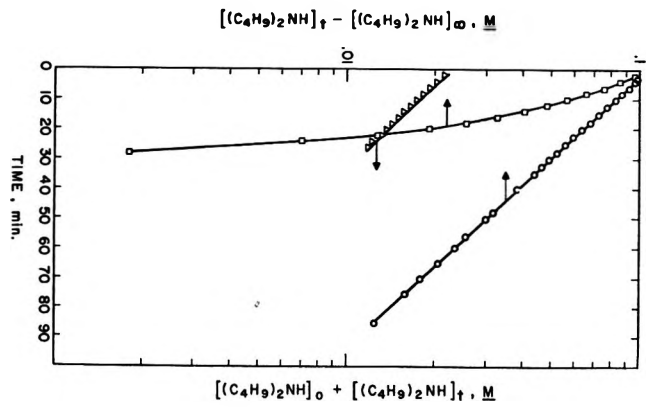


Figure 4.—Reaction of 1 with dibutylamine in toluene at 70°: O, $[polymer]_0$ = $[amine]_0$; □, $2[polymer]_0$ = $[amine]_0$; △, $2[polymer]_0$ = $[amine]_0$. Plot of $\log([amine]_t - [amine]_\infty)$ (O, □) or $\log([amine]_t + [amine]_0)$ (△) *vs.* time.

of equivalents of carbamate. When carbamate concentration exceeded that of the amine, however, the fractional change in concentration of amine with time increased markedly after ~50% reaction. A kinetic analysis of the pathway in eq 3 showed that, in the case where the number of equivalents of blocked isocyanate was twice that of the amine, an unusual, first-order-like variation of concentration with time would be observed. Specifically in this case, a plot of log of the sum of initial and remaining amine concentrations *vs.* time would give an initial straight line. The slope of such a line would be equal to the slope of the customary first-order plot for the reaction at the same temperature where the dibutylamine concentration was equal to or greater than the carbamate concentration.

This criterion was applied and the results at 70° are shown in Figure 4. As can be seen, a slope similar to that for a reaction where carbamate/amine = 1 was obtained. Interestingly, the effect was independent of absolute concentration, as the same line was obtained with initial polymer concentrations 0.121 or 0.242 normal. Additionally, when an amount of triethylamine equal to the concentration of dibutylamine was added, no effect on rate was observed. If the amine were involved in catalysis of the rate-determining dissociation, one would expect to observe a rate enhancement by the triethylamine in this otherwise amine-deficient system. The above experiment thus substantiates the dissociation–addition pathway (eq 3) and also provides a clue to the manner in which this unblocking differs from those previously studied.

The requirements for the rate-determining transition state in the present reaction follow: it must be unimolecular, resulting in dissociation; it must not be attainable by (or be of much higher energy for) phenol blocked isocyanates; it is not subject to base catalysis despite the necessary proton transfers. These limitations seem to indicate an intramolecular activated complex. Examination of the transition state in Figure 5 shows that the nitrogen lone pair of the azomethine moiety is capable of interaction with the

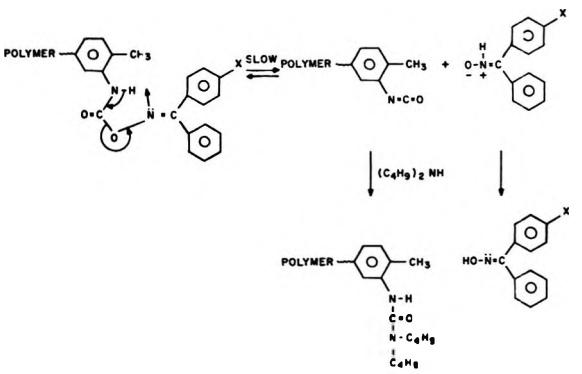


Figure 5.—Mechanism of unblocking in the presence of dibutylamine.

urethane hydrogen atom. This cyclic structure cannot form in the case of carbamates derived from phenols unless the aromatic ring participates which is energetically prohibitive under the conditions of this reaction. The intramolecular, cyclic nature of the postulated transition state is consistent with the insensitivity of the rate to added triethylamine and with the observed first-order kinetics. Since the azomethine nitrogen atom must act as a base in this reaction, electron-releasing substituents on the oxime moiety would increase the base strength and thus increase the rate. The lone pair is far removed from and not conjugated with the substituent, X, however, and one would thus expect a relatively small electronic effect. The transition state is pictured in Figure 5 proceeding to isocyanate and a relatively unstable tautomer of the oxime.

Molecular models show that the geometry necessary to form the cyclic transition state is probably not that of the ground state for the molecule. It may be attained, however, without greatly straining any bond. The steric hindrance to approach of a dibutylamine molecule is considerable, and consequently the cyclic transition state proposed is of lower energy than would be one which required higher order kinetics. There is an alternative unimolecular transition state for this reaction where proton transfer occurs *via* a four-center process. This is similar to the transition state usually pictured[7a] for uncatalyzed carbamate formation from an alcohol and an isocyanate. For the molecule at hand, the five-center geometry seems more favorable. Further, the reverse of alcohol addition is alcohol unblocking. Since alcohol unblocking has opposite electronic requirements,[7] we must conclude that a four-center transition state has a higher energy of activation than does the postulated transition state for unblocking of oxime carbamates.

Registry No.—Dibutylamine, 111-92-2.

Acknowledgments.—The authors are grateful to Dr. Joseph Blanc of RCA Laboratories for the kinetic analysis and for helpful discussions and to Dr. Peter Zanzucchi for determining the ir spectra.

Mechanisms of Induced Decomposition. I. Reactivity of Di-*tert*-butylperoxy Homoterephthalate[1]

AUGUSTINE I. DALTON AND THOMAS T. TIDWELL*

Department of Chemistry, University of South Carolina, Columbia, South Carolina 29208

Received December 21, 1971

Di-*tert*-butylperoxy homoterephthalate (6) reacts in toluene at 85° to give the perester products derived from the *p*-*tert*-butylpercarboxybenzyl radical 5. Calculations show that radical 5 has an average steady-state lifetime of 6×10^{-3} sec at 50% reaction, without undergoing observable intramolecular, induced decomposition. The rate constant of reaction of 6 in cumene at 79.6° is 2.38×10^{-5} sec^{-1}, which by comparison with the rates of reaction of other substituted phenylperacetates leads to a σ^+ value of 0.51 for the *p*-carbo-*tert*-butylperoxy substituent.

Induced decomposition is a pervasive phenomenon in the reactions of free radical precursors, and is most commonly considered[3] as the reaction of radicals derived from the radical source with the source itself, thereby accelerating the consumption of the precursor. The classic case of this process is the thermolysis of benzoyl peroxide in a solvent such as diethyl ether which possesses abstractable hydrogens (eq 1–3).[4] This example has been shown by kinetic studies,[4a-c] product isolation,[4d] and isotope labeling[4e] to occur by

$$PhC(=O^*)OOC(=O^*)Ph \xrightarrow{\Delta} 2PhC(=O^*)O\cdot \quad (1)$$

$$PhC(=O^*)O\cdot + CH_3CH_2OEt \longrightarrow PhC(=O^*)OH + CH_3\dot{C}HOEt \quad (2)$$

$$CH_3\dot{C}HOEt + PhC(=O^*)OOC(=O^*)Ph \longrightarrow PhC(=O^*)OCH(CH_3)OEt + PhC(=O^*)O\cdot \quad (3)$$

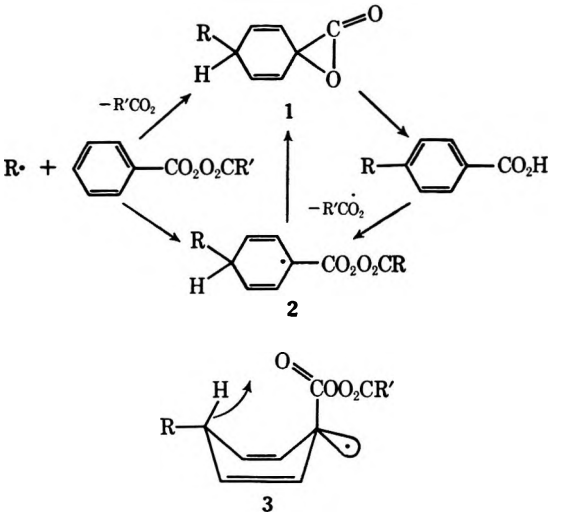
initial thermal cleavage of the benzoyl peroxide to form benzoyloxy radicals, which abstract hydrogen from the solvent to give α-ethoxyethyl radicals, which displace at peroxidic oxygen to form an ester and another benzoyloxy radical. This induced decomposition constitutes an SH2 displacement at peroxidic oxygen,[5] and numerous cases of such intermolecular reactions have been reported for diacyl peroxides, peresters, dialkyl peroxides, and perhaps other initiators.[5]

Another type of intermolecular, radical-induced decomposition involves bimolecular hydrogen atom transfer, for example to di-*tert*-butyl peroxide (eq 4).[5,6] A related process is the direct reaction between two nonradicals to give radical products ("molecule-induced homolysis").[7]

$$R_2\dot{C}OH + \textit{tert}\text{-}BuOO\textit{-tert}\text{-}Bu \longrightarrow R_2C{=}O + \textit{tert}\text{-}BuOH + \textit{tert}\text{-}BuO\cdot \quad (4)$$

Radical additions to benzoyl peroxides lead to induced decomposition,[8] and this is considered (Scheme I) to occur either *via* a concerted process giving an

SCHEME I



α-lactone 1 directly,[8a-c] or by an initial addition and subsequent reaction of the intermediate α-percarboxy radical 2.[8d,e] The latter process itself could occur by formation of the α-lactone or by transannular hydrogen transfer as shown in structure 3.[8d] The case for the concerted addition–cleavage reaction rests most strongly on the lack of meta substitution in the reaction, suggesting acceleration of para attack.[8a,b] However, if meta attack were reversible, whereas ortho and para substitution led to formation of substitution products, the reaction could be nonconcerted, and reversible addition of benzoyloxy radicals to benzene is known.[9]

(1) Presented at the 160th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1970, Abstracts, ORGN 160. For part II, see ref 2. Supported by the U. S. Army Research Office, Durham, N. C.

(2) D. L. Cable, J. A. Ernst, and T. T. Tidwell, 162nd National Meeting of the American Chemical Society, Washington, D. C., Sept. 1971, Abstracts, ORGN 137; manuscript in preparation.

(3) (a) W. A. Pryor, "Free Radicals," McGraw-Hill, New York, N. Y., 1966, p 82; (b) C. Walling, "Free Radicals in Solution," Wiley, New York, N. Y., 1957, pp 475–480; (c) E. S. Huyser, "Free-Radical Chain Reactions," Wiley, New York, N. Y., 1970, Chapter 10.

(4) (a) K. Nozaki and P. D. Bartlett, *J. Amer. Chem. Soc.*, **68**, 1686 (1946); (b) W. E. Cass, *ibid.*, **68**, 1976 (1946); (c) P. D. Bartlett and K. Nozaki, *ibid.*, **69**, 2299 (1947); (d) W. E. Cass, *ibid.*, **69**, 500 (1947); (e) D. B. Denny and G. Feig, *ibid.*, **81**, 5322 (1959).

(5) K. U. Ingold and B. P. Roberts, "Free-Radical Substitution Reactions," Wiley, New York, N. Y., 1971.

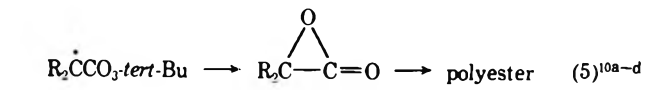
(6) (a) E. S. Huyser and C. J. Bredeweg, *J. Amer. Chem. Soc.*, **86**, 2401 (1964); (b) E. S. Huyser and A. A. Kahl, *J. Org. Chem.*, **35**, 3742 (1970); (c) W. F. Smith, Jr., and B. W. Rossiter, *Tetrahedron*, **25**, 2059 (1969); (d) D. F. De Tar, *J. Amer. Chem. Soc.*, **89**, 4058 (1967).

(7) (a) F. D. Greene, W. Adam, and J. E. Cantrill, *J. Amer. Chem. Soc.*, **83**, 3461 (1961); (b) C. Walling, L. Heaton, and D. D. Tanner, *ibid.*, **87**, 1715 (1965); (c) C. Walling and M. J. Mintz, *ibid.*, **89**, 1515 (1967); (d) G. R. Chalfont, D. H. Hey, K. S. Y. Liang, and M. J. Perkins, *J. Chem. Soc. B*, 233 (1971); (e) for a related case *not* involving molecule-induced homolysis see J. C. Martin, J. W. Taylor, and E. H. Drew, *J. Amer. Chem. Soc.*, **89**, 129 (1967).

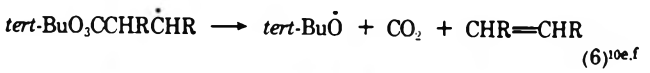
(8) (a) C. Walling and E. S. Savas, *J. Amer. Chem. Soc.*, **82**, 1738 (1960); (b) C. Walling and Z. Čeković, *ibid.*, **89**, 6681 (1967); (c) J. E. Leffler and R. G. Zepp, *ibid.*, **92**, 3713 (1970); (d) J. I. G. Cadogan, D. H. Hey, and P. G. Hibbert, *J. Chem. Soc.*, 3939 (1965); (e) D. F. De Tar and C. Weis, *J. Amer. Chem. Soc.*, **78**, 4296 (1957).

(9) J. Saltiel and H. C. Curtis, *J. Amer. Chem. Soc.*, **93**, 2056 (1971).

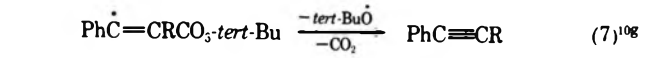
Intramolecular, induced decompositions between radical sites and acylperoxy functions have also been recorded (eq 5–9).[10] In these cases the radical was produced by atom abstraction, radical addition, or homolysis at another position one to four atoms removed in the molecule. For α-acylperoxy radicals lactone formation is the characteristic reaction (eq 5),



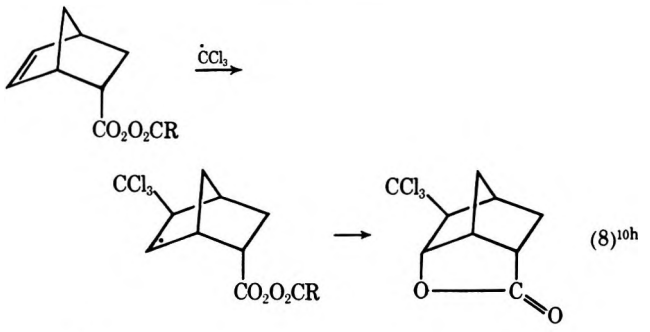
$R_2\dot{C}CO_3$-*tert*-Bu → $R_2C(-C(=O)-O-)$ → polyester (5)[10a–d]



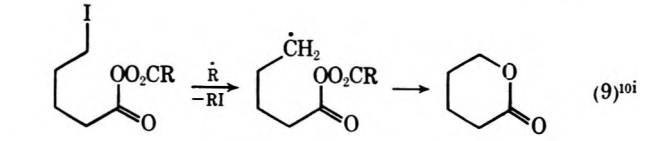
tert-$BuO_3CCHR\dot{C}HR$ → *tert*-$Bu\dot{O}$ + CO_2 + CHR=CHR (6)[10e,f]



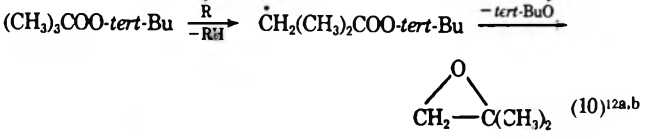
$PhC(\dot{)}=CRCO_3$-*tert*-Bu $\xrightarrow[-CO_2]{-\text{tert-}Bu\dot{O}}$ PhC≡CR (7)[10g]



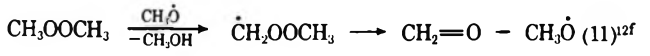
(8)[10h]



(9)[10i]



(10)[12a,b]



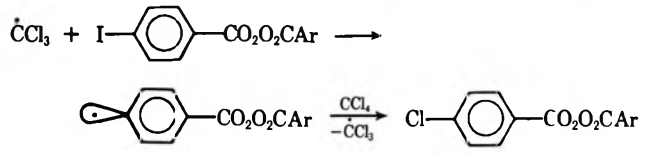
$CH_3OOCH_3 \xrightarrow[-CH_3OH]{CH_3\dot{O}}$ $\dot{C}H_2OOCH_3$ → $CH_2{=}O$ + $CH_3\dot{O}$ (11)[12f]

as was found in the case of additions to aromatic rings.[8] Radicals in β positions lead to decarboxylative elimination (eq 6–7) whereas γ and δ radicals lead to the formation of stable lactones (eq 8–9). In long-chain bisperesters, the peroxy groupings undergo reaction independently without induced decomposition if they are sufficiently removed from one another.[11] Dialkyl peroxides (eq 10, 11)[12] and hypochlorites[13] also give intramolecular induced decomposition where radicals are produced by abstraction.

Intramolecular analogies to "molecule-induced homolysis," in which substituents assist homolysis by anchimeric participation, exist in ortho-substituted *tert*-butylperoxy benzoates[14] and 5-aryl-4-pentenoyl peroxides.[15]

Azo compounds have also been observed to undergo radical-induced homolysis by a variety of mechanisms.[16]

A notable case of a free radical substituted with a percarboxylate function which does not undergo induced decomposition is the radical **4** generated from



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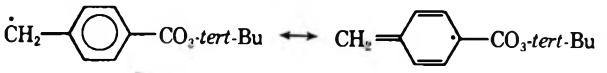
iodine atom abstraction from *p*-iodobenzoyl peroxide.[17] This radical survives for a sufficiently long period to abstract a chlorine atom from the solvent.

The prevalence of radical-induced decomposition, and its importance in the understanding of the properties of initiators, led us to initiate a study of the scope of this reaction. The present investigation, and that reported in part II,[2] deal with peresters.[18,19] Specifically, we chose to examine the reactivity of the *p*-*tert*-butylpercarboxybenzyl radical (**5**), which can interact through its π system to place electron spin density at the α position to the peracyl function, analogous to the structure which results from addition to the para position of benzoyl peroxides leading to induced decomposition (Scheme I). In the case of **5**



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it was of interest to determine if the driving force for induced decomposition was sufficient to overcome the resonance stabilization of the benzyl radical.

Results

As a precursor to radical **5** we prepared di-*tert*-butylperoxy homoterephthalate (**6**) by reaction of the acid chloride **7** of homoterephthalic acid (**8**)[20] with *tert*-

(10) (a) P. D. Bartlett and L. B. Gortler, *ibid.*, **85**, 1864 (1963); (b) P. D. Bartlett and J. M. McBride, *ibid.*, **87**, 1727 (1965); (c) L. B. Gortler and M. D. Saltzman, *J. Org. Chem.*, **31**, 3821 (1966); (d) C. Rüchardt and H. Schwarzer, *Chem. Ber.*, **99**, 1861 (1966); (e) L. M. Bobroff, L. B. Gortler, D. J. Sahn, and H. Wiland, *J. Org. Chem.*, **31**, 2678 (1966); (f) E. N. Cain, R. Vukov, and S. Masamune, *J. Chem. Soc. D*, 98 (1969); (g) N. Muramoto, T. Ochiai, O. Simamura, and M. Yoshida, *ibid.*, 717 (1968); (h) H. Hart and F. J. Chloupek, *J. Amer. Chem. Soc.*, **85**, 1155 (1963); (i) R. G. Woolford and R. N. Gedye, *Can. J. Chem.*, **45**, 291 (1967).

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(14) (a) T. H. Fisher and J. C. Martin, *ibid.*, **88**, 3382 (1966); (b) W. G. Bentrude and J. C. Martin, *ibid.*, **84**, 1561 (1962); (c) T. W. Koenig and J. C. Martin, *J. Org. Chem.*, **29**, 1520 (1964).

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(17) (a) M. M. Schwartz and J. E. Leffler, *J. Amer. Chem. Soc.*, **90**, 1368 (1968); (b) *ibid.*, **93**, 919 (1971).

(18) For recent reviews of perester reactivity see (a) L. A. Singer in "Organic Peroxides," Vol. 1, D. Swern, Ed., Wiley, New York, N. Y., 1970, Chapter 5; (b) S.-O. Lawesson and G. Schroll in "The Chemistry of Carboxylic Acids and Esters," S. Patai, Ed., Wiley, New York, N. Y., 1969, Chapter 14; (c) C. Rüchardt, *Angew. Chem., Int. Ed. Engl.*, **9**, 830 (1970); (d) C. Rüchardt, *Fortsch. Chem. Forsch.*, **8**, 251 (1967); (e) R. C. P. Cubbon, *Progr. React. Kinet.*, **5**, 29 (1970).

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SCHEME II

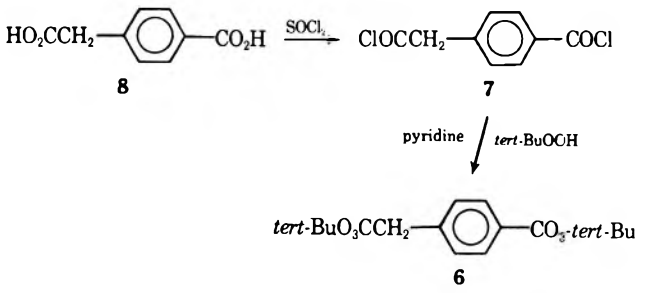
PRODUCT ANALYSIS FROM DI-*tert*-BUTYLPEROXY HOMOTEREPHTHALATE (6)

$$6 \xrightarrow[\text{toluene}]{85^\circ} CO_2 + \textit{tert}\text{-BuOH} + CH_4 + \text{acetone} + \text{bibenzyl} + \mathbf{9\text{–}12}$$

$$\text{bibenzyl} + \mathbf{9\text{–}12} \xrightarrow{H_2,\ Pd\text{–}C} \text{bibenzyl} + \text{soluble acids} + \mathbf{13}\ \text{(precipitate)}$$

$$\mathbf{13}\ \text{(trace)} + \text{bibenzyl} + \text{soluble acids} \xrightarrow{CH_2N_2} \mathbf{14} + \mathbf{15} + \text{methyl toluate} + \text{bibenzyl} + \mathbf{27}$$

$$\text{bibenzyl} + \mathbf{9\text{–}12} \xrightarrow{LiAlH_4} \mathbf{16} + \mathbf{17} + p\text{-MePhCH}_2\text{OH} + \text{bibenzyl (18 lost)}$$



butyl hydroperoxide and pyridine. New compounds **6** and **7** were characterized by spectral properties, elemental analyses, and conversion to known compounds (*vide infra*). Hammering, scratching, and heating of **6** produced no explosive behavior.

The rates of thermal decomposition of **6** were measured in toluene and cumene solvents by following the decrease of the peracetate carbonyl in the infrared. The peracetate and perbenzoate carbonyl bands were well resolved and at the temperatures used the peracetate band completely disappeared with good first-order kinetics, whereas no decrease was observed in the perbenzoate band. The observed rate constants and derived activation parameters are summarized in Table I, along with suitable data for comparison.

TABLE I

RATES OF THERMAL DECOMPOSITION OF PERESTERS

Perester	Temp, °C	Solvent	k_1, sec^{-1} × 10^5 [a]	ΔH^*, kcal/mol	ΔS^*, eu
6	100.5	Toluene	30.9	29.2[b]	3.1[b]
6	80.3	Toluene	2.80		
6	70.6	Toluene	0.944		
6	79.6	Cumene	2.38		
$PhCH_2CO_3$-*tert*-Bu	79.6	Cumene	7.21		
$PhCH_2CO_3$-*tert*-Bu[c]	79.6	Cumene	6.77[c]	27.9[d]	2.0[d]

[a] Average of two runs at each temperature, maximum deviation ±2.5%. [b] In toluene. Standard deviations of ΔH^* and ΔS^* are 0.03 kcal/mol and 0.07 eu, respectively. [c] Reference 23b. [d] Reference 23a, activation parameters from reaction in chlorobenzene.

Products were determined for the reaction of **6** at 85° in toluene and are given in Table II. A schematic diagram of the product separation is given in Scheme II. Gaseous products were analyzed by absorption of CO_2 on Ascarite and identification of the residual gas as methane by mass spectrometry. The only volatile products, *tert*-butyl alcohol and acetone, were analyzed by vpc. A small quantity of acids was detected in the nonvolatile residue by ir and by bicarbonate extraction, and constituted no more than 3% of the total. The acidic product was esterified by diazomethane, but no methyl toluate could be detected by vpc. The residual product consisted of a mixture of bibenzyl, *tert*-butylperoxy *p*-toluate (**9**), *p*-carbo-*tert*-butylperoxybibenzyl (**10**), and *tert*-butylperoxy *p*-(*tert*-butoxymethyl)benzoate (**11**).[21] This mixture was converted to the corresponding acids by hydrogenolysis with Pd/C catalyst. *p,p'*-Dicarboxybibenzyl (**13**) precipitated and was weighed to give the yield of the corresponding bisperester **12**, and the remaining acids were treated with diazomethane to give the methyl esters, which were analyzed by vpc to give the yields of **9**–**11**. Control experiments on authentic samples of **9** showed that this reaction proceeded in at least 90% yield, although the authentic sample of **11** was partially converted to toluic acid under these conditions. To confirm the source of the 5.2% of *p*-methyl toluate from the hydrogenolysis, a mixture of **9**–**12** from a separate reaction of **6** was treated with $LiAlH_4$, which converted the perester groupings to benzyl alcohols, but as shown by a control experiment did not disturb the *tert*-butyl ether. The yields of benzyl alcohols (determined by vpc analysis) were consistently lower than those from the hydrogenolysis, but showed 2.5% benzyl alcohol, corresponding to the minimum yield of **9** from **6**. The lower net yields were presumably caused by loss of material in the gelatinous precipitate formed during work-up of the $LiAlH_4$ reaction. An nmr of the reaction mixture from **6** after removal of the volatile material showed only peaks assigned to bibenzyl and **9**–**12**.

TABLE II

PRODUCTS FROM THERMAL DECOMPOSITION OF DI-*tert*-BUTYLPEROXY HOMOTEREPHTHALATE AT 85° IN TOLUENE

Product	Per cent, mol/mol **6** × 100
CO_2	99.0
CH_4	6.9[a]
Acetone	6.9
tert-BuOH	86.6
p-$MePhCO_3$-*tert*-Bu (**9**)	5.2[b,c]
p-$PhCH_2CH_2PhCO_3$-*tert*-Bu (**10**)	27.8[b,c]
Bibenzyl	*d*
tert-$BuOCH_2PhCO_3$-*tert*-Bu (**11**)	17.1[b,c]
p-$(CH_2PhCO_3$-*tert*-$Bu)_2$ (**12**)	16.9[c]
Acids	~2–3

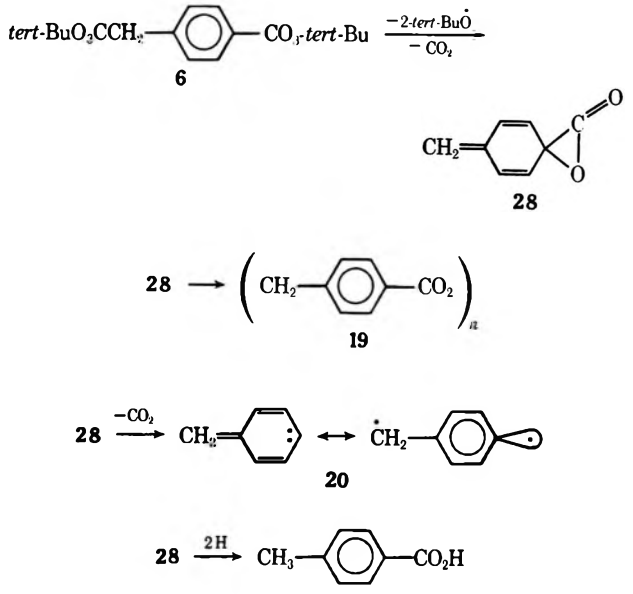
[a] Taken as equal to acetone. [b] Yields of **9**, **10**, and **11** from the work-up using $LiAlH_4$ were 2.5, 18.1, and 13.8%, respectively. [c] The sum of **9**, **10**, **11**, and 2 × **12** is 83.9, and equals the total residual perester. [d] The yield of bibenzyl corresponded to 17.1% (mol/mol) relative to **6**.

(21) These were identified in a separate experiment without prior base extraction. Due to the low solubility of several of the compounds present, it was advantageous to minimize handling of the solution.

Discussion

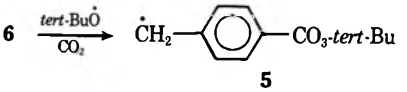
There are several reaction paths *a priori* open to **6**. One possibility would be concerted cleavage of both peroxide linkages to form the α-lactone **28**, which might react in several ways (Scheme III), for example

SCHEME III



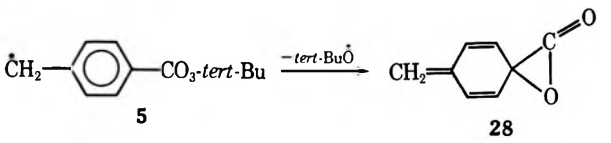
polymerizing to form poly(*p*-carboxybenzyl alcohol) (**19**), decarboxylation to form the diradical carbene **20**, or abstraction of two hydrogens to form toluic acid. However, the results exclude any significant contribution from this pathway. Thus, the reactivity of **6** is that expected for a normal phenylperacetate with an electron-withdrawing para substituent, with no evidence for an accelerated concerted reaction. None of the observed products was derived from reaction at the perbenzoate function. Polymer **19** was also prepared by an independent route and could not be detected in the product, although it is so insoluble that even a small amount would have been easily observed.

It may be concluded that **6** undergoes thermolysis



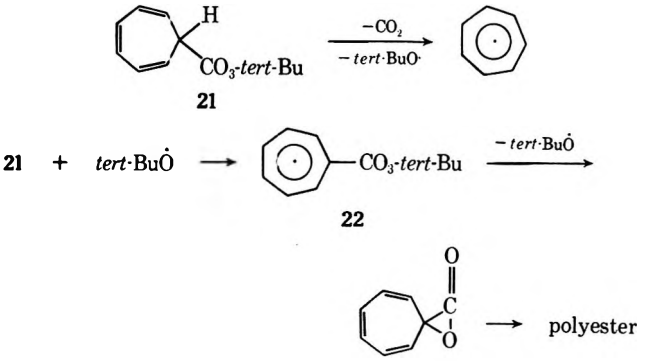
of the benzylic perester grouping to form **5**, presumably by an unimolecular two-bond scission.[22] Furthermore, **5** is sufficiently long-lived to undergo dimerization as well as coupling with solvent-derived benzyl radicals. A mechanism to account for the observed products is given in Scheme IV, where k_1 is the observed rate constant for disappearance of **6**, f is the fraction of the original cage pair which dissociates to free radicals, and k_2 is the rate constant for dimerization of **5**.

The survival of **5** so that it could undergo dimerization is of interest, because of the potential route for induced decomposition available to this compound to



form the α-lactone **28**. As discussed before, there is no evidence that any of the reaction proceeded through this intermediate, although α-lactone formation is the principal reaction pathway for other α-percarboxy radicals.[8,10a-d] The contribution of the resonance form of **5** which places the unpaired electron at the para position is certainly significant, as the esr spectrum of the benzyl radical reveals a hyperfine splitting of the para hydrogen of 6.3 G, and the observed hyperfine interactions are proportional to spin densities calculated by molecular orbital theory for this radical, with a calculated spin density at the para position of 0.231.[24]

It is interesting that **5** is isomeric to radical **22**, which



is formed by hydrogen abstraction from the cycloheptatrienyl perester **21** on thermal decomposition of the latter in chlorobenzene.[10d] However, **22** undergoes dimerization only to the extent of about one-fourth of the amount of polyester formed.[10d] The facile induced decomposition of **22** relative to **5** is striking, especially in view of the significant resonance stabilization of the cycloheptatrienyl radical (21 kcal/mol relative to cycloheptatriene).[25] The tropylium ion stabilization of the zwitterionic form of the α-lactone may aid its formation from **22**.

The reactions of the radicals **5** which escape from the solvent cage can be represented as shown ($k_1' = fk_1$) if the rates of combination of **5** with **5**, **5** with benzyl

$$6 \xrightarrow{k_1'} 5$$

$$25 \xrightarrow{k_2} 12$$

$$5 + PhCH_2 \xrightarrow{k_2} 10$$

$$2PhCH_2 \xrightarrow{k_2} \text{bibenzyl}$$

radicals, and benzyl radicals with benzyl radicals are the same. This is apparently true, because if equal numbers of **5** and benzyl radicals are formed the statistical distribution of **12**, **10**, and bibenzyl would be 1:2:1, and the actual yields are 1.00:1.65:1.02. It is possible to calculate the average steady-state lifetime for which the radical **5** survives without induced decomposition from the above scheme, using the relation-

(22) There is some controversy as to whether phenylperacetates with electron-withdrawing para substituents react by concerted two-bond[23a,b,c] scission or whether there is an appreciable contribution from one-bond scission, followed by decarboxylation.[23d] Either pathway would lead to **5**.

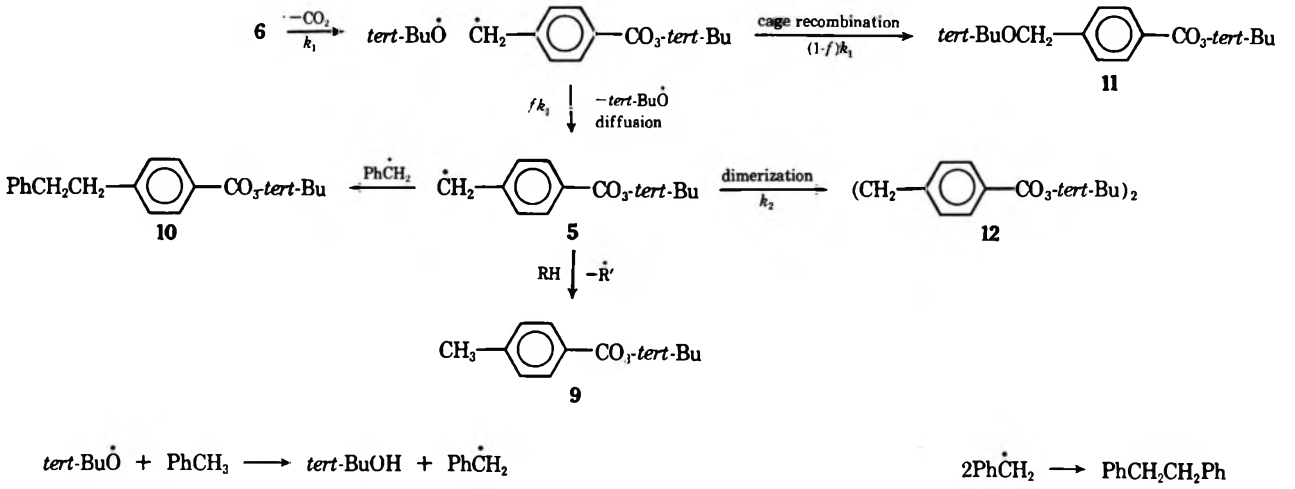
(23) (a) P. D. Bartlett and C. Rüchardt, *J. Amer. Chem. Soc.*, **82**, 1756 (1960); (b) R. C. Neuman, Jr., and J. V. Behar, *J. Org. Chem.*, **36**, 654 (1971); (c) T. Koenig, J. Huntington, and R. Cruthoff, *J. Amer. Chem. Soc.*, **92**, 5413(1970); (d) W. A. Pryor and K. Smith, *ibid.*, **92**, 5403 (1970).

(24) W. T. Dixon and R. O. C. Norman, *J. Chem. Soc.*, 4857 (1964).

(25) G. Vincow, H. J. Dauben, Jr., F. R. Hunter, and W. V. Volland, *J. Amer. Chem. Soc.*, **91**, 2823 (1969).

SCHEME IV

FORMATION AND REACTIONS OF *p*-*tert*-BUTYLPERCARBOXYBENZYL RADICAL (5)



tert-$BuO + PhCH_3 \longrightarrow$ tert-$BuOH + PhCH_2$

$2PhCH_2 \longrightarrow PhCH_2CH_2Ph$

ship (average lifetime) = (steady-state concentration of **5**)/(rate of disappearance of **5**). Thus, $[5] = (k_1'[6]/3k_2)^{1/2}$ and the average lifetime $\tau = (3k_1' \cdot k_2[6])^{-1/2}$.

The rate constant k_2 for combination of benzyl radicals in benzene at 25° has been reported[26] as 4.1×10^9 M^{-1} sec^{-1}, less than a factor of two smaller than the calculated[26] diffusion-controlled rate constant (7.2×10^9 M^{-1} sec^{-1}). Equation 12 was used for

$$k = \frac{4\pi\tau D_{rel}(N/1000)}{1 + 4\pi\tau D_{rel}(N/1000k_c)} \qquad (12)$$

calculating the rate constant, where D_{rel} is the diffusion coefficient of the benzyl radical. This diffusion coefficient was taken to be the same as that for toluene, and was estimated graphically from a plot of diffusion coefficient *vs.* the reciprocal of the solvent viscosity for a series of linear alkanes.[27a] Following this procedure and using the viscosity extrapolated for toluene at 85° (0.312 cP) from data at lower temperatures[27b] gives a diffusion coefficient of 4.36×10^{-5} cm^2/sec for the benzyl radical at 85°. If the only difference in k_2 for benzyl radicals in benzene at 25° and toluene at 85° arises from the difference in diffusion coefficients, eq 12 can be used to correct the reported value of k_2 given above to a value of 6.9×10^9 M^{-1} sec^{-1} for benzyl radicals at 85°, and the same value can be taken for the dimerization of **5**. At 85° the interpolated k_1 for **5** is 5.26×10^{-5} sec^{-1}; so k_1' is 0.83 times this or 4.36×10^{-5} sec^{-1}. The average lifetimes of **5** under these conditions and at the initial concentration of **6** used (0.061 M) are 5×10^{-3} sec at 25% reaction and 6×10^{-3} sec at 50% reaction.

The failure of **5** to undergo induced decomposition during its lifetime of about 10^{-2} sec surely reflects at least in part the loss of resonance energy that would result from conversion of **5** to **28**. By contrast **22** undergoes induced decomposition due to its lower loss in resonance energy, and perhaps also to a slower rate of dimerization of **22**. At reduced concentrations the lifetime of **5** could be prolonged, unless side reactions with solvent intervened, and the formation of **28** might compete with the diffusion-controlled dimerization.

In an independent study[17b] radical **5** and some related radicals have been generated by NBS bromination of **9** and other peresters and diacyl peroxides. Benzyl bromides were formed, without decomposition of the peroxides, in harmony with the results of this investigation. The mechanism of NBS bromination is apparently now established as involving bromine atoms as the chain-carrying agent,[28] but, since the rate constants for the individual steps are not known, it is not now feasible to estimate the lifetime of **5** under these conditions. In a related study the decomposition of toluyl peroxide in bromotrichloromethane was proposed to involve formation of a radical peroxide similar to **5**, which abstracted a bromine atom from the solvent.[8d]

Using the measured rate constant for **6** in cumene at 79.6°, and the plot of log k *vs.* σ^+ for substituted phenylperacetates in cumene of Neuman and Behar,[23b] a σ^+ constant of 0.51 is derived for the *p*-carbo-*tert*-butylperoxy substituent. This compares to the value of 0.48 cited[29] for ester functions.

Experimental Section

General.—Elemental analyses were performed by the Galbraith Laboratories, Knoxville, Tenn., and Mead Laboratories, Amherst, Mass. Qualitative infrared spectra wre determined using a Perkin-Elmer 337 spectrophotometer. Nmr spectra were measured using a Varian A-60 instrument with TMS as an internal standard. Melting points (open capillary) and boiling points are not corrected. Quantitative vapor phase chromatographic (vpc) analyses were carried out using a Varian-Aerograph 1800 temperature-programmed instrument and a Disc integrator mounted on a Sargent SRG recorder.

Reagents.—Cumene and toluene were purified by the procedure published for cumene.[30] Pyridine was distilled from BaO and stored over KOH. Pentane was distilled from calcium hydride and stored over sodium. Lucidol 90% *tert*-butyl hydroperoxide was purified by dissolving in pentane, extracting with saturated NaCl, drying over $MgSO_4$, and evaporating the solvent at aspirator pressure and 25°. The hydroperoxide was distilled twice through a 12-cm glass helix packed column and

(26) R. D. Burkhart, *J. Amer. Chem. Soc.*, **90**, 273 (1968).

(27) (a) P. Chang and C. R. Wilke, *J. Phys. Chem.*, **59**, 592 (1955); (b) "Handbook of Chemistry and Physics," 51st ed, Chemical Rubber Publishing Co., Cleveland, Ohio, p F-42.

(28) J. H. Incremona and J. C. Martin, *J. Amer. Chem. Soc.*, **92**, 627 (1970).

(29) C. D. Ritchie and W. F. Sager, *Progr. Phys. Org. Chem.*, **2**, 323 (1969).

(30) P. D. Bartlett, E. P. Benzing, and R. E. Pincock, *J. Amer. Chem. Soc.*, **82**, 1762 (1960).

the fraction boiling at 26–30° (13 Torr) was collected, $n^{23}D$ 1.4002. Iodometric titration[31] indicated a purity of 98.9%. Tetrahydrofuran was distilled from $LiAlH_4$ into the reaction vessels just prior to use.

Homoterephthalic acid (**8**) was prepared by the reported method in overall 25% yield, mp 238–240° (lit.[20] mp 239–241°). Later samples were prepared by custom synthesis at Columbia Organic Chemicals Co.

Homoterephthalyl chloride (**7**) was prepared by adding 138 ml (225 g, 1.9 mol) of thionyl chloride to 10 g (0.0056 mol) of **8**, stirring for 24 hr at 25°, and then refluxing for 4 hr. The thionyl chloride was removed under vacuum, leaving a red oil which gave 8.2 g (68%) of **7** as white crystals from pentane: mp 35–37°; ir (CCl_4) 1790 and 1815 cm^{-1} (C=O); nmr δ 4.15 (s, 2, $ArCH_2$) and 7.66[32] (quartet, 4, J = 8 Hz, Δ 0.72).

Anal. Calcd for $C_9H_6Cl_2O_2$ (217.05): C, 49.80; H, 2.66. Found: C, 49.53; H, 2.66.

Di-*tert*-butylperoxy homoterephthalate (**6**) was prepared by stirring 8.2 g (0.0038 mol) of **7** and 27.2 g (0.0302 mol) of *tert*-butyl hydroperoxide in 186 ml of 7.5:1 pentane–ether solution in a dry flask under N_2 at −5° for 10 hr. Then 23.8 g (0.0303 mol) of pyridine in 25 ml of pentane was added dropwise over 30 min with rapid stirring. A transient violet color was obtained on addition which faded to yellow. After stirring for 4 hr at −5° the solution was filtered and washed successively with water, cold 5% H_2SO_4, cold 5% NaOH, and water and then dried over $MgSO_4$ at 0°. The solvent was removed *in vacuo* to give a clear oil which was crystallized from ether–pentane at 0° to give 6.2 g (0.0019 mol, 51%) of **6**, mp 94–96°. This compound does not decompose on melting, scratching, or shock, but detonates without report on flash pyrolysis: ir (CCl_4) 1780 and 1770 cm^{-1} (peracetate and perbenzoate C=O, respectively); nmr (CCl_4) δ 1.21 (s, 9, peracetate *tert*-Bu), 1.35 (s, 9, perbenzoate *tert*-Bu), 3.55 (s, 2, $ArCH_2$), and 7.52[32] (quartet, 4, J = 8 Hz, Δ 0.52).

Anal. Calcd for $C_{17}H_{24}O_6$ (324.38): C, 62.95; H, 7.46. Found: C, 63.18; H, 7.58.

***tert*-Butyl *p*-(*tert*-butoxymethyl)benzoate** (**24**) was obtained by addition of 5.8 g (0.052 mol) of potassium *tert*-butoxide in 125 ml of anhydrous *tert*-butyl alcohol to 5.5 g (0.024 mol) of α-bromotoluyl chloride[33] in 50 ml of *tert*-butyl alcohol at 75°. The mixture was refluxed for 8 hr, stirred for 12 hr at 25°, poured into 500 ml of water, extracted with ether, and dried over $MgSO_4$. After the ether was evaporated the residue was distilled, yielding 3.5 g (56%) of **24**: bp 113–116° (0.6 Torr); ir (CCl_4) 1725 cm^{-1} (C=O); nmr (CCl_4) δ 1.35 (s, 9, CH_2O *tert*-Bu), 1.66 (s, 9, CO_2 *tert*-Bu), 4.48 (s, 2, $ArCH_2$), and 7.57[32] (quartet, 4, J = 8 Hz, Δ 0.58).

***p*-(*tert*-Butoxymethyl)benzoic acid** (**23**) was obtained by refluxing 3.5 g (0.00132 mol) of **24** with a solution of 2.1 g (0.0053 mol) of NaOH in 20% MeOH for 3 hr. After cooling the solution was acidified to yield 2.6 g of **23** as a white solid, mp 140–141° after recrystallization from aqueous ethanol. Treatment of 1.97 g of this material with excess diazomethane in ether at 0° and evaporation of the solvent gave 2 g of **methyl *p*-(*tert*)-butoxymethyl)benzoate** (**15**) which was recrystallized from hexane to give white plates: mp 135–137°; ir (CCl_4) 1735 cm^{-1} (C=O); nmr ($CHCl_3$) δ 1.18 (s, 9, *tert*-Bu), 3.76 (s, 3, OMe), 4.35 (s, 2, $ArCH_2$), and 7.47[32] (quartet, 4, J = 8 Hz, Δ 0.61).

***p*-(*tert*-Butoxymethyl)benzoyl chloride** (**25**) was prepared by addition of 1 equiv of aqueous NaOH to 3.85 g (0.00185 mol) of **23** in methanol. The methanol was removed under vacuum and benzene was added. After drying by distilling off part of the benzene, 30.2 g (0.0240 mol) of oxalyl chloride in 30 ml of dry benzene was added at 25°. After gas evolution ceased the mixture was refluxed for 30 min and the solvent was distilled away, leaving 4.1 g (98%) of crude **25**. Distillation gave a center fraction: bp 89–92° (0.25 Torr); ir (CCl_4) 1785 and 1765 cm^{-1} (C=O); nmr (CCl_4) δ 1.25 (s, 9, *tert*-Bu), 4.43 (s, 2, $ArCH_2$), and 7.62[32] (quartet, 4, J = 8 Hz, Δ = 0.60).

***tert*-Butylperoxy *p*-(*tert*-butoxymethyl)benzoate** (**11**) was obtained by dropwise addition of 3.1 g (0.0014 mol) of **25** in a solution of 5 ml of ether and 20 ml of pentane to a stirred mixture of 2.7 g (0.0030 mol) of 93% *tert*-butyl hydroperoxide and 2.4 g (0.0030 mol) of pyridine in 50 ml of pentane at 0°. After stirring for 4 hr at 0° the solution was filtered, washed with cold 10% KOH and then water, and dried, and the solvent was evaporated yielding a clear oil which was chromatographed on a 15-g Florisil with 5% ether–hexane. The first 100-ml eluent contained 1.1 g (0.004 mol, 29%) of **11** as a clear oil: ir (CCl_4) 1760 cm^{-1} (C=O); nmr (CCl_4) δ 1.24 (s, 9, *tert*-$BuOCH_2$), 1.35 (s, 9, CO_3-*tert*-Bu), 4.40 (s, 2, $ArCH_2$), and 7.53[32] (quartet, 4, J = 8 Hz, Δ 0.46).

Anal. Calcd for $C_{16}H_{24}O_4$ (280.37): C, 68.55; H, 8.63. Found: C, 68.62, H, 8.62.

***p*-(*tert*-Butoxymethyl)benzyl alcohol** (**17**) was obtained as the only product (vpc) from $LiAlH_4$ reduction of **24** in THF. Recrystallization from hexane gave white needles: mp 47–47.5°; nmr (CCl_4) δ 1.22 (s, 9, *tert*-Bu), 2.88 (broad s, 1, OH), 4.28 and 4.33 (each s, 2, $ArCH_2$), and 7.05 (s, 4, aromatic).

Anal. Calcd for $C_{12}H_{18}O_2$ (194.28): C, 74.19; H, 9.34. Found: C, 73.55; H, 9.02.

***p*-Carboxybibenzyl** (**26**) was prepared by the reported[34] procedure, mp 169–172° (lit.[34] mp 170–172°). Esterification with methanol and sulfuric acid gave the methyl ester **14**, bp 142° (0.6 Torr), which solidified on prolonged standing: mp 132–133°; nmr (CCl_4) δ 2.94 (s, 4, CH_2CH_2), 3.83 (s, 3, Me), 7.1 (m, 5, C_6H_5), and 7.37[32] (quartet, 4, J = 8 Hz, Δ 0.73). Reduction of **14** by $LiAlH_4$ in THF gave ***p*-(hydroxymethyl)bibenzyl** (**16**) which after recrystallization from 3% benzene in hexane gave mp 67–68° (lit.[35] mp 57–58° *sic*); nmr (CCl_4) δ 1.76 (s, 1, OH), 2.90 (s, 4, CH_2CH_2), 4.52 (s, 2, CH_2OH), and 7.10 (br s, 9, aromatic).

Anal. Calcd for $C_{15}H_{16}O$ (212.29): C, 84.87; H, 7.60. Found: C, 85.00; H, 7.69

***p,p'*-Dicarboxybibenzyl** (**13**) was prepared by the reported[36] procedure as a white amorphous solid which did not melt below 320°. Treatment with diazomethane in ether at 5° gave the dimethyl ester **27**: mp 115–117° (lit.[37] mp 115–119°); nmr (CCl_4) δ 2.94 (s, 4, CH_2CH_2), 3.80 (s, 6, Me), and 7.43[32] (quartet, 4, J = 8 Hz, Δ 0.74). Reduction of **27** with $LiAlH_4$ in refluxing THF gave ***p,p'*-di(hydroxymethyl)bibenzyl** (**18**), mp 151–154° (lit.[37] mp 157–159°).

***tert*-Butylperoxy *p*-toluate** (**9**) was prepared by the reported method.[38] ***p*-Methylbenzyl alcohol** was prepared by reduction of toluic acid with $LiAlH_4$, mp 57.5–58.5° (lit.[39] mp 61.0–62.1°).

Poly(*p*-carboxybenzyl alcohol) (**19**) was prepared by heating *p*-carboxybenzyl alcohol[40] in a sealed evacuated tube at 250° to give **19** as a brittle crystalline solid, mp 202–210° (lit.[41] mp 200–210°), insoluble in toluene, methylene chloride, and other common solvents and with an ir band (KBr) at 1725 cm^{-1} (C=O).

Kinetic Method.—Rate runs were carried out by the infrared method.[42] Sample tubes were washed first with nitric acid, then ammonium hydroxide, and were thoroughly dried. In each tube was placed 0.5 ml of a 0.06 *M* solution of perester and the tubes were sealed without degassing. Tubes were placed in the constant-temperature bath and after 15 min to equilibrate were removed at intervals. The transmittance of each sample between 1900 and 1650 cm^{-1} was scanned using a Perkin-Elmer 621 spectrophotometer and 0.1-mm NaCl cells. Rate constants were calculated as the least-squares slope of 2.303 log $(A_t - A_\infty)/(A_0 - A_\infty)$ *vs.* time, where A is the measured absorbance of the band at 1780 cm^{-1}. Reactions were followed for 60% reaction and gave no residual absorbance after 10 half-lives (taken as A_∞).

Product Studies.—Gaseous, volatile, and nonvolatile products were determined in separate experiments. Gaseous and volatile product yields are the average of three separate determinations carried out using 0.8-g samples of **6** in 15 ml of degassed

(31) R. D. Mair and A. J. Graupner, *Anal. Chem.*, **36**, 194 (1964).

(32) The aromatic protons are a typical AA'XX' pair of perturbed doublets, and are reported as δ (midpoint of spectrum), J (spacing of the doublets in Hz), and Δ (chemical shift difference between the midpoints of the two doublets in parts per million): L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, New York, N. Y., 1969, pp. 134–137; D. H. Williams and I. Fleming, "Spectroscopic Methods in Organic Chemistry", McGraw-Hill, New York, N. Y., 1966, pp 120–122.

(33) A. F. Titley, *J. Chem. Soc.*, 2571 (1928).

(34) A. Meisters and P. C. Wailes, *Aust. J. Chem.*, **19**, 1215 (1966).

(35) V. G. Cavallini, E. Massarani, and D. Nardi, *Farmaco, Ed. Sci.*, **11**, 378 (1956); *Chem. Abstr.*, **53**, 9194*i* (1959).

(36) G. J. Sloan and L. R. Vaughan, *J. Org. Chem.*, **22**, 750 (1957).

(37) D. J. Cram and H. Steinburg, *J. Amer. Chem. Soc.*, **73**, 5691 (1951).

(38) A. T. Blomquist and I. A. Bernstein, *ibid.*, **73**, 5546 (1951).

(39) J. K. Kochi and G. S. Hammond, *ibid.*, **75**, 3443 (1953).

(40) W. S. Emerson and R. A. Heimsch, *ibid.*, **72**, 5152 (1950).

(41) J. G. Cook, J. T. Dickson, A. R. Lowe, and J. R. Whinfield, British Patent 604,985 (1948); *Chem. Abstr.*, **43**, P1223*g* (1949).

(42) P. D. Bartlett and P. R. Hiatt, *J. Amer. Chem. Soc.*, **80**, 1398 (1958).

toluene. The evacuated sample was sealed in a tube equipped with a break seal and placed in an 85° bath for 36 hr (10 half-lives); then the sample was opened on a vacuum line and the CO_2 was determined by absorption on Ascarite. Methane was identified by mass spectrometry. The products that were volatile at 25° and 0.05 Torr were collected in a Dry Ice cooled trap and made up to 25 ml with toluene. Cyclohexane was added as an internal standard and the vpc analysis (10 ft × $^3/_8$ in. 30% Carbowax 20M on Chromosorb W, 90°, 60 ml/min He) gave cyclohexane, acetone, *tert*-butyl alcohol, and toluene in that order. Identification was confirmed by isolation and spectral comparison with authentic samples.

In a separate experiment the product from 0.846 g (2.16 mmol) of **6** in 15 ml of toluene was treated as before, and 10 ml of toluene was removed by distillation. The residue was removed from the vacuum line and estimated to contain a 2.2% yield of acids (based on toluic acid) by comparison of the ir spectrum with those of authentic mixtures. This material was dissolved in 40 ml of ethanol and treated in the Brown[2] hydrogenator (1 atm of H_2, 5% Pd/C catalyst), 10 hr at 0°. The solution was filtered, the solvent was evaporated at room temperature, and the residue was dissolved in methylene chloride. An amorphous solid remained and after being rinsed several times with methylene chloride was identified as **13** (0.118 g, 0.44 mmol) by comparison with authentic material and conversion to the dimethyl ester **27**, also compared with authentic material. The methylene chloride solution was treated with excess diazomethane, made up to 25 ml, and dichlorobenzene was added as an internal standard. Vpc analysis (10 ft × $^3/_8$ in. 30% SE-30 on Chromosorb W, 75 ml/min He, programmed from 170 to 310°) gave the following peaks in order: dichlorobenzene (170°), *p*-methyl toluate (225°), bibenzyl (225°), **15** (225°), **14** (310°), and **27** (0.03 mmol) (310°).

In another experiment the product from 0.750 g (2.28 mmol) of **6** in 15 ml of toluene was concentrated under vacuum to 5 ml, and added very slowly to a solution of 1 g (0.03 mol) of powdered $LiAlH_4$ in 40 ml of dry THF at 0°. The solution was refluxed for 11 hr and cautiously hydrolyzed with water. The material was filtered through glass wool to remove the gelatinous precipitate, and the precipitate and glass wool were boiled with methylene chloride, which was filtered and combined with the previous extract. The solvent was evaporated, the residue was made up to 25 ml in CH_2Cl_2, and benzyl alcohol was added as an internal standard. Vpc analysis (10 ft × $^1/_8$ in. 5% Carbowax 20 M on Chromosorb G, 24 ml/min He, programmed from 175 to 245°) gave in order benzyl alcohol (175°), *p*-methylbenzyl alcohol (175°), bibenzyl (245°), and **17** (245°). Compound **18** was not detectably soluble in the solvents used, and *tert*-butyl benzyl ether was specifically shown to be absent.

The yields of products reported in Table II were determined from the integrations of the vpc curves. In all cases the integration was calibrated using weighed quantities of authentic materials with the internal standards.

Registry No.—**6**, 34201-98-4; **7**, 3965-62-6; **11**, 34202-00-1; **14**, 14518-67-3; **15**, 34224-28-7; **16**, 34224-29-8; **17**, 34224-30-1; **23**, 34224-31-2; **24**, 34224-32-3; **25**, 34224-33-4.

Cyclobutyl Sulfonate Solvolysis. Leaving Group Study

DONALD D. ROBERTS

Department of Chemistry, Louisiana Tech University, Ruston, Louisiana 71270

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The solvolysis rates of a series of cyclobutyl para-substituted arenesulfonates have been determined in ethanol, acetic acid, and 2,2,2-trifluoroethanol. In addition, the solvolysis rates of cyclobutyl methanesulfonate have been determined in the same series of solvents. The data indicate that the partitioning of the carbonium ion among solvolysis and internal return isomerization routes is insensitive to anion solvation and charge dispersal effects but is sensitive to the steric bulk of the leaving group. The product distributions are also insensitive to the changes in the leaving group.

Recently, it was established[1] that cyclobutyl β-naphthalenesulfonate suffers solvolysis in a spectrum of solvents with little nucleophilic assistance by solvent but with considerable anchimeric assistance.

The nature of the cationic species responsible for the observed anchimeric assistance is interpreted[2] in terms of a rapidly equilibrating bicyclobutonium ion system which is common to solvolysis of cyclopropylcarbinyl and allylcarbinyl derivatives as well as cyclobutyl substrates.

The proposed cationic species have open three options: internal return (k_{-1}), internal return isomerization (k_R), and solvolysis (k_2), as illustrated in Scheme I.

SCHEME I

$$\text{ROTs} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \text{R}^+\text{OTs}^- \xrightarrow[\text{HOS}]{k_2} \text{ROS} + \text{HOTs}$$

$$\text{R}^+\text{OTs}^- \xrightarrow{k_R} \text{R'OTs}$$

The internal return isomerization route is well documented for the cyclopropylcarbinyl system.[3,4]

The presence of internal return isomerization has also been observed in the solvolysis reactions of cyclobutyl derivatives.[1,5] In keeping with the common cationic species postulated for both the cyclopropylcarbinyl and cyclobutyl derivatives in acetolysis reactions, about 10% of both substrates isomerize by the k_R route to allylcarbinyl derivatives.[1,4]

An examination of the literature suggests that the relative importance of the competing reactions, k_2/k_R, is sensitive to change in the nature of the leaving group. For example, the acetolysis of cyclobutyl chloride is accompanied by 40% internal return isomerization[5] while the acetolysis of cyclobutyl β-naphthalenesulfonate is accompanied by only 8% internal return isomerization.[1] Both cyclobutyl derivatives, however, exhibit the same solvent dependency behavior, *i.e.*, reduced internal return isomerization with increased solvent ionizing strength.[1,6]

These results contrast with the findings of related work. Thus Goering and coworkers,[7] using a combination of polarimetric and titrimetric kinetic techniques, demonstrated that the relative rates of com-

(1) D. D. Roberts, *J. Org. Chem.*, **36**, 1913 (1971).
(2) K. L. Servis and J. D. Roberts, *J. Amer. Chem. Soc.*, **86**, 3773 (1964).
(3) K. L. Servis and J. D. Roberts, *Tetrahedron Lett.*, 1369 (1967).
(4) D. D. Roberts, *J. Org. Chem.*, **35**, 4059 (1970).
(5) J. D. Roberts and R. H. Mazur, *J. Amer. Chem. Soc.*, **73**, 2509 (1951).
(6) C. Y. Wu and R. E. Robertson, *ibid.*, **88**, 2666 (1966).
(7) H. L. Goering and E. F. Silversmith, *ibid.*, **77**, 6249 (1955), and previous papers cited therein.

TABLE I

SOLVOLYSIS RATES FOR CYCLOBUTYL SULFONATES

Registry no.	Sulfonate	Solvent	Temp, °C	k_1, 10^6 sec^{-1}	Infinity, %
34236-40-3	*p*-Nitrobenzene	EtOH	40	74 ± 0.8	100
			50	233 ± 3	100
			60	740 ± 8	
	p-Nitrobenzene	AcOH	30	92 ± 1	92
			40	195 ± 2	
			50	610 ± 6	90
	p-Nitrobenzene	CF_3CH_2OH	25	920 ± 8	92
34236-41-4	*p*-Bromobenzene	EtOH	40	11 ± 0.2	
			50	33 ± 0.3	100
			50	33 ± 0.3[a]	100
			60	117 ± 2	
	p-Bromobenzene	AcOH	30	9.7 ± 0.1	92
			40	36 ± 0.3	93
			50	120 ± 2	90
			50	120 ± 2[b]	90
			50	127 ± 2[c]	92
			50	123 ± 2[d]	98
			60	380 ± 4	92
	p-Bromobenzene	CF_3CH_2OH	25	172 ± 3	92
			35	520 ± 6	91
34236-42-5	Benzene	EtOH	40	3.6 ± 0.04	
			50	11 ± 0.2	99
			60	39 ± 0.4	
	Benzene	AcOH	30	4.3 ± 0.04	94
			40	16 ± 0.2	88
			50	50 ± 0.5	92
			50	55 ± 0.2[e]	92
	Benzene	CF_3CH_2OH	25	83 ± 2	93
34236-43-6	*p*-Methylbenzene	EtOH	40	1.8 ± 0.01	
			50	6.1 ± 0.3	100
			50	6.1 ± 0.4[f]	100
			60	20 ± 0.4	
	p-Methylbenzene	AcOH	30	2.6 ± 0.03	92
			40	8.9 ± 0.1	
			50	33 ± 0.2	92
			50	34 ± 0.3[g]	92
	p-Methylbenzene	CF_3CH_2OH	25	53 ± 0.1	92
34236-44-7	*p*-Methoxybenzene	EtOH	40	1.39 ± 0.03	
			50	3.6 ± 0.1	100
			60	12.5 ± 0.2	
	p-Methoxybenzene	AcOH	30	1.7 ± 0.03	93
			40	6.1 ± 0.04	
			50	21 ± 0.2	87
	p-Methoxybenzene	CF_3CH_2OH	25	36 ± 0.5	90
34236-45-8	Methane	EtOH	50	4.7 ± 0.1[h]	100
	Methane	AcOH	50	47 ± 0.5[h]	80
	Methane	CF_3CH_2OH	25	50 ± 0.3	80

[a] Sample 0.05 *M* in urea and 0.030 *M* in ester. [b] Sample 0.033 *M* in *p*-toluenesulfonic acid and 0.030 *M* in ester. [c] Sample 0.0475 *M* in KOAc and 0.030 *M* in ester. [d] Sample 0.05 *M* in NaOAc and 0.030 *M* in ester. [e] Sample 0.0475 *M* in KOAc and 0.030 *M* in ester. [f] Sample 0.05 *M* in urea and 0.030 *M* in ester. [g] Sample 0.0475 *M* in KOAc and 0.030 *M* in ester. [h] Duplicate runs.

peting solvolysis and internal return rearrangement of various 5-methyl-2-cyclohexenyl derivatives were insensitive to changes in the nature of the leaving group (chloride, acid phthalate, and *p*-nitrobenzoate). Winstein and collaborators[8] also found that the relative rates of competing solvolysis and internal return racemization of norbornyl derivatives were insensitive to changes in the nature of the leaving group (chloride, bromide, iodide, and brosylate).

For some time the arenesulfonate group has been regarded by various authors[9] as well solvated relative to a monatomic leaving group, since it contains oxygen atoms which are capable of hydrogen bonding. The resulting increase in the solvation forces associated with the arenesulfonate leaving group should promote solvolysis and retard internal return relative to the chloride leaving group. This tendency should be modified as the charge density on the oxygen atoms in the arenesulfonate group is modified. To test the validity of this rationale the solvolysis study of a series of cyclobutyl para-substituted arenesulfonates was undertaken. During the course of this study some related aspects were investigated and are included in this paper in order to gain further insight as to the behavior of the cationic species involved in the cyclopropylcarbinyl–cyclobutyl solvolysis reactions.

(8) S. Winstein and G. C. Robinson, *J. Amer. Chem. Soc.*, **80**, 169 (1958), and previous papers cited therein.

(9) For example, see S. Winstein, A. H. Fainberg, and E. Grunwald, *ibid.*, **79**, 4146 (1957).

The data indicate that the partitioning of the carbonium ion among solvolysis and internal return isomerization routes is insensitive to anion solvation and charge dispersal effects but is sensitive to the size of the leaving group.

The first-order rate constants for solvolysis of cyclobutyl mesylate and a series of para-substituted arenesulfonates in various solvents are summarized in Table I. The reaction progress was followed by titrating the liberated alkyl and arylsulfonic acid. The solvolysis reactions in ethanol were unaccompanied by internal return isomerization and were cleanly first order up to 90% reaction. The solvolysis reactions in acetic acid and 2,2,2-trifluoroethanol were accompanied by internal return isomerization and consequently the apparent first-order rate constants, k_t, in these two solvents were computed on the basis of the acid infinity titer. The fact that the infinity titers in buffered and unbuffered reactions were identical supports an internal return isomerization and not a competing acid-catalyzed isomerization.

The sign and response of the calculated ρ valves, 1.75 for ethanolysis, 1.43 for acetolysis, and 1.38 for 2,2,2-trifluoroethanolysis, support a varying negative charge density at the oxygen atoms in the arenesulfonate leaving group; *i.e.*, the observed rate constant, k_t, is enhanced by para substituents with $+\sigma^n$ values.[10,11] For example, the *p*-nitrobenzenesulfonate relative to the *p*-methoxybenzenesulfonate is some 65 times more reactive in ethanol, 29 times more reactive in acetic acid, and 25 times more reactive in 2,2,2-trifluoroethanol.

The product distribution data listed in Table II

TABLE II

ACETOLYSIS PRODUCTS FOR CYCLOBUTYL SULFONATES[a]

Sulfonate	c-C_4H_7OS, %	c-C_3H_5-CH_2OS, %	CH_2=$CHCH_2CH_2$-OS, %
p-Bromobenzene	41	55	4
p-Methane	41	55	4
p-Methoxybenzene	42	54	4

[a] At 50° with urea buffer present.

reveal no dependency upon the nature of the leaving group. This marked insensitivity of the product distribution upon leaving group is consistent with the solvolytic behavior of the cyclopropylcarbinyl substrates.[12]

These results strongly suggest that the charge dispersal distribution in the reactive intermediate captured by solvent varies little with anion; *i.e.*, the nature of the anion in the intimate ion pair has little apparent affect upon the partitioning of the nonclassical cation[14-16] among the various product pathways.

(10) P. R. Wells, *Chem. Rev.*, **63**, 178 (1963).

(11) Not unexpectedly, the *p*-methoxy substituent fits this correlation only when a regular σ value (−0.268) is used which includes the resonance contribution.

(12) For example, the acetolysis of both cyclopropylcarbinyl chloride[5] and tosylate[13] yield essentially the same product distribution.

(13) D. D. Roberts, *J. Org. Chem.*, **29**, 294 (1964).

(14) P. D. Bartlett, "Nonclassical Ions," W. A. Benjamin, New York, N. Y., 1965.

(15) W. Bruce Kover and J. D. Roberts, *J. Amer. Chem. Soc.*, **91**, 3687 (1969).

(16) The nonclassical ion postulated for both the cyclopropylcarbinyl and cyclobutyl systems is obviously in a state of rapid development; for an alternative view see Z. Majerski and P. v. R. Scleyer, *J. Amer. Chem. Soc.*, **93**, 665 (1971).

An examination of the competing solvolysis and internal return isomerization reactions (k_2/k_R) is afforded by the derived data in Table III. The k_2/k_R ratio is sensitive to the solvent change from ethanol to acetic acid but insensitive to the change from acetic acid to 2,2,2-trifluoroethanol, while the observed rate constant, k_t, exhibits the opposite solvent sensitivity, a small twofold increase in changing from ethanol to acetic acid and a 40-fold increase in changing from acetic acid to 2,2,2-trifluoroethanol. This observation is true for the entire spectrum of leaving groups investigated in this study.

TABLE III

SOLVOLYSIS–INTERNAL RETURN ISOMERIZATION RATE RATIOS FOR c-C_4H_7X

X	Solvent	Temp, °C	% rearrangement	k_2/k_R
Cl[a]	AcOH	100	43	1.32
OSO_2CH_3	AcOH	50	20	4.00
	EtOH	50	0	
	CF_3CH_2OH	25	20	4.00
p-$YC_6H_4OSO_2$[b]	AcOH	50	8	11.5
	EtOH	50	0	
	CF_3CH_2OH	25	8	11.5

[a] Taken from data of ref 5. [b] Y = NO_2, Br, H, CH_3, OCH_3.

More significantly, the data in Table III reveal that the magnitude of the k_2/k_R ratio is insensitive to charge dispersal in the arenesulfonate leaving group, but is sensitive to change in steric bulk of the leaving group. Thus, in acetic acid the value of k_2/k_R is 1.32 for cyclobutyl chloride, 4.0 for cyclobutyl mesylate, and 11.5 for the various para-substituted cyclobutyl arenesulfonates.

This result clearly indicates that variation of the k_2/k_R ratio is not due to enhanced solvation of the arenesulfonate leaving group. It is unlikely that the tosylate group, with its greater steric bulk and charge dispersal, would be more strongly solvated than the methanesulfonate group, yet in acetolysis reactions, 20% of the cyclobutyl mesylate undergoes internal return isomerization as compared to only 8% of cyclobutyl tosylate. Both esters suffer acetolysis at approximately the same rate as does cyclobutyl β-naphthalenesulfonate, an ester whose acetolysis is also accompanied by only 8% internal return isomerization.

Inspection of models of the various cyclobutyl derivatives provides a convenient organization of the leaving groups into three steric bulk groups: small (chloride), medium (methanesulfonate), and large (arenesulfonate). The tempting correspondence between the leaving group steric bulk and the extent of internal return isomerization is readily apparent.

An appreciation of the proposal[2] that the intimate ion pair is described as a set of rapidly equilibrating ion pairs sheds some light on this correspondence. It is possible that in this dynamic situation the blend of electrostatic, polarization, and covalencey forces[17] that stabilizes as well as leads to the collapse of the ion pair intermediate is responsive to the change in anion steric bulk, which in turn affects the relative heights of the energy barriers for internal return and solvolysis.

(17) S. Winstein and G. C. Robinson, *J. Amer. Chem. Soc.*, **80**, 169 (1958).

Experimental Section

A Beckman GC-4 chromatographic instrument equipped with a thermal conductivity detector and an 8 ft × 0.25 in. column of 20% diethylene glycol succinate on Chromosorb W, AW-DMCS (45–60 mesh) and a Bausch and Lomb IR 270 spectrophotometer were used for analytical work.

Cyclobutyl *p*-nitrobenzenesulfonate resulted when *p*-nitrobenzenesulfonyl chloride (7.2 g, 35 mmol) was mixed with cyclobutanol (2.16 g, 30 mmol) and 40 ml of dry pyridine at 0°. After standing for 20 hr at 0°, the thick reaction mixture was carefully hydrolyzed by the slow addition of 20 ml of cold water at 0–5° followed by the rapid addition of sufficient cold, dilute HCl to acidify the mixture. The precipitated ester was separated on a Buchner funnel and washed several times with cold, dilute HCl, several times with cold water and then with cold petroleum ether (bp 30–60°) to yield the crude ester. Recrystallization from petroleum ether–benzene gave 5.0 g (65%) of light yellow crystals, mp 64–68°. Two additional recrystallizations yielded the analytical sample, mp 68–69°.

Anal. Calcd for $C_{10}H_{11}NO_5S$: C, 46.69; H, 4.31; N, 5.45. Found: C, 46.63; H, 4.39; N, 5.60.

Cyclobutyl *p*-bromobenzenesulfonate was prepared from *p*-bromobenzenesulfonyl chloride as described above in 63% yield: mp (after two recrystallizations from 33:1 petroleum ether–benzene) 53–54° (lit.[18] mp 52–53.5°).

Cyclobutyl Benzenesulfonate.—To 3.6 g (50 mmol) of cyclobutanol in 50 ml of dry pyridine cooled to 0° was added 9.7 g (55 mmol) of benzenesulfonyl chloride. After standing for 24 hr at 5° and an additional 28 hr at 18°, the mixture was carefully hydrolyzed by the slow addition of 20 ml of cold water at 0–5° followed by the rapid addition of sufficient cold, dilute HCl to acidify the mixture. The separated oil was taken up in 40 ml of methylene chloride, washed twice with cold, dilute HCl and once with cold, saturated $NaHCO_3$, dried over Na_2SO_4, and concentrated to yield an oil. The crude ester was purified twice by stirring with petroleum ether, freezing the undissolved oil at −78°, decanting off the solvent, and removing the last traces of solvent under reduced pressure (*ca.* 0.1 mm) to yield 5.5 g (52%) of an oil. The purity, calculated from infinity titers of the ethanolyses, was 99%. The ir spectrum, ν_{SO_2} (asymmetric) 1360 and ν_{SO_2} (symmetric) 1170 cm^{-1}, was consistent with the assigned structure.

Cyclobutyl *p*-toluenesulfonate was prepared in 50% yield by published procedure:[19] mp 25° (lit.[19] mp 24–25°); ir (neat) 1357 (ν_{SO_2}, asymmetric) and 1173 cm^{-1} (ν_{SO_2} symmetric).

Cyclobutyl *p*-methoxybenzenesulfonate was prepared from *p*-methoxybenzenesulfonyl chloride as described for cyclobutyl benzenesulfonate in 59% yield. The purity of the oil, calculated from infinity titers of the ethanolyses, was 99%. The ir spectrum, ν_{SO_2} (asymmetric) 1358 and ν_{SO_2} (symmetric) 1170 cm^{-1}, was consistent with assigned structure.

Cyclobutyl methanesulfonate was prepared from methanesulfonyl chloride as described for cyclobutyl benzenesulfonate in 40% yield. The purity of the oil, calculated from infinity titers of the ethanolyses, was 99%; ir (neat) 1340 (ν_{SO_2}, asymmetric) and 1170 cm^{-1} (ν_{SO_2}, symmetric).

Solvents.—Absolute ethanol was prepared according to the method of Fieser.[20] Acetic acid solvent was prepared from 994.9 ml of glacial acetic acid (Matheson Scientific, 99.8%) and 5.1 ml of acetic anhydride. 2,2,2-Trifluoroethanol (Aldrich Chemical Co.) was redistilled just prior to use.

Acetolysis Product Studies. A. Cyclobutyl *p*-Bromobenzenesulfonate.—Cyclobutyl *p*-bromobenzenesulfonate (1.5 g, 5 mmol) was dissolved in sufficient acetic acid solvent (containing 7 mmol of urea) to give 25 ml of solution. After 10 half-lives at 50°, the solution was diluted with 150 ml of water and continuously extracted with ether for 24 hr. The ether extract was neutralized with $NaHCO_3$ and dried (Na_2SO_4), and most of the solvent was removed by distillation. Analysis by gc revealed, in addition to solvent, the presence of allylcarbinyl acetate, cyclobutyl acetate, and cyclopropylcarbinyl acetate in the ratio 1.0:10.2:13.7, respectively.

B. Cyclobutyl *p*-Methoxybenzenesulfonate.—Cyclobutyl *p*-methoxybenzenesulfonate (1.2 g, 5 mmol) was solvolyzed in 25 ml of acetic acid solvent (containing 7 mmol of urea) for 10 half-lives at 50°. The material was worked up as before and analysis by gc revealed, in addition to solvent, the presence of allylcarbinyl acetate, cyclobutyl acetate, and cyclopropylcarbinyl acetate in the ratio 1.0:10.5:13.5, respectively.

C. Cyclobutyl Methanesulfonate.—Cyclobutyl methanesulfonate (0.53 g, 5 mmol) was solvolyzed as above for 10 half-lives at 50°. The material was worked up as before and analysis by gc revealed, in addition to solvent, the presence of allylcarbinyl, cyclobutyl, and cyclopropylcarbinyl acetate in the ratio 1.0:10.2:13.7, respectively.

Rate measurements were accomplished by usual ampoule techniques.[21] The titrating solutions were, for ethanolysis and 2,2,2-trifluoroethanolysis, 0.020 *N* sodium methoxide in anhydrous methanol and, for acetolysis, 0.020 *N* sodium acetate in acetic acid. The indicators used were bromthymol blue (in water), bromphenol blue (in 20% aqueous EtOH), and bromphenol blue (in acetic acid), respectively.

Registry No.—EtOH, 64-17-5; AcOH, 64-19-7; CF_3CH_2OH, 75-89-8.

(18) I. Lillien and L. Handloser, *J. Amer. Chem. Soc.*, **93**, 1682 (1971).
(19) J. D. Roberts and V. C. Chambers, *ibid.*, **73**, 5034 (1951).
(20) L. F. Fieser, "Experiments in Organic Chemistry," 3rd ed, D. C. Heath, Boston, Mass., 1957, p 285.
(21) D. D. Roberts, *J. Org. Chem.*, **29**, 294 (1964).

The Electrochemical Reduction of Aromatic Acids to the Corresponding Aldehydes

JOHN H. WAGENKNECHT

Central Research Department, Monsanto Company, St. Louis, Missouri 63166

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A number of aromatic carboxylic acids have been found to undergo electrochemical reduction to the corresponding aldehydes. Electron-donating substituents in the para position inhibit the reaction. It is possible to predict from the pK_a value of the acid or, more accurately, from the polarographic half-wave potential of the corresponding methyl ester whether or not the method is applicable for the preparation of an aldehyde.

The chemical reduction of a carboxylic acid to the corresponding aldehyde generally involves initial formation of a derivative of the acid other than a salt and subsequent reduction of the derivative. Calcium or manganese salts of carboxylic acids can be converted to the aldehydes by pyrolysis in the presence of the corresponding formate salts.[1,2] Similarly, the vapor phase reaction of a mixture of a carboxylic acid and formic acid over TiO_2 or ThO_2 leads to the aldehyde.[3] Although the reduction of carboxylic acids to the aldehydes by $(i\text{-Bu})_2AlH$ has been reported,[4] aluminum and boron hydrides generally reduce acids to the corresponding alcohols. However, acids such as perfluoroaliphatic acids, oxalic acid, or salicylic acid are re-

(1) E. Müller, "Methoden der Organische Chemie" (Houben-Weyl), Vol. VII, Part 1, Georg Thieme Verlag, Stuttgart, 1954, p 277.
(2) P. Mastagli, P. Lambert, and C. Hirigoyen, *C. R. Acad. Sci.*, **248**, 1830 (1959).
(3) P. Sabatier and A. Mailhe, *ibid.*, **154**, 561 (1912).
(4) L. I. Zakharkin and I. M. Khorlina, *Zh. Obshch. Khim* **34**, 1029 (1964).

duced to the aldehydes by $LiAlH_4$.[5] Lithium in ethylamine reduces aliphatic acids to the corresponding aldehydes[6] and sodium amalgam has been used to reduce aromatic acids to the corresponding aldehydes.[7]

It is generally believed that the electrochemical reduction of aromatic acids leads to the corresponding benzyl alcohol, since the intermediate aldehyde is more easily reduced than the parent acid.[8] There are several reported examples, however, of reductions in which the aldehyde has been trapped to protect it from further reduction. The most widely studied example is the reduction of salicylic acid to salicylaldehyde. In this case, the aldehyde is usually protected by *in situ* formation of the bisulfite addition complex.[9]

$$ArCO_2H \xrightarrow[-H_2O]{2e + 2H^+} ArCHO \xrightarrow[2H^+]{2e} ArCH_2OH$$

The reductions of several heterocyclic carboxylic acids to the corresponding aldehydes have been reported.[10] This is possible because the aldehydes exist in solution partially as the nonreducible hydrated species.

The aldehyde formed on reduction of 2,3-naphtholcarboxylic acid has been trapped with *p*-toluidine to form the insoluble Schiff base, but only in poor yield.[11]

The reduction of benzoic acid to benzaldehyde has been reported to occur in 30–50% yield in an undivided cell using benzene to extract the aldehyde.[12] However, other workers have been unable to reproduce these results.[13] This paper is a report of a simple general method for the electroreduction of aromatic carboxylic acids to the aldehydes and the methods of predicting the applicability of the reaction to a given acid.

Results and Discussion

The results of the attempted electroreduction of various aromatic carboxylic acids to the corresponding aldehydes are shown in Table I. The method (when boric acid is indicated as the buffer) is essentially that described by Mettler[12] except that a divided cell was used, the pH was continually controlled at pH 6 ± 0.2, and ammonium ion was substituted for sodium ion. These changes resulted in a considerable improvement over previously reported results in the initial current efficiency for salicylaldehyde formation. The use of benzene to extract the aldehyde from the catholyte as described by Mettler allows for more convenient recovery of the product than is possible using the bisulfite method of protecting the aldehyde.[9]

The method is limited in general to acids with carboxyl groups directly attached to an aromatic ring, and the current efficiency is poor for compounds with para electron-donating substituents. Of course, substituents more easily reduced than carboxylate, such as nitro groups, would also be reduced.

Table I
Reductions of Various Carboxylic Acids to the Aldehydes

Acid	Registry no.	Current efficiency,[a] %	Buffer	pK_a[b]	$E_{1/2}$ vs. sce[c]
Benzoic	65-85-0	55	H_3BO_3	4.20	−2.12[c,d]
Benzoic		8	None		
Benzoic		42	Phosphate		
Salicylic	69-72-7	73	H_3BO_3	3.00	−2.02[d]
Salicylic		Trace	None		
Salicylic		Trace	Phosphate		
p-Hydroxybenzoic	99-96-7	3	H_3BO_3	4.48	−2.32[d]
o-Methoxybenzoic	586-38-9	55	H_3BO_3	4.08	
o-Methoxybenzoic		7	None		
o-Methoxybenzoic		43	Phosphate		
p-Methoxybenzoic	100-09-4	1.75	H_3BO_3	4.47	−2.31[d]
o-Toluic	118-90-1	3	H_3BO_3	3.91	−2.21[c]
p-Toluic	99-94-5	15	H_3BO_3	4.37	−2.20[c,d]
o-Acetoxybenzoic	50-78-2	41	H_3BO_3	3.49	
o-Acetoxybenzoic		1.5	None		
o-Acetoxybenzoic		3.5	Phosphate		
p-Cyanobenzoic	619-65-8	37	H_3BO_3	3.55	
o-Fluorobenzoic	445-29-4	41	H_3BO_3	3.27	
o-Fluorobenzoic		14	None		
o-Fluorobenzoic		46	Phosphate		
Vanillic	121-34-6	5	H_3BO_3	4.48	
Phenylacetic		None	H_3BO_3	4.31	
Phenoxyacetic		None	H_3BO_3	3.17	

[a] To the corresponding aldehyde. [b] Values taken from "Handbook of Tables for Organic Compound Identification," 3rd ed, Chemical Rubber Co., Cleveland, Ohio, 1967. [c] Values determined for the methyl esters in 50% ethanol containing 0.1 *M* $Et_4N^+ClO_4^-$. [d] Values taken from T. Arai, *Nippon Kagaku Zasshi*, 89, 188 (1968), were converted to the numbers shown by addition of −0.42 V as determined from the two overlapping compounds, methyl benzoate and methyl *p*-toluate.

It is possible to predict the efficiency of the reduction of a given acid to the aldehyde from the pK_a value of the acid. From values shown in Table I one can see that acids with pK_a values greater than 4.40 undergo reduction to the aldehyde with very poor current efficiency.

A more accurate prediction of the result with a given acid may be obtained by the comparison of polarographic half-wave reduction potentials of the corresponding methyl esters (Table I). Thus, if a methyl ester has an $E_{1/2}$ value of −2.20 (*vs.* sce in 50% ethanol containing 0.1 *M* $Et_4N^+ClO_4^-$) or a more negative value, the current efficiency for the reduction of the acid to the aldehyde will be very low.

The assumption is made that the species being reduced is the carboxylic acid, a carboxylate ion pair, or a complexed carboxylate. Free carboxylate anion does

(5) Reference 1, p 303.
(6) A. W. Bergstohler, L. R. Worden, and T. B. Lewis, *J. Org. Chem.*, **28**, 2918 (1963).
(7) H. Weil, M. Traun, and S. Marcel, *Chem. Ber.*, **55**, 2664 (1922).
(8) M. J. Allen, "Organic Electrode Processes," Reinhold, New York, N. Y., 1958, p 71.
(9) (a) J. A. May and K. A. Kobe, *J. Electrochem. Soc.*, **97**, 183 (1950), and references cited therein; (b) K. S. Udupa, G. S. Subramanian, and H. V. K. Udupa, *Ind. Chem.*, **39**, 238 (1963).
(10) (a) H. Lund, *Acta Chem. Scand.*, **17**, 972 (1963); (b) P. E. Iversen and H. Lund, *ibid.*, **21**, 279, 389 (1967); (c) P. E. Iversen, *ibid.*, **24**, 2459 (1970).
(11) N. M. Przhiyalgovskaya, L. N. Lavrishcheva, G. T. Mondodoev, and V. N. Belov, *J. Gen. Chem. USSR*, **31**, 2163 (1960).
(12) C. Mettler, *Chem. Ber.*, **41**, 4148 (1908).
(13) K. S. Tesh and A. Lowy, *Trans. Electrochem. Soc.*, **45**, 37 (1924).

not reduce, as can be determined by the polarography of quaternary ammonium carboxylates.[14]

The reduction normally occurs near the electrode potential at which ammonium ion reduces and it appears that difficultly reducible compounds reduce at more negative potentials than ammonium ion. They cannot compete favorably in the electrode reaction, allowing the majority of the current to be consumed by ammonium ion and proton reduction.

The reduction of ammonium ion causes an operational problem during long-term electrolysis. Ammonium ion is reduced to ammonium amalgam,[15] which slowly decomposes to ammonia and hydrogen, which form a mercury foam on the cathode surface. The foam may be removed physically or by simply stopping the electrolysis for a few minutes, at which time the gases will escape, the mercury surface will return to normal, and the electrolysis can be resumed.

Steric Effects.—One would predict from the pK_a value of *o*-toluic acid that it would be reduced with good current efficiency to the aldehyde. Further, one would predict from Hammett substituent constants that methyl *o*-toluate would be more easily reduced than methyl *p*-toluate.[16] Although neither of these predictions is correct, the relative reduction potential of methyl *o*-toluate does correctly predict the result of the *o*-toluic acid reduction. Apparently the *o*-methyl group sterically inhibits coplanarity between the carboxyl group and the aromatic ring, making the reduction occur at a more negative potential than would be predicted from inductive effects. The carboxylate can be reduced only if π overlap with the aromatic ring can occur, as is shown by the inertness of phenylacetic and phenoxyacetic acids to reduction, even though the magnitude of the inductance is similar to that of reducible acids. Steric inhibition to coplanarity with the ring by *o*-methyl groups has also been shown to occur in other reductions.[16] From the small difference between $E_{1/2}$ values for methyl *o*-toluate and methyl *p*-toluate, less difference in the current efficiencies for the acid reductions would be expected. This may indicate that the species being reduced is more bulky than the methyl ester, *e.g.*, an ion pair with ammonium ion.

Effects of Buffering.—In several examples the reductions were carried out with the boric acid omitted or replaced with a phosphate buffer. From the results (Table I) it is clear that salicylic acid and acetylsalicylic acid are reduced as borate complexes (in agreement with previous results[9]) and the uncomplexed carboxylates are not reduced. None of the other acids tried were particularly sensitive to the type of buffering agent and, therefore, must be reduced as the free acid or an ion pair. In the absence of a buffer the pH at the cathode surface has been shown to be very high.[17] Even under these conditions some aldehyde was formed in most cases, and it is highly unlikely that free carboxylic acid would have been available at the electrode surface. Therefore, the most likely reaction is the reduction of an ion pair, since, as stated previously, the free carboxylate anion is not reducible.

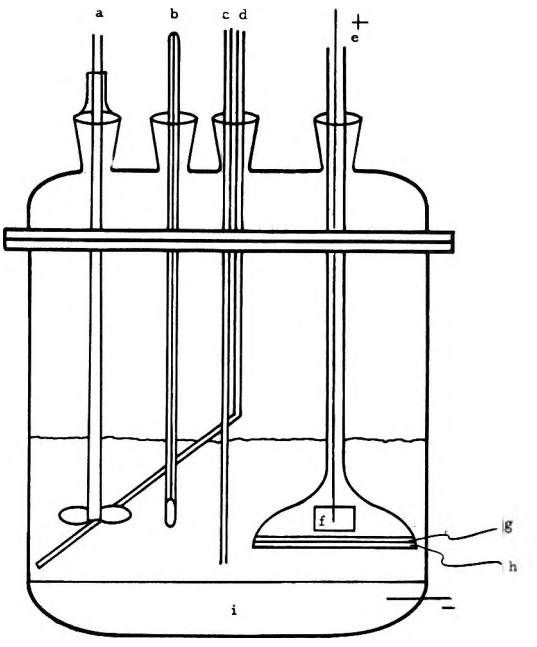

Figure 1.—Electrolysis cell: (a) stirrer; (b) thermometer; (c) entrance for pH meter side stream; (d) exit stream; (e) anode compartment; (f) anode; (g) agar layer; (h) glass frit; (i) Hg pool.

Protection of the Aldehyde.—The efficiency of aldehyde removal by benzene extraction is remarkable. In the case of salicylaldehyde, only about 4% of the alcohol, saligenin, was obtained in a reduction carried out to more than 50% conversion of the acid. Further, the yield of salicylaldehyde based on unrecovered starting material was 80%. The initial reduction product of an aromatic acid is probably the hydrated aldehyde I. Since aromatic aldehydes are known to be

$$\mathrm{ArCO_2H} \xrightarrow[2\mathrm{H^+}]{2e} \underset{\mathrm{H}}{\overset{\mathrm{OH}}{\mathrm{ArCOH}}} \xrightarrow{-\mathrm{H_2O}} \mathrm{ArCHO}$$

I

reducible, it would seem that any formed at the electrode surface would be immediately reduced to the benzyl alcohol derivative. Thus, apparently the rate of dehydration of I is slow enough to allow the species I to leave the electrode surface. Dehydration in the bulk solution to the aldehyde is followed by rapid extraction into the organic solvent. The fact that a buffer is necessary for the reaction is consistent with the above scheme, since aldehyde hydration reactions are base catalyzed.[18]

Experimental Section

All acids and aldehydes were obtained commercially and used as received. Polarography was carried out with a Sargent XXI polarograph using a conventional H cell with a saturated calomel reference electrode. Gas chromatographic analyses were performed on a Varian Series 1200 chromatograph or an F & M Model 5750 chromatograph, both with flame detectors.

Electrolysis Cell.—The electrolyses were carried out in the apparatus shown in Figure 1. Power was supplied by a Sorensen Nobatron DCR 300-2.5 constant-current power supply. A portion of the catholyte was cycled *via* 1/4-in. polyethylene tub-

(14) In the presence of excess tetraethylammonium hydroxide, benzoate and salicylate show no polarographic reduction waves. Certain substituted benzoates, such as bromobenzoates, are reducible but the substituent is probably being reduced (J. H. Wagenknecht, Ph.D. Dissertation, University of Iowa, Feb 1964).

(15) A. J. Deyrup, *J. Amer. Chem. Soc.*, **56**, 2594 (1934).

(16) P. Zuman, "Substituent Effects in Organic Polarography," Plenum Press, New York, N. Y., 1967.

(17) M. R. Ort and M. M. Baizer, *J. Org. Chem.*, **31**, 1646 (1966).

(18) J. Hine, "Physical Organic Chemistry," McGraw-Hill, New York, N. Y., 1962, p 250.

ing to a small, magnetically driven centrifugal pump with a polypropylene head, through a small flask containing pH meter probes and back to the electrolysis cell. The calomel electrode used for pH measurements was separated from the catholyte by an agar plug prepared from 3% agar in 10% aqueous tetramethylammonium chloride. The anode compartment was made from a coarse sintered-glass filter funnel with the walls removed and stem lengthened. A layer of fresh hot solution of 3% agar in 10% aqueous tetramethylammonium chloride was poured onto the anode side of the sintered glass for each experiment. The cell was cooled with an isopropyl alcohol bath to which Dry Ice was added as needed.

General Procedure.—The electrolyses were carried out as follows. Acid (0.15 mol) was neutralized with ammonium hydroxide and diluted to about 250 ml. To this solution was added 18.6 g of boric acid or 20 g of $(NH_4)H_2PO_4$, if a buffer was used. The solution was diluted to 300 ml and adjusted to pH 6 with ammonium hydroxide or dilute hydrochloric acid. This solution, along with 200 ml of benzene, was added to the electrolysis cell. The anolyte consisted of 10% tetramethylammonium chloride with some ammonium hydroxide added to keep the solution basic. The catholyte was stirred vigorously to maintain a good emulsion.

After the solution had been cooled to about 10°, the electrolysis was started with the current set at 0.8 A (current density about 10 mA/cm²). During the electrolysis the temperature was maintained near 10° and the pH was kept at 6 ± 0.2 by the addition of dilute HCl. After 0.5 hr, the electrolysis was stopped, an internal standard was added to the benzene, and that solution was analyzed by gas chromatography for the desired aldehyde. It was on this basis that the current efficiencies shown in Table I were determined.

In a longer experiment using salicylic acid with boric acid present, the electrolysis was carried out at 1.5 A for 5 hr. After each hour, the mercury pool was replaced because of the large amount of mercury foam which had formed on the surface.

Analysis.—After the electrolysis, the benzene was separated and analyzed for salicylaldehyde as below. The aqueous catholyte was divided into two equal portions. One-half was acidified to pH 1 with concentrated HCl and extracted with ether. Gas chromatographic analysis of the ether solution for saligenin indicated that a 4% current efficiency to saligenin was obtained. The other portion of the catholyte was taken to pH 9 with NaOH, diluted, and analyzed for salicylate with a salicylate ion selective electrode[19] by the known addition technique[20] and comparing to known solutions containing approximately the same composition. Of the initial salicylic acid, 90% was accounted for either as unreacted salicylic acid, salicylaldehyde (80% yield, 50% current efficiency), or saligenin.

The analyses of the aldehydes except for hydroxy aldehydes were carried out on a 10 ft × 1/8 in. gas chromatography column packed with 10% Carbowax 20M on Chromosorb G using biphenyl or naphthalene as internal standards.

Salicylaldehyde, saligenin, *p*-hydroxybenzaldehyde, and vanillin were treated in benzene (or ether) solution with Regisil [bis(trimethylsilyl)trifluoroacetamide] and then analyzed by gas chromatography on a 10 ft × 1/8 in. column packed with 10% SE-52 on Chromosorb W using naphthalene or biphenyl as the internal standards.[21]

Acknowledgment.—The author wishes to thank Mr. W. O. Jackson for technical assistance and Drs. M. M. Baizer and D. A. Tyssee for helpful discussions.

(19) W. M. Haynes and J. H. Wagenknecht, *Anal. Lett.*, **4**, 491 (1971).

(20) Orion Newsletter, July 1969, p 9.

(21) Since this paper was submitted, an article has appeared [J. A. Harrison and D. W. Shoesmith, *J. Electroanal. Chem.*, **32**, 125 (1971)] showing significant improvements in the yields of aldehydes in the reduction of aromatic acids by Udupa's method[5b] (rotating Cu amalgam cathode). This was accomplished by replacing metal ions with tetramethylammonium ions and by adding ethanol to the catholyte.

Exchange of Aryl Ligands to Polyvalent Iodine[1]

F. MARSHALL BERINGER* AND LYDIA L. CHANG

Department of Chemistry, Polytechnic Institute of Brooklyn, Brooklyn, New York 11201

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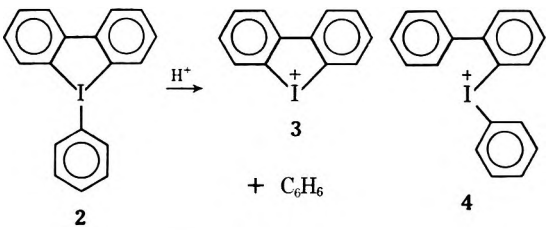
By treatment with aryllithium reagents (RLi) and then acid, diaryliodonium salts ($Ar_2I^+X^-$) have been converted to ArI^+X^- and $R_2I^+X^-$. With $[RLi]/[Ar_2I^+]$ near unity, a triaryliodine can be isolated. The product ratio from its acid cleavage reflects the relative susceptibility of Ar and R to protodeiodination and the selectivity of the reagent. Results include cases where Ar_2 = 2,2′-biphenylene (*i.e.*, Ar_2I^+ is the dibenziodolium ion) and R = C_6H_5, and where Ar = 4-chlorophenyl and R = C_6H_5. With $[RLi]/[Ar_2I^+] > 1$, aryl groups can be exchanged through three- and four-coordinated iodine intermediates, such as $Ar_2R_2I^-Li^+$. Treatment of the reaction mixture with acid gives iodonium salts whose amounts depend on the equilibria and on the cleavage ratios. Successful replacements include 4-ClC_6H_4 by C_6H_5 and C_6H_5 by 4-$(CH_3)_2NC_6H_4$ and by 2,2′-biphenylene.

Wittig and Clauss[2] reported the formation of the unstable triphenyliodine (**1**) by the addition of 1 equiv of phenyllithium solution to an ether suspension of a diphenyliodonium halide at −80°. Similarly, when a dibenziodolium halide **3** was treated with phenyllithium at 0°, a more stable triaryliodine, 5-phenyl-5*H*-dibenziodole (**2**), was produced.[3,4] Treatment of triaryliodines **1** and **2** with acids had been reported to regenerate the starting iodonium salts.[2,3] However, in a recent investigation of the acid cleavage of 5-phenyl-5*H*-dibenziodole (**2**) we found that, in addition to the starting cyclic dibenziodolium salt (**3**), a new acyclic 2-



biphenylylphenyliodonium salt (**4**) was also formed.[1] The dependence of the product distribution on the protonic or Lewis acid used has been reported.[1]

We should now like to note that this two-step process, formation of a triaryliodine and its cleavage by acid, may be used to replace one aryl group with another in a

(1) (a) Preceding paper: F. M. Beringer and L. L. Chang, *J. Org. Chem.*, **36**, 4055 (1971). (b) Taken from the dissertation of Lydia L. Chang submitted to the Polytechnic Institute of Brooklyn in partial fulfillment of the requirements for the degree of Doctor of Philosophy (Chemistry), 1971. (c) Supported by National Institutes of Health, 1968–1969, through Grant No. 5-SO5-FR-07063-04.

(2) G. Wittig and K. Clauss, *Justus Liebigs Ann. Chem.*, **578**, 136 (1952).

(3) K. Clauss, *Chem. Ber.*, **88**, 268 (1955).

(4) Diphenyliodonium chloride and *n*-butyllithium form an unstable trivalent organoiodine which decomposes in solution at approximately −40°: F. M. Beringer, J. W. Dehn, Jr., and M. Winicov, *J. Amer. Chem. Soc.*, **82**, 2948 (1960).

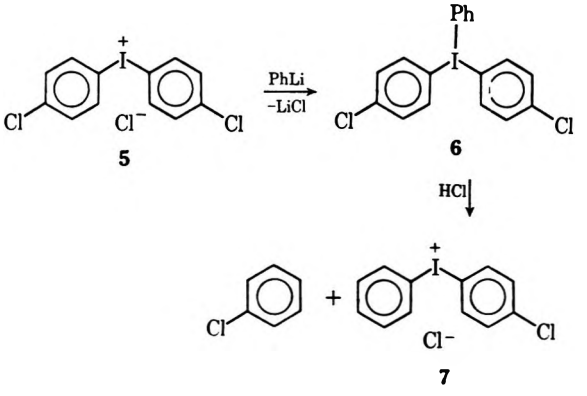
TABLE I

EXCHANGE OF ARYL GROUPS ATTACHED TO POLYVALENT IODINE. REACTION[a] OF ARYLLITHIUM WITH IODONIUM SALTS, FOLLOWED BY QUENCHING

Ar_2I^+	RLi	[RLi]/[Ar_2I^+]	Time, min	Quenching reagent	% R in iodonium product[b]	Other products
$(4\text{-}ClC_6H_4)_2I^+$	PhLi	1	15	HCl	50[c]	*d*
$(4\text{-}ClC_6H_4)_2I^+$	PhLi	1	15	PhCOOH	50[e]	*f*
$(4\text{-}ClC_6H_4)_2I^+$	PhLi	1.3	30	PhCOOH	77	*g*
$(4\text{-}ClC_6H_4)_2I^+$	PhLi	1.46	30	CO_2 then HCl	76	*h*, *i*
$(4\text{-}ClC_6H_4)_2I^+$	PhLi	2.3	30	PhCOOH	86	*j*
$(4\text{-}ClC_6H_4)_2I^+$	PhLi	4	30	PhCOOH	100[k]	*l*
$(4\text{-}ClC_6H_4)_2I^+$	PhLi	4	30	CO_2 then HCl	100[k]	*m*
Ph_2I^+	$4\text{-}ClC_6H_4Li$	1	30	CO_2 then HCl	0[n]	*o*
Ph_2I^+	$4\text{-}(CH_3)_2N\text{-}C_6H_4Li$	4	30	CO_2 then HCl	100[p]	*q*, *r*

[a] All reactions were run in diethyl ether at Dry Ice–acetone temperature under argon. [b] Based on the amount of RI from the pyrolysis of the mixture of iodonium iodides. [c] The product was pure 4-chlorodiphenyliodonium cation precipitated as iodide (86%). [d] Chlorobenzene in 83.5% yield based on the milliequivalents of chlorophenyl group that exchanged. [e] The product was 4-chlorodiphenyliodonium cation precipitated as iodide (89%). [f] Chlorobenzene in 86% yield. [g] Chlorobenzene in 73% yield. [h] Benzoic acid in 27% yield based on the unreacted phenyllithium. [i] 4-Chlorobenzoic acid in 21% yield based on the 4-chlorophenyl group that exchanged. [j] Chlorobenzene in 58% yield. [k] The product was pure diphenyliodonium cation precipitated as the iodide (87%). [l] Chlorobenzene in 77% yield. [m] 4-Chlorobenzoic acid in 70% yield determined as the methyl ester by vpc. [n] Diphenyliodonium cation in 69% yield recovered as the iodide. [o] 4-Chlorobenzoic acid in 74% yield determined as the methyl ester by vpc. [p] Pure 4,4′-di(dimethylamino)diphenyliodonium iodide in 72.5% yield. [q] Benzoic acid in 23.6% yield determined as the methyl ester. [r] 4-Dimethylaminobenzoic acid in 43% yield.

diaryliodonium salt. Thus bis(4-chlorphenyl)phenyliodine (**6**), obtained from 4,4′-dichlorodiphenyliodonium chloride (**5**) and 1 equiv of phenyllithium, gave on



5 **6** **7**

cleavage with hydrogen chloride unsymmetrical 4-chlorodiphenyliodonium chloride (**7**). The preferential cleavage of the 4-chlorophenyl group is striking, but no explanation is advanced now.

Consideration of this two-step process for aryl exchange on iodine led to the formulation of another possible route. Central to this idea was the likelihood that in a triaryliodine the large iodine atom, with unfilled d orbitals, would accept another ligand as from an aryllithium.

$$\underset{}{Ar_2I} \underset{+\ RLi}{\rightleftharpoons} \underset{Li^+}{Ar_2\bar{I}R} \underset{+\ ArLi}{\rightleftharpoons} Ar_2IR$$

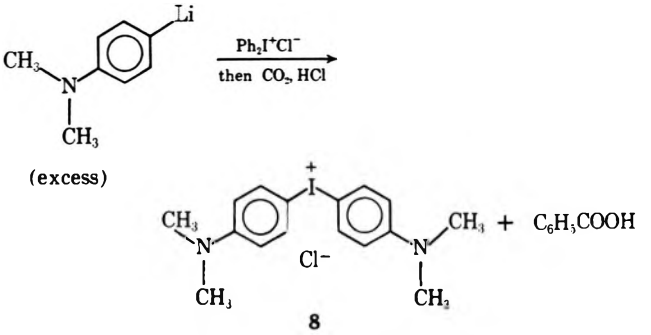
Further, it seemed probable that such a tetraryliodate ion would also be in equilibrium with a new triaryliodine and aryllithium. The triaryliodine might be formed *in situ*, as before, and then allowed to exchange with aryllithium reagent.

In the first successful example of this aryl exchange, 4,4′-dichlorodiphenyliodonium chloride (**5**) was treated with excess phenyllithium in various ratios; quenching with acid then gave mixtures of iodonium salts bearing phenyl and 4-chlorophenyl groups. As the excess of

$$\begin{array}{ccc} Ar_2I^+X^- & \xrightarrow{-LiX} & Ar_2IR \\ +\ 2RLi & & +\ RLi \\ & & \downarrow\uparrow \\ & & Ar_2\bar{I}R_2Li^+ \\ & & \downarrow\uparrow \\ X^-\dot{I}R_2 & \xrightarrow{-LiX} & ArIR_2 \\ +\ 2ArLi & & +\ ArLi \end{array}$$

phenyllithium increased, the replacement of 4-chlorophenyl groups was more extensive (Table I); with a fourfold excess of phenyllithium the exchange was essentially complete. If the reaction mixtures containing excess phenyllithium were treated with carbon dioxide before acidification, 4-chlorobenzoic acid was formed along with benzoic acid.

In another exchange reaction, of more synthetic interest, the phenyl groups in the readily available diphenyliodonium chloride were replaced; treatment with excess 4-dimethylaminophenyllithium followed by acidification gave a previously unknown salt, 4,4′-di(dimethylamino)diphenyliodonium chloride (**8**).



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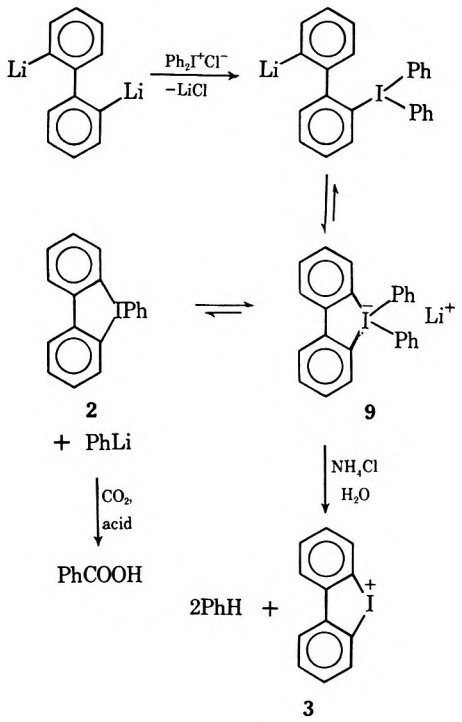
A final series of experiments indicates that, in at least some circumstances, at equilibrium the tetraaryliodate ion may be formed in substantial amount from the triaryliodine and aryllithium. When a suspension of diphenyliodonium chloride in tetrahydrofuran was

treated with a slight excess of 2,2′-dilithiobiphenyl at low temperature, a bright citrus-yellow suspension resulted, which gave a good yield (74%) of dibenziodolium iodide (3) after acidification but only 2% of benzoic acid after carbonation and acidification. This shows the absence of substantial amounts of aryllithium in the reaction mixture and supports the formulation of a tetraaryliodate intermediate (9), in which the diphenyliodonium ion has accepted a new bidentate ligand.



It is hoped that the further development of this approach utilizing tetraryliodate ions will open up the synthesis of new organoiodines bearing two, three, or four aryl or other organic groups.

Experimental Section

Analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Gas chromatography was done on 6-ft columns, packed with 20% OV-1 on 60/80 Chromosorb W with an Aerograph 1520-A gas chromatograph. Melting points were taken in capillary tubes on a Thomas-Hoover apparatus and are corrected.[5] All reactions involving organolithium reagents or triaryliodines were performed in an inert atmosphere.

Diphenyliodonium chloride,[6] 4,4-dichlorodiphenyliodonium chloride,[7] dibenziodolium chloride,[8] 4-dimethylaminodiphenyllithium,[9] 4-chlorophenyllithium,[10] and 2,2′-dilithiobiphenyl[11] were prepared by previously reported procedures. 5-Phenyl-5*H*-dibenziodole, prepared according to Clauss,[3] is sensitive to air and heat but may be kept for a few days in a vacuum desiccator at 0°.

Reaction of 5-Phenyl-5*H*-dibenziodole (2) with Hydrogen Chloride.—A solution of 2 was prepared under argon, standardized with benzoic acid,[1] and used for reaction immediately.

When a solution of 1.84 mmol of 2 in 50 ml of tetrahydrofuran was added to a solution of 3.44 mmol of hydrogen chloride in tetrahydrofuran, a white precipitate formed immediately. After stirring for 30 min, the solid was collected, washed with tetrahydrofuran, dried, and weighed (0.63 g). After this white solid was redissolved in 100 ml of hot water and treated with concentrated potassium iodide solution, the pale yellow mixed iodonium iodides that precipitated were collected, washed with water, and dried. This mixture was then heated at 200° for 5 min to give a dark oil, which was shown by vpc to contain 0.79 mmol of iodobenzene, 0.75 mmol of 2-iodobiphenyl, and 0.79 mmol of 2,2′-diiodobiphenyl, indicating 0.79 mmol (50%) of 2-biphenylylphenyliodonium ion (4) and 0.79 mmol (50%) of dibenziodolium ion (3) in the product mixture.[1]

4,4′-Dichlorodiphenyliodonium Chloride (5) with Phenyllithium.—To a suspension of 5 (1.23 g, 3.18 mmol) in 5 ml of anhydrous ether, 2 ml of 1.59 *M* phenyllithium solution (3.18 mmol) was added dropwise at −73°. The bright citrus-yellow mixture was stirred for 0.5 hr at −73° and treated with 20 ml (11 mmol) of 0.52 *M* hydrogen chloride in ether, giving a white precipitate. The mixture was stirred for 0.5 hr while warming to room temperature. The precipitate was collected, dissolved in hot water, and treated with potassium iodide to give 1.26 g (2.86 mmol, 90%) of 4-chlorodiphenyliodonium iodide, mp 160° dec. Vpc analysis of the products of pyrolysis of this iodonium iodide showed 1.00 equiv of iodobenzene for each 1.01 equiv of 4-chloroiodobenzene.

Anal. Calcd for $C_{12}H_8I_2Cl$: C, 32.77; H, 2.03; I, 57.40; Cl, 7.80. Found: C, 32.46; H, 1.98; I, 57.69; Cl, 7.75.

The ethereal mother liquor was washed with dilute NaOH solution and dried over $MgSO_4$, and was shown to contain 2.63 mmol (83.5%) of chlorobenzene.

When the above reaction was run with a 1:4 mole ratio of salt 5 to phenyllithium, pure diphenyliodonium iodide was obtained in 81% yield, mp 176° dec (lit.[5] mp 182–183° dec). Pyrolysis gave iodobenzene only. The infrared spectrum was in accord with that of an authentic sample.

Reactions run at mole ratios between 1:1 and 1:4 of 5 and phenyllithium, after quenching with acid, gave mixtures of 4-chlorodiphenyliodonium and diphenyliodonium salts; see Table I. The per cent of iodobenzene from the pyrolysis of the iodonium iodides was used as the per cent of the exchange reaction.

To demonstrate that 4-chlorophenyllithium was present in the reaction mixture, quenching with carbon dioxide was performed as in the following example. Through the citrus-yellow mixture from 2.38 mmol of 5 and 3.5 mmol of phenyllithium in anhydrous ether, stirred at −73° for 0.5 hr, dry carbon dioxide gas was passed for 15 min with vigorous stirring. The resulting mixture was treated with 10 mmol of hydrogen chloride in ether. The white solid was collected, dissolved in hot water, and treated with KI to give 0.31 g of iodonium iodides, which decomposed on pyrolysis to 2.65 mmol of iodobenzene and 0.84 mmol of 4-chloroiodobenzene, indicating 76% of phenyl groups in the iodonium salts.

The organic phase was separated into acidic and nonacidic components by extraction with dilute NaOH. The aqueous phase was separated and neutralized with dilute HCl to give a white solid. The mixture was then extracted three times with ether, esterified with diazomethane in ether, and analyzed by vpc to give 0.23 mmol (27% based on the millimoles of unreacted phenyllithium) of methyl benzoate and 0.82 mmol (21% based on the milliequivalents of 4-chlorophenyl groups exchanged) of methyl 4-chlorobenzoate.

Diphenyliodonium Chloride and 4-Chlorophenyllithium.—Reaction between 0.733 g (2 mmol) of diphenyliodonium chloride and 2.2 mmol of 4-chlorophenyllithium in ether was carried out under the same conditions as described above. After quenching and usual work-up, 0.560 g (1.38 mmol, 69%) of diphenyliodonium iodide was isolated. The acidic organic product was esterified with diazomethane to give 1.48 mmol (67.3%) of methyl 4-chlorobenzoate.

Quenching a solution of 2.2 mmol of 4-chlorophenyllithium with carbon dioxide under the same reaction conditions gave 1.63 mmol (74.1%) of 4-chlorobenzoic acid (analyzed on vpc as methyl ester).

Diphenyliodonium Chloride with 4-Dimethylaminophenyllithium.—A suspension of 1.27 g (4 mmol) of diphenyliodonium chloride in ether and 20 mmol of 4-dimethylaminophenyllithium solution was allowed to react under the conditions described above. The resulting citrus-yellow suspension was subsequently quenched with carbon dioxide and hydrogen chloride in ether to give a pale yellow suspension. After the addition of

(5) F. M. Beringer, *et al.*, *J. Amer. Chem. Soc.*, **81**, 342 (1959).
(6) F. M. Beringer, E. J. Geering, I. Kuntz, and M. Mausner, *J. Phys. Chem.*, **60**, 141 (1956).
(7) F. M. Beringer, M. Drexler, E. M. Gindler, and C. C. Lumpkin, *J. Amer. Chem. Soc.*, **75**, 2705 (1953).
(8) J. Collette, D. McGreer, R. Crawford, F. Chubb, and R. B. Sandin, *ibid.*, **78**, 3819 (1956).
(9) H. Gilman and I. Banner, *ibid.*, **62**, 344 (1940).
(10) H. Gilman in "Organic Reactions," Vol. VIII, Wiley, New York, N. Y., 1954, p 285.
(11) F. M. Beringer and R. A. Nathan, *J. Org. Chem.*, **34**, 685 (1969).

100 ml of water, two clear phases were separated. Treating the aqueous phase with concentrated potassium iodide solution gave a crude yellow solid. Recrystallization from ethanol gave 1.43 g (2.9 mmol, 72.5%) of fine yellow crystalline flakes of 4,4'-di(dimethylamino)diphenyliodonium iodide, mp 159° dec.

Anal. Calcd for $C_{16}H_{20}N_2I_2$: C, 38.87; H, 4.05; N, 5.66; I, 51.42. Found: C, 39.22; H, 3.91; N, 5.59; I, 51.38.

The infrared spectrum (KBr) has aliphatic C–H stretching at 2900 cm^{-1}, CH_3–N stretching at 2805 cm^{-1}, CH_3 rocking at 1500 and 1440 cm^{-1}, and an aromatic para-disubstitution pattern at 805 cm^{-1}.

The aqueous filtrate was then neutralized with dilute sodium hydroxide solution to give an off-white precipitate, which after recrystallization from water gave 1.02 g (6.1 mmol, 43% based on unexchanged 4-dimethylaminophenyllithium) of 4-dimethylaminobenzoic acid, mp 239–240° (lit.[12] mp 240–241°).

The acidic product in the organic phase was separated by acid–base extractions and esterified with diazomethane to give 0.595 g of methyl benzoate (2.29 mmol, 28.6% based on the milliequivalents of phenyl group in the starting diphenyliodonium salt, 57.2% based on the millimoles of diphenyliodonium chloride).

Dibenziodolium Iodide from Diphenyliodonium Chloride and 2,2'-Dilithiobiphenyl.—To a white suspension of 1.27 g (4 mmol) of diphenyliodonium chloride in 40 ml of tetrahydrofuran at −73°, there was added 4.25 mmol of 2,2'-dilithiobiphenyl in ether. The resulting bright yellow semitransparent solution was stirred at −73° for 15 min and filtered rapidly into aqueous potassium iodide with stirring. The pale yellow solid that separated between two phases was collected, washed with ether and water, and dried to give 1.2 g (2.86 mmol, 71.5%) of dibenziodolium iodide, mp 220° dec (lit.[13] mp 210–215°). The infrared spectrum was in agreement with that of an authentic sample. The pyrolysis product was pure 2,2'-diiodobiphenyl, identified by vpc peak enhancement with an authentic sample. Analysis of the ether layer also showed 27% of biphenyl, apparently arising from unreacted 2,2'-dilithiobiphenyl.

When a similar reaction mixture was treated first with carbon dioxide and then with aqueous acid, the yield of benzoic acid was only 2%.

Registry No.—**2**, 32174-73-5; **5**, 34220-01-4; phenyllithium, 591-51-5; diphenyliodonium chloride, 1483-72-3; 4-chlorophenyllithium, 14774-78-8; 4-dimethylaminophenyllithium, 13190-50-6; 4,4'-di(dimethylamino), diphenyliodonium iodide, 34220-05-8.

(12) C. A. Bischoff, *Ber.*, **22**, 343 (1889).

(13) L. Mascarelli and G. Benati, *Gazz. Chim. Ital.*, **38**, 619 (1908).

Oxidation of Arylpropenes by 2,3-Dichloro-5,6-dicyanoquinone[1]

EDGAR F. KIEFER* AND FRANK E. LUTZ

Department of Chemistry, University of Hawaii, Honolulu, Hawaii 96822

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Oxidation of anethole, estragole, or 1-phenylpropene by DDQ in benzene gives mono- and/or bis(arylpropenyl) ethers of dichlorodicyanohydroquinone (DDHQ). These highly reactive intermediates can be further oxidized by DDQ to arylpropenals, converted to allylically rearranged alkyl arylpropenyl ethers by alcoholysis, or converted to arylpropenyl chlorides by treatment with HCl. No esr or CIDNP evidence for free-radical intermediates could be detected, and it is assumed from solvent and substituent kinetic effects that the initial oxidation involves hydride ion abstraction by DDQ. Exclusive incorporation of ^{18}O-labeled water into the aldehyde oxidation product implicates an acetal intermediate in this transformation. The allylic rearrangement which takes place on alcoholysis is postulated to proceed *via* a cyclic S_N2' mechanism in which hydrogen bonding of the alcohol to the departing hydroquinone anion determines the geometry of the transition state.

In addition to its widespread use for the introduction of conjugated double bonds in steroidal ketones and hydroaromatic systems,[4] 2,3-dichloro-5,6-dicyanoquinone (DDQ) has been used to generate stable carbonium ions (*e.g.*, cycloheptatrienyl and triphenylcyclopropenyl) and free radicals (*e.g.*, perinaphthenyl) from the parent hydrocarbons.[5] In cases where an intermediate ion or radical is of lower stability and simple dehydrogenation to an alkene is blocked, the intermediate may either undergo rearrangement (*e.g.*, 1,1-dimethyltetralin to 1,2-dimethylnaphthalene[6]) or collapse to a covalent adduct (*e.g.*, 2,2-dimethylindan,[7] diphenylmethane[8]). We have characterized the reaction of DDQ with arylpropenes, which falls into the latter category. Because of the ability of DDQ to abstract either hydride ions or hydrogen atoms, we have also investigated briefly the mechanism of this reaction, as well as that of the oxidation to arylpropenals by excess DDQ. Finally, we have explored some synthetically useful transformations based on these reaction.

Results and Discussion

Reactions of DDQ with *trans*-1-(*p*-methoxyphenyl)-propene (anethole), 3-(*p*-methoxyphenyl)propene (estragole), *trans*-1-phenylpropene, 2-phenylpropene, and *p*-methoxystyrene were carried out under a variety of conditions. Intensely colored molecular complexes formed immediately in all cases, but oxidation rates varied widely; the reactions could be conveniently followed by observing the disappearance of color and precipitation of the quinone reduction product, 2,3-dichloro-5,6-dicyanohydroquinone (DDHQ). Reaction of anethole with tetrachloro-*p*-benzoquinone (chloranil) in benzene was also carried out for comparative purposes; in this case, no oxidation occurred within 5 days at room temperature. Since oxidation of anethole by DDQ under these conditions proceeds measurably within 1 sec (see below), it can be concluded that DDQ is at least 10^5 times as reactive as chloranil in this case.

2-Phenylpropene was not oxidized by DDQ within 8 days under the above conditions, nor was any po-

(1) Abstracted from the Ph.D. thesis of F. E. Lutz, University of Hawaii, 1970. Parts of this work have been published in preliminary form[2,3] and presented at the 26th Northwest Regional Meeting of the American Chemical Society, Bozeman, Mont., June 17, 1971. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and to the U. S. Public Health Service, National Institutes of Health, for support of this research.

(2) F. E. Lutz and E. F. Kiefer, *Tetrahedron Lett.*, 4851 (1970).

(3) F. E. Lutz and E. F. Kiefer, *Chem. Commun.*, 1723 (1970).

(4) D. Walker and J. D. Hiebert, *Chem. Rev.*, **67**, 153 (1967).

(5) D. H. Reid, M. Frazer, B. B. Molloy, H. A. S. Payne, and R. G. Sutherland, *Tetrahedron Lett.*, 530 (1961).

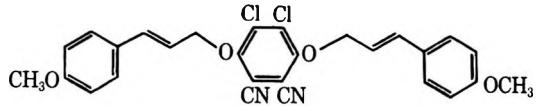
(6) R. P. Linstead, E. A. Braude, L. M. Jackman, and A. N. Beames, *Chem. Ind. (London)*, 1174 (1954).

(7) E. A. Braude, L. M. Jackman, R. P. Linstead, and G. Lowe, *J. Chem. Soc.*, 3123 (1960).

(8) H.-D. Becker, *J. Org. Chem.*, **34**, 1203 (1969).

lymerization observed. *p*-Methoxystyrene was substantially converted to a benzene-insoluble polymer within 20 hr by DDQ, probably *via* a change-transfer mechanism.[9] This type of polymerization was a minor side reaction in the oxidation of anethole by DDQ, and the only reaction observed with chloranil.

The DDQ oxidation of anethole has been described previously.[2] Benzene is the preferred solvent owing to the relatively high solubility (68 g/l.)[4] of DDQ and the very low solubility (0.6 g/l.)[4] of DDHQ. The immediate oxidation product, 2,3-dichloro-5,6-dicyano-1,4-bis(3-*p*-anisyl-2-propenyloxy)benzene (**1**), can be isolated only with difficulty (most conveniently after



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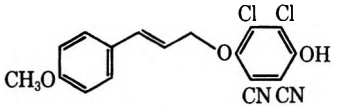
repeated extraction with aqueous dioxane) owing to its high reactivity toward polymerization and solvolysis; higher overall yields are obtained in subsequent transformations starting with the initial yellow solution of **1** in benzene after filtration of DDHQ. Further oxidation to *p*-methoxycinnamaldehyde is best accomplished by stirring a benzene solution of anethole and 2 equiv of DDQ with a small amount of water, and destroying unreacted DDQ by titration with aqueous sodium borohydride. Conversion to aldehyde may be nearly quantitative; the isolated yield in one run on a less than 1-g scale was 85%.

The DDQ oxidation of estragole also gives *p*-methoxycinnamaldehyde under the above conditions, though about 50 times as slowly. The difference in rate is attributed to the absence of extended conjugation in estragole, which significantly lowers the equilibrium constant for π-complex formation with DDQ. The aldehyde yield from estragole was remarkably constant at about 50% under a variety of conditions.

p-Methoxycinnamaldehyde is also produced when DDQ and estragole are present in equimolar amounts. In this case, the major oxidation product isolated was the mono ether of DDHQ, 2,3-dichloro-5,6-dicyano-4-(3-*p*-anisyl-2-(propenyloxy)phenol (**2**, below). Since **2** is presumably an intermediate in the formation



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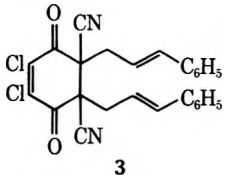
of **1** from anethole also, its more rapid disproportionation to **1** in the anethole reaction might be rationalized on the basis of acid catalysis: the very high initial reaction rate in the anethole reaction might produce a temporarily supersaturated solution of the strong acid DDHQ. Indeed, a tendency of DDHQ to precipitate only slowly from benzene solution has been noted in our work, and can be inferred in this case by the fact that the color change in the reaction substantially precedes DDHQ precipitation.

The DDQ oxidation of 1-phenylpropene, which serves to demonstrate that an activating substituent is not essential in this reaction, resembled that of estragole in rate and product distribution. In this case, both mono and bis ether products analogous to **1** and **2** were isolated, along with cinnamaldehyde, when the reagents were present in equimolar amounts. In addition, a small yield of a high-melting orange solid was obtained which was isomeric with the bis ether and was assigned the structure **3** on the basis of its spectral properties. The enedione chromophore is evident from the ir and uv–visible spectra, and the presence



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of two cinnamyl units per molecule is indicated by the uv extinction coefficient, microanalysis, and mass spectra. The nmr spectrum shows both cinnamyl units to be in identical environments and bonded to carbon rather than oxygen. Somewhat surprisingly, the methylene groups appear as a simple doublet rather than the expected AB quartet of doublets, in spite of the fact that the adjacent pseudoasymmetric carbon atoms bear highly anisotropic substituents. The cinnamyl groups are assigned to the cyano- rather than chloro-substituted carbon atoms (with unknown stereochemistry) largely because no thermal dehydrohalogenation could be observed at the melting point (217°).

Mechanism.—Because of the proven ability of DDQ to generate free radicals by hydrogen atom abstraction[5] and a proposed free-radical mechanism for the DDQ oxidation of diphenylmethane,[8] a careful search was made for evidence of a free-radical intermediate in the oxidation of anethole. Simultaneous injection of benzene solutions of DDQ and of anethole into an esr probe with rapid scanning[10] produced no esr signal attributable to a free radical derived from anethole. The broadened singlet due to semiquinone radical (DDSQ), together with a weak, superimposed triplet of unknown origin, were the only signals detected. Both signals were time- and concentration-independent and also shown to be present when DDQ and DDHQ were mixed in the absence of anethole.

In an even more sensitive test, rapid scanning of the pmr spectrum of a freshly mixed solution of DDQ and anethole also failed to detect any nmr emission or enhanced absorption due to nuclear polarization by unpaired electrons (CIDNP).[11] Further indirect evidence against a radical meechanism can be found in kinetic substituent and solvent effects: a *p*-methoxy substituent causes an approximately 100-fold rate enhancement, compared with typical factors of only 2–3 for analogous free-radical reactions,[12] and more polar solvents also exert substantial rate enhancements. It can thus be concluded with reasonable assurance that the initial step in this reaction is hydride ion abstrac-

(9) H. Nomori, M. Hatano, and S. Kambara, *J. Polym. Sci. Part B*, **4**, 623 (1966); H. Scott, G. A. Miller, and M. M. Labes, *Tetrahedron Lett.*, 1073 (1963).

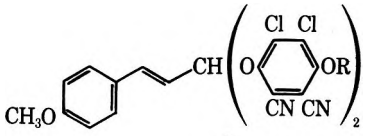
(10) I. Yamazaki and L. H. Piette, *J. Amer. Chem. Soc.*, **87**, 986 (1965), and earlier papers. We wish to thank Professor Piette for his assistance in performing the esr experiments.

(11) K. H. Hausser and D. Stehlik, *Advan. Mag. Res.*, **3**, 79 (1968), and references cited therein.

(12) R. L. Huang and S. Singh, *J. Chem. Soc.*, 3183 (1959); C. Walling, "Free Radicals in Solution", Wiley, New York, N. Y., 1957, p 139.

tion, as is the case in typical dehydrogenation reactions. Since subsequent proton transfer in our case is energetically disfavored, the initially formed ion pair[13] collapses to the ether **2**. As indicated above, the disproportionation of **2** to **1** and DDHQ appears to be acid catalyzed, though no studies bearing specifically on this point were made.

The further oxidation of **1** or **2** to aldehyde may be assumed to proceed initially by a repetition of the above steps, leading to an acetal, *e.g.*, **4** (R = H or *p*-methoxycinnamyl).[2] As might be expected, **4** is extremely



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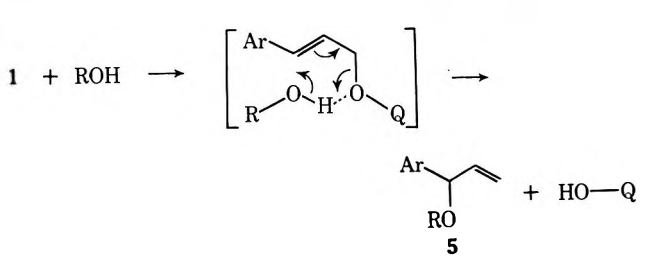
labile; attempts to isolate it failed. Addition of ^{18}O-enriched water to the reaction gave an 85% yield of *p*-methoxycinnamaldehyde in which at least 94% of the carbonyl oxygen was derived from water. The rate of oxidation of **1** or **2** to **4** by DDQ appears to be about 50 times as slow as that of anethole; *i.e.*, comparable to that of estragole.

Enedione **3** is believed to arise *via* alkylation of DDHQ or mono ether of type **2** by the cinnamyl carbonium ion, since no tendency for the biscinnamyl ether of DDHQ to rearrange to **3** could be observed. The fact that the *p*-methoxy analog of **3** was not found is presumably a reflection of the greater stability (*i.e.*, higher selectivity) of the *p*-methoxycinnamyl cation.

Conversion to Other Products.—The alcoholysis of **1** has been previously noted.[3] In this reaction, which is advantageously carried out starting with anethole and DDQ without isolation of **1**, allylically rearranged ethers (**5**) are produced *via* a proposed[3] S_N2' mechanism involving the cyclic, hydrogen-bonded transition state shown below (Ar = *p*-methoxyphenyl). The yield of rearranged ethers **5** drops from 65–70% with methanol (**5a**) and ethanol (**5b**) to 2% with 2-



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methyl-2-propanol (**5d**), while the yield of unrearranged alkyl *p*-methoxycinnamyl ethers (**6**) correspondingly rises from 4–5% to 17%. As the unconjugated ethers **5** could be quantitatively isomerized to the more stable conjugated ethers by treatment with dilute acid, this reaction constitutes a useful synthesis of both types of compound. The uniqueness of this system as a precursor for the unconjugated 1-arylallyl ethers was demonstrated by the ethanolysis of *p*-methoxycinnamyl chloride, which gave only the conjugated isomer, 3-*p*-methoxycinnamyl ethyl ether.

DDQ oxidation of anethole to **1** in benzene solution followed by treatment with aqueous hydrochloric acid gave *p*-methoxycinnamyl chloride in approximately 50% yield, the remainder being converted to a hexane-insoluble polymer. Reaction of **1** with diethylamine or aniline in benzene solution required prolonged heating and gave only intractable products. In a single experiment, crude **1** reacted at room temperature with excess pyrrolidine in acetonitrile to produce traces of a compound tentatively identified as N-(*p*-methoxycinnamyl)pyrrolidine on the basis of its ir spectrum and basicity. Compound **1** failed to react with cyanide ion in the absence of added acid, even in dimethyl sulfoxide. It thus appears that nucleophilic displacement on **1** requires the presence of a proton donor, *i.e.*, that the anion of DDHQ (or its mono ether) is a poor leaving group.

Experimental Section

Uv, ir, nmr, esr, and mass spectra were recorded on Cary 14, Beckman IR-5A, Varian HA-100, Varian E4, and Hitachi Perkin-Elmer RMU-6D spectrometers, respectively. Glpc separations were carried out on a Varian Aerograph Model 200 gas chromatograph, using a 0.25 in. × 5 ft stainless steel column packed with 20% SE-30 silicone fluid on 60–80 mesh Chromosorb W at 185°. Melting points were determined on a Fisher-Johns apparatus and are uncorrected; boiling points were determined by the inverted capillary method and are corrected. Mass spectral analyses were performed by Sr. Mary Roger Brennan and microanalyses by the Berkeley Analytical Laboratory unless otherwise noted. Arylpropenes were the best available commercial grade, redistilled before use. DDQ (Arapahoe Chemical Co.) was recrystallized from 3:2 benzene–petroleum ether (bp 30–60°) and displayed the expected spectral properties.[4] Analytical reagent grade solvents were used without further purification.

2,3-Dichloro-5,6-dicyano-1,4-bis(3-*p*-anisyl-2-propenyloxy)benzene (1).—A solution of 3.72 ml (25 mmol) of anethole in 20 ml of benzene was added to a solution of 5.67 g (25 mmol) of DDQ in 230 ml of benzene. Within 1 min, the initially black color of the molecular complex had faded a bright yellow, whereupon 2.84 g (50%) of precipitated DDHQ was collected by filtration and identified by its mass spectrum (*m/e* 228, base, M^+) and by conversion to the diacetate,[14] mp 182–183°. The filtrate was used directly for the conversion of **1** to other products (see below). For the isolation of **1**, 50 ml of dioxane was added to the filtrate, which was then washed with five 50-ml portions of water, dried ($MgSO_4$), and evaporated to dryness *in vacuo*. The residue, after brief trituration with 50 ml of ice-cold MeOH to remove residual DDHQ and colored polymeric material, weighed 3.0–3.5 g (45–55%) and displayed erratic melting behavior. Six recrystallizations from 1:3 dioxane–hexane were required to obtain a 20% yield of pure **1** of constant melting point (124°) uv max (dioxane) 268 nm (ε 44,200), 325 (4980); ir (KBr) 972 (*trans*-CH=CH), 1244 (COC), 2222 cm^{-1} (CN); nmr ($CDCl_3$) δ 7.08 (q, 4, J = 9.0, C_6H_4), 6.59 (d, 1, J = 16.0 Hz, CH=$CHCH_2$), 6.29 (d of t, 1, J = 16.0, 6.5 Hz, CH=$CHCH_2$), 4.87 (d, 2, J = 6.5 Hz, CH_2), and 3.78 (s, 3, OCH_3).

Anal. Calcd for $C_{28}H_{22}Cl_2N_2O_4$: C, 64.60; H, 4.27; Cl, 13.64; N, 5.38. Found: C, 64.52; H, 4.00; Cl, 13.71; N, 5.40.

Independent synthesis of **1** was accomplished in 40% yield by stirring a solution of the disodium salt of DDHQ in 50% aqueous dioxane with a benzene solution of 2 equiv of *p*-methoxycinnamyl chloride (see below) at 60° for 20 min, followed by isolation and purification as described above. This sample was identical (mixture melting point, ir, uv, nmr) with that prepared by the oxidation of anethole.

***p*-Methoxycinnamaldehyde.**—In the best preparative procedure a solution of 6 mmol of anethole in 20 ml of benzene was added to a solution of 12 mmol of DDQ in 230 ml of benzene to which 1 ml of water had been added. The heterogeneous mixture was stirred vigorously for 1 hr at room temperature and 1 hr at 50°, cooled, and treated dropwise with 2% aqueous sodium borohydride to reduce excess DDQ (yellow end point). After removal of DDHQ by filtration, the benzene solution was concentrated to about 20 ml and chromatographed on a 1.7 × 38 cm silica gel column. Elution with chloroform gave, after an

(13) B. M. Trost, *J. Amer. Chem. Soc.*, **89**, 1847 (1967).

(14) J. Thiele and F. Günther, *Justus Liebigs Ann. Chem.*, **349**, 55 (1906).

initial, bright orange oil (0.06 g, discarded), 0.79 g (78% yield) of *p*-methoxycinnamaldehyde: mp 58–59° after sublimation [50° (0.1 mm)]; uv (dioxane) max 314 nm (ε 22,700); ir (KBr) 1670 (C=O), 968 cm^{-1} (*trans*-CH=CH); nmr (CCl_4), δ 9.71 (d, 1, CHO); mass spectrum (70 eV) *m/e* 162 (M^+, base), 161. Reaction of the purified bis ether **1** with equimolar DDQ in benzene also gave *p*-methoxycinnamaldehyde in 73% yield, identical in all respects with that prepared directly from anethole.

***p*-Methoxycinnamaldehyde-^{18}O.**—The above procedure was followed except that 0.905 g of water containing 20.0% ^{18}O (Bio-Rad Laboratories) was used, and the excess DDQ was destroyed by adding 0.4 ml of anethole before work-up instead of aqueous sodium borohydride. The yield of aldehyde was 0.86 g (85%). Comparison of the relative intensities due to the ions at *m/e* 162 and 164 with those of unlabeled material indicated 18.8% ^{18}O-containing ions, corresponding to 94% incorporation of oxygen from water.

2,3-Dichloro-5,6-dicyano-4-(3-*p*-anisyl-2-propenyloxy)phenol (2).—Reaction of estragole with equimolar DDQ under the conditions and on the same scale described for anethole gave a 72% yield of DDHQ after 1 hr. Dioxane–water extraction of the filtrate and solvent removal gave a benzene-insoluble solid (2.0 g) which could not be recrystallized without decomposition to DDHQ. This was purified by precipitation from chloroform solution by slow addition of hexane to give white, crystalline **2** mp 100° dec, distinguishable from the bis ether **1** by its ir [3195 cm^{-1} (OH)] and uv [$\lambda_{max}^{dioxane}$ 267 nm (ε 24,800), 340 (5850)] spectra, and by microanalysis. Neither **1** nor **2** gave a usable mass spectrum.

Anal. Calcd for $C_{18}H_{12}Cl_2N_2O_3$: C, 57.80; H, 3.23; N, 7.50; Cl, 18.95. Found: C, 57.58; H, 3.18; N, 7.42; Cl, 18.91.

Other compounds isolated from the benzene filtrate by silica gel chromatography were *p*-methoxycinnamylaldehyde (0.7 g, 17% yield) and unreacted estragole (0.8 g, 22% recovery). The yield of aldehyde increased to 50% with 2 equiv of DDQ and to 60% with 3 equiv and was essentially unchanged by changing the reaction solvent to dioxane or dichloromethane or by dropwise addition of reagents or a nitrogen atmosphere.

DDQ Oxidation of 1-Phenylpropene.—In a typical experiment, a solution of 3.23 ml (0.025 mol) of 1-phenylpropene in 20 ml of benzene was added to 5.67 g (0.025 mol) of DDQ in 230 ml of benzene. Precipitation of DDHQ began within 2 min; filtration after 20 hr yielded 2.2 g (38%) of DDHQ. Concentration of the filtrate to a volume of about 20 ml caused precipitation of a pale green solid (2.2 g), identified as the monocinnamyl ether of DDHQ (**7**), mp 130° dec, on the basis of the following evidence: uv max (dioxane) 254 nm (ε 26,250) 340 (6050); ir (KBr) 969 (*trans*-CH=CH), 1195 (CO), 2227 (CN), 3245 cm^{-1} (OH); nmr (DMSO-d_6), δ 7.36 (m, 5, C_6H_5), 6.76, 6.50, 4.82 (ABX_2, 1, 1, 2, J_{AB} = 16.0 Hz, J_{BX} = 6.0 Hz, CH=$CHCH_2$). Like the *p*-methoxy analog **2**, **7** could not be crystallized, but was precipitated from chloroform–hexane; it did not give satisfactory analytical data.

Silica gel chromatography of the filtrate from **7** yielded four fractions (A–D), the first three of which contained cinnaldehyde and traces of 1-phenylpropene. Cinnamaldehyde was isolated by fractional distillation of fraction B combined with the hexane-soluble portion of semisolid fraction A, total yield 0.5 g (15%), bp 41° (0.15 mm), identified by nmr, ir, and uv spectra. The solid hexane-insoluble portion of fraction A (0.8 g) was further separated by fractional crystallization. Addition of 3 vol. of hexane to an acetone solution of the solid caused long, white needles, mp 148–149°, to separate within 1 hr at 4°, followed after addition of hexane to turbidity by short, orange needles, mp 216–217°. The white compound was identified as the biscinnamyl ether of DDHQ by its uv, ir, and nmr spectra, which resembled those of **7** except for the absence of features attributed to the phenolic hydroxyl group, and by microanalyses.

Anal.[15] Calcd for $C_{26}H_{18}Cl_2N_2O_2$: C, 67.69; H, 3.93. Found: C, 68.03; H, 3.71. (Calcd for **7**: C, 59.15; H, 2.92.)

The orange compound above was assigned the structure 2,3-dichloro-5,6-dicyano-5,6-dicinnamyl-2-cyclohexene-1,4-dione (**3**) on the basis of the following evidence: nmr (acetone-d_6) δ 7.33 (m, 5, C_6H_5), 6.71, 6.06, and 3.39 (d, d of t, d, ABX_2, 1, 1, 2, J_{AX} = 16.0 Hz, J_{BX} = 7.5 Hz, *trans*-CH=CHCH$_2$); uv max (dioxane) 257 nm (ε 39,000), 370 (1100); ir (KBr) 1560, 1704 (enedione), 2222 cm^{-1} in addition to the expected cinnamyl bands; mass spectrum (20 eV) *m/e* 460 (M^+), 117 (base).

Anal.[15] Calcd for $C_{26}H_{18}Cl_2N_2O_2$: see above. Found: C, 68.77; H, 4.26.

The total yield of isomers **7** and **3** was 14%, in the approximate ratio of 4:1.

3-*p*-Anisyl-3-alkoxypropenes (5) and 1-*p*-Anisyl-3-alkoxypropenes (6).—In the standard procedure for the conversion of anethole to the above ethers, the initial filtrate containing **1** (see above) was treated with 50 ml of an alcohol and heated under reflux for 0.5–3 hr (see below). After removal of the solvent *in vacuo*, benzene was added to facilitate removal of DDHQ by filtration and the filtrate was passed through a Florisil column (chloroform eluent) to remove polymeric materials, distilled *in vacuo*, and analyzed by glpc. Preparative separation of **5** and **6** was accomplished by collecting and analyzing *ca.* thirty 30-ml fractions from a 1.7 × 40 cm silica gel column with benzene as eluent; the unconjugated ethers **5** eluted first. Spectral data below are given for the ethyl ethers **5b** and **6b**. The nmr chemical shifts for the other six ethers are the same as those below within ±0.08 ppm except for the R groups and the benzylic proton in **5**, which shifts 0.38 ppm to lower field as the size of R increases from methyl to *tert*-butyl as would be expected from conformational considerations. The ir, uv, and mass spectra of these spectra of these homologues also show the expected similarities and differences. **5b**: nmr (CCl_4) δ 6.92 (q, 4, J = 9.0 Hz, C_6H_4), 5.80 (octet, 1, J = 17, 10, and 6 Hz, CHCH=CH_2), 5.10 and 5.00 (m, 2, J = 17, 10, 2, 1.5, and 1.3 Hz, CHCH=CH_2), 4.53 (octet, 1, J = 6, 1.5, and 1.3 Hz, CHCH=CH_2), 3.71 (s, 3, OCH_3), 3.40 and 3.30 (q_{AB} of q, 2, J = 9 and 7 Hz, OCH_2CH_3), 1.16 (t, 3, J = 7 Hz, CH_2CH_3); mass spectrum (70 eV) *m/e* (rel intensity) 192 (90 M^+), 163 (50), 147 (100), 135 (90). **6b**: nmr (CCl_4) δ 6.95 (q, 4, J = 9.0 Hz, C_6H_4), 6.39 (d of t, 1, J = 16 and 1.0 Hz, CH=CHCH$_2$), 6.01 (d of t, 1, J = 16 and 5.5 Hz, CH=CHCH$_2$), 3.98 (d of d, J = 5.5 and 1.0 Hz, CH=CHCH$_2$), 3.72 (s, 3, OCH_3), 3.42 (q, 2, J = 7 Hz, CH_2CH_3), 1.18 (t, 3, J = 7 Hz, CH_2CH_3); uv max (cyclohexane) 263 nm (ε 17,200); mass spectrum (70 eV) *m/e* (rel intensity) 192 (25, M^+), 136 (50), 135 (100). The reflux times for the preparation of isomeric ethers **5** and **6** are given in Table I along with isolated yields of chromatographically purified products. None of those compounds has been previously characterized.

TABLE I

Compd (R)	Reflux, hr	% 5	% 6
a (CH_3)	0.5	65	5
b (C_2H_5)	0.5	68	4
c (*i*-C_3H_7)	1.0	31	14
d (*tert*-C_4H_9)	3.0	2	17

Isomerization of 5b to 6b.—A solution of **5b** (1 g) in 20 ml of ethanol was treated with 5 ml of 0.1 *M* perchloric acid and heated under reflux for 1 hr. After evaporation of most of the ethanol, the solution was extracted three times with ether and the combined ether solution was washed with water, dried ($MgSO_4$), and distilled, providing gas chromatographically pure **6b**, bp 76–78° (1.0 mm), identified by its ir and nmr spectra.

***p*-Methoxycinnamyl Chloride.**—The initial benzene solution of compound **1** (see above) was stirred vigorously with 40 ml of concentrated HCl for 30 min and chilled in ice, and the acid was neutralized cautiously with 6 *N* NaOH to dissolved suspended DDHQ. The organic phase was washed twice with water, dried ($MgSO_4$), and evaporated at aspirator pressure. The oily residue was triturated thoroughly with warm hexane, and the hexane solution was evaporated to yield 2.36 g (52%) of solid *p*-methoxycinnamyl chloride, which after sublimation at 50° (0.1 mm) had mp 73.5–74.5° (lit.[16] mp 73°); uv max (cyclohexane) 268 nm (ε 20,400); ir (KBr) 654 (CCl), 972 (*trans*-CH=CH), 1645 cm^{-1} (C=C); nmr (CCl_4) δ 4.11 (d, 2, J = 6.5 Hz, CH_2Cl), otherwise similar to that of **1**; mass spectrum (70 eV) *m/e* 182 (M^+), 147 (base).

Registry No.—**1**, 33904-07-3; **2**, 31186-79-5; **3**, 33904-09-5; **5b**, 30225-71-9; **6b**, 33904-11-9; **7**, 33904-12-0; *p*-methoxycinnamaldehyde, 24680-50-0; biscinnamyl ether of DDHQ, 33904-14-2.

(15) This analysis was by C. F. Geiger, Ontario, Calif.

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Substituted Benzopyranopyridopyrimidine Ring Syntheses by the Ternary Condensation of Malononitrile, Salicylaldehyde, and Aromatic Ketones in the Presence of Ammonium Acetate

AKIO SAKURAI,* YOSHITO MOTOMURA,[1] AND HIROSHI MIDORIKAWA

The Institute of Physical and Chemical Research, Wako-shi, Saitama, Japan

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Various 2,5-diarylbenzopyranopyridopyrimidines (1) and substituted 4-amino-5-iminobenzopyranopyridine (2 and 3) were prepared directly by condensation of malononitrile, salicylaldehyde, and aromatic ketones in the presence of ammonium acetate. Moreover, reaction of the resulting 2 and 3 with acetic anhydride in boiling pyridine led to such benzopyranopyridopyrimidines as 2-aryl-5-methyl derivatives 5 and 2-acetamino-1-cyano-5-methyl derivatives 6, respectively.

Previous papers have shown that ethyl cyanoacetate condensed with salicylaldehyde and ketones or aldehydes in the presence of ammonium acetate afford substituted benzopyranopyridines[2,3] (from ketone or aliphatic aldehyde) and benzopyranopyrimidines[3] (from aromatic aldehyde).

The present paper deals with syntheses of 2,5-diaryl, 2-aryl-5-methyl, and 2-acetamino-1-cyano-5-methyl derivatives of [2,3,4-*de*]benzopyrano[2,3-*d*]pyridopyrimidine, 4-amino-5-imino[1]benzopyrano[3,4-*c*]pyridine derivatives by condensation of malononitrile, salicylaldehyde, or 3-methoxysalicylaldehyde, and aromatic ketones, *e.g.*, acetophenone, *o*- and *p*-hydroxy-, *p*-methyl-, *p*-methoxy-, and *m*-nitroacetophenone, in the presence of ammonium acetate.

The reaction of malononitrile, salicylaldehyde, and aromatic ketones (molar ratio of 1:1:1) in the presence of ammonium acetate (slight excess) gave a mixture of ~10–17% 2-aryl-5-(*o*-hydroxyphenyl)[2,3,4-*de*]-benzopyrano[2,3-*d*]pyridopyrimidines (**1**) and ~4–10% 1-cyano-2,4-diamino-5-imino[1]benzopyrano[3,4-*c*]pyridine (**3a**) except for the reactions when *m*-nitroacetophenone or *p*-methylacetophenone were used as the ketone reactant.

The use of 3-methoxysalicylaldehyde instead of salicylaldehyde gave a mixture of ~9–11% type **1** (R = OCH_3), ~8–10% **3b**, and ~6–10% 4-amino-2-aryl-5-imino-7-methoxy[1]benzopyrano[3,4-*c*]pyridines (**2**). In addition, on treatment with acetic anhydride in refluxing pyridine, both **2** and **3** gave good yields of cyclization products such as 2-aryl-5-methyl- (**5**) or its 8-methoxy derivative (57–95%) and 2-acetamino-1-cyano-5-methyl[2,3,4-*de*]benzopyrano[2,3-*d*]pyridopyrimidine (**6**) or its 8-methoxy derivative (79–94%), respectively, as indicated in Scheme I (yields based on **2** or **3**). When heated with hydrochloric acid in ethanol, **2c** was converted to 5-oxo derivative **7b** (Scheme I), which was proved to be the same type as those obtained by the condensation of ethyl cyanoacetate, salicylaldehyde, and ketones[2] or aliphatic aldehydes[3] previously reported, on the basis of their ir spectral studies.

It seems reasonable to assume that the formation of **1**, **2**, and **3** may be achieved by the following process. Malononitrile first condensed with salicylaldehyde to give 3-cyanocoumarinimide (**8**), which is in turn converted to 3-amidinocoumarinimide (**9**). Then, **9** condenses with ketones to afford **2**, which further reacts with salicylaldehyde, finally yielding **1**. Also, when intermediate **9** was treated with malononitrile, **3** was formed as indicated in Scheme II. Indeed, when heated with acetophenone and ammonium acetate in ethanol, crude **8a** gave **2a**. Furthermore, in the same reaction with salicylaldehyde, **2a** gave **1a**. Reaction of malononitrile, salicylaldehyde, or 3-methoxysalicylaldehyde with *m*-nitroacetophenone afforded mainly **2** (18–24%) accompanied by a small amount of **1** (5%) and **3** (6–8%).

The use of *p*-methylacetophenone as the ketone reactant afforded **1b**, **3a**, and **7a**, respectively. In this case, when the reaction was carried out in ethanol, **1b** was formed as the main product, while the reaction in ethanol–pyridine (2:1) gave **7a** as the main product. Reaction of malononitrile, 3-methoxysalicylaldehyde, and acetophenone afforded **1f**, **2c**, and **3b** under reflux, while in the same reaction at room temperature **1f** was not obtained. These facts are taken to indicate that in many cases in the present study the course of the reaction was markedly influenced by choice of solvent and/or reaction temperature. However, type **3** compounds (4–10%) were formed under all conditions.

The ir spectra of type **1** compounds showed absorption bands in the 1630–1500-cm^{-1} region attributed to a hetero ring, but they did not show any band in the amino, imino, or cyano region. However, **4** (acetyl derivatives of **1**) exhibited new absorption bands at 1770–1750 cm^{-1}. This indicates the presence of a hydroxy group in type **1**, since their bands can be attributed to the carbonyl band of acetoxy group. This acetoxy group showed doublet carbonyl absorption except for **4e** (Table I). It is probably attributable to the rotational isomerism around the C—C bond or the Fermi resonance. On the other hand, compounds **2** showed absorption bands at 3450–3150 cm^{-1} (three to four bands) (Table II) due to a primary amino and imino groups and at 1650 cm^{-1} due to a C=N bond, whereas compounds **5** (obtained when **2** was refluxed with acetic anhydride in pyridine) gave no absorption bands for a amino or imino groups, and their spectra were very similar to those of compounds **1**. The nmr spectrum (CF_3CO_2H) of compound **5b** indicated a methyl singlet corresponding to three protons at 3.2 ppm, while the ir spectrum gave no absorption band for an acetyl carbonyl group. This suggests that the 4 position of amino group and the 5 position of imino group of type **2** were involved in this cyclization;

(1) Tokyo Electrical Engineering College, Nishikicho, Chiyoda-ku, Tokyo, Japan.

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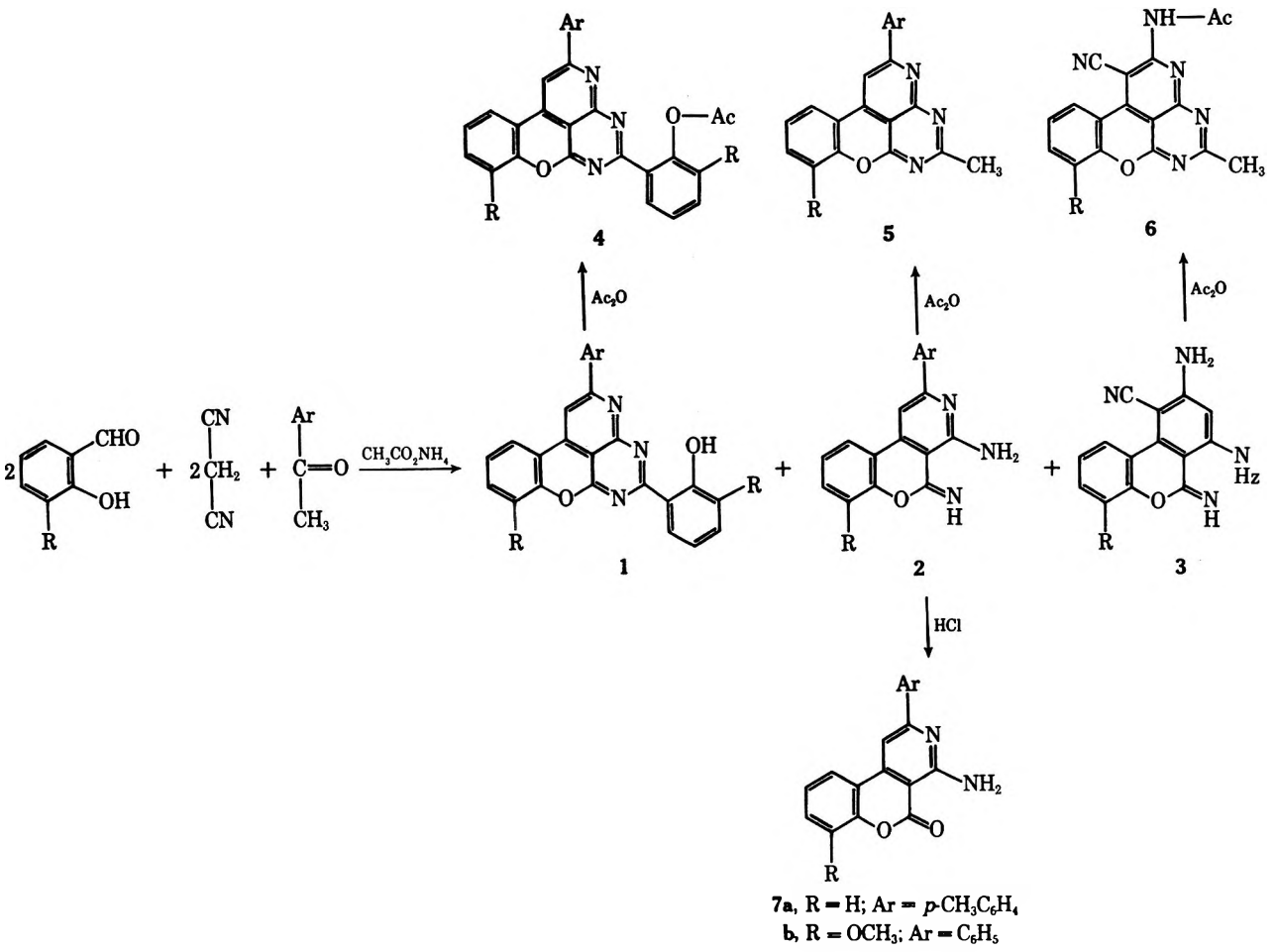
SCHEME I



SCHEME II

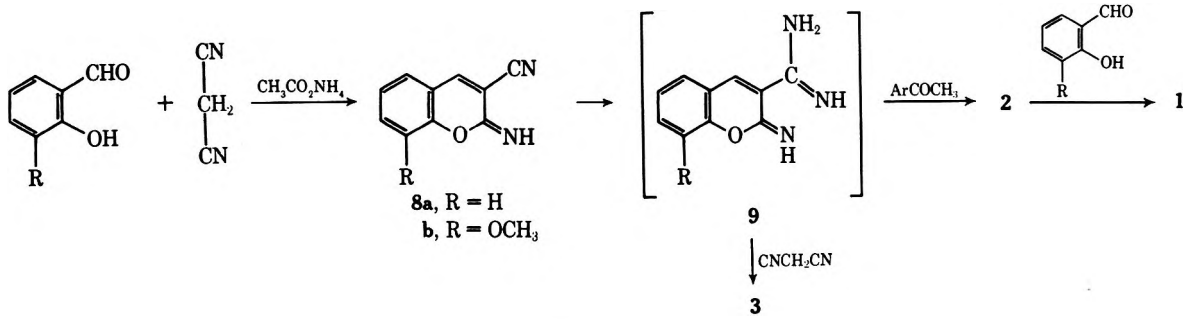


TABLE I

2-ARYL-5-(*o*-HYDROXYPHENYL)[2,3,4-*de*]BENZOPYRANO[2,3-*d*]PYRIDOPYRIMIDINE (1) and ITS ACETYL DERIVATIVES 4[a]

Compd	R	Ar	Mp, °C	Yield, %	Ir (KBr), $\nu_{C=O}$, cm^{-1}	Nmr (CH_3), ppm[b]
1a	H	C_6H_5	303–304	12		
1b	H	*p*-$CH_3C_6H_4$	299–300	12		
1c	H	*p*-OHC_6H_4	>340	11		
1d	H	*o*-OHC_6H_4	>340	10		
1e	H	*p*-$CH_3OC_6H_4$	278–279	17		
1f	OCH_3	C_6H_5	291–294	11		
1g	OCH_3	*p*-$CH_3OC_6H_4$	273–275	10		
4a	H	C_6H_5	248–251	91	1765, 1750	2.25 (s, 3 H)
4b	H	*p*-$CH_3OC_6H_4$	224–226	91	1770, 1750	2.25 (s, 3 H)
4c	H	*p*-$AcOC_6H_4$	262–264	67	1765, 1755	2.3 (s, 3 H), 2.6 (s, 3 H)
4d	H	*m*-$O_2NC_6H_4$	>335	82	1770, 1760	
4e	OCH_3	C_6H_5	270–271	73	1770	

[a] Satisfactory analytical values (±0.4% for C, H, N) for all compounds were reported: Ed. [b] Parts per million downfield from tetramethylsilane in CF_3CO_2H; s, singlet.

TABLE II

4-AMINO-5-IMINO[1]BENZOPYRANO[3,4-*c*]PYRIDINE DERIVATIVES 2 AND 3[a]

Compd	R	Ar	Mp, °C	Yield, %	Ir (KBr) $\nu_{NH_2, NH}$, cm^{-1}
2a	H	C_6H_5	193–196	29[b]	3330, 3300, 3160
2b	H	*m*-$O_2NC_6H_4$	261–263	24	
2c	OCH_3	C_6H_5	214–215	10	3450, 3310, 3240
2d	OCH_3	*m*-$O_2NC_6H_4$	228–229	18	
2e	OCH_3	*p*-$CH_3OC_6H_4$	216–217	6	
3a	H		293–295 dec	4–10	3420, 3330, 3310, 3140[c]
3b	OCH_3		>320	8–10	

[a] Satisfactory analytical values (±0.4% for C, H, N) for all compounds were reported: Ed. [b] Yield based on **8a**. [c] ν_{CN} 2200.

TABLE III

5-METHYL[2,3,4-*de*]BENZOPYRANO[2,3-*d*]PYRIDOPYRIMIDINE DERIVATIVES 5 AND 6[a]

Compd	R	Ar	Mp, °C	Yield, %	Ir (KBr), cm^{-1} ν_{NH}	Ir (KBr), cm^{-1} $\nu_{C\equiv N}$	Nmr δ_{CF_3}[b]
5a	H	C_6H_5	219–220	95			
5b	H	*m*-$O_2NC_6H_4$	330–333	57			3.2 (s, 3 H)
5c	OCH_3	C_6H_5	255–257	95			
5d	OCH_3	*m*-$O_2NC_6H_4$	313–314	67			
6a	H		296–298 dec	79	3240	2230	
6b	OCH_3		>320	94	3230	2220	3.15 (s, 3 H) 2.75 (s, 3 H)

[a] Satisfactory analytical values (±0.4% for C, H, N) for all compounds were reported: Ed. [b] Parts per million downfield from tetramethylsilane in CF_3CO_2H; s, singlet; br, broad. In **6b** spectrum, δ_{NH} 8.7–9.1 ppm (br, 1 H).

therefore, the above spectral characteristics are taken as evidence for assignment of the structure **5**. The ir spectrum of compound **3b** showed absorption bands in the 3470–3140-cm^{-1} region (four to five bands) for a primary amino and imino groups and at 2200 cm^{-1} for a conjugated cyano group. On the other hand, compound **6b** (obtained when **3b** was heated with acetic anhydride in pyridine) revealed absorptions at 3230, 2220, and at 1685 cm^{-1} (Table III). These observations show that the same cyclization occurred as in the case of the compounds **2**, since the bands at 3230 and 1685 cm^{-1} were assigned to a imino and carbonyl bands of the acetamino group (2 position), respectively. Thus, the structure of **6b** was deduced from the above ir data, the elemental analysis, and the nmr spectrum which has two methyl singlets at 3.15 and 2.75 ppm corresponding to three protons, respectively. The former signal (3.15 ppm) was assigned to a methyl group of the 5 position, by a comparison of nmr chemical shift observed for the methyl proton in **5b** (3.2 ppm). Therefore, the latter signal (2.75 ppm) was assigned to a methyl proton due to the acetamino group of the 2 position (Table III).

Experimental Section

All melting points are uncorrected. The ir spectra were determined by means of potassium bromide pellets. Nmr spectra were determined in trifluoroacetic acid at 60 Mc, using tetramethylsilane as the internal standard. Chemical shifts are reported as parts per million downfield from TMS.

Reaction of Malononitrile, Salicylaldehyde, and Aromatic Ketones.—A mixture of malononitrile (0.03 mol), aldehyde (0.03 mol), ketone (0.03 mol), and ammonium acetate (0.03–0.04 mol) in ethanol (20–30 ml) was refluxed for 0.5–2 hr. Yellow-orange crystals which precipitated during the reaction were collected and washed with hot ethanol. Compounds **1a–e** and **3a** were isolated by means of fractional crystallizations from pyridine, dimethyl sulfoxide, or ethanol.

Anal. Calcd for $C_{25}H_{15}N_3O_2$ (**1a**): C, 77.11; H, 3.88; N, 10.79. Found: C, 76.93; H, 3.95; N, 10.99. Calcd for $C_{26}H_{17}N_3O_2$ (**1b**): C, 77.40; H, 4.25; N, 10.42. Found: C, 77.46; H, 4.27; N, 10.75. Calcd for $C_{25}H_{15}N_3O_3$ (**1c**): C, 74.06; H, 3.73; N, 10.37. Found: C, 73.67; H, 3.88; N, 10.42. Calcd for $C_{25}H_{15}N_3O_3$ (**1d**): C, 74.06; H, 3.73; N, 10.37. Found: C, 73.88; H, 3.79; N, 10.65. Calcd for $C_{26}H_{17}N_3O_3$ (**1e**): C, 74.45; H, 4.09; N, 10.02. Found: C, 74.33; H, 3.87; N, 10.33. Calcd for $C_{13}H_9N_5O$ (**3a**): C, 62.14; H, 3.61; N, 27.88. Found: C, 62.03; H, 3.65; N, 28.06.

The use of *m*-nitroacetophenone as the ketone reactant afforded **2b** and **3a** along with a small amount of type **1** when treated as above. This substance **1** (R = H; Ar = *m*-$O_2NC_6H_4$) was confirmed by the acetylated compound (**4d**) owing to the insolubility in common organic solvents. Experimental results are summarized in Tables I and II.

Anal. Calcd for $C_{18}H_{12}N_4O_3$ (**2b**): C, 65.05; H, 3.64; N, 16.86. Found: C, 65.18; H, 3.77; N, 17.05.

Reaction of Malononitrile, Salicylaldehyde, and *p*-Methylacetophenone.—To a mixture of malononitrile (2.64 g, 0.04 mol), salicylaldehyde (4.88 g, 0.04 mol), and *p*-methylacetophenone (5.36 g, 0.04 mol) in ethanol (25 ml), ammonium acetate (3.08 g, 0.04 mol) was added and heated for 5 min. The reaction mixture gave 1 g (12%) of **1b**, 0.5 g (10%) of **3a**, and 0.5 g (4%) of **7a**, mp 233–235°. When this reaction was carried out in ethanol (20 ml) and pyridine (10 ml), the reaction mixture afforded 1.5 g (10%) of **7a**, 0.7 g (7%) of **1b**, and 0.4 g (6%) of **3a**. The ir spectrum of **7a** gave bands at 3430, 3330 (NH_2), and 1700 cm^{-1} (C=O).

Anal. Calcd for $C_{19}H_{14}N_2O_2$: C, 75.48; H, 4.67; N, 9.27. Found: C, 75.78; H, 4.70; N, 9.34.

Reaction of Malononitrile, 3-Methoxysalicylaldehyde, and Aromatic Ketones.—A mixture of malononitrile (0.04 mol), aldehyde (0.04 mol), ketone (0.04 mol), and ammonium acetate (0.05 mol) in ethanol (40 ml) was refluxed for 1–2 hr. The reaction mixture gave **1f–g** (10–11%), **2c–e** (6–18%), and **3b** (8–10%) when treated as in the case of salicylaldehyde mentioned above. Experimental results are summarized in Tables I and II.

Anal. Calcd for $C_{27}H_{19}N_3O_4$ (**1f**): C, 72.15; H, 4.26; N, 9.35. Found: C, 72.17; H, 4.30; N, 9.22. Calcd for $C_{28}H_{21}N_3O_5$ (**1g**): C, 70.14; H, 4.41; N, 8.76. Found: C, 69.82; H, 4.48; N, 8.81. Calcd for $C_{19}H_{15}N_3O_2$ (**2c**): C, 71.91; H, 4.76; N, 13.24. Found: C, 71.91; H, 4.83; N, 13.13. Calcd for $C_{19}H_{14}N_4O_4$ (**2d**): C, 62.98; H, 3.89; N, 15.46. Found: C, 63.20; H, 3.80; N, 15.52. Calcd for $C_{20}H_{17}N_3O_3$

(2e): C, 69.15; H, 4.93; N, 12.10. Found: C, 69.00; H, 5.03; N, 12.06. Calcd for $C_{14}H_{11}N_5O_2$ (3b): C, 59.78; H, 3.94; N, 24.90. Found: C, 59.56; H, 4.14; N, 24.57.

3-Cyanocoumarinimide (8a) and Its 8-Methoxy Derivative 8b.—To a solution of malononitrile (3.3 g, 0.05 mol) and salicylaldehyde (6.1 g, 0.05 mol) in ethanol (30 ml), ammonium acetate (2.31 g, 0.03 mol) was added and stirred for few minutes. This mixture afforded 5.5 g (65%) of **8a**, mp 162–164° dec (lit.[4] mp 163–165° dec). When 3-methoxysalicylaldehyde was used instead of salicylaldehyde, the condensation afforded 89% **8b**: mp 172–174° dec; ν_{max}^{KBr} 3290 (NH), 2220 (C≡N), 1650 cm^{-1} (C=NH).

Anal. Calcd for $C_{11}H_8N_2O_2$: C, 65.99; H, 4.03; N, 13.99. Found: C, 65.93; H, 3.97; N, 14.20.

Formation of 4-Amino-5-imino-2-phenyl[1]benzopyrano[3,4-c]pyridine (2a) by the Reaction of 8a and Acetophenone.—To a mixture of **8a** (0.8 g) and acetophenone (0.72 g) in ethanol (5 ml), ammonium acetate (1 g) was added and heated for 0.5 hr. After cooling, deposited crystals were collected and recrystallized from ethanol–pyridine to give 0.4 g of pale yellow needles (Table II).

Anal. Calcd for $C_{18}H_{13}N_3O$: C, 75.24; H, 4.56; N, 14.63. Found: C, 74.92; H, 4.52; N, 14.87.

Reaction of 2a and Salicylaldehyde.—To a mixture of **2a** (0.2 g) and salicylaldehyde (0.2 g) in ethanol (5 ml), ammonium acetate (0.5 g) was added and heated for 0.5 hr. Yellow-orange crystals precipitated out during the reaction. Recrystallization from pyridine gave 0.2 g of yellow crystals, mp 301–302°. This compound was proved to be identical with **1a** by a study of their ir spectra.

Reaction of 4-Amino-5-imino-7-methoxy-2-phenyl[1]benzopyrano[3,4-c]pyridine (2c) and Hydrochloric Acid.—To a mixture of **2c** (0.3 g) and ethanol (7 ml), hydrochloric acid (3 ml) was added and heated for 1 hr. After the mixture cooled, the resulting precipitate was collected and recrystallized from pyridine–ethanol to afford 0.2 g of 4-amino-7-methoxy-5-oxo-2-phenyl[1]benzopyrano[3,4-c]pyridine (**7b**): mp 219–220°; ν_{max}^{KBr} 3400, 3280, 3170 (NH_2), 1700 cm^{-1} (C=O).

Anal. Calcd for $C_{19}H_{14}N_2O_3$: C, 71.69; H, 4.43; N, 8.80. Found: C, 71.44; H, 4.61; N, 9.08.

Formation of 2-Aryl-5-methyl[2,3,4-*de*]benzopyrano[2,3-*d*]-pyridopyrimidine (5) by the Reaction of 2 and Acetic Anhydride.—A mixture of **2** (0.7 mmol) and acetic anhydride (4–6 ml) in pyridine (2–4 ml) was heated for 1–2 hr. After the mixture cooled, the resulting precipitate was collected and washed with dilute methanol. Experimental results are summarized in Table III.

Anal. Calcd for $C_{20}H_{13}N_3O$ (**5a**): C, 77.15; H, 4.21; N, 13.50. Found: C, 76.87; H, 4.21; N, 13.48. Calcd for $C_{20}H_{12}N_4O_3$ (**5b**): C, 67.41; H, 3.39; N, 15.72. Found: C, 67.53; H, 3.26; N, 15.75. Calcd for $C_{21}H_{15}N_3O_2$ (**5c**): C, 73.89; H, 4.43; N, 12.31. Found: C, 73.62; H, 4.44; N, 12.40. Calcd for $C_{21}H_{14}N_4O_4$ (**5d**): C, 65.28; H, 3.65; N, 14.50. Found: C, 64.93; H, 3.51; N, 14.28.

Formation of 2-Acetamino-1-cyano-5-methyl[2,3,4-*de*]benzopyrano[2,3-*d*]pyridopyrimidine (6) by the Reaction of 3 and Acetic Anhydride.—To a solution of **3** (0.4 mmol) suspended in pyridine (2 ml), acetic anhydride (2 ml) was added and heated for 1 hr. A pale yellow crystals began to separate from the solution. Experimental results are also listed in Table III.

Anal. Calcd for $C_{17}H_{11}N_5O_2$ (**6a**): C, 64.35; H, 3.49; N, 22.07. Found: C, 64.21; H, 3.57; N, 22.24. Calcd for $C_{18}H_{13}N_5O_3$ (**6b**): C, 62.24; H, 3.78; N, 2 0.17. Found: C, 61.88; H, 3.60; N, 19.89.

Acetylation of 1.—Acetic anhydride (3–6 ml) was added to a solution of **1** (0.2 g) suspended in pyridine (2–3 ml) and refluxed for 2 hr. After the mixture cooled, deposited crystals were collected and recrystallized from pyridine or dimethyl sulfoxide to afford **4** as pale yellow crystals. Experimental results and spectral data (ir and nmr) are summarized in Table I.

Anal. Calcd for $C_{27}H_{17}N_3O_3$ (**4a**): C, 75.17; H, 3.94; N, 9.74. Found: C, 74.89; H, 3.72; N, 9.88. Calcd for $C_{28}H_{19}N_3O_4$ (**4b**): C, 72.87; H, 4.15; N, 9.11. Found: C, 72.63; H, 4.23; N, 8.86. Calcd for $C_{29}H_{19}N_3O_5$ (**4c**): C, 71.16; H, 3.91; N, 8.59. Found: C, 71.13; H, 3.98; N, 8.81. Calcd for $C_{27}H_{16}N_4O_5$ (**4d**): C, 68.06; H, 3.36; N, 11.76. Found: C, 67.87; H, 3.42; N, 11.66. Calcd for $C_{29}H_{21}N_3O_5$ (**4e**): C, 70.87; H, 4.31; N, 8.55. Found: C, 70.92; H, 4.28; N, 8.70.

Registry No.—**1a**, 34035-64-8; **1b**, 34035-65-9; **1c**, 34035-66-0; **1d**, 34035-67-1; **1e**, 34035-68-2; **1f**, 34035-69-3; **1g**, 34035-70-6; **2a**, 30144-15-1; **2b**, 34035-72-8; **2c**, 34035-73-9; **2d**, 34035-74-0; **2e**, 34035-75-1; **3a**, 34035-76-2; **3b**, 34035-77-3; **4a**, 34035-78-4; **4b**, 34035-79-5; **4c**, 34035-80-8; **4d**, 34035-81-9; **4e**, 34087-68-8; **5a**, 34035-82-0; **5b**, 34035-83-1; **5c**, 34035-84-2; **5d**, 34035-85-3; **6a**, 34033-67-5; **6b**, 34033-68-6; **7a**, 34033-69-7; **7b**, 34033-70-0; **8b**, 34033-71-1; malononitrile, 109-77-3; salicylaldehyde, 90-02-8; ammonium acetate, 631-61-8.

Acknowledgment.—The authors wish to express their thanks to Dr. Taro Hayashi and Dr. Tatsuo Takeshima for their kind advice. Thanks are also due to Dr. Haruo Homma and his staff for their microanalyses, to Mr. Jun Uzawa for his measurements of the nmr spectra, and to Mr. Hironori Ogawa for his measurements of the ir spectra.

(4) G. P. Schiemenz, *Chem. Ber.*, **98**, 483 (1962).

Chemistry of α,α-Dichlorosulfenyl Chlorides

W. GARY PHILLIPS* AND K. WAYNE RATTS

Monsanto Company, Agricultural Division, Research Department, St. Louis, Missouri 63166

Received September 20, 1971

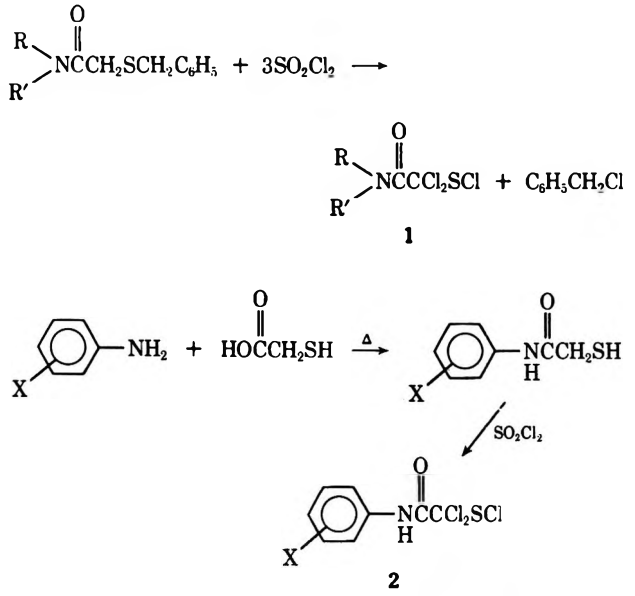
A convenient two-step general synthesis of α(carbamoyl)-α,α-dichloromethyl sulfenyl chlorides is described. These sulfenyl chlorides have been shown to undergo normal displacement of chloride from sulfur upon reaction with primary and secondary amines, alcohols and phenols, sulfinates, *O,O*-diethyldithiophosphoric acid, and phosphites. With liquid ammonia the sulfenyl chlorides yield 1-cyanoformamides. Other characteristic sulfenyl chloride reactions of these compounds include synthesis of (1) 1,2,4-thiadiazoles from amidines, (2) carbonylsulfenyl chlorides upon treatment with sulfuric acid–water, and (3) 2-chloro-2-thioxoacetamides with triphenylphosphine. Ring closure of these sulfenyl chlorides catalyzed by aluminum chloride produces 2-indolinones.

In a recent paper[1] we reported a general synthesis of functionalized α,α-dichlorosulfenyl chlorides (*e.g.*, **1**) *via* chlorination of the appropriate benzyl sulfide.

Presently we wish to report a new route for the synthesis of related compounds (**2**) and our studies of the chemical reactivity of dichlorosulfenyl chlorides (**1**).

Chlorination of α-Mercaptoacetanilides.—Chlorination of α-mercaptoacetanilides has been found to produce α-carbamoyl-α,α-dichlorosulfenyl chlorides (**2**) in good yield. The sequence initially involves simply

(1) W. G. Phillips and K. W. Ratts, *J. Org. Chem.*, **36**, 3145 (1971).

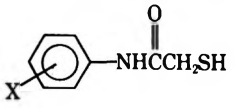


X = 4-Cl, 4-Br, 3-Br, 3-CF_3, 4-OCH_3, 4-CH_3, H, 2,6-di-C_2H_5, 2,6-di-CH_3

heating the appropriate aniline with readily available thioglycolic acid to produce the corresponding α-mercaptoacetanilide. Addition of 3 equiv of sulfuryl chloride to the α-mercaptoacetanilide yields the sulfenyl chloride. The reaction is general in that a variety of substituents on the aniline may be employed (Tables I and II).

Table I

α-Mercaptoacetanilides[a]

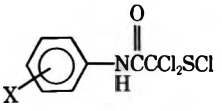


Registry no.	X	Mp, °C	Yield, %
	H	107–110[b]	93
34282-25-2	4-Cl	127–129	20
34282-26-3	3-CF_3	35–40	67
34282-27-4	2,6-Di-C_2H_5	120–124	37
34282-28-5	2,6-Di-CH_3	101–109	55
34282-29-6	4-OCH_3	111–115	90
34282-30-9	4-CH_3	117–123	95

[a] Satisfactory analytical data (±0.4% for C, H, N) were reported for all new compounds listed in the table. [b] Lit. mp 107–110°; W. Pacha and H. Erlenmeyer, *Helv. Chim. Acta*, **135**, 1156 (1956).

Table II

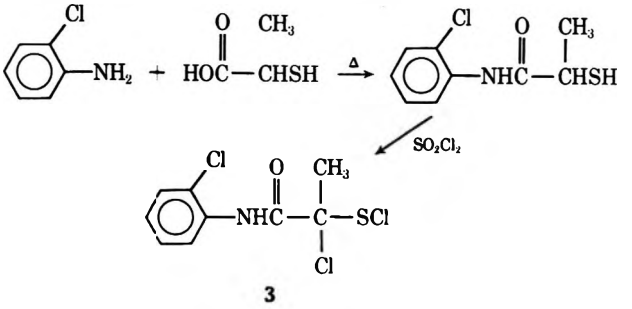
Dichlorosulfenyl Chlorides[a]



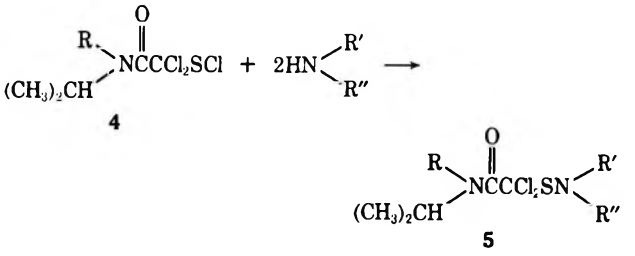
Registry no.	X	Mp, °C	Yield, %
34282-31-0	H	71–76	92
34282-32-1	4-Cl	71–73	40
34282-33-2	3-CF_3	60–62	65
34282-34-3	2,6-Di-C_2H_5	159–162	81
34282-35-4	2,6-Di-CH_3	115–117	50
34282-36-5	4-OCH_3	72–74	27
34282-37-6	4-CH_3	96–97	14

[a] Satisfactory analytical data (±0.4%) were reported for all compounds listed in the table.

A monochlorosulfenyl chloride (**3**) was synthesized simply by substituting α-mercaptopropionic acid for thioglycolic acid.



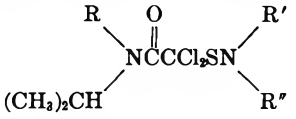
Reaction with N Nucleophiles.—The reaction of dichlorosulfenyl chlorides (**4**) with 2 equiv of a primary or secondary amine yields the dichlorosulfenamide **5**. Some representative examples are shown in Table III.

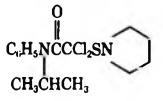
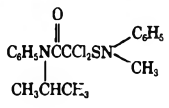
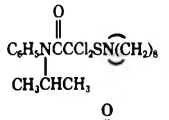
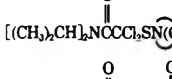
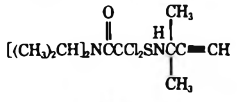
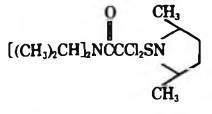


a, R = C_6H_5
b, R = $(CH_3)_2CH$

Table III

α,α-Dichlorosulfenamides[a]

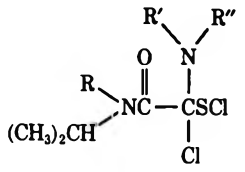


Registry no.	Structure	Mp, °C	Yield, %
34282-38-7		77–79	90
34282-39-8		Oil	
34282-40-1		63–64	30
34282-41-2		116–119	70
34282-55-8		81–83	63
34282-56-9		50–52	59

[a] Satisfactory analytical data (±0.4% for C, H) were reported for all compounds listed in the table.

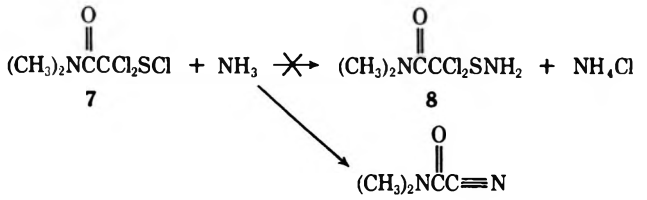
An isomeric sulfenyl chloride structure (**6**) is considered unlikely since trichloromethylsulfenyl chloride has been shown to give sulfenamides with amines.[2]

(2) J. Connolly and G. Dyson, *J. Chem. Soc.*, 679 (1935).



6

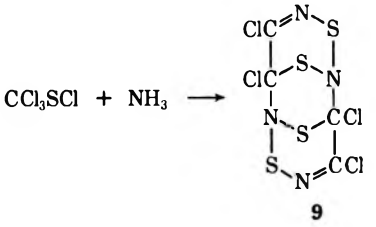
When liquid ammonia is employed as the amine the reaction takes a different course: treatment of **7** with liquid ammonia did not yield the expected sulfenamide **8**. Instead a 10% yield of 1-



7 8

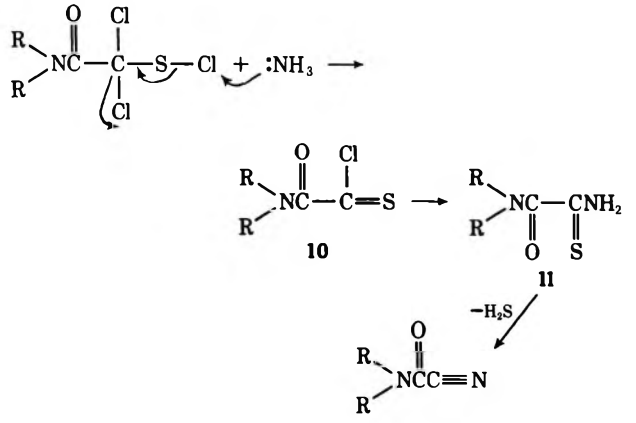
cyano-*N*,*N*-isopropylformamide was obtained. Likewise, when **4b** was treated with liquid ammonia 1-cyano-*N*,*N*-diisopropylformamide was isolated.

In contrast the reaction of trichloromethylsulfenyl chloride in benzene with aqueous ammonia takes a third course. Senning and Kelly reported[3] that **9** is formed in 9% yield under the above conditions. They suggest that trichloromethylsulfenamide is an intermediate in the formation of **9**.



9

A possible mechanism for the formation of the 1-cyanoformamides involves a 2-chloro-2-thioxoacetamide (**10**) as an intermediate, which could form a thioamide (**11**).



10 11

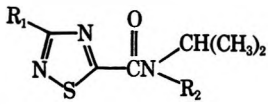
Elimination of hydrogen sulfide from **11** would yield the observed products. That **10** is a likely intermediate was shown when 2-chloro-2-thioxo-*N*,*N*-dimethylacetamide yielded 1-cyano-*N*,*N*-dimethylformamide under the reaction conditions.

The reaction of amides with α-carbamoyl-α,α-dichlorosulfenyl chlorides (**4**) produces 5-carbamoyl-

(3) A. Senning and P. Kelly, *Acta Chem. Scand.*, **20**, 2261 (1966).

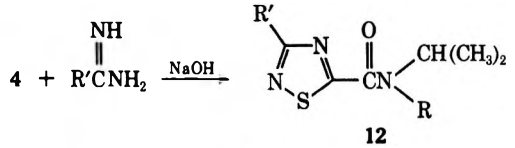
TABLE IV

1,2,4-THIADIAZOLES[a]



Registry no.	R_1	R_2	Mp, °C	Yield, %
34297-85-3		C_6H_5	102–107	20
		$CH(CH_3)_2$	68–72	42
	4-ClC_6H_4	C_6H_5	98–102	13

[a] Satisfactory analytical data (±0.4% for C, H) were reported for all compounds listed in the table.



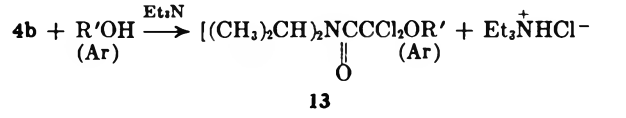
12

a, R = C_6H_5
b, R = $(CH_3)_2CH$

1,2,4-thiadiazoles (**12**) in moderate yield (see Table IV).

Goerdeler, Groschopp, and Sommerlad[4] have reported that amidines and trichloromethylsulfenyl chloride yield 5-chloro-1,2,4-thiadiazoles in a similar manner.

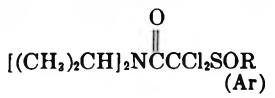
Reaction with O Nucleophiles.—An α,α-dichlorosulfenyl chloride (**4b**) when treated with methanol and substituted phenols in the presence of triethylamine reacts with displacement on sulfur to yield α,α-dichlorosulfenyl esters (**13**). Several representative examples are shown in Table V. In the case of metha-



13

TABLE V

α,α-DICHLOROSULFENYL ESTERS[a]



Registry no.	R	Mp, °C	Yield, %
34282-59-2	CH_3	77–79	90
34297-86-4	3-$CF_3C_6H_4$	38–40	19
34297-87-5	3,4,5-Tri-$CH_3C_6H_2$	96–98	69
34282-60-5	3-ClC_6H_4	85–89	72

[a] Satisfactory analytical data (±0.4% for C, H) were reported for all compounds listed in the table.

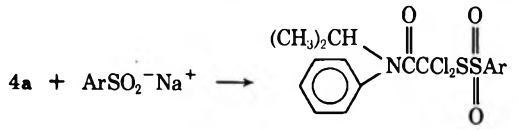
nol, the isomeric sulfoxide structure could be eliminated, since the product gave an nmr absorption at τ 6.5, the region expected for a methoxyl group.[5] A sulfoxide methyl group would be expected to appear at higher field (*e.g.*, DMSO absorbs at τ 7.4[5]). In the case of substituted phenols, reaction with the aromatic

(4) J. Goerdeler, H. Groschopp, and V. Sommerlad, *Chem. Ber.*, **90**, 182 (1957).

(5) Varian NMR Spectra Catalogs.

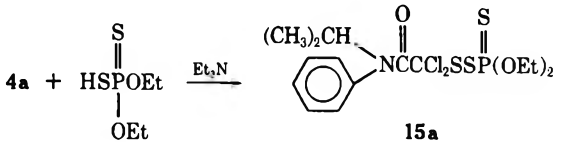
nucleus was precluded by integration of the relative areas of the absorptions in their nmr spectra.

Reaction with S Nucleophiles.—The reaction of an α,α-dichlorosulfenyl chloride (**4a**) with sodium arylsulfonates and *O,O*-diethyldithiophosphoric acid each proceeded *via* displacement on sulfur to yield α,α-dichlorothiolsulfonates (**14**) and a thioperoxyphosphoryldithioate (**15**), respectively.



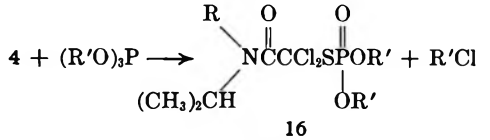
14

a, Ar = C_6H_5
b, Ar = p-$CH_3C_6H_4$



15a

Reaction with P Nucleophiles.—With trialkyl phosphites, α,α-dichlorosulfenyl chlorides (**4**) were found to give *S*-dichlorocarbamoylmethyl *O,O*-dialkylphosphorothioates (**16**). Apparently nucleophilic displacement occurs on sulfur followed by an Arbuzov reaction (see Table VI).[6]

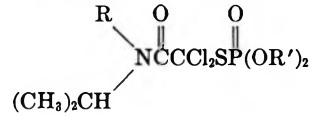


16

a, R = C_6H_5
b, R = $(CH_3)_2CH$

TABLE VI

S-DICHLOROCARBAMOYLMETHYL *O,O*-DIALKYLPHOSPHOROTHIOATES[a]



Registry no.	R	R′	Mp, °C	Yield, %
34282-61-6	C_6H_5	CH_3	91–92	34
34282-62-7	C_6H_5	CH_2CH_3	53–55	91
34282-63-8	$CH(CH_3)_2$	CH_3	129–131	93
34282-64-9	$CH(CH_3)_2$	CH_2CH_3	76–78	25
34282-65-0	$CH(CH_3)_2$	$CH(CH_3)_2$	83–87	70

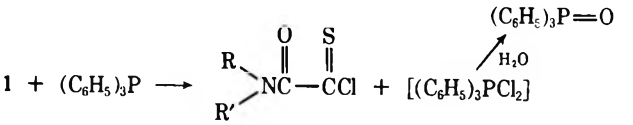
[a] Satisfactory analytical data (±0.4% for C, H, or Cl, S) were reported for all compounds listed in the table.

Dialkyl phosphites more slowly undergo the same reaction with the loss of hydrogen chloride to produce the same products.

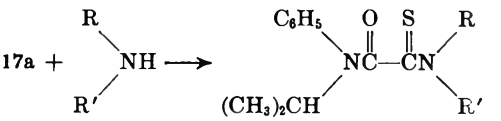
The carbamoyl dichlorosulfenyl chlorides (**1**) upon treatment with triphenylphosphine yield a salt (presumably triphenylphosphonium dichloride) and 2-chloro-2-thioxoacetamides (**17**).

Addition of chlorine to **17a** regenerated the starting sulfenyl chloride.

Treatment of the 2-chloro-2-thioxoacetamide **17a** with various amines yielded the corresponding monothiooxamides (**18**) (see Table VII).

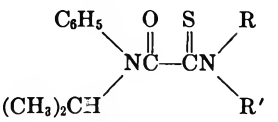


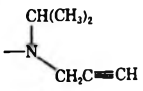
17a, R = C_6H_5; R′ = $(CH_3)_2CH$
b, R = $(CH_3)_2CH$; R′ = $(CH_3)_2CH$
c, R = CH_3; R′ = CH_3



18

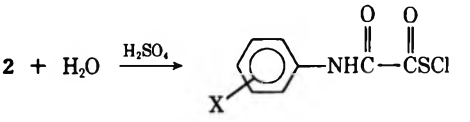
TABLE VII[a]



Registry no.	NRR′	Mp, °C	Yield, %
34282-66-1		108–109	91
34282-67-2		113–115	77
34282-68-3		131–132	99

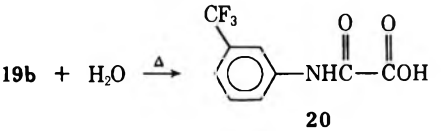
[a] Satisfactory analytical data (±0.4% for C, H) were reported for all compounds listed in the table.

Acid Hydrolysis.—Strong acid hydrolysis of α-carbamoyl-α,α-dichlorosulfenyl chlorides (**2**) yields carbamoylcarbonylsulfenyl chlorides (**19**). The reaction



19a, X = 4-Cl
b, X = 3-CF_3
c, X = 3-Br

appears somewhat general and proceeds in good yields. In one instance, when no care was exercised to keep the reaction temperature cool, a considerable amount of a carboxylic acid **20** was formed. Presumably this was formed *via* hydrolysis of **19b**.



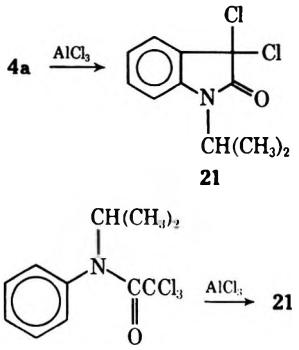
20

Trichloromethylsulfenyl chloride has been shown to undergo an analogous reaction to yield chlorocarbonylsulfenyl chloride.[7]

Aluminum Chloride Cyclization.—Treatment of **4a** with aluminum chloride produces 3,3-dichloro-1-isopropyl-2-indolinone (**21**). 3,3-Dichloro-1-isopropyl-2-indolinone was prepared authentically from ring closure of *N*-isopropyl-2,2,2-trichloroacetanilide.

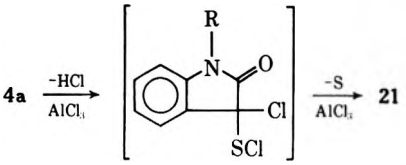
(6) The occurrence of the Arbuzov reaction with phosphites and sulfenyl chlorides has been reported. See P. Asinger, M. Thiel, and W. Schafer, *Justus Liebigs Ann. Chem.*, **637**, 146 (1960).

(7) W. Weiss, German Patent 1,224,720 (Nov. 11, 1964); (Farbenfabriken Bayer A. G).



21

The product **21** is likely formed as follows.



The catalytic influence of aluminum chloride is known[8] to convert trichloromethanesulfenyl chloride to carbon tetrachloride with loss of sulfur.

Experimental Section

General.—Melting points were determined with a Mel-Temp apparatus and are uncorrected. Infrared spectra were measured with a Beckman IR-5A spectrometer. Nuclear magnetic spectra were obtained on a Varian A-60 or T-60 spectrometer. Synthetic procedures for sulfenyl chlorides not described below are given in an earlier paper.[1]

General Procedure for Preparation of α-Mercaptoacetanilides.—To 92 g (0.95 mol) of 95% thioglycolic acid was added 1.0 mol of the appropriate aniline followed by heating at 130° for 3 hr under nitrogen. The mixture was poured into *ca.* 200 ml of 10% hydrochloric acid, whereupon it crystallized and was collected and air dried overnight. Chloroform proved to be a general recrystallizing solvent, although the resulting crude solid could be used directly in the chlorination step (see Table I).

General Procedure for the Preparation of α,α-Dichlorosulfenyl Chlorides (2).—To 0.1 mol of the appropriate α-mercaptoacetanilide in *ca.* 300 ml of methylene chloride was added 0.3 mol of sulfuryl chloride dropwise (exothermic). After the addition the mixture was stirred for an additional 1 hr. The solvent was then removed and the resulting mass was recrystallized from petroleum ether (bp 30–75°). No effort was made to optimize the yields (see Table II).

o-Chloro-α-mercapto-α-methylacetanilide.—To 53 g (0.5 mol) of α-mercaptopropionic acid was added 65 g (0.5 mol) of *o*-chloroaniline. After heating at 130° for 3 hr, the solution was poured into *ca.* 500 ml of 10% hydrochloric acid and the solid was collected and air dried, yield 26% after recrystallization from chloroform, mp 83–90°.

Anal. Calcd for $C_9H_{10}ClNOS$: C, 50.11; H, 4.67; N, 6.49. Found: C, 50.19; H, 4.86; N, 6.35.

2-(Chlorothio)2,2′-dichloropropionanilide (3).—The general procedure for chlorination of α-mercaptoacetanilides was followed employing *o*-chloro-α-mercaptopropionanilide. The oil was purified by low-temperature recrystallization from petroleum ether, yield 65%.

Anal. Calcd for $C_9H_8Cl_3NOS$: C, 37.98; H, 2.83; N, 4.92. Found: C, 38.03; H, 2.94; N, 4.76.

Treatment of 2-Chloro-2-thioxo-*N*-isopropylacetanilide with Chlorine.—Chlorine was bubbled through a solution of 1.5 g (6.2 mmol) of **17a** in 100 ml of methylene chloride until the red color was discharged. Removal of solvent gave **4a**, which was washed with pentane, yield 1.6 g (83%), mp 121–123° (lit.[1] mp 121–122°).

General Procedure for Preparation of α,α-Dichlorosulfenamides.—To 20 mmol of the sulfenyl chloride in *ca.* 100 ml of benzene was added 40 mmol of the appropriate amine. A precipitate formed immediately, after which the solution was stirred for *ca.* 1 hr. After filtration the solvent was removed and the crude product was recrystallized from petroleum ether (see Table III).

1-Cyano-*N*,*N*-diisopropylformamide.—Into *ca.* 50 ml of ammonia condensed in a three-neck flask was slowly poured 15.0 g of **4b**. Cooling was maintained by a Dry Ice bath for 1 hr, after which the ammonia was allowed to evaporate slowly. The gum which remained was extracted with petroleum ether. Cooling of the petroleum ether in Dry Ice gave a solid which was purified by distilling through a short-path column at low pressure, nmr ($CDCl_3$) τ 5.6 [heptet (h), CH], 6.3 (h, CH), 8.7 (q, CH_3).

Anal. Calcd for $C_8H_{14}N_2O$: C, 62.31; H, 9.15. Found: C, 62.25; H, 9.26.

1-Cyano-*N*,*N*-dimethylformamide.—A procedure analogous to that above was followed. The crude product was distilled at 55° (2 mm), yield 10%, nmr ($CDCl_3$) τ 6.85 (d, CH_3).

Anal. Calcd for $C_4H_6N_2O$: C, 48.97; H, 6.16. Found: C, 48.85; H, 6.21.

Treatment of 2-Chloro-2-thioxo-*N*,*N*-dimethylacetamide (10, R = CH_3) with Liquid Ammonia.—This procedure was analogous to that for the prepartion of 1-cyanoformamides. The product was distilled at reduced pressure, yield 0.5 g (9%). The ir of the product was the same as that of 1-cyano-*N*,*N*-dimethylformamide.

General Procedure for Preparation of Thiadiazoles (12).—The procedure of Goerdeler, Groschopp, and Sommerlad[4] for trichloromethylsulfenyl chloride was followed. Extraction of the crude oil with hot petroleum ether followed by cooling yielded the pure product (see Table IV). No attempt was made to optimize the yields.

General Procedure for Preparation of α,α-Dichlorosulfenyl Esters.—To 20 mmol of the appropriate sulfenyl chloride in *ca.* 100 ml of benzene was added 20 mmol of the appropriate alcohol (or phenol) followed by 20 mmol of triethylamine. A precipitate formed immediately and the reaction was stirred for *ca.* 30 min. After filtration, the solvent was removed and the crude product was recrystallized from petroleum ether (see Table V).

α,α-Dichloro-α-mercapto-*N*-isopropylacetanilide, *p*-Toluenethiolsulfonate (14b).—To 20 g (excess) of sodium *p*-toluenesulfinate in 100 ml of water was added a carbon tetrachloride solution of 15.6 g (0.05 mol) of **4a**. After stirring overnight, the layers were separated. Removal of the carbon tetrachloride gave a solid: mp 98–100°; nmr ($CDCl_3$) τ 2.4 (Ar, m), 7.55 ($ArCH_3$, s), 8.9 (CH_3, d).

Anal. Calcd for $C_{18}H_{19}Cl_2NO_3S_2$: C, 50.00; H, 4.43. Found: C,-50.05; H, 4.39.

α,α-Dichloro-α-mercapto-*N*-isopropylacetanilide Phenylthiolsulfonate (14a).—The same procedure as that above was followed: mp 86–90° (washed with petroleum ether); yield 71%; nmr ($CDCl_3$) τ 2.3 (Ar, m), 5.1 (CH, h), 8.9 (CH_3, d).

Anal. Calcd for $C_{17}H_{17}Cl_2NO_3S_2$: C, 48.80; H, 4.10. Found: C, 48.88; H, 4.18.

***S*,*S*-Dichloro(diisopropylcarbamoyl)methyl *O*,*O*-Diethylthioperoxyphosphoryldithioate (15b).**—To 3.8 g (20 mmol) of **4b** in benzene was added 5.6 g (20 mmol) of *O*,*O*-diethyldithiophosphoric acid followed by 2.0 g (20 mmol) of triethylamine. After stirring for 1 hr, the solution was filtered and the solvent was removed. The product was recrystallized from petroleum ether, mp 60–63°, yield 5.4 g (64%).

Anal. Calcd for $C_{12}H_{24}Cl_2NO_3PS_3$: C, 33.64; H, 5.65. Found: C, 33.68; H, 5.68.

General Procedure for the Preparation of *S*-Dichlorocarbamoylmethyl *O*,*O*-Dialkylphosphorothioates (16).—To 1 equiv of the sulfenyl chloride in benzene (or methylene chloride) was added 1 equiv of the trialkyl phosphite. After stirring for *ca.* 1 hr, the solvent was removed and the solid was recrystallized from petroleum ether (see Table VI).

2-Chloro-2-thioxo-*N*-isopropylacetanilide (17a).—To 6.2 g (0.02 mol) of α,α-dichloro-α-chlorothiol-*N*-isopropylacetanilide in *ca.* 100 ml of benzene was added 5.2 g (0.02 mol) of triphenylphosphine. After stirring for *ca.* 1 hr, the solvent was removed and a red oil remained. Addition of ether (with cooling) gave a gummy solid which gave off HCl when collected. Addition of water to this gummy solid gave a 97% yield of triphenylphosphine oxide, mp 144–147° (lit.[9] mp 153–156°). The nmr showed only aromatic protons.

(8) F. Boberg, *Justus Liebigs. Ann. Chem.*, **679**, 109 (1964).

(9) "Handbook of Chemistry and Physics," 37th ed, Chemical Rubber Publishing Co., Cleveland, Ohio.

The ether solution was evaporated and an oil remained. Addition of petroleum ether to the oil followed by filtration and cooling to −70° gave an orange solid: mp 35–37°; yield 73%; nmr ($CDCl_3$) τ 2.6 (m, aromatic), 5.1 (h, methane), 8.8 (d, methyl); mass spectrum *m/e* 241 (M^+), 206 (M − HCl), 162 [M − C(=S)Cl], 120 (PhNHC=O), 79 (ClC=S), 77 (Ph).

Anal. Calcd for $C_{11}H_{12}ClNOS$: C, 54.65; H, 5.00. Found: C, 54.80; H, 5.12.

2-Chloro-2-thioxo-*N*,*N*-diisopropylacetamide (17b).—This procedure was identical with that for **17a**: mp 30–63° (petroleum ether); yield 27%; nmr ($CDCl_3$) τ 6.0 (h, 1), 6.5 (h, 1), 8.55 (d, 6), 8.75 (d, 6).

Anal. Calcd for $C_8H_{14}ClNOS$: C, 46.26; H, 6.79; N, 6.74. Found: C, 46.02; H, 6.73; N, 6.62.

2-Chloro-2-thioxo-*N*,*N*-dimethylacetamide (17c).—To 13.2 g (0.061 mol) of α-(*N*,*N*-dimethylcarbamoyl)-α,α-dichloromethylsulfenyl chloride in *ca.* 250 ml of benzene was added 16.0 g (0.061 mol) of triphenylphosphine. After stirring for 1 hr, the solvent was stripped and the product was distilled at reduced pressure, nmr ($CDCl_3$) τ 6.95 (d), yield 67%.

Anal. Calcd for C_4H_6ClNOS: C, 31.69; H, 3.99. Found: C, 32.11; H, 4.04.

General Procedure for the Preparation of Monothiooxamides (18).—To 20 mmol of 2-chloro-2-thioxo-*N*-isopropylacetanilide in *ca.* 100 ml of benzene was added 40 mmol of the appropriate amine. After stirring for *ca.* 1 hr, the precipitate was filtered off and the solvent was removed. The product was recrystallized from petroleum ether (see Table VII).

***p*-Chlorophenylcarbamoylcarbonylsulfenyl Chloride (19a).**—To 6.1 g (0.02 mol) of α,α-dichloro-α-(*p*-chlorophenylcarbamoyl)-methylsulfenyl chloride was added *ca.* 75 ml of concentrated sulfuric acid. After stirring for *ca.* 10 min, the mixture was poured onto ice and the precipitate was collected and air dried, yield 94%. After recrystallization from chloroform the yield was 50%: mp 172–174°; ir ($CHCl_3$) 5.83, 5.90 cm^{-1} (C=O, C=O); nmr (DMSO-d_6) τ 2.3 (q, aromatic).

Anal. Calcd for $C_8H_5Cl_2NO_2S$: C, 38.42; H, 2.02; N, 5.60. Found: C, 38.23; H, 1.94; N, 5.57.

***m*-Trifluoromethylphenylcarbamoylcarbonylsulfenyl Chloride (19b).**—This procedure was analogous to that for **19a**, yield 90%, mp 108–114° (chloroform).

Anal. Calcd for $C_9H_5ClF_3NO_2S$: C, 38.11; H, 1.78; N, 4.94. Found: C, 38.32; H, 1.80; N, 4.86.

When the reaction was repeated on a 125-g scale an attempt was made to recrystallize the product from benzene. A white solid precipitated out which was identified as **20**: yield 25 g; mp 170–171°; mass spectrum *m/e* 233 (M^+), mol wt (benzene) 234 (calcd 233).

Anal. Calcd for $C_9H_6F_3NO_3$: C, 46.36; H, 2.57; N, 6.01. Found: C, 46.52; H, 2.65; N, 6.08.

3-Bromophenylcarbamoylcarbonylsulfenyl Chloride (19c).—This procedure was analogous to that for **19a**, yield 25%, mp 157–161° (chloroform).

Anal. Calcd for $C_8H_5BrClNO_2S$: C, 32.62; H, 1.71; N, 4.76. Found: C, 32.63; H, 1.76; N, 4.73.

$AlCl_3$-Catalyzed Ring Closures. A. From Sulfenyl Chloride.—*N*-Isopropyl *N*-phenylcarbamoyldichloromethylsulfenyl chloride (31.0 g, 0.1 mol) was dissolved in 200 ml of methylene chloride and cooled in an ice bath. Aluminum chloride (26.6 g, 0.2 mol) was added in small portions with stirring over 10 min. After 5 min of additional stirring the red solution was poured onto 500 ml of ice. The organic layer was separated and the aqueous phase was washed with 290 ml of methylene chloride. The combined organic layers were dried over magnesium sulfate and concentrated to an oil. Addition of hot petroleum ether (bp 30–75°) crystallized 4.8 g of 3,3-dichloro-1-isopropyl-2-indolinone (**21**). Concentration of the filtrate gave a gummy solid which was recrystallized from methylene chloride–petroleum ether to give an additional 5.0 g of solid for which the nmr was identical with that of the original solid, total yield 9.8 g (25%). Recrystallization of the product (4.8 g) from petroleum ether gave 3.7 g of **21**, mp 78–79°.

Anal. Calcd for $C_{11}H_{11}Cl_2NO$: C, 54.12; H, 4.54; Cl, 29.05; N, 5.74. Found: C, 54.19, 54.14; H, 4.62, 4.65; Cl, 28.47, 28.48; N, 5.81, 5.62.

The nmr spectrum ($CDCl_3$) exhibits peaks for CH_3 at τ 8.53 (d, J = 7 cps, A = 6), CH at 5.57 (septet, J = 7 cps, A = 1), ArH at 2.2–3.1 (multiplet, A = 4). The ir spectrum ($CHCl_3$) exhibits a single peak for C=O at 1730 cm^{-1}. Mass spectral characteristics are *m/e* 243 (44%, M^+ for ^{35}Cl), 228 (14%, M − CH_3), 208 (90%, M − Cl), 200 (27%, M − C_3H_7), 166 (100%, M − C_3H_6Cl).

B. From Trichloroacetanilide.—*N*-Isopropyl-2,2,2-trichloroacetanilide (2.8 g, 0.01 mol) was dissolved in 20 ml of methylene chloride, and aluminum chloride (2.7 g, 0.02 mol) was added in portions. After stirring overnight the mixture was poured onto ice (400 ml) and the layers were separated. The aqueous layer was washed with two 50-ml portions of methylene chloride and the combined organic layers were dried over magnesium sulfate. Removal of solvent gave an oil which was crystallized from petroleum ether to give 0.6 g (25%) of product identical with the above material **21**.

***N*-Isopropyl-2,2,2-trichloroacetanilide.**—*N*-Isopropylaniline (135.2 g, 1.0 mol) was dissolved in 250 ml of benzene, and trichloroacetyl chloride (181.1 g, 1.0 mol) was added slowly with stirring. Triethylamine (101.2 g, 1.0 mol) was added dropwise with vigorous stirring to the boiling mixture over 30 min. The mixture was filtered, the filter cake was washed with benzene, and the combined organic filtrate was washed twice with 10% hydrochloric acid (250 ml). The benzene solution was washed twice with 250 ml of water and dried over magnesium sulfate. Removal of the benzene *in vacuo* gave an oil which was crystallized from methanol to give 101.3 g (36%) of product, mp 45–47°.

Registry No.—**3**, 34282-69-4; **14a**, 34282-70-7; **14b**, 34282-71-8; **15**, 34282-72-9; **17a**, 34282-73-0; **17b**, 34282-74-1; **17c**, 34282-75-2; **19a**, 34282-76-3; **19b**, 34282-77-4; **19c**, 34282-78-5; **20**, 6890-83-1; **21**, 34282-79-6; *O*-chloro-α-mercapto-α-methylacetanilide, 34282-80-9; 1-cyano-*N*,*N*-diisopropylformamide, 34282-81-0; 1-cyano-*N*,*N*-dimethylformamide, 16703-51-8; *N*-isopropyl-2,2,2-trichloroacetanilide, 34282-83-2.

The Reaction of S-Methiodide Derivatives of Activated Thioureas with Hydroxylic Compounds. A Novel Synthesis of Mercaptans

DANIEL L. KLAYMAN,* ROBERT J. SHINE, AND J. DAVID BOWER

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

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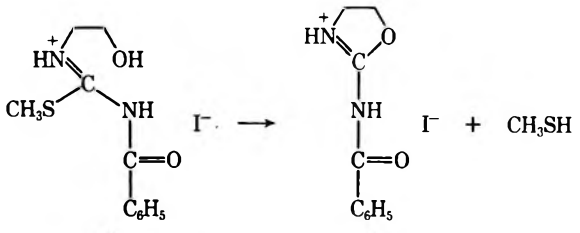
2-Methyl-2-thiopseudourea hydriodides activated by electron-withdrawing groups undergo attack by alcohols and water to give several types of products whose formation is dependent on the nature of the hydroxylic reactant. When 1-benzoyl-2-methyl-2-thiopseudourea hydriodide (5) was heated with alcohols, methyl mercaptan was evolved and there was formed 1-benzoylurea (2) and the iodide corresponding to the alcohol. The yield of 2 was diminished and the formation of 1-benzoyl-2-thiourea (1) took on greater prominence in going from a primary to a tertiary alcohol. Methyl *N*-benzoylthiolcarbamate (6) and NH_4I were also formed when the more hindered alcohols were used and were essentially the only products obtained in the reaction of 5 with water. *S*-Methiodide derivatives of other activated thioureas, *i.e.*, 1-acetyl-2-methyl-2-thiopseudourea (9), 2-methyl-2-thiopseudobiuret (10), 2-methyl-2,4-dithiopseudobiuret (11), and 1-(4-nitrophenyl)-2-methyl-2-thiopseudourea (12) hydriodides, reacted with ethanol and water in a similar manner as 5. Thiols could be generated in moderate yields by the reaction of 1-acetyl-2-thiourea (14) with primary alkyl halides in ethanol.

In the course of a recent study,[1] it was necessary to prepare *S*-methiodide derivatives of numerous thioureas. This was accomplished by heating the thioureas with methyl iodide in ethyl alcohol, a solvent eminently suitable for this purpose.[2] When the formation of *S*-methyl derivatives of acylthioureas such as 1-benzoyl-2-thiourea (1) was attempted in ethyl alcohol, however, there was unexpectedly noted a copious evolution of methyl mercaptan and from the reaction mixture was isolated a high yield of 1-benzoylurea (2). Recently, we described[3] a somewhat related reaction with 1-(2-hydroxyethyl)-3-benzoyl-2-methyl-2-thiopseudourea hydriodide (3) which cyclized *via* an intramolecular displacement of the methylthio group by the hydroxyl to give 2-benzamido-2-oxazoline hydriodide (4) with the concomitant evolution of methyl mercaptan.

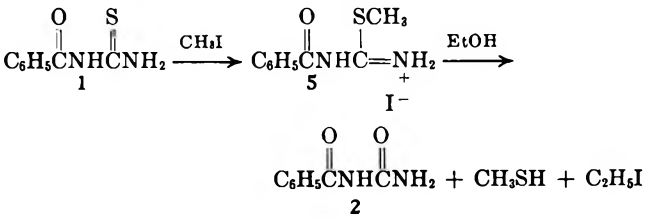


3 4

The investigation of the reaction between 1-benzoyl-2-methyl-2-thiopseudourea hydriodide (5), chosen as a model acylthiourea derivative, and some representative hydroxylic compounds is reported here. In addition, the results obtained in the reaction of compounds structurally related to 5 with both ethyl alcohol and water are described.

Results

The desired 1-benzoyl-2-methyl-2-thiopseudourea hydriodide (5) could be readily prepared in a nonhydroxylic medium such as acetonitrile. The free base of 5[4] was found to be virtually unaffected by boiling ethyl alcohol over a 24-hr period as evidenced by a negligible evolution of methyl mercaptan and recovery



1 5 2

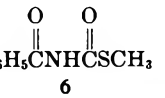
TABLE I

INTERACTION OF 1-BENZOYL-2-METHYL-2-THIOPSEUDOUREA HYDRIODIDE (5) WITH ALCOHOLS

5 + ROH ⟶ 1 + 2 + 6

R	Reflux time, hr	Yields, % 1	2	6	Other products (%)
CH_3–	3		94	<1	
CH_3CH_2–	3		90	1	
$CH_3CH_2CH_2$–	3		82	4	
	24		55		$C_6H_5C(=O)NHC(=O)OC_3H_7$ (31)
$(CH_3)_2CH$–	16	28	61	7	$C_6H_5C(=O)NHC(=O)OCH(CH_3)_2$ (4)
$(CH_3)_3C$–	16	64	15	21	

of ~90% of the starting material. Compound 5 was heated under reflux with methyl and ethyl alcohols for 3 hr to give >90% yields of 2 (*cf.* Table I). A somewhat lower yield of 2 was obtained with *n*-propyl alcohol after an identical heating period and, in addition, methyl *N*-benzoylthiolcarbamate (6) was isolated as a minor product.



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The decomposition of 5 in a secondary alcohol, *i.e.*, isopropyl alcohol, was considerably slower than had been seen with primary alcohols. After 3 hr, more than half of the starting material could be recovered and a 20% yield of the starting thiourea, 1, was obtained. When the reflux period was extended to 16 hr, the yield of 2 was 61%. In addition, a somewhat increased quantity of 1-benzoyl-2-thiourea (1) was isolated. Thiourea 1 was shown not to be the precursor of 2 in the above-described reactions by heating it for 24 hr with ethyl alcohol. Whereas extensive ethanolysis of the benzoyl group occurred, the formation of 2 or urea could not be detected.

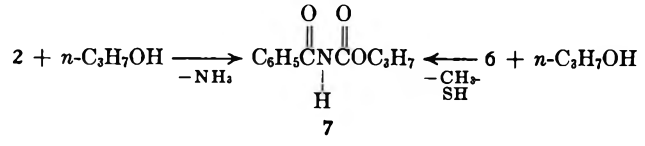
(1) D. L. Klayman and R. J. Shine, *Anal. Chim. Acta*, **41**, 408 (1968).
(2) E. E. Reid, "Organic Chemistry of Bivalent Sulfur," Vol. V, Chemical Publishing Co., New York, N. Y., 1963, p 28.
(3) D. L. Klayman, R. J. Shine, and A. E. Murray, Jr., *J. Pharm. Sci.*, **59**, 1515 (1970).
(4) G. Ito, *Chem. Pharm. Bull. (Tokyo)*, **9**, 245 (1961).

tert-Butyl alcohol also reacted much slower with **5** than did the primary alcohols. Most of the starting material could be recovered after a 3-hr reflux period; however, at the end of 16 hr there was obtained a 64% yield of the thiourea **1** and moderate quantities of **2** and **6**.

The components of the reaction mixtures obtained from the isopropyl and *tert*-butyl alcohols runs were extremely difficult to separate cleanly by crystallization methods. Column chromatography could not be used inasmuch as the products were insoluble in the solvents generally used with this technique. The most satisfactory method devised to quantitate the products was through the use of nmr spectroscopy in conjunction with sulfur microanalysis. This method gave the relative proportions of the products but not their absolute values.

Since the urea oxygen atom of **2** could only arise by transfer from the hydroxylic reactant, it was of interest to learn the fate of the alkyl moiety of the alcohol in this process. On distillation of the reaction mixtures from the ethyl, *n*-propyl, and isopropyl alcohol runs, the corresponding alkyl iodides were isolated and identified. The evolution of isobutylene, detected from the *tert*-butyl alcohol experiment, is ascribed to the breakdown of the thermally unstable *tert*-butyl iodide into the olefin and hydrogen iodide.[5]

Secondary crystalline transformation products were observed in those mixtures which had been permitted to reflux >12 hr. It was demonstrated that *n*-propyl *N*-benzoylcarbamate (**7**), a constituent of the

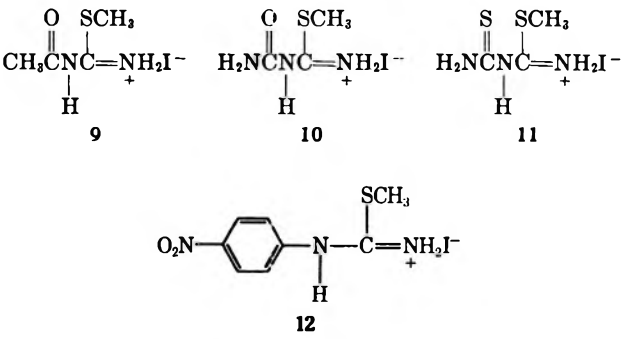


7

mixture from the *n*-propyl alcohol experiment, arose from the interaction of the alcohol with either of the primary products of the reaction, *i.e.*, **2** or **6**. The conversion of ureas to carbamic esters has been reported by earlier workers.[6] The related isopropyl *N*-benzoylcarbamate (**8**) was obtained in very low yield and *tert*-butyl *N*-benzoylcarbamate does not appear to have been formed at all.

The reaction of **5** with water resulted in its rapid and quantitative conversion to methyl *N*-benzoylthiolcarbamate (**6**) and ammonium iodide with only trace amounts of methyl mercaptan being evolved. Thus, the reaction course in water sharply contrasts with that which occurs in alcohols.

Compounds in which the benzoyl group of **5** was replaced by other electron-withdrawing groups, *i.e.*, acetyl, carbamoyl, thiocarbamoyl, and 4-nitrophenyl, were studied to determine if the resultant compounds would react similarly with hydroxylic nucleophiles. 1-Acetyl-2-methyl-2-thiopseudourea (**9**), 2-methyl-2-thiopseudobiuret (**10**), 2-methyl-2,4-dithiopseudobiuret (**11**), and 1-(4-nitrophenyl)-2-methyl-2-thiopseudourea (**12**) hydriodides were synthesized and each was heated under reflux with ethyl alcohol for 24 hr. In all instances the evolution of methyl mercaptan was



9 **10** **11**

12

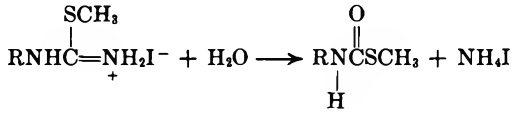
observed with the formation of acetylurea from **9**, biuret from **10** and **11**, and 1-(4-nitrophenyl)urea from **12**, respectively. The formation of biuret rather than thiobiuret from **11** was surprising and, therefore, it was necessary to confirm that thiobiuret is stable to boiling ethyl alcohol over a 24-hr period.

The essentiality of the 4-nitro group of **12** was dramatically demonstrated when the related 1-phenyl-2-methyl-2-thiopseudourea hydriodide was refluxed in ethyl alcohol for 24 hr. No methyl mercaptan evolution was detected and all the starting material was recovered unchanged. The *S*-methiodide derivative of 1-guanyl-2-thiourea was similarly unaffected.

When **9**–**12** were each heated in water, ammonium iodide was eliminated to give the corresponding methyl thiolcarbamate derivatives, generally in excellent yield (*cf.* Table II).

TABLE II

THE FORMATION OF METHYL THIOLCARBAMATES BY THE REACTION OF *S*-METHYLTHIOPSEUDOUREA HYDRIODIDES WITH WATER

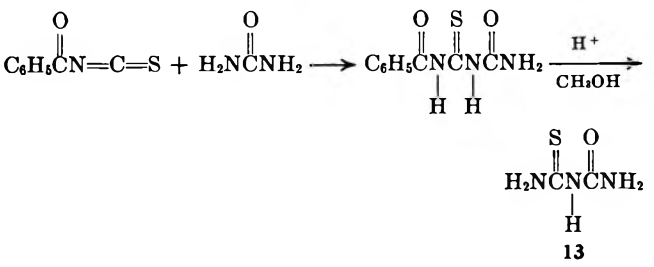


R	Reflux time, hr	Yield, %	Mp, °C	Recrystn solvent	Molecular formula[a]
CH_3CO–	0.5	78	152–154[b]	EtOH	$C_4H_7NO_2S$
C_6H_5CO–	1	96	162–164[c]	CH_3CN	$C_9H_9NO_2S$
H_2NCO–	3	82	209–211 dec[d]	CH_3CN	$C_3H_6N_2O_2S$
H_2NCS–	3	95	171–172 dec	CH_3CN	$C_3H_6N_2OS_2$
p-$NO_2C_6H_4$–	13	75	200–204	CH_3CN–H_2O	$C_8H_8N_2O_3S$

[a] Satisfactory analytical data (±0.3% for C, H, N, S) were reported for all compounds listed in the table: Ed. Registry numbers are, respectively, 34277-65-1, 13996-86-6, 34277-67-3, 34277-68-4, and 34277-69-5. [b] Lit.[21] mp 145.5–146°. [c] Lit.[21] mp 152–153°. On recrystallization, the melting point is lowered and broadened with no change in ir or nmr spectra. [d] Heating above the melting point gives cyanuric acid.

A new synthesis of thiobiuret (**13**) was developed incidental to this investigation which is considerably simpler than the existing method[7] which employs the reaction of hydrogen or ammonium sulfide with cyanourea. In our preparation, benzoyl isothiocyanate was condensed with urea to give 1-benzoyl-2-thiobiuret whose benzoyl group was easily removed by methanolysis to give thiobiuret in good yield.

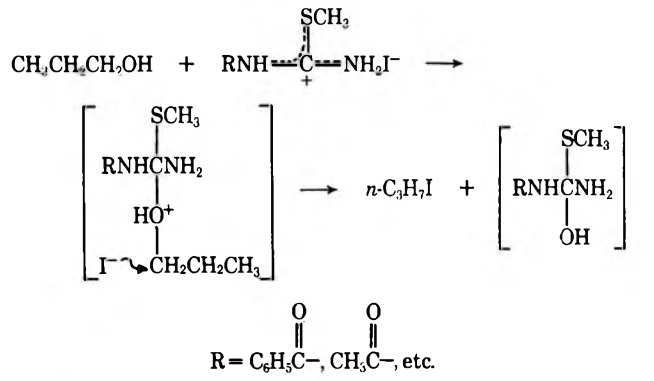
(5) J. L. Jones and R. A. Ogg, Jr., *J. Amer. Chem. Soc.*, **59**, 1943 (1937).
(6) R. A. Jacobson, *ibid.*, **60**, 1742 (1938), and references cited therein.
(7) A. Wunderlich, *Ber.*, **19**, 448 (1866); O. Hecht, *ibid.*, **25**, 749 (1892).



13

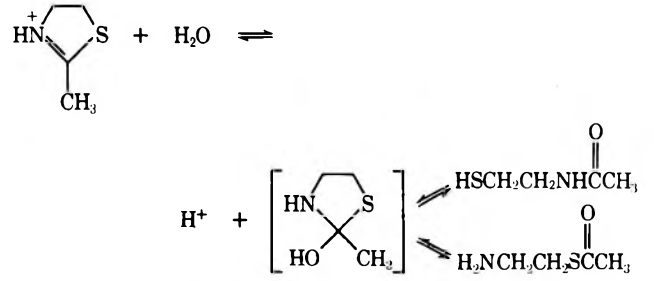
Discussion

An *S*-methiodide derivative of a thiourea which is N-substituted by an electron-withdrawing group undergoes addition by an alcohol, ordinarily a poor nucleophile, at the activated 2-carbon atom. This addition to the cationic substrate yields, in all probability, a

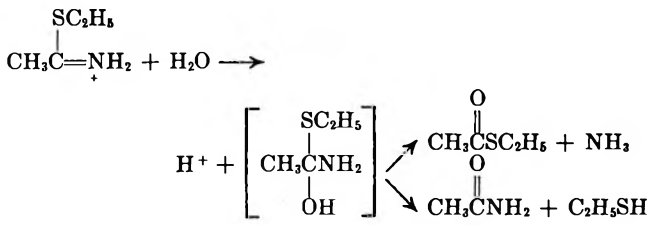


tetrahedral intermediate in the rate-determining step. The carbon adjacent to the protonated oxygen atom then is attacked by iodide ion under conditions which are highly favorable for ether cleavage, resulting in the formation of the alkyl iodide corresponding to the alcoholic reactant.

The uncharged carbinolamine intermediate, thus formed, closely resembles other tetrahedral intermediates possessing both a sulfur and a nitrogen atom about the central carbon whose mode of decomposition is highly dependent on the pH of the medium. For example, Martin, *et al.*,[8] proposed a hydroxythiazolidine intermediate to explain the formation of *N*- and *S*-

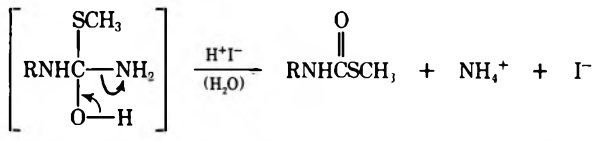


acetyl-2-mercaptoethylamine in the course of the hydrolysis of 2-methyl-2-thiazoline. In studying the hydrolysis of thioimidate esters, Schmir, *et al.*,[9] found that, in general, C–N bond fission of the proposed tetrahedral intermediate occurs under acidic conditions to yield thiol esters and amines, whereas under neutral or alkaline conditions C–S fission takes place resulting in the formation of amides with the loss of



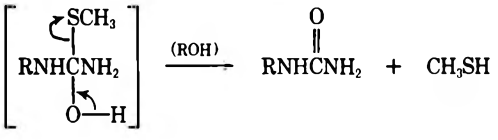
mercaptan. By adjusting the pH and buffer concentrations it was possible to obtain yields of the order of 90% of either the thiol ester or the amide. We have reported[10] a similar reaction in which the attack of hydroselenide ion on certain *S*-methylthiopseudoureas, when conducted under acid conditions (pH 5–6), results in C–N bond cleavage and under basic conditions (pH 8–9) leads to C–S bond fission.

In the present case, the variables, in addition to hydrogen ion concentration, were the polarity and molecular configuration of the hydroxylic reactants. With water, the most polar reactant, the collapse of the tetrahedral intermediate proceeds at *ca.* pH 7 by the cleavage of the C–N bond to form an ionic by-product, ammonium iodide, and the thiolcarbamic ester (6). As part of each mechanism proposed for the hydrolysis of thiazolines,[8] thioimidate esters,[9] iminolactones,[11] and aliphatic Schiff bases[12] there is a step in which the positively charged carbinolamine intermediate loses a proton before conversion to the final product. Here too, there is little reason to believe that



another mechanism is operative since the reaction we have observed seems to possess the essential characteristics of the hydrolyses mentioned above.

Alcohols, being considerably less polar than water, favor the decomposition of the tetrahedral intermediate by a route leading to nonionic products *via* C–S



bond cleavage. Methyl mercaptan and acylurea formation takes place with methyl and ethyl alcohols with approximately equal ease, the slight steric disadvantage of the latter being apparently overcome by its higher boiling point. Reactivity of the alcohols used in this reaction than falls in the order *n*-propyl > isopropyl > *tert*-butyl as crowding increases about the carbinol carbon atom.

The competitive formation of the thiourea **1** as a minor but significant product in the reaction of **5** with isopropyl alcohol and as the major product in the reaction with *tert*-butyl alcohol probably does not involve the direct participation of the medium in intermediate formation. This decomposition follows the order of the thermal lability of the alkyl halides formed,

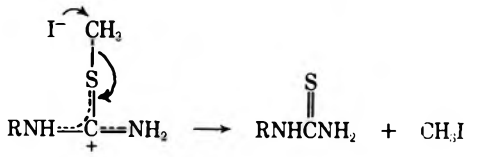
(8) R. B. Martin, S. Lowey, E. L. Elson, and J. T. Edsall, *J. Amer. Chem. Soc.*, **81**, 5089 (1959).

(9) R. K. Chaturvedi, A. E. MacMahon, and G. L. Schmir, *ibid.*, **89**, 6984 (1967); R. K. Chaturvedi and G. L. Schmir, *ibid.*, **91**, 737 (1969).

(10) D. L. Klayman and R. J. Shine, *J. Org. Chem.*, **34**, 3549 (1969).

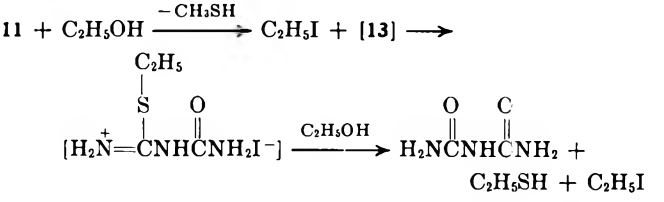
(11) G. L. Schmir and B. A. Cunningham, *J. Amer. Chem. Soc.*, **87**, 5692 (1965); B. A. Cunningham and G. L. Schmir, *ibid.*, **88**, 551 (1966).

(12) E. H. Cordes and W. P. Jencks, *ibid.*, **85**, 2843 (1963).

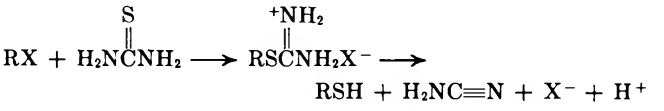


i.e., *tert*-butyl > isopropyl. Because iodide is not removed as a stable covalent compound, reaction mixtures from these alcohols have a more abundant quantity of ionic iodide to render the above reaction possible. It is interesting that, of the alcohols, only *tert*-butyl alcohol gives any significant amount of the thiolcarbamic ester **6**. This may also be a consequence of the increased acidity of the reaction medium due to the hydriodic acid formed in the decomposition of *tert*-butyl iodide.

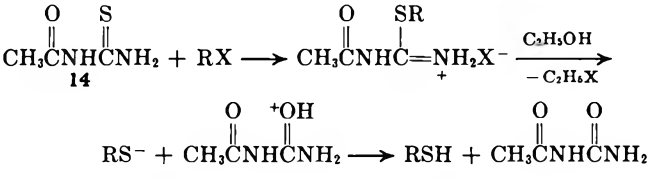
Compounds **9–12**, possessing electron-withdrawing groups other than benzoyl, eliminated methyl mercaptan or ammonium iodide when heated with ethanol or water, respectively. The only unexpected result was the reaction of *S*-methyldithiobiuret (**11**) with ethanol in which both sulfur atoms were separated from the molecule to give biuret. The loss of the second thiocarbonyl group can be hypothesized as occurring by the S-alkylation of thiobiuret (**13**) by ethyl iodide formed as a by-product of the first step, followed by reattack by an ethanol molecule.



Synthesis of Mercaptans.—The condensation of thiourea with alkyl halides to form thiopseudoureas, followed by their hydrolysis with aqueous alkali[13] or amines[14] is a well-known method for the production



of mercaptans. We have applied the above-described findings with activated thioureas to the synthesis of mercaptans. The procedure which was found most satisfactory consisted of heating alkyl halides (X = Br, I) with 1-acetyl-2-thiourea (**14**) in ethyl alcohol for



24 hr (*cf.* Table III). This method obviates the need for a separate hydrolysis step and may prove useful for the generation of thiols which are water or alkali sensitive. Acetyl- rather than benzoylthiourea was found preferable inasmuch as the partial ethanolysis of the amide function which occurs in the course of the reaction leads to the readily removable ethyl acetate rather than ethyl benzoate (bp 211–213°). This competing reaction, which deactivates **14**, prevents the quantitative formation of mercaptans regardless of how long the reflux time is extended beyond ~24 hr.

In comparison with thiourea, the thiocarbonyl group of **14** is deactivated as an S nucleophile owing to the electron-withdrawing effect of the *N*-acetyl group. Its diminished nucleophilicity could be demonstrated in its reaction with 2-bromooctane in acetonitrile. Whereas this secondary alkyl halide combined almost completely with thiourea in 24 hr, the reaction went to only ~20% completion with **14**.

Also, the yields of mercaptans derived from primary halides and **14** were considerably higher than those obtained from secondary halides (*e.g.*, 53% from 1-bromooctane *vs.* 12% from 2-bromooctane). There was no observed mercaptan formation from *tert*-butyl bromide. The use of alkyl iodides in place of the bromides resulted in only a slight increase in the yields of the mercaptans.

Several alkyl halides containing additional functional groups did not give the desired mercaptans on reaction with **14** but instead led to products reported to be obtained with thiourea. For example, the reaction of **14** with 2-bromoethylamine hydrobromide in ethanol gave 2-amino-2-thiazoline hydrobromide.[15] There was evidence that 2-acetamido-2-thiazoline was initially formed, with the acetyl group being lost by ethanolysis. Bromoacetic acid and **14** resulted in the formation of 2-amino-2-thiazolin-4-one hydrobromide.[16]

TABLE III

MERCAPTAN FORMATION FROM 1-ACETYL-2-THIOUREA (**14**) AND ALKYL HALIDES IN ETHANOL

$RX + 14 + C_2H_5OH \longrightarrow RSH + CH_3CONHCONH_2$

RX	RSH, % yield
1-Bromooctane	53
1-Bromododecane	50
1-Iododecane	52
1-Bromohexadecane	47
2-Bromooctane	12
α-Bromotoluene	76[a]
2-Bromoethylbenzene	38
2-Iodoethylbenzene	44
N-(2-Bromoethyl)phthalimide[b]	21
2-Bromoethoxybenzene	37
1,5-Dibromopentane	36

[a] Complete oxidation of the reaction product with iodine resulted in a 73% isolated yield of dibenzyl disulfide. [b] Owing to problems with solubility in petroleum ether, CH_2Cl_2 was used to elute the mercaptan from the column. Sulfur analysis of the chromatographed product was in good agreement with the value obtained by the iodine titration.

Experimental Section[17]

1-Benzoyl-2-thiourea (**1**).—To a solution of 89.2 g (1.1 mol) of sodium thiocyanate in 500 ml of warm acetone was slowly added 140 g (1 mol) of benzoyl chloride and the resulting mixture was

(13) E. E. Reid, "Organic Chemistry of Bivalent Sulfur," Vol. I, Chemical Publishing Co., New York, N. Y., 1958, p 32.

(14) B. C. Cossar, J. O. Fournier, D. L. Fields, and D. D. Reynolds, *J. Org. Chem.*, **27**, 93 (1962).

(15) D. G. Doherty, R. Shapira, and W. T. Burnett, Jr., *J. Amer. Chem. Soc.*, **79**, 5667 (1957).

(16) C. F. H. Allen and J. A. Allen, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 751.

(17) Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Microanalyses were performed by Mr. Joseph F. Alicino, New Hope, Pa. Ir spectra of solids were determined as KBr pellets on a Beckman IR-5 spectrometer. Nmr spectra were run on trifluoroacetic acid solutions using TMS as an internal standard on a Varian A-60 spectrometer. Mass spectra were measured either on an AEI MS-9 or a Varian EM-600 mass spectrometer at 70 eV.

heated (~10 min) until the odor of benzoyl chloride disappeared. Sodium chloride which precipitated as a fine powder was removed by filtration from the cooled mixture and to the filtrate was slowly added with agitation 150 ml of 28% aqueous ammonia. The mixture was evaporated to dryness and the residue was extracted with hot EtOH to give 87 g (48%) of 1-benzoyl-2-thiourea, mp 175° (lit.[18] mp 169–170°). The analytical sample was recrystallized from EtOH.

Anal. Calcd for $C_8H_8N_2OS$: C, 53.30; H, 4.47; N, 15.55; S, 17.79. Found: C, 53.52; H, 4.57; N, 15.64; S, 17.77.

1-Benzoyl-2-methyl-2-thiopseudourea Hydriodide (5).—To a solution of 27.8 g (0.154 mol) of 1-benzoyl-2-thiourea in 400 ml of dry acetonitrile was added 28.5 g (0.21 mol) of methyl iodide. The solution was refluxed for 45 min and cooled and the crystals which formed were collected to give 45.7 g (92%) of **5**, mp 185–189°. The analytical sample (from CH_3CN) melted at 190–195° (lit.[4] mp 186–190°).

Anal. Calcd for $C_9H_{11}IN_2OS$: C, 33.53; H, 3.44; N, 8.70; S, 9.96. Found: C, 33.44; H, 3.60; N, 8.56; S, 10.17.

Reaction of 5 with Hydroxylic Compounds. A. Methyl Alcohol.—A solution of 3.22 g (0.01 mol) of **5** in 50 ml of MeOH was heated under reflux until methyl mercaptan was no longer evolved to any appreciable extent. MeSH could be detected by not only its distinctive odor, but also by the yellow lead mercaptide which formed on moistened lead acetate paper placed at the top of the reflux condenser, and was identified by its ir spectrum (3.82 μ, –SH).[19] The solution was cooled giving white crystals of benzoylurea (**2**), the yield of which was increased by working up the mother liquors: mp 220–222° (lit. mp 215°,[20] 214–215°[21]) on recrystallization from EtOH. The ir spectrum was identical with that of an authentic sample.

B. Ethyl Alcohol.—The reaction of **5** with EtOH was run and worked up as described above. The contents of the flask were distilled through a Vigreux column at atmospheric pressure. The first 0.5 ml of distillate, an azeotrope rich in ethyl iodide, was collected. Ir indicated it to be a mixture of ethyl iodide and ethyl alcohol; a mass spectrum of the mixture gave a parent ion at m/e 156 $[C_2H_5I]^+$.

This procedure was also followed in the reaction of **5** with *n*-propyl and isopropyl alcohols. The *n*-propyl and isopropyl iodides collected gave the anticipated ir spectra and m/e 170 $[C_3H_7I]^+$.

C. *n*-Propyl Alcohol.—When *n*-PrOH was heated with **5** as described above, there was isolated some starting material, much **2**, and a small quantity of methyl *N*-benzoylthiolcarbamate (**6**) whose melting point and ir spectrum was identical with those of the material prepared by the reaction of **5** with water (*cf.* Table II).

The same reaction performed for an extended period of time gave, in addition, a moderate quantity of *n*-propyl *N*-benzoylcarbamate (**7**), mp 122–124°, whose ir spectrum was identical with that of **7** made from **6** by the method described below.

D. Isopropyl Alcohol.—A solution of 0.81 g (0.0025 mol) of **5** in 40 ml of *i*-PrOH was heated under reflux. The solvent was removed under reduced pressure and the residue was triturated with a minimum of cold water to remove the ammonium iodide present. Tlc of the dried water-insoluble residue (0.40 g) showed the presence of **1**, **2**, **6**, and **8**. The relative quantities of each component of this complex mixture was obtained by means of nmr and elemental analysis. Nmr integration gave the percentage of **6** by comparing the S-CH_3 peak area at δ 2.55 with that of the aromatic protons at 7.60–8.35. A further comparison of the *gem*-dimethyl peak areas of the isopropyl group at δ 1.48 with the aromatic proton area gave the percentage of **8**. Microanalysis gave the sulfur content of the mixture. Since sulfur is contained only in **1** and **6** and since the percentage of **6** was obtained by nmr, the percentage of **1** could be calculated by the following relationship: $(\%\ 1)[\%\ S_1] = \%\ S_{found} - (\%\ 6)\cdot[\%\ S_6]$. (Percentages in brackets are calculated from empirical formulas.) Finally, the percentage of **2** was assumed to be the difference between 100% and the total of the percentages found for **1**, **6**, and **8**.

E. *tert*-Butyl Alcohol.—A solution of 0.81 g (0.0025 mol) of **5** in 50 ml of *tert*-BuOH was heated under reflux. After the solvent was removed and the residue was triturated with water, three components were found by tlc. The relative amounts of these components (**1**, **2**, and **6**) were determined as described above for the reaction of **5** with *i*-PrOH. The percentage of **6** in the reaction product was found by means of nmr. By use of this quantity and the sulfur analysis, the percentage of **1** was determined. Finally, the percentage of **2**, which is the difference between 100% and the combined percentages of **1** and **6**, was calculated.

The effluent gases formed in the course of the reaction were passed through an aqueous solution of lead acetate to remove CH_3SH and into a solution of Br_2 in $CHCl_3$. The latter, decolorized by isobutylene, was evaporated to dryness leaving an oil whose ir was identical with that of an authentic sample of 1,2-dibromo-2-methylpropane and whose nmr was the same as the published spectrum[22] of this compound.

F. Water. Formation of Methyl Thiolcarbamates.—A solution of 0.01 mol of **5** in 20 ml of H_2O was heated near the reflux temperature during which time there was little evolution of methyl mercaptan detected. From the reaction mixture there was isolated **6** in excellent yield. Ammonium iodide was contained in the mother liquors.

Compounds **9**–**12** were treated with H_2O in a like manner to give methyl thiolcarbamates (*cf.* Table II).

***n*-Propyl *N*-Benzoylcarbamate (7).**—A solution of 1.95 g (0.01 mol) of **6** in 30 ml of *n*-PrOH was heated under reflux for 24 hr. Methyl mercaptan was slowly evolved and from the solution, which contained some unreacted starting material, was isolated 0.64 g (31%) of *n*-propyl 1-benzoylcarbamate, mp 122–124° (from *n*-PrOH).

Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.75; H, 6.32; N, 6.76. Found: C, 64.08; H, 6.52; N, 6.80.

The ir spectrum was identical with that of the product, mp 122–124°, obtained by the reaction of benzoyl isocyanate with *n*-propyl alcohol.

Isopropyl *N*-Benzoylcarbamate (8).—An *i*-PrOH solution of **6** was heated for 48 hr as described above. After removal of several crops of starting material from the solution, 0.25 g (12%) of isopropyl *N*-benzoylcarbamate was obtained, mp 100–102° (lit.[23] mp 99–100°). The analytical sample was recrystallized from *i*-PrOH.

Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.75; H, 6.32; N, 6.76. Found: C, 63.85; H, 6.09; N, 7.02.

1-Acetyl-2-methyl-2-thiopseudourea Hydriodide (9).—The title compound was synthesized in 81% yield from 1-acetyl-2-thiourea and methyl iodide as described above for the benzoyl derivative, **5**. Compound **9** melted at 161–164° (lit.[24] mp 148–149°) and was recrystallized from CH_3CN.

Anal. Calcd for $C_4H_9IN_2OS$: C, 18.47; H, 3.49; N, 10.77; S, 12.33. Found: C, 18.54; H, 3.58; N, 10.60; S, 12.50.

Reaction of 9 with Ethyl Alcohol.—A solution of 1-acetyl-2-methyl-2-thiopseudourea in EtOH was heated for 3 hr causing the evolution of methyl mercaptan. From the solution was isolated 83% acetylurea, mp 225–226° (lit.[25] mp 217°), whose ir was identical with that of an authentic sample.

1-Benzoyl-2-thiobiuret.—Benzoyl chloride (14.0 g, 0.1 mol) was slowly added to 9.7 g (0.12 mol) of sodium thiocyanate in 70 ml of warm acetone and the mixture was heated an additional 15 min. The benzoyl isothiocyanate solution was cooled to room temperature and the NaCl which formed was removed by suction with the assistance of a filter aid. The filtrate was then heated for 1 hr with 6.0 g (0.1 mol) of urea. The resultant solution was cooled and the product was collected and then recrystallized from CH_3CN to give 10.5 g (47%) of 1-benzoyl-2-thiobiuret as yellow crystals, mp 173–175°. The analytical sample was recrystallized from MeOH.

Anal. Calcd for $C_9H_9N_3O_2S$: C, 48.42; H, 4.06; N, 18.82; S, 14.37. Found: C, 48.17; H, 4.09; N, 18.87; S, 14.44.

Thiobiuret (13).—1-Benzoyl-2-thiobiuret (1.12 g, 0.005 mol) in 20 ml of MeOH containing 1 drop of concentrated HCl was heated under reflux for 24 hr. The solution was evaporated under reduced pressure to dryness and the residue was extracted with hexane to remove the methyl benzoate. The hexane-insoluble material was recrystallized from H_2O (charcoal) to

(18) W. H. Pike, *Ber.*, **26**, 755 (1893).
(19) Methyl mercaptan was collected in a 5-cm CaF_2 gas cell.
(20) H. Rupe, *Ber.*, **28**, 251 (1895).
(21) H. L. Wheeler and Y. B. Johnson, *Amer. Chem. J.*, **24**, 189 (1900).
(22) N. S. Bhacca, D. P. Hollis, L. F. Johnson, and E. A. Pier, "NMR Spectra Catalog," Vol. 2, Varian Associates, 1963, Spectrum No. 412.
(23) C. L. Arcus and B. S. Prydal, *J. Chem. Soc.*, 1091 (1957).
(24) T. K. Liao, F. Baiocchi, and C. C. Cheng, *J. Org. Chem.*, **30**, 560 (1965).
(25) R. W. Stoughton, *ibid.*, **2**, 514 (1938).

give 0.44 g (75%) of **13** as white crystals, mp 189–193° (lit.[7] mp 186°).

Anal. Calcd for $C_2H_5N_3OS$: C, 20.16; H, 4.23; N, 35.27; S, 26.92. Found: C, 20.31; H, 4.39; N, 34.97; S, 26.69.

2-Methyl-2-thiopseudobiuret Hydriodide (10).—To 5.95 g (0.05 mol) of thiobiuret suspended in 50 ml of CH_3CN was added 8.52 g (0.06 mol) of methyl iodide and the mixture was heated under reflux for 0.5 hr. The product, which separated as white shiny plates from the hot medium, was collected from the cooled mixture to give (11.3 g, 87%) of 2-methyl-2-thiopseudobiuret hydriodide, mp 181–183° (from CH_3CN).

Anal. Calcd for $C_3H_8IN_3OS$: C, 13.80; H, 3.09; N, 16.09; S, 12.28. Found: C, 13.87; H, 2.96; N, 16.11; S, 12.20.

Reaction of 10 with Ethyl Alcohol.—A solution of 1.31 g (0.005 mol) of **10** in 25 ml of EtOH was heated under reflux for 24 hr during which time methyl mercaptan was evolved. The solution was then concentrated and cooled giving 0.44 g (85%) of biuret (from EtOH), mp 193–194° (lit.[26] mp 193°); its ir spectrum was identical with the spectrum of an authentic sample.

Reaction of 2-Methyl-2,4-dithiopseudobiuret Hydriodide (11) with Ethyl Alcohol.—A 25-ml EtOH solution of 2-methyl-2,4-dithiopseudobiuret hydriodide (**11**)[10] was heated under reflux for 24 hr. From the concentrated solution was isolated 0.30 g (58%) of biuret.

1-(4-Nitrophenyl)-2-thiourea.—A suspension of 7.2 g (0.04, mol) of 4-nitrophenyl isothiocyanate in 35 ml of MeOH and 15 ml of 28% ammonium hydroxide was warmed on a steam bath for 20 min. The cooled mixture was filtered and the precipitate washed with MeOH to give 6.8 g (85%) 1-(4-nitrophenyl)-2-thiourea, mp 215–218° (lit.[27] mp 189–190°).

Anal. Calcd for $C_7H_7N_3O_2S$: C, 42.63; H, 3.58; N, 21.31; S, 16.26. Found: C, 42.31; H, 3.64; N, 21.31; S, 16.04.

2-Methyl-1-(4-nitrophenyl)-2-thiopseudourea Hydriodide (12).—A suspension of 1.06 g (0.0075 mol) of methyl iodide and 0.98 g (0.005 mol) of 1-(4-nitrophenyl)-2-thiourea in 10 ml of CH_3CN was heated under reflux for 2 hr. The cooled mixture was filtered and the solid was washed with CH_3CN to give 1.45 g (85%) of 2-methyl-1-(4-nitrophenyl)-2-thiopseudourea hydriodide, mp 188–190°.

Anal. Calcd for $C_8H_{10}IN_3O_2S$: C, 28.33; H, 2.97; N, 12.39; S, 9.45. Found: C, 28.10; H, 2.91; N, 12.37; S, 9.83.

Reaction of 12 with Ethyl Alcohol. Formation of 4-Nitrophenylurea.—A 17-ml EtOH solution containing 1.0 g (0.003 mol) of **12** was heated under reflux for 24 hr and cooled. From the solution was isolated 0.3 g (65%) of 4-nitrophenylurea, mp 228–230°, which resolidifies and then remelts at 328–330° (lit.[28] mp 237–238°). The analytical sample was recrystallized from $(CH_3)_2CO$–EtOH.

Anal. Calcd for $C_7H_7N_3O_3$: C, 46.41; H, 3.89; N, 23.20. Found: C, 46.59; H, 3.94; N, 22.94.

From the concentrated mother liquors was also isolated 120 mg (12%) of methyl *N*-(4-nitrophenyl)thiolcarbamate whose ir spectrum was identical with that of the material which was synthesized by the reaction of **12** with H_2O (*cf.* Table II).

Mercaptan Synthesis from 1-Acetyl-2-thiourea (14) and Alkyl Halides.—Each of a series of alkyl halides (*cf.* Table III) was heated under reflux with 1.1 equiv of **14** in ethanol (~1000 ml/mol of halide). After 24 hr, the solvent was removed under reduced pressure and the residue containing the mercaptan, 1-acetylurea, and the unreacted starting materials was transferred to an alumina (activity II) chromatography column by means of petroleum ether (bp 30–60°). Elution of the column with this solvent permitted the passage of only the mercaptan and the unreacted alkyl halide. The yields of the mercaptans were determined iodometrically.

Registry No.—**1**, 614-23-3; **5**, 6966-84-3; **7**, 15146-42-6; **8**, 34277-73-1; **9**, 924-51-6; **10**, 34277-75-3; **12**, 34277-76-4; **13**, 23228-74-2; 1-benzoyl-2-thiobiuret, 34277-78-6; 1-(4-nitrophenyl)-2-thiourea, 3696-22-8; 4-nitrophenylurea, 556-10-5.

Acknowledgments.—We are grateful to Drs. T. E. Fink and J. E. Tomaszewski and A. E. Murray, Jr., for technical assistance.

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Halomethyl Metal Compounds. LIII. Reactions of Phenyl(trihalomethyl)mercury Compounds with Thiocarbonyl Derivatives[1]

DIETMAR SEYFERTH,* WOLFGANG TRONICH,[2] ROBERT S. MARMOR,[3] AND WILLIAM E. SMITH[4]

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

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The reaction of phenyl(bromodichloromethyl)mercury with thiophosgene gave tetrachlorothiirane in excellent yield. This product also was formed in the reaction of this mercury reagent with elemental sulfur; its thermolysis gave tetrachloroethylene and sulfur. Similar reactions of $PhHgCCl_2Br$, $PhHgCClBr_2$, and $PhHgCBr_3$ with thiobenzophenone gave 2,2-dichloro-, 2-bromo-2-chloro-, and 2,2-dibromo-3,3-diphenylthiirane, respectively, in good yield. The first of these underwent extrusion of sulfur on thermolysis, but the second and third lost HBr on being heated to give 2-chloro-3-phenylbenzo[*b*]thiophene and 2-bromo-3-phenylbenzo[*b*]thiophene, respectively. The latter was converted to the Grignard reagent which was hydrolyzed and carboxylated.

The addition of CX_2 (X = halogen), either as the free carbene or *via* a carbenoid reagent, to the C=C and C=C bonds is well known.[5] Some examples are known of such additions to the C=N bond[6] and to the C=O bond,[7] but CX_2 addition to the C=S bond has been restricted to a few examples involving difluorocarbene derived from pyrolysis of perfluoropropylene oxide (eq 1).[8] Addition of dichloro- or dibromocarbene, or of an appropriate "dihalocarbenoid," to any kind of C=S bond had not been reported.

Various diazoalkanes are known to react with thio-

(1) (a) Preliminary communication: D. Seyferth and W. Tronich, *J. Amer. Chem. Soc.*, **91**, 2138 (1969). (b) Part LII of this series: D. Seyferth and H. Shih, *Organometal. Chem. Syn.*, in press.

(2) Postdoctoral Research Associate, 1968–1969.

(3) Postdoctoral Research Associate, 1971–1972.

(4) National Institutes of Health Postdoctoral Fellow, 1969–1970.

(5) W. Kirmse, "Carbene Chemistry," Academic Press, New York, N. Y., 1964; "Carbene, Carbenoide und Carbenanaloge," Verlag Chemie, Weinheim/Bergstr., Germany, 1969.

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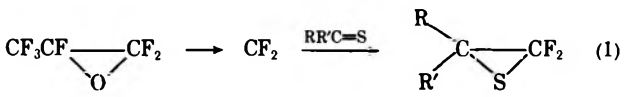
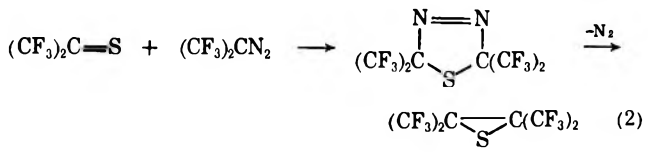
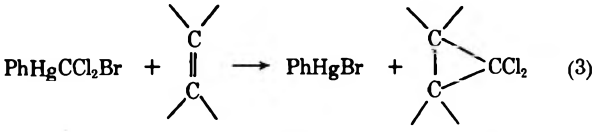
(8) (a) W. R. Brasen, H. N. Chipps, C. G. Bottomley, M. W. Farlow, and C. G. Krespan, *J. Org. Chem.*, **30**, 4188 (1965); (b) F. C. McGrew, U. S. Patent 3,136,744 (1964); *Chem. Abstr.*, **61**, 4312*b* (1964).



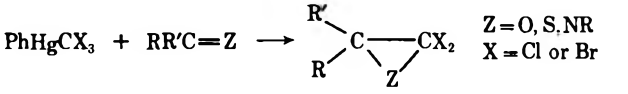
carbonyl compounds to give thiiranes (episulfides),[9] but recent work has shown that these products are formed *via* an intermediate thiadiazoline (eq 2).[10]



Our application of phenyl(trihalomethyl)mercury reagents to the synthesis of *gem*-dihalocyclopropanes had been very successful (eq 3),[11] and we became in-



terested in the possible use of these reagents (especially of $PhHgCCl_2Br$, $PhHgCClBr_2$, and $PhHgCBr_3$) in the synthesis of three-membered heterocyclic systems.

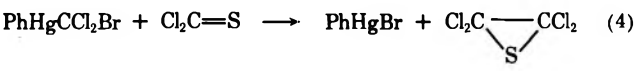


In view of the advantages associated with the use of the phenyl(trihalomethyl)mercury compounds (compared with other dihalocarbene-generating systems),[11b] we felt that such a study would have a good chance for success. We report here the results of our investigations of reactions of these organomercury reagents with selected thiocarbonyl compounds.

Results and Discussion

We chose to study the reactions of our phenyl(trihalomethyl)mercury reagents with thiophosgene and thiobenzophenone, feeling that these should serve adequately as representative members of the class of thiocarbonyl derivatives.

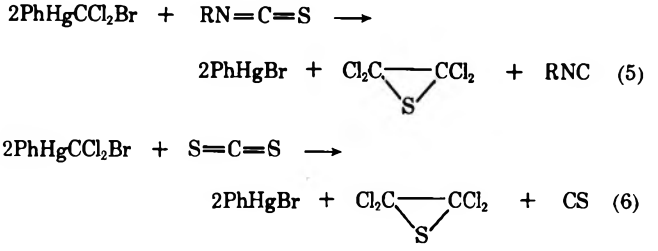
Thiophosgene.—Phenyl(bromodichloromethyl)mercury was found to react with a twofold excess of thiophosgene in benzene at 70–75° to give phenylmercuric bromide (88%) and tetrachlorothiirane (96% by glc) (eq 4). Isolated yields of the latter invariably were



lower because of its thermal instability. Thus in a reaction carried out on a 33.5-mmol scale (at 60° for 4 hr) phenylmercuric bromide was obtained in 90% yield, but the yield of tetrachlorothiirane isolated by distillation was only 57%.

During the course of another project, three other routes to tetrachlorothiirane were discovered. The remarkable reaction of elemental sulfur with phenyl(bromodichloromethyl)mercury in benzene at 70° to give this compound in 34% yield when 2 molar equiv of $PhHgCCl_2Br$ per gram-atom of sulfur were used is of special interest. A reaction sequence involving conversion of the sulfur to thiophosgene by reaction with CCl_2 or $PhHgCCl_2Br$ followed by CCl_2 addition to the C=S bond thus formed seems reasonable. However, nothing is known concerning the course of the $PhHgCCl_2Br$–S_8 reaction and a better understanding of this novel process would be desirable.

The reactions of phenyl(bromodichloromethyl)mercury with isothiocyanates and with carbon disulfide also result in formation of tetrachlorothiirane (eq 5 and 6). In both cases thiophosgene is formed first



and then reacts further with the mercurial. Details of these two reactions have been reported.[12]

Tetrachlorothiirane, a new compound, is a malodorous liquid which also is a lachrymator. It appears to be stable at room temperature and analytically pure samples could be obtained by glc. However, larger samples isolated by distillation or preparative glc invariably were contaminated with small quantities (up to 10%) of tetrachloroethylene, the volatile product of its thermal decomposition. The fragmentation of tetrachlorothiirane in the mass spectrometer at 70 eV gave the expected chlorinated equivalents of the principal species observed in the mass spectrum of thiirane itself. Desulfurization of tetrachlorothiirane also could be accomplished by treatment with phosphorus trichloride in slight excess at room temperature or with triphenylphosphine in diethyl ether. The latter reaction is complicated; only low yields of triphenylphosphine sulfide were obtained and only trace yields of tetrachloroethylene. Instead, much polymeric material appeared to be formed. Reaction with diethylamine in benzene at 50° gave no volatile products; only yellow-brown nonvolatiles which could not be crystallized were produced. Anhydrous hydrogen chloride was without effect on tetrachlorothiirane at room temperature, but chlorination at room temperature resulted in desulfurization, giving hexachloroethane as the organic product. Further study of the chemistry of tetrachlorothiirane should be of interest but is beyond the scope of this investigation.

Thiobenzophenone.—The reaction of equimolar quantities of phenyl(bromodichloromethyl)mercury and thiobenzophenone required about 3 hr at 70°. During this time the blue color of the thiobenzophenone was not discharged completely; however, phenylmercuric bromide was filtered off in 98% yield. 2,2-Dichloro-3,3-diphenylthiirane was formed in this reaction in 75% yield (eq 7). This product is a known compound,

(9) (a) H. Staudinger and J. Siegwart, *Helv. Chim. Acta*, **3**, 833 (1920); (b) A. Schönberg and S. Nickel, *Ber.*, **64**, 2323 (1931); (c) A. Schönberg and E. Frese, *Chem. Ber.*, **96**, 2420 (1963); (d) W. J. Middleton and W. H. Sharkey, *J. Org. Chem.*, **30**, 1384 (1965).

(10) W. J. Middleton, *J. Org. Chem.*, **34**, 3201 (1969).

(11) (a) D. Seyferth, J. M. Burlitch, R. J. Minasz, J. Y.-P. Mui, H. D. Simmons, Jr., A. J.-H. Treiber, and S. R. Dowd, *J. Amer. Chem. Soc.*, **87**, 4259 (1965); (b) D. Seyferth, *Accounts Chem. Res.*, **5**, 65 (1972).

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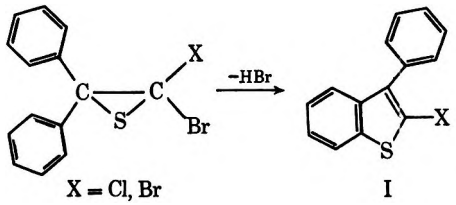
$$PhHgCCl_2Br + Ph_2C{=}S \longrightarrow PhHgBr + Ph_2C\!\!<\!\!\begin{matrix}S\\ \\ \end{matrix}\!\!>\!\!CCl_2 \quad (7)$$

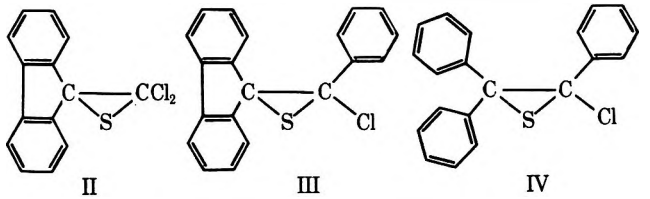
having been prepared by Staudinger and Siegwart[9a] by reaction of diphenyldiazomethane with thiophosgene. The behavior of 2,2-dichloro-3,3-diphenylthiirane on being heated (200° for 4 hr) was similar to that of tetrachlorothiirane; formed were 1,1-dichloro-2,2-diphenylethylene and sulfur.

The reactions of $PhHgCClBr_2$ and $PhHgCBr_3$ with thiobenzophenone also were investigated. In both cases similar reactions occurred, giving 2-bromo-2-chloro-3,3-diphenylthiirane and 2,2-dibromo-3,3-diphenylthiirane, respectively. These, however, were less stable than 2,2-dichloro-3,3-diphenylthiirane and were difficult to purify. Of special interest is that their thermolysis takes takes an entirely different course, as shown in eq 8. The appropriate 2-halo-3-



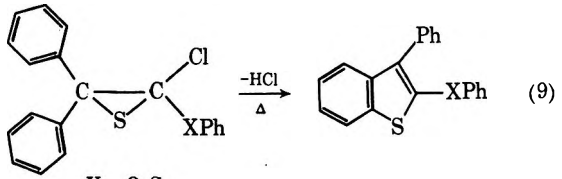
X = Cl, Br I (8)

phenylbenzo[*b*]thiophene (I) was produced in good yield in each case. Such a mode of decomposition of phenyl-substituted thiiranes had been reported already by earlier workers. Staudinger and Siegwart[13] found that the thiiranes II and III decomposed *via* sulfur extrusion but that IV decomposed at 100° with



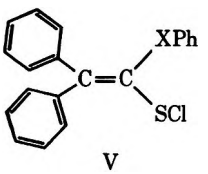
II III IV

loss of hydrogen chloride, giving a product which was presumed to be 2,3-diphenylbenzo[*b*]thiophene. Schönberg and Vargha[14] described a similar decomposition of other substituted thiiranes (eq 9). It was

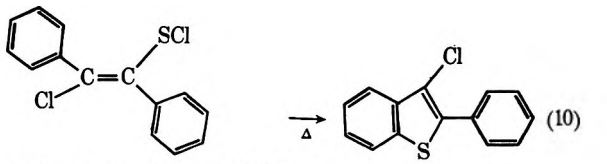


X = O, S (9)

suggested (but not proven) that this decomposition proceeded *via* the sulfenyl chloride intermediate V. In support of this suggestion, we note the recent report of the decomposition of an appropriate sulfenyl chloride

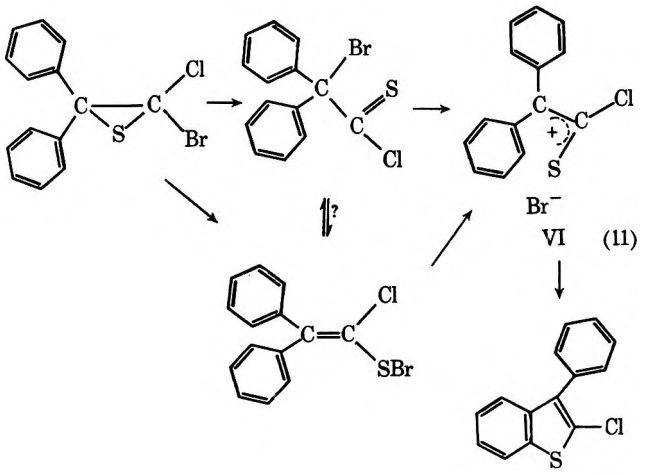


V

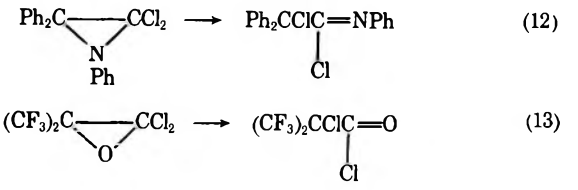


(prepared *via* PhC≡CPh + SCl_2) (10)

in this fashion (eq 10).[15] Another possibility is that ring opening of the thiirane gives the thio acid chloride and that this is the intermediate which forms the benzo[*b*]thiophene (eq 11). The ionic species VI should be accessible both from the thio acid chloride and from the sulfenyl bromide; so it also is possible that both ring-opened species are formed in the course of the thiirane decomposition, as shown in eq 11. In indirect support



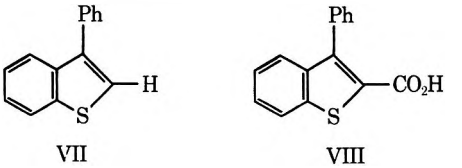
of this idea, it may be noted that analogous aziridines[16] and oxiranes[7d] undergo similar ring opening upon thermolysis (eq 12 and 13).



(12)

(13)

2-Bromo-3-phenylbenzo[*b*]thiophene (I, eq 8) was converted to the Grignard reagent in THF solution. Hydrolysis of this reagent gave 3-phenylbenzo[*b*]thiophene (VII), while its carboxylation produced 2-carboxy-3-phenylbenzo[*b*]thiophene (VIII). The forma-



VII VIII

tion of VII by hydrolysis of the Grignard reagent from I (X = Br) serves to confirm the structure of I (X = Br) and, by interference, of I (X = Cl). We obtained VII as a colorless oil, in agreement with the report by Rao and Tilak[17] that 3-phenylbenzo[*b*]thiophene is an oil and 2-phenylbenzo[*b*]thiophene is a solid, mp 171–

(13) H. Staudinger and J. Siegwart, *Helv. Chim. Acta*, **3**, 840 (1920).

(14) A. Schönberg and L. v. Vargha, *Justus Liebigs Ann. Chem.*, **483**, 176 (1930); *Ber.*, **64**, 1390 (1931).

(15) T. J. Barton and R. G. Zika, *J. Org. Chem.*, **35**, 1729 (1970).

(16) (a) H. W. Heine and A. B. Smith, *Angew. Chem.*, **75**, 669 (1963); (b) R. E. Brooks, J. O. Edwards, G. Levey, and F. Smyth, *Tetrahedron*, **22**, 1279 (1966).

(17) D. S. Rao and B. D. Tilak, *J. Sci. Ind. Res.*, **18B**, 77 (1959); *Chem. Abstr.*, **54**, 1484f (1960).

172°.[18] In confirmation of the report by Rao and tilak,[17] we found that VII underwent acid-catalyzed thermal rearrangement to give 2-phenylbenzo[*b*]thiophene.

Conclusions.—This study has shown that phenyl(trihalomethyl)mercury compounds react with thiocarbonyl compounds to add CX_2 to the C=S bond to give thiiranes. The exact nature of this addition process is not known. One mechanistic extreme involves a two-step process, decomposition of the organomercury reagent to give a dihalocarbene which subsequently adds to the C=S bond. Such an addition could either occur as a concerted cycloaddition or as a process in which an ylide intermediate, $R_2C{=}\overset{+}{S}{-}\overset{-}{C}X_2$, is formed prior to ring closure to the thiirane. At the other extreme is a noncarbene process in which a direct interaction between the organomercurial and the thiocarbonyl compound is involved in the CX_2 transfer.[19]

This research, which had purely exploratory synthetic objectives, has brought the first synthesis of tetrachlorothiirane, an interesting new compound whose chemistry remains largely unexplored. It has made available a new route to 1,1-dihalo-2,2-diarylthiiranes and as an added dividend has provided what may be a fairly general entry to 3-aryl-2-halobenzo[*b*]thiophenes. The latter have a reactive "handle" in the 2 position which allows further transformations. The reactions described in this report thus provide new examples of the wide-ranging synthetic utility of the phenyl(trihalomethyl)mercury reagents.

Experimental Section

General.—All reactions were carried out under an atmosphere of dry argon or prepurified nitrogen using flame-dried glassware. Carefully dried solvents were used in all reactions. Nmr spectra were recorded using a Varian Associates A-60 or T-60 spectrometer. Chemical shifts are given in δ units, downfield from internal TMS. Infrared spectra were recorded using a Perkin-Elmer 237B, 337, or 257 grating infrared spectrophotometer. Gas–liquid partition chromatography (glpc) was used for yield determinations and collection of liquid samples. Commercial stainless steel columns were employed with either an F & M Model 700, 720, or 5754 gas chromatograph. Yields were determined by the internal standard procedure. The standard apparatus used in these reactions of phenyl(trihalomethyl)mercury compounds consisted of a three-necked flask of appropriate size equipped with a reflux condenser (topped with a gas inlet tube), a thermometer, and a magnetic stirring assembly. The phenyl(trihalomethyl)mercurials were prepared by our improved THF procedure.[20] The progress of the reactions involving these reagents was followed using thin layer chromatography.[11a]

Reaction of Phenyl(bromodichloromethyl)mercury with Thiophosgene.—The standard apparatus was charged with 4.41 g (10 mmol) of $PhHgCCl_2Br$, 2.30 g (20 mmol) of thiophosgene (Aldrich), and 25 ml of dry benzene. The reaction mixture was stirred and heated under nitrogen for 1 hr at 70–75°. The resulting suspension was chilled to 10° and filtered under nitrogen through a Schlenk tube to remove 3.2 g (88%) of phenylmercuric bromide, mp 274–279°. The filtrate was trap-to-trap distilled after 5.7 g of *n*-dodecane had been added as a "chaser" (at 0.1 mm, pot temperature below 70°). Glpc analysis of the distillate (6-ft Dow Corning DC-200 silicone oil on Chromosorb W, 135°) showed that tetrachlorothiirane had been formed in 81% yield.

Experiments were carried out on a larger scale in order to accumulate more of this compound. In a typical reaction, 33.5 mmol each of the mercury reagent and freshly distilled thiophosgene in 60 ml of benzene were stirred and heated at 60° for 4 hr. After filtration of PhHgBr (90%), the filtrate was trap-to-trap distilled at 0.1 mm (pot temperature to 50°). The resulting distillate was redistilled using an 8-in. Vigreux column, first at room temperature and approximately 0.2 mm to remove most of the benzene and subsequently at 25° and 0.1 mm to obtain the product, 3.79 g (57%), $n^{25}D$ 1.5665, in analytical purity. The compound has an unpleasant odor and is an intense lachrymator. Glc analysis (as above) showed the presence of a minor (~5%) impurity, identified as tetrachloroethylene.

Anal. Calcd for C_2Cl_4S: C, 12.14; Cl, 71.66; S, 16.20. Found: C, 12.12; Cl, 71.05; S, 16.08.

The product was isolated as a colorless to faint yellow liquid which became yellow on long standing. A boiling point determination by slow distillation gave 36–38° (0.1 mm). Its ir spectrum (film) showed bands at 1145 (vs), 1110 (w), 920 (w), 910 (w), 835 (w), 815 (vs), 770 (vw), 750 (vs), 745 (w), 705 (vw), 675 (vs), 670 (w), and 650 cm^{-1} (vw). The fragmentation of tetrachlorothiirane in the mass spectrometer at 70 eV gave the chlorinated equivalents of the principal species observed in the mass spectrum of thiirane itself:[21] $C_2Cl_4S^+$ (17.5), $C_2Cl_3S^+$ (29.8), $C_2Cl_2S^+$ (62.9), CCl_2S^+ (3.2), C_2ClS^+ (12.3), $CClS^+$ (100.0), Cl_2S^+ (0.58), S^+ (3.2), $C_2Cl_4^+$ (78.8), $C_2Cl_3^+$ (46.2), $C_2Cl_2^+$ (26.8), C_2Cl^+ (8.7), CCl_3^+ (21.0), CCl_2^+ (23.5), and CCl^+ (21.7).

Reaction of Phenyl(bromodichloromethyl)mercury with Sulfur.—The standard apparatus was charged with 10 mmol of the mercury compound and 5 mg-atoms (0.16 g) of yellow sulfur (S_8) in 30 ml of benzene. The reaction mixture was stirred and heated at 70° for 1 hr. Phenylmercuric bromide was filtered off in 93% yield. The filtrate was concentrated at 30° (14 mm) and the residue, a yellow semisolid, was trap-to-trap distilled at 0.05 mm (to 30°). Glpc analysis of the distillate indicated the presence of tetrachlorothiirane in 34% yield.

Chemical Properties of Tetrachlorothiirane. A. Thermolysis.—Tetrachlorothiirane (260 mg) was placed in a vacuum-sealed tared flask and entirely immersed in an oil bath at 130° for 24 hr. All volatiles were trap-to-trap distilled at 0.1 mm to leave 105 mg of a viscous orange residue, a mixture of elemental sulfur (burns with blue flame and odor of SO_2) and polymer. The distillate (155 mg) was analyzed by glc (6-ft DC-200, at 85°). Only one component, tetrachloroethylene, was present, and this represents an isolated yield of 71%. The product was identified on the basis of its glpc retention time and mass spectrum.

B. Desulfurization with Phosphorus Trichloride.—Tetrachlorothiirane (431 mg, 2.17 mmol) and 497 mg (3.62 mmol) of PCl_3 were stirred under nitrogen at room temperature for 3 days. Glc analysis was difficult; on an Apiezon L column there was no separation between $PSCl_3$ and tetrachloroethylene; on a DC-200 column slight separation was observed. On a polar General Electric Co. XF-1112 cyanoethylsilicone rubber gum column adequate separation of these products occurred. However, PCl_3 was partially retained in the column and gave irregular peaks. Also, $POCl_3$ appeared, even though the reaction mixture was protected from the air. In any case, smooth conversion to only two products, $PSCl_3$ and C_2Cl_4, was indicated. These products were present in equivalent amounts (DC-200 column analysis) and were identified by means of their glpc retention times and their ir spectra.

C. Chlorination.—Tetrachlorothiirane (752 mg) in 20 ml of CCl_4 was stirred at room temperature while the solution was saturated with an excess of chlorine in a sealed system. The solution was stirred for 3 days, after which time the resulting orange solution was distilled to remove unconverted chlorine and solvent at 2 mm. The remaining white residue was sublimed *in vacuo* (heat lamp) to give 592 mg of white crystals, mp 174–176°. Recrystallization from ether at −78° gave pure hexachloroethane: mp 185–186° (sealed tube); mmp with authentic material, 184–186° (sealed tube); "Handbook of Chemistry and Physics" mp 187°.

(18) The structure of 2-phenylbenzo[*b*]thiophene has been proven by independent synthesis and by degradation: J. E. Banfield, W. Davies, N. W. Gamble, and S. Middleton, *J. Chem. Soc.*, 4791 (1956). (The structure of 3-phenylbenzo[*b*]thiophene also was confirmed by independent synthesis.[17]) Melting points as high as 176° have been reported: G. M. Badger, N. Kowanko, and W. H. F. Sasse, *ibid.*, 2969 (1960).

(19) Note the evidence in favor of such a process in the case of the reaction of $PhHgCCl_2Br$ with benzophenone.[7f]

(20) D. Seyferth and R. L. Lambert, Jr., *J. Organometal. Chem.*, **4**, 127 (1965).

(21) E. Gallegos and R. W. Kiser, *J. Phys. Chem.*, **65**, 1177 (1961).

Reactions of Phenyl(trihalomethyl)mercury Compounds with Thiobenzophenone. A. Phenyl(bromodichloromethyl)mercury.—The standard apparatus was charged with 4.41 g (10 mmol) of the mercurial and 10 mmol (1.98 g) of thiobenzophenone[22] in 50 ml of dry benzene. The resulting blue solution was stirred and heated at 70° under nitrogen for 3 hr. During this time the blue color of the thiobenzophenone was not completely discharged, but tlc indicated complete consumption of the organomercury reagent. The reaction mixture was cooled and filtered to remove 3.5 g (98%) of phenylmercuric bromide, mp 275–278°. The filtrate was concentrated at 50° (14 mm) to leave a solid residue. Unconverted thiobenzophenone was washed out from the latter by treatment with cold ethanol, leaving yellow crystals (2.1 g, 75%) of 2,2-dichloro-3,3-diphenylthiirane, mp 88–90° dec. Two recrystallizations from ethanol gave 1.7 g of fine, faintly yellow needles, mp 88.5–89.5° dec. 2,2-Dichloro-3,3-diphenylthiirane prepared by reaction of diphenyldiazomethane and thiophosgene was reported to have mp 89–90° dec.[9a] The ir spectrum (Nujol) showed the following bands below 1600 cm^{-1}: 1595 (w), 1580 (w), 1485 (m), 1445 (s), 1335 (w), 1310 (w), 1225 (w), 1100 (m), 1070 (m), 1030 (m), 1000 (w), 930 (m), 895 (w), 810 (s), 770 (s), 745 (m), 720 (s), 705 (s), and 690 cm^{-1} (s).

B. Phenyl(dibromochloromethyl)mercury.—The organomercury reagent (10 mmol) and thiobenzophenone (10 mmol) in 40 ml of benzene were stirred and heated at 40° for 3 days. The initially blue solution became gray-violet during this time. Filtration gave PhHgBr (90%). The filtrate was evaporated at reduced pressure (pot temperature to 50°) to leave a colored solid residue. Extraction of unconverted thiobenzophenone left a yellow residue (2.8 g, 86%), which was recrystallized (with difficulty) from ethanol to give 2.4 g (74%) of pale yellow crystals, mp 80–81° dec, of 2-bromo-2-chloro-3,3-diphenylthiirane: ir (Nujol) 1595 (w), 1580 (w), 1485 (w), 1445 (s), 1330 (w), 1095 (m), 1075 (m), 1045 (w), 1030 (w), 1000 (w), 925 (m), 890 (w), 810 (m), 770 (s), 720 (s), 710 (s), 700 (s), 690 (s), and 680 cm^{-1} (s).

Anal. Calcd for $C_{14}H_{10}ClBrS$: C, 51.65; H, 3.09. Found: C, 51.36; H, 3.36.

C. Phenyl(tribromomethyl)mercury.—The same procedure as described in B was used in the reaction of 10 mmol each of $PhHgCBr_3$ and thiobenzophenone in 40 ml of benzene. The crude product (3.3 g, 89%) had mp 74–76° dec. Material recrystallized twice from ethanol had mp 76–77° dec. In another preparation the crude product was dissolved in hot methanol and filtered through Celite. On cooling, yellow needles of 2,2-dibromo-3,3-diphenylthiirane crystallized: ir (Nujol) 1600 (w), 1585 (w), 1490 (m), 1445 (s), 1155 (w), 1095 (m), 1080 (w), 1030 (w), 1000 (w), 920 (w), 795 (w), 770 (s), 755 (s), 715 (m), 705 (s), 690 (m), and 680 cm^{-1} (s).

Anal. Calcd for $C_{14}H_{10}Br_2S$: C, 45; H, 2.73. Found: C, 45.64; H, 3.04.

Thermolysis of the 2,2-Dihalo-3,3-diphenylthiiranes. A. 2,2-Dichloro-3,3-diphenylthiirane.—A 585-mg sample was stirred in a sealed flask in a 200° oil bath for 4 hr. The resulting brown oil was extracted with four 5-ml portions of boiling hexane under nitrogen, leaving behind undissolved polymers and sulfur. Refrigeration of the combined hexane extracts precipitated some sulfur. The filtered solution was evaporated at reduced pressure and the residue was triturated under nitrogen with several small portions of Dry Ice cooled ether. The remaining white solid was dried *in vacuo*, giving 352 mg of 1,1-dichloro-2,2-diphenylethylene, mp 79–80° (lit.[23] mp 79–80°); ν(C=C) 1610 cm^{-1}.

B. 2-Bromo-2-chloro-3,3-diphenylthiirane.—A solution of 1.6 g (4.9 mmol) of the thiirane in 10 ml of dry benzene was stirred and heated at reflux under nitrogen for 24 hr. During this time the originally yellow solution became brown. The solvent was removed at reduced pressure and the residual oil was distilled using a short-path distillation apparatus to give a colorless oil, boiling range 160–170° (0.05 mm), yield 0.9 g (75%, based on eq 8). Two recrystallizations at low temperature from a minimum amount of pentane gave white crystals, mp 39–40°, of 2-chloro-3-phenylbenzo[*b*]thiophene.[24] This compound also could be purified by glc (6-ft Carbowax W on Chromosorb W at 175°): ir (molten film) 3105 (sh), 3090 (sh), 3070 (s), 3035 (m), 1960 (w), 1910 (w), 1670 (w), 1610 (m), 1580 (w), 1540 (w), 1490 (s), 1460 (m), 1450 (s), 1435 (s), 1345 (s), 1320 (m), 1315 (w), 1285 (w), 1270 (s), 1190 (w), 1180 (w), 1165 (m), 1140 (w), 1080 (m), 1040 (s), 1020 (s), 975 (w), 950 (w), 930 (m), 915 (s), 860 (w), 850 (w), 825 (w), 810 (w), 780 (s), 775 (s), 760 (s), 740 (s), 725 (s), 705 (s), 670 (m), and 650 cm^{-1} (m).

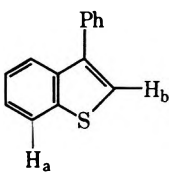
Anal. Calcd for $C_{14}H_9ClS$: C, 68.71; H, 3.71; Cl, 14.48; S, 13.10. Found: C, 68.40; H, 3.63; Cl, 14.51; S, 13.01.

C. 2,2-Dibromo-3,3-diphenylthiirane.—A solution of 940 mg of the thiirane in 10 ml of dry benzene was stirred at reflux under nitrogen for 24 hr, during which time HBr evolution was evident. The solvent was removed at reduced pressure and the violet residue was extracted with two 10-ml portions of hot hexane, leaving undissolved a small amount of black polymer. The yellow hexane solution was evaporated and the residue (665 mg, 91% crude) was sublimed at 110° (0.03 mm), giving 530 mg of pale yellow crystals, mp 62–69°. Recrystallization from pentane gave an analytically pure sample, mp 73–74°, of 2-bromo-3-phenylbenzo[*b*]thiphene: ir (Nujol) 1595 (w), 1570 (w), 1525 (w), 1425 (s), 1330 (m), 1260 (m), 1155 (w), 1130 (w), 1070 (m), 1030 (w), 990 (s), 940 (w), 920 (w), 890 (w), 860 (w), 850 (w), 765 (s), 755 (s), 735 (s), 715 (m), and 700 cm^{-1} (s).

Anal. Calcd for $C_{14}H_9BrS$: C, 58.14; H, 3.14; Br, 27.64; S, 11.09. Found: C, 58.39; H, 3.21; Br, 27.68; S, 11.11.

In another experiment, the intermediate thiirane was not isolated. A solution of 40 mmol of thiobenzophenone and 52 mmol of $PhHgCBr_3$ in 200 ml of dry benzene was stirred under nitrogen in an oil bath kept at 45° for 4 days, at the end of which time the blue color had been discharged. The brown solution was filtered to remove 13.4 g of phenylmercuric bromide (72%, based on the mercurial). The filtrate was heated at reflux with the exclusion of atmospheric moisture for 28 hr. The solvent was removed at reduced pressure and the black residue was extracted with three 50-ml portions of hot hexane. The hexane extracts were concentrated and the remaining oil was short-path distilled to give a semisolid oil, boiling range 110° (0.07 mm)–140° (0.03 mm). The distillate was dissolved in 200 ml of pentane, treated with activated charcoal, filtered through Celite, and concentrated to 70 ml. Refrigeration gave a first crop of 3.78 g, mp 72–74°. A second crop of 1.34 g was obtained on concentrating the mother liquor to 20 ml, mp 70–73°. Total yield of 5.12 g represented at 45% yield.

Reduction of 2-Bromo-3-phenylbenzo[*b*]thiophene to 3-Phenylbenzo[*b*]thiophene.—This reduction was carried out to confirm the structure of the 2,2-dibromo-3,3-diphenylthiirane pyrolysis product. The Grignard reagent was prepared by heating at reflux a THF solution (12 ml) of 1.157 g (4.0 mmol) of 2-bromo-3-phenylbenzo[*b*]thiophene with 120 mg (5.0 mg-atom) of magnesium for 22 hr under nitrogen. The reaction mixture was hydrolyzed by addition of 1 ml of concentrated HCl diluted with 5 ml of water. The resulting mixture was evaporated at reduced pressure until the THF was removed. The residue was extracted twice with hexane and the extracts were dried (Na_2SO_4) and evaporated to leave 880 mg of product as a yellow oil. Short-path distillation gave 740 mg of pure product as a colorless oil (88%) at 103–108° (0.02 mm): $n^{25}D$ 1.6789; ir (neat) 3040 (m), 3000 (m), 1600 (m), 1520 (w), 1480 (m), 1440 (m), 1420 (s), 1345 (m), 1300 (w), 1255 (w), 1210 (w), 1140 (w), 1070 (w), 1060 (w), 1020 (w), 940 (w), 910 (w), 830 (m), 790 (w), 765 (s), 750 (m), 730 (s), and 700 cm^{-1} (s); nmr (CCl_4) δ 7.6–8.0 (multiplet, area 2, a and b) and 7.1–7.6 ppm (multiplet, area 8).



Anal. Calcd for $C_{14}H_{10}S$: C, 79,96; H, 4.79; S, 15.25. Found: C, 80.01; H, 4.83; S, 15.24.

The 3-phenylbenzo[*b*]thiophene thus obtained (354 mg) and a very small drop of concentrated H_2SO_4 were placed in a sealed flask under nitrogen and heated at 200–210° for 22 hr. Only a hard, black residue remained on the bottom of the flask, but

(22) "Organic Syntheses," Collect. Vol. IV, N. Rabjohn Ed., Wiley, New York, N. Y., 1963, p 927.

(23) A. Baeyer, *Ber.*, **6**, 223 (1873).

(24) The isomeric 3-chloro-2-phenylbenzo[*b*]thiophene has mp 67°.[15]

crystals of 2-phenylbenzo[b]thiophene had sublimed to the top of the flask. These were recrystallized from 10 ml of absolute ethanol, giving 110 mg of white plates, mp 170–171°. Another recrystallization raised the melting point to 171.5–172° (lit.[17] mp 171–172°, lit.[18] 172–173°; note also footnote 18).

No rearrangement of 2-phenylbenzo[b]thiophene took place in the absence of an acid catalyst, and the starting material was recovered unchanged.

Preparation of 2-Carboxy-3-phenylbenzo[b]thiophene.—The Grignard reagent was prepared as above from 868 mg (3.0 mmol) of 2-bromo-3-phenylbenzo[b]thiophene and 100 mg (4.0 mg-atoms) of magnesium in 9 ml of dry THF. The nitrogen atmosphere was replaced with dry tank carbon dioxide and the solution was heated at reflux for 25 hr under positive CO_2 pressure. The solution was evaporated at reduced pressure and the residue was treated with 2 ml of concentrated HCl in 15 ml of water. Extraction with two 15-ml portions of diethyl ether followed. The ether solution was extracted with three 10-ml portions of saturated sodium bicarbonate solution, which gave an aqueous suspension of the product sodium salt. The combined bicarbonate layers were acidified with dilute HCl and extracted with three 20-ml portions of ether. The combined ether extracts were dried and evaporated and the remaining yellow powder was recrystallized from 15 ml of 70% aqueous ethanol. A first crop of 394 mg, mp 198–199°, and a second crop of 121 mg were obtained, a total yield of 68%. Recrystallization from 50% aqueous ethanol gave an analytical sample, mp 199.0–199.5°, with prior softening at about 175°: ir (Nujol) 2550 (broad, OH), 1650 (s), 1520 (s), 1485 (m), 1340 (m), 1295 (s), 1250 (m), 1180 (w), 1125 (w), 1080 (m), 1050 (w), 920 (m), 860 (w), 780 (w), 755 (s), 745 (m), 740 (s), 715 (m), and 700 cm^{-1} (s).

Anal. Calcd for $C_{15}H_{10}O_2S$: C, 70.84; H, 3.96; S, 12.61. Found: C, 70.68; H, 4.29; S, 12.49.

Registry No.—VII, 14315-12-9; VIII, 29491-86-9; phenylmercuric bromide, 1192-89-8; tetrachlorothiirane, 22706-41-8; 2,2-dichloro-3,3-diphenylthiirane, 34281-40-8; 2-bromo-2-chloro-3,3-diphenylthiirane, 34281-41-9; 2,2-dibromo-3,3-diphenylthiirane, 34281-42-0; 2-chloro-3-phenylbenzo[b]thiophene, 34281-43-1; 2-bromo-3-phenylbenzo[b]thiophene, 34281-44-2.

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Selective Hydrogenation of α,β-Unsaturated Carbonyl Compounds *via* Hydridoiron Complexes

R. NOYORI,* I. UMEDA, AND T. ISHIGAMI

Department of Chemistry, Nagoya University, Nagoya, Japan

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A reagent generated *in situ* from iron pentacarbonyl and a small amount of base in moist solvents serves as a new, efficient agent for selective hydrogenation of α,β-unsaturated carbonyl compounds (ketones, aldehydes, esters, and lactones, etc.) under mild reaction conditions. The characteristics and the possible mechanisms of the reduction are described.

The reduction of α,β-unsaturated carbonyl compounds (eq 1) has been effected *chemically* by dissolving alkali metals such as Li, Na, and K in liquid ammonia (Birch conditions),[1] and amalgamated zinc in hydrochloric acid (Clemmensen conditions).[2] Because such reductions require strongly basic or acidic conditions, which often cause undesired side reactions, their synthetic utility has been restricted. Sodium borohydride also has been employed in certain cases, but lacks general utility.[3] The homogeneous, transition metal catalyzed reduction of unsaturated compounds, most of which proved to involve metal hydride complexes, is the subject of current interest.[4] However, there have so far been few attempts to gain selectivity for homogeneous reduction of α,β-unsaturated carbonyl compounds.[5,6] This paper describes a new, selective reduction of α,β-unsaturated carbonyl compounds by means of iron-based complexes under mild reaction conditions.

$$RCH{=}CHCOR' \longrightarrow RCH_2CH_2COR' \qquad (1)$$

Results and Discussion

Treatment of unsaturated carbonyl derivatives with a reagent generated *in situ* from iron pentacarbonyl [$Fe(CO)_5$] and a small amount of NaOH in 95% CH_3OH at 0–60° under nitrogen atmosphere gave the corresponding saturated derivatives in high yield (condition A). A mixture of ether and H_2O (4:1 v/v) which provides a two-layer reaction system may be used in place of 95% CH_3OH (condition B). Besides NaOH, 1,4-diazabicyclo[2.2.2]octane (DABCO) in moist dipolar solvents such as *N*,*N*-dimethylformamide (DMF) or *N*,*N*,*N*′,*N*′,*N*″,*N*″-hexamethylphosphoric triamide (HMPA) gave satisfactory results (condition C). As exemplified in Table I, this reduction method is applicable to a wide variety of α,β-unsaturated carbonyl compounds including ketones, aldehydes, esters, lactones, etc.

The present procedure, within limits of the experiments examined, possesses the following characteristics: (1) overreductions of the ketonic group into >CHOH or $>CH_2$ groups are negligible; (2) ester

(1) (a) A. J. Birch, *Quart. Rev., Chem. Soc.*, **4**, 69 (1950); (b) H. Smith, "Organic Reactions in Liquid Ammonia," Interscience, New York, N. Y., 1963; (c) M. Smith in "Reduction," R. L. Augustine, Ed., Marcel Dekker, New York, N. Y., 1968, p 95.

(2) J. G. St. C. Buchanan and P. D. Woodgate, *Quart. Rev., Chem. Soc.*, **23**, 522 (1969).

(3) (a) W. R. Jackson and A. Zurqiyah, *J. Chem. Soc.*, 5280 (1965); (b) K. Iqbal and W. R. Jackson, *J. Chem. Soc. C*, 616 (1968), and references cited therein.

(4) Reviews: (a) Collected papers presented at the symposium on homogeneous catalysis, Liverpool, U. K., Sept 17 and 18, 1968, in *Discuss. Faraday Soc.*, **46** (1968); (b) M. E. Vol'pin and I. S. Kolomnikov, *Russ. Chem. Rev.*, **38**, 273 (1969).

(5) $Ru(II)Cl_2$ in aqueous HCl exhibited marked selectivity: J. Halpern, J. F. Harrod, and B. R. James, *J. Amer. Chem. Soc.*, **88**, 5150 (1966).

(6) For heterogeneous, *catalytic* hydrogenation systems, see R. L. Augustine, "Catalytic Hydrogenation," Marcel Dekker, New York, N. Y., 1965, p 60.

Table I

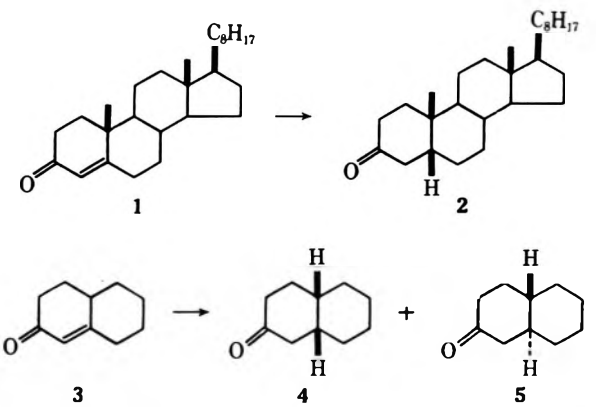
Selective Hydrogenation with Iron Carbonyl

Registry no.	Substrate	Condition[a]	Reaction temp, °C	Reaction time, hr	Product	Yield, %[b]
122-57-6	Benzalacetone	A	20	12	Benzylacetone	>98
		B	20	48		91
		C	20	48		>98
94-41-7	Benzalacetophenone	A	20	12	Benzylacetophenone	>98
		B	20	12		>98
495-41-0	Crotonophenone	A	0	3	Butyrophenone	>98
		B	20	12		>98
		C	20	17		>98
78-94-4	Methyl vinyl ketone	A	0	3	Ethyl methyl ketone	>98
141-79-7	Mesityl oxide	A	60	24	Isobutyl methyl ketone	96
		C	20	36		>98
930-68-7	2-Cyclohexenone	A	20	10	Cyclohexanone	96
		C	20	36		>98
		C[c]	20	20		93
1121-18-2	2-Methyl-2-cyclohexenone	A	60	24	2-Methylcyclohexanone	35[d]
1193-18-6	3-Methyl-2-cyclohexenone	A	60	24	3-Methylcyclohexanone	52[d]
601-57-0	4-Cholesten-3-one	B	20	36	Coprostanone[e]	32[d]
1196-55-0	$\Delta^{1,9}$-2-Octalone	B	20	24	2-Decalones[f]	35[d]
1728-25-2	2-Cyclooctenone	A	20	12	Cyclooctanone	>98
		B	20	18		>98
		C	20	24		>98
4170-30-3	Crotonaldehyde	A	0	2	Butyraldehyde	>98
104-55-2	Cinnamaldehyde	A	20	12	3-Phenylpropionaldehyde	98
103-26-4	Methyl cinnamate	A	20	48	Methyl 3-phenylpropionate	90
624-48-6	Dimethyl maleate	A	0	12	Dimethyl succinate	96
624-49-7	Dimethyl fumarate	A	0	12	Dimethyl succinate	92
108-54-3	5-Hydroxy-2-hexenoic acid δ-lactone	C	60	12	5-Hydroxyhexanoic acid δ-lactone	90
4360-47-8	Cinnamonitrile	A	20	36	3-Phenylpropionitrile	92
7187-01-1	3-(2-Furyl)acrylonitrile	C	60	9	3-(2-Furyl)propionitrile	75

[a] See Experimental Section for details. Under condition C, unless otherwise stated, DMF was used as solvent. [b] Determined by glpc analysis. [c] Moist HMPA was used as solvent. [d] The remainder consisted mainly of the starting material. Side reactions were negligible. [e] Isomeric purity 95%. [f] Cis:trans 37:63.

functions are not reduced; (3) reductive coupling of ketones to pinacols, frequently encountered under Birch conditions, is not observed; (4) no skeletal rearrangements, often promoted under Clemmensen conditions, take place; (5) phenyl and furyl groups are not affected; and (6) the rate of the reduction is profoundly influenced by steric environments around double bonds (competition experiments demonstrated that relative reactivities of 2-cyclohexenone 2-methyl-2-cyclohexenone, and 3-methyl-2-cyclohexenone are 1.00, 0.10, and 0.017, respectively).[7]

As to the stereochemistry of the reduction, 4-cholesten-3-one (1) was converted selectively into coprostanone (2) having cis stereochemistry at the A/B ring juncture (condition B), whereas $\Delta^{1,9}$-2-octalone (3) was reduced to afford a stereoisomeric mixture of 2-decalones 4 and 5 (37:63 ratio).[8]



The reduction in deuterated solvents serves as a convenient method for specific deuteration at the position β to the carbonyl group.[11] For instance, reduction of crotonophenone under condition A using NaOD–D_2O–CH_3OD gave crude butyrophenone-α,β-d_2. Treatment of the product with CH_3ONa–CH_3OH gave butyrophenone-β-d_1, while work-up with CH_3ONa–CH_3OD afforded butyrophenone-α,α,β-d_3. Deuterium incorporation into the unreacted ketone was not observed.[12]

Noteworthy are the facts observed in the reaction of dimethyl fumarate and maleate in CH_3OD: (1) maleate isomerizes to fumarate during the reduction (2) recovered fumarate contains a considerable amount of deuterium atom, whereas only a slight incorpora-

(7) Isolated double bonds are not hydrogenated, but positionally isomerize slowly. This might offset to some extent the advantages of the present method.

(8) Catalytic reduction of 1 on PdO gave a stereoisomeric mixture, the cis/trans ratio depending on the nature of the solvent used: *e.g.*, 11.5:1 in C_2H_5OH–20% aqueous NaOH and 1.44:1 in C_2H_5OH–3 *N* HCl. Hydrogenation of 3 on 10% Pd–C or PtO_2 yielded a mixture of isomeric decalones in favor of the cis isomer 4.[10]

(9) S. Nishimura, M. Shimahara, and M. Shiota, *J. Org. Chem.*, **31**, 2394 (1966).

(10) (a) A. Marchant and A. R. Pinder, *J. Chem. Soc.*, 327 (1956); (b) R. L. Augustine, *J. Org. Chem.*, **23**, 1853 (1958).

(11) Previous methods: (a) (Li–ND_3) D. H. Williams, J. M. Wilson, H. Budzikiewicz, and C. Djerassi, *J. Amer. Chem. Soc.*, **85**, 2091 (1963); (b) (Li–$C_5H_7ND_2$) M. Fetizon and J. Gore, *Tetrahedron Lett.*, 471 (1966).

(12) H. W. Whitlock, Jr., C. R. Reich, and R. L. Markezich, *J. Amer. Chem. Soc.*, **92**, 6665 (1970).

TABLE II
REACTION OF DIMETHYL FUMARATE AND MALEATE IN CH_3OD–D_2O[a]

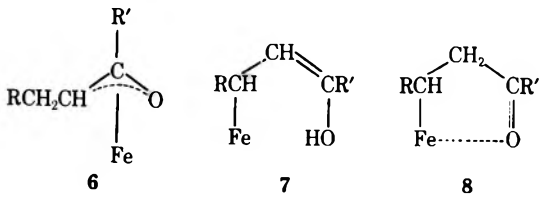
Substrate	Recovered fumarate, %	Recovered maleate, %	Dimethyl succinate, %
Dimethyl fumarate	86 (0.14 D)[b]	0	14 (2.10 D)[c]
Dimethyl maleate	33 (0.22 D)[d]	54 (0.04 D)[e]	13 (2.00 D)[c]

[a] Results of the reaction using 2 equiv of $Fe(CO)_5$ under condition A (0°, 12 hr). Product composition was determined by glpc. Deuterium content of the esters shown in parentheses was obtained by nmr (error <5%). Isotope distribution was determined by mass spectral analysis. [b] 87% d_0, 12% d_1, and 1% d_2. [c] Consists mainly of *meso*- and *dl*-succinate-2,3-d_2: C. R. Childs, Jr., and K. Bloch, *J. Org. Chem.*, **26**, 1630 (1961). [d] 79% d_0, 20% d_1, and 1% d_2. [e] 96% d_0 and 4% d_1.

tion was observed in unreacted maleate (Table II). These phenomena are reminiscent of the recently reported reaction of $HCo(CO)_4$ and dimethyl maleate, where hydrogenation to succinate was claimed to proceed *via* fumarate.[13] In the present case, however, maleate also seems susceptible to the hydrogenation, because (1) reduction of fumarate induced a higher, or at least comparable, extent of deuterium incorporation in the product compared with the case of maleate; (2) apparently both esters were reduced at a comparable rate without an appreciable induction period.

Although the exact nature of the species responsible for the reduction remains unspecified, the reaction most probably proceeds by way of hydridoiron complexes.[14] The present reaction conditions would be expected to produce a complicated mixture of mono-, di-, and trinuclear iron complexes [$H_2Fe(CO)_4$, $H_2Fe_2(CO)_8$, and $H_2Fe_3(CO)_{11}$, respectively], and their salts,[15,16] the composition being subtly influenced by various factors, *e.g.*, kind of solvent and base, ratio of $Fe(CO)_5$ and the base, temperature, and reaction time. The appearance of the characteristic wine-red color suggests the formation of anionic di- and trinuclear complexes ($[HFe_2(CO)_8]^-$ and $[HFe_3(CO)_{11}]^-$),[16] and control experiments demonstrated that these species do reduce 2-cyclohexenone. However, the possibility that feebly colored mononuclear complexes are the major reducing agents could not be excluded. The anionic species is produced according to the stoichiometry $Fe(CO)_5 + 3OH^- \rightarrow [HFe(CO)_4]^- + CO_3^{2-} + H_2O$, and then oxidatively converted to the di- and trinuclear complexes.[15] However, the use of a ratio of NaOH:$Fe(CO)_5$ higher than 1:2 (under condition A) induced significant side reactions and gave decreased yields of the reduction products.[17]

The reaction intermediate might have a π-enolate structure of type **6**.[14] Alternatively, the reduction might proceed *via* the organoiron complexes of type **7**[13] or **8**.[18] However, the s-cis conformation, which facilitates the conjugate addition or the carbonyl chelation, would not be a necessary condition for the reaction since cyclic unsaturated compounds are readily reduced.



6 **7** **8**

Experimental Section

General.—Commercial $Fe(CO)_5$ (Strem Chemicals, Inc.) and CH_3OD (99%, Merck) were used without further purification. Reagent grade CH_3OH, DMF, and HMPA were used after distillation. Ether was purified before use by passing through a column of basic alumina. Benzalacetophenone,[19] crotonophenone,[20] 2-methyl-2-cyclohexenone,[21] $\Delta^{1,9}$-2-octalone,[22] 2-cyclooctenone,[23] 5-hydroxy-2-hexenoic acid δ-lactone,[24] cinnamonitrile,[25] and 3-(2-furyl)acrylonitrile[25] were prepared according to the known procedures. Other starting materials were obtained commercially, and, in most instances, liquid reagents were distilled and solids were recrystallized before use.

Nuclear magnetic resonance (nmr) spectra were taken with a JEOLCO C-60H spectrometer in CCl_4 solution with tetramethylsilane as internal standard. Mass spectra were obtained on a Hitachi RMU 6C mass spectrometer at 70 eV using a heating inlet system. Analytical gas–liquid partition chromatography (glpc) was performed on a Yanagimoto Model G8 instrument with flame ionization detector and nitrogen carrier gas. The columns (3 mm × 2 m) used were 5% diisodecyl phthalate on Celite 545, 5% polyethylene glycol 4000 (with and without $AgNO_3$) on Celite 545, 5% polyethylene glycol succinate on Neopak 1A, 2% silicone OV-17 on Chromosorb W, and 5% silicone SE-30 on Chromosorb W. Yields of the products were determined by cut-and-weigh integration of glpc traces using added standards for correction for detector response differences. Preparative glpc was carried out on a Yanagimoto Model 3D instrument with thermal conductivity detector and a column (5 mm × 1 m) of 5% polyethylene glycol succinate on Neopak 1A using helium carrier gas. Analytical and preparative thin layer chromatography (tlc) was carried out on silica gel plates (Merck silica gel GF_{254}, buffered at pH 7, 0.25-mm and 1.0-mm thickness, respectively).

Procedure.—$Fe(CO)_5$ is toxic, and great care must be exercised in its handling. All reactions and work-ups must be carried out in a well-ventilated hood. All reactions were conducted in a 10-ml round-bottomed flask with a neck and a sidearm to accommodate a three-way stopcock and a rubber serum cap, respectively. Stirring was effected magnetically. Liquid reagents and solutions in the case of solids were transferred with a hypodermic syringe.

The general execution of the present method (condition A) is illustrated by the procedure for the conversion of benzalacetone to benzylacetone. A mixture of $Fe(CO)_5$ (784 mg, 4.0 mmol) and NaOH (80 mg, 2.0 mmol) in a 95:5 v/v mixture of CH_3OH and H_2O (2.0 ml) was flushed with nitrogen and stirred for 5 min at room temperature to ensure the complete depletion of NaOH. To the resulting dark-red solution was added benzalacetone (146 mg, 1.0 mmol) in one portion, and the mixture was allowed to stir at ambient temperature. After a reaction time of 12 hr, the excess reducing agents were decomposed by adding an ethereal solution of I_2 (*Caution:* vigorous foaming occurred), and the mixture was treated with H_2O and extracted with ether. The combined extracts were washed with sodium thiosulfate solution, dried over Na_2SO_4, and concentrated *in vacuo*. The residual oil was subjected to preparative tlc (R_f 0.39, 1:1 *n*-hexane–benzene mixture) to give pure benzylacetone (134 mg, 90% yield; >98% by glpc). The identity was established by comparison of the

(13) P. Taylor and M. Orchin, *J. Organometal. Chem.*, **26**, 389 (1971).
(14) Reduction with $HCo(CO)_4$: R. W. Goetz and M. Orchin, *J. Amer. Chem. Soc.*, **85**, 2782 (1963).
(15) H. W. Sternberg, R. Markby, and I. Wender, *ibid.*, **79**, 6116 (1957), and references cited therein.
(16) J. R. Case and M. C. Whiting, *J. Chem. Soc.*, 4632 (1960).
(17) A reaction aliquot diluted with a 20-fold volume of H_2O showed pH *ca.* 9.
(18) For the related ir complex, see M. McPartlin and R. Mason, *J. Chem. Soc. A*, 2206 (1970).
(19) E. P. Kohler and H. M. Chadwell, "Organic Syntheses, Collect. Vol. I, Wiley, New York, N. Y., 1956, p 78.
(20) R. C. Fuson, R. E. Christ, and G. M. Whitman, *J. Amer. Chem. Soc.*, **58**, 2450 (1936).
(21) E. W. Warnhoff, D. G. Martin, and W. S. Johnson, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 162.
(22) G. Stork, A. Brizzolara, H. Landesman, J. Szmuzkovicz, and R. Terrell, *J. Amer. Chem. Soc.*, **85**, 207 (1963).
(23) E. W. Garbisch, Jr., *J. Org. Chem.*, **30**, 2109 (1965).
(24) R. Kuhn and D. Jerchel, *Ber.*, **76**, 413 (1943).
(25) J. M. Patterson, *Org. Syn.*, **40**, 46 (1960).

spectral data (ir and nmr) and retention time of glpc with those of an authentic sample.

Under condition B, a heterogeneous mixture of ether (1.6 ml) and H_2O (0.4 ml) was used instead of 95% CH_3OH. Condition C refers to the use of DMF (or HMPA)–H_2O mixture (98:2 v/v, 2.0 ml) containing DABCO (224 mg, 2.0 mmol). Unless otherwise stated, the reaction scale and the procedure were as above described. The progress of the reaction was conveniently monitored by glpc or tlc. In general, volatile products were purified by distillation and preparative glpc, whereas nonvolatile materials were isolated in pure state by preparative tlc. The structure was confirmed by comparison of the retention times of glpc and the spectral data (ir, nmr, uv, and mass) with those of authentic specimen. Isomeric purity of coprostanone (2) (95%) derived from 4-cholesten-3-one (1) was determined according to the standard procedure[26] after converting the whole ketonic products into the 2,4-dinitrophenylhydrazones.

Reduction of 2-Cyclohexenones.—The rates of hydrogenation were compared individually and competitively. When 2-cyclohexenone, 2-methyl-2-cyclohexenone, and 3-methyl-2-cyclohexenone were treated separately with 4 equiv of $Fe(CO)_5$ under condition A at 20°, the corresponding saturated ketones were formed. Yields of cyclohexanone, 2-methylcyclohexanone, and 3-methylcyclohexanone were 43, 3.8, and 1.0% after 30 min, and 96, 15, and 22% after 12 hr, respectively. Although 2-methyl-2-cyclohexenone was reduced more rapidly than 3-methyl-2-cyclohexenone at the early stage of the reaction, the final yield of 2-methylcyclohexanone was lower than that of 3-methylcyclohexanone.

Reaction under condition A using 2-cyclohexenone (10 mg, 0.11 mmol), 2-methyl-2-cyclohexenone (112 mg, 1.0 mmol), $Fe(CO)_5$ (796 mg, 4.1 mmol), NaOH (80 mg, 2.0 mmol), and 95% CH_3OH (2.0 ml) was performed at 20°. A similar competition experiment was conducted using 2-cyclohexenone (10 mg, 0.11 mmol), 3-methyl-2-cyclohexenone (330 mg, 3.0 mmol), $Fe(CO)_5$ (268 mg, 1.3 mmol), NaOH (25 mg, 0.63 mmol), and 95% CH_3OH (6.0 ml). The reaction aliquot was taken up at appropriate intervals and analyzed by glpc. Yields of the reduction products were plotted against reaction time, and the competition figure, 2-cyclohexenone:2-methyl-2-cyclohexenone:3-methyl-2-cyclohexenone = 1.00:0.10:0.017, was obtained from the slope of the traces (conversion <30%).

Preparation of Deuteriobutyrophenones.—To a solution prepared by dissolving Na (35 mg, 1.5 mg-atoms) in a mixture of CH_3OD (1.5 ml) and D_2O (0.075 ml) was added $Fe(CO)_5$ (588 mg, 3.0 mmol), and the mixture was stirred for 5 min at room temperature and then cooled to 0°. Crotonophenone (100 mg, 0.69 mmol) was added in one portion, and the mixture was stirred at 0° for 3 hr. After quenching with an ethereal solution of I_2, the mixture was treated with aqueous sodium thiosulfate solution and extracted with ether. Concentration of the extracts *in vacuo* followed by preparative tlc (R_f 0.29 after two developments with 1:1 *n*-hexane–benzene mixture) gave pure butyrophenone (85 mg, 82% yield). The nmr indicated that the major component was $CH_3CHDCHDCOC_6H_5$: δ 0.98 (d, J = 6.7 Hz, 3 H, CH_3), 1.3–2.0 (m, 1 H, β-CH), 2.6–3.0 (m, 1 H, α-CH), and 7.1–8.0 (m, 5 H, C_6H_5). Crotonophenone recovered from the incomplete reaction (tlc R_f 0.15 after two developments with 1:1 *n*-hexane–benzene mixture) did not contain deuterium atom, as confirmed by nmr and mass analyses.

Butyrophenone-α,β-d_2 above prepared (26 mg, 0.17 mmol) was treated with 0.1 *N* CH_3ONa in CH_3OD (0.17 ml) at room temperature for 3 hr. The reaction mixture was directly chromatographed on a silica gel plate to afford butyrophenone-α,α,β-d_3 (24 mg, 92% recovery). Mass spectral analysis using $CH_3CH_2COC_6H_5$ and $CH_3CH_2CD_2COC_6H_5$ (86% d_2 and 14% d_1) as reference indicated the composition of 3% d_4, 81% d_3, 15% d_2, and 1% d_1: nmr δ 0.98 (d, J = 6.7 Hz, 3 H, CH_3), 1.3–2.0 (m, 1 H, β-CH), 2.6–3.0 (m, 0.04 H, α-CH), and 7.1–8.0 (m, 5 H, C_6H_5). Butyrophenone-β-d_1 was obtained in a similar fashion using 0.1 *N* CH_3ONa in CH_3OH: mass spectrum 3% d_2, 92% d_1, and 5% d_0; nmr δ 0.98 (d, J = 6.7 Hz, 3 H, CH_3), 1.3–2.0 (m, 1 H, β-CH), 2.6–3.0 (d, J = 6.7 Hz, 2 H, α-CH_2), and 7.1–8.0 (m, 5 H, C_6H_5).

Reaction of Dimethyl Maleate and Fumarate in Deuterated Solvent.—$Fe(CO)_5$ (590 mg, 3.0 mmol) was added to a solution prepared by dissolving Na (35 mg, 1.5 mg-atoms) in CH_3OD (3.0 ml)–D_2O (0.18 ml), and the mixture was stirred at ambient temperature for 5 min. To the resulting dark-red solution kept at 0° was added dimethyl maleate (or fumarate) (224 mg, 1.5 mmol) in one portion, and the mixture was stirred at 0° for 12 hr. The reaction mixture was subjected directly to bulb-to-bulb distillation. The ester fraction obtained at 25° (1 mm) was dissolved in $CDCl_3$, dried by passing through a short column of Na_2SO_4, and analyzed by nmr to determine the deuterium content of succinate. The isotope distribution of succinate could not be specified by mass spectral analysis. Isotope exchange of succinate during the reaction and the work-up proved to be negligible. Samples of maleate and fumarate for mass and nmr analyses were obtained by preparative glpc (5% polyethylene glycol succinate on Neopak 1A, 95°). The results are summarized in Table II.

Reduction of 2-Cyclohexenone with Polynuclear Hydridoiron Complexes.—Treatment of $Fe_3(CO)_9$ (369 mg, 1.0 mmol) with KOH (172 mg, 3.1 mmol) in CH_3OH (2.0 ml) at 20° for 1.5 hr gave a mixture of dinuclear complexes, $[HFe_2(CO)_8]^-$ and $[Fe_2(CO)_8]^{2-}$.[16] 2-Cyclohexenone (98 mg, 1.0 mmol) was added in one portion, and the mixture was stirred at 20° for 6 hr. Glpc analysis of the aliquot quenched by ethereal solution of I_2 indicated the formation of cyclohexanone in 56% yield.

Treatment of 2-cyclohexanone (98 mg, 1.0 mmol) with $(C_2H_5)_3NH^+$–$[HFe_3(CO)_{11}]^-$ (546 mg, 1.0 mmol)[16] in CH_3OH (2.0 ml) at room temperature for 6 hr afforded cyclohexanone in 23% yield.

(26) F. J. McQuillin, W. O. Ord, and P. L. Simpson, *J. Chem. Soc.*, 5996 (1963).

Registry No.—Iron pentacarbonyl, 13463-40-6.

An Improved Synthesis of Indenes[1]

WILLIAM E. PARHAM* AND DAVID C. EGBERG

Department of Chemistry, University of Minnesota, Minneapolis, Minnesota 55455

Received November 2, 1971

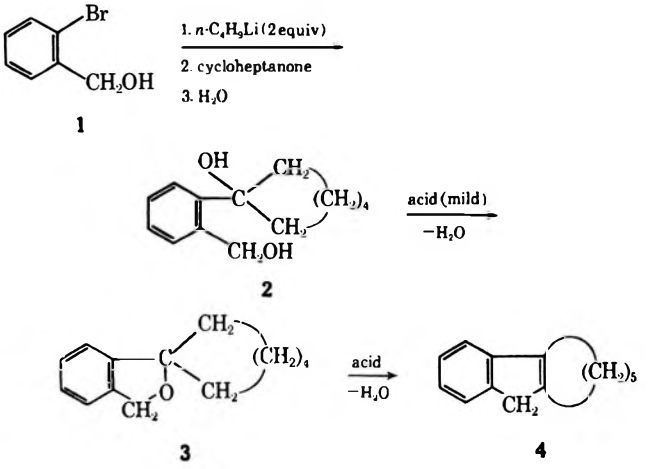
Diols of type **2** or ethers of type **3** are prepared in high yield from readily available *o*-bromobenzyl alcohol and are converted to indenes of type **4** by action of protonic acids such as sulfuric acid in glacial acetic acid, *p*-toluenesulfonic acid in hot glacial acetic acid, polyphosphoric acid, or Lewis acids such as boron trifluoride etherate in refluxing benzene. Boron trifluoride etherate is the current acid of choice for the cyclic ketones studied (C_7, C_8, C_9, C_{12}), and high yields of indenes (49–73%) of type **4** are prepared conveniently and without isolation of intermediates. The reaction gives 3-phenylindene when acetophenone is employed. Under certain conditions indan formation has been noted as a side product.

We wish to report a new synthesis of indenes which is illustrated by the synthesis of 6,7,8,9,10-pentahydro-5*H*-cyclohept[*a*]indene (**4**) as shown in Scheme I.

(1) Supported by U. S. Army Medical Research and Development Command, DADA-17-70-C-0008.

The procedure involves addition of alkyllithium (2 equiv) to the 2-bromobenzyl alcohol in an appropriate nonprotonic solvent such as tetrahydrofuran and hexane. The temperature of addition is not critical; however, the reaction is exothermic and is usually

SCHEME I



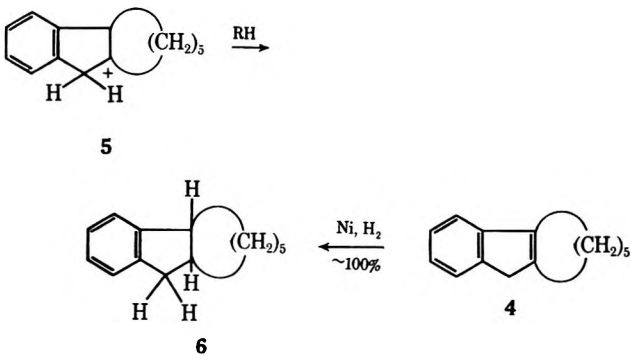
effected in the cold. The ketone, in solution of an inert solvent such as hexane, is added at a rate sufficient to control the exothermic reaction (cooling −10 to −20° is recommended). The intermediate diol **2** can be isolated by conventional methods, or the crude diol can be used without purification for direct conversion to the cyclic ether **3** or to the indene **4** by action of appropriate acid. All acids studied (hot formic acid, *p*-toluenesulfonic acid in acetic acid, sulfuric acid in acetic acid, and boron trifluoride etherate in benzene) effect rapid conversion of diol **2** to cyclic ether **3**; formic acid is the reagent of choice of those studied when isolation of the ether is desired (74% yield of **3**).

Optimum reaction conditions (acid, time, temperature) vary for the conversion to each indene and either the diol **2** or the cyclic ether **3** can be employed; more conveniently the crude diol can be converted directly to indene in essentially a *one-pot* reaction without isolation of intermediates. Boron trifluoride etherate in boiling benzene is currently the acid of choice for the cyclic ketones employed (C_7, C_8, C_9, C_{12}) and the yield of indenes of type **4** has consistently been 49–73%.

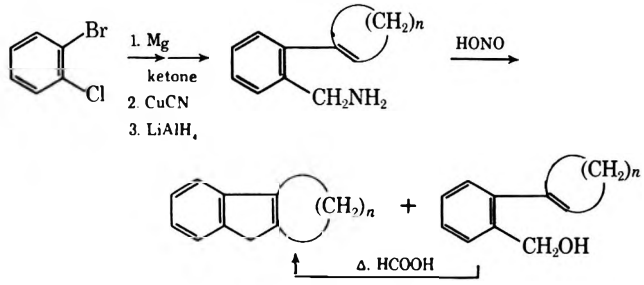
Conversion of diols of type **2** into indenes of type **4** is also practical using sulfuric acid in glacial acetic acid; however, such reactions are accompanied by more tar formation and the yield of indenes is lower (generally 23–38%). Reaction of the diol **2** with polyphosphoric acid (22–31°) gave a mixture of indene **4** (30%) and reduced indene **6** (26%). Indan **6** was observed as a by-product in all acid systems studied; however, its formation was decreased by decreasing the concentration of the reacting diol **2**. The indan **6** was assumed to be formed by hydride transfer involving an intermediate carbonium ion **5**; the structure of **6** was established by its independent synthesis from **4** (Scheme II). Indene **4** does not give rise to indan **6** in polyphosphoric acid or boron trifluoride etherate in benzene; thus, it was established that the by-product indans do not originate from the indenes as they are formed. Reaction of **2** (1.23 mmol) with *p*-toluenesulfonic acid (0.28 mmol) in hot glacial acetic acid proceeded slowly (after 3 hr, 51% conversion to **3**, 40% conversion to 4) but cleanly, and this procedure may prove to be a suitable alternative to use of boron trifluoride etherate in benzene.

Fused indenes of type **4** are of particular interest to us as intermediates for the preparation of metacyclophanes by addition of halocarbenes with subsequent ring expansion of the derived cyclopropanes.[2] The present method for the preparation of such indenes is superior to that previously reported[3] since the preparation can be carried out rapidly, fewer steps are involved and intermediates need not be isolated or purified. The alternative method[3] starting with *o*-bromochlorobenzene (Scheme III) involves six steps, requires rather tedious isolation procedures, and gives overall yields of indenes (C_6–C_{12}) of only 4–15%.

SCHEME II



SCHEME III



This synthesis of indenes can be extended to noncyclic ketones. Treatment of the crude diol obtained from acetophenone with boron trifluoride etherate did not give indene(s); however, use of sulfuric acid in glacial acetic acid gave 3-phenylindene in 23% yield. Possible extension of this new indene synthesis to the use of aldehydes, unsymmetrical ketones, and for the preparation of polycyclic indenes is the subject of further study.

Experimental Section

Methyl *o*-Bromobenzoate.—Esterification of *o*-bromobenzoic acid using molecular sieves was fashioned after the method used by Harrison and coworkers[4] for the synthesis of methyl nonanoate. The yield of pure methyl *o*-bromobenzoate was 91%. The yield was 80–84% when molecular sieves were not employed.

***o*-Bromobenzyl alcohol** was prepared (93% yield) by reduction of methyl *o*-bromobenzoate (0.462 mol) with lithium aluminum hydride, mp 78.5–80.5° (lit.[5] mp 80°).

1-(*o*-Hydroxymethylphenyl)cycloheptanol (2).—Dry *o*-bromobenzyl alcohol (10.00 g, 0.0535 mol) was added to a flame-dried 500-ml three-neck round-bottom flask, equipped with an addition funnel, alcohol thermometer, nitrogen inlet, and mechanical

(2) (a) W. E. Parham, *Rec. Chem. Progr.*, **29**, (1968); (b) W. E. Parham, D. R. Johnson, C. T. Hughes, M. K. Meilahn, and J. K. Rinehart, *J. Org. Chem.*, **35**, 1048 (1970).

(3) W. E. Parham, C. D. Wright, and D. A. Bolon, *J. Amer. Chem. Soc.*, **83**, 1751 (1961).

(4) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Vol. I, Wiley, New York, N. Y., 1967, p 705.

(5) C. Mettler, *Ber.*, **39**, 2938 (1906).

stirrer. Tetrahydrofuran (40 ml, distilled from $LiAlH_4$) and 10 ml of hexane (stored over sodium) was added and the solution was cooled to −15° in a Dry Ice–aqueous isopropyl alcohol bath under positive nitrogen pressure. Recently standardized[6] *n*-butyllithium (Alpha) (55 ml, 0.123 mol, 15% molar excess) was slowly added over a 75-min period, forming a thick white precipitate, and the mixture was stirred for an additional 2 hr under nitrogen at −10 to −20°. Cycloheptanone (Aldrich) (9.00 g, 0.080 mol, 15% molar excess based on dilithium salt and excess *n*-butyllithium) in 25 ml of hexane was added to the cold slurry over a 30-min period while maintaining the temperature between −10 and −20°, and a large portion of the white precipitate vanished. The mixture was stirred at −15° for another 2 hr and then was allowed to warm to room temperature and stirred under nitrogen for an additional 16 hr. The clear reaction solution was hydrolyzed (80 ml of saturated aqueous NH_4Cl) and the two phases were separated. The aqueous layer was extracted with two 50 ml-portions of ether and the combined organic extracts were washed with 50 ml of water, dried (Na_2SO_4), filtered, and the solvent removed (rotary evaporation) to a yellow oil (15.29 g). Benzyl alcohol and unreacted cycloheptanone were distilled at 55–88° (10 mm) from the crude diol with a short path column to give 4.04 g of distillate (18 mol % benzyl alcohol and 82% cycloheptanone by nmr). After removal of unreacted ketone and benzyl alcohol, the distillation flask contained 10.55 g (90% yield) of crude diol which crystallized upon cooling to room temperature (22°). The solid material was dissolved in 90 ml of petroleum ether (bp 60–70°) and cooled to −25° with the formation of pink needles (8.30 g, mp 61–64.5°, 71% yield). The mother liquor was concentrated to 2.15 g of red oil which showed the presence of additional dialcohol by nmr spectroscopy.

An analytical sample of **2** was prepared by recrystallizing the diol (0.50 g) two times from petroleum ether to give 0.34 g of small, white needles, mp 62.5–64°, which showed the following spectral properties: ir (neat) 3620–3100 cm^{-1} (broad and strong, associated OH); uv max (95% C_2H_5OH) 211 mμ (log ε 3.94), 254 (sh, 2.20), 259 (2.30), 265 (sh, 2.24), 270 (sh, 2.03); nmr ($DCCl_3$) (with areas relative to 20 protons) τ 2.54–2.86 (m, 4.0, aromatic H), 5.16 (s, 2.0, benzylic CH_2O), 6.36 (s, 2.1, alcohol OH) (disappeared when D_2O added to sample), 7.67–8.57 (two broad peaks, 11.9, aliphatic CH_2).

Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15. Found: C, 76.51; H, 9.03.

Spiro[cycloheptane-1,1′(3′*H*)-isobenzofuran] (Cyclic Ether Intermediate 3).—The crude diol **2** (14.82 g) obtained from *o*-bromobenzyl alcohol (0.0535 mol) as described above which still contained benzyl alcohol and cycloheptanone was added to 65 ml of 88% formic acid (Baker) and heated at the reflux temperature for 80 min. The solution turned deep red and a yellow oil separated on the surface. The reaction mixture was then added with stirring to 250 ml of ice water and the resulting aqueous mixture was extracted with two 100-ml portions of petroleum ether and one 100-ml portion of benzene. The combined organic extracts were washed with 100 ml of water, 100 ml of saturated aqueous sodium bicarbonate, and another 100 ml of water in succession and then dried ($MgSO_4$). The mixture was filtered and the solvent was removed (rotary evaporator) to give a yellow oil (15.41 g). Glpc analysis (5 ft × 0.25 in., 20% DC710 on Chromosorb W, 60–80 mesh, 190°, 60 ml/min He) and nmr analysis of the crude oil showed the presence of the pentahydrocyclohept[*a*]indene (**4**, retention time 14 min 24 sec), benzyl formate, unreacted cycloheptanone, and cyclic ether (retention time 11 min 36 sec). No *o*-bromobenzyl formate was observed, indicating complete reaction of *o*-bromobenzyl alcohol with *n*-butyllithium.

The crude oil was subjected to fractional distillation through a short path column. The first fraction (3.02 g) distilled between 45 and 70° (8 mm) and was shown to be composed of benzyl formate and cycloheptanone by glpc analysis (retention times compared with authentic samples on the column described above). The second fraction (8.67 g) distilled at 79° (0.05 mm) and was shown by glpc analysis (internal standard heptadecane) to be 8 wt % indene **4** (0.69 g, 7.0% yield) and 92% cyclic ether **6** (7.98 g, 74% yield). The distillation flask contained 1.344 g of a red viscous oil which contained additional pentahydrocyclohept[*a*]indene and cyclic ether by glpc analysis.

The cyclic ether was purified by preparative glpc and exhibited the following properties: refractive index $n^{27}D$ 1.5412; ir (neat) 1035 cm^{-1} (CO); uv max (95% C_2H_5OH) 209 mμ (sh, log ε 3.98), 234 (sh, 2.90), 257 (sh, 2.79), 262 (2.92), 269 (2.90), 278 (sh, 2.26); nmr ($DCCl_3$) (with areas relative to 18 protons) τ 2.73–2.90 (with intense peak at 2.79) (m, 4.0, aromatic H), 4.96 (s, 1.9 benzylic CH_2O–), 7.87–8.60 (two broad peaks, 12.1, aliphatic CH_2); mass spectrum *m/e* 202 (molecular ion).

Anal. Calcd for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 83.16; H, 9.00.

Direct Conversion of *o*-Bromobenzyl Alcohol to Indenes of Type 4. A. Use of Boron Trifluoride Etherate. 6,7,8,9,10-Pentahydro-5*H*-cyclohept[*a*]indene (4).—Crude 1-(*o*-hydroxymethylphenyl)cycloheptanol (**2**, 4.15 g, 0.0189 mol), obtained as described above, subsequent to removal of benzyl alcohol and cycloheptanone, was added to 175 ml of benzene contained in a 250-ml three-neck flask equipped with a magnetic stirrer, condenser, and nitrogen inlet. Distilled boron trifluoride etherate (2.68 g, 0.0189 mol) was added, and glpc analysis (5 ft × 0.25 in., 20% DC 710 on 60–80 mesh Chromosorb W, 210°, 60 ml/min He) showed the immediate presence of ether **3**. The reaction mixture was heated to the reflux temperature and after 7 hr (solution turned dark red) at that temperature glpc showed complete conversion to the pentahydrocyclohept[*a*]indene with no indan by-product observed. The reaction was hydrolyzed by adding the red benzene solution to 175 ml of ice water and shaking the mixture thoroughly in a separatory funnel (red color changed to light yellow upon hydrolysis). The layers were separated and the benzene layer was washed with a 150-ml portion of saturated aqueous sodium bicarbonate followed by 150 ml of water, dried ($MgSO_4$), and filtered, and the solvent was removed by rotary evaporation to yield 4.101 g of an orange oil (less tar formation than with H_2SO_4). The oil was chromatographed over 120 g of 80–200 mesh alumina (Matheson Coleman and Bell) by elution with 300 ml of petroleum ether to give a pale yellow oil which solidified on standing (2.726 g, mp 35–46°, 70% yield from *o*-bromobenzyl alcohol). Glpc analysis showed only trace impurities and the nmr spectrum was essentially that of the pure compound. The solid was crystallized from ethanol–water to give white needles (1.389 g, mp 48–50°). The mother liquor was concentrated, crystallized from absolute ethanol and recrystallized from ethanol–water to give desired indene (0.399 g, mp 49–51°). The mother liquors were concentrated to an oil which was chromatographed over silica gel (60 g) with petroleum ether and then crystallized from ethanol–water to give additional indene (0.145 g, mp 49–51.5°) which was combined with the above in the same melting point range to give pentahydrocyclohept[*a*]indene (1.933 g, 50% yield from *o*-bromobenzyl alcohol, lit.[3] mp 50.5–51.5°).

B. 6,7,8,9,10,11-Hexahydro-5*H*-cyclooct[*a*]indene.—*o*-Bromobenzyl alcohol (0.0535 mol) was treated with *n*-butyllithium (0.123 mol) and cyclooctanone (10.08 g, 0.080 mol, 15% molar excess) essentially as described for cycloheptanone above. The crude diol (9.52 g, 76% yield) obtained subsequent to removal of benzyl alcohol and cyclooctanone was treated with boron trifluoride etherate (5.77 g, 0.0407 mol) in hot benzene (407 ml) as described in A above. After 4 hr nmr spectroscopy indicated complete conversion. The solution was diluted with water (100 ml), washed with aqueous sodium bicarbonate, dried ($MgSO_4$), and concentrated to give 8.23 g of yellow oil. The oil was distilled through a short path column, and a center cut (4.86 g, 46% yield from *o*-bromobenzyl alcohol) was collected. Glpc analysis of this product (5 ft × 0.25 in., 20% DC 710 of 60–80 mesh Chromosorb W, 198°, 60 ml/min He, 10 min 24 sec retention time) showed it to be 99% pure hexahydrocyclooct[*a*]indene, $n^{25}D$ 1.5760 (lit.[7] $n^{25}D$ 1.5784). The ir and nmr spectra of this product were identical with those of an authentic sample.[7]

C. 6,7,8,9,10,11,12-Heptahydro-5*H*-cyclonona[*a*]indene.—The product (8.53 g) obtained from *o*-bromobenzyl alcohol (7.60 g, 0.041 mol) and cyclonanone (6.00 g, 0.043 mol) as described above, obtained subsequent to removal of benzyl alcohol and cyclonanone, was treated with boron trifluoride etherate (4.87 g, 0.034 mol) in hot benzene (343 ml). The reaction was monitored by nmr (prolonged heating was found to reduce the yield of indene) and was complete after refluxing for 6.5 hr. The mixture was quenched by pouring the reaction mixture into a separatory funnel containing 350 ml of ice water (vigorous shaking). The layers were separated and the aqueous layer was washed with two

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(7) W. E. Parham and J. K. Rinehart, *ibid.*, **89**, 5668 (1967).

50-ml portions of ether. The combined organic layers were washed with four 100-ml portions of water and two 100-ml portions of saturated aqueous sodium bicarbonate. The solution was dried ($MgSO_4$) and filtered, and the solvent was removed by rotary evaporation to a light orange oil (8.17 g) which was primarily desired indene by nmr. The indene was distilled at 96–97° (0.025 mm) through a short path column to give 5.12 g (59% yield) of a light yellow oil, $n^{19}D$ 1.5769, which was 97% pure by glpc analysis (5 ft × 0.25 in., 20% DC 710 on Chromosorb W 60–80 mesh, 220°, 60 ml/min He, 5 min retention time). The analytical sample was prepared by using preparative glpc.

The distilled indene showed the following spectral properties: ir (neat) 1628 (w, ν C=C), 1609 (w), 1468 (s), 1445 (m), 1395 (m), 760 (s) and 720 cm^{-1} (s); uv max (95% C_2H_5OH) 207 mμ (log ϵ 4.25), 220 (sh, 4.08), 226 (sh, (3.92), 260 (4.12), 266 (sh, 4.08), 270 (sh) (4.02), 286 (sh, 3.16); nmr (20% CCl_4) (with areas relative to 20 protons); τ 2.61–3.16 (with intense peak at 2.89) (m, 3.9, aromatic H), 6.84 (s, 1.9, CH_2 in indene 5 position), 7.27–7.59 (m, 3.7 benzylic CH_2), 7.84–9.24 (with intense peak at 8.53) (m, 10.5, bridge aliphatic CH_2).

Anal. Calcd for $C_{16}H_{20}$: C, 90.50; H, 9.50. Found: C, 90.59; H, 9.78.

D. Use of Sulfuric Acid in Glacial Acetic Acid. 6,7,8,9,10-Pentahydro-5*H*-cyclohept[*a*]indene (4).—The crude alcohol (4.15 g, 0.0189 mol) obtained as described in A above was added to 145 ml of glacial acetic acid (low concentration decreases indane by-product formation) containing concentrated sulfuric acid (1.48 g, 0.015 mol). The reaction was heated to reflux and monitored by nmr (disappearance of $-CH_2O$). After 16 hr, sodium acetate trihydrate (4.1 g, 0.03 mol) was added to neutralize the sulfuric acid. Acetic acid (100 ml) was removed (rotary evaporator) and 100 ml of water was added to the dark oil. The remaining acetic acid in the resulting mixture was neutralized with 10% aqueous sodium hydroxide. The suspension was extracted with two 200-ml portions of petroleum ether and one 200-ml portion of benzene. The combined organic extracts were washed with 300 ml of water, dried ($MgSO_4$), and filtered, and the solvent was removed by rotary evaporation to a black oil (2.34 g). The oil was chromatographed over 80 g of 80–200 mesh alumina (Matheson Coleman and Bell) with 200 ml of petroleum ether as eluent to give a yellow oil (1.50 g, 39% yield from *o*-bromobenzyl alcohol) which was essentially pure pentahydrocyclohept[*a*]indene by nmr spectroscopy. Glpc analysis showed only desired indene with no indan side product present. The oil was crystallized from ethanol (−25°) to give white needles (0.658 g, mp 49.5–51.5°). The mother liquor was concentrated and crystallized from ethanol and then recrystallized from ethanol–water to give white needles (0.248 g, mp 49–51°). The combined mother liquors were concentrated to an oil which was chromatographed over 60 g of 100–200 mesh silica gel. The resulting oil (0.189 g) was crystallized from ethanol–water to white needles (0.091 g, mp 49–51.5°) which were combined with the above in the same melting point range to give pure indene (0.997 g, mp 49–51.5, 26% yield from *o*-bromobenzyl alcohol, lit.[4] mp 50.5–51.5°).

6,7,8,9,10,11,12,13,14,15-Decahydro-5*H*-cyclododec[*a*]indene.—The reaction of *o*-bromobenzyl alcohol (0.0535 mol) and cyclododecanone was carried out as described in B above. The acidic solution (H_2SO_4 in acetic acid) was heated for 22 hr and the crude product (7.20 g) was chromatographed to give 4.62 g (35% yield from *o*-bromobenzyl alcohol) of essentially pure (glpc) decahydrocyclododec[*a*]indene as an oil which crystallized. There was obtained from the oil 3.58 g (26% yield) of decahydrocyclododec[*a*]indene, mp 49–52° (lit.[7] mp 53.5–55°). The ir and nmr spectra were identical with those of an authentic sample.[7]

3-Phenylindene.—The reaction of *o*-bromobenzyl alcohol (0.0535 mol) with acetophenone was carried out as described for other ketones. The crude solid diol (10.85 g) showed only minor impurities (nmr) but was not further characterized. The product was treated first with boron trifluoride etherate (total of 10.10 g, 0.71 mol) for 24 hr in boiling benzene; however, the nmr spectrum of the only product (9.51 g) showed no indene and was consistent with the corresponding cyclic ether. The crude ether was treated with sulfuric acid (3.54 g, 0.036 mol) in hot (reflux temperature) glacial acetic acid (455 ml) for 12 hr as described above. The brown oil (7.16 g) thus obtained was distilled, bp 93–99° (0.03 mm), through a short path column to give 3.62 g (35.2% yield) of a light yellow oil. Glpc analysis (5 ft × 0.25 in., 20% DC 710 on Chromosorb W 60–80 mesh, 210°, 60 ml/min He) with internal standard *n*-octadecane showed the distillate to contain 65.5 wt % (2.37 g, 23%) yield of 3-phenylindene (retention time 6 min 10 sec).

A pure sample of 3-phenylindene was obtained by preparative glpc and had the following properties: refractive index $n^{25}D$ 1.6308 (lit. $n^{20}D$ 1.6320,[8] $n^{24}D$ 1.6313,[9] $n^{18}D$ 1.6357[10]); uv max (95% C_2H_5OH) 204 mμ (log ϵ 4.52), 228 (4.33), 257 (sh, 3.89), 282 (sh, 3.27), 293 (2.87); nmr ($DCCl_3$) (with areas relative to 12 protons) τ 2.22–2.86 (complex multiplet, 9.0, aromatic H), triplet centered at 3.40 (J = 2 Hz, 1.0 proton in 2 position), doublet centered at 6.51 (J = 2 Hz, 2.0 protons in 1 position).

Reaction of 3 with Sulfuric Acid in Formic Acid. Isolation of Indene and By-product Indan.—The cyclic ether **3** (6.53 g, 0.0323 mol) and 52 ml of 88% formic acid (Baker) were added to a 100-ml round-bottom flask equipped with a condenser and magnetic stirrer. Concentrated sulfuric acid (5.9 g, 0.60 mol) was added and the mixture was heated to reflux temperature (reaction mixture turned red). After 30 min at reflux temperature the reaction was quenched by adding it to 75 ml of ice water with stirring. The aqueous mixture was extracted with two 100-ml portions of petroleum ether and one 100-ml portion of benzene. The combined organic extracts were washed with 100 ml of water, 100 ml of saturated aqueous sodium bicarbonate, and 100 ml of water in succession and then dried ($MgSO_4$) and filtered. The solvent was removed by rotary evaporation to 6.31 g of orange oil which showed primarily desired indene and no unreacted ether (benzylic CH_2O) by nmr spectroscopy. The crude oil was chromatographed (fraction analyzed by tlc every 125 ml) over 200 g of 100–200 mesh silica gel (Matheson Coleman and Bell) with petroleum ether as eluent. The first 1.3 l. of eluent were concentrated (rotary evaporation) to a colorless oil (0.259 g, 4.3% yield). The oil was purified by preparative glpc and showed the following properties: refractive index $n^{26}D$ 1.5459; ir (neat), 3050 (w), 3000 (w), 2900 (s), 2832 (s), 1480 (m), 1460 (m), 1440 (w), 1020 (w), 740 cm^{-1} (s); uv max (95% C_2H_5OH) 209 mμ (log ϵ 3.94), 212 (3.94), 217 (sh, 3.87), 253 (sh, 2.77), 260 (2.99), 266 (3.16), 273 (3.21); nmr (5% w/v $DCCl_3$) (with areas relative to 18 protons) τ 2.80 (s, 4.0, aromatic H), 6.43–7.80 (complex, 4.4, benzylic CH_2 and methine CH), 7.80–8.90 (complex, 9.6, bridge CH_2); mass spectrum m/e 186 (parent peak, 58% of base peak), P − 57 (base peak).

This product was identical with that obtained (97% yield) by reduction (absorption of 1 molar equiv of hydrogen) of pentahydrocyclohept[*a*]indene (absolute ethanol, Raney nickel, 22°, 24 hr, 45 psi).

Anal. Calcd for $C_{14}H_{18}$: C, 90.26; H, 9.74. Found: C, 90.52; H, 9.68.

The next 1.9 l. of eluent were concentrated to 2.40 g (40% yield) of yellow oil which crystallized to a solid (mp 44–51°) which yielded white needles of **4** (1.80 g, 30% yield, mp 50.5–52°, lit.[3] mp 50.5–51.5°) upon recrystallization from an ethanol and water mixture at −22°.

Conversion of Pure 1-(*o*-Hydroxymethylphenyl)cycloheptanol (2) to 6,7,8,9,10-Pentahydro-5*H*-cyclohept[*a*]indene. With Polyphosphoric Acid.—A sample of **2** (0.500 g, 2.27 mmol) was added to 9.5 g of polyphosphoric acid (9.5 g, City Chemical) at 22°. The mixture turned dark and the temperature rose to 31°. After 20 min the reaction was hydrolyzed (25 ml ice water). Analysis of the oil (0.428 g), obtained subsequent to washing, drying, and solvent removal, by glpc (5 ft × 0.25 in., DC 710 on Chromosorb W, 60–80 mesh, 210°, 60 ml/min He) with *n*-heptadecane as an internal standard showed the product to contain 29 wt % (0.12 g, 30% yield) of **4** and 26 wt % (0.11 g, 26% yield) of reduced pentahydrocyclohept[*a*]indene (the indan **6**).

With Boron Trifluoride Etherate.—The reaction was carried out as described above in section A using 1.73 mmol of **2** and 1.73 mmol of boron trifluoride etherate in 9 ml of benzene. The reaction progress was followed by glpc analysis (see section A) using *n*-heptadecane as an internal standard (the relative response[11] factors of the cyclic ether **3** and the indene **4** were determined with pure samples). Glpc analysis showed the following prior to reflux: immediately after mixing, **3** (80%), **4** (10%); after 2.5 hr, **3** (88%), **4** (10%). The mixture was heated

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(10) P. A. Plattner, R. Sandrin, and J. Wyss, *Helv. Chim. Acta*, **29**, 1604 (1946).

(11) H. M. McNair and S. J. Bonelli, "Basic Gas Chromatography," Varian Aerograph, Walnut Creek, Calif., 1969, p 150.

to reflux and glpc analysis showed, after 15 min, **3** (60%), **4** (36%), indan **6** (0%); after 2 hr, **3** (14%), **4** (70%), **6** (6%); after 3 hr, **3** (10%), **4** (73%), **6** (7%); after 6 hr, **3** (0%), **4** (68%), **6** (7%).

Additional boron trifluoride etherate (0.260 g, 1.82 mmol) was added to the refluxing solution. Glpc analysis showed a steady decrease in **4** to 18% yield after 13.5 hr with no detectable increase in the amount of indan formation.

With *p*-Toluenesulfonic Acid in Glacial Acetic Acid.—1-(*o*-Hydroxymethylphenyl)cycloheptanol (**2**) (0.270 g, 1.23 mmol), *p*-toluenesulfonic acid monohydrate (0.0534, 0.281 mmol), an internal standard *n*-heptadecane (0.0563 g), and 8 ml of glacial acetic acid were added to a 50-ml two-neck round-bottom flask equipped with magnetic stirrer, condenser, and nitrogen inlet. The solution was heated to reflux temperature and the reaction process was followed by glpc analysis (5 ft × 0.25 in. 20% DC 710 on 60–80 mesh Chromosorb W, 210°, 60 ml/min He) with the following results: after 1 hr, **3** (68%), **4** (31%); after 3 hr, **3** (51%), **4** (40%). No indan by-product (**6**) was observed by glpc.

Reaction with Sulfuric Acid in Glacial Acetic Acid.—Concentrated sulfuric acid (0.09 g, 0.92 mmol) was added to a solution of *o*-(1-cycloheptanol) benzyl alcohol **2** (0.135 g, 0.610 mmol), *n*-heptadecane (0.0563 g) (internal standard) and 8 ml of acetic acid at the reflux temperature. Glpc analysis (5 ft 0.25 in. 20% DC 710 on 60–80 mesh Chromosorb W, 210°, 60 ml/min He) showed, after 5 hr, **3** (20%), **4** (60%); after 17 hr, **3** (0%), **4** (73%). None of the side product **6** was detected by glpc.

Registry No.—**2**, 34219-85-7; **3**, 32921-59-8; **4**, 34219-87-9; **6**, 34219-89-1; 6,7,8,9,10,11,12-heptahydro-5*H*-cyclonone[*a*]indene, 34219-88-0; 3-phenylindene, 1961-97-3

Homogeneous Hydrogen-Transfer Reactions Catalyzed by Tricarbonylchromium Complexes. Hydrogenation of Trienes[1]

E. N. FRANKEL

Northern Regional Research Laboratory,[2] Peoria, Illinois 61604

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Hydrogenating 1,3,5-cycloheptatriene with methyl benzoate-$Cr(CO)_3$ yields a mixture of 1,3-cycloheptadiene and cycloheptene. The formation of 1,3- instead of 1,4-cycloheptadiene is in contrast to the results obtained with acyclic conjugated trienes. Deuteration experiments rule out 1,6 addition and support a mechanism involving 1,4 reduction followed by rapid isomerization of 1,4- to 1,3-cycloheptadiene (1,3-hydrogen-deuterium shift). Catalytic hydrogenation of *trans*-1,3,5-hexatriene with methyl benzoate-$Cr(CO_3)$ yields *cis*-1,4-hexadiene as the most important intermediate, the product expected from 1,4 addition. Hydrogenation of *cis*-1,3,5-hexatriene gives mainly cyclohexene. This product is derived from 1,3-cyclohexadiene formed by thermal cyclization of the cis hexatriene.

The homogeneous hydrogenation of unsaturated compounds continues to be the subject of intensive investigation. A high degree of selectivity is probably the most important practical characteristic of homogeneous hydrogenation catalysts.[3] Our studies of the catalytic activity of arene–$Cr(CO)_3$ complexes have demonstrated a selectivity approaching 100% in the hydrogenation of 1,3 and 1,4 dienes to monoenes.[4] Selectivity, kinetic, and deuterium tracer studies[4c,5] have provided ample evidence for 1,4 addition of hydrogen as the dominant mechanism of reduction catalyzed by these arene–$Cr(CO)_3$ complexes. With 1,4 dienes and monoenes, double-bond isomerization by 1,3-hydrogen shift was indicated.[5b]

Hydrogenation of methyl β-eleostearate (*all-trans*-9,11,13-octadecatrienoate) with these complexes yielded the diene products expected from 1,4 addition (*trans*-9,*cis*-12- and *cis*-10,*trans*-13-octadecadienoates).[6] With α-eleostearate (*cis*-9,*trans*-11,*trans*-13-octadecatrienoate) stereoselective 1,4 reduction producing up to 60% linoleate (*cis*-9,*cis*-12-octadecadienoate) was observed, but concurrent isomerization to β-eleostearate yielded also the corresponding cis,trans-1,4-diene products. This paper reports an extension of these studies to the hydrogenation of 1,3,5-cycloheptatriene and 1,3,5-hexatriene.

Results and Discussion

1,3,5-Cycloheptatriene.—Hydrogenations and deuterations were catalyzed by methyl benzoate–$Cr(CO)_3$ as in earlier work.[4c,5] Figure 1 plots results of kinetic runs with H_2 and D_2. 1,3-Cycloheptadiene was the main initial product detected by glc. Cycloheptene was formed in only minor amounts at 160°, but at 175° it was formed in significant amounts after 1,3-cycloheptadiene reached a maximum concentration of 80%. On the basis of previous work,[5] no significant kinetic isotopic effect would be expected. Identification of 1,3-cycloheptadiene by glc was confirmed by uv and ^1H nmr analyses of the hydrogenation products. That there was no 1,4-cycloheptadiene in the products was demonstrated by the absence of resonance corresponding to the α,α-methylene proton ($C{=}CCH_2C{=}C$) on C-3 (τ 7.20).

The formation of 1,3- instead of 1,4-cycloheptadiene

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(6) (a) Paper 72;[1] (b) E. N. Frankel and F. L. Thomas, *J. Amer. Oil Chem. Soc.*, **49**, 70 (1972).

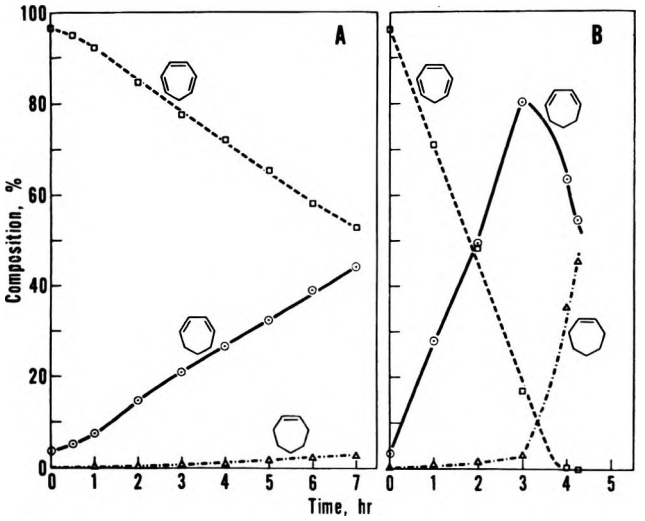
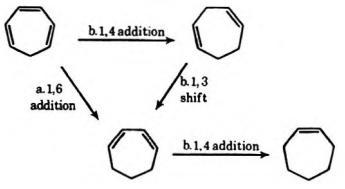


Figure 1.—Catalytic hydrogenation and deuteration of 1,3,5-cycloheptatriene with methyl benzoate–$Cr(CO)_3$: (A) run 1, 9.5 mmol of substrate, 0.5 mmol of catalyst, 50 ml of *n*-hexane, 160°, 30 atm of H_2; (B) run 2, 0.2 mol of substrate, 0.005 mol of catalyst, no solvent, 175°, 30 atm of D_2.

from 1,3,5-cycloheptatriene is in contrast to methyl eleostearate in which 1,4-diene fatty esters are the only initial products of hydrogenation with $Cr(CO)_3$ complexes.[6] Two possible routes can be considered for 1,3,5-cycloheptatriene, namely, (a) 1,6 addition or (b) 1,4 addition followed by rapid isomerization of 1,4- to the more stable 1,3-cycloheptadiene (Scheme I). It has been shown[7] that the 1,3 isomer represents

SCHEME I



nearly 100% of the equilibrium mixture of cycloheptadienes. The internuclear C_1–C_6 distance of the triene system (2.5 Å) and the C_1–C_4 distance of the 1,3-diene system (3.0 Å) of 1,3,5-cycloheptatriene are within 0.5 Å of each other in a model. Therefore, 1,6 addition (a) is not an unlikely path in a cyclic conjugated triene. Deuteration experiments were carried out to examine the two alternative reduction routes (a and b) in greater detail.

The products of run 2 (Figure 1) were separated by preparative glc and the fractions were analyzed at two levels of reduction. Mass spectral analyses showed the deuteration mixture to consist of cycloheptatriene-d_0, cycloheptadiene-d_2, and cycloheptane-d_4. The absence of deuterated cycloheptatriene species after partial reduction demonstrates that no exchange occurs before addition. The absence of d_1 and d_3 species in the reduced products indicates further that no scrambling of deuterium occurred after they are formed. If exchange and scrambling of hydrogen and deuterium do not occur, it is possible to elucidate the reduction mechanism with a reasonable degree of certainty by determining the deuterium distribution in the products. On the one hand, 1,6 addition (a)

(7) R. B. Bates, University of Arizona, personal communication, 1971.

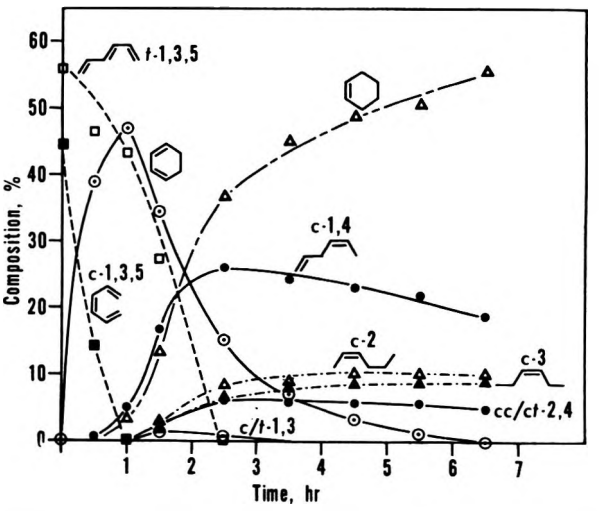
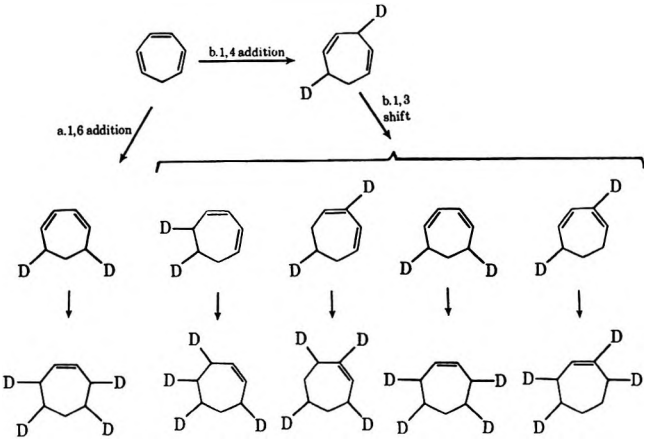


Figure 2.—Catalytic hydrogenation of *cis*- and *trans*-1,3,5-hexatriene (9.5 mmol) with methyl benzoate–$Cr(CO)_3$ (0.5 mmol) in *n*-pentane solution (50 ml) at 170° under 30 atm of H_2.

followed by 1,4 addition would yield 1,3-cycloheptadiene-d_2 with deuterium located all on the α-methylenes and cycloheptene-d_4 with deuterium distributed half on the α-methylenes and half on the β-methylenes (Scheme II). On the other hand, 1,4 addition followed

SCHEME II



by isomerization (b) would yield 1,3-cycloheptadiene-d_2 with deuterium located on the α- (50%) and β- (25%) methylenes and on the vinyl carbons (25%). It is assumed here that 1,4-cycloheptadiene-d_2 is formed as a reactive intermediate which undergoes rapid isomerization to 1,3-cycloheptadiene-d_2 by a 1,3 shift involving both hydrogen and deuterium in equal amounts. Further reduction of 1,3-cycloheptadiene-d_2 by 1,4 addition would yield cycloheptene-d_4 with deuterium located on the α- (50%) and β- (37.5%) methylenes and on the vinyl carbons (12.5%).

The deuterium distribution in the products determined by ^2H nmr is shown in Table I. The results are consistent with a mechanism involving reduction of 1,3,5-cycloheptatriene by 1,4 addition followed by isomerization (b). The direct 1,6-addition path (a) is ruled out by these results. These deuteration experiments have afforded a way of establishing the formation of an intermediate (1,4-cycloheptadiene) which is too reactive to be determined directly by standard techniques such as glc, uv, and ^1H nmr. The inter-

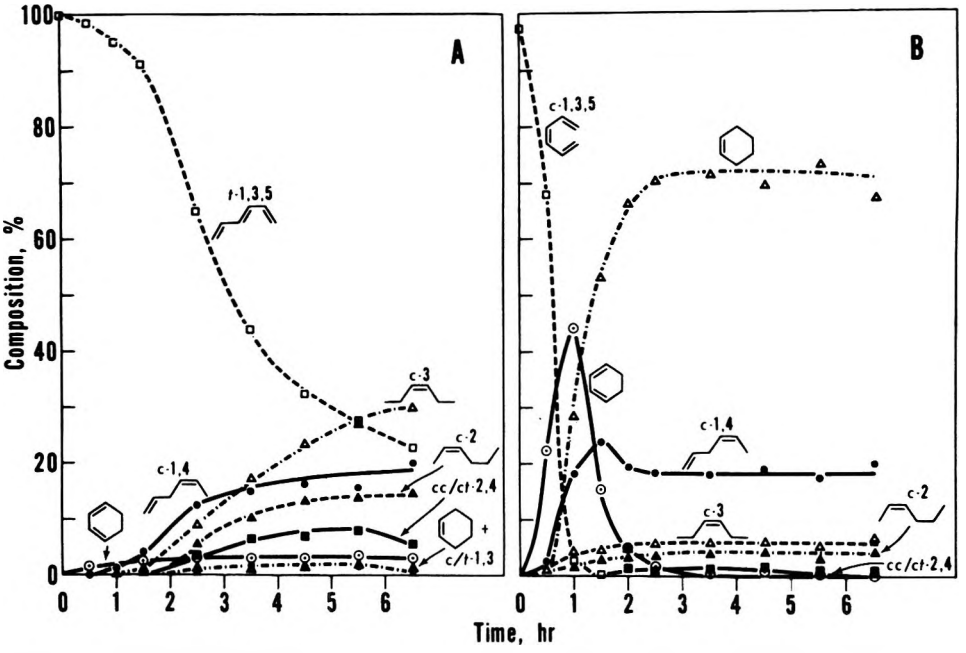


Figure 3.—Catalytic hydrogenation of (A) *trans*-1,3,5-hexatriene (1 mmol) and of (B) *cis*-1,3,5-hexatriene (1 mmol), with methyl benzoate–$Cr(CO)_3$ (0.05 mmol) in *n*-pentane solution (25 ml) at 160° under 30 atm of H_2.

TABLE I

DEUTERIUM DISTRIBUTION BY ^2H NMR

Deuterium in following positions[a]	1,3-Cycloheptadiene-d_2,[b] % After 2 hr	After 4 hr	Calcd[c] 1,6 Addn	Calcd[c] 1,4 Addn	Cycloheptene-d_4,[b] % After 4 hr	Calcd[c] 1,6 Addn	Calcd[c] 1,4 Addn
α-Methylene	40	45	100	50	50	50	50
β-Methylene	25	25		25	40	50	37.5
Vinyl carbon	35	30		25	10		12.5

[a] α-Methylene CDC=C, δ_{CDCl_3} 76–80 cps; β-methylene $CDCH_2C$=C, 80–84; vinyl CD=C, 22. [b] Fractions separated by preparative glc (run 2, Figure 1B). [c] See Scheme II, (a) 1,6 addition, (b) 1,4 addition followed by 1,3 shift.

mediate 1,4 dienes from noncyclic conjugated trienes are stable and their formation from methyl eleostearate has been established.[6] Further evidence of 1,4 diene formation from 1,3,5-hexatriene is reported below.

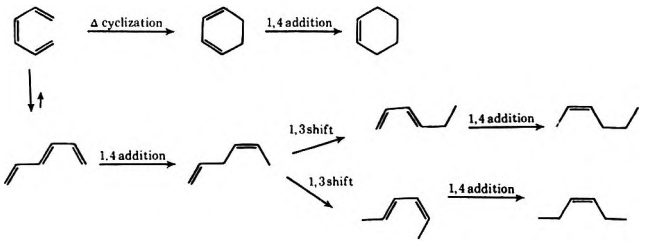
1,3,5-Hexatriene.—This simplest of acyclic conjugated trienes provided a suitable model. Rate studies with a mixture of *cis*- and *trans*-1,3,5-hexatriene showed the cis isomer to be more rapidly converted with methyl benzoate–$Cr(CO)_3$ than the trans isomer (Figure 2). 1,3-Cyclohexadiene and cyclohexene were important cyclic products. Acyclic products included *cis*-1,4-hexadiene, *cis,cis*- and *cis,trans*-2,4-hexadienes, and *cis*-2- and *cis*-3-hexenes. *cis*- and *trans*-1,3-hexadienes were also formed in minor amounts initially. 1,3-Cyclohexadiene is the product expected from cyclization of *cis*-1,3,5-hexatriene and *cis*-1,4-hexadiene, the product expected from 1,4 reduction of *trans*-1,3,5-hexatriene. 1,3-Cyclohexadiene is the valence tautomer of *cis*-1,3,5-hexatriene resulting from a Cope-type cyclization which is known to be a facile thermal reaction.[8] Control experiments demonstrated that this cyclization of *cis*-1,3,5-hexatriene occurs readily and irreversibly in the absence of catalyst. In a mixture of *cis*- and *trans*-1,3,5-hexatriene, complete conversion of the cis isomer to 1,3-cyclohexadiene occurred within 0.5–1 hr at 170° under either nitrogen or hydrogen pressure. Since the relative concentration of trans isomer remained unchanged, no cis → trans isomerization took place under these conditions. When pure 1,3-cyclohexadiene was heated under the same conditions, no ring opening was observed either.

To elucidate the reaction course further, *cis*- and *trans*-1,3,5-hexatriene were separated and purified by preparative glc and hydrogenated separately. Hydrogenation of pure *trans*-1,3,5-hexatriene proceeded as expected by 1,4 addition and yielded predominantly *cis*-1,4-hexadiene as the most important intermediate (Figure 3A). Other dienes included in decreasing concentration 2,4-hexadiene, 1,3-cyclohexadiene, and 1,3-hexadienes. The monoenes were composed of *cis*-3- and *cis*-2-hexenes, together with minor amounts of cyclohexene. Since cyclohexadiene would be derived from cyclization of *cis*-1,3,5-hexatriene, this evidence indicates that a trans → cis isomerization of hexatriene occurs to a small, but significant, degree. Hydrogenation of *cis*-1,3,5-hexatriene (97% pure) resulted in cyclization as the main reaction (Figure 3B). 1,3-Cyclohexadiene reached a maximum of 45% within 1 hr and was rapidly converted to cyclohexene, which leveled off at 70–73%. Cyclization was accompanied by 1,4 reduction as evidenced by the formation of *cis*-1,4-hexadiene, which peaked at 25% and leveled off at 18%. The corresponding conjugation and reduction products were observed (2,4-hexadiene, 2- and 3-hexenes).

These results clearly support the reaction sequence in Scheme III. On the one hand, cyclization of *cis*-1,3,5-hexatriene is followed by 1,4 reduction of 1,3-cyclohexadiene. On the other hand, hydrogenation of *trans*-1,3,5-hexatriene by 1,4 addition is followed by isomerization of *cis*-1,4-hexadiene to a mixture of 1,3- and 2,4-hexadienes, which are in turn reduced to *cis*-2- and *cis*-3-hexenes, respectively. There is also clear evidence for an equilibration between *trans*- and *cis*-1,3,5-hexatrienes that favors the trans isomer.

(8) (a) K. E. Lewis and H. Steiner, *J. Chem. Soc.*, 3080 (1964); (b) D. S. Glass, J. W. H. Watthey, and S. Winstein, *Tetrahedron Lett.*, 377 (1965); (c) E. N. Marvell, G. Caple, and B. Schatz, *ibid.*, 385 (1965); (d) E. Vogel, W. Grimme, and E. Dinne, *ibid.*, 391 (1965).

SCHEME III



Evidence for this type of geometric isomerization has already been observed with α- and β-eleostearate.[6] Equilibrium K (trans/cis) values of 3.97 (0°) and 2.97 (5°) were reported[9] for the iodine-catalyzed isomerization of 1,3,5-hexatriene. We have also reported on the reduction by 1,4 addition of 1,3-cyclohexadiene and 1,4-hexadiene[4c] and on the isomerization of 1,4 dienes[5b,10] catalyzed by $Cr(CO)_3$ complexes. The mechanisms advanced involve a diene–$H_2Cr(CO)_3$ intermediate in the 1,4 addition, and allyl–$HCr(CO)_3$ or pentadienyl–$HCr(CO)_3$ intermediates in the isomerizations by 1,3-hydrogen shift. The catalytic isomerization of *trans*-1,4-hexadiene occurred much more readily than that of *cis*-1,4-hexadiene, and steric hindrance was invoked in the pentadienyl hydride intermediate from the cis isomer.[10] The same steric hindrance in the hydride complex from the *cis*-1,4-hexadiene intermediate would account for its slow rate of hydrogenation and the slow conversion of its precursor, *trans*-1,3,5-hexatriene.

Experimental Section

Materials.—The catalyst methyl benzoate–$Cr(CO)_3$ was purchased (Strem Chemicals, Inc.).[11] Cycloheptatriene (Chemical Samples Co.) was distilled and chromatographed through a short alumina column. It was 98% pure by glc on a 1,2,3-tris(2-cyanoethoxy)propane (TCEP) column. An unidentified impurity (2%) was inert under hydrogenation conditions. 1,3,5-Hexatriene (Aldrich Chemical Co., K & K Laboratories, Inc.) was pure by glc and consisted of 56–64% trans and 36–44% cis isomers (TCEP column). Isomer identification was based on glc after reaction with iodine and maleic anhydride.[12] The cis and trans isomers were separated by preparative glc on a β,β′-oxydipropionitrile (ODPN) column (14 ft × 0.25 in.; 20% on Chromosorb W, 60–80 mesh). The trans fraction, which emerged first, was pure (by glc on an ODPN column). The cis fraction (97%) contained 3% trans isomer. Other hydrocarbons of high-purity grade used for identification were purchased (Chemical Samples Co.).

Hydrogenation and Separation.—The hydrogenation and deuteration procedures were the same as before.[4c,5] Products from from cycloheptatriene deuteration were first distilled and then separated by preparative glc on a Carbowax 20M column (8 ft × 0.25 in.; Chromosorb W, 60–80 mesh; 20% liquid phase). Control runs were made to check the thermal valence isomerization of *cis*-1,3,5-hexatriene. A 44:56% mixture of *cis*- and *trans*-1,3,5-hexatriene (1 g) in *n*-pentane (50 ml) was heated in a 150-ml autoclave at 170° in the absence of catalyst. In one run under hydrogen pressure (200 psi), the cis isomer was completely converted to 1,3-cyclohexadiene during a heat up of 30 min and the trans isomer was left unchanged. In another run under nitrogen pressure (50 psi), this conversion occurred within 1 hr after the temperature of the reaction mixture was reached. When pure 1,3-cyclohexadiene was heated under the same conditions, no formation of *cis*-1,3,5-hexatriene was observed within 6 hr.

Analyses.—Analyses and product identification were carried out by glc on three different columns (TCEP, ODPN, and Carbowax 20M) as before.[4c] The uv spectrum (cyclohexane) of a fraction distilled from partially hydrogenated cycloheptatriene (glc analysis: 26.5% cycloheptatriene, 70.8% cycloheptadiene, and 2.7% cycloheptene) showed a maximum at 247.5 nm (ε 6125) due to 1,3-cycloheptadiene [lit.[13] λ_{max} 248 nm (ε 7150)] and a shoulder at 265 nm due to unreacted 1,3,5-cycloheptatriene.

Mass spectral analyses of deuterated products were done on a Nuclide 12-90-DF mass spectrometer at 70 eV with a 150° metal inlet. Deuterium analyses were calculated as atoms per molecule in excess of natural abundance. The mass spectrum of 1,3,5-cycloheptatriene obtained by preparative glc (Carbowax 20M column) after partial reduction with D_2 (Figure 1B, 2 hr) was the same in the parent peak region as that of the starting material. It contained, therefore, no deuterium (cycloheptatriene-d_0). 1,3-Cycloheptadiene was separated by preparative glc from deuteration mixtures after 2 hr and 4 hr and cycloheptene was separated after 4 hr (Figure 1B). Fractions of deuterated 1,3-cycloheptadiene had an M peak of 96 corresponding to cycloheptadiene-d_2. Relative isotopic peaks, d_0, d_1, d_2, and d_3 were of the same order of intensity or below the corresponding peaks M − 2, M − 1, M, and M + 1 in a nondeuterated 1,3-cycloheptadiene standard. The deuterated cycloheptene fraction had an M peak of 100 corresponding to cycloheptene-d_4. Relative isotopic distribution d_3, d_4, and d_5 was of the same order of magnitude as the distribution M − 1, M, and M + 1 in nondeuterated cycloheptene.

^1H nmr spectra ($CDCl_3$, 100 MHz, in τ values relative to tetramethylsilane) showed the following resonances in 1,3-cycloheptadiene fractions: τ 8.16 (β-methylene, 2 H), 7.72 (α-methylene, 4 H), 4.34 (vinyl, 4 H) [1,4-cycloheptadiene reference:[14] τ 7.82 (α-methylene, 4 H), 7.20 (α,α-methylene), 4.35 (vinyl 4 H)]. ^2H nmr spectra ($CDCl_3$, 15.4 MHz in cycles per second relative to $CDCl_3$) showed three resonances: in 1,3-cycloheptadiene-d_2 fractions, δ 83.6 (D on β-methylene, $CDCH_2$-C=C), 75.8 (D on α-methylene CDC=C), and 22.3 (D on vinyl carbon, –CD=C–); in cyclohexene-d_4, δ 88.1 (D on β-methylene), 79.6 (D on α-methylene), and 22.1 (D on vinyl carbon). Relative magnitude of these deuterium resonances are reported in Table I.

Registry No.—1,3,5-Cycloheptatriene, 544-25-2; *cis*-1,3,5-hexatriene, 2612-46-6; *trans*-1,3,5-hexatriene, 821-07-8.

Acknowledgment.—The author is grateful to Professor R. B. Bates, University of Arizona, for the reference 1,3- and 1,4-cycloheptadienes[14] and for helpful discussions; to W. K. Rohwedder for mass spectral analyses; and to C. A. Glass for nmr analyses.

(9) C. W. Spangler, *J. Org. Chem.*, **31**, 346 (1966).

(10) E. N. Frankel, *J. Catal.*, **24**, 358 (1972).

(11) The mention of firm names or trade products does not imply that they are endorsed or recommended by the Department of Agriculture over other firms or similar products not mentioned.

(12) C. W. Spangler and G. F. Woods, *J. Org. Chem.*, **30**, 2218 (1965).

(13) A. P. TerBorg and A. F. Bickel, *Recl. Trav. Chim. Pays-Bas*, **80**, 1229 (1961).

(14) R. B. Bates, W. H. Deines, D. A. McCombs, and D. E. Potter, *J. Amer. Chem. Soc.*, **91**, 4608 (1969), especially footnote 9.

A Comparative Study of Some Reactions of Dimethylvinylidene and Dimethylmethylidene

TIMOTHY B. PATRICK,*[1] EDWARD C. HAYNIE, AND W. J. PROBST

Faculty of Chemistry, Southern Illinois University, Edwardsville, Illinois 62025

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Dimethylvinylidene and dimethylmethylidene have been compared with respect to their addition reactions with styrenes and insertion reactions into several R-H bonds in aprotic solvents. The results show that dimethylvinylidene is much more reactive than dimethylmethylidene in addition reactions with styrenes under the conditions used. Attention is brought to sight of a possible alkyl substituent effect in the insertion of alkylvinylidenes into Si-H bonds. Relative rates for thermal conversion of 1-(2-methylprop-1-enylidene)-2-phenylcyclopropanes to 1-isopropylidene-2-methylene-3-phenylcyclopropanes were determined and used as additional support for a radical mechanism for the thermal rearrangement. An attempt to prepare 1-lithio-1-bromo-3-methyl-1,2-butadiene, a possible precursor to dimethylvinylidene carbene, was not successful. A useful method for preparing 1,2-dibromo-3-methyl-1,3-butadiene is reported.

Reactions which proceed by transfer of an unsaturated divalent carbon intermediate to various substrates have received much attention.[2] We have directed our attention to a study which would allow some comparisons to be made between the reactivities of dimethylvinylidene A[3] and dimethylmethylidene B.[3] Our aim was to compare the reactivities of A and B in aprotic media with regard to their addition reactions with styrenes and insertion reactions into C–H and metal–H bonds. In addition, we sought to generate and identify an organometallic intermediate which could be a precursor or directly responsible for reactions of A. The results of our studies are the subject of this paper.

$(CH_3)_2C{=}C{=}C:$ A $(CH_3)_2C{=}C:$ B

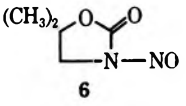
Results and Discussion

Dimethylvinylidene (A) was generated from 1-bromo-3-methyl-1,2-butadiene (**1**)[4] and trapped with para-substituted styrenes (**2a–c**) to give 1-(2-methylprop-1-enylidene)-2-phenylcyclopropanes (**3a–c**)[5] in approximately 30% yields.

$(CH_3)_2C{=}C{=}CHBr$ (**1**) $CH_2{=}CHPhR$ (**2a**, R = H; **b**, R = CH_3; **c**, R = Cl) $(CH_3)_2C{=}C{=}C{-}C(CPhR)$ (**3a**, R = H; **b**, R = CH_3; **c**, R = Cl)

Dimethylmethylidene (B) was obtained from 1,1-dibromo-2-methylpropene (**4**)[6] or 1-bromo-2-methylpropene (**5**)[7] and trapped with **2a–c** to give 2-phenylisopropylidenecyclopropanes (**7a–c**) in 11–20% yields. Compounds **7a–c** have been previously reported by the reaction of B generated from 5,5-dimethyl-*N*-nitroso-2-oxazolidone (**6**)[2d] with **2a–c**.

$(CH_3)_2C{=}CBr_2$ **4** $(CH_3)_2C{=}CHBr$ **5**



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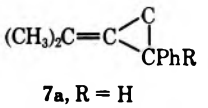


7a, R = H; **b**, R = CH_3; **c**, R = Cl

Relative rates of reaction of both A and B with styrenes were obtained by generating A from **1** or B from **4** and **5** in the presence of large excesses of the styrenes. The molar amounts of products from A were determined by mass spectrometry. The actual products analyzed were **8a–c**, which occur from rearrangement of **3a–c**, respectively[14] (see later discussion). The molar amounts of products from B were determined by vpc analysis. The results are given in Table I.

TABLE I

RELATIVE RATES OF ADDITION OF DIMETHYLVINYLIDENE AND DIMETHYLMETHYLIDENE TO STYRENES[a]

Styrene	$(CH_3)_2C{=}C{=}C:$[b]	$(CH_3)_2C{=}C:$[c]	$(CH_3)_2C{=}C:$[d]	$(CH_3)_2C{=}C:$[e]
p-H	1.0	1.0	1.0	1.0
p-CH_3	1.9	21	19	12
p-Cl	0.78	0.34	0.32	0.42
ρ[f]	−0.95	−4.3	−4.3	−3.4

[a] The approximate error is ±5%. [b] Generated from 1 (heterogeneous reaction). [c] Generated from 4 (homogeneous reaction). [d] Generated from 5 (heterogeneous reaction). [e] Data taken from ref 2d where B was generated from 6 (homogeneous reaction). [f] From Hammett equation using σ^+ values.

Certain points regarding the reactivities of A and B can be made from inspection of the data in Table I. The Hammett ρ values show that both A and B are reacting as electrophiles.[8] The ρ values for B indicate that B is sensitive to the substituents on the phenyl ring, whereas the low ρ value for A shows that the substituents influence the reactivity of A very little. The low electrophilic nature of A found here in *aprotic* media is in sharp contrast to the high polar character found for A in *protic* solvents.[9] Thus one should expect to

(1) Address correspondence to this author.

(2) For some leading references see (a) W. Kirmse, "Carbene Chemistry," Academic Press, New York, N. Y., 1964, pp 67–75; (b) M. S. Newman and A. O. M. Okorodudu, *J. Org. Chem.*, **34**, 1220 (1969); (c) H. D. Hartzler, *J. Amer. Chem. Soc.*, **93**, 4527 (1971); (d) M. S. Newman and T. B. Patrick, *ibid.*, **91**, 6461 (1969); (e) J. C. Gilbert and J. R. Butler, *ibid.*, **92**, 7493 (1970).

(3) The chemistry of A has been described as carbene chemistry.[2c] The actual nature of A in *aprotic* media has been questioned by W. J. le Noble, Y. Tatsukani, and H. F. Morris, *ibid.*, **92**, 5681 (1970). The intermediate described by B is also questionable.[2d,e] We prefer to name both A and B in a manner which is noncommital as to the actual nature of the intermediate. Thus the names dimethylvinylidene and dimethylmethylidene do not infer carbene or organometallic character to the intermediates involved.

(4) D. K. Black, S. R. Landor, A. N. Patel, and P. F. Whiter, *Tetrahedron Lett.*, 483 (1963).

(5) S. R. Landor and P. F. Whiter, *J. Chem. Soc.*, 5625 (1966).

(6) H. D. Hartzler, *J. Amer. Chem. Soc.*, **86**, 526 (1964).

(7) M. Tanabe and R. A. Walsh, *ibid.*, **85**, 3522 (1963).

(8) H. H. Jaffe, *Chem. Rev.*, **53**, 191 (1953).

(9) W. le Noble *J. Amer. Chem. Soc.*, **87**, 2434 (1965).

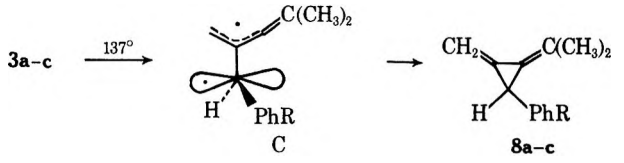
find the reactions of A to be influenced to a large extent by the nature of the solvent in which A is generated. The reactions of A and B reported by us are carried out in the same solvent system (styrene). The comparisons made between A and B are therefore valid.

The reactivity of B is nearly the same when B is generated homogeneously from **4** or heterogeneously from **5**. Although care should be exercised when comparing heterogeneous reactions, it appears as if the cation has little effect on the reactivity of B (Li^+ in **4**, K^+ in **5**). However, comparison of homogeneously generated B from both **4** and **6** where the cation is the same (Li^+) shows that the leaving group does affect the reactivity of B (Br^- in **4**, N_2 in **6**).[10]

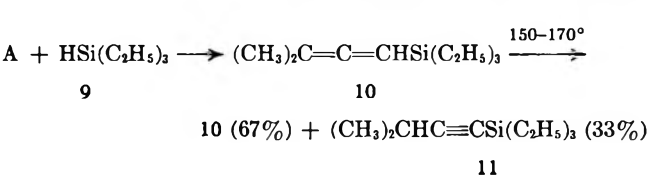
There have been no reports of A being generated homogeneously in *aprotic* media. However, where comparisons of the reactivity of A from various precursors in heterogeneous media have been made, it is found that the cation and leaving group have little effect on the reactivity of A.[11,12]

For completeness in comparing the reactions of A and B we repeat here the already known facts that steric effects from substituents on A are small[12] whereas the substituents attached to B influence the reactions of B very markedly.[13]

We mentioned earlier in this paper that the analysis for products **3a–c** were carried out by mass spectrometry and that the products actually analyzed were 1-isopropylidene-2-methylene-3-phenylcyclopropanes (**8a–c**) which are formed by thermal rearrangements of **3a–c**.[14–16] This rearrangement was determined to occur quantitatively under the mass spectrometric conditions used. The mechanism of this rearrangement is considered to proceed through the nonplanar diradical C.[17,18] Having samples of **3a–c** on hand, we measured their rates of rearrangement to **8a–c** at 137°. (See Experimental Section.) The relative rates of rearrangement of **3a** (1.0), **3b** (1.1), and **3c** (1.3) give additional support for a radical mechanism.[19]



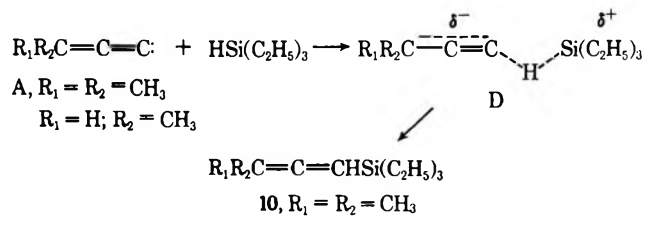
Reaction of A with triethylsilane (**9**) gave 1-(triethylsilyl)-3-methyl-1,2-butadiene (**10**) in 68% yield. Compound **10** underwent a thermal protrotropic rearrangement at 150–170° to give a 2:1 equilibrium mixture of **10** and 1-(triethylsilyl)-3-methyl-1-butyne (**11**).



The reaction of A with **9** is the first example of a dialkylvinylidene insertion reaction. A recent communication has reported the insertion of monoalkylvinylidene into Si–H and certain activated C–H bonds.[20] The fact that A inserts into **9** in 68% yield whereas methylvinylidene[20] inserts into **9** in 29% yield is of particular significance regarding vinylidene insertion reactions if these yields are a true reflection of the reactivity of the vinylidene involved. Insertion reactions of the highly electrophilic dichlorocarbene[21] into Si–H[22,23a] and C–H[23b,c] bonds have been postulated as proceeding by a concerted three-centered mechanism which may have some polar character.[23a,c]

Disubstituted vinylidenes have shown nearly the same reactivity regardless of their method of preparation.[10] The yield of Si–H insertion product from dimethylvinylidene (68%) compared with the yield of insertion product for methylvinylidene (29%)[20] suggests that the substituents cause vinylidenes to have *different* reactivity.

We offer here a suggestion as to reactivity differences which could occur in vinylidene insertion reactions. Reaction of the electrophilic vinylidene with a silicon hydride involve a transition state (D) which has dipolar character in which the negative portion of dipolar character in which the negative portion of the dipole is spread over the allylic system. Increasing alkyl substitution should lead to a decrease in the stability of the negatively charged part of the transition state.[24] Thus a difference in the reactivity of disubstituted alkyl vinylidenes *vs.* monosubstituted alkyl vinylidenes is to be expected. Our suggestion concerning the reactivity differences is based now on yield differences. We are presently testing the suggestion by obtaining more quantitative data. Similar dipolar mechanisms have been used to explain divalent carbon insertion into Si–H bonds.[12,23a]



We were unable to find products from insertion of A in C–H bonds of cumene or the Sn–H bond of tri-*n*-butyltin hydride. Insertion of methylidenes into Si–H bonds are well known.[12] Methylidenes are known to undergo intramolecular[25] C–H insertion and inter-

(10) The general reaction sequence for generation of unsaturated divalent carbon is $RRC{=}CLK \xrightarrow{MN} RRC{=}CLM \xrightarrow{-ML} RRC{=}C:$, where L is the leaving group, K is a proton or halogen, M is the cation portion of a strong base N, and R is an alkyl or R-substituted vinyl group.

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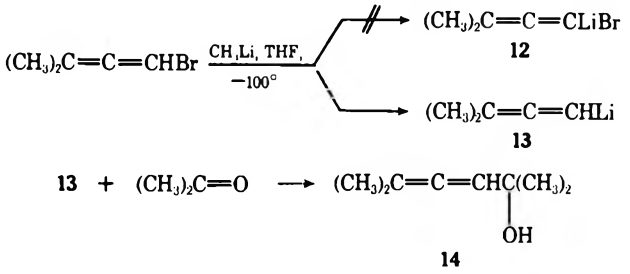
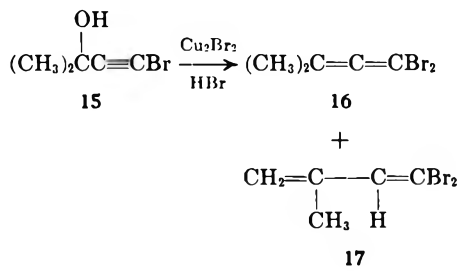
molecular C–H insertion when the methylidene is especially reactive.[2e]

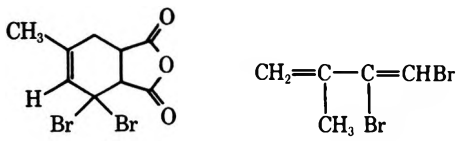
The extensive work reported by Kobrich[26] on the preparation and trapping of 1-lithio-1-haloethylene derivatives by reaction of vinyl halides with organolithium reagents in tetrahydrofuran (THF) at −100° prompted us to attempt the preparation and trapping of 1-lithio-1-bromo-3-methyl-1,2-butadiene (**12**) by treating **1** with methyllithium in THF at −100° followed by trapping with acetone. The only characterizable product from this attempt was 2-hydroxy-2,5-dimethyl-3,4-hexadiene (**14**), indicating that the reaction had proceeded by halogen–metal exchange to produce **13** which reacted with the acetone. No spectral evidence was found for the presence of a product resulting from **12**.



Efforts were made to synthesize 1,1-dibromo-3-methyl-1,2-butadiene (**16**), which could yield **12** on low-temperature treatment with methyllithium. The method used to prepare **16** was treatment of 1-bromo-3-methyl-1-butyne (**15**)[27] with Cu_2Br_2–HBr in a manner similar to that for the preparation of **1**.[4] The products from this reaction were a mixture of **16** (10%) and 1,1-dibromo-3-methyl-1,3-butadiene (**17**, 52%). On standing for seveal hours at room temperature, this mixture converted entirely to **17**. We were unable to isolate pure **16**.



The structure of **17** was based on its method of preparation, its Diels–Alder maleic anhydride adduct (**18**), and its nonidentity with isomeric 1,2-dibromo-3-methyl-1,3-butadiene (**19**), prepared by a reported procedure.[28]



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Experimental Section[29]

Competitive Reactions with Styrenes. A. Dimethylvinylidene (A).—The method of Landor and Whiter[5] was used to generate dimethylvinylidene.

A stirred mixture containing 0.06 mol each of *p*-chlorostyrene, *p*-methylstyrene, and styrene and 0.006 mol of 1-bromo-3-methylbuta-1,2-diene (**1**) was cooled to −10° in a nitrogen atmosphere. *tert*-BuOK·*tert*-BuOH (0.006 mol) was added all at once. After stirring at −10° for 45 min, the mixture was filtered and analyzed directly by mass spectrometry to determine the molar amounts of **8a–c** present.

The mass spectra of **3a–c** were identical with their respective rearrangement products **8a–c**. Thus rearrangement occurred quantitatively under the mass spectrometer conditions used. Mass spectra[30] were recorded on mixtures containing known molar quantities of **8a–c** and the respective styrenes.

Intensities of the ions at *m/e* 155 (**8a**), 184 (**8b**), and 189 (**8c**) were found to serve as reliable measures of the molar quantities of products present. Values of molar quantities found by mass spectrometry were within 0.1% of the value expected from several standard mixtures.

Relative rates were obtained from the expression $k_2/k_1/k_0 = P_2/P_1/P_0$, where k's are the rate constants and P's are the molar amounts of products present. The values reported in Table I are an average of three runs.

B. Dimethylmethylidene (B) from 1,1-Dibromo-3-methylpropene (4).—To a stirred mixture of 0.1 mol of *p*-chlorostyrene (or *p*-methylstyrene), 0.1 mol of styrene, and 0.01 mol of **4**[6] (bp 154–156°) at −40° under nitrogen was added 10 ml (0.01 mol) of 1.0 *N* ethereal methyllithium. The mixture was stirred for 1 hr and then poured into water. The organic products were extracted into ether, washed with saturated sodium chloride solution, and dried by filtration through anhydrous magnesium sulfate. Most of the ether was removed by distillation and the remaining liquid was analyzed by vpc. A 5 ft × 0.25 in. column of 20% FFAP on Chromosorb W, 60–80 mesh at 150° and nitrogen flow of 60 ml/min, was used for separation on an Aerograph Model A-705 flame ionization gas chromatograph. Peak areas were standardized with solutions of known molar amounts of the products. Relative reactivities were determined from the expression $k/k_0 = P/P_0$, where P is the moles of products from competing substituted styrene (**7b** and **7c**) and P_0 is the moles of products formed from styrene (**7a**).

C. Dimethylmethylidene (B) from 1-Bromo-2-methylpropene (5).—A mixture of 0.1 mol of substituted styrene, 0.1 mol of styrene, and 0.01 mol of *tert*-BuOK·*tert*-BuOH at −10° under nitrogen was treated dropwise with 0.01 mol of **5**[7] during 30 min. The mixture was stirred for an additional 1 hr at 0° and poured into water, and the organic products were extracted into ether. After drying, the ether was removed and the products were analyzed by vpc according to the method described in part B.

1-(2-Methylprop-1-enylidene)-2-phenylcyclopropane (3a) was obtained in 35% yield by treating styrene with 1-bromo-3-methylbuta-1,2-diene and *tert*-BuOK·*tert*-BuOH according to the procedure described by Landor and Whiter.[4]

1-(2-Methylprop-1-enylidene)-2-(4-chlorophenyl)cyclopropane (3c) was prepared in 30% yield by the above procedure[4] except that 4-chlorostyrene was used: bp 98–99° (0.5 mm); $n^{26}D$ 1.5681; ir (neat) 2020 cm^{-1} (allene); nmr (CCl_4) multiplets at τ 2.65 and 2.82 (4 H, aromatic), 7.3 (1 H, four peaks, CH), 7.8–9.0 with a sharp peak at 8.20 (8 H, CH_2 and CH_3). *Anal.* Calcd for $C_{13}H_{15}Cl$: C, 76.1; H, 6.3; Cl, 17.6. Found: C, 76.3; H, 6.3; Cl, 17.3.

1-(2-Methylprop-1-enylidene)-2-(4-methylphenyl)cyclopropane (3b) was prepared as above in 49% yield except that 4-methylstyrene was used: bp 90–92° (0.4 mm); $n^{25}D$ 1.5509; ir (neat) 2020 cm^{-1} (allene); nmr (CCl_4) τ 3.05 (4 H, s, aromatic CH_3), 7.29 (1 H, four peaks, CH), 7.82 (3 H, s, CH_3) 8.0–9.0 with sharp singlet at 8.20 (8 H, CH_2 and CH_3). *Anal.* Calcd for $C_{14}H_{16}$: C, 91.8; H, 8.2. Found: C, 91.6; H, 8.1.

(29) All temperature readings are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Nmr spectra were recorded on a Varian T-60 spectrometer using tetramethylsilane as an internal standard (τ 10). Ir spectra were recorded on a Perkin-Elmer Model 337 grating spectrometer. Spectra were calibrated with polystyrene film.

(30) A Varian M-66 mass spectrometer was used. We thank Dr. P. Gaspar, Chemistry Department, Washington University, St. Louis, Mo., for making arrangements for us to use the instrument.

Thermal Rearrangements of 1-(2-Methylprop-1-enylidene)-2-phenylcyclopropanes (3a–c). Method A.—A solution of 1.0 g of 1-(2-methylprop-1-enylidene)-2-arylcyclopropane and 10 ml of mesitylene was heated under reflux (163°) for 2 hr. The infrared spectrum showed complete absence of allene absorption at 2020 cm^{-1}. The product was isolated by short path distillation. Vpc analysis of the mesitylene solutions prior to distillation showed the presence of solvent, rearranged product, and less than 1% of unidentified materials which had long retention times. Isolated yields follow: **8a**, 89%; **8b**, 96%; **8c**, 91%.

Method B.—A 50-μl sample of **3a**, **b**, or **c** was injected onto a 5 ft × 0.25 in. column of 20% SE-30 on Chromosorb W (60/80) at 170°. The eluent was collected at −60°. In all cases, more than 45 μl (90%) of product was collected. Nmr and vpc analysis showed the material to be completely homogeneous.

The following physical and analytical properties were found. **8a**: bp 70–71° (0.25 mm); ir (neat) 1795 and 1740 cm^{-1};[31] nmr ($CDCl_3$) τ 2.84 (5 H, s, aromatic), 4.60 and 4.80 (1H each, rounded, vinyl), 7.00 (1 H, broad, benzylic), 7.97 and 8.12 (3 H each, broad singlets, CH_3). *Anal.* Calcd for $C_{13}H_{14}$: C, 91.7; H, 8.3. Found: C, 91.6; H, 8.3. **8b**: bp 98–99° (0.25 mm); ir (neat) 1800 and 1730 cm^{-1};[30] nmr ($CDCl_3$) τ 3.00 (4 H, aromatic), 4.46, 4.83 (1 H each, vinyl), 7.10 (1 H, broad, benzylic), 7.78 (3H, *p*-CH_3), 8.06, 8.17 (3 H each, allylic CH_3). *Anal.* Calcd for $C_{14}H_{16}$: C, 91.8; H, 8.2. Found: C, 92.0; H, 8.1. **8c**: bp 89–90° (0.25 mm); ir (neat) 1800 and 1740 cm^{-1};[31] nmr τ 2.5–3.0 (4 H, m, aromatic), 4.60, 4.75 (1 H each, vinyl), 7.10 (1 H, broad, benzylic), 7.95, 8.10 (3 H each, CH_3). *Anal.* Calcd for $C_{13}H_{13}Cl$: C, 76.1; H, 6.3; Cl, 17.6. Found: C, 76.0; H, 6.4; Cl, 17.7.

Rearrangement Rates for 3a–c.—The 2-phenylalkenylidenecyclopropanes were mixed with dry mesitylene to give solutions with allene absorbance in the infrared spectrum of about 0.5 using a 0.15-mm path length sodium chloride cell. Sealed steam-cleaned glass tubes containing the degassed solution were immersed in an oil bath maintained at 137 ± 1.5°. Samples were removed at various time intervals and the reaction was quenched at −60°. Absorbance values for the allene band at 2040 cm^{-1} were obtained in the 0.15 mm solution cell. An infinity reading was made about 24 hr after the initial reading. First-order rate plots were linear for the entire reaction. Rate constants were obtained from the expression $k = 0.693/t_{1/2}$, where $t_{1/2}$ is the half-life of the reaction in minutes. Rate constants obtained follow: **3c**, 1.9 ± 0.1 × 10^{-2} min^{-1}; **3b**, 1.7 ± 0.1 × 10^{-2} min^{-1}; **3a**, 1.5 ± 0.1 × 10^{-2} min^{-1}. Two runs were made on each reaction.

1-(Triethylsilyl)-3-methyl-1,2-butadiene (10) and 1-(Triethylsilyl)-3-methyl-1-butyne (11).—Potassium *tert*-butoxide–*tert*-BuOH (9.3 g, 0.05 mol) was added all at once to a stirred solution of **1** (7.3 g, 0.05 mol) and 20 ml of triethylsilane (Pierce Chemical Co.) in 50 ml of dry benzene. An exothermic reaction ensued. After 30 min the cooled reaction mixture was poured into cold water and extracted with ether. The organic solution was worked up in the usual manner and the ether was distilled. Short-path distillation of the remaining liquid yielded 7.9 g (68%) of **10**: bp 108–109° (20 mm); $n^{19}D$ 1.4499; ir (neat) 1960 cm^{-1} (allene); nmr ($CDCl_3$) τ 7.3 (1 H, m, vinyl), 8.35 (6 H, d, allylic CH_3, $J \sim 4H$), 8.8–9.8 (15 H, m, C_2H_5). *Anal.* Calcd for $C_{11}H_{22}Si$: C, 75.3; H, 12.1; Si, 12.6. Found: C, 75.1; H, 12.1; Si, 12.9.

A 0.5-ml sample of **10** was heated for 2 hr at 150–170° in a steam-cleaned, closed glass tube. Nmr analysis of the mixture showed the presence of a 2:1 mixture of **10** and 1-(triethylsilyl)-3-methyl-1-butyene (**11**). An analytical sample of **11** was obtained by preparative vpc: ir (neat) 2100 cm^{-1} (C≡C); nmr (CCl_4) τ 6.4 (1 H, m, CH), complex pattern at 8.6–9.8 (21 H) containing a doublet centered at 8.04 (CH_3, J = 6 Hz). *Anal.* Found: C, 75.2; H, 12.0.

Reaction of 1-Bromo-3-methyl-1,2-butadiene (1) with Methyllithium at −100°.—A solution of 7.4 g (0.05 mol) of **1** in 50 ml of dry tetrahydrofuran under a dry nitrogen atmosphere was cooled to −100° (liquid nitrogen–bromoethane). Ethereal methyllithium (1.0 *N*, 50 ml, 0.05 mol) was added dropwise over a period of 1 hr. A white solid appeared in the flask. After 0.5 hr, 50 ml of dry acetone was added rapidly. The mixture was allowed to warm to room temperature and was then extracted with ether. The ether extract was washed with potassium carbonate solution and saturated sodium chloride solution and then dried by filtration through magnesium sulfate. After removing the ether by distillation, the remaining liquid was distilled through a short-path apparatus, yielding 2-hydroxyl-2,5-dimethylhexa-3,4-diene (**15**, 6.5 g, 35%): bp 50–54° (20 mm); ir (neat) 3450 (broad OH), 1960 cm^{-1} (allene); nmr (CCl_4) τ 4.85 (1 H, m, vinyl), 8.17 (6 H, d, allylic CH_3, J = 2 Hz), 9.60 (6 H, s, CH_3). *Anal.* Calcd for $C_8H_{14}O$: C, 78.9; H, 9.9. Found: C, 78.7; H, 9.8.

1,1-Dibromo-3-methyl-1,2-butadiene (16) and 1,1-Dibromo-3-methyl-1,3-butadiene (17).—A mixture of 40.0 g (0.25 mol) of 1-bromo-3-methyl-1-butyn-3-ol (**15**), 200 ml of 48% hydrobromic acid, 32 g of cuprous bromide, 3.2 g of copper powder, and 32 g of sodium bromide was stirred at 27° for 1.5 hr. The mixture was filtered and the organic material was taken up in ether. After a usual work-up and removal of ether by distillation at atmospheric pressure, the remaining dark oil was subjected to short-path distillation. The first fraction obtained boiled at 72–78° (25 mm) and amounted to 11.5 g of approximately equal amounts of **16** and **17**. The presence of **16** in the mixture was determined by absorption bands in the nmr (sharp singlet at τ 8.0) and ir (1960 cm^{-1}) spectra. On standing at room temperature for several hours, **16** completely converted to **17**.

A second fraction boiling at 78–80° (25 mm) yielded 23.3 g of pure **17**. The total yield of **17** was 34.7 g (62%); $n^{27}D$ 1.5601; ir (neat) 1601 cm^{-1} (C=C); nmr (CCl_4) τ 3.00 (1 H, broad singlet, vinyl), 4.84 (2 H, m, vinyl CH_2), and 7.96 (3 H, m, CH_3); mol wt 224 (mass spectrum).[32] *Anal.* Calcd for $C_5H_6Br_2$:[32] C, 26.5; H, 2.7; Br, 70.8. Found: C, 26.6; H, 2.5; Br, 70.9.

A mixture of *cis*- and *trans*-1,2-dibromo-3-methyl-1,3-butadiene (**19**) prepared by a described procedure[28] showed absorptions in its nmr spectrum (CCl_4) at τ 3.71 (vinyl CH), 4.75 (vinyl CH_2), and 8.00 (CH_3).

6,6-Dibromo-2-methylcyclohexene-*cis*-4,5-dicarboxylic Anhydride (18).—A mixture of 1,1-dibromo-3-methyl-1,3-butadiene (3.7 g, 16 mmol) and maleic anhydride (1.57 g, 16 mmol) in 20 ml of benzene was heated at reflux overnight. On cooling, 1.5 g (29%) of **18** crystallized, mp 264–265°. The nmr spectrum (acetone-d_6) showed peaks at τ 3.2 (1 H, vinyl), 6.0–6.6 (4 H, m, aliphatic), and 7.9 (3 H, m, CH_3). *Anal.* Calcd for $C_9H_8Br_2O_3$: C, 33.3; H, 2.5; Br, 49.4. Found: C, 33.0; H, 2.4; Br, 49.5.

Registry No.—A, 4209-13-6; B, 26265-75-8; **2a**, 100-42-5; **2b**, 622-97-9; **2c**, 1073-67-2; **3a**, 4544-23-4; **3b**, 32571-02-1; **3c**, 32571-01-0; **8a**, 30896-86-7; **8b**, 34220-33-2; **8c**, 34220-34-3; **10**, 34220-35-4; **11**, 34220-36-5; **14**, 2424-45-5; **17**, 34220-38-7; **18**, 34220-39-8.

Acknowledgments.—We thank the Research Corporation and Research and Projects department of SIU, Edwardsville, for financial support of this research.

(31) R. F. Bleiholder and H. Shechter, *J. Amer. Chem. Soc.*, **86**, 5032 (1964), report 5.52 μ (1812 cm^{-1}) and 6.0 μ (1667 cm^{-1}) as characteristic absorptions for dimethylenecyclopropanes.

(32) The molecular weight and formula were determined by mass spectrometry at the Morgan-Schaffer Corp., Montreal, Canada.

Nuclear Magnetic Resonance Studies of Isobutylene, Propylene, and 2,3-Butanediol Phosphites and Phosphates

R. H. COX, BRADLEY S. CAMPBELL, AND M. GARY NEWTON*

Department of Chemistry, University of Georgia, Athens, Georgia 30601

Received October 26, 1971

The nmr spectra of seven five-membered ring phosphites and three phosphates have been analyzed exactly in terms of chemical shifts and coupling constants. Both the proton and phosphorus spectra were utilized in the analysis. The phosphorus–proton coupling constants are consistent with a twist-envelope conformation for the five-membered ring. Data obtained from the isobutylene phosphites indicate that the twist in the five-membered ring increases with increasing alkyl substitution of the ring.

Our interests in the synthesis of cyclic five-membered ring phosphate esters from analogous phosphite precursors have led us to examine the stereochemical stability of trivalent phosphorus and the conformational preferences in these systems. All recent nmr studies[1-4] of cyclic phosphites have agreed that inversion at phosphorus is very slow. Haake, *et al.*,[3] have reported a detailed nmr analysis of ethylene sulfite and a series of ethylene phosphites and concluded that these systems exist in a twist–envelope conformation with a ring O–C–C–O dihedral angle of approximately 30°. We have examined a series of isobutylene and propylene phosphites and the corresponding phosphates by detailed nmr analysis and now report our findings in this paper.

Experimental Section

Spectra.—Proton and phosphorus nmr spectra were obtained using a Varian Associates HA-100 spectrometer operating at 100 and 40.5 MHz, respectively, with a probe temperature of 29°. Neat solutions containing 2% TMS as lock signal source and internal reference were used for the proton spectra of the phosphites. Identical solutions were used for the phosphorus spectra except that P_4O_6 was used as an external reference and lock signal source. ^{31}P chemical shifts were not corrected for bulk susceptibility differences. Spectra of the phosphates were obtained from 10% solutions in chloroform-*d*. All measurements were made in the frequency sweep mode. Calibration of the spectra was by the frequency difference technique. Line positions were obtained by averaging the results of two upfield and downfield scans. A scan width of 50 Hz was used with a sweep time of 1000 sec. Variable temperature experiments were performed on a Hitachi R-20 spectrometer.

Methyl Isobutylene Phosphite[5,6] **(Ia).**—The procedure described for preparation of this ester is typical for synthesis of esters Ib, Ic, and Id also. To a 250-ml three-necked flask equipped with a mechanical stirrer, thermometer, nitrogen inlet, and dropping funnel was added 0.25 mol of isobutylene phosphorochloridite (If) dissolved in 90 ml of dry ether. The dropping funnel was charged with 0.25 mol of dry methanol and 0.25 mol of dry pyridine. The alcohol–pyridine solution was added dropwise over a period of 1 hr maintaining the temperature between 0 and 10°. After the addition was completed, the amine hydrochloride was removed by suction filtration and the solvent was evaporated under vacuum. The crude phosphite ester was distilled: bp 35° (4.3 mm), yield 65%.

Isopropyl isobutylene phosphite (Ib) had bp 33° (1.7 mm), yield 41%.

tert-**Butyl isobutylene phosphite** (Ic) had bp 30° (0.8 mm), yield 61%.

Phenyl isobutylene phosphite (Id) had bp 60° (0.2 mm), yield 75%.

Isobutylene Phenylphosphonite (Ie).—A procedure similar to that used for the preparation of isobutylene phosphorochloridite was employed with dichlorophenylphosphine replacing phosphorus trichloride, bp 61° (0.2 mm), yield 37%.

Isobutylene Phosphorochloridite (If).—The preparation followed the procedure given by Azubuzov and Azanovskaya[7] with modification. In a 1000-ml three-necked flask equipped with a mechanical stirrer, alcohol thermometer, nitrogen inlet, and two 250-ml dropping funnels was placed 400 ml of dry ether and 80 g (1 mol) of dry pyridine. The flask and its contents were cooled to −20 to −30° in an acetone–Dry Ice bath. 2-Methyl-1,2-propanediol (45 g, 0.5 mol), dried over potassium carbonate, was dissolved in 200 ml of dry ether and placed in one dropping funnel. Freshly distilled phosphorus trichloride (69 g, 0.5 mol) dissolved in 200 ml of dry ether was added to the remaining dropping funnel. Both solutions were added dropwise, simultaneously, over a period of approximately 6 hr. The temperature of the reaction was maintained between −10 to 0° during the addition. Upon completion of the addition, the solution was heated under reflux for 30 min. The pyridinium chloride was removed by suction filtration and the solvent was evaporated under vacuum. The crude material was then vacuum distilled, bp 33° (4.5 mm), yield 20 g (26%).

tert-**Butyl Propylene Phosphite** (II).—Propylene phosphorochloridite was prepared in a manner similar to that given for If, using 1,2-propanediol in place of 2-methyl-1,2-propanediol. The chloridite was then treated with *tert*-butyl alcohol to produce the corresponding *tert*-butyl ester. The crude product was vacuum distilled, bp 32° (3.6 ml), quantitative yield (based on the phosphorochloridite).

tert-**Butyl** (*dl*)-**2,3-Butanediol Phosphite** (III).—A mixture of meso and *dl* isomers of methyl 2,3-butanediol phosphite was prepared by the method of Denney, *et al.*[8] A solution of 20 g of the mixture of esters in a large excess of *tert*-butyl alcohol was heated under reflux for about 12 hr in a dry nitrogen atmosphere. The alcohol solvent was removed by distillation and the resulting isomeric mixture of *tert*-butyl 2,3-butanediol phosphites was separated by vacuum distillation on a Teflon spinning band column. The *dl* phosphite distilled at 38° (10 mm) and the meso at 42° (10 mm).

Preparation of the Phosphate and Phosphonate Esters (IVa–c).—The appropriate phosphite or phosphonite ester was dissolved in 50 ml of petroleum ether (bp 30–60°) and the solution was cooled in an ice bath. Nitrogen dioxide was bubbled through the mixture until a light green color was observed in the solution. The solvent was removed under vacuum and the phosphate was purified on a modified Hickman still at 0.15 mm. Yields were about 90–95% of theory.

Results

The numbering used in this paper corresponds to the following structure.

(1) B. Fontal and H. Goldwhite, *Tetrahedron*, **22**, 3275 (1966).

(2) D. Gagnire, J. B. Robert, J. Verrier, and R. Wolf, *Bull. Soc. Chim. Fr.*, 3719 (1966).

(3) P. Haake, J. P. McNeal, and E. J. Goldsmith, *J. Amer. Chem. Soc.*, **90**, 715 (1968).

(4) H. Goldwhite, *Chem. Ind. (London)*, 495 (1964).

(5) For an alternative method of preparation, see ref 8

(6) We have chosen to use the nomenclature system which emphasizes the phosphorus portion of the molecule rather than the more exact, yet more cumbersome, heterocyclic nomenclature. Thus, the alkyl isobutylene phosphite esters correspond to 2-alkoxy-4,4-dimethyl-1,3,2-dioxaphospholanes, the alkyl propylene phosphites to 2-alkoxy-4-methyl-1,3,2-dioxaphospholanes, and the alkyl 2,3-butanediol phosphites to 2-alkoxy-4,5-dimethyl-1,3,2-dioxaphospholanes.

(7) A. E. Arbuzov and M. M. Azanovskaya, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 473 (1949).

(8) D. Z. Denney, G. Y. Chen, and D. B. Denney, *J. Amer. Chem. Soc.*, **91**, 6838 (1969).

TABLE I

^{1}H NMR PARAMETERS FOR THE ISOBUTYLENE PHOSPHITES AND PHOSPHATES[a]

Compd	ν_1[b]	ν_2	ν_3	ν_4	J_{34}[c]	J_{35}	J_{45}
Methyl isobutylene phosphite (Ia)	1.447	1.248	3.796	3.802	−8.45	13.43	0.29
Isopropyl isobutylene phosphite (Ib)	1.437	1.228	3.738	3.826	−8.32	12.99	0.27
tert-Butyl isobutylene phosphite (Ic)	1.440	1.206	3.714	3.874	−8.25	13.20	0.32
Phenyl isobutylene phosphite (Id)	1.479	1.336	3.723	3.803	−8.32	13.12	0.31
Isobutylene phenylphosphonite (Ie)	1.215	1.211	3.726	3.331	−8.80	13.95	0.39
Isopropyl isobutylene phosphate (IVa)	1.487	1.524	4.114	4.036	−8.75	14.26	9.28
Phenyl isobutylene phosphate (IVb)	1.383	1.485	4.108	3.965	−9.08	11.35	11.01
Isobutylene phenylphosphonate (IVc)	1.472	1.618	4.286	4.095	−8.99	13.55	8.05

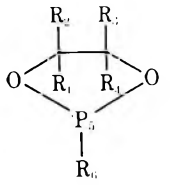
[a] Numbering used is that given in the text. [b] In parts per million downfield from internal TMS. [c] In hertz.

TABLE II

^{1}H NMR PARAMETERS FOR *tert*-BUTYL PROPYLENE AND *tert*-BUTYL (*dl*)-2,3-BUTANEDIOL PHOSPHITE[a]

Compd	ν_1[b]	ν_2	ν_3	ν_4	J_{12}[c]	J_{13}	J_{14}	J_{24}	J_{34}	J_{15}	J_{25}	J_{35}	J_{45}
tert-Butyl propylene phosphite (II)	4.486	1.217	3.368	4.167	6.17	6.57	6.53		−8.22	0.40	0.74	8.17	1.94
tert-Butyl (*dl*)-2,3-butanediol phosphite (III)	1.328	3.593	1.279	4.027	6.09			8.20	6.07	0.72	4.20	0.48	0.72

[a] Numbering used is that given in the text. [b] In parts per million downfield from internal TMS. [c] In hertz.



Ia, R_1, R_2 = CH_3; R_3, R_4 = H; R_6 = OCH_3
Ib, R_1, R_2 = CH_3; R_3, R_4 = H; R_6 = $OCH(CH_3)_2$
Ic, R_1, R_2 = CH_3; R_3, R_4 = H; R_6 = $OC(CH_3)_3$
Id, R_1, R_2 = CH_3; R_3, R_4 = H; R_6 = OC_6H_5
Ie, R_1, R_2 = CH_3; R_3, R_4 = H; R_6 = C_6H_5
If, R_1, R_2 = CH_3; R_3, R_4 = H; R_6 = Cl
II, R_1, R_3, R_4 = H; R_2 = CH_3; R_6 = $OC(CH_3)_3$
III, R_1, R_3 = CH_3; R_2, R_4 = H; R_6 = $OC(CH_3)_3$
IVa, R_1, R_2 = CH_3; R_3, R_4 = H; R_6 = O, $OCH(CH_3)_2$
IVb, R_1, R_2 = CH_3; R_3, R_4 = H; R_6 = O, OC_6H_5
IVc, R_1, R_2 = CH_3; R_3, R_4 = H; R_6 = O, C_6H_5
V, R_1, R_2, R_3, R_4 = H; R_6 = OCH_2CH_3

Spectra were analyzed in terms of chemical shifts and coupling constants using the computer program LAOCN3.[9] Both the ^{1}H and ^{31}P spectra were utilized in the analysis. Results obtained for the proton parameters are given in Tables I and II. Chemical shifts and coupling constants for the methyl protons on the five-membered ring and for the alkoxyl groups of all compounds are those obtained from a first-order analysis. A typical spectrum is that of *tert*-butyl isobutylene phosphite (Ic) shown in Figure 1. Results obtained at 60 MHz confirm that the appearance of the spectrum is not due to an unusually large phosphorus coupling constant but is due to the magnetic nonequivalence of the two methylene hydrogens and of two methyl groups. The methylene protons show a typical AB pattern when the spectrum is obtained while decoupling phosphorus.

The protons of the isobutylene phosphites were assigned from comparison of the parameters of the various compounds and from considerations of models of the compounds. All the isobutylene phosphites studied, with the exception of Ie, have similar chemical shifts and coupling constants. In Ie, one methyl group and methylene proton are shifted upfield considerably, whereas the other methyl group and methylene proton have shifts similar to one of the methyl and methylene protons in Ia–d. Inspection of a model of Ie in the envelope conformation reveals that the methyl and methylene protons cis to the phenyl ring are located in a position such that they should be upfield due to the anisotropic effect of the phenyl substituent.[10] The phenyl substituent should have little effect on the shifts of the methyl and methylene protons trans to the substituent. Therefore, those protons shifted upfield in Ie are assigned to those cis to the phenyl ring and those protons unaffected are assigned as being trans to the phenyl substituent. Thus, the methyl and methylene protons trans to the substituent on phosphorus in Ia–d are assigned as those appearing at highest field. Similar conclusions are reached on the basic of steric arguments. The assignment of II and III follows from the above arguments. This assignment is in complete agreement with that of Gagnaire, *et al.*,[2] who assigned the proton with the largest P–H coupling in the *meso*- and *dl*-2,3-butanediol phosphorochloridites as cis to the electron pair on phosphorus.

The spectra of the isobutylene phosphates (IVa–c) also show two nonequivalent methylene protons and methyl groups. However, the two P–O–C–H coupling constants are quite different in IVa and IVc and approximately equal in IVb. Ramirez, *et al.*,[11] have also observed a large difference between the phosphorus–proton coupling constants of a similar compound and attributed this to a difference in the dihedral angle between phosphorus and the ring protons. The methyl group and methylene proton appearing a lower field in IVa–c are assigned as those cis to the phosphoryl oxygen. It is reasonable that a reversal in chemical shifts should occur between I and IV as a result of the phosphoryl–oxygen bond in IV. This assignment of the protons in IV is consistent with the assignment in I in that the larger phosphorus–proton coupling constant results from the proton trans to the

(9) S. Castellano and A. A. Bothner-By, Mellon Institute, Pittsburgh, Pa., 1966.

(10) J. A. Pople, W. G. Schneider, and H. J. Berstein, "High-Resolution Nuclear Magnetic Resonance," McGraw-Hill, New York, N. Y., 1959, p 180.

(11) F. Ramirez, A. V. Patwardham, N. B. Desai, and S. R. Heller, *J. Amer. Chem. Soc.*, **87**, 549 (1965).

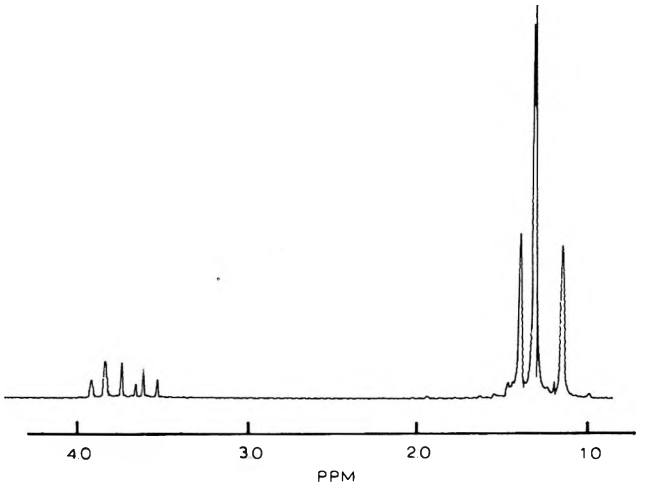


Figure 1.—The 100-MHz nmr spectrum of *tert*-butyl isobutylene phosphite (Ic).

alkoxyl group on phosphorus. A long-range coupling $^4J_{H-H}$ of 0.35 and 0.55 Hz is observed between the methyl protons cis to the alkoxyl substituent and the methylene proton trans to the substituent on phosphorus in IVa and IVc, respectively.

Discussion

Conformation of the Five-Membered Ring.—The complete analysis of the nmr spectra of compounds I–IV clearly demonstrates the nonequivalence of the methyl and methylene protons. Earlier studies on alkyl pinacol phosphites,[1] ethylene phosphites, ethylene chlorophosphites,[2,3] and propylene chlorophosphite[10] have shown that these compounds also possess nonequivalent protons. However, two explanations of the different magnetic environments in these compounds have been offered: (1) a stable pyramidal stereochemistry at phosphorus with an essentially planar five-membered ring[1,2,4] and (2) a twist–envelope conformation of the five-membered ring with a O–C–C–O dihedral angle of ~30°.[3] While it is true that a stable pyramidal configuration at phosphorus would account for the nonequivalence of the methyl and methylene protons in I–IV, there are other factors which require a nonplanar five-membered ring. Furthermore, earlier investigations of ethylene phosphorochloridites[2,3] have resulted in two explanations of the different P–O–C–H coupling constants observed in compounds of this type. It has been suggested that the different couplings arise from a dependence of the coupling on dihedral angle[3] and from the influence on the lone pair on phosphorus.[2]

Recent nmr data from six-membered ring phosphites,[12] phosphates,[12,13] and phosphonates[14] indicate a dependence of vicinal proton–phosphorus coupling constants on dihedral angle similar to that observed for proton–proton coupling constants.[15] The different values observed for J_{PH_3} and J_{PH_4} (13 and 0.3 Hz, respectively) in Ia–e could be taken to indicate different dihedral angles (~180 and 90°, respectively, based on models[3]). The observed coupling constants necessitate an important contribution of the envelope conformation, since different P–O–C–H dihedral angles would be found only when the five-membered ring is in an envelope conformation. Since the above arguments have been based on the different phosphorus–proton coupling constants observed in Ia–e, one cannot rule out the possibility that the different coupling constants arise from the orientation of the protons with respect to the lone pair on phosphorus.[2] While this interpretation has been shown for the different P–C–H couplings in phosphines,[16,17] the influence of the phosphorus lone pair on the coupling constants has been shown to be negligible in six-membered ring phosphites. There are at least two factors which necessitate some contribution from twisting of the five-membered ring. (1) If the five-membered ring were either planar or in an envelope conformation, expected P–O–C–H couplings in the isobutylene phosphites, I, would be of similar magnitude to those observed for the ethylene phosphites.[2,3] The larger P–O–C–H couplings observed in I (13.0 *vs.* 9.0 Hz) are therefore incompatible with a planar five-membered ring. (2) Considering the propylene phosphite (II) as a model, replacement of a proton trans to the phosphorus lone pair with a methyl group, as in the isobutylene phosphites Ia–e, should not alter the influence of the phosphorus lone pair on the coupling constant between the remaining cis proton (H-3) and phosphorus. However, significantly different P–O–C–H coupling constants are observed in I compared to II.

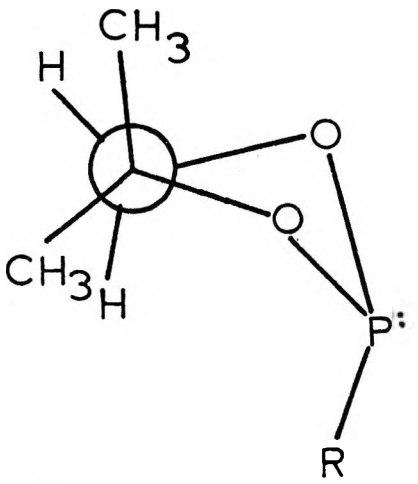


Figure 2.—Twist–envelope conformation of five-membered ring phosphites.

The different P–O–C–H coupling constants (Table I) observed for IVa–c most likely arise from different phosphorus–proton dihedral angles, as suggested by Ramirez, *et al.*[11] Different dihedral angles would be obtained if the five-membered ring were in twist–envelope conformation. The data for IVa and IVc indicate that the degree of twist is similar to that in I. For IVb, however, the phosphorus–proton coupling constants indicate that the ring is closer to being planar on the average than in IVa and IVc. The long-range $^4J_{H-H}$ coupling constants also support this

(12) E. J. Boris, K. J. Coskran, R. W. King, and J. G. Verkade, *J. Amer. Chem. Soc.*, **88**, 1140 (1966); J. G. Verkade and R. W. King, *Inorg. Chem.*, **1**, 948 (1962); J. G. Verkade, R. W. King, and C. W. Heitsch, *ibid.*, **3**, 884 (1964); J. G. Verkade, T. D. Huttermann, M. K. Fung, and R. W. King, *ibid.*, **4**, 83 (1965).

(13) M. Tsuboi, F. Kuriyouawa, K. Matsuo, and Y. Kyogoku, *Bull. Chem. Soc. Jap.*, **40**, 1813 (1967).

(14) C. Benezra and G. Ourisson, *Bull. Soc. Chim. Fr.*, 1825 (1966).

(15) A. A. Bothner-By, *Advan. Magn. Resonance*, **1**, 195 (1965).

(16) D. Gagnaire, J. B. Robert, and J. Verrier, *Chem. Commun.*, 819 (1967).

(17) H. Goldwhite and D. G. Rowsell, *ibid.*, 1665 (1968).

view. In the sterically more favorable twist conformation of IV, the methyl group trans to the alkoxyl group on phosphorus and the cis methylene proton have a dihedral angle of ~180°. Couplings of 0.35 and 0.55 Hz are observed in IVa and IVc, respectively. As the ring becomes more planar, the CH_3–C–C–H dihedral angle decreases towards 90°. The $^4J_{HH}$ long-range coupling was not observed in IVb. Therefore, both the phosphorus–proton and proton–proton coupling constants support the view that IVa and IVc exist in a twist–envelope conformation similar to I while in IVb the twist in the five-membered ring is, on the average, smaller.

Thus, the nmr data for Ia–e and IVa–c are not consistent with a planar ring but are in accord with a twist–envelope conformation of the five-membered ring similar to that proposed for methyl ethylene phosphite[3] (Figure 2). Haake, *et al.*,[3] have proposed a value of ~30° for the twist in the ring based on considerations of the vicinal H–H coupling constants. The coupling constants in II and III are consistent with this value, whereas the larger P–O–C–H couplings in I and IV suggest a somewhat larger degree of twist.[18] Increased twisting of the ring is not unexpected, since the steric interactions of ring substituents with the alkyl group on phosphorus are greater for isobutylene phosphites and phosphates than for the ethylene phosphites.

The question of the orientation of the alkoxyl group attached to phosphorus with respect to the five-membered ring is significant. X-Ray analysis of methyl ethylene phosphate[19] shows the methyl group to be centered over the ring between the two ring oxygen atoms, whereas in methyl pinacol phosphate[20] the methyl group is directed away from the ring because of steric crowding by the ring methyl groups. If the phenyl group in Id were folded back over the ring, some shielding of the methyl and methylene protons cis to the phenyl group should be observed, since they would be located directly over the plane of the phenyl ring.[10] Such a conformation would result in considerable steric crowding. Since the chemical shifts in Id are similar to those in Ia–c, II, III, and IVa–c, the alkyl groups must be directed away from the five-membered ring in these phosphites and phosphates.

The spectra of all compounds reported here were examined at various temperatures up to 150°. No significant changes were observed in any of the spectra, indicating that inversion at phosphorus is extremely slow within this temperature range relative to the nmr time scale. For *tert*-butyl propylene phosphite, both cis and trans isomers are present. The ratio of trans to cis isomers is 2.03:1, a value slightly larger than that found for methyl propylene phosphite (1.55:1).[4]

Nmr Parameters.—The magnitude of the geminal H–H coupling constants (Tables I and II) agree with those obtained from other five-membered ring compounds and are in accord with the theory of geminal coupling constants.[15] Although little data is available on the dependence of P–O–C–H coupling constants on dihedral angle in phosphites, recent work with rigid six-membered ring compounds indicates values of 6 and 2 Hz for the trans and gauche coupling,[12] respectively. In ethylene phosphites, P–O–C–H coupling constants of 9.0 and 1.8 Hz were observed.[3] It appears that J_{trans} is larger in five-membered rings than in six-membered ring phosphites.[12] Slight differences in hybridization at phosphorus and carbon and in bond angles in the two systems could be responsible for this difference in coupling constants. It seems that the increase in one of the coupling constants results in a decrease in the other coupling constant. For example, in II the $J_{P-O-C-H}$ values are 8.17 and 1.94 Hz, in ethylene phosphites 9.0 and 1.8 Hz, and in Ia–e ~13.0 and 0.3 Hz. This observation would seem to support the suggestion[3] that the cyclic phosphites have P–O–C–H dihedral angles of ~180 and 90°, respectively. However, it is doubtful that the value of J_{trans} of 13 Hz is a limiting value.

The ^{31}P chemical shifts for Ia–e are given in Table III along with that of ethyl ethylene phosphite (V) for comparison.[21] With the exception of Ie, the shifts agree with those predicted from "group shift" values.[22] Jones and Katritzky[21] have pointed out the limitations of the additivity relationship; other investigators[23] have noted anomalous ^{31}P chemical shifts when an aromatic ring is attached directly to phosphorus. Although this and similar shifts[23] cannot be explained in terms of ring currents, some probable factors are a change in hybridization at phosphorus and a change in the O–P–O bond angle.

TABLE III
^{31}P CHEMICAL SHIFTS OF CYCLIC FIVE-MEMBERED RING PHOSPHITES

Compd	$\phi^{31}P^a$
Ia	−28.88
Ib	−30.55
Ic	−29.55
Id	−23.60
Ie	−57.50
II	−25.11
III	−27.42
V[b]	−18.5

[a] In parts per million downfield from P_4O_6 external reference. [b] Reference 21.

Registry No.—Ia, 26964-02-3; Ib, 33835-20-0; Ic, 33835-21-1; Id, 33835-22-2; Ie, 33835-23-3; If, 31539-64-7; II, 33835-25-5; (±)-III, 33835-63-1; *meso*-III, 33835-64-2.

(18) Examination of models of I indicate that one P–O–C–H dihedral angle increases towards 180° with increasing twist of the ring.

(19) T. A. Steitz and W. N. Lipscomb, *J. Amer. Chem. Soc.*, **87**, 2488 (1965).

(20) M. G. Newton, J. R. Cox, Jr., and J. A. Bertrand, *ibid.*, **88**, 1503 (1966).

(21) R. A. Y. Jones and A. R. Katritzky, *Angew. Chem., Int. Ed. Engl.*, 1, 32 (1962).

(22) J. T. Van Wazer, C. F. Callis, J. N. Shoolery, and R. C. Jones, *J. Amer. Chem. Soc.*, **78**, 5717 (1956).

(23) H. Finegold, *Ann. N. Y. Acad. Sci.*, **70**, 875 (1958).

Reactions of Phosphorus Compounds. 31.[1] Reactions of Substituted α-Imino Ketones with Vinyltriphenylphosphonium Bromide

EDWARD E. SCHWEIZER* AND CHARLES M. KOPAY

Department of Chemistry, University of Delaware, Newark, Delaware 19711

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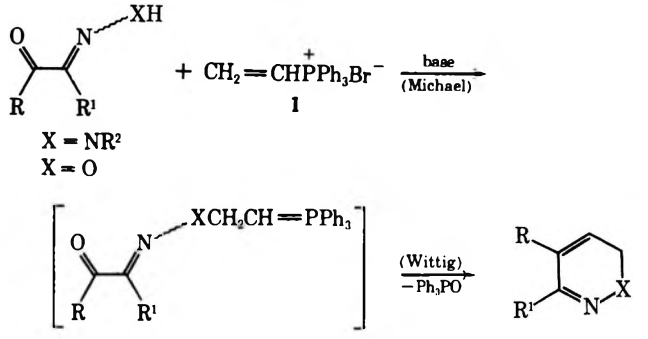
Treatment of substituted α-imino ketones with vinyltriphenylphosphonium bromide (1) gave moderate yields of 1-hydroxypyrroles, 1-aminopyrroles, or 2,3-dihydropyridazines. A mechanism for the formation of the five- and six-membered rings is provided and appears to be dependent upon the geometry of the α-imino ketone.

Continuing our interest in the use of vinyltriphenylphosphonium bromide (**1**) for the syntheses of heterocyclic compounds,[2] we undertook a study of the reactions of some substituted α-imino ketones (oximes and hydrazones) with **1** in the hopes of forming substituted 6*H*-oxazines and 2,3-dihydropyridazines (Scheme I).[3]

SCHEME I
PROPOSED REACTIONS OF
1 WITH SUBSTITUTED α-IMINO KETONES

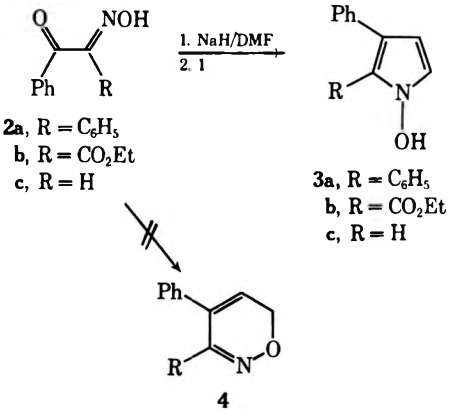


Oximes.—Treatment of (*E*)-benzil monoxime (**2a**) with 1 equiv of NaH in DMF followed by 1 equiv of **1** gave the unexpected 1-hydroxy-2,3-diphenylpyrrole (**3a**)[4] in 26% yield. An nmr spectrum of the crude reaction mixture gave no indication of the presence of 6*H*-oxazine (**4**). The structure of **3a** was based on the following spectral data. The infrared spectrum (Nujol) of **3a** exhibited a broad OH stretching frequency at 3320 cm^{-1}; nmr ($CDCl_3$) δ 6.23 (1, d, J = 3.0 Hz), 6.86 (1, d, J = 3.0 Hz), and 7.0–7.5 (10, m). The proton resonances at δ 6.23 and 6.86 were assigned to the AB pattern of the pyrrole ring positions 4 and 5, respectively. The OH resonance was not detected in **3a**, a phenomenon that had previously been noted in the case of 1-hydroxyindoles.[5]

The mass spectrum showed the molecular ion m/e 235) as the base peak. Fragmentation took place by the loss of HO· from the molecular ion $(M - HO\cdot)^+$, this pattern of fragmentation being in accord with the fragmentation occurring in substituted 1-hydroxyindoles.[5]

Likewise monoximes **2b** and **2c** gave the 1-hydroxypyrroles **3b** and **3c** in yields of 44 and 29%, respectively (Scheme II, Tables I and II).

SCHEME II
FORMATION OF 1-HYDROXYPYRROLES



A mechanism for the formation of the 1-hydroxypyrroles can be rationalized as occurring through the attack of nitrogen on **1** to generate the ylide **5** (pathway 1, Scheme III). Attack of ylide **5** on the benzoyl carbonyl in a normal Wittig reaction would lead to the amine oxide **6b**, which is a tautomeric form of **3** (Scheme III).

An alternative mechanism (pathway 2, Scheme III), assuming $E \rightarrow Z$ conversion, would occur through the attack of the oxygen anion with the formation of ylide **7**, which would then undergo a Wittig reaction with the benzoyl carbonyl to form the 6*H*-oxazine (**8**). The oxazine (**8**) could in turn undergo an electrocyclic ring opening to the nitrosobutadiene **9**; ensuing reattack by the nitroso nitrogen would lead to the amine oxide **6**. The alternative mechanism (pathway 2) was dismissed on the basis of the following reactions. When (*Z*)-benzil monoxime was employed as the starting material, no 1-hydroxypyrrole (**3a**) was obtained and only polymeric material isolated. Under the reaction conditions the *E* and *Z* oximes were not isomerized. Therefore it appears necessary to have the *E* isomer in order to synthesize the 1-hydroxypyrroles.

Nmr studies of the 1-hydroxypyrroles **3a–c** in various solvents, both protic and aprotic, did not indicate the presence of substantial quantities of the tautomeric forms **6a** and/or **6b**.[6] However, the addition of D_2O to a $CHCl_3$ solution of **3a** showed, after 2 hr, a com-

(1) Previous paper in this series: E. E. Schweizer and C. S. Kim, *J. Org. Chem.*, **36**, 4041 (1971).

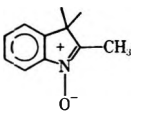
(2) E. E. Schweizer, J. Liehr, and D. T. Monaco, *J. Org Chem.*, **33**, 2416 (1968); E. E. Schweizer, *J. Amer. Chem. Soc.*, **86**, 2744 (1964).

(3) Part of this work was presented at the 6th Middle Atlantic Regional Meeting of the American Chemical Society, Baltimore, Md., Feb 1971, p 83.

(4) This product was first prepared by J. G. Thompson and isolated and characterized by G. Hollander in these laboratories.

(5) R. M. Acheson, R. G. Bolton, and I. Hunter, *J. Chem. Soc. C*, 1067 (1970).

(6) Studies of the 1-hydroxy-2-methylindole[5] showed that in phenol and other acidic solvents



could be shown to exist in quantities up to 100%.

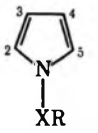
TABLE I

PREPARATION OF N-SUBSTITUTED PYRROLES AND PYRIDAZINES

Starting material	Reaction time, hr (temp, °C)	Product (% yield, solvent)		Analysis, % C	H	N
2a	4 (25)	3a (26, hexane)	Calcd	81.68	5.57	5.93
			Found	82.07	5.55	5.98
2b	3 (25)	3b (44, hexane)	Calcd	67.52	5.67	6.06
			Found	67.82	5.65	6.13
2c	2.5 (25)	3c (29, hexane)	Calcd	75.45	5.70	8.80
			Found	75.19	5.85	8.89
11a	2 (25)	12a (67, EtOH)	Calcd	85.13	5.85	9.03
			Found	85.17	5.87	8.72
11b	2 (25)	12b (27, sublimed)	Calcd	82.33	6.50	11.28
			Found	82.45	6.39	11.21
11c	1 (25)	12c (74, hexane)	Calcd	74.49	5.92	9.15
			Found	74.39	5.97	9.11
11d	40 (50)	13 (31, EtOAc–hexane)	Calcd	81.63	5.36	8.28
			Found	81.56	5.23	8.21

TABLE II

SPECTRA OF SUBSTITUTED PYRROLES

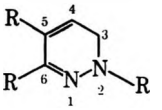


Compd	Ir,[a] cm^{-1}	Nmr,[b] δ 2	3	4	5	Other protons
3a	3320 (w), 1595 (w), 1075 (m)		6.23 (d, 1, J = 3.0 Hz)		6.86 (d, 1, J = 3.0 Hz)	C_6H_5 (m, 10) 7.0–7.5 OH not detectable
3b	3370 (w), 1660 (s), 1575 (s)		5.97 (d, 1, J = 2.8 Hz)		6.93 (d, 1, J = 2.8 Hz)	C_6H_5 (m, 5) 7.1–7.6 $-OCH_2$ (q, 2, J = 7.0 Hz) 4.12 $-CH_3$ (t, 3, J = 7.0 Hz) 1.07 -OH (s, 1) 10.2[c]
3c	3325 (w), 1595 (w), 1080 (m)	6.86 (m, 1)	6.19 (m, 1)		6.61 (m, 1)	C_6H_5 (m, 5) 7.0–7.5 -OH (s, 1) 10.1[c]
13	3250 (w), 1660 (s), 1075 (w)		6.38 (d, 1, J = 3.0 Hz)		6.65 (d, 1, J = 3.0 Hz)	C_6H_5 (m, 15) 6.9–7.7 NH (s, 1) 9.31[c]

[a] All ir spectra were run as a Nujol mull. [b] $CDCl_3$ solvent; all chemical shifts reported in parts per million followed by the splitting patterns, the number of protons, and the coupling constants. [c] Proton exchangeable with D_2O.

TABLE III

SPECTRA OF 2,3-DIHYDROPYRIDAZINES



Compd	Ir,[a] cm^{-1}	Nmr,[b] δ 3	4	Other protons
12a	1590 (m), 1190 (s), 955 (s)	4.25 (d, 2, J = 5.0 Hz)	5.99 (t, 1, J = 5.0 Hz)	C_6H_5 (m, 15) 6.9–7.6
12b	1595 (w), 1160 (m), 1120 (m)	3.42 (d, 2, J = 5.3 Hz)	6.10 (t, 1, J = 5.3 Hz)	NCH_3 (s, 3) 3.05 C_6H_5 (m, 10) 6.9–7.6
12c	1710 (s), 1180 (s), 1125 (m)	4.43 (d, 2, J = 5.0 Hz)	6.22 (t, 1, J = 5.0 Hz)	OCH_2CH_3 (t, 3, J = 7.0 Hz) 1.37 OCH_2CH_3 (q, 2, J = 7.0 Hz) 4.35 C_6H_5 (m, 10) 6.9–7.6

[a] All ir spectra were run as a Nujol mull. [b] $CDCl_3$ solvent; all chemical shifts reported in parts per million followed by the splitting patterns, the number of protons, and the coupling constants.

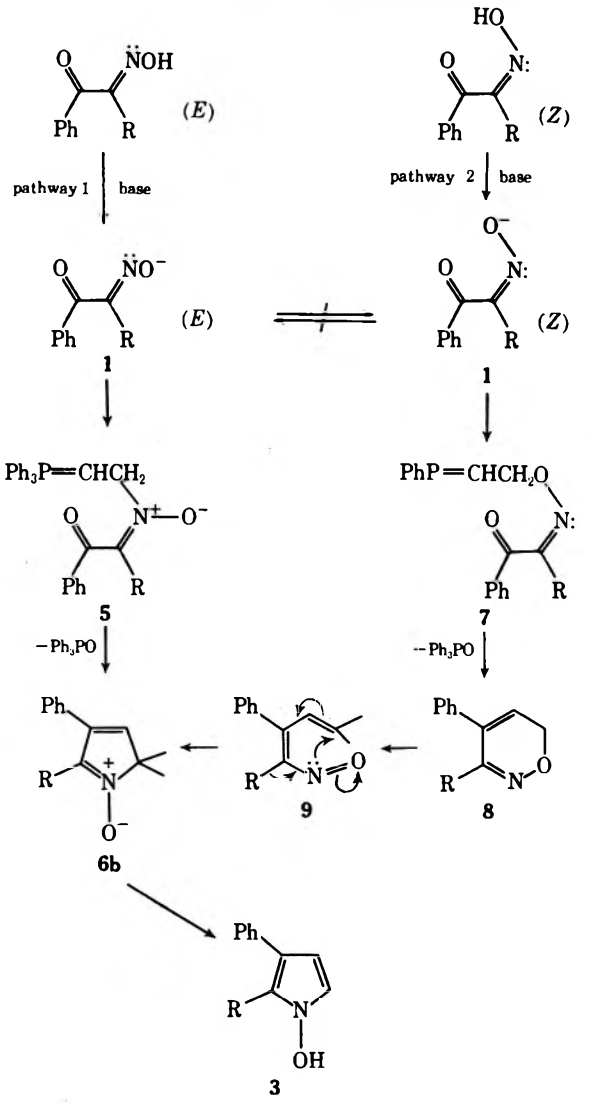
plete deuterium exchange in the 4 and 5 positions of the pyrrole ring, exchange taking place five times faster in the 5 position. The deuterium exchange experiment thus indicates the contribution of tautomeric forms **6a** and **6b** to the hydroxypyrrole **3** (Scheme IV).

Treatment of **3a** with either benzoyl chloride or acetic anhydride in pyridine gave the expected O-acylated products **10a** and **10b** in yields of 78 and 80%, respectively.

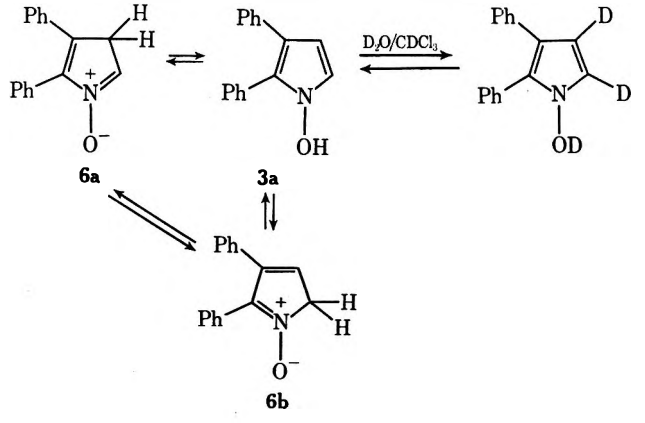
Monohydrazones.—Treatment of monohydrazones **11a–c** with **1** gave exclusively the substituted 2,3-dihydropyridazines **12a–c** in good yields (Scheme V, Table III), without any indication as to the presence of any 1-aminopyrrole **13**. Although the geometric configurations of the hydrazones **11a** and **11b** are not known, it must be assumed that they exist as the *Z* isomer[7] in order to yield pyridazines. It is known

(7) If they do not exist as the *Z* isomer, the energy of isomerization to the *Z* isomer from the *E* must lie sufficiently low for this to occur under reaction conditions.

SCHEME III
MECHANISMS OF 1-HYDROXYPYRROLE FORMATION



SCHEME IV
TAUTOMERIC 1-HYDROXYPYRROLES

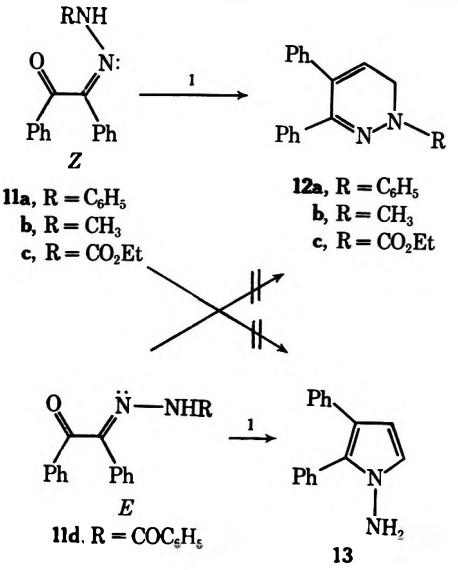


that the *N*-carboethoxybenzil monohydrazone (**11c**) used in our work exists as the *Z* isomer;[8] sufficient quantities of the *E* isomer could not be obtained in order to test its reactivity with **1**.

Benzoylation of benzil monohydrazone with benzoyl chloride in pyridine gave a 42% yield of (*E*)-*N*-benzoyl-

(8) M. Rosenblum, V. Nayak, S. K. Das Gupta, and A. Longroy, *J. Amer. Chem. Soc.*, **85**, 3874 (1963).

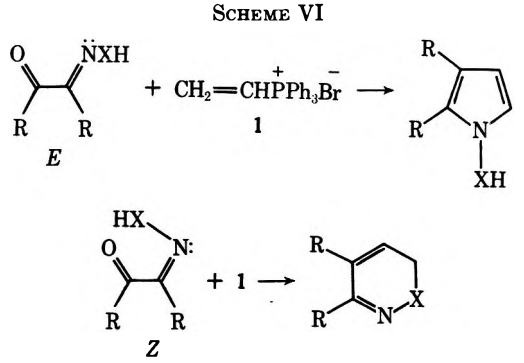
SCHEME V
REACTION OF BENZIL MONOHYDRAZONES WITH 1



benzil monohydrazone (**11d**), mp 139–140°. Refluxing the *E* isomer in dry toluene for 43 hr gave a 52% yield (based on nmr integration of the NH resonances) of the *Z* isomer **14**. The *E* and *Z* isomers were differentiated on the basis of their nmr NH resonances. The *Z* isomer, capable of intramolecular hydrogen bonding, exhibited a broad singlet (exchangeable with D_2O) at δ 10.17; the *E* isomer, not capable of intramolecular hydrogen bonding, at δ 9.37. This same trend had appeared in the (*E*)- and (*Z*)-*N*-carboethoxybenzil monohydrazones. However, only small amounts of *Z* isomer could be obtained pure by fractional crystallization from ether. Isolation and identification of the *Z* and *E* isomers of the *N*-benzoylhydrazone, and the reaction of **11d** (the *Z* isomer) to give only the 1-aminopyrrole **13** (Scheme V) was totally predictable, and paralleled the reactions of the oximes **2a–c** with vinyl salt **1**.

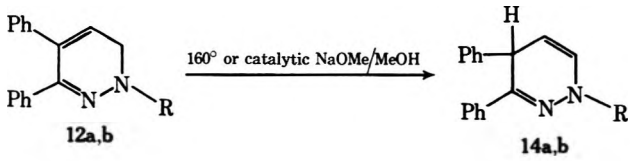
A more general scheme for the reactions of α-imino ketones with vinyl salt **1** can be written, the *E* isomer leading to the 1-substituted pyrroles and the *Z* isomer giving the pyridazine (Scheme VI).

SCHEME VI



The thermal rearrangement of pyridazines **12a** and **12b** at 160° in a sealed tube gave 1,4-dihydropyridazines **14a** and **14b** in 52 and 44% yields (by nmr integration). This apparent [1,3] sigmatropic rearrangement cannot be considered as such, since the heating of **12a** and **12b** as a dilute solution in refluxing mesitylene gave no 1,4-dihydropyridazine and starting material

SCHEME VII
THERMAL AND BASE-CATALYZED REARRANGEMENT OF 12a AND 12b



was recovered. Treatment of **12a** and **12b** with a catalytic amount of NaOMe in refluxing MeOH gave the 1,4-dihydropyridazine in quantitative yield (Scheme VII).

Thus the use of vinyltriphenylphosphonium bromide as a versatile reagent for the synthesis of heterocyclic species has been expanded to include N-substituted pyrroles and pyridazines.

Experimental Section

General Procedure for the Preparation of 1-Hydroxypyrroles (3a–c), N-Substituted 2,3-Dihydropyridazines (12a–c), and *N*-Benzamidopyrrole.—To a slurry of 480 mg of NaH dispersion (57% in mineral oil) in 10 ml of dry DMF was added dropwise 10 mmol of the appropriate monoxime (**2a–c**) or monohydrazone (**11a–d**) in 30 ml of DMF. The deeply colored reaction mixture was stirred at room temperature until all hydrogen evolution had ceased, and vinyltriphenylphosphonium bromide (**1**) (3.69 g, 10 mmol) was introduced all at once; the reaction mixture became almost colorless. After stirring for the appropriate time (Table I) the reaction mixture was poured into 800 ml of H_2O and extracted with two 200-ml portions of ether. The ether extracts were combined, backwashed with 600 ml of H_2O, dried over anhydrous $MgSO_4$, and evaporated *in vacuo* to an oil. The oil was chromatographed on silica gel powder, eluting with benzene. The chromatographic fractions were monitored by tlc to ensure the separation from triphenylphosphine oxide. The pure fractions were combined, concentrated *in vacuo* to a solid material, and recrystallized from the appropriate solvent (Table I).

Acylation of 3a with Benzoyl Chloride and Acetic Anhydride.—To a solution of 1.0 mmol of **3a** in 5 ml of dry pyridine was added 1.1 mmol of benzoyl chloride or acetic anhydride. The reaction mixture was allowed to stand for 3 days at −10°. The reaction mixture, with small amounts of pyridine hydrochloride present, was poured onto 40 g of crushed ice. Stirring and scratching afforded a white solid, which was filtered and washed with 20 ml of ice water. The product was air dried and recrystallized from small amounts of petroleum ether (bp 30–60°) to give an analytically pure sample.

Compound **10a** (*O*-benzoyl) was obtained in 78% yield: mp 80–83°; ν (Nujol) 1760 (s), 1575 cm^{-1} (m); nmr ($CDCl_3$) δ 6.43 (d, 1, J = 3.3 Hz, 4 proton), 6.82 (d, 1, J = 3.3 Hz, 5 proton), 7.0–8.1 (m, 15, C_6H_5).

Anal. Calcd for $C_{23}H_{17}NO_2$: C, 81.39; H, 5.05; N, 4.13. Found: C, 81.10; H, 5.20; N, 4.08.

Compound **10b** (*O*-acetyl) was obtained in 80% yield: mp 104–107°; ν (Nujol) 1700 (s), 1595 cm^{-1} (m); nmr ($CDCl_3$) δ 2.20 (s, 3, $CDCH_3$), 6.37 (d, 1, J = 3.3 Hz, 4 proton), 6.78 (d, 1, J = 3.3 Hz, 5 proton), 6.9–7.4 (m, 10, C_6H_5).

Anal. Calcd for $C_{19}H_{15}NO_2$: C, 77.96; H, 5.45; N, 5.00. Found: C, 77.64; H, 5.55; N, 5.01.

(*E*)-*N*-Benzoylbenzil Monohydrazone (11d).—To a solution of 21.0 g (0.1 mol) of benzil monohydrazone in 200 ml of dry pyridine was added 14.0 g (0.1 mol) of benzoyl chloride over a period of 10 min. The solution was stirred for 14 hr at room temperature. The reaction mixture was poured onto 600 g of cracked ice and stirred until all of the ice had melted. The water was decanted and the remaining gummy yellow residue was dissolved in CH_2Cl_2 and washed with three 100-ml portions of water. The CH_2Cl_2 was dried over anhydrous Na_2SO_4 and evaporated *in vacuo* to a volume of 50 ml, and 100 ml of ether was added. Scratching and chilling furnished 13.2 g (42%) of **11d**. Recrystallization from EtOH–Et_2O furnished an analytical sample: mp 139.5–140°; ν (Nujol) 3320 (w), 1690 (s), 1640 cm^{-1} (m); nmr ($CDCl_3$) δ 7.1–8.3 (m, 15, C_6H_5), 9.37 (s, 1, NH).

Anal. Calcd for $C_{21}H_{16}N_2O_2$: C, 76.81; H, 4.91; N, 8.53. Found: C, 76.56; H, 4.95; N, 8.88.

(*Z*)-*N*-Benzoylbenzil Monohydrazone.—A solution of 2 g of **11d** in 20 ml of dry toluene was refluxed for a period of 24 hr. The isomerization was monitored by nmr following the NH resonances, until the per cent of *Z* isomer reached a maximum. After 24 hr the percentages of *Z* and *E* isomers were 52 and 48%, respectively. The toluene was removed *in vacuo* and the solid residue was fractionally crystallized from ether–hexane to yield 230 mg of pure **14**: mp 123–125°; ν (Nujol) 3310 (w), 1690 (s), 1630 cm^{-1} (m); nmr ($CDCl_3$) δ 7.1–8.2 (m, 15, C_6H_5), 10.17 (s, 1, NH).

Anal. Calcd for $C_{21}H_{16}N_2O_2$: C, 76.81; H, 4.91; N, 8.53. Found: C, 76.76; H, 5.01; N, 8.85.

***N*-Methylbenzil Monohydrazone (11b).**—To a solution of 21.0 g (0.10 mol) of benzil dissolved in a minimum amount of dry CH_3CN (200 ml) was added 4.2 g (0.10 mol) of methyl hydrazine. The reaction became extremely exothermic and the acetonitrile began to reflux. After the exotherm had subsided the mixture was allowed to remain at room temperature for 10 hr. Evaporation *in vacuo* to a yellow oil gave upon addition of 100 ml of ether a white solid, mp 136–137°. Recrystallization from CH_2Cl_2–Et_2O afforded 16.2 g (65%) of **11b**: mp 138–140°; ν (Nujol) 3260 (w), 1650 (s), 1590 cm^{-1} (m); nmr ($CDCl_3$) δ 2.95 (s, 3, $-NCH_3$), 4.36 (s, 1, NH), 7.0–8.2 (m, 10, C_6H_5).

Anal. Calcd for $C_{15}H_{14}N_2O$: C, 75.60; H, 5.92; N, 11.76. Found: C, 75.91; H, 5.87; N, 12.02.

(*Z*)-*N*-Carboethoxybenzil Monohydrazone (11c).—To a slurry of 22.4 g (0.10 mol) of benzil monohydrazone in 120 ml of dry pyridine cooled to 0° was added dropwise 0.11 mol of ethyl chloroformate. Immediately a red solution formed and a crystallization of pyridine hydrochloride occurred. The slurry was stirred for 4 hr at 0° and then 4 days at room temperature. The reaction mixture was then poured into 600 ml of water and extracted with ether. The ether layer was washed five times with water, dried (Na_2SO_4), and evaporated *in vacuo* to a pale pink solid. Recrystallization from CH_2Cl_2–hexane afforded 11.2 g (37%) of **11c**, mp 123.5–124° (lit.[8] mp 124–125°).

Base-Catalyzed Isomerization of 2,3-Dihydropyridazines (12a,b) to 1,4-Dihydropyridazines (14a,b).—To a solution of 12 mg of sodium in 40 ml of dry EtOH was added 2 mmol of the 2,3-dihydropyridazine (**12a,b**). The yellow solution was refluxed for 7 days, tlc indicating the complete disappearance of starting material. The solution was concentrated *in vacuo* to a yellow oil, and water and ether were added. The ether extract was dried over anhydrous Na_2SO_4 and evaporated *in vacuo* to a yellow solid, which upon recrystallization from EtOH–hexane afforded the 1,4-dihydropyridazines in quantitative yield.

1,3,4-Triphenyl-1,4-dihydropyridazine (14a) had mp 131–133°; ν (Nujol) 1590 (m), 1310 (s), 1250 cm^{-1} (m); nmr ($CDCl_3$) δ 4.85 (d, 1, J = 6.0 Hz, 4 proton), 5.31 (dd, 1, J = 7.5, 6.0 Hz, 5 proton), 6.93 (d, 1, J = 7.5 Hz, 6 proton), 7.0–8.1 (m, 15, C_6H_5).

Anal. Calcd for $C_{22}H_{18}N_2$: C, 85.13; H, 5.85; N, 9.03. Found: C, 84.84; H, 5.78; N, 8.92.

1-Methyl-3,4-diphenyl-1,4-dihydropyridazine (11b) had mp 69–70°; ν (Nujol) 1595 (m), 1315 (s), 1250 cm^{-1} (m); nmr ($CDCl_3$) δ 3.28 (s, 3, NCH_3), 2.60 (d, 1, J = 5.5 Hz, 4 proton), 4.91 (dd, 1, J = 7.3, 5.5 Hz, 5 proton), 6.13 (d, 1, J = 7.5 Hz, 6 proton).

Anal. Calcd for $C_{17}H_{16}N_2$: C, 82.22; H, 6.50; N, 11.28. Found: C, 82.62; H, 6.35; N, 10.99.

Heating **12a** and **12b** at 160° neat for 1.5 hr gave approximately 60% of **14a** and **14b**, respectively, before extensive decomposition occurred. Yields were determined by nmr integration with an internal standard and identification of **14a** and **14b** was accomplished by peak enhancement with authentic samples.

Registry No.—**1**, 5044-52-0; **3a**, 34288-44-3; **3b**, 34288-45-4; **3c**, 34288-46-5; **10a**, 34288-47-6; **10b**, 34288-48-7; **11b**, 34289-86-6; **11d**, 34289-87-7; **11d** *Z* isomer, 34289-88-8; **12a**, 34288-49-8; **12b**, 34288-50-1; **12c**, 34288-51-2; **13**, 34288-52-3; **14a**, 34288-53-4; **14b**, 34288-54-5.

Acknowledgment.—This work was supported by a U. S. Public Health Service Grant (CA 11000) for which we are most grateful.

Bicyclic Enamines. VI.[1] Homoallylic Participation in the Formation and Properties of Some Bicyclic Enamines[2,3]

A. GILBERT COOK,* WARREN M. KOSMAN, THOMAS A. HECHT, AND WILLIAM KOEHN

Department of Chemistry, Valparaiso University, Valparaiso, Indiana 46383

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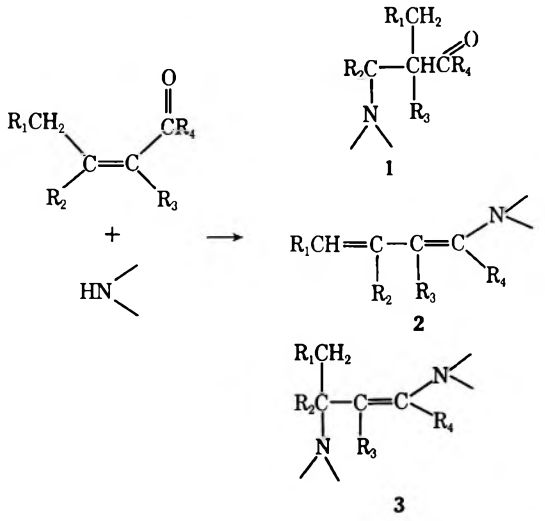
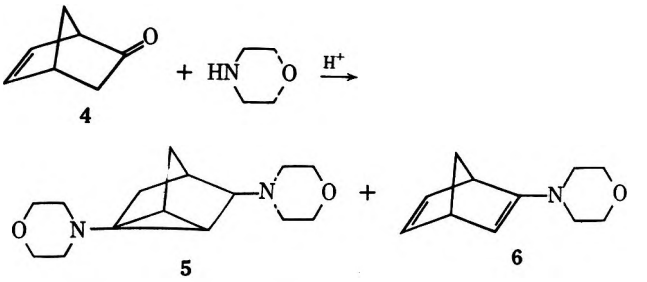
The reaction of norbornenone and morpholine without an acid catalyst results in formation of a tricycloenamine, a normal enamine, an enamine reduction product, and an amino ketone. The amino ketone is apparently formed *via* a homoenolate ion. Treatment of bicyclo[2.2.2]oct-5-en-2-one with morpholine and an acid catalyst gives the thermodynamic product, *N*-phenylmorpholine, in refluxing xylene and the kinetic product, 2-*N*-morpholinobicyclo[2.2.2]octa-2,5-diene, at room temperature.

Secondary amines react with α,β-unsaturated ketones or aldehydes in one of the following three ways: (1) nucleophilic attack of the amine on the β carbon resulting in a β-amino ketone or aldehyde such as structure **1**;[4-7] (2) a combination of nucleophilic attacks of the amine on both the β carbon and the carbonyl carbon to form a γ-aminoenamine such as structure **3** or an isomer thereof;[8,9] (3) nucleophilic attack of the amine on the carbonyl carbon alone to form dienamine such as structure **2** or an isomer thereof[10] (although many dienamines are formed *via* a γ-aminoenamine such as structure **3**).



The reaction of secondary amines with the bicyclo[2.2.1]heptyl homoallylic ketone system by pathway types 2 and 3 has been observed when it was found that the acid-catalyzed reaction between morpholine and norbornenone (**4**) produced 2,5-bis(*N*-morpholino)-tricyclo[2.2.1.$0^{2,6}$]heptane (**5**) (*via* pathway 2) and 2-*N*-morpholinobicyclo[2.2.1]hepta-2,5-diene (**6**) (probably *via* pathway 3).[5]



We have found that the reaction of norbornenone (**4**) with morpholine *without acid catalyst* gives four products which are formed by all three pathway types. These four products include tricyclic amine **5** and bicyclic enamine **6**, which were observed in the acid-catalyzed reaction mentioned above,[5] and two new products. The two new products are bicyclic amine **7** and amino ketone **8** (Scheme I).

Tricyclic amine **5** (*via* pathway 2) was identified by comparison with an authentic sample.[5] The yield of tricyclic amine **5** increases the most markedly of the four products as the reaction time is extended as seen in Table I. Enamine **6** (probably formed *via* pathway 3) was identified by its ir and nmr spectra (see Table II), gas chromatography, hydrogenation to produce the identified saturated amine **9**, and a low yield synthesis by the Diels–Alder reaction of 1,1-dimorpholinoethene (**10**)[11] with cyclopentadiene followed by elimination of morpholine. *endo*-2-*N*-Morpholinobicyclo[2.2.1]hept-5-ene (**7**) was probably produced by the reduction of enamine **6** with excess morpholine which reduction has been shown to give the endo isomer.[5,12,13] The structure of **7** was demonstrated by glc and ir comparison with an authentic sample obtained by reduction of iminium salt **11**.[12]

TABLE I

REACTION OF NORBORNENONE WITH MORPHOLINE IN REFLUXING XYLENE (NO ACID CATALYST)

Time, hr	% Yield 5	6	7	8
50	4	2	1	1
114	17	2	3	1
261	23	2	3	1

The structure of *exo*-5-*N*-morpholinobicyclo[2.2.1]-

(1) For the previous article in the series, see A. G. Cook, S. B. Herscher, D. J. Schultz, and J. A. Burke, *J. Org. Chem.*, **35**, 1550 (1970).

(2) For a preliminary communication of this work, see A. G. Cook and W. M. Kosman, *Tetrahedron Lett.*, 5847 (1966).

(3) Support of this work by a grant from the Petroleum Research Fund, administered by the American Chemical Society, and by Valparaiso University research grants is gratefully acknowledged.

(4) S. I. Suminov and A. N. Kost, *Russ. Chem. Rev.*, **38**, 884 (1969).

(5) A. G. Cook, W. C. Meyer, K. E. Ungrodt, and R. H. Mueller, *J. Org. Chem.*, **31**, 14 (1966).

(6) H. Shenhav, Z. Rappoport, and S. Patai, *J. Chem. Soc. B*, 469 (1970).

(7) E. Rouvier, J. C. Giacomoni, and A. Cambon, *Bull. Soc. Chim. Fr.*, 1717 (1971).

(8) C. Mannich, K. Handke, and K. Roth, *Ber.*, **69**, 2112 (1936).

(9) For a comprehensive review of the formation and structure of enamines, see "Enamines: Synthesis, Structure, and Reactions," A. G. Cook, Ed., Marcel Dekker, Inc., New York, N. Y., 1969.

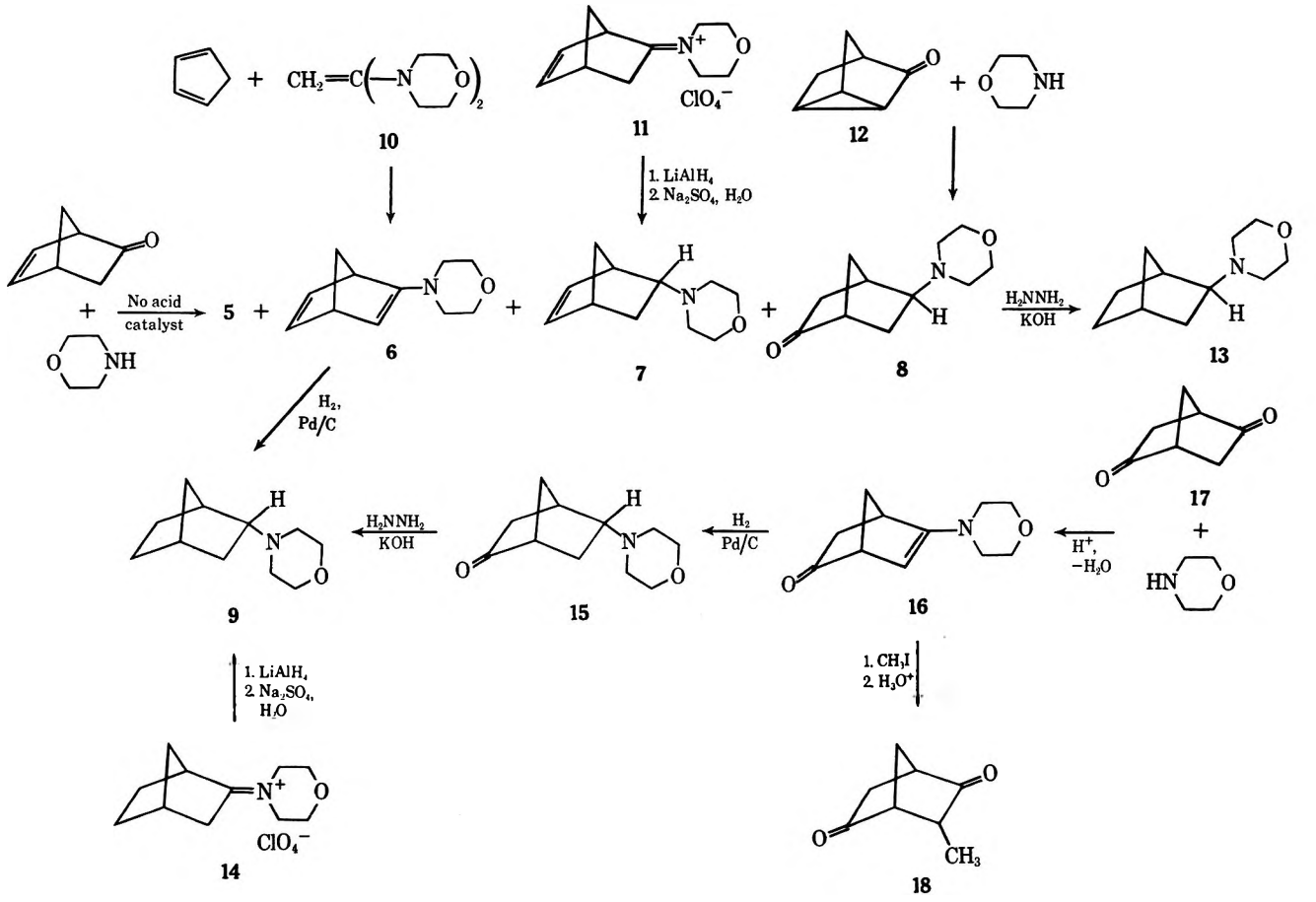
(10) G. Optiz and W. Merz, *Justus Liebigs Ann. Chem.*, **653**, 139 (1962).

(11) H. Baganz and L. Domaschke, *Chem. Ber.*, **93**, 2095 (1962).

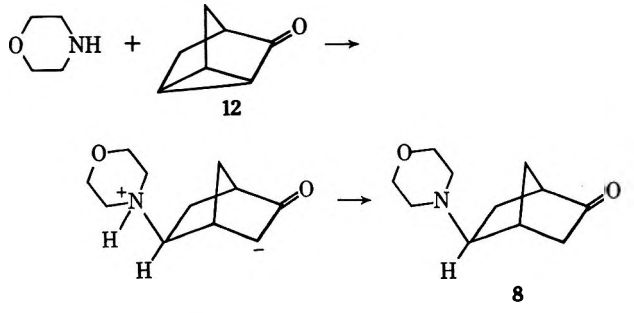
(12) A. G. Cook and C. R. Schulz, *J. Org. Chem.*, **32**, 473 (1967).

(13) The observation that morpholine is also among those secondary amines that reduce amines in the presence of an acid catalyst was first reported by E. L. Patmore and H. Chafetz, *ibid.*, **32**, 1254 (1967). Morpholine has also been observed to reduced enamines in the absence of acid catalyst when heated with the enamine over an extended period of time as reported by Stephen and Marcus (see Table II, ref *e*).

SCHEME I



heptan-2-one (**8**) (formed *via* pathway 1) was demonstrated by comparison of physical, spectral, and chromatographic properties with those of an authentic sample. The authentic sample was synthesized by treatment of tricyclo[2.2.1.$0^{2,6}$]heptan-3-one (**12**) with



morpholine.[5] The same product is obtained whether an acid catalyst is present or not. Since the presence of acid is not necessary for this reaction, it probably proceeds by a nucleophilic backside attack of morpholine on **12** to produce a carbanion followed by proton removal and addition to give amino ketone **8**. This would mean that the compound produced (**8**) is the exo isomer. Proof of its being the exo isomer was obtained by reducing amino ketone **8** by the Wolff–Kishner reduction to the corresponding amine (**13**). The gas chromatogram and ir spectrum of this amine were compared with those of an authentic sample of *endo*-2-morpholinobicyclo[2.2.1]heptane (**9**), synthesized by reduction of iminium salt **14** with lithium aluminum hydride. This type of reduction has been shown to produce the endo isomer.[12] The peaks on the gas chromatograms have different retention times under identical conditions, and the ir spectra have several distinct differences showing them to be nonidentical. The endo isomer possesses strong bands at 1180, 1030, and 798 cm^{-1} which the exo isomer does not exhibit whereas the exo isomer shows strong bands at 1010 and 865 cm^{-1} which the endo isomer does not show. Therefore amino ketone **8** and its corresponding amine **13** are indeed exo isomers. Further proof is seen by glc and ir comparison of *endo*-5-*N*-morpholinobicyclo[2.2.1]heptan-2-one (**15**) with the exo amino ketone, **8**. This comparison shows the nonidentity of amino ketones **8** and **15**. Wolff–Kishner reduction of amino ketone **15** produces endo amine **9** as additional proof of the stereochemistry of amino ketone **15**. *endo*-5-*N*-Morpholinobicyclo[2.2.1]heptan-2-one (**15**) was produced by catalytic reduction of 5-*N*-morpholinobicyclo[2.2.1]hept-5-en-2-one (**16**) (hydrogenation takes place on the less hindered exo side of the bicyclic systems), which in turn was synthesized in the usual manner[9] from diketone **17** and morpholine. The structure of enamine **16** was demonstrated by alkylation with methyl iodide followed by hydrolysis to yield 3-methylbicyclo[2.2.1]hepta-2,5-dione (**18**).

The most plausible explanation for the formation of amino ketone **8** from norbornenone (**4**) and morpholine is *via* a homoenolate ion intermediate (**19**)[14] in a Michael-type addition reaction. The ketone group must exert a homoconjugative effect on the carbon–

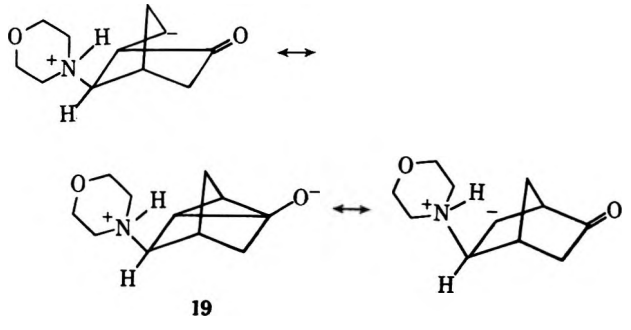
(14) A. Nickon, J. L. Lambert, R. O. Williams and N. H. Werstuik, *J. Amer. Chem. Soc.*, **88**, 3354 (1966), and previous articles.

TABLE II

PHYSICAL PROPERTIES OF SOME MORPHOLINE ENAMINES

Component ketone	Uv spectrum: Solvent[a]	λ_{max}, nm	ϵ	ν^{film}_{max}, cm^{-1} (>C=C<N)	Nmr, δ (HC=CN)	Synthesis[b]	Yield, %	Bp, °C (mm)	n^tD (t)	Formula	C, % Calcd	C, % Found	H, % Calcd	H, % Found
Norbornenone (4)	A	203	4680	1600 (m), 1660 (s)		c								
Norcamphor	A	None above 200		1600 (s)[d]	4.60 (d)[e]	f								
Bicyclo[2.2.1]-heptane-2,5-dione (17)	A	None above 200		1600 (s)	4.32 (d)	A	54	118 (0.4)						
Bicyclo[2.2.2]-oct-2-en-5-one (20)	E, A, C	217 and 244 (sh), none above 200, 243 (sh)	4000 and 2200, 1700	1600 (m), 1630 (s)	4.93 (m)	B	50	81–82 (0.3)	1.5288 (24)	$C_{12}H_{17}NO$	75.35	75.16	8.96	8.86
Bicyclo[2.2.2]-octan-2-one (23)	E, A	217, none above 200	5600	1620 (s)		B	71	93–94 (0.5)	1.5224 (21)	$C_{12}H_{19}NO$	74.57	74.44	9.91	9.87

[a] E, diethyl ether; A, ethanol; C, cyclohexane. [b] A, amine, ketone and acid catalyst in refluxing xylene;[9] B, amine, ketone and $TiCl_4$ at room temperature.[15] [c] See Experimental Section. [d] An incorrect assignment reported in ref 5 was first corrected by M. Mazarguil and A. Lattes, *Bull. Soc. Chim. Fr.*, 319 (1969). [e] J. F. Stephen and E. Marcus, *J. Org. Chem.*, **34**, 2535 (1969). [f] See ref 5.



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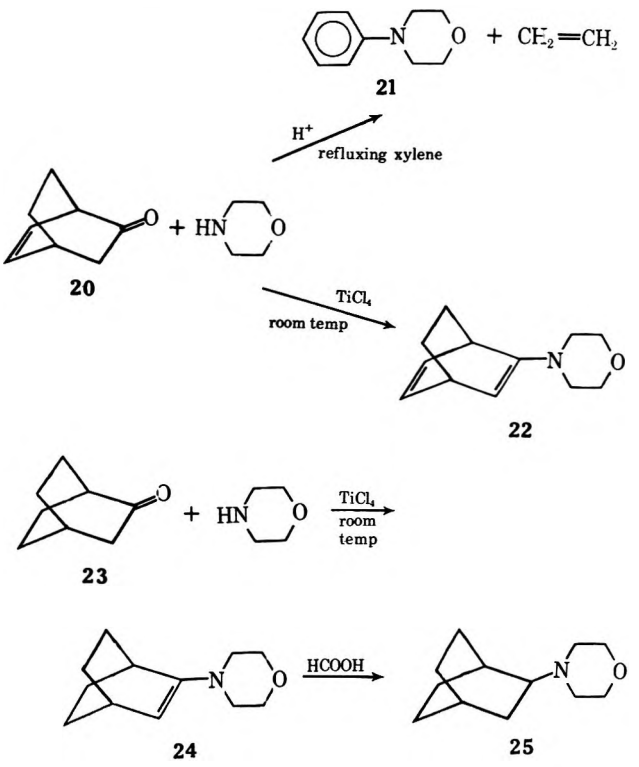
carbon double bond since neither norbornene nor nobornadiene react with morpholine under these conditions.[5] Michael addition reactions involving secondary amines and α,β-unsaturated carbonyl compounds have been reported before[4–7], but this is the first example of such a reaction involving the homoenolate ion.

An extension of this study into the bicyclo[2.2.2]-octyl system was carried out to determine the generality of these reactions. Homoallylic participation in the bicyclo[2.2.2]octyl system has been shown to be important in solvolysis reactions.[15] Treatment of bicyclo[2.2.2]oct-5-en-2-one (**20**) with morpholine in the presence of an acid catalyst in refluxing xylene results in the loss of a mole of ethylene along with the expected mole of water producing *N*-phenylmorpholine (**21**) in a 78% yield. Using titanium tetrachloride catalyst in benzene at room temperature, according to the method of White and Weingarten,[16a] with ketone **20** and morpholine gives the kinetically controlled product,[16b] 2-*N*-morpholinobicyclo[2.2.2]octa-2,5-diene (**22**), in a 50% yield. No sign of homoallylic products, such as were discovered in the bicyclo[2.2.1]-heptyl system, was found. Bicyclo[2.2.2]octan-2-one (**23**) is readily converted to 2-*N*-morpholinobicyclo[2.2.2]oct-2-ene (**24**) in a 71% yield by the same method. Enamine **24** is readily reduced to 2-*N*-morpholinebicyclo[2.2.2]octane (**25**) with 98–100% formic acid.



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Listed in Table II are the physical properties and elemental analyses of those enamines reported for the first time.

Experimental Section

The instruments used in this work were the Beckman DK-2A recording spectrophotometer, the JEOL C-60HL high resolution nmr spectrometer, the Perkin-Elmer Model 137 and the Beckman IR-20A ir spectrometers, and the Hewlett-Packard Model 7620A research chromatograph. The elemental analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

Starting Bicyclic Ketones.—Bicyclo[2.2.1]hept-2-en-5-one (**4**) and bicyclo[2.2.2]oct-2-en-5-one (**20**) were made by the method of Freeman, *et al.*[17] Bicyclo[2.2.2]octan-2-one (**23**) was synthesized using the method of Krieger.[18] The synthesis of bicyclo[2.2.1]heptane-2,5-dione (**17**) was carried out according to the method described by Meinwald, *et al.*[19]

(15) J. B. Lambert and A. G. Holcomb, *J. Amer. Chem. Soc.*, **93**, 3952 (1971).

(16) (a) W. A. White and H. Weingarten, *J. Org. Chem.*, **32**, 213 (1967); (b) D. Pocar, R. Stradi, and G. Bianchetti, *Gazz. Chim. Ital.*, **100**, 1135 (1970).

(17) P. K. Freeman, D. M. Balls, and D. J. Brown, *J. Org Chem.*, **33**, 2211 (1968).

(18) H. Krieger, *Suom. Kemistilehti B.*, **35**, 180 (1962).

(19) J. Meinwald, J. K. Crandall, and P. G. Gassman, *Tetrahedron*, **18**, 815 (1962).

Reaction of Norbornenone with Morpholine (No Acid Catalyst.)—A stirred solution of 10.8 g (0.1 mol) of norbornenone, 8.7 g (0.1 mol) of morpholine, and 150 ml of xylene was refluxed under a nitrogen atmosphere for 114 hr. Water was removed during this time by means of a Dean-Stark trap. At the end of this time the solvent and excess starting materials were removed and the residual oil was fractionally distilled. The product distribution is 0.19 g (1%) of *exo*-5-*N*-morpholinobicyclo[2.2.1]heptan-2-one (**8**) (identified by glc and ir spectral comparison with an authentic sample[5]), 0.54 g (3%) of *endo*-2-*N*-morpholinobicyclo[2.2.1]hept-5-ene (**7**) (identified by glc and ir spectral comparison with an authentic sample, see below), 0.55 g of 2-*N*-morpholinobicyclo[2.2.1]hepta-2,5-diene (**6**) (identified by hydrogenation to a known saturated amine, ir spectra, and independent synthesis, see below), and 4.45 g (17%) of 2,5-bis-(*N*-morpholino)tricyclo[2.2.1.$0^{2,6}$]heptane (**5**) (identified by comparison with an authentic sample[5]). See Table I for comparison of yields for different reaction times. The balance of the reactants were recovered as unreacted starting materials.

exo-2-*N*-**Morpholinobicyclo[2.2.1]heptane** (**13**).—A solution of 18.4 g (0.094 mol) of *exo*-5-*N*-morpholinobicyclo[2.2.1]heptan-2-one (**8**),[5] 135 ml of diethylene glycol, 34 g of potassium hydroxide, and 24 ml of 85% hydrazine hydrate was stirred at 60–120° for 6 hr and at 220° for 3 hr. Then ~1.5 l. of steam distillate was obtained and extracted with ether, the combined extracts were dried over anhydrous magnesium sulfate and filtered, and the solvent was removed and distilled. A total of 5.6 g (37%) of colorless product was obtained, bp 80° (0.6 mm), n^{27}D 1.4972.

Anal. Calcd for $C_{11}H_{19}NO$: C, 72.88; H, 10.56. Found: C, 73.03; H, 10.57.

endo-2-*N*-**Morpholinobicyclo[2.2.1]heptane** (**9**).—A stirred slurry of 5.1 g (0.018 mol) of the perchlorate salt of 2-*N*-morpholinobicyclo[2.2.1]hept-2-ene (**14**), 3.8 g (0.1 mol) of lithium aluminum hydride and 500 ml of ether was refluxed for 21 hr. The reaction mixture was treated with an aqueous saturated sodium sulfate solution and filtered, the solvent was removed, and residual oil was distilled. A total of 2.3 g (71%) of colorless liquid product was obtained, bp 76° (0.65 mm), n^{26}D 1.4953.

Anal. Calcd for $C_{11}H_{19}NO$: C, 72.88; H, 10.56. Found: C, 72.95; H, 10.60.

endo-5-*N*-**Morpholinobicyclo[2.2.1]heptan-2-one** (**15**).—A solution of 5.34 g (0.03 mol) of 5-*N*-morpholinobicyclo[2.2.1]hept-5-en-2-one (**16**)[20] and 75 ml of ethyl acetate was hydrogenated using 10% palladium-on-carbon catalyst and 40-psi pressure. After filtration and solvent removal, the residual liquid was distilled to give 3.6 g (66%) of a colorless product, bp 111° (0.35 mm).

Anal. Calcd for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78. Found: C, 67.37; H, 8.99.

A Wolff–Kishner reduction was run on this product by a procedure identical with that used to reduce amino ketone **8**. *endo*-2-*N*-Morpholinobicyclo[2.2.1]heptane (**9**) was the product obtained in a 30% yield.

3-Methylbicyclo[2.2.1]heptane-2,5-dione (**18**).—A stirred mixture of 2.43 g (0.013 mol) of 5-*N*-morpholinobicyclo[2.2.1]-hept-5-en-2-one (**16**)[20] and 226 g of methyl iodide was refluxed for 16 hr. The cooled solution was filtered, the solid residue as refluxed with dilute hydrochloric acid for 1.5 hr and extracted with ether, the combined extracts were dried over anhydrous magnesium sulfate and filtered, and solvent was removed. A total of 0.6 g (33%) of colorless liquid product was obtained, bp 124° (15 mm). It solidified on standing, mp 35–36.5°.

Anal. Calcd for $C_8H_{10}O_2$: C, 69.54; H, 7.30. Found: C, 69.71; H, 7.32.

Reaction of 1,1-Dimorpholinoethene with Cyclopentadiene.—A mixture of 3.3 g (0.05 mol) of freshly distilled cyclopentadiene, 9.9 g (0.05 mol) of 1,1-dimorpholinoethene[11] and a trace of hydroquinone was heated in a reaction bomb at 120–130° for 7 hr. At the end of this time the bomb was cooled, and a total of 0.22 g (3%) of 2-*N*-morpholinobicyclo[2.2.1]hepta-2,5-diene (**6**) was found. It was identified by ir and glc with an authentic sample.

endo-2-*N*-**Morpholinobicyclo[2.2.1]hept-5-ene** (**7**).—A stirred mixture of 6.0 g (0.055 mol) of norbornenone (**4**), 10.3 g (0.055 mol) of morpholine perchlorate, and 100 ml of xylene was refluxed under nitrogen for 2 hr, and water was removed with a Dean-Stark trap. The solvent was decanted, and 120 ml of ether and 3.8 g (0.1 mol) of lithium aluminum hydride was added. The stirred reaction mixture was refluxed for 17 hr, after which it was treated with a saturated solution of sodium sulfate. The mixture was filtered, the solvent was removed, and the residual oil was distilled. A total of 3.83 g (39%) of product was obtained as a colorless liquid, bp 62° (0.15 mm), n^{23}D 1.5057, nmr δ 5.90 (2 H, m, HC=CH), $\lambda_{max}^{cyclohexane}$ 203 nm (ε 5700).

Anal. Calcd for $C_{11}H_{17}NO$: C, 73.71; H, 9.56. Found: C, 73.85; H, 9.64.

Registry No.—**7**, 34201-83-7; **9**, 20238-39-5; **13**, 34217-00-0; **15**, 34217-01-1; **16**, 34219-66-4; **18**, 34219-67-5; **22**, 34219-68-6; **24**, 34219-69-7.

(20) See Table II for synthetic method and physical properties.

Distal Effects in E2 Eliminations. Elimination of Hydrogen Chloride from Epimeric 8-Trichloromethyldibenzobicyclo[3.2.1]octadienes[1]

BRUCE B. JARVIS* AND JOHN P. GOVONI

Department of Chemistry, University of Maryland, College Park, Maryland 20742

Received August 6, 1971

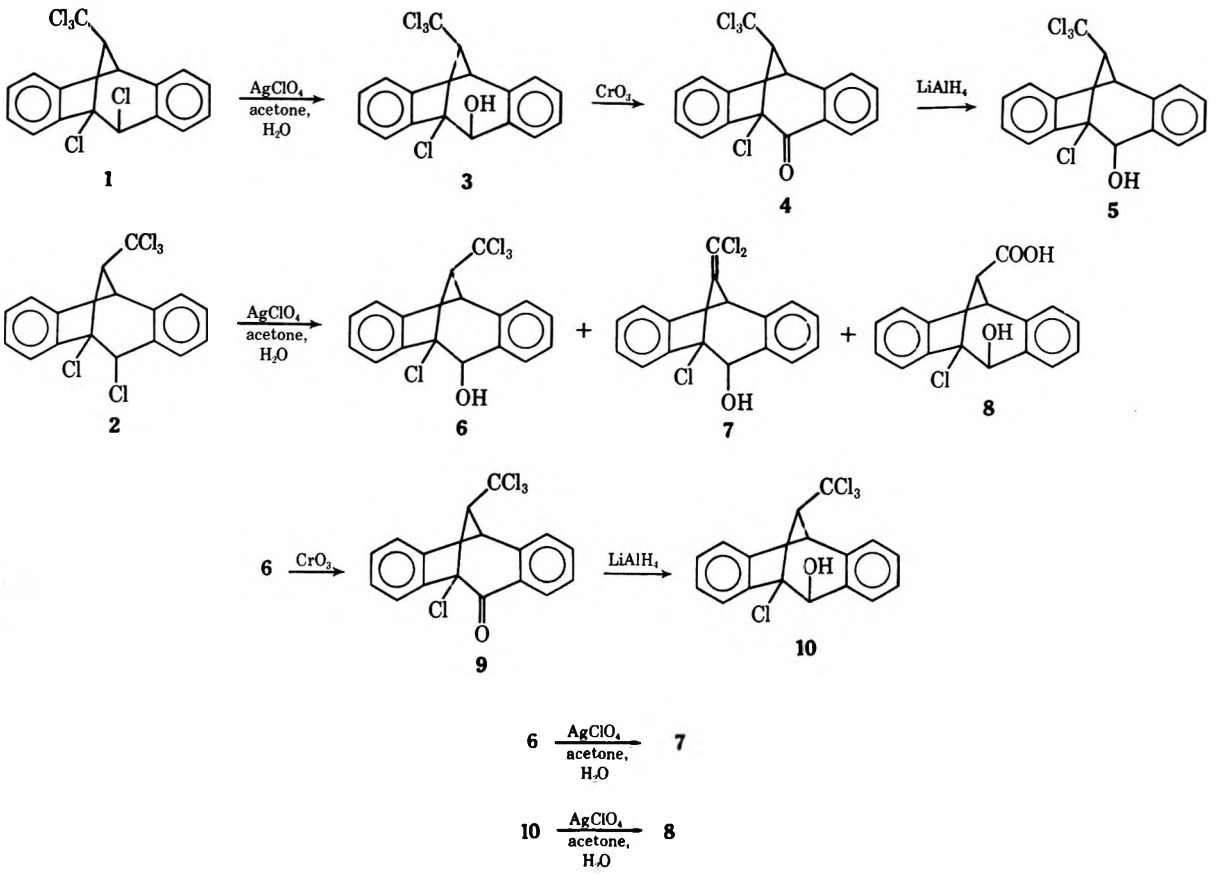
A series of C-4 substituted epimeric 8-trichloromethyldibenzobicyclo[3.2.1]octadienes were synthesized and their rates of elimination with lithium chloride in dimethylacetamide (DMA) measured. The substituents at C-4 have a marked effect on the rates for loss of hydrogen chloride from the *anti*-8-trichloromethyl epimers but have no apparent effect on the rates for the syn epimers. The k_{syn}/k_{anti} ranged from 48 to 2300 depending upon the substituent at C-4. This large ratio could be accounted for in terms of steric hindrance to approach by base to the C-8 hydrogen atom from the syn direction.

A great deal of data have been amassed on the variables associated with 1,2-elimination reactions.[2] Most of these data are concerned with how the nature of these reactions vary with changes either at the site of the leaving group (α and β positions) or in the base system employed. Little effort has been made to study what effect groups removed from the reaction sites (α and β) would have on the course of E2 eliminations. In particular, we wished to study the effect in β eliminations of groups removed from the reaction site in a sterically constrained system.

(1) (a) Taken in part from the M.S. thesis of J. P. Govoni, University of Maryland, 1970. (b) Presented in part at the 6th Middle Atlantic Regional Meeting of the American Chemical Society, Baltimore, Md., Feb 1971.

(2) (a) D. V. Banthorpe, "Elimination Reactions," Elsevier, Amsterdam, 1963; (b) J. F. Bunnett, *Angew. Chem., Int. Ed. Engl.*, **1**, 225 (1962); (c) R. F. Hudson, *Chimia (Aarau)*, **16**, 173 (1962); (d) D. J. McLennan, *Quart. Rev. (London)*, **21**, 490 (1967); (e) J. F. Bunnett, *Surv. Progr. Chem.*, **5**, 53 (1969).

SCHEME I



6 $\xrightarrow[\text{acetone, } H_2O]{AgClO_4}$ 7

10 $\xrightarrow[\text{acetone, } H_2O]{AgClO_4}$ 8

Results and Discussion

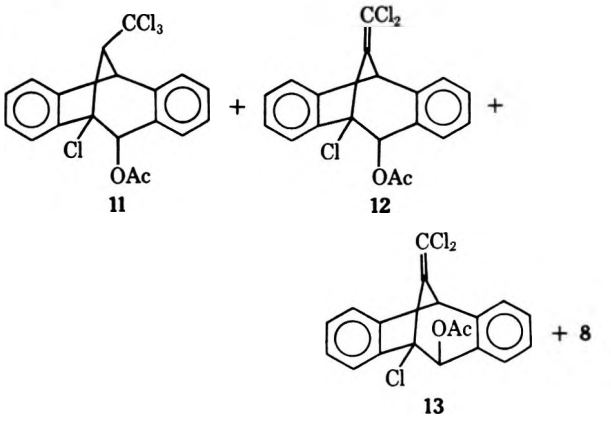
The epimeric trichloromethyl compounds (**1** and **2**) were available from a previous study.[3] These compounds appeared to be good candidates for studying the effect of substituents at the C-4 position on the rates of dehydrochlorination. Since the proton at C-8 is fixed in space with respect to the C-4 position, the electrostatic and/or steric effect of the groups at C-4 can be ascertained.

Scheme I outlines the syntheses of the alcohols and ketones whose rates of dehydrochlorination were measured.

Silver ion assisted solvolysis of **1** gives **3** cleanly. Oxidation of **3** to ketone **4** goes smoothly as does the reduction of **4** (lithium aluminum hydride) to give the endo alcohol **5**. However, solvolysis of the chloride **2** in aqueous acetone in the presence of an excess of silver perchlorate gives 60% **6**, 10% olefin **7**, and 30% acid **8**. Subsequently, it was shown that the endo alcohol **6** is converted slowly to the olefin **7** under the reaction conditions while the exo alcohol **10**[4] is converted very rapidly to the hydroxy acid **8**.

The rapid reaction of **10** with silver perchlorate in aqueous acetone (immediate precipitate of silver chloride is formed when aqueous silver perchlorate is mixed with **10** dissolved in aqueous acetone) is a clear example of neighboring-group participation in the solvolysis of the trichloromethyl group by an un-ionized hydroxyl group. It is felt that the hydroxyl group in **10** remains un-ionized during the course of these reactions for a number of reasons: (1) the presence of 0.1 *M* perchloric acid has no apparent effect on the rate of reaction of **10** or **6** with silver perchlorate in aqueous acetone; (2) **10** reacts only slowly with potassium carbonate in aqueous acetone and does not yield the acid **8**; (3) solvolysis of **2** with silver acetate in glacial acetic acid gives 20% endo acetate **11**, 55% *endo*-acetoxy olefin **12**, 20% of the acid **8** and ~5% of the *exo*-acetoxy olefin **13** (**11** → **12** under the reaction conditions). The transesterification of the acetate **12** yields the alcohol **7**. Formation of acid **8** presumably in-

2 $\xrightarrow[HOAc]{AgOAc}$

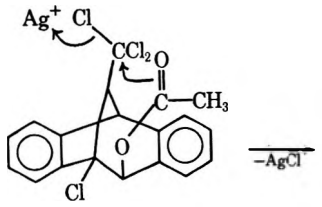


(3) B. B. Jarvis, J. P. Govoni, and P. J. Zell, *J. Amer. Chem. Soc.*, **93**, 913 (1971).

(4) The alcohol **10** is synthesized in high yield in two steps (see Scheme I) starting with **6**. Reduction of ketone **9** with lithium aluminum hydride occurs *via* hydride transfer from the sterically less hindered endo position.[5] The stereoelectronically more favored exo approach[5,6] is blocked by the bulky trichloromethyl group.

(5) (a) S. J. Cristol, F. P. Parungo, and D. E. Plorde, *J. Amer. Chem. Soc.*, **87**, 2870 (1965); (b) S. J. Cristol, R. J. Bopp, and A. E. Johnson, *J. Org. Chem.*, **34**, 3574 (1969).

(6) S. J. Cristol, F. P. Parungo, D. E. Plorde, and K. Schwarzenbach, *J. Amer. Chem. Soc.*, **87**, 2879 (1965).



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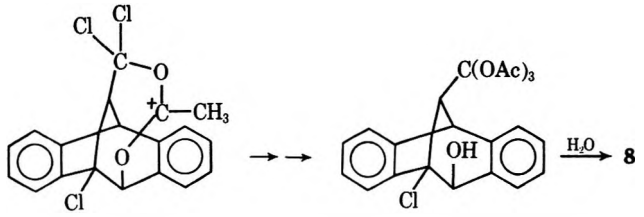


volves participation by the *exo*-acetoxy group in the intermediate acetate **14**. Such participation by an acetoxy group is known to lead eventually to an alcohol if any water is present in the acetic acid.[7]

Interestingly, trichloromethylphenylcarbinol gives no reaction with silver perchlorate in aqueous acetone at reflux for extended periods of time. Normally, epoxides are formed less readily than tetrahydrofurans,[8,9] but the difference in reactivity between trichloromethylphenylcarbinol and **10** must be extremely large. This difference can be accounted for mainly in the entropy factor ($\Delta S^{\pm}$), since in **10** the hydroxyl group is held in close proximity to the incipient carbonium ion owing to the rigidity of the carbon skeletal system.

What is less clear, though, is why a number of these *syn*-trichloromethyl compounds (**6** and **11**) undergo loss of hydrogen chloride upon treatment with silver perchlorate in aqueous acetone. The *anti*-trichloromethyl epimeric alcohols **3** and **5** and 2,2-bis(4-chlorophenyl)-1,1,1-trichloroethane (DDT) show no sign of reacting with silver perchlorate under these conditions. The syn ketone **9** also reacts, albeit slowly, with silver perchlorate in refluxing aqueous acetone. It would appear that these reactions of **6**, **9**, and **11** are E1 reactions, but what is not clear is why the corresponding SN1 reactions, which normally accompany E1 reactions,[10,11] are not observed.

The trichloromethyl compounds react with a variety of bases with loss of hydrogen chloride to give the corresponding dichloromethylene compounds (**7**, **15**, and **16**). However, the olefins are sensitive to strong base,[13] and it was most convenient to use the relatively mild base system, lithium chloride in dimethylacetamide (DMA), for both syntheses and kinetic studies.

(7) S. Winstein, H. U. Hess, and R. E. Buckles, *J. Amer. Chem. Soc.*, **64**, 2796 (1942).

(8) B. Capon, *Quart. Rev. (London)*, **18**, 45 (1964).

(9) S. Winstein, E. Allred, R. Heck, and R. Glick, *Tetrahedron*, **3**, 1 (1958).

(10) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," 2nd Ed., Cornell University Press, Ithaca, N. Y., 1969, Chapter IX.

(11) Chlorine atoms are known[12] to have a stabilizing effect on carbon–carbon double bonds. This may account in part for high ratio of E1/SN1 products.

(12) A. N. Nesmeyanov, R. K. Freidlina, and V. I. Firstov, *Dokl. Akad. Nauk SSSR*, **78**, 717 (1951).

(13) Ketones **4** and **16** react instantly with 1.0 *M* potassium *tert*-butoxide in *tert*-butyl alcohol at room temperature to give a deep purple solution. No identifiable organic compounds could be isolated from these solutions. All of the 8-trichloromethyldibenzob:cyclo[3.2.1]octadienes (and the corresponding olefins derived from these compounds) reported in this work behaved in a similar manner upon treatment with strong bases. The ketones were the most sensitive compounds.

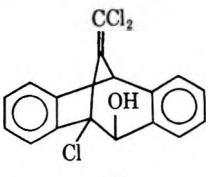
TABLE I

RATE DATA[a] FOR LOSS OF HYDROGEN CHLORIDE FOR THE TETRACHLORIDES **3**, **4**, **5**, **6**, **9**, AND **10**[b] WITH LITHIUM CHLORIDE[c,d] IN DMA AT 130.2°

Compd	k_2 (l. mol^{-1} sec^{-1})[e]	k^{rel}
anti-**4** (ketone)	7.0×10^{-5}	50
anti-**3** (*exo*-OH)	5.6×10^{-6}	4.0
anti-**5** (*endo*-OH)	1.4×10^{-6}	1.0
syn-**9** (ketone)	3.4×10^{-3}	2400
syn-**10** (*exo*-OH)	3.2×10^{-3}	2300
syn-**6** (*endo*-OH)	3.2×10^{-3}	2300

[a] Reaction rates were followed by titration with standard base for liberated acid. [b] 0.03 *M*. [c] 0.308 *M*. [d] Reactions were first order in chloride ion as shown by a linear plot of k_{obsd} *vs.* [Cl$^-$], where [Cl$^-$] varied from 0.902 to 0.094 *M*. [e] Precision of ±2–4% for k_2.

Table I gives the rate data for dehydrochlorination of the tetrachlorides with lithium chloride in DMA at 130.2°.



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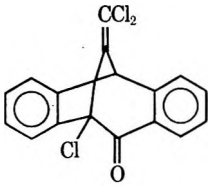

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The behavior of the anti epimers (**3**–**5**) can be contrasted to that of the syn compounds (**6**, **9**, and **10**). Whereas the reactivities of the syn isomers (**6**, **9**, and **10**) toward lithium chloride in DMA are all about the same, the reactivities of the anti epimers vary by a factor of 50 going from the endo alcohol **5** to the ketone **4**. This variation in rate for the anti series can be explained by the electronic nature of the substituent at C-4 (>C=O more electron withdrawing than the >CHOH group). Furthermore, this electrostatic effect appears to be transmitted through space (field effect[14]) rather than through the carbon chain.

The sensitivity of the elimination reactions in the *anti*-trichloromethyl compounds is also evident in compounds lacking the C-5 bridgehead chlorine atom. Five compounds in this series were synthesized as outlined below (Scheme II). Treatment of these trichlorides with lithium chloride in DMA gave the corresponding dichloro olefins (**25**–**29**) in high yields. Table II lists the rate data for the reactions of **18**–**22** with lithium chloride in DMA at 130.2°.

From a comparison of Tables I and II it is clear that the bridgehead chlorine atom in **3**–**5** has little effect on the behavior of these compounds in the elimination reactions. Furthermore, the effect of the substituents at C-4 on the rates of elimination (Table II) is that anticipated from the electron-withdrawing ability of these groups (>C=O > >CHOH > >CH_2).[15]

(14) (a) R. Golden and L. M. Stock, *J. Amer. Chem. Soc.*, **88**, 5928 (1966); (b) C. F. Wilcox and C. Leung, *ibid.*, **90**, 336 (1968); (c) M. J. S. Dewar and A. P. Marchand, *ibid.*, **88**, 3318 (1966); (d) M. J. S. Dewar and T. G. Squires, *ibid.*, **89**, 210 (1967); (e) W. Adcock and M. J. S. Dewar, *ibid.*, **89**, 379 (1967); (f) C. L. Liotta, W. F. Fisher, and G. H. Green, *Chem. Commun.*, 1251 (1969).

(15) (a) The rate of elimination decreases going from **22** to *exo*-methoxy **21**, contrary to what might be expected from the electron-withdrawing ability of a methoxyl group compared with a hydrogen atom. The more bulky *exo*-methoxyl group may impede approach of base to the syn-C-8 proton. (b) The relatively large effect of the carbonyl group is consistent with the expected field effect; see P. G. Gassman and F. V. Zolar, *J. Amer. Chem. Soc.*, **88**, 3070 (1968), and R. M. Moriarty, C. R. Romain, and T. O. Lovett, *ibid.*, **89**, 3927 (1967).

SCHEME II

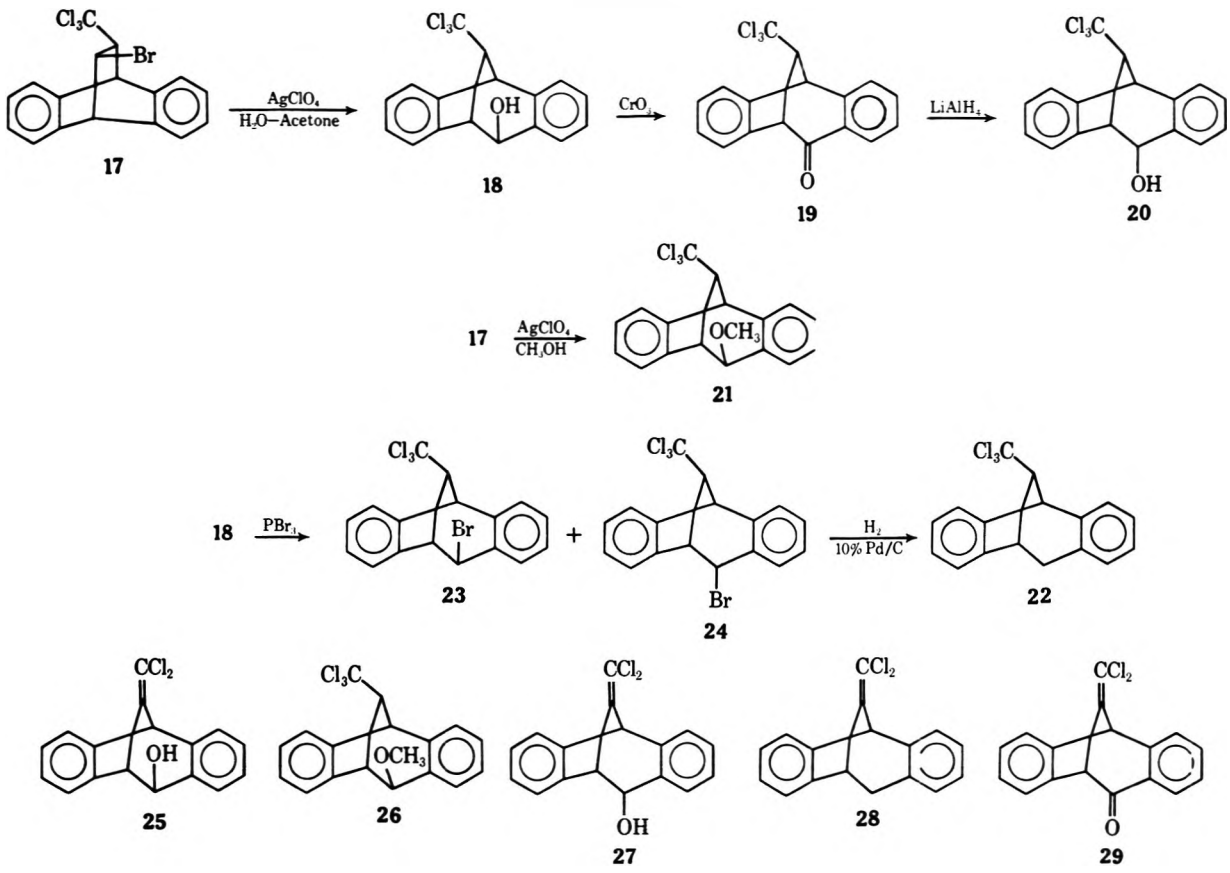


TABLE II

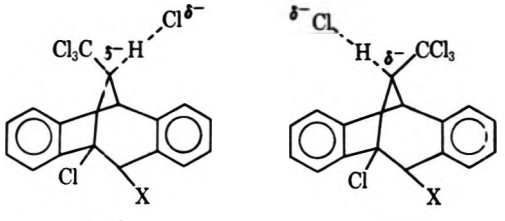
RATE DATA[a] FOR LOSS OF HYDROGEN CHLORIDE FOR THE TRICHLORIDES 18–22[b] WITH LITHIUM CHLORIDE[c,d] IN DMA AT 130.2°

Compd	k_2 (l. mol^{-1} sec^{-1})	k_{rel}
19	8.4×10^{-5}	35
18	6.8×10^{-6}	5.2
20	1.7×10^{-6}	1.3
22	1.3×10^{-6}	1.0
21	4.0×10^{-7}	0.33

[a] Reaction rates were followed by titration with standard base for liberated acid. [b] 0.03 *M*. [c] 0.308 *M*. [d] Reactions were first order in chloride ion as shown by a linear plot of K_{obsd} *vs.* [Cl$^-$], where [Cl$^-$] varied from 0.902 to 0.094 *M*.

Compounds **18**–**22** were also treated with potassium hydroxide in methanol at 65°. Attempts to obtain reproducible kinetic data past ~1 half-life for these reactions were unsuccessful presumably owing to significant product decomposition.[13] However, crude data (see Experimental Section) showed that the spread in reactivity (compared with data in Table II) between the methyl ether **21** and the ketone **19** had increased by a factor of only about 2.

The invariance in the rates of elimination in the *syn*-trichloromethyl ketone and alcohols (**6**, **9**, and **10**, Table I) can be contrasted with 50-fold range [k_4/k_5 (Table I) ~ k_{19}/k_{20} (Table II) = 50] observed in the epimeric *anti*-trichloromethyl series. The difference can be attributed to a number of effects but again a simple field effect would appear to be most consistent with the data; *i.e.* in the transition state in the anti series (**3**, **4**, and **5**) a partial negative charge is being generated in the C–H bond situated directly over the C-4 position while in the transition state in the syn series (**6**, **9**, and **10**) the partial negative charge is developing in an area more removed from the substituents at C-4. This suggestion implies that for

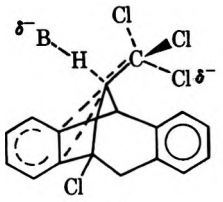


these E2 eliminations the transition states lies somewhat toward the paenecarbanion[2e] extreme rather than exactly at the central position. Previous work with chloride ion initiated E2 eliminations in aprotic solvents[16] have suggested that such eliminations lie very close to the "central"[17] transition state; *i.e.*, a good deal of double bond character between C_α and C_β has already developed in the transition state. Recent work on hydrogen chloride elimination from meta- and para-substituted DDT with chloride ion in DMF has yielded a ρ of +1.23 for these eliminations,[18] indicating at least some negative charge buildup on the benzhydryl carbon (C_β). The ρ for such eliminations is considerably larger for the stronger base systems, *e.g.*, ethoxide ion in ethanol.[19] We observe only a modest increase in the spread of the relative rates in the *anti*-trichloromethyl series (**18**–**22**) going from chloride ion in DMA to hydroxide ion in methanol. There

(16) A. J. Parker, *Chem. Rev.*, **69**, 1 (1969).
(17) E. Baciocchi and A. Schirali, *J. Chem. Soc. B*, 554 (1969).
(18) D. J. McLennan and R. J. Wong, *Tetrahedron Lett.*, 881 (1970).
(19) S. J. Cristol, *J. Amer. Chem. Soc.*, **67**, 1494 (1945).

in fact may be a good deal of double-bond character developed in the transition state for loss of hydrogen chloride from these dibenzobicyclo[3.2.1]octadienes, but the data available do not require such a conclusion.[20]

The relatively large k_{syn}/k_{anti} ratios for these eliminations (Table I) may be due to a number of factors. One aspect that is often invoked in explaining rate differences is anchimeric assistance. Two different transition states (**30** and **31**) might be suggested which would



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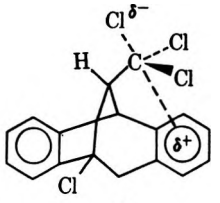

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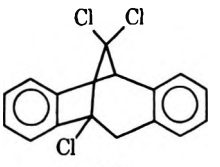
account for the syn epimers' reacting more rapidly than the anti epimers. Both of these models can be rejected. **30** actually should be higher in energy than a transition state not involving participation of the benzene ring since **30** would represent an anti aromatic system;[21] **31** would suggest that the transition state would lie toward the paenecarbonium ion extreme[2e] a fact not in accord with experimental observations (*vide supra*). Furthermore, the anti benzene ring probably is more favorably disposed toward participation,[22] and, even if the syn benzene ring were oriented correctly for participation, evidence is available in analogous systems[23] to suggest that the reaction would still not make use of such participation.

The most reasonable explanation for the large k_{syn}/k_{anti} ratio noted in Table I is the steric argument.[24] Reduction of the trichloride **32** with tri-*n*-butyltin hydride (*n*-Bu_3SnH) gives only the syn chloride **33**.[26] The product-determining step in this reaction is the chain transfer of a hydrogen atom from *n*-Bu_3SnH[27] to the radical **34**; this transfer takes place ~100% from the anti direction. Reduction of **32** with chromium(II) in aqueous DMF, a reaction believed to involve protonation of an intermediate carbanion as the product-determining step,[28a] also gives only **33**.[28b] Clearly, a variety of reagents prefer to approach the C-8 position in the dibenzobicyclo[3.2.1]octadiene system from the anti direction.[29]



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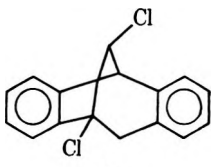

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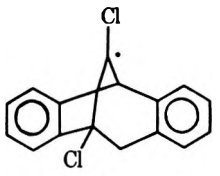

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Models show that reagents have a significantly more open approach from the anti direction than from the syn direction. Steric hindrance to attack by base from the syn direction then would seem to be the most reasonable explanation for the greater ease for E2 elimination of hydrogen chloride from the *syn*-8-trichloromethyldibenzobicyclo[3.2.1]octadienes in comparison with the anti epimers.[30]

Experimental Section[32]

Preparation of *exo*-4-Hydroxy-*anti*-8-trichloromethyldibenzobicyclo[3.2.1]octadiene (18).—To 10 g (0.025 mol) of **17**[33] dissolved in 100 ml of reagent grade acetone was added 10 g (0.048 mol) of silver perchlorate dissolved in 25 ml of water. The homogeneous mixture was stirred at reflux (65°) for 3 hr (a greenish yellow precipitate of silver bromide was formed). The mixture was allowed to cool, and 15 ml of concentrated hydrochloric acid was added to precipitate the excess silver ion. The inorganic precipitate was removed by filtration, water was added to the filtrate, and the filtrate was extracted twice with 100 ml of ether. The combined ether extracts were washed with water and saturated sodium carbonate solution and dried over anhydrous magnesium sulfate. The ether was removed by rotary evaporation, and a pmr spectrum of the resulting solid showed only the exo alcohol present. After recrystallization from Skellysolve B–carbon tetrachloride, the yield was 8.5 g (83%) of **18**, mp 159–160°, ν_{OH} 3590 cm^{-1}.

The pmr spectrum of **18** shows a singlet (1 H) at τ 5.68 (J_{18} = 0 Hz), two slightly broadened singlets (2 H and 1 H, respectively at 6.20 (H-5 and H-8 have the same chemial shift) and 6.53,[34] a doublet (1 H) at 5.37 (J_{45} = 2.5 Hz), and a complex multiplet (8 H) from 2.4 to 3.0.

Anal. Calcd for $C_{17}H_{13}Cl_3O$: C, 60.12; H, 3.86. Found: C, 59.87; H, 3.90.

Oxidation of 18 with Jones Reagent.—The alcohol **18** (8.0 g, 0.024 mol) was dissolved in 25 ml of reagent grade acetone and stirred at 25° under nitrogen. Jones reagent (15 ml, prepared from 26.72 g of chromium trioxide in 25 ml of concentrated sulfuric acid and diluted to 100 ml with water) was added dropwise over a 5-min period. Greenish chromium salts were seen to

(20) F. G. Bordwell, *Accounts Chem. Res.*, **3**, 281 (1970).

(21) R. Breslow, R. Pagni, and W. N. Washburn, *Tetrahedron Lett.*, 547 (1970); however, others have suggested that such an electronic array might be a source of stabilization. See C. K. Alden and D. I. Davies, *J. Chem. Soc. C*, 700 (1968).

(22) (a) S. J. Cristol, J. R. Mohrig, F. P. Parungo, D. E. Plorde, and K. Schwarzenbach, *J. Amer. Chem. Soc.*, **85**, 2675 (1963); (b) G. W. Klumpp, G. Ellen, and F. Bickelhaupt, *Recl. Trav. Chim. Pays-Bas*, **88**, 474 (1969).

(23) R. K. Bly and R. S. Bly, *J. Org. Chem.*, **31**, 1577 (1966).

(24) A number of studies[25] of E2 eliminations in bridged bicyclic systems has shown that elimination reactions in these systems are rather sensitive to steric hindrance.

(25) N. A. LeBel, P. D. Beirne, T. R. Karger, J. C. Powers, and P. M. Subramanian, *J. Amer. Chem. Soc.*, **85**, 3199 (1963); D. I. Davies and L. T. Parfitt, *J. Chem. Soc. C*, 2691 (1967).

(26) B. B. Jarvis and J. B. Yount, III, *Chem. Commun.*, 1405 (1969).

(27) (a) H. G. Kuivila, *Accounts Chem. Res.*, **1**, 299 (1968); (b) D. J. Carlsson and K. U. Ingold, *J. Amer. Chem. Soc.*, **90**, 7047 (1968).

(28) (a) J. K. Kochi and J. W. Powers, *ibid.*, **92**, 137 (1970); (b) J. B. Yount, III, M.S. Thesis, University of Maryland, 1970.

(29) The C-8 anti chlorides solvolyze much more readily than do the epimeric syn chlorides;[29a] however, these reactions are not comparable with those reported above since solvolysis of the anti chlorides leads to carbon skeletal rearranged products.

(30) Torsional strain[26,31] might also be envoked to account for the rate differences observed in these epimers. However, contribution by torsional strain is believed to be minimal in the formation of exocyclic double bonds.[31c]

(31) (a) C. L. Osborn, J. V. Van Auken, and D. J. Treker, *J. Amer. Chem. Soc.*, **90**, 5806 (1968); (b) F. R. Jensen, J. H. Gale, and J. E. Rogers, *ibid.*, **90**, 5739 (1968); (c) P. v. R. Schleyer, *ibid.*, **89**, 701 (1967).

(32) Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Pmr spectra were run in carbon tetrachloride solutions (unless otherwise noted) and measured with a Varian A-60D spectrometer with tetramethylsilane (τ 10.00) as the internal standard. *J* values are "observed" ones. Ir spectra were taken on a Perkin-Elmer 337 infrared spectrometer in 0.5-mm matched cells with carbon tetrachloride as the solvent. The uv spectra of **3** and **4** were obtained on a Cary 15 spectrometer in 1.0-mm matched quartz cells with ethanol as the solvent. Microanalyses were performed by Dr. F. K. Kasler, University of Maryland.

(33) B. B. Jarvis, *J. Org. Chem.*, **33**, 4075 (1968).

(34) Since the chemical shift associated with the hydroxyl group does not remain constant when the concentration of the compound in solution is changed, this peak is not reported for the other alcohols (**3**, **5**, **6**, **7**, **8**, **10**, **15**, **20**, **25**, and **27**.

precipitate. The reaction solution was allowed to stir for an additional 5 min at which time 75 ml of water was added to dissolve the chromium salts and the entire mixture was extracted twice with 50-ml portions of ether. The ethereal portions were washed with saturated sodium chloride and dried over anhydrous magnesium sulfate. The ether was removed by rotary evaporation, and the resulting solid was found to be entirely the *anti*-8-trichloromethyldibenzobicyclo[3.2.1]octadien-4-one (**19**) by pmr spectroscopy. Recrystallization from a methanol–methylene chloride mixture gave 6.0 g (75%) of ketone: mp 155–156°; $\nu_{C=O}$ 1750 cm^{-1}; λ 211 nm (ϵ 24,700), 227 (14,300), 242 (12,300), 278 (2750), 300 (1200), 338 (400), 351 (340) and 365–370 (160).

The pmr spectrum of **19** shows a singlet (1 H) at τ 6.06, a pair of doublets (1 H each) at 5.42 and 5.58 (J_{15} = 1.4 Hz, long range coupling;[35] J_{18} = 0 Hz), and a complex multiplet from 2.2 to 3.0.

Anal. Calcd for $C_{17}H_{11}Cl_3O$: C, 60.48; H, 3.28. Found: C, 60.78; H, 3.38.

Preparation of *endo*-4-Hydroxy-*anti*-8-trichloromethyldibenzobicyclo[3.2.1]octadiene (20).—To 100 mg (2.6 mmol) of lithium aluminum hydride dissolved in 15 ml of dry ether at room temperature and under nitrogen was slowly added 1.4 g (4.1 mmol) of the ketone **19** as a solid. The mixture was stirred for an additional 5 min at which point water was added dropwise to destroy the excess lithium aluminum hydride. The inorganic precipitate which formed was removed by filtration, and water was added to the filtrate. Two 50-ml ether extractions were taken, and the combined ethereal portions were washed with water and saturated sodium chloride and dried over magnesium sulfate. Rotary evaporation of the solvent yielded a yellow oil whose pmr spectrum showed only the endo alcohol **20** present. This was crystallized from a pentane–carbon tetrachloride mixture to give 1.2 g (86%) of **20**, mp 150–151°.

The pmr spectrum for **20** shows two singlets (1 H each) at τ 5.72 and 6.67 (J_{18} = 0 Hz), two doublets (1 H each) at 5.28 and 6.17 (J_{45} = 5.6 Hz), and a complex multiplet (8 H) from 2.3 to 3.0.

Anal. Calcd for $C_{17}H_{13}Cl_3O$: C, 60.12; H, 3.86. Found: C, 60.08; H, 3.93.

Preparation of *exo*-4-Methoxy-*anti*-8-trichloromethyldibenzobicyclo[3.2.1]octadiene (21).—To a solution of 4.5 g (0.011 mol) of **17** in 100 ml of absolute methanol, held at reflux, was added 4.5 g (0.022 mol) of silver perchlorate dissolved in 25 ml of methanol. The mixture was held at reflux for 3 hr and cooled, and 150 ml of water was added. Two 100-ml ether extractions were taken, and the combine ethereal portions were washed with water and saturated with sodium chloride and dried over magnesium sulfate. Rotary evaporation of the ether yielded a solid, which was found by pmr spectroscopy to be the *exo*-methoxy compound **21**. This was recrystallized from ethanol to yield 3.6 g (79%) of **21**, mp 114–115°.

The pmr spectrum of **21** shows three singlets (1 H, 1 H, and 3 H, respectively) at τ 5.90 (J_{45} < 0.5 Hz), 6.15 (J_{18} = 0 Hz), and 6.36 (OCH_3), a pair of broadened overlapping singlets (2 H) from 5.67 to 5.75, and a complex multiplet (8 H) from 2.5 to 3.0.

Anal. Calcd for $C_{18}H_{15}Cl_3O$: C, 61.13; H, 4.28. Found: C, 61.15; H, 4.34.

Reaction of 18 with Phosphorus Tribromide.—To 3.0 g (8.9 mmol) of the exo alcohol **18**, dissolved in 20 ml of dry ether, was added a solution of 10 ml of phosphorus tribromide and 5 ml of dry ether. The mixture was held at reflux for 15 hr. The excess phosphorus tribromide was destroyed by slow addition of saturated sodium carbonate. Water was added, and two 50-ml ether extracts were taken. The combined ethereal portions were washed with saturated sodium carbonate and water, dried over magnesium sulfate, and decolorized with charcoal. The ether was removed by rotary evaporation to yield a yellow oil (2.9 g, 81%). A pmr spectrum showed approximately 60% exo bromide **23** and 40% an isomer believed to be the endo bromide **24**. Slow crystallization of the mixture from ethanol gave 0.4 g of pure exo compound **23**, mp 125–126°. A second recrystallization gave 2.3 g of a 50:50 mixture of the isomers. An attempt to isolate the endo isomer by chromatography on silica gel gave no separation. No further attempts were made since the bromide was an intermediate in the synthesis of the hydrocarbon described next.

The pmr spectrum for **23** shows two singlets (1 H each) at τ 5.68 and 5.90, a pair of doublets (1 H each) at τ 4.56 and 5.82 (J_{45} = 2.2 Hz), and a complex multiplet (8 H) from τ 2.4 to 30.

Anal. Calcd for $C_{17}H_{12}BrCl_3$: C, 50.72; H, 3.01. Found: C, 50.48; H, 3.02.

Preparation of *anti*-8-Trichloromethyldibenzobicyclo[3.2.1]octadiene (22).—One gram (2.5 mmol) of a 50:50 mixture of exo and endo bromides **23** and **24**, dissolved in 35 ml of absolute ethanol was placed in a hydrogenation apparatus[36] with 200 mg of 10% palladium on charcoal as a catalyst. After 2 hr, addition of hydrogen had ceased with 65.0 ml of hydrogen gas consumed by the ethanol solution. Removal of the catalyst by filtration was followed by addition of water and two extractions with 50-ml portions of ether. The ethereal portions were washed with saturated sodium chloride and dried over magnesium sulfate. Removal of the ether by rotary evaporation resulted in a solid whose pmr spectrum indicated that it was pure hydrocarbon **22**. Recrystallization from ethanol gave 0.58 g (71%) of **22**, mp 152°.

The pmr spectrum of **22** shows two singlets (1 H each) at τ 5.73 and 6.57 (J_{18} = 0 Hz), two doublet of doublets (1 H each) at 6.63 (J_{gem} = 17.0 Hz; $J_{exo\text{-}45}$ = 1.7 Hz) and 7.18 (J_{gem} = 17.0 Hz; $J_{endo\text{-}45}$ = 5.0 Hz), a complex multiplet (1 H) from 6.06 to 6.22, and another complex multiplet (8 H) from 2.8 to 3.1.

Anal. Calcd for $C_{17}H_{13}Cl_3$: C, 63.09; H, 4.05. Found: C, 62.80; H, 4.11.

Dehydrochlorination of 18–22.—Treatment of the trichlorides **18–22** with 1 *M* lithium chloride in dimethylacetamide (DMA) at 130° gave the corresponding olefins **25–29**. Reaction times varied from 1 hr for the ketone **19** to 10 days for the methyl ether **21**. Reaction mixtures were worked up by quenching with water followed by ether extraction. The products were isolated in 75–90% yield and the materials were recrystallized from ethanol. Pertinent physical data for **25–29** are given below. Treatment of **18–22** with 1 *M* potassium *tert*-butoxide in *tert*-butyl alcohol at reflux gave **26** and **28** in moderately good yields (50–70%), and **25** and **27** in poor yields (5–10%). **29** could not be observed in the reaction of **19** with this base system. Under the conditions of the reaction (1 *M* base at room temperature), **29** was rapidly destroyed. The other olefins (**25–28**) were also slowly destroyed under these conditions.

The pmr spectrum of **25** (mp 146–147°; $\nu_{C=C}$ 1660 cm^{-1}, ν_{OH} 3580 cm^{-1}) shows two singlets (1 H and 2 H, respectively) at τ 5.46 and 5.38 (H-4 and H-5 have the same chemical shift) and a complex multiplet from 2.3 to 3.0.

Anal. Calcd for $C_{17}H_{12}Cl_2O$: C, 67.35; H, 3.99. Found: C, 67.40; H, 4.06.

The pmr spectrum for **26** (mp 156–157°; $\nu_{C=C}$ 1655 cm^{-1}, $\nu_{C=O}$ 1090 cm^{-1}) shows two singlets (1 H and 3 H, respectively) at τ 5.38 (J_{18} = 0 Hz) and 6.39 (OCH_3), a multiplet (2 H) from 5.55 to 5.70, and another multiplet (8 H) from 2.3 to 3.0.

Anal. Calcd for $C_{18}H_{14}Cl_2O$: C, 68.16; H, 4.45. Found: C, 68.06; H, 4.53.

The pmr spectrum of **27** (mp 131–132°; $\nu_{C=C}$ 1645 cm^{-1}, ν_{OH} 3570 cm^{-1}) shows a singlet (1 H) at τ 5.43, a pair of doublets (1 H each) at 5.10 and 5.72 (J_{45} = 5.8 Hz), and a complex multiplet from 2.3 to 3.0.

Anal. Calcd for $C_{17}H_{12}Cl_2O$: C, 67.35; H, 3.99. Found: C, 67.10; H, 4.06.

The pmr spectrum of **28** (mp 148–149°, $\nu_{C=C}$ 1650 cm^{-1}) shows a singlet (1 H) at τ 5.40, a pair of doublet of doublets (1 H each) at 6.61 (J_{gem} = 17.0, $J_{exo\text{-}45}$ = 1.6 Hz) and 7.17 (J_{gem} = 17.0; $J_{endo\text{-}45}$ = 5.0 Hz), a complex multiplet (1 H) from 5.72 to 5.88, and another complex multiplet (8 H) from 2.7 to 3.0.

Anal. Calcd for $C_{17}H_{12}Cl_2$: C, 71.10; H, 4.21. Found: C, 70.99; H, 4.27.

The pmr spectrum for **29** [mp 153–154°; $\nu_{C=C}$ 1650 cm^{-1}, $\nu_{C=O}$ 1700 cm^{-1}; λ 208 nm (ϵ 36,300), 223 (31,600), 262–272 (4440), 295–308 (760), 340 (410), 355 (380), 372 (180)] shows two singlets (1 H each) at τ 5.15 and 5.27 and a complex multiplet (8 H) from 2.2 to 3.0.

Anal. Calcd for $C_{17}H_{10}Cl_2O$: C, 67.80; H, 3.34. Found: C, 67.52; H, 3.52.

Preparation of *exo*-4-Hydroxy-5-chloro-*anti*-8-trichloromethyldibenzobicyclo[3.2.1]octadiene (3).—To a solution of 2.0 g (5.1 mmol) of anti-exo chloride 1[3] in 30 ml of acetone, held at reflux, was added 1.6 g (7.8 mmol) of silver perchlorate dissolved in 15 ml of water. The homogeneous mixture was held at reflux (65°) for 6 hr and worked up as usual. (The reaction was in-

(35) S. J. Cristol, J. R. Mohrig, and D. E. Plorde, *J. Org. Chem.*, **30**, 1956 (1965).

(36) K. B. Wiberg, "Laboratory Technique in Organic Chemistry," McGraw Hill, New York, N. Y., 1960, p 228.

complete after 4 hr.) Recrystallization from Skellsolve B–ether gave 1.6 g (87%) of the alcohol **3**, mp 158–159°, ν_{OH} 3650 cm^{-1}.

The pmr spectrum of **3** shows three singlets (1 H each) at τ 5.32, 5.34, and 5.80 (J_{18} = 0 Hz) and a complex multiple (8 H) from 2.3 to 3.0.

Anal. Calcd for $C_{17}H_{12}Cl_4O$: C, 54.58; H, 3.23. Found: C, 54.77; H, 3.30.

Preparation of 5-Chloro-*anti*-8-trichloromethyldibenzobicyclo[3.2.1]octadien-4-one (4).—To 2.2 g (0.059 mol) of alcohol **3** dissolved in 15 ml of acetone under nitrogen was slowly added 7 ml of Jones reagent at 25°. The rest of the procedure is like that for the preparation of **19**. The yield was 2.0 g (91%) of **4**, mp 195° (from ethanol), $\nu_{C=O}$ 1702 cm^{-1}.

The pmr spectrum for **4** shows two singlets (1 H each) at τ 4.98 and 5.87 (J_{18} = 0 Hz) and a complex multiplet (8 H) from 2.1 to 3.0.

Preparation of *endo*-4-Hydroxy-5-chloro-*anti*-8-trichloromethyldibenzobicyclo[3.2.1]octadiene (5).—To 90 mg (2.5 mmol) of lithium aluminum hydride dissolved in 15 ml of dry ether under nitrogen at room temperature was added slowly 1.0 g (2.7 mmol) of ketone **4** as a solid. The rest of the procedure is like that for the preparation of **20**. The yield was 0.82 g (82%) of pure **5**, mp 179° (Skellysolve B–ether), ν_{OH} 3550 cm^{-1}.

The pmr spectrum for **5** shows three singlets (1 H each) at τ 4.98, 5.34, and 6.32 (J_{18} = 0 Hz) and a complex multiplet (8 H) from 2.4 to 3.0.

Anal. Calcd for $C_{17}H_{12}Cl_4O$: C, 54.58; H, 3.23. Found: C, 54.34; H, 3.30.

Reaction of *endo*-4,5-Dichloro-*syn*-8-trichloromethyldibenzobicyclo[3.2.1]octadiene (2) with Silver Perchlorate in Aqueous Acetone.—To 2.0 g (5.1 mmol) of **2**[3] in 30 ml of acetone was added 2.4 g (11.7 mmol) of silver perchlorate in 15 ml of water. The homogeneous mixture was held at reflux (65°) for 6 hr. After the solution was allowed to cool, concentrated hydrochloric acid was added, and the silver chloride was removed by filtration. The remaining procedure was identical with that used for the preparation of **18**. Removal of the ether by rotary evaporation yielded an oil, but addition of 10 ml of carbon tetrachloride resulted in the formation of a precipitate. The insoluble material (0.45 g) was collected, and a pmr spectrum of the *filtrate* was taken. This revealed a mixture of 85% **6** and 15% **2**. The total weight of the mixture as an oil was 1.15 g. The oil was crystallized from Skellysolve B–ether to give 0.91 g (48%) of **6**, mp 149–150°, ν_{OH} 3555 cm^{-1}.

The pmr spectrum of **6** shows a singlet (1 H) at τ 4.54, a pair of doublets (1 H each) at 5.50 and 5.86 (J_{18} = 3.6 Hz), and a complex multiplet (8 H) from 2.4 to 3.0.

Anal. Calcd for $C_{17}H_{12}Cl_4O$: C, 54.58; H, 3.23. Found: C, 54.30; H, 3.27.

The solid which was collected was found to be soluble in saturated sodium carbonate solution, and an ir spectrum of this solid (KBr pellet) showed the unknown substance to be an acid. After two recrystallizations from acetic acid–water, 0.20 g (13%) of **8** was obtained, mp 286–287°, ν_{OH} 3550 cm^{-1}.

The pmr spectrum of **8** [in $CD_3S(=O)CD_3$] shows a singlet (1 H) at τ 4.42, a pair of doublets (1 H each) at 5.62 and 6.20 (J_{18} = 4.5 Hz), and a complex multiplet (8 H) from 2.3 to 3.0.

Anal. Calcd for $C_{17}H_{13}ClO_3$: C, 67.89; H, 4.36. Found: C, 67.59; H, 4.47.

It was found that the reaction of **2** with silver perchlorate did not proceed when stirred at room temperature for 4 hr. The reaction of **2** with silver perchlorate in aqueous acetone that was 0.1 *M* in perchloric acid gave essentially identical results as the reaction run in the absence of perchloric acid. Also, addition of potassium carbonate (forming a basic solution) slowed the reaction (50% completion after a 20-hr reflux period with 2 equiv of silver perchlorate to 1 equiv of potassium carbonate).

Preparation of 5-Chloro-*syn*-8-trichloromethyldibenzobicyclo[3.2.1]octadien-4-one (9).—The alcohol **6** (0.80 g, 2.2 mmol) was dissolved in 10 ml of acetone under nitrogen. Jones reagent (5 ml) was added and the reaction was run in the same manner as described previously. The yield was 0.71 g (89%) of ketone **9**, mp 182–183° (from ethanol–methylene chloride), $\nu_{C=O}$ 1710 cm^{-1}.

The pmr spectrum of **9** shows a pair of doublets (1 H each) at τ 5.25 and 5.42 (J_{18} = 3.7 Hz) and a complex multiplet (8 H) from 2.1 to 3.0.

Anal. Calcd for $C_{17}H_{10}Cl_4O$: C, 54.88; H, 2.69. Found: C, 54.89; H, 2.81.

Preparation of *exo*-4-Hydroxy-5-chloro-*syn*-8-trichloromethyldibenzobicyclo[3.2.1]octadiene (10).—The ketone **9** (0.60 g, 1.6 mmol) was added slowly as a solid to 50 mg (1.3 mmol) of lithium aluminum hydride in 15 ml of dry ether. The procedure for the preparation of **20** was followed, and the resulting oil was crystallized from pentane–ether to give 0.55 g (92%) of the exo alcohol **10**, mp 128°, ν_{OH} 3555 cm^{-1}.

The pmr spectrum of **10** shows a singlet at τ 5.41, a pair of doublets (1 H each) at 5.43 and 5.92 (J_{18} = 3.5 Hz), and a complex multiplet (8 H) from 2.3 to 3.0.

Anal. Calcd for $C_{17}H_{12}Cl_4O$: C, 54.58; H, 3.23. Found: C, 54.52; H, 3.32.

Reaction of the Four 4-Hydroxy-5-chloro-8-trichloromethyldibenzobicyclo[3.2.1]octadienes (3, 5, 6, and 10) with Silver Perchlorate in Aqueous Acetone.—To 0.200 g (0.54 mmol) of each of the alcohols dissolved in 20 ml of acetone was added 0.350 g (1.69 mmol, 3 equiv) of silver perchlorate dissolved in 10 ml of water. The mixture was held at reflux for the time specified below, and the solution was allowed to cool. Hydrochloric acid was added, and the inorganic precipitate was removed by filtration. The filtrate after addition of water was extracted with two 50-ml portions of ether. The combined ethereal portions were washed three times with saturated sodium carbonate solution, dried over magnesium sulfate, and rotary evaporated. The resulting oil was dissolved in carbon tetrachloride solution and a pmr spectrum was taken. The three sodium carbonate washings and the aqueous layer were combined, made acidic with hydrochloric acid, and extracted twice with 100-ml portions of ether. The ethereal portions were washed with saturated sodium chloride, dried over magnesium chloride, and rotary evaporated. The following results were obtained.

For **3** and **5** (after 48 hr), only starting material was observed in the initial ether layer, and no organic material was found in the ether extracts of the aqueous layer.

For **6** (after 24 hr), 60% **7** was found present in the ether layer, and no acid was observed in the aqueous layer. Reflux of the recovered material for another 30 hr under the same conditions resulted in complete conversion of **6** to **7**. The oil was crystallized from Skellysolve B–ether to give 0.125 g (69%) of pure **7**, mp 147–148°, $\nu_{C=C}$ 1640 cm^{-1}, ν_{OH} 3650 cm^{-1}.

The pmr spectrum of **7** shows two singlets (1 H each) at τ 4.92 and 5.17 and a complex multiplet (8 H) from 2.4 to 3.0.

Anal. Calcd for $C_{17}H_{11}Cl_3O$: C, 60.48; H, 3.28. Found: C, 60.50; H, 3.39.

For **10**, instantaneous precipitation of silver chloride was observed when the silver perchlorate was added to the acetone solution of **10** at room temperature. After a 30-min period of reflux, the reaction was worked up to yield no material in the ether layer and 0.120 g (75%) of acid **8** from the water layer (recrystallization from acetic acid–water). The structure was proven by ir spectroscopy and a mixture melting point with an analytical sample of **8**.

Reaction of Syn-Endo Chloride 2 with Silver Acetate in Glacial Acetic Acid.—A mixture of 2.5 g (6.4 mmol) of **2** and 2.0 g (12 mmol) of silver acetate in 50 ml of glacial acetic acid was held at reflux for 19 hr. At this time most of the glacial acetic acid was removed by distillation, the silver chloride removed by filtration, and water added to the filtrate. After two extractions with 100-ml portions of ether, the combined extracts were washed three times with saturated sodium carbonate and dried over magnesium sulfate. Removal of the ether by rotary evaporation resulted in an oil that was found (by pmr spectroscopy) to consist of 25% acetate **11**, 70% olefin **12**, and 5% olefin **13** (configuration not actually proven). The oil weighed 1.9 g.

The aqueous layers were combined, made acidic, and worked up with ether to give 0.5 g of the acid **8** (structure confirmed by mixture melting point and ir spectroscopy after recrystallization from acetic acid–water). The oil (*vide supra*) was recrystallized from pentane and then recrystallized from methanol to give 0.640 g of **12**: mp 190°; $\nu_{C=C}$ 1640 cm^{-1}, $\nu_{C=O}$ 1690 cm^{-1}, ν_{C-O} 1220 cm^{-1}). Further fractional crystallizations from pentane and methanol failed to separate the remaining olefin **12** from the acetate **11** and from the unconfirmed olefin **13**.

The pmr spectrum of **12** shows three singlets (1 H, 1 H, and 3 H, respectively) at τ 4.12, 5.16, and 7.84 [$OC(=O)CH_3$], and a complex multiplet (8 H) from 2.3 to 3.0.

Anal. Calcd for $C_{19}H_{13}Cl_3O$: C, 60.11; H, 3.46. Found: C, 60.19; H, 3.53.

Treatment of the Acetoxy Olefin 12 with Hydrochloric Acid in Methanol.—A solution of 0.50 g (1.3 mmol) of **12** in 25 ml of concentrated hydrochloric acid was held at reflux for 7 hr. Water

was then added, and two 50-ml ether extractions were taken. The extracts were combined and washed with saturated sodium chloride, dried over magnesium sulfate, and decolorized with charcoal. Removal of the ether by rotary evaporation resulted in an oil, whose pmr spectrum was identical with that of the hydroxy olefin **7**. Crystallization from pentane–ether gave 0.41 g (93%), mp 188–190°.

Reaction of Trichloromethylphenylcarbinol with Silver Perchlorate in Aqueous Acetone.—To 2.0 g (0.16 mol) of trichloromethylphenylcarbinol[37] dissolved in 60 ml of acetone was added 3 equiv (10.0 g) of silver perchlorate in 30 ml of water to form a homogeneous solution. No silver chloride precipitate was observed during a 36-hr period of reflux. Work-up gave only unreacted starting material.

Reaction of DDT with Silver Perchlorate in Aqueous Acetone.—2,2-Bis(4-chlorophenyl)-1,1,1-trichloroethane (DDT, 1 g, 2.8 mmol) in 20 ml of acetone was heated to reflux. To this was added 1.75 g (8.4 mmol) of silver perchlorate in 10 ml of water, and the refluxing was continued for 48 hr. The standard work-up revealed only starting material in the ether layer and only traces of unidentifiable material in the water layer.

Reaction of the Syn Ketone 9 with Silver Perchlorate in Aqueous Acetone.—A solution of 0.20 g (0.54 mmol) of **9** and 0.34 g (16.2 mmol) of silver perchlorate in 20 ml of acetone and 10 ml of water was held at reflux for 48 hr. The reaction was worked up in the usual manner. The ether layer showed that ~10% of the ketone had reacted to give the corresponding olefin (*vide infra*). The aqueous layer yielded no organic material.

Synthesis of Olefins 15 and 16.—Olefins **15** and **16** were synthesized from **10** and **9**, respectively, in the same fashion (1 *M* lithium chloride in DMA at 130°) as in the case of the olefins **25** and **29** (*vide supra*). The olefins were obtained in 80–90% and were recrystallized from ethanol.

The pmr spectrum for the olefin **15** (mp 169°; $\nu_{C=C}$ 1650 cm^{-1}, ν_{OH} 3560 cm^{-1}) shows two singlets (1 H each) at τ 5.15 and 5.36 and a complex multiplet (8 H) from 2.3 to 3.0.

Anal. Calcd for $C_{17}H_{11}Cl_3O$: C, 60.48; H, 3.28. Found: C, 60.24; H, 3.36.

The pmr spectrum of the ketone **16** (mp 200°; $\nu_{C=C}$ 1620 cm^{-1}, $\nu_{C=O}$ 1690 cm^{-1}) shows a singlet (1 H) at τ 4.85 and a complex multiplet (8 H) from 2.2 to 3.0.

(37) Kindly provided by Dr. E. W. Reeve, University of Maryland.

Anal. Calcd for $C_{17}H_9Cl_3O$: C, 60.84; H, 2.73. Found: C, 60.95; H, 2.81.

Kinetic Procedure.—Dimethylacetamide (reagent grade and twice distilled *in vacuo* from P_2O_5) solution (0.03 *M* in alkyl halide and 0.308 *M* in lithium chloride, standardized against silver nitrate by potentiometric titration) was placed in sealed ampoules and heated at 130.2° (±0.05°) in a constant temperature silicone oil bath. Samples (5.0 ml) were withdrawn at varying times and quenched in 50 ml of water. The solutions were analyzed by potentiometric titration (Sargent–Welch Model DG recording titrator) against a standardized solution of sodium hydroxide. A plot of log (liberated acid) *vs.* time gave a straight line, the slope of which was $k_{obsd}/2.303$. The second-order rate constant (k_2) is $k_{obsd}/[Cl^-]$. By variation of [LiCl] from 0.902 to 0.094 *M*, it was shown that each run gave the same k_2 to within ±10%.

Attempts at accurately measuring the rates of reactions of the alkyl halides (0.03 *M*) with 0.312 *M* sodium hydroxide in methanol at 65.1° (sealed ampoules) were not successful. Plots of log (liberated Cl^-) *vs.* time gave fairly straight lines for only ~20–40% reaction times. Rough data on the relative half-lives of the reactions of **18**–**22** with 0.312 *M* sodium hydroxide in methanol at 65.1° were obtained by quenching the reactions at ~15, 25, and 40% reaction times and measuring the extent of reaction by pmr spectroscopy. The relative rates for disappearance of starting materials as measured in this fashion follow: hydrocarbon **22** (1.0), methyl ether **21** (0.4), endo alcohol **20** (1.5), exo alcohol **18** (8), ketone **19** (150).

Registry No.—**3**, 27995-04-6; **4**, 27995-05-7; **5**, 27948-20-5; **6**, 27948-21-6; **7**, 34226-23-8; **8**, 34226-24-9; **9**, 27948-22-7; **10**, 34226-26-1; **12**, 34226-27-2; **15**, 34226-28-3; **16**, 34220-44-5; **18**, 34226-29-4; **19**, 34226-30-7; **20**, 34226-31-8; **21**, 34226-32-9; **22**, 34226-33-0; **23**, 34226-34-1; **25**, 34226-35-2; **26**, 34226-36-3; **27**, 34226-37-4; **28**, 34220-45-6; **29**, 34220-46-7.

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Synthetic Routes to Polyspiro Compounds with a Central Cyclobutane Ring

A. PAUL KRAPCHO,* D. E. HORN, D. R. RAO, AND B. ABEGAZ[1]

Department of Chemistry, University of Vermont, Burlington, Vermont 05401

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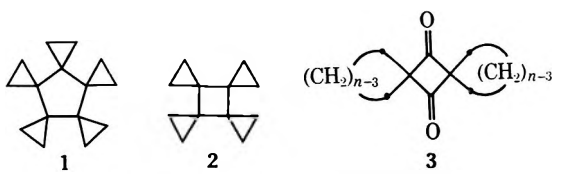
The reaction of dione **3** (n = 6) with triphenylphosphinemethylene in a benzene solution leads to **4** (n = 6) in 15–20% yields along with **9** (n = 6). On the other hand, **3** (n = 5) on treatment with this ylide leads only to the ring-opened product **9** (n = 5). Treatment of **6** with dimethylsulfoxonium methylide leads to **12**. The diepisulfides **13** and **14** (n = 5 or 6) undergo smooth desulfurization on heating with tri-*n*-butylphosphine to yield **7** and **4** (n = 5 or 6), respectively, in good yields. The dienes **7** and **4** (n = 5 or 6) on treatment with the Simmons–Smith reagent lead to **16** and **5** (n = 5 or 6). The trispirenes **15** (n = 5) and **17** were also isolated. The nmr data for the trispiro and tetraspiro systems along with **16** and **17** are presented and briefly discussed.

The synthesis of pentaspiro[2.0.2.0.2.0.2.0.2.0]pentadecane (**1**) has recently been described by Ripoll and Conia.[2] This was the first report of the preparation of this type of polyspiro system and the general name "rotane" was suggested because of the paddle-wheel-like arrangement of the outer cyclopropane rings. Shortly thereafter, the synthesis of tetraspiro[2.0.2.0.2.0.2.0]dodecane (**2**) was reported.[3,4]



1 **2** **3**

We wish to report synthetic routes to "rotanes" possessing an internal four-membered ring flanked by "blades" of varying ring size. The original synthetic scheme centered on the readily available polymethyleneketene dimers **3** (n = 5 or 6) as potential starting materials.[5] It was envisioned that treatment

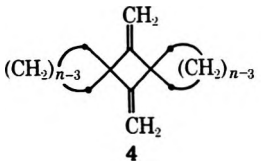
(1) Ethiopian Fellow of the African Graduate Fellowship Program (AFGRAD).

(2) (a) J. L. Ripoll and J. M. Conia, *Tetrahedron Lett.*, 979 (1969); (b) J. L. Ripoll, J. C. Limasset, and J. M. Conia, *Tetrahedron*, **27**, 2431 (1971).

(3) J. M. Conia and J. M. Denis, *Tetrahedron Lett.*, 3545 (1969).

(4) P. Le Perchec and J. M. Conia, *ibid.*, 1587 (1970).

(5) J. L. E. Erickson, F. E. Collins, Jr., and B. L. Owen, *J. Org. Chem.*, **31**, 480 (1966).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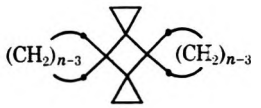
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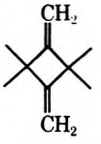
6

of the dimers **3** (n = 5 or 6) with excess methylenetriphenylphosphorane might lead to **4** (n = 5 or 6). These latter compounds could then be converted to the "paddlewheel" systems **5** (n = 5 or 6) *via* the Simmons–Smith procedure.[6] However, this approach suffers from the problem that ring-opened products generally have been reported in various reactions of tetramethylcyclobutane-1,3-dione (**6**).[7] For example, treatment of **6** with triphenylphosphinemethylene (methyltriphenylphosphonium bromide and *n*-butyllithium in THF) leads to the ring-opened product **8**.[7c]

Dione–Ylide Reactions.—Treatment of **6** with 2 equiv of triphenylphosphinemethylene (generated in DMSO from the phosphonium salt and Na^+DMSO^-) led to **8** in 77% yield. No diene **7** could be detected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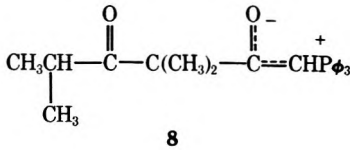
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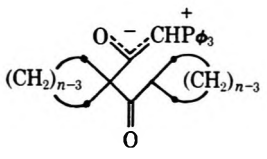
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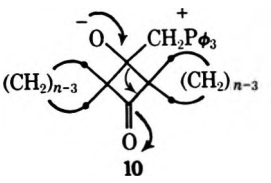
in the reaction mixture. In a similar manner, **3** (n = 5) led to a 75% yield of **9** (n = 5). The structure of **9** (n = 5) could readily be ascertained by an nmr comparison of its spectrum with that previously reported for **8**.[7c] When **3** (n = 5) was treated with 3 equiv of triphenylphosphinemethylene (generated in benzene from the phosphonium salt using *n*-butyllithium) a 75% yield **9** (n = 5) was isolated and no diene was detectable. Nevertheless, dione **3** (n = 6) on treatment with excess ylide (2–2.5 equiv prepared from methyltriphenylphosphonium bromide using *n*-butyllithium or potassium *tert*-butoxide in benzene) led to diene **4** (n = 6) in 15–20% yields along with the ring-opened ylide **9** (n = 6).

Thus in our hands only the dione **3** (n = 6) led to poor yields of the desired diene **4** (n = 6) while diones **3** (n = 5) and **6** led almost totally to the ring-opened products. The ring-opening reaction of an intermediate[7c] such as **10** (n = 5 or 6) would be expected to proceed more readily in the case of n = 5 than for n = 6.

(6) See A. P. Krapcho and D. E. Horn, *Tetrahedron Lett.*, 4537 (1969), for a preliminary communication.

(7) (a) J. L. E. Erickson and G. C. Kitchens, *J. Amer. Chem. Soc.*, **68**, 492 (1946); (b) J. C. Combret, *Ann. Chim. (Paris)*, **4**, 481 (1969); (c) E. A. LaLancette, *J. Org. Chem.*, **29**, 2957 (1964).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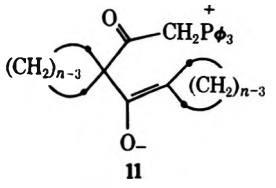
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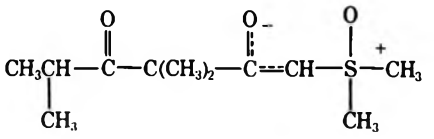
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Intermediate **10** has less internal angle strain in the central cyclobutanone ring when n = 6 than when n = 5; hence the ring-opening reaction leading to **11** (n = 5) would be expected to proceed more rapidly and dominate the formation of the transient methylene ketone. A nonpolar solvent such as benzene appears to favor the methylene ketone.

It was also of interest to investigate the reaction of the dione **6** with dimethyloxosulfonium methylide.[8] Treatment of **6** with this reagent led to the ring-opened product **12** in 37% yield. No diepoxide could be isolated in this reaction.

Desulfurizations.—In order to circumvent the facile ring-opening processes exhibited by the 1,3-diones in the Wittig reaction, our attention was next focused on the conversion of the diepisulfides **13** and **14** (n = 5 or 6) into the corresponding dimethylene systems **7** and **4** (n = 5 or 6), respectively. Recently we have prepared the stereoisomeric diepisulfides **13** and **14** (n = 5 or 6) by treatment of the thiones **6** (O = S) and **3** (O = S, n = 5 or 6) with diazomethane followed by thermal decomposition of the resulting Δ^3-1,3,4-thiadiazolines.[9] On heating the diepisulfides in tri-*n*-butylphosphine at 80–100° for 18–36 hr, a smooth desulfurization occurred[10] and the dimethylene systems could be obtained in good yields.

Treatment of the mixture of cis and trans diepisulfides **13** with tri-*n*-butylphosphine (80° for 60 hr)


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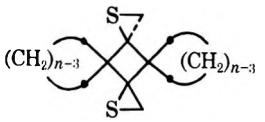
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led to **7** in 67% yield. The compound collected in the condenser and was identical in melting point and nmr spectrum with those of a previously reported sample.[11] Treatment of the stereoisomeric mixture of diepisulfides **14** (n = 5 or 6) with tri-*n*-butylphosphine (100° for 36 and 18 hr, respectively) followed by addition of pentane and chromatography on alumina led to **4** (n = 5 or 6) in yields of 73 and 70%, respectively. Compound **4** (n = 6) was identical in all respects with the sample prepared by the di-Wittig procedure.

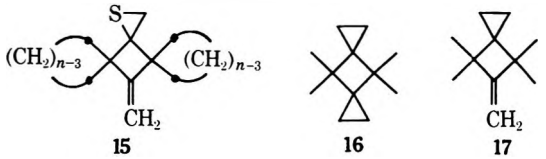
(8) (a) M. Fieser and L. Fieser, "Reagents for Organic Synthesis," Vol. 2, Wiley-Interscience, New York, N. Y., 1969, p 171; (b) E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **87**, 1353 (1965).

(9) A. P. Krapcho, D. R. Rao, M. P. Silvon, and B. Abegaz, *J. Org. Chem.*, **36**, 3885 (1971).

(10) (a) D. B. Denney and M. J. Boskin, *J. Amer. Chem. Soc.*, **82**, 4736 (1960); (b) R. E. Davis, *J. Org. Chem.*, **23**, 1767 (1958).

(11) D. P. G. Hamon, *J. Amer. Chem. Soc.*, **90**, 4513 (1968).

Tetraspiro Compounds.—Treatment of **4** (n = 6) with the Simmons–Smith reagent prepared according to the procedure of Shank and Shechter[12] led to tetraspiro **5** (n = 6) in 90% yield. The dienes **4** (n = 5) and **7** appeared to react much more slowly with the couple prepared by the above procedure and the method recently suggested by Rawson and Harrison[13] was utilized. Treatment of **4** (n = 5) for 36 hr led to a mixture of **5** (n = 5) (57%), the trispiro compound **15** (n = 5) (26%), and starting diene **4** (n = 5) (18%).



15 **16** **17**

These percentages were readily obtained by nmr integrations of the areas in the spectrum of the reaction product. Pure **5** (n = 5) was obtained in a 26% yield by vpc collection, and a pure sample of **15** (n = 5) was also collected. Treatment of **7** in a similar fashion (48 hr) led to 16 (67%) and **17** (33%). Pure **16** (24% yield) and **17** were obtained by vpc collection. The nmr spectral data for the tri- and tetraspiro compounds along with **16** and **17** are tabulated in Table I for comparative purposes.

TABLE I

NMR DATA FOR THE TRISPIRO AND TETRASPIRO SYSTEMS

Compd[a]	δ, Cyclopropyl $-CH_2-$	δ, $=CH_2$	δ, Cycloalkyl $-CH_2-$ or CH_2-
5 (n = 5)	0.37 (s)		1.37 (m)
5 (n = 6)	0.50 (s)		1.30 (broad s)
15 (n = 5)	0.37 (s)	4.67 (s)	1.60 (m)
16	0.38 (s)		0.77 (s)
17	0.38 (s)	4.75 (s)	1.00 (s)

[a] CCl_4 as solvent.

It is of interest to note the chemical shift for the methyl resonances in **7**, monospirene **17**, and dispiro **16**. The Δδ of the methyl resonances in **7** (δ 1.24) and **17** is 0.24 ppm, while the Δδ of the methyl resonances in **17** and **16** is 0.23 ppm. The effect of adding the second cyclopropane ring shows nearly the same upfield shift as the first. Similarly, the ring methylenes for the five-membered ring of **4** (n = 5) (δ 1.77, m) shift to 1.60 (m) in **15** (n = 5), Δδ 0.17, while the change from **15** (n = 5) to **5** (n = 5) shows Δδ of 0.23. The anisotropic shielding effect exhibited by the cyclopropanes rings can be rationalized by the ring-current model[14] or on the basis of the bond anisotropy exhibited by the carbon–carbon bonds of the ring.[15]

Experimental Section

All melting points and boiling points are uncorrected. Infrared spectra were determined on a Perkin-Elmer Model 237B grating spectrophotometer. Nmr spectra were obtained on a Varian Associates A-60 spectrophotometer, and the peak positions are reported as parts per million values relative to internal TMS. Gas chromatographic separations were performed on an Aerograph Model A-90-P instrument. Microanalyses were done by Robertson Laboratory, Florham Park, N. J.

Ylide Reactions. Preparation of 4 (n = 6). **Procedure A.**—To a stirred suspension of methyltriphenylphosphonium bromide (11.1 g, 0.031 mol) in 80 ml of dry benzene was added under a nitrogen atmosphere, *via* a syringe, 13 ml of a 2.37 *M* *n*-butyllithium solution in hexane (0.030 mol) over a period of 5 min. After the evolution of butane ceased (5 min), a solution of the dione **3** (n = 6) (3.0 g, 0.014 mol) in 40 ml of benzene was added dropwise over a period of 10 min. A precipitate appeared and the mixture was heated at reflux for 20 hr. The mixture was cooled and then filtered. The benzene was removed by distillation and the remaining viscous residue was washed repeatedly with pentane. The pentane extracts were chromatographed on 25.0 g of alumina (Camag, Brockmann Number 1) to yield 0.55 g (18%) of **4** (n = 6): mp 57–58°; nmr (CCl_4) δ 1.50 (broad singlet, 20 H, ring $-CH_2-$) and 4.85 ppm (sharp singlet, 4 H, $=CH_2$); ir (CCl_4) 1640 (m, $-C=CH_2$ stretch) and 870 cm^{-1} (s, $-C=CH_2$ bending).

The analytical sample was crystallized from methanol–pentane, mp 57–57.5°.

Anal. Calcd for $C_{16}H_{24}$: C, 88.82; H, 11.18. Found: C, 89.01; H, 11.01.

Procedure B.—To a suspension of potassium *tert*-butoxide (5.6 g, 0.05 mol) and *tert*-butyl alcohol (3.7 g, 0.05 mol) in 160 ml of dry benzene methyltriphenylphosphonium bromide (17.9 g, 0.05 mol) was added under a nitrogen atmosphere. The dione **3** (n = 6) (4.4 g, 0.02 mol) was added to the yellow mixture and the mixture was refluxed for 20 hr. After cooling in an ice bath the mixture was filtered. The benzene was distilled until 100 ml was collected and the mother liquor was cooled and filtered. The syrupy benzene solution was added to an alumina column and then eluted with pentane. Four 250-ml fractions were collected and fraction 2 on concentration yielded 0.65 g (15%) of **4** (n = 6), mp 54–56°.

Preparation of 8.—Sodium hydride (1.2 g, 52 mmol as a 58.6% dispersion in mineral oil) was washed five times with pentane to remove the oil.[16] The reaction was kept under a nitrogen blanket and 20 ml of dry dimethyl sulfoxide was introduced *via* a syringe. The mixture was warmed to 75–80° and stirred for 30 min. The solution was cooled in an ice–water bath and methyltriphenylphosphonium bromide (18.5 g, 52 mmol) dissolved in 50 ml of DMSO was added dropwise. The mixture was stirred at room temperature for 10 min and **6** (3.0 g, 26 mmol) in 40 ml of DMSO was added. The reaction mixture was warmed to 65° and stirred at this temperature for 16 hr. The DMSO was then removed under vacuum and 100 ml of ice–water was added. The residual solid was filtered and dried under vacuum to yield 6.9 g (77%) of **8**. The sample was crystallized from ligroin–benzene to give 5.1 g, mp 138–139° (lit.[7a] mp 136–137°).

Preparation of 9 (n = 5).—The reaction was run as above. From **3** (n = 5) (2.0 g, 10 mmol) there was obtained 3.6 g (75%) of **9** (n = 5). The sample was crystallized from ligroin–benzene to yield 2.1 g: mp 140–141°; nmr ($CDCl_3$) δ 1.65 (broad m, 12 H), 2.1 (broad m, 4 H), (ring $-CH_2-$), 3.05 (m, 1 H, O=CCH), 3.6 (d, 1 H, J = 25 Hz, $^-O=C=CHPPh_3^+$), and 7.5 ppm (m, 15 H, aromatic protons).

Anal. Calcd for $C_{31}H_{33}PO_2$: C, 79.45; H, 7.09. Found: C, 79.73; H, 7.37.

Preparation of 9 (n = 6).—A solution of triphenylphosphinemethylene was prepared under a nitrogen atmosphere from methyltriphenylphosphonium bromide (1.6 g, 4.6 mmol) in 25 ml of dry benzene and 2.0 ml of 2.37 *M* *n*-butyllithium in hexane (4.6 mmol). The dione **3** (n = 6) (1.0 g, 4.6 mmol) in 20 ml of benzene was added *via* a syringe. The yellow mixture was refluxed for 15 hr and cooled. The benzene was washed twice with cold water and dried over anhydrous sodium sulfate. The benzene was concentrated by distillation and the residual material was crystallized. On addition of pentane followed by filtration 1.5 g of crude **9** (n = 6) (65%), mp 140–155°, was obtained. On solution in ligroin (60–90°) followed by filtration 1.3 g of **9** (n = 6) was obtained: mp 161–162°; nmr ($CDCl_3$) δ 7.6 (complex m, 15 H, aromatic protons), 3.78 (d, 1 H, J = 25 Hz, H adjacent to phosphorus), 2.90 (complex

(12) R. S. Shank and H. Shechter, *J. Org. Chem.*, **24**, 1825 (1959).

(13) R. J. Rawson and I. T. Harrison, *ibid.*, **35**, 2057 (1970).

(14) (a) D. J. Patel, M. E. H. Howden, and J. D. Roberts, *J. Amer. Chem. Soc.*, **85**, 3218 (1963); (b) J. J. Burke and P. C. Lauterbur, *ibid.*, **86**, 1870 (1964).

(15) K. Tori and K. Kitahonoki, *ibid.*, **87**, 386 (1965), and references cited therein.

(16) E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **84**, 866 (1962).

m, 1 H, H adjacent to carbonyl), 1.95 and 1.45 ppm (broad multiplets, 20 H, ring $-CH_2-$).

Anal. Calcd for $C_{33}H_{37}PO_2$: C, 79.71; H, 7.51. Found: C, 79.74; H, 7.31.

Reaction of Dimethylsulfoxonium Methylide with 6. Preparation of 12.—A solution of the ylide was prepared under nitrogen from trimethylsulfoxonium iodide (9.2 g, 42 mmol), sodium hydride (2.2 g of a 58.6% dispersion in mineral oil, 42 mmol) and 50 ml of dry DMSO.[8] A solution of **6** (2.8 g, 20 mmol) in 40 ml of DMSO was added with stirring *via* a syringe. The mixture was stirred at room temperature for 2 hr and then heated to 50–55° for 1 hr. The mixture was poured into cold water (250 ml) and extracted with two 150-ml portions of methylene chloride. After drying the extracts over potassium carbonate, the solvent was removed on a rotary evaporator. The residue was further concentrated under vacuum pump pressure. The crude product was treated with ether to yield a crystalline solid, 1.7 g (37%), mp 63–65°. The solid was crystallized from pentane–benzene: mp 64–65°; nmr ($CDCl_3$) δ 4.52 (s, 1 H, OS^+C^-H-), 3.41 [s, 6 H, $(CH_3)_3S^+O$], 3.0 (septet, 1 H, $-CH-$), 1.30 [s, 6 H, $O{=}CC(CH_3)_2C{=}O$], and 1.05 ppm [d, 6 H, $(CH_3)_2CH-$]; ir (CCl_4) 1705 ($-C{=}O$) and 1550 cm^{-1} ($-CH{=}C^-{=}O$).

Anal. Calcd for $C_{11}H_{20}O_3S$: C, 56.86; H, 8.68; S, 13.82. Found: C, 57.17; H, 9.00; S, 14.11.

Diepisulfide Desulfurizations. Preparation of 7.—The mixture of *cis*- and *trans*-**13** (0.9 g, 4.5 mmol) and tri-*n*-butylphosphine (3.0 g, 15 mmol) was heated with stirring in an oil bath at 80° for 60 hr under a nitrogen atmosphere. The diene **7** sublimed and collected in the lower part of the condenser. The solid was removed from the condenser and purified by sublimation at atmospheric pressure and room temperature: yield 0.41 g (67%); mp 65–66° (lit.[11] mp 66–68°); nmr ($CDCl_3$) δ 1.24 (s, 12 H, CH_3-) and 4.75 ppm (s, 4 H, $=CH_2$).

Preparation of 4 (n = 5).—*cis*- and *trans*-**14** (n = 5) (1.2 g, 4.8 mmol) and tri-*n*-butylphosphine (2.0 g, 10 mmol) were heated with stirring at 100° for 36 hr in a nitrogen atmosphere. The reaction mixture was chromatographed on alumina (100 g, neutral) using pentane to yield 0.70 g (73%) of **4** (n = 5). The diene was purified by distillation: bp 45–50° (0.1 mm); nmr ($CDCl_3$) δ 1.77 (broad peak, 16 H, cyclopentyl $-CH_2-$) and 4.78 ppm (s, 4 H, $=CH_2$); ir (CCl_4) 1640 (m, $-C{=}CH_2$ stretch) and 875 cm^{-1} (s, $-C{=}CH_2$ bending).

Anal. Calcd for $C_{14}H_{20}$: C, 89.40; H, 10.60. Found: C, 89.10; H, 10.80.

Preparation of 4 (n = 6).—The diepisulfides **14** (n = 6) (0.4 g, 1.4 mmol) and tri-*n*-butylphosphine (1.4 g, 7 mmol) were heated with stirring at 100° for 18 hr in a nitrogen atmosphere. The residue was chromatographed on neutral alumina with pentane to yield 0.21 g (70%) of **4** (n = 6), mp 55–56°. This product was identical in all respects with the compound obtained by the Wittig procedure.

Simmons–Smith Reaction. Preparation of 16 and 17.—Zinc dust (8.5 g, 0.13 mol) and cuprous chloride (1.3 g, 0.13 mol) in 40 ml of anhydrous ether were refluxed with stirring for 30 min under a nitrogen atmosphere.[13] Methylene iodide (5.2 ml, 0.065 mol) was added and the mixture was refluxed for 30 min. The diene **7** (0.7 g, 0.005 mol) in 5 ml of ether was added and the mixture was refluxed for 48 hr. The ether was removed by decantation, washed with two 10-ml portions of a 5% ammonium chloride solution and two 10-ml portions of a saturated sodium bicarbonate solution, and dried over anhydrous magnesium sulfate. Removal of the ether under water aspirator pressure yielded 0.5 g of crude product: nmr (CCl_4) δ 0.38 (s), 0.77 (s), 1.00 (s), and 4.75 (s). From the peak areas one can calculate the composition of the crude product to be 33% of monocyclopropane **17** and 67% of dispirocyclopropane **16**. Pure **16** was obtained by vpc collection on a 6-ft column of 20% silicone oil on firebrick at 80°: yield 0.18 g (24%); mp 134–135°; nmr (CCl_4) δ 0.38 (s, 8 H, cyclopropane $-CH_2-$) and 0.77 ppm (s, 12 H, CH_3-).

Anal. Calcd for $C_{12}H_{20}$: C, 87.73; H, 12.27. Found: C, 87.57; H, 12.47.

A reasonably pure sample of the monocyclopropane **17** (mp 108–109°) was collected from the vpc column: nmr (CCl_4) δ 0.38 (s, 4 H, cyclopropane $-CH_2-$), 1.00 (s, 12 H, CH_3-), and 4.75 ppm (s, 2 H, $-CH_2$).

Preparation of 5 (n = 5) and 15 (n = 5).—The above procedure was followed for the preparation of the Simmons–Smith reagent. Compound **4** (n = 5) (0.35 g, 1.8 mmol) in 5 ml of ether was added to the reagent and the mixture was refluxed for 36 hr. The ether was removed by decantation and washed as above. On removal of the ether the crude mixture which was obtained consisted of **5** (n = 5) (57%), the monocyclopropane **15** (n = 5) (26%), and starting material (18%). Pure **5** (n = 5) was obtained by vpc separation on a 6-ft column of 20% silicone oil on firebrick at 150°: yield 0.1 g (28%); mp 34–34.5°; nmr (CCl_4) δ 0.37 (s, 8 H, cyclopropane $-CH_2-$), and 1.37 ppm (m, 16 H, cyclopentane $-CH_2-$).

Anal. Calcd for $C_{16}H_{24}$: C, 88.90; H, 11.10. Found: C, 88.94; H, 11.29.

A sample of the monocyclopropane **15** (n = 5) was also collected from the vpc column: nmr (CCl_4) δ 0.37 (s, 4 H, cyclopropane $-CH_2-$), 1.60 (m, 16 H, cyclopentyl $-CH_2-$), and 4.67 ppm (s, 2 H, $=CH_2$).

Anal. Calcd for $C_{15}H_{22}$: C, 89.04; H, 10.96. Found: C, 89.37; H, 10.98.

Preparation of 5 (n = 6).—The zinc–copper couple was prepared from zinc (0.68 g, 10 g-atoms) following the procedure of Shank and Shechter.[12] Methylene iodide (2.06 g, 7.4 mmol) in 50 ml of ether was added to the couple and the mixture was refluxed for 30 min. A solution of **4** (n = 6) was added to the reagent. The mixture was refluxed for 18 hr and then filtered. The ethereal filtrate was washed with two 5-ml portions of saturated ammonium chloride, two 5-ml portions of 5% sodium bicarbonate, and two 5-ml portions of water. After drying over anhydrous magnesium sulfate the ether was removed to yield 0.40 g (90%) of crude **5** (n = 6). On solution in pentane and cooling to −25° colorless crystals were obtained: mp 45–46°; nmr (CCl_4) δ 0.50 (s, 8 H, cyclopropane $-CH_2-$) and 1.30 ppm (s, 20 H, cyclohexane $-CH_2-$); ir (CCl_4) 2050 (s) and 905 cm^{-1} (m).

The analytical sample was crystallized from ethanol, mp 45–46°.

Anal. Calcd for $C_{18}H_{28}$: C, 88.45; H, 11.55. Found: C, 88.40; H, 11.60.

Registry No.—**4** (n = 5), 34202-02-3; **4** (n = 6), 34220-26-3; **5** (n = 5), 34226-15-8; **5** (n = 6), 25517-28-6; **9** (n = 5), 34219-90-4; **9** (n = 6), 34219-91-5; **12**, 34219-92-6; **15** (n = 5), 34202-04-5; **16**, 34219-93-7; **17**, 34219-94-8.

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Unexpected n–π* Absorption of a Spiro Ketone from 2-Phenylcyclohexanone-2-acetic Acid

Mary Ellen Scanlan and S. MacKenzie*

Pastore Chemical Laboratory, University of Rhode Island, Kingston, Rhode Island 02881

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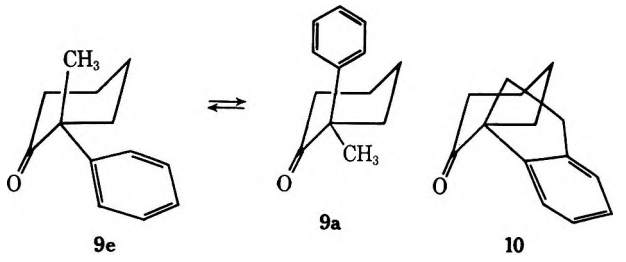
2-Phenylcyclohexanone-2-acetic acid, when treated with either sulfuric acid or polyphosphoric acid, rearranged with loss of water to form the lactone of 3-(1-hydroxy-1-cyclopentyl)cinnamic acid. The lactone was synthesized by ozonolysis of the glycol obtained by addition of allylmagnesium chloride to 1-benzoylcyclopentanol. The rearrangement of the keto acid was prevented by protection of the ketone group with ethanedithiol. The dithioketal was cyclized to the indanone; this was reduced to the indanol, and this was hydrolyzed to spiro(cyclohexan-2-one-1,1′-indan-3′-ol). In contrast to expectation, the n–π* absorption of this ketone was substantial.

Cookson originally proposed[1] that exalted n–π* transitions arose most significantly in α-phenyl ketones when the planes of the carbonyl group and the phenyl group faced each other. This idea has been supported in recent reports.[2,3] Reconciliation of the data for certain ketones remains difficult, however. For example, the spectrum of 2-phenylcyclohexanone (290 mμ, 17, EtOH)[4] is easily explicable (the planes are orthogonal and the phenyl group is equatorial) but that for 2-methyl-2-phenylcyclohexanone (294 mμ, 100, EtOH)[5] is not. True, a conformational equilibrium can be proposed,[5] but this seems quantitatively unsatisfactory. Conformation **9e**, surely the major



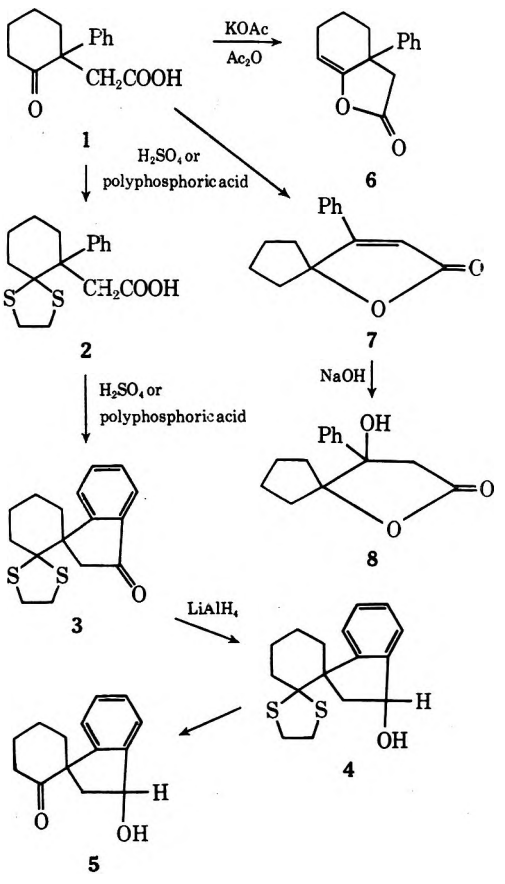
9e **9a** **10**

one, would have no exaltation in the 290-mμ region, while **9a** would have an extinction coefficient of about 125.[6] An extinction coefficient of 50–60 would seem more appropriate for **9e**–**9a**. The validity of this argument, however, rests upon the correctness of the assumed value for **9e**. For this reason, spiro ketone **10**, which must be equivalent to **9e** for steric reasons, was desired.

Results

The synthetic route to spiro ketone **5**, a hydroxylated variation of **10**, is shown in Scheme I. The starting compound, 2-phenylcyclohexanone-2-acetic acid (**1**), was prepared from 2-phenylcyclohexanone[7] by two different routes: (1) the formate blocking method of Ireland[8] and (2) direct alkylation of the ketone with sodamide and ethyl iodoacetate.[9] Treatment of keto

Scheme I



acid **1** with polyphosphoric acid or sulfuric acid gave a lactone, **7**. The nmr spectral properties (5, s, δ 7.5; 1, s, 6.3; 8, m, 2.1) and the intense uv spectrum (275 mμ, ε 16,500, EtOH) suggested strongly the cinnamate structure. The lactone was resistant in the extreme to saponification.[10] Boiled with 20% sodium hydroxide, it gave a hydroxy derivative,[11] **8**. These properties strongly indicated structure **7**. This proposal is examined in detail in the third paragraph of this section. The ketone group in **1** therefore required protection prior to treatment with acids. With ethanedithiol,[12] **1** gave the dithioketal **2**, mp 162–164°. The ketone could not be made to react with the new reagent, 1,2-dimethyl-4,5-di(mercaptomethyl)benzene.[13] The di-

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(2) S. MacKenzie, S. F. Marsocci, and H. C. Lampe, *J. Org. Chem.*, **30**, 3328 (1965).
(3) R. Gencarelli, H. Abajian, P. Irving, and S. MacKenzie, *ibid.*, **35**, 2673 (1970).
(4) W. C. Wildman and R. B. Wildman, *ibid.*, **17**, 581 (1952).
(5) P. Colard, I. Elphimoff-Felkin, and M. Verrier, *Bull. Soc. Chim. Fr.*, 516 (1961).
(6) The value chosen is based on the spectrum of 2,2-diphenylcyclohexanone: W. B. Bennet and A. Burger, *J. Amer. Chem. Soc.*, **75**, 84 (1953).
(7) M. S. Newman and M. D. Farbman, *ibid.*, **66**, 1550 (1944).
(8) R. A. Ireland and J. A. Marshall, *J. Org. Chem.*, **27**, 1615 (1962).
(9) D. Ginsburg and R. Pappo, *J. Chem. Soc.*, 1524 (1953).
(10) This is generally typical for α,β-unsaturated lactones of tertiary alcohols: F. Korte and D. Scharf, *Chem. Ber.*, **95**, 443 (1962); W. C. Bailey, *et al.*, *J. Org. Chem.*, **33**, 2819 (1968).
(11) Such a reaction was seen for triphenylcrotonolactone: Dutch Patent 6,412,872 (1965); *Chem. Abstr.*, **63**, p16429*f* (1965).
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(13) I. Shahak and E. D. Bergmann, *J. Chem. Soc. C*, 1005 (1963).

thioketal gave, on treatment with sulfuric or polyphosphoric acid, the indanone **3**, mp 144–146°. Reduction of this with lithium aluminum hydride gave the indanol **4**. Chromatography on silica gave the two isomers, mp 80–83° (10 parts) and 162–164° (1 part). The major isomer, when treated with $HgCl_2$ and $CdCO_3$,[14] gave the spiro ketone **5**. This liquid had an nmr spectrum which suggested that it was a mixture of stereoisomers arising by racemization at the benzyl alcohol site. The ketone had an exalted uv spectrum (290 mμ, ε 183, EtOH).

An explanation for this exaltation must be sought. Provisionally advanced is the suggestion that the cyclohexane ring of this ketone has adopted a twist or a flattened chair conformation. Little support is found in the literature for this idea. The best known cases of nonchair conformations involve 1,3-diaxial alkyl interactions.[15] These are present in 3,3,5-trimethyl-5-phenylcyclohexanones.[16] The simpler 2-methyl-2-phenylcyclohexanones appear not to have been studied in this regard. Table I gives the results of an inspection of Dreiding models of spiro[2,2-indanocyclohexanone] (**10**). Of the six boat forms listed in Table I,

TABLE I

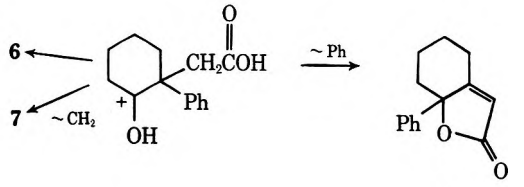
TABULATION OF SHORTER H–H REPULSION DISTANCES FOR SPIRO[INDANOCYCLOHEXANONE]

Prow[a]	Eclipsed H[b]	Methylene[c]	Phenyl[c]	d
2	3, 4	1.6, 1.6	2.25	0°
3	4, 5	2.0, 3.0	2.25, 2.5	60°
e		2.25, 2.5	2.0, 2.25	90°
4	5, 6	2.0	1.5, 2.0	120°
5	3, 4	2.5, 2.5	Short	120°
6	4, 5	2.5, 2.5	1.5, 1.75	60°
e		2.0, 2.25	2.25	20–30°
1	5, 6	2.0, 2.0	2.5, 2.6	0°
f		2.0, 2.0	2.25	0°

[a] Given is the number of the carbon atom in the cyclohexane ring which is the prow of the boat form. [b] For additional identification, given is the location of the cyclohexane carbon atoms which have eclipsed hydrogen atoms. [c] Several of the shorter H–H repulsion distances, measured in Dreiding models, are given for the methylene group and for the phenyl group of the indano system. [d] The angle made by the carbonyl group with the plane containing carbons 1 and 2 and the carbon of phenyl attached to the cyclohexane ring. [e] Twist–boat forms placed in the table where a different repulsion phenomenon becomes more important. [f] For comparison of repulsion distances, given are data for the chair conformation with the phenyl group equatorial.

three have very serious repulsion between the hydrogen atom of the phenyl ring and the hydrogens of the cyclohexane ring. The other three boat forms have less serious repulsion between the indan methylene group and the hydrogens of the cylcohexane ring as a main factor. The cyclic path of rotatory change connecting these boat forms has two transition points which represent a change of the principal factor of repulsion. At these two transition points, twist boat forms can be found which have lower repulsion energies. Of course, the boat forms also have two sets of eclipsed hydrogen atoms at a distance of about 2.25 Å but this energy is no longer the major factor. Table I admits the possibility, then, that twist–boat forms may contribute to the conformational population of **10**. One of the full-boat forms (prow 3) may also contribute.

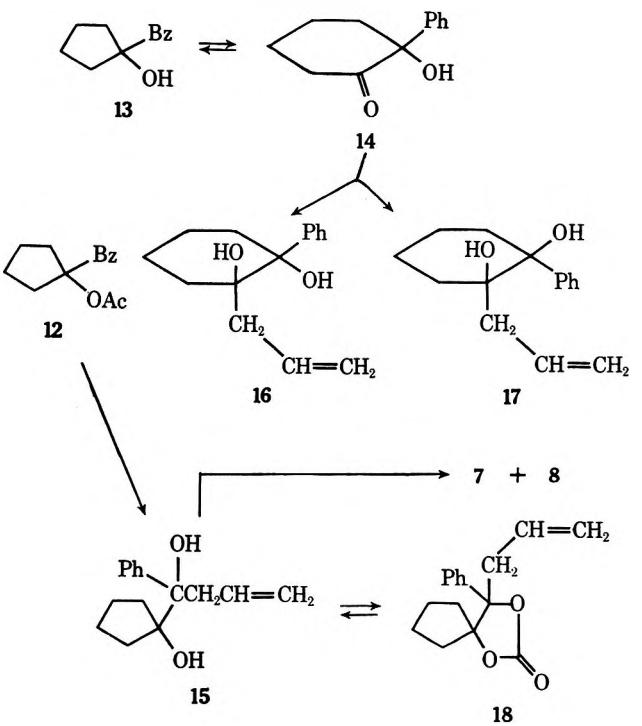
Various workers have studied the rearrangement of ketones. It was originally noted[17] that only tetra- or trisubstituted cycloalkanones rearranged in acid, but subsequently many exceptions have been observed. Ketones having lesser degrees of substitution can rearrange when additional factors favorable to such reaction exist. Such factors can be increased resonance energy,[18] relief of steric strain,[18] relief of small-ring strain,[19] and, most appropriate to the present study, the formation of lactone rings. 2-Methylcycloheptanone-2-acetic acid with incidental substituents rearranged[20] to a spiro[5.6]lactone. The present circumstance is different in the fact that the ring contraction is 6 to 5, not 7 to 6, and that a phenyl group, normally prone to migrate easily, is also present. Several possible acid-catalyzed events should be considered.



11

Although neither the enol lactone **6** nor lactone **11** would be expected to have the spectral properties of the rearrangement product, it was advisable to seek an independent structure proof for **7**. The synthetic work is outlined in Scheme II.

SCHEME II



(14) J. English, Jr., and P. H. Griswold, *J. Amer. Chem. Soc.*, **67**, 2040 (1945).

(15) N. L. Allinger and M. A. Rogers, *ibid.*, **84**, 4561 (1962).

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(17) S. Barton and C. R. Porter, *J. Chem. Soc.*, 2483 (1956).

(18) H. D. Zook, W. E. Smith, and J. L. Greene, *J. Amer. Chem. Soc.*, **79**, 4436 (1957).

(19) R. L. Cargill, D. M. Pond, and S. D. LeGrand, *J. Org. Chem.*, **35**, 359 (1970).

(20) B. W. Roberts, S. C. Welch, and D. A. Steed, *J. Chem. Soc. D*, 535 (1969).

The obvious synthesis (**12** + NaH) failed, as did additions of various ester anions to **12** or **13**. Isolated in such instances was the mixture of **13** and **14**. Allylmagnesium chloride reacted with **13** to give a liquid glycol, **15**. Reaction with **14** (containing some **13**) gave three glycols,[21] easily separated by chromatography. Table II suggested, in analogy to the work of

Table II

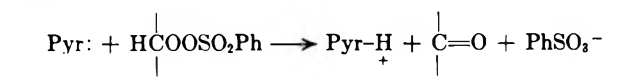
Per Cent Reaction of Glycols with Periodate, 2 Min,[a] 25°

	pH[b]				
Glycol	7	8.5	11.5	11.9[c]	12
17			84	85	88
15				67	
16	68	79	50		13
Propylene	70	33			
Ethylene	14	4			
Pinacol	4	9			

[a] Reactions were not quenched; they stopped due to pH change. [b] The pH is that of the aqueous 0.02 *M* periodate which was added to the glycol in 50% diglyme. [c] Glycol was dissolved in 100% diglyme.

Price,[22] that the glycol of mp 57–60° is **17** (cis) and that of mp 80–82° is **16** (trans). The liquid glycol, which gave cyclopentanone when treated with lead tetraacetate, must be **15**.

The liquid glycol **15** was also prepared from the solid 1-acetoxy-1-benzoylcyclopentane, prepared from benzoylcyclopentane and lead tetraacetate, and also by regeneration from the solid cyclic carbonate, **18**. Ozonolysis of **15**, followed by decomposition, distillation, and chromatography, gave lactone **7**. All three specimens of glycol **15** had the same ir spectrum and gave identical results on ozonolysis. The crystalline character of lactone **7** facilitated final purification. Since the initial six ozonolyses (two with each of the three glycol preparations) gave such disappointing yields (9–11% in each case) of **7**, an alternative to the thermal decomposition of the ozonide was sought. Under the assumption that the products of ozonolysis contained cyclic hydroperoxide,[23] decomposition by polar means was explored. Addition of benzenesulfonyl chloride caused a pyridine solution of the peroxidic material to boil. The yield of lactones was 47% (45% of **8** and 2% of **7**). The mechanism shown below is plausible.



Experimental Section

2-Phenylcyclohexanone-2-acetic Acid (from Ethyl Iodoacetate).—To a suspension of sodamide (from 10.7 g of sodium) in ether was added a solution of 83 g (0.475 mol) of 2-phenylcyclohexanone[7] in 100 ml of ether and 200 ml of benzene over a period of 2 hr. The mixture was refluxed for 10 hr, cooled, and treated with a solution of 100 g (0.47 mol) of ethyl iodoacetate in 100 ml of ether over a period of 1.5 hr. The mixture was refluxed for 4 hr and hydrolyzed with cold water. After extraction, the combined organic layers were washed four times with solutions of sodium thiosulfate and dried, and the solvents were removed by evaporation. The oil residue was refluxed for 4 hr with 500 ml of 10% NaOH, cooled, and extracted with ether. Evaporation gave 17 g of recovered ketone. Acidification of the aqueous layer gave 39.8 g (47%) of keto acid **1**: mp 134–136° (lit.[9] mp 133–134°); uv max (95% EtOH) 251 mμ (ε 202), 257 (260), 263 (203), 290 (97); nmr (CCl_4) δ 2.9 (d, 2, J = 2 Hz, CH_2COOH).

2-Phenylcyclohexanone-2-acetic Acid (from Blocked Ketone).—A solution of 57 g (1.46 mol) of potassium in 1.4 l. of dry *tert*-butyl alcohol was stirred under nitrogen. After addition of 88 g (0.364 mol) of 2-*n*-butylthiomethylene-6-phenylcyclohexanone,[8] the mixture was stirred at room temperature for 5 min. It was cooled in an ice bath and 357 g (2.33 mol) of methyl bromoacetate was added all at once. After the initial reaction had subsided, the mixture was refluxed for 2 hr. The excess *tert*-butyl alcohol was removed by distillation and 500 ml of water was added to the residue. After extraction with ether and solvent removal, the oily residue was treated with 500 ml of ethylene glycol and 500 ml of 25% KOH and refluxed for 15 hr. Cooling and extraction with ether gave 14 g of 2-phenylcyclohexanone. The aqueous layer was acidified to precipitate 38 g (67%) of **1**.

The Enol Lactone (6) of 2-Phenylcyclohexanone-2-acetic Acid.—One gram of 2-phenylcyclohexanone-2-acetic acid was mixed with 3 ml of acetic anhydride and 0.1 g of KOAc and refluxed for 4 hr. After standing overnight, the liquid was poured into water, extracted with ether, and washed liberally with portions of sodium bicarbonate solution. Distillation in a small glass tube gave colorless liquid: $n^{25}D$ 1.5630; uv max (C_6H_{12}) 205 mμ (ε 13,700), 252 (217), 258 (236), 261 (211), 263 (186), 268 (155); nmr (CCl_4) δ 5.4 (t, 1, vinyl H), 2.7 (s, 2, CH_2COO–).

Anal. Calcd for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59. Found:[24] C, 78.29; H, 6.52.

3-(1′-Hydroxycyclopentyl)-3-phenylpropenoic Acid Lactone (7).—A solution of 11.5 g (0.049 mol) of 2-phenylcyclohexanone-2-acetic acid in 130 g of polyphosphoric acid was heated in an oil bath maintained at 84–92° for 3 hr. The solution became brown. After addition of water, extraction, and washing of organic layers, evaporation gave 10 g of neutral material. After four recrystallizations from ethanol–water, the yield of solid was 6.4 g (61%). Use of 90% sulfuric acid in place of polyphosphoric acid gave about the same yield of colorless solid: mp 74–76°; nmr (CCl_4) δ 7.5 (s, 5, Ph), 6.3 (s, 1, vinyl), 2.0–2.2 (m, 8, cyclopentane); uv max (95% EtOH) 275 mμ (ε 16,500).

Anal. Calcd for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59. Found: C, 78.66; H, 6.74.

In a kinetic experiment, 0.5346 g (0.0025 mol) of the lactone was mixed with 200 ml of 0.106 *N* NaOH and the mixture was diluted to 500 ml with methanol. After 20 days at 20°, the titer was unchanged.

3-(1′-Hydroxycyclopentyl)-3-hydroxy-3-phenylpropanoic Acid Lactone (8).—A mixture of 3 g of the unsaturated lactone **7** and 50 ml of 20% NaOH was made homogeneous with ethanol and then refluxed for 5 days. Cooling gave 1 g of recovered **7**. Acidification and further cooling caused precipitation of 1.9 g of crude material, mp 102–124°. After five recrystallizations from ethanol–water, there was obtained 1.4 g (43%) of colorless solid: mp 123–124°; nmr (CCl_4) δ 7.45 (m, 5, Ph), 3.08 (q, 2, J = 17 Hz, CH_2COO), 3.2 (s, 1, OH), 1.3–2.3 (m, 8, cyclopentane). The uv spectrum was benzenoid.

Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94; O, 20.66. Found: C, 72.16; H, 7.04; O, 20.77.

Ethylene Dithioketal of 2-Phenylcyclohexanone-2-acetic Acid (2).—To a mixture of 10 g (0.043 mol) of the acid **1** and 20 ml of ethanedithiol was added with stirring 4 ml of boron trifluoride etherate. Within 5 min, the acid had dissolved and the solution became yellow. After stirring for another 5 min, the solution became cloudy. Stirring was continued at room temperature for 2 hr. Methanol was added to produce a clear solution which was then added to 400 ml of 10% NaOH. After filtration, acidification gave 10.5 g (80%) of crystals: mp 162–164°; nmr (CCl_4) δ 11.0 (s, 1, COOH), 7.6–7.2 (m, 5, Ph), 3.3 (d, 2, J = 7 Hz, CH_2COO), 3.0–1.4 (m, 12, ring H atoms). The uv spectrum was benzenoid.

Anal. Calcd for $C_{16}H_{20}O_2S_2$: C, 62.31; H, 6.52; S, 20.79. Found: C, 62.40; H, 6.33; S, 21.1.

(21) The reaction of 2-hydroxy-2-phenylcyclohexane with phenyllithium gave only *trans*-diphenylcyclohexanediol: P. Tomboulian, *J. Org. Chem.*, **26**, 2652 (1961).

(22) C. C. Price and M. Knell, *J. Amer. Chem. Soc.*, **64**, 552 (1942), showed that *cis*-cyclohexanediol reacted 60 times faster than the trans isomer at pH 10.

(23) A. Rieche, M. Schulz, and D. Becker, *Chem. Ber.*, **98** (11), 3627 (1965).

(24) All analyses were performed by Micro-Analysis, Inc., Wilmington, Del. 19808.

Dispiro[1,3-dithiolane-2,1′-cyclohexane-2′,1″-indan-3″-one] (3).—To 6.5 g (0.021 mol) of finely powdered ketal 2 was added with mechanical stirring 140 g of warm (50–60°) polyphosphoric acid. With continued stirring, the contents were heated over 1 hr to 73–78° and maintained at this temperature for 5.5 hr. The oil bath was then removed and the stirring was continued for an additional 1 hr. The contents were cooled by an ice bath and ice water was added. The contents became warm and the odor of sulfur compounds was apparent. The solid which precipitated was dissolved in ether and the aqueous layer was extracted with ether. The combined ether portions were extracted with 100 ml of 10% NaOH and four times further with 50-ml portions. Acidification of the aqueous layer gave 0.6 g (0.002 mol) of recovered keto acid 1. The ether was evaporated to give solid which was recrystallized from ethanol. Obtained was 2.85 g (52.5%) of colorless solid: mp 144–146°; uv max (95% EtOH) 242 mμ (ε 11,286), 285 (2943); nmr (CCl_4) δ 8.2–7.5 (m, 4, aromatic), 3.05–2.0 (m, 14, aliphatic).

Anal. Calcd for $C_{16}H_{18}OS_2$: C, 66.16; H, 6.25; S, 22.08. Found: C, 66.27; H, 6.15; S, 22.10.

Dispiro[1,3-dithiolane-2,1′-cyclohexane-2′,1″-indan-3″-ol] (4).—To a stirred suspension of 0.73 g (0.019 mol) of lithium aluminum hydride in 50 ml of anhydrous ether was added a solution of 3.16 g (0.011 mol) of **3** in ether over a period of 30 min. The mixture was refluxed overnight, cooled, and hydrolyzed with saturated ammonium chloride solution. Evaporation of the ether gave a solid which was added to a column made up in a 1-in. tube with 100 g of silica and benzene. Elution with benzene gave ten parts of the more abundant isomers: mp 80–83°; nmr ($CDCl_3$) δ 7.75 (m, 1, aromatic), 7.25 (m, 3, aromatic), 4.95 (q, 1, J = 4 Hz, CHOH), 3.72 (s, 1, OH), 3.3–1.2 (m, 14, aliphatic); uv max (95% EtOH) 251 mμ (ε 459), 258 (489), 265 (543), 272 (453).

Anal. Calcd for $C_{16}H_{20}OS_2$: C, 65.71; H, 6.89; S, 21.93. Found: C, 65.77; H, 6.94; S, 21.89.

Continued elution gave one part of the less abundant isomer: mp 162–164°; nmr (CCl_4) δ 7.8 (m, 1, aromatic), 7.4 (m, 3, aromatic), 5.7 (t, 1, J = 7 Hz, CHOH), 3.4–1.5 (m, 15, aliphatic + OH); uv max (95% EtOH) 252 mμ (ε 450), 257 (527), 263 (615), 272 (534).

Anal. Calcd for $C_{16}H_{20}OS_2$: C, 65.71; H, 6.89; S, 21.93. Found: C, 65.75; H, 6.83; S, 21.94.

Spiro[cyclohexan-2-one-1,1′-indan-3′-ol] (5).—To a solution of 0.6 g of dispiro compound **4**, mp 80–83°, in 60 ml of acetone and 3 ml of water were added 1.3 g of cadmium carbonate and 1.3 g of mercuric chloride. The reaction mixture was stirred for 6 days and 0.2 g of each of the inorganic salts was added four times during that period. The solid was filtered off, the acetone was removed by distillation, and the solid was extracted with ether. Ether-insoluble material was discarded. The ether solution was washed three times with 100-ml portions of 10% KI, once with water, and once with saturated NaCl solution. The oil which remained after removal of the ether was placed in a Kragen tube under high vacuum and distilled. A small amount of material which distilled below a bath temperature of 160° was discarded. Obtained was a highly viscous oil: nmr ($CDCl_3$) δ 7.4 (m, 4, aromatic), 5.15 (m, 1, CHOH), 3.0–1.8 (m, 11, aliphatic + OH); uv max (95% EtOH) 257 mμ (ε 548), 263 (693), 268 (646), 290 (183).

Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46; O, 14.8. Found: C, 77.58; H, 7.18; O, 14.86.

The ketone formed a 2,4-dinitrophenylhydrazone, mp 153–155°.

Anal. Calcd for $C_{20}H_{20}N_4O_5$: C, 60.6; H, 5.09; N, 14.13. Found: C, 60.46; H, 4.90; N, 14.09.

Benzoylcyclopentane (19).—To the cyclopentylmagnesium bromide prepared from 89.3 g (0.6 mol) of bromocyclopentane, 14.58 g (0.6 g-atom) of magnesium, and 2 l. of ether, was added slowly with mechanical stirring 41.2 g (0.4 mol) of benzonitrile. Solid precipitated. After standing overnight, the mixture was poured into water and acidified with 100 ml of concentrated HCl. The water layer was separated, heated to 90°, recooled, and extracted with ether. The combined ether portions gave, on distillation, a yield of 50 g (72%) of ketone[25] **19**.

1-Acetoxy-1-benzoylcyclopentane (12).—Following the procedure of Henbest,[26] 53.8 g (0.1336 mol) of lead tetraacetate was dissolved in 2 l. of anhydrous benzene. There was added all at once with mechanical stirring 21 g (0.1215 mol) of **19**. This was followed by 50 g of boron trifluoride etherate. The solution, originally orange, became yellow. It was heated slowly to 65° and then allowed to stand for 2 weeks. Cold water (500 ml) was added and the organic layer was separated and dried. Distillation gave 35% of recovered **19** and 45% of liquid boiling at 140–144° (1 mm) which soon solidified. Obtained from cyclohexane were colorless crystals: mp 49–50°; nmr (CCl_4) δ 7.8–7.3 (m, 5, aromatic), 1.75 (s, 3, OAc), 2.6–1.2 (m, 8, aliphatic).

Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.95. Found: C, 72.43; H, 6.84.

1-(1′-Hydroxycyclopentyl)-1-phenyl-3-butenol-1 (15).—To the Grignard reagent prepared from 15.5 g (0.2 mol) of allyl chloride, 9.7 g (0.4 g-atom) of magnesium, and 350 ml of anhydrous ether was added a solution of 5.7 g (0.025 mol) of 1-acetoxy-1-benzoylcyclopentane. The mixture was allowed to stand overnight. The mixture was then poured into 1 l. of ice–water slush. After the ice melted, the mixture was poured into a separatory funnel and the layers were allowed to separate over an hour or two. Neither acid nor ammonium chloride was added. The thick water layer was extracted twice with ether, considerable time again being allowed for layer separation. After removal of the ether, the oil was subjected to chromatography on silica. Only one fraction was obtained. Repeated efforts to cause the oil to solidify were unsuccessful. Obtained was 3.1 g (55%) of viscous oil, bp 145–148° (1 mm), $n^{20}D$ 1.5446.

Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.54; H, 8.68.

One gram of the glycol was treated with 2.0 g of lead tetraacetate and 20 ml of acetic acid. The mixture was allowed to stand overnight. Steam distillation was conducted until 60 ml of distillate was collected. Addition of 2,4-dinitrophenylhydrazine reagent gave an orange precipitate which was impure. After three recrystallizations from ethanol, the derivative, mp 141–143°, was bright yellow. The yield at this point was 9%. A mixture melting point with the derivative prepared from cyclopentanone was not depressed.

Cyclic Carbonate 18.—Into an ice-cold solution of 25 g (0.107 mol) of glycol **15**, 32 g of pyridine, and 125 ml of chloroform was bubbled 19.8 g (0.20 mol) of phosgene. The solution was kept in ice for 5 hr and then allowed to warm up to room temperature overnight. It was poured into much ice (brisk reaction) and the chloroform layer separated. It was washed with water and twice with portions of sodium bicarbonate solution. The chloroform was evaporated and the liquid residue, previously found to smoke badly on attempted distillation, was added to a 1 × 24 in. column of silica made up with benzene. Elution with benzene (1500 ml) gave 21.6 g, bp 176–180° (1 mm). It solidified on cooling and was recrystallized from 25 ml of cyclohexane and then from 25 ml of ethanol. Obtained was 15.9 g (57%) of large blocks: mp 80–82°; nmr (CCl_4) δ 7.4 (s, 5, Ph), 5.0 (m, 3, vinyl), 2.9 (d, 2, J = 5 Hz, allylic), 2.4–1.3 (m, 8, cyclopentane); ir (Nujol) 1790 cm^{-1} (ester), no OH band.

Anal. Calcd for $C_{16}H_{18}O_3$: C, 74.39; H, 7.02. Found: C, 74.38; H, 7.00.

To a solution of 2.58 g (0.01 mol) of cyclic carbonate **18** in 10 ml of dry tetrahydrofuran was added 0.38 g (0.01 mol) of lithium aluminum hydride. After 2 hr of stirring at room temperature, the liquid was treated with a few milliliters of ethanol and poured into cold water. Extraction with ether gave a liquid which was distilled in a small apparatus. The ir spectrum of this preparation was identical with that of the glycol prepared from 1-acetoxy-1-benzoylcyclopentane.

1-Benzoylcyclopentanol (13) and 2-Hydroxy-2-phenylcyclohexanone (14).—Compound **13** was made by the addition of the tetrahydropyranyl ether of cyclopentanone cyanohydrin to phenylmagnesium bromide.[5,27] The hydroxy ketone gave, on retreatment with dihydropyran, the tetrahydropyranyl ether, bp 127–130° (1 mm), $n^{25}D$ 1.5335.

Anal. Calcd for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08. Found: C, 74.45; H, 7.95.

There was no advantage, however, to using this ether in place of **13** itself in the preparation of glycol **15**. Benzoylcyclo-

(25) Due to the tendency of cyclopentylmagnesium bromide to reduce carbonyl compounds, the ketone has usually been made by the Friedel–Crafts synthesis: D. H. Hey and O. C. Musgrave, *J. Chem. Soc.*, 3156 (1949).

(26) H. B. Henbest, D. N. Jones, and G. P. Slater, *ibid.*, 4472 (1961).

(27) I. Elphimoff-Felkin, *Bull. Soc. Chim. Fr.*, 784 (1955).

pentanol was isomerized to a mixture which was largely **14** by powdered KOH.[5]

cis- and *trans*-1-Allyl-2-phenyl-1,2-cyclohexanediol.—Into the Grignard reagent prepared from 30.6 g (0.40 mol) of allyl chloride, 12.1 g (0.50 g-atom) of magnesium, and 700 ml of anhydrous ether was added a solution of 8.7 g (0.05 mol) of ketone, largely 2-hydroxy-2-phenylcyclohexanone, in 125 ml of ether. The reaction was vigorous and a thick paste formed. After standing overnight, the mixture was poured into ice water. No acid or ammonium chloride was added. After layer separation, the thick aqueous layer was extracted twice with ether. The ether portions were combined and distilled. Vacuum distillation gave 7.5 g of highly viscous oil. A portion (2.25 g) was placed on a column of silica,[28] 1 × 25 in., made up with benzene. Elution was with benzene, and 250-ml portions were collected. The residues of bottles 4–8, after several cycles of cooling and rewarming, finally solidified. Large lumps (0.7 g, mp 57–60°) were obtained from cyclohexane.

Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.83; H, 8.82.

The residues from bottles 9–16 remained liquid. When the flow of 5% ethyl acetate in benzene was started, a second series of bottles (17–21) gave residues which solidified still more slowly than those of bottles 4–8. Seeding was most advantageous. Fractions 17–21, when dissolved in hot cyclohexane, gave fine hairs, mp 82–83°.

Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.74; H, 8.78.

A larger run (5.8 g) on the same size column gave 2.1 and 1.7 g.

Ozonolysis of Glycol 15.—The glycol, prepared from 2.58 g of cyclic carbonate as described above, was dissolved in 100 ml of ethyl acetate, cooled to −70° in a bath of ethyl acetate and Dry Ice, and treated with oxygen containing 1% ozone until the solution developed a faint blue color. Evaporation of the ethyl acetate under reduced pressure (20 mm) without heating gave a colorless, thick oil. It could be stored at room temperature for several days but gradually became tan, then darker brown. Its ir spectrum showed that hydroxyl, carbonyl, and perhaps lactone groups were present. When, in an earlier run, the liquid was heated, it decomposed abruptly but without detonation. The presence of zinc dust made no difference in this property. The mixture became black. A portion (1.18 g) of the thick oil was, directly after preparation, dissolved in 10 ml of pyridine. Faint heat evolution was noted. When 2 ml of benzenesulfonyl chloride was added with stirring, the pyridine came to a boil rapidly. It was allowed to cool to room temperature and then allowed to stand overnight. A small amount of precipitate formed. The mixture was poured into water and extracted with ether. Evaporation of the ether and traces of residual pyridine gave an extremely viscous liquid, no longer sensitive to heat. Addition of 1 ml of cyclohexane and 1 ml of benzene permitted direct crystallization of 0.384 g (32.5%) of hydroxylactone **8**. Chromatography on silica of the residue from the crystallization gave 2% of unsaturated lactone **7** and an additional 12.7% of **8**. The total yield was thus 47%. The lactones so prepared did not depress the melting points of the lactones produced by rearrangement.

Registry No.—**1**, 3645-89-4; **2**, 34219-59-5; **3**, 34201-78-0; **4**, 34201-79-1; **5**, 34201-80-4; **5** 2,4-DNP, 34219-60-8; **6**, 34219-61-9; **7**, 34219-62-0; **8**, 34201-81-5; **12**, 34219-63-1; **14** tetrahydropyranyl ether, 34219-64-2; **15**, 34219-65-3; **16**, 34216-97-2; **17**, 34216-98-3; **18**, 34201-82-6.

(28) Size was 70–325 mesh. EM Laboratories, Inc., Elmford, N. Y. 10523.

Structural and Conformational Studies of 2-Phenyl-1,3,2-diaza- and -dioxaboracycloalkanes

FRANKLIN A. DAVIS,[1a] IGNATIUS J. TURCHI,[1b] BRUCE E. MARYANOFF, AND ROBERT O. HUTCHINS*[1a]

Department of Chemistry, Drexel University, Philadelphia, Pennsylvania 19104

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A series of 1,3,2-diaza- and -dioxaboracyclohexanes have been investigated by means of proton and boron nmr in order to obtain information concerning the conformation of the rings, hybridization and stereochemistry of the nitrogens, and effects of ring substitution on boron chemical shifts. The data suggest that the N-C_4-C_5-C_6-N and the O-C_4-C_5-C_6-O regions adopt normal rapidly inverting chair type conformations. Substituents on nitrogen appear to strongly prefer equatorial orientations presumably because of extensive nitrogen to boron π bonding. The difference in boron chemical shifts observed for five- and six-membered rings in the diazaboracycloalkanes may be explained by assuming pyramidal hybridization of the nitrogens.

During the past five years considerable interest has been directed toward structural and conformational studies of various six-membered ring heterocycle containing more than one heteroatom including dioxa-,[2,3] dithia-,[2,4] and diazacyclohexanes.[2a,5] In contrast, relatively little conformational and structural information is available concerning boron-containing heterocycles. Of particular interest in this area are boron heterocycles containing additional adjacent heteroatoms such as nitrogen or oxygen which have lone electron pairs and thus are capable of π overlap with the vacant p orbital on boron, a topic of considerable interest.[6] In line with our general interest in conformational analysis of heterocyclic compounds[4,5a] and in bonding between boron and other heteroatoms,[6] we have undertaken a proton and ^{11}B nmr spectral study of a series of 2-phenyl-1,3,2-diazabora- and -dioxaboracyclohexanes with the aim of obtaining information concerning the shape of the rings, the stereochemistry about the nitrogens in the diaza derivatives, and the bonding between boron and other heteroatoms.

A considerable amount of evidence has been accumulated which indicates that substantial π bonding occurs between boron and adjacent atoms which bear lone electron pairs.[6,7] In cases where the adjacent atom is

(1) (a) Senior coauthors to whom correspondence should be addressed. (b) NSF Undergraduate Research Participant, 1969.

(2) Excellent reviews concerning conformational analysis of heterocyclic compounds containing more than one heteroatom are available. See (a) E. L. Eliel, *Accounts Chem. Res.*, **3**, 1 (1970), and references cited therein; (b) C. Romers, C. Altona, H. R. Buys, and E. Havinga, "Topics in Stereochemistry," Vol. 4, Wiley, New York, N. Y., 1969, and references cited therein; (c) C. H. Bushweller, "Mechanisms of Reactions of Sulfur Compounds," Vol. 5, Intra-Science Research Foundation, Santa Monica, Calif., 1969, p 75, and references cited therein.

(3) F. W. Nader and E. L. Eliel, *J. Amer. Chem. Soc.*, **92**, 3050 (1970).

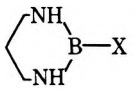
(4) E. L. Eliel and R. O. Hutchins, *ibid.*, **91**, 2703 (1969).

(5) (a) R. O. Hutchins, L. D. Kopp, and E. L. Eliel, *ibid.*, **90**, 7174 (1968); (b) P. J. Halls, R. A. Y. Jones, A. R. Katritzky, M. Snarey, and D. L. Trepanier, *J. Chem. Soc. B*, 1320 (1971); (c) H. Booth and R. M. Lemieux, *Can. J. Chem.*, **49**, 779 (1971).

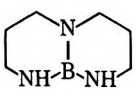
(6) For a review of the pertinent literature see F. A. Davis, I. J. Turchi, and D. N. Greeley, *J. Org. Chem.*, **36**, 1300 (1971).

(7) K. Niedenzu and J. W. Dawson in "The Chemistry of Boron and Its Compounds," E. L. Muetterties, Ed., Wiley, New York, N. Y., 1967, p 392.

nitrogen, however, there is some question as to the hybridization of the nitrogen atom. Goubeau and Zappel[8] concluded from Raman data that the B–N bond in 2-methyl-1,3,2-diazaboracyclohexane (**1a**) is similar to that in planar borazine, and additional spectroscopic evidence supports a high B–N bond order in this compound.[9] The similarity of the ^{11}B chemical shift of



1a, X = CH_3
b, X = C_6H_5
c, X = H



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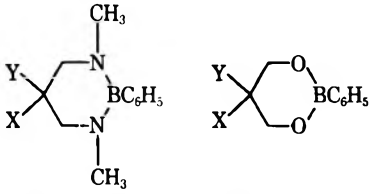
1a (−29.9 ppm)[10a] and borazine (−30.4 ppm)[10b] also suggests similar boron to nitrogen bonding. The independence of the nmr spectrum of **1a** (1,3-d_2 derivative) over a temperature range from −70 to 90° was put forth as evidence for planarity of the N–B–N region and thus for essentially sp^2 hybridization of the nitrogen atoms.[11] However, the introduction of sp^2 hybridized boron may reduce the barrier such that the lower temperature (−70°) reached may be insufficient to slow ring inversion.[12]

X-Ray crystallographic studies have demonstrated nearly planar nitrogen geometries in various compounds containing B–N bonds including $[(CH_3)_2N-B=CH_2]_3$,[13] $(CH_3)_2N-B(CH_3)_2$,[14] $(C_6H_4O_2B)_3N$,[15] and 1,8,10,9-triazaboradecaline[16] (**2**).

A B C

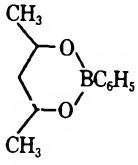
On the other hand, Dewar and Rona have argued on theoretical grounds that nitrogen will usually prefer a pyramidal (sp^3) geometry unless the delocalization energy gained by assuming a planar geometry is large.[17] These authors concluded that effective overlap with adjacent unsaturated systems can occur despite sp^3 hybridization of nitrogen. The conclusions are supported by the structure of trisdimethylaminoborane,[18] in which the CNC angle and C–N bond length are nearly identical with those in dimethylamine.[19]

Irrespective of the nitrogen hybridization in 1,3,2-diazaboracyclohexanes, the most effective overlap of the nitrogen lone pairs with the vacant p orbital on boron occurs when the respective orbitals are coplanar, or nearly so, as represented by conformations A or B. However, in these forms the lone pairs are located syn axial to each other. In corresponding 1,3-diazacyclohexane systems this situation leads to unfavorable dipole interactions which force one *N*-methyl group into an axial orientation,[5a,20] as in conformation C. This latter conformation should reduce the nitrogen π overlap. Detection of conformations such as C would provide strong evidence against sp^2 hybridization of the nitrogens. Our approach was to investigate the proton and ^{11}B nmr spectra of 2-phenyl-1,3,2-diazaboracyclohexanes **3** and **4**, in which the N substituents may adopt equatorial or axial positions (as in C), and the spectrum of the corresponding 5,5-dimethyl derivative **5**, in which the *N*-methyl groups are constrained to equatorial sites (as in A or B). Boron chemical shifts are largely dependent upon the electron occupancy of the vacant boron orbital (*i.e.*, an increase in electron density increases the shielding on boron) and are quite sensitive to changes in the conformation of alkylamino groups attached to boron.[6] Consequently, any difference in conformation of the *N*-methyl groups in **3** and **4** should be reflected by a change in the boron chemical shift. In particular, the presence of an appreciable population of conformation C should produce a downfield ^{11}B shift of **5** compared to **3**. In addition, the corresponding 1,3,2-dioxaboracyclohexanes **6–9**



3, X = Y = H
4, X = H, Y = CH_3
5, X = Y = CH_3

6, X = Y = H
7, X = H, Y = CH_3
8, X = Y = CH_3



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were also investigated in order to preclude any boron chemical shift changes caused by ring deformations introduced by 5,5-dimethyl substituents.

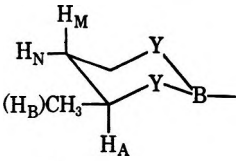
Results and Discussion

Compounds **3–5** were prepared from the appropriate *N*,*N*′-dimethyl-1,3-propanediamines and bis(dimethylamino)phenylboron by transamination. Compounds **6–9** were synthesized from phenylboric acid and 1,3-propanediols by azeotropic removal of water. Identification and characterization were accomplished by elemental analysis and by infrared and proton nmr

(8) J. Goubeau and A. Zappel, *Z. Anorg. Allg. Chem.*, **278**, 38 (1955).
(9) (a) K. Niedenzu and P. Fritz, *ibid.*, **340**, 329 (1965); (b) J. Goubeau and H. Snedider, *Justus Liebigs Ann. Chem.*, **675**, 1 (1964).
(10) (a) K. Niedenzu, P. Fritz, and S. W. Dawson, *Inorg. Chem.*, **3**, 1077 (1964); (b) W. D. Phillips, H. C. Miller, and E. L. Muetterties, *J. Amer. Chem. Soc.*, **81**, 4496 (1959).
(11) K. Niedenzu, C. D. Miller, and S. L. Smith, *Z. Anorg. Allg. Chem.*, **372**, 337 (1970).
(12) F. R. Jensen and B. H. Beck, *J. Amer. Chem. Soc.*, **90**, 1066 (1968). Introduction of an sp^2 carbon into a six-membered ring lowers the inversion barrier to *ca.* 7.7 kcal/mol (T_{coal} = *ca.* −115°) in methylenecyclohexane and 15.1 kcal/mol (T_{coal} = *ca.* −170°) in cyclohexanone compared to *ca.* 10 kcal/mol for cyclohexane: G. Binsch in "Topics in Stereochemistry," Vol. 3, E. Eliel and N. Allinger, Ed., Wiley, New York, N. Y., 1968, p 97. The effect of an sp^2 boron atom on the ring inversion barrier is unknown but probably should cause a similar decrease.
(13) H. Hess, *Acta Crystallogr., Sect. B*, **25**, 2334 (1969).
(14) G. J. Bullen and N. H. Clark, *J. Chem. Soc. A*, 992 (1970).
(15) G. J. Bullen and P. R. Mallinson, *ibid.*, 2213 (1970).
(16) G. J. Bullen and N. H. Clark, *ibid.*, 404 (1969).
(17) M. J. S. Dewar and P. Rona, *J. Amer. Chem. Soc.*, **91**, 2259 (1969).
(18) A. H. Clark and G. A. Anderson, *J. Chem. Soc. D*, 1082 (1969).
(19) B. Beagley and T. G. Hewitt, *Trans. Faraday Soc.*, **64**, 2561 (1968).
(20) The phenomenon is found in various systems and has been termed the "Rabbit-ear,"[21] "Edward-Lemieux,"[22] or "Generalized Anomeric"[23] effect and attributed to syn-axial lone pair repulsions[21,24] or polar bond repulsions.[22]
(21) E. L. Eliel, *Sv. Kem. Tidskr.*, **81**, 22 (1969); E. L. Eliel, L. D. Kopp, J. E. Dennis, and S. A. Evans, Jr., *Tetrahedron Lett.*, 3409 (1971).
(22) S. Wolfe, A. Rauk, L. Tel, and I. Csizmadia, *J. Chem. Soc. B*, 136 (1971).
(23) H. Booth and R. M. Lemieux, *Can. J. Chem.*, **49**, 779 (1971).
(24) F. P. Chen and R. G. Jesaitis, *J. Chem. Soc. D*, 1573 (1970).

TABLE I

PROTON NMR PARAMETERS FOR 2-PHENYL-1,3,2-DIAZABORACYCLOHEXANES AND 2-PHENYL-1,3,2-DIOXABORACYCLOHEXANES[a]



Compd	δ_A	δ_B	δ_M	δ_N	J_{AB}	J_{MN}	J_{AM}	J_{BM}	J_{AN}	δ_{NCH_3}
3	2.92[b]	2.92[b]	1.92[c]	1.92[c]						2.45
4	2.78[d]	2.78[d]		(0.96)			*d*	*d*		2.48
5	2.71[e]	2.71[e]	(1.00)	(1.00)						2.48
6	4.02[f]	4.02[f]	1.84[g]	1.84[g]						
7	3.64	4.06	2.27	(0.83)	11	(7)	10.0	4.4		
8	3.79	3.79	(1.02)	(1.02)						
9	4.18		1.33	1.87		14	11		2.3	

[a] Measured as $CDCl_3$ solutions; chemical shifts in parts per million from TMS internal standard. [b] H_A, H_B appear as a triplet, J = 5.5 Hz. [c] H_M, H_N appear as a pentet, J = 5.5 Hz. [d] H_A, H_B appear as a "deceptively simple" doublet, $J = (J_{AM} + J_{BM})/2$ = 7 Hz. [e] H_A, H_B are isochronous. [f] H_A, H_B appear as a triplet, J = 5.4 Hz. [g] H_M, H_N appear as a pentet, J = 5.4 Hz.

data. The 1,3,2-diazaboracyclohexanes showed strong absorption at 1500 cm^{-1}, attributable to the antisymmetrical BN_2 stretching mode.[25] Compounds **6–9** all showed strong bands in the 1310–1350 cm^{-1} region, indicative of B–O stretching.[26] The nmr spectra of compounds **3–9** were recorded at 60 or 100 MHz and the parameters were extracted by first-order analysis presented in Table I. Compounds **3** and **6** displayed similar patterns for the ring protons consisting of two sets of isochronous absorptions, a two-proton pentet representing the C_5 hydrogens, and a four-proton triplet at higher field for the $C_{4,6}$ protons. Compounds **5** and **8** both showed a singlet for the $C_{4,6}$ protons and a second high-field singlet for the 5,5-dimethyl groups. The spectrum of 5-methyl-1,3,2-dioxaboracyclohexane (**7**) showed a more complex $(AB)_2X$ pattern for the ring protons. The presence of a relatively large vicinal coupling ($J_{AX} \cong 10$ Hz) was indicative of an H_{axial}–H_{axial} coupling[27] and allowed the assignment of the H_A and H_B chemical shifts. The smaller J_{BX} (4.4 Hz) was indicative of an $H_{4\ equatorial}$–$H_{5\ axial}$ coupling and was consistent with the assignment. The spectrum of the analogous diaza derivative **4** was much less complex. The $C_{4,6}$ region appeared as a "deceptively simple"[28] doublet from which only $(J_{AX} + J_{BX})/2$ could be obtained. The average value (*ca.* 7 Hz) suggested the presence of a large and a small coupling similar to those obtained for **7**. The spectrum of **9** appeared as an $(A)_2MN$ pattern (excluding the $C_{4,6}$ methyl coupling) with $J_{AM} \cong 11$ and $J_{AN} \cong 2.3$ Hz, again suggestive of an axial–axial and an axial–equatorial coupling.[29,30]

All of the above nmr data are most consistent with a chairlike X–C_4–C_5–C_6–X region of the molecules for X = O and N. The relatively simple spectra obtained for **3**, **5**, **6**, and **8** point strongly to the presence of rapid ring inversion at ordinary temperatures which renders the $C_{4,6}$ and the C_5 proton sets isochronous. Only slight broadening was observed in the spectrum of compound **3** upon cooling to −80°, indicating that the inversion barrier is probably quite low.

In an attempt to obtain information concerning the nitrogen stereochemistry and hence the shape of the N–B–N region of the rings, the boron chemical shifts were determined and the data are presented in Table II.

TABLE II

BORON-11 CHEMICAL SHIFTS OF 1,3,2-DIAZA- AND DIOXABORACYCLOALKANES

Compd	Ref	Solvent	Chemical shift,[a] ppm	Line width,[b] Hz
1b	*c*		−27.2[c]	
3	*d*	Neat	−30.6	359
		Benzene	−29.5	144
4		Neat	−29.0	520
		Benzene	−29.4	136
5		Neat	−28.8	306
		Benzene	−29.0	126
6	*e*	Neat	−27.0 (−27.7)[f]	407
7		Benzene	−26.6	226
8	*e*	Benzene	−26.2	157
		Acetonitrile	−26.4	93
9		Acetonitrile	−26.9	135
10	*g*	Benzene	−31.1	111
11	*e*	Benzene	−31.2 (−31.9)[f]	100

[a] In parts per million relative to boron trifluoride etherate. Estimated error, ±0.15 ppm for line width <100 Hz, ±0.3 ppm for line width <200 Hz, ±1.0 ppm for wider lines. [b] At Half-height; estimated error ±5%. [c] Reference 10a. [d] Reference 25. [e] Reference 33. [f] Unpublished results reported in W. R. Henderson and E. F. Mooney, *Annu. Rev. NMR (Nucl. Magn. Resonance) Spectrosc.*, **2**, 219 (1969). [g] Reference 32.

Replacing hydrogen by methyl in compound **1** to give **3** produced a downfield shift of 2 ppm, in contrast to the expected inductive shielding effect produced by alkyl groups on boron.[6] The deshielding observed is probably due to nonbonded interactions between the *N*-methyl substituents and the ortho hydrogens of the *B*-phenyl ring. Such interactions apparently twist the phenyl group so that conjugation with boron is less effective. Compounds **3** and **4** should have the same stereochemistry at the nitrogen atoms and thus overlap of the lone pairs with boron should be the same in both.

(25) W. Weber, J. W. Dawson, and K. Niedenzu, *Inorg. Chem.*, **5**, 726 (1966).

(26) R. L. Werner and K. G. O'Brian, *Aust. J. Chem.*, **8**, 355 (1955); **9**, 137 (1955).

(27) N. Bhacca and D. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, Calif., 1964, p 51.

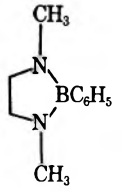
(28) J. W. Emsley, J. Feeney, and L. H. Sutcliff, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Vol. I, Pergamon Press, New York, N. Y., 1965, p 363. In this case, simplification probably arises as a consequence of $\delta_{AB} \simeq 0$ and $^1/_2\ (J_{AX} - J_{BX})/J_{AB}$ small compared to J_{AB}.

(29) The $C_{4,6}$ region of **9** was very similar to that of other analogous heterocyclic systems including 1,3-dioxacyclohexanes[30] and 1,3-dithiacyclohexanes.[4]

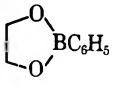
(30) E. L. Eliel and Sr. M. C. Knoeber, *J. Amer. Chem. Soc.*, **90**, 3444 (1968).

As expected, the boron chemical shifts of **3** and **4** are essentially the same (Table I). The presumably equatorial 5-methyl substituent in **4** apparently has no measurable effect. The introduction of the second, necessarily axial, methyl group at position 5 should greatly disfavor any population of axial *N*-methyl conformations[31] (as C) and any conformational change should appear as a shielding of the boron in **5** and a shift to higher field. The nearly identical chemical shifts for **3**, **4**, and **5** (*ca.* −29.0 ppm) strongly suggests that all three have similar, diequatorial orientations for the *N*-methyl groups. Any "Rabbit-ear"[20,21] or "Anomeric"[23] effect apparently is overshadowed by stabilization due to π bonding or to sp^2 hybridization of the nitrogens. The corresponding dioxa derivatives **6–9** also exhibited practically identical boron chemical shifts, indicating that ring substitution plays very little role in determining such shifts. A similar result has been observed in a series of trialkyl borates which showed no dependence of the boron chemical shift on the type of alkyl substituent.[6]

To obtain a more definitive answer concerning the hybridization of the nitrogen atoms in compounds **3–5**, we measured the boron chemical shifts of the diaza- and dioxaboracyclopentane derivatives **10**[32] and **11**.[33] The chemical shift of **10** (−31.1 ppm) is deshielded by 2



10



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ppm compared with that of **3–5**. If nitrogen in compounds **10** and **3–5** were sp,[2] then the chemical shifts of these compounds should be nearly identical. However, if the nitrogen atoms in **3–5** and **10** are sp^3 then Drieding models show that in the cyclopentane derivative **10** the lone pairs on nitrogen and the vacant orbital on boron cannot be coplanar without severely deforming the ring. The models further suggest that in **3–5** coplanarity of the orbitals on boron and nitrogen are much better. This downfield shift can then be attributed to lower π bonding in the five- than in the six-membered ring compounds.

A similar argument can be used to explain the large downfield shift (−5 ppm) observed between the five- and six-membered ring 1,3,2-dioxaboracycloalkanes (**11** and **6–9**). In these compounds oxygen will be sp^3 hybridized. The much larger difference in chemical shift observed between the 1,3,2-dioxaboracycloalkanes and the 1,3,2-diazaboracycloalkanes may be attributed to the greater electronegativity of oxygen over nitrogen.

The above argument, therefore, suggests that the nitrogens in the 1,3,2-diazaboracycloalkanes are sp^3 hybridized provided that the boron chemical shifts in these compounds are primarily determined by the degree of π electron density on boron and not to some additional parameters.[34]

(31) The syn-axial methyl–methyl interaction in these systems is unknown but should be close to the value of 3.7 kcal/mol found in cyclohexyl derivatives.

(32) K. Niedenzu, H. Beyer, and J. W. Dawson, *Inorg. Chem.*, **1**, 738 (1962).

(33) R. A. Bowie and O. C. Musgrave, *J. Chem. Soc.*, 3945 (1963).

Experimental Section

^{11}B nmr chemical shifts were measured with a Varian HR-100 at 32.1 MHz referenced against a capillary containing boron trifluoride etherate. Proton nmr spectra were measured on Varian A-60A and HR-100 instruments, and infrared spectra were measured on a Perkin-Elmer 457 spectrometer.

General Procedure for Preparation of the 2-Phenyl-1,3,2-diazaboracyclohexanes.—The 1,3,2-diazaboracyclohexanes were prepared by transamination between bis(dimethylamino)phenylboron[25] and the appropriate *N,N'*-dimethyl-1,3-propanediamine in benzene.

2-Phenyl-1,3,5-trimethyl-1,3,2-diazaboracyclohexane (4).—Bis(dimethylamino)phenylboron (0.71 g, 0.0041 mol) and *N,N'*-2-trimethyl-1,3-propanediamine (Ames Laboratories) (0.47 g, 0.0041 mol) gave 0.61 g (73%) of **4**, bp 75° (1 mm).

Anal. Calcd for $C_{12}H_{19}BN_2$: C, 71.31; H, 9.48. Found: C, 71.16; H, 9.35.

Compound **4** has the following properties: infrared (thin film) 3080–2800 (s), 1950 (w), 1870 (w), 1810 (w), 1690 (m), 1510 (s), 1440 (s), 1410 (s), 1370 (s), 1280 (s), 1210 (s), 1190 (s), 1140 (m), 1120 (w), 1090 (s), 1060 (s), 1030 (s), 970 (m–w), 930 (m), 890 (w), 870 (w), 750 (s), 705 (s), 650 (m–s), and 618 cm^{-1} (m).

2-Phenyl-1,3,5,5-tetramethyl-1,3,2-diazaboracyclohexane (5).—Bis(dimethylamino)phenylboron (0.90 g, 0.005 mol) and *N,N'*-2,2-tetramethyl-1,3-propanediamine (see below) (0.64 g, 0.005 mol) gave 0.97 g (90%) of **5**, bp 108–111° (2 mm).

Anal. Calcd for $C_{13}H_{21}BN_2$: C, 72.24; H, 9.79. Found: C, 72.06; H, 9.91.

Compound **5** had the following properties: infrared (thin film) 3200 (w), 2980–2795 (s), 1595 (w), 1500 (s), 1440 (s), 1405 (s), 1380 (s), 1355 (s), 1290 (s), 1235 (s), 1190 (s), 1125 (w), 1090 (w), 1065 (s), 1035 (m), 955 (w), 940 (w), 910 (w), 750 (s), 700 (s), and 645 cm^{-1} (m).

***N,N'*-2,2-Tetramethyl-1,3-propanediamine.**—The parent diamine was prepared in 45–49% yield by reduction of 2,2-dimethyl-1,3-dinitropropane[35] with iron filings and hydrochloric acid,[36] bp 72–75° (37 mm), $n^{25}D$ 1.4532 [lit.[37] bp 151–153° (737 mm), $n^{20}D$ 1.4536]. This material was treated with ethyl chloroformate according to standard procedures[39] to give the dicarbamate in 89–90% yield, mp 68–69° (lit.[40] mp 62–64°). Reduction of the dicarbamate with lithium aluminum hydride in ether gave *N,N'*,2,2-tetramethyl-1,3-propanediamine in 51–54% yield, bp 82–84° (68 mm), $n^{22}D$ 1.4388. Analysis was performed on a derivative of this compound, *N,N'*,5,5-tetramethyl-2-phenyl-1,3-diazacyclohexane, which was prepared by treating the diamine with benzaldehyde.

Anal. Calcd for $C_{14}H_{22}N_2$: C, 77.01; H, 10.16. Found: C, 77.12; H, 10.13.

The final product had the following properties: infrared (thin

(34) The major parameters affecting the ^{31}P chemical shift in symmetrically substituted phosphorus compounds have been suggested as being the bond angles and the degree of π bonding to phosphorous. See J. H. Letcher and J. R. Van Wazer, *J. Chem. Phys.*, **44**, 815 (1966), and V. Mark and J. R. Van Wazer, *J. Org. Chem.*, **32**, 1187 (1967). Since boron has a vacant orbital, π bonding to boron in trivalent organoboron compounds would be expected to be the dominant parameter affecting the boron chemical shift. Experimental evidence bears this out.[6]

(35) A. Lambert and A. Lowe, *J. Chem. Soc.*, 1517 (1947).

(36) M. Senkus, *Ind. Eng. Chem.*, **40**, 506 (1948). This transformation may be carried out *via* catalytic hydrogenation.[37] An attempt to reduce the dinitro compound with $LiAlH_4$ in ether afforded a mixture (30–40% yield), *ca.* 35% of which proved to be a cyclized product, 4,4-dimethyl-2-pyrazoline,[38] isolated as the 1-carboethoxy derivative: bp 68–71° (0.35 mm); $n^{25}D$ 1.4700; ir (neat) olefinic 3050 (w), C=O 1705 (vs), C=N 1592 cm^{-1} (m); pmr (CCl_4) δ 1.20 (s, 6, *gem*-Me), 1.30 (t, 3, Me, J = 7 Hz), 3.50 (s, 2, ring methylene), 4.17 (q, 2, methylene), 6.65 (s, 1, olefinic H); mass spectrum *m/e* (rel intensity) 170 (parent, 21), 111 (28), 83 (87), 42 (22), 32 (32), 30 (23), 29 (42), 28 (100). *Anal.* Calcd for $C_8H_{14}N_2O_2$: C, 56.45; H, 8.29. Found: C, 56.55; H, 8.28.

(37) J. Rockett and F. C. Whitmore, *J. Amer. Chem. Soc.*, **71**, 3249 (1949)

(38) R. J. Crawford, A. Mishra, and R. J. Dummel, *J. Amer. Chem. Soc.*, **88**, 3959 (1966).

(39) W. W. Hartman and M. R. Brethen, "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1944, p 279.

(40) G. S. Skinner, R. H. Hall, and P. V. Susi, *ibid.*, **79**, 3786 (1957).

film) 3320 (m), 2960–2790 (s), 1470 (s), 1390 (m–s), 1365 (m), 1310 (w), 1270 (w–m), 1245 (m), 1150 (s), 1110 (s), 1030 (w), 965 (w), 940 (w), 910 (m), 880 (w), 800 (m–s), 850 (s), and 640 cm^{-1} (w); nmr (C_6D_6) δ 0.9 (s, 6 H), 0.95 (s, 2 H), and 2.4 (d, 10 H).

General Procedure for Preparation of the 2-Phenyl-1,3,2-dioxaboracyclohexanes.—The dioxaboracyclohexanes were prepared from the appropriate 1,3-propanediol and phenylboric acid in benzene by azeotropic removal of water.

2-Phenyl-5-methyl-1,3,2-dioxaboracyclohexane (7).—Phenylboric acid (2.6 g, 0.021 mol) and 2-methyl-1,3-propanediol[39] (1.9 g, 0.021 mol) gave 3.5 g (95%) of **7**, bp 103–105° (3 mm), mp 30–31°.

Anal. Calcd. for $C_{10}H_{13}BO_2$: C, 68.22; H, 7.45. Found: C, 68.28; H, 7.58.

Compound **7** had the following properties: infrared (thin film) 3060 (w), 2960 (m), 2900 (m), 1600 (m–s), 1480 (s), 1445 (s), 1415 (s), 1380 (w), 1350 (s), 1320 (s), 1300 (s), 1255 (s), 1220 (w), 1170 (s), 1140 (s), 1080 (m), 1030 (m), 950 (w), 880 (w), 765 (m), 730 (m–s), 700 (s), 670 (m), and 650 cm^{-1} (s).

2-Phenyl-4,6-dimethyl-1,3,2-dioxaboracyclohexane (9).—Phenylboric acid (1.2 g, 0.01 mol) and *meso*-2,4-pentanediol[41] (1.0 g, 0.01 mol) in toluene gave 1.5 g (88%) of **8**, mp 45°, purified by sublimation at 60° (0.5 mm).

Anal. Calcd for $C_{11}H_{15}BO_2$: C, 69.47; H, 7.89. Found: C, 69.64; H, 7.94.

Compound **9** had the following properties: infrared (KBr) 3050 (w), 2990 (m), 2930 (m–w), 1605 (m), 1450 (s), 1410 (s), 1385 (m), 1370 (m), 1360 (m), 1310 (s), 1270 (m–s), 1180 (m), 1155 (s), 1140 (s), 1070 (w), 1030 (m), 900 (w), 830 (w), 780 (m), 715 (s), 660 (m–w), and 650 cm^{-1} (s).

(41) J. G. Pritchard and R. L. Vollmer, *J. Org. Chem.*, **28**, 1545 (1963).

Registry No.—**3**, 6063-69-0; **4**, 29173-11-3; **5**, 34288-22-7; **6**, 4406-77-3; **7**, 34288-24-9; **8**, 5123-13-7; **9**, 7317-42-2; 1-carboethoxy-4,4-dimethyl-2-pyrazoline, 34288-27-2; *N,N'*-2,2-tetramethyl-1,3-propanediamine, 31892-15-6; *N,N'*-5,5-tetramethyl-2-phenyl-1,3-diazacyclohexane, 34288-29-4.

Acknowledgment.—The authors wish to thank Dr. Ben A. Schoulders, University of Texas, for running the boron spectra and Cynthia A. Milewski for a sample of *meso*-2,4-pentanediol.

Azimines. I. Reinvestigation of Some Alleged Azimines

ROBERT C. KERBER

Department of Chemistry, State University of New York at Stony Brook, Stony Brook, New York 11790

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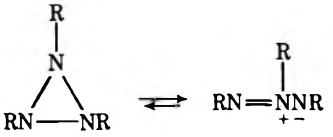
Azimines are the 1,3-dipolar isomers of the unknown triaziridines. Some previously proposed azimine structures are reassigned, based on new spectroscopic evidence. The product formed by bromination and dehydrobromination of *o*-nitrobenzaldehyde phenylhydrazone is assigned structure **5b**; reduction with stannous chloride gives **6b**, *anhydro*-2-(*p*-bromophenyl)-3*H*-benzo-1,2,3-triazinium-4-one hydroxide. Reaction of *o*-aminobenzamide with *N,N*-dimethyl-4-nitrosoaniline gives 4,4'-azoxy-*N,N*-dimethylaniline, not the previously proposed **6c**. Condensation of indazolinone with *N,N*-dimethyl-4-nitrosoaniline does give **6c**, presumably *via* an intermediate triaziridine.

1,3 dipoles have been of substantial interest, originally as intermediates in the synthesis of five-membered heterocycles,[1] and more recently as valence isomers of three-membered heterocycles.[2,3] The three-nitrogen valence isomer pair comprising the cyclic triaziridines and the open dipolar azimines remains, however, almost unexplored. The literature reveals no extant reports of triaziridines,[4] and only scattered examples of azimines (see below). Expecting the latter to be more



stable, we here report the establishment of structure of some cyclic azimines. An accompanying paper[5] reports on the reactions of nitrenes with azo compounds, a potential synthetic route to azimines.[6] Other synthetic routes are also being investigated, and will be reported subsequently.[7]

Products from *o*-Nitrobenzaldehyde Phenylhydrazone.—In a series of papers in 1925–1931, Chattaway[8–11] reported that halogenation of *o*-nitrobenzaldehyde phenylhydrazone, followed by treatment with base, gave a series of compounds A, to which he assigned structure **1**[9] (Scheme I). Reduction of compounds A with stannous chloride gave a series of compounds B, assigned triaziridine structures **2**. This work was subsequently reinvestigated by Gibson,[12] who proposed the new structures **3a** and **4a** for materials A and B (Ar = 2,4-dibromophenyl), respectively. The anthranil *N*-oxide structure **3a** was apparently based on mechanistic considerations and ultraviolet and infrared spectra, especially bands at 1248 and 1570 cm^{-1} in the latter, assigned as $\overset{+-}{>NO}$ and –N=N– stretching frequencies, respectively. Compound B was assigned the azimine structure **4a**, since the possibility of B being the straightforward reduction product of **3a**, the

(1) R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, **2**, 565, 633 (1963). Most recent paper: R. Knorr, R. Huisgen, and G. K. Staudinger, *Chem. Ber.*, **103**, 2639 (1970).

(2) Oxaziridine–nitrone pair: J. S. Splitter and M. Calvin, *J. Org. Chem.*, **23**, 651 (1958); E. Schmitz, "Dreiringe mit Zwei Heteroatomen," Springer-Verlag, West Berlin, 1967, pp 14–15, 19–20, 35–36.

(3) General discussion, especially oxadiaziridine–azoxy compound pair: (a) F. D. Greene and S. S. Hecht, *J. Org. Chem.*, **35**, 2482 (1970); (b) H. Mauser, G. Gauglitz, and F. Stier, *Justus Liebigs Ann. Chem.*, **739**, 84 (1970).

(4) One uncorroborated report: M. Colonna and A. Risaliti, *Gazz. Chim. Ital.*, **91**, 204 (1961).

(5) R. C. Kerber and P. J. Heffron, *J. Org. Chem.*, **37**, 1592 (1972).

(6) A recent example of this reaction: K.-H. Koch and E. Fahr, *Angew. Chem., Int. Ed. Engl.*, **9**, 634 (1970).

(7) Unpublished work by S.-M. Liu, L. Colen, and R. Liotta in these laboratories.

(8) F. D. Chattaway and A. J. Walker, *J. Chem. Soc.*, 2407 (1925). 323 (1927).

(9) F. D. Chattaway and A. J. Walker, *ibid.*, 323 (1927).

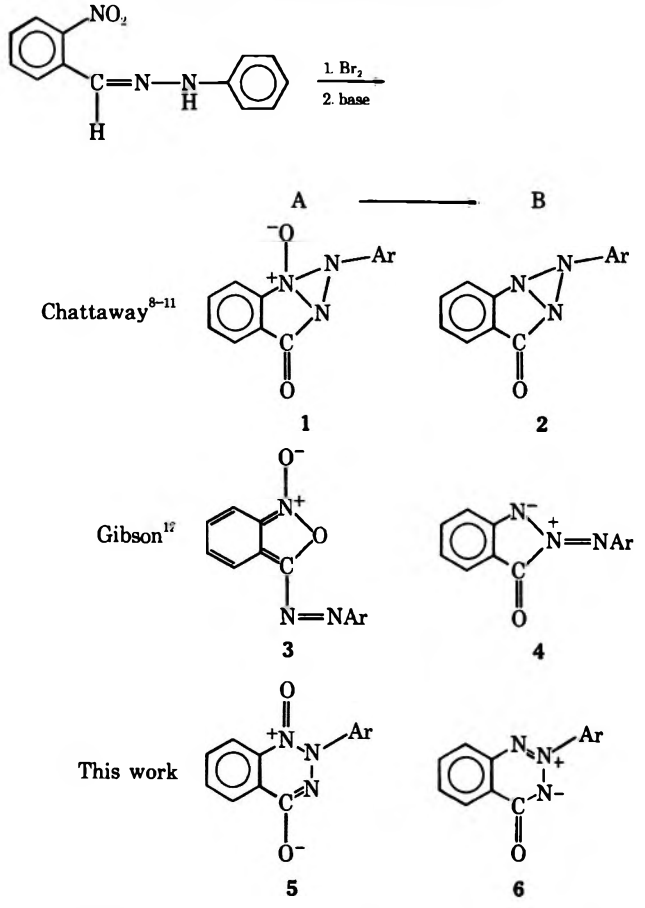
(10) (a) F. D. Chattaway and A. B. Adamson, *ibid.*, 157 (1930); (b) *ibid.*, 2787, 2792 (1931).

(11) For a review, see J. G. Erickson in "The Chemistry of Heterocyclic Compounds," Vol. 10, A. Weissberger, Ed., Interscience, New York, N. Y., 1956, p 27.

(12) M. S. Gibson, *Tetrahedron*, **18**, 1377 (1962); *Nature (London)*, **193**, 474 (1962).

SCHEME I

PROPOSED STRUCTURES FOR PRODUCTS FROM HALOGENATION OF *o*-NITROBENZALDEHYDE PHENYLHYDRAZONE

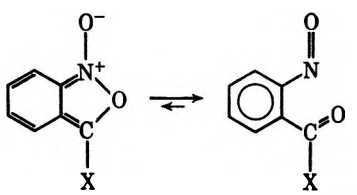


a, Ar = 2,4-$Br_2C_6H_3$; b, Ar = 4-BrC_6H_4; c, Ar = 4-$(Me_2N)C_6H_4$

3-(arylazo)anthranil, was excluded by the chemical and spectral properties of **4a**, especially by the presence of a carbonyl stretching band in the infrared at 1655 cm^{-1}.

However, this reported >C=O stretching frequency appeared also to be inconsistent with the proposed five-membered ring azimine structure **4a** for material B, inasmuch as the carbonyl stretching frequency for indazolone falls at 1792 cm^{-1},[13] and the positive charge on the 2 nitrogen might be expected to raise the frequency even higher. Consequently, we undertook a reinvestigation of these materials.

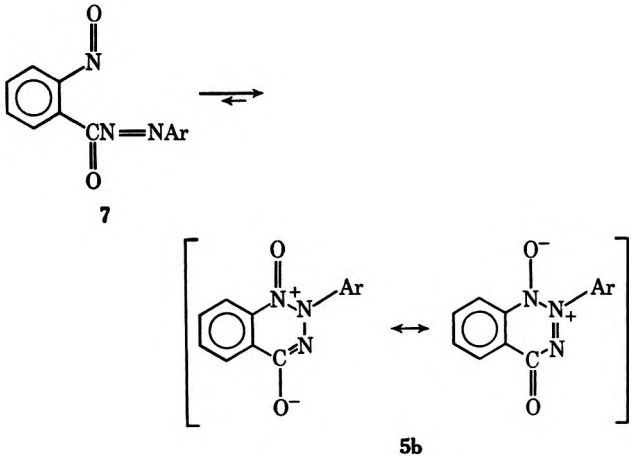
Reaction of *o*-nitrobenzaldehyde phenylhydrazone with 2 equiv of bromine in acetic acid containing excess sodium acetate[8] gave directly the material A (Ar = *p*-bromophenyl), assigned the anthranil *N*-oxide structure **3b** by Gibson.[12] Anthranil *N*-oxides are an unknown[14] class of compound thought to be unstable



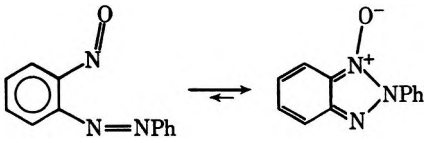
7, X = N=NC_6H_4Br

with respect to the isomeric *o*-nitroso carbonyl compounds.[15] Nonetheless, structure **3b** provides an adequate explanation of the principal feature of the infrared spectrum of A (Ar = *p*-bromophenyl), a strong band at 1630 cm^{-1}, which may be assigned to >C=N–, by analogy with benzofuroxans[16] and nitronic esters.[17] In contrast, the isomeric nitroso compound **7** does not fit the spectra; for example, A lacks the carbonyl stretching band found at about 1715 cm^{-1} in (aroylazo)benzenes,[18] the strong nitroso stretching frequency normally found near 1500 cm^{-1},[19] or the n → π^* absorption of the nitroso group, found at 765 nm (ϵ 6060) in *o*-nitrosobenzophenone.[20]

One additional structure which should be considered for A is **5b**, which may be formed by intramolecular cyclization of the azo and nitroso groups of **7**. Such a



cyclization evidently occurs spontaneously in the *o*-nitrosoazobenzenes, which exist in the form of 2-arylbenzotriazole 1-oxides.[15,21]



The structure **5b** for material A is reconcilable with the spectral data and, assuming a mobile equilibrium between **7** and **5b**, with the chemical reactions reported by Chattaway[9] (formation of ArH on treatment with ethanolic KOH; oxidation to *o*-nitrobenzoic acid with $KMnO_4$; and, especially, reduction to B with stannous chloride).

Material B (Ar = *p*-bromophenyl) was obtained in 57% yield on reduction of A (**5b**) with stannous chloride. The infrared spectrum showed a carbonyl stretching band at 1675 cm^{-1} [*cf.* Gibson's value of

(13) E. F. Ullman and E. A. Bartkus, *Chem. Ind. (London)*, 93 (1962).

(14) One reported exception: H. H. Szmant and C. M. Harmuth, *J. Amer. Chem. Soc.*, **81**, 962 (1959).

(15) K. H. Wünsch and A. J. Boulton, *Advan. Heterocycl. Chem.*, **8**, 332 (1967).

(16) A. R. Katritzky, Ed., "Physical Methods in Heterocyclic Chemistry," Vol. II, Academic Press, New York, N. Y., 1963, p 239.

(17) N. Kornblum and R. A. Brown, *J. Amer. Chem. Soc.*, **86**, 2681 (1964).

(18) E. Fahr and H. Lind, *Angew. Chem., Int. Ed. Engl.*, **5**, 372 (1966).

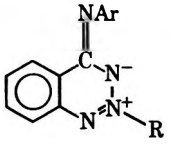
(19) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Methuen & Co., London, 1958, p 306.

(20) S. Kim, S. S. Friedrich, L. J. Andrews, and R. M. Keefer, *J. Amer. Chem. Soc.*, **92**, 5452 (1970).

(21) This may be inferred from the numerous (colorless) benzotriazole *N*-oxides which are reported, and the lack of *o*-nitrosoazo compounds: F. R. Benson and W. L. Savell, *Chem. Rev.*, **46**, 1 (1950). However, no infrared spectra seem to be reported for the supposed benzotriazole *N*-oxides.

1655 for B (Ar = 2,4-dibromophenyl)]. Since 3-arylbenzo-1,2,3-triazin-4-ones have carbonyl stretching frequencies at about 1685 cm^{-1},[22] and since 3-(*p*-bromophenyl)benzotriazinone has nearly the same reported melting point (196°)[9] as B (199–200°), an authentic sample of the former was prepared for comparison. The two materials were not identical, as shown by infrared comparison and depressed mixture melting point. However, the spectra showed many similarities, suggesting a six-membered azimine structure **6b** for material B. This was also consistent with the 60-MHz pmr spectrum of B in DMSO at 100°, which showed a two-proton doublet at τ 1.8 ($J \approx 9$ Hz), a four-proton singlet at τ 2.0, and another two-proton doublet at τ 2.2 ($J \approx 9$ Hz); the substantial deshielding of the *p*-bromophenyl ring is consistent with structure **6**, in which the ring is bonded to the positive central nitrogen of the azimine grouping, but not with **4**.

Confirmation that the material B had structure **6b** was obtained from the mass spectrum, which showed, in addition to a substantial (24%) parent peak at *m/e* 301 and 303, important fragments at *m/e* 273 and 275 (P − N_2 or CO), 245 and 247 (P − N_2 − CO), 183 and 185 (*p*-$BrC_6H_4N_2^+$), 166 (P − N_2 − CO − Br), and 155 and 157 ($BrC_6H_4^+$). The fragmentation pattern observed is analogous to those of the recently reported iminoazimines **8**.[23]



8

Ar = *o*-CNC_6H_4, *o*-ClC_6H_4, *o*-$O_2NC_6H_4$
R = Me, Et, Pr

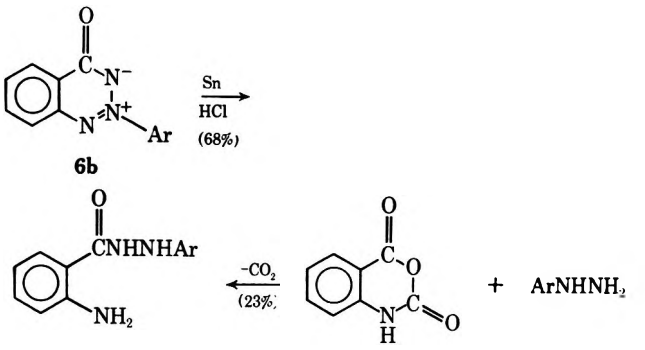
Fragments such as $BrC_6H_4N^+$, $C_5H_4Br^+$, $C_7H_4N_2O^+$, and $C_7H_4O^+$, which would be expected from a material of structure **4b**, are absent from the observed mass spectrum of B. These data appear to support structure **6b** for this material. The structure **6b** is also supported by recent reports of alkylation of salts of benzo-1,2,3-triazin-4-one to give, in addition to the expected O- and N(3)-alkylated products, products which appear to be N(2)-alkylated azimines, **6** (Ar = CH_3, CH_3CH_2).[24] The spectroscopic data for these compounds [ν_{CO} 1630 cm^{-1}, λ_{max} *ca.* 340 nm (log ϵ 3.9), deshielded methyl group in the nmr (τ 5.55)] are consistent with those of **6b**, allowing for the differences between a 2-alkyl and a 2-aryl substituent.

Reduction of compound B (**6b**) with tin in hydrochloric acid gave the *p*-bromophenylhydrazide of anthranilic acid, identical with an authentic sample.[9]

Reaction of **6b** with ethanolic KOH[9] gave a complex mixture from which pure products could not be isolated.

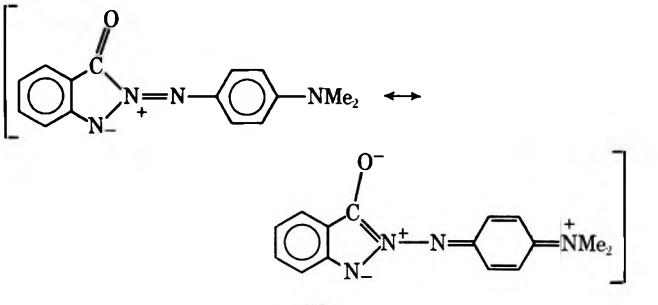
The six-membered ring azimine structure **6b** for B, which is uniquely consistent with the spectroscopic and chemical information, appears also to lend support to the proposed structure **5b** for material A.

Product from Anthranilamide and 4-Nitrosodimethylaniline.—Jennen has reported that condensation of anthranilamide with 4-nitroso-*N*,*N*-dimethylaniline (**9**) gave rise to a material C, mp 249°, assigned the structure **6c**.[25] However, the reported analysis did not fit the formula $C_{15}H_{14}N_4O$, and no other support for the structure **6c** for C was offered. Repetition of this reaction gave a product, mp 243–244°, which was apparently that obtained by Jennen. The infrared spectrum of this material showed neither carbonyl nor ortho-substituted benzene ring absorption. A doublet at 813 and 824 cm^{-1} indicated only para-substituted rings.[26] The 60-MHz pmr spectrum (DMSO-d_6 at 150°) showed a singlet at τ 7.00 (area 6) for the dimethylamino groups, a doublet at τ 3.25 ($J \approx 9$ Hz, area 2), and a pair of overlapping doublets at τ 1.89 and 2.05 ($J \approx 9$ Hz, area 2). These data and a correct analysis for $C_{16}H_{20}N_4O$ showed the material C to be 4,4′-azoxy-*N*,*N*-dimethylaniline (lit.[27] mp 244.5°).



6b

Product from Indazolinone and Nitrosodimethylaniline.—Jennen also reported the synthesis of another azimine, by condensation of indazolinone and **9**. The product, material D, was assigned the structure **10**



10

(analogous to Gibson's **4**), and was described initially as a blue dye[28] and later as a red-purple compound, mp 198°.[25]

Condensation of indazolinone with **9**, using methanolic KOH, gave a very dark solution from which a purple, crystalline product, mp *ca.* 186°, was obtained after recrystallization from chloroform, and then from DMSO. Chromatography of the residue from the recrystallizations led to isolation of several by-products, including *N*,*N*-dimethyl-*p*-phenylenediamine, 4,4′-azo-*N*,*N*-dimethylaniline, and *N*-benzoyl-*N*′,*N*′-dimethyl-*p*-phenylenediamine.

Evaporation of a saturated solution of the purple material D in methanol containing 5% carbon tetra-

(22) M. S. Gibson, *J. Chem. Soc.*, 3539 (1963).

(23) R. A. W. Johnstone, *et al.*, *J. Chem. Soc. C*, 1238 (1970); H. N. E. Stevens and M. F. G. Stevens, *ibid.*, 2289 (1970).

(24) G. Wagner and H. Gentzsch, *Pharmazie*, **23**, 629 (1968). The authors do not firmly decide between the 1- and 2-alkylated structures for these materials, but the bulk of the evidence favors the latter.

(25) J. J. Jennen *Meded. Vlaam. Chem. Ver.*, **18**, 43 (1956).

(26) J. R. Dyer, "Applications of Absorption Spectroscopy of Organic Compounds," Prentice-Hall, Englewood Cliffs, N. J., 1965, p 33.

(27) E. Bornstein, *Ber.*, **29**, 1479 (1896).

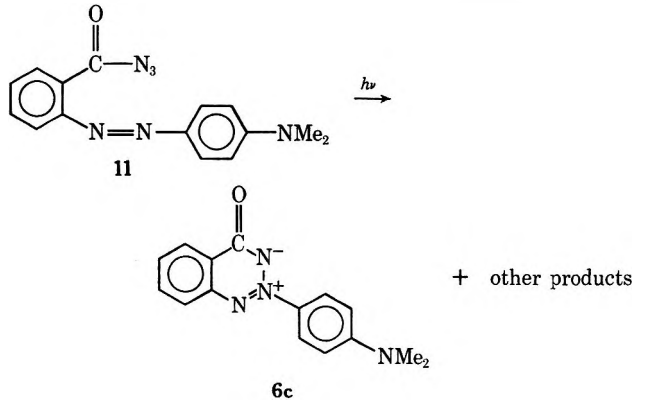
(28) J. J. Jennen, *Ind. Chim. Belge*, **16**, 472 (1951). D has been shown to be different from 2[4′-(dimethylamino)phenylazo]benzamide: L. Moelants and R. Janssen, *Bull. Soc. Chim. Belg.*, **66**, 209 (1957).

chloride gave shiny blue-black needles, mp 199–200°, which showed the same infrared spectrum as the less pure purple materials. This spectrum showed a carbonyl stretching band at 1655 cm^{-1}, and bands at 817 and 781 cm^{-1} for the para- and ortho-substituted rings. The nmr spectrum (in DMSO-d_6 at 150°) of D was similar to that of B (**6b**), showing a sharp singlet at τ 6.84 for the dimethylamino protons, a doublet (2H, $J \approx 10$ Hz) at τ 3.08, a multiplet (4H) at τ 2.3, and another doublet (2H, $J \approx 10$ Hz) at τ 1.56. These data suggested the analogous structure **6c** for D.

The color of D is due to an intense long-wavelength absorption which appears at 548 nm in ethanol, 530 nm in chloroform, and 522 nm in dioxane. The absence of such a band in B in contrast to D and the solvent dependence of its wavelength suggest that this is a charge transfer absorption analogous to the long-wavelength band (λ_{max} 390 nm in ethanol, 380 nm in dioxane, 352 nm in hexane) found in *p*-nitro-*N*,*N*-dimethylaniline.[29] Its appearance in D (**6c**) appears to support the notion that the aryl group is bonded to the electron-deficient 2 nitrogen in **6c** rather than a terminal nitrogen of the azimine group, as in **10**.

The structural analogy between B (**6b**) and D (**6c**) was confirmed by their very similar mass spectra. Thus, both feature large parent peaks, small fragments corresponding to loss of 28 and 56 amu, and large fragments at masses corresponding to $C_6H_4NAr^+$, Ar^+, $C_6H_4N^+$, and $C_5H_3^+$.

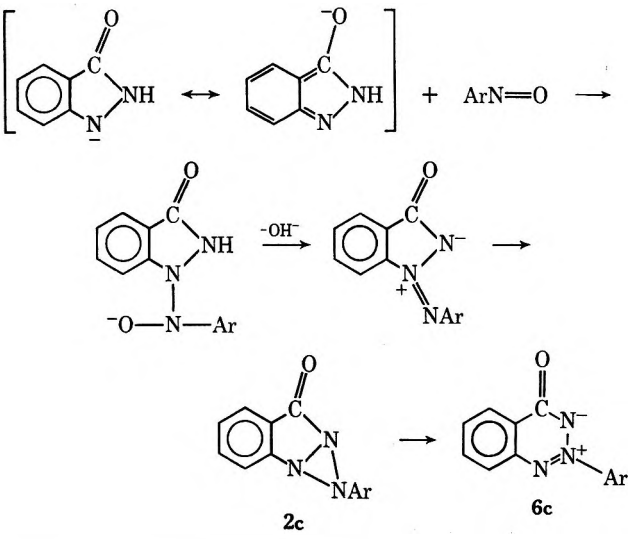
Reduction of **6c** with tin and hydrochloric acid gave an air-sensitive product which appeared by infrared and vapor phase chromatographic analysis to be a mixture of *N*,*N*-dimethyl-*p*-phenylenediamine and *p*-(*N*,*N*-dimethylamino)phenylhydrazine.[30] An attempt to synthesize authentic **6c** by photolysis of the azide **11** gave only 3% of **6c**, in addition to a number of other products, which will be reported on subsequently.[5]



Discussion

Our results suggest that materials B and D, both previously assigned five-membered ring azimine structures **4**, in fact have the isomeric six-membered ring azimine structures **6**. The production of **6b** on reduction of material A is to be expected, based on the proposed structure **5b** for A.[31] However, the six-membered ring structure for the product D, from condensation of the five-membered ring starting material, indazolinone, with **9** is more surprising, even though the stability of structures such as **6** relative to **4** may be expected based on lesser ring strain and greater aromatic character of the heterocyclic ring in **6**.

Jennen's proposal of the structure **4c** for the product was evidently based on the idea that reaction of an electrophile such as **9** with the conjugate base of indazolinone would occur most readily at the 2-nitrogen.[25] More recent studies, however, have shown that electrophiles, including acyl chlorides[33] and alkylating agents,[34] react primarily at the 1 nitrogen. It seems probable that reaction of the nitroso compound **9** should begin in the same way. Loss of hydroxide ion from the first intermediate should then give an azimine isomeric with **4** and **6**. Rearrangement to the presumably most stable azimine **6c** may then occur *via* a triaziridine intermediate, **2c**.



In addition to the azimines reported here, a number of others can be found on inspection of the literature.[35–42]

In all of these examples, the azimine grouping is part of an aromatic ring, which no doubt lends stability to the system.[43] However, this structural feature also makes closure of the azimine to a triaziridine more difficult for both electronic and steric reasons.[44] The

(29) W. D. Kumler, *J. Amer. Chem. Soc.*, **68**, 1184 (1946); H. Labhart and G. Wagniere, *Helv. Chim. Acta*, **46**, 1314 (1963).

(30) R. Stolle and K. T. Gunzert, *J. Prakt. Chem.*, **139**, 141 (1934).

(31) The structure **5b** remains hypothetical pending crystallographic study. It would be formed *via* **3b** and **7**. **3b** could arise by nucleophilic attack of the nitro group[20] on an intermediate nitrilimine.[12,32]

(32) R. Huisgen, M. Seidel, G. Wallbillich, and H. Knupfer, *Tetrahedron*, **17**, 3 (1962).

(33) R. M. Anderson and J. K. Way, *J. Chem. Soc. C*, 1139 (1967).

(34) J. Schmutz, F. Hunziker, and W. Michaelis, *Helv. Chim. Acta*, **47**, 1986 (1964).

(35) M. P. Schmidt and A. Hagenbocker, *Ber.*, **54**, 2191, 2201 (1921).

(36) For reviews, see M. Ohta and H. Kato in "Nonbenzenoid Aromatics," J. P. Snyder, Ed., Academic Press, New York, N. Y., 1969, pp 117–248, and L. C. Behr in "The Chemistry of Heterocyclic Compounds," Vol. 17, A. Weissberger, Ed., Interscience, New York, N. Y., 1962, p 323.

(37) M. J. Perkins, *J. Chem. Soc.*, 3005 (1964).

(38) P. Tavs, H. Sieper, and H. Beecken, *Justus Liebigs Ann. Chem.*, **704**, 150, 161, 166, 172 (1967).

(39) C. W. Rees and R. C. Storr, *J. Chem. Soc. C*, 756 (1969).

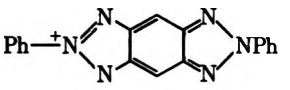
(40) R. A. Carboni, J. C. Kauer, J. E. Castle, and H. E. Simmons, *J. Amer. Chem. Soc.*, **89**, 2618, 2626, 2633, 2638 (1967).

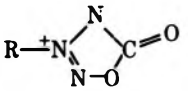
(41) R. A. Carboni, U. S. Patent 3,190,886 (1965); *cf. Chem. Abstr.*, **63**, 11749*d* (1965).

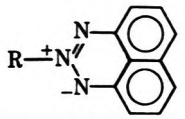
(42) A. W. Murray and K. Vaughan, *Chem. Commun.*, 1282 (1967).

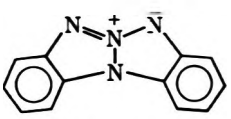
(43) A strong case can also be made that 2*H*-triazoles and 2*H*-benzotriazoles are best represented as cyclic azimines. For evidence, see A. J. Boulton, P. J. Halls, and A. R. Katritzky, *Org. Mag. Resonance*, **1**, 311 (1969), and H. Günther and H.-H. Hinrichs, *Justus Liebigs Ann. Chem.*, **706**, 1 (1967). For reviews, see J. H. Boyer in "Heterocyclic Compounds," Vol. VII, R. C. Elderfield, Ed., Wiley, New York, N. Y., 1961, p 384, and F. R. Benson and W. L. Savell, *Chem. Rev.*, **46**, 1 (1950).

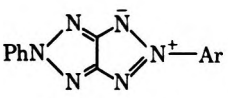
(44) However, see H. Kato, T. Shiba, H. Yoshida, and S. Fujimori, *Chem. Commun.*, 1591 (1970).

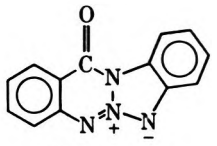

Reference 35


Reference 36


R = alkyl,[37] aryl,[37,38] NH_2[39]


Reference 40


Reference 41


Reference 42

only acyclic azimines reported have been found by Fahr[6] to decompose *in situ*, in contrast to more stable semicyclic ones prepared by an analogous route. Further attempts to obtain acyclic azimines will be reported subsequently.[5,7]

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer Infracord Model 137, ultraviolet–visible spectra on a Beckman DK-2A, and pmr spectra on a Varian A-60. Solvents used for spectra were Spectro Grade, except for DMSO, which was reagent grade, redistilled from calcium hydride at reduced pressure. Reaction and chromatographic solvents were redistilled before use. Drying of wet solutions was by means of magnesium sulfate unless otherwise noted.

***o*-Nitrobenzaldehyde Phenylhydrazone.**—*o*-Nitrobenzaldehyde (20.0 g, 0.132 mol) was dissolved in a mixture of 40 ml of water and 65 ml of ethanol, and added to a solution of 14.3 g (0.132 mol) of phenylhydrazine in 100 ml of water containing 30 ml of acetic acid. After 1 hr, the mixture was cooled in ice and filtered, and the precipitated product was washed with water and then ethanol. Drying over potassium hydroxide left 30.78 g of bright red solid, mp 154–156° (97%) (lit.[45] mp 154°).

Formation of A (5b).—The hydrazone (5.00 g, 20.7 mmol) and anhydrous sodium acetate (12.0 g, 146 mmol) were suspended in 50 ml of glacial acetic acid. A solution of bromine (6.72 g, 42.0 g-atoms) in 20 ml of acetic acid was added dropwise while the solution was stirred. After 1 hr, there remained a brown solution containing a red precipitate, which was poured into 200 ml of water and stirred until the precipitate had become completely yellow. The mixture was then filtered, and the precipitate was washed with water, 5% $NaHCO_3$ solution, water, and ethanol. After drying over KOH, the solid was recrystallized from chloroform, leaving yellow needles, mp 138° dec, yield 3.33 g (46%). The mother liquor yielded an additional 0.93 g, mp 134° dec, on evaporation (lit.[8] mp 144° dec): ir (KBr disc) 3.26 (w, CH), 6.14 (vs, C=N or C=O), 6.36 (m) and 6.76 (m) (Ar), 7.61 (s), 7.94 and 8.03 (d, s), 8.37 (s, $=N^+-O^-$?), 8.67 (m), 9.92 (m), 11.47 (m), 12.17 (m, para-substituted), and 13.18 μ (s, ortho-substituted); uv (95% EtOH) λ_{max} 400 nm (ϵ 5.56×10^3), 286 (1.17×10^4); nmr (CF_3COOH) two multiplets of equal intensity at τ 1.52 and 2.26.

Reduction of A (5b) to B (6b).—Material A (3.13 g, 9.87 mmol) was dissolved in a mixture of 15 ml of acetic acid and 40 ml of concentrated aqueous HCl. The solution was cooled in ice and stirred magnetically while a solution of $SnCl_2 \cdot 2H_2O$ (3.00 g, 13.3 mmol) in 10 ml of concentrated HCl was added dropwise. The mixture was allowed to warm to room temperature and filtered, and the precipitate was washed with 3% HCl (twice) and then with warm (60°) water. The product was recrystallized from methanol–ethanol, yielding 1.69 g (57%) of yellow powder, mp 199–200° (lit.[9] mp 197°). Filtration of the hot alcohol solution during recrystallization gave an orange solid, mp >270°, which showed no carboryl group in the infrared. Ir of **6b** (KBr disc) 3.25–3.35 (w, CH), 5.97 (vs, C=O), 6.38 (w) and 6.79 (m) (Ar), 7.12 (m), 7.50 (m), 7.74 (m), 7.86 (s), 8.82 (m), 9.07 (m), 9.37 and 9.45 (d, m), 9.92 (m), 11.98 (s, para-substituted), and 12.96 μ (s, ortho-substituted); uv (95% EtOH) λ_{max} *ca.* 350 nm (sh, ϵ 13,500), 312 (17,400), 285 (sh, 14,200), and 237 (12,200); nmr (DMSO, 100°) given in text; nmr (CF_3COOH) τ 1.54 (d, $J \approx 9$ Hz, 2 H), 1.42 (s, 4 H), 2.18 (d, $J \approx 9$ Hz, 2 H); mass spectrum (direct inlet at 90°, 50 V ionizing voltage) *m/e* (rel intensity) 303, 301 (24.1,[46] P), 273, 275 (1.4,[46] P − N_2 or CO), 245, 247 (1.2,[46] P − N_2 − CO), 222 (1.3, P − Br), 194 (2.5, P − N_2 or CO − Br), 183, 185 (23.3,[46] $BrC_6H_4N_2^+$), 166 (13.8, P − Br − N_2 − CO), 155, 157 (100.0,[46] $Br-C_6H_4^+$), 90 (62, $C_5H_4N^+$), 76 (91, $C_6H_4^+$), 75 (74, $C_6H_3^+$), 64 (25.8, $C_5H_4^+$), 63 (38.8, $C_5H_3^+$), 50 (53.4, $C_4H_2^+$), 39 (34.4, $C_3H_3^+$), 31 (37.9).

3-(*p*-Bromophenyl)benzo-1,2,3-triazin-4-one.—1-(*o*-Carbomethoxyphenyl)-3-(*p*-bromophenyl)triazene was prepared by coupling of diazotized methyl anthranilate (1.4 g, 20 mmol) with *p*-bromoaniline (3.0 g, 18 mmol) according to the method of Chattaway.[9] The crude triazene was refluxed for 2 hr in 60 ml of 67% aqueous ethanol containing 3 ml of triethylamine. Cooling to room temperature gave a precipitate which was washed with ethanol and recrystallized from ethanol, yielding white benzotriazinone, yield 1.80 g (33% overall), mp 204–206° (lit.[9] mp 196°). The infrared spectrum was clearly different from that of **6** (for example, $\nu_{C=O}$ at 1689 cm^{-1} or 5.92 μ). A mixture melting point of **6** and the triazinone was *ca.* 160–175°. Uv (95% EtOH) showed λ_{max} 315 nm (ϵ 10,000), 301 (10,200), and *ca.* 285 (sh, 9300).

Reduction of 6b.[9]—The azimine **6b** (0.201 g, 0.67 mmol) was suspended in a mixture of 5 ml of acetic acid and 4 ml of concentrated HCl, and mossy tin (0.499 g, 4.1 mg-atoms) was added. The mixture was stirred at room temperature for 19 hr, diluted with 10 ml of water, and neutralized with sodium bicarbonate until a precipitate just began to form. The mixture was then extracted with four 25-ml portions of ether, which were washed with water and sodium bicarbonate solution until neutral, and then dried over $MgSO_4$ and evaporated, leaving 0.149 g of light brown solid, mp 162–167° (68% crude yield). Recrystallization from ethanol gave white needles, mp 184.5–185°, of *o*-aminobenzoyl-*p*-bromophenylhydrazide. The ir spectrum (KBr disc) showed important bands at 3.15 (s, NH), 6.14 (s, >C=O), 12.1 (s, para-substituted), and 13.3 (s, ortho-substituted).

***o*-Aminobenzoyl-*p*-bromophenylhydrazide.**—*p*-Bromophenylhydrazine (mp 104–106°, prepared in 60% yield by the method of Michaelis[47]) (0.873 g, 4.67 mmol) and 0.762 g (4.67 mmol) of isatoic anhydride were refluxed for 20 hr in 20 ml of dioxane. The mixture was poured into 50 ml of 5% aqueous HCl, and extracted with three 20-ml portions of ether. The aqueous layer was made alkaline with sodium hydroxide, and extracted again with three 20-ml portions of ether. The latter ether layers were combined, dried over $MgSO_4$, and evaporated, leaving 0.33 g (23%) of crude product. Recrystallization from ethanol gave mp 180–183°, mixture melting point with the previous sample, 180–183°. The infrared spectra of the two samples were identical.

Reaction of Anthranilamide with 9.[25]—Anthranilamide (2.72 g, 20.0 mmol) was suspended in 20 ml of absolute ethanol and added dropwise to a solution of *p*-nitroso-*N*,*N*-dimethylaniline (**9**, 3.00 g, 20.0 mmol) in 20 ml of 50% ethanol–acetic acid. The mixture was refluxed for 10 min, and then allowed to stand in a refrigerator (5–10°) for 19 hr. Filtration gave a small amount of brown solid, mp 231–237°. Addition of ether to the filtrate yielded a larger quantity of precipitate, which was also collected, giving a total of 0.88 g of crude **C** (36%). Recrystallization from dimethyl sulfoxide (three times) gave red needles (blue reflection), mp 243–244° (lit. mp[27] for *p*,*p*′-bis(dimethylamino)azoxybenzene, 244.5°; reported by Jennen,[25] 249°).

Anal. Calcd for $C_{16}H_{20}N_4O$: C, 67.61; H, 7.04; N, 19.72. Found: C, 67.58; H, 6.97; N, 19.69. Found:[25] C, 67.32; H, 7.05; N, 20.34.

The ir spectrum showed bands at *ca.* 3.4 (w, CH), 6.25 (s), 6.60 (m), 6.95 (w), 7.34 (s, −N=NO), 7.95 (w), 8.14 (w), 8.60

(45) C. Paal and A. Bodewig, *Ber.*, **25**, 2903 (1892).

(46) Intensity of ^{79}Br peak, relative to base peak at *m/e* 155. The ^{81}Br isotopic peak had an intensity of *ca.* 97% that of the ^{79}Br for all bromine-containing peaks.

(47) L. Michaelis, *Ber.*, **26**, 2190 (1893).

(s), 10.59 (m), 12.15 and 12.30 μ (s, para-substituted). The nmr spectrum is given in the text.

Reaction of 9 with Indazolinone.—Indazolinone (2.68 g, 20.0 mmol) was suspended in 20 ml of methanol, and dissolved by adding 1.2 g (21 mmol) of KOH. A nitrogen atmosphere was established, and then a solution of 3.00 g (20.0 mmol) of 9 in 40 ml of methanol was added dropwise. After 2 hr, the methanol solvent was stripped off, the nearly black residue was added to 100 ml of water, and the mixture was extracted repeatedly with methylene chloride until the coloration of the organic layer was only light purple. The methylene chloride solutions were combined, dried with $MgSO_4$, and evaporated, leaving a dark purple residue. This was triturated with carbon tetrachloride, and the residue was recrystallized from chloroform and then dimethyl sulfoxide, giving a purple compound, mp *ca.* 186°. This was further purified by slow evaporation of a saturated 95% methanol–5% CCl_4 solution to give blue needles, mp 199–200° (lit.[25] mp for D, 198°).

Anal. Calcd for $C_{15}H_{14}N_4O$: C, 67.66; H, 5.26; N, 21.05. Found: C, 67.43; H, 5.37; N, 20.98.

Chromatography of the combined residue from evaporation of the CCl_4 triturate and the mother liquors from the recrystallizations on silica gel produced (1) *p,p'*-bis(dimethylamino)-azobenzene, yield 0.21 g (8%), mp 264–268° (from benzene), identified by ir comparison with authentic[48] spectrum (lit.[49] mp 273°); (2) *N*-benzoyl-*N',N'*-dimethyl-*p*-phenylenediamine, yield 0.14 g (3%), mp 220–225°, identified by ir and mixture melting point comparison with authentic material; (3) *N,N*-dimethyl-*p*-phenylenediamine, yield 0.25 g (9%), identified by vpc (150°, 15% SF-96 column) and ir comparison with authentic material; (4) additional D. Spectral data for D follow: ir (KBr disc) 3.35 (w, CH), 6.04 (s, C=O), 6.24 (s), 6.52 (m), 6.90 (s), 7.26 (s), 7.50 (m), 7.81 (s), 8.71 (s), 9.29 (s), 9.58 (s), 10.60 (m), 11.48 (m), 12.30 (s), 12.80 (m), 14.12 (m), 14.70 μ (m); nmr (DMSO-d_6), see text; nmr (CF_3COOH) τ 1.54 (d, $J \approx 10$ Hz, 2 H), 2.1 (m, 4 H), 2.78 (d, $J \approx 10$ Hz, 2 H), and 6.42 (s, 6 H); uv (95% EtOH) λ_{max} 548 nm (ε 86,000), 322 (sh, 5000), 298 (8800), 292 (9600), 238 (14,600), 228 (15,700) (The long-wavelength maximum appeared at 530 nm in $CHCl_3$, 522 nm in dioxane.); mass spectrum (direct inlet, 120°, 70 eV ionizing voltage) *m/e* (rel intensity) 267 (18.2, P + 1), 266 (100.0, P), 265 (9.4, P − H), 250 (2.9, P − H − CH_3), 238 (11.5, P − N_2 or CO), 237 (14.6, P − N_2 or CO − H), 223 (6.2, P − N_2 or CO − CH_3), 222 (5.7, P − N_2 or CO − CH_3 − H), 209 (7.8, P − N_2 − CO − H), 195 (15.6, P − N_2 − CO − CH_3), 167 (9.4, $C_6H_5NC_6H_4^+$), 134 (14.6, $Me_2NC_6H_4N^+$), 133 (16.2, P^{2+} or 134 H), 120 (43.2, $Me_2NC_6H_4^+$), 119 (19.8), 105 (26.0), 104.5 (9.9), 104 (18.8), 93 (9.4), 92 (8.9), 91 (9.9), 90 (10.4, $C_6H_4N^+$), 79 (13.5), 78 (13.0), 77 (24.5), 65 (7.8), 63 (10.4), 51 (4.2), 42 (31.8), 39 (9.9).

Reduction of 6c.—6c (0.205 g, 0.77 mmol) was reduced with tin in the same manner as 6b, but no product was obtained from the ether extracts of the acidic solution. Therefore, the aqueous layers were made basic with sodium hydroxide and extracted with four additional 25-ml portions of ether. Drying and evaporating the latter ether layers left 0.107 g of liquid, which darkened rapidly on exposure to air. The infrared spectrum was essentially identical with that of *N,N*-dimethyl-*p*-phenylenediamine, but vpc analysis (SE-30, 135°) showed an additional, higher boiling component in addition to the diamine. The ir spectrum and air sensitivity suggested that the latter might be *p*-(dimethylamino)phenylhydrazine.[30] An attempt to obtain a hydrazone by reaction of the material with benzaldehyde[30] failed.

Registry No.—6b, 33986-95-7; *o*-aminobenzoyl-*p*-bromophenylhydrazide, 33986-96-8; *N*-benzoyl-*N,N'*-dimethyl-*p*-phenylenediamine, 33986-97-9; *N,N*-dimethyl-*p*-phenylenediamine, 99-98-9.

Acknowledgment.—We gratefully acknowledge support from Rohm and Haas Co. and from the Research Foundation of State University of New York.

(48) Sadtler Standard Infrared Spectra, Sadtler Research Laboratories, Inc., Philadelphia, Pa., 1970, No. 18592.

(49) D. Vorländer and E. Wolferts, *Ber.*, **56**, 1238 (1923).

Azimines. II. Reactions of Nitrenes with Azo Compounds

ROBERT C. KERBER* AND PETER J. HEFFRON

Department of Chemistry, State University of New York at Stony Brook, Stony Brook, New York 11790

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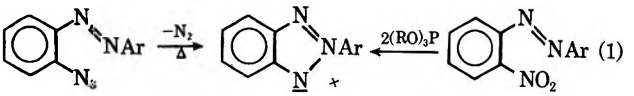
Syntheses of azimines by reaction of nitrenes with azo compounds are explored. The major product from the thermolysis of ethyl azidoformate in azobenzene is ethyl 2-(phenylazo)carbanilate, apparently formed by rearrangement of an azimine intermediate, 5. No reaction occurred between *N*-phthalimidylnitrene and diethyl azodicarboxylate. The reaction of 2-(4'-dimethylaminophenylazo)benzhydrazide with nitrous acid did not give isolable 2-(4'-dimethylaminophenylazo)benzazide; the major product of the reaction was 3-(4'-dimethylaminophenyl)-3*H*-benzo-1,2,3-triazin-4-one (15). The expected azimine, *anhydro*-2-(4'-dimethylaminophenyl)-3*H*-benzo-1,2,3-triazinium-4-one hydroxide (12), was only obtained in low yield and did not undergo conversion to 15 under the reaction conditions.

Having studied a number of aromatic heterocycles containing the 1,3-dipolar azimine grouping,[1] RN=N⁺(R)N⁻R, we wished to explore possible synthetic routes to acyclic azimines. One such route which appeared promising was addition of a nitrene to an azo group.

Electrophilic nitrenes add readily to pyridines, sulfides, and sulfoxides to give dipolar adducts.[2-5] Analogous addition to the azo group therefore appeared plausible, despite the low basicity of azo compounds. Formal intramolecular examples of such a reaction



(1)

have been reported (*e.g.*, eq 1);[6,7] however, the actual intermediacy of nitrenes in these reactions is not probable.[8] Moreover, the isolation of azobenzenes in good yields from reactions producing arylnitrenes[9] suggests that the reactivity of these nitrenes toward azobenzenes cannot be high.

Early attempts to study the reaction of carbethoxy-

(1) R. C. Kerber, *J. Org. Chem.*, **37**, 1587 (1972).

(2) K. Hafner, D. Zinser, and K. L. Moritz, *Tetrahedron Lett.*, 1733 (1964).

(3) T. L. Gilchrist and C. W. Rees, "Carbenes, Nitrenes, and Arynes," Appleton-Century-Crofts, New York, N. Y., 1969, p 98.

(4) W. Lwowski in "Nitrenes," W. Lwowski, Ed., Interscience, New York, N. Y., 1970, p 216.

(5) D. S. Breslow, ref 4, pp 277–279.

(6) R. A. Carboni, J. C. Kauer, J. E. Castle, and H. E. Simmons, *J. Amer. Chem. Soc.*, **89**, 2618, 2633, 2638 (1967).

(7) J. I. G. Cadogan, M. Cameron-Wood, R. K. Mackie, and R. J. G. Searle, *J. Chem. Soc.*, 4831 (1965).

(8) P. A. S. Smith, ref 4, pp 138–141; J. H. Hall, 15th Annual Report on Research, Petroleum Research Fund, 1970, p 37.

(9) P. A. S. Smith, ref 4, pp 114–119.

nitrene with diethyl azodicarboxylate were reported by Hancock[10] and by Lwowski.[11] Photolysis of ethyl azidoformate in the presence of diethyl azodicarboxylate gave triethyl nitrilotricarboxylate; the intermediacy of a triaziridine or an azimine was postulated. However, an attempt to generate the singlet nitrene by α elimination in the presence of the azo compound failed to produce the same product, owing to decomposition of the azo compound.[11] It appeared to us that reaction of the electrophilic intermediate, carbethoxynitrene, with a more nucleophilic azo compound would have a better chance of success, and hence we chose to study initially the reaction of carbethoxynitrene with azobenzene. Thermolysis of the azide, which gives initially only the singlet nitrene, appeared preferable to photolysis, which gives both singlet and triplet.[12]

Reaction of Carbethoxynitrene with Azobenzene.—When ethyl azidoformate was thermolyzed in the presence of excess azobenzene at 115–117°, 78% of the azobenzene was recovered by chromatography on acid-washed alumina. The recovered azobenzene was found to contain a higher boiling contaminant by vpc. Isolation by preparative gas chromatography gave a red oil, which was identified by ir and uv as 2-(phenylazo)biphenyl (**1**).

An additional minor product eluted from the column after the azobenzene. This proved to be 4-(phenylazo)-biphenyl (**2**), obtained in 0.4% yield. Initial identification by ir and melting point was supported by a mass spectrum which showed important peaks at *m/e* 258 (parent), 181 ($C_6H_5C_6H_4N_2^+$), 153 (base, C_6H_5-$C_6H_4^+$), 105 ($C_6H_5N_2^+$), and 77 ($C_6H_5^+$), as reported elsewhere for **2**.[13]

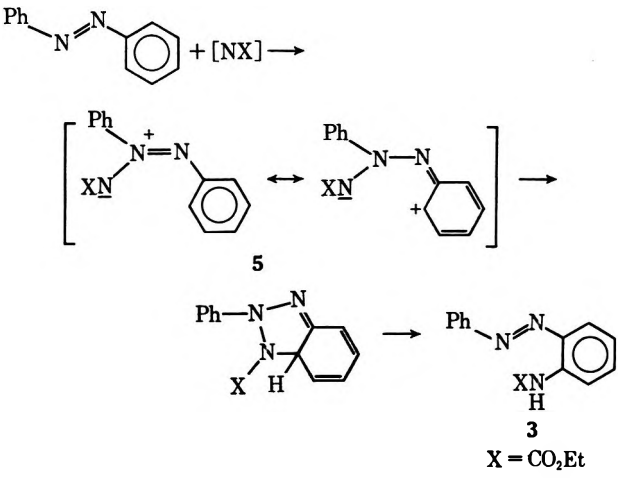
The only product directly arising from the nitrene was obtained as red-orange needles melting at 68.0–69.2°. The spectral data and microanalysis are consistent with structure **3**, ethyl 2-(phenylazo)carbanilate. The ir spectrum showed carbonyl absorption at 1736, a strong N–H stretch at 3311, and mono- and *o*-phenyl substitution at 773, 686, and 732 cm^{-1}, respectively. The pmr spectrum (CCl_4) showed an N–H absorption at τ 1.65, which disappeared after a solution of **3** was shaken with D_2O. The carbethoxy protons absorbed at τ 5.83 (q, $J \approx 7$ Hz, 2 H) and 8.73 (t, $J \approx 7$ Hz, 3 H). The aromatic region showed a one-proton doublet at τ 1.56 ($J \approx 8$ Hz), a three-proton multiplet at 2.3, a four-proton multiplet at 2.7, and another one-proton doublet at 3.03 ($J \approx 8$ Hz). The yield of **3** in a number of runs of the reaction fell in the 3–10% range.

Further elution of the column failed to yield any additional characterizable products. Comparisons of the eluate with an authentic sample (vpc, tlc) showed that it did not contain any ethyl *p*-(phenylazo)carbanilate (**4**). A quantity of **4** corresponding to 2% was readily detectable.

The formation of the carbanilate **3** was at first surprising, since singlet carbethoxynitrene does not ordinarily insert into aromatic C–H bonds.[14] Carbanilate products, when formed, have been found to arise primarily from acid-catalyzed rearrangement of initially formed azepines.[2,14] Since acidic alumina was used on work-up (**3** being unstable to basic alumina), we suspected that **3** might have been produced during chromatography. This possibility was excluded by demonstrating that (a) *N*-carbethoxyazepine could be recovered in 94% yield on chromatography on acidic alumina, no ethyl carbanilate being formed; and (b) **3** was present in the crude product prior to chromatography, as shown by vpc analysis. Again, **4** could not be detected. Formation of **3** by thermal rearrangement of an azepine under the reaction conditions cannot be absolutely excluded; however, the absence of any para isomer, **4**, makes this route (or direct insertion) seem improbable.

The exclusive formation of the ortho carbanilate **3** seems to us to suggest involvement of the azo group with the nitrene in the course of the reaction (Scheme I). We propose initial formation of the azimine **5**,

SCHEME I



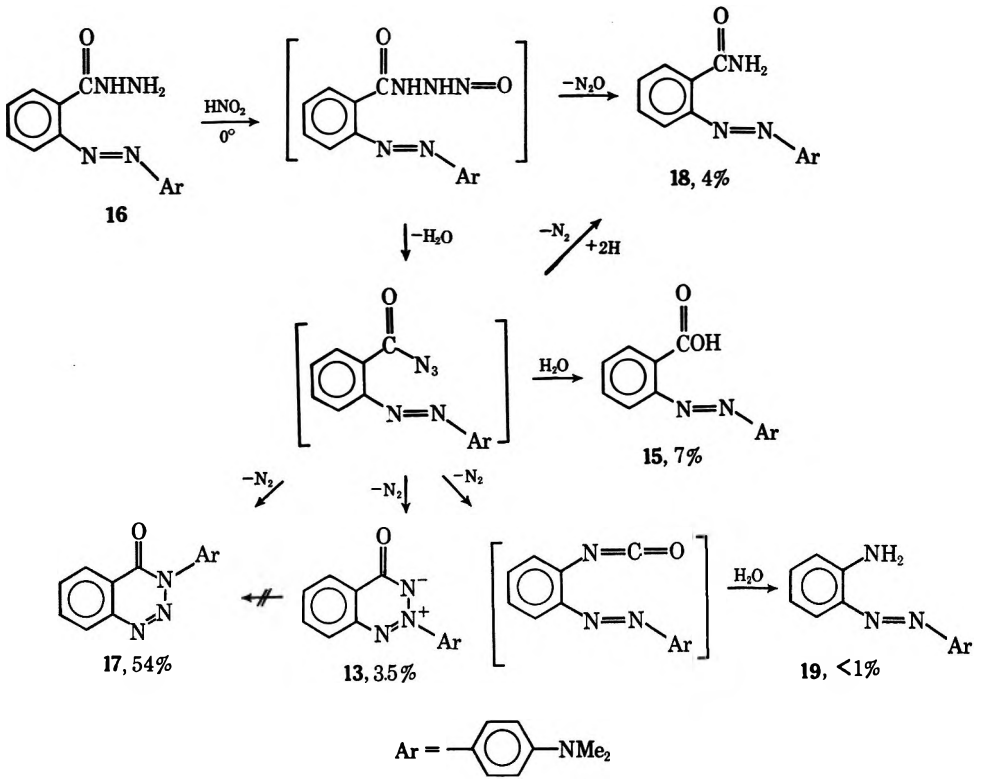
which rearranges to **3** under the reaction conditions. Such a rearrangement is analogous to the well-known Wallach rearrangement of azoxybenzenes to 2-hydroxyazobenzenes.[15] The phenylazobiphenyl products produced must be formed by means of phenyl radicals arising from some reaction intermediate. (Azobenzene itself does not decompose to phenyl radicals below 600°.)[16]

Decomposition of **5** by a route analogous to that proposed by Lwowski[11] and Hancock[10] would have yielded ethyl diphenylcarbamate, which could not be detected in the crude reaction product nor among the chromatographic fractions by tlc or vpc.

Attempted Reaction of *N*-Phthalimidylnitrene with Diethyl Azodicarboxylate.—A number of nucleophilic aminonitrenes have recently been shown to add to electrophilic alkenes, giving aziridines.[17] Since the simplest aminonitrenes, 1,1-dialkyldiazenes, apparently do not add in this fashion,[18] we chose to study the reaction of *N*-phthalimidylnitrene with the electrophilic diethyl azodicarboxylate (**6**). The nitrene was generated by *in situ* oxidation of *N*-aminophthalimide (**7**) with lead tetraacetate. The products obtained, phtha-

(10) J. Hancock, *Tetrahedron Lett.*, 1585 (1964).
(11) W. Lwowski, *ibid.*, 1591 (1964).
(12) W. Lwowski, *Angew. Chem., Int. Ed. Engl.*, **6**, 897 (1967).
(13) N. S. Vul'fson, V. A. Puchkov, and Y. S. Nekrasov, *J. Gen. Chem. USSR*, **38**, 1337 (1968); *cf. Zh. Obshch. Khim.*, **38**, 1385 (1968).
(14) Reference 4, p 206.
(15) G. G. Spence, E. C. Taylor, and O. Buchardt, *Chem. Rev.*, **70**, 231 (1970).
(16) M. T. Jaquiss and M. Szwarc, *Nature (London)*, **170**, 312 (1952).
(17) D. J. Anderson, T. L. Gilchrist, D. C. Horwell, and C. W. Rees, *J. Chem. Soc.*, 576 (1970).
(18) D. M. Lemal, ref 4, p 363.

SCHEME II



lic anhydride (**8**), 4%, phthalimide (**9**), at least 53%, and 1,4-bisphthaloyltetrazene (**10**), 14%, were the same as obtained in the absence of **6**. The recovery of **6** was only 54% due to substantial decomposition. Some diethyl hydrazinedicarboxylate (**11**) was also formed, apparently by reaction of **6** with the intermediate, 1,4-diphthaloyltetrazane.[19,20]

Subsequent to this work, Koch and Fahr[21] reported successful reactions of even more nucleophilic 1,1-dialkyldiazenes with **6** and with the cyclic azo compound, 4-phenyl-1,2,4-triazoline-3,5-dione. From their results, it is probable that any azimine formed in our reaction would have decomposed to *N*-carbethoxyphthalimide[22] and ethyl azidoformate. The apparent absence of these products in our mixtures confirms the failure of *N*-phthalimidylnitrene to react with **6** to form an azimine. Dreiding[23] has reported the reaction of the nitrene with azoalkanes and azoarenes to form azimines, in contrast to **6**.

We next attempted to observe an intramolecular reaction of a nitrene with an azo group, because of the apparent greater stability of cyclic azimines.[1] Preparation of the previously examined,[1] stable azimine, *anhydro*-2-(*p*-dimethylaminophenyl)-3*H*-benzo-1,2,3-triazinium-4-one hydroxide (**13**), was therefore undertaken.

Synthesis and Decomposition of 2-(4′-Dimethylaminophenylazo)benzazide (14).—Numerous attempts to prepare azide **14** directly from the acid **15** (methyl red) failed. **15** could not be converted to its acid chloride using thionyl chloride, with or without sodium carbonate present,[24] or phosphorus pentachloride. In all cases only deeply colored tars were produced. An attempt to prepare the azide *via* the mixed carbonic anhydride[25] gave only recovered acid (92%). Consequently, an alternative route *via* the hydrazide **16** was used (Scheme II). **16** was synthesized from methyl anthranilate by standard reactions (overall yield 50%).

Inasmuch as photolysis of an acyl azide generally gives the nitrene whereas thermolysis gives Curtius rearrangement *via* a concerted route,[26] we proposed to study the former. However, the products obtained directly from the nitrosation of 2-(4′-dimethylaminophenylazo)benzhydrazide (**16**) were found to be the same as when the reaction was followed by photolysis. Evidently the azide **14** is susceptible to direct intramolecular thermal reaction (or is unstable even to room light). Facile intramolecular displacement of N_2 from *o*-arylazophenyl azides is well documented.[6,7]

When **16** was treated with nitrous acid at 0°, the azide **14** could not be detected by ir. The reaction mixture proved to contain 3-(4′-dimethylaminophenyl)-3*H*-benzo-1,2,3-triazin-4-one (**17**) as the major product (54%) and not the expected cyclic azimine **13**, which was obtained in 3.5% yield. A number of other minor products were also obtained (Scheme II). The carboxylic acid **15** presumably arises from nucleophilic displacement of the azide ion from **14** by water, whereas 2-(4′-dimethylaminophenylazo)benzamide (**18**) can be produced either by hydrogen abstraction by the nitrene or directly from the nitrosated benzhydrazide.[27] The 2-(4′-dimethylaminophenylazo)aniline (**19**) is envisioned as the final product of a Curtius rearrangement[26]

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followed by hydrolysis of the isocyanate. One unidentified material, **20**, was also obtained (see Experimental Section).

The mechanism of formation of the benzotriazinone **17** is under investigation at the present time. The "obvious" route, rearrangement of azimine **13**, is excluded by the thermal stability of **13**; moreover, photolysis of **13** under the same conditions as used in the photolytic reaction failed to convert **13** to **17**; **13** was quantitatively recovered.

Conclusions

Although reaction of nitrenes with azo compounds is on paper the simplest route to azimines, it appears to lack synthetic generality. Indeed, in the three cases we have examined, only the intramolecular reaction gives any isolable azimine at all. The failure to isolate azimines in the other cases evidently arises from too low reactivity of nitrene toward azo compound and instability of azimine toward reaction conditions. The latter is a particularly serious problem, since it appears that acyclic azimines may frequently be too unstable to survive the high-energy conditions (high temperatures or photolysis) necessary to generate nitrenes.

Experimental Section

All melting points were measured on a Mel-Temp melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Infracord Model 137 NaCl spectrophotometer. Ultraviolet–visible spectra were obtained on a Beckman DK-2A and pmr spectra on a Varian Model A-60, using tetramethylsilane as internal standard unless otherwise noted. Solvents used for spectra were Spectro Grade except for DMSO, which was reagent grade, redistilled from calcium hydride at reduced pressure. Reaction and chromatographic solvents were redistilled before use. Solutions were dried using sodium sulfate except as noted. The vapor phase chromatographic measurements were performed on a Varian Aerograph Series 1200 chromatograph equipped with a flame ionization detector. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn., and Meade Microanalytical Laboratory, Amherst, Mass. Mass spectra were obtained from Morgan-Schaffer Corp., Montreal, on a Hitachi Perkin-Elmer RMU-6D.

Thermolysis of Ethyl Azidoformate in Azobenzene.—Azobenzene (25.68 g, 141 mmol, mp 66–67.5°) and ethyl azidoformate (6.66 g, 57.9 mmol) were heated slowly in a flask equipped with a magnetic stirrer, thermometer, condenser with Nujol bubbler gas exit tube, and a dropping funnel. No appreciable N_2 evolution occurred until the temperature reached 115°. The contents of the flask were allowed to come to room temperature after a total reaction time of 3 hr at 115°, by which time nitrogen evolution had ceased. Chromatography of the resulting mixture on acidic alumina afforded, first, unreacted azobenzene, 19.97 g (77.6% recovery), eluted with benzene, and identical with starting material by ir and mixture melting point. However, a vpc analysis (5 × 1/8 in. 5% SE-30 column, programmed from 130 to 230°) showed a higher boiling contaminant. Partial sublimation of the azobenzene fraction at 74–76° (0.20 Torr) gave a residue (18 mg) enriched in the unknown material (*ca.* 75%). Preparative vpc collection of this unknown (5 ft × 1/4 in. 3% SE-30 on Varaport column) yielded 9.6 mg of red oil **1**: ir (neat film) 3.3 (m) and 3.45 (m, CH), 13.16 (m, monosubstituted), 13.65 (s, ortho-substituted), 14.35 (s), and 14.55 (s, monosubstituted) (lit.[28] mp 37–39°); uv (95% EtOH) λ_{max} 231 nm (ϵ 26,300), 322 (18,500), 440 (810).

Contained elution of the column with benzene increasingly rich in CCl_4 afforded a fraction (8.27 mg) of crude **2**, mp 50–83°. Recrystallization from CCl_4–pentane gave orange platelets: yield 14.68 mg (0.4%, based on azobenzene consumed); mp 154–155° (lit.[29] mp 154–155°); ir (Nujol) 3.32 (w, CH), 3.47 (w, CH), 11.80 (s, para-substituted), 12.98 (s, monosubstituted), and 14.5 (s, monosubstituted); uv (95% EtOH) λ_{max} 340 nm (ϵ 27,000) and 234 (14,300); mass spectrum[13] (indirect inlet at 250°, 70 eV ionizing voltage) *m/e* (rel intensity) 259 (8.1, P + 1), 258 (39.2, P), 230 (3.0, P − N_2), 228 (3.6, P − N_2 − H_2), 182 (1.9, P − C_6H_4), 181 (9.4, P − C_6H_5), 154 (13.3, P − $C_6H_5N_2$), 153 [100, P − $C_6H_5N_2$ ($C_{12}H_9^+$)], 152 (51.1, $C_{12}H_8^+$), 151 (13.3), 128 (1.8), 127 (7.1, $C_{10}H_7^+$), 105 (9.8, $C_6H_5N_2^+$), 78 (5.0), 77 (62.7, $C_6H_5^+$), 51 (13.4, $C_4H_3^+$), 43 (4.4), 28 (13.4), 18 (9.4).

Continued elution with carbon tetrachloride gave a red-orange oil, **3** (0.861 g, 3.20 mmol, 10%), which decomposed slowly in solution at room temperature. An analytical sample obtained by crystallization from ethanol–water was obtained as deep orange needles, mp 68.0–69.2°. (The reported melting points of the meta and para isomers of **3** are 102–103°[30] and 153°,[31] respectively.)

Anal. Calcd for $C_{15}H_{13}N_3O_2$: C, 66.90; H, 5.62; N, 15.60. Found: C, 66.74; H, 5.70; N, 15.36.

The ir spectrum (neat melt) showed bands at 3.02 (m, NH), 3.27 (w), 3.31 (m, CH), 5.76 (s, C=O), 12.93 and 14.57 (s, monosubstituted), and 13.62 μ (m, ortho-substituted). The pmr spectrum is given in the text: uv (95% EtOH) 227 nm (ϵ 16,300), 245 (sh, 13,700), 321 (12,200), 365 (sh, 7000), 450 (sh, 1250).

Further elution of the column with increasing amounts of ether in CCl_4 and then methylene chloride afforded a deep red oily fraction (*ca.* 1 g). Vpc analysis of this material (5% SE-30, 180°) showed that it contained at least five components. Attempts to isolate pure components failed. The ir spectrum of the mixture showed a broad carbonyl absorption at 5.82 μ and broad peaks at 13.1 and 14.4 μ. A comparison of this mixture with anticipated possible products by vpc and tlc showed the absence of ethyl phenylazocarboxylate, ethyl carbamate, ethyl carbanilate, ethyl diphenylcarbamate, and ethyl *p*-(phenylazo)-carbanilate.

Final elution of the column with increasing amounts of ethanol yielded 10.85 g of a tarry brown residue from which no characterizable materials could be obtained.

Various runs employing excess azobenzene gave 3–10% yields of **3**. Yields of **1** and **2** fell always below 1%. The recovery of azobenzene in all runs fell in the range of 78–89%.

Attempted Reaction of *N*-Phthalimidylnitrene with Diethyl Azodicarboxylate.—To a suspension of *N*-aminophthalimide[32] (**7**, 0.504 g, 3.11 mmol) in a 20-ml dichloromethane solution of diethyl azodicarboxylate (**6**) [Aldrich, distilled at 85° (3.5 Torr), 0.543 g, 3.11 mmol] was added 1.38 g (3.11 mmol) of lead tetraacetate in small portions over a 10-min period. The mixture was allowed to stir at room temperature for 1 hr, then evaporated to dryness to remove acetic acid. Addition of 50 ml of dichloromethane allowed the collection of precipitated lead diacetate (1.03 g, 100%). A concentrated benzene solution of the filtrate was then placed on a silica gel column. Elution with benzene, followed by mixtures increasingly rich in dichloromethane, afforded first a yellow band of unreacted **6**, 0.3119 g, from which 0.018 g (0.122 mmol) of phthalic anhydride (**8**) crystallized out upon standing (3.9% yield), mp 130–131° (lit.[33] mp 130.8°), ir spectrum identical with that of an authentic sample. The total recovery of unreacted **6** was 54%. Continued elution with dichloromethane and 1% ethanol in dichloromethane gave an oily solid (0.444 g). Fractional crystallization with CH_2Cl_2–PhH–ether afforded 0.243 g (53%) of phthalimide **9**, mp 230–238°. Recrystallization from ether gave mp 236–238° (lit.[34] mp 238.5–240°), ir spectrum identical with that of an authentic sample. The viscous filtrate (0.2 g) obtained from the recrystallization of **9** was shown by vpc analysis (5% SE-30, 160°) to contain additional phthalimide and a minimum of eight other components, two of which were identified as diethyl hydrazinedicarboxylate (**11**) and triethyl hydrazinetricarboxylate (**12**) by vpc comparison with authentic samples. Further elution with 5% ethanol in dichloromethane gave after drying a

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semisolid (119 mg). Washing this material with anhydrous ether left a beige solid which gave long platelets from a slowly evaporating dichloromethane solution. Obtained was 73.6 mg (0.214 mmol, 14%) of 1,4-bisphthaloyltetrazene (10): mp 267–269° dec (lit.[19] mp 263–268° dec); ir (KBr) 3.32 (w, CH), 5.59 (m), 5.74 (s, C=O), 7.90 (s, br), 14.0 (s); nmr (CH_2Cl_2) τ 2.06 (symmetrical m). Evaporation of the ether washings from the crude 10 left 44 mg of residue which proved to contain more phthalimide and unknown material in about 1:1 ratio.

Additional experimental runs gave comparable yields of recovered azo compound 6 (50–56%). Yields of phthalimide 9 and tetrazene 10 fell in the ranges 40–55% and 9–15%, respectively. In all cases, small quantities of 11 and 12 were detected in the 150–225 mg of viscous material which eluted along with 9. 12, but not 11, was produced by decomposition of 6 on the column; pure 6 could be recovered in 74% quantity from a silica gel column. 6 and 7 did not react spontaneously in 12 days at room temperature or in 3 hr at 80°, 7 being 92% recovered.

Methyl 2-(4′-Dimethylaminophenylazo)benzoate.[35]—In a 400-ml beaker were placed 7.0 g (46 mmol) of methyl anthranilate, 15 ml of H_2O, and 6 ml of concentrated HCl, followed by a slurry of 25 g of ice and 7 ml of concentrated HCl. When the temperature reached −5°, a solution of 3.6 g (50 mmol) of $NaNO_2$ in 10 ml of water was added dropwise, while the temperature was held at <5° (*ca.* 1 hr). To the clear yellow diazonium solution was then added 8.5 ml (8.1 g, 67 mmol) of *N,N*-dimethylaniline. The solution was stirred at 0–5° for 30 min, then treated with a solution of 6.80 g (83 mmol) of sodium acetate in 10 ml of water (a small amount of ethyl acetate was added to prevent foaming). The mixture was kept at 4° for 20 hr, then warmed to room temperature. The mixture was neutralized with sodium carbonate and left at room temperature for 8 hr. It was then extracted with four 50-ml portions of chloroform. The organic extracts were dried over $MgSO_4$ and evaporated, leaving a deep red oil, yield 17.6 g. A concentrated benzene solution of this material was placed on a basic alumina column, elution of which with benzene gave 1.1 g of unreacted *N,N*-dimethylaniline. Elution with ether–benzene mixtures afforded 6.76 g (52%) of red crystalline methyl 2-(4′-dimethylaminophenylazo)benzoate. Recrystallization from benzene–hexane gave mp 92–94°. Further recrystallization from hexane–CCl_4–$CHCl_3$ gave mp 94.5–96°; ir (KBr) 3.46 and 3.6 (w, CH), 5.8 (s, C=O), 12.08 (m, para-substituted), 13.0 μ (m, ortho-substituted); pmr ($CDCl_3$) τ 2.47 (m, 4 H), 2.17 (2 H, d, $J \approx 9$ Hz), 3.37 (2 H, d, $J \approx 9$ Hz), 6.17 (s, 3 H), 7.12 (s, 6 H).

Anal. Calcd for $C_{16}H_{17}N_3O_2$: C, 67.83; H, 6.05; N, 14.82. Found: C, 67.75; H, 5.93; N, 14.91.

2-(4′-Dimethylaminophenylazo)benzhydrazide (16).—Methyl 2-(4′-dimethylaminophenylazo)benzoate (3.25 g, 11.5 mmol) and 2.00 ml (62 mmol) of hydrazine (95+%) were dissolved in 25 ml of methanol, and the solution was refluxed for 90 min while being magnetically stirred. By this time a voluminous, bright red precipitate had separated. The mixture was cooled to room temperature, then filtered to give 3.15 g (97%) of fluffy red needles, mp 170–171°. An analytical sample obtained by recrystallization from chloroform–carbon tetrachloride had mp 173–174°; ir (KBr) 3.0 (w, NH), 3.21 (w, NH), 3.52 (w, CH), 6.08 (m, C=O), 12.38 (m, (para-substituted), and 13.21 μ (w, ortho-substituted); pmr (DMSO-d_6) τ 0.48 (br s, 1 H, NH), 2.48 (m, 6 H), 3.21 (2 H, d, $J \approx 9$ Hz), *ca.* 5.4 (very broad), 6.92 (s, 6 H).

Anal. Calcd for $C_{15}H_{17}N_5O$: C, 63.58; H, 6.05; N, 24.72. Found: C, 63.87; H, 6.12; N, 24.93.

Nitrosation of 16. Method A.—2-(4′-Dimethylaminophenylazo)benzhydrazide (16, 1.75 g, 6.18 mmol) was dissolved in 75 ml of water by the addition of about 1.5 ml of 12 *M* HCl. Dichloromethane (60 ml) was added. While the heterogeneous mixture was stirred and kept below 5°, a solution of 0.621 g (9.0 mmol) of $NaNO_2$ in 6 ml of cold water was added. A red precipitate formed and was extracted into the CH_2Cl_2 layer. The organic layer was separated and the aqueous layer was washed with three 50-ml portions of CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and filtered to yield a deep red solution. The solution was then flushed with nitrogen and irradiated for 3 hr through the Pyrex flask using a GE UA-3 360-W medium pressure mercury lamp. The solvent was allowed to reflux. During this time only a slight amount of gas was evolved through a bubbler. The solution was then evaporated to dryness, and a suspension of the red-brown material in benzene was chromatographed on a silica gel column. Elution with benzene and 2% ether in benzene afforded 7.8 mg (<1%) of 2-(4′-dimethylaminophenylazo)aniline (19) as orange platelets: mp 104–106° (lit.[36] mp 105–106°); ir (KBr) 3.03 (w, br, NH), 3.5 (w, CH), 3.59 (sh, w), 12.18 (m, para-substituted), 13.29 μ (w, ortho-substituted).

Further elution with 2% ether in benzene afforded a minor yellow product, 8.9 mg, fluffy needles, mp 240–241° dec (EtOH), which was not identified: ir (KBr) 3.03 (m, br), 3.5 (w, br), 4.28 (w), 6.00 (m), 6.30 (m), 6.62 (s), 6.94 (m), 13.11 μ (m). Elution with 5–40% ether in benzene gave 0.7493 g (46%) of a deep orange solid, mp 242–244° dec. Recrystallization from dichloromethane gave 0.330 g (1.24 mmol) of 3-(4′-dimethylaminophenyl)-3*H*-benzo-1,2,3-triazin-4-one (17): mp 246–247° dec [(lit.[37] mp 249–250° (EtOH)]; ir (KBr) 3.34 (w, CH), 3.54 (w), 5.99 (s, C=O), 12.29 (m, para-substituted), 13.71 (m, br), and 14.6 (m, br); visible ($CHCl_3$) λ_{max} 362 nm (ϵ 5260); pmr ($CDCl_3$) τ 1.45–2.28 (m, 4 H), 2.49 (d, $J \approx 9$ Hz, 2 H), 3.17 (d, $J \approx 9$ Hz, 2 H), and 6.96 (s, 6 H). The red-colored filtrates from the recrystallizations contained (by tlc analysis) additional 17. Crystallization of the residue from these filtrates from dioxane gave 9 mg of deep red needles, mp 240–242°. Comparison of ir spectra and tlc behavior (neutral alumina, CH_2Cl_2) demonstrated that this material was impure 20 (see below).

Elution of the column with ether and dichloromethane–ether mixtures brought down a deep red-brown band which weighed 0.443 g; the crude melting point was 176–194°. Tlc (silica gel) showed four major components. Crystallization of this material from CH_2Cl_2–CCl_4 afforded 0.1384 g of crude 2-(4′-dimethylaminophenylazo)benzamide (18), mp 186–189° (8%). Recrystallization from CH_2Cl_2–methylcyclohexane gave 0.120 g of 18: mp 196–197°; ir (KBr) 3.09 (m, NH), 3.22 (w), and 3.50 (w, CH), 6.05 (m, C=O), 6.28 (s), 12.09 (m, para-substituted), 13.08 μ (w, ortho-substituted); visible (95% EtOH) 443 nm (ϵ 44,700). Upon addition of concentrated HCl, λ_{max} shifted to 527 nm and the absorbance more than doubled.[38]

Anal. Calcd for $C_{15}H_{16}N_4O$: C, 67.15; H, 6.01; N, 20.87. Found: C, 66.93; H, 6.30; N, 20.64.

The filtrate from the first recrystallization of 18 was concentrated; on addition of benzene, 70 mg of a material melting at 161–163° was obtained. Recrystallization from a slowly evaporating benzene–methylcyclohexane solution gave 20 mg of deep violet needles, mp 174–175°. This material was identical (ir, tlc comparison, and mixture melting point) with authentic methyl red, mp 175–176° (Pfaltz & Bauer, recrystallized from acetic acid, then benzene–methylcyclohexane), crude yield 4%.

Continued elution of the column with methanol yielded a deep violet material. Recrystallization from slowly evaporating dichloromethane–benzene afforded 9 mg of blue-black material, mp 198–200°. Recrystallization from slowly evaporating 95% methanol–5% CCl_4 solution gave deep blue needles of *anhydro*-2-(*p*-dimethylaminophenyl)-3*H*-benzo-1,2,3-triazinium-4-one hydroxide (13), mp 199–200°, yield 8.6 mg (<1%). The spectral data were identical with those previously described.[1]

The filtrate from 13 was evaporated; successive recrystallization (CH_2Cl_2–CCl_4) gave 45 mg of 20, mp 238–241°. Recrystallization from a slowly evaporating 5% CH_2Cl_2–95% ethanol mixture gave orange needles: yield 25 mg; mp 250–251° dec; ir (KBr) 3.25 (w) 3.52 (w) (CH), 6.29 (s), 12.14 (m, para-substituted), 13.1 μ (w, ortho-substituted); uv–visible (EtOH–$CHCl_3$) 471, 315 (sh), 280 nm; after addition of concentrated HCl, λ_{max} shifted to 493 nm, absorption doubled in intensity; uv ($CHCl_3$) 483 nm.

Anal. Calcd for $C_{16}H_{16}N_4O_2$: C, 64.80; H, 5.44; N, 18.90. Found: C, 64.85; H, 5.41; N, 19.02.

The mass spectrum (70 eV ionizing voltage, 220° direct inlet) exhibited an apparent parent peak at *m/e* 290 (14.7%). The peak at *m/e* 291 had a relative intensity of 3.1%. Although 20 remains unidentified, the intact skeletal structure of 16 is substantiated by fragments appearing at *m/e* (rel intensity) 224 (16.7, $ArN{=}NC_6H_4^+$), 148 (28, ArN_2^+), 134 (19.7, $Me_2NC_6H_4N^+$), and 120 (100, $Ar^+ = Me_2NC_6H_4^+$). Other important fragments appeared at *m/e* (rel intensity) 268 (7.3), 254 (15.2), 253

(35) Synthesis adapted from H. T. Clarke and W. R. Kirner, "Organic Syntheses," Collect. Vol. I, Wiley, New York, N. Y., 1941, p 374.

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(46), 252 (43), 239 (10.7), 238 (13.4), 210 (10.4), 181 (16.3), 147 (46), 146 (36.5), 145 (12.7, P^{2+}?), 136 (82.3), 135 (79), 132 (20), 122 (53), 121 (56), 119 (38), 108 (18.7), 107 (37), 106 (14.5), 105 (23), 104 (17.6), 94 (16.3), 93 (31), 92 (41), 78 (16.3), 77 (41), 76 (19.5), 65 (34), 42 (26.8), 39 (21.4), 28 (31), and 18 (18.7).

The pmr spectrum (CF_3CO_2H) follows: τ 2.05–3.55 (m, 8H), 6.92 (s, 6H); two doublets can be discerned within the multiplet, at τ 2.55 and 3.30 ($J \approx 9$ Hz).

Method B (in the Dark).—The previous reaction was performed with the flask wrapped in aluminum foil. An ir spectrum of the crude product mixture showed no azide absorption in the 4.0–5.0 μ region. The same work-up procedure was performed, giving **17** (54.5%), unknown **20** (96 mg), and acid **15** (7.5%), amide **18** (4%), and **13** (3.5%). The higher yield of **17** is obtainable if **17** is not left in solution for prolonged periods.[39] The aniline **19** was not detected in this run.

Photolysis of 13.—Azimine **13** (0.5866 g, 2.2 mmol) in 250 ml of N_2-saturated dichloromethane was photolyzed for 3 hr. During this time the solution was allowed to reflux. No appreciable gas evolution was observed through the N_2 bubbler. The solution showed no visible color change. Evaporation of the solvent gave back **13** (0.585 g, >99%).

Synthesis of 17.[37] **A. *N'*-Anthranilyl-*N*,*N*-dimethyl-*p*-phenylenediamine.**—Isatoic anhydride (Aldrich, 1.35 g, 8.30 mmol) and *N*,*N*-dimethyl-*p*-phenylenediamine (Eastman, 1.15 g, 8.50 mmol) were heated together on a steam bath until gas evolution ceased (15 min). This left a black solid mass (2.10 g, 99%), mp 134–138°. Two recrystallizations from ethanol gave a gray solid (0.94 g, 45%): mp 147–148° (lit.[37] mp 146–148°); ir (KBr disc) 2.85 and 2.96 μ (m, NH_2), 3.30 (w, NH), 3.40 and 3.49 (w, CH), 6.06 (vs, C=O), 12.22 and 12.39 (s, para), and 13.35 (s, ortho); pmr ($CDCl_3$) τ 2.3 (br, s, 1 H), 2.7 (m, 4 H), 3.3 (m, 4 H), 4.7 (broad s, 2 H), 7.10 (1 s, 6 H).

B.—The amide (0.724 g, 2.84 mmol) was dissolved in 30 ml of 1 *M* H_2SO_4, cooled to 0°, and treated with 0.20 g (2.84 mmol) of $NaNO_2$. After 10 min, the solution was neutralized with $NaHCO_3$ and filtered. The precipitate was washed with water and air dried, leaving 0.762 g (100%) of yellow powder, mp 235–238° dec. Recrystallization from acetone gave **17**, mp *ca.* 245° dec (lit.[37] mp 249–250°). The mixture melting point with **17** from nitrosation of **16** was 244–245° dec. The ir spectra were identical.

(39) Benzotriazinones are unstable to light: E. M. Burgess and G. Milne, *Tetrahedron Lett.*, 93 (1966).

Registry No.—**3**, 33986-91-3; **13**, 33986-92-4; **16**, 33986-93-5; **18**, 33986-94-6; methyl 2-(4'-dimethylaminophenylazo)benzoate, 20412-23-1; methyl red, 493-52-7.

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Reactions of the Nitrosonium Ion. IV. Nitrosative Cleavage of the Carbon–Nitrogen Double Bond. The Reaction of *N*-Arylimines and Ketimines with Nitrosonium Salts[1a]

MICHAEL P. DOYLE,* WENDELL WIERENGA,[1b] AND MARY A. ZALETA

Department of Chemistry, Hope College, Holland, Michigan 49423

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N-Benzylideneanilines react with nitrosonium salts at or below room temperature to produce benzaldehydes and benzenediazonium salts. These reactions proceed with initial N-nitrosation and are proposed to involve the intermediacy of N-substituted oxadiazetine compounds. Competing reactions are observed only with *p*-methoxy substituents. When a proton is produced in these reactions, as when benzophenonimine undergoes nitrosative cleavage, protonation of the imine occurs to the exclusion of further reaction with the nitrosonium ion.

Reactions of nitrosonium compounds with compounds containing the carbon–carbon double bond have been well characterized.[2] Similar reactions with other functional groups, however, have received less attention. Although imines represent the simplest class of organic compounds for use in a study of the reactions of nitrosonium compounds with the carbon–nitrogen double bond, few examples of such reactions have been reported.[3–5] Turcan in 1935 reported that nitrosyl chloride, dinitrogen tetroxide, and nitrosyl sulfuric acid react with *N*-benzylideneaniline under mild conditions to produce benzaldehyde and the corresponding benzenediazonium salt (eq 1).[3] Since these reactions

$$C_6H_5CH{=}NC_6H_5 + XNO \longrightarrow C_6H_5CHO + C_6H_5N_2{}^+X^- \quad (1)$$
$$X = Cl, NO_3, HSO_4$$

were run under anhydrous conditions in benzene or ether, the production of benzaldehyde and the benzenediazonium salt could not have involved prior hydrolysis of the imine followed by diazotization of aniline. Similar results were obtained when *N*-heptylideneaniline, *N*-benzylidene-*p*-bromoaniline, and *N*-benzylidene-α-naphthylamine were treated with nitrosyl chloride under mild conditions, although no yields were given.[3] The reaction of *N*-benzylideneaniline with dinitrogen tetroxide was recently shown, however, to proceed in high yield to benzaldehyde and benzenediazonium nitrate.[4]

Unlike the carbon–carbon double bond, which undergoes initial electrophilic addition with nitrosyl halides and related compounds,[2] aldimines react with nitrosonium compounds with cleavage to form carbonyl and diazonium compounds.[6] Since aldimines are formed from aldehydes and amines and the parent aldehyde re-formed, the net effect of the reaction of aldimines with nitrosonium compounds is an efficient diazotization of the amine. The mechanism of carbon–nitrogen double bond cleavage may be represented as involving the intermediacy of an N-substituted oxa-

(1) (a) For part III, see M. P. Doyle and W. Wierenga, *J. Amer. Chem. Soc.*, in press; (b) National Science Foundation Undergraduate Research Participant, summer 1969.

(2) (a) L. J. Beckham, W. A. Fessler, and M. A. Kise, *Chem. Rev.*, **48**, 319 (1951); (b) J. Meinwald, Y. D. Meinwald, and T. N. Baker, *J. Amer. Chem. Soc.*, **86**, 4074 (1964); (c) H. C. Hamann and D. Swern, *ibid.*, **90**, 6181 (1968); (d) E. F. Schoenbrunn and J. H. Gardner, *ibid.*, **82**, 4905 (1960).

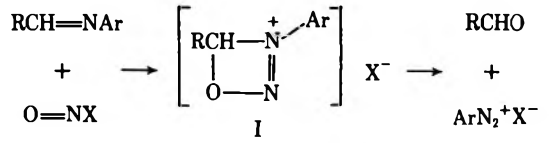
(3) J. Turcan, *Bull. Soc. Chim. Fr.*, **2**, 627 (1935).

(4) R. M. Scribner, *J. Org. Chem.*, **29**, 3429 (1964).

(5) (a) C. J. Thoman and I. M. Hunsberger, *ibid.*, **33**, 2852 (1968); (b) J. Jappy and P. N. Preston, *Tetrahedron Lett.*, 1157 (1970).

(6) Only one example of an apparent addition reaction has been reported: E. P. Goldberg and H. R. Nace *J. Amer. Chem. Soc.*, **75**, 6260 (1953).

SCHEME I



diazetine compound (I), as shown in Scheme I, although no such intermediate has been directly observed.

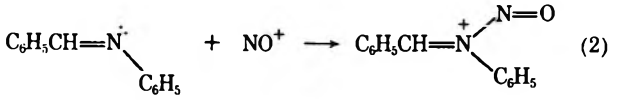
The cleavage reaction is not unique to *N*-aryl aldimines, however. When ketimines are treated with nitrosyl chloride, *N*-nitrosoketimines are formed and may be isolated.[5] On standing at room temperature these compounds decompose to nitrogen and the parent ketone in a manner consistent with formation of an intermediate similar to I.[5a]

Since only a limited number of imines have been examined in their reactions with nitrosonium compounds and no attempt has been made to study the scope of the reaction, we undertook our present investigation of imines. Nitrosonium salts, including $NO^+BF_4^-$ and $NO^+SbF_6^-$, were chosen for this study since the nitrosonium ion represents the apparent reactive species in the cleavage of the carbon–nitrogen double bond. In addition, the counterion is sufficiently nonnucleophilic so as to minimize side reactions.

Results

Treatment of *N*-benzylideneaniline with 1 equiv of $NO^+BF_4^-$ or $NO^+SbF_6^-$ in anhydrous acetonitrile or nitromethane at room temperature or below produced benzaldehyde and benzenediazonium tetrafluoroborate or hexafluoroantimonate nearly quantitatively. Benzaldehyde was identified in the reaction mixture by pmr, ir, and glpc analysis. The benzenediazonium ion was confirmed by both pmr and ir spectroscopy and by *in situ* conversion to fluorobenzene (Schiemann reaction)[7] and chlorobenzene (Sandmeyer reaction).[8] Yields of products were determined of aliquots removed from the reaction mixture by integration of specific pmr absorptions.[9] Isolated yields of benzaldehyde averaged 95%.

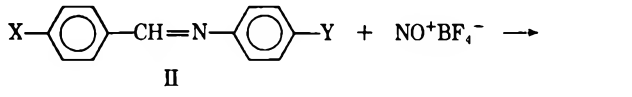
N-Benzylideneaniline reacts rapidly with $NO^+BF_4^-$ even at temperatures below 25°. At 25° the production of benzaldehyde and benzenediazonium tetrafluoroborate is complete within 10 min. The pmr spectrum of *N*-benzylideneaniline in acetonitrile before addition of the nitrosonium salt shows the C hydrogen as a singlet at δ 8.65 relative to internal TMS. Upon addition of $NO^+BF_4^-$ the C hydrogen is shifted to δ 9.18, and a new proton resonance due to benzaldehyde appears at δ 10.0. The benzaldehyde signal increases in intensity with time at the expense of the δ 9.18 absorption. Protonated *N*-benzylideneaniline, produced by adding *N*-benzylideneaniline to 1 equiv of FSO_3H–SbF_5 in acetonitrile, shows a doublet for the C hydrogen, centered at δ 9.30 (J = 17.5 Hz).[10] These data



(2)

indicate that nitrosation of the imine (eq 2) occurs as a discrete step prior to cleavage of the carbon–nitrogen double bond, a conclusion reasonable in terms of the strong Lewis acidity of the nitrosonium ion and the observation by Olah and coworkers that *N*-nitrosopyridinium salts are readily prepared from nitrosonium salts and pyridines.[11]

Treatment of a series of substituted *N*-benzylideneanilines (IIa–j) at room temperature with 1 equiv of $NO^+BF_4^-$ in anhydrous acetonitrile produced the corresponding aldehyde and diazonium compound in yields usually greater than 90% (eq 3). The amounts



(3)

a, X = H; Y = H
b, X = H; Y = NO_2
c, X = H; Y = Cl
d, X = H; Y = CH_3
e, X = H; Y = OCH_3
f, X = NO_2; Y = H
g, X = Cl; Y = H
h, X = CH_3; Y = H
i, X = OCH_3; Y = H
j, X = OCH_3; Y = OCH_3

of aldehyde and diazonium compound were identical within experimental error. Only with the methoxy-substituted compounds (IIe,i,j) were product yields less than 90%: with IIe and IIi the yield of aldehyde and diazonium ion was 83%, and with IIj only a 75% yield of products was obtained. With methoxy-substituted imines processes such as nitrosation of the aromatic ring[12] and hydrogen abstraction[13] may compete with nitrosative cleavage. When, for example, *p*-anisaldehyde was treated with 1 equiv of $NO^+BF_4^-$ under the same reaction conditions used for nitrosative cleavage, only 58% of the aldehyde remained intact after 40 min. Benzaldehyde was unaffected by $NO^+BF_4^-$ in acetonitrile at room temperature over the same period of time.

At 25° or below the diazonium salts produced from II in acetonitrile are stable for prolonged periods of time. However, heating above 35° effects the loss of nitrogen accompanying decomposition of the diazonium compound. For example, within 20 min at 40° the amount of benzenediazonium tetrafluoroborate, produced from IIa,f–i, was reduced by 20%. In addition to fluorobenzene, mentioned earlier, decomposition of benzenediazonium tetrafluoroborate yielded 23% of acetanilide, isolated after work-up and identified from its pmr and ir spectrum and by glpc analysis.

When water is present in trace amounts in the reaction mixture, the yield of products from reaction 3 is

(7) A. Roe in "Organic Reactions," Vol. V. R. Adams, Ed., Wiley, New York, N. Y., 1949, Chapter 4.

(8) S. C. Dickerman, D. J. DeSouza, and N. Jacobson, *J. Org. Chem.*, **34**, 710 (1969), and references cited therein.

(9) Reactants and products are soluble in the solvents used. The aldehydic proton resonance signal of benzaldehyde (δ 10.0) and the signals for the ortho hydrogens of the benzenediazonium ion (δ 8.2–8.5) were used with reference to a standard to calculate absolute yields.

(10) This observation is in accord with the spectra of protonated *N*-benzylideneaniline reported in different solvents: G. A. Olah and P. Kreienbuhl, *J. Amer. Chem. Soc.*, **89**, 4756 (1967).

(11) G. A. Olah, J. A. Olah, and N. A. Overchuk, *J. Org. Chem.*, **30**, 3373 (1965).

(12) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p 531.

(13) Hydrogen abstraction reactions by the nitrosonium ion have been observed with aliphatic ethers[14] and are inferred in the nitric acid oxidation of 2-methoxyethanol.[15] Evidence for hydride abstraction from cumene by nitrosonium salts has also been given.[16]

(14) Unpublished results of M. P. Doyle.

(15) E. J. Stojny, R. I. Iwamasa, and L. K. Frevel, *J. Amer. Chem. Soc.*, **93**, 1171 (1971).

(16) G. A. Olah and N. Friedman, *ibid.*, **88**, 5330 (1966).

decreased due to formation of the corresponding protonated imine, observed by pmr spectroscopy by the characteristic doublet[9] at δ 8.9–9.4 (J = 17–18 Hz).[17] The protonated imine does not undergo nitrosative cleavage. In a separate experiment 1 equiv of $NO^+BF_4^-$ was added to protonated benzylideneaniline, formed when IIa was treated with 1 equiv of FSO_3H–SbF_5 in anhydrous acetonitrile. Production of either benzaldehyde or benzenediazonium tetrafluoroborate was not observed over a 90-min period. These results show that the nitrosonium ion is a weaker Lewis acid than a proton and that, for reactions of the nitrosonium ion with basic compounds in which a proton is produced in the course of the reaction, protonation of the substrate will serve to quench further reaction with the nitrosonium ion.

Protonic quenching of nitrosative cleavage of imines was readily observed in the reaction of benzophenonimine with $NO^+BF_4^-$. Dropwise addition of benzophenonimine to 1 equiv of $NO^+BF_4^-$ in anhydrous acetonitrile at 20° produced a deep blue-purple colored solution. The dark color, characteristic of N-nitrosobenzophenonimine,[5a] changed rapidly to give a yellow reaction solution with evolution of approximately 0.5 equiv of a gaseous product, assumed to be nitrogen. The pmr spectrum was characteristic of benzophenone with the exception that a sharp singlet was observed at δ 7.75 in an integral ratio of approximately 1:1 with the benzophenone multiplet at δ 7.3–8.0.[18] Glpc analysis confirmed the identity of benzophenone and showed the presence of another product having the same retention time as benzophenonimine, formed in an amount equal to benzophenone. Neither addition of an additional 1 equiv of $NO^+BF_4^-$, heating at 80° for 30 min, nor standing at room temperature for over 20 hr had any effect on the glpc product ratio or the pmr spectrum. The ir spectrum of the products isolated after evaporation of the solvent exhibited strong, broad absorptions at 3400–3100 cm^{-1} (N–H stretching) and 1100–1020 cm^{-1} (BF_4^-) and a sharp absorption at 1605 cm^{-1} (C=N stretching), characteristic of benzophenoniminium tetrafluoroborate, $(C_6H_5)_2C{=}NH_2^+BF_4^-$.[19] The addition of methanol did not change the product composition. However, benzophenone was the only product observed when water was added to the reaction solution. These results are consistent with the stoichiometry and products given in eq 4.

$$2(C_6H_5)_2C{=}NH + NO^+BF_4^- \longrightarrow (C_6H_5)_2C{=}O + N_2 + (C_6H_5)_2C{=}NH_2^+BF_4^- \quad (4)$$

N-Arylketimines also undergo nitrosative cleavage with nitrosonium salts. N-Benzhydrylideneaniline (III) gave both benzophenone and benzenediazonium tetrafluoroborate when treated with 1 equiv of $NO^+BF_4^-$, and benzil dianil (IV) produced benzil quantitatively when treated with 2 equiv of $NO^+BF_4^-$ at room temperature.

III IV

(17) Chemical shift varies with the individual compound.

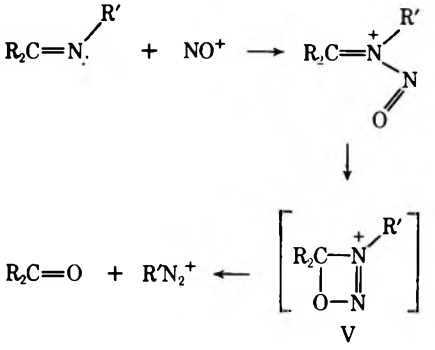
(18) The NH absorption of benzophenonimine, observed at δ 9.61, was not found in the pmr spectrum of the reaction solution.

(19) Characteristic absorptions for benzophenone were also observed.

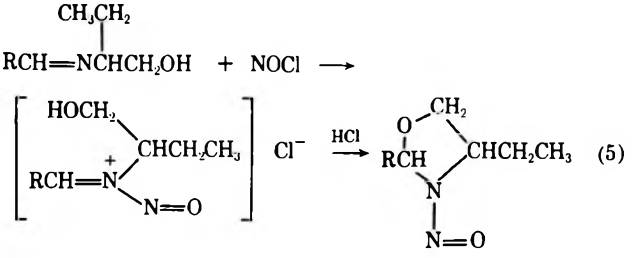
Discussion

The reaction of imines with nitrosonium compounds may be represented by the sequence of steps given in Scheme II. Our observation of N-nitrosated N-benzylideneaniline and the previously reported isolation of N-nitrosoketimines[5] suggests that nitrosation of the imine occurs as a rapid step prior to rate-limiting product formation. In addition, the conversion of substituted 2-imino-1-butanols to oxazolidines with nitrosyl chloride[6] indicates the intermediacy of an N-nitrosated imine that is prevented from undergoing cleavage by intramolecular trapping (eq 5). We speculate that the production of carbonyl and diazonium compounds is preceded by rate-limiting formation of an N-substituted oxadiazetine compound (V), although we have no evidence to support the independent existence of such an unusual compound.

SCHEME II



V



(5)

Although we have given evidence here for the reactions of only a select class of organic compounds, a mechanism similar to that given in Scheme II may be used to explain a larger number of previously observed reactions of compounds containing the carbon–nitrogen double bond with nitrosonium salts. The production of alkyl cations and acylium ions in the reactions of nitrosonium salts with isocyanates, thioisocyanates, and sulfinylamines (eq 6–8), first observed by Olah and coworkers,[20] are prime examples of nitrosative cleavage of the carbon–nitrogen and sulfur–nitrogen double bond. Bott had previously found that aryl sulfinylamines produce the corresponding aryldiazonium compounds and sulfur dioxide when treated with nitrosonium perchlorate and hexachloroantimonate (eq 9).[21] We have also found evidence which suggests

$$RN{=}C{=}O + NO^+ \longrightarrow R^+ + N_2 + CO_2 \quad (6)$$

$$RN{=}C{=}S + NO^+ \longrightarrow R^+ + N_2 + COS \quad (7)$$

$$RN{=}S{=}O + NO^+ \longrightarrow R^+ + N_2 + SO_2 \quad (8)$$

(20) G. A. Olah, N. Friedman, J. M. Bollinger, and J. Lukas, *J. Amer. Chem. Soc.*, **88**, 5328 (1966).

(21) K. Bott, *Angew. Chem.*, **77**, 132 (1965).

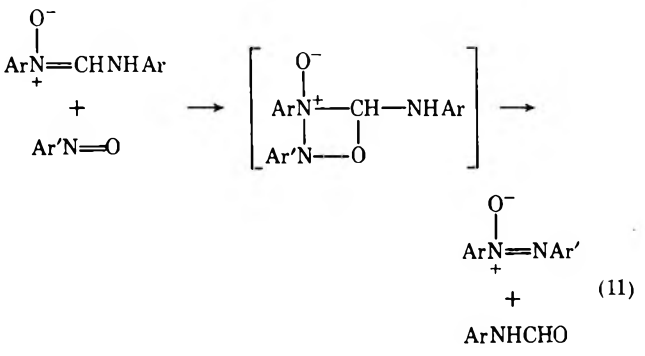
$$ArN{=}S{=}O + NO^+ \longrightarrow ArN_2^+ + SO_2 \quad (9)$$

that carbodiimides lead to isocyanates and alkyl cations according to eq 10.[14] Nitrosyl chloride sim-

$$RN{=}C{=}NR + NO^+ \longrightarrow RN{=}C{=}O + R^+ + N_2 \quad (10)$$

ilarly effects nitrosative cleavage of phosphineimines[22] and sulfinylamines.[23] These reactions point to the generality of nitrosative cleavage of the carbon–nitrogen double bond and suggest that compounds containing the S=N and P=N bonds react in a similar manner.

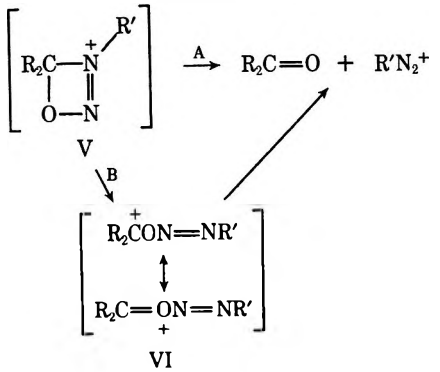
The formation of carbonyl and diazonium compounds from N-nitrosated imine appears to involve an oxadiazetine intermediate.[4,5a] A similar compound may be used to explain the production of carbonyl compounds and nitrous oxide from oximes and nitrous acid,[24] and Taylor has recently proposed that a discrete 1,2,3-oxadiazetidine intermediate may be involved in the reaction of nitrosobenzenes with α-arylamino-*N*-arylnitrones (eq 11).[25] Ring opening of V may be written



(11)

as producing the observed products by either of two extremes (Scheme III): directly in a concerted process

SCHEME III



(A), the pathway usually written,[4,5] or by initial heterolytic cleavage of the C–N bond (B) to give VI. Since thermal cycloreversion (path A) would require a relatively high activation energy,[26] a mechanism involving VI appears to be more reasonable.

The only serious limitation to nitrosative cleavage by nitrosonium salts is the protonic quenching reaction. This is especially evident in the reaction of benzophenonimine with $NO^+BF_4^-$. Competing reactions of the nitrosonium ion with aldehyde, ketone, or methyl substituents on benzene do not occur under our reaction conditions, and even a methoxy group provides for only a limited loss of products.

The facile reaction of nitrosonium salts with *N*-arylimines and ketimines suggests that alkyl cations would be produced from *N*-alkylimines. In this regard, we have found that the trityl cation is quantitatively formed from *N*-benzylidenetriphenylmethylamine and $NO^+BF_4^-$. The reactions of *N*-alkylimines and those of other unsaturated compounds with nitrosonium compounds will be presented in subsequent publications.

Experimental Section

General.—Instrumentation has been described.[27] Use was made of 5 ft columns of 10% Carbowax 20M and 20% SE-30 on Chromosorb P and of 3% SE-30 on Varaport 30. Nitrosonium salts were obtained from Ozark Mahoning Co. and were dried over phosphorus pentoxide in a vacuum desiccator at 1.0 Torr for several hours prior to use. Spectral grade acetonitrile and nitromethane were distilled twice from calcium hydride and stored over molecular sieves. Substituted *N*-benzylideneanilines were prepared from the corresponding benzaldehydes and anilines in refluxing benzene by removal of water with a Dean-Stark trap and purified by recrystallization or distillation. Benzhydrylideneaniline was commercially available. Benzophenonimine was prepared by the method of Pickard and Tolbert.[28]

Benzil Dianil (IV).—A mixture of 10.5 g (0.05 mol) of benzil, 7.0 g (0.075 mol) of aniline, and 0.3 ml of 10% hydrochloric acid was heated to 140–150° for 3 hr under a constant flowing nitrogen atmosphere. Water vapor was allowed to escape through an unstoppered opening in the reaction flask. After cooling the solution to 50° ethanol was added and the crude monoanil was allowed to crystallize. Recrystallization from ethanol afforded the yellow monoanil in 79% yield, mp 103–104° (lit.[29] mp 103–106°). Repeating the above procedure using benzil monoanil gave the dianil in 63% yield, mp 142.5–143.5° (lit.[29] mp 143–145°).

General Procedure for Nitrosation of Imines.—To 5.5 mmol of nitrosonium salt in 3 ml of anhydrous acetonitrile or nitromethane was added 5.0 mmol of imine in 7 ml of the same solvent, usually over a 15-min period. Prior to addition of imine the entire system was flushed with dry nitrogen, and, except for those runs where gas evolution was measured, the reaction was run under a nitrogen atmosphere. The solution was constantly stirred and temperature control was effected using an appropriate cooling bath. Reactions were usually run at 25°. No difference in yields or composition of products was observed when the nitrosonium salt was added to the imine (reverse addition), when the reaction was run at 0°, or when a greater volume of solvent was used. For benzophenonimine total gas evolution (0.52 equiv) was measured on the closed system by water displacement from a calibrated gas buret.

Reaction of *N*-Benzylideneaniline (IIa) with $NO^+BF_4^-$ and $NO^+SbF_6^-$.—After treatment of IIa with $NO^+BF_4^-$ in acetonitrile, benzaldehyde was identified by pmr, ir, and glpc analysis of the reaction solution. The benzenediazonium ion was detected by comparison of the pmr spectrum of the reaction solution with a comparable mixture of benzaldehyde and benzenediazonium tetrafluoroborate in acetonitrile. When the same reaction was run in nitromethane, the absorption band in the ir for the diazonium group at 2300 cm^{-1} was clearly visible. Heating the acetonitrile solution of products from IIa and $NO^+BF_4^-$ or $NO^+SbF_6^-$ to 70° for 15 min produced fluorobenzene in 40% yield. Fluorobenzene was confirmed by glpc, ir, and pmr comparison to an authentic sample as well as by its boiling point. In a separate experiment heating to 50° for 2 hr produced, after work-up, acetanilide in 23% yield. Production of chloro-

(22) H. Zimmer and G. Singh, *Angew. Chem.*, **75**, 574 (1963).
(23) M. Kobayashi and K. Honda, *Bull. Chem. Soc. Jap.*, **39**, 1778 (1966).
(24) T. Wieland and D. Grimm, *Chem. Ber.*, **96**, 275 (1963).
(25) E. C. Taylor and R. E. Buntrock, *J. Org. Chem.*, **36**, 634 (1971).
(26) See R. B. Woodward and R. Hoffman, "The Conservation of Orbital Symmetry," Springer-Verlag, New York, N. Y., 1970, for a discussion of 2+2 cycloaddition reactions.
(27) M. P. Doyle and W. Wierenga, *J. Amer. Chem. Soc.*, in press.
(28) T. L. Tolbert and P. L. Pickard, *J. Org. Chem.*, **26**, 4886 (1961).
(29) P. L. Julian, E. W. Meyer, A. Magnani, and W. Cole, *J. Amer. Chem. Soc.*, **67**, 1203 (1945).

benzene in 40% yield from benzenediazonium tetrafluoroborate was effected by adding cuprous chloride to the reaction mixture.

Product Analyses.—After complete addition of $NO^+BF_4^-$ or $NO^+SbF_6^-$ to the imine in acetonitrile a measured amount of a standard, usually nitromethane, was added to the reaction solution and an aliquot was removed for pmr analysis. Analyses were usually performed within 1 hr after initiation of reaction, although no change in product composition was observed over longer periods of time. A pmr spectrum was taken and integrated within 10 min after the sample was placed in the probe at 41° so as to minimize decomposition of diazonium salt. For spectra taken within 10 min no noticeable decomposition was observed. Another spectrum was recorded after 20 min in the nmr probe; only when the unsubstituted benzenediazonium ion was produced was there a noticeable change in the spectrum. Products were identified by spectral comparison to the authentic materials under comparable conditions. Yields were determined by averaging several integrations of the absorption signals for products. Reproducibility was ±2% when averaged over several reactions of the same components. Comparison was made both to the added standard and to the total phenyl region with no noticeable difference. Except for III and IV, absorptions for both the carbonyl compound and benzenediazonium ion were clearly distinguishable by pmr spectroscopy. Product per cent yields determined by this method follow: IIa, 95; IIb, 95; IIc, 95; IId 90; IIe, 83; IIf, 90; IIg, 95; IIh, 90; IIi, 83; IIj, 75. Products from the reaction of III with $NO^+BF_4^-$ were detected by glpc and ir analyses. Benzil was recovered in good yield after treatment of IV with $NO^+BF_4^-$ in acetonitrile and work-up in dichloromethane under conditions where both monoanil and dianil could have been detected.

Registry No.—Nitrosonium ion, 33904-18-6.

Acknowledgment.—This work was supported by a Frederick Cottrell Grant from the Research Corporation and by Grant No. GP-27587 from the National Science Foundation. We are grateful to Mr. James E. DeBoer for some preliminary results. We wish to thank Dr. L. M. Stephenson for helpful discussions concerning this work.

The Novel Reaction of 1,3-Dimethyl-6-amino-5-nitrosouracil with Lead Tetraacetate[1]

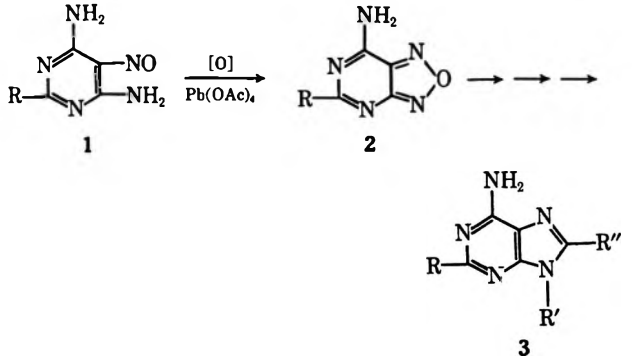
EDWARD C. TAYLOR,* YOSHIFUMI MAKI,[2] AND ALEXANDER MCKILLOP[3]

Department of Chemistry, Princeton University, Princeton, New Jersey 08540

Received September 13, 1971

Lead tetraacetate oxidation of 1,3-dimethyl-6-amino-5-nitrosouracil (**4**) in glacial acetic acid solution results in rapid discharge of the purple color of **4**, evolution of nitrogen, and the formation of 1,3,6,8-tetramethyl-2,4,5,7-(1*H*,3*H*,6*H*,8*H*)-pyrimido[5,4-*g*]pteridinetetrone 10-oxide (**6**), along with a minor amount of 4,6-dimethyl-5,7-(4*H*,6*H*)-furazano[3,4-*d*]pyrimidinedione (**5**). The structure of **6** was established by reductive and hydrolytic studies.

We have described in a recent paper[4] the lead tetraacetate oxidation of a series of 4,6-diamino-5-nitrosopyrimidines (**1**) to 7-aminofurazano[3,4-*d*]pyrimidines (**2**), and the subsequent utilization of the latter as versatile intermediates for the unequivocal synthesis of 9-substituted adenines (**3**). The present paper describes the novel and unexpected result of lead tetraacetate oxidation, under identical conditions, of 1,3-dimethyl-6-amino-5-nitrosouracil (**4**).



1 **2** **3**

Addition of lead tetraacetate to an acetic acid solution of **4** at room temperature resulted in nitrogen evolution, rapid discharge of the purple color of **4**, and the separation of a yellow, crystalline solid, mp 360–362° dec. Evaporation of the filtrate and recrystallization of the residue gave the expected[4] product, 4,6-dimethyl-5,7(4*H*,6*H*)-furazano[3,4-*d*]pyrimidinedione (**5**), in low (19%) yield. Microanalytical and mass spectral data on the yellow solid, mp 360–362° dec, established the molecular formula $C_{12}H_{12}N_6O_5$, while a strong M − 16 peak in the mass spectrum indicated the presence of a labile oxygen, most probably an *N*-oxide.[5] This conclusion was confirmed by chemical reduction with sodium dithionite at room temperature to give a pale yellow solid, mp 385°, which was shown to be 1,3,6,8-tetramethyl-2,4,5,7(1*H*,3*H*,6*H*,8*H*)-pyrimido[5,4-*g*]pteridinetetrone (**8**) by comparison with an authentic sample fortuitously available in our own laboratory.[6] Thus the lead tetraacetate oxidation product of **4** must be one of the two possible *N*-oxides **6** or **7** of **8**. That the major oxidation product of **4** was the 10-oxide (**6**) and not the 9-oxide (**7**) was demonstrated unequivocally by hydrolytic and other degradative reactions which are summarized below.

Although dilute alkaline hydrolysis of **8** is known to give 3,5-bis(methylamino)-*N*,*N*′-dimethylpyrazine-2,6-dicarboxamide (**9**) in excellent yield,[6] analogous hydrolysis of **6** yielded three products, 3,5-bis(methylamino)-*N*,*N*′-dimethylpyrazine-2,6-dicarboxamide 1-oxide (**10**), 3,5-bis(methylamino)-6-carboxy-*N*-methylpyrazine-2-carboxamide 1-oxide (**11**), and 1,3-dimethyl-5-methylaminocarbonyl-6-methylamino-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one (**12**) in yields of 20, 20, and 50%, respectively. Compound **10** was readily deoxygenated to the known **9** with triethyl phosphite. Re-

(1) We are indebted for partial support of this work to the National Science Foundation, Office of International Programs, U. S.–Japan Committee on Scientific Cooperation, Grant No. GF-390.

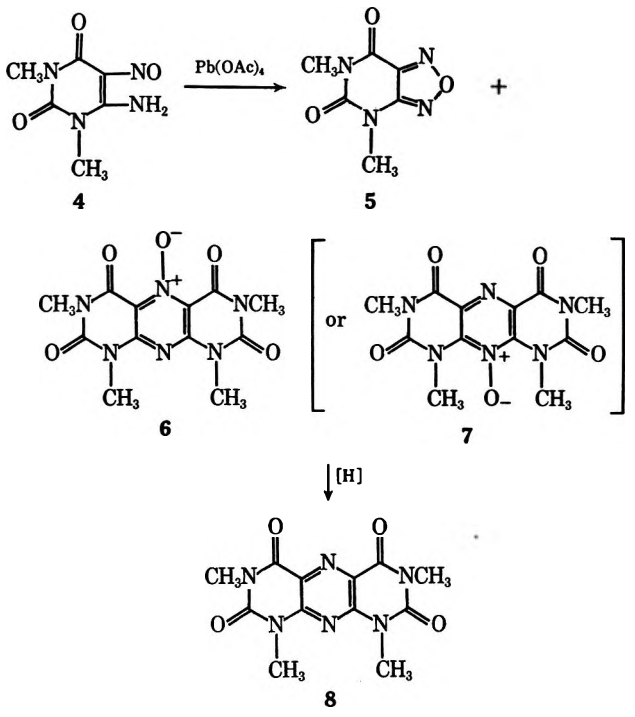
(2) Gifu College of Pharmacy, Gifu, Japan.

(3) School of Chemical Sciences, University of East Anglia, Norwich, England.

(4) E. C. Taylor, G. P. Beardsley, and Y. Maki, *J. Org. Chem.*, **36**, 3211 (1971).

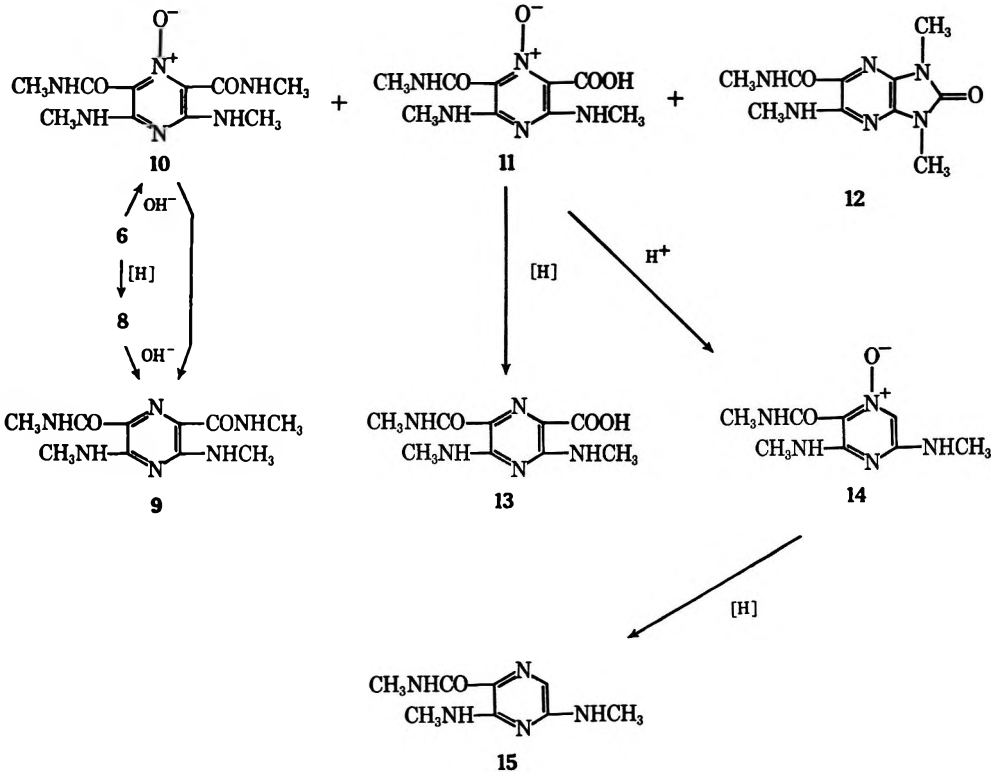
(5) T. A. Bryce and J. R. Maxwell, *Chem. Commun.*, 206 (1965).

(6) E. C. Taylor, C. K. Cain, and H. M. Loux, *J. Amer. Chem. Soc.*, **76**, 1874 (1954). The melting point of **8** was reported to be 403–404°, but a redetermination using a corrected thermometer showed it to be 385°.



duction of **11** with sodium dithionite gave 3,5-bis(methylamino)-6-carboxy-*N*-methylpyrazine-2-carboxamide (**13**), while treatment of **11** with trifluoroacetic acid at room temperature resulted in rapid decarboxylation to give 3,5-bis(methylamino)-*N*-methylpyrazine-2-carboxamide 1-oxide (**14**). Reduction of the latter compound with sodium dithionite gave 3,5-bis(methylamino)-*N*-methylpyrazine-2-carboxamide (**15**).

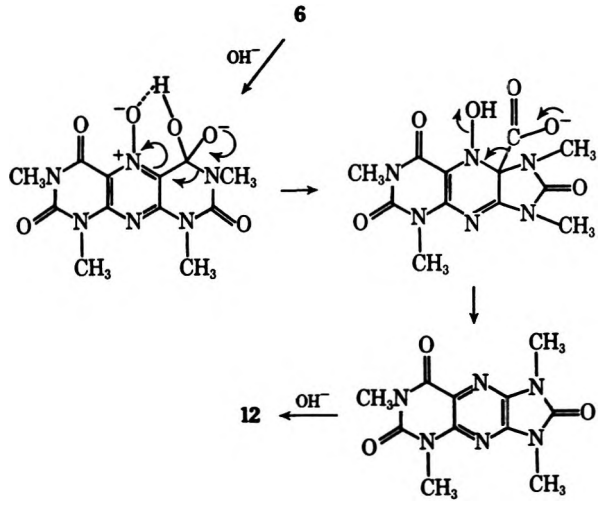
The position of the *N*-oxide function in the above pyrazine degradation products of **6** (and, as a consequence, the establishment of the position of the *N*-oxide grouping in **6** itself) was deduced from the following observations. (a) There is a marked difference between the position of the carboxylic acid C=O stretching bands of **11** and **13** (1695 and 1725 cm^{-1}, respectively), which is explicable only in terms of the effect of the *N*-oxide grouping on the ortho-situated carboxyl grouping, and would not be expected if the *N*-oxide grouping were on N_4 rather than N_1. (b) The nmr spectrum of **14** shows the C_6 H at δ 6.99, whereas the C_6 H in the deoxygenated pyrazine **15** appears at δ 7.06. The slight upfield shift of the ring proton in **14** is consistent with previous observations[7] on the effect of an *N*-oxide grouping on the chemical shift of α-ring protons. (c) Although **11** underwent smooth decarboxylation upon treatment with trifluoroacetic acid at room temperature, the corresponding deoxygenated pyrazine **13** was stable under the same conditions. This is again in accord with placement of the *N*-oxide grouping on the ring nitrogen adjacent to the carboxyl grouping.[8] (d) The formation of **12** is consistent only with the *N*-10-oxide structure **6** and cannot be explained satisfactorily on the basis of the alternate 9-oxide structure **7**. The structure of **12**, $C_{10}H_{14}N_6O_2$, was derived on the basis of combustion analysis and ir, nmr, and mass spectral data. Thus, **12** exhibited ir bands at 3390, 3310, 1695, and 1650 cm^{-1}, indicating clearly that both pyrimidine rings in the parent compound **6** had suffered cleavage by the action of alkali. The nmr spectrum of **12** showed that all four *N*-methyl groupings were still present (δ 3.30, 3.14, 3.00, and 2.86 in trifluoroacetic acid), although these chemical shifts were all different from those exhibited by the *N*-methyl groups in **6**. Compound **12** could be converted into a monoacetate with acetic anhydride which still, however, showed an NH band in its ir spectrum (3325 cm^{-1}). The absence of an *N*-oxide grouping in **12**,



(7) For leading references, see A. R. Katritzky and J. M. Logowski, "Chemistry of the Heterocyclic N-Oxides," Academic Press, New York, N. Y., 1971, p 16.

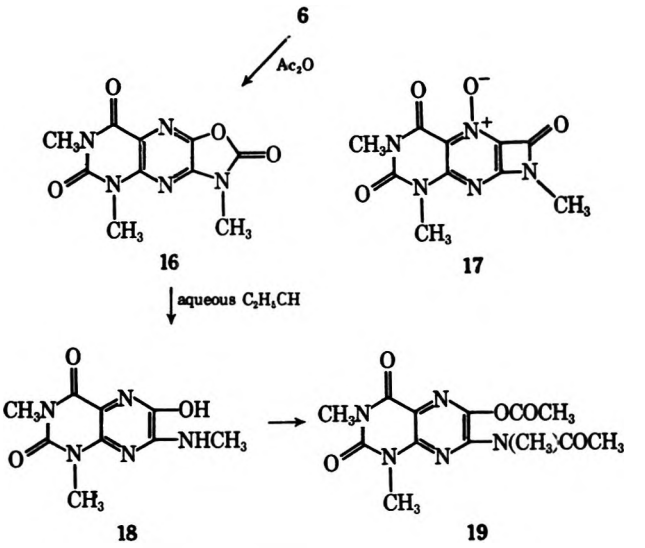
(8) See ref 7, pp 382–383.

indicated by the absence of an M − 16 peak in its mass spectrum, was confirmed by its stability to Raney nickel and to sodium dithionite. We suggest that **12** is formed from **6** by the mechanism outlined below, in which the ring contraction step is a benzylic acid type rearrangement similar to that firmly established for the conversion of alloxan to alloxanic acid.[9] The unique feature of the rearrangement in the present case is that concerted decarboxylation and dehydration lead to aromatization of the pyrazine ring. The transformation of **6** to **12** is possible only if the *N*-oxide grouping is placed on N-10.



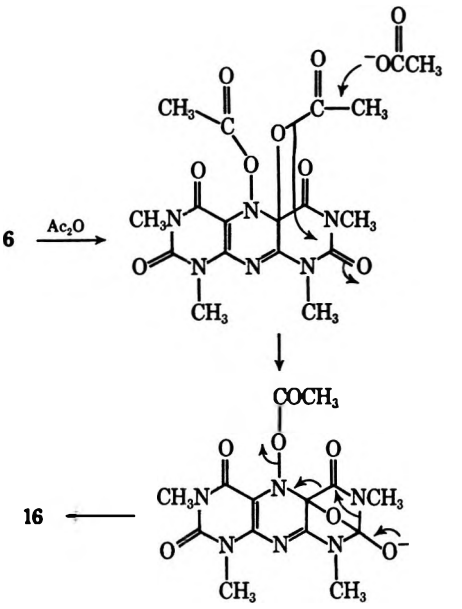
Further evidence in support of **6** (as opposed to **7**) for the lead tetraacetate oxidation product of **4** was obtained upon treatment of **6** with acetic anhydride. One of the two products formed was the deoxygenated pyrimidopteridine **8**; there is precedent for this deoxygenation in the conversion of phenazine *N*-oxide to phenazine with acetic anhydride.[10] The other product, mp 248°, was shown by microanalytical and mass spectral data (*m/e* 263) to have the molecular formula $C_{10}H_9N_5O_4$. This compound was not an *N*-oxide, as evidenced by the absence of an M − 16 peak. Its ir spectrum showed three carbonyl bands at 1825, 1720, and 1675 cm^{-1}; its nmr spectrum showed only three methyl groups at δ 3.7, 3.55, and 3.5. These three methyl groups account for all of the protons in the molecule.

These data suggest that this product contains two rings in addition to a pyrazine ring; one is apparently an unchanged fused 1,3-dimethyluracil and the other must result from the loss of methyl isocyanate from **6**. We suggest that this compound possesses structure **16**; although the high frequency carbonyl band at 1825 cm^{-1} might be explicable in terms of the *N*-methylazetinone structure (**17**),[11] such a formulation is inconsistent with mechanistic considerations (*vide infra*), with the absence of an M − 16 peak in its mass spectrum, and with its conversion with hot aqueous alcohol to 1,3-dimethyl-6-hydroxy-7-methylaminolumazine (**18**). Treatment of this latter compound with acetic anhydride gave the diacetate **19**, whose structure was confirmed by microanalysis, its ir spectrum (which revealed the lactim *O*-acetate grouping at



1775 cm^{-1}),[12] and its nmr spectrum (see Experimental Section).

We suggest that **16** is formed from **6** as depicted below. It should be noted that this interpretation requires that the *N*-oxide grouping on **6** be positioned at N-10; no reasonable mechanism leading to **16** from **7** could be envisaged.



It should be noted that **5** is apparently *not* an intermediate in the formation of **6** (from **4**). Thus, oxidation of 1,3-di(*n*-butyl)-6-amino-5-nitrosouracil (**20**) with lead tetraacetate in glacial acetic acid gave 1,3,6,8-tetra(*n*-butyl)-2,4,5,7(1*H*,3*H*,6*H*,8*H*)-pyrimido[5,4-*g*]pteridinetetrone 10-oxide (**21**). Oxidation of a mixture of 1,3-dimethyl- and 1,3-di(*n*-butyl)-6-amino-5-nitrosouracils (**4** and **20**, respectively) gave, as major products, a mixture of **6**, **21**, and the crossed product, 1,3-dimethyl-6,8-di(*n*-butyl)-2,4,5,7(1*H*,3*H*,6*H*,8*H*)-pyrimido[5,4-*g*]pteridinetetrone 10-oxide (**22**). On the other hand, oxidation of a mixture of **5** and **20** gave only the tetra(*n*-butyl) oxide **21**; **5** was recovered unchanged in 90% yield.

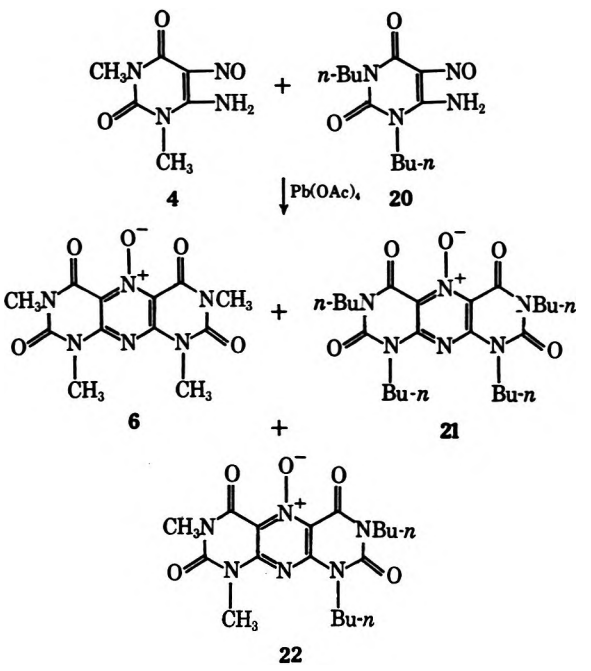
Although a number of different mechanisms (both

(9) H. Kwart and I. M. Sarasohn, *J. Amer. Chem. Soc.*, **83**, 909 (1961).

(10) C. A. Swan and D. G. I. Felton, "Phenazines," Interscience, New York, N. Y., 1957, p 12.

(11) E. M. Burgess and G. Milne, *Tetrahedron Lett.*, 93 (1966).

(12) For example, the 1770-cm^{-1} band exhibited by 1-phenyl-3-acetoxy-5-pyrazolecarboxylic acid has been attributed to the lactim *O*-acetate grouping: Y. Maki, H. Kizu, and K. Obata, *Yakugaku Zasshi*, **83**, 725 (1963).



free radical and ionic) can be written for the lead tetraacetate oxidation of 4 to 6, we are unable at present to advance evidence favoring any one over the others. Work is underway in an effort to clarify the course of this intriguing transformation.

Experimental Section[13]

Oxidation of 1,3-Dimethyl-6-amino-5-nitrosouracil (4) with Lead Tetraacetate. Formation of 1,3,6,8-Tetramethyl-2,4,5,7-(1*H*,3*H*,6*H*,8*H*)-pyrimido[5,4-*g*]pteridinetetrone 10-Oxide (6).—To a solution of 13.8 g (0.075 mol) of 1,3-dimethyl-6-amino-5-nitrosouracil (4) in 200 ml of glacial acetic acid was added 33.24 g (0.075 mol) of lead tetraacetate in portions over a period of 5 min. The reaction was mildly exothermic and proceeded with evolution of nitrogen. The color of the reaction mixture had changed from deep violet to pale yellow by the time addition of the lead tetraacetate was complete, and during this period a light yellow crystalline solid separated from the reaction mixture. The mixture was stirred (nitrogen atmosphere) at room temperature for 18 hr to ensure complete reaction and the precipitated pale yellow crystalline solid was collected by filtration, washed well with water, and dried. Recrystallization from a large volume of dimethylformamide with the use of decolorizing charcoal gave 8.0 g (67%) of long yellow needles: mp 360–362° dec; ir 1725, 1680 (br), 1585, 1550 cm^{-1} (br); mass spectrum *m/e* 320, 304 (M − 16).

Anal. Calcd for $C_{12}H_{12}N_6O_5$: C, 45.00; H, 3.78; N, 26.24. Found: C, 45.03; H, 3.98; N, 25.98.

4,6-Dimethyl-5,7(4*H*,6*H*)-furazano[3,4-*d*]pyrimidinedione (5). Method A.—Evaporation to dryness of the acetic acid filtrate above gave an oily residue which, on trituration with water, gave a colorless, crystalline solid. This compound was collected by filtration and recrystallized from acetone to give 2.6 g (19%) of colorless platelets: mp 225–226°; ir 1750, 1700, 1645, 1565 cm^{-1}; nmr (CF_3COOH) δ 3.49 (3 H, N_4 CH_3), 3.60 (3 H, N_6 CH_3); mass spectrum *m/e* 182, 152.

Anal. Calcd for $C_6H_6N_4O_3$: C, 39.56; H, 3.32; N, 30.76. Found: C, 39.32; H, 3.45; N, 30.65.

Method B.—To a suspension of 4.60 g (0.025 mol) of 1,3-dimethyl-6-amino-5-nitrosouracil (4) in 130 ml of benzene was added an equivalent amount of lead tetraacetate in small portions over a period of 6 hr. During this time the reaction mixture was maintained at 60°; some evolution of nitrogen was observed. The reaction mixture was then allowed to stir at room temperature for an additional 24 hr (nitrogen atmosphere). The suspended solids (containing some unreacted 4 as indicated by its red-violet color) were collected by filtration, washed well with water, dried, and recrystallized from dimethylformamide to give 0.40 g of 1,3,6,8-tetramethyl-2,4,5,7(1*H*,3*H*,6*H*,8*H*.)-pyrimido[5,4-*g*]pteridinetetrone 10-oxide (6), mp 361–362° dec, identical with the material obtained above by oxidation of 4 in glacial acetic acid solution. The benzene filtrate was washed with water, dried with anhydrous magnesium sulfate, and evaporated to dryness. The residual solid was recrystallized from acetone to give 2.71 g (60%) of 5 as colorless plates, mp 225–226°, identical in all respects with the compound obtained by oxidation of 4 in glacial acetic acid.

1,3,6,8-Tetramethyl-2,4,5,7(1*H*,3*H*,6*H*,8*H*)-pyrimido[5,4-*g*]-pteridinetetrone (8).—To a suspension of 0.5 g of 6 in 35 ml of 70% aqueous ethanol was added dropwise at room temperature 0.5 g of sodium dithionite. The reaction mixture was stirred for 2 hr, diluted with 30 ml of water, and filtered. The pale yellow crystals which were collected were recrystallized from glacial acetic acid to give 0.5 g of 8, mp 385°, identical in all respects (ir, nmr, melting point, and mixture melting point) with an authentic sample.[6]

Alkaline Hydrolysis of 1,3,6,8-Tetramethyl-2,4,5,7(1*H*,3*H*,-6*H*,8*H*)-pyrimido[5,4-*g*]pteridinetetrone 10-Oxide (6).—A suspension of 4.00 g of 6 in 50 ml of 4 *N* sodium hydroxide solution was warmed gently with swirling at 60–70°. As the hydrolysis proceeded, the reaction mixture first formed a hard mass and then became pasty. After about 1 hr, the alkaline mixture was cooled to room temperature and the light yellow solid which separated was collected by filtration, washed well with water, and dried. Recrystallization of the collected solid from aqueous dimethylformamide gave 1.50 g (50%) of **1,3-dimethyl-5-methylaminocarbonyl-6-methylamino-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one (12)** as pale yellow crystals: mp 355° dec; ir 3390, 3310 (NH), 1695 (imidazolone C=O), 1650 cm^{-1} (amide C=O); nmr (CF_3COOH) δ 3.30, 3.14, 3.00, 2.86; mass spectrum *m/e* 250.

Anal. Calcd for $C_{10}H_{14}N_6O_2$: C, 47.99; H, 5.64; N, 35.58. Found: C, 47.90; H, 5.71; N, 35.56.

The monoacetate of 12, prepared by heating with acetic anhydride, was recrystallized from acetone: mp 295° dec; ir 3325 (NH), 1710 (imidazolone C=O), 1690 (acetyl C=O), 1670 cm^{-1} (amide C=O).

The aqueous dimethylformamide mother liquors obtained as described above were concentrated to dryness and the solid residue was recrystallized from acetone to give 0.65 g (20%) of **3,5-bis(methylamino)-*N*,*N*′-dimethylpyrazine-2,6-dicarboxamide 1-oxide (10)**, in the form of long yellow needles: mp 158–159°; mass spectrum *m/e* 268, 252 (M − 16); ir 3350, 3150 (NH), 1650 cm^{-1} (amide C=O); nmr (CF_3COOH) δ 2.99, 3.32 (N CH_3).

The alkaline filtrate of the initial hydrolysis mixture, obtained as described above, was acidified at 0° with concentrated hydrochloric acid. The precipitated amorphous solid was recrystallized from methanol to give 0.64 g (20%) of **3,5-bis(methylamino)-6-carboxy-*N*-methylpyrazine-2-carboxamide 1-oxide (11)**, in the form of pale yellow feathery crystals: mp 218° dec; mass spectrum *m/e* 255, 239 (M − 16); ir 3345, 3250 (NH), 3200–3000 (br, carboxyl OH), 1695 (carboxyl C=O), 1650 cm^{-1} (amide C=O).

Anal. Calcd for $C_9H_{13}N_5O_4$: C, 42.35; H, 5.13; N, 27.44. Found: C, 42.09; H, 5.11; N, 27.10.

3,5-Bis(methylamino)-*N*,*N*′-dimethylpyrazine-2,6-dicarboxamide (9).—A mixture of 0.20 g of 3,5-bis(methylamino)-*N*,*N*′-dimethylpyrazine-2,6-dicarboxamide 1-oxide (10) and 20 ml of triethyl phosphite was heated under reflux for 3 hr. Excess triethyl phosphite was then removed by distillation *in vacuo*, and the residue was dissolved in chloroform–acetone (8:2) and chromatographed on silica gel. The column was diluted with additional chloroform–acetone (8:2), the eluate was evaporated to dryness, and the residue was recrystallized from acetone to give 0.066 g (35%) of 9, mp 232°, as bright yellow crystals. The product was identical in all respects (ir, nmr, melting point, and mixture melting point) with an authentic sample of 9.[6,14]

3,5-Bis(methylamino)-6-carboxy-*N*-methylpyrazine-2-carboxamide (13).—A mixture of 0.20 g of 3,5-bis(methylamino)-6-carboxy-*N*-methylpyrazine-2-carboxamide 1-oxide (11) and 0.45 g of sodium dithionite in 40 ml of 70% aqueous ethanol was heated with stirring at 90° for 3 hr. After cooling and acidifying

(13) Melting points are uncorrected and were determined on a Thomas-Hoover apparatus. Infrared data refer to Nujol mull spectra taken on a Perkin-Elmer Model 237B grating infrared spectrometer. Nmr data were obtained on a Varian A-60A instrument, using TMS as internal standard.

(14) Belgium Patent 568,115 (J. R. Geigy S. A.), May 29, 1957.

with hydrochloric acid, the reaction mixture was concentrated to a small volume under reduced pressure. On standing overnight, a yellow crystalline solid separated which was collected by filtration and recrystallized from alcohol to give 0.10 g (56%) of **13**: mp 190°;[15] ir 3425–3100 (NH and carboxyl OH), 1725 (carboxyl C=O), 1675 cm^{-1} (amide C=O).

Anal. Calcd for $C_9H_{13}N_5O_3$: C, 45.18; H, 5.48; N, 29.28. Found: C, 44.82; H, 5.71; N, 29.50.

3,5-Bis(methylamino)-*N*-methylpyrazine-2-carboxamide 1-Oxide (14).—To 5 ml of trifluoroacetic acid was added 0.50 g of 3,5-bis(methylamino)-6-carboxy-*N*-methylpyrazine-2-carboxamide 1-oxide (**11**) and the mixture was swirled at room temperature. Rapid decarboxylation took place, as evidenced by vigorous evolution of CO_2. The trifluoroacetic acid was removed by evaporation under reduced pressure and the solid residue was recrystallized from ethanol to give 0.32 g (77%) of pale yellow crystals of **14**: mp 235–236°; ir 3325, 3250, 3150 (NH), 1650 cm^{-1} (amide C=O); nmr ($DCCl_3$) δ 2.95, 3.03, 3.09 (N CH_3), 6.99 (1 H, C_6 H).

3,5-Bis(methylamino)-*N*-methylpyrazine-2-carboxamide (15). Method A.—A mixture of 0.50 g of 3,5-bis(methylamino)-*N*-methylpyrazine-2-carboxamide 1-oxide (**14**) and 0.8 g of sodium dithionite in 50 ml of water was heated under reflux for 2.5 hr with stirring. The cooled reaction mixture deposited yellow crystals which were collected by filtration and recrystallized from water to give 0.31 g (67%) of **15**: mp 151–152°; ir 3400, 3350 (NH), 1650 cm^{-1} (amide C=O); nmr ($DCCl_3$) δ 2.85, 2.93, 3.01 (N CH_3), 7.06 (1 H, C_6 H).

Anal. Calcd for $C_8H_{13}N_5O$: C, 49.23; H, 6.67; N, 35.89. Found: C, 49.26; H, 6.96; N, 35.86.

Method B.—**14** (300 mg) was heated at 190–200° (0.25 mm). The residual solid was extracted with hot water, and the extract was treated with charcoal, filtered, and concentrated to a small volume. Cooling resulted in the separation of 0.05 g of **15**, identical in all respects with the product obtained by method A.

Treatment of 1,3,6,8-Tetramethyl-2,4,5,7(1*H*,3*H*,6*H*,8*H*)-pyrimido[5,4-*g*]pteridinetetrone 10-Oxide (6) with Acetic Anhydride. Formation of 16.—A mixture of 2.0 g of **6** was heated under reflux with 20 ml of acetic anhydride for 20 hr. As the reaction proceeded, the suspended solid gradually went into solution and the color of the reaction mixture changed from yellow to light brown. A small amount of unreacted **6** was removed by filtration, and the clear acetic anhydride filtrate was allowed to stand at room temperature for several hours. Filtration then gave 0.5 g of 1,3,6,8-tetramethyl-2,4,5,7(1*H*,3*H*,6*H*,8*H*)-pyrimido[5,4-*g*]-pteridinetetrone (**8**), identical with an authentic sample prepared as described above by sodium dithionite reduction of **6**. Concentration of the acetic anhydride filtrate and recrystallization of the solid residue from ethanol then gave 0.6 g (40%) of **16**: mp 248°; mass spectrum *m/e* 263; ir 1825 (oxazolidone C=O), 1720, 1675 cm^{-1} (uracil C=O); nmr ($DCCl_3$) δ 3.7, 3.55, 3.5 (N CH_3).

Anal. Calcd for $C_{10}H_9N_5O_4$: C, 45.63; H, 3.45; N, 26.61. Found: C, 45.94; H, 3.63; N, 26.62.

1,3-Dimethyl-6-hydroxy-7-methylaminolumazine (18).—A suspension of 0.3 g of **16** in 30 ml of 50% aqueous ethanol was heated under reflux for 1 hr. The reaction mixture was concentrated to dryness and the residual solid was recrystallized from glacial acetic acid to give 0.2 g of **18** as fine colorless crystals: mp 370° dec; ir 3320, 3160 (NH), 1710, 1680 (uracil C=O), 1655 cm^{-1} (C_6 C=O); nmr (CF_3COOH) δ 3.80, 3.58, 3.28 (N CH_3).

(15) This compound has previously been reported (as the hemihydrate) to melt at 214° dec (ref 14).

1,3-Dimethyl-6-acetoxy-7-(*N*-methylacetamido)lumazine (19).—This compound was prepared in quantitative yield by refluxing **18** with acetic anhydride in the presence of anhydrous potassium acetate. Recrystallization of the crude product from methanol–ether (1:1) gave colorless crystals: mp 165°; ir 1775 (lactim *O*-acetate), 1720, 1675 cm^{-1} (br, uracil and amide C=O).

Anal. Calcd for $C_{13}H_{15}N_5O_5$: C, 48.59; H, 4.68; N, 21.78. Found: C, 48.67; H, 4.89; N, 21.79.

1,3,6,8-Tetra(*n*-butyl)-2,4,5,7(1*H*,3*H*,6*H*,8*H*)-pyrimido[5,4-*g*]pteridinetetrone 10-Oxide (21).—A solution of 5.26 g (0.02 mol) of 1,3-di(*n*-butyl)-6-amino-5-nitrosouracil (**20**) in 100 ml of glacial acetic acid was treated in small portions with 8.8 g (0.02 mol) of lead tetraacetate. The reaction was mildly exothermic and proceeded with evolution of nitrogen. After addition of lead tetraacetate was complete, the reaction mixture was stirred at room temperature (nitrogen atmosphere) for 18 hr and then concentrated to dryness under reduced pressure. The oily residue was triturated with water to give a solid mass which was pressed dry on a filter and recrystallized from acetone to give 3.70 g (90%) of pale yellow crystals of **21**: mp 158°; mass spectrum *m/e* 489, 473 (M − 16); ir 1725, 1680 cm^{-1}.

Anal. Calcd for $C_{24}H_{36}N_6O_5$: C, 59.00; H, 7.43; N, 17.20. Found: C, 58.87; H, 7.32; N, 17.34.

Lead Tetraacetate Oxidation of a Mixture of 1,3-Dimethyl- and 1,3-Di(*n*-butyl)-6-amino-5-nitrosouracil (4 and 20).—A mixture of 1.84 g (0.01 mol) of 1,3-dimethyl-6-amino-5-nitrosouracil (**4**) and 2.68 g (0.01 mol) of 1,3-di(*n*-butyl)-6-amino-5-nitrosouracil (**20**) in 70 ml of glacial acetic acid was treated with 8.8 g (0.02 mol) of lead tetraacetate in small portions over a period of 15 min. The reaction mixture was then stirred under nitrogen for 24 hr. Cooling of the crude reaction mixture resulted in the separation of 0.30 g of **6**, mp 360–362° dec, identical with authentic **6** prepared as described above. The filtrate was evaporated to dryness under reduced pressure and the residue was triturated with water to dissolve excess lead tetraacetate. The suspended solids were collected by filtration and dissolved in 30 ml of hot acetone. The acetone solution was allowed to stand at room temperature for several hours and filtered to remove a small amount of an insoluble impurity, and the filtrate was diluted with 20 ml of chloroform. The solution thus obtained was chromatographed on silica gel and the column was eluted with chloroform–acetone (7:3) to give the following compounds, listed in their order of elution: 4,6-dimethyl-5,7(4*H*,6*H*)-furazano[3,4-*d*]pyrimidinedione (**5**) (0.21 g), 1,3,6,8-tetra(*n*-butyl)-2,4,5,7-(1*H*,3*H*,6*H*,8*H*)-pyrimido[5,4-*g*]pteridinetetrone 10-oxide (**21**) (0.90 g), and 1,3-dimethyl-6,8-di(*n*-butyl)-2,4,5,7-(1*H*,3*H*,6*H*,8*H*)-pyrimido[5,4-*g*]pteridinetetrone 10-oxide (**22**) (0.19 g). Recrystallization of the latter compound from acetone gave pale yellow crystals: mp 203°; mass spectrum *m/e* 388, 372 (M − 16); ir 1725, 1675 cm^{-1} (br, uracil C=O).

Anal. Calcd for $C_{18}H_{24}N_6O_5$: C, 53.45; H, 5.98; N, 20.78. Found: C, 53.55; H, 5.91; N, 20.57.

Further elution of the column with chloroform–ethanol (1:1) gave an additional 0.22 g of **6**.

Registry No.—**4**, 6632-68-4; **5**, 33070-47-2; **6**, 33070-48-3; **10**, 33070-49-4; **11**, 33070-50-7; **12**, 33070-51-8; **12** monoacetate, 33070-52-9; **13**, 33122-32-6; **14**, 33070-53-0; **15**, 33070-54-1; **16**, 33070-55-2; **18**, 33070-56-3; **19**, 33070-57-4; **21**, 33070-58-5; **22**, 33070-59-6; lead tetraacetate, 546-67-8.

Routes of Conversion of D-Xylose, Hexuronic Acids, and L-Ascorbic Acid to 2-Furaldehyde[1]

MILTON S. FEATHER,* DONALD W. HARRIS, AND SUSAN B. NICHOLS

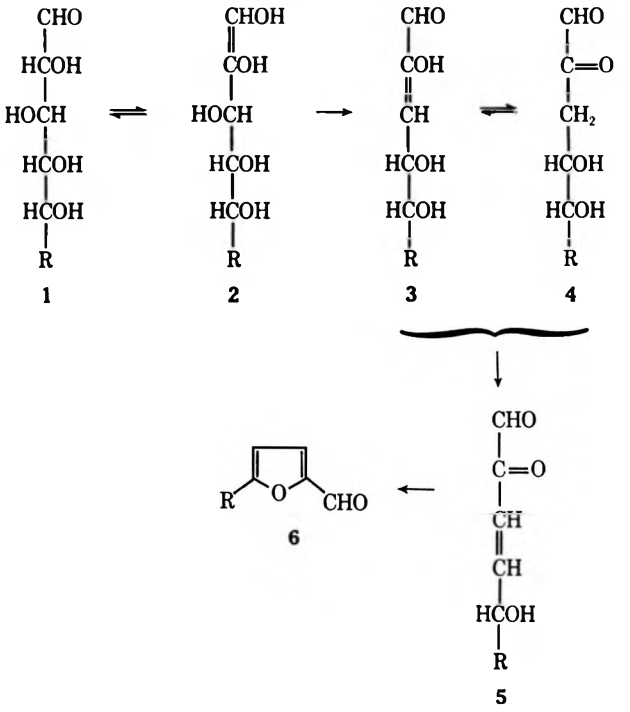
The Department of Agricultural Chemistry, The University of Missouri, Columbia, Missouri 65201

Received October 13, 1971

Investigations into the mechanism by which a number of carbohydrates are converted to 2-furaldehyde were undertaken by performing the conversions in acidified, tritiated water followed by a determination of the carbon-bound tritium incorporated into the product. The 2-furaldehyde derived from D-xylose contained essentially no carbon-bound tritium while that obtained from L-ascorbic acid and the related 2-oxo-D-*arabino*-hexonic acid had about 60% the radiochemical activity of the solvent. In the latter two cases, further degradation studies showed that nearly all of the activity was situated at the aldehyde carbon atom of the 2-furaldehyde. The 2-furaldehyde derived from L-sorburonic acid contained 17% the activity of the solvent and that from D-glucuronic acid 19%. In both cases none of the activity is located at the aldehyde carbon atom, and further degradation of the D-glucuronic acid derived 2-furaldehyde showed that the activity resides at either position 3 or 4 or a combination of both positions on the furan ring. The data are discussed in terms of mechanisms which are now in print. 2-Amino-2-deoxy-D-glucose was also investigated as a potential source of 2-furaldehyde but, in both cases, none was produced in detectable amounts.

The acid-catalyzed production of 2-furaldehyde from pentoses, hexuronic acids, and ascorbic acid and of 5-(hydroxymethyl)-2-furaldehyde from hexoses represent well-known dehydration reactions in the field of carbohydrate chemistry. The mechanism of carbohydrate dehydration reactions has been the subject of a number of studies in recent years, and it has been concluded[2] that for hexoses (R = CH_2OH, Chart I) and pentoses (R = H, Chart I) the pathway involves an initial con-

CHART I



version of the aldose **1** or related 2-ketose to the 1,2-enediol **2** in a reversible reaction followed by a dehydration of **2** to the enolic form **3** of a 3-deoxyglycosulose **4** which further dehydrates to **5** and thence to the 2-furaldehyde **6**. Evidence for such a mechanism rests on the isolation of **4** and **5** (R = CH_2OH) from D-fructose after treatment with acid[3] and further studies of these compounds. Kinetic studies indicate[4] that **4** is not a necessary intermediate in the dehydration reaction, but as much as 40% of the reaction involves this intermediate with the remaining 60% proceeding directly *via* **3**. Recent studies[5] involving deuterium exchange experiments are not consistent with this conclusion, however, and indicate a pathway involving only **1**, **2**, **3**, **5**, and **6**.

It is noteworthy that an analog of **4**[6,7] has been suggested as an intermediate in the decarboxylation of hexuronic acids during which 2-furaldehyde is produced, and 3-deoxy-D-pentosulose[8] (**3**, R = H) has been reported produced during the acid-catalyzed degradation of ascorbic acid, which also produces carbon dioxide and 2-furaldehyde.

Thus, for a number of dehydration reactions involving a variety of reactants, structurally similar reaction intermediates have been proposed.

The purpose of the present study was to evaluate a number of carbohydrates as potential sources of 2-furaldehyde and to determine the importance of the reversible equilibration between compounds having the general structures **1** and **2**, and the importance 3-deoxyglycosuloses (**4**) as reaction intermediates during such dehydration reactions. The compounds investigated were D-xylose (**7**), D-glucuronic acid (**8**), L-sorburonic acid (**9**), L-ascorbic acid (**10**), 2-oxo-D-*arabino*-hexonic acid (**11**), and 2-amino-2-deoxy-D-glucose (**12**). Compounds **7** through **11** were readily converted to 2-furaldehyde in yields in excess of 20% on treatment with aqueous acid.

Zimmerman and Cosmatos[9] have reported that 2-furaldehyde is the product of dehydration of **12** when the reaction is performed at a pH near neutrality in a sodium borate solution and that the 2-furaldehyde so produced can be distilled from the solution. Spectrophotometric measurements of distillates of such a reaction, which was repeated under these conditions, did not verify this and indicated that only small amounts of volatile ultraviolet-absorbing materials are produced.

(1) Journal Paper No. 6210 of the University of Missouri Agricultural Experiment Station.

(2) E. F. L. J. Anet, *Advan. Carbohyd. Chem.*, **19**, 181 (1964).

(3) E. F. L. J. Anet, *Chem. Ind. (London)*, 262 (1962).

(4) E. F. L. J. Anet, *Aust. J. Chem.*, **18**, 240 (1965).

(5) (a) M. S. Feather and J. F. Harris, *Tetrahedron Lett.*, 5807 (1968). (b) M. S. Feather and J. F. Harris, *Carbohyd. Res.*, **16**, 304 (1970).

(6) D. M. W. Anderson and S. Garbutt, *J. Chem. Soc.*, 3204 (1963).

(7) E. Stutz and H. Deuel, *Helv. Chim. Acta*, **41**, 1722 (1958).

(8) T. Kurata and Y. Sakurai, *Agr. Biol. Chem., (Tokyo)*, **31**, 170 (1967).

(9) H. K. Zimmerman and A. Cosmatos, *Z. Physiol. Chem.*, **326**, 73 (1961).

Assuming that all the ultraviolet-absorbing material was 2-furaldehyde, the maximum yield was less than 0.24% under these conditions.

The importance of the suggested reaction intermediates was examined by converting the compounds to 2-furaldehyde in acidified, tritiated water followed by a determination of the distribution of carbon-bound tritium in the product. For **7**, **8**, and **9** an equilibration between the reactant and 1,2-enediol would be expected to involve aldose, ketose, and enediol and would involve the acquisition of carbon-bound tritium at C-1 which ultimately would reside on the α carbon atom of 2-furaldehyde. The participation of **4** (or an analog thereof) in the reaction would involve tritium incorporation at C-3, which would ultimately reside at position 3 of the furan ring.

In the case of ascorbic acid (**10**) and the related 2-oxo-D-*arabino*-hexonic acid (**11**) it is presumed[8] that C-1 is lost as carbon dioxide during the conversion and that C-2 corresponds to the α carbon atom of 2-furaldehyde. Thus, for these cases, an incorporation at the α carbon of 2-furaldehyde represents an evaluation of the extent of reversible 2,3 enolization of the starting material with its 3-keto form, and an incorporation at position 3 of the furan ring represents an evaluation of the importance of 3-deoxypentosulose as a reaction intermediate.

The tritium content and distribution (Table I) was

TABLE I

SPECIFIC ACTIVITIES OF 2-FURALDEHYDE DERIVATIVES PREPARED FROM SUGARS IN ACIDIFIED, TRITIATED WATER

	2-Furaldehyde phenylhydrazone		2-Furoic acid	
Sugar	Specific activity, μCi/mmol	Activity of solvent, %	Specific activity, μCi/mmol	Activity of solvent, %
D-Xylose	0.03[a]	4.3	0.009[b]	0.5
D-Glucuronic Acid	0.14[a]	19.4	0.34[b]	18.9
L-Sorburonic Acid	0.30[b]	16.7	0.25[b]	13.9
L-Ascorbic Acid	0.42[a]	58.3	0.056[b]	3.1
2-Oxo-D-*arabino*-hexonic acid	0.41[a]	56.9	0.067[b]	3.7

[a] Prepared in tritiated water having a specific activity of 0.72 μCi/mmol. [b] Prepared in tritiated water having a specific activity of 1.80 μCi/mmol.

determined by isolating and counting 2-furaldehyde as its phenylhydrazone, a procedure which allowed the determination of the total amount of isotope incorporated, followed by a similar determination of 2-furoic acid, which allowed a determination of the combined activity at position 3, 4, and 5 of the furan ring.

The possibility of solvent and primary isotope effects must be considered when the collected data are used to interpret mechanisms. For isotope exchange experiments, such effects will affect the validity of a direct comparison of reactions in water with similar ones in tritiated water. Thus, the extent of equilibration of starting material or intermediates might be substantial in water and less so as evidenced by tritium incorporation. The results as obtained, however, are consistent with a direct conversion of D-xylose to 2-furaldehyde involving only **1**, **2**, **3**, and **5** (R = H) and, in this respect, the data is identical with that obtained for the conversion of D-glucose and D-fructose to 5-(hydroxymethyl)-2-furaldehyde in deuterium oxide solution.[5]

The 2-furaldehyde derived from the hexuronic acids (compounds **8** and **9**) is interesting in that only negligible amounts of the tritium incorporated during the reaction is located at the α carbon atom (Table I). A further conversion of the 2-furoic acid obtained from D-glucuronic acid to methyl 5-nitro-2-furoate with retention of all the radiochemical activity indicates that the isotope is located at position 3 or 4, or both positions. It thus appears possible, at least in a portion of the reaction pathway, that analogs of **4** could participate in the reaction. It is interesting to note that existing mechanism proposals predict, aside from proton exchange[6] at C-3 (corresponding to position 3 of the furan ring), that exchange would occur at C-5 (corresponding to position 5 of the furon ring)[8] and no exchange would necessarily occur during the reaction.[10]

In an earlier report[11] on the conversion of D-glucuronic acid to 2-furaldehyde, we reported that the conversion in tritiated water (0.49 μCi/mmol) resulted in only an 8% incorporation of tritium relative to the solvent and the conversion in deuterium oxide resulted in no measurable incorporation on the furan ring, as evidenced by nmr measurements. While the absence of deuterium relative to tritium incorporation can be explained on the basis of isotope effects, we cannot, at present, explain the discrepancy between the radiochemical measurements except to point out that the measurements made herein used much higher activity water and hence would constitute a more accurate measurement.

Kurata and Sakurai[8] in a recent investigation of ascorbic acid decarboxylation considered two possible mechanisms, one which involved a dehydration sequence followed by decarboxylation and 2-furaldehyde formation, and another which involved a rearrangement to the 3-keto form followed by a β-keto acid decarboxylation to give a pentose 1,2-enediol which is then converted to 2-furaldehyde. These investigators preferred the former mechanism, which predicts solvent proton exchange at C-4 of the ascorbic acid (corresponding to position 3 of the furan ring). In the case of the 2-furaldehyde derived from **10** and **11**, the labeling distribution is consistent only with the latter pathway, however. It is interesting to note that the predicted product of L-ascorbic acid decarboxylation is the pentose 1,2-enediol, which would be expected to dehydrate with no further isotope exchange. Such a mechanism explains the reported isolation of pentosuloses (**4**, R = H) during ascorbic acid dehydration since, although the reaction apparently proceeds *via* **3** (R = H), this compound would be isolated as its more stable keto form **4** (R = H). It is also noteworthy that the results relative to the L-ascorbic acid reaction are entirely consistent with the Isbell mechanisms[10,12] which also predict isotope exchange corresponding to acquisition at the α carbon atom of the 2-furaldehyde.

Experimental Section

Materials and Methods.—Radiochemical determinations were performed in Brays solution using a tritiated toluene internal standard. At least 10,000 total counts were obtained for each sample. Thin layer chromatography was performed using silica

(10) H. S. Isbell, *J. Res. Nat. Bur. Stand.*, **33**, 45 (1944).
(11) M. S. Feather, *Tetrahedron Lett.*, 4143 (1970).
(12) H. S. Isbell, *Ann. Rev. Biochem.*, **12**, 205 (1943).

gel HF supports with benzene–methanol (99:1) as an irrigant for phenylhydrazones and chloroform–acetic acid (9:1) for furoic acid samples. Spots were visualized by uv light or by spraying with 10% ethanolic sulfuric acid followed by heating at 110° for 10 min.

Carbohydrates were commercially obtainable samples, with the exception of L-sorburonic acid, which was obtained from Northern Regional Research Laboratories, Peoria, Ill., as a gift.

Ultraviolet spectra were obtained on a recording Coleman Model 124 double beam grating spectrometer.

Preparation of 2-Furaldehyde.—Essentially the same procedure was followed for the preparation of 2-furaldehyde for all sugars tested. In a typical experiment 2.0 g of carbohydrate was placed in a 1-l. round-bottom flask containing 500 ml of 6 *N* sulfuric acid. The solution was brought to boiling, an operation which required about 30 min, and 250 ml of distillate was then collected over a 3-hr period. The 2-furaldehyde contained by the distillate was readily identified by its ultraviolet spectrum, which showed maxima at 227 and 278 mμ[13] and which was identical with the spectrum of an authentic sample. Yields of 2-furaldehyde in the distillate were estimated by a spectrophotometric measurement at 278 mμ based on a molar absorptivity of 2-furaldehyde of 18,000. The 2-furaldehyde was further identified by conversion to the phenylhydrazone and to 2-furoic acid in radiochemical experiments described below.

Reaction of 2-Amino-2-deoxy-D-glucose (12) in Borate Buffer.—The procedure of Zimmerman and Cosmatos[9] was repeated in this experiment. **12** (2.15 g), boric acid (9.27 g), and sodium hydroxide (6.0 g) were dissolved in 1 l. of water and held at 25° for 30 hr. The solution was then adjusted to pH 7 with concentrated hydrochloric acid and distilled as described above. The distillate contained a small amount of uv-absorbing material which showed maxima at 235 and 265 mμ. Assuming that all the absorbance at 265 mμ was due to 2-furaldehyde the total yield was 0.24%.

Preparation of 2-Furaldehyde-^{3}H Phenylhydrazone.—In a typical experiment, 2-furaldehyde was obtained from 3.0 g of D-xylose by distillation as described above with the exception that the solution contained 20 mCi of tritiated water. An equimolar amount of phenylhydrazine hydrochloride in 20 ml of water was added and the resulting precipitate was collected on a filter. This material was recrystallized from ethanol–water (1:1) to constant radiochemical activity. The 2-furaldehyde phenylhydrazone had mp 94° (lit.[14] mp 97°) and had a thin layer chromatographic flow rate identical with that of an authentic sample. Identical procedures were used in subsequent experiments using compound **8**, **9**, **10**, and **11**.

Preparation of 2-Furoic Acid-^{3}H.—A solution of 2-furaldehyde-^{3}H was obtained from D-xylose in tritiated water as described above. To the distillate was added 2.0 g of freshly prepared silver oxide and the pH was adjusted to 10 with sodium hydroxide solution. The suspension was stirred for 30 min with aeration and filtered, and the filtrate was passed through a column of Dowex 50 (hydrogen form). The eluate was evaporated to dryness and alternately sublimed at 110° (0.3 mm) and reevaporated from water until constant radiochemical activity was reached. The final product had mp 131° (lit.[15] mp 133°) and had a chromatographic mobility identical with that of an authentic specimen. Identical results were obtained using compounds **8**, **9**, **10**, and **11** as starting materials.

Preparation of Methyl 5-Nitro-2-furoate-^{3}H from 2-Furoic Acid-^{3}H.—A sample (12 mg) of 2-furoic acid-^{3}H derived from D-glucuronic acid as described above was diluted with inert material and recrystallized to give a sample having a specific activity of 0.357 μCi/mmol. This sample (936.8 mg) was esterified with diazomethane and the resulting ester was converted to methyl 5-nitro-2-furoate as described by Freure and Johnson.[16]

This compound after two recrystallizations from methanol and one from hexane had mp 79.5° (lit.[16] mp 81.6°) and ran as a single spot on thin layer chromatograms.

Anal. Calcd for $C_6H_5O_5N$: N, 8.18. Found: N, 7.90.

The specific activity of this derivative was 0.353 uCi/mmol and was not changed on further purification.

Registry No.—**7**, 58-86-6; **8**, 6556-12-3; **9**, 488-34-6; **10**, 50-81-7; **11**, 669-90-9; **12**, 3416-24-8; 2-furaldehyde, 98-01-1.

Acknowledgment.—This research was supported, in part, by a grant from the Corn Industries Research Foundation, a division of the Corn Refiners Association.

(13) A. P. Dunlop and F. Peters, "The Furans," Wiley, New York, N. Y., 1953, p 13.

(14) Reference 13, p 364.

(15) Reference 13, p 489.

(16) B. T. Freure and J. R. Johnson, *J. Amer. Chem. Soc.*, **53**, 1142 (1931).

New Route to Branched-Chain Sugars. Photoamidation and Photohydroxyalkylation of 3-Deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-*erythro*-hex-3-enofuranose

ALEX ROSENTHAL* AND KOICHI SHUDO

Department of Chemistry, The University of British Columbia, Vancouver, British Columbia, Canada

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The acetone-initiated photochemical addition of formamide to 3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-*erythro*-hex-3-enofuranose (**1**) afforded trans 1:1 adducts, namely, 3-*C*-carbamoyl-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**2**), 3-carbamoyl-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-gulofuranose (**3**), and 3-deoxy-3-*C*-(1-hydroxy-1-methylethyl)-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**4**) in 16, 15, and 7% yields (after chromatography), respectively. Irradiation of **1** in the presence of isopropyl alcohol and acetone gave the hydroxyisopropyl 1:1 adduct **4** in 31% yield and, in addition, a novel 1:2 adduct **6** which is tentatively assigned the structure of 3-deoxy-3,4-*C*-bis(1-hydroxy-1-methylethyl)-1,2:5,6-di-*O*-isopropylidene-α-D-gulofuranose in 8% yield. The proton magnetic resonance and high-resolution infrared spectra of these substances are described. Lithium aluminum hydride reduction of the carbamoyl sugar **3** afforded 3-*C*-aminomethyl-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-gulofuranose, isolated as its trifluoroacetamido derivative **7**.

In continuation of our studies on the chemistry of branched-chain sugars[1] we now wish to report a different approach to the synthesis of these novel sugars by photoaddition of formamide and of isopropyl alcohol to unsaturated carbohydrates.

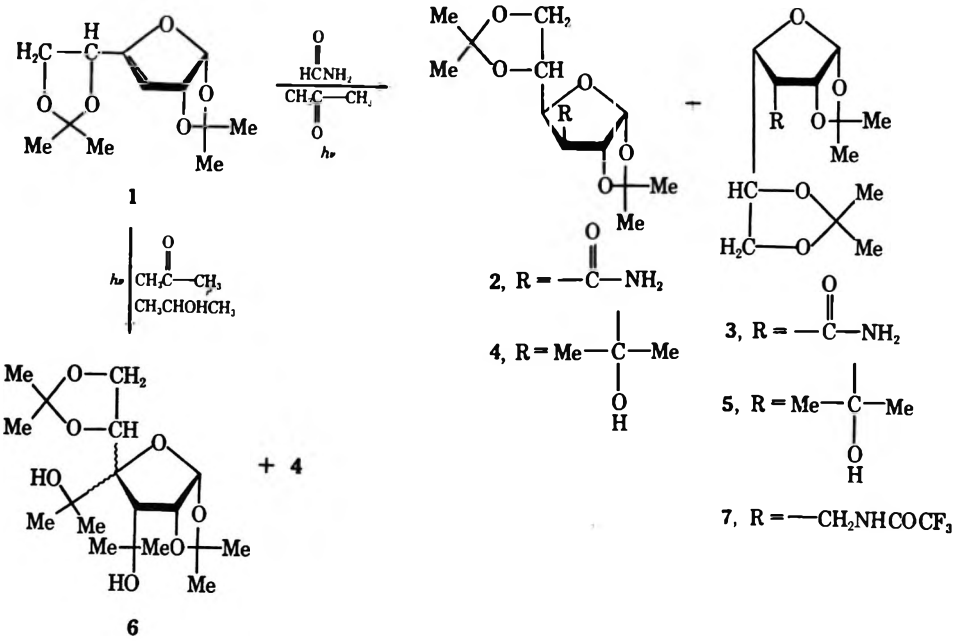
Formamide has been shown to undergo acetone-initiated photochemical addition to terminal[2] and nonterminal olefins[3] to yield 1:1 carbamoyl adducts. In the case of norbornene the reaction has been found to be stereospecific, leading exclusively to the exo isomer. This reaction, termed photoamidation, has also been

(1) (a) A. Rosenthal, *Advan. Carbohyd. Chem.*, **23**, 59 (1968); (b) A. Rosenthal and M. Sprinzl, *Carbohyd. Res.*, **16**, 337 (1971); (c) A. Rosenthal, K. S. Ong, and D. A. Baker, *ibid.*, **13**, 113 (1970); (d) A. Rosenthal and G. Schöllnhammer, *ibid.*, **15**, 421 (1970); (e) A. Rosenthal, and D. A. Baker, *Tetrahedron Lett.*, 397 (1969).

(2) (a) D. Elad and J. Rokach, *J. Org. Chem.*, **29**, 1855 (1964); (b) D. Elad and J. Rokach, *J. Chem. Soc.*, 800 (1965).

(3) D. Elad and J. Rokach, *J. Org. Chem.*, **30**, 3361 (1965).

SCHEME I



extended successfully to α,β-unsaturated esters.[4] The point of attachment of the carbamoyl [$\cdot C(=O)NH_2$] radical to the carbon–carbon double bond depends on the structure of the olefin. With terminal olefins, the 1:1 adduct was predominately the anti-Markovnikov one, but with nonterminal olefins mixtures of the two possible amides were obtained.

Because of the great importance of the amino sugars[5] as constituents of many antibiotics,[6] our laboratory has been interested in developing new general methods for the synthesis of analogues of the amino sugars which occur as moieties in some of the antibiotics. Photoamidation of unsaturated carbohydrates appeared to offer promise for the synthesis of carbohydrate carboxamides, structurally related to gougerotin.[7] Reduction of the blocked carbamoyl sugars might be expected to yield branched-chain amino sugars which would be homologues of the amino sugar moiety of puromycin.[7] An alternative approach to this synthesis, *via* the application of the nitromethane synthesis to a ketose, has been reported recently.[8]

When a solution of 3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-*erythro*-hex-3-enofuranose (**1**),[9] *tert*-butyl alcohol, formamide, and acetone was irradiated through a Pyrex filter for 22 hr, a mixture of three main products, **2**, **3**, and **4**, was formed (Scheme I). After work-up of the reaction mixture the chloroform-soluble components (part of the product was water soluble and not recovered) were separated by silica gel column chromatography using benzene–ethyl acetate as developer to afford two photoamidation adducts, **2** and **3**, in about equal yields (total yield ~31%) and a hydroxyisopropyl adduct, **4**, in ~7% yield. The structures of the phctoproducts were readily deduced from an analysis of their infrared (ir) and proton magnetic resonance (pmr) spectra. The pmr spectra (see Figure 1 and Experimental Section) of all three compounds clearly showed a single H-3 methine hydrogen at τ 6.9–7.9, thus establishing that the carbamoyl and ketyl radical [$(CH_3)_2\cdot COH$] had added exclusively to C-3 of **1**. The C-2 hydrogen of both **2** (Figure 1A) and **4** gave doublets at τ 5.05 and 5.45, respectively ($J_{2,1}$ = 3.5 and 4.0 Hz), which collapsed to singlets on irradiation of the C-1 hydrogen. On the other hand, the C-2 hydrogen of **3** (Figure 1B) exhibited four peaks at τ 4.97 ($J_{2,1}$ = 4.0 and $J_{2,3}$ = 2.5 Hz) which collapsed to a doublet on irradiation of the C-3 hydrogen. Trans H_2–H_3 of the 1,2-*O*-isopropylidenefuranose sugars have small couplings of <0.5 Hz, whereas cis H_1–H_2 or H_2–H_3 have couplings of >2.5 Hz;[10] therefore the C-3 hydrogen of compounds **2** and **4** are trans to the C-2 hydrogen, whereas the C-3 hydrogen of **3** must be cis to the C-2 hydrogen. Similar consideration of the coupling constants of the C-3 hydrogen with the C-4 hydrogen must lead to the configuration of the C-4 of each of the compounds. Because the C-3 hydrogen of **2** gave a doublet at τ 6.87 ($J_{3,4}$ = 4.0 Hz), H-3 and H-4 must be cis oriented, and, because the C-3 hydrogen of **3** at a τ 6.96 exhibited four peaks with $J_{3,2}$ = 2.5 and $J_{3,4}$ = 7.0 Hz, H-3, H-4, and H-2 of the latter compound must also be cis oriented. Therefore, compounds **2** and **3** are undoubtedly 3-*C*-carbamoyl-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose and 3-*C*-carbamoyl-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-gulofuranose, respectively. Interestingly, the photoamidation products must have been formed *via* a trans addition of the carbamoyl and hydrogen radicals (hydrogen atom is abstracted from the formamide in the last step[2]) to the carbon–carbon double bond of **1**. Here the addition of the carbamoyl radical took place stereoselectively to C-3 and almost with equal

(4) J. Rokach and D. Elad, *J. Org. Chem.*, **31**, 4210 (1966).

(5) (a) A. B. Foster and M. Stacey, *Advan. Carbohyd. Chem.*, **7**, 247 (1952); (b) A. B. Foster and D. Horton, *ibid.*, **14**, 213 (1959); (c) A. B. Foster, and J. M. Webber, *ibid.*, **15**, 371 (1960).

(6) (a) J. D. Dutcher, *ibid.*, **18**, 259 (1963); (b) L. Hough and A. C. Richardson in "Rodd's Chemistry of Carbon Compounds," Vol. 1, Part F, S. Coffey, Ed., Elsevier, Amsterdam, 1967.

(7) J. J. Fox, K. A. Watanabe, and A. Bloch, *Progr. Nucleic Acid Res. Mol. Biol.*, **5**, 251 (1966).

(8) H. P. Albrecht and J. G. Moffatt, *Tetrahedron Lett.*, 1053 (1970).

(9) (a) F. Weygand and H. Wolz, *Chem. Ber.*, **85**, 256 (1952); (b) J. Prokop and D. H. Murray, *J. Pharm. Sci.*, **54**, 359 (1965).

(10) R. J. Abraham, L. D. Hall, L. Hough, and K. A. McLauchlin, *J. Chem. Soc.*, 3699 (1962).

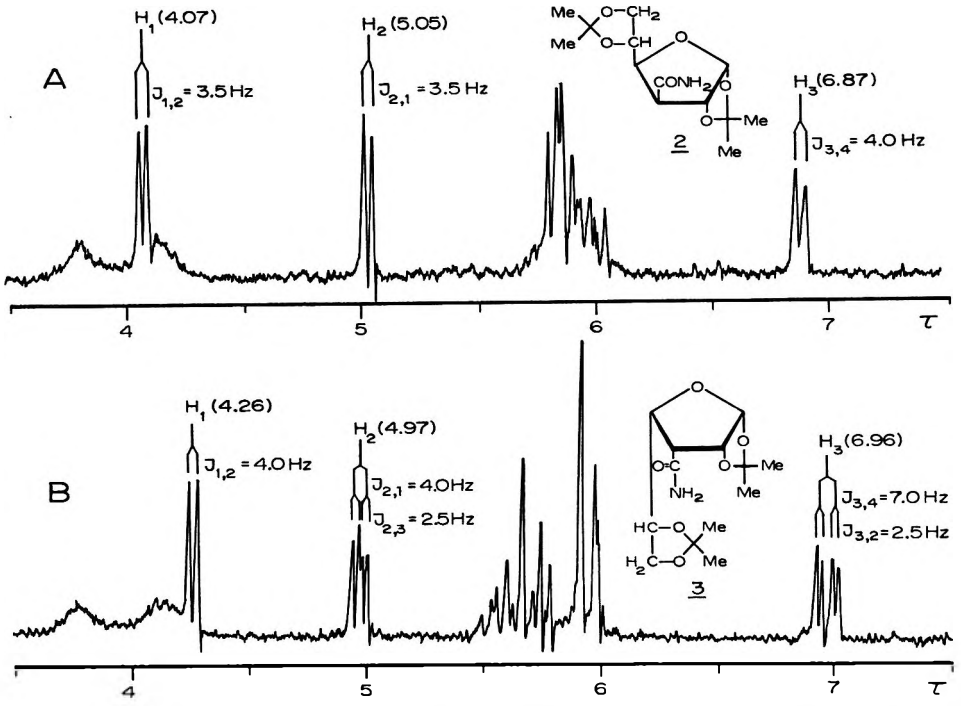


Figure 1.—Partial nmr spectra of (A) 3-*C*-carbamoyl-3-deoxy1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**2**) and (B) 3-*C*-carbamoyl-3-deoxy-1.2:5,6-di-*O*-isopropylidene-α-D-gulofuranose (**3**) in $CDCl_3$ at 100 MHz.

facility from both sides of the double bond as evidenced by the almost equal yield of **2** and **3**. The complete structure of the branched-chain hydroxyisopropyl sugar **4** was similarly deduced from its pmr spectrum (similar to that of **2**) and therefore it must be 3-deoxy-3-*C*-(1-hydroxy-1-methylethyl)-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose. Presumably, **4** must have been formed *via* a trans addition of the ketyl group and hydrogen atom to **1**. In contrast to the photoamidation reaction the photohydroxyalkylation reaction was stereoselective since the ketyl group added stereoselectively to **1** to afford **4** only. Although 2-methylalkan-2-ols have been isolated from some reaction mixtures encountered in the light-induced amidation of terminal olefins,[2] the stereochemistry of these photoreactions has hitherto not been elaborated.

The second part of this investigation deals with the photoaddition of isopropyl alcohol to the same unsaturated sugar **1** to yield novel branched-chain hydroxyalkyl sugars. The light-induced addition of alcohols to olefins to afford homologous alcohols and telomers has been known for almost two decades.[11] When a solution of 3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-*erythro*-hex-3-enose (**1**) in isopropyl alcohol and acetone was irradiated for 26 hr through a Pyrex filter, the unsaturated sugar was converted mainly into a 1:1 and a 1:2 adduct to afford 3-deoxy-3-*C*-(1-hydroxy-1-methylethyl)-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**4**) and an unexpected novel adduct **6** in 31 and 8% yields, respectively. In addition, pinacol was produced. These substances were separated by silica gel column chromatography using benzene–ethyl acetate as developer. The identity of pinacol was established by direct comparison with an authentic sample. The structure of **6** was deduced from its mass, pmr, and ir spectra. Its mass spectrum gave a peak at *m/e* 345 and a very small peak at *m/e* 360. Because isopropylidene derivatives of carbohydrates are known to lose a methyl group during their initial mass breakdown,[12] the molecular weight of **6** was 360. This molecular weight suggested strongly that compound **6** was an adduct of 1 mol of **1** and 2 mol of the ketyl group. Elemental analysis of **6** agreed with the molecular constitution $C_{18}H_{32}O_7$. The pmr spectrum of **6** in $CDCl_3$ clearly showed the presence of two hydroxyl peaks which disappeared on addition of D_2O and the presence of six high-field signals at τ 8.38–8.86 equal to eight methyl groups. These findings confirmed that two ketyl radicals must have added to the C_3–C_4 double bond of **1**. The configuration of C-3 of **6** was readily deduced from its pmr spectrum which showed a doublet at τ 4.09 (J = 4.5 Hz), four peaks at 5.01 ($J_{2,1}$ = 4.5 Hz and 7 Hz), and one doublet at 7.05 (J = 7 Hz). These signals were assigned to C-1, C-2, and C-3 hydrogens, respectively, because irradiation at τ 5.0 collapsed the doublets at 4.09 and 7.05 to singlets. Therefore, the C-3 hydrogen of compound **6** must be cis to the C-2 hydrogen. Because there is no hydrogen on C-4 of **6**, pmr could not be used to deduce the configuration of C-4. On the other hand, intramolecular hydrogen-bonding studies[13] carried out by high resolution ir spectroscopy on dilute carbon tetrachloride solutions and molecular model studies strongly suggested the configuration at C-4 of **6**. The broad intense peak at 3458 cm^{-1} indicated the presence of a hydroxyl group bonded to oxygen in a six-membered ring.[13] This obviously could arise from the bonding of the hydroxyl group on the C-3 hydroxyisopropyl group with the C-2 oxygen or from the bonding of the two hydroxyl groups if both

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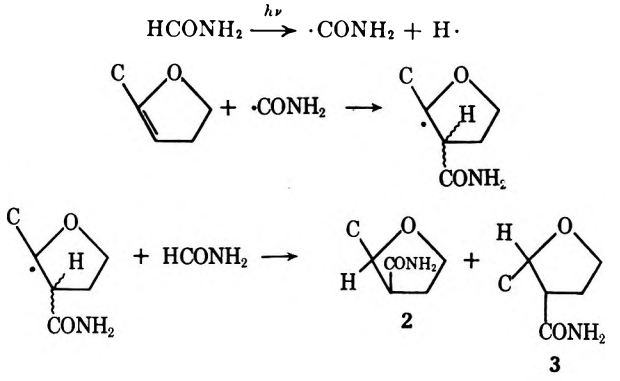
hydroxyisopropyl groups were cis oriented. However, the presence of a sharp intense peak at 3623 cm^{-1} indicated that one of the hydroxyisopropyl groups must be free, and furthermore, because the configuration of the C-3 hydroxyisopropyl group is known, the C-4 hydroxyisopropyl group must be trans to its C-3 counterpart; **6** is thus tentatively assigned as 3-deoxy-3,4-*C*-bis(1-hydroxy-1-methylethyl)-1,2:5,6-di-*O*-isopropylidene-α-D-gulofuranose.[14] From a stereochemical viewpoint, **6** might have been formed *via* a trans addition of the two ketyl groups to **1**. The omission of the hydrogen-abstraction step has been noted by other workers;[2] as an example, alkylated succinamides have been isolated in low yields from the photoamidation of terminal olefins. These trace compounds might have arisen from an addition of two carbamoyl free radicals to the olefin or else from a radical addition to formamide.

The course of the reaction for the photochemical synthesis of 1:1 adducts[2] of formamide and the unsaturated sugar **1** may be illustrated as follows.



The ease of converting **3** into a branched-chain amino sugar having the L configuration by selective periodate degradation of the 5,6-diol of **3** followed by reduction of the aldehydo compound makes this synthesis potentially attractive.

Lithium aluminum hydride reduction of the carboxamide sugar **3** readily afforded a branched-chain amino sugar, namely 3-*C*-aminomethyl-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-gulofuranose. Quite unexpectedly, the corresponding branched-chain amino sugar from **2** proved to be unstable and could not be characterized.

Experimental Section

Irradiations were made with a 450-W Hanovia medium pressure mercury vapor lamp with Pyrex filter under oxygen-free nitrogen. The reaction mixture was cooled internally with running water. Agitation of the reaction mixture was achieved with magnetic stirring. Purified nitrogen was bubbled for 2 hr through the reaction mixture before irradiation. The progress of reactions and purity of products were checked by tlc on silica gel G. Grace silica gel and Woelm neutral alumina were used for column chromatography. Ir spectra were recorded in Nujol or in CCl_4 with a Perkin-Elmer Model 337 spectrometer, and pmr spectra were determined in deuteriochloroform solution with TMS as the internal standard using a Varian HA-100 spectrometer, ionizing potential 70 eV. Mass spectroscopy was obtained with a HMS-9 spectrometer. Optical rotations were measured at room temperature with a Perkin-Elmer Model 141 automatic polarimeter. Chemical analysis were performed by Mr. P. Borda of the Microanalytical Laboratory, University of British Columbia.

Photoamidation of 3-Deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-*erythro*-hex-3-enose (1)[9] to Yield Compounds 2, 3 and 4.—A solution of the unsaturated carbohydrate **1** (4.8 g) in anhydrous formamide (200 ml), *tert*-butyl alchohol (60 ml) and acetone (20 ml) was irradiated for 22 hr (or until all starting material was consumed as evidenced by tlc), after which the solution was diluted with 300 ml of saturated aqueous sodium chloride and then extracted with chloroform (3 × 200 ml). The combined chloroform extracts were washed with a saturated aqueous sodium chloride solution, dried over sodium sulfate, filtered, and concentrated to give a syrup (5.0 g). Investigation of the syrup by tlc (on silica gel using 1:1 benzene–ethyl acetate) showed three main products, corresponding to compounds **2**, **3**, and **4**, with R_f 0.65, 0.50, and 0.70, respectively. The syrup was applied to a silica gel column (700 g) and eluted with benzene–ethyl acetate (1:1 v/v). Progress was checked by tlc. About 70 l. of eluent was required. The fastest moving zone contained pure compound **4** (0.283 g) and the first part of the second zone (0.250 g) consisted of an almost equal mixture of compounds **4** and **2**. The main part of the second zone (0.673 g) consisted of pure **2**. The first part of the third zone consisted of an almost equal mixture (0.150 g) of compounds **2** and **3** and the principal portion of the third zone (0.747 g) contained pure compound **3**.

3-*C*-Carbamoyl-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (2).—The fraction containing pure **2** was recrystallized from hexane–benzene (2:1): mp 110–111.5°; $[\alpha]^{22}D$ −1.4° (c 4.7, chloroform); ir 1675 cm^{-1} (amide C=O); mass spectrum (70 eV) *m/e* 287 (calcd *m/e* 287); for τ^{CDCl_3} see Figure 1A (irradiation at τ 5.8 collapsed the doublet at 6.87 to a singlet and irradiation at τ 4.07 collapsed the doublet at 5.05 to a singlet; irradiation at τ 6.8 did not affect the doublet at τ 5.05).

Anal. Calcd for $C_{13}H_{21}NO_6$: C, 54.35; H, 7.37; N, 4.88. Found: C, 54.31; H, 7.50; N, 4.68.

3-*C*-Carbamoyl-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-gulofuranose (3).—The fraction containing pure compound **3** was recrystallized from carbon tetrachloride and from water: mp 152–154°; $[\alpha]^{22}D$ +19.0° (*c*, 1.8, chloroform); ir 1670 cm^{-1} (amide C=O); mass spectrum *m/e* 287 (calcd *m/e* 287); for τ^{CDCl_3} see Figure 1B (irradiation at τ 4.97 collapsed the signals at 6.96 to a doublet having J = 7 Hz and collapsed the doublet at τ 4.26 to a singlet; irradiation at τ 6.9 collapsed the signals at τ 4.97 to a doublet, J = 4 Hz).

Anal. Calcd for $C_{13}H_{21}NO_6$: C, 54.35; H, 7.37; N, 4.88. Found: C, 54.21; H, 7.24; N, 4.64.

3-Deoxy-3-*C*-(1-hydroxy-1-methylethyl)-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (4).—The first fraction containing 4 (homogeneous by tlc) was distilled at bp 110–120° (0.1 mm): $[\alpha]^{22}D$ −15.6° (*c* 1.8, chloroform); mass spectrum *m/e* 287 (M − CH_3) (calcd *m/e* 302); ir (0.005 and 0.001 *M* in CCl_4) 3700 (small peak), 3610 (strong peak), 3500 cm^{-1} (sh); τ^{CDCl_3} 4.28 (d, H-1, $J_{1,2}$ = 4.0 Hz), 5.45 (d, H-2, $J_{2,1}$ = 4.0 Hz), 5.56 (t, J = 7.5 Hz), 5.82 (q, H-4, $J_{4,3}$ = 3.0 Hz, $J_{4,5}$ = 7.5 Hz), 6.00 and 6.11 (m), 7.92 (d, H-3, $J_{3,4}$ = 3.0 Hz), 7.9–8.0 (OH peak, disappears on addition of D_2O), 8.40, 8.50, 8.58, 8.65, 8.67, 8.69 (6-Me) (irradiation of the doublet at τ 7.92 collapsed the quartet at 5.82 to a doublet; irradiation at τ 5.45 collapsed the doublet at 4.28 to a singlet).

Anal. Calcd for $C_{15}H_{26}O_6$: C, 59.58; H, 8.67. Found: C, 58.99; H, 8.88.

Reduction of 3-*C*-Carbamoyl-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-gulofuranose (3) to Yield 3-Deoxy-1,2:5,6-di-*O*-isopropylidene-3-*C*-trifluoroacetamidomethyl-α-D-gulofuranose (7).—The amide **3** (0.280 g) in anhydrous tetrahydrofuran (25 ml) was reduced with lithium aluminum hydride (0.370 g). After the reaction mixture was allowed to stand at room temperature for 1 hr, it was refluxed for 3 hr. Excess lithium aluminum hydride was then decomposed by dropwise addition of water. The solids were removed by filtration and washed with tetrahydrofuran. The combined filtrates were dried (Na_2SO_4) and evaporated under reduced pressure to yield a syrup which was treated with trifluoroacetic anhydride (1 ml) and pyridine (2 ml) at room temperature overnight. After evaporation of the acetylation mixture under reduced pressure, the syrup was partitioned between an equal volume mixture of dichloromethane–

(14) One referee has commented that, if the two –OH groups were H bonded together, one of the H atoms would still be free and would give rise to absorption at >3600 cm^{-1}. Furthermore, regardless of the stereochemistry at C-4, the –OH of the C-4 hydroxyisopropyl can bond in a six-membered ring to O-5. Thus, the C-3 hydroxyisopropyl group could be the free one (it is apparently free in compound **4**). Thus the complete structure of compound **6**, is not known.

water. The dichloromethane extract was dried over sodium sulfate, filtered, and evaporated to dryness. The residue was purified by chromatography on silica gel using benzene–ethyl acetate (1:1) as eluent. The main zone was crystallized from hexane: mp 131–132°; $[\alpha]^{22}D$ +8.8° (c 2.2, chloroform); τ^{CDCl_3} 4.28 (d, H-1, $J_{1,2}$ = 4.0 Hz), 5.5 (two d, H-2, $J_{1,2}$ = 4.0 Hz, $J_{2,3}$ = 1.5 Hz), 6.5 (2 H, CH_2N), 7.5 (m, H-3).

Anal. Calcd for $C_{15}H_{22}NO_6F_3$: C, 48.78; H, 5.97; N, 3.79. Found: C, 48.65; H, 6.09; N, 3.84.

Attempted Reduction of 3-*C*-Carbamoyl-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (2).—The amide 2 was subjected to lithium aluminum hydride reduction and the product was treated with trifluoroacetic anhydride and pyridine according to the same procedure as described above. Chromatographic (tlc) examination of the product showed a complex mixture of products which could not be separated. Pmr of the impure main fractions indicated that the sugar moiety had changed.

Photohydroxyalkylation of 3-Deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-erythro-hex-3-enose (1) to Yield Compounds 4 and 6.—A solution of 1 (4.0 g) in isopropyl alcohol (200 ml) and acetone (100 ml) was irradiated for 26 hr through a Pyrex filter. The product was worked up as described previously and then chromatographed on a silica gel comumn (1000 g) using benzene–ethyl acetate (1:3 to 2:1) as developer. The fastest moving zone 6 (0.500 g, 8%) was followed by a zone consisting of a mixture of compound 4 (1.59 g, 31%) and pinacol (1.0 g). The latter two compounds were separated by distillation at 0.1 mm and 100°. The pinacol was compared with an authentic sample of pinacol and shown to be identical (ir spectrum).

3-Deoxy-3,4-*C*-bis(1-hydroxy-1-methylethyl)-1,2:5,6-di-*O*-isopropylidene-α-D-gulofuranose (6).—Product 6 was recrystallized from benzene–hexane (1:9): mp 174–175° (crystal form changes at 147–149° from prisms to needles); $[\alpha]^{22}D$ +73° (c 1, chloroform); mass spectrum *m/e* 360 and 345 (M − CH_3) (calcd *m/e* 360); ir (0.005 and 0.001 *M* in CCl_4) 3623 (sharp intense peak due to free OH), 3458 cm^{-1} (intense broad peak); τ^{CDCl_3} 4.09 (d, H-1, $J_{1,2}$ = 4.5 Hz), 5.01 (two d, H-2, $J_{2,1}$ = 4.5 Hz, $J_{2,3}$ = 7.0 Hz), 5.62–6.1 (H-5 and H-6), 6.3–6.85 (broad OH peaks, disappear on addition of D_2O), 7.05 (d, H-3, $J_{3,2}$ = 7.0 Hz), 8.38, 8.46, and 8.50 (3-Me), 8.60 and 8.63 (4-Me), 8.86 (1-Me) (irradiation at τ 5.0 collapsed the doublets at 4.09 and 7.05 to singlets).

Anal. Calcd for $C_{18}H_{32}O_7$: C, 59.98; H, 8.95. Found: C, 59.68; H, 9.30.

Registry No.—1, 10368-85-1; 2, 34289-95-7; 3, 34289-96-8; 4, 34297-59-1; 6, 34289-97-9; 7, 34289 98-0.

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Nucleosides. XIII.[1] Synthesis and Interconversions of *C*-Methyl-Branched 1-(3-Amino-3-deoxy-β-D-hexopyranosyl)uracils. An Empirical Method for Configurational Assignments at the Branch Point by Nuclear Magnetic Resonance[2]

FRIEDER W. LICHTENTHALER* AND HORST ZINKE

Institut für Organische Chemie, Technische Hochschule Darmstadt, 61 Darmstadt, Germany

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C-Methyl-branched 3′-nitrohexosyl uracils of gluco, galacto, manno, and allo configuration (4–7) were prepared from uridine by treatment with metaperiodate and subsequent base-catalyzed cyclization with nitroethane. Hydrogenation afforded the title compounds 12–15 which were further characterized as the *N*-acetyl (20–22) and the fully acetylated derivatives (16–19). While coupling patterns of the ring protons readily provided configurational proof for the arrangement of the hydroxyl groups at C-2′ and C-4′, the stereochemistry at the branch point was established chemically by conversion of the *gluco-N*-acetate 20 into derivatives of manno (22) and galacto configuration (33) in a series of reactions which involved as decisive steps a displacement *via* oxazolines of mesyl functions, introduced at C-2′ and C-4′, respectively. In the gluco → manno conversion, both intermediates possible, the O^2,2′ cyclonucleoside 28 and the 2′,3′-oxazoline 29, were isolated and their structures established by chemical and spectroscopical means. Tertiary acetoxy and acetamido resonances at a *C*-methyl branch, as compared to their secondary counterparts, are shifted toward higher field by about 0.1 ppm in $CDCl_3$ or in DMSO-d_6. This provides a facile and surprisingly accurate means for determining configurations at the tertiary center of *C*-methyl-branched cyclitol and pyranose peracetates.

Branched-chain sugar nucleosides, which were virtually unknown prior to 1966, have since attained considerable chemical interest,[3-10] no doubt mainly evoked by the cytotoxic and antiviral activities of some compounds of this type.[3] The prevailing synthetic route[3-10] consisted in linking nucleobase and branched-chain sugar *via* standard procedures of nucleoside synthesis, an approach which is encumbered by the still limited availability of branched-chain sugars and by certain unsuccessful attempts[11] to convert them into nucleosides. As an alternate approach toward the synthesis of branched-chain sugar nucleosides, we exploited the applicability of the dialdehyde–nitroalkane

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(2) Taken in part from the Doctoral Dissertation of H.Z., Technische Hochschule Darmstadt, June 1969. (b) Financial support of this work by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie is gratefully acknowledged. (c) A preliminary account of this work has appeared: F. W. Lichtenthaler and H. Zinke, *Angew. Chem.*, **78**, 774 (1966); *Angew. Chem., Int. Ed. Engl.*, **5**, 737 (1966).

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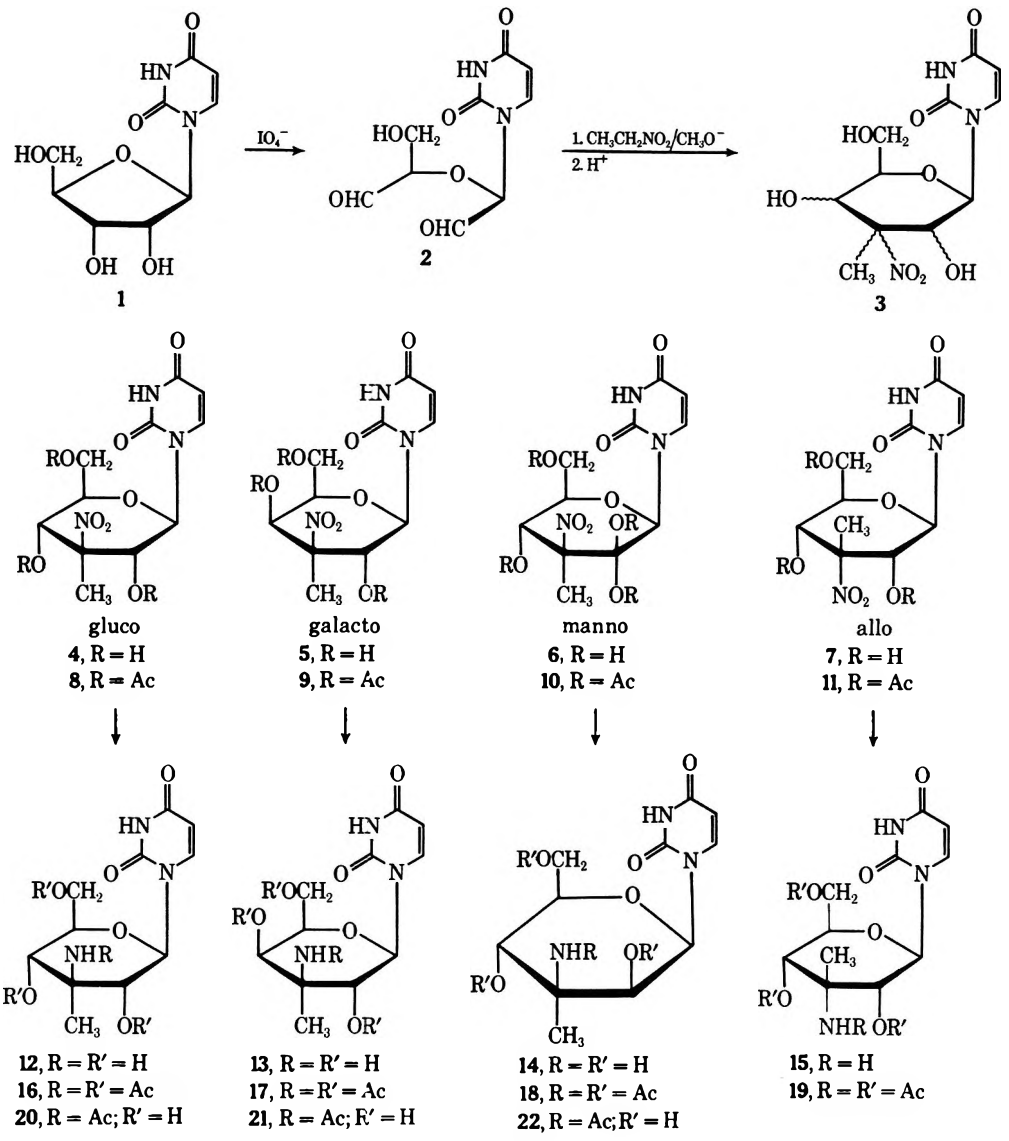


cyclization[12] to "nucleoside dialdehydes." If feasible, this would allow one to start from readily available ribo nucleosides and would simultaneously introduce a nitro (and thus amino) group and an alkyl branch into the sugar portion of the molecule. In this paper, we report the details[2c] of the reaction of 2-*O*-[(*R*)-formyl-(1-uracilyl)methyl]-(*R*)-glyceraldehyde (2) ("uridine dialdehyde") with nitroethane and of entailing studies which were required to unequivocally establish the configurations at the branch point of the products formed.

When 2, obtained by oxidation of uridine (1) with sodium metaperiodate, is allowed to react with nitroethane–sodium methoxide in methanol (6 hr, 25°) followed by deionization of the reaction mixture with an acidic resin, a crystalline mixture of cyclization products **3** is obtained in a yield of 80%.[13] Thin layer chromatography revealed the presence of one major and three minor compounds, together with traces of two other substances. By combination of fractional recrystallizations from several solvents and column chromatography separation was achieved. The main product, 1-(3-deoxy-3-*C*-methyl-3-nitro-β-D-glucopyranosyl)uracil (**4**), is obtained in 40% yield, whereas the minor components, having galacto (**5**), manno (**6**), and allo configuration (**7**), are isolated in yields of 5, 5, and 1%,[13] respectively. Though these yields are preparative, they rather concisely reflect the composition of the cyclization mixture **3**.

The nitro sugar nucleosides **4–7** were readily converted into 2′,4′,6′-tri-*O*-acetates **8–11** by acid-catalyzed acetylation; their hydrogenation over Raney nickel in aqueous methanol afforded the corresponding 1-(3-amino-3-deoxy-3-*C*-methyl-β-D-hexopyranosyl)uracils **12–15** in yields of 70–90%, which were further characterized by their tetraacetyl derivatives **16–19** and, except for the allo compound, by their *N*-acetyl compounds **20–22**.

The stereochemistry at C-2′ and C-4′ of each of these nucleosides was deduced from the coupling patterns of the ring protons which are best resolved in the nitrotri-*O*-acetates **8–11** and in the corresponding tetraacetyl derivatives of the amino compounds **16–19** (*cf.* Table I).

In the gluco series (**8** and **16**) large couplings of 9–10 Hz are exhibited by each of the doublets obtained for H-1′, H-2′, and H-4′, and clearly indicate their axial orientation. In the galacto derivatives **9** and **17**, H-4′ gives rise to a 2-Hz doublet as expected from a 4′e,5′a

(12) For a recent review, see F. W. Lichtenthaler, *Fortschr. Chem. Forsch.*, **14**, 556 (1970).

(13) Yields given are based on uridine (**1**).

TABLE 1

NMR ASSIGNMENTS[a,b]

Series	Compd	Solvent	Uracil NH	H-6[c]	H-5[c]	3'-NH	H-1' ($J_{1',2'}$)	H-2'	H-4' ($J_{4',5'}$)	OAc	NHAc	3'-CH_3
gluco	8	$CDCl_3$	0.51	2.56	*d*		*d*	*d*	*d*	7.93, (2), 8.02		8.11
	16	$CDCl_3$	0.50	2.49	4.21	4.51	3.75 (9)	4.12	3.99 (10)	7.90, 7.93, 7.99	8.15	8.53
		DMSO-d_6	−1.36	2.58	4.26	2.62	3.78 (9)	4.16	4.05 (10)	7.96, 8.00, 8.06	8.33	8.66
galacto	9	$CDCl_3$	0.49	2.64	*e*		*e*	*e*	4.41 (2)	7.86, 7.96 (2)		8.05
	17	$CDCl_3$	0.53	2.73	4.19	?	4.00 (9)	4.92	?	7.83, 7.91, 7.96	8.16	8.22
		DMSO-d_6	−1.26	2.63	4.35	2.59	4.15 (9)	4.98	4.49 (2)	7.89, 8.02, 8.05	8.29	8.32
manno	10	$CDCl_3$	0.47	2.75	4.36		4.09 (2)	4.18	4.40 (10)	7.87, 7.91, 8.02		8.05
	18	$CDCl_3$	0.56	2.73	4.40	4.05	3.81 (2)	4.17	5.00 (10)	7.82, 7.91, 7.96	8.19	8.25
		DMSO-d_6	−1.30	2.70	4.50	2.90	4.06 (2)	4.41	5.05 (10)	7.91, 7.98 (2)	8.29	8.31
allo	11	$CDCl_3$	0.99	2.62	4.18		3.30 (9)	4.77	4.65 (10)	7.90, 7.92, 7.96		8.40
	19	$CDCl_3$	0.07	2.59	4.20	3.85	3.73 (9)	5.01	4.98 (10)	7.90, 7.93 (2)	7.95	8.36
		DMSO-d_6	?	2.09	4.34	2.71	3.81 (9)	4.80	4.93 (10)	7.94, 7.99, 8.02	8.06	8.51

[a] Chemical shifts are expressed in parts per million (τ scale) from tetramethylsilane as an internal standard. [b] H-5' and C-6' CH_2, not listed in Table I, generally appear as complex 3 H multiplets in the region of τ 5.6–6.1. [c] Obtained as doublets with $J_{5,6}$ = 7–8 Hz. [d] 4 H multiplet at τ 4.1–4.4. [e] 3 H multiplet centered around τ 4.08.

arrangement, whereas the 1'a,2'e orientation in the manno compounds **10** and **18** gives rise to doublets with small couplings ($J_{1',2'}$ = 2 Hz) for H-1' and H-2'. The allo derivatives **11** and **19**, being C-3' epimers of the corresponding gluco compounds, expectedly exhibit the same coupling features as **8** and **16** ($J_{1',2'}$ = 9 and $J_{4',5'}$ = 10 Hz); yet there are characteristic differences in the chemical shifts of the ring protons at C-2' and C-4'. For example, when going from the gluco compound **16** to its C-3' epimer **19** of allo configuration, the chemical shift of H-1' remains virtually constant in the two solvents measured, whereas considerable upfield shifts are observed for H-2' (by 0.89 ppm in $CDCl_3$ and 0.64 ppm in DMSO-d_6) and H-4' (0.99 and 0.75 ppm, respectively). This effect must be entirely due to the different steric arrangement at C-3', *i.e.*, the anisotropy of the nitro group, which in an equatorial arrangement (gluco configuration) will exert a quite different shielding on vicinal axial protons than when oriented axially as in the allo derivatives.

The configurational assignments at C-2' and C-4' are supported by the chemical shifts of the acetoxy resonances (*cf.* Table I), which nicely comply with the empirical principles laid down in the "acetyl resonance rule" for cyclitols,[14] carbohydrates,[15] and hexopyranosyl nucleosides.[15] Thus, the gluco and allo derivatives show no acetyl resonances below τ 7.90, whereas in the galacto compounds **9** and **17** one of the *O*-acetyl signals appears at lower field (τ 7.83 and 7.86 in $CDCl_3$; τ 7.89 in DMSO-d_6) clearly falling into the range for axial acetoxy groups, in accord with all other polyacetyl galactopyranosyl nucleosides known.[16,17] Similarly, the manno derivatives show one acetoxy resonance at lower field, which can be attributed to the *O*-acetyl group at C-2'.

Configurational Assignments at the *C*-Methyl Branch by Chemical Means.—At present, all of the cyclic compounds bearing a *C*-methyl branch and an amino function at the same ring carbon atom, have been prepared *via* dialdehyde–nitroethane cyclization followed by hydrogenation.[19-22] It might be surmised from the steric course of the cyclizing additions of nitromethane onto dialdehydes[21] that, here too, the nitro group will preferentially adopt the equatorial orientation in the cyclization step rather than the less bulky methyl substituent. However, no rigorous chemical proof has been advanced concerning the configuration at the branch point. Since hydroxyl functions, when situated trans to an adjacent acetamido group, can be inverted stereospecifically *via* oxazoline intermediates, a procedure which has found extensive use in the field of aminocyclitols,[23] amino sugars,[24] and amino sugar nucleosides,[25,26] it seemed appropriate to utilize this method for firmly establishing the stereochemical relationships between the *C*-methyl branch and its vicinal OH functions.

Inversion at C-2'.—For the synthesis of the 2'-*O*-mesylate **24** required for displacement reactions at C-2', the *N*-acetate **20** was converted to the 4',6'-*O*-benzylidene derivative **23** by treatment with benzaldehyde–zinc chloride, in which the remaining hydroxyl group is subsequently mesylated to give **24**. When allowed to react with sodium acetate in refluxing 2-methoxyethanol–water (9:1) for 3 days, **24** yields an approximate 1:1 mixture of the 4',6'-*O*-benzylidene-*manno*-*N*-acetate (**26**) and its de-N-acetylated derivative **25** separable by fractional crystallization in moderate yields (15 and 23%, respectively). The structure and configuration of **25** were ascertained by N-acetylation to **26** with acetic anhydride in methanol. Compound **26** was proved to be of manno configuration by its non-

(14) F. W. Lichtenthaler and P. Emig, *Carbohyd. Res.*, **7**, 121 (1968).

(15) F. W. Lichtenthaler, G. Bambach, and P. Emig, *Chem. Ber.*, **102**, 994 (1969).

(16) F. W. Lichtenthaler, G. Bambach, and U. Scheidegger, *ibid.*, **102**, 986 (1969).

(17) Findings by Cushley, *et al.*,[18] that the axial C-4'-acetoxy resonance of 1-(3-acetamido-3-deoxy-2,4,6-tri-*O*-acetyl-β-D-galactopyranosyl)uracil and its 5,6-dihydrouracil derivative appear in the equatorial range (τ 8.03 and 8.11, respectively), have been shown[16] to be incorrect.

(18) R. J. Cushley, K. A. Watanabe, and J. J. Fox, *J. Amer. Chem. Soc.*, **89**, 394 (1967).

(19) H. H. Baer and G. V. Rao, *Justus Liebigs Ann. Chem.*, **686**, 210 (1965).

(20) F. W. Lichtenthaler and H. K. Yahya, *Carbohyd. Res.*, **5**, 485 (1967).

(21) F. W. Lichtenthaler, H. Leinert, and U. Scheidegger, *Chem. Ber.*, **101**, 1819 (1968).

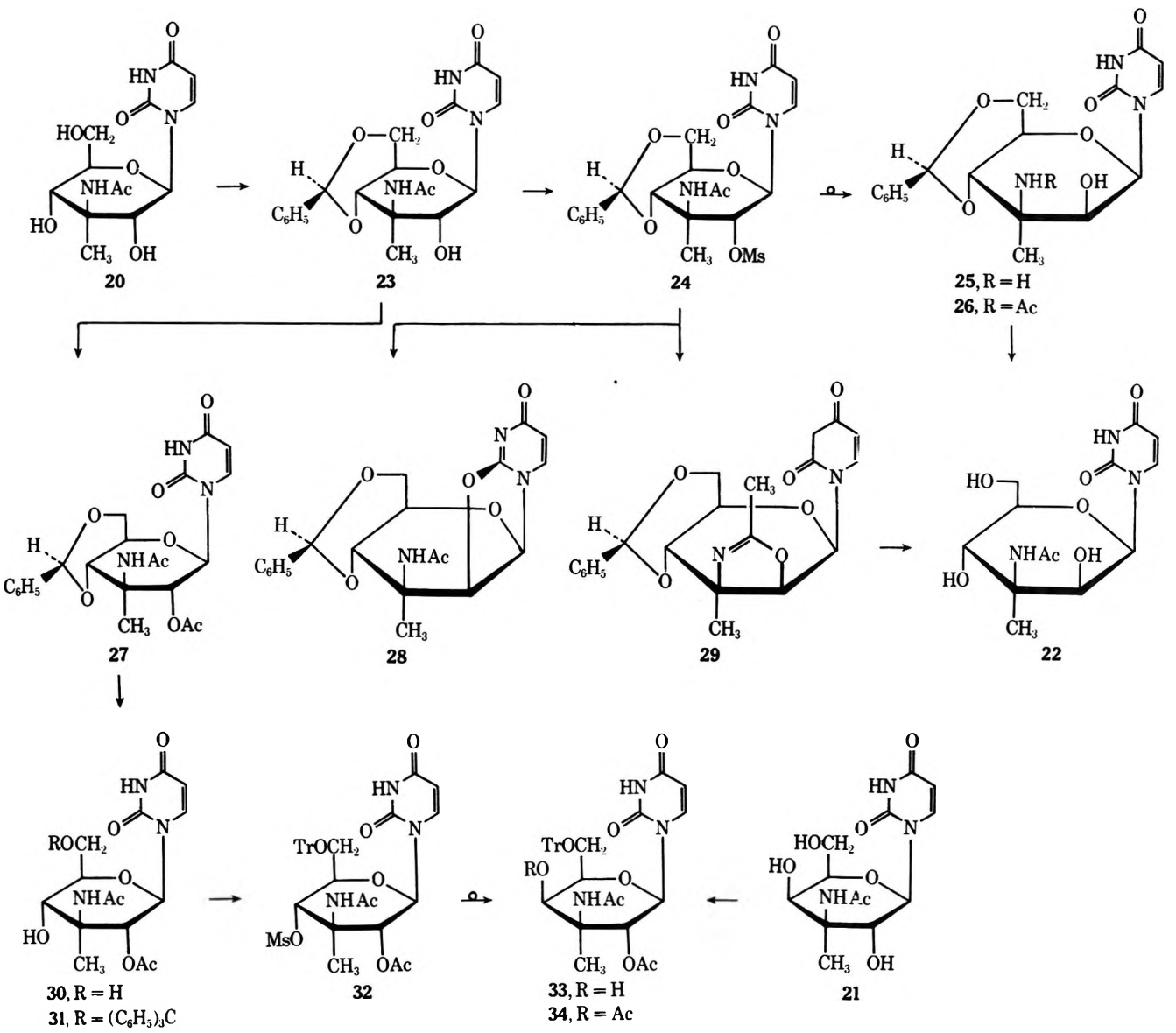
(22) S. W. Gunner, R. D. King, W. G. Overend, and N. R. Williams, *J. Chem. Soc.*, 1954 (1970).

(23) F. W. Lichtenthaler, *Chem. Ber.*, **94**, 3071 (1961); **96**, 2047 (1963).

(24) (a) B. R. Baker, *Methods Carbohyd. Chem.*, **2**, 444 (1963); A. C. Richardson and H. O. L. Fischer, *J. Amer. Chem. Soc.*, **83**, 1132 (1961). (b) D. H. Buss, L. Hough, and A. C. Richardson, *J. Chem. Soc.*, 5295 (1963); W. Meyer zu Reckendorf, *Chem. Ber.*, **97**, 325 (1964).

(25) B. R. Baker and R. E. Schaub, *J. Amer. Chem. Soc.*, **77**, 2396, 5900 (1955); F. J. McEvoy, M. J. Weiss, and B. R. Baker, *ibid.*, **82**, 205 (1960); F. W. Lichtenthaler, T. Nakagawa, and J. Yoshimura, *Chem. Ber.*, **100**, 1833 (1967); F. W. Lichtenthaler, P. Emig, and D. Bommer, *ibid.*, **102**, 971 (1969).

(26) K. A. Watanabe and J. J. Fox, *J. Org. Chem.*, **31**, 211 (1966).



identity with **23**, by its nmr data, exhibiting the anomeric proton at τ 4.36 as a 3-Hz doublet, and by its conversion on acidic de-O-benzylidenation to a product, identical in all respects with compound **22**, obtained from the manno derivative **14** on N-acetylation. However, since displacement of the sulfonyloxy group in **24** can occur either with participation of the nucleobase *via* the cyclonucleoside **28**, or with participation of the acetamido group through the oxazoline **29**, the origination of **25** and **26**, and hence the steric relationship between C-2′ and the branch point, cannot be deduced unequivocally from these results. Yet, when modifying the de-O-mesylation conditions to sodium ethoxide–95% 2-methoxyethanol (80 hr, 130°),[27] a mixture of four products is obtained, from which, aside from **25** and **26** (15 and 38%), both of the intermediates **28** and **29** can be isolated in yields of 11 and 15%, respectively.

The structure of the O²,2′ cyclonucleoside **28** was shown by its conversion, on hydrolysis, to the *manno-N*-acetate **26**, and by spectral data. The ultraviolet spectrum of **28** in methanol displayed two maxima (227 and 242 nm) as required for a cyclonucleoside of this type;[28] in the nmr spectrum of **28** in DMSO-d_6, which except for the 3′-*C*-methyl group is highly reminiscent of the one observed for the unbranched analog of **28**,[26] the anomeric proton and H-2′ are easily identified as 3-Hz doublets at τ 3.96 and 4.53, respectively, whereas the amide hydrogen is obtained as a singlet at τ 1.86.

The structure of **29**, which represents the first example of an oxazoline in the hexosyl nucleoside area, was based on the distinct absence of NH stretching and amide II absorption at 3300–3100 and 1540 cm^{-1}, respectively, on a uv maximum at 260 nm, convincingly corresponding to an intact uracil moiety, and on the nmr spectrum in DMSO-d_6, exhibiting the expected features, *e.g.*, a singlet for the uracil NH at τ −1.49. As **28**, the methyl oxazoline is converted to *manno-N*-acetate **26** on hydrolysis.

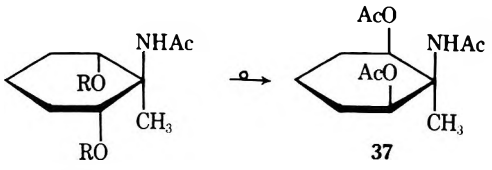
These results clearly demonstrate the trans arrangement of C-2′ OH and C-3′ NH_2 groups in **12** and its ensuing products and firmly establish that **14** and its derivatives are C-2′ epimers thereof.

(27) Under milder conditions, *i.e.*, hot ethanolic sodium ethoxide[24b] or sodium ethoxide in ethanol–pyridine,[26] only unchanged starting material was recovered.

(28) J. F. Codington, I. L. Doerr, and J. J. Fox, *J. Org. Chem.*, **30**, 476 (1965), and earlier papers referred to therein.

Inversion at C-4′.—The 4′-mesyloxy group in the gluco derivative **32**, obtained from **23** in four steps, using standard procedures for acetylation (to **27**), de-O-benzylidenation (to **30**), tritylation (to **31**), and mesylation, can only be displaced with participation of the vicinal acetamido group *via* an oxazoline derivative similar to **29**. The fact that on de-O-sulfonylation with sodium acetate in refluxing 2-methoxyethanol–water (9:1) only one uniform product is isolated in 90% yield, identical in all respects with **33** obtained from the *galacto-N*-acetate on tritylation, clearly establishes the stereochemical relationship between the C-4′ OH group and the amino function at the *C*-methyl branch.

Similarly, the configuration at the branch point of 1-acetamido-1-methylcyclohexane-2,6-diol (**35**), obtained on cyclization of glutaraldehyde with nitroethane, followed by hydrogenation and N-acetylation,[21] can be established chemically. On treatment of its di-*O*-mesylate **36** with sodium acetate in 90% 2-methoxyethanol (17 hr, 130°), both sulfonyloxy groups are displaced with inversion, to give, after acetylation, 1-acetamido-2*t*,6*t*-diacetoxy-1*c*-methylcyclohexane (**37**) in 60% yield, as evidenced by the nmr data (*cf.* Table III).



35, R = H
36, R = Ms
37

Assignment of Configuration at the *C*-Methyl Branch by Nmr.—At the tertiary center of branched-chain sugars and cyclanols, nmr analysis of coupling patterns will not provide any information concerning the stereochemistry at the branch point. In view of the "acetyl resonance rule" for secondary acetoxy and acetamido groups,[14,15] it is to be surmised that similar relationships between chemical shift and steric arrangement exist for C(CH$_3$)OAc and C(CH$_3$)NHAc groups on cyclohexane or pyranoside rings, where the influence of the *C*-methyl group, as compared with that of a hydrogen atom, must be taken into account.

On the basis of eight *C*-methyl-branched cyclanol acetates it was found that replacement of a ring hydrogen by a methyl group causes an upward shift of the acetoxy resonance by about 0.1 ppm.[29] These findings have been supported[30] and are further substantiated by the data presented in Table II, in which the substituent resonances of four *C*-methyl-branched cyclanol acetates, tri-*O*-acetyl-1*c*-methylcyclohexane-1,2*t*,6*t*-triol (**39**), and the hexa-*O*-acetyl derivatives of mytilitol (**41**), laminitol (**43**), and 2-*C*-methyl-*epi*-inositol (**45**), are compared with those of their unbranched counterparts. As expected,[29] no stereochemical information is provided by the chemical shift of the *C*-methyl protons, apparently being under the influence of too many shielding effects to show distinct differences between axial (*e.g.*, **43**) and equatorial orientation (*e.g.*, **45**). However, when comparing the acetoxy resonances of the compound pairs

(29) F. W. Lichtenthaler and P. Emig, *Tetrahedron Lett.*, 577 (1967).

(30) A. Hasegawa and H. Z. Sable, *J. Org. Chem.*, **33**, 1608 (1968); G. B. Howarth, W. A. Szarek, and J. K. N. Jones, *Carbohyd. Res.*, **7**, 284 (1968).

TABLE II

CHEMICAL SHIFTS OF SUBSTITUENT RESONANCES IN FULLY ACETYLATED CYCLANOLS, IN CDCl$_3$ AND DMSO-d_6.[a]

	τ (CDCl$_3$)[b]		τ (DMSO-d_6)[b]	
Compd	OAc	CCH$_3$	OAc	CCH$_3$
38	7.96 (2), 7.99		8.04 (2), 8.07	
39	7.97 (2), 8.12	8.58	8.02 (2), 8.19	8.67
40	8.02 (6)		8.10 (6)	
41	8.00 (2), 8.04 (3), 8.14	8.50	8.06 (2), 8.10 (3), 8.20	8.58
42	7.80, 8.00 (5)		7.85, 8.04 (3), 8.06 (2)	
43	7.85, 7.94 (2), 7.99, 8.03, 8.10	8.42	7.87, 7.99 (2), 8.04, 8.07, 8.17	8.53
44	7.85 (2), 7.98, 8.02 (3)		7.88 (2), 8.00 (2), 8.04, 8.07	
45	7.88, 7.93 (3), 8.02, 8.04	8.43	7.91, 7.98 (3), 8.05, 8.09	8.51

[a] The nmr data of the unbranched polyacetates are from ref 14; compound **39** was prepared *via* addition of methylmagnesium iodide to 1,3-diacetoxycyclohexan-2-one and subsequent acetylation (*cf.* Experimental Section); the other branched polyacetates, **41**, **43**, and **45**, were prepared according to known procedures (*cf.* T. Posternak, "The Cyclitols," Holden-Day, San Francisco, Calif., 1965, pp 252–259). [b] Ciphers in parantheses refer to the number of coincident COCH$_3$ signals.

38/39, **40/41**, and **42/43**, in each of the *C*-methyl-branched derivatives one of the signals appears at higher field (τ 8.10–8.14 in CDCl$_3$, 8.17–8.20 in DMSO-d_6), attributable to an equatorically oriented tertiary acetoxy group. As revealed from the substituent resonances obtained for **44** and **45** (*cf.* Table II), axial acetoxy groups at the *C*-methyl branch show a similar upfield shift by about 0.1 ppm (τ 7.85 → 7.93 and 7.88 → 7.98, respectively). On the basis of these results, the configuration at the branch point of cyclohexane or pyranoside derivatives can be deduced from the chemical shift of a C(CH$_3$)-acetoxy group, provided that substituents next to the branch do not exert any extraordinary shielding. Thus, while this method may safely be applied to compounds having acetoxy, acetamido, or methoxy groups next to the tertiary center, aryl substituents are apt to considerably change the position of a vicinal acetoxy signal, owing to the anisotropy of the aromatic ring. This effect has been demonstrated with *O*-benzyl,[31] *O*- and *N*-benzoyl,[31,32] *O*-tosyl, *O*-trityl, *N*-benzyloxycarbonyl, and *N*-(2,4-dinitrophenyl) groups;[33] hence it seems questionable to assign the allo configuration to compounds **46**[34] and **47**[35] on the basis of their acetoxy resonance at τ 7.89 and 8.03, respectively, without recourse to adequate supporting evidence.

For acetamido resonances, a similar upward shift of about 0.1 ppm is observed, when going from CHNHAc to C(CH$_3$)NHAc derivatives, as is demonstrated by the data summarized in Table III. The CCH$_3$ resonances of the branched compounds listed vary considerably within a rather broad range of τ 8.22–8.68

(31) T. D. Inch and H. G. Fletcher, Jr., *J. Org. Chem.*, **31**, 1810, 1815, 1821 (1966).

(32) T. D. Inch, J. R. Plimmer and H. G. Fletcher, Jr., *ibid.*, **31**, 1827 (1966).

(33) D. Horton, J. B. Hughes, J. S. Jewell, K. D. Philips, and W. N. Turner, *ibid.*, **32**, 1073 (1967).

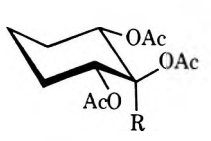
(34) B. R. Baker and D. H. Buss, *ibid.*, **31**, 217 (1966).

(35) G. B. Howarth, W. A. Szarek, and J. K. N. Jones, *Can. J. Chem.*, **46**, 3376 (1968).

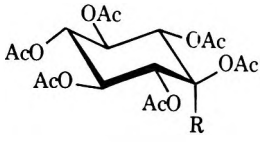
Table III
Chemical Shifts of Substituent Resonances of Fully Acetylated Amino Sugar Derivatives and Their C-Methyl-Branched Counterparts

Compd	τ (CDCl₃)[a] OAc	NHAc	CCH₃	τ (DMSO-d₆)[a] OAc	NHAc	CCH₃	Ref
48	7.95 (2)	8.07		8.07 (2)	8.26		14
49	7.97 (2)	8.17	8.68	8.04 (2)	8.34	8.86	21
50	7.94 (2), 7.97 (3)	8.08		8.10 (5)	8.29		14
51	7.99 (2), 8.04 (3)	8.20	8.57	8.03 (2), 8.07 (3)	8.37	8.75	20
52	7.91, 7.93	8.10					b
53	7.88 (2)	8.15	?				22
54	7.92 (2)	8.16	8.54				19
55	7.88, 7.92	8.17	8.45				19
56	7.92, 7.96 (2)	8.08		8.00, 8.01, 8.03	8.25		15
57	7.92 (3)	8.17	8.53				19
58	7.92, 7.95 (2)	8.09		8.00 (2), 8.04	8.26		15
59	7.88, 7.91 (2)	8.17	8.46				19
60	7.93, 7.95, 7.99	8.08		7.99, 8.02, 8.11	8.23		15
16	7.90, 7.93, 7.99	8.15	8.53	7.96, 8.00, 8.06	8.33	8.66	
61	7.81, 7.97, 8.00	8.08		7.84, 8.02, 8.09	8.23		16, 17
17	7.83, 7.91, 7.89	8.16	8.22	7.89, 8.02, 8.05	8.29	8.32	
62				7.92, 7.97 (2)	8.21		18
18	7.82, 7.91, 7.96	8.19	8.25	7.91, 7.98 (2)	8.29	8.31	
19	7.90, 7.93 (2)	7.95	8.36	7.94, 7.99, 8.02	8.06	8.51	
37	7.92 (2)	8.09	8.55	7.97 (2)	8.14	8.55	

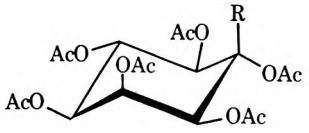
[a] Ciphers in parentheses refer to the number of coincident $COCH_3$ signals. [b] A. C. Richardson and K. A. McLauchlan, *J. Chem. Soc.*, 2499 (1962).



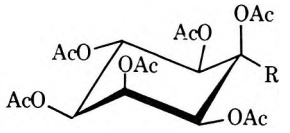
38, R = H
39, R = CH_3



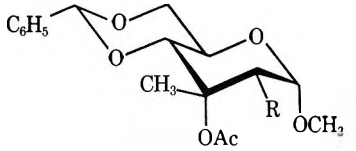
40, R = H
41, R = CH_3



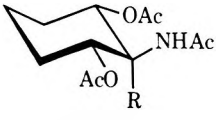
42, R = H
43, R = CH_3



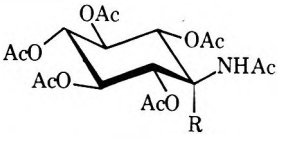
44, R = H
45, R = CH_3



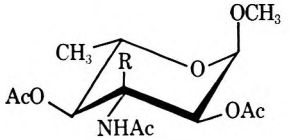
46, R = C_6H_5CONH—
47, R = $CH_3C_6H_4SO_3$—



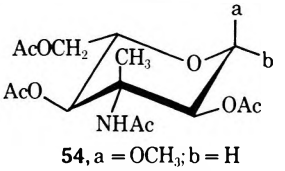
48, R = H
49, R = CH_3



50, R = H
51, R = CH_3

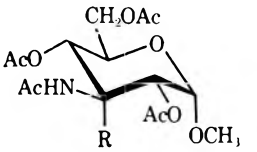


52, R = H
53, R = CH_3

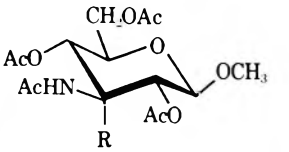


54, a = OCH_3; b = H
55, b = OCH_3; a = H

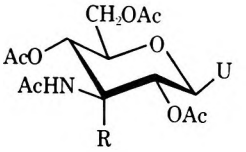
(CDCl₃) and 8.31–8.86 (DMSO-d_6), hence excluding any stereochemical deductions from their chemical shift differences. However, the tertiary acetamido resonances of the nucleosides **16–18**, and of compounds



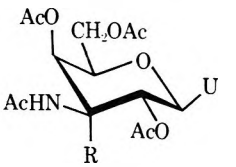
56, R = H
57, R = CH_3



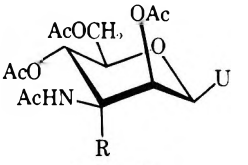
58, R = H
59, R = CH_3



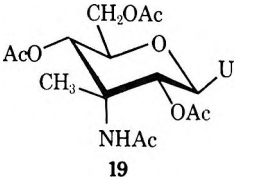
60, R = H
16, R = CH_3



61, R = H
17, R = CH_3



62, R = H
18, R = CH_3



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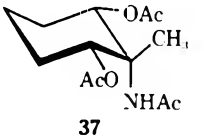
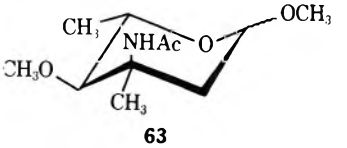


37



63

49, **51**, **53–55**, **57**, and **59**, which were similarly prepared *via* dialdehyde–nitroethane cyclizations,[19–22] appear within a very narrow range (τ 8.15–8.20 in $CDCl_3$, 8.29–8.37 in DMSO-d_6), clearly separated from the other acetyl resonances. This strongly indicates an identical steric orientation. When comparing these acetamido resonances with those of their equatorial CHNHAc counterparts (compounds **48**, **50**, **52**, **56**, **58**, and **60–62** in Table III), the expected upward shift of about 0.1 ppm is clearly revealed, suggesting an equa-

torial orientation in each case. Convincing support for this deduction is given by the fact that in four of these *C*-methyl-branched derivatives, namely **49** and **16–18**, the configuration at the tertiary center has been established by chemical means (*cf.* above).

Additional proof of these conclusions is obtained from the chemical shifts of the tertiary acetamido resonances in compounds **19** and **37**, of which the configuration of the latter has also been established chemically (*cf.* above). They appear at τ 7.95 and 8.09 ($CDCl_3$, *cf.* Table III) and τ 8.06 and 8.14 (DMSO-d_6), respectively, clearly indicating an axial orientation. On the basis of these results, it seems very likely that compound **63**, obtained on reduction and acetylation of evernitrose, a component of the everninomycin antibiotics B and D, has the L-ribo rather than the alternate L-xylo configuration owing to its acetamido resonance, in $CDCl_3$, at τ 8.05.[36]

Experimental Section

Thin layer chromatography (tlc) on Kieselgel PF_{254} (E. Merck AG, Darmstadt) was used to monitor the reactions and to ascertain the purity of the reaction products; developers employed (A) butyl acetate–acetic acid–water (55:16:5); (B) butyl acetate–acetic acid (100:1); (C) ethanol–concentrated ammonia (4:1); (D) ethyl acetate–ethanol–water (15:2:1). Dectection was by uv or in iodine vapor (free amines with ninhydrin).

Melting points were determined on a Bock Monoskop and were not corrected. Spectra were recorded on Perkin-Elmer 125 (ir), Perkin-Elmer 137 (uv), and Varian A-60A (nmr) instruments.

Nitroethane Cyclization of "Uridinedialdehyde" to Mixture 3.—To a magnetically stirred ice-cooled solution of 32.1 g (0.15 mol) of sodium metaperiodate in 450 ml of water was added 36.6 g (0.15 mol) of uridine (**1**) in small portions during 15 min. Stirring was continued for 6 hr at room temperature, and the solution was concentrated *in vacuo* at 35° to about 100 ml. Addition of methanol (300 ml) precipitated most of the sodium iodate formed; this was removed by filtration and washed with methanol (100 ml). The filtrate and washings were combined and evaporated to dryness under diminished pressure below 40°. The residue was dissolved in 200 ml of methanol, and a small amount of inorganic material was removed by filtration. The resulting solution of the dialdehyde **2** was diluted with 400 ml of methanol, and nitroethane (10.7 ml, 0.15 mol) was added, followed by dropwise addition, with vigorous stirring and ice-cooling, of 0.1 *M* sodium methoxide in methanol (100 ml). The mixture was allowed to warm to room temperature, and was kept for 24 hr. Following deionization of the solution with a strongly acidic ion-exchange resin (Merck) which was filtered off and washed with 600 ml of methanol, the filtrate and washings were combined and concentrated under diminished pressure at 35° to about 200 ml. The product, which separated after standing for 2 days at room temperature,[37] was filtered off and washed with a little methanol to give "fraction F_1" (14.6 g), representing an approximate 10:1 mixture of **4** and **5** (tlc in A). By concentrating the filtrate to about half of its original volume and subsequent standing, three further fractions (F_2, F_3, and F_4, together 11.5 g) were obtained, containing **4** and **5** in an approximate 1:1 ratio. The remaining mother liquor was taken to dryness *in vacuo*. The residue was dissolved in 200 ml of water, treated with charcoal, and set aside for 1–2 days to give fraction F_5 and, upon reducing the volume of the filtrate to about 100 ml, fraction F_6 (F_5 + F_6, 7.2 g), consisting mainly of **5** and **6** aside from traces of **4** and **7**. The mother liquor remaining (filtrate M) contained (tlc in A) the allo isomer **7** with **4**, **5**, and **6** as minor components. Total yield was 33.3 g (70%).

(36) A. K. Ganguly, O. Z. Sarre, and H. Reimann, *J. Amer. Chem. Soc.*, **90**, 7129 (1968).

(37) Crystallization of the various fractions of mixture **3** proceeds rather slowly, requiring 1–2 days in each case for completion. Tlc in solvent system A to follow the separation of the individual isomers is indispensable; the nitro nucleosides appear in the order allo (**7**), galacto (**5**), manno (**6**), and gluco (**4**), from the starting point.

1-(3-Deoxy-3-*C*-methyl-3-nitro-β-D-glucopyranosyl)uracil (4).[38]—Fraction F_1 (see above) was dissolved in methanol (45 ml/g) and the solution was evaporated *in vacuo* to about one-tenth of its initial volume. The crystals that separated after 2 days were collected (filtrate M_1) and recrystallized from methanol by the same procedure (filtrate M_2) to give 7.5 g of pure **4** (tlc in A). In similar fashion, the combined fractions F_2, F_3, and F_4 were recrystallized from methanol (filtrates M_3 and M_4, respectively), yielding another 7.1 g of **4**. From the combined mother liquors M_1–M_4, when concentrated to about 50 ml, a further crop of crystals was obtained to give, after three recrystallizations (filtrates M_6, M_7, and M_8), 4.2 g. Total yield of chromatographically pure **4** was 18.8 g (40%, based on uridine) as colorless prisms, mp 226–240° dec, $[\alpha]^{20}D$ +25.5° (*c* 1, water).

Anal. Calcd for $C_{11}H_{15}N_3O_8$: C, 41.64; H, 4.77; N, 13.25. Found: C, 41.61; H, 4.69; N, 13.25.

1-(3-Deoxy-3-*C*-methyl-3-nitro-β-D-galactopyranosyl)uracil (5).—The combined filtrates M_5–M_8 were concentrated to a volume of about 40 ml, and the crystals precipitating after standing for 2 days were collected (filtrate M_9) to give 1.7 g of **5**. An analogous work-up of filtrate M_{11} (see below) afforded another 0.6 g (filtrate M_{13}). Total yield was 2.3 g (5% based on **1**) of **5** as colorless needles, mp 232–235° (after drying at 50° and 0.1 mm for 6 hr[39]), $[\alpha]^{20}D$ +52° (*c* 1, MeOH).

Anal. Calcd for $C_{11}H_{15}N_3O_8$: C, 41.64; H, 4.77; N, 13.25. Found: C, 41.78; H, 5.09; N, 13.12.

1-(3-Deoxy-3-*C*-methyl-3-nitro-β-D-mannopyranosyl)uracil (6).—The crystal fractions F_5 and F_6 (7.2 g, see above) were dissolved in the minimum amount of hot water and kept for 2 days at room temperature. The precipitate was filtered off (filtrate M_{11}) and recrystallized from water (filtrate M_{12}) to give 2.61 g (5%, based on **1**) of **6** monohydrate as colorless rhombs, mp 186–190°, $[\alpha]^{20}D$ +121° (*c* 1, MeOH).

Anal. Calcd for $C_{11}H_{15}N_3O_8 \cdot H_2O$: C, 39.38; H, 5.11; N, 12.54. Found: C, 39.66; H, 5.23; N, 12.55.

1-(3-Deoxy-3-*C*-methyl-3-nitro-β-D-allopyranosyl)uracil (7).—The filtrates M, M_{10}, M_{12}, and M_{13}, containing **7** as the major component (tlc in A), were combined and taken to dryness *in vacuo*. The residue was subjected to a silica gel column (130 × 4 cm) and eluted with ethyl acetate–methanol–water (40:2:1). A distinct separation was achieved between the nitro nucleosides **4**, **5**, and **6**, eluted first, and the allo compound **7**. The fraction containing **7** was evaporated to dryness to give, after recrystallization from a small amount of methanol, 620 mg (1.2%, based on **1**) of **7** as colorless crystals, mp 225–227° dec, $[\alpha]^{20}D$ +44° (*c* 1, water).

Anal. Calcd for $C_{11}H_{15}N_3O_8$: C, 41.64; H, 4.77; N, 13.25. Found: C, 41.64; H, 4.95; N, 12.98.

1-(3-Deoxy-3-*C*-methyl-3-nitro-2,4,6-tri-*O*-acetyl-β-D-glucopyranosyl)uracil (8).—To 3.0 g (9.5 mmol) of **4**, in acetic anhydride (10 ml), was added, with cooling, 2 drops of concentrated H_2SO_4. After 4 hr at room temperature the mixture was stirred into ice–water and the precipitate was removed by filtration. Recrystallization from ethyl acetate afforded 2.6 g (62%) of **8** as prisms, mp 228°, $[\alpha]^{20}D$ −8° (*c* 1, $CHCl_3$).

Anal. Calcd for $C_{17}H_{21}N_3O_{11}$: C, 46.05; H, 4.77; N, 9.48. Found: C, 46.04; H, 5.10; N, 9.37.

1-(3-Deoxy-3-*C*-methyl-3-nitro-2,4,6-tri-*O*-acetyl-β-D-galactopyranosyl)uracil (9).—To 5 ml of acetic anhydride containing 2 drops of concentrated H_2SO_4 was added 600 mg of **5** and the mixture was stirred. After 4 hr the clear solution was poured into ice–water, which was subsequently extracted with chloroform (3 × 40 ml). The extracts were washed with $NaHCO_3$ solution, dried (Na_2SO_4), and evaporated to dryness. On trituration of the sirupy residue with cold benzene, **9** slowly crystallized to afford 513 mg (61%) of colorless, chromatographically (B) pure crystals, mp 107–110°, $[\alpha]^{20}D$ +24° (*c* 1, $CHCl_3$)

Anal. Calcd for $C_{17}H_{21}N_3O_{11}$: C, 46.05; H, 4.77; N, 9.48. Found: C, 46.03; H, 4.96; N, 9.39.

1-(3-Deoxy-3-*C*-methyl-3-nitro-2,4,6-tri-*O*-acetyl-β-D-mannopyranosyl)uracil (10).—Acetylation of **6** (400 mg, 1.2 mmol), in a manner identical with that described for **9**, afforded 340 mg (55%) of **10** as colorless needles, mp 106–109°, crystallizing with 1 mol of benzene, $[\alpha]^{20}D$ +124° (*c* 1, $CHCl_3$).

(38) A more simplified procedure, concentrating only on the isolation of **4**, has been described: F. W. Lichtenthaler and H. Zinke, *Syn. Proc. Nucleic Acid Chem.*, **1**, 366 (1968).

(39) Air-dried preparations of **5** contain varying amounts of methanol, melting considerably lower (~160°).

Anal. Calcd for $C_{17}H_{21}N_3O_{11}\cdot C_6H_6$: C, 52.95; H, 5.22; N, 8.06. Found: C, 52.94; H, 5.34; N, 8.14.

1-(3-Deoxy-3-*C*-methyl-3-nitro-2,4,6-tri-*O*-acetyl-β-D-allopyranosyl)uracil (11).—To a suspension of 150 mg (0.45 mmol) of **7** in acetic anhydride (4 ml) was added 5 drops of BF_3 etherate, resulting in a clear solution on stirring. After 2 days at room temperature, the reaction mixture was evaporated to dryness *in vacuo* (0.1 mm) and the residue was triturated with ice–water (20 ml). The crystals separating were collected and recrystallized from water–ethanol (10:1) to give 97 mg (49%) of **11** as colorless prisms, mp 203–204° dec, $[\alpha]^{20}D$ +12° (*c* 1, $CHCl_3$).

Anal. Calcd for $C_{17}H_{21}N_3O_{11}$: C, 46.05; H, 4.77; N, 9.48. Found: C, 46.14; H, 4.64; N, 9.36.

Catalytic Hydrogenation of the Nitrohexosyluracils.—The nitro compounds **4**, **5**, **6**, or **7** (5 mmol) were dissolved in a sufficient quantity of methanol–water (1:1) (*ca.* 25 ml/mmol), added to a prehydrogenated suspension of 1 ml of freshly prepared Raney nickel T4 catalyst[40] in 15 ml of water, and the hydrogenation was continued. After uptake of the calculated amount of H_2 (6–15 hr) the catalyst was filtered off and washed with hot methanol–water (1:1) and the combined filtrate and washings were evaporated to a small volume. For isolation of **12** and **14** the solution was kept overnight at room temperature to effect crystallization. To isolate **13** and **15**, the solution was evaporated to dryness and the residue was precipitated by addition of ether to an ethanolic solution. The compounds were obtained in chromatographically pure form (tlc in C).

1-(3-Amino-3-deoxy-3-*C*-methyl-β-D-glucopyranosyl)uracil (12).—Recrystallization from water afforded **12** as the monohydrate in 69% yield in the form of colorless crystals, mp 146–148°, $[\alpha]^{20}D$ +39° (*c* 1, water).

Anal. Calcd for $C_{11}H_{17}N_3O_6\cdot H_2O$: C, 43.29; H, 6.28; N, 13.77. Found: C, 43.22; H, 6.41; N, 13.75.

1-(3-Amino-3-deoxy-3-*C*-methyl-β-D-galactopyranosyl)uracil (13) was obtained as a solid, amorphous product, $[\alpha]^{20}D$ +63° (*c* 1, water), yield 92%.

1-(3-Amino-3-deoxy-3-*C*-methyl-β-D-mannopyranosyl)uracil (14) was obtained as colorless crystals, mp 154–155°, $[\alpha]^{20}D$ +93° (*c* 1, Me_2NCHO), yield 75%.

Anal. Calcd for $C_{11}H_{17}N_3O_6$: C, 45.99; H, 5.97; N, 14.63. Found: C, 45.73; H, 6.12; N, 14.47.

1-(3-Amino-3-deoxy-3-*C*-methyl-β-D-allopyranosyl)uracil (15) was obtained as a solid, amorphous product, $[\alpha]^{20}D$ +25° (*c* 1, MeOH).

N-Acetylation of the Aminohexosyluracils.—To a solution of 5 mmol of amine **12**, **13**, or **14** in methanol (150 ml) was added 2 ml of acetic anhydride. The mixture was kept at room temperature for 48 hr and subsequently evaporated to dryness *in vacuo* with repeated addition of ethanol. The residue was crystallized by trituration with ethanol to give a first crop of product, the second being obtained after concentration of the mother liquors. The compounds **10–22** are homogeneous by tlc in solvent system D.

1-(3-Acetamido-3-deoxy-3-*C*-methyl-β-D-glucopyranosyl)uracil (20) was obtained as prisms, mp 248°, $[\alpha]^{20}D$ +72° (*c* 1, water), yield 87%.

Anal. Calcd for $C_{13}H_{19}N_3O_7$: C, 47.41; H, 5.82; N, 12.76. Found: C, 47.14; H, 5.83; N, 12.72.

1-(3-Acetamido-3-deoxy-3-*C*-methyl-β-D-galactopyranosyl (21) was obtained as crystals, mp 213–125°, $[\alpha]^{20}D$ +104° (*c* 1, water) after recrystallization from ethanol, yield 52%.

Anal. Calcd for $C_{13}H_{19}N_3O_7$: C, 47.41; H, 5.82; N, 12.76. Found: C, 47.58; H, 6.05; N, 12.52.

1-(3-Acetamido-3-deoxy-3-*C*-methyl-β-D-mannopyranosyl)uracil (22).—Crystallization occurring rather sluggishly, the product was precipitated from an ethanolic solution by addition of ether to give an amorphous solid, $[\alpha]^{20}D$ +86° (*c* 1, water).

Anal. Calcd for $C_{13}H_{19}N_3O_7$: C, 47.41; H, 5.82; N, 12.76. Found: C, 47.41; H, 6.02; N, 12.65.

Peracetylation of Acetamidohexosyluracils.[41]—A solution of 1 mmol of the *N*-acetates **20**, **21**, or **22** in 5 ml of acetic anhydride containing 1 drop of concentrated H_2SO_4 was kept at room temperature for 24 hr followed by stirring the reaction mixture into ice–water. Extraction with chloroform (3 × 40 ml), washing of the extracts with $NaHCO_3$ solution and water, and subsequent evaporation to dryness yielded the tetraacetyl derivatives **16–18** as amorphous, chromatographically (tlc in C) pure products, which resisted crystallization from the usual organic solvents. For nmr data *cf.* Table I.

1-(3-Acetamido-3-deoxy-3-*C*-methyl-2,4,6-tri-*O*-acetyl-β-D-glucopyranosyl)uracil (16) was obtained in 38% yield, $[\alpha]^{20}D$ +21° (*c* 2, $CHCl_3$).

Anal. Calcd for $C_{19}H_{25}N_3O_{10}$: C, 50.11; H, 5.53; N, 9.23. Found: C, 49.97; H, 5.69; N, 9.20.

1-(3-Acetamido-3-deoxy-3-*C*-methyl-2,4,6-tri-*O*-acetyl-β-D-galactopyranosyl)uracil (17) was obtained in 63% yield, $[\alpha]^{20}D$ +93° (*c* 1, $CHCl_3$).

Anal. Calcd for $C_{19}H_{25}N_3O_{10}$: C, 50.11; H, 5.53; N, 9.23. Found: C, 50.07; H, 5.50; N, 8.99.

1-(3-Acetamido-3-deoxy-3-*C*-methyl-2,4,6-tri-*O*-acetyl-β-D-mannopyranosyl)uracil (18) was obtained in 60% yield, $[\alpha]^{20}D$ +41° (*c* 1, $CHCl_3$).

Anal. Calcd for $C_{19}H_{25}N_3O_{10}$: C, 50.11; H, 5.53; N, 9.23. Found: C, 49.92; H, 5.63; N, 9.01.

1-(3-Acetamido-3-deoxy-3-*C*-methyl-2,4,6-tri-*O*-acetyl-β-D-allopyranosyl)uracil (19).—A solution of 250 mg (0.8 mmol) of **15** in a mixture of 25 ml of methanol and 0.5 ml of acetic anhydride was allowed to stand at room temperature for 40 hr and evaporated to dryness *in vacuo*. The residue was dissolved in acetic anhydride (5 ml) containing 2 drops of concentrated H_2SO_4 and the mixture was kept for 24 hr at 60°. Addition of ice–water, extraction with chloroform (3 × 30 ml), and evaporation of the extracts afforded a brownish sirup, which was applied to a silica gel column (75 × 4 cm) and eluted with ethyl acetate–methanol–water (40:2:1). The fraction containing **19** was taken to dryness and reevaporated twice with ethanol to yield 143 mg (38%) of an amorphous product, $[\alpha]^{20}D$ +9° (*c* 1, $CHCl_3$).

Anal. Calcd for $C_{19}H_{25}N_3O_{10}$: C, 50.11; H, 5.53; N, 9.23. Found: C, 49.81; H, 5.65; N, 9.12.

1-(3-Acetamido-4,6-*O*-benzylidene-3-deoxy-3-*C*-methyl-β-D-glucopyranosyl)uracil (23).—Anhydrous zinc chloride (9.0 g) and 5.80 g (17.6 mmol) of **20** in 60 ml of benzaldehyde were stirred at ambient temperature for 36 hr, after which the excessive benzaldehyde was removed by evaporation *in vacuo* (0.1 mm). The resulting sirup was triturated twice with water (100 ml), followed by decantation to give a semisolid mass, which was extracted with petroleum ether (2 × 50 ml) and subsequently suspended in 30 ml of benzene. Filtration, washing with cold benzene and ether, and recrystallization from water yields 6.51 g (85%) of **23** as a monohydrate in the form of colorless prisms, mp 294–296° dec, $[\alpha]^{20}D$ −12° (*c* 1, Me_2CO).

Anal. Calcd for $C_{20}H_{23}N_3O_7\cdot H_2O$: C, 55.17; H, 5.79; N, 9.65. Found: C, 55.12; H, 5.82; N, 9.53.

1-(3-Acetamido-4,6-*O*-benzylidene-3-deoxy-2-*O*-mesyl-3-*C*-methyl-β-D-glucopyranosyl)uracil (24).—To a cooled solution (0°) of 4.3 g (9.9 mmol) of **23** monohydrate in pyridine (80 ml), 2 ml of methanesulfonyl chloride was added slowly, followed by storage at ambient temperature for 24 hr. After removal of a precipitate by filtration, the mixture is taken to dryness *in vacuo* (0.1 mm). The crystals appearing on trituration of the residue with water were collected and recrystallized successively from methanol–water (1:1) and water to yield 3.1 g (60%) of **24** monohydrate as colorless needles, mp 179°, $[\alpha]^{20}D$ +13° (*c* 1, MeOH).

Anal. Calcd for $C_{21}H_{25}N_3O_9S\cdot H_2O$: C, 49.12; H, 5.30; N, 8.18. Found: C, 49.13; H, 5.31; N, 8.18.

1-(3-Amino-4,6-*O*-benzylidene-3-deoxy-3-*C*-methyl-β-D-mannopyranosyl)uracil (25) and Its *N*-acetate (26) by De-*O*-mesylation of 24.—A mixture of sodium acetate (2.5 g), **24** monohydrate (3.0 g, 5.9 mmol), and 20 ml of β-methoxyethanol–water (9:1) was refluxed (140° bath temperature) for 70 hr and evaporated to dryness *in vacuo* (0.1 mm). The residue was triturated with water to afford 2.3 g of an approximate 1:1 mixture of **25** and **26** (tlc in solvent system D). Two recrystallizations from methanol–water (1:1) (filtrates M_1 and M_2) and one from ethanol–water (1:1) yielded 360 mg (15%) of chromatographically pure (tlc in D) **26** as crystals, mp 268–272° dec, $[\alpha]^{20}D$ +17° (*c* 1, MeOH).

Anal. Calcd for $C_{20}H_{23}N_3O_7$: C, 57.55; H, 5.55; N, 10.07. Found: C, 57.36; H, 5.46; N, 10.08.

(40) S. Nishimura, *Bull. Chem. Soc. Jap.*, **32**, 61 (1959).

(41) Attempted peracetylation of the free aminohexosyluracils (**16–19**) with acetic anhydride in the presence of pyridine or acidic catalysts (BF_3, H_2SO_4) yields mixtures of the peracetate and two or three other products (tlc in C), seemingly resulting from incomplete acetylation under these conditions.

The mother liquors M_1 and M_2 were evaporated to a yellowish residue, which was dissolved in a little methanol, applied to a silica gel column, and eluted with 90:2:1 ethyl acetate–methanol–water. After elution of **26** and fractions consisting of mixtures of **25** and **26**, the final eluate contained only **25**. Evaporation gave 510 mg (23%) of **25** as colorless rhombs, mp 249–253° dec, $[\alpha]^{20}D$ +29° (*c* 1, MeOH) and +35° (*c* 1, Me_2NCHO).

Anal. Calcd for $C_{18}H_{21}N_3O_6$: C, 57.59; H, 5.64; N, 11.20. Found: C, 57.34; H, 5.64; N, 10.99.

De-*O*-mesylation of 24 in Sodium Ethoxide–2-Methoxyethanol.—To 1.22 g (2.4 mmol) of mesylate **24** in 2-methoxyethanol (20 ml) was added 2.45 ml (1.02 molar equiv) of 1 *N* sodium ethoxide in ethanol and the mixture was refluxed (140° bath temperature). As evidenced by tlc (solvent system D), 80 hr are required for complete reaction, the mixture then consisting of four components, the anhydro nucleoside **28** (R_f in D 0.15), the amine **25** (0.30), the *N*-acetate **26** (0.47), and the oxazoline **29** (0.62). After evaporation to dryness *in vacuo* at 0.1 mm, the residue was subjected to chromatography on silica gel (75 × 2.5 cm column) with ethyl acetate–methanol–water (90:2:1). Elution occurred in the order **29**, **26**, **25**, and **28** as monitored by a uv recording instrument. The appropriate fractions were then evaporated to afford compounds **25**, **26**, **29**, and **28**.

A. Amino nucleoside **25**, yield 281 mg, had melting point, $[\alpha]D$, and ir spectrum identical with those of the product obtained by sodium acetate evoked de-*O*-mesylation.

B. **3-Acetamido nucleoside 26**, yield 150 mg (15%), was identical (melting point, $[\alpha]D$, ir) with the compound described above. Treatment of **25** with acetic anhydride in methanol under conditions used for N-acetylation of the aminohexosyluracils afforded **26** in yields of 75–80%.

C. **1-[4,6-*O*-Benzylidene-2,3-dideoxy-3,2-(2-methyl-1-oxa-3-azaprop-2-eno)-β-D-mannopyranosyl]uracil (29).**—After recrystallization from methanol, 140 mg (15%) of colorless rhombs was obtained: mp 310–320°; $[\alpha]^{20}D$ −51° (*c* 1, Me_2NCHO); λ_{max}^{MeOH} 256 mμ; nmr (DMSO-d_6) τ −1.49 (s, 1, uracil NH), 2.36 and 4.31 (two d, 1, J = 8 Hz, uracil H-6 and H-5), 3.81 (d, 1, $J_{1',2'}$ = 3 Hz, H-1'), 5.80 (d, 1, J = 3 Hz, H-2'), 8.06 (s, 3, oxazoline CH_3), 8.57 (s, 3,3'-CH_3).

Anal. Calcd for $C_{20}H_{21}N_3O_6$: C, 60.14; H, 5.30; N, 10.52. Found: C, 60.13; H, 5.23; N, 10.55.

Hydrolysis of **29** by refluxing with sodium acetate in 9:1 2-methoxyethanol–water for 16 hr, evaporation to dryness, and purification of the residue by chromatography on silca gel with ethyl acetate–methanol–water (40:2:1) afforded the *N*-acetate **26**, mp 268–270° dec, in 56% yield.

D. **O^2,2'-Anhydro-1-(3-acetamido-4,6-*O*-benzylidene-3-deoxy-3-*C*-methyl-β-D-mannopyranosyl)uracil (28).**—Recrystallization from methanol afforded 103 mg (11%) of colorless crystals: mp 330° dec; $[\alpha]^{20}D$ −15° (*c* 1, MeOH); λ_{max}^{MeOH} 227 nm (ε 9900) and 242 (8400); ir (KBr) 3300 (NH), 1640 (amide I), 1535 cm^{-1} (amide II); nmr (DMSO-d_6) τ 1.86 (s, 1,3'-NH), 2.13 and 4.13 (two d, 1, J = 8 Hz, H-6 and H-5), 2.56 (s, 5, C_6H_5), 3.96 (d, 1, J = 3 Hz, H-1'), 4.37 (s, 1, C_6H_5CH), 4.53 (d, 1, J = 3 Hz, H-2'), 5.76 (m, 1, H-4'), 8.10 (s, 3, $NHCOCH_3$), 8.38 (s, 3, 3'-CH_3).

Anal. Calcd for $C_{20}H_{21}N_3O_6$: C, 60.14; H, 5.30; N, 10.52. Found: C, 60.08; H, 4.94; N, 10.37.

Refluxing a mixture of **28** (30 mg) with sodium acetate in 9:1 methoxyethanol–water for 16 hr, followed by evaporation and purification on a silica gel column with ethyl acetate–methanol–water (40:2:1), gave the *N*-acetate **26** in 64% yield.

De-*O*-benzylidenation of 26.—A solution of 270 mg of **26** in 10 ml of acetic acid–water (1:1) was kept at 80° for 3 hr, followed by extraction with light petroleum ether (3 × 20 ml) to remove the benzaldehyde formed. The aqueous phase was evaporated to dryness and the residue, after three reevaporations from ethanol, was dissolved in a little ethanol. Addition of ether affords 170 mg (80%) of **22** as an amorphous solid, identical in R_f (tlc in D), $[\alpha]D$, and ir spectrum with the product obtained by N-acetylation of amino nucleoside **14**.

1-(3-Acetamido-2-*O*-acetyl-4,6-*O*-benzylidene-3-deoxy-3-*C*-methyl-β-D-glucopyranosyl)uracil (27).—A mixture of 1.50 g (3.5 mmol) of **23** monohydrate and 4 ml of acetic anhydride in pyridine (20 ml) was stored overnight at room temperature and subsequently evaporated to dryness. Trituration of the residue with ice–water afforded a crystalline solid which was recrystallized twice from methanol–water (1:1) to give 820 mg (52%) of **27**: mp 174–176°; $[\alpha]^{20}D$ 15° (*c* 1, $CHCl_3$); nmr (DMSO-d_6) τ 2.46 (s, 1, 3'-NH), 2.52 and 4.27 (d, 1, $J_{5,6}$ = 8 Hz, H-6 and H-5), 2.60 (s, 5, C_6H_5), 3.98 (d, 1, $J_{1',2'}$ = 9 Hz, H-1'), 4.11 (d, 1, J = 9 Hz, H-2'), 4.41 (s, 1, ArCH), 5.06 (d, 1, $J_{3',4'}$ = 9 Hz, H-4'), 5, 6–6.3 (m, 3, H-5' and C-6' CH_2), 8.03 and 8.23 (s, 3, 2'-OAc and 3'-NHAc), 8.61 (s, 3,3'-CH_3).

Anal. Calcd for $C_{22}H_{25}N_3O_8$: C, 57.51; H, 5.48; N, 9.15. Found: C, 57.34; H, 5.66; N, 9.15.

1-(3-Acetamido-2-*O*-acetyl-3-deoxy-3-*C*-methyl-β-D-glucopyranosyl)uracil (30).—A solution of 99 mg (2 mmol) of **27** in 1:1 acetic acid–water (10 ml) was kept at 80° for 3 hr, and subsequently extracted with light petroleum ether (3 × 25 ml) to remove the benzaldehyde formed. The aqueous layer was evaporated to dryness to give a residue, which crystallized on trituration with ethanol to give 460 mg of **30**. A further crop (120 mg) was obtained by evaporation of the mother liquor, followed by recrystallization from ethanol. Total yield was 580 mg (80%) of **30**, mp 232–234° after sintering around 170°, $[\alpha]^{20}D$ +103° (*c* 1, MeOH).

Anal. Calcd for $C_{15}H_{21}N_3O_8$: C, 48.51; H, 5.70; N, 11.32. Found: C, 48.48; H 5.92; N, 11.19.

1-(3-Acetamido-2-*O*-acetyl-3-deoxy-3-*C*-methyl-6-*O*-trityl-β-D-glucopyranosyl)uracil (31).—Triphenylchloromethane (2.3 g, 8.3 mmol) was added to 440 mg (1.2 mmol) of **30** in pyridine (10 ml) and kept at ambient temperature for 5 days. After removal of a precipitate by filtration, the mixture was evaporated to dryness and repeatedly reevaporated from dioxane. The residue was applied to a silica gel column (2.5 × 75 cm) and first eluted with ethyl acetate to remove excessive trityl chloride, subsequently with ethyl acetate–methanol–water (90:2:1). Evaporation of the appropriate fraction and recrystallization of the residue from 2:1 methanol–water afforded 254 mg (35%) of **31** as colorless crystals, mp 244–247°, $[\alpha]^{20}D$ +52° (*c* 1, MeOH),

Anal. Calcd for $C_{34}H_{35}N_3O_8$: C, 66.34; H, 5.75; N, 6.85. Found: C, 66.44; H, 5.83; N, 6.81.

1-(3-Acetamido-2-*O*-acetyl-3-deoxy-4-*O*-mesyl-3-*C*-methyl-6-*O*-trityl-β-D-glucopyranosyl)uracil (32).—The trityl derivative **31** (200 mg, 0.3 mmol) was suspended in pyridine (5 ml), and with cooling (0°) and stirring 0.25 ml of methanesulfonyl chloride was added. The mixture, after being kept for 3 days in the refrigerator, was evaporated to dryness *in vacuo* (1 mm), followed by trituration of the residue with ice–water, filtration, and purification by chromatography on silica gel with ethyl acetate–methanol–water (40:1:1). After evaporation of the appropriate fraction, 201 mg (89%) of **32** was obtained as a chromatographically uniform (tlc in D), amorphous product: $[\alpha]^{20}D$ +64° (*c* 1, MeOH); nmr ($CDCl_3$) τ 2.37 and 4.16 (d, 1, $J_{5,6}$ = 8 Hz, H-6 and H-5), 2.7 (m, 15, 3 C_6H_5), 3.52 (d, 1, $J_{1',2'}$ = 9.5 Hz, H-1'), 4.05 (d, 1, $J_{3',4'}$ = 10 Hz, H-4'), 4.12 (d, 1, J = 9.5 Hz, H-2'), 4.70 (s, 1,3'-NH), 6.2–6.8 (m, 3, H-5' and C-6' CH_2), 7.50 (s, 3, 4'-OMs), 7.99 and 8.07 (s, 2, 2'-OAc and 3'-NHAc), 8.60 (s, 3, 3'-CH_3).

Anal. Calcd for $C_{35}H_{37}N_3O_{10}S$: C, 60.77; H, 5.39; N, 6.07. Found: C, 60.51; H, 5.40; N, 5.91.

1-(3-Acetamido-3-deoxy-3-*C*-methyl-6-*O*-trityl-β-D-galactopyranosyl)uracil (33). A. **Tritylation of *galacto*-*N*-Acetate 21.**—A mixture of 560 mg (1.7 mmol) of **21** and 2.0 g (6.2 mmol) of triphenylchloromethane in pyridine are stored overnight at ambient temperature, followed by evaporation to dryness, trituration with ice–water (60 ml), filtration, and purification of the solid material by chromatography on silica gel in a manner identical with that described for **31**. Recrystallization from methanol gave 710 mg (73%) of **33** as colorless crystals, mp 223–225°, $[\alpha]^{20}D$ +1° (*c* 1, MeOH).

Anal. Calcd for $C_{32}H_{33}N_3O_7$: C, 67.23; H, 5.82; N, 7.35. Found: C, 67.09; H, 5.86; N, 7.34.

B. **De-*O*-mesylation of 32 with Subsequent De-*O*-acetylation.**—A mixture of sodium acetate (80 mg), **32** (132 mg, 0.19 mmol), and 9:1 2-methoxyethanol–water (15 ml) was refluxed for 20 hr and subsequently evaporated to dryness. The residue was purified by chromatography on silica gel with ethyl acetate–methanol–water (20:2:1). Evaporation of the appropriate fraction and recrystallization from methanol yielded 48 mg (43%) of colorless crystals, identical in melting point, $[\alpha]D$, tlc in solvent D, and ir spectrum with **33**, described under A.

1-(3-Acetamido-3-deoxy-2,4-di-*O*-acetyl-3-*C*-methyl-6-*O*-trityl-β-D-galactopyranosyl)uracil (34).—A solution of 295 mg of **33** and 0.5 ml of acetic anhydride in pyridine (8 ml) was kept at ambient temperature for 2 days and subsequently evaporated to dryness. Trituration of the residue with ice–water induced

crystallization to give, after recrystallization from methanol, 280 mg (84%) of **34**: mp 188–190°; $[\alpha]^{20}D$ −9°(*c* 1, MeOH); nmr ($CDCl_3$) τ 4.01 (d, 1, $J_{1',2'}$ = 9.5 Hz, H-1'), 7.93 and 8.04 (s, 3,2'- and 4'-OAc), 8.18 (s, 3, NHAc), 8.27 (s, 3,3'-CH_3).

Anal. Calcd for $C_{36}H_{37}N_3O_9$: C, 65.94; H, 5.69; N, 6.41. Found: C, 65.84; H, 5.49; N, 6.48.

***C*-Methyl-Branched Cyclanols. 1*r*-Methylcyclohexane-1,2*c*,6*c*-triol.**—To an ethereal solution of methylmagnesium iodide, prepared from 3.4 g of magnesium and methyl iodide (11.4 ml) in ether (80 ml), was added a solution of 4.3 g of 1,3-diacetoxycyclohexan-2-one[42] in chloroform (140 ml). The mixture was refluxed for 30 min and subsequently stirred into an excess of 2 *N* H_2SO_4. After evaporation of the organic solvents and addition of the calculated amount of silver carbonate, the mixture was neutralized with 1 *N* sodium hydroxide (pH 7), filtered to remove the silver iodide formed, and evaporated to dryness. The residue was extracted with ether overnight, to give, after evaporation and recrystallization from ethyl acetate, 900 mg (31%) of a product melting at 122–124°.

Anal. Calcd for $C_7H_{14}O_3$: C, 57.51; H, 9.65. Found: C, 57.43; H, 9.68.

Tri-*O*-acetyl-1*r*-methylcyclohexane-1,2*c*,6*c*-triol (39).—To a mixture of 5 ml of acetic anhydride and 3 drops of concentrated H_2SO_4 was added 300 mg of 1*r*-methylcyclohexane-1,2*c*,6*c*-triol. After 4 hr at ambient temperature, the solution was stirred into ice–water, which was repeatedly extracted with chloroform. The extracts were washed with $NaHCO_3$ solution, dried (Na_2SO_4), and evaporated to dryness. Recrystallization of the residue from ethyl acetate afforded 240 mg (45%) of **39** as colorless prisms, mp 102–103°; for nmr *cf.* Table II.

Anal. Calcd for $C_{13}H_{20}O_6$: C, 57.34; H, 7.40. Found: C, 57.22; H, 7.30.

1-Acetamido-2*c*,6*c*-dimethanesulfonyloxy-1*r*-methylcyclohexane (36).—To a cooled solution of 22.2 g (0.12 mol) of the *N*-acetate **35**[21] in pyridine (300 ml) was added gradually 40 ml (0.52 mol) of methanesulfonyl chloride with stirring. The mixture was stored at 0° for 20 hr, then concentrated to a crystalline solid *in vacuo* (finally 0.1 mm), and triturated with ice–water. The product was filtered off, thoroughly washed with acetone–methanol (2:1), and recrystallized from water–methanol (10:1) with the addition of activated carbon, to give 34.0 g (81%) of **36** as colorless crystals: mp 147°; nmr (DMSO-d_6) τ 2.30 (s, 1, NH), 4.52 (q, 2, $J_{a,a}$ = 10 and $J_{a,e}$ = 5 Hz, H-2 and H-6), 6.92 (s, 6, 2- and 6-OMs), 8.18 (s, 3, NHAc), 8.87 (s, 3, 1-CH_3).

Anal. Calcd for $C_{11}H_{21}NO_7S_2$: C, 38.47; H, 6.16; N, 4.08. Found: C, 38.35; H, 6.13; N, 4.05.

1-Acetamido-2*t*,6*t*-diacetoxy-1*r*-methylcyclohexane (37).—The dimesylate **36** (3.0 g) was refluxed for 17 hr with sodium acetate (3.6 g) in 150 ml of 2-methoxyethanol–water (9:1), and then concentrated. The resulting residue was extracted several times with hot acetone and the combined extracts were then evaporated to dryness to give a pale yellow sirup, which is acetylated by treatment with acetic anhydride (5 ml) and pyridine (30 ml) at room temperature overnight. The mixture was concentrated to a semicrystalline solid, which, after trituration with water, was filtered off and recrystallized twice from water to yield 1.42 g (60%) of **37** as colorless crystals: mp 156–158°; nmr ($CDCl_3$) τ 4.13 (s, 1, NH), 4.50 (m, 2, H-2 and H-6); nmr (DMSO-d_6) 2.67 (s, 1, NH), 4.70 (m, 2, H-2 and H-6); for other data *cf.* Table III.

Anal. Calcd for $C_{13}H_{21}NO_5$: C, 57.55; H, 7.80; N, 5.16. Found: C, 57.50; H, 7.71; N, 5.17.

Registry No.—**4**, 13184-57-1; **5**, 13184-60-6; **6**, 13184-59-3; **7**, 34280-68-7; **8**, 13184-58-2; **9**, 13184-65-1; **10**, 13184-64-0; **11**, 34280-72-3; **12**, 13184-61-7; **13**, 34280-74-5; **14**, 34280-75-6; **15**, 34280-76-7; **16**, 13184-63-9; **17**, 34280-78-9; **18**, 34297-61-5; **19**, 34280-79-0; **20**, 34297-62-6; **21**, 34280-80-3; **22**, 34280-81-4; **23**, 34280-82-5; **24**, 34280-83-6; **25**, 34280-84-7; **26**, 34280-85-8; **27**, 34280-86-9; **28**, 34280-87-0; **29**, 34280-88-1; **30**, 34280-89-2; **31**, 34297-63-7; **32**, 34280-90-5; **33**, 34280-91-6; **34**, 34280-92-7; **36**, 34280-93-8; **37**, 34280-94-9; **39**, 34280-95-0; 1*r*-methylcyclohexane-1,2*c*,6*c*-triol, 34280-96-1.

(42) G. W. Cavill and D. H. Solomon, *J. Chem. Soc.*, 4426 (1955).

C → O Migration of an Ethoxycarbonyl Group[1,2]

Frieder W. Lichtenthaler* and Gerd Bambach

Institut für Organische Chemie, Technische Hochschule Darmstadt, 61 Darmstadt, Germany

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The first example of a base-catalyzed C → O ethoxycarbonyl shift is described, occurring during the reaction of dialdehyde **1** (obtained from methyl α-D-glucopyranoside by periodation) with ethyl nitroacetate in the presence of base. The reaction products were proved to be methyl 3-deoxy-6-*O*-ethoxycarbonyl-3-nitro-α-D-hexosides of gluco (**8**) and manno configuration by preparation of a number of derivatives **9**–**12** by hydrolysis of the ethoxycarbonyl group in **9** and **12** to give known glucosides and by nmr and mass spectral data. Mechanistic aspects of this C → O migration are discussed.

While the occurrence of C → C migrations of alkoxycarbonyl groups is exceedingly well documented in the literature,[3] only one example each of an N → O[4] and of an O → O alkoxycarbonyl shift[5] has been disclosed. We now wish to report on yet another type, namely, on the first example of a C → O migration of an ethoxycarbonyl group. This rearrangement took place in a product formed from reaction of ethyl nitroacetate with a 1,5-dialdehyde.

The reaction of 2-*O*-(*S*-methoxyformyl)methyl-(*R*)-glyceraldehyde[6] (readily accessible from methyl α-D-glucoside by periodate oxidation) with ethyl nitroacetate in aqueous ethanol at pH 8.6 has been reported to give a substance to which the 1,4-dioxane structure **2** was assigned. Though structure **2** was further supported by derivatives **3**–**5**, and though some nmr data were cited as proof,[7] these findings neither explain why addition should preferentially occur at one aldehyde function nor why two pentose dialdehydes,[8] differing from **1** only in the absence of a hydroxymethyl sub-

(1) Nitromethane Condensation with Dialdehydes. XIX. Paper XVIII: F. W. Lichtenthaler and H. Zinke, *J. Org. Chem.*, **37**, 1612 (1972).

(2) (a) Taken in part from the doctoral dissertation of G. Bambach, submitted to the Technische Hochschule Darmstadt, Oct 1971. (b) Financial support of this work by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie is gratefully acknowledged.

(3) R. M. Acheson, *Accounts Chem. Res.*, **4**, 177 (1971).

(4) J. H. Ransom, *Chem. Ber.*, **33**, 199 (1900).

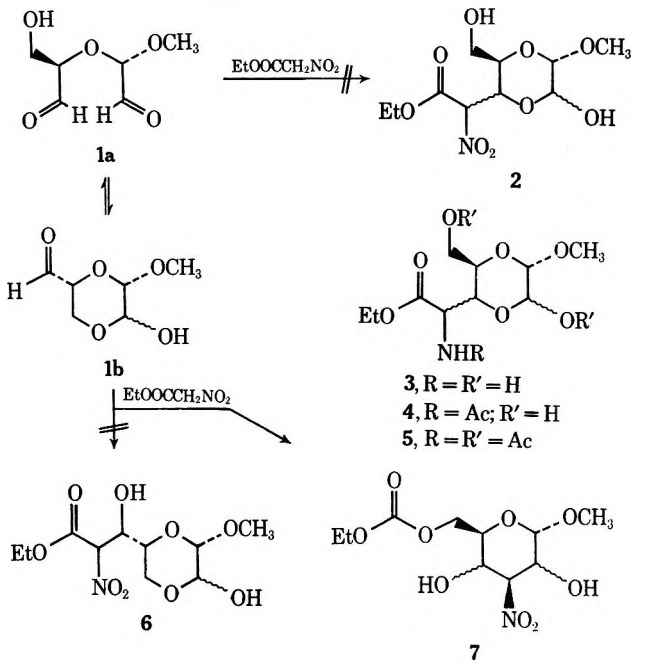
(5) D. Trimnell, W. M. Doane, C. R. Russel, and C. E. Rist, *Carbohyd. Res.*, **13**, 301 (1970).

(6) In naming **5** we prefer this designation derived from *R*-glyceraldehyde rather than the previous system of E. L. Jackson and C. S. Hudson, *J. Amer. Chem. Soc.*, **59**, 994 (1937), according to which **5** would be a "D'-methoxy-D-hydroxymethyldiglycolaldehyde."

(7) S. Zen, A. Yasuda, H. Hashimoto, and Y. Takeda, *Nippon Kagaku Zasshi*, **90**, 110 (1969); *Chem. Abstr.*, **70**, 97153 (1969).

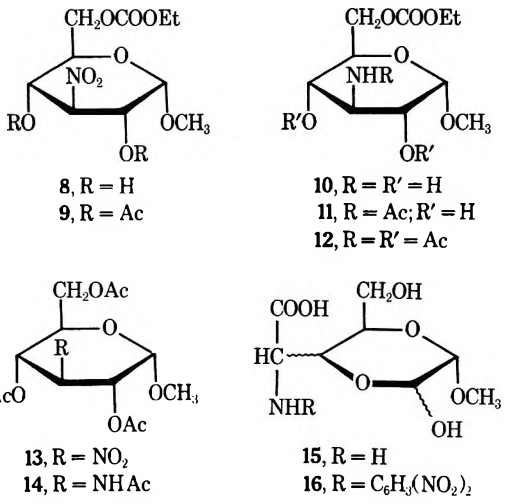
(8) H. Yanagisawa, M. Kinoshita, and S. Umezawa, *Bull. Chem. Soc. Jap.*, **42**, 1719 (1969).

stituent, as well as other dialdehydes[9] yield products of the normal dialdehyde–nitroalkane cyclization type on reaction with ethyl nitroacetate under essentially identical conditions. As has been pointed out,[10] these queries might be answered satisfactorily by invoking structure 6, formed by addition of ethyl nitroacetate to the free aldehyde function in the internal hemiacetal **1b**. However, as shown by the results presented below, the products from this reaction have neither structure 2 nor 6, but are tetrahydropyran derivatives of general structure 7.



When dialdehyde **1a** ⇌ **1b** was treated with ethyl nitroacetate in aqueous ethanol in the presence of either sodium acetate or sodium carbonate (pH 8.6)[7] or, experimentally more convenient, 1 molar equiv of sodium hydroxide, a sirupy mixture was obtained on deionization which consisted (tlc) of two major components in a 5:2 ratio (nmr). This material was later shown to be the nitroglucoside **8** and its C-2-epimeric manno analog. Two minor products amounting to about 5% of the total mixture were not further characterized, but by analogy with the product distribution of the nitromethane cyclization of **1**[11] may be the galacto and the talo isomers of **8**. Elution of the product mixture from silica gel afforded **8** as a colorless sirup that was contaminated with only traces of the manno analog. A crystalline di-*O*-acetate was obtained on treatment of **8** with BF_3–acetic anhydride. Catalytic hydrogenation yielded the aminoglucoside **10** which on acetylation gave the triacetate **12**. Despite minor differences in melting points and rotations, the properties of **10** and **12** are sufficiently close to those of the alleged compounds **3** and **5** described by Zen, *et al.*,[7] to lead to the conclusion that the products obtained are the same substances and, hence, that structures **3**–**5** will have to be revised to **10**–**12**, respectively, based on the evidence to be presented.

Structural and configurational assignments for compounds **8**–**12** rest on chemical as well as on spectroscopic evidence. Firstly, hydrolysis of the 6-*O*-ethoxycarbonyl group in the nitroglucoside **8** with methanolic ammonia afforded methyl 3-deoxy-3-nitro-α-D-glucopyranoside,[12] characterized as its crystalline triacetate **13**. Similarly, the 6-*O*-ethoxycarbonyl aminoglucoside **12** on treatment with methanolic ammonia and subsequent acetylation gave a crystalline tetraacetate, shown to be methyl 3-acetamido-3-deoxy-2,4,6-tri-*O*-acetyl-α-D-glucopyranoside (**14**) by melting point, rotation,[11] and nmr data.[13,14] On the basis of these results, the structure of the supposed **15**, obtained on hydrolysis of the alleged **3** (revised, **10**) with barium hydroxide[7] and its 2,4-dinitrophenyl derivative **16**, must be revised to that of methyl 3-amino-3-deoxy-α-D-glucopyranoside and its 2,4-DNP derivative, despite discrepancies in the reported[7] analytical data.



Secondly, comparison of the mass spectral fragmentation patterns of methyl 3-deoxy-3-nitro-2,4,6-tri-*O*-acetyl-β-D-glucopyranoside[15] or its α anomer **13**, which are expectedly[16] identical, except for intensity differences, with those of the 6-ethoxycarbonyl nitroglucoside **9** showed only minor deviations of 30 mass units (C_2H_5O *vs.* CH_3) in the region of higher mass numbers, in which the C-acyl moiety is still present. Below *m/e* 200, the spectra of **9** and **13** (or its β anomer) become essentially identical, showing significant peaks at *m/e* 81, 99, and 141. These peaks can readily be attributed to ions stemming from a series, initiated by rupture of the C-1–C-2 and/or C-5–C-6 bonds followed by loss of the nitro, acetoxy, and C-6 acyloxy groups.[17] Since very similar relationships were revealed in the mass spectra of the aminoglucosides **12** and **14**, the alternative structures, *i.e.*, **2** and **5**, can be ruled out unequivocally.

Finally, the nmr data of the 6-*O*-ethoxycarbonyl glucosides **9** and **12**, when compared with those of their

(9) S. Yen, Y. Takeda, A. Yasuda, and S. Umezawa, *Bull. Chem. Soc. Jap.*, **40**, 431 (1967); S. Zen and A. Nishikai, *ibid.*, **42**, 1761 (1969).

(10) F. W. Lichtenthaler, *Fortschr. Chem. Forsch.*, **14**, 572 (1970).

(11) H. H. Baer, *J. Amer. Chem. Soc.*, **84**, 83 (1962).

(12) H. H. Baer, F. Kienzle, and T. Neilson, *Can. J. Chem.*, **43**, 1829 (1965).

(13) H. Agahigian, G. D. Vickers, M. H. von Saltza, J. Reid, A. I. Cohen, and H. Gauthier, *J. Org. Chem.*, **30**, 1085 (1965).

(14) The anomeric proton in **14** appears within the complex 4 H multiplet centered around τ 5.2, and not at τ 5.83, as previously reported.[13]

(15) H. H. Baer, F. Kienzle, and F. Rajabalee, *Can. J. Chem.*, **46**, 80 (1968).

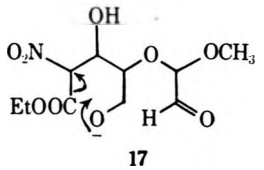
(16) K. Heyns, H. F. Grützmacher, H. Scharmann, and D. Müller, *Fortschr. Chem. Forsch.*, **5**, 448 (1966); N. K. Kochetkov and O. S. Chizhov, *Advan. Carbohyd. Chem.*, **21**, 39 (1966).

(17) For a detailed discussion of the various fragmentation routes of peracetylated 3-deoxy-3-nitrohexopyranosides *cf.* ref 2a and W. Fischer, Doctoral Dissertation, Technische Hochschule Darmstadt, April 1972.

6-*O*-acetyl analog **13** and **14**, correspond convincingly to what one expects for an α-D-gluco configuration in these compounds. In the 100-MHz spectrum of the nitroglucoside **9** in $CDCl_3$, the multiplet splittings of the ring protons, despite partial overlapping, allowed a first-order interpretation, showing at τ 4.90 a small coupling (3.5 Hz) for the anomeric proton, while the 2,3-, 3,4-, and 4,5-coupling constants were in the range of 9.5–10.5 Hz, as expected for an axial orientation of H-5. These assignments are strongly supported by the nmr data of the tri-*O*-acetyl nitroglucoside **13**, in which the multiplet patterns for H-1–H-4 in the τ 4.4–5.2 range were superimposable on those of **9**. Similarly, the nmr features of **12** and **14**, in $CDCl_3$ and in DMSO-d_6, were identical, except for the signals caused by the ethyl group in **12** *vs.* the C-6-acetoxy resonance in **14**.

Several intermediates and/or mechanisms may be postulated to account for the conversion **1** → **7**. Of these, a direct ethoxycarbonyl transfer from the ethyl nitroacetate to the primary hydroxyl group in **1** prior to attack on a carbonyl function can be ruled out. If this occurred, a similar transfer to the ethanol or water present in the reaction medium would take place, giving, owing to the liberation of nitromethane, a mixture of products which would include methyl 3-deoxy-3-nitro-α-D-hexopyranosides. However, a direct comparison of the reaction mixture obtained on nitromethane cyclization of **1**[11] with the corresponding reaction mixture from **1** and ethyl nitroacetate showed (by tlc in several solvents) that none of the tlc spots were due to identical compounds.

Two mechanistic formulations appear to satisfy the experimental data presently available. In the first, which has good analogies with the readily occurring 4 → 6, O → O acyl migrations in hexopyranosides,[18] the C → O ethoxycarbonyl shift occurs in an intermediate of type **17**, formed from preferential attack of the nitroacetate carbanion at the unblocked aldehyde function (**1b** → **6**) with subsequent opening of the hemiacetal ring. The resulting 1-aldehydo-6-nitro derivative is then converted into **7** by cyclizing addition. In the alternative mechanism, a normal dialdehyde–nitroalkane cyclization to **18** takes place, followed by the C → O migration of the ethoxycarbonyl moiety.



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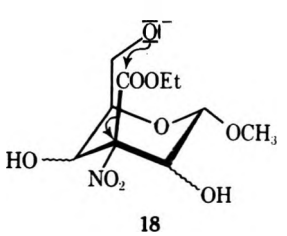

18

There seems to be no way at present to decide which of these mechanisms is operating. However, the C → O ethoxycarbonyl shift may be circumvented by blocking the primary hydroxyl function in **1**, *e.g.*, by tritylation of the dialdehyde precursor. Since compounds of type **18** will then be accessible by detritylation of the products, an investigation of their behavior towards base will decide between the two mechanisms. These aspects are currently being studied.

(18) R. U. Lemieux, in P. de Mayo, Ed., "Molecular Rearrangements," Part 2, Interscience, New York, N. Y., 1964, p 763 ff, and literature cited therein.

Experimental Section[19]

Reaction of Ethyl Nitroacetate with 2-*O*-(*S*-Methoxyformyl)-methyl-(*R*)-glyceraldehyde.[6] (1). **Mixture of Methyl 3-Deoxy-6-*O*-ethoxycarbonyl-3-nitro-α-D-hexopyranosides (7).**—To a solution of dialdehyde **1** [obtained from 7.8 g (0.04 mol) of methyl α-D-glucopyranoside by periodate oxidation[20]] and 5.3 g (0.04 mol) of ethyl nitroacetate in 50 ml of ethanol was added 20 ml (1 molar equiv) of 2 *N* sodium hydroxide and the mixture was kept at ambient temperature for 1 hr. Deionization with a strongly acidic ion exchange resin (Merck I), filtration, and evaporation afforded a reddish sirup, which was dissolved in a little ethanol and purified by chromatography on silica gel with 5:1 benzene–2-propanone. After evaporation of the appropriate fractions a yellowish "sirup A" (6.3 g, 53%, based on methyl α-D-glucoside) was obtained. Sirup A was composed of two minor components of R_f 0.53 and 0.72 (tlc in 1:1 benzene–ethyl acetate), that amount to 5% of the mixture, and two major products, the gluco compound **8** and its manno analog of R_f 0.61 and 0.68, in a 5:1 ratio, as evidenced by the intensities of the two methoxy signals at τ 6.65 and 6.68, respectively, in DMSO-d_6. Elution of sirup A from silica gel with the same eluent gave two fractions; the first contained mainly the manno derivative,[21] whereas the second, on evaporation, afforded 4.8 g of a colorless oil (sirup B), being practically pure (tlc) gluco derivative **8**, contaminated with traces of manno compound. Sirup B, which was not amenable to crystallization from the usual solvents, was used for the further experiments: nmr (DMSO-d_6) τ 3.95 and 4.23 (d, 1, J = 7 Hz, C-2 and C-4 OH), 5.28 (d, 1, $J_{1,2}$ = 3.5 Hz, H-1), 5.37 (m, 2, H-2 and H-3), 5.80 (complex m, 6, H-4, H-5, C-6 CH_2, $EtCH_2$), 6.65 (s, 3, OCH_3), 8.77 (t, 3, J = 7 Hz, $EtCH_3$). Addition of trifluoroacetic acid eliminated the two OH doublets.

Anal. Calcd for $C_{10}H_{17}NO_9$: C, 40.68; H, 5.80; N, 4.74. Found: C, 40.45; H, 5.69; N, 4.60.

Methyl 3-Deoxy-2,4-di-*O*-acetyl-6-*O*-ethoxycarbonyl-3-nitro-α-D-glucopyranoside (9).—A solution of 1.65 g of sirup B in acetic anhydride (5 ml), containing 3 drops of boron trifluoride etherate, was kept for 2 hr at ambient temperature and subsequently taken to dryness *in vacuo* with repeated reevaporations from benzene. After treatment with activated carbon in benzene solution, the residue was triturated with ethanol, causing crystallization. Recrystallization from ethanol afforded 1.34 g (63%) of **9** as colorless crystals: mp 94–95°; $[\alpha]^{23}D$ +112° (*c* 1, $CHCl_3$); nmr (100 MHz in $CDCl_3$) τ 4.53 (t, 1, $J_{3,4} = J_{4,5}$ = 9.5 Hz, H-4), 4.69 (q, 1, $J_{1,2}$ = 3.5, $J_{2,3}$ = 10.5 Hz, H-2), 4.90 (d, 1, $J_{1,2}$ = 3.5 Hz, H-1), 4.99 (t, 1, H-3), 5.78 (m, 4, C-6 CH_2 and $EtCH_2$), 6.01 (m, 1, H-5), 6.56 (s, 3, OCH_3), 7.92 (s, 6, C-2 and C-4 OAc), 8.68 (t, 3, J = 7 Hz, $EtCH_3$); assignments were made by double resonance experiments.

Anal. Calcd for $C_{14}H_{21}NO_{11}$: C, 44.33; H, 5.58; N, 3.69. Found: C, 44.44; H, 5.44; N, 3.49.

Hydrolysis of the Ethoxycarbonyl Group in 9. Methyl 3-Deoxy-3-nitro-2,4,6-tri-*O*-acetyl-α-D-glucopyranoside (13).—Sirup B (220 mg) was kept in 10 ml of methanolic ammonia for 12 hr at room temperature and the solution was then taken to dryness followed by several reevaporations from methanol. After treatment with charcoal in water, a colorless sirup (80 mg, 53%) was obtained, which was allowed to stand for 2 hr in 3 ml of acetic anhydride containing a few drops of BF_3 etherate. Work-up as described for **9** afforded a sirup which was crystallized from water–ethanol to give 60 mg (25%) of **13** as needles: mp 83°; $[\alpha]^{23}D$ +122° (*c* 1, $CHCl_3$); nmr (100 MHz in $CDCl_3$) τ 4.50 (t, 1, $J_{3,4} = J_{4,5}$ = 9.5 Hz, H-4), 4.67 (q, 1, $J_{1,2}$ = 3.5, $J_{2,3}$ = 10.5 Hz, H-2), 4.90 (d, 1, H-1), 4.99 (t, 1, H-3), 5.78 (m, 2, C-6 CH_2), 6.02 (m, 1, H-5), 6.55 (s, 3, OCH_3), 7.88 (s, 3, C-6 OAc), 7.92 (s, 6, C-2 and C-4 OAc); the multiplet patterns in the

(19) Melting points were determined in a Bock Monoskop apparatus and are uncorrected. Nmr spectra were obtained on a Varian A-60 and Varian HA-100 spectrometer with tetramethylsilane as an internal standard; mass spectra were determined on an Atlas CH4 instrument.

(20) H. H. Baer and H. O. L. Fischer, *J. Amer. Chem. Soc.*, **82**, 3709 (1960).

(21) When subjected to BF_3-catalyzed acetylation, analogous to the conversion of **8** to **9**, a sirupy mixture was obtained containing approximately 30% of **9**. The manno configuration of the major part was clear from nmr data in $CDCl_3$, which showed, when compared to **9**, distinct differences in the splitting patterns of the ring protons: a quartet for H-2 at τ 4.46 with $J_{1,2}$ = 2.0 and $J_{2,3}$ = 3.5 Hz and, similarly, a quartet for H-3 at τ 5.02 with couplings of 10.5 and 3.5 Hz.

τ 4.4–5.2 region were superimposable with the corresponding ones of the 6-ethoxycarbonyl compound **9**.

Anal. Calcd for $C_{13}H_{19}NO_{10}$: C, 44.70; H, 5.48; N, 4.01. Found: C, 44.68; H, 5.39; N, 3.88.

Acid-catalyzed hydrolysis of the ethoxycarbonyl group in **9** could be effected, though rather retardedly, by refluxing sirup B with a strongly acidic ion exchange resin (Merck I) in methanol. As monitored by tlc (1:1 benzene–ethyl acetate) the reaction was still incomplete after 5 days, giving after work-up and acetylation as performed above, a tri-*O*-acetate in very low yield (3%), identical in all respects with **13**.

Methyl 3-Amino-3-deoxy-6-*O*-ethoxycarbonyl-α-D-glucopyranoside (10).—Sirup B (900 mg, 3.0 mmol) in 80 ml of ethanol was hydrogenated in the presence of 5 ml of Raney nickel T4 catalyst[22] for 3 hr at 100 atm. Removal of the catalyst followed by evaporation to dryness afforded a solid residue, which was chromatographically not homogeneous. After two recrystallizations from ethyl acetate, 200 mg (25%) of **10** was obtained as colorless crystals: mp 122–125° (reported[7] for alleged **3** mp 128.5–129.5°); nmr (D_2O) τ 5.24 (d, 1, $J_{1,2}$ = 3.5 Hz, H-1), 5.55 (m, 2, C-6 CH_2), 5.76 (q, 2, J = 7 Hz, $EtCH_2$), 6.15 (m, 1, H-5), 6.51 (q, 1, $J_{1,2}$ = 3.5, $J_{2,3}$ = 10 Hz, H-2), 6.59 (s, 3, OCH_3), 6.68 (t, 1, $J_{3,4} = J_{4,5}$ = 10 Hz, H-4), 7.05 (t, 1, H-3), 8.73 (t, 3, $EtCH_3$).

Anal. Calcd for $C_{10}H_{19}NO_7$: C, 45.28; H, 7.22; N, 5.28. Found: C, 45.12; H, 7.10; N, 5.35.

Methyl 3-Acetamido-3-deoxy-2,4-di-*O*-acetyl-6-*O*-ethoxycarbonyl-α-D-glucopyranoside (12).—To a prehydrogenated suspension of platinum (1 g) in 1:1 methanol–acetic anhydride (40 ml) was added 420 mg of nitrodi-*O*-acetate **9**, and the hydrogenation was continued in an autoclave at 100 atm of H_2 for 2 hr. Removal of the catalyst, which was thoroughly washed with methanol, and concentration of the combined filtrate and washings *in vacuo*, followed by repeated reevaporations from benzene, left a crystalline residue, which was filtered off (440 mg, quantitative). The crude product was recrystallized twice from ethanol to give 170 mg (40%) of **12** as colorless crystals: mp 179°; $[\alpha]^{23}D$ +102° (*c* 1, $CHCl_3$) [reported for alleged 5[7] mp 177–178° from 2-propanol and $[\alpha]^{25}D$ +119° (*c* 1.1, $CHCl_3$)]; nmr (DMSO-d_6) τ 2.21 (d, 1, $J_{3,NH}$ = 9 Hz, NH), 5.1–5.4 (complex m, 3, H-1, H-2, and H-4), 5.7–6.2 (m, 6, H-3, H-5, C-6 CH_2 and $EtCH_2$), 6.66 (s, 3, OCH_3), 8.01 and 8.04 (s, 3, C-2 and C-4 OAc), 8.27 (s, 3, NHAc), 8.78 (t, 3, J = 7 Hz, $EtCH_3$).

Anal. Calcd for $C_{16}H_{25}NO_{10}$: C, 48.86; H, 6.41; N, 3.58. Found: C, 49.02; H, 6.55; N, 3.42.

Overnight treatment of the aminoglycoside **10** with pyridine–acetic anhydride at room temperature similarly afforded a triacetate, identical in all respects with **12**, as obtained above.

Methyl 3-Acetamido-3-deoxy-2,4,6-tri-*O*-acetyl-α-D-glucopyranoside (14).—A solution of 300 mg of triacetyl glucoside **12** in 20 ml of methanolic ammonia was kept at room temperature overnight, and subsequently taken to dryness with repeated reevaporations from methanol. The sirupy residue was dissolved in 2:1 pyridine–acetic anhydride (15 ml), and the resulting solution was kept overnight and then evaporated to dryness *in vacuo*. Several reevaporations from benzene and treatment with activated carbon in the same solvent left a residue on evaporation which crystallized on trituration with ethanol. Recrystallization from ethanol afforded 180 mg (65%) of **14**: mp 178–179°; $[\alpha]^{23}D$ +105° (*c* 1, $CHCl_3$) (mp 178–179°, $[\alpha]^{23}D$ +109°, reported previously[11]); nmr (DMSO-d_6) τ 2.23 (d, 1, $J_{3,NH}$ = 9 Hz, NH), 5.2 (m, 3 H-1, H-2, and H-4), 5.73 (broad m, 1, H-3), 5.96 (m, 3, H-5 and C-6 CH_2), 6.67 (s, 3, OCH_3), 8.00, 8.01, and 8.03 (s, 3, C-2, C-4, and C-6 OAc), 8.25 (s, 3, NHAc).

Anal. Calcd for $C_{15}H_{23}NO_9$: C, 49.86; H, 6.42; N, 3.88. Found: C, 49.97; H, 6.25; N, 3.61.

Registry No.—**8**, 34246-31-6; **8** manno derivative, 34280-29-0; **9**, 34246-26-9; **10**, 34246-27-0; **12**, 34280, 30-3; **13**, 34246-28-1; **14**, 2595-38-2.

(22) S. Nishimura, *Bull. Chem. Soc. Jap.*, **32**, 61 (1959).

Studies Related to the Synthesis of (±)-Dihydro-β-santalol[1]

WAYNE I. FANTA* AND WILLIAM F. ERMAN

The Procter & Gamble Company, Miami Valley Laboratories, Cincinnati, Ohio 45239

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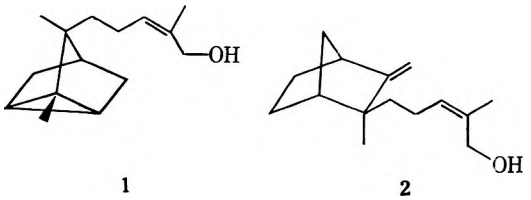
Several related schemes for the synthesis of the novel sesquiterpene dihydro-β-santalol (**3**), a material possessing the powerful, woody fragrance of East Indian sandalwood oil, are described. A preferred sequence utilizes boric acid esters as a means of protecting reactive hydroxyl groups during hydrobromination, alkylation, and Wittig reactions. A novel Meerwein–Ponndorf–Verley reduction discovered during these synthetic studies is also described.

East Indian sandalwood oil, an isolate of *Santalum album L.*, is a prized essential oil known for its powerful, sweet woody fragrance.[2] Although numerous minor components are important for the reproduction of the natural aroma of the oil, the two major components—α-santalol (**1**) and β-santalol (**2**)—are responsible for the basic sandalwood note. While syntheses of these two materials have been accomplished,[3] these schemes do not permit the accumulation of large amounts of material owing to the complexity of the natural sesquiterpene structures. The greater synthetic accessibility of compounds in the β series and the challenge to construct a simpler molecule with a powerful sandalwood note prompted us to synthesize dihydro-β-santalol (**3**).



1 **2**

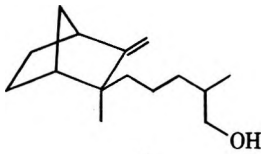
Corey has shown[4] that either of the epimeric methylnorcamphors **4** or **5** undergoes stereoselective alkylation from the exo face to produce 3-*exo*-alkyl-3-*endo*-methylnorcamphors. Using this information, our synthetic scheme was to preconstruct a side chain—such as **6**—which on condensation with ketone **4** or **5** would be expected to yield stereoselectively a dihydro-β-santalol

(1) For a preliminary communication of this work, see W. I. Fanta and W. F. Erman, *Tetrahedron Lett.*, 4155 (1969).

(2) (a) E. Guenther, "The Essential Oils," Vol. V, Van Nostrand, Princeton, N. J., 1952, pp 173–186; (b) J. L. Simonsen and D. H. R. Barton, "The Terpenes," 2nd ed, Vol. 3, University Press, Cambridge, England, 1951, pp 98, 178–188; (c) F. V. Wells, *Soap Chem. Spec.*, **43** (12), 74, 76–78, 149–151 (1967).

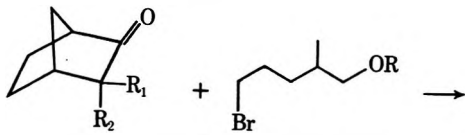
(3) (a) R. G. Lewis, D. H. Gustafson, and W. F. Erman, *Tetrahedron Lett.*, 401 (1967); (b) S. Y. Kamat, K. K. Chakravarti, and S. C. Bhattacharyya, *Tetrahedron*, **23**, 4487 (1967); (c) H. C. Kretschmar and W. F. Erman, *Tetrahedron Lett.*, 41 (1970); (d) J. Colonge, G. Descotes, Y. Bahurel, and A. Menet, *Bull. Soc. Chim. Fr.*, 374 (1966); (e) E. J. Corey, H. A. Kirst, and J. A. Katzenellenbogen, *J. Amer. Chem. Soc.*, **92**, 6314 (1970); (f) E. J. Corey and H. Yamamoto, *ibid.*, **92**, 226 (1970).

(4) E. J. Corey, R. Hartmann, and P. A. Vatakencherry, *ibid.*, **84**, 2611 (1962).



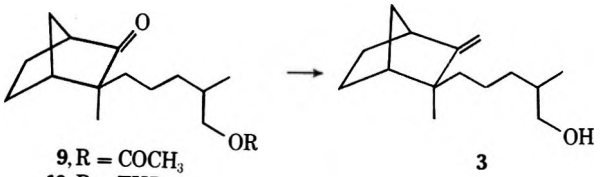
3

precursor such as **9**.[5] Introduction of a methylene function and removal of the alcohol blocking group would yield the synthetic goal **3**.



4, $R_1 = CH_3$; $R_2 = H$
5, $R_1 = H$; $R_2 = CH_3$

6, R = $COCH_3$
7, R = THP
8, R = H

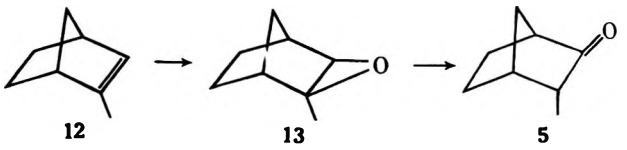


9, R = $COCH_3$
10, R = THP
11, R = H

3

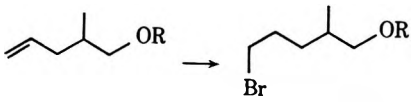
The construction of 3-*exo*-methylnorcamphor (**4**) can be accomplished through the alkylation of norcamphor as described by Corey.[4] We chose to examine an alternate preparative scheme to 3-methylnorcamphor which we felt would more conveniently allow preparation of large quantities of the required ketone from readily available starting materials. The olefin, 2-methylbicyclo[2.2.1]hept-2-ene (**12**), available in quantity through Diels–Alder condensation of methylcyclopentadiene and ethylene,[6a] offered promise as a precursor to 3-methylnorcamphor. Epoxidation of olefin **12** with *m*-chloroperbenzoic acid[6b] or sodium acetate buffered peracetic acid afforded the exo epoxide **13** in excellent yield.[7] We found that, of the several catalysts examined, boron trifluoride etherate was most efficient and consistent for opening the oxide to methylnorcamphor. This process selectively forms the endo isomer **5**.[8]

With a ready supply of the methylnorcamphor available, we turned our attention to construction of suitable side-chain precursors. Since our intent was to



12 **13** **5**

construct the total side chain prior to its addition to 3-methylnorcamphor, we were interested in the recently reported one-step preparation of 2-methyl-4-pentenol (**14**) by Cherest and coworkers.[9] Although the alcohol had been previously described,[10] this new synthetic scheme offered, more directly, a material ideally suited for simple modifications to side chains such as **6** and **7**.

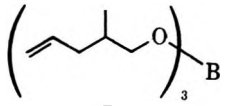


14, R = H
15, R = $COCH_3$
16, R = THP

6, R = $COCH_3$
7, R = THP

Our attention was next directed toward the reactions necessary to convert alcohol **14** into a properly functionalized side-chain precursor. In considering various alcohol blocking groups, we concluded it would be advantageous to employ a group which would protect the alcohol during both a hydrobromination reaction and subsequent combination with methylnorcamphor, and yet be easily removed at a latter stage in the scheme. Some of the problems encountered with the use of standard blocking groups for this multipurpose role are elaborated below.

While the acetate **15** and the tetrahydropyranyl ether **16** were available through standard procedures, the borate **17** proved to be the most versatile in sub-



17

sequent synthetic work. Although borates have been used as blocking groups, extensive use in synthetic organic chemistry has not been described.[11]

Free-radical hydrobromination of unsaturated alcohol **14** offers a simple method for introduction of the desired leaving group. We expected, and subsequently demonstrated experimentally, however, that free-radical hydrobromination of **14** was not practical owing to the inhibitory effect of the free hydroxyl group. We also found that, while the anti-Markovnikov hydrobromination of acetate **15** could be carried out in high yield, attempts to hydrobrominate tetrahydropyranyl ether **16** met with little success. In the latter case, hydrogen abstraction adjacent to the ether oxygen most likely terminates the free-radical process and bromo ether **18** is the only observed product.

Anti-Markovnikov hydrobromination of borate **17**

(5) The alkylation of ketone **4** or **5** with side chains such as **6**, which contain an asymmetric carbon atom, would be expected to produce diastereomeric mixtures. No attempt was made to separate the two diastereomers in products such as **9**, **10**, **11**, and **3**.

(6) (a) K. Alder and H. J. Ache, *Chem. Ber.*, **95**, 503 (1962); (b) H. C. Kretschmar, unpublished observation.

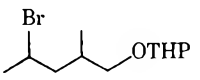
(7) It was anticipated that the epoxidation would occur specifically from the less hindered exo face as has been observed in the epoxidation of bicyclo-[2.2.1]hept-2-ene: H. Kwart and W. G. Vosburgh, *J. Amer. Chem. Soc.*, **76**, 5400 (1954); H. M. Walborsky and D. F. Lonerini, *ibid.*, **76**, 5396 (1954); H. C. Brown, J. H. Kawakami, and S. Ikegami, *ibid.*, **92**, 6914 (1970).

(8) In the carbonium ion formed by oxide opening, the exo-hydrogen transfer is greatly favored over the endo-hydrogen transfer. As a consequence, the methyl group is oriented endo in the product. For a discussion of methylnorbornyl cation equilibria, see (a) J. A. Berson, J. H. Hammons, A. W. McRowe, R. G. Bergman, A. Ramanick, and D. Houston, *ibid.*, **89**, 2561 (1967); (b) J. A. Berson, A. W. McRowe, R. G. Bergman, and D. Houston, *ibid.*, **89**, 2563 (1967); (c) J. A. Berson and R. G. Bergman, *ibid.*, **89**, 2569 (1967); (d) J. A. Berson, A. W. McRowe, and R. G. Bergman, *ibid.*, **89**, 2573 (1967); (e) J. A. Berson, R. G. Bergman, J. H. Hammons, and A. W. McRowe, *ibid.*, **89**, 2581 (1967); (f) J. A. Berson, J. H. Hammons, A. W. McRowe, R. G. Bergman, A. Remanick, and D. Houston, *ibid.*, **89**, 2590 (1967).

(9) M. Cherest, H. Felkin, C. Frajerman, C. Lion, G. Roussi, and G. Swierczewski, *Tetrahedron Lett.*, 875 (1966).

(10) G. I. Fray and N. Polgar, *J. Chem. Soc.*, 2036 (1956).

(11) See J. Staněk, M. Černý, J. Kocourek, and J. Pacák, "The Monosaccharides," Academic Press, New York, N. Y., 1963, pp 40 and 254 and references therein for applications in carbohydrate chemistry. L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, pp 64–66 and references therein which describe limited applications in hydroxylation and condensation reactions and in monoglyceride chemistry. W. C. Agosta, *J. Amer. Chem. Soc.*, **89**, 3926 (1967).



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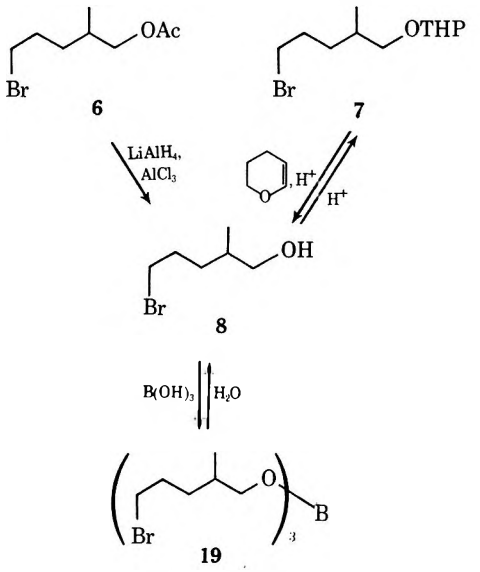
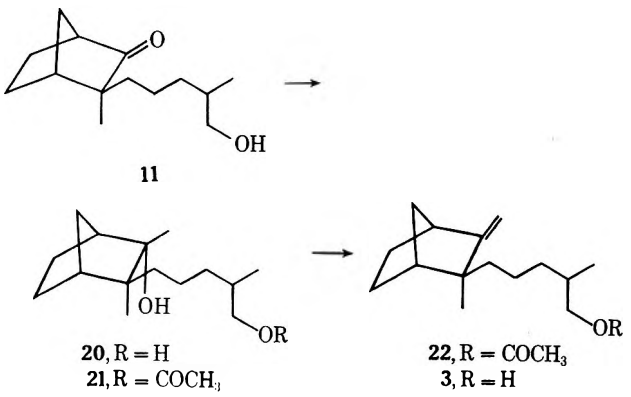
proceeded smoothly and an aqueous isolation procedure afforded directly the bromo alcohol **8**. With these materials available certain interconversions were undertaken which afforded additional compounds for potential use in the remainder of the sequence. For example, while direct saponification of bromo acetate **6** led only to 3-methyltetrahydropyran, reduction with lithium aluminum hydride–aluminum chloride under mild conditions afforded a nearly quantitative yield of bromo alcohol **8**. This material could be converted by standard procedures to the bromo ether **7**. In addition, bromo borate **19** was readily available through interaction of bromo alcohol **8** and boric acid.



With three potential alkylating agents (**6**, **7**, and **19**) available, we turned our attention to the alkylation of 3-methylnorcamphor. Although an alkylation procedure previously described[4] was used in initial studies, we found that improved yields and product purity resulted when sodium hydride was used in place of sodium amide. We discovered, however, that the readily available bromoacetate **6**, or the corresponding iodoacetate, could not be successfully added to the methylnorcamphor system. While a considerable amount of polymer was formed the major volatile products were identified as starting materials and dehydrohalogenated products such as **15**.

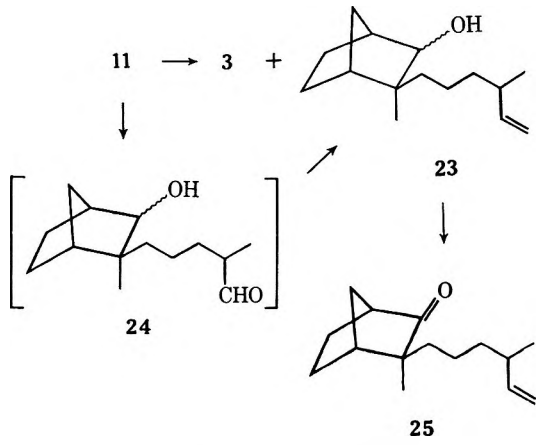
Bromo ether **7**, on the other hand, was smoothly added to methylnorcamphor using either the sodium amide–tetrahydrofuran combination or, preferably, a sodium hydride–benzene system. While the alkylation product **10** could not be effectively purified because of chromatographic instability, we found that removal of the ether blocking group afforded the readily analyzable ketol **11**. This material was also available through alkylation of methylnorcamphor with bromo borate **19**. As noted previously, the borate, being extremely water sensitive, was readily cleaved during an aqueous work-up and the ketol **11** was isolated directly in 60–70% yield.

The final conversion (**11** → **3**), which we approached in several different ways, remained to complete the synthesis. Application of Corey's procedure[4] to ketol **11** required certain modifications owing to the side-chain hydroxyl function. Interaction of the ketol **11** with 3 equiv of methyllithium or methylmagnesium bromide followed by monoacetylation of diol **20** afforded hydroxy acetate **21**. Subsequent dehydration to dihydro-β-santalol acetate (**22**) followed by saponifi-

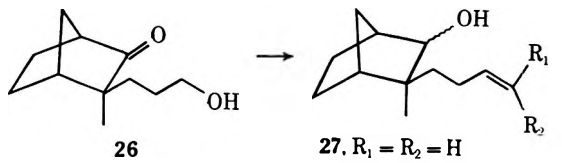


cation afforded dihydro-β-santalol (**3**) as a colorless viscous oil.

Alternately, one can visualize the use of a Wittig reaction for a more direct conversion of **11** to the desired santalol **3**. We found that condensation of ketol **11** with excess methylenetriphenylphosphorane in dimethyl sulfoxide afforded, in addition to **3**, substantial amounts of a second product. This side product was identified as the isomeric hydroxy olefin **23** which undoubtedly arises from a Wittig reaction on hydroxyaldehyde **24**. (Although an intramolecular Ponndorf–Verley reduction can be recognized as one reasonable pathway for formation of **24**, the actual mechanistic details have not been defined.) The identity of product **23** was further established by oxidation to keto olefin **25** in high yield.



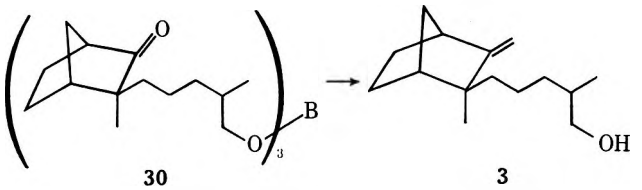
While one can visualize several possible applications in the area of santalol synthesis for this interesting rearrangement, the reaction appears to be quite specific for the methylene Wittig reagent. We attempted to interact ketol **26** with three different Wittig reagents but found that only the simplest would react to give hydroxy olefin **27**. Since neither isopropylidenetriphenylphosphorane nor α-carboethoxyethylidenetriphenylphosphorane could be successfully used, we were unable to gain what initially appeared to be a novel entrance into other santalol systems.



26

27, $R_1 = R_2 = H$
28, $R_1 = R_2 = CH_3$
29, $R = CH_3$; $R = CO_2Et$

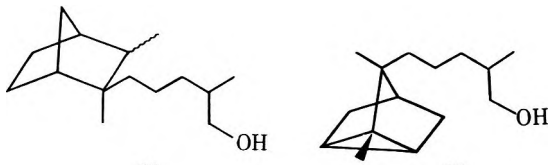
The interaction of the hydroxyl and the keto groups in bicyclic ketol **11** could be circumvented by blocking the hydroxyl as the borate. Subsequent treatment of keto borate **30** with excess methylenetriphenylphosphorane in dimethyl sulfoxide afforded, on hydrolysis, a 90% yield of dihydro-β-santalol (**3**).



30 3

Pure **3** was also obtained directly in high yield from diol **20** using boron trifluoride etherate as a dehydration catalyst. This latter conversion has the advantages of requiring no blocking group, using inexpensive reagents, and proceeding in high yield.

It is of interest at this point to compare the odor properties of dihydro-β-santalol (**3**), tetrahydro-β-santalol (**31**), and dihydro-α-santalol (**32**). Although



31 32

alcohols **31** and **32** have been previously described,[12] we have independently synthesized[13] samples of these materials for direct comparison to dihydro-β-santalol (**3**). While the odor of dihydro-α-santalol is sandalwood in character, it is very much weaker than dihydro-β-santalol. Moreover, the odor of the α isomer is short lived and on dry down the strength is greatly diminished while a sample of dihydro-β-santalol retains its strong and characteristic sandalwood note for an extended period of time. Tetrahydro-β-santalol exhibits a "chemical, earthy, musty" odor and dries down to a very weak, neutral woody odor.[14]

Experimental Section

General.—Ir spectra were recorded on a Perkin-Elmer Model 137 spectrophotometer; nmr spectra were determined with a Varian Model HA-100 spectrometer with chemical shifts measured relative to tetramethylsilane (τ 10) (s, singlet; b s, broad singlet; d, doublet, etc.). Gas–liquid partition chromatography (glpc) was carried out on an Aerograph Model 202B using a flow rate of 100 cc/min on 5 ft × 0.25 in. columns packed with 20% FFAP on 60/80 Chromosorb P column or 20% SE-30 on 60/80 Chromosorb W. The apparatus described by Johnson and Schneider[15] was used to maintain a nitrogen atmosphere. Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. Boiling points are taken on standard thermometers and are uncorrected.

2-Methylbicyclo[2.2.1]hept-2-ene (12).—Condensation of 80 g (1 mol) of methyl cyclopentadiene dimer with a large excess of ethylene according to the procedure of Alder and Ache[5] and subsequent distillation afforded 38 g (35%) of colorless product, bp 115–117° (lit.[5] bp 117°), which showed 96% purity by glpc analysis.

2-Methyl-*exo*-2,3-epoxybicyclo[2.2.1]heptane (13).—A mixture of 54 g (0.5 mol) of olefin **12** and 60 g (0.75 mol) of sodium acetate in 180 ml of methylene chloride was cooled in an ice bath. The temperature was maintained at 5–10° and 104 ml (0.625 mol) of a 40% peracetic acid solution in acetic acid was added with good stirring over 80 min. The resulting solution was stirred for an additional 10 min and poured into excess 5% aqueous sodium hydroxide, and the layers were separated. The aqueous layer was extracted several times with ether and the combined organic layers were washed with 5% aqueous sodium hydroxide until basic and with brine solution to neutrality and dried ($MgSO_4$). The solvent was evaporated to afford 56.5 g (92%) of epoxide **13** which was suitable for subsequent reactions.

The epoxide could be purified by distillation, bp 95° (100 mm), or preparative glpc[6b] to afford material with the following spectral characteristics: ir (film) 7.6, 8.85, 9.2, 10.0, 10.5, 11.15, 11.6, 11.95 μ; nmr (CCl_4) τ 7.41 (s, 1, C_3 endo H), 8.7 (s, C_2 endo CH_3), 8.4–8.95 (m, CH_2's).

***endo*-3-Methylbicyclo[2.2.1]heptan-2-one (5).**—A solution of 51 g (0.41 mol) of crude epoxide **13** dissolved in 200 ml of benzene was treated, under nitrogen over ~1 min, with 8.3 ml of boron trifluoride etherate. The dark solution was stirred at 60° for 5 hr and cooled slightly, and most of the solvent was removed at reduced pressure. The residual oil, 70.3 g, was distilled to afford 23.7 g (46%) of ketone **5**: bp 80–90° (30 mm); ir (neat) 5.8, 7.7, 8.5, 9.0, 9.6, 10.5 μ; nmr (CCl_4) τ 9.05 (d, 3, J = 7 Hz, $CHCH_3$). The material exhibited greater than 95% purity by glpc.[8]

2-Methyl-4-pentenol (14).—A modification of the procedure of Cherest and coworkers was employed.[9] A solution of 23.2 g (0.4 mol) of allyl alcohol in 60 ml of anhydrous ether was treated with 150 ml of a 3 *M* ethereal methylmagnesium bromide solution (0.45 mol) over a 3–4-hr period. The resulting clear brown solution was subsequently treated in one portion with 360 ml of a 1.4 *M* ethereal allylmagnesium bromide solution and refluxed under nitrogen for 50 hr. The cooled reaction was decomposed by slow addition to ice and solution was subsequently effected by cautious addition of 10% aqueous hydrochloric acid. The solution was saturated with salt, the product was isolated with ether, and the combined extracts were washed with brine and dried ($MgSO_4$). Removal of the solvent and subsequent distillation afforded 25.4 g (64%) of unsaturated alcohol **14**, bp 53–58° (14 mm), which showed 96% purity by glpc.

Material purified by redistillation and glpc exhibited the following physical properties: bp 57–58° (12 mm); $n^{21.5}$D 1.4319 (lit.[10] n^{18}D 1.4345); ir (neat) 3.00, 3.28, 6.10, 9.68, 10.04, 10.91 μ; nmr (CCl_4) τ 4.00–4.51 (m, 1, –CH=), 4.90–5.20 (m, 2, CH=CH_2), 5.60 (s, 1, OH), 6.40–6.80 (m, 2, CH_2OH), 9.10 (d, 3, J = 7 Hz, $CHCH_3$).

Anal. Calcd for $C_6H_{12}O$: C, 71.95; H, 12.08. Found: C, 72.1; H, 12.2.

2-Methyl-4-pentenyl Acetate (15).—A solution of 3.44 g (34.4 mmol) of alcohol **14** in 35 ml of anhydrous pyridine was treated under a nitrogen atmosphere with 10.78 g (10 ml, 100 mmol) of acetic anhydride. The reaction was stirred at room temperature for 24 hr and poured into brine, and the product was isolated with ether. The extracts were washed with 3% aqueous hydrochloric acid and brine and dried ($MgSO_4$). The solvent was removed and the residual crude oil was distilled to afford 4.3 g (88%) of acetate **15**, bp 60–65° (17 mm), which showed 99% purity by glpc.

A sample of the material subjected to redistillation exhibited the following physical properties: bp 54–56° (13 mm), n^{26}D 1.4140; ir (neat) 3.28, 5.71, 6.10, 8.06, 9.62, 10.05, 10.91 μ; nmr (CCl_4) τ 4.10–4.55 (m, 1, –CH=), 4.90–5.19 (m, 2, CH=

(12) V. Herout, V. Jarolím, and J. Pliva, *Chem. Listy*, **50**, 1271 (1956); *Chem. Abstr.*, **51**, 296*de* (1957).

(13) The preparation of dihydro-α-santalol (**32**) was carried out by R. G. Lewis using precursors prepared by R. G. Lewis, D. H. Gustafson, and W. F. Erman, *Tetrahedron Lett.*, 401 (1967). A mixture of *cis*- and *trans*-ethyl-α-santalates was catalytically reduced and the resulting saturated ester was reduced with lithium aluminum hydride to afford the required santalol **32**.

(14) We are indebted to E. J. Matre, W. A. Whitehead, J. B. Dacey, and R. W. Martin, Senior Perfumers of The Procter & Gamble Co., for these odor evaluations.

(15) W. S. Johnson and W. P. Schneider, *Org. Syn.*, **30**, 18 (1950).

CH_2), 6.05–6.36 (m, 2, CH_2O), 8.08 (s, 3, $COCH_3$), 9.11 (d, 3, J = 6 Hz, $CHCH_3$).

Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.93. Found: C, 67.3; H, 10.0.

2-Methyl-4-pentenyl Tetrahydropyranyl Ether (16).—A mixture of 1.4 g (14 mmol) of alcohol **14** and 1.12 g (14 mmol) of dihydropyran was cooled in an ice bath and treated under nitrogen with 5 drops of phosphorus oxychloride. The resulting reaction was stirred at room temperature for 2.5 hr and added to 100 ml of 2% aqueous sodium hydroxide and the product was isolated with ether. The combined extracts were washed with brine and dried ($MgSO_4$), and the solvent was removed to afford crude product. Subsequent distillation afforded 2.14 g (84%) of ether **16**, bp 66–68° (3 mm), which showed 99% purity by glpc.

Material collected from glpc analysis exhibited the following physical properties: $n^{25}D$ 1.4446; ir (neat) 3.28, 6.10, 8.30, 8.90, 9.25, 9.39, 9.65, 10.18, 10.91, 11.43, 12.19 μ; nmr (CCl_4) τ 4.00–4.50 (m, 1, $-CH=$), 4.90–4.25 (m, 2, $=CH_2$), 5.51 (b s, 1, OCHO), 6.10–7.05 (m, 4, $-CH_2OCHOCH_2$), 9.12 (d, 3, J = 6 Hz, $CHCH_3$).

Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.69; H, 10.94. Found: C, 71.8; H, 11.0.

Tris-2-methyl-4-pentenyl Borate (17).—A mixture of 25 g (0.25 mol) of alcohol **14** and 5.25 g (0.084 mol) of boric acid in 250 ml of benzene was refluxed with constant removal of water. When the theoretical amount of water (4.5 ml, 0.25 mol) had separated, the solution was cooled slightly and the solvent was removed at reduced pressure to afford 27.2 g (100%) of colorless borate **17**: ir (neat) 3.30, 6.11, 6.78, 7.08, 7.51, 9.61, 10.06, 10.94 μ; nmr (CCl_4) τ 3.95–4.42 (m, 1, $-CH=$), 4.85–5.15 (m, 2, $=CH_2$), 6.35 (d, 2, J = 6 Hz, CH_2O), 7.65–8.50 [m, 3, $-CH_2CH(CH_3)-$], 9.08 (d, 3, J = 6 Hz, $CHCH_3$). This material was used without further purification.

2-Methyl-5-bromopentyl Acetate (6).—A solution of 12.84 g (0.09 mol) of acetate **15** and 0.22 g of benzoyl peroxide in 100 ml of hexane (98%) was cooled in an ice bath and anhydrous hydrogen bromide was rapidly passed through the solution for 15 min. The reaction was stirred for an additional 15 min, the excess gas was removed by a nitrogen sweep, and the total solution was washed well with a saturated aqueous solution of sodium bicarbonate and then brine until neutral. The hexane solution was dried ($MgSO_4$), concentrated under reduced pressure, and distilled to give 17.4 g (85%) of product, bp 69–72° (0.85 mm).

Further purification by distillation and glpc afforded material with the following physical properties: bp 69–71° (0.9 mm); $n^{33}D$ 1.4533 [lit.[16] bp 77° (3 mm); $n^{33}D$ 1.4539]; ir (neat) 5.73, 8.10, 9.63 μ; nmr (CCl_4) τ 6.14 (d, 2, J = 6.5 Hz, CH_2OAc), 6.63 (t, 2, J = 7 Hz, CH_2Br), 8.03 (s, 3, $COCH_3$), 9.06 (d, 3, J = 6.5 Hz, $CHCH_3$).

Anal. Calcd for $C_8H_{15}BrO_2$: C, 43.06; H, 6.78; Br, 35.82. Found: C, 43.0; H, 6.75; Br, 35.8.

2-Methyl-5-bromopentanol (8). A. From Tris-2-methyl-4-pentenyl Borate (17).—The procedure described for hydrobromination of acetate **13** was employed. From 0.24 mol of crude ester **17** there was obtained after 1 hr of reaction and aqueous work-up (washing with brine, saturated sodium bicarbonate solution, and brine) 41.5 g of crude product. Distillation afforded 36.8 g (86%) of clear bromo alcohol **8**, bp 70° (0.1 mm).

Redistillation afforded material with the following physical properties: bp 62° (0.02 mm); $n^{25}D$ 1.4829; ir (neat) 2.99, 9.68 μ; nmr (CCl_4) τ 4.30 (s, 1, OH), 6.61 (d, 2, J = 6 Hz, CH_2OH), 6.63 (t, 2, J = 6 Hz, CH_2Br), 9.07 (d, 3, J = 6 Hz, $CHCH_3$).

Anal. Calcd for $C_6H_{13}BrO$: C, 39.79; H, 7.23; Br, 44.14. Found: C, 39.9; H, 7.2; Br, 44.1.

B. From 2-Methyl-5-bromopentyl Acetate (6).—The procedure of Nystrom[17] was employed. A mixture of 0.95 g (25 mmol) of lithium aluminum hydride and 25 ml of ether was treated in an anhydrous atmosphere with a solution of 3.33 g (25 mmol) of aluminum chloride in 38 ml of ether. A solution of 5.53 g (25 mmol) of bromo acetate **6** in 50 ml of ether was added dropwise over a 15-min period. The reaction mixture after stirring at room temperature for 1 hr was decomposed by the cautious addition of 9 ml of water followed by 35 ml of 6 N aqueous sulfuric acid in 25 ml of water. The resulting mixture was extracted with ether and the combined extracts were washed once with brine. Evaporation of the dried ($MgSO_4$) solvent and subsequent distillation afforded 4.18 g (94%) of bromo alcohol which was identical in all respects with the product **8** described above.

Tris-2-methyl-5-bromopentyl Borate (19).—The procedure described for preparation of borate ester **17** was employed on bromo alcohol **8**. From 18 g of crude bromo alcohol there was obtained 18.8 g (100%) of crude bromo borate **19**: ir (neat) 6.75, 7.05; 7.48, 9.68 μ; nmr (CCl_4) τ 6.38 (d, 2, J = 5.5 Hz, CH_2OB), 6.63 (t, 2, J = 6.5 Hz, CH_2Br), 9.10 (d, 3, J = 6 Hz, $CHCH_3$).

This material could be used directly without further purification.

2-Methyl-5-bromopentyl Tetrahydropyranyl Ether (7).—The procedure described for the preparation of ether **16** from the corresponding alcohol was employed. From 10.5 g (0.058 mol) of alcohol **8** there was obtained 15.4 g of crude product which was distilled to afford 15 g (96%) of colorless bromo ether **7**: bp 83–5° (0.02 mm); $n^{25}D$ 1.4729; ir (neat) 8.34, 8.91, 9.29, 9.41, 9.67, 10.21, 11.02, 11.46, 12.20 μ; nmr (CCl_4) τ 5.55 (s, 1, $-OCHO$), 6.10–7.05 (m, $-CH_2OCHOCH_2-$) 6.68 (t, J = 7 Hz, CH_2Br), 9.08 (d, 3, J = 6 Hz, $CHCH_3$).

Anal. Calcd for $C_{11}H_{21}BrO_2$: C, 49.82; H, 7.98; Br, 30.14. Found: C, 49.9; H, 8.1; Br, 30.1.

***endo*-3-Methyl-3-(4-methyl-5-hydroxypentyl)bicyclo[2.2.1]-heptan-2-one Tetrahydropyranyl Ether (10),**—A nitrogen-blanketed suspension of 4.9 g (0.125 mol) of a 61% mineral oil dispersion of sodium hydride in 60 ml of benzene was treated with a solution of 12.4 g (0.1 mol) of 3-methylnorcamphor in 60 ml of benzene. The resulting mixture was heated at 125° for 2 hr and then treated with a solution of 26.5 g (0.1 mol) of bromo ether **7** in 60 ml of benzene. The reaction was refluxed for an additional 61 hr, cooled, added to brine, and extracted with ether. The combined extracts were washed with brine and dried ($MgSO_4$), and the solvent was removed to afford 33.5 g of oil. The crude product was distilled, bp 30–100° (0.02 mm), to remove starting materials, and the residual oil, 20.8 g (67%), composed mainly of product, was treated as described in the following experiment.

Pure keto ether **10** could be obtained by distillation: bp 135–140° (0.02 mm); ir (neat) 5.72, 8.31, 8.90, 9.28, 9.39, 9.67, 10.19, 11.00, 11.48, 12.19 μ; nmr (CCl_4) τ 5.53 (s, 1, OCHO), 6.11–7.10 (m, 4, $-CH_2OCHOCH_2$), 7.55, 7.68 (2 b s, 2, C_1 H, C_4 H), 9.02 (s, 3, CH_3), 9.06 (d, 3, J = 6 Hz, $CHCH_3$).

Anal. Calcd for $C_{19}H_{32}O_3$: C, 73.98; H, 10.46. Found: C, 73.9; H, 10.5.

***endo*-3-Methyl-3-(4-methyl-5-hydroxypentyl)bicyclo[2.2.1]heptan-2-one (11). A. From Keto Ether 10.**—A solution of 20.8 g (67 mmol) of crude keto ether **10** and 1.5 g of *p*-toluenesulfonic acid monohydrate in 250 ml of absolute ethanol was refluxed under nitrogen for 2 hr. The cooled reaction was added to brine and the product was isolated with ether. Removal of the dried ($MgSO_4$) solvent afforded 19.1 g of crude ketol **11** which on subsequent distillation afforded 14 g (96%) of product. Further purification by distillation and glpc gave ketol exhibiting the following physical characteristics: bp 127–130° (0.07 mm); ir (neat) 2.90, 5.73, 7.30, 9.60, 10.92, 13.02 μ; nmr (CCl_4) τ 6.72 (d, 2, J = 6 Hz, CH_2OH), 7.06 (s, 1, OH), 7.57, 7.71 (2 b s, 2, C_1 H, C_4 H), 9.07 (s, 3, CH_3), 9.16 (d, 3, J = 6.5 Hz, $CHCH_3$).

Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 74.8; H, 10.8.

B. From Keto Borate 30.—A nitrogen-blanketed mixture of 4.9 g (0.125 mol) of a 61% mineral oil dispersion of sodium hydride and 60 ml of dry toluene was treated with a solution of 12.4 g (0.1 mol) of 3-methylnorcamphor in 60 ml of dry toluene and the resulting mixture was heated at 130° for 2.25 hr. The refluxing enolate solution was treated as rapidly as possible with a solution of 18.8 g (0.1 mol) of crude bromo borate **19** in 60 ml of dry toluene and subsequently refluxed for 68 hr. The cooled reaction was added to brine and the product was isolated with ether. Removal of the dried ($MgSO_4$) solvent and subsequent distillation afforded 13.9 g (62%) of ketol **11**, bp 117–130° (0.08 mm), which showed 90% purity by glpc. The material isolated by this process exhibited spectral properties identical with those of the ketol isolated from keto ether **10**.

***trans*-2,3-Dimethyl-*exo*-3-(4-methyl-5-hydroxypentyl)bicyclo-[2.2.1]heptan-2-ol (20). A. Using Methyllithium.**—A solution of 4.5 ml of 2.4 M ethereal methyllithium (0.11 mol) in 110 ml of ether was slowly treated (1 hr) with a solution of 8.0 g (35.7 mmol) of ketol **11** in 55 ml of ether. The reaction was stirred at room temperature for 3 hr and poured slowly onto crushed ice. The aqueous solution was saturated with salt and the product isolated with ether. Removal of the dried (Mg-

(16) S. V. Kessar and A. L. Rampal, *Chem. Ind. (London)*, 1957 (1963).

(17) R. F. Nystrom, *J. Amer. Chem. Soc.*, **77**, 2544 (1955).

SO_4) solvent and distillation afforded 8.2 g (96%) of product, bp 132° (0.18 mm). This material (95% purity by glpc) could be further purified by glpc: $n^{26.5}D$ 1.5019; ir (neat) 2.97, 7.31, 8.87, 9.69, 10.51, 10.60, 11.04 μ; nmr (CCl_4) τ 6.50–6.85 (m, 2, CH_2OH), 8.81 (s, 3, $HOCCH_3$), 9.11 (d, 3, J = 6 Hz, $CHCH_3$), 9.14 (s, 3, CH_3).

Anal. Calcd for $C_{15}H_{28}O_2$: C, 74.95; H, 11.74. Found: C, 75.0; H, 11.9.

B. Using Methylmagnesium Bromide.—A solution of 5.7 g (25 mmol) of ketol **11** in 50 ml of ether was added over 15 min to a nitrogen-blanketed solution of 33 ml of 3 *M* ethereal methylmagnesium bromide in 100 ml of ether. The mixture was refluxed for 5 hr and decomposed by the cautious dropwise addition of 20 ml of saturated aqueous sodium sulfate. The ethereal layer was decanted and the solid material was washed well with several portions of ether. The combined organic layers were washed once with the sodium sulfate solution and dried ($MgSO_4$), and the solvent removed. The crude oil (7.7 g) was distilled to give 5.58 g (93%) of 95% pure diol **20** possessing physical properties identical with those of material prepared in the proceeding experiment. The crude material could be used in subsequent reactions.

***trans*-2,3-Dimethyl-*exo*-3-(4-methyl-5-acetoxypentyl)bicyclo[2.2.1]heptan-2-ol (21).**—A nitrogen-blanketed solution of 2.6 g (11 mmol) of crude diol **20** in 13 ml of pyridine (distilled from barium oxide) was treated with 3.5 ml of acetic anhydride and the total was stirred at room temperature for 24 hr. The reaction was poured into brine and the product was isolated with ether. The combined extracts were washed with brine, 5% hydrochloric acid, and brine and dried ($MgSO_4$). Solvent removal and distillation afforded 2.8 g (89%) of hydroxy acetate **21**, bp 124–125° (0.05 mm). Material purified by glpc exhibited the following physical properties: ir (neat) 2.88, 5.72, 7.31, 8.05, 9.63 μ; nmr (CCl_4) τ 6.00–6.40 (m, 2, CH_2OAc), 8.04 (s, 3, $OCOCH_3$), 8.81 (s, 3, $HOCCH_3$), 9.08 (d, 3, J = 6 Hz, $CHCH_3$), 9.13 (s, 3, CH_3).

Anal. Calcd for $C_{17}H_{30}O_3$: C, 72.30; H, 10.71. Found: C, C, 73.6; H, 11.0.[18]

Dihydro-β-santalol Acetate (22).—The procedure described by Corey and coworkers[4] was employed. From 2.6 g of hydroxy acetate **21** (70% pure) there was obtained after distillation 2.06 g (77%) of product **22**, bp 120–125° (0.05 mm), which showed 85% purity by glpc. Redistillation and subsequent glpc purification afforded santalol acetate **22**: bp 90° (0.02 mm); $n^{32}D$ 1.4727; ir (film) 3.30, 5.72, 6.04, 7.32, 8.09, 9.65, 11.39 μ; nmr (CCl_4) τ 5.39, 5.64 (2 s, 2, $=CH_2$), 6.05–6.41 (m, 2, CH_2OAc), 7.41, 7.95 (2 b s, 2, C_1 H, C_4 H), 8.10 (s, 3, $OCOCH_3$), 8.99 (s, 3, CH_3), 9.09 (d, 3, J = 6 Hz, $CHCH_3$).

Anal. Calcd for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67. Found: C, 77.0; H, 10.7.

This acetate was also prepared from dihydro-β-santalol in 82% distilled yield by routine procedures.

Dihydro-β-santalol (3). A. From Saponification of Acetate 22.—A mixture of 1.7 g (6.5 mmol) of acetate **22** (85% pure), 1.0 g (six pellets) of potassium hydroxide, and 15 ml of ethanol was stirred under nitrogen for 24 hr. The product was isolated with ether and distilled to afford 1.24 g (87%) of colorless dihydro-β-santalol, bp 93–103° (0.03 mm). The alcohol could be further purified by column chromatography (Florisil elution with 2–5% ether in hexane) or redistillation, bp 106–107° (0.1 mm), on larger scale. Material purified by glpc exhibited the following: $n^{26}D$ 1.4920; ir (neat) 3.00, 3.29, 6.03, 7.21, 9.01, 9.65, 11.37 μ; nmr (CCl_4) τ 5.31, 5.57 (s, 2, $=CH_2$), 5.87 (s, 1, OH), 6.65 (q, 2, J_1 = 6 Hz, J_2 = 4 Hz, CH_2OH), 7.35, 7.89 (2 s, 2, C_1 H, C_4 H), 8.96 (s, 3, CH_3), 9.09 (d, 3, J = 6 Hz, $CHCH_3$); mass spectrum parent ion m/e 222.

Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 80.9; H, 11.8.

B. From Wittig Reaction on Borate 30.—The preparation of borate **30** from ketol **11** *via* azeotropic removal of water was accomplished as previously outlined. From 9.4 g (42 mmol) of ketol and 0.88 g (14 mmol) of boric acid there was obtained 10.4 g of crude borate **30**: ir (film) 5.72, 7.08, 7.50, 9.69, 10.59, 10.98 μ. The crude borate was used directly as follows. A mixture of 4.9 g (12.5 mmol) of a 61% mineral oil dispersion of sodium hydride and 100 ml of anhydrous dimethyl sulfoxide was heated at 70° under nitrogen for 1 hr. The resulting solution was cooled to 0° and treated with a warm solution of 49 g (137 mmol) of methyltriphenylphosphonium bromide in 150 ml of anhydrous dimethyl sulfoxide. The resulting mass was allowed to warm to room temperature, was stirred for 0.5 hr, and was treated with a solution of 10.4 g (42 mmol) of borate **30** in a small amount of ether. The reaction was stirred for 0.5 hr at room temperature and 24 hr at 70°. The cooled reaction was added to water and the product was isolated with pentane. The organic solution was washed with water and brine and dried ($MgSO_4$) and the solvent was removed at reduced pressure. Subsequent distillation afforded 8.87 g (95%) of clear santalol product **3** (87% pure by glpc) identical with the product previously isolated.

C. From Boron Trifluoride Etherate Dehydration of Diol 20.—A solution of 5.58 g (23.3 mmol) diol **20** in 23 ml of ether was rapidly treated under nitrogen with 2.33 ml of a 47% boron trifluoride etherate solution. The dark reaction was refluxed for 2 hr, cooled, and cautiously added to an excess of saturated aqueous sodium bicarbonate solution. The product was isolated with ether, washed with brine, and dried ($MgSO_4$) and the solvent was removed at reduced pressure. The residual oil was distilled to afford 4.55 g (87%) of santalol **3** which showed 98% purity by glpc. This material exhibited spectral properties identical with those previously described.

The conversion of ketol **11** to santalol **3** could be carried out by removing most of the ether solvent from the crude, dried solution of diol **20** and treating this solution (0.03 mol of **20**/30 ml of ether) with boron trifluoride etherate as described above. This treatment afforded, on work-up and distillation, bp 111–118° (0.08 mm), a 75% yield of 96% pure dihydro-β-santalol (**3**).

D. From Wittig Reaction on Ketol 11.—Essentially the same procedure employed on keto borate **30** was used in an effort to convert ketol **11** to santalol **3**. From 0.91 g of ketol **11** there was obtained 2.55 g of crude Wittig product which was chromatographed on 100 ml of Florisil. Several early 5% ether in hexane fractions containing rearranged product **23** were combined (225 mg) and pure material was isolated by preparative glpc. The purified hydroxy olefin **23** exhibited the following spectral properties: ir (neat) 2.96, 3.28, 6.10, 9.42, 10.03, 10.96 μ; nmr (CCl_4) τ 4.45 (m, AA'BX, 1, J_{AB} = 17 Hz, $J_{A'B}$ = 10 Hz, J_{BX} = 7 Hz, $>CH_XCH_B{=}CH_AH_{A'}$), 5.18 (d, 1, J_{AB} = 17 Hz, $=CH_AH_{A'}$), 5.21 (d, 1, $J_{A'B}$ = 10 Hz, $=CH_AH_{A'}$), 6.50 (d, 1, J = 4 Hz, CHOH), 9.02 (d, 3, J = 7 Hz, $CHCH_3$), 9.21 (s, 3, CH_3).

Latter 5% ether in hexane and 10% ether in hexane fractions yielded 278 mg of santalol product **3** which was subsequently evaporatively distilled to give 210 mg of oil identical with santalol isolated from the experiments described above.

***endo*-3-Methyl-3-(4-methyl-5-hexenyl)bicyclo[2.2.1]heptan-2-one (25).**—An ice-cooled solution of 100 mg of hydroxy olefin **23** in 5 ml of acetone was treated dropwise with Jones reagent[19] until a persistent red color developed. The reaction was stirred for an additional 15 min and the product was isolated with ether. The ether was washed with saturated sodium bicarbonate and brine and dried ($MgSO_4$), and the solvent was removed at reduced pressure to afford 89 mg (90%) of keto olefin **25**. Evaporative distillation afforded a purified sample which exhibited the following spectral properties: ir (neat) 3.30, 5.73, 6.11, 10.03, 10.95 μ; nmr (CCl_4) τ 4.46 (m, AA'BX, 1, J_{AB} = 17 Hz, $J_{A'B}$ = 10 Hz, J_{BX} = 7 Hz, $>CH_XCH_B{=}CH_AH_{A'}$), 5.19 (d, 1, J_{AB} = 17 Hz, $=CH_AH_{A'}$), 5.22 (d, 1, $J_{A'B}$ = 10 Hz, $=CH_AH_{A'}$), 9.05 (d, 3, J = 7 Hz, $CHCH_3$), 9.09 (s, 3, CH_3).

Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.8; H, 11.1.

Tetrahydro-β-santalol (31).—A solution of 0.67 g (3 mmol) of dihydro-β-santalol (**3**) in 15 ml of ethanol was hydrogenated over 1 hr using 50 mg of prereduced platinum oxide in 10 ml of ethanol. The catalyst was removed by filtration and the solvent was removed at reduced pressure to afford 0.76 g of oily residue. Hickman distillation, bp 120–145° (0.1 mm), afforded 0.56 g (84%) of colorless product which showed >95% purity by glpc.

Material collected by preparative glpc exhibited the following physical properties: $n^{27}D$ 1.4866 (lit.[12] $n^{20}D$ 1.4918); ir (neat) 3.00, 7.22, 7.26, 9.60 μ; nmr ($CDCl_3$) τ 5.65 (s, 1, OH), 6.68 (m,

(18) Efforts to obtain a carbon analysis consistent with the assigned structure **21** were unsuccessful. The method of synthesis and the properties exhibited by the compound, however, leave no doubt as to the assigned structure.

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2, CH_2OH), 9.08, 9.12, 9.18, 9.25 ($CHCH_3$'s); mass spectrum parent ion m/e 224.

Anal. Calcd for $C_{15}H_{28}O$: C, 80.29; H, 12.58. Found: C, 80.3; H, 12.5.

Registry No.—**3**, 34289-89-9; **5**, 4154-60-3; **6**, 17142-58-4; **7**, 33454-43-2; **8**, 26496-79-7; **10**, 34288-62-5; **11**, 34288-63-6; **13**, 34289-91-3; **14**, 5673-98-3; **15**, 17142-57-3; **16**, 34288-66-9; **17**, 26496-78-6; **19**, 26496-80-0; **20**, 26133-24-4; **21**, 34289-93-5; **22**, 34288-69-2; **25**, 34288-70-5; **31**, 34288-71-6.

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Conformations of Acetylated Glyculose Phenylosotriazoles and Para-Substituted Phenylosotriazoles[1-3] in Solution

H. El Khadem, Derek Horton,*[4] and J. D. Wander

Department of Chemistry, The Ohio State University, Columbus, Ohio 43210

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Phenylosotriazoles and some para-substituted phenylosotriazoles of D-*erythro*- and L-*threo*-pentulose, D-*arabino*-, D-*lyxo*-, and L-*xylo*-hexulose, and 6-deoxy-L-*arabino*-hexulose have been examined as their peracetates by nmr spectroscopy at 100 MHz in chloroform-*d* solution. In each example, shielding of the protons along the side chain increases with distance from the heterocycle. From the spin–spin coupling data it can be inferred that the carbohydrate chain adopts a planar, zigzag arrangement of carbon atoms unless an eclipsed, 1,3 interaction between polar groups would thereby be generated or unless the polar substituent at C-2 (of the side chain) would thereby bisect the angle between the substituents on C-1, namely, the heterocycle and an acetoxyl group. Except for the arabino derivatives, which appear to be stabilized by stereochemical factors further along the chain, the favored conformations adopted when either or both of the aforementioned features would be present in the planar, zigzag arrangement are derived from the planar form by rotation about one or more of the carbon–carbon bonds along the chain. The variations of conformational preference displayed by the various acetylated, acyclic sugar derivatives examined to date are not presently amenable to more than superficial rationalization on the basis of apparent "size" of the chain-terminal group.

Conformational analysis of acyclic molecules can be traced back to van't Hoff[5] and to a casual observation by Rosanoff.[6] The statements of these authors were as general as they were fundamental, and the validity of their interpretations has not declined in the intervening years. Later interpretations of phenomena related to conformational properties of acyclic sugar molecules[7] drew specific conclusions that have been refuted.[8,9]

Recent work[2,9-20] has employed nmr spectroscopy to determine the conformational preferences of a variety of acyclic carbohydrate derivatives. In the initial paper of this series[10] the planar, zigzag arrangement of the carbon atoms in the side chain of 2-(D-*arabino*-tetrahydroxybutyl)quinoxaline and its tetraacetate was inferred to be the favored conformation by consideration of vicinal, proton–proton spin couplings as they relate to approximate angular dependences.[21] Implicit, qualitative corrections for the effects of substituent electronegativity[22] were made by assuming couplings of 2–4 Hz for gauche, vicinal protons and 8–9 Hz for vicinal, antiparallel protons, by analogy with data for acetylated, cyclic, carbohydrate systems.[23-25] Similarly, for a series of nonacetylated phenylosotriazole derivatives, the planar, zigzag arrangement of the carbohydrate chain was shown[11] to be favored, except when this would lead to a parallel, 1,3 interaction between oxygen atoms on the chain; such an interaction, as arising in L-*xylo*-hexulose phenylosotriazole, is alleviated by the molecule's adopting a different rotameric form about one or more of the carbon–carbon bonds of the chain.

Examination of a configurationally complete series of acetylated diethyl dithioacetals confirmed[12] the influence of parallel, 1,3 interactions in determining favored conformations of acyclic molecules. Coupling data for members having the ribo and xylo configurations indicate that, by rotation about C-3–C-4 or C-2–C-3, respectively, stabilization is achieved by the generation of "sickle" conformers free of 1,3 interactions. The corresponding acetylated diphenyl dithioacetals[13,14] show essentially identical behavior, except for

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a diminution in the magnitude of $J_{1,2}$, and a downfield shift of the H-1 signal. The variation in $J_{1,2}$ might reflect a sterically induced change of rotamer populations about C-1–C-2, but the attendant, large change of field position of the H-1 resonances suggested[13] that differences in electronic character[21,26] between the C-1 substituents influence the value of $J_{1,2}$. A series of acetylated dimethyl acetals showed[2] conformational behavior entirely analogous to that of the diethyl dithioacetals.

Although the steric size of the aldehyde group might be expected to be less than that of the bis(ethylthio)-methyl group, no substantial changes of chemical shifts or couplings were observed[14] between members of a configurational series of *aldehydo*-aldose peracetates and the corresponding dithioacetals, except for a shift of the H-1 signal to below τ 0.5 and a decrease in $J_{1,2}$ to near zero. The $J_{1,2}$ coupling was considered in terms of the Karplus relationship,[21] with reservations expressed about the effect of the electronegative O-1 and the trigonal hybridization at C-1; the conformations thus indicated were consistent with those deduced by various methods for simpler carbonyl derivatives.[27] For the xylo derivative there was indication that two sickle forms were contributing significantly to the conformational equilibrium.[25,28] As noted by Chilton and Krahn[15] in a conformational study of some acetylated quinoxaline derivatives having acyclic, carbohydrate side chains, coupling data can be accommodated by more than one conformer. However, an equilibrium between forms having eclipsed 1,3 interactions is not considered probable when an equilibrium between forms free of such interactions can accommodate the observed couplings.

In analyzing the nmr spectra of several 3 4,5,6-tetraacetoxy-*trans*-1-nitro-1-hexenes, Williams[16] displayed cautious reserve in assigning rotamer states about the C-2–C-3 bond, because of shortage of available reference information; however, the conformational behavior of the chain of tetrahedrally hybridized carbon atoms was shown to accord with previous[10–12] and contemporary[9,13–15,17] reports.

The elegance and simplicity of the Karplus expression provides an extreme temptation for incautious overinterpretation of the significance of coupling data. The interdependence of vicinal couplings, dihedral angles, and substituent electronegativity has been demonstrated in cyclic carbohydrate derivatives,[22,24] but a definitive treatment of this relationship in acyclic molecules is currently lacking. Extraction of exact dihedral bond angles in acyclic molecules[17] is certainly an overapplication of the Karplus equation, and the deduction of quantitative values for the distributions of rotameric states about each carbon–carbon bond along the acyclic chain[18] requires perspicacious consideration of the limits of its precision, as it is predicated upon the implied conditions (1) that ideal bond geometry prevails, (2) that only the three fully staggered rotameric forms around each bond are represented, (3) that there is angular independence of the effect of acetoxyl substituents upon vicinal couplings and (4) that the couplings between antiparallel and gauche pairs of protons invariably adopt those values assumed by analogy with cyclic derivatives.

X-Ray crystallographic studies on alditols[29,30] suggest that ideal bond geometry in these molecules is the exception rather than the rule, and the observed vicinal, dihedral angles in crystalline ribitol range[30] from 46.6 to 77.9°. In solution, rapid time averaging presumably takes place among all possible rotameric states along each carbon–carbon bond; positional time averaging between minimum-energy rotamers is an approximation to this condition. It is well documented that vicinal couplings for a given orientation are dependent upon substituent electronegativity;[22,24] furthermore, the report[9] that the *field positions* of signals in the nmr spectra of the methyl 2,3,4,6-tetra-*O*-acetyl-5-hexulosonates are dependent upon the orientation of the corresponding protons (with respect to the adjacent acetoxyl group) suggests that the *couplings* of such protons will be affected simultaneously. This implies that the coupling constants for the two different rotamers having vicinal, gauche protons will normally be different. Finally, the model couping values used[18] (9.5 Hz antiparallel, 2.0 Hz gauche) are inadequate for uncritical generalization; for example, 2,3,4,5-tetra-*O*-acetyl-6-deoxy-*aldehydo*-L-galactose shows[14] couplings more extreme ($J_{2,3}$ = 1.5 Hz, $J_{3,4}$ = 9.8 Hz) than these estimates.

Conformational equilibria of pyranoid sugar derivaatives have been measured quantitatively[25,28] by performing nmr studies at a temperature low enough for interconversion to be slow on the nmr time scale, so that spectra of individual conformers can be observed ("conformational freeze-out"), and also by "averaging of spin couplings" by use of model compounds of demonstrated conformational homogeneity.[25,31] Because of the greater mobility of acyclic systems, a similar low-temperature study has not yet been applied successfully to acyclic sugar derivatives, nor have true, limiting values for couplings been established. At present, it seems, therefore, excessively speculative to attempt quantitative description of conformational equilibria in these acyclic systems. A qualitative identification of conformers as major or minor is a conservative, but more realistic, application of existing methods and information and can be expected to generate fewer errors of concept than a detailed quantitative treatment based on unsound foundations. An error limit of the order of 10%, as implied in the level of differentiation attributed to the analytical method of Lee and Scanlon[18] and applied with other systems,[9] is clearly unrealistic. Likewise, attempts[18] to calculate conformational behavior, from interaction energies between substituents

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Table I
Chemical Shift Data for Osotriazole Peracetates

Compd	Confign	Chemical shifts, τ, in chloroform-d: Triazole proton	H-1	H-2	H-3[a]	H-3′	H-4[a]	H-4′	Acetyl groups	Aromatic[b]
1	Arabino	2.23	3.60	4.24	4.65		5.64	5.82	7.94, 7.92, 7.90, 7.84	2.57, 1.96
2	Arabino	2.25	3.65	4.28	4.69		5.66	5.85	7.94 (2), 7.91, 7.85	2.42, 2.08
3	Arabino	2.24	3.64	4.28	4.68		5.67	5.86	7.97, 7.95, 7.93, 7.87	1.84, 1.58
4	Lyxo	2.21	3.80	4.19	4.48		5.67	5.96	8.04, 7.97 (2), 7.94	2.63, 1.96
5	Lyxo	2.09	3.79	4.19	4.45		5.64	5.93	7.98, 7.92, 7.90, 7.87	1.77, 1.61
6	Xylo	2.26	3.76	4.25	4.81		5.69	5.99	7.99, 7.92, 7.91, 7.88	2.65, 1.98
7	Xylo	2.18	3.84	4.28	4.63		5.66	5.86	7.97, 7.95, 7.92, 7.85	1.83, 1.66
8	Arabino	2.23	3.63	4.37	4.88		8.75		8.00, 7.96, 7.91	2.63, 1.95
9	Arabino	2.08	3.76	4.35	4.66		8.71		7.96, 7.94, 7.90	1.75, 1.61
10	Erythro	2.23	3.71	4.33	5.56	5.73			7.97 (2), 7.90	2.63, 1.94
11	Erythro	2.25	3.75	4.35	5.57	5.75			7.95 (2), 7.87	2.81, 1.97
12	Threo	2.19	3.66	4.29	5.53	5.90			7.93, 7.89, 7.86	2.57, 1.92

[a] When two protons are present on the same carbon atom, the one whose signal resonates at higher field is designated by a prime, *e.g.*, H-3′. [b] Of the substituent on N-2 of the 1,2,3-triazole ring.

Chart I

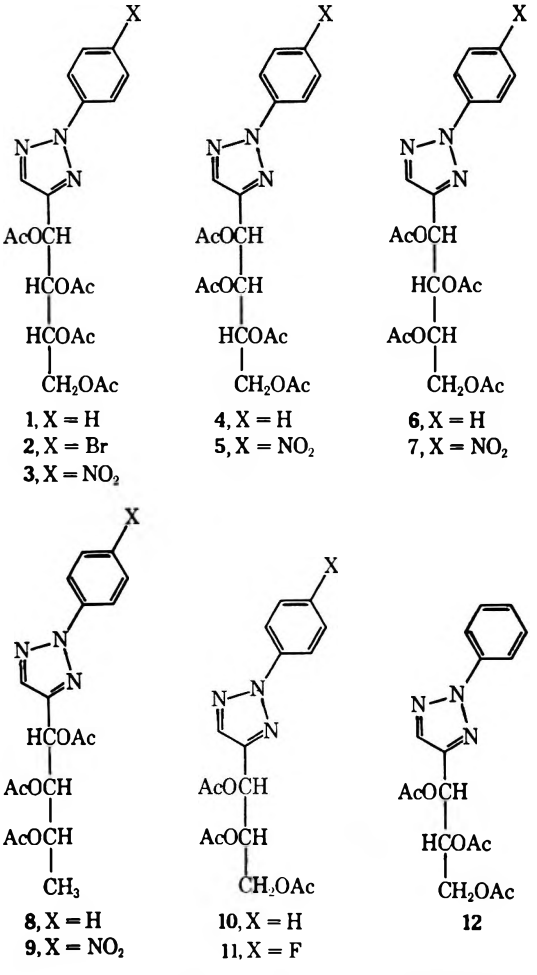

Table II
First-Order Coupling Constants for Osotriazole Peracetates

Compd	Confign	Coupling constants, Hz: $J_{1,2}$	$J_{2,3}$[a]	$J_{2,3'}$[a]	$J_{3,3'}$[a]	$J_{3,4}$[a]	$J_{3,4'}$[a]	$J_{4,4'}$[a]
1	Arabino	3.8	8.2			3.4	4.5	12.2
2	Arabino	3.6	8.0			3.6	5.5	12.2
3	Arabino	3.6	7.9			3.1	6.0	12.3
4	Lyxo	7.8	3.1			4.7	7.0	12.0
5	Lyxo	7.7	3.3			5.0	6.8	12.0
6	Xylo	7.5	3.8			5.4	6.4	11.8
7	Xylo	3.6	8.0			3.4	5.5	12.2
8	Arabino	5.4	6.2			6.2		
9	Arabino	7.8	3.4			6.2		
10	Erythro	5.4	4.0	6.0	12.4			
11	Erythro	5.6	4.0	6.1	12.1			
12	Threo	6.4	4.4	5.6	12.0			

[a] See footnote *a* of Table I.

originally defined for cyclic systems, appear premature at this stage.

The present report enumerates the favored conformations in solution, as determined by nmr spectroscopy, of tetra-*O*-acetyl-D-*arabino*-hexulose phenylosotriazole[32] (**1**) and its *p*-bromophenyl[33] (**2**) and *p*-nitrophenyl[34] (**3**) analogs, of tetra-*O*-acetyl-D-*lyxo*-hexulose phenylosotriazole[35] (**4**) and its *p*-nitrophenyl derivative[36] (**5**), of tetra-*O*-acetyl-L-*xylo*-hexulose phenylosotriazole[35] (**6**) and its *p*-nitrophenyl analog[36] (**7**), of tri-*O*-acetyl-6-deoxy-L-*arabino*-hexulose phenylosotriazole[37,38] (**8**) and its *p*-nitrophenyl analog[36] (**9**), of tri-*O*-acetyl-L-*erythro*-pentulose phenylosotriazole[38] (**10**) and its *p*-fluorophenyl analog[39] (**11**), and of tri-*O*-acetyl-D-*threo*-pentulose phenylosotriazole[35] (**12**) (Chart I).

Spectral Measurements and Analysis.—The 100-MHz nmr spectrum of each compound (**1**–**12**) was measured at ~24° in chloroform-*d* containing 5% (v/v) of tetramethylsilane as an internal standard. Coupling patterns that could not be interpreted by inspection were resolved by double irradiation, and double irradiation was also used to verify assignments made by inspection. The chemical shifts and coupling constants measured for **1**–**12** are recorded in Tables I and II, respectively. The acetoxyl methyl groups resonated as a series of sharp singlets between τ 7.84 and 8.04. Aryl-proton resonances were observed near τ 2.0 as an AA′BB′ system in the spectra of **2**, **3**, **5**, **7**, and **9**, or near τ 2.2 as a pair of complex multiplets in the seven unsubstituted examples. A singlet at about τ 2.23 was caused by H-5 of the triazole ring (H-1 of

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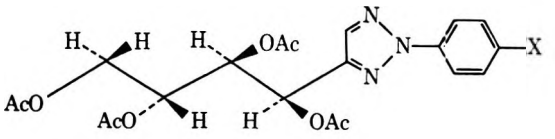
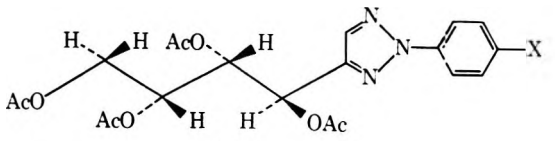
(38) W. T. Haskins, R. M. Hann, and C. S. Hudson, *J. Amer. Chem. Soc.*, **69**, 1461 (1947).
(39) B. B. Bishay, H. El Khadem, and Z. M. El-Shafei, *J. Chem. Soc.*, 4980 (1960).

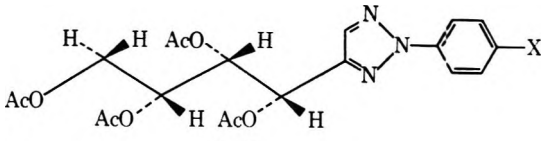
CHART II



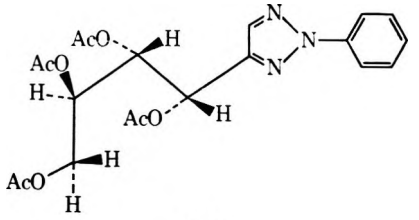
1a, 2a, 3a



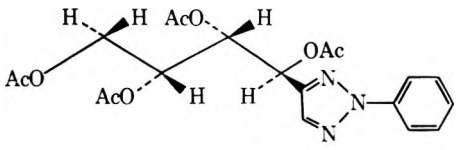
4a, 5a



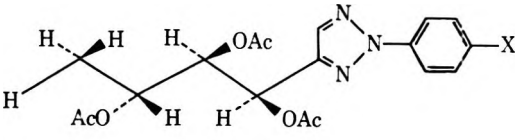
6a, 7a



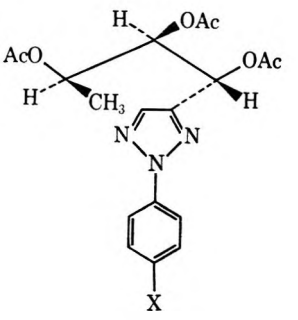
6b, 7b



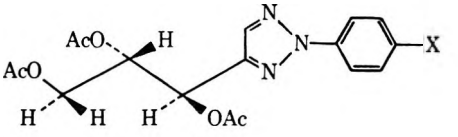
6c



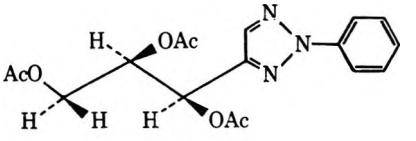
8a, 9a



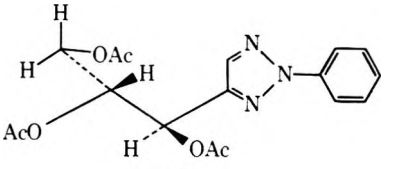
8b, 9b



10a, 11a



12a



12b

the original sugar); it was shifted slightly downfield in the nitro-substituted derivatives.

The C-1 proton of the polyacetoxyalkyl side chain (H-3 of the original sugar) gave rise to a sharp doublet near τ 3.7 whose spacing gave $J_{1,2}$ directly. The signal next upfield of H-1 was assigned to H-2; it appeared as a complex multiplet in **10–12** but as a well-defined quartet yielding $J_{1,2}$ and $J_{2,3}$ in **1–9**. Also, in **1–9**, H-3 resonated at somewhat higher field than H-2, near τ 4.6 as a well-resolved multiplet split by H-2 and the protons on C-4; this signal appeared as a quintet in the spectrum of **8** because $J_{2,3}$ and $J_{3,4}$ were fortuitously equal. The methylene protons of the terminal acetoxymethyl group (at C-4 of **1–9**, C-3 of **10–12**) resonated at highest field of the protons on the chain, near τ 5.6 and 5.9, as the A and B portions of an ABX system, from which the remaining coupling constants were measured. The proton resonating at higher field of the methylene protons is indicated by a primed number. The protons of the C-4 methyl group (in **8** and **9**) gave rise to a doublet at τ ~8.75 showing the coupling $J_{3,4}$.

In all examples the ratio of chemical-shift difference to coupling constant for coupled protons was of sufficient magnitude to ensure that the spacings measured approximate closely to the true coupling constants. The results are discussed for each configurational series in turn.

Tetra-*O*-acetyl-D-*arabino*-hexulose Phenylosotriazole (1), *p*-Bromophenylosotriazole (2), and *p*-Nitrophenylosotriazole (3).—The spin couplings and chemical shifts for protons on the chain in **1–3** vary only slightly as a function of the para substituent on the phenyl group. The magnitudes of $J_{1,2}$ and $J_{3,4}$ are small, indicating gauche relationships between H-1 and H-2, and between H-3 and H-4, and the large (8 Hz) $J_{2,3}$ coupling indicates that H-2 and H-3 are antiparallel in the favored conformer. The $J_{3,4}$ coupling is rather small (4.5–6.0 Hz) and shows that, as found in the *aldehydo*-pentose tetraacetates,[14] C-3–C-4 rotamer states having H-3 gauche disposed to H-4′ compete with the antiparallel conformer; the effectiveness of this competition appears to decrease somewhat as the electronegativity of the para substituent increases, but detailed speculation on this point is not warranted. Compounds **1–3** thus favor the extended, planar, zigzag conformations **1a–3a** (Chart II), respectively, in line with earlier results[2,9–13,15–18] for acetylated, acyclic carbohydrate derivatives having the arabino stereochemistry.

In the absence of potential hydrogen-bonding interactions,[11] the bulky triazole ring structure would be

expected to extend away from the acyclic side chain in the favored conformation. The relative invariance of chemical shift of the acetoxyl methyl signals (and of the protons along the chain) as the para substituent is changed supports this hypothesis.

Tetra-*O*-acetyl-D-*lyxo*-hexulose Phenylosotriazole (4) and *p*-Nitrophenylosotriazole (5).—The coupling data for **4** and **5** accord with invocation of the anticipated[2,9-13,15-17] extended planar, zigzag structures **4a** and **5a**, respectively, as the favored conformations. The required, small value of $J_{2,3}$ and the predictably large values of $J_{1,2}$ and $J_{3,4}$, accord completely with this formulation, and the slight increase in magnitude of $J_{3,4}$ suggests a moderate representation by the C-3–C-4 rotamer state having H-3 antiparallel to H-4, although possible effects from slight bond distortion cannot be excluded.

Tetra-*O*-acetyl-L-*xylo*-hexulose Phenylosotriazole (6) and *p*-Nitrophenylosotriazole (7).—In acetylated, acyclic sugar chains that in the extended form would have an eclipsed, 1,3 interaction between substituent groups it is now well established[2,9,11-14,16,18] that rotation about an internal carbon–carbon bond to alleviate this interaction generates a "sickle" conformation as the favored form. In systems having the xylo configuration and having only tetrahedrally hybridized carbon atoms along the chain, rotation occurs[10-13] largely along C-2–C-3. Data from the literature indicate that introduction of a trigonally hybridized center into such molecules leads to unpredictable conformational behavior. In tetra-*O*-acetyl-D-xylonothioamide,[18] rotation appears to be favored about the C-3–C-4 bond, but in 2-(D-*xylo*-tetraacetoxybutyl)-4-(*p*-bromophenyl)-1,3-thiazole[18] the C-1–C-2 bond (of the side chain) appears to be the axis for rotation. Coupling data measured for *aldehydo*-D-xylose tetraacetate,[14] D-*xylo*-3,4,5,6-tetraacetoxy-*trans*-1-nitro-1-hexene,[16] and methyl 2,3,4,6-tetra-*O*-acetyl-D-*xylo*-hex-5-ulosonate[9] are best reconciled in terms of a conformational equilibrium between two sickle conformers. A method proposed[18] for quantitative prediction of the carbon–carbon bond along which rotation will occur appears altogether speculative when reliable values for the energies of interaction between substituents are lacking.

The coupling data for **7** indicate that, as in the tetra-*O*-acetyl-D-xylose dithioacetals,[12,13] the favored conformation is derived from the extended form **7a** by rotation about the second C–C bond of the chain removed from the larger end group; in compound **7** this bond is C-2–C-3 and the favored form is the sickle conformation **7b**. The relative magnitudes of $J_{1,2}$ (3.6 Hz) and $J_{2,3}$ (8.0 Hz) are consistent with **7b** and indicate a considerable degree of conformational homogeneity. However, in **6** the magnitudes of $J_{1,2}$ (7.5 Hz) and $J_{2,3}$ (3.8 Hz) are interchanged, indicating that the corresponding sickle form (**6b**) does not contribute significantly to the conformational equilibrium[28] of **6** and that there preponderates the alternative sickle form **6c**, obtained by rotation about the C-1–heterocycle bond in **6a**, which likewise provides relief from 1,3 interactions. It is surprising, and somewhat disconcerting in attempts to generalize, to note the radical change in the conformational behavior of the chain that results from such an apparently minor change as nitration at the remote para position of the phenyl moiety. A similar drastic change is observed in the 6-deoxy-L-*arabino*-hexulose derivatives considered next.

Tri-*O*-acetyl-6-deoxy-L-*arabino*-hexulose Phenylosotriazole (8) and *p*-Nitrophenylosotriazole (9).—The coupling data observed for **8** ($J_{1,2}$ = 5.4 Hz, $J_{2,3}$ = 6.2 Hz) are in qualitative accord with the planar, zigzag conformation **8a**, but the intermediate magnitudes of these couplings indicate substantial contributions by other rotameric forms. The corresponding couplings in the *p*-nitro derivative **9** are, however, altogether inconsistent with the planar, zigzag conformation **9a**. The large value of $J_{1,2}$ (7.8 Hz) and the small value (3.4 Hz) of $J_{2,3}$ suggest that **9** may adopt a conformation **9b**, obtained by rotating **9a** along C-1–C-2 and along the C-2–C-3 bond and in which H-2 is antiparallel to H-1 and gauche disposed to H-3. This conformation is free of eclipsed 1,3 interactions and corresponds to an extended, planar zigzag form if the steric requirement at the 1- and 3-acetoxyl groups be reckoned greater than that of the methyl and *p*-nitrophenylosotriazolyl groups. If the *p*-nitrophenylosotriazolyl group has a steric effect smaller than the unsubstituted phenylosotriazolyl group, as already suggested for **5** and **6**, the conformational behavior of **8** can be rationalized in terms of an equilibrium between **8a** and **8b**.

Tri-*O*-acetyl-L-*erythro*-pentulose Phenylosotriazole (10) and *p*-Fluorophenylosotriazole (11).—It has been suggested by Angyal and James[9] that the acetylated, four-carbon sugar chains are conformationally less predisposed toward a single, favored conformation than are five-carbon analogs wherein a terminal hydrogen atom has been replaced by a terminal acetoxymethyl group. The data for **10** and **11** accord with this view; the magnitudes of $J_{1,2}$ indicate extensive, but definitely not exclusive, population of the planar, zigzag forms **10a** and **11a** wherein H-1 is antiparallel to H-2. The argument of stabilization by prolongation of the chain would also seem to predispose **10** and **11** (and **12**) to moderate torsional deviations from ideal geometry, an important consideration before making any attempt to calculate conformational populations. The intermediate values of $J_{2,3}$ and $J_{2,3'}$ suggest that the rotamers about C-2–C-3, especially the two having H-2 antiparallel to one C-3 proton, are separated by relatively small energy differences, so that there is substantial population of more than one rotameric state along this terminal C–C bond, as previously suggested for tetra-*O*-acetyl-*aldehydo*-L-arabinose.[14]

Tri-*O*-acetyl-D-*threo*-pentulose Phenylosotriazole (12).—Considerations made for **10** and **11** also apply to **12**, with a notable exception that the coupling data do not support the planar, zigzag form **12a** as the major conformer. This molecule appears to represent a situation where vicinal, gauche interactions are sufficient to dictate rotational alteration. The large magnitude (6.4 Hz) of $J_{1,2}$ is accommodated only by a major representation from the form **12b**, in which H-1 and H-2 are antiparallel, and in which the 1,2-gauche interaction between the phenylosotriazolyl group and the acetoxymethyl group on C-2 is alleviated. Again the idea of conformational stabilization by chain extension[9] is supported by comparing the behavior of **12** with that of its 3-acetoxymethyl homolog **1**, which favors the fully extended form to a much greater extent.

Conclusions

These data further establish that rotamers of acyclic carbohydrate derivatives that involve an eclipsed 1,3 interaction between substituents are energetically disfavored, a situation that is generally alleviated by rotation about an internal carbon–carbon bond to a different, gauche rotamer (sickle form). The short (three carbon) chains are more prone to populate more than one conformational state to a substantial extent, whereas prolongation of the chain tends to cause the molecule to favor one conformation more exclusively, this being the most extended arrangement compatible with avoidance of 1,3 interactions.

It is suggested that application of the Karplus equation, to quantitative determinations of dihedral angles on rotamer populations, from data obtainable by present methods, is less likely to advance the understanding of conformational behavior of polysubstituted, acyclic chains in solution than a conservative, qualitative treatment, at least until experimental methods of greater finesse are developed.

Registry No. —**1**, 7770-63-0; **2**, 34297-73-9; **3**, 34297-74-0; **4**, 16346-56-8; **5**, 34297-75-1; **6**, 34297-76-2; **7**, 34290-22-7; **8**, 34297-77-3; **9**, 34297-78-4-**10**, 7599-11-3; **11**, 34288-31-8; **12**, 6631-64-7.

A Convenient Synthesis of Myosmine

BRADFORD P. MUNDY,* BRENT R. LARSEN, LEE F. MCKENZIE,[1] AND GARY BRADEN

Department of Chemistry, Montana State University, Bozeman, Montana 59715

Received October 7, 1971

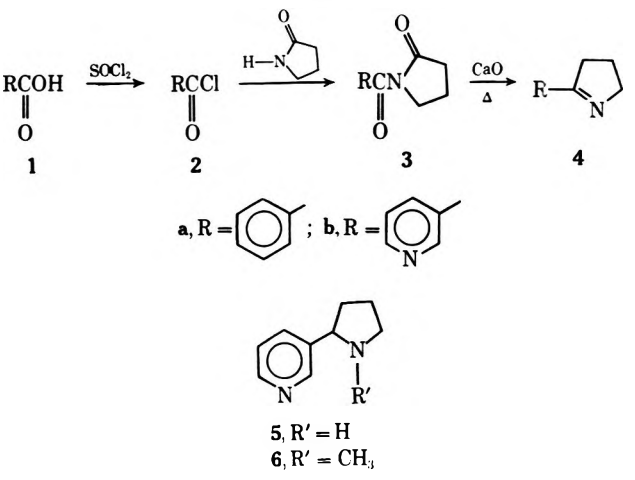
A three-step synthesis of myosmine, one of the pyrrolidine alkaloids found in various *Nicotiana species*, is described.

Myosmine (**4b**) is one of the tobacco alkaloids, and its structure has been elucidated by degradation[2] and spectral methods.[3] It has been previously synthesized by other research groups.[2b,4] We wish now to report a convenient three-step synthesis of this alkaloid (Scheme I).

The envisioned synthesis required, as the critical step, the pyrolysis of *N*-nicotinoyl-2-pyrrolidone (**3b**). Because of the wealth of data available for 2-phenylpyrroline (**4a**),[5] this proved to be a useful model for the initial evaluation of synthetic procedures. The reaction of benzoyl chloride with 2-pyrrolidone yielded the expected product, *N*-benzoyl-2-pyrrolidone (**3a**). Pyrolysis of an equal weight mixture of **3a** and calcium oxide resulted in a crude distillate, shown to be primarily 2-pyrrolidone.[6] However, the simplicity of the procedure more than compensated for the low yield of **4a** and encouraged us to apply the method, without trying to maximize yields, to the synthesis of myosmine.

Nicotinoyl chloride (**2b**) was prepared by treating nicotinic acid with an excess of thionyl chloride. Acylation of 2-pyrrolidone with **2b** afforded **3b**, which when subjected to the conditions of pyrolysis resulted in a crude product mixture which contained 67% **4b** and 33% 2-pyrrolidone.[7] The identity of **4b** was confirmed by analysis of its nmr spectrum, mass spectrum,[8] and the melting point of the picrate derivative.[4] The reported conversion of myosmine to nornicotine (**5**) and nicotine (**6**)[8] thus realizes a simple synthesis of the tobacco alkaloids.

SCHEME I
SYNTHESIS OF MYOSMINE



Experimental Section[9]

N-**Benzoyl-2-pyrrolidone** (**3a**).—A solution of 2-pyrrolidone (85.1 g) and pyridine (158 g) was added to 140 g of benzoyl chloride. After 3 days at room temperature, the pyridine was removed and the residue was suspended in benzene. This solution was washed with water, dried, and concentrated. The crude product was crystallized from hot ethanol to give 81.2 g (56%) of **3a**, mp 91° (lit.[5] mp 92°).

2-Phenylpyrroline (**4a**).—The general procedure for carrying out the pyrolysis involved intimately mixing **3a** with an equal weight of calcium oxide and placing the reactants in a distilling flask. After being heated with a free flame, the crude product mixture was collected and purified. The melting point (35–39°, lit.[5] mp 44°) and the melting point of the picrate derivative (198°, lit.[5] mp 198°), buttressed by nmr, ir, and uv spectral data, confirmed the identity of the product from this sequence.

(1) Undergraduate research participant during the summer of 1970 (NSF Grant GY 7358).

(2) (a) E. Späth, A. Wenusch, and E. Zajic, *Ber.*, **69**, 393 (1936); (b) C. F. Woodward and A. Eisner, *J. Amer. Chem. Soc.*, **66**, 911 (1944).

(3) B. Witkop, *ibid.*, **76**, 5597 (1954).

(4) E. Späth and L. Mamoli, *Ber.*, **69**, 757 (1936).

(5) F. Korte and H.-J. Schulze-Steiner, *Chem. Ber.*, **95**, 2444 (1962).

(6) We have not thoroughly investigated the mechanistic course of this reaction. However, we have noted considerable reductive cleavage occurring, finding benzene, toluene, and trimethylamine in low yields in the reaction products. The yield of **4a** was generally in the order of 15–20%, as much as 85% 2-pyrrolidone having been observed in the reaction product.

(7) This constitutes a 65% yield of **4b**, based on **3b**.

(8) A. M. Duffield, H. Budzikiewicz, and C. Djerassi, *J. Amer. Chem. Soc.*, **87**, 2926 (1965).

(9) The boiling points and melting points are uncorrected.

N-Nicotinoyl-2-pyrrolidone (3b).—Nicotinoyl chloride hydrochloride, prepared from 20 g of nicotinic acid and 40 g of thionyl chloride, was dissolved in 10 g of pyridine and was stirred at room temperature for 1 hr. After this time, 40 g of 2-pyrrolidone was slowly added to the reaction flask and the mixture was stirred for ~15 hr at room temperature. The reaction mixture was dissolved in methylene chloride and was washed with dilute hydrochloric acid. The aqueous solution was adjusted to pH 9 and extracted with methylene chloride. After the mixture dried, the solvent was removed and the crude solid was crystallized from chloroform–hexane. The crystalline product (25.5 g, 73%) exhibited mp 104–105° (lit.[5] mp 103°).

Anal. Calcd for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.78; H, 5.03; N, 14.82.

Myosmine (4b).—*N*-Nicotinoyl-2-pyrrolidone (1.5 g) was mixed with an equal weight of calcium oxide, and the mixture was subjected to free-flame distillation. The crude product from this procedure (1.3 g) was shown by glc analysis (6-ft column of 2% OV-17) to be 67% myosmine and 33% 2-pyrrolidone.[10] Distillation of the crude product yielded myosmine [0.75 g 65%)], bp 82–86° (0.5 mm) [lit.[4] mp 82–84° (0.5 mm)]. This material was shown by glc to be uncontaminated with 2-pyrrolidone. Myosmine was characterized by its mass spectrum,[8] and a dipicrate derivative (mp 184–185, lit.[4] mp 184–185°). The nmr spectrum was consistant with the structure.

Registry No.—3b, 34236-73-2; 4b, 532-12-7.

Acknowledgments.—We would like to express our appreciation to the National Science Foundation for support of L. F. M. and to Professor Henry Rapoport for helpful discussions. We acknowledge the financial assistance of The Endowment and Research Foundation of Montana State University.

(10) Other possible reaction products which might constitute the remainder of the crude product were not found from this glc analysis; only the two reported products were noted, in the ratio of 67:33.

LL-D253α, -β, and -γ, Novel Chromanones from the Fungus *Phoma Pigmentivora*

W. J. McGahren,* G. A. Ellestad, G. O. Morton, and M. P. Kunstmann

Process and Analytical Research Section, Lederle Laboratories, A Division of American Cyanamid Company, Pearl River, New York 10965

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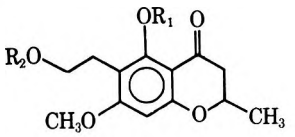
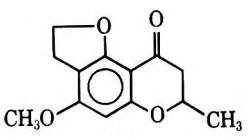
The fungus *Phoma pigmentivora* elaborates (2*R*)-5-hydroxy-6-(2′-hydroxyethyl)-7-methoxy-2-methylchromanone (LL-D253α, I) in good yield in both surface and agitated fermentations. In surface fermentation, the culture also produces in lower yield the monoacetate of this material or (2*R*)-5-hydroxy-6-(2′-acetoxyethyl)-7-methoxy-2-methylchromanone (LL-D253β, II). Treatment of the major metabolite with concentrated sulfuric acid gives 7-methoxy-5,6-(2′,3′-dihydrofuro)-2-methylchromanone (LL-D253γ, III) which is also produced in low yield in agitated fermentations of the fungus. The basic degradation of these chromanones is discussed.

In our quest for novel metabolites of pharmacological interest, we investigated the fungus *Phoma pigmentivora* or Lederle culture D253. Culture D253 was grown both by the surface and deep fermentation methods which are described in the Experimental Section. The still fermentation process in the presence of beechwood shavings[1] yielded the metabolites LL-D253α and LL-D253β which are represented respectively by structures I and II.

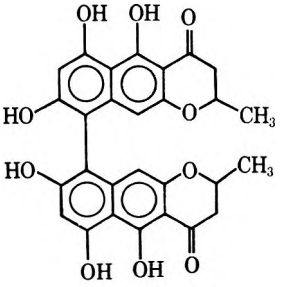




III

I, $R_1 = R_2 = H$
II, $R_1 = H$; $R_2 = CH_3CO$
IV, $R_1 = R_2 = CH_3CO$
V, $R_1 = CH_3$; $R_2 = H$
VI, $R_1 = CH_3CO$; $R_2 = H$

Agitated fermentations of the fungus yielded I as the major product and LL-D253γ or III. These metabolites are 2-methylchromanones and on tlc give a characteristic yellow spot when sprayed with sulfuric acid and heated for 1 min or so. To our knowledge, only two microbial metabolites have been isolated so far which have been characterized as chromanones. Allport and Bu'Lock isolated 5-hydroxy-2-methylchromanone from the ascomycete *Daldinia concentrica*.[2] This natural product was optically inactive. The other chromanone, rosellinic acid, was isolated from culture filtrates of *Rosellinia necatrix Berlese*[3] and shown to be 6-carboxy-8-hydroxy-2-methylchromanone.[4] A yellow pigment called cephalochromin[5] has been briefly reported. This material is a dimer in which the 2-methylchromanone nucleus is fused to an aryl group as shown below.



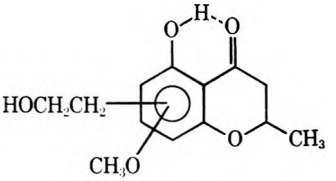
cephalochromin

The major metabolite I melts at 188–189°, is optically active, and has the empirical formula $C_{13}H_{16}O_5$. A uv maximum of the material in methanol at 287 nm is shifted to 325 nm in basic solution in addition to displaying a large hyperchromic effect. The ir spectrum shows a carbonyl frequency at 1655 cm^{-1} which is shifted to 1699 cm^{-1} in the diacetate IV. All of these features point to a chelated phenolic ketone.

The nmr spectrum of the monomethyl ether V was

(1) F. Kavanagh, A. Hervey, and W. J. Robbins, *Proc. Nat. Acad. Sci.*, **37**, 570 (1951).
(2) D. C. Allport and J. D. Bu'Lock, *J. Chem. Soc.*, 654 (1960).
(3) Y. Chen, *Agr. Biol. Chem.*, **24**, 372 (1960).
(4) Y. Chen, *ibid.*, **28**, 431 (1964).
(5) G. Tertzakina, R. H. Haskins, G. P. Slater, and L. R. Nesbitt, *Proc. Chem. Soc.*, 195 (1964).

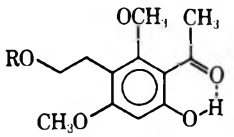
easier to interpret than that of the parent compound. A split methyl signal at δ 1.48 ($J \sim 7$ cps) and a complex quartet at δ 4.50 account for a methyl group and a single proton on a carbon bearing an oxygen. A sharp exchangeable singlet at δ 1.85 is due to a relatively nonacidic hydroxyl proton. Two almost coincidental signals around δ 2.51 and a singlet at δ 2.63 together account for a methylene group adjacent to a carbonyl, while a benzylic methylene group is represented by a triplet centered at δ 2.87 ($J \sim 7$ cps). Another triplet at δ 3.73 ($J \sim 7$ cps) may be attributed to a methylene group attached to an oxygen and coupled with the adjacent benzylic protons. Sharp singlets at δ 3.89 and 3.90 integrating for three protons each indicate two aromatic methoxyl groups. The remaining signal in the spectrum is a singlet at δ 6.12 which represents a single aromatic proton. Based on the evidence presented so far, partial structure i may be written for I. Placement of the ethanolic side chain at C-6 as opposed to C-7 or C-8 is shown by the formation of the dihydrofuran III on cyclization of I in sulfuric acid. In the ir spectrum of III, the O–H stretch frequencies have virtually vanished and the carbonyl band appears at 1680^{-1} cm. The nmr spectrum of III shows the remaining chromanone features still intact. The methoxyl group is placed at the 7 position as a result of two pieces of evidence. The material gives a positive Gibbs test which indicates that the position para to the phenolic group in the aromatic ring is open and secondly fusion of I with sodium hydroxide yields phloroglucinol. Hence, the structure of LL-D253α is unequivocally I or 5-hydroxy-6-(2′-hydroxyethyl)-7-methoxy-2-methylchromanone.



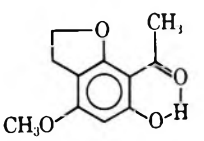
i

It has already been mentioned that I gives a diacetate which melts at 121–122°. In the nmr of this derivative in deuterated chloroform the acetyl methyl groups are located at δ 2.0 and 2.35, respectively. If I is treated with 1 equiv of acetic anhydride in pyridine, two products are formed, the diacetate IV and a monoacetate, mp 129°. The shift in the frequency of the chromanone carbonyl from 1655 to 1690 cm^{-1} in the monoacetate indicates that it is the chelated phenolic group which had been acetylated. The acetyl methyl signal in the nmr of this derivative VI is located at δ 2.33. Metabolite LL-D253β, which was isolated from surface fermentation only, has a molecular ion at m/e 294 and carbonyl frequencies in the ir spectrum at 1655 and 1740 cm^{-1}, respectively. In the nmr spectrum the acetyl methyl signal is present at δ 2.0 and hence this metabolite has structure II. Compound II could be synthesized in good yield by the reaction of I with acetic acid in ethyl acetate saturated with dry hydrogen chloride.

The reaction of the monomethyl ether V with strong alkali gave some unexpected products in addition to the expected degradation compound VII.[2,4] Methylation of VII using methyl iodide and silver oxide yielded



VII, R = H
VIII, R = CH_3
IX, R = CH_3CO



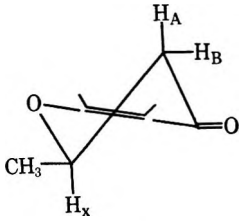
X

VIII indicating that in this compound the chelation of the phenolic group is very strong.[6,7]

In the nmr spectrum of VII, the primary hydroxy proton signal is at δ 1.87 while the strongly chelated phenolic proton is a ringing singlet at δ 13.93. Among the unexpected products of the alkaline degradation is IX which has the empirical formula $C_{14}H_{18}O_6$ and melts at 97°. The nmr spectrum has the acetyl methyl signal at δ 2.0 and the chelated phenolic proton singlet at δ 13.92. Evidently, the acetyl fragment cleaved during alkaline degradation acetylates the primary hydroxyl group during the subsequent acidic work-up of the reaction. The chemical preparation of II from I confirms this observation. The other unusual product isolated from the alkaline degradation is X which was also obtained by similar degradation of III.

As has already been mentioned, the nmr spectrum of the monomethyl ether V was more amenable to interpretation than that of the parent metabolite. Nevertheless, from the normal spectra in deuterated chloroform or benzene, the coupling constants of the carbon three methylene protons with the carbon two methine proton were not discernable. However, the use of as much of the shift reagent dipivalomethanatoeuropium-(III) as is consistent with solubility in chloroform[8] results in resonance peak shifts so that nearly all the lines associated with this ABX system can be seen. Under these conditions, the values observed are $J_{AB} = 16.5$ cps for the geminal coupling, $J_{AX} = 4.0$ cps for the axial–equatorial coupling, and $J_{BX} = 11.2$ cps for the trans axial–axial coupling. Consequently, the methine proton of position 2 is axial while the methyl group at the same position is equatorial as would be expected.

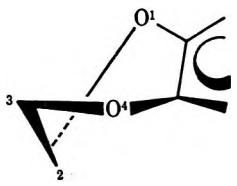
The absolute stereochemistry at C-2 is determined to be R from the positive Cotton effect $[\theta]_{322.5} = +6710$ in the CD spectrum of III since the relative stereochemistry is known. Flavanones show a uv maximum at



270–290 nm and an inflection at 320–330 nm. These absorptions have been assigned $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ origins, respectively.[9,10] Clearly the same assignments can be made for the maximum at 287 nm and the shoulder at 320 nm in the uv spectra of I–III. Snatzke[11] has derived a relationship between the chirality of

(6) J. F. Garden and R. H. Thomson, *J. Chem. Soc.*, 2483 (1957).
(7) W. J. McGahren and L. A. Mitscher, *J. Org. Chem.*, **33**, 1577 (1968).
(8) C. C. Hinckley *J. Amer. Chem. Soc.*, **91**, 5160 (1969).
(9) H. H. Jaffe and M. Orchin, "Theory and Application of Ultraviolet Spectroscopy," Wiley, New York, N. Y., 1962, p 204.
(10) W. Gaffield, *Tetrahedron*, **26**, 4093 (1970).
(11) G. Snatzke, *ibid.*, **21**, 413 (1965).

α,β-unsaturated ketones and the sign of their n → π^* Cotton effects. Extension of this rule to aryl ketones[12] and flavanones[10] suggests that chromanones of the conformation shown below will exhibit a positive n → π^* Cotton effect.



Experimental Section

Uv spectra were recorded using a Cary 11 spectrophotometer. Nmr spectra were run on a Varian A-60 instrument. Ir spectra were made using a Perkin-Elmer Infracord. Mass spectra were run on AEI MS9 high-resolution direct inlet spectrometer. CD data were obtained using a Cary 60 spectropolarimeter with CD attachment.

Fermentations.—A slant of Lederle culture D253 was used to inoculate 50 ml of sterile medium consisting o 0.2% ammonium tartrate, 0.05% $MgSO_4 \cdot 7H_2O$, 0.1% KH_2PO_4, 0.05% KCl, 0.001% $FeSO_4 \cdot 7H_2O$, 5.0% glucose, and 1% corn steep liquor (pH adjusted to 6.5 with NaOH) in 250-ml Erlenmeyer flasks and incubated for 3 days on a rotary shaker at 22°. Three Fernbach flasks, each containing 1.5 g of KH_2PO_4, 5.0 g of corn steep liquor, 0.5 g of KCl, 0.5 g of $MgSO_4 \cdot 7H_2O$, 3.0 g of $NaNO_3$, 40 g of dextrose, and 5 g of beechwood shavings in 1 l. of distilled water with pH adjusted to 6.5 before sterilization, were inoculated using 10 ml per flask of the preformed inoculum. The flasks were incubated at ambient temperature. After 5 weeks, the contents of the flasks were extracted with ethyl acetate at harvest pH to give 300 mg of gum. The pH of the mash was then adjusted to pH 2.5 and extraction with $CHCl_3$ gave another 200 mg of gum. Both lots of gum were combined and upon trituration with ether yielded 110 mg of off-white crystals. Recrystallization from ethyl acetate–hexane gave white crystals, mp 188–188.5°, of LL-D253α (I): $[\alpha]^{25}D$ +25.2 ± 0.42 (*c* 0.477, MeOH); λ_{max}^{MeOH} 213 nm (ϵ 22,700), 233 (sh, 13,500), 287 (18,900), 320 (sh, 5670); λ_{max}^{NaOH} 245 nm (ϵ 8500) and 325 (25,100); mass spectrum *m/e* 252.

Anal. Calcd for $C_{13}H_{16}O_5$: C, 61.90; H, 6.34. Found: C, 62.14; H, 6.31.

The filtrate from which 110 mg of I was obtained was concentrated and put on two 2.0-mm thick-layer silica gel plates and developed for two passes using 10% MeOH in $CHCl_3$. Two uv positive bands were scraped off and eluted with MeOH. The more polar band yielded 50 mg of I. The less polar band yielded 50 mg of white solid which was difficult to recrystallize. Finally, 27 mg of white solid material was recovered which softened at 180° and slowly darkened thereafter. The mass spectrum indicated a pure material with a molecular ion *m/e* 294 and a peak at *m/e* 251 indicating the loss of an acetyl fragment. This material was called LL-D253β (II). A 30-l. stirred, aerated tank was grown for 117 hr at 28° on the ammonium tartrate medium previously described and extracted with ethyl acetate and chloroform as mentioned before. The solvent extracts yielded about 3.7 g of a gum from which about 800 mg of I crystallized. The remainder was passed over 160 g of Davison grade 62 acid-washed silica gel using $CHCl_3$ as eluting solvent. Fractions of 80–90 ml volume were collected. Fractions 3–15 upon evaporation gave 400 mg of crystals which upon recrystallization from ethyl acetate–hexane yielded a first crop of 250 mg of LL-D253γ (III): mp 158–159°; $[\alpha]^{25}D$ +26.2 ± 0.27 (*c* 0.715, MeOH); λ_{max}^{MeOH} 213 nm (ϵ 22,200), 240 (15,000), 289 (17,100), 310 (sh, 7000); mass spectrum *m/e* 234.

Anal. Calcd for $C_{13}H_{14}O_4$: C, 66.65; H, 6.02. Found: C, 66.80; H, 5.98.

The CD curve of III was run on a methanol solution of concentration 2.225 mg/ml in a cell of 0.1-mm width: $[\theta] \times 10^3$ 322.5 nm (+6.71), 306 (±0), 287.5 (−14.80), 245 (±0), 235 (+3.50, inflection), 216 (+16.37); δ ($CDCl_3$) 1.47 [3 H, doublet ($J \sim 6.5$ cps)] methyl, 2.60 [2 H, doublet ($J \sim 7.5$ cps)] methylene adjacent to carbonyl, 3.12 [2 H, triplet ($J \sim 8.5$ cps)] benzylic methylene, 3.86 (3 H, singlet) methoxyl, 4.57 (1 H, irregular quartet) methine proton, 4.65 [2 H, triplet ($J \sim 8.5$ cps)] 2′-methylene of dihydrofuran ring, 6.06 (1 H, singlet) aromatic proton.

Preparation of Diacetate IV.—About 100 mg of I was treated with 2 ml of Ac_2O and a drop of pyridine and heated for a few minutes on a steam bath. The solvents were evaporated under reduced pressure and the resultant gum was passed over 20 g of grade 62 silica gel using 50:50 ethyl acetate–hexane as solvent. Fractions of 20-ml volume were collected and fractions 3 and 4 yielded 70 mg of solids which upon recrystallization from ether–hexane gave the diacetate IV: mp 121–122°; $[\alpha]^{25}D$ +23.1 ± 0.18 (*c* 0.238, $CHCl_3$); ν (KBr) 1772, 1740, and 1699 cm^{-1}.

Anal. Calcd for $C_{17}H_{20}O_7$: C, 60.71; H, 5.99. Found: C, 61.28; H, 6.18.

Methyl Ether V.—Approximately 2.0 g of I was refluxed overnight in 20 ml of acetone with 5 g of K_2CO_3 and 3 ml of CH_3I. Work-up included passage of the reaction concentrate over 90 g of acid-washed silica gel using 50:50 ethyl acetate–$CHCl_3$. Fraction volume was 75–80 ml. Evaporation of fractions 4–16 yielded 1.8 g of white crystals which were recrystallized from ethyl acetate to 1.5 g of V: mp 165–166°; $[\alpha]^{25}D$ +36.0 ± 0.36 (*c* 0.545, MeOH); λ_{max}^{MeOH} 213 nm (ϵ 22,200), 240 (15,000), 289 (17,100), 310 (sh, 7000); λ_{max}^{NaOH} 216 nm (ϵ 45,800), 240 (12,600), 292 (16,400), 320 (sh, 7000).

Anal. Calcd for $C_{14}H_{18}O_5$: C, 63.14; H, 6.81. Found: C, 63.29; H, 6.75.

Monoacetate VI.—Exactly 252 mg or 1 mmol of I was dissolved in 0.5 ml of pyridine and 0.12 ml or 1.1 mmol of Ac_2O was added. After 10 min the reaction solution was evaporated to an oil which was passed over 15 g of acid-washed silica gel using 20% hexane in $CHCl_3$ as eluting solvent. Fraction size was 15–18 ml. Fractions 3–5 gave 90 mg of diacetate IV. Fractions 12–23 gave 120 mg of material which was recrystallized from ether–hexane to get 90 mg of monoacetate VI: mp 128.5–129°; $[\alpha]^{25}D$ +51.4 ± 0.34 (*c* 0.584, MeOH); ν (KBr) 1760 and 1695 cm^{-1}; δ ($CDCl_3$) 1.50 [3 H, doublet ($J \sim 7$ cps)] methyl, 1.70 (1 H, exchangeable singlet] OH, 2.33 (3 H, singlet) acetyl methyl, 2.67 (2 signals) and 2.70 (1 signal) (2*H*)methylene group adjacent to carbonyl, 2.82 [2 H, triplet ($J \sim 7$ cps)] benzylic methylene, 3.73 [2 H, triplet ($J \sim 7$ cps)] hydroxymethylene, 3.85 (3 H, singlet) methoxyl, 4.57 (1 H, irregular quartet) methine proton, 6.28 (1 H, singlet) aromatic H.

Anal. Calcd for $C_{15}H_{18}O_6$: C, 61.21; H, 6.17. Found: C, 61.28; H, 6.03.

Fusion of I with NaOH.—About 0.5 g of I was mixed with 2.0 g of powdered NaOH and the mixture heated under N_2 in a stainless steel vessel for 15 min up to a temperature of 280°. The fused mass was cooled, treated with H_2O, and acidified with 4 *N* HCl and subjected to liquid–liquid extraction overnight with ethyl acetate. Work-up of the extract yielded 170 mg of a gum which was put on a thick-layer silica gel plate (2.0 mm) and developed using 20% MeOH in $CHCl_3$. A broad uv positive band was scraped off and eluted with MeOH to yield 70 mg of off-white solid. Attempts to recrystallize this material following Darco treatment failed. By evaporation of solvent, 42 mg of white crystals was obtained, mp 203–206°. The nmr, ir, and uv spectra of this material were identical with those of phloroglucinol.

Anal. Calcd for $C_6H_6O_3$: C, 56.25; H, 4.68. Found: C, 56.04; H, 5.34.

Reaction of I with Concentrated H_2SO_4.—About 500 mg of I was dissolved in 2 ml of concentrated H_2SO_4 to give a distinctly yellow solution which was refrigerated overnight. The solution was carefully diluted to 25 ml with ice water, neutralized with 4 *N* NaOH, and subjected to liquid–liquid extraction with ethyl acetate overnight to yield upon work-up 250 mg of white solid. Recrystallization from ethyl acetate–hexane gave pure III, mp 159°. The ir and nmr of this material were identical with those of III isolated from agitated fermentations.

Preparation of II from I.—About 0.5 g of I was dissolved in 25 ml of dry ethyl acetate and 2 ml of acetic acid was added. The solution was then saturated with dry HCl gas and the yellow solution was allowed to sit overnight at room temperature. The solution was extracted with 20 ml of H_2O and the organic phase was dried and evaporated to a solid residue which was recrystallized from ethyl acetate–hexane to give a first crop of 290 mg of

(12) G. Snatzke, *Tetrahedron*, **21**, 439 (1965).

white crystals: mp 207–208°; $[\alpha]^{25}D$ +20.99 ± 1.18 (*c* 1.091, MeOH). The ir and nmr spectra of this material were identical with those of the natural product II.

Anal. Calcd for $C_{15}H_{18}O_6$: C, 61.27; H, 6.17. Found: C, 61.30; H, 6.01.

Alkaline Degradation of V.—A 4.1-g aliquot of V was dissolved in 200 ml of absolute EtOH, 20 g of solid KOH was added, and the mixture refluxed overnight under N_2. The cooled reaction mixture was filtered, concentrated to small volume, acidified, and extracted with ethyl acetate to get upon work-up a brown gum which was passed over 200 g of grade 62 acid-washed silica gel and eluted with 70:30 $CHCl_3$–hexane solution. Fraction volume was 80–85 ml. Fractions 3–25 were combined to give 2.5 g of a viscous oil which was a mixture and labeled fraction A. Fractions 26–38 yielded about 2.0 g of an oil which solidified. The material was recrystallized from ethyl acetate–hexane to give a first crop of 1.2 g of faintly yellow crystals which spectral data showed to be VII or 1-hydroxy-3,5-dimethoxy-4-(2′-hydroxyethyl)acetophenone: mp 133–134°; λ_{max}^{MeOH} 213 nm (ε 18,000), 230 (sh, 12,200), 290 (19,200), 330 (sh, 3600); λ_{max}^{NaOH} 215 nm (ε 36,000), 235 (sh, 18,600), 295 (6000), 330 (sh, 3300); δ ($CDCl_3$) 1.85 (1 H, exchangeable singlet) ethanolic OH, 2.60 (3 H, singlet) methyl ketone, 2.92 [2 H, triplet ($J \sim 7$ cps)] hydroxy methylene, 3.84 and 3.89 (3 H and 3 H, singlets) two aromatic methoxyls, 5.98 (1 H, singlet) aromatic H, 13.98 (1 H, exchangeable singlet) aromatic OH.

Anal. Calcd for $C_{12}H_{16}O_5$: C, 60.00; H, 6.66. Found: C, 60.38; H, 6.63.

Fraction A was again passed over silica gel. This time 90 g of acid-washed material was used and elution was carried out using a gradient of 10–50% ethyl acetate in hexane solution. Fraction size was 80–90 ml. Fractions 2–5 gave 0.6 g of residue which was recrystallized from ethyl acetate–hexane to give a first crop of 300 mg of faintly yellow crystals which were subsequently shown to be X or 1-hydroxy-3-methoxy-4,5-(2′,3′-dihydrofuro)acetophenone: mp 106–107°; λ_{max}^{MeOH} 212 nm (ε 18,700), 238 (sh, 10,400), 292 (18,500); λ_{max}^{NaOH} 214 nm (ε 38,000), 238 (sh, 15,600), 300 (6200); δ ($CDCl_3$) 2.57 (3 H, singlet) methyl ketone, 3.12 [2 H, triplet ($J \sim 7$ cps)] benzylic methylene, 3.83 (3 H, singlet) aromatic methoxyl, 4.67 [2 H, triplet ($J \sim 7$ cps)] methylene of ether linkage, 5.95 (1 H, singlet) aromatic proton, 14.00 (1 H, exchangeable singlet) phenolic proton.

Anal. Calcd for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.30; H, 5.67.

Fraction 8–16 on evaporation gave 1.0 g of a viscous oil which partially solidified. The solid was recrystallized from ethyl acetate–hexane to yield 300 mg of faintly yellow crystals, mp 97°, which spectral data showed to be IX: λ_{max}^{MeOH} 213 nm (ε 21,100), 230 (sh, 15,500), 290 (21,300), 330 (sh, 4200); λ_{max}^{NaOH} 213 nm (ε 49,000), 235 (sh, 16,900), 295 (7000), 240 (sh, 4100); ν (KBr) 1740 and 1635 cm^{-1}; δ ($CDCl_3$) 2.00 (3 H, singlet) acetyl methyl, 2.63 (3 H, singlet) aryl methyl ketone, 2.95 [2 H, triplet ($J \sim 7$ cps)] benzylic methylene, 3.90 and 3.92 (3 H and 3 H, singlets) aromatic methoxyls, 4.20 [2 H, triplet ($J \sim 7$ cps)] acetoxy methylene, 5.98 (1 H, singlet) aromatic proton, 13.93 (1 H, singlet) chelated phenolic proton.

Anal. Calcd for $C_{14}H_{18}O_6$: C, 59.56; H, 6.43. Found: C, 59.26; H, 6.36.

Work-up of fractions 27–37 yielded 250 mg of VII.

Alkaline Degradation of III.—About 0.4 g of III was dissolved in 25 ml of EtOH, 3 g of KOH was added, and the mixture was refluxed overnight under N_2. The solvent was evaporated and the mixture acidified with 4 *N* HCl and then extracted with ethyl acetate. Work-up of the ethyl acetate extract gave 270 mg of yellow solids which were passed over 18 g of acid-washed grade 62 silica gel and eluted with 5% ethyl acetate in hexane. The second holdback volume yielded 200 mg of material which upon recrystallization gave 110 mg of X, mp 107–108°.

Preparation of VIII.—About 1.2 g of VII was stirred overnight in 200 ml of $CHCl_3$ with 15 g of Ag_2O and 20 ml of CH_3I. The reaction mixture was filtered and the solvent evaporated to get 1.2 g of solid material which was passed over 90 g of acid-washed grade 62 silica gel and eluted with a gradient of 5–20% ethyl acetate in hexane. Fraction size was 80–85 ml. Fractions 9–12 gave 0.7 g of crystals which were recrystallized to give a first crop of 320 mg, mp 94–94.5°, which spectral data showed to be VIII: λ_{max}^{MeOH} 213 nm (ε 18,000), 230 (sh, 12,700), 287 (20,300), 330 (sh, 3800); δ ($CDCl_3$) 2.62 (3 H, singlet) methyl ketone, 2.93 [2 H, split triplet ($J \sim 7$ cps)] benzylic methylene, 3.37 (3 H, singlet) aliphatic methoxyl, 3.48 [2 H, split triplet ($J \sim 7$ cps)] $-OCH_2$, 3.90 (6 H, singlet) 2 aromatic methoxyls, 5.98 (1 H, singlet) aromatic proton, 13.93 (1 H, singlet) chelated phenolic proton.

Anal. Calcd for $C_{13}H_{18}O_5$: C, 61.52; H, 7.14. Found: C, 61.40; H, 7.06.

Registry No.—I, 34288-33-0; II, 34288-34-1; III, 34288-35-2; IV, 34288-36-3; V, 34288-37-4; VI, 34288-38-5; VII, 34288-73-8; VIII, 34288-74-9; IX, 34288-75-0; X, 34288-76-1; phloroglucinol, 108-73-6.

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Chemical Modifications of Zearalenone. I

N. P. JENSEN,* R. D. BROWN, S. M. SCHMITT, T. B. WINDHOLZ, AND A. A. PATCHETT

Department of Synthetic Chemical Research, Merck Sharp & Dohme Research Laboratories, Rahway, New Jersey 07065

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Chemical transformations of the aliphatic portion of the mold metabolite zearalenone were examined. Reactions at the C′-6 ketone and the C′-1 double bond and positions adjacent to these reaction centers are reported. The reactions proved to be quite regioselective.

The mold metabolite zearalenone (1),[1] which has shown hormonal and growth-promotant activities,[1a] has previously been synthesized,[2] its absolute configuration has been determined,[3] and modifications in the aromatic ring with the resulting changes in biological activity have been reported.[4] In this report some transformations of the lactone ring are examined. Although one might expect a 14-member ring to have several conformations of relatively equal energies, we

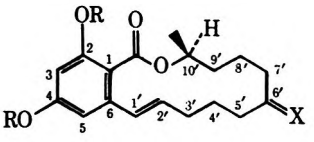
(1) (a) M. Stab, R. S. Baldwin, J. Tuite, F. N. Andrews, and K. G. Gillette, *Nature (London)*, **196**, 1318 (1962); (b) W. H. Urry, H. L. Wehrmeister, E. B. Hodge, and P. H. Hidy, *Tetrahedron Lett.*, 3109 (1966); (c) zearalenone used in these experiments was supplied by Commercial Solvents Corp.

(2) (a) D. Taub, N. N. Girotra, R. D. Hoffsommer, C. H. Kuo, H. L. Slates, S. Weber, and N. L. Wendler, *Tetrahedron*, **24**, 2443 (1968); (b) I. Vlattas, I. T. Harrison, L. Tökes, J. H. Fried, and A. D. Cross, *J. Org. Chem.*, **33**, 4176 (1968).

(3) C. H. Kuo, D. Taub, R. D. Hoffsommer, N. L. Wendler, W. H. Urry, and G. Mullenback, *Chem. Commun.*, 761 (1967).

(4) D. B. R. Johnston, C. A. Sawicki, T. B. Windholz, and A. A. Patchett, *J. Med. Chem.*, **13**, 941 (1970).

were gratified to find that various reactions showed selectivities indicative of definitely preferred conformations. It should be noted that cyclization to dideoxyzearalane, which lacks zearalenone's double bond, ketone, and aromatic hydroxyls, has been reported to be difficult,[5] and hence typical of rings in the 7- to 13-member class,[6] while formation of the lactone in dimethoxyzearalenone under less dilute conditions has been achieved in as high as 80% yield.[2a] This comparison demonstrates the importance of the additional functional groups in conferring preferred conformations in zearalenone and its derivatives.



1, R = H; X = O

2, R = H; X = 

3, R = CH_3; X = O

4. R = CH_2Ph; X = O

5, R = CH_2OCH_3; X = O

6, R = CH_2OCH_3; X = 

7, R = CH_2OCH_3; X = 

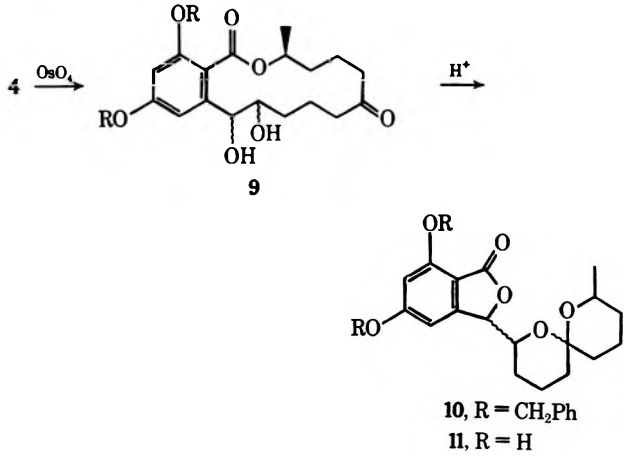
8, R = CH_2OCH_3; X = 

In order to effect reactions on the aliphatic portion of zearalenone, various groups were used to block the aromatic hydroxyls. Besides the use of a methyl group, which was used in the syntheses of zearalenone,[2] benzyl and methoxymethyl groups were used. The benzyl groups were used if the concomitant double bond reduction on hydrogenolytic removal was acceptable. If retention of the double bond was desired a methoxymethyl group was used. We found that a combination of *p*-toluenesulfonic acid, water, and ethylene glycol in refluxing benzene cleanly removed this group as well as a 6′ ketal protecting group. This is demonstrated in the conversion of **15** to **16** and **12** to **13**.

The 1′,2′ trans double bond of zearalenone appears to be quite electron poor. Exposure of **3** to either perphthalic or *m*-chloroperbenzoic acid in chloroform solution for 2 weeks gave no significant reaction. This is in accord with the general observation that a *m*-methoxy substituent has no electron-supplying or electron-withdrawing effect.[7] It is therefore the electron-withdrawing inductive effect of the *o*-carboxy group which is the important factor in the electron availability of the double bond.

The more reactive reagent osmium tetroxide reacted smoothly with the double bond of **4** to give a diol mixture **9** (R = CH_2Ph) which was not fully characterized owing to the great ease with which it rearranged to the isomeric mixture **10** in the presence of acid[8] (Scheme I). While this is an unusual rearrangement in that one ring-opening and three ring-forming reactions take place, all the elements of this transformation

SCHEME I



9

10, R = CH_2Ph
11, R = H

have already been demonstrated in similar molecules and the 1,6 nature of the ketone and lactone alcohol has been used as a means of protecting these functions in the synthesis of zearalenone.[2a]

Hydroboration of the double bond was also sluggish and was complicated by formation of products (**14**) identified as phthalides by the 5.71-μ carbonyl frequency in their infrared spectrum. In this case, it was found that phthalide formation could be reduced by running the reaction at lower concentrations. As in the case of other benzylic boranes[7] oxidation had to be run at low temperatures to avoid hydrolysis. Since a 1′ alcohol had already been found to be acid-labile, the product from hydrogen peroxide oxidation of the borane was converted immediately to ketone **12** by Sarett oxidation.[9] The product was then purified by chromatography in order to remove starting material (**6**) and phthalides (**14**) and to see if any 2′ ketone could be detected. Although no 2′ ketone was found[10] an interesting side product (**15**) of Sarett oxidation was identified (Scheme II).

The minor product **15** was thought to arise from allylic oxidation of unreacted starting material **6**. This hypothesis proved correct inasmuch as exposure of **6** to excess Sarett reagent for 2 days gave a good yield of **15**. Although chromic acid has long been used as an allylic oxidant,[11] until recently chromium trioxide in pyridine had not been generally considered a reagent for allylic oxidation. While allylic oxidation with Sarett reagent is slow compared to the oxidation of an alcohol, it can be a useful preparative reaction.[12] In the case of zearalenone, allylic oxidation with Sarett reagent was very sensitive to changes at C-6′. The compound **5** in which the C-6′ ketal is replaced with a ketone was 85% unreacted under the conditions which give an 85% yield of **15** from **6**. A likely explanation for this difference is that an sp^3 instead of an sp^2 center at C-6′ allows a more active

(5) H. L. Wehrmeister and D. E. Robertson, *J. Org. Chem.*, **33**, 4173 (1968).

(6) *Cf.* (a) K. Ziegler and R. Aurnhammer, *Justus Liebigs Ann. Chem.*, **513**, 43 (1933); (b) N. J. Leonard and C. W. Schimelpfenig, Jr., *J. Org. Chem.*, **23**, 1708 (1958).

(7) H. C. Brown and R. L. Sharp, *J. Amer. Chem. Soc.*, **88**, 5851 (1966).

(8) This rearrangement was first noted when the diol mixture was dissolved in deuteriochloroform for examination by nmr.

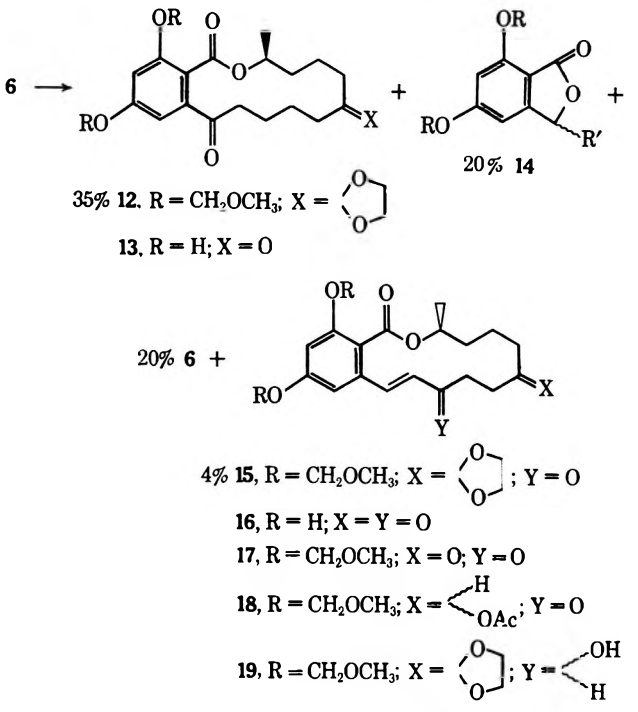
(9) (a) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Amer. Chem. Soc.*, **75**, 422 (1953); (b) J. R. Holem, *J. Org. Chem.*, **26**, 4814 (1961).

(10) H. C. Brown and G. Zweifel, *J. Amer. Chem. Soc.*, **82**, 4708 (1960), find that β-methylstyrene gives 15% of 2′ product.

(11) (a) F. C. Whitmore and G. W. Pedlow, Jr., *ibid.*, **63**, 758 (1941); (b) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, New York, N. Y., 1965, p 94.

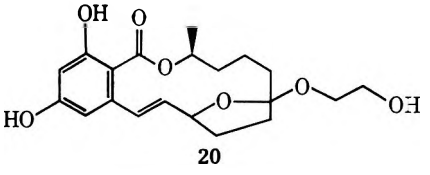
(12) Subsequent to this work it has been shown that the Collins modification of chromium trioxide–pyridine oxidation [J. C. Collins, W. W. Hess, and F. J. Frank, *Tetrahedron Lett.*, 3363 (1968)] is an effective allylic oxidant [W. G. Dauben, M. Lorber, and D. S. Fullerton, *J. Org. Chem.*, **34**, 3587 (1969)].

SCHEME II



ring conformation to exist. When the epimeric acetate **8**, which also has an sp^3 center at C-6′, was submitted to the Sarett oxidation conditions, a good yield of a product of allylic oxidation (**18**) was again obtained.

An alternative or additional explanation for the favorable reactivity of **6** and **8** is that an sp^3 oxygen attached to C-6′ assists attack at C-3′. The fact that such oxygens at C-3′ and C-6′ can be in proximity to each other is attested to by the formation of **20**, which was prepared by reduction of **15** with $NaBH_4$ to give **19** followed by attempted simultaneous cleavage of the methoxymethyl and ketal protecting groups. Although the combination of ethylene glycol, water, and *p*-toluenesulfonic acid was found to be very good for removing these groups from **12** and **15**, in the case of **19** the tetrahydrofuran **20** was formed.[13] The structure



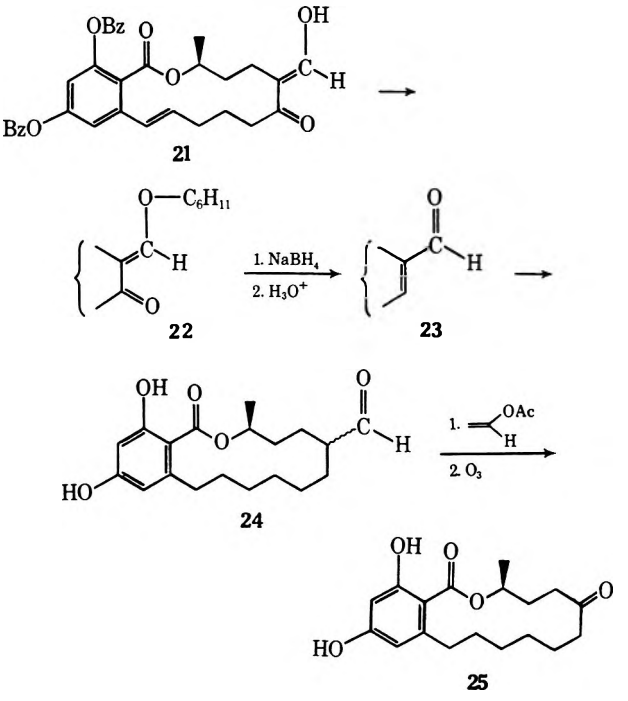
20

of this compound is based on its mass spectrum and analysis as well as the nmr of its triacetate,[14] which distinguishes it from other structure possibilities which do not have primary alcohols.

Reactions of the 6′-keto group of zearalenone were also environment sensitive. Although the α positions of this ketone are both secondary, it was found that reactions at this center showed considerable "regioselectivity."[15] One of the most useful reactions which displayed this regioselectivity was formylation in benzene using sodium hydride and *tert*-butyl alcohol as a base. Although the intermediate hydroxymethylene products of this reaction were not very stable and were therefore not characterized, isomer ratios could easily be determined by tlc and it was subsequently established (see below) that the C-7′ product (**21**) was the major isomer by a 8:1 margin.[16] Whether this selectivity is kinetic or thermodynamic has not been proven. Under the conditions of sodium ethoxide–ethanol, which are reported to be equilibrium conditions for hydroxymethylene formation,[17] the product was not stable with respect to starting ketone.

The predominance of C-7′ isomer in hydroxymethylene formation provided a starting point for the synthesis of the C-7′ ketone isomer of zearalanone. The synthetic objective of moving a ketone to an α carbon is a common one for which there are a variety of schemes.[18] In this instance the double bond was eliminated to permit the use of ozone. The attractiveness of this route (see Scheme III) lay in its utilization

SCHEME III



of the hydroxymethylene derivative and in the unambiguous course of the acid rearrangement step. This allylic rearrangement of proven course[19] has been used in diterpene synthesis.[20] Hydrogenation of **23** was accompanied by some reduction of the aldehyde **24**,[21] but it was found that purification by chromatog-

(13) The inability to hydrolyze a six-membered ether in a zearalenone derivative under acid conditions has been reported in ref 2b.

(14) We wish to acknowledge Dr. B. Arison's invaluable help and suggestions regarding nmr spectra.

(15) A. Hassner, *J. Org. Chem.*, **33**, 2684 (1968).

(16) The product ratio, while always greatly favoring the C-7′ isomer, was somewhat capricious. In one larger scale preparation only the C-7′ isomer could be detected.

(17) (a) L. M. Roch and N. Boulay, *C. R. Acad. Sci.*, **253**, 2375 (1961); (b) L. M. Roch, *Ann. Chim. (Paris)*, **6**, 105 (1961); (c) R. O. Clinton, R. L. Clark, F. W. Stonner, A. J. Manson, K. F. Jennings, and D. K. Phillips, *J. Org. Chem.*, **27**, 2800 (1962).

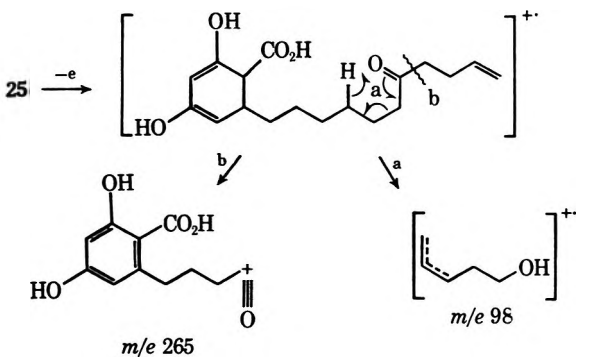
(18) *Cf.* (a) J. A. Marshall and H. Roebke, *J. Org. Chem.*, **34**, 4188 (1969); (b) A. Hassner, J. M. Larkin, and J. E. Dowd, *ibid.*, **33**, 1733 (1968); (c) G. Just and Y. C. Lin, *Chem. Commun.*, 1350 (1968).

(19) M. Stiles and A. Lonroy, *Tetrahedron Lett.*, 337 (1961); *J. Org. Chem.*, **32**, 1095 (1967).

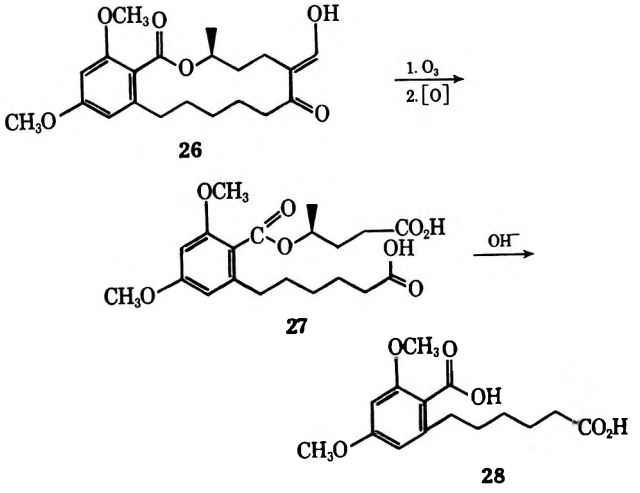
(20) R. E. Ireland and P. W. Schiess, *J. Org. Chem.*, **28**, 6 (1963).

(21) The aldehyde **24** showed increased hormonal activity [J. R. Brooks, S. L. Steelman and D. J. Patanelli, *Proc. Soc. Exp. Biol. Med.*, **137**, 101 (1971)]. This epimeric mixture (**24**) of aldehydes was separated by fractional recrystallization from benzene and epimeric purity was confirmed by nmr (see Experimental Section).

SCHEME IV



SCHEME V



raphy gave better yields than protecting the aldehyde *via* a ketal.[22]

The position of the ketone in 7′-ketozearalane (**25**) is easily seen by comparing its mass spectrum with that of its isomer zearalanone.[23a] The mass spectra of these two isomers have essentially the same peaks with the exception of two strong sets of homologous peaks.[23b] The 7′-keto compound has peaks at *m/e* 265 and 98, while zearalanone has corresponding peaks at *m/e* 251 and 112.[24] These peaks can be seen to arise from a McLafferty rearrangement at the lactone followed by α cleavage or a McLafferty rearrangement at the ketone (Scheme IV shows these cleavages for the 7′-keto isomer). Peaks at *m/e* 237 and 126 which would arise from a 5′-keto isomer are negligible in the spectrum of zearalanone and the 7′-keto isomer.

This preference for C-7′ formylation was also seen in a saturated series. Zearalanone bismethyl ether gave a 3:1 ratio of products which, while not characterized by analysis, could easily be separated by preparative tlc. The major isomer **26** thus purified was degraded *via* Scheme V to the known acid **28**,[1b] thus proving **26** to be the 7′ isomer.[25]

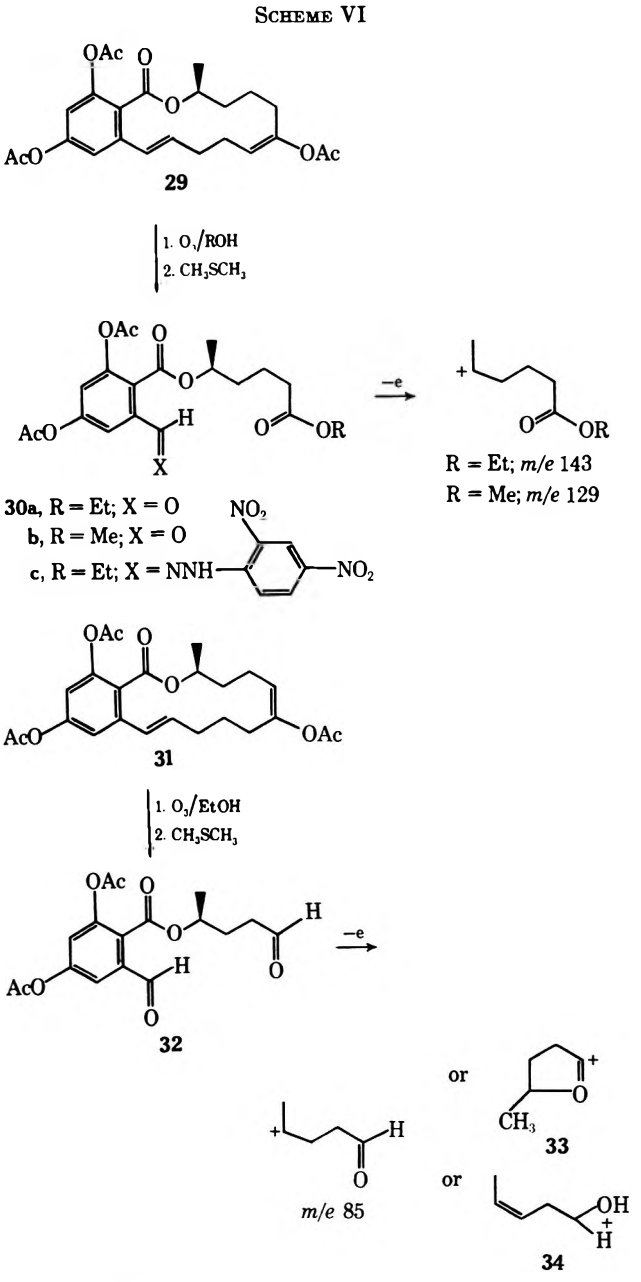
(22) This general scheme was reported in the synthesis of samandarone: S. Hara and K. Oka, *J. Amer. Chem. Soc.*, **89**, 1041 (1967).

(23) (a) We wish to thank Dr. G. Albers-Schonberg for determining and discussing with us the mass spectra reported in this paper. (b) The mass spectrum of zearalanone (see ref 1b for preparation) is given for comparison: *m/e* (rel intensity) 320 (82), 302 (59), 251 (53), 177 (35), 163 (100), 150 (40), 125 (88), 124 (26), 123 (27), 112 (86), 69 (401), 55 (65), 41 (70).

(24) This peak has been identified as coming from the aliphatic portion of zearalenone (see ref 1b).

(25) It should be noted that dimethylzearalenone preferentially gave the 7′-hydroxymethylene derivative by a ratio of 5:1 and that the relationship between saturated and unsaturated series was shown by interrelation of their pyrazole derivatives: T. B. Windholz and R. B. Brown, unpublished.

SCHEME VI



A reaction that showed even greater regioselectivity was the formation of enol acetates at the C-6′ ketone in diacetyl zearalenone. In this case the major product was one derived from enolization in the C-5′ direction to give **29**[26] in 61% isolated yield. The higher melting, less soluble Δ-6′ isomer (**31**) was isolated in ~4% yield.

The identities of the two isomers **29** and **31** were determined by ozonolysis followed by reduction with dimethyl sulfide[27] to the aldehydes **30** and **32**, respectively (Scheme VI). These degradation products were then examined by nmr and mass spectrometry and in the case of **30a** by conversion to **30c**. As expected, the mass spectra of **30a**, **30b**, and **32** exhibit strong peaks at *m/e* 143, 139, and 85, respectively. These peaks are base peaks and result from cleavage of the respective C–O ester bonds.

The conditions under which the enol acetates **29**

(26) Examination of various types of molecular models indicates that the C-5′–C-6′ double bond involves less steric interactions if it is trans.

(27) J. J. Pappas, W. D. Keaveney, E. Gancher, and M. Berger, *Tetrahedron Lett.*, 4273 (1966).

and **31** are formed are not ones which are known[28] to lead cleanly to kinetic products because of the prolonged reaction times necessary for complete conversion of the starting material. Preparation of **29** and **31** using conditions involving the use of *p*-toluenesulfonic acid and acetic anhydride over an extended period of time which gives thermodynamically favored products[28] were preparatively unsuccessful because of slow conversion and a large number of products as determined by tlc. In this case and in the preparation of **21** the fact that conditions known to give thermodynamic product were not successful in producing the desired product suggests kinetic control.

Experimental Section[29]

6-(6-Ethylenedioxy-10-hydroxy-*trans*-1-undecenyl)-β-resorcylic Acid μ-Lactone (2).—Zearalenone[1] (1, 10.0 g, 31.6 mmol) was stirred and refluxed for 26 hr with 220 ml of benzene, 30 ml of ethylene glycol, and 0.25 g of *p*-toluenesulfonic acid monohydrate using a water separator. After cooling the mixture, 200 ml of ether and 400 ml of saturated brine were added. The organic layer was separated, washed four times with saturated brine, dried, and concentrated to 11.5 g of white foam. An analytical sample was obtained as a glass by sublimation at 100° (50 μ): uv max 236 mμ (ε 26,300), 274 (11,600), 313 (5760); ir 6.10, 6.22, 6.33 μ; nmr τ 2.14 (s, 1, OH), 2.4 (s, 1, OH), 2.92 (d, 1, J = 16 Hz, =CH), 2.15 (m, 2, ArH), 4.18 (d, 1, J = 16 cps, =CH), 5.0 (m, 1, CO_2CH), 6.06 (s, 4, OCH_2), and 8.63 (d, 3, J = 6 Hz, CH_3).

Anal. Calcd for $C_{20}H_{26}O_6$: C, 66.20; H, 7.23. Found: C, 66.31; H, 7.35.

2-(10-Hydroxy-6-oxo-*trans*-undecenyl)-4,6-dibenzyloxybenzoic Acid μ-Lactone (4).[30]—A mixture of 50 g of **1**, 81 g of benzyl chloride, and 98 g of potassium carbonate was stirred and refluxed for 5 days in 1 l. of acetone. After cooling, the mixture was filtered and the filtrate was concentrated to an oil which was triturated with 1 l. of *n*-hexane to give 70 g of product: mp 130–132°; nmr τ 2.61 (s, 5, C_6H_5), 2.64 (s, 5, C_6H_5), 3.29 (d, 1, J = 2 Hz, ArH), 3.50 (d, 1, J = 2 Hz, ArH), 3.55 (d, 1, J = 16 Hz, =CH), 3.7–4.4 (m, 1, =CH), 4.5–5.1 (m, 1, CO_2CH), 4.96 (s, 2, OCH_2Ph), 4.98 (s, 2, OCH_2Ph), and 8.76 (d, 2, J = 6 Hz, CH_3).

Anal. Calcd for $C_{32}H_{34}O_5$: C, 77.08; H, 6.87. Found: C, 76.91; H, 6.62.

2-(10-Hydroxy-6-oxo-*trans*-undecenyl)-4,6-bismethoxymethoxybenzoic Acid μ-Lactone (5).—A 3.18-g (10.0 mmol) portion of zearalenone was dissolved in 75 ml of dimethylformamide (dried with 3A molecular sieves). The stirred solution was cooled with an ice bath and 0.89 g (20.3 mmol) of 54.7% sodium hydride in mineral oil was added. After stirring for 30 min at 0°, 1.7 g (21 mmol) of chloromethylmethyl ether in 25 ml of dimethylformamide was added dropwise with stirring over a period of 20 min. Stirring was continued for 30 min at 0° and about 50% of the solvent was removed *in vacuo*. The remainder was then poured onto 150 g of ice. The resulting precipitate was collected, washed well with water, and dissolved in methylene chloride. The methylene chloride solution was dried and concentrated to 4.3 g of solid, which was recrystallized from methylene chloride–*n*-hexane to give 2.96 g (73%) of light yellow crystalline chunks: mp 140.5–143.0°; uv max 222.5 mμ (ε 26,800), 254 (12,700), 296 (1880); ir (Nujol mull) 5.84, 5.91 μ; nmr τ 3.15 (d, 1, J = 2.5 Hz, ArH), 3.28 (d, 1, J = 2.5 Hz, ArH), 3.57 (d, 1, J = 16 Hz, =CH), 3.86 (m, 1, =CH), 4.83 (s, 4, OCH_2O), 6.52 (s, 6, OCH_3), and 8.67 (d, 3, J = 6 Hz, CH_3).

Anal. Calcd for $C_{23}O_{30}O_7$: C, 65.01; H, 7.44. Found: C, 65.11; H, 7.48.

2-(6-Ethylenedioxy-10-hydroxy-*trans*-1-undecenyl)-4,6-methoxymethoxybenzoic Acid μ-Lactone (6).—Using 29 g of crude **2**, crude **6** was prepared in essentially the same manner as **5**. Chromatography on 600 g of Fluorisil using benzene–ethyl acetate as an eluent yielded crystalline material in early fractions. The entire eluent was then concentrated to a gum and recrystallized from methanol at −5° (using a seed crystal) to give 30 g of product: mp 70–72°; uv max 221 mμ (ε 31,500), 255 (13,200), 295 (31,500), 255 (13,200), 295 (ε 1710); ir 5.83 μ; nmr τ 3.18 (d, 1, J = 2.5 Hz, ArH), 3.33 (d, 1, J = 2.5 Hz, ArH), 3.6–3.8 (m, 2, =CH), 4.86 (s, 4, OCH_2O), 6.12 (s, 4, OCH_2), 6.55 (s, 6, OCH_3), and 8.65 (d, 3, J = 6 Hz, CH_3).

Anal. Calcd for $C_{24}H_{34}O_8$: C, 63.98; H, 7.61. Found: C, 64.07; H, 7.58.

2-(6,10-Dihydroxy-*trans*-undecenyl)-4,6-bismethoxymethoxybenzoic Acid μ-Lactone (7).—A solution of 4.65 g of **5** in 50 ml of methanol was cooled in an ice bath and 1.0 g of $NaBH_4$ was added portionwise over a period of 5 min. After stirring for 15 min at 0° and 0.5 hr at room temperature the mixture was taken up in 400 ml of saturated brine which contained excess hydrochloric acid. The mixture was extracted with ether and the ether extracts were washed with saturated brine, dried, and concentrated to 4.5 g of a solid of low crystallinity.

Anal. Calcd for $C_{22}H_{32}O_7$: C, 64.68; H, 7.90. Found: C, 64.73; H, 7.91.

2-(6-Acetoxy-10-hydroxy-*trans*-undecenyl)-4,6-bismethoxymethoxybenzoic Acid μ-Lactone (8).—A 4.3-g portion of **7** was treated with 20 ml of pyridine and 15 ml of acetic anhydride for 18 hr before pouring into ice. The mixture was extracted with ether, which was washed with dilute HCl and saturated brine before *in vacuo* concentration to 4.6 g of semisolid.

Anal. Calcd for $C_{24}H_{34}O_8$: C, 63.98; H, 7.61. Found: C, 63.82; H, 7.54.

5,7-Dibenzyloxy-1,3-dihydro-1-oxo-3-(10-methyl-1,11-dioxaspiro[5.5]undecan-2-yl)benzo[*c*]furan (10).—A 5.73-g (1.15 mmol) portion of **4** was treated with 3.00 g (1.18 mmol) of osmium tetroxide and worked up essentially according to the procedure of Corey, *et al.*,[31] to give 6.3 g of gummy residue **9** which was much more polar on tlc than starting material. A 0.83-g portion of this residue was dissolved in 10 ml of chloroform, and 2 drops of concentrated hydrochloric acid were added. After standing for 15 hr at room temperature, the mixture was concentrated *in vacuo* to a foam which was dissolved in ether. The ether solution was decanted from an insoluble yellow oil, filtered, concentrated to 15 ml of hot ether, and precipitate. After cooling, 0.41 g of colorless needles were collected: mp 152–156°; ir 5.72 μ; nmr τ 2.63 (s, 10, C_6H_5), 3.3–3.45, (m, 2, ArH), ~4.7 (m, 1, OCHAr), 4.78 (s, 2, $PhCH_2O$), 4.92 (s, 2, $PhCH_2O$), 4.92 (s, 2, $PhCH_2O$), ~5.4 (m, 1, OCH), and ~6.2 (m, 1, OCH).

Anal. Calcd for $C_{32}H_{34}O_6$: C, 74.68; H, 6.06. Found: C, 74.42; H, 6.55.

1,3-Dihydro-5,7-dihydroxy-1-oxo-3-(10-methyl-1,11-dioxaspiro[5.5]undecan-2-yl)benzo[*c*]furan (11).—A 4.15-g (8.1 mmol) portion of **10** was hydrogenated in 200 ml of ethyl acetate in the presence of 0.5 g of 10% palladium on carbon catalyst. The reaction was carried out in a Parr bomb at 35-lb pressure. Uptake stopped at theory after 2.5 hr. The catalyst was removed by filtration, and the filtrate was concentrated to a solid which was triturated with *n*-hexane and collected on a filter to give 2.45 g (89%) of wide-melting solid: ir 5.8 μ; nmr (DMSO) τ −1 to 0 (very broad, 2, OH), 3.66 (s, 2, ArH), 4.78 (d, 1, J = 4 Hz, OCHAr), 5.7 (d of d, 1, J = 4 and 9 Hz, OCH), and 6.35 (m, 1, OCH).

Anal. Calcd for $C_{18}H_{22}O_6$: C, 64.65; H, 6.63. Found: C, 64.85; H, 6.69.

2-(6-Ethylenedioxy-10-hydroxy-1-oxoundecanyl)-4,6-bismethoxymethoxybenzoic Acid μ-Lactone (12).—A 4.5-g (10.0 mmol) portion of **6** was dissolved in 150 ml of tetrahydrofuran

(28) H. O. House and B. M. Trost, *J. Org. Chem.*, **30**, 2502 (1965).

(29) Unless stated otherwise, drying of solutions was with anhydrous magnesium sulfate, and concentration was by removal of the solvent at reduced pressure using a rotary evaporator. Infrared spectra were determined on Perkin-Elmer 137 and 237B recording spectrophotometers in chloroform solution. Nuclear magnetic resonance spectra were determined in deuteriochloroform on a Varian Associates A60 recording spectrometer using tetramethylsilane as an internal standard. Ultraviolet spectra were determined in methanol using a Cary 14 recording spectrophotometer. Mass spectra were run at 70 eV using an LKB 9000 mass spectrograph. Thin layer chromatograms were run on Analtech, Inc., silica gel G plates utilizing iodine or ceric sulfate development. Melting points were run on a Koffler block and are uncorrected. Analyses were performed by R. Boos and associates of these laboratories.

(30) Procedure of Dr. R. Czaza of these laboratories. This compound was first prepared and characterized by workers at Commercial Solvents Co. (see ref 1b for these workers).

(31) E. J. Corey, M. Ohno, R. B. Mitra, and P. A. Vatakencherry, *J. Amer. Chem. Soc.*, **86** 478 (1964).

(distilled from lithium aluminum hydride and stored over 3A molecular sieves). The mixture was stirred under a nitrogen atmosphere and cooled to 0° before 20 ml of 0.5 *M* diborane in tetrahydrofuran was added dropwise over a period of 5 min. The temperature was kept below 1° during addition. After stirring for 1 hr at 0° the cooling bath was removed and stirring was continued for 23 min as the temperature rose to 18°. At this time the reaction mixture was cooled to −12° and 10 ml of water was added dropwise over a period of 11 min while the temperature was maintained below −10°. Stirring and cooling was continued as 25 ml of 2.5 *N* sodium hydroxide was added dropwise over a period of 3 min (temperature < −4°) followed by dropwise addition of 25 ml of 30% hydrogen peroxide over a period of 2 min (temperature < −2°). The cooling bath was then removed and the mixture was stirred for 30 min before being extracted with 400, 200, and 100 ml of ether. The combined ether extracts were washed with saturated brine, dried, and concentrated to 4.9 g of colorless oil. This residue was stirred for 14 hr with pyridine–chromium trioxide complex formed from 5.0 g of chromium trioxide and 50 ml of pyridine. After dilution with 50 ml of ether the insoluble salts were removed by filtration and washed ten times with 300-ml portions of saturated brine, dried, and concentrated to 4.66 g of viscous yellow oil. A 10.6-g portion of this residue (from runs of 5.0 and 6.0 g) was chromatographed on a 4.4-cm dry column of 350 g of silica gel using 30% ethyl acetate in benzene as an eluent. Fractions containing product (3.9 g) were then rechromatographed on an identical column. In this manner, 3.5 g of product was isolated. Also found in the crude reaction product were about 20% of starting material 6, 4% of compound 15, and about 20% of material 14 whose ir showed a 5.71-μ (phthalide) carbonyl. An analytical sample of the product was obtained as a glass by sublimation: uv max 217 mμ (ϵ 25,500), 253 (6350), 312 (2720); ir 5.82, 5.95 μ; nmr τ 2.90 (d, 1, J = 2.5 Hz, ArH), 2.98 (d, 1, J = 2.5 Hz, ArH), 4.80 (s, 4, OCH_2O), 6.12 (s, 4, OCH_2), 6.51 (s, 6, OCH_3), and 7.05 (m, 2, $ArCOCH_2$).

Anal. Calcd for $C_{24}H_{34}O_9$: C, 61.79; H, 7.35. Found: C, 61.90; H, 7.30.

6-(1,6-Dioxo-10-hydroxyundecanyl)-β-resorcylic Acid μ-Lactone (13).—A 2.1-g portion of 12 was refluxed and stirred under a nitrogen atmosphere for 4 hr with 240 mg of *p*-toluenesulfonic acid monohydrate, 35 ml of benzene, 6.5 ml of ethylene glycol, and 1 ml of water. After being cooled the mixture was taken up in 200 ml of ether. The ether solution was washed five times with saturated brine, dried, and concentrated to 1.4 g of foam which was chromatographed on 170 g of activity 3 neutral alumina on a 2.5-cm column. Elution with 2% methanol in ethyl acetate gave an impurity and elution with 10% methanol plus 1% acetic acid in ethyl acetate yielded 1.1 g (73%, mp 167–171°) of product. An analytical sample was obtained by washing with ether: mp 172.5–174.5°; ir 5.85, 6.03, 6.19 μ; nmr τ −0.93 (s, 1, OH), ~2 (very broad, 1, OH), 3.57 (d, 1, J = 2.5 Hz, ArH), and 3.85 (d, 1, J = 2.5 Hz, ArH).

Anal. Calcd for $C_{18}H_{22}O_6$: C, 64.65; H, 6.63. Found: C, 64.68; H, 6.73.

2-(6-Ethylenedioxy-10-hydroxy-3-oxo-*trans*-1-undecenyl)-4,6-bismethoxymethoxybenzoic Acid μ-Lactone (15).—A 4.00-g (8.9 mmol) portion of 6 was stirred for 47 hr at 27–28° with chromium trioxide–pyridine complex formed from 8.0 g of chromium trioxide and 100 ml of pyridine. The mixture was then added to 600 ml of ether and the insoluble precipitate was removed by filtration and washed well with ether. The combined filtrate and washings were then washed five times with 800-ml portions of saturated brine, dried with sodium sulfate, and concentrated to 4.0 g of viscous yellow oil which was 85% one spot on tlc (30% methyl ethyl ketone–70% *n*-hexane as an eluent). This residue was chromatographed on a 4.4-cm dry column of 300 g of silica gel using 35% ethyl acetate in benzene as an eluent. In this manner 2.4 g (59%) of pure material was separated. An analytical sample was obtained as a colorless glass by sublimation: uv max 231 mμ (ϵ 18,100), 291 (17,850); ir 5.83, 6.03, 6.11, 6.24 μ; nmr τ 2.56 (d, 1, J = 16 Hz, =CH), 2.96 (d, 1, J = 2.5 Hz, ArH), 3.14 (d, 1, J = 2.5 Hz, ArH), 3.46 (d, 1, J = 16 Hz, =CHCO), 4.83 (s, 4, OCH_2O), 5.86 (m, 1, CO_2CH), 6.10 (s, 4, OCH_2), 6.54 (s, 6, OCH_3), and 8.63 (d, 3, J = 6.5 Hz, CH_3).

Anal. Calcd for $C_{24}H_{32}O_9$: C, 62.05; H, 6.94. Found: C, 62.03; H, 6.94.

6-(3,6-Dioxo-10-hydroxy-*trans*-1-undecenyl)-β-resorcylic Acid μ-Lactone (16).—A 1.9-g portion of 15 was refluxed for 6 hr under nitrogen with 35 ml of benzene, 8 ml of ethylene glycol, 260 mg of *p*-toluenesulfonic acid monohydrate, and 1 ml of water. After cooling the mixture was taken up in 100 ml of ether and 100 ml of saturated brine. The ether layer was separated, washed four times with saturated brine, dried, and concentrated to 1.3 g of yellow foam. To this residue, under nitrogen, was added 20 ml of acetone, 20 ml of ethanol, 2 ml of water, and 0.3 g of *p*-toluenesulfonic acid monohydrate. The mixture was stirred and refluxed for 3 hr and concentrated *in vacuo*. The residue was triturated with water and the insoluble precipitate was collected on a filter and washed ten times with 10-ml portions of water to give 0.98 of crude product. Two recrystallizations from nitromethane gave 0.98 g of crude product. Two recrystallizations from nitromethane gave 0.48 g of analytical sample: mp 214.5–216.0°; uv max 216 mμ (ϵ 20,750), 247.5 (26,200), 286 (9030), 300 (8420); ir (Nujol mull) 5.92, 6.04, 6.2 μ; nmr τ −0.75 (broad, 2, OH), 2.23 (d, 1, J = 16 Hz, =CH), 3.53 (d, 1, J = 16 Hz, =CH), 3.57 (s, 2, ArH), and 8.73 (d, 3, J = 6 Hz, CH_3).

Anal. Calcd for $C_{18}H_{20}O_6$: C, 65.05; H, 6.07. Found: C, 64.80; H, 6.33.

2-(3,6-Dioxa-10-hydroxy-*trans*-1-undecenyl)-4,6-bismethoxymethoxybenzoic Acid μ-Lactone (17).—A 1.0-g portion of 5 was stirred for 11 days at 25–30° with chromium trioxide–pyridine complex formed from 2.0 g of chromium trioxide and 30 ml of pyridine. The mixture was worked up as described in the preparation of 15 to give 0.69 g of yellow solid whose tlc (20% ethyl acetate on benzene as an eluent) showed it to be 50% starting material (after only 2 days reaction, about 85% starting material was still unreacted), 10% unknown material, and 40% product. The product was isolated by preparative tlc and recrystallized from methanol to give an analtycal sample: mp 117–119.5°; uv max 227.5 mμ (ϵ 17,600), 290 (12,600); ir 5.84, 6.01, 6.14, 6.25 μ; nmr τ 2.56 (d, 1, J = 16 Hz, ArCH=), 3.03 (d, 1, J = 2.5 Hz, ArH), 3.13 (d, 1, J = 2.5 Hz, ArH), 3.47 (d, 1, J = 16 Hz, =CHCO), 4.82 (s, 2, OCH_2), 6.53 (s, 6, OCH_3), and 8.65 (d, 3, J = 6.5 Hz, CH_3).

Anal. Calcd for $C_{22}H_{28}O_8$: C, 62.84; H, 6.71. Found: C, 62.55; H, 6.89.

2-(6-Acetoxy-10-hydroxy-3-oxo-*trans*-1-undecenyl-4,6-bismethoxymethoxybenzoic Acid μ-Lactone (18).—A 387-mg portion of 8 was treated as in the preparation of 15 to give 0.35 g of crude product which was ~60% one spot on tlc (30% ethyl acetate–benzene). Purification of preparative tlc gave 0.18 g of one-spot material which was purified for analysis by sublimation at 190° (50 μ): uv max 227 mμ (ϵ 15,400); ir 5.84, 6.02, 6.13, 6.23 μ; nmr τ 2.56 (d, 1, J = 15.5 Hz, ArCH=), 2.95 (d, 1, J = 2 Hz, ArH), 3.12 (d, 1, J = 2 Hz, ArH), 3.46 (d, 1, J = 15.5 Hz, =CHCO), 4.82 (s, 4, OCH_2O), and 6.54 (s, 6, OCH_3).

Anal. Calcd for $C_{24}H_{32}O_9$: C, 62.05; H, 6.94. Found: C, 61.84; H, 6.87.

2-(3′,10′-Dihydroxy-6′-ethylenedioxy-*trans*-1′-undecenyl)-4,6-bismethoxymethoxybenzoic Acid μ-Lactone (19).—A 1.85-g sample of 15 was dissolved in 25 ml of methanol and the solution was stirred as 0.33 g of sodium borohydride was added. The mixture was stirred for 30 min, 200 ml of chloroform was added, and the mixture was washed with dilute hydrochloric acid and saturated brine. The chloroform solution was then dried and concentrated to 1.83 g of colorless gum. An analytical sample was obtained as a glass by sublimation: uv max 221 mμ (ϵ 30,700), 252.5 (12,500), 295 (1970); ir 5.83 μ.

Anal. Calcd for $C_{24}H_{34}O_9$: C, 61.79; H, 7.35. Found: C, 62.05; H, 7.33.

6-[10-Hydroxy-6-(2-hydroxylethoxy)-3,6-oxy-*trans*-1-undecenyl]-β-resorcylic Acid μ-Lactone (20).—To 513 mg of 19 was added 5 ml of acetone, 5 ml of ethanol, 0.5 ml of water, and 100 mg of *p*-toluenesulfonic acid monohydrate. The mixture was stirred and refluxed under nitrogen for 6 hr and the solvent was removed *in vacuo*. The residue was taken up in ether and the ether solution was washed with saturated brine, dried, and concentrated to 0.45 g of foam. To this foam was added 13 ml of benzene, 3 ml of ethylene glycol, 0.5 ml of water, and 100 mg of *p*-toluenesulfonic acid monohydrate. The mixture was stirred and refluxed under nitrogen for 7 hr. Work-up as before gave 375 mg of colorless foam. This material was dissolved in 10 ml of chloroform. On standing at −5°, a precipitate separated and was collected on a filter to give 86 mg, mp 243–248°. An analytical sample was prepared by two recrystallizations from chloroform: mp 245–246°; uv max 235 mμ (ϵ 28,400), 274 (12,300), 316 (5860; with base added 256 (21,600), 305 (15,290), 315

(15,400); ir (Nujol mull) 5.89, 6.07; 6.24 μ; nmr (DMSO) τ −1.83 (broad, 1, OH), −0.4 (very broad, 1, OH), 2.84 (d, 1, J = 16 Hz, =CH), 3.52 (d, 1, J = 2.5 Hz, ArH), 3.68 (d, 1, J = 2.5 Hz, ArH), 4.41 (d of d, 1, J = 16 and 9 Hz, =CH), 5.1 (m, 1, CO_2CH), 5.4 (m, 1, OH, disappears on spiking with D_2O), 6.2 (m, 1, OCH), 6.5 (m, 4, OCH_2), and 8.64 (d, 3, J = 6 Hz, CH_3); mass spectrum of tristrimethylsilyl derivative m/e 594.

Anal. Calcd for $C_{20}H_{26}O_7$: C, 63.48; H, 6.93. Found: C, 63.70; H, 7.16.

Acetylation of 20.—A 30-mg sample of **20** was dissolved in 0.6 ml of pyridine, and 0.4 ml of acetic anhydride was added with stirring. After standing for 15 hr the mixture was diluted with 10 ml of ice–water. The water was decanted from the resultant gum, which was washed with water and taken up in ether. The ether solution was dried and concentrated to 35 mg of colorless gum which was examined by nmr: τ 2.87 (d, 1, J = 2 Hz, ArH), 3.15 (d of d, 1, J = 1.5 and 16 Hz, =CH), 3.23 (d, 1, J = 2 Hz, ArH), 4.23 (d of d, 1, J = 16 and 5 Hz, =CH), 4.80 (m, 1, CO_2CH), 5.85 (m, 2, OCH_2), 5.9 (m, 1, OCH), 6.4 (m, 2, OCH_2), 7.73 (s, 3, $COCH_3$), 7.76 (s, 3, $COCH_3$), 7.93 (s, 3, $COCH_3$), and 8.66 (c, 3, J = 6.5 Hz, CH_3).

2-{7-[(Cyclohexyloxy)methylene]-10-methyl-6-oxo-1-undecenyl}-4,6-dibenzyloxybenzoic Acid μ-Lactone (22).—A 19-g portion of **4**, 4.2 g of 54.7% sodium hydride in mineral oil, and 300 ml of benzene (dried with 3A molecular sieves) were stirred under a nitrogen atmosphere for 5 min, and 1 ml of *tert*-butyl alcohol (dried with 3A molecular sieves) was added. After stirring for 15 min at room temperature, the mixture was refluxed for 15 min and cooled to room temperature, and 9.6 ml (8.4 g) of ethyl formate (dried with 3A molecular sieves) was added. The mixture was then stirred for 18 hr and 2 ml of additional ethyl formate was added. After stirring for 3 hr more the mixture was added to 1 l. of water and 500 ml of ether. The water layer was separated and made acidic with sodium dihydrogen phosphate before extraction with ether. The ether extract was dried and concentrated to 20 g of pink gum whose tlc (30% acetone–70% *n*-hexane) showed an 8:1 mixture of **21** and its C-5′ isomer. Pure **21** was obtained by preparative tlc: ir 5.72, 5.82, and 6.25 μ; nmr τ −5.16 (d, 1, J = 5.5 Hz, C=COH), 1.70 (d, 1, J = 5.5 Hz, C=CHOH), 2.65 (s, 5, ArH), 2.68 (s, 5, ArH), 3.35 (d, 1, J = 2.5 Hz, ArH), 3.44 (d, 1, J = 16 Hz, C=CH), 3.49 (d, 1, J = 2.5 Hz, ArH), 3.8–4.1 (m, 1, C=CH), 4.5–4.9 (m, 1, CO_2CH), 4.95 (s, 4, $ArCH_2$), and 8.75 (d, 3, J = 6.5 Hz, CH_3).

A mixture of 14.5 g of the crude **21** and its C-5′ isomer and 400 ml of benzene was boiled as 50 ml of distillate was removed by a Dean–Stark water separator. The mixture was cooled, and 50 mg of *p*-toluenesulfonic acid monohydrate and 3.6 ml of cyclohexanol was added. The mixture was then refluxed for 15 hr with the use of a Dean–Stark water separator. The Dean–Stark trap was then drained and filled with 3A molecular sieves and refluxing was continued for 45 hr. After cooling and addition of 400 ml of ether, the mixture was washed with dilute sodium hydroxide followed by saturated brine. After being dried the organic layer was concentrated to 13 g of orange gum whose tlc (10% ethyl acetate–90% benzene) exhibited two spots in a ~8:1 ratio. This residue was chromatographed on a 6.6-cm dry column of 390 g of silica gel H using 10% ethyl acetate–90% benzene as an eluent. In this manner, 6.8 g of **22**, which was free of C-5′ isomer, was isolated as a glass. An analytical sample was obtained by grinding a sample to a powder and drying at 50 μ: uv max 227 mμ (ε 36,000) and 258 (26,700); ir 5.83, 6.01, 6.16, 6.26, and 6.34 μ.

Anal. Calcd for $C_{39}H_{44}O_6$: C, 76.94; H, 7.29. Found: C, 76.87; H, 7.34.

2-(7-Formyl-10-hydroxy-*trans*-1,6-undecadienyl)-4,6-dibenzyloxybenzoic Acid μ-Lactone (23).—To a stirred solution of 5.7 g (9.4 mmol) of **22** in 110 ml of methanol was added, in small portions over a period of 10 min, 2.5 g of sodium borohydride. The mixture was then stirred for 75 min and concentrated *in vacuo* to a solid residue which was taken up in 200 ml each of ether and saturated brine. The layers were separated and the aqueous layer was extracted once with ether. The combined ether layers were then washed with saturated brine, dried, and concentrated *in vacuo* to 5.45 g of colorless gum. This gum was stirred under nitrogen for 4 hr in a mixture of 100 ml of ether and 100 ml of 3 *N* hydrochloric acid. An additional 200 ml of ether was then added and the organic layer was separated, washed with saturated brine, and dried before concentration *in vacuo* to 5.0 g of slightly colored gum. This residue was shown by tlc (10% ethyl acetate–90% benzene) to be ~75% product. Purification of a 4.5-g portion of this residue was achieved by chromatography on 200 g of silica gel H in a 4.5-cm dry column (10% ethyl acetate–90% benzene). This procedure gave 3.16 g (73%) of a colorless gum which was one spot on tlc. An analytical sample was obtained as a glass by sublimation at 170° (50 μ): uv max 222 mμ (ε 47,800), 264 (7800), and 290 (2780); ir 3.67, 5.82, 5.95, 6.06, and 6.10 μ; nmr τ 0.64 (s, 1, CHO), 2.66 (s, 5, C_6H_5), 2.69 (s, 5, C_6H_5), 3.33 (d, 1, J = 2.5 Hz, ArH), 3.51 (d, 1, J = 2.5 Hz, ArH), 4.98 (s, 4, OCH_2Ph), and 8.77 (d, 3, J = 6 Hz, CH_3).

Anal. Calcd for $C_{33}H_{34}O_5$: C, 77.62; H, 6.71. Found: C, 77.36; H, 6.57.

6-(7-Formyl-10-hydroxyundecyl)-β-resorcylic Acid μ-Lactone (24).—A 2.20-g portion of **23** was hydrogenated at atmospheric pressure in 50 ml of ethyl acetate in the presence of 1.1 g of 10% palladium on carbon (no prehydrogenation of the catalyst). Hydrogenation was stopped after 3 hr and 413 ml uptake. The catalyst was removed by filtration. Concentration of the filtrate *in vacuo* gave 1.31 g of slightly colored tacky gum which was 70% one spot (R_f 0.3) on tlc (10% ethyl acetate–90% benzene). This material was purified by chromatography on 60 g of silica gel H in a dry 3.5-cm column (10% ethyl acetate–90% benzene). Early fractions yielded material with one benzyl group remaining, [ir 3.67, 5.75, 6.03, and 6.14 μ; nmr τ 2.65 (s, 5, C_6H_5) and 4.97 (s, 2, CH_2Ar)], while later fractions gave material with a reduced formyl group [ir 2.79, 3.08, 6.10, and 6.17 μ; nmr τ 6.5 (m, 2, CH_2OH)]. The intermediate fractions yielded 0.72 g (50%) of pure product which was epimeric at C-7: mp 40–140°; uv max 219.5 mμ (ε 21,900), 265 (13,100), and 303 (ε 5280); ir 2.74, 2.81, 3.0, 3.70, 5.82, 6.10, and 6.18 μ; nmr τ −2.23 (s, 0.6, OH), −2.17 (s, 0.4, OH), 0.30 (s, 0.4, CHO), and 0.35 (s, 0.6, CHO).

Anal. Calcd for $C_{19}H_{26}O_5$: C, 68.24; H, 7.84. Found: C, 68.17; H, 7.89.

Isolation of Epimers of 24.—The crude hydrogenation product from three runs as described in the preparation of epimeric **24** (10.3 g) was recrystallized twice from benzene to give 1.2 g of crude isomer b which was not pure by tlc, mp 152–155°. This sample was chromatographed on 120 g of Baker silica gel packed in benzene and gave 1.09 g of material that was one spot on tlc (R_f 0.4, 10% ethyl acetate–90% benzene). This material was recrystallized from benzene to give 820 mg of pure isomer **24b**: mp 148–152°; nmr τ −2.5 (s, 1, OH), and 0.30 (s, 1, CHO).

Anal. Calcd for $C_{19}H_{26}O_5$: C, 68.24; H, 7.81. Found: C, 68.42; H, 7.77.

To the filtrate of the first recrystallization of the 10.3 g of crude **24** mentioned above, *n*-hexane was added and 1.0 g of precipitate separated and was collected on a filter. Recrystallization from benzene gave 600 mg of crude isomer **24a** which was impure by tlc. Chromatography in 60 g of silica gel as described in the purification of isomer **24b** gave 0.40 g of pure isomer **24a**: mp 141–146°; nmr τ −2.13 (s, 1, OH), and 0.35 (s, 1, CHO).

Anal. Calcd for $C_{19}H_{26}O_5$: C, 68.24; H, 7.84. Found: C, 68.54; H, 7.82.

6-(10-Hydroxy-7-oxoundecyl)-β-resorcylic Acid μ-Lactone (25).—The epimeric mixture **24** (445 mg) was dissolved in 5 ml of pyridine (dried with 3A molecular sieves) and 7 ml of acetic anhydride. After standing for 15 hr the mixture was poured onto ice. The resultant gum was extracted with ether and the ether extracts were washed with saturated brine, dried, and concentrated *in vacuo* to 475 mg of slightly colored gum. This residue was added to 100 mg of *p*-toluenesulfonic acid monohydrate and 20 ml of freshly distilled isopropenyl acetate. The mixture was slowly distilled for 10 hr (5 ml of distillate collected), refluxed for 13 hr, and distilled for another hour (5 ml of distillate collected). The remainder of the isopropenyl acetate was removed *in vacuo*, and the residue was taken up in ether. The ether solution was washed with saturated brine, dried, treated with activated charcoal, and concentrated to 554 mg (90%) of yellow gum, which was one spot on tlc (R_f 0.25, 10% ethyl acetate–90% benzene). An analytical sample of the enol acetate of **24** diacetate was prepared by purification by preparative tlc followed by sublimation at 150° (50 μ) to give a colorless glass: ir 5.6–5.7 μ; nmr τ 3.13 (s, 1, =CH), 3.17 (d, 1, J = 2.5 Hz,

ArH), 3.26 (d, 1, J = 2.5 Hz, ArH), 7.82 (s, 3, $COCH_3$), 7.83 (s, 3, $COCH_3$), and 7.95 (s, 3, $COCH_3$).

Anal. Calcd for $C_{25}H_{32}O_8$: C, 65.20; H, 7.00. Found: C, 65.44; H, 7.13.

A 400-mg sample of the crude enol acetate was ozonized in methanol and treated with dimethyl sulfide as described in the ozonolysis of **10**. Concentrations *in vacuo* gave 489 mg of brown oil. To this residue was added 8 ml of methanol, 8 ml of dioxane, and 3 ml of 2.5 *N* sodium hydroxide. After standing for 2 hr the solvent was removed *in vacuo* and the residue was dissolved in 50 ml of water. The aqueous solution was washed with ether, acidified with concentrated hydrochloric acid, and extracted with ether. The ether extract was washed with saturated brine, dried, and concentrated *in vacuo* to 278 mg of pink gum whose tlc (20% ethyl acetate–80% benzene) showed it to be ~85% one spot at R_f 0.4. This material was purified by preparative tlc (4% methanol–96% chloroform) to give 155 mg (56%) of crystalline product, mp 167–170°. An analytical sample was obtained by partial recrystallization from benzene: mp 168–170.5°; ir 5.86, 6.10, and 6.17 μ; nmr τ −1.65 (s, 1, OH), 0.93 (s, 1, OH), 3.68 (d, 1, J = 3 Hz, ArH), 3.75 (d, 1, J = 3 Hz, ArH), 4.82 (q, 1, J = 6 Hz, COCH), and 8.63 (d, 3, J = 6 Hz, CH_3); mass spectrum m/e (rel intensity) 320 (11), 302 (5), 265 (51), 177 (15), 163 (48), 150 (23), 124 (39), 123 (33), 111 (100), 98 (35), 69 (32), 55 (67), 41 (34).

Hydroxymethylation of Dimethoxyzearalanone and Degradation of the Main Isomer to Diacid 28.—In 21 ml of dry benzene, 1044 mg of dimethoxyzearalanone[1b] was dissolved and 330 mg of sodium hydride (51% dispersion in mineral oil) was added, followed by 0.15 ml of *tert*-butyl alcohol. The mixture was heated for 3 min to 60° and allowed to stir for 15 min at room temperature. After addition of 0.75 ml of freshly distilled ethyl formate, it was stirred overnight and became dark brown. Work-up consisted of quenching by pouring onto 25 g of ice and adddition of 2 ml of 2.5 *N* sodium hydroxide followed by two extractions with ether. The aqueous portion was acidified with sodium dihydrogen phosphate and extracted three times with ether. Upon drying and concentrating, the residue was only 1020 mg.

A total of 1000 mg was chromatographed on ten silica gel plates (8 × 8 × 1000 μ) and developed with 20% acetone in hexane, giving good separation into two bands. The less polar fraction (R_f 0.3) was homogeneous but still oily and weighed 460 mg (**26**).

The homogeneous, more polar fraction (R_f 0.45) was also oily, 150 mg, and undistinguished by ir, uv, or nmr from either the more abundant isomer or the total crude: uv max 281 mμ (ϵ 5000); with base added 302.5 (15,100), 245 (4980); ir (neat) 5.83, 5.88, 6.25 μ.

Degradation to 28.—A 230-mg portion of **26** was dissolved in 8 ml of ethyl acetate, cooled to −70°, and exposed for a total of 12 min to a stream of ozone. During this period the initially orange-colored solution became light yellow. After purging the mixture with nitrogen at 0°, 6 ml of glacial acetic acid was added at this temperature, followed by 1.5 ml of 30% hydrogen peroxide solution. The mixture was allowed to warm to room temperature and stirred for 3 hr. It was worked up after the addition of 30 ml of water containing 4 g of sodium bisulfite and final acidification to pH 2. The combined ethyl acetate extracts were dried and concentrated to dryness, yielding 180 mg of amorphous solid (**27**).

(A 70-mg sample of this solid was purified by chromatography on silica gel plates using a 50:50 mixture of acetone–hexane as an eluent. The major band yielded 40 mg of noncrystalline material which had a molecular ion at m/e 396, corresponding to **27**.)

A 100-mg sample of crude **27** was hydrolyzed by treatment with 5 ml of 2.5 *N* sodium hydroxide on the steam bath for 16 hr.

The ether extracts, after acidification, yielded 80 mg of viscous oil.

On preparative tlc the latter separated into two bands; the major product was crystallized from ether, yielding 40 mg of material, mp 110–111°. Its mass spectrum was very similar to that of **27** if the latter's molecular ion is disregarded. It was assigned to diacid structure **28**, and its identity was confirmed by melting point, mixture melting point, and ir and tlc with an authentic specimen[1b] kindly supplied by Dr. Hodge from CSC.

2-(6-Acetoxy-10-hydroxy-*trans*-1,5-undecadienyl)diacetoxybenzoic Acid μ-Lactone (29).—A 12.5-g (30 mmol) portion of zearalenone diacetate,[1b] 200 g of *p*-toluenesulfonic acid monohydrate, and 200 ml of isopropenyl acetate were stirred and warmed with gradual distillation through a 2.5 × 25 cm Vigreux column for 45 hr. During this time 50 ml of distillate was collected at a stillhead temperature of about 60°. The distillate temperature was then raised to 95° and 50 ml of distillate was collected. The cooled residue was then taken up in a mixture of 400 ml of ether, 350 ml of saturated brine, and 50 ml of 2.5 *N* NaOH. The ether layer was separated, washed four times with saturated brine, dried with sodium sulfate, and concentrated to 18 g of viscous brown oil which was dissolved in 75 ml of methanol and cooled to −5°. The precipitate was collected to give 8.46 g (61%) of slightly colored crystals, mp 120–123°. Recrystallization from methanol gave an analytical sample: mp 124–125°; uv max 219.5 mμ (ϵ 24,800), 252 (14,300); ir 5.66, 5.75, 5.84 μ; nmr τ 2.89 (d, 1, J = 2 Hz, ArH), 3.16 (d, 1, J = 2 Hz, ArH), 3.48 (d, 1, J = 15 Hz, =CH), 3.8–4.3 (m, 1, =CH), 4.5–5.1 (m, 2, OCH), 7.74 (s, 3, $COCH_3$), 7.77 (s, 3, $COCH_3$), 7.88 (s, 3, $COCH_3$), and 8.81 (d, 3, J = 7 Hz, CH_3); mass spectrum m/e (rel intensity) 112 (1), 125 (100), 176 (30), 218 (40), 300 (3), 342 (5), 402 (3), 444 (2).

Anal. Calcd for $C_{24}H_{28}O_8$: C, 64.85; H, 6.35. Found: C, 65.10; H, 6.16.

Ozonolysis of 29.—A 400-mg portion of **29** was added to 65 ml of ethanol. The mixture was stirred, cooled in a Dry Ice–acetone bath, and saturated with ozone. After 10, 20, and 60 min of stirring, the mixture was again saturated with ozone. The cooling bath was then removed, and the mixture was stirred at room temperature for 15 min before flushing with nitrogen. Dimethyl sulfide[27] (1 ml) was added, and the solution was stirred for 65 hr at room temperature (an aliquot taken after 15 hr exhibited an ir with a 5.47 μ carbonyl of moderate strength which was not present after 65 hr). The mixture was then concentrated to an oil whose tlc (30% ethyl acetate in benzene) indicated a small amount of starting material (R_f 0.50), a major spot at R_f 0.45, and a large amount of very polar material. This residue was dissolved in ether and extracted with saturated sodium bicarbonate. The ether layer was dried and concentrated to 147 mg of residue which contained (tlc) ~90% of the material at R_f 0.45 and starting material. A 37-mg sample of oil containing only material of R_f 0.45 and a more polar spot was separated by preparative tlc and treated with 20 ml of pyridine and 400 ml of acetic anhydride. This gave 37 mg of colorless oil that was one spot at R_f 0.45 and is assigned structure **30a**: ir 3.67, 5.64, and 5.80 μ; nmr τ −0.06 (s, 1, CHO), 2.42 (d, 1, J = 2.5 Hz, ArH), 2.71 (d, 1, J = 2.5 Hz, ArH), 4.8 (m, 1, CO_2CH), 5.86 (q, 2, J = 7 Hz, CO_2CH_2), 7.80 (s, 3, $COCH_3$), 7.82 (s, 3 $COCH_3$), 8.62 (d, 3, J = 6 Hz, CH_3), and 8.76 (t, 3, J = 7 Hz, CH_3); mass spectrum m/e (rel intensity) 249 (22), 143 (100).

The 2,4-dinitrophenylhydrazone (**30c**) of **30a** was prepared and recrystallized from methanol, mp 163–165°.

Anal. Calcd for $C_{26}H_{28}O_{12}N_4$: C, 53.06; H, 4.80; N, 9.52. Found: C, 52.82; H, 4.90; N, 9.46.

A 200-mg sample of **29** was ozonized in methanol and worked up in the manner described above to give 330 mg of crude product which showed only a nonpolar spot at R_f ~0.5 (30% ethyl acetate in benzene). From 50% of the crude product, 32 mg of material was isolated by preparative tlc and was assigned structure **30b**: ir 3.67, 5.64, and 5.80 μ; nmr τ 0.03 (s, 1, CHO), 2.53 (d, 1, J = 2.5 Hz, ArH), 2.83 (d, 1, J = 2.5 Hz, ArH), 4.87 (m, 1, CO_2CH), 6.39 (s, 3, CO_2CH), 7.77 (s, 6, $COCH_3$), and 8.86 (d, 3, J = 7 Hz, CH_3); mass spectrum m/e (rel intensity) 249 (11), 129 (100).

2-(6-Acetoxy-10-hydroxy-*trans*-1,6-undecadienyl)-4,6-diacetoxybenzoic Acid μ-Lactone (31).—From the mother liquors **29** there was isolated after several days at room temperature 0.3 g (2%) of fine needles, mp 174–178°. Recrystallization from methanol gave 0.23 g of analytical sample: mp 178.5–180°; uv max 219.5 mμ (ϵ 22,800), 258 (15,900); ir same as ir of **29** except in 10–12-μ region; nmr τ 2.76 (d, 1, J = 2 Hz, ArH), 3.11 (d, 1, J = 2 Hz, ArH), 3.46 (d, 1, J = 15 Hz, =CH), 3.7–4.2 (m, 1, =CH), 4.5–5.0 (m, 2, =CH and COCH), 7.69 (s, 3, $COCH_3$), 7.73 (s, 3, $COCH_3$), and 8.64 (d, 3, J = 6 Hz, CH_3); mass spectrum m/e (rel intensity) 112 (50), 125 (11), 141 (66), 176 (9), 218 (22), 300 (89), 342 (100), 402 (28), 444 (7).

Anal. Calcd for $C_{24}H_{28}O_8$: C, 64.85; H, 6.35. Found: C, 64.59; H, 6.41.

Ozonolysis of 31.—A 167-mg portion of **31** was ozonized and worked up according to the procedure described for ozonolysis

of **29** to give 277 mg of residue which was purified by preparative tlc (30% ethyl acetate in benzene) to yield 96 mg (83%) of an oil that was 95% one spot (R_f 0.35) on tlc. A second preparative tlc of this material did not increase its purity. This material is assigned structure **32** on the basis of its spectral properties: ir 3.67 (twice the strength of the same band in the spectra of **30a**, **30b**), 5.64, and 5.78 μ; nmr τ 0.03 (s, 1, CHO), 0.27 (t, 1, J = 1 Hz CHO), 2.45 (d, 1, J = 2.5 Hz, ArH), 2.73 (d, 1, J = 2.5 Hz, ArH), 4.75 (q, 1, J = 6 Hz, CO_2CH), 7.40 (t, 2, J = 6.5 Hz, CH_2CHO), 7.69 (s, 3, $COCH_3$), 7.71 (s, 3, $COCH_3$), 7.98 (t, 2, J = 6.5 Hz, CH_2), and 8.62 (d, 3, J = 6 Hz, CH_3); mass spectrum m/e (rel intensity) 265 (7), 249 (6), 85 (100).

Registry No.—**1**, 17924-92-4; **2**, 34289-99-1; **4**, 34297-69-3; **5**, 34290-00-1; **6**, 34297-70-6; **7**, 34288-78-3; **8**, 34288-79-4; **10**, 34288-80-7; **11**, 34288-81-8; **12**, 34290-01-2; **13**, 34290-02-3; **15**, 34290-03-4; **16**, 34290-04-5; **17**, 34290-05-6; **18**, 34288-82-9; **19**, 34288-83-0; **20**, 34297-71-7; **20** triacetate, 34297-72-8; **21**, 34290-06-7; **22**, 34290-07-8; **23**, 34290-08-9; **24** α isomer, 29181-06-4; **24** β isomer, 29181-19-9; **24** cis isomer diacetate, 34290-11-4; **24** trans isomer diacetate, 34290-12-5; **25** dimethyl ether, 34290-13-6; **28**, 10513-52-7; **29**, 34290-14-7; **30a**, 34290-15-8; **30b**, 34290-16-9; **30c**, 34290-17-0; **31**, 34290-18-1; **32**, 34290-19-2.

Chemical Modifications of Zearalenone. II

T. B. WINDHOLZ* AND R. D. BROWN

Department of Synthetic Chemical Research, Merck Sharp & Dohme Research Laboratories, Rahway, New Jersey 07065

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Substitution of carboxyl and formyl groups into the aromatic portion of zearalenone is described and the new structures are unambiguously determined. Elimination reactions occurring during Birch reduction are investigated and a mechanism is proposed that accounts for the obtained products and intermediates.

As part of a program directed toward chemical modifications of zearalenone[1] (**1**) we investigated some of its aromatic substitution and elimination products. Available literature data[2] seemed insufficient to predict, with assurance, the outcome of a Kolbe–Schmitt reaction on **1** since the carbonation of resorcinol is described as leading primarily to 2,4-dihydroxybenzoic acid, while a 90% yield of 2,6-dihydroxy-4-methylbenzoic acid had been obtained from 3,5-dihydroxy-1-methylbenzene. Because of the sensitivity of zearalenone, we decided on relatively short reaction times for carbonation, and found that using potassium carbonate at 175° and 800 psi carbon dioxide for 3 hr,[3] a single carboxylic acid **2a** was obtained in better than 50% yield.

Since physical data could not safely distinguish between the two possible positions for the carboxy group in the aromatic ring, chemical degradation had to be undertaken. The sequence of reactions is shown in Scheme I. Successive methylations of the purified Kolbe–Schmitt product with methyl sulfate and diazomethane afforded a dimethoxymethyl ester **2b**, which was submitted to ozonization. It was found best to oxidize immediately the presumed dialdehyde **3** to a crude diacid **4a**, which was esterified to **4b** and purified by chromatography. Hydrolysis of this triester gave a tricarboxylic acid **5a** which was best purified by reesterification to **5b**, chromatography, and renewed hydrolysis to the crystalline triacid. Although the nmr signal for the single aromatic proton at τ 2.6 was a clear indication that it is flanked by a methoxy and a carboxy group [*cf.* the signals at τ 2.8 and 3.25 of the two types of easily identifiable protons in 2,4-dimethoxybenzoic acid (**6**)[4]], we have been able to identify **5a** with an authentic sample[5] of 2,4-dimethoxybenzene-1,3,6-tricarboxylic acid, mp 240–241°.

It was of further interest to determine the structure of a monoformyl derivative **7** of zearalenone, which was obtained by a Friedel–Crafts type formylation.[6] To this end, both the purified formylation product **7** and the carboxylic acid **2a** were converted to the same carboxamide **9** as shown in Scheme I. Since the aldehyde **7** did give a monoxime **8a**, its further conversion to the nitrile **8b** and the corresponding carboxamide **9** did not present difficulties. This carboxamide was found to be identical with the one obtained directly from the methyl ester of acid **2a**, proving that both carboxylation and formylation of zearalenone have occurred at the same carbon atom.

Birch reduction of the aromatic nucleus was investigated using the ethylene ketal **10** of the saturated macrocycle. Reaction with 4 equiv of sodium (the minimum required for significant reduction) in liquid ammonia and *tert*-butyl alcohol afforded two homogeneous, oily products, each in *ca.* 30% yield. Both were rather unstable to conventional manipulations because of a marked tendency to aromatize.

The more polar product, which had retained one methoxy group, was assigned[7] structure **11a** on spectral grounds. On treatment with CrO_3 in pyridine it was converted into the aromatic, noncrystalline ketal **12a**, which was further characterized by acid hydrolysis to 2-(10-hydroxy-6-oxoundecyl)-6-methoxybenzoic acid μ-lactone (**12b**), mp 96–97°, identical in all respects with a sample prepared by methylation of authentic[8] 2-(hy-

(1) For leading references regarding isolation, structure, and total syntheses of this fungal metabolite see paper I: N. P. Jensen, R. D. Brown, S. M. Schmitt, T. B. Windholz, and A. A. Patchett, *J. Org. Chem.*, **37**, 1639 (1972). This paper also describes specifics of physical measurements and standard procedures.

(2) (a) A. S. Lindsey and H. Jeskey, *Chem. Rev.*, **57**, 583 (1957); (b) F. Wessely, K. Benedikt, H. Benger, G. Friedrich, and F. Prillinger, *Monatsh. Chem.*, **81**, 1071 (1950).

(3) We thank Dr. W. H. Jones and associates for performing this reaction.

(4) Kindly supplied by Mr. H. L. Slates of these laboratories.

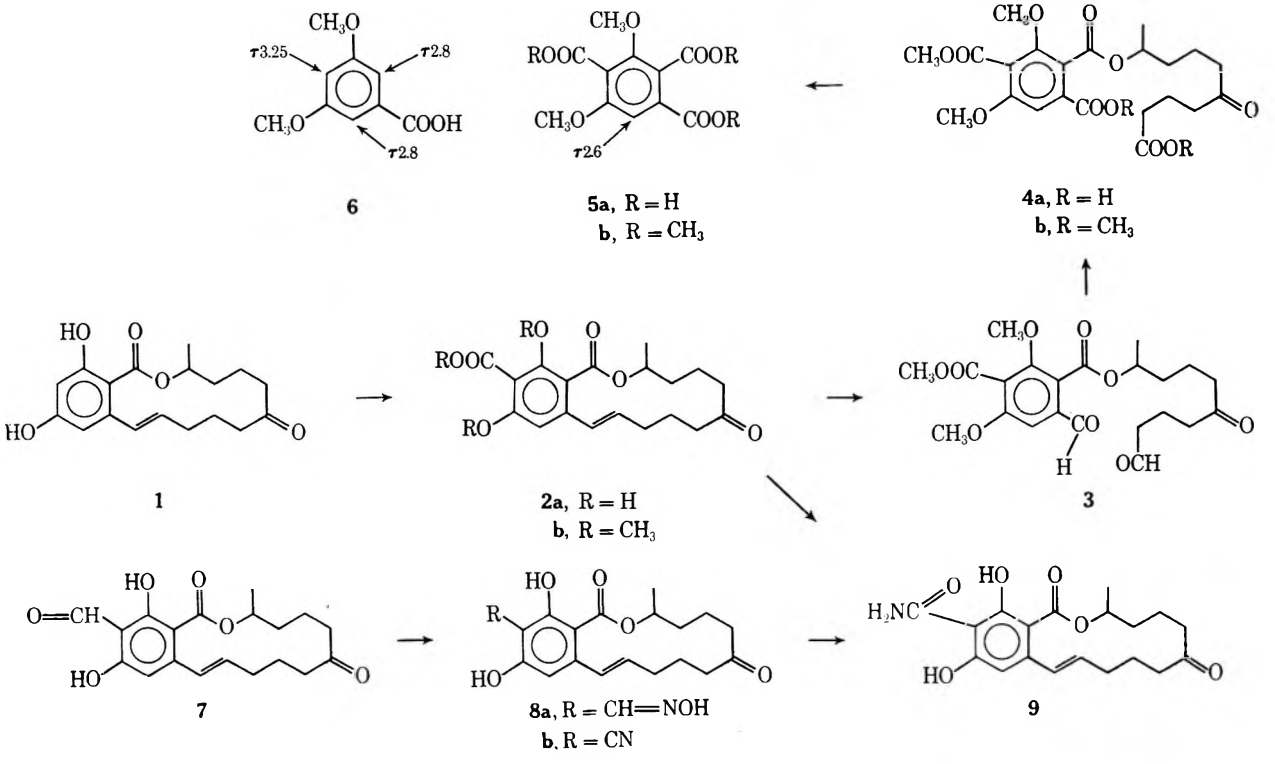
(5) I. Iwai and H. Mishima, *Chem. Ind. (London)*, 186 (1965). We are greatly indebted to Drs. Iwai and Mishima of Sankyo, Ltd. (Tokyo), for providing us with an authenticated sample for comparison.

(6) H. Gross, A. Fieche, and G. Matthey, *Chem. Ber.*, **96**, 308 (1963).

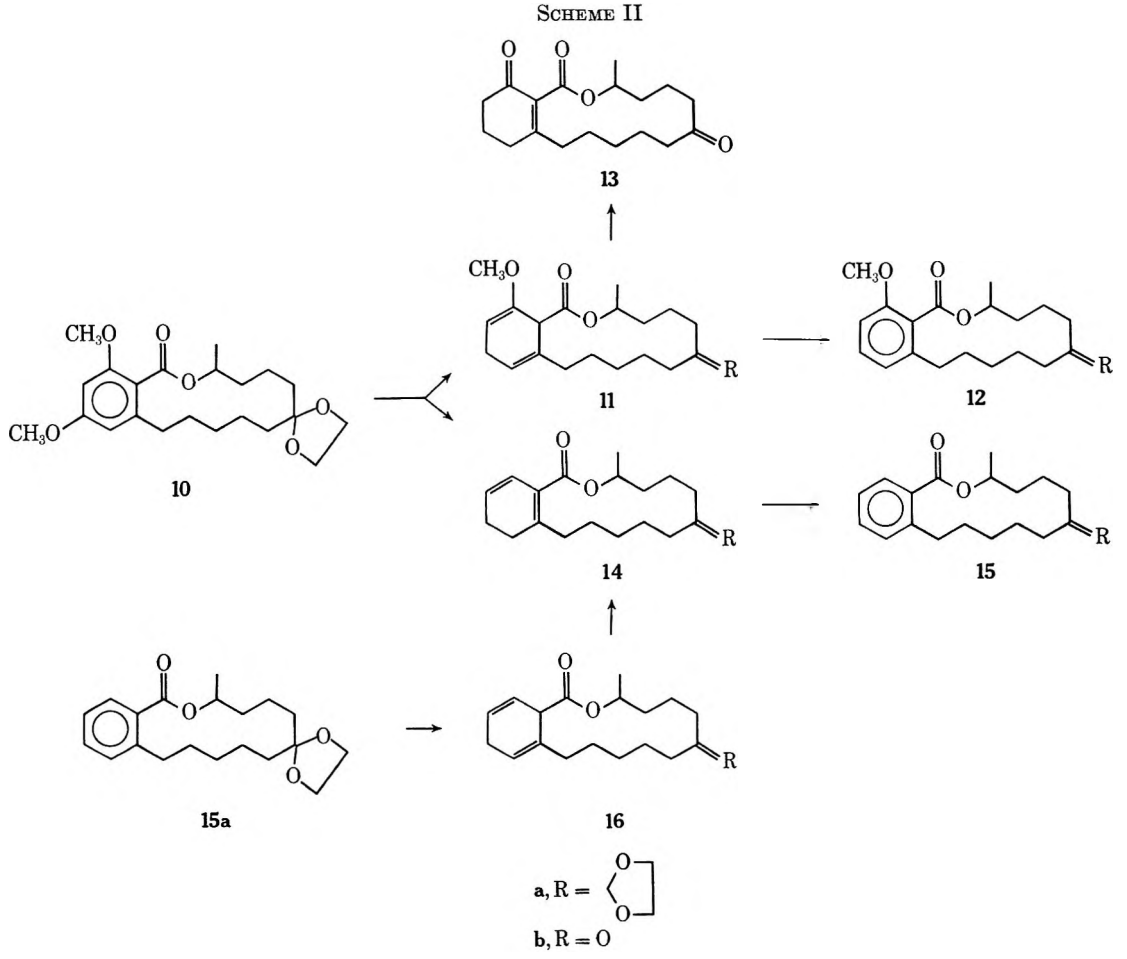
(7) Uv data of dihydroaromatic compounds are omitted, since they reflect the presence of small amounts of aromatic contaminants also detected in the nmr spectra.

(8) D. B. R. Johnston, C. A. Sawicki, T. B. Windholz, and A. A. Patchett, *J. Med. Chem.*, **13**, 941 (1970).

SCHEME I



SCHEME II



droxy-6-oxoundecyl)-6-hydroxybenzoic acid μ-lactone. Acid treatment of **11a** yields 2-(10-hydroxy-6-oxoundecyl)-6-oxo-1-cyclohexene-1-carboxylic acid μ-lactone (**13**).

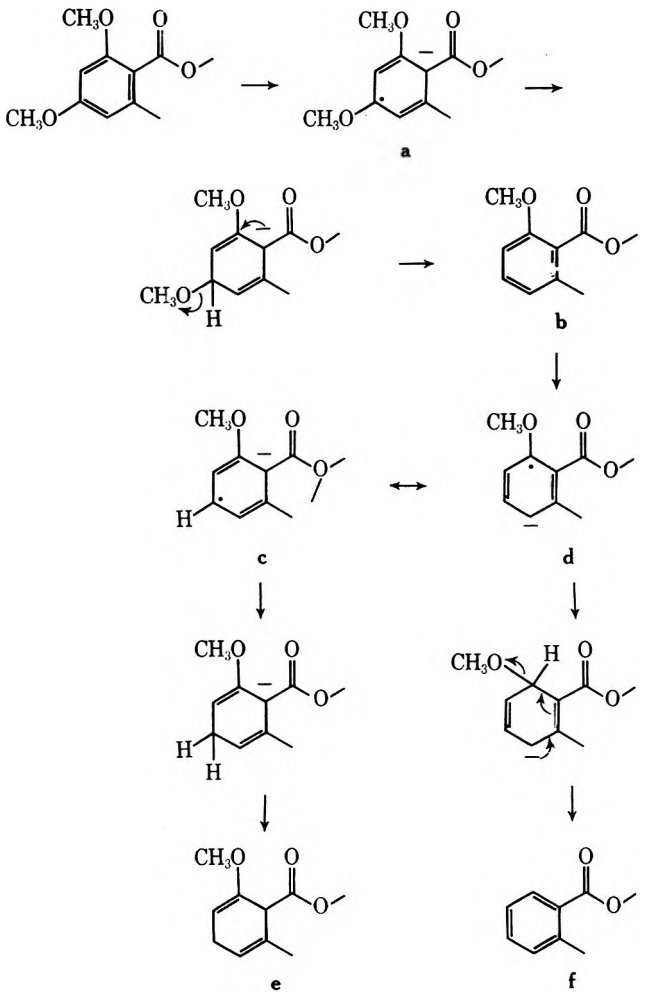
The less polar product from the Birch reduction (see Scheme II) had no methoxy group and was assigned the dihydroaromatic structure **14a**. Aromatization (CrO_3–pyridine) followed by mild acidic hydrolysis converts **14a** into the known[8] 2-(10-hydroxy-6-oxoundecyl)-benzoic acid μ-lactone (**15b**), mp 89–91°. The sup-

position that **14a** was obtained by subsequent reduction of the initially formed dideoxy zearalenone ketal **15a** was confirmed when, upon Birch reduction of an independently prepared[8] sample of **15a**, a new dehydroaromatic product was isolated in 90% yield. It was assigned structure **16a**, based on its spectral data. Base treatment of **16a** (KOH–methanol, room temperature) resulted in rearrangement to **14a**, confirming the possibility that, during work-up of the mixture[9] resulting from the Birch reduction of **10**, the initially formed **16a** was isomerized to **14a**. On the other hand, acid treatment of **16a** had no effect on the double bonds, and only caused ketal reversal to **16b**.

When **10** was subjected to Birch reduction using 8–18 equiv of sodium, only small amounts of **11a** were found, **14a** being the major identifiable product, isolated in *ca.* 36% yield.

Scheme III shows our interpretation of the course and mechanism[10] of the reactions reported above. Single-electron addition to the dimethoxy derivative **10** forms the anion radical a, which upon protonation and further reduction causes immediate elimination of the para-situated 4-methoxy group, with facile rearomatization to b. Under the conditions of the reaction, electron addition to b leads to an anion radical to which c and d are major contributing structures. Further reduction and protonation (see Scheme III) leads to both e and f, the latter product apparently favored by an excess of sodium metal. The dehydroaromatic product **2**, actually isolated from the reaction, must result from further reduction of the initially formed derivative f.

SCHEME III



Experimental Section

2,4-Dihydroxy-6-(10-hydroxy-6-oxoundec-1-enyl)-1-isophthalic Acid μ-Lactone (2a).—A mixture of 3.18 g of zearalenone[1] and 10 g of anhydrous potassium carbonate was heated at 175° under 800-psi carbon dioxide pressure for 3 hr. The resulting solid was pulverized and stirred with 200 ml of saturated monosodium phosphate solution for 2 hr. The remaining solid was filtered, dried, and washed with acetone. The crude salt (2.7 g) was suspended in 50 ml of methanol, and 4.5 ml of 2.5 *N* hydrochloric acid was gradually added. Partial solution followed by reprecipitation was observed, and the suspension was stirred for 2 hr at room temperature, then poured into 300 ml of water. The obtained precipitate was filtered and dried, yielding 1.8 g (50% yield) of **2a**. A sample was crystallized from methanol: mp 158–160°; uv max 330 mμ (ε 3800), 280 (17,500), and 227.5 (17,900); ir 5.90 (C=O), 6.09 (C=O), and 6.19 μ (C=O); nmr τ −2.70 (s, 1, exchangeable), −1.0 (s, 1, exchangeable), 3.00 (d, 1, *J* = 16 Hz, C=CH), 3.41 (s, 1, ArH), 8.55 (d, 3, *J* = 6.5 Hz, CH_3); mass spectrum (70 eV) *m/e* 362.

Anal. Calcd for $C_{19}H_{22}O_7$: C, 62.97; H, 6.12. Found: C, 62.93; H, 6.09.

2,4-Dimethoxy-6-(10-hydroxy-6-oxoundec-1-enyl)-1-isophthalic Acid μ-Lactone 3-Methyl Ester (2b).—A 1.0-g sample of **2a** was suspended in 4 ml of dimethyl sulfate and 15 ml of a 20% solution of sodium hydroxide was added. An exothermic reaction followed. The temperature was maintained at 90° for 60 min, during which time 2 ml of dimethyl sulfate and 5 ml of the sodium hydroxide solution were added. The reaction mixture was cooled to 0° and neutralized with concentrated hydrochloric acid. The crude product was collected on a filter and washed with water. The dried solid was dissolved in 10 ml of tetrahydrofuran and 20 ml of ether and directly treated with 20 ml of a 1 *M*, ethereal diazomethane solution. After standing for 45 min, the excess diazomethane was destroyed with acetic acid and the solution was concentrated. The crude product (800 mg, 70%) was characterized as **2b**: ir 5.75 (C=O), 5.85 μ (C=O); nmr τ 3.23 (s, 1, ArH), 3.56 (d, 1, *J* = 16 Hz, C=CH), 6.13 (s, 3, OCH_3), 6.16 (s, 3, OCH_3), 6.19 (s, 3, OCH_3), 8.68 (d, 3, *J* = 6.5 Hz, CH_3).

A crystalline sample was obtained by preparative tlc (1000-μ plates, 4:1 mixture of methylene chloride–ether) and recrystallized from ether, mp 111–113°.

Anal. Calcd for $C_{22}H_{28}O_7$: C, 65.33; H, 6.98. Found: C, 65.57; H, 7.01.

Degradation of 2,4-Dimethoxy-6-(10-hydroxy-6-oxoundec-1-enyl)-1-isophthalic Acid μ-Lactone 3-Methyl Ester (2b).—A 500-mg sample of **2b** dissolved in 60 ml of methanol at −80° was treated with O_3 until the effluent gas gave a positive starch iodide test and then continued for another 10 min. The solution was flushed with nitrogen, 1 ml of dimethyl sulfide was added, and the cold solution was allowed to stand overnight at room temperature. The solution was concentrated and the obtained product was purified by preparative tlc (1000-μ plates, with a 4:1 mixture of methylene chloride–ether). The isolated 460 mg of presumed dialdehyde **3** was immediately oxidized in 25 ml of acetone at 0° with the dropwise addition of 1.62 ml of Jones reagent. After 20 min the reaction mixture was diluted with water and extracted with ethyl acetate. The organic phase was dried and concentrated *in vacuo*. The product (460 mg, 85%) was characterized as the diacid **4a**: ir 2.85, 3.10 (COOH), 5.72, 5.80, 5.85 μ (C=O); nmr τ 2.61 (s, 1, ArH), 6.07 (s, 3, OCH_3), 6.12 (s, 3, OCH_3), 6.17 (s, 3, OCH_3), 8.68 (d, 3, *J* = 6.5 Hz, CH_3).

The diacid was best purified as its methyl ester. To this effect, 285 mg of **4a** was dissolved in 5 ml of ether, treated with 20 ml of 1 *M* solution of diazomethane, and worked up as above. The isolated 280 mg of crude **4b** was purified by preparative tlc (1000-μ plates, 4:1 mixture of CH_2Cl_2–ether).

The isolated product (210 mg) was homogeneous on repeat

(9) While it is not possible to state that compound **16** was initially present in the mixture obtained from the Birch reduction of **10**, only compounds **11** and **14** were isolated in significant amounts and satisfactory purity.

(10) *Cf.* H. E. Zimmerman, *Tetrahedron*, **16**, 169 (1961), and F. J. Kakis in "Steroid Reactions," C. Djerassi, Ed., Holden-Day, San Francisco, Calif., 1968, p 267.

tlc: ir 5.79 μ (C=O); nmr τ 2.70 (s, 1, ArH), 6.11 (m, 12, four OCH_3), 6.33 (s, 3, OCH_3), 8.65 (d, 3, J = 6.5 Hz, CH_3). This sample was hydrolyzed by dissolving it in 2 ml of DMSO, adding 1.2 ml of 20% NaOH solution, and refluxing for 2 hr under nitrogen. The reaction product was poured into water and extracted with chloroform. The aqueous phase was acidified with 2.5 N hydrochloric acid and extracted with chloroform. This chloroform solution was washed with water and saturated salt solution, dried, and concentrated *in vacuo*. The crude product (150 mg) was reesterified in 5 ml of tetrahydrofuran with 4 ml of 1 M diazomethane, worked up as usual, and applied on three preparative tlc plates of 250 μ. It was developed with 4:1 CH_2Cl_2–ether and the material (**5b**) of R_f 0.6 (40 mg, 32%) was isolated: ir 5.72, 5.77 μ (C=O); nmr τ 2.72 (s, 1, ArH), 6.09 (m, 15, five OCH_3); nmr (acetone-d_6) τ 2.63 (s, 1, ArH), 6.06 (s, 3, OCH_3), 6.12 (two s, 6, OCH_3), 6.16 (two s, 6, OCH_3).

For identification, 35 mg of **5b** was hydrolyzed in 2 ml of methanol with 0.5 ml of 2.5 N sodium hydroxide by heating on the steam bath for 3 hr. The reaction mixture was poured into water and extracted with ether. The aqueous phase was acidified with 2.5 N hydrochloric acid and extracted three times with ethyl acetate. The organic solutions were combined, dried, and concentrated. The crude crystalline product was recrystallized from ethyl acetate–hexane to give 15 mg (50%) of the triacid **5a**, mp 239–240°, identical in all respects (mixture melting point, ir, and nmr) with an authentic sample of 2,4-dimethoxybenzene-1,3,6-tricarboxylic acid, mp 240–241°.[5]

2,4-Dihydroxy-6-(10-hydroxy-6-oxoundec-1-enyl)-isophthalaldehydic Acid μ-Lactone (7).—A 21-g sample of zearalenone (**1**) was dissolved in 400 ml of ethyl orthoformate and heated to 60°, and 13.2 g of aluminum chloride was added in small portions over 0.5 hr. The temperature was kept at 60° for an additional 1.5 hr, then lowered to 25°, and a 525-ml solution of 2.5 N HCl was added dropwise at such a rate that the temperature never exceeded 25°. The acidified reaction mixture was extracted four times with ethyl acetate, and the combined extracts were washed three times with water, dried ($MgSO_4$), and concentrated *in vacuo*. The crude product (24.8 g) was dissolved in 150 ml of methylene chloride and absorbed on a dry column (90 mm d) of 1.5 kg of silica gel (E. Merck, grade H). The column was eluted with a 7:1 mixture of methylene chloride–ether, and 200 fractions of 20 ml each were collected.

Fractions 42–87 contained 7.2 g (31%) of aldehyde **7**, which crystallized spontaneously: uv max (dioxane) 3375 mμ (ε 5800), 3030 (15,700), 251 (26,800); ir 5.92 (C=O) and 6.05 μ (C=O); nmr τ −3.22 (s, 1, ArOH), −2.43 (s, 1, ArOH), −0.40 [s, 1, C(=O)H], 2.98 (d, 1, J = 16 Hz, C=CH), 3.58 (s, 1, ArH), 8.60 (d, 3, J = 6 Hz, CH_3). The analytical sample, recrystallized from isopropyl alcohol, had mp 160–164°.

Anal. Calcd for $C_{19}H_{22}O_6$: C, 65.88; H, 6.40. Found: C, 65.48; H, 6.48.

2-(10-Hydroxy-6-oxoundec-1-enyl)-4,6-dihydroxy-5-hydroxyiminomethylbenzoic Acid μ-Lactone (8a).—A 2-g sample of aldehyde **7** was dissolved in a cold solution containing 60 ml of pyridine, 80 ml of absolute ethanol, and 440 mg of hydroxylamine hydrochloride. The reaction mixture was stirred at 0° for 45 min under nitrogen, poured into ice water, neutralized with 2.5 N HCl, extracted with ether, dried ($MgSO_4$), and concentrated *in vacuo*. The crude product (2.7 g) was dissolved in 20 ml of methylene chloride and absorbed on a 1.75-in.-diameter column which had been packed under vacuum with 200 g of dry silica gel H. The column was eluted with 1500 ml of a solution containing a 6:1 ratio of methylene chloride to ether and 150 fractions were collected using an automatic fraction collector. Fractions 13–22 contained 1.1 g of crystalline oxime **8a**: uv max 337.5 mμ (ε 7250), 297.5 (14,500), 257 (37,500); ir 3.12 (OH), 3.80 (C=O), 6.05 (C=O), 6.15 μ (C=N); nmr τ 1.21 [s, 1, C(=NOH)H], 2.98 (d, 1, J = 16 Hz, C=CH), 3.48 (s, 1, ArH), 8.61 (d, 3, J = 6 Hz, CH_3).

An analytical sample recrystallized from ether–hexane had mp 180–182°.

Anal. Calcd for $C_{19}H_{23}O_6N$: C, 63.14; H, 6.42; N, 3.88. Found: C, 63.37; H, 6.14; N, 3.96.

2-(10-Hydroxy-6-oxoundec-1-enyl)-4,6-dihydroxy-5-cyanobenzoic Acid μ-Lactone (8b).—A 500-mg sample of oxime **8a** was refluxed in 20 ml of acetic anhydride for 3.5 hr under nitrogen. The reaction mixture was poured into ice–bicarbonate solution, extracted with ethyl acetate, washed with water, dried ($MgSO_4$), and concentrated *in vacuo*. The crude product was dissolved in 200 ml of ether and an impurity crystallized from the solution. The ether solution was concentrated, leaving 600 mg of an amorphous material which was identified as **8b** diacetate: ir 4.50 (C=N), 5.60 (C=O), 5.80 μ (C=O); nmr τ 2.68 (s, 1, ArH), 3.47 (d, 1, J = 16 Hz, C=CH), 7.60 [s, 3, $CH_3C(=O)O$], 7.65 (s, 3, $CH_3C=O$).

A sample crystallized from ether–hexane had mp 73–75°.

Anal. Calcd for $C_{23}H_{25}NO_7$: C, 64.62; H, 5.90; N, 3.28. Found: C, 65.02; H, 5.83; N, 3.37.

A 500-mg sample of **8b** diacetate was dissolved in 15 ml of methanol containing 3.5 ml of 2.5 N sodium hydroxide and stirred for 2 hr at room temperature under nitrogen. The reaction mixture was poured into ice water, neutralized with 2.5 N hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate solution was dried ($MgSO_4$) and concentrated *in vacuo* and yielded 420 mg of crude dihydroxy nitrile **8b**. A sample of 270 mg of clean product was isolated after preparative tlc (9:1 solution of methylene chloride–methanol) using 1000-μ silica gel G commercial plates.

A sample was recrystallized from ether–methylene chloride: mp 120–122°; uv max 3250 mμ (ε 7100), 2780 (15,100), 2425 (34,000); ir 3.15 (OH), 4.51 (C≡N), 5.88 (C=O), 6.07 μ (C=O); nmr τ 2.98 (d, 1, J = 16 Hz, C=CH), 3.40 (s, 1, ArH), 8.59 (d, 3, J = 6.5 Hz, CH_3).

Anal. Calcd for $C_{19}H_{21}NO_5$: C, 66.46; H, 6.16; N, 4.08. Found: C, 66.15; H, 6.36; N, 3.82.

2,4-Dihydroxy-6-(10-hydroxy-6-oxoundec-1-enyl)isophthalamic Acid μ-Lactone (9). A.—A 900-mg sample of the acid **2a** was dissolved in 15 ml of pyridine and 2 ml of acetic anhydride. The reaction mixture was heated on the steam bath for 2 hr under nitrogen, cooled to room temperature, poured into ice water, and acidified to pH 3 using 2.5 N hydrochloric acid. The resulting amorphous solid was filtered and dissolved in ethyl acetate, and the solution was washed with water, dried, and concentrated to a foam. This crude diacetate (1.0 g, 90%) was identified: ir 3.20, 5.65, 5.83, and 5.90 μ; nmr τ −0.75 (s, 1, COOH, exchangeable), 2.77 (s, 1, ArH), 3.46 (d, 1, J = 16 Hz, C=CH), 7.68 [s, 3, $CH_3C(=O)O$], 7.72 [s, 3, $CH_3C(=O)O$], and 8.65 (d, 3, J = 6.5 Hz, CH_3).

A 500-mg sample of the crude diacetate was dissolved in 50 ml of tetrahydrofuran and then cooled to 0°, and 4 ml of an approximately 1 M diazomethane solution was added.

After 10 min the excess reagent was decomposed with acetic acid in the usual way. The reaction mixture was concentrated *in vacuo*, yielding 540 mg of a crude methyl ester which was characterized by its ir and nmr spectrum: ir 5.68 (2, C=O) and 5.86 μ (2, C=O); nmr τ 2.83 (s, 1, ArH), 3.02 (d, 1, J = 16 Hz, C=CH), 6.18 (s, 3, OCH_3), 7.70 [s, 3, $CH_3C(=O)O$], 7.76 [s, 3, $CH_3C(=O)O$], and 8.67 (d, 3, J = 6 Hz, CH_3).

This methyl ester (540 mg) was dissolved in 5 ml of methanol and transferred into a stainless steel pressure tube which contained 5 ml of liquid ammonia. After heating for 6 hr at 70°, the reaction mixture was cooled to room temperature, poured into cold water, and acidified with 2.5 N hydrochloric acid. The obtained precipitate was filtered, washed with water, and dried to yield 540 mg of crude material. The latter was recrystallized from methanol, yielding a total of 220 mg of crystalline product, mp 175–178°, which was homogeneous by tlc and was recognized as the isophthalamic acid lactone **9**: uv max 328 mμ (ε 5100), 2800 (14,400), and 2500 (26,400); ir 2.97 (NH_2), 5.88 (C=O), 6.08 (C=O), 6.21 μ (O=CNH_2); nmr τ −4.54 (s, 1, ArOH), −4.46 (s, 1, ArOH), 3.02 (d, 1, J = 16 Hz, C=CH), 3.49 (s, 1, ArH), 8.59 (d, 3, J = 6.5 Hz, CH_3).

A sample recrystallized for analysis had mp 180–182°.

Anal. Calcd for $C_{19}H_{23}O_6N$: C, 63.14; H, 6.42; N, 3.88. Found: C, 63.24; H, 6.52; N, 3.70.

B.—A 150-mg sample of cyano diacetate (**8b** diacetate) was dissolved in 10 ml of 75% sulfuric acid and stirred for 40 hr at room temperature. The reaction mixture was poured over ice and the precipitate was filtered. The crude product (100 mg) was purified by preparative tlc on a 1000-μ silica gel G commercial plate developed in a 4:1 mixture of methylene chloride–ether. A recovered sample was recrystallized from methanol and afforded material of mp 180–181° that was identical with the above prepared amide **9** by mixture melting point and ir and nmr spectra.

2-(10-Hydroxy-6,6-ethylenedioxyundecyl)-4,6-dimethoxybenzoic acid μ-lactone (10) was prepared from the corresponding ketone, as previously described.[1] It was recrystallized from ether–petroleum ether (bp 30–60°) and isolated in 78% yield: mp 91–93°; uv max 282.5 mμ (ε 2560) and 24 (4500); ir 5.87

μ (C=O); nmr τ 3.68 (m, 2, ArH), 6.11 (s, 4, OCH_2CH_2O), 6.22 (s, 6, CH_3O), 8.64 (d, 3, J = 6.5 Hz, CH_3).

Anal. Calcd for $C_{22}H_{32}O_6$: C, 67.32; H, 8.22. Found: C, 67.21; H, 8.21.

2-(10-Hydroxy-6,6-ethylenedioxyundecyl)benzoic acid μ-lactone (15a) which was prepared as above, from compound **15** previously described,[8] was crystallized from petroleum ether in 61% yield: mp 61–63°; uv max 2770 mμ (ε 840), 227 (5950); ir 5.83 μ (C=O); nmr τ 2.35 (m, 1, ArH), 2.80 (m, 3, ArH), 6.7 (s, 4, OCH_2CH_2O), and 8.68 (d, 3, J = 6.5 Hz, CH_3).

Anal. Calcd for $C_{20}H_{28}O_4$: C, 72.26; H, 8.49. Found: C, 72.49; H, 8.25.

Birch Reduction of 10.—A 1.5-g sample of **10** was dissolved in 20 ml of dry tetrahydrofuran and added to a solution of 120 ml of distilled dry liquid ammonia and 20 ml of *tert*-butyl alcohol. Sodium metal (465 mg) was added in small portions. All the sodium had reacted after 8 min and the color of the reaction mixture turned yellow. Ammonium chloride (1 g) was added, the ammonia was evaporated, and a liter of water was added to this mixture. After extracting it three times with ether, the organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to a crude oily mixture of 1.45 g.

A 485-mg sample of this mixture was applied onto five 1000-μ tlc plates (eluent acetone–hexane 3:7). A homogeneous, more polar, oily product of 125 mg was identified as **2-(10-hydroxy-6,6-ethylenedioxyundecyl)-6-methoxy-2,5-cyclohexadiene-1-carboxylic acid μ-lactone (11a)**: ir 5.80 (C=O), 5.90, and 6.00 μ (C=COMe); nmr τ 4.37 and 5.20 (m, C=CH), 6.12 (s, 4, $-OCH_2CH_2O-$), 6.48 (s, 3, OCH_3), 7.18 (m, 2, $C=CCH_2$), 8.75 (d, J = 6.5 Hz, CH_3), and 8.83 (d, J = 6.5 Hz, CH_3).

A second, less polar, homogeneous oil (150 mg) was characterized as **2-(10-hydroxy-6,6-ethylenedioxyundecyl)-1,5-cyclohexadiene-1-carboxylic acid μ-lactone (14a)**: ir 5.83 μ (C=O); nmr τ 3.76 (d, 1, J = 9 Hz, C=CH), 4.24 (d, 1, J = 9 Hz, C=CH), 6.12 (s, 4, $-OCH_2CH_2O-$), 7.83 (s, 4, $C=CCH_2$), and 8.71 (d, 3, J = 6.5 Hz, CH_3).

Aromatization Experiments.—A 45-mg sample of **11a** was dissolved in 0.5 ml of pyridine and added to an ice cold suspension of 45 mg of CrO_3 in 0.5 ml of pyridine. The mixture was stirred at room temperature overnight and worked up by adding 5 ml of ethyl acetate and filtering the insoluble salts. The filtrate was repeatedly washed with water, dried, and concentrated *in vacuo*. The obtained product (37 mg) was characterized as **2-(10-hydroxy-6,6-ethylenedioxyundecyl)-6-methoxybenzoic acid μ-lactone (12a)**: ir 5.82 μ (C=O); nmr τ 2.70, 3.20, 3.22 (m, 3, ArH), 6.10 (s, 4, $-OCH_2CH_2O-$), 6.21 (s, 3, OCH_3), and 8.63 (d, 3, J = 6.5 Hz, CH_3).

A sample of ketal **14a** (80 mg) was similarly treated with 80 mg of CrO_3 in pyridine. The resulting product (64 mg) had all the spectral characteristics of **15a** prepared independently by ketalization of the ketone **15b**.

Acidic Hydrolyses.—A 55-mg sample of **11a** was dissolved in 5 ml of dioxane containing 4 drops of 2.5 *N* hydrochloric acid. The solution was kept for 16 hr under nitrogen and then poured into ice water. The mixture was extracted with ether, and the solvent solution was dried and concentrated. The obtained product (36 mg) was crystallized from methanol. It had mp 48–50° and was identified as **2-(10-hydroxy-6-oxoundecyl)-6-oxo-1-cyclohexene-1-carboxylic acid μ-lactone (13)**: uv max 238 mμ (ε 12,000); ir 5.73, 5.80, 5.92, and 6.10 μ (C=O); nmr τ 8.66 (d, 1, J = 6.5 Hz, CH_3).

Anal. Calcd for $C_{18}H_{26}O_4$: C, 70.56; H, 8.44. Found: C, 70.41; H, 8.55.

Ketal **12a** (37 mg) was treated with HCl as shown above and the obtained 25 mg of product was found to be identical with an authentic sample of **2-(10-hydroxy-6-oxoundecyl)-6-methoxybenzoic acid μ-lactone (12b)** prepared as shown further below. Similarly, a 43-mg sample of the crude ketal **15a** was hydrolyzed to the known[8] **2-(10-hydroxy-6-oxoundecyl)benzoic acid μ-lactone (15b)**, mp 89–91°.

The remaining 970 mg of crude product isolated from the Birch reaction described above was hydrolyzed under identical conditions using 2 ml of 2.5 *N* hydrochloric acid in 33 ml of dioxane. The total crude mixture obtained was absorbed on a 30-g dry column of silica gel and eluted with a 3:7 mixture of acetone–hexane. Fractions containing material of uv max 238 mμ were combined and crystallized, yielding 265 mg (32%) of lactone **13** identical in all respects with the product described above.

2-(10-Hydroxy-6-oxoundecyl)-6-methoxybenzoic Acid μ-Lactone (12b).—A 400-mg sample of 2-(10-hydroxy-6-oxoundecyl)-6-hydroxybenzoic acid μ-lactone[8] was suspended in 1 ml of dimethyl sulfate, and 4 ml of a 20% NaOH solution was added in one portion. An exothermic reaction set in after a few minutes and the mixture was stirred without further heating for 2 hr. The product crystallized during this period and was filtered, washed with water, dried, and recrystallized from methanol to yield 300 mg (72%) of **12b**: mp 96–97°; ir 5.79 and 5.82 μ (C=O); nmr τ 2.76, 3.20, and 3.31 (m, 3, ArH), 6.22 (s, 3, OCH_3), and 8.65 (d, 3, J = 6.5 Hz, CH_3).

Anal. Calcd for $C_{19}H_{26}O_4$: C, 71.67; H, 8.23 Found: C, 71.39; H, 8.42.

Birch Reduction of 10 with a Large Excess of Reagent.—A 300-mg sample of dimethoxy ketal **10** dissolved in 5 ml of tetrahydrofuran was added to a solution of 40 ml of distilled dry ammonia and 5 ml of *tert*-butyl alcohol. Then 320 mg of sodium metal was added and the blue reaction mixture was stirred for 15 min at −40°. The reaction was then quenched with 0.5 ml of methanol, the ammonia was evaporated, and 30 ml of water was added. The aqueous phase was extracted with methylene chloride and the organic phase was washed with water, dried, and concentrated *in vacuo*. The crude product was purified by preparative tlc (on 250-μ plates, solvent system 0.5% methanol in chloroform). The major product, which was the least polar one, was isolated in 36% yield; it was the only fully characterized compound, **2-(10-hydroxy-6,6-ethylenedioxyundecyl)-1,5-cyclohexadiene-1-carboxylic acid μ-lactone (14a)**, having ir and nmr spectra identical with those of the previously isolated sample.

The balance of the isolated material contained a mixture of **14b** and **15b** in *ca.* 30% yield, as well as approximately 15% of unchanged hydrolyzed starting material **10**.

A 43-mg sample of **14a** was dissolved in 3 ml of dioxane containing 3 drops of 2.5 *N* hydrochloric acid. The solution was kept for 16 hr under nitrogen and then poured into ice water. The mixture was extracted with ether and the ethereal solution was dried and concentrated *in vacuo*. The obtained product, 32 mg (86%), was characterized as **2-(10-hydroxy-6-oxoundecyl)-1,5-cyclohexadiene-1-carboxylic acid μ-lactone (14b)**: ir 5.88 μ (C=O); nmr τ 3.68 (d, 1, J = 9 Hz, C=CH), 4.25 (m, 1, C=CH), 7.80 (s, 4, $C=CCH_2$), and 8.67 (d, 3, J = 6.5 Hz, CH_3).

Birch Reduction of 15a.—A 900-mg sample of **15a** dissolved in 15 ml of tetrahydrofuran was added to a mixture of 120 ml of dry ammonia and 15 ml of *tert*-butyl alcohol. Then 1 g of sodium metal was added in small portions, the blue reaction mixture was stirred for 30 min, and finally 2 g of ammonium chloride was added. The ammonia was evaporated and the reaction was worked up as usual. An oil (800 mg, 89%) was isolated and characterized as **2-(10-hydroxy-6,6-ethylenedioxyundecyl)-2,5-cyclohexadiene-1-carboxylic acid μ-lactone (16a)**: ir 5.82 μ (C=O); nmr τ 2.72, 4.21, and 4.40 (3, C=CH), 6.14 (s, 4, $-OCH_2CH_2O-$), 7.25 (m, 2, $C=CHCH_2$), 8.77 (d, J = 6.5 Hz, CH_3), and 8.83 (d, J = 6.5 Hz, CH_3).

An 30-mg sample of compound **16a** was hydrolyzed with HCl–dioxane as usual.

The isolated product (60 mg, 85%) was characterized as **2-(10-hydroxy-6-oxoundecyl)-2,5-cyclohexadiene-1-carboxylic acid μ-lactone (16b)**: ir 5.78 and 5.82 μ (C=O); nmr τ 2.70, 4.28 (m, C=CH), 4.30 (m, C=CH), 7.22 (m, 2, $C=CCH_2$), 8.72 (d, J = 6.5 Hz, CH_3), and 8.80 (d, J = 6.5 Hz, CH_3). When the ketal **16a** (30 mg) was treated for 16 hr at room temperature under nitrogen, with a solution of 40 mg of KOH in 2 ml of MeOH and 0.5 ml of water, and the obtained product (20 mg) was isolated by dilution with water and ether extraction. It was found to be identical in all respects with ketal **14a**.

Registry No.—**1**, 17924-92-4; **2a**, 34246-32-7; **2b**, 34246-33-8; **4a**, 34246-34-9; **4b**, 34246-35-0; **5a**, 2411-45-2; **5b**, 34246-37-2; **7**, 34246-38-3; **8a**, 34246-39-4; **8b**, 34246-40-7; **8b** diacetate, 34246-41-8; **9**, 34246-42-9; **10**, 34246-43-0; **11a**, 34246-44-1; **12a**, 34246-45-2; **12b**, 34246-46-3; **13**, 34246-47-4; **14a**, 34280-39-2; **14b**, 34246-48-5; **15a**, 34246-49-6; **15b**, 28684-53-9; **16a**, 34246-51-0; **16b**, 34246-52-1.

Steroid Total Synthesis. V.[1] (±)-Estr-4-ene-3,17-dione and (±)-13β-Ethylgon-4-ene-3,17-dione[2]

J. W. SCOTT AND G. SAUCY*

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

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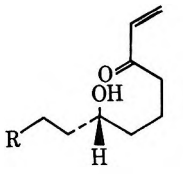
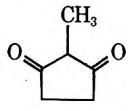
Condensation of (±)-9-(3,5-dimethyl-4-isoxazolyl)-7-hydroxynon-1-en-3-one (12), as its Mannich base 18, with 2-methyl- and 2-ethylcyclopentane-1,3-dione gave mixtures of *trans*- and *cis*-(±)-3-[2-(3,5-dimethyl-4-isoxazolyl)ethyl]-6a-methyl-1,2,3,5,6,6a-hexahydrocyclopenta[*f*][1]benzopyran-7(8*H*)-one (**20a**, **21a**) and (±)-3-[2-(3,5-dimethyl-4-isoxazolyl)ethyl]-6a-ethyl-1,2,3,5,6,6a-hexahydrocyclopenta[*f*][1]benzopyran-7(8*H*)-one (**20b**, **21b**) in which the trans isomers predominated. These dienol ether mixtures were converted in five steps to (±)-19-(3,5-dimethyl-4-isoxazolyl)-de*A*-androst-9-ene-5,17-dione (**26a**) and (±)-19-(3,5-dimethyl-4-isoxazolyl)-18-methyl-de*A*-androst-9-ene-5,17-dione (**26b**). A modified procedure for hydrogenolysis of the isoxazole group and ring closure then gave (±)-estr-4-ene-3,17-dione (**5a**) and (±)-13β-ethylgon-4-ene-3,17-dione (**5b**) in high yield.

Recently, one of us reported[3] the unique asymmetric induction obtained during the condensation of (±)-7-hydroxynon-1-en-3-one (**1a**) with 2-methylcyclopentane-1,3-dione (2). One of the two isomers of (±)-3-ethyl-6a-methyl-1,2,3,5,6,6a-hexahydrocyclopenta[*f*]-[1]benzopyran-7(8*H*)-one was obtained as the predominant product of this reaction. This major component, later shown[4] to be the trans dienol ether **3a**,[5] was readily converted[3] to (±)-17β-hydroxy-de*A*-androst-9-en-5-one (**4a**). The (−) antipode[4] of this compound has been employed as an intermediate in syntheses of retrotestosterone[6] and retroprogesterone.[7]

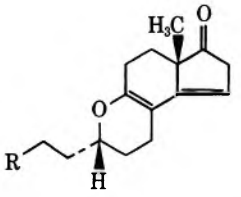
The trans configuration of the dienol ethers **3** was determined[4] by using the vinyl ketone **1b** of known absolute configuration in the condensation reaction, and converting the resulting dienol ether **3b** to the tricyclic enone **4b**, also of known absolute configuration. It can be seen that, if the vinyl ketone **1b** were substituted by a properly positioned, masked keto function (as in the hypothetical intermediate **1c**), one would obtain the tricyclic enone **4c**, a type of compound employed in an elegant synthesis[8] of 19-nor steroids. In this paper, we wish to report our efforts in this direction, which have culminated in total syntheses of (±)-estr-4-ene-3,17-dione (**5a**)[9] and (±)-13β-ethylgon-4-ene-3,17-dione (**5b**).[10]



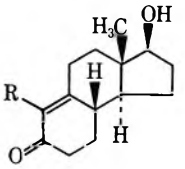
1a, R = H
b, R = $CH_2CH_2CH_3$
c, R = $CH_2C[O]CH_3$



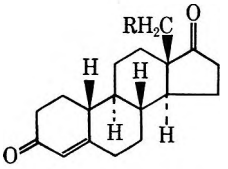
2



3a, R = H
b, R = $CH_2CH_2CH_3$
c, R = $CH_2C[O]CH_3$



4a, R = H
b, R = $CH_2CH_2CH_3$
c, R = $CH_2C[O]CH_3$



5a, R = H
b, R = CH_3

Results and Discussion

In choosing the type of masked 3-oxobutyl function to employ in the vinyl ketone **1c**, we were guided by the necessity of having a moiety which would be easy to prepare, stable to the wide variety of reaction conditions[3] involved in the sequence **1c** → **4c** (*vide infra*), and yet easily reconverted to the free ketone. The 3,5-dimethylisoxazole group[11] seemed admirably suited to our needs. Isoxazoles are known[12] to be stable to most reagents but are readily opened by hydrogenation under the proper conditions. We thus set out to synthesize the desired δ-hydroxy vinyl ketone **12**. We have developed two syntheses (outlined in Scheme I) of this compound.

In one approach, the anion of diethyl β-oxopimelate (**7**)[13] was alkylated in benzene with 4-chloromethyl-3,5-dimethylisoxazole (**6**).[14,15] The crude alkylated

(1) Part IV: M. Rosenberger, T. P. Fraher, and G. Saucy, *Helv. Chim. Acta*, **54**, 2857 (1971).

(2) Presented in part at the Joint Chemical Institute of Canada–American Chemical Society Meeting, Toronto, Canada, May 1970.

(3) Part I: G. Saucy, R. Borer, and A. Fiirst, *Helv. Chim. Acta*, **54**, 2034 (1971).

(4) Part II: G. Saucy and R. Borer, *Helv. Chim. Acta*, **54**, 2121 (1971).

(5) All compounds reported in this paper, with the exceptions of **1b**, **3b**, and **4b**, are racemic. Only one enantiomer is shown.

(6) Part III: G. Saucy, and R. Borer, *Helv. Chim. Acta*, **54**, 2517 (1971).

(7) A. M. Krubiner, G. Saucy, and E. P. Oliveto, *J. Org. Chem.*, **33**, 3548 (1968).

(8) L. Velluz, J. Mathieu, and G. Nominé, *Tetrahedron, Suppl. 8*, Part II, 495 (1966).

(9) K. K. Koshoev, S. N. Ananchenko, and I. V. Torgov, *Khim. Prir. Soedin.*, 180 (1965); *Chem. Abstr.*, **63**, 13346f (1965).

(10) H. Smith, Belgian Patent 608,370 (1961).

(11) G. Stork, S. Danishefsky, and M. Ohashi, *J. Amer. Chem. Soc.*, **89**, 5459 (1967).

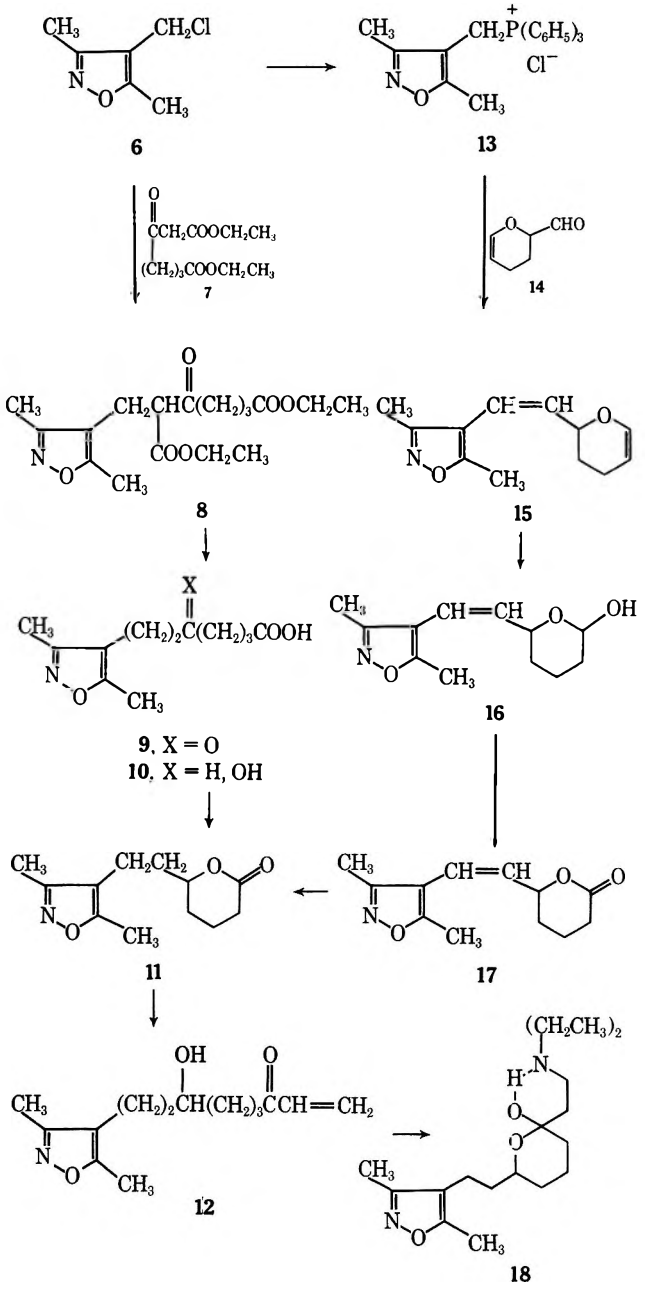
(12) For general reviews of isoxazole preparations and reactions, see (a) N. K. Kochetkov and S. D. Sokolov in "Advances in Heterocyclic Chemistry," Vol. 2, A. R. Katritzky, Ed., Academic Press, New York, N. Y., 1963, pp 365–422; (b) A. Quilico, "The Chemistry of Heterocyclic Compounds," Vol. 17, A. Weissberger, Ed., Interscience, New York, N. Y., 1963, pp 1–230.

(13) M. Guha and D. Nasipuri, *Org. Syn.*, **42**, 41 (1962).

(14) N. K. Kochetkov, E. D. Khomutova, and M. V. Bazilevskii, *J. Gen. Chem. USSR*, **28**, 2762 (1958).

(15) J. E. McMurry, Ph.D. Thesis, Columbia University, New York, N. Y., 1967.

SCHEME I



diester **8** was saponified with dilute sodium hydroxide solution and was then acidified to effect decarboxylation. It was thus possible to isolate crystalline keto acid **9**, mp 61.5–62°. Usually, however, the noncrystalline acid, purified only by acid–base extraction, was reduced with sodium borohydride. The resulting hydroxy acid **10** was distilled with loss of water to give lactone **11**, mp 61–62.5°, in 32% yield from the diester **7**. Reaction[4] of this lactone with 1.75–2 equiv of vinylmagnesium chloride[16] at −60°[5] gave the vinyl ketone **12**. Since this compound proved to be relatively unstable, it was treated with diethylamine[5] to give the corresponding Mannich base. The infrared spectrum of this compound (hydrogen-bonded hydroxyl absorption at 3100 cm^{-1}, weak carbonyl absorption at 1705 cm^{-1}) indicated that it existed mostly in the bicyclic, internally hydrogen-bonded form **18**. After purification by acid–base extraction, the oily base **18** was obtained in 80–85% yield from the lactone **11**.

The first step of an alternate approach to the lactone **11**, and thus the vinyl ketone **12**, consisted in converting the chloride **6** to the phosphonium salt **13**. Conversion of this salt to the corresponding ylide with methylsulfinyl carbanion,[17] followed by reaction with freshly distilled acrolein dimer (**14**),[18] gave **15** in 82% yield. The Wittig product **15** was treated with dilute sulfuric acid in dioxane to give the hemiacetal **16**. Oxidation[19] of the crude material so produced with activated manganese dioxide gave lactone **17** in 39% yield. Hydrogenation of this unsaturated lactone over palladium on carbon proceeded smoothly to give lactone **11** in 76% yield. The isoxazole ring was not reduced under these conditions.

Condensation of the Mannich base **18** with 2-methylcyclopentane-1,3-dione (**2**)[4] (Scheme II) in a toluene–acetic acid mixture at reflux[3] afforded a mixture of trans and cis dienol ethers **20a** and **21a**. The major component of this mixture, assigned the trans configuration **20a** in analogy with previous work,[3,5] could be isolated in pure form by crystallization. The nmr spectrum of the oily residue from this crystallization indicated that the sample was a mixture of the crystalline trans dienol ether **20a** and a second compound, differing only in the position of the signal of the C-3 proton. This second compound, presumably the cis dienol ether **21a**, could not be isolated in pure form. By integration of the C-3 proton signal of the crude dienol ether mixture, it was possible to estimate that the ratio of trans to cis dienol ethers was approximately 4:1. The extent of asymmetric induction observed with the vinyl ketone **12** was thus considerably less than when the vinyl ketone **1a** was used. We have no explanation for this difference, but presumably it depends upon steric factors in the transition state leading to the dienol ethers.[3]

Reduction of the mixture[20] of dienol ethers **20a** and **21a** with lithium aluminum hydride in tetrahydrofuran gave the trans and cis dienol ether alcohols **22a**.[21] The 7β configuration of the hydroxyl groups is assigned on the basis of our own previous work,[3] as well as literature analogy.[22] Hydrogenation of the crude reduction product over a palladium catalyst[3,23] in tetrahydrofuran at atmospheric pressure gave a mixture showing C-6a methyl signals in the nmr spectrum at δ 0.80 and 0.98 ppm in a ratio of 7:1. No hydrogenolysis of the isoxazole ring was observed when these relatively mild reaction conditions were employed. The major nmr signal was due to the trans anti enol

(16) H. E. Ramsden, J. R. Leebrick, S. D. Rosenberg, E. H. Miller, J. J. Walburn, A. D. Balint, and R. Cserr, *J. Org. Chem.*, **22**, 1602 (1957).

(17) R. Greenwald, M. Chaykovsky, and E. J. Corey, *ibid.*, **28**, 1128 (1963).

(18) G. Büchi and J. E. Powell, Jr., *J. Amer. Chem. Soc.*, **92**, 3126 (1970). We wish to thank Professor Büchi for communicating the experimental details of this work prior to publication.

(19) R. J. Highet and W. C. Wildman, *J. Amer. Chem. Soc.*, **77**, 4399 (1955).

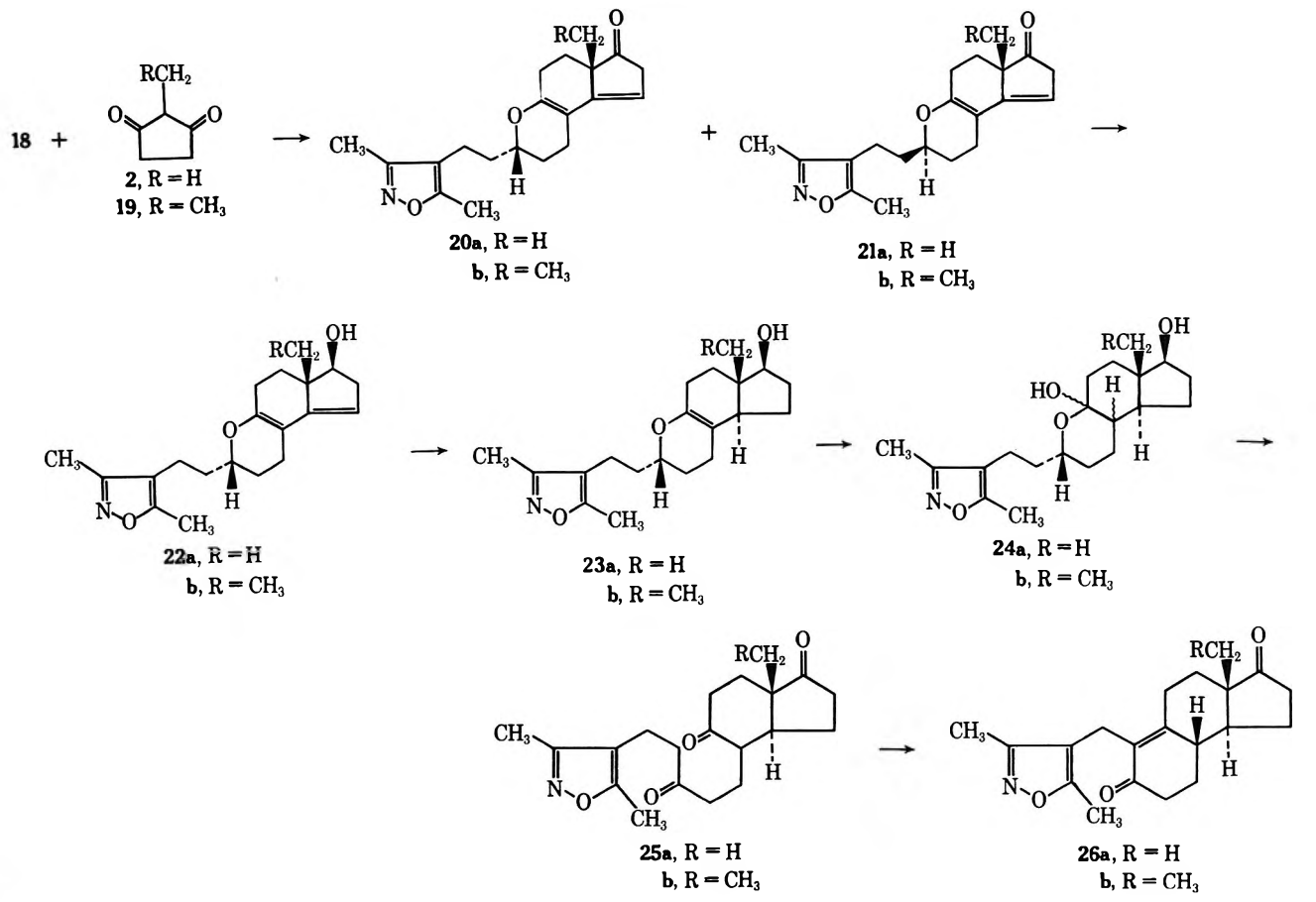
(20) Either the mixture of trans and cis dienol ethers or the pure trans isomer could be carried through the synthesis. Since the original asymmetric center at C-3 is eventually destroyed (*vide infra*), both trans and cis dienol ethers give the same deA-androstenone **26a** *when racemic compounds are involved*, as is here the case. For this reason, the isomers were not usually separated.

(21) For convenience, only the trans isomers of compounds **22**, **23**, and **24** are shown.

(22) L. J. Chinn, *J. Org. Chem.*, **27**, 54 (1962).

(23) A 5% palladium on carbon catalyst prepared at F. Hoffmann-La Roche and Co., AG, Basle, Switzerland, was employed for this hydrogenation.

SCHEME II



ether **23a**, while the minor signal may have been due to material having a cis ring fusion. The trans ring fused product had been expected to predominate on the basis of previous analogous reactions.[3] That α-face hydrogenation had occurred was confirmed at the end of the synthesis when the C/D trans steroid **5a** was obtained. The mixture of products from the hydrogenation was hydrated with 1 *N* sulfuric acid in acetone to give the hemiketal **24a** as a mixture of compounds with unknown configurations at C-3a and C-9b. It was not necessary to isolate this mixture; rather, it was oxidized with Jones reagent[24] to give the trione **25a**. This oxidation destroyed the original center of asymmetry (C-7 of the vinyl ketone **12**), again giving a homogeneous compound, rather than the trans–cis mixtures encountered with compounds **20a**–**24a**.[21] Since the trione **25a** was not crystalline, it was cyclized with methanolic sodium hydroxide solution to give the racemic tricyclic dione (**26a**),[25] mp 141.5–143.5°. This compound was obtained in 33% yield from the lactone **11** when the crude trans–cis dienol ether mixture **20a**, **21a** was used.

Condensation of the Mannich base **18** with 2-ethylcyclopentane-1,3-dione (**19**)[26] in the same manner as described above gave the trans and cis 6a-ethyl dienol ethers **20b** and **21b**. The ratio of isomers was again approximately 4:1, as determined by nmr. This mixture of dienol ethers was converted, *via* intermediates **22b**–**25b**, to dione **26b**. This compound, mp 111–115.5°, was obtained in 37% yield from the lactone **11**.

To complete the synthesis of (±)-estr-4-ene-3,17-dione[9] (**5a**) and (±)-13β-ethylgon-4-ene-3,17-dione[10] (**5b**), it was necessary only to stereoselectively saturate the Δ^9 double bond of the de*A*-andostenones **26a** and **26b** and elaborate ring A. This was done as shown in Scheme III. Hydrogenation of the enones **26a,b** over palladium on carbon in a 3:1 ethanol–triethylamine mixture gave the expected[8] diones **27a**, mp 137.5–139.5°, and **27b**, mp 143.5–146°. As before, no hydrogenolysis of the isoxazole ring was observed. When the hydrogenation mixture containing the dione **27a** was made alkaline to the extent of 0.1 *N* in potassium hydroxide, a second equivalent of hydrogen was rapidly taken up. The resulting vinylogous amide **28**,[27] upon heating with aqueous base, was converted to (±)-estr-4-ene-3,17-dione (**5a**).[9] The yield from the enone **26a** could not be raised above 45% when this procedure was employed. It seemed to us that the reason for this relatively low yield might lie in the instability of the carbinolamine **28**. Stork[27] has shown that vinylogous amides of this type rapidly dehydrate upon treatment with base to give dihydropyridines, which are susceptible to oxidation and possibly also disproportionation to give pyridines and/or other compounds of no use to us. We theorized that if we prevented cyclization of the initial isoxazole hydrogenolysis product[27] to the carbinolamine form **28**, the yield of steroid

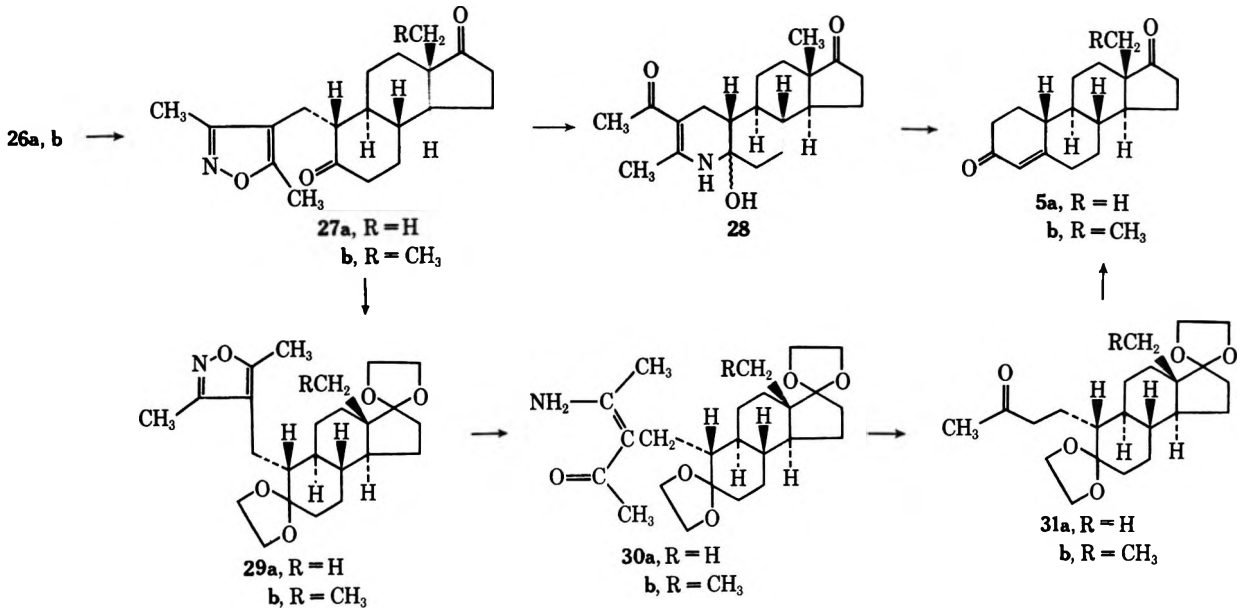
(24) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 2548 (1953).

(25) This compound has been disclosed in Syntex Corp., Netherlands Patents 6,817,384 and 6,817,385 (1969). No physical or spectral data were given.

(26) H. Shick, G. Lehmann, and G. Hilgetag, *Angew. Chem.*, **79**, 378 (1967).

(27) G. Stork and J. E. McMurry, *J. Amer. Chem. Soc.*, **79**, 5463 (1967).

SCHEME III



end product might be significantly higher. This, in fact, proved to be the case.

The hydrogenation of the enone **26a** was carried out as before, and the crude dione **27a** was then ketalized to give the bisketal **29a**, mp 145.5–148°. Hydrogenolysis of this diketal over palladium on carbon in 4% ethanolic potassium hydroxide solution proceeded smoothly. The vinylogous amide **30a** was not isolated. The hydrogenation solution, after removal of the catalyst, was concentrated to approximately one-third its original volume. Addition of 20% aqueous potassium hydroxide solution, followed by heating at reflux, gave the heretofore unknown keto bisketal **31a**, mp 126.5–128°. Heating this material with methanolic hydrochloric acid caused deketalization and cyclization to give the desired steroid **5a**.[9] The yield for the five-step sequence, when none of the intermediates was purified, was 80–85%. In a similar manner, the 18-methyl enone **26b** was converted, *via* the dione **27b**, the diketal **29b** (mp 140–143°), the vinylogous amide **30b**, and the keto diketal **31b** (mp 117.5–119.5°), to (±)-13β-ethylgon-4-ene-3,17-dione[10] (**5b**, mp 158–161°), in 70% yield. The same compound, which may serve as a precursor for the synthesis of *Norgestrel*,[28] had been prepared earlier by a related route.[1]

Experimental Section[29]

(±)-7-(3,5-Dimethyl-4-isoxazolyl)-5-hydroxyheptanoic Acid Lactone (11). A.—In a dry flask under nitrogen, 35 g (0.080 mol) of 55% NaH suspension was washed with pentane to remove the mineral oil and was then suspended in 800 ml of dry benzene. A solution of 180 g (0.785 mol) of diethyl β-oxopimelate (7)[13] in 250 ml of benzene was added dropwise over 2.0 hr. The greenish-brown suspension was stirred at 20° for 3.0 hr and then a solution of 117 g (0.80 mol) of 4-chloromethyl-3,5-dimethylisoxazole (6)[14,15] in 200 ml of benzene was added over 2.0 hr. The resulting suspension was stirred at 20° overnight and was then heated at reflux for 24 hr. The cooled solution was washed with 2 *N* HCl, H_2O, and saturated brine and was dried (Na_2SO_4). Solvent removal gave the crude alkylated diester **8** as 280 g of light orange oil. A solution of this material in 2 l. of 5% NaOH was stirred at 20° for 4 hr. To the flask was cautiously added 250 ml of 18 *N* H_2SO_4 and the resulting mixture was heated at reflux for 2.0 hr. The solution was cooled, saturated with NaCl, and extracted with ethyl acetate. The organic solutions were washed with saturated brine, dried (Na_2SO_4), and stripped of solvent to give the crude keto acid **9** as 200 g of orange oil. A similarly prepared sample was crystallized twice from ethyl acetate–hexane to give analytically pure 7-(3,5-dimethyl-4-isoxazolyl)-5-oxoheptanoic acid as white microprisms: mp 61.5–62°; uv max (C_2H_5OH) 220 nm (ε 5000); ir ($CHCl_3$) 3500–2500 (acid OH), 1720 (strong, acid and ketone C=O), and 1640 cm^{-1} (isoxazole); nmr ($CDCl_3$) δ 2.21 (s, 3) and 2.32 (s, 3, 2 isoxazole-CH_3), and 10.5 ppm (s, 1, COOH).

Anal. Calcd for $C_{12}H_{17}NO_4$: C, 60.24; H, 7.16; N, 5.85. Found: C, 60.15; H, 7.29; N, 5.78.

To a solution of the crude keto acid **9** in 1 l. of isopropyl alcohol was slowly added 50 g (1.48 mol) of $NaBH_4$. The resulting mixture was stirred at 20° for 3.0 hr, slowly heated to reflux, and then held at reflux for 1.5 hr. The cooled solution was stripped of solvent, diluted with H_2O, cautiously acidified with 4 *N* HCl, and extracted with benzene. The benzene solutions were washed with saturated brine and dried (Na_2SO_4). Solvent removal gave crude hydroxy acid **10** as 150 g of pale yellow resin. Distillation of this material through a short-path apparatus gave 84 g of pale yellow oil, bp 160–185° (0.25 mm). Crystallization of this material from 400 ml of ether gave 57.2 g (32%) of the lactone **11** as small, white prisms, mp 61–62.5°. A similarly prepared sample was crystallized an additional time from ether to give analytically pure material as white microprisms: mp 61–62.5°; uv max (C_2H_5OH) 220 nm (ε 5350); ir ($CHCl_3$) 1735 (lactone C=O) and 1640 cm^{-1} (isoxazole); nmr ($CDCl_3$) δ 2.18 (s, 3) and 2.29 (s, 3, 2 isoxazole-CH_3), and 4.19 ppm (m, 1, >CHOC=O).

Anal. Calcd for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.68; N, 6.27. Found: C, 64.59; H, 7.77; N, 6.12.

B.—A solution of 59.6 g (0.40 mol) of 4-chloromethyl-3,5-dimethylisoxazole (6)[14,15] and 116 g (0.44 mol) of triphenylphosphine in 1 l. of toluene was heated at reflux under nitrogen for 6.0 hr. The suspension was cooled and filtered. The filtrate was heated at reflux for an additional 20 hr. The precipitate was again removed by filtration and the combined solids were washed with ether and benzene. Crystallization from ethanol–ether gave the phosphonium salt **13** as 149.5 g (91%) of cream-white solid, mp 313–316° dec. A sample from a similar preparation was

(28) (±)-13β-Ethyl-17α-ethinyl-17β-hydroxygon-4-en-3-one: H. Smith, G. A. Hughes, G. H. Douglas, G. R. Wendet, G. C. Buzby, Jr., R. A. Edgren, J. Fisher, T. Foell, B. Gadsby, D. Hartley, D. Herbst, A. B. A. Jansen, K. Ledig, B. J. McLoughlin, J. McMenamin, T. W. Pattison, P. C. Phillips, R. Rees, J. Siddall, J. Siuda, L. L. Smith, J. Tokolics, and D. H. P. Watson, *J. Chem. Soc.*, 4472 (1964).

(29) Melting points were determined on a Kofler hot stage, except for mixture melting points, which were determined in capillaries on a Thomas-Hoover apparatus, and are not corrected. A Varian A-60 spectrometer was used to obtain the nmr spectra and tetramethylsilane was used as the internal standard. Infrared spectra were recorded on a Beckman IR-9 spectrophotometer. The uv spectra were recorded on a Cary Model 14M spectrophotometer.

crystallized again from ethanol–ether to give analytically pure material as small, white prisms: mp 303–305° dec;[30] ir (KBr) 1625 cm^{-1} (isoxazole); nmr (D_2O) δ 1.83 (s, 3, isoxazole-5-CH_3), 2.05 (d, 3, J = 3 Hz, isoxazole-3-CH_3), 4.90 (d, 2, J = 12 Hz, isoxazole-CH_2), and 7.7–8.2 ppm (m, 15, 3-C_6H_5).

Anal. Calcd for $C_{24}H_{23}ClNOP$: C, 70.67; H, 5.68; Cl, 8.69; N, 3.44. Found: C, 70.73; H, 5.69; Cl, 8.66; N, 3.55.

Methylsulfinyl carbanion was prepared under nitrogen in the usual manner[17] from 8.75 g (0.20 mol) of 55% NaH dispersion and 600 ml of dimethyl sulfoxide. The gray-green solution was cooled to 15° and 91.6 g (0.20 mol) of the phosphonium salt **13** was added in one portion. After 5 min, a bright orange precipitate formed in the initially dark red solution. This suspension was stirred at 20° for 45 min. To the mixture was then added, dropwise *via* syringe, 25.0 g (0.223 mol) of acrolein dimer **14** (Shell Chemical Co.; freshly distilled from and into hydroquinone) at such a rate that the temperature remained less than 30° (10–15 min, with water bath cooling). The orange-brown solution was stirred at 25° for 20 min, and then at 60–65° for 3.0 hr.[18] The reaction mixture was cooled, poured onto ice, and slurried until all the dark oil solidified. The suspension was filtered and the filter cake was washed well with pentane. The combined filtrates were washed with H_2O and saturated brine and dried (Na_2SO_4). Solvent removal gave a light orange oil which was distilled from a few milligrams of anhydrous K_2CO_3 to give 33.5 g (82%) of the Wittig product **15** as a colorless liquid, bp 83–85° (0.1 mm). A similarly prepared sample, bp 77–85° (0.2 mm), was submitted for analysis: uv max (hexane) 221 nm (ϵ 8830); ir ($CHCl_3$) 1665 (sh, C=C), 1655 (C=CO–), and 1625 cm^{-1} (isoxazole); nmr (CCl_4) δ 2.16 (s, 3) and 2.34 (s, 3, 2 isoxazole-CH_3), 4.24 (m, 1, CHO–), 4.62 (m, 1, CH=CHO–), 5.87 (q, 2, J = 11 Hz, CH=CH), and 6.30 ppm (d, 1, CH=CHO–).

Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.45; H, 7.44; N, 6.60.

To a solution of 33.5 g (0.163 mol) of the Wittig product **15**, bp 83–85° (0.1 mm), in 400 ml of dioxane was added 400 ml of 1 N H_2SO_4 and the cloudy solution, which soon cleared, was stirred at 20° for 1.0 hr. The mixture was poured into 2 l. of saturated $NaHCO_3$ solution and extracted with ether. The ether extracts were washed with saturated brine and dried (Na_2SO_4). Solvent removal gave the crude hemiacetal **16** as a colorless oil. To a solution of this material in 2 l. of benzene was added 400 g of activated MnO_2 (Sterwin Chemical Co.) and the resulting suspension was stirred at 20° under nitrogen for 40 hr. The mixture was filtered and the solids were carefully washed with fresh benzene. Solvent removal from the filtrates gave 23 g of yellow solid which was crystallized twice from benzene–ether to give 14.30 g (40%) of the unsaturated lactone **17** as a cream-white powder, mp 90–91.5°. A similarly prepared sample was crystallized again from benzene–ether to give the analytical sample as fine, white needles: mp 91–92.5°; uv max 222 nm (ϵ 8100); ir ($CHCl_3$) 1735 (lactone C=O), 1665 (C=C), and 1624 cm^{-1} (isoxazole); nmr ($CDCl_3$) δ 2.15 (s, 3) and 2.32 (s, 3, 2 isoxazole-CH_3), 4.77 (t, 1, CHO–), and 5.82 and 6.15 ppm (AB q, 2, CH=CH).

Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 64.93; H, 6.71; N, 6.06.

To a solution of 16.80 g (76 mmol) of the unsaturated lactone **17**, prepared as described above, in 400 ml of ethyl acetate was added 500 mg of 10% palladium on carbon catalyst and the resulting suspension was hydrogenated at atmospheric pressure and 20°. After 2.0 hr, the uptake of hydrogen had ceased. The catalyst was removed by filtration and washed with fresh ethyl acetate. Solvent removal from the filtrates gave a colorless oil which was crystallized from ether to give 12.07 g (76%) of the lactone **11** as white microprisms, mp 59–62°, which were identical in all respects with the sample prepared in part A.

(±)-*trans*-3-[2-(3,5-Dimethyl-4-isoxazolyl)ethyl]-6a-methyl-1,2,3,5,6,6a-hexahydrocyclopenta[*f*] [1]benzopyran-7(8*H*)-one (**20a**).—A solution of 10.0 g (44.8 mmol) of the lactone **11** in 150 ml of tetrahydrofuran (freshly distilled from $LiAlH_4$) was cooled in a Dry Ice–isopropyl alcohol bath under nitrogen to −60°. A 25% solution of vinylmagnesium chloride[15] (25 ml, 75 mmol) was added *via* syringe at a rate such that the temperature remained at −50 to −55°. The mixture was stirred at −60° for 15 min, cooled to −70°, and quenched by the slow addition of 5 ml of methanol (temperature < −50°). It was then poured into ice, 24 g of NH_4Cl, and 8 ml of acetic acid. The resulting solution was extracted with ether and the ether solutions were washed with saturated $NaHCO_3$ solution and saturated brine and were dried (Na_2SO_4). After 10 min, 10 ml of diethylamine was added to the etheral solution of the vinyl ketone **12**. The solution was allowed to stand at 20° for 15 min, and was then stripped of solvent to give the crude Mannich base **18** as a yellow oil. This material was taken up in ether and extracted with a total of 100 ml of 1 N HCl followed by 25 ml of H_2O. The aqueous solutions were washed with ether and placed under a layer of ether in an ice bath. The solution was made basic with 3 N NaOH and then extracted with ether. The ether extracts were washed with saturated brine and dried (Na_2SO_4). Solvent removal gave the Mannich base **18** as a pale yellow oil: ir (film) 3400–2700 (NH and OH, hydrogen bonded), 1705 (weak, C=O), and 1640 cm^{-1} (isoxazole).

A solution of 5.30 g (47.2 mmol) of 2-methylcyclopentane-1,3-dione (**2**)[4] in 150 ml of toluene and 50 ml of acetic acid was degassed, placed under nitrogen, and heated at reflux for 5 min. A solution of the Mannich base prepared above in 50 ml of toluene was added, and refluxing was continued for 2.0 hr. The cooled solution was washed with H_2O, saturated $NaHCO_3$ solution, and saturated brine and dried (Na_2SO_4). Solvent removal gave a reddish-orange gum which was filtered through 150 g of Woelm neutral alumina III with benzene to give 12.0 g (81%) of the trans,cis dienol ether mixture (**20a**, **21a**) as a light orange solid.

Normally, this mixture was used without further purification. The sample from one experiment was, however, crystallized from ether–hexane and then from ether to give an analytically pure sample of the trans dienol ether **20a** as light yellow prisms: mp 113–116°; uv max (C_2H_5OH) 227 nm (sh, ϵ 10,200) and 252 (18,200); ir ($CHCl_3$) 1740 (cyclopentanone) and 1640 cm^{-1} (C=CC=CO and isoxazole); nmr ($CDCl_3$) δ 1.13 (s, 3, CH_3), 2.21 (s, 3) and 2.32 (s, 3, 2 isoxazole-CH_3), 3.11 (q, 2, =CH-CH_2C=O), 3.73 (m, 1, >CHOC), and 5.44 ppm (t, 1, =$CHCH_2$).

Anal. Calcd for $C_{20}H_{25}NO_3$: C, 73.36; H, 7.70; N, 4.28. Found: C, 73.64; H, 7.72; N, 4.57.

In a separate experiment, 2.23 g of lactone **11** was converted to 2.38 g of dienol ether mixture. The nmr of this sample was the same as that of the pure trans isomer **20a**, except that the C-3 proton was two multiplets (total 1 H) at δ 3.73 and 3.85 ppm in a ratio of approximately 4:1. The sample was crystallized twice from isopropyl ether to give 1.545 g of trans dienol ether **20a** as light-orange prisms, mp 111–115°. Concentration of the mother liquors gave 730 mg of orange semicrystalline resin which was shown to contain the trans and cis isomers in a ratio of approximately 45:55. Thus, the original mixture contained 1545 + 0.45(730)/2275 = 83% of trans dienol ether **20a**.

(±)-19-(3,5-Dimethyl-4-isoxazolyl)-de*A*-androst-9-ene-5,17-dione (**26a**).—A suspension of 1.60 g (41 mmol) of lithium aluminum hydride in 150 ml of freshly distilled tetrahydrofuran was cooled under nitrogen in an ice bath as a solution of 12.0 g of the mixture of trans and cis dienol ethers (**20a**, **21a**), the preparation of which is described in the preceding experiment, in 50 ml of tetrahydrofuran was added over 10 min. The suspension was stirred at 0° for another 10 min and then without cooling for 30 min. The mixture was cooled again in an ice bath, carefully hydrolyzed with saturated Na_2SO_4 solution, and dried (Na_2SO_4). The salts were removed by filtration and washed with tetrahydrofuran and chloroform. Solvent removal from the filtrates gave 10.4 g of cream-white solid. Normally, the hydroxy dienol ether **22a** thus prepared was used without purification. However, the material obtained by reduction of the pure trans dienol ether **20a** was crystallized from ether and then from ether–tetrahydrofuran to give analytically pure trans hydroxy dienol ether **22a** as a cream-white crystalline powder: mp 158.5–165° dec; uv max (C_2H_5OH) 230 nm (sh, ϵ 12,000) and 252 (20,000); ir ($CHCl_3$) 3620 and 3450 (OH) and 1640 cm^{-1} (C=CC=CO and isoxazole); nmr ($CDCl_3$) δ 0.96 (s, 3, CH_3), 2.22 (s, 3) and 2.32 (s, 3, 2 isoxazole-CH_3), 3.72 (m, 1, >CHOC), 4.05 (t, 1, >CH-OH), and 5.09 ppm (m, 1, =$CHCH_2$).

Anal. Calcd for $C_{20}H_{27}NO_3$: C, 72.92; H, 8.26; N, 4.25. Found: C, 73.22; H, 8.26; N, 4.03.

The crude hydroxy dienol ether prepared above was dissolved in 350 ml of tetrahydrofuran. To this solution was added 750 mg of 5% palladium on carbon catalyst[23] and the resulting mixture was hydrogenated at atmospheric pressure and room temperature. After 4.0 hr, the uptake of H_2 (1.1 equiv) had ceased. The catalyst was removed by filtration and washed with fresh tetra-

(30) The melting point of this compound depends upon the rate of heating.

hydrofuran. Solvent removal gave the enol ether **23a** as a pale green resin: ir (film) 3150 (OH), 1675 (C=CO–), and 1630 cm^{-1} (isoxazole); nmr ($CDCl_3$) δ 0.80 and 0.98 ppm (s, ratio 7:1, CH_3).

A solution of the crude enol ether **23a** in 400 ml of acetone was stirred at 20° with 100 ml of 1 *N* H_2SO_4 for 1.5 hr. This solution of the hemiketal **24a** was cooled in an ice bath as 100 ml of freshly prepared, cold Jones reagent[24] was added over 30 min. The mixture was stirred with cooling for 30 min and then for another 1.5 hr after removal of the cooling bath. It was then poured into H_2O and extracted with benzene. The benzene solutions were washed with saturated $NaHCO_3$ solution and saturated brine and dried (Na_2SO_4). Solvent removal gave the crude trione **25a** as a pale yellow resin. A solution of this material in 100 ml of methanol was degassed, placed under nitrogen, and, after the addition of 1.0 g of KOH, heated at reflux for 1.5 hr. The dark mixture was cooled, poured into H_2O, and extracted with benzene. The benzene extracts were washed with H_2O and saturated brine and dried (Na_2SO_4). Solvent removal gave 8.33 g of orange solid which was filtered through 150 g of Woelm neutral alumina I. Elution with 3:1 benzene–ether gave the enedione **26a** as a cream-white solid. Crystallization from benzene–hexane gave 4.80 g (33% from lactone 11) of white prisms, mp 141–143.5°. A sample from a similar preparation was crystallized again from benzene–hexane to give analytically pure material: mp 141.5–143.5°; uv max (C_2H_5OH) 226 nm (ϵ 11,300) and 243 (13,350); ir ($CHCl_3$) 1735 (cyclopentanone), 1660 (cyclohexenone), and 1630 cm^{-1} (sh, isoxazole); nmr ($CDCl_3$) δ 1.03 (s, 3, CH_3), 2.14 (s, 3) and 2.27 (s, 3, 2 isoxazole-CH_3), and 3.38 ppm (s, 2, isoxazole-CH_2).

Anal. Calcd for $C_{20}H_{25}NO_3$: C, 73.36; H, 7.70; N, 4.28. Found: C, 73.39; H, 7.64; N, 4.38.

(±)-Estr-4-ene-3,17-dione[9] (5a).—A solution of 654 mg (2.0 mmol) of the enedione **26a** in 50 ml of 3:1 ethanol–triethylamine containing 60 mg of 10% palladium on carbon catalyst was hydrogenated at atmospheric pressure and room temperature. After 1.0 hr, the uptake of H_2 (50 ml) had ceased. The catalyst was removed by filtration and washed with fresh ethanol. Solvent removal from the filtrates gave the dione **27a** as a colorless foam. This material was taken up in 15 ml of ethylene glycol and 50 ml of benzene containing 400 mg of *p*-toluenesulfonic acid monohydrate. This solution was degassed, placed under nitrogen, and heated at reflux, with azeotropic removal of H_2O (water-jacketed Dean–Stark trap) for 21 hr. The cooled solution was washed with saturated $NaHCO_3$ solution, H_2O, and saturated brine and dried (Na_2SO_4). Solvent removal gave the diketal **29a** as a pale yellow resin. To a solution of this material in 40 ml of ethanol containing 1.5 g of KOH was added 80 mg of 10% palladium on carbon catalyst. The resulting solution was hydrogenated at atmospheric pressure and room temperature. The uptake of hydrogen stopped after 4 hr. The catalyst was removed by filtration and washed with fresh ethanol. The solvent was removed from the filtrates until a residue of approximately 20 ml remained. To this solution of the vinylogous amide **30a** was added 50 ml of 20% aqueous KOH solution. The resulting mixture was degassed, placed under nitrogen, and heated at reflux for 18 hr. The cooled solution was extracted with benzene and the benzene solutions were washed with saturated brine and dried (Na_2SO_4). Solvent removal gave the keto diketal **31a** as a pale yellow solid. To a solution of this material in 30 ml of methanol was added 3 ml of 4 *N* HCl. The resulting solution was heated at reflux under nitrogen for 3.0 hr, cooled, diluted with H_2O, and extracted with benzene. The benzene solutions were washed with saturated $NaHCO_3$ solution and saturated brine and dried (Na_2SO_4). Solvent removal gave 540 mg of pale tan solid which was chromatographed on 25 g of E. Merck 0.05–0.2 mm silica gel. The material eluted with 9:1 and 8:2 benzene–ether was triturated with hot isopropyl ether and then cooled to give 474 mg (85%) of the desired steroid **5a** as white prisms, mp 157–159.5° (lit.[9] mp 156–157°). The ir, nmr, and uv spectra of a similarly prepared sample were identical with those of (+)-estr-4-ene-3,17-dione.[31]

The following intermediates were isolated from a similar preparation.

Isoxazole dione 27a was obtained as white prisms from benzene–hexane: mp 137.5–139.5°; uv max (C_2H_5OH) 223 nm (ϵ 4680) and 292 (65); ir ($CHCl_3$) 1740 (cyclopentanone), 1705 (cyclohexanone), and 1630 cm^{-1} (isoxazole); nmr ($CDCl_3$) δ 1.00 (s, 3, CH_3) and 2.26 (s, 3) and 2.41 ppm (s, 3, 2 isoxazole-CH_3).

Anal. Calcd for $C_{20}H_{27}NO_3$: C, 72.92; H, 8.26; N, 4.25. Found: C, 72.89; H, 7.93; N, 4.34.

Isoxazole diketal 29a was obtained as colorless microprisms from ether: mp 145.5–148°; uv max (C_2H_5OH) 225 nm (ϵ 4500); ir ($CHCl_3$) 1640 cm^{-1} (isoxazole); nmr ($CDCl_3$) δ 0.82 (s, 3, CH_3), 2.25 (s, 3) and 2.32 (s, 3, 2 isoxazole-CH_3), and 3.92 ppm (m, 8, 2 $-OCH_2CH_2O-$).

Anal. Calcd for $C_{24}H_{35}NO_5$: C, 69.03; H, 8.45; N, 3.35. Found: C, 69.34; H, 8.64; N, 3.35.

Keto diketal 31a was obtained as fine, white needles from ether: mp 126.5–128°; no uv max; ir ($CHCl_3$) 1715 cm^{-1} (CH_3CO-); nmr ($CDCl_3$) δ 0.85 (s, 3, CH_3), 2.10 (s, 3, CH_3CO-), and 3.90 ppm (d, 8, J = 4 Hz, 2 $-OCH_2CH_2O-$).

Anal. Calcd for $C_{22}H_{34}O_5$: C, 69.81; H, 9.05. Found: C, 70.11; H, 8.99.

(±)-13β-Ethylgon-4-ene-3,17-dione (5b).—A solution of Mannich base **18** (25.0 g, prepared as described above from 20.0 g of lactone **11**) and 12.6 g (0.01 mol) of 2-ethylcyclopentane-1,3-dione (**19**)[26] in 300 ml of toluene and 100 ml of acetic acid was degassed, placed under nitrogen, and heated at reflux for 2.5 hr, the last 1 hr with azeotropic removal of H_2O (Dean–Stark trap). The solution was cooled under nitrogen, washed with saturated brine, saturated $NaHCO_3$ solution, and saturated brine, and dried (Na_2SO_4). Solvent removal at reduced pressure gave the trans and cis dienol ethers **20b** and **21b** as 26.2 g of orange semisolid.

A suspension of 2.6 g (78 mmol) of $LiAlH_4$ in 300 ml of tetrahydrofuran was cooled in an ice–salt bath under nitrogen as a solution of the dienol ether mixture prepared above in 80 ml of tetrahydrofuran was added dropwise over 30 min. The solution was stirred for an additional 10 min with cooling and then for 2.0 hr at room temperature. The mixture was again cooled in an ice bath and cautiously hydrolyzed with saturated aqueous Na_2SO_4 solution until a light yellow solution containing a white precipitate was obtained. This suspension was filtered and the salts were carefully washed with eight portions of fresh tetrahydrofuran. The filtrates were dried (Na_2SO_4) and stripped of solvent to give the hydroxy dienol ether **22b** as 27 g of extremely viscous yellow resin.

To a solution of the hydroxy dienol ether **22b** in 400 ml of tetrahydrofuran (filtered through Woelm neutral alumina I) was added 1.5 g of 5% palladium on carbon catalyst[23] and the resulting suspension was hydrogenated at atmospheric pressure and room temperature. After 7.0 hr, the uptake of H_2 (1650 ml) had virtually ceased. The catalyst was removed by filtration and washed with fresh tetrahydrofuran. Solvent removal from the filtrates gave the enol ether **23b** as a greenish resin.

To a solution of this material in 400 ml of acetone was added 100 ml of 1 *N* H_2SO_4 and the resulting solution was stirred at room temperature under nitrogen overnight. The solution of the hemiketal **24b** was cooled in an ice bath as 75 ml of cold, freshly prepared Jones reagent[24] was added dropwise over 30 min (more slowly at first until a brown color persisted). The mixture was stirred for another 15 min with cooling and then at room temperature for an additional 3.5 hr. Sufficient saturated $NaHSO_3$ solution was added to destroy the remaining oxidizing agent and the resulting green mixture was diluted with H_2O and extracted with benzene. The benzene solutions were washed with saturated brine, saturated $NaHCO_3$ solution, and saturated brine and dried (Na_2SO_4). Solvent removal at reduced pressure gave the trione **25b** as an orange oil.

To a solution of the crude trione **25b** in 300 ml of methanol was added 2.0 g of NaOH and the resulting dark solution was degassed, placed under nitrogen, and heated at reflux for 2.0 hr. The mixture was cooled, diluted with H_2O, and extracted with benzene. The benzene solutions were washed with H_2O and dried (Na_2SO_4). Solvent removal gave the crude tricyclic enedione **26b** as 18.0 g of reddish-orange resin. This material was taken up in benzene, treated with decolorizing carbon, filtered, concentrated, and finally crystallized from 100 ml of benzene–ether to give 11.35 g of the enedione **26b** as an off-white powder, mp 110–113°.

To a solution of the crystallized tricyclic enedione **26b** prepared above in 300 ml of ethanol and 100 ml of triethylamine was added 500 mg of 5% palladium on carbon catalyst and the resulting suspension was hydrogenated at atmospheric pressure and room temperature. After 2.0 hr, the uptake of hydrogen (895 ml) had ceased. The catalyst was removed by filtration and washed with

(31) Part VI: J. W. Scott, R. Borer, and G. Saucy, *J. Org. Chem.*, **37**, 1659 (1972).

fresh ethanol. The solvent was removed at reduced pressure (finally at 50° and 0.01 mm to remove the last traces of triethylamine) to give the isoxazole dione **27b** as a cream-white solid.

A solution of the isoxazole dione **27b** and 5.0 g of *p*-toluenesulfonic acid monohydrate in 50 ml of ethylene glycol and 500 ml of benzene was degassed, placed under nitrogen, and heated at reflux, with azeotropic removal of H_2O (water-jacketed Dean–Stark trap), for 20 hr. The solution was cooled, washed twice with saturated $NaHCO_3$ solution, twice with H_2O, and saturated brine, and dried (Na_2SO_4). Solvent removal gave the diketal **29b** as a pale yellow resin, the infrared spectrum of which indicated that ketalization was complete.

The isoxazole diketal **29b** was dissolved in a solution of 16.0 g of sodium hydroxide in 400 ml of ethanol. To this mixture was added 1.5 g of 5% palladium on carbon catalyst and the resulting suspension was hydrogenated at atmospheric pressure and room temperature. After 2.5 hr, the uptake of hydrogen (880 ml) had ceased. The catalyst was removed by filtration and washed with fresh ethanol. The solvent was removed from the filtrates until a residue of approximately 100 ml remained. To this solution of the vinylogous amide **30b** was added 400 ml of 20% aqueous NaOH solution and the resulting mixture was degassed, placed under nitrogen, and heated at reflux for 18 hr. The solution was cooled and extracted with benzene. The benzene solutions were washed with saturated brine and dried (Na_2SO_4). Solvent removal at reduced pressure gave the keto diketal **31b** as a yellowish-orange resin.

To a solution of the ketal diketal **31b** in 250 ml of methanol was added 25 ml of 3 *N* HCl and the resulting solution was heated at reflux under nitrogen for 3.0 hr. The solution was cooled, poured into H_2O–brine, and extracted with benzene. The benzene solutions were washed with saturated brine, saturated $NaHCO_3$ solution, and saturated brine and dried (Na_2SO_4). The solvent was removed until a residue of approximately 300 ml remained. This solution was treated with decolorizing carbon, filtered, and stripped of solvent to give 9.6 g of yellow solid. Crystallization from acetone gave 6.10 g of pale yellow prisms, mp 156–160°. A second crystallization from acetone gave 5.86 g (23% from the lactone **11**) of (±)-13β-ethylgon-4-ene-3,17-dione (**5b**) as large white prisms: mp 158–161° (lit.[10] mp 159–161°); uv max (C_2H_5OH) 240 nm (ε 17,000); ir 1734 (cyclopentanone), 1668 (cyclohexenone), and 1619 cm^{-1} (C=C); nmr ($CDCl_3$) δ 0.81 (t, 3, J = 7 Hz, CH_2CH_3) and 5.87 ppm (s, 1, C=CH). The compound was found to be identical with the product obtained[1] by another route.

The following intermediates were isolated from a similar preparation.

Trans dienol ether 20b was obtained as yellow-orange prisms from isopropyl ether: mp 101–104°; uv max (C_2H_5OH) 222 nm (sh, ε 9500) and 253 (19,600); ir ($CHCl_3$) 1737 (cyclopentanone) and 1640 cm^{-1} (dienol ether and isoxazole); nmr ($CDCl_3$) δ 0.85 (t, 3, J = 7 Hz, CH_2CH_3), 2.25 (s, 3), and 2.33 (s, 3, 2 isoxazole-CH_3), 2.97 (m, 2, CH_2C=O), 3.70 (s, 1, >CHO–), and 5.55 ppm (t, 1, C=C**H**CH_2).

Anal. Calcd for $C_{21}H_{27}NO_3$: C, 73.87; H, 7.97; N, 4.10. Found: C, 73.91; H, 7.95; N, 4.11.

Trans hydroxy dienol ether 22b was obtained as pale orange prisms from ether: mp 105–109.5°; uv max (C_2H_5OH) 224 nm (sh, ε 11,000) and 251 (18,800); ir ($CHCl_3$) 3625 and 3445 (OH) and 1647 cm^{-1} (dienol ether and isoxazole); nmr ($CDCl_3$) δ 0.95 (t, 3, J = 7 Hz, CH_3CH_2), 2.22 (s, 3), and 2.31 (s, 3, 2 isoxazole-CH_3), 3.65 (m, 1 >CHO), 4.10 (t, 1, CHOH), and 5.15 ppm (t, 1, C=C**H**CH_2).

Anal. Calcd for $C_{21}H_{29}NO_3$: C, 73.43; H, 8.51; N, 4.08. Found: C, 73.65; H, 8.50; N, 3.74.

Hydroxy enol ether 23b was obtained as a clear, colorless glass: ir ($CHCl_3$) 3618 and 3442 (OH), 1680 (enol ether), and 1639 cm^{-1} (isoxazole); nmr ($CDCl_3$) δ 1.05 (t, 3, J = 7 Hz, CH_2CH_3), 2.19 (s, 3) and 2.29 (s, 3, 2 isoxazole-CH_3) and 3.5 ppm (m, 1, >CHO–).

Isoxazole enedione 26b was obtained as fine, white needles from benzene–ether: mp 111–115.5°; uv max (C_2H_5OH) 228 nm (ε 12,350) and 242 (13,900); ir ($CHCl_3$) 1739 (cyclopentanone), 1669 (cyclohexenone), 1635 (isoxazole), and 1605 cm^{-1} (C=C); nmr ($CDCl_3$) δ 0.85 (t, 3, J = 7 Hz, CH_2CH_3), 2.15 (s, 3) and 2.28 (s, 3, 2 isoxazole-CH_3), and 3.39 ppm (s, 2, isoxazole-CH_2).

Anal. Calcd for $C_{21}H_{27}NO_3$: C, 73.87; H, 7.97; N, 4.10. Found: C, 73.71; H, 7.85; N, 4.02.

Isoxazole dione 27b was obtained as small, white needles from methylene chloride–ether: mp 143.5–146°; uv max (C_2H_5OH) 224 nm (ε 4650); ir ($CHCl_3$) 1735 (cyclopentanone), 1715 (cyclohexanone), and 1640 cm^{-1} (isoxazole); nmr ($CDCl_3$) δ 0.84 (t, 3, J = 7 Hz, CH_2CH_3), 2.25 (s, 3), and 2.40 ppm (s, 3, 2 isoxazole-CH_3).

Anal. Calcd for $C_{21}H_{29}NO_3$: C, 73.43; H, 8.51; N, 4.08. Found: C, 73.77; H, 8.74; N, 4.17.

Isoxazole diketal 29b was obtained as white prisms from ether: mp 140–143° (clear melt at 170°); uv max (C_2H_5OH) 225 nm (ε 4600); ir ($CHCl_3$) 1639 cm^{-1} (isoxazole); nmr ($CDCl_3$) δ 0.90 (t, 3, J = 7 Hz, CH_2CH_3), 2.24 (s, 3) and 2.31 (s, 3, 2 isoxazole-CH_3), and 3.92 ppm (m, 8, 2 -OCH_2CH_2O–).

Anal. Calcd for $C_{25}H_{37}NO_5$: C, 69.57; H, 8.64; N, 3.25. Found: C, 69.41; H, 8.70; N, 3.11.

Keto diketal 31b was obtained as fine, white needles from ether: mp 117.5–119.5°; no uv max; ir ($CHCl_3$) 1711 cm^{-1} (CH_3C=O); nmr ($CDCl_3$) δ 0.95 (t, 3, J = 7 Hz, CH_2CH_3), 2.11 (s, 3, CH_3-C=O), 2.56 (t, 2, J = 6 Hz, -CH_2C=O), and 3.90 ppm (d, 8, 2 -OCH_2CH_2O–).

Anal. Calcd for $C_{23}H_{36}O_5$: C, 70.37; H, 9.24. Found: C, 70.10; H, 9.30.

Registry No.—**5a**, 5972-59-8; **5b**, 23477-67-0; **9**, 31612-44-9; **10**, 34769-88-5; **11**, 33587-68-7; **13**, 28241-32-0; **15**, 34769-91-0; **17**, 34769-92-1; **18**, 33282-03-0; **20a**, 34769-94-3; **20b**, 34769-95-4; **22a**, 34769-96-5; **22b**, 34769-97-6; **23a**, 34769-98-7; **23b**, 34769-99-8; **26a**, 27510-08-3; **26b**, 29282-22-2; **27a**, 34770-02-0; **27b**, 34770-03-1; **29a**, 29371-34-4; **29b**, 34770-05-3; **31a**, 29371-35-5; **31b**, 34770-07-5.

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Steroid Total Synthesis. VI.[1] (+)-Estr-4-ene-3,17-dione[2]

J. W. SCOTT, R. BORER, AND G. SAUCY*

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

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Reaction of (±)-9-(3,5-dimethyl-4-isoxazolyl)-7-hydroxynon-1-en-3-one (**1**) with (+)- and (−)-α-phenethylamine gave mixtures of the (2*S*,6*R*)- and (2*R*,6*S*)-2-[2-(α-phenethylamino)ethyl]-6-[2-(3,5-dimethyl-4-isoxazolyl)-ethyl]tetrahydropyran-2-ols **2**–**5**. The determination of the absolute configurations and optical purities of these Mannich bases is described. The resolved Mannich base **2** was converted, *via* (−)-*trans*-3-[2-(3,5-dimethyl-4-isoxazolyl)ethyl]-6a-methyl-1,2,3,5,6,6a-hexahydrocyclopenta[*f*][1]benzopyran-7(8*H*)-one (**8**) and (+)-19-(3,5-dimethyl-4-isoxazolyl)-de*A*-androst-9-ene-5,17-dione (**14**), to (+)-estr-4-ene-3,17-dione (**23**).

In the accompanying paper,[1] we have described a total synthesis of racemic 19-nor steroids. In this paper we present the results of our attempts to modify this synthesis to allow the preparation of optically active 19-nor steroids, in particular (+)-estr-4-ene-3,17-dione (**23**).[3]

Results and Discussion

Reaction[4] of the racemic vinyl ketone **1**[1] with (−)-α-phenethylamine (Scheme I) gave the diastereomeric Mannich bases (2*S*,6*R*)- and (2*R*,6*S*)-2-[2-(*S*-α-phenethylamino)ethyl]-6-[2-(3,5-dimethyl-4-isoxazolyl)ethyl]tetrahydropyran-2-ol (**2**, **3**). Similar reaction with (+)-α-phenethylamine gave the antipodal Mannich bases **4** and **5**. All four compounds were crystalline and were obtained in 50–70% of theoretical yield by fractional crystallization, once seed crystals were available.[5]

We believe that the Mannich bases possess the conformations and absolute configurations shown for the following reasons. That the Mannich bases exist mainly in the spirocyclic, internally hydrogen bonded hemiketal form is indicated by their infrared spectra (strong hydrogen bonded OH and NH absorption at 3200 cm^{-1}; weak carbonyl absorption at 1710 cm^{-1}). The absolute configurations of the α-phenethylamines are known.[6] The configurations at C-6 were determined by conversion of the Mannich bases to either (+)- or (−)-19-(3,5-dimethyl-4-isoxazolyl)-de*A*-androst-9-ene-5,17-dione (*vide infra*). Our previous work[4] with related systems has shown that 6*R* Mannich bases give tricyclic compounds, and eventually steroids, of the natural series. Application of the principles of conformational analysis then allowed us to determine the absolute configurations at C-2, as well as the conformations of the molecules. Owing to the spirocyclic nature of these Mannich bases, each ring can individually undergo conformational inversion. Since the configuration of the hemiketal center C-2 is clearly invertible, at least under the reaction conditions under which it is formed (heating with excess α-phenethylamine in benzene at 50° for 3 hr), there are eight possible chair–chair forms for each of the Mannich bases **2**–**5**. The application of free-energy differences determined in cyclohexane systems to heterocyclic rings is a hazardous undertaking, at best. It is thus rather difficult to estimate by how much each of the conformations shown is more stable than its seven other forms. What is clear, however, is that these are the most stable conformers, since the three ethylidene substituents are in the more stable equatorial positions while the oxygen substituents at the anomeric center C-2 are in favored[7] axial orientations. An interesting consequence of this analysis is that the configuration at C-6 determines that at C-2. Since there are two asymmetric centers in addition to that of the α-phenethylamine in each Mannich base, it would be expected *a priori* that four diastereomers would be obtained with each amine. The fact that only two diastereomers were found provides support for our conformational arguments.

The nmr spectra of the Mannich bases present evidence of their homogeneity and optical purity. The spectra of the four compounds **2**–**5** are identical, except for the positions of the isoxazole methyl signals. In the spectra of the 6*R* bases **2** and **4**, these signals are at 134 and 140 Hz, while the corresponding signals of the 6*S* bases **3** and **5** are at 127 and 133 Hz. Diastereomeric mixtures of compounds show the expected summation of signals. In addition, there is a smaller set of signals (15–20% of the total) at 133 and 139 Hz in the spectrum of each Mannich base or mixture of Mannich bases. We assign this second set of signals to the open form **6** of the Mannich bases. The presence of compounds of type **6** in solution, which was previously shown by the infrared spectra of these compounds, indicates that the acyclic forms **6** are probably more stable than any of the ring-inverted conformers of the bases **2**–**5**. Molecular models indicate that the phenyl and isoxazole rings can come in quite close proximity in the spirocyclic forms **2**–**5**. Such immediate nearness would not be expected to occur in the open configuration **6**. If the isoxazole signals at 133 and 139 Hz are thus considered to be "normal," it appears that the isoxazole rings of the 6*S* bases **3** and **5** are being shielded, presumably by the phenyl ring, while those of the diastereomeric 6*R* bases are virtually unaffected. As yet, we have no explanation for this selective shielding. It has, however, allowed us to determine that we have obtained each of the Mannich bases in an optical purity of at least 95%.

With the optically pure Mannich bases in hand, we turned our attention to the condensation of these materials with 2-methylcyclopentane-1,3-dione (**7**).[8]

(1) Part V: J. W. Scott and G. Saucy, *J. Org. Chem.*, **37**, 1652 (1972).

(2) Presented in part at the Third International Congress on Hormonal Steroids, Hamburg, Germany, 1970.

(3) A. L. Wilds and N. A. Nelson, *J. Amer. Chem. Soc.*, **75**, 5366 (1953).

(4) Part III: G. Saucy and R. Borer, *Helv. Chim. Acta*, **54**, 2517 (1971).

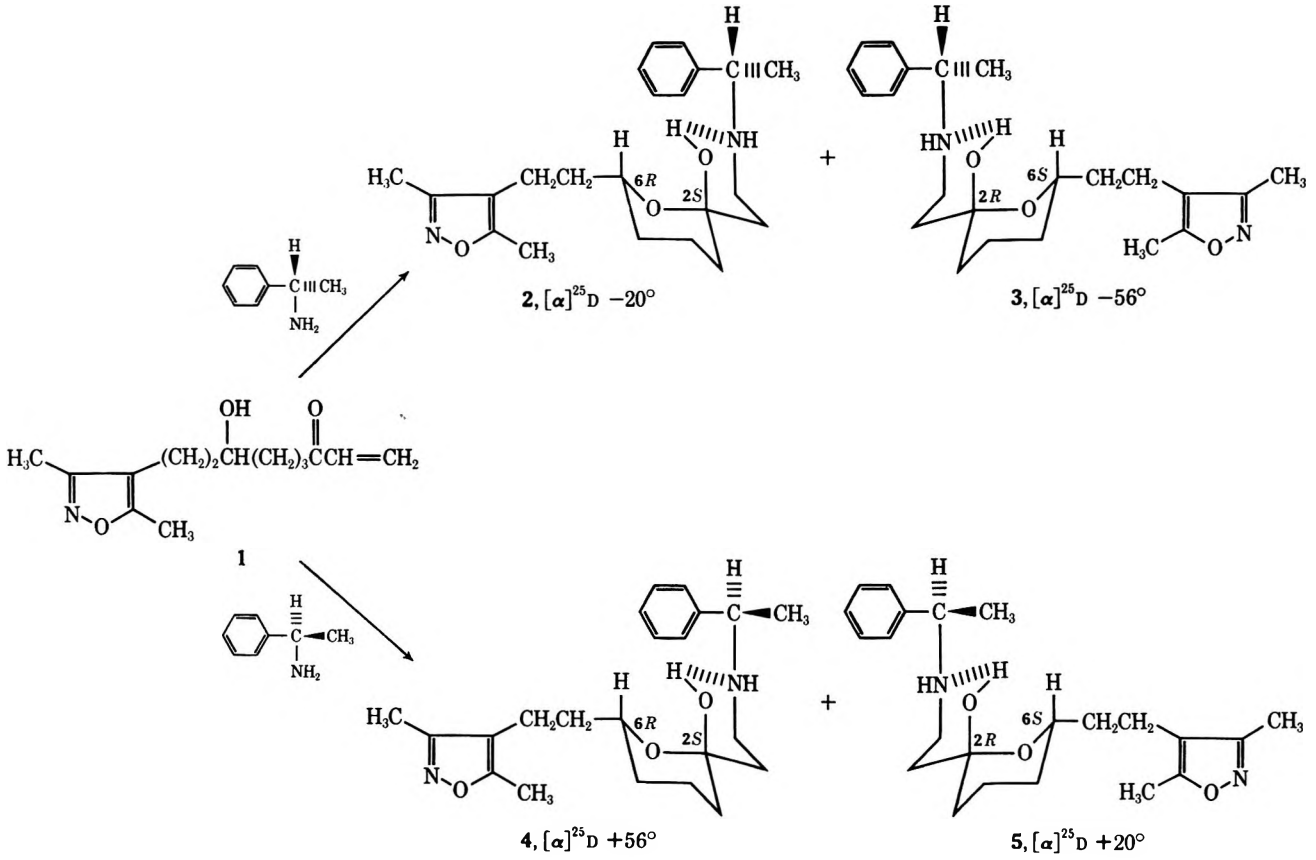
(5) The initial resolution was obtained by fractional crystallization of the oxalate salts of the diastereomeric mixtures. Regeneration of the free amines with dilute base then gave the pure crystalline Mannich base seed crystals.

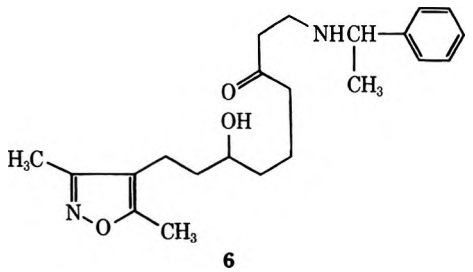
(6) J. C. Craig, R. P. K. Chan, and S. K. Roy, *Tetrahedron*, **23**, 3573 (1967).

(7) C. B. Anderson and D. T. Sepp, *Tetrahedron*, **24**, 1707 (1968); E. L. Eliel and C. A. Giza, *J. Org. Chem.*, **33**, 3754 (1968).

(8) J.-J. Panouse and C. Sannié, *Bull. Soc. Chim. Fr.*, 1036 (1955).

SCHEME I





6

Reaction of the base **2** with the dione **7** in a toluene–pyridine–acetic acid mixture (Scheme II) gave a mixture of trans and cis dienol ethers (**8**, **9**), $[\alpha]^{25}D$ −171°. In the racemic series,[1] it had been possible to isolate the pure trans dienol ether by crystallization, but unfortunately this was not possible with compounds **8** and **9**. Since we thus had no means of accurately determining the extent of optical induction obtained during the condensation reaction,[9] the mixture of dienol ethers was converted, as previously described[1] in the racemic series, to the (+) enedione **14**. Thus, the dienol ethers **8** and **9** were reduced with lithium aluminum hydride (→**10**[10]), hydrogenated over palladium on carbon (→**11**), hydrated with dilute sulfuric acid in acetone (→**12**), oxidized with Jones reagent[11] (→**13**), and cyclized with methanolic sodium hydroxide. An optically pure comparison sample of the (+) dione **14**, $[\alpha]^{25}D$ +93.6°, was synthesized by alkylation of enone **17**[12] with 4-chloromethyl-3,5-dimethylisoxazole,[13] followed by acid-catalyzed cleavage of the ether group and oxidation[11] of the resulting alcohol **16**. The rotation of the crude enone **14** prepared from the dienol ether mixture indicated that this material was approximately 44% optically pure; in other words, an optical induction of 72% had occurred. The extent of optical induction was quite sensitive to the reaction conditions.[4] After considerable experimentation, we were able to obtain dienol ether mixtures of $[\alpha]^{25}D$ −186.5°, corresponding to 89% optical induction. This was done by first quaternizing the Mannich base **2** with methyl iodide and potassium carbonate. The crude quaternary salt was then treated with 2-methylcyclopentane-1,3-dione in aqueous *tert*-butyl alcohol to give a mixture of compounds whose spectral data were in accord with the general structure **18**.[4] Treatment of this mixture with *p*-toluenesulfonic acid then gave the dienol ethers **8** and **9** in 46% yield from the Mannich base **2**. The enone **14** prepared from this mixture was fractionally crystallized to give optically pure (+)-19-(3,5-dimethyl-4-isoxazolyl)-de*A*-androst-9-ene-5,17-dione, mp 85.5–88.5°, in 31% yield from the dienol ether mixture.

Conversion of the optically pure enedione **14** to (+)-estr-4-ene-3,17-dione (**23**) was carried out (Scheme III) as previously described for the racemic series.[1] Thus, hydrogenation of compound **14** over palladium on carbon in ethanol–triethylamine gave the dione **19**, mp 107–110.5°. Ketalization (→**20**, mp 148–150°),

(9) The nmr method previously described[1] was probably accurate at best to ±10%, owing to the overlap of the signals to be integrated. Despite numerous attempts, the materials could not be separated by gas chromatography.

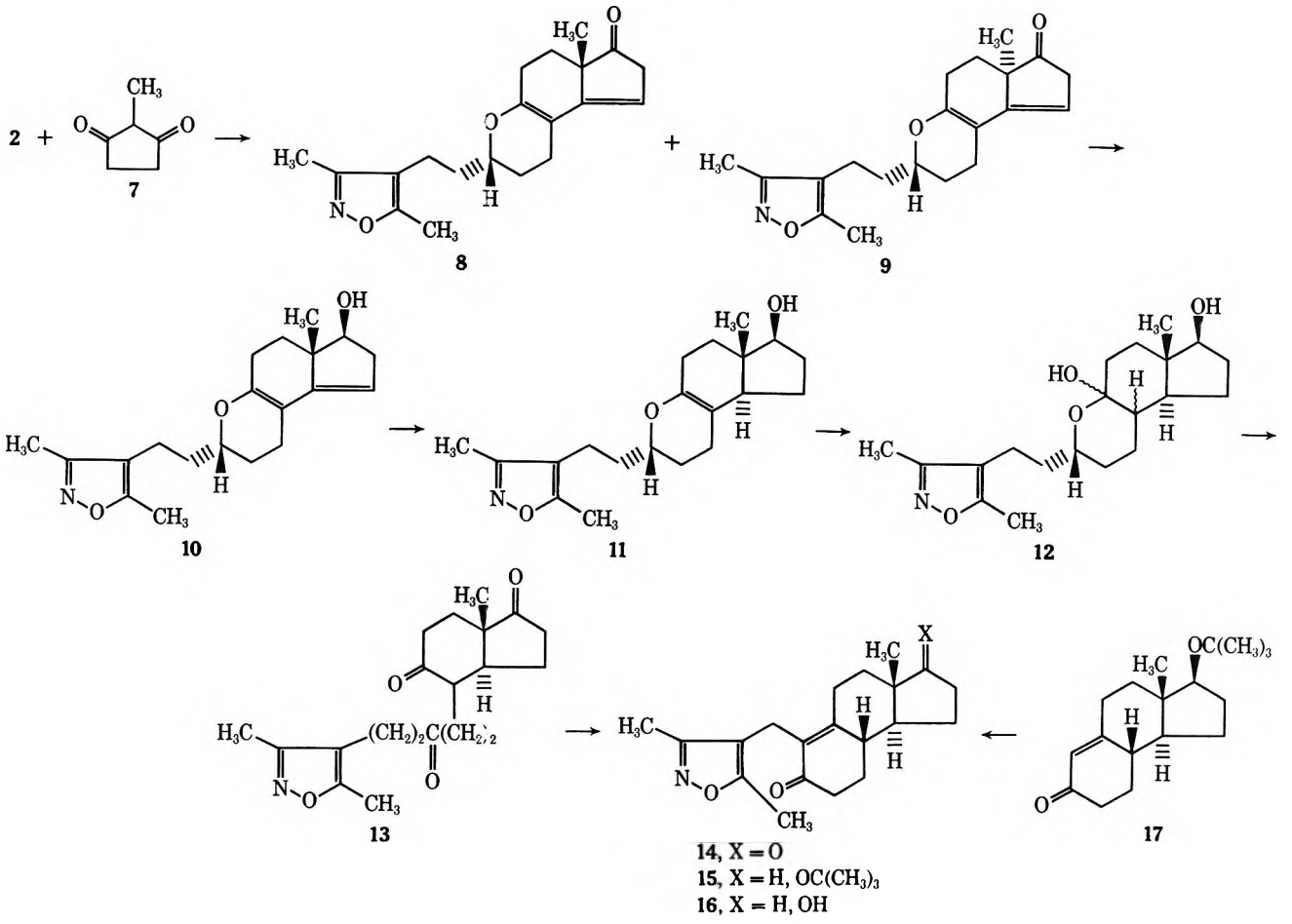
(10) For convenience, only the trans isomers of compounds **10**–**12** are shown.

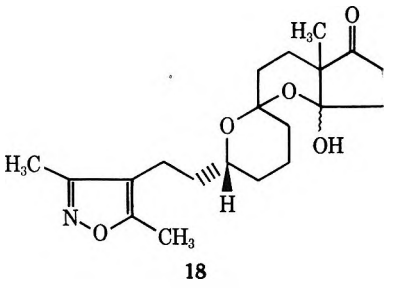
(11) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 2548 (1953).

(12) J. W. Scott, W. Vetter, W. E. Oberhänsli, and A. Furst, *Tetrahedron Lett.*, in press.

(13) N. K. Kochetkov, E. D. Khomutova, and M. V. Bazilevskii, *J. Gen. Chem. USSR*, **28**, 2762 (1958).

SCHEME II





followed by hydrogenation in 4% ethanolic sodium hydroxide solution, gave the vinylogous amide **21**. Treatment of this compound with aqueous base at reflux (→**22**, mp 85.5–86.5°) and then heating with methanolic hydrochloric acid to effect deketalization and ring closure gave (+)-estr-4-ene-3,17-dione (**23**)[3] in 66% yield. The material thus obtained was identical in all respects with a sample obtained by Jones oxidation of 17β-hydroxyestr-4-en-3-one.[14]

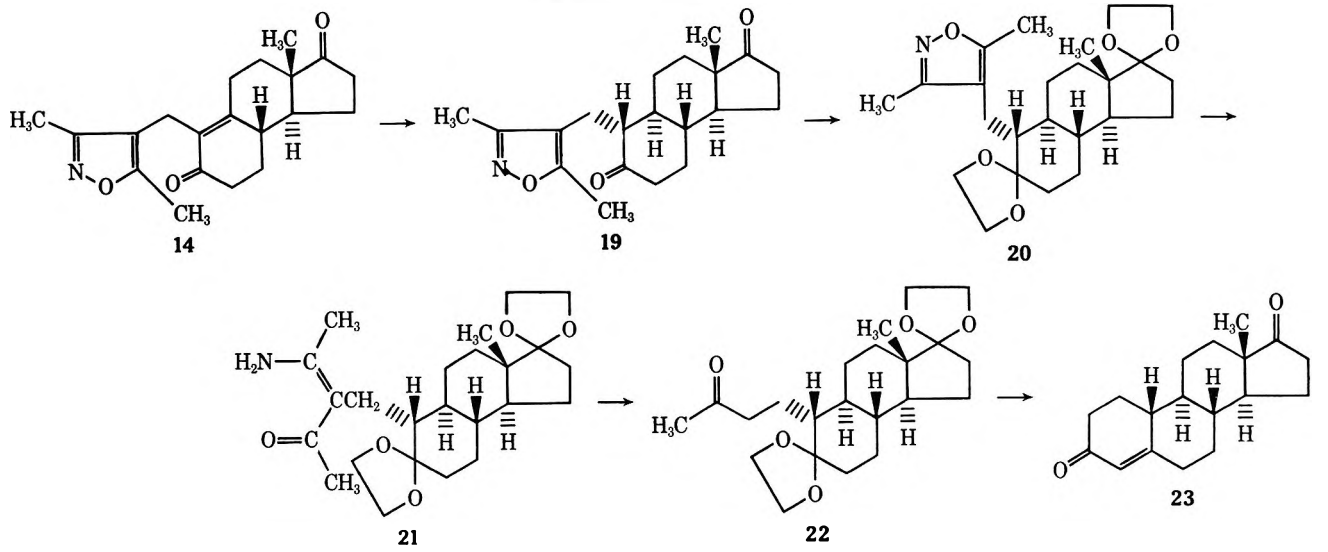
Experimental Section[15]

(2*S*,6*R*)-2-[2-(*S*-α-Phenethylamino)ethyl]-6-[2-(3,5-dimethyl-4-isoxazolyl)ethyl]tetrahydropyran-2-ol (2) and (2*R*,6*S*)-2-[2-(*S*-α-Phenethylamino)ethyl]-6-[2-(3,5-dimethyl-4-isoxazolyl)ethyl]-tetrahydropyran-2-ol (3).—A solution of 13.4 g (0.06 mol) of (±)-7-(3,5-dimethyl-4-isoxazolyl)-5-hydroxyheptanoic acid lactone[1] in 200 ml of tetrahydrofuran (freshly distilled from $LiAlH_4$) was cooled under nitrogen in a Dry Ice–isopropyl alcohol bath to −60°. A 2 *N* vinylmagnesium chloride in tetrahydrofuran solution (55 ml = 0.11 mol; Peninsular ChemResearch, Inc.) was added at a rate such that the temperature remained at −50 to −55° (5 min). The resulting pale yellow solution was stirred at −55 to −60° for 20 min, cooled to −70°, and cautiously hydrolyzed with 15 ml of methanol (temperature < −50°). The solution was poured into a mixture of ice, 30 g of NH_4Cl, and 10 ml of acetic acid and extracted with ether. The ether solutions were washed with saturated brine, saturated $NaHCO_3$ solution, and saturated brine and dried (Na_2SO_4). Solvent removal at 30° gave the vinyl ketone **1** as a pale yellow oil. This material was taken up in 100 ml of benzene, degassed, and placed under nitrogen. To the flask was added 7.50 g (0.062 mol) of (−)-α-phenethylamine (Aldrich Chemical Co.) and the resulting solution was stirred at 50–55° for 3 hr. The solvent was removed at reduced pressure and the residual orange resin was chromatographed on 1.5 kg of Woelm neutral alumina III. After prior elution with 1:1 hexane–benzene and benzene, benzene–ether mixtures gave a mixture of diastereomeric Mannich bases **2** and **3** as 18.0 g of pale yellow resin. To a solution of this material in 90 ml of ether was added a solution of 7.55 g (0.060 mol) of oxalic acid dihydrate in 60 ml of ether, at which point an oil precipitated. The ether layer was decanted and the oil was shaken twice with 50-ml portions of ether. The oil was then crystallized from 50 ml of acetone and 100 ml of benzene to give 15.4 g of white solid, mp 111–114°,[15] $[\alpha]^{20}D$ −28.2° (*c* 1.0, CH_3OH). Four crystallizations of this material from methanol–ether gave the pure oxalate of the Mannich base **2** as heavy, white needles, mp 118–120°, $[\alpha]^{20}D$ −28.5° (*c* 1.0, CH_3OH). A 110-mg sample of this material was shaken with benzene and 20 ml of 1 *N* KOH until all the solid dissolved. The benzene layer was washed with saturated brine and dried (Na_2SO_4). Solvent removal gave 82 mg of pale yellow resin which was crystallized from isopropyl ether to give the Mannich base **2** as 50 mg of white prisms, mp 65.5–69.5°, $[\alpha]^{25}D$ −19.8° (*c* 1.2, C_6H_6). The mother liquors from the

(14) G. D. Searle and Co.

(15) Melting points were determined on a Kofler hot stage and are not corrected. A Varian A-60 spectrometer was used to obtain the nmr spectra and tetramethylsilane was used as the internal standard. Infrared spectra were recorded on a Beckman IR-9 spectrophotometer. The uv spectra were recorded on a Cary Model 14M spectrophotometer. Optical rotations were taken on a Perkin-Elmer Model 141 polarimeter.

SCHEME III



initial oxalate crystallization were shaken with benzene and 1 *N* KOH as above to give 12.0 g of yellow oil. A 3.0-g sample of this material was chromatographed on 90 g of Woelm neutral alumina I. The material eluted with benzene was crystallized twice from isopropyl ether to give the Mannich base **3** as 115 mg of white prisms, mp 70–72.5°, $[\alpha]^{25}D$ −55.2° (*c* 1.0, C_6H_6).

A sample of the mixed diastereomers **2** and **3** (30.75 g), which was prepared as described above, was dissolved in 100 ml of hot isopropyl ether, cooled to 20°, and seeded with isomer **2**. Crystallization was allowed to proceed at 20° overnight and then for 48 hr at 0°. Careful decantation of the mother liquors (to avoid initiation of crystallization of isomer **3**) gave 10.60 g of Mannich base **2** as large, white prisms. Recrystallization of this material from 150 ml of 2:1 hexane–ether gave 9.35 g (61%) of large white prisms, mp 69.5–75°, $[\alpha]^{25}D$ −20.4° (*c* 1.26, C_6H_6).[16] Seeding of the mother liquors from the original crystallization of compound **2** with isomer **3** gave, after 3 hr at 0°, 10.5 g of slightly orange solid. Two recrystallizations of this material from 120 and 90 ml of 2:1 hexane–ether gave 7.40 g (48%) of the Mannich base **3** as long white prisms, mp 68.5–75.5°, $[\alpha]^{25}D$ −56.2° (*c* 1.14, C_6H_6). An additional 1.58 g (10%) of Mannich base **2**, mp 69.5–75.5°, $[\alpha]^{25}D$ −21.1° (*c* 1.33, C_6H_6), was obtained by fractional crystallization of the material recovered from the mother liquors.

The analytical samples of compounds **2** and **3** were obtained respectively as large white prisms, mp 69.5–73.5°, $[\alpha]^{25}D$ −21.3° (*c* 1.26, C_6H_6), and as a white, crystalline solid: mp 70–72.5°; $[\alpha]^{25}D$ −55.2° (*c* 1.0, C_6H_6); uv max (C_2H_5OH) 220 nm (ε 7500), 250 (280), 256 (285), and 262–263 (200); ir ($CHCl_3$) 3400–2400 (OH and NH, hydrogen bonded), 1710 (C=O, weak), and 1640 cm^{-1} (isoxazole).

Anal. Calcd for $C_{22}H_{32}N_2O_3$: C, 70.92; H, 8.66; N, 7.52. Found: **2**, C, 71.10; H, 8.47; N, 7.40; **3**, C, 71.07; H, 8.69; N, 7.52.

The isoxazole methyl nmr signals for these compounds are given and discussed fully in the discussion. Other signals ($CDCl_3$) are at δ 1.39 (d, 3, $CHCH_3$) and 7.25 ppm (s, 5, C_6H_5).

(+)-19-(3,5-Dimethyl-4-isoxazolyl)-de*A*-androst-9-ene-5,17-dione (14). A. From 17β-*tert*-Butoxy-de*A*-estr-9-en-5-one (17).—In a dry flask under nitrogen, a mixture of 520 mg (12.0 mmol) of 55% NaH in mineral oil and 2.76 g (10.0 mmol) of the enone **17**[12] in 100 ml of 1,2-dimethoxyethane (freshly distilled from $LiAlH_4$) was heated at reflux for 1.0 hr to give a cloudy, light brown solution. Heating was continued as a solution of 1.75 g (12.0 mmol) of 4-chloromethyl-3,5-dimethylisoxazole[13] in 20 ml of 1,2-dimethoxyethane was added over 4.5 hr. The resulting suspension was heated at reflux for another 1.5 hr, cooled, poured into H_2O, and extracted with benzene. The benzene solutions were washed with saturated brine and dried (Na_2SO_4). Solvent removal gave an orange resin which was chromatographed on 200 g of E. Merck 0.05–0.2 mm silica gel. Elution with 19:1 benzene–ether gave 619 mg (22.5%) of enone **17**. Continued elution with this solvent mixture gave the desired isoxazole enone **15** as a light yellow solid. Crystallization from ether–hexane gave 1.72 g (45%) of white prisms: mp 125.5–126.5°; $[\alpha]^{25}D$ +18.4° (*c* 1.06, C_2H_5OH); uv max (C_2H_5OH) 220 nm (sh, ε 8000) and 244 (13,300); ir ($CHCl_3$) 1660 (C=CC=O and isoxazole) and 1600 cm^{-1} (C=C); nmr ($CDCl_3$) δ 0.88 (s, 3, CH_3), 2.15 (s, 3) and 2.28 (s, 3, 2 isoxazole-CH_3), and 3.39 ppm (m, 3, isoxazole-CH_2 and C_{17} H).

Anal. Calcd for $C_{24}H_{35}NO_3$: C, 74.76; H, 9.15; N, 3.63. Found: C, 74.88; H, 9.38; N, 3.67.

A solution of 1.159 g (3.0 mmol) of the alkylated enone **15** and 1.10 g of *p*-toluenesulfonic acid monohydrate in 100 ml of benzene was heated at reflux for 1.0 hr. The cooled solution was washed with saturated $NaHCO_3$ solution and saturated brine and dried (Na_2SO_4). Solvent removal gave 1.03 g of yellowish resin which was crystallized from isopropyl ether to give 697 mg (71%) of hydroxy enone **16** as small, white needles: mp 127–127.5°; $[\alpha]^{25}D$ −3.6° (*c* 1.12, $CHCl_3$); uv max (C_2H_5OH) 225 nm (ε 10,200) and 244 (13,600); ir ($CHCl_3$) 3600 and 3400 (OH), 1660 (C=CC=O and isoxazole), and 1600 cm^{-1} (C=C); nmr ($CDCl_3$) δ 0.90 (s, 3, CH_3), 2.13 (s, 3) and 2.26 (s, 3, 2 isoxazole-CH_3), 3.39 (s, 2, isoxazole-CH_2), and 3.75 ppm (t, 1, $C_{17}H$).

Anal. Calcd for $C_{20}H_{27}NO_3$: C, 72.92; H, 8.26; N, 4.25. Found: C, 73.25; H, 8.49; N, 4.16.

A solution of 415 mg (1.26 mmol) of the hydroxy enone **16** in 25 ml of acetone was cooled in an ice bath as 1.0 ml of Jones reagent[11] was added over 5 min. The mixture was stirred with cooling for 10 min, diluted with $NaHSO_3$ solution, and extracted with benzene. The benzene solutions were washed with H_2O, saturated $NaHCO_3$ solution, and saturated brine and dried (Na_2SO_4). Solvent removal gave 430 mg of colorless foam which was crystallized from isopropyl ether to give 280 mg (68%) of enedione **14** as white needles: mp 85.5–87.5°; $[\alpha]^{25}D$ +93.6° (*c* 1.04, $CHCl_3$); uv max (C_2H_5OH) 225 nm (ε 10,600) and 242 (12,700); ir ($CHCl_3$) 1740 ($C_{17}C$=O), 1664 (C=CC=O), 1640 (sh, isoxazole), and 1600 cm^{-1} (C=C); nmr ($CDCl_3$) δ 1.03 (s, 3, CH_3), 2.15 (s, 3) and 2.28 (s, 3, 2 isoxazole-CH_3), and 3.40 ppm (s, 2, isoxazole-CH_2).

Anal. Calcd for $C_{20}H_{25}NO_3$: C, 73.36; H, 7.70; N, 4.28. Found: C, 73.67; H, 7.95; N, 4.15.

B. From Mannich Base 2.—To a solution of 1.86 g (5.0 mmol) of optically pure Mannich base **2**, $[\alpha]^{25}D$ −20.36° (*c* 1.26, C_6H_6), in 40 ml of acetone was added 3.0 g of granular anhydrous K_2CO_3 and 5 ml of methyl iodide. The resulting suspension was stirred at room temperature overnight, filtered, and stripped of solvent at reduced pressure to give the Mannich base quaternary salt as a white, semicrystalline mass. To a solution of this material in 75 ml of 4:1 *tert*-butyl alcohol–H_2O was added 1.12 g (10.0 mmol) of 2-methylcyclopentane-1,3-dione[8] and the resulting mixture was degassed, placed under nitrogen, and heated at reflux for 24 hr. The cooled solution was diluted with H_2O and extracted with benzene. The benzene solutions were washed twice with saturated oxalic acid, H_2O, saturated $NaHCO_3$ solution, and saturated brine and dried (Na_2SO_4). Solvent removal

(16) The rotations of the Mannich bases are difficult to reproduce exactly and seem to depend to some extent upon the length of time the material is in solution before the determination is made. Presumably these variations in rotation reflect, at least partially, differing concentrations of the acyclic forms **6**.

gave a pale yellow resin which was chromatographed on 100 g of E. Merck 0.05–0.2 mm silica gel. Elution with benzene–ether mixtures (3:2, 2:3, 1:4) gave the mixture of isomeric hemiketals **18** as 1.27 g (70%) of pale yellow resin: ir (film) 3450 (OH), 1740 (cyclopentanone), and 1640 cm^{-1} (isoxazole). To a solution of the hemiketals **18** in 100 ml of benzene was added 100 mg of *p*-toluenesulfonic acid monohydrate and the resulting solution was stirred at 20° for 30 min. An additional 100 mg of acid was added and stirring was continued for another 2.5 hr. The mixture was washed with H_2O, saturated $NaHCO_3$ solution, and saturated brine and dried (Na_2SO_4). The pale yellow resin obtained upon solvent removal was filtered through 100 g of Woelm neutral alumina III with benzene to give 842 mg of cream-white solid. Two crystallizations of this material from isopropyl alcohol–H_2O gave 754 mg (46%, based on Mannich base **2**) of dienol ether **8** as fine, colorless (white) needles, mp 86.5–91.5°, $[\alpha]^{25}D$ −186.5° (*c* 1.19, $CHCl_3$). The melting point and rotation were unchanged by a further recrystallization. The material had ir and uv spectra and tlc behavior identical with those of racemic dienol ether.[1] That the sample contained cis dienol ether **9** was shown by its further conversion (*vide infra*) to a mixture of (±)- and (+)-enediones **14**.

The series of reactions converting the dienol ether mixture **8** and **9** to the crude enedione **14** is essentially that previously described for the racemic series.[1] Thus, 654 mg (2.0 mmol) of the mixed dienol ethers, $[\alpha]^{25}D$ −186.5°, was reduced with lithium aluminum hydride in tetrahydrofuran to give the 17-hydroxy dienol ether **10** as a pale yellow resin. Hydrogenation over palladium on carbon in tetrahydrofuran gave the enol ether **11** as a pale yellow glass: ir (film) 3480 (OH), 1675 (C=CO–), and 1640 cm^{-1} (isoxazole). Hydration of the enol ether with 1 *N* H_2SO_4 in acetone, followed by Jones oxidation[11] of the hemiketal **12**, gave the trione **13** as a pale yellow oil. Cyclization with KOH in methanol gave the crude enedione **14**, which was chromatographed on 50 g of Woelm neutral alumina III. Elution with benzene and 95:5 benzene–ether gave 410 mg (63%) of pale yellow resin, $[\alpha]^{25}D$ +74.0° (*c* 4.05, $CHCl_3$). This material was triturated with 12 ml of ether and cooled to −20°. The mother liquors were decanted and the process was repeated to give 39 mg of (±)-19-(3,5-dimethyl-4-isoxazolyl)-de*A*-androst-9-ene-5,17-dione:[1] mp 141–144°; mixture melting point with an authentic sample[1] undepressed; ir, uv, and nmr spectra identical with those of the authentic sample; $[\alpha]^{25}D$ 0° (*c* 1.10, $CHCl_3$).

The mother liquors from the trituration of the racemic material were stripped of solvent to give 340 mg of yellowish resin. Crystallization of this material from 20 ml of isopropyl ether gave 203 mg (31%) of (+)-enedione **14** as long, white prisms, mp 85.5–88.5°. Recrystallization from ether–hexane gave fine white needles: mp 85.5–89°; mixture melting point with material from part A undepressed; $[\alpha]^{25}D$ +93.82° (*c* 1.0, $CHCl_3$); ir, uv, and nmr spectra identical with those of the sample prepared in part A.

(+)-Estr-4-ene-3,17-dione (23). A. From (+)-17β-Hydroxyestr-4-en-3-one.—To a cold (ice bath) solution of 558 mg (2.0 mmol) of 17β-hydroxyestr-4-en-3-one[14] in 25 ml of acetone was added 2.0 ml of Jones reagent.[11] The mixture was stirred with cooling for 10 min, diluted with $NaHSO_3$ solution, and extracted with benzene. The benzene solutions were washed with saturated brine and dried (Na_2SO_4). Solvent removal gave a white solid which was crystallized from acetone–hexane to give the dione **23** as 475 mg (85%) of shiny platelets, mp 173–174°, $[\alpha]^{25}D$ +139.2° (*c* 1.20, $CHCl_3$) (lit.[3] mp 170–171°, $[\alpha]^{25}D$ +147 ± 1°).

B. From (+)-Enedione 14.—The procedure employed in this preparation is that described previously[1] for the preparation of (±)-estr-4-ene-3,17-dione. Thus, hydrogenation of 6.55 g (20 mmol) of the (+)-enedione **14** over palladium on carbon in 3:1 ethanol–triethylamine gave the dione **19** as an off-white glass. A purified sample was obtained as white needles: mp 107–110.5° from isopropyl ether; $[\alpha]^{25}D$ −0.76° (*c* 1.45, $CHCl_3$); uv max (C_2H_5OH) 223 nm (ε 4500); ir ($CHCl_3$) 1739 (cyclopentanone), 1713 (cyclohexanone), and 1639 cm^{-1} (isoxazole); nmr ($CDCl_3$) δ 0.99 (s, 3, CH_3), 2.26 (s, 3), and 2.40 ppm (s, 3, 2 isoxazole-CH_3).

Anal. Calcd for $C_{20}H_{27}NO_3$: C, 72.92; H, 8.26; N, 4.25. Found: C, 73.01; H, 8.20; N, 4.04.

Ketalization of the crude dione **19** gave the diketal **20** as a colorless oil. A purified sample was obtained as white rods: mp 148–150° from methylene chloride–isopropyl ether; $[\alpha]^{25}D$ +3.5° (*c* 1.05, $CHCl_3$); uv max (C_2H_5OH) 224 nm (ε 4600); ir ($CHCl_3$) 1638 cm^{-1} (isoxazole); nmr ($CDCl_3$) δ 0.82 (s, 3, CH_3), 2.25 (s, 3) and 2.32 (s, 3, 2 isoxazole-CH_3), and 3.92 ppm (m, 8, 2 $-OCH_2CH_2O-$).

Anal. Calcd for $C_{24}H_{35}NO_5$: C, 69.04; H, 8.45; N, 3.35. Found: C, 68.91; H, 8.52; N, 3.22.

The crude diketal was hydrogenated over 5% palladium on carbon in 4% ethanolic NaOH solution. The vinylogous amide **21** was cleaved with aqueous base to give the keto diketal **22** as a light yellow oil. A purified sample was obtained as irregular white prisms: mp 83.5–86.5° from ether–hexane; $[\alpha]^{25}D$ −16.0° (*c* 1.17, C_6H_6); no uv absorption; ir ($CHCl_3$) 1710 cm^{-1} (CO-CH_3); nmr ($CDCl_3$) δ 0.88 (s, 3, CH_3), 2.14 (s, 3, $COCH_3$), and 3.92 ppm (d, 8, 2 $-OCH_2CH_2O-$).

Anal. Calcd for $C_{22}H_{34}O_5$: C, 69.81; H, 9.05. Found: C, 69.74; H, 9.10.

The crude keto diketal was treated with methanolic HCl to give the crude steroid **23** as 5.85 g of light yellow solid. Chromatography of this material on 500 g of E. Merck 0.05–0.2 mm silica gel (elution with 85:15 benzene–ether) gave 4.28 g of pale yellow solid. Crystallization from 15 ml of acetone and 100 ml of hexane gave 3.34 g (61%) of shiny, colorless plates: mp 172–173°; mixture melting point with material from part A undepressed; $[\alpha]^{25}D$ +139.5° (*c* 0.95, $CHCl_3$). An additional 328 mg (5%) of material, mp 165–171°, was obtained by concentration of the mother liquors.

Registry No.—**2**, 33276-61-8; 2 oxalate, 34770-09-7; **3**, 34770-10-0; **8**, 34770-11-1; **14**, 34770-12-2; **15**, 34770-13-3; **16**, 34770-14-4; **19**, 34770-15-5; **20**, 34770-16-6; **22**, 34770-17-7; **23**, 734-32-7.

Acknowledgment.—We would like to express our gratitude to the personnel of the Physical Chemistry Department of Hoffmann-La Roche Inc. for their assistance in this work.

Notes

An Improved Procedure for Ring Annelation with 3,5-Dimethylisoxazoles

J. W. SCOTT, B. L. BANNER, AND G. SAUCY*

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

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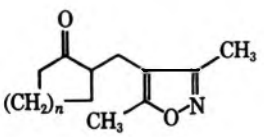
In two accompanying papers[1,2] on steroid total synthesis we have outlined a method for obtaining significantly higher yields in the Stork isoxazole ring annelation reaction.[3] In order to test the generality of this sequence, we have investigated the conversion of 2-[(3,5-dimethyl-4-isoxazolyl)methyl]cyclopentanone (**1a**)[4] and 2-[3,5-dimethyl-4-isoxazolyl)methyl]cyclohexanone (**1b**)[3] to 2,3,7,7a-tetrahydroindan-5(6*H*)-one (**5a**)[5] and 4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one (**5b**).[5]

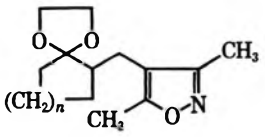
The ketones **1a** and **1b** were ketalized with ethylene glycol in the usual fashion. The desired ketals **2a** and **2b** could be obtained in analytically pure form by distillation in 85 and 86% yield, respectively.[6] The distilled ketals **2a,b** were hydrogenated over palladium on carbon in 3–4% ethanolic potassium hydroxide solution. The uptake of hydrogen proceeded smoothly, stopping after the uptake of 1 equiv in 4–10 hr. The resulting vinylogous amides **3a** and **3b** were not isolated; rather, the hydrogenation solutions, after removal of the catalyst by filtration, were concentrated at reduced pressure. Addition of 20% aqueous potassium hydroxide solution, followed by heating at reflux for 12–16 hr, gave the keto ketals **4a** and **4b**. These materials could be isolated in analytically pure form in 83 and 84% yield, respectively, from the isoxazole ketals **2a** and **2b**.

When the crude keto ketal **4b** was heated with methanolic hydrochloric acid, the octalone **5b**, bp 70–76° (0.25 mm), was obtained in 76% yield from the distilled isoxazole ketal **2b**. The material was, as expected,[5] a mixture containing approximately 20% of the isomeric β,γ-unsaturated ketone **6b**. When the product was isolated as its 2,4-dinitrophenylhydrazone, the yield was 78%. These yields compare favorably with the 50% previously reported[3] for the conversion **1b** → **5b**.

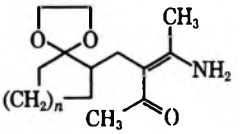
Treatment of the crude keto ketal **4a** with methanolic hydrochloric acid caused deketalization to give 2-(3-oxobutyl)cyclopentanone (**7**),[7] which was not cyclized under these conditions. Heating this dione with methanolic sodium hydroxide gave indenone **5a**, bp 60–68° (0.25 mm), of 95% gc purity[8] in 57% yield from the isoxazole ketal **2a**. Since the lower yield in this second example clearly arose only from difficulties in cyclization of the dione **7**, extensive attempts to raise the yield in this step were not made.[9]



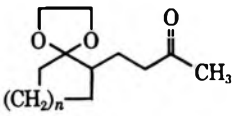
1a, $n = 1$
b, $n = 2$



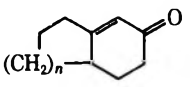
2a, $n = 1$
b, $n = 2$



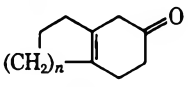
3a, $n = 1$
b, $n = 2$



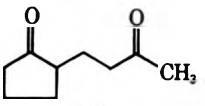
4a, $n = 1$
b, $n = 2$



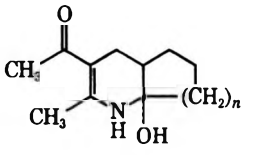
5a, $n = 1$
b, $n = 2$



6a, $n = 1$
b, $n = 2$



7



8, $n = 1,2$

In our opinion, the improved yields in the procedure here described are traceable to the suppression of formation of the carbinolamines **8**.[10] As noted previously,[2,10] these compounds, upon treatment with base, rapidly dehydrate to dihydropyridines, which are susceptible to oxidation and/or disproportionation to give, for annelation purposes, useless by-products.

Experimental Section[11]

1,1-Ethylenedioxy-2-[(3,5-dimethyl-4-isoxazolyl)methyl]cyclopentane (2a).—To a solution of 25.0 g (0.13 mol) of 2-[(3,5-dimethyl-4-isoxazolyl)methyl]cyclopentanone[4] in 50 ml of ethylene glycol and 300 ml of benzene was added 3.0 g (16 mmol) of *p*-toluenesulfonic acid monohydrate. The resulting solution was degassed, placed under nitrogen, and heated at reflux, with azeotropic removal of H_2O (water-jacketed Dean–Stark trap),

(1) J. W. Scott and G. Saucy, *J. Org. Chem.*, **37**, 1652 (1972).
(2) J. W. Scott, R. Borer, and G. Saucy, *ibid.*, **37**, 1659 (1972).
(3) G. Stork, S. Danishefsky, and M. Ohashi, *J. Amer. Chem. Soc.*, **89**, 5459 (1967).
(4) M. Ohashi, H. Kamachi, H. Kakisawa, and G. Stork, *ibid.*, **89**, 5460 (1967).
(5) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *ibid.*, **85**, 207 (1963).
(6) The crude ketals, obtained in quantitative yield, had infrared spectra identical with those of the distilled materials. Either sample was suitable for further reaction.
(7) H. O. House, B. M. Trost, R. W. Magin, R. A. Carlson, R. W. Franck, and G. N. Rasmussen, *J. Org. Chem.*, **30**, 2513 (1965).
(8) The impurity presumably[7] was the β,γ-unsaturated ketone **6a**. Spectral measurements were in agreement with this assumption (see Experimental Section).
(9) Cyclization with pyrrolidine, followed by cleavage of the resulting enamine with acetate buffer,[7] gave the indenone **6a** in 49% yield from the ketal **2a**.
(10) G. Stork and J. E. McMurry, *J. Amer. Chem. Soc.*, **89**, 5463 (1967).
(11) Melting points were determined on a Kofler hot stage and are uncorrected. A Varian A-60 spectrometer was used to obtain the nmr spectra and tetramethylsilane was used as the internal standard. Infrared spectra were recorded on a Beckman IR-9 spectrophotometer. The uv spectra were recorded on a Cary Model 14M spectrophotometer.

for 16 hr. The cooled mixture was washed twice with saturated $NaHCO_3$ solution and three times with H_2O and saturated brine and dried ($MgSO_4$). The benzene solutions were concentrated and then distilled through a short Vigreux column to give 26 g (85%) of **2a** as a colorless liquid: bp 125–129° (0.4 mm); uv max (C_2H_5OH) 221 nm (ϵ 4970); ir ($CHCl_3$) 1642 cm^{-1} (isoxazole); nmr ($CDCl_3$) δ 2.24 (s, 3) and 2.34 ppm (s, 3, 2 isoxazole-CH_3) and 3.95 ppm (s, 4, $-OCH_2CH_2O-$).

Anal. Calcd for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07; N, 5.90. Found: C, 66.10; H, 8.42; N, 5.72.

1,1-Ethylenedioxy-2-[(3,5-dimethyl-4-isoxazolyl)methyl]cyclohexane (2b).—This compound, prepared as described in the previous experiment from 2-[(3,5-dimethyl-4-isoxazolyl)methyl]-cyclohexanone,[3] was obtained in 86% yield as a colorless liquid: bp 126–132° (0.25 mm); uv max (C_2H_5OH) 222–223 nm (ϵ 4880); ir ($CHCl_3$) 1645 cm^{-1} (isoxazole); nmr ($CDCl_3$) δ 2.35 (s, 3) and 2.34 (s, 3, 2 isoxazole-CH_3), and 4.04 ppm (s, 4, $-OCH_2CH_2O-$).

Anal. Calcd for $C_{14}H_{21}NO_3$: C, 66.90; H, 8.42; N, 5.57. Found: C, 66.95; H, 8.25; N, 5.58.

1,1-Ethylenedioxy-2-(3-oxobutyl)cyclopentane (4a).—To a solution of 5.0 g (21 mmol) of **2a** in 100 ml of 3.2% ethanolic KOH solution was added 100 mg of 10% palladium on carbon catalyst and the resulting mixture was hydrogenated at atmospheric pressure and room temperature. After 8 hr, the uptake of hydrogen had ceased. The catalyst was removed by filtration and washed with fresh ethanol. The filtrates were concentrated at reduced pressure to approximately 30 ml. To this solution of the vinylogous amide **3a** was added 100 ml of 20% aqueous KOH solution and the resulting mixture was degassed, placed under nitrogen, and heated at reflux overnight. The cooled solution was extracted with benzene. The benzene solutions were washed with saturated brine and dried ($MgSO_4$). Solvent removal, followed by distillation, gave 3.52 g (83%) of **4a** as a colorless liquid: bp 85–90° (0.35 mm); no uv absorption; ir ($CHCl_3$) 1723 cm^{-1} (CH_3CO-); nmr ($CDCl_3$) δ 2.12 (s, 3, CH_3CO-), 2.45 (t, 2, J = 7 Hz, $-CH_2COCH_3$) and 3.90 ppm (s, 4, $-OCH_2CH_2O-$).

Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.73; H, 8.98.

1,1-Ethylenedioxy-2-(3-oxobutyl)cyclohexane (4b).—This compound, prepared by the method described in the previous experiment, was obtained in 84% yield as a colorless liquid, bp 96–101° (0.3 mm), which solidified upon standing to a white solid: mp 38–40°;[11] no uv absorption; ir ($CHCl_3$) 1710 cm^{-1} (CH_3CO-); nmr, ($CDCl_3$) δ 2.15 (s, 3, CH_3CO-), 2.45 (t, 2, J = 7 Hz, $-CH_2COCH_3$), and 3.96 ppm (s, 4, $-OCH_2CH_2O-$).

Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 68.19; H, 9.70.

4,4a,5,6,7,8-Hexahydronaphthalen-2(3*H*)-one (5b).—To a solution of crude keto ketal **4b**, prepared as described above from 6.00 g of isoxazole ketal **2b**, in 60 ml of methanol was added 6 ml of 4 *N* HCl and the resulting mixture was heated at reflux under nitrogen for 3 hr. The solution was cooled, poured into H_2O, and extracted with benzene. The benzene solutions were washed with saturated $NaHCO_3$ solution and saturated brine and dried ($MgSO_4$). Solvent removal followed by distillation gave 2.73 g (76%) of colorless liquid: bp 70–76° (0.25 mm) [lit.[5] bp 135–138° (15 mm)]; uv max (C_2H_5OH) 237 nm (ϵ 14,100) and 308–310 (60); ir ($CHCl_3$) 1719, 1675 (~1:4, $-CH_2CO-$ and C=CHCO–) and 1625 cm^{-1} (C=C); nmr ($CDCl_3$) δ 5.85 ppm (s, 0.8, =CHCO–).

In a separate preparation, the crude octalone mixture was treated with 2,4-dinitrophenylhydrazine to give 4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one 2,4-dinitrophenylhydrazone, mp 170–172° (lit.[5] mp 168–170°), in 78% yield after crystallization from ethyl acetate.

2,3,7,7a-Tetrahydroindan-5(6*H*)-one (5a).—Crude 1,1-ethylenedioxy-2-(3-oxobutyl)cyclopentane (**4a**), prepared from 5.0 g of isoxazole ketal **2a**, was treated with HCl in ethanol as described in the preceding experiment. The resulting colorless oil [2-(3-oxobutyl)cyclopentanone (**7**), ir ($CHCl_3$) 1748 (cyclopentanoe C=O) and 1710 cm^{-1} (CH_3CO-)] was dissolved in 50 ml of 2% methanolic NaOH. The resulting solution was heated at reflux under nitrogen for 3 hr, cooled, diluted with H_2O, and extracted with benzene. The benzene extracts were washed with saturated brine and dried ($MgSO_4$). Solvent removal and distillation gave 1.64 g (57%) of **5a** as a colorless liquid: bp 60–38° (0.25 mm) [lit.[5] bp 80–81° (0.4 mm)]; uv max (C_2H_5OH) 237 nm (ϵ 13,090) and 310 (60); ir ($CHCl_3$) 1750 (weak, cyclopentanone C=O) and 1670 cm^{-1} (C=CHO–); nmr ($CDCl_3$) δ 3.20 (q, ~0.1, J = 14 Hz, $CH_2C=O$) and 5.88 ppm (q, ~0.95, J = 1 Hz, =CHC=O); semicarbazone mp 217–219° (1-butanol) (lit.[5] mp 214–219°).

Registry No.—**2a**, 34803-84-4; **2b**, 34769-83-0; **4a**, 34803-85-5; **4b**, 34769-84-1; **5a**, 1489-28-7; **5b**, 1196-55-0.

Acknowledgment.—We would like to express our gratitude to the members of the Physical Chemistry Department of Hoffmann-La Roche for their assistance in this work.

Compounds Affecting the Central Nervous System. I. Tropane-2β,3β-diol Derivatives. A Reverse Ester of Cocaine

SOL J. DAUM,* CATHERINE M. MARTINI, RUDOLPH K. KULLNIG, AND ROBERT L. CLARKE

Sterling-Winthrop Research Institute, Rensselaer, New York 12144

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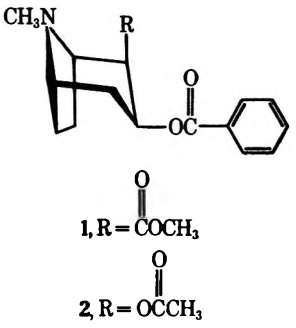
Investigation of all possible modifications of a known drug has been one of the approaches used to find better therapeutic agents. A drug having an ester group can typically be modified by formation of a "reverse ester." It appeared to us that the reverse ester **2** of cocaine (**1**)



might have an activity profile more interesting than that of cocaine.

The most convenient intermediate for the preparation of **2** was tropane-2β,3β-diol (**7**), a compound first prepared by Einhorn and Fischer[1] and later characterized fully by Davies, Jones, and Pinder.[2] Large-scale preparation of **7** has now been achieved by permanganate oxidation of ethyl nortrop-2-ene-8-carboxylate (**5**) followed by reduction with $LiAlH_4$.

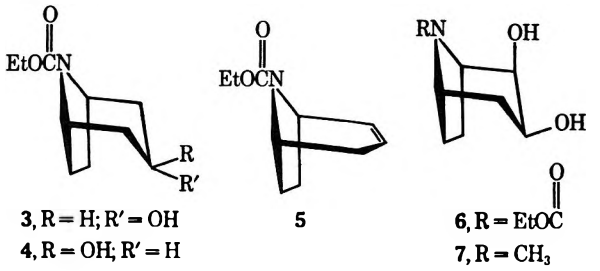
A method for the preparation of precursor **5** (see Experimental Section) involved dehydration of alcohol **3**. This alcohol, with its hydroxyl group in the axial position, was formed along with the equatorial epimer **4** (3:1 ratio) when ethyl 3-oxonortropane-8-carboxylate[3] was reduced catalytically (Pt in EtOH or HOAc) or by hydrides [$NaBH_4$ in MeOH or LiAl (*tert*-OBu)$_3$H in THF]. The role of the basic nitrogen in steric control of catalytic hydrogenation was illustrated here when tropan-3-one (basic N) was reduced catalytically (Pt in

(1) A. Einhorn and L. Fischer, *Chem. Ber.*, **26**, 2008 (1893).
(2) W. A. M. Davies, J. B. Jones, and A. R. Pinder, *J. Chem. Soc.*, 3504 (1960).
(3) B. J. Calvert and J. D. Hobson, *ibid.*, 2723 (1965).

TABLE I
CHEMICAL SHIFTS, PPM ($CDCl_3$)

Compd	H_1	H_5	H_2	H_3	NCH_3	$OCCH_3$	C_6H_5
8[a,b]	3.1	3.1	3.8	4.9	2.4		7.3–8.3
9[c,d]	3.4	3.1	5.0	3.9	2.3		7.5–8.1
10[a,b]	3.3	3.1	5.0–5.5	5.0–5.5	2.4		7.0–8.1
12[a,d]	3.1	3.1	3.7	4.8	2.3	2.0	
13[a,d,e] (HCl salt)	4.0	4.0	5.2	5.2	2.9	2.3, 2.0	
2[a,b]	3.2	3.2	5.2	5.2	2.3	2.1	7.1–8.3
11[c,f]	3.4	3.2	5.1	5.1	2.3	1.9	7.3–8.2

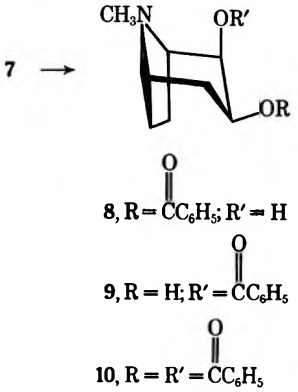
[a] 60 MHz. [b] 20% solution. [c] 100 MHz. [d] 10% solution. [e] 11.7 ppm (NH^+), vanishes in D_2O; 2.9 ppm (d, 3 H, NCH_3) $\xrightarrow{D_2O}$ 2.9 ppm (s, 3 H, NCH_3). [f] 7% solution.



EtOH or HOAc) to give tropan-3α-ol as the exclusive product.[4]

The next phase of the problem involved benzoylation at C-3. On the basis of the difference in rates for acylation of equatorial *vs.* axial hydroxyl groups,[5] the desired 3β-benzoate (equatorial) should predominate. However, House, *et al.*,[6] have shown that a tertiary nitrogen atom adjacent to an axial hydroxyl group can increase the rate of acylation of the latter through acyl transfer from an intermediate acyl ammonium ion.

When diol **7** was treated with 1 equiv of benzoic anhydride in pyridine and the reaction mixture was worked up in the customary manner, the 3β-benzoate **8**



was isolated as the major product, together with a small amount of the 2β-benzoate **9** and a very small amount of dibenzoate **10**.

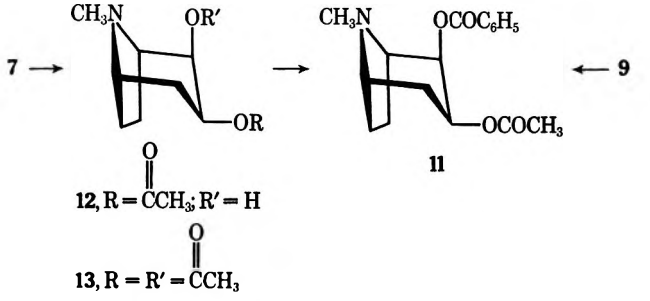
The 3β-benzoate **8** was readily identified by its physical properties. The infrared spectrum (CCl_4) of this 3-benzoate with its axial hydroxyl group at C-2 had a band at 3465 cm^{-1} that persisted even on dilution to a 0.001 *M* concentration, a characteristic of expected intramolecular hydrogen bonding with the nitrogen.[2]

Its nmr spectral signals are recorded in Table I and corroborating spin-decoupling experiments are described in the Experimental Section. Additionally, the C-1 and C-5 hydrogen signals were not separated. This symptom precludes the presence of a 2β-benzoyloxy group (see below and Table I).

The 2β-benzoate structure **9** was substantiated similarly. The infrared spectrum (CCl_4) had a band at 3610 cm^{-1}, which is characteristic of a nonbonded hydroxyl group.[2] When the benzoate is at the C-2 position, the C-1 hydrogen is deshielded and is resolved from the C-5 hydrogen (see Table I). Spin-decoupling experiments are described in the Experimental Section.

Acetylation of the 3-benzoate **8** then furnished the desired reverse ester **2**. It is evident that an axial C-2 acetoxyl group does not have a deshielding effect on the C-1 hydrogen, since the C-1 and C-5 hydrogens are unresolved. Thus it seems that the aromatic ring of compound **9** must be involved. Yet the 2β-carbomethoxy group of cocaine and the 2α-carbomethoxy group of pseudococaine both produce deshielding of the C-1 hydrogen; the C-1 and C-5 hydrogens are separated.[7]

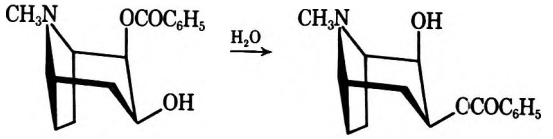
In like manner, acetylation of the 2-benzoate **9** furnished a sort of backwards reverse ester, diester **11**.



The nmr spectrum showed an unresolved multiplet for the hydrogens at C-2 and C-3, but showed resolved signals for the C-1 and C-5 hydrogens (Table I).

It is appropriate at this point to mention some observations related to the mechanism of benzoylation alluded to earlier. A sample of crude benzoylation product obtained after the usual work-up, which consisted of evaporation of the excess pyridine by warming *in vacuo* followed by addition of dilute aqueous base and extraction with ether, was converted directly to the monobenzoate monosilyl ether with *N*,*O*-bis(trimethylsilyl)acetamide. A glpc analysis indicated that the crude reaction mixture contained 3-monobenzoate **8**

(4) S. P. Findlay, *J. Org. Chem.*, **24**, 1540 (1959).
(5) L. F. Fieser and M. Fieser, "Steroids," Reinhold, New York, N. Y., 1959, p 216.
(6) H. O. House, H. C. Müller, C. G. Pitt, and P. P. Wickham, *J. Org. Chem.*, **28**, 2407 (1963).
(7) A. Sennema, L. Moat, A. J. Van Der Gugten, and H. C. Beyerman, *Recl. Trav. Chim. Pays-Bas*, **87**, 1027 (1968).



9 8

and 2-monobenzoate **9** in a 6:1 ratio. It was found that a sample of the 2β-monobenzoate **9** in acetone-d_6 or $CDCl_3$, when treated with a drop of D_2O for 15 hr, had an nmr spectrum compatible with a 75% conversion to the 3β-monobenzoate **8**. There was an 80% conversion after 40 hr (ratio of methyl peak heights).

Therefore it appeared as if the ratio of monobenzoates produced after work-up reflected an equilibrium mixture of compounds, and that perhaps the 2β-monobenzoate **9** is the kinetic product as would be expected on the basis of the difference in rates of acetylation due to acyl ammonium involvement. To test this assumption, a sample of diol **7** in pyridine was treated with 1 equiv of benzoic anhydride in the usual manner. At the end of the time allotted for benzoylation an excess of acetic anhydride was added. Work-up in the usual manner, including thick layer chromatography, afforded an approximately 3:1 mixture of acetate benzoates. The minor product corresponded to **2** while the major compound was **11**. It is quite evident from this experiment that usual work-up of the benzoylation reaction caused the 2β-monobenzoate, the kinetic product, to rearrange to the more stable 3β-monobenzoate.

When this tandem experiment of benzoylation and acetylation without intermediate work-up was done in $CHCl_3$ instead of pyridine, **2** was the major product.

Acetylation of the diol **7** with 1 equiv of acetic anhydride gave 50% of recovered starting material and about 15% of the 3β-monoacetate **12**. Substantiation of the structure of **12** was accomplished by the same series of spin-decoupling experiments used to identify the 3-monobenzoate **8**. The infrared spectrum (CCl_4) had a band at 3464 cm^{-1} (persisting even after dilution to a 0.001 *M* concentration) which corresponded to the band observed in the spectrum of compound **8**.

Although tlc analysis of the mother liquor showed a major spot corresponding to diacetate **13** together with a minor spot of monoacetate **12**, preparative tlc furnished this diacetate in only 10% yield.

The reverse ester **2** of cocaine (**1**) was devoid of stimulative activity.

Experimental Section[8]

Ethyl (±)-1α*H*,5α*H*-Nortrop-2-ene-8-carboxylate (5). Method A.—A solution of 313.5 ml (3.33 mol) of ethyl chloroformate in 650 ml of C_6H_6 was added in 1 hr to 136.8 g (1.11 mol) of tropidine in 750 ml of C_6H_6 which was heated at 70°.[9] The mixture was then heated under reflux for 3 hr, diluted with Et_2O, and washed with 2 *N* HCl. The solution was dried (Na_2SO_4) and concentrated to an oily residue which was distilled under reduced pressure, affording **5** (48.4 g, 74% yield), bp 83–92° (0.25–1.0 mm).

Method B.—To a solution of 231.8 g (2.12 mol) of nortropidine[10] in 2.8 l. of H_2O held at 15° was added dropwise with stirring 228 g (2.12 mol) of ethyl chloroformate followed by a solution of 42.2 g (1.05 mol) of NaOH in 300 ml of H_2O. Another 228 g (2.12 mol) of ethyl chloroformate followed by 42.2 g (1.05 mol) of NaOH in 300 ml of H_2O was added. The two-phase system was stirred for another 0.5 hr at 15°. Et_2O was added, the layers were separated, and the organic layer was washed (dilute HCl) and dried (Na_2SO_4). Evaporation of the solvents and distillation of the residue gave 369.8 g (96%) of **5**, bp 68–74° (0.30–0.34 mm). The analytical sample boiled at 70–72° (0.15–0.20 mm), $n^{25}D$ 1.4875.

Anal. Calcd for $C_{10}H_{15}NO_2$: C, 66.28; H, 8.33; N, 7.72. Found: C, 66.5; H, 8.5; N, 7.6.

Method C.—Ethyl 3α-hydroxy-1α*H*,5α*H*-nortropane-8-carboxylate (**3**) (43.8 g, 0.22 mol) in 150 ml of $SOCl_2$ was heated under reflux for 2 hr and let stand overnight. The excess $SOCl_2$ was removed and the residue was distilled under reduced pressure to give **5** (20.5 g, 51% yield), bp 87° (0.5 mm).

Mixture of Ethyl (±)-1α*H*,5α*H*-Nortropan-3ξ-ol-8-carboxylates (3 and 4).—A solution of 100 g (0.50 mol) of ethyl (±)-3-oxo-1α*H*,5α*H*-nortropane-8-carboxylate[3] in 100 ml of THF was added dropwise to a suspension of 151.2 g (0.5 mol + 20% excess) of Li(*tert*-OBu)$_3$AlH with stirring at room temperature. After 3 hr of stirring, a saturated Na_2SO_4 solution was added carefully together with Et_2O. The layers were separated and the Et_2O layer was washed (2 *N* HCl and saturated NaCl), dried (Na_2SO_4), and concentrated. The residue (109.5 g) was crystallized from Et_2O–pentane, affording 43.8 g of 3α-ol **3**, mp 73–74°. The mother liquor was chromatographed on 2 kg of silica gel. The least polar fraction, obtained by elution with 3:1 Et_2O–pentane, gave (from Et_2O) another 24 g (68% yield) of **3**, mp 73–74°, R_f 0.3 (silica gel, Et_2O). In a repeat run a polymorph was obtained with mp 88–89.5°.

Anal. Calcd for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60; N, 7.03. Found: C, 60.3; H, 8.5; N, 7.1.

The more polar fractions, eluted with Et_2O, gave 22.8 g (23%) of 3β-ol **4**, mp 63–64.5° (from Et_2O), R_f 0.17 (silica gel, Et_2O).

Anal. Calcd for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60; N, 7.03. Found: C, 60.0; H, 8.7; N, 7.0.

$NaBH_4$ in MeOH with work-up similar to that just described gave approximately the same isomer ratio. Low-pressure hydrogenation (PtO_2 in HOAc or EtOH) with monitoring by tlc appeared to give this same isomer ratio.

Preparation of (±)-1α*H*,5α*H*-Tropan-3α-ol from Ethyl (±)-3α-Hydroxy-1α*H*,5α*H*-nortropane-8-carboxylate (3).—A solution of 1.00 g of **3** in 30 ml of Et_2O was added to 0.5 g of $LiAlH_4$ in 100 ml of Et_2O with stirring. After 15 hr of reflux, 3 ml of H_2O was added and the mixture was filtered. Concentration of the filtrate afforded 0.74 g of (±)-1α*H*,5α*H*-tropan-3α-ol, the ir spectrum of which was identical with that of an authentic sample. Recrystallization from Et_2O–EtOH gave material of mp 63–64° (reported[4] mp 63–64°; the melting point of (±)-1α*H*,5α*H*-tropan-3β-ol is 109–110°[4]).

Ethyl (±)-2β,3β-Dihydroxy-1α*H*,5α*H*-nortropane-8-carboxylate (6).—A solution of 91 g of $KMnO_4$ and 91 g of $MgSO_4$ in 1.5 l. of H_2O was added to a solution of 100 g of ethyl (±)-1α*H*,5α*H*-nortrop-2-ene-8-carboxylate (**5**) in 4 l. of 95% EtOH over a period of 1.5 hr while the temperature was maintained at −5 to −2°. The mixture was stirred for 3 min. A solution of 62 g of sodium metabisulfite in 185 ml of H_2O was added over 5 min. The mix was filtered through Sulka Flox and the filtrate was concentrated *in vacuo*.

The residue was dissolved in 600 ml of $CHCl_3$ and the solution was washed with 100 ml of H_2O, dried over K_2CO_3, and treated with Darco G-60. The $CHCl_3$ was evaporated and the residue was dissolved in 150 ml of Et_2O. This solution was cooled and filtered. The product weighed 55.6 g (47%), mp 88–89° after drying at 40° *in vacuo*. No more product could be obtained from the filtrate. The analytical sample, recrystallized from Et_2O, melted at 93–94°.

Anal. Calcd for $C_{10}H_{17}NO_4$: C, 55.80; H, 7.96; N, 6.51. Found: C, 55.8; H, 7.9; N, 6.4.

(8) All melting points were determined in capillary tubes and are uncorrected. The ir spectra were recorded on a Perkin-Elmer Model 21 spectrophotometer except for the high-dilution measurements, which were done with a Beckman IR-7 instrument. Nmr spectra were measured in $CDCl_3$ with a Varian A-60 spectrometer using Me_4Si as an internal reference. Spin-decoupling experiments were done with a Varian HA-100 instrument using a Hewlett-Packard audiooscillator 4204A. The mass spectrum reported was measured with a Jeolco JMS-1-OSC mass spectrograph. Column chromatography was done with 100–200 mesh silica gel obtained from the Davison Co., Baltimore, Md. Preparative tlc was done using 20 × 40-cm plates coated with a 1-mm thickness of Brinckmann PF 254 silica gel. The analytical plates were coated with the same gel.

(9) Method of E. Jucker and A. Lindenmann, Swiss Patent 442,318 (1967).

(10) R. Willstätter and F. Iglauer, *Chem. Ber.*, **33**, 1640 (1900).

(±)-1αH,5αH-Tropane-2β,3β-diol (7).[1,2]—A solution of 2.15 g (0.01 mol) of diol 6 in 30 ml of THF was added to 100 ml of THF containing 1 g of $LiAlH_4$. The solution was heated under reflux for 15 hr. (It was found later that reflux for 1 hr was sufficient.) H_2O was carefully added and the mixture was extracted with a 2:1 mixture of $CHCl_3$–EtOH. The organic layer was dried (Na_2SO_4) and concentrated to afford 1.45 g of residue. The residue crystallized from a small volume of Et_2O to give 1 g of diol 7, mp 104–108°. Concentration of the filtrate gave another 0.18 g, mp 104–108° (77% yield).

The analytical sample, obtained from a similar experiment, melted at 105–107°.

Anal. Calcd for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 61.0; H, 9.6; N, 8.8.

Benzoylation of (±)-1αH,5αH-Tropane-2β-3β-diol (7).—A solution of 8.9 g (0.04 mol) of benzoic anhydride in 62 ml of pyridine was treated with 6.2 g (0.04 mol) of the diol 7 all at once and the resulting solution was heated on a steam bath for 2 hr. The excess pyridine was removed by heating *in vacuo*. Et_2O and dilute NaOH were added to the residue and the layers were separated. The Et_2O was washed (saturated NaCl), dried (Na_2SO_4), and concentrated *in vacuo* to afford 7 g of oily residue which crystallized. Recrystallization from Et_2O afforded 3.57 g of impure (±)-1αH,5αH-tropane-2β,3β-diol 3-benzoate (8), mp 92–95°. A second crop of crude 3-benzoate (0.36 g, mp 90–91°) was also obtained. The mother liquor was put on ten silica gel thick-layer plates which were developed with 25:24:1 Et_2O–pentane–*i*-$PrNH_2$. Elution of the more polar uv-absorbing band with Et_2O and recrystallization of it from Et_2O afforded another 1.0 g of monobenzoate 8, mp 93–95° (46% total). Recrystallization of the total 8 from Et_2O gave 4.3 g, mp 93–94°. The filtrate will be referred to below as mother liquor A.

Further recrystallization of 8 in a similar experiment gave an analytical sample, mp 95–97°, ir (CCl_4, 0.05–0.001 *M*) 3465 and 1722 cm^{-1}.

In a spin-decoupling experiment on 8, irradiation of the methylene region caused the signal of the furthest downfield aliphatic hydrogen (–$CHOCOC_6H_5$, 4.9 ppm) to be simplified from a multiplet to a doublet [*J* = 3.5 Hz, H-2(e), H-3(a) coupling]. There was no change in the character of the H-2 signal. Irradiation of the H-2 triplet at 3.8 ppm collapsed the H-3 multiplet at 4.9 ppm to a quartet having *J* = 7 and 10 Hz [H-3(a), H-4(e) and H-3(a), H-4(a) coupling, respectively]. Irradiation of the H-3 multiplet at 4.9 ppm collapsed the H-2 triplet to a doublet [*J* = 3.5 Hz, H-1(e), H-2(e)]. There was no change in the character of the H-1 signal.

Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.95; H, 7.33; N, 5.36. Found: C, 69.1; H, 7.4; N, 5.3.

The cyclohexanesulfamate salt of 8, prepared in acetone, melted at 205–207° dec (from MeOH).

Anal. Calcd for $C_{15}H_{19}NO_3 \cdot C_6H_{13}NO_3S$: C, 57.24; H, 7.33; S, 7.28. Found: C, 57.4; H, 7.5; S, 7.2.

Partial concentration of mother liquor A caused precipitation of 0.1 g of (±)-1αH,5αH-tropane-2β,3β-diol 2-benzoate (9), mp 128–132°. Glpc analysis of the trimethylsilyl ether derivative prepared with *N*,*O*-bis(trimethylsilyl)acetamide (on a methyl silicone gum column, OV-1) indicated that this sample contained 7% of the 3-benzoate 8. An analytical sample, prepared by recrystallization from Et_2O in an identical experiment, melted at 136.5–137.5°: ir (CCl_4, 0.05–0.001 *M*) 3610 and 1726 cm^{-1}.

In a spin-decoupling experiment, irradiation of the H-3 signal at 3.9 ppm collapsed the triplet at 5.0 ppm to a doublet [*J* = 3 Hz, H-1(e), H-2(e)]. Irradiation of the H-2 signal at 5.0 ppm simplified the H-3 multiplet at 3.9 ppm and the H-1 multiplet at 3.4 ppm. Irradiation of the H-1 signal at 3.4 ppm collapsed the H-2 signal at 5.0 ppm to a doublet [*J* = 4.2 Hz, H-2(e), H-3(a)]. Irradiation of the methylene region simplified the H-3 signal at 3.9 ppm.

Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.95; H, 7.33; N, 5.36. Found: C, 69.0; H, 7.3; N, 5.3.

In an identical experiment a portion of the crude reaction mixture was silylated and put through an OV-1 glpc column as described above. The process indicated a 6:1 ratio of 3-monobenzoate 8 to 2-monobenzoate 9.

The partially concentrated mother liquor A, from which 9 was removed, was subjected to preparative plate chromatography. The less polar uv-absorbing band afforded 0.60 g of (±)-1αH,5αH-tropane-2β,3β-diol dibenzoate (10), mp 92–93° from hexane–Et_2O. This product was analyzed as its hydrochloride salt, mp 273° dec (from acetone).

Anal. Calcd for $C_{22}H_{23}NO_4 \cdot HCl$: C, 65.73; H, 6.02; Cl, 8.83. Found: C, 65.6; H, 6.0; Cl, 8.9.

Equilibration of 2-Monobenzoate 9 to a Mixture of 2- and 3-Monobenzoates 8 and 9.—A 5% solution of 1αH,5αH-tropane-2β,3β-diol 2-benzoate (9) in acetone-d_6 in an nmr tube was treated with a drop of D_2O. The solution was scanned at 0, 15, and 40 hr and after 6 days (Table II).

TABLE II

Compd	0 hr	15 hr	40 hr	6 days
	Aromatic peak height			
2-Benzoate 9	100	20	23	15
3-Benzoate 8	0	80	77	85
	Methyl peak height			
2-Benzoate 9	100	25	20	21
3-Benzoate 8	0	75	80	79

This conversion was also observed in $CDCl_3$ with a drop of D_2O.

Acetylation of (±)-1αH,5αH-Tropane-2β,3β-diol (7).—A solution of 4 g (0.025 mol) of diol 7 in 25 ml of pyridine was treated with 2.54 g (0.25 mol) of Ac_2O at room temperature overnight. The excess pyridine was removed by heating *in vacuo*. Dilute NH_4OH and Et_2O were added. The layers were separated and the Et_2O was washed (saturated NaCl), dried (Na_2SO_4), and concentrated to afford 2.7 g of oily residue A. The aqueous layer was extracted with a mixture of $CHCl_3$–EtOH (2:1) to give 2.02 g (50%) of starting glycol 7.

Residue A crystallized in Et_2O–pentane to give 0.76 g (15%) of (±)-1αH,5αH-tropane-2β,3β-diol 3-acetate (12), mp 85–88°. Tlc analysis of the mother liquor (silica gel, Et_2O–*i*-$PrNH_2$ 98:2) showed a large spot at R_f 0.45 corresponding to diacetate 13 and a small spot at R_f 0.40 corresponding to 3-monoacetate 12.

The recovered glycol 7 was reprocessed with Ac_2O to give another 0.22 g (9%) of 3-monoacetate 12, mp 84–86°. Recrystallization from Et_2O gave the analytical sample, mp 85–86.5°, ir (CCl_4, 0.05–0.001 *M*) 3464 and 1744 cm^{-1}.

Anal. Calcd for $C_{10}H_{17}NO_3$: C, 60.21; H, 8.63; N, 7.02. Found: C, 60.2; H, 8.6; N, 7.0.

In a spin-decoupling study on 12, irradiation of the H-2 signal at 3.7 ppm collapsed the H-3 signal at 4.8 ppm to a quartet [*J* = 10 and 8 Hz, H-3(a), H-4(a) and H-3(a), H-4(e), respectively]. Irradiation of the H-3 signal at 4.8 ppm collapsed the H-2 signal at 3.7 ppm to a doublet (*J* = 3.5 Hz; H-1, H-2). Irradiation of the methylene region collapsed the H-3 signal at 4.8 ppm to a doublet (*J* = 3.5 Hz, H-2, H-3). The signals of the C-1 and C-5 hydrogens were not resolved.

The total mother liquor residues (2.3 g) from isolation of the 3-monoacetate were further acetylated with 10 ml of Ac_2O and 15 ml of C_5H_5N overnight at room temperature. Work-up as above afforded 1.03 g of oily (±)-1αH,5αH-tropane-2β,3β-diol diacetate (13). Chromatography on four silica gel preparative plates (Camag DSFO coating) using two passes of 97:3 Et_2O–*i*-$PrNH_2$ gave a principal band containing 0.62 g (10%) of oily diacetate 13. Its HCl salt melted at 253° dec (from acetone).

Anal. Calcd for $C_{12}H_{19}NO_4 \cdot HCl$: C, 51.87; H, 7.27; Cl, 12.78. Found: C, 51.8; H, 7.3; Cl 12.7.

(±)-1αH,5αH-Tropane-2β,3β-diol 2-Acetate 3-Benzoate (2).—A solution of 10 g (0.038 mol) of 3-monobenzoate 8 in 100 ml of C_5H_5N was treated with 50 ml of Ac_2O and heated on the steam bath for 4.5 hr. Excess reagents were removed by warming *in vacuo*. Dilute NaOH and Et_2O were added. The layers were separated and the Et_2O layer was washed (saturated NaCl), dried (Na_2SO_4), and concentrated to give 11.5 g of oil that crystallized when fresh ether was added. Filtration afforded 6.3 g of 2, mp 101.5–103°. A second crop of 3.5 g, mp 99–101.5°, was obtained upon concentration of the mother liquor (85% yield).

The analytical sample from an identical experiment melted at 101.5–103.5° (from Et_2O); R_f 0.21 (silica gel; Et_2O–pentane–*i*-$PrNH_2$ 50:47:3).

Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.30; H, 6.98; N, 4.61. Found: C, 67.5; H, 7.1; N, 4.6.

The cyclohexanesulfamate salt of 2, prepared in and recrystallized from acetone, melted at 159–165°.

Anal. Calcd for $C_{17}H_{21}NO_4 \cdot C_6H_{13}NO_3S$: C, 57.25; H, 7.11; S, 6.65. Found: C, 57.2; H, 7.2; S, 6.3.

(±)-1α*H*,5α*H*-Tropane-2β,3β-diol 2-Benzoate 3-Acetate (11). Method A (from the 3-Acetate).—A solution of 0.80 g (4 mmol) of (±)-1α*H*,5α*H*-tropane-2β,3β-diol 3-acetate (**12**) in 5 ml of C_5H_5N was treated with 0.91 g (4 mmol) of benzoic anhydride at room temperature overnight. The usual work-up afforded 1.1 g of oily residue. Chromatography on four silica preparative plates using 50:47:3 Et_2O–pentane–*i*-$PrNH_2$ (R_f 0.36) followed by recrystallization from hexane gave 0.50 g of poorly formed crystals of 2-benzoate 3-acetate **11**, mp 91–95°. From wet ether, **11** formed a hydrate as beautiful, massive prisms which reverted to an oil when dried *in vacuo*. The air-dried prisms melted at 90–102° with bubbling and their nmr spectrum showed an excess of two hydrogens, presumably from H_2O. The mass spectrum gave a molecular ion peak at *m/e* 303 with abundant ions at *m/e* 244 ($M^+ - OAc$), 198 ($M^+ - OBz$), and 105 (OBz), and very intense peaks at *m/e* 17 (OH) and 18 (H_2O).

Anal. Calcd for $C_{17}H_{21}NO_4 \cdot H_2O$: C, 63.53; H, 7.22; N, 4.35. Found: C, 63.5; H, 7.3; N, 4.2.

Method B (from the 2-Benzoate).—A solution of 0.10 g (0.4 mmol) of (±)-1α*H*,5α*H*-tropane-2β,3β-diol 2-benzoate (**9**) in 5 ml of C_5H_5N and 2.5 ml of Ac_2O was heated on the steam bath for 2 hr. The usual work-up afforded 0.12 g of **11** as an oil that crystallized from hexane, mp 96–99°. A sample recrystallized from wet ether melted at 92–102° (bubbling). The nmr and ir spectral curves and the tlc R_f value were all identical with those of **11** prepared by method A. A mixture melting point was undepressed.

Method C (from the Diol).—A solution of 0.48 g (3.1 mmol) of diol **7** in 20 ml of C_5H_5N was treated with 0.72 g (3 mmol) of benzoic anhydride and the solution was heated on a steam bath for 2.5 hr. Ac_2O (4 ml) was added and the mixture was heated for 2 hr more. The usual work-up afforded 0.72 g of an oily residue. Tlc analysis (silica gel; Et_2O–pentane–*i*-$PrNH_2$ 50:47:3) showed a major spot with R_f 0.36 and a minor spot with R_f 0.21. Chromatography on four preparative plates using the same solvent system gave 0.50 g (54%) of the R_f 0.36 oil which crystallized as prisms from wet Et_2O. It was found to be identical with **11** by means of nmr, ir, mixture melting point, and tlc.

The band of R_f 0.21 material furnished 0.17 g of oil which crystallized from Et_2O and proved identical with the 2-acetate 3-benzoate **2** by the usual criteria.

When the experiment just described was repeated using $CHCl_3$ as the solvent instead of pyridine, tlc analysis of the product indicated that **2** was the major product.

Registry No.—**2**, 33780-46-0; 2 cyclohexanesulfamate, 33780-47-1; **3**, 33780-48-2; **4**, 33780-49-3; **5**, 33780-50-6; **6**, 33780-51-7; **7**, 33780-52-8; **8**, 33886-15-6; **8** cyclohexanesulfamate, 33886-16-7; **9**, 33872-63-8; **10**, 33780-53-9; **10** HCl, 33780-54-0; **11**, 33780-55-1; **12**, 33780-56-2; **13** HCl, 33780-57-3.

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A Simple Synthesis of 4-Hydroxycyclohexanone

PHILLIP RADLICK*[1] AND HERSCHEL T. CRAWFORD

Department of Chemistry, University of California, Riverside, California 92502

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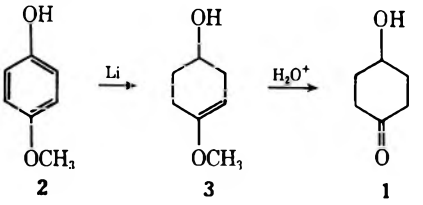
Recently in our laboratory we have found it desirable to prepare synthetically useful quantities of 4-hydroxycyclohexanone (**1**). We therefore had need of a simple high-yielding route to this compound. Jones and Sondheimer[2] developed a route, later modified by Trager,[3] which required the selective oxidation of a protected 1,4-cyclohexanediol. This multistep synthesis gave only a 25% yield based upon the starting diol and was not suited to our purpose.

Fried[4] has shown that phenols can be reduced under Birch conditions provided that high enough concentrations of Li in ammonia are used. The high concentrations of Li are required presumably because of the high potential barrier to formation of the dianion radical, which must come from the initially produced phenoxide anion.

When *p*-methoxyphenol (**2**) was subjected to reduction with lithium in ammonia (3.6 *M* Li), there was isolated after work-up the crude enol ether **3** which was directly hydrolyzed in 0.1 *N* HCl to afford **1** in 89% yield after distillation. The mole ratio of lithium to the phenol appears to be critical. When the mole



2 **3** **1**

ratio was reduced from 11:1 to 6:1 (both still 3.6 *M* in Li), considerable quantities of 1,4-cyclohexanedione are formed. This high-yielding simple route can be easily adapted to large scale reactions and renders this valuable synthetic intermediate (**1**) readily available.

Experimental Section

4-Hydroxycyclohexanone (1).—Liquid ammonia (100 ml) after distillation through a KOH tower was collected with stirring in a thoroughly dry three-neck flask at −78°. The NH_3 inlet was replaced by a N_2 inlet and the remainder of the reaction was run under nitrogen. The reaction flask was allowed to warm to −50° and Li (2.5 g, 0.36 g-atom) was added all at once. After this, *p*-methoxyphenol (4.0 g, 32.2 mmol) in anhydrous ether (25 ml) was added to the ammonia solution over a period of 5 min. The reaction mixture was stirred at −50° for 45 min, absolute ethanol (1.9 ml, 32 mmol) was added, and stirring was continued for an additional ½ hr. Absolute ethanol (4 ml) was added at 30-min intervals until the blue color was discharged. A total of 25 ml of ethanol was used.

After the ammonia had been evaporated, saturated NH_4Cl (200 ml) was added to the residue, and the resulting brown solution was cooled in an ice bath. Concentrated HCl was added dropwise until the pH of the solution was approximately 1. This acidic solution was then heated to 50° for 1 hr to effect hydrolysis of the enol ether **3**. The cooled aqueous solution was extracted with $CHCl_3$ (8 × 50 ml), saturated with NaCl, and then reextracted. After drying and removal of solvent, 4.96 g of a brown oil was isolated. Distillation at 93° (0.3 mm) yielded 3.25 g (89%) of 4-hydroxycyclohexanone: M^+ 114; ir (neat) 5.95 (C=O), 2.98 μ (OH); nmr ($CDCl_3$–TMS) δ 4.16 (m, α to hydroxyl), 1.77–2.84 (m, ring CH_2 protons); 2,4-dinitrophenylhydrazone mp 152–153° (lit.[1] mp 150–151°).

Registry No.—**1**, 13482-22-9.

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Formation of Cyclohexane vs. Tetrahydropyran Derivatives on Reaction of Glutaraldehyde with Nitroalkanes[1,2]

FRIEDER W. LICHTENTHALER* AND DIETRICH FLEISCHER

Institut für Organische Chemie, Technische Hochschule Darmstadt, 61 Darmstadt, Germany

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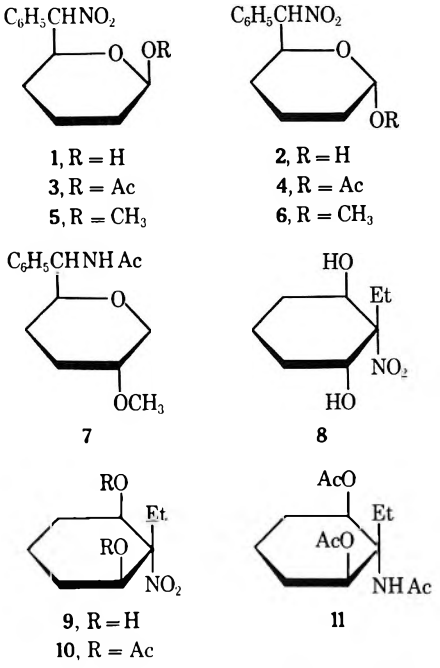
Considerable evidence has accumulated that the base-catalyzed addition of nitroalkanes to dialdehydes proceeds *via* cyclization to yield carbocyclic nitrodiols,[3] although these educts may give rise to a variety of other reactions. Examples are the Cannizzaro reaction which takes place in the case of glyoxyl[4] and naphthalene-1,8-dicarboxaldehyde,[5] and the addition of one nitroalkane per aldehyde group in glyoxal[6,7] and succinic dialdehyde.[7] Monoaddition of a nitromethylene compound to only one of the carbonyl functions has been observed in the reaction of *o*-phthalaldehyde with nitromethane which yields carbocyclic products under the common conditions,[8,9] yet can give a 1-hydroxy-3-nitromethylphthalane when performed in anhydrous nitromethane.[9] Inasmuch as three products differing in melting points have been described for the reaction of glutaraldehyde with phenylnitromethane[10-12] and, since structural assignments were only tentative, we re-examined this reaction in order to determine whether, and if so under which conditions, acyclic diaddition products or products resulting from usual dialdehyde–nitroalkane cyclization or monoaddition products may be formed.

Surprisingly, under a variety of conditions which ranged in pH from 7 to 13, the only products detectable by tlc from the reaction of phenylnitromethane with glutaraldehyde turned out to be the C-2-epimeric 2-hydroxy-6-(α-nitrobenzyl)tetrahydropyrans **1** and **2**, from stabilization of the initial monoadduct by internal hemiacetalization. The cis (**1**) and trans isomers (**2**) could be isolated as crystalline mixtures in yields of up to 50%. The cis/trans ratio varied from 2:1 to 1:3, depending on the mode of isolation and the number of recrystallizations. As a consequence, melting points vary between 120 and 140°, hence easily explaining the discrepancies observed previously. By chromatography on silica gel, the cis isomer **1**, mp 143–145°, was separated in 24% yield. It is stable in neutral solutions of ethanol or dimethyl sulfoxide, but becomes spontaneously equilibrated with **2** on addition of traces of acid (*i.e.*, trifluoroacetic acid) or base (sodium methoxide). Treatment of the epimeric mixture of **1** and **2** or the cis isomer **1** with 2,4-dinitrophenylhydrazine afforded a crystalline product in low yield (20%), which analyzed correctly for a 2,4-dinitrophenylhydrazone of 5-hydroxy-6-nitro-6-phenylhexanal, of which the structure is as yet tentative, since cyclic phenylhydrazino forms cannot be excluded unequivocally by ir or nmr. Acid-catalyzed reactions of the epimers **1** and **2** with acetic anhydride and methanol yielded the corresponding *O*-acetyl **3** and **4** and *O*-methyl derivatives (**5** and **6**) in the form of cis–trans mixtures, in which, as expected from the anomeric effect,[13] the trans isomers predominated. Of these, compounds **4**, **5**, and **6** were obtained in a form free of their anomers. Whereas **1** and **2** are resistant toward hydrogenation with the usual catalysts under normal pressure, more forcing conditions (Raney nickel in water at 100 atm H_2 and 50°) yielded benzylamine isolable in low yield and characterized as its hydrochloride. The methoxy derivative, however, could readily be hydrogenated over Raney nickel to give after acetylation *trans*-2-methoxy-6-(α-acetamidobenzyltetrahydropyran (**7**) in 57% yield.

Structures of compounds **1**–**7** and their configurations at the anomeric center clearly followed from the nmr data. In DMSO-d_6 the cis isomer **1** showed, aside from an OH doublet at τ 3.36, only one distinct doublet for the benzylic proton (H-7) at τ 4.26 with $J_{6,7}$ = 10 Hz, whereas two are observed in the anomeric mixtures of **1** and **2**, the signal for the trans compound expectedly[14] appearing at higher field (τ 4.40). Similar results with respect to the chemical shift of H-7 are ob-



(1) Last communication of the series "Nitromethane Condensation with Dialdehydes." Paper XIX: F. W. Lichtenthaler and G. Bambach, *J. Org. Chem.*, **37**, 1621 (1972).

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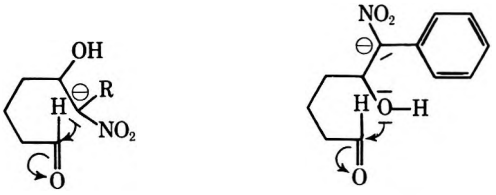
tained for the epimeric mixtures **3** and **4** and **5** and **6**. The anomeric proton in the trans series (*i.e.*, **2**, **4**, and **7**) appears as a narrow multiplet with a half-width of 6 Hz, as anticipated for ee and ea couplings. In the cis isomers, H-2 appears at higher field, the expected quartet overlapping with the broad multiplet obtained for H-6 in each case. Additional configurational evidence can be derived from the chemical shifts of the acetoxy resonances at τ 7.91 for equatorial (**3**) and 7.84 for axial orientation (**4**), which is in accord with the acetyl resonance rule.[15]

Two main components in an approximate 2:1 ratio, together with traces of other substances, can be detected by tlc in the reaction mixture of glutaraldehyde with 1-nitropropane. The major product (36% yield) has been characterized and shown to be 1-nitro-1*r*-ethylcyclohexane-2*c*,6*t*-diol (**8**) by nmr and derivatization.[10] The other component (**9**) has now been isolated in low yield due to high-loss fractional crystallizations. Acetylation of **9** gave the di-*O*-acetate **10**, whereas hydrogenation of **9** followed by acetylation yielded the triacetate **11**. The nmr data of these compounds clearly established them to be configurational isomers of **8** and its corresponding derivatives rather than products of other conceivable structures, *i.e.*, those of the lactol type (**1**, Et instead of C_6H_5). The identical steric arrangement of H-2 and H-6 in **10** and **11** readily evolved from their identical chemical shifts and splitting patterns, thus proving a meso configuration for **9** and its ensuing products. The configuration at the ethyl branch pictured in the formula was derived from steric reasoning on the basis of molecular models and hence is tentative. In contrast to **8**, compound **9** is rather unstable, showing a distinct tendency to epimerize to **8** on melting or on short heating in aqueous solution to afford mixtures of **8** and **9** ranging in their ratios from 2:1 to 1:1.

Thus, the base-catalyzed reaction of 1-nitropropane with glutaraldehyde, yields carbocyclic products exclusively by a normal type dialdehyde–nitroalkane cyclization, while phenylnitromethane, also exclusively, gives heterocyclic products by monoaddition to one of the aldehyde functions and subsequent internal hemiacetalization. These differences may be rationalized by the concept that when R is hydrogen or alkyl the carbanion nucleophilicity in the *aci*-nitro anion **12**,



12 **13**

R = H, alkyl, CH_2OH, COOR

formed initially, is high enough to exclusively effect attack on the second aldehyde function. With hydroxymethyl or even alkoxycarbonyl residues at the nitromethyl carbon, the course of the reaction is still the same, though probably not as exclusive, as evidenced by a number of dialdehyde cyclizations with nitroethanol[16,17] and alkyl nitroacetate.[17,18] With R = C_6H_5, however, the nucleophilicity of carbanion **13**, whose electron pair is delocalized by the nitro group and the aromatic ring, is sufficiently reduced so as to allow exclusive internal hemiacetalization to tetrahydropyran derivatives.[19] From this it may be concluded that other nitromethylene compounds, whose reactions, with didaldehydes have not yet been studied, *i.e.*, nitroacetone or ω-nitroacetophenone, conceivably will yield both carbocyclic products *via* **12** and heterocyclic products *via* **13**.

Experimental Section[20]

2-Hydroxy-6-(α-nitrobenzyl)tetrahydropyran. 1:1 Mixture of Cis and Trans Isomers 1 and 2.—Phenylnitromethane (27.4 g, 0.2 mol), 25% aqueous glutaraldehyde (80 ml, 0.2 mol), methanol (100 ml), and 1 *N* sodium methoxide (5 ml) were mixed to give a solution of pH 7.0–7.5. After 3 hr at ambient temperature, the felted needles, which had separated, were filtered off and recrystallized from ethanol to give 20.2 g (50%) of **1** and **2** as an approximate 1:1 mixture (nmr): mp 123–125°; ir ($CHCl_3$) 3590 and 3410 (OH), 1555 and 1350 cm^{-1} (NO_2); nmr (DMSO-d_6), τ 2.51 (m, 5, C_6H_5), 4.26 (cis isomer **1**), and 4.40 (trans isomer **2**) (d, 0.5, $J_{6,7}$ = 10 Hz, H-7), 4.82 (narrow m, 0.5, H-2 of **1**), ~5.5 (broad m, 1.5, H-2 of **2** and H-6), ~8.5 [m, 6, $(CH_2)_3$].

Anal. Calcd for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37; N 5.90. Found: C, 60.90; H, 6.36; N, 5.94.

Further recrystallizations from ethanol or ethyl acetate gave higher melting mixtures of **1** and **2** (*i.e.*, mp 129–130°, 133–135°[21]) with ratios ranging between 3:1 and 1:2.

Isolation of Cis Isomer 1.—A solution of 25% aqueous glutaraldehyde (20 ml, 0.05 mol) and phenylnitromethane (6.9 g, 0.05 mol) in 100 ml of methanol–water (1:1) was brought to pH 11–11.5 by the dropwise addition of 1 *N* sodium hydroxide with stirring. A precipitate, separating after 1 hr at ambient temperature, redissolved on further stirring. After another 3 hr, the solution was freed from methanol by evaporation, subsequently acidified with 2 *N* HCl to about pH 4, and extracted with three 100-ml portions of chloroform. Evaporation of the combined extracts left a yellow oil, containing **1** and **2** in an approximate 2:1 ratio (nmr), which was purified by chromatography on silica gel with chloroform. The main fraction afforded a yellowish sirup on evaporation, which crystallized on trituration with ethanol. Recrystallization from the same solvent gave 2.9 g (24%) of **1** as colorless needles: mp 142–144°; ir ($CHCl_3$), 3590 (OH), 1545, and 1350 cm^{-1} (NO_2); nmr (DMSO-d_6) τ 3.36 (d, 1, $J_{2,OH}$ = 6 Hz, OH), 4.26 (d, 1, $J_{6,7}$ = 10 Hz, H-7), 5.40 (broad m, 2, H-2 and H-6).

Anal. Calcd for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37; N, 5.90. Found: C, 60.79; H, 6.30; N, 5.84.

On addition of trifluoroacetic acid (2 drops) to the above solution of **4** in DMSO-d_6, not only the OH doublet at τ 3.36 disappeared, but the nmr signals of the trans isomer **2** (τ 4.40 and 4.82) emerged, their intensity indicating a 1:1 mixture of **1** and **2**.

Treatment of cis isomer **1** or the epimeric mixture of **1** and **2** with dinitrophenylhydrazine under usual conditions,[22] followed by two recrystallizations of the product that had separated from ethanol, afforded yellow crystals, mp 126° in low yield (20%), that analyzed correctly for a 2,4-dinitrophenylhydrazone of 5-hydroxy-6-nitro-6-phenylhexanal.

2-Acetoxy-6-(α-nitrobenzyl)tetrahydropyran (3 and 4).—To a

(15) F. W. Lichtenthaler and P. Emig, *Carbohyd. Res.*, **7**, 121 (1968); F. W. Lichtenthaler, G. Bambach, and P. Emig, *Chem. Ber.*, **102**, 994 (1969).

(16) F. W. Lichtenthaler and H. Leinert, *Chem. Ber.*, **101**, 1815 (1968).

(17) S. Zen and A. Nishikai, *Bull. Chem. Soc. Jap.*, **42**, 1761 (1969).

(18) S. Zen, Y. Takeda, A. Yasuda, and S. Umezawa, *ibid.*, **40**, 431 (1967); H. Yanagisawa, M. Kinoshita, and S. Umezawa, *ibid.*, **42**, 1719 (1969).

(19) Although it cannot be excluded that steric factors are codetermining in the reaction leading to **13**, inspection of molecular models indicates that they are not of primary importance.

(20) Melting points were determined in a Bock Monoskop apparatus and are uncorrected. Nmr spectra were obtained on a Varian A-60 spectrometer with tetramethylsilane as a internal standard, the chemical shifts being given in τ parts per million.

(21) Attempts to again isolate a product of mp 99°, as described previously,[11] were unsuccessful; presumably a free *aci*-nitro form of **1** had been obtained.

(22) L. F. Fieser in "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, p 330.

cooled solution of 62.0 g of the anomeric mixture of 1 and 2 (as obtained above) in acetic anhydride (10 ml) was added 2 drops of concentrated H_2SO_4. After 1 hr at room temperature the solution was stirred into ice–water and the precipitate formed was recrystallized from ethanol to afford 1.0 g (42%) of trans isomer 4: mp 143–145°; nmr ($CDCl_3$) τ 2.67 (s, 5, C_6H_5), 3.78 (m, 1, H-2), 4.66 (d, 1, $J_{6,7}$ = 10 Hz, H-7), 5.15 (broad m, 1, H-6), 7.84 (s, 3, OAc), 8.22 (m, 4, CH_2 at C-3 and C-5), 8.70 (m, 2, CH_2 at C-3); nmr (DMSO-d_6) τ 4.00 (m, 1, H-2) and 4.40 (d, 1, $J_{6,7}$ = 10 Hz).

Anal. Calcd for $C_{14}H_{17}NO_5$: C, 60.20; H, 6.14; N, 5.02. Found: C, 60.36; H, 6.37; N, 4.93.

The ethanolic mother liquors, remaining after the isolation of 4, yielded on evaporation and five recrystallizations a product, melting at 235°, which, on the basis of the intensities of the acetoxy resonances in $CDCl_3$ (7.84 for 4 and 7.91 for 3) contained approximately 80% of the cis isomer 3.

2-Methoxy-6-(α-nitrobenzyl)tetrahydropyran (5 and 6).—To 1.0 g of an anomeric mixture of 1 and 2 (*cf.* above) in 10 ml of methanol was added 0.5 g of a strongly acidic ion exchange resin, and the solution was refluxed for 12 hr. Removal of the resin, evaporation to dryness, and filtration of the crystalline residue with a little cold methanol afforded 750 mg (68%) of a product, composed of 5 and 6 in a 1:4 mixture (nmr). Separation was achieved by elution of the mixture from a silica gel column (2.5 × 60 cm) with chloroform. Examination of the 10-ml samples collected, by tlc [R_f values 0.73 (6) and 0.50 (5) in chloroform], evaporation of the appropriate fractions, and recrystallization, in both cases, from isopropyl alcohol afforded 520 mg (70%) of the trans isomer 6 as felted needles, mp 105°, and 140 mg (19%) of the cis compound 5 as needles: mp 125–127°; nmr ($CDCl_3$) for 6, τ 2.55 (m, 5, C_6H_5), 4.63 (d, 1, $J_{6,7}$ = 10 Hz, H-7), 5.25 (broad m, 2, H-2 and H-6), 6.59 (s, 3, OCH_3), 8.32 (m, 4, CH_2 at C-3 and C-5), 8.80 (m, 2, CH_2 at C-4). The cis isomer 5 had analogous nmr features except for the chemical shifts for H-7 (τ 4.40) and the methoxy group (6.47).

Anal. Calcd for $C_{13}H_{17}NO_4$: C, 62.08; H, 6.77; N, 5.58. Found: C, 62.20; H, 6.74; N, 5.51 (cis isomer). Found: C, 62.12; H, 6.82; N, 5.66 (trans isomer).

***trans*-2-Methoxy-6-(α-acetamidobenzyl)tetrahydropyran (7).**—To a suspension of Raney nickel T4 catalyst[23] (2 ml) in 50 ml of methanol was added 750 mg of the epimeric mixture of methoxy compounds 5 and 6, as obtained above, followed by hydrogenation under pressure (100 atm H_2) at room temperature for 1 day. After removal of the catalyst the solution was concentrated to about 10 ml, and, upon addition of 2 ml of acetic anhydride, kept overnight at ambient temperature. Evaporation to dryness *in vacuo* (finally 0.2 mm) and trituration of the residue with a small amount of methanol induced crystallization, to afford, after recrystallization from ethanol–water, 530 mg (57%) of 7 as colorless crystals: mp 84–85°; nmr (DMSO-d_6) τ 1.80 (d, 1, $J_{7,NH}$ = 9 Hz, NH), 2.66 (m, 5, C_6H_5), 5.08 (q, 1, $J_{2,7}$ = 4 and $J_{7,NH}$ = 9 Hz, H-7), 5.36 (narrow m, 1, H-2), 6.16 (broad m, 1, H-6), 7.08 (s, 3, OCH_3), 8.07 (s, 3, NHAc), 8.5 (m, 6, ring CH_2).

Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.41; H, 8.04; N, 5.32. Found: C, 68.35; H, 7.96; N, 5.26.

Cyclization of Glutaraldehyde with 1-Nitropropane.—To a mixture of 120 g (0.3 mol) of 25% aqueous glutaraldehyde and 40 ml (0.425 mol) of 1-nitropropane was added, with cooling, 1 *N* NaOH (20 ml). The solution was kept at ambient temperature for 3 days and subsequently deionized with a strongly acidic ion exchange resin (Merck I, H^+ form). After removal of the resin and thorough washing with methanol (200 ml) the combined filtrate and washings were evaporated to about 100 ml and, after treatment with activated carbon, taken to dryness, followed by repeated reevaporations from ethanol. Trituration of the residue with chloroform caused crystallization to give on filtration 21.7 g of crude product. Recrystallization from chloroform–petroleum ether (bp 60–80°) (1:2) afforded 20.2 g (36%) of 8 as colorless crystals, mp 90–91°, nmr in ref 10. The mother liquor, remaining after isolation of crude 8, was evaporated to dryness and the sirupy residue was dissolved in a little ethanol followed by gradual addition of petroleum ether. The crystals that had separated after standing for 2 days consisted of an approximate 1:1 mixture of 8 and 9 (tlc in 20:1 chloroform–methanol, R_f 0.45 (8) and 0.62 (9), and were subjected to another three recrystallizations from the same solvent mixture, the separation being followed by tlc. Thus, 1.6 g (3%) of 9 was obtained as colorless rhombs. Since partial epimerization of 9 into 8 occurs on melting, as evidenced by tlc, the observed melting point on fast heating of 102–109° does not represent the melting point of pure 9: nmr ($CDCl_3$) τ 5.60 (m, 2, $W_{1/2}$ = 18 Hz, H-2 and H-6), 6.15 (d, 2, J = 8 Hz, C-2 and C-6 OH), 8.1 (m, 8, 4 CH_2), 9.11 (t, 3, J = 7 Hz, $EtCH_3$); addition of trifluoroacetic acid eliminates the OH doublet, and reduces the half-width of the τ 5.60 multiplet to 10 Hz.

Anal. Calcd for $C_8H_{15}NO_4$: C, 50.78; H, 7.99; N, 7.40. Found (9): C, 50.80; H, 7.91; N, 7.24.

2,6-Diacetoxy-1-nitro-1-ethylcyclohexane (10).—A solution of 500 mg of 9 in acetic anhydride (2 ml) containing a trace of concentrated H_2SO_4 was kept at room temperature for 1 hr, and subsequently stirred into ice–water. Recrystallization of the resulting precipitate from petroleum ether–ethyl acetate (10:1) afforded 310 mg (54%) of 10 as colorless spears: mp 88–89°; nmr ($CDCl_3$) τ 4.64 (q, 2, J = 6 and 3 Hz, H-2 and H-6), 7.95 (s, 6, OAc), ~8.1 (m, 8, CH_2), 9.02 (t, 3, $EtCH_3$).

Anal. Calcd for $C_{12}H_{19}NO_6$: C, 52.74; H, 7.01; N, 5.13. Found: C, 52.80; H, 7.04; N, 4.98.

1-Acetamido-2,6-diacetoxy-1-ethylcyclohexane (11).—To a prehydrogenated suspension of 500 mg of PtO_2 in 10 ml of glacial acetic acid was added a solution of 1.0 g of nitrodiol 9 in acetic acid (30 ml) and the hydrogenation was continued. After uptake of the theoretical amount of H_2 (380 ml, 2 days) the catalyst was filtered off and washed with acetic acid (25 ml) and the combined filtrate and washings were taken to dryness with repeated reevaporations from ethanol. The remaining sirup was acetylated in a mixture of acetic anhydride (10 ml) and pyridine (25 ml) by standing overnight at ambient temperature. Removal of the solvents *in vacuo* (0.1 mm) and trituration of the residue with ice–water (50 ml) afforded a first crop of crystals, concentration of the mother liquor similarly a second, to give 890 mg of crude 11. Two recrystallizations from water–methanol (10:1) gave 310 mg (24%) of 11 as rhombs: mp 149–151°; nmr ($CDCl_3$) τ 4.31 (s, 1, NH), 4.79 (m, 2, $W_{1/2}$ = 10 Hz, H-2 and H-6), 7.91 (s, 6, OAc), 8.07 (s, 3, NHAc), ~8.15 (broad m, 8, CH_2), 9.21 (t, 3, J = 8 Hz, $EtCH_3$); DMSO-d_6 shifts the NH signal to τ 3.09 and the acetyl resonances to 7.99 (OAc) and 8.16 (NHAc), respectively.

Anal. Calcd for $C_{14}H_{23}NO_5$: C, 58.93; H, 8.13; N, 4.91. Found: C, 58.82; H, 8.16; N, 4.85.

Registry No.—1 and 2, 21891-46-3; 3 and 4, 21891-47-4; 5 and 6, 34288-57-8; 7, 34288-58-9; 8, 34289-82-2; 9, 34289-83-3; 10, 34289-84-4; 11, 34289-85-5.

(23) S. Nishimura, *Bull. Chem. Soc. Jap.*, **32**, 61 (1959).

Oxidation of 4-Alkyl-2,6-di-*tert*-butylphenols with β-Manganese Dioxide

HANS DIETL* AND HOWARD S. YOUNG

Research Laboratories, Tennessee Eastman Company, Division of Eastman Kodak Company, Kingsport, Tennessee 37662

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The preparation of 2,6-di-*tert*-butyl-*p*-benzoquinone (1) by the salcomine-catalyzed air oxidation of 2,6-di-*tert*-butylphenol (2) was recently reported.[1,2] The oxidation of 2 or 4-alkyl-2,6-di-*tert*-butylphenols (3a) with most oxidizing agents gives only a low yield of 1.[3-5]

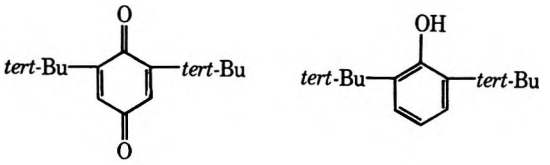
(1) H. M. van Dort and H. J. Geursen, *Recl. Trav. Chim. Pays-Bas*, **86**, 520 (1967).

(2) L. H. Vogt, Jr., J. G. Wirth, and H. L. Finkbeiner, *J. Org. Chem.*, **34**, 273 (1969).

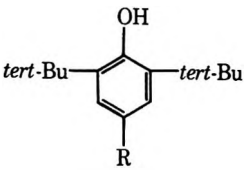
(3) M. S. Kharasch and B. S. Joshi, *ibid.*, **22**, 1439 (1957), and references cited therein.

(4) G. R. Yohe, J. E. Dunbar, R. L. Pedrotti, F. M. Scheidt, F. G. H. Lee, and E. C. Smith, *ibid.*, **21**, 1289 (1956), and references cited therein.

(5) T. Matsura, K. Omura, and R. Nakashima, *Bull. Chem. Soc. Jap.*, **38**, 1359 (1965).

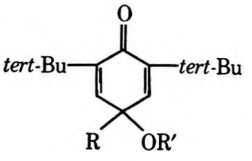


1 2



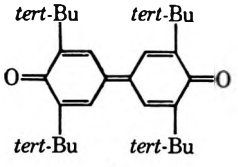
3a, R = alykl
b, R = CH_3
c, R = *tert*-Bu

Therefore, it is surprising that β-manganese dioxide (pyrolusite) oxidizes 2,6-di-*tert*-butyl-4-methylphenol (**3b**) in good yields either to **1** or to 4-alkoxy-2,6-di-*tert*-butyl-4-methyl-2,5-cyclohexadien-1-ones (**4a**), depending on the reaction conditions.



4a, R = CH_3; R′ = alykl
b, R = R′ = CH_3
c, R = CH_3; R′ = CH_3CH_2; $CH_3CH_2CH_2$
d, R = *tert*-Bu; R′ = CH_3

We obtained **1** in 74% yield by treating **3b** with finely divided β-manganese dioxide in a mixture (2/1 w/w) of 40% aqueous sulfuric acid and acetic acid at 60° for 5 hr. Oxidation of **2** under the same conditions gave only a 10% yield of **1**; the main product was 3,3′5,5′-tetra-*tert*-butyldiphenoquinone (**5**). To obtain a good yield of **1** from **3b**, the presence of both water and acetic acid (besides sulfuric acid) is essential. For example, in 40% aqueous sulfuric acid (without acetic acid), only a 15% yield of **1** was obtained after treatment of **3b** with β-manganese dioxide at 60° for 18 hr; in 40% sulfuric acid in acetic acid (water absent), only an 11% yield of **1** was obtained.



5

By oxidation of **3b** with β-manganese dioxide in 40% aqueous sulfuric acid containing methanol (1.5/1 w/w) at 55° for 4 hr, 2,6-di-*tert*-butyl-4-methoxy-4-methyl-2,5-cyclohexadien-1-one (**4b**) was obtained in 60% yield. As by-products, 11% of **1** and 12% of **5** were obtained. Replacement of methanol by ethanol or propanol gave the corresponding ethoxy and propoxy compounds **4c**. When the reaction was carried out in 40% methanolic sulfuric acid (no water present), a 25% yield of **1** was obtained in addition to **5**. No **4b** was detected in this case.

Oxidation of 2,6-di-*tert*-butylphenol (**2**), in which the para position is not blocked by a methyl group, in a 40% aqueous sulfuric acid–methanol mixture at 50° gave no cyclohexadienone. The main product was **5**, and a trace of **1** was found.

The oxidation of 2,4,6-tri-*tert*-butylphenol (**3c**) in a 40% aqueous sulfuric acid–acetic acid mixture gave **1** in 70% yield. In a 40% aqueous sulfuric acid–methanol mixture, a 40% yield of **4d** and a 40% yield of **1** were obtained.

Experimental Section

Oxidation of 2,6-Di-*tert*-butyl-4-methylphenol (3b) to 2,6-Di-*tert*-butyl-*p*-benzoquinone (1).—Twenty grams of **3b** was added to a mixture containing 150 g of 40% aqueous sulfuric acid and 75 g of glacial acetic acid. The mixture was heated to 60° with stirring, and 40 g of finely divided β-MnO_2 (pyrolusite) was added over a period of 2 hr at 60°. After the addition of MnO_2 was completed, stirring was continued for 3 hr at 60°. After the reaction mixture was cooled to room temperature, it was diluted with 600 ml of water and steam distilled. The distillate was extracted with ether, and the ether was allowed to evaporate to give 15 g (75% yield) of **1**.

Oxidation of 2,6-Di-*tert*-butyl-4-methylphenol (3b) to 2,6-Di-*tert*-butyl-4-methoxy-4-methyl-2,5-cyclohexadien-1-one (4b).—Twenty grams of **3b** was added to a mixture containing 150 g of 40% aqueous sulfuric acid and 100 g of methanol. The mixture was heated to 55° with stirring, and 40 g of finely divided β-MnO_2 was added over a period of 2 hr at 55°. After the reaction mixture was cooled to room temperature, it was diluted with 600 ml of water and steam distilled. The distillate was extracted with ether, and the ether was evaporated. Recrystallization of the residue from ethanol gave a 60% yield of **4b**, mp 92–94°.

Registry No.—**1**, 719-22-2; **3b**, 128-37-0; **4b**, 2411-18-9; β-manganese dioxide, 14854-26-3.

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A New Method for the Methylation of Amines

RICHARD F. BORCH*[1] AND AVIV I. HASSID

Department of Chemistry, University of Minnesota, Minneapolis, Minnesota 55455

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The introduction of methyl groups into a primary or secondary amine by reductive alkylation with formaldehyde and formic acid derivatives (the Clarke–Eschweiler method[2]) has proved to be a useful method for the preparation of tertiary methylated amines. In some cases, however, complex mixtures have resulted from the multiplicity of side reactions which can occur.[3] Our need for a milder procedure in connection with another problem currently under investigation, coupled with our earlier interest in the chemistry of the cyanoborohydride (BH_3CN^-)[4] ion, led us to examine the feasibility of a formaldehyde–cyanoborohydride system for amine methylation. We describe here a mild and efficient method for the synthesis of tertiary methylated amines of high purity in good yield.

(1) Alfred P. Sloan Foundation Fellow.
(2) M. L. Moore, *Org. React.*, **5**, 301 (1949).
(3) S. H. Pine and B. L. Sanchez, *J. Org. Chem.*, **36**, 829 (1971).
(4) (a) R. F. Borch, M. D. Bernstein, and H. D. Durst, *J. Amer. Chem. Soc.*, **93**, 2897 (1971); (b) R. F. Borch and H. D. Durst, *ibid.*, **91**, 3996 (1969).

TABLE I

REPRESENTATIVE REDUCTIVE METHYLATIONS WITH FORMALDEHYDE–$NaBH_3CN$ IN ACETONITRILE AT 25°

Entry	Compd[a]	Time, hr	Registry no.	Product	Yield, %	Product (deriv) mp, °C[b]
1	Cyclohexylamine	2	34201-87-1	*N,N*-Dimethylcyclohexylamine	84	(178–180)[c]
2	2-Heptylamine	2	34224-22-1	*N,N*-Dimethyl-2-heptylamine	82	(140–142)[d]
3	*endo*-Norbornylamine	2	34287-03-1	*endo*-*N,N*-Dimethylnorbornylamine	75	(218–219)[c]
4	*N*-Isopropylcyclohexylamine	2	34224-23-2	*N*-Methyl-*N*-isopropylcyclohexylamine	87	(123–124)[c]
5	α-Methylbenzylamine	2	3160-90-5	*N,N*-Dimethyl-α-methylbenzylamine	81	(139–140)[c]
6	*N*-Ethylbenzylamine	1	34224-25-4	*N*-Methyl-*N*-ethylbenzylamine	85	(113–114)[c]
7	Aniline	2	2554-80-5	*N,N*-Dimethylaniline	92	(162–163)[c]
8	*p*-Phenetidine	1	34201-88-2	*N,N*-Dimethyl-*p*-phenetidine	85	(138–139)[c]
9	*N*-Propylaniline	2	34201-89-3	*N*-Methyl-*N*-propylaniline	83	(111–112)[c]
10	*m*-Chloroaniline	3	34201-90-6	*N,N*-Dimethyl-*m*-chloroaniline	86	(143–144)[c]
11	*p*-Bromoaniline	1	586-77-6	*N,N*-Dimethyl-*p*-bromoaniline	87	56–57
12	*m*-Nitroaniline	2.5	619-31-8	*N,N*-Dimethyl-*m*-nitroaniline	68	56–58
13	*p*-Nitroaniline	5	100-23-2 + 100-15-2	*N,N*-Dimethyl-*p*-nitroaniline + *N*-Methyl-*p*-nitroaniline	46 + 18	162–163 + 148–150

[a] Ratio of amine:formaldehyde:$NaBH_3CN$: entries 1–9, 1:5:1.6; entries 10–12, 1:10:3; entry 13, 1:20:6. [b] All values are in accord with published values where known; satisfactory elemental analyses were obtained for unknown derivatives. [c] Picrate. [d] Hydrochloride.

Reaction of an aliphatic or aromatic amine with aqueous formaldehyde and $NaBH_3CN$ in methanol (our previously reported[4] conditions for reductive amination) afforded a mixture of starting material and partially methylated products. Presumably the formaldehyde is tied up as the hemiacetal in the methanol system, rendering it less reactive in imine formation. A survey of aprotic solvents which were capable of solubilizing $NaBH_3CN$ was undertaken; acetonitrile proved to be the solvent of choice. The results are summarized in Table I.

This procedure is general for a wide variety of aliphatic and aromatic amines. Amines ranging in basicity from pK_a 10.66 (cyclohexylamine) to 2.47 (*m*-nitroaniline) were successfully methylated under these conditions. Even the very weak base *p*-nitroaniline (pK_a 1.00) was converted to a mixture of mono- and dimethylated products (entry 13). Steric hindrance seems to pose no problem; the hindered amine *N*-isopropylcyclohexylamine (entry 4) underwent methylation without difficulty. Because of the mild conditions, the ease of experimental manipulation, and the high yields of pure products, this reaction appears to be the method of choice for reductive methylation of amines.

Experimental Section

Reductive Methylation of "Reactive" Amines ($pK_a > 4$).—The preparation of *N*-methyl-*N*-ethylbenzylamine is typical. To a stirred solution of 675 mg (5 mmol) of *N*-ethylbenzylamine and 2 ml (25 mmol) of 37% aqueous formaldehyde in 15 ml of acetonitrile was added 500 mg (8 mmol) of sodium cyanoborohydride.[5] A vigorous exothermic reaction ensued, and a dark residue separated. The reaction mixture was stirred for 15 min, and then glacial acetic acid was added dropwise until the solution tested neutral on wet pH paper. Stirring was continued for an additional 45 min, glacial acetic acid being added occasionally to maintain the pH near neutrality. The solvent was evaporated at reduced pressure, and 20 ml of 2 *N* KOH was added to the residue. The resulting mixture was extracted with three 20-ml portions of ether. The combined ether extracts were washed with 20 ml of 0.5 *N* KOH and then extracted with three 10-ml portions of 1 *N* HCl. The acid extracts were combined and neutralized with solid KOH and then extracted with three 20-ml portions of ether. The combined ether extracts were dried (K_2CO_3) and evaporated *in vacuo* to give 735 mg (98%) of *N*-methyl-*N*-ethylbenzylamine as a colorless, glpc-pure oil. Reaction with 1.5 g of picric acid in ethanol afforded 1.61 g (85%) of picrate, mp 110–112°. One recrystallization from ethanol gave an analytical sample, mp 113–114°.

Anal. Calcd for $C_{16}H_{18}N_4O_7$: C, 50.79; H, 4.80; N, 14.81. Found: C, 51.00; H, 4.79; N, 14.79.

Reductive Methylation of "Unreactive" Amines ($pK_a < 4$).—The preparation of *N,N*-dimethyl-*m*-nitroaniline is typical. To a stirred solution of 690 mg (5 mmol) of *m*-nitroaniline and 4 ml (50 mmol) of 37% aqueous formaldehyde in 20 ml of acetonitrile was added 950 mg (15 mmol) of sodium cyanoborohydride. Glacial acetic acid (0.5 ml) was added over 10 min, and the reaction was stirred at room temperature for 2 hr. An additional 0.5 ml of glacial acetic acid was added, and stirring was continued for 30 min more. The reaction mixture was poured into 75 ml of ether and then washed with three 20-ml portions of 1 *N* KOH and one 20-ml portion of brine. The ether solution was dried (K_2CO_3) and evaporated *in vacuo* to give 840 mg of crude product as a semisolid. Thin layer chromatographic analysis (alumina, benzene) showed one major spot corresponding to the desired product and a trace of monomethylated material. Crystallization from aqueous ethanol afforded 565 mg (68%) of *N,N*-dimethyl-*m*-nitroaniline as an orange solid, mp 56–58° (lit.[6] mp 60°), homogeneous on tlc.

Acknowledgment.—Acknowledgment is made to the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this work.

(5) Available from Alfa Inorganics, Inc.

(6) "Dictionary of Organic Compounds," Oxford University Press, Cambridge, 1965, p 1190.

Kinetics of Azo Dye Formation. Micellar Effects

MARK POINDEXTER[1] AND BRUCE MCKAY*

Department of Chemistry, Harvey Mudd College, Claremont, California 91711

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Few references appear in the literature concerning the effects of micelle-forming surfactants on electrophilic

(1) National Science Foundation Undergraduate Research Participant, 1971.

aromatic substitution reactions.[2] These reactions are in the main available only in nonaqueous solvents, and micellar studies are not far advanced in other than water solvent. Nevertheless, at least one reaction class of interest for both mechanistic and synthetic reasons is amenable to aqueous solution study. We refer to the formation of azo dyes through coupling of aryldiazonium ions to naphthylamines and naphthols, particularly. Kinetic investigations of these reactions have been initiated and we wish to report some preliminary results.

As a representative reaction we chose the couplings of *p*-nitrobenzenediazonium ion with R salt (2-naphthol-3,6-disulfonate) and S salt (2-naphthol-6-sulfonate).[3] Effects of cationic (CTAB), anionic (NaLS), and nonionic (Triton X-100) surfactants on the coupling rates have been determined.[4] Table I displays

TABLE I

FIRST-ORDER RATE CONSTANT RATIOS. COUPLING OF *p*-NITROPHENYLDIAZONIUM ION WITH NAPHTHOLS

	S salt, k/k_0[c]	R salt, k/k_0[c]
[CTAB][a]		
0.001	0.695	0.732
0.002	0.471	0.380
0.003	0.427	
0.005		0.0705
0.010	0.321	
0.20	0.318	0.0556
[NaLS][a]		
0.002	0.556	
0.004	0.221	
0.010	0.124	
0.020	0.0655	
[Triton X-100][b]		
1.0	0.692	0.828
3.0	0.540	0.786
5.0	0.518[d]	0.759[d]

[a] Molar concentration. [b] Concentration in volume per cent. [c] Rate constant in surfactant solution/rate constant in absence of surfactant. [d] Rate ratio is depressed little more in 10% Triton solution.

our results in the form of rate constant ratios (rate in surfactant solution/rate in absence of surfactant). Coupling rates were determined at a single temperature (26.0°) in acetate-buffered solutions (pH 4.59) and with potassium chloride added to maintain ionic strength, except for solutions containing NaLS. These latter solutions were inhomogeneous if potassium chloride was present, owing to insolubility of the surfactant. The chloride salt was omitted. Basal rates (no surfactant) were variable, within narrow limits, but all rates were reproducible.

Inclusion of a surfactant of each charge type (cationic, anionic, nonionic) in the coupling medium results in a depression of the rate constant associated with azo dye formation. As the present system was designed only for demonstration of the susceptibility of a typical coupling to the presence of micelles, a number of features inhibit detailed interpretation of results. For example, increases in pK_a of phenols and naphthols have been found when these substrates are associated with micelles of Triton X-100.[5] Thus, we are unable at present to distinguish rate effects due to naphtholate ion concentration changes from other factors, for both uncharged and ionic detergent systems.

In the absence of requisite physical property data we would only suggest that the results of this study are at least consistent with more general observations regarding the activity of micellar species. In particular, electrostatic repulsions and attractions often appear to be dominating factors influencing reactions of charged species in the presence of micelles.[2,6] If both naphtholate and diazonium ions associate with micelles of the opposite charge type the electrostatic argument becomes more tenable.[6]

A consideration in undertaking this preliminary study was that substrate structures and charges in coupling reactions are variable over a rather wide range, and this feature might be advantageous for elucidating general aspects of micellar catalysis. We intend to make use of structure–charge variations in extending our investigations. Zollinger has shown that coupling of a charged naphthylamine with aryldiazonium ions bearing net formal charges of +1, 0, and −1 obeys, quantitatively, Debye–Hückel salt effect theory.[7] Use of Zollinger's substrates in the presence of micelles should prove very useful in determining how charge–charge interactions in couplings are affected by micelles.

Experimental Section

Standard, published procedures were followed for recrystallizations of cetyltrimethylammonium bromide,[8] sodium lauryl sulfate,[8] sodium 2-naphthol-6-sulfonate,[3] and *p*-nitrobenzenediazonium fluoroborate.[9] Both Triton X-100 and disodium 2-naphthol-3,6-disulfonate were used as received from their suppliers.

Stock solutions were prepared and kinetic data were obtained following the procedures of Cox and Kumamoto.[3] All solutions were maintained at pH 4.59 with 0.01 *M* acetic acid–0.01 *M* sodium acetate. Ionic strength for each solution was kept at 0.22 by addition of potassium chloride, except for solutions containing NaLS (see text).

In a typical experiment 8.7 ml of stock acetate buffer, containing potassium chloride, was mixed with 1.0 ml of 0.012 *M* naphthol solution, also acetate buffered. To the mixed solutions 0.3 ml of diazonium salt solution, buffered, was added. The concentration of diazonium ion was such that the infinite absorbance reading for each run was about 1.0. An aliquot of this solution was placed in a cuvette and this was inserted into the thermostated cell compartment of a Cary 13 recording spectrophotometer. The increase in absorbance at 485–490 nm, λ_{max} for the dyes, was measured as a function of time. Pseudo-first-order rate constants were calculated from plots of $\log (A_\infty - A_t)$ *vs.* *t*.

Reaction temperatures were 26.0 ± 0.3°. Rate constants were reproduced to at least ±4%. Generally, the higher the detergent concentration the better the rate constant reproduction, since the reaction half-life becomes very short (*ca.* 1 min or less) as the detergent concentration approaches zero.

(2) A recent comprehensive review of micellar catalysis contains only one such example: coupling of halonaphthols with quinonediimenes. E. J. Fendler and J. H. Fendler, *Advan. Phys. Org. Chem.*, **8**, 271 (1970).

(3) R. J. Cox and J. Kumamoto, *J. Org. Chem.*, **30**, 4254 (1965).

(4) CTAB = cetyltrimethylammonium bromide; NaLS = sodium lauryl sulfate.

(5) L. K. J. Tong and M. C. Glesman, *J. Amer. Chem. Soc.*, **79**, 4305 (1957).

(6) A more fully developed argument applicable to our results is to be found in a recent report of micellar effects on Meisenheimer complex equilibria: J. H. Fendler, E. J. Fendler, and M. V. Merritt, *J. Org. Chem.*, **36**, 2172 (1971).

(7) H. Zollinger, *Helv. Chim. Acta*, **36**, 1723 (1953).

(8) E. F. J. Dunstee and E. Grunwald, *J. Amer. Chem. Soc.*, **81**, 4540 (1959).

(9) E. B. Starkey, "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1943, p 225.

Solutions containing ionic detergents were made up by adding the desired weight of the solid to the stock solutions just before mixing with diazonium salt solutions. No volume change effects were observable. Because of the larger quantities of Triton X-100 needed this detergent was added to the stock acetate buffer before the final dilution to the mark with water.

Registry No.—*p*-Nitrophenyldiazonium ion, 14368-49-1; S salt, 93-01-6; R salt, 148-75-4.

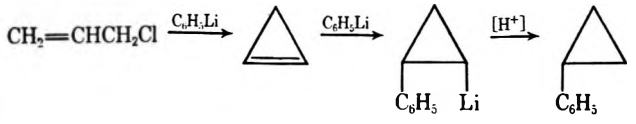
The Reaction of Phenyllithium with Allyl Chloride. Addition of Phenyllithium to Lithiated Cyclopropenes

DOUGLAS E. APPLEQUIST* AND EDWARD G. SAURBORN

Department of Chemistry, University of Illinois, Urbana, Illinois 61801

Received October 26, 1971

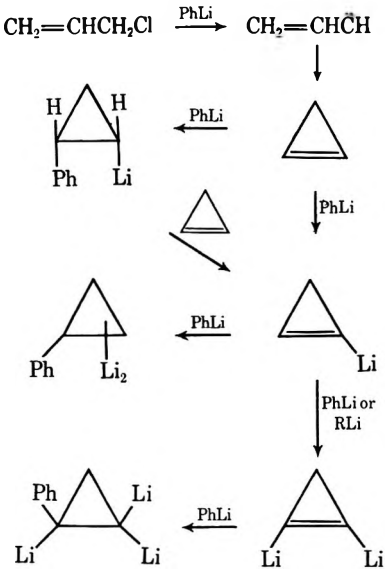
The formation of phenylcyclopropane from the reaction of phenyllithium with allyl chloride in ether has been the subject of at least four proposed mechanisms.[1,2] The mechanism which has gained the most impressive confirmation[3] is 1,1 elimination to form cyclopropene, followed by addition of phenyllithium to the double bond and protolysis of the 2-phenylcyclopropyllithium thus formed. The principal difficulty with this mechanism is that the source of the proton in the



last step has not been found. It has been reported by two groups[2,3] that, if reaction mixtures were treated with deuterium oxide, the phenylcyclopropane isolated contained no deuterium, apparently ruling out water in the isolation procedure as the proton source. Magid[3] has suggested ether, allylbenzene, and allyl chloride as proton sources, but the first two are too slow in their reactions with phenylcyclopropyllithium[3] to account for the lack of deuterium incorporation with D_2O after a reaction run under mild conditions,[2] and the last is unsuitable under at least some conditions since allyl-1,1-d_2 chloride gives phenylcyclopropane containing only one deuterium[3] (confirmed in this work).

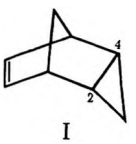
The source of the proton for the last step and hence a strong confirmation of the cyclopropene mechanism has now been found to be cyclopropene itself. If the reaction is run with a 1.50 mole ratio of phenyllithium to allyl chloride (as opposed to ratios 0.75–1.20 previously used), followed by a deuterium oxide quench, the isolated phenylcyclopropane contains an average deuterium content of 1.47 atoms (combustion analysis) and includes d_1, d_2, and d_3 species (mass spectrometry). The deuterium atoms were shown to be exclusively on the cyclopropane ring by quantitative integration of the H nmr and D nmr spectra, with 0.37 atoms in the α position and 1.10 atoms in the β positions. A control showed that treatment of phenylcyclopropane with phenyllithium, followed by a deuterium oxide quench, gave no detectable deuterium incorporation. It is concluded that phenylcyclopropane does in fact arise from addition of phenyllithium to cyclopropene, and that di- and trideuterated phenylcyclopropanes form as a result of addition of phenyllithium to the metalated cyclopropenes, 1-lithiocyclopropene and 1,2-dilithiocyclopropene (Scheme I).

SCHEME I



The source of protons to make phenylcyclopropane in the absence of sufficient phenyllithium is then seen to be cyclopropene, certainly the best proton acid in the medium.

Two other observations serve to confirm the mechanism shown in Scheme I. The first is that, when a reaction mixture of allyl chloride and methyllithium was quenched with deuterium oxide and the resulting cyclopropene was allowed to react with cyclopentadiene, the adduct I was obtained with 1.48 atoms/molecule of deuterium, all of it being in the 2 and 4 positions, according to H nmr and D nmr spectra, in which the multiplet at δ 1.31 was assigned to C_2 and C_4. The presence of 1,2-dilithiocyclopropene in a reaction mixture very similar to the phenyllithium mixture was thus supported, although the experiment did not exclude



I

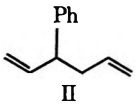
the possiblility of base-catalyzed exchange of unlithiated or monolithiated cyclopropene with deuterium oxide.

A second observation pertinent to the mechanism in Scheme I is the finding that 3-phenyl-1,5-hexadiene (II) is a minor (2–5%) product of the reaction of phenyllithium with allyl chloride. When the reaction was run with allyl-1,1-d_2 chloride, the II formed contained almost no proton at C_3, while positions C_1 and C_6

(1) S. Wawzonek, B. Studnicka, H. J. Bluhm, and R. E. Kallio, *J. Amer. Chem. Soc.*, **87**, 2069 (1965).

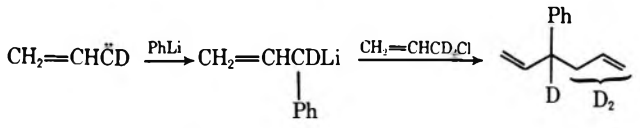
(2) D. E. Applequist and M. A. Lintner, *J. Org. Chem.*, **31**, 3062 (1966).

(3) R. M. Magid and J. G. Welch, *J. Amer. Chem. Soc.*, **90**, 5211 (1968), and earlier references cited therein.



II

shared two deuterium atoms (by pmr integration). A reasonable explanation is that the vinylcarbene or carbenoid intermediate is trapped by phenyllithium to give 1-phenylallyllithium, which couples with allyl chloride.



It is pertinent that allylbenzene isolated from a phenyllithium–allyl chloride reaction with a deuterium oxide quench shows no deuterium incorporation.

Experimental Section[4]

The Reaction of Allyl Chloride with Phenyllithium.—To 50 ml of a 1.2 *N* solution of phenyllithium (0.06 mol) at 0° in ether[5] was added dropwise 3.06 g (0.04 mol) of allyl chloride in 5 ml of ether, while the vapor above the stirred solution was swept slowly (60 min) with argon through a dewar condenser at −70° into a solution of 6.60 g (0.100 mol) of freshly distilled cyclopentadiene in 150 ml of methylene chloride at 0°. The mixture in the first flask was then treated with 50 g of water and heated to reflux for 5 min, while the argon flow was continued, now through the Dewar condenser at 0°. The phases were then separated, the aqueous phase was washed with 10 ml of ether, and the ether phases were combined and dried ($MgSO_4$).

Distillation and analytical gc (0.25 in. × 10 ft 20% 1,2,3-tris(2-cyanoethoxy)propane on 60/80 Chromosorb P column at 125°, flow rate 100 ml/min) showed allylbenzene at 7.0 min, phenylcyclopropane at 13.3 min, and 3-phenyl-1,5-hexadiene at 19.6 min in a ratio of 68:22:10, respectively. Preparative gc (0.375 in. × 5 ft 20% 1,2,3-tris(2-cyanoethoxy)propane on 45/60 Chromosorb A column at 135°, flow rate 100 ml/min) gave 1.184 g (0.01004 mol, 25.2%) of allylbenzene, 0.334 g (0.00284 mol, 7.1%) of phenylcyclopropane, and 0.156 g (0.00099 mol, 4.9%) of 3-phenyl-1,5-hexadiene. Comparison of the published nmr and infrared spectra of allylbenzene[6,7a] and phenylcyclopropane[7b,8] with those of the isolated samples established their respective identities. The 3-phenyl-1,5-hexadiene was identified by comparison of the infrared spectrum with the published spectrum:[7c] nmr (CCl_4) δ 7.19 (s, 5, phenyl), 5.86 (m, 2, −CH=), 5.02 (m, 4, CH_2=), 3.30 (m, 1, PhCH), and 2.46 (m, 2, $-CH_2-$); mass spectrum (25 eV) *m/e* 158.

Anal. Calcd for $C_{12}H_{14}$: C, 91.09; H, 8.91. Found: C, 89.93; H, 8.72.

Distillation of the methylene chloride from the contents of the second flask and preparative gc of the higher boiling material (0.375 in. × 7 ft 20% SE-30 on 45/60 Chromosorb A column) gave 0.492 g (0.00464 mol, 11.6%) of the known[9] *endo*-tricyclo[3.2.1.$0^{2,4}$]oct-6-ene: 220-MHz nmr (CCl_4) δ 5.66 (m, 2, $C_{6,7}$), 2.76 (m, 2, $C_{1,5}$), 1.80 (m, 1, C_8), 1.71 (m, 1, C_8), 1.31 (m, 2, $C_{2,4}$), 0.56 (m, 1, C_3), and 0.35 (m, 1, C_3).

The deuterium oxide quench was carried out in the same manner (without the cyclopropene trap) with the exception that 75 g (3.75 mol) of deuterium oxide (99.5%) was used as the quenching agent. Preparative gc gave phenylcyclopropane with average deuterium content (falling-drop analysis) 1.47; 220-MHz nmr (CCl_4) δ 7.02 (m, 5, phenyl), 1.82 (m, 0.61, benzylic), 0.86 (m, 1.68, trans to phenyl), and 0.63 (m, 1.24, cis to phenyl); mass spectrum (20 eV) *m/e* (rel intensity) 118 (35.57), 119 (87.35), 120 (100.00), 121 (39.36), 122 (4.43); 15.351-MHz D nmr (CD_2Cl_2) 3.52 (m, 0.37, benzylic) and 4.60 ppm upfield of CD_2Cl_2 (m, 1.10, ring methylene). In the mass spectrum, the ratio of the *m/e* 118 peak to the *m/e* 119 peak was 0.408. The ratio of the *m/e* 117 peak to the *m/e* 118 peak in a reference spectrum was 0.388, indicating few, if any, d_0 molecules (within the experimental error). The nmr and mass spectra of the isolated allylbenzene and 3-phenyl-1,5-hexadiene showed no evidence of deuterium incorporation.

The reaction of allyl-1,1-d_2 chloride with phenyllithium was carried out as described above, without the cyclopropene trap, utilizing 3.11 g (0.0396 mol) of the dideuterated allyl chloride[10] and 76.2 ml of a 0.78 *N* solution of phenyllithium (0.0594 mol) in ether. Analytical gc of the product showed only the allylbenzene, but isolation of the products *via* preparative gc (0.900-ml injections) gave small amounts of the phenylcyclopropane and 3-phenyl-1,5-hexadiene. The phenylcyclopropane mass spectrum (20 eV) showed *m/e* (rel intensity) 118 (33), 119 (100), 120 (13), indicating at least 97% d_1 (*vide supra*). Allylbenzene showed nmr (CCl_4) δ 7.17 (s, 5, phenyl), 5.90 (m, 1.0, −CH=), 5.00 (m, 0.6, CH_2=), and 3.34 (d, 1.3, PhCH−); mass spectrum (20 eV) *m/e* (rel intensity) 119 (5), 120 (100), 121 (11); indicating 68% 3,3-d_2-allylbenzene and 32% 1,1-d_2-allylbenzene. 3-Phenyl-1,5-hexadiene showed nmr (CCl_4) δ 7.19 (s, 5.0, phenyl), 5.86 (m, 2.0, −CH=), 5.02 (m, 3.5, CH_2=), 3.30 (broad m, maximum of 0.1, PhCH−), and 2.46 (m, 0.4, $-CH_2-$).

The reaction of methyllithium with allyl chloride was carried out as described for the phenyllithium reaction, with the second flask charged with 23.3 g (0.353 mol) of freshly distilled cyclopentadiene in 300 ml of methylene chloride, and the first flask charged with 505 ml of a 1.07 *N* solution of methyllithium in ether (0.540 mol). The allyl chloride (13.78 g, 0.180 mol) in 25 ml of ether was added to the cooled methyllithium solution over a 40-min period, and the resulting solution was stirred at room temperature for 30 min, heated to gentle reflux for 7 min, and stirred for an additional 60 min at room temperature. The ice water bath was then replaced, the condenser coolant was changed to Dry Ice and carbon tetrachloride, and the reaction mixture was quenched with 18.30 g (0.916 mol) of deuterium oxide. The volatile products were swept into the second flask, which was cooled with an ice water bath. After the deuterium oxide addition was complete, the first flask was heated at gentle reflux for 15 min, and the second flask was then disconnected. Preparative gc gave 0.800 g (0.00754 mol, 4.2%) of *endo*-tricyclo[3.2.1.$0^{2,4}$]oct-6-ene, whose 220-MHz nmr spectrum was identical with that described above, the only exception being that the signal at δ 1.31 integrated for only 0.52 protons. The average deuterium content (falling-drop analysis) was found to be 1.48, and the D nmr spectrum showed only one absorption at 5.89 ppm upfield of deuteriochloroform, corresponding to the C_2 and C_4 positions.

Registry No.—Phenyllithium, 591-51-5; allyl chloride, 107-05-1; 3-phenyl-1,5-hexadiene, 1076-66-0; phenylcyclopropane, 873-49-4; allylbenzene, 300-57-2; methyllithium, 917-54-4.

Acknowledgments.—This work was supported in part by National Science Foundation Grant GP-8372, and in part by the Petroleum Research Fund administered by the American Chemical Society. Grateful acknowledgment is made to the National Science Foundation and to the donors of the Petroleum Research Fund.

(4) The nuclear magnetic resonance spectra were obtained by Mr. Robert L. Thrift, Mr. Joseph M. Timko, and Mr. Steven K. Silber. The microanalyses were determined by Mr. Josef Nemeth and his associates.

(5) Prepared from lithium metal (0.01% sodium, Lithium Corp. of America) and bromobenzene according to R. G. Jones and H. Gilman, *Org. React.*, **6**, 339 (1951).

(6) "JEOLCO NMR Spectra," Japan Electron Optics Laboratory Co., Ltd., New Tokyo Bldg., Marunouchi, Chiyoda-ku, Tokyo, Japan, spectrum 100–112.

(7) "Sadtler Standard Spectra," The Sadtler Research Laboratories, Philadelphia, Pa., 1962, (a) spectrum 13701; (b) spectrum 12108; (c) spectrum 2792.

(8) N. S. Bhacca, D. P. Hollis, L. F. Johnson, and E. A. Pier, "NMR Spectra Catalog," Vol. 2, Varian Associates, Palo Alto, Calif., 1963, spectrum 528.

(9) K. B. Wiberg and W. J. Bartley, *J. Amer. Chem. Soc.*, **82**, 6375 (1960).

(10) Allyl-1,1-d_2 alcohol was obtained by the procedure of R. D. Schuetz and F. W. Millard, *J. Org. Chem.*, **24**, 297 (1959), and converted to the chloride according to S. H. Sharman, F. F. Caserio, R. F. Nystrom, J. C. Leak, and W. G. Young, *J. Amer. Chem. Soc.*, **80**, 5965 (1958).

The Thermal Decarboxylation of 2-Furoic Acids

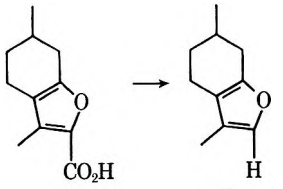
JERRY A. HIRSCH* AND DALE E. STERNER

Department of Chemistry, Seton Hall University, South Orange, New Jersey 07079

Received November 15, 1971

One solution to the problem of introducing a deuterium into a specific position on a furan ring[1] would be by thermal decarboxylation of a furoic acid subjected to prior exchange of the carboxyl hydrogen with deuterium oxide.

Little is known about the thermal decarboxylation of furoic acids. Eastman and Wither[2] reported the decarboxylation of menthofuroic acid (**1**) to menthofuran (**2**) under "illuminating gas" at 230°. The only other

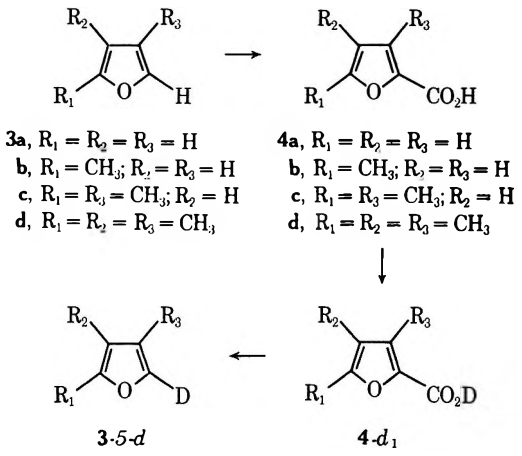


1 **2**

report of a thermal decarboxylation[3] does not discuss isolation of the product furan.

The general synthetic route used is shown in Scheme I. Conversion of a furan (**3**) to a 2-furoic acid (**4**) was

SCHEME I



effected in low yields[4] by lithiation[5] with phenyllithium or, a better choice in all instances,[4] *n*-butyllithium followed by carbonation,[5] or *via* the anilide by the method of Eastman and Wither[2] in better yields.[6] After purification of the 2-furoic acids by sublimation,[7] exchange of the carboxyl hydrogen with deuterium oxide was performed neat or in various solvents,[6] and the decarboxylation proceeded with good efficiency at reasonably accessible temperatures. Of the five 2-furoic acids (**4a–d**, **1**) subjected to an exchange–decarboxylation procedure, only 2-furoic acid (**4a**) failed to decarboxylate. The product from each reaction mixture was purified by distillation and/or preparative vapor phase chromatography.

The furans were analyzed for deuterium incorporation by mass spectrometry[6,8] and, in each instance, the presence of dideuterated and trideuterated furans was indicated[6] (Table I). A combination of proton magnetic resonance spectroscopy and mass spectrometry was used to evaluate the distribution of the deuterium. In each instance, deuterium incorporation at the α position in each furan was found to equal the sum of all of the monodeuterated product, one deuterium from all the dideuterated product, and one deuterium from all of the trideuterated product (Table II). Most of the remaining deuterium in the polydeuterated species was located in the methyl group occupying the other α position. Thermal decarboxylation is therefore not a reasonable method for the introduction of a deuterium into a specific position on a furan ring.

TABLE I

DEUTERIUM CONTENT BY MASS SPECTROMETRY[a]

Compd	% d_1	% d_2	% d_3
2-Methylfuran	62	11	2
2,4-Dimethylfuran	49	13	3
2,3,4-Trimethylfuran	57	19	5.5
2,3,4-Trimethylfuran[b]	50	23	9
Menthofuran	41	16	3.6

[a] All deuterium percentages are corrected for natural isotopic abundances. [b] This sample was inefficiently dried in order to evaluate the possible influence of traces of deuterium oxide.

TABLE II

DEUTERIUM DISTRIBUTION BY PROTON MAGNETIC RESONANCE SPECTROSCOPY

Compd	% at α[a]	% in C-2 methyl[b]	% in C-4 methyl
2-Methylfuran	(75)	(15)	
2,4-Dimethylfuran	75 (65)	26 (19)	
2,3,4-Trimethylfuran	79 (81)	30 (30)	
2,3,4-Trimethylfuran[c]	82 (82)	42 (41)	7
Menthofuran	60 (60)		

[a] Number in parentheses is per cent deuterium predicted from mass spectrometry from ($d_1 + d_2 + d_3$). [b] Number in parentheses is per cent deuterium predicted from mass spectrometry from ($d_2 + 2d_3$). [c] This sample was inefficiently dried in order to evaluate the possible influence of traces of deuterium oxide.

Several alternatives must be considered to account for the formation of polydeuterated products and to evaluate the mechanism in such thermal decarboxylations. As a control experiment, menthofuran (**2**) was subjected to the conditions of the exchange–decarboxylation sequence and no deuterium was incorporated. Hence, for the decarboxylation reaction, intro-

(1) For straightforward systems, see D. H. Williams, R. G. Cooks, J. Ronayne, and S. W. Tam, *Tetrahedron Lett.*, 1777 (1968); B. Bak, L. Hansen, and J. Rastrey-Anderson, *Discuss. Faraday Soc.*, **19**, 30 (1955).

(2) R. H. Eastman and R. P. Wither, *J. Amer. Chem. Soc.*, **75**, 1492 (1953); R. P. Wither, Dissertation, Stanford University, 1955.

(3) K. Kato, *Agr. Biol. Chem. (Tokyo)*, **31**, 657 (1967).

(4) The choice of organolithium and exact reaction conditions resulted in wide fluctuations in yields and extensive amounts of ketonic materials.[5] For analogous results with aryllithiums, see D. S. Sethi, M. R. Smith, Jr., and H. Gilman, *J. Organometal. Chem.*, **24**, C41 (1970).

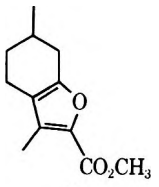
(5) P. H. Boyle, W. Cocker, J. B. H. McMurry, and A. C. Pratt, *J. Chem. Soc. C*, 1993 (1967).

(6) J. A. Hirsch, Dissertation, Stanford University, 1966.

(7) The parent 2-furoic acid (**4a**) was obtained from Matheson Coleman and Bell.

(8) D. H. Williams, R. G. Cooks, J. Ronayne, and S. W. Tam, *Tetrahedron Lett.*, 1777 (1968); K. Heyns, R. Stute, and H. Scharmann, *Tetrahedron*, **22**, 2223 (1966); H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, San Francisco, Calif., 1967, Chapter 23; K. Biemann, "Mass Spectrometry," McGraw-Hill, New York, N. Y., 1962, p 106.

duction of deuterium must occur prior to product formation. This does not rule out the possibility that furoic acid-*O*-*d* reacts with the furan by some mechanism to give exchanged product.[9] Another possibility—deuterium incorporation prior to decarboxylation—was eliminated from consideration in two ways. Methyl menthofuroate (**5**), prepared from menthofuroic acid (**1**) by treatment with diazomethane[6] or boron trifluoride–methanol complex, was subjected to the exchange–decarboxylation sequence without deuterium uptake. Subsequent to this experiment, Zoltewicz



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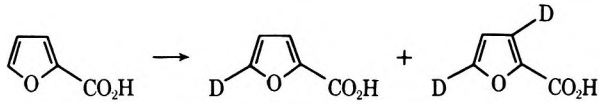
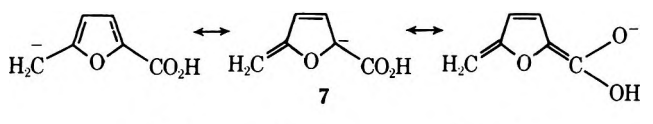
and Jacobson[10] reported that 2-furoic acid (**3a**) could be converted to 2-furoic-*5*-*d* acid (**3a**-*5*-*d*) and 2-furoic-*3*,*5*-d_2 acid (**6**) by heating the carboxylic acid in a deu-



3a **3a**-*5*-*d* **6**

terium oxide–carbonate buffer at 165° in a bomb or by heating the *O*-deuterated carboxylic acid in a bomb at 250°. We have repeated their work under the latter reaction conditions using O-deuterated 2-furoic acid (**4a**-d_1) as the substrate with similar results. However, placing the same furoic acid or 5-methyl-2-furoic acid (**4b**-d_1) in our apparatus at 240° for 1–2 hr, cooling the flask to room temperature, and back-exchanging the carboxyl deuterium, produced furoic acid containing only 2–3% deuterium. These experiments demonstrate that very little deuterium is being introduced at any furan carbon atom prior to decarboxylation by our procedure.

The only remaining alternative is deuterium incorporation during decarboxylation. As shown by decarboxylation of O-deuterated 3,4,5-trimethylfuroic acid (**4d**-d_1) in an incompletely dried medium (Tables I and II), the presence of an external base increases the amount of polydeuteration, thereby reinforcing the intermolecular character of the process leading to polydeuteration. The lack of decarboxylation with 2-furoic acid (**4a**) and the primary incorporation of the second and third deuterium atoms of the polydeuterated species in the α-methyl groups both suggest the involvement of an anion formed by proton abstraction from an α-methyl group (**7**), an enol (**8**), or an intermediate formed by a type of electrophilic substitution[9] (**9**).



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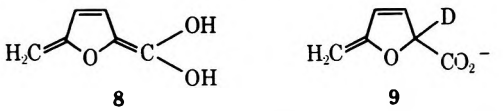

8 **9**

(9) We are indebted to a reviewer for pointing out this possibility.

(10) J. A. Zoltewicz and H. L. Jacobson, *J. Heterocycl. Chem.*, **8**, 331 (1971).

Experimental Section

Melting points and boiling points are uncorrected. Nmr spectra were recorded on a Varian A-60A instrument using approximately 10% solutions in deuteriochloroform unless otherwise indicated and are reported in parts per million downfield from tetramethylsilane as an internal standard. Only distinct absorptions will be reported herein. Infrared spectra were determined with a Beckman IR-10 spectrophotometer, with only major absorptions being cited. Elemental analyses were performed by Alfred Bernhardt Mikroanalytisches Laboratorium, Elbach, West Germany. Mass spectral analyses were performed by Morgan Schaeffer Corporation, Montreal, Canada, and were obtained at 70 eV. Lower voltages were not useful, as desired minimization of M − 1 species was accompanied by sufficient broadening of molecular ion peaks to introduce new errors.

Preparation of 2-Furoic Acids.—A solution containing an equal volume of Na_2SO_4-dried hexane and the appropriate furan was added dropwise to an equivalent amount of 2.2 *M* *n*-butyllithium in hexane (Alfa Inorganics) under a nitrogen stream. The reaction mixture was mechanically stirred until the color changed to a dark blood-red. If this color change did not occur within 15 min, the temperature was raised by 10° intervals with a temperature-controlled oil bath until the color change began. The contents were returned to room temperature and poured over Dry Ice. The residue was dissolved in 10% NaOH, while the solution was extracted with ether to remove unreacted furan and ketonic material. The basic solution from the residue was acidified with cold dilute HCl until the 2-furoic acid no longer precipitated. The solid material was dissolved in ether and dried ($MgSO_4$), and the solvent was removed. The residue was dissolved in boiling water, filtered hot, and extracted with ether. The organic layer was dried ($MgSO_4$) and the solvent was removed. The product was then sublimed at reduced pressures.

2-Furoic acid (**4a**) was purchased from Matheson Coleman and Bell.

5-Methyl-2-furoic Acid (**4b**).—This acid was prepared by the above procedure from 2-methylfuran (**3b**) (Aldrich) in 6.6% yield: mp 108–110° (lit.[11] mp 108–109°); nmr (CCl_4) δ 2.3 (s, 3), 6.0 (d, 1, J = 3 Hz), 7.1 (d, 1, J = 3 Hz), 12.3 (s, 1, COOH).

Anal. Calcd for $C_6H_6O_3$: C, 57.14; H, 4.80. Found: C, 57.18; H, 4.62.

3,5-Dimethyl-2-furoic Acid (**4c**).—This acid was prepared by the above procedure in 11.7% yield from 2,4-dimethylfuran (**3c**) prepared by the method of Morel and Verkade:[12] mp 140–145° (lit.[13] mp 146–147°); nmr δ 6.05 (broad s, 1), 2,3 (broad s, 6), 10.7 (broad s, 1, COOH).

Anal. Calcd for $C_7H_8O_3$: C, 60.00; H, 5.75. Found: C, 59.89; H, 5.83.

3,4,5-Trimethyl-2-furoic Acid (**4d**).—This acid was prepared by the above procedure in 9.6% yield from 2,3,4-trimethylfuran (**3d**) prepared by the method of Hirsch:[6] mp 188° dec (lit.[14] mp 185° dec); nmr δ 1.9 (s, 3), 2.3 (broad s, 6), 11.6 (broad s, 1, COOH).

Anal. Calcd for $C_8H_{10}O_3$: C, 62.33; H, 6.54. Found: C, 62.51; H, 6.69.

Menthofuroic Acid (**1**).—This acid was prepared from menthofuran (**2**) by the above procedure in 8.4% yield and by the method of Wither and Eastman[2] in 46.5% yield: mp 178–182° dec (lit.[2] mp 179–180° dec); ir (KBr) 1660, 1595, 3000–2500 cm^{-1} uv λ_{max}^{EtOH} 270 mμ (log ϵ 4.12) (as reported);[2] nmr δ 1.0 (d, 3, J = 5 Hz), 2.2 (s, 3), 11.5 (broad s, 1, COOH).

Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.07; H, 7.04.

Exchange and Decarboxylation of 2-Furoic Acids.—An ethereal solution of 0.5 g of a 2-furoic acid was magnetically stirred in a stoppered flask with 2 ml of deuterium oxide (Bio-Rad Laboratories, 99.8%). The deuterium oxide was removed with a pipette, and the exchange was performed two more times. The ether was removed by distillation under nitrogen. Dried benzene was added in sufficient amount for azeotropic removal of

(11) Hill and Sawyer, *J. Amer. Chem. Soc.*, **20**, 171 (1898).

(12) J. Morel and P. E. Verkade, *Recl. Trav. Chim. Pays-Bas*, **70**, 35 (1951).

(13) T. Reichstein, H. Zschokke, and A. Georg, *Helv. Chim. Acta*, **14**, 1277 (1931).

(14) T. Reichstein, H. Zschokke, and W. Syz, *ibid.*, **15**, 1117 (1932).

any remaining deuterium oxide. Nitrogen was passed over the acid for 10 min, and then the flask was heated to 220–250° for a few hours in a flask fitted with an acetone–Dry Ice condenser. The flask was then cooled to room temperature, and the furan was removed by molecular distillation and collected in a Dry Ice trap. The furan was then purified by preparative gas chromatography if impurities were present.

2-Furoic Acid (4a).—Decarboxylation did not occur under these reaction conditions. Decarboxylation by method B of Zoltewicz and Jacobson[10] in a bomb produced 32% of 5-deuterio-2-furoic acid (**3a**-5-*d*) and 4% of 3,5-dideuterio-2-furoic acid (6).

5-Methyl-2-furoic Acid (4b).—Decarboxylation proceeded smoothly to 2-methylfuran (**3b**): mass spectrum, molecular ion *m/e* 82, base peak *m/e* 83.

When decarboxylation was stopped prior to completion, unreacted starting material was recovered, back-exchanged with water, dried, and sublimed. Less than 2% deuterium was evident in the resulting acid.

3,4-Dimethyl-2-furoic Acid (4c).—Decarboxylation to 2,4-dimethylfuran (**3c**) proceeded smoothly: mass spectrum, molecular ion and base peak *m/e* 96; nmr δ 1.9 (s, 3), 2.2 (s, 2.22), 5.6 (s, 1), 6.9 (s, 0.25).

3,4,5-Trimethyl-2-furoic Acid (4d).—Decarboxylation by the above procedure produced 2,3,4-trimethylfuran (**3d**): mass spectrum, molecular ion *m/e* 110, base peak *m/e* 111; nmr δ 1.8 (s, 3), 1.9 (d, 3), 2.1 (s, 2.1), 6.9 (s, 0.21).

The exchange and decarboxylation procedure was performed with the omission of the azeotropic distillation. The resulting 2,3,4-trimethylfuran (**3d**) exhibited nmr δ 1.8 (s, 3), 1.9 (d, 2.79), 2.1 (s, 1.74), 6.9 (3, 0.18).

Menthofuroic Acid (1).—Decarboxylation of menthofuroic acid (**1**) using the general exchange–decarboxylation sequence mentioned above or a variety of other exchange techniques[6] produced menthofuran (**2**) of roughly the same isotopic composition. Submission of menthofuran (**2**) to the exchange–decarboxylation procedure did not lead to deuterium incorporation.

Registry No.—**1**, 34289-48-0; **2**-*2-d*, 34289-49-1; **3a**-*5-d*, 6142-86-5; **3b**-*5-d*, 23451-00-5; **3c**-5-*d*, 34289-51-5; **3d**-5-*d*, 34289-52-6; **4a**, 88-14-2; **4b**, 1917-15-3; **4c**, 34297-68-2; **4d**, 34289-53-7.

Acknowledgment.—We wish to thank Dr. R. H. Eastman for helpful comments during the early phases of this work.

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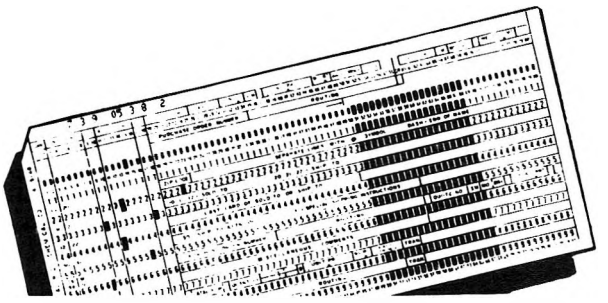

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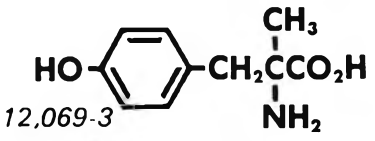

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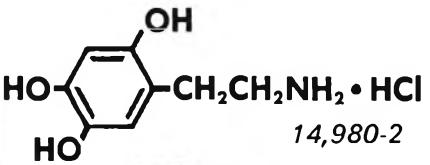

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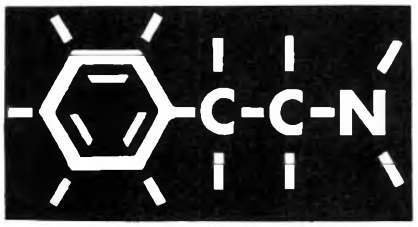

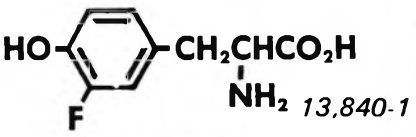

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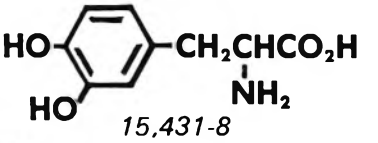

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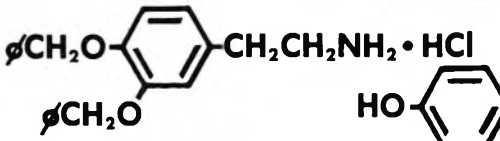

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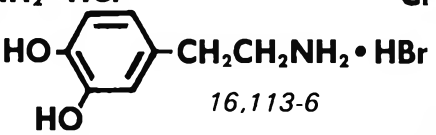

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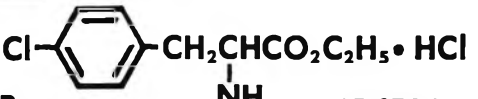

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