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THE JOURNAL OF Organic Chemistry®

VOLUME 37, NUMBER 19

SEPTEMBER 22, 1972

Guanine, Thioguanine, and Related Nucleosides by the Mercuric Cyanide–Silyl Method. An Improved Synthesis of α-2′-Deoxythioguanosine[1]

WILLIAM W. LEE,* ABELARDO P. MARTINEZ, LEON GOODMAN, AND DAVID W. HENRY

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Received March 17, 1972

The silyl derivatives of 2-amino-6-chloropurine and 2-acetamido-6-chloropurine react readily with halo sugars in the presence of mercuric cyanide to afford nucleosides in high yields. These can be converted to guanine, thioguanine, and other related nucleosides by standard procedures. By this new and improved method and through a column chromatographic separation described here, α-2′-deoxythioguanosine has been obtained in excellent yield and high anomeric purity, and 9-β-D-xylofuranosylguanine has been obtained in almost twice the yield previously attainable.

α-2′-Deoxythioguanosine (α-TGdR, α-**5**[2a]) is the only α anomer of a nucleoside known to have antitumor activity.[3] The β anomer (β-TGdR, β-**5**) is also an interesting antitumor agent.[3] Studies have shown that both β- and α-TGdR can be phosphorylated and incorporated into the DNA of some murine tumors *in vivo*[4] and of some murine and human tumor extracts *in vitro*.[5] Unlike the β anomer, α-TGdR is not phosphorylated to a significant extent by extracts of normal bone marrows;[5] hence, α-TGdR is less toxic than the β anomer. For these reasons, there is great interest in α-TGdR, and large amounts are needed for additional studies. This article reports a new, improved synthesis of α-TGdR and a means of separating its precursor from that of the β anomer. The new method of synthesis seems generally useful for guanine, thioguanine, and other 2-amino 6-substituted purine nucleosides.[6]

Of the general methods of guanine nucleoside synthesis,[6] none could assure a better yield of α-**5** and a more favorable α:β anomer ratio than the original.[2a] However, the silyl method of nucleoside synthesis merited consideration. It has been extremely useful for pyrimidine nucleosides.[7] Although the silyl method was originally less attractive for purine nucleosides, a recent modification has given improved yields of adenine nucleosides.[8] The silyl method also afforded the possibility of altering the ratio of α:β anomers,[9] at least with pyrimidine nucleosides. On this basis, we investigated the silyl method for the synthesis of α-**5**.

In our first experiments with the silyl derivatives (**1b**) of 2-acetamido-6-chloropurine (**1a**) and 2-deoxy-3,5-di-*O*-*p*-toluoyl-D-*erythro*-pentofuranosyl chloride (**2**) we followed the method of Kotick, Szantay, and Bardos,[9a] to see whether the absence or presence of trimethylchlorosilane (TMCS) would allow stereospecific synthesis of α or β nucleosides from purines as well as from pyrimidines.[9a] Our experiments with TMCS are given in Table I. The main conclusion was that the yield of 2-acetamido-6-chloro-9-(2-deoxy-3,5-di-*O*-*p*-toluoyl-D-*erythro*-pentofuranosyl)-9*H*-purine (**3**) was not sufficient for our purposes, although some variation in α:β ratio (generally *ca.* 1) can be achieved. The yields of **3** represented the anomeric mixture freed of unreacted base and sugar products by column chromatography.

Other pertinent data from Table I show that the use of solvents other than benzene offer no advantages.

(1) (a) This work was carried out under the auspices of Drug Research and Development, National Cancer Institute, National Institutes of Health, Public Health Service, Contract No. NIH-71-2070. The opinions expressed in this paper are those of the authors and not necessarily those of Drug Research and Development. (b) Part of this work was presented at the 162nd National Meeting of the American Chemical Society, Washington, D. C., Sept 12–17, 1971.

(2) (a) R. H. Iwamoto, E. M. Acton, and L. Goodman, *J. Med. Chem.*, **6**, 684 (1963), synthesized α-**5**, 9-(2-deoxy-α-D-*erythro*-pentofuranosyl)-thioguanine, *via* the mercury derivative of 2-acetamido-6-chloropurine. (b) Recently, the L isomers were prepared by the fusion method. See M. J. Robins, T. A. Khwaja, and R. K. Robins, *J. Org. Chem.*, **35**, 636 (1970).

(3) G. A. LePage, I. G. Junga, and B. Bowman, *Cancer Res.*, **24**, 835 (1964).

(4) (a) G. A. LePage and I. G. Junga, *Mol. Pharmacol.*, **3**, 37 (1967); (b) G. A. LePage, *Can. J. Biochem.*, **46**, 655 (1968).

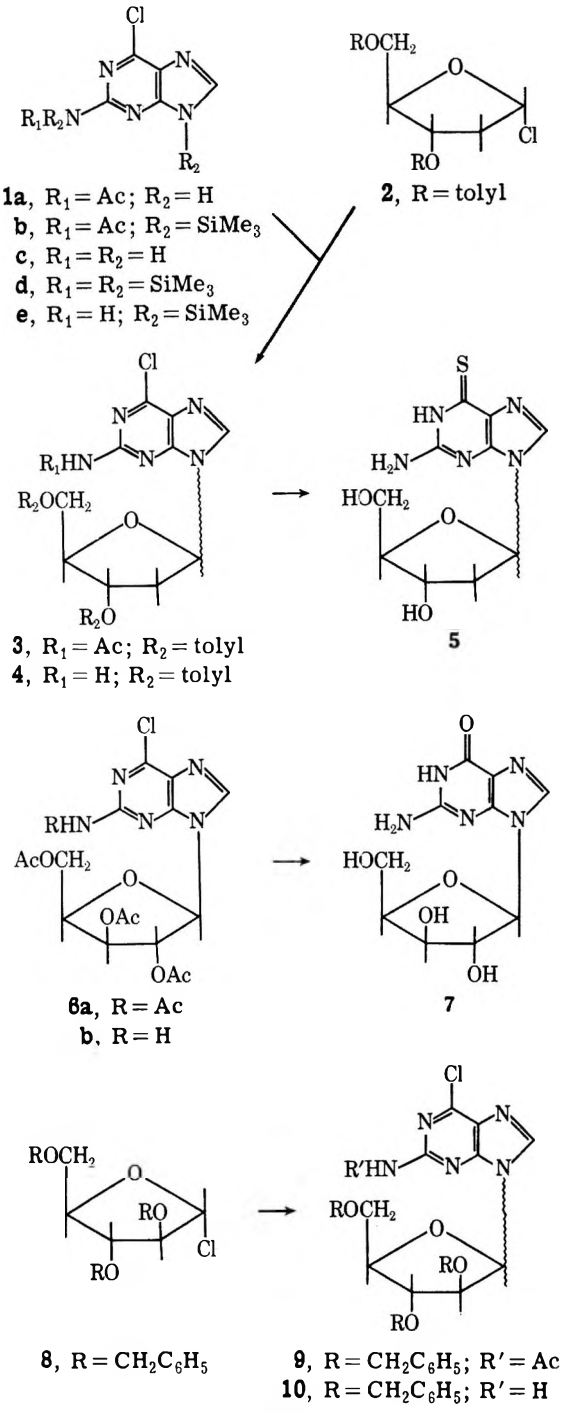
(5) A. Peery and G. A. LePage, *Cancer Res.*, **29**, 617 (1969).

(6) For general methods of guanine nucleoside synthesis, see discussion in G. L. Tong, K. J. Ryan, W. W. Lee, E. M. Acton, and L. Goodman, *J. Org. Chem.*, **32**, 859 (1967).

(7) C. A. Dekker and L. Goodman in "The Carbohydrates Chemistry and Biochemistry," 2nd ed, Vol. 2A, W. Pigman and D. Horton, Ed., Academic Press, New York, N. Y., 1970, p 1.

(8) (a) B. Shimizu and A. Saito, *Agr. Biol. Chem. (Tokyo)*, **33**, 119 (1969). (b) K. J. Ryan, E. M. Acton, and L. Goodman, *J. Org. Chem.*, **36**, 2646 (1971). (c) After the portion of this work on α-**3** was completed, W. Hutzenlaub, R. L. Tolman, and R. K. Robins reported the use of the silyl procedure in the preparation of 8-azaguanosine at the 161st National Meeting of the American Chemical Society, Los Angeles, Calif., March 28–April 2, 1971.

(9) (a) M. P. Kotick, C. Szantay, and T. J. Bardos, *J. Org. Chem.*, **34**, 3806 (1969); (b) E. Wittenburg, *Chem. Ber.*, **101**, 1095 (1968).



Additives such as mercuric acetate or mercuric cyanide in the presence of excess TMCS promoted decomposition, probably because the salts could not function as HCl acceptors under these conditions.[10] Excess base **1b** was harmless, but excess halo sugar **2** gave lower yields. A long reaction time (expt 7) resulted in some N-deacylation to 2-amino-6-chloro-9-(2-deoxy-3,5-di-*O*-toluoyl-D-*erythro*-pentofuranosyl)-9*H*-purine (**4**), contaminated by a second nucleoside that was not investigated. Initially the mixture of **4** and its contaminant was thought to be the two **7** isomers of **3** on the basis of our experience with N^2-acylguanine nucleosides[11a] and the observations of Miyaki and Shimizu[11b] on 7-substituted and 9-substituted N^2-acetylguanines. However, the **4** in this mixture was later found to be identical with the authentic **4**.

TABLE I

FORMATION OF **3** FROM **1b**[a] AND **2** WITH TMCS PRESENT

Expt	Mole ratio of 1b:2	Solvent	Temp, °C	Time, hr	Yield, %
1	1	B	80	0.5	48
2	2.2	B	80	6	45
3	1	B	80	18	44
4	1	B	80	7.5	44[b]
5	1	B	80	5	33[c]
6	1	B	80	12	31[d]
7	1	B	30, 45	20, 24	13[d,e]
8	1	DMF	55	60	*f*
9	1	CH_3CN	82	5	*g*
10	1	CH_3CN	25	60	*c, h*
11	1	PhCl	80	18	*c*
12	1	B	80, 25	2, 18	18[i]
13	1	B	50	1	18[j]
14	0.67	B	80	1	23[k,l]
15	0.67	B	80	0.5	22[l]
16	0	B	80	0.5	X[m]

[a] 5–10 mmol. Procedure in Experimental Section. Solvent B is benzene. [b] 30-mmol scale. [c] No excess TMCS used. [d] $Et_3N \cdot HCl$ not removed. [e] Also 6.5% of **4** that contained another unidentified component. [f] $Hg(OAc)_2$ added; black decomposition products and **1a**. [g] Decomposition of sugar. [h] Trace of **4**. [i] $Hg(CN)_2$ added. [j] Reduced pressure. Ratio of $\alpha:\beta \sim 2$. [k] Distilled and added 15% TMCS solution simultaneously. [l] Ratio of $\alpha:\beta \sim 1.5$. [m] No decomposition of **2**.

When no excess TMCS was used (expt 5) the yield was lower. Experiment 16 confirmed the considerable stability of **2** in the presence of TMCS.[9a] While TMCS had no adverse effect on the stability of **2**, hydrogen, chloride did; the same decomposition products, *e.g.*, furfuryl *p*-toluate, observed by previous investigators[12] were found.

In another series of experiments, we examined the condensation of **1b** and **2** under other conditions. Wittenburg[13] had successfully altered the $\alpha:\beta$ ratio of anomers by the use of added salts in the synthesis of pyrimidine nucleosides by the silyl method. His studies included some 3,5-di-*O*-acyl-2-deoxyribofuranosyl chlorides.[9b] Pyrstas, *et al.*,[12,14] have altered the yields of $\alpha:\beta$ ratio of anomers in the Hilbert–Johnson reaction of pyrimidines with **2** through proper choice of solvents. We found that with no excess TMCS, but with mercuric cyanide present, **1b** and **2** condensed to give high yields of **3**. The results are given in Table II. The crude yields included the by-products (**4** and others) as well as **3**. In some of the larger runs, there may be several per cent of solvent left in the product. Again, for **3**, the ratio of $\alpha:\beta$ anomers was slightly greater than one. It is noteworthy that the yields were high and reproducible on scaling up; this consistency has not been always observed with some other methods of nucleoside synthesis, *e.g.*, the fusion method.[15]

(10) The excess trimethylchlorosilane could negate the mercury salts as HCl acceptors by these reactions: $Hg(OAc)_2 + 2HCl \rightarrow HgCl_2 + 2HOAc$; $2HOAc + 2Me_3SiCl \rightarrow 2Me_3SiOAc + 2HCl$.

(11) (a) W. W. Lee, A. P. Martinez, and L. Goodman, *J. Org. Chem.*, **36**, 842 (1971); (b) M. Miyaki and B. Shimizu, *Chem. Pharm. Bull.*, **18**, 1446 (1970).

(12) M. Prystaš and F. Šorm, *Collect. Czech. Chem. Commun.*, **30**, 1900 (1965).

(13) E. Wittenburg, *Chem. Ber.*, **101**, 1614 (1968), and prior work; *e.g.*, ref 9b.

(14) M. Prystaš, J. Farkaš, and F. Šorm, *Collect. Czech. Chem. Commun.*, **30**, 3123 (1965).

(15) W. W. Lee, A. P. Martinez, G. L. Tong, and L. Goodman, *Chem. Ind. (London)*, 2007 (1963).

TABLE II

FORMATION OF 3[a] FROM 1b AND 2 WITH MERCURIC CYANIDE PRESENT

Expt	Millimoles 1b	Mole ratio of 1b:2	$Hg(CN)_2$, mmol	Solvent	Time, min	Yield,[b] %
1	5.0	1	4.8	B	120	84
2	2.5	0.97	6.0	B	45	75
3	5.0	1.2	12.0	B	60	~100
4	17.2	1.2	41	B	60	~100
5	2.4	1.5	4.0	CH_3CN[c]	60	~100
6	42.6	0.83	79	B	60	~100
7	63.8	0.85	127	B	50/60	~100

[a] Procedure in Experimental Section; solvent B is benzene. [b] Crude yield after rapid Florisil columning. Larger runs not always free of solvent. [c] Less by-product (by tlc) than with benzene.

Separation of the anomers at **3** rather than at **5** seemed more feasible from our past experience with similar nucleosides.[11a,16] Also, LePage[4b] had demonstrated that the anomers of **3** could be separated to give α-**3** free of β-**3** (<0.1%) by thick plate chromatography. The method, though laborious and unsuitable for large scale preparative work, does suggest that a practical chromatographic method may be found by further study. After considerable experimentation, the following process was deemed the best. The crude product containing **3** and some nucleoside by-products was crystallized from chloroform–carbon tetrachloride to remove most of the relatively insoluble β-**3**. The mother liquors were then rapidly chromatographed through a short Florisil column to separate sugar by-products and the other nucleoside by-products from **3**. A final separation using a higher ratio of adsorbent to nucleoside afforded the pure α anomer in one fraction and a fraction containing unseparated α- and β-**3** that could be recycled. The yields of pure α-**3** and β-**3** each ranged between 25 and 40% in several runs, tending toward the higher side as the separation process was improved. The anomeric purity of α-**3** obtained by this process was found to be at least 99.5% (the limits of detection) by quantitative chromatography and uv measurement.[4b] The α-**3** and β-**3** were converted to α-**5** and β-**5** by the literature procedure,[2a] thus providing further confirmation of their structures.

The anomeric purity of the α-**3** and β-**3** fractions was monitored during separations by tlc and nmr. The H-8 protons of α-**3** and β-**3** were separable in the nmr obtained with $DCCl_3$ or DMSO-d_6–$DCCl_3$ mixtures as solvent, but not in DMSO-d_6 alone.

Reaction of the silyl derivative **1b** with other halo sugars was examined. Reaction with 2,3,5-tri-*O*-acetyl-D-xylofuranosyl bromide gave 2-acetamido-6-chloro-9-(2,3,5-tri-*O*-acetyl-β-D-xylofuranosyl)-9*H*-purine (**6a**) in consistently higher yields and higher purity than were obtainable from the mercury derivative of 2-acetamido-6-chloropurine.[16] Reaction of **1b** with 2,3,5-tri-*O*-benzyl-D-arabinofuranosyl chloride (**8**) gave a 67% yield of an anomeric mixture of 2-acetamido-6-chloro-9-(2,3,5-tri-*O*-benzyl-D-arabinofuranosyl)-9*H*-purine (**9**). This crude product required immediate column purification; otherwise, extensive darkening took place. The anomeric ratio, $\alpha:\beta$, of **9** was about 1, although nmr suggests it to be slightly richer in the β anomer. By contrast, the reaction of **1b** with the above arabinofuranosyl chloride (**8**) in the *absence* of mercuric cyanide by the method of Glaudeman and Fletcher method[17] gave less than 20% yield of **9**, but with the β anomer predominating. The reaction of unsilylated **1a** with **8** under the same conditions[17] gave negligible amounts of **9** because of poor solubility of **1a**.

The results immediately raised another question: Is the acetyl group in the silyl derivative of **1a** necessary? If not, this would eliminate the need for **1a**. Its preparation from **1c** proceeds only in moderate yield (small scale, 64%;[2a] many larger runs, about 50%) and requires the elimination of overacetylated product.

Treatment of **1c** with hot hexamethyldisilazane afforded a silyl derivative of undetermined structure (probably **1d**, **1e**, or both) which was combined immediately with **2** in hot benzene containing mercuric cyanide. A nucleoside product was formed and gave, after purification, an 80% yield of analytically pure **4** ($\alpha:\beta \sim 1$). A comparison on the same tlc plate showed that the anomeric mixture of **4** was more difficult to separate than that of **3**. However, **4** should be reacetylatable to **3** for the separation. Furthermore, there is the possibility that treatment of **4** with a different acylating agent might give an anomeric mixture easier to separate than **3**.

The silyl derivative of **1c** also reacted with 2,3,5-tri-*O*-acetyl-D-xylofuranosyl bromide to give, after column purification, an 84% yield of **6b**. That this was a 9-substituted nucleoside was shown by its conversion to authentic **7** in 51% overall yield from **1c**. This represents double the yield of **7** previously obtained *via* the mercury derivative of **1a** (23% from **1c**).[16] Furthermore, the **6b** prepared by this route is so pure that in larger scale runs no column purification was needed before conversion to **7** (see Acknowledgments).

In the same way, the silyl derivative of **1c** reacted with **8** to afford 2-amino-6-chloro-9-(2,3,5-tri-*O*-benzyl-D-arabinofuranosyl)-9*H*-purine (**10**) in excellent yield after purification. The ratio of $\beta:\alpha$ was about 1, though slightly richer in β, according to nmr results. The crude **10** was more stable than the crude **9** (obtained *via* TMCS). An interesting side observation is that **1c** itself can be used for nucleoside condensation if it can be dissolved. Thus, heating **1c** in DMF with **2** and triethylamine afforded a 15% yield of **4**, which was identical with an authentic sample, together with another 15% of product assumed to be a nucleoside (by ir and tlc), which was not investigated.

These experiments with several halo sugars show that the silyl derivatives of both **1a** and **1c** are suitable for the preparation of nucleoside intermediates that lead to guanine, thioguanine, and other 2-amino 6-substituted nucleosides in high yields. The use of the silyl derivative of **1a** may be advantageous in cases where anomer separation is required. However, in other cases, the silyl derivative of **1c** is advantageous; it is simpler to obtain. Silylation with hexamethyldisilazane gives cleaner nucleoside products than TMCS. The silyl method is a new, general, and superior method for synthesizing such nucleosides. By this method and

(16) W. W. Lee, A. P. Martinez, R. W. Blackford, V. J. Bartuska, E. J. Reist, and L. Goodman, *J. Med. Chem.*, **14**, 819 (1971).

(17) C. P. J. Glaudemans and H. G. Fletcher, Jr., *J. Org. Chem.*, **28**, 3004 (1963).

the separation technique described, α-2′-deoxythioguanosine can be prepared in quantity.

Experimental Section

Optical rotations were measured with a Perkin-Elmer Model 141 automatic polarimeter. Thin layer chromatograms were run in cyclohexane–ethyl acetate (6:4) on silica gel HF (E. Merck AG Darmstadt) with multiple development (usually five times). All spots were detected by uv light. All solutions were dried with anhydrous magnesium sulfate and were concentrated in a rotatory spin evaporator *in vacuo* with a bath temperature of <50° unless otherwise noted. Celite is a diatomaceous earth product of Johns-Manville. Florisil, an activated magnesium silicate product of the Floridin Co., of 100–200 mesh was used in the column chromatography.

Formation of 3 with TMCS Present.—The general procedure for the preparation of 2-acetamido-6-chloro-9-(2-deoxy-3,5-di-*O*-*p*-toluoyl-D-ribofuranosyl)-9*H*-purine is illustrated by expt 4 in Table I. A solution of 10.0 ml (72 mmol) of triethylamine in 30 ml of benzene was added dropwise over 30 min to a stirred mixture of 6.33 g (30 mmol) of 2-acetamido-6-chloropurine (1a),[2a] 6 g of 3A molecular sieves, 80 ml of dry (over 3A sieves) benzene, and 8.0 g (74 mmol) of TMCS. The mixture was stirred for 24 hr at room temperature while protected from moisture. [In some cases, this mixture containing the silyl derivative (1b) of 1a and the triethylamine hydrochloride was used directly in the nucleoside condensation. See expt 6 and 7, Table I.] The mixture was filtered, the residue was washed with 80 ml of dry benzene, and the combined filtrate and wash were evaporated to dryness. (In some experiments, this solution was not evaporated, but was was used directly.)

To the residue was added a warm solution of 11.7 g (30.0 mmol) of the chloro sugar 2[18] in 310 ml of benzene containing 15% TMCS and 10 g of 3A molecular sieves. The mixture was heated at reflux for 7.5 hr (some experiments were heated with distillation of some TMCS and benzene; see expt 13 and 14) and then evaporated to dryness *in vacuo*. The residue was stirred for 30 min in 175 ml of methanol and 250 ml of ethyl acetate and filtered; the filtrate was evaporated to dryness, leaving 16.4 g of residue. This was dissolved in chloroform–ethyl acetate (4:1) and chromatographed through a 3.2 × 61 cm column containing 237 g of Florisil. After the sugar by-products were eluted with 600 ml of chloroform, further elution with 725 ml of ethyl acetate afforded the anomeric mixture of nucleosides (7.2 g, 44%). Recrystallization from 59 ml of chloroform afforded 2.94 g (17.5%) of the β anomer of **3** (which contains a trace of the α anomer), R_f 0.30 and 0.20 (trace). The mother liquors were concentrated and rechromatographed through a column of the same size, eluting with 4.5 l. of chloroform and then 1.2 l. of 5% ethyl acetate in chloroform, to obtain 3.20 g (19%) of the α anomer of **3**, R_f 0.20.

Preparation of 3 with Mercuric Cyanide Present.—The general procedure is illustrated by expt 7 in Table II. The 2-acetamido-6-chloropurine (1a, 13.5 g, 63.8 mmol) was silylated as described above. The filtered solution of 1b and benzene washes (total, about 850 ml) and 32 g of mercuric cyanide were stirred and heated (oil bath, temperature 120°) to 60–65°. The 29.0 g (74.5 mmol) of the chloro sugar 2 was added in one portion, and the stirred mixture was rapidly brought to reflux (about 5 min) and maintained at reflux temperature for 50 min.

The reaction mixture was evaporated to dryness. The residual amber gums were dissolved in 500 ml of methylene chloride, filtered to remove the mercuric cyanide, washed successively with 250 ml of 30% potassium iodide solution and 150 ml of water, dried, and evaporated.

The crude **3** (contains solvent; over 36 g, the theoretical yield) was dissolved in a hot solution of 500 ml of chloroform and 800 ml of carbon tetrachloride, left at room temperature overnight, then chilled for 4 hr in Dry Ice and filtered. The white crystalline β-**3** was thoroughly washed with 800 ml of cold (chilled over Dry Ice) chloroform–carbon tetrachloride (2:3) and dried for 3 hr at 56° (1 mm) to afford 16.4 g (45%) of β-**3** (this contains a little α-**3**). Some amber gums on the walls of the crystallization flask were discarded.

The filtrate from the crystallization was passed through a 5.4 × 32.5 cm column containing 300 g of Florisil, eluting with chloroform–carbon tetrachloride. The first 2.87 l. of eluate contained 3.78 g of sugar products, the next 1.20 l., about 0.27 g of sugar plus other material. When product began to appear in the next 0.375 l., the solvent was changed to ethyl acetate–chloroform–carbon tetrachloride (5:2:3) and the product was rapidly stripped off with 2.13 l., affording fraction A, 21.5 g of mainly crude α-**3** (contains solvent; theoretical yield is 19.6 g). This chromatography operation took about 3.5 hr.

A 9.0-g portion of fraction A was chromatographed through 300 g of Florisil on a 5.4-cm diameter column eluting with chloroform (1.0 l.) and 5% ethyl acetate in chloroform (3.7 l.). Traces of α-**3** appeared toward the end of that fraction. The next two fractions, 10 l. of 7% ethyl acetate in chloroform and 6.0 l. of 10–13% ethyl acetate in chloroform, afforded 6.0 g (equivalent to 14.3 g of fraction A) of α-**3**, which was at least 99.5% anomerically pure by the quantitative chromatography and uv measurement techniques employed by LePage.[4b] The properties of α-**3** agreed with literature values except the rotation: $[\alpha]^{21}D$ −62° (*c* 0.5, $CHCl_3$) and lit.[2a] $[\alpha]^{24}D$ −55° ($CHCl_3$); uv max (EtOH) 225 nm (ε 30,600), 245 (sh, 37,400) and 284 (10,600);[19] nmr ($DCCl_3$–DMSO-d_6) δ 10.20 (s, 1, NHAc), 8.38 (s, 1, H-8), other features compatible with structure. For comparison, into the same tube was added some β-**3**: nmr (above tube) δ 10.32 (s, 1, NHAc), 8.32 (s, 1, H-8). For β-**3** alone: nmr (DMSO) δ 10.65 (s, 1, NHAc), 8.42 (s, 1, H-8), 7.9–6.95 (4 d, 8, 2 COC_6H_4-Me), 6.42 (t, 1, $J_{1'-2'}$ = 7 Hz, H-1′), 5.75 (m, 1, H-3′), 4.50 (m, 3, H-4′, 2 H-5′), 3.15 (m, 2, H-2′), 2.25 and 2.21 (both s, 6, 2 $C_6H_4CH_3$), 2.04 (s, 3, $COCH_3$). Other properties agreed with literature values.[2] In the succeeding fractions, β-**3** began to appear, so that all the remaining nucleosides were rapidly stripped off with ethyl acetate to afford 1.33 g (equivalent to 2.86 g of fraction A) of α-**3** and β-**3**. Total material recovered, 7.33 g. The overall yields are β-**3** (contains little α-**3**), 45%; α-**3**, 40%; mixture of α-**3** and β-**3**, 8%.

2-Acetamido-6-chloro-9-(2,3,5-tri-*O*-acetyl-β-D-xylofuranosyl)-9*H*-purine (6a).—A 3.5-g (16.5 mmol) portion of 1a was silylated as above and filtered. The filtrate and benzene washes (total, 350 ml) were treated with 10.0 g (39.5 mmol) of mercuric cyanide and 40 ml of a benzene solution containing 8.02 g (23.1 mmol) of 2,3,5-tri-*O*-acetyl-D-xylofuranosyl bromide.[20] After 2 hr at reflux temperature, the reaction was worked up as above. Purification through a 125 g column of Florisil gave, on elution with methylene chloride and then ethyl acetate, 5.76 g (62%) of **6a**, R_f 0.50 in methanol–ethyl acetate (2:8), identical by tlc, ir, uv, and other properties with **6a** prepared from the mercury derivative of 1a.[16]

2-Acetamido-6-chloro-9-(2,3,5-tri-*O*-benzyl-D-arabinofuranosyl)-9*H*-purine (9). A. Silylation with TMCS.—A small portion (0.53 g, 2.5 mmol) of 1a was silylated as above. The filtered benzene solution was evaporated to dryness. The residue of silylated base was taken up in 75 ml of dry ethylene dichloride, and combined with 20 g of mercuric cyanide, 2.0 g of molecular sieves, and 3.0 mmol of 2,3,5-tri-*O*-benzyl-D-arabinosyl chloride (**8**).[17] The mixture was heated at reflux for 17 hr. The reaction mixture was filtered, and the filtrate was *immediately* chromatographed through 45 g of Florisil in a 1.6 × 60 cm column. After elution of by-products in 1.0 l. of ethylene dichloride–methylene chloride (1:9), the product was eluted in 800 ml of methylene chloride containing an increasing amount of ethyl acetate (initially, 10%; finally, 20%). Evaporation of the solvent left 1.0 g (67%) of an anomeric mixture of **9**: R_f 0.83 and 0.70 in ethyl acetate, after four passes.

B. Silylation with Hexamethyldisilazane.—A mixture of 4.23 g (20.0 mmol) of 1a and 0.9 g of ammonium sulfate in 70 ml of hexamethyldisilazane was stirred and heated at reflux for 4 hr, with protection from moisture. The solution was evaporated to dryness at 50°, leaving the silylated 1a as a colorless syrup. To this was added 6.72 g (26.5 mmol) of mercuric cyanide and 80 ml of dry benzene. This mixture was stirred and heated to incipient reflux; to this was rapidly added an 80-ml benzene solution of 20.7 mmol of **8** [from 13.85 g (20.7 mmol) of 2,3,5-tri-*O*-benzyl-1-*O*-(*p*-nitrobenzoyl)-D-arabinose[17]]. The mixture was stirred and heated at reflux for 16 hr under a nitrogen atmosphere. The reaction mixture was worked up as for **3** (with mercuric

(18) (a) M. Hoffer, *Chem. Ber.*, **93**, 2777 (1960); (b) C. C. Bhat in "Synthetic Procedures in Nucleic Acid Chemistry," Vol. 1, W. W. Zorbach and R. S. Tipson, Ed., Interscience, New York, N. Y., 1968, p 521.

(19) The literature[2a] values for the uv of α-**3** were determined in ethanol, not $CHCl_3$.

(20) O. P. Crews, Jr., and L. Goodman, ref 18b, p 139.

cyanide present). The residue in 125 ml of methylene chloride was chromatographed through 200 g of Florisil on a 3.5 × 32 cm column. The product 9 (11.2 g, 91%) was eluted in fractions totaling 1.4 l. of 10% ethyl acetate in methylene chloride. A portion of a central fraction was evaporated to give the analytical sample of 9: R_f 0.85 (α anomer) and 0.72 (β anomer) in ethyl acetate, four passes; ir (neat) 3.05 (NH), 5.88 (NAc), 6.21, 6.32, 6.60 μ (characteristic of all 2-AcNH-6-Cl-9-R-purines, with areas under 6.21 and 6.32 peaks approximately equal); nmr ($DCCl_3$) δ 8.47 (broad, NHAc), 8.40 and 8.22 (both s, 1, H-8 of anomers), 7.38 and 7.26 (both s, 12, 3 C_6H_4Me), 6.43 (d, $J_{1',2'}$ = 4 Hz, H-1' of β-9), 6.26 (d, $J_{1',2'}$ = 2 Hz, H-1' of α-9), 4.68, 4.67, 4.62, 4.58, and 4.55 (all s, 6, $CH_2C_6H_5$), 4.3–3.80 (several m, 5, H-2'–H-5'), 2.52 (s, 3, $NCOCH_3$); uv max (pH 1) 225 nm (sh) (ϵ 24,800), 260 (sh) (17,100), 288 (15,100); (pH 7) 225 nm (sh) (ϵ 25,300), 260 (sh) (18,900), 291 (17,100); (pH 13) 267 nm (9300).

Anal. Calcd for $C_{33}H_{32}ClN_5O_5 \cdot 1.5\ H_2O$: C, 61.8; H, 5.50; N, 10.9. Found: C, 61.6; H, 5.41; N, 10.78.

Another portion of 9, 2.43 g, was chromatographed through a 3.2 × 45 cm column of silica gel (110 g) eluting with 40% ethyl acetate–cyclohexane to afford first 0.75 g of pure α-9, R_f 0.29, then 1.04 g of anomeric mixture, R_f 0.18–0.29, and finally 0.53 g of pure β-9, R_f 0.18 (all R_f's on same tlc plate after two passes). CD results[21] as well as nmr confirmed the structural assignments of these anomers. α-9 had nmr ($DCCl_3$) δ 8.20 (s, H-8), 6.21 (d, 1, $J_{1',2'}$ = 2 Hz, H-1'); uv, identical with that of the anomeric mixture. *Anal.* Calcd for $C_{33}H_{32}ClN_5O_5$: C, 64.5; H, 5.25; N, 11.4. Found: C, 64.6; H, 5.31; N, 11.1. β-9 had nmr ($DCCl_3$) δ 8.37 (s, H-8), 6.37 (d, 1, $J_{1',2'}$ = 4 Hz, H-1'); uv, identical with that of the anomeric mixture. Found: N, 11.4%.

2-Amino-6-chloro-9-(2-deoxy-3,5-di-*O*-toluoyl-D-ribofuranosyl)-9*H*-purine (4).—Hexamethyldisilazane was used to silylate 2.00 g (11.6 mmol) of 2-amino-6-chloropurine (1c); and the product was treated for 1.5 hr at reflux with 4.65 g (12 mmol) of 2, as described in procedure B for 9, above. The reaction mixture was worked up as above to give 5.99 g (99%) of 4. A portion (1.0 g) was chromatographed through 70 g of Florisil on a 3.2 × 27.5 cm column with ethyl acetate–methylene chloride (1:4). The first 500 ml of eluent was discarded. The next 400 ml afforded 0.85 g (84%) of the analytically pure 4: R_f 0.39 and 0.48 (multiple passes); $[\alpha]^{21}D$ −41° (*c* 0.5, $CHCl_3$); ir (Nujol) 2.35 (sh), 3.00, 3.11 (NH_2), 5.78 (C=O, esters), 5.88 (sh, NHAc), 6.18, 6.36, and 6.58 μ (characteristic of all 2-NH_2-6-Cl-9-R-purines; area under 6.18 peak is much greater than that under 6.36); uv max (pH 1) 218 nm (ϵ 25,400), 242 (28,200), 317 (13,100); (pH 7) 219 nm (ϵ 24,200), 243 (27,500), 317 (14,500); (pH 13) 230 nm (sh) (ϵ 30,300), 307 (7000); nmr ($DCCl_3$) δ 8.20, 8.08 (both s, H-8 of α- and β-4; some overlapping with COC_6H_4Me), 7.5 (both m, 1, H-1' anomers), 6.4 (2, NH_2), 2.44, 2.42 (both s, 6, $2C_6H_4CH_3$) with satisfactory integration for the eight aryl and five other furanose protons.

Anal. Calcd for $C_{26}H_{24}ClN_5O_5$: C, 59.8; H, 4.63; N, 13.4. Found: C, 59.8; H, 4.67; N, 13.2.

The formation of 4 from 3 by refluxing in ethanol containing sodium acetate was followed by tlc. The time for conversion of half of 3 to 4 was 30 min for the α anomer and 3 hr for the β anomer. Methanol solutions of 3 exposed to the atmosphere had formed detectable amounts of 4 (by tlc) after 2 or 3 days.

2-Amino-6-chloro-9-(1,3,5-tri-*O*-acetyl-β-D-xylofuranosyl)-9*H*-purine (6b).—A portion (0.43 g, 2.5 mmol) of 1c was silylated with hexamethyldisilazane as above and treated with the xylosyl bromide [prepared from 1.00 g (3.14 mmol) of 1,2,3,5-tetra-*O*-acetyl-β-D-xylofuranose] for 2.3 hr at reflux temperature of benzene. This reaction gave a theoretical yield of 6b, which was purified through a column of 60 g of Florisil, eluting with methanol–methylene chloride (1:9) to afford 0.89 g (84%) of 6b as a white foam, R_f 0.45 in ether–ethyl acetate (4:6). The analytical sample of 6b was from another run that had been chromatographed through Florisil and eluted with 2% methanol in benzene. This 6b had $[\alpha]D$ +13.9° (*c* 0.5, $CHCl_3$); ir (Nujol) 2.86 (sh), 2.98, 3.10 (NH_2), 5.69 (CO, ester), 6.18, 6.36, 6.57 μ (like those in 4); uv max (pH 1) 219 nm (ϵ 28,800), 247 (7700), 307 (8270); (pH 7) 221 nm (ϵ 29,100), 247 (7500), 307 (8400); (pH 13) 245 nm (sh) (ϵ 7100), 308 (7900); nmr ($DCCl_3$) δ 8.10 (s, 1, H-8), 6.12 (d, $J_{1',2'}$ = 2.5 Hz, H-1'), 6.4 (broad, NH_2), 2.15 and 2.10 (both s, 9, $3COCH_3$) with satisfactory integration for the other five furanose protons. Some benzene was also present.

Anal. Calcd for $C_{16}H_{18}ClN_5O_7 \cdot 0.2\ C_6H_6$: C, 46.6; H, 4.37; N, 15.2. Found: C, 46.1; H, 4.69; N, 15.2.

9-β-D-Xylofuranosylguanine (7). A. **From 6b.**—A solution of 0.53 g (1.24 mmol) of 6b and 0.32 ml (4.5 mmol) of mercaptoethanol in 10 ml of MeOH was treated with 4.4 ml of 1 *N* sodium methoxide in methanol and 0.04 ml of water, and heated at reflux for 3.5 hr. After cooling at 5°, the crystalline sodium salt of 7 was collected and slurried with 5 ml of MeOH and 0.4 ml of glacial acetic acid to give, in two crops, 0.18 g (51%) of 7: mp 234–240° (lit.[15] mp 238–240°); R_f 0.10 in methanol–ethyl acetate (2:8), identical with that of authentic 7; $[\alpha]^{21}D$ −34° (*c* 0.25, H_2O) [lit.[15] $[\alpha]^{21}D$ −36.5° (*c* 0.25, H_2O)]; uv max (pH 1) 255 nm (ϵ 11,700), 275 (sh) (8000); (pH 7) 252 (ϵ 12,600), 275 (sh) (8700); (pH 13) 257 (ϵ 10,600), 264 (sh) (10,700), identical with that of authentic 7; uv max (pH 1) 255 nm (ϵ 11,600), 275 (sh) (8000); (pH 7) 252 (ϵ 12,900), 270 (sh) (9200); (pH 13) 257 (ϵ 10,800), 265 (sh) (10,800); identical by ir with authentic 7. The mother liquors still contained 7 by tlc.

The overall yield of 7 from 1c was 43% as compared with 23% by the previous method.[15]

B. **From 6a.**—An 8.96-g (19.1 mmol) portion of 6a was treated with mercaptoethanol and base, as above, to yield 3.05 g (56%) of 7, identical with authentic 7[15] by ir, tlc, uv, and rotation.

2-Amino-6-chloro-9-(2,3,5-tri-*O*-benzyl-D-arabinofuranosyl)-9*H*-purine (10).—The silyl derivative of 1c [prepared from 1.04 g (5.81 mmol) of 1c and hexamethyldisilazane] and 6.00 mmol of 8 [prepared from 4.00 g (6.00 mmol) of 2,3,5-tri-*O*-benzyl-1-*O*-(*p*-nitrobenzoyl)-D-arabinofuranose][17] were heated in refluxing benzene for 2 hr, worked up as above, and chromatographed through 100 g of Florisil on a 3.4 × 29.5 cm column, with 10% ethyl acetate in Skellysolve B as eluent. From 850 ml of the eluent was obtained 3.05 g (92%) of analytically pure 10 as a gum: R_f 0.36 in cyclohexane–ethyl acetate (6:4); ir (Nujol) 2.85 (sh), 3.00, 3.11 (NH_2), 6.19, 6.37, and 6.59 μ (characteristic of 2-NH_2-6-Cl-9-R-purines); uv max (pH 1) 209 nm (ϵ 26,000), 237 (21,700), 260 (sh) (20,100), 321 (15,700); (pH 7) 215 nm (ϵ 26,000), 236 (25,000), 260 (22,400), 321 (17,100); (pH 13) 250 nm (sh) (ϵ 24,500), 314 (15,300); nmr ($DCCl_3$) δ 8.18 and 8.08 (both s, 1, H-8 of β- and α-10, respectively), 6.35 (d, ~0.5, $J_{1',2'}$ = 4 Hz, H-1' of β), 6.17 (d, ~0.5, $J_{1',2'}$ = 2 Hz, H-1' of α-10), 5.3 (broad, 2, NH_2), 4.60, 4.57, and 4.56 (all s, 6, 2 $C_6H_4CH_3$) with satisfactory integration for the 15 aryl and 5 other furanose protons. The ratios of anomers is about 1, but slightly richer in β. The H-8 and H-1' protons are assigned by analogy to those of 9.

Anal. Calcd for $C_{31}H_{30}ClN_5O_4$: C, 65.2; H, 5.29; N, 12.2. Found: C, 65.2; H, 5.50; N, 12.2.

Registry No.—**1b,** 35095-89-7; **2,** 4330-21-6; **α-3,** 35129-57-8; **β-3,** 7356-40-3; **α-4,** 35095-92-2; **β-4,** 35095-93-3; **α-5,** 35085-15-5; **6b,** 35085-16-6; **α-9,** 35085-17-7; **β-9,** 35085-18-8; **α-10,** 35085-19-9; **β-10,** 35085-24-6; guanine, 73-40-5; thioguanine, 154-42-7.

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(21) J. Ingwall, manuscript in preparation.

Synthesis of [4′,4′-Bis(glycine),5′,5′-bis(valine)]actinomycin D, a Tetra-*N*-demethylactinomycin[1a,b]

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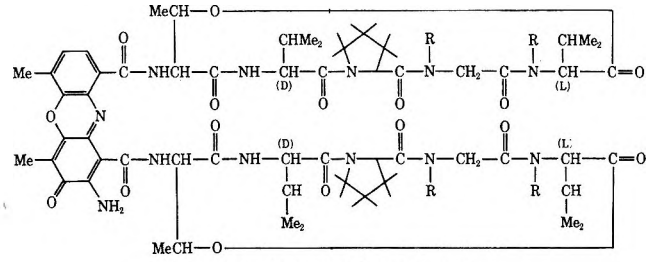
An analog of actinomycin D, lacking the four *N*-methyl groups in the peptide lactone rings, has been synthesized by a route involving *first* the cyclization of the tetra-*N*-demethyl linear pentapeptide; condensation of this cyclic peptide with the benzoyl moiety, followed by successive reduction and oxidation by standard procedures, led to [Gly⁴′,Val⁵′]actinomycin D. CD spectra indicate that this analog has a conformation different from that of actinomycin D in methanol, chloroform, and acetonitrile solutions, but a very similar conformation in hexafluoroacetone. Biologically, [Gly⁴′,Val⁵′]actinomycin D showed no antimicrobial or cytotoxic activity in several tests.

Because several members of the actinomycin group, particularly actinomycins C_3 and D (C_1),[1c] have shown considerable activity as antitumor agents, studies to elucidate their structures, to characterize them completely, and to synthesize them and numerous analogs have been reported, notably by Brockmann and coworkers[2] and Meienhofer.[3] We are now reporting our synthesis of a tetra-*N*-demethyl analog, [4′,4′-bis(glycine),5′,5′-bis(valine)]actinomycin D (**1a**), in which



1a, R = H, [Gly⁴′, Val⁵′]actinomycin D
b, R = CH_3, actinomycin D

the four *N*-methyl groups of the cyclic peptide lactones in actinomycin D have been replaced by hydrogens.

Heretofore, reported syntheses involved condensation of linear peptide with a benzoyl moiety, followed by cyclization of the peptide chain, either *via* ester bond formation (lactonization)[2c,2e,2f] or *via* peptide bond formation.[2a,2b,2d,3b] Cyclization of the peptide by either method was either preceded or followed by formation of the chromophore involving catalytic hydrogenation and finally controlled oxidation. We proposed a slightly different approach, *i.e.*, *first* cyclizing a suitably protected linear peptide **9**, *via* peptide bond formation, and then condensing the deblocked cyclic peptide **14** with the benzoyl residue, followed finally by hydrogenation and oxidation[4] (Scheme I).

The first steps were suggested by Meienhofer's synthesis[3b,5] but differed in methods of coupling.

The benzyl ester of *tert*-butyloxycarbonyl-L-threonine (**2**) was prepared by the method of Baer.[6] After removal of the major portion of excess benzyl chloride, dry pyridine was added and the mixture was heated to quaternize the last traces of benzyl chloride. Condensation of **2** with benzyloxycarbonyl-L-valine by the DCC method, in acetone containing dry pyridine, afforded the protected didepsipeptide (**3a**) as a colorless syrup, which was hydrogenolyzed to yield the partially deblocked **3b**. Crystallization from water gave the purified material, with overall yields of 55–70%, based on **2**. Action of the active ester, benzyloxycarbonylglycine *N*-hydroxysuccinimide,[7] on the triethylamine salt of **3b** gave **4**, a sticky material, which was used directly in the next step. A small amount was converted to the crystalline, analytically pure dicyclohexylammonium salt. A salt of similar purity was prepared from the product obtained by DCC coupling of benzyloxycarbonylglycine with **3b**. Hydrogenolysis of **4** produced **5**, a crystalline solid, which was converted to **6**, also an analytically pure solid, *via* condensation with benzyloxycarbonyl-L-proline-*N*-hydroxysuccinimide ester. Hydrogenolysis of **6** gave the partially blocked tetrapeptide **7**. Since this tetrapeptide swelled in organic solvents to a gelatinous material, it was not purified but was used as the air-dried solid. Molar ratios of the amino acids, after acid hydrolysis, were in the expected range.

The best method found for preparing the linear pentapeptide **9** utilized the reaction of benzyloxy-D-valine *p*-nitrophenyl ester with the triethylammonium salt of **7** to give **8**, followed by hydrogenolysis of that pentapeptide. Compound **8** was obtained in 78% yield after purification on a Sephadex LH-20 column, using methanol as eluent and uv spectra of the fractions to follow the purification. Attempts to condense benzyloxycarbonyl-D-valine with the triethylammonium salt of **7** by other standard coupling methods (use of DCC or Woodward's Reagent K, or *N*-hydroxysuccinimide ester) gave poor results. In particular, the mixed anhydride method gave, as a major product, based on nmr evidence, *O*-(isobutyloxycarbonyl-L-prolylglycyl-

(1) (a) Abbreviations follow the rules of the IUPAC–IUB Commission on Biochemical Nomenclature in *J. Biol. Chem.*, **241**, 2491 (1966), and in *Biochemistry*, **5**, 1445, 2485 (1966); **6**, 362 (1967). (b) This work was supported by Public Health Service Research Grant No. 5 R01 CA10571 from the National Cancer Institute. (c) Actinomycin D was so designated by L. C. Vining and S. A. Waksman [*Science*, **120**, 389 (1954)]; subsequently it was found to be identical with actinomycin C_1, so identified by H. Brockmann and H. Gröne, *Naturwissenschaften*, **41**, 65 (1954).

(2) (a) H. Brockmann and H. Lackner, *Naturwissenschaften*, **47**, 230 (1960); (b) *ibid.*, **48**, 555 (1961); (c) *ibid.*, **51**, 435, 384 (1964); (d) *Chem. Ber.*, **100**, 353 (1967); (e) *ibid.*, **101**, 1312 (1968); (f) H. Brockmann, H. Lackner, R. Mecke, G. Troemel, and H.-S. Petras, *ibid.*, **99**, 717 (1966).

(3) (a) J. Meienhofer, *J. Org. Chem.*, **32**, 1143 (1967); (b) *Experientia*, **24**, 776 (1968); (c) *J. Amer. Chem. Soc.*, **92**, 3771 (1970).

(4) Recently, after our yet-unpublished work had been completed, a similar approach was reported by E. Atherton, R. P. Patel, and J. Meienhofer, XXIIIrd IUPAC Meeting, Boston, Mass., 1971.

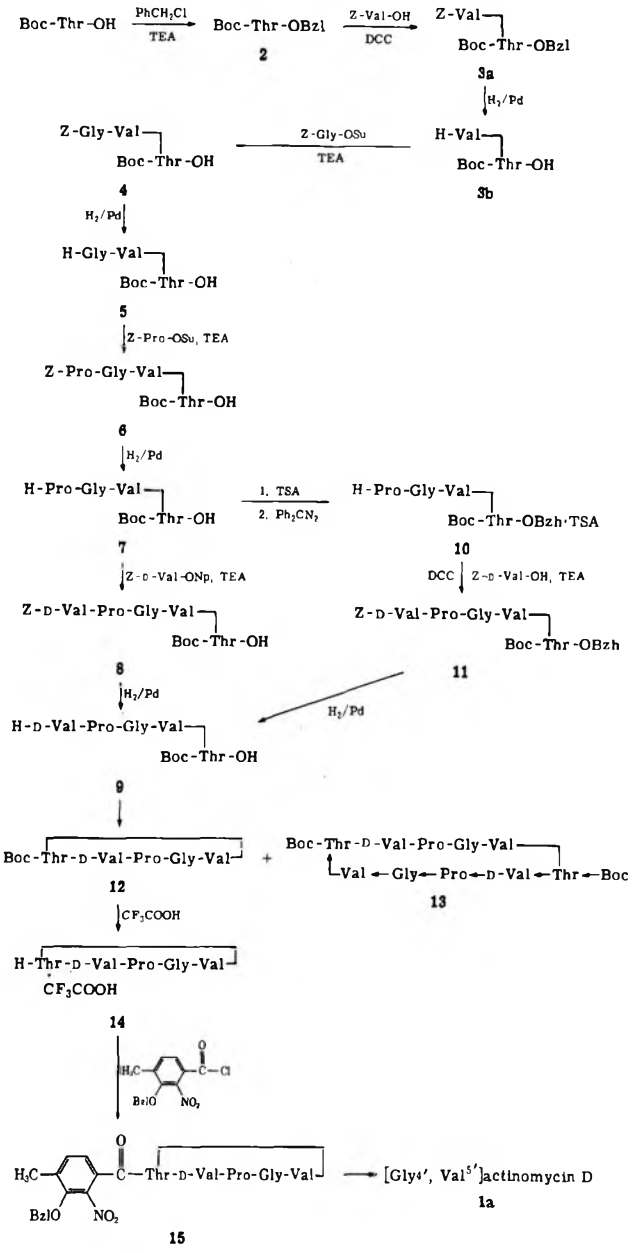
(5) We thank Dr. J. Meienhofer for sending us a preprint[3b] and also for details of preparation of *O*-(L-*N*-methylvalyl)-*N*-*tert*-butyloxycarbonyl-L-threonine and a sample for comparison with the identical product which we had prepared by DCC condensation.

(6) E. Baer and F. Eckstein, *J. Biol. Chem.*, **237**, 1451 (1962).

(7) G. W. Anderson, J. E. Zimmerman, and F. M. Callahan, *J. Amer. Chem. Soc.*, **86**, 1839 (1964).

SCHEME I

SYNTHESIS OF TETRA-*N*-DEMETHYLACTINOMYCIN[a]



[a] All amino acids are of L configuration unless otherwise noted; DCC = dicyclohexylcarbodiimide; TEA = triethylamine; TSA = *p*-toluenesulfonic acid.

L-valyl)-*N*-*tert*-butyloxycarbonyl-L-threonine, resulting from "reverse" opening of the anhydride intermediate.

Another approach to **9** was successful but less convenient. The benzhydryl ester **10** was prepared from **7** by the method of Aboderin[8] to give a broadly melting solid. This was coupled with benzyloxycarbonyl-D-valine by the DCC method, affording a syrup that could be purified by preparative thick layer chromatography. Similar results and yields were obtained when benzyloxycarbonyl-D-valine *p*-nitrophenyl ester[9,10] was allowed to react with **10**. The blocked pentapeptide **11** so obtained was a sticky solid that could be converted to **9** by hydrogenolysis.

(8) A. A. Aboderin, G. R. Delpierre, and J. S. Fruton, *J. Amer. Chem. Soc.*, **87**, 5469 (1965).

(9) M. Bodanszky and V. du Vigneaud, *ibid.*, **81**, 5688 (1959).

(10) B. Iselin, W. Rittel, P. Sieber, and R. Schwyzer, *Helv. Chim. Acta*, **40**, 373 (1957).

Cyclization of **9** by several different methods was attempted. The presence of cyclic pentapeptide in crude reaction mixtures was readily determined by mass spectroscopy; uncyclized **9** and cyclic decapeptide **13** were not sufficiently volatile to be detected. Thus it was determined that only small amounts of **12** were produced when DCC, alone or with *N*-hydroxysuccinimide, was used. Slightly better yields were indicated when *o*-phenylene chlorophosphite[11] in diethyl phosphite was used, but lower molecular weight, volatile products were also produced. Since this procedure involved heating at 140° for about 5 hr, it is quite likely that cleavage of the *tert*-butyloxycarbonyl group in the slightly acidic medium occurred to some extent.

Crude yields of 30–55% resulted from cyclization[12] of the *p*-nitrophenyl ester of **9** (prepared by reaction of di-*p*-nitrophenylsulfite[13] with the *p*-toluenesulfonate salt of **9**) in pyridine at high dilution (about 0.05%, 5×10^{-4} *M* final concentration), the ester being slowly added over a period of several hours. The crude cyclization product was purified on a Sephadex LH-20 column;[14] only a very small amount of **13** was present; yields of purified **12** were in the 23–47% range.

Removal of the *tert*-butyloxycarbonyl blocking group with trifluoroacetic acid at room temperature proceeded cleanly to give **14**, which was then coupled, in the dark, with 2-nitro-3-benzyloxy-4-methylbenzoyl chloride[15] in the presence of *N*-methylmorpholine.[3b] Purification of the product **15** on Sephadex LH-20 gave a 69% yield of slightly discolored solid from which the analytical sample was obtained.

Tetra-*N*-demethylactinomycin (**1a**) was obtained by catalytic reduction followed by controlled oxidation.[16] The orange-red product, purified by precipitation from ethyl acetate solution with hexane (79%), had uv and ir spectra very similar to those of actinomycin D.

The CD spectra of **1a** in methanol, acetonitrile, and chloroform are very similar (Figure 1). It appeared that in methanol solution there was a concentration dependence, but detailed studies were not carried out. The *position* and *magnitudes* of the envelopes are very much like those in the spectra of actinomycin D in the same solvents, but *reversals* of the signs are observed in each case (Figure 2). This is most strikingly seen in the methanol solutions (Figure 3). In hexafluoroacetone hydrate, the CD spectra of actinomycin D and **1a** were very similar; the sign of the Cotton effects in both spectra were the same as those in the spectra of methanol, acetonitrile, or chloroform solutions of **1a** (Figure 4).[17] Thus, we conclude that **1a** essentially has the same conformation in these four solvents, while actinomycin D has similar conformation in hexa-

(11) M. Rothe and F. Eisenbeiss, *Z. Naturforsch. B*, **21**, 814 (1966).

(12) R. Schwyzer and P. Sieber, *Helv. Chim. Acta*, **40**, 624 (1957).

(13) B. Iselin and R. Schwyzer, *ibid.*, **43**, 1763 (1960).

(14) (a) H. Aoyagi, T. Kato, M. Waki, O. Abe, R. Okawa, S. Makisumi, and N. Izumiya, *Bull. Chem. Soc. Jap.*, **42**, 782 (1969); (b) M. Kondo and N. Izumiya, *ibid.*, **43**, 1850 (1970).

(15) B. Weinstein, O. P. Crews, M. A. Leaffer, B. R. Baker, and L. Goodman, *J. Org. Chem.*, **27**, 1389 (1962).

(16) W. G. Hanger, W. C. Howell, and A. W. Johnson, *J. Chem. Soc.*, 496 (1958).

(17) It should be noted that the CD spectrum of actinomycin D in hexafluoroacetone sesquihydrate obtained in these laboratories is somewhat different from that reported by Ascoli,[18] particularly in that his spectrum showed a strong absorption maximum ($\Delta\epsilon$ +30) at about 290 nm, while we found no such absorption.

(18) F. Ascoli, P. De Santis, and M. Savino, *Nature (London)*, **227**, 1237 (1970).

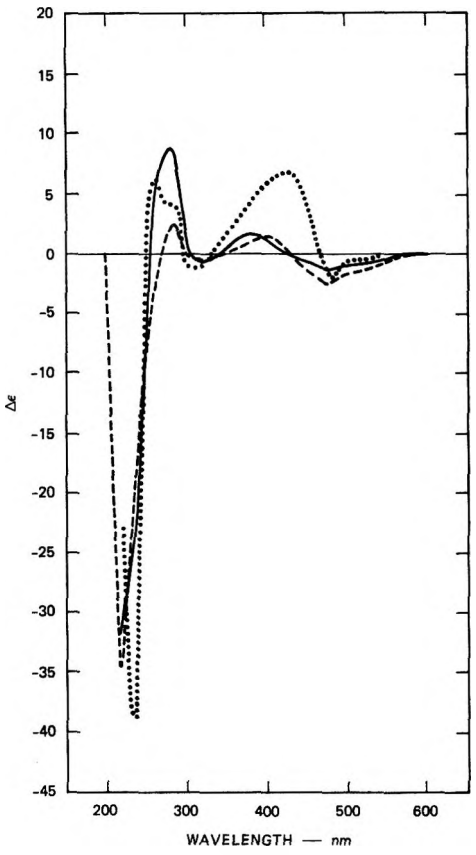


Figure 1.—CD spectra of tetra-*N*-demethylactinomycin: (——) CH_3OH solution, 6×10^{-5} *M*; (· · · ·) CH_3CN solution, 3.9×10^{-5} *M*; (- - - -) HFA solution, 9×10^{-5} *M*.

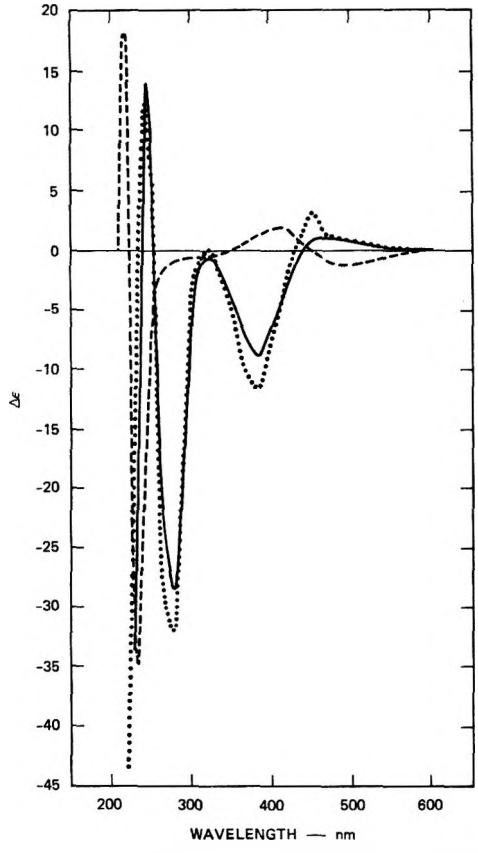


Figure 2.—CD spectra of actinomycin D: (——) CH_3OH solution, 6.5×10^{-5} *M*; (· · · ·) CH_3CN solution, 3.7×10^{-5} *M*; (- - - - -) HFA solution, 1×10^{-4} *M*.

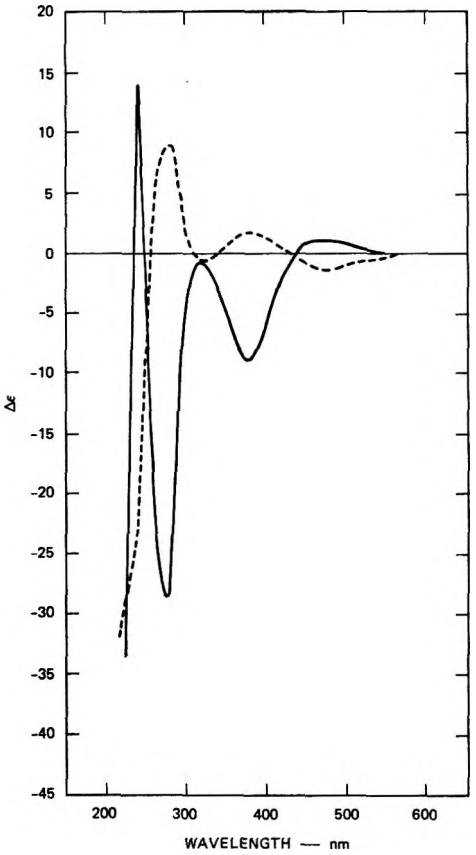


Figure 3.—CD spectra in CH_3OH solution: (——) actinomycin D, 6.5×10^{-5} *M*; (- - - -) **1a**, 6×10^{-5} *M*.

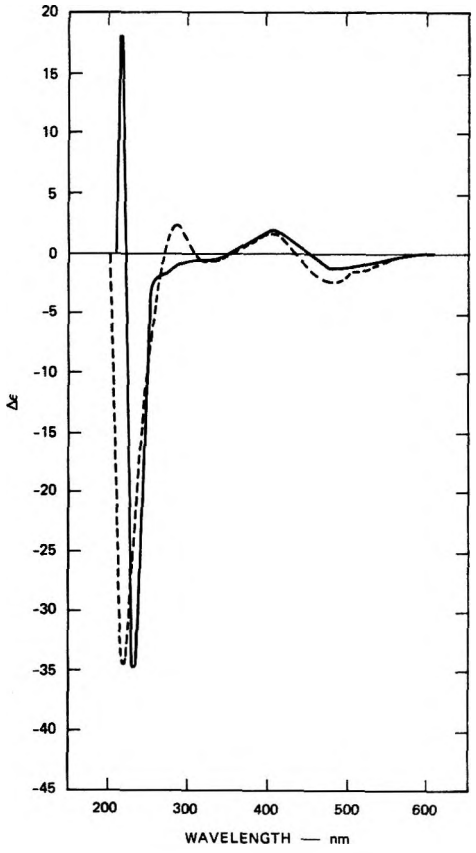


Figure 4.—CD spectra in hexafluoroacetone sesquihydrate solution: (——) actinomycin D, 1×10^{-4} *M*; (- - - -) **1a**, 9×10^{-5} *M*.

fluoroacetone, but a different conformation in methanol, chloroform, and acetonitrile. The increased potential for hydrogen bonding in **1a**, which has two more –NH groups in each peptide lactone ring, may be an important factor.

The nmr spectrum of **15** was very similar to that of (2-nitro-3-methoxy-4-methylbenzoyl)-L-threonyl-D-valyl-L-prolylsarcosyl-*N*-methyl-L-valine (threonine-hydroxyl) lactone, reported by Lackner.[19] However, the nmr spectrum of **1a** was different in many areas from that of actinomycin, which has been variously interpreted.[20-25] Again, these differences reflect increased or changed hydrogen bonding and other conformational changes in the peptide lactone rings.

Antibacterial tests showed **1a** to be inactive against *B. subtilis*, *Staph. aureus*, and a number of other organisms; also, it was noncytotoxic to KB cells in tissue culture tests.

Experimental Section

Methods.—Melting points, uncorrected, were determined on a Fisher-Johns apparatus. Ultraviolet spectra were obtained on a Cary 14 recording spectrophotometer; circular dichroism, on a Durrum-Jasco ORD/UV-5 spectropolarimeter equipped with a Sproul Scientific SS-20 CD modification. Optical rotations were determined at the D line on a Perkin-Elmer 141 polarimeter. Thick layer preparative chromatography was accomplished on Brinkman silica gel HF, 2 mm thick; thin layer chromatography, on silica gel 0.25 mm thick; detection was accomplished by ultraviolet light, by iodine, and by acidic ninhydrin solution. Compounds containing the *tert*-butyloxycarbonyl moiety were detected by first spraying with trifluoroacetic acid, heating at 100° for 5 min, and then spraying with ninhydrin solution and heating again. The following solvent systems were used: (A) methanol–chloroform (3:1); (B) water; (C) 2-butanol–formic acid–water (75:13.5:11.5). Purifications on the Sephadex LH-20 column (2.5 × 72 cm) were accomplished with methanol, flow rate 100 ml/hr, collecting 3-ml fractions; separation was followed by weighing of residues after solvent removal from individual fractions and by thin layer chromatography. Hydrogenolyses were carried out over palladium black (Engelhard) at 1 atm and room temperature. Magnesium sulfate was used as drying agent, and all evaporations were done under reduced pressure (water aspirator). Molecular weight determinations were performed by E. Meier, Department of Chemistry, Stanford University, Stanford, Calif.

***N*-*tert*-Butyloxycarbonyl-L-threonine Benzyl Ester (2).**—Using the method of Baer and Eckstein,[6] *N*-*tert*-butyloxycarbonyl-L-threonine was converted to **2** in 90% yields, mp 40–41°, tlc R_f 0.88 (A). A sample for analysis was recrystallized from ether–petroleum ether (bp 30–60°): $[\alpha]^{21}D$ −19.6° (*c* 1, CH_3OH).

Anal. Calcd for $C_{16}H_{23}NO_5$: C, 62.1; H, 7.49; N, 4.53. Found: C, 62.4; H, 7.60; N, 4.71.

***O*-(Benzyloxycarbonyl-L-valyl)-*N*-*tert*-butyloxycarbonyl-L-threonine Benzyl Ester (3a).**—To a stirred solution of **2** (10.2 g, 33 mmol) and benzyloxycarbonyl-L-valine (12.55 g, 50 mmol) in dry acetone (30 ml), cooled in ice, was added dry pyridine (3.13 ml, 50 mmol) and DCC (7.25 g, 35 mmol). The mixture was stirred at 0° for 1 hr and then overnight at room temperature. After removal of dicyclohexylurea, which was washed with acetone, the combined filtrates were concentrated; the residual syrup was dissolved in ethyl acetate and washed successively with 1 *M* citric acid solution (twice), dilute $NaHCO_3$ solution, and finally saturated NaCl solution (three times), dried, and concentrated; the crude, syrupy product [19 g, tlc R_f 0.8 (alumina, $CHCl_3$) with trace impurity, mass spectral data confirming the expected structure] was used without further purification in the next step.

***O*-(L-Valyl)-*N*-*tert*-butyloxycarbonyl-L-threonine (3b).**—The crude **3a** (19 g) was dissolved in absolute ethanol (200 ml) and subjected to hydrogenolysis; the white solid that separated was dissolved by addition of alcohol. After the catalyst was removed and washed with ethanol, the combined filtrates were concentrated. The solid white product was thoroughly triturated with ether several times, collected on a filter (7.38 g, mp 173–178°), and recrystallized from water (50 ml): yield 6.11 g (60% based on **2**); mp 180.5–181.5°; tlc R_f 0.42 (B), 0.72 (C); $[\alpha]^{21}D$ +42.4° (*c* 1, CH_3OH).

Anal. Calcd for $C_{14}H_{26}N_2O_6 \cdot 3H_2O$: C, 45.2; H, 8.66; N, 7.52. Found: C, 45.4; H, 8.58; N, 7.58.

***O*-(Benzyloxycarbonylglycyl-L-valyl)-*N*-*tert*-butyloxycarbonyl-L-threonine (4).**—To a suspension of **3b** (7.28 g, 22.9 mmol) in dry tetrahydrofuran (50 ml) was added triethylamine (3.2 ml, 22.9 mmol) and then a solution of benzyloxycarbonylglycine *N*-hydroxysuccinimide ester[7] (7.0 g, 22.9 mmol) in dry tetrahydrofuran (25 ml). After the mixture had been stirred overnight at room temperature, the clear solution was concentrated to a syrupy residue, which was dissolved in ethyl acetate and washed with 1 *M* citric acid solution and then with water (three times). It was dried and concentrated, yielding a sticky foam, 11.7 g, which was not purified further. Mass spectral data obtained from the crude methyl ester (prepared by the action of diazomethane[26]) indicated that the expected structure was obtained. A small portion in ether solution was converted to its dicyclohexylammonium salt (96%) and recrystallized from ethanol–ethyl acetate: mp 165–168°; $[\alpha]^{19.5}D$ −9.4° (c 0.7, CH_3OH); tlc R_f 0.9 (A), 0.9 (C).

Anal. Calcd for $C_{36}H_{58}N_4O_9$: C, 62.6; H, 8.46; N, 8.11. Found: C, 62.8; H, 8.62; N, 8.16.

***O*-(Glycyl-L-valyl)-*N*-*tert*-butyloxycarbonyl-L-threonine (5).**—Hydrogenolysis of **4** in ethanol yielded **5** in 65–75% yield after recrystallization from water: mp 185–187° dec; tlc R_f 0.4 (B), 0.6 (C); $[\alpha]^{22}D$ −1.11 ± 0.3° (*c* 1, CH_3OH).

Anal. Calcd for $C_{16}H_{29}N_3O_7 \cdot {}^1/_2H_2O$: C, 50.0; H, 7.87; N, 10.9. Found: C, 49.7; H, 7.77; N, 10.8.

***O*-(Benzyloxycarbonyl-L-prolylglycyl-L-valyl)-*N*-*tert*-butyloxycarbonyl-L-threonine (6).**—To a suspension of **5** (6.24 g, 16.6 mmol) in dry tetrahydrofuran (50 ml) was added triethylamine (2.33 ml, 16.6 mmol) and then a solution of benzyloxycarbonyl-L-proline *N*-hydroxysuccinimide ester[7] (5.74 g, 16.6 mmol) in dry tetrahydrofuran. It was stirred overnight at room temperature and then worked up as described for **4**. The crude, solid white product was recrystallized from ethyl acetate (450 ml): yield 6.76 g; mp 183–184.5°; $[\alpha]^{23}D$ −44.5° (*c* 1, CH_3OH); tlc R_f 0.83 (A); second and third crops (1.93 g) raised the total yield to 8.69 g (87%). A small sample was converted to the methyl ester; its mass spectrum confirmed the expected structure.

Anal. Calcd for $C_{29}H_{42}N_4O_{10}$: C, 57.4; H, 6.98; N, 9.25. Found: C, 57.3; H, 6.76; N, 9.17.

***O*-(L-Prolylglycyl-L-valyl)-*N*-*tert*-butyloxycarbonyl-L-threonine (7).**—Hydrogenolysis of **6** in ethanol gave a very gelatinous material in 83–91% yield; after ether trituration and air-drying, mp 136–141°; tlc R_f 0.2 (B), 0.46 (C). Amino acid analysis (6 *N* HCl, 110°, 22 hr) gave the following molar ratios: valine:proline:glycine:threonine, 1.1:1.1:1.1:1.0.

***O*-(Benzyloxycarbonyl-D-valyl-L-prolylglycyl-L-valyl)-*N*-*tert*-butyloxycarbonyl-L-threonine (8).**—A solution of benzyloxycarbonyl-D-valine *p*-nitrophenyl ester[9,10] (5.57 g, 15 mmol) in dry tetrahydrofuran (50 ml) was added, with stirring, to a solution of **7** (7.08 g, 15 mmol) and triethylamine (2.10 ml, 15 mmol) in dry tetrahydrofuran (100 ml) and dry dimethylformamide (75 ml); a yellow color developed immediately. After standing for 20 hr at room temperature, the solution was concentrated *in vacuo* to a yellow syrup, which was dissolved in ethyl acetate and washed with 1 *M* citric acid solution and then saturated NaCl solution. Solvent was removed from the dried solution, yielding 12.82 g of a friable foam, which was divided into four portions. Each portion was purified on the Sephadex LH-20 column, using methanol solvent. The fractions were collected and combined according to their ultraviolet spectra; from the four reproducible runs, the material obtained in elution volumes of 208–280 ml totalled 9.0 g.

(19) H. Lackner, *Tetrahedron Lett.*, 3189 (1970).
(20) B. H. Arison and K. Hoogsteen, *Biochemistry*, **9**, 3976 (1970).
(21) F. Conti and P. De Santis, *Nature (London)*, **227**, 1239 (1970).
(22) T. A. Victor, F. E. Hruska, C. L. Bell, and S. S. Danyluk, *Tetrahedron Lett.*, 4721 (1969).
(23) T. A. Victor, F. E. Hruska, K. Hikichi, S. S. Danyluk, and C. L. Bell, *Nature (London)*, **223**, 302 (1969).
(24) P. De Santis, R. Rizzio, and G. Ughetto, *Tetrahedron Lett.*, 4309 (1971).
(25) H. Lackner, *ibid.*, 2221 (9171).
(26) The simplified techniques used in preparing peptide derivatives suitable for mass spectral determinations were suggested by Dr. David W. Thomas, who also obtained and interpreted the spectra.

Crystallization from ethyl acetate yielded 8.0 g, mp 109–115° with softening around 104°, and a second crop of 0.29 g (total yield, 78%): $[\alpha]^{23}D$ −11.7° (c 1, CH_3OH); tlc R_f 0.85 (A), 0.88 (C); uv max (CH_3OH) 252 mμ (ε 180), 257 (215), 261 (166), 264 (179), 267 (117).

Anal. Calcd for $C_{34}H_{51}N_5O_{11}$: C, 57.9; H, 7.28; N, 9.93. Found: C, 57.8; H, 7.64; N, 9.98.

O-(L-Prolylglycyl-L-valyl)-N-*tert*-butyloxycarbonyl-L-threonine Benzhydryl Ester p-Toluenesulfonate (10).—The *p*-toluenesulfonic acid salt of **7** was prepared by lyophilizing a solution of **7** (1.89 g, 4 mmol) and *p*-toluenesulfonic acid monohydrate (0.76 g, 4 mmol) in water (15 ml): mp 114–118°; nmr spectrum showed no loss of *tert*-butyloxycarbonyl. The benzhydryl ester (according to the method of Aboderin[8]) was obtained by treating the tosylate salt of **7** (419 mg, 0.65 mmol) with diphenyldiazomethane[27] (188 mg, 0.97 mmol) in dimethylformamide (2 ml) at 50°. After removal of solvent, addition of ether caused separation of an oil which, upon trituration with petroleum ether, solidified to a white solid (320 mg) with a broad melting point below 115°.

O-(Benzyloxycarbonyl-D-valyl-L-prolylglycyl-L-valyl)-N-*tert*-butyloxycarbonyl-L-threonine Benzhydryl Ester (11).—A solution of **10** (305 mg, 0.38 mmol) in ethyl acetate was treated with triethylamine (0.10 ml, 0.76 mmol) and water (3–4 ml). The ethyl acetate layer was separated, washed with water (three times), dried, and concentrated to yield a friable foam (234 mg), which was coupled with benzyloxycarbonyl-D-valine (113 mg, 0.45 mmol) in methylene chloride (3 ml), using DCC (82 mg, 0.4 mmol). After the mixture had been stirred overnight, it was worked up as described for **3a**; the crude product (330 mg) showed on tlc (ethyl acetate) one spot near the front and one with R_f about 0.4. Attempted purification on a silica column, ethyl acetate eluent, yielded 198 mg of still impure syrup, collected in the first half of the eluate, and 50 mg of sryup, homogeneous on tlc, collected in the second half of the eluate. The impure material was purified on a thick layer chromatographic plate to give 131 mg of sticky product, homogeneous on tlc, R_f 0.4 (ethyl acetate), total yield 181 mg (56%).

O-(D-Valyl-L-prolylglycyl-L-valyl)-N-*tert*-butyloxycarbonyl-L-threonine (9). A. From 11.—Hydrogenolysis of **11** (130 mg, 0.15 mmol) in absolute ethanol gave a syrup (106 mg), which solidified upon trituration with ether, yielding a white solid (84 mg, 100%), mp 138–141°. The mass spectrum of a derivatized sample (*tert*-butyloxycarbonyl group removed and the product acetylated and permethylated) showed the presence of the tetrapeptide expected upon cleavage of the ester bond in **9** during permethylation.

Anal. Calcd for $C_{26}H_{45}N_5O_9 \cdot 1^1/_2H_2O$: C, 52.2; H, 8.08; N, 11.7. Found: C, 52.2; H, 8.10; N, 11.4.

B. From 8.—Hydrogenolysis of **8** (4.0 g, 5.67 mmol) in ethanol produced, after removal of ethanol and trituration with ether, a white solid (3.12 g, 96%), mp 136.5–138°, tlc R_f 0.17 (B).

N-(*tert*-Butyloxycarbonyl)-L-threonyl-D-valyl-L-prolylglycyl-L-valine (Threonine Hydroxy) Lactone (12).—A solution of **9** (228 mg, 0.4 mmol) and *p*-toluenesulfonic acid monohydrate (130 mg, 0.4 mmol) in water (5 ml) was lyophilized, leaving a white powder, which was then mixed with di-*p*-nitrophenyl sulfite[13] (130 mg, 0.4 mmol) and dissolved in a solution of dry pyridine (0.07 ml, 0.8 mmol) in ethyl acetate (6 ml). After the solution had been heated (drying tube) at 50° for 3 hr, it was concentrated to a syrup, which was triturated several times with dry ether. A solution of the sticky residue in dry dimethylformamide (3 ml) containing a drop of glacial acetic acid was added dropwise, with stirring, over a 2-hr period to dry pyridine (500 ml) at 55–60°. Stirring at this temperature was continued for 2.5 hr, the pyridine was removed by distillation, and the residue was dissolved in ethyl acetate. After the solution had been washed successively with 1 *M* citric acid solution, dilute $NaHCO_3$ solution, and saturated NaCl solution (until washings were neutral), it was dried and concentrated, yielding a yellow syrup. Purification on Sephadex LH-20 column gave a small amount of material (about 8 mg, decapeptide **13**) in the fractions of elution volume 190–208 ml, and in later fractions (elution volumes 232–259 ml), a much larger amount of **12** (112 mg, 50% yield), mp 118–128°. After two recrystallizations from ethyl acetate–petroleum ether, a first crop (50 mg, mp 128–130°) and a second crop (30 mg, mp 124–128°) were obtained: tlc (acetone–$CHCl_3$, 2:1) R_f 0.72; tlc (CH_3OH–$CHCl_3$, 1:20) R_f 0.40 (R_f 0.0 for **13** in these two systems); $[\alpha]^{22}D$ +15.0° (c 1, CH_3OH).

Anal. Calcd for $C_{26}H_{43}N_5O_8$: C, 56.4; H, 7.83; N, 12.7. Found: C, 56.6; H, 8.04; N, 12.7.

Amino acid analysis (6 *N* HCl, 110°, 22 hr) gave the following molar ratios: glycine:valine:threonine:proline, 0.9:1.7:0.8:1.0.

Microbiological assay[28] (4 *N* HCl, 120°, 16 hr hydrolysis) gave the following molar ratios: L-valine:L-threonine:L-proline, 1.0:0.8:1.0.

A sample of **12**, mp 126–130°, obtained in another preparation, was found to have a molecular weight of 546 (theoretical value 553), while **13**, mp 172–175°, had a molecular weight of 1113 (theoretical value 1106).

The mass spectrum of **12** showed a parent peak of *m/e* 553 and various other peaks representing expected fragments upon loss of $-OC_4H_9$, $-C_4H_8-$, and $-CO_2$ and cleavages of the molecule.

L-Threonyl-D-valyl-L-prolylglycyl-L-valine (Threonine Hydroxyl) Lactone Trifluoroacetic Acid Salt (14).—A solution of **12** (60 mg) in trifluoroacetic acid (2 ml), after standing for 1 hr at room temperature, was concentrated to a tan syrup; several triturations with ether yielded a white solid (53 mg), mp 138–141°.

Anal. Calcd for $C_{21}H_{35}N_5O_6 \cdot CF_3CO_2H \cdot {}^1/_2H_2O$: C, 47.9; H, 6.47; N, 12.2 F, 9.89. Found: C, 47.9; H, 6.60 N, 12.1; F, 9.82.

(2-Nitro-3-benzyloxy-4-methylbenzoyl)-L-threonyl-D-valyl-L-prolylglycyl-L-valine (Threonine Hydroxyl) Lactone (15).—Light was excluded as much as possible during preparation and purification of **15**, since it is very light sensitive. To an ice-cooled, stirred solution of **14** (1.19 g, 2.1 mmol) in a mixture of dry tetrahydrofuran (5 ml) and dry dimethylformamide (2 ml) was added *N*-methylmorpholine (0.74 ml, 6.4 mmol) followed by a solution of 2-nitro-3-benzyloxy-4-methylbenzoyl chloride (641 mg, 2.1 mmol) in dry tetrahydrofuran (5 ml). The turbid mixture was stirred, cold, for 1 hr and then stored in the refrigerator overnight. After it was diluted with ethyl acetate (100 ml), the reaction mixture was washed successively with 1 *N* HCl (twice) and saturated NaCl solution (four times), dried, and concentrated to yield a crude, friable foam (1.56 g). Purification on the Sephadex LH-20 column yielded 1.04 g (69%) of a pale yellow solid. Precipitation from ethyl acetate solution with hexane gave a white solid (630 mg), mp 131–136°. A sample was reprecipitated for analysis, mp 134–139°.

Anal. Calcd for $C_{36}H_{46}N_6O_{10}$: C, 59.8; H, 6.41; N, 11.6. Found: C, 59.9; H, 6.67; N, 11.4.

Tetra-*N*-demethylactinomycin. 2-Amino-4,6-dimethylphenoxazinone-(3)-1,9-bis[carbonyl-L-threonyl-D-valyl-L-prolylglycyl-L-valine (Threonine Hydroxyl) Lactone] (1a).—A solution of **15** [529 mg, 0.73 mmol, dried for 18 hr at 80° (0.1 mm) over KOH pellets and P_2O_5] in methanol (20 ml) was hydrogenated over 5% palladium on carbon, in the dark. After 2 hr, the mixture was filtered, under nitrogen, through Celite, collecting the filtrate in a flask containing phosphate buffer solution, pH 7.2 (27 ml) and potassium ferricyanide (700 mg, 2.12 mmol). The red-brown mixture was stirred for 20 min, and then diluted with water (80 ml) and ethyl acetate (80 ml). The aqueous layer was separated and extracted three times with ethyl acetate (30-ml portions). The combined ethyl acetate layers were washed successively with 5% $NaHCO_3$ solution (twice), 1 *M* HCl solution (twice), and saturated NaCl solution until washings were neutral. After the solution had been dried and concentrated, the residue was dissolved in ethyl acetate and precipitated with hexane to give 350 mg (79%): mp 213–220°; uv max (CH_3OH) 443 mμ (ε 21,500), 426 (20,900), 237 (38,800), 205 (41,200); $[\alpha]^{28}D$ −433.6° (*c* 0.25, CH_3OH).[29]

Anal. Calcd for $C_{58}H_{78}N_{12}O_{16} \cdot 2H_2O$: C, 56.4; H, 6.69; N, 13.6. Found: C, 56.6; H, 6.39; N, 13.4.

Microbiological assay of tetra-*N*-demethylactinomycin using a number of different organisms in *in vitro* tests carried out at Stanford Research Institute showed it to be totally inactive. Thus, for actinomycin D, the minimal inhibitory concentration for antimicrobial activity (μg/ml), using *B. subtilis*, was 0.5; for tetra-*N*-demethylactinomycin, >1000; using *Staph. aureus*, for actinomycin D, 20; for tetra-*N*-demethylactinomycin, >200.

(27) J. B. Miller, *J. Org. Chem.*, **24**, 560 (1959).

(28) Stereospecific assays for L-threonine, L-valine, and L-proline were done by Shankman Laboratories, Los Angeles, Calif.

(29) This rotation value was obtained on a Durrum-Jasco ORD/UV-5 spectropolarimeter, since the Perkin-Elmer instrument gave irreproducible results, presumably because the solution was so highly colored.

Also cytotoxic tests against KB cells in tissue culture tests carried out under the auspices of the National Cancer Institute showed the tetra-*N*-demethylactinomycin to be completely inactive (at 100 μg/ml). Actinomycin D strongly inhibits KB cells (ID_{50}, 0.002 μg/ml).[3c]

Registry No.—**1a**, 35085-42-8; **2**, 33662-26-9; **3b**, 35085-44-0; **4**, 35085-45-1; **5**, 35085-46-2; **6**, 35085-47-3; **7**, 35085-48-4; **8**, 35085-49-5; **9**, 35085-50-8; **10**, 35085-51-9; **12**, 35085-52-0; **13**, 35085-55-3; **14**, 35085-53-1; **15**, 35085-54-2.

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The Solid-State Dehydrogenation of L-1,4-Cyclohexadiene-1-alanine Hydrate to L-Phenylalanine

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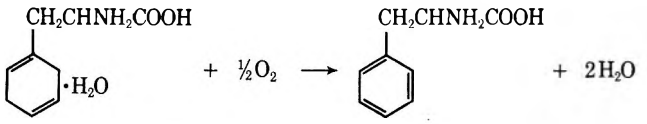
The solid-state dehydrogenation of L-1,4-cyclohexadiene-1-alanine (I) to phenylalanine is shown to be associated with a hydrated form of I. Crystalline, unhydrated, L-, D-, and DL-1,4-cyclohexadiene-1-alanine products are stable, as are the solid cupric and the newly prepared hydrochloride and sodium salts of I. Dehydrogenation requires molecular oxygen. The reaction is accelerated by reducing the pressure in the presence of desiccant, or, at atmospheric pressure, by heating. It takes place at 100° without racemization. The reaction is interpreted to be a transfer of allylic hydrogen to atmospheric oxygen facilitated by aquation.

Organic reactions known to occur in the solid state include largely cyclization and elimination reactions at temperatures below the melting point and radiation-induced decomposition and polymerization reactions. Uncatalyzed, facile dehydrogenation of hydroaromatics at room temperature or below, to our knowledge, has not been described as a solid-state reaction. This communication describes a novel solid-state reaction occurring at room temperature with no catalyst present, the dehydrogenation of L-1,4-cyclohexadiene-1-alanine hydrate to L-phenylalanine (eq 1). In this facile



solid/gas reaction aquation appears to be a means of lowering the activation energy.[1]

L-1,4-Cyclohexadiene-1-alanine (L-DiHPhe, I) is a new and effective antagonist of phenylalanine; it is obtained simply by a one-step Birch reduction of commercial phenylalanine (Phe).[2-4] Soon after its synthesis and properties had been described, L-DiHPhe was identified in three separate laboratories as a new, naturally occurring inhibitor in bacterial sources.[5] Although L-DiHPhe is stable in solution, as a solid at or below room temperature it was observed sometimes to dehydrogenate to Phe.[2] In contrast, DL-DiHPhe was stable in the solid state as well as in solution, which suggested stereospecificity in the solid-state dehydrogenation. Although a crystallization procedure was provided for preparing L-DiHPhe as a stable solid,[2] the side reaction was expected to limit the usefulness of this Phe antagonist for biological purposes.[6] Thus a systematic investigation of the dehydrogenation of DiHPhe was undertaken.

The dehydrogenation product had been identified originally as Phe on the basis of its chromatographic behavior. The product has now been isolated in crystalline form after preparative chromatography on the amino acid analyzer. Its nmr spectrum, optical rotation, and ability to support the growth of *Escherichia coli* 9723f mutant were the same as those of an authentic sample of L-Phe, thus confirming its identity and establishing that it forms without racemization.

The first reproducible observation of dehydrogenation came when material to be dried had been placed in a high vacuum over phosphorus pentoxide at room temperature. In 3 days, as much as 44% transformation to Phe had occurred, whereas another portion of L-DiHPhe left under atmospheric conditions for the same time had undergone only a small change.[7] L-DiHPhe was then observed to separate into two crystalline forms. Stable prisms formed from a dilute solution in 80% ethanol, and unstable needles formed from a hot, saturated solution in 80% ethanol or from a solution in methanol–ethyl acetate. When dissolved at different concentrations in the same solvent (80%

(1) The conversion of 1,4-cyclohexadiene to benzene is carried out at temperatures of 350–500° [see V. A. Mironov and A. A. Akhrem, *Chem. Abstr.*, **68**, 2607f (1968)].

(2) M. L. Snow, C. Lauinger, and C. Ressler, *J. Org. Chem.*, **33**, 1774 (1968).

(3) B. A. Shoulders, R. M. Gipson, R. J. Jandacek, S. H. Simonsen, and W. Shive, *J. Amer. Chem. Soc.*, **90**, 2992 (1968).

(4) (a) C. Ressler, D. S. Genghof, C. Lauinger, and M. L. Snow, *Fed. Proc., Fed. Amer. Soc. Exp. Biol.*, **27**, 764 (1968); (b) D. S. Genghof, *Can. J. Microbiol.*, **16**, 545 (1970).

(5) Private communications: T. Yamashita, Fujisawa Pharmaceutical Co., Ltd., Osaka, Japan, 1968 [see also T. Yamashita, N. Miyairi, K. Kunugita, K. Shimizu, and H. Sakai, *J. Antibiot.*, **23**, 537 (1970)] and G. E. Mallett, Lilly Research Laboratories, 1968. J. P. Scannell, D. L. Pruess, T. C. Demny, T. H. Williams, and A. Stempel, Abstracts, 160th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1970.

(6) Amino acid antagonists of phenylalanine suitable for incorporation into peptides have been needed for efforts to modify hormone activity. *p*-Fluorophenylalanine has been used in this way for the synthesis of bradykinin analogs: E. D. Nicolaides, M. K. Craft, and H. A. DeWald, *J. Med. Chem.*, **6**, 524 (1963).

(7) Observed by Miss C. Lauinger.

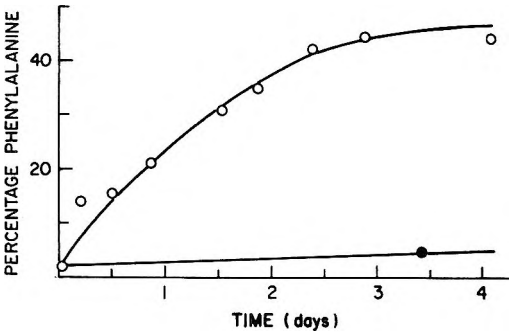


Figure 1.—Pressure dependence of the rate of the dehydrogenation of L-1,4-cyclohexadiene-1-alanine hydrate to L-phenylalanine at 25°: compound allowed to stand over P_2O_5 in a desiccator evacuated to 2 Torr, O—O; compound allowed to stand at 1 atm in a sealed tube, ●—●; and over P_2O_5 in an unevacuated desiccator (not shown) when 6.5% Phe formed (see "Kinetics of Dehydrogenation").

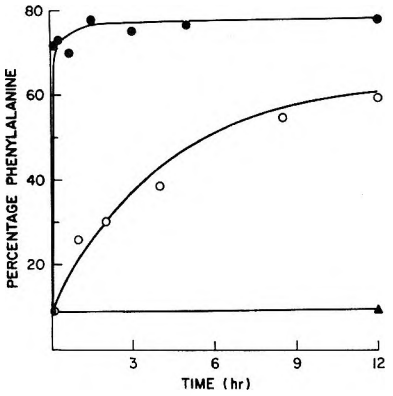


Figure 2.—Temperature dependence of the rate of the dehydrogenation of L-1,4-cyclohexadiene-1-alanine hydrate to L-phenylalanine at atmospheric pressure: 25°, ▲—▲; 60°, O—O; 100°, ●—● (see "Kinetics of Dehydrogenation").

ethanol) and recrystallized, either form could be converted into the other and, in so doing, could adopt the stability characteristic of the new form. Both forms had essentially identical ir spectra and remained stable in 0.2% aqueous solution (5 hr, 100°), suggesting that these were allotropic crystalline forms having different reactivities.[8]

Elemental analysis of the unstable crystalline form of L-DiHPhe indicated that it was a hydrate. Nuclear magnetic resonance spectra in D_2O, which showed an enhanced HDO peak of the expected intensity for the needles but for both forms were otherwise identical, supported this conclusion.

Figure 1 shows the kinetics of dehydrogenation of L-DiHPhe hydrate under reduced pressure and in the presence of desiccant. Dehydrogenation at atmospheric pressure could be accelerated markedly by heating. After 2 hr at 60°, the product contained 30% Phe; after 10 min at 100° the per cent of Phe was 70% (Figure 2). Rates were determined by automatic amino acid analysis.[9]

The stability of various other preparations was then examined by heating several milligrams of solid material in a test tube at 100° for 5 or 8 hr[10] or by placing it over P_2O_5 in an evacuated deisscator for 3.5 days (Table I). The copper complex of L-DiHPhe, which is stable under prolonged storage,[2] was also highly stable when heated or placed in a vacuum. The newly prepared recrystallized hydrochloride and the sodium salt obtained by titration with 1 equiv of 1 *N* NaOH were also much more stable than the hydrate. Unhydrated L-DiHPhe was stable both when heated and under reduced pressure. Even when unhydrated L-DiHPhe was heated in a small, sealed tube in the presence of 0.5–1 part (4.8–9.3 equiv) of added water, less than 1% dehydrogenation resulted, thus showing that for effective dehydrogenation water must be bound intramolecularly in L-DiHPhe.

D-DiHPhe, likewise, crystallized into an unstable form and a stable unhydrated form. Since DL-DiHPhe was known to be stable, equal amounts of the unstable forms of L- and D-DiHPhe were dissolved in water and the solution was concentrated to dryness. On being heated, the residue increased in Phe content from 4.4% to only 7.4%. When recrystallized and then heated, the residue increased from 1.3% to only 2.3% Phe. Originally, DL-DiHPhe had been isolated directly from the Birch reduction mixture of DL-Phe by washing with water to remove salts, whereas L-DiHPhe, because of its greater solubility, had been isolated *via* its copper chelate.[2] L-DiHPhe, therefore, was isolated directly, and DL-DiHPhe was now isolated *via* its copper chelate; their stability characteristics, however, remained unchanged. These experiments were carried out before the unstable form of L-DiHPhe was identified as a hydrate and helped rule out the possibility that an impurity present only in L- and D-DiHPhe was responsible for the dehydrogenation. The stereospecificity of the dehydrogenation is only apparent; it may be accounted for by the observation that, in contrast to the L isomer, DL-DiHPhe does not readily form a molecular hydrate.

When solid samples of L-DiHPhe hydrate were well equilibrated with N_2 gas in sealed, dry ampoules before being heated for 4 hr at 100°, the content of Phe rose from 1% to only 2.7% whereas with O_2 gas the Phe content rose to 63%. Under the same conditions, moreover, DiHPhe or DiHPhe hydrate in 0.2% aqueous solutions saturated with O_2 gas increased in Phe content from 3.3% to less than 5%. Thus atmospheric oxygen, as well as water of hydration, participates in the solid-state dehydrogenation of I.

Repeated analysis showed 0.75 equiv of water to be bound as the hydrate. Since the maximum extent of dehydrogenation on heating has been near 75%, one might speculate that the water of hydration participates stoichiometrically in the dehydrogenation.[11] So far, all attempts to desiccate L-DiHPhe hydrate have

(8) For a discussion of this problem, see H. Morawetz, *Science*, **152**, 705 (1966).

(9) D. H. Spackman, W. H. Stein, and S. Moore, *Anal. Chem.*, **30**, 1190 (1958).

(10) These experiments were carried out before determination of the dehydrogenation kinetics. Heating for 30–60 min should be adequate.

(11) A possible role for the peroxy radical in the dehydrogenation of the hydrate was investigated. L- and DL-DiHPhe as well as L-DiHPhe hydrate, representing both stable and unstable compounds, and the dehydrogenation mixture all had detectable amounts of peroxide (1–3%), as determined by I_2–thiosulfate titrimetry: V. R. Kokatnur and M. Jelling, *J. Amer. Chem. Soc.*, **63**, 1432 (1941). One sample of L-DiHPhe hydrate that had been left in air for 2 months, with occasional evacuation, had 64% Phe and close to 10% peroxide. Peroxide was not detected in cyclohexadiene, hydroquinone, L-3,4-dihydroxyPhe, or L-Phe. 2,6-Di-*tert*-butyl-4-methylphenol, *n*-propylgallate, and hydroxyurea (1:10 w/w) added as peroxide scavengers were ineffective in retarding the dehydrogenation occurring under reduced pressure over P_2O_5 of the solid L-DiHPhe hydrate.

TABLE I

SELECTIVE DEHYDROGENATION OF 1,4-CYCLOHEXADIENE-1-ALANINE TO PHENYLALANINE IN THE SOLID STATE

Compd	Untreated		Heated at 100°		Evacuated over P_2O_5 (84 hr at 25°)	
	Phe, %[a]	$[\alpha]_D$[b]	Phe, %[a]	$[\alpha]_D$[b]	Phe, %[a]	$[\alpha]_D$[b]
L-DiHPhe	1.7[c]	−58.6	1.3[d]	−60.1	1.8	−60.6
D-DiHPhe	3.6[e]	+58.5	3.9[d]	+57.9	4.0	+57.5
DL-DiHPhe	1.0		1.4[d]		1.0	
L-DiHPhe·0.75H_2O	2.6[f]	−64.1[g]	78	−36.3[g,h]	46[i]	−49.4[g,i]
D-DiHPhe·0.75H_2O	0.7	+60.8[g]	74	+36.8[g,k]		
L- and D-DiHPhe·0.75H_2O						
Mixed	4.4	+0.1	7.4			
Mixed and recrystallized	1.3	−1.4	2.3		1.4	
L-DiHPhe						
1/2 Cupric salt	0.2		0.8		0.4[l]	
Sodium salt	0.2[m]		5.5			
Hydrochloride	0.2[m]		2.5		1.9	
	3.8		6.9		4.5	

[a] Compounds also contained 2–4% Ene. [b] Observed rotations are in 1 *N* acetic acid, *c* 0.5, unless indicated otherwise. Calculated rotations of treated hydrated samples are based on amino acid and water analyses; for L-Phe, $[\alpha]_D$ −34.5°[15] was used; for L- and D-DiHPhe, $[\alpha]_D$ of starting DiHPhe hydrate was corrected for content of Phe, Ene, and water; for Ene, $[\alpha]_D$ of DiHPhe was used. [c] After storage for 4 years at 5°, Phe content was 2.5%. [d] Heated for 5 hr; others, for 8 hr. [e] *Anal.* Calcd for $C_9H_{13}NO_2$ containing 3.6% Phe and 2.1% Ene: C, 64.3; H, 7.82; N, 8.38. Found: C, 64.5; H, 7.9; N, 8.33. [f] After storage for 4 years at 5°, Phe content was 25%. [g] Rotation in water, *c* 0.5–1.0. [h] Calcd $[\alpha]_D$ −35.8°. [i] A portion standing simultaneously at atmospheric pressure contained 4.6% Phe. [j] Calcd $[\alpha]_D$ −49°. [k] Calcd $[\alpha]_D$ +35.6°. [l] After 7 months at 5°, Phe content was unchanged. [m] Phe content in starting DiHPhe hydrate.

resulted in dehydrogenation.[12] Moreover, little dehydrogenation of the hydrate occurred in a vacuum when the P_2O_5 was omitted from the desiccator. Perhaps the lattice water tends to solubilize oxygen within or at the surface of the crystal by hydrogen bonding.[13] Protected by such hydrogen bonding to the water, the oxygen reacts only slowly with the allylic ring hydrogen of L-DiHPhe unless the water is removed or thermal energy is supplied. When the hydrate was equilibrated with N_2 gas before the water of hydration was removed quantitatively, dehydrogenation was considerably less than if no attempts had been made to replace O_2 with N_2 (22% after 1 hr over P_2O_5 at 110° in an evacuated Alderhalden pistol). When heated further in air for 1 hr, however, such desiccated material underwent additional dehydrogenation, the Phe content rising to 78%. Perhaps desiccation of the hydrate leaves L-DiPhe in a conformation that is more susceptible to proton transfer to atmospheric oxygen than is the anhydrous L-DiHPhe obtained directly by crystallization. The described oxidation–reduction reaction can be considered to provide general support for various speculations that structured water plays a role in biological systems.[14]

Experimental Section

Elemental analyses were carried out by Micro-Tech Laboratories, Skokie, Ill. Water analyses were done by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y., or were carried out as given under "Attempts to Dry DiHPhe·0.75H_2O." Nuclear magnetic resonance spectra were obtained on a Varian A-60A or EM-300 spectrometer. Infrared spectra, melting points, which are corrected, and optical rotations were determined and automatic amino acid analyses were performed as described elsewhere.[2]

Preparation of Compounds.—DL-DiHPhe, L-DiHPhe·1/2Cu, and L-DiHPhe were prepared as described.[2] L-DiHPhe was crystallized from a 2% solution of 80% ethanol; D-DiHPhe and its hydrate were synthesized from D-Phe, $[\alpha]_D$ +33.3° (c 2, water) (lit.[15] $[\alpha]_D$ +34.5°), Mann Research Laboratories, N. Y., in the same manner as the L compounds. Analyses and properties are given in Table I.

L-DiHPhe·HCl.[16]—Concentrated HCl (0.83 ml, 10 mequiv) was added to a solution of L-DiHPhe·0.75H_2O (0.5 g, 2.77 mmol, 2.3% Phe) in 10 ml of water, and the solution was concentrated to dryness. The solid residue was crystallized from 95% tetrahydrofuran–ethyl acetate, yield 472 mg (85%), mp 194–198°. For analysis, the material was recrystallized twice, mp 193–195° (very rate dependent), $[\alpha]^{26}_D$ −39.9° (*c* 1, water). It contained 2.5% Phe and 3.7% cyclohexene-1-alanine (Ene).

Anal. Calcd for $C_9H_{14}ClNO_2$: C, 53.1; H, 6.93; N, 6.88; Cl, 17.4. Found: C, 52.9; H, 6.87; N, 7.00; Cl, 17.3.

L-DiHPhe·0.75H_2O.—L-DiHPhe was dissolved in a minimum of warm 80% ethanol and was allowed to crystallize at 25°. The solution was then placed in the cold no longer than overnight. Preparations were examined under the microscope for crystal type and uniformity. The hydrate tended to pack the solution with long needles, in contrast to L-DiHPhe, which had been known to separate well at the bottom of the solution into dense aggregates. The needles were collected and washed first with 80% ethanol, then with absolute ethanol, and finally with ether. The material also could be crystallized from a solution of it in warm methanol containing 1% H_2O and diluted with ethyl acetate. For analysis, samples were dried to constant weight by evacuation at the water pump in the absence of desiccant or under a stream of N_2 gas at atmospheric pressure.

Anal. Of seven samples obtained from L-DiHPhe solutions in 80% ethanol or methanol–ethyl acetate, six had CHN analyses for L-DiHPhe·0.75H_2O and one for L-DiHPhe·H_2O. Calcd for DiHPhe: C, 64.7; H, 7.84; N, 8.38. Calcd for DiHPhe·H_2O: C, 58.4; H, 8.12; N, 7.57. Calcd for DiHPhe·0.75H_2O containing 2.6% Phe and 3.1% Ene: C, 60.1; H, 8.04; N, 7.79. Found: C, 59.9; H, 7.51; N, 7.65. Calcd for DiHPhe·0.75 H_2O containing 1.05% Phe and 3.7% Ene: C, 60.1; H, 8.07; N, 7.78. Found: C, 59.7; H, 7.61; N, 8.02.

Nmr Confirmation of Hydration.—L-DiHPhe in 12.5% solution in D_2O containing 50 μl of NaOD, both 99.7 atom % D, showed after 20 min 3 vinyl H, 6 allylic H, 1 α-CH, and 3.0 HDO; calcd 3 HDO (exchangeable H). L-DiHPhe·0.75H_2O in

(12) A recent report describes an inorganic solid-phase transformation that involves hydration and has some characteristics in common with the dehydrogenation of L-DiHPhe. Isomerization of *trans*-$[Co(NH_3)_4Cl_2]IO_3 \cdot 2H_2O$ to *cis*-$[Co(NH_3)_4Cl_2]IO_3$ is accelerated by heating, and it occurs with samples kept at room temperature in a vacuum over P_2O_5 and on all attempts at desiccation. Moreover, the similar unhydrated trans bromate does not isomerize: H. E. LeMay, Jr., and J. C. Bailar, Jr., *J. Amer. Chem. Soc.*, **89**, 5577 (1967).

(13) In response to a query by a referee, it is noted that the various analytical data for the hydrate can also be reconciled reasonably well with a hemihydrate structure containing 0.125 g-mol O_2.

(14) D. T. Warner, *Annu. Rep. Med. Chem.*, 256 (1969).

(15) A. Meister, "Biochemistry of the Amino Acids," 2nd ed, Academic Press, New York, N. Y., 1965, p 141.

(16) This compound was prepared by Miss L. Diamond.

equimolar solution showed 3 vinyl H, 6 allylic H, 1 α-CH, and 4.4 HDO; calcd 4.5 HDO. Correction was made for the HDO in D_2O–NaOD and for the Phe + Ene content.

Attempts to Dry L-DiHPhe·0.75H_2O.—When heated on a hot block under a stream of H_2 gas at 100°, DiHPhe hydrate lost 3.5% in weight, at 120° 4.7–4.8%, and at 155° 6.9% (Micro-Tech). At 100 and 110° in a vacuum it lost 6.8 and 7.04%, respectively (Schwarzkopf); calcd (cor) for DiHPhe·0.75H_2O: 7.1%. The latter procedure was adopted for the determination of water. Heating at 139° with constant evacuation at 0.05 Torr was unreliable, since some material, which contained Phe and DiHPhe, condensed onto the cool portion of the Abderhalden pistol.

Kinetics of Dehydrogenation.—The timed experiment showing the effect of reduced pressure was carried out by placing 100–200 mg of L-DiHPhe·0.75H_2O in a 30-ml crystallizing dish over P_2O_5 in a desiccator (10-cm diameter) that was evacuated to 2 Torr for 2 min, closed, and then allowed to stand at 25°. At the times indicated in Figure 1, several milligrams were removed and dissolved in water for analysis. The desiccator was reevacuated to 2 Torr and allowed to stand, and the process was repeated. For comparison, one sample was kept at 1 atm in a sealed tube and another sample over P_2O_5 in an unevacuated desiccator.

The timed experiment showing the effect of temperature was conducted by heating 2- to 3-mg samples of L-DiHPhe·0.75H_2O in corked 3-ml test tubes in an oil bath heated to 60 or 100 ± 1.5°. At the times indicated in Figure 2, 1 ml of water was added, and the solutions were kept frozen until placed on the amino acid analyzer.

Isolation of L-Phenylalanine as the Dehydrogenation Product.—In batches of 20–30 mg per test tube, 448 mg of L-DiHPhe hydrate were heated for 5 hr in an oil bath at 100°, with approximately 78% conversion to Phe. Each batch was chromatographed on the amino acid analyzer in system 1.[2] Fractions of 1 ml were collected and analyzed with ninhydrin.[17] Phe, eluting at 69–78 ml, separated from DiHPhe, eluting at 87–92 ml. The combined eluate containing 281 mg of Phe was desalted on a column of 150 ml of Dowex 50 W X8 (H^+) resin, 100–200 mesh.[18] Two recrystallizations from 50% ethanol yielded 130 mg of L-Phe, a homogeneous product on the analyzer, $[\alpha]_D$ −33.6° (c 0.85, water) [lit.[15] $[\alpha]_D$ −34.5° (c 1, water)]. Its nmr spectrum as the carboxylate ion in D_2O was identical with that of commercial L-Phe. At concentrations of 5, 10, and 15 μg/ml in Anderson's asparagine medium[19] supplemented with 1.5 mg of $FeNH_4SO_4 \cdot 6H_2O$/l., it afforded the same growth for *E. coli* 9723f as did L-Phe.

Registry No.—L-1,4-Cyclohexadiene-1-alanine hydrate, 16055-12-2; L-phenylalanine, 63-91-2; L-DiHPhe·HCl, 32507-80-5.

Acknowledgments.—This work was aided by Grant NS 04316 from the U. S. Public Health Service and by the Muscular Dystrophy Associations of America. The author is indebted to Dr. Dorothy S. Genghof and Mr. Alan Shiffrin for the microbiological comparison, Dr. L. Wilson of Varian Associates and Mrs. Barbara Cottrell for obtaining the nmr spectra, and Miss Christine Lauinger and Miss Lillian Diamond for valuable assistance.

(17) S. Moore and W. H. Stein, *J. Biol. Chem.*, **211**, 907 (1954).
(18) E. Ratti, C. Lauinger, and C. Ressler, *J. Org. Chem.*, **33**, 1309 (1968).
(19) E. H. Anderson, *Proc. Nat. Acad. Sci. U. S.*, **32**, 120 (1946).

The Synthesis of Atheroline. A Route to Phenolic Oxoaporphines

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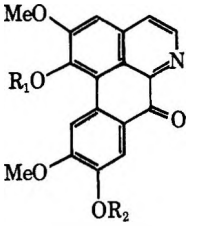
The alkaloid antheroline (II) has been synthesized. This work represents the first synthesis of a phenolic oxoaporphine base.

The yellow alkaloid atheroline occurs in the bark of *Atherosperma moschatum* L.[1] It was at first assigned the phenolic oxoaporphine structure I,[1] but this formulation was later modified to II as a result of direct comparison of *O*-ethylatheroline (IV) with a series of



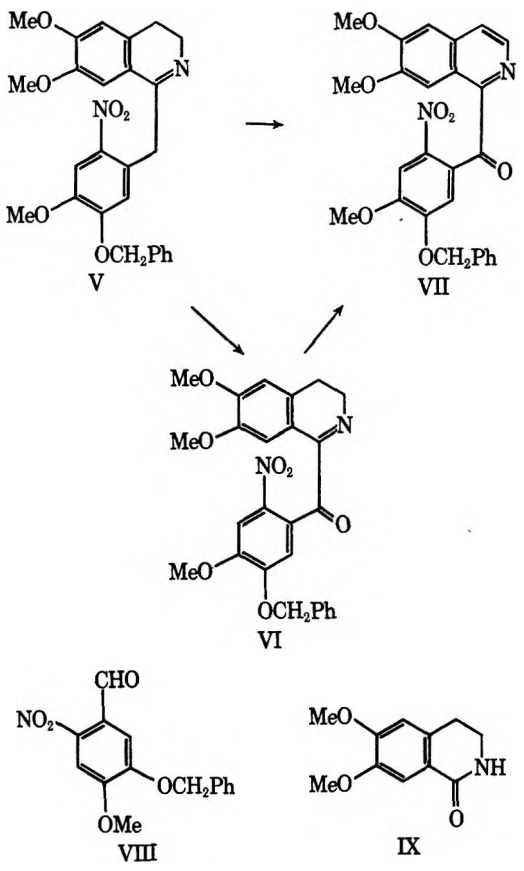
I, $R_1 = H; R_2 = Me$
II, $R_1 = Me; R_2 = H$
III, $R_1 = Me; R_2 = COMe$
IV, $R_1 = Me; R_2 = Et$

synthetic trimethoxyethoxyoxoaporphines.[2] We now report the first synthesis of atheroline; this represents also the first synthesis of any phenolic oxoaporphine.

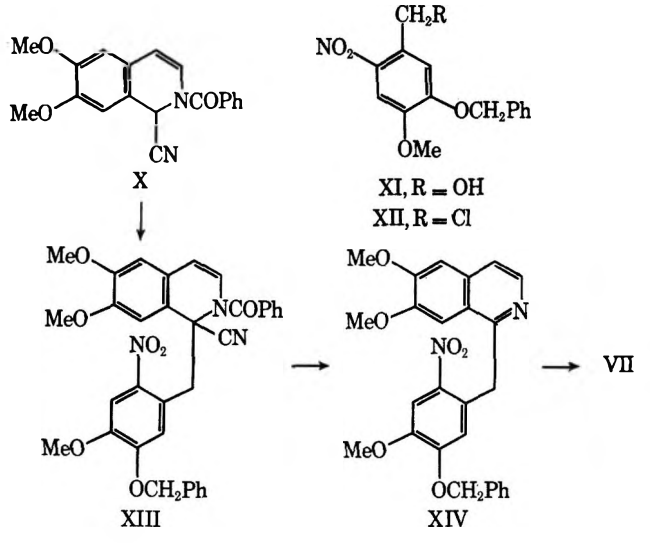
1-(5-Benzyloxy-4-methoxy-2-nitrobenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (compound V) was prepared starting from 3,4-dimethoxyphenethylamine and 5-benzyloxy-4-methoxy-2-nitrobenzaldehyde[3] (VIII) as described in the literature.[4] Mild oxidation of V with chromic acid in acetic acid afforded the corresponding benzoylisoquinoline (VI) in 53% yield; the aldehyde VIII and the isocarbostyryl[5] IX were obtained as minor products. Dehydrogenation of VI with 10% palladium on charcoal under nitrogen yielded 1-(5-benzyloxy-4-methoxy-2-nitrobenzoyl)-6,7-dimethoxyisoquinoline (VII), mp 168–169°, in 71% yield. The success of this reaction is worthy of note, in view of the survival in the product of both the readily hydrogenolyzed benzyl group and the readily reduced nitro function. A minor proportion of VII (or V) is, in fact, undoubtedly destroyed by acting as the hydrogen acceptor in the dehydrogenation.

A direct one-step conversion of V to VII could also be achieved by heating V with palladium on charcoal in *p*-cymene in the presence of air. In this practical reaction (~50% yield), dehydrogenation of the dihydroisoquinoline system is accompanied by the catalytic oxidation of the activated benzylic methylene group.

(1) I. R. C. Bick and G. K. Douglas, *Tetrahedron Lett.*, 2399 (1965).
(2) I. R. C. Bick and G. K. Douglas, *ibid.*, 4655 (1965).
(3) M. Tomita and I. Kikkawa, *Chem. Pharm. Bull.*, **4**, 230 (1956).
(4) I. Kikkawa, *J. Pharm. Soc. Jap.*, **79**, 83 (1969).
(5) K. Wiesner, Z. Valenta, A. J. Manson, and F. W. Stonner, *J. Amer. Chem. Soc.*, **77**, 675 (1955).

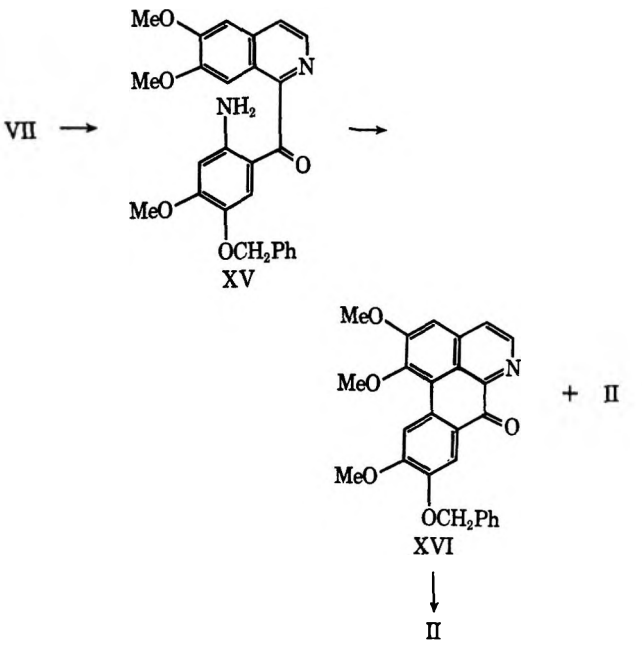


A quite different synthesis of intermediate VII was also carried out in the following manner. Borohydride reduction of aldehyde VIII, followed by treatment of the corresponding benzyl alcohol (XI) with thionyl chloride, afforded the benzyl chloride XII. The Reissert compound X, prepared from 6,7-dimethoxyisoquinoline[6] by reaction with benzoyl chloride and potassium cyanide, was alkylated with halide XII to



give mainly the 1,2-dihydroisoquinoline XIII, mp 176–177°, along with some of the hydrolysis product, 1-(5-benzyloxy-4-methoxy-2-nitrobenzyl)-6,7-dimethoxyisoquinoline (XIV). The nitrile XIII was then hydrolyzed cautiously with Triton B in dimethylformamide[7,8] to give an additional quantity of XIV. Finally, oxidation of XIV with sodium dichromate in acetic acid gave the benzoylisoquinoline VII. Despite careful study, the best yield obtained in this oxidation was rather low (16%), probably due to attack of the benzyl ether function of XIV by the oxidant.

Catalytic hydrogenation of VII in the presence of Raney nickel catalyst, followed by Pschorr cyclization of the resulting keto amine XV, gave not only the desired oxoaporphine, 9-benzyloxy-1,2,10-trimethoxydibenz[*de*,*g*]quinolin-7-one (XVI), mp 228° dec, in 10% yield but also 9-hydroxy-1,2,10-trimethoxydibenz[*de*,*g*]quinolin-7-one (II), mp 252° dec, in 1% yield. The ir spectrum of II showed hydroxyl and carbonyl signals at 2.93 and 6.00 μ, respectively. Its mass spectrum showed a molecular ion peak at *m/e* 337. Furthermore, its uv–visible region spectrum showed absorption bands at 243, 273, 292, 354, 380, and 435 nm which shifted bathochromically in aqueous ethanolic alkali. These spectral properties were in accord with those reported for natural atheroline[1,2] and compatible with structure II.



Catalytic debenzylation of XVI was attempted under a variety of conditions, but II could not be isolated from these reactions. Hydrolysis of XVI in hydrochloric acid and tetrahydrofuran was, however, successful and afforded the desired phenol II in good yield.

As a final proof of identity, II was treated with acetic anhydride to give the corresponding crystalline acetyl derivative III, mp 216–218° dec.[9] The ir spectrum of our synthetic III was superimposable upon that of a sample of *O*-acetylatheroline prepared from the natural base. Furthermore, all of the signals in the nmr spectrum of III were identical within 0.04 ppm with those of *O*-acetylatheroline as reported in the literature.[1,2]

(6) E. Spath and N. Polgar, *Monatsh. Chem.*, **51**, 190 (1929).

(7) M. P. Cava and M. V. Lakshmikantham, *J. Org. Chem.*, **35**, 1867 (1970).

(8) M. P. Cava and M. Srinivasan, *Tetrahedron*, **26**, 4649 (1970).

(9) The melting point (190–195°) recorded for *O*-acetylatheroline in ref 1 is apparently in error. Recrystallization from chloroform–ether–*n*-hexane of an authentic sample of III donated by Professor Bick gave yellow needles, mp 217–219° dec.

In conclusion, the work described above suggests several approaches which should be of general applicability to the synthesis of phenolic oxoaporphines. The one-step oxidation dehydrogenation of V to VII, in particular, may be the prototype of a very useful conversion in oxoaporphine synthesis.

Experimental Section

Analyses were carried out by Midwest Microlab, Inc., Indianapolis, Ind. All melting points are uncorrected. Nmr spectra were measured on a Varian A-60 and a Varian A-100 instrument in $CDCl_3$ using tetramethylsilane as an internal standard unless noted. Mass spectra were measured on a Perkin-Elmer Model 270 instrument. Ultraviolet spectra were measured on a Perkin-Elmer 202 spectrophotometer.

1-(5-Benzyloxy-4-methoxy-2-nitrobenzoyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (VI).—To a stirred solution of 1-(5-benzyloxy-4-methoxy-2-nitrobenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (V, 6.0 g) in AcOH (250 ml) was added portionwise chromic acid (4.8 g). After stirring for 1.5 hr at 15–20°, the reaction mixture was poured into ice–water and the precipitate was extracted into $CHCl_3$. Work-up in the usual manner gave a brownish gum (5.6 g), which was chromatographed on silica gel (300 g, $CHCl_3$ eluent). The first fraction yielded 5-benzyloxy-4-methoxy-2-nitrobenzaldehyde (VIII, 690 mg) as yellow prisms, mp 129–131°[3] ($CHCl_3$–ether–*n*-hexane).

The second fraction contained the benzoyl derivative VI (3.2 g), which was recrystallized from $CHCl_3$–*n*-hexane to give yellow needles: mp 148–149°; ir (KBr) 5.85 (CO), 13.45, 14.30 μ (monosubstituted benzene); nmr δ 7.58 (1 H, s, $C_{3'}$ H), 7.84 (1 H, s, $C_{6'}$ H), 7.34 (5 H, s, C_6H_5), 7.12 (1 H, s, C_8 H), 6.65 (1 H, s, C_5 H), 5.20 (2 H, s, OCH_2Ph), 3.92, 3.90, 3.88 (each 3 H, s, 3 OCH_3); mass spectrum *m/e* 476 (M^+).

Anal. Calcd for $C_{26}H_{24}N_2O_7$: C, 65.54; H, 5.08; N, 5.88. Found: C, 65.53; H, 5.03; N, 5.91.

The third fraction gave the isocarbostyryl IX (170 mg) as colorless needles, mp 172–174° (lit.[5] mp 175°).

1-(5-Benzyloxy-4-methoxy-2-nitrobenzoyl)-6,7-dimethoxyisoquinoline (VII).—A mixture of the 3,4-dihydroisoquinoline VI (700 mg), *p*-cymene (200 ml), and 10% Pd/C (800 mg) was heated at 140–145° under N_2 for 4 hr. The catalyst was filtered off, and ether saturated with HCl gas was then added dropwise to the filtrate to afford a yellowish precipitate, which was basified with ammonia and extracted into $CHCl_3$. The usual work-up gave a brownish gum, which crystallized from MeOH to give compound VII (502 mg) as yellow needles: mp 168–169°; ir (KBr) 5.85 (CO), 13.35, 14.30 μ (monosubstituted benzene); nmr δ 8.60, 7.62, 7.18, 7.06 (each 1 H, s, aromatic protons), 8.19, 7.57 (each 1 H, d, J = 6.0 Hz, C_3 and C_4 H), 7.38 (5 H, broad singlet, C_6H_5), 5.22 (2 H, s, OCH_2Ph), 4.10, 4.02, 3.97 (each 3 H, s, 3 OCH_3); λ_{max}^{EtOH} 232 nm (log ϵ 4.42), 349 (3.95); mass spectrum *m/e* 474 (M^+), 91 (tropylium ion).

Anal. Calcd for $C_{26}H_{22}N_2O_7$: C, 65.82; H, 4.67; N, 5.90. Found: C, 65.38; H, 4.84; H, 5.90.

Dehydrogenative Oxidation of V.—A stirred mixture of the 3,4-dihydroisoquinoline V (1.7 g), *p*-cymene (300 ml), and 10% Pd/C (3.5 g) was heated at 140–145° for 4.5 hr. The catalyst was filtered off, and ether saturated with HCl gas was then added to the filtrate to afford a yellowish precipitate, which was basified with ammonia and extracted into $CHCl_3$. The washed extract was evaporated to afford a yellowish gum, which crystallized from MeOH to give yellow needles of 1-(5-benzyloxy-4-methoxy-nitrobenzoyl)-6,7-dimethoxyisoquinoline (VII, 910 mg), mp 169–170°. Its ir spectrum was superimposable on that of the authentic sample.

5-Benzyloxy-4-methoxy-2-nitrobenzyl Alcohol (XI).—To a stirred solution of 5-benzyloxy-4-methoxy-2-nitrobenzaldehyde[3] (VIII, 2.0 g) in MeOH (150 ml) was added portionwise sodium borohydride (0.5 g). The solvent was evaporated and water (200 ml) was added. The yellow precipitate was dissolved in $CHCl_3$ and after washing (H_2O) and removal of the solvent, the resulting residue was crystallized from $CHCl_3$–ether–*n*-hexane to give the benzyl alcohol XI (1.41 g) as yellow needles: mp 132–134°; ir (KBr) 2.75 (OH), 6.60, 7.55 (NO_2), 13.30, 14.40 μ (monosubstituted benzene); nmr δ 7.73 (1 H, s, C_3 H), 7.43 (5, H, broad singlet, C_6H_5), 7.27 (1 H, s, C_6 H), 5.24 (2 H, s, OCH_2Ph), 4.94 (2 H, broad, CH_2OH), 3.94 (3 H, s, OCH_3).

Anal. Calcd for $C_{15}H_{15}NO_5$: C, 62.28; H, 5.23; N, 4.84. Found: C, 61.99; H, 5.40; N, 4.88.

2-Benzoyl-1-cyano-6,7-dimethoxy-1,2-dihydroisoquinoline (X).—To a stirred mixture of 6,7-dimethoxyisoquinoline[6] (3.1 g), CH_2Cl_2 (35 ml), potassium cyanide (4.2 g), and water (10 ml) was added dropwise benzoyl chloride (3 ml) at 0–5°. After stirring for an additional 4 hr, CH_2Cl_2 (50 ml) was added and the organic layer was separated. The washed (H_2O) and dried (Na_2SO_4) solvent was evaporated to afford a gum, which crystallized from EtOH to give the Reissert compound X (1.7 g) as colorless needles: mp 167–168°; ir (KBr) 4.35 (CN), 5.95 (CO), 6.05 μ (C=C); nmr δ 7.57 (5 H, broad singlet, C_6H_5), 6.91 (1 H, s, C_8 H), 6.77 (1 H, s, C_5 H), 6.54 (1 H, s, methylene proton), 6.58 (1 H, d, J = 8.0 Hz, C_4 H), 6.00 (1 H, d, J = 8.0 Hz, C_3 H), 3.90 (6 H, s, 2 OCH_3).

Anal. Calcd for $C_{19}H_{16}N_2O_3$: C, 71.24; H, 5.03; N, 8.75. Found: C, 71.27; H, 5.26; N, 8.87.

Alkylation of X with XII.—To a stirred suspension of the benzyl alcohol XI (3.0 g) and sodium acetate (1.2 g) in dry benzene (200 ml) was added dropwise thionyl chloride (6 ml). After stirring for 1 hr at room temperature, the filtered solution was evaporated to give the benzyl chloride XII as a brownish gum. To a solution of chloride XII and the Reissert compound X (3.0 g) in dimethylformamide (100 ml) was added portionwise sodium hydride (50% in mineral oil, 0.9 g) with stirring at 0–5°. After stirring for a further 4 hr at 0–5°, aqueous ammonium chloride was added to the reaction mixture, which was then poured into a large amount of ice–water. The resulting solid was dissolved in $CHCl_3$ and worked up as usual to give a brownish gum (3.7 g). Chromatography on silica ($CHCl_3$ eluent) gave the following compounds. The first fraction afforded 1-(5-benzyloxy-4-methoxy-2-nitrobenzyl)-6,7-dimethoxyisoquinoline (XIV, 0.7 g) as pale yellow needles: mp 254° dec ($CHCl_3$–*n*-hexane); ir (KBr) 6.08 (C=C and C=N), 6.52, 7.42 (NO_2), 13.55, 14.35 μ (monosubstituted benzene); nmr δ 8.28 (1 H, d, J = 6.0 Hz, C_3 H), 8.14, 7.92 (each 1 H, s, aromatic protons), 7.30 (6 H, broad singlet, C_6H_5 and C_4 H), 4.05, 3.96, 3.64 (each 3 H, s, 3 OCH_3); uv λ_{max}^{EtOH} 241 nm (log ϵ 4.54), 315 (sh, 3.57), 329 (3.63), 344 (3.53).

Anal. Calcd for $C_{26}H_{24}N_2O_6$: C, 67.81; H, 5.25; N, 6.08. Found: C, 67.35; H, 5.17; N, 6.15.

The second fraction gave 2-benzoyl-1-(5-benzyloxy-4-methoxy-2-nitrobenzyl)-1-cyano-6,7-dimethoxy-1,2-dihydroisoquinoline (XIII, 1.9 g) as yellow needles: mp 176–177° (EtOH); ir (KBr) 5.85 (CO), 5.97 (C=C), 6.50, 7.48 (NO_2), 13.25, 14.35 μ (monosubstituted benzene); nmr δ 7.38, 7.10 (each 1 H, s, $C_{3'}$ and $C_{6'}$ H), 6.58, 6.53 (each 1 H, s, C_5 and C_8 H), 6.37 (1 H, d, J = 8.0 Hz, C_3 H), 5.68 (1 H, d, J = 8.0 Hz, C_4 H), 5.24, (2 H, s, OCH_2Ph), 3.94 (6 H, s, 2 OCH_3), 3.66 (3 H, s, OCH_3); uv λ_{max}^{EtOH} 228 nm (log ϵ 4.45), 245 (4.42), 313 (4.07).

Anal. Calcd for $C_{34}H_{29}N_3O_7$: C, 69.02; H, 4.94; N, 7.10. Found: C, 69.27; H, 5.21; N, 6.86.

1-(5-Benzyloxy-4-methoxy-2-nitrobenzyl)-6,7-dimethoxyisoquinoline (XIV).—To a stirred solution of XIII (1.0 g) in dimethylformamide (30 ml) was added Triton B (3.0 ml) at room temperature. After stirring for 1 hr, the reaction mixture was poured into ice–water to afford a yellowish precipitate. Work-up as usual gave a brownish gum, which crystallized from MeOH to afford the isoquinoline XIV (205 mg) as pale yellow needles, mp 254° dec.

Oxidation of XIV with Sodium Dichromate.—A mixture of XIV (300 mg), AcOH (15 ml), and sodium dichromate (600 mg) was refluxed for 30 min. The reaction mixture was poured into ice–water to afford a yellowish precipitate, which was filtered and extracted with $CHCl_3$. The usual work-up gave a brownish gum, which was chromatographed on silica ($CHCl_3$ eluent) to give compound VII (51 mg), mp 168–170°.

Hydrogenation of VII and Pschorr Reaction of XV.—The nitrobenzoylisoquinoline VII (500 mg) was dissolved in tetrahydrofuran (100 ml) and hydrogenated in the presence of Raney nickel (W-2) at atmospheric pressure for 20 hr. The catalyst was removed and the solvent was then evaporated to afford a yellow residue, which was dissolved in ether (200 ml). Ether saturated with HCl gas was added to the solution to give the hydrochloride of amine XV (490 mg) as a yellow, amorphous powder. This hydrochloride (480 mg) was dissolved in a mixture of 10% H_2SO_4 (5 ml), MeOH (20 ml), and water (15 ml) and then diazotized with 10% $NaNO_2$ (5 ml) at 0–5°. After stirring for a further 30 min at 0–5°, copper powder (50 mg) was added to the reaction mixture. After heating at 45–50°

for 30 min, the reaction mixture was basified with ammonia and extracted with $CHCl_3$. The extract was washed with 10% NaOH in order to separate the products into nonphenolic and phenolic fractions. Purification of the nonphenolic material by tlc (silica, using 1:1 benzene–acetone as developer) gave 9-benzyloxy-1,2,10-trimethoxydibenz[*de*,*g*]quinolin-7-one (XVI, 47 mg): mp 228° dec ($CHCl_3$–MeOH); ir (KBr) 5.95 (CO), 13.60, 14.45 μ (monosubstituted benzene); nmr δ 8.82 (1 H, d, J = 6.0 Hz, C_5 H), 8.73 (1 H, s, C_{11} H), 8.06 (1 H, s, C_8 H), 7.68 (1 H, d, J = 6.0 Hz, C_4 H), 7.60–7.25 (5 H, m, C_6H_5), 7.12 (1 H, s, C_3 H), 5.30 (2 H, s, OCH_2Ph), 4.07, 4.03, 4.00 (each 3 H, s, 3 OCH_3); uv λ_{max}^{EtOH} 243 nm (log ε 4.04), 272 (4.03), 291 (sh, 3.85), 355 (3.65), 380 (sh, 5.95), 428 (sh, 3.45); mass spectrum *m/e* 427 (M^+), 336, 91 (tropylium ion).

Anal. Calcd for $C_{26}H_{21}NO_5$: C, 73.05; H, 4.95; N, 3.28. Found: C, 72.55; H, 4.84; N, 3.28.

The aqueous alkaline layer was neutralized with ammonium chloride and then extracted with $CHCl_3$. The extract was dried over sodium sulfate. The usual work-up gave a brownish gum, which was purified by tlc (silica, using 10:1 $CHCl_3$–MeOH as developer) to give 9-hydroxy-1,2,10-trimethoxydibenz[*de*,*g*]-quinolin-7-one (II, 6 mg) as an amorphous powder: mp 252° dec ($CHCl_3$–*n*-hexane); ir (KBr) 2.93 (OH), 6.00 μ (CO); uv λ_{max}^{EtOH} 243 nm (log ε 4.12), 273 (4.11), 292 (3.92), 354 (3.70), 380 (sh), (3.67), 435 (3.55); $\lambda_{max}^{EtOH-NaOH}$ 251 nm (log ε 4.07), 296 (3.99), 324 (3.97), 390 (3.42), 535 (3.30); $\lambda_{max}^{EtOH-HCl}$ 256 nm (log ε 4.08), 286 (4.01), 380 (3.68), 500 (3.17); mass spectrum *m/e* 337 (M^+).

Hydrolysis of XIX.—A mixture of *O*-benzylatheroline (XVI, 22 mg), tetrahydrofuran (3 ml), and hydrochloric acid (5 ml) was refluxed for 2 hr. The solvent was evaporated to afford a dark purple hydrochloride, which was washed with ether, suspended in $CHCl_3$, and basified with ammonia. The $CHCl_3$ extract was dried (Na_2SO_4) and the solvent was then concentrated to 5 ml. Addition of a small amount of *n*-hexane gave atheroline (II, 11 mg) as an amorphous yellow powder, mp 252° dec.

9-Acetoxy-1,2,10-trimethoxydibenz[*de*,*g*]quinolin-7-one (III).—A mixture of synthetic atheroline (II, 10 mg), tetrahydrofuran (15 ml), acetic anhydride (10 drops), and potassium carbonate (300 mg) was stirred for 20 hr at room temperature. The inorganic salt was filtered off and the solvent was then evaporated to give a gum which was extracted into $CHCl_3$. The extract was washed with 5% $NaHCO_3$ and water and dried (Na_2SO_4), and the solvent was evaporated. Trituration with ether gave crystals which were recrystallized ($CHCl_3$–ether) to give 9-acetoxy-1,2,10-trimethoxydibenz[*de*,*g*]quinolin-7-one (III) (9 mg) as yellow needles: mp 216–218° dec; ir (KBr) 5.54 ($OCOCH_3$), 5.92 μ (CO); nmr ($CDCl_3$) δ 8.82 (1 H, s, C_{11} H), 8.82 (1 H, d, J = 6.0 Hz, C_5 H), 8.20 (1 H, s, C_8 H), 7.68 (1 H, d, J = 6.0 Hz, C_4 H), 7.14 (1 H, s, C_3 H), 4.04 (3 H, s, OCH_3), 4.02 (6 H, s, 2 OCH_3), 2.37 (3 H, s, $OCOCH_3$); nmr (CF_3COOH) δ 9.08 (1 H, s, C_{11} H), 8.73 (1 H, d, J = 6.0 Hz, C_5 H), 8.50 (1 H, d, J = 6.0 Hz, C_4 H), 8.26 (1 H, s, C_8 H), 7.68 (1 H, s, C_3 H), 4.37, 4.31, 4.18 (each 3 H, s, 3 OCH_3), 2.50 ppm (3 s, H, $OCOCH_3$). Its spectral properties (ir, nmr) were identical with those of *O*-acetylatheroline derived from natural atheroline, and a mixture melting point (216–219° dec) showed no depression.[9]

Registry No.—II, 1349-20-8; III, 5140-36-3; VI, 35096-38-9; VII, 35096-39-0; X, 35096-40-3; XI, 35096-42-5; XIII, 35096-41-4; XIV, 35096-43-6; XVI, 35096-44-7.

Acknowledgment.—We are grateful to Professor I. R. C. Bick for a generous sample of *O*-acetylatheroline. We also thank the National Institutes of Health for a grant (CA 11445) in support of this work.

Reduction and Hydrolysis of Triethyl α-Phosphonocinnamate and Its Derivatives

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Received February 3, 1972

The triethyl ester of α-phosphonocinnamic acid and some of its derivatives can be reduced with sodium borohydride to the corresponding triethyl α-phosphonohydrocinnamates. Hydrolysis of both the unsaturated and the saturated esters in concentrated hydrochloric acid causes dephosphonation and the formation of cinnamic acid and hydrocinnamic acid and their derivatives, respectively.

A number of aromatic aldehydes, **1**, undergo condensation with triethyl phosphonoacetate (**2**) to give triethyl α-phosphonocinnamates (**3**)[2] (Scheme I); however, the chemistry of compounds of type **3** has been examined only cursorily to date. As a part of an attempt to find a convenient general method for the synthesis of β-styryl- (**10**) and β-phenethylphosphonic acids[3] (**11**), we have examined some of the chemical properties of these compounds.

Reduction.—The selective reduction of the carbon–carbon double bond of the phosphonocinnamate esters **3** to give the corresponding phosphonopropionates **4** has been accomplished by treating the unsaturated esters with a 1:1 molar ratio of $NaBH_4$.[4] The results of these reductions are summarized in Table I. Both ethanol and pyridine were used as solvents; it may be deduced from Table I that pyridine is the superior solvent. The reduction reactions were relatively simple to carry out; however, some decomposition occurred during distillation and considerable difficulty was experienced in obtaining analytically pure products. Due to the minor differences in the percentage composition of starting materials and products, more emphasis was placed on nmr data than on elemental analysis. In the case of the unsaturated esters **3**, absorption due to the vinylic hydrogen occurred as a doublet (J = 24 ± 1 cps) at δ 7.52–8.42; in the reduced esters **4**, the absorption in this region disappeared with the emergence of new absorption at δ 2.7–3.3 (multiplet) due to the new methylene and methine hydrogens.

In addition to the compounds listed in Table I, attempts were made to reduce three other compounds: triethyl *p*-methyl-α-phosphonocinnamate, triethyl 3,4-dimethoxy-α-phosphonocinnamate, and the diethyl ester of courmarin-3-phosphonic acid (**15**). Decomposition during distillation of the reduced products was so extensive that reasonable analyses could not be obtained; however, the vinylic proton absorption in the nmr spectra of the crude products was reduced in size or disappeared entirely and the expected absorption appeared in the δ 2.7–3.3 region. Additional evidence for

(1) (a) The authors gratefully acknowledge the support of this work by the National Institutes of Health, U. S. Public Health Service (GM-12480). (b) Part of the work discussed in this article is abstracted from work presented for the M.S. Thesis by P. K. Li.

(2) C. N. Robinson and J. F. Addison, *J. Org. Chem.*, **31**, 4325 (1966).

(3) This problem has now largely been solved by the work of G. H. Jones, E. K. Hamamura, and J. G. Moffatt, *Tetrahedron Lett.*, 5731 (1968).

(4) Reduction procedures were patterned after the work of S. B. Kadin, *J. Org. Chem.*, **31**, 620 (1966).

SCHEME I

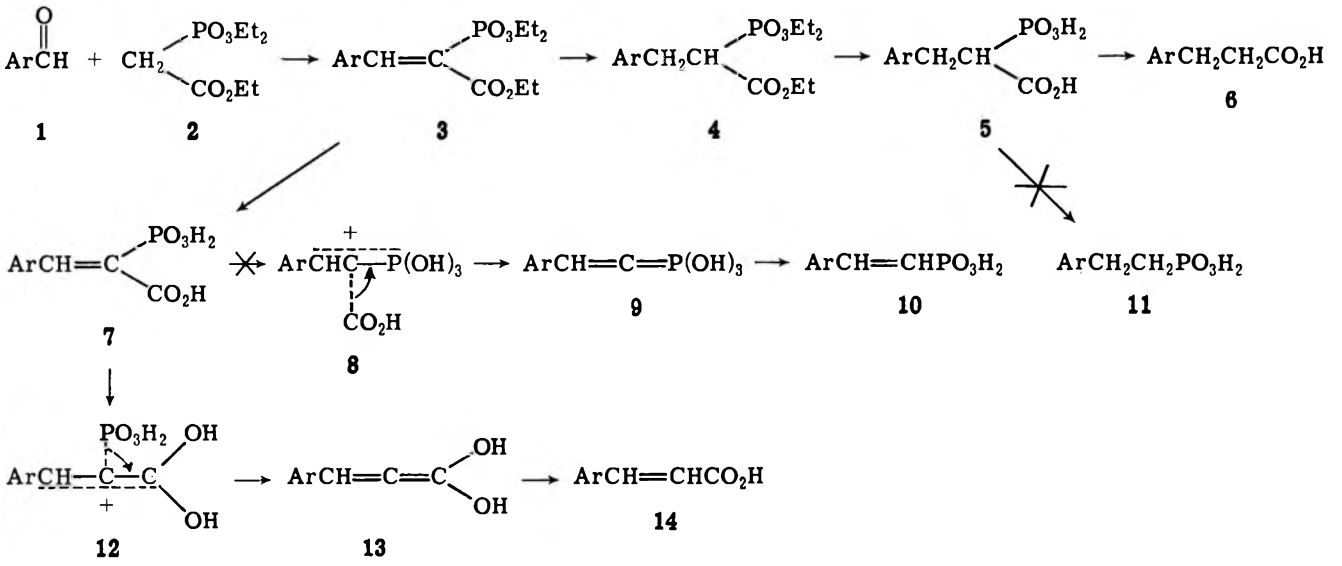
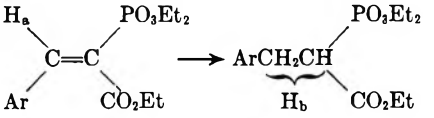


TABLE I

REDUCTION OF TRIETHYL α-PHOSPHONOCINNAMATES



Registry no.	No.	Aryl group	Product bp, °C (mm)	Yield, %	Formula	Anal., % Calcd P	Anal., % Found P	Nmr, δ H_a	Nmr, δ H_b, estd[a]
35085-32-6	1	C_6H_5	145–149 (0.35)	70[b]	$C_{15}H_{23}O_5P$			7.60	3.12
			189–191 (5.00)	70[c]		9.86	9.86		
35085-33-7	2	p-$CH_3OC_6H_4$	134–137 (0.30)	83[b]	$C_{16}H_{25}O_6P$	9.00	9.10	7.52	2.70
			122–124 (0.05)	71[c]					
35085-34-8	3	p-ClC_6H_4	166–167 (0.30)	74[b]	$C_{15}H_{22}O_5PCl$	8.88	8.74	7.52	3.19
			151–153 (0.15)	70[c]			8.72		
35085-35-9	4	1-$C_{10}H_7$	124–126 (0.05)	52[b]	$C_{19}H_{25}O_5P$	8.50	8.71	8.41	3.30
			131–134 (0.10)	34[c]					

[a] The multiplet for the methylene and methine protons represent the ABC portion of an ABCX pattern and the chemical shift shown is an estimate of the center of the ABC portion. [b] Pyridine as the solvent. [c] Ethanol as the solvent.

the reduction of the coumarin derivative is presented below.

Hydrolysis of Unsaturated Esters.—In 1960 Patai and Schwartz[5] reported that hydrolysis of triethyl α-phosphonocinnamate under a variety of conditions gave only cinnamic acid (**14**), contrary to the original report of Pudovik and Lebedeva[6] that α-phosphonocinnamic acid (**7**) was formed. We have previously reported[2] that the hydrolysis of **15** gave reasonably good yields of coumarin-3-phosphonic acid (**16**) (Scheme II), which lost the phosphonic acid group with difficulty (at >250°) to produce coumarin (**21**). This indicated that there was a possibility, however slight, that varying the substituent attached to the aromatic ring might alter the course of the reaction. The C–C bond and the C–P bond are reported to be of about equal strength[5] and, if decarboxylation rather than dephosphonation could be effected, the desired β-styrylphosphonic acids (**10**) would be produced.

Several of these unsaturated esters (Table II, type A) were therefore hydrolyzed, but in each case only the dephosphonated product was formed. Evidently, substitution may affect the stability of the phosphonic acid but not the course of the reaction. Two possible reasons can be advanced for dephosphonation in preference to decarboxylation. In the protonation of the phosphonic acids **7**, transition state **12** would be more stable than **8** because of the poor p–d overlap required for resonance stabilization in **8**. Also, in the completed decomposition, **13** would be more stable than **9** for the same reason. The stability of the coumarin-3-phosphonic acid (**16**), on the other hand, is enhanced by the fact that the protonated acid, **17** ↔ **18**, probably cannot lose the phosphono group directly to give the unstable enol **19**, which would be an angular allene. A more likely route for this more difficult decomposition involves either tautomerization of the protonated acid to **20** or direct protonation of the double bond.

As mentioned earlier, **15** was also reduced with $NaBH_4$ and, although the intermediate ester, **22**, could not be purified for analysis, the hydrolysis of the crude product resulted in dephosphonation and the formation of 3,4-dihydrocoumarin (**26**). In this case there is no steric inhibition to formation of **25** such as exists for the formation of **19**.

(5) S. Patai and A. Schwartz, *J. Org. Chem.*, **25**, 1232 (1960).

(6) A. N. Pudovik and N. M. Lebedeva, *Dokl. Akad. Nauk SSSR*, **90**, 799 (1953); *Chem. Abstr.*, **50**, 2429d (1956).

SCHEME II

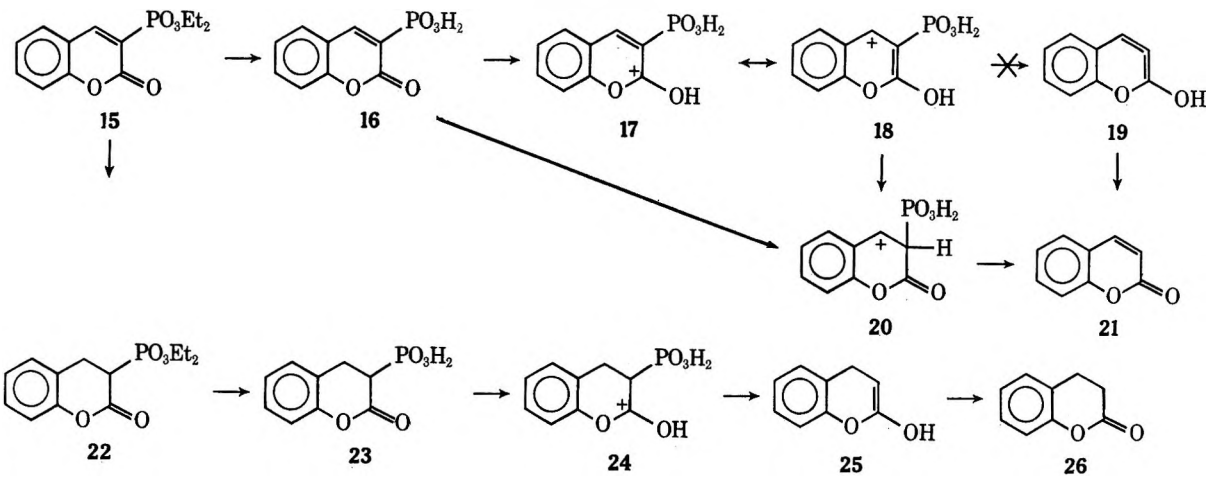


TABLE II

HYDROLYSIS OF ESTERS

No.	Aryl group	Product mp, °C	Reported mp, °C
Type A	$ArCH=C(PO_3Et_2)(CO_2Et) \longrightarrow ArCH=CHCO_2H$		
1	C_6H_5	134–135	132–134[a]
2	p-$CH_3C_6H_4$	198–202	199[b]
3	p-$CH_3OC_6H_4$	170	174[b]
4	p-ClC_6H_4	237–240	241[c]
5	1-$C_{10}H_7$	208–210	209–212[d]
Type B	$ArCH_2CH(PO_3Et_2)(CO_2Et) \longrightarrow ArCH_2CH_2CO_2H$		
6	C_6H_5	47–48	49[e]
7	p-ClC_6H_4	123	125[f]

[a] C. F. Koelsch, *J. Amer. Chem. Soc.*, **65**, 57 (1943). [b] J. F. J. Dippy and J. E. Page, *J. Chem. Soc.*, 362 (1938). [c] J. v. Braun and J. Nelles, *Chem. Ber.*, **66**, 1467 (1933). [d] B. L. West, *J. Amer. Chem. Soc.*, **42**, 1664 (1920). [e] K. Kindler and W. Peschke, *Justus Liebigs Ann. Chem.*, **497**, 196 (1932). [f] K. Kindler and T. Li, *Chem. Ber.*, **74**, 321 (1941).

Arbusov and Razumov[7] have prepared triethyl α-phosphonohydrocinnamate (**4**) (unsubstituted) by the benzylation of triethyl phosphonoacetate (**2**), and hydrolyzed the product with HCl in a sealed tube at 150° to produce α-phosphonohydrocinnamic acid (**5**). We have hydrolyzed this ester and its *p*-chloro derivative (Table II, type B) with concentrated hydrochloric acid at atmospheric pressure and, as would be expected, obtained the dephosphonated products **6**, but none of the decarboxylation products, **11**.

(7) A. E. Arbusov and A. I. Razumov, *J. Russ. Phys. Chem. Soc.*, **61**, 623 (1929).

Experimental Section

The triethyl α-phosphonocinnamates were prepared by the method of Robinson and Addison.[2] Melting points (uncorrected) were obtained on a Fisher-Johns melting point apparatus. Analyses were by M-H-W Laboratories, Garden City, Mich. Nmr spectra were taken in deuteriochloroform with tetramethylsilane as an internal standard, using a Varian HA-60 spectrometer.

All of the reductions listed in Table I were carried out in essentially the same manner illustrated by procedures 1 and 2 below. The hydrolysis reactions referred to in Table II were conducted according to procedure 3 below.

Procedure 1. Reduction of Triethyl α-Phosphonocinnamate in Pyridine.—A solution of 1.9 g (0.05 mol) of $NaBH_4$ in 30 ml of cold, dry pyridine was added dropwise to a mixture of 15.6 g (0.05 mol) of triethyl α-phosphonocinnamate and dry pyridine at 0–5°. This mixture foamed vigorously and changed from light brown to colorless. After the addition was complete, the mixture was stirred at 0–5° for 1 hr and at room temperature for 1 hr; 300 ml of 1 *N* HCl was added and the resulting solution was extracted three times with ether. The combined ether extracts were dried over anhydrous magnesium sulfate. After filtration, the ether was removed and the residue was distilled *in vacuo*. The fraction boiling at 145–149° (0.35 mm) weighed 11.4 g (70.4%).

Procedure 2. Reduction of Triethyl α-Phosphonocinnamate in Ethanol.—A solution of 15.6 g (0.05 mol) of triethyl α-phosphonocinnamate in 30 ml of cold, absolute ethanol was added dropwise over 20 min to a mixture of 1.9 g (0.05 mol) of $NaBH_4$ in absolute ethanol at 0–5°. After the addition, the reaction mixture was stirred for 1 hr in the cold and 2 hr at room temperature. Water (400 ml) was then added and the solution was extracted with three 60-ml portions of ether. The combined ether extracts were dried over anhydrous magnesium sulfate. After the $MgSO_4$ and ether were removed the product was distilled *in vacuo* at 189–191° (5 mm). The product weighed 11.2 g (70.2%).

Procedure 3. Hydrolysis of Triethyl α-Phosphonocinnamate.—A mixture of 6.3 g (0.02 mol) of triethyl α-phosphonocinnamate and 20 ml of concentrated hydrochloric acid was heated at reflux temperature for 24 hr, allowed to cool to room temperature, and placed in a refrigerator overnight. The dark brown solid was recrystallized from 70% ethanol, producing 1.9 g (64.2%) of product. Two further recrystallizations from dilute ethanol gave white crystals of cinnamic acid, mp 134–135°.

Registry No.—**3** (Ar = Ph), 13507-49-8.

Selective Reductions. XVII. Reaction of Thexylborane in Tetrahydrofuran with Selected Organic Compounds Containing Representative Functional Groups. Comparison of the Reducing Characteristics of Diborane and Its Alkyl Derivatives

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The approximate rates and the stoichiometry of the reaction of excess thexylborane with 56 selected organic compounds containing representative functional groups under standard conditions (tetrahydrofuran solution, 0°) were determined in order to establish the utility of the reagent as a selective reducing agent and to compare its characteristics with those of diborane and disiamylborane previously studied. Alcohols evolve hydrogen rapidly, phenol only in moderate speed, and benzenethiol slowly. No hydrogen evolution is observed with *n*-hexylamine and 1-hexanethiol. Aldehydes and ketones are reduced rapidly. Among the ketones, 2-heptanone and acetophenone are reduced rapidly, while the reaction with benzophenone is quite sluggish. *p*-Benzoquinone consumes one hydride rapidly, but further reaction becomes very slow. On the other hand, anthraquinone is reduced very sluggishly. Caproic acid liberates hydrogen immediately and is then reduced at a moderate rate, whereas benzoic acid shows practically no reduction at standard conditions. However, both acids afford good yields of the corresponding aldehydes under special conditions. Acid chlorides and anhydrides react sluggishly with the reagent. Ethyl caproate is reduced very slowly, whereas ethyl benzoate, phenyl acetate, and phthalide undergo practically no reductions under standard conditions. However, γ-butyrolactone is reduced at a moderate rate. 1,2-Butylene oxide and cyclohexene oxide react very slowly, while styrene oxide and 1-methyl-1,2-cyclohexene oxide react at a moderate rate, but not in a simple manner. Amides and nitriles are all reduced slowly, indicating the possibility of a potential aldehyde synthesis. 1-Nitropropane is inert, whereas nitrobenzene is reduced at a moderate rate. Azobenzene reacts very slowly. Azoxybenzene is reduced slowly without hydrogen evolution. Cyclohexanone oxime liberates hydrogen, with only very slow reduction thereafter. Pyridine is inert; however, pyridine *N*-oxide is reduced at a moderate rate, consuming three hydrides per mole. Of the sulfur compounds tested, only dimethyl sulfoxide is reduced to dimethyl sulfide at a moderate rate. Thus, under the standard conditions, disulfide, sulfide, sulfone, sulfonic acids, and cyclohexyl tosylate are all inert to this reagent.

Thexylborane[2,3] (2,3-dimethyl-2-butylborane) has been prepared by the hydroboration of 2,3-dimethyl-2-butene with borane in the ratio of 1:1. And it has been demonstrated that thexylborane is a convenient reagent for the cyclic hydroboration of dienes.[4-6] Recently we carried through systematic studies of the approximate rates and stoichiometry of the reaction of diborane[7] and disiamylborane[8] in tetrahydrofuran solution at 0° with a standard list of compounds representative of the more common functional groups. We have observed many differences in reducing characteristics between these two hydrides. Thexylborane carries a bulky alkyl group and has two hydrogens attached to boron. It exists as a dimer in tetrahydrofuran[3] solution. From these structural considerations, we anticipated that there might result unique reducing characteristics for thexylborane different from those of diborane and disiamylborane.

In order to compare the reducing characteristics of thexylborane with those of diborane and disiamylborane, we adopted the same standard conditions, tetrahydrofuran solutions (1.0 *M* in "hydride," 0.25 *M* in organic compound) at 0°.

(1) (a) Postdoctoral research associate, 1962–1964, on research grants supported by the Atomic Energy Commission, AT(11-1)-70, and the National Institutes of Health, GM 10937; (b) Graduate research assistant, 1963–1967, and postdoctoral research associate, 1967–1969, on Research Grants DA-31-124, ARO(D)-117, and -453 supported by the U. S. Army Research Office (Durham).

(2) H. C. Brown and A. W. Moerikofer, *J. Amer. Chem. Soc.*, **84**, 1478 (1962).

(3) H. C. Brown and G. J. Klender, *Inorg. Chem.*, **1**, 204 (1962).

(4) H. C. Brown and C. D. Pfaffenberger, *J. Amer. Chem. Soc.*, **89**, 5475 (1967).

(5) H. C. Brown and E. Negishi, *ibid.*, **89**, 5477 (1967).

(6) H. C. Brown and E. Negishi, *Chem. Commun.*, 594 (1968).

(7) H. C. Brown, P. Heim, and N. M. Yoon, *J. Amer. Chem. Soc.*, **92**, 1637 (1970).

(8) H. C. Brown, D. B. Bigley, S. K. Arora, and N. M. Yoon, *ibid.*, **92**, 7161 (1970). Disiamylborane is bis(3-methyl-2-butyl)borane, prepared in the reaction of 2 mol of 2-methyl-2-butene with 1 mol of borane in THF.

Results and Discussion

Procedure for Rate and Stoichiometry Studies.—Thexylborane was prepared by adding diborane to a cooled solution of tetramethylethylene in tetrahydrofuran in the ratio of one borane to one olefin. The reagent was stable at 0°, showing no significant change in hydride concentration for 14 days.

The procedure adopted for the rate and stoichiometric studies was to add 12.5 mmol of the organic compound to 25 mmol of thexylborane in sufficient tetrahydrofuran to give 50 ml of solution. This made the reaction mixture 0.5 *M* in thexylborane (*i.e.*, 1.00 *M* in hydride) and 0.25 *M* in the compound under examination. Thus hydride was present in excess, with a ratio of hydride to compound of 4:1.

The solution was maintained at 0° and aliquots were removed at appropriate time intervals and analyzed for residual hydride. In this manner it was possible to establish both the rate at which the reduction proceeds and the stoichiometry of the reaction, *i.e.*, the number of hydrides utilized per mole of the compound. When the reaction comes to an effective halt, the sample was analyzed for tetramethylethylene in order to make certain that no displacement had taken place. All reductions were carried out under nitrogen atmosphere.

Alcohols, Phenols, Amines, and Thiols.—All the alcohols tested liberated hydrogen rapidly and quantitatively. However, phenol liberated hydrogen only at a moderate rate, and *n*-hexylamine was inert. The aliphatic thiol, 1-hexanethiol, was inert to this reagent, whereas the aromatic thiol, benzenethiol, liberated hydrogen slowly, the evolution of hydrogen being almost complete in 24 hr. The results are summarized in Table I.

Aldehydes and Ketones.—All of the aldehydes and ketones consumed one hydride, indicating reduction to the corresponding alcohols. The aldehydes were re-

TABLE I

REACTION OF THEXYLBORANE WITH REPRESENTATIVE "ACTIVE HYDROGEN" COMPOUNDS IN TETRAHYDROFURAN AT 0°

Compound[a]	Time, hr	Hydrogen evolved[b]	Hydride used[b]	Hydride used for reduction[b]
1-Hexanol	0.25	0.99	0.99	0.00
	0.5	1.00	1.00	0.00
Benzyl alcohol	0.25	0.98	0.98	0.00
	0.5	1.00	1.00	0.00
3-Hexanol	0.25	0.97	0.97	0.00
	0.5	1.00	1.00	0.00
3-Ethyl-3-pentanol	0.25	0.92	0.92	0.00
	0.5	0.98	0.98	0.00
	1.00	1.00	1.00	0.00
Phenol	0.25	0.30	0.30	0.00
	0.5	0.44	0.44	0.00
	1.0	0.63	0.63	0.00
	3.0	0.94	0.94	0.00
	6.0	1.00	1.00	0.00
n-Hexylamine	14.0	0.00	0.00	0.00
1-Hexanethiol	10.0	0.00	0.00	0.00
Benzenethiol	1.0	0.13	0.13	0.00
	3.0	0.38	0.38	0.00
	6.0	0.65	0.65	0.00
	12.0	0.82	0.82	0.00
	24.0	0.92	0.92	0.00

[a] 12.5 mmol of a compound to 25 mmol of thexylborane (50 mmol of hydride) in 50 ml of solution; 0.25 *M* in compound and 1.00 *M* in hydride. [b] Millimoles/millimole of compound.

duced very rapidly, with the reaction being over in 15 min. Benzophenone was reduced at a much slower rate than the corresponding rates exhibited by 2-heptanone and acetophenone.[9] A similar trend is observed with diborane and disiamylborane. Cinnamaldehyde consumed one hydride rapidly, while the rate of uptake of a second hydride was moderate. An experiment, carried out in the ratio of 1 equivalent of hydride per mole of compound, established that the aldehyde group was attached faster than the double bond. The stoichiometry also established that almost no elimination[10] occurred following hydroboration. The stereochemistry of the reduction of norcamphor is very similar to that observed in the reduction with disiamylborane,[8] showing 91% *endo*- and 9% *exo*-norbornanol. The results are summarized in Table II.

Quinones.—*p*-Benzoquinone consumed rapidly approximately one hydride per mole of compound, of which 43% was utilized for hydrogen evolution and the remaining 57% for reduction. Afterward the reaction became very sluggish, showing a total of 1.12 mmol of hydride consumption after 12 hr, a value which did not increase over 24 hr. The reaction of the reagent with anthraquinone was very sluggish. These results are similar to the reactions observed with disiamylborane, and further study is required before any sound interpretation can be given to the reaction involving *p*-benzoquinone. The results are summarized in Table III.

Carboxylic Acids and Derivatives.—Both caproic acid and benzoic acid liberated hydrogen rapidly and quantitatively. The reaction with caproic acid then proceeded at a moderate rate to achieve reduction, whereas

(9) In contrast to this reagent, lithium tetrakis(*N*-dihydropyridyl)-aluminate is reported to reduce benzophenone remarkably rapidly (95% in 5 min) compared with the corresponding reduction of acetophenone (32% in 12 hr). P. T. Lansbury and J. O. Peterson, *J. Amer. Chem. Soc.*, **85**, 2236 (1963).

(10) K. Kratze and P. Claus, *Monatsh. Chem.*, **94**, 1140 (1963).

TABLE II

REACTION OF THEXYLBORANE WITH REPRESENTATIVE ALDEHYDES AND KETONES IN TETRAHYDROFURAN AT 0°

Compound[a]	Time, hr	Hydrogen evolved[b]	Hydride used[b]	Hydride used for reduction[b]
Caproaldehyde	0.25	0.00	0.99	0.99
	0.5	0.00	0.99	0.99
Benzaldehyde	0.25	0.00	1.05	1.05
	0.5	0.00	1.05	1.05
2-Heptanone	0.25	0.00	0.70	0.70
	0.5	0.00	0.83	0.83
	1.0	0.00	0.93	0.93
	3.0	0.00	0.99	0.99
	6.0	0.00	1.05	1.05
Norcamphor	0.5	0.03	0.97	0.94
	1.0	0.03	1.01	0.98
	3.0	0.03		
Acetophenone	0.25	0.00	0.58	0.58
	0.5	0.00	0.77	0.77
	1.0	0.00	0.90	0.90
	3.0	0.00	0.97	0.97
	6.0	0.00	0.97	0.97
Benzophenone	1.0	0.00	0.13	0.13
	3.0	0.00	0.26	0.26
	6.0	0.00	0.45	0.45
	48.0	0.00	0.96	0.96
Cinnamaldehyde	0.25	0.00	1.24	1.24
	0.5	0.00	1.36	1.36
	1.0	0.00	1.50	1.50
	3.0	0.00	1.94	1.94
	6.0	0.00	2.00	2.00

[a, b] See corresponding footnotes in Table I.

TABLE III

REACTION OF THEXYLBORANE WITH REPRESENTATIVE QUINONES IN TETRAHYDROFURAN AT 0°

Compound[a]	Time, hr	Hydrogen evolved[b]	Hydride used[b]	Hydride used for reduction[b]
p-Benzoquinone	0.5	0.33	0.90	0.57
	1.0	0.36	0.94	0.58
	3.0	0.43	1.00	0.57
	6.0	0.46	1.09	0.66
	12.0	0.46	1.12	0.66
	24.0	0.46	1.13	0.67
Anthraquinone	3.0	0.00	0.16	0.16
	24.0	0.00	0.23	0.23
	48.0	0.00	0.28	0.28
	72.0	0.00	0.32	0.32

[a, b] See corresponding footnotes in Table I.

practically no reduction of benzoic acid was observed under the same conditions. However, using 2.5 mol of thexylborane per mole of acid, addition of acid at −20°, followed by refluxing of the THF solution, it was possible to obtain a 98% yield of caproaldehyde from caproic acid and a 82% yield of benzaldehyde from benzoic acid, both after extended refluxing (36 hr). (The yields were determined by analysis for aldehyde with 2,4-dinitrophenylhydrazine.) This simple reduction of carboxylic acids to aldehydes is a promising development, and we plan to undertake research to improve the procedure and to examine the scope of the reaction.

Acetic anhydride consumed two hydrides very rapidly, with only a slow reduction thereafter. However, no aldehyde could be detected. The two cyclic anhydrides and the two acid chlorides reacted only very sluggishly. No aldehydes could be detected in the acid

chloride reactions. The results are summarized in Table IV.

TABLE IV
REACTION OF THEXYLBORANE WITH REPRESENTATIVE CARBOXYLIC ACIDS AND ACYL DERIVATIVES IN TETRAHYDROFURAN AT 0°

Compound[a]	Time, hr	Hydrogen evolved[b]	Hydride used[b]	Hydride used for reduction[b]
Caproic acid	0.5	1.00	1.27	0.27
	1.0	1.00	1.55	0.55
	3.0	1.00	1.85	0.85
	6.0	1.00	2.12	1.12
	12.0	1.00	2.40	1.40
Benzoic acid	0.5	1.00	1.00	0.00
	6.0	1.00	1.08	0.08
	48.0	1.00	1.08	0.08
Acetic anhydride	0.5	0.00	2.00	2.00
	6.0	0.00	2.12	2.12
	24.0	0.00	2.50	2.50
Succinic anhydride	0.5	0.00	0.10	0.10
	1.0	0.00	0.12	0.12
	3.0	0.00	0.21	0.21
	6.0	0.00	0.25	0.25
	12.0	0.00	0.32	0.32
	24.0	0.00	0.51	0.51
	48.0	0.00	0.75	0.75
Phthalic anhydride	0.5	0.00	0.12	0.12
	1.0	0.00	0.16	0.16
	6.0	0.00	0.35	0.35
	12.0	0.00	0.41	0.41
	24.0	0.00	0.46	0.46
	48.0	0.00	0.52	0.52
Caproyl chloride	12.0	0.00	0.05	0.05
	24.0	0.00	0.10	0.10
	48.0	0.00	0.20	0.20
Benzoyl chloride	12.0	0.00	0.20	0.20
	24.0	0.00	0.35	0.35
	48.0	0.00	0.55	0.55

[a, b] See corresponding footnotes in Table I.

Esters and Lactones.—The reduction of esters by thexylborane was sluggish. γ-Butyrolactone underwent a relatively slow reduction. However, no aldehyde could be detected when 1 mol of the lactone was treated with 0.5 mol of thexylborane for 24 hr at 0°. The reduction of phthalide was very slow at 0°. Isopropenyl acetate utilized two hydrides rapidly. However, following the initial reaction, reduction proceeded only slowly. Presumably the reaction involves an initial hydroboration, followed by a rapid elimination and hydroboration of the propylene produced in the elimination step, as shown in the following equations (R = thexyl). The reaction intermediate, thexylacetoxyborane, shown in the above possible mechanism, may also be present in the acetic anhydride reduction. The reaction is believed to follow the course indicated. The very slow reaction after the uptake of two hydrides in both cases can be correlated with a unique characteristic of this species. It appears that the thexylacyloxyborane moiety undergoes reduction intermolecularly rather than intramolecularly in the reaction of carboxylic acids with thexylborane, resulting in the formation of the aldehyde in high yield. The results are summarized in Table V.

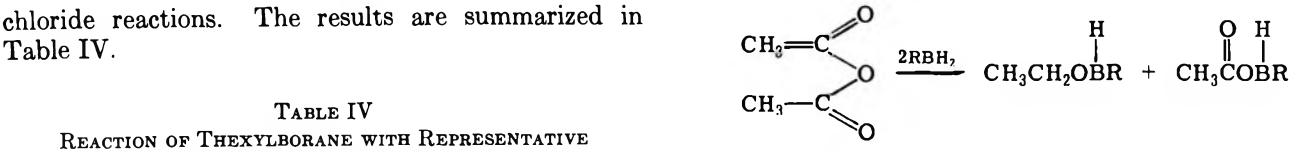


TABLE V
REACTION OF THEXYLBORANE WITH REPRESENTATIVE ESTERS AND LACTONES IN TETRAHYDROFURAN AT 0°

Compound[a]	Time, hr	Hydrogen evolved[b]	Hydride used[b]	Hydride used for reduction[b]
Ethyl caproate	1.0	0.00	0.23	0.23
	3.0	0.00	0.21	0.21
	6.0	0.00	0.25	0.25
	12.0	0.00	0.31	0.31
	24.0	0.00	0.47	0.47
	48.0	0.00	0.65	0.65
Ethyl benzoate	1.0	0.00	0.04	0.04
	3.0	0.00	0.07	0.07
	6.0	0.00	0.12	0.12
	12.0	0.00	0.23	0.23
	24.0	0.00	0.30	0.30
	48.0	0.00	0.34	0.34
Phenyl acetate	1.0	0.00	0.15	0.15
	3.0	0.00	0.20	0.20
	6.0	0.00	0.20	0.20
	12.0	0.00	0.21	0.21
	24.0	0.00	0.22	0.22
	48.0	0.00	0.25	0.25
γ-Butyrolactone	1.0	0.00	0.12	0.12
	3.0	0.00	0.32	0.32
	6.0	0.00	0.60	0.60
	12.0	0.00	1.04	1.04
	24.0	0.00	1.50	1.50
Phthalide	1.0	0.00	0.01	0.01
	3.0	0.00	0.03	0.03
	6.0	0.00	0.06	0.06
	12.0	0.00	0.14	0.14
	24.0	0.00	0.25	0.25
	48.0	0.00	0.34	0.34
Isopropenyl acetate	1.0	0.00	2.02	2.02
	3.0	0.00	2.08	2.08
	6.0	0.00	2.10	2.10
	12.0	0.00	2.20	2.20
	24.0	0.00	2.24	2.24

[a, b] See corresponding footnotes in Table I.

Epoxides.—The reactions of the reagent with simple epoxides, 1,2-butylene oxide and cyclohexene oxide, were very sluggish. However, styrene oxide consumed more hydride than expected from the stoichiometric requirement for reduction to the corresponding alcohols. (Reduction to 1- and 2-phenylethanol requires one hydride.) 1-Methyl-1,2-cyclohexene oxide consumed two hydrides, one involving hydrogen evolution and the other involving reduction. These results are very similar to those realized in the corresponding reactions in-

TABLE VI

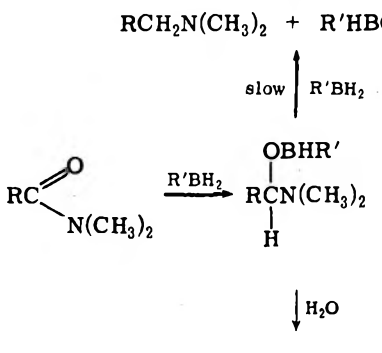
REACTION OF THEXYLBORANE WITH REPRESENTATIVE EPOXIDES IN TETRAHYDROFURAN AT 0°

Compound[a]	Time, hr	Hydrogen evolved[b]	Hydride used[b]	Hydride used for reduction[b]
1,2-Butylene oxide	1.0	0.00	0.03	0.03
	3.0	0.00	0.08	0.08
	6.0	0.00	0.17	0.17
	12.0	0.00	0.25	0.25
	24.0	0.00	0.37	0.37
	48.0	0.00	0.55	0.55
Styrene oxide	1.0	0.00	0.16	0.16
	3.0	0.00	0.31	0.31
	6.0	0.00	1.19	1.19
	24.0	0.00	1.68	1.68
Cyclohexene oxide	1.0	0.00	0.03	0.03
	6.0	0.00	0.12	0.12
	12.0	0.00	0.21	0.21
	24.0	0.00	0.31	0.31
	48.0	0.00	0.41	0.41
1-Methyl-1,2-cyclohexene oxide	1.0	0.49	0.76	0.27
	3.0	0.84	1.55	0.71
	6.0	0.97	1.34	0.97
	12.0	0.97	2.01	1.04
	24.0	0.97	2.02	1.05

[a, b] See corresponding footnotes in Table I.

volving diborane and disiamylborane. The results are summarized in Table VI.

Amides and Nitriles.—Primary amides underwent reduction slowly. Caproamide did not evolve hydrogen, whereas benzamide revealed partial hydrogen evolution (0.9 mol per mole of compound). This difference in behavior is presumably due to the difference in acidity of the amide hydrogen atoms. Tertiary amides were reduced slowly. Even though the rate data do not reveal any indication of a halt at the aldehyde stage (one hydride uptake), we were able to establish the preparation of some aldehydes under these conditions. Thus, a 44% yield of benzaldehyde (2,4-DNP analysis) was realized after 2 hr (0.95 hydride consumed) or after 8 hr (1.5 hydride consumed) in the reaction of thexylborane with *N*,*N*-dimethylbenzamide. Similarly, a 55% yield of crotonaldehyde was indicated in 4 hr (1.04 hydride consumed) and a 65% yield in 8 hr (1.3 hydride consumed) in the reaction of the reagent with *N*,*N*-dimethylcaproamide. These data suggest that the tertiary amides are much more easily attacked than the intermediate corresponding to aldehyde.



Since we had previously observed that disiamylborane reacts with tertiary amides even more cleanly to give aldehydes, we did not study this feature further.

Finally, nitriles were reduced very slowly, indicating relatively stable intermediates which can be hydrolyzed to aldehydes. Thus, using 1 mol of thexylborane per mole of nitrile at room temperature, we observed a 40% yield of benzaldehyde after 3 days and a 60% yield of caproaldehyde after 12 hr, as measured with 2,4-DNP. The results are summarized in Table VII.

TABLE VII

REACTION OF THEXYLBORANE WITH REPRESENTATIVE AMIDES AND NITRILES IN TETRAHYDROFURAN AT 0°

Compound[a]	Time, hr	Hydrogen evolved[b]	Hydride used[b]	Hydride used for reduction[b]
Caproamide[c]	0.5	0.00	0.25	0.25
	1.0	0.00	0.34	0.34
	6.0	0.00	0.75	0.75
	12.0	0.00	1.35	1.35
	24.0	0.00	1.62	1.62
Benzamide[c]	1.0	0.11	0.40	0.30
	3.0	0.30	1.02	0.72
	6.0	0.50	1.57	1.07
	12.0	0.73	2.11	1.38
	24.0	0.90	2.58	1.68
N,*N*-Dimethyl[d] caproamide	0.5	0.00	0.48	0.48
	1.0	0.00	0.60	0.60
	3.0	0.00	0.93	0.93
	6.0	0.00	1.17	1.17
	12.0	0.00	1.40	1.40
	24.0	0.00	1.60	1.60
	48.0	0.00	1.80	1.80
	72.0	0.00	1.92	1.92
N,*N*-Dimethyl[d] benzamide	0.5	0.00	0.48	0.48
	1.0	0.00	0.80	0.80
	3.0	0.00	1.15	1.15
	6.0	0.00	1.40	1.40
	12.0	0.00	1.72	1.72
	24.0	0.00	1.95	1.95
	48.0	0.00	1.99	1.99
Capronitrile[d]	1.0	0.00	0.20	0.20
	3.0	0.00	0.25	0.25
	6.0	0.00	0.28	0.28
	12.0	0.00	0.38	0.38
	24.0	0.00	0.42	0.42
Benzonitrile[d]	1.0	0.00	0.15	0.15
	3.0	0.00	0.18	0.18
	6.0	0.00	0.23	0.23
	12.0	0.00	0.25	0.25
	24.0	0.00	0.32	0.32

[a, b] See corresponding footnotes in Table I. [c] Compound was added as a solid. [d] Hydrolyzed with a mixture of concentrated hydrochloric acid and tetrahydrofuran (2:1).

Nitro Compounds and Their Derivatives.—1-Nitropropane was inert to this reagent. However, nitrobenzene was reduced at a moderate rate without hydrogen evolution. Azobenzene was reduced only sluggishly, whereas azoxybenzene underwent slow reduction without hydrogen evolution. The results are summarized in Table VIII.

Other Nitrogen Compounds.—Cyclohexanone oxime liberated 0.44 mmol of hydrogen rapidly, but uptake of hydride for reduction was very slow. With diborane also the hydrogen evolution was only partial, but reduction then proceeded at a moderate rate. On the other hand, with disiamylborane, cyclohexanone oxime liberated hydrogen quantitatively, but no reduction was observed. Phenyl isocyanate was slowly reduced,

TABLE VIII

REACTION OF THEXYLBORANE WITH NITRO COMPOUNDS AND THEIR DERIVATIVES IN TETRAHYDROFURAN AT 0°

Compound[a]	Time, hr	Hydrogen evolved[b]	Hydride used[b]	Hydride used for reduction[b]
1-Nitropropane	40.0	0.00	0.00	0.00
Nitrobenzene[c]	0.5	0.00	0.14	0.14
	1.0	0.00	0.23	0.23
	3.0	0.00	0.38	0.38
	6.0	0.00	0.54	0.54
	12.0	0.00	0.92	0.92
	24.0	0.00	1.45	1.45
	48.0	0.00	1.95	1.95
Azobenzene	0.5	0.00	0.01	0.01
	6.0	0.00	0.04	0.04
	12.0	0.00	0.12	0.12
	24.0	0.00	0.18	0.18
	48.0	0.00	0.25	0.25
Azoxybenzene[c]	3.0	0.00	0.30	0.30
	6.0	0.00	0.40	0.40
	24.0	0.00	0.89	0.89
	48.0	0.00	1.54	1.54

[a,b] See corresponding footnotes in Table I. [c] Hydrolyzed with a mixture of concentrated hydrochloric acid and tetrahydrofuran (2:1).

consuming two hydrides in 48 hr, with the consumption of the third hydride very sluggish. Pyridine did not react with this reagent. However, pyridine-*N*-oxide consumed three hydrides in 24 hr. This behavior is similar to that observed with diborane, but the reaction proceeds at a faster rate. The results are summarized in Table IX.

TABLE IX

REACTION OF THEXYLBORANE WITH OTHER NITROGEN COMPOUNDS IN TETRAHYDROFURAN AT 0°

Compound[a]	Time, hr	Hydrogen evolved[b]	Hydride used[b]	Hydride used for reduction[b]
Cyclohexanone[c] oxime	0.5	0.44		
	15.0	0.44	0.62	0.18
	20.0	0.44	0.75	0.31
	120.0	0.44	1.29	0.85
	144.0	0.44	1.42	0.98
Phenyl isocyanate[c]	0.5	0.00	1.31	1.31
	1.0	0.00	1.35	1.35
	6.0	0.00	1.44	1.44
	48.0	0.00	2.03	2.03
	168.0	0.00	2.47	2.47
Pyridine[c]	1.0	0.00	0.00	0.00
	3.0	0.00	0.00	0.00
	6.0	0.00	0.04	0.04
Pyridine *N*-oxide[c]	0.5	0.00	1.28	1.28
	1.0	0.00	1.78	1.78
	3.0	0.00	2.65	2.65
	6.0	0.00	2.80	2.80
	24.0	0.00	2.90	2.90

[a,b] See corresponding footnotes in Table I. [c] Hydrolyzed with a mixture of concentrated hydrochloric acid and tetrahydrofuran (2:1).

Sulfur Compounds.—Of the sulfur compounds tested only dimethyl sulfoxide underwent reduction, forming dimethyl sulfide. Both the sulfonic acids liberated hydrogen quantitatively, but no reduction occurred. Disulfides, sulfide, sulfone, and cyclohexyl tosylate were all inert to the reagent. These results are very similar to those realized with diborane and disiamylborane previously explored. The results are summarized in Table X.

TABLE X

REACTION OF THEXYLBORANE WITH REPRESENTATIVE SULFUR DERIVATIVES IN TETRAHYDROFURAN AT 0°

Compound[a]	Time, hr	Hydrogen evolved[b]	Hydride used[b]	Hydride used for reduction[b]
Di-*n*-butyl disulfide	20.0	0.00	0.00	0.00
Diphenyl disulfide	20.0	0.00	0.00	0.00
Phenyl *n*-propyl sulfide[c]	24.0	0.00	0.00	0.00
Dimethyl sulfoxide	0.25	0.23	0.62	0.39
	0.5	0.35	0.95	0.60
	1.0	0.55	1.30	0.75
	3.0	0.93	1.90	0.97
	6.0	1.00	2.00	1.00
	12.0	1.00	2.00	1.00
Diphenyl sulfone	40.0	0.00	0.00	0.00
Methanesulfonic acid	0.25	1.00	1.00	0.00
	0.5	1.00	1.00	0.00
	3.0	1.00	1.00	0.00
p-Toluenesulfonic acid monohydrate	0.25	2.96	2.96	0.00
	0.5	3.00	3.00	0.00
	3.0	3.00	3.00	0.00
Cyclohexyl tosylate[c]	24.0	0.00	0.00	0.00

[a,b] See corresponding footnotes in Table I. [c] Hydrolyzed with a mixture of concentrated hydrochloric acid and tetrahydrofuran (2:1).

Comparison of the Reducing Characteristics of Diborane, Thexylborane, and Disiamylborane.—Diborane was first applied for the reduction of organic compounds[11] some 30 years ago. A valuable feature proved to be its characteristics as an electrophilic or acid-type reducing agent,[12] in contrast to the nucleophilic reducing characteristics of sodium borohydride and lithium aluminum hydride.

The introduction of bulky alkyl groups into diborane produces borane-reducing agents which retain the acidic characteristics of the parent system, but exhibit numerous differences in reducing behavior, especially demonstrating a far greater selectivity.

In the hope of systematizing our knowledge of the reducing characteristics of the various hydridic reagents now available and ultimately arriving at simple generalizations governing their behavior, we initiated some time ago a program to examine the rate and stoichiometry of the reaction of these hydrides with a representative list of derivatives. We have previously achieved a comparison of the four aluminohydride reagents.[13] It appears appropriate for the objectives of this program to analyze our findings on diborane, thexylborane, and disiamylborane and point out the relative advantages of each of the reagents for specific reductions.[14]

I. Active Hydrogen Compounds.—Changes in the nature of the organic grouping attached to the hydroxyl

(11) H. C. Brown, H. I. Schlesinger, and A. B. Burg, *J. Amer. Chem. Soc.*, **61**, 673 (1939).

(12) H. C. Brown and B. C. Subba Rao, *ibid.*, **82**, 681 (1960).

(13) H. C. Brown and N. M. Yoon, *ibid.*, **88**, 1464 (1966).

(14) Unless specific mention of other conditions is made, it should be understood that these conclusions reached are based on comparative data for tetrahydrofuran solution at 0°. We shall attempt to generalize on the basis of the data obtained with the standard list, as well as such other data that may be available in the literature. While the conclusion should be valid for the average derivatives, it should be recognized that the rich variations possible in organic chemistry will doubtless result in the need to apply the generalizations cautiously to new systems which are quite different chemically from the model compounds.

group of alcohols result in major changes in the rate of hydrogen evolution observed with diborane (BH_3) but not with thexylborane ($ThBH_2$). However, disiamylborane (Sia_2BH) liberates 1 mol of hydrogen instantly with primary and secondary alcohols but fails to react with 3-ethyl-3-pentanol, a hindered tertiary alcohol. Phenol evolves hydrogen with Sia_2BH rapidly. However, $ThBH_2$ and BH_3 require 6 and 12 hr, respectively, for complete hydrogen evolution. *n*-Hexylamine evolves hydrogen only very slowly with BH_3, but fails to react with $ThBH_2$ and Sia_2BH.

Thiols exhibit major differences between these reagents. There is also a considerable difference between the reactivity of an aliphatic and aromatic thiol. Thus, BH_3 evolves one hydrogen in 1 hr with benzenethiol, but requires 12 hr with 1-hexanethiol, whereas $ThBH_2$ gives 0.92 hydrogen in 24 hr with benzenethiol, but is inert to 1-hexanethiol. Finally Sia_2BH does not evolve hydrogen with either of these thiols. These results indicate that hydrogen evolution in the reaction of these boranes with active hydrogen compounds is dependent upon two factors: the ease of coordination (between boron atom of the hydride and the electron donor atom to which the active hydrogen atom is attached in the substrate) and the acidity of the active hydrogen.

An alcohol such as 3-ethyl-3-pentanol requires prior coordination between the oxygen and boron atoms in order to react with liberation of hydrogen. Consequently, no reaction occurs with Sia_2BH. On the other hand, an acidic molecule such as phenol does not require prior coordination. Thus, Sia_2BH reacts rapidly with phenol to liberate hydrogen.

II. Aldehydes and Ketones.—All of the aldehydes and ketones included in the list, except benzophenone, are reduced rapidly by all three reagents. Benzophenone is reduced only at a moderate rate. The stereochemistry of reduction of norcamphor is quite interesting. Thus, BH_3 gives good stereospecificity (98% *endo*-norbornanol and 2% *exo*-norbornanol), whereas both $ThBH_2$ and Sia_2BH achieve less stereospecificity (91% endo and 9% exo).

The reduction of the aldehyde group in cinnamaldehyde with excess BH_3 is accompanied by hydroboration of the double bond and some elimination. However, the more bulky alkyl-substituted boranes do not exhibit such elimination, providing a route to good yields of 1,3-diols from α,β-unsaturated aldehydes.[15]

III. Quinones.—The reduction of *p*-benzoquinone with BH_3 gives hydroquinone exclusively, consuming two hydrides per mole, one for hydrogen evolution and the other for reduction. However, both the $ThBH_2$ and Sia_2BH consume approximately one hydride rapidly, but subsequent utilization of hydride is sluggish. These reactions require further study. The reduction of anthraquinone is very slow with all three reagents.

IV. Carboxylic Acids and Acyl Derivatives.—Carboxylic acids are reduced with BH_3 with remarkable speed. With $ThBH_2$ and Sia_2BH hydrogen evolution is rapid, but reduction is very slow. Thus the carboxylic acid group can be reduced preferentially with BH_3 in the presence of many other functional groups, such as ester, nitro, disulfide, and tosylate. On the other hand, with Sia_2BH it is possible to reduce many functional groups such as carbonyl, *tert*-amide (to aldehydes), and azoxy groups without reducing the carboxylic acid group. The formation of aldehydes in excellent yields from reaction in refluxing THF of carboxylic acids with $ThBH_2$, observed in the present study, should find major application in organic synthesis. The reduction of cyclic anhydrides and acyl chlorides is very slow with BH_3, still slower with $ThBH_2$, and essentially absent with Sia_2BH.

V. Esters and Lactones.—Toward the esters the order of reactivity follows the order $BH_3 > ThBH_2 > Sia_2BH$. Lactones are readily reduced to hydroxyaldehydes with Sia_2BH.[8] Aromatic esters and lactones are more inert than aliphatic esters and lactones toward all these hydrides.

These results are in marked contrast with the rapid reduction of these functional groups with lithium aluminum hydride and related aluminohydrides.[13]

VI. Epoxides.—Simple epoxides such as 1,2-butylene oxide and cyclohexene oxide react very slowly with each of these three hydrides. Therefore, many other more reactive functional groups should be reduced selectively by these reagents without significant attack of the epoxide ring. However, these epoxide rings can be reduced rapidly by diborane by using sodium borohydride in catalytic amounts in BH_3 solution. When one of the carbon atoms of epoxide ring is either benzylic or tertiary, the addition of borohydride is recommended for simple reductions leading to the corresponding alcohols, preferentially in the anti-Markovnikov fashion.[16] Styrene oxide gives almost exclusively α-phenylethanol with lithium aluminum hydride. However, we could obtain 2-phenylethanol almost exclusively by the addition of boron trifluoride to the BH_3 solution.[17]

VII. Amides and Nitriles.—BH_3 reduces primary and tertiary amides to the corresponding amines in excellent yield.[18] Sia_2BH does not reduce primary amides. However, *tert*-amides are reduced to the corresponding aldehydes with this reagent. Since these hydrides can tolerate many other groups, such as halogen, nitro, and disulfide, the application of this reagent should have advantages in some instances over aluminum hydride[19] for the selective conversion of tertiary amides to amines and over lithium diethoxyaluminohydride[20] for the conversion of such amides to aldehydes.

VIII. Nitro Compounds and Derivatives.—1-Nitropropane is not reduced by any of the three reagents under the standard conditions. However, $ThBH_2$ and Sia_2BH react slowly with nitrobenzene, whereas BH_3 is inert. Therefore, BH_3 is the reagent of choice for the selective reduction of other groups in the presence of an aromatic nitro substituent. Azobenzene is reduced to aniline with BH_3, but azoxybenzene is not reduced. This behavior contrasts with that of Sia_2BH, which

(15) H. C. Brown and R. M. Gallivan, *J. Amer. Chem. Soc.*, **90**, 2906 (1968).

(16) The reaction of 1-methylcycloalkene oxides with diborane results in 1-methylol-2-cycloalkanols (after oxidation of the intermediate). However, in the presence of borohydrides, *cis*-2-methylcycloalkanols are the major products, with a minor amount of some 1-methylcycloalkanol formed. H. C. Brown and N. M. Yoon, *J. Amer. Chem. Soc.*, **90**, 2686 (1968).

(17) H. C. Brown and N. M. Yoon, *Chem. Commun.*, 1549 (1968).

(18) H. C. Brown and P. Heim, *J. Amer. Chem. Soc.*, **86**, 3566 (1964).

(19) N. M. Yoon and H. C. Brown, *ibid.*, **90**, 2927 (1968).

(20) H. C. Brown and A. Tsukamoto, *ibid.*, **86**, 1089 (1964).

TABLE XI

REACTION OF REPRESENTATIVE ORGANIC DERIVATIVES WITH EXCESS DIBORANE, THEXYLBORANE, AND DISIAMYLBORANE IN TETRAHYDROFURAN AT 0°

Compound[a]	Diborane[b] — Hydride used: Evoln	Diborane[b] — Hydride used: Redn	Diborane[b] — Time, hr	Thexylborane[c] — Hydride used: Evoln	Thexylborane[c] — Hydride used: Redn	Thexylborane[c] — Time, hr	Disiamylborane[a] — Hydride used: Evoln	Disiamylborane[a] — Hydride used: Redn	Disiamylborane[a] — Time, hr
I. Active Hydrogen									
1-Hexanol	1.00	0	0.5	1.00	0	0.5	1.07	0	0.5
Benzyl alcohol	0.98	0	0.5	1.00	0	0.5	0.99	0.04	0.5
3-Hexanol	0.98	0	1.0	1.00	0	0.5	0.99	0.04	0.5
3-Ethyl-3-pentanol	1.00	0	12.0	0.98	0	0.5	0.00	0	1.0
Phenol	1.00	0	12.0	1.00	0	6.0	1.05	0.01	0.5
n-Hexylamine	0.13	0	20.0	0.00	0	14.0	0.00	0	1.0
1-Hexanethiol	1.00	0	12.0	0.00	0	10.0	0.00	0	1.0
Benzenethiol	1.00	0	1.0	0.92	0	24.0	0.00	0	1.0
II. Aldehydes and Ketones									
Caproaldehyde	0	1.00	2.0	0	0.99	0.5	0	0.97	3.0
Benzaldehyde	0	1.00	0.5	0	1.05	0.5	0	1.00	3.0
2-Heptanone	0	1.00	1.0	0	1.05	6.0	0	1.00	3.0
Norcamphor	0.03	0.96	1.0	0.03	0.99	3.0	0.04	0.97	1.0
Acetophenone	0	1.00	2.0	0	0.97	3.0	0	1.03	6.0
Benzophenone	0	1.00	24.0	0	0.96	48.0	0	0.98	24.0
Cinnamaldehyde	0	2.10	1.0	0	2.00	6.0	0	1.98	24.0
III. Quinones									
p-Benzoquinone	0.90	1.05	6.0	0.46	0.66	12.0	0.71	0.27	3.0
Anthraquinone	0	0.95	1680	0	0.32	72.0	0.11	0.34	24.0
IV. Carboxylic Acids and Acyl Derivatives									
Caproic acid	1.00	1.96	0.5	1.00	1.40	12.0	1.00	0.06	3.0
Benzoic acid	1.00	2.00	24.0	1.00	0.08	48.0	1.03	0	3.0
Acetic anhydride	0	3.82	24.0	0	2.00	0.5	0	1.97	0.5
Succinic anhydride	0	1.32	48.0	0	0.75	48.0	0	0.04	3.0
Phthalic anhydride	0	0.87	48.0	0	0.52	48.0	0	0.02	3.0
Caproyl chloride	0	1.13	48.0	0	0.20	48.0	0	0	3.0
Benzoyl chloride	0	0.98	48.0	0	0.55	48.0	0	0.03	3.0
V. Esters and Lactones									
Ethyl caproate	0	2.00	24.0	0	0.65	48.0	0	0	3.0
Ethyl benzoate	0	0.18	24.0	0	0.34	48.0	0.02	0.03	3.0
Phenyl acetate	0	1.67	24.0	0	0.25	48.0	0.03	0.02	3.0
γ-Butyrolactone	0	2.00	24.0	0	1.50	24.0	0	1.02	1.0
Phthalide	0	0.13	24.0	0	0.34	48.0	0	0.05	3.0
Isopropenyl acetate	0	3.95	24.0	0	2.02	1.0	0	2.01	6.0
VI. Epoxides									
1,2-Butylene oxide	0.04	0.99	72.0	0	0.55	48.0	0	0.07	3.0
Styrene oxide	0.04	1.85	24.0	0	1.68	24.0	0.05	2.56	72.0
Cyclohexene oxide	0	0.94	48.0[e]	0	0.41	48.0	0	0.04	3.0
1-Methyl-1,2-cyclohexene oxide	0.96	0.96	24.0[e]	0.97	1.04	12.0	0.85	1.11	48.0
VII. Amides and Nitriles									
Caproamide	1.10	1.00	48.0	0	1.62	24.0	1.96	0	24.0
Benzamide	1.38	1.20	48.0	0.90	1.68	24.0	1.99	0	24.0
Dimethylcaproamide	0	2.00	12.0	0	1.92	72.0	0	1.01	6.0
Dimethylbenzamide	0	2.00	24.0	0	1.99	48.0	0	1.01	3.0
Capronitrile	0	1.94	120.0	0	0.42	24.0	0.05	1.29	72.0
Benzonitrile	0	1.97	80.0	0	0.32	24.0	0.04	1.85	72.0
VIII. Nitro Compounds and Derivatives									
1-Nitropropane	0	0	96.0	0	0	40.0	0	0	24.0
Nitrobenzene	0	0	20.0	0	1.95	48.0	0.39	1.27	72.0
Azobenzene	0	2.00	48.0	0	0.25	48.0	0	0.01	3.0
Azoxybenzene	0	0.05	24.0	0	0.89	24.0	0.97	1.00	24.0
IX. Other Nitrogen Compounds									
Cyclohexanone oxime	0.56	1.22	48.0	0.44	0.98	144.0[c]	1.02	0.01	6.0
Phenyl isocyanate	0	2.05	24.0	0	2.03	48.0	0	1.98	24.0
Pyridine	0	0	48.0	0	0.04	6.0	0.05	0.03	24.0
Pyridine *N*-oxide	0	2.76	48.0	0	2.90	24.0	0.97	1.03	24.0
X. Sulfur Compounds									
Di-*n*-butyl disulfide	0	0	24.0	0	0	20.0	0	0.07	3.0
Diphenyl disulfide	0	0	72.0	0	0	20.0	0	0.04	3.0
Phenyl *n*-propyl sulfide	0	0	40.0	0	0	24.0	0	0	3.0[e]

TABLE XI (*Continued*)

Compound[a]	Diborane[b] Hydride used Evoln	Redn	Time, hr	Thexylborane[c] Hydride used Evoln	Redn	Time, hr	Disiamylborane[d] Hydride used Evoln	Redn	Time, hr
Dimethyl sulfoxide	0.83	0.77	48.0	1.00	1.00	6.0	0.96	1.04	3.0
Diphenyl sulfone	0	0	24.0	0	0	40.0	0	0	3.0
Methanesulfonic acid	1.00	0	0.5	1.00	0	0.5	0.99	0.04	0.5
Toluenesulfonic acid[f]	2.97	0	3.0	3.00	0	0.5	3.06	0.01	0.5
Cyclohexyl tosylate	0	0	40.0	0	0	24.0	0	0	3.0

[a] Hydride to compound ratio, 4:1. [b] 0.33 *M* BH_3 (1.00 *M* hydride). [c] 0.50 *M* RBH_2 (1.00 *M* hydride). [d] 1.00 *M* $R_2'BH$ (1.00 *M* hydride). [e] At 25°. [f] Monohydrate. [g] Methyl-*p*-tolyl sulfide.

reduces azoxybenzene but not azobenzene. Both of these substrates are reduced slowly by $ThBH_2$.

IX. Other Nitrogen Compounds.—Cyclohexanone oxime is reduced slowly with BH_3.[21] However, no significant reductions are observed with $ThBH_2$ and Sia_2BH. Phenyl isocyanate undergoes reduction slowly, but only to an intermediate stage, with further reduction being extremely slow. Pyridine is not attacked by any of these three reagents. However, pyridine *N*-oxide reacts at a moderate rate with both BH_3 and $ThBH_2$, both without accompanying hydrogen evolution. However, Sia_2BH apparently reduces this compound cleanly to the pyridine stage, as indicated by the evolution of 1 mol of hydrogen and the uptake of one hydride for reduction.

X. Sulfur Compounds.—All of the three reagents react in similar manner with various sulfur functional groups. Of all the sulfur compounds tested, only dimethyl sulfoxide is reduced to dimethyl sulfide. Sulfonic acids evolve hydrogen quantitatively, but no reduction is observed. Thus disulfide, sulfide, sulfone, and tosylate are all inert.

The experimental data supporting these conclusions and generalizations are summarized in Table XI.

In this table are reported the moles of hydrogen evolved and the hydride utilization observed per mole of compound under the standard conditions. In cases where no significant reduction was observed, in spite of the evident possibility for such reduction, the values reported are for the longest period for which the observation was made. Where reaction occurred, the data are for the shortest period, where essentially constant values of hydrogen evolution and hydride uptake were realized. Thus the values do not necessarily give maximum evolution of hydrogen nor the maximum possible utilization of hydride. They merely define the point where further reduction either does not occur or proceeds so slowly as to provide a convenient stopping place for the reaction.

Experimental Section

Materials.—The compounds used were the same collection[7,8] used in the earlier studies. The standard solutions of thexylborane were prepared by the following procedure. In a flask equipped with a thermometer and a side arm, capped by a rubber septum, was placed 100 ml of a solution of tetrahydrofuran containing 25.2 g (0.3 mol) of tetramethylethylene. The reaction flask was immersed in a mixture of Dry Ice–CCl_4; 74.7 ml of 2.04 *M* (0.3 mol of borane) diborane solution in THF was added slowly with stirring, keeping the temperature below 0°. The flask was permitted to remain overnight at 0°. The glpc analysis of the thexylborane solution indicated a slight excess (2–5%) of tetramethylethylene.

The thexylborane solution was periodically checked for active hydrogen by standard techniques.[22] No significant change in the hydride concentration was observed when a solution of thexylborane was kept at 0° for 14 days. At room temperature it has been reported that approximately 0.8 *M* solution of thexylborane did not undergo significant change in the hydride concentration in 16 days. Moreover, oxidation of the thexylborane indicated that isomerization of the tertiary boron to the primary position is very slow, 3% after 8 days and 8–9% after 16 days at room temperature. Even at the refluxing temperature of tetrahydrofuran (65°), the hydride concentration changed only 2% in 24 hr and 8% in 48 hr. However, no 1-butanol could be detected.[23] However, when the THF solution of thexylborane was exposed to the air through a drying tube at room temperature, the hydride concentration decreased to 70% in 48 hr.

Procedure.—In a 100-ml flask fitted with a side arm, capped by a rubber septum, 45 ml of a solution of thexylborane in THF (50 mmol in hydride) was placed. The flask was immersed in an ice bath. The reaction mixture was diluted with 5 ml of THF containing 12.5 mmol of the compound to be reduced.

At different time intervals 5-ml samples were withdrawn and quenched in a glycerol–water hydrolyzing mixture (1:3). The hydrogen evolved was measured volumetrically. The reaction was stopped when two or more analyses indicated that no more hydride was taken up. At the end of reduction the sample was analyzed for tetramethylethylene by glpc analysis in order to make certain that no displacement had occurred during the reduction. Solutions were transferred by means of a hypodermic syringe.

The reduction of isopropenyl acetate is described as representative. After 30 min reaction at 0°, the 5-ml aliquot of reaction mixture indicated 2.6 mmol of residual hydride, revealing that 1.85 mmol of hydride per mmole of compound had been consumed. After 1 hr the residual hydride decreased to 2.48 mmol, indicating that 2.02 hydride per mole of compound had been consumed. The reaction then became very slow. Thus, 1.76 mmol of residual hydride was observed after 48 hr, indicating an uptake of 2.4 hydride per mole of compound. Glpc analysis established that no displacement of the alkyl group of thexylborane had taken place during the course of the reaction.

Quantitative Determination of Aldehydes.—The following method was used for determination of aldehydes in samples of the reaction mixtures after treating various compounds with thexylborane.

In a 100-ml erlenmeyer flask 0.4 g of 2,4-dinitrophenylhydrazine was dissolved in a mixture of 2 ml of concentrated sulfuric acid and 3 ml of water. To this solution was added 5 ml of methanol, followed by the addition of 1–5 ml of the reaction mixture under investigation. After a short time the expected 2,4-dinitrophenylhydrazone crystallized out. After 15 min, 10 ml of water was added and the mixture was allowed to stand for 1 hr at room temperature. The crystals were separated from the liquid by a glass filter and washed several times with 2 *N* HCl, followed by a mixture of water–methanol (3:1). The substance was dried over P_2O_5 under vacuum to constant weight. Test experiments were carried out by using authentic aldehydes, caproaldehyde, and benzaldehyde. In these cases yields of 97–98% of the pure derivatives were realized.

Reduction of Carboxylic Acids to Aldehydes.—In a 100-ml flask, equipped with a reflux condenser, magnetic stirring bar, and a thermometer, were placed 22.5 ml of thexylborane solution in THF, containing 25 mmol of hydride. This solution was then

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(23) Unpublished observation by W. E. Rieder in this laboratory.

allowed to cool to −20° (CCl_4 + Dry Ice bath). Five millimoles of benzoic acid dissolved in 2.5 ml of THF (cooled to −20°) was then added slowly under vigorous stirring. After 10 min the mixture was heated up and kept under reflux. After different time intervals the mixture was cooled to 0° and 5-ml aliquots were withdrawn and analyzed for aldehyde. After 12 hr 0.197 g of 2,4-DNP derivative was obtained (70%); after 24 hr 0.232 g (82%) was obtained; and this remained constant after 36 hr. From caproic acid, using the same procedure as from benzoic acid, a 68% yield after 12 hr, 88% yield after 24 hr, and 98% yield after 36 hr were realized.

Registry No.—Thexylborane, 3688-24-2; diborane, 13283-31-3; disiamylborane, 1069-54-1.

Nonclassical Oxidation of Aromatics. II. Cobaltic Ion Catalyzed Oxidations of 1,1-Di(*p*-tolyl)ethane and 1,1-Di(3,4-dimethylphenyl)ethane

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Co^{III} ion catalyzed oxidation with oxygen in acetic acid has been extended to the 1,1-diarylalkanes. Major and novel products are carboxylic acids in which the bridging ethylidene group survives the oxidation. 1,1-Di(*p*-tolyl)ethane gave 1,1-di(4-carboxyphenyl)ethane (70%) as the major product. 1,1-Di(3,4-dimethylphenyl)ethane afforded isomeric dimethyl, dicarboxylic acids (85%). The products of this oxidation are unexpected, assuming a free-radical pathway. An electron transfer mechanism involving radical cation intermediates is therefore proposed.

Inorganic oxidants including chromic acid, potassium permanganate, and nitric acid are known to oxidize 1,1-diarylalkanes to benzophenone polycarboxylic acids.[1-3] Air oxidation, however, has been limited to di(*p*-tolyl)methane[4,5] and 2,2-diarylalkanes.[6,7] Di(*p*-tolyl)methane was oxidized to a benzophenone dicarboxylic acid. Attempts to oxidize 1,1-di(*p*-tolyl)ethane or 1,1-di-(3,4-dimethylphenyl)ethane with oxygen in the liquid phase led to low conversion of almost exclusively nonacidic oxidation products.[8] Similar difficulties were encountered in the attempted oxidation of alkoxytoluenes in acetic acid.[9] In these cases, initially formed hydroperoxide cleaves into phenolic materials which then terminate the reaction. A recent paper describes the synthesis of 1,1-di(*p*-tolyl)ethyl hydroperoxide and its subsequent cleavage to form *p*-cresol and *p*-methylacetophenone.[10]

We have proposed an electron transfer mechanism for the selective oxidation of alkyltoluenes in which methyl groups are preferentially attacked.[11] Extending this work, liquid phase oxidation of 1,1-di(*p*-tolyl)ethane (DTE) and 1,1-di(3,4-dimethylphenyl)ethane (DXE) was examined.

Results

Oxidations were carried out in acetic acid using cobaltous acetate catalyst and methyl ethyl ketone (MEK)–butane as the promotors. Reactants, experimental conditions, and the results obtained are summarized in Table I.

Oxidation of DTE in the presence of cobaltous acetate without a promotor was slow, nonselective, and incomplete, even after 20 hr (expt 1). A mixture of monoacids, including 1-(4-carboxyphenyl)-1-(4-methylphenyl)ethane (I) and 4-methyl-4′-carboxybenzophenone, was isolated (21%) along with 4,4′-dimethylbenzophenone (26%). A similar experiment, but with MEK, afforded I in 45.4% yield (expt 2). Oxidation of DTE in the presence of MEK–butane gave 1,1-di(4-carboxyphenyl)ethane (EDB) and I in yields of 67.3 and 8.3%, respectively (expt 3). Extension of the reaction time beyond a 5–6-hr period did not improve the yields of I or EDB significantly.

Oxidation of DXE under conditions used for DTE gave an isomeric mixture of the corresponding ethylidenedi- and -monocarboxylic acids exclusively (expt 5).

Recovery of products in all experiments was above 85%, whereas cleavage into fragments was between 5 to 10%. Cleavage products from DTE oxidation were (vpc) *p*-acetobenzoic acid, *p*-toluic acid, terephthalic acid, some *p*-methylacetophenone, and traces of *p*-cresol.

Discussion

Oxidation of 1,1-di(*p*-tolyl)ethane and 1,1-di(3,4-dimethylphenyl)ethane in the system earlier described for alkyltoluenes was investigated.[11] Major and novel products are carboxylic acids in which the bridging ethylidene group remains intact. Large amounts of catalyst in the higher valency state were required to effect selective methyl group oxidation. With Co^{II} ions alone, reaction did not proceed readily and showed no selectivity. Peroxy radicals derived from the substrate were apparently not sufficient to maintain the active Co^{III} species. If the overall rate of reaction is

$$RO_2\cdot + Co^{II} \longrightarrow R'CHO + Co^{III} + OH^-$$

governed by the reoxidation of Co^{II} to Co^{III}, it should be helped by peroxy radical-forming promoters. Adding for this purpose MEK or cyclohexanone showed an increase in rate and shortening of the induction period. As methylenic ketones are rapidly consumed, precursor

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(5) V. B. Fal'kovskii, R. A. Nurmukhamedova, S. V. L'vov, *Izobret., Prom. Obraztsy, Tovarnye Znaki*, **43** (2), 26 (1966); *Chem. Abstr.*, **64**, 19501 (1966).
(6) U. S. Patent 3,281,459 (1966).
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(11) A. Onopchenko, J. G. D. Schulz, and R. Seekircher, *J. Org. Chem.*, **37**, 1414 (1972).

TABLE I

Expt no.	1	2	3	4	5
Reactants, g					
$Co(OAc)_2 \cdot 4H_2O$	21.5	20	20	31.5	20
MEK		15	15	20	30
HOAc	403	400	400	535	460
n-Butane			105	45	18
Substrate	DTE (38.8)	DTE (48.8)	DTE (52.5)	DTE (37.5)	DXE (84.0)
Conditions					
Temp, °C	105	105	105	118	105
Total pressure, atm[c]	24	28	20	26	20
Reaction time, hr	20	4.5	17	5.5	22
Product data, g (% yield)[d]					
I	9.4 (21)[a]	25.1 (45.4)	4.9 (8.3)	1.8 (4.3)	
II			45.3 (67.3)	35.2 (73)	
4,4′-Dimethylbenzophenone	10.5 (26)				
Dimethyldicarboxylic acids					52 (50%)[b]
Trimethylcarboxylic acids					23 (25)
Methyltricarboxylic acids					Trace

[a] *Ca.* a 50:50 mixture of I and 4-methyl-4′-carboxybenzophenone. [b] Continued reaction for 6 hr with added butane; yield, 85%. [c] Mostly partial pressures of butane and oxygen. [d] Based on aromatic feed.

hydrocarbons such as *n*-butane and cyclohexane were used as promotors of greater permanency.

Products obtained were not expected from a normal free-radical pathway. By this mechanism, hydrogen on the bridging ethylidene group would have been preferentially abstracted.[12] That simple radical abstraction was not involved is shown by the different nature of the products formed, the dependence of the reaction rate on catalyst concentration,[11] and the relative reactivities of different substrates toward Co^{III} ions (Table II). Most striking is the inertness of the

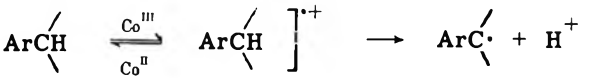
TABLE II

RELATIVE REACTIVITIES OF AROMATICS TOWARD COBALTIC ION[a]

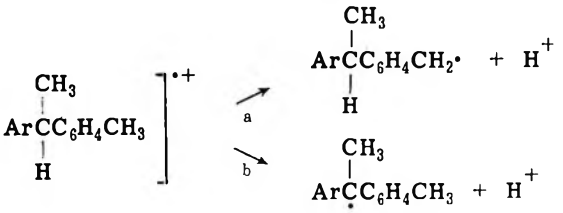
	Reactivity per molecule	Reactivity/ methyl group
1,1-Di(*p*-tolyl)ethane	12	(6.0)[c]
1,1-Di(3,4-dimethylphenyl)ethane	23	(5.8)[c]
p-Cymene	2.4	(2.4)[c,d]
Toluene	1.00[b,f]	1.00[b]
Diphenylmethane	0.5[e]	
3,4,3′,4′-Tetramethylbenzophenone	1.6	0.4
4,4′-Dimethylbenzophenone	0.6	0.3
p-Tolyl sulfone	0.6	0.3
3,4-Dimethylphenyl sulfone	0.8	0.2
4,4′-Dimethylbiphenyl	0.3	0.15
Triphenylmethane	0.2[e]	
Cumene	0.1[f]	
Phenyl ether	0.0[g]	

[a] 100°, 22-atm total pressure, in presence of MEK–C_4H_{10}. [b] Assumed standard, reactivity = 1.00. [c] Assumed negligible contribution from reactivity of the tertiary hydrogen, based on low reactivity of cumene and triphenylmethane. [d] 90% of the reaction was at the methyl group.[11] [e] 40°, from Table I of ref 14. [f] Our values agree with those of footnote *e*. [g] Internal standard.

benzylic tertiary hydrogens. This has been observed in electrophilic chlorination and diazotizations[13] for systems in which a positive charge is developed either at or adjacent to an aromatic ring. Sakota, *et al.*,[14] rationalized this observation in terms of an entropy decrease of the substrate in the transition state. Lack of available σ^+ values for our compounds prevented us from obtaining a reliable ρ value. The data show, however, that electron-withdrawing substituents retard oxidation in this system. Consistent with a positively charged transition state is an anticipated negative ρ value. The following mechanism for 1,1-diarylalkanes oxidation would agree with our line of reasoning. Loss of proton appears to be controlled by stereo-



electronic factors rather than the thermodynamic stability of the product. Results are therefore best rationalized by path a. To account for this unusual selectivity,



a steric configuration is proposed with tertiary hydrogen located in the node plane of the benzene ring, where any action upon it in the transition state would be minimized. This is supported by recent esr studies which show that groups such as isopropyl exhibit no free rotation in radical cations when compared to methyl or ethyl.[15]

Benzyl radicals produced are trapped by oxygen to give peroxy radicals which then terminate. Termination of such radicals can occur through various pathways which do not necessarily proceed *via* a hydroperoxide route.[16] In the absence of kinetic data we do not wish to speculate on the mechanism of termination.

During more recent work with aliphatic substrates in the same system, rates and general characteristics of this type of oxidation were almost identical with those with the alkyltoluenes and diarylalkanes. Formation of radical cations is therefore not a prerequisite for

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electron transfer, but rather an accompanying phenomenon in aromatic systems.

Experimental Section

Apparatus and Materials.—Oxidations were carried out in a 1-l., 316 stainless steel, magnetically stirred autoclave (Autoclave Engineers, Inc., Erie, Pa.) under conditions described in Table I. The autoclave was equipped with a cooling coil and a heating mantle, and was connected to an oxygen supply system, temperature and pressure controllers, and recording instruments.

The nmr spectra were obtained on a Varian T-60 spectrometer (solvent, TMS). Chemical shifts are in δ units, parts per million. The ir spectra were recorded either on Perkin-Elmer Infracord or Model 237B spectrometers. The products were analyzed by vapor phase chromatography (vpc) as trimethylsilyl derivatives (4 ft × 0.25 in., OV-1 column, programmed from 50 to 250° at 10°/min).

All aromatic hydrocarbons used in our work were available in this laboratory or prepared by standard procedures.

Oxidation of DTE.—A typical procedure used for the oxidation of diarylalkanes is described for DTE (expt 4). A mixture of 31.5 g of cobaltous acetate tetrahydrate, 525 g of acetic acid, 20 g of MEK, 37.5 g (0.178 mol) of DTE, and 45 g of *n*-butane was placed into the autoclave. The autoclave was pressured with oxygen to ~10 atm, and heated to 118°. Additional oxygen was introduced to bring the pressure inside the autoclave to 26 atm. After an induction period of 1 hr, the reaction was continued for 5.5 hr. The autoclave was cooled and depressured, and the product mixture was removed.

Filtration of crude product afforded 25 g of solids (first crop). The filtrate was evaporated to dryness on a rotary evaporator, and the residue was extracted with acetone to afford a second crop of solids. The acetone insoluble material, mostly catalyst, was treated with concentrated hydrochloric acid and filtered to afford a third crop of solids. The combined solids were washed with water and then dried (vacuum oven) to give 44 g of product. Analysis by vpc had indicated that 35.2 g (0.13 mol, 73%) of EDB, and 1.6 g (0.007 mol, 4.3%) of I were present in the mixture. About 6.6 g of material consisted of *p*-toluic acid, *p*-methylacetophenone, *p*-acetobenzoic acid, a trace of 4,4-dimethylbenzophenone and terephthalic acid, and unknowns. The entire product was dissolved in acetone from which EDB was obtained by repeated crystallization [mp 278° (lit.[17] mp 280°); ir ν_{COOH}^{Nujol} 1695 (s), ν_{ring} 1610 cm^{-1}], present in benzoates but not in terephthalates or benzophenones: nmr ($Cl_2HCCOOH$, TMS) 8.0 (d, 4, ring), 7.3 (d, 4, ring), 4.3 (q, 1, =CH–), and 1.72 (d, 3, CH_3).

Anal. Calcd for $C_{16}H_{14}O_4$: C, 71.1; H, 5.22. Found: C, 70.8; H, 5.3; neut equiv, 135.5.

Isolation of I.—Oxidation of 48.8 g of DTE (expt 2) for 4.5 hr afforded a partially oxidized product. The solvents were removed on a rotary evaporator and the residue was treated with aqueous sodium hydroxide to precipitate the catalyst. After filtering, the filtrate was acidified with hydrochloric acid to give 36 g of acids. Analysis by vpc indicated 25.1 g (0.1 mol, 45.4%) of I to be in the mixture. A 10-g sample of crude product was purified by base-acid treatment and recrystallized from aqueous methanol to give 5.6 g of I: mp 95–8°; ir ν_{COOH}^{Nujol} 1695 (s), ν_{ring} 1610 cm^{-1} (m); nmr (acetone-d_6, TMS) 7.0 (s, 4, ring), 7.25 (d, 2, ring), 7.9 (d, 2, ring), 4.11 (q, 1, =CH–), 2.27 (s, 3, CH_3), and 1.61 (d, 3, CH_3CH=).

Anal. Calcd for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 80.2; H, 6.9; neut equiv, 241.6.

Oxidation of DXE.—Oxidation of DXE (expt 5) was carried out under conditions used for DTE. At the end of this experiment, a sample of product mixture was withdrawn and analyzed by vpc (internal standard method). Analysis indicated that 52 g (50%) of dicarboxylic acids and 23 g (24.5) of monocarboxylic acids were formed. Continued oxidation of mixture in the presence of added butane afforded dicarboxylic acids predominantly (85%). Neutral equivalent determination and the nmr data were consistent with the vpc analysis. The absence of benzophenone derivatives was shown by the absence of the 1650 band in the infrared spectrum.

Competitive Rate Study.—Competitive rate study on mixtures of substrates was done under conditions used for oxidation of DTE alone. The initial concentration of each substrate in a mixture was held at a low value (~0.1 *M*).

The mixture was analyzed directly before and after the reaction for the disappearance of starting substrates (vpc, internal standard method). In addition to OV-1 column, 20 ft × 1/8 in., 5% Bentone 24 and DC 200 on Chrom W was also used at 95°. All reactivities were related to toluene, assumed reactivity = 1.00, by the following expression, where subscripts refer to final and initial concentrations (wt %).

$$\frac{k_A}{k_B} = \frac{\log([A]_f/[A]_i)}{\log([B]_f/[B]_i)}$$

Registry No.—I, 35026-55-2; DTE, 530-45-0; DXE, 1742-14-9; EDB, 35026-58-5; Co^{III} ion, 22541-63-5.

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Kinetics of the Baeyer–Villiger Reaction of Aromatic Ketones with Perbenzoic Acid[1]

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The Baeyer–Villiger reaction of acetophenones with perbenzoic acid has been studied kinetically in 40% aqueous ethanol and in organic solvents at 25.0°. The rate–pH profiles are similar to those for the reaction of benzaldehydes with aryl migration.[2] Acid catalysis by perchloric acid in 40% ethanol is not correlated with acidity function but is proportional to $[HClO_4]$ at its higher concentration. The Baeyer–Villiger reaction with pure perbenzoic acid is very slow in organic solvents and acetic acid catalyzes only the carbonyl addition, while trifluoroacetic acid effectively establishes the addition equilibrium and catalyzes also the migration. Carbonyl addition is rate-determining under some conditions for the Baeyer–Villiger reaction of the ketones especially with strongly electron-releasing groups, and the addition rate of perbenzoate ion to *o*- and *p*-HOC_6H_4COR satisfies the Taft equation to give $\rho^* = 1.3$–1.6 (σ^*) and $\delta = 0.6$–0.8. The rate of the Baeyer–Villiger reaction in the presence of a suitable catalyst is governed by that of migration step, and the apparent rate for ring-substituted acetophenones affords ρ values of 1.5–2.4 (σ^+). The kinetic suggests that the acid catalyst is not proton but general acid.

Most features of the Baeyer–Villiger (B–V) reaction are well understood.[3–6] The rate for peracid oxidation of ketones is, for most cases, first order both in peracid and ketone and is acid catalyzed by strong acid.[5,7] A rate-determining, concerted migration in the peracid–carbonyl adduct (I) was demonstrated[7] and recently confirmed by ^{14}C-isotope effect,[8] where no observation of the isotope effect for the exceptional case of *p*-methoxyacetophenone was explained on the basis of strong electron-releasing power of *p*-methoxy group,[8] but an alternative explanation seems also to be possible, of a rate-controlling carbonyl addition of peracid, as demonstrated in our hands for the B–V reaction of benzaldehydes having a strong electron-releasing group.[2a]

Another obscure point in the B–V reaction is about the nature of acid catalysis, *i.e.*, general or specific, and which step is subject to the catalysis, carbonyl addition, and/or migration step. The present report summarizes our kinetic results for the B–V reaction of aromatic ketones with perbenzoic acid (PBA), and states that carbonyl addition is rate determining in some cases and that general acid catalysis is operative both for carbonyl addition and migration.

Results

The reaction of acetophenones in 40 vol. % ethanol was undertaken in the presence of 10^{-4} *M* ethylenediaminetetraacetate (EDTA) to minimize the catalytic decomposition of PBA, although the effect of EDTA is usually very small. The B–V reaction satisfied the second-order kinetics shown in eq 1. The rate was

$$v = k_{obsd}[ArCOR][PBA] \quad (1)$$

mostly followed by iodometry of PBA with reproducibility of ±5%, the rates of which were identical with these obtained from the decrease of carbonyl absorbance of the ketone. The migrating group in the present reaction is practically the aryl alone as reported with trifluoroperacetic acid.[7,9]

Effect of Acids and Bases in 40% Aqueous Ethanol.—The rates varies with the substituent and pH (Figure 1). For example, *o*-hydroxyacetophenone is highly reactive at pH >2, but almost inactive at pH <2. Also, the relative reactivity of *p*-hydroxy- *vs.* *p*-methoxyacetophenone is reversed at pH range of 1–5.

The observed rate in 40% ethanol is expressed as

$$k_{obsd} = k_{HA}[HA] + k_0 + k_{PBA^-}[PBA^-] \quad (2)$$

Here, PBA^- is perbenzoate ion and HA is general acid (perchloric acid in this case). The lines for *o*- and *p*-hydroxyacetophenones in Figure 1 are those calculated from the values of k_{HA}, k_0, and k_{PBA^-} in Table I.

TABLE I

SUMMARY OF RATE DATA FOR PBA OXIDATION OF ACETOPHENONES, XC_6H_4COMe, IN 40% ETHANOL AT 25.0°

X	k_{HA},[a] M^{-2} sec^{-1}	k_0, M^{-1} sec^{-1}	k_{PBA^-}, M^{-1} sec^{-1}
p-HO	1.33×10^{-3}	$<0.05 \times 10^{-3}$	1.10
o-HO	Very small	$\sim 0.13 \times 10^{-3}$	27.0
p-MeO	0.54×10^{-3}	(0.50×10^{-3})[b]	
p-Me	Very small	$\sim 0.15 \times 10^{-3}$	

[a] Here HA = $HClO_4$. [b] Value at pH 6.

As shown in the discussion section, a rate-determining step for *o*- and *p*-hydroxyacetophenones is a carbonyl addition of PBA^-. Hence, the apparent rate at pH 4–11 gives the rate for the carbonyl addition of PBA^- (Table II), which fits the Taft equation[10]

$$\log (k/k_0) = \rho^* + \delta E_s$$

giving ρ^* and δ values listed at the bottom of Table II.

As apparent in Figure 1, the acid catalysis is rather small and cannot be correlated by acidity function, H_0, which demonstrates no intervention of any conjugate acid of reactants. The plot of k_{obsd} *vs.* $[HClO_4]$ is a curve up to ~0.5 *M* acid and then a straight line at its higher concentration above 0.5 *M* (Figure 2). The slope of this plot gives a catalytic constant, k_{HA}, of 1.33×10^{-3} and 0.54×10^{-3} M^{-2} sec^{-1}, and the intercept of this line is 0.26×10^{-3} and 0.49×10^{-3} M^{-1}

(1) Contribution No. 181.

(2) (a) Y. Ogata and Y. Sawaki, *J. Amer. Chem. Soc.*, **94**, 4189 (1972); (b) Y. Ogata and Y. Sawaki, *J. Org. Chem.*, **34**, 3985 (1969).

(3) C. H. Hassall, *Org. React.*, **9**, 73 (1957).

(4) A. G. Davies, "Organic Peroxides," Butterworths, London, 1961, p 144.

(5) P. A. S. Smith, "Molecular Rearrangements," Vol. I, P. de Mayo, Ed., Interscience, New York, N. Y., 1963, p 579.

(6) S. B. Lee and B. C. Uff, *Quart. Rev.*, **21**, 429 (1967).

(7) M. F. Hawthorne and W. D. Emmons, *J. Amer. Chem. Soc.*, **80**, 6393, 6398 (1958).

(8) B. W. Palmer and A. Fry, *ibid.*, **92**, 2580 (1970).

(9) E. E. Smissman, J. P. Li, and Z. H. Israili, *J. Org. Chem.*, **33**, 4231 (1968).

(10) R. W. Taft, Jr., "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, p 648.

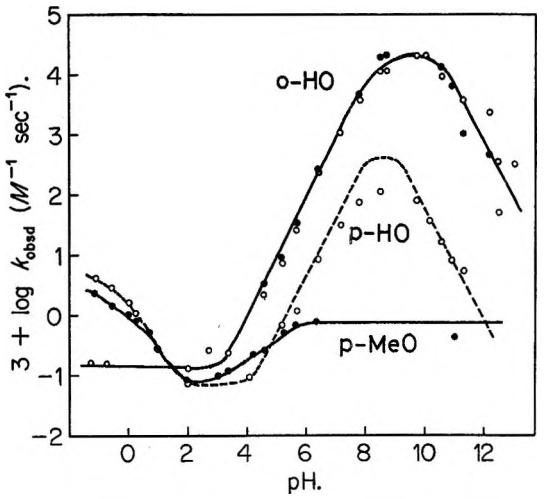


Figure 1.—Rate–pH profiles for the PBA oxidation of substituted acetophenones in 40% ethanol at 25.0°. The lines for *o*-HO and *p*-HOC$_6$H$_4$COMe are calculated from the data in Table I.

TABLE II

SUBSTITUENT EFFECT ON THE RATE OF ADDITION OF PERBENZOATE ION TO *o*- AND *p*-HOC$_6$H$_4$COR IN 40% ETHANOL AT 25.0°

	pK_a[a]		$k_1^{PBA^-}$, M^{-1} sec^{-1}	
R	*p*-HOC$_6$H$_4$-COR[b]	*o*-HOC$_6$H$_4$-COR[c]	*p*-HOC$_6$H$_4$-COR	*o*-HOC$_6$H$_4$-COR
H	8.21	8.45	112[d]	1050[d]
Me	8.72	10.50	1.12	27
Et	8.90	10.73	0.82	22
n-Pr	8.86	10.88	0.56	16
i-Pr	8.92	10.75	0.33	~3
CH_2Cl	8.40		35.4	
Ph	8.63		0.25	
ρ^*[e]			1.63[f]	1.31
δ[e]			0.63[f]	0.81
r[g]			0.991[f]	0.991

[a] Titrated in 40% ethanol at 25 ± 1°. [b] Registry numbers are, respectively, 123-08-0, 99-93-4, 70-70-2, 1009-11-6, 34917-91-4, 6305-04-0, and 1137-42-4. [c] Registry numbers are, respectively, 90-02-8, 118-93-4, 610-99-1, 2887-61-8, and 6640-69-3. [d] Data from ref 2a. [e] Correlated by the Taft equation, log (k/k_0) = $\rho^*\sigma^* + \delta E_S$, where σ^* was taken from ref 10. [f] These were calculated from the substituents except R = H and Ph. If H's are incorporated in the correlation, the values of ρ = 1.05, δ = 0.99, and r = 0.977 are obtained. [g] Correlation coefficient.

sec^{-1} for acetophenones with *p*-HO and *p*-MeO groups, respectively. Other interesting points are as follows. First, the intercept of 0.49 × 10^{-3} M^{-1} sec^{-1} for *p*-MeO is very close to the rate constant of 0.50 × 10^{-3} M^{-1} sec^{-1} at pH ~6. Second, the rate of *p*-HO at [HClO$_4$] < 0.5 M is identical or slightly less than that of *p*-MeO, a more electron-attracting group.

Effect of Acid and Base in Organic Solvents.—Acid catalysis in organic solvents revealed the similar features of the B–V reaction. The reaction with pure PBA was very slow. Although catalysis by acetic or *m*-chlorobenzoic acid is not appreciable up to 3 M concentration in 40% aqueous ethanol, the reaction in benzene is sensitive to these weak acids. The catalysis by acetic acid shows no linear relation between the rate and the acid concentration (see Figure 3A), but at higher concentration the observed rate in benzene gradually approaches to limiting k_{obsd} values of

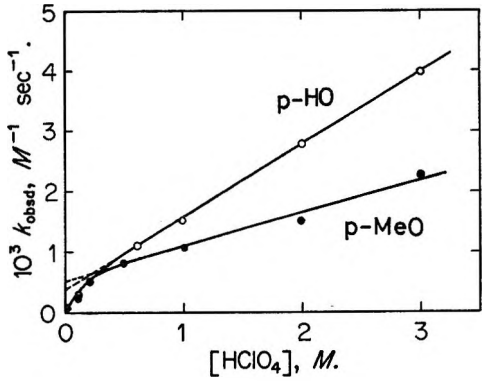


Figure 2.—Dependence of k_{obsd} on perchloric acid concentration for PBA oxidation of substituted acetophenones in 40% ethanol at 25.0°.

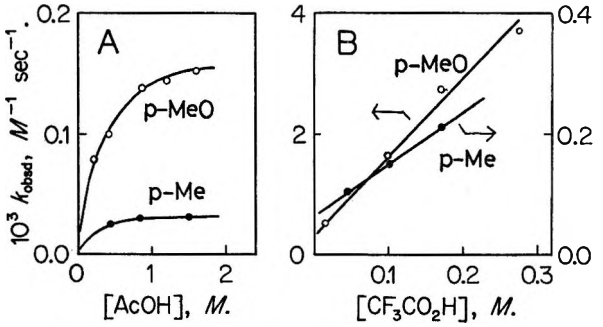


Figure 3.—Dependence of the apparent rate on acid concentration for PBA oxidation of *p*-methoxy- and *p*-methylacetophenones in benzene at 25.0°.

0.18 × 10^{-3} and 0.04 × 10^{-3} M^{-1} sec^{-1} for *p*-methoxy- and *p*-methylacetophenones, respectively.

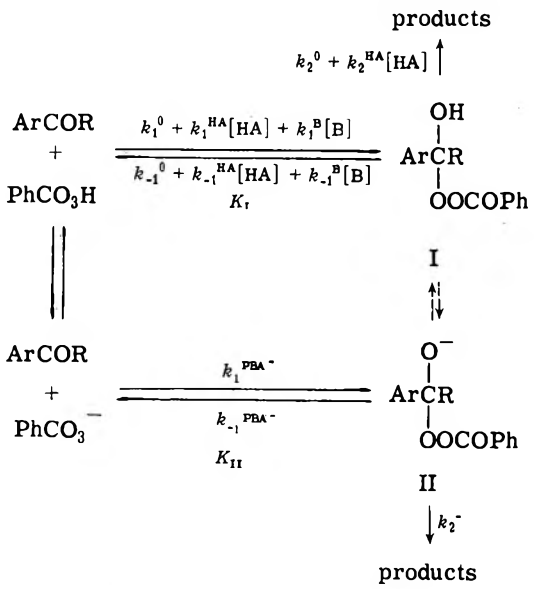
On the other hand, the catalysis by trifluoroacetic acid affords a linear relationship between the rate and the acid concentration. The plot in Figure 3B gives k_{HA} of 2.7 × 10^{-3} and 0.17 × 10^{-3} M^{-2} sec^{-1} for *p*-methoxy- and *p*-methylacetophenones, respectively. The intercept gives k_0 of ~0.3 × 10^{-3} for *p*-MeO and 0.07 × 10^{-3} M^{-1} sec^{-1} for *p*-Me, which agree in order with the above limiting values at higher concentration of acetic acid.

For comparison, the B–V reaction of benzaldehydes has been examined, where the acid catalysis similar to the case of acetophenone is observed as shown in Figure 4A. The reaction of anisaldehyde in ethanol is much slower than that in benzene, a more efficient solvent for acid catalysis. The base catalysis by sodium acetate for the establishment of carbonyl addition equilibrium is remarkable; the PBA oxidation of anisaldehyde reaches a constant rate constant of 1.5 × 10^{-3} M^{-1} sec^{-1} only with 0.002 M acetate (Figure 4B). As for the base catalysis of B–V reaction of acetophenones, no reliable data could be obtained because of simultaneous decomposition of PBA.

Discussion

The B–V reaction of acetophenones showed features similar to the case of benzaldehydes.[2a] The reaction is heterolytic, since the oxidation gave high yields of phenols (>90%) and was not affected by addition of oxygen or other radical scavengers, *e.g.*, phenols or EDTA. Probable steps in the present B–V oxidation are shown in Scheme I.

SCHEME I



Rate-Determining Step in 40% Aqueous Ethanol.—Rate-determining, concerted migration was proved by ^{14}C-isotope effect on the *m*-ClPBA oxidation of acetophenones.[8] The absence of isotope effect for the case of *p*-methoxyacetophenone was explained by a strong electron-releasing power of p-methoxy group,[8] but an alternative explanation seems to be more probable as discussed below that carbonyl addition is rate determining.

Evidences for the rate-determining addition to *o*- and *p*-hydroxyacetophenones are as follows. (i) The rate–pH profile at pH >2 is explicable by assuming the rate-controlling carbonyl attack of perbenzoate ion, PBA^- (see Figure 1). That is, the observed rate–pH profiles can be reproduced assuming that the data (k's) for *o*- and *p*-HO in Table I are those of first step (k_1's) in Scheme I (*i.e.*, $k_{obsd} = k_1^0 + k_1^{HA}[HA] + k_1^{PBA^-}[PBA^-]$). (ii) If the unit slope at pH 4–7 for *o*- and *p*-HO were OH^--catalyzed migration in the carbonyl adduct I, *i.e.*, $k_2 = k_2^{OH}[OH^-]$, catalytic constant k_2^{OH} for the migration step should be $\geq 80 \times 10^{10}$ and $>0.5 \times 10^{10}\ M^{-1}\ sec^{-1}$ for *o*- and *p*-HO in 40% ethanol. The rate constants extrapolated to pure water are *ca.* sixfold greater than those in 40% ethanol, *i.e.*, $\sim 500 \times 10^{10}$ and $3 \times 10^{10}\ M^{-1}\ sec^{-1}$, respectively, which are too fast to be actual.[11] This assumes that a relative ratio of equilibrium constant (K_I) of carbonyl addition of PBA[12] to ArCHO *vs.* that to ArCOMe is ≥ 100, which is not unreasonable in view of other carbonyl addition,[13] and, even if ArCHO/ArCOMe is ~1, the assumed constant of 500×10^{10} for *o*-HOC_6H_4COMe is decreased to $5 \times 10^{10}\ M^{-1}\ sec^{-1}$ which is still too large to be actual.[11] (iii) Relative rates $k_{m\text{-ClPBA}}/k_{PBA}$ ($\Delta pK_a = 0.35$)[14a] are 2.0 ± 0.1 at pH <8 and 1.05 ± 0.20 at pH >10, which may also be explained by a rate-determining carbonyl addition of PBA^-. That is, ΔpK_a of 0.35 corresponds to *ca.* twofold concentration of *m*-ClPBA anion compared to PBA anion and then to the observed twofold increase of rate constant in going from PBA to *m*-ClPBA at pH <8, while little increase in the rate observed at pH >10 is explicable in view of no change in the concentration of peracid ion because of 100% dissociation of PBA's at this pH region. (iv) Relative rate of *p*-hydroxy- and *p*-methoxyacetophenones is reversed at pH 2–5 (Figure 1). The reversion suggests a change of rate-controlling steps from C=O addition to migration. Expected order is *p*-HO > *p*-MeO in view of σ value if the overall rate (k_{obsd}) contained the rate of migration step (k_2). These reversion of relative rates are generally understood as a change of rate-determining steps.[14b] (v) The change of dependence of k_{obsd} on $[HClO_4]$ at ~0.5 *M* acid (Figure 2) suggests a change of rate-determining step. These lead to the conclusion of rate-determining carbonyl addition of PBA at least at pH >1. The insensitivity of *o*-hydroxyacetophenone to acid catalysis for the carbonyl addition may be understood by the decrease of basicity of carbonyl oxygen owing to the intramolecular hydrogen bonding. Similar results have also been obtained for the B–V reaction of salicylaldehyde.[2a]

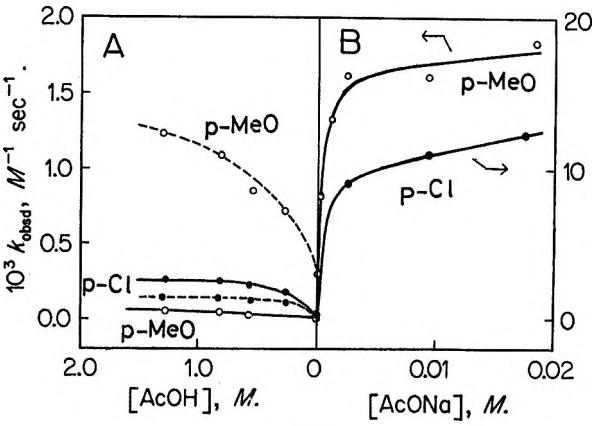


Figure 4.—Acid and base catalyses for the PBA oxidation of substituted benzaldehydes in ethanol (solid line) and in benzene (dotted line) at 25.0°.

PBA oxidation of *p*-methoxyacetophenone showed a rate–pH profile similar to that of anisaldehyde[2a] and seems likewise to be of an intermediary case. At pH >5.5 the rate constant holds a constancy, suggesting a rate-determining migration.[15] The reaction at pH 0.7–5.5 is probably controlled both by addition (k_1) and migration (k_2), but the data were not so reliable as to deduce k_1 value because of the spontaneous decomposition of PBA. The acid-catalyzed migration becomes rate determining at higher acidity, since the intercept at zero acid concentration (Figure 2) is close to the rate at pH ~6.

Rate-Determining Step in Organic Solvents.—The PBA oxidation of acetophenones in benzene and in pure ethanol was very slow without added acid and two types of acid catalyses are shown in Figure 3. The limiting rate constant at very high concentration of acetic acid is of the same magnitude as that at very low

(11) M. Eigen, *Angew. Chem.*, **75**, 489 (1963).

(12) The equilibrium constants for carbonyl addition of PBA to *o*- and *p*-hydroxybenzaldehydes were assumed to be $\sim 10^{-2}\ M^{-1}$ which is slightly smaller than those of hydrogen peroxide.[2a]

(13) For example, relative equilibrium constants for ArCHO *vs.* ArCOMe are ~470 for cyanohydrin formation [A. Lapworth, R. H. F. Manske, and E. B. Robinson, *J. Chem. Soc.*, 1976 (1930)] and ~570 for acetal formation [J. M. Bell, D. G. Kubler, P. Sartwell, and R. G. Zepp, *J. Org. Chem.*, **30**, 4284 (1965)].

(14) (a) J. F. Goodman, P. Robson, and E. R. Wilson, *Trans. Faraday Soc.*, **58**, 1846 (1962); P. Robson, *J. Chem. Soc.*, 5170 (1964). (b) W. P. Jencks, "Progress in Physical Organic Chemistry," Vol. 2, Interscience Publishers, New York, N. Y., 1964, p 63.

(15) Carbonyl addition of hydrogen peroxide is catalyzed by H^+ and OH^-: E. G. Sander and W. P. Jencks, *J. Amer. Chem. Soc.*, **90**, 4377 (1968).

concentration of trifluoroacetic acid. These results are explicable by a shift of a rate-determining step from addition to migration.

This is supported by the following treatment of the acetic acid catalyzed data for the reaction of *p*-methoxyacetophenone in benzene. Assuming (i) a steady-state concentration of I, (ii) that $k_1 = k_1^0 + k_1^{HA}[HA] + k_1^B[B] \simeq k_1^{HA}[HA]$, and $k_2 = k_2^0 + k_2^{HA}[HA] \simeq k_2^0$, the observed rate may be written as eq 3 (see Scheme I for notation). The plot of $1/k_{obsd}$ *vs.* $1/[AcOH]$ is linear for 0.1–1.59 *M* acetic acid (*cf.* Figure 3A).[16] This affords k_1^{HA} of $0.595 \times 10^{-3}\ M^{-2}\ sec^{-1}$ and $K_1k_2^0 = 5.3 \times 10^{-3}\ M^{-2}\ sec^{-1}$.

$$\frac{1}{k_{obsd}} = \frac{k_{-1}^{HA}}{k_1^{HA} \times k_2^0} + \frac{1}{k_1^{HA}} \times \frac{1}{[AcOH]} \qquad (3)$$

A similar plot for the B–V reaction of anisaldehyde is also linear and gives $k_1^{HA} = 6.85 \times 10^{-3}\ M^{-2}\ sec^{-1}$ and $K_1k_2^0 = 7.5 \times 10^{-2}\ M^{-2}\ sec^{-1}$. The ratio of k_1^{HA} (HA = AcOH) for *p*-methoxybenzaldehyde *vs.* *p*-methoxyacetophenone is then 11.5, which is of reasonable magnitude, since a similar ratio of 10–20 has been found for the acid-catalyzed addition of semicarbazide.[17] It is another evidence for the shift of the rate-determining step for the B–V reaction of acetophenone that the similar change is also observed for benzaldehydes with greater facility to carbonyl addition.

In conclusion, acetic acid ($pK_a = 4.76$)[18] may catalyze only the carbonyl addition of PBA (*i.e.*, $k_1 = k_1^{HA}$), but not the migration ($k_2 = k_2^0$). On the other hand, trifluoroacetic acid ($pK_a = 0.23$)[18] establishes rapidly the addition equilibrium (effective even at 0.002 *M*) and catalyzes also the migration ($k_2 = k_2^0 + k_2^{HA}$).

So far many kinetic results for the B–V reaction of ketones, especially with PBA and peracetic acid, has not been explicable straightforwardly.[3-6,19] This apparently complex kinetics seem to be due to the shift of the rate-determining step and sometimes to the different susceptibilities of the two steps to acid catalysis. Actually, the rate–pH profile in aqueous ethanol (see Figures 1 and 2) and acid–base catalysis (see Figures 3 and 4) seem to demonstrate that the kinetic data might be complex and the resulting Hammett relationship cannot be explained straightforwardly at moderate acidity because of the shift of rate-determining step. Especially, Figure 3 shows that acetic acid can catalyze only C=O addition, but trifluoroacetic acid can catalyze both C=O addition and migration from I. Hence, it is apparent that the observed rate constant in the presence of acetic or benzoic acid with moderate acidity would be consisted of terms of k_1, k_{-1}, and k_2, affording complex results. On the other hand, stronger peracids, *e.g.*, trifluoroperacetic acid[7] and *m*-ClPBA,[8] have resulted in rather clear kinetics probably because of fast establishment of the addition equilibrium in the presence of stronger parent acids.[20]

(16) The rate constant at 3.50 *M* AcOH (benzene:AcOH, ~2:1) is $0.250 \times 10^{-3}\ M^{-1}\ sec^{-1}$, which is ~25% higher than the expected value from the above correlation. This is probably due to solvent effect.

(17) E. H. Cordes and W. P. Jencks, *J. Amer. Chem. Soc.*, **84**, 4319 (1962).

(18) The values in water at 25°: J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," Wiley, New York, N. Y., 1963, p 372.

(19) For example, S. L. Fries and A. H. Soloway, *J. Amer. Chem. Soc.*, **73**, 3968 (1951); Y. Yukawa and T. Yokoyama, *J. Chem. Soc. Jap.*, **73**, 371 (1952).

(20) Although Palmer and Fry[8] did not noted the purity of *m*-ClPBA, the purchased peracid is usually not of high purity.

Carbonyl Addition of PBA.—Rate-determining addition of PBA^- to *o*- and *p*-hydroxyacetophenones is shown above. Similar rate–pH profiles were also obtained for the PBA oxidation with other *o*- and *p*-hydroxyphenyl alkyl ketones and hence gave the addition rate of PBA^- to these ketones at pH range of 5–12. The addition rate satisfied the Taft equation (Table II), showing the operation of both steric and electronic effects.

The ρ^* value of 1.3–1.6 seems to reflect an importance of electronic effect of a similar extent as observed with typical alkaline hydrolysis.[21] Related data is the addition of hydrogen peroxide ion to benzaldehydes;[15] the relative rate constant for *p*-methoxy- *vs.* *p*-chlorobenzaldehydes (1.08:3.74) corresponds to an approximate ρ value of 1.1. The present data of δ 0.6–0.8 seems to reflect a less importance of steric effects in a nucleophilic attack of peroxide. Similar δ of 0.57 was obtained for the acid-catalyzed attack of hydrogen peroxide on aliphatic carboxylic acids while $\rho^* \sim 0$.[22] Although there has been no explicit explanation for the nature of α effects,[23] the present data show at least a trend of peroxidic nucleophiles that a steric requirement is less important and an electric effect is needed to the same extent as with the other nucleophiles.

The acid catalysis for the addition of PBA is more effective in benzene than in pure or aqueous ethanol, because of the preferred hydrogen bonding of the acid catalysts with the more basic solvents.

Aryl Migration.—Rate data for the B–V reaction of ring-substituted acetophenones are summarized in Table III. The reaction conditions are those of rate-determining aryl migration, and the data are correlated with σ^+ to give an apparent ρ value of ~2. In the last column in Table III are listed the data with *m*-ClPBA from the literature;[8] although the data were stated to be well correlated with σ^+, the correlation is rather poor in view of the downward deviation by ~0.5 log unit for *p*-MeO, which seems to us to be due to the change of rate-determining step for *p*-methoxyacetophenone.[24]

TABLE III

APPARENT SECOND-ORDER RATE CONSTANTS ($k_{obsd} \times 10^3$, M^{-1} sec^{-1}) FOR THE REACTION OF XC_6H_4COMe WITH PBA AT 25.0°

X[a]	σ^+[b]	2 *M* $HClO_4$ in 40% EtOH	1.2 *M* AcOH in C_6H_6	0.17 *M* CF_3CO_2H in C_6H_6	*m*-ClPBA[c] in $CHCl_3$
p-HO	−0.92	2.78			
p-MeO	−0.778	1.48	0.145	2.75	40.3
p-Me	−0.311	0.13	0.033	0.210	19.1
H	0.00	<0.05	~0.009	~0.035	4.5
p-Cl	0.112	<0.05		~0.022	3.39
ρ	(σ^+)	2.05	~1.5	2.39	~1.8

[a] Registry numbers for the last four entries are, respectively, 100-06-1, 122-00-9, 98-86-2, and 99-91-2. [b] Reference 18, p 204. [c] The B–V reaction with *m*-chloroperbenzoic acid at 32°;[8] the rate was reported to be well correlated with σ^+ to give a ρ value of −1.36, but the correlation is rather poor, *p*-methoxyacetophenone being deviated by ~0.5 log unit.

(21) Reference 10, p 605.

(22) Y. Ogata and Y. Sawaki, *Tetrahedron*, **20**, 2065 (1964).

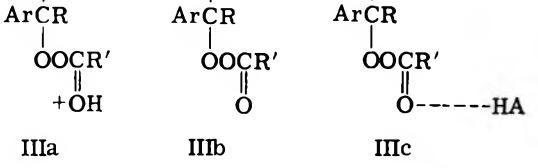
(23) T. C. Bruice, A. Donzel, R. W. Huffman, and A. R. Butler, *J. Amer. Chem. Soc.*, **89**, 2106 (1967); R. A. Firestone, *J. Org. Chem.*, **36**, 702 (1971).

(24) Another uncertain point is the reported unreactivity[8] of *p*-nitroacetophenone in spite of the small difference in σ^+ values between *p*-NO_2 and *p*-CN ($\Delta\sigma^+ = 0.131$).

It is also not proper to correlate directly the uncorrected data for a strong electron-attracting group such as NO_2 and CN where methyl group is also a competitive migration one.[7,25]

The ρ value for the migration step cannot be obtained directly from the above data because K_I is unknown. An approximately estimated ρ value for K_I might be near 0.9 if compared with ρ values for other carbonyl addition equilibria in aqueous ethanol (at 20–30°), *e.g.*, ArCHO + H_2O_2 (ρ = 1.6),[2a] ArCHO + $H_2NNHCONH_2$ (ρ = 1.64),[26] and ArCOMe + $H_2NNHCONH_2$ (ρ = 0.91).[27] Thus, the migration in the B–V reaction should possess an approximate ρ value of −3 (σ^+), which is comparable to the ρ value of −4 to −5 for the B–V migration of benzaldehydes[2a] and to other peroxide rearrangements (ρ = −5.1,[28] −4.57,[29] and −3.78[30]).

As for the nature of acid catalysis for the migration step, the protonation on the carbonyl (IIIa),[7] acyloxy



IIIa IIIb IIIc

(25) E. E. Smissman, J. P. Li, and Z. H. Israili, in ref 9 reported an exceptional facile migration of *o*-nitrophenyl group for the B–V reaction of acetophenones, but strangely the anchimerie assistance was not observed for propiophenones.

(26) R. Wolfenden and W. P. Jencks, *J. Amer. Chem. Soc.*, **83**, 2763 (1961).

(27) R. P. Cross and P. Fugassi, *ibid.*, **71**, 223 (1949).

(28) K. Nelson, quoted by S. Winstein and G. C. Robinson, *ibid.*, **80**, 169 (1958).

(29) A. W. De R. Van Stevenick and E. C. Kooyman, *Recl. Trav. Chim. Pays-Bas*, **79**, 413 (1960).

(30) G. H. Anderson and J. G. Smith, *Can. J. Chem.*, **46**, 1553, 1561 (1968).

oxygen,[7] or hydroxyl oxygen (IIIb)[5,6] has been assumed. However, the present study demonstrates no intervention of conjugate acid of I, *i.e.*, IIIa or IIIb of specific proton catalysis, since the rate is not correlated with H_0 function (the slope of log k_{obsd} *vs.* $-H_0$ is less than 0.4) but accelerated slightly by perchloric acid in aqueous ethanol. The catalysis suggests IIIc of general acid catalysis, the position of hydrogen bonding being either on carbonyl (IIIc) or acyloxy oxygen. Finally, the data in the presence of acetic acid clearly reveals that the uncatalyzed migration from I is also operative.

Experimental Section

Materials.—Perbenzoic acids were prepared by the reaction of benzoyl peroxides or chlorides with alkaline hydrogen peroxide[31] and recrystallized from *n*-hexane. *o*- and *p*-hydroxyacetophenones were prepared by the Fries rearrangement of corresponding phenyl esters.[32] Alkyl group and melting or boiling points for *p*-hydroxyphenyl alkyl ketones are as follows: Me, mp 108.8–109.2°; Et, mp 153°; *n*-Pr, mp 90.5–91.5°; *i*-Pr, bp 196–198° (21 mm); CH_2Cl, mp 148–149°; *i*-Bu, bp 175–180° (6 mm); Ph, mp 132–133°. Boiling points for *o*-HOC_6H_4COR are as follows: Me, 109–110° (23 mm); Et, 120–122° (21 mm); *n*-Pr, 91–98° (5 mm); *i*-Pr, bp 121–123° (20 mm). Other ketones were synthesized by Friedel–Crafts acylation and purified by fractional distillation.

Rate and Products.—The B–V reaction of acetophenones in 40 vol. % aqueous ethanol was conducted in the presence of 10^{-4} *M* EDTA to suppress metallic ion catalyzed decomposition of PBA. The rate was determined by iodometry of peracid and/or by uv spectrophotometry of ketone as reported previously.[2]

The produced phenols were determined by uv spectrophotometry or by glc after methylation as reported previously.[2b]

Registry No.—PBA, 93-59-4; *p*-hydroxyphenyl isobutyl ketone, 34887-83-7.

(31) Y. Ogata and Y. Sawaki, *Tetrahedron*, **23**, 3327 (1967).

(32) E. Miller and W. H. Hartung, "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1955, p 543.

Nonbenzenoid Aromatic Systems. VII.[1a] Reactions of Azulenes with Ethylene Oxide or Trimethylene Oxide and Lewis Acids

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A direct β-hydroxyethylation method applied to azulene, 5-methylazulene, and certain 6-substituted (OCH_3, CH_3, Br) azulenes is reported. Reaction of azulene and trimethylene oxide with aluminum chloride yielded 3-(1-azulyl)-1-propanol and 1,1-di(1-azulyl)propane.

Presently, only one literature method is available for the introduction of the 2-hydroxyethyl side chain into the 1 position of azulene (**1a**).[2] Since this procedure is rather lengthy (*N*,*N*-dimethylamino methylation, quaternization, cyanide displacement, hydrolysis, and reduction), our interest in the solvolytic behavior of 2-(1-azulyl)ethyl tosylate and ring-substituted derivatives[3] prompted us to examine a more direct route for introducing this side chain. We report here such a procedure, which involves reaction of the azulene with ethylene oxide and Lewis acids.

The reaction is a modification of the procedure by Searles[4] for the β-hydroxyethylation of benzene and anisole; the modifications involve the use of methylene chloride as solvent and shorter reaction times. As can be seen from the results listed in Table I, 2-(1-azulyl)-ethanol (**2a**) was produced in 41–47% yield (81–85% net yield) with either aluminum chloride or stannic chloride as the Lewis acid. A minor component was identified as the disubstitution product, 1,3-bis(2-hydroxyethyl)azulene (**3**), on the basis of its nmr spectrum. Increasing or decreasing the amounts of Lewis

(1) (a) For paper VI see R. N. McDonald and R. R. Reitz, *J. Org. Chem.*, **37**, 2703 (1972); (b) Phillips Petroleum Co. Fellowship, 1968–1969.

(2) A. G. Anderson, R. G. Anderson, and T. S. Fujita, *J. Org. Chem.*, **27**, 5435 (1962).

(3) R. N. McDonald and J. R. Curtis, *J. Amer. Chem. Soc.*, **93**, 2530 (1971).

(4) S. Searles, *ibid.*, **76**, 2313 (1954).

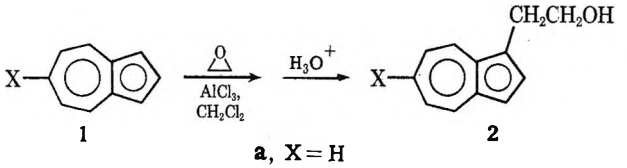
Table I

Conditions and Yields for β-Hydroxyethylation of Azulenes[a]

Starting azulene	Solvent	Catalyst	Reaction time	Yield, %	Net yield,[b] %
Azulene	CH_2Cl_2	$AlCl_3$	10 min	47	81
Azulene	CS_2	$AlCl_3$	10 min	20	70
Azulene	CH_2Cl_2	$SnCl_4$	10 min	41	85
Azulene	CH_3NO_2	$AlCl_3$	2 min	0	0
Azulene	CH_2Cl_2	$AlCl_3$	10 hr	45	68
6-Methylazulene	CH_2Cl_2	$AlCl_3$	10 min	46	73
5-Methylazulene	CH_2Cl_2	$AlCl_3$	10 min	45	
6-Bromoazulene	CH_2Cl_2	$AlCl_3$	1 hr	41	90
6-Methoxyazulene	CH_2Cl_2	$AlCl_3$	20 min	48	93
6-Cyanoazulene	CH_2Cl_2	$AlCl_3$	1 hr	0	0[c]

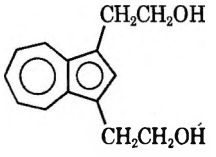
[a] After chromatography of the products 2 on basic alumina, nmr spectral analysis showed the presence of impurities, presumably ethylene chlorohydrin and/or ethylene glycol. The impurities can be removed by (1) repeated, careful chromatography of the product on alumina and recrystallization of solid alcohols 2; (2) preparation and chromatography of the acetates of 2 followed by hydrolysis; and (3) preparation and recrystallization of the 1,3,5-trinitrobenzene complexes of 2 followed by chromatography. Of these three methods, (2) is the most convenient and gives the best recoveries of alcohols 2. [b] Based on recovered starting material. [c] 6-Cyanoazulene recovered in 70%.

acid and increasing reaction times led to reduced amounts of **2a**. The procedure has been successfully applied to the β-hydroxyethylation of 6-methoxy- (**1b**), 6-methyl- (**1c**), 6-bromo- (**1d**), and 5-methylazulene;



1 2

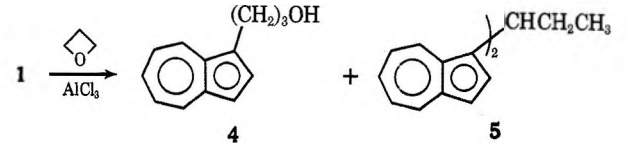
a, X = H
b, X = OCH_3
c, X = CH_3
d, X = Br
e, X = CN



3

the last example gives rise to a mixture of 2-[5- and 2-(7-methylazulyl)]ethanol.[5] 6-Cyanoazulene (**1e**) failed to produce **2e** in this reaction, apparently due to complexation of the cyano group and aluminum chloride with accompanying increased electron withdrawal by the complexed group.

The success of the β-hydroxyethylation of **1** led us to try γ-hydroxypropylation using trimethylene oxide in place of ethylene oxide. 3-(1-Azulyl)-1-propanol (**4**)



4 5

(5) Since this original work, we have successfully used this reaction with several 2-substituted (Cl, Br, CH_3, OCH_3) azulenes.[6]

(6) J. M. Richmond, unpublished results.

was indeed formed, but only in minor amounts. The major product was 1,1-di(1-azulyl)propane (**5**), which was identified on the basis of its nmr and mass spectra; the 100% abundance peak in the mass spectrum of **5** involved the loss of $\cdot C_2H_5$, the process expected for structure **5**.[7] By increasing the amount of aluminum chloride (and trimethylene oxide), the isolated ratio of **5**:**4** increased, as is shown in Table II. Replacing

Table II

Reaction of Azulene with Trimethylene Oxide

Azulene, mmol	$AlCl_3$, mmol	$(CH_2)_3O$, mmol	Yield of **4**, %	Yield of **5**, %
2.0	4.0	4.0	1.6	4.8
4.4	9.5	13.8	5.5	12.5
3.2	16.2	16.2	2.2	15.2
4.0	20.0	41.0	0.0	20.0

aluminum chloride with stannic chloride gave neither **4** nor **5**. While the mechanism of formation **5** is unknown, if we assume that **4** or its aluminate ester is the precursor to **5**, a number of mechanistic pathways to **5** appear reasonable, probably involving formation of a 1-azulylcarbinyl cation followed by electrophilic substitution on unreacted azulene.

Experimental Section[8]

β-Hydroxyethylation of Azulene.—To 100 mg (0.78 mmol) of azulene in 25 ml of dichloromethane was added 0.216 g (1.6 mmol) of anhydrous aluminum chloride with stirring at ice bath temperature. After a few minutes the color of the mixture changed from blue to light yellow. Into this was injected 8.0 ml of a 1% (v/v) ethylene oxide–dichloromethane solution by means of syringe. The color of the solution changed immediately back to blue. The mixture was stirred for 10 min and poured onto 500 ml of iced 10% hydrochloric acid. The organic layer was extracted with 10% hydrochloric acid and washed with ten 100-ml portions of water. The dichloromethane layer was dried (Na_2SO_4), the solvent was evaporated, and the blue residue was chromatographed on 40 g of alumina. A mixture of 9:1 hexane–dichloromethane eluted 42 mg of azulene, chloroform eluted a second blue band, and a third smaller blue band was eluted with 1:1 ethanol–chloroform. Solvent removal from the second band yielded 63 mg (47%; 81% net yield) of 2-(1-azulyl)ethanol (**2a**) recrystallized from carbon tetrachloride as blue needles, mp 57–58° (lit.[2,3] mp 57–58°), which was identical in all respects with that previously reported. The third band, 15 mg (9%; 15% net yield), was characterized as 1,3-bis(2-hydroxyethyl)azulene (**3**), assigned on the basis of the nmr spectrum ($CDCl_3$) τ 1.85 (d, 2), 2.36 (s, 1), 2.50–3.25 (m, 3), 6.22 (t, J = 6.0 Hz, CH_2CH_2OH, 4), 6.83 (t, J = 6.0 Hz, CH_2CH_2OH, 4), and 7.66 (s, OH, 2).

2-(6-Methoxy-1-azulyl)ethanol (2b).—To 0.300 g (1.90 mmol) of 6-methoxyazulene dissolved in 150 ml of dichloromethane was added 0.508 g (3.80 mmol) of aluminum chloride at ice bath temperature. After a few minutes stirring, the color changed from violet-red to deep blue. To this mixture was added 10 ml of 2% (v/v) ethylene oxide–dichloromethane, causing the solution to change back to violet-red. After stirring the solution for 20 min, the color had gradually faded to a light pink. Isolation and purification of the product as described previously resulted in 0.145 g of recovered 6-methoxyazulene and 0.184 g (48%; 93% net yield) of **2b**: mp 59.5–61.0°; ir (KBr) 3.04 (s, OH), 6.35 (s), and 12.05 μ (s); nmr ($CDCl_3$, internal TMS) τ 1.82 and 1.86 (2 superimposed d's, J = 11.5 Hz, $C_{4,8}$ ring H's, 2), 2.46 (d, J = 4.0

(7) R. G. Cooks, A. N. Yeo, and D. H. Williams, *Org. Mass Spectrom.*, **2**, 985 (1969).

(8) Melting points were determined on a Kofler hot stage and are uncorrected. Spectra were determined with commercial instruments (ir, P-E 137; nmr, Varian A-60 and T-60; uv, Cary 11; mass, AEI MS-9). Nmr spectral data are listed as centers except for multiplets, where the range of the signals is given. All alumina is F-20 Alcoa, basic alumina, activity I, unless otherwise specified.

Hz, C_2 ring H, 1), 2.78 (d, J = 4.0 Hz, C_3 ring H, 1), 3.28 (broad d, J = 11.5 Hz, $C_{5,7}$ ring H's, 2), 6.11 (t, J = 6.0 Hz, CH_2CH_2-OH, 2), 6.13 (s, OCH_3, 3), 6.76 (t, J = 6.0 Hz, CH_2CH_2OH, 2), and 8.30 (s, OH, 1).

For analysis, a 1,3,5-trinitrobenzene complex was prepared and recrystallized from 1:1 ethyl acetate–hexane: mp 90.0–91.5°; λ_{max} (CH_2Cl_2) 541 (log ϵ 2.42), 371 (3.38), 358 (3.87), 350 (3.80), 342 (3.78), 297 (4.93), and 291 nm (4.93).

Anal. Calcd for $C_{19}H_{17}N_3O_8$: C, 54.91; H, 4.13. Found: C, 55.00; H, 4.10.

2-(6-Methyl-1-azulyl)ethanol (2c).—Following the above procedure, 100 mg (0.705 mmol) of 6-methylazulene, 188 mg (1.41 mmol) of aluminum chloride, and 7.3 ml of 1% ethylene oxide–dichloromethane solution were allowed to react. This reaction netted 37 mg of recovered 6-methylazulene, 60 mg (46%; 73% net yield) of 2c, identical to that of an authentic sample,[9] and 12 mg (7%; 12% net yield) of what is probably 1,3-bis(2-hydroxyethyl)-6-methylazulene from its nmr spectrum.

2-(6-Bromo-1-azulyl)ethanol (2d).—To 126 mg (0.61 mmol) of 6-bromoazulene in 25 ml of dichloromethane cooled to ice bath temperature 165 mg (1.22 mmol) of aluminum chloride was added, with a corresponding color change from blue to green. Upon addition of 6.3 ml of a 1% (v/v) ethylene oxide–dichloromethane solution, the blue color returned. After 0.5 hr of stirring, 83 mg (0.61 mmol) of aluminum chloride and 3.2 ml of the 1% ethylene oxide solution were added to the solution, with stirring for another 0.5-hr period. The product was isolated and purified as described previously to yield 68 mg of 6-bromoazulene and 63 mg (41%; 90% net yield) of 2d. This product was crystallized from carbon tetrachloride–hexanes to yield pale blue plates: mp 113–116°; ir (KBr) 3.10 (s, OH), 6.41 (s), 11.27 (m), 12.13 (s), and 12.76 μ (m); nmr ($CDCl_3$, internal TMS) τ 1.80–2.70 (m, 6), 6.05 (t, J = 6.5 Hz, CH_2CH_2OH, 2), 6.85 (t, J = 6.5 Hz, CH_2CH_2OH, 2), and 8.42 (s, OH, 1); λ_{max} (CH_2Cl_2) 724 (log ϵ 1.91), 654 (2.27), 603 (2.47), 430 (1.75), 353 (3.72), 333 (3.62), 292 (4.83), and 286 nm (4.81).

Anal. Calcd for $C_{12}H_{11}OBr$: C, 57.39; H, 4.42. Found: C, 57.10; H, 4.60.

2-[5- and 2-(7-Methyl-1-azulyl)]ethanol.—Following the procedure outlined with azulene, 180 mg (1.27 mmol) of 5-methylazulene in 50 ml of dichloromethane was allowed to react with 366 mg (2.66 mmol) of anhydrous aluminum chloride and 13 ml of a 1% (v/v) ethylene oxide–dichloromethane solution. Upon isolation of the product, 108 mg (45.5%) of a 1:1 mixture of 2-[5- and 2-(7-methyl-1-azulyl)]ethanol was collected as a blue-green oil, containing an impurity.

Purification of the compounds was achieved by recrystallization of the ethanols as their mixed 1,3,5-trinitrobenzene complexes. To 108 mg (0.58 mmol) of product in 3 ml of ethyl acetate was added 124 mg of 1,3,5-trinitrobenzene in 3 ml of ethyl acetate. The solvent volume was reduced to approximately one-half, 3 ml of hexanes was added, and the product was allowed to crystallize at freezer temperature. Recrystallization of the brown solid from 1:1 hexanes–ethyl acetate yielded a red-brown solid: mp 80.0–82.0°; ir (KBr) 3.00 (m, OH) and 7.47 μ (s); nmr ($CDCl_3$, internal TMS) τ 0.71 (s, TNB H's, 3), 1.84–3.30 (m, 6), 6.03 (t, J = 6.0 Hz, CH_2CH_2OH, 2), 6.70 (t, J = 6.0 Hz, CH_2CH_2-OH, 2), 7.33 and 7.37 (s, CH_3, each 1.5), and 8.42 (s, OH, 1); λ_{max} (CH_2Cl_2) 658 (log ϵ 2.52), 610 (2.57), 361 (3.58), 346 (3.70), and 283 nm (4.77).

Anal. Calcd for $C_{19}H_{17}N_3O_7$: C, 57.14; H, 4.29. Found: C, 56.99; H, 4.48.

Reaction of Azulene with Trimethylene Oxide.—To azulene (415 mg, 3.24 mmol) in 200 ml of dichloromethane was added 2.160 g (16.2 mmol) of anhydrous aluminum chloride with stirring at ice bath temperature. After being stirred a few minutes, the solution became bright yellow. To this mixture was added 940 mg (16.2 mmol) of trimethylene oxide (Farchan Research Laboratories) dissolved in 50 ml of dichloromethane, causing an immediate color change from yellow to blue. The mixture was stirred for 10 min and isolation of the blue residue was achieved as described previously. The blue residue was chromatographed on 60 g of alumina with hexanes eluting, after careful solvent volume reduction, 29 mg of azulene. A second band eluted with 9:1 hexanes–dichloromethane gave 73 mg of a bright blue solid, mp 77–77.5°. Chloroform eluted 13 mg of a blue oil after solvent evaporation.

The blue solid was identified as 1,1-di(1-azulyl)propane (5) (15%; 51% net yield) based on its analysis and spectral properties: ir (KBr) 6.38 (s), 12.93 (s), 13.08 (s), and 13.62 μ (s); nmr (CCl_4, internal TMS) τ 1.55–3.30 (m, 14), 4.88 (t, J = 7.0 Hz, $CHCH_2CH_3$, 1), 7.63 (m, J = 7.0 Hz, $CHCH_2CH_3$, 2), and 9.00 (t, J = 7.0 Hz, $CHCH_2CH_3$, 3); λ_{max} (cyclohexane) 735 (log ϵ 2.27), 693 (2.38), 662 (2.73), 631 (2.72), 605 (2.80), 584 (2.72), 362 (3.89), 346 (3.94), 292 (4.74), 288 (4.73), 271 (4.85), and 241 nm (4.47); mass spectrum (70 eV, heated inlet) m/e (rel intensity), 296 ($M\cdot^+$, 27), 267 (100), 265 (24), 252 (8), and 239 (5).

Anal. Calcd for $C_{13}H_{20}$: C, 93.20; H, 6.80. Found: C, 93.20; H, 6.82.

The second product band was identified as 3-(1-azulyl)-1-propanol (4) (2%; 7% net yield): ir (film) 3.04 (s, OH) and 6.34 μ (s); nmr (CCl_4, internal TMS) τ 1.60–3.30 (m, 7), 6.43 (t, J = 6.0 Hz, CH_2OH, 2), 6.88 (t, J = 6.0 Hz, $CH_2CH_2CH_2$-OH, 2), and 7.90–8.30 (m, $CH_2CH_2CH_2OH$, 2); λ_{max} (CH_2Cl_2) 718 (log ϵ 1.97), 654 (2.40), 602 (2.48), 359 (3.50), 345 (3.73), 289 (4.55), 284 (4.66), and 280 nm (4.69); mass spectrum (70 eV, heated inlet) m/e (rel intensity), 186 ($M\cdot^+$, 25), 155 (9), and 141 (100). A trinitrobenzene complex was prepared from the above oil to aid in its purification which was recrystallized from ethyl acetate–hexanes to give brown needles, mp 102.5–103.5°.

Registry No.—**1a**, 275-51-4; **1b**, 35046-03-8; **1c**, 1654-52-0; **1d**, 35046-05-0; **2b**, 35046-06-1; **2b** (1,3,5-trinitrobenzene complex), 35046-07-2; **2d**, 35096-49-2; **3**, 35046-08-3; **4**, 35046-09-4; **4** (1,3,5-trinitrobenzene complex), 35046-10-7; **5**, 35046-11-8; ethylene oxide, 75-21-8; 5-methylazulene, 1654-55-3; trimethylene oxide, 75-56-9; 2-(5-methyl-1-azulyl)ethanol, 35046-13-0; 2-(7-methyl-1-azulyl)ethanol, 35046-14-1.

Acknowledgment.—The authors wish to thank the National Science Foundation (GP-7818, GP-10691) for support of this research.

(9) J. R. Curtis, Ph.D. Thesis, Kansas State University (1971).

Pyridazines. LI. Synthetic Approaches to Pyridazino[2,3-a]-1,3,5-triazines, a Novel Heterocyclic System[1]

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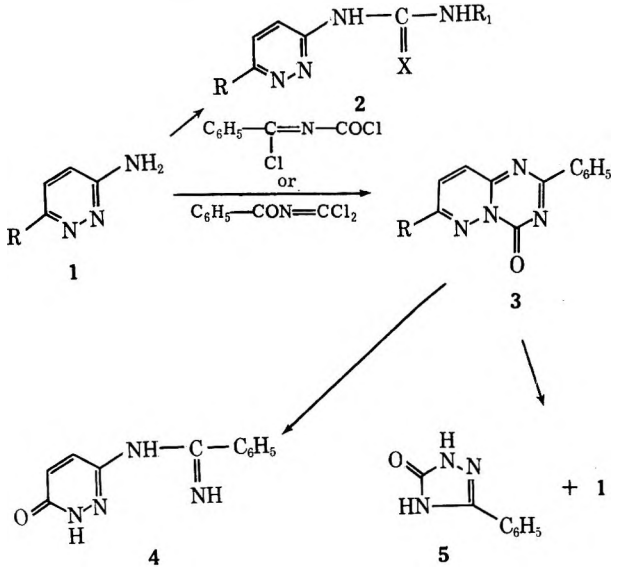
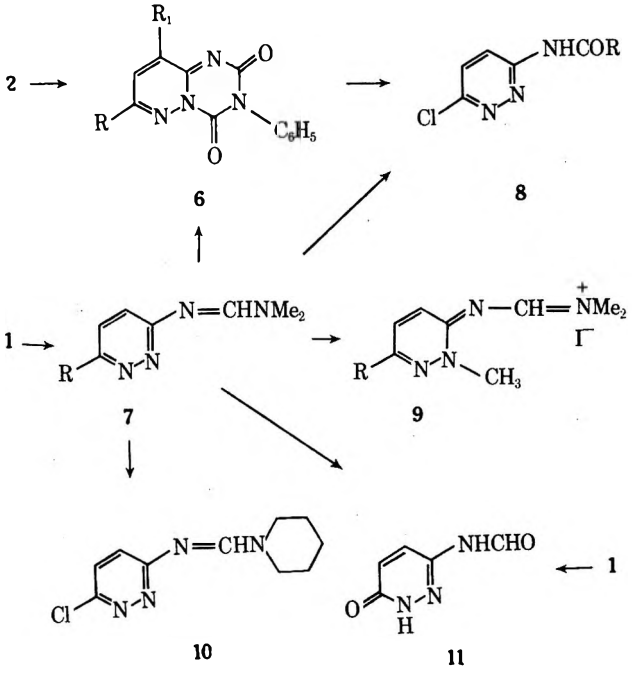
Three synthetic pathways leading to a novel heterocyclic system, pyridazino[2,3-a]-1,3,5-triazine, and some of its transformations are described.

Neither the parent heteroaromatic pyridazino[2,3-*a*]-1,3,5-triazinium system nor its derivatives have so far been synthesized. Earlier work in this laboratory directed towards azolo- and azinoazines with bridgehead nitrogen[2,3] stimulated the investigation on pyridazino-[2,3-*a*]-1,3,5-triazines. We would like to report on several synthetic approaches toward this bicyclic system, as well as on some investigations concerning its reactivity.

All syntheses which we have developed use 3-aminopyridazines as starting material. In this manner, 3-amino-6-chloropyridazine with either *N*-(phenylchloromethylene)carbamic acid chloride or benzoyl isocyanide dichloride formed the bicyclic compound (**3**, R = Cl) in moderate yield. The system is stable in the presence of bases and the halogen atom at position 7 could be replaced by nucleophiles. A similar reaction took place with hydrazine at low temperature, but at room temperature and in particular when heat was applied, the bicyclic system was degraded to 3-phenyl-1,2,4-triazol-5(4*H*)-one (**5**) and 3-amino-6-chloropyridazine. Similar ring cleavage could be observed also when **3** was treated with boiling diluted hydrochloric acid and the substituted formamidine (**4**) could be isolated and characterized.

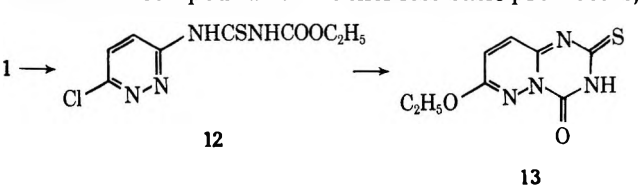


A second approach to this bicyclic system consisted of condensing either the corresponding *N*-(pyridazinyl-2′)-*N*′-phenylurea (**2**, X = O; R_1 = Ph) or *N*,*N*-dimethyl-*N*′-(pyridazinyl-3′)formamidine (**7**) with phenyl isocyanate. In both cases the corresponding 3-phenylpyridazino[2,3-*a*]-1,3,5-triazine-2,4-diones (**6**) were formed, and they undergo electrophilic substitution (bromination) at position 9. This may be anticipated if we take into account that this position is most susceptible for electrophilic attack also with related pyrimido[1,2-*b*]pyridinazines, as shown from the calculated electron densities.[2] On the other hand, the stability of this system toward bases is greatly diminished by the introduction of the 3-phenyl group, and attempted nucleophilic displacement of the 7-chlorine atom with sodium ethoxide proceeded by ring opening to give the pyridazine (**8**, R = OEt).



N,*N*-Dimethyl-*N*′-(pyridazinyl-3′)formamidine or its 6′-chloro analog (**7**) formed a quaternary salt with methyl iodide, and nmr spectroscopic investigation revealed that the methyl group entered in the pyridazine ring to give the conjugated formamidinium salt (**9**). On the other hand, the formamidine **7** can undergo a displacement of the dimethylamino group with piperidine to give **10**.

Finally, another convenient preparative route to the bicyclic system was developed by preparing *N*-carbethoxy-*N*′-(6′-chloropyridazinyl-3′)thiourea (**12**) which, upon heating in the presence of sodium ethoxide, afforded the compound **13**. Other less basic promotors,



(1) Heterocycles. Part XCVII.

(2) A. Pollak, B. Stanovnik, and M. Tišler, *J. Org. Chem.*, **36**, 2457 (1971).

(3) B. Stanovnik, M. Tišler, and B. Stefanov, *ibid.*, **36**, 3812 (1971), and other references cited therein.

such as pyridine or triethylamine, proved to be ineffective as cyclizing agents. We have observed the same situation recently when synthesizing the related pyrido[1,2-*a*]-1,3,5-triazines.[4]

Experimental Section

Melting points were taken on a Kofler micro hot stage. Infrared spectra were recorded on a Perkin-Elmer 137 Infracord as KBr disks, nmr spectra were taken on a JEOL JNM-C-60HL spectrometer (TMS as internal standard), and mass spectra were recorded on a CEC 21-110C instrument using direct sample insertion into the ion source.

***N*-(6′-Chloropyridazinyl-3′)-*N*′-benzoylurea (2, R = Cl; X = O; R_1 = PhCO).**—A filtered solution of 3-amino-6-chloropyridazine (2.0 g) in dioxane (80 ml) was treated with benzoyl isocyanate (2.4 g), and the reaction mixture was heated under reflux for 15 min. The separated product was filtered and crystallized from dioxane (3.3 g, 78%): mp 245°; ir (KBr) 1709 and 1689 (CO), 3300 and 3165 cm^{-1} (NH); mass spectrum M^+ = 276.

Anal. Calcd for $C_{12}H_9ClN_4O_2$: C, 52.24; H, 3.28; N, 20.30. Found: C, 52.24; H, 3.72; N, 20.40.

If the compound was heated with polyphosphoric acid at 120° for 3 hr, a sublimate was identified as benzoic acid and the mixture, after being diluted with water, afforded 3-amino-6-chloropyridazine.

2-Phenyl-7-chloropyridazino[2,3-*a*]-1,3,5-triazin-4-one (3, R = Cl). A.—A suspension of 1 (R = Cl) (1.0 g) in a mixture of chloroform (30 ml) and toluene (30 ml) was vigorously stirred under nitrogen. An ethereal solution of *N*-(phenylchloromethylene)carbamic acid chloride[5] (1.0 g) was added portionwise and, after being stirred for 4 hr at room temperature, the mixture was then heated under reflux for 30 min. The solvent was evaporated *in vacuo* and the product was crystallized from dimethyl sulfoxide (0.2 g, 25%): mp 310–312°; ir (KBr) 1740 cm^{-1} (CO); mass spectrum M^+ = 258; nmr (DMSO-d_6, 130°) τ 2.33 (s, H_8, H_9), 2.33, and 1.45 (m, Ph).

Anal. Calcd for $C_{12}H_7ClN_4O$: C, 55.71; H, 2.73; N, 21.65. Found: C, 55.99 H, 3.06; N, 21.65.

B.—A suspension of 1 (R = Cl) (1.0 g) in dry ethyl acetate (10 ml) was stirred and benzoyl isocyanide dichloride[5] (1.0 g) was added. Stirring under nitrogen was continued for 3 hr and, upon filtration, the residue was suspended in ethyl acetate (30 ml) and filtered again. This procedure was repeated twice. The filtrates were combined and dried, and the solvent was evaporated *in vacuo*. The residue was treated with cyclohexane and, after 1 hr, the product was filtered off (0.3 g, 15%). It is essentially pure, mp 310–312°, and identical with the product obtained as described under A.

7-Methoxy-2-phenylpyridazino[2,3-*a*]-1,3,5-triazin-4-one (3, R = OCH_3).—To a cooled (0°) solution of sodium methylate (prepared from 0.1 g of sodium and 8 ml of methanol) the chloro compound (3, R = Cl) (1.0 g) was added portionwise under stirring. The suspension was stirred at 0° for 2 hr and the product was filtered off (0.8 g, 81%). It was crystallized from *N*,*N*-dimethylformamide and ethanol: mp 274–276°; ir (KBr) 1718 cm^{-1} (CO); nmr (DMSO-d_6, 139°) τ 2.13 (d, H_8), 2.42 (d, H_9), 5.92 (s, CH_3O), 2.50 and 1.65 (m, C_6H_5), $J_{8,9}$ = 9.0 Hz.

Anal. Calcd for $C_{13}H_{10}N_4O_2$: C, 61.41; H, 3.96; N, 22.04. Found: C, 61.67; H, 4.34; N, 21.66.

The same product was obtained if the chloro compound was stirred at room temperature in a methanolic solution of potassium hydroxide.

7-Phenylthio-2-phenylpyridazino[2,3-*a*]-1,3,5-triazin-4-one (3, R = C_6H_5–S–) was prepared in a likewise manner with sodium thiophenolate: mp 275° (from *N*,*N*-dimethylformamide and ethanol); ir (KBr) 1736 cm^{-1} (CO); nmr (DMSO-d_6, 154°) τ 2.22 (d, H_8), 2.48 (d, H_9), 2.5 (m, C_6H_5S–), 2.5 and 1.65 (m, 2-C_6H_5), $J_{8,9}$ = 9.0 Hz.

Anal. Calcd for $C_{18}H_{12}N_4OS$: C, 65.05; H, 3.64; N, 16.86. Found: C, 64.62; H, 3.68; N, 16.83.

7-Hydrazino-2-phenylpyridazino[2,3-*a*]-1,3,5-triazin-4-one (3, R = $NHNH_2$).—A suspension of the chloro compound (3, R = Cl) (1.0 g) in methanol (10 ml) was cooled to 0°, hydrazine hydrate (3 ml of 100%) was added, and the mixture was stirred at 0° for 3 hr. The product (0.7 g, 71%) had mp 250–252°; ir (KBr) 3322 (NH_2) and 1700 cm^{-1} (CO); nmr (DMSO-d_6, 130°) τ 2.50 (s, H_8, H_9), 2.60 and 2.25 (m, C_6H_5), 6.8 (broad, NH).

Anal. Calcd for $C_{12}H_{10}N_6O$: C, 56.68; H, 3.96; N, 33.06. Found: C, 56.50; H, 4.10; N, 32.83.

The compound formed a **benzylidene derivative** (3, R = $NHN{=}CHC_6H_5$) which was prepared in the usual way: mp 320° (from *N*,*N*-dimethylformamide and toluene); nmr (DMSO-d_6, 107°) τ 2.10 (s, H_8, H_9), 2.5 and 1.8 (m, C_6H_5CH).

Anal. Calcd for $C_{19}H_{14}N_6O$: C, 66.65; H, 4.12; N, 24.55. Found: C, 66.39; H, 4.36; N, 24.10.

If the reaction between the chloro compound and hydrazine was conducted at room temperature, a mixture of the 7-hydrazino compound (0.58 g) and the triazolone (5) (0.3 g) was obtained.

Degradation of 7-Chloro-2-phenylpyridazino[2,3-*a*]-1,3,5-triazin-4-one with Hydrazine Hydrate.—A suspension of compound 3 (R = Cl) (1.0 g) in methanol (30 ml) and hydrazine hydrate (2 ml of 100%) was heated under reflux for 1 hr. The solvent was evaporated *in vacuo* to half of its original volume; the product was filtered off and crystallized from ethanol (0.5 g). The compound was identified as 3-phenyl-1,2,4-triazol-5(4*H*)-one, mp 315–320° (dec), when compared with an authentic specimen prepared according to literature[6] (lit.[6] mp 321–322°): ir (KBr) 1730 cm^{-1} (CO); mass spectrum M^+ = 161; nmr (DMSO-d_6) τ 2.70 and 2.35 (m, C_6H_5), −2.0 (broad, NH).

Anal. Calcd for $C_8H_7N_3O$: C, 59.62; H, 4.38; N, 26.07. Found: C, 59.04; H, 4.26; N, 26.19.

When the filtrate from the above experiment was evaporated to dryness, the remaining product (0.3 g) was identified as 3-amino-6-chloropyridazine.

3-(Phenylformamidino)pyridazin-6(1*H*)-one (4).—A mixture of compound 3 (R = Cl) (0.5 g) and hydrochloric acid (7 ml of 1:4) was heated under reflux for 2 hr. The cooled solution was then neutralized with solid sodium bicarbonate. The separated product was filtered off and sublimed at 270° (1 mm) (0.3 g, 72%): mp 273–274°; ir (KBr) 3311 (NH), 1679 cm^{-1} (CO); mass spectrum M^+ = 214.

Anal. Calcd for $C_{11}H_{10}N_4O$: C, 61.67; H, 4.71; N, 26.16. Found: C, 62.09; H, 4.83; N, 26.13.

***N*-(Pyridazinyl-3′)-*N*′-phenylthiourea (2, R = H; X = S; R_1 = C_6H_5).**—3-Aminopyridazine (1.0 g), methanol (15 ml), and phenyl isothiocyanate (1.0 g) were mixed together and the mixture was heated under reflux for 2 hr. The solvent was evaporated *in vacuo* and the residue crystallized from 25% ethanol (1.2 g, 45%), mp 180°.

Anal. Calcd for $C_{11}H_{10}N_4S$: C, 57.38; H, 4.38; N, 24.34. Found: C, 57.80; H, 4.42; N, 23.74.

***N*-(6′-Chloropyridazinyl-3′)-*N*′-phenylurea (2, R = Cl; X = O; R_1 = C_6H_5).** A.—A solution of 3-amino-6-chloropyridazine (1.0 g) in dioxane (60 ml) and phenyl isocyanate (1.0 g) was heated under reflux for 2 hr. The separated product (1.4 g, 72%) was crystallized from *N*,*N*-dimethylformamide and water (1:5): mp 280°; ir (KBr) 1712 cm^{-1} (CO); nmr (DMSO-d_6, 108°) τ 1.95 (d, $H_{4'}$), 2.42 (d, $H_{5'}$), 2.7 (m, C_6H_5), $J_{4',5'}$ = 9.5 Hz.

Anal. Calcd for $C_{11}H_9ClN_4O$: C, 53.21; H, 3.64; N, 22.60. Found: C, 53.19; H, 4.04; N, 22.68.

B.—The same compound was obtained when 7-chloro-3-phenylpyridazino[2,3-*a*]-1,3,5-triazine-2,4-dione (0.5 g) was heated with water (10 ml) and ethanol (1 ml) for 10 min.

If the product was heated with acetic anhydride under reflux for 3 hr, the separated product was identified as 3-acetylamino-6-chloropyridazine, mp 252–254°.

***N*-(Pyridazinyl-3′)-*N*′-phenylurea (2, R = H; X = O; R_1 = C_6H_5).** A.—The same procedure as above under A was applied: mp 290° (dec) (from dioxane, 57% yield); ir (KBr) 1718 cm^{-1} (CO); nmr (DMSO-d_6) τ 2.12 (dd, $H_{4'}$), 2.55 (dd, $H_{5'}$), 1.28 (dd, $H_{3'}$), 2.75 (m, C_6H_5), 0.2 (broad, NH), $J_{4',5'}$ = 9.0, $J_{4',6'}$ = 1.5, $J_{5',6'}$ = 4.5 Hz.

B. The compound was obtained in a similar experiment as described above under B from 3-phenylpyridazino[2,3-*a*]-1,3,5-triazine-2,4-dione.

C.—A mixture of the thiourea (2, R = H; X = S; R_1 = C_6H_5) (1.0 g), ethanol (10 ml), hydrogen peroxide (6 g of 3%), and some diluted hydrochloric acid was heated for 2 min. Upon cooling, water (5 ml) was added and neutralized with ammonia. The product (0.6 g) was identical in all respects with the compound prepared as described under A or B.

(4) B. Stanovnik and M. Tišler, *Synthesis*, 308 (1972).

(5) R. Neidlein and W. Haussmann, *Chem. Ber.*, **99**, 239 (1966).

(6) D. A. Peak and F. Stansfield, *J. Chem. Soc.*, 4067 (1952).

N,N-**Dimethyl-*N'*-(pyridazinyl-3)formamidine** (**7**, **R** = **H**).—A mixture of 3-aminopyridazine (1.0 g) and *N,N*-dimethylformamide dimethyl acetal (1.2 g) was heated under reflux for 1 hr. After excess of the reagent was removed *in vacuo*, the residue was treated with ethyl acetate (1 ml) and the separated product was filtered off and purified by distillation at 120° (1 mm) (1.2 g, 76%): mp 42–46°; ir (KBr) 1631 cm^{-1} (C=N); nmr (DMSO-d_6) τ 3.12 (dd, H_4), 2.78 (dd, H_5), 1.40 (dd, H_6), 1.59 (s, CH), $J_{4,5} = 9.0$, $J_{5,6} = 4.5$, $J_{4,6} = 2.0$ Hz.

Anal. Calcd for $C_7H_{10}N_4$: C, 55.98; H, 6.71; N, 37.31. Found: C, 55.68; H, 7.03; N, 36.94.

N,N-**Dimethyl-*N'*-(6-chloropyridazinyl-3)formamidine** (**7**, **R** = **Cl**).—The compound was prepared in the same manner as described above for the unsubstituted analog: mp 115° (from ethyl acetate); ir (KBr) 1626 cm^{-1} (C=N); nmr (DMSO-d_6) τ 2.96 (d, H_4), 2.55 (d, H_5), 1.62 (s, CH), $J_{4,5} = 9.4$ Hz.

Anal. Calcd for $C_7H_9ClN_4$: C, 45.55; H, 4.91 N, 30.34. Found: C, 46.00; H, 5.17; N, 30.34.

7-Chloro-3-phenylpyridazino[2,3-*a*]-1,3,5-triazine-2,4-dione (**6**, **R** = **Cl**; R_1 = **H**). **A.**—A suspension of **2** (R = Cl; X = O; $R_1 = C_6H_5$) (1.0 g) in dioxane (35 ml) and pyridine (5 ml) was treated with phenyl isocyanate (0.8 g) and the mixture was then heated under reflux for 48 hr. Upon filtration, the filtrate was evaporated to dryness and the crude product was sublimed at 150° (1 mm) to separate the unchanged urea. The residue was thereafter sublimed at 210° (1 mm) (0.05 g, 4.5%): mp 280°; ir (KBr) 1757, 1683 cm^{-1} (CO); nmr (TFAA) τ 1.70 (d, H_8), 1.82 (d, H_9), 2.40 (m, C_6H_5), $J_{8,9} = 9.5$ Hz.

Anal. Calcd for $C_{12}H_7ClN_4O_2$: C, 52.47; H, 2.57; N, 20.40. Found: C, 52.23; H, 2.94; N, 20.20.

B.—The method, as described for the following example, was applied and the compound was obtained from the formamidine **7** (R = Cl) in 81% yield, mp 280° (from toluene). It was identical with the product obtained as described under A.

3-Phenylpyridazino[2,3-*a*]-1,3,5-triazine-2,4-dione (**6**, **R** = R_1 = **H**).—A solution of the formamidine **7** (R = H) (1.0 g) in dry toluene (20 ml) was treated with phenyl isocyanate (2.0 g) and the mixture was heated under reflux for 3 hr. The product (1.4 g, 87%) was for analysis sublimed at 230° (1 mm): mp 252–253°; ir (KBr) 1757 and 1683 cm^{-1} (CO); nmr (TFFA) degenerated ABX τ 0.92 (t, H_7), 1.70 (d, H_8, H_9), $J_{7,8} = 4.0$, $J_{8,9} = 9.2$, $J_{7,9} = 1.0$ Hz.

Anal. Calcd for $C_{12}H_8N_4O_2$: C, 60.00; H, 3.36; N, 23.33. Found: C, 60.23; H, 3.63; N, 23.16.

9-Bromo-7-chloro-3-phenylpyridazino[2,3-*a*]-1,3,5-triazine-2,4-dione (**6**, **R** = **Cl**; R_1 = **Br**).—A solution of **6** (R = Cl; R_1 = H) (0.5 g) in glacial acetic acid (10 ml) was treated with bromine (0.3 g) and the mixture was left at room temperature for 2 hr. The separated bromo complex was filtered off, suspended in acetic acid, and then heated under reflux for 2 hr. The obtained product was crystallized from acetic acid (0.35 g, 55%): mp 255° dec; ir (KBr) 1757 and 1689 cm^{-1} (CO); nmr (TFFA) τ 1.83 (s, H_8), 2.40 (m, C_6H_5).

Anal. Calcd for $C_{12}H_6BrClN_4O_2$: C, 40.76; H, 1.71; N, 15.85. Found: C, 40.33; H, 2.01; N, 15.62.

9-Bromo-3-phenylpyridazino[2,3-*a*]-1,3,5-triazine-2,4-dione (**6**, **R** = H; R_1 = **Br**) was prepared similarly in 44% yield: mp 240° dec (from acetic acid); ir (KBr) 1757 and 1681 cm^{-1} (CO); nmr (DMSO-d_6) τ 1.72 (d, H_7), 1.85 (d, H_8), 2.60 (m, C_6H_5), $J_{7,8} = 4.5$ Hz.

Anal. Calcd for $C_{12}H_7BrN_4O_2$: C, 45.16; H, 2.21; N, 17.55. Found: C, 45.02; H, 2.28; N, 17.50.

3-Carbethoxyamino-6-chloropyridazine (**8**, **R** = **OEt**).—A mixture of **6** (R = Cl; R_1 = H) (1.0 g) and ethanolic sodium ethylate (prepared from 0.3 g of sodium and 7 ml of ethanol) was heated under reflux for 15 min, cooled, acidified to pH 5, and the product was filtered off (0.5 g, 67%). For analysis it was sublimed at 120° (1 mm): mp 192–193°; ir (KBr) 3279 (NH) and 1718 cm^{-1} (COOEt); nmr (DMSO-d_6, 79°) τ 1.90 (d, H_4), 2.30 (d, H_5), 5.80 (q, CH_2CH_3), 8.68 (t, CH_2CH_3), −0.5 (broad, NH), $J_{4,5} = 9.5$, $J_{Et} = 7.5$ Hz.

Anal. Calcd for $C_7H_8ClN_3O_2$: C, 41.71; H, 4.00; N, 20.84. Found: C, 42.21; H, 4.03; N, 20.90.

N-(**2-Methyl-6-chloropyridazinylene-3**)-*N',N'*-**dimethylformamidinium Iodide** (**9**, **R** = **Cl**).—A mixture of the formamidine **7** (R = Cl) (1.0 g), methanol (10 ml), and methyl iodide (1.0 g) was heated under reflux for 3 hr. The solvent was evaporated *in vacuo*, ethyl acetate (2 ml) was added, the product was filtered off and dissolved in hot glacial acetic acid, the acid was evaporated *in vacuo*, and the residue was treated with ethyl acetate (1 ml). The product was crystallized from ethyl acetate and ethanol (1:3) (0.8 g, 45%): mp 178–179°; nmr (DMSO-d_6) τ 1.70 (d, H_5), 1.80 (d, H_4), 1.13 (s, CH), 5.96 (s, 2-NCH_3), 6.63 (s) and 6.76 (s) for $N(CH_3)_2$, $J_{4,5} = 9.4$ Hz.

Anal. Calcd for $C_8H_{12}ClIN_4$: C, 29.52; H, 3.71; N, 17.21. Found: C, 29.43; H, 3.65; N, 17.26.

N-(**2-Methylpyridazinylene-3**)-*N',N'*-**dimethylformamidinium Iodide** (**9**, **R** = **H**).—The compound was prepared in a similar manner as above in 66% yield: mp 192–193° (from ethyl acetate and ethanol, 1:3); nmr (DMSO-d_6) τ 2.26 (d, H_4), 1.85 (dd, H_5), 0.75 (d, H_6), 1.55 (s, CH), 5.67 (s, 2-NCH_3), 6.80 (s) and 6.94 (s) for $N(CH_3)_2$, $J_{4,5} = 9.2$, $J_{5,6} = 6.0$ Hz.

Anal. Calcd for $C_8H_{13}IN_4$: C, 32.89; H, 4.48; N, 19.18. Found: C, 33.21; H, 4.85; N, 18.90.

6-Chloro-3-[(*N'*-piperidinomethylene)amino]pyridazine (**10**).—The formamidine **7** (R = Cl) (1.0 g) and piperidine (1.3 g) were heated at 120° for 1 hr, with dimethylamine being evolved. The cooled reaction mixture was treated with ethyl acetate (3 ml) and the product was filtered off and crystallized from ethyl acetate (0.9 g, 74%): mp 104–105°; nmr (DMSO-d_6) τ 2.63 (d, H_4), 3.03 (d, H_5), 1.66 (s, CH), 6.50 and 8.40 (m, piperidine CH_2), $J_{4,5} = 9.0$ Hz.

Anal. Calcd for $C_{10}H_{13}ClN_4$: C, 53.45; H, 5.83; N, 24.94. Found: C, 53.05; H, 6.06; N, 25.52.

3-Formylamino-6-chloropyridazine (**8**, **R** = **H**).—A mixture of **7** (R = Cl) (1.0 g) and glacial acetic acid (5 ml) was heated just to boiling, the solvent was evaporated *in vacuo*, and the residue, when treated with ethyl acetate (3 ml), afforded the formyl derivative (0.6 g, 70%). For analysis it was sublimed at 130° (1 mm): mp 208–210°; ir (KBr) 3247 (NH) and 1692 cm^{-1} (CO); nmr (DMSO-d_6, 95°) τ 2.12 (d, H_4), 2.35 (d, H_5), 1.22 (s, CHO), −1.0 (broad, NH), $J_{4,5} = 9.4$ Hz.

Anal. Calcd for $C_5H_4ClN_3O$: C, 38.36; H, 2.58; N, 26.83. Found: C, 38.57; H, 3.10; N, 26.55.

3-Formylaminopyridazin-6(1*H*)-one (**11**).—If the same procedure as above was applied, but with heating for 2 hr, the compound was obtained in 34% yield: mp 285–286° (sublimed at 200° (1 mm); nmr (DMSO-d_6, 83°) τ 2.56 (d, H_4), 3.30 (d, H_5), 1.70 (s, HCO), 7.10 (broad, NH, OH), $J_{4,5} = 9.0$ Hz.

Anal. Calcd for $C_5H_5N_3O_2$: C, 43.17; H, 3.62. Found: C, 42.80; H, 3.72.

The same compound could be prepared if 3-amino-6-chloropyridazine was heated with formic acid under reflux for 18 hr (74% yield).

N-**Carbethoxy-*N'*-(6-chloropyridazinyl-3)thiourea** (**12**).—3-Amino-6-chloropyridazine (1.29 g) was dissolved in *N,N*-dimethylformamide (15 ml) with gentle warming and a solution of carbethoxy isothiocyanate (1.31 g) in the same solvent (3 ml) was added. The mixture was warmed to 80° for 5 min, and cooled, water (50 ml) was added, and the product filtered off (0.82 g). It was crystallized from 70% ethanol, mp 168–170°.

Anal. Calcd for $C_8H_9ClN_4O_2S$: C, 36.86; H, 3.48; N, 21.49. Found: C, 36.96; H, 3.34; N, 21.12.

7-Ethoxy-2-thioxopyridazino[2,3-*a*]-1,3,5-triazin-4(3*H*)-one (**13**).—The above thiourea (**12**) (1.16 g) and a solution of sodium ethylate (prepared from 0.12 g of sodium and 15 ml of ethanol) was heated under reflux for 1 hr. The obtained product was treated with diluted hydrochloric acid to pH 4 and then crystallized from ethanol (1.0 g): mp 223–226°; mass spectrum M^+ 224; nmr (TFAA) τ 2.06 (d, H_8), 2.24 (d, H_9), 5.40 (q, CH_2CH_3), 8.49 (t, CH_2CH_3), $J_{8,9} = 9.4$, $J_{Et} = 6.7$ Hz.

Anal. Calcd for $C_6H_8N_4O_2S$: C, 42.86; H, 3.60; N, 24.99. Found: C, 42.96; H, 3.79; N, 25.01.

Registry No.—**2** (R = Cl; X = O; R_1 = PhCO), 35053-39-5; **2** (R = H; X = S; R_1 = Ph), 35053-40-8; **2** (R = Cl; X = O; R_1 = Ph), 35053-41-9; **2** (R = H; X = O; R_1 = Ph), 35053-42-0; **3** (R = Cl), 35053-43-1; **3** (R = OCH_3), 35053-44-2; **3** (R = PhS), 35053-45-3; **3** (R = $NHNH_2$), 35053-46-4; **3** (R = NH–N=CHPh), 35053-47-5; **4**, 35053-48-6; **5**, 939-07-1; **6** (R = Cl; R_1 = H), 35053-50-0; **6** (R = R_1 = H), 35053-51-1; **6** (R = Cl; R_1 = Br), 35053-52-2; **6** (R = H; R_1 = Br), 35053-53-3; **7** (R = H), 35053-54-4; **7** (R = Cl), 35053-55-5; **8** (R = CH_3), 14959-31-0; **8** (R = OEt), 35053-57-7; **8** (R = H), 35053-

58-8; **9** (R = Cl), 35053-59-9; **9** (R = H), 35053-60-2; **10**, 35053-61-3; **11**, 35053-62-4; **12**, 35053-63-5; **13**, 35053-64-6.

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Alkaline Sodium Dithionite and Catalytic Reduction of Di-, Tri-, and Tetraalkoxycarbonylpyrazines. The Synthesis of 1,2-Dihydropyrazines

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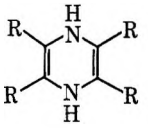
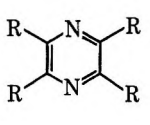
Catalytic reduction of di-, tri- and tetraalkoxycarbonylpyrazines afford 1,2-, not 1,4-dihydropyrazines, as the major products. 2,3,5,6-Tetraethoxycarbonylpyrazine (**2b**) and 3,5-dimethoxycarbonylpyrazine (**9**) yield only the 1,2-dihydropyrazines **3b** and **10**, respectively. 2,3,5,6-Tetramethoxycarbonylpyrazine (**2a**) gave tetramethoxycarbonyl-1,2-dihydropyrazine (**3a**) together with the tetra- and hexahydro products **4** and **5**, respectively. 2,3,5-Trimethoxycarbonylpyrazine (**6**) afforded the 1,2-dihydropyrazine **7** and the tetrahydropyrazine **8**. The 3,5-dimethoxycarbonylpyrazine **9** afforded the 1,2-dihydropyrazine **10**, whereas the 2,5-dimethoxycarbonylpyrazine **11** gave the tetrahydropyrazine **12**. The unstable tetrahydropyrazines **8** and **12** were identified by spectral data. Alkaline sodium dithionite reduction of tetra- and trialkoxycarbonylpyrazines **3a**, **3b**, and **6** yielded their 1,2-dihydropyrazines as the only product. Attempted reduction of disubstituted pyrazines led to hydrolysis of the esters.

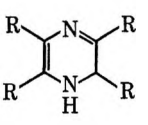
According to quantum mechanical calculations, systems with $4n$ π electrons ought to have antiaromatic character, *i.e.*, be destabilized by resonance.[1] This prediction has been extensively examined for the simplest system having $4n$ π electrons where $n = 1$.[1b] The 1,4-dihydropyrazine ring system **1a**, a cyclic conjugated system with $4n$ π electrons ($n = 2$), is generally thought to be a known structure.[2] However, recent results have cast doubt on the structures of many previously reported 1,4-dihydropyrazines.[3] We have reexamined the reduction of alkoxycarbonylpyrazines reported to yield 1,4-dihydropyrazines and find the original structural assignments to be in error. We now wish to report a convenient method for the synthesis of 1,2-dihydropyrazines.



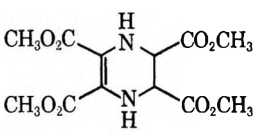
1a, R = H
b, R = $CO_2C_2H_5$



2a, R = CO_2CH_3
b, R = $CO_2C_2H_5$



3a, R = CO_2CH_3
b, R = $CO_2C_2H_5$



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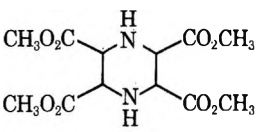

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Mager and Berends[4,5] reported that alkaline sodium dithionite and catalytic reduction under vigorous conditions of 2,3,5,6-tetraethoxycarbonylpyrazine (**2b**) yielded the 1,4-dihydropyrazine **1b**. In contrast, we find that catalytic reduction occurs readily at room temperature to yield the same yellow product as was isolated previously.[4,5] The nmr spectrum of this product showed two doublets, δ 5.50 (1 H, J = 5.0 Hz) and 6.85 (1 H, J = 5.0 Hz), together with two very complex multiplets due to the different environments of the four ethyl ester groups. This spectrum is clearly inconsistent with **1b**. Deuteration caused the peak at δ 6.85 to disappear and that at δ 5.50 to collapse to a singlet. The ir spectrum confirmed the presence of a secondary amine. Therefore, the yellow product is assigned the 1,2-dihydropyrazine structure **3b**.

To simplify the nmr spectrum, the tetramethoxycarbonylpyrazine **2a** was reduced under identical conditions. In contrast to the single product formed in the ethyl case, the tetramethyl ester was reduced further to yield a mixture of the di-, tetra-, and hexahydro derivatives. In the nmr spectrum of the 1,2-dihydropyrazine **3a** the C-2 hydrogen, initially a singlet at δ 5.55, changed to a multiplet upon hydration.

The nmr spectrum of the second product showed two absorption peaks at δ 3.74 and 3.78 for the four methyl esters. Peaks at δ 4.28 were assigned to the hydrogens on the carbon next to nitrogen and the ester, and a broad absorption at 4.30 was due to the NH proton, which disappeared upon deuteration. This data is consistent with the 1,2,3,4-tetrahydropyrazine structure **4**, for the second product.

The third product showed a singlet at δ 3.69 for the four methyl esters, a singlet at δ 3.87 (4 H) for the hydrogens on the carbon next to nitrogen and the ester, and a broad 2 H multiplet at δ 2.82 due to the NH. There was no absorption maximum in the uv above 210 nm, confirming the structure of the compound as 2,3,5,6-tetramethoxycarbonylpiperazine (**5**).

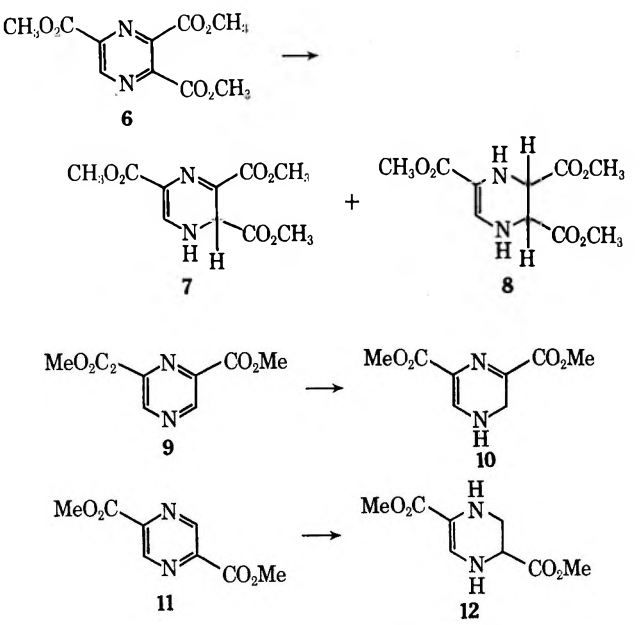
Disproportionation, previously observed for 1,2-dihydropyridine,[6] did not occur in the case of the 1,2-dihydropyrazine **3a**.

To test the generality of this reaction, catalytic reduction of tri- and dimethoxycarbonyl-substituted pyrazines was investigated.

Catalytic reduction of 2,3,5-trimethoxycarbonylpy-

(1) For leading references see (a) J. F. Labarre and F. Crasnier, *Fortschr. Chem. Forsch.*, **24**, 33 (1971); (b) R. Breslow, *Angew. Chem.*, **7**, 565 (1968).
(2) Y. T. Pratt and R. C. Elderfield, *Heterocycl. Compounds*, **6**, 414 (1957).
(3) S. J. Chen and F. W. Fowler, *J. Org. Chem.*, **35**, 3987 (1970).
(4) H. I. X. Mager and W. Berends, *Recl. Trav. Chim., Pays-Bas*, **79**, 282 (1960).
(5) H. I. X. Mager and W. Berends, *ibid.*, **76**, 28 (1957).
(6) U. Eisner, *Chem. Commun.*, 1348 (1969).

razine (6) occurred with the uptake of 1.3 mol of hydrogen and yielded a mixture of reduction products. Upon standing, 2,3,5-trimethoxycarbonyl-1,2-dihydropyrazine (7) crystallized out of the mixture. Deuteration of the NH proton in 7 caused both the C-2 and C-6 protons in the nmr spectrum to collapse to singlets.



The nmr spectrum of the yellow gum immediately after reduction was different from either that of the starting material or 1,2-dihydro product. A singlet at δ 4.32 integrating for two hydrogens and a doublet at δ 6.84 (J = 4.0 Hz) due to an olefinic hydrogen indicates that reduction has occurred at the C-2 and C-3 positions. Furthermore, the ultraviolet spectrum, λ_{max} (MeOH) 295 nm (ϵ 7700), is different from either that of 6 or 7. Mass spectra, both by electron impact ionization and chemical ionization, indicate addition of 2 mol of hydrogen, and therefore the unstable product is the tetrahydropyrazine 8. Attempts to obtain 8 crystalline were unsuccessful due to its ready oxidation to 6 and 7.

Catalytic reduction of 3,5-dimethoxycarbonylpyrazine (9) yielded the corresponding 1,2-dihydropyrazine 10. 2,5-Dimethoxycarbonylpyrazine 11 yielded the tetrahydropyrazine 12 in low yield. The nmr spectrum of 12 showed an ABX pattern due to the C-2 and C-3 protons. This coupling pattern was confirmed by irradiation at δ 4.01, causing the AB part of the ABX to collapse to a typical AB quartet. Attempts to purify and isolate 12 resulted in oxidation and formation of the aromatic starting material.

From the above results it appears that catalytic hydrogenation using palladium on charcoal results in initial formation of a 1,2-dihydropyrazine. It is interesting to note that reduction of the tetraethyl ester stops after 1 mol of hydrogen has been taken up, whereas for the methyl ester both the tetra- and hexahydropyrazines are isolated. This is probably due to the smaller size of the methyl group, allowing the pyrazine molecule to get closer to the catalyst surface. Recently, catalytic reduction of pyridine has also been shown to occur to give 1,2-dihydropyridines.[6]

Mager and Berends[4] also examined the alkaline sodium dithionite reduction of the tetraethoxycarbonylpyrazine 2b. They obtained the same yellow product as from the catalytic reduction which they reported[4] to be the 1,4-dihydropyrazine 1b but now is shown to be the 1,2-dihydropyrazine 3b. Alkaline sodium dithionite reduction of the tetra- and trimethoxycarbonylpyrazines 2a and 6 also afforded the corresponding 1,2-dihydropyrazines 3a and 7, respectively, as the only products. Dithionite reduction of the disubstituted esters led to hydrolysis of the esters, with very little reduction of the ring.

Therefore, sodium dithionite offers a convenient method for the reduction of pyrazines and synthesis of 1,2-dihydropyrazines in good yield (60–70%). This result is in contrast to the extensively examined dithionite reduction of the pyridine nucleus, which has been shown to occur 1,4.[7]

To our knowledge this is the first reported method for the synthesis of 1,2-dihydropyrazines by reduction from the corresponding pyrazine. Previous reduction methods have resulted in the formation of saturated piperazines.[2] The 1,2-dihydropyrazines 3a, 3b, 7, and 10 are stable, since they are not antiaromatic as the corresponding 1,4-dihydropyrazines would be predicted to be.[1] Furthermore, it should be noted that the reduction products become much more sensitive to oxidation as the number of electron-withdrawing substituents is reduced.

Experimental Section[8]

2,3,5,6-Tetraethoxycarbonylpyrazine (2b).—2,3,5,6-Pyrazinetetracarboxylic acid was obtained as colorless needles, mp 230° (lit.[5] mp 205°), using the method of Mager and Berends.[5] Esterification of the tetraacid yielded the tetraethyl ester 2b, mp 103–104° (lit.[5] mp 104°), uv max (MeOH) 277–279 nm (ϵ 8500).

2,3,5,6-Tetramethoxycarbonylpyrazine (2a).—A solution of 2.23 g of 2,3,5,6-pyrazinetetracarboxylic acid in 70 ml of methanol saturated with HCl was refluxed for 16 hr. The solvent was evaporated and the residue was filtered through alumina (neutral activity 1) in ethyl acetate. Recrystallization from methanol afforded 2,3,5,6-tetramethoxycarbonylpyrazine (2a) as colorless needles: mp 181–182°; uv max (MeOH) 278 nm (ϵ 11,060); ir (Nujol) 1740 and 1730 cm^{-1} (ester C=O).

Anal. Calcd for $C_{12}H_{12}N_2O_8$: C, 46.16; H, 3.87; N, 8.97. Found: C, 46.36; H, 3.84; N, 8.93.

General Procedure for 5% Palladium on Charcoal Reduction of Alkoxycarbonylpyrazines.—To 100 mg of alkoxycarbonylpyrazine dissolved in 25 ml of 95% ethanol was added with stirring 25 mg of 5% palladium on charcoal, under hydrogen at atmospheric pressure and room temperature. The reaction was allowed to continue until hydrogen absorption ceased, usually about 70 min. The catalyst was filtered off, and the filtrate was concentrated.

2,3,5,6-Tetraethoxycarbonyl-1,2-dihydropyrazine (3b).—Catalytic hydrogenation of 2,3,5,6-tetraethoxycarbonylpyrazine proceeded with the absorption of 10.0 ml (1.67 molar equiv) of hydrogen to yield 78 mg (77%) of 2,3,5,6-tetraethoxycarbonyl-1,2-dihydropyrazine (3b) as yellow needles: mp 128–129° (lit.[2] mp 127–127.5°); uv max (MeOH) 278 nm (ϵ 9280), 374 (6280); ir (Nujol) 4200 (NH), 1755, 1735, 1680 cm^{-1} (ester C=O); nmr ($CDCl_3$)δ 1.3 (m, 12, 4 CH_3CH_2), 4.25 (m, 8, CH_2CH_3), 5.50 (d, 1, J = 5.0 Hz, NCHCO$_2$Me), 6.85 (d, 1, J = 5.0 Hz, NH).

(7) For leading references see J. F. Biellmann and H. J. Callot, *Bull. Soc. Chim. Fr.*, 1299 (1969).

(8) Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. Ir spectra were recorded with a Perkin-Elmer Infracord Model 137 spectrometer fitted with sodium chloride prisms. Ultraviolet spectra were determined in methanol with a Cary 14 recording spectrometer. Nmr spectra were obtained with Varian A-60A and XL100 spectrometers. The mass spectra were measured on an AE1 MS-9 mass spectrometer at an ionizing energy of 70 eV. Microanalyses were performed by Micro-Analysis Inc., Wilmington, Del.

Anal. Calcd for $C_{16}H_{22}N_2O_8$: C, 51.89; H, 5.95; N, 7.56. Found: C, 51.67; H, 6.02; N, 7.36.

2,3,5,6-Tetraethoxycarbonyl-1,2-dihydropyrazine (3a).—Catalytic hydrogenation of 2,3,5,6-tetraethoxycarbonylpyrazine proceeded with the absorption of 17.9 ml (2.5 molar equiv) of hydrogen. Recrystallization of the residue from methanol afforded 51 mg of **2,3,5,6-tetraethoxycarbonyl-1,2,3,4-tetrahydropyrazine (4)** as pale yellow prisms: mp 165–166°; uv max 277 nm (ϵ 10, 130), 372 (4290); ir (Nujol) 3380, 3350, (NH), 1735, 1730, 1670 (ester C=O), and 1620 cm^{-1} (C=C); nmr ($CDCl_3$) δ 3.74 (6, s, 2 CO_2Me) 3.78 (6, s, 2 CO_2Me) 4.28 (2, s, $NCHCO_2Me$), and 4.30 (2, m, NH).

Anal. Calcd for $C_{12}H_{16}N_2O_8$: C, 45.57; H, 5.10; N, 8.86. Found C, 45.75; H, 5.06; N, 8.72.

A further crop (21 mg) of the tetrahydropyrazine, mp 160–164°, was obtained from the filtrate. Upon standing, the above filtrate afforded 64 mg of **2,3,5,6-tetramethoxycarbonylpiperazine (5)**, which upon recrystallization from methanol yielded colorless needles: mp 162–163°; uv (MeOH) no absorption maximum; ir (Nujol) 3380, 3250 (NH), 1755 and 1725 cm^{-1} (ester C=O); nmr ($CDCl_3$) δ 3.69 (12, s, 4 CO_2Me), 3.87 (4, s, $NCHCO_2Me$), 2.82 (2, m, NH).

Anal. Calcd for $C_{12}H_{18}N_2O_8$: C, 45.28; H, 5.70 N, 8.80. Found: C, 45.51; H, 5.51; N, 8.85.

The mother liquors were all combined, reduced in volume, and cooled to −10°. Deep yellow crystals (1.01 g) of **2,3,5,6-tetramethoxycarbonyl-1,2-dihydropyrazine (3a)**, mp 144–145°, were obtained: uv max (MeOH) 276 nm (ϵ 8800), 371 (6160); ir (Nujol) 3200 (NH), 1755, 1730, 1685 cm^{-1} (ester C=O); nmr ($CDCl_3$) δ 3.68 (3, s, CO_2Me), 3.79 (3, s, CO_2Me), 3.87 (3, s, CO_2Me), 3.90 (3, s, CO_2Me), 5.55 (1, s, $NCHCO_2Me$).

Anal. Calcd for $C_{12}H_{14}N_2O_8$: C, 45.87; H, 4.49 N, 8.91. Found: C, 45.61; H, 4.53; N, 8.93.

Treatment of **3a** in methanol with Pd/C yielded only starting material.

Catalytic Reduction of 2,3,5-Trimethoxycarbonylpyrazine (6).—Catalytic reduction of **6** proceeded with the absorption of 11.8 ml (1.34 molar equiv) of hydrogen. The yellow residue would not crystallize: uv max (MeOH) 289 nm (ϵ 7700); ir (liquid film) 3360 (NH), 1740, 1670 (ester C=O), 1648 cm^{-1} (C=C); nmr δ 3.72 (3, s, CO_2Me), 3.98 (3, s, CO_2Me), 4.30 (2, s, $NCHCO_2Me$), 4.70 (1, m, NH), 6.84 (1, d, C=CHN, J = 4.2 Hz). Deuteration caused the peak at δ 4.70 to disappear and the peak at δ 6.84 to become a singlet.

The oil was taken up in methanol and upon standing crystallized as yellow prisms, mp 182–184°, of **2,3,5-trimethoxycarbonyl-1,2-dihydropyrazine (7)**: uv max (EtOH) 270 nm (ϵ 14,400), 369 (5800); ir (Nujol) 3200 (NH), 1735 and 1695 cm^{-1} (C=O, ester); nmr ($CDCl_3$) δ 3.75 (3, s, CO_2Me), 3.87 (3, s, CO_2Me), 3.98 (3, s, CO_2Me), 5.49 (1, d, $NCHCO_2Me$, J = 4.0 Hz), 7.64 (1, d, C=CHN, J = 6.0 Hz), 6.54 (m, 1, NH).

Anal. Calcd for $C_{10}H_{12}N_2O_6$: C, 46.88; H, 4.72; N, 10.93. Found: C, 46.64; H, 4.86; N, 10.75.

Catalytic Reduction of 3,5-Dimethoxycarbonylpyrazine (9).—Catalytic reduction of **9** (500 mg) proceeded with the absorption of 64 ml (1.12 molar equiv) of H_2. The residue was crystallized from methanol to yield **3,5-dimethoxycarbonyl-1,2-dihydropyrazine (9)** (320 mg) as orange needles: mp 202–204° (evacuated capillary); uv max (MeOH) 275 nm (ϵ 15,000), 386 (5400); ir (Nujol) 3280 (NH), 1705 (CO_2Me), 1675 (CO_2Me), 1615 cm^{-1} (C=C); nmr (DMSO-d_6) δ 3.62 (3, s, CO_2Me), 3.72 (3, s, CO_2Me), 3.95 (2, s, NCH_2), 7.48 (1, s, C=HN), 8.20 (m, 1, NH); mass spectrum m/e (rel intensity) 198.0634 (46), 197 (14), 167 (22), 166 (24), 165 (10), 159 (9), 140 (13), 139 (49), 138 (100), 137 (25).

Anal. Calcd for $C_8H_8N_2O_4$: C, 48.98; H, 4.11; N, 14.28. Found: C, 49.26; H, 5.04; N, 14.52.

Catalytic Reduction of 2,5-Dimethoxycarbonylpyrazine (11).—Catalytic reduction of 11 (200 mg) proceeded with the absorption of 23.0 ml (1.01 molar equiv) of H_2. The residue was very unstable and was readily oxidized by the oxygen of the air, back to the starting aromatic ester. The residue had the following nmr ($CDCl_3$): δ 3.12 (1, q, J_{AB} = 11.4, J_{AX} = 6.0 Hz), 3.47 (1, q, J_{AB} = 11.4, J_{BX} = 3.5 Hz), 4.01 (1, q, J_{AX} = 11.2, J_{BX} = 3.5 Hz), 3.67 (3, s, CO_2Me), 3.74 (3, s, CO_2Me), 6.91 (1, d, J = 2.5 Hz), attributable to 2,5-dimethoxycarbonyl-1,2,3,4-tetrahydropyrazine (12).

Alkaline Sodium Dithionite Reduction of 2,3,5,6-Tetraethoxycarbonylpyrazine (2b).—The method of Mager and Berends[4] was used. Reduction of **2b** yielded the 1,2-dihydropyrazine **3b** (67%), mp 128–129° (lit.[4] mp 129.5–131°), identical (ir, uv, nmr, melting point, mixture melting point) with the 1,2-dihydropyrazine obtained by catalytic reduction of **2b**.

Alkaline Sodium Dithionite Reduction of 2,3,5,6-Tetramethoxycarbonylpyrazine (2a).—Using the above method, reduction of **2a** yielded 2,3,5,6-tetramethoxycarbonyl-1,2-dihydropyrazine (**2b**), mp 146–148°, in 82% yield, identical with the product obtained by catalytic reduction of **2a**.

Alkaline Sodium Dithionite Reduction of 2,3,5-Trimethoxycarbonylpyrazine (6).—Using the above method, 2,3,5-trimethoxycarbonyl-1,2-dihydropyrazine (**7**), mp 182–184°, was obtained as yellow needles in 68% yield.

Alkaline Sodium Dithionite Reduction of 2,3-, 2,5-, and 3,5-Dimethoxycarbonylpyrazines.—Using the above method resulted in hydrolysis of the ester functions.

Registry No.—**2a**, 35042-21-8; **3a**, 35042-22-9; **4**, 35042-23-0; **5**, 35042-24-1; **7**, 35042-25-2; **9**, 35042-26-3; **12**, 35042-27-4.

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Cyanogen Azide

F. D. MARSH

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The preparation of cyanogen azide (1) from sodium azide and cyanogen chloride in anhydrous media is described. In aqueous media these same reagents can also give either sodium 5-azidotetrazole (6) or (diazidomethylene)cyanamide (8). A probable reaction path leading to the various products is proposed.

The brief but rich history of cyanogen azide (N_3CN) (1) has already established it as a highly reactive and useful reagent in synthetic and theoretical chemistry. Our preliminary reports of its synthesis[1] and decomposition to cyanonitrene (NCN) (2)[2,3] were the bases for two broad areas of research in cyanogen azide and cyanonitrene chemistry. The unique reactivity of 1 with olefins[1,4,5] at 0–35° to give alkylidene cyanamides and *N*-cyanoaziridines had led to a better understanding of azide–olefin reactions[4] and to a convenient method for converting selected olefins to ketones under exceptionally mild conditions.[4] The azide–olefin reaction has been adapted to a new method for contracting rings of steroid ketones.[6] In addition, the azide 1 has broad utility as an intermediate to a number of new heterocyclic systems through reaction with acetylenes,[7] ketones,[8] and nucleophiles,[8] and yields new classes of ylides and substituted cyanamides through reaction with Lewis bases.[8]

The second class of cyanogen azide reactions occurs at *ca.* 50° where 1 loses nitrogen to give cyanonitrene (2), a common intermediate in the reactions of cyanogen azide with aliphatic and aromatic hydrocarbons which furnish alkylcyanamides[2] and *N*-cyanoazepines,[9] respectively. Cyanonitrene has also been proposed as an intermediate in selected olefin reactions[10] to give aziridines and is the only known precursor to azodinitrile.[11] The symmetry and ease of preparation of this new first-row triatomic molecule has led to several fundamental studies of its structure and reactivity in the singlet and triplet states.[12]

This paper describes the synthesis and properties of 1 and offers an explanation for the formation of a compound, $(CN_4)_2$, originally reported[13] to be 1.

Synthesis and Properties of Cyanogen Azide.—Cyanogen azide is obtained in virtually quantitative yield from sodium azide and cyanogen chloride in anhydrous media.

$$NaN_3 + ClCN \longrightarrow \underset{1}{N_3CN} + NaCl$$

The pure azide 1 *is a colorless oil which detonates with great violence when subjected to mild mechanical, thermal, or electrical shock.* Solutions of cyanogen azide, however, can be prepared and handled safely in a number of solvents where most of its properties have been determined.

The pure azide 1 is too sensitive for combustion analysis but it has been characterized both physically and chemically. The infrared spectrum in carbon tetrachloride shows absorptions at 2240 (s), 2199 (vs), 2143 (s), and 2090 cm^{-1} (s) (associated with nitrile and azide stretching vibrations) and at 1245 cm^{-1} (vs) (C–N stretching). In cyclohexane, 1 has two resolved absorptions at 275 mμ (ϵ 103) and 220 (2157). The mass spectrometric cracking pattern of 1 (Table I) shows a peak of 48% relative abundance for the parent ion and is entirely consistent with the formulated structure. The molecular weight (freezing point in benzene) is 69 (calcd, 68). The boiling point and vapor pressure have not been determined, but 1 is estimated to boil at 90° and its vapor pressure at 25° lies between 70 and 100 mm.

TABLE I
MASS SPECTRUM OF N_3CN[a]

m/e	Intensity relative to $NCN^{\cdot+}$	Probable ion
12	94.7	$C^{\cdot+}$
13	0.9	^{13}C isotope
14	24.2	$N^{\cdot+}$
26	20.1	CN^+
28	42.4	$N_2^{\cdot+}$
34	1.2	N_3CN^{2+}
40	100	$NCN^{\cdot+}$
41	2.0	^{13}C and ^{15}N isotopes
42	3.9	N_3^+
54	0.4	N_3C^+ and/or N_3CN^+
68	48.1[b]	$N_3CN^{\cdot+}$
69	1.4	^{13}C and ^{15}N isotope

[a] Consolidated Electrodynamics Corp. 21-103C mass spectrometer operated with 10.5-μA ionizing current at 70 eV. [b] Parent ion.

For characterization, 1 was reduced to cyanamide in 80% yield and treated with triphenylphosphine and trimethyl phosphite to give, respectively, ylides 3 and 4 nearly quantitatively.

$$N_3CN + H_2S \longrightarrow NH_2CN + S + N_2$$
$$N_3CN + R_3P \longrightarrow R_3P{=}NCN + N_2$$
$$\mathbf{3},\ R = C_6H_5$$
$$\mathbf{4},\ R = CH_3O$$

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(13) M. G. Darzens, *C. R. Acad. Sci.*, **154**, 1232 (1912).

Cyanogen azide (1) is soluble in most organic solvents and water and can be recovered unchanged from aqueous solutions after 24 hr at room temperature. When heated in water, 1 is slowly hydrolyzed to carbamazide in low yield (40°, 54 hr). In 10% sodium hydroxide solution, 1 is slowly converted at room temperature to sodium 5-azidotetrazole (6) in 50% yield. The tetrazole presumably arises from initial hydrolysis of 1 to cyanate and azide ions. The azide ion reacts with 1 to give tetrazole 6, as discussed below.

Solutions of 1 decompose with loss of nitrogen, and the rate depends on temperature and to a lesser degree on the solvent (Table II). The half-life of 1 in acetonitrile (27 wt %) is 15 days at 25°, but solutions in acetonitrile or ethyl acetate have been stored for up to 1 year at 0 to −20° without change. Polar solvents appear to stabilize 1 with respect to thermal decomposition.

TABLE II
THERMAL STABILITY OF CYANOGEN AZIDE IN POLAR AND NONPOLAR SOLVENTS

Solvent	N_3CN, wt %	Temp, °C	N_3CN half-life
Acetonitrile	27	25	15 days
Acetonitrile	27	0 to −20	Indefinite
Acetonitrile	2.8	55	6.5 hr
Benzene	2.2	55	2.1 hr
Cyclohexane	2.8	55	1.6 hr

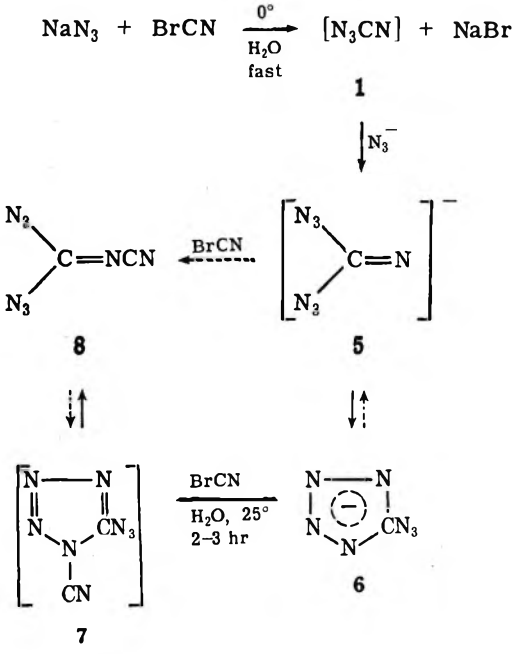
Reaction of Sodium Azide and Cyanogen Bromide in Water.—The older literature[13] describes the synthesis of a compound, $(CN_4)_2$, originally thought to be 1. We have reinvestigated this work and propose an explanation for the earlier findings.

Darzens[13] added 1 equiv of cyanogen bromide to aqueous sodium azide and obtained a white, crystalline solid, mp 35.5–36°, to which he assigned the structure 1 and the name carbon pernitride. Hart[14] reinvestigated this product and from molecular weight data and chemical studies reported that Darzens' product was a dimer of cyanogen azide, $(CN_4)_2$, having the (diazidomethylene)cyanamide structure 8. Hantzsch[15] later concluded from spectral data that Darzens' product was 1 and that Hart's findings resulted from an associated dimer of 1 in solution.

Our findings confirm the structure of Darzens' product as 8. Cyanogen azide has shown no tendency to dimerize as implied by Hart, and we suggest that 8 may arise as shown in Scheme I. When 1 equiv of cyanogen bromide was added to aqueous sodium azide at 0°, an initial rapid reaction consumed all the azide and 0.5 equiv of cyanogen bromide and gave nearly quantitatively a water-soluble, highly explosive CN_7 anion. This product was shown to be sodium 5-azidotetrazole (6) by elemental analysis, infrared spectrum, and reduction of the parent acid to the known 5-aminotetrazole.

When the reaction is allowed to continue at 25°, the remaining 0.5 equiv of cyanogen bromide slowly reacts (2–3 hr) and an oil separates, which when crystallized from ether gives the white, explosive solid, mp 42.1–42.9°, first isolated by Darzens. The structure of this solid was confirmed as 8 by elemental analysis, infrared spectrum, and reduction to the known dicyandiamide.

SCHEME I
REACTION OF SODIUM AZIDE AND CYANOGEN BROMIDE IN WATER



The initial fast reaction of sodium azide and cyanogen bromide in water at 0° appears to result from nucleophilic displacement on cyanogen bromide by azide ion and may give 1 as an intermediate. Repeated attempts to isolate or detect 1 in the aqueous reaction mixture or in the organic layer of two-phase reactions failed. Cyanogen azide prepared in acetonitrile, however, reacted rapidly with aqueous sodium azide to give tetrazole 6 in 80% yield. The tetrazole is presumed to form from attack of azide ion on the electron-deficient carbon of 1 to give the hypothetical *gem*-diazide 5, in a manner similar to the reaction of azide ion with nitriles bearing electron-withdrawing groups.[16] One of the azide groups then closes on the azomethine group in a well-documented reaction[17,13] to give 6. The second, slower step involves displacement on cyanogen bromide by the tetrazole anion 6 to give 7, which was not isolated but apparently opens spontaneously to the *gem*-diazide 8 in a reaction characteristic of many tetrazoles.[14,18c]

An equilibrium between 5 and 6 and reaction of the *gem*-diazide 5 with cyanogen bromide as shown by broken arrows in Scheme I can also account for 8. Other workers have demonstrated that certain tetrazoles, particularly those containing electron-withdrawing substituents, are in equilibrium with the isomeric azide.[18–20]

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(18) (a) C. Temple, Jr., C. L. Kussner, and J. A. Montgomery, *J. Org. Chem.*, **31**, 2210 (1966); (b) H. Limpricht, *Chem. Ber.*, **21**, 3409 (1888); (c) F. R. Benson in "Heterocyclic Compounds," 1st ed, Vol. 8, R. C. Elderfield, Ed., Wiley, New York, N. Y., 1967, p 65.
(19) J. H. Boyer and E. J. Miller, Jr., *J. Amer. Chem. Soc.*, **81**, 4671 (1959).
(20) J. H. Boyer and W. H. Hyde, *J. Org. Chem.*, **25**, 458 (1960).

Experimental Section[21]

Synthesis and Handling of Cyanogen Azide.—Synthesis and handling variables depend largely on the choice of the solvent for 1. Solutions of 1 are usually prepared by adding cyanogen chloride or cyanogen bromide to a well-stirred suspension of sodium azide at 0–12° in anhydrous media. Good yields are obtained in either polar or nonpolar media, including acetonitrile, ethyl acetate, methylene chloride, dibutyl phthalate, cyanogen chloride, toluene, benzene, cyclohexane, or pentane. *Careful consideration must be given to the properties of the solvent used for* 1, *since in some solutions the azide may separate and detonate if low-boiling solvents evaporate, saturated solutions are cooled, or the solvent is frozen.*

With polar media such as acetonitrile or ethyl acetate the exothermic reaction is complete in less than 1 hr after the reaction mixture is brought to room temperature. The solubility of 1 in polar solvents is good, and solutions containing up tp 30% (wt) of 1 in acetonitrile do not detonate on instantaneous exposure to a 250° hot bar or under a 480 kg-cm drop test (6-kg weight dropped 80 cm) and have been used routinely in our laboratory without event. Cyanogen azide is not readily separated from these solvents in normal laboratory manipulations, since the vapor pressures of 1 and these solvents are nearly the same. These solutions, however, should not be cooled below the freezing point of the solvent. Acetonitrile solutions of 1 are toxic when ingested by rats, producing cyanosis and death at a level of less than 72 mg/kg of body weight, but are absorbed only slowly through unbroken skin of rabbits or by inhalation of solution vapors.

In nonpolar media such as aliphatic and aromatic hydrocarbons, the synthesis of 1 requires up to 24 hr at room temperature and good yields are obtained only with activated[22] sodium azide and a 0.5 to 4 molar excess of cyanogen chloride. Cyanogen azide has a limited solubility in nonpolar solvents, and solutions in aliphatic hydrocarbons containing more than 5% (wt) of 1 are not safe to handle; if cooled, 1 may separate from such solutions and detonate.

Cyanogen azide solutions thus prepared contain sodium chloride, cyanogen chloride, and traces of by-products which can be removed or avoided if desired. Excess cyanogen chloride is removed under vacuum (caution[23]) or avoided by using a small excess of sodium azide. The reaction mixture is filtered (caution[24]) under nitrogen pressure to remove sodium chloride and any unreacted sodium azide. *Dry solvents are important to obtain good yields.* Traces of moisture or excess sodium azide lead to by-products 6 and 8, which may be isolated in subsequent manipulations as shock-sensitive solids. Solutions of essentially pure 1 are obtained nearly quantitatively when cyanogen chloride is used as the sole reaction media. These solutions are dangerous to handle because the cyanogen chloride (bp 12.7°) may evaporate, leaving pure 1, but this solvent can be readily exchanged for a higher boiling solvent when the reaction is complete.

Pure cyanogen azide is a lachrymator which has been isolated only *in small quantities* from solutions by gas–liquid chromatography and by evaporating the solvent from cyanogen chloride solutions under reduced pressure.

For many purposes, cyanogen azide can be most conveniently and safely prepared *in situ* where it is frequently consumed as formed. This method of synthesis, for example, is particularly useful in preparing alkylidene cyanamides or *N*-cyanoaziridines from olefins,[4] cyanamides from hydrocarbons,[2] and azepines from aromatic compounds.[9]

Cyanogen azide can also be prepared in high yield from cyanogen bromide or cyanogen fluoride and most ionic azides including lithium, potassium, ammonium, and tetraethylammonium zaides, but sodium azide and cyanogen chloride are used routinely in our laboratory.

Cyanogen Azide–Acetonitrile Solution.—A 1-l. flask equipped with a magnetic stirrer, thermometer, condenser, and gas inlet adapter was flame dried and cooled under nitrogen. Sodium azide (65 g, 1.0 mol) and dry acetonitrile (250 ml) were added and the flask, under a positive nitrogen pressure, was cooled in an ice–salt bath. A coolant at −5 to 0° was circulated through the condenser, and cyanogen chloride (82 g, 1.2 mol) was distilled into the flask above the level of the well-agitated sodium azide–acetonitrile slurry at such a rate as to maintain a temperature between 0 and 12°. When addition was complete, the mixture was stirred for 30 min at 0–12°, then warmed to room temperature over 1 hr and stirred for an additional 1 hr. The system was slowly evacuated (caution[23]) through the cooled condenser (−5 to 0°) to a pressure of 120 mm and a pot temperature of 25° to remove excess cyanogen chloride. The solution was filtered under nitrogen pressure and the filter cake (caution[24]) was washed with two 50-ml portions of dry acetonitrile. The combined filtrates (350–375 ml) were stored at −20° in a bottle fitted with a serum stopper. An aliquot (1–2 ml) of the solution was added to trimethyl phosphite at 0° and the yield (98%) was determined by measuring the nitrogen evolved.

Cyanogen Azide–Toluene Solution.—Cyanogen chloride (120 g, 1.95 mol) was added to activated[22] sodium azide (32.5 g, 0.50 mol) suspended in dry toluene (60 ml) at 0–12° as described above. When addition was complete, the mixture was warmed slowly to room temperature (1 hr) and stirred for 20 hr. Dry toluene (100 ml) was added through the condenser and the mixture was evacuated slowly through the cooled (0°) condenser to 120 mm and a pot temperature of 25° (caution[23]). The mixture was filtered and the filter cake (caution[24]) was washed twice with dry toluene (2 × 25 ml). The combined filtrates (190–220 ml) were analyzed (yield 89–92%) and stored as described above at −20°.

Reduction of Cyanogen Azide.—Cyanogen azide prepared from sodium azide (3.25 g, 0.05 mol) and excess cyanogen chloride was dissolved in ether (50 ml) and treated with hydrogen sulfide at 0° for 1.5 hr and at 25° for 40 min. The solution was filtered and the filtrate was evaporated to dryness. The residue was taken up in water (20 ml), warmed on a steam bath, and filtered to remove sulfur. The filtrate was evaporated to dryness and the solid was sublimed (0.1 mm, 75°) to give analytically pure cyanamide, 1.7 g (80%), mp 46–47°, mmp 46–47° (lit.[25] mp 42°), having an infrared spectrum identical with that of an authentic sample.

***N*-Cyanotriphenylphosphine Imide (3).**—Triphenylphosphine (5.2 g, 0.02 mol) in acetonitrile (40 ml) was added slowly to cyanogen azide (0.02 mol) in acetonitrile (30 ml). When nitrogen evolution was essentially complete, acetone (10 ml) was added and the mixture was heated at 40° for 45 min. The mixture was filtered, and the filtrate was concentrated and cooled to separate 3 (5.3 g, 88%) which was recrystallized from acetonitrile, mp 193–195°, λ_{max}^{KBr} 4.58 (–C≡N), 6.59 μ (C_6H_5P).

Anal. Calcd for $C_{19}H_{15}N_2P$: C, 75.5; H, 5.0; N, 9.3; P, 10.3. Found: C, 75.7, 75.5; H, 5.4, 5.3; N, 9.6, 9.5; P, 10.1.

Trimethyl *N*-Cyanophosphorimidate (4).—Cyanogen azide (0.10 mol) in acetonitrile (40 ml) was added slowly to trimethyl phosphite (12.4 g, 0.10 mol) in ether (200 ml) with cooling at 15°. When nitrogen evolution was complete, volatiles were removed under reduced pressure and the crystalline residue was washed with cold ether to give the pure ylide (13.1 g, 80%), mp 56.4–56.8°, λ_{max}^{KBr} 4.42, 4.52 μ (–C≡N).

Anal. Calcd for $C_4H_9N_2O_3P$: C, 29.3; H, 5.5 N, 17.1; P, 18.9. Found: C, 29.3, 29.1; H, 5.7, 5.7; N, 17.2, 17.3; P, 18.4.

(21) Cyanogen chloride was obtained from the American Cyanamid Co. and was stabilized with trisodium phosphate (~7% wt). Eastman Organic Chemicals practical-grade sodium azide of 97–99% purity was used unless otherwise specified. Melting points were determined in a Mel-Temp apparatus and are not corrected.

(22) Activated sodium azide, necessary to give good yields of 1 in nonpolar media, was prepared as follows. Sodium azide (70 g) was dissolved in distilled water (280 ml) and stirred with hydrazine hydrate (10 ml) for 15 min. The solution was filtered and added dropwise to rapidly stirred dry acetone (3 l.). Excess acetone was decanted and the solid was collected in a pressure funnel and washed with dry acetone (100 ml). The fine powder (40–60 g) was dried under vacuum at 50° for 2 hr. Sodium azide is extremely toxic and the fine powder should be handled with care to avoid breathing the dust.

(23) Traces of cyanogen azide codistil with cyanogen chloride and may detonate if the cyanogen chloride evaporates from the condensate. This step can be avoided when cyanogen chloride does not interfere with the intended use. The volatiles are safely collected in a trap containing an acetone solution of a "deactivating" agent such as ethyl vinyl ether, norbornene, or trimethyl phosphite and cooled at −78°. The vacuum tubes are cut near the trap and both are rinsed into the trap with acetone. The trap is allowed to warm to room temperature and when nitrogen evolution ceases, the solution can be discarded with regard only for the toxic cyanogen chloride.

(24) The filter cake contains absorbed cyanogen azide and may detonate if dried. It is safely deactivated by leaching with excess acetone or by washing with acetone and finally a solution of one of the above "deactivators." The acetone extract is collected in a receiver containing one of the "deactivating" reagents. Washings and filter cake are safely discarded when nitrogen evolution ceases.

(25) W. Traube, F. Kegel, and H. E. P. Schulz, *Z. Angew. Chem.*, **39**, 1465 (1926).

Reduction of (Diazidomethylene)cyanamide (8) to Dicyandiamide.—Compound **8** was prepared according to the procedure of Hart:[16] mp 42.1–42.9° (lit.[16] mp 40.3°); $\lambda_{max}^{CHCl_3}$ 4.30 (w), 4.52 (sh), 4.63 (s), 6.25 (s), 7.56 (s), 8.90, 9.04 (m), 9.40 μ (w).

Compound **8** was reduced with hydrogen sulfide[14] to give dicyandiamide (75%), which was identified by melting point (210°), mixture melting point (210°) (lit.[26] mp 207–290°), and comparison of its infrared spectrum with that of an authentic sample.

Sodium 5-Azidotetrazole (6) from Cyanogen Azide and Sodium Azide.—*Caution: Sodium 5-azidotetrazole is exceptionally shock sensitive. See footnote 27 before attempting this synthesis.*

Cyanogen azide prepared in acetonitrile (20 ml) from sodium azide (3.25 g, 0.05 mol) and cyanogen chloride (12 g, 0.22 mol) was evacuated to 120 mm and a pot temperature of 25° to remove excess cyanogen chloride. The resulting solution was cooled at 5–10° while sodium azide (3.5 g, 0.05 mol) in water (15 ml) was added dropwise and then stirred at room temperature for 1.5 hr. The resulting solution was diluted with water (20 ml) and extracted with ether (3 × 25 ml). Sodium 5-azidotetrazole (2.65 g, 80%) was isolated from one-half of the aqueous layer as described below and identified by comparison of its infrared spectrum with that of an authentic sample.

Sodium 5-Azidotetrazole (6) from Cyanogen Bromide and Sodium Azide.—To a solution of sodium azide (3.8 g, 0.058 mol) in water (10 ml) at 0–5° was added (15 min) finely pulverized cyanogen bromide (6.8 g, 0.064 mol). The mixture was stirred at 0–5° for 30 min, and the cold solution was then extracted with ether (2 × 15 ml). The water layer was evaporated to dryness at 50° (1 mm). (*Caution:* The product may detonate if pressure is changed rapidly when the product is dry.) The resulting salt was extracted with hot acetone (3 × 25 ml). The extract was concentrated to about 35 ml and ether was added to precipitate **6** (2.56 g, 66%), λ_{max}^{KBr} 4.67, 6.84, 7.09, 8.15, 13.57 (s), 8.45, 8.86, 12.56 (m), 7.49, 8.96, 9.52, 9.82 μ (w).

Anal. Calcd for CN_7Na: C, 9.03; N, 73.70; Na, 17.28. Found: N, 73.61, 73.86; Na, 16.6.

5-Azidotetrazole.—*Caution: This compound is shock sensitive. See footnote 27 before attempting synthesis.*

An aqueous solution of **6** prepared as described above from sodium azide (7.6 g, 0.117 mol) and cyanogen bromide (6.2 g, 0.058 mol) was cooled in ice water and acidified with concentrated hydrochloric acid to pH 1. The solution was extracted with ether (3 × 50 ml), and the ether layer was dried and evaporated to dryness at room temperature under nitrogen to give 5-azidotetrazole (4.2 g, 65%) as white needles which were recrystallized once from chloroform, mp 79.6–80.2° (lit.[29] mp 72–73°), λ_{max}^{KBr} 3.25–4 (broad weak multiple bands), 4.67, 6.30, 7.08, 8.34 (s), 9.65, 12.76,13.78, 14.43 μ (m).

Anal. Calcd for CN_7H: N, 88.29. Found: N, 88.16.

Ammonium-5-azidotetrazole.—An aqueous solution of **6** prepared as described above from cyanogen bromide (6.2 g, 0.059 mol) and sodium azide (7.6 g, 0.117 mol) was acidified to pH 1 and extracted with ether (3 × 50 ml). The dried ether extract was saturated with anhydrous ammonia and filtered to separate pure ammonium-5-azidotetrazole[28] (caution[27]) as a white, crystalline solid (15 2 g, 95%), mp 185–186, λ_{max}^{KBr} 4.63, 6.77, 7.14 (s), 3.62, 3.19, 3.35, 7.03, 8.09, 8.74, 13.15 (m), 8.41, 9.52, 12.67 μ (w).

Anal. Calcd for CH_4N_8: N, 87.51. Found: N, 87.42.

Registry No.—**1**, 764-05-6; **3**, 4027-82-1; **4**, 17167-30-5; **6**, 35038-45-0: 5-azidotetrazole, 35038-46-1; ammonium-5-azidotetrazole, 35038-47-2.

Acknowledgment.—The phosphorus ylides were prepared and characterized by Dr. M. E. Hermes.

(26) E. C. Franklin, *J. Amer. Chem. Soc.*, **44**, 501 (1922).

(27) The explosive properties of sodium 5-azidotetrazole are described by E. Lieber and D. R. Levering, *J. Amer. Chem. Soc.*, **73**, 1313 (1951). The dry salt is extremely sensitive to friction, heat, electrical shock, and pressure. For example, a dry sample of **6** at 1-mm pressure will usually detonate if brought rapidly to atmospheric pressure. Great care and adequate protective equipment (shields, leather gloves, and jacket) should be used when preparing even small quanties of the *dry* compound. Samples larger than 0.1 g are best handled remotely. The salt can be prepared and handled safely in aqueous solution or as a free-flowing solid when moistened with water or mixed with an equal weight of mineral oil. We have prepared acetone solutions without event, but Lieber reports that such solutions containing traces of acetic acid may detonate and in this respect our procedure is safer.

Pure dry 5-azidotetrazole is less sensitive than its sodium salt but the same handling precautions apply. Ammonium-5-azidotetrazole is still less sensitive to shock but detonates when heated rapidly to ~190°.

(28) F. D. Marsh and D. W. Thatcher, U. S. Patent 3,374,188 (1968).

N-Cyanoaziridines and 1-Alkylalkylidenecyanamides from Cyanogen Azide and Olefins

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The reaction of molecular cyanogen azide with hydrocarbon olefins at 0–35° gives 1-alkylalkylidenecyanamides and/or 1-cyanoaziridines in high yields. Evidence is presented favoring a 1,3-dipolar concerted addition of the azide followed by opening of the resulting triazoline to a diazonium zwitterion and loss of nitrogen from this labile species to yield products. Linear and simple cyclic olefins generally produce alkylidenecyanamides as the major product, often to the exclusion of *N*-cyanoaziridines. With selected cyclic olefins this reaction is an effective means of forming either ring-enlarged or ring-contracted product. Ring-enlargement products and aziridines are also formed by reacting cyclic alkylidenecyanamides with diazomethane. The 1-alkylalkylidenecyanamides are readily hydrolyzed to ketones; the cyanogen azide reaction thus permits facile, low-temperature conversion of olefins to ketones. More highly substituted olefins often produce *N*-cyanoaziridines, and these compounds are obtained in high yield from polycyclic olefins such as norbornene and dicyclopentadiene. The *N*-cyanoaziridine produced from norbornene, 3-cyano-3-azatricyclo[4.2.1.0^{2,4}]octane, is cleaved with $LiAlH_4$ to the parent aziridine, which is readily converted to 7-aminonorbornane (by hydrolysis and dehalogenation) and *syn*-7-aminonorbornene (by hydrolysis and dehydrochlorination).

Since we reported the synthesis of cyanogen azide (N_3CN) in 1964,[1] two broad areas of chemical reactivity for this highly reactive compound have been defined. We disclosed at that time the facile addition of the molecular azide to olefins accompanied by nitrogen loss and formation of alkylidenecyanamides and *N*-cyanoaziridines. The reaction of cyanogen azide with acetylenes was recently reported[2] to give 1-cyanotriazoles which are in equilibrium with tautomeric α-diazo-*N*-cyanoimines. Other reported reactions of molecular

(1) F. D. Marsh and M. E. Hermes, *J. Amer. Chem. Soc.*, **86**, 4506 (1964); F. D. Marsh, U. S. Patent 3,410,658 (1968).

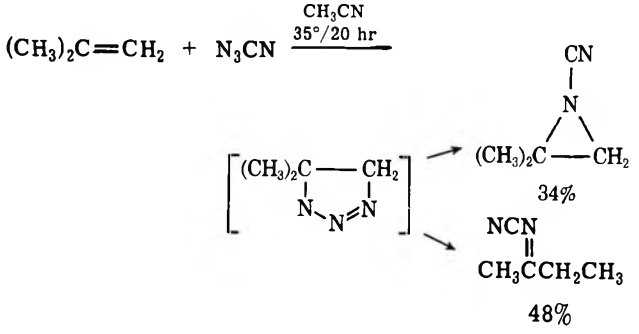
(2) M. E. Hermes and F. D. Marsh, *J. Amer. Chem. Soc.*, **89**, 4760 (1967); F. D. Marsh, U. S. Patent 3,322,782 (1967).

cyanogen azide include addition to norbornadiene[3] and polycyclic enamines.[4]

The second broad area of cyanogen azide chemistry grew from the observation that cyanogen azide decomposes to cyanonitrene[5] and nitrogen under very mild conditions. The nitrene reacts with alkanes to form cyanamides, with aromatics to form azepines, and with cyclooctatetraene, and "dimerizes" to form azodicarbonitrile. This paper will present results of addition of cyanogen azide to over 30 hydrocarbon olefins and discuss the chemistry of *N*-cyanoaziridines and 1-alkylalkyli denecyanamides, which are the products.

Results

Cyanogen azide solutions react with olefinic hydrocarbons within 24 hr at 0–35° to give high conversion to *N*-cyanoaziridines and/or 1-alkylalkylidenecyanamides with loss of nitrogen. Reaction conditions are chosen so that molecular cyanogen azide is the reacting species rather than thermally generated cyanonitrene. The reaction is illustrated for isobutylene.[6]



Cyanogen azide apparently adds exclusively in a single direction to an unsymmetrical olefin. In all cases, the nitrogen bearing the cyano group becomes attached to the more highly substituted olefinic carbon in the Markovnikov fashion.

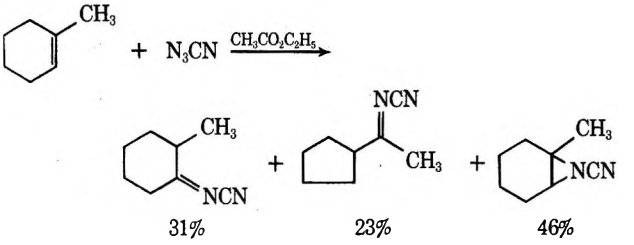
Formation of *N*-cyanoaziridines occurs by nitrogen loss and ring closure, and 1-alkylalkylidenecyanamides arise by rearrangement from the carbon bearing the –NCN group. Table I reports the products from 24 olefins, the yields, the per cent ring closure *vs.* rearrangement, and the structure and properties of alkylidenecyanamides obtained. Table II reports the properties of five *N*-cyanoaziridines obtained from olefins in Table I along with aziridines derived from norbornene, dicyclopentadiene, and tricyclopentadiene. The Experimental Section presents representative synthetic procedures.

The ratio of cyanoaziridine to alkylidenecyanamide varies greatly from olefin to olefin. In general, linear olefins, both terminal and internal, give high yields of alkylidenecyanamide by hydrogen migration, often to the exclusion of cyanoaziridines. Ethylene, propylene, 1-butene, 2-butene, 1-hexene, 1-decene, and 1-dodecene fall into this class. Simple cyclic olefins such as cyclopentene, cyclohexene, and cyclooctene are also converted exclusively to alkylidenecyanamides.

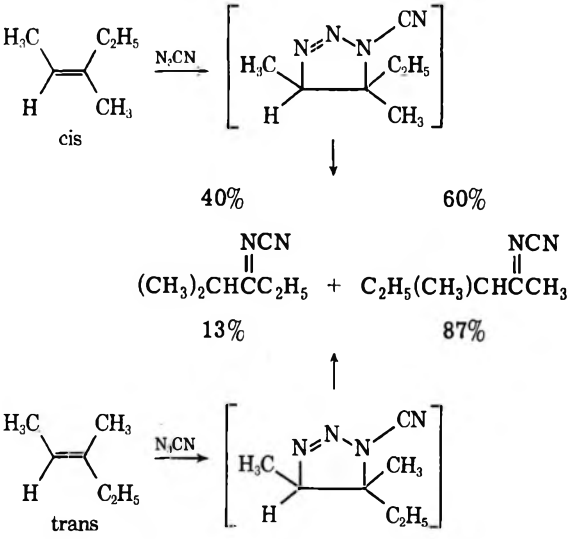
(3) A. G. Anastassiou, *J. Org. Chem.*, **31**, 1131 (1966).
(4) R. M. Scribner, *Tetrahedron Lett.*, **No. 47**, 4737 (1967).
(5) Pertinent references to the chemistry and properties of cyanonitrene are given by F. D. Marsh, *J. Org. Chem.*, **37**, 2966 (1972).
(6) In addition about 1% $(CH_3)_2C{=}NCN$ is formed from isobutylene. This C–C bond fragmentation is a major factor in only one olefin studied (1,1-dicyclopropylethylene).

More highly substituted olefins, particularly those having no hydrogen on the carbon to which the cyano-bearing nitrogen becomes attached, such as isobutylene, 2-methyl-1-butene, 3-methyl-1-butene, 3,3-dimethyl-1-butene, 1-methylcyclopentene, 1-methylcyclohexene, and methylenecyclohexane, often give significant yields of cyanoaziridine along with alkylidenecyanamides.

If two different alkyl groups are present at the carbon to which the –NCN becomes bonded, both may migrate. Thus, 1-methylcyclohexene gives in addition to the *N*-cyanoaziridine two alkylidenecyanamides, one a product of methyl migration, the other formed by methylene migration and ring contraction.



It is not possible to give a strict ordering of migratory aptitudes for the most substituted carbon, although hydrogen migrates to the exclusion of alkyl in all cases studied so far. However, steric factors play a role in determining to what extent each of two alkyl groups will migrate in a particular case. Thus, *cis*- and *trans*-3-methyl-2-pentene, in which methyl and ethyl may migrate, give different product mixtures.



We have studied the reaction of methylenecyclohexane with cyanogen azide in a variety of solvents and have noted a moderate effect on the product ratio (Table III).

Addition of cyanogen azide to the highly reactive double bond in the bicycloheptene system of norbornene, dicyclopentadiene, and tricyclopentadiene results in high yields of the corresponding *N*-cyanoaziridines.

The properties of these aziridines are given in Table II and the spectra are discussed in a later section in connection with proof of structure and chemistry of these compounds.

There are two general procedures for the olefin–cyanogen azide reaction. Cyanogen azide solutions may be combined directly with the olefin, or cyanogen

Table I

Alkylidenecyanamides from Olefins and N_3CN[h]

Olefin	Solvent	Product yield, %	Registry no.[i]	Alkylidene-cyanamide, %[a]	NCN– on carbon no.	Rearranged group	Bp, °C (mm)	$n^{25}D$
$CH_2=CH_2$	CH_3CN	14		0				
$CH_2=CH_2$	C_6H_6	53	35092-61-6; 35092-62-7	~90[b]	1	H	Amorphous solid	
$CH_2=CHCH_3$	CH_3CN	53	3285-27-6	~90	2	H	30 (0.1)[d]	1.4480
$CH_2=CHCH_2CH_3$	CH_3CN	86[c]	35092-64-9; 35092-65-0	100	2	H	31 (0.3)	1.4532
cis-$CH_3CH=CHCH_3$	CH_3CN	88	35092-64-9; 35092-65-0	100	2	H	35 (0.2)[d]	1.4538
trans-$CH_3CH=CHCH_3$	CH_3CN	78		100	2	H		1.4540
$CH_2=C(CH_3)_2$	CH_3CN	82[c]		59	2	CH_3	30 (0.4)	1.4517[e]
$(CH_3)_2C=CHCH_3$	CH_3CN	88[c]	35095-95-5; 35095-96-6	~85	2	CH_3	30 (0.2)	1.4528
$CH_2=CHCH(CH_3)_2$	CH_3CN	86[c]		~40	2	H	41 (0.35)	
$CH_2=C(CH_3)C_2H_5$	CNCl	65		~80	2	CH_3 ~50[f,i] C_2H_5 ~50[k]	45 (0.005)[d]	1.4514–1.4561
$CH_2=CH(CH_2)_3CH_3$	CNCl	38	35096-00-5; 35147-22-9	100	2	H	46–47 (0.07)	1.4570
$CH_3CH=CH(CH_2)_2CH_3$	CNCl	65	35096-01-6; 35096-02-7	100	2 ~40 3 ~60	H[f]	45 (0.05)	1.4560
$(CH_3)_2C=C(CH_3)_2$	CH_3CN	98	35096-03-8; 35096-04-9	92	2	CH_3	40 (0.05)	1.4570
$H_2C=CHC(CH_3)_3$	CH_3CN	96		74	2	H	34 (0.03)	1.4571
cis-$CH_3CH=C(CH_3)C_2H_5$	CH_3CN	54		100	3	CH_3 40[f,l] C_2H_5 50[m]	33 (5 μ)[d]	1.4576
trans-$CH_3CH=C(CH_3)C_2H_5$	CH_3CN	61		100	3	CH_3 17[f] C_2H_5 83	32 (5 μ)[d]	1.4578
$CH_2=CH(CH_2)_7CN_3$	CH_3CN	44	35096-08-3; 35096-09-4	100	2	H	70–71 (0.4 μ)	
$CH_2(CH_2)_2CH=CH$	CNCl	96	3550-39-8	100	1	H	52–57 (0.05)	1.4944
$CH_2(CH_2)_2CH=CCH_3$[g]	CH_3CN	~100		~65	1	CH_3		
$CH_2(CH_2)_3CH=CH$	CNCl	94	3285-19-6	100	1	H	25–26 (0.2 μ)	1.5025
$CH_2=C(CH_2)_3$	CH_3CN	79		100	1	~CH_2–	62–63.5 (0.05)	1.4937
$CH_2=C(CH_2)_5$	CH_3CN	61	3281-33-2	77	1	–CH_2–	96–103 (1)	
$CH_2(CH_2)_3CH=CCH_3$	EtOAc	79		54	1	CH_3 63[f,n]	69–77 (0.05)	
					1	–CH_2[o] 37		
$CH_2(CH_2)_5CH=CH$	CH_3CN	78	35096-17-4	100	1	H	78–94 (0.4 μ)	1.5113
Bicyclo[2.2.2]octene	EtOAc	~100		94	2	H	Isolated bicyclo[2.2.2]octanone after alumina hydrolysis	

[a] (Aziridine %) = 100 − (alkylidenecyanamide %). [b] Solid material, probably trimeric. [c] Crude, before distillation. [d] Pot temperature in short-path still. [e] Contaminated with aziridine. [f] Isomer mixture. [g] Product analyzed by proton magnetic resonance only. [h] Satisfactory analytical values (±0.4% for C, H, and N) were reported for all compounds except the ethylene adduct: Ed. [i] First registry number is for syn isomer; second is for anti isomer. [j] Registry number: 35095-99-9. [k] Registry numbers: 35095-97-7; 35095-98-8 (anti). [l] Registry numbers: 35096-05-0 (syn); 35096-06-1 (anti). [m] Registry numbers: 35096-07-2 (syn); 35147-23-0 (anti). [n] Registry numbers: 35147-24-1 (syn); 35096-14-1 (anti). [o] Registry numbers: 35096-15-2 (syn); 35096-16-3 (anti).

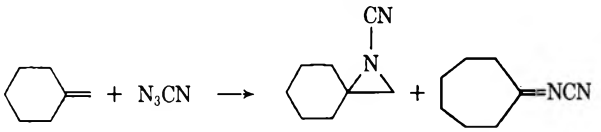
Table II

N-Cyanoaziridines[a]

Compd	Bp °C (mm)	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
N-Cyanoaziridine (1)	30–25 (0.2)	52.9	5.9	41.2	51.8	5.9	41.3
2-Methyl-*N*-cyanoaziridine (2)		Polymerized[c]					
2,2-Dimethyl-*N*-cyanoaziridine (3)		62.5	8.4	29.1	62.4	8.3	29.3
2,2-Pentamethylene-*N*-cyanoaziridine (4)		Polymerized					
2-Methyl-2,3-tetramethylene-*N*-cyanoaziridine (5)	55 (5 μ)[b]	70.6	8.9	20.6	69.6	8.9	20.3[c]
3-Cyano-3-azatricyclo-[3.2.1.$0^{2,4}$]octane (6)	72–74 (0.1)	71.6	7.5	20.9	71.6	7.8	20.8
9-Cyano-9-azatetracyclo-[5.3.1.$0^{2,6}$.$0^{8,10}$]-undecene-3 (7)	70[d]	76.6	7.0	16.3	76.7	7.2	16.6
13-Cyano-13-azapentacyclo-[9.3.1.$1^{3,9}$.$0^{4,8}$.$0^{12,14}$]-hexadecene-5 (8)	162–164[d]	80.7	7.6	11.8	79.8	7.4	12.1

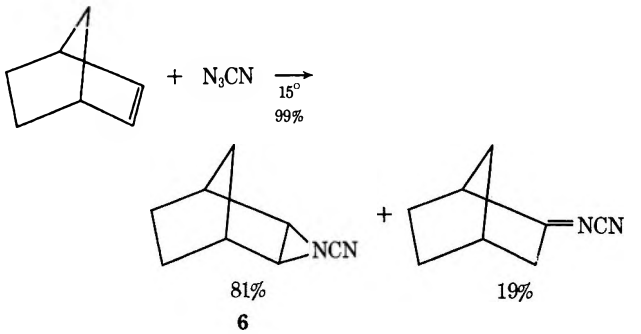
[a] Nmr data are collected in Tables V and VI. [b] Pot temperature of short-path molecular still. [c] Analyses were obtained on isomer mixtures before separation. [d] Melting point.

TABLE III

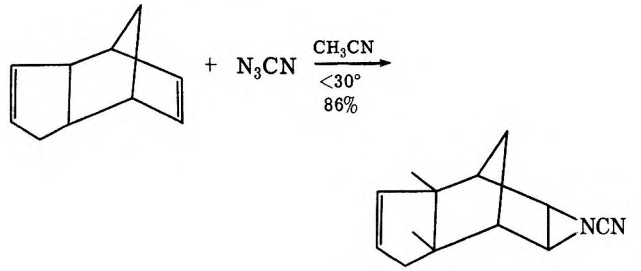


solvent	%	%
3:1 DMF–ethyl acetate	25	75
Ether	23	77
CH_3CN	30	70
Ethyl acetate	39	61
CH_3OH	48	52
3:1 acetic acid–ethyl acetate	75	25

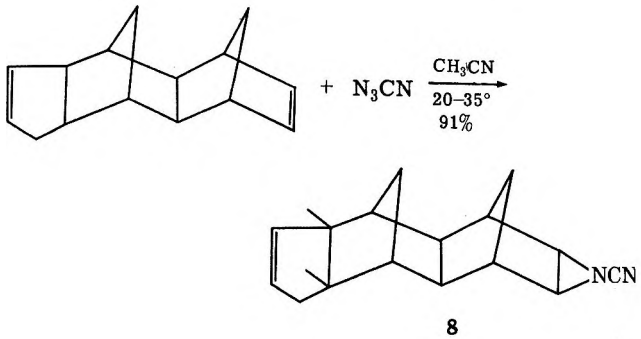
chloride may be added to a mixture of sodium azide and olefin, with or without added solvent. In this latter procedure, cyanogen azide reacts as it is formed. More volatile olefins (<5 C atoms) are best handled in barricaded steel pressure vessels.



6



7

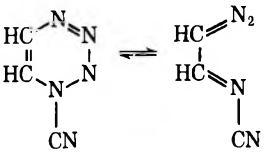


8

Mechanism.—The olefin and cyanogen azide form a cyanotriazoline as the first step, but this unstable triazoline decomposes instantaneously to products with nitrogen evolution by a mechanism believed to involve zwitterionic intermediates.

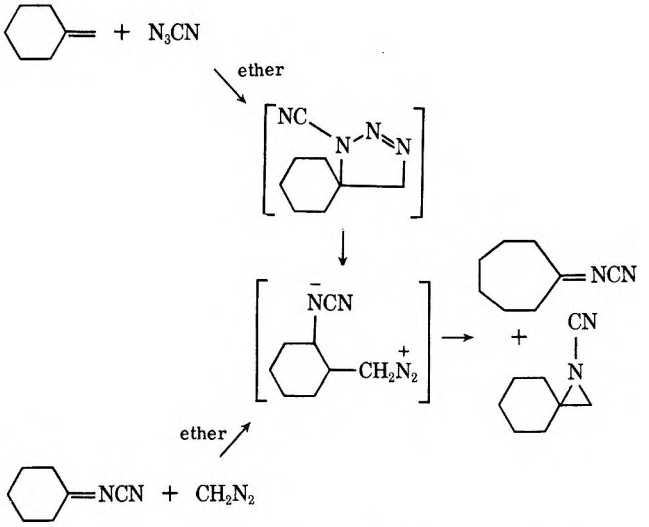
Cyanotriazolines have not been isolated as intermediates, but evidence indicates that the azide–oelfin reaction is a 1,3-dipolar, concerted addition. The evolved nitrogen is a measure of a second-order reaction, first order in each component, over essentially the whole conversion range. In addition, the rate is not greatly dependent on solvent polarity as would be expected for reactions involving highly polar intermediates in the rate-determining step. Table IV shows rate constants obtained from nitrogen evolution data.

In view of the demonstrated lability of 1-cyanotriazoles, prepared from N_3CN and acetylenes, which are in equilibrium with α-diazo-*N*-cyanoimines at room temperature involving heterolytic cleavage of the N-1–N-2 bond,[2] it is not surprising that cyanotriazolines are



unstable. Heterolytic N–N bond cleavage would lead to diazonium betaines, logical precursors of the formed products. Evidence has accumulated that such ionic intermediates are involved, and some description of this evidence is presented below.

A second method of preparing 1-cyanotriazolines was attempted. Addition of diazomethane to 1-methylethylidenecyanamide and to cyclohexylidene cyanamide did not give the expected triazoline; instead, elimination of nitrogen immediately occurred and alkylidenecyanamide and cyanoaziridine products results in ratios similar to those obtained by addition of cyanogen azide to the appropriate olefin. The following reaction path is suggested.



	Aziridine, %	Alkylidene cyanamide, %
N_3CN path	23	77
CH_2N_2 path	29	71

The inability to form stable triazolines by two atomic combinations reinforces the idea that they are unstable with respect to intermediates leading to alkylidene cyanamides and aziridines. Consideration of diazomethane addition mechanisms also indicates that the intermediate may well be the zwitterionic species shown, since such diazomethane reactions have been postulated

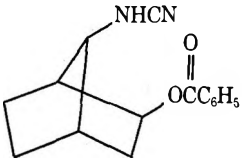
Table IV

Representative Cyanogen Azide–Olefin Reaction Rate Constants at 25°

Registry no.	Olefin	Solvent	$k \times 10^5$, l. mol^{-1} sec^{-1}
563-79-1	2,3-Dimethyl-2-butene	CH_3CN	2.8
		$C_2H_5O_2CCH_3$	2.0
		$C_6H_5CH_3$	4.9
1192-37-6	Methylenecyclohexane	CH_3CN	8.0
		$CH_3CO_2C_2H_5$	5.3
		$C_6H_5CH_3$	13.7
142-29-0	Cyclopentene	CH_3CN	18.6
108-87-2	1-Methylcyclohexane	CH_3CN	0.63

to proceed by nucleophilic attack on carbon to give ionic intermediates.[7]

A possible ionic intermediate has been intercepted in the N_3CN–norbornene reaction which produces **6** and bicycloheptylidenecyanamide. Cyanogen azide, in the presence of equimolar amounts of norbornene and benzoic acid, produces a reduced yield of **6** and the related cyanamide, in approximately 4:1 ratio, along with 23% of *syn*-7-cyanamido-*exo*-1-norborneol benzoate.



This benzoate, synthesized under conditions under which the normal reaction products are stable, is probably formed by protonation of the diazonium cyanamide, loss of nitrogen, and attack of the benzoate anion at the 7 position of the resulting carbonium ion. The fact that loss of nitrogen occurs to form the *unrearranged* aziridine, rather than rearranged azetidine, indicates that the products may arise from an ion-pair structure.

That the postulated ionic intermediate is not a planar carbonium zwitterion is shown by the addition of N_3CN to *cis*- and *trans*-3-methyl-2-pentene. Generation of different product ratios from the isomeric olefins shows that the intermediates cannot be identical and retain at least some steric integrity throughout the reaction.

The preferred explanation is ring closure or rearrangement with simultaneous nitrogen loss from a diazonium zwitterion.

Properties and Chemistry of Alkylidenecyanamides. —1-Alkylalkylidenecyanamides are high-boiling, unstable oils. Separation and isolation generally involve short-path distillation at low pressure because the compounds easily resinify.

Alkylidenecyanamides absorb strongly at 2200 ± 5 and 1620 ± 10 cm^{-1} and these bands have been assigned to the carbon–nitrogen triple and double bonds. The intensity of the >C=N– band is surprisingly high; it is the strongest band in the spectrum of the crude product mixture from norbornene, even though the product contains only 19% alkylidenecyanamide.

The nmr spectra of 1-methylalkylidenecyanamides reveal syn–anti isomers that interconvert only slowly at room temperature. Table V details the absorbances

Table V

Nmr of Methylalkylidenecyanamides

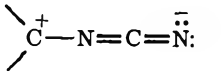
$CH_3\overset{NCN}{\overset{\|}{C}}R$,[a] R =	Syn CH_3, τ (%)	Anti CH_3, τ (%)
CH_3	7.59 (50)	7.72 (50)
C_2H_5	7.58 (79–84)	7.71 (16–21)
$(CH_3)_2CH$	7.58 (89)	7.78 (11)
$(CH_3)_3C$	7.58 (100)	(0)

[a] Neat samples.

observed for four of these compounds. 1-Methylethylidenecyanamide (from propylene) exhibits a chemical shift of 0.13 ppm between the two methyl resonances. The deshielded methyl is assigned syn to the cyano group on the basis of its coincidence with the 1-methyl resonance of 1-methyl-2,2-dimethylpropylidenecyanamide (from 2,3-dimethyl-2-butene) in which the bulky *tert*-butyl group determines the geometry and only one methyl resonance is observed.

In intermediate cases in which the methylidenecyanamide group is flanked by a single methyl and an ethyl or isopropyl group, both syn and anti isomers are observed. It is interesting to note that the syn/anti ratios are undoubtedly equilibrium values, since similar ratios are observed in the synthesis of 1-methylpropylidenecyanamide from four different butenes (1-butene, *cis*- and *trans*-2-butene, and isobutylene), in which case four different triazoline intermediates are postulated and the cyano group is directed exclusively adjacent to the methyl in three of them and adjacent to the ethyl in the fourth (1-butene). Similar isomeric ratios were found by Karabatsos for 2,4-dinitrophenylhydrazones, phenylhydrazones, and semicarbazides of methyl ethyl ketone, methyl isopropyl ketone, and methyl *tert*-butyl ketone and substituted *N*-nitrosoamines.[8]

The nmr spectra of the alkylidenecyanamides are temperature dependent. At elevated temperatures, the resonances of 1-methylethylidenecyanamide broaden and begin to coalesce. True coalescence has not been observed, since the compound is temperature sensitive and measurements have been limited to below 90°. This indication of low-temperature isomerization may be explained by the contribution of polar resonance structures to the stabilization of linear transition states.



Shechter has recently reported temperature dependency of alkylidenesulfonamides of similar structure, in which two methyl resonances (2:1 ratio) coalesce to a single line on heating to 140°.[9]

Alkylidenecyanamides are readily converted to the corresponding ketones by dilute aqueous acid or base, or silver nitrate solution.

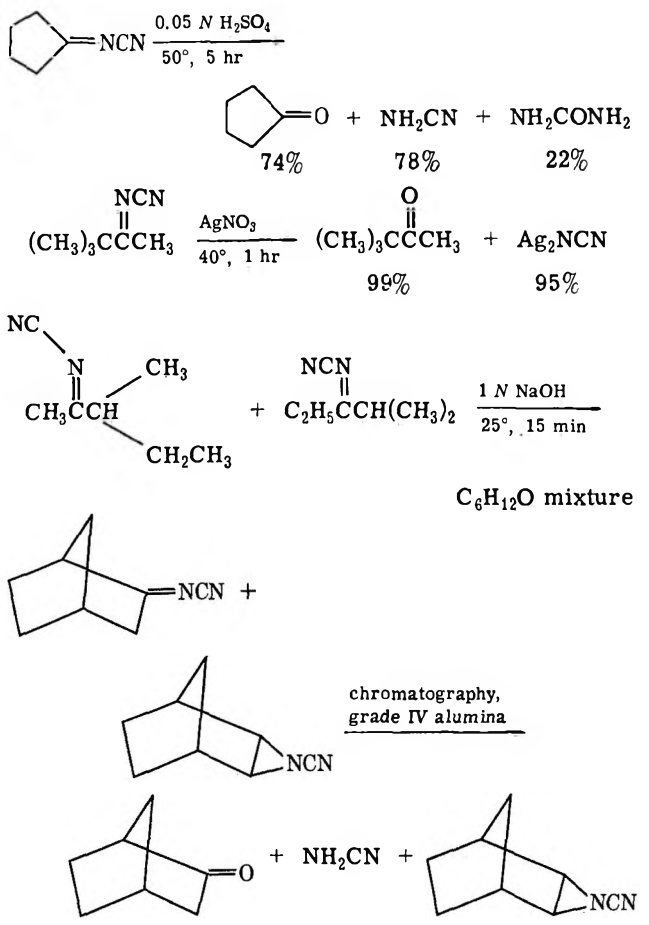
Cyanogen azide thus affords a convenient route from olefin to ketone, and high yields may be obtained using concentrated solutions and simple work-up procedures.

Semicarbazides, oximes, and phenylhydrazones may be obtained directly from alkylidenecyanamides on

(7) P. Kadaba and J. O. Edwards, *J. Org. Chem.*, **26**, 2331 (1961). H. House, E. Grubbs, and W. F. Gannon, *J. Amer. Chem. Soc.*, **82**, 4099 (1960).

(8) G. J. Karabatsos, *et al.*, *ibid.*, **84**, 753 (1962); **85**, 3624 (1963); **86**, 3351 (1964); **86**, 4373 (1964).

(9) R. F. Bleiholder and H. Shechter, *ibid.*, **90**, 2131 (1968).



treatment with standard reagents. Methylalkylidenecyanamides are oxidized with sodium hypoidite (iodoform test). A number of *tert*-alkylcyanamides have been prepared by addition of Grignard reagents to isopropylidenecyanamide.

$$(CH_3)_2C{=}NCN + RMgBr \longrightarrow R(CH_3)_2CNHCN$$

$$R = CH_3,\ C_2H_5,\ C_6H_5$$

Properties and Chemistry of *N*-Cyanoaziridines.—Several *N*-cyanoaziridines[10] have been isolated and purified during this study. Cyanoaziridines are somewhat lower boiling than alkylidenecyanamides formed from the same olefins, and separation can sometimes be achieved by careful distillation. Chromatography of olefin–N_3CN product mixtures on activated neutral alumina has afforded *N*-cyanoaziridine–ketone mixtures from which the pure *N*-cyanoaziridines **2**–**6** have been isolated (Table II). These aziridines show strong C≡N absorption near 2200 cm^{-1} with no C=N at 1640 cm^{-1}. Nmr spectra are consistent with the structures proposed (Table VI).

In all cases the nmr spectra are consistent with rapid inversion about the pyramidal nitrogen, in marked contrast to the spectra of the *N*-chloro analogs of **2** and **3** and the *N*-amino analogs of **1** and **3**, which show slow nitrogen inversion on the nmr time scale up to 120[11] and ~150°, respectively. In fact, the invertomers of the chloro analog of **2** have been isolated by Brois. The

(10) B. R. Balser and T. Neilson, *J. Org. Chem.*, **29**, 1057 (1964), prepared the only previously reported cyanoaziridine, methyl 4,6-*O*-benzylidene-*N*-cyano-2,3-dideoxy-2,3-imino-α-D-allopyranoside.

(11) S. J. Brois, *J. Amer. Chem. Soc.*, **90**, 506, 508 (1968); S. J. Brois, *Tetrahedron Lett.*, 997 (1968).

TABLE VI
PROTON MAGNETIC RESONANCE OF SIMPLE CYANOAZIRIDINES (τ)

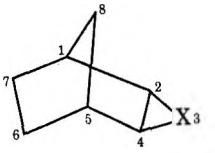
Compd	$-CH_2N$	CHN	CH_3CN	Others
1	7.53			
2	(6.95 to 7.83; 3 H) (12 line)		8.58 (doublet) (J = 5 cps)	
3	7.66		8.57	
4	7.61			$-(CH_2)_5-$ 8.39 (10 H)
5		7.25 (triplet) (J = 3 cps)	8.44	$-CH_2CN$ 8.05 multiplet (4 H) $-CH_2CH_2-$ 8.55 multiplet (4 H)

rapid nitrogen inversion in *N*-cyanoaziridines as compared to the halo compounds is not surprising in view of the ready thermal isomerization of the alkylidenecyanamides.

The cyanoaziridines **1**–**5** are unstable oils which decompose readily, particularly under basic conditions.

The aziridines **6**, **7**, and **8**, which are the major products formed from norbornene, dicyclopentadiene, and tricyclopentadiene, are much more stable and are readily isolated by distillation or crystallization.

The nmr spectrum of **6** (Table VII lists nmr spectra of several polycyclic aziridines) is similar to those of the norbornene–benzenesulfonyl azide adduct **9**,[12] norbornene oxide (**10**),[13] and 3,3-dichlorotricyclo[3.2.1.$0^{2,4}$]-octane (**11**).[14] In all cases the anti 8 proton is observed



6, X = NCN
9, X = NSO_2Ph
10, X = O
11, X = CCl_2

at τ 9.1–9.4 coupled to the syn proton with $J \cong 10$ cps. The syn 8 proton is generally hidden by ethano bridge absorption. Moore has suggested that this high-field absorption is caused by bending of the methano bridge under steric pressure of the group at position 3 so that the anti H proton is crowded toward the exo protons at C_6 and C_7, thus becoming highly shielded. The syn 8 hydrogen has been identified in two ways. In the dichlorocarbene–norbornene adduct **11**,[14] proximity of the syn 8 hydrogen to the chlorine at C-3 deshields it sufficiently so that it appears at τ 7.85 (downfield from hydrogens at C-2, C-4, C-6, and C-7. In addition, Moore found for **11** and Franz, Osuch, and Dietrich[12c] for **9** and **10** that spectra run in benzene solution[15] show large shifts to higher field for all protons save syn-C-8.

(12) (a) J. E. Franz and C. Osuch, *Tetrahedron Lett.*, 837 (1963); (b) L. H. Zalkow and A. C. Oehlschlager, *J. Org. Chem.*, **28**, 3303 (1963); (c) J. E. Franz, C. Osuch, and M. W. Dietrich, *ibid.*, **29**, 2922 (1964).

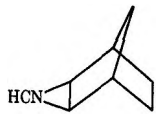
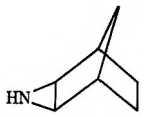
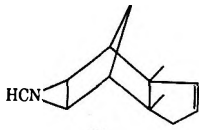
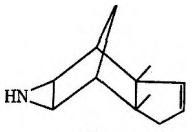
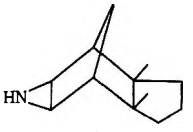
(13) K. Tori, K. Kitahonoki, Y. Takano, H. Tanida, and T. Tsuji, *Tetrahedron Lett.*, 559 (1964).

(14) W. R. Moore, W. R. Moser, and J. E. LaPrade, *J. Org. Chem.*, **28**, 2200 (1963).

(15) P. Laszlo and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **86**, 1171 (1964), have discussed the large solvent effect of benzene on substituted norbornene spectra.

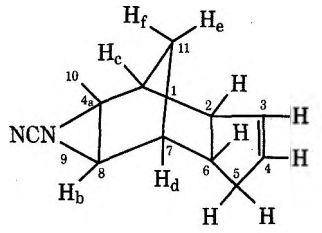
TABLE VII

NMR SPECTRA OF POLYCYCLIC AZIRIDINES (τ)

Compd	HCN	Bridgehead CH	Methano bridge CH	Others
 6	7.0 (2 H)	7.4 (2 H)	Anti, 9.2 doublet J = 10 cps (1 H)	Ethano bridge and anti methano bridge CH 8.4–8.8 (5 H)
 12	8.0 (2 H)	7.6 (2 H)	Anti, 9.3 doublet J = 10 cps (1 H)	Ethano bridge and anti methano bridge CH 8.3–8.7 (5 H)
 17	6.9 doublet J = 5 cps (1 H) 7.2 doublet J = 5 cps (1 H)	6.8 multiplet (1 H)	Anti, 9.1 doublet J = 10 cps (1 H) Syn, 8.5 doublet J = 10 cps (1 H)	Olefinic 4.3 multiplet (2 H) Remainder 6.9–7.9 (5 H)
 18	8.1 doublet J = 5 cps (1 H) 7.8 doublet J = 5 cps (1 H)	6.7 multiplet (1 H) 7.2 multiplet (1 H)	Anti, 9.0 doublet J = 10 cps (1 H) Syn, 8.4 doublet J = 10 cps (1 H)	Olefinic 4.1 singlet (2 H) NH 9.6 (1 H) Remainder 7.3–7.7 (4 H)
 19	7.9 (2 H)	7.7 (2 H)	Anti, 9.2 doublet J = 10 cps (1 H)	NH 10.0 (1 H) CH 7.6 (2 H) Trimethylene bridge } 8.0–8.7 Anti methano CH } (7 H)

This proton appears as a doublet, $J \cong 10$ cps, split to pentuplets ($J \cong 1$ cps). We have repeated this latter experiment on **6** with similar results.

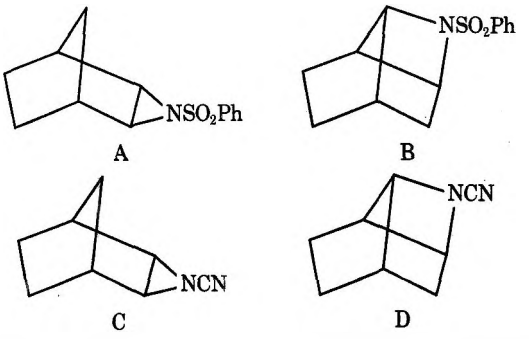
The nmr spectrum of **7**[16] is similar to that of **6**; how-



7

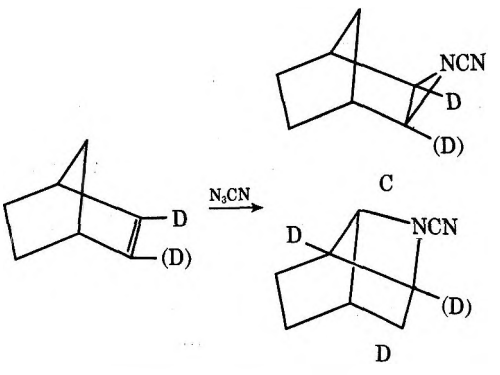
ever, protons H_a and H_b on the carbon α to nitrogen are chemically shifted because of the asymmetry introduced by the double bond. The bridgehead protons H_c and H_d also are chemically shifted, one at τ 6.8, the other under the peak at τ 6.9–7.9 which contains four other saturated CH. The anti 11 proton is at τ 9.1 (J = 10 cps) and the syn 11 stands clear of other saturated CH at τ 8.5 (J = 10 cps).

It became necessary to prove the structures of **6** and **9** after Zalkow[12b] alleged on the basis of ring-opening reactions that the structure of **9** could best be explained as the azetidine B rather than the aziridine A. Osuch[12c] demonstrated conclusively that **9** is A and we have used a similar method to show that **6** is C rather than D. Norbornene was treated with amylsodium and then



A B C D

deuterium oxide to give norbornene-*2*-*d*[17] containing 0.9 deuterium per molecule. Deuterated **6** obtained from this compound showed the τ 7.0 peak to be diminished to 1.1 H compared to the bridgehead absorption at τ 7.4 (2.0 H). Rearrangement to D requires one-half of the deuterium to terminate at the bridgehead



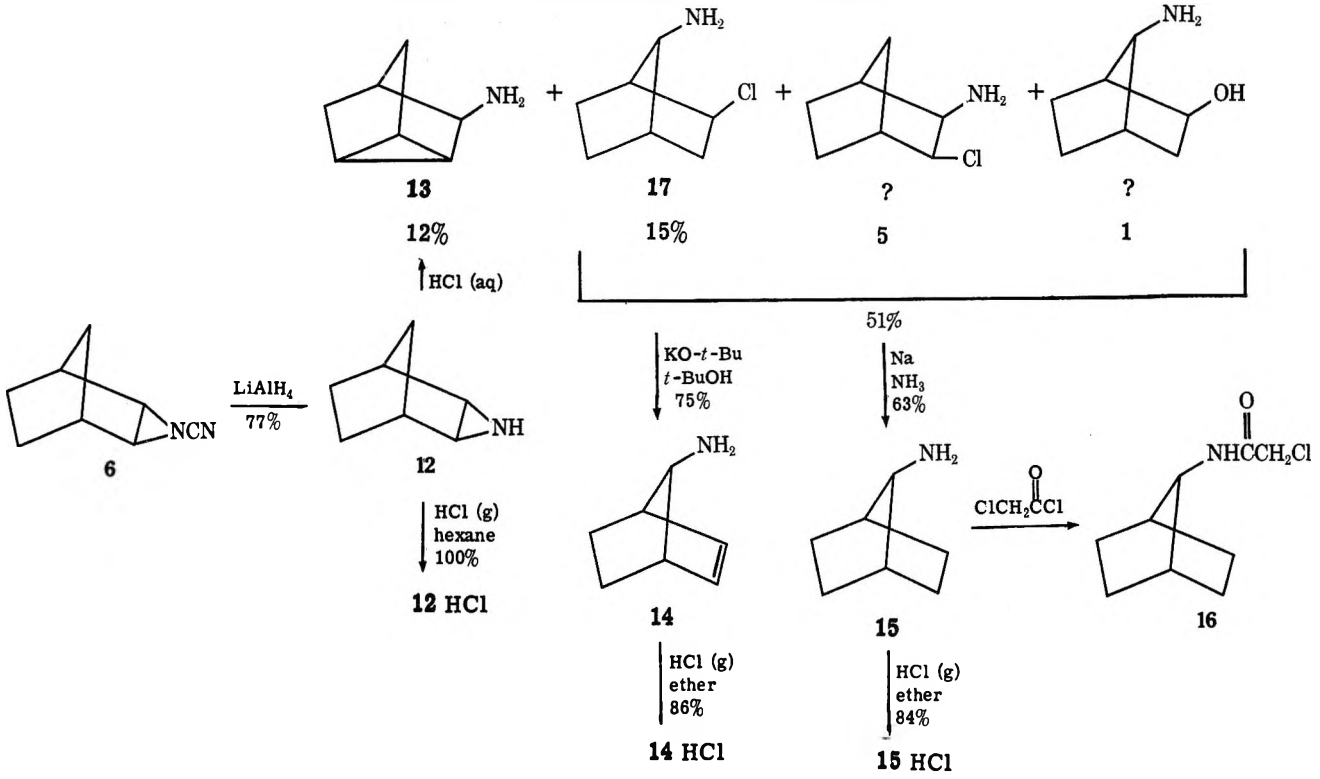
C D

(16) L. H. Zalkow, A. C. Oehlschlager, G. A. Cabat, and R. L. Hale, *Chem. Ind. (London)*, 1556 (1964), have commented briefly on the nmr of the dicyclopentadiene–benzenesulfonyl azide adduct similar to **7**.

(17) R. A. Finnegan and R. S. McNees, *ibid.*, 1450 (1961); *J. Org. Chem.*, **29**, 3234 (1964), have shown that on carbonation of the alkyl sodium–norbornene product only norbornene-2-carboxylic acid results.

CHART I

CHEMISTRY OF 3-CYANO-3-AZATRICYCLO[3.2.1.0^{2,4}]OCTANE (6) AND DERIVATIVES



with the remainder on the carbon α to nitrogen, thus decreasing each of these peaks an equal amount ($\sim^3/_4$ of their undeuterated intensity). Aziridine formation results in no rearrangement and explains the ratio observed.

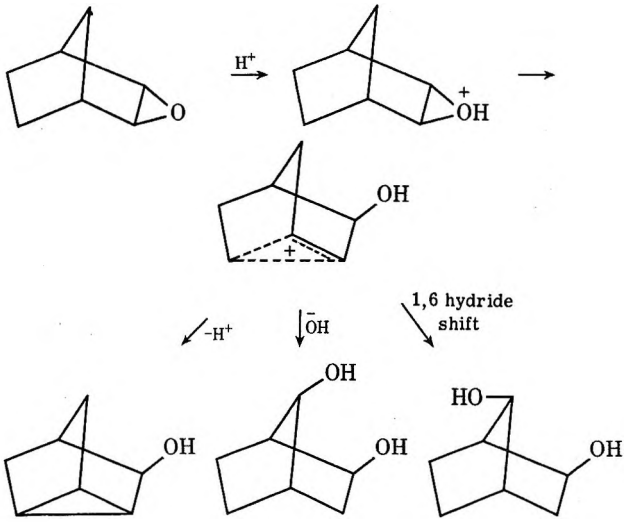
Reduction of **6** with lithium aluminum hydride (Chart I) produces the aziridine **12** in 77% yield.[18] The hydrochloride may be prepared quantitatively from hexane solution. The nmr spectrum of **12** is similar to that of **6**; however, removal of the cyano group causes an upfield shift of the HCN of 1.0 ppm.

Hydrochloric acid hydrolysis of **12** gives at least four amines. Distillation of the product yielded 3-aminonortricyclene (**13**) (containing a minor unsaturated impurity) in 12% yield. The structure of **13** was deduced from elemental analysis, spectra, and comparison with authentic material. Authentic **13** was prepared from nortricyclanone[19] and had identical infrared and nmr spectra with those of **13** obtained from **12**.

The higher boiling fraction from this hydrolysis (41–51%) was shown by gas chromatography to consist of three amines in the ratio 15:5:1. Elemental analysis indicated a chloroamine mixture containing an oxygenated material. The amine mixture was dehydrochlorinated with potassium *tert*-butoxide in 1-butanol at 80°. Only the major component reacted and a 75% yield of *syn*-7-aminonorbornene (**14**) was obtained and converted to the hydrochloride in 86% yield. The nmr and infrared spectra of **14** are identical with the spectra reported for the compound by Tanida, *et al.*[18]

The amine mixture was treated with sodium in liquid ammonia. All components reacted and a 63% yield of 7-aminonorbornane (**15**) contaminated with ~10% of **14** was obtained. Pure **15** was obtained by crystallization of **15** HCl from nitromethane. The structure of **15** was established by analysis, spectra, and conversion to the chloroacetamide **16**.[20] Thus, the major hydrolysis product of the amine **12** appears to be *syn*-7-amino-*exo*-2-chloronorbornane (**17**).

Winstein and Stafford[21] studied hydrolysis of 2,3-epoxynorbornane by perchloric acid. Three products were obtained: nortricyclanol (7%), *syn*-7-*exo*-2-dihydroxynorbornane (51%), and 12% of an isomeric diol formed by 1,6 hydride shift, *anti*-7-*exo*-2-hydroxynorbornane. Hydrolysis of the epoxide with 48% hydrogen bromide led to a 15–20% (isolated) yield of *syn*-7-bromo-*exo*-2-hydroxynorbornane along with several



(18) H. Tanida, T. Tsuji, and T. Irie, *J. Org. Chem.*, **31**, 3941 (1966), prepared **12** by hydrolysis of the carbomethoxyaziridine.

(19) We thank Dr. J. R. Roland of this laboratory for the sample of **13**.

(20) W. R. Boehme, M. L. Graeme, W. G. Scharpf, E. Siegmund, E. Schipper, and M. Tobkes, *J. Med. Pharmacol. Chem.*, **4**, 183 (1961).

(21) E. T. Stafford, Dissertation, University of California at Los Angeles, 1958.

other products not further investigated, although the authors assume that nortricyclanol and *anti*-7-bromo-*exo*-2-hydroxynorbornane are present.

These results are similar to hydrolysis of **12** except for the identity of the second and third components of the high-boiling mixture. It is unlikely that either of the high-boiling materials accompanying **17** is *anti*-7-amino-*exo*-2-chloronorbornane, since simultaneous dehydrohalogenation should occur. A more likely explanation is that the minor of the two is *syn*-7-amino-*exo*-2-hydroxynorbornane (supported by elemental analysis), and the more abundant is probably 2-amino-3-chloronorbornane, which may not dehydrohalogenate under the conditions of the reaction.

Lithium aluminum hydride reduction of **7** produced the aziridine **18** in 93% yield. Reduction of **18** with hydrogen over PtO_2 gave the saturated aziridine **19** in which the hydrogens at C-2 and C-3 are magnetically equivalent, consistent with aziridine rather than azetidine structures for **7**, **18**, and **19** (Table VI).

Experimental Section

Warning.—Cyanogen azide is a hazardous material. It should be handled only in solution. Concentration to give pure material will result in volent detonation by heat or shock.

General Synthetic Methods.—Two procedures have been used for the olefin–cyanogen azide reaction. The first involves synthesis and simultaneous reaction of the azide with the olefin; excess olefin is often used as the reaction medium. Examples of this procedure given are the reactions with isobutylene and cyclopentene. This procedure is a convenient, one-step synthesis of alkylidenecyanamides and aziridines and avoids accumulation of large amounts of the azide.

In the second procedure, cyanogen azide is prepared in a solvent and the olefin is added to the preformed cyanogen azide solution with cooling or heating as dictated by the reactivity of the particular olefin. The procedures for preparation of cyanogen azide solutions are reported by Marsh.[22]

1,2,2-Trimethylpropylidenecyanamide. Reaction of an Olefin with Preformed Cyanogen Azide.—A 500-ml flask equipped with an ice-cooled condenser, magnetic stirrer, dropping funnel, thermometer, nitrogen bubbler, and gas inlet tube was flame dried and cooled to room temperature under nitrogen. The exit of the condenser was attached through a Dry Ice trap to a wet-test meter. Activated sodium azide (32.5 g, 0.5 mol) and dry acetonitrile (200 ml, 156.6 g) were added and the flask was cooled in an ice–salt bath. Cyanogen chloride (97.4 g, 1.58 mol) was distilled into the stirred reaction mixture over 1.75 hr at such a rate as to maintain a reaction temperature between 4 and 18°. When addition was complete, the reaction mixture was allowed to warm slowly to room temperature and pure 2,3-dimethyl-2-butene (88.3 g, 1.05 mol) was added. The mixture was heated at 30–38° for 16 hr, during which time approximately 0.5 mol of nitrogen was liberated. The solution was then cooled to room temperature, diluted with ether (100 ml), and filtered. Removal of the solvent and unreacted olefin from the filtrate at 0.3 mm and room temperature on a rotary evaporator gave a light straw-colored oil (60.65 g, yield 98%). Distillation of this product in a short-path still at 0.2-mm pressure and a pot temperature of 37–38° gave four colorless fractions (60.34 g, yield 97.2%, $n^{25}D$ 1.4568–1.4581).

Infrared and nmr analysis of the combined fractions indicated that the product consisted of 1,2,2-trimethylpropylidenecyanamide (92%) and *N*-cyanotetramethylaziridine (8%). Fractionation of a 31.7-g aliquot of the oil in a 17 in. × 8 mm spinning-band column separated 13 g of pure 1,2,2-trimethylpropylidenecyanamide [bp 36–38° (0.1 mm), $n^{25}D$ 1.4571] having only two unsplit resonance peaks in a 1:3 ratio at τ 7.58 and 8.79.

The lowest boiling fraction boiled very close to the main product and was not obtained in a pure form. Analysis of this fraction by nmr indicated that it contained approximately 18% of *N*-cyanotetramethylaziridine, as indicated by a single unsplit resonance at τ 8.60, and 82% of 1,2,2-trimethylpropylidenecyanamide.

Cyclopentylidenecyanamide. Simultaneous Generation and Use of Cyanogen Azide.—A 300-ml flask equipped with an ice-cooled condenser, gas inlet, nitrogen bubbler, and magnetic stirrer was flame dried and cooled to room temperature under nitrogen. Sodium azide (9.75 g, 0.15 mol) and cyclopentene (23 g) were added and the flssk was cooled in a Dry Ice–acetone bath. Cyanogen chloride (48.8 g, 0.78 mol) was added and the mixture was allowed to warm to reflux temperature (16–18°) and stirred at this temperature for 22 hr, during which time nitrogen was liberated. The reaction mixture was cooled to 10°, diluted with dry ether (50 ml), and filtered under nitrogen. The solvent was removed from the filtrate on a rotary evaporator at 1-mm pressure and 40° to give a clear yellow oil (15.85 g, 98% yield). Distillation of the oil in an acid-washed short-path still gave a colorless product (15.2 g, 94% yield), the main fractions of which had essentially constant refractive indices and melting points (determined by differential thermal analysis). A freezing-point curve showed a melting point of −20°.

Absorption bands in the infrared spectrum at 4.55 (C≡N) and 6.1 μ (>C=N–) and the mass spectrometric pattern were in agreement with the proposed cyclopentylidenecyanamide structure. A complex envelope in the nmr pattern at τ 7.17–7.63 and a second and equal weight complex pattern at τ 7.75–8.2 are in agreement with those expected for the four protons most remote from the functional group and the four protons flanking the CN=CN group.

1-Cyano-2,2-dimethylaziridine and 1-Methylpropylidenecyanamide. Pressure Tube Reaction.—Two 80-ml Hastelloy-lined pressure vessels were charged with 6.5 g (0.1 mol) of sodium azide and 20.3 g (26 ml) of acetonitrile and cooled, and to each was added 12 g (0.20 mol) of cyanogen chloride and 16 g (0.29 mol) of isobutylene. After the tubes were shaken for 20 hr at 35–36°, the contents were removed, combined, and filtered to remove the salt, and the filtrate was evaporated to remove the volatiles. Distillation through a molecular-type still gave a 50% yield of a mixture of 2,2-dimethyl-1-cyanoaziridine and 1-methylpropylidenecyanamide, boiling at a pot temperature of 40–50° (0.25 mm).

In a similar experiment at 26–27°, an 82% yield of the $C_5H_8N_2$ mixture was obtained and was shown by nmr to be 41% of 2,2-dimethyl-1-cyanoaziridine and 59% of 1-methylpropylidenecyanamide.

In a third experiment the isomer mixture was distilled through a 24 in. × 8 mm spinning-band column, and an essentially pure sample of 2,2-dimethyl-1-cyanoaziridine was obtained, bp 24–25° (0.4 mm), $n^{25}D$ 1.4422.

3-Cyano-3-azatricyclo[3.2.1.0^{2,4}]octane (6).—A solution of 50 g (0.54 mol) of norbornene in 100 ml of acetonitrile was added slowly to 0.3 mol of cyanogen azide in 100 ml of acetonitrile. The temperature of the solution was kept below 30° with ice cooling. The theoretical amount of nitrogen was evolved in 1 hr. The mixture was then warmed to 55° for about 15 min to remove excess cyanogen chloride, diluted with acetone (50 ml), and filtered under nitrogen to separate the by-product, sodium chloride. This salt gave a negative test for azide ion with 5% ferric chloride solution. Removal of the solvent and unreacted bicyclo[2.2.1]heptene on a rotary evaporator at 50° (0.3 mm) gave a light straw-colored, mobile oil (39.8 g, 99%) having an infrared spectrum essentially identical with that of the distilled product. Distillation of this product through a short-path still at 0.2 mm pressure gave four fractions (34.4 g, 96%), bp 72–74° (0.1 mm), $n^{25}D$ 1.5142–1.5150. The infrared spectrum of each fraction was essentially identical, showing strong absorptions at 4.52 (CN) and 6.07 μ (C=N).

Nmr analysis of the product shows it to be 81% aziridine **6** and 19% alkylidenecyanamide.

Pure **6** can be obtained as follows. The crude product mixed in ether solution is shaken with 1 *N* NaOH solution, which hydrolyzes the alkylidenecyanamide to norcamphor. The resulting ether solution is dried, solvents are removed, and distillation easily separates the lower boiling ketone from **6**.

Reaction of Cyanogen Azide with Norbornene in the Presence of Benzoic Acid.—A solution containing 0.076 mol of cyanogen azide in 50 ml of acetonitrile was added to a stirred suspension of 12.2 g (0.1 mol) of benzoic acid and 9.4 g (0.1 mol) of norbornene in 100 ml of acetonitrile. External cooling was employed to keep the reaction temperature below 30°. Over a 0.5-hr period 1.89 l. (100%) of nitrogen was evolved. The solvents were evaporated

(22) F. D. Marsh, *J. Org. Chem.*, **37**, 2966 (1972).

and the residual oil was dissolved in ether and extracted with sodium bicarbonate solution until there was no further evolution of carbon dioxide. From the water extracts on acidification was obtained 5.6 g (46%) of benzoic acid. The ether solution was dried over magnesium sulfate and evaporated to give 14.6 g of an oil. On cooling to −20°, a crystalline solid was formed and on treatment with 50 ml of cooled carbon tetrachloride and filtration 4.50 g (23%) of *syn*-7-cyanamido-*exo*-1-norborneol benzoate, mp 105–106°, was obtained.

Anal. Calcd for $C_{15}H_{16}N_2O_2$: C, 70.3; H, 6.3; N, 10.9. Found: C, 69.8; H, 6.4; N, 11.0.

The nmr spectrum of this material (20% in deuterioacetone) showed the aromatic protons (5) at τ 2.4 and 2.9 and showed NH (1) at τ 4.7. A triplet appears at τ 5.5 (1) and a quartet (1) appears at τ 7.0. A multilined band envelope appears at τ 7.85–9.4 (8).

9-Cyano-9-azatetracyclo[5.3.1.0.^{2,6}.0^{8,10}]undec-3-ene (7).—Cyanogen chloride was distilled at 1 g/min into an agitated slurry of 66 g (0.50 mol) of dicyclopentadiene, 32.5 g (0.50 mol) of sodium azide, and 300 ml of acetonitrile. The initial temperature was 25° and the reaction temperature was held below 30° with ice cooling. After 45 g (~0.75 mol) of cyanogen chloride was added, the mixture was allowed to stand for 5 hr, after which 12.4 l. of nitrogen had evolved (99%). The precipitated salt was removed by filtration, and a mixture of 150 ml of alcohol and 150 ml of ammonium chloride solution was added to hydrolyze any alkylidenecyanamides present. After 1 hr, the organic solvents were removed by evacuation and ether was added to the two-phase system (water–product) which remained. The water was removed; the ether solution was extracted with water, sodium bisulfite, and finally water, and was dried over magnesium sulfate; and the ether was removed on a rotating evaporator. Crystalline **7**, 74 g (86%), resulted which was recrystallized from 5:1 hexane–ether, mp 69.8–70.2°. The ir spectrum of this material showed it to be pure aziridine containing no ketones or alkylidenecyanamide.

Distillation of the crude reaction mixture without removing the isomeric alkylidenecyanamides by hydrolysis gave a 66% yield of $C_{10}H_{12}N_2$ isomers, bp 91–105° (1 μ). This mixture probably contains the alkylidenecyanamides formed by addition in both directions to both double bonds.

13-Cyano-13-azapentacyclo[9.3.1.1^{3,9}.0^{4,8}.0^{12,14}]hexadec-5-ene (8).—A solution of 0.15 mol of cyanogen azide in 88 ml of acetonitrile was added to a slurry of 29.7 g (0.15 mol) of tricyclopentadiene in 75 ml of acetonitrile at such a rate that the temperature remained below 35°. After 2 hr, 0.15 mol of nitrogen was evolved. Filtration yielded 29.2 g (82%) of off-white, crystalline **8**, mp 155–160°. Concentration of the acetonitrile solution gave an additional 3.3 g of **8** for a total of 32.5 g (91%). The compound was recrystallized from acetonitrile, mp 162–164°. Infrared and nmr spectra are consistent with the aziridine structure.

Hydrolysis of Cyclopentylidenecyanamide. A. Sulfuric Acid.—Cyclopentylidenecyanamide (5.4 g, 0.05 mol) was added to 25 ml of distilled water and the mixture was acidified with 6 drops of 10% sulfuric acid. The solution was stirred at 45–59° for 5 hr. After standing at room temperature for 16 hr, evaporation of the mixture to dryness under reduced pressure (0.03 mm, 40°) gave 2.35 g of a white, crystalline solid. Extraction of this solid with ether and evaporation of the extract gave crystalline cyanamide (1.65 g, 78.6% yield) which was identified by infrared analysis. An aqueous solution of an aliquot of this material when added to silver nitrate gave a yellow salt which analyzed correctly for silver cyanamide.

Anal. Calcd for CN_2Ag_2: N, 10.95. Found: N, 11.36, 11.44.

The ether-insoluble portion (0.65 g, yield 21.6%) after recrystallization from acetone gave long, white needles (0.55 g) which melted at 131–133.5°. Recrystallization from alcohol and a trace of ether gave pure urea (0.40 g, 13.3% yield) which was identified by melting point (135–136°) and mixture melting point (135–136°) with an authentic sample.

The volatile fraction was extracted with ether in a continuous extractor for 24 hr. The extract was dried over anhydrous magnesium sulfate and filtered, and the ether was removed from the filtrate on an efficient column. There remained 3.1 g (74% yield) of essentially pure cyclopentanone, which was identified by comparison of its infrared spectrum with that of an authentic sample. The 2,4-dinitrophenylhydrazone prepared from an aliquot of this product melted at 145.6–146.2°. A mixture of this product and an authentic sample of the 2,4-dinitrophenylhydrazone of cyclopentanone melted at 145.6–146.5°.

B. Silver Nitrate Solution.—To a flask equipped with a condenser, dropping funnel, magnetic stirrer, and thermometer was added silver nitrate (17.0 g, 0.1 mol) and distilled water (50 ml). When solution was complete, cyclopentylidenecyanamide (5.41 g, 0.05 mol) was added over 5 min. A mild exothermic reaction occurred and a small amount of yellow precipitate formed. Ether (5 ml) was added and the reaction mixture was heated at 40–50° for 20 min and then cooled to room temperature. Addition of ammonium hydroxide (20 ml, 14%) caused additional yellow precipitate to form. The solid product was separated by filtration, washed on a filter with distilled water, and dried over phosphorus pentoxide at 60–70° (0.1 mm) (12.70 g, yield 99.3%) The infrared spectrum of this compound was identical with that of silver cyanamide. The filtrate was extracted with ether on a continuous extractor for 20 hr and the ether layer was dried over anhydrous magnesium sulfate. Separation of the ether on an efficient column gave 4.0 g (95% yield) of cyclopentanone having an infrared spectrum identical with that of a known sample.

***tert*-Butylcyanamide from 1-Methylethylidenecyanamide and Methylmagnesium Bromide.**—A solution containing 0.10 mol of methylmagnesium bromide in 33 ml of ether was slowly added to 8.2 g (0.10 mol) of 1-methylethylidenecyanamide in 100 ml of ether so that the temperature was held below 20°.

The mixture was then added to 250 ml of 2 *N* hydrochloric acid; the ether layer was separated and dried over magnesium sulfate; and the ether was removed. Distillation gave 2.66 g (27%) of *tert*-butylcyanamide, n^{25}D 1.4282, bp 54.5–57° (0.2 mm) [reported[23] bp 62–63° (0.3 mm)].

1-Cyanoaziridine.—An acetonitrile solution (55 ml) containing 13.6 g (0.20 mol) of cyanogen azide was placed in a 240-ml Hastelloy-lined pressure tube which was pressured with 18 g (0.64 mol) of ethylene. The tube was held at 21–27° for 20 hr, during which the internal pressure rose from 480 to 740 psi.

The resulting solution was poured into 500 ml of ether and about 3 g of polymeric material was filtered off. After the filtrate was evaporated to 5.5 g, the residue was distilled through a short-path still at a pot temperature of 30–35° (0.2 mm) to give about 2 g (15%) of 1-cyanoaziridine, a colorless oil.

Infrared analysis of this product showed strong absorptions at 4.50 (−C≡N) and 6.80 and 6.90 μ (−CH_2−) with no absorption at 6.0–6.2 μ characteristic of the >C=N− group and none at 7.2–7.4 μ (−CH_3).

Isolation of 1-Cyano-2-methyl-2,3-tetramethyleneaziridine (5).—A solution of 0.068 mol of cyanogen azide in 40 ml of acetonitrile was added to 9.62 g (0.10 mol) of 1-methylcyclohexene. After 5 days at room temperature 1.21 l. of nitrogen was evolved. After evaporation of the solvent and excess reactant, 7.24 g (79%) of an oil was obtained. Nmr analysis of this crude product as outlined in the discussion showed 46% of 1-cyano-2-methyl-2,3-tetramethyleneaziridine, 31% of 2-methylcyclohexylidenecyanamide, and 23% of 1-methyl-2,2′-tetramethyleneethylidenecyanamide. Analysis was performed on a distilled portion of this mixture.

Five grams of this mixture was dissolved in 25 ml of benzene and chromatographed on grade IV neutral alumina. Elution with benzene gave 3.3 g of a mixture of ketones and aziridine with no alkylidenecyanamide. Distillation gave 0.4 g of **5**, bp 55° (0.5 μ) and 1.1 g of polymeric residue. Elemental analyses and nmr spectra are given in Tables II and V.

3-Azatricyclo[3.2.1.0^{2,4}]octane (12).—A solution of 62 g (0.46 mol) of **6** in ether was added to 9.5 g (0.25 mol) of lithium aluminum hydride in 350 ml of ether over 2 hr. After an additional 0.5 hr with stirring, saturated sodium sulfate solution was added over 0.5 hr until the complexes and excess hydride were decomposed and a creamy white slurry resulted. This mixture was filtered and the solvent was evaporated from the resulting solution on a rotating evaporator.

Simple trap-to-trap distillation of the resulting solution gave 37.2 g (74%) of **12** shown by glc to contain one component.

In another run a 45% yield of **12**, bp 40° (1 mm), was obtained.

Anal. Calcd for $C_7H_{11}N$: C, 77.1; H, 10.1; N, 12.8. Found: C, 77.6, 77.2; H, 10.4, 10.4; N, 12.2, 12.4.

The aziridine **12** in hexane solution is readily converted to the hydrochloride quantitatively by the action of gaseous HCl. (In ether a discrete hydrochloride is not obtained.) The hydro-

(23) E. Schmidt and K. Wamsler, German Patent 1,018,858 (1960); *Chem. Abstr.*, **54**, 5479g (1960).

chloride, mp 148–149°, can be recrystallized from isopropyl alcohol.

Anal. Calcd for $C_7H_{12}ClN$: C, 57.7; H, 8.3; N, 9.6. Found: C, 57.4; H, 8.9; N, 9.7.

Hydrolysis of 12 with Aqueous HCl.—To 43 g (0.30 mol) of **12** was added 100 ml of concentrated hydrochloric acid. The solution was heated briefly to reflux, and then most of the hydrochloric acid was evaporated. To the solution was added ammonium hydroxide until it remained basic, and then the solution was extracted with three 100-ml portions of methylene chloride. This organic material was dried over magnesium sulfate and distilled through a 24-in. spinning-band column to give 5.2 g (12%) of impure nortricyclamine, bp 41–44.5° (10 mm), $n^{25}D$ 1.4868–1.4878.

Anal. Calcd for $C_7H_{11}N$: C, 77.1 H, 10.1, N, 12.8. Found: C, 76.9, 76.5; H, 11.6, 11.4; N, 12.3.

The nmr spectrum of this material was nearly identical with that of an authentic sample.

Continued distillation gave 23.6 g (41%) of a mixture, bp 84–85° (10 mm), $n^{25}D$ 1.5095–1.5108.

Anal. Calcd for $C_7H_{12}ClN$: C, 57.7; H, 8.3; N, 9.6. Found: C, 58.3, 58.3; H, 8.5, 8.6 N, 10.0.

Gas–liquid chromatography of this mixture showed three components present in a ratio approximating 1:5:15.

***syn*-7-Aminonorbornene (14) by Dehydrohalogenation of *exo*-2-Chloro-*syn*-7-aminonorbornane (17).**—A solution of 27 g of the above mixture and 30 g of potassium *tert*-butoxide in 250 ml of *tert*-butyl alcohol was refluxed for 44 hr. Glc indicated at this point that the major component had reacted completely, and the two lesser components were unchanged. The precipitated salt was filtered, the solution was concentrated to a volume of 70 ml, and 200 ml of 10% potassium hydroxide was added. This two-phase system was extracted three times with ether; the ether solution was dried and carefully distilled to give 11.5 g (57%, 75% based on most abundant compound) of *syn*-7-amino-2-norbornene (**14**), bp 49–51° (18 mm), along with 2.5 g of the unreacted portion of the starting materials, bp 73–75° (4 mm).

The amine **14** carbonated readily, and analytical data were determined on the hydrochloride.

Hydrogen chloride was passed into a solution of 3 g (28 mmol) of **14** in 150 ml of ether. The precipitated solid was filtered to give 3.50 g (86%) of hydrochloride.

Recrystallization of 2.5 g of the hydrochloride from 150 ml of boiling nitromethane gave 2.3 g of **14** HCl.

Anal. Calcd for $C_7H_{12}ClN$: C, 57.7; H, 8.3; Cl, 24.4; N, 9.6. Found: C, 57.3, 57.5; H, 8.2, 8.2; Cl, 24.0, 23.8; N, 9.8, 10.0.

The following nmr spectrum of **14** HCl in D_2O was obtained: τ 3.87 (2) olefinic –CH, 5.22 (3) HOD, 6.74 (1) HCN, 6.97 (2) bridgehead, 8–8.3 (2) and 8.9–9.2 (2) ethano bridge.

7-Aminonorbornane (15) and 15·HCl.—To a solution of 11.3 g (0.078 mol) of the hydrolysis mixture containing **17** in 70 ml of liquid ammonia was added sodium metal over 1 hr until a blue color persisted. A precipitate slowly formed during the addition. Ammonium chloride was added until the color faded and the ammonia was then allowed to evaporate.

The solid residue was taken up in potassium hydroxide solution (the amine separated), ether was added, and the ether layer was removed and dried. Glc showed that none of the starting materials survived this reaction.

On distillation, 5.5 g (63%) of oily solid, **15**, bp 95° (77 mm), was obtained. This material reacted readily with carbon dioxide. The nmr spectrum showed the presence of about 10% of the unsaturated amine in this sample.

To a solution of 3.0 g (27 mmol) of **15** in ether was added anhydrous hydrogen chloride. On filtration, 3.34 g (84%) of hydrochloride was obtained. Recrystallization of 2.7 g from 220 ml of 10:1 nitromethane–isopropyl alcohol gave 1.7 g. After a second crystallization, the following was obtained.

Anal. Calcd for $C_7H_{14}ClN$: C, 56.9; H, 9.6; Cl, 24.0; N, 9.5. Found: C, 56.8, 56.9; H, 9.2, 9.4; Cl, 23.9; N, 9.5, 9.7.

Aziridine 18 by $LiAlH_4$ Treatment of 7.—A solution of 83.3 g (0.48 mol) of **7** in 150 ml of ether was added to 20 g of lithium aluminum hydride in 350 ml of ether over 1 hr. The solution was allowed to stand for 1 hr; saturated sodium sulfate was added until the exothermic reaction ceased. The salts were easily filtered from the light-colored ether solution, and, on evaporation of the ether, 65 g (93%) of an oil, **18**, was obtained. (This material may be reduced to **19** without further treatment.)

Distillation at 52–54° (7 μ) through a 2-ft spinning-band column gave 27 g (39%) of impure 9-azatetracyclo[5.3.1.$0^{2,6}$.$0^{8,10}$]-undec-3-ene (**18**), $n^{23}D$ 1.5428, with extensive decomposition.

Anal. Calcd for $C_{10}H_{13}N$: C, 81.6; H, 8.9; N, 9.5. Found: C, 79.8, 79.8; H, 8.7, 9.1; N, 9.2, 9.3.

9-Azatetracyclo[5.3.1.$0^{2,6}$.$0^{8,10}$]undecane (19).—A solution of 34.6 g (0.24 mol) of crude **18** in 75 ml of ethanol was hydrogenated for 40 hr at 40 psi using 0.3 g of PtO_2 catalyst. A total of 0.22 mol of hydrogen was absorbed. Distillation of the resulting product gave 26.0 g (74%) of **19**, bp 71–74° (0.2 mm), $n^{25}D$ 1.5191.

Anal. Calcd for $C_{10}H_{15}N$: C, 80.5 H, 10.1; N, 9.4. Found: C, 80.2, 80.5; H, 10.2, 10.2; N, 9.0, 9.1.

Registry No.—**1**, 3285-26-5; **2**, 35092-47-8; **3**, 3285-28-7; **4**, 35092-49-0; **5**, 3281-02-5; **6**, 35092-51-4; **7**, 35092-52-5; **8**, 35092-53-6; **12**, 1121-38-6; **12** HCl, 35092-55-8; **14**, 14173-90-1; **14** HCl, 35092-57-0; **15**, 35092-58-1; **15** HCl, 35092-59-2; **18**, 25129-62-5; **19**, 35092-60-5; *syn*-7-cyanamido-*exo*-1-norborneol benzoate, 35096-18-5.

The Synthesis and Reactions of Some 1-(Nitroaryl)diaziridines

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1-(2,4-Dinitrophenyl)- and 1-(2,4,6-trinitrophenyl)diaziridines are prepared by treating appropriate diaziridines with 2,4-dinitrofluorobenzene and 2,4,6-trinitroanisole, respectively. The 1-(2,4-dinitrophenyl)-3,3-dialkyl- and 1-(2,4,6-trinitrophenyl)-3,3-dialkyldiaziridines are isomerized in refluxing toluene into 2,4-dinitrophenyl- and 2,4,6-trinitrophenylhydrazones. However, 1-(2,4-dinitrophenyl)-2,3-dialkyldiaziridines and 1-(2,4-dinitrophenyl)-2,3,3-trialkyldiaziridines are converted in refluxing toluene into 2-alkyl-6-nitrobenzotriazole 1-oxides and ketones. Acid hydrolysis of the 1-(nitroaryl)-2-alkyldiaziridines forms 1-nitroaryl-2-alkylhydrazines.

Previous work in this laboratory has shown that 1-(nitroaryl)aziridines are easily synthesized by treating an aziridine bearing an NH group with either 2,4,6-trinitroanisole or 2,4-dinitrofluorobenzene.[1] We now report that 1-(2,4-dinitrophenyl)- and 1-(2,4,6-trinitrophenyl)diaziridines can be similarly prepared. Some reactions of these compounds are also described. The only other 1-aryldiaziridine that has been made, but not isolated, is 1-phenyl-3,3-pentamethylenediaziridine.[2]

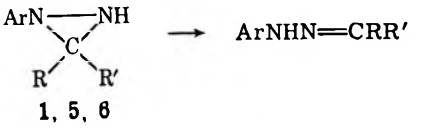
Results

Reaction of diaziridines having one or two NH groups with 2,4-dinitrofluorobenzene in ether containing triethylamine at room temperature or with 2,4,6-trinitroanisole in methanol led to 1-(2,4-dinitrophenyl)- and 1-(2,4,6-trinitrophenyl)diaziridines. These diaziridines are characterized in Table I. Picryl chloride was used in place of 2,4,6-trinitroanisole in a few instances, but the crude products that were obtained were less pure than when the anisole was employed.

The nmr spectra of the 1-(2,4-dinitrophenyl)- or 1-(2,4,6-trinitrophenyl)diaziridines were consistent with the proposed structures. This conclusion is based on the similar splitting patterns observed for the 3,3-pentamethylene protons in diaziridines **1**, **2**, **6**, and **7** and their progenitors, 3,3-pentamethylene- and 1-methyl-3,3-pentamethylenediaziridines. In both series of compounds the 3,3-pentamethylene group appears as a broad multiplet extending from δ 1.1 to 2.3. By contrast, the protons for this group in cyclohexanone 2,4-dinitrophenylhydrazone and cyclohexanone 2,4,6-trinitrophenylhydrazone [into which some of the 1-(nitroaryl)diaziridines can be isomerized; see below] form two multiplets, the four protons α to the carbon of the >C=N- group being separate and downfield at δ 2.0–2.7 while the remaining six protons are at δ 1.5–2.0.

Interestingly, each of the two aromatic hydrogens of 1-(2,4,6-nitrophenyl)-3,3-pentamethylenediaziridine (**6**) and 1-(2,4,6-trinitrophenyl)-2-methyl-3,3-pentamethylenediaziridine (**7**) appears as a sharp doublet. Models indicate that free rotation of the *o*-nitroaryl group is inhibited by the 3,3-pentamethylene group, thus rendering the aryl protons nonequivalent.

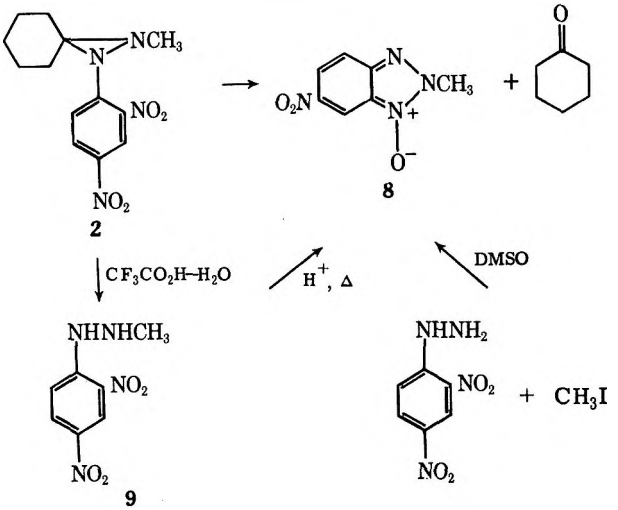
The 1-(2,4-dinitrophenyl)- and 1-(2,4,6-trinitrophenyl)diaziridines bearing an NH group (**1**, **5**, **6**) upon heating in toluene for about 3 hr rearrange into the corresponding known 2,4-dinitrophenyl- or 2,4,6-trinitrophenylhydrazones.



1, **5**, **6**

Heating of the 1-(2,4-dinitrophenyl)-2,3,3-trialkyldiaziridines **2**, **3**, and **4** did not give hydrazones but afforded instead 2-alkyl-6-nitrobenzotriazole 1-oxides and ketones. Thus 1-(2,4-dinitrophenyl)-2-methyl-3,3-pentamethylenediaziridine (**2**) was converted after 7 hr in refluxing toluene into 2-methyl-6-nitrobenzotriazole 1-oxide (**8**) and cyclohexanone (Scheme I).

SCHEME I



The cyclohexanone was identified by gas chromatography. The structure of **8** was confirmed by contrasting its nmr, ir, and mass spectra with those of the known isomeric 3-methyl-6-nitro-1,2,3-benzotriazole 1-oxide,[3] by elemental analyses, and by alternate syntheses. One synthesis involved treatment of 2,4-dinitrophenylhydrazine with methyl iodide in dimethyl sulfoxide at room temperature, while the other synthesis involved the acid-catalyzed dehydration of 1-methyl-2-(2,4-dinitrophenyl)hydrazine (**9**) (Scheme I). The acid-catalyzed dehydration of 1-aryl-2-(*o*-nitroaryl)-hydrazines into 2-arylbenzotriazole 1-oxides is a known reaction.[4,5] Compound **9**, although easily transformed into **8** by acid, remained unchanged after 7 hr in refluxing toluene. This clearly established that **9** was not a reaction intermediate in the conversion of **2** to **8**.

(1) H. W. Heine, G. J. Blosick, and G. B. Lowrie, *Tetrahedron Lett.*, 4801 (1968).

(2) E. Schmitz and R. Ohme, *Chem. Ber.*, **94**, 2166 (1961).

(3) O. L. Brady and C. V. Reynolds, *J. Chem. Soc.*, 1273 (1931).

(4) A. Mangini, *Gazz. Chim. Ital.*, **65**, 1191 (1935).

(5) (a) H. Goldstein and A. Jaquet, *Helv. Chim. Acta*, **24**, 30 (1941); (b) H. Goldstein and R. Stamm, *ibid.*, **35**, 1470 (1952).

TABLE I

1-(NITROARYL)DIAZIRIDINES FROM THE REACTION OF 2,4-DINITROFLUOROBENZENE AND 2,4,6-TRINITROANISOLE WITH DIAZIRIDINES[a]

ArNNCR²R³
|
R¹

Compd	Ar	R¹	R²		R³	Crude yield, %	Mp, °C
1	$2,4(O_2N)_2C_6H_3$	H		$-(CH_2)_5-$		81	123–125
2	$2,4(O_2N)_2C_6H_3$	CH_3		$-(CH_2)_5-$		81	92–93
3	$2,4(O_2N)_2C_6H_3$	$CH(CH_3)_2$	CH_3		CH_3	93	100–103
4	$2,4(O_2N)_2C_6H_3$	C_6H_{11}	H		C_2H_5	88	115–116
5	$2,4(O_2N)_2C_6H_3$	H	CH_3		C_2H_5	75	73–75
6	$2,4,6(O_2N)_3C_6H_2$	H		$-(CH_2)_5-$		71	132–134
7	$2,4,6(O_2N)_3C_6H_2$	CH_3		$-(CH_2)_5-$		94	108–109

[a] Satisfactory analytical data (±0.4% for C, H, and N) were reported for all new compounds listed in the table: Ed.

Compound **9** was obtained by the hydrolysis of **2** in commercial trifluoroacetic acid (Scheme I). The structure of **9** was proved by mass spectrometry, elemental analyses, and comparison of its infrared and nmr spectra with those of the known isomeric 1-methyl-1-(2,4-dinitrophenyl)hydrazine prepared according to the method of Blanksma and Wackers.[6] The acid-catalyzed hydrolysis of compounds **3** and **4** to the corresponding 1-(2,4-dinitrophenyl)-2-isopropylhydrazine and 1-(2,4-dinitrophenyl)-2-cyclohexylhydrazine was also achieved in high yield. The acid hydrolysis of 1,2-dialkyldiaziridines to 1,2-dialkylhydrazines is a known reaction,[7] as is the hydrolysis of 1-alkyldiaziridines to 1-alkylhydrazines.[8]

The conversions of diaziridines **3** and **4** to the corresponding 2-alkylbenzotriazole 1-oxides were also achieved in good yields, but attempts to convert **7** to 2-methyl-4,6-dinitrobenzotriazole 1-oxide (**10**) were thwarted by extensive decomposition. Compound **10** was extracted from the reaction mixture with difficulty and in low yield.

Discussion

The rearrangement of the 1-(2,4-dinitrophenyl)- and 1-(2,4,6-trinitrophenyl)diaziridines bearing an NH group into hydrazones probably proceeds through the cleavage of the carbon–nitrogen bond of the diaziridine ring to give the dipolar intermediate **11**. Intermediate **11** subsequently forms the hydrazone. Other diaziridine derivatives have been shown to rearrange into hydrazones. For example, a number of 1,2-dibenzoyldiaziridines isomerized under mild conditions to ketone dibenzoylhydrazones.[9]

ArNHN=CRR′

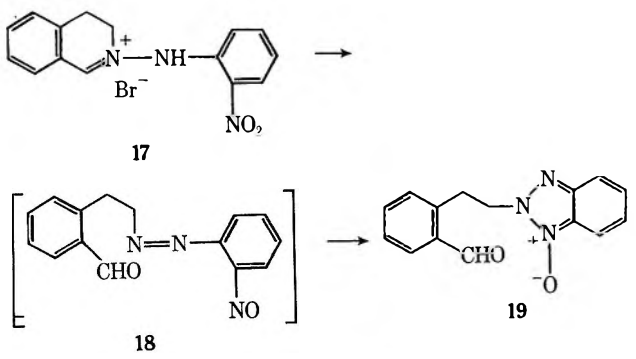
One possible mechanism for the conversion of 1-(2,4-dinitrophenyl)-2,3,3-trialkyldiaziridines into benzotriazole 1-oxides and ketones involves the formation of a dipolar intermediate **12**, which undergoes ring closure to the intermediate **13**. Elimination of cyclohexanone from **13** would give the ortho nitroso azo intermediate **14**, which cyclizes into the benzotriazole 1-oxide (Scheme II).

SCHEME II

That an intermediate such as **14** could isomerize to a benzotriazole 1-oxide is supported by the observations that reducing agents such as sodium hydrosulfite, sodium sulfide, or hydrazine react with ortho nitro azo derivative **15** to form **16**.[10]

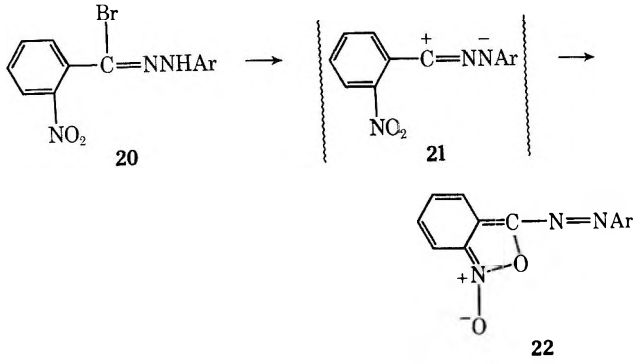
The ortho nitroso azo intermediate **18** similar to **14** has been proposed to account for the formation of the benzotriazole 1-oxide **19** when 2-(o-nitrophenylamino)-3,4-dihydroisoquinolinium bromide (**17**) is treated with pyridine.[11] Prior to this paper compound **19** was the only 2-alkylbenzotriazole 1-oxide reported.

(6) J. J. Blanksma and M. L. Wackers, *Recl. Trav. Chim. Pays-Bas*, **55**, 655 (1936).
(7) E. Schmitz, *Angew. Chem.*, **73**, 23 (1961).
(8) E. Schmitz and D. Habisch, *Chem. Ber.*, **95**, 680 (1962).
(9) E. Schmitz, D. Habisch, and Ch. Grundemann, *ibid.*, **100**, 142 (1967).
(10) E. Bamberg and R. Hubner, *Ber.*, **36**, 3822 (1903).
(11) R. Grashey, *Angew. Chem., Int. Ed. Engl.*, **1**, 158 (1962).



17 18 19

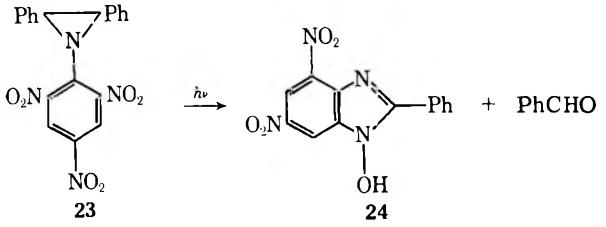
The solvolysis of *N*-(4-nitrophenyl)-*o*-nitrobenzhydrazonyl bromide (**20**) affords the azomethine imine **21**, an interesting counterpart to intermediate **12**. Interaction of the nitro group of **21** with the neighboring positive carbon yields 3-(4-nitrophenylazo)-anthranil 1-oxide (**22**).[12]



20 21 22

Ar = *p*-$O_2NC_6H_4$

The formation of 2-alkylbenzotriazole 1-oxides from 1-(2,4-dinitrophenyl)-2,3,3-trialkyldiaziridines resembles the photochemical conversion of 1-(2,4,6-trinitrophenyl)-2,3-diphenylaziridine (**23**) into 1-hydroxy-2-phenyl-4,6-dinitrobenzimidazole (**24**) and benzaldehyde.[1]



23 24

Experimental Section

Compounds 1–5.—To a mixture of 4 mmol of triethylamine and 4 mmol of the appropriate diaziridine (3,3-pentamethylene-, 1-methyl-3,3-pentamethylene-, 1-isopropyl-3,3-dimethyl-, 1-cyclohexyl-3-ethyl-, 3-methyl-3-ethyldiaziridines) in 200 ml of dry ether was added all at once a solution of 4 mmol of 2,4-dinitrofluorobenzene in 40 ml of ether. The reaction mixture was allowed to stand for 18 hr and then the solvent was evaporated. One milliliter of CH_3OH was added to the residue and the mixture was slurried until a fine yellow powder was obtained which was filtered. The 1-(2,4-dinitrophenyl)diaziridines were recrystallized from a small quantity of methanol, special care being taken that the period of recrystallization was of short duration and that the recrystallizing solution was cooled immediately after the dissolution of the diaziridine.

Compounds 6 and 7.—A solution of 4 mmol of either 3,3-pentamethylene- or 1-methyl-3,3-pentamethylenediaziridine in 10 ml of CH_3OH was added to 4 mmol of 2,4,6-trinitroanisole in 10 ml of CH_3OH. The reaction mixture was allowed to stand at room temperature overnight and then the solvent was evaporated. The same care was taken in recrystallizing **6** and **7** as with compounds **1–5**.

Rearrangements of 1, 5, and 6.—A solution of **1**, **5**, or **6** in toluene was refluxed for 4 hr. Evaporation of the toluene gave the known cyclohexanone 2,4-dinitrophenylhydrazone, butanone 2,4-dinitrophenylhydrazone, and cyclohexanone 2,4,6-trinitrophenylhydrazone, respectively, in quantitative yields.

Conversion of 2 to 8.—A solution of 223 mg of **2** in 10 ml of toluene was refluxed for 7.5 hr. Evaporation of the solvent gave 144 mg (97%) of **8**, mp 200–201°. After two recrystallizations from ethanol **8** had mp 200–202°; molecular ion *m/e* 194; uv max (absolute EtOH) 271 nm (ε 18,000), 204 (14,000); ir (Nujol) 6.21, 6.70, 7.44, 7.66, 7.95, 8.10, 8.59, 9.40, 9.73, 10.89, 11.16, 12.00, 12.70, 13.20, 13.59, 14.54 μ; nmr ($CDCl_3$) δ 4.30 (s, 3, CH_3), 7.80 (d, 1, J = 9.5 Hz, 4-H), 8.20 (pair of d's, 1, $J_{4,5}$ = 9.5, $J_{5,7}$ = 2.0 Hz, 5-H), 8.70 (d, 1, J = 2.0 Hz, 7-H).

Anal. Calcd for $C_7H_6N_4O_3$: C, 43.29; H, 3.11; N, 28.85. Found: C, 43.38; H, 3.28; N, 28.72.

Conversion of 3 to 2-Isopropyl-6-nitrobenzotriazole 1-Oxide.—A solution of 200 mg of **3** in 10 ml of toluene was refluxed for 3 hr and the toluene was then evaporated to give a quantitative yield of **22**. After recrystallization from ethanol **22** melted at 151–153°; uv max (absolute EtOH) 271 nm (ε 20,000), 204 (16,000); nmr ($CDCl_3$) δ 1.70 (d, 6, 2 CH_3's), 5.63 [m, 1, $(CH_3)_2$**CH**], 7.92 (d, 1, J = 9.5 Hz, 4-H), 8.30 (pair of d's, 1, $J_{4,5}$ = 9.5, $J_{5,7}$ = 2.0 Hz, 5-H), 8.85 (d, 1, J = 2.0 Hz, 7-H).

Anal. Calcd for $C_9H_{10}N_4O_3$: C, 48.65; H, 4.53; N, 25.21. Found: C, 48.67; H, 4.74; N, 24.85.

Conversion of 4 to 2-Cyclohexyl-6-nitrobenzotriazole 1-Oxide.—A solution of 202 mg of **4** in 10 ml of toluene was refluxed for 14 hr. Evaporation of the solvent gave 174 mg (98%) of **23**. Recrystallization from ethanol gave **23**, mp 120–122°.

Anal. Calcd for $C_{12}H_{14}N_4O_3$: C, 54.93; H, 5.37; N, 21.36. Found: C, 55.28; H, 5.35; N, 21.48.

Reaction of Methyl Iodide with 2,4-Dinitrophenylhydrazine. Preparation of 8.—To 1.982 g (0.01 mol) of 2,4-dinitrophenylhydrazine in 11 ml of DMSO was added 1.420 g (0.01 mol) of CH_3I. The reaction mixture was allowed to stand at room temperature for 42 hr. The mixture was cooled in an ice bath and about 5 ml of H_2O was added gradually. The precipitate of **8** (270 mg) was collected and water was added to the filtrate until an oil settled out. This oil solidified after 12 hr and an additional 905 mg of **8** was filtered. The total yield of **8** was 1.175 g (60%).

Conversion of 2 to 9.—A solution of 273 mg of **2** in 1 ml of commercial CF_3CO_2H was allowed to stand overnight at room temperature. The solvent was evaporated and 0.5 ml of CH_3OH was added to the residue. Trituration of the mixture gave 137 mg (69%) of **9**. These recrystallizations from CH_3OH gave **9**, mp 125–127°.

Anal. Calcd for $C_7H_8N_4O_4$: C, 39.63; H, 3.80; N, 26.41. Found: C, 39.72; H, 4.06; N, 26.37.

Conversion of 3 to 1-(2,4-Dinitrophenyl)-2-isopropylhydrazine.—A solution of 378 mg of **3** in 4 ml of CF_3CO_2H was stirred for 2 hr and then the solvent was evaporated in a hood. The residue was recrystallized from ethanol to give 278 mg (86%) of **24**, mp 106–108°.

Anal. Calcd for $C_9H_{12}N_4O_4$: C, 45.00; H, 5.03; N, 23.32. Found: C, 45.30; H, 4.97; N, 22.90.

Conversion of 4 to 1-(2,4-Dinitrophenyl)-2-cyclohexylhydrazine.—A mixture of 1.099 g of **4** and 5 ml of CF_3CO_2H was stirred for 5 min and then the solvent was evaporated. A small quantity of MeOH was added to the dark brown oil. Trituration of the mixture gave 732 mg of **25**. Recrystallization from acetonitrile gave **25**, mp 160–162.5°.

Anal. Calcd for $C_{12}H_{16}N_4O_4$: C, 51.42; H, 5.75; N, 19.99. Found: C, 51.54; H, 6.03; N, 19.89.

Preparation of 8 from 9.—A mixture of 50 mg of **9**, 10 ml of CH_3OH, and 3 drops of concentrated hydrochloric acid was stirred for 7 hr. The solvent was evaporated to give 39 mg of crude **8**. Recrystallization gave dark-colored crystals of **8**, mp 195–198°. The infrared spectrum was identical with that of **8** prepared by heating **2** in toluene.

Preparation of 22 from 25.—A mixture of 67 mg of **24**, 10 ml of EtOH, and 1 drop of concentrated hydrochloric acid was refluxed for 3.5 hr. The solvent was evaporated to give 49 mg (79%) of crude **22**.

(12) A. F. Hegarty, M. Cashman, J. B. Aylward, and F. L. Scott, *J. Chem. Soc. B*, 1879 (1971).

Synthesis of 23 from 25.—A mixture of 130 mg of 25, 10 ml of MeOH, and 1 drop of concentrated hydrochloric acid was refluxed for 2 hr. Evaporation of the solvent gave 98 mg (81%) of crude 23, mp 105–110°.

Registry No.—1, 35042-51-4; 2, 35040-15-4; 3, 35040-16-5; 4, 35040-17-6; 5, 35040-18-7; 6, 35040-19-8; 7, 35040-20-1; 8, 35040-21-2; 9, 35040-22-3; 23, 35040-27-8; 2-isopropyl-6-nitrobenzotriazole 1-oxide, 35040-23-4; 2-cyclohexyl-6-nitrobenzotriazole 1-oxide, 35040-24-5; 1-(2,4-dinitrophenyl)-2-isopropylhydrazine 35040-25-6; 1-(2,4-dinitrophenyl)-2-cyclohexylhydrazine, 35040-26-7.

Acknowledgment.—We thank the Camille and Henry Dreyfus Foundation, Inc., and the Petroleum Research Fund for financial aid and Professor C. C. Sweeley for several mass spectra.

cis-8,9-Dihydroisoxazolo[5,4-*d*]pyrimidine-4,6(5*H*,7*H*)-diones

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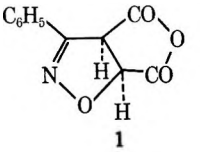
The Lossen rearrangement of *cis*-3-phenyl-2-isoxazoline-*N*-benzenesulfonyloxy-4,5-dicarboximide with aqueous ammonia or methylamine produced a mixture of *cis*-3-phenyl-5-ureido-2-isoxazoline-4-carboxamides and the corresponding 4-carboxylic acids (80–90% yield). Cyclization of these ureido acids with 3.3 *N* hydrochloric acid at 100° furnished the title compounds. Structures of all products were established *via* their pmr and mass spectra; the stereochemistry of the 4,5-disubstituted 2-isoxazolines was shown to be *cis* with $J_{4,5}$ consistently between 9 and 12 Hz. Mechanisms for this selective Lossen degradation are discussed.

As part of our continuing interest in condensed uracils[2] as potential antimetabolites, we explored syntheses of isoxazolo[4,5- and 5,4-*d*]pyrimidinediones.[3] The initial plan to utilize 4,5-isoxazoledicarboxylic esters[4] and to convert these by the standard method[2] to the corresponding bishydroxamates, was thwarted when the latter could not be isolated. Thus, this approach to build the uracil system onto the isoxazole ring *via* the modified Lossen rearrangement of the 4,5-bishydroxamates[2] was abandoned. An alternate route to the isoxazolo pyrimidine system is reported below.

1,3-Dipolar addition of benzonitrile oxide to maleic anhydride produced *cis*-3-phenyl-2-isoxazoline-4,5-dicarboxylic anhydride (**1**).[6,7] It was planned to degrade **1**, *via* the Lossen reaction, to one, or both, of the corresponding β-amino acids[8,9] and then build up, in this instance, the dihydrouracil system. Hydroxylamine smoothly transformed **1** to the corresponding *N*-hydroxyimide, **2a**, which was characterized by an acetate, **2b**, and sulfonate, **2c**. An instantaneous reaction took place between **2c** and ammonia to give the ureido acid and amide, **3a** and **3b**, respectively. The isomers **4a** and **4b** could not be detected. This type of Lossen degradation parallels that of *N*-sulfonyloxyphthalimides with amines reported by Kühle and Wegler.[9] However, these authors found their intermediate *o*-ureidobenzoic acid derivatives spontaneously cyclized to 2,4-quin-



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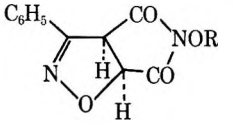
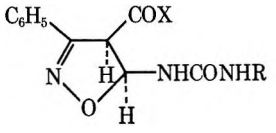
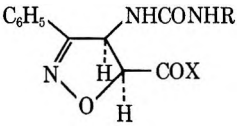


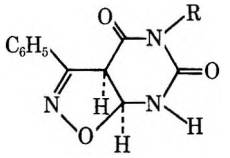
2a, R = H
b, R = $COCH_3$
c, R = $SO_2C_6H_5$



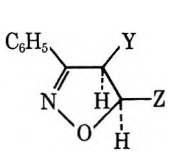
3a, X = OH; R = H
b, X = NH_2; R = H
c, X = OH; R = CH_3
d, X = $NHCH_3$; R = CH_3



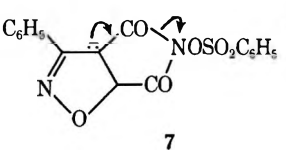
4a, X = OH; R = H
b, X = NH_2; R = H



5a, R = H
b, R = CH_3



6a, Y = CO_2H; Z = $CONH_2$
b, Y = H; Z = $CONH_2$
c, Y = CO_2H; Z = CONHOH



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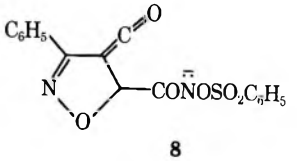

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(1) Abstracted from the Ph.D. Dissertation of W. J. T., University of Illinois (Medical Center), 1972.

(2) L. Bauer and C. S. Mahajanshetti, *J. Heterocycl. Chem.*, **5**, 331 (1968), and references cited therein.

(3) Recent papers in this field are by G. Desimoni and P. Grünanger, *Gazz. Chim. Ital.*, **98**, 25 (1968); *Tetrahedron*, **23**, 687 (1967); P. Rajagopalan and C. N. Talaty, *ibid.*, **23**, 3541 (1967).

(4) These esters are readily available from the addition of acetylenedicarboxylic esters to nitrile oxides; see ref 5.

(5) C. Grundmann and P. Grünanger, "The Nitrile Oxides," Springer-Verlag, New York, N. Y., 1971.

(6) (a) This anhydride was synthesized in somewhat larger scale from the original paper of A. Quilico, G. S. D'Alcontres, and P. Grünanger, *Gazz. Chim. Ital.*, **80**, 479 (1950); N. S. Isaacs, "Experiments in Physical Organic Chemistry," Macmillan, London, 1969, p 261.

(7) A. Quilico, "Five- and Six-Membered Compounds with Nitrogen and Oxygen," Interscience, New York, N. Y., 1962 p 95.

(8) This approach was demonstrated originally by us [L. Bauer and S. Miarka, *J. Amer. Chem. Soc.*, **79**, 1983 (1957)], later by Kühle and Wegler (ref 9). A recent example of this type of degradation is described by V. L. Plakidin, N. M. Zadorozhnyi and Z. I. Krasota, *J. Org. Chem. USSR*, **6**, 1493 (1970).

(9) E. Kühle and R. Wegler [*Justus Liebigs Ann. Chem.*, **616**, 183 (1958)] found that *N*-(*p*-chlorobenzenesulfonyloxy)phthalimide rearranged with gaseous ammonia at 25° in benzene–dioxane and gave *o*-ureidobenzamide (72%), but cyclized in 10% aqueous ammonia solution. It is plausible that the driving force for this cyclization was the formation of the aromatic 2,4-quinazolinedione.

azolinediones.[9] The rearrangement of **2c** with amines stopped at the ureido acid stage and subsequent cyclization to **5** had to be conducted separately.

The reaction of **2c** with ammonia produced both **3a** and amide, **3b**, the proportion depending upon the concentration of ammonia. With concentrated ammonium hydroxide, alone or in tetrahydrofuran, or ammonia gas in *N,N*-dimethylformamide, **3b** proved to be the major product (80–90%). On reducing the concentration of ammonia, the yield of the acid, **3a**, increased over that of the amide, **3b**. Cyclization of the more readily available ureidoamide, **3b**, with dilute acid produced a negligible quantity of **5a**, accompanied by a large quantity of reddish-brown material. As a matter of fact, all 2-isoxazolines in this study turned bright red on boiling with hydrochloric acid and decomposed subsequently. By contrast, the ureido acid, **3a**, cyclized to **5a** with great ease, which is in line with the acid-catalyzed cyclization of β-ureido acids to dihydrouracils.[10]

A similar series of reactions was initiated when **2c** was treated with methylamine to give **3c** and **3d**. Of these, only the acid **3c** cyclized readily to **5b**, while the amide, **3d**, could not be induced to yield any **5b**.

Structure Proof.—Proton magnetic resonance (pmr) spectra readily distinguished between the series based on **3** from isomers **4**, and at the same time established the stereochemistry. It had been demonstrated that in 3-phenyl-2-isoxazolines, in $CDCl_3$, H-5 is the most deshielded proton, irrespective of the type of substituents on C-4 and C-5.[11] A similar anisotropic effect was reported for H-5 in 3-phenylisoxazolidines. Our pmr spectra were all recorded in $(CD_3)_2SO$ due to limited solubilities in $CDCl_3$, and, for each member of series **3** and **5**, the signal furthest downfield consisted of a doublet of doublets, or triplet, readily exchanged with D_2O to a doublet. This pattern arises from the –CHCH(O–)NH– grouping, which proves that the Lossen degradation of the 5-carboxylic acid function in **2** was involved to form **3**. The magnitude of the spin–spin coupling constant, $J_{4,5}$, in **1–6** (9–12 Hz) is in excellent agreement with the cis coupling constant established for a series of 3-phenyl-2-isoxazolines.[11]

Related Compounds.—The reaction of **1** with ammonia yielded the acid amide **6a**, which was thermally decarboxylated to the known amide **6b**, and hydrolyzed by concentrated HCl to the acid, 3-phenyl-2-isoxazoline-5-carboxylic acid.[6a] The ease of decarboxylation of the 4 acid in **6a** is attributed to its position in the β-oximino acid system. Ring opening of **1** with aniline also gave anilide analogous to **6a**.[6a] The initial product from **1** and hydroxylamine was isolated (after mild acidification) and was a hydroxamic acid to which structure **6c** was assigned, based on analogous ring opening of **1** with amines. Attempts to decarboxylate **6c** yielded **2a**, and dilute hydrochloric acid produced **2a** in the cold and the 5-carboxylic acid on heating.

The known *cis*-methyl 3-phenyl-2-isoxazoline-4,5-dicarboxylate[6a] was resynthesized and its pmr spectrum in $(CD_3)_2SO$ was compared to the one published in $CDCl_3$.[11] Treatment of this ester with aqueous ammonia produced the bisamide, which possessed the trans configuration as evident from its pmr spectrum. This isomerization of the ring protons on prolonged exposure of the ester or amide to concentrated aqueous ammnoium hydroxide solution was perhaps unexpected, since we had only encountered cis products. However, it had been recorded that the 4,5-dicarboxylic acid and esters are readily epimerized by bases. The active methylene proton at C-4 is thought to be responsible for the ease of such a process and creates the thermodynamically most stable isomer.[12]

Mechanism of Ring Openings.—It is reasonable to assume that ammonia and aniline react most rapidly with the more electrophilic CO group at C-5 to give the identified acid amides of type **6a**. However, during the Lossen rearrangement of **2c**, it would appear that nucleophilic attack on the CO at C-4 initiates the degradation. In the absence of steric factors, an alternate mechanism is suggested. Abstraction of H-4 in **2c** generates **7**, which opens to the ketene hydroxamate ion **8**. To form the products, **3**, the ketene function adds either water or ammonia, while the hydroxamate sulfonate portion of **8** is degraded to the isocyanate,[13] which reacts with ammonia to form the urea. This mechanism explains the formation of the large amount of the ureido acid. This contrasts with the Lossen degradation of *N*-hydroxyphthalimide sulfonates to *o*-ureidobenzamides only.[9] In their mechanism, Kühle and Wegler initiate their Lossen reaction by attack of ammonia on one of the imide CO, followed by ring opening to the amide hydroxamate sulfonate anion, which in turn rearranges to an isocyanate group capable of then adding ammonia or an amine to form the ureidoamide.

This mechanism *via* **8** would encourage the formation of both the cis and trans isomers of **3**. The formation of the cis isomer might well be favored in terms of the highly hydrogen-bonded products **3**, which could account for either stereoselective addition to the intermediate unsaturated systems or epimerization of final products to produce the most stable isomers.

Experimental Section[14]

cis-3-Phenyl-2-isoxazoline-4,5-dicarboxylic anhydride (**1**) was prepared in 62% yield (0.6 mol scale) using Isaac's method.[6] Extreme care must be exercised in handling the intermediate benzohydroximyl chloride, which is a powerful vesicant and lachrymator. The anhydride melted at 161–163° (lit.[6] mp 162°); ir 1800 and 1870 cm^{-1}; pmr δ 4.93 (d, H-4), 5.50 (d, H-5,

(10) I. G. Pojarlieff, R. Z. Mitova-Chernaeva, I. Blagoeva, and B. J. Kourtev, *C. R. Acad. Bulg. Sci.*, **21**, 131 (1968); *Chem. Abstr.*, **69**, 51283b (1968).

(11) R. Sustmann, R. Huisgen, and H. Huber, *Chem. Ber.*, **100**, 1802 (1967).

(12) Reference 7, p 107.

(13) C. D. Hurd and L. Bauer, *J. Amer. Chem. Soc.*, **76**, 2791 (1954).

(14) Melting points were determined on a Thomas-Hoover Unimelt capillary melting point apparatus and are uncorrected. Microanalysis were performed by Micro-Tech Laboratories, Inc., Skokie, Ill., and those for elemental nitrogen by Mr. Richard Dvorak using a Coleman Nitrogen Analyzer, Model 29. Infrared spectra were obtained in Nujol mulls with either Perkin-Elmer Models 337 or 700 recording spectrophotometers. Only strong to medium absorption bands between 1600 and 1900 cm^{-1} are reported. No C=O or C=N stretching band assignments are made, since 2-isoxazolines show a strong band at 1725 cm^{-1}: R. P. Barnes, G. E. Pinkney, and G. M. Phillips, *J. Amer. Chem. Soc.*, **76**, 276 (1954). Pmr spectra were recorded in $(CD_3)_2SO$ (unless otherwise stated) at 60 MHz by means of a Varian A-60 spectrometer or at 100 MHz by Dr. Richard Egan, Abbott Laboratories, on a Varian HA-100 spectrometer. Signals are reported in parts per million (δ) downfield from internal Me_4Si. Only those spin–spin coupling constants (J) are reported which are relevant to the problem. Exchangeable protons were detected on addition of D_2O. Mass spectra were obtained at 70 eV by Mr. Richard Dvorak using a Hitachi Perkin-Elmer RMU-6D mass spectrometer equipped with a Honeywell Visicorder and Hitachi Perkin-Elmer mass marker. Solids were introduced by the direct inlet system at the lowest possible temperature for all parts of the system. Only fragment ions, m/e, present in excess of 5% of the base peak, other than the P + 1, P + 2 ions, are reported. The relative intensities of the ions are shown in parentheses.

$J_{4,5}$ = 11 Hz), 7.25–7.92 (m, C_6H_5); mass spectrum *m/e* (rel intensity) 218 (8), 217 (69), 146 (6), 145 (50), 144 (100), 117 (16), 116 (10), 115 (11), 103 (8), 91 (5), 90 (13), 89 (15), 78 (6), 77 (66), 76 (11), 75 (6), 72 (18), 65 (6), 64 (6), 63 (17), 62 (7), 57 (7), 55 (7), 54 (10), 51 (31), 50 (14), 45 (12), 44 (8), 39 (15), 32 (9).

***cis*-*N*-Hydroxy-3-phenyl-2-isoxazoline-4,5-dicarboximide (2a). Method A.**—A stirred solution of hydroxylamine hydrochloride (4.4 g, 0.65 mol) in 25% aqueous tetrahydrofuran (80 ml) was neutralized with sodium carbonate (3.4 g, 0.33 mol) at 25°. Addition of **1** (10.85 g, 0.5 mol) over 1 min produced initially a solution which set to a paste (3–5 min). The mixture was then heated at 60–70° for 0.25 hr and diluted with water (10 ml), pH ≤ 4. The product (8.2 g, 71%) was crystallized from water: mp 206–208°; ir 1720, 1740, 1800 cm^{-1}; pmr δ 5.22 (d, H-4), 5.60 (d, H-5, $J_{4,5}$ = 10 Hz), 7.30–8.05 (m, C_6H_5); mass spectrum *m/e* (rel intensity) 233 (12), 232 (90), 216 (20), 146 (10), 145 (60), 144 (100), 120 (50), 119 (9), 117 (25), 116 (13), 115 (11), 105 (6), 104 (17), 103 (51), 93 (9), 91 (11), 90 (14), 89 (16), 78 (6), 77 (86), 76 (26), 75 (8), 70 (25), 65 (7), 64 (11), 63 (19), 62 (6), 52 (8), 51 (45), 50 (22), 44 (24), 43 (11), 42 (9), 39 (22), 38 (6), 29 (10).

Anal. Calcd for $C_{11}H_8N_2O_4$: C, 56.90; H, 3.45; N, 12.07. Found: C, 57.12; H, 3.33; N, 12.01.

Method B.—A solution of hydroxylamine hydrochloride (15.8 g, 0.225 mol) in methanol (100 ml) was neutralized by sodium ethoxide solution (5.17 g of Na in 100 ml of methanol). Salt was filtered off and **1** (16.36 g, 0.75 mol) was added to the filtrate over 5 min. After the mixture was stirred for 1 hr, the solid (19.1 g) was filtered. A part of this solid (0.5 g) was dissolved in water (5 ml) and acidified with concentrated HCl to produce **6c** (0.32 g): mp 180–183° (intense purple color with $FeCl_3$); ir 1640 and 1710 cm^{-1}; pmr δ 4.90 (d, H-4) 5.37 (d, H-5, $J_{4,5}$ = 12 Hz), 7.30–8.01 (m, C_6H_5); mass spectrum *m/e* (rel intensity) 232 (16, M − 18), 218 (9), 217 (66), 216 (6), 146 (14), 145 (49), 144 (100), 118 (11), 117 (17), 116 (10), 115 (10), 104 (7), 103 (15), 91 (6), 90 (12), 89 (13), 78 (6), 77 (71), 76 (13), 65 (13), 63 (15), 51 (30), 50 (13), 44 (22), 39 (11), 33 (33).

Anal. Calcd for $C_{11}H_{10}N_2O_5$: N, 11.20. Found: N, 11.31.

When the above solid from method B was either heated in dilute HCl solution (90° for 0.10 hr) or such a solution was permitted to stand at 25° for 24 hr, **2a** was isolated in 50–65% yield. Also, on heating this solid from B at 110–115° for 0.25 hr *in vacuo* (20 Torr) and treating the residue with cold dilute HCl, **2a** was precipitated immediately in poorer yield.

***cis*-*N*-Acetoxy-3-phenyl-2-isoxazoline-4,5-dicarboximide (2b).**—A solution of **2a** (6.96 g, 0.03 mol) in acetic anhydride (80 ml) containing pyridine (3 ml) was heated at 100° for 1 hr. After solvents were removed *in vacuo*, the residue was crystallized from ethanol–ethyl acetate (2:1) to give 7.55 g (92%): mp 156–157°; ir 1700, 1740, 1800 cm^{-1}; pmr δ 5.47 (d, H-4), 5.85 (d, H-5, $J_{4,5}$ = 10 Hz), 7.37–8.11 (m, C_6H_5); mass spectrum *m/e* (rel intensity) 275 (4), 274 (26), 232 (36), 144 (10), 77 (11), 43 (100), 36 (6).

Anal. Calcd for $C_{13}H_{10}N_2O_5$: N, 10.22. Found: N, 10.21.

***cis*-*N*-Benzenesulfonoxy-3-phenyl-2-isoxazoline-4,5-dicarboximide (2c).**—To aqueous 2.5% sodium carbonate (160 ml) was added **2a** (11.6 g, 0.05 mol). The solution was filtered to remove a small amount of insoluble material, and benzenesulfonyl chloride (6.5 ml, 0.05 mol) was added dropwise at 25° over 20 min. The mixture was stirred for 3 hr and the solid (11.3 g, 60%), mp 158–161°, was collected. It was crystallized from ethyl acetate: mp 168–171°; ir 1740, 1775, 1840 cm^{-1}; pmr δ 5.30 (d, H-4), 5.65 (d, H-5, $J_{4,5}$ = 10 Hz), 7.28–8.03 (m, 10 Ar H); mass spectrum *m/e* (rel intensity) 373 (5), 372 (24), 216 (3), 145 (8), 144 (15), 142 (6), 141 (80), 103 (8), 78 (7) 77 (100), 76 (5), 70 (9), 51 (17).

Anal. Calcd for $C_{17}H_{12}N_2C_6S$: C, 54.84; H, 3.23; N, 7.53. Found: C, 54.68; H, 3.42; N, 7.42.

***cis*-3-Phenyl-5-ureido-2-isoxazoline-4-carboxylic Acid (3a) and *cis*-3-Phenyl-5-ureido-2-isoxazoline-4-carboxamide (3b).**—A suspension of **2c** (3.72 g, 0.01 mol) in water (50 ml) containing concentrated NH_4OH (3 ml) was heated in the steam bath for 20 min, cooled, and filtered to give 0.7 g (28%) of **3b**, which is identified below. The filtrate was acidified with concentrated HCl and **3a** was collected. It was recrystallized from methanol to provide 1.28 g (51%): mp 218–220°; ir 1620, 1650, 1730 cm^{-1}; pmr δ 5.08 (d, H-4), 6.20 (d of d, H-5, $J_{4,5}$ = 9.5, $J_{NH,5}$ = 10.5 Hz), 5.45 (broad singlet, NH_2), 6.73 (d, NH at C-5), 7.33–7.88 (m, C_6H_5); mass spectrum *m/e* (rel intensity) 231 (3, M − 18), 159 (5), 158 (74), 145 (7), 144 (8), 141 (8), 135 (9), 128 (6), 119 (11), 104 (8), 103 (28), 95 (7), 94 (86), 93 (8), 91 (5), 78 (9), 77 (100), 76 (18), 75 (8), 74 (9), 66 (15), 65 (22), 57 (7), 55 (7), 51 (56), 50 (25), 44 (21), 43 (7), 41 (6), 39 (12), 36 (7), 32 (24), 29 (6).

Anal. Calcd for $C_{11}H_{11}N_3O_4$: C, 53.01; H, 4.45; N, 16.86. Found: C, 53.10; H, 4.42; N, 17.13.

When the same reaction was conducted in concentrated NH_4OH (50 ml), **3b** (2.1 g, 85%) was obtained: mp 250–251° (from ethanol); ir 1630, 1660, 1680 cm^{-1}; pmr δ 4.88 (d, H-4), 6.03 (t, H-5, $J_{4,5}$ = $J_{NH,5}$ = 10 Hz), 5.67 (NH_2), 6.48 (d, NH at C-5), 7.30–7.80 (m, C_6H_5 and other NH_2); mass spectrum *m/e* (rel intensity) 248 (2), 231 (6), 205 (13), 204 (100), 160 (8), 144 (7), 133 (8), 105 (16), 104 (94), 103 (81), 101 (14), 77 (38), 76 (33), 75 (14), 74 (7), 73 (7), 71 (10), 70 (10), 69 (8), 59 (30), 58 (48), 57 (19), 56 (8), 55 (12), 51 (10), 50 (15), 45 (9), 44 (45), 43 (18), 41 (13), 39 (10), 30 (24), 29 (15).

Anal. Calcd for $C_{11}H_{12}N_4O_3$: C, 53.22; H, 4.87; N, 22.57. Found: C, 53.17; H, 4.96; N, 22.89.

Concentration of the mother liquor from this reaction and acidification afforded a small quantity of the acid **3a**.

When a solution of **2c** in tetrahydrofuran (1.86 g, 0.005 mol in 15 ml) was treated with 15 ml of concentrated NH_4OH at 90° for 0.5 hr, **3b** was precipitated in 93% yield.

***cis*-3-Phenyl-5-(3-methylureido)-2-isoxazoline-4-carboxylic Acid (3c) and *cis*-3-Phenyl-5-(3-methylureido)-2-isoxazoline-4-(*N*-methylcarboxamide) (3d).**—A suspension of **2c** (1.86 g, 0.005 mol) in water (25 ml) was heated (10 min) with aqueous 40% methylamine (1.15 ml, 0.015 mol). The precipitate of **3d** (0.35 g, 25.2%) was filtered (see below for identification). Acidification of the filtrate afforded a white solid (0.81 g). Crystallization from methanol (5 ml) yielded **3c** (0.62 g, 48%): mp 199–202°; ir 1610, 1640, 1730 cm^{-1}; pmr δ 2.57 (d, CH_3, $J_{CH_3,NH}$ = 4 Hz), 5.05 (d, H-4), 6.11 (t, H-5, $J_{4,5}$ = $J_{NH,5}$ = 10 Hz), 5.68 (q, $NHCH_3$), 6.66 (d, NH at C-5), 7.35–7.78 (m, C_6H_5); mass spectrum *m/e* (rel intensity) 245 (M − 18, 12), 142 (5), 119 (25), 105 (5), 104 (15), 103 (100), 98 (18), 85 (8), 77 (11), 76 (35), 75 (8), 69 (7), 58 (9), 51 (10), 50 (13), 44 (50), 42 (11), 39 (5), 30 (7).

Anal. Calcd for $C_{12}H_{13}N_3O_4$: C, 54.75; H, 4.98; N, 15.96. Found: C, 54.53; H, 4.95; N, 15.80.

Crystallization of **3d** (from above) from 95% ethanol raised the melting point to 255–256° (270 mg, 19.5%). The same product was isolated in 80% yield when a large excess of methylamine was present: ir 1600, 1660, 1680 cm^{-1}; pmr δ 2.52, 2.63 (d, $NHCH_3$, both J = 5 Hz), 4.91 (d, H-4), 6.07 (d of d, H-5, $J_{4,5}$ = 9.5, $J_{NH,5}$ = 10 Hz), 5.86, 7.59 (q, both due to $NHCH_3$), 7.30–7.80 (m, C_6H_5); mass spectrum *m/e* (rel intensity) 276 (4), 245 (4), 218 (64), 188 (4), 161 (5), 146 (7), 133 (7), 116 (6), 115 (19), 105 (6), 104 (48), 103 (44), 89 (6), 88 (5), 77 (18), 65 (16), 70 (6), 59 (40), 58 (100), 57 (6), 51 (9), 50 (7), 42 (6), 30 (25), 29 (6).

Anal. Calcd for $C_{13}H_{16}N_4O_3$: C, 56.51; H, 5.84; N, 20.28. Found: C, 56.48; H, 5.82; N, 20.19.

***cis*-3-Phenyl-8,9-dihydroisoxazolo[5,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (5a).**—A mixture of **3a** (0.24 g, 0.001 mol) and 3.3 *N* HCl (3.0 ml) was boiled for 7 min. On chilling to 5°, the solid 0.21 g) was collected and recrystallized from 35 ml of 2-propanol. There was obtained 0.092 g (40%): mp 254–255°; ir 1700, 1740 cm^{-1}; pmr δ 5.15 (d, H-4), 5.64 (d of d, H-5, $J_{4,5}$ = 10, $J_{NH,5}$ = 4 Hz), 7.40–7.90 (m, C_6H_5), 8.32 (d, NH); mass spectrum *m/e* (rel intensity) 232 (4), 231 (28), 144 (5), 128 (9), 120 (9), 119 (100), 105 (7), 104 (19), 103 (29), 91 (16), 85 (12), 77 (20), 76 (12), 69 (9), 64 (8), 63 (7), 57 (9), 51 (11), 50 (6), 39 (6), 38 (9), 36 (29), 32 (6).

Anal. Calcd for $C_{11}H_9N_3O_3$: C, 57.14; H, 3.92; N, 18.17. Found: C, 57.25; H, 4.06; N, 18.08.

***cis*-3-Phenyl-5-methyl-8,9-dihydroisoxazolo[5,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (5b).**—A suspension of **3c** (0.263 g, 0.001 mol) in 3.3 *N* HCl (3 ml) was heated at reflux for 2 min. A purple solution resulted. On cooling, the product was filtered off and washed with cold 3.3 *N* HCl. It weighed 0.24 g, mp 264–265°. Recrystallization from acetic acid (70% recovery) raised the melting point to 268–270°: ir 1680 and 1720 cm^{-1}; pmr δ 3.00 (NCH_3), 5.27 (d, H-4), 5.65 (d of d, H-5, $J_{4,5}$ = 10, $J_{NH,5}$ = 3 Hz), 7.40–7.85 (m, C_6H_5), 8.60 (d, NH, $J_{NH,5}$ = 3 Hz); mass spectrum *m/e* (rel intensity) 246 (5), 245 (36), 144 (10), 142 (20), 126 (15), 120 (8), 119 (100), 113 (7), 105 (24), 104 (22), 103 (32), 91 (17), 85 (32), 77 (20), 76 (14), 69 (16), 64 (7), 59 (18), 57 (13), 51 (10), 32 (18), 29 (7).

Anal. Calcd for $C_{12}H_{11}N_3O_3$: C, 58.77; H, 4.52; N, 17.13. Found: C, 58.49; H, 4.54; N, 16.91.

Prolonged heating or an increase in the concentration of HCl diminished the yield of **5b**.

***cis*-5-Carboxamido-3-phenyl-2-isoxazoline-4-carboxylic Acid (6a).**—To concentrated ammonium hydroxide (10 ml) at 10° was added 1 (1.08 g, 0.005 mol) in small portions, keeping the temperature below 10°. The reaction mixture was filtered and acidified with cold concentrated hydrochloric acid in an ice bath. The colorless solid (0.86 g, 73.5%) was collected and dried: mp 165–166°; ir 1650 and 1725 cm^{-1}; pmr δ 4.84 (d, H-4), 5.25 (d, H-5, $J_{4,5}$ = 12 Hz), 6.5–7.18 (m, 5, Ar H); mass spectrum *m/e* (rel intensity) 234 (1), 218 (8), 217 (62), 191 (5), 190 (6), 159 (16), 147 (7), 146 (64), 145 (40), 144 (76), 119 (7), 118 (32), 117 (19), 116 (11), 115 (12), 104 (15), 103 (20), 91 (19), 90 (12), 89 (15), 78 (10), 77 (100), 76 (16), 75 (7), 66 (7), 65 (6), 64 (16), 63 (6), 57 (8), 52 (6), 51 (40), 50 (15), 44 (62), 43 (9), 41 (8), 39 (15), 36 (10), 32 (19), 29 (5).

Anal. Calcd for $C_{11}H_{10}N_2O_4$: N, 11.96. Found: N, 11.82.

3-Phenyl-2-isoxazoline-5-carboxamide (6b).—On heating 5-carboxamido-3-phenyl-2-isoxazoline-4-carboxylic acid (**6a**) (0.75 mg, 0.0032 mol) for 15 min *in vacuo* until the oil bath temperature had risen to 190°, a solid material formed which was triturated with saturated aqueous sodium bicarbonate solution (10 ml), collected, and washed with three portions of cold water (5 ml). The solid was extracted with boiling benzene to afford 0.2 g (33%) of **6b**: mp 200–201° (lit.[6] mp 204°); ir 1650 and 1660 cm^{-1}; pmr δ 3.1–3.6 (m, 2 H at C-4), 4.67–5.13 (m, H-5, the X part of an ABX pattern), 7.1–7.84 (m, C_6H_5); mass spectrum *m/e* (rel intensity) 190 (13), 159 (33), 147 (10), 146 (100), 119 (10), 118 (75), 117 (13), 115 (6), 104 (14), 103 (9), 91 (30), 78 (15), 77 (95), 76 (10), 63 (6), 51 (32), 50 (10), 44 (19), 32 (7).

Anal. Calcd for $C_{10}H_{10}N_2O_2$: N, 14.73. Found: N, 14.45.

3-Phenyl-2-isoxazoline-5-carboxylic Acid.—To concentrated hydrochloric acid (10 ml) was added **6a** (0.468 g, 0.002 mol), and the solution was warmed on a steam bath for 20 min. The reaction mixture was allowed to stand for 12 hr to furnish **6c**: 0.21 g (55%); mp 140–143° (lit.[6] mp 143°); ir 1720 cm^{-1}; pmr, computer-checked spectrum for ABX pattern of ring protons offers this solution:[15] δ 5.203 (H-5), 3.745, 3.613 (H-4, J_{gem} = −17.27, $J_{4,5}$ = 11.83 and 6.77 Hz), 7.20–7.80 (m, C_6H_5); mass spectrum *m/e* (rel intensity) 191 (30), 147 (8), 146 (64), 119 (10), 118 (86), 117 (12), 115 (7), 104 (14), 103 (19), 91 (32), 89 (8), 78 (13), 77 (100), 76 (16), 75 (6), 74 (5), 65 (6), 63 (11), 52 (6), 51 (40), 50 (17), 46 (7), 39 (11).

Anal. Calcd for $C_{10}H_9NO_3$: N, 7.33. Found: N, 7.51.

Methyl *cis* 3-Phenyl-2-isoxazoline-4,5-dicarboxylate.—This ester was prepared in 44% yield by the literature[6] method: mp 89–92° (lit.[6] mp 91°); pmr ($CDCl_3$) δ 3.73, 3.87 (OCH_3), 4.80 (H-4), 5.43 (H-5, $J_{4,5}$ = 12 Hz); lit.[11] pmr ($CDCl_3$) δ 3.65, 3.80 (OCH_3), 4.81 (H-4), 5.29 (H-5, $J_{4,5}$ = 12 Hz), pmr $(CD_3)_2SO$ δ 3.65, 3.77 (OCH_3), 5.23 (H-4), 5.66 (H-5, $J_{4,5}$ = 12 Hz); mass spectrum *m/e* (rel intensity) 264 (11), 263 (62), 231 (5), 204 (27), 178 (21), 177 (14), 176 (100), 172 (23), 160 (14), 146 (6), 144 (85), 134 (18), 119 (11), 118 (9), 117 (12), 116 (12), 115 (6), 113 (16), 105 (8), 104 (6), 103 (15), 91 (18), 89 (9), 77 (51), 76 (9), 59 (31), 51 (22), 39 (6), 31 (11), 29 (5).

***trans*-3-Phenyl-2-isoxazoline-4,5-dicarboxamide.**—A mixture of methyl *cis*-3-phenyl-2-isoxazoline-4,5-dicarboxylate (2.61 g) and concentrated NH_4OH (20 ml) was allowed to react for 8 hr at 25°. The solid (2.1 g, 91%) was collected and dried: mp 250–252°; ir 1660 cm^{-1}; pmr δ 4.73 (d, H-4), 5.07 (d, H-5, $J_{4,5}$ = 6 Hz), 7.33–7.92 (m, C_6H_5); mass spectrum *m/e* (rel intensity) 234 (3), 233 (13), 190 (10), 189 (80), 172 (29), 147 (10), 146 (100), 145 (5), 144 (24), 130 (16), 118 (12), 117 (7), 116 (7), 115 (6), 104 (17), 103 (10), 91 (30), 89 (7), 87 (6), 86 (74), 78 (7), 77 (58), 76 (7), 63 (6), 51 (23), 50 (5), 44 (31), 39 (5) ir (Nujol) 1660 cm^{-1} (C=O).

Anal. Calcd for $C_{11}H_{11}N_3O_3$: N, 18.02. Found: N, 18.20.

Registry No.—**2a**, 35053-65-7; **2b**, 35053-66-8; **2c**, 35053-67-9; **3a**, 35053-68-0; **3b**, 35053-69-1; **3c**, 35053-70-4; **3d**, 35053-71-5; **5a**, 35053-72-6; **5b**, 35053-73-7; **6a**, 35053-74-8; **6b**, 35053-75-9; **6c**, 35053-76-0; 3-phenyl-2-isoxazoline-5-carboxylic acid, 4872-58-6; *trans*-3-phenyl-2-isoxazoline-4,5-dicarboxamide, 35053-78-2.

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(15) We are grateful to Dr. Richard S. Egan for this spectrum and solution. The ABX spectrum was calculated using LAOCN3 [S. Castellano and A. A. Bothner-by, *J. Chem. Phys.*, **41**, 3853 (1964)], as modified by Mr. W. C. Bass, Abbott Laboratories.

The Synthesis of 2,5- and 4,5-Dihydroxyxanthone[1]

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The photo-Fries rearrangement of *p*-methoxyphenyl 2,3-dimethoxybenzoic acid was advantageously employed in the preparation of 2-hydroxy-2′,3′,5-trimethoxybenzophenone which, after demethylation and cyclodehydration, provided the previously unknown 2,5-dihydroxyxanthone. Similarly, the irradiation of *o*-methoxyphenyl 2,3-dimethoxybenzoate provided the Fries rearrangement products 4-hydroxy- and 2-hydroxy-2′,3,3′-trimethoxybenzophenone. Demethylation and cyclization of the latter yielded 4,5-dihydroxyxanthone, also previously unknown.

We have already described research on the constituents of *Mammea americana* L. which led to the isolation of some simple mono- and dihydroxyxanthones.[4] Among the 16 possible dihydroxyxanthones, we noted that the 1,5, 2,5, and 4,5 isomers were unknown in the literature. The 1,5 isomer was synthesized and shown to be identical to one of the *Mammea* constituents.[4] Here we report the synthesis of the remaining two isomers and describe two new examples of the photo-Fries reaction.

2,5-Dihydroxyxanthone (Ia).—A simple and obvious pathway to Ia would involve treatment of the tetramethoxybenzophenone II with a Lewis acid in order to

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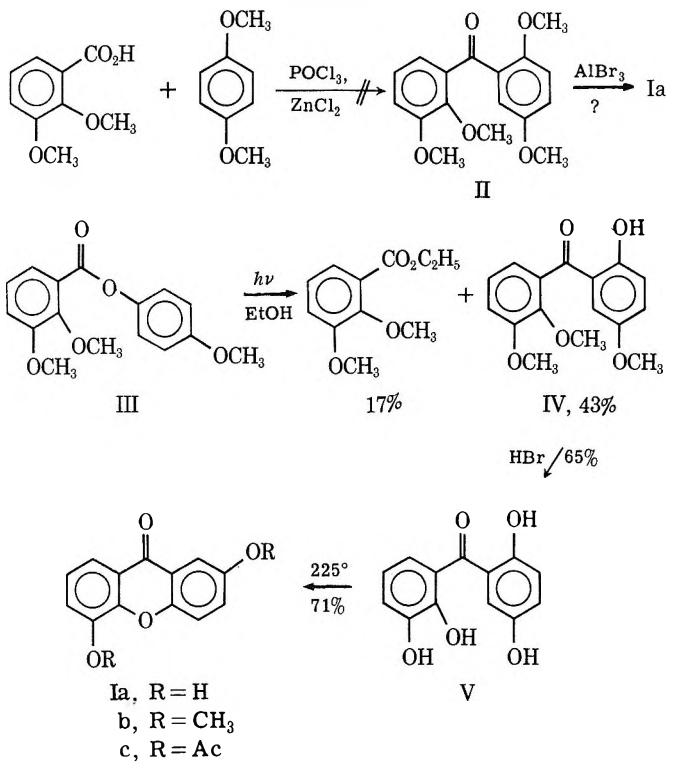
(2) This article was written while the author was a Guest Professor at the Institut für Pharmazeutische Arzneimittellehre der Universität München, and he wishes to thank the Directors of the Institute for their hospitality during this period.

(3) The experiments on which this article is based were taken from the Ph.D. thesis of K. E. M., presented to the Department of Medicinal Chemistry, State University of New York at Buffalo, April 1970.

(4) R. A. Finnegan and J. K. Patel, *J. Chem. Soc., Perkin Trans. 1*, (1972); see also R. A. Finnegan, J. K. Patel, and P. L. Bachman, *Tetrahedron Lett.*, 6087 (1966).

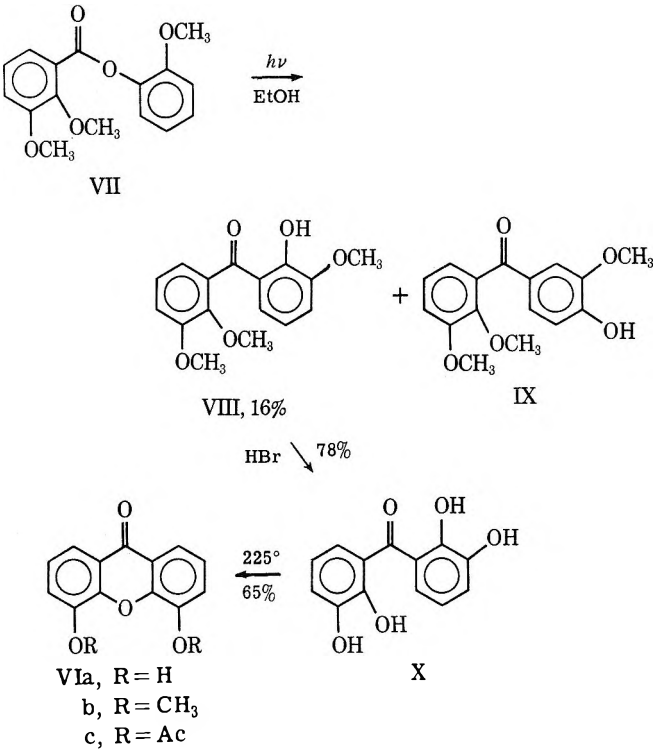
cause demethylation and cyclodehydration in a single operation,[5] as suggested at the top of Scheme I. Furthermore, the preparation of II was thought to be merely a matter of the condensation of 2,3-dimethoxybenzoic acid with *p*-dimethoxybenzene. In the event, however, neither of these reactions were directly realized. When the benzoic acid was condensed with the dimethoxybenzene, using the conditions established by Grover, Shah, and Shah,[6] a multicomponent mixture was produced which showed OH absorption in the infrared. Treatment of this product with dimethyl sulfate and alkali produced the ester III, identified by comparison with an authentic sample prepared separately. This indicates that even under the relatively mild conditions of the condensation reaction, demethylation was a primary reaction. This acid-catalyzed side reaction was avoided and the equally useful benzophenone IV was obtained indirectly by application of the photo-Fries reaction[7] to the ester III, as outlined in Scheme I. In addition to IV, there was formed a 17% yield of solvolysis product, the corresponding ethyl benzoate, which is of interest since this type of photosolvolysis is usually a very minor process except in the case of certain nitrobenzoates.[8] An attempt to convert IV directly to Ia with aluminum bromide[5] gave black tar. Compound IV was therefore demethylated by reaction with hydrogen bromide and the resultant tetrahydroxybenzophenone V was smoothly converted to the desired xanthone Ia, mp 303–305°, by heating it in water in a bomb at 225°.[9] The product Ia was further characterized by formation of its dimethyl ether Ib, mp 178–179°, and its diacetate derivative Ic, mp 159–160°.

SCHEME I



4,5-Dihydroxyxanthone (VIa).—Following the precedent set above for the preparation of Ia, the synthesis of VIa began with the preparation and irradiation of an ethanol solution of *o*-methoxyphenyl 2,3-dimethoxybenzoate (VII). In this case the photo-Fries rearrangement can and does lead to both the *o*- and *p*-hydroxy ketones VIII and IX, as shown in Scheme II.

SCHEME II



(Curiously, less than 2% of the photosolvolysis product, ethyl 2,3-dimethoxybenzoate, was formed in this reaction.) Treatment of VIII with aluminum bromide did not give the desired xanthone Va as expected, but only a low yield of 2,2′,3,3′-tetrahydroxybenzophenone (X). When VIII was refluxed with hydrobromic acid, however, compound X was produced in 78% yield. Cyclodehydration of X then afforded the xanthone VIa which was derivatized by preparation of the dimethyl ether VIb, mp 273–274°, and the diacetate VIc, mp 270–272°.

Experimental Section[10]

Methylation Procedure.—A mixture of the hydroxyxanthone (0.20–0.25 g), anhydrous potassium carbonate (3 g), acetone (50 ml), and dimethyl sulfate (4 ml) was refluxed for 15–20 hr. The potassium carbonate was filtered and the filtrate was evaporated nearly to dryness. Excess dimethyl sulfate was decomposed by addition of aqueous 2 *N* NaOH solution (5 ml) and by heating the resulting mixture on the steam bath. The

(5) G. V. Rao and T. R. Seshadri, *Proc. Indian Acad. Sci. Sect. A*, **37**, 710 (1953).

(6) P. K. Grover, G. D. Shah, and R. C. Shah, *J. Chem. Soc.*, 3982 (1955).

(7) For an excellent review, see D. Bellus, *Advan. Photochem.*, **8**, 109 (1971).

(8) R. A. Finnegan and D. Knutson, *J. Amer. Chem. Soc.*, **90**, 1670 (1968).

(9) J. M. Dutta, and E. R. Watson, *J. Chem. Soc. Ind.* **30**, 196 (1911).

(10) Melting points are uncorrected and were determined on a Fisher-Johns block for melting points below 300° and with a Mel-Temp apparatus for those above 300°. Infrared spectra were determined with a Perkin-Elmer Model 237 spectrophotometer. Only characteristic and/or strong absorptions (75% of the strongest) are reported. Ultraviolet and visible spectra were obtained with a Beckman DB-G grating spectrophotometer. Nmr spectra were determined with a Varian A-60 instrument using tetramethylsilane (TMS) as internal standard. Photolyses were carried out using a 450-W Hanovia medium pressure mercury arc lamp housed in a double-walled quartz immersion well. Additional details may be found in ref 3.

products were collected by filtration of the reaction mixture through a sintered glass funnel, washed extensively with water, dried, and purified by recrystallization or sublimation.

Acetylation Procedure.—A mixture of hydroxyxanthone (0.20–0.25 g), pyridine (4 ml), and acetic anhydride (4 ml) was allowed to stand for 24 hr at room temperature. The mixture was then poured into ice water and the resulting precipitate was collected on a filter. The solid was washed extensively with water, dried, and purified by recrystallization or sublimation.

***p*-Methoxyphenyl 2,3-Dimethoxybenzoate (III).**—A solution of 2,3-dimethoxybenzoyl chloride, bp 146–147° at 13 mm (lit.[11] bp 142–143° at 13 mm) (10.41 g), in pyridine (20 ml) was added to a solution of *p*-methoxyphenol (5.97 g) in pyridine (30 ml). The reaction mixture was refluxed for 4.5 hr, allowed to cool to room temperature, and poured into 200 ml of ice water. The aqueous mixture was extracted with ether (5 × 40 ml) and the combined ether extracts were washed with 10% aqueous HCl (3 × 50 ml), water (4 × 25 ml), 5% aqueous sodium carbonate solution (5 × 25 ml), water (4 × 25 ml), and saturated sodium chloride solution (2 × 25 ml). The ether solution was dried with anhydrous magnesium sulfate and evaporated to dryness. The oily residue was distilled under reduced pressure to afford a colorless liquid (11.78 g, 85%), bp 172°, at 0.025 mm. The distillate solidified and had mp 68–70°. Recrystallization from chloroform–hexane furnished white needles: mp 71–72°; ν_{max}^{KBr} 1733, 1511, 1477, 1263, 1193, 1043, 1007 cm^{-1}; λ_{max}^{EtOH} 242 (sh), 275, 283 (sh), 290 (sh), mμ (log ε 3.90, 3.62, 3.60, 3.49); nmr (CDCl$_3$–TMS) τ 2.3–3.3 (7 H, m), 4.01 (3 H, s), 4.11 (3 H, s), 4.20 (3 H, s).

Anal. Calcd for $C_{16}H_{16}O_5$: C, 66.66; H, 5.59. Found: C, 66.80; H, 5.43.

Photolysis of *p*-Methoxyphenyl 2,3-Dimethoxybenzoate (III). The Preparation of 2-Hydroxy-2′,3′,5-trimethoxybenzophenone (IV).—A solution of III (10.05 g) was irradiated at 30–40° for 9 hr. Progress of the reaction was followed by ir and vpc by periodic examination of aliquots. The ethanol solution was evaporated to dryness and the residue was chromatographed on 320 g of neutral alumina (Woelm, activity grade II). The initial hexane eluents (fractions 1 and 2) gave a yellow oil (1.67 g, 16.5%) which was identified as ethyl 2,3-dimethoxybenzoate by its ir and nmr spectra. It was not further purified. Further elution of the column with hexane and hexane–benzene mixtures (fractions 3–21) furnished yellow crystalline IV (4.47 g, 42.5%), mp 65–75°, which showed one spot on tlc. One recrystallization from aqueous pyridine provided IV with mp 74–76°: ν_{max}^{KBr} 1613, 1481, 1312, 1289, 1272, 1252, 1229, 1066, 826, 805, 781 cm^{-1}; λ_{max}^{EtOH} 225, 238 (sh), 371 mμ (log ε 4.34, 4.19, 3.61); $\lambda_{max}^{EtOH-NaOH}$ 227, 262, 408 mμ (log ε 4.33, 3.96, 3.85); nmr (CDCl$_3$–TMS) τ −1.9 (1 H, s), 2.6–3.2 (6 H, m), 6.03 (3 H, s), 6.14 (3 H, s), 6.33 (3 H, s).

Anal. Calcd for $C_{16}H_{16}O_5$: C, 66.66; H, 5.59. Found: C, 66.56; H, 5.56.

Further elution of the column with benzene, chloroform, ethanol, and mixtures of these solvents (fractions 22–51) gave a total of 2.2 g (22% by weight) of oily material. Analysis (tlc) showed this to be a mixture containing IV and two other materials of lower mobility. This was not further examined.

2,2′,3,5′-Tetrahydroxybenzophenone (V).—A solution of IV (2.00 g) in glacial acetic acid (30 ml) and 48% hydrobromic acid (20 ml) was refluxed for 4 hr. The resulting green solution was concentrated to 25 ml, diluted with water, and filtered. The filtrate was evaporated to dryness and the resulting residue was dissolved in ethyl acetate (200 ml), treated with charcoal, and again evaporated to dryness. The resultant yellow oil was triturated with water and the yellow solid which formed was separated by filtration, washed with water, and dried to give crude V, mp 187–189° (1.28 g, 79%). After sublimation and recrystallization from aqueous ethanol, there was obtained 1.05 g (64%) of V: mp 190–191°; ν_{max}^{KBr} 1634, 1613, 1600, 1580, 1458, 1330, 1269, 1221 cm^{-1}; nmr (acetone-d_6, TMS) τ 2.7–3.4 (6 H, m), 0.56–1.57 (4 H, s).

Anal. Calcd for $C_{13}H_{10}O_5$: C, 63.41; H, 4.09. Found: C, 62.76; H, 4.22.

2,5-Dihydroxyxanthone (Ia).—A mixture of V (1.05 g) and water (10 ml) in a stainless steel bomb was kept for 17 hr at 225°. After the mixture cooled to room temperature the material was separated by filtration and dried to give brown needles of Ia, 295–300° (0.70 g, 72%). This product was dissolved in ethyl acetate and treated with charcoal. The solution was evaporated and the residue was sublimed to give yellow needles: mp 303–305°; ν_{max}^{KBr} 1639, 1616 (sh), 1600, 1585 (sh), 1495, 1471, 1460 (sh), 1316, 1248, 1208, 766 cm^{-1}; $\lambda_{max}^{EtOH-0.01\ N\ HCl}$ 253, 282 (sh), 372 mμ (log ε 4.58, 3.45, 3.79); $\lambda_{max}^{EtOH-0.01\ N\ NaOH}$ 252 (sh), 275, 430 mμ (log ε 4.44, 4.58, 3.72); nmr (pyridine-d_5, TMS) τ −1.75 (2 H, s), 1.93–3.21 (6 H, m).

Anal. Calcd for $C_{13}H_8O_4$: C, 68.42; H, 3.53. Found: C, 68.24; H, 3.66.

2,5-Dimethoxyxanthone (Ib).—Methylation of Ia (0.20 g) afforded tan needles (0.21 g, 98%), mp 167–170°. This crude material was sublimed, chromatographed through neutral alumina, and recrystallized from chloroform–hexane to give fine white needles of Ib (0.17 g, 78%), mp 176.5–177°. Two additional recrystallizations from chloroform–hexane raised the melting point to 178–179°: ν_{max}^{KBr} 1661, 1645, 1600, 1490, 1439, 1431, 1314, 1269, 1148, 752 cm^{-1}; nmr (CDCl$_3$–TMS) τ 2.14–2.90 (6 H, m), 6.04 (3 H, s), 6.13 (3 H, s).

Anal. Calcd for $C_{15}H_{12}O_4$: C, 70.30; H, 4.72. Found: C, 70.07; H, 4.71.

2,5-Diacetoxyxanthone (Ic).—Acetylation of Ia (0.15 g) afforded a tan solid (0.20 g, 97%), mp 150–154°. Sublimation and three recrystallizations from chloroform–hexane gave pure Ic: mp 159–160°; ν_{max}^{KBr} 1779, 1761, 1669, 1481, 1451, 1314, 1252, 1221, 1143, 912, 882, 766 cm^{-1}; nmr (CDCl$_3$–TMS) τ 1.85–2.89 (6 H, m), 7.62 (3 H, s), 7.72 (3 H, s).

Anal. Calcd for $C_{17}H_{12}O_6$: C, 65.38; H, 3.87. Found: C, 65.19; H, 3.83.

***o*-Methoxyphenyl 2,3-Dimethoxybenzoate (VII).**—A mixture of *o*-methoxyphenol (16.00 g), 2,3-dimethoxybenzoyl chloride (22.77 g), and pyridine (75 ml) was refluxed for 5 hr. Excess pyridine was removed under reduced pressure and the remaining liquid was dissolved in ether (800 ml). The ether solution was washed with water (2 × 50 ml), 2 *N* hydrochloric acid (3 × 40 ml), water (3 × 50 ml), 10% aqueous sodium bicarbonate solution (2 × 50 ml), water (2 × 50 ml), and saturated sodium chloride solution (2 × 50 ml). The ether solution was dried with anhydrous magnesium sulfate and the ether was evaporated under reduced pressure. The residual yellow oil was distilled, bp 174–178° at 0.2 mm, to give 29.38 g (90%) of colorless VII. This material crystallized from a hexane suspension to give 27.47 g (83%) of crystalline white solid: mp 49–50°; ν_{max}^{KBr} 1748, 1504, 1486, 1312, 1285 (sh), 1261, 1238, 1170, 1111, 1044, 757 cm^{-1}; λ_{max}^{EtOH} 242 (sh), 273, 279, 298 mμ (log ε 3.66, 3.42, 3.43, 3.24); nmr (CDCl$_3$–TMS) τ 2.3–3.4 (7 H, m), 6.10 (3 H, s), 4.27 (3 H, s), 4.29 (3 H, s).

Anal. Calcd for $C_{16}H_{16}O_5$: C, 66.66; H, 5.59. Found: C, 66.53; H, 5.63.

Photolysis of *o*-Methoxyphenyl 2,3-Dimethoxybenzoate (VII). Preparation of the Benzophenones VIII and IX.—A solution of VII (9.34 g) in absolute ethanol (320 ml) was irradiated for 22 hr. The solvent was then evaporated under reduced pressure and the residue was chromatographed on 320 g of neutral alumina (Woelm, activity grade III). The initial hexane eluents (fractions 1–4) gave no residues. A yellow oil (0.16 g) was obtained from fractions 5–7 which were eluted with hexane and hexane–benzene mixtures. Thin-layer chromatography indicated the presence of three components and no attempt was made to further purify this product. Further elution of the column with hexane–benzene mixtures (fractions 8–16) furnished crystalline yellow residues. The residue from fraction 8 (0.62 g) was recrystallized from absolute ethanol to give fine yellow needles of VIII, mp 70–90° (0.46 g, 5%). The residues from fractions 9–16 showed a single spot on tlc and were combined to give an additional amount of VIII (1.05 g, 11%), mp 90–100°. Six recrystallizations from absolute ethanol raised the melting point of VIII to 110–110.5°: ν_{max}^{KBr} 1634, 1475, 1466, 1445, 1346, 1312, 1269, 1250, 999, 992, 758, 749, 741 cm^{-1}; nmr (CDCl$_3$–TMS) τ −2.3 (1 H, s), 2.7–3.4 (6 H, m), 6.08 (6 H, s), 6.22 (3 H, s); $\lambda_{max}^{EtOH-0.01\ N\ HCl}$ 227, 272, 355 mμ (log ε 4.41, 4.11, 3.49); $\lambda_{max}^{EtOH-0.01\ N\ NaOH}$ 235 (sh), 275, 392 mμ (log ε 4.32, 3.95, 3.86).

Anal. Calcd for $C_{16}H_{16}O_5$: C, 66.66; H, 5.59. Found: C, 66.58; H, 5.63.

Further elution of the column with benzene (fractions 17–23) gave mixtures of VIII and IX (1.28 g, 14%). Fractions 24–31, showing two spots on tlc, and having a combined weight of 0.93 g (10%), were recrystallized from benzene to afford IX, 0.62 g, mp 137–142°, as a tan solid. Five recrystallizations from benzene furnished white crystalline IX: mp 143–143.5°; ν_{max}^{KBr} 1650, 1595, 1582, 1513, 1477, 1466, 1427, 1316, 1279, 1248,

(11) F. Mauthner, *J. Prakt. Chem.*, **112**, 63 (1926).

1159, 1086, 1002, 998, 766, 745 cm^{-1}; nmr ($CDCl_3$–TMS) τ 2.3–3.3 (6 H, m), 3.48 (1 H, s), 6.10 (6 H, s), 6.23 (3 H, s); $\lambda_{max}^{EtOH-0.01\ N\ HCl}$ 228, 283, 312 mμ (log ϵ 4.29, 4.04, 4.08); $\lambda_{max}^{EtOH-0.01\ N\ NaOH}$ 255, 285 (sh), 360 mμ (log ϵ 4.04, 3.57, 4.44).

Anal. Calcd for $C_{16}H_{16}O_5$: C, 66.66; H, 5.59. Found: C, 66.84; H, 5.79.

Further elution of the column with benzene, chloroform, ethyl acetate, and mixtures of these solvents gave mixtures (2.9 g, 32%) which contained both VIII and IX and at least two other components (tlc) which were not identified. Three additional portions (10 g each) of VII were photolyzed and provided, after work-up, an additional 4.1 g (14%) of VIII, mp 107–108°.

2,2′,3,3′-Tetrahydroxybenzophenone (X).—A solution of VIII (4.0 g) in glacial acetic acid (60 ml) and 48% hydrobromic acid (40 ml) was refluxed for 5 hr. The solution was concentrated to *ca.* 50 ml, diluted with water (150 ml), and filtered. The filtrate was allowed to stand for 12 hr at room temperature, whereupon the precipitate was collected by filtration, washed with water, and dried to give fine yellow needles of X (2.65 g, 78%), mp 120–121°. Sublimation followed by recrystallization from water gave X with mp 121–122°: ν_{max}^{KBr} 3600–2700 (broad), 1626, 1475, 1449, 1332, 1279, 1442, 1190, 854, 752, 740 cm^{-1}; $\lambda_{max}^{EtOH-0.01\ N\ HCl}$ 223, 275, 350 mμ (log ϵ 4.30, 4.08, 3.56); $\lambda_{max}^{EtOH-0.01\ N\ NaOH}$ 240, 273 (sh), 308, 365 mμ (log ϵ 4.35, 4.04, 4.05, 3.38).

Anal. Calcd for $C_{13}H_{10}O_5$: C, 63.41; H, 4.09. Found: C, 63.03; H, 4.12.

4,5-Dihydroxyxanthone (VIa).—A mixture of X (1.5 g) and water (15 ml) was heated in a stainless steel bomb for 19 hr between 220–230°. The mixture was then cooled and the solid material was separated by filtration, washed with water, and dried. Sublimation afforded crystalline yellow VIa (0.91 g, 65%) which decomposed at 350°. Recrystallization from absolute alcohol furnished fine yellow needles: mp >350° (dec); ν_{max}^{KBr} 1600, 1468, 1374, 1350, 1255, 1170, 742 cm^{-1}; $\lambda_{max}^{EtOH-0.01\ N\ HC}$ 247, 300, 358 mμ (log ϵ 4.66, 3.82, 3.77); $\lambda_{max}^{EtOH-0.01\ N\ NaOH}$ 264, 316, 350, 410 mμ (log ϵ 4.62, 3.76, 3.63, 3.61); nmr (DMSO-d_6, TMS) τ 2.15–3.15 (m).

Anal. Calcd for $C_{13}H_8O_4$: C, 68.42; H, 3.53. Found: C, 68.01; H, 3.85.

4,5-Dimethoxyxanthone (VIb).—Methylation of 4,5-dihydroxyxanthone (VIa) (0.20 g) afforded 0.15 g (68%) of a crystalline white solid, mp 273–275° (subl). Sublimation followed by recrystallization furnished fine white needles of VIb (0.12 g): mp 273–274° (subl); ν_{max}^{KBr} 1660, 1490, 1441, 1360, 1339, 1282, 1230, 1078, 750 cm^{-1}; nmr ($CDCl_3$–TMS) τ 2.03–2.76 (6 H, m), 5.93 (6 H, s).

Anal. Calcd for $C_{15}H_{12}O_4$: C, 70.30; H, 4.72. Found: C, 70.14; H, 4.92.

4,5-Diacetoxyxanthone (VIc).—Acetylation of VIa (45 mg) afforded a white crystalline solid (58 mg, 94%), mp 263–268°. Sublimation furnished fine white needles of VIc: mp 270–272°; ν_{max}^{KBr} 1764, 1669, 1493, 1475, 1447, 1372, 1326, 1230, 1178, 753 cm^{-1}; nmr ($CDCl_3$–TMS) τ 1.80–2.78 (6 H, m), 7.59 (6 H, s).

Anal. Calcd for $C_{17}H_{12}O_6$: C, 65.38; H, 3.87. Found: C, 65.32; H, 4.04.

Registry No.—Ia, 35040-32-5; Ib, 35040-33-6; Ic, 35040-34-7; III, 35040-35-8; IV, 35040-36-9; V, 35040-37-0; VIa, 35040-38-1; VIb, 35040-39-2; VIc, 35040-40-5; VII, 35040-41-6; VIII, 35040-42-7; IX, 35042-49-0; X, 35042-50-3.

Semihydrogenation of 1-Phenyl-4-penten-2-yn-1-one and of 1-Phenyl-3-(cyclohexen-1-yl)-2-propynone[1]

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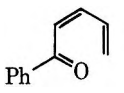
Semihydrogenation of 1-phenyl-4-penten-2-yn-1-one gave mainly 1-phenyl-2-penten-1-one. Addition of 1 mol of hydrogen to 1-phenyl-3-(cyclohexen-1-yl)-2-propynone (4) gave a mixture in which 6-phenyl-2,3-cyclohexa-2*H*-pyran and *cis*-2,3-cyclohexa-6-phenyl-3,4-dihydro-2*H*-pyran were identified by spectral methods and from which *cis*-2,3-cyclohexa-6-phenyltetrahydropyran and 3-cyclohexyl-1-phenyl-1-propanone could be isolated.

The synthesis of some cis dienones was a crucial part of a project aimed at elucidation of the electrocyclic equilibrium between α-pyrans and cis dienones. Some early studies by Schinz and his students[2] have shown that semihydrogenation of some enynones gave mixtures which appeared to contain at least the α-pyran valence isomer, and perhaps both the pyran and the cis dienone. We have investigated this semihydrogenation route to cis dienones with considerable care, and the results described here will show why we have become disenchanted with this beguilingly simple process.

Schinz[2c] indicated that partial reduction of dodec-5-en-3-yn-2-one gave mainly 2-hexyl-6-methyl-2*H*-pyran. To enhance the value of ultraviolet spectroscopy as an *a priori* device for distinguishing between cis dienone and α-pyran forms, we decided to employ phenyl rather than methyl ketones. Ring closure would then be expected to lead to a large (*ca.* 40 nm) bathochromic shift.



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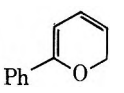

3

1-Phenyl-4-penten-2-yn-1-one (1) was prepared by Jones oxidation of the corresponding alcohol,[3] and it was reduced over a variety of palladium catalysts under varying conditions. The product inevitably contained unreacted 1, and, when its uv absorption was subtracted from that of the mixture, the difference spectrum had a λ_{max} at 257 nm. 1-Phenyl-2-buten-1-one absorbs at 256 nm.[4] Thus the 257-nm band along with a band at 734 cm^{-1} identified the main product as *cis*-1-phenyl-2-penten-1-one. Clearly a terminal vinyl group and the triple bond are reduced competitively.

$$\underset{1}{PhCOC{\equiv}CCH{=}CH_2} \xrightarrow[Pd]{H_2} 1 + \underset{cis}{PhCOCH{=}CHEt}$$

1-Phenyl-3-(cyclohexen-1-yl)-2-propynone (4) was selected as a second substrate to reduce the competition by the double bond. Semihydrogenation of 4 gives a

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(2) (a) V. Theus, W. Surber, L. Colombi, and H. Schinz, *Helv. Chim. Acta*, **37**, 239 (1955); (b) V. Theus and H. Schinz, *ibid.*, **39**, 1290 (1956); (c) W. Surber, V. Theus, L. Colombi, and H. Schinz, *ibid.*, **39**, 1299 (1956).

(3) Y. S. Zal'kind and A. I. Kulikov, *Zh. Obshch. Khim.*, **15**, 643 (1945).

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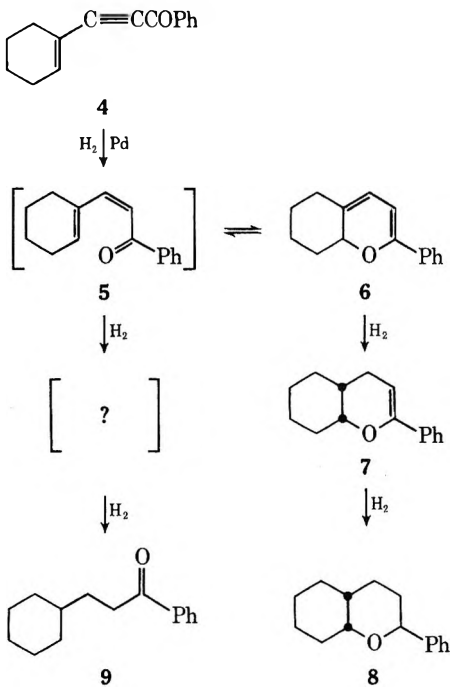
complex mixture. Persistent attempts to isolate either a pyran or a cis dienone were of little avail. Both fully saturated products **8** and **9** were isolated, but a combination of separative methods and spectral measurements provided strong support for the reaction series of Scheme I. No products of initial reduction of the cyclohexene

SCHEME I



bond or of a reduction level between **5** and **9** were uncovered.

Evidence for the Presence of 6.—An unstable compound can be separated in impure form from the semihydrogenation mixture by column chromatography. This substance has λ_{max} 338 nm ($\epsilon \sim 10{,}000$). Removal of the solvent gave a gummy residue having ir bands at 1660, 1600, 1575, 1500, 1083, 755, and 686 cm^{-1}. The nmr spectrum of the material was characterized by two bands at δ 5.49 (2 H) and 4.85 (1 H). While we were unable to isolate the pure compound because of its instability, we can assign the structure **6** to this substance. The most revealing piece of evidence is the uv band at 338 nm. This eliminates **5** from consideration since *trans*-3-(cyclohexen-1-yl)-1-phenyl-2-propen-1-one (**10**) has a λ_{max} at 308 nm, while *trans*-chalcone and its cis isomer absorb at 299 and 290 nm, respectively.[5] Recently Dreux[6] has reported that 2,6-diphenyl-2,4-dimethyl-α-pyran absorbs at 323 nm while 2,4,6-triphenyl-α-pyran has a λ_{max} at 340 nm.

The nmr and ir spectra add support to this assignment. If it is assumed that the phenyl region in the nmr corresponds to five protons, then the total proton count is 16. The olefinic protons in all known α-pyrans except 2,2,4,6-tetraphenyl-α-pyran lie between 4.5 and 5.7 ppm.[6,7] Generally the protons at C_3 and C_4 are separated by *ca.* 0.3 ppm and have $J \cong 6$ Hz, but apparently those in **6** coincidentally have the same chemical shift. In accord with this suspicion the singlet at δ 5.49 disappears almost completely if partial reduction is carried out with deuterium. Attempts to trap **6** by formation of a stable Diels–Alder adduct failed. Use of tetracyanoethylene, dimethyl acetylenedicarboxylate, or *N*-phenylmaleimide led in all cases to recovery of starting material.

Evidence of the Presence of 7.—The lack of clean selectivity for reduction of the triple bond of **4** leads to overhydrogenation products. Most interesting is the compound **7**, never isolated in pure form, which was identified by spectral means. Column chromatography of the semihydrogenation mixture gives a mixture whose main component has a doublet of doublets at δ 5.13 and a broad singlet at δ 4.09. Decoupling showed that the δ 5.13 peak is the X portion of a modified AMX pattern. The A proton appears as a doublet of doublets (broadened by further unresolved coupling) at δ 1.82, and the M proton as a doublet of quartets at δ 2.41. First-order analysis gives $J_{AX} \cong 6$, $J_{MX} \cong 3$, and $J_{AM} = 17$ Hz (probably a negative sign). In view of its magnitude[8] J_{AM} must represent the geminal coupling constant for an allylic CH_2 group. The M proton is coupled to an additional proton with $J = 6.5$ Hz, while the A proton coupling is too small to be resolved. These data suggest that a $CHCH_2CH{=}C<$ group must be part of a ring system sufficiently rigid to fix the dihedral angle between the methine and the A proton close to 90°. The structure **7** fits this requirement, and inspection of models shows that only the cis ring juncture will permit the necessary dihedral angle. Further support for the cis ring juncture is provided by the hydrogenolysis experiment (see below).

Isolation and Identification of 8 and 9.—Both **8** and **9** can be separated from the semihydrogenation mixture by either vapor phase or column chromatography. However, they were isolated and identified from deliberate overhydrogenation experiments. If the normal semihydrogenation mixture was chromatographed to obtain a solution having λ_{max} 338 nm, complete hydrogenation over either palladium or platinum oxide gave both **8** and **9**. **8** was identified by its nmr spectrum, which contains a doublet of doublets at δ 4.30 and a broad singlet at δ 3.70. Hydrogenolysis of **8** gave the known[9] *cis*-2-(γ-phenylpropyl)cyclohexanol. **9** was identified by comparison with an authentic sample prepared by complete hydrogenation of **4** over platinum oxide. Its presence can be ascertained by the characteristic triplet at δ 2.84 for the CH_2COPh protons.

Conclusions.—These results show that the selectivity of a palladium catalyst for the triple bond of an enynone with the acetylenic bond directly attached to the carbonyl group is discouragingly low. The reaction might be useful for preparation of either a cis dienone or the corresponding α-pyran provided (a) the double bond provides no competition to the triple bond for primary hydrogen uptake and (b) the reduction products are stable enough to survive separation from the reaction mixture. Catalyst selectivity is much better for enynones if the triple bond is terminal in the conjugated

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system.[10-12] Success has also been achieved in cases where the triple bond, while not terminal in a conjugated system, was not adjacent to the carbonyl group.[13-15] During the course of this study we also found that the Diels–Alder route to cis dienones failed when **4** proved unreactive toward cyclopentadiene and 2,3-dimethyl-1,3-butadiene.

Experimental Section

1-Phenyl-4-penten-2-yn-1-ol.—A cold ether solution of vinylacetylene (61 g, 1.18 mol) was added to a solution containing 0.8 mol of ethylmagnesium bromide under a nitrogen atmosphere. The solution was heated for 3 hr under reflux, and then 85 g (0.8 mol) of benzaldehyde was added. The reaction was stirred for 6 hr and the mixture was decomposed with saturated ammonium chloride. The ether solution was dried ($MgSO_4$) and the product was isolated as a yellow oil, bp 125° (5 mm), $n^{18}D$ 1.5730 [lit.[3] bp 125° (5 mm), $n^{17}D$ 1.5747]. The yield was 40 g (32%).

1-Phenyl-4-penten-2-yn-1-one (1).—A solution containing 2.18 g (0.22 mol) of chromium trioxide and 1.8 ml of concentrated sulfuric acid in 6.0 ml of water was added slowly to a cold solution of 5.0 g (0.032 mol) of 1-phenyl-4-penten-2-yn-1-ol in 10 ml of acetone. The product was extracted with ether and the extracts were dried ($MgSO_4$). After the ether had been removed the residue was chromatographed over 125 g of activity III alumina using petroleum ether (bp 30–60°) as eluent. A light yellow oil was isolated: yield 3.25 g; λ_{max} 270 nm (ϵ 5480); ir (neat) 2219, 1640, 1598, 1580, 1260 cm^{-1}. *Anal.* Calcd for $C_{11}H_8O$: C, 84,63; H, 5.13. Found: C, 84.43; H, 5.30.

A 2,4-dinitrophenylhydrazone was prepared according to the procedure of Shriner, Fuson, and Curtin,[16] mp 192–192.5°. *Anal.* Calcd for $C_{17}H_{12}N_4O_4$: C, 60.71; H, 3.57. Found: C, 60.91; H, 3.62.

Semihydrogenation of 1.—Solutions of **1** containing between 1.33 and 2.00 mmol of **1** were hydrogenated in the dark until between 0.9 and 1.2 molar equiv of hydrogen had been absorbed. About 20–30% of catalyst (by weight) compared with **1** was used. For most runs 5% palladium on calcium carbonate was employed either alone or with added zinc acetate or quinoline. Lindlar[17] catalyst gave no better results. Ethyl acetate, heptane, and methanol were used as solvents; no advantage was noted for any one of these. During the reaction ir bands at 2210, 1640, and 1260 cm^{-1} diminished but did not disappear; bands at 1665, 1612, and 1225 cm^{-1} appear. In the uv the λ_{max} at 270 nm diminishes and a new λ_{max} at 259 nm appears.

1-Phenyl-3-(cyclohexen-1-yl)-2-propynone (4).—Ethynylcyclohexene[18] (65.0 g, 0.61 mol) in ether was added to a solution containing 0.61 mol of ethylmagnesium bromide, and the reaction mixture was heated under reflux for 4 hr. This solution was cooled and 64.6 g (0.61 mol) of benzaldehyde in 100 ml of ether was added. After having been stirred for 6 hr, the solution was decomposed with saturated ammonium chloride. The crude 1-phenyl-3-(cyclohexen-1-yl)-2-propynol, mp 42°, was obtained by evaporation of the ether and was used in the next step.

This alcohol (41.0 g, 0.19 mol) was oxidized according to the procedure for preparation of **1**. The ketone **4** was isolated by chromatography over activity III alumina using petroleum ether as eluent. A light yellow oil was obtained: $n^{25}D$ 1.6040; uv max (EtOH) 304 nm (ϵ 10,800); ir (thin film) 1630, 1608, 1580, 1280 cm^{-1}; nmr (CCl_4) δ 8.0 and 7.36 (two m, 5 H), 6.43 (m, 1 H), 2.25 (m, 4 H), and 1.69 (m, 4 H). It was isolated in 84% yield. *Anal.* Calcd for $C_{15}H_{14}O$: C, 85.71; H, 6.66. Found: C, 85.64; H, 6.69.

A 2,4-dinitrophenylhydrazone prepared by the procedure of Shriner, Fuson, and Curtin[16] melted at 213–214°. *Anal.* Calcd for $C_{21}H_{18}N_4O_4$: C, 64.62; H, 4.61. Found: C, 64.47; H, 4.83.

Semihydrogenation of 4.—A series of runs under varied conditions using the infrared spectrum of the crude product as an analytical measure suggested that the outcome was influenced only in small measure whether palladium on calcium carbonate or Lindlar catalyst was used, whether ethyl acetate or cyclohexane was the solvent, and whether quinoline was present or absent. The following procedure was then adopted.

The catalyst, 5% palladium on calcium carbonate (200 mg), was prehydrogenated under cyclohexane. A solution of 400 mg of *freshly chromatographed* **4** in cyclohexane was added *via* a serum cap and hydrogenation was allowed to proceed at 1 atm hydrogen pressure until 1 molar equiv had been added. The catalyst was removed by filtration and the solvent by evaporation. The crude product was treated as described below.

Identification of 2,3-Cyclohexa-6-phenyl-2*H*-pyran (6).—The crude product from semihydrogenation of **4** was chromatographed on 25 times its weight of Mallinckrodt 100 mesh silicic acid using hexane as an eluent. Overreduced products eluted first followed by an unstable yellow oil: uv max (cyclohexane) 338 nm (ϵ ~10,000); ir (thin film) 1660, 1600, 1575, 1373, 1265, 1083 cm^{-1}; nmr (CCl_4) δ 7.48 and 7.19 (two m), 5.51 (s), 4.86 (m), and 2.3–1.2 (broad m) with relative areas of 5:1.8:0.8:8.8. The oil was unstable and could not be isolated in a pure state. *Anal.* Calcd for $C_{15}H_{16}O$: C, 84.95; H, 7.59. Found: C, 84.10; H, 7.62; C, 83.84; H, 7.61.

Attempted Formation of Diels–Alder Adducts of 6.—A solution containing 0.125 g of the semihydrogenation product of **4** and 0.080 g of dimethyl acetylenedicarboxylate in 10 ml of benzene was heated at reflux under nitrogen for 10 hr. Examination of the reaction mixture by vpc on a 20% Apiezon on Chromosorb W column at 162° before and after heating showed that no reaction had occurred. The same mixture was heated in xylene with an equivalent result.

A mixture of 170 mg of *N*-phenylmaleimide and 210 mg of the semihydrogenation product of **4** was heated under reflux for 16 hr. Examination *via* vpc on a 20% SE-30 on 45/60 mesh Chromosorb W column at 188° showed that no reaction took place.

Identification of *cis*-2,3-Cyclohexa-6-phenyl-3,4-dihydropyran (7).—If the mixture from semihydrogenation of **4** (450 mg of **4** and 1.26 molar equiv of hydrogen added) was chromatographed over silicic acid as described above except that 10% benzene in petroleum ether was used as the eluent, a fraction having uv max (EtOH) 218, 227, 239, 263, and 336 nm was isolated, nmr (CCl_4) δ 7.5 and 7.19 (2 m), 5.46 (s), 5.13 (d of d), 4.09 (broad s), 2.84 (t, J = 6.5 Hz), and 2.5–1.0 (complex m). Irradiation of the δ 5.13 band collapsed two quartets at δ 2.51 and 2.34 to a pair of doublets and a pair of doublets at δ 1.90 and 1.73 to a pair of singlets. Irradiation of the δ 4.09 band causes a change in a part of the complex multiplet near δ 2.08, and conversely irradiation in this region sharpens the broad singlet at δ 4.09 quite effectively. Interpretation is given in the discussion section of this paper.

Direct vpc separation of the semihydrogenation mixture on a 5 ft × 0.25 in. 20% SE-30 on Chromosorb W column at 182° gave four peaks, the second of which was mainly **7**, nmr (CCl_4) δ 5.13 and 4.09, mol wt 214 (mass spectrum).

***cis*-2,3-Cyclohexa-6-phenyltetrahydropyran (8). A. From Hydrogenation of 6.**—After 1.14 molar equiv of hydrogen had been added to 110 mg of **4** as described earlier, the product mixture was divided into two halves. To the first half 0.20 g of platinum oxide catalyst was added, and the mixture was hydrogenated until absorption ceased. The catalyst was removed by filtration and the solvent by evaporation. Vpc analysis on the SE-30 column at 188° gave three peaks. The first to elute was a liquid, nmr (CCl_4) δ 7.20 (s, 5 H), 4.31 (m, 1 H), 3.68 (broad s, 1 H), 2.0–1.0 (m, 13 H).

The second half of the semihydrogenation mixture was chromatographed over silicic acid as described for identification of **6**. The main material isolated was hydrogenated over platinum oxide until saturated. This material was chromatographed over activity II–III alumina using a gradient elution with pentane containing increasing amounts of benzene. The early fractions (20%) contained an oil, ir (thin film) 1095, 1060, 988, 950, 750, 696 cm^{-1}, nmr (CCl_4) as above. *Anal.* Calcd for $C_{15}H_{20}O$: C, 83.28; H, 9.32. Found: C, 83.00; H, 9.12.

B. From Semihydrogenation of 4.—A sample (400 mg) of **4** was hydrogenated (1.01 molar equiv) as described above. The

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(15) R. Ahmad and B. C. L. Weedon, *ibid.*, 3299 (1953).

(16) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 5th ed, Wiley, New York, N. Y., 1964, p 253.

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(18) J. C. Hamlet, H. B. Henbest, and E. R. H. Jones, *J. Chem. Soc.*, 2652 (1951).

product was separated by vpc on the SE-30 column, and the first peak had spectral properties which identified it as **8**.

3-Cyclohexyl-1-phenylpropan-1-one (9). A. From 4.—A mixture of 2.66 g of platinum oxide and 39.0 g (0.18 mol) of **4** was hydrogenated at 20 psig initial hydrogen pressure in a Parr shaker. Chromatography of the crude product over activity III alumina gave a white solid: mp 43°; ir (CCl_4) 1676, 1593, 736, 690 cm^{-1}; nmr (CCl_4) δ 7.3 (m, 5 H), 2.84 (t, J = 6.7 Hz, 2 H), and 1.9–1.0 (broad m, 14 H); 80% yield. *Anal.* Calcd for $C_{15}H_{20}O$: C, 83.28; H, 9.32. Found: C, 83.54; H, 9.15.

B. From Hydrogenation of 6.—The product described under part A of the preparation of **8** above was separated by vpc into three fractions. The third fraction (last to elute) was identified spectrally as **9**.

C. From Semihydrogenation of 4.—The semihydrogenation product described in part B of the preparation of **8** was separated by vpc. The last material to elute was identified spectrally as **9**.

***trans*-3-(Cyclohexen-1-yl)-1-phenyl-2-propen-1-ol.**—A solution of 5.0 g (0.03 mol) of **4** in 100 ml of ether was added to a suspension of 0.82 g (0.024 mol) of lithium aluminum hydride in ether. The mixture was stirred for 5 hr at room temperature and for 30 min at reflux. The mixture was carefully treated with saturated ammonium chloride, and the ether layer was separated and dried ($MgSO_4$). After the ether layer had been concentrated to *ca.* 100 ml, an equal volume of petroleum ether was added and a white solid was precipitated: mp 64–65; ir (CCl_4) 3160, 1630, 1185, 1088, 960, 755, 600 cm^{-1}; nmr (CCl_4) δ 6.99 (s, 5 H), 5.88 and 5.40 (modified AB, J_{AB} = 15 Hz, 2 H), *ca.* 5.48 (?, 1 H), 4.79 (m, 1 H), 3.31 (OH), 1.78 (m, 4 H), and 1.49 (m, 4 H); yield 3.09 g. *Anal.* Calcd for $C_{15}H_{18}O$: C, 84.61; H, 8.46. Found: C, 84.30; H, 8.46.

***trans*-3-(Cyclohexen-1-yl)-1-phenyl-2-propen-1-one (10). From the Alcohol.**—The above alcohol was oxidized as described for the preparation of **4**. The crude reaction product was chromatographed an activity II alumina with 5% benzene in petroleum ether. The main fraction, a yellow oil, was recrystallized from petroleum ether to give a white solid: mp 68.5–69.5°; uv max (EtOH) 307.5 nm (ϵ 23,900); ir (CCl_4) δ 7.88 and 7.46 (two m, 5 H), 7.27 and 6.76 (AB, J = 16.0 Hz), 6.18 (m, 1 H), 2.22 (broad s, 4 H), 1.69 (broad s, 4 H). *Anal.* Calcd for $C_{15}H_{16}O$: C, 84.95; H, 7.59. Found: C, 85.05; H, 7.77.

***cis*-2-(3-Phenylpropyl)cyclohexanol.**—A sample (100 mg) of **8** was hydrogenated at atmospheric pressure over 25 mg of palladium on charcoal in 5 ml of glacial acetic acid. The product, a colorless oil, was heated with 125 mg of 2,4-dinitrobenzoyl chloride for several minutes and the crystalline product was recrystallized from 95% ethanol, mp 101–102° (lit.[9] mp 101–102°).

Attempted Preparation of Diels–Alder Adducts of 4.—A solution of 131 mg of **4** and 100 mg of 2,3-dimethylbutadiene in 20 ml of benzene was heated under reflux for 12 hr. Vpc analysis showed that no reaction had occurred. The solution was then heated for 4 days at 105° in a sealed tube. Analysis again showed no reaction.

A solution of 600 mg of **4** and 600 mg of cyclopentadiene in 3 ml of xylene was heated in a sealed tube at 145° for 12 hr. Again no reaction occurred.

Registry No.—**1**, 16278-55-0; **1** DNP, 21961-16-0; **4**, 16616-44-7; **4** DNP, 35030-87-6; **6**, 35030-88-7; **8**, 35030-89-8; **9**, 28861-24-7; **10**, 35030-91-2; *trans*-3-(cyclohexen-1-yl)-1-phenyl-2-propen-1-ol, 35030-92-3.

Rates of Electrocyclic Reactions. Conversion of α-Pyrans to Cis Dienones[1]

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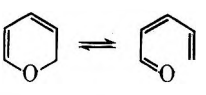
The equilibrium constant, K_{18} = 0.094, for the interconversion of 1-oxa-2,5,5,8a-tetramethyl-5,6,7,8-tetrahydronaphthalene (**3**) and *cis*-β-ionone (**2**) was measured at several temperatures, ΔH° = 5.5 kcal/mol and ΔS° = 14 eu. Both the rate of conversion of **3** to **2** (k_1) and the reverse rate (k_{-1}) were measured directly by nmr at several temperatures. At 18° k_{-1} equals 1.39 × 10^{-3} sec^{-1} and k_1 is 1.31 × 10^{-4} sec^{-1} with $\Delta H^{\pm} \cong$ 19 kcal/mol for the reverse reaction. An indirect method of determining the rate (k_1) of ring-opening of an α-pyran *via* rapid selective reduction of the cis dienone was developed. Tested on **3** this method gave k_1 as 3.2 × 10^{-5} sec^{-1} at 15°. At 14.6° the rate of the retroelectrocyclic reaction of 2,2,4,6-tetramethyl-α-pyran is 1.6 × 10^{-4} sec^{-1}, while the rate for 2,4-dimethyl-2,6-diphenyl-α-pyran is 5.35 × 10^{-4} sec^{-1}. In all cases it was established that reduction occurred solely at the carbonyl group.

The number of simple unstrained molecules with five or fewer carbons which have proved synthetically inaccessible must be vanishingly small; so α-pyran, a member of this select group, merits some attention. Preparation of a simple α-pyran was first reported[2] in 1917, but the report and the pyran proved equally short-lived, since von Auwers[3] showed that the compound was 2-vinyl-2,5-dihydrofuran and not methyl-α-pyran. Interestingly, the first authentic relatively simple α-pyran was inadvertently brought to light in 1957.[4] Recently Dreux[5] has notably lengthened the list of known α-pyrans, but α-pyran itself still has eluded all pursuers.[6]

Failure of our early attempts to prepare some α-pyrans[7] was quite reasonably attributable to the often postulated[8] rapid and reversible equilibrium between the α-pyran and cis dienones. Though the evidence leading to the postulation of this equilibrium is persua-



(1) The authors are pleased to acknowledge financial support for this study by the Public Health Service under Grant CA-AM10385, and by the National Science Foundation through Grants G-23702 and GP4985. A preliminary account of part of this work has been published: E. N. Marvell, G. Caple, T. A. Gosink, and G. Zimmer, *J. Amer. Chem. Soc.*, **88**, 619 (1966).

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(3) K. von Auwers, *Justus Liebigs Ann. Chem.*, **422**, 133 (1921).

(4) G. Büchi and N. C. Yang, *J. Amer. Chem. Soc.*, **79**, 2318 (1957).

(5) (a) A. Hinnen and J. Dreux, *C. R. Acad. Sci., Ser. C*, **255**, 1747 (1962); (b) P. Rouiller and J. Dreux, *ibid.*, **258**, 5228 (1964); (c) J. Royer and J. Dreux, *ibid.*, **258**, 5895 (1964); (d) A. Hinnen and J. Dreux, *Bull. Soc. Chim. Fr.*, 1492 (1964); (e) J. Royer and J. Dreux, *C. R. Acad. Sci., Ser. C*, **262**, 927 (1966); (f) J.-P. Schirrmann and J. Dreux, *ibid.*, **262**, 652 (1966); (g) P. Rouiller, D. Gagnaire, and J. Dreux, *Bull. Soc. Chim. Fr.*, 689 (1966); (h) J.-P. Montillier and J. Dreux, *C. R. Acad. Sci., Ser. C*, **264**, 891 (1967); (i) J.-P. Schirrmann and J. Dreux, *Bull. Soc. Chim. Fr.*, 3896 (1967); (j) J. Royer and J. Dreux, *Tetrahedron Lett.*, 5589 (1968); (k) J.-P. Griot, J. Royer, and J. Dreux, *ibid.*, 2195 (1968).

(6) See P. Schiess and H. L. Chia, *Helv. Chim. Acta*, **53**, 485 (1970), and references cited therein, for studies of the unsubstituted molecule.

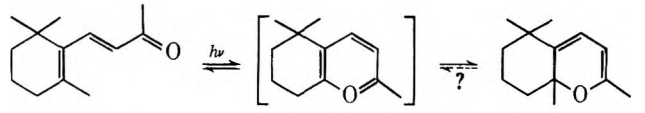
(7) E. N. Marvell, T. Gosink, P. Churchley, and T. H. Li, *J. Org. Chem.*, **37**, 2989 (1972).

(8) See, for example, (a) J. A. Berson, *J. Amer. Chem. Soc.*, **74**, 358 (1952); (b) K. H. Hafner and H. Kaiser, *Justus Liebigs Ann. Chem.*, **618**, 141 (1958); (c) A. T. Balaban, G. Mihai, and C. D. Nenitzescu, *Tetrahedron*, **18**, 257 (1962); (d) G. Köbrich, *Angew. Chem.*, **72**, 348 (1960); (e) K. Dimroth, *ibid.*, **72**, 331 (1960); (f) J. C. Anderson, D. G. Lindsay, and C. B. Reese, *Tetrahedron*, **20**, 2091 (1964); (g) S. Sarel and J. Rivlin, *Tetrahedron Lett.*, 821 (1965), and references to earlier work listed in these papers.

(9) E. N. Marvell, G. Caple, and B. Schatz, *Tetrahedron Lett.*, 385 (1965).

sive indeed, there existed no direct corroboration of the idea. Indeed, recent measurement of the rate of electrocyclization of some trienes[9] indicated that, if the theory were correct, it would require that replacement of a terminal carbon by an oxygen in a triene system cause a very substantial rate enhancement. Consideration of some of the possible causes of such a rate change (see discussion of this point below) convinced us that this question deserved serious study.

cis-β-**Ionone (2) and 1-Oxa-2,5,5,8a-tetramethyl-5,6,7,8-tetrahydronaphthalene (3).**—Attempting to prepare *cis*-β-ionone (2) from *trans*-β-ionone (1) by irradia-



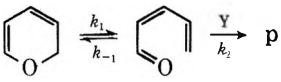
1 2 3

tion, Büchi and Yang[4] isolated instead the stable pyran **3**. Our examination of **3** as a model pyran led us by fortunate chance to the first directly observable equilibrium between a pyran and a dienone.[1] At *ca.* 40° in an nmr probe **3** exhibits a spectrum in full accord with its assigned structure (see Experimental Section). The pleasant surprise afforded by this spectrum came from a series of bands of low intensity which were not removed by further purification. These consisted of two singlets at δ 1.02 and 2.09 and an AB pattern at δ 6.03 and 6.38. We attributed these to the hitherto unknown **2**, and confirmed this by showing that, when heated in a variable-temperature probe, the mixture showed a temperature-dependent spectrum. An increase in temperature increased the intensity of the bands attributed to **2** and decreased those due to **3**. In addition one further band at δ 1.52 was identified in the spectrum of **2**, and J_{AB} was found to be 12.5 Hz, in good agreement with the cis geometry of the double bond. Several heating and cooling cycles could be carried out without appreciable degradation of the spectrum.

Since both valence isomers are present in measurable concentration, it is possible to determine the rates of their interconversion directly. The protons at C_3 and C_1 of **3** lie at δ 4.89 and 5.60 while the equivalent pair in **2** are at δ 6.03 and 6.38. The patterns do not overlap and no other bands lie in the region. Integration of the multiplet for each pair was used to measure the relative concentrations of the isomers at equilibrium. Rate constants for the formation of **2** from **3** (k_1) and for the reverse reaction (k_{-1}) were obtained by heating a solution of **3** to 120°, quenching in a Dry Ice bath, allowing the solution to reach thermal equilibrium at the desired temperature, and measuring the change in the peak height of the main peak in the doublet at δ 6.03. This gives $k_1 + k_{-1}$ and using $K = k_1/k_{-1}$ both rates are obtained. Values for the equilibrium and rate constants at various temperatures are given in Table I.[10]

Indirect Rate Measurement.—As was illustrated above, it is easy to determine both rate constants when the pyran and cis dienone are present in sufficient amount at equilibrium to permit analysis of each isomer. Generally it appears that the free-energy difference between the isomers is so delicately balanced that small structural changes can shift the equilibrium constant by several orders of magnitude. If $K > 100$ or $K < 0.01$, direct measurement of the isomerization rates is no longer possible. Clearly development of generally applicable indirect methods of measuring these rates is important. A general technique for doing this when the α-pyran is the sole observable isomer is described here. A procedure for the case of the stable cis dienone has been described recently.[11]

Huisgen[12] has shown elegantly how to utilize a bimolecular reaction of the less stable of a pair of valence isomers to measure the rate of conversion of the more stable to the less stable isomer. In the present case, if Y is a selective reagent which reacts with the dienone, the scheme involved is shown in eq 1. When Y is pres-



product (1)

ent in considerable excess the observed rate will be first order with

$$k_{obsd} = \frac{k_1 k_2[Y]}{k_{-1} + k_2[Y]}$$

When $k_2[Y] \gg k_{-1}$, k_{obsd} is equal to k_1 and the desired rate is obtained directly. Where this limiting result does not pertain, the equation can be rearranged to

$$k_{obsd} = k_1 - \frac{k_{-1}}{k_2}\frac{k_{obsd}}{[Y]}$$

and a plot of k_{obsd} *vs.* $k_{obsd}/[Y]$ gives a straight line with k_1 as intercept. Use of this equation is limited to cases where $k_2[Y]$ is of the same order of magnitude as k_{-1}, since if $k_{-1} \gg k_2[Y]$ the equation reduces to

$$k_{obsd} = k_1 k_2[Y]$$

and no information about k_1 can be obtained.

As possible choices for the reagent Y several organometallic compounds seem reasonable. We chose initially a borohydride in order to maximize selectivity. Lithium borohydride in THF was necessitated by solubility considerations. To check the value of the procedure a series of runs using **3** as substrate was made. The rates were followed spectrophotometrically, and the results are shown as runs 1–8 in Table II. The data

TABLE I

EQUILIBRIUM AND RATE CONSTANTS FOR THE PROCESS 3 ⇌ 2 AT VARIOUS TEMPERATURES

Solvent	Temp, °C	K	$k_1 \times 10^4$	$k_{-1} \times 10^4$
TCE[a]	0	0.054	0.086	1.58
Pyridine	0	0.091	0.062	0.68
TCE	8	0.070	0.25	3.57
Pyridine	8	0.14		
TCE	18	0.0943	1.31	13.9
Pyridine	18	0.17	1.30	7.5
TCE	54	0.217		
TCE	113	0.658		

[a] Tetrachloroethylene.

(10) Note that in the earlier publication[1] equilibrium and rate constants were defined for reaction i (below), while in this paper these are defined for

reaction ii in order to accord with the most reasonable definition for these constants in the indirect rate studies.

(11) P. Schiess, H. L. Chia, and C. Suter, *Tetrahedron Lett.*, 5747 (1968); P. Schiess, R. Seeger, and C. Suter, *Helv. Chim. Acta*, **53**, 1713 (1970).

(12) R. Huisgen and F. Mietsch, *Angew. Chem.*, **76**, 36 (1964); R. Huisgen, G. Boche, A. Dahmen, and W. Hechtl, *Tetrahedron Lett.*, 5215 (1968).

TABLE II
RATES OF REACTION OF 3 WITH HYDRIDE REDUCING AGENTS[a]

Run	Reagent	Concn, M	Solvent	Temp, °C	$k \times 10^5$, sec^{-1}
1	$LiBH_4$	0.0085	THF	40.0	47
2	$LiBH_4$	0.027	THF	40.0	67
3	$LiBH_4$	0.032	THF	40.0	75
4	$LiBH_4$	0.045	THF	40.0	80
5	$LiBH_4$	0.048	THF	40.0	81
6	$LiBH_4$	0.104	THF	40.0	87
7	$LiBH_4$	0.162	THF	40.0	90
8	$LiBH_4$	0.232	THF	40.0	91
9	$LiBH_4$	0.120	THF	15.0	3.75
10	$LiBH_4$	0.120	THF	15.0	3.22
11	$LiAlH_4$	0.057	Et_2O	15.0	2.5
12	$LiAlH_4$	0.056	Et_2O	15.0	3.3
13	$LiAlH_4$	0.056	Et_2O	15.0	3.1
14	$LiAlH_4$	0.415	Et_2O	15.0	3.98

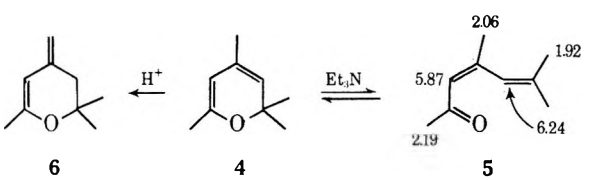
[a] Concentration of 3 was 1.8–2.2 × 10^{-4} M.

give a reasonable fit to the straight line $k_{obsd} = 9.5 \times 10^{-4} - 0.90 \times 10^{-4} k_{obsd}/[BH_4^-]$, which indicates that runs 6–8 are very close to limiting (k_{obsd} independent of $[BH_4^-]$). Under similar conditions at 15° runs 9 and 10 give $k_1 = 3.5 \times 10^{-5}$ sec^{-1}. This value in THF may be compared with $k_1 = 1.3 \times 10^{-4}$ sec^{-1} in TCE as measured by nmr. Clearly the indirect measurement provides a reasonable value for the desired rate.

Since $K = k_1/k_{-1}$ is approximately 5 at 40° in TCE (Table I), the slope of the above line, k_{-1}/k_2, in conjunction with the assumption that $K \sim 5$ in THF as well, gives $k_2 \cong 52\ M^{-1}$ sec^{-1} as the rate of reduction of 2 at 40°. This estimate might appear rather high in view of the rates reported for sodium borohydride in isopropyl alcohol.[13] However, lithium borohydride is a considerably more reactive agent than the sodium salt,[14] which leads us to believe that the estimate is reasonable.

The success of lithium borohydride prompted us to try lithium aluminum hydride. The very high rate of reaction of this reagent suggested that, under conditions of first-order kinetics, k_{obsd} should equal k_1, but that the reactivity of the reagent toward ethers would limit the useful temperature range. Runs 12 and 13 (Table II) confirm the former suggestion, since essentially the same rate was observed in this case as in runs 9 and 10. Though some experimental problems were experienced with lithium aluminum hydride solutions (erratic results because of turbidity), its use is recommended because the desired rate can usually be obtained from a single kinetic run.

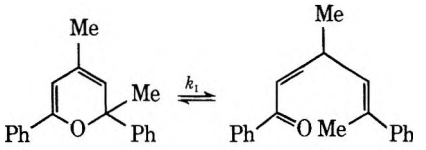
2,2,4,6-Tetramethyl- and 2,4-Dimethyl-2,6-diphenyl-α-pyran.—A sample of 2,2,4,6-tetramethyl-α-pyran (**4**)



6 **4** **5**

was prepared by the method of Hinnen and Dreux,[5a,d] and an attempt was made to ascertain the content of 4,6-dimethyl-3,5-heptadien-2-one (**5**) by nmr. In carbon tetrachloride the only observable result was the acid-catalyzed conversion of **4** to 2,6,6-trimethyl-4-methylenetetrahydropyran (**6**), a reaction previously observed by Hinnen and Dreux.[5a,d] In anhydrous pyridine **4** does not undergo the hydrogen migration, but no clear indications of the electrocyclic process were found. A more comprehensive examination in anhydrous triethylamine using repetitive scanning uncovered five peaks at δ 1.92, 2.06, 2.19, 5.87, and 6.24 ppm whose intensity is increased slightly with elevation in temperature. These peaks can be assigned to **5**, and with but one exception are in excellent agreement with the expected chemical shifts. Thus, the carbonyl methyl lies at δ 2.21 in **1** and 2.09 in **2**. A methyl at C_4 which is trans to a carbonyl group normally appears between δ 1.8 and 2.1 ppm.[15] A trans terminal methyl resonance lies at δ 1.81 in 4-methyl-*cis*-3,*trans*-5-heptadien-2-one (**7**),[7,16] while the proton at C_3 in that dienone gives a singlet at δ 5.98 ppm. The δ 6.24 peak, which must be assigned to the C_5 proton, provides the difficulty since its equivalent in **7** is at 7.63 ppm. We suggest that the additional methyl at C_6 alters the conformation and thus the stereorelation between that proton and the carbonyl group. In any event the evidence indicates that at equilibrium a small amount of **5** is present but it is not sufficient to permit quantitative analysis.

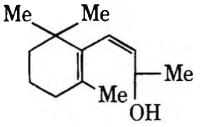
The rate of the retroelectrocyclic reaction of **4** was measured in ether at 15° using lithium aluminum hydride as the reagent. Under these conditions the rate constant is 1.60 × 10^{-4} sec^{-1}. A sample of 2,4-dimethyl-2,6-diphenyl-α-pyran (**8**)[5] was prepared and its



8 **9**

rate of ring opening was measured under the same conditions, giving $k_1 = 5.35 \times 10^{-4}$ sec^{-1}.

Reduction Products.—The three pyrans **3**, **4**, and **8** were reduced with lithium aluminum hydride on a preparative scale and the products were isolated. In all cases reduction gave the conjugated dienol derived from direct reduction of the carbonyl group. No indication of any conjugate reduction product was found. Structures were clearly delineated by the nmr spectra in all cases. The spectrum of *cis*-β-ionol (**10**) shows two



10

singlets for the geminal methyls. The nonequivalence of these methyl groups was most unexpected since the two are equivalent in *trans*-β-ionol and in **2**. Thus this nonequivalence must result from restricted rotation about the single bond between the ring and the cis

(13) See, for example, B. Rickborn and M. T. Wuesthoff, *J. Amer. Chem. Soc.*, **92**, 6894 (1970).

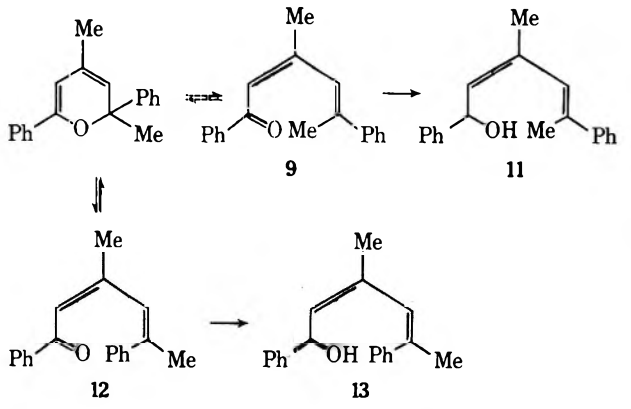
(14) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, New York, N. Y., 1965, p 24.

(15) (a) K. S. Brown and S. M. Kupchan, *J. Amer. Chem. Soc.*, **84**, 4592 (1962); (b) R. W. Benn and R. M. Dodson, *J. Org. Chem.*, **29**, 1142 (1964); (c) R. H. Wiley, P. F. G. Nau, and T. H. Crawford, *ibid.*, **26**, 4285 (1961); (d) E. E. Boehm and M. C. Whiting, *J. Chem. Soc.*, 2591 (1963).

(16) A. F. Kluge and C. P. Lillya, *J. Org. Chem.*, **36**, 1977 (1971).

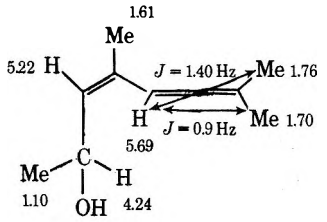
double bond. That the diene chromophore is not planar is clearly indicated by the λ_{max}, 219 nm (ϵ 3400).

Ring opening of **8** may occur in two ways, leading to either **9** or **12**. In view of the steric problems involved,



ring opening to **9** should be preferred. Indeed our results support this expectation, since only a single alcohol was obtained. The alcohol gives one spot on analysis by tlc, and the nmr spectrum is that of a single substance. We assign this the structure **11** for the following reasons.

The alcohol from reduction of **4** must have the formula **14**. The hydrogens at C_3 and C_5 are clearly dis-



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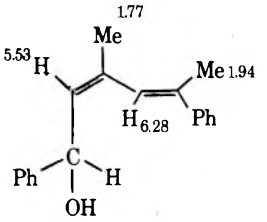


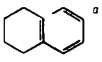
11

tinguishable and permit us to assign the three methyl singlets as is shown in **14** on the basis of coupling constants. Again in **11** the C_2 and C_4 protons are readily identified. The δ 1.94 Me is coupled to a proton by 1.25 Hz, while the δ 1.77 Me has $J \cong 1.0$ Hz. This evidence is not sufficient to provide unequivocal assignments; so double-resonance experiments were used to show that the δ 1.94 Me was indeed coupled to the C_4 proton. The 1.25-Hz coupling suggests that these are trans oriented. That geometry is supported by a calculation[17] of the shift expected for the C_4 proton of **14** if the cis methyl were replaced by a phenyl (calcd +0.63) and if the trans methyl were similarly replaced (calcd +0.28). The observed value of +0.59 is in excellent agreement with the former value, which supports the assignment shown in 11.

(17) C. Pascual, J. Meier, and W. Simon, *Helv. Chim. Acta*, **49**, 164 (1966).

Possible Causes of the Rate Enhancement.—It is very satisfying to find that the chemically reasonable route for conversion of cis dienones and α-pyrans is indeed confirmed by the experimental study. However, this result now requires that we return to a consideration of the rate enhancement caused by replacing a carbon by an oxygen in the triene system. The present work gives in one case a quantitative measure of this rate effect, and in two other cases sets a lower limit to the rate increase. The data are given in Table III.

TABLE III
COMPARATIVE RATES FOR SOME ELECTROCYCLIC REACTIONS OF TRIENES AND CIS DIENONES

Compd	Rate, sec^{-1}	Temp, °C	$\Delta H^{\pm}$	$\Delta S^{\pm}$
2	1.39×10^{-3}	18	20	−5
 [a]	2.6×10^{-5}	173	34	−5
5	*ca.* 1×10^{-2} [b]	15		
 [c]	2.2×10^{-5}	178	33	−5
9	$>5 \times 10^{-2}$ [b]	15		

[a] N. Polston, M.S. Thesis, Oregon State University, 1966. [b] The rate is a lower limit for k_{-1} which was estimated from the k_1 rate measured in the present work and assuming that $K = k_1/k_{-1} \geq 100$. [c] See ref 9.

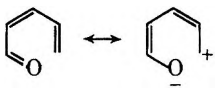
In all cases the rate increase between the dienone and a triene as nearly comparable as is presently possible corresponds to a factor of 1×10^8 or larger. For 2 and its comparable triene the rate change corresponds to a $\Delta\Delta G^{\pm}$ of 14 kcal/mol, which Table III shows is entirely due to the $\Delta\Delta H^{\pm}$.

What factors are responsible for this dramatic change? Undoubtedly a steric factor contributes, since replacement of a C=CH unit by a C=O group reduces the compressions in the disrotatory transition state. We consider that this is a minor contributor, since replacement of a terminal cis hydrogen by a methyl group reduces the triene rate by only 100-fold. Surely what amounts effectively to a replacement of the hydrogen by a nonbonded electron pair must produce a very much smaller rate change. Thus, we are driven to the conclusion that the major cause must be the substitution of the oxygen atom for the carbon.

Introduction of the oxygen must bring into play one factor which would be expected to reduce rather than increase the rate. Electrocyclization converts a π bond to a σ bond which for the triene leads to a bond energy increase of *ca.* 19 kcal/mol, but for the dienone leads to a decrease in bond energy of *ca.* 4 kcal/mol.[18] This fact is clearly evident in the equilibrium constants for the two series, and to the extent that the difference might be reflected in the rates it would lead to a slower reaction for the dienone. This influence must obviously be counterbalanced by some further factor. To the extent that the enhanced electronegativity of the oxygen can be represented by contributing forms such as **15b**, this would be expected to increase the rate of ring closure. Two observations raise some question about the efficacy of this influence. First, the presence of a phenyl group on the terminal carbon, though it will

(18) T. L. Cottrell, "The Strengths of Chemical Bonds," 2nd ed, Butterworths, London, 1958.

delocalize the positive charge, should increase the contribution of **15b**, and probably should thus increase the



15a **15b**

rate. Measured by the retro process rates, the factor of sevenfold (statisticalf actors taken into account) does not offer much support for the electronegativity effect as a major factor. This view is supported by the lack of any strong solvent influence on the dienone rates.[19]

Finally, there exists the very interesting possibility that the oxygen atom perturbs the orbital system sufficiently strongly to remove the symmetry restrictions and to permit a concerted conrotatory path.[20] The conrotatory route, which at the transition state brings the six-atom chain nearly to a one-turn helix, does not seriously distort the dihedral angles between orbitals on adjacent atoms. On the contrary, a calculation of the geometry of the disrotatory transition state[21] indicates a severe dislocation (dihedral angle of *ca.* 50°) between the C_2–C_3 and C_4–C_5 orbitals. In the absence of the orbital symmetry control the conrotatory path should be preferred. It seems very likely that the very favorable geometry of the conrotatory process is the reason for the very rapid electrocyclic reaction of tetraenes.[22] Unfortunately, the obvious test of the stereo path used is not capable of being checked experimentally.

A very recent paper[23] shows that 2,3,4,4-tetramethyloxetene rearranges to 3,4-dimethyl-3-penten-2-one some several powers of ten faster than *cis*-1,2,3,4-tetramethylcyclobutene opens to give *cis,trans*-3,4-dimethyl-2,4-hexadiene. In this case it would appear that alteration of the stereochemistry direction of the ring opening would provide no particular rate increase. On the other hand the bond energy influence is favorable in this ring-opening reaction.

Experimental Section

cis-β-**Ionol** (**10**).—A sample (1.67 g, 8.7 mmol) of the pyran **3**[4] was added rapidly to a solution of 2 *M* lithium aluminum hydride (20 ml) in ether. The flask was purged with dry nitrogen, sealed, and held at 16° for 3 days. Water was added cautiously and after the initial violent reaction had subsided 20 ml of 2 *M* sodium hydroxide was added. The ether layer was decanted and dried ($MgSO_4$), and the ether was removed by evaporation. The crude alcohol (1.29 g, 78%) was purified by glc on a 15 ft × 0.375 in. Carbowax 20M column (20% liquid phase on 30/50 mesh firebrick): uv max (95% EtOH) 219 nm (ε 2300), ir (neat) 3350 (OH), 1640 (C=C), and 750 cm^{-1} (cis olefin); nmr (CCl_4) δ 5.73 (d, 1 H, *J* = 12 Hz), 5.39 (d of d, 1 H, *J* = 12, 10 Hz), 4.13 (d of d, 1 H, *J* = 10, 6 Hz,) 1.35–2.30 (m, 7 H), 1.53 (s, 3 H), 1.09 (d, 3 H, *J* = 6 Hz), 0.95 (s, 3 H), 0.90 (s, 3 H). *Anal.* Calcd for $C_{13}H_{22}O$: C, 80.35; H, 11.41. Found: C, 80.29; H, 11.24.

trans-β-**Ionol**.—This was prepared by the procedure of Inhoffen and Bohlmann.[24] β-Ionone (1.04 g, 5.4 mmol) was added dropwise to 50 ml of cold 2 *M* lithium aluminum hydride. The alcohol was isolated as above, giving 1.0 g of an oil: ir (neat) 3340 (OH), 962 cm^{-1} (trans double bond); nmr (CCl_4) δ 5.94 (d, 1 H, *J* = 15 Hz), 5.28 (d of d, 1 H, *J* = 15, 6 Hz), 4.21 (m, 1 H), 3.92 (s, 1 H), 1.40–2.13 (m, 6 H), 1.54 (s, 3 H), 1.25 (d, 3 H, *J* = 6 Hz), 0.97 (s, 6 H); uv max (95% EtOH) 234 nm (ε 4800) [lit.[25] 234 nm (ε 5099)].

4,6-Dimethyl-*cis*-3,5-heptadien-2-ol (**14**).—A solution containing 97.4 mg (0.70 mmol) of 2,2,4,6-tetramethyl-2*H*-pyran (**4**),[5a,d] purified by glc on a 3 m × 0.25 in. 10% Apiezon M on Chromosorb W column at 85°, in 10 ml of ether was added to 25 ml of 0.2 *M* lithium aluminum hydride. The reaction mixture was allowed to stand for 24 hr at 16°. The product was isolated as described for **10** above: uv max (95% EtOH) 219 nm (ε 6500); ir (neat) 3450 (OH), 1640 cm^{-1} (C=C); nmr (CCl_4) δ 5.69 (broad s, 1 H), 5.22 (d of q, 1 H, *J* = 8.75, 1.25 Hz), 4.24 (m, 1 H, *J* = 8.75, 6.3 Hz), 3.68 (s, OH), 1.76 (d, 3 H, *J* = 1.40 Hz), 1.70 (d, 3 H, *J* = 0.9 Hz), 1.61 (d, 3 H, *J* = 1.25 Hz), 1.10 (d, 3 H, *J* = 6.3 Hz); mol wt, 140 (mass spectrum). *Anal.* Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 76.94; H, 11.43.

1,5-Diphenyl-3-methyl-*cis*-2,4-hexadien-1-ol (**11**).—A 390-mg (1.46 mmol) sample of the pyran **8**, mp 81–82° (lit.[5] mp 84°), was reduced as described for **10** above. The crude alcohol was purified by preparative tlc using Woelm PF_{254} alumina and benzene as eluent: R_f 0.2; uv max (95% EtOH) 253 nm (ε 12,300); ir (neat) 3450, 1642, 1590, 1570, 750, 690 cm^{-1}; nmr (CCl_4) δ 7.18 (m, 10 H), 6.28 (broad s, 1 H), 5.53 (d, 1 H, *J* = 9 Hz), 5.19 (d, 1 H, *J* = 9 Hz), 4.28 (s, OH), 1.94 (d, 3 H, *J* = 1.25 Hz), 1.77 (d, 3 H, *J* = 1.0 Hz). *Anal.* Calcd for $C_{19}H_{20}O$: C, 86.32; H, 7.63. Found: C, 86.17 H, 7.75.

Kinetic Measurements. A. Direct Measurement *via* Nmr.—All studies were carried out in a Varian A-60 nmr spectrometer equipped with a variable-temperature probe.[26] A sample, *ca.* 150 mg, of **3** was dissolved in about 0.5 ml of the appropriate solvent, tetrachloroethylene or pyridine, and the solution in an nmr tube was heated at 120° for about 10 min. The mixture was quenched in a Dry Ice bath in which it was kept until ready to use. The variable-temperature probe was adjusted to the desired temperature, which was determined by measurement of the relative chemical shifts of the methanol protons. The sample tube was placed in the probe and the solution was allowed to reach thermal equilibrium. The AB patterns for the C_3 and C_4 protons in **2** and **3** are separated cleanly from each other and from all other bands in the spectrum of the mixture. The rate of reversion to equilibrium can be determined from the integrations of these two patterns or by measuring the decrease in the peak height of the larger peak of the doublet near δ 6.03.

Using the equation

$$2.3 \log \frac{x_o - x_e}{x_t - x_e} = (k_1 + k_{-1})t$$

where x = peak height or the integral for the AB pattern of **2** divided by the sum of the integrals for the AB patterns of **2** and **3**, the data give a good first-order plot[27] from which the sum $k_1 + k_{-1}$ could be derived. The equilibrium concentrations of **2** and **3** could be determined from the integration. For runs at low temperature where the concentration of **2** was too small to permit accurate assessment of the equilibrium value, the equilibrium constant was calculated from values determined at higher temperatures using ΔH° = 5.5 kcal/mol. The results are given in Table I.

B. Indirect Measurement Using Metal Hydride Reduction.—Solutions of lithium borohydride were prepared in a dry box under nitrogen atmosphere by dissolving a weighed amount of commercial lithium borohydride (Ventron) in anhydrous tetrahydrofuran. The solution was clarified by filtration and the concentration was determined by hydrolysis of an aliquot and titration of the liberated base with standard hydrochloric acid.

(19) See J. B. Flannery, Jr., *J. Amer. Chem. Soc.*, **90**, 5660 (1968), footnote 46, along with the data in the present paper.

(20) For a recent case where a similar explanation has been advanced for a very different system, see R. C. Cookson and J. E. Kemp, *Chem. Commun.*, 385 (1971).

(21) E. N. Marvell, E. Heilbronner, and H. Baumann, Abstracts, 153rd National Meeting of the American Chemical Society, Miami, Fla., April 1967.

(22) R. Huisgen, A. Dahmen, and H. Huber, *Tetrahedron Lett.*, 1461 (1969).

(23) L. E. Friedrich and G. B. Schuster, *J. Amer. Chem. Soc.*, **93**, 4602 (1971).

(24) H. H. Inhoffen, F. Bohlmann, and M. Bohlmann, *Justus Liebigs Ann. Chem.*, **665**, 35 (1947).

(25) B. N. Joshi, R. Seshadri, K. K. Chakravarti, and S. C. Bhattacharyya, *Tetrahedron*, **20**, 2911 (1964).

(26) We are indebted to the National Science Foundation for financial assistance in the purchase of this instrument.

(27) A. A. Frost and R. G. Pearson, "Kinetics and Mechanisms of Homogeneous Chemical Reactions," 2nd ed, Wiley, New York, N. Y., 1961, p 186.

A stock solution of lithium aluminum hydride in ether was prepared by heating the solid with anhydrous ether under nitrogen for several hours. The solution was clarified by settling and the clear supernatant solution was standardized by the iodometric procedure of Felkin.[28] Solutions of the desired concentration were prepared by dilution of the stock solution in a dry box under nitrogen.

Method A.—A silica ultraviolet cell having a ground glass top closure was filled in the drybox under nitrogen with a known volume of hydride solution. The cell was then capped with a serum stopple which was wired in place. If necessary the solution was clarified by centrifugation and then allowed to equilibrate thermally. A measured volume of a solution of the pyran of known concentration was added to the cell *via* a syringe. The solution was mixed by brief shaking, and the mixture was centrifuged and then placed in the thermostatted cell compartment of a Cary 15 spectrophotometer. The reaction was followed by monitoring the disappearance of the pyran absorption band. The temperature in an oil filled cell at thermal equilibrium in the cell compartment was measured just prior to each run.

Method B.—Measured volumes of solutions of pyran and lithium aluminum hydride of known concentration were brought to thermal equilibrium and then mixed in a vessel permitting withdrawal of aliquots. Aliquots were withdrawn at intervals and the reaction solution was immediately mixed with a measured volume of a solution of durene of known concentration. Reaction was quenched by careful addition of water, and the organic layer was separated from the precipitated salts. The salts were washed with ether, and the washings were combined with the main solution. The solution was carefully concentrated and the concentrations of durene, pyran, and alcohol were determined by glc. Analysis was carried out with a 7 ft × 0.125 in. 5% Carbowax 20M on 60/80 mesh firebrick using a Disc integrator to determine relative peak areas. A plot of log $A_p/(A_p + A_{al})$ *vs.* time gave a straight line (A_p = area of pyran peak; A_{al} = area of alcohol peak). Constancy of the ratio $A_D/(A_p + A_{al})$ (A_D = area of the durene peak) provided a check against loss of material or incursion of side reactions. The rate constants determined by this method were in good agreement with those ascertained by method A.

(28) H. Felkin, *Bull. Soc. Chim. Fr.*, 347 (1951).

Registry No.—**2**, 35031-06-2; **3**, 5552-30-7; **4**, 5526-16-9; **5**, 35031-09-5; **8**, 5631-86-7; **9**, 35031-10-8; **10**, 35031-11-9; **10** trans isomer, 472-80-0; **11**, 35031-13-1; **14**, 35031-14-2.

Ozonation of Amines. VI.[1] Primary Amines

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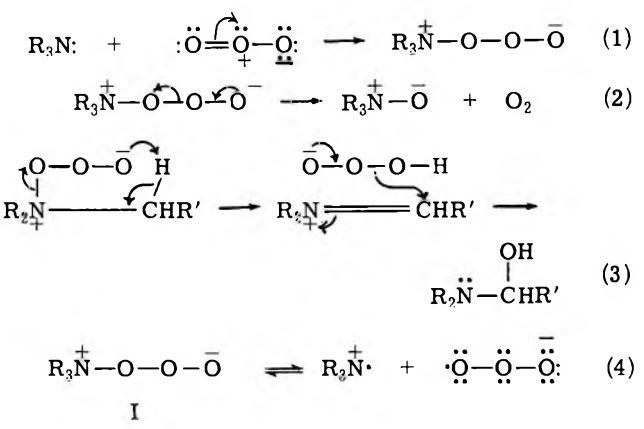
A detailed study of the ozonation of two primary amines, *n*-butylamine (having a primary alkyl group) and isopropylamine (having a secondary alkyl group), has been made and the results have been compared with those of *tert*-butylamine in regard to the three principal fates of the initial amine–ozone adduct.

In preceding papers in this series, the ozonations of *tert*-butylamine,[2,3] tri-*n*-butylamine,[2,4] di-*tert*-butylamine,[5] and di-*tert*-butyl nitroxide[1] were reported. The results of the ozonations of the amines were rationalized by means of an initial electrophilic ozone attack (eq 1) followed by four competing fates of the initial amine–ozone adduct.[2,5] Three of these fates, loss of oxygen to form an amine oxide product or intermediate, intramolecular side-chain oxidation, and dissociation to cation and anion radicals (followed by further reactions of these intermediates), are described by eq 2–4.



(1) For paper V of this series, see P. S. Bailey and J. E. Keller, *J. Org. Chem.* **35**, 2782 (1970).

(2) P. S. Bailey, J. E. Keller, D. A. Mitchard, and H. M. White, *Advan. Chem. Ser.*, **77**, 58–64 (1968).

(3) P. S. Bailey and J. E. Keller, *J. Org. Chem.*, **33**, 2680 (1968).

(4) P. S. Bailey, D. A. Mitchard, and A. Y. Khashab, *ibid.*, **33**, 2675 (1968).

(5) P. S. Bailey, J. E. Keller, and T. P. Carter, Jr., *ibid.*, **35**, 2777 (1970).

The purpose of the presently reported research was to study the ozonation of two additional primary amines with which a competition among all three of the pathways was possible, in order to gain information concerning the factors which affect this competition, as was done with the tertiary amine, tri-*n*-butylamine.[4] One of the primary amines chosen was *n*-butylamine, having a primary alkyl group, and the other was isopropylamine, which has a secondary alkyl group.

The ozonation of isopropylamine was studied in chloroform solution at three different temperatures (−65, −30, and 0°), in methylene chloride at −78°, and in pentane at −78°. The ozonations were carried out with a slight excess of ozone over a 1:1 amine–ozone ratio; on the average slightly less than 1 mol of ozone reacted per mole of amine. In addition, a less detailed study of the ozonation of isopropylhydroxylamine was made. All results are shown in Table I.

The production of 2-nitropropane (II) is analogous to the formation of 2-methyl-2-nitropropane from ozonation of *tert*-butylamine[3] and almost certainly occurs by the amine oxide route, involving a total of 3 molar equiv of ozone (eq 5), as proposed previously.[3] Ex-

pected intermediates in this reaction are isopropylhydroxylamine (IV) and 2-nitrosopropane (V). Evidence for the proposed reaction pathway is that the major product from ozonation of IV is 2-nitropropane (Table I, expt 10–13) and that the pale blue color of 2-nitrosopropane (V) was evident throughout the ozonations of both isopropylamine and the hydroxyl-

TABLE I

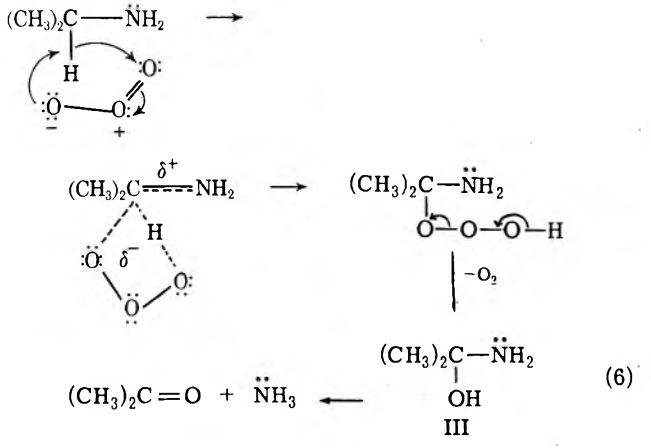
OZONATION OF ISOPROPYLAMINE AND ISOPROPYLHYDROXYLAMINE[a]

Expt[a]	Solvent[b]	Temp, °C	O_3/amine[c]	O_2 evolved/O_3 reacting	Acetone[d]	2-Nitropropane[d]	Isopropyl isocyanate[d]	Isopropylammonium chloride[d]	Total yield,[e] %
1	$CHCl_3$	−65	1.1	*f*	4	25	18	48	95
2	$CHCl_3$	−65	1.0	*f*	5	27	15	51	98
3	$CHCl_3$	−65	0.9	0.7	6	28	15	49	97
4	$CHCl_3$	−30	0.8	0.7	10	23	5[g]	40	86
5	$CHCl_3$	−30	0.8	0.9	10	22	5[h]	47	89
6	$CHCl_3$	0	0.9	*f*	15	19	5[i]	42	90
7	$CHCl_3$	0	0.9	0.7	14	22	5[i]	46	97
8	CH_2Cl_2[j]	−78	1.1	0.8	12	36	5[k]	43	96
9	Pentane	−78	1.4	*f*	8	53	0	6[l]	67[m]
10[a]	$CHCl_3$	−65	2.0	*f*	15	51	*f*	*f*	*f,n*
11[a]	$CHCl_3$	0	1.2	*f*	11	44	*f*	*f*	*f, n*
12[a]	CH_2Cl_2[j]	−78	1.4	1.0	Trace	76	*f*	*f*	*f, n*
13[a]	CH_2Cl_2[j]	0	1.0	*f*	5	28	*f*	*f*	*f, n*

[a] In expt 1–9, the amine was isopropylamine, while in expt 10–13, isopropylhydroxylamine was employed. [b] Approximately 6–8 ml of solvent per 5 mmol of amine was employed. [c] Unless otherwise stated, each run employed 5 ± 1 mmol of amine and 6 ± 1 mmol of ozone from an ozone–nitrogen stream (see Experimental Section), which was an excess of ozone. The ratio shown is of ozone reacting to amine employed, all of which reacted. [d] Per cent yield based on amine employed, all of which reacted. [e] Total per cent yield. This equals the total amount of the isopropyl group of the amine accounted for. The total nitrogen accounted for is equal to this value minus the acetone yield. [f] Not determined. [g] In addition, an 8% yield of *N,N*-diisopropylurea was obtained. Yield is based on percentage of original amine ending up as urea. [h] Plus 5% diisopropylurea. See footnote *g*. [i] Plus 9–10% diisopropylurea. See footnote *g*. [j] The results constitute an average of 2–3 runs. [k] With CH_2Cl_2 solvent the product was *N*-isopropylformamide. In two of the three runs averaged in this experiment 18 ± 3 mmol of amine was employed. [l] The isopropylammonium salt cannot be the chloride, of course. It appears to be largely nitrate. [m] In addition, 2-pentanone and 3-pentanone were identified. These products are not obtained when ozone is passed into pure pentane under the same conditions. [n] No acetone oxime was detected.

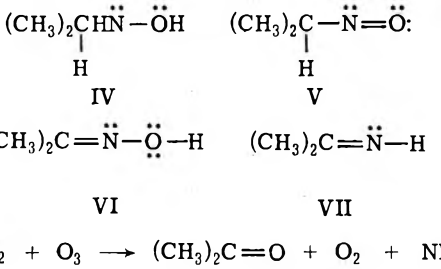
amine IV. Similar observations were made during the ozonation of *tert*-butylamine.[3] The fact that, unlike the nitrosoalkane, the alkylhydroxylamine has not been isolated or observed in the ozonations of primary amines does not cast doubt on its role as an intermediate. Because of the α effect[6] it would be expected to react with ozone faster than the parent amine.

The acetone obtained is a product expected from side-chain oxidation of the isopropylamine, whether it be by the mechanism of eq 3 (or a similar mechanism[4]) or by 1,3-dipolar insertion[7] (eq 6).



(6)

Another conceivable source of acetone is ozonation or hydrolysis of acetone oxime (VI) obtained by rearrangement of 2-nitrosopropane (V).[8] Ozonation of oximes has been found to yield the corresponding aldehyde or ketone as the major product.[9] This is thought not to be the source in the present case, however, because no indication of the presence of the oxime was observed from ozonation of either isopropylamine or isopropylhydroxylamine, even when less than 1 equiv of ozone was employed. In contrast, ozonation of *n*-butylamine did give a low yield of the corresponding oxime (Table II), but this was due to the fact that the ozonations were not carried out to completion and some nitrosobutane probably was present at the end of the ozonations. The oxime did not appear until the reaction mixture had stood overnight. Most likely, the acetone obtained from ozonation of isopropylhydroxylamine also arose from side-chain oxidation. The overall side-chain oxidation of isopropylamine to acetone, whether it be by the mechanism of eq 3 or 6, can be expressed by eq 7.



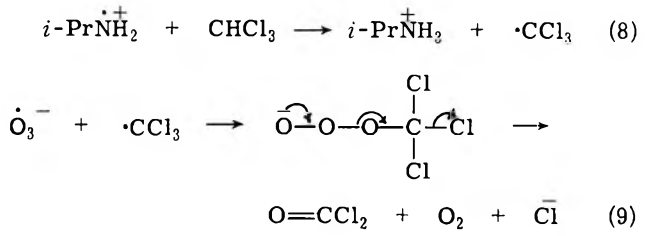
$$i\text{-PrNH}_2 + O_3 \longrightarrow (CH_3)_2C{=}O + O_2 + NH_3 \quad (7)$$

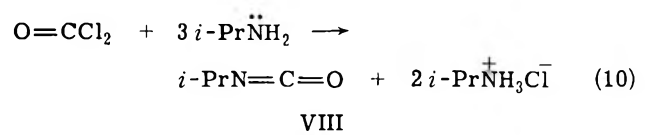
Alternatively, it is conceivable that decomposition of amino alcohol III to imine VII and water rather than to acetone and ammonia occurs. The acetone then would be derived from either ozonation or hydrolysis of VII. This route is probably minor in a protic solvent like chloroform, however, as will be discussed later in regard to ozonations of isopropylamine and *n*-butylamine in pentane.

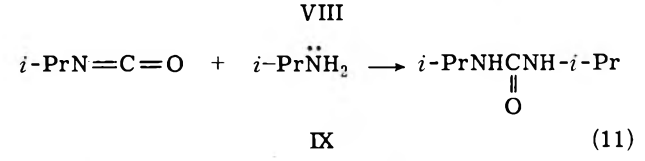
Similar to the ozonation of *tert*-butylamine in chlorinated solvents,[3] a major product of the ozonation of isopropylamine in chloroform and methylene chloride was the corresponding ammonium chloride. Accompanying this in chloroform was isopropyl isocyanate (VIII) and (at −30 and 0°, but not at −65°) diiso-

(6) J. O. Edwards and R. G. Pearson, *J. Amer. Chem. Soc.*, **84**, 16 (1962).
(7) J. E. Batterbee and P. S. Bailey, *J. Org. Chem.*, **32**, 3899 (1967).
(8) G. B. Bachman and K. G. Strawn, *ibid.*, **33**, 313 (1968).
(9) R. E. Erickson, P. J. Andrulis, Jr., J. C. Collins, M. L. Lungle, and G. D. Mercer, *ibid.*, **34**, 2961 (1969).

propylurea (IX),[10] whereas the companion product in methylene chloride was *N*-isopropylformamide (X). These are exactly the results expected by the cation radical, ozonate anion radical pathway (initial steps expressed by eq 1 and 4, followed by eq 8–11 for the ozonation in chloroform and eq 12–14 for the ozonation in methylene chloride). Our interpretation of reactions 4 followed by 8 and 9 or 12 and 13 is that the dissociation of the amine–ozone adduct (eq 4) is reversible and goes to products only if the cation radical can readily abstract a hydrogen atom from its environment (eq 8 or 12). The ozonate anion radical and the solvent radicals of eq 9 and 13 are then in a solvent cage and react immediately at the reaction temperatures employed.

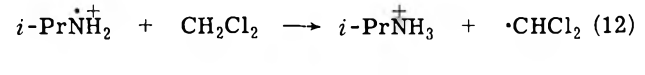


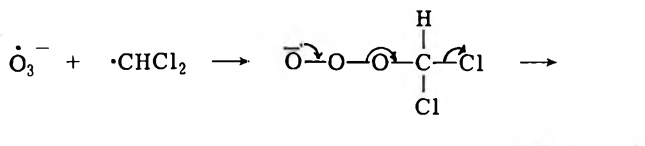


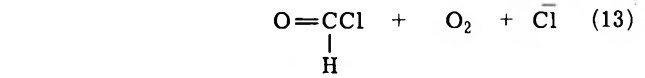


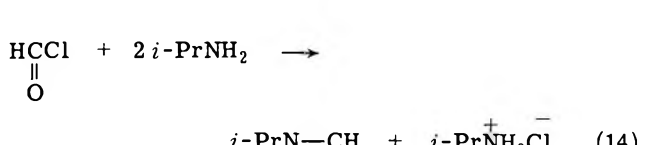
VIII

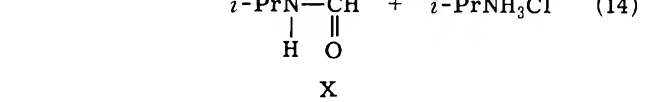
IX

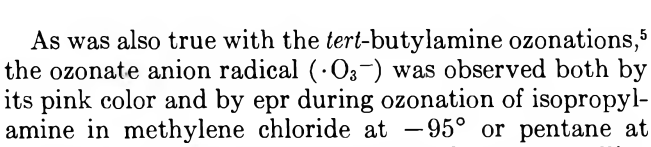








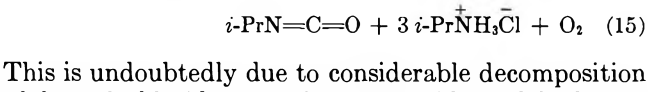


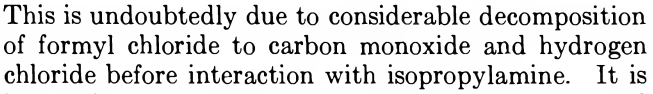


X

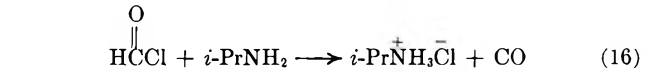
As was also true with the *tert*-butylamine ozonations,[5] the ozonate anion radical ($\cdot O_3^-$) was observed both by its pink color and by epr during ozonation of isopropylamine in methylene chloride at −95° or pentane at −120°. In these cases an actual buildup of crystalline isopropylammonium ozonate occurs. This should deter reaction 13 from occurring. However, no 1,1,2,2-tetrachloroethane was found in the methylene chloride reaction mixture. Under these conditions the solvent radical is probably destroyed by interaction with molecular oxygen, which is a product of reaction pathways 5 and 7. Oxygen has been shown to be a powerful scavenger of these radicals in similar situations.[11] It is possible that even under ordinary conditions oxygen competes with the ozonate anion radical (eq 9 and 13) for the solvent radical, to give $\cdot OOCCl_3$. This radical then could decompose to phosgene and $\cdot OCl$. Additional data and arguments favoring the ion-radical mechanisms can be found elsewhere.[2,3,5]

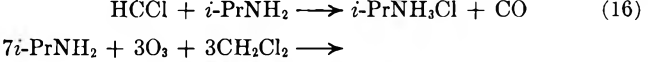
A combination of eq 1, 4, 8, 9, and 10 gives eq 15, which expresses the ion-radical pathway for the isopropylamine ozonation in chloroform at −65°. The data of expt 1–3 (Table I) fit fairly well the ammonium chloride/isocyanate ratio predicted by eq 15, although on the average the experimental ratio is slightly high. This possibly is due to some loss of isocyanate through hydrolysis, or to minor side reactions which produce hydrogen chloride. A similar summation for the ozonation in methylene chloride predicts a higher formamide/ammonium salt ratio than found in expt 6 (Table I).

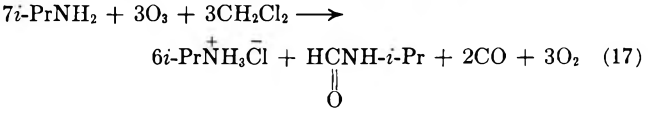




This is undoubtedly due to considerable decomposition of formyl chloride to carbon monoxide and hydrogen chloride before interaction with isopropylamine. It is interesting to note that formamide was not observed at all as a product of the ozonation of *tert*-butylamine in methylene chloride;[3] the more hindered amine apparently has no chance at all of reacting with the formyl chloride before it decomposes. The reaction of isopropylamine with the decomposed formyl chloride is represented by eq 16. Summation of eq 1, 4, 12, 13, 14, and 16, giving twice as much weight to eq 16 as eq 14, results in eq 17 as a reasonable representation of the ion-radical pathway in methylene chloride at −78°.







Equation 18 is the summation of eq 5 (amine oxide pathway), 7 (side-chain oxidation), and 15 (ion-radical pathway) for the ozonation of isopropylamine in chloroform at −65°, assuming approximate weightings of 55, 10, and 35%, respectively, for the above pathways. Equation 19 is a similar summation of eq 5, 7, and 17, giving weights of 50, 20, and 30%, respectively, for the three pathways in the −78° methylene chloride ozonation. Below each product in these equations is the theoretical yield as dictated by the equation (below ozone is the ozone/amine ratio). It can be seen that the equations describe the data of expt 1–3 (chloroform) and 8 (methylene chloride) of Table I quite adequately, with the exceptions that the experimental O_3/amine ratios are slightly low and the oxygen yield is low, especially considering that the equations do not include any ozonation of ammonia. These discrepancies are perhaps caused by the fact that the oxygen evolved

(10) Isopropyl isocyanate was found to react very slowly with isopropylamine at −65° to give the urea. *tert*-Butyl isocyanate does not react at all with *tert*-butylamine at −65°.

(11) W. J. Lautenberger, E. N. Jones, and J. G. Miller, *J. Amer. Chem. Soc.*, **90**, 1110 (1968).

TABLE II

OZONATION OF *n*-BUTYLAMINE

Expt[a]	Solvent	Temp, °C	O_3/amine[b]	O_2/O_3[c]	Products[m] A[d,e]	B[d]	C[d,f]	D[d,e]	E[d,e]	F[d]	G[d,e]	H[d,e]	Total C[g,h]	Total N[g]
14	Pentane[i]	−60	1.5	0.7	11	14	18[e,f]	0	*j*	0	2.5	4	67	67
15	$CHCl_3$	−60	1.1	0.6	2	18	36	7.5[k]	5	4	0.5	3	94	84
16	$CHCl_3$	0	1.1	0.7	7.5	14	29	5.5[k]	2.5	0	*l*	*l*	74	65
17	CH_2Cl_2	−60	1.1	0.7	4	17	20	2.5[k]	0	6.5	*l*	*l*	56	52
18	CCl_4	−25	1.0	0.7	6	13	27	5[k]	0	0	*l*	*l*	62	56

[a] Reactions were run on a 5-, 10-, or 20-mmol scale employing approximately 2.5 ml of solvent per millimole of amine. The results shown were obtained from several different runs in each solvent, as described in the Experimental Section. [b] In each case 1 mmol of ozone (in a nitrogen stream) per millimole of starting amine was employed and reacted completely. Unreacted amine was determined and the ratio is that of ozone reacting to amine reacting. [c] Ratio of molecular oxygen evolved per mole of ozone reacting. [d] These values equal the number of moles of product (rounded off to the nearest half mole) obtained per 100 mol of *n*-butylamine (see footnote *e*). [e] In these cases the actual percentage yield is twice the value shown, since 2 mol of amine were required to produce 1 mol of product (see footnote *d*). [f] In expt 14 the salt is in the form of the nitrate and arose from 2 mol of amine, one to form the ammonium ion and one to form the nitrate. [g] The total C is the total percentage yield based on an accounting of the butyl group; the total N is the total percentage yield based on an accounting of nitrogen. [h] Small amounts of butyraldehyde and butyric acid also were detected in all cases. In expt 15, propionic acid also was detected. [i] Also detected among the products were 1–2% yields of a mixture of 2- and 3-pentanol and 8% yields of 2- and 3-pentanone. Yields are based on ozone reacting, since these are oxidation products of the solvent. [j] A trace was detected. [k] It is possible that these values are high by the amount of formamide and butyramide present, since the NH peak used in the nmr determination could have included all three amides through hydrogen exchange. [l] Not determined. [m] A is PrCH=NBu; B is $BuNO_2$; C is $BuNH_3^+$, Cl^-, or NO_3^-; D is BuNH(C=O)NHBu; E is PrCH=N^+O^-Bu; F is PrCH=NOH; G is Pr(C=O)-NHBu; H is H(C=O)NHBu.

is singlet oxygen,[12] and it may be reacting in place of ozone as an oxidant to some extent.

$$\underset{1.02}{41i\text{-PrNH}_2} + 42O_3 + 7CHCl_3 \longrightarrow$$

$$\underset{27\%}{11i\text{-PrNO}_2} + 2Me_2C{=}O + \underset{51\%}{21i\text{-Pr}\overset{+}{N}H_3\bar{Cl}} +$$

$$\underset{17\%}{7i\text{-PrN}{=}C{=}O} + \underset{100\%}{42O_2} + 2NH_3 + 11H_2O \quad (18)$$

$$\underset{1.4}{14i\text{-PrNH}_2} + 20O_3 + 3CH_2Cl_2 \longrightarrow$$

$$\underset{36\%}{5i\text{-PrNO}_2} + 2Me_2C{=}O + \underset{43\%}{6i\text{-Pr}\overset{+}{N}H_3\bar{Cl}} +$$

$$i\text{-PrNHCH}(=O) + 20O_2 + 5H_2O + 2NH_3 + 2CO \quad (19)$$

$$\underset{7\%}{\qquad} \qquad \underset{100\%}{\qquad}$$

A comparison of expt 4 and 5 (ozonation at −30°) and 6 and 7 (ozonation at 0°) with expt 1–3 (ozonation at −65°) reveals that there is a temperature effect in the ozonation of isopropylamine similar to the one found eariler in the ozonation of tri-*n*-butylamine,[4] although not as great. If one does a similar summation with the −30 and 0° chloroform data as was done with the −65° data, it can be seen that the ratios of amine oxide to side-chain oxidation to ion-radical pathways are approximately 50:30:20 for the −30° reaction and 40:30:30 for the 0° ozonation, compared to 55:10:35 for the −65° reaction.

The data obtained from ozonation of isopropylamine in pentane is more difficult to interpret, since the total accounting of starting material in terms of products is not as great. The same is true with the ozonation of *n*-butylamine in pentane, and these reactions will be discussed together later.

The ozonation of *n*-butylamine required 1.6–1.9 molar equiv of ozone compared to less than 1.0 for isopropylamine. This difference is due to the greater reactivity of the primary ozonation products toward ozone in the case of butylamine. Table II contains the data obtained from the ozonation of *n*-butylamine in various solvents. In each case only 1 mol of ozone per mole of amine was employed. The amount of unreacted amine was determined and the product yields are based on unrecovered amine.

Since the only good accounting of reacting starting material in terms of determined products occurred with the ozonation in chloroform at −60°, only these data will be discussed in detail. The *n*-butylammonium chloride and *N,N'*-di-*n*-butylurea (XI) are products expected from the ion-radical pathway. In this case only the urea and no isocyanate was observed, due largely to the fact that amine was still present to react with any isocyanate when the reaction mixture was allowed to come to room temperature. When the ozonation of *n*-butylamine was carried out at −60° using 1.6–1.9 molar equiv of ozone, a small amount of isocyanate was observed in the reaction mixture. A summation of the *n*-butylamine equivalents of eq 1, 4, and 8–11 gives eq 20 for the ion-radical pathway in the ozonation of *n*-butylamine. As with the *tert*-butylamine[5] and isopropylamine ozonations, the ozonate

$$5BuNH_2 + O_3 + CHCl_3 \longrightarrow$$

$$3Bu\overset{+}{N}H_3\bar{Cl} + BuNHC(=O)NHBu + O_2 \quad (20)$$

XI

anion radical was identified by epr during low-temperature ozonations in pentane at −100°.

By analogy to the other primary amine ozonations, 1-nitrobutane (XII) is the expected major product of the amine oxide pathway, as expressed by eq 21.[3] The

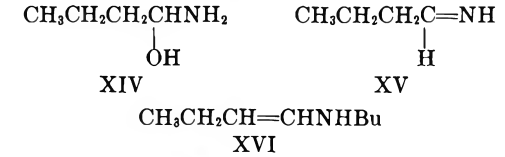
$$BuNH_2 + 3O_3 \longrightarrow \underset{\text{XII}}{BuNO_2} + 3O_2 + H_2O \quad (21)$$

butyraldoxime XIII, found in low yield, must also be a product of the amine oxide route, *via* isomerization of the nitrosobutane intermediate, as proposed previously by Bachman and Strawn.[8] The amine oxide route to the oxime can be expressed by eq 22.

$$BuNH_2 + 2O_3 \longrightarrow \underset{\text{XIII}}{PrCH{=}NOH} + HOH + 2O_2 \quad (22)$$

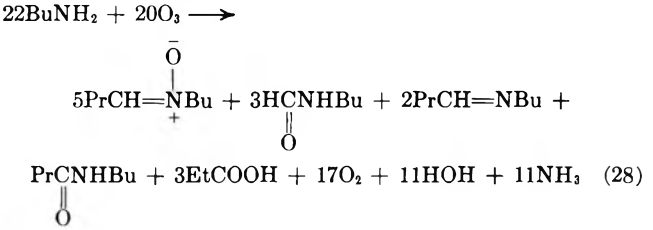
(12) R. W. Murray, W. C. Lumma, Jr., and J. W.-P. Lin, *J. Amer. Chem. Soc.*, **92**, 3205 (1970).

The other observed products are best explained by the side-chain oxidation pathway involving the formation of amino alcohol XIV as the primary product (*via* either the mechanism of eq 3 or of eq 6). Dehydration of XIV would give imine XV, whereas deamination would give butyraldehyde. In a protic solvent the latter would appear more likely, at least at low temperatures, as will be discussed later. This is thought to be the explanation for the better accounting of products in expt 15 (Table II) than in expt 14 or 16, where unstable XV was probably an important intermediate. Butyraldehyde was observed as a minor product, as was its oxidation product, butyric acid. Addition of butylamine to butyraldehyde yields amino alcohol XVII, which appears to be the key intermediate in the formation of at least three of the remaining determined products. Dehydration of XVII could occur in two ways, to give imine XX, a minor product, or

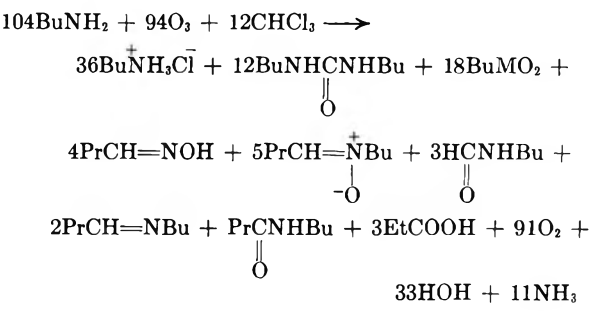


enamine XVI, which could undergo ozonolysis to formamide XIX, another minor product. Further side-chain oxidation of amino alcohol XVII (*via* a geminal diol) would produce *N*-butylbutyramide (XXI), also a minor product. The intermediacy of XVII in the formation of XIX and XXI finds analogy in the earlier reported results of ozonation of tri-*n*-butylamine.[4] The probable route to nitrone XVIII is *via* the amine oxide of XVII, followed by dehydration.

The reactions just discussed can be expressed by eq 23, followed by eq 24–27. If one sums these equations, multiplying eq 24, 25, 26, and 27 by 5, 3, 2, and 1, respectively (see Table II), and eq 23, consequently, by 11, eq 28 results as a representation of the side-chain oxidation pathway in the ozonation of *n*-butylamine.



By summation of eq 28 with 12 times eq 20 for the ion-radical pathway, 18 times eq 21 and 4 times eq 22, for the amine oxide pathways (see Table II), one arrives at eq 29 for the ozonation of *n*-butylamine. It can be seen that this fits the data of Table II quite well, except for the urea yield, the ozone to amine ratio, and



the oxygen to ozone ratio. The low urea yield most likely is due to some loss of phosgene during the ozonation and the low oxygen yield is perhaps due to some involvement of singlet oxygen in the amine oxidation, as was also suggested for the ozonation of isopropylamine. The fact that more ozone was actually used in the ozonation than implied by equation 29 most likely is due largely to the fact that the equation does not take into account any ozonation of ammonia. Undoubtedly, some of the ammonia escaped, but some was oxidized. The oxidation would require between 2 and 4 molar equiv of ozone.

If eq 29 is a reasonable representation of the *n*-butylamine ozonation, it and the equations leading up to it show that the ratio of moles of amine initially attacked by ozone *via* the amine oxide, the ion-radical, and the side-chain ozonation pathways is 22:12:11, respectively, or, on a percentage basis, 49, 27, and 24%.

As has already been mentioned, the accounting of both isopropylamine (Table I) and *n*-butylamine (Table II) in terms of products from the ozonations in pentane is poor. The identity and source of the missing products are uncertain, but it seems most likely that they are side-chain oxidation products. It is quite likely that major products of side-chain oxidation of both isopropylamine and *n*-butylamine in pentane are the corresponding imines VII and XV, from expulsion of water rather than ammonia from the corresponding amino alcohols III and XIV. In a nonprotic solvent hydroxyl should be a better leaving group than amino, whereas the opposite might be expected to be true in a protic solvent such as chloroform, at least at the temperature of expt 15 (Table II), due to the greater basicity of the amino group over that of the hydroxyl group. The chemistry expected of simple imines such as VII and XV is not clear. The most likely fate for VII or XV is polymerization.[13] Polymeric material was detected in the ozonation products of both isopropylamine and *n*-butylamine. Low yields of identified products from dye-sensitized photochemical autoxidation of butylamine are also thought to be due to polymerization of imine XV.[14]

The detection of pentanols and pentanones from ozonations of isopropylamine and of *n*-butylamine in

(13) E. M. Smolin and L. Rapoport in "The Chemistry of Heterocyclic Compounds," Vol. 13, A. Weissberger, Ed., Interscience, New York, N. Y., 1969, pp 505–509.

(14) F. C. Schaefer and W. D. Zimmermann, *J. Org. Chem.*, **35**, 2165 (1970).

pentane is analogous to similar findings with *tert*-butylamine.[3] Since the pentanones were not observed from ozonations of pentane in the absence of an amine, they are thought to evolve from the ion-radical pathway by mechanisms previously described.[3] These involve no overall loss of amine. It is noteworthy that the yield of isopropylammonium salt determined in the ozonation of isopropylamine in pentane is approximately equal to the acetone yield (Table I, expt 9) and that a similar correlation can be seen between the *n*-butylammonium salt yield and the sum of the yields of imine XX, *N*-butylbutyramide, and *N*-butylformamide from ozonation of *n*-butylamine in pentane (Table II, expt 14). These salts are thought to be nitrates and probably arise from oxidation of the ammonia expelled during formation of the stated products, followed by reaction of the resulting nitric acid with unreacted amine, rather than by an ion-radical pathway.

Thus, it appears that the products resulting from ozonation of isopropylamine and *n*-butylamine in pentane arise by the amine oxide and side-chain oxidation routes only. If the assumption is made that the products not accounted for in these ozonations are side-chain oxidation products, it can be shown, by calculations similar to those already made, that the proportions of amine oxide to side-chain oxidation occurring during attack of ozone on isopropylamine and *n*-butylamine in pentane are 56:44 and 22:78, respectively, as shown in Table III.

TABLE III

COMPETITIONS IN OZONATIONS OF PRIMARY AMINES HAVING TERTIARY, SECONDARY, AND PRIMARY ALKYL GROUPS

Amine	Solvent	Temp, °C	Amine oxide pathway[a]	Ion radical pathway[a]	Side-chain oxidation[a]
t-Bu	$CHCl_3$	−65, −60	50	50	*b*
i-Pr	$CHCl_3$	−65	55	35	10
n-Bu	$CHCl_3$	−60	49	27	24
i-Pr	$CHCl_3$	−30	50	20	30
i-Pr	$CHCl_3$	0	40	30	30
t-Bu	Isooctane	−78	100	*c*	*b*
i-Pr	Pentane	−78	56	*c*	44
n-Bu	Pentane	−60	22	*c*	78

[a] Approximate percentages by each pathway. [b] Not possible in this case. [c] Occurs to some extent, but does not show up in products derived from the amine.

Table III compares the results of ozonation of *tert*-butylamine,[3] isopropylamine, and *n*-butylamine in chloroform at −60 to −65° and in pentane at −60 to −78°. In the ozonations in chloroform solution the amine oxide pathway is the major pathway in all three cases. The ion-radical pathway decreases in importance in going from *tert*-butyl to isopropyl to *n*-butyl. This could simply reflect the increasing side-chain oxidation, but also may indicate a steric factor; the equilibrium between the adduct and the ion radicals may shift slightly in favor of the ion radicals as bulk around the nitrogen increases.

Table III also shows that there is a much greater solvent effect with *n*-butylamine than with isopropylamine. With isopropylamine there is no change in the percentage of amine oxide pathway and only a 34% variation in the side-chain oxidation pathway in going from chloroform to pentane at −65 to −78°. In contrast, with *n*-butylamine there is a 27% decrease in the amine oxide pathway and a 54% increase in the side-chain oxidation pathway in going from chloroform to pentane. The *n*-butylamine solvent effect is similar to that of tri-*n*-butylamine.[4] This suggests that side-chain attack with isopropylamine may occur to a large extent by the 1,3-dipolar insertion mechanism (eq 6), whereas that with *n*-butylamine and tri-*n*-butylamine occurs predominantly by the mechanism of eq 3. A solvent effect is expected in the competition between reactions 2 and 3, but not between reactions 2 and 6.[4] There are also indications of this difference in the ozonation of triisopropylamine.[15] The increase in the side-chain oxidation pathway in going from isopropylamine to *n*-butylamine in chloroform appears to be largely a statistical factor, but also may reflect this difference in mechanism. The small temperature effect noted in the ozonation of isopropylamine is possibly due to a decreasing stability of the amine–ozone adduct with increasing temperature and a consequential increase in 1,3-dipolar insertion at the side chain. It is not possible to judge from Table II whether there is a temperature effect in the ozonation of *n*-butylamine or whether there is a solvent effect involving methylene chloride and carbon tetrachloride.

Experimental Section

Materials.—The isopropylamine and *n*-butylamine were J. T. Baker reagent grade. They were dried over potassium hydroxide and distilled before use. *N,N'*-Di-*n*-butylurea[16] and *N,N'*-diisopropylurea[17] were prepared by treatment of the corresponding primary amine with phosgene or the corresponding isocyanate in ether or chloroform solution. Formylation of *n*-butylamine with chloral afforded *N*-*n*-butylformamide.[18,19] Isopropylhydroxylamine,[20,21] *N*-isopropylformamide,[22,23] *N*-*n*-butylbutyramide,[24,25] and *N*-*n*-butylidene-*n*-butylamine[26,27] were prepared and purified by standard procedures. *C*-propyl-*N*-butyl nitrone was synthesized by the general method of Utzinger,[28] involving hydrogen peroxide oxidation of the corresponding hydroxylamine (di-*n*-butylhydroxylamine), which was, in turn, synthesized by the amine oxide pyrolysis method of Cope[29] starting with tributylamine.[3] The dibutylhydroxylamine melted at 51–52°.[29] The nitrone gave important ir absorptions (CCl_4) at 1587 (C=N) and 1178 cm^{-1} (N^+O^-) and nmr absorptions (CCl_4) at δ 6.52 (t, 1, J = 6 Hz, CH=N), 3.60 (t, 2, J = 7 Hz, CH_2N), 2.35 (m, 2, CH_2CH=N), 1.57 (m, 6, CH_2CH_2CH=$NCH_2CH_2CH_2$), 1.00 (t, 3, CH_3), and 0.98 ppm (t, 3, CH_3). The other materials used were obtained commercially and purified, when necessary, by standard procedures.

General Equipment and Procedures.—The ozonation setup and procedures, including the use of ozone–nitrogen and the determination of molecular oxygen yields, are described in

(15) P. S. Bailey, D. E. Lerdal, and T. P. Carter, Jr., results to be reported shortly.
(16) F. Cramer and M. Winter, *Chem. Ber.*, **92**, 2761 (1959).
(17) T. Curtius, *J. Prakt. Chem.*, **125**, 152 (1930).
(18) F. F. Blicke and C. J. Lu, *J. Amer. Chem. Soc.*, **74**, 3933 (1952).
(19) P. L. deBenneville, J. S. Strong, and V. T. Elkind, *J. Org. Chem.*, **21**, 772 (1956).
(20) W. R. Dunslan and E. Goulding, *J. Chem. Soc.*, **75**, 792 (1899).
(21) P. A. S. Smith, H. R. Alul, and R. L. Baumgarten, *J. Amer. Chem. Soc.*, **86**, 1139 (1964).
(22) H. Morawetz and P. S. Otaki, *ibid.*, **85**, 463 (1963).
(23) L. A. LaPlanche and M. T. Rogers, *ibid.*, **86**, 337 (1964).
(24) A. I. Vogel, "A Textbook of Practical Organic Chemistry," 2nd ed, Longmans, Green and Co., London, 1951, pp 396–397.
(25) K. Heyns and W. von Bebenburg, *Justus Liebigs Ann. Chem.*, **595**, 55 (1955).
(26) K. N. Campbell, A. H. Sommers, and B. K. Campbell, *J. Amer. Chem. Soc.*, **66**, 82 (1944).
(27) W. S. Emerson, S. M. Hess, and F. C. Uhle, *ibid.*, **63**, 872 (1941).
(28) G. E. Utzinger, *Justus Liebigs Ann. Chem.*, **556**, 50 (1944);
(29) A. C. Cope and H.-H. Lee, *J. Amer. Chem. Soc.*, **79**, 964 (1957).

earlier papers.[30] Ir spectra were recorded with a Beckman IR-5A double-beam infrared spectrophotometer and mass spectra were obtained with a Consolidated Engineering Corp. 21-491 double-focusing medium-resolution mass spectrograph.

Epr Procedures.—All spectra were recorded with a Varian Associated V-4502 spectrometer equipped with a Varian field dial and a 9-in. magnet using a modulation frequency of 100 kcps.[31] Special techniques for recording spectra while ozonating were described earlier.[5]

Glpc determinations were made with either a Varian Aerograph 1520B dual-column chromatograph equipped with hydrogen flame ionization detectors and a Beckman recorder and disk integrator or with an F & M 500 gas chromatograph, equipped with a disk integrator. Yields were determined by the internal standard method with the Aerograph 1520B and by comparison with standard solutions of known compounds with the F & M 500. With the Aerograph 1520B the following columns were employed: (1) 20% Dowfax 9N9, 2.5% NaOH on Chromosorb W, 1/16 in. × 10 ft; (2) 30% silicone gum rubber SE-30 on Chromosorb P, acid washed, 1/16 in. × 10 ft; (3) 15% Carbowax 20M on Chromosorb W (AW), 1/16 in. × 10 ft; (4) 5% DEGS, 2% H_3PO_4 on Chromosorb P, 1/16 in. × 10 ft; (5) 5% Versamid 900 on Chromosorb G (AW), 1/16 in. × 5 ft. With the F & M 500 the following columns were employed: (6) 20% Carbowax 20M on Chromosorb P, 1/4 in. × 15 ft; (7) 10% Carbowax 20M–10% NaOH on Chromosorb P, 1/4 in. × 20 ft; (8) 5% Celanese ester #9 on Haloport F, 1/4 in. × 10 ft; (9) 30% silicone gum rubber SE-30 on Chromosorb P, 1/4 in. × 10 ft.

A Varian Aerograph A-90-P3 gas chromatograph was used for preparative work.

Nmr Spectra and Procedures.—A Varian A-60 spectrometer was used for ordinary spectra, whereas a Varian HA-100 instrument was used for most quantitative analyses using, usually, 1-nitropropane as an internal standard. Chemical shifts are reported on the δ scale, with TMS internal standard. Important spectra observed follow: *n*-butylamine (CCl_4), 2.64 (t, 2, J = 6 Hz, CH_2N), 1.52 (s, 2, NH_2), 1.40 (m, 4, $CH_2CH_2CH_2N$), 0.92 (t, 2, CH_3); *N*-*n*-butyl-*n*-butyramide ($CDCl_3$), 6.49 (1, NH), 3.24 (m, 2, CH_2N), 2.18 (t, 2, J = 7 Hz, CH_2CO), 1.48 (m, 6, $CH_2CH_2CH_2NCOCH_2CH_2$), 0.94 (t, 3, CH_3), 0.91 (t, 3, CH_3); *N*-*n*-butylformamide ($CDCl_3$), 8.16 (s, 1, CHO), 3.30 (m, 2, CH_2N), 1.42 (m, 4, $CH_2CH_2CH_2N$), 0.94 (t, 3, CH_3); *N*,*n*-butylidene-*n*-butylamine (CCl_4), 7.57 (t, 1, J = 4 Hz, CH=N), 3.29 (t, 2, J = 6 Hz, CH_2N), 2.17 (m, 2, CH_2CH=N), 1.43 (m, 6, CH_2CH_2CH=$NCH_2CH_2CH_2$), 0.94 (t, 3, CH_3), 0.92 (t, 3, CH_3); *n*-butyraldoxime (CCl_4), 9.91 (broad s, 1, OH), 7.34 (t, 0.5, J = 6 Hz, CH=N), 6.65 (t, 0.5, J = 6 Hz, CH=N), 2.27 (m, 2, CH_2CH=N), 1.52 (m, 2, CH_2CH_2CH=N), 0.96 (t, 1.5, CH_3), 0.94 (t, 1.5, CH_3); *N*,*N*'-di-*n*-butylurea ($CDCl_3$), 5.67 (2, NH), 3.16 (m, 4, CH_2N), 1.39 (m, 8, $CH_2CH_2CH_2N$), 0.92 (t, 6, CH_3); 1-nitrobutane (CCl_4), 4.37 (t, 2, J = 7 Hz, CH_2NO_2), 2.00 (m, 2, $CH_2CH_2NO_2$), 1.42 (m, 2, $CH_2CH_2CH_2NO_2$), 0.98 (t, 3, CH_3); *N*-isopropylformamide (CCl_4), 1.16 (d, CH_3), 4.00 (heptet, CHN), 7.93 (s, CHO).

Ozonation of Isopropylamine and Isopropylhydroxylamine.—Ozonations were generally run on a 5 ± 1 mmol scale in 6–8 ml of solvent[32] and using 6 ± 1 mmol of ozone (a slight excess), from an ozone–nitrogen stream, at the designated (Table I) temperature. A pale blue color (of 2-nitrosopropane) developed immediately and persisted until the ozonation was nearly complete and, in the methylene chloride and chloroform runs with isopropylamine, a white solid (the ammonium chloride) precipitated. An excess of ozone was employed because of difficulty in determining unreacted isopropylamine by glpc, due to tailing with some columns and conversion of isopropylammonium chloride to free amine by others. The amount of excess ozone was determined by titration of the iodine produced in the iodide trap. The reaction mixture was brought to room temperature and diluted to a known volume of solvent, and the liquid components were determined by glpc, using the F & M 500. Column 6 (above) was used for the determinations of acetone, 2-nitropropane, and isopropylformamide (at column temperatures of 75, 125, and 200°, respectively), and column 8 was used for the isopropyl isocyanate determination at a column temperature of 50°. The isopropylammonium chloride was determined by evaporating the reaction mixture, drying the residue for 24 hr in a vacuum desiccator, and weighing it. It was completely water soluble and was shown to be the salt by comparing its ir spectrum with that of an authentic sample and by conversion to isopropylamine with base. The isopropylamine was determined by glpc using column 7. In one instance a chloride determination was made. Results are shown in Table I.

Infrared spectra of the reaction mixture confirmed the presence of the above substances, showing peaks at 1720 (acetone carbonyl), 1675 (isopropylformamide carbonyl), 1543 and 1357 (nitro group), and 2275 cm^{-1} (isocyanate). A qualitative test for ammonia in the effluent from one reaction mixture was made by using an ethereal hydrogen chloride trap at −78° and evaporating the ether to give a white solid, which gave a positive test.[33]

In ozonations of isopropylamine in chloroform at −30 and 0°, *N*,*N*'-diisopropylurea was a product. It was determined by weighing the residue from evaporation of the reaction material after the isopropylammonium chloride had been extracted with water. It melted at 186–188°[17] and absorbed at 1661 cm^{-1} (urea carbonyl) in the ir.

From isopropylamine ozonations in pentane, 2- and 3-pentanone was qualitatively identified by glpc using column 6 at a column temperature of 145°. These were not produced when pentane alone was ozonized. Evaporation of the pentane ozonation solution to dryness gave a residue which was shown by mass spectroscopy to contain some polymeric material (m/e over wide range, continuing in excess of 200), perhaps from polymerization of imine VII. Part of the residue, however, was soluble in water and gave a positive nitrate ion test.[34] Treatment with base converted it to isopropylamine, which was determined by glpc on column 7. On this basis the residue was listed in Table I as isopropylammonium nitrate.

Ozonation of isopropylamine in methylene chloride at −95° gave a reddish solution which became colorless when the temperature was allowed to rise. The reaction mixture was analyzed for 1,1,2,2-tetrachloroethane by glpc, using column 9, but none was found. By epr the red solution was shown to contain the ozonate anion radical.[5] The anion radical also was shown to be strongly present from ozonation of isopropylamine in pentane at −120°. In this case, a red precipitate formed.

Ozonation of *n*-butylamine in chlorinated solvents afforded a pale yellow solution containing a white solid. The data shown in Table II resulted from numerous runs employing 5, 10, or 20 mmol of amine in 2.5 ml of solvent per millimole of amine and utilizing 1 mol of ozone (in a nitrogen stream) per mole of amine. Product determinations were performed as follows. Determinations by glpc were carried out with 1-nitrobutane (column 2 at a column temperature of 90° and toluene as an internal standard), butyraldehyde (column 3, column temperature 90°, ethylbenzene as internal standard), and *N*-*n*-butylbutyramide and *N*-*n*-butylformamide (column 5, 170°, phenyl propyl ketone internal standard). It was impossible to determine unreacted butylamine by glpc with chloroform as solvent because the two came off together. After these determinations were made, the reaction mixture was extracted with aqueous potassium hydroxide. The extract was acidified and carefully extracted with ether. Butyric acid was determined on the ether extract, using column 4 at a temperature of 120° with phenyl propyl ketone as internal standard. A small propionic acid peak was also detected, but not determined quantitatively. With 1-nitrobutane as the internal standard (peak at δ 4.38 ppm) the following substances were then determined by nmr from a $CDCl_3$ ozonation solution and using the HA-100 spectrometer: unreacted *n*-butylamine (δ 2.89, CH_2N), *N*-*n*-butylidene-*n*-butylamine (δ 7.72, CH=N), *C*-*n*-propyl-*N*-*n*-butylnitrone (δ 6.67, CH=N), and *n*-butyraldoxime (δ 7.39, CH=N); the butyraldoxime peak did not show up until the reaction mixture had been kept in the refrigerator overnight. The *n*-butylammonium chloride was determined in a 10-mmol run by partially evaporating the solvent, extracting the salt with water, and determining chloride ion in the aqueous extract by standard methods. A D_2O extract of the residue was shown to contain largely the butylammonium salt, by comparison with an authentic sample (nmr). The organic layer was then

(30) A. M. Reader, P. S. Bailey, and H. M. White, *J. Org. Chem.*, **30**, 784 (1965), and references cited therein.

(31) This instrument was made available to the Chemistry Department through NSF Grant GP-2090.

(32) During ozonations carried out in nonpolar solvents (pentane, isooctane, and carbon tetrachloride) a black, particulate material appeared in the iodide trap.

(33) N. D. Cheronis and J. B. Entrikin, "Semimicro Qualitative Organic Analysis," 2nd ed, Interscience, New York, N. Y., 1960, Chapter 5.

(34) P. Arthur and O. M. Smith, "Semimicro Qualitative Analysis," 3rd ed, McGraw-Hill, New York, N. Y., 1952, p 263.

evaporated to a thick oil, $CDCl_3$ was added, and the *N,N'*-di-*n*-butylurea was determined by nmr (δ 5.55, NH), using 1,4-dioxane (δ 3.69) as an internal standard. Although the urea peak employed appears to be distinctive in comparison to those of the other amides, it is possible that a mixture of all three amides would have a common NH peak due to hydrogen exchange, thereby causing the urea value to be high. Molecular oxygen analyses were carried out by standard procedures already referenced.

In a few instances the amine was ozonized in chloroform at −60° with an excess (2–3 molar equiv) of ozone, resulting in the reaction of 1.6–1.9 molar equiv of ozone. The major products were the nitrobutane and the *tert*-butylammonium chloride. Small amounts of *n*-butyric acid, *N*-*n*-butyl-*n*-butyramide, and *n*-butyl isocyanate (column 2, 90°) were detected by glpc. Quantitative determinations were made, however, only in the case of the *n*-butylammonium chloride (36% yield).

Ozonation of *n*-butylamine (20 mmol) in pentane at −60° with 1 molar equiv of ozone resulted in the formation of a white solid which melted and settled to the bottom as a small yellow aqueous layer when the reaction mixture was allowed to warm to room temperature. The two layers were separated and analyzed independently. The *pentane layer* was analyzed for 1-nitrobutane, *N*-*n*-butyl-*n*-butyramide, and *N*-*n*-butylformamide by glpc in the same manner as described for ozonations in chlorinated solvents. Glpc determinations were also employed for unreacted butylamine and *N*-*n*-butylidene-*n*-butylamine (column 1, 75° for 4 min and 75–175° at 6°/min, propylbenzene as internal standard), and the pentanones and pentanols (column 3, 90°, ethylbenzene as internal standard); the 2- and 3-pentanones were not separable from each other and are reported together in Table II. A trace of *C*-*n*-propyl-*N*-*n*-butylnitrone was shown to be present by nmr (see details under chlorinated solvent experiments).

A portion of the *aqueous phase* was dissolved in acetone and traces of pentanones and pentanols were determined by glpc using the procedure already described. The aqueous phase was concentrated at room temperature under reduced pressure (6 mm) for 40 min and the volatile material was trapped at −70° and weighed. This was shown to be composed of water and unreacted amine; the amounts were obtained by integration. The residue from the aqueous phase was extracted with chloroform and analyzed by glpc for *N*-*n*-butyl-*n*-butyramide and *N*-*n*-butylformamide, using the procedure already described. The *n*-butylammonium cation was determined by nmr ($BuNH_3^+$ peak at δ 7.09) on a portion of the original residue, using the butyramide as an internal standard ($EtCH_2CONHBu$ at δ 2.17). Since the residue gave a positive nitrate anion test,[34] the salt is reported in Table II as the nitrate. In a separate experiment, a trace of butyric acid was identified in the aqueous phase by acidification, extraction with ether, and glpc analysis of the ether extract, using the procedure already described. The values for unreacted amine, the butyramide, and the formamide reported in Table II are the sums of the determinations in the pentane and aqueous phases.

Ozonation of *n*-butylamine in pentane at −100° gave a colorless solution which, however, gave a strong epr signal for the ozonate anion radical.

Registry No.—Isopropylamine, 75-31-0; isopropylhydroxylamine, 5080-22-8; *n*-butylamine, 109-73-9.

Acknowledgment.—This work was supported by grants from the Robert A. Welch Foundation (F-042) and the National Science Foundation (GP-7351), for which the authors are grateful. Acknowledgment is also made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of the research.

Addition of Pseudohalogens to 1,5-Cyclooctadiene[1]

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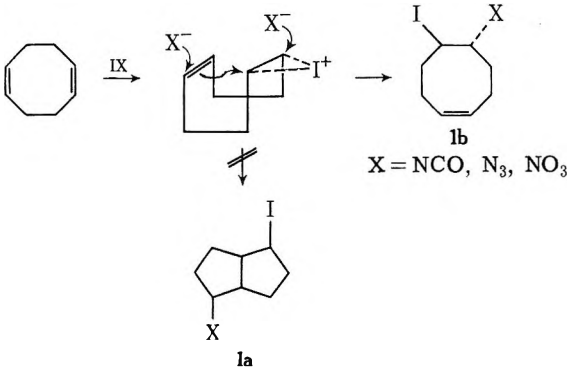
The addition of pseudohalogens IX, where X = NCO, N_3, NO_3, to 1,5-cyclooctadiene (mole ratio 1:1) yields 1,2-monocyclic adducts. In contrast, addition of iodine in methanol activates the second double bond, resulting in the direct formation of *endo,endo*-2,6-diiodo-9-oxabicyclo[3.3.1]nonane (**2**). The complete analysis of the nmr spectrum of **2** with the help of chemical shift reagents confirms the chair conformation for this fused ring system Similarly, the reaction of 5-methoxycyclooctene (**5**) with iodine in methanol gives *endo*-2-iodo 9-oxabicyclo[3.3.1]-nonane (**7**), whereas cyclooct-1-en-5-ol (**6**) gives only *endo*-2-iodo-9-oxabicyclo[4.2.1]nonane (**8**).

The addition of various reagents to 1,5-cyclooctadiene (COD) can lead to either monocyclic or bicyclic products. The monocyclic products arise by simple addition of the reagent to one of the double bonds, while the formation of bicyclic products involves transannular π participation, a well-documented pathway.[2] Recently, a detailed study of ionic additions to COD outlined some of the requirements for formation of bicyclic *vs.* monocyclic products and also presented information on the stereochemistry of the substituents on the bicyclic ring skeleton.[3]

We were interested in the preparation of 2-amino-6-iodobicyclo[3.3.0]octanes (**1a**) (Scheme I) and felt that

SCHEME I



1b
X = NCO, N_3, NO_3

1a

these could be obtained by the addition of pseudohalogens of type IX to COD.[4] It was visualized that the initial formation of an iodonium ion might be followed by transannular π participation to form a bicyclo[3.3.0]octane. However in all cases, where X^- =

(1) (a) This work was supported in part by U. S. Public Health Service Grants CA-05222, 07803, and 07174 of the National Cancer Institute. Pseudohalogens. XVIII. Paper XVII: *Amer. Chem. Soc., Div. Petrol. Chem., Prepr.*, **15**, E39 (1970). (b) Presented at the 162nd National Meeting of the American Chemical Society, Washington, D. C., Sept 1971, Paper 169, Organic Chemistry Division.

(2) R. Dowbenko, *Tetrahedron*, **20**, 1843 (1964); L. Friedman, *J. Amer. Chem. Soc.*, **86**, 1885 (1964); G. Pregaglia and G. Gregorio, *Chim. Ind. (Milan)*, **45**, 1065 (1963); M. Julia and E. Colomer, *An. Quim.*, **67**, 199 (1971); T. Cantrell and B. L. Strasser, *J. Org. Chem.*, **36**, 670 (1971).

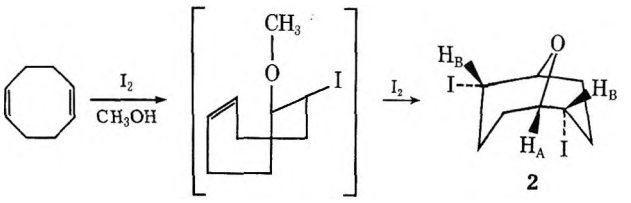
(3) I. Tabushi, K. Fujita, and R. Oda, *J. Org. Chem.*, **35**, 2376 (1970).

(4) (a) S. Rosen and D. Swern, *Anal. Chem.*, **38**, 1392 (1966); (b) F. W. Fowler, A. Hassner, and L. A. Levy, *J. Amer. Chem. Soc.*, **89**, 2077 (1967).

NCO^-, N_3^-, or NO_3^-, only 1,2-addition products (**1b**) are observed. This is believed due in part to the "closed nature" of the iodonium ion where so little positive charge resides on the carbon atoms of the iodonium ring that the remaining double bond cannot compete with the anion.[5] We have observed similar 1,2-adduct formation in the addition of *N*,*N*-dichlorourethane to COD.[6]

In contrast, the reaction of COD with I_2 in methanol (Scheme II) gives a single crystalline product char-

SCHEME II

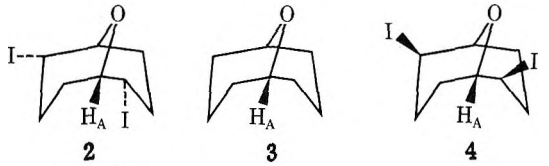


acterized as *endo,endo*-2,6-diiodo-9-oxabicyclo[3.3.1]-nonane (**2**) by analysis, its infrared spectrum with peaks at 1490 cm^{-1} characteristic of 9-oxabicyclo[3.3.1]-nonanes[7] and at 1030 cm^{-1} for an ether, its nmr spectrum [δ 4.6 (2, p), 3.95 (2, t), 2.8–2.0 (8)],[8] and its reduction with $LiAlH_4$ to 9-oxabicyclo[3.3.1]nonane (**3**). The nmr coupling pattern, $J_{H_AH_B}$ = 5 cps, is compatible with the conclusion that H_B is in the exo position.

An isomeric compound, formed from the reaction of mercuric acetate, potassium iodide, and iodine with COD, has $J_{H_AH_B} < 1$ cps and is thus *exo,exo*-2,6-diiodo-9-oxabicyclo[3.3.1]nonane (**4**).[9,10]

In order to distinguish clearly between structures **2** and **4**, we examined their nmr spectra with the help of chemical shift reagents.[11] Chart I shows the chemical

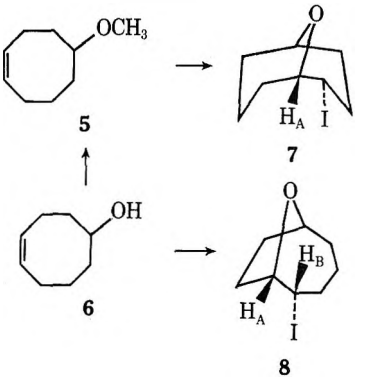
CHART I



shift gradient (Δ_{Eu}) of H_A in three 9-oxabicyclononanes with $Eu(thd)_3$. The values of the α hydrogens H_A in **2** and **3** show that these ethers are complexed about three and four times stronger, respectively, than alicyclic ethers ($\Delta_{Eu} \sim 10$). Also, the weakness of complexation with **4** confirms that it has the exo,exo configuration, since the iodines in this configuration could readily interfere with complexation. Further, the use of $Eu(thd)_3$ allowed a first-order analysis of the six different hydrogens in **2**. The coupling constants thus determined confirmed the chair cyclohexane geometry for this ring system.[12]

The mechanism of formation of **2** (Scheme II) can be visualized as proceeding through an intermediate iodine–methoxy adduct a in which the ether oxygen activates the remaining π bond, which adds a second iodine atom followed by loss of methyl iodide. This result is similar to that with sulfenyl halide additions to COD where diadducts are formed almost exclusively unless high dilution techniques are employed.[13] To test this mechanism, 5-methoxycyclooctene (**5**) was treated with iodine in methanol (Scheme III). A new

SCHEME III



product was formed which was characterized as *endo*-2-iodo-9-oxabicyclo[3.3.1]nonane (**7**) on the basis of spectral data and its reduction with $LiAlH_4$ to give 9-oxabicyclo[3.3.1]nonane (**3**).[14]

In contrast with this result, under the same conditions **6** gives *endo*-2-iodo-9-oxabicyclo[4.2.1]nonane (**8**).[14] The infrared spectrum of **8** has an ether peak at 1064 cm^{-1} while its nmr pattern shows δ 4.5 (2, m), 4.15 (1, m) (splitting identical with that of **2** and **7** suggesting the endo configuration), and 2.3–1.2 (10). The α hydrogens H_A in the [4.2.1] ring system are deshielded by ~0.5 ppm compared with those in the [3.3.1] ring system; thus in **8** H_A gives a signal at lower field than H_B.[15] This feature of sizable differences in the chemical shifts of bridgehead protons between ring systems has also been found in the 9-thiabicyclonanes and has been attributed to differences in ring strain.[16]

These results support the mechanism for formation of **2**. Reaction of iodine with **6** is faster than with **5** and this may explain in part the difference in the products formed. Thus, before the methyl group is lost (Scheme IV), a second-order reaction, the more stable bridged structure b may be formed, whereas in the formation of **8** simple proton loss is required from a species like a and this reaction may be under kinetic control. This in-

(5) For a discussion of iodonium ions as intermediates see A. Hassner, *Accounts Chem. Res.*, **4**, 9 (1971), and references cited therein.

(6) T. A. Foglia and D. Swern, *J. Org. Chem.*, **31**, 3625 (1966).

(7) (a) E. D. Weil, K. J. Smith, and R. J. Gruber, *ibid.*, **31**, 1669 (1966); (b) F. G. Bordwell and M. L. Douglass, *J. Amer. Chem. Soc.*, **88**, 993 (1966).

(8) This isomer of diiodo-9-oxabicyclononane is identical with one of the six isomers formed in the iododemercuration of the mercuric acetate adduct of COD.[9]

(9) C. Ganter, K. Wicker, W. Zwahlen, and K. Schaffner-Sabba, *Helv. Chim. Acta*, **53**, 1618 (1970).

(10) H. Stetter, H. J. Meissner, and W. D. Last, *Chem. Ber.*, **101**, 2889 (1968).

(11) J. K. M. Sanders and D. K. Williams, *J. Amer. Chem. Soc.*, **93**, 641 (1971).

(12) E. J. Corey and E. Block, *J. Org. Chem.*, **31**, 1663 (1966).

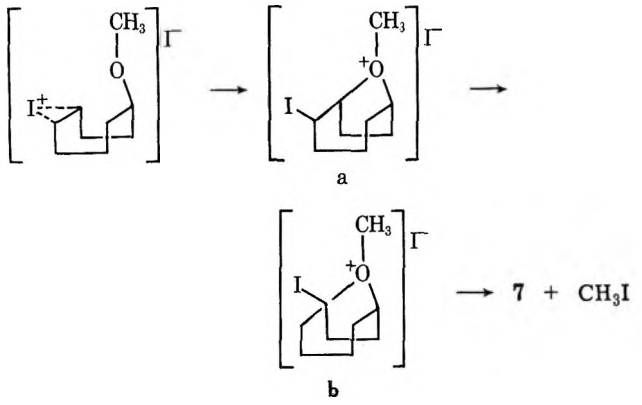
(13) W. H. Mueller, *J. Amer. Chem. Soc.*, **91**, 1223 (1969).

(14) C. Ganter, R. O. Duthaler, and W. Zwahlen, *Helv. Chim. Acta*, **54**, 578 (1971).

(15) The δ values for the parent systems are 3.9 for **3** and 4.4 for 9-oxabicyclo[4.2.1]nonane.[16]

(16) H. J. Franz, W. Höbold, R. Höhn, G. Müller-Hagen, R. Müller, W. Pritzkow, and H. Schmidt, *J. Prakt. Chem.*, **3**, 622 (1970).

SCHEME IV



terpretation is supported by results on the addition of mercuric acetate to **6** where, under buffered conditions, a [4.2.1] ring system is formed, while under acidic conditions the [3.3.1] ring system is formed since added acid inhibits proton loss, thus leading to the thermodynamic product.[7b]

Experimental Section

Nmr spectra were obtained on a Varian XL-100 spectrometer. Infrared spectra were recorded on a Perkin-Elmer Model 137. 1,5-Cyclooctadiene was obtained from Aldrich Chemical Co.

Addition of Pseudohalogens to 1,5-COD.—Literature procedures were followed for the preparation of INCO,[4a] IN_3,[4b] INO_3 (solvent acetonitrile), and *N,N*-dichlorourethane,[6] and their addition to COD. A 1:1 molar ratio of reagent to COD was used. After removal of unreacted COD, the products were analyzed by nmr for the presence of olefinic hydrogens. In all cases proton ratios indicated one remaining double bond.

Methyl (5-iodo-6-cyclooctenyl)carbamate, mp 114°, was prepared from the INCO adduct by reaction with methanol, nmr δ 5.7 (2), 5.1 (1), 4.6 (1), 4.0 (1), 3.5 (3, s), 2.7–1.8 (8).

Anal. Calcd for $C_{10}H_{16}NIO_2$: C, 38.6; H, 5.17; N, 4.52; I, 41.3. Found: C, 38.6; H, 5.15; N, 4.27; I, 41.3.

5-Iodo-6-azidocyclooctene had nmr δ 5.7 (2), 4.6 (1), 4.0 (1), 3.0–2.0 (8); **5-iodo-6-nitratocyclooctene** had mp 110°, nmr δ 5.6 (2), 5.3 (1), 4.5 (1), 2.5–2.0 (8) (compare $-CH_2ONO$, δ 4.8); **ethyl (5-chloro-6-cyclooctenyl)carbamate**[6] had bp 105° (0.02 mm), nmr δ 5.8–5.5 (2), 4.5–3.8 (4), 2.7–1.8 (8), 1.2 (3, t).

***endo,endo*-2,6-Diiodobicyclo[3.3.1]nonane (2).**—A solution of 1,5-COD (5 g, 0.05 mol) and iodine (22 g, 0.09 mol) in methanol was refluxed for 3–4 hr. On cooling a precipitate formed, which was filtered and washed with a solution of sodium thiosulfate. Recrystallization from ether or hexane gave crystals (5 g, 30%): mp 124°; ir 2980, 1490, 1150, 1030, 905, 860, 790 cm^{-1}; nmr δ 4.6 (2, p), 4.0 (2, t), 2.8–2.0 (8, b).

Anal. Calcd for $C_8H_{12}I_2O$: C, 25.5; H, 3.19; I, 67.0. Found: C, 25.5; H, 3.15; I, 66.9.

The same yield was obtained in methanol–water (80:20). **2** gave an immediate precipitate with $AgNO_3$ and a quantitative yield of AgI. Reaction of **2** (1 g) with $LiAlH_4$ (0.4 g) in ether gave a residue which after work-up was identical with 9-oxabicyclo[3.3.1]nonane (**3**) by ir and nmr [δ 3.8 (2), 7.9–8.6 (12)]. Further purification by sublimation gave crystals, mp 50–52° (lit. mp 52–52.5°).[7b]

***endo*-2-Iodo-9-oxabicyclo[4.2.1]nonane (8).**—Cyclooct-1-en-5-ol (**6**) (1 g) was dissolved in methanol (25 ml), and iodine (2.5 g excess) was added; the reaction mixture was stirred at 25° for 4 days. Sodium thiosulfate solution was added to destroy excess iodine and the mixture was extracted with hexane, washed, and dried. On evaporation of hexane a residue (1.5 g) was formed: bp 56° (0.03 mm); ir 2980, 1475, 1458, 1060, 960, 920 cm^{-1}; nmr δ 4.5 (2, m), 4.15 (1, m) (six peaks), 2.3–1.2 (10).

Anal. Calcd for $C_8H_{13}IO$: C, 38.1; H, 5.16. Found: C, 38.26; H, 5.17.

5-Methoxycyclooctene (5).[16]—**6** was treated with NaH and methyl iodide. The product after work-up and distillation [43° (1.5 mm)] showed ir 2980, 1100, 995, 879 cm^{-1} and nmr δ 5.6 (2), 3.8 (1), 3.2 (3), 2.4–1.2 (10).

Anal. Calcd for $C_9H_{16}O$: C, 77.3; H, 11.4. Found: C, 77.2; H, 11.4.

***endo*-2-Iodo-9-oxabicyclo[3.3.1]nonane (7).**—**5** was treated with iodine in methanol for 1 week and worked up as previously described. The product showed ir 1490 and 1028 cm^{-1} and nmr δ 4.55 (1, p), 3.93 (2, q), 2.7–1.7 (10), with a pattern identical with that reported.[14] The ether **5** reacts slower than the alcohol **6** with iodine, as determined from a competition reaction. When a 70:30 mixture of ether–alcohol was treated with excess iodine for 24 hr, unreacted ether **5** was still present. Distillation [56° (0.03 mm)] afforded a mixture of the iodo ethers **7** and **8** as determined from nmr. A sample of **7** was treated with $LiAlH_4$ in ether to give 9-oxabicyclo[3.3.1]nonane (**3**) identical with an authentic sample.[7b]

Registry No.—**2**, 29417-22-9; **5**, 32160-45-5; **8**, 35048-89-6; 1,5-COD, 111-78-4; methyl (5-iodo-6-cyclooctenyl)carbamate, 35048-90-9.

Acknowledgment.—The authors acknowledge with gratitude the capable assistance of Michael Luddy and Robert Johnson, participants in the Undergraduate Honors Research Program, Temple University, and also to Donald F. Busky.

Intramolecular Nucleophilic Participation. IX. Solvolysis of *o*- and *p*-Thiolcarbophenoxybenzyl Bromides

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In 80% aqueous dioxane *o*-thiolcarbophenoxybenzyl bromide hydrolyzes significantly faster than does its para isomer (8.11 times at 65°). In acetic acid at 85° the ortho/para solvolysis rate constant ratio is exceptionally high (534) when compared with that for the *o*- and *p*-methoxybenzyl bromides (0.0017 at 60°), a system in which ortho substituent participation does not occur. The high reactivity of *o*-thiolcarbophenoxybenzyl bromide is attributed to the favorable influence of the S atom on the capacity of the *o*-$COSC_6H_5$ group to function as an internal nucleophile. The rate influence of the substituent becomes larger as the medium becomes less nucleophilic in character.

Both *o*-carbophenoxy and *o*-nitro substituents function as internal nucleophiles in promoting the hydrolysis and also the acetolysis of benzhydryl bromide.[1-3] However, these substituents participate much less effectively in benzyl halide hydrolysis.[1,2,4] Presumably in the reactions of the benzyl systems in question the geometry at the transition state provides for substantial dispersal of positive charge at the reaction center through delocalization of ring π electrons rather than through involvement of the neighboring ortho substituents.[1,4]

Recently it has been reported that the acetolysis of *o*-dithiacyclopentylbenzyl chloride is subject to pronounced rate enhancement through participation of the $-CH(SCH_2)_2$ group.[5] Apparently when, as in this case, the ortho substituent contains a strongly nucleophilic atom (S) at a proper distance from the reaction center, the geometry at the transition state is such that the influence of that substituent on reactivity is appreciable.

To explore further the matter of the effectiveness of sulfur containing ortho nucleophiles as participants in the solvolysis of benzyl halides, a comparison has been made of the hydrolysis and acetolysis rates of the *o*- and *p*-carbophenoxy- and *o*- and *p*-thiolcarbophenoxybenzyl bromides. In the acetolysis reactions a dramatic difference in the capacities of *o*-$COOC_6H_5$ and *o*-$COSC_6H_5$ to serve as internal nucleophiles has been observed.

Experimental Section

Analytical Procedures.—Melting points and boiling points are uncorrected. Nuclear magnetic resonance spectra were obtained using a Varian Associates Model A-60A instrument. Microanalyses were performed by Mr. V. Tashinian and Associates, Berkeley, Calif.

Materials.—Benzyl bromide (Eastman Organic Chemicals) was distilled under reduced pressure prior to use.

To prepare the *o*- and *p*-carbophenoxytoluenes, a stoichiometric quantity of thionyl chloride was added slowly to a solution of *o*- or *p*-toluic acid (Eastman Organic Chemicals), respectively, in pyridine solvent. When the reaction mixture had cooled to room temperature, a stoichiometric amount of phenol was added and the mixture was heated on a steam bath for *ca.* 2 hr in a system protected from atmospheric moisture. The reaction mixture was diluted with water and extracted with ether. The products were obtained in 85% yield upon work-up of the ether solutions: *o*-carbophenoxytoluene, bp 117–118° (0.6 mm) [lit.[6] bp 306° (754 mm)]; *p*-carbophenoxytoluene, mp 77–79° (lit.[6] mp 83°).

The *o*- and *p*-carbophenoxybenzyl bromides were prepared through the benzoyl peroxide induced reaction of equimolar quantities of *N*-bromosuccinimide and *o*- or *p*-carbophenoxytoluene, respectively, in carbon tetrachloride solvent at reflux temperature. Recrystallization of both isomers from mixed hexanes gave white crystals in *ca.* 50% yield. *o*-Carbophenoxybenzyl bromide had mp 51–52.5°; nmr (CCl_4) δ 4.92 (s, 2, CH_2), 7.32 (m, 8, arom), and 8.11 ppm (m, 1, arom, ortho to C=O).

Anal. Calcd for $C_{14}H_{11}BrO_2$: C, 57.75; H, 3.82; Br, 27.45. Found: C, 57.76; H, 3.72; Br, 27.58.

p-Carbophenoxybenzyl bromide had mp 93–95°; nmr (CCl_4) δ 4.40 (s, 2, CH_2), 7.30 (m, 7, arom), and 8.10 ppm (m, 2, arom, ortho to C=O).

Anal. Calcd for $C_{14}H_{11}BrO_2$: C, 57.75; H, 3.82; Br, 27.45. Found: C, 57.65; H, 3.90; Br, 27.60.

To prepare *p*-thiolcarbophenoxytoluene, 9.0 g of thionyl chloride was added slowly to a solution of 10 g of *p*-toluic acid (Eastman Organic Chemicals) in 35 ml of dry pyridine in a system protected from atmospheric moisture. When the reaction mixture had cooled to room temperature, 8.2 g of thiophenol was added slowly and the mixture was heated on a steam bath for *ca.* 2 hr. Approximately 100 ml each of ether and water were added to the cooled reaction mixture, and the ether layer was washed successively with water, dilute hydrochloric acid, water, 3 *N* sodium hydroxide, and water. The ether solution was dried (Na_2SO_4) and concentrated. Recrystallization of the residual solid from *ca.* 100 ml of mixed hexanes provided 12 g (71%) of *p*-thiolcarbophenoxytoluene as white crystals: mp 91–93°; nmr (CCl_4) δ 2.40 (s, 3, CH_3), 7.29 (m, 7, arom), and 7.88 ppm (m, 2, arom, ortho to C=O).

Anal. Calcd for $C_{14}H_{12}OS$: C, 73.65; H, 5.31; S, 14.04. Found: C, 73.48; H, 5.25; S, 13.94.

o-Thiolcarbophenoxytoluene was prepared from *o*-toluic acid (Eastman Organic Chemicals), thionyl chloride, and thiophenol in 69% yield by much the same procedure described for the synthesis of the para isomer: mp 45–47°; nmr (CCl_4) δ 2.44 (s, 3, CH_3), 7.33 (m, 8, arom), and 7.89 ppm (m, 1, arom, ortho to C=O).

Anal. Calcd for $C_{14}H_{12}OS$: C, 73.65; H, 5.31; S, 14.04. Found: C, 73.73; H, 5.16; S, 14.01.

The *o*- and *p*-thiolcarbophenoxybenzyl bromides were synthesized through the light-induced reaction of equimolar quantities of *N*-bromosuccinimide and *o*- or *p*-thiolcarbophenoxytoluene, respectively, in carbon tetrachloride solvent. The crude products from the preparation of both isomers were contaminated with a significant quantity of the corresponding dibromide. The pure monobromides were obtained in *ca.* 30% yield by fractional recrystallization from mixed hexanes–carbon tetrachloride mixed solvent. *o*-Thiolcarbophenoxybenzyl bromide had mp 92–94°; nmr (CCl_4) δ 4.72 (s, 2, CH_2), 7.46 (m, 8, arom), and 7.92 ppm (m, 1, arom, ortho to C=O).

Anal. Calcd for $C_{14}H_{11}BrOS$: C, 54.73; H, 3.62; Br, 26.01; S, 10.44. Found: C, 54.53; H, 3.66; Br, 26.28; S, 10.37.

p-Thiolcarbophenoxybenzyl bromide had mp 96–99°; nmr (CCl_4) δ 4.42 (s, 2, CH_2), 7.48 (m, 7, arom), and 7.95 ppm (m, 2, arom, ortho to C=O).

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Anal. Calcd for $C_{14}H_{11}BrOS$: C, 54.73; H, 3.62; Br, 26.01; S, 10.44. Found: C, 54.58; H, 3.62; Br, 26.26; S, 10.32.

Kinetic Studies.—Acetic acid was purified for use as a solvent by the method described previously.[3] Spectroquality dioxane (Matheson Coleman and Bell) was dried by distilling from calcium hydride through a Widmer column. In preparing 80% aqueous dioxane 80 volumes of dioxane was mixed with 20 volumes of doubly distilled water at room temperature.

The kinetics of acetolysis of benzyl bromide, *o*- and *p*-carbophenoxybenzyl bromides, and *p*-thiolcarbophenoxybenzyl bromide were investigated through analysis of rate samples for excess acetate ion by titration with a standard solution of perchloric acid in acetic acid. The method has been described previously.[3] In studying acetolysis of *o*-thiolcarbophenoxybenzyl bromide an alternate method of analysis was employed, since the color of the mixture turns yellow as the reaction progresses. In this case 5-ml samples of the reaction mixtures were analyzed for bromide ion through extraction with water and titration of the aqueous extract by the Volhard procedure. Details of the method are given elsewhere.[1] The acetolysis rate constants for all bromides except for *o*-carbophenoxybenzyl and *o*-thiolcarbophenoxybenzyl bromides were calculated from the slopes of lines obtained by plotting values of log $[RBr]_t$ *vs.* time (eq 1). The

$$2.303 \log ([RBr]_i/[RBr]_t) = kt \qquad (1)$$

rate constants for the *o*-carbophenoxybenzyl and *o*-thiolcarbophenoxybenzyl bromides exhibit significant downward drifts during the course of the reactions. For these compounds the reported rate constants apply to early phases of the reactions. They were obtained by extrapolation of a plot of point-to-point rate constants (calculated using eq 1) *vs.* percentage reaction.

To study the rate of hydrolysis of *o*- and *p*-thiolcarbophenoxybenzyl bromides in 80% aqueous dioxane, a sample of the bromide was weighed into a volumetric flask, and the temperature of the flask was adjusted to the temperature of the rate run. Solvent, which had been equilibrated to this same temperature, was added to the mark. Samples (5 ml) were withdrawn from time to time and quenched in *ca.* 50 ml of chilled acetone. The solutions were analyzed for hydrogen ion by titrating with standard sodium hydroxide solution to the green end point of bromothymol blue indicator. Rate constants were calculated from the slopes of plots of log $[RBr]_t$ *vs.* time (eq 1).

Products of Acetolysis of *o*-Carbophenoxybenzyl and *o*-Thiolcarbophenoxybenzyl Bromides.—Small samples of the bromides in question were solvolyzed in 0.04 *M* sodium acetate in dry acetic acid under conditions comparable to those used in studying the reaction kinetics. After about 10 half-lives for reaction the acetic acid was removed under vacuum, and anhydrous ether was added to the residue. The undissolved salts were filtered off and the ether solution was concentrated by use of a rotary vacuum evaporator. The sole product obtained from *o*-carbophenoxybenzyl bromide was recrystallized from mixed hexanes and was identified as *o*-carbophenoxybenzyl acetate: mp 68.5–70°; nmr (CCl_4) δ 2.05 (s, 3, CH_3), 5.51 (s, 2, CH_2), 7.37 (m, 8, arom), and 8.17 ppm (m, 1, arom, ortho to C=O).

Anal. Calcd for $C_{16}H_{14}O_4$: C, 71.04; H, 5.23. Found: C, 71.09; H, 5.00.

The oily residue which resulted from the work-up of the acetolysis of *o*-thiolcarbophenoxybenzyl bromide proved to be a mixture of at least four products as shown by nmr analysis. The major product, comprising about 50% of the mixture, was isolated by alumina column chromatography and was identified as *o*-thiolcarbophenoxybenzyl acetate. Because of the small quantities available, however, it could not be completely purified: mp 86–89°; nmr (CCl_4) δ 2.05 (s, 3, CH_3), 5.50 (s, 2, CH_2), 7.78 (m, 8, arom), and 8.29 ppm (m, 1, arom, ortho to C=O).

Anal. Calcd for $C_{16}H_{14}O_3S$: C, 67.10; H, 4.94; S, 11.20. Found: C, 68.15; H, 5.16; S, 10.26.

Product of Hydrolysis of *o*-Thiolcarbophenoxybenzyl Bromide.—A small sample of the bromide was hydrolyzed in 80% aqueous dioxane at 65.0°. At the end of reaction time most of the solvent was evaporated under vacuum. The organic material was extracted into ether. Removal of the ether resulted in a solid residue. Recrystallization from mixed hexanes provided white crystals identified as phthalide: mp 72–73.5° (lit.[7] mp 73°); nmr (CCl_4, trace $CDCl_3$) δ 5.30 (s, 2, CH_2) and 7.68 ppm (m, 4, arom).

(7) J. H. Gardner and C. A. Naylor, Jr., *Org. Syn.*, **16**, 71 (1936).

Results

The results of the rate runs on the several substituted benzyl bromides which have been investigated are summarized in Table I. The acetolyses of the *o*-$COOC_6H_5$ and *o*-$COSC_6H_5$ derivatives are subject to marked common ion rate depression. Therefore the rate constants reported for these halides (based only on the initial phases of the runs) are to be regarded only as approximate, and if anything on the low side.

TABLE I
RATE CONSTANTS FOR SOLVOLYSIS OF BENZYL BROMIDES

Registry no.	X	$10^2[RBr]_i$,[a] mol/l.	10^2-[NaOAc], mol/l.	10^6k, sec^{-1}
	$XC_6H_4CH_2Br$ in Acetic Acid at 85.0°			
100-39-0	H	1.37–2.30	2.00	1.23 ± 0.01[b]
	H	3.18	4.00	1.54[b]
34124-08-8	*o*-$COOC_6H_5$	1.17–2.06	2.00	4.76 ± 0.10[c]
	o-$COOC_6H_5$	2.45	4.00	5.80[c]
	o-$COOC_6H_5$	1.43	2.00[d]	1.44[c]
35092-35-4	*p*-$COOC_6H_5$	1.08–2.02	2.00	0.332 ± 0.012[b]
	p-$COOC_6H_5$	2.46	4.00	0.464[b]
	p-$COOC_6H_5$	1.51	2.00[d]	0.287[b]
35092-36-5	*o*-$COSC_6H_5$	1.08–1.54	2.00	173 ± 13[c]
	o-$COSC_6H_5$	1.93	4.00	173[c]
	o-$COSC_6H_5$	1.59	2.00[d]	43[c]
35129-59-0	*p*-$COSC_6H_5$	1.01–2.04	2.00	0.324 ± 0.007[b]
	p-$COSC_6H_5$	2.00	4.00	0.507[b]
	p-$COSC_6H_5$	1.05	2.00[d]	0.300[b]
	$XC_6H_4CH_2Br$ in 80% Aqueous Dioxane at 65.0°			
	o-$COSC_6H_5$	1.41–2.62		120 ± 2[e]
	p-$COSC_6H_5$	1.13–1.90		14.8 ± 0.2

[a] In most instances, two or more runs were made in which $[RBr]_i$ was varied over the indicated range. [b] These values are based on the first 30–40% reaction. Rate constants are somewhat less beyond this point. [c] These values are based on data recorded in early phases of the runs. The reported rate constant at zero per cent reaction was obtained by extrapolation of a plot of point-to-point rate constants (eq 1) *vs.* percentage reaction. [d] $[NaBr]_i$ = 0.006 *M*. [e] Included in the runs for which the average rate constant is reported is one in which the medium contained 2,6-lutidine (0.0214 mol/l., $[RBr]_i$ = 0.0141 mol/l.). The value of the rate constant was not noticeably altered when lutidine was present.

In Table II a summary is made of the *k*(ortho)/*k*(para) rate constant ratios for the substituted benzyl halides investigated in the present work and also for those obtained in earlier studies which are relevant for

TABLE II
RATE CONSTANT RATIOS FOR SOLVOLYSIS OF *o*- AND *p*-$XC_6H_4CH_2Br$

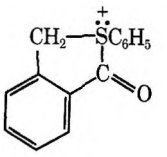
Medium	*k*(ortho)/*k*(para) (Temp, °C) 80% Aqueous dioxane	Acetic acid
X		
CH_3O		0.0017 (60)[a]
CH_3S		0.018 (60)[a]
$OCOC_6H_5$	0.21 (71.4); 0.20 (87.7)[b]	
$COOCH_3$	3.61 (71.4); 4.54 (87.7)[b]	
$COOC_6H_5$		14.3 (85.0)[c]
$COSC_6H_5$	8.11 (65.0)	534 (85.0)[c]

[a] From ref 5. The reported values are based on reactions of benzyl chlorides (rather than bromides) in acetic acid with $[RCl]_i$ = 0.05 *M* and $[NaOAc]_i$ = 0.06 *M*. [b] Values from ref 1. [c] Based on runs (Table I) in which $[NaOAc]_i$ = 0.0200 *M*.

comparative purposes. For reaction in 80% aqueous dioxane the rate constant ratios for the thiolcarbophenoxybenzyl bromides and the carbomethoxybenzyl bromides are comparable in magnitude. Though the ratios in both cases are not dramatically large, they are substantially greater than in cases in which the ortho substituent is nonparticipating, as for example when it is $-OCOC_6H_5$.

In acetic acid both the o-$COOC_6H_5$ and o-$COSC_6H_5$ substituted benzyl bromides solvolyze significantly faster than the corresponding para isomers. It is also noteworthy (Table I) that both ortho isomers, in contrast to the para analogs, are significantly more reactive in the acetolysis reactions than benzyl bromide itself (a fourfold difference in the case of o-$COOC_6H_5$ and *ca.* 140-fold for o-$COSC_6H_5$). On the other hand, the acetolysis rate constant at 60° for p-methoxybenzyl bromide is about 590 times that for the ortho isomer under the same conditions.[5] The relatively low reactivity of the latter is associated with steric hindrance to solvation at the reaction center by the o-methoxy substituent. If this value is used as an estimate of the magnitude of the rate constant ratio for acetolysis of substituted benzyl bromides when the ortho substituent is nonparticipating, it can be concluded that o-thiolcarbophenoxybenzyl bromide is *ca.* 310,000 times as reactive as it would be if the o-$COSC_6H_5$ group did not function as an internal nucleophile. It can be argued similarly that o-carbophenoxybenzyl bromide is *ca.* 8000 times as reactive as it would be if the o-$COOC_6H_5$ substituent were nonparticipating.

The fact that the o-$COSC_6H_5$ group is a substantially more effective participant than o-$COOC_6H_5$ is attributed to the differences in the capacities of oxygen and sulfur atoms to undergo positive polarization. Presumably forms such as I or II make very important contribution to structure at the transition state for acetolysis of o-thiolcarbophenoxybenzyl bromide. Significant common ion rate depression observed in the acetolyses of the o-$COSC_6H_5$ and o-$COOC_6H_5$ substituted benzyl



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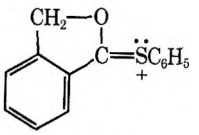

II

bromides (Table I) is considered to be a reflection of the stabilizing influence of the participating ortho substituents on structure at the transition state during the activation process[3] (either as shown in forms I and II, or through related involvement of oxygen atoms of the $COOC_6H_5$ group).

The fact that the ortho/para rate constant ratios for $-COSC_6H_5$ substituted benzyl bromides are much larger in acetic acid than in 80% aqueous dioxane brings to mind similar medium effects observed earlier in studies of the solvolyses of o- and p-NO_2 and o- and p-$COOC_6H_5$ substituted benzhydryl bromides.[3] It is also noteworthy that for reaction in acetic acid the k(ortho)/k(para) rate constant ratio for the $-COSC_6H_5$ substituted benzyl bromides is *ca.* 40 times larger than the ratio for the o- and p-carbophenoxybenzyl bromides. That is, in the solvolyses of the benzyl halides in question, as the medium becomes less suited to function as a solvating agent and as the nucleophilicity of the ortho substituent becomes stronger (through replacement of an O atom by S), the influence of the nucleophilic ortho substituent in stabilizing the developing positive charge at the reaction center through internal solvation is strikingly magnified.

Registry No.—p-Thiolcarbophenoxytoluene, 3128-42-5; o-thiolcarbophenoxytoluene, 35092-37-6; o-carbophenoxybenzyl acetate, 35092-38-7; o-thiolcarbophenoxybenzyl acetate, 35092-39-8.

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Meisenheimer Complexes. Stopped-Flow Study of the Interaction of 3,5-Dinitro-4-methoxypyridine with Methoxide Ion in Methanol and Methanol–Dimethyl Sulfoxide Mixtures[1]

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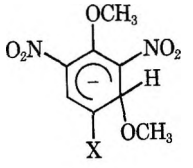
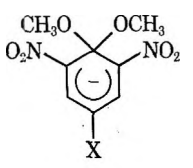
The kinetics of the reaction of methoxide ions with 3,5-dinitro-4-methoxypyridine (**3**) in methanol has been studied by the stopped-flow technique. When the methoxide ion concentration is greater than about 0.01 *M*, the appearance of the stable 1,1 complex **4** is preceded by the faster formation of the thermodynamically less stable 1,3 complex **5**. The rate and equilibrium constants for the formation of complexes **4** (k_2, K_2) and **5** (k_1, K_1), together with the rate constants for their decomposition (k_{-2}, k_{-1}) have been determined at four different temperatures, allowing a determination of the energies and entropies of activation for the reactions. A similar study has been also carried out in various methanol–dimethyl sulfoxide (DMSO) mixtures. The results are compared with previously reported data on the reactions of 2,4,6-trinitroanisole (**6**) and 4-cyano-2,6-dinitroanisole (**9**) with methoxide ions to give analogous 1,1 complexes **7** and **10** as well as 1,3 complexes **8** and **11**. The pyridinic 1,3 complex **5** appears to be the most stable transient 1,3 complex detected to date.

The reaction of methoxide ions with substituted 4-X-2,6-dinitroanisoles in DMSO often results in the fast initial formation of 1,3 complexes **1** followed by the slower appearance of the classical Meisenheimer 1,1 complexes **2** which are thermodynamically more stable.[2-5]



1



2

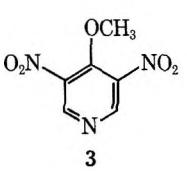
Recent kinetic studies of this interaction in CH_3OH–DMSO mixtures shed some light on its mechanism.[5,6] Whatever the composition of the solvent mixture, methoxide ions attack the unsubstituted 3 carbon faster than the substituted 1 carbon. The formation of 1,3 complexes **1** is thus initially favored and their detection, in a given medium, requires only that they be sufficiently stable and that their lifetime be sufficiently important. Since the equilibrium constants for their formation as well as their lifetime increase strongly with addition of DMSO to the methanolic solutions, 1,3 complexes are consequently more easily observed in mixtures rich in DMSO, but the minimum DMSO amount necessary to their detection is dependent on the electron-withdrawing power of the X substituent. Whereas 1,3 complexes formed from 4-fluoro- and 4-chloro-2,6-dinitroanisoles can be seen only in the mixtures with as much as 70% DMSO by weight, the 1,3 complex formed from 4-cyano-2,6-dinitroanisole can be observed in 25% DMSO.

From these results, it appeared of special interest to study a 4-X-2,6-dinitroanisole with an X substituent, such as a nitro group or an aza group, the electron-withdrawing power of which is stronger than that of a cyano group. Thus we could expect to obtain spectral evidence for a 1,3 complex as well as to follow kinetically the formation of such a transient species in the absence of DMSO cosolvent. Though a calorimetric study, recently reported by Fendler, *et al.*,[7] of the interaction of 2,4,6-trinitroanisole with methoxide ions in methanol has given some indication that a 1,3 complex is formed prior to the stable 1,1 complex, the behavior of this compound was not found very convenient for the stopped-flow method. We have thus investigated in pure methanol and various CH_3OH–DMSO mixtures the reaction of 3,5-dinitro-4-methoxypyridine (**3**) with potassium methoxide. Following a preliminary communication,[1] we wish now to report detailed results and additional data for this kinetic study.

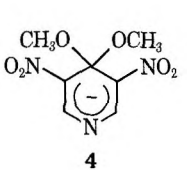
Indeed, at the same time as our preliminary communication, a report by Bernasconi[8] appeared describing the study, by the temperature-jump method, of the transient 1,3 complex formed by the reaction of 2,4,6-trinitroanisole with methoxide ion in methanol. This study provides complementary data to our work and we have used it for the purpose of comparison in our discussion.

Results

Reaction of 3 with CH_3O^- in Methanol.—When the methoxide ion concentration b is kept below 0.01 *M*, the reaction of methoxide ions with 3,5-dinitro-4-methoxypyridine (**3**) in methanol gives directly, according to the



3



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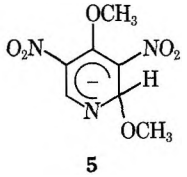


5

scheme below, the stable 1,1 complex **4**, which shows an absorption band at 455 mμ (ϵ_{max} 1.85 × 10^4 cm^{-1} l. mol^{-1}) and whose structure has been confirmed by nmr

(1) Presented, in part, at the 23rd IUPAC Meeting, Boston, Mass., July 25–30, 1971.

(2) (a) K. L. Servis, *J. Amer. Chem. Soc.*, **87**, 5495 (1965); (b) *ibid.*, **89**, 1508 (1967).

(3) M. R. Crampton and V. Gold, *J. Chem. Soc. B*, 893 (1966).

(4) (a) E. J. Fendler, J. H. Fendler, and C. E. Griffin, *Tetrahedron Lett.*, 5631 (1968); (b) J. H. Fendler, E. J. Fendler, and C. E. Griffin, *J. Org. Chem.*, **34**, 689 (1969); (c) E. J. Fendler, J. H. Fendler, C. E. Griffin, and J. W. Larsen, *ibid.*, **35**, 287 (1970).

(5) (a) F. Terrier and F. Millot, *C. R. Acad. Sci., Ser. C*, **268**, 808 (1969); (b) F. Millot and F. Terrier, *Bull. Soc. Chim. Fr.*, 2694 (1969).

(6) (a) F. Terrier and F. Millot, *ibid.*, 1743 (1970); (b) F. Terrier, C. Dearing, and R. Schaal, "Reaction Transition States," Gordon and Breach, London, 1972, in press; (c) F. Millot and F. Terrier, *Bull. Soc. Chim. Fr.*, 3897 (1971).

(7) J. W. Larsen, J. H. Fendler, and E. J. Fendler, *J. Amer. Chem. Soc.*, **91**, 5903 (1969).

(8) (a) C. F. Bernasconi, paper presented at the IUPAC meeting, Boston, Mass., July 25–30, 1971; (b) C. F. Bernasconi, *J. Amer. Chem. Soc.*, **93**, 6975 (1971).

$$3 + CH_3O^- \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} 4$$

spectroscopy.[9] All the rate measurements were carried out under pseudo-first-order conditions with an excess of the methoxide reagent. The observed first-order rate constant λ_2 for the equilibrium attainment is thus given by eq 1, where k_2 is the second-order rate constant for the formation of **4** and k_{-2} is the first-order rate constant for its decomposition. Using eq 1, plots of

$$\lambda_2 = k_{-2} + k_2 b \quad (1)$$

λ_2 against the base concentration at the four temperatures studied gave good straight lines whose slopes are k_2 and intercepts k_{-2}. Since the intercepts were susceptible to large errors, more accurate values for k_{-2} have been determined either directly, by following the decomposition of the solid complex **4** which is easily isolable,[9a] or indirectly by using the value of the equilibrium constant K_2 which could be spectrophotometrically measured. The agreement between the values of k_{-2} obtained by the two methods is reasonable.

As soon as the base concentration reaches 0.01 M, the form of the interaction becomes very different. As can be seen from Figure 1, the oscilloscope pictures reveal that the appearance of the 1,1 complex **4** is preceded by the fast formation of another complex which is completely formed in a solution of potassium methoxide 0.5 M and which shows an absorption band at 435 mμ (ϵ_{max} 2.36 $\times$ 10^4 cm^{-1} l. mol^{-1}). This thermodynamically less stable complex can reasonably be considered as being the 1,3 complex **5** due to an initial attack by CH_3O^- ions of the unsubstituted carbon of **3**. Indeed, Illuminati and Miller have observed such a complex by nmr spectroscopy in DMSO-d_6.[9]

The kinetic scheme of two competitive reactions which corresponds then to this interaction involves in fact two separated steps. The first step is the equilib-

$$3 + CH_3O^- \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} 5 \qquad 3 + CH_3O^- \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} 4$$

rium attainment for complex **5** with an observed first-order rate constant λ_1 expressed by eq 2. Values of k_1

$$\lambda_1 = k_{-1} + k_1 b \quad (2)$$

and k_{-1} were obtained from slopes and intercepts of plots of λ_1 *vs.* b, which are linear. We calculated the equilibrium constant K_1 from $K_1 = k_1/k_{-1}$.

The second step is the slow equilibrium formation of the stable 1,1 complex **4**, from the molecule which is considered as being in instantaneous equilibrium with **5**. As previously shown in different papers concerning the formation of 1,1 and 1,3 complexes derived from other 4-X-2,6-dinitroanisoles,[6,8] the rate equation again gives pseudo-first-order relationships with an observed first-order rate constant λ_2' expressed by eq 3, which can

$$\lambda_2' = k_{-2}\frac{1 + K_1 b + K_2 b}{1 + K_1 b} \quad (3)$$

$$\lambda_2' = k_{-2}\frac{1 + K_2 b}{1 + K_1 b} = \frac{\lambda_2}{1 + K_1 b}\ (K_1 \ll K_2) \quad (3a)$$

(9) (a) P. Bemporad, G. Illuminati, and F. Stegel, *ibid.*, **91**, 6742 (1969); (b) M. E. C. Biffin, J. Miller, A. G. Moritz, and D. B. Paul, *Aust. J. Chem.*, **21**, 1267 (1968).

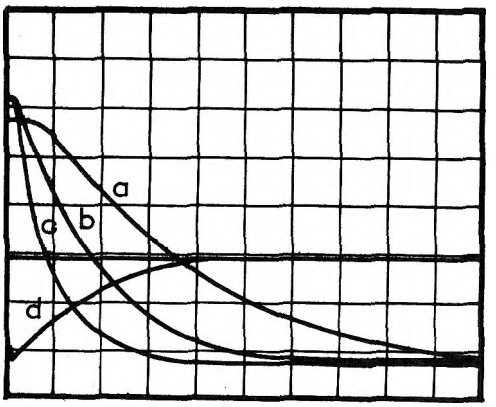


Figure 1.—Representative oscilloscope picture of the reaction of **3** with potassium methoxide in methanol at 20°; [**3**] = 3.4 $\times$ 10^{-5} M, b = 0.16 M. The plots (a, b, c) show the appearance of **5** (5, 10, 20 msec/horizontal division) and the plot (d) illustrates its disappearance (0.5 sec/horizontal division).

be reduced to eq 3a because the equilibrium constant K_2 is much greater than K_1.

From the measured values of λ_2' and knowing K_1, we calculated the values of the first-order rate constant λ_2 which would be observed in the same experimental conditions if **4** were formed directly by reaction of CH_3O^- ions with **3**. These values allow the plots of λ_2 *vs.* b obtained at the very low base concentrations to be extended and confirm the value previously determined for k_2.

Reaction of 3 with CH_3O^- Ions in CH_3OH–DMSO Mixtures.—Except for the mixture containing 13.35% DMSO by weight, where again it was possible to study directly the equilibrium **3** + $CH_3O^- \rightleftarrows$ **4** at the lowest methoxide ion concentrations, the formation of the less stable 1,3 complex **5** was found always to precede the appearance of **4**, whatever the amount of DMSO and the base concentration of the used solution might be.

In the mixtures where the amount of DMSO is equal to or less than 37% by weight, values of k_1 and k_{-1}, and consequently those of K_1, were obtained in all cases from the linear plots of λ_1 *vs.* b. Above 37% DMSO, k_{-1} became too small for a good determination from intercepts of such plots and we could only calculate k_{-1} in the mixtures containing 47.5 and 57.5% DMSO by weight, where the equilibrium constant K_1 could be thermodynamically measured.

Figure 2 illustrates the variations of the observed first-order rate constant λ_2' for the appearance of the stable complex **4**. At the highest base concentrations used in the mixtures with as much as 37% DMSO by weight, the graphs of λ_2' *vs.* b show a characteristic flat line of slope 0 corresponding to the maximum value given by eq 4. Thus, when the equilibrium constant

$$\lambda_2'^{max} = k_{-2}\frac{K_2}{K_1} = \frac{k_2}{K_1} = k_{-1}\frac{k_2}{k_1} \quad (4)$$

K_1 was known, it was possible to obtain the rate constant k_2 directly from this maximum. In mixtures with 13.35 and 25.3% DMSO, k_2 was determined, as above in methanol, through the variations of the first-order rate constant λ_2 calculated from the measured values of λ_2' by using eq 3a. In these mixtures, we were also able to follow directly the decomposition of **4** and thus to obtain k_{-2}.

TABLE I

RATE AND EQUILIBRIUM CONSTANTS FOR THE REACTIONS OF 3,5-DINITRO-4-METHOXYPYRIDINE WITH CH_3O^- IONS IN METHANOL AND VARIOUS METHANOL–DMSO MIXTURES AT 20°

Solvent composition, % DMSO by weight	1,3 complex 5			1,1 complex 4				
	k_1, M^{-1} sec^{-1}	k_{-1}, sec^{-1}	K_1, M^{-1}	k_2, M^{-1} sec^{-1}	k_{-2}, sec^{-1}	K_2, M^{-1}	$\lambda'_2{}^{max}$, sec^{-1}	$t_{1/2}$, sec
					5.2×10^{-3} [c]	3,180[b]		
0	275	25	11[a]	16.5	5.75×10^{-3} [d]	2,870[a]	1.5[f]	0.46
				13.8[e]	5.00×10^{-3} [e]	2,770[e]		
13.35	398	17.3	23[a]	25.7	3.56×10^{-3} [d]	7,230[a]	1.12[f]	0.62
25.3	630	6.95	91[a]	48	2.37×10^{-3} [d]	20,200[a]	0.527[f]	1.32
37	1,175	3.25	361[a]	90			0.25	2.77
47.5	2,000	1.6[c]	1250[b]	180			0.144	4.8
57.5	3,710	0.7[c]	5300[b]	330			6.25×10^{-2}	11.1
67	6,900						2.75×10^{-2}	25.2
76	22,000						1.00×10^{-2}	69.3
84.8							1.82×10^{-3}	380
92.6							4.65×10^{-4}	1490

[a] Calculated from $K_1 = k_1/k_{-1}$ or $K_2 = k_2/k_{-2}$. [b] From equilibrium measurements. [c] Calculated from $k_{-1} = k_1/K_1$ or $k_{-2} = k_2/K_2$. [d] Decomposition of the solid complex 4. [e] Reference 9a. [f] Calculated from $\lambda'_2{}^{max} = k_2/K_1$.

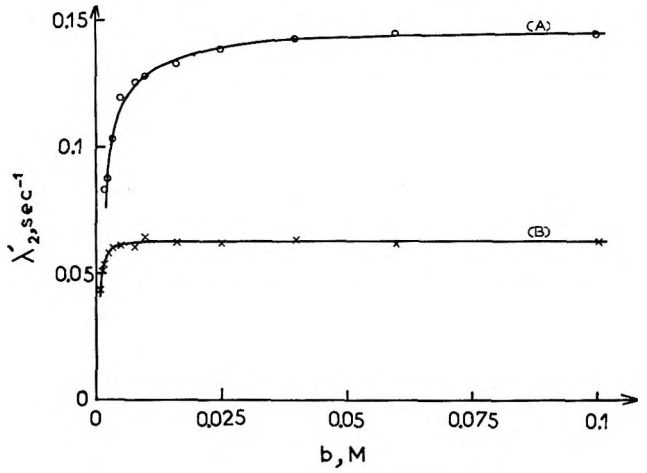


Figure 2.—Plots of λ'_2 against potassium methoxide concentration b for the appearance of 4 in 47.5 (A) and 57.5% DMSO (B).

In Table I are listed the specific rate constants and equilibrium constants associated with the formation and decomposition of the two complexes **4** (k_2, k_{-2}, K_2) and **5** (k_1, k_{-1}, K_1) and obtained at 20° in methanol and all the CH_3OH–DMSO mixtures studied. The values previously reported by Illuminati, *et al.*,[9] for k_2, k_{-2}, and K_2 in methanol are included in the table; as can be seen, the agreement with our results is fairly good.

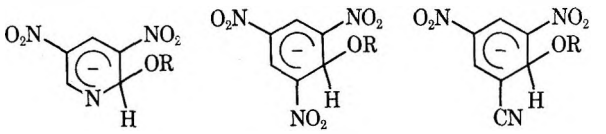
Rate coefficients and equilibrium constants determined at different temperatures in methanol and 63% CH_3OH–37% DMSO (by weight) are summarized in Table II. Table III allows a comparison of kinetic and thermodynamic data for the formation and decomposition of complexes **4** and **5** with analogous data reported on the reactions of 2,4,6-trinitroanisole[4b,7] (**6**) and 4-cyano-2,6-dinitroanisole[4b,6b] (**9**) with methoxide ions.

Discussion

Influence of the Aza Group on Stability of Adducts 4 and 5.—Considering 3,5-dinitro-4-methoxypyridine (**3**) to be an 4-aza-2,6-dinitroanisole, a comparison of the rate and equilibrium constants for the formation as well as the rate constants for the decomposition of 1,1 and 1,3 complexes **4** and **5** to the corresponding parameters found for the benzenic analogs derived from 2,4,6-trinitroanisole (**6**) and 4-cyano-2,6-dinitroanisole (**9**) allows a quantitative analysis of the influence of the aza group on the stability of adducts.

With respect to the 1,1-complex formation, the rate of methoxide ion attack on carbon carrying the methoxy group is very similar for **3** and **6** ($k_2^3/k_2^6 = 1.4$) and somewhat slower for **9** ($k_2^3/k_2^9 = 4$; $k_2^6/k_2^9 = 2.8$). On the other hand, the trinitro adduct **7** is decomposed, respectively 8- and 21-fold more slowly than the pyridinic and cyano adducts **4** and **10**. Thus, in agreement with earlier observations of Illuminati, *et al.*,[9a] the influence of the aza group para to the geminal position on the stability of the 1,1 complex appears to be intermediate between that of the nitro and cyano groups ($K_2^4/K_2^7 = 0.158$; $K_2^4/K_2^{10} = 9.6$). This result is consistent with a more effective delocalization of the negative charge by a nitro group than by an aza group.

Replacing a nitro or a cyano by an aza group in the ortho position of the sp_3 carbon causes, respectively, a 4.3- and 60-fold increase in the equilibrium constant for the formation of adduct. Consequently, the pyridinic 1,3 complex **5** appears to be the most stable 1,3 transient complex which has so far been detected. Since the rate of formation of **5** is 2.5-fold slower than that of trinitro 1,3 adduct **8** and only 2.9-fold faster than that of cyano 1,3 adduct **11**, the greater thermodynamic stability of **5** relative to its benzenic analogs arises essentially from its significantly slower rate of decomposition ($k_{-1}^8/k_{-1}^5 = 10.5$; $k_{-1}^{11}/k_{-1}^5 = 20.4$). This situation is similar to one we have encountered by comparing the stabilities of complexes resulting from the reaction of methoxide or hydroxide ions with 3,5-dinitropyridine (**12a**,**12b**) on the one hand, and with 1,3,5-trinitrobenzene (**13a**,**13b**) or 3,5-dinitrobenzonitrile (**14a**,**14b**) on the other hand.[10]



12a, R = CH_3 **13a**, R = CH_3 **14a**, R = CH_3
b, R = H **b**, R = H **b**, R = H

(10) (a) R. Schaal, F. Terrier, J. C. Halle, and A. P. Chatrousse, *Tetrahedron Lett.*, 1393 (1970); (b) F. Terrier, F. Millot, and M. P. Simonnin, *ibid.*, 2933 (1971); (c) F. Terrier and A. P. Chatrousse, *Bull. Soc. Chim. Fr.*, submitted for publication.

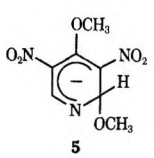
TABLE II

RATE AND EQUILIBRIUM CONSTANTS OF MEISENHEIMER COMPLEXES 4 AND 5 IN METHANOL AND IN 63% CH_3OH–37% DMSO AT DIFFERENT TEMPERATURES

	CH_3OH				63% CH_3OH–37% DMSO		
	2°	10°	20°	31°	7°	20°	32°
k_1, M^{-1} sec^{-1}	86.5	146	275	548	470	1175	2500
k_{-1}, sec^{-1}	8.5	14	25	46	1.5	3.25	6.5
$K_1 = k_1/k_{-1}$, M^{-1}	10.2	10.4	11	11.9	313	361	385
k_2, M^{-1} sec^{-1}		8	16.5	35	35	90	215
$10^3\ k_{-2}$, sec^{-1}		2.3	5.75	13.8			
$K_2 = k_2/k_{-2}$, M^{-1}		3480	2870	2540			

TABLE III

KINETIC AND THERMODYNAMIC PARAMETERS OF MEISENHEIMER COMPLEXES AT 25°



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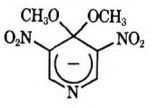

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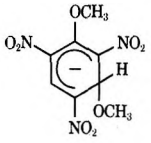

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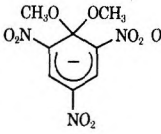

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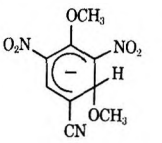

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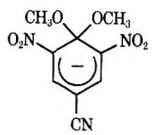

10

	In CH_3OH[a]	In 37% DMSO[a]	In CH_3OH[a]	In 37% DMSO[a]	In CH_3OH[b]	In CH_3OH[c]	In 37% DMSO[d]	In CH_3OH[c]	In 37% DMSO[d]
$\vec{k}$, M^{-1} sec^{-1}	390	1640	23	136	950	17.3	560	6.1	22.4
$\overleftarrow{k}$, sec^{-1}	33.2	4.4	8.6×10^{-3}		350	1.04×10^{-3}	90	2.2×10^{-2}	5.02×10^{-3}
K, M^{-1}	11.7	372	2680		2.71	17,000	6.25	280	4450
$\Delta\vec{H}^{\ddagger}$, kcal mol^{-1}	10.3 ± 0.8	10.55 ± 0.6	11.4 ± 0.4	11.55 ± 0.4	10.4 ± 1	12.9 ± 1	9.7 ± 0.5	13.3 ± 0.8	12.7 ± 0.5
$\Delta\vec{S}^{\ddagger}$, eu	−12.1 ± 2.7	−8.5 ± 2.3	−14 ± 1.4	−10 ± 1.4	−10.8 ± 3.4	−9.4 ± 3.4	−13.3 ± 1.7	−10.4 ± 2.7	−9.8 ± 1.7
$\Delta\overleftarrow{H}^{\ddagger}$, kcal mol^{-1}	9.3 ± 0.8	9.45 ± 0.6	13.85 ± 0.4		8.2 ± 0.5	18.4 ± 1	10.6 ± 0.5	9.3 ± 0.8	10.1 ± 0.5
$\Delta\overleftarrow{S}^{\ddagger}$ eu	−20.4 ± 2.7	−23.8 ± 2.3	−21.5 ± 1.4		−19.3 ± 1.7	−4.8 ± 3.4	−14 ± 1.7	−32 ± 2.7	−35 ± 1.7
ΔH, kcal mol^{-1}	1 ± 1.6	1.1 ± 1.2	−2.45 ± 0.8		2.2 ± 1.5	−5.5 ± 2	−0.9 ± 1	4.3 ± 1.6	2.6 ± 1
ΔS, eu	8.3 ± 5.4	15.3 ± 4.6	7.5 ± 2.8		8.5 ± 5.1	−4.6 ± 6.8 −4.6 ± 4[e]	0.6 ± 3.4	21.6 ± 5.4	25.2 ± 3.4

[a] This work. [b] Reference 8. [c] Reference 4b. [d] Reference 6b. [e] Reference 7.

1,3- and 1,1-Complex Formation.—From an inspection of Table III, it is clear that the reaction of 3,5-dinitro-4-methoxypyridine (**3**) to give the 1,3 complex **5** is strongly different from the reaction to give the 1,1 complex **4**. Whereas the rate of formation of **5** is about a factor of 17 faster than that of **4**, its rate of decomposition is about a factor of 5000 greater than that observed for the latter. Consequently, the thermodynamic stability of **5** is relatively low compared to that of **4**. Changes in both the forward and reverse reactions for these complexes appear to be mainly dependent on the changes in the enthalpies of activation. The much higher value of $\Delta\overleftarrow{H}^{\ddagger}$ for **4** relatively to that for **5** is particularly significant. These results agree well with the general features reported for similar nucleophilic attacks of methoxide ions at substituted or unsubstituted 1 and 3 positions of various 4-X-2,6-dinitroanisoles.[2-6,11] Nevertheless, as can be seen from Table III, entropy changes were found to play an important role in the reactions of 2,4,6-trinitroanisole and 4-cyano-2,6-dinitroanisole.

The mechanism of the interaction has been extensively discussed in the case of 2,4,6-trinitroanisole. On the one hand, Crampton and Gold[3,11c] have attributed the slower attack of methoxide ions on the 1 carbon carrying the methoxy group, as compared to that on the unsubstituted 3 carbon, to a larger steric strain in the transition state leading to the 1,1 adduct than in the transition state leading to the 1,3 adduct. On the other hand, Bernasconi has interpreted this kinetic effect through resonance stabilization involving the methoxy group, which lowers the energy of the ground state of the 1,3 complex and of the transition state leading to its formation but not of the 1,1 complex.[8,12] The higher stability of the 1,1 complex relative to the 1,3 complex was attributed to the release of steric strain from the molecule and to the stabilizing influence of multiple alkoxy substitution at the sp^3 1 carbon.[11]

Taking into consideration the fact that all the 4-X-2,6-dinitroanisoles present the same steric strain around the carbon bearing the methoxy group, we wish to point out the major role played by the nature of the X substituent in the interaction. Since the activating as well as delocalizing influence of a nitro group is greater in the para than in the ortho position, the replacement of a nitro group at the 4 position of 2,4,6-trinitroanisole by another substituent could be expected to affect the rates of formation as well as rates of decomposition of 1,1 complexes to a greater extent than those of 1,3 complexes. Indeed, in Table IV, we observe that the ratio k_1/k_2 of the rates of formation of the two sorts of complexes increases from 4-aza- to 4-fluoro-2,6-dinitroanisole, *i.e.*, as the electron-withdrawing effect of the X substituent on the 1 carbon decreases; the value of this ratio for the trinitro derivative appears, however, abnormally high with respect to the series. On the other hand, the ratio k_{-1}/k_{-2} is found to decrease going from 2,4,6-trinitroanisole to 4-fluoro-2,6-

(11) For recent reviews see (a) R. Foster and C. A. Fyfe, *Rev. Pure Appl. Chem.*, **16**, 61 (1966); (b) E. Buncel, A. R. Norris, and K. E. Russell, *Quart. Rev., Chem. Soc.*, **22**, 123 (1968); (c) M. R. Crampton, *Advan. Phys. Org. Chem.*, **7**, 211 (1969); (d) M. J. Strauss, *Chem. Rev.*, **70**, 667 (1970).

(12) C. F. Bernasconi, *J. Amer. Chem. Soc.*, **92**, 4682 (1970).

(13) (a) C. M. Grammacioli, R. Destro, and M. Simonetta, *Chem. Commun.*, 331 (1967); (b) R. Destro, C. M. Grammacioli, and M. Simonetta, *Acta Crystallogr.*, **24**, 1369 (1968).

(14) H. Ueda, N. Sakabe, J. Tanaka, and A. Furusaki, *Bull. Chem. Soc. Jap.*, **41**, 2866 (1968).

(15) F. Terrier, J. C. Halle, and M. P. Simonnin, *Org. Magn. Resonance*, **3**, 361 (1971).

TABLE IV

INFLUENCE OF THE 4-X SUBSTITUENT ON THE EQUILIBRIUM AND RATE CONSTANTS FOR THE FORMATION AND DECOMPOSITION OF 1,3 AND 1,1 COMPLEXES DERIVED FROM 4-X-2,6-DINITROANISOLES

	X					
	NO_2[a]	Aza[b]	CN[c]	CF_3[c]	Cl[c]	F[c]
k_1/k_2	55	16.6	26	36	130	360
k_{-1}/k_{-2}	3.5×10^5	4.35×10^3	1.5×10^4	200	430	225
K_1/K_2	1.6×10^{-4}	3.80×10^{-3}	1.75×10^{-3}	0.18	0.3	1.6

[a] Reference 8. [b] This work at 20° in methanol. [c] Reference 6.

dinitroanisole. The greater thermodynamic stability of the fluoro 1,3 complex compared to that of the 1,1 complex emphasizes clearly the important influence of both these variations on the interaction. As to the abnormal value of the ratio k_1/k_2 for 2,4,6-trinitroanisole, an explanation might be that resonance stabilization involving the methoxy group, as described by Bernasconi,[8,12] would be much more important in this compound and its 1,3 complex than in the other 4-X-2,6-dinitroanisoles because of the higher capacity to resonance of a *p*-nitro group relative to the other substituents.

Effect of Solvent Composition on the Interaction.—There is a strong increase in the equilibrium constants K_1 and K_2 for the formation of complexes **4** and **5** with addition of DMSO to the methanolic solutions due to an increase in the rate constants of formation k_1 and k_2 and a decrease in the rate constants of decomposition. Furthermore, the variations of k_1 and k_{-1} are, in a first approximation, respectively analogous to those observed for k_2 and k_{-2}. Consequently, the relative thermodynamic stability of **4** and **5** probably does not change very much with increasing DMSO amount. Since these findings are similar to those found for the formation of various benzenic Meisenheimer complexes and have been already discussed in earlier papers,[4c,6,16,17] it is more interesting to appreciate their influence on the lifetime of the transient 1,3 complex **5**. Taking into account that the ratios K_1/K_2 and k_1/k_2 are approximately independent of the DMSO amount and that the maximum value $\lambda'_2{}^{max}$ of the apparent rate constant for the conversion from **5** to the stable 1,1 complex **4** can be used as reference for the lifetime of **5**, eq 4 shows that the influence of the DMSO amount on its lifetime is analogous to that observed on the rate constants k_{-1} and k_{-2} for the decomposition of complexes. Whereas the half-life of **5** is about 0.46 sec in pure methanol, it is about 1500 sec in a mixture containing 92.6% DMSO by weight, *i.e.*, 3000-fold longer than in the absence of DMSO cosolvent. This result, which can be seen from Table I where the values of $\lambda'_2{}^{max}$ are listed with the corresponding half-lives, is very important because it allows an understanding of the easier nmr observation of such transient 1,3 complexes in DMSO than in CH_3OH–DMSO mixtures.[2,3,4,11]

(16) J. W. Larsen, K. Amin, and J. H. Fendler, *J. Amer. Chem. Soc.*, **93**, 2910 (1971).

(17) M. R. Crampton, *J. Chem. Soc. B*, 1208 (1968).

Experimental Section

Materials.—The solvents and reagents were prepared, purified, and standardized as previously described.[5,6,18] Solutions of potassium methoxide in methanolic DMSO were freshly prepared from the purified solvents by the appropriate dilutions.

3,5-Dinitro-4-methoxypyridine (**3**) and potassium 4-aza-1,1-dimethoxy-2,6-dinitrocyclohexadienate (**4**) were prepared by the methods described by Illuminati and Miller.[9]

Rate Measurements.—Stopped-flow determinations were performed on a Durrum stopped-flow spectrophotometer, the cell compartment of which was maintained to ±1°. The reported rate constants represent average values obtained from two or three independent determinations. The slow rates for the decomposition of the 1,1 complex **4** were carried out, using 1-cm cells, on a Beckman DU-2 spectrophotometer with a cell compartment thermostated within ±0.1°.

Registry No.—**3**, 26738-20-5; **4**, 28927-60-8; **5**, 28927-61-9; methoxide ion, 3315-60-4; methanol, 67-56-1; dimethyl sulfoxide, 67-68-5.

Acknowledgment.—We wish to thank Professor C. F. Bernasconi (University of California, Santa Cruz) for reading the manuscript and for valuable suggestions.

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Diels-Alder Reaction between Dimethylfulvene and Vinylene Carbonate. Configurational Assignments of and Magnetic Anisotropic Studies in Adducts and Related Compounds[1]

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Nine new 7-isopropylidenebicyclo[2.2.1]hept-5-ene 2,3-disubstituted derivatives were synthesized. Successful approaches include the reaction of dimethylfulvene with vinylene carbonate to afford exo and endo diastereoisomers of 7-isopropylidenebicyclo[2.2.1]hept-5-ene-2,3-diol carbonate, **1a** and **1b**, in the ratio of 3:2, respectively. Hydrolysis of **1a** and **1b** gave the corresponding diols, **2a** and **2b**. Treatment of the latter two with thiocarbonyldiimidazole resulted in the formation of the thionocarbonate, **3a** and **3b**. Catalytic hydrogenation of **1a**, **2a**, **2b**, and **3a** reduced the $\Delta^{5,6}$ double bond. As expected, the $\Delta^{5,6}$ double bond showed a shielding effect on the isopropylidene methyl protons, a deshielding on the H-2,3 exo pair, and a shielding influence on the corresponding endo pair. Desulfurization–decarboxylation of **3** with trimethyl phosphite or Raney nickel to produce 7-isopropylidenebicyclo[2.2.1]hepta-2,5-diene (**4**) was unsuccessful. Anisotropic effects of the double bonds on cyclopropyl protons in 7,7-dimethylenebicyclo[2.2.1]hept-5-ene and -hepta-2,5-diene are discussed.

Various aspects of the nuclear magnetic resonance spectra of bicyclo[2.2.1]heptane ring systems have been studied in recent years. Initial investigations[3] furnished relations between spin–spin coupling constants of ring protons and the stereochemistry. Fraser[4] established a method of configurational assignment in 5- and 6-substituted norbornenes.

Effects of magnetic anisotropy[5] of the double bond on the bridge methylene protons in norbornene and nonbornadiene, however, have been inconsistent and anomalous. Tori and coworkers[6] in 1964 incorrectly ascribed the multiplets centered at τ 8.92 and 8.67 to the H-7 syn and H-7 anti, respectively. This assignment was based on the anticipated larger diamagnetic shielding of the double bond for H-7 syn compared to H-7 anti. This assignment was later reversed,[7] since long-range coupling was observed between the multiplet at τ 8.67 and H-5,6 endo pair; stereospecific coupling between the latter and H-7 syn in accord with the "W-letter" rule[3e,8] was responsible for this reassignment. More recently, other workers[9] have clearly demonstrated that H-7 syn in nonbornene absorbs[10] at lower field than H-7 anti, thus confirming Tori's later results.[7] Furthermore, in norbornadiene,[6] the bridge methylene protons experience an unusual deshielding and appear at τ 8.02, whereas in norbornane these protons absorb at τ 8.80. If the additivity principle of shielding effects could be applied, the signal of bridge methylene protons should appear at τ 8.80. This unexpected shielding and deshielding influence of the bridge protons prompted us to undertake the present study.

We originally wished to synthesize 7-isopropylidene derivatives of norbornane, norbornene, and norbornadiene to study the anisotropic effects of the double bonds on the isopropylidene methyl protons and see if unusual deshielding similar to that observed in norbornadiene is encountered. This aim, however, could not be accomplished, since we were not successful in synthesizing these compounds.

This paper reports (i) syntheses and configurational assignments of 7-isopropylidenebicyclo[2.2.1]hept-5-ene-2,3-diol carbonates and their derivatives, and (ii) anisotropic effects of the $\Delta^{5,6}$ double bond on the isopropylidene methyl protons and H-2,3 exo–endo pairs. In addition, effects of the double bonds on the chemical shifts of the cyclopropyl protons in 7,7-dimethylenebicyclo[2.2.1]hept-5-ene[15] and -hepta-2,5-diene have been examined and the results compared with those of Tori[6,7] on norbornanes.

Results and Discussion

The reaction of dimethylfulvene with vinylene carbonate afforded a mixture of exo and endo isomers of

(1) (a) This work constituted, in part, the Ph.D. dissertation of M. Z. Haq, University of Ottawa, Ottawa, Canada, 1967, and was done under the supervision of Professor Robert R. Fraser. The author wishes to thank Professor Fraser for his stimulating guidance during the course of this work, for kindly suggesting that he submit the paper as sole author, and for providing invaluable comments and suggestions on the manuscript. Financial help of the National Research Council of Canada in support of this work is also gratefully acknowledged. (b) M. Z. Haq, Abstracts, 163rd National Meeting of the American Chemical Society, Boston, Mass., April 1972, ORGN-100.

(2) Meloy Laboratories, Inc., 6715 Electronic Drive, Springfield, Va. 22151.

(3) (a) W. D. Kumler, N. J. Schoolery, and F. B. Bruchter, Jr., *J. Amer. Chem. Soc.*, **80**, 2533 (1958); (b) E. J. Corey, M. Ohno, S. W. Chow, and R. A. Scherrer, *ibid.*, **81**, 6305 (1959); (c) F. A. L. Anet, *Can. J. Chem.*, **39**, 789 (1961); (d) M. M. Anderson and P. M. Henry, *Chem. Ind. (London)* 2053 (1961); (e) J. Meinwald and A. Lewis, *J. Amer. Chem. Soc.*, **83**, 2769 (1961); (f) K. B. Wiberg, B. R. Lowny, and B. Nist, *ibid.*, **84**, 1954 (1962); (g) K. L. Williamson, *ibid.*, **85**, 516 (1963); (h) J. I. Musher, *Mol. Phys.*, **6**, 93 (1963); (i) J. Meinwald, Y. C. Meinwald, and T. N. Baker, III, *J. Amer. Chem. Soc.*, **85**, 2513 (1963); (j) J. C. Davis, Jr., and T. V. Van Auken, *ibid.*, **87**, 3900 (1965); (k) F. A. L. Anet, H. H. Lee, and J. L. Sudmeier, *ibid.*, **89**, 4431 (1967).

(4) R. R. Fraser, *Can. J. Chem.*, **40**, 78 (1962).

(5) Magnetic anisotropic effects can be calculated employing Nakagawa and coworkers[6] equation provided that the molecular geometry is known.

(6) K. Tori, Y. Hata, R. Muneyuki, Y. Takano, T. Tsuji, and H. Tanida, *Can. J. Chem.*, **42**, 926 (1964).

(7) K. Tori, A. K. Aono, Y. Hata, R. Muneyuki, T. Tsuji, and H. Tanida, *Tetrahedron Lett.*, **No. 1**, 9 (1966).

(8) For a review, see S. Sternhell, *Rev. Pure Appl. Chem.*, **14**, 15 (1964).

(9) (a) B. Franzus, W. C. Baird, Jr., N. F. Chamberlain, T. Hines, and E. I. Snyder, *J. Amer. Chem. Soc.*, **90**, 3721 (1968); (b) A. P. Marchand and J. E. Rose, *ibid.*, **90**, 3724 (1968).

(10) The reverse should be expected according to the suggestions of Jackman,[11] Pople,[12] and ApSimon and coworkers.[13] For a detailed account of magnetic anisotropy of the double bond and theoretical consideration, see ref 11–14.

(11) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1969, p 83.

(12) (a) J. A. Pople, *J. Chem. Phys.*, **37**, 53 (1962); (b) *ibid.*, **37**, 60 (1962).

(13) (a) J. W. ApSimon, W. G. Craig, P. V. Demarco, D. W. Mathieson, L. Saunders, and W. B. Whalley, *Chem. Commun.*, **No. 12**, 359 (1966); (b) J. W. ApSimon, W. G. Craig, P. V. Demarco, D. W. Mathieson, and W. B. Whalley, *Tetrahedron*, **23**, 2375 (1967).

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(16) K. Alder, H. J. Ache, and F. H. Flock, *Chem. Ber.*, **93**, 1888 (1960).

TABLE I

NMR SPECTRAL DATA IN τ UNITS[a] OF 7-ISOPROPYLIDENEBICYCLO[2.2.1]HEPTANE DERIVATIVES

Compd	H-5, H-6	OH	H-2, H-3	H-1, H-4	H methyls
1a	3.81 (t, sp 2 Hz)		5.60 (s)	6.50 (t, sp 2 Hz)	8.33 (s)
1b	3.70 (t, sp 2 Hz)		5.22 (t, sp 2 Hz)	6.32 (qi, sp 2 Hz)	8.42 (s)
2a	3.82 (t, sp 2 Hz)	7.12 (br s)	6.34 (s)	6.84 (t, sp 2 Hz)	8.34 (s)
2b	3.62 (t, sp 2 Hz)	7.46 (br s)	5.92 (t, sp 2 Hz)	6.50 (qi, sp 2 Hz)	8.46 (s)
3a	3.78 (t, sp 2 Hz)		5.18 (s)	6.37 (t, sp 2 Hz)	8.35 (s)
3b	3.64 (t, sp 2 Hz)		4.82 (t, sp 2 Hz)	6.21 (qi, sp 2 Hz)	8.41 (s)

[a] Peak multiplets are represented by br, broad band; m, multiplet; qi, quintet; s, singlet; sp, spacing; t, triplet.

the adduct **1** in the ratio of 3:2, respectively (Scheme I). This conclusion was based on the nmr spectrum of the product, which showed two sets of bands (four peaks each) in the intensity ratio of 3:2. Fractional crystallization of the mixed adduct **1** gave pure carbonates **1a** and **1b**. Hydrolysis of **1a** and **1b** gave rise to **2a** and **2b**, which on treatment with thiocarbonyldiimidazole resulted in the formation of **3a** and **3b**, respectively. Compounds **5a**, **6a**, **6b**, and **7a** (see Table II) were prepared by the catalytic reduction of **1a**, **2a**, **2b**, and **3a**, respectively.

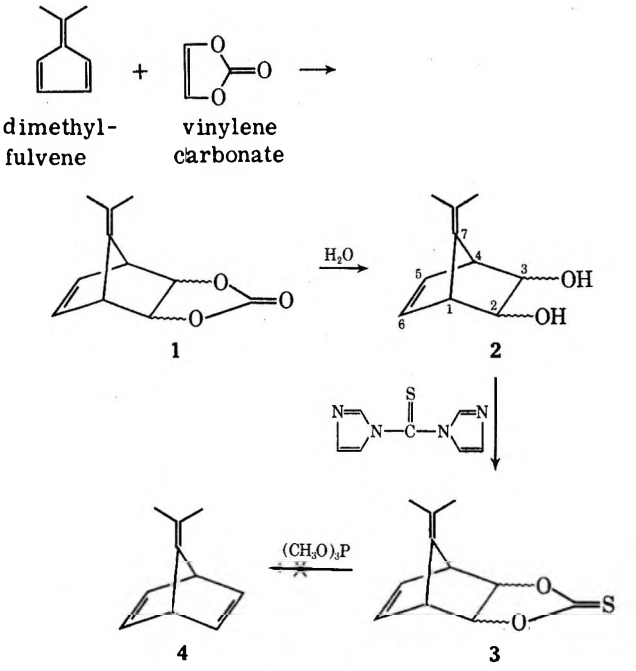
Attempts to produce **4** through the reaction of **3** with trimethyl phosphite[17] or Raney nickel were unsuccessful. Attempted oxidative decarboxylation[18] of 7-isopropylidenebicyclo[2.2.1]hept-5-ene-*exo*-2,3-dicarboxylic acid[19] using lead tetraacetate also failed.

Configurational Assignments of 7-Isopropylidenebicyclo[2.2.1]hept-5-ene-2,3-diol Carbonate (1) and Its Derivatives.—Elemental analysis and mass, infrared, and nmr spectral data confirmed the gross structure of **1** (see Experimental Section for details). In **1a** a singlet at τ 5.60 (2 protons) was ascribed to the H-2,3 endo pair, since no coupling with the bridgehead protons is observed.[4] In **1b**,[20] there appeared a triplet at τ 5.22 (2 protons) reasonably ascribed[3a-e,4,6,9] to the H-2,3 exo pair now spin coupled to the bridgehead protons; the latter now appeared as a quintet. The configurations of **2a**, **2b**, **3a**, and **3b** follow from their precursors and were confirmed by the multiplicities of the H-2,3 pair (see Experimental Section and Table I).

Reduction Products of 7-Isopropylidenebicyclo[2.2.1]-hept-5-ene-2,3-diol Carbonate (1) and Its Derivatives.—The structures of the hydrogenation products **5a**, **6a**, **6b**, and **7a** follow from their respective unsaturated counterparts and were confirmed by their elemental analyses and infrared and nmr spectral data (see Experimental Section). In a representative example of the nmr spectrum of **5a**, a singlet at τ 5.57 was assigned to the H-2,3 endo pair. The bridgehead protons appeared as a triplet at τ 7.20 due to the coupling with the H-5,6 exo pair. The multiplets centered at τ 8.57 and 8.79 were ascribed to the H-5,6 exo and H-5,6 endo pairs, respectively, in accordance with the known chemical shifts of these protons in similar systems.[7]

Magnetic Anisotropic Effects of the Double Bond in Derivatives of 1.—Anisotropic effects of the $\Delta^{5,6}$ double bond on the isopropylidene methyl protons and on the H-2,3 exo–endo pairs in the reduction products of **1** and its derivatives merit discussion. Changes in the chemical shifts of various protons upon hydrogenation are obtained from Tables I and II and are summarized in Table III. It can be seen that isopropylidene methyls which lie above the plane of the double bond absorb at lower field in all the dihydro compounds (**5a**, **6a**, **6b**, and **7a**) than in their unsaturated counterparts. Thus the $\Delta^{5,6}$ double bond exerts a diamag-

SCHEME I[a]



[a] **1a** = exo carbonate; **1b** = endo carbonate; **2a** = exo hydroxyls; **2b** = endo hydroxyls; **3a** = exo thionocarbonate; **3b** = endo thionocarbonate; **5a** = **1a**, **6a** = **2a**, **6b** = **2b**, and **7a** = **3a**, respectively, with double bond at C-5 reduced in each case.

(17) Olefinic bonds can be obtained smoothly from 1,2-diols. See E. J. Corey and R. A. E. Winter, *J. Amer. Chem. Soc.*, **85**, 2677 (1963).

(18) Numerous examples of oxidative decarboxylation of dicarboxylic acids to produce double bonds including examples in bicyclic systems are known, *e.g.*, (a) C. A. Grob and A. Weiss, *Helv. Chim. Acta*, **43**, 1390 (1960); (b) E. E. van Tamelen and S. P. Pappas, *J. Amer. Chem. Soc.*, **85**, 3297 (1963); (c) E. J. Corey and J. Casanova, Jr., *Ibid.*, **85**, 165 (1963); (d) R. Criegee, C. O. Edens, Jr., and B. Graham in "Newer Methods of Preparative Organic Chemistry," Interscience, New York, N. Y., 1948, p 1.

(19) (a) D. Craig, J. J. Shipman, J. Kiehl, F. Widmer, R. Fowler, and A. Hawthorne, *J. Amer. Chem. Soc.*, **76**, 4573 (1954); (b) K. Alder and R. Ruhrmann, *Justus Liebigs Ann. Chem.*, **566**, 1 (1950).

(20) An elemental analysis of **1b** itself was not obtained since it was available in very small quantity, but the diol **2b**, which was derived from **1b** on hydrolysis, analyzed correctly. This, therefore, established the structure of **1b** as well.

TABLE II

NMR SPECTRAL DATA IN τ UNITS[a] OF REDUCTION PRODUCTS OF 7-ISOPROPYLIDENEBICYCLO[2.2.1]HEPTANE DERIVATIVES

Compd	OH	H-2, H-3	H-1, H-4	H-5, H-6 (exo)	H-5, H-6 (endo)	H methyls
5a[b]		5.57 (s)	7.20 (t, sp 2 Hz)	8.57 (m)	8.79 (m)	8.27 (s)
6a	7.47 (br)	6.31 (s)	7.43 (distorted t)	8.63 (m)	8.82 (m)	8.29 (m)
6b	7.28 (br)	6.15 (t, sp 2 Hz)	7.14 (br)	8.68 (m)	9.12 (m)	8.36 (s)
7a		5.22 (s)	7.05 (t, sp 2 Hz)	8.51 (m)	8.77 (m)	8.29 (s)

[a] Peak multiplets are represented by br, broad band; m, multiplet; qi, quintet; s, singlet; sp, spacing; t, triplet. [b] In CCl_4.

TABLE III

CHANGES IN CHEMICAL SHIFT ($\Delta\tau$)[a] ON HYDROGENATION

Compd	H-2, H-3 (exo)	H-2, H-3 (endo)	H methyls
1a → 5a		−0.03	−0.06
2a → 6a		−0.03	−0.05
3a → 7a		+0.04	−0.06
2b → 6b	+0.23		−0.10

[a] $\Delta\tau = \tau_2 - \tau_1$, where τ_1 = the chemical shift in the unsaturated compound, and τ_2 = the chemical shift in the dihydro compound.

netic (shielding) effect on the isopropylidene protons. This result is in accord with the familiar shielding phenomenon[11] of the double bond above its plane.

The H-2,3 exo pair lies near the plane of the double bond and should, therefore, be expected to be shifted downfield, whereas the corresponding endo pair lying below the plane of the double bond should be expected[21] to be shifted upfield by the double bond. Inspection of Table III reveals that the $\Delta^{5,6}$ double bond exerts a paramagnetic (deshielding) effect on the H-2,3 exo pair and in two cases out of three a diamagnetic effect on the H-2,3 endo pair. These results serve to substantiate Fraser's earlier findings.[4] The fact that **3a** on hydrogenation shows a positive rather than negative $\Delta\tau$ may be a result of the anisotropic effect of the thionocarbonate group. A previous exception had also been noted by Wong and Lee.[23]

Anisotropic Effects of Double Bonds on Cyclopropyl Protons in 11 and 12.—Anisotropic effects of the double bonds on the chemical shifts of cyclopropyl protons in 7,7-dimethylenebicyclo[2.2.1]hept-5-ene[15] (**11**) and -hepta-2,5-diene (**12**) have been examined. Singlets for these protons in **10** and **12** appeared at τ 9.58 and

10 **11** **12**

9.57, respectively (see Experimental Section). Multiplets centered at τ 9.62 and 9.71 in **11** are assigned to the two anti and syn cyclopropyl protons, respectively; this assignment is suggested by the geometry of **11**, in which the syn cyclopropyl protons lie above the plane of the double bond and thus experience an appreciable diamagnetic shift. The anti cyclopropyl protons are almost insensitive[24a] to the anisotropy of the double bond. This observation is contrary to the reported paramagnetic shift for the H-7 syn and diamagnetic shift for the H-7 anti in norbornene.[7] Furthermore, the present study reveals no anomalous deshielding of the cyclopropyl protons in going from **10** to **12**, whereas an unusual deshielding of the bridge methylene protons was reported in proceeding from norbornane (τ 8.80) to norbornadiene (τ 8.02). Our results are consistent with the shielding phenomenon of the double bond, but differ from those of Tori because of the difference in orientation of the respective protons in the two systems. This study, qualitatively, demonstrates that geometric factors in norbornanes are important in affecting the chemical shifts of protons at the 7 position and is consistent with previous work.[9a,24b]

In summary, we have (i) synthesized and established configurations of several 7-isopropylidenebicyclo[2.2.1]-hept-5-ene 2,3-disubstituted derivatives, (ii) observed a diamagnetic effect of the $\Delta^{5,6}$ double bond on the seven isopropylidene methyls, and on the H-2,3 endo and a paramagnetic effect on the H-2,3 exo, and (iii) found a diamagnetic effect of the $\Delta^{5,6}$ double bond on the seven cyclopropyl syn protons in 7,7-dimethylenebicyclo[2.2.1]hept-5-ene. The results are consistent with the predicted anisotropic effects of the double bond.

Experimental Section[25]

7-Isopropylidenebicyclo[2.2.1]hept-5-ene-2,3-diol Carbonate (Exo and Endo Isomers 1a and 1b).—Dimethylfulvene[26] (10.6 g,

(21) ApSimon and coworkers[22] find no significant influence of C–H anisotropy on shielding effects of the carbonyl group on substituting the latter for CH_2 group in a series of steroids [see also J. Homer and D. Callaghan, *J. Chem. Soc. A*, 439 (1968)]. Thus in our [2.2.1] system where the geometry is similar in olefinic and dihydro derivative, the C–H bond effect should not be an influence.

(22) J. W. ApSimon and H. Beierbeck, *Can. J. Chem.*, **49**, 1328 (1971).

(23) E. W. Wong and C. C. Lee, *ibid.*, **42**, 1245 (1964).

(24) (a) The magnitude of shielding on the anti cyclopropyls is small (0.04 ppm) and could fall within the error (±0.02 ppm) involved in the determination of peak positions in this case. (b) N. Inamoto, S. Masuda, K. Tori, K. Aono, and H. Tanida, *Can. J. Chem.*, **45**, 1185 (1967).

(25) Melting points were determined on a Leitz hot-stage apparatus and are uncorrected. Ir spectra were obtained on a Perkin-Elmer Infracord double beam instrument. Unless otherwise stated, nmr spectra were recorded in $CDCl_3$ on a Varian V4302 high-resolution spectrometer operating at 60 MHz. Tetramethylsilane was used as an internal standard and the spectra were calibrated by the side-band technique. Uv spectra were taken on a Perkin-Elmer ultraviolet-visible spectrophotometer. Vpc curves were obtained on a Perkin-Elmer gas chromatograph. Elementary analyses were performed by Midwest Microlab, Inc., Indianapolis, Ind.

(26) (a) J. Thiele and H. Balhorn, *Justus Liebigs Ann. Chem.*, **348**, 5 (1906); (b) J. Thiele, *Chem. Ber.*, **33**, 666 (1900).

0.1 mol) was added dropwise[27] to a refluxing solution of vinylene carbonate[28] (8.6 g, 0.1 mol) in *p*-xylene (40 ml), under nitrogen, and the heating was continued for 18 hr. The solvent was then removed under vacuum; the residual syrup was distilled at 110–130° (0.05 mm) to give a pale yellow crystalline material (6.66 g, 35%). The nmr[29] spectrum of this material (CCl_4 + trace amount of $CDCl_3$) had two sets of absorptions in the intensity ratio of 2:3. The weaker set of bands appeared at 3.70 (t, H-5,6, sp 2 Hz), 5.22 (t, H-2,3, sp 2 Hz), 6.32 (qi, H-1,4, sp 2 Hz), and 8.42 (s, methyls). The more intense absorptions were at 3.81 (t, H-5,6, sp 2 Hz), 5.60 (s, H-2,3), 6.50 (t, H-1,4, sp 2 Hz), and 8.33 (s, methyls).

The mixture on recrystallization from carbon tetrachloride–petroleum ether (bp 30–60°) gave white crystals of pure **1a**: mp 108–109°; ir[30] ($CHCl_3$) 3050 (w), 1850, 1810 cm^{-1} (vs); nmr, see Table I; uv (CH_3OH) λ_{max} 207 nm (ϵ 2500); mol wt, 192 (mass spectrum). *Anal.* Calcd for $C_{11}H_{12}O_3$: C, 68.73; H, 6.29. Found: C, 68.99; H, 6.18. Compound **1b** was obtained by sublimation of the mixture at 35–40° (0.05 mm), followed by recrystallization from ether: mp 74–76°; ir[30] (CCl_4) 3050 (w) 1850, 1810 cm^{-1} (vs); nmr, see Table I; uv (CH_3OH) λ_{max} 207.5 nm (ϵ 3100); mol wt, 192 (mass spectrum).

***exo*-2,3-Dihydroxy-7-isopropylidenebicyclo[2.2.1]hept-5-ene (2a).**—**1a** (358 mg, 1.865 mmol) was stirred with a solution of potassium hydroxide (10%) at room temperature for 2 hr. The solution was made acidic (HCl, 10%) and extracted with ether. The combined ether extracts were washed with water, dried (Na_2SO_4), and concentrated, giving a crystalline residue (300 mg, 84%) of **2a** which was recrystallized from CCl_4: mp 124–126°; ir[30] ($CHCl_3$) 3600–3300 (br), 3050 cm^{-1} (w); nmr assignments in Table I; uv (CH_3OH) λ_{max} 207 nm (ϵ 5000). *Anal.* Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.14; H, 8.32.

***endo*-2,3-Dihydroxy-7-isopropylidenebicyclo[2.2.1]hept-5-ene (2b).**—The endo diol **2b** was obtained by the hydrolysis of the endo carbonate **1b** in exactly the same way as the exo diol **2a** from the exo carbonate, **1a**. **2b** after recrystallization from ethanol or sublimation [100–110° (0.05 mm)] afforded white crystals: mp 132–133°; ir[30] ($CHCl_3$) 3600–3300 (br), 3050 cm^{-1} (w); nmr data in Table I; uv (CH_3OH) λ_{max} 207 nm (ϵ 5400). *Anal.* Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.20; H, 8.46.

7-Isopropylidenebicyclo[2.2.1]hept-5-ene-*exo*-2,3-diol Thionocarbonate (3a).—A solution of **2a** (166 mg, 1.0 mmol) in *p*-xylene (5 ml) was heated under reflux with a solution of thiocarbonyldiimidazole[31] (178 mg, 1.0 mmol) in *p*-xylene (5 ml) for 0.5 hr. The reaction mixture was cooled and filtered and the solvent from the filtrate was evaporated to afford crystals of **3a** (200 mg, 96%). After sublimation [110–115° (0.05 mm)], needlelike crystals were obtained: mp 176–178°; ir[30] ($CHCl_3$), 3050 (w), 1330, 1300, 1275 cm^{-1} (vs); see Table I for nmr data; uv (CH_3OH) λ_{max1} 205 nm (ϵ 13,300), λ_{max2} 241 nm (ϵ 19,900). *Anal.* Calcd for $C_{11}H_{12}O_2S$: C, 63.45; H, 5.81; S, 15.37. Found: C, 63.63; H, 5.73; S, 15.38.

Mixture of 7-Isopropylidenebicyclo[2.2.1]hept-5-ene-*exo*-2,3- and -*endo*-2,3-diol Thionocarbonate (3a and 3b).—Starting from a mixture of **1a** and **1b**, a mixture of **2a** and **2b** was obtained. This mixture was then converted into the mixed thionocarbonates **3a** and **3b**. The crude crystalline material was sublimed at 120–130° (0.05 mm), giving a pure mixture of **3a** and **3b** in the ratio of 3:2 respectively, as shown by its nmr spectrum (Table I).

Attempted Desulfurization–Decarboxylation of 7-Isopropylidenebicyclo[2.2.1]hept-5-ene-*exo*- and -*endo*-2,3-diol Thionocarbonate Mixture, Using Trimethyl Phosphite.—The mixture of thionocarbonates **3a** and **3b** (1.04 g, 5.0 mmol) in trimethyl phosphite (10 ml, 85.0 mmol) in a two-neck flask equipped with a gas inlet tube and a condenser, was refluxed under nitrogen for 84 hr. The condenser, in turn, was connected to two traps containing carbon tetrachloride. A potassium hydroxide solution (30 ml of 20%) was added to the reaction mixture and the contents were refluxed for 0.5 hr. The solution was extracted with ether several times and the ether extracts were washed with water and dried (Na_2SO_4). After evaporation of ether, a dark brown residue (50 mg) consisting of the starting material was obtained. The nmr spectra of materials in the two carbon tetrachloride traps did not show bands of the expected product, **4**.

Attempted Desulfurization–Decarboxylation of 7-Isopropylidenebicyclo[2.2.1]hept-5-ene-*exo*- and -*endo*-2,3-diol Thionocarbonate Mixture, Using Raney Nickel.—A solution of the exo and endo thionocarbonate mixture, **3a** and **3b** (95 mg), in ether (10 ml) was stirred with Raney nickel (60–90 mg) for 12 hr. The filtered ether solution, on evaporation, gave only the starting material as shown by its nmr spectrum. A complicated nmr spectrum of the reaction product was observed when the reaction was carried out for 2 hr in refluxing tetrahydrofuran or dioxane.

7-Isopropylidenebicyclo[2.2.1]heptane-*exo*-2,3-diol Carbonate (5a).—A solution of **1a** (50 mg) in ethanol (10 ml) was hydrogenated in the presence of Adams' catalyst (9 mg) at atmospheric pressure. One equivalent of hydrogen was taken up in 5 min. The solvent was removed under reduced pressure to obtain a white residue (48 mg, 95%). The product after sublimation at 90–100° (0.05 mm) melted at 113–114°: ir[30] (CCl_4) 1845, 1810 cm^{-1} (s); nmr, see Table II; uv (CH_3OH) λ_{max} 205 nm (ϵ 3100). *Anal.* Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.02; H, 7.12.

***exo*-2,3-Dihydroxy-7-isopropylidenebicyclo[2.2.1]heptane (6a).**—Hydrogenation of **2a** (60 mg) in ethanol (10 ml) was carried out as described above. The solvent was removed, giving white amorphous material (56 mg, 92%); the product after sublimation at 80–90° (0.05 mm) afforded white crystals of **6a**: mp 96–97°; ir[30] (CCl_4) 3500 cm^{-1} (br); nmr assignments in Table II; uv (CH_3OH) λ_{max} 205 nm (ϵ 4300). *Anal.* Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.61; H, 9.47.

***endo*-2,3-Dihydroxy-7-isopropylidenebicyclo[2.2.1]heptane (6b).**—A solution of **2b** (30 mg) in ethanol (10 ml) was hydrogenated. The product (28 mg, 92%) after sublimation at 90–100° (0.05 mm), had mp 129–130°; ir[30] (CCl_4) 3600–3300 cm^{-1} (br); nmr, see Table II; uv (CH_3OH) λ_{max} 205 nm (ϵ 3800). *Anal.* Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.21; H, 9.71.

7-Isopropylidenebicyclo[2.2.1]heptane-*exo*-2,3-diol Thionocarbonate (7a).—A solution of **3a** (66 mg) in ethyl acetate (15 ml) was hydrogenated as before; the uptake of hydrogen was extremely slow and was complete after 24 hr. The product (60 mg, 90%) was purified by sublimation at 100–110° (0.05 mm): mp 145–146°; ir[30] ($CHCl_3$) 1340, 1305, 1275 cm^{-1} (vs); nmr, see Table II; uv (CH_3OH) λ_{max} 205 nm (ϵ 8300) and 241 (14,300). *Anal.* Calcd for $C_{11}H_{14}O_2S$: C, 62.84; H, 6.71; S, 15.22. Found: C, 62.68; H, 6.57; S, 15.09.

Spiro[2.4]hepta-1,3-diene.—Spiro[2.4]hepta-1,3-diene, bp 43–45° (70 mm) [lit.[16] bp 57° (100 mm)], was prepared according to the method of Alder and coworkers:[16] ir[30] (neat) 3120, 3050 cm^{-1} (w); nmr[29] (CCl_4) 3.66 and 4.07 (two symmetrical multiplets for vinylics, 4 protons), 8.51 (cyclopropyl, s, 4 protons).

***endo*[32]-2,3-Dibromo 7,7-dimethylenebicyclo[2.2.1]hept-5-ene (8).**—The reaction of spiro[2.4]hepta-1,3-diene with dibromoethylene was done in a Carius combustion tube, sealed under high vacuum. The adduct was purified by sublimation at 40–50° (0.05 mm): mp 73° (reported[16] mp 75°); ir[30] (CCl_4) 3110, 3050 cm^{-1} (w); nmr[29] (CCl_4) 3.71 (t, H-5,6, sp 2 Hz), 5.48 (t, H-2,3 exo, sp 2 Hz), 7.43 (qi, H-1,4, sp 2 Hz), 9.46 (s, H cyclopropyls).

***endo*-2,3-Dibromo-7,7-dimethylenebicyclo[2.2.1]heptane (9).**—Hydrogenation of **8** afforded white, crystalline material of **9** after sublimation at 80–90° (0.05 mm): mp 104° (reported[16] mp 76°); ir[30] (CCl_4) 3100 cm^{-1} (w); nmr[29] (CCl_4) 5.33[33] (br, H-2,3 exo), 9.39 (s, H cyclopropyls).

7,7-Dimethylenebicyclo[2.2.1]heptane (10).—Debromination of **9** gave **10**: mp 40–42° (reported[16] mp 44°); ir[30] (CCl_4) 3100 cm^{-1} (w); nmr[29] (CCl_4) 9.58 (s, H cyclopropyls), 8.5 (br m, 10 protons).

(27) Several preliminary experiments were carried out to establish optimum reaction conditions. Reactions in a Carius combustion tube or metallic bomb gave only black tarry material.

(28) M. S. Newman and R. W. Addor, *J. Amer. Chem. Soc.*, **75**, 1263 (1953).

(29) Signal positions in τ units; br, broad; m, multiplet; qi, quintet; s, singlet; t, triplet. Chemical shifts are accurate to ±0.02 ppm. All these assignments are confirmed by the integrated areas of various peaks.

(30) Abbreviations: br, broad; s, sharp; vs, very strong; w, weak.

(31) H. A. Staab and G. Walther, *Justus Liebigs Ann. Chem.*, **657**, 98 (1962).

(32) Alder, *et al.*, first reported **8** but did not comment on its configuration. On the basis of the triplet nature of the signal for H-2,3 due to coupling with the bridgehead protons, we have assigned the endo configuration to this compound.

(33) This unexpected downfield shift may result from the anisotropic effects of Br-2,3.

7,7-Dimethylenebicyclo[2.2.1]hept-5-ene (11).—Purification of 11, bp 57–60° (50 mm) [lit.[16] bp 63° (60 mm)], was accomplished by vpc (silicone oil column at 98°): ir[30] (CCl_4) 3100 (w), 3020 cm^{-1} (w); nmr (CCl_4) 3.97 (t, H-5,6, sp 2 Hz), 7.92 (br, H-1,4), 8.22 (m, H-2,3 exo), 8.98 (m, H-2,3 endo), 9.62 (m, H cyclopropyls anti), 9.71 (m, H cyclopropyls syn).

7,7-Dimethylenebicyclo[2.2.1]hepta-2,5-diene (12).—Purification of 12, bp 30–31° (18 mm) [lit.[16] bp 37° (20 mm)], was achieved by vpc using a silicone oil column at 91°: ir[30] (CCl_4) 3100, 3010 cm^{-1} (w); nmr[29] (CCl_4) 3.26 (t, H-2,3,5,6, sp 2 Hz), 7.08 (t, H-1,4, sp 2 Hz), 9.57 (s, H cyclopropyls).

Registry No.—**1a**, 35092-24-1; **1b**, 35129-58-9; **2a**, 35092-25-2; **2b**, 35092-26-3; **3a**, 35092-27-4; **3b**, 35092-28-5; **5a**, 35092-29-6; **6a**, 35092-30-9; **6b**, 35092-31-0; **7a**, 35092-32-1; dimethylfulvene, 2175-91-9; vinylene carbonate, 872-36-6.

Preparation and Stereochemistry of 1-Methyl-2-methylenebenzonorbornene and 1,2-Dimethyl-2-benzonorbornenyl Derivatives

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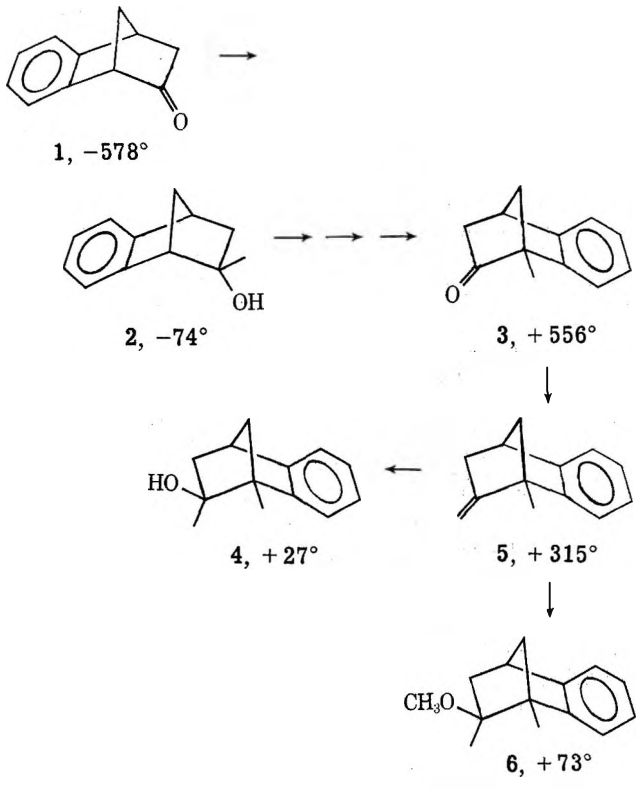
Optically active 2-benzonorbornenone (1) has been converted to active 1-methyl-2-methylenebenzonorbornene (5) in five steps and the latter has been converted to active 1,2-dimethyl-*exo*-2-benzonorbornenol (4) and 1,2-dimethyl-*exo*-2-benzonorbornenyl methyl ether (6). Absolute configurations and rotations of 4, 5, and 6 are established by correlation with 1.

We have recently investigated the symmetry properties of ionic intermediates in the 1,2-dimethyl-2-benzonorbornenyl system[1] This paper reports our synthetic entry into this system and the correlation of optical configurations and rotations required for that investigation.

The 1,2-dimethyl-*exo*-2-benzonorbornenyl system was derived from 2-benzonorbornenone (1)[2] as outlined in Chart I. The key intermediate in this synthesis is 1-methyl-2-methylenebenzonorbornene (5), which was prepared from 1-methyl-2-benzonorbornenone (3) by the Wittig reaction. The latter was prepared from 1 by the series of reactions used earlier[3,4] to convert norcamphor to 1-methyl-2-norbornanone. This sequence involves conversion of 1 to 2-methyl-*endo*-2-benzonorbornenol (2) with methylmagnesium bromide followed by acid-catalyzed rearrangement of 2 in acetic acid to 1-methyl-*exo*-2-benzonorbornenyl acetate. This step results in configurational change of the bicyclic system, as illustrated in Chart I. Reductive cleavage of the acetate with lithium aluminum hydride followed by Oppenauer oxidation[5] of the resulting 1-methyl-*exo*-2-benzonorbornenol gave 3.

CHART I



Absolute configurations and rotations[6] are shown in Chart I. These were determined directly starting with optically active 1. The absolute configuration and rotation of the latter had been established earlier.[2] Optically active 1 was prepared[2] by asymmetric hydroboration of benzonorbornadiene with tetraisopinocamphenyldiborane[7] followed by oxidation of the resulting active *exo*-2-benzonorbornenol. The most active samples were about 68% optically pure.

Optically active 5 was converted to active 1,2-dimethyl-*exo*-2-benzonorbornenol (4) by oxymercuration–demercuration[8] and to active 1,2-dimethyl-*exo*-2-benzonorbornenyl methyl ether (6) by methoxymercuration–demercuration.[9] There is evidence[3,7] that this type of addition does not result in rearrangement in a similar system, and from this and the reproducible changes in rotations, we conclude that these transformations do not result in loss of optical purity.

Experimental Section

Materials.—Racemic and optically active 2-benzonorbornenone (1) were prepared in about 80% yield from benzonorborna-

(1) H. L. Goering and J. V. Clevenger, to be submitted for publication.

(2) D. J. Sandman, K. Mislow, W. P. Giddings, J. Dirlam, and G. C. Hanson, *J. Amer. Chem. Soc.*, **90**, 4877 (1968).

(3) H. L. Goering, C. Brown, S. Chang, J. V. Clevenger, and H. Humski, *J. Org. Chem.*, **34**, 624 (1969).

(4) J. A. Berson, J. S. Walia, A. Remanick, S. Suzuki, P. Reynolds-Warnhoff, and D. Willner, *J. Amer. Chem. Soc.*, **83**, 3986 (1961).

(5) P. D. Bartlett and W. P. Giddings, *ibid.*, **82**, 1240 (1960).

(6) Rotations are for chloroform solutions at 25°.

(7) H. C. Brown, N. R. Ayyangar, and G. Zweifel, *J. Amer. Chem. Soc.*, **86**, 397 (1964).

(8) H. C. Brown, J. H. Kawakami, and S. Ikegami, *ibid.*, **89**, 1525 (1967), and references cited therein.

(9) H. C. Brown and M.-H. Rei, *ibid.*, **91**, 5646 (1969).

diene[10] as described earlier.[2] This method involves hydroboration with diborane in tetrahydrofuran for racemic products or with tetraisopinocamphenyldiborane in diglyme for active products, followed by oxidation of the resulting *exo*-2-benzonorbornenol. Asymmetric hydroboration with tetraisopinocamphenyldiborane[2,7] derived from (−)-α-pinene, $[\alpha]^{20}D$ −46.7° (neat) (~91% optically pure[2]), led to (−)-**1**, $[\alpha]^{25}D$ −368° (*c* 1.25, isooctane) (~65% optically pure[2]). Similar results were obtained with (+)-pinene, $[\alpha]^{25}D$ 40.2° (neat). In this case (+)-**1**, $[\alpha]^{25}D$ 321° (isooctane), was obtained. For several preparations the optical purity of **1** was about 70% of that of the pinene.

2-Methyl-*endo*-2-benzonorbornenol (2).—A solution of 24.8 g (0.157 mol) of 2-benzonorbornenone (**1**) in 35 ml of ether was slowly added to 62.5 ml (0.187 mol) of 3 *M* methylmagnesium bromide in ether. During the addition the reaction flask was cooled with an ice bath. After the solution was stirred for an additional 1 hr at room temperature, saturated aqueous ammonium chloride was added, after which the clear ether solution was decanted from the precipitate. The solid material was washed with ether and the extracts were combined, dried (magnesium sulfate), and concentrated to dryness under reduced pressure. The yield of crude solid 2-methyl-*endo*-2-benzonorbornenol (**2**) was 26.5 g (97%). Recrystallization from pentane gave pure **2**, mp 61–62°. The nmr spectrum had an aromatic multiplet at τ 2.56–3.12 (4 H), a bridgehead proton (C-4) multiplet at τ 6.68–6.88 (1 H), a bridgehead proton (C-1) multiplet at τ 6.86–7.10 (1 H), methylene and hydroxyl absorption at τ 7.82–9.12 (5 H), and a methyl singlet at τ 8.48 (3 H).

Anal. Calcd for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 82.53; H, 7.93.

By the above procedure 36 g of (−)-**1**, $[\alpha]^{25}D$ −391° (*c* 2.32 $CHCl_3$), $[\alpha]^{25}D$ −385 (isooctane) (68% optically pure[2]), was converted to 40 g of (−)-**2**. A pure sample of (−)-2-methyl-*endo*-2-benzonorbornanol (**2**), mp 58–71°, $[\alpha]^{25}D$ −50.0° (*c* 9.19, $CHCl_3$), was obtained by preparative gc (20% KOH, 1% Carbowax 40 M on firebrick) followed by sublimation.[11] This corresponds to an absolute rotation of about $[\alpha]^{25}D$ −74° ($CHCl_3$) for **2**.

Anal. Calcd for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 82.72; H, 8.11.

1-Methyl-2-benzonorbornenone (3).—A solution of 26.5 g (0.152 mol) of **2** in 67 ml of acetic acid was treated with 1 ml of sulfuric acid and 0.5 ml of water. The resulting purple solution was heated at 100° for 1 hr and then poured onto 200 g of ice. A solution of 40 g (1 mol) of sodium hydroxide in 200 ml of water was slowly added, after which saturated sodium carbonate solution was added to completely neutralize the reaction mixture. The mixture was extracted with ether. After drying, the ether was removed under reduced pressure, leaving 31.2 g (95%) of crude 1-methyl-*exo*-2-benzonorbornenyl acetate as a brown oil. Gas chromatography showed that this acetate fraction consisted of ~80% 1-methyl-*exo*-2-benzonorbornenyl acetate.

The crude acetate was taken up in 60 ml of dry ether and reduced with 5.08 g (0.134 mol) of lithium aluminum hydride. After work-up in the usual manner, 24.6 g of crude solid 1-methyl-*exo*-2-benzonorbornenol was obtained. Gas chromatography indicated that this material was about 80% pure and contained about 10% each of two other components.

The crude 1-methyl-*exo*-2-benzonorbornenol was oxidized to 1-methyl-2-benzonorbornenone (**3**) with *p*-benzoquinone and aluminum *tert*-butoxide by a procedure described earlier.[2,6] The crude product was shown to be 86% **3** by analytical gc. A pure sample of **3** was obtained by preparative gc (30% cyanosilicone XF-1150 on Chromosorb). The nmr spectrum exhibited absorptions at τ 2.80–3.13 (m, Ar H, 4 H), 6.42 (m, C-4 H, 1 H), 7.53–8.48 (m, CH_2, 4 H), and 8.60 (s, CH_3, 3 H).

Anal. Calcd for $C_{12}H_{12}O$: C, 83.69; H, 7.02. Found: C, 83.80; H, 7.12.

By the above procedure 34 g (0.195 mol) of (−)-**2**, derived from 68% optically pure (−)-**1**, $[\alpha]^{25}D$ −391° (*c* 2.32, $CHCl_3$), was converted to 23.3 g (69%) of (+)-1-methyl-2-benzonorbornenone (**3**), which after purification (gc) had $[\alpha]^{25}D$ 376° (*c* 4.74, $CHCl_3$[11]). This corresponds to an absolute rotation of about $[\alpha]^{25}D$ 556° ($CHCl_3$) for **3**.

Anal. Calcd for $C_{12}H_{12}O$: C, 83.69; H, 7.02. Found: C, 83.70; H, 7.14.

1-Methyl-2-methylenebenzonorbornene (5).—This compound was prepared from 1-methyl-2-benzonorbornenone (**3**) by the procedure[3] used to prepare 1-methyl-2-methylenenorbornane from 1-methyl-2-norbornanone. In a typical experiment 19.9 g (0.114 mol) of **3** gave 16.5 g of crude **5**. Fractionation with a spinning-band column gave 13 g (67%) of 1-methyl-2-methylenebenzonorbornene, bp 52–53° (0.1 mm). The nmr spectrum had an aromatic multiplet at τ 2.78–3.10 (4 H), olefin proton triplets at τ 5.11 with J = 3.3 Hz (1 H) and 5.31 with J = 3.3 Hz (1 H), a bridgehead proton multiplet at τ 6.62–6.82 (1 H), a methylene multiplet at τ 7.13–8.37 (4 H), and a methyl singlet at τ 8.43 (3 H).

Anal. Calcd for $C_{13}H_{14}$: C, 91.71; H, 8.29. Found: C, 91.73; H, 8.11.

Optically active 1-methyl-2-methylenebenzonorbornene (**5**) was prepared from active 2-benzonorbornenone (**1**) without purification of the intermediates. In one experiment 23.4 g (0.148 mol) of (−)-**1**, $[\alpha]^{25}D$ −368° (*c* 1.25, isooctane) (~64% optically pure[2]), gave 12.63 g (50%) of (+)-1-methyl-2-methylenebenzonorbornene (**5**), $[\alpha]^{25}D$ 202° (*c* 2.72, $CHCl_3$). In another case (+)-**1**, $[\alpha]^{25}D$ 292° (isooctane), gave (−)-1-methyl-2-methylenebenzonorbornene (**5**), $[\alpha]^{25}D$ −163° (*c* 2.63, $CHCl_3$).[11] These results indicate an absolute rotation of about $[\alpha]^{25}D$ 315° ($CHCl_3$) for **5**.

1,2-Dimethyl-*exo*-2-benzonorbornenol (4).—Oxymercuration–demercuration of **5** according to a previously described procedure[12] gave **4** in 97% yield. The crude product was ~96% pure according to gc. Sublimation at 80° (14 mm) gave pure **4**, mp 54–55.5°. The nmr spectrum had an aromatic multiplet at τ 7.67–8.50 (4 H), a bridgehead proton multiplet at τ 6.73–6.96 (1 H), methylene absorption at τ 7.67–8.50 (5 H), and methyl singlets at τ 8.60 (3 H) and 9.18 (3 H).

Anal. Calcd for $C_{13}H_{16}O$: C, 82.93; H, 8.57. Found: C, 82.70; H, 8.45.

By the above procedure (+)-**5**, $[\alpha]^{25}D$ 213° ($CHCl_3$), was converted to (+)-1,2-dimethyl-*exo*-2-benzonorbornenol (**4**), which after purification by gc (20% KOH, 1% Carbowax 40M on firebrick) and sublimation had mp 62–63°, $[\alpha]^{25}D$ 18.45° (*c* 5.92, $CHCl_3$).[11] This corresponds to an absolute rotation of about $[\alpha]^{25}D$ 27° ($CHCl_3$) for **4**.

Anal. Calcd for $C_{13}H_{16}O$: C, 82.93; H, 8.57. Found: C, 83.11; H, 8.55.

(+)-1,2-Dimethyl-*exo*-2-benzonorbornenyl Methyl Ether (6). Optically active 1-methyl-2-methylenebenzonorbornene (**5**) was converted to active **6** directly by methoxymercuration–demercuration[9] as follows. To a stirred suspension of 2.91 g (9.12 mmol) of mercuric acetate in 18 ml of methanol was slowly added a solution of 1.55 g (9.12 mmol) of (+)-**5**, $[\alpha]^{25}D$ 202° ($CHCl_3$), in 5 ml of methanol. The resulting colorless solution was stirred for 10 min at room temperature and then cooled and treated with 9 ml of 3 *M* sodium hydroxide. To the resulting yellow suspension was added (dropwise) a solution of 0.15 g (3.97 mmol) of sodium borohydride in 9 ml of 3 *M* sodium hydroxide solution. This gave a grey-black suspension that was stirred for 2 hr to coagulate the mercury. The resulting mixture was extracted with pentane. After drying ($MgSO_4$) the pentane was removed under reduced pressure. The residual liquid ether, 1.84 g (100%), was purified by column chromatography (Florisil with hexane as eluent). This gave (+)-**6**, $[\alpha]^{25}D$ 46.8° (*c* 4.10, $CHCl_3$). This corresponds to an absolute rotation of about $[\alpha]^{25}D$ 73° ($CHCl_3$) for **6**. The nmr spectrum had a singlet at τ 2.91 (4 H), a multiplet at τ 6.75–6.91 (1 H), a methyl singlet at τ 6.75 (3 H), a multiplet at τ 7.61–7.97 (2 H), a doublet (with unresolved fine splitting) at τ 8.32 with J = 9 cps (1 H), a methyl singlet at τ 8.60 (3 H), a doublet of doublets centered at τ 8.87 with J = 12 and J = 2.5 cps (1 H), and a methyl singlet at τ 9.27 (3 H).

Registry No.—(−)-**1**, 35001-30-0; (+)-**1**, 21159-73-9; (−)-**2**, 35001-32-2; (±)-**2**, 34969-22-7; (±)-**3**, 34969-23-8; (±)-**3**, 34969-24-9; (±)-**5**, 35001-33-3; (±)-**5**, 34993-32-3; (−)-**5**, 34969-25-0; (±)-**4**, 34993-33-4; (±)-**4**, 34993-34-5; (±)-**6**, 34969-26-1.

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(10) Prepared from anthranilic acid and cyclopentadiene by the method of L. F. Friedman, F. M. Logullo, and D. M. Smith. We thank Professor Friedman for experimental details prior to publication.

(11) Optically active samples had the same spectral properties as racemic samples.

Thermal Decomposition of *exo*- and *endo*-Norbornylcarbonic–*p*-Nitrobenzoic Anhydrides

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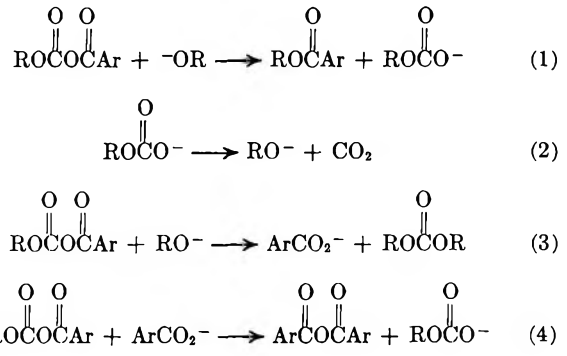
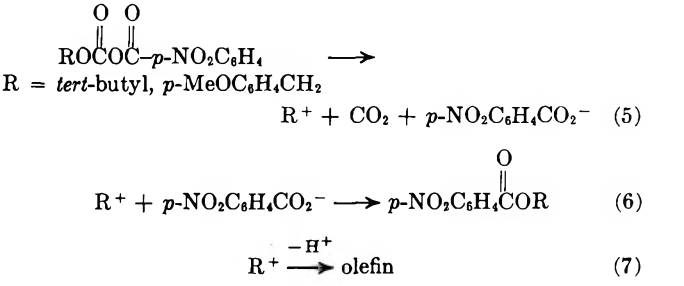
The ability of the norbornyl system to stabilize a positive charge prompted the study of the mechanism of the thermal decomposition of *exo*-norbornylcarbonic–*p*-nitrobenzoic anhydride **1** and its endo isomer **2**. Anhydrides **1** and **2** were prepared from the corresponding oxygen-18-labeled norborneols and **1** was also prepared from optically active norborneol. When the thermal decomposition was carried out in nitrobenzene or acetonitrile at 130–140°, **1** decomposed with approximately 20% alkyl–oxygen cleavage. The alkyl-oxygen cleavage could be quenched by addition of triethylamine. The decomposition of **1** in xylene and **2** in all three solvents proceeded exclusively by acyl–oxygen cleavage. Semiquantitative analysis of the products of the decompositions indicated large differences in product distributions when the decompositions were carried out in xylene as compared to acetonitrile. The product distribution in xylene could be altered by addition of catalytic amounts of triethylamine. The rate measurements were not very reproducible but indicated that the rate differences between the decomposition of **1** in xylene and nitrobenzene were very small. The decomposition of **2** was actually faster in xylene than in nitrobenzene. The data lead to a conclusion that in polar solvents **1** decomposes partly by a unimolecular process, which leads to the formation of the norbornyl cation, but the bulk of the decomposition proceeds by an ionic chain mechanism. Anhydride **2** decomposes exclusively by the ionic chain mechanism in nitrobenzene and acetonitrile. In xylene both anhydrides decompose by a cyclic SNi-like mechanism which leads to the formation of the respective norbornyl esters and carbon dioxide as the principal products.

The thermal decomposition of mixed carboxylic–carbonic anhydrides has been studied exhaustively by Tarbell and his coworkers.[1] These workers found that, when the mixed anhydride was derived from a primary or secondary alcohol, the decomposition proceeded by an ionic chain mechanism in which the alkoxide ion was the chain carrier. The products of the



reaction were the ester (produced in step 1), the symmetrical carbonate and the symmetrical anhydride (produced in steps 3 and 4, respectively), and carbon dioxide. The ratios of the products formed were an invariant property of each anhydride and depended on the structure of R and Ar. One feature of this mechanism was that the alkyl–oxygen bond remained intact throughout the reaction.[2,3]

A different situation exists if the group R is capable of stabilizing a carbonium ion. Thus it was found that, when R was *tert*-butyl and Ar was *p*-nitrophenyl, the anhydride decomposed mainly by alkyl–oxygen cleavage.[4] The same was true when the mixed anhydride was derived from *p*-methoxybenzyl alcohol and *p*-nitrobenzoic acid,[5] although here the course of the reaction depended on the conditions. Thus, a second mechanism may be written (eq 5 and 6 or 7), which takes the alkyl–oxygen cleavage into account. It must be added that the ionic chain mechanism, as



outlined, competes with unimolecular cleavage in all the cases studied.

In view of these data a study of the decomposition of the mixed anhydrides derived from *exo*- and *endo*-norborneols was undertaken. The unusual stability of the norbornyl cation is well known. The participation of the 1,6-σ bond in solvolysis reactions is well documented, although that concept is not without its opposition.[6] The study reported here sought to test the effect of the norbornyl system on the mechanism of the thermal decomposition of mixed anhydrides derived from it.

Results

Synthesis.—The mixed anhydrides **1** and **2** were prepared by the conventional procedure[7] from *exo*- and *endo*-norbornyl chloroformates, respectively, and *p*-nitrobenzoic acid, using triethylamine as the base. The chloroformates were prepared from *exo*- and *endo*-norborneols and phosgene, using standard procedures.

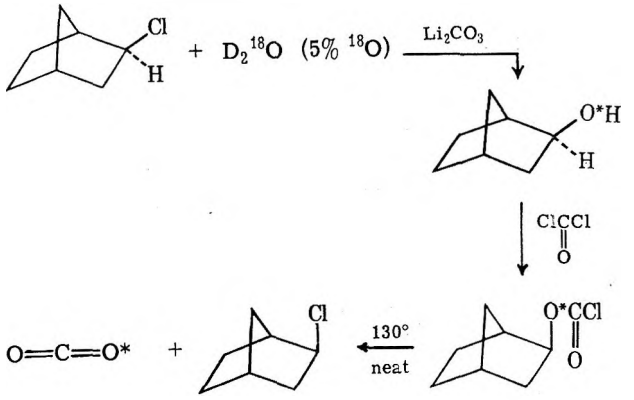
The oxygen-18-labeled anhydrides were prepared from the corresponding oxygen-18-labeled chloroformates, which were prepared, in turn, from the labeled norborneols. These preparations were carried out according to Schemes I and II.

The details of the preparation are given in the Experimental Section. The amount of labeling in each

(1) For a recent review of that work see D. S. Tarbell, *Accounts Chem. Res.* **2**, 296 (1969).
(2) E. J. Longosz and D. S. Tarbell, *J. Org. Chem.*, **26**, 2161 (1961).
(3) C. J. Michejda, D. S. Tarbell, and W. H. Saunders, Jr., *J. Amer. Chem. Soc.*, **84**, 4113 (1962).
(4) C. J. Michejda and D. S. Tarbell, *J. Org. Chem.*, **29**, 1168 (1964).
(5) R. C. L. Chow and D. S. Tarbell, *ibid.*, **32**, 2188 (1967).
(6) *Cf.* P. D. Bartlett, "Nonclassical Ions," W. A. Benjamin, New York, N. Y., 1965.
(7) D. S. Tarbell and N. A. Leister, *J. Org. Chem.*, **23**, 1149 (1958).

SCHEME I

exo-NORBORNYL CHLOROFORMATE-^{18}O



SCHEME II

endo-NORBORNYL CHLOROFORMATE-^{18}O

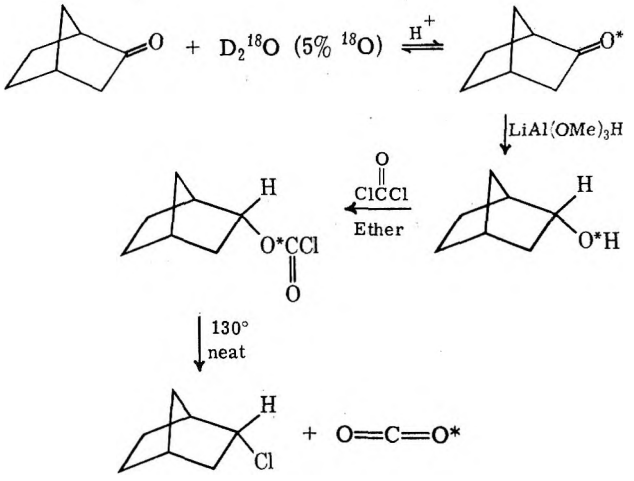


TABLE I

OXYGEN-18-LABELING DATA

Origin of CO_2	(*m/e* 46/*m/e* 44) × 100	Average (*m/e* 46/*m/e* 44) × 100	Relative average per cent enrichment
Natural (from tank)	0.55	0.54 ± 0.04	0
	0.48		
	0.58		
exo-Norbornyl chloroformate	5.16	5.14 ± 0.06	100.00
	5.21		
	5.05		
Exo anhydride 1			
In acetonitrile	0.98	1.45 ± 0.49	19.7
	1.12		
	1.43		
	2.69		
	1.02		
In xylene	0.58	0.54 ± 0.04	0
	0.51		
In nitrobenzene	1.79	1.42 ± 0.25	19.1
	1.25		
	1.21		
With trace of Et_3N	0.65	0.71 ± 0.06	3.7
In acetonitrile	0.77		
Neat	0.71	0.62 ± 0.09	1.7
	0.52		
Unlabeled exo anhydride (1)			
In nitrobenzene	0.59	0.59	
endo-Norbornyl chloroformate	4.35	4.34 ± 0.03	100.00
	4.30		
	4.38		
Endo anhydride 2			
In acetonitrile	0.58	0.53 ± 0.04	0
	0.47		
	0.55		
In xylene	0.50	0.50	0
In nitrobenzene	0.53	0.53	0
Neat	0.49	0.49	0

chloroformate was determined by heating the neat chloroformate at 130° or in the presence of quinoline at 80°. The former procedure gave more reproducible results. The carbon dioxide from each decomposition was trapped in a liquid N_2 trap. The carbon dioxide samples were then distilled on a vacuum line and, after degassing, were subjected to mass spectroscopic analysis. The ratio of *m/e* 46 to *m/e* 44 of the experimental sample, compared with this ratio for natural carbon dioxide, gave the amount of labeling. These results are tabulated in Table I. The labeled chloroformates were then converted to the labeled mixed anhydrides.

The optically active *exo*-norbornylcarbonic–*p*-nitrobenzoic anhydride was prepared from the optically active *exo*-norborneol. The latter was resolved by the procedure of Winstein and Trifan.[8] *exo*-Norborneol was converted to the acid phthalate by heating the alcohol with phthalic anhydride in pyridine. The acid phthalate was resolved using cinchonidine as the resolving agent. After four crystallizations the acid phthalate was liberated from the alkaloid. The mother liquors were also worked up. It was found, as in the original resolution, that the mother liquors contained the more highly resolved material. The resolved acid phthalate used in subsequent work had $[\alpha]^{27}D$ −8.68°.

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

This material was hydrolyzed with sodium hydroxide to give the optically active norborneol. The norborneol was immediately converted to the chloroformate which, in turn, was converted to the mixed anhydride, which had $[\alpha]^{27}D$ − 5.593° (*c* 5.68).

Part of the optically active norborneol was converted to *exo*-norbornyl *p*-nitrobenzoate. This material had $[\alpha]^{27}D$ −8.23° (*c* 9.677).

Decomposition of Oxygen-18-Labeled Anhydrides.— The mixed anhydrides were decomposed by two different methods, which are described in the Experimental Section. The carbon dioxide samples were collected in liquid nitrogen traps. At the end of a run the carbon dioxide was distilled on a vacuum line and degassed. The samples were analyzed mass spectroscopically. Measurements were made of the parent peak at *m/e* 44 and the isotope peak at *m/e* 46. Each sample was scanned 15–20 times and the ratio of *m/e* 46 to *m/e* 44 was recorded. These data are presented in Table I. It is readily apparent from the table that the decomposition of *exo*-norbornylcarbonic–*p*-nitrobenzoic anhydride (1) proceeds with about 20% alkyl–oxygen cleavage when the decomposition is carried out in acetonitrile and nitrobenzene.

There is no alkyl–oxygen cleavage during the decomposition of **1** in xylene, and there is a significant decrease in the amount of alkyl–oxygen cleavage when

the reaction is carried out in the presence of the nucleophile triethylamine or in the absence of solvent. In contrast the endo anhydride 2 decomposes without any alkyl–oxygen cleavage under all the conditions studied.

Decomposition of Optically Active Exo Anhydride 1.—The anhydride was decomposed in acetonitrile, nitrobenzene, and xylene. After being heated for 10 hr at 130–140° the solvent was removed and the *exo*-norbornyl *p*-nitrobenzoate was extracted and purified. Samples of the ester were analyzed polarimetrically. The ester was shown to be configurationally stable under the reaction conditions. The data are presented in Table II.

TABLE II

DECOMPOSITION OF OPTICALLY ACTIVE *exo*-NORBORNYLCARBONIC–*p*-NITROBENZOIC ANHYDRIDE (1)[a] AS A FUNCTION OF SOLVENT.[b] TEMPERATURE 130–140°

Source of *exo*-Norbornyl *p*-nitrobenzoate	Specific rotation, $[\alpha]^{27}D$, deg	% racemization
Original active norborneol[c]	−8.23	0
Decomposition of 1 in acetonitrile	−7.50	17.8
Decomposition of 1 in nitrobenzene	−7.85	9.2
Decomposition of 1 in xylene	−8.23	0
Decomposition of 1 in acetonitrile in the presence of triethylamine[d]	−8.17	1.6

[a] The specific rotation of the anhydride 1 was −5.39°. [b] The concentration of the anhydride 1 in the solvents used was approximately 0.3 *M*. [c] Preparation is given in the Experimental Section. [d] The concentration of the triethylamine was approximately 0.07 *M*.

Although the polarimeteic data do not mirror the labeling data exactly, particularly in the case of the decomposition of 1 in nitrobenzene, the correlation between the two sets of data is gratifying.

Products of Decomposition of Anhydrides 1 and 2.—The mixed anhydrides were heated in acetonitrile and xylene for 11–13 hr at 130–140° to effect complete decomposition. Table III gives the products as

TABLE III

PRODUCTS[a] OF DECOMPOSITION OF 1 AND 2 AS FUNCTIONS OF SOLVENT. TEMPERATURE 130–140°

Anhydride in solvent	Ester[b]	Anhydride[b]	Carbonate[b,d]
1 in acetonitrile	0.80	0.17	~0.1
	0.79[c]	0.25	
1 in xylene	0.82	0	0–trace
2 in acetonitrile	0.38	0.42	~0.15
	0.40		
2 in xylene	0.89	0.03	~0.02

[a] The product yields are expressed as mol of product/mol of mixed anhydride. [b] Ester is *exo*-norbornyl *p*-nitrobenzoate from 1 and the endo isomer from 2; anhydride is *p*-nitrobenzoic anhydride; carbonate is dinorbornyl carbonate (exo from 1, endo from 2). [c] Isolated yield. [d] The carbonate yields are very approximate and should be treated as a lower limit.

functions of solvent. The products were determined by a variety of methods, which are described in the Experimental Section. Most difficulty was encountered in the analysis for *p*-nitrobenzoic acid and *p*-nitrobenzoic anhydride in the presence of each other. The products from the decomposition in nitrobenzene were not analyzed quantitatively because of the difficulty of removing the last traces of the solvent. The major products from 1 and 2 in nitrobenzene, however, were the corresponding exo and endo esters. The yields of carbon dioxide produced in the reactions were not determined quantitatively, but it is obvious from the data in Table III that they were better than 90%.

Varying amounts of *p*-nitrobenzoic acid and norborneol were also found. These products were probably secondary, formed during the manipulation of the decomposition mixtures. In most cases only small amounts were found to be present.

The effect of added triethylamine on the thermal decomposition of 1 and 2 in xylene was very instructive. These data are presented in Table IV. It should be

TABLE IV

EFFECT OF TRIETHYLAMINE[a] ON THE PRODUCTS FROM 1 AND 2

Anhydride	Decomposition medium	Products (mol of product/mol of anhydride) Ester	Symmetrical anhydride	Carbonate
1	Xylene	0.82	0.00	0–trace
	Xylene + Et_3N	0.75	0.17	~0.12
2	Xylene	0.89	0.03	~0.02
	Xylene + Et_3N	0.27	0.37	~0.1

[a] Triethylamine concentration = 0.2 mol/mol of anhydride. Temperature of decomposition, 138°.

noted that the products of decomposition in the presence of triethylamine show virtually identical distributions with those found in the decomposition of the respective anhydrides in acetonitrile. This suggests that the presence of the nucleophilic catalyst in xylene causes the anhydrides to decompose in a similar manner as in the polar solvent.

Rates of Decomposition of 1 and 2.—An attempt was made to study the kinetics of the decomposition reactions in nitrobenzene and xylene. The rates were followed using the disappearance of the strong infrared carbonyl bands (1808 cm^{-1}) of the mixed anhydrides, according to the procedure of Bartlett and Hiatt.[9]

In some runs the reaction showed an induction period (up to 30 min at 138°) but then followed reasonably clean first-order kinetics. The rate constants, however, were not reproducible. For example, duplicate runs for the exo anhydride 1 at 138.5° in nitrobenzene were 2.7×10^{-4} sec^{-1} and 4.1×10^{-4} sec^{-1}. The rates of decomposition of endo anhydride 2 in nitrobenzene at the same temperature were approximately an order of magnitude slower than the rate of 1. The rate data are shown in Table V. Although it must be stressed

TABLE V

RATES OF DECOMPOSITION OF ANHYDRIDES 1 AND 2[a]

Anhydride	Solvent	$k \times 10^5$ sec^{-1}
1	Nitrobenzene	40.7, 27.4[b]
	Xylene	16.3
2	Nitrobenzene	4.96, 2.07[b]
	Xylene	14.5

[a] Decomposition temperature, 138.5°. [b] Duplicate runs.

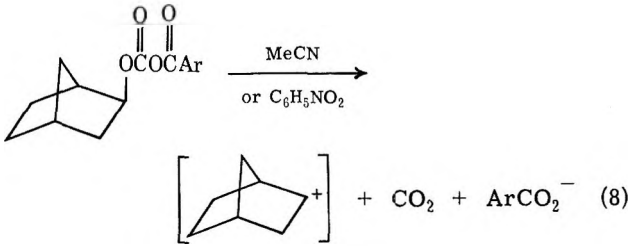
that the individual rate constants are suspect, Table V does show some startling results. There is remarkably little effect on the rate of decomposition of 1 in going from the highly polar nitrobenzene to the nonpolar xylene. Perhaps even more startling is the result

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

that the decomposition of 2 in xylene is actually faster than in nitrobenzene.

Discussion

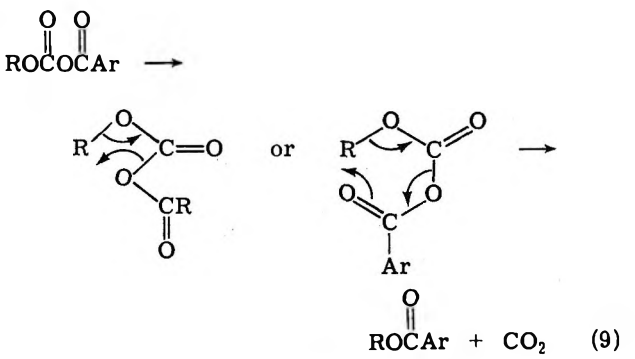
Decomposition in Polar Solvents.—It is clear from the oxygen-18-labeling data and the stereochemical experiment in the case of anhydride 1 that approximately 20% of the decomposition of 1 proceeds with alkyl–oxygen cleavage. An attractive explanation of this result is that, at least 20% of the time, the anhydride decomposes to give a norbornyl cation, carbon dioxide, and the *p*-nitrobenzoate ion. The cation and the anion then collapse to give the exo ester. It is



(8)

significant that no norbornene was ever found among the products. This may mean that the ester is formed rapidly by the collapse of an ion pair and that the cation never really gets free. This suggestion is supported by the fact that no dinorbornyl ether was ever found. The latter product could have arisen from the reaction of the cation with the anion of norborneol. The alkoxide ion is undoubtedly present in a steady state concentration during the reaction because the remaining 80% of the reaction, which occurs with retention of the alkyl–oxygen bonds, must proceed by the ionic chain mechanism discussed in the first part of this article. In that mechanism the alkoxide ion is the chain-carrying species. Thus, the decomposition of 1 in acetonitrile and nitrobenzene appears to be similar to the decomposition of *tert*-butylcarbonic–*p*-nitrobenzoic anhydride,[4] although the percentage of alkyl–oxygen cleavage in the case of 1 appears to be lower. This is consistent with the generally recognized lower stability of the norbornyl cation relative to the *tert*-butyl cation. It is interesting to note that this is the first example of a mixed anhydride derived from a nonbenzylic secondary alcohol which decomposes, at least in part, by alkyl–oxygen cleavage. This formation of the norbornyl cation, under nonsolvolytic conditions, points again to the extraordinary stability of this system. The alkyl–oxygen cleavage can be quenched, however, by addition of small amounts of triethylamine. The presence of the nucleophilic catalyst evidently speeds up the chain mechanism at the expense of the unimolecular cleavage. It could be argued on the basis of the oxygen-18-labeling data that the alkyl–oxygen cleavage in the decomposition of 1 was the result of cyclic processes such as the one shown in eq 9. Such a mechanism would require retention of configuration of the norbornyl system. Our stereochemical data indicate, however, that racemization roughly parallels the amount of alkyl–oxygen cleavage.

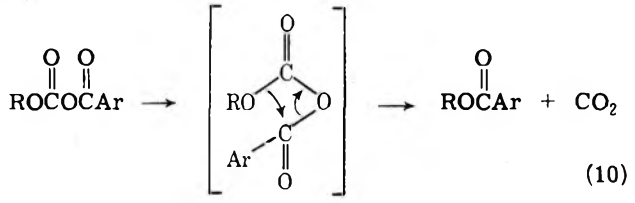
The decomposition of the mixed anhydride 2 in acetonitrile and nitrobenzene seems to proceed exclusively by the ionic chain mechanism. There is absolutely no alkyl–oxygen cleavage, as shown by the labeling data. It is interesting to note that the rate of decomposition of the endo anhydride 2 is an order of magnitude slower in nitrobenzene than the rate of the exo anhydride 1 (Table V).



(9)

Decomposition in Xylene.—Even a casual perusal of the data suggests that the decomposition of both 1 and 2 in xylene is completely different from the reaction in more polar solvents. The oxygen-18-labeling data and the stereochemical data show that the alkyl–oxygen bond remains unbroken in the decompositions of both 1 and 2 in xylene. Examination of the products of the decomposition indicates that the respective esters are, for all intents, the exclusive products in both anhydrides. The rates of the decompositions in xylene are remarkably similar to one another, and there is very little rate depression in going from the polar nitrobenzene to the nonpolar xylene. The kinetic data suggest strongly that the reactions do not involve ionic intermediates. Finally, the data shown in Table IV indicate that the reaction in xylene can be forced to behave in the manner of the reactions in polar solvents by the addition of the nucleophile triethylamine to the decomposition mixture.

These data lead us to conclude that the decomposition of both 1 and 2 in xylene and, by implication, in other nonpolar solvents, proceeds by yet another mechanism. We propose that this reaction is a unimolecular cyclic process that leads to the ester and carbon dioxide directly. Such a mechanism accounts



(10)

R = *exo*- and *endo*-norbornyl

for the retention of the alkyl–oxygen bond, the retention of configuration in 1, the relatively fast rate of decomposition, and the overwhelming preponderance of the ester in the products of both anhydrides. The small amounts of the symmetrical anhydride and carbonate observed in the decomposition of 2 were probably due to the presence of small amounts of adventitious nucleophiles, which directed part of the reaction *via* the chain decomposition route. The role of the added triethylamine was to force the reaction to proceed by the chain mechanism; hence we have the product distribution so similar to the one observed in acetonitrile.

The reaction, as indicated in eq 10, is favored by the presence of a nitro group on the aromatic ring, which makes the carbon of the carboxyl carbonyl more electron deficient. The substitution of a strongly electron donating group, such as a methoxyl, on the aromatic ring could be expected to produce the opposite effect and hence the reaction might be found to follow a more orthodox path. To test this hypothesis both the *exo*- and *endo*-norbornylcarbonic–*p*-methoxybenzoic anhydrides were prepared. It was gratifying to find that in the case of the endo anhydride the decomposition products in xylene and acetonitrile were very similar; almost exclusively, the symmetrical anhydride and the carbonate were found. The decomposition of the exo anhydride was examined in xylene only. Both ester and the symmetrical anhydride were formed. These data, however, are not so conclusive as they might appear. The reason for this is that the product ratios of the decomposition of the anhydrides derived from *p*-methoxybenzoic acid can be changed by addition of triethylamine. The reason for this unexpected result is still not clear.

The cyclic mechanism indicated in eq 10 has not been observed before in the decomposition carboyxlic–carbonic anhydrides. One might ask whether all the carboxylic–carbonic anhydrides derived from primary and secondary alcohols might not decompose by that mechanism in very nonpolar solvents. Recently, Wei and Tarbell[10] proposed a similar mechanism for the decomposition of *p*-nitrobenzoic–*tert*-butylthiocarbonic anhydride. That substance, however, seemed to decompose by the cyclic mechanism over a wide range of solvent polarities.

Experimental Section

Melting points are uncorrected. Infrared spectra were taken on Perkin-Elmer Models 21, 621, and 237 spectrophotometers. Proton magnetic resonance spectra were obtained on Varian Models A-60 and T-60. Mass spectra were obtained on a Perkin-Elmer Hitachi Model RMU6D double-focusing instrument. Varian Aerograph Models 1520 and A90P3 were used for the gas chromatography. Polarimetric measurements were carried out on a Perkin-Elmer Model 241M automatic polarimeter. Microanalyses were performed by A. Bernhardt, Elbach-uber-Engelskirchen, West Germany.

Purification of Solvents.—**Xylene** was heated at reflux over sodium and distilled from sodium. **Nitrobenzene** was chromatographed through alumina, then crystallized from ethanol, and finally distilled through a fractionating column. **Acetonitrile** was heated at reflux over P_2O_5 and then distilled.

Preparation of *exo*-Norborneol.—This compound was prepared by Schleyer's method[11] from norbornene and formic acid. The resulting formate ester was hydrolyzed with potassium hydroxide to *exo*-norborneol, mp 127–128 (lit.[11] 127–128°). The yield, based on norbornene, was 60%.

Preparation of *endo*-Norborneol.—The procedure of Schleyer was used to oxidize *exo*-norbornyl formate with chromic acid to give a 60% yield of **norcamphor** (mp 93°, lit.[12] 93–94°). The ketone was reduced with lithium aluminum trimethoxy hydride.[13] The hydride was prepared by the dropwise addition of 24 ml (0.6 mol) of dry methanol to 8.25 g (0.217 mol) of lithium aluminum hydride in 405 ml of dry tetrahydrofuran at 0°. To this mixture was added dropwise 15.0 g (0.136 mol) of norcamphor in tetrahydrofuran. After 1 hr of stirring, the excess hydride was decomposed with water. Ether was added and the mixture was treated with a saturated solution of sodium potassium tartrate. The organic layer was separated and dried. Evaporation of the solvent *in vacuo* and sublimation [40° (1.5 mm)] of the crude residue afforded 10.9 g (72% yield) of *endo*-norborneol, mp 150–151° (lit.[12] 152–153°).

Preparation of *exo*- and *endo*-Norbornyl Chloroformates.—The procedure for both compounds was identical. The preparation of the exo isomer will be described.

Into a 250-ml three-necked flask fitted with an addition funnel and a Dry Ice condenser and equipped with a magnetic stirrer was condensed 15 ml (0.2 mol) of phosgene. This was dissolved in 75 ml of dry ether. The solution was chilled in an ice bath and 15 g (0.134 mol) of *exo*-norborneol in a little ether was added dropwise with stirring. After the addition was complete the mixture was stirred at room temperature for about 3 hr. The excess phosgene and the ether were removed *in vacuo* to yield a clear, somewhat viscous liquid. No attempt was made to purify the product. The yield was virtually quantitative. Both isomeric chloroformates exhibited a strong band in the infrared spectrum at 1775 cm^{-1} (CCl_4).

Preparation of Anhydrides 1 and 2.—Again the procedures were virtually identical. The preparation of 1 will be described.

To a solution of 6.2 g (0.035 mol) of *exo*-norbornyl chloroformate and 5.0 g (0.035 mol) of *p*-nitrobenzoic acid in 200 ml of dry ether was added 3.8 g (0.038 mol) of dry triethylamine. After the dropwise addition was complete, the mixture was stirred for an additional 2.5 hr. The precipitated amine hydrochloride was filtered off and the ether solution was washed successively with dilute hydrochloric acid, sodium bicarbonate solution, and water. The solution was then dried over magnesium sulfate and the ether was evaporated *in vacuo* to give 7.25 g (67%) of *exo*-norbornylcarbonic–*p*-nitrobenzoic anhydride, mp 63.8–64°.

Anal. Calcd for $C_{15}H_{15}NO_6$: C, 59.01; H, 4.95; N, 4.59. Found: C, 59.06; H, 5.08; N, 4.48.

The endo isomer 2 was prepared in 64% yield, mp 71–72°.

Anal. Calcd for $C_{15}H_{15}NO_6$: C, 59.01; H, 4.95; N, 4.59. Found: C, 59.03; H, 4.91; N, 4.44.

Both anhydrides exhibited the characteristic strong double carbonyl bands at 1808 and 1748 cm^{-1} (CCl_4).

Preparation of *exo*- and *endo*-Norbornyl *p*-Nitrobenzoates.—Both the optically active and inactive esters were prepared in an identical fashion.

In a 100-ml three-necked flask equipped with an addition funnel, condenser, and a magnetic stirrer was placed 1.2 g (0.0065 mol) of *p*-nitrobenzoyl chloride and 0.67 g (0.006 mol) of *exo*-norborneol in approximately 40 ml of dry ether. To this solution was added dropwise over a 10-min period 0.47 g (0.006 mol) of pyridine in about 10 ml of ether. The mixture was stirred for 3 hr. The pyridine hydrochloride was filtered off and the ether solution was washed successively with dilute hydrochloric acid, sodium bicarbonate solution, and water. After drying, the ether was removed *in vacuo* to afford 0.95 g (57%) of *exo*-norbornyl *p*-nitrobenzoate, mp 83–84° (lit.[14] mp 84–85°) after recrystallization from hexane.

The *endo*-norbornyl–*p*-nitrobenzoate was prepared in 74% yield, mp 80° (lit.[14] mp 81°).

Preparation of *exo*-Norbornyl Carbonate.—Into a 250-ml flask was placed 4.0 g (0.036 mol) of *exo*-norborneol in 30 ml of pyridine. To this solution was added dropwise with stirring, at 0°, 6.3 g (0.036 mol) of *exo*-norbornyl chloroformate. The reaction was stirred for 1 hr at 0°, followed by stirring at room temperature for 6 hr. Ether was added to the mixture and the amine hydrochloride was filtered off. The ether solution was washed thoroughly with dilute hydrochloric acid and then water. After drying, the solvent was removed *in vacuo* to yield a yellow oily residue. This material was purified by chromatography on a Florisil column and was eluted by Skellysolve B (light petroleum ether). The product was a white waxy solid, mp 57–59°. The yield was 6.1 g (73%). The compound's infrared spectrum showed a strong carbonyl band at 1730 cm^{-1}.

Anal. Calcd for $C_{15}H_{22}O_3$: C, 70.55; H, 9.31. Found: C, 70.74; H, 9.17.

Preparation of *endo*-Norbornyl Carbonate.—This compound was prepared in similar manner to *exo*-norbornyl carbonate described above. Using 2.1 g (0.019 mol) of *endo*-norborneol and 3.4 g (0.020 mol) of *endo*-norbornyl chlorocarbonate in 16 ml of

(10) L. Wei and D. S. Tarbell, *J. Org. Chem.*, **33**, 1884 (1968).

(11) P. v. R. Schleyer, *Org. Syn.*, **42**, 79 (1962).

(12) "Dictionary of Organic Compounds," Vol. IV, Oxford University Press, New York, N. Y., 1965.

(13) H. C. Brown and P. M. Weissman, *J. Amer. Chem. Soc.*, **87**, 5614 (1965).

(14) N. J. Toivonen and K. Ojala, *Makromol. Chem.*, **18/19**, 414 (1956).

dry pyridine and the work-up described above, the crude product was obtained, yield 4.6 g (95%). An analytical sample was purified by sublimation at mp 165–166° (110°.2 mm).

The infrared spectrum (CCl_4) showed a carbonyl band at 1730 cm^{-1}.

Anal. Calcd for $C_{15}H_{22}O_3$: C, 70.55; H, 9.31. Found: C, 70.68; H, 9.21.

Preparation of Norbornyl Chloride.—The method of Schmerling[15] was used for the preparation of this compound. Into a flask fitted with a stirrer and gas bubbler was placed 25.0 g (0.265 mol) of norbornene in 95 ml of pentane. The flask was cooled in a Dry Ice–acetone bath and HCl was bubbled through for 20 min. The mixture was allowed to stand for several hours at room temperature. The pentane was removed by distillation, and the product was distilled at reduced pressure to yield 28.5 g (82%) of norbornyl chloride, bp 71° (20 mm) [lit.[15] bp 52° (11 mm)].

Preparation of *exo*-Norborneol-^{18}O.—A mixture of 21.3 g (0.162 mol) of *exo*-norbornyl chloride, 13.0 g (0.194 mol) of lithium carbonate, and 40 ml of $D_2{}^{18}O$ (Diaprep, ^{18}O 5.0%) was heated at reflux for 41 hr. The mixture was extracted with ether. The ether extracts were dried over anhydrous magnesium sulfate and evaporated to yield 17.6 g (97%) of *exo*-norborneol-^{18}O, mp 127–128°.

Preparation of Norcamphor-^{18}O.—To a mixture of 20 g (0.182 mol) of norcamphor and 25 ml of $D_2{}^{18}O$ (Diaprep, O^{18} 5.0%) was added three drops of concentrated H_2SO_4. The mixture was heated at reflux for 4.5 hr. After cooling a small amount of potassium carbonate was added. The mixture was extracted with ether. The ether was dried over magnesium sulfate and evaporated to yield 18.0 g (90% recovery) of norcamphor-^{18}O.

Preparation of *endo*-Norborneol-^{18}O.—The reduction of norcamphor-O^{18} to *endo*-norborneol-^{18}O was carried out in the same manner described for the unlabeled compound, using lithium aluminum trimethoxy hydride in THF, mp 149–150°.

Preparation of *exo*- and *endo*-Norbornyl Chlorocarbonates-^{18}O.—The preparation of both the *exo*- and *endo*-norbornyl chlorocarbonates-^{18}O was carried out in the same manner as the unlabeled compounds described above.

Preparation of *exo*- and *endo*-Norbornylcarbonic–*p*-Nitrobenzoic Anhydrides-^{18}O.—The preparation of both the *exo*- and *endo*-norbornylcarbonic–*p*-nitrobenzoic anhydrides-^{18}O was carried out in the same manner as the unlabeled compounds, using the corresponding oxygen-18-labeled chlorocarbonates.

Decomposition of the Labeled Mixed Anhydrides and Collection of the Carbon Dioxide for Mass Spectral Analysis.—The oxygen-18 content of the mixed anhydrides was determined by comparison with the corresponding labeled chlorocarbonates. Decomposition of the chlorocarbonates was carried out either neat at 130° or in the presence of an equimolar quantity of quinoline at 80°. The CO_2 evolved was subjected to mass spectral analysis. The mixed anhydrides were decomposed in solutions at 140 ± 5° and the carbon dioxide was collected for mass spectral analysis. The decompositions were carried out by one of the two following procedures.

A.—A 0.3-g sample of the anhydride in the appropriate solvent was decomposed in a 50-ml round-bottomed flask heated in an oil bath. The flask was equipped with a reflux condenser and a side arm for admission of a stream of dry nitrogen. The top of the condenser was connected to a U trap cooled with Dry Ice–acetone; this trap was connected in turn to a U trap cooled by liquid nitrogen. The liquid nitrogen trap was fitted with inlet and outlet stopcocks and standard taper joints. When sufficient carbon dioxide was condensed in the trap the stopcocks were closed, the N_2 flushing was stopped, and the sample of carbon dioxide was degassed and distilled. The ratio of m/e 46 to m/e 44 was then determined by mass spectral analysis.

B.—A 0.3-g sample of the anhydride in the appropriate solvent was placed in a thick-walled tube fitted with a vacuum stopcock and a standard taper joint. The sample was degassed on a vacuum line and the stopcock on the evacuated tube was closed. The tube was heated in an oil bath. Heating time varied from 1 to 3 hr. The tube was then connected to the vacuum line and the carbon dioxide was distilled out. The ratio of m/e 46 to m/e 44 was then determined by mass spectral analysis.

Mass Spectral Measurements.—The mass peaks used for the measurements were the parent peak at m/e 44 and the isotope parent peak at m/e 46. Each sample was repeatedly scanned over this region 15–20 times and the ratio of m/e 46 to m/e 44 was then calculated as an average of these scans.

Preparation of Optically Active 1.—The procedure of Winstein and Trifan[8] was followed for the resolution of norborneols. Starting with 168.0 g (1.5 mol) of *exo*-norborneol and 223 g (1.5 mol) of phthalic anhydride, there was obtained 255 g (65%) of *exo*-norbornyl acid phthalate, mp 97–99° (lit.[8] mp 98.6–99.7°). The acid phthalate was resolved by forming the diastereomeric mixture with cinchonidine. The resolved *exo*-norbornyl acid phthalate was obtained from the $CHCl_3$ mother liquors and crystallized from an ether–petroleum ether solution to yield 14.4 g of product, $[\alpha]^{27}D$ −8.68° (lit.[8] $[\alpha]^{24}D$ −8.49°), mp 89–90° (lit.[8] mp 89.3–90.3). The active ester was hydrolyzed by aqueous NaOH (25 g/100 ml) to give a yield of 6.1 g (98.3%) of the active norborneol, mp 126° (lit.[8] mp 126–226.6°). The optically active alcohol was immediately converted to *exo*-norbornyl *p*-nitrobenzoate, mp 77–78°, $[\alpha]^{27}D$ −8.23°, and to the optically active mixed anhydride 1, mp 53.5–55, $[\alpha]^{27}D$ −5.39°.

Decomposition of Optically Active 1.—Approximately 1-g samples of the optically active mixed anhydride, dissolved in the appropriate solvent, were decomposed at 130–140° in sealed tubes. After 10 hr of heating the tubes were opened, the solvent was removed under reduced pressure, and the *exo*-norbornyl *p*-nitrobenzoate was extracted and recrystallized from hexane. The optical activity of the *exo*-norbornyl *p*-nitrobenzoate thus obtained was measured.

Polarimetric Measurements.—The specific rotations of optically active compounds were determined on a Perkin-Elmer Model 141M polarimeter. The path length of the cell used was 1 dcm. The cell was thermostated at 27° during the runs. Chloroform was used as the solvent.

Kinetic Procedure.—The rate of the thermal decompositions of both the *exo*- and *endo*-norbornylcarbonic–*p*-nitrobenzoic anhydrides in xylene and nitrobenzene was followed by observing the decrease of the infrared anhydride carbonyl band at 1808 cm^{-1}. For each solvent and anhydride, a standard curve of known concentrations of anhydride *vs.* per cent transmittance was determined. A typical run is described.

Into a large test tube fitted with a serum cap was placed 0.6099 g of *exo*-norbornylcarbonic–*p*-nitrobenzoic anhydride in 20 ml of freshly distilled nitrobenzene. The tube was lowered into an oil bath at 138.5° ± 0.1° and after 2 min a sample was withdrawn with a syringe; this time was marked as zero time. Samples were then collected at regular intervals and frozen. When all the samples for a run were collected, the intensity of the infrared band at 1808 cm^{-1} was determined for each sample. Typically, 11 points were measured.

The rate constants were calculated using a linear least-squares fit of the integrated form of the first-order rate equation.

Quantitative Analysis of the Decomposition Products.—The appropriate mixed anhydride was decomposed in solution in a thick-walled tube fitted with a vacuum stopcock. The sample was degassed prior to heating. The samples were heated at a temperature of 130–140° for a period of 11–13 hr to effect complete decomposition.

***p*-Nitrobenzoic Anhydride, Acid, and Norbornyl Ester.**—The analytical procedure developed by Lukashevich[16] was used. The decomposition mixture was divided into two equal portions. The solvent was removed from each, under reduced pressure. Portion A was dissolved in 20 ml of dry methanol and 10 ml of dry pyridine, and was left to stand for 30 min. Portion B was dissolved in 10 ml of pyridine and 10 ml of water; this sample was immediately titrated with 0.098 *N* sodium hydroxide to the phenolphthalein end point. After 30 min, portion A was also titrated with 0.098 *N* sodium hydroxide. The titer of portion B was equivalent to all the free acid and two equivalents of acid per mole of anhydride. The titer of portion A yielded the acidity due to the free acid and one equivalent of acid per mole of anhydride. The amount of ester in the mixture was then determined by difference.

***exo*- and *endo*-Norbornyl Carbonates and Norborneol.**—These compounds were analyzed by glc, using a 6 ft × 1/4 in. glass column packed with 5% Carbowax 20M coated on Chromosorb W. The estimates were made by comparison of the glc peaks with those of appropriate standards.

(15) L. Schmerling, *J. Amer. Chem. Soc.*, **68**, 195 (1946).

(16) V. D. Lukashevich, *Khim. Prom. Moscow*, **8**, 1086 (1931), as quoted in C. W. Hammond, "Organic Analysis," Vol. III, Interscience, New York, N. Y., 1956, p 106.

Preparation of *endo*-Norbornylcarbonic-*p*-Methoxybenzoic Anhydride.—To a mixture of 3 g (0.017 mol) of *endo*-norbornyl chlorocarbonate and 2.61 g (0.017 mol) of *p*-anisic acid in 100 ml of dry ether at 0° was added, dropwise with stirring, 1.73 g (0.017 mol) of triethylamine in dry ether. The reaction mixture was stirred for 1 hr. The amine hydrochloride was filtered off and the ether solution was washed with dilute HCl, $NaHCO_3$, and water, and then dried over anhydrous magnesium sulfate. Upon evaporation of the ether an oil was obtained. Attempts to induce the oil to crystallize met with failure.

Anal. Calcd for $C_{16}H_{18}O_5$: C, 66.19; H, 6.25. Found: C, 66.04; H, 6.38.

The infrared spectrum (CCl_4) showed a double carbonyl band at 1805 and 1745 cm^{-1}, a separation of 60 cm^{-1}.

Preparation of *exo*-Norbornylcarbonic-*p*-Methoxybenzoic Anhydride.—This compound was prepared in the same manner as the endo isomer described above. An oil was obtained from the reaction mixture which crystallized upon cooling, mp 50.5–51.5°, yield, 94%.

Anal. Calcd for $C_{16}H_{18}O_5$: C, 66.19; H, 6.25. Found: C, 66.03; H, 6.36.

The infrared spectrum (CCl_4) showed a double carbonyl band at 1785 and 1727 cm^{-1}.

Registry No.—1 (exo), 35042-30-9; 2 (endo), 35042-31-0; *exo*-norbornyl carbonate, 35042-32-1; *endo*-norbornyl carbonate, 35042-33-2; *exo*-norbornyl *p*-nitrobenzoate, 10472-43-2; *endo*-norbornylcarbonic-*p*-methoxybenzoic anhydride, 35042-35-4; *exo*-norbornylcarbonic-*p*-methoxybenzoic anhydride, 35042-36-5.

Acknowledgments.—The authors are grateful to the University of Nebraska Research Council for financial support of this research.

Azaindolizines. 2. N-5 and C-1 and C-3 Protonation of 1,3-Disubstituted 5-Azaindolizines

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1,2,3,6-Tetramethyl-5-azaindolizine (**2e**) and 1,3,6-trimethyl-2-phenyl-5-azaindolizine (**2f**) have been shown by pmr studies in trifluoroacetic acid to protonate solely at C-3. The di-5-azaindolizinylmethane (**6**) in trifluoroacetic acid diprotonates to give the di C-3 cation (**7**, 32%) and the C-3/N-5′ dication (**8**, 68%). The perchlorates of **2e** and **2f**, when examined in trifluoroacetic acid, show protonation at N-5. Equilibration in solution leads to the formation of the 1-H (**4c** and **4d**) and 3-H cations (**3c** and **3d**) at the expense of the N-5 cations (**5a** and **5b**). The 3-H cation, initially observed in low concentration is eventually the sole cation established in solution.

Carbon protonation of heteroaromatic systems containing a π-equivalent nitrogen is exceptional and is shown solely by the 2*H*-cyclopenta[*d*]pyridazine and 5-azaindolizine structures **1a–c**[1] and **2a–d**.[2] Both these systems can be considered to be nitrogen heteroanologs of azulene which contain a π-excessive and a π-equivalent nitrogen.[3] Protonation of these compounds occurs at carbon with the establishment of a 6-π cation in the six-membered ring; other similarly structured nitrogen heteroanologs of azulene do not protonate at carbon but at the π-equivalent nitrogen with the formation of a 10-π cation.[2,4,5]

Previous pmr studies of 5-azaindolizines (**2a–d**) and their perchlorates[6] showed protonation of **2a** and **2b** to occur at C-3 to give the 3-H cations **3a** and **3b** whereas their corresponding 3-methyl derivatives **2c** and **2d** protonated solely and predominantly at C-1 to give the 1-H cations **4a** and **4b**. This suggests that the 3-methyl group sterically inhibits protonation at C-3 in a manner akin to that found in 3-alkylindolizines.[7,8] None of the 5-azaindolizines (**2a–d**) or their perchlorates in trifluoroacetic acid[9] showed signals which could be attributed to the presence of a N-5 protonated cation. This suggests that if the N-5 cation is formed it is either too transient or in concentrations too low to be detected by pmr spectroscopy. 1,3-Disubstituted 5-azaindolizines (**2e**, **2f**, and **6**) were synthesized to test whether this steric factor would sufficiently suppress C-1 and or C-3 protonation to cause protonation at the π-equivalent N-5 site with the formation of the corresponding 10-π cations.

Results

The pmr spectra of 1,3-dimethyl-5-azaindolizines (**2e** and **2f**) in trifluoracetic acid[10] showed them to protonate solely at the C-3 position to give the corresponding 6-π 3-H cations **3c** and **3d**. However, the pmr spectra of the isolated perchlorates of **2e** and **2f**, prepared by the addition of perchloric acid to an ethyl acetate solution of **2e** and **2f**, gave, when dissolved in trifluoracetic acid, spectra which differed from the corresponding spectra of the 3-H cations **3c** and **3d**. These first recorded spectra of the perchlorates[10] are considered to arise from protonation of **2e** and **2f** at the respective N-5 sites to give the 10-π cations **5a** and **5b**. The spectra of the cations **5a** and **5b** gradually became more complex with time. After approximately 6 hr at 25° or 1

(1) A. Anderson and D. Forky, *J. Amer. Chem. Soc.*, **91**, 924 (1969).

(2) M. Fraser, *J. Org. Chem.*, **36**, 3087 (1971).

(3) A π equivalent heteroatom provides one electron and a π-excessive heteroatom provides two electrons to the π structure.

(4) K. Hofner and M. Kreuder, *Angew. Chem.*, **73**, 657 (1961).

(5) W. Armarego, *J. Chem. Soc.*, 4226 (1964).

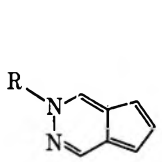
(6) Perchlorates of (**2a–d**) were prepared originally from ethanol; subsequently better yields were obtained using ethyl acetate as solvent.

(7) M. Fraser, S. McKenzie, and D. Reid, *J. Chem. Soc. B*, 44 (1966).

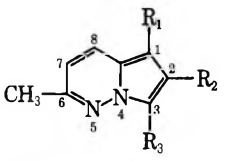
(8) W. Armarego, *ibid.*, 191 (1966).

(9) Spectra of the perchlorates of (**2a–f**) in $(CD_3)_2SO$ were identical in pattern with the spectra of (**2a–f**) in $CDCl_3$ due to the loss of perchloric acid.

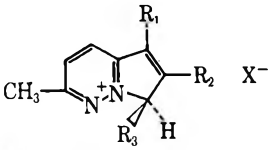
(10) Pmr spectra of **2e** in CF_3CO_2H (cation **3c**), **2e** $HClO_4$ in CF_3CO_2H (cation **5a**), **2e** $HClO_4$ in CF_3CO_2H after 15 min (**5a**, **3c**, and **4c**), and **6** in CF_3CO_2H (cations **7** and **8**), and ir spectra of **2a** $HClO_4$ and **2e** $HClO_4$ will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 Sixteenth St., N.W., Washington, D. C. 20036, by referring to code number JOC-37-3027. Remit cheek or money order for $3.00 for photocopy or $2.00 for microfiche.

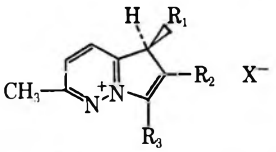


1a, R = H
b, R = CH_3
c, R = Ph



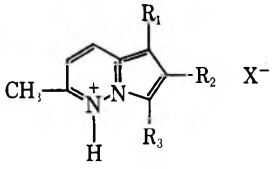
2a, $R_1 = R_3 = H$; $R_2 = CH_3$
b, $R_1 = R_3 = H$; $R_2 = Ph$
c, $R_1 = H$; $R_2 = R_3 = CH_3$
d, $R_1 = H$; $R_2 = Ph$; $R_3 = CH_3$
e, $R_1 = R_2 = R_3 = CH_3$
f, $R_1 = R_3 = CH_3$; $R_2 = Ph$
g, $R_1 = CHO$; $R_2 = R_3 = CH_3$
h, $R_1 = CHO$; $R_2 = Ph$; $R_3 = CH_3$

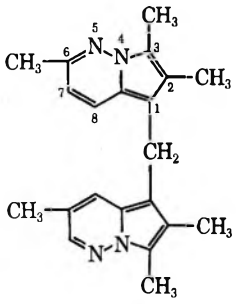




3a, $R_1 = R_3 = H$; $R_2 = CH_3$
b, $R_1 = R_3 = H$; $R_2 = Ph$
c, $R_1 = R_2 = R_3 = CH_3$
d, $R_1 = R_3 = CH_3$; $R_2 = Ph$

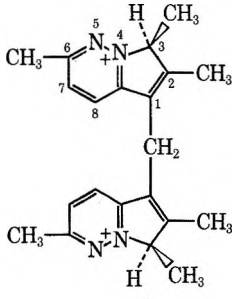
4a, $R_1 = H$; $R_2 = R_3 = CH_3$
b, $R_1 = H$; $R_2 = Ph$; $R_3 = CH_3$
c, $R_1 = R_2 = R_3 = CH_3$
d, $R_1 = R_3 = CH_3$; $R_2 = Ph$

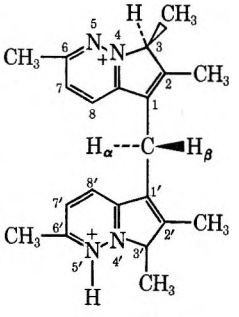




5a, $R_1 = R_2 = R_3 = CH_3$
b, $R_1 = R_3 = CH_3$; $R_2 = Ph$

6





7

8

hr at 50° they became identical with the spectra of the corresponding 3-H cations **3c** and **3d**. These observations show that the site of protonation of **2e** and **2f** depends upon the conditions of protonation. When trifluoroacetic acid is used as solvent and protonating agent the conditions of protonation are reversible and conducive to the selective formation of the thermodynamically more stable carbon protonated cations **3c** and **3d**.[11] On the other hand when the highly acidic medium of perchloric acid in ethyl acetate is used, the conditions of protonation are less reversible and protonation at the high-electron density[2,12] π-equivalent N-5 site is kinetically favored. In trifluoroacetic acid, proton exchange between cation and solvent is facile and the initially observed N-5 cations **5a** and **5b** of the perchlorates of **2e** and **2f** equilibrate to the more stable C-1- and C-3-protonated cations to give a complex spectra consisting of the superposed spectra of the three cations **3c**, **4c**, and **5a**[10] and **3d**, **4d**, and **5b**, respectively. The intensity of the signals of the 1-H cations **4c** and **4d**, though initially greater than those of the 3-H cations **3c** and **3d**, are transient and eventually the only cations established in trifluoroacetic acid are the 3-H cations.

The protonation of the 1,3-disubstituted 5-azaindolizine (**6**) in trifluoroacetic acid occurs with the formation of a mixture of the di C-3 protonated cation (**7**, 32%) and the C-3/N-5′ protonated dication (**8**, 68%).[10] The isolation of the perchlorates of **6** from ethyl acetate or other solvents was unsuccessful, but the percentages of the cations **7** and **8** did not materially alter either on standing or on the addition of perchloric acid to the trifluoroacetic acid solution of **6**.

Experimental Section

Melting points were determined by the capillary method and are uncorrected. Elemental analyses were performed by the analytical laboratories of Aberdeen University. Infrared spectra were measured with a Unicam SP200 spectrometer and absorption peaks were recorded in wave numbers (cm^{-1}). Ultraviolet spectra were measured with a Unicam SP800 spectrometer. Light absorption data refer to solutions in ethanol; principal maxima are italized; sh = shoulder, br = broad, and infl = inflection. Pmr 100-MHz spectra were recorded at *ca.* 25° with a Varian HA-100B spectrometer using tetramethylsilane as an internal standard. Unless otherwise stated values given on the δ scale refer to singlet absorptions, coupling constants in cycles per second (Hz), and integration values and signal assignment are in parentheses. For multiplets d = doublet, q = quartet, and t = triplet.

Procedures.—Solutions were dried over anhydrous magnesium sulfate and solvents evaporated at reduced pressure on a rotatory film evaporator. Perchloric acid refers to 70% w/w Analar perchloric acid. Petroleum ether was of boiling point range 40–60°.

The synthesis of azaindolizines (**2a–d**) has been previously reported.[2]

Formylation of 2,3,6-Trimethyl- (2c) and 3,6-Dimethyl-2-phenyl-5-azaindolizine (2d) to Give, Respectively, 1-Formyl-2,3,6-trimethyl- (2g) and 1-Formyl-3,6-dimethyl-2-phenyl-5-azaindolizine (2h).—A solution of phosphoryl oxychloride (1.69 g, 1.0 ml, 11 mmol) in dimethylformamide (10 ml) was slowly added with stirring to a solution of the 5-azaindolizines (**2c–2d**) (10 mmol) in dimethylformamide (10 ml). Once the exothermic reaction which ensued had subsided the resulting brown solution was gently warmed for 15 min, left overnight, and then poured into 2 *M* aqueous sodium hydroxide (150 ml). On cooling yellow needles of the crude aldehydes precipitated. These were filtered off, washed with water, and dried *in vacuo*. The crude aldehyde was recrystallized (benzene–petroleum ether 1:4) and then vacuum sublimed. 2,3,6-Trimethyl-5-azaindolizine (**2c**) (1.6 g) gave 1-formyl-2,3,6-trimethyl-5-azaindolizine (**2g**, 1.35 g, 72%) as long straw colored needles: mp 94°; λ_{max} 380 (br), 317 (br), 298 (br), 255 (br), 238 (infl), *232* nm (log ϵ 3.88, 3.92, 3.90, 4.04, 4.25, 4.27, respectively); ir (Nujol) 715, 805, 1310, 1650, (C=O) cm^{-1}; pmr ($CDCl_3$) 2.46 (3 H, 2-Me), 2.50 (3 H, 3-Me), 2.55 (3 H, 6-Me), 6.77 (d, J = 9.0 Hz, 1 H, H-7), 8.32 (d, J = 9.0 Hz, 1 H, H-8), and 10.09 (1 H, 1-formyl).

Anal. Calcd for $C_{11}H_{12}N_2O$: C, 70.2; H, 6.4; N, 14.9. Found: C, 70.3; H, 6.6; N, 14.6.

3,6-Dimethyl-2-phenyl-5-azaindolizine (**2d**, 2.02 g) gave 1-formyl-3,6-dimethyl-2-phenyl-5-azaindolizine (**2h**, 1.86 g, 78%) as bright yellow needles: mp 118°; λ_{max} 384 (br), 320 (br), 295 (br), 250 (infl), *235* (br) nm (log ϵ 4.93, 4.83, 4.89, 5.22, 5.35, respectively); ir (Nujol) 740, 1320, 1545, 1610, 1640 (C=O) cm^{-1}; pmr ($CDCl_3$) 2.51 (3 H, 3-Me), 2.58 (3 H, 6-Me), 6.86 (d, J = 9.0 Hz, 1 H, H-7), 7.43 (5 H, 2-Ph), 8.55 (d, J = 9.0 Hz, 1 H, H-8), and 9.83 (1 H, 1-formyl).

(11) Cotterall, "Strength of Chemical Bonds," Butterworths, 1954, p 272.
(12) M. Zupan, B. Stanovvick, and M. Tisler, *J. Heterocycl. Chem.*, **8**, 1 (1971).

Anal. Calcd for $C_{16}H_{14}N_2O$: C, 76.7; H, 5.6; N, 11.2. Found: C, 76.5; H, 5.7; N, 10.9.

Reduction of Aldehydes 2g and 2h to Give, Respectively, 1,2,3,6-Tetramethyl-5-azaindolizine (2e) and 1,3,6-Trimethyl-2-phenyl-5-azaindolizine (2f).—A solution of the aldehyde (2g–2h, 5 mmol) in ether (30 ml) was added dropwise during 30 min to a stirred solution of lithium aluminum hydride (1.0 g, 26 mmol) and aluminum chloride (5 g, 40 mmol) in ether (120 ml). The reaction mixture was stirred for 60 min before being poured into ice cold 0.05 *M* sulfuric acid. The acid solution was basified with potassium carbonate and extracted with ether and the ether extract washed, dried, and evaporated to leave the crude 5-azaindolizine.

1-Formyl-2,3,6-trimethyl-5-azaindolizine (2g, 0.94 g) gave the crude 1,2,3,6-tetramethyl-5-azaindolizine (2e) as a brown oil which on distillation, 155–165° (15 mm), gave 2e as a golden oil (0.31 g, 36%): λ_{max} 400 (br), 316 (br), 304 (br), *254*, 219 nm (log ϵ 3.51, 3.29, 3.25, 4.46, 4.37, respectively); ir (thin film) 780, 1160, 1315, 1620 cm^{-1}. The pmr ($CDCl_3$) of 2e showed 2.21 or 2.24 (3 H, 2-Me), 2.24 or 2.21 (3 H, 1-Me), 2.43 (3 H, 3-Me), 2.48 (3 H, 6-Me), 6.18 (d, J = 8.5 Hz, 1 H, H-7), and 7.45 (d, J = 8.5 Hz, 1 H, H-8). The assignment of the H-7 and H-8 AB doublet system is substantiated by a comparative examination of the pmr ($CDCl_3$) spectra of 2e with its precursor aldehyde 2g. In 2g the 1-formyl group by peri effect would be expected to cause a preponderantly greater shift in the H-8 doublet which occurs at δ 8.32, a downfield shift of 87 Hz from the position assigned to the H-8 doublet of 2e. The H-7 doublet of 2g is relatively less affected by the 1-formyl group and occurs at δ 6.71, a downfield shift of 59 Hz from the H-7 doublet of 2e: pmr (CF_3COOH)[10] 1.84 (d, J = 7.8 Hz, 3 H, 3-Me), 2.27 (3 H, 2-Me), 2.32 (3 H, 1-Me), 2.83 (3 H, 6-Me), 5.27 (q, J = 7.8 Hz, 1 H, 3-methine), 8.15 (1 H, H-7), and 8.15 (1 H, H-8). The AB doublet system of 2e in deuteriochloroform assigned to H-7 and H-8 with signals at δ 6.18 and 7.45 merge into a 2 H singlet at δ 8.15 in trifluoroacetic or deuteriotrifluoroacetic acid.

Anal. Calcd for $C_{11}H_{14}N_2$: C, 75.8; H, 8.1; N, 16.1. Found: 75.6; H, 8.3; N, 16.0.

1-Formyl-3,6-dimethyl-2-phenyl-5-azaindolizine (2h, 1.13 g) gave the crude 1,3,6-trimethyl-2 phenyl 5-azaindolizine (2f) as a brown oil which subsequently solidified. Vacuum sublimation gave 2f as a yellow solid (0.43 g, 38%): mp 67°; λ_{max} 395 (br), 310 (br), *262* nm (log ϵ 4.48, 3.25, 3.17, respectively); ir (Nujol) 700, 770, 1196, 1610 cm^{-1}; pmr ($CDCl_3$) 2.28 (3 H, 1-Me), 2.44 (3 H, 3-Me), 2.51 (3 H, 6-Me), 6.26 (d, J = 8.5 Hz, 1 H, H-7), 7.37 (5 H, 2-Ph), and 7.54 (d, J = 8.5 Hz, 1-H, H-8); pmr (CF_3COOH) 1.78 (d, J = 7.0 Hz, 3 H, 3-Me), 2.47 (3 H, 1-Me), 2.89 (3 H, 6-Me), 5.40 (q, J = 7.0 Hz, 1 H, 3-methine), 7.58 (5 H, 2-Ph), 8.17 (d, J = 9.0 Hz, 1 H, H-7), and 8.33 (d, J = 9.0 Hz, 1 H, H-8).

Anal. Calcd for $C_{16}H_{16}N_2$: C, 81.1; H, 6.8; N, 11.9. Found: C, 81.4; H, 6.8; N, 11.9.

By analogy with the 1- and 3-methine and methylene resonances of indolizines[7,8,12] and 5-azaindolizines[2,14] protonation of 2e and 2f in trifluoroacetic acid is inferred to occur at C-3. The deuteriotrifluoroacetic acid spectra of 2e and 2f are similar in pattern to their spectra in trifluoroacetic acid, apart from the absence of the 1 H quartets at δ 5.27 and 5.40 assigned to the 3-methine hydrogens and the spin coupled 3 H, 3-methyl, high-field doublets at δ 1.84 and 1.78, which appear as 3 H singlets at δ 1.86 and 1.80, respectively.

1,2,3,6-Tetramethyl-5-azaindolizinium Perchlorate (3c, 4c, and 5a, X = ClO_4) and 1,3,6-Trimethyl-2-phenyl-5-azaindolizinium Perchlorate (3d, 4d, and 5b, X = ClO_4).—Perchloric acid (3.0 ml, 37% excess) was added to a solution of 2e–2f (2 mmol) in ethyl acetate (5 ml). On cooling 5-azaindolizinium perchlorate precipitated and was collected.

1,2,3,6-Tetramethyl-5-azaindolizine (2e, 0.35 g) gave 1,2,3,6-tetramethyl-5-azaindolizinium perchlorate (0.32 g, 73%) as orange colored needles: mp 105–108°; ir (Nujol) 1100 (ClO_4), 1260, 1315, 1405, 1520, 1640, 3500 cm^{-1}; pmr (CF_3COOH), the first recorded spectrum was attributed to the N-5 cation 5a,[10] 2.37 or 2.44 (3 H, 1-Me), 2.44 or 2.37 (3 H, 2-Me), 2.69 (3 H, 3-Me), 2.80 (3 H, 6-Me), 6.64 (d, J = 8.5 Hz, 1 H, H-7), and 8.15 (d, J = 8.5 Hz, 1 H, H-8). A broad singlet or triplet which would be expected to arise from the proton bonded to nitrogen was not discernible, though it may be obscured by the broad acid–solvent peak below δ 9.50. The pmr spectrum of other azaindolizines, for which N-protonation has previously been established, have also characteristically shown the absence of a signal attributable to a proton bonded to nitrogen and other incidences of the nonappearance of a proton bonded to nitrogen have been cited.[1,2,15,16] The first recorded spectrum of 1,2,3,6-tetramethyl-5-azaindolizinium perchlorate in deuteriotrifluoroacetic acid was identical in pattern with its first spectrum in trifluoroacetic acid showing that the nitrogen-protonated cation 5a is formed rather than a carbon-protonated cation. When the first spectrum of 1,2,3,6-tetramethyl-5-azaindolizinium perchlorate in trifluoroacetic acid is retraced after approximately 15 min, a complex spectrum constituted of the three superposed spectra of the three cations 5a (15%), 3c (35%), and 4c (50%) is obtained.[10] The signals of the transient 1-H-cation 4c were located as the residual signals in this spectrum after assignment of the signals of the 3-H and N-5 cations 3c and 5a; they occurred at (CF_3COOH) 1.67 (d, J = 8.0 Hz, 3 H, 1-Me), 2.31 (3 H, 2-Me), 2.52 (3 H, 3-Me), 2.93 (3 H, 6-Me), 4.10 (q, J = 8.0 Hz, 1 H, 1-methine), 8.14 (d, J = 9.0 Hz, 1 H, H-7), and 8.44 (d, J = 9.0 Hz, 1 H, H-8); (CF_3COOD) 1.66 (3 H, 1-Me), 2.32 (3 H, 2-Me), 2.53 (3 H, 3-Me), 2.94 (3 H, 6-Me), 8.14 (d, J = 9.0 Hz, 1 H, H-7), and 8.44 (d, J = 9.0 Hz, 1 H, H-8). After approximately 6 hr the only signals remaining were identical in pattern with those of the spectrum of 2e in trifluoroacetic acid, due to the presence of the 3-H cation 3c.

Anal. Calcd for $C_{11}H_{15}ClN_2O_4$: C, 48.1; H, 5.1; N, 10.2; Cl, 12.9. Found: C, 47.8; H, 5.3; N, 10.4; Cl, 12.7.

1,3,6-Trimethyl-2-phenyl-5-azaindolizine (2f, 0.43 g) gave 1,3,6-trimethyl-2-phenyl-5-azaindolizinium perchlorate (0.38 g, 72%) as orange colored needles: mp 187°; ir (Nujol) 775, 1060 (ClO_4), 1100 (ClO_4), 1190, 1260, 1320, 1410, 1520, 1650, 3300 cm^{-1}. The first recorded spectrum, taken 15 min after dissolving the perchlorate in trifluoroacetic acid, showed a preponderance of the N-5-protonated cation 5b (80%) whose signals occur at 2.43 (3 H, 1-Me), 2.65 (3 H, 3-Me), 2.82 (3 H, 6-Me), 6.67 (d, J = 8.5 Hz, 1 H, H-7), 7.52 (5 H, 2-Ph), and 8.22 (d, J = 8.5 Hz, 1 H, H-8). The 1-H cation 4d was also present (on average *ca.* 20%, its low-field signals being recorded first were weaker than the high-field signals): 1.57 (d, J = 7.0 Hz, 3 H, 1-Me), 2.69 (3 H, 3-Me), 2.96 (3 H, 6-Me), 4.05 (q, J = 7.0 Hz, 1 H, 1-methine), 7.57 (5 H, 2-Ph), 8.16 (d, J = 9.0 Hz, 1 H, H-7), and 8.54 (d, J = 9.0 Hz, 1 H, H-8); pmr (CF_3COOD) 1.56 (3 H, 1-Me), 2.69 (3 H, 3-Me), 2.96 (3 H, 6-Me), 5.75 (5 H, 2-Ph), 8.16 (d, J = 9.0 Hz, 1 H, H-7), and 8.54 (d, J = 9.0 Hz, 1 H, H-8). This first recorded spectrum of the perchlorate of 2f, when retraced after a further 5 min, showed a marked increase in the concentration of the 1-H cation 4d (55%) and the emergence of the 3-H cation 3d (20%). After 1 hr the ratio of the three cations 3d, 4d, and 5b was approximately 82, 12, and 6%, respectively. Finally after about 6 hr the spectrum of 1,3,6-trimethyl-2-phenyl-5-azaindolizinium perchlorate became identical in pattern with the spectrum of 2f in trifluoroacetic acid which showed solely the presence of the 3-H cation 3d.

Anal. Calcd for $C_{16}H_{17}ClN_2O_4$: C, 56.8; H, 5.1; N, 8.3; Cl, 10.3. Found: C, 56.8; H, 5.0; N, 8.6; Cl, 10.5.

2,2′,3,3′,6,6′-Hexamethylmethylene-1,1′-di-5-azaindolizine (6).—Addition of 40% aqueous formaldehyde (2.0 ml) to a solution of 2,3,6-trimethyl-5-azaindolizine (2c, 0.8 g, 5 mmol) in ethanol (3 ml) gave on warming a cloudy solution. This solution, when heated a further 10 min and then cooled, precipitated brilliant yellow needles of the symmetrical di-5-azaindolizinylmethane (6, 0.81 g, 98%); recrystallization from ethyl acetate gave mp 158–159°; λ_{max} 397 (br), 315 (br), 303 (br), *251*, 238 (infl) nm (log ϵ 4.76, 4.54, 4.54, 5.62, 5.44, respectively), ir (Nujol) 700, 785, 800, 1150, 1260, 1290, 1310, 1325, 1530, 1550, 1620 cm^{-1}; pmr ($CDCl_3$) 2.13 (6 H, 2-Me), 2.39 (6 H, 3-Me), 2.46 (6 H, 6-Me), 4.11 (2 H, bridge methylene), 6.07 (d, J = 9.0 Hz, 2 H, H-7), and 7.10 (d, J = 9.0 Hz, 2 H, H-8); pmr (CF_3COOH)[10] cation 7 (32%), 1.92 (d, J = 7.5 Hz,

(13) M. Fraser, A. Malera, B. Malloy, and D. Reid, *J. Chem. Soc.*, 3288 (1962).

(14) W. Flitsch and U. Kramer, *Justus Liebigs Ann. Chem.*, **735**, 35 (1970).

(15) R. Himman and E. Whipple, *J. Amer. Chem. Soc.*, **84**, 2539 (1962).

(16) Pmr studies failed to reveal the presence of a proton bonded to nitrogen in trifluoroacetic acid solution possibly due to a rapid rate of exchange with solvent. However, the ir spectra of the perchlorates of **2e** and **2f** had in common with other N-protonated azaindolizinium perchlorates and in contrast to the perchlorates of **2a**, **2b**, and **2d**, a broad, medium strong absorption in the 3300–3500-cm^{-1} region attributable to a proton bonded to nitrogen.

6 H, 3-Me), 2.42 (6 H, 2-Me), 2.80 (6 H, 6-Me), 4.25 (2 H, bridge methylene), 5.52 (q, J = 7.5 Hz, 2 H, 3-methine), 8.16 (2 H, H-7), and 8.16 (2 H, H-8); cation **8** (68%), 1.93 (d, J = 7.5 Hz, 3 H, 3-Me), 2.30 (3 H, 2'-Me), 2.40 (3 H, 2-Me), 2.67 (3 H, 3'-Me), 2.80 (3 H, 6-Me), 2.85 (3 H, 6'-Me), 4.36 (t, J = 14 Hz, 2 H, $H_\alpha H_\beta$ bridge methylene), 5.44 (q, J = 7.5 Hz, 1-H, 3-methine), 6.82 (d, J = 8.5 Hz, 1 H, H-7'), 7.77 (d, J = 8.5 Hz, 1 H, H-7), 7.97 (d, J = 8.5 Hz, 1 H, H-8), and 8.32 (d, J = 8.5 Hz, H-8'). Cation **8** showed no signal arising from a proton bonded to nitrogen; the two hydrogens H_α and H_β of the bridging methylene though magnetically nonequivalent would appear to experience a similar magnetic environment since the anticipated AB quartet is observed rather as a broad singlet at δ 4.36 with small wings at δ 4.50 and 4.24, the latter wing being obscured by the bridging methylene signal of the cation **7**.

Anal. Calcd for $C_{21}H_{24}N_4$: C, 75.9; H, 7.3; N, 16.8. Found: C, 75.8; H, 7.2; N, 16.8.

Registry No.—**2e**, 34876-65-8; **2f**, 34876-66-9; **2g**, 34876-67-0; **2h**, 34876-68-1; **3c**, 34876-69-2; **3d**, 34876-70-5; **4c**, 34876-71-6; **4d**, 34876-72-7; **5a**, 34876-73-8; **5b**, 34876-74-9; **6**, 34876-75-0.

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Synthesis of β-Cyano-α,β-Unsaturated Isocyanates and Their Reactions with Hydrogen Chloride

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When enaminonitriles with a primary nitrogen atom were allowed to react with phosgene in refluxing ethyl acetate, N-acylation occurred to give the corresponding β-cyano-α,β-unsaturated isocyanates in 37–79% yield. The reaction of thus obtained isocyanates with hydrogen chloride in dioxane at 100° for 24 hr gave 5,6-disubstituted uracils in good yields. Reaction of isocyanate **2c** with hydrogen chloride at 60° for 6 hr afforded 6-chloro-5-methyl-4-phenyl-2(3*H*)-pyrimidinone in 74% yield.

The reactions of enaminonitriles having a primary or a secondary nitrogen atom with acylating agents such as carboxylic acid chlorides and carboxylic acid anhydrides have been reported.[1-3] In these reactions C-acylation or N-acylation products were obtained, depending on the nature of enaminonitriles and acylating agents.

Recently, Samaraj, *et al.*,[4] have reported the synthesis of α,β-unsaturated isocyanates from ketimine and phosgene. However, the reaction of primary enamines (tautomers of ketimines) with phosgene has not been reported yet.

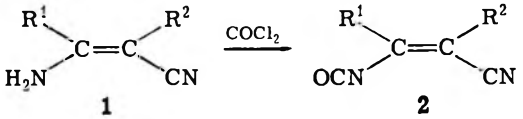
In addition, recently N-acylations of nitriles in the presence of hydrogen halide with acylating agents have been reported to yield various heterocycles. Simchen, *et al.*, have widely investigated the intramolecular cyclization reactions of various acid chlorides[5-9] or isocyanates[10] having a cyano group in the same molecule in the presence of hydrogen halide; for instance, they obtained quinazolones from *o*-cyanophenyl isocyanates.[10] In view of these studies intramolecular cyclization of β-cyano-α,β-unsaturated isocyanates is synthetically of interest.

We have now attempted the synthesis of β-cyano-α,β-unsaturated isocyanates by reacting phosgene with enaminonitriles, easily obtainable by condensation of nitriles in the presence of sodium.[11,12] In addition, the cyclization reaction of isocyanates thus obtained was carried out.

Results and Discussion

Synthesis of Unsaturated Isocyanates.—All the enaminonitriles used in this study were shown to exist predominantly as enamine tautomer in $CDCl_3$ by nmr analysis.

When enaminonitriles **1a–d** were allowed to react with phosgene in refluxing ethyl acetate, the expected N-acylation occurred to give the corresponding β-cyano-α,β-unsaturated isocyanates **2a–d** in 37–79% yield.



1 **2**

a, $R^1 = CH_3CH_2$; $R^2 = CH_3$
b, $R^1 = CH_3CH_2CH_2$; $R^2 = CH_3CH_2$
c, $R^1 = C_6H_5$; $R^2 = CH_3$
d, $R^1, R^2 = -(CH_2)_4-$

In the cases of **1a** and **1b**, considerable amounts of resinous substances were formed. They may be formed by polymerization of once-formed isocyanates or may be derived from C-phosgenated intermediates; this is not clear at present.

The structures of **2a–d** were established on the basis of ir and nmr spectra and elemental analysis. Yields and spectra are listed in Table I. Nmr spectra of **2a–c** showed that they are mixtures of the cis and trans isomer.

(1) E. Benary and M. Schmidt, *Chem. Ber.*, **54**, 2157 (1921).
(2) E. Benary and W. Lau, *ibid.*, **56**, 591 (1923).
(3) H. E. Schroeder and G. W. Rigby, *J. Amer. Chem. Soc.*, **71**, 2205 (1949).
(4) L. I. Samaraj, O. W. Wischenewski, and G. I. Derkatsch, *Angew. Chem.*, **80**, 620 (1968).
(5) G. Simchen, *ibid.*, **78**, 674 (1966).
(6) G. Simchen and W. Krämer, *Chem. Ber.*, **102**, 3656 (1969).
(7) G. Simchen, *ibid.*, **103**, 389 (1970).
(8) G. Simchen, *ibid.*, **103**, 407 (1970).
(9) G. Simchen and J. Wenzelburger, *ibid.*, **103**, 413 (1970).
(10) G. Simchen, G. Entenmann, and R. Zondler, *Angew. Chem.*, **82**, 548 (1970).
(11) H. Adkins and G. M. Whitman, *J. Amer. Chem. Soc.*, **64**, 150 (1942).
(12) G. A. Reynolds, W. J. Humphlett, R. W. Swamer, and C. R. Hauser, *J. Org. Chem.*, **16**, 165 (1951).

Table I

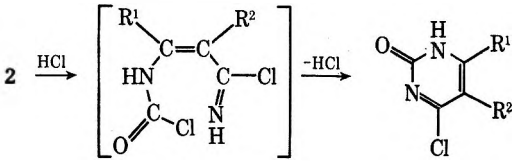
β-Cyano-α,β-Unsaturated Isocyanates 2[a,c]

Compd	Bp, °C (mm)	Yield, %	Ir,[b] cm⁻¹ NCO	CN	C=C
2a	85–87 (17)	37	2262	2212	1627
2b	89–90.5 (10)	55	2260	2221	1623
2c	121–123 (1.5)	72	2257	2210	1613
2d	108 (2)	79	2255	2215	1642

[a] Nmr (CCl_4): 2a, δ 1.24 (t, 3 H, J = 7.5 Hz), 1.89 (s) and 1.91 (s) (total 3 H), 2.62 (q, 2 H, J = 7.5 Hz); 2b, 1.04 (t, 3 H, J = 7.5 Hz), 1.14 (t, 3 H, J = 7.5 Hz), 1.65 (m, 2 H), 2.41 (m, 4 H); 2c, 1.85 (s) and 2.05 (s) (area ratio 1:2.6) (total 3 H), 7.40 (m, 5 H); 2d, *ca.* 1.7 (br, 4 H), *ca.* 2.3 (br, 4 H). [b] Liquid film. [c] Satisfactory analytical values (±0.4% for C, H, and N) were reported for 2a–c. The carbon value for 2d was 0.9% low: Ed.

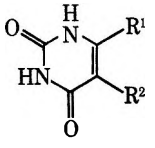
The reaction of 1-amino-2-cyanocyclopentene with phosgene also gave the corresponding isocyanate (22% yield), which was characterized only by ir spectroscopy since it was very unstable and became dark in a few days at room temperature.

Reactions of Isocyanates with Hydrogen Chloride.— In the reaction of isocyanate 2 with hydrogen chloride, the formation of 6-chloro-2(3*H*)-pyrimidinone **4** *via* intermediate **3** was expected.



3 4

The cyclization of 2 was carried out with a large excess of anhydrous hydrogen chloride in a glass tube. Dioxane was used as the solvent since hydrogen chloride is very soluble in it. The reaction at 100° for 24 hr did not give the expected 2-pyrimidinone **4**, but afforded 5,6-disubstituted uracil **5** in good yield (Table II).



5

In the cases of the reactions of **2b** and **2d** the yields of uracils were slightly low and much unidentified resinous substantces were formed; this is probably due to side reactions of the isocyanates such as degradation and polymerization. The structures of uracils were established by ir, nmr, and mass spectroscopy and elemental analysis. Yields and spectra are summarized in Table II.

The reaction of **2c** with hydrogen chloride in dioxane at 60° for 6 hr gave the expected 6-chloro-5-methyl-4-phenyl-2(3*H*)-pyrimidinone (**4c**) in 74% yield along with **5c** (10% yield).

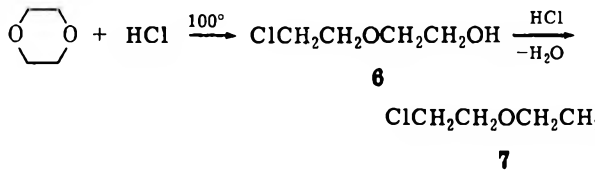
To clarify the reaction pathway to uracils, by-products of the reaction at 100° were analyzed; a small amount of a mixture of 2-(2-chloroethoxy)-ethanol (**6**) (minor) and bis(2-chloroethyl) ether (**7**) (major) was obtained in every case. The cleavage of the ether linkage by hydrogen halide to an alcohol and a halide and halogenation of the alcohol by hydrogen halide are well known.[13] In fact, the reaction of dioxane with hydrogen chloride at 100° for 24 hr in a glass tube gave a small amount of a mixture of **6** and **7**. In this case **6** was the major product.

Table II

5,6-Disubstituted Uracils[a,f]

Compd	Mp, °C	Recrystn solvent	Yield, %	Ir,[b] cm⁻¹	Mass (M⁺)
5a	258–260	EtOH–H_2O (1:3)	70	1710, 1645	154
5b	229–232[c]	EtOH	47	1735, 1670, 1643 (sh)	182
5c	241–243	Dioxane	95	1705, 1665,[e] 1640	202
5d	297–301[d]	MeOH	58	1705, 1640	166

[a] Nmr: 5a (DMSO-d_6) δ 1.09 (t, 3 H, J = 7.5 Hz), 1.75 (s, 3 H), 2.37 (q, 2 H, J = 7.5 Hz), 10.57 (br s, 1 H), 10.90 (br s, 1 H); 5b, (CF_3COOH) 1.20 (m, 6 H), 1.82 (m, 2 H), 2.65 (m, 4 H), 10.27 (br s, 1 H); 5c, (DMSO-d_6), 1.68 (s, 3 H), 7.42 (s, 5 H), 10.79 (br s, 1 H), 11.04 (br s, 1 H); 5d (CF_3COOH), 1.90 (br s, 4 H), 2.54 (br, 4 H), 10.14 (br s, 1 H). [b] Nujol. [c] Mp 228–229°: Z. Bukac and J. Sebenda, *Collect. Czech. Chem. Commun.*, **32**, 3537 (1967); *Chem. Abstr.*, **68**, 12940 (1968). [d] Mp 295–297°: Z. Budesinsky and F. Roubinec, *Collect. Czech. Chem. Commun.*, **29**, 2341 (1964); *Chem. Abstr.*, **62**, 555 (1965). [e] The crude product has different absorption bands in the C=O region, 1730, 1700 (sh), and 1675 cm^{-1}. When it was recrystallized from dioxane or heated around 240°, crystals which have absorption bands shown in the table were obtained. This phenomenon may be explained in terms of the difference of crystal structures. [f] Satisfactory analytical values (±0.3% for C, H, and N) were reported for all compounds in table: Ed.

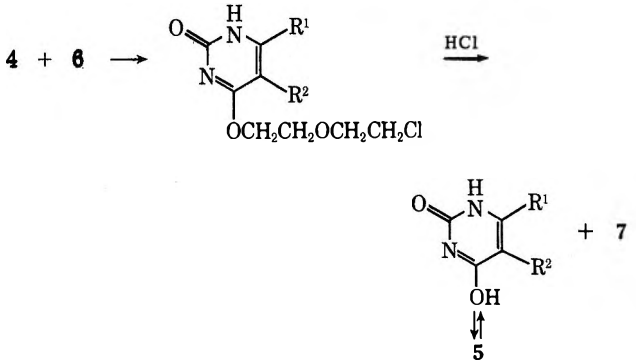


6

$ClCH_2CH_2OCH_2CH_2Cl$

7

Moreover, the reaction of **4c** with hydrogen chloride in dioxane at 100° for 20 hr afforded uracil **5c** in 88% yield. Pyrimidinone **4c** was easily hydrolyzed to **5c** upon refluxing in H_2O–MeOH for 30 min. On the basis of these facts, uracils were apparently formed *via* 2-pyrimidinone **4** according to the following reaction scheme.



5

Uracils might be formed in part by the reaction of **4** with water formed during chlorination of **6** to **7**.

Under such reaction conditions that the cleavage of dioxane by hydrogen chloride is suppressed, that is, at lower temperature and for shorter reaction time, it is possible to obtain 6-chloro-5-methyl-4-phenyl-2-(3*H*)-pyrimidinone (**4c**) exclusively.

(13) E. Staude and F. Patat, "The Chemistry of the Ether Linkage," S. Patai, Ed., Interscience, New York, N. Y., 1967, p 21.

In the case of 2a–c, mixtures of two geometrical isomers were used for cyclization. In view of the almost quantitative yield of 5c from 2c (ratio of two geometrical isomers, 3:1), it is clear that cis–trans equilibria between two isomers of isocyanates 2 are established in this reaction.

Experimental Section

Melting points were determined on a Yanagimoto micro melting point apparatus and are corrected. Boiling points are uncorrected. Nmr spectra were obtained using a JNM-G-60 spectrometer (Japan Electronic Optics Laboratory Co.) with tetramethylsilane as an internal reference. Ir spectra were recorded with a Japan Electronic IR-E spectrophotometer or with a Hitachi 225 spectrophotometer equipped with gratings. Mass spectra were recorded with a Hitachi RMU-6E mass spectrometer.

Materials.—Enaminonitriles 1 were prepared according to the known methods.[3,11,14]

Synthesis of Unsaturated Isocyanates 2.—A typical procedure is as follows. In a 100-ml round-bottomed four-necked flask, equipped with a stirrer, a condenser, a dropping funnel, and a gas inlet tube, was placed 30 ml of ethyl acetate and it was saturated with phosgene under reflux. To this solution was added 7.5 g (0.05 mol) of enaminonitrile 1c in 30 ml of ethyl acetate in 25 min; then the reaction mixture was heated under reflux with stirring for an additional 30 min. The introduction of phosgene was continued throughout these procedures. After phosgene was purged with dry N_2, the solvent was removed under reduced pressure to yield a viscous reddish liquid, which was distilled under reduced pressure to give 6.7 g (72%) of 2c (colorless liquid).

Reaction of Isocyanate 2 with HCl at 100°.—A typical procedure is as follows. In a 35-ml glass tube were placed 1.1 g (6 mmol) of 2c and 5 ml of dioxane; then to the mixture 1.45 g (40 mmol) of anhydrous HCl was allowed to be absorbed under cooling. The glass tube was sealed and heated at 100° for 24 hr. After removal of HCl, the precipitates formed were filtered, washed with a small portion of dioxane, and dried *in vacuo* to yield 1.0 g of uracil 5c. From the filtrate 0.15 g of 5c was obtained. The total yield was 95%.

Reaction of 2c with HCl at 60°.—In a 35-ml glass tube, a mixture of 0.63 g (3.4 mmol) of 2c, 1.3 g (36 mmol) of HCl, and 5 ml of dioxane was heated at 60° for 6 hr. After HCl was purged, the precipitates formed were filtered, washed with dioxane, and dried at 80° *in vacuo* to yield a white powder of 6-chloro-5-methyl-4-phenyl-2(3*H*)-pyrimidinone (4c) (0.56 g, 74%). The crude product was recrystallized from anhydrous CH_3CN to give colorless needles: mp 190–195°; ir (Nujol) 1665 cm^{-1} (C=O); nmr (CF_3COOH) δ 2.53 (s, 3 H) and 7.82 (s, 5 H); mass spectrum (70 eV) *m/e* (rel intensity) 220 (45, M^+) and 219 (100).

Anal. Calcd for $C_{11}H_9N_2OCl$: C, 59.87; H, 4.11; N, 12.70. Found: C, 59.70; H, 4.05; N, 12.80.

The dioxane was evaporated from the filtrate and the residue was washed with a small portion of dioxane and dried *in vacuo* to yield 0.076 g (10%) of 5c.

Reaction of Pyrimidinone 4c with HCl in Dioxane.—In a 35-ml glass tube a mixture of 0.119 g of 4c, 0.8 g of HCl, and 2 ml of dioxane was heated at 100° for 20 hr. The reaction mixture was evaporated to dryness and the resulting residue was washed with ether and dried *in vacuo* to give 0.096 g (88%) of 5c.

Reaction of Dioxane with HCl at 100°.—In a 50-ml glass tube a mixture of 9.0 g of dioxane and 3.2 g of HCl was heated at 100° for 24 hr. The dioxane was removed under reduced pressure to yield 0.6 g of a mixture of 6 (major) and 7 (minor) (glpc analysis).

Registry No.—*cis*-2a, 35042-37-6; *trans*-2a, 35042-38-7; *cis*-2b, 35042-39-8; *trans*-2b, 35042-40-1; *cis*-2c, 35042-41-2; *trans*-2c, 35042-42-3; 2d, 30542-43-4 4c, 35042-44-5; 5a, 32796-82-0; 5b, 16372-00-2; 5c, 35042-47-8; 5d, 35042-48-9.

(14) J. Kuthan, V. Jehlička, and E. Haker, *Collect. Czech. Chem. Commun.*, **32**, 4390 (1967).

A *p*-Fluoro Labeling Study of Partial Scrambling before Fragmentation in Some Five-Membered Heterocycles Containing Nitrogen

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Illustrative examples of *p*-fluoro labeled triphenyloxazole, -imidazole, -thiazole, and isoxazole were studied in the mass spectrometer to determine scrambling patterns in major fragmentations. No trends were observed which would have been analogous to the photochemical analogy in the scrambling patterns of furans and thiophenes.

Previously the *p*-fluoro substituent has been used as a label[1] to study scrambling in the decomposition of several five-[2,3] and six-membered[4] heterocycles in the mass spectrometer. Partial to complete scrambling before fragmentation was observed in the cases of tetraphenylfuran and tetraphenylthiophene,[3] in analogy to the behavior of furan and thiophene themselves in the mass spectrometer[5] and to the photochemical behavior of substituted thiophenes[6] and furans.[7] In distinction to the mass spectral behavior of pyridine,[8] however, the completely phenylated derivatives of pyridine, pyrazine, and 1,2,4-triazine were found not to scramble appreciably before decomposition.[4] We therefore thought it of interest to examine the extent of scrambling before fragmentation for several fully phenylated five-membered heterocycles containing nitrogen. This report is concerned with the scrambling in various fragment ions of 4,5-diphenyl-2-*p*-fluorophenyloxazole (I), 4,5-diphenyl-2-*p*-fluorophenylimidazole (II), 2,5-bis(*p*-fluorophenyl)-4-phenylthiazole (III), and 3,5-diphenyl-4-*p*-fluorophenylisoxazole (IV). Fragmentation of other substituted triphenyl isox-

(1) M. M. Bursey, R. D. Rieke, T. A. Elwood, and L. R. Dusold, *J. Amer. Chem. Soc.*, **90**, 1557 (1968).

(2) M. M. Bursey, T. A. Elwood, and P. F. Rogerson, *Tetrahedron*, **25**, 605 (1969).

(3) M. M. Bursey, T. A. Elwood, and P. F. Rogerson, *J. Org. Chem.*, **34**, 1138 (1969).

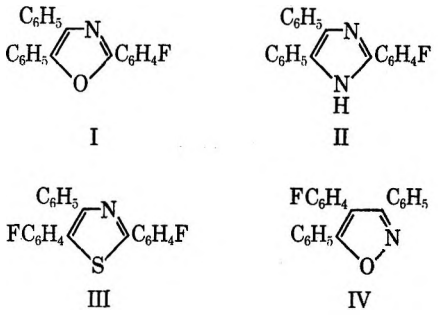
(4) M. M. Bursey and T. A. Elwood, *ibid.*, **35**, 793 (1970).

(5) (a) D. H. Williams, R. G. Cooks, J. Ronayne, and S. W. Tam, *Tetrahedron Lett.*, 1777 (1968); (b) F. de Jong, H. M. J. Sinnige, and M. J. Janssen, *Recl. Trav. Chim. Pays-Bas*, **89**, 225 (1970); (c) F. de Jong, H. M. J. Sinnige, and M. J. Janssen, *Org. Mass Spectrom.*, **3**, 1539 (1970); (d) A. S. Siegel, *Tetrahedron Lett.*, 4113 (1970).

(6) H. Wynberg, R. M. Kellogg, H. van Driel, and G. E. Beekhuis, *J. Amer. Chem. Soc.*, **89**, 3501 (1967).

(7) (a) A. Padwa and R. Hartman, *ibid.*, **88**, 3759 (1966); (b) E. E. van Tamelen and T. H. Whitesides, *ibid.*, **90**, 3894 (1968).

(8) D. H. Williams and J. Ronayne, *Chem. Commun.*, 1129 (1967).



I II III IV

azoles has been reported, and we specifically note the lack of important scrambling processes preceding several cleavages studied therein.[9]

Data for distribution of the label between fragment ions of similar composition for compounds I–IV are given in Table I.

TABLE I
RATIOS OF COMPARABLE FRAGMENT ION INTENSITIES IN THE MASS SPECTRA OF I–IV

	I	II	III	IV
$\frac{M - FC_6H_4CN}{M - C_6H_5CN}$	1.0	6.4[a]	1200	0.08
$\frac{C_{13}H_9F}{C_{13}H_{10}}$	2.5	0.08	30	0.9
$\frac{C_{13}H_8F}{C_{13}H_9}$	0.7	0.05	14	2.3
$\frac{FC_6H_4CN}{C_6H_5CN}$	20	2.0	18[b]	0.25
$\frac{FC_6H_4CO}{C_6H_5CO}$	0.18		0.7[c]	0.002
$\frac{FC_6H_4}{C_6H_5}$	0.22	0.4	1.4	0.07

[a] Ratio for ions $[M - FC_6H_4CNH]/[M - C_6H_5CNH]$. [b] Ratio for ions FC_6H_4CHNH/C_6H_5CHNH. The ratio for FC_6H_4CNH/C_6H_5CNH is 1.3. [c] Ratio for ions FC_6H_4CS/C_6H_5CS.

The loss of the elements of benzonitrile from the molecule ion (or, in the case of II, benzonitrile + H) is specific in the case of the thiazole III and fairly specific for the isoxazole IV, but is not specific (this need not imply scrambling) in the oxazole I and the imidazole II. In I, it may be argued that the aryl group on either side of N is lost equally easily (though other more complex arguments might be invented); in II, the substituent at C-2 is lost more frequently than the others; in III, a substituent at C-2 (or less likely C-5) is lost to the exclusion of that at C-4; and, in IV, the loss of the substituent at C-3 (or less likely C-5) is favored over the loss of the C-4 substituent. Sulfur, in this series of compounds, does not accelerate the rate of internal scrambling relative to the first-row elements. This is in decided contrast to the behavior of five-membered heterocycles containing only oxygen or sulfur, where the dominant effect of sulfur seems to be promotion of scrambling. Here the dominant effect of sulfur is to promote a specific cleavage.

The formation of the ions $C_{13}H_{10}\cdot^+$, $C_{13}H_9^+$, and their fluorinated analogs is reasonable against the background of ready formation of these ions in the decomposition of many classes of compounds containing at least two phenyl groups.[10] Since there are two ways of choosing one substituted ring and one unsubstituted ring, but only one way of choosing two unsubstituted rings in I, II, and IV, complete scrambling before production of this ion would produce a ratio of two monofluorinated to one unflorinated C_{13} ion. Hence, total scrambling is very nearly approached in the $C_{13}H_{10}$ ion of the oxazole I and the $C_{13}H_9$ ion (but not the $C_{13}H_{10}$ ion!) of the isoxazole IV. In all other cases, ions seem to be formed with only a small amount of scrambling; the data for III are reasonable in the minimal amount of unfluorinated ions formed, since it is not possible to choose two unsubstituted rings in III. The formation of any $C_{13}H_{10}$ or $C_{13}H_9$ must be complex process, but very little is formed of these ions. Incidentally, there is virtually no $C_{13}H_8F_2\cdot^+$ or $C_{13}H_7F_2^+$ produced by III, again suggesting that sulfur promotes cleavage, not scrambling, in the production of fragment ions in this series.

The data for the production of FC_6H_4CN/C_6H_5CN should be compared with the data for the expulsion of these fragments from the molecular ion. In every case, the scrambling is significantly different from that for loss of benzonitrile; consequently, the mechanisms for these two processes cannot be closely related. This is unexpected, because naive assumptions would have led to the only distinction as the placement of the charge. Again, the sulfur atom in the thiazole has not produced significantly greater scrambling than the oxygen atom in the oxazole.

Benzoyl ion formation in I from C-2 is discriminated against, relative to C-5, by a factor of 4 or 5 (or, relative to C-4 and C-5, by a factor of less than 3 if there is total scrambling); in the isoxazole, as noted before in cases with other substituents,[9] the process is specific. The thiobenzoyl ion III involves substantial contribution from C-4, and serves as one of the few ions produced after bond formation across the ring initiated by sulfur but not so much by oxygen.

Finally, the small fragment corresponding to the phenyl group is formed with less than statistical origin in each case, particularly IV.[9] Deviations from the statistical values of 2:1 are about 50% in the oxazole I, 25% in the imidazole II, and 35% in the thiazole.

There are several fragmentations peculiar to certain species, so that relative behavior across the series of compounds cannot be compared as in the above cases. In the imidazole, the ratio of loss of labeled to unlabeled (benzonitrile + H_2) is 4.7. This number suggests that the mechanism for loss of these components is closely related to that for the loss of (benzonitrile + H), but not to the formation of $C_6H_5CHNH\cdot^+$ or $C_6H_5CNH^+$, where the scrambling values are different. Peaks of mass corresponding to difluorodiphenylacetylene and fluorodiphenylacetylene appear in the spectrum of the thiazole III in the ratio of 0.07, indicating that only a small amount of bond formation across the ring occurs before formation of these virtual hydrocarbon ions.

Low-Voltage Studies.—Most of the processes noted are high-energy processes and do not lend themselves to study at reduced voltages. A study of spectra at

(9) C. F. Beam, M. C. D. Dyer, R. A. Schwarz, and C. R. Hauser, *J. Org. Chem.*, **35**, 1806 (1970).

(10) (a) J. H. Bowie, P. F. Donaghue, H. J. Rodda, and B. K. Simons, *Tetrahedron*, **24**, 3965 (1968); (b) P. C. Wszolek, F. W. McLafferty, and J. H. Brewster, *Org. Mass Spectrom.*, **1**, 127 (1968).

voltages between 40 and 12 V ionizing energy led to the following observations.

In the oxazole I, the $[C_{13}H_9F\cdot^-]/[C_{13}H_{10}\cdot^+]$ ratio increases from 2.5 at 70 V to 7 at 20 V; in the imidazole and thiazole, the $[C_{13}H_8F^+]/[C_{13}H_9^+]$ ratio remains constant at low voltage. The routes of formation of these ions are therefore convergent, since the oxazole begins to approach specificity and the others remain nearly specific.

In the oxazole, the $[FC_6H_4^+]/[C_6H_5^+]$ ratio exceeds 30 at 40 V; in the imidazole, it drops somewhat to 0.15 at 40 V. A specific process is therefore indicated involving the C-2 substituent in the oxazole, but the analogy does not hold in the imidazole.

The $[M - FC_6H_4CNH^+]/[M - C_6H_5CNH^+]$ ratio is 0.14 at 40 V in the imidazole, a striking reversal of the behavior at 70 V. This observation suggests that at least two specific processes may be involved in the formation of the ion, one dominant just above threshold and the other becoming more important at higher ionizing voltage. The most closely analogous process which could be studied, loss of benzonitrile from the thiazole, does not undergo such a reversal, the ratio dropping from 1200 at 70 V to 300 at 17.5 V ionizing energy.

Finally, in the thiazole, the difluorodiphenylacetylene/fluorodiphenylacetylene ratio drops by an order of magnitude at 20 eV.

Conclusions

The scrambling processes in these compounds do not follow the trend of greater scrambling as one moves down the periodic table in choosing a heteroatom, as might have been expected from the photochemical analogy in scrambling of furans and thiophenes in the mass spectrometer.[3,5] The introduction of a heteroatom seems to have the principal effect of making certain fragmentation routes more favorable. Usually the competition of this decomposition process with scrambling mechanisms is favorable to fragmentation.

Experimental Section

Mass Spectra.—The spectra were recorded on a Hitachi RMU-6E mass spectrometer, with sample introduction by direct-probe insertion at the minimum temperature required to produce a useable spectrum (160–275°). For conventional spectra the ionizing voltage was 75 V and the repeller voltage was 2 V, the temperature of the source being maintained at 190°. The ionizing current was 80 μA and the trap current 50 μA. Low-voltage spectra were collected with ionizing voltages of 40, 30, 25, 20, 17.5, and 15 V, with tied repellers set at 0 V.

Synthesis. 4,5-Diphenyl-2-*p*-fluorophenyloxazole (I).—This was prepared by the general method of Murray and Japp[11] and was recrystallized from EtOH, mp 118°.

Anal. Calcd: C, 80.0; H, 4.44. Found: C, 79.99; H, 4.55.

4,5-Diphenyl-2-*p*-fluorophenylimidazole (II).—A method adapted from that of Radziszewski[12] was used; benzil (0.05 mol), *p*-fluorobenzaldehyde (0.04 mol), and NH_3 (enough to saturate) were dissolved in the minimum of EtOH at 40° and left standing for 48 hr, mp 275° from EtOH.

Anal. Calcd: C, 80.25; H, 4.77. Found: C, 80.38; H, 4.81.

2,5-Bis(*p*-fluorophenyl)-4-phenylthiazole (III).—This was prepared by a procedure described by Hubacher,[13] mp 115.5° from ether, then EtOH.

Anal. Calcd: C, 72.20; H, 3.72. Found: C, 72.08; H, 3.66.

3,5-Diphenyl-4-*p*-fluorophenylisoxazole (IV).—The method of preparation was analogous to those described by Kohler and Barrett[14] and Meisenheimer and Weibezahn,[15] mp 231–232° from MeOH.

Anal. Calcd: C, 80.0; H, 4.44. Found: C, 80.27; H, 4.51.

Registry No.—I, 35040-28-9; II, 2284-96-0; III, 35040-30-3; IV, 35040-31-4.

Acknowledgments.—M. M. B. is a Research Fellow of the Alfred P. Sloan Foundation.

(11) F. R. Japp and T. S. Murray, *J. Chem. Soc.*, **63**, 469 (1893).
(12) B. Radziszewski, *Chem. Ber.*, **15**, 1493 (1882).
(13) K. Hubacher, *Justus Liebigs Ann. Chem.*, **259**, 228 (1890).
(14) E. P. Kohler and G. R. Barrett, *J. Amer. Chem. Soc.*, **46**, 2105 (1924).
(15) J. Meisenheimer and K. Weibezahn, *Chem. Ber.*, **54**, 3195 (1921).

Notes

N-Methylbicycloatalaphylline, a New Alkaloid from *Atalantia monophylla* Correâ

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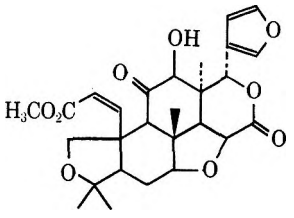
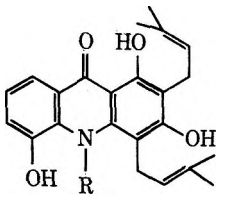
In the course of detailed analysis of the chemical constituents of *Atalantia monophylla* Correâ, a new acridone base, $C_{24}H_{27}NO_4$ (M^+ 393), has been isolated. The structure of this alkaloid has been established and is reported in the present communication.

Previous work on the roots of this botanical species collected from different parts of India by various groups of workers[1-3] did not furnish the same results. Sabata and coworkers[1] isolated the limonoid, atalantin (I), from *Atalantia* collected from Orissa and did not report the occurrence of any alkaloid, whereas Govindachari, *et al.*[2], could isolate two new acridone alkaloids, atalaphylline (IIa) and *N*-methylatalaphylline (IIb), but not atalantin (I). Xanthyletin (III) has also been reported[3] to occur in this species.

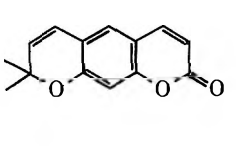
We collected the roots of the plant from Orissa, and from the petroleum ether (bp 60–80°) extract we could isolate all the aforesaid constituents besides a new alkaloid, *N*-methylbicycloatalaphylline (IV).



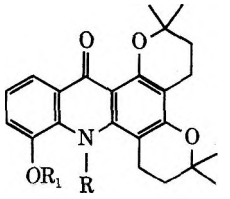
I



IIa, R = H
b, R = CH_3



III



IV, R = CH_3; R_1 = H
V, R = R_1 = CH_3
VI, R = H; R_1 = CH_3

The alkaloid *N*-methylbicycloatalaphylline, $C_{24}H_{27}NO_4$ (M^+ 393), mp 185°, appeared in the benzene eluates upon chromatographic resolution of petroleum ether extract of the roots over silica gel as well as alumina. That the base is not an artifact of its uncyclized isomer IIb was proved by the presence of tlc spots corresponding to both these bases among the seven constituents in the crude plant extract. Moreover, the isolation of this base also substantiates the earlier report by Govindachari, *et al.*,[2] of the presence of polar constituents other than atalaphylline and *N*-methylatalaphylline in the crude extract.

The alkaloid exhibited ultraviolet and infrared spectra (see Experimental Section) typical of 9-acridones and gave a positive ferric reaction, thereby indicating the presence of a phenolic hydroxyl group. This contention was further substantiated by the infrared absorption at 3475 cm^{-1}. In the nmr spectrum sharp singlets at δ 1.50 and 1.54 (6 H each) and broad multiplets at δ 1.85 and 2.80 (4 H each), respectively, were characteristic of the 2,2-dimethylchroman system. The signal of the methylimino group was clearly discernible at δ 3.94 (3 H, s) while the aromatic protons of the C_6 and C_7 locus merged with the phenolic hydroxyl at C_5 (which disappeared on D_2O exchange) as a complex multiplet at δ 7.34. The C_8 aromatic proton, deshielded by the neighboring peri carbonyl group, appeared at δ 7.8.

The mass spectrum of the alkaloid exhibited strong peaks at *m/e* 393 (M^+, 100%), 378 (M − 15), 350 (M − 43), 338 (M − 55), 322 (378 − 56), 294, 282 (338 − 56), and 268, which is in agreement with the structure IV.

On treatment with diazomethane IV formed a monomethyl ether V, $C_{25}H_{29}NO_4$ (M^+ 407), which gave superimposable ir spectra with the *N*-methyl derivative of *O*-methylbicycloatalaphylline[4] (VI), thereby confirming the structure of the new base as *N*-methylbicycloatalaphylline (IV).

Experimental Section

Melting points are uncorrected. Uv spectra were determined in a Beckman Model DU-2 and ir spectra in Perkin-Elmer 337 instruments. Nmr spectra were determined at 100 MHz in $CDCl_3$, a few drops of DMSO-d_6 being added where necessary. Tlc was done on silica gel G plates with benzene–ethyl acetate (9:1) as developer and iodine vapor as indicator.

Isolation.—The powdered root bark (5 kg) of *Atalantia monophylla* collected from the Chandka forest, Orissa, was extracted with petroleum ether (bp 60–80°). The concentrated petroleum extract on tlc examination showed seven distinct spots. The most polar constituent (R_f 0.61) showed an identical R_f value with that of pure *N*-methylbicycloatalaphylline. The crude extract was left in the refrigerator for 1 week, during which a dirty yellow solid separated out. It was filtered and repeatedly crystallized from methanol in needles, mp 185°, and was characterized as atalantin.

The concentrated mother liquor was diluted with benzene and chromatographed over silica gel (500 g). The column was eluted with solvents of increasing polarity. Fractions of about 50 ml each were collected and monitored by tlc and those giving identical spots were combined together. Xanthyletin and β-sitosterol migrated out of the column from 2 and 5% ethyl acetate in petroleum eluates, respectively. Early benzene fractions 24–30 yielded *N*-methylbicycloatalaphylline (50 mg), R_f 0.61, followed by *N*-methylatalaphylline (15 mg), R_f 0.56, from frac-

(1) M. R. Thakar and B. K. Sabata, *Indian J. Chem.*, **7**, 870 (1969).

(2) T. R. Govindachari, N. Viswanathan, B. R. Pai, V. N. Ramachandran, and P. S. Subramanium, *Tetrahedron*, **26**, 2905 (1970).

(3) S. K. Talapatra, S. Bhattacharyya, and B. Talapatra, *J. Indian. Chem. Soc.*, **47**, 600 (1970).

(4) The authors thank Dr. N. Viswanathan for this sample.

tions 34–38 and atalaphylline (20 mg), R_f 0.42, from fractions 42–47. The latter fractions furnished a tarry mass which still showed the presence of a number of less polar components.

N-**Methylbicycloatalaphylline.**—The alkaloid crystallized from benzene as yellow needles: mp 185°; λ_{max}^{EtOH} 228 nm (log ϵ 4.20), 274 (4.49), 340 (4.07), 420 (3.66); $\lambda_{max}^{EtOH + alkali}$ 245 nm (log ϵ 4.24), 308 (4.52), 375 (4.14); ν_{max} 3475, 1630, 1560, 1530, 1450 cm^{-1}.

Anal. Calcd for $C_{24}H_{27}NO_4$: C, 73.26; H, 6.92; N, 3.56. Found: C, 73.25; H, 6.46; N, 3.69.

Methylation of *N*-**Methylbicycloatalaphylline.**—A solution of IV (0.05 g) in MeOH (5 ml) was treated with excess CH_2N_2 and the product was chromatographed over silica gel, and a semisolid mass (V), homogeneous by tlc in several solvent systems, migrated out. It exhibited ν_{max}^{Nujol} 1640, 1600, 1575 cm^{-1} and a molecular ion peak (M^+) at *m/e* 407.

Methylation of *O*-**Methylbicycloatalaphylline.**—A solution of VI (0.02 g) in acetone (15 ml) was refluxed with MeI (2 ml) and anhydrous K_2CO_3 (0.1 g) over a steam bath for 96 hr. Usual work-up led to a gummy mass containing traces of starting material. Separation by preparative tlc over silica gel gave a semisolid mass which gave a superimposable ir spectrum with that of V.

Registry No.—IV, 35096-35-6.

Acknowledgments.—The authors wish to express their gratefulness to Professor A. Chatterjee for helpful discussions and for providing laboratory facilities, Dr. R. D. Bennett (California, U. S.) for nmr spectra. Professor B. R. Pai, Presidency College, Madras, for authentic samples, and CCRIMH, New Delhi, for financial assistance.

Valence Isomerization of 2,4,6-Trimethyl-2*H*-pyran[1]

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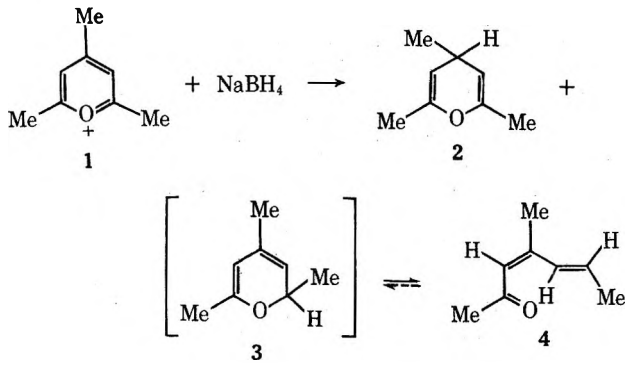
Balaban, Mikai, and Nenitzescu[2] showed that reaction of 2,4,6-trimethylpyryllium perchlorate with sodium borohydride gave two products to which they



assigned the structures 2 and 4 (stereochemistry not given). They made the reasonable assumption that 4 was formed by a rapid valence isomerization from 3. Because of our general interest in electrocyclic reactions, we investigated this reaction somewhat more thoroughly than had the previous workers.[2] The reaction proceeds exactly as they described and the two products were isolated in good yield. The nmr spectra are described in the Experimental Section, and these are in accord with the assigned structures. In addition the spectrum of 4 permits us to assign its stereochemistry. Thus the Δ^5 double bond must be trans, since J_{56} is 15.0 Hz, and the Δ^3 double bond is cis since the shift for H_5 (7.63 ppm) can be accounted for only if the acetyl and C_5H groups have a cis orientation.[3]

We were unable to ascertain satisfactorily whether an observable amount of 3 is in equilibrium with 4 or not. The nmr spectrum of 4 has peaks of low intensity at δ 1.18 (d), 4.77, and 4.85 which might be assigned to 3, but these do not exhibit the expected intensity increase and decrease on heating and cooling. Furthermore, there are a number of other small peaks which could not be associated with 3 which also appear in the spectrum.

Next we attempted to determine whether 3 could be identified as a transient intermediate. The presence of a transient intermediate was readily shown by spectral means. If the reduction is carried out under an overlayer of pentane at 0°, a diluted aliquot of the pentane layer has λ_{max} 277 nm, which disappears rapidly at room temperature, leaving the λ_{max} 272 nm of 4. The 277-nm band is quite reasonable for the α-pyran 3, since Hinnen and Dreux[4] have found λ_{max} (CH_3OH) 282 nm for 2,2,4,6-tetramethyl-α-pyran. Additional evidence to support a structural assignment for the intermediate was obtained from the nmr spectrum of a solution obtained by reducing 1 with an underlayer of carbon tetrachloride. At −22° the spectrum shows (in addition to bands due to 2 and 4) resonances at δ 1.18 (d, J = 6.5 Hz), 1.56 (s), 1.76 (s), 4.6 (m), 4.8 (broad s), and 4.9 (broad s). When the solution is warmed to 35°, these bands rapidly disappear and the final spectrum matches that of the crude reduction product obtained from the normal reaction procedure. These data provide strong support for the assignment of structure 3 to the transient intermediate.

An estimate of the rate of conversion of 3 to 4 was obtained by following the change in absorbance at 253.5 nm where the intermediate showed no absorption. With the assumption that 3 goes directly to 4 with no intermediate, the rate of disappearance of 3 can be calculated. The reaction shows good first-order kinetics with k (13°) $\cong 3 \times 10^{-3}$ sec^{-1}. More recently we have shown[5] that the rate of ring opening of 2,2,4,6-tetramethyl-α-pyran is 1.6×10^{-4} sec^{-1} at 14.6°. Since 3 is lacking the cis methyl group on the terminal carbon present in 2,2,4,6-tetramethyl-α-pyran, which is expected to reduce the rate of the latter, the rate difference of *ca.* 20-fold seems quite reasonable.

Experimental Section

2,4,6-Trimethyl-4*H*-pyran (2) and 4-Methyl-*cis*-3-*trans*-5-heptadien-2-one (4).—An aqueous solution of 1 was reduced with sodium borohydride according to the procedure of Balaban, Mikai, and Nenitzescu.[2] The two products were separated by fractional distillation using a Nester and Faust 30-cm spinning band column. The pyran 2, bp 30° (6 mm), nmr (CCl_4) δ 0.98 (d, J = 6.5 Hz, 3 H), 1.71 (d, J = 0.8 Hz, 3 H), 2.79 (m,

(1) Support of this study by the National Science Foundation under Grant GP-4985 is gratefully acknowledged.

(2) A. T. Balaban, G. Mikai, and C. D. Nenitzescu, *Tetrahedron*, **18**, 257 (1962).

(3) L. M. Jackman and R. H. Wiley, *J. Chem. Soc.*, 2881, 2886 (1960).

(4) A. Hinnen and J. Dreux, *C. R. Acad. Sci., Ser. C*, **255**, 1747 (1962).

(5) E. N. Marvell, T. Chadwick, G. Caple, T. Gosink, and G. Zimmer, *J. Org. Chem.*, **37**, 2992 (1972).

1 H), 4.38 (d, J = 3.8 Hz, 2 H), constituted about 1/3 to 1/4 of the distillate. The dienone 4, bp 53–54° (6 mm), nmr (CCl_4) δ 1.81 (d of d, J = 6.7, 1.0 Hz, 3 H), 1.91 (d, J = 1.0 Hz, 3 H), 2.1 (s, 3 H), 5.98 (s, 1 H), 6.17 and 7.63 (AB part of ABX pattern, J_{AB} = 15.0, $J_{AX} \cong 1.0$, J_{BX} = 6.7 Hz), was the major product.

2,4,6-Trimethyl-2*H*-pyran (3) as Transient Intermediate.—A mixture of 0.5 g (2.1 mmol) of 1, 100 ml of pentane, and 10 ml of water was cooled in an ice bath. To this was added 0.2 g (53 mmol) of sodium borohydride and the mixture was stirred vigorously for 20–30 sec. About 25 ml of the pentane layer was decanted into a test tube stored in a Dry Ice bath. The pentane solution had λ_{max} 277 nm, which disappeared rapidly (10 min at 25°), giving λ_{max} 272 nm for 4. The rate of change of the spectrum at 253.5 nm followed first-order kinetics, since a plot of 2.3 log $(A_\infty - A_t)/A_\infty$ *vs.* time gave a straight line.

Reduction was carried out as described above except that spectral grade carbon tetrachloride was used in place of the pentane. The organic layer was pipetted into a cold test tube and was dried briefly ($MgSO_4$). A nmr spectrum at −22° gave a complex spectrum containing, in addition to bands associated with 2 and 4, new bands at δ 1.18 (d, J = 6.5 Hz), 1.56 (s), 1.76 (s), 4.6 (m), 4.8 (s), and 4.9 (s). All of these bands disappear rapidly when the solution is warmed to 35°.

Registry No.—2, 35030-93-4; 3, 35030-94-5; 4, 29178-98-1.

Preparation of *trans*-2,3-*trans*-5,6-dioxane-d_4. Use of a Hindered Base to Prevent Acid-Catalyzed Side Reactions

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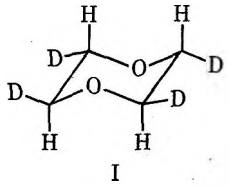
In the course of another investigation[1] it became necessary to synthesize a 1,4-dioxane, substituted with deuterium such that a definite geometric isomer, *trans*-2,3-*trans*-5,6-dioxane-d_4 (I), was obtained. The usual



I

preparations of 1,4-dioxane (*e.g.*, the acid-catalyzed self-condensation of ethylene glycol) were not expected to lead to pure geometric isomers, and preliminary results were in accord with this expectation.

A double displacement on an appropriately deuterated ethane, with leaving groups in the 1 and 2 positions, by the oxygens of an appropriately deuterated ethylene glycol, would be expected to give I.

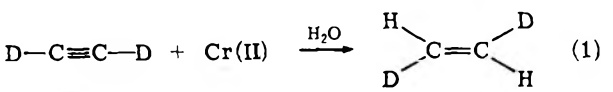
An attempt to displace the tosylate groups of ethylene glycol ditosylate with the dilithium salt of ethylene glycol in hexamethylphosphoramide yielded no 1,4-dioxane. Heating ethylene glycol directly with ethylene glycol ditosylate in *p*-dimethoxybenzene to 210° also yielded no 1,4-dioxane. When ethylene glycol and ethylene glycol ditosylate were heated together to 180°, without solvent, 1,4-dioxane was obtained in 20% yield. This dioxane may have arisen in part from the acid-catalyzed self-condensation of ethylene glycol (toluenesulfonic acid is obtained from the desired reaction and from decomposition of the tosylate). To test this possibility, 1,1,2,2-ethylene glycol-d_4 was synthesized and reacted with undeuterated ethylene glycol ditosylate. Mass spectral analysis of the dioxane product revealed parent peaks at 92 (dioxane-d_4) and 96 (dioxane-d_8), and none at 88 (dioxane-d_0). In the course of a reaction, the amount of the acid-catalyzed self-condensation product (dioxane-d_8) formed depended on the extent of conversion and varied between 25–50%.

It thus became necessary to eliminate the formation of the ethylene glycol self-condensation product. Since this undesired reaction apparently was acid-catalyzed, various bases were added to the reaction mixture. With quinoline as the added base, heating produced only a red tar and no volatiles. Evidently, base-catalyzed side reactions took precedence over the desired reaction.

Brown and Kanner[2] have reported that hindered pyridines, such as 2,6-di-*tert*-butylpyridine, act as normal bases toward free protons, but do not act as nucleophiles. Base-catalyzed eliminations would also be expected to be minimal with such a hindered base. When two equivalents of this base were heated with one equivalent each of ethylene glycol and ethylene glycol ditosylate, the yield of 1,4-dioxane went up dramatically to 70%. After removing the volatiles, the 2,6-di-*tert*-butylpyridinium-*p*-toluenesulfonate salt in the residue was recovered and recrystallized from acetone–carbon tetrachloride. When ethylene glycol-d_4 was substituted for the undeuterated ethylene glycol, mass spectral analysis of 1,4-dioxane product showed only dioxane-d_4 and no dioxane-d_8 or dioxane-d_0. As little as 2 or 3% of these side products could have been detected. When a less hindered base (2,6-lutidine) was used, a lower yield of 1,4-dioxane (20%) was obtained, although deuterium labeling experiments indicated that no or minimal self-condensation reactions had occurred.

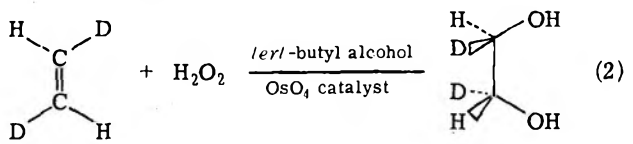
The reaction employing 2,6-di-*tert*-butylpyridine is therefore suitable for the preparation of geometric isomers of 1,4-dioxane. Synthesis of *dl*-1,2-ethylene glycol-d_2 and its ditosylate was accomplished by the following sequence of reactions.

Acetylene-d_2 was reduced to *trans*-1,2-ethylene-d_2 (eq 1) by water–chromium(II) chloride in a trans fashion.[3]



(1)

Cis hydroxylation of *trans*-1,2-ethylene-d_2, using the osmium tetroxide catalyzed hydrogen peroxide–*tert*-butyl alcohol reagent (eq 2) of Milas and Sussman,[4] gave



(2)

(1) F. R. Jensen and R. A. Neese, *J. Amer. Chem. Soc.*, **93**, 6329 (1971).

(2) H. C. Brown and B. Kanner, *ibid.*, **88**, 986 (1966).

(3) J. Bigeleisen, S. V. Ribnikar, and W. A. Van Hook, *Zh. Fiz. Khim.*, **38**, 489 (1963).

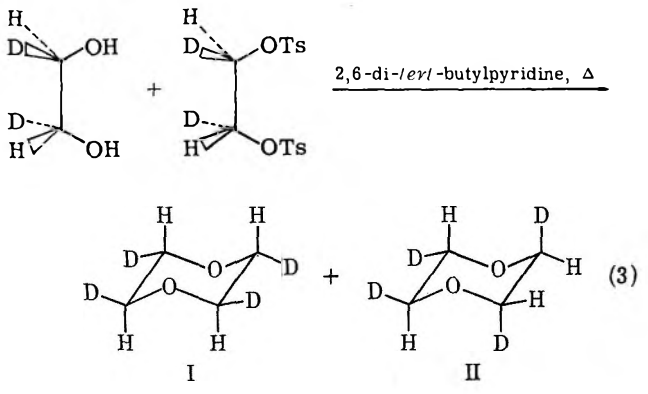
(4) N. A. Milas and S. Sussman, *J. Amer. Chem. Soc.*, **59**, 2345 (1937).

TABLE I
PREPARATION OF DIOXANE AND DEUTERATED DIOXANES

Glycol[a]	Ditosylate[b]	Base	Temp, °C	Yield, %	Product
Ethylene glycol	Ethylene glycol ditosylate		180	20	Dioxane
Ethylene glycol[c]	Ethylene glycol ditosylate		210	0	No volatiles obtained
Ethylene glycol-d_4	Ethylene glycol ditosylate		180	23	Dioxane-d_4 and dioxane-d_8
Ethylene glycol	Ethylene glycol ditosylate	Quinoline (3.14 g, 0.024 mol)	195	0	Decomposition began at 150° and no volatiles were observed
Ethylene glycol	Ethylene glycol ditosylate	2,6-Di-*tert*-butylpyridine (4.66 g, 0.024 mol)	180–190	70	Dioxane
Ethylene glycol-d_4	Ethylene glycol ditosylate	2,6-Di-*tert* butylpyridine (4.66 g, 0.024 mol)	180–190	67	Dioxane-d_4
Ethylene glycol-d_4	Ethylene glycol ditosylate	2,6-Lutidine (4.0 g, 0.037 mol)	180–190	20	Dioxane-d_4
dl-1,2-Ethylene glycol-d_2	*dl*-1,2-Ethylene glycol ditosylate-d_2	2,6-Di-*tert*-butylpyridine (4.74 g, 0.025 mol)	180–190	65	*trans*-2,3-*trans*-5,6-Dioxane-d_4

[a] 0.75 g, 0.012 mol of ethylene glycol. [b] 4.5 g, 0.012 mol of ethylene glycol ditosylate. [c] 15 g of *p*-dimethoxybenzene was used as a solvent.

the desired *dl*-1,2-ethylene glycol-d_2. Conversion of this glycol to the corresponding ditosylate was carried out with *p*-toluenesulfonyl chloride–pyridine by the method of Edgell and Parts.[5] The reaction of the *dl*-glycol with the *dl*-ditosylate in the presence of 2,6-di-*tert*-butylpyridine gave the desired *trans*-2,3-*trans*-5,6-dioxane-d_4 (I), which is presumably a mixture of two stereoisomers, I and II (eq 3).



(3)

Double inversion stereochemistry is assumed from the method of synthesis. The nmr spectral evidence supports this hypothesis.

Experimental Section

Ethylene Glycol Ditosylate.—This compound was prepared by the pyridine–*p*-toluenesulfonyl chloride method of Edgell and Parts.[5] Deuterated ethylene glycols were converted to their respective ditosylates by the same method, mp 124–126°, lit. 126–127°.

1,1,2,2-Ethylene Glycol-d_4.—To a solution of 10 g of lithium aluminum deuteride (0.238 mol) in 500 ml of dry tetrahydrofuran, was added 26.3 g of diethyl oxalate (0.18 mol) dissolved in 100 ml of dry tetrahydrofuran. The heat of reaction caused the mixture to reflux. After the addition was complete, the mixture was refluxed for 6 hr. The mixture was cooled, 10 g of water was added, followed by 10 ml of 15% sodium hydroxide solution, and finally 30 ml more water was added. The solid was removed by filtration and washed with tetrahydrofuran. The combined filtrates were distilled to remove tetrahydofuran and ethyl alcohol. The remaining ethylene glycol-d_4 was distilled: bp 92–96° (13 mm) [for $HOCH_2CH_2OH$, lit.[6] bp 93° (13 mm)]; yield, 5.8 g, 49%. The nmr spectrum revealed that less than 2 or 3% of the glycol existed as $HOCD_2CHDOH$.

2,6-Di-*tert*-butylpyridine.—This compound was prepared from *tert*-butyllithium and pyridine by the procedure of Brown and Kanner,[2] bp 100–101° (23 mm) [lit.[2] 100–101° (23 mm)].

***trans*-1,2-Ethylene-d_2.**—Acetylene-d_2 was reduced with chromous chloride by the procedure of Bigeleisen, *et al.*,[3] and was used without isolation to produce the *dl*-1,2-ethylene glycol-d_2.

***dl*-1,2-Ethylene Glycol-d_2.**—*trans*-1,2-Ethylene-d_2 was oxidized in a cis fashion with the osmium tetroxide–*tert*-butyl alcohol–H_2O_2 reagent of Milas and Sussman,[4] bp 93–97° (13 mm). In the nmr spectrum, the ratio of the areas under the hydroxyl protons compared to the remaining alkyl protons was 1:1.06. The alkyl protons appeared at δ 4.02 (neat, external capillary TMS). In ethylene glycol itself, this value is δ 4.03 (neat, external capillary TMS).

1,4-Dioxane.—All 1,4-dioxanes were prepared by a general procedure, using the appropriate ethylene glycol and ethylene glycol ditosylate (illustrated with added 2,6-di-*tert*-butylpyridine).

In a small round-bottomed flask, equipped with a magnetic stirring bar and a short distillation head, were placed 0.75 g (0.012 mol) of ethylene glycol, 4.5 g of ethylene glycol ditosylate (0.012 mol), and 4.66 g of 2,6-di-*tert*-butylpyridine (0.024 mol). The mixture was heated to 180° while stirring, and the volatiles were removed by distillation and collected. Purification of the 1,4-dioxane was accomplished by preparative glpc utilizing a 10 ft × 1/2 in. 20% QF-1 on 60/80 Chromosorb W column. Undeuterated 1,4-dioxane was identified by comparison of retention time, ir spectrum, nmr spectrum, and mass spectrum. The results of the various experiments are summarized in Table I.

Registry No.—2,6-Di-*tert*-butylpyridine, 585-48-8; *trans*-2,3-*trans*-5,6-dioxane-d_4, 35048-86-3.

(5) W. F. Edgell and L. Parts, *J. Amer. Chem. Soc.*, **77**, 4899 (1955).

(6) I. Heilbron, H. M. Bunbury, A. H. Cook, E. R. H. Jones, T. G. Halsall, and J. R. A. Pollock, "Dictionary of Organic Compounds," Vol. 2, Oxford University Press, New York, N. Y., 1953, p 503.

Metal–Amine Reactions.[1] The Effect of Continuous Sodium Dispersions during Reaction with Naphthalene

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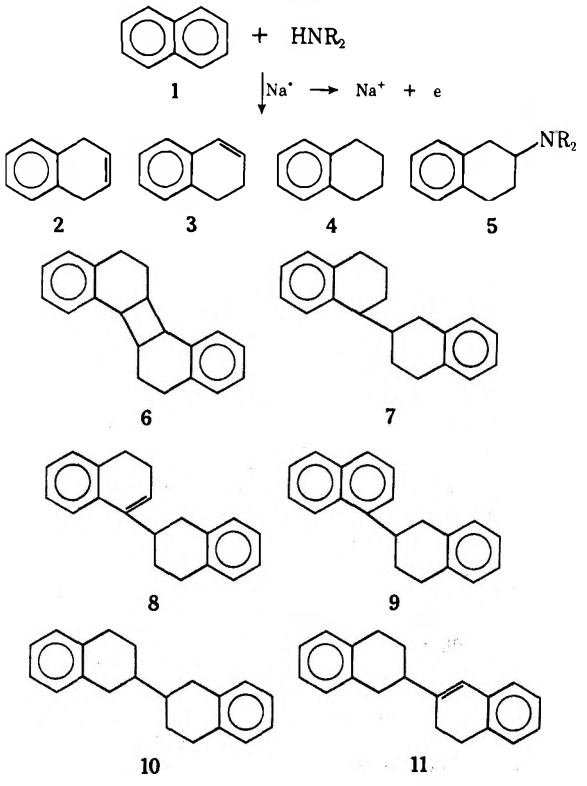
We previously demonstrated that, in addition to reduction products, naphthalene and alkylnaphthalenes in the presence of sodium and secondary amines give reductive amination (*e.g.*, **5**) and/or reductive dimerization products (*e.g.*, **6**, **7**, **8**, **9**, **10**, and **11**) of Scheme I.[1]

SCHEME I



We were also able to show that, with proper selection of an unhindered amine (cyclic secondary amine), reductive amination becomes the predominant route or, conversely, with a hindered secondary amine (*e.g.*, dipropylamine) or primary diamines (*e.g.*, ethylenediamine), reductive amination diminishes and reductive dimerization predominates.[1b] In some cases, formation of specific dimerized hydrocarbons is markedly selective.[1a,d]

With the techniques that had been developed in the earlier work, some reactions were sluggish and the yields were disappointingly low. We were dependent upon the use of dispersed sodium and a paddle stirrer or magnetic stirrer for agitation.

In either case, initially the reaction proceeded satisfactorily. However, the dispersed sodium soon agglomerated to a few shiny balls of metal. To overcome this difficulty, we developed a stir–shredding device which simultaneously stirs and disperses sodium, thus continuously exposing new surface and re-forming fine particles.[3] The development of this apparatus removed the need for using predispersed sodium, and it became possible to carry out reactions with sodium and an amine by periodically adding small pieces or pellets of sodium directly to the reaction mixture. The continuous shredding action provides fresh surface, increases solubility, and hence increases the possibility of reaction. The overall result is a reduction in reaction time and an increased yield of reductive amination product. The data from several selected reactions are compiled in Table I.

Our principal interest in this study was to increase the yield of reductive amination product. A 3-hr reaction period (*vs.* 12-hr previously used) was adequate to cause an increase in yield in all cases and even more than double the yield of reductive amination product in some cases.

It should be noted that extending the reaction period from 3 to 6 hr for *N*-methylpiperazine caused the yield of reductive amination product to drop from 95 to 57%. Similarly, the reaction with pyrrolidine after 20 hr showed 64% yield of reductive amination as compared to 78% after 3 hr. We attribute this lowering of yield to a reversal of reductive amination product formation.[1b] Hence, the best yields of reductive amination are to be expected in a rapid reaction using an unhindered amine. Accordingly, hindered secondary amines should not, and indeed do not, give high yields of reductive amination product. However, it is of interest that, through the use of the stir–shredding apparatus, hindered amines (2-methylpiperidine, 2,6-dimethylpiperidine, dipropylamine, and diisopropylamine) show small increases in reductive amination product, as compared to the yields reported in the earlier work.[1b]

Experimental Section[4]

General Reaction Conditions.—All reductions were carried out in a similar manner using the previously described stir–

(1) (a) L. E. Harris and E. J. Eisenbraun, *J. Org. Chem.*, **37**, 336 (1972); (b) E. J. Eisenbraun, R. C. Bansal, D. V. Hertzler, W. P. Duncan, P. W. K. Flanagan, and M. C. Hamming, *ibid.*, **35**, 1265 (1970); (c) R. C. Bansal, E. J. Eisenbraun, and P. W. Flanagan, *J. Amer. Chem. Soc.*, **88**, 1837 (1966); (d) E. J. Eisenbraun, D. V. Hertzler, R. C. Bansal, P. W. K. Flanagan, and M. C. Hamming, *Amer. Chem. Soc., Div. Petrol. Chem., Prepr.*, **13** (3), 55 (1968).

(2) (a) Continential Oil Company Graduate Research Fellow, 1970–1971; (b) National Science Foundation Science Faculty Fellow, Grant 68098, 1968–1969.

(3) E. J. Eisenbraun and H. Hall, *Chem. Ind. London*, 1158 (1971).

(4) (a) The solvent amines, obtained from Union Carbide Co. and Aldrich Chemical Co., were dried by stirring (24 hr) with KOH and distilling from fresh KOH. The high-purity naphthalene was a gift from Sun Oil Co. The sodium (Matheson Coleman and Bell Co.) was reagent grade, 0.1–0.25 in. spheres, and was washed with sulfuric acid treated and redistilled petroleum ether, bp 60–68°, before use. (b) The glc analyses of the dimeric hydrocarbons and the reductive amination products were obtained on a Hewlett-Packard 5750 glc apparatus fitted with thermal conductivity and hydrogen flame detectors using helium as the carrier gas. For the reductive amination products, a 0.25 in. × 10 ft column of 5% polyethylenimine on base-washed firebrick (80–120 mesh) at 190 to 230° was used. The dimer hydrocarbon mixtures were analyzed on a 0.25 in. × 11 ft column of 6% UC W-98 methyl–vinyl silicone rubber on acid-washed and DMCS-treated Chromosorb G (80–100 mesh) at 260°. (c) The nmr spectra (CCl_4) were obtained with Varian HR-60 and HA-100 instruments (TMS standard) and mass spectra were obtained with a Consolidated Electrodynamics Corp. Model 21-103C mass spectrometer. (d) The glc analyses of the steam-volatile hydrocarbons were obtained on a Beckman GC-2A glc apparatus fitted with a thermal conductivity detector using a 0.25 in. × 10 ft column of 25% Carbowax 20M on Chromosorb W (30–60 mesh) at 190°.

TABLE I
METAL–AMINE REACTIONS

Amine	Reaction time,[a] hr	Distilled reductive amination products, %[b,c]	Naphthalene recovered, %	Yield[b] of hydrocarbon, % 2	3	4	Nonvolatile	Glc ratio of C_{20} dimers 6	7	8	9	10	11	Unknown
Using the Stir–Shredding Device														
N-Methylpiperazine	3	95		<1	1	<1	1		17	36	35	12		
	6	57	1	1		1	1		25	39	14	22		
Piperidine	3	79	<1	2	2	<1	2	1	68	12	6	13		
Pyrrolidine	3	78	<1	<1	<1	4	8	2				98		
	20	64				6	13					100		
N-Methylbutylamine	3	78	<1	2	5	2	9		64	21	6			9
Diethylamine	3	13	2	2	13	13	56		42	39	10			9
Ethylenediamine	3	*d*	5	13	3	2	42	27	25	1		2	20	25
2-Methylpiperidine	3	13[e]	33	9	15	2	50		41	38	21			
2,6-Dimethylpiperidine	3	*f*	25		17	5	63		71	19	10			
Dipropylamine	23	12[g]	49			6	62		11	16	73			
Diisopropylamine	27		61			4	65		28		69		3	
Using Predispersed Sodium and Magnetic Stirring[h]														
N-Methylpiperazine	12	64		6	<1		5	1		17		71		11
Piperidine	12	46		4	<1		11	2				94		4
Pyrrolidine	12	35		20			36	2				98		
2-Methylpiperidine	12	5		42			36							
2,6-Dimethylpiperidine	12			5	4		85							

[a] At room temperature. [b] Yield based on consumed naphthalene. [c] Nonvolatile reductive amination products remained at still bottoms and were not measured. [d] Consisted of several products (1.6 g). [e] Consisted of two major products, 79% of the expected one and 17% of one with the same glc retention time as the amination product from piperidine. [f] Two products (1.3 g) which showed molecular ion *m/e* 229 in their mass spectra and not 243 as expected for the amination product. [g] Consisted of several unidentified products. [h] Ref 1b.

shredding device.[3] The equipment was dried before assembling and a flow of dry lamp-grade nitrogen was employed to flush the system for 10 min before any reactants were added. A thermocouple, inserted through one of the openings at the top and immersed in the solution, was used to monitor the temperature. A rubber cooling tube[5] wrapped around the outer wall of the reaction flask was used to maintain the reaction mixture at room temperature.

The amine and 1 were introduced through a port at the top of the flask and stirred until the solution was complete.[4a] Sodium was then added slowly over a period of 1–2 hr from a 125-ml erlenmeyer flask attached by Gooch tubing to one of the addition ports.[4a] The sodium addition was slow enough to allow the metal spheres of each portion to be shredded into small pieces before more was added. A yellow-orange color usually developed in less than 10 min with most amine solvents. This color darkened to red and then to a red-brown color within 1–2 min and the solution became opaque. The color of the reaction mixture usually remained dark red-brown to brown against a muddy-appearing background.

Reduction of Naphthalene (1) with Sodium and *N*-Methylbutylamine.—To 12.8 g (0.1 mol) of 1 and 250 ml of *N*-methylbutylamine[4a] (bp 88–90°) contained in the reaction flask was added 9.2 g (0.4 g-atom) of sodium over a period of 1.5 hr. A yellow color developed on the metal surface immediately and the solution turned red-orange in *ca.* 2 min. This color darkened to red-brown in 30 sec and after 8 min the solution had gradually darkened to an opaque brown. This appearance remained until the reaction mixture was decanted from the unreacted sodium at the end of 3 hr and was poured cautiously over 400 ml of crushed ice. The resulting orange mixture was extracted with 500 ml of ether in three portions, and the ether layer was washed once with water and then twice with 10% aqueous HCl. The ether layer, which retained the hydrocarbons, was then washed with water until neutral. The acidic extracts and water washings were combined, made basic with NaOH, and extracted with ether. The amine-carrying ether layer was washed with water, dried (Na_2SO_4), and concentrated to yield 17.9 g of amines. Distillation at reduced pressure yielded 16.7 g (78%) of *N*-butyl-*N*-methyl-1,2,3,4-tetrahydro-2-naphthylamine, which appeared pure by glc analysis:[4b] bp 86° (0.2 mm); mass spectrum[6] (70 eV) *m/e* (rel intensity) 217 (25), 174 (100), 131 (71), 70 (20), 44 (35), 42 (33); nmr (CCl_4) four aromatic protons at δ 6.92 (singlet) and 19 aliphatic protons at 0.3–3.1 (several overlapping multiplets), with a singlet at 2.21.[4c]

Anal. Calcd for $C_{15}H_{23}N$: C, 82.89; H, 10.67; N, 6.45. Found: C, 82.90; H, 10.61; N, 6.78.

The ether layer containing the hydrocarbons was concentrated and steam distilled. Both pot residues and distillate were extracted with ether and dried (Na_2SO_4). Distillation of the ether from the extract of the distillate yielded 1.3 g of steam-volatile hydrocarbons. These were shown by glc analysis to be a mixture of 1:2:3:4 (8:22:50:28).[4d]

The ether extract of the pot residue was concentrated (rotary evaporator) to yield 1.2 g of a dark viscous oil. This was shown by glc analysis to be a mixture of dimers 7, 8, and 9, in which dimer 7 is the major one.[4b]

The reaction procedure and product analysis techniques given above are identical to those used for the other reaction products shown in the first part of Table I. The reductive amination products were shown by instrumental methods to be identical in structure with authentic samples of the expected amines.

Registry No.—Naphthalene, 91-20-3; *N*-methylbutylamine, 110-68-9; sodium, 7440-23-5; *N*-butyl-*N*-methyl-1,2,3,4-tetrahydro-2-naphthylamine, 35046-15-2.

Acknowledgments.—We thank the American Petroleum Institute for partial support.

(5) The tubing is made of thermal conducting material with a hemispherical cross section which allows close fit to the flask surface.

(6) We thank Mr. M. C. Hamming, Continential Oil Co., for this determination.

An Improved Procedure for the Synthesis of Fluorodinitroethyl and Trinitroethyl Esters of Carboxylic Acids

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Recent investigations in this laboratory concerning structure–physical property relationships of nitroaliphatic and fluoronitroaliphatic compounds generated a need for the bistrinitroethyl and bisfluorodinitroethyl esters of a homologous series of dibasic acids. Furthermore, we desired to obtain certain of these esters in rather large quantities for testing of explosive properties.

A study of the literature available to us revealed several approaches which have been used to effect esterifications with 2,2,2-trinitroethanol (1) and 2-fluoro-2,2-dinitroethanol (2). The low basicity of these alcohols requires the use of a strong condensing agent or a reactive carboxylic acid derivative to effect esterification. The esterification methods generally used are: (1) transesterification of the methyl ester of the desired acid and the alcohol in fuming sulfuric acid,[1] (2) the acid and alcohol in fuming sulfuric acid solvent,[2] (3) the acid and alcohol in polyphosphoric acid solvent,[3] (4) the aluminum chloride catalyzed reaction of the acid chloride and the alcohol in an inert solvent,[4] and (5) the neat acid chloride and the alcohol.[5] The first two of these methods have been found to work well only in specific cases and the yields of ester have been found to vary widely depending on the carboxylic acid used. Esterification of malonic acid and trinitroethanol in polyphosphoric acid failed to give us the desired ester. Esterification *via* the aluminum chloride catalyzed reaction of the acid chloride appeared to us to be the most generally applicable procedure giving good yields.

Although the acid chloride–aluminum chloride procedure gave excellent yields of the bistrinitroethyl glutarate and bistrinitroethyl pimelate, we obtained a colored product in the preparation of bistrinitroethyl sebacate. Column chromatography and repeated recrystallization from a variety of solvent systems failed to give us the pure ester. This problem, as well as the difficulty in obtaining the requisite acid chlorides of the desired carboxylic acids, prompted us to seek another esterification procedure using the cheaper and more readily available carboxylic acids.

Trifluoroacetic anhydride has been used successfully as a condensing agent in esterification reactions for some time.[6,7] The acetate and trifluoroacetate of 2,2-dinitropropanol have been prepared using trifluoroacetic anydride as condensing agent.[8] It also has been shown to be an exceptionally powerful reagent for the esterification of sterically hindered acids and/or alcohols.[9] The reported procedures generally involve dissolving the carboxylic acid and alcohol in trifluoroacetic anhydride solvent. Esterification generally proceeds in high yield by merely stirring the solution a short time at ambient temperatures.

We have found that this general procedure gives, in most cases, quantitative yields of 2,2,2-trinitroethyl and 2-fluoro-2,2-dinitroethyl esters with a variety of mono- and dicarboxylic acids (Table I). A reaction time of 1.5 hr at ambient temperature was found sufficient for the esterification of all the acids in Table I with the exception of malonic and ethylmalonic acids.[10] In all cases, the product is isolated by merely pouring the trifluoroacetic anhydride solution into cold aqueous 1 *M* potassium hydrogen phosphate solution and filtering the crude solid ester. Since trifluoroacetic anhydride is, by far, the lowest boiling constituent (bp 40°) of the crude reaction mixture before work-up, it should be possible, on a larger scale, to recover part of it by distillation before work-up.

Succinic acid failed to yield any ester with 1 under the reaction conditions employed. This result is due presumably to intramolecular anhydride formation competing with esterification.[6] Likewise, glutaric acid gave lower yields of esterified products than might be expected. Oxalic acid was fragmented by trifluoroacetic anhydride and yielded no ester.

Experimental Section

Caution! Both 2,2,2-trinitroethanol (1) and 2-fluoro-2,2-dinitroethanol (2) are moderately shock sensitive explosives and should be handled with care. Compound 2 may cause painful burns upon contact with the skin.

All carboxylic acids were obtained from commercial sources and used without further purification. Fluorodinitroethanol[11,12] was obtained from the Naval Ordnance Laboratory, White Oak, Md., and was distilled [bp 55–56° (0.5 mm)] prior to use. Trinitroethanol was prepared from tetranitromethane, dried by azeotropic distillation, and crystallized (mp 70°) from carbon tetrachloride–methylene chloride solution, all by known procedures.[13] The crystalline trinitroethanol was stored under carbon tetrachloride in the refrigerator. Trifluoroacetic anhydride was obtained from Eastman Organics and was used as received.

All melting points were obtained on a Mel-Temp apparatus using sealed tubes and are uncorrected. Nuclear magnetic resonance spectra were obtained on a Varian A-60 instrument using deuteriochloroform as solvent and tetramethylsilane as internal reference. Infrared spectra were obtained in chloroform solution on a Beckman IR-20 spectrophotometer. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

General Esterification Procedure.—A 50-ml, single-necked, round-bottomed flask containing a Teflon-coated magnetic

(1) M. H. Gold and K. Klager, *Tetrahedron, Suppl. 1*, **19**, 81 (1963).

(2) (a) M. B. Frankel, *J. Org. Chem.*, **27**, 331 (1962); (b) J. C. Colby (to U. S. Rubber Co.), U. S. Patent, 3,160,654 (Dec 8, 1964); *Chem. Abstr.*, **62**, 7644 (1965).

(3) (a) Reference 1; (b) L. A. Kaplan in "The Chemistry of the Nitro and Nitroso Groups," Part 2, H. Feuer, Ed., Interscience, New York, N. Y., 1970, p 305.

(4) Reference 2a.

(5) (a) N. S. Marans and R. P. Zelinski, *J. Amer. Chem. Soc.*, **72**, 5329 (1950); (b) H. Feuer, H. B. Hass, and R. D. Lowrey, *J. Org. Chem.*, **25**, 2070 (1960).

(6) J. M. Tedder, *Chem. Rev.*, **55**, 787 (1955).

(7) P. F. E. Cook and A. J. Showler, *J. Chem. Soc.*, 4594 (1965).

(8) L. W. Kissinger, M. Schwartz, and W. E. McQuistion, *J. Org. Chem.*, **26**, 5203 (1961).

(9) R. C. Parish and L. M. Stock, *ibid.*, **30**, 927 (1965).

(10) Presumably for steric reasons, optimum yields of esters of malonic and ethylmalonic acids were obtained after 18 hr at ambient temperature.

(11) M. J. Kamlet and H. G. Adolph, *J. Org. Chem.*, **33**, 3073 (1968).

(12) V. Grakauskas and K. Baum, *ibid.*, **33**, 3080 (1968).

(13) NAVORD Report (Naval Ordnance Laboratory, White Oak, Md.) 6752, K. E. Shipp and M. E. Hill, "An Improved Process for the Preparation of 2,2,2-Trinitroethanol," Jan 5, 1960, pp 14–17.

TABLE I

TRINITROETHYL AND FLUORODINITROETHYL ESTERS[a]

Acid	Alcohol	Crude yield, % (recrystallized yield, %)[b]	Registry no.	Mp, °C	Nmr data, δ	Ir data, cm^{-1}
Malonic	1	100 (94)	35027-56-6	56.0–57.0	5.49 (s, 4), 3.65 (s, 2)	1785, 1600, 1290
Glutaric	1	80 (77)	35027-57-7	61.0–62.0	5.45 (s, 4), 2.52 (t, 4), 2.05 (q, 2)	1765, 1600, 1295
Adipic	1	99 (96)	35027-58-8	88.5–90.0	5.41 (s, 4), 2.45 (t, 4), 1.70 (m, 4)	1770, 1605, 1295
Pimelic	1	99 (94)	35027-59-9	55.0–56.2	5.40 (s, 4), 2.45 (t, 4), 2.0–1.1 (m, 6)	1770, 1600, 1295
Suberic	1	100 (96)	35027-60-2	58.0–59.0	5.40 (s, 4), 2.40 (t, 4), 1.90–1.15 (m, 8)	1770, 1600, 1295
Sebacic	1	100 (94)	20721-00-0	46.0–47.0	5.40 (s, 4), 2.40 (t, 4), 1.90–1.15 (m, 12)	1770, 1600, 1295
Dodecanedioic	1	98 (93)	35027-62-4	33.0–33.7	5.40 (s, 4), 2.40 (t, 4), 1.90–1.15 (m, 16)	1770, 1600, 1295
Ethylmalonic	1	63 (40)	35027-63-5	47.2–48.5	5.45 (s, 4), 3.50 (t, 1), 1.98 (quint, 2), 1.00 (t, 3)	1770, 1600, 1290
Malonic	2	68 (55)	25595-91-9	47.2–49.5 (lit.[c] 46–47°)	5.30 (d, 4, J = 16 Hz), 3.60 (s, 2)	1780, 1605, 1305 [lit.[c] ir (Nujol) 1780, 1610, 1315]
Glutaric	2	47 (44)	35027-65-7	53.5–55.0	5.22 (d, 4, J = 17 Hz), 2.50 (t, 4), 2.05 (q, 2)	1770, 1605, 1310
Adipic	2	100 (97)	35027-66-8	77.0–78.0	5.22 (d, 4, J = 17 Hz), 2.45 (t, 4), 1.68 (m, 4)	1770, 1605, 1310
Pimelic	2	89 (80)	35027-67-9	34.0–35.0	5.22 (d, 4, J = 17 Hz), 2.44 (t, 4), 1.95–1.15 (m, 6)	1765, 1605, 1310
Suberic	2	100 (89)	35027-68-0	46.0–47.5	5.21 (d, 4, J = 17 Hz), 2.45 (t, 4), 1.95–1.15 (m, 8)	1765, 1605, 1310
Sebacic	2	99 (88)	35027-69-1	31.5–32.0	5.20 (d, 4, J = 17 Hz), 2.40 (t, 4), 1.95–1.15 (m, 12)	1765, 1605, 1310
Dodecanedioic	2	99 (95)	35027-70-4	40.0–42.2	5.21 (d, 4, J = 17 Hz), 2.40 (t, 4), 1.90–1.20 (m, 16)	1765, 1605, 1310
Ethylmalonic	2	100 (95)	35027-71-5	49.0–50.0	5.30 (d, 4, J = 16 Hz), 3.50 (t, 1), 1.97 (quint, 2), 1.00 (t, 3)	1765, 1605, 1305
Benzoic	2	92 (74)	35027-72-6	47.0–48.5	8.15–7.25 (m, 5), 5.43 (d, 2, J = 17 Hz)	1745, 1605, 1310
Cinnamic	2	100 (96)	35027-73-7	63.0–64.0	7.78 (d, 1, J = 16 Hz), 7.45 (m, 5), 6.38 (d, 1, J = 16 Hz), 5.30 (d, 2, J = 17 Hz)	1735, 1630, 1600, 1305

[a] All compounds in this table gave satisfactory (±0.3%) analyses for C, H, N, and F. The analytical data were made available to the referees and to the Editor. [b] Recrystallized yields represent first and second crops of ester from methanol–water. [c] Bis(2-fluoro-2,2-dinitroethyl) malonate has been reported: M. E. Hill, D. L. Ross, C. L. Coon, and L. O. Ross, *J. Chem. Eng. Data*, 14, 410 (1969).

stirring bar was charged with 11 mmol of a dicarboxylic acid or 22 mmol of a monocarboxylic acid, 25 mmol of 1 or 2 (4.60 g of 1 or 3.85 g of 2), and 10 ml of trifluoroacetic anhydride. The reaction flask was then fitted with a drying tube and the reaction mixture was stirred at ambient temperature for 1.5 hr.[10] The reaction mixture was then poured into 75 ml of a cold (ice temperature) solution of 1 M aqueous dipotassium hydrogen phosphate. The reaction flask was rinsed twice with methanol and the rinsings were added to the phosphate solution. The phosphate solution containing the oily ester was stirred at 5° until the ester solidified. The solidified crude ester was filtered, washed with water, and vacuum dried to give the crude yield in Table I.

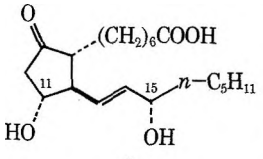
The crude esters were all recrystallized from methanol–water solution. The recrystallized yield in Table I is based only on the first and second crops from methanol–water.

See Editorial, *J. Org. Chem.*, **37**, No. 19, 4A (1972).

11,15-Epiprostaglandin E_2 and Its Enantiomer. Biological Activity and Synthesis

Summary: *ent*-11,15-Epiprostaglandin E_2 (**3**) has been synthesized starting from the hydroxy acid **4** *via* the lactone **6** (X = H; Y = OH). The bioactivity of **3** as measured by the stimulation of smooth muscle contraction was found to exceed by far that of its optical antipode 11,15-epiprostaglandin E_2 and to approach the activity of prostaglandin E_2 itself.

Sir: Prostaglandin E_1 (PGE_1) (**1**) stimulates contraction of a variety of smooth muscle tissues[1] at concentrations in the range 10^{-9} g/ml. The response of the same tissues to 15-epi-PGE_1 or 11-epi-PGE_1 is lower by one or two orders of magnitude.[2] It was of considerable interest therefore that racemic 11,15-epi-PGE_1 was found to exhibit approximately the same activity as PGE_1.[2] This observation brought into question the relative contributions of the two mirror image forms in the racemate to the measured biological activity. Preliminary tests with partially resolved material indicated that the *ent*-11,15-epi-PGE_1 component of the racemate might be more active than the antipode 11,15-epi-PGE_1.[2] These results prompted the synthetic and biological studies reported here for the PGE_2 series which have allowed an unambiguous conclusion. Both 11,15-epi-PGE_2 (**2**) and *ent*-11,15-epi-PGE_2 (**3**) have been synthesized, and the latter compound (**3**) has now been found to be far more active in smooth muscle stimulation than the former substance (**2**). Indeed, the activity of the *ent* form **3** approaches that of PGE_2 itself.



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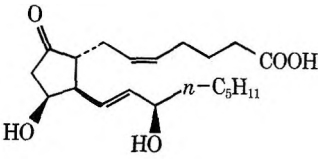

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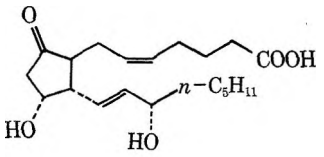
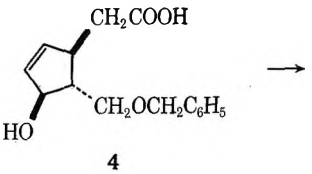


3

The synthesis of *ent*-11,15-epi-PGE_2 was carried out starting from the readily available salt of the levo acid **4** with (−)-amphetamine[3] by a modification of the scheme which has been employed for the synthesis of the various primary prostaglandins.[4] Iodolactonization[4] of **4** produced **5** [Z = I, R = H, X = $CH_2OCH_2C_6H_5$;[5] mp 120–121°; $[\alpha]^{28}D$ +36.1° (*c* 1.2, $CHCl_3$) (97%)], which was converted[4] to the *p*-phenylbenzoate ester **5** [Z = I, R = *p*-$C_6H_5C_6H_4CO$, X = $CH_2OCH_2C_6H_5$;[5] mp 164–166°; $[\alpha]^{28}D$ −1.43° (*c* 1.05, $CHCl_3$) (98% yield)], and further *sequentially* by deiodination using tributyltin hydride to **5** [Z = H, R = *p*-$C_6H_5C_6H_4CO$, X = $CH_2OCH_2C_6H_5$;[5] mp 98–100°; $[\alpha]^{25}D$ +88.2° (*c* 1.2, $CHCl_3$) (95%)], hydrogenation[4] (Pd/C catalyst) to the primary alcohol **5** [Z = H, R = *p*-$C_6H_5C_6H_4CO$, X = CH_2OH;[5] mp 130–131°; $[\alpha]^{24}D$ +88.3° (*c* 1.1, $CHCl_3$) (92%)], and oxidation[4] (Collins reagent) to the aldehyde **5** (Z = H, R = *p*-$C_6H_5C_6H_4CO$, X = CHO).[5a] This last intermediate was directly condensed with the sodio derivative of dimethyl 2-oxoheptylphosphonate[4] to yield (67% over two steps) the oily enone **5** [Z = H, R = *p*-$C_6H_5C_6H_4CO$, X = CH=CHCO-*n*-C_5H_{11}; $[\alpha]^{25}D$ +146.4° (*c* 1.2, $CHCl_3$)],[5a] reduction of which by sodium borohydride in ethanol at −20° afforded the 15*S* alcohol **6** (X = $OCOC_6H_4C_6H_5$, Y = H, R = H),[5] along with the 15*R* epimer.[6] The configuration at C-11 in this 15*S* derivative was inverted in ~50% overall yield by the sequence (1) tetrahydropyranylation of the 15-hydroxyl; (2) cleavage of the *p*-phenylbenzoate ester (1 equiv of potassium carbonate in methanol at 25° for 1 hr) to form **6** (X = HO, Y = H, R = THP);[5a] (3) tosylation (2.0 equiv of tosyl chloride in pyridine at 25° for 19 hr) to form **6** (X = TsO, Y = H, R = THP);[5a] (4) reaction with 6.7 equiv of tetrabutylammonium formate in acetone at 25° for 16 hr[7] to form **6** (X = H, Y = HCO_2, R = THP);[5a] and (5) formate cleavage (potassium carbonate in methanol) and tetrahydropyranylation to



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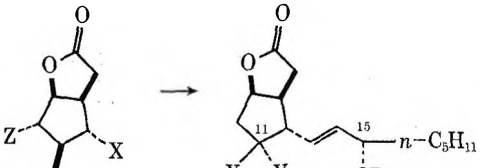

5 **6**

(1) For example, rat uterus, guinea pig ileum, gerbil colon.

(2) P. W. Ramwell, J. E. Shaw, E. J. Corey, and N. Andersen, *Nature*, **221**, 1251 (1969).

(3) This salt had mp 111–112.5°, $[\alpha]^{26}D$ −17.25° (*c* 1.0, $CHCl_3$). For the preparation of the enantiomeric salt, see E. J. Corey, S. M. Albonico, U. Koelliker, T. K. Schaaf, and R. K. Varma, *J. Amer. Chem. Soc.*, **93**, 1491 (1971).

(4) See (a) E. J. Corey, T. K. Schaaf, W. Huber, U. Koelliker, and N. M. Weinshenker, *ibid.*, **92**, 397 (1970); (b) E. J. Corey, N. M. Weinshenker, T. K. Schaaf, and W. Huber, *ibid.*, **91**, 5675 (1969).

(5) Satisfactory (a) ir and nmr spectra and (b) analytical data have been obtained for this substance.

(6) The 15*S*- and 15*R*-epimeric alcohols (which exhibited, respectively, R_f 0.23 and 0.44 upon thin layer chromatography using silica gel plates with benzene–ethyl acetate, 3:1) were separated chromatographically. The 15*S* alcohol **6** (X = OH, Y = H, R = H) was obtained as an oil, $[\alpha]^{28}D$ +99.3° (*c* 1.1, $CHCl_3$).

(7) E. J. Corey and S. Terashima, *Tetrahedron Lett.*, 111 (1972).

form 6 [X = H, Y = THPO, R = THP;[5a] $[\alpha]^{25}D$ $-103°$ (*c* 0.54, $CHCl_3$)] as a colorless oil. The synthesis of *ent*-11,15-epi-PGE_2 (**3**) from this last intermediate was accomplished by the standard[4] sequence (1) lactone → lactol reduction[4] (97% yield) using 2.0 equiv of diisobutylaluminum hydride in hexane at $-70°$ for 25 min; (2) Wittig reaction of the lactol with the ylide derived from 5-triphenylphosphoniopentanoic acid[4] (51% yield); (3) Jones oxidation of the resulting 11,15-bistetrahydropyranyl derivative of *ent*-11,15-epi-$PGF_{2\alpha}$ to form the 11,15-bistetrahydropyranyl derivative of **3** (90%); and finally (4) THP cleavage using 2:1 acetic acid–water to form *ent*-11,15-epi-PGE_2 (**3**) (80% yield), obtained as a colorless oil by thin layer chromatographic purification,[8] $[\alpha]^{22}D$ $+25.5°$ (*c* 1.04, tetrahydrofuran). The nmr and ir spectra of a purified sample of **3** synthesized in this way were identical with those obtained for its enantiomer **2**.[9]

The preparation of 11,15-epi-PGE_2 (**2**) was carried out from 15-epi-PGA_2[10] by a previously reported[11] sequence. The material so obtained was a colorless oil, $[\alpha]^{25}D$ $-26.7°$ (*c* 0.49, tetrahydrofuran), chromatographically and spectroscopically identical with a reference sample provided by Dr. John E. Pike of the Upjohn Co.

Tissue contraction in response to PGE_2 and the two test substances **2** and **3** were measured *in vitro* as previously[2] outlined for (a) isolated rat uterus and (b) isolated gerbil colon preparations.[12] For a given tissue preparation a log dose–response curve was obtained first for the standard PGE_2 and immediately thereafter for the test substance **2** or **3**, and in this way relative potencies were ascertained. These results are summarized in Table I. From these data it is apparent that *ent*-11,15-epi-PGE_2 (**3**) is considerably more active than 11,15-epi-PGE_2 (**2**) in agreement with the results of the preliminary studies reported earlier[2] for the corresponding PGE_1 isomers.

TABLE I

RELATIVE POTENCIES OF PROSTAGLANDINS IN SMOOTH MUSCLE CONTRACTION

Prostaglandin	Rat uterus	Gerbil colon
PGE_2 (standard)	1.0	1.0
11,15-Epi-PGE_2[a]	0.011–0.012[b]	0.01–0.02[b]
ent-11,15-Epi-PGE_2[c]	0.50–0.55[b]	0.18–0.20[b]

[a] Concentration range 50–100 ng/ml. [b] Range of potencies covers results from different muscle specimens. [c] Concentration range 1–4 ng/ml.

An interesting inhibitory behavior was also observed for substances **2** and **3**. These were found to inhibit strongly the action of PGE_2 on rat uterus and gerbil colon preparations. That is, after exposure of the tissue to either **2** or **3** at concentrations in the test range, replacement of the tissue bath and addition of PGE_2, little if any response could be measured. For example, addition of 1 ng/ml of PGE_2 to the treated tissue produced <5% of the normal response. Although pretreatment with **2** and **3** in effect desensitized the tissue to PGE_2, such tissue responded normally to addition of more of the original substrate **2** or **3**.

The high biological activity of *ent*-11,15-epi-PGE_2 is most intriguing. The many possibilities for rotation about the carbon–carbon bonds in the α and ω side chains lead to a substantial number of reasonable conformations which can in principle interact with a receptor site. This flexibility in fact allows the generation of conformers from PGE_2 and *ent*-11,15-epi-PGE_2 which have quite similar geometry, especially with regard to overall molecular shape and the relative disposition of polar groups.

It seems reasonable to conclude from the above results that the *ent*-11,15-epi series of prostaglandins deserves further study at least with regard to (1) biological activity in different tissues, (2) mode of interaction with receptor sites, and (3) inhibition of other prostaglandins.[13]

(8) Two successive chromatographic separations were used, one with silica gel using 10% methanol in chloroform for development and the second with silver nitrate impregnated silica gel using *n*-hexane–methylene chloride–tetrahydrofuran–acetic acid (6:2:2:1) for development. Because both **3** and **2** undergo slow dehydration to PGA_2-type products even upon storage at $-20°$, the samples employed for the biological tests were additionally purified by high pressure liquid chromatography on silica gel (Chromatronix instrument) shortly before use.

(9) *ent*-11,15-Epi-PGE_2 was prepared both in Cambridge and Palo Alto by essentially identical procedures and, after similar purification procedures, exhibited identical bioassay, tlc, high pressure chromatography, and nmr results. However, the Palo Alto sample had $[\alpha]D$ $+39.8°$ (*c* 0.67, tetrahydrofuran) which is as yet unexplained. The corresponding (−)-ephedrine salt of the levo methoxy ether,[4] $[\alpha]D$ $-36.0°$ (*c* 1.4, methanol), was used as starting material for this preparation.

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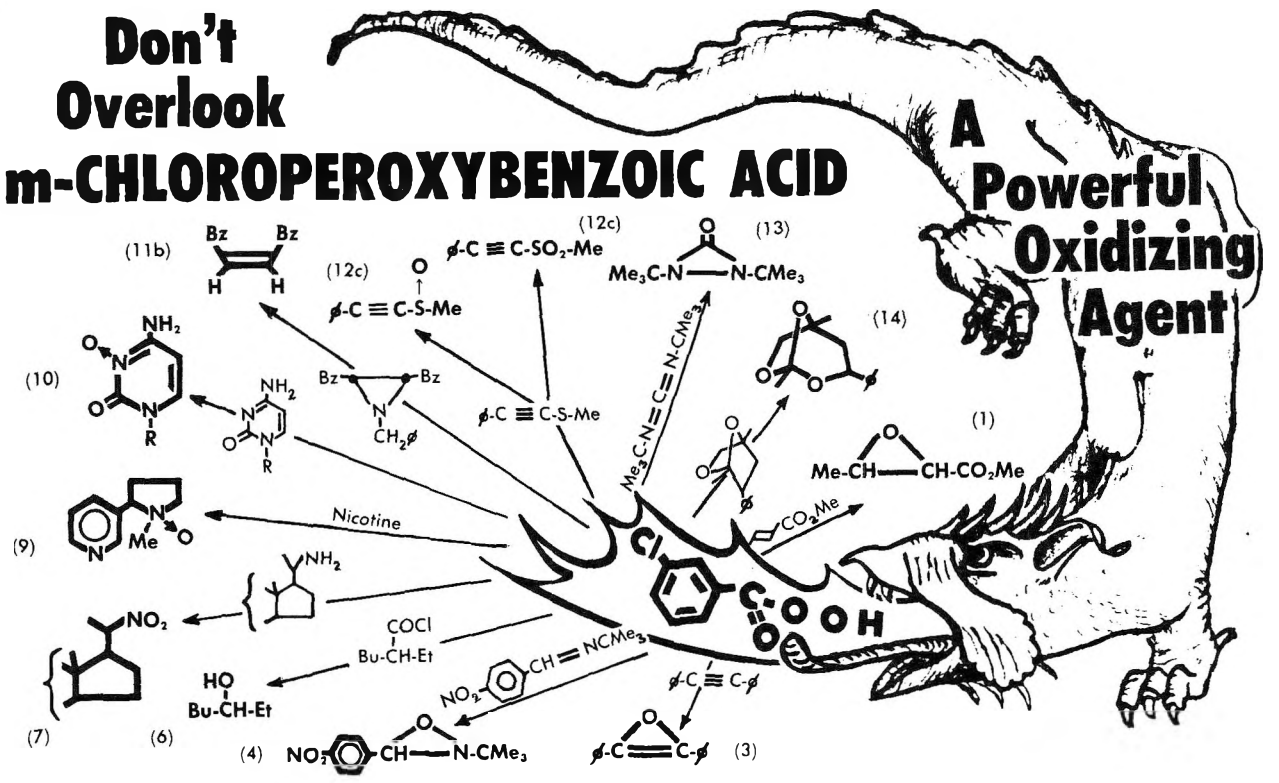
Don't Overlook m-CHLOROPEROXYBENZOIC ACID A Powerful Oxidizing Agent



m-CPBA is a superior oxidizing agent compared to hydrogen peroxide or other peracids in reactivity, stereoselectivity, and in purity and yield of products. Isolated **carbon-carbon double bonds** and the less reactive α,β-**unsaturated esters** are smoothly oxidized to **epoxides** in high yields.[1] In **nonconjugated dienes,** selective epoxidation occurs in the more substituted double bond.[2] Disubstituted **acetylenes** can be oxidized to **oxirenes** which break down to ketones, carboxylic acids, or esters depending on the reaction conditions.[3] Like olefins, **imines** are oxidized to the corresponding **oxaziranes.**[4]

m-CPBA is an excellent reagent for the **Baeyer-Villiger oxidation** of ketones to esters, such as acetylcyclanes[5a] and acetophenones.[5b] Related to this reaction is the conversion of **acid chlorides to alcohols in which -OH replaces -CO_2H.** For example, 3-heptanol was obtained in 73% overall yield from 2-ethylhexanoyl chloride.[6]

Primary amines can be converted to **nitroalkanes,** and the yields decrease in the order: **tert**-alkyl > **sec**-alkyl > n-alkyl.[7] **Secondary amines** give **nitroxide radicals,**[8] whereas **tertiary amines** afford the **N-oxides.**[9] Hence, nicotine is converted to the N'-oxide and to the N,N'-dioxide by 1 and 2 equivalents of m-CPBA, respectively. Among the nucleic acid bases, nucleosides, and nucleotides, only the **cytosine** and **adenine series** can be oxidized to **N-oxides.**[10] Uracil, thymine, and guanosine and their derivatives gave ring-cleavage products. N-substituted **aziridines** are presumably oxidized to the corresponding **N-oxides.**[11] This reaction is successfully used in the stereospecific **deamination of N-alkylaziridines** to **olefins.**[11b]

Sulfides can be selectively oxidized to **sulfoxides**[12] or **sulfones**[12a] in excellent yields, even in the presence of amine functions,[12b] or carbon-carbon double and triple bonds.[12c] Some **diaziridinones** have been prepared from **carbodiimides,**[13] and some **ortho esters** from **ketals.**[14]

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