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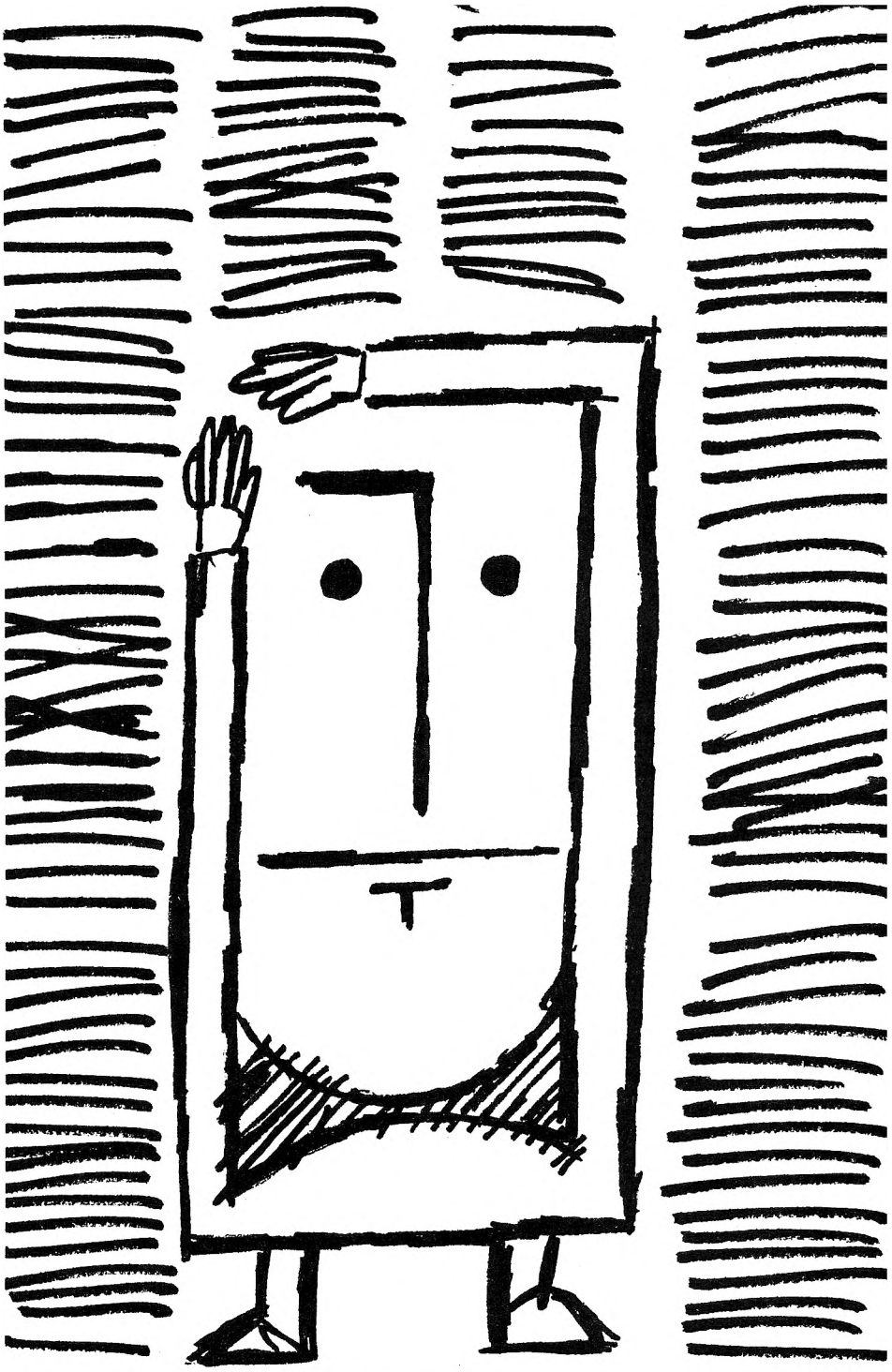

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Thermal Transformations of an Aminomalononitrile and of an Aminocyanoketenimine. Evidence for Homolysis and Heterolysis and for Aminocyanocarbenes

LOUIS DEVRIES

Chevron Research Company, Richmond, California 94802

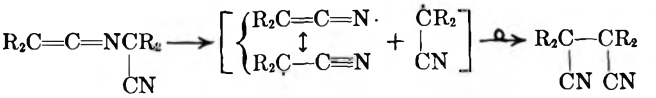
Received May 11, 1973

In refluxing toluene *N-tert*-octylaminocyanoketen-*N-tert*-octylimine (**3**) and *tert*-octylaminomalononitrile (**1**) both thermolyze. Additionally, **3** rearranges to give *tert*-octylamino-*tert*-octylmalononitrile (**10**). It is proposed that in each case the initial intermediate is a hybrid ion pair–radical pair in a solvent cage. This intermediate may either proceed directly to products or may—with increasing solvent separation—diverge into distinct ion and radical pairs. In the case of **3**, combination or disproportionation reactions can account for the formation of all identified products with the exception of *tert*-octylimino-*tert*-octylacetonitrile (**12**) and of di-*tert*-octylaminomaleonitrile (**16**). Stoichiometrically, these compounds are related to **3** as the products of elimination and addition of hydrogen cyanide. With β-cis elimination ruled out by MO-symmetry considerations, it is proposed that cyanide ion is generated by α elimination from the *tert*-octylaminomalononitrile anion which is the anionic component in the proposed ion pairs. Combination of the resulting *tert*-octylaminocyanocarbene (**11**) with the *tert*-octyl cation—the cationic component—and subsequent elimination of a proton gives **12**. In the case of **1**, Thorpe-type dimerization appears to compete with thermolysis since a triaminotricyanopyroline, **22**, was isolated. Formation of this compound may involve addition of hydrogen cyanide to an iminopyroline resulting from cyclization of the initial Thorpe dimer. Also obtained was an enaminoimine **23** which formally corresponds to the product of elimination of hydrogen cyanide from the dimer, but which may originate from insertion of the aminocyanocarbene **11** in the C–H bond of **1**. From the thermolysis of neat **1** a dehydrogenation product of the Thorpe dimer was isolated. It is proposed that **11** is responsible for the hydrogen abstraction.

In an earlier paper[1] the reactions of *tert*-octylaminomalononitrile (**1**) and of *N-tert*-octylaminocyanoketen-*N-tert*-octylimine (**3**) in basic media are described.

Esr evidence shows that under these conditions **1** gives the relatively stable *tert*-octylglycinonitrile radical (**18**). Additionally, the formation of the *tert*-octylaminomalononitrile radical (**5**) is indicated. The evidence points to initial α elimination of hydrogen cyanide from **1** to give the *tert*-octylaminocyanocarbene (**11**);[1] however, competing β elimination to give the tautomeric *tert*-octyliminoacetonitrile (**13**) is difficult to rule out.

Therefore, the uncatalyzed thermolysis of **1** and **3** became of interest. Under these conditions β elimination can be virtually ruled out. Concerted β-cis elimination is forbidden by the MO symmetry rules,[2,3] and the alternative nonconcerted β-trans elimination should be a high-energy process because it implies ionization without solvation. Moreover, as previously pointed out,[1] heterolysis of aminomalononitriles such as **1** is unlikely even in a solvating medium. These predictions are experimentally confirmed (see below). Homolytic paths are likely in the thermolysis of **3**, since a number of thermal rearrangements of ketenimines have been reported to involve the formation and recombination of radicals. Examples are R = CH_3,[5] R_2 = $-(CH_2)_5-$.[6]



Results and Discussion

Thermolysis of the Aminocyanoketenimine 3.—In the thermolysis of **3** (Scheme I) the major isolated products are 2,4,4-trimethylpentene-1 (**7**), 2,4,4-trimethylpentane (**8**), *tert*-octylimino-*tert*-octylaminomalononitrile (**10**), and *tert*-octylimino-*tert*-octylacetonitrile (**12**). Minor isolated products are di-*tert*-octylaminotricyanoethane (**19**), di-*tert*-octylaminomaleonitrile (**16**), and di-*tert*-octyliminosuccinonitrile (**25**). Additionally,

(1) L. de Vries, *J. Org. Chem.*, **38**, 2604 (1973).

(2) R. Hoffmann and R. B. Woodward, *Science*, **167**, 825 (1970).

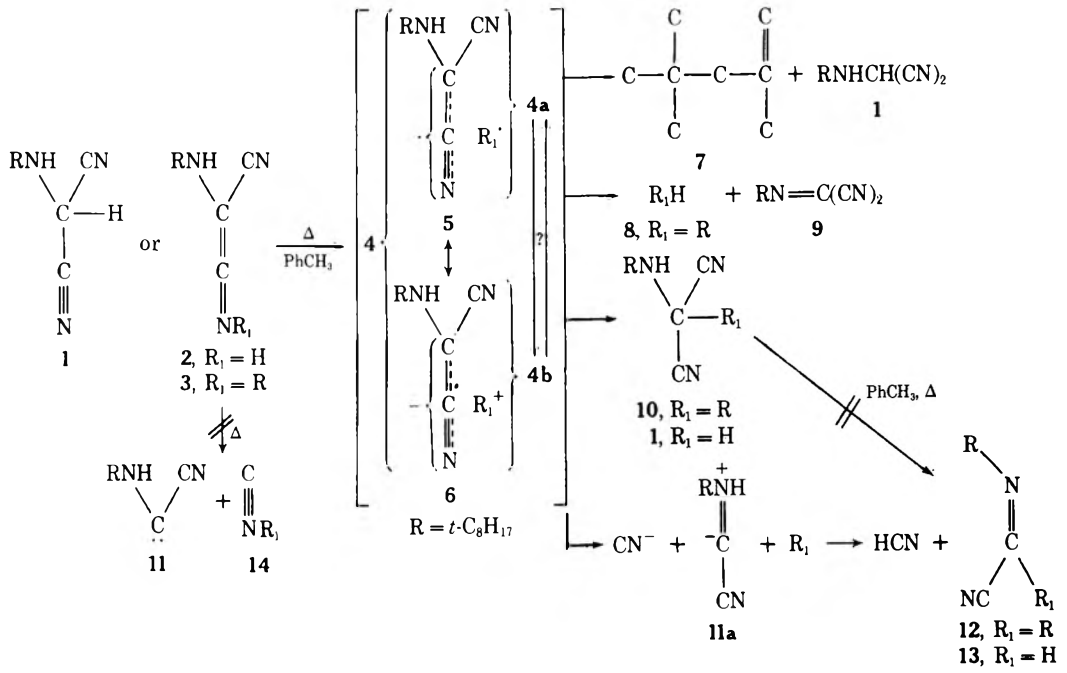
(3) It has recently been recognized that some reactions in which orbital symmetry is not conserved may yet occur in a concerted manner.[4] These are, however, likely to be high-energy processes, requiring conditions of considerably greater severity than those used in the present work.

(4) J. E. Baldwin, A. H. Andrist, and R. K. Pinschmidt, *Accounts Chem. Res.*, **5**, 402 (1972); J. A. Berson, *ibid.*, **5**, 406 (1972).

(5) G. S. Hammond, O. D. Trapp, R. T. Keys, and D. L. Neff, *J. Amer. Chem. Soc.*, **81**, 4878 (1959).

(6) H. D. Waits and G. S. Hammond, *J. Amer. Chem. Soc.*, **86**, 1911 (1964).

SCHEME I



the presence of small amounts of *tert*-octylaminomalononitrile (1) and of *tert*-octyliminomalononitrile (**9**)[7] is indicated by glpc.

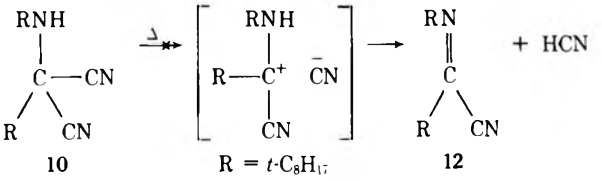
Moreover, hydrogen cyanide is evidently evolved as well, because among the above thermolysis products the diaminomaleonitrile **16** is the adduct of hydrogen cyanide to **3**,[8] while the iminoacetonitrile **12** is the (stoichiometric) product of elimination of hydrogen cyanide from **3**.

The restrictions imposed by the MO symmetry rules suggest that none of these products is formed by a concerted process. Specifically, the formation of the aminomalononitrile **10** by rearrangement of the aminocyanoketenimine **3** involves a 1,3 shift of a *tert*-octyl group from nitrogen to carbon. A concerted shift of this type is symmetry forbidden because it is equivalent to a suprafacial 1,3 shift in an allylic system with retention of configuration in the migrating group.[9] Steric considerations lead independently to the same conclusion: the linearity of the C–C–N system in both the initial ketenimine and the final nitrile makes it impossible for the migrating group to remain bonded to both ends of the unsaturated system throughout the rearrangement, as is required for a concerted process.

Concerted β-cis elimination is another symmetry-forbidden process. Concerted decomposition of the aminocyanoketenimine can, therefore, not account for the formation of the trimethylpentene **7** and the aminomalononitrile **1** (by way of its ketenimine tautomer **2**).

Similarly, the hydrogen cyanide that is formed in the thermolysis of **3** cannot originate by the forbidden β-cis-elimination route from the aminomalononitriles **1** or **10** (both of these are thermolysis products). For the case of **10**, this conclusion is experimentally verified. Upon β elimination of hydrogen cyanide **10** would give the iminoacetonitrile **12**. In the thermolysis of **3** in refluxing toluene for 18 hr **12** is a major product, but under identical conditions no **12**, and therefore no hydrogen cyanide, is produced from **10** which is quantitatively recovered.

In summary, a nonconcerted, rather than a concerted, mechanism is indicated for the thermolysis of **3**. That this process has homolytic features is suggested by the formation of thermolysis products such as 2,4,4-trimethylpentane (**8**) and the iminomalononitrile **9**, which is formally the product of dehydrogenation of **1**. On the other hand, the formation of hydrogen cyanide points to a heterolytic pathway, since the C≡N radical is a high-energy species.[10] The simplest nonconcerted heterolytic process leading to hydrogen cyanide and **12** is a β-trans elimination, involving initial ionization of aminomalononitrile **10** to give a cyanoimmonium cyanide and subsequent deprotonation of the immonium ion by the cyanide counterion to give **12**. This path is, however, *a priori* improbable for reasons mentioned above and is experimentally ruled out by the demonstrated thermal stability of **10** in refluxing toluene.



The formation of all isolated thermolysis products can be rationalized by a single mechanism with homolytic, as well as heterolytic, features if one assumes that the first intermediate is an intimate ion pair–radical pair hybrid in a solvent cage (**4**, Scheme I). This initial intermediate may directly proceed to products or, with increasing solvent separation, it may diverge into distinct ion pairs (**4b**) and radical pairs (**4a**). This seems a reasonable possibility, since both the radical and the anion derived from *tert*-octylamino-

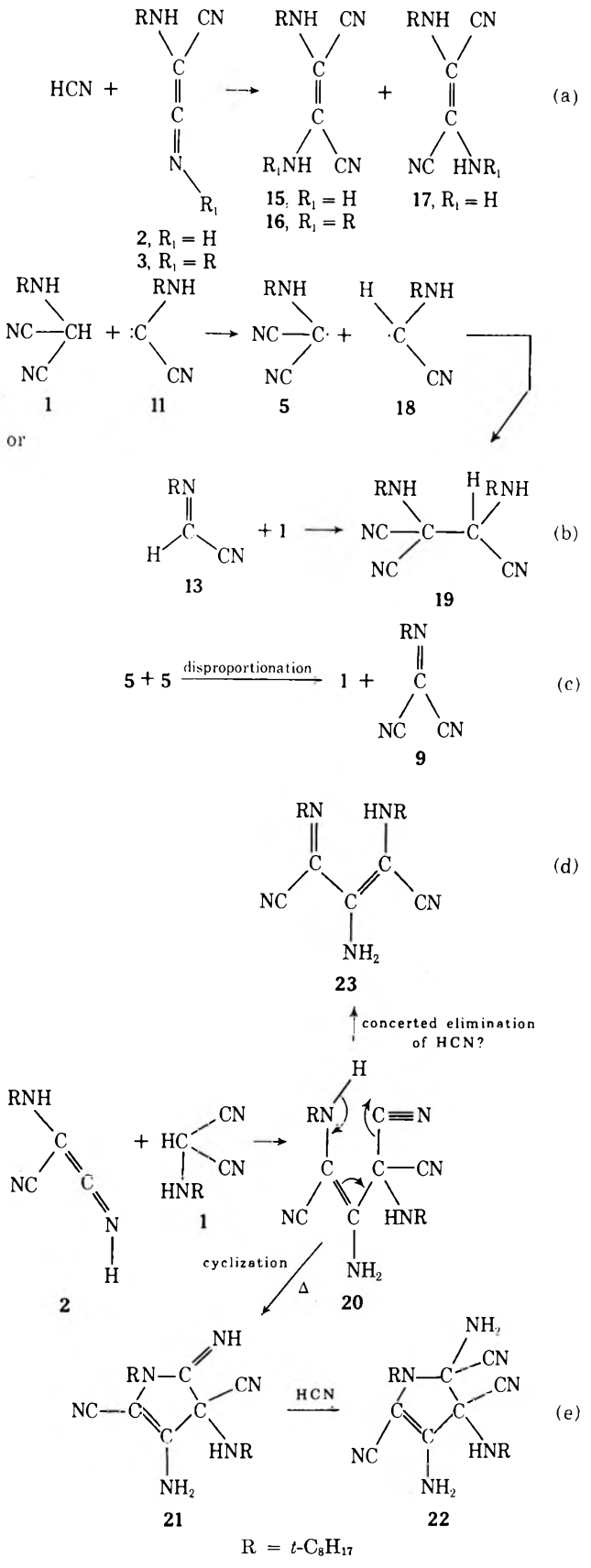
(7) Compound **9** is prepared in high yield by dehydrogenation of **1** with tetracyanoethylene or benzoyl peroxide.[1]

(8) L. deVries, *J. Org. Chem.*, **36**, 3442 (1971).

(9) R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry," Academic Press, New York, N. Y., 1970, p 114.

(10) J. C. Boden and B. A. Trush, *Proc. Roy. Soc., Ser. A*, **305**, 107 (1968).

SCHEME II



malononitrile (**5** and **6**) are presumably resonance-stabilized species.[1]

Walling[11] has proposed a similar ion pair–radical pair hybrid—later diverging into distinct ion pairs and radical pairs—in order to account for the competing homolytic and heterolytic decomposition paths of acyl peroxides.

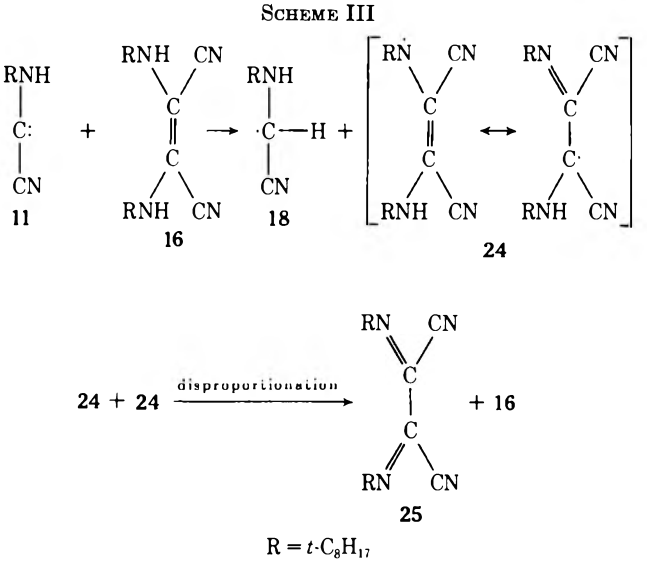
Recombination and disproportionation in **4**, **4a**, or **4b** can account for the formation of **7**, **8**, **9**, and **10**.

The ion pair **4b** also explains the formation of the iminoacetonitrile **12** and of hydrogen cyanide. Inside the solvent cage the aminomalononitrile anion **6** may expel a cyanide ion to give the aminocyanocarbene **11** (shown in the ylide form **11a**). Combination of **11** with R^+, followed by expulsion of a proton, results in formation of **12**. The hydrogen cyanide thus produced adds to **3** to give the isolated diaminomaleonitrile **16** (reaction a, Scheme II).

It may be significant that thermolysis of neat **3** (as opposed to **3** in refluxing toluene) gives no rearrangement product **10**. Under these conditions the main product is the iminoacetonitrile **12**.

Evidence presented earlier[1] suggests that the carbene **11** could be a fairly long-lived species, capable of diffusing out of the initial solvent cage to react with other molecules in the environment, primarily through hydrogen abstraction. The formation of the diiminosuccinonitrile **25** (Scheme III) can be rationalized in this manner,

SCHEME III



since under dehydrogenating conditions **25** is readily formed from the diaminomaleonitrile **16**. Esr shows that a stable radical is involved.[1]

It is proposed that abstraction of hydrogen from the diaminomaleonitrile **16** by the carbene **11** results in the initial formation of the radical **24**. Disproportionation of this radical then generates the diiminosuccinonitrile **25** and regenerates **16** (Scheme III). This mechanism is supported by the observation that the diiminosuccinonitrile **25** is also produced when the carbene **11** is generated (from the aminomalononitrile **1** and triethylamine) in the presence of an excess of the diaminomaleonitrile **16**.

Formation of the carbene **11** also suggests two routes —both discussed earlier[1]—to the diaminotricyanoethane **19** (reaction b, Scheme II).

(1) Hydrogen abstraction by the carbene **11** from the concomitantly formed aminomalononitrile **1** results in the formation of the glycinonitrile radical **18** and the

(11) C. Walling, H. D. Waits, J. Milanovic, and C. G. Pappiaonnou, *J. Amer. Chem. Soc.*, **92**, 4927 (1970); see also J. E. Leffler and A. A. More, *ibid.*, **94**, 2483 (1972).

aminomalononitrile radical **5**. These radicals may combine to yield **19**.

(2) The carbene **11** first rearranges to the more stable iminoacetonitrile **13**, to which **1** adds to give **19**.

In summary, the mechanism shown in Scheme I could account for the formation of all products identified in the thermolysis of the aminocyanoketenimine **3**. Proof is however needed that the carbene **11** is not formed by an alternative route that does not involve the ion pair–radical pair intermediate **4**. Such a route could be thermal dissociation of the aminocyanoketenimine **3** to give **11** and *tert*-octylisonitrile (**14**, Scheme I). This would constitute a reversal of a reaction observed by Ciganek,[12] *i.e.*, the addition of a carbene to an isonitrile to give a ketenimine.

Such a direct formation of **11** is, however, very improbable. According to Hoffmann, Gleiter, and Mallory,[13] orbital symmetry rules demand that two dimerizing singlet carbenes approach each other in perpendicular planes to give an olefin. The principle of microscopic reversibility implies, therefore, that coplanar dissociation of an olefin to give two singlet carbenes (or other singlet species) is symmetry forbidden and that the π bond must first be broken in an initial 90° twist. Such a high-energy process would be required for thermal dissociation of **3** since the isonitrile **14** is a ground-state singlet as is assumedly the carbene **11**.[1] Glpc analysis confirms the nonoccurrence of this process, since *tert*-octylisonitrile was shown to be absent among the thermolysis products.

The thermolysis of ketene-*N*-*tert*-butylimines, which are structurally similar to **3**, has been reported to give isobutene and a nitrile.

$$R_1R_2C{=}C{=}NC(CH_3)_3 \xrightarrow{\Delta} R_1R_2CHCN + H_2C{=}C(CH_3)_2$$

Ciganek[14] found first-order kinetics for this reaction and proposed that it may be analogous to a reverse ene reaction. However, the required cyclic, six-membered transition state appears to be highly strained owing to the linearity of the ketenimine moiety. (See, however, ref 14.) Disproportionation of an ion pair–radical pair intermediate similar to **4** is an attractive alternative. Such a mechanism would be analogous to that proposed above for the thermolysis of **3**. Ciganek considered a radical mechanism but dismissed it because neither isobutane nor the dimers of the *tert*-butyl radical and of the radical $R_1R_2\dot{C}C{\equiv}N$ are found among the products. (In this system isobutane would originate from disproportionation of a pair of *tert*-butyl radicals.[14b]) Formation of these products is not expected, however, if an initial ion pair–radical pair proceeds directly to products within the solvent cage and does not dissociate to give individual radicals.

Thermolysis of the Aminomalononitrile 1.—Thermolysis of **1** in toluene gave a product mixture from which six products have been isolated and identified (Scheme II). For one of these the triaminotricyanopyroline structure **22** is proposed; the others are the two diaminodicyanoethylene isomers **15** and **17** (the maleonitrile and fumaronitrile structures are unassigned), the diaminotricyanoethane **19**, the enaminoimine **23**, and the iminomalononitrile **9**. Several additional products were separated by chromatography but were not identified, since they could not be purified by crystallization.

The initial step in the formation of triaminotricyanopyroline **22** may be Thorpe-type dimerization of **1** to give **20**. It is hypothesized that cyclization of this dimer gives **21**, to whose imino group hydrogen cyanide adds to give **22** (reaction e, Scheme II). A mechanistically similar cyclization of the trimer of malononitrile has been reported.[15] Other structures fit the formula of **22** ($C_{23}H_{39}N_7$), which was determined by elemental analysis and mass spectra, but only the triaminotricyanopyroline is consistent with the nmr evidence. (See Experimental Section.)

Formation of the remaining products in the thermolysis of **1** can be explained by a mechanism analogous to that proposed for the thermolysis of **3**. This implies a hybrid ion pair–radical pair intermediate which, among other products, gives rise to the carbene **11** and to hydrogen cyanide.

Addition of the hydrogen cyanide to **1** accounts for the formation of the two isomeric *N*-alkyldiaminodicyanoethylenes **15** and **17**[16] (reaction a, Scheme II).

The enaminoimine **23** may originate from insertion of the carbene **11** into the C–H bond of **1**, as proposed earlier[1] for the formation of **23** from **1** in triethylamine.

Under thermolytic conditions 1,4 elimination of hydrogen cyanide from the Thorpe dimer **20** must be considered a possible alternative route to **23** (reaction d, Scheme II). An uncatalyzed, concerted process of this type is MO symmetry allowed, but appears questionable in view of the mildness of the conditions. Not only does it require a hydrogen to leave from a relatively basic amino group but, additionally, the nitrile group is a very poor leaving group.

Conceivably, elimination of hydrogen cyanide from the Thorpe dimer **20** could also be bimolecular and autocatalyzed by one of the amino groups. However, this appears improbable as well, because the basicity of these amino groups is lowered owing to inductive or tautomeric electron withdrawal by the nitrile groups.

The iminomalononitrile **9** could originate from direct disproportionation of the radical pair–ion pair intermediate **4** with generation of molecular hydrogen (Scheme I, R_1 = H). Although this may occur, there is no experimental evidence to support the evolution of hydrogen.

It seems more likely that the aminocyanocarbene **11** is the hydrogen-abstracting species. According to a mechanism discussed earlier[1] (reaction b Scheme II), **11** initially abstracts a hydrogen atom from the aminomalononitrile **1**, to yield simultaneously the glycinonitrile radical **18** and the aminomalononitrile radical **5**. Combination of **5** and **18** gives the diaminotricyanoethane **19**. Disproportionation of **5** gives **9** and regenerates **1** (reaction c, Scheme II).

When *tert*-octylaminomalononitrile (**1**) is heated in the absence of solvent at 60°, a thermolysis mixture results which differs profoundly from that obtained in refluxing toluene. Under the solvent-free conditions, the enaminoimine **23** is still formed, but the diamino-

(12) E. Ciganek, *J. Org. Chem.*, **35**, 862 (1970).

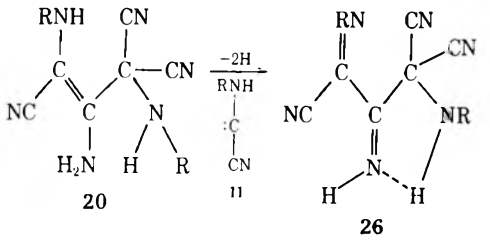
(13) R. Hoffmann, R. Gleiter, and F. B. Mallory, *J. Amer. Chem. Soc.*, **92**, 1460 (1970).

(14) (a) E. Ciganek, *Tetrahedron Lett.*, **59**, 5179 (1969); (b) ref 14a, footnote 8.

(15) H. Junek and H. Sterk, *Z. Naturforsch.*, **22**, 732 (1967).

(16) The assignment of a 1-*tert*-octylamino-2-aminodicyanoethylene structure to **17** is based on elemental analysis, on mass spectrum, and on the striking similarity of its ir and nmr spectra to those of the configurationally isomeric **15**, which was isolated earlier.[1]

tricyanoethane **19** is not found, although it is a major component in refluxing toluene. Similarly, neat **1** gives very little of the triaminotricyanopyroline **22** and only a trace of *tert*-octyliminomalononitrile (**9**) is shown by glpc. On the other hand, relatively more of the diaminodicyanoethylene isomers **15** and **17** is found and additionally a new compound is isolated. According to elemental analysis and spectral evidence (see Experimental Section) this is 1-*tert*-octylimino-2-imino-3-*tert*-octylamino-1,3,3-tricyanopropane (**26**), which is formally the product of dehydrogenation of the Thorpe dimer **20**. The hydrogen abstraction which is implied in this formula is attributed to the aminocyanocarbene **11**.



Conclusion

It thus appears that the intermediates involved in the thermolyses of **1** and **3** are either identical with or are closely related to those postulated for the reactions of these same compounds in basic media. Under the latter conditions, most of the evidence for the intermediacy of *tert*-octylaminocyanocarbene was of an indirect nature. In the thermolysis reactions, however, this intermediate appears more directly implicated owing to the mechanistic restrictions imposed by the MO symmetry requirements.

Experimental Section

Equipment.—The following instruments were used: a Perkin-Elmer 621 double-beam grating ir spectrometer, a Laser-Raman Cary 81 spectrometer, and a Varian HA-100 nmr spectrometer.

Materials.—*tert*-Octylaminomalononitrile (**1**)[1] and *tert*-octylaminocyanoketen-*N*-*tert*-octylimine (**3**)[8] were prepared as described in earlier papers.

***tert*-Octylamino-*tert*-octylmalononitrile (10) by Thermal Rearrangement of 3 in Toluene.**—An 11.4-g (0.037 mol) quantity of **3** was dissolved in 75 ml of toluene, and the solution was heated at reflux in a nitrogen atmosphere for 14 hr. The toluene and the volatile reaction products were collected by distillation *in vacuo*. The residue was diluted with 20 ml of pentane, chilled to −10°, and filtered to give 6.5 g of a crystalline product. With the exception of a small residue, this product could be redissolved in cold pentane. After three recrystallizations from this solvent at −10° (including a treatment with Norit), 4.1 g (36.0%) of pure **10** was recovered, mp 67.0–67.5°.

Anal. Calcd for $C_{19}H_{35}N_3$: C, 74.69; H, 11.54; N, 13.75. Found: C, 74.61; H, 11.63; N, 13.84.

Ir (CCl_4) 3405, 3360 (w, NH), 2235 cm^{-1} (vw, C≡N);[17] nmr (CCl_4) δ 0.97, 1.01 [18 H, 2 $C(CH_3)_3$], 1.26, 1.41 [each 6 H, $C(CH_3)_2$], 1.46, 1.54 ppm (each 2 H, CH_2); mass spectrum (70 eV) *m/e* 305 (M^+); mol wt 303 (Thermonam).

Formation of 1,2-Di-*tert*-octylamino-1,2,3-tricyanoethane (19) in Thermolysis of 3.—The pentane-insoluble part of the crystalline thermolysis residue of **3** was recrystallized from a benzene–hexane mixture. An 0.153-g amount (2.3%) of pure **19** was obtained, identified by ir spectrum and mixture melting point determination. Authentic **19**, prepared by thermolysis of **1** (see below), was used for comparison.

Glpc Analysis of Mother Liquors of 10. Identification of *tert*-Octylaminomalononitrile (1) and of *tert*-Octyliminomalononitrile (9).—The condensed mother liquors of **10** were analyzed by glpc. The support was 5% silicone SE-30 (General Electric Co.) on Chromosorb W (Johns-Manville). By means of the coinjection technique, three of the major components were identified as *tert*-octylimino-*tert*-octylacetonitrile (**12**), di-*tert*-octyliminosuccinonitrile (**26**), and di-*tert*-octylaminomaleonitrile (**16**). These substances were also isolated by column chromatography (see below).

Additionally, by means of the coinjection technique, two minor components were identified as *tert*-octylaminomalononitrile (**1**) and *tert*-octyliminomalononitrile[4] (**9**). Neither of these compounds could be isolated by column chromatography.

Chromatography of the Mother Liquors of 10.—The mother liquors of **10** were chromatographed through a silica column using mixed pentane–ether eluents of progressively increasing ether content.

***tert*-Octylimino-*tert*-octylacetonitrile (12) and Di-*tert*-octyliminosuccinonitrile (25) from Thermolysis of 3.**—Removal of the solvents from the pentane–ether (19:1) eluate left an oily residue. Distillation of this residue through a microstill yielded 1.1 g (10.7%) of **12** as a colorless oil, bp 82.0–82.5° (0.13 mm), $n^{20}D$ 1.4582.

Anal. Calcd for $C_{18}H_{34}N_2$: C, 77.60; H, 12.33; N, 10.06. Found: C, 77.46; H, 12.31; N, 10.25.

Ir (neat) 1622 cm^{-1} (m, C=N); nmr (CCl_4) δ 0.93, 0.96 [18 H unresolved, 2 $C(CH_3)_3$], 1.18, 1.42 [each 6 H, 2 $C(CH_3)_2$], 3.36, 3.38 ppm (4 H, unresolved, 2 CH_2).

The residue remaining after distillation of **12** was dissolved in pentane, and the solution was treated with decolorizing carbon. After condensation and cooling to −40°, a crystalline precipitate was obtained. One additional crystallization gave 0.33 g (2.7%) of **25**, identified by ir spectrum and mixture melting point determination using authentic **25**.[8]

Di-*tert*-octylaminomaleonitrile (16) from Thermolysis of 3.—The pentane–ether (85:15) eluate yielded a crystalline residue which was recrystallized from hot hexane, yield 0.57 g (4.6%) of **16**, identified by ir spectrum and mixture melting point determination using authentic **16**.[8]

2,4,4-Trimethylpentene-1 and 2,4,4-Trimethylpentane from Thermolysis of 3.—The combined toluene solvent and volatile reaction products from the thermolysis of **3** were redistilled through a spinning band distillation column. The fraction with bp 94–104° (760 mm) weighed 0.8 g and consisted, according to the coinjection glpc method, of 2,4,4-trimethylpentene-1 (93%) and 2,4,4-trimethylpentane (7%). The corresponding yields in the thermolysis are 17.9 and 1.3%.

Thermal Stability of *tert*-Octylamino-*tert*-octylmalononitrile (10).—A 0.53-g quantity of **10** was dissolved in 10 ml of toluene. The solution was blanketed with nitrogen and heated at reflux for 19 hr. Removal of the toluene *in vacuo* left a residue that was recrystallized from pentane. After 2 hr at −15°, filtration yielded 0.50 g (94.3%) of a crystalline precipitate which was identical with the starting material according to ir spectra and mixture melting point determination.

Thermolysis of 3 in the Absence of Solvent. Isolation of Di-*tert*-octylaminomaleonitrile (16).—An 18.7-g quantity of **3** was blanketed with nitrogen and heated at 100–105° for 18 hr. At that time the characteristic ketenimine band at 2025 cm^{-1} was no longer present in the ir spectrum. The dark green liquid was dissolved in 50 ml of pentane and cooled to −10°. After 10 hr, filtration yielded 3.57 g (17.5%) of a colorless precipitate which was identified as **16** by ir spectrum and mixture melting point determination using authentic **16**.[8]

Isolation of *tert*-Octylimino-*tert*-octylacetonitrile (12) from Thermolysis of Neat 3.—The mother liquors of **16** were chromatographed through a silica column. From the 95:5 pentane–ether eluent, 1.72 g (10.1%) of an oil was obtained which, according to ir spectrum (see above) and glpc (coinjection), was almost pure **12**.

Formation of Di-*tert*-octyliminosuccinonitrile (25) from 16, 1, and Triethylamine.—A solution of 2 g (0.01 mol) of **1** and 3.3 g (0.01 mol) of **16** in triethylamine under a nitrogen atmosphere was stirred at room temperature for 14 hr. The triethylamine was removed *in vacuo*, and the partially crystalline residue was extracted with 50 ml of pentane. The pentane-insoluble part of the residue consisted of **16** according to ir spectrum and mixture melting point determination. Upon cooling to −15°, the pentane extract deposited additional **16** which was removed by filtration. The filtrate was chromatographed through a silica column. Pentane–ether (98:2) eluted a fraction which was further purified

(17) Extremely weak C≡N bands are the rule in aminomalononitriles.[8]

by two crystallizations from pentane (3 ml) at −30° to yield 0.64 g (16.6%) of **25**, identified by ir spectrum and mixture melting point determination using an authentic sample.[8]

Thermolysis of 1 in Toluene. Isolation of 1-*tert*-Octyl-2,4-diamino-2,3,5-tricyano-3-*tert*-octylaminopyroline (22).—A 15-g quantity of **1** was dissolved in 100 ml of toluene, and the solution was kept at reflux for 15 hr in a nitrogen atmosphere. The toluene and the volatile products were removed by distillation *in vacuo*. The residue was diluted with 200 ml of pentane and allowed to stand for 15 hr in the refrigerator. Filtration gave a crystalline precipitate (A) and a filtrate (B). Extraction of the precipitate A with 200 ml of refluxing hexane gave an insoluble part (C) and a hexane solution (D). The hexane-insoluble part (C) was twice recrystallized from hot benzene to give 0.31 g (1.8%) of **22** as colorless crystals, mp 232–233°.

Anal. Calcd for $C_{23}H_{39}N_7$: C, 66.77; H, 9.52; N, 23.71. Found: C, 66.70; H, 9.61; N, 23.59.

Ir ($CHCl_3$) 3395, 3320 (m, NH_2, NH), 2172 (vs, C≡N), 1605, 1555, 1547, 1510 cm^{-1} (m, C=C and NH_2, NH deformation); nmr ($CDCl_3$) δ 0.792 [9 H, $C(CH_3)_3$], 1.016 [9 H, $C(CH_3)_3$], 1.592 [6 H, $C(CH_3)_2$], 1.97 [8 H, $C(CH_3)_2 + CH_2$], 2.218 [2 H, CH_2], 3.904 (4 H, 2 NH_2), 4.68 ppm (1 H, NHR); mass spectrum (70 eV) *m/e* 413 (M^+).

1,2-Di-*tert*-octylamino-1,2,3-tricyanoethane (19) from Thermolysis of 1 in Toluene.—The hexane solution D obtained in the thermolysis of **1** deposited a crystalline precipitate upon cooling to −10°. A second yield was obtained upon concentrating the mother liquors and cooling to −40°. Both precipitates were combined and after two recrystallizations from hot hexane, 1.14 g (18.2%) of **19** was obtained as colorless crystals, mp 116–116.5°.

Anal. Calcd for $C_{21}H_{37}N_5$: C, 70.13; H, 10.39; N, 19.48. Found: C, 70.47; H, 10.31; N, 19.32.

Ir (CCl_4) 3325 (mw with shoulders at 3365 and 3275, NH), 2245 and 2220 cm^{-1} (vw, C≡N); nmr ($CDCl_3$) δ 1.07 [18 H, 2 $C(CH_3)_3$], 1.28 and 1.32 [6 H, two heterosteric CH_3 in $C(CH_3)_2$], 1.50, 1.53, and 1.58 [10 H, unresolved multiplet, $C(CH_3)_2 + 2\,CH_2$], 1.85 and 2.05 (1 H, doublet, J = 12.0 Hz, NH, disappears on deuteration), 2.22 (1 H, singlet, NH, disappears on deuteration), 3.95 and 4.15 ppm (1 H doublet, J = 12.0 Hz, CH, replaced by singlet at 4.05 ppm on deuteration); partial mass spectrum above *m/e* 260 (70 eV) *m/e* (rel intensity) 359 (M^+, 0), 344 ($M^+ - CH_3$, 1.5), 332 (M^+ − HCN, 100), 317 ($M^+ - CH_3$ − HCN, 3.1), 307 [$M^+ - (CN)_2$, 25.6], 288 ($M^+ - C_5H_{11}$, 11.8), 261 ($M^+ - C_5H_{11}$ − HCN, 66.7).

1-*tert*-Octylamino-2-amino-3-*tert*-octylimino-1,3-dicyanopropene-1 (23) from Thermolysis of 1 in Toluene.—The orange-colored filtrate (B) obtained in the thermolysis of **1** was concentrated to a 75-ml volume and seeded with some crystals of **23** obtained in the decomposition of **1** in triethylamine.[1] After 10 hr in the refrigerator, filtration yielded a crystalline precipitate which was recrystallized from hexane (−10°), yield 1.08 g (5.9%) of yellow needles, identified as **23** by ir spectrum and mixture melting point determination using authentic **23**.[1]

Chromatography of the Mother Liquors of 23. Isolation of Additional Products of Thermolysis of 1 in Refluxing Toluene.—The mother liquors of **23** were chromatographed through a silica column using mixed pentane–ether eluents of progressively increasing ether content.

tert-Octyliminomalononitrile (9) from Thermolysis of 1.—From the pentane–ether (9:1) eluate 0.172 g (1.2%) of a brown oil was recovered which became almost colorless upon treatment with Norit. It was identified as slightly impure **9** by ir and nmr spectra[1] and by glpc (coinjection using authentic **9**).

Unchanged 1 and 1-*tert*-Octylamino-2-aminodicyanoethylenes (Cis or Trans) 17 and 15 from Pentane–Ether Eluate.—Pentane–ether (1:1) eluted two products. The brown residue from the initial fraction was extracted with pentane. Treatment of the pentane extract with Norit, followed by concentration and cooling to −78°, gave a crystalline precipitate. After two additional crystallizations from pentane (−78°) 0.237 g of unchanged **1** was recovered, melting at 35.0–35.5° and identified by ir spectrum and by the glpc coinjection technique using authentic **1**.

Similar treatment of the residue from a subsequent 1:1 pentane–ether fraction yielded 0.065 g (0.4%) of **17**, mp 83.7–84.2°.

Anal. Calcd for $C_{12}H_{20}N_4$: C, 65.45; H, 9.09; N, 25.46. Found: C, 65.46; H, 9.24; N, 25.57.

Ir (CCl_4) 3450 (m), 3360 and 3335 (doublet, ms), 3180 (w) (all NH_2 and NH), 2200 (ms), 2160 (sh, C≡N), 1615 (ms, C=C), 1580 cm^{-1} (sh, NH_2, NH deformation); nmr ($CDCl_3$) δ 1.05 [9 H, $C(CH_3)_3$], 1.33 [6 H, $C(CH_3)_2$], 1.58 (2 H, CH_2), 2.97 (1 H, NH), 3.90 ppm (2 H, NH_2); mass spectrum (70 eV) *m/e* 220 (parent).

Pentane–ether (1:3) eluted an additional product which was recrystallized from benzene, yield 0.18 g (1.1%) of **15**, identified by ir spectrum and by mixture melting point determination using a sample of authentic **15**.[1]

Thermolysis of Neat *tert*-Octylaminomalononitrile (1).—A 5.5-g quantity of **1** was blanketed with nitrogen and heated at 60° for 36 hr. The deep orange liquid was extracted by shaking with 50 ml of warm (50°) hexane to give a hexane extract (A) and a residue (B).

1-*tert*-Octylamino-2-amino-3-*tert*-octylimino-1,3-dicyanopropene-1 (23) from Thermolysis of Neat 1.—The hexane extract (A) was treated with Norit and condensed to a 10-ml volume. The solution was seeded with authentic **23** (see above). After 10 hr at −10°, the solution was filtered to give 0.21 g (3.1%) of **23** identified by ir spectrum and mixture melting point determination.

1-*tert*-Octylamino-2-amino-1,2-dicyanoethylene (17) from Thermolysis of Neat 1.—The mother liquors of **23** were chromatographed through a silica column. From the pentane–ether (1:3) eluent, 0.067 g (1.0%) of a crystalline product was obtained that was identified as **17** by ir spectrum and mixture melting point determination using a sample of authentic **17** (see above).

1-*tert*-Octyl-2,4-diamino-2,3,5-tricyano-3-*tert*-octylaminopyroline (22) from Thermolysis of Neat 1.—The hexane-insoluble residue B (see above) was dissolved in 25 ml of ether. Upon cooling to −10°, a crystalline precipitate formed, yield 0.072 g (1.2%) of **22**, identified by ir spectrum and mixture melting point determination.

1-*tert*-Octylamino-2-amino-1,2-dicyanoethylene (15) from Thermolysis of Neat 1.—The ether mother liquors of **22** were freed of solvent and the residue was dissolved in 10 ml of warm benzene. A 5-ml quantity of hexane was added, and the solution was cooled at −10° for 12 hr. Filtration yielded 0.53 g (8.5%) of **15**, identified by ir spectrum and mixture melting point determination using a sample of authentic **15**.[1]

1-*tert*-Octylimino-2-imino-3-*tert*-octylamino-1,3,3-tricyanopropane (26) from Thermolysis of Neat 1.—The mother liquors of **15** were freed of solvent *in vacuo*. The residue was extracted with 25 ml of refluxing hexane. The hexane extract was concentrated to a 5-ml volume and cooled to −10° for 12 hr. The crystalline precipitate was collected by filtration and once recrystallized from hot hexane (Norit treatment) to yield 0.093 g (1.7%) of **26** as yellow crystals, mp 131.5–132°.

Anal. Calcd for $C_{22}H_{36}N_6$: C, 68.70; H, 9.45; N, 21.85. Found: C, 68.76; H, 9.54; N, 22.07.

Ir ($CHCl_3$) 3475 (m), 3230 (w), and 3160 (w) (NH), 2215 (s, C≡N), 1610 (vs) and 1580 (s) (RN=CC=NH), 1515 cm^{-1} (NH deformation ?); nmr ($CDCl_3$) δ 0.90 [9 H, $C(CH_3)_3$], 0.97 [9 H, $C(CH_3)_3$], 1.56 [6 H, $C(CH_3)_2$], 1.93 [8 H, $CH_2 + C(CH_3)_2$], 2.06 (2 H, CH_2), 6.27 ppm (2 H, NH, disappears upon deuteration); mass spectrum (70 eV) *m/e* 384 (M^+).

Registry No.—**1**, 31819-52-0; **3**, 30768-56-0; **10**, 40127-69-3; **12**, 42271-33-0; **17**, 42271-34-1; **19**, 42271-35-2; **22**, 42447-97-2; **26**, 42447-98-3.

Formation of 2,4,6-Trinitrobenzonitrile and 4-Chloro-5,7-dinitro-2-(2,4,6-trinitrophenyl)quinazoline 1-Oxide by the Action of Nitrosyl Chloride on 2,4,6-Trinitrotoluene

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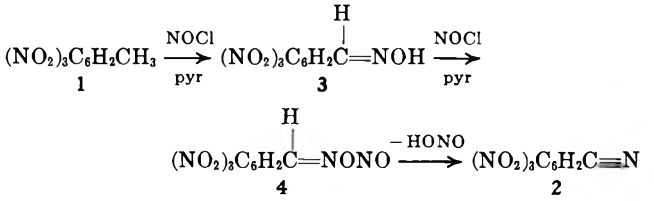
During an attempt to prepare 2,4,6-trinitrobenzonitrile by the action of nitrosyl chloride on 2,4,6-trinitrotoluene, the unexpected formation of the by-product 4-chloro-5,7-dinitro-2-(2,4,6-trinitrophenyl)quinazoline 1-oxide occurred. However, reaction conditions were found that gave the trinitrobenzonitrile free of the quinazoline. Mechanisms that account for the formation of the nitrile and the quinazoline are given.

The reaction of nitrosyl chloride with hydrocarbons is well established in the literature:[1] at low temperatures the products are nitroso compounds which often rearrange to oximes; at elevated temperatures, 100° and above, chlorinated products usually result. Heretofore, there has been no report in the literature of a nitrile isolated as a major product from nitrosyl chloride and a hydrocarbon.[2]

The action of nitrosyl chloride on 2,4,6-trinitrotoluene (1) in pyridine solution was investigated as a convenient method for the preparation of 2,4,6-trinitrobenzonitrile[3] (2). The nitrile 2 is obtained as the major product of the reaction *via* the intermediate 2,4,6-trinitrobenzaldoxime (3).



A pyridine solution of 1 and nitrosyl chloride would be expected to first give α-nitroso-2,4,6-trinitrotoluene. Loss of a proton forms 2,4,6-trinitrobenzaldoxime anion, which upon reaction with nitrosyl chloride yields the oxime nitrite 4. Elimination of the elements of nitrous acid from the oxime nitrite produces the nitrile 2.

As evidence for this reaction sequence, authentic 3 gave the same products (see Experimental Section) as obtained from 1. The conversion of 3 to 2 *via* the oxime nitrite seems logical in view of the fact that 3 in pyridine solution without nitrosyl chloride does not produce 2. The considerable gas evolution that occurs during the course of the reaction results from the reaction of nitrous acid (eliminated from 4) with nitrosyl chloride. The production of nitrous acid (pyridine salt) by addition of pyridine containing a small amount of water to a nitrosyl chloride–pyridine solution is accompanied by gas evolution. The unstable nitrous anhydride formed

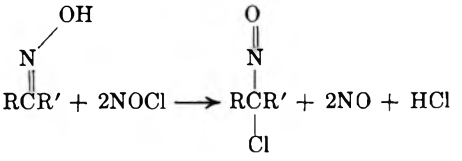
$$\text{Pyr HONO} + \text{NOCl} \longrightarrow \text{N}_2\text{O}_3 + \text{Pyr HCl}$$

$$\text{N}_2\text{O}_3 \longrightarrow \text{NO} + \text{NO}_2$$

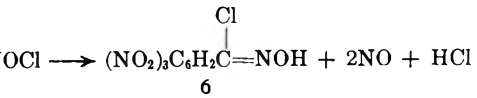
from nitrous acid and nitrosyl chloride decomposes to a mixture of nitric oxide and nitrogen dioxide.

When the reaction was run by adding 1 to a solution of nitrosyl chloride in pyridine at 0° and slowly allowing the mixture to warm to 20–25°, 4-chloro-5,7-dinitro-2-(2,4,6-trinitrophenyl)quinazoline 1-oxide (5) was formed in addition to 2. This made the isolation of pure 2 too difficult for a practical synthesis. At −10 to −5° the reaction gave no 5, but gave 2,4,6-trinitrobenzohydroximoyl chloride (6) as a by-product from which a 60% yield of pure 2 could readily be separated.

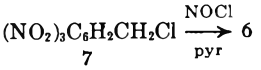
The formation of 6 can occur by reaction of 3 with nitrosyl chloride. Nitrosyl chloride reacts with ketoximes[4] and onimino esters[5] to give chloro nitroso compounds. Aliphatic aldoximes with nitrosyl chloride



give chloro nitroso compounds which can be converted by heating to the corresponding hydroximoyl chlorides, whereas aromatic aldoximes yield the hydroximoyl chlorides directly.[4] Thus 6 can be formed from the oxime 3 as shown. The reaction of 3 with nitrosyl chloride in pyridine did give 6 together with 2.

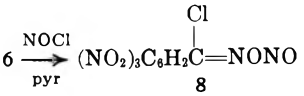


There is also the possibility that 6 produced from 1 results from nitrosation of 2,4,6-trinitrobenzyl chloride (7). Authentic 7 with nitrosyl chloride in pyridine did give 6. The formation of 7 would have to result from



chlorination rather than nitrosation of 1 by nitrosyl chloride.

It is likely that 6 exists in the pyridine reaction mixture as the nitrite derivative 8. The fact that 6 rather than 8 is isolated as a product from the reaction at −5 to −10° is probably due to hydrolysis of 8 during the



(1) L. J. Beckham, W. A. Fessler, and M. A. Kise, *Chem. Rev.*, **48**, 354 (1951).

(2) A small amount of benzoyl cyanide from the reaction of nitrosyl chloride with acetophenone in ethanol–pyridine was the result of thermal dehydration of phenylglyoxal aldoxime during the work-up distillation: D. T. Manning and H. A. Standbury, Jr., *J. Amer. Chem. Soc.*, **81**, 4885 (1959).

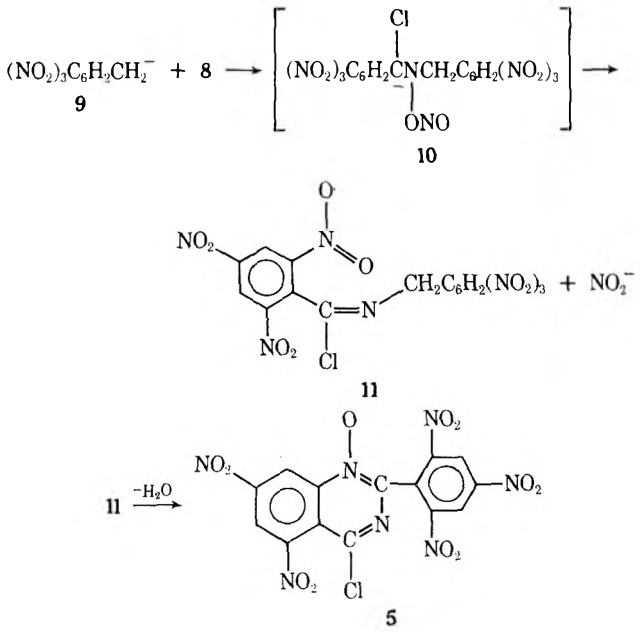
(3) Dr. Mortimer J. Kamlet of these laboratories obtained 2,4,6-trinitrobenzonitrile by dehydration of trinitrobenzaldoxime. Dehydration of 2,4,6-trinitrobenzamide also gives the trinitrobenzonitrile. Recently, Konarski and Graczyk described the preparation of 2,4,6-trinitrobenzonitrile in 60% yield by the reaction of picryl chloride with cuprous cyanide in nitrobenzene at 200°: J. Konarski and A. Graczyk, *Rocz. Chem.*, **46**, 745 (1972).

(4) Reference 1, pp 358–360.

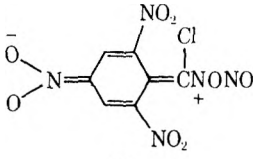
(5) L. W. Kissinger and H. E. Ungnade, *J. Org. Chem.*, **23**, 1517 (1958).

work-up procedure (the pyridine reaction mixture is poured into dilute hydrochloric acid).

The formation of the quinazoline **5** when the reaction temperature is allowed to rise above 0° can be rationalized as follows. The addition of 2,4,6-trinitrobenzyl anion[6] (**9**) to **8** gives the intermediate carbanion **10**; loss of nitrite ion from **10** produces **11**; the cyclization of **11** by the addition of the methylene carbon to the nitro group followed by dehydration yields **5**.



The apparent attack of **9** on the nitrogen of **8** is contrary to the usual mode of reaction of hydroximoyl chlorides.[7] This could be accounted for by resonance structures such as **12**, which show a positive charge on

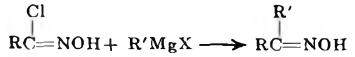


the nitrogen atom bearing the ONO group. Nucleophilic attack on this electron-deficient nitrogen atom by **9** produces the resonance-stabilized carbanion **10**.

The structure for **5** is consistent with all the analytical data obtained (elemental analysis, molecular weight, and nmr).[8] Hydrolysis products of **5** with refluxing 50% sulfuric acid included 2,4,6-trinitrobenzamide and 2,4,6-trinitrobenzoic acid. The trinitrobenzamide would be expected along with 2,4-dinitro-5-hydroxylaminobenzoic acid as products from hydrolytic cleavage of the bonds between positions 1 and 2 and 3 and 4 of the quinazoline ring. The trinitrobenzoic acid can arise from hydrolysis of the trinitrobenzamide.

(6) The use of 2,4,6-trinitrobenzyl anion as a nucleophile has been described in the literature: K. G. Shipp, L. A. Kaplan, and M. E. Sitzmann, *J. Org. Chem.*, **37**, 1966 (1972).

(7) Hydroximoyl chlorides normally react with carbanions to give ketoximes.



Alkoximoyl chlorides (RClC=NOR) react similarly. P. A. S. Smith, "The Chemistry of Open-Chain Organic Nitrogen Compounds," Vol. II, W. A. Benjamin, New York, N. Y., 1966, p 87.

(8) There are a number of positional isomers (heteroring) of **5** which are entirely consistent with the nmr, molecular weight, elemental analysis, etc. Mechanistically, however, **5** is the most likely product. The authors wish to thank a referee for suggesting these possibilities.

Experimental Section

General.—Caution! The compounds described herein are explosives and should be handled with care. Melting points were taken on a Thomas-Hoover apparatus and are corrected. Silica gel HF-254 was used for tlc and the spots were visualized with uv light. Nmr spectra were determined on a Varian HA-100 spectrometer. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

Work-up of the pyridine reaction mixtures was accomplished by pouring them into a stirred mixture of methylene chloride, dilute hydrochloric acid, and ice. The methylene chloride extract was dried ($MgSO_4$) and filtered. The solvent was removed under reduced pressure or in a current of air in the hood to give the product residue.

4-Chloro-5,7-dinitro-2-(2,4,6-trinitrophenyl)quinazoline 1-Oxide.—Six grams of 2,4,6-trinitrotoluene was added all at once to a solution of 7.5 g of nitrosyl chloride in 25 ml of pyridine cooled to 0°. The temperature was slowly allowed to rise to 15–18° to maintain a moderate rate of gas evolution. After *ca.* 45 min at 15–18°, the rate of gas evolution slowed considerably and the temperature was then maintained at 20–25° for 4 hr. Work-up (see above) gave a red oil which was stirred with 60 ml of methanol at 25°. The yellow solid (2.05 g, mp 182–188° dec) that formed was removed by filtration. Crystallization from acetone–methanol gave 1.75 g of the quinazoline: mp 198–199° dec; nmr (acetone-d_6) δ 9.45 (s, 2), 8.80 (d, 1), 8.54 (d, 1).

Anal. Calcd for $C_{14}H_4N_7O_{11}Cl$: C, 34.90; H, 0.84; N, 20.35; Cl, 7.36; mol wt, 481.67. Found: C, 34.85; H, 0.73; N, 20.14; Cl, 7.50; mol wt, 484, 482.

The methanol filtrate (60 ml of methanol above) was concentrated to 10 ml, after which 20 ml of benzene was added. Cooling gave 1.8 g of product, mp 115–127°. The product was mainly 2,4,6-trinitrobenzonitrile with a small amount of the quinazoline (as analyzed by tlc). Pure trinitrobenzonitrile was not obtained by repeated crystallizations.

2,4,6-Trinitrobenzonitrile from 2,4,6-Trinitrotoluene.—To a solution of 18.7 g of nitrosyl chloride in 55 ml of pyridine cooled to −10° was added 18 g of 2,4,6-trinitrotoluene. The dark mixture was stirred at −10 to −5° (evolution of gas occurs) for 6 hr. Work-up (see above) gave 19.8 g of residue which was crystallized from methanol–benzene to give 11.5 g (60.9%) of 2,4,6-trinitrobenzonitrile, mp 132–135°. Recrystallization from methanol–benzene raised the melting point to 134–135°. The trinitrobenzonitrile separates as solvates; drying for several hours at 60° removed the benzene of solvation. Nmr (acetone-d_6) showed δ 9.38 (s).

2,4,6-Trinitrobenzohydroximoyl Chloride. A. From 2,4,6-Trinitrotoluene.—In a parallel run at −10 to −5° as above, the residue from the methylene chloride extract was stirred with 60 ml of benzene at 25°. The insoluble solid (2,4,6-trinitrobenzonitrile containing a small amount of the hydroximoyl chloride) was removed by filtration. The benzene filtrate was treated with charcoal and filtered. Removal of the solvent under reduced pressure left a residual oil, which after two crystallizations from methylene chloride gave 1.0 g of crystals, mp 145–147° dec. A final crystallization (charcoal) from benzene by slow addition of hexane gave 0.75 g of 2,4,6-trinitrobenzohydroximoyl chloride: mp 151–152° dec; ir (film) 3525 cm^{-1} (OH); nmr (acetone-d_6) δ 9.21 (s), 12.30 (s, disappears with D_2O).

Anal. Calcd for $C_7H_3N_4O_7Cl$: C, 28.93; H, 1.04; N, 19.28; Cl, 12.20. Found: C, 29.06; H, 0.95; N, 19.11; Cl, 12.01.

B. From 2,4,6-Trinitrobenzaldoxime.—To a solution of 2.0 g of nitrosyl chloride in 5 ml of pyridine cooled to −30° was added 0.5 g of 2,4,6-trinitrobenzaldoxime. After the solution was stirred for 5 hr at −30 to −20°, work-up gave an oil which was shown by tlc (benzene) to be a mixture of the trinitrobenzohydroximoyl chloride and trinitrobenzonitrile. Separation of the products as before yielded 75 mg of the hydroximoyl chloride, mp 148–150° dec. Mixture with the hydroximoyl chloride from trinitrotoluene did not depress the melting point.

C. From 2,4,6-Trinitrobenzyl Chloride.—A solution of 1 g of nitrosyl chloride in 5 ml of pyridine was cooled to 0° before the addition of 0.5 g of 2,4,6-trinitrobenzyl chloride. After the mixture was stirred at 0–5° for 2 hr, work-up gave an oil which

tlc (benzene) showed to be mostly hydroximoyl chloride along with some origin material. The oil was crystallized twice by solution in benzene (charcoal) and precipitation by the slow addition of hexane to give 125 mg, mp 147–148° dec. A third crystallization yielded 100 mg, mp 150–152° dec. The melting point was not depressed by mixture with the product from trinitrotoluene.

Hydrolysis of 4-Chloro-5,7-dinitro-2-(2,4,6-trinitrophenyl)quinazoline 1-Oxide.—The quinazoline (0.3 g) was stirred at reflux temperature (*ca.* 160°) with 15 ml of 50% sulfuric acid for 2 hr before all the solid dissolved. The solution was heated at reflux temperature for an additional 1 hr, then was cooled and diluted with water. The small amount of dark solid that precipitated was removed by filtration, and the filtrate was extracted with ether. The ether solution, after extraction with aqueous sodium bicarbonate, was concentrated and hexane was added to precipitate the 2,4,6-trinitrobenzamide (identified by tlc and mixture melting point with an authentic sample). The bicarbonate extract contained 2,4,6-trinitrobenzoic acid which was identified by decarboxylation to 1,3,5-trinitrobenzene, mp 119–122°. Mixture with authentic trinitrobenzene did not depress the melting point.

Registry No.—1, 118-96-7; 2, 37841-25-1; 3, 42449-44-5; 5, 42449-45-6; 6, 42449-46-7; 7, 7176-28-5.

Iron Pentacarbonyl and the Hydridoundecacarbonyltriferrate Anion as Reagents for Converting Benzohydroxamoyl Chlorides to Nitriles. The Deoxygenation of Nitrile Oxides

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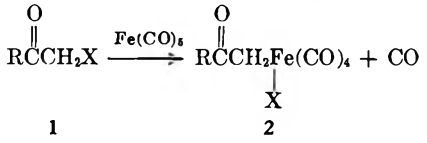
Received July 5, 1973

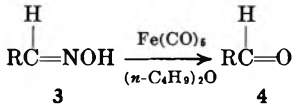
Several new convenient syntheses of nitriles are described. Reaction of benzohydroxamoyl chlorides with iron pentacarbonyl in refluxing tetrahydrofuran affords nitriles in moderate yields. Higher yields of nitriles can be realized by treating the organic reactant with triiron dodecacarbonyl and methanol in hot benzene. The *in situ* generated hydridoundecacarbonyltriferrate anion is the active species in the latter reaction. Iron pentacarbonyl can also deoxygenate nitrile oxides to nitriles.

Iron pentacarbonyl [$Fe(CO)_5$] has recently been shown to be a useful reagent for converting α-halo ketones to 1,4-diketones.[1] Also isolated in these reactions were monoketones and, in several instances, β-epoxy ketones. A mechanistic study of the reaction indicated initial oxidative addition to the α-halo ketone **1** to give the iron tetracarbonyl halide **2**.



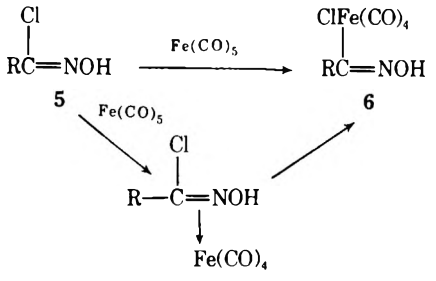
1 **2**

Treatment of oximes with the same metal carbonyl in di-*n*-butyl ether results in the regeneration of the corresponding carbonyl compound (*e.g.*, **3** → **4**) in



3 **4**

reasonable yields.[2] Although the mechanism of this reaction has yet to be fully elucidated,[3] it clearly does not involve initial oxidative addition. If, however, the vinylic hydrogen of **3** was replaced by a halogen,



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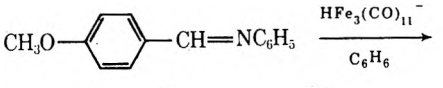
specifically chlorine (**5**), then oxidative addition may now occur to give **6** either directly or, more likely, *via* the π complex **7**. Regarding the latter, irradiation of related vinyl halides with $Fe(CO)_5$ (or thermal reaction with diiron enneacarbonyl) has been reported to give iron tetracarbonyl complexes with π complexation to the double bond.[4,5] These mononuclear π complexes are convertible to binuclear complexes *via* analogs of **6**. Such transformations can be effected thermally[5] or photolytically,[4,5] subject to the stereochemistry of the mononuclear π-complexed vinyl halides. This paper describes the reaction of benzohydroxamoyl chlorides with $Fe(CO)_5$. It was of considerable interest to learn the fate of **6**, if formed, in these reactions.

One of us has demonstrated the utility of the hydridoundecacarbonyltriferrate anion (generated from triiron dodecacarbonyl and methanol in benzene) as a reagent for reducing the carbon–nitrogen double bond in heterocycles (*e.g.*, phthalazine) and in Schiff bases (*e.g.*, **8** → **9**).[6] Several benzohydroxamoyl chlorides



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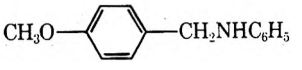

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were also exposed to the iron hydride in order to determine whether hydrogenation would occur here, as was observed for **8**.

(1) H. Alper and E. C. H. Keung, *J. Org. Chem.*, **37**, 2566 (1972).
(2) H. Alper and J. T. Edward, *J. Org. Chem.*, **32**, 2938 (1967).
(3) H. Alper, unpublished results.
(4) C. Kruger, Y. H. Tsay, F. W. Grevels, and E. K. von Gustorf, *Israel J. Chem.*, **10**, 201 (1972), and references cited therein.
(5) F. W. Grevels, E. K. von Gustorf, and G. Bor, "Procedings of the Third International Symposium on Reactivity and Bonding in Transition Organometallic Compounds, Venice, 1970," Inorganica Chimica Acta, E4.
(6) H. Alper, *J. Org. Chem.*, **37**, 3972 (1972).

TABLE I

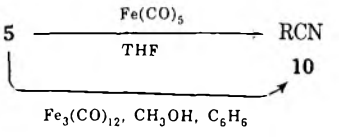
YIELDS OF NITRILES OBTAINED FROM REACTION OF BENZOHYDROXAMOYL CHLORIDES WITH $Fe(CO)_5$ AND WITH THE *in situ* GENERATED $HFe_3(CO)_{11}^-$

5, R =	Registry no.	Product(s)	Registry no.	$Fe(CO)_5$ yield, %[a]	$HFe_3(CO)_{11}^-$ yield, %[a]
C_6H_5	698-16-8	Benzonitrile	100-47-0	76	
4-ClC_6H_4	28123-63-9	4-Chlorobenzonitrile	623-03-0	60	86
4-$C_6H_5C_6H_4$	42202-94-8	4-Cyanobiphenyl	2920-38-9	33	76
2,6-$Cl_2C_6H_3$	6579-27-7	2,6-Dichlorobenzonitrile	1194-65-6	62	90
4-FC_6H_4	42202-95-9	4-Fluorobenzonitrile	1194-02-1	67	
2,4,6-$(CH_3O)_3C_6H_2$	2904-65-6	2,4,6-Trimethoxybenzonitrile	2571-54-2	44	
4-$NO_2C_6H_4$	1011-84-3	4-Nitrobenzonitrile	619-72-7	40	58[b]
4-$NH_2C_6H_4$	42202-97-1	4-Aminobenzonitrile	873-74-5	0	19

[a] Yields are of sublimed, recrystallized, or distilled material. The melting or boiling points and spectral data were in good agreement with data reported in the literature. [b] Use of a 2:1 mole ratio of $Fe_3(CO)_{12}$ to **5**, R = 4-$NO_2C_6H_4$, gave 4-aminobenzonitrile in 68% yield.

Results and Discussion

Treatment of benzohydroxamoyl chlorides (**5**, R = aryl) with $Fe(CO)_5$ [2:1 mole ratio of $Fe(CO)_5$:**5**] in refluxing anhydrous tetrahydrofuran (THF) for 18–24 hr results in the formation of nitriles in 33–76% yields (Table I). This reaction is very simple both in execution and work-up, thus providing a convenient synthesis of nitriles under neutral conditions. The reaction is not catalytic in the metal carbonyl.



Nitriles were also formed when **5** was treated with an approximately equimolar amount of triiron dodecacarbonyl [$Fe_3(CO)_{12}$] and methanol in boiling benzene. As indicated in Table I, the yields of nitriles are superior using this reagent combination as compared with the results with $Fe(CO)_5$. However, there are several differences between the two processes. First, $Fe(CO)_5$ is a more economical reagent than $Fe_3(CO)_{12}$. Secondly, while $Fe(CO)_5$ is uncharged, the iron hydride is anionic (and of moderate nucleophilicity).

The results for 4-nitrobenzohydroxamoyl chloride (**5**, R = 4-$NO_2C_6H_4$) are noteworthy. Iron pentacarbonyl is known to deoxygenate nitrobenzenes to azo, azoxy, and/or amino compounds, subject to the nature and position of substitution on the benzene ring.[7] The formation of only 4-nitrobenzonitrile from treatment of **5**, R = 4-$NO_2C_6H_4$, with $Fe(CO)_5$ is indicative of the substantially greater reactivity of the ClC=NOH group as compared with the nitro function. In addition, Landesberg and coworkers[8] have reported that nitrobenzenes, bearing a variety of substituents, can be reduced to anilines with $Fe_3(CO)_{12}$ and methanol in benzene. Here, however, reaction occurs primarily at the hydroxamic acid site of **5**, R = 4-$NO_2C_6H_4$, when equimolar quantities of reactants are used. 4-Aminobenzonitrile was obtained in 68% yield using a 2:1 mole ratio of $Fe_3(CO)_{12}$:**5**, R = 4-$NO_2C_6H_4$.

Solid evidence for the intermediacy of nitrile oxides in the $Fe(CO)_5$ reaction was obtained by conducting the reaction of benzohydroxamoyl chloride and the metal carbonyl in the presence of excess benzaldehyde. The 1,3-dipolar cycloaddition product, 2,5-diphenyl-1,3,4-dioxazole,[9] was isolated in 40% yield, along with some nitrile. In addition, treatment of 2,6-dichlorobenzohydroxamoyl chloride with $Fe_2(CO)_9$ at room temperature for 2 hr afforded a mixture of an iron tetracarbonyl complex [**6** or **7**, ν_{CO}(KBr) 2083 (w-m), 2036 (s), and 1982 cm^{-1} (m-s)], 2,6-dichlorobenzonitrile, and 2,6-dichlorobenzonitrile oxide (the infrared spectrum showed intense bands at 2294 and 1366 cm^{-1} characteristic of nitrile oxides).[10]

The above results suggest the deoxygenation of nitrile oxides. Treatment of 2,4,6-trimethoxybenzonitrile oxide with an equimolar quantity of $Fe(CO)_5$ gave 2,4,6-trimethoxybenzonitrile in 47% yield. Similarly, mesitonitrile was obtained in 64% yield from 2,4,6-trimethylbenzonitrile oxide and $Fe(CO)_5$. Therefore, $Fe(CO)_5$ is capable of deoxygenating nitrile oxides to nitriles in moderate yields. The use of excess $Fe(CO)_5$ in these deoxygenations should be avoided, since such conditions lead to the ligand substitution products $(RCN)Fe(CO)_4$ and/or $(RCN)_2Fe(CO)_3$. The latter complexes, however, undergo partial or complete decomposition to nitriles after standing for 3–6 weeks.

It is not clear how the hydridoundecacarbonyltriferrate anion converts benzohydroxamoyl chlorides to nitriles. 2,6-Dichlorobenzaldoxime failed to react with $Fe_3(CO)_{12}$ and methanol in benzene using identical reaction conditions with those for the 2,6-dichlorobenzohydroxamoyl chloride–$Fe_3(CO)_{12}$–methanol reaction. Therefore, oximes are not involved in the benzohydroxamoyl–$HFe_3(CO)_{11}^-$ reaction.

Experimental Section

Melting points were determined using a Fisher-Johns apparatus and are uncorrected. Microanalyses were performed by Hoffmann-La Roche, Inc. Infrared spectra were obtained on a Perkin-Elmer 457 grating spectrophotometer. Polystyrene was used for calibration. Nuclear magnetic resonance spectra were determined on Varian A-60 (TMS as internal standard) and/or HA-100 spectrometers.

Iron pentacarbonyl, diiron enneacarbonyl, and triiron dodecacarbonyl were purchased from Pressure Chemical Co. and used as received. Solvents were dried and purified by standard techniques. *All reactions were run under an atmosphere of dry nitrogen.*

Benzohydroxamoyl Chlorides (5).—Except for **5**, R = 2,4,6-$(CH_3O)_3C_6H_2$, all of the benzohydroxamoyl chlorides were readily prepared by chlorination of the corresponding oxime in commercial chloroform. The following general procedure is a modification of that described by Chiang.[11] To commercial

(7) H. Alper and J. T. Edward, *Can. J. Chem.*, **48**, 1543 (1970).
(8) J. M. Landesberg, L. Katz, and C. Olsen, *J. Org. Chem.*, **37**, 930 (1972).
(9) R. Huisgen and W. Mack, *Tetrahedron Lett.*, 583 (1961).
(10) R. H. Wiley and B. J. Wakefield, *J. Org. Chem.*, **26**, 546 (1960).
(11) Y. Chiang, *J. Org. Chem.*, **36**, 2146 (1971).

chloroform (225 ml) was added 15 drops of absolute ethanol. After the solution was cooled to −15 to −20° (Dry Ice–CCl_4) the oxime (2.8–4.0 g) was added and then chlorine gas was bubbled through the solution at a moderate rate for 25–35 min. The reaction mixture was allowed to stand at −20° for 2 hr, and then at room temperature for 6–8 hr. The solution was flushed with nitrogen gas to remove excess chlorine. Filtration and subsequent evaporation of the filtrate gave an oil. The benzohydroxamoyl chloride was crystallized by adding pentane and immersing the solution in a Dry Ice–acetone bath for 15 min. The crystals were filtered and dried in a vacuum desiccator. Yields of pure **5** follow: R = C_6H_5, 56%; R = 4-ClC_6H_4, 79%; R = 4-$C_6H_5C_6H_4$, 42%; R = 4-$NO_2C_6H_4$, 84%; R = 2,6-$Cl_2C_6H_3$, 62% [mp 92–93° (lit.[12] mp 93–94°). *Anal.* Calcd for $C_7H_4Cl_3NO$: C, 37.44; H, 1.80; N, 6.24. Found: C, 37.44; H, 1.76; N, 6.31 (Dondoni and coworkers[12] claimed that this compound could not be prepared by direct chlorination of the oxime)]; R = 4-FC_6H_4, 74% (mp 72–73°. *Anal.* Calcd for C_7H_5ClFNO: C, 48.44; H, 2.90; N, 8.07. Found: C, 48.09; H, 2.73; N, 8.29.).

Compound **5**, R = 2,4,6-$(CH_3O)_3C_6H_2$, was prepared from the nitrile oxide following the procedure of Grundmann and Dean.[13]

General Procedures for Conversion of Benzohydroxamoyl Chlorides to Nitriles. A. $Fe(CO)_5$.—To a dried, deoxygenated solution to THF (40–50 ml) was added the benzohydroxamoyl chloride (5.0–8.7 mmol) followed by $Fe(CO)_5$ [2:1 mole ratio of $Fe(CO)_5$:**5**]. The mixture was refluxed (expect for **5**, R = 4-$NO_2C_6H_4$, where a reaction temperature of 60° was used) with stirring for 18–24 hr, cooled, and filtered, and pentane (100 ml) was then added to the filtrate. After standing in the refrigerator overnight, the solution was filtered, and the filtrate was flash evaporated. The residual nitrile (**10**) obtained from flash evaporation was then purified, if necessary, by sublimation, recrystallization (*n*-heptane), or distillation. The yields of nitrile are given in Table I.

B. $Fe_3(CO)_{12}$–CH_3OH.—A mixture of $Fe_3(CO)_{12}$ (2.92 g, 4.3 mmol) and methanol (1.0 ml) in benzene (55 ml) was refluxed with stirring for 8 hr. The solution was cooled, the benzohydroxamoyl chloride (4.52 mmol) was added, and the resulting mixture was refluxed for 17–22 hr. The solution was cooled and filtered, and the filtrate was evaporated to afford reasonably pure nitrile. Further purification, if required, could be effected as described in A. The two products obtained from 4-nitrobenzohydroxamoyl chloride were separated by chromatography on Florisil or by trituration with hexane. 2,6-Dichlorobenzaldoxime failed to react with $Fe_3(CO)_{12}$–methanol under these conditions.

Reaction of 2,6-Dichlorobenzohydroxamoyl Chloride with $Fe_2(CO)_9$.—A mixture of $Fe_2(CO)_9$ (1.72 g, 4.72 mmol) and 2,6-dichlorobenzohydroxamoyl chloride (0.825 g, 3.60 mmol) in benzene (50 ml) was stirred at room temperature for 2 hr. The solution was filtered and evaporation of the filtrate gave 2,6-dichlorobenzonitrile and the nitrile oxide. The benzene-insoluble solid apparently was an iron tetracarbonyl complex (see Results and Discussion) but was of low stability and could not be isolated in analytically pure form. Reactant **5**, R = 4-$C_6H_5C_6H_4$, behaved similarly when treated with $Fe_2(CO)_9$.

2,5-Diphenyl-1,3,4-dioxazole.—The general procedure described for the reaction of **5** and $Fe(CO)_5$ was repeated for **5**, R = C_6H_5, in the presence of a fivefold excess of benzaldehyde. Work-up as above gave 2,5-diphenyl-1,3,4-dioxazole, mp 38–40° (lit.[9] mp 41–42°), in 40% yield and benzonitrile in 14% yield.

General Procedure for Deoxygenation of Nitrile Oxides by $Fe(CO)_5$.—An equimolar mixture of nitrile oxide[13] (0.5–4.0 mmol) and $Fe(CO)_5$ in THF (20–50 ml) was refluxed with stirring for 1–2 hr. The reaction was worked up as described for the benzohydroxamoyl chloride–$Fe(CO)_5$ reaction. The nitriles were identified by comparison with authentic samples and by comparison with melting points and spectral data. Rearrangement of nitrile oxides to isocyanates[13] does not occur to a significant extent under these reaction conditions.

Acknowledgments.—Acknowledgment is made to the Research Foundation of the State University of New York, and to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research. We are indebted to Hoffmann-La Roche, Inc., for carrying out the microanalytical determinations. Ms. R. Cartmell was kind enough to run some nmr spectra on the HA-100 spectrometer.

Registry No.—$Fe(CO)_5$, 13463-40-6; $HFe_3(CO)_{11}^-$, 25948-56-5.

(12) A. Dondoni, G. F. Pedulli, and G. Barbaro, *J. Org. Chem.*, **37**, 3564 (1972).

(13) C. Grundmann and J. M. Dean, *J. Org. Chem.*, **30**, 2809 (1965).

A New Method for the Conversion of Nitro Groups into Carbonyls

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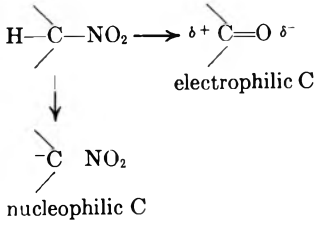
Received July 16, 1973

When a primary or secondary nitro compound is treated with aqueous $TiCl_3$, reduction occurs yielding an imine which hydrolyzes to the corresponding ketone or aldehyde. A study of the scope and mechanism has been carried out. A variety of functional groups including ketone, ester, nitrile, ketal, and hydroxyl survive the reaction conditions. Yields range between 45 and 90%. The reaction probably proceeds through a nitroso intermediate which then tautomerizes to an oxime and is further reduced to imine. Evidence in support of this mechanism is presented. The use of the reaction in organic synthesis is illustrated by a synthesis of *cis*-jasmone.

The nitro group is a function of great synthetic potential in organic chemistry because of the versatility with which it may react.[1] Acting as a strong electron withdrawer, a nitro group can activate a neighboring C–H bond for aldol or Michael-type additions to suitable acceptors. Conversely, nitro olefins can themselves act as excellent Michael acceptors. Nitro groups β to carbonyls can also act as leaving groups in β-elimination reactions—a property which we recently took advantage of in our synthesis of α-methylenebutyrolactones.[2] Acting in yet other ways, nitro groups can be converted into other useful functional groups such as amines or carbonyls. This latter conversion is of considerable interest and utility because it in effect reverses



(1) For a review of the chemistry of nitro groups, see H. Feuer, Ed., "The Chemistry of the Nitro and Nitroso Groups," Wiley-Interscience, New York, N. Y., 1969.

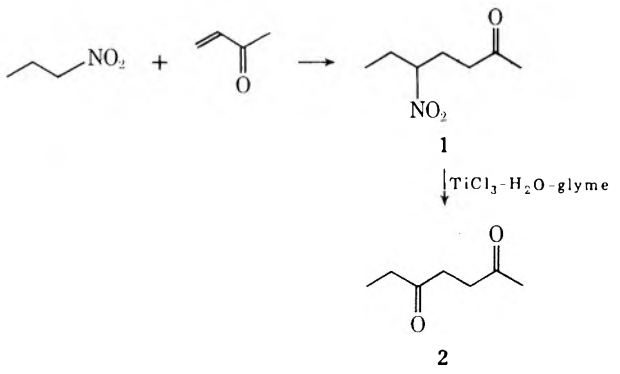
(2) J. W. Patterson and J. E. McMurry, *Chem. Commun.*, 488 (1971).

the polarity of the neighboring carbon from nucleophilic to electrophilic, thus allowing a wide range of transformations to be carried out.

Current methods for effecting this conversion, however, are either incompatible with the presence of other sensitive functionality within the molecule or proceed in low yield. Thus the Nef reaction[3] is an acidic method which is incompatible with the presence of a ketal function; permanganate oxidation of nitronate anions[4] is incompatible with other easily oxidized functional groups; persulfate oxidation of nitronates[5] proceeds in low yield. We therefore sought an effective, mild method for performing the nitro → carbonyl transformation.

In a recent communication, Timms and Wildsmith reported[6] that oximes are rapidly reduced by aqueous titanium trichloride to imines which are then hydrolyzed to carbonyl compounds in high overall yield. Since oximes might be expected to occur as intermediates in the reduction of primary and secondary nitro compounds, we investigated the action of aqueous Ti^{III} on aliphatic nitro compounds in the hope that they too might be reduced to imines, and thence, by hydrolysis, to ketones.

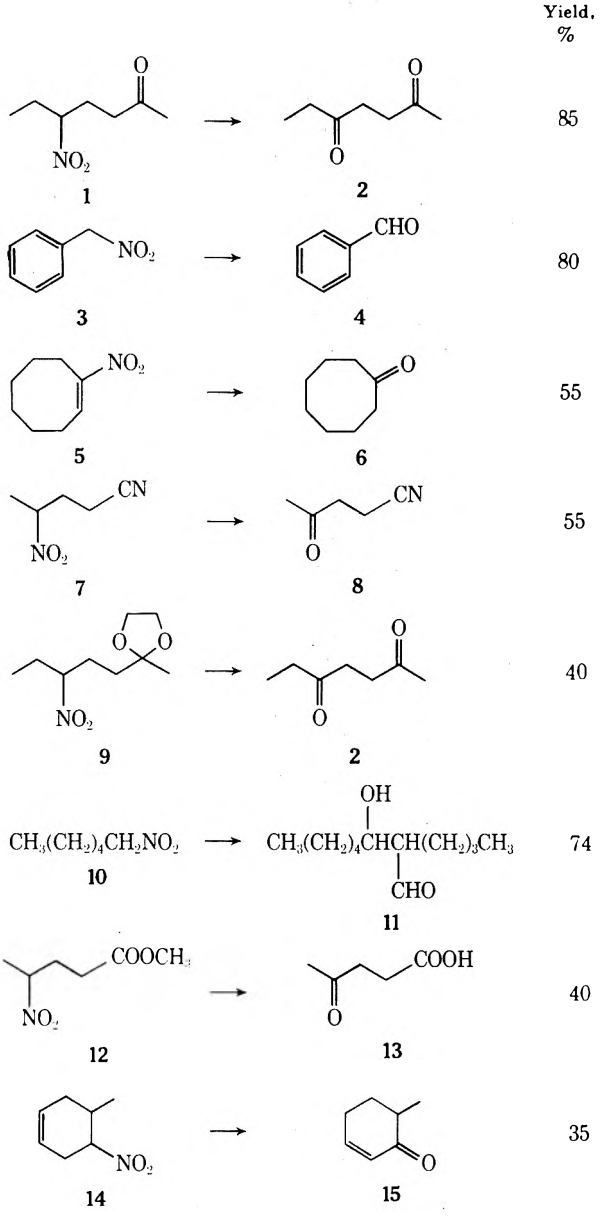
For a model system, we examined the reduction of 5-nitroheptan-2-one (**1**) prepared by diisopropylamine-catalyzed addition of 1-nitropropane to methyl vinyl ketone (MVK). Addition of an aqueous solution of 4 equiv of $TiCl_3$ to a solution of **1** in glyme at room temperature resulted in the slow disappearance of the deep purple Ti^{III} color. After 6 hr, vpc analysis indicated the absence of starting material and the presence of a single new product. After work-up, 2,5-heptanedione was isolated in 85% yield.[7]



The feasibility of this new method had therefore been established and we began a study of the reaction's scope.

It quickly became apparent that, although simple nitro compounds underwent ready transformation to the corresponding ketones in good yields (**1** → **2**, 85%; α-nitrotoluene → benzaldehyde, 80%; nitrocyclooctene → cyclooctanone, 55%), our conditions were still too vigorous (pH <1) for acid-sensitive functional groups to survive. For example, nitro ketal **9** was reduced and hydrolyzed to diketone **2** in the course of the reaction; hexanal (from 1-nitrohexane) aldolized during the reaction to give the dimer **11**; nitro ester **12** was reduced and hydrolyzed to the corresponding keto acid **13**; nitro olefin **14** was reduced and isomerized to α,β-enone **15** under the reaction conditions. These transformations are summarized in Table I.

TABLE I
REACTION OF NITRO COMPOUNDS WITH AQUEOUS $TiCl_3$ SOLUTIONS (pH <1)



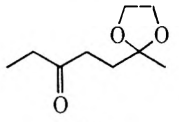
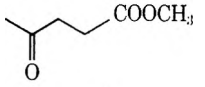
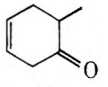
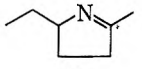
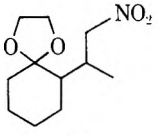
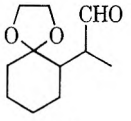
Because of these difficulties, we therefore sought milder conditions under which we could carry out the reaction. The obvious solution was to raise the pH of the reaction medium, and we chose to do this by adding ammonium acetate as a buffer. In the proportion $NH_4OAc:TiCl_3$ of 6:1, the pH of the reaction was approximately 6 and reduction still occurred at a rate similar to that at pH <1. We immediately found that under these near neutral conditions a marked improvement in some of the reactions could be made. For example, the nitro ketal **9** now gave the desired keto ketal **16** in 70% yield. Similarly, the nitro ester **12** gave the desired keto ester **17** (35%) and nitro olefin **14** gave β,γ-enone **18** (30%), although yields were still not acceptable.

(3) For a review of the Nef reaction, see W. E. Noland, *Chem. Rev.*, **55**, 137 (1955).
(4) H. Shechter and F. T. Williams, *J. Org. Chem.*, **27**, 3699 (1962).
(5) A. H. Pagano and H. Shechter, *J. Org. Chem.*, **35**, 295 (1970).
(6) G. H. Timms and E. Wildsmith, *Tetrahedron Lett.*, 195 (1971).
(7) A preliminary account of this work has already appeared: J. E. McMurry and J. Melton, *J. Amer. Chem. Soc.*, **93**, 5309 (971).

Much to our surprise, however, several nitro compounds gave worse results under these neutral conditions than under acidic conditions. For example, nitro ketone **2** gave none of the expected diketone **3** but gave rather, as the only isolable organic compound, the pyrroline **19** (20%). Similarly, 1-nitrohexane now gave aldol dimer plus azoxy-*n*-hexane. These results are given in Table II.

TABLE II

REACTION OF NITRO COMPOUNDS WITH $TiCl_3$–NH_4OAc (1:6) AT pH 6

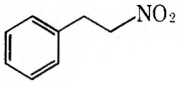
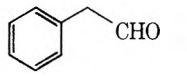
			Yield, %
5	→	6	70
9	→	 **16**	70
12	→	 **17**	35
14	→	 **18**	30
10	→	**11** (45%) + $C_6H_{13}N{=}NC_6H_{13}$ (O↑)	20
1	→	 **19**	20
 **23**	→	 **24**	70

These unexpected results are saying something about the mechanism of the reduction but, leaving this aside for the moment, it is still clear that better conditions are needed in some cases. After considering the possible mechanism of the reaction (*vide infra*), and after further experimentation, we found that, if we first formed the sodium salt of the nitro compound (1 equiv of $NaOCH_3$ in CH_3OH) and then added this salt to an aqueous solution of $TiCl_3$–NH_4OAC (1:3, pH ~ 5–6), reaction occurred within minutes at room temperature and the desired carbonyl compounds could be isolated in good yields in all cases.

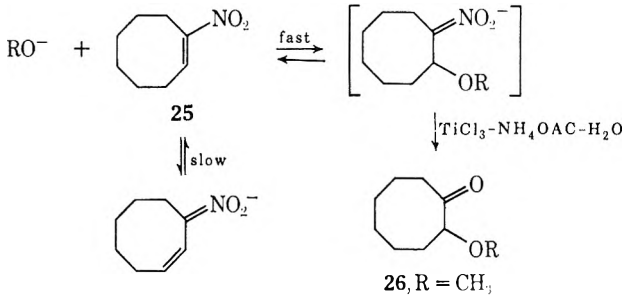
Thus, to dwell on only the more delicate cases, the nitro ester **12** could be transformed into methyl levulinate (**17**, 90%); nitro nitrile **7** similarly was converted in 90% yield to keto nitrile **8**; β-nitrophenylethane was converted to phenylacetaldehyde (70%); 1-nitrohexane gave hexanal (45%); and nitro olefin **14** was transformed into the β,γ-unsaturated ketone **18** in 60% yield. This last case is particularly noteworthy, because, in effect, a nitro olefin has served as a ketene equivalent in the Diels–Alder reaction with butadiene. This simple synthesis of β,γ-unsaturated cyclohexenones is thus complementary to the well-known Birch reduction of anisoles. These and other examples are shown in Table III.

TABLE III

REACTION OF NITRONATE ANIONS WITH $TiCl_3$–NH_4OAc (1:3) AT pH 6

			Yield, %
9	→	16	70
12	→	17	90
7	→	8	90
14	→	18	60
10	→	$CH_3(CH_2)CHO$ **22**	45
 **20**	→	 **21**	70
23	→	**24**	90

One further point we wanted to investigate was the reaction of conjugated nitro olefins with Ti^{III}. *A priori*, one might expect to obtain an α,β-unsaturated ketone from such a reaction. In fact, however, when we treated 1-nitrocyclooctene (**25**) with 1 equiv of $NaOCH_3$ in CH_3OH followed by treatment with 1:3 $TiCl_3$–NH_4OAc in water, a 70% yield of 2-methoxycyclooctanone (**26**) was formed. Similarly, if we used hydroxide in aqueous dioxane as the base, a 90% yield of 2-hydroxcyclooctanone could be isolated. Presumably the alkoxide adds to the olefin to give the 2-alkoxynitronate anion, which then reduces normally.



26, R = CH_3
27, R = H
28, R = *t*-Bu

Synthetically, this appears to be quite an attractive way to generate these rather difficultly accessible systems.

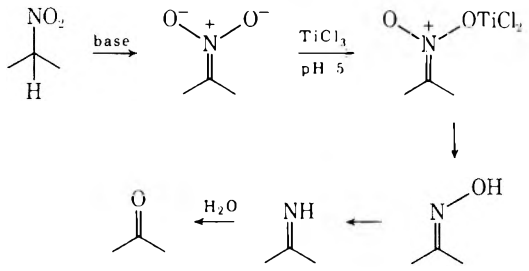
Mechanistically, however, this was a most unexpected result, since it has been reported[8] that treatment of a nitro olefin with ethoxide leads to the conjugated nitronate anion, not to the addition product. Interestingly, however, we have been able to show that the product obtained by treating a nitro olefin with alkoxide depends on the conditions used. When we treated 1-nitrocyclooctene with 1 equiv of $NaOCH_3$ in methanol followed rapidly by quenching the dilute acetic acid–sodium acetate buffer at 0°, we isolated 2-methoxy-1-nitrocyclooctane in near-quantitative yield. If, on the other hand, we allowed the base to react with 1-nitrooctene overnight followed by quenching, we recovered largely 1-nitrocyclooctene. Evidently the

(8) A. T. Neilsen, *J. Org. Chem.*, **27**, 2001 (1962).

addition product is kinetically formed whereas the conjugated nitronate anion is thermodynamically favored.

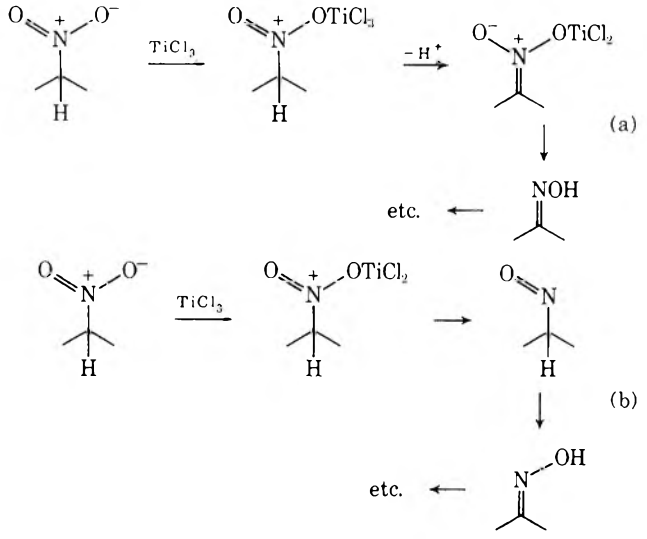
Mechanism.—As reported above, we have carried out two basic kinds of reactions: reactions on free nitro compounds at different pH's and reactions on nitronate anions. These two cases may well proceed by different mechanisms and we will consider them separately.

Reduction of Nitronate Anions.—Since Timms and Wildsmith have conclusively shown[6] that oximes reduce rapidly to imines with aqueous $TiCl_3$, we see no reason to assume that the reduction of nitronate anions is anything other than analogous. It can be written in the following way.



The details of the N–O bond cleavage steps are not clear (although radicals are probably involved since Ti^{III} is a one-electron reducing agent) but the general picture seems secure.

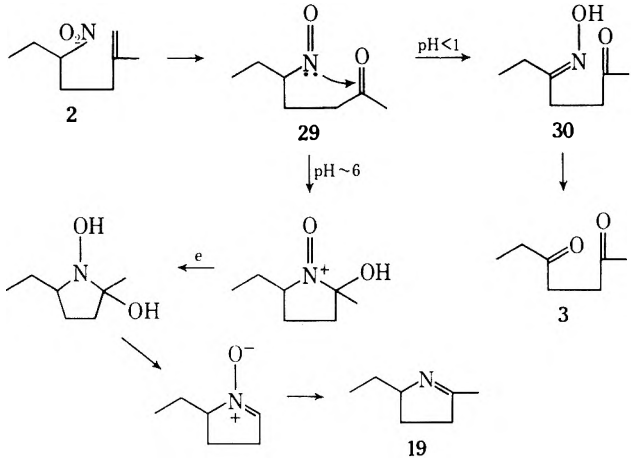
Reduction of Free Nitro Compounds.—The mechanism of reduction of free nitro groups is considerably less obvious, since one must deal with the question of when the C=N double bond is formed. Assuming that at some stage the titanium is covalently bound to nitro oxygen, we can conceive of two routes, a and b.



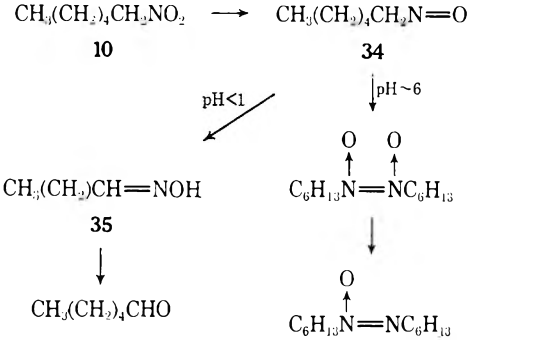
The major difference between the two concerns the timing of C=N double bond formation. In a, C=N double bond formation takes place while the titanium is still bound to oxygen, whereas in b the C=N double bond is formed *via* tautomerization of a discrete nitroso intermediate. We have found evidence pointing to b as the correct mechanism, and we believe that a nitroso compound is in fact an intermediate in the reaction. Our evidence is the following.

(1) The initial step in a is simply a Lewis acid (Ti^{III}) catalyzed tautomerization of the nitro compound to its acidform. It has been shown, however, that acid-catalyzed tautomerizations of nitro compounds are extremely slow.[9] Thus this mechanism is probably incorrect.

(2) As shown in Tables I and II, 5-nitroheptan-2-one (**2**) reduces normally to the diketone **3** at low pH, but gives only pyrroline **19** at neutral pH. We feel that this is best explained by assuming that nitroso compound **29** is an intermediate. At low pH, tautomerization to the oxime **30** would be rapid[10] and further reduction to the diketone would occur normally. At neutral pH, however, tautomerism of **29** to oxime **30** is slower,[10] and the nitroso group can therefore be trapped internally by the ketone carbonyl. Further reduction of the N–O bond followed by dehydration gives the observed pyrroline (**19**).



(3) The third piece of evidence in support of a nitroso intermediate comes from reduction of 1-nitrohexane. At pH <1, reaction occurs normally and hexanal is produced. At neutral pH, however, a mixture of hexanal (as the aldol dimer) and azoxy-*n*-hexane is formed. It is well known that nitroso compounds, particularly primary ones, dimerize quite readily to azodioxy compounds.[11] Evidently, 1-nitrosohexane (**34**) is an intermediate in the reduction of **10**. At low pH, **34** tautomerizes rapidly to oxime **35**, but, at neutral pH where tautomerization is slow, dimerization intervenes and further reduction occurs. It is interesting that only in the case of a primary nitro compound does this dimerization of the nitroso intermediate occur, but this is just what one would expect on steric grounds.

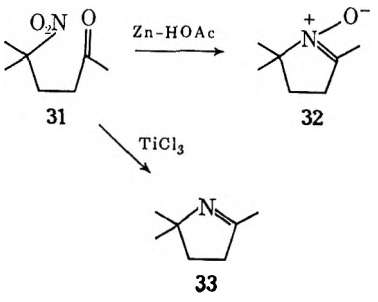


(9) A. T. Neilsen in "The Chemistry of the Nitro and Nitroso Groups," Vol. 1, H. Feuer, Ed., Wiley-Interscience, New York, N. Y., 1969, pp 370–372.

(10) M. H. Palmer and E. R. R. Russell, *Chem. Ind. (London)*, 157 (1966).

(11) J. H. Boyer in "The Chemistry of the Nitro and Nitroso Groups," Vol. 1, H. Feuer, Ed., Wiley-Interscience, New York, N. Y., 1969, pp 252–255.

There is good analogy in the literature for this cyclization. Zinc–acetic acid reduction of 5-methyl-5-nitrohexan-2-one (**31**) has been reported to yield the pyrroline 1-oxide **32**, presumably also through the intermediacy of a nitroso ketone.[12] Aqueous $TiCl_3$ is evidently able to carry the reduction one step further, for, when **31** is treated with $TiCl_3$, pyrroline **33** is the sole product isolated.



31 **32** **33**

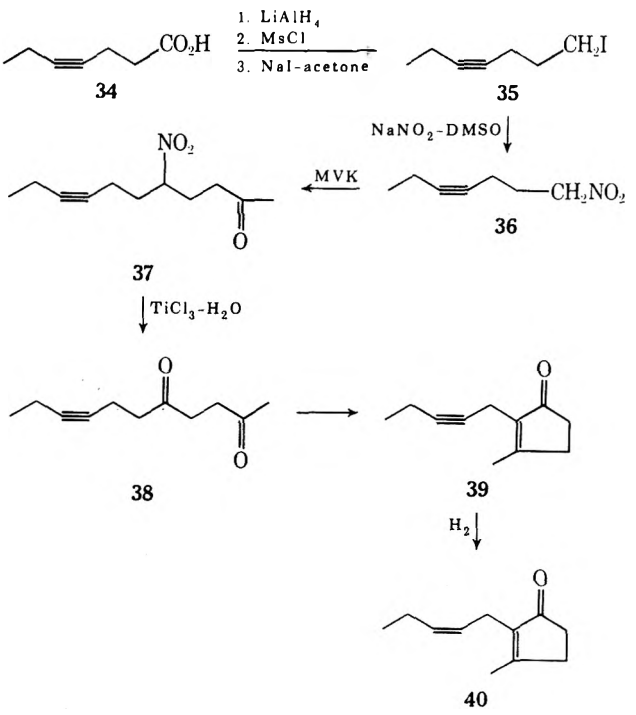
(4) Finally, one further point which should be made is that we have shown that hexanal oxime reduces normally to hexanal at pH ~6 and does not dimerize. Thus it cannot be an intermediate in the formation of azoxyhexane at this pH.

Synthesis of *cis*-Jasmone.—As stated at the outset, the nitro → carbonyl conversion is of great synthetic importance because it allows one to alter the polarity of the neighboring carbon atom. One consequence of this is the ability of a primary nitro compound to serve as a "carbonyl anion" equivalent.[13] We decided to demonstrate this process in a simple synthesis of the naturally occurring *cis*-jasmone (**40**).

4-Heptynoic acid[14] was reduced ($LiAlH_4$), and the resulting alcohol was mesylated. This mesylate was converted into the iodide by treatment with NaI in acetone, and the iodide was readily converted into the required primary nitro compound **36** with $NaNO_2$ in DMSO.[15] Taking advantage of the nucleophilic character of the nitro-bearing carbon, the diisopropylamine-catalyzed addition of **36** to MVK gave the desired nitro ketone **37** in 83% yield. Treatment of **37** in glyme with 4.5 equiv of aqueous $TiCl_3$ then gave the desired diketone **38** (85%), which was cyclized to dehydrojasmone (**39**) in 90% yield by treatment with refluxing 5% NaOH in aqueous ethanol. Hydrogenation of **39** over Lindlar catalyst[16] gave pure *cis*-jasmone (**40**, 95%), identified by comparison with an authentic sample[17] (Scheme I).

Summary.—In summary, we have developed, and refined conditions on, a new method of transforming a nitro group into a carbonyl. If the specific case is not acid sensitive, the simplest procedure is to treat the nitro compound with an unbuffered aqueous solution of $TiCl_3$. For sensitive cases, however, one should first form the nitronate anion, and then treat it with a buffered $TiCl_3$ solution.

SCHEME I



34 **35** **36** **37** **38** **39** **40**

Experimental Section

Preparation of Nitro Compounds.—4-Nitrovaleronitrile and methyl 4-nitrovalerate were prepared by the procedure of von Schickh.[18] 1-Nitrocyclohexene and 1-nitrocyclooctene were prepared according to Seifert.[19]

5-Nitroheptan-2-one (**1**).—1-Nitropropane (0.2 mol, 17.8 g) and diisopropylamine (10 ml) in 200 ml of chloroform were stirred at 60° under a nitrogen atmosphere. Methyl vinyl ketone (0.1 mol, 7.0 g) was added dropwise to this solution. After 3 hr, another portion of MVK (0.1 mol, 7.0 g) was added and the reaction was further stirred for 24 hr. The solution was then washed sequentially with water, 10% aqueous HCl, 5% $NaHCO_3$, and saturated brine, then dried (Na_2SO_4), concentrated, and distilled to yield nitro ketone **1** (17.0 g, 55%): bp 120° (10 mm); ir (neat) 1715, 1545 cm^{-1}; nmr (CCl_4) δ 0.97 (t, 3 H, J = 7 Hz), 2.7–2.5 (m, 6 H), 2.13 (s, 3 H), 4.38 (m, 1 H).

5-Nitroheptan-2-one Ethylene Ketal (**9**).—The nitro ketone **1** (10 mmol, 1.59 g) was dissolved in 5 ml of benzene, and ethylene glycol (12 mmol, 0.75 g) and 5 mg of *p*-toluenesulfonic acid monohydrate were added. The mixture was refluxed for 5 hr in a flask fitted with a Dean–Stark trap. The reaction solution was cooled and diluted with ether. After washing with 5% aqueous $NaHCO_3$ and brine, the organic phase was dried (Na_2SO_4) and concentrated, giving 1.98 g (98%) of crude nitro ketal **9**: ir (neat) 1545, 1040 cm^{-1}; nmr (CCl_4) δ 0.93 (t, 3 H, J = 7 Hz), 1.20 (s, 3 H), 2.2–1.3 (m, 6 H), 3.75 (s, 4 H), 4.5–4.0 (m, 1 H).

4-Nitro-5-methylcyclohexene (**14**).—A thick-walled glass tube was charged with 1-nitropropene[20] (9.0 g, 0.10 mol) and butadiene (4.5 ml). The tube was sealed and heated on a steam bath for 4 days to yield 6.54 g (46%) of **14**: bp 90° (10 mm); ir (neat) 3050, 1650, 1545 cm^{-1}; nmr (CCl_4) δ 0.95 (d, 3 H, J = 5.5 Hz), 3.0–1.5 (m, 4 H), 4.30 (m, 1 H), 5.53 (d, 2 H, J = 1.5 Hz). *Anal.* Calcd for $C_7H_{11}NO_2$: C, 59.56; H, 7.85. Found: C, 59.64; H, 7.87.

Nitro Ketal 23.—1-Nitropropene (2.0 g, 27.5 mmol) in 20 ml of acetonitrile was added dropwise to a stirred solution of morpholinocyclohexene (6.0 g) in 20 ml of acetonitrile at −20° and the reaction was let stir for 1 hr under a nitrogen atmosphere. Hydrolysis of the enamine was effected by addition of 30 ml of 1.5 *M* HCl. After extraction with ether, distillation gave 2.64 g (65%) of nitro ketone corresponding to **23**: bp 90° (7 mm); ir (neat) 1710, 1545 cm^{-1}; nmr (CCl_4) δ 1.00 (d, 3 H, J = 6 Hz), 3.5–1.30 (m, 9 H), 4.33 (d, 2 H, J = 6 Hz). The 2,4-DNP had

(12) R. F. C. Brown, V. M. Clark, and A. Todd, *Proc. Chem. Soc., London*, 97 (1957).
(13) For a general discussion of carbonyl anion equivalents, see D. Seebach, *Angew. Chem., Int. Ed. Engl.*, **9**, 639 (1969).
(14) M. F. Ansell, J. C. Emmett, and R. V. Coombs, *J. Chem. Soc. C*, 217 (1968).
(15) N. Kornblum and J. W. Powers, *J. Org. Chem.*, **22**, 455 (1957).
(16) Purchased from Fluka, A. G., Buchs, Switzerland.
(17) J. E. McMurry and T. E. Glass, *Tetrahedron Lett.*, 2575 (1971).
(18) *Chem. Abstr.*, **52**, 5455*f* (1958).
(19) W. Seifert, *J. Org. Chem.*, **28**, 125 (1963).
(20) G. D. Buckley and C. W. Scaife, *J. Chem. Soc.*, 1471 (1947).

mp 139–140°. *Anal.* Calcd for $C_{15}H_{19}N_3O_6$: C, 49.31; H, 5.24. Found: C, 49.41; H, 5.21.

General Procedures for $TiCl_3$ Reduction of Nitro Compounds. A. Reductions with Aqueous $TiCl_3$ at pH 1.—The alkyl nitro compound in an appropriate solvent (THF or dimethoxyethane, 0.2 *M*) was treated with 4 equiv of $TiCl_3$ (20% aqueous solution) and stirred under nitrogen at room temperature for the indicated time. The reaction mixture was then poured into ether and separated into phases. The aqueous phase was extracted several times with ether; the organic extracts were combined, washed with 5% $NaHCO_3$ and with brine, then dried (Na_2SO_4), concentrated, and distilled. The following examples were run.

α-Nitrotoluene (3).—Benzaldehyde was isolated in 80% yield after allowing α-nitrotoluene (**3**) to react for 18 hr in THF.

5-Nitroheptan-2-one (1).—Dione **2** was isolated in 66% yield after allowing **1** to react for 24 hr in THF: ir (neat) 1710 cm^{-1}; nmr (CCl_4) δ 2 60 (s, 4 H), 3.41 (q, 2 H, J = 7 Hz), 2.10 (s, 3 H), 1.00 (t, 3 H, J = 7 Hz). Dione **2** was further identified by cyclization with 5% aqueous NaOH to the known 2,3-dimethylcyclopentenone (85%), 2,4-DNP mp 226–227° (lit.[21] mp 226–227°).

1-Nitrohexane (10).—Hexanal aldol dimer (**11**) was isolated in 74% yield after allowing **10** to react for 18 hr in THF: ir ($CHCl_3$) 2730, 1680, 1640 cm^{-1}; nmr (CCl_4) δ 9.35 (s, 1 H), 6.4 (t, 1 H, J = 7.5 Hz), 2.5–2.0 (m, 4 H), 1.8–1.1 (m, 6 H), 1.1–0.8 (m, 6 H).

4-Nitrovaleronitrile (7).—Levulinonitrile (**8**) was isolated in 55% yield after allowing **7** to react for 2 days in THF, 2,4-DNP mp 146° (lit.[22] mp 146°).

Methyl 4-Nitrovalerate (12).—Methyl levulinate was isolated in 16% yield, plus 32% levulinic acid after allowing **12** to react for 12 hr in THF.

1-Nitrocyclooctene (5).—Allowing **5** to react for 2 hr in THF gave 55% **6**.

5-Nitroheptan-2-one Ethylene Ketal (9).—Keto ketal **16** was isolated in 40% yield after allowing **9** to react for 12 hr in THF.

4-Nitro-5-methylcyclohexene (14).—After reaction for 12 hr in THF, 6-methylcyclohex-2-en-1-one (**15**) was isolated in 35% yield.

B. Reduction of Nitro Compounds with Aqueous $TiCl_3$ at pH 5.—A buffered $TiCl_3$ solution was prepared by adding NH_4OAc (4.6 g, 0.06 mol) in 15 ml of H_2O to 20% aqueous $TiCl_3$ (0.01 mol) under nitrogen. Nitro compound in the appropriate solvent was added rapidly and the mixture was stirred for the indicated period at room temperature. Product isolation was carried out as in procedure A. The following examples were run.

2-Nitroheptan-2-one Ethylene Ketal (9).—Keto ketal **16** was isolated in 67% yield after reaction of **9** for 12 hr in dimethoxyethane: ir (neat) 1715, 1100, 1030 cm^{-1}; nmr (CCl_4) δ 0.97 (t, 3 H, J = 7 Hz), 1.18 (s, 3 H), 2.0–1.3 (m, 2 H), 3.6–2.0 (m, 2 H), 3.75 (s, 4 H). Ketal **16** was further identified by acidic hydrolysis to diketone **2**.

Nitro Ketal 23.—Ketal aldehyde **24** was isolated in 70% yield after stirring nitro ketal **23** for 12 hr in methanol: ir (neat) 2750, 1725 cm^{-1}; nmr (CCl_4) δ 0.96 and 1.00 (two doublets, 3 H, J = J' = 7 Hz), 3.84 (s, 4 H), 9.1 and 11.1 (two doublets, 1 H, J = J' = 4 Hz). *Anal.* Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.60; H, 9.14.

1-Nitrohexane (10).—After reaction of **10** for 3 hr in methanol, hexanal dimer (45%) and azoxy-*n*-hexane (20%) were isolated. Azoxy *n*-hexane had ir ($CHCl_3$) 1500 cm^{-1}; nmr ($CDCl_3$) δ 4.15 (t, 2 H, J = 7 Hz), 3.40 (t, 2 H, J = 7 Hz), 2.0–1.0 (m, 10 H), 1.0–0.6 (m, 6 H). An authentic sample was prepared for comparison purposes by the procedure of Greene,[23] and was identical in all respects.

5-Nitroheptan-2-one (1).—After 12 hr reaction in THF, 2-methyl-5-ethyl-Δ¹-pyrroline (**19**) was isolated (20%): ir (neat) 2975, 2940, 2880, 1650 cm^{-1}; nmr (CCl_4) δ 3.6 (m, 1 H), 2.20 (m, 2 H), 1.9 (d, 3 H, J = 1.5 Hz), 1.7–1.2 (m, 4 H), 1.2–0.7 (m, 3 H); picrate mp 126.5–127.5°. *Anal.* Calcd for $C_{13}H_{16}N_4O_7$: C, 45.89; H, 4.74. Found: C, 46.14; H, 4.80.

1-Nitrocyclohexene.—After reaction for 12 hr in methanol, a 42% yield of cyclohexanone was found.

1-Nitrocyclooctene (5).—After reaction for 12 hr in methanol, cyclooctanone was produced in 70% yield.

Methyl 4-Nitrovalerate (12).—After 12 hr in THF, methyl levulinate (**17**) was isolated (35%).

4-Nitro-5-methylcyclohexene (14).—After 12 hr reaction in THF, 6-methylcyclohex-3-en-1-one (**18**) was isolated (30%).

C. Reduction of Nitronate Anions with Aqueous $TiCl_3$ at pH 5.—The nitro compound was dissolved in methanol (0.5 *M*) and treated with 1 equiv of $NaOCH_3$. A buffered $TiCl_3$–NH_4OAc solution prepared as in procedure B was then added in one portion to the anion solution at room temperature under a nitrogen atmosphere. After an appropriate period, the reaction was worked up as in procedure A. The following examples were examined.

4-Nitro-5-methylcyclohexene (14).—After reaction for 45 min, 6-methylcyclohex-3-en-1-one (**18**) was isolated in 60% yield: ir (neat) 3040, 1715 cm^{-1}; nmr (CCl_4) δ 1.05 (d, 3 H, J = 6 Hz), 5.71 (m, 2 H); 2,4-DNP mp 142°. *Anal.* Calcd for $C_{13}H_{14}N_4O_4$: C, 53.79; H, 4.86. Found: C, 53.75; H, 4.77.

Methyl 4-Nitrovalerate (12).—A 90% yield of methyl levulinate was isolated after 30-min reactions, 2,4-DNP mp 141° (lit.[24] mp 141°).

4-Nitrovaleronitrile (7).—A 90% yield of levulinonitrile was isolated after 45-min reaction, 2,4-DNP mp 146° (lit.[22] mp 146°).

Nitro Ketal 23.—A 90% yield of ketal aldehyde was isolated after 45 min reaction.

β-Nitrophenylethane (20).—Phenylacetaldehyde (**21**, 70%) was isolated after 30-min reaction.

1-Nitrohexane (10).—Hexanal (45%) was isolated after 30-min reaction.

1-Nitrocyclooctene (5).—After 1 hr reaction, 2-methyoxycyclooctanone (70%) was isolated: ir (neat) 1710, 1100 cm^{-1}; nmr (CCl_4) δ 3.54 (m, 1 H), 3.28 (s, 3 H), 2.8–0.8 (12 H); 2,4-DNP mp 136°. *Anal.* Calcd for $C_{15}H_{20}N_4O_5$: C, 53.57; H, 5.99. Found: C, 53.56; H, 6.11.

When aqueous NaOAc–dioxane was used to form the nitronate anion, 2-hydroxycyclooctane (90%) was formed.

5-Nitroheptan-2-one Ethylene Ketal (9).—Keto ketal **16** was isolated in 70% yield after 2-hr reaction in methanol.

4-Heptyn-1-ol.—A slurry of lithium aluminum hydride (1.93 g, 0.051 mol) in 75 ml of dry ether was mechanically stirred in a 250-ml flask and a solution of 4-heptynoic acid (6.13 g, 0.049 mol) in 75 ml of ether was slowly added. After addition was complete, the reaction was further stirred for 30 min and then cautiously quenched by sequential addition of water (2.5 ml), 15% NaOH (2.5 ml), and water (7.5 ml). The reaction mixture was then filtered, dried (Na_2SO_4), concentrated, and distilled to yield the desired alcohol (5.18 g, 95%) as a colorless oil: bp 91° (15 mm); ir (neat) 3350, 1050 cm^{-1}; nmr (CCl_4) δ 3.58 (t, 2 H, J = 6.5 Hz), 3.6 (s, 1 H), 2.15 (m, 4 H), 1.68 (m, 2 H), 1.08 (t, 3 H, J = 7.5 Hz).

1-Iodo-4-heptyne (35).—4-Heptyn-1-ol (1.0 g, 8.9 mmol) was dissolved in 40 ml of methylene chloride and 15 ml of triethylamine at −10°. Methanesulfonyl chloride (10 mmol) was slowly added, and, after 15 min of additional stirring, the mixture was transferred to a separatory funnel and washed sequentially with water, 10% HCl, 5% $NaHCO_3$, and saturated brine. The solution was then dried (Na_2SO_4) and concentrated to yield crude mesylate (1.67 g, 100%).

Without further purification, the crude mesylate (3.54 g, 18.6 mmol) was added to a mixture of NaI (4.15 g, 28 mmol) in acetone (20 ml) and the reaction mixture was stirred overnight at room temperature. The mixture was then filtered and concentrated. The residue was taken up in ether and washed with water, 10% $NaHSO_3$, and saturated brine, and then was dried (Na_2SO_4) and concentrated. The residual oil was distilled to give iodide **35** (3.0 g, 73%): bp 91–94° (15 mm); ir (neat) 2980, 1240, 1165 cm^{-1}; nmr (CCl_4) δ 3.12 (m, 2 H), 2.7 (m, 2 H), 2.17 (m, 2 H), 1.12 (t, 3 H, J = 7.5 Hz).

1-Nitro-4-heptyne (36).—A solution of iodide **35** (2.77 g, 12.5 mmol) and $NaNO_2$ (1.52 g, 21.7 mmol) in DMSO (10 ml) was mechanically stirred for 1 hr at room temperature. The reaction mixture was diluted with 30 ml of ice water and extracted with petroleum ether (bp 30–60°) (5 × 10 ml). The combined extracts were washed with water, dried ($MgSO_4$), filtered, concentrated, and distilled to give the nitro compound **36** (0.8 g, 45%): bp 60–70° (5 mm); ir (neat) 1550 cm^{-1}; nmr (CCl_4) δ 4.25 (t, 2 H, J = 7 Hz), 2.5–1.4 (m, 6 H), 1.10 (t, 3 H, J = 7 Hz).

(21) S. Dev and C. Rai, *J. Indian Chem. Soc.*, **34**, 266 (1957).
(22) G. D. Buckley and T. J. Elliott, *J. Chem. Soc.*, 1505 (1947).
(23) F. D. Greene and S. S. Hecht, *J. Org. Chem.*, **35**, 2482 (1970).
(24) M. A. Cowley and H. S. Schuette, *J. Amer. Chem. Soc.*, **55**, 3463 (1933).

5-Nitro-8-undecyn-2-one (37).—1-Nitro-4-heptyne (0.79 g, 5.62 mmol), diisopropylamine (0.3 ml), and methyl vinyl ketone (0.43 g, 6.1 mmol) in 6 ml of chloroform were stirred at 40° for 16 hr under nitrogen. The solution was then distilled to give 980 mg (83%) of product **37**: bp 110° (0.001 mm); ir (neat) 1715, 1545 cm^{-1}; nmr (CCl_4) δ 1.09 (t, 3 H, J = 7 Hz), 2.10 (s, 3 H), 4.6 (m, 1 H); mass spectrum m/e (rel intensity) 162 (P^+, 50), 147 (100). *Anal.* Calcd for $C_{11}H_{17}NO_3$: C, 62.53; H, 8.13. Found: C, 62.53; H, 8.10.

8-Undecyne-2,5-dione (38).—This compound was prepared by reduction of **37** with $TiCl_3$ according to procedure A above; an 85% yield was obtained after 18-hr reaction in dimethoxyethane as solvent.

Dehydrojasmone (39).—Diketone **38** (0.38 g, 2.1 mmol) was dissolved in 10 ml of 5% ethanolic KOH solution and the solution was refluxed for 2 hr under nitrogen. The solution was then poured into a separatory funnel, diluted with water, and extracted with ether. The extracts were washed with brine, dried ($MgSO_4$), concentrated, and distilled to yield dehydrojasmone (**39**, 0.34 g, 85%): bp 103–105° (0.1 mm); ir (neat) 1705, 1650 cm^{-1}; nmr (CCl_4) δ 1.13 (t, 3 H, J = 7 Hz), 2.15 (s, 3 H), 2.25 (m, 6 H), 2.95 (t, 2 H, J = 1.5 Hz); 2,4-DNP mp 165° (lit.[25] mp 166°).

(25) K. Sisido, Y. Kawasima, and T. Isida, *Perfum. Essent. Oil. Rec.*, **57**, 364 (1966).

***cis*-Jasmone (40).**—Lindlar catalyst[16] (50 mg) in 2 ml of ethyl acetate was equilibrated under 1 atm of hydrogen for 12 hr and dehydrojasmone (0.050 g, 0.003 mol) in 1 ml of ethyl acetate was added. After 5 min, hydrogen uptake stopped, and the reaction was filtered free of catalyst and concentrated to yield *cis*-jasmone (**40**, 47 mg, 95%): ir 1705, 16.50 cm^{-1}; nmr (CCl_4) δ 0.97 (t, 3 H, J = 7.5 Hz), 2.02 (s, 3 H), 2.20 (m, 6 H), 2.84 (d, 2 H, J = 5 Hz), 5.22 (triplet of doublets, 2 H, J = 4, J' = 6 Hz); 2,4-DNP mp 116° (lit.[26] mp 117.5°).

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Registry No.—**1**, 42397-25-1; **2**, 1703-51-1; **3**, 622-42-4; **5**, 1782-03-2; **7**, 16506-99-3; **9**, 42397-27-3; **10**, 646-14-0; **11**, 42397-28-4; **12**, 10312-37-5; **14**, 42397-30-8; **16**, 42397-31-9; **18**, 32863-04-0; **18** 2,4-DNP, 42397-33-1; **19**, 42397-34-2; **19** picrate 42397-12-6; **20**, 6125-24-2; **23**, 42397-13-7; **23** 2,4-DNP, 42397-14-8; **24**, 42397-15-9; **26**, 42397-16-0; **26** 2,4-DNP, 42397-17-1; **34**, 42441-83-8, and **35**, 18498-36-7 (Scheme I); **36**, 42397-19-3; **37**, 42397-20-6; **38**, 7051-43-6; **39**, 7051-37-8; **40**, 488-10-8; $TiCl_3$, 7705-07-9; 1-nitropropane, 108-03-2; methyl vinyl ketone, 78-94-4; 1-nitropropene, 3156-70-5; butadiene, 106-99-0; morpholinocyclohexene, 670-80-4; azoxy-*n*-hexane, 42441-84-9; 1-nitrocyclohexene, 2562-37-0; 4-heptyn-1-ol, 42397-24-0.

(26) L. Crombie and S. H. Harper, *J. Chem. Soc.*, 869 (1952).

Synthesis of *N*-(2-Triphenylstannylethyl)amines and Their Reactivities

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The reactions of seven *N*-(2-triphenylstannylethyl)amines (**3a–g**), prepared from the corresponding 2-chloroethylamines (**1a–e,g**) and triphenyltinlithium (**2**), with methyl halides (MeX) or hydrogen halides (HX) were investigated. In the case of X = I or Br, the quaternary ammonium salts or the amine hydrohalides, produced from *N*-(2-triphenylstannylethyl)alkylamines (**3a** and **3b**), were unstable and were cleaved by nucleophilic attack of X^- at tin atom which resulted in the formation of triphenyltin halides and alkylamines with the loss of ethylene. On the contrary, **3a–c** hydrochlorides were stable, but the presence of excess hydrogen chloride led quantitatively to (2-alkylaminoethyl)phenyltin dichloride hydrochlorides (**8a–c**) by electrophilic attack of H^+ on the phenyl groups. However, the reaction of *N*-(2-triphenylstannylethyl)arylamines (**3d** and **3e**) with hydrogen chloride gave a mixture of triphenyltin chloride, diphenyltin dichloride, phenyltin trichloride, and *sec*-arylamines, as a result of the competition between the nucleophilic attack of Cl^- at tin atom and the electrophilic attack of H^+ on phenyl group.

Previous investigations of aminoalkyltin compounds have dealt with the chemistry of the α-[1] and γ-amino[2] derivatives. While a few of the β-aminoalkyltin compounds have been obtained by additions of triorganotin hydrides to vinylamines[2a,3] or by carbon–carbon insertion reaction into tin–nitrogen bonds,[4] little is known about their chemical properties. We now report the preparation of several new alkylamino- and arylaminoethyltriphenyltin compounds as well as some of the reactions that they undergo.

Seven *N*-(2-triphenylstannylethyl)amines (**3a–g**) were synthesized in 60–80% yields from reactions of the corresponding 2-chloroethylamines (**1a–e,g**) with triphenyltinlithium (**2**) in tetrahydrofuran (see Table I). Their structures were confirmed by elemental and ^1H nmr spectral analyses (see Table IV). *N*-(2-Triphenylstannylethyl)aniline (**3f**) was isolated in low yield from the reaction of *N*-(2-chloroethyl)acetanilide (**1g**) with **2**. Hydrolysis of *N*-(2-triphenylstannylethyl)acetanilide (**3g**) in alcoholic potassium hydroxide also gave **3f**. The reduction of **3g** with lithium aluminum hydride gave **3f** in high yield. No *N*-(2-triphenylstannylethyl)-*N*-ethylaniline was obtained. The acetylation of **3f** with acetic anhydride led to **3g**. However, the methylation of **3f** with an equimolar amount of methyl bromide or methyl iodide in ethanol did not produce *N*-(2-triphenylstannylethyl)-*N*-methylaniline (**3d**) as expected, but gave mixtures which consisted of *N*-methylaniline, triphenyltin bromide, or triphenyltin iodide, respectively, as major products, and aniline and *N*,*N*-dimethylaniline as minor products along with unreacted **3d**. These products are regarded as resulting from the following reactions (Scheme I).

The reaction of **3f** with MeX (X = Br, I) initially gives **3d** hydrohalide (**3d**-HX). Proton transfer from **3d**-HX to **3f** affords **3f** hydrohalide (**3f**-HX) and **3d**, which subsequent reacts with additional MeX to give *N*-(2-triphenylstannylethyl)-*N*,*N*-dimethyl-*N*-phenylammonium halide (**5d**). These three ammonium

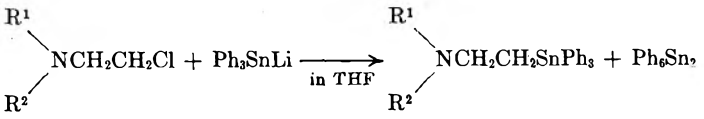
(1) D. J. Peterson, *J. Organometal. Chem.*, **21**, P63 (1970); *J. Amer. Chem. Soc.*, **93**, 4027 (1971). R. G. Kostyanovskii and A. K. Prokofev, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 175 (1965).

(2) (a) G. J. M. van der Kerk and J. G. Noltes, *J. Appl. Chem.*, **9**, 106 (1959); (b) *ibid.*, **9**, 176 (1959).

(3) G. J. M. van der Kerk, J. G. Noltes, and J. G. A. Luijten, *J. Appl. Chem.*, **7**, 356 (1957); W. P. Neumann, H. Niermann, and R. Sommer, *Justus Liebigs Ann. Chem.*, **659**, 27 (1962).

(4) G. Chandra, T. A. George, and M. F. Lappert, *Chem. Commun.*, 116 (1967).

TABLE I



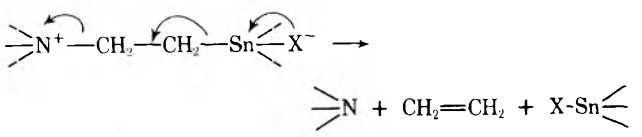
1a–e,g 2 3a–g 4

Compd	R¹	R²	Reaction conditions: Temp	Reaction conditions: Time, hr	3: Mp, °C	3: Yield, %	4, Yield, %
a	CH_3	CH_3	Room	7	81–83	85.3	5
b	C_2H_5	C_2H_5	Room	18	48.5–49.5	63.5	5
			Reflux	2			
c	$(-CH_2CH_2)_2O$		Room	18	125–126	56.1	7
			Reflux	2			
d	CH_3	C_6H_5	Room	20	59.5–60.0	62.4	5
			Reflux	2			
e	C_6H_5	C_6H_5	Room	19	98–100	78.5	5
			Reflux	3			
f	H	C_6H_5			91–92.5	*a*	
g	CH_3CO	C_6H_5	Room	18	106–108	65.0	9
			Reflux	2			

[a] 3f was isolated from the reaction of 1g with 2 as a by-product in 4% yield.

halides, 3d-HX, 3f-HX, and 5d, are cleaved by nucleophilic attack of the X^- at the tin atom to give the amines, triphenyltin halide, and ethylene (path a, b, and c). Evidence in support of these three postulated reaction paths is found in the following experimental results. The addition of an equimolar solution of hydrogen bromide in ether to 3d afforded *N*-methylaniline and triphenyltin bromide, accompanied by a small amount of 3d hydrobromide (3d-HBr). Similarly, the addition of an equimolar amount of hydrogen bromide to 3f gave 3f hydrobromide (3f-HBr) quantitatively, which was readily cleaved to aniline and triphenyltin bromide by heating in ethanol. The reaction of 3d with an equimolar amount of methyl iodide gave *N*,*N*-dimethylaniline, triphenyltin iodide, and no 5d.

The other β-aminoethyltin compounds, *N*-(2-triphenylstannylethyl)dimethylamine (3a) and *N*-(2-triphenylstannylethyl)diethylamine (3b), gave, upon reaction with excess methyl bromide, the corresponding amine methobromides (6a and 6b) and triphenyltin bromide, respectively. Attempts to isolate quaternary ammonium bromides from any of the reactions were unsuccessful. *N*-(2-Triphenylstannylethyl)diphenylamine (3e) and 3g did not react with the methyl halide to form quaternary ammonium salts. There is no doubt from these results that the cleavage of *N*-(2-triphenylstannylethyl)amines by methyl halides proceeds *via* the quaternary ammonium salts.



Early observations in organosilicon chemistry indicated that substituted organosilanes, $R_3SiCH_2CH(R')X$ (X = halogen or hydroxyl, R′ = H or alkyl), react rapidly with acid, base, and a variety of other reagents to generate the corresponding alkene and R_3SiX.[5] Davis, *et al.*,[6] recognized that β-triphenylstannyl alcohols readily undergo an acid-catalyzed deoxymetalation reaction in an acidic medium.

$$Ph_3SnCH_2CH_2OH \xrightarrow{H^+} Ph_3SnCH_2CH_2O^+H_2 \xrightarrow{MeOH-H_2O} Ph_3SnOH + CH_2{=}CH_2 + H_2O + H^+$$

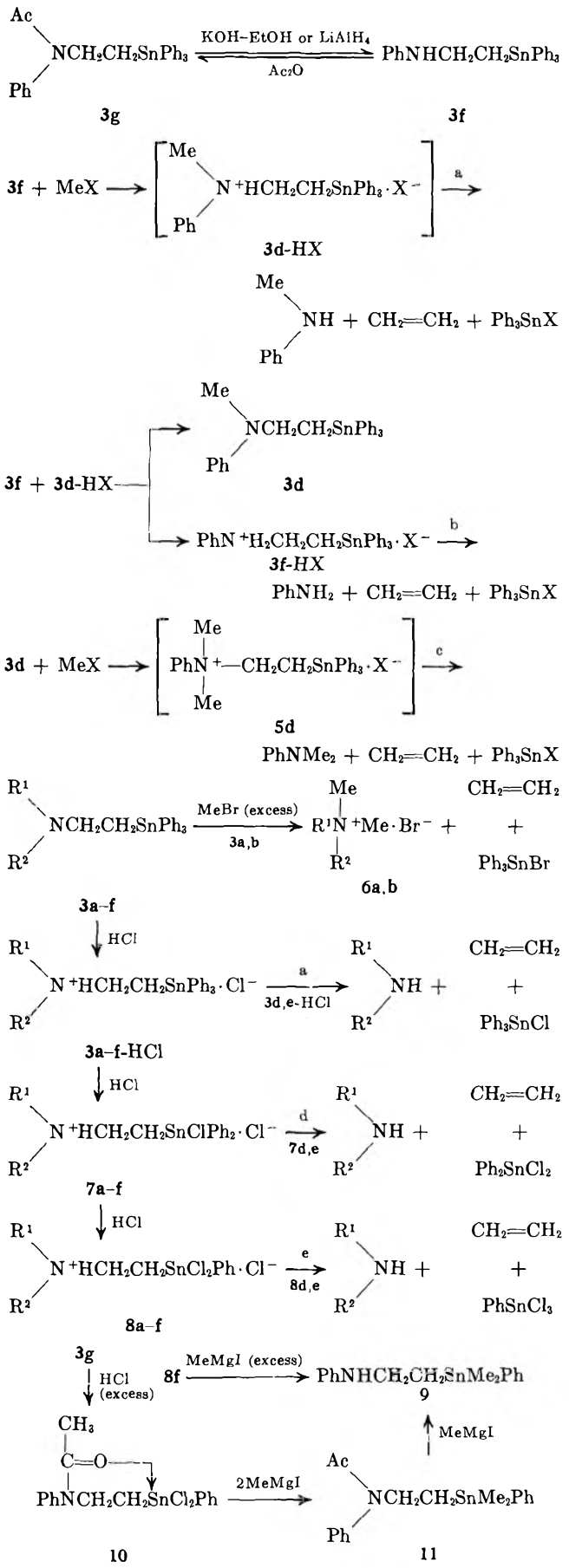
Addition of an equimolar amount of ethereal hydrogen bromide to 3a gave a mixture of 3a hydrobromide (3a-HBr), dimethylamine, and triphenyltin bromide, whereas stable crystals of 3a hydrochloride (3a-HCl) were formed upon treatment of 3a with an equimolar amount of ethereal hydrogen chloride (Table II). Two equivalents of hydrogen chloride and 3a in ether gave quantitatively (2-dimethylaminoethyl)diphenyltin chloride hydrochloride (7a). When further excess hydrogen chloride in ether was treated with 3a, (2-dimethylaminoethyl)phenyltin dichloride hydrochloride (8a) only was isolated quantitatively. These results suggest that the phenyl–tin bonds are cleaved stepwise by electrophilic attack of H^+ to give 7a from 3a-HCl, then 8a from 7a, but one phenyl–tin bond remains. These three amine hydrochlorides are stable and the nucleophilic attack of Cl^- at the tin atom is not observed. The same results were also obtained in the other (2-triphenylstannylethyl)amines: 3b, *N*-(2-triphenylstannylethyl)morpholine (3c) and 3f to give (2-diethylaminoethyl)phenyltin dichloride hydrochloride (8b), (2-morpholinoethyl)phenyltin dichloride hydrochloride (8c), and (2-anilinoethyl)phenyltin dichloride hydrochloride (8f) in a quantitative yield, respectively.

N-(2-Triphenylstannylethyl)acetanilide (3g) also reacted quantitatively with excess hydrogen chloride in ether to give the crystals, mp 149–150°, whose elemental analysis, molecular weight determination, and nmr spectrum showed reasonable agreement with (2-acetylphenylaminoethyl)phenyltin dichloride (10). The carbonyl absorption of 10 shifted extremely to low frequency, at 1565 and 1575 cm^{-1} in carbon tetrachloride. The carbonyl band of *N*-(2-dimethylphenylstannylethyl)acetanilide (11), derived by the reaction of 10 with 2 equiv of methylmagnesium iodide, was observed again at 1660 cm^{-1} in the same region as 3g. Therefore it seems reasonable to assume that the low-frequency shift of the carbonyl stretching vibration of

(5) C. Eaborn and R. W. Bott in A. G. MacDiarmid, Ed., "Organometallic Compounds of the Group IV Elements, Vol. 1: The Bond to Carbon," Part 1, Marcel Dekker, New York, N. Y., 1968, pp 378–391, and references cited therein.

(6) D. D. Davis and C. E. Gray, *J. Org. Chem.*, **35**, 1303 (1970).

SCHEME I



10 is due to the formation of an intramolecular six-membered ring by the coordination of the carbonyl oxygen to the tin atom, which acidity was enhanced by the two chlorine atoms. A similar intramolecular cyclization has been reported on [2,3-bis(ethoxycarbonyl)propyl]-*n*-butyltin dibromide by Matsuda and coworkers.[7]

Two organic groups in a tetraorganotin compound can be replaced stepwise by free halogen under appropriate condition to give diorganotin dihalides;[8] however, the cleavage of the tin–carbon bonds of alkyltriphenyltin derivatives by hydrogen halides has not been studied in detail. From the results mentioned above, it seems general that alkyltriphenyltin compounds will give the corresponding alkylphenyltin dichlorides by excess ethereal hydrogen chloride. The following experiments are performed on this point of view. When six alkyltriphenyltin compounds (**12a–f**) were treated with excess hydrogen chloride in ether at room temperature, the corresponding alkylphenyltin dichlorides (**13a–f**) were given quantitatively as shown in Table III. This procedure provides an excellent method to prepare alkylphenyltin dichlorides.

The reaction of either **3d** or **3e** with 3 mol of hydrogen chloride[9] in ether led to a mixture, whose nmr spectra showed the absence of N–CH_2CH_2Sn linkage. *Glc* analysis of each reaction mixture suggested the presence of phenyltin chlorides and secondary amine instead of (2-methylphenylaminoethyl)phenyltin dichloride hydrochloride (**8d**) or (2-diphenylaminoethyl)-phenyltin dichloride hydrochloride (**8e**), expected from the results described above. In order to obtain a more definite conclusion, each reaction mixture was methylated by an excess of methylmagnesium bromide. Separation of the products gave the following compounds: methyltriphenyltin (56%), dimethyldiphenyltin (31%), trimethylphenyltin (4%), and *N*-methylaniline (78%) from the reactant of **3d**; methyltriphenyltin (56%), dimethyldiphenyltin (34%), trimethylphenyltin (1%), and diphenylamine (85%) from the reactant of **3e**. The ratios of these tin compounds were apparently consistent with the original ratios of phenyltin chlorides.

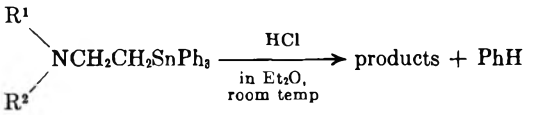
Each of the reactions probably takes place in the following stages. At first, nearly half of the **3d** hydrochloride (**3d**-HCl) or **3e** hydrochloride (**3e**-HCl) is cleaved to form triphenyltin chloride and secondary amine with the loss of ethylene by nucleophilic attack of Cl^- on the triphenyltin moiety (path a). (In fact, independent **3d**-HCl, prepared from **3d** and 1 equiv of hydrogen chloride, was unstable at room temperature decomposing readily to triphenyltin chloride and *N*-methylaniline.) On another half, electrophilic attack of H^+ on the phenyl group results in the formation of (2-methylphenylaminoethyl)diphenyltin chloride hydrochloride (**7d**) or (2-diphenylaminoethyl)diphenyltin chloride hydrochloride (**7e**). At the second stage, a part of **7d** or **7e** is cleaved to give diphenyltin dichloride, secondary amine and ethylene (path d). A few remaining parts lead to **8d** or **8e**. **8d** or **8e** cleavage then gives phenyltin trichloride, secondary

(7) I. Omae, S. Onishi, and S. Matsuda, *J. Organometal. Chem.*, **22**, 623 (1970).

(8) G. P. Van Der Kelen, E. V. Van Den Berghe, and L. Verdonck in A. K. Sawyer, Ed., "Organotin Compounds," Vol. 1, Marcel Dekker, New York, N. Y., 1971, pp 58–88.

(9) This amount is a theoretical mole for the preparation of **8d** or **8e**. When excess hydrogen chloride is employed, initially produced triphenyltin chloride is converted to diphenyltin dichloride.

TABLE II

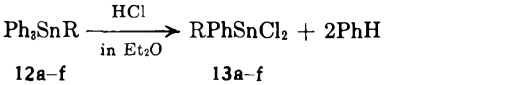


3a–g

3	Reaction conditions: HCl, mol	Time, hr	Products	Mp, °C	Yield, %	
a	1	4	$Me_2N^+HCH_2CH_2SnPh_3 \cdot Cl^-$	106–107.5	100	3a-HCl
a	2	4	$Me_2N^+HCH_2CH_2SnClPh_2 \cdot Cl^-$	156–157	100	7a
a	Excess	4	$Me_2N^+HCH_2CH_2SnCl_2Ph \cdot Cl^-$	177–180	100	8a
b	Excess	17	$Et_2N^+HCH_2CH_2SnCl_2Ph \cdot Cl^-$	177–178	100	8b
c	Excess	14	$OCH_2CH_2N^+HCH_2CH_2SnCl_2Ph \cdot Cl^-$ (–CH_2CH_2–)	201–203	100	8c
d	3	27	Ph_3SnCl		56[a]	
			Ph_2SnCl_2		31[a]	
			$PhSnCl_3$		4[a]	
			$PhMeN^+H_2 \cdot Cl^-$		78	
			$CH_2=CH_2$			
e	3	14	Ph_3SnCl		56[a]	
			Ph_2SnCl_2		34[a]	
			$PhSnCl_3$		1[a]	
			$Ph_2N^+H_2 \cdot Cl^-$		84	
			$CH_2=CH_2$			
f	Excess	20	$PhN^+H_2CH_2CH_2SnCl_2Ph \cdot Cl^-$	95–100 dec	100	8f
g	Excess	5	Ac, Ph, $NCH_2CH_2SnCl_2Ph$	149–150	100	10

[a] These compounds were isolated from the mixture as the corresponding methylphenyltin derivatives.

TABLE III



12a–f 13a–f

	R	Reaction conditions: Temp	Time, hr		Products (13a–f)[a]: Mp or bp, °C (mm)	Yield, %
a	Me	Room	5	$MePhSnCl_2$	41–43	100
b	Et	Room	4	$EtPhSnCl_2$	54.5–60	100
c	*n*-Pr	Room	4	*n*-$PrPhSnCl_2$	35–37	100
d	*i*-Pr	Room	2	*i*-$PrPhSnCl_2$	153–157 (10)	100
e	*n*-Bu	Room	3.5	*n*-$BuPhSnCl_2$	43.5–45	100
f	Bz	Room	2	$BzPhSnCl_2$	82–84	100

[a] Satisfactory analytical data (±0.4% for C, H) were reported for all new compounds listed in the table: Ed.

amine, and ethylene (path e). Thus the competition between the electrophilic aromatic substitution and the nucleophilic cleavage reaction occurs by *N*-(2-triphenylstannylethyl)arylamines. If redistribution reactions were slow enough among the phenyltin chlorides produced *via* paths a, d, and e, the contribution of these paths could be estimated as 56%, path a; 31–34%, d; and 1–4%, e.

Experimental Section

Nuclear magnetic resonance spectra were recorded using a JNM-MH-60 (JOEL) spectrometer employing tetramethylsilane as an internal standard. Infrared spectra were obtained using an IR-A-2 (JASCO) spectrophotometer. Gas–liquid chromatographic analyses were performed on JGC-750 and JGC-1100 (JOEL). All boiling points and melting points are uncorrected.

Diphenylaminoethyl Chloride (1e).—A solution of diphenylaminoethanol (21.3 g, 0.1 mol) and triphenylphosphine (26.2 g, 0.1 mol) in 110 ml of carbon tetrachloride was stirred at room temperature for 7 hr, then heated under reflux for 3 hr. After the removal of the solvent, the residue was extracted with petroleum ether (bp 30–60°). The extract was concentrated and distilled, giving 18.2 g (78%) of a pale yellow oil, bp 105–108° (0.05 mm).

Anal. Calcd for $C_{14}H_{14}ClN$: C, 72.13; H, 6.09; N, 6.05. Found: C, 72.39; H, 6.05; N, 6.40.

***N*-(2-Hydroxyethyl)acetanilide.**—Sodium borohydride (0.6 g, 0.014 mol) was added in small portions with stirring to a cold solution of *N*-(2-acetoxyethyl)acetanilide (5 g, 0.023 mol) in 45 ml of methanol. The mixture was stirred below 10° for 2.5 hr, and then at room temperature for 4 hr. After the addition of 30 ml of a saturated sodium chloride solution, the methanol was removed. The residue was extracted with benzene. The extract was dried and concentrated. Recrystallization of the residue from petroleum ether–carbon tetrachloride gave 3.2 g (78%) of *N*-(2-hydroxyethyl)acetanilide, mp 61–62° (lit.[10] mp 62–63°).

***N*-(2-Chloroethyl)acetanilide** (1g).—A solution of thionyl chloride (10.0 g, 0.084 mol) in 20 ml of dry toluene was added to an ice-cold solution of *N*-(2-hydroxyethyl)acetanilide (10.0 g, 0.056 mol) in 30 ml of dry toluene. After the addition, the mixture was stirred at room temperature for 18 hr and distilled, giving 9.0 g (81.8%) of 1g: bp 83–86° (0.07 mm); nmr ($CDCl_3$) δ 1.85 (s, 3, $NCOCH_3$), 3.70 (t, J = 6 Hz, 2, CH_2Cl), 4.10 (t, J = 6 Hz, 2, NCH_2).

Anal. Calcd for $C_{10}H_{12}ClNO$: C, 60.87; H, 6.13; N, 7.10. Found: C, 61.17; H, 6.32; N, 7.10.

***N*-(2-Triphenylstannylethyl)dimethylamine** (3a).—A solution of triphenyltinlithium (2, 0.03 mol) in THF[11] was added to an ice-cold solution of dimethylaminoethyl chloride (1a, 2.26 g, 0.021 mol) in 15 ml of THF. After the addition, the mixture was stirred at room temperature for 7 hr, and then it was hydrolyzed with a saturated ammonium chloride solution. The THF layer was separated and the aqueous layer was extracted with ether. The combined organic layer was dried and concentrated. Recrystallization of the residue from ethanol gave 7.75 g (85.3%) of 3a: mp 81–83°; nmr (CCl_4) δ 1.63 (t, J = 7 Hz, 2, $SnCH_2$), 2.06 (s, 6, NCH_3), 2.60 (t, J = 7 Hz, 2, NCH_2), 7.0–8.0 (m, 15 aromatic protons). The ethanol-insoluble solid was recrystallized from petroleum ether to give 0.53 g (5%) of hexaphenylditin (4). Nmr data are given in Table IV.

(10) A. B. Boese, Jr., U. S. Patent 2,355,141 (1944).

(11) C. Tamborski, F. E. Ford, and E. J. Soloski, *J. Org. Chem.*, **28**, 181 (1963).

Table IV

N-(2-Triphenylstannylethyl)amines (3)

3	R¹	R²	Formula[a]	Nmr, δ, —NCH₂CH₂Sn—	
a	CH_3	CH_3	$C_{22}H_{25}NSn$	2.60	1.63
b	C_2H_5	C_2H_5	$C_{24}H_{29}NSn$	2.79	1.73
c	$(-CH_2CH_2)_2O$		$C_{24}H_{27}NOSn$	2.70	1.75
d	CH_3	C_6H_5	$C_{27}H_{27}NSn$	3.68	1.72
e	C_6H_5	C_6H_5	$C_{32}H_{29}NSn$	4.20	1.93
f	H	C_6H_5	$C_{26}H_{25}NSn$	3.50	1.75
g	CH_3CO	C_6H_5	$C_{28}H_{27}NOSn$	4.10	1.6–2.2

[a] Satisfactory analytical data (±0.3% for C, H, N) and vapor-pressure molecular weight data were reported for all new compounds listed in the table: Ed.

N-(2-Triphenylstannylethyl)diethylamine (3b).—In a similar manner as described for 3a, the reaction of diethylaminoethyl chloride (1b, 4.418 g, 0.033 mol) with 2 (0.03 mol) gave 8.570 g (63.5%) of 3b [mp 48.5–49.5° (recrystallized from ethanol); nmr (CCl_4) δ 0.80 (t, 6, CH_3CH_2N), 1.73 (t, J = 7.5 Hz, 2, $SnCH_2$), 2.43 (q, 4, CH_3CH_2N), 2.79 (t, J = 7.5 Hz, 2, NCH_2CH_2Sn), 6.8–8.0 (m, 15 aromatic protons)] and 0.52 g (5%) of 4.

N-(2-Triphenylstannylethyl)morpholine (3c).—In a similar manner as described for 3a, the reaction of β-4-morpholinoethyl chloride (1c, 4.170 g, 0.027 mol) with 2 (0.03 mol) gave 7.031 g (56.1%) of 3c [mp 125–126° (recrystallized from ethanol); nmr ($CDCl_3$) δ 1.75 (t, J = 7.5 Hz, 2, $SnCH_2$), 2.2–2.6 (m, 4, CH_2NCH_2), 2.70 (t, J = 7.5 Hz, 2, $SnCH_2CH_2$), 7.0–8.0 (m, 15, aromatic protons)] and 0.74 g (7%) of 4.

N-(2-Triphenylstannylethyl)-*N*-methylaniline (3d).—In a similar manner as described for 3a, the reaction of *N*-(2-chloroethyl)-*N*-methylaniline (1d, 3.2 g, 0.019 mol) with 2 (0.023 mol) gave 5.92 g (62.0%) of 3d [mp 59.5–60° (recrystallized from ethanol); nmr ($CDCl_3$) δ 1.72 (t, J = 7.5 Hz, 2, $SnCH_2$), 2.80 (s, 3, NCH_3), 3.68 (t, J = 7.5 Hz, 2, NCH_2), 6.5–8.2 (m, 20, aromatic protons)] and 0.40 g (5%) of 4.

N-(2-Triphenylstannylethyl)diphenylamine (3e).—In a similar manner as described for 3a, the reaction of 1e (2.42 g, 0.01 mol) with 2 (0.015 mol) gave 4.50 g (78.5%) of 3e [mp 98–100° (recrystallized from ethanol); nmr (CCl_4) δ 1.93 (m, 2, $SnCH_2$), 4.20 (m, 2, NCH_2), 6.4–7.7 (m, 25, aromatic protons)] and 0.26 g (5%) of 4.

N-(2-Triphenylstannylethyl)acetanilide (3g) and *N*-(2-Triphenylstannylethyl)aniline (3f).—A solution of 2 (0.03 mol) was added to a cold solution of 1g (4.10 g, 0.021 mol) in 15 ml of THF. The mixture was stirred at room temperature for 18 hr and then refluxed for 2 hr. After the addition of a saturated ammonium chloride solution, the THF layer was separated and the aqueous layer was extracted with ether. The combined organic layer was dried. Removal of the solvent afforded a mixture which was separated on a silica gel column eluting with benzene. The first elution gave 0.411 g (4%) of 3f: mp 91–92.5° (recrystallized from ethanol); nmr ($CDCl_3$) δ 1.75 (t, J = 7.5 Hz, 2, $SnCH_2$), 3.34 (s, 1, NH), 3.50 (t, J = 7.5 Hz, 2, NCH_2), 6.3–8.2 (m, 20, aromatic protons); ir (CCl_4) 3500 cm^{-1} (NH). The second elution gave 6.811 g (65%) of 3g: mp 106–108° (recrystallized from ethanol); nmr (CCl_4) δ 1.76 (s, 3, $NCOCH_3$), 1.6–2.2 (m, 2, $SnCH_2$), 4.10 (m, 2, NCH_2), 6.9–8.2 (m, 20, aromatic protons); ir (CCl_4) 1660 cm^{-1} (C=O).

Hydrolysis of 3g.—A mixture of 3g (0.63 g) and 30% potassium hydroxide–ethanol (35 ml) was refluxed for 7.5 hr. After the addition of water, the ethanol was removed under reduced pressure. The residue was extracted with chloroform, washed with water, and dried. Removal of the solvent afforded 0.27 g (47%) of 3f.

Lithium Aluminum Hydride Reduction of 3g.—A solution of 3g (1.00 g, 1.95 mmol) and lithium aluminum hydride (77 mg, 2.03 mmol) in 70 ml of ether was heated under reflux for 7 hr and then hydrolyzed with a saturated ammonium chloride solution. The reaction mixture was extracted with ether. The extract was washed with water, dried, and then concentrated. Recrystallization of the residue from ethanol gave 0.75 g (81.5%) of 3f.

Acetylation of 3f with Acetic Anhydride.—A mixture of 3f (100 mg), acetic anhydride (2 ml), and glacial acetic acid (30 ml) was stirred at room temperature for 3 hr, and then made alkaline by adding of a saturated sodium carbonate solution. The reaction mixture was extracted with ether. The extract was washed with water, dried, and concentrated to give 90 mg (82%) of 3g.

Reaction of 3f with Methyl Halides. A.—A mixture of 3f (47 mg, 0.1 mmol), methyl bromide (9.5 mg, 0.1 mmol) in absolute ethanol (2 ml), and dry ether (1 ml) was heated in a sealed tube at 40–50° for 2 hr, and then at 70–80° for 2 hr. After the addition of 20 ml of water, the organic solvent was removed under reduced pressure. The aqueous layer was made slightly alkaline (pH 8) by adding of a sodium bicarbonate solution and it was extracted with ether. The extract was dried and concentrated. Glc analysis of the residue on Lubrol-MO column and silicon SE-30 column showed the presence of *N*-methylaniline (18%), *N*,*N*-dimethylaniline (2%), aniline (3%), triphenyltin bromide (20%), and unreacted 3f (60%).

B.—A mixture of 3f (94 mg, 0.2 mmol), methyl iodide (30 mg, 0.2 mmol) in absolute ethanol (4 ml), and dry ether (2 ml) was heated in a sealed tube at 40–50° for 5 hr. The treatment of the products in the same manner as described above showed the presence of *N*-methylaniline (36%), *N*,*N*-dimethylaniline (6%), aniline (6%), triphenyltin iodide (43%), and unreacted 3f (40%).

Reaction of 3d with Hydrogen Bromide.—A mixture of hydrogen bromide (0.5 mmol) in dry ether (2 ml) and 3d (0.242 g, 0.5 mmol) in dry ether (15 ml) was allowed to stand at room temperature for 1.5 hr. The precipitated white crystals were filtered to give 35 mg (12%) of 3d hydrobromide (3d-HBr), mp 78–80° dec. Glc analysis of the filtrate on Lubrol-MO and silicone SE-30 showed the presence of *N*-methylaniline (75%) and triphenyltin bromide (84%).

N-(2-Triphenylstannylethyl)aniline Hydrobromide (3f-HBr).—A mixture of hydrogen bromide (1.0 mmol) in dry ether (14 ml) and 3f (0.470 g, 1.0 mmol) in dry ether (20 ml) was allowed to stand for 1.5 hr to give 0.550 g (100%) of 3f-HBr, mp 124–125°.

Anal. Calcd for $C_{26}H_{25}BrNSn$: C, 56.67; H, 4.76; N, 2.54. Found: C, 56.39; H, 4.81; N, 2.62.

A solution of 3f-HBr (55 mg, 0.1 mmol) in 10 ml of ethanol was refluxed for 2 hr. The ethanol was removed and the residue was extracted with ether. The ethereal extract was dried and concentrated. Column chromatography of the residue on silica gel gave aniline (7 mg, 75%) and triphenyltin bromide (36 mg, 83%).

Reaction of 3d with Methyl Iodide.—A solution of 3d (0.315 g, 0.65 mmol) and methyl iodide (93 mg, 0.65 mmol) in 10 ml of absolute ethanol was heated in a sealed tube at 70–80° for 4 hr. After the removal of the ethanol, column chromatography of the residue on silica gel gave *N*,*N*-dimethylaniline (53 mg, 67%), triphenyltin bromide (198 mg, 71%), and unreacted 3d (47 mg, 15%).

Reaction of 3a or 3b with Methyl Bromide.—Methyl bromide gas was conducted into a solution of 3a or 3b (1 mmol) in 30 ml of dry ether for 7 hr, and then the mixture was allowed to stand overnight. The precipitate was filtered and it was identified with an authentic sample of tetramethylammonium bromide (6a) or dimethyldiethylammonium bromide (6b), respectively, yield 90–100%. Each filtrate was concentrated to give triphenyltin bromide in 90–100% yield.

N-(2-Triphenylstannylethyl)dimethylamine Hydrobromide (3a-HBr).—The addition of hydrogen bromide (1 mmol) in 11 ml of dry ether to 3a (0.422 g, 1 mmol) in 25 ml of dry ether gave 0.352 g (70%) of 3a-HBr, mp 138–141°.

Anal. Calcd for $C_{22}H_{26}BrNSn$: C, 52.53; H, 5.21; N, 2.68. Found: C, 52.08; H, 4.92; N, 2.77.

The filtrate was concentrated to give 0.122 g (28.4%) of triphenyltin bromide.

N-(2-Triphenylstannylethyl)dimethylamine Hydrochloride (3a-HCl).—The addition of hydrogen chloride (1.05 mmol) in 2 ml of dry ether to 3a (0.444 g, 1.05 mmol) in 30 ml of dry ether gave 0.572 g (100%) of 3a-HCl, mp 106–107.5°.

Anal. Calcd for $C_{22}H_{26}ClNSn$: C, 57.61; H, 5.51; N, 3.05. Found: C, 57.35; H, 5.47; N, 3.07.

(2-Dimethylaminoethyl)diphenyltin Chloride Hydrochloride (7a).—A mixture of hydrogen chloride (2.04 mmol) in 8.7 ml of dry ether and 3a (0.430 g, 1.02 mmol) in 30 ml of dry ether was allowed to stand at room temperature for 4 hr. The precipitate was separated by filtration, giving 0.430 g (100%) of 7a: mp 156–157° (recrystallized from methanol); nmr (DMSO-d_6–$CDCl_3$) δ 1.8–2.1 (m, 2, $SnCH_2$), 2.60 (s, 6, NCH_3), 7.2–8.2 (m, 10, aromatic protons).

Anal. Calcd for $C_{16}H_{21}Cl_2NSn$: C, 46.10; H, 5.08; N, 3.36. Found: C, 46.04; H, 5.19; N, 3.33.

(2-Substituted aminoethyl)phenyltin Dichloride Hydrochloride (8a–c,f) and (2-Acetylphenylaminoethyl)phenyltin Dichloride (10).—A mixture of a solution of 3a–c,f or 3g in dry ether and a saturated solution of hydrogen chloride (excess) in dry ether was allowed to stand at room temperature for 4–20 hr. Removal of the solvent and the excess hydrogen chloride under reduced pressure afforded 8a–c,f or 10 in quantitative yield, respectively. Their data are shown in Tables II and V.

TABLE V

(2-SUBSTITUTED AMINOETHYL)PHENYLTIN DICHLORIDE HYDROCHLORIDE (8a–c–f) AND (2-ACETYLPHENYLAMINOETHYL)PHENYLTIN DICHLORIDE (10)

Compd	R^1	R^2	Formula[a]	Nmr, δ
				DMSO-d_6–$CDCl_3$
8a	CH_3	CH_3	$C_{10}H_{16}Cl_3NSn$	1.5–2.0 (2, $SnCH_2$) 3.1–3.6 (2, NCH_2) 6.8–7.8 (5, aromatic H)
				DMSO-d_3
8b	C_2H_5	C_2H_5	$C_{12}H_{20}Cl_3NSn$	1.6–2.2 (2, $SnCH_2$) 7.0–8.0 (5, aromatic H)
				DMSO-d_3
8c	$(-CH_2CH_2)_2O$		$C_{12}H_{18}Cl_3NOSn$	1.7–2.2 (2, $SnCH_2$) 6.7–7.8 (5, aromatic H)
8f	H	C_6H_5	$C_{14}H_{16}Cl_3NSn$	
				$CDCl_3$
10	CH_3CO	C_6H_5	$C_{16}H_{17}Cl_2NOSn$	1.9–2.3 (2, $SnCH_2$) 4.0–4.4 (2, NCH_2) 7.0–8.3 (10, aromatic H)

[a] Satisfactory analytical data (±0.4% for C, H, N) were reported for all new compounds listed in the table, except for compound 8f, which was too hygroscopic: Ed.

N-(2-Dimethylphenylstannylethyl)aniline (9). A.—A solution of methylmagnesium iodide (25 mmol) in dry ether was added to a stirred suspension of 8f (0.450 g, 1.60 mmol) in dry ether (15 ml). The mixture was stirred at room temperature for 2.5 hr and then heated under reflux for 2 hr. The reaction mixture was hydrolyzed with a saturated ammonium chloride solution and extracted with ether. The extract was dried and concentrated and the residue was then purified by column chromatography on silica gel to give 0.323 g (87.8%) of a pale yellow oil (9): nmr (CCl_4) δ 0.30 (s, 6, $SnCH_3$), 1.30 (t, J = 9 Hz, 2, $SnCH_2$), 3.32 (t, J = 9 Hz, 2, NCH_2), 3.20 (s, 1, NH), 6.2–7.5 (m, 10, aromatic protons); ir (CCl_4) 3400 cm^{-1} (NH).

Anal. Calcd for $C_{16}H_{21}NSn$: C, 55.54; H, 6.12; N, 4.05. Found: C, 55.46; H, 5.92; N, 3.86.

B.—A solution of 10 (800 mg, 1.86 mmol) in dry ether was added to a solution of methylmagnesium iodide (10.7 mmol) in ether. After the mixture was heated under reflux for 3 hr, the reaction temperature was raised to 80° by addition of dry benzene and evaporation of the ether. The reaction mixture was hydrolyzed with a saturated ammonium chloride solution and extracted with ether. The ethereal extract was dried and concentrated, and the residue was purified by preparative thin layer chromatography on silica gel to give 0.240 g (37.2%) of 9.

N-(2-Dimethylphenylstannylethyl)acetanilide (11).—A solution of 10 (1.340 g, 3.12 mmol) and methyl iodide (5 ml) in THF (30 ml) was added slowly to magnesium turnings (157 mg, 6.46 mg-atoms). After the addition, the mixture was stirred at room temperature for 5 hr and then heated under reflux for 3 hr. The reaction mixture was hydrolyzed with a saturated ammonium chloride solution. The THF layer was separated and the aqueous layer was extracted with ether. The combined organic layer was dried and concentrated, and the residue was purified by column chromatography on silica gel to give 0.848 g (70%) of a pale yellow oil (11): nmr (CCl_4) δ 1.22 (t, J = 8 Hz, 2, $SnCH_2$), 1.71 (s, 3, $NCOCH_3$), 0.32 (s, 6, $SnCH_3$), 3.92 (t, J = 8 Hz, 2, NCH_2), 6.9–7.6 (aromatic protons); ir (CCl_4) 1660 cm^{-1} (C=O).

Anal. Calcd for $C_{18}H_{23}NOSn$: C, 55.71; H, 5.97; N, 3.61. Found: C, 55.51; H, 5.90; N, 3.58.

Reaction of 3d with Hydrogen Chloride. A.—A mixture of a solution of 3d (0.534 g, 1.1 mmol) in dry ether (30 ml) and a solution of hydrogen chloride (1.1 mmol) in dry ether (2.7 ml) was stirred at room temperature for 1.5 hr. After removal of the ether, the residue was neutralized with a sodium bicarbonate solution and extracted with benzene. The benzene extract was dried and concentrated. Preparative thin layer chromatography of the residue on silica gel gave 49.9 mg (46.2%) of *N*-methylaniline, 0.229 g (53.8%) of triphenyltin chloride, and 0.109 g (20.4%) of 3d.

B.—A mixture of a solution of 3d (1.010 g, 2.09 mmol) in dry ether (30 ml) and a solution of hydrogen chloride (6.27 mmol) in dry ether (30 ml) was stirred at room temperature for 27 hr. After removal of the ether, the residue which was dissolved in 15 ml of THF was added to a solution of methylmagnesium bromide (25 mmol) in THF (20 ml). The mixture was heated under reflux for 5 hr, hydrolyzed with a saturated ammonium chloride solution, and extracted with ether. The ethereal extract was dried and concentrated. Glc analysis (silicone SE-30) of the residue showed the presence of *N*-methylaniline (78%), methyltriphenyltin (56%), dimethyldiphenyltin (31%), and trimethylphenyltin (4%).

Reaction of 3e with Hydrogen Chloride.—A mixture of a solution of 3e (0.982 g, 1.79 mmol) in dry ether (25 ml) and a solution of hydrogen chloride (5.37 mmol) in dry ether (27 ml) was stirred at room temperature for 14 hr. Treatment of the reaction mixture in a similar manner as described above showed the presence of diphenylamine (84%), methyltriphenyltin (56%), dimethyldiphenyltin (34%), and trimethylphenyltin (1%).

Alkylphenyltin Dichlorides (13a–f).—A mixture of a solution of alkyltriphenyltin compounds (12a–f) (3 mmol) in dry ether (60 ml) and a saturated solution of hydrogen chloride in dry ether (12 ml) was allowed to stand at room temperature for 2–5 hr. The ether and the excess hydrogen chloride were removed under reduced pressure to yield alkylphenyltin dichlorides (13a–f) in quantitative yield, respectively. Their data are shown in Table III.

Acknowledgment.—We are grateful to Professor Y. Ishii and Dr. K. Ito (Nagoya University) for valuable suggestions.

Registry No.—1a, 107-99-3; 1b, 100-35-6; 1c, 3240-94-6; 1d, 1669-85-8; 1e, 42393-65-7; 1g, 36842-84-9; 2, 4167-90-2; 3a, 42393-67-9; 3a-HBr, 42393-68-0; 3a-HCl, 42393-69-1; 3b, 42393-70-4; 3c, 42393-71-5; 3d, 42393-72-6; 3d-HBr, 42393-73-7; 3e, 42393-74-8; 3f, 42428-60-4; 3f-HBr, 42393-75-9; 3g, 42428-61-5; 7a, 42393-76-0; 8a, 42428-62-6; 8b, 42393-77-1; 8c, 42393-78-2; 8f, 42393-79-3; 9, 42393-80-6; 10, 42428-63-7; 11, 42393-81-7; 12a, 1089-59-4; 12b, 5424-25-9; 12c, 42428-64-8; 12d, 1446-45-3; 12e, 2847-57-6; 12f, 20451-88-1; 13a, 15649-26-0; 13b, 15649-27-1; 13c, 15649-28-2; 13d, 42393-84-0; 13e, 26340-42-1; 13f, 42393-85-1; diphenylaminoethanol, 6315-51-1; *N*-(2-hydroxyethyl)acetamilide, 28358-86-3.

Dimetalated Heterocycles as Synthetic Intermediates. IV. Dilithio Derivatives of 2-Methylbenzimidazole, 2-Benzylbenzimidazole, and Related Compounds[1]

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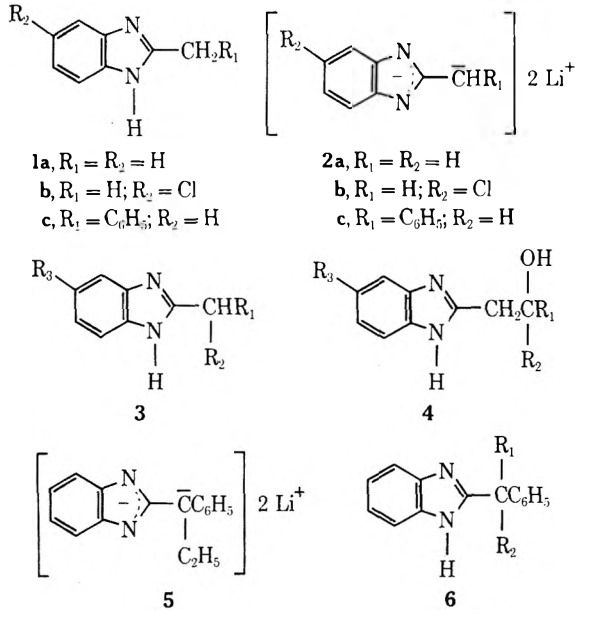
Treatment of 2-methylbenzimidazole (**1a**), 2-methyl-5-chlorobenzimidazole (**1b**), 2-benzylbenzimidazole (**1c**), and 1-(2-benzimidazolyl)-1-phenylpropane (**3g**) with 2 mol equiv of *n*-butyllithium in THF–hexane at 0° resulted in abstraction of the heterocyclic NH proton as well as an α hydrogen of the 2-alkyl substituent. Reactions of the resulting dilithio derivatives with alkyl halides, aldehydes, and ketones took place selectively at the side-chain carbanion center to produce 2-alkylbenzimidazoles and 2-(2-hydroxylalkyl)benzimidazoles, respectively. Attempted twofold deprotonation of 2-propylbenzimidazole (**3a**) with *n*-butyllithium afforded only the monolithio salt (**7**) even in the presence of TMEDA or HMPA.

The weakly acidic character of the methyl protons of 2-methylbenzimidazole (**1a**) has been demonstrated on a number of occasions.[2] For example, **1a** reacts with aromatic aldehydes in the presence of both acidic and basic catalysts to form 2-styrylbenzimidazoles.[2c] Although the base-catalyzed reactions presumably involve an intermediate possessing carbanion character at the 2-methyl position,[2a] active hydrogen condensations at this site have previously been limited to those in which unfavorable ionization of a side-chain proton is compensated for by a later, irreversible step such as dehydration of an intermediate aldol product. It occurred to us that treatment of **1a** with a suitable strong base should effect rapid ionization of the NH proton and that the benzimidazole nucleus might provide sufficient delocalization of negative charge to then allow secondary ionization of a methyl hydrogen to form dianion **2a**. If such a dual ionization process could be driven to completion by utilizing an essentially irreversible acid–base reaction, and if dianion **2a** were to possess reasonable stability in aprotic solvents, it seemed possible that this and similar intermediates might be useful for the synthesis of a variety of 2-substituted benzimidazole derivatives *via* simple carbanion condensations.



1a, $R_1 = R_2 = H$
b, $R_1 = H$; $R_2 = Cl$
c, $R_1 = C_6H_5$; $R_2 = H$

2a, $R_1 = R_2 = H$
b, $R_1 = H$; $R_2 = Cl$
c, $R_1 = C_6H_5$; $R_2 = H$

3

4

5

6

We now wish to report that **1a** can be readily converted into dianion **2a** by means of 2 mol equiv of *n*-butyllithium in THF–hexane at 0°, as shown by deuteration and selective condensations with various electrophiles at the exocyclic carbanion site. These results represent the first example of simultaneous ring and side-chain metalation of a 2-alkylbenzimidazole.[3]

Alkylation of **2a** with a series of primary halides as well as isopropyl bromide afforded *C*-alkyl derivatives **3a–e** (Table I). These results are in contrast to alkylations of 2-alkylbenzimidazoles in the presence of weaker bases, which afford N-substituted derivatives.[4] Reactions of **2a** with a representative series of aromatic, aliphatic, and α,β-unsaturated aldehydes produced carbinols **4a–d**, rather than the styryl derivatives obtained under more vigorous conditions.[2c] Similarly, benzophenone, cyclohexanone, and acetophenone afforded tertiary alcohols **4e–f** and **4h**, while benzalacetophenone gave a mixture of 1,2 and 1,4 adducts **4g** and **3f**, respectively. Twofold lithiation of 5-chloro-2-methylbenzimidazole (**1b**) to form dianion **2b** also took place smoothly, as demonstrated by condensations with anisaldehyde and benzophenone to form **4i** and **4j**, respectively.

Exposure of 2-propylbenzimidazole (**3a**) to 2 mol equiv of *n*-butyllithium in THF–hexane at 0° afforded a light yellow slurry. Treatment of such reaction mixtures with benzyl chloride or benzophenone failed to yield the expected side-chain condensation products, and **3a** was recovered unchanged. The absence of detectable quantities of addition and/or reduction[5] products resulting from reaction of residual *n*-butyl-

(1) (a) The following papers constitute parts I–III of this series: J. F. Wolfe, G. B. Trimitsis, and D. R. Morris, *J. Org. Chem.*, **34**, 3263 (1969); J. F. Wolfe and T. G. Rogers, *ibid.*, **35**, 3600 (1970); J. D. Taylor and J. F. Wolfe, *Synthesis*, 310 (1971). (b) Abstracted in part from the Ph.D. dissertation of D. E. Portlock, Virginia Polytechnic Institute and State University, April 1972. (c) Supported by Grant No. NS-10197 from the National Institute of Neurological Diseases and Stroke. (d) Presented at the 166th National Meeting of the American Chemical Society, Chicago, Ill., Aug 30, 1973.

(2) (a) For reviews see K. Hofmann in "The Chemistry of Heterocyclic Compounds," Part I, A. Weissberger, Ed., Interscience, New York, N. Y., 1953; A. F. Pozharskii, A. D. Garnovskii, and A. M. Simonov, *Russ. Chem. Rev.*, **35**, 122 (1966). (b) For a report of H–D exchange at the methyl group of **1a** see N. N. Zatsepina, Y. L. Kaminskii, and I. F. Tupitsyr, *Reakts. Sposobnost Org. Soedin.*, 433 (1967); *Chem. Abstr.*, **69**, 85848e (1968). (c) For examples of aldol condensations involving **1a** see W. R. Sullivan, *J. Med. Chem.*, **13**, 784 (1970), and references cited therein.

(3) Several investigators have found previously that 1-alkyl- or 1-arylbenzimidazoles undergo metalation of the heterocyclic ring and/or addition to the azomethine linkage on treatment with organolithium reagents. See (a) R. C. Elderfield and V. B. Meyer, *J. Amer. Chem. Soc.*, **76**, 1891 (1954); (b) P. W. Alley and D. A. Shirley, *J. Org. Chem.*, **23**, 1791 (1958); (c) B. A. Tertov, N. A. Ivankova, and A. M. Simonov, *Zh. Obshch. Khim.*, **32**, 2989 (1962); (d) B. A. Tertov and S. E. Panchenko, *ibid.*, **33**, 3671 (1963); (e) A. V. Koblik, *Mater. Nauch. Konf. Aspir., Rostov-na-Donu Gos. Univ.*, 7th, 8th, 235 (1967) [*Chem. Abstr.*, **71**, 13061m (1969)].

(4) For example see M. Mousseron, J. M. Kamenka, and A. Stenger, *J. Med. Chem.*, **11**, 889 (1968).

(5) J. D. Buhler, *J. Org. Chem.*, **38**, 904 (1973).

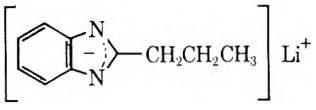
TABLE I

CONDENSATIONS OF DIANIONS 2a–e AND 5 WITH ALKYL HALIDES AND CARBONYL COMPOUNDS

Di-anion	Halide or carbonyl Registry no.	Halide or carbonyl Compd	No.	R_1	R_2	R_3	Yield, %[a]	Recrystn solvent
2a	74-96-4	CH_3CH_2Br	3a	CH_3CH_2	H	H	78	EtOH–H_2O
2a	100-44-7	$C_6H_5CH_2Cl$	3b	$C_6H_5CH_2$	H	H	44	EtOH–H_2O
2a	926-57-8	$ClCH_2CH{=}C(Cl)CH_3$	3c	$CH_3C(Cl){=}CHCH_2$	H	H	40	EtOH–H_2O
2a	106-95-6	$CH_2{=}CHCH_2Br$	3d	$CH_2{=}CHCH_2$	H	H	33	Me_2CO–hexane
2a	75-26-3	$(CH_3)_2CHBr$	3e	$(CH_3)_2CH$	H	H	43	EtOH–H_2O
2a	111-71-7	$CH_3(CH_2)_6CHO$	4a	$CH_3(CH_2)_4CH_2$	H	H	61	EtOH
2a	100-52-7	C_6H_5CHO	4b	C_6H_5	H	H	65	EtOH
2a	123-11-5	p-$CH_3OC_6H_4CHO$	4c	p-$CH_3OC_6H_4$	H	H	48	EtOH
2a	107-02-8	$C_6H_5CH{=}CHCHO$	4d	$C_6H_5CH{=}CH$	H	H	68	EtOH
2a	119-61-9	$(C_6H_5)_2C{=}O$	4e	C_6H_5	C_6H_5	H	70	EtOH
2a	108-94-1	c-$C_6H_{11}O$	4f	$-CH_2CH_2CH_2CH_2CH_2-$		H	49	EtOAc
2a	94-41-7	$C_6H_5CH{=}CHCOC_6H_5$	4g	C_6H_5	$C_6H_5CH{=}CH$	H	59	Me_2CO–hexane
	779-51-1	Benzalacetophenone	3f	$C_6H_5COCH_2CH(C_6H_5)$	H	H	32	Me_2CO–hexane
2a	98-86-2	$C_6H_5COCH_3$	4h	C_6H_5	CH_3	H	65	EtOAc–hexane
2b		p-$CH_3OC_6H_4CHO$	4i	p-$CH_3OC_6H_4$	H	Cl	46	EtOH
2b		$(C_6H_5)_2C{=}O$	4j	C_6H_5	C_6H_5	Cl	62	EtOH
2c		CH_3CH_2Br	3g	CH_3CH_2	C_6H_5	H	69	EtOH–H_2O
2c		$C_6H_5CH_2Cl$	3h	$C_6H_5CH_2$	C_6H_5	H	70	EtOH–H_2O
5	105-65-9	$CH_3(CH_2)_2CH_2Br$	6	$CH_3(CH_2)_2CH_2$	CH_3CH_2		88	EtOAc–hexane

[a] Yields are based on isolated, constant-melting material and have not been subjected to optimization.

lithium with benzophenone raised the question as to whether the precipitate was the desired dianion or perhaps an insoluble complex consisting of monoanion **7**



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and 1 equiv of lithium reagent.[6] The first of these possibilities was eliminated by deuterium oxide quenching, which returned **3a** containing no side-chain deuterium. The second premise was shown to be suspect by isolation of valeric acid (17%) upon treatment of the inhomogeneous reaction mixture with excess, gaseous carbon dioxide. However, this experiment was complicated by rapid dissolution of the precipitate as carbon dioxide was added. The identity of the precipitate was established as uncomplexed monoanion **7** by separating it from the reaction mixture, followed by hydrolysis and titration of the resulting aqueous solution against standard hydrochloric acid.

Several subsequent attempts were made to effect side-chain metalation of **3a** utilizing *n*-butyllithium complexed with *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA)[7] and by solubilizing monoanion **7** with hexamethylphosphoric triamide (HMPA). The first of these approaches again gave only the insoluble monoanion as shown by deuterium oxide quenches. Use of HMPA resulted in the production of a homogeneous solution, but addition of benzyl chloride to the reaction mixture afforded a nearly quantitative recovery of **3a** and a 64% yield of stilbene. Excess *n*-butyllithium (3 mol equiv/mol equiv of **3a**) effected a small amount of metalation at the α-methylene position of **3a** as evidenced by incorporation of 0.29 D per α-methylene group of **3a**. However, these experimental conditions appear to offer limited possibilities for the synthesis of benzimidazoles bearing α-alkyl substituents in the 2 position.

Although substitution of alkyl groups larger than methyl at the 2 position of the benzimidazole nucleus appears to surpress, almost completely, side-chain metalation, the α-phenyl substituent of 2-benzylbenzimidazole (**1c**) is compatible with formation of dianion **2c** as shown by alkylations with ethyl bromide and benzyl chloride to afford **3g** and **3h** in yields of 69 and 70%, respectively. The α-phenyl substituent of **3g** provides sufficient activation to allow abstraction of the methinyl hydrogen to form tertiary dianion **5**, which underwent alkylation with butyl bromide to form **6** in 88% yield.

In conclusion, it should be pointed out that the present reactions involving dianions **2a–c** and **5** represent a mild and seemingly versatile alternative to more classical methods[8] for the synthesis of 2-substituted benzimidazoles. Moreover, such dianions should prove to be useful intermediates for introduction of the biologically interesting[2,4] 2-benzimidazolemethyl and related moieties into various molecules containing appropriate electrophilic centers.

Experimental Section

General.—Melting points were obtained on a Thomas-Hoover apparatus in open capillaries and are uncorrected. All evaporations were carried out *in vacuo*.

Materials.—Tetrahydrofuran (THF) was distilled from lithium aluminum hydride immediately before use. *N*,*N*,*N*′,*N*′-Tetramethylethylenediamine (TMEDA) and hexamethylphosphoric triamide (HMPA) were distilled from calcium hydride and stored over Linde type 3A molecular sieves. *n*-Butyllithium (as a solution in hexane) was obtained from Ventron Corp., Beverly, Mass. 5-Chloro-2-methylbenzimidazole (**1b**) was obtained from Aldrich Chemical Co., Inc., Milwaukee, Wis., and was recrystallized from water. All other commercial reagents were used without further purification.

(6) R. G. Harvey and L. N. H. Cho, *J. Amer. Chem. Soc.*, **95**, 2376 (1973), have recently proposed such a 1:1 complex between the monolithio salt of 9,10-dihydrophenanthrene and *n*-butyllithium.

(7) A. W. Langer, Jr., *Trans. N. Y. Acad. Sci.*, **27**, 741 (1965).

(8) For examples of such methods, which normally involve condensations of *o*-phenylenediamines with acids, aldehydes, and imino ethers, respectively, see (a) M. A. Phillips, *J. Chem. Soc.*, 2393 (1928); (b) D. Jerchez, H. Fischer, and M. Kracht, *Justus Liebigs Ann. Chem.*, **575**, 162 (1952); (c) F. E. King and R. M. Acheson, *J. Chem. Soc.*, 1396 (1949).

2-Methylbenzimidazole (**1a**) was prepared in 43% yield by condensation of acetic acid with *o*-phenylenediamine according to the procedure of Phillips,[8a] and had mp 178–179° (lit.[8a] mp 176°); pmr (DMSO-d_6) δ 2.63 (s, 3, CH_3), 7.02 (m, 2, aromatic), and 7.32 ppm (m, 2, aromatic).

2-Benzylbenzimidazole (**1c**) was prepared by the method of King and Acheson[8c] from o-phenylenediamine and the hydrochloride salt of methyl iminophenylacetate in 55% yield: mp 190–191° (lit.[8c] mp 191°); pmr (DMSO-d_6) δ 4.16 (s, 2, CH_2), 7.04 (m, 2, aromatic), and 7.30 ppm (m, 8, aromatic and NH).

General Procedure for Preparation of Dianions 2a–c and 5.—The 2-alkylbenzimidazole **1a–c** and **3g** (1–15 mmol) was dissolved in 50–75 ml of THF under nitrogen. The magnetically stirred solution was cooled to 0° in an ice bath, and *n*-butyllithium (2.1–32.0 mmol) was added *via* syringe. The resulting reaction mixture was stirred for 1 hr at 0° to ensure complete formation of the respective dianion. Dianion **2a** appeared as a tan slurry; dianions **2b** and **2c** formed red-brown solutions, while dianion **5** formed a blood-red solution.

Deuteration of Dianion 2a.—A slurry of **2a** in THF was quenched with 0.5 ml of D_2O. The precipitated lithium deuterioxide was removed by filtration, the filtrate was diluted with ether and dried over $MgSO_4$ and the solvent was evaporated, giving deuterated **1a**. Analysis of the pmr spectrum of this material ($CDCl_3$) indicated incorporation of 0.84 D per methyl group of **1a**.

Alkylations of Dianions 2a–c and 5.—A solution of the appropriate alkyl halide (5–15 mmol) in 10–15 ml of THF was added to the respective dianion. The reaction mixture was stirred for 2 hr while warming to room temperature. The reaction was processed by quenching with 50 ml of water, neutralization with concentrated HCl, and extraction with ether. The crude isolated products were recrystallized from the appropriate solvent (Table I). The following 2-alkyl benzimidazoles were prepared by this method.

2-Propylbenzimidazole (3a) had mp 156–157.5° (lit.[9] mp 152–153°); pmr (DMSO-d_6) δ 0.96 (s, 3, CH_3), 1.81 (m, 2, CH_2), 2.80 (t, 2, CH_2), 7.01 (m, 2, aromatic), and 7.36 ppm (m, 2, aromatic).

2-Phenethylbenzimidazole (3b) had mp 190–191° (lit.[10] mp 189–190°); pmr (DMSO-d_6) δ 3.16 (m, 4, CH_2) and 7.25 ppm (m, 9, aromatic).

5-(2-Benzimidazolyl)-2-chloro-2-pentene (3c) had mp 143–144°; pmr (DMSO-d_6) δ 2.05 (s, 3, CH_3), 2.63 (t, 2, CH_2), 2.82 (m, 2, CH_2), 5.61 (t, 1, =CH), 7.04 (m, 2, aromatic), and 7.41 ppm (m, 2, aromatic).

Anal. Calcd for $C_{12}H_{13}N_2Cl$: C, 65.30; H, 5.93; N, 12.70. Found: C, 65.38; H, 5.80; N, 12.62.

4-(2-Benzimidazolyl)-1-butene (3d) had mp 165–166°; pmr (DMSO-d_6) δ 2.51 (t, 2, CH_2), 2.86 (m, 2, CH_2), 4.94 (m, 2, $=CH_2$), 5.78 (m, 1, =CH), 7.01 (m, 2, aromatic), and 7.37 ppm (m, 2, aromatic).

Anal. Calcd for $C_{11}H_{12}N_2$: C, 76.71; H, 7.03; N, 16.27. Found: C, 76.89; H, 6.77; N, 16.35.

2-Isobutylbenzimidazole (3e) had mp 185.5–187° (lit.[11] mp 186–187°); pmr (DMSO-d_6) δ 0.97 (d, 6, CH_3), 2.21 (m, 1, CH), 2.72 (d, 2, CH_2), 7.13 (m, 2, aromatic), and 7.52 ppm (m, 2, aromatic).

4-(2-Benzimidazolyl)-1,3-diphenyl-1-butanone (3f)[12] had mp 194–195.5°; pmr (DMSO-d_6) δ 3.19 (m, 2, CH_2), 3.48 (m, 2, CH_2), 3.92 (m, 1, CH), 7.21 (m, 12, aromatic), and 7.81 ppm (d, 2, aromatic).

Anal. Calcd for $C_{23}H_{20}N_2O$: C, 81.15; H, 5.92; N, 8.23. Found: C, 80.85; H, 5.96; N, 8.27.

1-(2-Benzimidazolyl)-1-phenylpropane (3g) had mp 189–191° (lit.[13] mp 189–190°); pmr (DMSO-d_6) δ 0.87 (t, 3, CH_3), 2.14 (m, 2, CH_2), 4.07 (t, 1, CH), and 7.29 ppm (m, 10, aromatic and NH).

1-(2-Benzimidazolyl)-1,2-diphenylethane (3h) had mp 244–245°; pmr (DMSO-d_6) δ 3.31 and 3.62 (2 AB, 2, CH_2), 4.52 (t, 1, CH), and 7.29 ppm (m, 15, aromatic and NH).

Anal. Calcd for $C_{21}H_{18}N_2$: C, 84.53; H, 6.05; N, 9.39. Found: C, 84.25; H, 6.19; N, 9.44.

3-(2-Benzimidazolyl)-3-phenylheptane (6) had mp 211–213°; pmr (DMSO-d_6) δ 0.96 (m, 10, CH_2 and CH_3), 2.30 (m, 4, CH_2), 7.23 (m, 8, aromatic), and 7.62 ppm (m, 1, aromatic).

Anal. Calcd for $C_{20}H_{24}N_2$: C, 82.14; H, 8.27; N, 9.58. Found: C, 82.43; H, 8.56; N, 9.27.

Carbonyl Condensations of Dianions 2a–b.—A solution of the aldehyde or ketone (5–15 mmol) in 10–15 ml of THF was added to the respective dianion. After 2 hr the reaction mixture was poured into 100 ml of iced water, and the crude product was isolated by ether extraction, or, in cases where a precipitate formed, filtration. The crude product was purified by recrystallization from the appropriate solvent (Table I). The following carbinols were prepared in this manner.

1-(2-Benzimidazolyl)-2-octanol (4a) had mp 192–193°; pmr (DMSO-d_6) δ 0.85 (t, 3, CH_3), 1.30 (m, 10, CH_2), 2.50 (s, 1, OH), 2.90 (d, 2, CH_2), 4.03 (t, 1, CH), 7.03 (m, 2, aromatic), and 7.38 ppm (m, 2, aromatic).

Anal. Calcd for $C_{15}H_{22}N_2O$: C, 73.12; H, 9.02; N, 11.37. Found: C, 73.26; H, 8.86; N, 11.24.

1-Phenyl-2-(2-benzimidazolyl)ethanol (4b) had mp 213.5°; pmr (DMSO-d_6) δ 3.18 (d, 2, CH_2), 5.18 (t, 1, CH), 5.72 (s, 1, OH), and 7.36 ppm (m, 9, aromatic).

Anal. Calcd for $C_{15}H_{14}N_2O$: C, 75.61; H, 5.93; N, 11.76. Found: C, 75.72; H, 6.08; N, 11.88.

1-*p*-Anisyl-2-(2-benzimidazolyl)ethanol (4c) had mp 212.5–213°; pmr (DMSO-d_6) δ 3.06 (d, 2, CH_2), 3.67 (s, 3, OCH_3), 5.04 (t, 1, CH), 5.50 (broad, 1, OH), 6.82 (d, 2, aromatic), 7.05 (m, 2, aromatic), 7.25 (d, 2, aromatic), and 7.38 ppm (m, 2, aromatic).

Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.65; H, 5.85; N, 10.26.

1-(2-Benzimidazolyl)-4-phenyl-3-buten-2-ol (4d) had mp 214.5–215°; pmr (DMSO-d_6) δ 3.03 (d, 2, CH_2), 4.67 (2 d, 1, CH), 5.43 (s, 1, OH), 6.30 (2 d, 1, =CH), 6.58 (d, 1, =CH), and 7.26 ppm (m, 9, aromatic).

Anal. Calcd for $C_{17}H_{16}N_2O$: C, 77.24; H, 6.10; N, 10.61. Found: C, 76.93; H, 6.18; N, 10.37.

1,1-Diphenyl-2-(2-benzimidazolyl)ethanol (4e) had mp 199–201°; pmr (DMSO-d_6) δ 3.36 (broad, 1, OH), 3.85 (d, 2, CH_2), and 7.29 ppm (m, 14, aromatic).

Anal. Calcd for $C_{21}H_{18}N_2O$: C, 80.22; H, 5.78; N, 8.91. Found: C, 80.03; H, 5.91; N, 9.15.

2-(1-Hydroxycyclohexylmethyl)benzimidazole (4f) had mp 200–201.5°; pmr (DMSO-d_6) δ 1.44 (s, 10, CH_2), 2.85 (s, 2, CH_2), 4.72 (s, 1, OH), 7.04 (m, 2, aromatic), and 7.42 ppm (m, 2, aromatic).

Anal. Calcd for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.16. Found: C, 73.28; H, 8.08; N, 12.13.

1-(2-Benzimidazolyl)-2,4-diphenyl-3-buten-2-ol (4g) had mp 139.5–140.5°; pmr (DMSO-d_6) δ 3.51 (s, 2, CH_2), 6.49 (s, 1, OH), 6.60 (d, 1, =CH), and 7.22 ppm (m, 15, aromatic and =CH).

Anal. Calcd for $C_{23}H_{20}N_2O$: C, 81.15; H, 5.92; N, 8.23. Found: C, 81.25; H, 5.75; N, 8.52.

1-(2-Benzimidazolyl)-2-phenyl-2-propanol (4h) had mp 157.5–159°; pmr (DMSO-d_6) δ 1.53 (s, 3, CH_3), 3.27 (s, 2, CH_2), 5.91 (s, 1, OH), and 7.38 ppm (m, 9, aromatic).

Anal. Calcd for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.11. Found: C, 76.44; H, 6.09; N, 11.20.

1-*p*-Anisyl-2-(5-chloro-2-benzimidazolyl)ethanol (4i) had mp 235–236°; pmr (DMSO-d_6) δ 3.08 (d, 2, CH_2), 3.70 (s, 3, OCH_3), 5.04 (t, 1, CH), 5.64 (s, 1, OH), 6.84 (d, 2, aromatic), 7.01 (m, 1, aromatic), 7.28 (d, 2, aromatic), and 7.47 ppm (d, 2, aromatic).

Anal. Calcd for $C_{16}H_{15}ClN_2O_2$: C, 63.47; H, 4.99; N, 9.25. Found: C, 63.28; H, 5.06; N, 9.28.

2-(5-Chloro-2-benzimidazolyl)-1,1-diphenylethanol (4j) had mp 204.5–206°; pmr (DMSO-d_6) δ 3.89 (s, 2, CH_2), 6.89 (s, 1, OH), and 7.36 ppm (m, 13, aromatic).

Anal. Calcd for $C_{21}H_{17}ClN_2O$: C, 72.30; H, 4.91; N, 8.03. Found: C, 72.51; H, 4.76; N, 8.16.

Attempted Dimetalation of 2-Propylbenzimidazole (3a) with *n*-Butyllithium.—*n*-Butyllithium (2.1–21.0 mmol) was added *via* syringe to a solution of 2-propylbenzimidazole (**3a**, 1–10 mmol) in 25–50 ml of THF at 0° under nitrogen. After stirring for 1 hr, the yellow slurry was quenched with one of the following electrophiles.

(9) R. Sera and R. H. Müller, *Monatsh. Chem.*, **57**, 97 (1931).

(10) B. A. Porai-Koshits and G. M. Kharkhova, *Zh. Obshch. Khim.*, **25**, 2138 (1955).

(11) R. Weidenhagen, *Ber.*, **69B**, 2263 (1936).

(12) **3f** was obtained from reaction of **2a** with benzalacetophenone and was separated from the 1,2-addition product **4g** by column chromatography on silica gel, employing ether–hexane as the eluent.

(13) A. Hunger, J. Kerble, A. Rossi, and K. Hoffman, *Helv. Chim. Acta*, **43**, 800 (1960).

A. Deuterium Oxide.—The reaction slurry formed from 2 mmol of **3a** was quenched with 0.5 ml of deuterium oxide. The precipitated lithium deuterioxide was removed by filtration; the filtrate was diluted with ether, dried over $MgSO_4$, and concentrated. Analysis of the pmr spectrum (DMSO-d_6) of the residue indicated no deuterium incorporation at the α-methylene position of **3a**.

B. Benzyl Chloride.—To a reaction slurry formed from 10 mmol of **3a** was added a 1:1 v/v solution of benzyl chloride (11 mmol) in THF, and the resulting mixture was stirred for 2 hr. The reaction mixture was poured into 50 ml of water and neutralized with concentrated HCl. The organic phase was separated, and the aqueous phase was extracted with two 50-ml portions of ether. The organic solution was dried over $MgSO_4$, and the solvent was evaporated. Tlc analysis (benzene–acetone–hexane, 1:1:1) of the resulting gummy solid indicated the presence of only unreacted **3a** and benzyl chloride.

C. Butyl Bromide.—Butyl bromide (1 mmol) in 2 ml of THF was added to the slurry formed from 1 mmol of **3a**. After 2 hr, the reaction mixture was processed in a manner similar to that of the preceding experiment. Tlc analysis (benzene–acetone–hexane, 1:1:1) of the crude reaction product indicated the presence of only unreacted **3a**.

D. Benzophenone.—To a reaction slurry formed from 10 mmol of **3a**, benzophenone (11 mmol) in 25 ml of THF was added. After 2 hr, the reaction was processed in the usual manner. Tlc analyses (benzene–acetone–hexane, 1:1:1, and ether) showed only the presence of unreacted **3a** and benzophenone in the crude reaction product; no diphenylbutylcarbinol could be detected.

E. Carbon Dioxide.—Carbon dioxide was bubbled through a slurry formed from 3.5 mmol of **3a** and 7.1 mmol of *n*-butyllithium for 3 min, causing dissolution of the yellow slurry. The reaction mixture was poured into 50 ml of iced water. The organic phase was separated, and the aqueous phase was extracted with two 50-ml portions of ether. The organic solution was dried over $MgSO_4$ and the solvent was evaporated, giving 0.55 g (98% recovery) of **3a**. The alkaline aqueous solution was acidified to pH ~2 and was continuously extracted with ether for 22 hr. The ethereal solution was dried over $MgSO_4$, and the solvent was evaporated to afford 0.06 g (17%) of valeric acid; ir and pmr spectra were identical with those of authentic material.

F. Water.—The precipitate formed from 1 mmol of **3a** was allowed to settle, and the yellow supernatant solution was withdrawn with a syringe and added to 25 ml of water. The precipitate was washed with 5 ml of THF, and the washing was added to the hydrolyzed supernatant. The basic solution was titrated with 0.05 *M* HCl to the end point of phenolphthalein, 29.50 ml of acid being required to reach the end point. This volume of acid represents 1.475 mmol of total base present in the supernatant.

The precipitate was suspended in 5 ml of THF and hydrolyzed with 25 ml of water. Titration of this solution with 0.05 *M* HCl to the end point of phenolphthalein required 23.45 ml, indicating that hydrolysis of the precipitate liberated 1.173 mmol of hydroxide ion.

Attempted Dimetalation of 2-Propylbenzimidazole (3a) with 2 Mol Equiv of *n*-Butyllithium–TMEDA Complex.—*n*-Butyllithium (1.1 ml of 1.9 *M* hexane solution, 2.1 mmol) was added *via* syringe to a solution of **3a** (0.160 g, 1 mmol) and TMEDA (0.232 g, 2 mmol) in 15 ml of THF at 0° under nitrogen. The resulting yellow slurry was stirred for 1 hr before the addition of 0.5 ml of deuterium oxide. After stirring for 1 min, lithium deuteroxide was removed by filtration, the filtrate was diluted with 50 ml of ether and dried over $MgSO_4$, and the solvent was evaporated. The recovered **3a** was dried at 50° (3 mm) for 3 hr to remove residual TMEDA. Analysis of the pmr spectrum (DMSO-d_6) of this material indicated no deuterium incorporation at the α-methylene group of **3a**.

Attempted Benzylation of 2-Propylbenzimidazole (3a) with 2 Mol Equiv of *n*-Butyllithium in the Presence of HMPA.—*n*-Butyllithium (5.8 ml of 1.9 *M* hexane solution, 11 mmol) was added *via* syringe to a solution of **3a** (0.800 g, 5 mmol) in 20 ml of THF and 2 ml of HMPA at 0° under nitrogen. The yellow-brown solution was stirred for 1 hr, and benzyl chloride (0.633 g, 5 mmol) in 5 ml of THF was added. The reaction solution immediately became deep red-black. After approximately 30 sec, this color was discharged, being replaced by the original yellow-brown color. The reaction solution was stirred for 2 hr before being poured into 100 ml of iced water containing 2.5 ml of concentrated HCl. The organic phase was separated, and the acidic aqueous phase was extracted with two 50-ml portions of ether. The organic solution was dried over $MgSO_4$, and the solvent was evaporated. The resulting tan, oily solid was recrystallized from ethanol, giving 0.29 g (64%) of stilbene, mp 119–121° (lit.[14] mp 124°).

The acidic solution was neutralized with concentrated NH_4OH and then was extracted with two 50-ml portions of ether. The organic solution was dried over $MgSO_4$ and the solvent was evaporated, giving 0.77 g (96.5% recovery) of **3a**.

Attempted Dimetalation of 2-Propylbenzimidazole (3a) with 3 Mol Equiv of *n*-Butyllithium.—*n*-Butyllithium (3.3 ml of 1.9 *M* hexane solution, 6.3 mmol) was added *via* syringe to a solution of **3a** (0.320 g, 2 mmol) in 25 ml of THF at 0° under nitrogen. The resulting yellow slurry was stirred for 1 hr before the addition of 1 ml of deuterium oxide. The resulting reaction mixture was processed as in other deuteration experiments. Analysis of the pmr spectrum (DMSO-d_6) of the recovered material indicated incorporation of 0.29 D per α-methylene group of **3a**.

Registry No.—**1a**, 615-15-6; **1b**, 2818-69-1; **1c**, 621-72-7; **3a**, 5465-29-2; **3b**, 5805-30-1; **3c**, 42449-70-7; **3d**, 5838-57-3; **3e**, 5851-45-6; **3f**, 42449-72-9; **3g**, 24893-44-5; **3h**, 42449-74-1; **4a**, 42449-75-2; **4b**, 42449-76-3; **4c**, 42449-77-4; **4d**, 42449-78-5; **4e**, 42449-79-6; **4f**, 42449-80-9; **4g**, 42449-81-0; **4h**, 42449-82-1; **4i**, 42449-83-2; **4j**, 42449-84-3; **6**, 42449-85-4.

(14) T. W. J. Taylor and A. R. Murray, *J. Chem. Soc.*, 2079 (1938).

Studies in the Heterocyclic Series. VII. The Use of Kaufmann's Reaction as a Route to o-Aminomercaptopyridines

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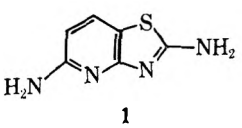
Received June 29, 1973

The Kaufmann's thiocyanation of 6-substituted 2-amino- and 3-aminopyridines has now been fully studied and analytically pure compounds obtained therefrom. A study of their uv, ir, pmr, and mass spectra establishes the products as 6-substituted 2-amino-3-thiocyanatopyridine and 5-substituted 2-aminothiazolo[5,4-*b*]pyridine, respectively. The action of 20% sodium hydroxide on the thiazolo[5,4-*b*]pyridines led to analytically pure 6-substituted 3-aminopyridin-2[1*H*]-thiones required for azaphenothiazine synthesis. Our modified procedures gave yields better than 90% overall. Isomerization and acetylation of 6-substituted 2-amino-3-thiocyanatopyridine to 5-substituted 2-acetamidothiazolo[4,5-*b*]pyridine was accomplished by prolonged heating in acetic anhydride.

The importance of phenothiazine compounds in medicine has prompted a lot of attention, not only on the aza- and thiaphenothiazines[2] themselves but also on their precursors.[3] A convenient method of synthesizing one of these precursors, o-aminomercaptopyridine, patterned after Kaufmann's reaction,[4] was developed, but contradictory results on both the structure[5,6] and purity[7] of the products were reported. Maggiolo's claim[5] that the thiocyanation of 2,6-diaminopyridine gave 2,5-diaminothiazolo[4,5-*b*]pyridine (**1**) was shown to be incorrect; the product is 3-thiocyanato-2,6-diaminopyridine (**2**).[6] Baker and Hill[6] therefore concluded that the reported base-catalyzed hydrolysis of thiazolopyridine could well be the hydrolysis of o-aminothiocyanatopyridine, since cleavage of the thiazole ring is unlikely owing to the aromatic stabilization of the ring. There is also a possibility that the thiocyanation of 3-aminopyridines should occur preferentially in the 4 position owing to greater reactivity of the 4 carbon center to nucleophiles such as thiocyanogen. All these reports and counterreports on the thiocyanation site, the purity and structure of the products, the isomerization of the thiocyanato derivative, and the cleavage of the thiazole ring led us to investigate these reactions, as they are crucial in our azaphenothiazine studies.



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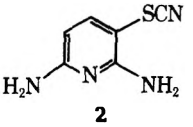

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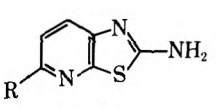
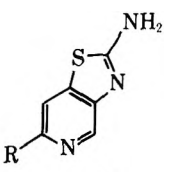
The action of potassium thiocyanate and bromine on 6-substituted 3-aminopyridine in glacial acetic acid led to a single product recrystallizable from methanol. From 3-amino-6-methoxy- (**3**) and 3-amino-6-chloropyridines (**4**), the products **5** and **6**, of molecular formulas $C_7H_7N_3OS$ and $C_6H_4N_3SCl$, respectively, were obtained. Their ultraviolet absorption spectra showed no maxima in the visible, but in the ultraviolet region, absorption maxima around 311 and 270 mμ were observed. The two spectra are nearly superimposable, indicating similarities in structure. There was no absorption in the 2000–2200-cm^{-1} region in their infrared spectra, thus showing the absence of the thiocyanato group. If, however, the thiocyanato derivatives were postulated as intermediates, isomerization of the 2- and 4-thiocyanato derivatives will lead to thiazolo[5,4-*b*]pyridine (**7**) and thiazolo[4,5-*c*]pyridine (**8**), respectively. Isomerization of the third possibility, 3-amino-5-thiocyanatopyridine, to a cyclic structure appears improbable owing to the rigidly planar structure of the pyridine ring. Spectral studies are in agreement with the structure **7** rather than **8**. In the proton magnetic resonance spectrum of the product **5**, taken in hexadeuteriodimethyl sulfoxide (DMSO-d_6), a large coupling constant is expected if the correct structure is **7** owing to strong coupling of the 6 and 7 protons, which are in close proximity. From structure **8**, a low coupling constant will be expected (0–3 Hz) owing to large separation between the protons at the 4 and 7 positions[8] and the planarity of the aromatic ring. As the observed coupling constant is quite large (J = 10 Hz), the alternative structure **8** was therefore ruled out and structure **7** (R = OCH_3) was assigned to this product. A similar effect was observed in the pmr spectrum of the product **6**. Here, the coupling constant is less (J = 8 Hz) than what was observed in the methoxy analog (J = 10 Hz) in agreement with the observation in the vinyl compounds that electronegative substituents tend to diminish the magnitude of J_{cis}.[9,10] The areas of the peaks are in agreement with the assigned structures **7** (R = OCH_3 and Cl). The absence of additional peaks in the spectrum led to the elimination of such imino tautomeric structures as **9**. The strong infrared absorption be-



7



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(4) H. P. Kaufmann and P. Schulz, *Arch. Pharm. (Weinheim)*, **273**, 31 (1935); H. P. Kaufmann, *Ber.*, **62B**, 390 (1929); H. P. Kaufmann and M. Schubert, German Patent 493,025 (1927) [*Chem. Abstr.*, **24**, 2754 (1930)].

(5) A. Maggiolo, *J. Amer. Chem. Soc.*, **73**, 5815 (1951).

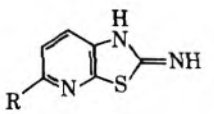
(6) J. A. Baker and S. A. Hill, *J. Chem. Soc.*, 3464 (1962).

(7) T. Takahashi and Y. Maki, *Chem. Pharm. Bull.*, **3**, 92 (1955).

(8) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, London, 1969, pp 305–311.

(9) P. Laszlo and P. R. Schleyer, *Bull. Soc. Chim. Fr.*, 87 (1964).

(10) T. Schaefer, *Can. J. Chem.*, **40**, 1 (1962).

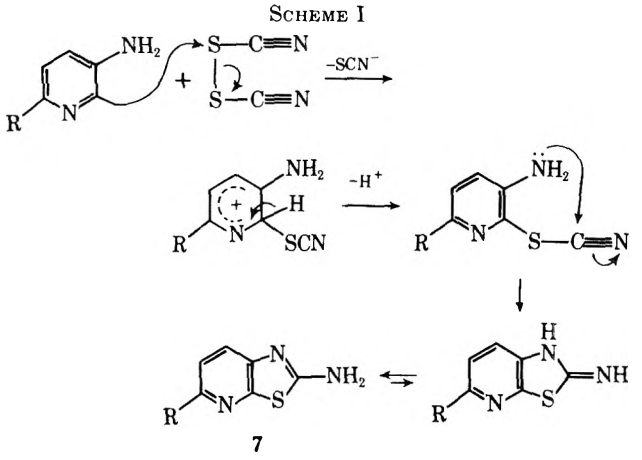


9

tween 810 and 820 cm^{-1} is consistent with structure **7**, in which two aromatic protons are in adjacent carbons.[11] The mass spectra of these compounds were also taken and the observed fragmentation patterns were rationalized with the assigned structures **7** (R = OCH_3 and Cl).

From the molecular orbital calculations of the π-electron densities in 3-amino-6-chloropyridine,[12] the 4 position is the most positive center. As the attack, however, was on the 2 position, which is the electrophilic center, it is probable that thiocyanogen, being a pseudohalogen, behaves as an electrophile by attacking this electrophilic center (the 2 position). It is equally plausible to consider the 2 position as mounting a nucleophilic attack on thiocyanogen as the substrate. Thus the reactions which led to the structures **7** can be formulated according to Scheme I.

SCHEME I



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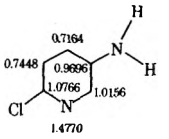
The structures of the products of the base-catalyzed reactions were also investigated. When these thiazolo[5,4-*b*]pyridines were refluxed in 20% sodium hydroxide followed by acidification, massive yellowish precipitates were formed. Upon recrystallization from methanol, yellow, glistening needles of the product of each reaction were collected in near-quantitative yields. Analyses of these products are in agreement with the formulas $C_6H_8N_2OS$ and $C_5H_5N_2SCl$, which were confirmed by an examination of their mass spectra. A study of their uv, ir, and particularly pmr spectra confirmed that these products are 3-aminopyridine-2[1*H*]-thiones **10**.

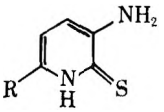
(11) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed, Methuen and Co., London, 1964, pp 65, 277.

(12) The π-electron densities given were calculated by the LCAO–MO method. The figures in the structure show a higher electron density in the 2 position compared to the 4 and 5 positions.



A. Streitwieser, Jr., "Molecular Orbital Theory for Organic Chemists," Wiley, New York, N. Y., 1967, pp 97–135; J. Ridd in "Physical Methods in Heterocyclic Chemistry," A. R. Katritzky, Ed., Vol. I, Academic Press, New York, N. Y., 1963, pp 27–43, 109–160.

The ready solubility in dilute base and the absence of the SH group in the ir spectra are further evidence of the structures **10** (R = OCH_3, Cl).



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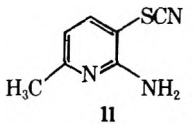
The thiocyanation of the isomeric 2-aminopyridine was also investigated for comparison with the 3-amino isomer. In the 2-aminopyridine series, the 4-methyl and 5-methyl derivatives failed to react and in both cases nearly 50% of the starting amines was recovered. When 2-amino-6-picoline was, however, thiocyanated, a single product of molecular weight 165 and molecular formula $C_7H_7N_3S$ was isolated in 35% yield. The infrared spectrum of this compound showed a strong SCN peak at 2145 cm^{-1}. The large spin–spin coupling constant in the pmr spectrum (J = 9 Hz) and the ready conversion of the product to thiazolo[4,5-*b*]-pyridine prove that this compound is 2-amino-3-thiocyanato-6-picoline (**11**) rather than 2-amino-5-thiocyanato-6-picoline or 2-amino-4-thiocyanato-6-picoline. This structure is also in conformity with the mass spectrum.

Although the acetylation of 2-amino-3-thiocyanato-6-picoline (**11**) is expected to give the 2-acetamido derivative, the product obtained showed no thiocyanate peak between 2000 and 2200 cm^{-1} in the ir spectrum but gave the expected single NH peak at 3290 cm^{-1} and the amide II band at 1665 cm^{-1}. This product was therefore formulated as 2-acetamido-5-methylthiazolo-[4,5-*b*]pyridine (**12**), which is formed by isomerization and acetylation of compound **11**.



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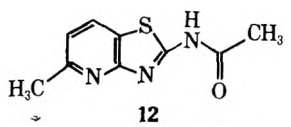

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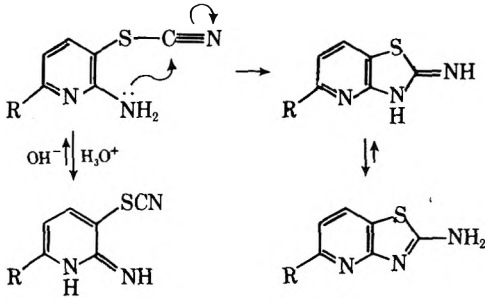
These results therefore show that, although the thiocyanation of 2- and 3-aminopyridines gives the thiocyanato derivatives, isomerization of the 3-amino-2-thiocyanatopyridine takes place with much ease, leading to the isolated 2-aminothiazolo[5,4-*b*]pyridines, while the 2-amino-3-thiocyanatopyridine does so only on prolonged heating. The difficulty in the isomeriza-



tion of 2-amino-3-thiocyanato-6-picoline is probably a result of amino–imino tautomerism in which the imino form hinders the intramolecular nucleophilic attack on the positive carbon of the thiocyanate group. In the isomeric 3-amino-2-thiocyanatopyridine, no such tautomerism can be formulated, as the amino group is

meta and remote from the ring nitrogen, and therefore the isomerization to the 2-aminothiazolo[5,4-*b*]pyridine will proceed with ease.

Experimental Section

General.—Melting points were determined with a Thomas-Hoover apparatus in open capillaries and are corrected. Uv absorption spectra were measured with a Cary Model 14 spectrophotometer in methanol solutions using matched 1-cm quartz cells. Ir spectra were determined on a Perkin-Elmer Model 137 spectrophotometer in Nujol (Kaydol) pastes. Pmr spectra were recorded at 60 MHz on a Varian Associates A-60 spectrometer. Chemical shifts were reported on the τ scale relative to tetramethylsilane (TMS) used as an internal standard. The mass spectra of these compounds were obtained on an AEI MS-9 (ion source temperature 190°, 70 eV) mass spectrometer.

2-Amino-5-methoxythiazolo[5,4-*b*]pyridine (7, R = OCH_3).—This compound was prepared by a modification of the previously described methods.[13,14]

2-Methoxy-5-nitropyridine was prepared by the condensation of 2-chloro-5-nitropyridine with sodium methoxide in methanol. Reduction of the nitrogroup was accomplished by slow addition of 15.4 g (0.1 mol) of 2-methoxy-5-nitropyridine to a well-stirred and ice-cooled solution of 113 g (0.5 mol) of stannous chloride dihydrate and 150 ml of concentrated hydrochloric acid (*d* 1.42). The addition of the nitro compound was carried out in small quantities and at such a rate that the temperature never exceeded 85°. The reduction was highly exothermic and a cooling bath was therefore used.

After all the nitro compound had been added, the mixture was stirred for 4 hr and allowed to stand overnight. Neutralization with sodium carbonate followed by the use of concentrated ammonia solution gave 3-amino-6-methoxypyridine, which was isolated by successive extraction with four 200-ml portions of ether. After removal of the solvent by distillation followed by purification by fractional distillation *in vacuo*, 11.6 g (94%) of the red liquid was isolated, $n^{20}D$ 1.5729, dipicrate mp 128–129°.

To glacial acetic acid (100 ml) precooled to 5° were added 40 g (0.41 mol) of potassium thiocyanate and 6.2 g (0.05 mol) of 3-amino-6-methoxypyridine. The mixture was placed in a freezing mixture of ice and salt and mechanically stirred while 8 ml of bromine in 30 ml of glacial acetic acid was added from a dropping funnel at such a rate that the temperature never rose beyond 0°. After all the bromine has been added (105 min), the solution was stirred for an additional 2 hr at 0° and at room temperature for 10 hr. It was then allowed to stand overnight, during which period an orange precipitate settled at the bottom. Water (30 ml) was added quickly and the slurry was heated to 85° on a steam bath and filtered hot. The orange residue was placed in the reaction flask and treated with 50 ml of glacial acetic acid, heated again to 85°, and filtered hot. The combined filtrates were cooled and neutralized with concentrated ammonia solution to pH 6, when a dark yellow precipitate was collected. Recrystallization from methanol (twice) after treatment with activated charcoal gave colorless plates of 2-amino-5-methoxythiazolo[5,4-*b*]pyridine after drying in a vacuum oven at 50° (0.02 mm). The dry material (8.7 g, 96%) melted at 192–193°: uv spectrum (MeOH) λ_{max} 314 mμ (log ϵ 3.8603), λ_{min} 293 (3.6033), λ_{max} 267 (4.1037), λ_{min} 240 (3.5102); uv (HCl) λ_{max} 302 (4.0378), λ_{min} 285 (3.8902), λ_{max} 270 (3.9535); uv (NaOH) λ_{max} 314 (3.8202), λ_{min} 293 (3.5398), λ_{max} 267 (4.1170); ir spectrum (Nujol) ν_{max} 3330, 3100, 1640, 1580, 1565, 1544, 1403, 1290, 1280, 1247, 1170, 1122, 1108, 1078, 1020, 949, 907, 845, 815, 743, 700 cm^{-1}; pmr spectrum (DMSO-d_6) τ 5.87 (singlet, 5-OCH_3), 2.04 (broad peak, 2-NH_2), 2.87 (doublet, J = 10 Hz, 6-H), 1.85 (doublet, J = 10 Hz, 7-H); mass spectrum *m/e* (rel intensity) 52 (13), 80 (33), 107 (33), 111 (5), 122(4), 138 (10), 151 (11), 152 (42), 154 (4), 166 (21), 181 (M^+, 100).

Anal. Calcd. for $C_7H_7N_3SO$: C, 46.41; H, 3.87; N, 23.21; S, 17.68. Found: C, 46.28; H, 3.96; N, 22.84; S, 17.70.

2-Amino-5-chlorothiazolo[5,4-*b*]pyridine (7, R = Cl).—The synthesis of this compound from 2-chloro-5-nitropyridine is similar to what was reported for the 5-methoxy analog. From 31.7 g (0.2 mol) of 2-chloro-5-nitropyridine, 225 g (1.0 mol) of stannous chloride dihydrate, and 300 ml of concentrated hydrochloric acid, 25.0 g (97%) of white needles of 3-amino-6-chloropyridine was obtained, mp 82–83°.

This product (12.85 g, 0.1 mol) was treated with 80 g (0.82 mol) of potassium thiocyanate in 200 ml of glacial acetic acid and 6 ml of bromine to yield 15.2 g (95%) of 2-amino-5-chlorothiazolo-[5,4-*b*]pyridine as glistening, light-yellow needles melting at 243–244° dec: uv spectrum (MeOH) λ_{max} 310 mμ (log ϵ 3.9164), λ_{min} 292 (3.7029), λ_{max} 272 (4.1606), λ_{min} 246 (3.6101); uv (HCl) λ_{max} 297 (4.0803), λ_{min} 277 (3.8801), λ_{max} 260 (4.0661), λ_{min} 233 (3.7503); uv (NaOH) λ_{max} 310 (3.9507), λ_{min} 292 (3.7765), λ_{max} 272 (4.1910), λ_{min} 246 (3.7366); ir spectrum (Nujol) ν_{max} 3310, 1640, 1577, 1525, 1400, 1316, 1300, 1280, 1240, 1138, 1120, 1082, 940, 895, 813, 769, 736, 690 cm^{-1}; pmr spectrum (DMSO-d_6) τ 1.48 (broad peak, 2-NH_2), 1.77 (doublet, J = 8 Hz, 6-H), 2.20 (doublet, J = 8 Hz, 7-H); mass spectrum *m/e* (rel intensity) 96 (7), 108 (7), 123 (15), 150 (13), 158 (15), 185 (M^+, 100), 187 (39).

Anal. Calcd for $C_6H_4N_3SCl$: C, 38.81; H, 2.16; N, 22.64; S, 17.25; Cl, 19.14. Found: C, 38.90; H, 2.28; N, 22.62; S, 17.46; Cl, 19.18.

2-Amino-3-thiocyanato-6-picoline (11).—This compound was prepared by the same procedure used for the 2-aminothiazolo-[5,4-*b*]pyridines 7.

From 10.8 g (0.1 mol) of 2-amino-6-picoline, 80 g (0.82 mol) of potassium thiocyanate in 100 ml of glacial acetic acid, and 16 ml of bromine in 60 ml of glacial acetic acid, 5.8 g (35%) of white needles of 2-amino-3-thiocyanato-6-picoline (11), melting at 161–162°, were obtained after recystallization twice from methanol (more products were collected by keeping the volume of the partially neutralized solution to a minimum and for several days at 0–3°): uv spectrum (MeOH) λ_{max} 302 mμ (log ϵ 3.7462), λ_{min} 282 (3.6309), λ_{max} 256 (4.2015), λ_{min} 220 (3.4883); ir spectrum ν_{max} 3330, 3150, 2145, 1640, 1572, 1547, 1390, 1339, 1292, 1186, 1134, 1020, 960, 928, 822, 750 cm^{-1}; pmr spectrum (DMSO-d_6) τ 7.37 (singlet, 6-CH_3), 2.95 (broad based singlet, 2-NH_2), 3.17 (doublet, J = 9 Hz, 5-H), 1.91 (doublet, J = 9 Hz, 4-H); mass spectrum *m/e* (rel intensity) 53 (12), 70 (12), 97 (26), 106 (8), 124 (20), 138 (15), 165 (M^+, 100).

Anal. Calcd for $C_7H_7N_3S$: C, 50.91; H, 4.21; N, 25.46; S, 19.39. Found: C, 50.81; H, 4.28; N, 25.19; S, 19.48.

2-Acetamido-5-methylthiazolo[4,5-*b*]pyridine (12).—2-Amino-3-thiocyanato-6-picoline (1.65 g, 0.01 mol) was refluxed in 40 ml of acetic anhydride for 7 hr, during which period there was complete dissolution.

After cooling in an ice bath, a few ice cubes were added and the mixture was stirred with constant cooling until a precipitate was formed. Upon filtration and recrystallization of the material from aqueous acetone after treatment with activated charcoal, 1.95 g (94%) of glistening white needles of 2-acetamido-5-methylthiazolo[4,5-*b*]pyridine melting at 193–194° was obtained: uv spectrum (MeOH) λ_{max} 292 mμ (log ϵ 4.1516), λ_{min} 277 (3.9664), λ_{max} 255 (4.1361), λ_{min} 223 (3.8493); ir spectrum (Nujol) ν_{max} 3290, 1665, 1576, 1540, 1420, 1292, 1268, 1235, 1139, 1038, 1003, 956, 912 (doublet), 826, 775, 742, 677 cm^{-1}; mass spectrum *m/e* (rel intensity) 41 (8), 42 (9), 97 (9), 111 (3), 124 (14), 138 (9), 165 (100), 207 (M^+, 30), 208 (4), 209 (3).

Anal. Calcd. for $C_9H_9N_3OS$: C, 52.17; H, 4.35; N, 20.29; S, 15.46. Found: C, 52.02; H, 4.47; N, 20.00; S, 15.70.

3-Amino-6-methoxypyridine-2[1*H*]-thione (10, R = OCH_3).—2-Amino-5-methoxythiazolo[5,4-*b*]pyridine (7, R = OCH_3) (18.1 g, 0.1 mol) containing 1 g of sodium sulfite was refluxed in 20% sodium hydroxide (150 ml) for 3 hr. Complete dissolution was achieved after 1 hr. The clear, yellowish brown solution was treated with activated charcoal, boiled, and filtered. Upon cooling and neutralizing with glacial acetic acid, a massive yellowish precipitate was obtained. It was purified quickly[15] by recrystallization from methanol after treating with charcoal again. Long, yellowish needles of 3-amino-6-methoxypyridine-2[1*H*]-thione (15.2 g, 97%) melting at 178–179° dec were obtained after drying in a vacuum oven at 5-mm pressure for 24 hr: uv spectrum (MeOH) λ_{max} 388 mμ (log ϵ 4.0947), λ_{min} 297 (2.4282), λ_{max} 270 (3.8102), λ_{min} 235 (3.5743); ir spectrum (Nujol) ν_{max} 3400, 3300, 1600, 1560, 1400, 1360, 1283, 1272, 1260, 1120, 1103, 1056, 1028, 1020, 890, 875, 778, 765 cm^{-1}; pmr spectrum (DMSO-d_6) τ 6.0 (singlet, 6-OCH_3), 3.50 (doublet, J = 9 Hz, 5-H),

(13) T. Takahashi and E. Yoshii, *Chem. Pharm. Bull.*, **2**, 382 (1954).

(14) C. O. Okafor, *J. Org. Chem.*, **32**, 2006 (1967); C. O. Okafor, *J. Med. Chem.*, **10**, 126 (1967).

(15) These 3-aminopyridine-2-thiones are unstable to heat and light. They are best recrystallized from methanol and oven dried at 50° (10 mm) and preserved in brown bottles wrapped with aluminium foil.

2.63 (doublet, J = 9 Hz, 4-H), 1.70 (singlet, 1-NH); pmr (pyridine-d_5) τ 6.13 (singlet, 6-OH_3), 3.80 (doublet, J = 9 Hz, 5-H), 2.67 (doublet, J = 9 Hz, 4-H), 0.90 (broad singlet, 3-NH_2 and 1-NH); mass spectrum m/e (rel intensity) 52 (36), 53 (44), 54 (36), 80 (40), 97 (22), 114 (78), 141 (100), 156 (M^+, 94).

Anal. Calcd for $C_6H_8N_2OS$: C, 46.15; H, 5.13; N, 17.95; S, 20.51. Found: C, 46.26; H, 5.14; N, 17.84; S, 20.43.

3-Amino-6-chloropyridine-2[1*H*]-thione (10, R = Cl).—The base-catalyzed hydrolysis of 2-amino-5-chlorothiazolo[5,4-*b*]-pyridine (7, R = Cl) was carried out by the same method described for the preparation of the 6-methoxy analog.

From 18.55 g (0.10 mol) of this compound (7, R = Cl), 1 g of sodium sulfite, and 150 ml of 20% NaOH, 15.4 g (96%) of 3-amino-6-chloropyridine-2[1*H*]-thione[15] was obtained as glistening yellow needles melting at 210–211° dec: uv spectrum (MeOH) λ_{max} 355 mμ (log ϵ 3.5463), λ_{min} 292 (3.1362), λ_{max} 256 (3.8992), λ_{min} 237 (3.7832); ir spectrum (Nujol) ν_{max} 3480, 3311, 3180, 1600, 1550, 1545, 1300, 1250, 1136, 1108, 1088, 1030, 855, 815, 728 cm^{-1}; pmr spectrum (pyridine-d_5) τ 3.03 (singlet with broad base, 3-NH_2), 2.50 (doublet, J = 2 Hz, 4-H and5-H), 0.80 (singlet with broad base, 1-NH); pmr (DMSO-d_6) τ 3.53 (singlet with broad base, 3-NH_2), 2.33 (singlet, 4-H and 5-H); mass spectrum m/e (rel intensity) 44 (6), 64 (11), 81 (6), 98 (9), 115 (21), 116 (9), 125 (28), 132 (13), 133 (11), 159 (11), 160 (M^+, 100), 161 (13), 162 (39).

Anal. Calcd for $C_5H_5N_2SCl$: C, 37.38; H, 3.12; N, 17.45; S, 19.94; Cl, 22.12. Found: C, 37.76; H, 2.72; N, 17.46; S, 20.04; Cl, 22.35.

Acknowledgment.—The author is indebted to Professor R. B. Woodward for his financial assistance and useful suggestions during the duration of this project. Grateful acknowledgment is also extended to the Department of Chemistry, Harvard University, for providing the facilities for this work. The assistance of Professor J. Wuest and W. Pegg is also gratefully acknowledged.

Registry No.—7 (R = OCH_3), 13797-77-8; 7 (R = Cl), 31784-71-1; 10 (R = OCH_3), 42362-14-1; 10 (R = Cl), 42362-15-2; 11, 42449-30-9; 12, 42449-31-0; 2-methoxy-5-nitropyridine, 5446-92-4; 3-amino-6-methoxypyridine, 6628-77-9; 3-amino-6-methoxypyridine dipicrate, 42449-34-3; 2-chloro-5-nitropyridine, 4548-45-2; 3-amino-6-chloropyridine, 5350-93-6; 2-amino-6-picoline, 1824-81-3.

Studies in the Heterocyclic Series. VIII. The First Synthesis of a Triazaphenothiazine Ring

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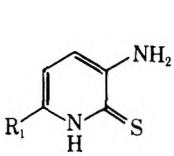
Compounds of 1,3,6-triazaphenothiazine, a new heterocyclic ring, are hereby described. Previously, no triazaphenothiazine compound was known. The synthesis of these compounds was achieved by acid-catalyzed reaction of suitably placed 3-aminopyridine-2[1*H*]-thiones with 5,6-dihalopyrimidines. Optimum yields were obtained in dilute sulfuric acid at concentrations between 0.12 and 0.50 *N*. Their uv, ir, pmr, and mass spectra were taken and used along with certain reactions to establish their structures. The related "open" 1,3,6-triazaphenothiazines were also synthesized and characterized and the abnormal appearance of their parent peaks in their mass spectra was rationalized. Many derivatives of these "open" and "closed" 1,3,6-triazaphenothiazines were also reported.

In continuation of our search for new azaphenothiazine drugs, a new azaphenothiazine ring was considered desirable, as previously reported azaphenothiazine rings are only the monoaza- and the diazaphenothiazine systems.[2] This work becomes even more important in the study of the mechanism of action of phenothiazine drugs where a correlation between tranquilizing activity and electron-donor property in charge-transfer complexes has been made. The stronger electron-donor property and hence the higher psychopharmacological activity have been associated with the heterocyclic ring, phenothiazine, and evidence for this conclusion has been provided.[3] More systematic studies in this direction will require a greater variety of phenothiazine rings. In an earlier paper[4] in this series, the synthesis of some 3,6-diazaphenothiazine compounds was described, and in continuation of this work, we present the first synthesis of a triazaphenothiazine system.

These compounds were obtained from 3-aminopyridine-2[1*H*]-thiones (1)[5] and 5-bromo-4-chloropyrimidines (2) prepared by an adaptation of Phillips'



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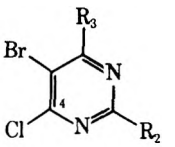

2

procedure.[6] The pmr spectra of the latter products showed no evidence for imino structures, contrary to the situation in related dihydroxypyrimidines.[7] In the crucial step involving the nucleophilic attack of the aminopyridinethione on the dihalopyrimidine followed by cyclization of the intermediate diarylamine **3**, several condensing agents were tried. Most promising results were obtained by acid-catalyzed procedures.[8] Using concentrated acid techniques, no reaction took place in concentrated hydrochloric and sulfuric acids, as all basic points were protonated. The insolubility of compound **1** in concentrated acids also posed a serious problem. However, upon dilution, it was possible to dissolve the compound and to protonate selectively the tertiary and secondary amino groups only, as these are more basic than the primary NH_2 group. The protona-

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(2) C. O. Okafor, *Int. J. Sulfur Chem.*, *B*, **6**, 237 (1971).

(3) G. Karreman, I. Isenberg, and A. Szent-Gyorgyi, *Science*, **130**, 1191 (1959); R. Foster and C. A. Fyfe, *Biochim. Biophys. Acta*, **112**, 490 (1966); R. Foster and P. Hanson, *ibid.*, **112**, 482 (1966).

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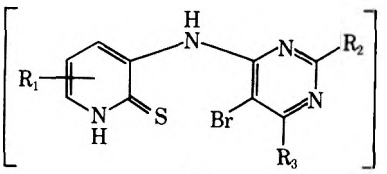
(5) C. O. Okafor, *J. Org. Chem.*, **38**, 4383 (1973).

(6) A. P. Phillips, N. B. Mehta, and J. Z. Strelitz, *J. Org. Chem.*, **28**, 1488 (1963).

(7) G. M. Kneifets, N. V. Khromov-Borisov, A. I. Koltsov, and M. V. Volkenstein, *Tetrahedron*, **23**, 1197 (1967).

(8) C. K. Banks, *J. Amer. Chem. Soc.*, **66**, 1127 (1944); O. R. Rodig, R. E. Collier, and R. K. Schlatzer, *J. Org. Chem.*, **29**, 2652 (1964).

tion of the pyrimidine ring nitrogens enhances the positive characters of the 2,4 and 6 carbons both by inductive and conjugative mechanisms. The 5 carbon is relatively less reactive, as it is only affected by the inductive effect of the ring nitrogens, which are, even then, relatively more remote. Under these conditions, therefore, the 3-NH_2 group in structure **1** mounts a nucleophilic attack on the positive pyrimidine carbon bearing the active halogen (C-4) leading to the formation of the *o*-thioxopyridylpyrimidinylamine **3** as the intermediate. These diarylamines, bearing both ortho-halo and mercapto groups, are sufficiently reactive in the acid medium and spontaneously cyclize to the 1,3,6-triazaphenothiazines (**4**).



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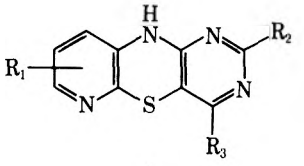

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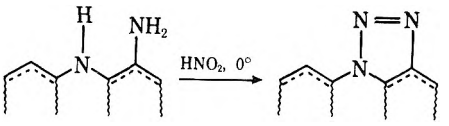
The conditions for optimum yields were also investigated. Best yields and purest products were obtained in aqueous solutions of 0.12 and 0.50 *N* H_2SO_4. Addition of a little amount of sodium sulfite helped to prevent the autoxidation of the aminopyridinethione which diverts the reaction to the undesirable disulfide. By refluxing for 3 hr, reproducible yields better than 70–95% were obtained in most cases.

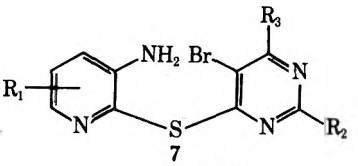
The reaction of 3-amino-6-methoxypyridine-2[1*H*]-thione (**1**, R_1 = 6-OCH_3) and 5-bromo-4-chloro-2,6-diaminopyrimidine (**2**, R_2 = R_3 = NH_2) under these conditions led to a triazaphenothiazine of molecular weight 262. Elemental analysis and molecular weight determination are consistent with the formula $C_{10}H_{10}N_6OS$. The uv spectrum gave three maximum absorptions at 335, 300, and 252 mμ; the strong band in the neighborhood of 252 mμ is consistent with similar observation in phenothiazinoid systems.[9] The infrared spectrum showed the NH_2 (doublet) and NH (singlet) stretching bands expected from structure **4**. The pmr and mass spectra of this compound were rationalized on the basis of the assigned structure **4** (R_1 = 7-OCH_3; R_2 = R_3 = NH_2).

Using 3-amino-6-chloropyridine-2[1*H*]-thione in place of **1** (R_1 = OCH_3), 7-chloro-2,4-diamino-1,3,6-triazaphenothiazine was obtained. These two triazaphenothiazines have similar uv spectra and the substitution of chlorine for the 7-methoxy group did not affect the characteristic phenothiazine band at 252 mμ. Owing to the stronger inductive effect of chlorine compared with the methoxy group, there was a general deshielding of all the proton absorptions found in the pmr spectrum. Diazotization of these diaminotriazaphenothiazines (**4**, R_2 = R_3 = NH_2) did not give the 1,10-diazoles (**5**) characteristic of *o*-aminodiarylamines (**6**).[10] 1-Amino-



6 **5**

3-azaphenothiazine[11] and 1-amino-3-azaphenoxazine,[12] structurally related to the alternative structure **8**, gave the corresponding 1,10-diazoles (**5**). It can be inferred from these reactions, therefore, that the *o*-thioxodiarylamine **3** does not undergo Smiles rearrangement to *o*-aminodiaryl sulfide **7**, which will lead to the alternative structure **8** expected to give the nitrous acid reaction. This is evidence for the assigned structures **4**.



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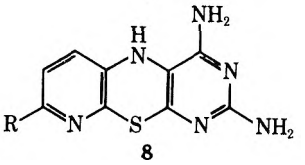

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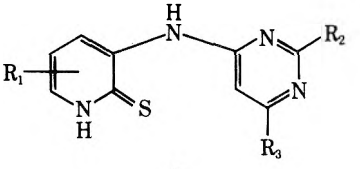
The synthesis of systems in which the central ring has been "opened" was also carried out, since many such systems are reported to be biologically active.[13] Furthermore, the determination of their structures as *o*-thioxodiarylamines will lend further support to the assigned structures of the "closed" systems, as this implies that Smiles rearrangement did not occur. These compounds were generally obtained by treating the 3-aminopyridine-2[1*H*]-thiones with 4-chloropyrimidines under the reaction conditions used for obtaining the "closed" systems. The uv spectra of these "open" products resemble those of the "closed" systems. In the ir spectrum, the absence of an SH band in the region of 2600–2550 cm^{-1} even in concentrated solutions and the appearance of NH bands as singlets rather than doublets show that these compounds exist as the thioxo form **9** rather than **10**. Examination of their pmr



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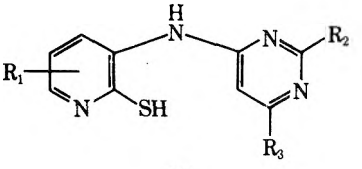

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(9) F. Yoneda, T. Ohtaka, and Y. Nitta, *Chem. Pharm. Bull.*, **13**, 580 (1965); D. E. Ames and N. D. Griffiths, *J. Chem. Soc. C*, 2672 (1970); F. H. Clarke, G. B. Silverman, C. M. Watnick, and N. Sperber, *J. Org. Chem.*, **26**, 1126 (1961).

(10) F. Kehrmann and J. Steinberg, *Ber.*, **44**, 3011 (1911); G. R. Clemo, W. H. Perkin, Jr., and R. Robinson, *J. Chem. Soc.*, **125**, 1754 (1924).

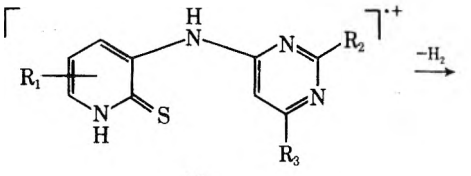
(11) V. A. Petrow and E. L. Rewald, *J. Chem. Soc.*, 591 (1945).

(12) V. A. Petrow and E. L. Rewald, *J. Chem. Soc.*, 313 (1945); C. O. Okafor, *Int. J. Sulfur Chem., B*, **6**, 345 (1971).

(13) A. Burger and J. F. Stanmyer, Jr., *J. Org. Chem.*, **21**, 1382 (1956); B. Roth and G. H. Hitchings, *ibid.*, **26**, 2770 (1961).

spectra confirmed the structures as **9**. The formation of these "open" nonrearranged structures, which are related to and formed by the same method used for the closed systems, is further evidence that the diaryl intermediate **3** did not rearrange to the diaryl sulfide **7**, which should yield 2,4,6-triazaphenothiazine **8** upon cyclization.

One interesting observation in the mass spectra of these "open" 1,3,6-triazaphenothiazines is the appearance of the parent peak (**11**) consistently at two mass units lower than the expected value. In all the four compounds whose mass spectra were examined, the parent peak appeared at two mass units lower than the expected charge to mass ratio. It appears therefore that the elimination of hydrogen occurs readily under the condition in which the mass spectra were run, thereby leading to the tricyclic ion **12**. This shows that,



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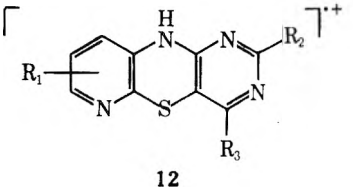

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in the excited state, the diarylamine intermediate **3** is in a favorable steric arrangement within the molecule, which ensures cyclization in the acid medium. Many other derivatives of both the "closed" and "open" 1,3,6-triazaphenothiazines were also described.

Experimental Section

Melting points were determined with a Thomas-Hoover apparatus in open capillaries. Uv spectra were taken with a Cary Model 14 spectrophotometer in methanol solutions using matched 1-cm quartz cells. Ir spectra were determined on a Perkin-Elmer Model 137 spectrophotometer in Nujol (Kaydol) pastes. Nmr spectra were obtained with a Varian Associates A-60 spectrometer. Chemical shifts are reported on the τ scale relative to tetramethylsilane (TMS) used as an internal standard except in the case of compound **13**, where TMS was used as an external reference. The mass spectra were obtained on an AEI MS-9 mass spectrometer at 70 eV.

3-Aminopyridine-2[1*H*]-thiones (1).—This class of compounds was obtained by the thiocyanation of substituted 3-aminopyridines with potassium thiocyanate and bromine in glacial acetic acid. The now formed 2-aminothiazolo[5,4-*b*]pyridine was treated with 20% sodium hydroxide solution to give excellent yields of 3-aminopyridine-2[1*H*]-thiones, fully described in the preceding paper.[5]

4-Chloro-2,6-diaminopyrimidine.—2,4-Diamino-6-hydroxypyrimidine (28.9 g, 0.2 mol) was treated with phosphoryl chloride (45 ml) and phosphorus pentachloride (40 g) and the mixture was refluxed in an oil bath maintained at 120–130° for a 3-hr period. Excess phosphorus halides were removed by distillation *in vacuo*. The gummy brown solid was poured *cautiously* into a few chips of ice in an ice bath. The solution was then partially neutralized with concentrated ammonia solution while cooling. The product was collected by filtration and recrystallized from methanol. White, glistening needles of 4-chloro-2,6-diaminopyrimidine (11.6 g, 80%) melting at 202–203° were obtained.

2-Amino-4-chloro-6-methylpyrimidine.—Dried and powdered 2-amino-4-hydroxy-6-methylpyrimidine (12.5 g, 0.1 mol) was refluxed with phosphoryl chloride (30 ml) and phosphorus pentachloride (40 g) as previously described. Long white needles of 2-amino-4-chloro-6-methylpyrimidine (11.7 g, 81.5%) melting at 182–183° were obtained after recrystallization from aqueous methanol (Norit).

5-Bromo-4-chloro-2,6-dimethoxypyrimidine (2, $R_2 = R_3 = OCH_3$).—4-Chloro-2,6-dimethoxypyrimidine (17.45 g, 0.1 mol) was slurried with 12 g of sodium bicarbonate in 300 ml of 50% methanol. Bromine (9 ml) was added with efficient stirring during a period of 1 hr. After 30 min of bromine addition, an additional 7 g of sodium bicarbonate was added and the mixture was stirred at room temperature for a total of 2 hr. The white precipitate obtained (mp 95–96°) was collected by filtration and recrystallized from aqueous methanol, yielding 24.1 g (95.1%) of white crystalline plates of 5-bromo-4-chloro-2,6-dimethoxypyrimidine melting at 97–98°. The analytical sample was purified by sublimation (sublimes at 98°): uv spectrum λ_{max} 273 mμ (log ϵ 3.84), λ_{min} 250 (3.40), λ_{max} 223 (3.97), λ_{min} 210 (3.84); ir spectrum (Kaydol) ν_{max} 1563, 1545, 1320, 1238, 1195, 1106, 1027, 1008, 937, 866, 772 cm^{-1}; pmr spectrum ($CDCl_3$) τ 5.73 (singlet, 6-OCH_3), 5.65 (singlet, 2-OCH_3).

Anal. Calcd for $C_6H_6N_2O_2BrCl$: C, 28.41; H, 2.37; N, 11.05; Cl, 14.01; Br, 31.53. Found: C, 28.45; H, 2.45; N, 10.97; Cl, 14.10; Br, 31.52.

5-Bromo-4-chloro-2,6-diaminopyrimidine (2, $R_2 = R_3 = NH_2$).—4-Chloro-2,6-diaminopyrimidine (14.45 g, 0.1 mol) was brominated with 16 ml of bromine in 750 ml of 50% methanol in the presence of a total of 20 g of sodium bicarbonate as described for 5-bromo-4-chloro-2,6-dimethoxypyrimidine. White needles of 5-bromo-4-chloro-2,6-diaminopyrimidine (15.87 g, 71%) melting at 217.5–218° were obtained: uv spectrum λ_{max} 294 mμ (log ϵ 3.78), λ_{min} 264 (2.79), λ_{max} 233 (4.05); ir spectrum (Kaydol) ν_{max} 3350 (doublet), 3200, 1670, 1645, 1605, 1530, 1328, 1270, 1063, 988, 886, 762 cm^{-1}.

Anal. Calcd for $C_4H_4N_4ClBr$: C, 21.48; H, 1.79; N, 25.07; Cl, 15.89; Br, 35.76. Found: C, 21.58; H, 1.68; N, 25.05; Cl, 15.92; Br, 35.68.

2-Amino-5-bromo-4-chloro-6-methylpyrimidine (2, $R_2 = NH_2$; $R_3 = CH_3$).—2-Amino-4-chloro-6-methylpyrimidine (10.76 g, 75 mmol) was treated with 15 g of sodium bicarbonate in 500 ml of 50% aqueous methanol. Bromine (14 ml) was added as described for 5-bromo-4-chloro-2,6-dimethoxypyrimidine. White needles of 2-amino-5-bromo-4-chloro-6-methylpyrimidine (16.9 g, 96.5%) melting at 206–207° were obtained after recrystallization from methanol (Norit): uv spectrum λ_{max} 310 mμ (log ϵ 3.57), λ_{min} 270 (2.88), λ_{max} 237 (4.22), λ_{min} 216 (3.68); ir spectrum (Kaydol) ν_{max} 3380, 3250, 1640, 1550, 1526, 1280, 1217, 1044, 1020, 888, 862, 771 cm^{-1}; pmr spectrum ($CDCl_3$) τ 7.33 (singlet, 6-CH_3), 2.22 (singlet, 2-NH_2).

Anal. Calcd for $C_5H_5N_3ClBr$: C, 26.98; H, 2.25; N, 18.88; Cl, 15.96; Br, 35.91. Found: C, 27.08; H, 2.21; N, 18.84; Cl, 15.83; Br, 36.02.

2-Amino-5-bromo-4,6-dichloropyrimidine (2, $R_2 = NH_2$; $R_3 = Cl$).—2-Amino-4,6-dichloropyrimidine (32.8 g, 0.2 mol) was mixed with 20 g of sodium bicarbonate and slurried in 600 ml of 50% methanol. Bromine (16 ml) was added as described for 5-bromo-4-chloro-2,6-dimethoxypyrimidine followed by addition of an additional 15 g of sodium bicarbonate. 2-Amino-5-bromo-4,6-dichloropyrimidine (46.2 g, 95%) was collected after recrystallization from methanol (Norit): mp 235–236°; uv spectrum λ_{max} 314 mμ (log ϵ 3.62), λ_{min} 277 (2.95), λ_{max} 238 (4.26), λ_{min} 217 (3.63); ir spectrum (Kaydol) ν_{max} 3290 (doublet), 1640, 1545, 1490, 1325, 1270, 1250, 1210 (doublet), 1050, 1023, 953, 815, 762 cm^{-1}; pmr spectrum ($CDCl_3$) τ 2.25 (singlet, 2-NH_2).

Anal. Calcd for $C_4H_2N_3Cl_2Br$: C, 19.76; H, 0.82; N, 17.29; Cl, 29.23; Br, 32.90. Found: C, 19.70; H, 0.87; N, 17.40; Cl, 29.11; Br, 33.08.

5-Bromo-2,4-diamino-6-hydroxypyrimidine.—2,4-Diamino-6-hydroxypyrimidine monohydrate (28.8 g, 0.2 mol) was dissolved in 5% aqueous sodium hydroxide (480 ml). The solution was cooled to 20° and 12.5 ml of bromine was added with efficient stirring during a 3-hr period. The temperature was maintained at 20° throughout the addition and for an additional 0.5 hr. The clear solution was stirred at room temperature for an additional 3 hr and allowed to stand overnight.

Upon acidification with concentrated hydrochloric acid while cooling, a massive white precipitate of 5-bromo-2,4-diamino-6-hydroxypyrimidine resulted. It was recrystallized from water after treating with activated charcoal, yielding glistening white

needles: mp 264–265°; ir spectrum ν_{max} 3300, 3190, 1650, 1600, 1550, 1430, 1160, 1088, 998, 875, 764, 683 cm^{-1}.

Anal. Calcd for $C_4H_5N_4OBr$: C, 23.43; H, 2.44; N, 27.32; Br, 38.99. Found: C, 23.44; H, 2.51; N, 27.21; Br, 39.06.

5-Bromo-6-chloro-2,4-diaminopyrimidine from 5-Bromo-2,4-diamino-6-hydroxypyrimidine.—To an intimate mixture of 5-bromo-2,4-diamino-6-hydroxypyrimidine (20.5 g, 0.1 mol) and phosphorus pentachloride (41.7 g, 0.2 mol) was added 60 ml of phosphoryl chloride and the mixture was refluxed in an oil bath maintained at 120–130° for 2.5 hr. The phosphorus halides were removed by vacuum distillation, leaving a yellow, gummy residue. It was then transferred to a beaker to which some ice chips were cautiously added. Upon neutralization with concentrated ammonia solution while cooling, a yellow precipitate was collected after filtration. Recrystallization from water after treating with activated charcoal (Norit) gave white, microcystalline plates of 5-bromo-6-chloro-2,4-diaminopyrimidine (15.2 g, 68%) melting at 217.5–218°. A mixture melting point with the product, obtained by the alternative method already described, did not show any depression. Furthermore, their spectra are superimposable.

2,4-Diamino-7-methoxy-1,3,6-triazaphenothiazine (4, R_1 = **7-OCH$_3$**; R_2 = R_3 = **NH$_2$**).—3-Amino-6-methoxypyridine-2-[1*H*]-thione (1.56 g, 10 mmol) was intimately mixed with 2.46 g (11 mmol) of 5-bromo-6-chloro-2,4-diaminopyrimidine in a mortar and placed in a 250-ml three-necked flask equipped with an efficient mechanical stirrer. Some 100 ml of water and 1 g of sodium sulfite were added and the mixture was refluxed with stirring for 2 hr in the presence of 1 ml. of concentrated sulfuric acid (*d* 1.84). Complete dissolution was achieved within 30 min followed by massive precipitation of a yellowish-green product.[14] The pH of the solution was checked from time to time to ensure that the solution remained acidic.[15]

The mixture was allowed to cool in an ice bath and neutralized with dilute ammonia and the residue was collected by filtration. Upon recrystallization from acetone after addition of activated charcoal (Norit), light, yellowish-green plates of 2,4-diamino-7-methoxy-1,3,6-triazaphenothiazine (2.38 g, 91%) melting at 255–256° were obtained: uv spectrum λ_{max} 335 mμ (log ϵ 3.79), λ_{min} 307 (3.65), λ_{max} 300 (3.65), λ_{min} 283 (3.55), λ_{max} 252 (4.36), λ_{min} 234 (4.22); ir spectrum ν_{max} 3390 (doublet), 3200, 1630, 1602, 1565, 1500, 1478, 1417, 1332, 1300, 1280, 1260, 1220, 1173, 1155, 1105, 1088, 1057, 1028, 980, 903, 818, 810, 740 cm^{-1}; pmr spectrum (DMSO-d_6) τ 6.00 (singlet, 7-OCH$_3$), 3.78 (broad peak, 4-NH$_2$), 3.50 (broad peak, 2-NH$_2$), 3.12 (doublet, J = 8.4 Hz, 9-H), 2.40 (doublet, J = 8.4 Hz, 8-H), 0.82 (broad peak, 10-NH); mass spectrum *m/e* (rel intensity) 150 (5), 177 (6), 178 (8), 219 (18), 220 (8), 247 (24), 262 (M$^+$, 100).

Anal. Calcd for $C_{10}H_{10}N_6OS$: C, 45.78; H, 3.84; N, 32.04; S, 12.22. Found: C, 45.95; H, 4.01; N, 31.97; S, 12.22.

7-Chloro-2,4-diamino-1,3,6-triazaphenothiazine (4, R_1 = **7-Cl**; R_2 = R_3 = **NH$_2$**).—This compound was prepared from 3-amino-6-chloropyridine-2[1*H*]-thione (1.61 g, 10 mmol) and 5-bromo-4-chloro-2,6-diaminopyrimidine (2.46 g, 11 mmol) as described for 2,4-diamino-7-methoxy-1,3,6-triazaphenothiazine. Yellow microcrystals of 7-chloro-2,4-diamino-1,3,6-triazaphenothiazine (2.35, g, 88%) melting at 309–310° were collected: uv spectrum λ_{max} 353 mμ (log ϵ 3.64), λ_{min} 313 (3.11), λ_{infl} 290 (3.61), λ_{max} 254 (4.47), λ_{min} 230 (4.12); ir spectrum ν_{max} 3395, 3240, 1640, 1588, 1555, 1500, 1440, 1400, 1340, 1285, 1260, 1224, 1173, 1140, 1110, 1092, 1060, 992, 934, 877, 814, 790, 760, 730 cm^{-1}; pmr spectrum (DMSO-d_6) τ 3.63 (broad peak 4-NH$_2$), 3.32 (broad peak, 2-NH$_2$), 2.48 (singlet, 8-H and 9-H), 0.40 (broad peak, 10-NH); mass spectrum *m/e* (rel intensity) 192 (6), 199 (8), 234 (23), 266 (M$^+$, 100), 268 (37).

Anal. Calcd for $C_9H_7N_6SCl$: C, 40.53; H, 2.65; N, 31.51; S, 12.00; Cl, 13.29. Found: C, 40.59; H, 2.80; N, 31.30; S, 11.92; Cl, 13.48.

2,4,7-Trimethoxy-1,3,6-triazaphenothiazine (4, R_1 = **7-OCH$_3$**; R_2 = R_3 = **OCH$_3$**).—To a mixture of 1.56 g (10 mmol) of 3-amino-6-methoxypyridine-2[1*H*]-thione (5, R_1 = 6-OCH$_3$) and 5.07 g (20 mmol) of 5-bromo-4-chloro-2,6-dimethoxypyrimidine 7 (6, R_2 = R_3 = OCH$_3$) in 100 ml of water was added 1 ml of concentrated sulfuric acid and 1 g of sodium sulfite. The mixture was refluxed with efficient stirring for 6 hr. There was complete dissolution after 5 min followed by extensive sublimation of 7. It was washed down with water followed by reduction in heating to reduce its reappearance at 96°. At the end of the reaction, a tarry, greenish product, which solidified upon cooling, was formed. It was collected by decanting off the hot supernatant liquid, neutralized with concentrated ammonia, and filtered. The bulk of this product was the unreacted pyrimidine compound 7, which was removed by extraction with boiling methanol. The greenish residue was recrystallized from ethanol to give 0.32 g (11%) of 2,4,7-trimethoxy-1,3,6-triazaphenothiazine (10, R_1 = 7-OCH$_3$; R_2 = R_3 = OCH$_3$) as green plates melting at 187–188°: uv spectrum λ_{max} 308 mμ (log ϵ 4.21), λ_{max} 250 (4.00); ir spectrum ν_{max} 3250 (singlet), 1600, 1535, 1280, 1219, 1192, 1178, 1141, 1111, 1103, 1077, 1030, 1021, 939, 926, 901, 840, 826, 786, 771, 690 cm^{-1}.

Anal. Calcd for $C_{12}H_{12}N_4O_3S$: C, 49.32; H, 4.11; N, 19.18; S, 10.96. Found: C, 49.49; H, 4.30; N, 19.01; S, 11.05.

7-Chloro-2,4-dimethoxy-1,3,6-triazaphenothiazine (4, R_1 = **7-Cl**; R_2 = R_3 = **OCH$_3$**).—A mixture of 1.61 g (10 mmol) of 3-amino-6-chloropyridine-2[1*H*]-thione and 3.80 g (15 mmol) of 5-bromo-4-chloro-2,6-dimethoxypyrimidine in 200 ml of water was refluxed for 4 hr in the presence of 1 g of sodium sulfite and 1 ml of concentrated sulfuric acid as was described for compound 4 (R_1 = 7-OCH$_3$; R_2 = R_3 = NH$_2$). Recrystallization from ethanol after treatment with activated charcoal afforded 2.82 g (95%) of 7-chloro-2,4-dimethoxy-1,3,6-triazaphenothiazine as green plates: mp 202–203°; uv spectrum λ_{max} 343 mμ (log ϵ 3.89), λ_{min} 333 (3.87), λ_{max} 308 (4.19), λ_{min} 281 (3.90), λ_{max} 261 (4.05), λ_{min} 247 (4.03), λ_{infl} 224 (4.14); ir spectrum ν_{max} 3200 (singlet), 1600, 1570, 1525, 1476, 1350, 1309, 1281, 1270, 1223, 1189, 1174, 1153, 1101, 1070, 1022, 1004, 930, 870, 845, 820, 808, 770, 689 cm^{-1}.

Anal. Calcd for $C_{11}H_9N_4SOCl$: C, 44.52; H, 3.04; N, 18.89; S, 10.79; Cl, 11.98. Found: C, 44.66; H, 2.89; N, 18.69; S, 10.76; Cl, 12.08.

2-Amino-7-chloro-4-methyl-1,3,6-triazaphenothiazine (4, R_1 = **7-Cl**; R_2 = **NH$_2$**; R_3 = **CH$_3$**).—A mixture of 1.61 g (10 mmol) of 3-amino-6-chloropyridine-2[1*H*]-thione and 2.45 g (11 mmol) of 2-amino-5-bromo-4-chloro-6-methylpyrimidine was treated as described earlier except that the reflux period was increased to 3.5 hr. Green plates of 2-amino-7-chloro-4-methyl-1,3,6-triazaphenothiazine (1.94 g, 73%) were collected after recrystallization from aqueous acetone (Norit): mp 247–249°; uv spectrum λ_{max} 321 mμ (log ϵ 3.47), λ_{max} 245 (3.45); ir spectrum ν_{max} 3420, 1660, 1608, 1565, 1525, 1500, 1320, 1270, 1200, 1150, 1116, 1066, 1050, 853, 813, 803, 772, 736 cm^{-1}.

Anal. Calcd for $C_{10}H_8N_5SCl$: C, 45.21; H, 3.01; N, 26.37; S, 12.05; Cl, 13.38. Found: C, 44.99; H, 2.89; N, 26.41; S, 12.11; Cl, 13.47.

2-Amino-7-methoxy-4-methyl-1,3,6-triazaphenothiazine (4, R_1 = **7-OCH$_3$**; R_2 = **NH$_2$**; R_3 = **CH$_3$**).—3-Amino-6-methoxypyridine-2[1*H*]-thione (3.12 g, 20 mmol) was treated with 2.45 g (11 mmol) of 2-amino-5-bromo-4-chloro-6-methylpyrimidine in the presence of sodium sulfite and sulfuric acid as was described for 2,4-diamino-7-methoxy-1,3,6-triazaphenothiazine. This time the reflux period was extended to 5 hr. White plates of 2-amino-7-methoxy-4-methyl-1,3,6-triazaphenothiazine were obtained after recrystallization from aqueous acetone: mp 243–244°; uv spectrum λ_{max} 308 mμ (log ϵ 3.91), λ_{min} 278 (3.57), λ_{max} 232 (4.07), λ_{min} 217 (4.05); ir spectrum ν_{max} 3340, 3200, 1640, 1600, 1570, 1540, 1500, 1400, 1327, 1280, 1270, 1260, 1238, 1220, 1058, 1042, 1020, 984, 973, 884, 858, 825, 806, 776, 770 cm^{-1}.

Anal. Calcd for $C_{11}H_{11}N_5SO$: C, 50.58; H, 4.21; N, 26.82; S, 12.26. Found: C, 50.25; H, 3.37; N, 26.90; S, 12.25.

2-Amino-4,7-dichloro-1,3,6-triazaphenothiazine (4, R_1 = **7-Cl**; R_2 = **NH$_2$**; R_3 = **Cl**).—2-Amino-5-bromo-4,6-dichloropyrimidine (1.34 g, 5.5 mmol) and 3-amino-6-methoxypyridine-2[1*H*]-thione (0.78 g, 5 mmol) were refluxed in 0.43 *N* H_2SO_4 as described for the 4-amino analog. Yellow microplates of 2-amino-4,7-dichloro-1,3,6-triazaphenothiazine (1 g, 70%) were collected; mp >300°; uv spectrum λ_{max} 318 mμ (log ϵ 4.07), λ_{min} 287 (3.77), λ_{max} 234 (4.21), λ_{min} 222 (4.19); ir spectrum ν_{max} 3380, 3230, 1606, 1550, 1530, 1410, 1342, 1261, 1220, 1138, 1065, 1050, 1003, 913, 838, 827, 770 cm^{-1}.

Anal. Calcd for $C_9H_5N_5SCl_2$: C, 37.76; H, 1.75; N, 24.47; S, 11.19; Cl, 24.82. Found: C, 37.70; H, 1.96; N, 24.22; S, 11.28; Cl, 24.65.

2,4-Diamino-6-(6-methoxy-2[1*H*]-thion-3-pyridyl)pyrimidinylamine (9, R_1 = **6-OCH$_3$**; R_2 = R_3 = **NH$_2$**).—This "open" 1,3,6-triazaphenothiazine was prepared as described for the corresponding closed system. From 1.56 g (10 mmol) of 3-

(14) There was excessive frothing and foaming if an efficient stirrer was not used.

(15) Alternatively, a 0.22 *N* H_2SO_4 solution was used satisfactorily.

amino-6-methoxypyridine-2[1*H*]-thione (1, R_1 = 6-OCH_3) and 4-chloro-2,6-diaminopyrimidine in 0.50 *N* H_2SO_4, 1.36 g (94% yield) of 2,4-diamino-6-(6-methoxy-2[1*H*]-thion-3-pyridyl)pyrimidinylamine was obtained as yellow plates: mp 270–272°; uv spectrum λ_{max} 384 mμ (log ε 3.54), λ_{min} 342 (3.36), λ_{max} 311 (3.88), λ_{min} 280 (3.62), λ_{max} 249 (3.87), λ_{min} 242 (3.85); ir spectrum ν_{max} 3200, 1675, 1595, 1404, 1290, 1260, 1225, 1200, 1163, 1130, 1080, 1060, 1030, 1012, 980, 900, 865, 796, 774 cm^{-1}; mass spectrum *m/e* (rel intensity) 147 (16), 178 (10), 218 (8), 220 (14), 231 (30), 262 (M^+, 100).

Anal. Calcd for $C_{10}H_{12}N_6OS$: C, 45,45; H, 4.55; N, 31.82; S, 12.12. Found: C, 45.20; H, 4.49; N, 32.00; S, 12.19.

2,4-Diamino-6-(6-chloro-2[1*H*]-thion-3-pyridyl)pyrimidinylamine (9, R_1 = 6-Cl; R_2 = R_3 = NH_2).—This compound was again prepared as described for the closed analog **4**. From 0.80 g (5 mmol) of 3-amino-6-chloropyridine-2[1*H*]-thione (1, R_1 = 6-Cl) and 0.80 g (5.5 mmol) of 4-chloro-2,6-diaminopyrimidine, 1.22 g (91% yield) of yellow plates of 2,4-diamino-6-(6-chloro-2[1*H*]-thion-3-pyridyl)pyrimidinylamine was collected: mp >300°; uv spectrum λ_{max} 345 mμ (log ε 3.72), λ_{min} 333 (3.67), λ_{max} 306 (3.96), λ_{min} 283 (3.79), λ_{max} 251 (4.15), λ_{min} 232 (4.10); ir spectrum ν_{max} 3400, 3250, 1675, 1600, 1575, 1525, 1273, 1232, 1240, 975, 885, 870, 832, 786, 776, 745 cm^{-1}; mass spectrum *m/e* (rel intensity) 199 (10), 224 (9), 231 (8), 234 (25), 266 (M^+ 100), 268 (40).

Anal. Calcd for $C_9H_9N_6SCl$: C, 40.23; H, 3.35; N, 31.29; S, 11.92; Cl, 13.22. Found: C, 40.32; H, 3.11; N, 31.50; S. 12.03; Cl, 13.19.

6′-Methoxy-2′[1′*H*]-thion-3′-pyridyl-2,4-dimethoxy-6-pyrimidinylamine 13 (9, R_1 = 6-OMe; R_2 = R_3 = OCH_3).—The reaction of 1.56 g (10 mmol) of 3-amino-6-methoxypyridine-2[1*H*]-thione and 1.59 g (11 mmol) of 4-chloro-2,6-dimethoxypyrimidine was carried out as described for "closed" 1,3,6-triazaphenothiazine compounds. A 2.56-g (87%) yield of 2,4-dimethoxy-6-(6-methoxy-2[1*H*]-thion-3-pyridyl)pyrimidinylamine was obtained as white plates: mp 163–164°; uv spectrum λ_{max} 272 μ (log ε 4.16); ir spectrum ν_{max} 3440, 1608, 1580, 1520, 1418, 1340, 1284, 1257, 1202, 1193, 1162, 1132, 1120, 1105, 1094, 1073, 1048, 1026, 1000, 984, 976, 940, 888, 868, 834, 810, 802, 772, 733, 701 cm^{-1}; pmr spectrum [$(CD_3)_2SO$] τ 5.93 (singlet, 2-OMe, 4-OMe, 6′-OMe), 4.02 (singlet, 5-H), 3.27 (singlet, 1′-NH), 2.58 (doublet, *J* = 9.6 Hz, 4′-H), 1.53 (doublet, *J* = 9.6 Hz, 5′-H), 0.45 (singlet, 6-NH); mass spectrum *m/e* (rel intensity) 247 (3), 260 (12), 261 (58), 262 (10), 277 (35), 292 (100).

Anal. Calcd for $C_{12}H_{14}N_4O_3S$: C, 48.98; H, 4.76; N, 19.05; S, 10.88. Found: C, 49.15; H, 4.63; N, 19.22 S, 11.00.

6′-Chloro-2′[1′*H*]-thion-3′-pyridyl-2,4-dimethoxy-6-pyrimidinylamine (9, R_1 = 6-Cl; R_2 = R_3 = OCH_3).—This compound was obtained by the reaction of 3-amino-6-chloropyridine-2[1*H*]-thione (1.6 g, 10 mmol) and 4-chloro-2,6-dimethoxypyrimidine (1.59 g, 11 mmol) as described for the closed triazaphenothiazines. White plates of 6′-chloro-2′[1′*H*]-thion-3′-pyridyl-2,4-dimethoxy-6-pyrimidinylamine (2.39 g, 80%) were obtained: mp 270–271°; uv spectrum λ_{max} 348 mμ (log ε 3.67), λ_{min} 320 (3.47), λ_{max} 295 (3.72), λ_{min} 270 (3.47), λ_{max} 244 (4.39), λ_{min} 225 (4.19), λ_{max} 209 (4.37); ir spectrum ν_{max} 3320, 3250, 1620, 1590, 1570, 1530, 1440, 1420, 1337, 1290, 1272, 1238, 1196, 1173, 1148, 1133, 1110, 1048, 978, 960, 938, 886, 816, 809, 774 cm^{-1}; pmr spectrum (DMSO-d_6) τ 5.95 (singlet, 4-OCH_3), 5.90 (singlet, 2-OCH_3), 2.60 (singlet, 4-H and 5-H), −0.25 (singlet, 3-NH); mass spectrum *m/e* (rel intensity) 252 (3), 261 (4), 265 (53), 266 (8), 281 (28), 296 (M^+ 100), 298 (61).

Anal. Calcd for $C_{11}H_{11}N_4O_2SCl$: C, 44.23; H, 3.68; N, 18.76; S, 10.72; Cl, 11.90. Found: C, 44.51; H, 3.36; N, 18.81; S, 10.70.

2-Amino-4-methyl-6-(6-methoxy-2[1*H*]-thion-3-pyridyl)pyrimidinylamine (9, R_1 = 6-OCH_3; R_2 = NH_2; R_3 = CH_3).—This compound was prepared by acid-catalyzed condensation of 3-amino-6-methoxypyridin-2[1*H*]-thione (4.68 g, 30 mmol) and 2-amino-4-chloro-6-methylpyrimidine (4.74 g, 33 mmol) as described for the closed systems. A 90% (7.10 g) yield of white 2-amino-4-methyl-6-(6-methoxy-2[1*H*]-thion-3-pyridyl)pyrimidinylamine was obtained: mp >300; ir spectrum ν_{max} 3400, 3230, 1650, 1595, 1550, 1412, 1290, 1262, 1058, 1020, 969, 890, 866, 810, 788 cm^{-1}.

Anal. Calcd for $C_{11}H_{13}N_5OS$: C, 50.19 H, 4.94; N, 26.62; S, 12.16. Found: C, 49.97; H, 5.09; N, 26.71; S, 12.10.

2-Amino-4-methyl-6-(6-chloro-2[1*H*]-thion-3-pyridyl)pyrimidinylamine (9, R_1 = 7-Cl; R_2 = NH_2; R_3 = CH_3).—The preparation of this compound from 3-amino-6-chloropyridine-2[1*H*]-thione (0.80 g, 5 mmol) and 2-amino-4-chloro-6-methylpyrimidine (0.79 g, 5.5 mmol) was carried out as described for the closed 1,3,6-triazaphenothiazine analog. White plates of 2-amino-4-methyl-6-(6-chloro-2[1*H*]-thion-3-pyridyl)pyrimidinylamine (1.19 g, 89%) were obtained: mp 275–276°; uv spectrum λ_{max} 315 mμ (log ε 4.06), λ_{min} 286 (3.65), λ_{infl} 280 (3.66), λ_{max} 245 (3.89), λ_{min} 240 (3.89), λ_{max} 220 (3.96), λ_{min} 210 (3.96); ir spectrum ν_{max} 3390, 3240, 1647, 1590, 1550, 1515, 1420, 1292, 1271, 1248, 1211, 1148, 1120, 1070, 1028, 974, 965, 874, 856, 827, 794, 784, 768 cm^{-1}.

Anal. Calcd for $C_{10}H_{10}N_5SCl$: C, 44.86; H, 3.74; N, 26.17; S, 11.96; Cl, 13.27. Found: C, 44.67; H, 3.92; N, 26.15; S, 12.11.

2-Amino-4-chloro-6-(6-methoxy-2[1*H*]-thion-3-pyridyl)pyrimidinylamine (9, R_1 = 6-OCH_3; R_2 = NH_2; R_3 = Cl).—This compound was prepared in the usual way, starting with 1.56 g (10 mmol) of 3-amino-6-methoxypyridine-2[1*H*]-thione and 1.80 g (11 mmol) of 2-amino-4,6-dichloropyridmidine. Yellow platelets of 2-amino-4-chloro-6-(6-methoxy-2[1*H*]-thion-3-pyridyl)pyrimidinylamine (2.04 g, 72%) were obtained: mp 270–272°; ir spectrum ν_{max} 3400, 3290, 1660, 1625, 1520, 1420, 1350, 1309, 1263, 1020, 974, 888, 815 cm^{-1}.

Anal. Calcd for $C_{10}H_{10}N_5OSCl$: C, 42.33; H, 3.53; N, 24.69; S, 11.29; Cl, 12.52. Found: C, 42.51; H, 3.33; N, 24.59; S, 11.42; Cl, 12.44.

2-Amino-4-chloro-6-(6-chloro-2[1*H*]-thion-3-pyridyl)pyrimidinylamine (9, R_1 = 6-Cl; R_2 = NH_2; R_3 = Cl).—By acid-catalyzed condensation of 1.60 g (10 mmol) of 3-amino-6-chloropyridine-2[1*H*]-thione and 1.80 g (11 mmol) of 2-amino-4,6-dichloropyrimidine, yellow plates of 2-amino-4-chloro-6-(6-chloro-2[1*H*]-thion-3-pyridyl)pyrimidinylamine (2.65 g, 92%) were obtained as described for the closed system: mp >300°; ir spectrum ν_{max} 3400, 3280, 1625, 1575, 1550, 1405, 1267, 1220, 1138, 975, 910, 835, 790 cm^{-1}.

Anal. Calcd for $C_9H_7N_5SCl_2$: C, 37.50; H, 2.43; N, 24.31; S, 11.11; Cl, 24.65. Found: C, 37.74; H, 2.30; N, 24.19; S, 11.25; Cl, 24.61.

Acknowledgment.—The author is indebted to Professor R. B. Woodward for his financial assistance and useful suggestions during the duration of this project. Grateful acknowledgment is also extended to the Department of Chemistry, Harvard University, for providing the facilities for this work. The assistance of Professor J. Wuest, W. Pegg, and all of the other members of Professor Woodward's research team is also gratefully acknowledged.

Registry No.—1 (R_1 = 6-OCH_3), 42362-14-1; 1 (R_1 = 6-Cl), 42362-15-2; 2 (R_2 = R_3 = OCH_3), 42362-16-3; 2 (R_2 = R_3 = NH_2), 7150-68-7; 2 (R_2 = NH_2; R_3 = CH_3), 6314-12-1; 2 (R_2 = NH_2; R_3 = Cl), 7781-26-2; 4 (R_1 = 7-OCH_3; R_2 = R_3 = NH_2), 42362-20-9; 4 (R_1 = 7-Cl; R_2 = R_3 = NH_2), 42362-21-0; 4 (R_1 = 7-OCH_3; R_2 = R_3 = OCH_3), 42362-22-1; 4 (R_1 = 7-Cl; R_2 = R_3 = OCH_3), 42362-23-2; 4 (R_1 = 7-Cl; R_2 = NH_2; R_3 = CH_3), 42362-24-3; 4 (R_1 = 7-OCH_3; R_2 = NH_2; R_3 = CH_3), 42362-25-4; 4 (R_1 = 7-Cl; R_2 = NH_2; R_3 = Cl), 42362-24-3; 9 (R_1 = 6-OCH_3; R_2 = R_3 = NH_2), 42362-27-6; 9 (R_1 = 6-Cl; R_2 = R_3 = NH_2), 42362-28-7; 9 (R_1 = 6-OCH_3; R_2 = R_3 = OCH_3), 42362-29-8; 9 (R_1 = 6-Cl; R_2 = R_3 = OCH_3), 42362-30-1; 9 (R_1 = 6-OCH_3; R_2 = NH_2; R_3 = CH_3), 42362-31-2; 9 (R_1 = 7-Cl; R_2 = NH_2; R_3 = CH_3), 42362-32-3; 9 (R_1 = 6-OCH_3; R_2 = NH_2; R_3 = Cl), 42362-33-4; 9 (R_1 = 6-Cl; R_2 = NH_2; R_3 = Cl), 42362-34-5; 4-chloro-2,6-diaminopyrimidine, 156-83-2; 2,4-diamino-6-hydroxypyrimidine, 56-06-4; 2-amino-4-chloro-6-methylpyrimidine, 5600-21-5; 2-amino-4-hydroxy-6-methylpyrimidine, 3977-29-5; 4-chloro-2,6-dimethoxypyrimidine, 6320-15-6; 2-amino-4,6-dichloropyrimidine, 56-05-3; 5-bromo-2,4-diamino-6-hydroxypyrimidine 6312-72-7.

Localization or Delocalization of Nonbonded Electrons in Unsaturated Heterocycles[1]

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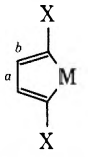
The pmr couplings for the vinyl H's have been obtained for several fully unsaturated nitrogen heterocycles, including 1-methyl-1,2-dihydro-2-diphenylmethylidinepyridine (**16**), indolizine (**9**), 4-quinolizone (**11**), and 1,3-diphenyl-2-methylisoindole (**8a**). These data are discussed in terms of the average (J_{av}), and ratio (J_{ratio}) of the J's across adjacent bonds and long-range ^4J couplings, and they are compared with the known values for other unsaturated six-membered heterocycles. The results of these comparisons indicate that nmr J values offer a simple method for obtaining a semiquantitative picture of the extent of interaction between olefin residues and a nitrogen electron pair.

Unsaturated organic molecules containing group VA or VIA heteroatoms have sparked numerous investigations aimed at defining the nature of the interaction between a heteroatom lone pair and adjacent trigonal carbons.[3,4] The five-membered family of fully unsaturated heterocycles has received a large amount of attention and some interesting similarities and diversions in structure can be implied for members of this series from data in the literature. For example, perusal of experimental bond lengths (Å) a and b for cyclopentadiene (**1**)[5] and a series of five-membered heterocycles (**2–5**)[6] shows for **1** $a = 1.47$ and $b = 1.34$ as compared with **2–5** wherein $a = 1.42$–1.44 and $b = 1.34$—1.37. The fairly close similarity of these respective data, in contrast to the idealized approach to $a = b = 1.39$ upon complete delocalization between the M lone pair and double bonds, suggests that only a small interaction occurs between the olefinic function and the heteroatomic electrons for **2–5**. Semiempirical MO calculations for furan, pyrrole, indole (**7**), and isoindole (**8**) have led to the proposition, based on estimates of both bond lengths and delocalization energies, that in furan there is essentially no heteroatom electron pair–carbon p orbital interaction, whereas a sizable such interaction of this type exists for the latter molecules.[4] Comparison of the observed planar configuration about the pyrrole nitrogen,[6b,7] relative to the pyramidal ground state observed for phosphole [$\Delta G^{\ddagger}_{inv}$ (**4a**) = 16 kcal/mol][8] and thiophene sulfoxide [$\Delta G^{\ddagger}_{inv}$ (**6**) = 15 kcal/mol],[9] might suggest that the degree of interaction between carbon p orbitals and heteroatomic electrons is in some way directly a function of nonbonded orbital types. A variety of pmr data involving proton chemical shifts for pyrrole and isoindole derivatives has been interpreted as being in support of a fully delocalized trigonal carbon–heteroatom lone pair constellation.[10]



1, M = CH_2; X = H
2, M = O; X = CO_2H
3, M = $\ddot{N}H$; X = H
4, M = $\ddot{P}CH_2Ph$; X = H
4a, M = $\ddot{P}CD_2C(OCH_3)_2HPh$; X = Ph, CH_3
5, M = $\ddot{S}$:; X = H
6, M = O=S:; X = $C(CH_3)_2CH_2C(CH_3)_3$

Most recently the similarity of ^{13}C chemical shifts between indolizine (**9**) and the isoelectronic indenide anion has been put forth as evidence that the bridgehead nitrogen does not perturb full π-electron delocalization in the former molecule.[12]

We have recently utilized both vicinal and long-range pmr coupling constants as convenient guides for achieving moderately precise estimates of both conformation and electronic configuration in polyolefins.[13] Accurate pmr coupling constant data can be found in the literature for each member of the series **1–5**.[14] For cyclopentadiene (**1**) the ^3J's across bonds b and a are 5.1 and 1.9 Hz, respectively,[14a] while for **2–5** the individual ^3J's range across bond b from a low of 1.7 Hz (furan) to a high of 7.2 Hz (1-methylphosphole) and across

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(2) On leave at UCSC (1971–1972) from Austana College, Sioux Falls, S. Dak.

(3) (a) A. Albert "Heterocyclic Chemistry," Atholone Press, University of London. 1968, Chapter 3; (b) E. M. Evleth, *Theor. Chim. Acta.*, **16**, 22 (1970); (c) J. A. Berson, E. M. Elveth, and S. L. Manatt, *J. Amer. Chem. Soc.*, **87**, 2901 (1965); (d) E. Lippmaa, M. Mägi, S. S. Novikov, L. I. Khmelnitski, A. S. Prihodko, O. V. Lebedev, and L. V. Epishina, *Org. Magn. Resonance*, **4**, 153 (1972), and references cited therein; (e) R. J. Pugmire and D. M. Grant, *J. Amer. Chem. Soc.*, **90**, 4232 (1968).

(4) M. J. S. Dewar, A. J. Harget, N. Triajstic, and S. D. Worley, *Tetrahedron*, **26**, 4505 (1970); M. J. S. Dewar and N. Trinajstic, *J. Amer. Chem. Soc.*, **92**, 1453 (1970); however, see also N. C. Baird, *Can. J. Chem.*, **47**, 3535 (1969).

(5) J. F. Chiang and S. H. Bauer, *J. Amer. Chem. Soc.*, **92**, 261 (1970).

(6) Structural data (Å) for bonds a and b, respectively, follow. (a) **2**, 1.442, 1.354: E. Martuscelli and C. Pedone, *Acta Crystallogr., Sect. B*, **24**, 175 (1968). (b) **3**, 1.429, 1.371: B. Bak, D. Christensen, L. Hansen, and J. Andersen, *J. Chem. Phys.*, **24**, 720 (1956). (c) **4**, 1.438, 1.343: P. Coggon, T. F. Engel, A. T. McPhail, and L. D. Quin, *J. Amer. Chem. Soc.*, **92**, 5779 (1970). (d) **5**, 1.423, 1.370: B. Bak, D. Christensen, L. Nygaard, and J. Andersen, *J. Mol. Spectrosc.*, **7**, 58 (1961).

(7) A planar structure at nitrogen for pyrrole has been inferred from a variety of data: R. A. Jones, *Advan. Heterocycl. Chem.*, **11**, 384 (1970); see also H. L. Ammon and L. H. Jensen, *J. Amer. Chem. Soc.*, **88**, 681 (1966).

(8) W. Egan, R. Tang, G. Zon, and K. Mislow, *J. Amer. Chem. Soc.*, **93**, 6205 (1971).

(9) W. L. Mock, *J. Amer. Chem. Soc.*, **92**, 7610 (1970).

(10) (a) J. A. Elvidge and L. M. Jackman, *J. Chem. Soc.*, 859 (1961); (b) J. A. Elvidge, *Chem. Commun.*, 160 (1965); (c) J. D. White, M. E. Mann, H. D. Krishenbaum, and A. Mitra, *J. Org. Chem.*, **36**, 1048 (1971); (d) J. J. Eisch and G. Gupta, *Tetrahedron Lett.*, 3273 (1972). However, data from two separate studies imply that observations of a ring current in five-membered ring heterocycles or cyclic six-π-electron systems does not necessarily imply a direct relationship to enhanced resonance stabilization or electron delocalization.[11]

(11) (a) R. J. Abraham and W. A. Thomas, *J. Chem. Soc. B*, 127 (1966); (b) J. A. Pople and K. G. Untch, *J. Amer. Chem. Soc.*, **88**, 4811 (1966).

(12) R. J. Pugmire, M. J. Robins, D. M. Grant, and R. K. Robins, *J. Amer. Chem. Soc.*, **93**, 1887 (1971).

(13) (a) P. Crews, *J. Amer. Chem. Soc.*, **95**, 636 (1973); (b) P. Crews, *Chem. Commun.*, 583 (1971).

(14) (a) M. A. Cooper, D. D. Elleman, C. D. Pearce, and S. L. Manatt, *J. Chem. Phys.*, **53**, 2343 (1970); (b) G. S. Reddy and J. H. Goldstein, *J. Amer. Chem. Soc.*, **84**, 583 (1962); (c) H. Fukui, S. Shimukawa, and J. Sohma, *Mol. Phys.*, **18**, 217 (1970); (d) D. M. Grant, R. C. Hirst, and H. S. Gutowski, *J. Chem. Phys.*, **38**, 470 (1963); (e) L. D. Quin, J. G. Bryson, and C. G. Moreland, *J. Amer. Chem. Soc.*, **91**, 3308 (1969).

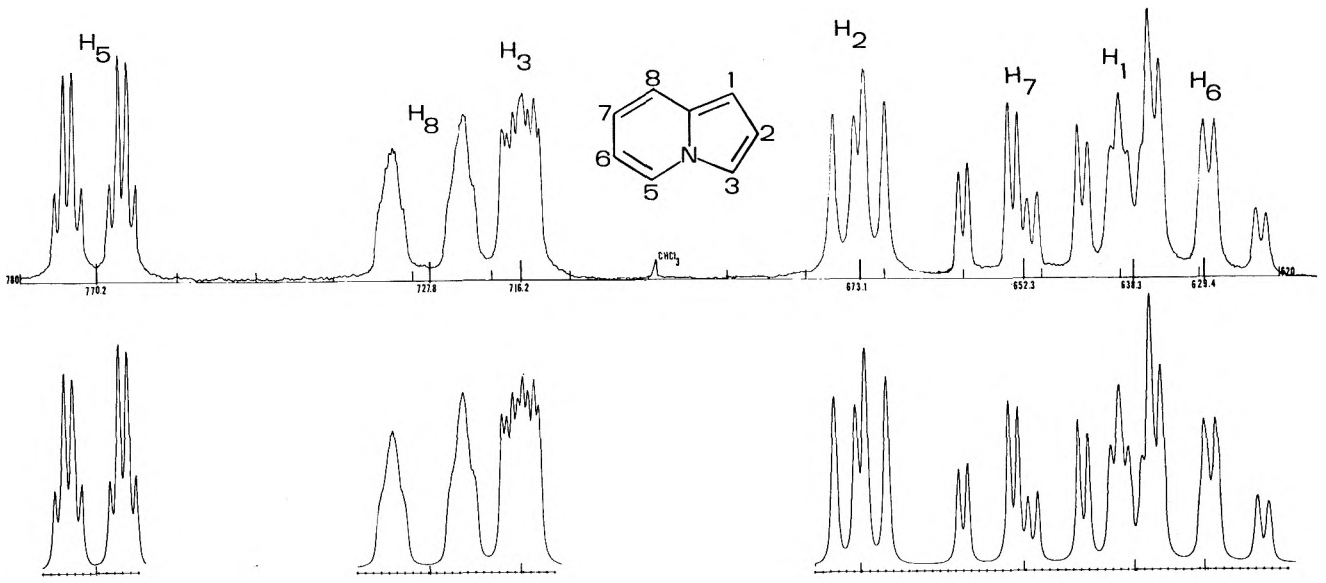
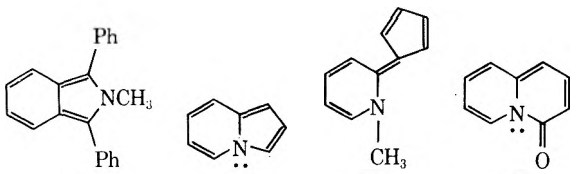


Figure 1.—Experimental (100 MHz) and calculated pmr spectrum of indolizine (as 15% solution in $CDCl_3$). Chemical shifts (Hz) are relative to TMS.

bond *a* from a low of 1.9 Hz (1-methylphosphole) to 3.6 Hz (pyrrole). Large variations can also be observed for the ^4J's and ^5J's for ring systems **1**–**5**.[14b-e] Thus the M center exerts a substantial influence on the J's in compounds **1**–**5**; consequently, these vicinal or long-range pmr J's have only limited utility as a useful probe of structure. Alternatively, there are several isomeric 5,6-fused ring heterocycles known which are electronic homologs of ring skeletons **2** and **3**. In these systems the heteroatom effect upon several J's should be negligible owing to the large number of heteroring bonds separating the coupled protons and heteroatom. We therefore felt that a systematic comparison of pmr J's among several bicyclic and fully unsaturated nitrogen heterocycles would be an attractive starting point in a program to provide a sound basis for attempting to index the extent of long pair–trigonal carbon interaction. In this regard we describe below data obtained from pmr analyses of 1,3-diphenyl-2-methylisoindole (**8a**), indolizine (**9**), 1-methyl-2-cyclopentadienylidene-1,2-dihydropyridine (**10**), and 4-quinolizone (**11**).



8a **9** **10** **11**

Spectral Analyses.—Pmr coupling constant data for indolizine (**9**) was first reported by Black, *et al.*, some years ago.[15] The protons of **9** are representative of an ABCDEFG type spin system with a maximum of 21 coupling constants, and obtaining an accurate solution for such a complex spin system tests the limits of most of the available iterative computer programs. In order to simplify the analysis of this specta, Black approximated nine of the long-range J's as being equal to zero; however, there are examples in the literature which demonstrate that significant errors can be present in ^3J's derived from analyses in which certain long-range couplings are arbitrarily ignored.[13a,16] Our 100-MHz pmr experimental spectrum of indolizine is shown in Figure 1. By treating it as a closely coupled seven-spin system we were successful in obtaining an acceptable fit of the computer-generated spectrum and the experimental, following several trial calculations and a final iterative run in which 456 transitions were assigned. It should be noted that only one of the possible 21 couplings is equal to zero (Table I).

The pmr spectrum of the interesting amide 4-quinolizone (**11**) (see paragraph at end of paper regarding supplementary material) was also treated as a closely coupled seven-spin system and 472 transitions were assigned in the final iterative run. Treatment of the spectrum of isoindole **8a** as an AA'BB' spin system gave a computer-generated spectra which was an exact fit of the experimental. Although pmr J's had been previously published for **10**, inspection of these data revealed that the ^4J for the nitrogen ring had been assumed to be zero.[17] The results of our analyses of the pmr J's for this compound are given in Table I.

Discussion

Before attempting to evaluate the trends exhibited by the pmr J's (Table I) obtained for the nitrogen heterocycles described in the previous section, it is necessary to briefly summarize several simultaneously operating effects. The major influences upon the pmr J's of vinyl H's in unsaturated ring systems can be ascribed to variations in (a) electron delocalization (even though $^3J_{total}$ can be approximately partitioned in terms of $^3J_\sigma$ and $^3J_\pi$, it has been shown by several groups that good linear correlations can be drawn between changes in ^3J and C–C bond length);[16b,18] (b) H–H dihedral

(15) P. J. Black, M. L. Heffernan, L. M. Jackman, Q. N. Porter, and G. R. Underwood, *Aust. J. Chem.*, **17**, 1128 (1964).

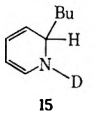
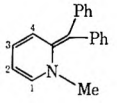
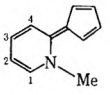
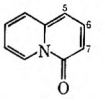
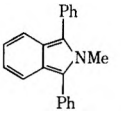
(16) (a) R. E. Rondeau, H. M. Rosenberg, and D. J. Dunbar, *J. Mol. Spectrosc.*, **26**, 139 (1968); (b) M. A. Cooper and S. L. Manatt, *J. Amer. Chem. Soc.*, **91**, 6325 (1969).

(17) J. H. Crabtree and D. J. Bertelli, *J. Amer. Chem. Soc.*, **89**, 5384 (1967).

(18) (a) D. J. Bertelli and P. Crews, *Tetrahedron*, **26**, 4717 (1970); (b) J. B. Pawliczek and H. Gunther, *ibid.*, **26**, 1755 (1970).

TABLE I

EXPERIMENTAL PMR COUPLING CONSTANTS[a]

$J_{H,H}$	 15	 16	 10	 9	 11	 8a		
1,2	7.11	7.00	6.74 (6.50)	7.06	7.36	8.63	4.86	4.84
1,3	1.39	1.64	1.47 (1.60)	1.07	1.30	0.98	1.85	1.79
1,4	0.89	0.76	0.76 (0)	1.21	0.97	1.02	0.98	1.00
2,3	5.40	5.96	6.61 (6.50)	6.45	6.50	6.39	7.66	7.62
2,4	1.27	1.44	1.43 (1.50)	1.30	1.52	0.98	1.36	1.45
3,4	9.80	9.72	9.27 (9.30)	9.07	8.91	8.63	7.66	7.62
5,6				3.93	7.47			
5,7				1.39[d]	1.27			
6,7				2.70	8.75			
1,5				±0.95	±0.98			
1,6				±0.10	−0.30			
1,7				±0.15	±0.17			
2,5				±0.20	±0.34			
2,6				±0.32	±0.09			
2,7				±0.25	±0.10			
3,5				±0.14	±0.19			
3,6				±0.21	±0.16			
3,7				0.00	±0.17			
4,5				±0.35	±0.22			
4,6				±0.21	±0.18			
4,7				±0.68	±0.32			
Ref	*e*	This work[c]	This work, *f*	This work[b]	This work[c]	This work[c]	*g*	

[a] J's are in hertz. [b] Experimental proton chemical shifts (in hertz) are in Figure 1. [c] Chemical shifts (hertz) relative to TMS: **8a**, $\nu_{1,4}$ = 757.8, $\nu_{2,3}$ = 693.2; **16**, ν_1 = 645.9, ν_2 = 541.1, ν_3 = 610.6, ν_4 = 676.9; and **11**, ν_1 = 903.5, ν_2 = 692.8, ν_3 = 725.8, ν_4 = 740.3, ν_5 = 657.7, ν_6 = 759.0, ν_7 = 655.7. [d] The relative sign could not be determined (see Experimental Section) but a + sign is preferred based upon calculations: M. Bacon and G. E. Maciel, *Mol. Phys.*, 21, 257 (1971). [e] G. Fraenkel and J. C. Cooper, *Tetrahedron Lett.*, 1825 (1968). [f] J. H. Crabtree and D. J. Bertelli, *J. Amer. Chem. Soc.*, 89, 5384 (1967). [g] S. Castellano, C. Sun, and R. Kostelnik, *J. Chem. Phys.*, 46, 327 (1967); J. B. Merry and J. H. Goldstein, *J. Amer. Chem. Soc.*, 88, 5560 (1966).

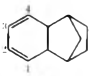
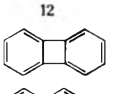
angles[19] (both ^3J and ^4J are directly sensitive to such angle changes, and ^3J follows a Karplus-type function, across sp^2–sp^2 single bonds while ^4J passes from positive to negative in sign as the angle H–CCC–H increases);[14a] (c) ring strain (using benzenoids as models, increasing ring strain affects ^3J couplings in a random way, ^4J decreases, and ^5J increases);[20] and (d) ring size (*i.e.*, changes in angle HCC).[21]

Since we wish to capitalize upon the sensitivity of J_{vic} to variations of bond or electron delocalization in our analysis of fused-ring nitrogen heterocycles, it is imperative that only this parameter change over a related series of compounds. To illustrate how some of these above-mentioned factors can be easily recognized, the pmr J's for several planar, unsaturated six-membered rings have been collected in Table II. To facilitate our discussion of the trends in the tabulated vicinal couplings we include the computed average and ratio of the ^3J's across adjacent bonds. The data for the unsaturated C-6 rings of Table II will be briefly discussed below in order to specifically illustrate how J_{av} and J_{ratio} can provide a convenient assay of variations in a–d and also to point out their limitations in this end.

In principle the invarance of parameter $J_{av} = {}^1/_2 \cdot (J_{23} + J_{24})$ for a series of related polyenes reflects that

TABLE II

PROTON COUPLINGS FOR VINYL H'S OF PLANAR SIX-MEMBERED RINGS

Compd	J_{23}	J_{34}	J_{24}	Ref	$J_{av} = 0.5 (J_{23} + J_{34})$	$J_{ratio} = J_{23}/J_{34}$
 12	5.47	9.69	0.99	13a	7.58	0.56
	8.23	6.89	1.00	20	7.56	0.84[a]
	8.83	8.30	1.20	16b	7.57	0.92
	7.54	7.54	1.37	*b*	7.54	1.00

[a] $(J_{23}/J_{34})^{-1}$. [b] J. M. Read, R. E. Mayo, and J. H. Goldstein, *J. Mol. Spectrosc.*, 22, 419 (1967).

factors b–d remain constant, whereas the invariance of $J_{ratio} = J_{23}/J_{24}$ reflects that factors a–d are constant. The similarity of J_{av} [$= {}^1/_2(J_{23} + J_{34}) = 7.57 \pm 0.03$ Hz] for the compounds in Table II reflects that each of the unsaturated C-6 rings have a planar conformation with approximately the same component of ring strain. Moreover, the average of the bond lengths across the two adjacent olefinic bonds can be assumed to be approximately identical. That the term J_{av} is specifically sensitive to variation in b and c can be shown by the J_{av} = 7.25 and 6.24 Hz, respectively, for 1,3-cyclohexadiene[13a] and benzocyclopropene (**13**).[20] In 1,3-cyclohexadiene the H_2–H_3 dihedral angle is known to be

(19) (a) S. Sternhell, *Quart Rev., Chem. Soc.*, **23**, 236 (1969); (b) M. Bacon and G. E. Maciel, *Mol. Phys.*, **21**, 257 (1971).

(20) M. A. Cooper and S. L. Manatt, *J. Amer. Chem. Soc.*, **92**, 1605 (1970).

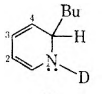
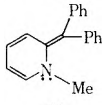
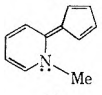
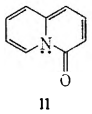
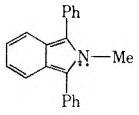
(21) O. L. Chapman, *J. Amer. Chem. Soc.*, **85**, 2014 (1963); G. V. Smith and H. Kriloff, *ibid.*, **85**, 2016 (1963); P. Laszlo and P. v. R. Schleyer, *ibid.*, **85**, 2017 (1963).

18°[22] and **13** has been concluded to exhibit extreme ring strain as evidenced by the unusually small $^4J_{24}$ = 0.33 Hz.[20] It has, however, been pointed out that ^3J's may not vary in a predictable fashion as the component of ring strain changes;[20] therefore, to fully assess variation in this term (*i.e.*, c) it is evident that both the J_{av} and $^4J_{HH}$ values must be monitored. Tricyclic undecadiene **14**, which can be assumed to have a planar diene conformation, represents a particularly dramatic example in which J_{av} = 7.60 Hz is almost identical with that observed in Table II, whereas the diminished $^4J_{24}$ = 0.58 Hz indicates that the diene ring is moderately strained.[23] Turning to J_{ratio} (J_{23}/J_{34}), the regular increase in this parameter from 0.56 to 1.0 in progressing down Table II directly reflects the convergence of the adjacent bond lengths from fully bond alternant in tricyclo[4.4.1.0]undecadiene (**12**) to delocalized in benzene.[24]

In order to utilize J_{ratio} as an index of electron delocalization for the fused-ring nitrogen compounds one must first have estimates of this parameter for the two limiting heterocyclic structural types. Pmr J's for the vinyl H's of 2-*n*-butyl-1,2-dihydropyridine-d_1 (**15**) are known[25] (Table I), and comparison of these data with those from tricycloundecadiene (**12**, Table II) shows that ^3J's (J_{23} and J_{34}), J_{av}, and J_{ratio} (Tables II and III)

TABLE III

PMR J'S FOR VINYL HYDROGENS

Compd	Ref	J_{24}	J_{av} = $(J_{23} + J_{34})/2$	J_{ratio} = J_{23}/J_{34}
 15	25	1.27	7.60	0.55
 16		1.44	7.84	0.61
 10		1.43	7.94	0.71
 9		1.30	7.76	0.71
 11		1.52	7.71	0.73
 8a		0.98	7.51	0.74
	*a*	1.37 1.45	7.66 7.62	1.0

[a] S. Castellano, C. Sun, and R. Kostelnik, *J. Chem. Phys.*, **46**, 327 (1967); J. B. Merry and J. H. Goldstein, *J. Amer. Chem. Soc.*, **88**, 5560 (1966).

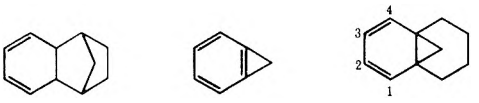
(22) H. Oberhammer and S. H. Bauer, *J. Amer. Chem. Soc.*, **91**, 10 (1969); S. S. Butcher, *J. Chem. Phys.*, **42**, 1830 (1965).

(23) Computed J_{av} and J_{24} from couplings reported by H. Gunther and H. H. Hinrichs, *Tetrahedron Lett.*, 787 (1966).

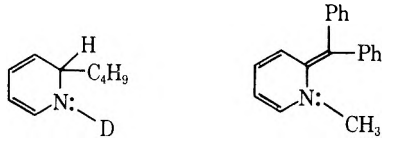
(24) Gunther has previously proposed J_{ratio} as a qualitative index of π-bond delocalization: H. Gunther, *Tetrahedron Lett.*, 2967 (1967).

(25) G. Fraenkel and J. C. Cooper, *Tetrahedron Lett.*, 1825 (1968).

are, within experimental error, identical. The large variation in J_{12} of 1.6 Hz between **12** and **15** and the difference in their $^4J_{24}$'s of 0.4 Hz can be ascribed to the substituent effect of nitrogen.[26] Models show the diene carbons of **12** to be entirely coplanar, and the similarity of J_{av} and J_{24} (corrected for the N substituent) between **12** and **15** implies near coplanarity of the diene array in the latter. The coincidence of J_{ratio} for these two compounds indicates that dihydropyridine **15** displays pmr J's characteristic of an approximately planar olefin–nitrogen chromophore in which the lone pair is entirely localized at nitrogen. As might be anticipated, the J_{av} term computed for pyridine (Table III) is essentially identical with that of **15**, and the pmr J's of pyridine provide values to be expected for complete delocalization. To further test the sensitivity of J_{ratio} and J_{av} to substitution upon the dihydropyridine ring nucleus we prepared 1-methyl-1,2-dihydro-2-diphenylmethylidinepyridine (**16**). By



12 **13** **14**



15 **16**

matching a computer-generated spectrum to the 100-MHz pmr spectrum of the vinyl H's of **16** we obtained the J's reported in Table I (see paragraph at end of paper regarding supplementary material). The computed J_{av} = 7.84 and $^4J_{24}$ = 1.4 Hz for **16** (Table III) are quite similar to the corresponding values of J_{av} = 7.60 and $^4J_{24}$ = 1.3 Hz for dihydropyridine **15**. The very slight increase of J_{ratio} = 0.61 for the former *vs.* J_{ratio} = 0.55 for the latter indicates that only a minor interaction of the nitrogen lone pair with the carbon p orbitals results when the length of the adjacent olefinic chromophore is significantly increased. In contrast, replacement of the diphenylmethilidine function by a fulvene group on the *N*-methyldihydropyridine ring system, *i.e.*, **16** → **10**, causes a significant increase in the parameter J_{ratio} to 0.71, while J_{av} (7.84 *vs.* 7.94) and $^4J_{24}$ (1.4 *vs.* 1.4 Hz) are essentially invariable.

Additional changes in the architecture of the dihydropyridine skeleton are embodied in indolizine (**9**) and 4-quinolizone (**11**). Scrutiny of the data summarized in Table III shows that for compounds **10**, **9**, and **11** each of the parameters J_{av} (7.94, 7.76, 7.71 Hz), J_{24}

(26) Based on pmr J's of benzene[27] *vs.* pyridine[28] and naphthalene[16b] *vs.* quinoline,[29] the nitrogen substituent effect upon ^3J is almost negligible at the β–γ bond [^3J (benzene) = 7.54 Hz *vs.* $^3J_{34}$ (pyridine) = 7.66 Hz, and $^3J_{34}$ (naphthalene) = 8.30 Hz *vs.* $^3J_{34}$ (quinoline) = 8.3 Hz], but $^4J_{24}$ is slightly increased [^4J (benzene) = 1.37 Hz and $^4J_{24}$ (pyridine) = 1.37 or 1.45 Hz)]. It is also noteworthy that the relative input of $^4J_\pi$ (− sign) and $^4J_\sigma$ (+ sign)[13a] upon $^4J_{total}$ appears to be slightly changed upon going from a diene to a fully delocalized system, as evidenced by $^4J_{24}$ = 0.99 Hz for **12** increasing to $^4J_{24}$ = 1.37 Hz for benzene and $^4J_{24}$ = 1.27 Hz for **15** increasing to $^4J_{24}$ = 1.37 or 1.45 Hz for pyridine.

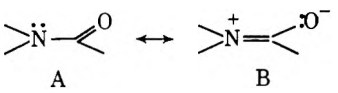
(27) J. M. Read, R. E. Mayo, and J. H. Goldstein, *J. Mol. Spectrosc.*, **22**, 419 (1967).

(28) S. Castellano, C. Sun, and R. Kostelnik, *J. Chem. Phys.*, **46**, 327 (1967); J. B. Merry and J. H. Goldstein, *J. Amer. Chem. Soc.*, **88**, 5560 (1966).

(29) P. J. Black and M. L. Heffernan, *Aust. J. Chem.*, **17**, 558 (1964).

(1.4, 1.3, and 1.5 Hz), and J_{ratio} (0.71, 0.71, and 0.73) are almost identical. A similar coincidence in these respective data is also observable for isoindole **8a** ($^4J_{24}$ corrected for an adjacent nitrogen substituent effect). Thus, an overall view of the data of Table III in terms of J_{ratio} reveals three catagories of nitrogen heterocycles **8a**, **9**, **10**, and **11** which are bordered on one side by dihydropyridines **15** and **16** and by pyridine on the other.

As a first approximation quinolizone (**11**) can be considered to be an extended vinylogous amide. In simple amides dynamic magnetic resonance studies have revealed a barrier of 20 kcal/mol for rotation about the C–N bond,[30] which is consistent with Pauling's conclusion that charged resonance structures such as B, representing total N lone pair delocalization, contribute 40% to the ground state.[31]



A B

The ground-state structure of quinolizone (**11**) can be expressed in similar terms with the aid of the J_{ratio}. In Table III descending from dihydropyridine **15** the J_{ratio} for **11** has progressed *ca.* 40% of the distance toward a value of unity, which implies that the extent of delocalization of the nitrogen lone pair in a simple amide is not further increased when it is inserted into a cyclooctetraene-type chromophore to give quinolizone (**11**). Similarly, isoindole (**8**) and indolizine (**9**) can be viewed, based on their respective J_{ratio} values, as having a magnitude of N lone pair delocalization which is nearly identical with that of quinolizone. The electronic structure of cyclopentdienylidenedihydropyridine (**10**) has been discussed previously. On the basis of its observed and calculated dipole moment[3c] and measured C–N rotational barrier from dnmr experiments[17] charge-separated structures have been envisioned as making approximately a 30% contribution to the structure of **10**. It is satisfying to note that our pmr J data suggest an entirely similar conclusion for this molecule in that J_{ratio} has progressed *ca.* 35% toward the limiting value of unity.

Thus, it appears that the measurement of pmr J's for unsaturated heterocycles, wherein the effects of the heteroatom upon J are minimal, can provide a rapid, semiquantitative method for evaluation of the influence of the heteroatom lone pair on their electronic constitution. We feel that this method has distinct advantages over the more classical methods involving interpretation of dipole moments or barriers of dynamic behavior, and we are currently expanding this approach to the further study of second and higher row unsaturated heterocycles.

Experimental Section

The nmr spectra were determined on a Jeol PS-100 spectrometer (100 MHz), and computer analyses were performed with the aid of iterative least-squares programs, LAOCN 3 or NMRIT[32] on spectra recorded at 54 Hz sweep width. An experimental coupling constant error is estimated at ±0.1 Hz based upon our ability to detect significant changes in the computed spectra as a function of different imput values. The relative signs of the coupling constants were assumed to be positive for dihydropyridines **10** and **16** and for isoindole **8a** based upon analogy to the known relative signs in other unsaturated six-membered rings[13,20,28] and upon the good agreement between the calculated and experimental spectra. The proton chemical shifts of the multiplets in the indolizine (**9**) spectra were solvent sensitive, but they did not show a large downfield shift in the presence of Eu(thd)$_3$. Exact chemical shift assignments were derived by inspection of the 15% $CDCl_3$ spectrum in which H's 2, 5, 6, 7, and 8 (Figure 1) were assignable entirely on first-order coupling considerations. The assignment[33] of H_1 (*vs.* H_3) at δ 6.38 was suggested by double irradiation at H_8 (δ 7.27) and this assignment was confirmed by trial and error computer runs. Relative to the experimental the computed spectra were quite sensitive to alterations in long-range J's. For example, switching[33] J_{25} and J_{26} resulted in unacceptable changes in the multiplet shapes of H_5 and H_6, and a switch of the ^4J couplings among H's 1, 3, 5, and 8 in that $J_{15} \rightarrow J_{35}$, $J_{18} \rightarrow J_{15}$, $J_{35} \rightarrow J_{38}$, and $J_{38} \rightarrow J_{18}$ caused perceptible deterioration of the multiplets associated with H_1, H_3, H_5, and H_8. In contrast, systematic variation of the relative signs of all of the cross-ring couplings and intraring coupling J_{13} produced essentially no variation in the appearance of the multiplet sets. The relative signs for the remaining intraring long-range couplings for **9** were derived by trial and error input of both plus and minus values. The multiplet structure of the 4-quinolizone (**11**) spectra showed with only one exception (J_{16}) insensitivity to variation in the relative signs of the cross-ring coupling constants. The signs of the intraring couplings for **11** were derived by input of both possible signs.

The compounds analyzed in this work, 2-methyl-1,2-dihydro-2-diphenylmethilidinepyridine (**16**),[34] 1-methyl-2-cyclopentadienylidene-1,2-dihydropyridine (**10**),[35] indolizine (**9**),[36] 4-quinolizone (**11**),[37] and isolindole (**8a**),[10a] were prepared according to literature methods.

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Registry No.—**8a**, 4276-24-8; **9**, 274-40-8; **10**, 704-20-1; **11**, 491-42-9; **15**, 20180-26-1; **16**, 1916-50-3.

Supplementary Material Available.—The 100-MHz pmr sectrum for quinolizone (**11**) and for the vinyl H's of 1-methyl-1,2-dihydro-2-diphenylmethylidene pyridine (**16**) along with their respective computer-generated spectrum will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 20× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N. W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code numbers JOC-73-4391.

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(31) L. Pauling, "The Nature of the Chemical Bond," 3rd ed, Cornell University Press, Ithaca, N. Y., 1960, pp 281–282.

(32) These programs are described in D. F. Detar, Ed., "Computer Programs for Chemistry," Vol. I. W. A. Benjamin, New York, N. Y., 1968.

(33) Numbering system of Figure 1.

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(35) J. A. Berson, E. M. Evleth, and Z. Hamlet, *J. Amer. Chem. Soc.*, **87**, 2887 (1965).

(36) V. Boekelheide and R. J. Windgassen, Jr., *J. Amer. Chem. Soc.*, **81**, 1456 (1959).

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Nucleophilic and Bifunctional Catalysis. Mechanism, Reactivity, and Transition-State Structure in the Hydrolysis of 2-Chloro-4-isopropylamino-6-cyclopropylamino-*s*-triazine by *N*-Hydroxysuccinimide and 1-Hydroxy-2-piperidone

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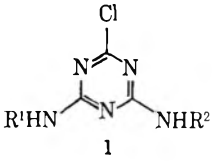
The hydrolysis in water at 70° of the herbicide 2-chloro-4-isopropylamino-6-cyclopropylamino-*s*-triazine (Cyprazine) is nucleophilically catalyzed by *N*-hydroxysuccinimide and 1-hydroxy-2-piperidone, which are models for natural plant resistance factors. *N*-Hydroxysuccimimide ($pK_a \sim 6$), which is more acidic than the transition state for its attack on the triazine nucleus ($pK_a \sim 7$), is 10-fold more nucleophilically reactive than its conjugate base, while 1-hydroxy-2-piperidone ($pK_a \sim 9$), which is less acidic than the transition state, is 25-fold less reactive than its conjugate base, in agreement with a general rule. Structural analysis of the transition states shows that the reduced acidity results from a bifunctional catalytic proton bridge in a reactant-like transition state. Application of the findings to the *in vivo* action of the corn-plant resistance factor demonstrates that the mechanism is adequate to describe the biological detoxification of the herbicide.

The ability of resistant plants to metabolize and detoxify 2-chlorobis(alkylamino)-*s*-triazine (1) herbi-



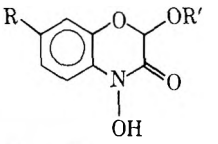
1

Compd	R^1	R^2
a, Simazine	C_2H_5	C_2H_5
b, Atrazine	i-C_3H_7	C_2H_5
c, Cyprazine	i-C_3H_7	-CH(CH$_2$)CH$_2$

cides is now considered to be the basis for the selectivity of this class of herbicides rather than the degree of absorption of the herbicide by resistant plants or selective interference with certain biochemical processes by the herbicides in susceptible plants.[1-3] Three metabolic pathways for **1** are now known to exist, with the major pathway found in corn being dechlorination to give the 2-hydroxy analogs, which are relatively nonphytotoxic.[4-7]

The compound which is responsible for this metabolic inactivation reaction was isolated and identified as a benzoxazinone hydroxamic acid (**2**) which occurs as the glucoside.[8-12]

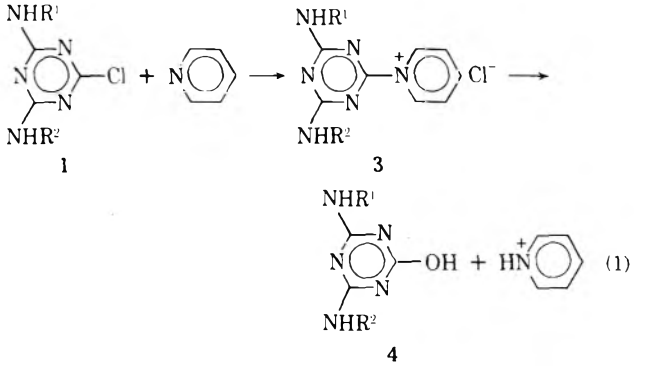
The dechlorination reaction caused by this cyclic hydroxamic acid has also been demonstrated to occur *in vitro*.[5,13] In resistant crops such as sorghum[6,14] and



2a, R = R′ = H
b, R = CH_3O; R′ = H
c, R = CH_3O; R′ = glucose

pea plants,[15,16] which do not contain the hydroxamic acid **2**, an N-dealkylation pathway has been shown to be responsible for the resistance to the chlorotriazine herbicides. Another metabolic pathway which has recently been reported is the formation of a glutathione conjugate of the triazine herbicide in the sorghum plant.[17]

Although evidence exists regarding the detoxification of the chlorotriazines (**1**) by the cyclic hydroxamic acids, **2a** and **2b**, studies concerning the mechanism of this process are very limited. Castelfranco and Brown[18] screened many nucleophilic agents for their ability to react with Simazine (**1a**) but found that only pyridine and hydroxylamine were effective. They suggested that nucleophilic attack occurred at carbon 2. The resulting intermediate **3** may undergo hydrolysis to give the 2-hydroxytriazine, **4** (eq 1). Tipton



1 3 4 (1)

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(2) M. L. Montgomery and V. H. Freed, *J. Agr. Food Chem.*, **12**, 11 (1964).
(3) R. H. Shimabukuro and H. R. Swanson, *J. Agr. Food Chem.*, **17**, 199 (1969).
(4) P. Castelfranco, C. P. Foy, and D. B. Deutch, *Weeds*, **9**, 580 (1961).
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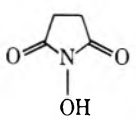
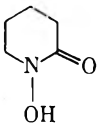
(18) P. Castelfranco and M. S. Brown, *Weeds*, **10**, 131 (1962).

and coworkers[19] have recently studied the reaction of Simazine with the hydroxamic acid **2b** and suggested that a molecular aggregate of **2b** may catalyze the reaction.

Since the reaction of the chlorotriazines **1** and the natural detoxifying agents **2** is slow[13] and **2** is unstable in hydroxylic solvents,[10,20,21] we decided to examine the reaction of 2-chloro-4-isopropylamino-6-cyclopropylamino-*s*-triazine (Cyprazine, **1c**) with more stable hydroxamic acids. The two cyclic hydroxamic acids which were selected as models for the natural system **2** were *N*-hydroxysuccinimide (**5**) and 1-hydroxy-2-piperidone (**6**). The absence of strong chromophores



5



6

in **5** and **6** permitted us to obtain detailed kinetic data by ultraviolet spectrophotometry.

Results

***N*-Hydroxysuccinimide-Catalyzed Hydrolysis of Cyprazine.**—The ultraviolet absorption change with time during the reaction of Cyprazine (**1c**, 3.0×10^{-4} *M*) with *N*-hydroxysuccinimide (**5**) (20.0×10^{-4} *M*) at 70° in water containing 2% methanol is presented in Figure 1. The initial absence of isosbestic points shows that an intermediate (λ_{max} ~260 nm) accumulates during the first 2 hr. It then proceeds over a longer period to 2-hydroxy-4-isopropylamino-6-cyclopropylamino-*s*-triazine (**4**), to which the final spectrum corresponds exactly. If **4** arises from hydrolysis of an intermediate generated by reaction of Cyprazine and **5**, it should be isolable from their reaction in a nonaqueous medium. In fact, the product of the reaction in acetonitrile has λ_{max} 258 nm and a spectrum which resembles the 2-hr spectrum in Figure 1 (where the maximum at 258 nm can be seen as a shoulder) so that the isosbestic points observed after 2 hr at 228 and 255 nm corresponds to conversion of this compound to **4**.

Neither the intermediate compound **7** nor the product **4** nor *N*-hydroxysuccinimide (**5**) absorb at wavelengths beyond 280 nm, so that the decrease in absorbance at 285 or 290 nm gives a direct measure of the rate of disappearance of **1c**. Similarly, the increase in absorbance at 243 nm is specific for appearance of **4**. First-order plots of the data at 285 or 290 nm are linear with slopes independent of the initial concentration of reactant **1c**. The first-order rate constants, k_1' (Table I), are proportional to the concentration of *N*-hydroxysuccinimide (present in 6.7-fold to 27-fold excess) in both water and 0.1 *M* acetate buffer (pH 3.94) and are unaltered by the buffer at this pH. A plot of k_1' *vs.* concentration of **5** yields a second-order rate constant k_1 of 480 M^{-1} hr^{-1} at 70°.

First-order plots of the data at 243 nm show an initial lag time of 1–4 hr (depending on the concentration of **5**), followed by good first-order behavior. The first-order rate constant (Table I) is independent of the concentration of **1c**, **5**, and acetate buffer at pH 3.94, and is identical with that obtained in separate experiments for hydrolysis of the intermediate **7** to **4** and **5** under the same conditions.

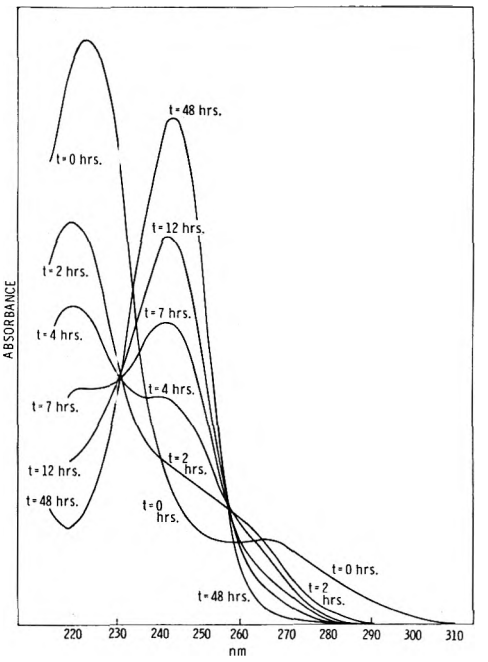


Figure 1.—Ultraviolet absorption as a function of time during the reaction of Cyprazine (**1c**, 3×10^{-4} *M*) with *N*-hydroxysuccinimide (**5**, 2×10^{-3} *M*) at 70° in water containing 2% methanol.

TABLE I

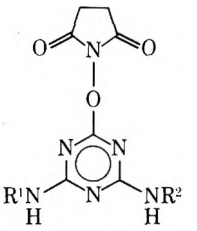
FIRST-ORDER RATE CONSTANTS IN THE REACTION OF CYPRAZINE (**1c**) WITH *N*-HYDROXYSUCCINIMIDE (**5**) IN WATER (1% METHANOL) AT 70°

10^4[**1c**], *M*	10^3[**5**], *M*	Buffer	k_1', hr^{-1}	k_2, hr^{-1}
1.50	1.00	None	0.444	0.130
1.50	2.00	None	0.820	
1.50	3.00	None	1.20	
3.0	4.00	None	2.01	0.126
1.50	2.00	Acetate[a]	0.94	0.128
1.50	3.00	Acetate[a]	1.50	
1.50	4.00	Acetate[a]	1.88	
1.50	0.00	Acetate[a]	0.023	

[a] Acetate buffer composed of 0.084 *M* acetic acid, 0.016 *M* sodium acetate (pH 3.9 at 70°), μ = 0.5 with added potassium chloride.

These data thus indicate a second-order reaction of Cyprazine with *N*-hydroxysuccinimide to form an intermediate **7**, which slowly hydrolyzes to **4** with regeneration of **5**. *N*-Hydroxysuccinimide is therefore a catalyst for the hydrolysis of Cyprazine.

Structure of the Intermediate 7.—The product **7** of the reaction of Cyprazine and *N*-hydroxysuccinimide



7

(19) C. L. Tipton, R. R. Husted, and F. H. C. Tsao, *J. Agr. Food Chem.*, **19**, 484 (1971).

(20) J. B-Son Brendenberg, E. Honkanen, and A. I. Virtanen, *Acta Chem. Scand.*, **16**, 135 (1962).

(21) M. D. Corbett, Ph.D. Thesis, University of Kansas, 1970.

in acetonitrile is a monohydrochloride (silver nitrate, titration with 0.1 N NaOH) with a pK_a of 2.07 at 26° (*vs.* 1.6 for **1c**). It hydrolyzes to **4** and N-hydroxysuccinimide in water, as shown by thin layer chromatography. The nmr spectrum of the salt in $CDCl_3$ indicates the absence of a free OH group. These results and the analytical data are all consistent with the product **7** [R^1 = i-C_3H_7, R^2 = $CH(CH_2)_2$] from nucleophilic attack by the oxygen on **1c**.

Effect of pH.—The rate of attack of N-hydroxysuccinimide (**5**) on Cyprazine (**1c**) is independent of buffer concentration but varies with pH as shown in Table II. If the fall-off at higher pH is assumed to result

TABLE II

pH DEPENDENCE OF RATE CONSTANTS IN THE REACTION OF CYPRAZINE (**1c**) WITH N-HYDROXYSUCCINIMIDE (**5**) IN WATER (1% METHANOL) AT 70°

Buffer	[HA], M	[MA], M	pH	10^3 [5], M	k_1', hr^{-1}
CH_3CO_2H–	0.084	0.016	3.94	2.00	0.94
CH_3CO_2Na	0.084	0.016	3.94	0.00	0.023
	0.016	0.084	5.40	2.00	0.73
	0.016	0.084	5.40	0.00	0.002
KH_2PO_4–					
$Na_2HPO_4 \cdot 7H_2O$	0.050	0.050	6.8[a]	2.00	0.21

[a] Measured at 26°.

from ionization of N-hydroxysuccinimide to its conjugate base, then eq 2 should hold where k_{HA}' and k_A'

$$k_1' = k_{HA}'f_{HA} + k_A'(1 - f_{HA}) \quad (2)$$

are the pseudo-first-order rate constants for reaction of the acid and base forms, respectively, and f_{HA} is the fraction of **5** present as acid. Taking the pK_a of **5** as about 6 at 70° (it is 5.95 at 25°), eq 2 is obeyed for the three available points and gives k_{HA}' = 0.9 hr^{-1} and k_A' = 0.08 hr^{-1}. This remarkable result indicates that the neutral form of **5** is ten times more nucleophilic than its conjugate base toward Cyprazine.

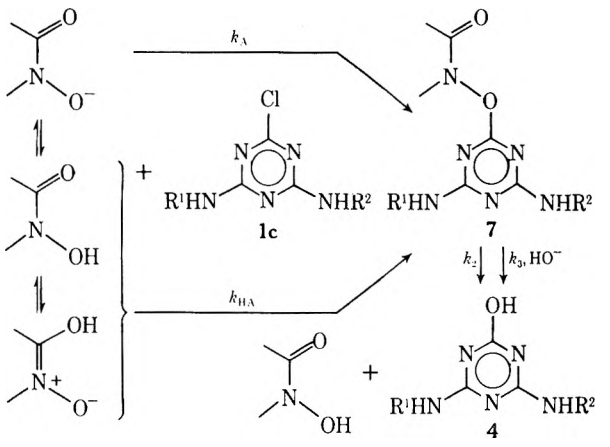
1-Hydroxy-2-piperidone Catalyzed Hydrolysis of Cyprazine.—The time variation of the ultraviolet spectrum in the course of the reaction of 1-hydroxy-2-piperidone (**6**) with Cyprazine is identical in character with that described for the N-hydroxysuccinimide reaction. Analysis of the data at 290 nm yields a rate constant k_1' for disappearance of **1c** at 70° in water of 0.01 hr^{-1} (0.002 M **6**, pH 4.4–6) while k_2 for conversion of the intermediate to **4** is 0.0027 hr^{-1}. At pH 10.0 in 0.1 M carbonate buffer, both rate constants greatly increased, k_1' to 0.25 hr^{-1}, k_2 to about 0.2 hr^{-1}. Thus, contrary to the situation with N-hydroxysuccinimide, nucleophilic attack by **6** on Cyprazine is base catalyzed. If this results from formation of the conjugate base of **6**, this species is about 25 times more reactive than neutral **6**. The increase in k_2 at high pH is indicative of base catalysis in the hydrolysis of **7**.

Activation Parameters.—A rough determination of the rate of the N-hydroxysuccinimide reaction with Cyprazine at 40° yields a rate constant $k_1 \cong 95$ M^{-1} hr^{-1}. Together with the value of 480 M^{-1} hr^{-1} at 70°, this gives the approximate activation parameters $\Delta G_{343}^* = 2.16$ kcal/mol, $\Delta H^* = 11$ kcal/mol, and $\Delta S^* = -31$ gibbs/mol. From these, we estimate $k_1 \cong 37$ M^{-1} hr^{-1} at 25°.

Discussion

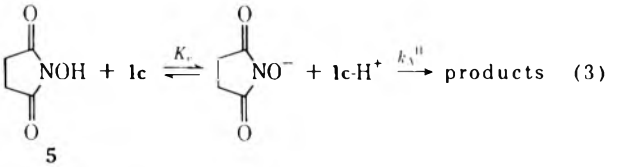
Mechanism.—All data given above are consistent with the mechanism of Scheme I for hydroxamic acid

SCHEME I



catalyzed hydrolysis of Cyprazine. Both the anion and the neutral form of the hydroxamic acid are capable of displacing chloride from the chlorotriazine nucleus to give intermediate **7**. The latter then undergoes acid-, neutral, and base-catalyzed hydrolysis; the mechanistic details of this process will be treated in another report.

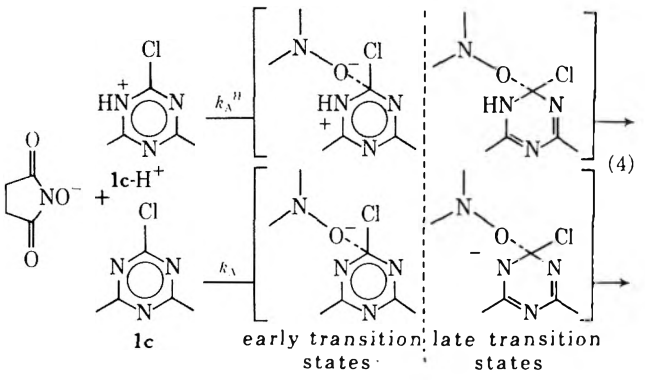
Relative Reactivities of Neutral and Anionic Forms.—One of the notable features of these findings is that the anion of 1-hydroxy-2-piperidone is about 25 times more nucleophilically reactive than its neutral form toward Cyprazine, while the neutral form of N-hydroxysuccinimide is ten times more reactive than its anion. A conventional explanation for the latter kind of observation (greater nucleophilic reactivity of the conjugate acid than the nucleophile itself) is that the rate constant k_{HA} does not reflect direct attack of N-hydroxysuccinimide on **1c** but rather an initial exchange of a proton between the reactants, followed by attack of the anion of N-hydroxysuccinimide on **1c**-H^+ (eq 3). Then the rate



(3)

constant $k_{HA} = K_e k_A^H$ and since $K_e = K_a^5/K_a^{1c\text{-}H}$, $k_{HA} = K_a^5 k_A^H / K_a^{1c\text{-}H}$. It is possible in this case for k_{HA} to exceed k_A, the rate constant for attack of the anion of **5** directly on **1c**, but there is no *a priori* way to tell whether it will or not. It is likely that $k_A^H > k_A$, since protonation of **1c** should activate it toward nucleophilic attack, but the question is whether this activation is sufficient to overcome the effect of the initial unfavorable proton transfer from **5** (p$K_a \sim 6$) to **1c** (p$K_a^{1c\text{-}H} \sim 1.6$). In other words, $k_{HA} \cong 10^{-4.4} k_A^H$ on this model, and unless $k_A^H > 10^{4.4} k_A$, then the conventional wisdom must fail to explain why $k_{HA} > k_A$. In fact, the relative magnitudes of k_A^H and k_A depend on the structure of the transition

state for nucleophilic attack (eq 4). Early transition states resemble the reactants **1c** and **1c**-H^+ strongly, so



that transition-state free-energy differences will be cancelled by reactant-state differences and $k_A^H \sim k_A$. Late transition states greatly favor protonation of the ring nitrogen, so that now k_A^H will tend to become larger than k_A. Transition states for nucleophilic attack on substrates like **1c** are often thought, from the Hammond postulate for example, to have product-like structures because of the instability of the nucleophilic adduct (tetrahedral intermediate, Meisenheimer complex, etc.) relative to reactants. Thus the conventional wisdom may succeed in cases where this prediction is accurate.

However, it is important to notice that it is very difficult to establish or even to test mechanisms of the form of eq 3 for processes of this type. One is attempting to infer the route by which molecules leave the reactant state and travel to the transition state from data which in general refer only to free-energy differences between the initial and final states. It is therefore more desirable to formulate the problem of relative *phenomenological reactivities* of nucleophiles and their conjugate acids (*i.e.*, relative magnitudes of k_A and k_{HA}) in terms which are independent of the route by which reactants reach the transition state. This is particularly true because there are other reasons for greater reactivity of nucleophile conjugate acids than the conventional one reviewed above. We find that the concept of transition-state acidities[22] offers a convenient method for treating the problem.

Scheme II shows the thermodynamic cycle from which the transition-state acidities can be deduced.[22] As in other thermodynamic cycles, the free-energy changes are state functions and no mechanistic knowledge of the route from one state to another is implied by the scheme. In Scheme II, transition state **8** contains one more proton than transition state **9** and the two are therefore a conjugate acid–base pair, connected by the ionization constant K_a^*. The exact position of the proton in **8** is not specified but is discussed below. The ionization constant K_a^* can be calculated from experimental data because Scheme II constitutes a closed thermodynamic cycle; thus $K_a^* = K_a k_A / k_{HA}$, or $pK_a^* = pK_a - \log k_A/k_{HA}$. For *N*-hydroxysuccinimide (R_2 = O in Scheme II), $pK_a \sim 6$ and $k_A/k_{HA} \sim 0.1$ so that $pK_a^* \sim 7$ for **8b**. For 1-hydroxy-2-piperidone (R_2 = H_2 in Scheme II), $pK_a \sim 9$ and $k_A/k_{HA} \sim 25$ so that $pK_a^* = 7.6$ for **8a**.

(22) J. L. Kurz, *Accounts Chem. Res.*, **5**, 1 (1972).

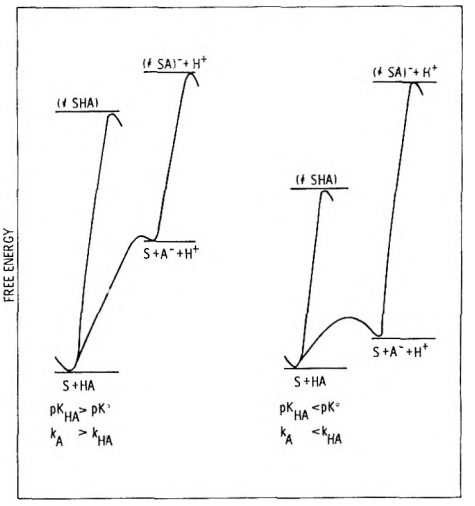
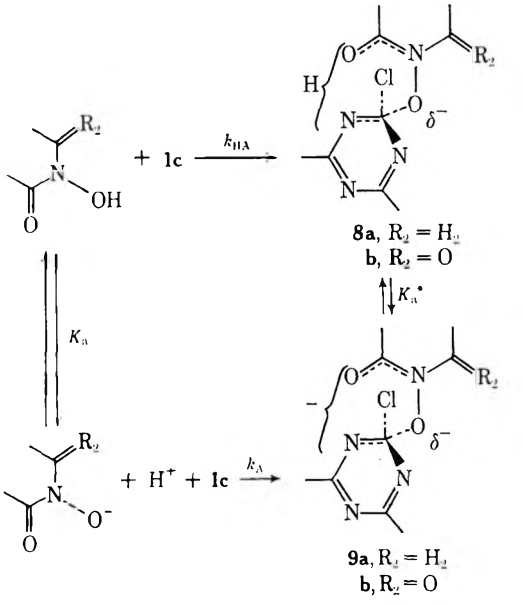


Figure 2.—Free-energy diagram illustrating that nucleophiles which are more acidic than the transition states for their nucelophilic attack ($pK_a < pK_a^*$) are also more reactive than their conjugate bases ($k_{HA} > k_A$) and vice versa.

SCHEME II



The transition states for attack by both neutral nucleophiles are thus about equally acidic, the pK_a^*'s being 7.6 for **8a** and 7 for **8b**. Now *N*-hydroxysuccinimide, with a pK_a of about 6, is a somewhat stronger acid than these transition states, while 1-hydroxy-2-piperidone, with a pK_a of about 9, is a considerably weaker acid than the transition states. As Figure 2 shows schematically, this situation is covered by the following general rule.

Whenever a nucleophile is more acidic than the transition state for its nucleophilic attack, it will be more nucleophilically reactive than its conjugate base; if a nucleophile is less acidic than the transition state for its nucleophilic attack, it will be less reactive nucleophilically than its conjugate base.

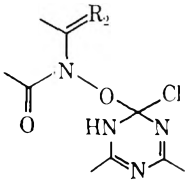
As can be seen from Figure 2, ionization of a relatively weak reactant acid produces a conjugate base closer to its corresponding transition state in free energy and thus more reactive than the conjugate acid. A relatively strong acid, on the other hand, ionizes to a species more

distant in free energy from its transition state and therefore less reactive than its conjugate acid.

Usually transition states for nucleophilic attack by ionizable nucleophiles are stronger acids than the free nucleophile because the proton remains bound to the nucleophilic atom in the transition state. The latter is becoming more positive and thus the proton is more acidic. Then the nucleophilic reactivity of the anion always exceeds that of its conjugate base. Here the opposite is true in the case of *N*-hydroxysuccinimide, for which reasons are considered below.

The correctness of the rule we state above is obvious from the method of calculation of K_a^* (*i.e.*, $k_{HA}/k_A = K_a^*/K_a^{HA}$ so that $k_{HA} > k_A$ only when $K_a^* > K_a^{HA}$) but it is by no means a restatement of this equation or a mere tautology. K_a^* is a good thermodynamic property of the transition state and the molecular structure of the transition state determines its value; thus some transition-state structures can lead to $k_{HA} > k_A$ while others cannot.

What is the factor (or factors) which makes transition state **8** so weakly acidic? One explanation, corresponding to the conventional picture of eq 3 and 4, is that **8** has a structure approaching **11**, which might have a pK_a (for loss of the proton from the ring NH) as large[23] as 12. On this model, the acidity constant of **8**, K_a^*, will vary from $10^{-1.6}$ (when it exactly resembles reactant **1c**-H$^+$) to 10^{-12} (when it exactly resembles **11**).



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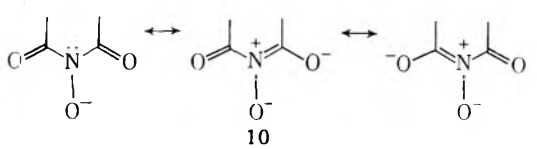
Thus $K_a^* = (10^{-1.6})^{1-x}\,(10^{-12})^x$ where x is an index of transition state structure which varies from 0 (reactant like) to 1 (product like). In fact, if the O–C bond order from nucleophile to ring is a good measure of transition-state structure, as it should be, then the negative charge δ on the nucleophilic oxygen of **8** will vary from $-\delta = -1$ (reactant-like) to $-\delta = 0$ (product-like), so that $\delta = 1 - x$, $1 - \delta = x$. Therefore $K_a^* = (10^{-1.6})^{\delta}\cdot(10^{-12})^{1-\delta}$ and, since $pK_a^* = 7$ for **8a** and 7.6 for **8b**, we obtain $-\delta = -0.5$ (**8a**), $-\delta = -0.4$ (**8b**) *if the conventional model of eq 3–4 is correct.*

Now the conventional model can be tested because the charges δ in **8** and δ' in **9** (Scheme II) of the nucleophilic oxygens can also be inferred in the following independent way. *N*-Hydroxysuccinimide is 10^3 times more acidic than 1-hydroxy-2-piperidone because the additional carbonyl group stabilizes the negative charge in the conjugate base as in **10**. If the two neutral

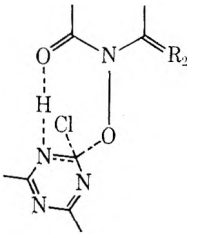


10

nucleophiles were converted into a transition state with a full negative charge on the nucleophilic oyxgen, then the same stabilizing effects should come into play and *N*-hydroxysuccinimide should react 10^3 times faster. Actually the ratio k_{HA} (**5**)/k_{HA} (**6**) is about 90. The usual linear free energy concepts thus suggest that $\delta = \log 90/\log 10^3 \sim 0.7$, *i.e.*, that transition state **8** has a charge $-\delta$ of -0.7 on its nucleophilic oxygen. A similar argument indicates that, if the anionic nucleophiles were converted to a transition state with *zero* negative charge on the nucleophilic oxygen, then the less stable 1-hydroxy-2-piperidone anion should react 10^3 times faster. In fact, it reacts only three times faster, meaning that the charge has decreased only a fraction $\log 3/\log 10^3$ or about 0.2 of the way from one to zero. That is, $-\delta' = -(1 - 0.2) = -0.8$ in **9**, about the same as $-\delta = -0.7$ in **8**. The large quantity of charge still on this oxygen shows that the bond to the triazine ring is only slightly (20–30%) formed in both **8** and **9**.

Returning now to the conventional model discussed above, we notice that only if $-\delta$ were as small as -0.4 in **8b** (transition state C–O bond about 60% formed) would the NH bond be sufficiently lacking in acidity in **8b** to permit $k_{HA} > k_A$. Since the independent measure of δ just made shows that $-\delta$ is actually about -0.7 in **8** (transition state C–O bond only 30% formed), the conventional model does not account for the findings.

We conclude that the transition state for nucleophilic attack on **1c** is an early one, so early that *N*-hydroxysuccinimide would react more slowly than its conjugate base, *even by prior proton transfer*, unless some special interaction were present to stabilize the proton of **8** and render it less acidic.[24] The most reasonable interaction is a bridging of the proton between O and N as in **12**, a form of bifunctional catalysis in which one function performs a protolytic role, the other a nucleophilic role.



Application to the *in Vivo* Action of the Natural Resistance Factor.—The natural detoxifying agent present in corn, **2b**, has a pK_a of 6.4 at room temperature. Assuming that the transition-state acidities are related to the hydroxamic acid acidities by a linear free energy equation, and knowing that the transition states for the reaction of *N*-hydroxysuccinimide ($pK_a = 6$) and 1-hydroxy-2-piperidone ($pK_a = 9$) have pK_a's of 7 and 7.6, respectively, we estimate that $pK_a^* = 7.1$ for **2b**. This is turn tells us that (since $pK_a < pK_a^*$) the neutral form of **2b** should be more reactive than its anion; in fact $k_{HA}/k_A \sim 5$ ($= K_a/K_a^*$). From the separate linear free energy relations for k_A *vs.* K_a and k_{HA} *vs.* K_a, we obtain that k_{HA} for **2b** is about 1.8-fold smaller than k_{HA} for *N*-hydroxysuccinimide while k_A is about 1.1-fold larger than k_A for *N*-hydroxysuccini-

(23) This estimate is based on analogies tabulated by G. Kortum, W. Vogel, and K. Andrussow, "Dissociation Constants of Organic Acids in Aqueous Solution," Butterworths, London, 1961, by A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases," Methuen, London, 1962, and by G. Yagil, *Tetrahedron*, **23**, 2855 (1967), and should be regarded as a maximum value. Note that a smaller, more realistic value will intensify the argument offered below.

(24) This concept has some affinities with the ideas of J. Hine, "Physical Organic Chemistry," McGraw-Hill, New York, N. Y., 1962, p 111, and of W. P. Jencks, *Chem. Rev.*, **72**, 705 (1972).

mide. The temperature dependence of k_{HA} for *N*-hydroxysuccinimide gives $k_{HA} \sim 37\ M^{-1}\ hr^{-1}$ at 25°, approximating *in vivo* conditions and the correction factor of 1.8 for **2b** yields $k_{HA} \sim 21\ M^{-1}\ hr^{-1}$ for the natural resistance factor *in vivo*. The ratio $k_{HA}/k_A \sim 5$ then provides $k_A \sim 4\ M^{-1}\ hr^{-1}$. Thus the effective *in vivo* rate constant for action of the corn plant resistance factor against Cyprazine varies from $\sim 21\ M^{-1}\ hr^{-1}$ below pH 5.4 to about $4\ M^{-1}\ hr^{-1}$ above pH 7.4. Small's summary[25] of pH measurements on tissues of *Zea mays* indicates a range from 5.19 to 5.68 in normal plants. The effective rate constant thus varies only from about 21 to about $18\ M^{-1}\ hr^{-1}$, giving an average around $20\ M^{-1}\ hr^{-1}$.

To find the time required for detoxification by this mechanism we assume that the resistance factor is in large excess over intracellular Cyprazine. The loss of Cyprazine will proceed with a first-order rate constant $k_{eff} = 20\ M^{-1}\ hr^{-1}$ (concentration of **2b**, *M*). Various measurements of tissue levels of corn plant resistance factors indicate an average concentration of approximately $5 \times 10^{-3}\ M$, which gives $k_{eff} = 0.10\ hr^{-1}$. This corresponds to a half-life of about 7 hr for intracellular Cyprazine, or complete (99%) detoxification in about 2–3 days.

The fact that the natural resistance factor is more acidic ($pK_a = 6.4$) than its nucleophilic transition state ($pK_a^* = 7.1$) is of some significance since it is responsible for the high efficiency of detoxification even under the relatively acidic conditions prevailing in the corn tissue.

Experimental Section

Materials.—Cyprazine (**1c**) supplied by Gulf Research and Development Co. was recrystallized twice from toluene followed by two recrystallizations from chloroform–petroleum ether (bp 60–68°), mp 161–164° (lit.[26] mp 167–168).

N-Hydroxysuccinimide (**5**) (Aldrich Chemical Co.) was purified by repeated crystallization from methanol–ethyl acetate to correct elemental analysis. The pK_a was determined to be 5.95 by titration with 0.1 *N* NaOH.

1-Hydroxy-2-piperidone (**6**) was prepared according to the method of Panizzi, *et al.*,[27] by reaction of *N*-hydroxybenzenesulfonamide with cyclopentanone at 0°. It was purified by repeated sublimation at 50–55° (0.1 mm), mp 55°, $pK_a = 9.15$ (determined spectrophotometrically at 26°).

Basic alumina, chromatographic grade (E. Merck A. G., Darmstadt) and reagent grade chemicals were utilized.

Reaction of Cyprazine (1c) with *N*-Hydroxysuccinimide (5) in Acetonitrile.—Cyprazine (**1c**, 9.79 g, 0.043 mol) and *N*-hydroxysuccinimide (**5**, 4.95 g, 0.043 mol) were placed in a 500-ml erlenmeyer flask and enough acetonitrile was added to effect solution. The flask was maintained at 70° for 3 days, after which the solvent was removed *in vacuo* and the residue was dissolved in chloroform. The solution was warmed and ether was added to the cloud point. Upon cooling an oily substance separated as the lower layer. The addition of ethyl acetate to the oil caused the precipitation of the desired substance. The precipitate was collected and washed with ether–ethyl acetate. The chloroform–ether solution from which the oily substance separated was evaporated to dryness and the residue was washed with ethyl acetate and combined with the solid obtained previously. The yield of the crude product as the hydrochloride salt was 9.80 g (66.5%), mp 191–194° dec. Purification of the salt by recrystallization was not successful; thus it was converted to the free base by chromatography on basic alumina. The crude salt (6.0 g) was eluted with ethyl acetate from 210 g of basic alumina to give 3.8 g (71%) of a residue which was recrystallized from ethyl acetate–ether: mp 179–181°; λ_{max} 220 nm (acetate buffer, pH 4.0, ϵ 3.8×10^4), 217 (0.01 *N* $HClO_4$, 2.9×10^4), 257 (0.01 *N* $HClO_4$, 7.9×10^3); nmr ($CDCl_3$) δ 2.82 (s, 4, O=CCH_2CH_2C=O); ir (KBr) 1745 cm^{-1} (C=O); *m/e* 3.06.3.

Anal. Calcd for $C_{13}H_{18}N_6O_3$: C, 50.96; H, 5.91; N, 27.49. Found: C, 50.73; H, 5.93; N, 27.18.

Kinetic Procedure.—An aliquot of the hydroxamic acid solution in water (2–8 ml, 0.05 *M*) was placed into each of two 100-ml volumetric flasks and diluted to about 95 ml with water. When the reaction was performed in buffers the calculated amounts of buffer components were added together with the calculated amount of KCl to maintain the ionic strength at 0.5 *M* and the contents of the flasks were then diluted to about 95 ml with water. The flasks were immersed in a constant-temperature bath at 70.00 ± 0.5°. After thermal equilibration an aliquot (1 or 2 ml) of a stock solution of chlorotriazine ($1.5 \times 10^{-2}\ M$ in MeOH) was added to one flask and the same volume of methanol was added to the other flask. The flasks were then filled to the mark with water maintained at the same temperature, shaken, and returned to the constant-temperature bath. Zero time samples (5 ml) were withdrawn immediately and sampling was continued at appropriate time intervals. The samples were acidified by addition of 0.5–2.0 ml of 1 *N* $HClO_4$ or H_2SO_4 and diluted to 50 ml with water. The spectra or absorbances at a fixed wavelength were obtained on a Cary 14 spectrophotometer against the control sample solutions which were obtained in the identical manner from the control reaction mixture. Absorbance was measured using 10-cm cells at either 285 or 290 nm, and in 2- or 1-cm cells at 243 nm.

Thin Layer Chromatography.—Samples were spotted on precoated silica gel F 254 plates (Brinkmann Instruments) and developed to a distance of 7 cm using two solvent systems: (1) *n*-butyl alcohol–acetic acid–water (5:1:4) upper layer; and (2) isopropyl alcohol–ammonia–water (80:5:15) upper layer.

The fact that the salt hydrolyzes in water to 2-hydroxytriazine **4** and regenerates *N*-hydroxysuccinimide (**5**) was confirmed by tlc. The salt solution in water was allowed to stand for several days at room temperature, spotted on silica plates, and developed with two different solvent systems, 1 and 2. The R_f's observed with solvent systems 1 and 2, respectively, were 0.74 (**7**), 0.60 (**4**), and 0.41 (**5**) and 0.44 (**7**), 0.56 (**4**), and 0.11 (**5**). The reaction mixture gave a faint red-purple color with $FeCl_3$, indicating the possible presence of **5**.

Acknowledgment.—The authors gratefully acknowledge support of this project by the National Institutes of Health Grant NS 09399. R. L. S. acknowledges receipt of a Research Career Development Award from the National Institutes of General Medical Sciences. We also wish to thank the Gulf Research and Development Co., Agricultural Division, for generous supplies of Cyprazine.

Registry No.—**1c**, 22936-86-3; **5**, 6066-82-6; **7**, 42449-58-1; **7** HCl, 42449-59-2.

(25) J. Small, "Hydrogen-Ion Concentration in Plant Cells and Tissues," Verlag Gebrüder Borntraeger, Berlin, 1929.

(26) R. P. Neighbors and L. V. Phillips, South African Patent 6,802,975 (Oct 21, 1968); *Chem. Abstr.*, **71**, 39013x (1969).

(27) L. Panizzi, G. DiMaio, P. A. Tardella, and L. d'Abbiero, *Ric. Sci.*, **1**, IIA, 312 (1961); *Chem. Abstr.*, **57**, 9658 (1962).

Reaction of Diazonium Salts with Nucleophiles. XVIII. Dimethyl Phosphonate in Base[1]

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The rates of reaction of diazonium salts with dimethyl phosphonate have been followed in two cases. The kinetics, almost but not exactly third order, indicate that the ionization of dimethyl phosphonate by base occurs before the attack of diazonium salt on the phosphonate anion, but neither step is rate determining at accessible concentrations. Most of the isolated arylazophosphonates probably have syn stereochemistry.

Aromatic diazonium salts react with nucleophiles at the terminal nitrogen, yielding covalent diazo compounds which have the syn configuration in those cases when both stereoisomers are known. Studies in this area are usually complicated by side reactions, and, because both the desired and side reactions are very sensitive to substituent, often the reactions can be studied only over a small range of substituents. A type of nucleophile not yet extensively studied quantitatively in this reaction includes phosphorus compounds in lower oxidation states. Some of these, such as hypophosphorous acid and phosphorous acid, lead to replacement of the diazonium group by hydrogen by way of a free radical chain reaction.[3] In contrast, triphenylphosphine reacts with diazonium salts, again with ultimate reduction but with the intermediacy of the covalent diazo compound, $ArN_2P(C_6H_5)_3^+$.[4] Dialkyl phosphonates react to form stable dialkyl diazophosphonates,[5] which are the subject of this paper, and the preparation is shown in reaction 1. We were

$$(MeO)_2PHO + ArN_2^+ \longrightarrow ArN_2PO(OMe)_2 + H^+ \quad (1)$$

able to prepare several of these compounds (1) following the literature methods[5] in which 1 precipitates from an aqueous mixture of diazonium salt and dimethyl phosphonate at about pH 7, but the change to conditions suitable for a kinetic study was difficult. When the solvent was changed to methanol the reaction in most cases followed a different course, as indicated by uv absorption, and when very dilute solutions were used in water various side reactions in most cases overwhelmed the desired process. With Ar = *p*-$O_3SC_6H_4$, the product 1 is water soluble, and the reactions could be studied and, with Ar = *p*-$N{\equiv}CC_6H_4$, the side reactions were slow enough to allow the study. With Ar = *p*-CH_3O, *p*-CH_3, H, *p*-NO_2, and *p*-Cl-phenyl, the only other ones tried, no reasonably accurate study was possible in either water or methanol, although the product could be readily prepared.

The reaction 1 was not detectably reversed in water, but, when 1 was dissolved in concentrated sulfuric acid, the product showed the coupling reaction after neutralization. We may conclude that the equilibrium lies very far to the right.

The reaction rates were readily followed; they were very strongly pH dependent and reminiscent of some other chemistry of dialkyl phosphonates, the oxidation with halogens[6] and the deuterium exchange,[7] in which the anion $(MeO)_2PO^-$ (2) or its O-protonated conjugate acid, dialkyl phosphite, is implicated as a reactive intermediate. Using this analogy as a basis for the present work, the mechanism would be that given by eq 2 and 3. This leads to the rate equation (eq 4),

$$(MeO)_2PHO + B^- \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} \underset{2}{(MeO)_2PO^-} + BH \quad (2)$$

$$(MeO)_2PO + ArN_2^+ \xrightarrow{k_3} \underset{1}{ArN{=}NPO(OMe)_2} \quad (3)$$

$$\frac{d[1]}{dt} = \frac{k_3[ArN_2^+][(MeO)_2PHO]\Sigma_i k_{2i}[B_i^-]}{k_3[ArN_2^+] + \Sigma_i k_{-2i}[B_iH]} \quad (4)$$

where the summations recognize the multiplicity of bases and conjugate acids, and this equation reduces to two limiting forms, depending on which term in the denominator is predominant. If the second term predominates, the equation reduces to one specific hydroxide ion catalysis, eq 5,[8] and, if the first term predominates, eq 6 applies, showing general base catalysis

$$d[1]/dt = k[OH^-][ArN_2^+][(MeO)_2PHO] \quad (5)$$

$$d[1]/dt = [(MeO)_2PHO]\Sigma_i k_{2i}[B_i^-] \quad (6)$$

and a rate-determining first step. The first experiments showed that the rate is insensitive to a twofold buffer concentration and dependent on diazonium ion concentration, excluding the limit (eq 6). However, the distinction between the limit (eq 5) and the more general eq 4 was more difficult, for the range of concentrations without serious side reactions was limited. The method of accounting for a minor side reaction is described in the Experimental Section. The pseudo-first-order rate constant, k_ψ, for the reaction (1) was calculated by the method of Guggenheim[9] from the absorbance *vs.* time curves. At constant $[ArN_2^+]$, a plot of log k_ψ *vs.* pH is linear with a slope of +1, and a plot of k_ψ *vs.* $[ArN_2^+]$ at constant pH was linear.[10] We therefore calculated $k' = k_\psi/[OH^-][ArN_2^+]$, which

(1) Paper XVII: E. S. Lewis and D. J. Chalmers, *J. Amer. Chem. Soc.*, **93**, 3267 (1971). This work was supported by a grant from the Robert A. Welch Foundation which we gratefully acknowledge.

(2) From a portion of the Ph.D. Thesis of Edward C. Nieh, Rice University, 1972.

(3) N. Kornblum, G. D. Cooper, and J. E. Taylor, *J. Amer. Chem. Soc.*, **72**, 3013 (1950); N. Kornblum, A. E. Kelley, and G. D. Cooper, *ibid.*, **74**, 3074 (1952).

(4) L. Horner and H. Stöhr, *Ber.*, **86**, 1066, 1073 (1953); L. Horner and H. Hoffmann, *Angew. Chem.*, **68**, 473 (1956).

(5) F. Suckfull and H. Haubrick, *Angew. Chem.*, **70**, 238 (1958); see also German Patents 1,008,313 (1955), 1,011,432 (1955), 1,015,443 (1955), and 1,075,627 (1956). We thank Drs. Suckfull and Haubrick for copies of these patents.

(6) P. Nylen, *Z. Anorg. Allg. Chem.*, **235**, 161 (1938).

(7) Z. Luz and B. Silver, *J. Amer. Chem. Soc.*, **84**, 1095 (1962).

(8) This reduction is not an algebraic identity; it requires further relations between the terms in the summation such as is required by microscopic reversibility.

(9) E. A. Guggenheim, *Phil. Mag.*, **2**, 538 (1926).

(10) Although diazonium salts react with high pH buffers to give diazotates, this does not occur perceptibly at these pH's: E. S. Lewis and H. Suhr, *Chem. Ber.*, **91**, 2350 (1958).

would be pH and concentration independent if eq 5 holds exactly. The results are shown in Table I. The

TABLE I

RATES OF DIAZOPHOSPHONATE FORMATION AT 6.0 ± 0.1° FROM p-$XC_6H_4N_2^+$ AND $(MeO)_2PHO$[a]

X	$(ArN_2^+) \times 10^2$, M	pH	$k_\psi \times 10^{-3}$, sec^{-1}	$k' \times 10^{-6}$, M^{-2} sec^{-1}
SO_3^-	0.8	7.0	3.75	4.46
SO_3^-	1.0	7.0	3.99	3.99
SO_3^-	1.2	7.0	4.33	3.60
SO_3^-	1.4	7.0	4.87	3.47
SO_3^-	1.6	7.0	5.32	3.32
SO_3^-	1.8	7.0	5.77	3.20
SO_3^-	1.6	6.2	0.93	3.65
SO_3^-	1.6	7.4	14.70	3.68
CN	1.0	6.4	2.86	11.4
CN	1.2	6.4	3.25	10.8
CN	1.4	6.4	3.54	10.1
CN	1.6	6.4	3.82	9.55
CN	1.8	6.4	4.28	9.51

[a] All runs were done with an initial 6.8×10^{-4} M $(MeO)_2PHO$; a more extensive set is to be found in E. C. Nieh's thesis (ref 2). Registry number for $(MeO)_2PHO$, 868-85-9.

pH effect (as shown by the virtual identity of k' at pH 6.2 and 7.4 at constant $[ArN_2^+]$) is very clearly of the correct form, but the rate dependent on $[ArN_2^+]$ less than is demanded by eq 5.

Equation 4 will clearly give a better fit, and only the term with $B^- = OH^-$ is very significant. We use these data to calculate the limiting rate at high diazonium salt concentrations most easily as the slope of a plot of $1/k'$ *vs.* $[ArN_2^+]$, since eq 4 with only an OH^- term becomes eq 7, and using the data with $X = SO_3^-$ we

$$k' = \frac{k_3 k_2}{k_{-2} + k_3[ArN_2^+]} \quad (7)$$

find $k_2 = 3.3 \times 10^5$ M^{-1} sec^{-1}, and that from X = CN gives $k_{-2} = 1.4 \times 10^5$ M^{-1} sec^{-1}. Making suitable corrections for pH and temperature, and counting only the $[OH^-]$ term, we get from Nylen's iodine oxidation data $k_2 = 7 \times 10^5$. The roughness of our calculation, severely limited by the small range of variation of $[ArN_2^+]$ imposed by solubility, together with other uncertainties of comparison make the better than order of magnitude agreement satisfactory, and we therefore believe that the mechanism of eq 2 and 3 is adequately demonstrated.

The separate constants k_3 or k_2 are not firmly established, although the ratio of k_3/k_{-2} is determined; for the sulfonate case a value between 0.01 and 0.1 results. The equilibrium constant, K_2, for reaction 2 with $B^- = OH^-$ is k_2/k_{-2}; it is available from the pK_a of dimethyl phosphonate, *i.e.*, $K_2 = K_a/K_w$. Hammond[11] has estimated the pK_a of diethyl phosphonate as about 15, but without a clear basis. Using this value we find $k_{-2} = 10k_2 = 3 \times 10^6$ sec^{-1} and k_3 is then of the order of 10^5 M^{-1} sec^{-1}. Dimethyl phosphite as an intermediate rather than its anion is possible if its reactivity is very high and its acidity is improbably low. Since we did not find evidence of acid catalysis, and since acid catalyzes the iodine reaction, a reaction probably passing through this tautomer, the anion is a more acceptable intermediate.

(11) P. R. Hammond, *J. Chem. Soc.*, 1365 (1962).

A question of product stereochemistry appears; the observation that with Ar = p-$CH_3OC_6H_4$ the uv spectrum changed with time may be relevant. The intensity of the visible band increased from a value with ϵ *ca.* 100 at 475 nm to ϵ 240 at 475 nm in an hour or so. The other bands [λ_{max} 345 nm (ϵ 2 × 10^4), λ_{max} 242 (ϵ 1.3 × 10^4)] were unaltered. If this corresponds to a syn–anti change, then the other substances are rearranged either too fast to see or too slow to see; an extremum for the rate with p-OCH_3 substituent is reasonable. The nmr spectrum does not change noticeably, so that we rule out a reaction far more extensive than this stereoisomerization. Since the phosphonate group is electron withdrawing, it is most reasonable to assume that the fastest isomerization will be with para electron-rich substituents (like that of the diazo cyanides[12]) rather than the reverse characteristic of electron-supplying groups on nitrogen, such as in the diazotates[13] which isomerize most rapidly with the p-nitro substituent. It is thus reasonable that all the diazophosphonates studied are syn, and that isomerization to the anti form is detectable only for the p-methoxy case. A further support for this argument lies in the extinction coefficients. All the substances had extinction coefficients at the longest wavelength absorption maximum in the range 73–107, including the early measurements on the p-methoxy compound. After the spectrum became time stable, the p-methoxy compound was well outside this range with ϵ 240.

Experimental Section

Materials.—Dimethyl phosphonate, Matheson Coleman and Bell practical grade, was dried over Drierite and then distilled through a 14-in. column packed with glass helices. The fraction with bp 62–63° was collected and used; proton nmr found no contaminants.

Diazonium salts were prepared as the fluoroborates and purity was assayed by the uv absorption.[14] The diazotization of sulfanilic acid yielded the inner salt, not requiring any external anion.

Dimethyl Arylazophosphonates.—To a suspension of 0.2 mol of diazonium salt with 0.2 mol of dimethyl phosphonate in 30 ml of water at 0° was added in small portions 15 g of sodium bicarbonate over a period of 15 min. After stirring for an additional 15 min at 0°, the solution was extracted several times with dichloromethane, and evaporation of the solvent left the azophosphonates as red oils in 75–80% yields. The p-nitro and the p-cyano compounds were recrystallized [mp 114–116° (lit.[5] mp 119°) and 74–75°, respectively] from dichloromethane–pentane. The uv spectra are presented in Table II, and in the two cases where recrystallization was possible no significant change was found.

Kinetic Procedures.—A buffer solution with total phosphate 0.1 M made up according to Britten[15] and cooled to 0° was added to a weighed sample of diazonium salt in a volumetric flask. After mixing, the solution was used to fill a 10-cm cell in the thermostated (at 6.0°) compartment of the spectrophotometer. Temperature equilibrium was attained in a few minutes. After about 15 min a 2-μl sample of dimethyl phosphonate was added, the cell was shaken, and then absorbance was recorded at the absorption maximum (485 nm for the p-SO_3^- compound, 505 nm for the p-CN compound).

The absorbances used to calculate the rate constances contained a small correction for a side reaction. Diazotized sulfanilic acid is slightly unstable at the pH used, and an absorbing species is produced. In the times used this change in absorbance

(12) R. J. W. LeFévre and J. Northcott, *J. Chem. Soc.*, 944 (1949).
(13) E. S. Lewis and H. Suhr, *Chem. Ber.*, **92**, 3031 (1959).
(14) E. S. Lewis and M. P. Hanson, *J. Amer. Chem. Soc.*, **89**, 6268 (1967).
(15) H. S. T. Britten, "Hydrogen Ions," Vol. 1, 3rd ed, Van Nostrand, Princeton, N. J., 1943, p 135.

TABLE II

ULTRAVIOLET ABSORPTION MAXIMA OF p-$XC_6H_4N_2PO(OMe)_2$[a]

Registry no.	X	λ_1, nm (ϵ)	λ_2, nm (ϵ)	λ_3, nm (ϵ)
42334-47-4	NO_2	510 (108)	257 (21,800)	
42334-48-5	CN	505 (84)	286 (16,000)	235 (11,000)
42334-49-6	Cl	496 (96)	310 (17,000)	230 (10,900)
e	OCH_3	475 (240)[b]	345 (20,000)	242 (12,600)
42398-38-9	SO_3^-	485 (~100)[c]		
42334-52-1	CH_3	490 (107)	304 (14,700)	22 (9370)
42334-53-2	H	485 (73)[d]	293 (12,000)	

[a] In methanol solutions; extinction coefficients are in parentheses. [b] This extinction coefficient was that obtained after several hours of standing; the initial value was about 100. [c] In water solution assuming a quantitative reaction, the pure azophosphonate was not isolated. Shorter wavelength absorption was not studied because of possible contamination. [d] This maximum was at 487 nm in dioxane solution, with the same extinction coefficient. [e] 42334-51-0 (anti), 42334-50-9 (syn).

is essentially linear with time, *i.e.*, $A = A_0 + k_0t$, where k_0 is a zero-order rate constant for change of absorbance (A) with time (t). The absorbance was then measured for a while to establish A_0 and k_0 before the dimethyl phosphonate was added. After the reaction with dimethyl phosphonate was virtually complete, the absorbance continued to increase with the same slope. The corrected absorbances were those calculated by subtracting those due to the zero-order process. This correction was typically up to about 10% of the absorbance change resulting from reaction 1 over about 3 or 4 half-lives. If the extinction coefficient is the same as that of **1**, this corresponds to a loss of about 0.5% of the diazonium salt. The correction increased with pH; it is presumably the known decomposition of diazonium salts near pH 7.[16] This correction was negligible with p-cyanobenzenediazonium ion, but another absorbance change after the reaction was complete was presumed to represent the hydrolysis of the methoxy groups of the azophosphonate. The effect was minimized by using data from the first two half-lives only.

This known hydrolytic instability, characteristic of all these substances, prevented the study of these methods over very long periods which would have answered questions about possible isomerization rates.

Registry No.—p-$XC_6H_4N_2^+$: X = SO_3^-, 305-80-6; X = CN, 19262-72-7; X = NO_2, 14368-49-1; X = Cl, 17333-85-6; X = OMe, 17333-79-8; X = Me, 14597-45-6; X = H, 2684-02-8.

(16) See, for example, C. Rüchardt and E. Merz, *Tetrahedron Lett.*, 2431 (1964).

Anomalous Photocyclization of Methyl 2-(1-Naphthyl)-3-(4-pyridyl)acrylate[1]

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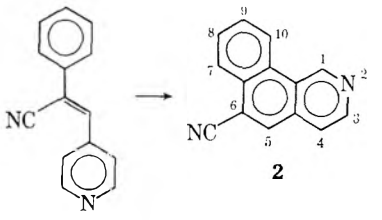
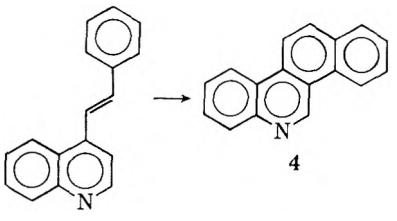
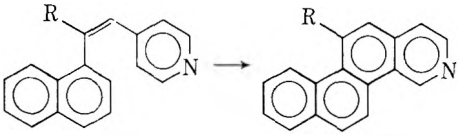
Oxidative photocyclization of methyl 2-(1-naphthyl)-3-(4-pyridyl)acrylate (**5b**) gave acenaphthene and acenaphthylene derivatives by cyclization to the 8 position of the naphthalene ring rather than the expected azachrysene that would result from cyclization into the 2 position. Chemical and spectral evidence is presented to support structural assignments of the products.

The oxidative photocyclization of stilbene and related compounds is a useful synthetic route to many polycyclic compounds.[2] For example, oxidative photocyclization of 2-phenyl-3-(4-pyridyl)acrylonitrile (**1**) is reported to yield 6-cyanobenz[*h*]isoquinoline (**2**) in good yield,[3] and likewise, 1-styrylnaphthalene has been reported to yield chrysene.[4] In a similar manner, photocyclization of 4-styrylquinoline (**3**) gave benzo[*i*]phenanthridine (**4**).[5] Based on these reactions, oxidative photocyclization of **5b** appeared to be a reasonable synthetic approach to the naphth[1,2-*h*]isoquinoline **6a**.





An attempt to prepare azachrysene **6a** by oxidative photocyclization of **5b** in methanol (see Experimental Section) led to isolation of a yellow solid in low yield. The 60-MHz nmr spectrum of the yellow product was not consistent with structure **6a**, as it lacked a singlet near δ 10.0 expected for H_4,[6] and 100-HMz nmr revealed that the 4-pyridyl group was unchanged from **5b**. The mass spectrum showed a molecular ion at m/e 287, indicating a loss of 2 in molecular weight from **5b**.



5a, R = CO_2H
b, R = CO_2CH_3
c, R = CN (trans)

6a, R = CO_2CH_3
b, R = CN

Examination of the photocyclization products (Scheme I) from **5b** by chromatography on silica gel gave as the major fraction (75–80% by weight) a yellow oil, which exhibited two overlapping spots on tlc (ethyl acetate or chloroform), one of which corresponded to the yellow solid. Nmr examination of the oil revealed a set of doublets not present in the crystalline solid.

(1) Supported by Contract NIH-71-2070 from the Division of Cancer Treatment, National Cancer Institute, National Institutes of Health.

(2) See, for example, A. Schönberg, "Preparative Organic Photochemistry," Springer-Verlag, New York, N. Y., 1968, p 126; E. V. Blackburn and C. J. Timmons, *Quart. Rev., Chem. Soc.*, **23**, 482 (1969).

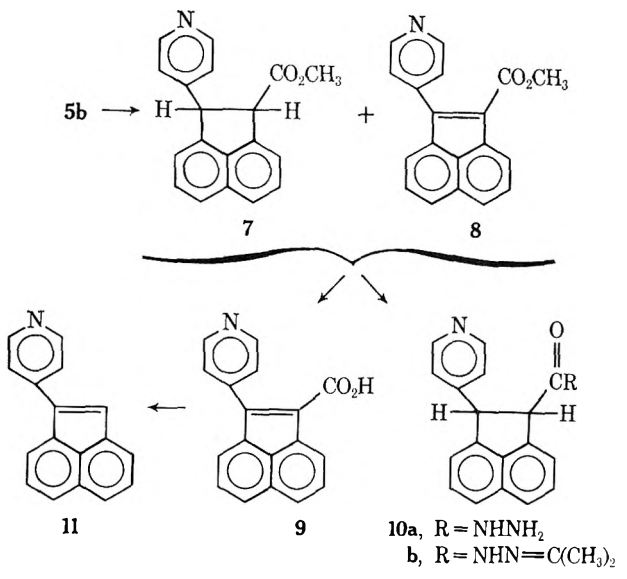
(3) P. L. Kumler and R. A. Rybas, *J. Org. Chem.*, **35**, 3825 (1970).

(4) C. S. Wood and F. B. Mallory, *J. Org. Chem.*, **29**, 3373 (1964).

(5) C. E. Loader and C. J. Timmons, *J. Chem. Soc. C*, 1457 (1967); 330 (1968).

(6) H_4 in **2**, prepared during the course of this investigation, was found at δ 10.08. See also O. De Silva and V. Snieckus, *Synthesis*, 254 (1971).

SCHEME I



These doublets, centered at δ 4.50 (J = 5 Hz) and 5.35 (J = 5 Hz), integrated for slightly less than one proton each, indicating that the two products of the photocyclization might be quite similar, with one being a dihydro derivative of the other.[7] By comparison of peak height in the nmr spectrum, the dihydro component was estimated to account for about 75% of the mixture, and the yellow solid, 25%. Photocyclization in *tert*-butyl alcohol gave the same mixture, while use of benzene as solvent led to amorphous insoluble powders and tars. Addition of iodine did not appear to affect the course of the reaction or the product ratios.[8]

Attempts to separate the mixture cleanly were unsuccessful, and the major component could not be obtained in crystalline form. Acid or base hydrolysis of the chromatographed mixture led to a solid acid, but repeated recrystallization failed to remove the minor component. Hydrazinolysis of the nixture led to a light yellow power which showed only one spot in tlc, but did not give satisfactory elemental analyses. The uv spectrum of this hydrazide was nearly identical with that of acenaphthene (Figure 1), and it was assigned structure **10a** on this basis. The mass spectrum of **10a** showed a molecular ion at m/e 289 and fragments at m/e 230 and 152 which are accounted for by Scheme II. The acenaphthylene fragment **13** has been observed as a major peak in the mass spectrum of another substituted acenaphthylene.[9] The assignment of structure **10a** then led to the assignment of structures **7** and **8** for the original mixture.[10] Hydrazide **10a** was further characterized as the hydrazone **10b**, which gave correct elemental analyses and was spectrally quite similar.

A literature search revealed the preparation of the closely related acenaphthylene **15** by Ghigi.[11] During the course of structure proof, Ghigi degraded **15** to acid

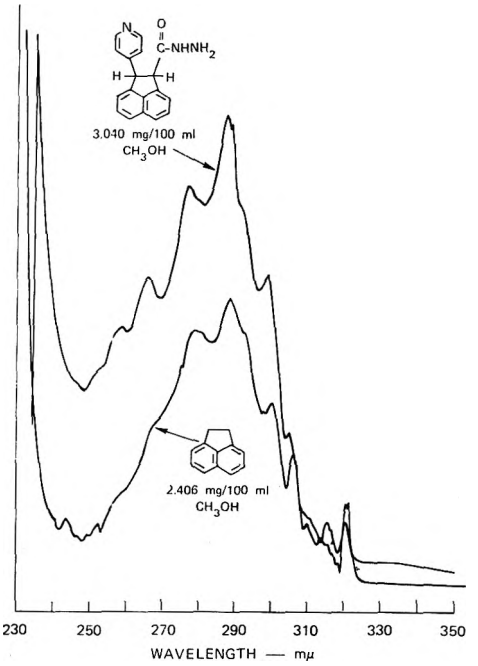
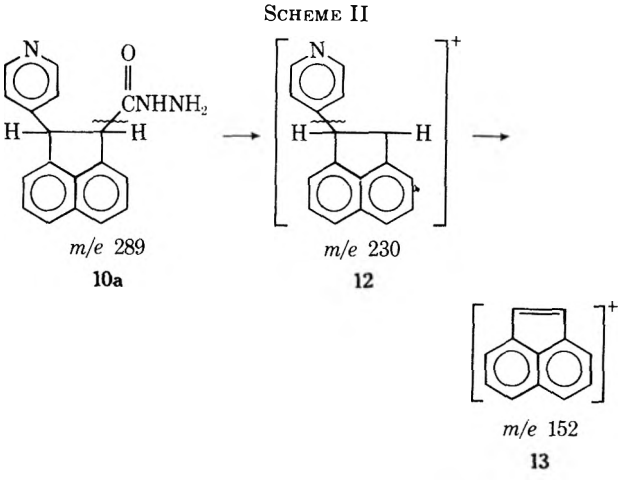
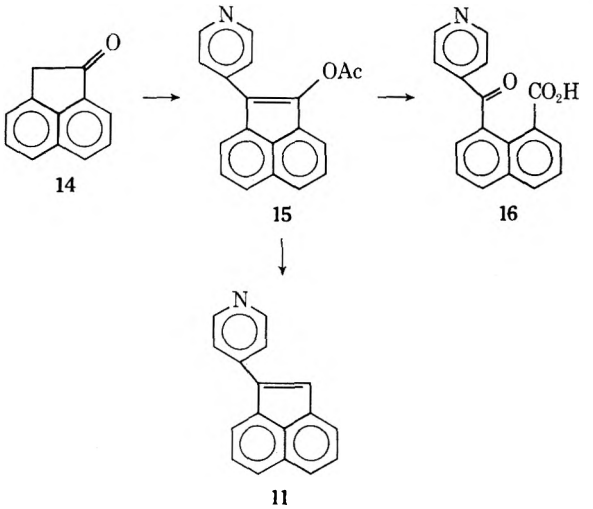


Figure 1.—Uv comparison of **10a** with acenaphthene.

SCHEME II



16 and to acenaphthylene **11**. Attempts to oxidize the mixture of **7** and **8** to acid **16**, with various oxidizing



agents including excess acidic dichromate or basic permanganate, did not yield isolable products. However, the careful use of a limited amount of basic

(7) This assumption was originally made on the grounds that related photocyclizations proceed through a dihydro intermediate. See F. B. Mallory, C. S. Wood, and J. T. Gordon, *J. Amer. Chem. Soc.*, **86**, 3094 (1964).

(8) C. E. Loader and C. J. Timmons, *J. Chem. Soc. C*, 1078 (1966); see also ref 4.

(9) J. Meinwald and J. W. Young, *J. Amer. Chem. Soc.*, **93**, 725 (1971).

(10) The excess hydrazine used in the preparation of **10a** may have reduced the double bond in **8**. See L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, p 1074.

(11) E. Ghigi, *Chem. Ber.*, **75**, 764 (1942).

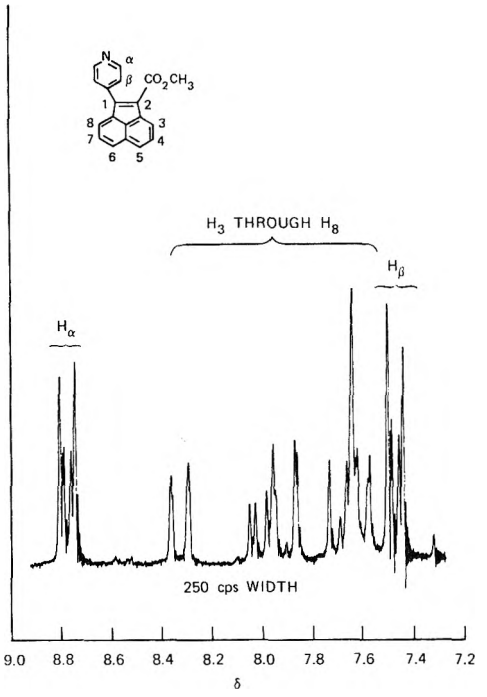


Figure 2.—100-MHz nmr spectrum of aromatic protons in acenaphthylene 8 before addition of shift reagent.

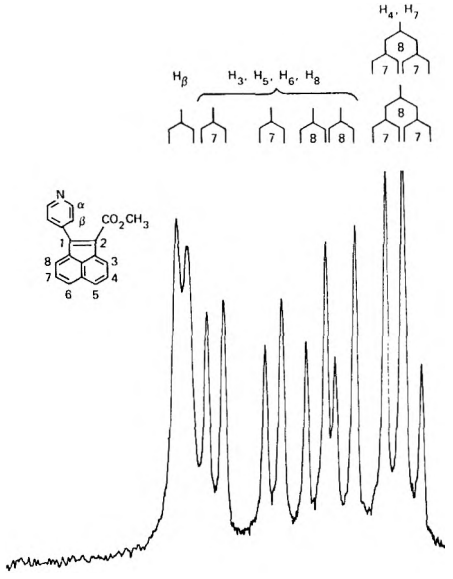


Figure 3.—100-MHz spectrum of 8 after addition of about 5 mg of Euroshift F reagent. H_α appears about 400 Hz downfield.

permanganate gave a good yield of a bright yellow acid, which melted well above the value reported for **16**. On the basis of elemental analyses and nmr spectra data, this acid was assigned structure **9**. Decarboxylation of **9** gave a low yield of yellow oil which was assigned the structure **11**. This oil was treated with a saturated picric acid solution to yield a yellow solid whose melting point (266–268° dec) compared well with the melting point reported for the picrate of **11** (264–265°).[11]

Further confirmation of the structure of the minor product (**8**) was sought. Since nmr examination of pure **8** using 60- or 100-MHz instruments did not resolve the six acenaphthylene protons sufficiently for definitive interpretation (Figure 2), the use of shift reagents was tried. Addition of Rondeau's reagent (Prashift F, Pierce Chemical Co.) shifted the acenapthylene protons even closer together, but Sievers' reagent (Euroshift F, Pierce Chemical Co.) gave a 60-MHz spectrum with the protons reasonably well separated. Finally, using the Euroshift F reagent and 100-MHz nmr with decoupling gave definitive evidence for the acenaphthylene system. Dewar and Fahey report the following coupling constants for acenaphthylene.[12]

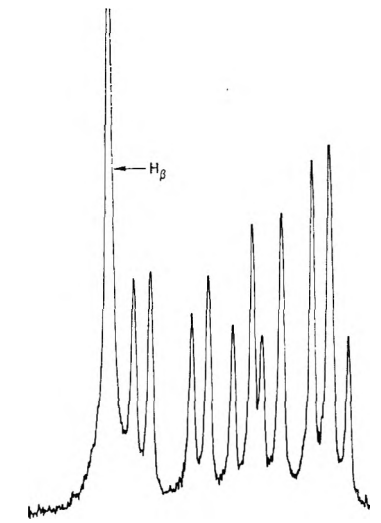
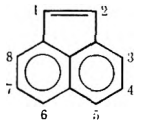


Figure 4.—Changes in the 100-MHz spectrum of **8** from Figure 3. H_β doublet collapsed by irradiation of H_α protons which are about 400 Hz downfield.



$J_{6,7} = 8.3$ Hz
$J_{6,8} = 0.6$ Hz
$J_{7,8} = 6.9$ Hz

Thus, the spectrum of **8**, once the pyridyl protons are shifted away, should consist of four doublets and two quartets (or apparent triplets) as seen in Figure 3.

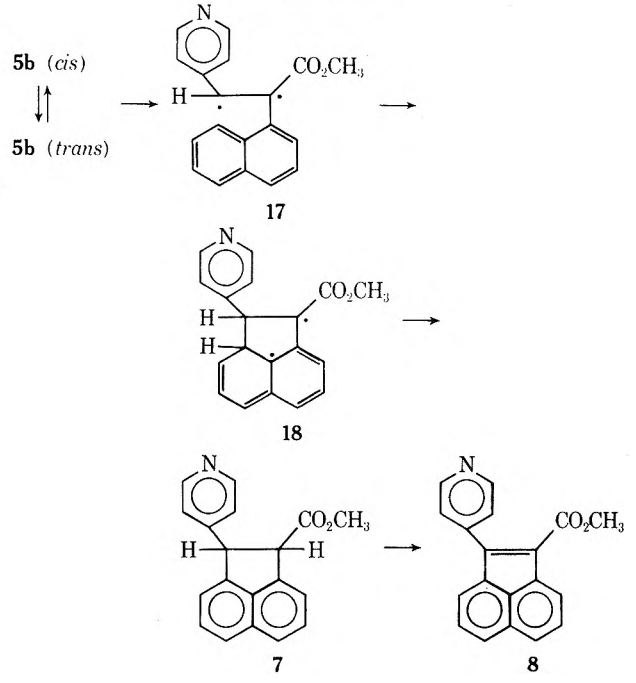
Before addition of Sievers' reagent, a small (<1 Hz) 1,3 aromatic splitting was observed (Figure 2). In practice, Sievers' reagent was added in small portions (about 5 mg) until sufficient separation was obtained for decoupling. Figure 3 shows the six acenaphthylene protons and a doublet assumed to be the H_β protons on the 4-pyridyl group. Irradiation of the H_α protons, which have been shifted nearly 400 Hz downfield, collapsed the doublet, as seen in Figure 4, but left the rest of the spectrum unchanged, confirming that this doublet is due to the pyridine ring. Irradiation of H_4 and H_7 collapsed all four doublets, as shown in Figure 5, indicating that the four doublets were all coupled to H_4 and H_7 with $J = 7$ or 8 Hz. The only arrangement of protons that could give this result is two independent ABC systems as in acenaphthylene **8**. Thus, the nmr data substantiate structure **8** for the minor product and support the assignment of structure **7** to the minor product. As additional confirmation of the structure of **8**, the acid **9** was reesterified to give an ester that was identical with **8** in all respects. Since **9** was obtained in 59% yield from a 3:1 mixture of **7**:**8**, some **9** must have come from **7**. This is additional confirmation of the relationship of **7** to **8**.

(12) M. J. S. Dewar and R. C. Fahey, *J. Amer. Chem. Soc.*, **85**, 2704 (1963).

This cyclization to the 8 position in naphthalene is in contrast to the reported cyclization of 1-styrylnaphthalene to the 2 position to give chrysene.[4] An examination of models shows that to obtain the azachrysene structure **6a**, the carbomethoxy group must be in a quite hindered environment, which may account for the direction of cyclization. If steric effects are important, cyclization of the sterically less demanding nitrile **5c** would be more likely to give the desired azachrysene. Irradiation of **5c** led to a complex mixture. The nmr spectrum of the crude mixture showed a small peak at δ 10.14[6] that may have been H_4 of **6b**. There was also evidence for a small amount of an acenaphthene (two small doublets at δ 4.45 and δ 5.10 with J = 5 Hz). Yields of both products appeared to be less than 10%, and thus the photocyclization route to **6b** did not appear to be practical.

A possible mechanism for formation of **7** and **8** is presented in Scheme III.

SCHEME III



Irradiation of **5b** produces a resonance-stabilized diradical **17**, which then cyclizes to **18**.[13] A 1,3 hydrogen shift would lead to **7**, while **8** could be formed by oxidation of either **7** or **18**.

Experimental Section

Melting points were observed on a Fisher-Johns hot stage and were not corrected. Ultraviolet (methanol solution, Cary 11 instrument) and 60-MHz nmr (Varian Associates, A-60 spectrometer) measurements were performed by the Pharmaceutical Analysis Group under the direction of Dr. Peter Lim. Mass spectra were recorded by Dr. D. W. Thomas with an LKB Model 9000 mass spectrometer. Decoupling experiments were performed by Dr. H. C. Barret, using a Varian HA-100 spectrometer, and elemental microanalyses were provided by E. M. McCarthy of SRI.

Thin layer chromatography plates were prepared, using silica gel HF-254, and visualized with uv or iodine. Photocyclizations were performed using either a 100-W GE high-pressure mercury vapor lamp or a 450-W Hanovia high-pressure mercury vapor lamp in Pyrex glassware. Solvents were evaporated *in vacuo*.

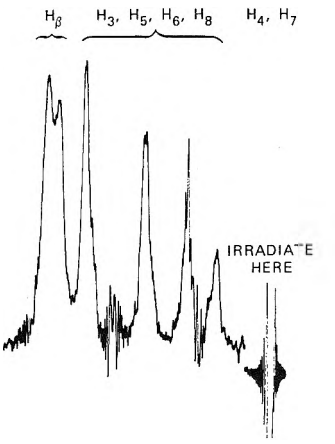


Figure 5.—Changes in the 100-MHz spectrum of **8** from Figure 3. Irradiation of H_4 and H_7 has collapsed H_3, H_5, H_6, and H_8 to singlets.

***cis*-2-(1-Naphthyl)-3-(4-pyridyl)acrylic Acid (5a).**[14]—Sodium methoxide (1.5 g, 27.8 mmol) was added slowly, with stirring, to acetic anhydride (20 ml). After 5 min, α-naphthylacetic acid (5.0 g, 26.9 mmol) was added and the solution was stirred for 20 min. Pyridine-4-carboxaldehyde (2.5 ml, 22.2 mmol) was added and the solution was heated slowly to 100° over about 1 hr. After 20 hr at 100°, the solution was cooled to 80° and water (100 ml) was added slowly over about 15 min. The solution was cooled, made basic with concentrated ammonium hydroxide, and filtered to remove tars. The filtrate was adjusted to pH 4 with concentrated hydrochloric acid and cooled in ice. The light yellow solid that separated was collected (3.60 g, 56%), mp 290–300° Recrystallization from methanol–water gave a yellow, crystalline solid, mp >300°, nmr (TFA) δ 6.70–8.00 (m).

Anal. Calcd for $C_{18}H_{13}NO_2$: C, 78.53; H, 4.76; N, 5.09. Found: C, 78.41; H, 4.80; N, 5.32.

***cis*-Methyl 2-(1-Naphthyl)-3-(4-pyridyl)acrylate (5b).**—A solution of 2-(1-naphthyl)-3-(4-pyridyl)acrylic acid (0.40 g, 1.45 mmol) in methanol (40 ml) containing concentrated sulfuric acid (1.0 ml, 17.6 mmol) was heated at reflux for 2 hr. The solution was poured into water (150 ml) and excess sodium bicarbonate, and the suspension was extracted with two 75-ml portions of chloroform. The chloroform was washed with water (50 ml) and evaporated to leave a yellow oil, which crystallized from benzene–hexane as a yellow solid (0.21 g, 50%), mp 98–101°. Recrystallization from the same solvent gave a white, crystalline solid: mp 106–107°; nmr ($CDCl_3$) δ 3.70 (s, 3) and 6.65–8.40 (m, 12); uv max (MeOH) 222 and 262 nm.

Anal. Calcd for $C_{19}H_{15}NO_2$: C, 78.87; H, 5.23; N, 4.84. Found: C, 79.02; H, 5.23; N, 4.97.

***trans*-2-(1-Naphthyl)-3-(4-pyridyl)acrylonitrile (5c).**[15]—A solution of 1-naphthylacetonitrile (2.0 ml, 12 mmol) in dry tetrahydrofuran (30 ml) was treated with 0.7 g (17 mmol) of 58.1% sodium hydride dispersed in oil and heated to reflux. Pyridine-4-carboxaldehyde (1.6 ml) was added slowly; after 10 min, an additional 0.5 ml (2.1 ml total, 19 mmol) was added. Refluxing was contlnued for 1.5 hr; then the solution was cooled, diluted with water (100 ml), and extracted with two 75-ml portions of benzene. Evaporation of the benzene left a yellow oil, which was dissolved in benzene (20 ml) and applied to a column of silica gel (80–200 mesh, 80 g). The column was washed with benzene (200 ml) and then eluted with ethyl acetate (150 ml). Evaporation of the ethyl acetate left a yellow oil, which crystallized slowly from 1:1 ethanol–water to give a sticky yellow solid, mp 45–50° (0.89 g, 29%). A sample was recrystallized from methanol–water, then from acetone–water to give a yellow solid, mp 63–66°. Tlc ($CHCl_3$) still showed trace impurities; nmr ($CDCl_3$), δ 7.25–8.30 (m, 10) and 8.60–8.90 (m, 2).

(13) For an example of another type of 1,8 photocyclization in naphthalene, see H. H. Ong and E. L. May, *J. Org. Chem.*, **35**, 2544 (1970).

(14) Assumed to be cis based on method of synthesis. See H. E. Zimmerman and L. Ahramjian, *J. Amer. Chem. Soc.*, **81**, 2086 (1959).

(15) Assumed to be trans based on method of synthesis. See F. H. Clarke, G. A. Felock, G. B. Silverman, and C. M. Watnick, *J. Org. Chem.*, **27**, 533 (1962).

Anal. Calcd for $C_{18}H_{12}N_2$: C, 84.35; H, 4.72; N, 10.93. Found: C, 83.96; H, 4.66; N, 10.66.

Photocyclization of Methyl 2-(1-Naphthyl)-3-(4-pyridyl)-acrylate.—A solution of methyl 2-(1-naphthyl)-3-(4-pyridyl)-acrylate (1.0 g, 3.46 mmol) in methanol (400 ml) was irradiated with a 100-W mercury vapor lamp through a Pyrex well for 18 hr. Air was bubbled slowly through, and the solution was stirred during the irradiation. The solvent was evaporated and the residual oil was dissolved in benzene (20 ml) and poured onto a 1.5 × 10 cm column of basic alumina. The column was washed with benzene (~100 ml) until a yellow band approached the end of the column, then eluted with chloroform (~200 ml) until no more yellow product was obtained. Evaporation of the chloroform left 0.75 g of yellow oil (7 and 8, two spots on tlc with ethyl acetate), which was dissolved in a large volume of hot hexane. On long cooling, 0.13 g (13%) of yellow crystals of 8 formed, mp 97–100°. Recrystallization from hexane gave yellow needles: mp 110–113°; ir 5.82, 6.24, 6.99, 8.09, 8.25, 8.82, 9.42, 11.76, 12.10, and 12.98 μ; nmr ($CDCl_3$) δ 3.82 (s, 3), 7.25–8.40 (m, 8), and 8.85 (d, 2); mass spectrum m/e 287, 256, 227, 200, and 100; uv λ_{max} 316 nm (ϵ 7350) and 343 (9950).

Anal. Calcd for $C_{19}H_{13}NO_2$: C, 79.43; H, 4.56; N, 4.88. Found: C, 79.33; H, 4.59; N, 5.07.

Different runs gave approximately the same mixture of 7 and 8. However, the relative amount of 8 appeared to slowly increase in solutions left exposed to air.

The photocyclizations with other solvents were run under the same experimental conditions.

2-(4-Pyridyl)acenaphthene-1-carbonylhydrazide (10a).—A chromatographed mixture of 7 and 8 (0.75 g), ethanol (20 ml), and 95% hydrazine (1.5 ml) was heated on a steam bath for 2 hr. The solution was evaporated to dryness, treated with benzene (20 ml), and again evaporated to dryness. The residual yellow oil was crystallized twice from methylene chloride–carbon tetrachloride to afford 0.21 g (28%) of 10a as a sticky yellow powder: mp 135–138°; nmr ($CDCl_3$) δ 3.80 (s, 2), 4.32 (d, 1, J = 4 Hz), 5.25 (d, 1, J = 4 Hz), 7.00–8.00 (m, 9), and 8.47 (d, 2, J = 6 Hz); mass spectrum m/e 289, 230, 152, 121, 119, 117. Satisfactory elemental analyses were not obtained.

Acetone 1-(4-Pyridyl)acenaphthene-2-carbonylhydrazone (10b).—A sample of crude hydrazide 10a (prepared from 0.5 g of ester 5b) was crystallized from acetone–hexane to give a light yellow powder, mp 235–238°. Recrystallization from acetone–ethanol gave 0.15 g (26%) of white solid: mp 242–245°; nmr (TFA) δ 2.10 (s, 3), 2.25 (s, 3), 4.35 (m, 1), 5.15 (m, 1), and 6.65–8.35 (m, 10).

Anal. Calcd for $C_{21}H_{19}N_3O$: C, 76.57; H, 5.81; N, 12.76. Found: C, 76.35; H, 6.02; N, 12.70.

2-(4-Pyridyl)acenaphthylene-1-carboxylic Acid (9).—A crude chromatographed mixture of 7 and 8 (0.75 g) was suspended in 10% sodium hydroxide (20 ml), and potassium permanganate (1.0 g) was added. The mixture was heated on a steam bath for 2.5 hr, with occasional swirling, and then cooled and filtered. The solids were washed with water (20 ml). The combined filtrates were acidified with acetic acid and cooled to give 0.56 g (59% from 5b) of bright yellow solid. Recrystallization from methanol–water gave an analytical sample: mp >300° dec; nmr (DMSO-d_6) δ 7.55–8.45 (m, 8) and 8.65–8.90 (m, 2).

Anal. Calcd for $C_{18}H_{11}NO_2$: C, 79.11; H, 4.06; N, 5.13. Found: C, 78.89; H, 4.06; N, 5.36.

Reesterification of 9 with methanol and HCl afforded 8, identical with 8 obtained by photocyclization above on comparison of melting point, mixture melting point (no depression), ir, and tlc.

1-(4-Pyridyl)acenaphthylene (11) Picrate.—A finely powdered mixture of 1-(4-pyridyl)acenaphthylene-2-carboxylic acid (0.2 g, 0.7 mmol) in a small sublimation apparatus (no vacuum) was placed in an oil bath preheated to 260°. After 20 min, the mixture was cooled and the entire apparatus was washed out with benzene (50 ml). The benzene was filtered and evaporated to leave a yellow oil. The oil was dissolved in ethanol (20 ml), and a saturated picric acid solution in ethanol (20 ml) was added. The suspension was heated to boiling on a steam bath and cooled. The yellow solid was collected. Recrystallization from ethanol gave tiny yellow needles (0.04 g, 12%): mp 266–268° dec[16] (lit.[11] mp 264–265°); nmr (DMSO-d_6) δ 6.80–9.10 (m).

Anal. Calcd for $C_{23}H_{14}N_4O_7$: C, 60.26; H, 3.08; N, 12.22. Found: C, 60.45; H, 3.43; N, 12.03.

Acknowledgments.—We thank Mr. R. B. Bicknell and his staff for the large-scale preparations of intermediates, as well as those already named in the Experimental Section.

Registry No.—5a, 42245-94-3; 5b, 42245-95-4; 5c, 42245-96-5; 7, 42245-97-6; 8, 42245-98-7; 9, 42245-99-8; 10a, 42246-00-4; 10b, 42246-01-5; 11 picrate, 42246-02-6; 1-naphthylacetic acid, 86-87-3; pyridine-4-carboxaldehyde, 872-85-5; 1-naphthylacetonitrile, 132-75-2.

(16) Corrected melting point.

Optical Resolution of DL-Amino Acids by Preferential Crystallization Procedure

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To make preferential crystallization procedure more generally applicable for optical resolution of racemic amino acids, the resolution was carried out in the form of aromatic sulfonates of amino acids. Aromatic sulfonic acids were chosen because they vary greatly in properties and easily form salts with any kind of amino acids. Moreover it seemed very likely that some of these salts would form racemic mixtures suitable for preferential crystallization procedure. As a result of extensive studies, a method was developed for the resolution of amino acids in high yields such as DL-alanine, DL-leucine, DL-lysine, DL-serine, DL-3,4-dihydroxyphenylalanine, DL-tryptophan, and DL-3-(3,4-methylenedioxyphenyl)-2-methylalanine through the use of different aromatic sulfonic acids. These results indicate that the present method can be applied more generally for resolution of amino acids.

Although a number of methods for optical resolution of DL-amino acids have been reported, most of them have employed chemical or enzymatic procedures and only a few reports on preferential crystallization procedure have appeared.[1] If successfully applied, preferential crystallization procedure is a very advantageous method for the production of optically active amino acids, since the procedure can be easily accomplished by providing seed crystals of one antipode in a supersaturated solution of the racemic modification.[2] However, in nearly a century since the first example of this type of resolution was reported, satisfactory application of this simple procedure has been restricted to several amino acids such as asparagine,[3] histidine,[4]

(1) J. P. Greenstein and M. Winitz, "Chemistry of the Amino Acids," Vol. 1, Wiley, New York, N. Y., 1961, pp 715–716.

(2) R. M. Secor, *Chem. Rev.*, **63**, 297 (1963).

(3) A. Piutti, *C. R. Acad. Sci.*, **103**, 134 (1886).

(4) R. Duschinsky, *Chem. Ind. (London)*, **53**, 10 (1934); "Festschrift Emil Barell," Friedrich Reinhardt A. G., Basel, 1936, p 375.

threonine,[5] glutamic acids,[6,7] and aspartic acid.[8,9] The reason for this limited applicability is that most amino acids form racemic compounds instead of racemic mixtures and have no properties suitable for this resolution procedure. Although it was suggested[10] that resolution is possible when the solubility of each of the pure optical isomers is less than that of the racemic modification, resolution by preferential crystallization is more easily accomplished when the racemic modification forms a racemic mixture. Therefore, if it becomes possible to find out the conditions under which respective amino acid crystallizes as a racemic mixture, this convenient method is expected to be applied for all synthetic amino acids as a general method. To realize this expectation, the optical resolution of amino acids was carried out in the form of their aromatic sulfonates. Aromatic sulfonic acids were chosen because they vary greatly in properties and easily form salts with any kinds of amino acids, so that it is very likely that some of their salts will form racemic mixtures and can be resolved by preferential crystallization procedure. Previously, it was found that dl-lysine, as an example of basic amino acids, was resolved in the form of the salt with *p*-aminobenzenesulfonic acid.[11] Subsequently, under this idea, optical resolution of other amino acids was investigated, and it became possible to resolve many amino acids, for example, dl-alanine and dl-leucine as typical aliphatic amino acids, dl-serine as a hydroxy amino acid, dl-3,4-dihydroxyphenylalanine as an aromatic amino acid, dl-tryptophan as a heterocyclic amino acid, and dl-3-(3,4-methylenedioxyphenyl)-2-methylalanine as an α-alkyl amino acid. The optically active forms of these amino acids are important in nutritional and pharmaceutical fields. Especially, l-3,4-dihydroxyphenylalanine (l-DOPA) has been in large commercial demand as a specific drug for treatment of Parkinson's disease and l-3-(3,4-methylenedioxyphenyl)-2-methylalanine (l-MDPMA) is useful for an intermediate of the antihypertensive drug, l-3,4-dihydroxyphenyl-2-methylalanine (l-α-methyl DOPA).

Generally it is well recognized that the solid state infrared spectra of respective optical isomers are identical but different from that of the corresponding racemic compound.[12] However, in the case where racemic amino acids exist as a racemic mixture, the infrared spectrum of a racemic modification should be identical with that of the respective optical isomers. Thus the above amino acids were converted to the wide variety of the salts with aromatic sulfonic acids and the spectra of their optically active salts were compared with those of the respective racemic modifications. This method was very useful for screening the salts which form racemic mixtures. As a result, the spectra of dl-alanine *p*-chlorobenzenesulfonate (dl-Ala-*p*-ClBS), dl-leucine benzenesulfonate (dl-Leu-BS), dl-serine *m*-xylene-4-sulfonate (dl-Ser-*m*-XS), dl-3,4-dihydroxyphenylalanine 2-naphthol-6-sulfonate (dl-DOPA-NS·$^3/_2H_2O$), dl-tryptophan benzenesulfonate (dl-Trp-BS), and dl-3-(3,4-methylenedioxyphenyl)-2-methylalanine *p*-phenolsulfonate (dl-MDPMA-*p*-PS·H_2O), were found to be exactly identical with those of the corresponding optical isomers. The result suggests that these racemic modifications exist as racemic mixtures. This was also supported by the melting point–composition diagram. In each case, the melting point of the racemic modification was identical with that of the mechanical mixture of equal amount of the two antipodes, and admixture of one of the pure isomers to the racemic modification increased the melting point. Also, the solubility of the racemic modifications was much higher than that of the corresponding isomers. The saturated solution of the racemic modifications no longer dissolved the optically active isomers. Thus, dl-Ala-*p*-ClBS, dl-Leu-BS, dl-Ser-*m*-XS, dl-DOPA-NS·$^3/_2H_2O$, dl-Trp-BS, and dl-MDPMA-*p*-PS·H_2O could be easily screened as the simple salts forming the racemic mixtures.

The resolutions of these salts were accomplished in the usual manner. Seeding a supersaturated solution of each racemic modification with the crystals of the desired isomer (for example, l isomer) brought about preferential crystallization of the l isomer, while the nonseeded d isomer remained in the mother liquor as supersaturation. The resolutions were also carried out without seeding by spontaneous crystallization of an excess isomer (l isomer) from a supersaturated solution containing an excess of one isomer (l isomer). This procedure of using an excess of one isomer in the initial solution was equivalent, in principle, to adding seed crystals because the l isomer present in higher concentration began to crystallize initially and it played a role of seed crystals. However, the most favorable resolution procedure in a practical purpose was that described in the Experimental Section. This was started with a supersaturated solution containing an excess of one isomer (l isomer). Furthermore, the solution was nucleated with the isomer (l isomer) present in excess. In this case, preferential crystallization of l isomer occurred more rapidly and smoothly without crystallization of d isomer. The presence in the initial solution of an excess of the isomer being crystallized seemed to be important for the successful functioning of the resolution procedure. It was also desirable that the amount of an excess isomer (l isomer) dissolved initially in a supersaturated solution of racemic modification was adjusted to almost the same amount of l isomer resolved in a single cycle, and that the amount of crystallization was controlled to about twofold of the excess of l isomer employed initially. In that case, almost the same conditions as the first, except that the solution contained d isomer in excess, could be obtained by adding the same amount of the racemic modification as that of the l isomer previously separated into the mother liquor. Then d isomer was separated in the same way. Thus, the entire cycle could be repeated and both l and d isomers were obtained reciprocally. However, the amount of a desired isomer resolved in a single cycle should be limited in order to avoid crystallization of the antipode. As shown in Table IV, optimal conditions for resolution were dependent on the properties of the individual racemic modification. The iso-

(5) L. Velluz and G. Amiard, *Bull. Soc. Chim. Fr.*, **20**, 903 (1953).
(6) F. Kögl, H. Erxleben, and G. J. van Veersen, *Z. Physiol. Chem.*, **277**, 260 (1943).
(7) T. Akashi, *Nippon Kagaku Zasshi*, **83**, 417 (1962).
(8) T. Haga, M. Sato, and K. Miura, Japanese Patent 42-3290 (1967).
(9) K. Harada, *Bull. Chem. Soc. Jap.*, **38**, 1552 (1965).
(10) A. Werner, *Ber.*, **47**, 2171 (1914).
(11) S. Yamada, M. Yamamoto, and I. Chibata, *J. Agr. Food Chem.*, **21**, 889 (1973).
(12) R. J. Koegel, R. A. McCallum, J. P. Greenstein, M. Winitz, and S. M. Birnbaum, *Ann. N. Y. Acad. Sci.*, **69**, 94 (1957).

mers obtained by this procedure were almost optically pure. If the optical purity is not satisfactory and further purification is required, the crude products can be easily purified by recrystallization without loss of the optically active isomer. The optically active enantiomorph no longer dissolves in the saturated solution of the racemic modification. Therefore, this purification can be performed by dissolving the mixture in a minimum amount of water required to dissolve the racemic modification in the crude crystals, and allowing the pure crystals to crystallize out. However, the operation is not so easy because the amount of water required to dissolve the racemic impurity is very small. So it was convenient to carry out the above operation by adding an appropriate amount of the solution saturated with the racemic modification. Thus, obtained optically pure sulfonates were easily converted to optically pure amino acids by neutralization with alkali or by use of ion exchange resin.

In the present work we cannot establish a theory to predict what kind of racemic modification forms a racemic mixture suitable for the resolution by preferential crystallization. By the use of aromatic sulfonates, however, it becomes easy to find out the simple salts which form racemic mixtures and can be resolved by the preferential crystallization procedure. Consequently, it is very likely that the present simple method using aromatic sulfonates may be applied more generally for resolution of synthetic amino acids.

Experimental Section

Materials.—Analytical standard grade amino acids manufactured by our company, Tanabe Seiyaku Co., Ltd., were used, except MDPMA.[13] All aromatic sulfonic acids were obtained from Tokyo Kasei Kogyo Co., Ltd., and E. Merck AG. These were used without further purification.

Analyses.—All samples for analyses were dried overnight *in vacuo* at 45–50° unless otherwise noted. Melting points were measured with a Yamato MP-21 melting point apparatus in an unsealed capillary tube and were uncorrected. Infrared spectra of samples were determined in KBr disks using a Shimazu infrared spectrophotometer, Model IR-27G. Optical rotations were measured with a Perkin-Elmer 141 automatic polarimeter. Elemental analyses were performed by a Perkin-Elmer 240 elemental analyzer. Solubility was determined by approaching saturation equilibrium from both sides of undersaturation and supersaturation. Concentration of solutes was measured by a Karl Zeiss immersion refractometer.

Preparation of Aromatic Sulfonates of Amino Acids.—DL-Alanine *p*-chlorobenzenesulfonate (DL-Ala-*p*-ClBS), DL-3,4-dihydroxyphenylalanine 2-naphthol-6-sulfonate (DL-DOPA-NS·$^3/_2H_2O$), DL-leucine benzenesulfonate (DL-Leu-BS), DL-lysine *p*-aminobenzenesulfonate (DL-Lys-*p*-ABS), DL-3-(3,4-methylenedioxyphenyl)-2-methylalanine *p*-phenolsulfonate (DL-MDPMA-*p*-PS·H_2O), DL-serine *m*-xylenesulfonate (DL-Ser-*m*-XS), and DL-tryptophan benzenesulfonate (DL-Trp-BS) were easily prepared from amino acids and the corresponding aromatic sulfonic acids.

A mixture of 1 mol of amino acids and 1.03 mol of aromatic sulfonic acids was dissolved in water by heating, treated with charcoal, concentrated *in vacuo*, and cooled in a refrigerator. The resulting precipitates and further crops obtained by successive concentrations of the combined filtrate were collected, washed with cold water, and dried *in vacuo* at 45°. The products were almost pure and could be used for optical resolution without further purification. The optically active isomers were prepared in the same way. The total yields based on the amino acids were from 95 to 98%. The elemental analyses are summarized in Table I.

TABLE I

AROMATIC SULFONATES OF AMINO ACIDS

Aromatic sulfonate of amino acids (elemental composition)		Elemental analysis, % Calcd	Found DL	Found L
Ala-*p*-ClBS ($C_9H_{12}ClNO_5S$)	C	38.37	38.48	38.23
	H	4.29	4.40	4.42
	N	4.97	4.87	4.80
	S	11.38	11.52	11.20
DOPA-NS·$^3/_2H_2O$ ($C_{19}H_{19}NO_8S·^3/_2H_2O$)	C	50.89	50.83	50.95
	H	4.97	4.70	4.97
	N	3.12	3.03	3.13
	S	7.15	7.27	7.29
Leu-BS ($C_{12}H_{19}NO_5S$)	C	49.81	50.04	50.06
	H	6.62	6.65	6.64
	N	4.84	4.97	4.82
	S	11.08	10.93	11.20
Lys-*p*-ABS ($C_{12}H_{21}N_3O_5S$)	C	45.12	45.20	45.00
	H	6.63	6.73	6.74
	N	13.16	13.09	13.14
	S	10.04	10.01	10.06
MDPMA-*p*-PS·H_2O[a] ($C_{17}H_{19}NO_8S·H_2O$)	C	49.15	49.27	49.27
	H	5.10	5.21	5.10
	N	3.37	3.32	3.32
	S	7.72	7.70	7.66
Ser-*m*-XS ($C_{11}H_{17}NO_6S$)	C	45.35	45.38	45.43
	H	5.88	5.91	5.92
	N	4.81	4.70	4.76
	S	11.01	11.06	10.93
Ser-*m*-XS·$2H_2O$[b] ($C_{11}H_{17}NO_6S·2H_2O$)	C	40.36	40.25	40.55
	H	6.47	6.32	6.47
	N	4.28	4.33	4.23
	S	9.80	9.78	9.75
Trp-BS ($C_{17}H_{18}N_2O_5S$)	C	56.34	56.63	56.53
	H	5.01	5.04	5.07
	N	7.73	7.88	7.80
	S	8.85	8.57	8.82

[a] Recrystallized from 0.25 mol of an aqueous solution of *p*-phenolsulfonic acid. [b] Dried in air at room temperature.

The samples for elemental analysis were recrystallized from water except for MDPMA-*p*-PS·H_2O. Recrystallization of DL-MDPMA-*p*-PS·H_2O from water gave DL-MDPMA-$^1/_2$*p*-PS (hemisulfonate) as colorless prisms, mp 237–238° dec. *Anal.* Calcd for $C_{11}H_{13}O_4N·^1/_2(C_6H_6O_4S)$: C, 54.19; H, 5.20; N, 4.51; S, 5.17. Found: C, 53.99; H, 5.28; N, 4.45; S, 4.96. On the other hand, recrystallization from 0.25 mol of an aqueous solution of *p*-phenolsulfonic acid gave a monosulfonate as needles. It was stable as a hydrate and melted at 110–120, 184–186, and 192–193° with decomposition. For the optically active MDPMA-*p*-PS·H_2O, the hemisulfonates were not obtained. The optically active and racemic Ser-*m*-XS·$2H_2O$ crystallized from water as dihydrate. Elemental analyses of the samples dried in air at room temperature corresponded to $C_{11}H_{17}NO_6S·2H_2O$. Drying the samples *in vacuo* over P_2O_5 or at elevated temperatures yielded their anhydrates.

The properties of the aromatic sulfonates of amino acids thus obtained are shown in Table II.

Optical Resolution.—A typical experiment for the resolution was carried out as follows. DL-Ser-*m*-XS (94.00 g) and L-Ser-*m*-XS (6.00 g) were dissolved in 100 ml of water at elevated temperature. The mixture was cooled to 25°, seeded with L-Ser-*m*-XS·$2H_2O$ (0.10 g), and stirred for 50 min at the same temperature. The precipitated crystals were collected by filtration, washed with small amount of cold water, and dried. The crystals thus obtained were optically pure, yield 12.66 g, $[\alpha]^{26}D$ +4.1° (*c* 4, H_2O), mp 172–173°. *Anal.* Found: C, 45.37; H, 5.87; N, 4.85; S, 11.14. After the separation of the L isomer, DL-Ser-*m*-XS (13.88 g) and a small amount of water were added to the mother liquor. The amounts of the addition were adjusted by refractometric measurement and weighing

(13) DL-MDPMA was prepared from 3,4-methylenedioxyphenylacetone according to the method of G. A. Stein, H. A. Bronner, and K. Pfister, III, *J. Amer. Chem. Soc.*, **77**, 700 (1955). Optically pure L- and D-MDPMA were prepared by the optical resolution of the *N*-acetyl menthyl ester according to the method of S. Terashima, K. Achiwa, and S. Yamada, *Chem. Pharm. Bull.*, **13**, 1399 (1965).

Table II

Properties of Aromatic Sulfonates of Amino Acids

Aromatic sulfonate of amino acids	Isomer	Mp, °C	$[\alpha]^{25}_{D}$, deg (c 2, water)	$[\alpha]^{25}_{365}$, deg (c 2, water)	Solubility in water, g/100 ml (°C)		
Ala-*p*-ClBS	dl	190–192			50.2 (15)	86.3 (30)	139.2 (45)
	l	222–223	+3.6	+15.4	24.2 (15)	37.2 (30)	67.5 (45)
DOPA-NS·$^3/_2H_2O$	dl	152–154			1.6 (10)	3.3 (30)	9.0 (50)
	l	162–164	−8.6	−19.7	1.1 (10)	2.0 (30)	5.3 (50)
Leu-BS	dl	152–154			39.4 (15)	58.0 (25)	
	l	172–173	+3.2	+18.6	17.0 (15)	22.9 (25)	
Lys-*p*-ABS	dl	238–239			54.0 (15)	66.1 (25)	90.6 (45)
	l	250–251	+6.2	+23.0	33.8 (15)	42.7 (25)	63.1 (45)
MDPMA-*p*-PS·H_2O[c]	dl	192–193			10.8 (10)	18.6 (25)	76.3 (45)
	l	212–213	+0.8[a]	+14.0[a]	5.0 (10)	8.3 (25)	25.0 (45)
Ser-*m*-XS	dl	157–158			45.1 (15)	80.9 (25)	175.4 (40)
	l	172–173	+4.1[b]	+19.6[b]	23.5 (15)	39.5 (25)	86.8 (40)
Trp-BS	dl	210–211			5.7 (15)	10.7 (35)	20.9 (50)
	l	234–235	−2.9	+16.8	3.5 (15)	5.6 (35)	8.9 (50)

[a] 1% in 1 *N* HCl. [b] 4%. [c] Solubility was determined in 0.25 mol of *p*-phenolsulfonic acid aqueous solution.

Table III

Successive Resolution of dl-Ser-*m*-XS[a]

Expt	Amount of addition		Composition of solution		Crystals separated	
	dl form, g	Active form, g	dl form, g	Active form g	Yield, g	Optical purity, %
1 (l)	94.00	6.00	94.00	6.00	12.66	100
2 (d)	13.88		93.84[b]	6.16[b]	12.52	98
3 (l)	13.08		94.02[b]	5.98[b]	11.34	100
4 (d)	13.34		94.74[b]	5.26[b]	13.24	98
5 (l)	14.24		92.36[b]	7.64[b]	12.20	97
6 (d)	12.20		95.92[b]	4.08[b]	12.42	98
7 (l)	14.40		92.04[b]	7.96[b]	13.10	97
8 (d)	14.84		95.36[b]	4.64[b]	13.54	97
9 (l)	15.32		91.62[b]	8.38[b]	12.56	98
10 (d)	14.42		96.14[b]	3.86[b]	12.18	96
Mean	13.97		94.00	6.00	12.58	98

[a] Resolution was carried out on a 100-ml scale. Crystallization time was 50 min in every case. [b] Values calculated theoretically from analysis of separated crystals.

Table IV

Optical Resolution of Aromatic Sulfonates of Amino Acids[a]

Aromatic sulfonate of amino acids	Resoln no.	Registry no.	Amount of addition: dl form, g	Amount of addition: Registry no.	Amount of addition: Active form, g	Composition of solution: dl form, g	Composition of solution: Active form, g	Crystn: Temp, °C	Crystn: Time, min	Separated crystals: Yield, g	Separated crystals: Optical purity, %
Ala-*p*-ClBS	1 (l)	36760-85-7	97.00	42334-78-1	5.00	97.00	5.00	30	40	10.56	98
	2 (d)	36760-86-8	11.00			96.71[b]	5.29[b]	30	40	10.34	98
DOPA-NS·$^3/_2H_2O$	1 (l)	42334-82-7	16.00	42334-81-6	3.00	16.00	3.00	50	25	6.44	100
	2 (d)	42334-83-8	6.50			15.66[b]	3.34[b]	50	25	6.52	100
Leu-BS	1 (l)	42398-40-3	66.50	42398-39-0	1.00	66.50	1.00	25	50	2.23	93
	2 (d)	42398-41-4	2.32			66.53[b]	0.97[b]	25	50	2.12	93
Lys-*p*-ABS	1 (l)	27168-73-6	77.00	42719-79-9	5.00	77.00	5.00	25	65	11.04	98
	2 (d)	42398-44-7	11.54			76.26[b]	5.74[b]	25	65	11.72	98
MDPMA-*p*-PS·H_2O[c]	1 (l)	42334-84-9	50.00	42398-45-8	7.50	50.00	7.50	25	120	17.83	95
	2 (d)	42398-46-9	18.40			48.36[b]	9.14[b]	25	120	17.92	97
Ser-*m*-XS[d]	1 (l)	27168-77-0	94.00	27168-75-8	6.00	94.00	6.00	25	50	12.66	100
	2 (d)	27168-76-9	13.88			93.84[b]	6.16[b]	25	50	12.52	98
Try-BS	1 (l)	42719-78-8	16.00	42719-79-9	1.20	16.00	1.20	35	50	2.84	92
	2 (d)	42746-61-2	2.93			15.88[b]	1.32[b]	35	50	2.78	92

[a] Resolution was carried out on a 100-ml scale by use of 0.10 g of seed crystals. [b] Values calculated theoretically from analysis of separated crystals. [c] Resolution was carried out in 0.25 mol of *p*-phenolsulfonic acid aqueous solution. [d] Dihydrates of this compound were used as seed crystals.

according to a standard curve previously constructed. Thus, almost the same composition as in the previous resolution was obtained, except that the predominant enantiomorph was d isomer. This supersaturated solution was seeded with d-Ser-*m*-XS·$2H_2O$ (0.10 g) at 25° and stirred for 50 min. Drying the precipitated crystals yielded d-Ser-*m*-XS (12.52 g) which had 98% optical purity. By repeating these procedures, l and d isomers were successively obtained as shown in Table III.

Other sulfonates of amino acids could also be resolved in the same manner as described above. Conditions for the resolution and the analyses for separated crystals are summarized in Table IV.

Optical Purification of Optically Impure Isomers.—The isomers obtained by the above procedure were practically pure. If the optical purification is, however, required, it can be performed as follows. Crude l-Ser-*m*-XS (10.00 g, optical purity 87.7%) was mixed with 1.5 ml of water and an appropriate amount (30 ml) of the solution saturated with dl-Ser-*m*-XS at 25° and dissolved at elevated temperature. The mixture was then stirred for 2 hr at 25°. The resulting crystals were collected

TABLE V
OPTICALLY ACTIVE AMINO ACIDS PREPARED FROM THEIR AROMATIC SULFONATES

Amino acid	Registry no. D	Registry no. L	Method	Yield, %	N analysis, % Calcd	N analysis, % Found L	N analysis, % Found D	[α]²⁵D, deg (c 2, 5 N HCl) L	[α]²⁵D, deg (c 2, 5 N HCl) D
Alanine	338-69-2	56-41-7	Ion exchange	96	15.72	15.72	15.73	+14.6	−14.6
DOPA	5796-17-8	59-92-7	LiOH	96	7.10	7.08	7.11	−12.2[a]	+12.3[a]
Leucine	328-38-1	61-90-5	Ion exchange	95	10.68	10.63	10.64	+15.9	−16.0
Lysine HCl	42334-88-3	10098-89-2	Ion exchange	96	15.34	15.41	15.45	+20.8	−20.8
MDPMA	42334-90-7	42334-89-4	NH_4OH	96	6.28	6.27	6.27	+25.4[b]	−25.4[b]
Serine	312-84-5	56-45-1	Ion exchange	98	13.33	13.37	13.35	+15.0[c]	−15.1[c]
Tryptophan	153-94-6	73-22-3	NH_4OH	95	13.72	13.74	13.73	−32.4[d]	+32.5[d]

[a] 4%, in 1 N HCl, at 20°. [b] $[\alpha]^{25}_{365}$, 1% in 1 N HCl. [c] In 1 N HCl. [d] 1% in H_2O.

by filtration, washed with a small amount of cold water, and dried. By this operation, optically pure crystals of L-Ser-*m*-XS were obtained, yield 8.62 g, $[\alpha]^{25}D$ +4.1° (*c* 4, H_2O).

Preparation of Optically Active Amino Acids.—From optically pure aromatic sulfonates of amino acids, the free amino acids were easily obtained either by neutralization with alkali or by use of an ion exchange resin. In the former, an aqueous solution of aromatic sulfonates was adjusted with alkali to the isoelectric point of the amino acids and cooled in a refrigerator overnight. The crystallized free amino acids were filtered off, washed with cold water, and dried. This method was convenient for sparingly soluble amino acids. For readily soluble amino acids, the latter method was employed. Aromatic sulfonates were taken up in a tenfold amount of water. The solution was passed through an ion exchange column of Amberlite IR-120 (in H form). The column was washed with water and the amino acid was eluted with 2 *N* NH_4OH. The eluate was concentrated, treated with charcoal, and concentrated again until the crystalline precipitate appeared. To the residue MeOH was added and the mixture was allowed to stand in a refrigerator overnight to give the colorless amino acid.

Table V indicates the yields and the specific rotations of optically active amino acids obtained by this process.

For the preparation of L-α-methyl DOPA, the L-MDPMA (50.0 g) obtained above was hydrolyzed with 20% hydrochloric acid (930 ml) and phenol (47 g) for 17 hr. After evaporation, the residue was dissolved in 120 ml of water and adjusted to pH 5.8 with 5 *N* NH_4OH containing a small amount of sodium bisulfite. The precipitate was collected, and further crops were obtained by successive concentrations of the filtrate. The total yield of L-α-methyl DOPA·$^3/_2H_2O$ was 43.6 g (81.6%). Recrystallization from sulfurous acid solution (0.5%) gave a white powder of L-α-methyl DOPA·$^3/_2H_2O$, and drying of the sesquihydrate *in vacuo* at 100° gave the anhydrous form, mp 306–307° dec, $[\alpha]^{25}D$ −5.2°, $[\alpha]^{25}_{578}$ −5.5° (*c* 2, 0.1 *N* HCl). *Anal.* Calcd for $C_{10}H_{13}NO_4$: C, 56.86; H, 6.20; N, 6.63. Found: C, 56.63; H, 6.24; N, 6.59.

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Registry No.—DL-MDPMA·$^1/_2$ *p*-PS, 42398-50-5; L-α-methyl DOPA, 555-30-6.

Total Synthesis of *dl*-Prostaglandin E_1

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dl-Prostaglandin E_1 (PGE_1) (**61**) has been synthesized in 14 steps from 2-carboxy-5-oxo-1-cyclopentenehexanoic acid (**15**). The synthesis required the development of two mild procedures and a new protecting group. A Moffatt oxidation using a water-soluble carbodiimide converted the carbinol **52** to aldehyde **53**. The Wittig reaction of aldehyde **53** with the tributylphosphorane **36** was used to obtain the enone **54**. Protection of the cyclopentanone carbonyl group was achieved *via* the phenylthiomethyl oxime **48**. This derivative is unaffected by mild oxidative (Moffatt or Collins) or reductive (borohydride) procedures and yet can be readily cleaved back to the unsubstituted oxime with mercury ion catalysis and hence in turn to the ketone.

The prostaglandins have, during the past decade, become a major area of biological[1] and clinical investigation.[2] As a consequence of their limited accessibility from natural sources, and the desire to explore the structural requirements for their biological activity, the prostaglandins have become the synthetic targets of many groups.[3] Several of these groups have reported specific syntheses of prostaglandin E_1 (PGE_1)[4] (**61**). We now describe the details of our synthesis of PGE_1.[5]

At the time our efforts commenced there was no significant clinical work published on the prostaglandins which would indicate any important differences between PGE_1 and PGE_2. PGE_1 seemed to be the most appropriate target compound, as it had been converted to PGA_1 and $PGF_1\alpha$[3] and the additional double bond in the carboxylic acid side chain of PGE_2 seemed to pose additional synthetic limitations.

The preparation of an appropriate starting material, **15**, was anticipated as being possible by a process analogous to one of those used to synthesize isosarkomycin, 2-methyl-3-carboxycyclopentenone. The synthesis of Shemyakin[6] was briefly investigated but discarded in favor of the procedure used by Newman.[7]

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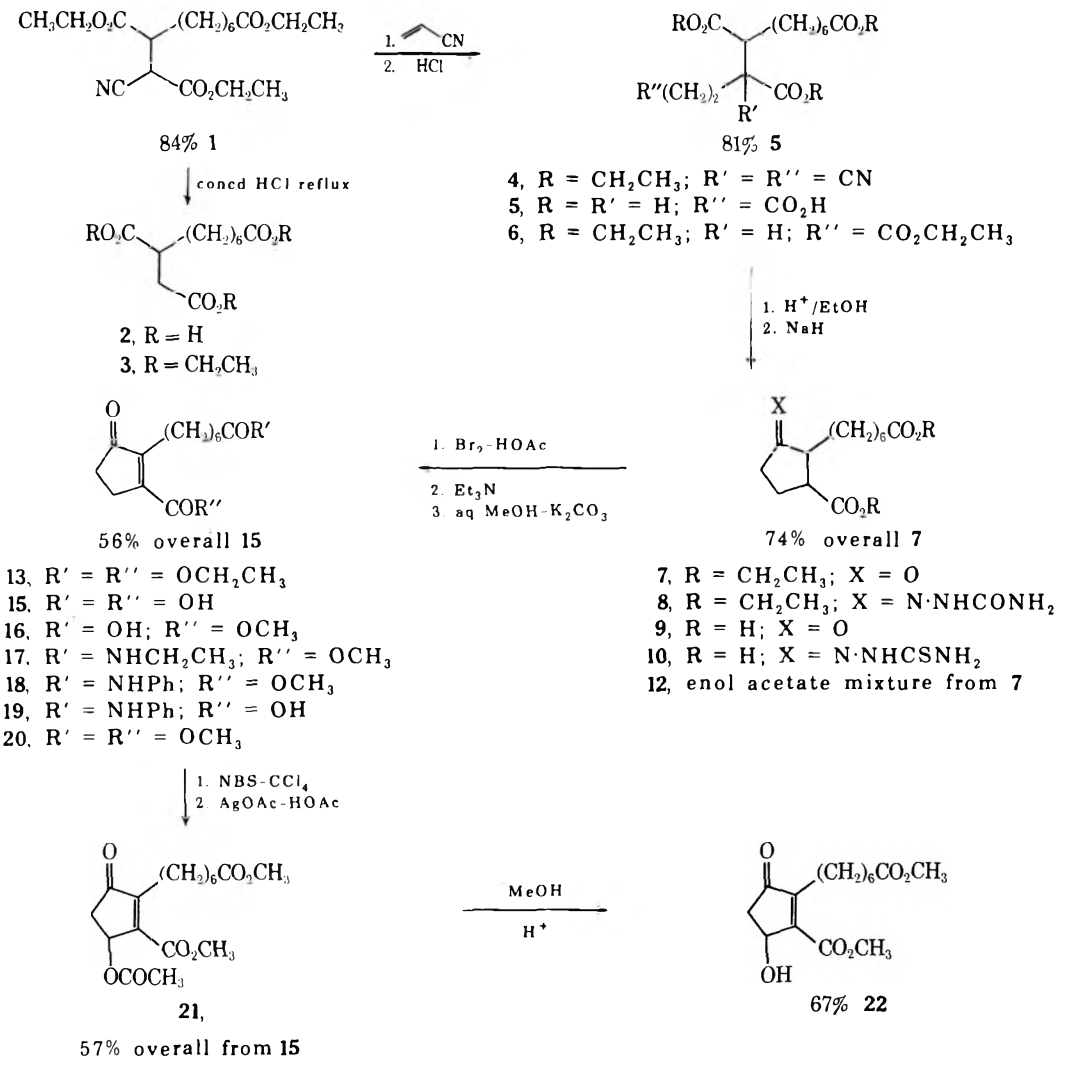
SCHEME I



Substituting readily available diethyl α-bromoazelate[8] for the ethyl α-bromopropionate used by Newman gave access in good yield to the cyclopentenone diacid **15** (Scheme I). The only critical step in this procedure was to ensure that the addition of acrylonitrile to compound **1** goes to completion (tlc). If adduct **4** is contaminated with unreacted starting material, **1**, hydrolysis gives a crystalline mixture of tetraacid **5** and triacid **2**. The acids **5** and **2** cocrystallize and the presence of **2** in **5** becomes easily evident only after esterification, when the presence of the triester **3** in the tetraester **6** can be readily detected by vpc. After Dieckmann cyclization of **6**, the resultant cyclopentanone diester, **7**, was hydrolyzed to the diacid.[9] Conversion of **7** to the cyclopentenone diester **13** was explored both *via* bromination of the enol acetate mixture **12** and directly of **7** followed by dehydrobromination. Both procedures gave comparable overall yields, and the latter procedure was one step less, so this was employed for the large scale preparations.

Introduction of the hydroxyl group into the cyclopentenone diester **13** (Scheme I), to obtain **22**, also employed well-established procedures.[10] The only ambiguity possible, *i.e.*, that the hydroxyl group of **22** was in position 5 rather than 4 of the cyclopentenone ring, was removed by spectral comparison (particularly the uv shift with base) of the precursor to **22**, the acetoxycyclopentenone diester **21**, with 2-methyl-3-carbomethoxy-4-acetoxycyclopentenone whose structure has been firmly established.[11]

To obtain the appropriate stereochemistry for PGE_1, *i.e.*, trans,trans, it was presumed that silylation of the hydroxycyclopentenone diester **22** would create a functionality, *i.e.*, the siloxy group, large enough to influence the direction of hydrogenation. Thus cis addition of hydrogen to the double bond of siloxycyclopentenone **25** from the side opposite to the siloxy group would yield an all-cis siloxycyclopentanone. Epimerization then at the center α to the carbomethoxy group should lead predominantly to the desired all-trans arrangement. In fact, hydrogenation of the siloxycyclopentanone diester, **25**, over Raney nickel gave a crystalline siloxycyclopentanone, **26**, in almost quantitative yield. A single spot on tlc and crystallinity were taken as indicators of homogeneity. Reaction with methoxyamine in pyridine gave a crystalline

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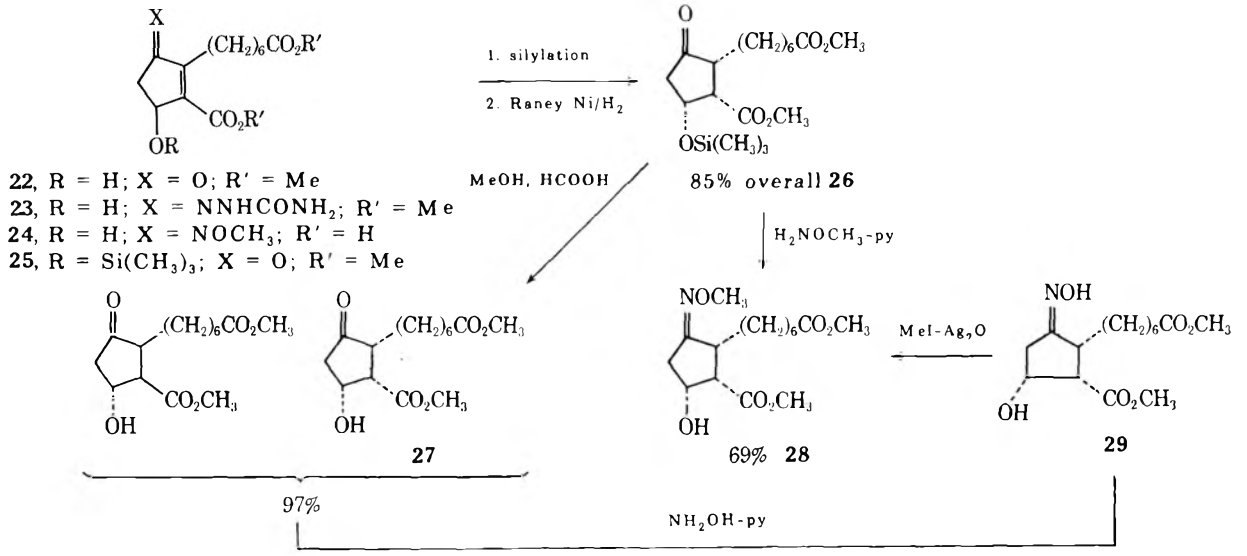
SCHEME II



methyl oxime, **28**, in 69% yield. The mother liquor material contained a second compound, which was assumed to be a syn or anti isomer of **28**. Reaction of siloxycyclopentanone, **26**, with hydroxylamine gave an oxime, **29**, which could be O-methylated to give the same methyl oxime, **28**, as had been obtained directly from **26** with methoxyamine. Serious doubts, for several reasons, developed about whether the methyl oxime mother liquor material was indeed a syn or anti isomer and as epimerization during methyl oxime formation had been excluded[12] these doubts necessarily extended to the homogeneity of **26**. Treatment of this substance with methanolic formic acid at room temperature, to remove the silyl group, yielded a crystalline hydroxycyclopentanone, which by tlc was clearly a mixture of two substances. Both isomers cocrystallized and several recrystallizations were necessary to obtain a homogeneous sample of the major isomer **27** (Scheme II). Compound **27** yielded the same oxime derivatives as could be obtained directly from the siloxycyclopentanone, **26**. The minor isomeric hydroxycyclopentanone was subsequently shown to be a cis,-trans compound derived by hydrogenation from the same side as the siloxy group. This was therefore the origin of the "mother liquor" methyl oxime, rather than syn–anti isomerism. Despite our disappointment in the lack of stereospecificity at the hydrogenation step, our expectations were completely fulfilled on treatment of the major all-cis crystalline methyl oxime, **28**, with base. Hydrolysis with aqueous methanolic potassium carbonate and reesterification with diazomethane yielded an isomeric compound, **32**, which contained only traces of the starting material **28**. That this change involved epimerization at the carbomethoxy group was confirmed by an ir dilution study of the OH region. The crystalline methyl oxime, **28**, showed a concentration-independent behavior expected for a cis arrangement of hydroxyl group and ester, which makes possible a strong *intra*molecular hydrogen bond. The isomeric methyl oxime, **32**, exhibited concentration-dependent behavior and can be reasonably assigned a trans stereochemistry at these centers.[12] Independent work[12] on methyl oximes derived from configurationally unstable ketones demonstrated that under these conditions epimerization α to the methyl oxime was unlikely. Thus the stereochemistry of the epimerized methyl oxime, **32**, can be assigned all trans, assuming cis addition of hydrogen at the reduction step.

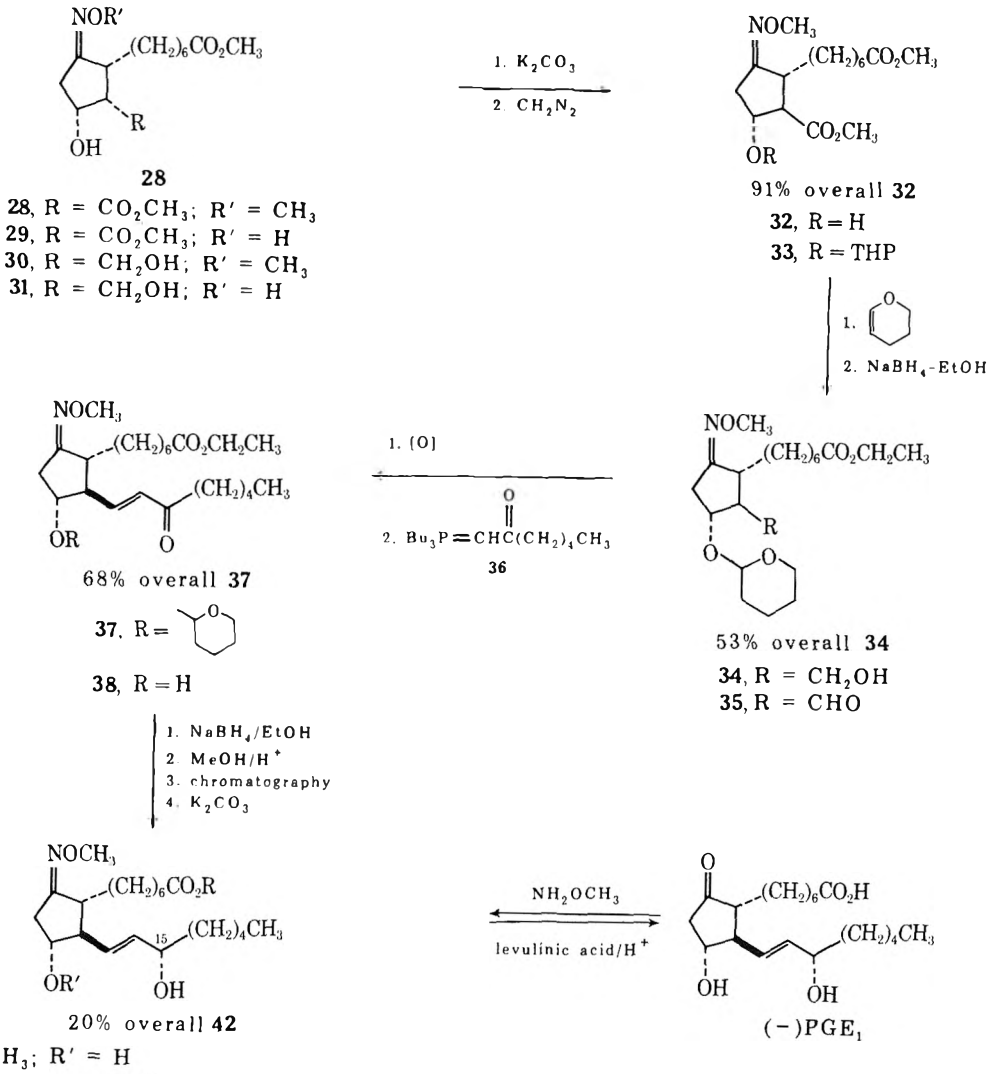
The next step in the sequence called for selectivity between the ester at the end of the chain and that on the ring. Earlier efforts (Scheme I) had provided half-ester acid derivatives of cyclopentenone diacid **15**, *e.g.*, compounds **17** and **18**. Nevertheless, based both on the yields by which they were obtained and the ease of their conversion to the hydroxycyclopentenones, these compounds, **17** and **18**, were not regarded as being useful intermediates, which would provide this selectivity. Therefore, an alternative approach was explored. It had been anticipated that selectivity between the esters would be possible *via* an internal assist from the hydroxy group, *e.g.*, sodium borohydride might be expected to reduce the ester attached to the ring *via* an intermediate alkoxy borohydride. Alas the stereochemical differences evident in the ir study, discussed above, now worked against us. The all-cis crystalline methyl oxime, **28**, was reduced rapidly in good yield to the crystalline diol methyl oxime ester **30**, but epimerized methyl oxime **32** reacted only sluggishly with borohydride and no discrimination was evident in the reduction of the esters. In desperation the dihydropyran addition step was carried out and borohydride reduction repeated on THP ether **33**. For reasons we do not completely understand, **33** gave selective reduction of the ester on the ring and the desired THP methyl oxime ester carbinol, **34**, could be readily separated by chromatography from overreduced material. Nevertheless this step is the poorest in the scheme, except for the cleavage of PGE_1 oxime.

Oxidation of carbinol **34** to aldehyde **35** could be effected in almost quantitative yield by a modified Moffatt oxidation[13] using the water-soluble 1-cyclo-

(12) Configurational stability of methyl oximes from epimerizable ketones, the stereochemical assignments to substituted 2-hydroxycyclopentanecarboxylic acids, and other model studies will be discussed in more detail in a subsequent paper.

(13) (a) J. G. Moffatt, *Org. Syn.*, **47**, 25 (1967); (b) N. M. Weinshenker and C. M. Shen, *Tetrahedron Lett.*, 3285 (1972).

SCHEME III



hexyl-3-(2-morpholinoethyl)carbodiimide metho-*p*-toluenesulfonate (Aldrich C-10, 640-2). The excess reagent was readily removed by an ice water wash. In this instance the product would be affected by oxalic acid treatment, normally used to remove excess DCC, the reagent used by Moffatt.[13a] Other modifications of the Moffatt oxidation have been developed by the Alza group.[13b] Reaction of aldehyde **35** with the tributylphosphorane **36** gave the enone **37**. The use of **36** was developed by us because of the instability of the reactant aldehyde **35**. Tributylphosphoranes were known to be more reactive than the conventional triphenylphosphoranes.[14] Thus a Wittig reaction with the tributylphosphorane **36** is possible under milder conditions.

The enone **37** was reduced with sodium borohydride in ethanol at room temperature. Under these conditions with the THP group still present, little conjugate reduction (estimated by nmr) was evident. The mixture of allylic alcohols **40** was treated with methanolic hydrochloric acid to remove the THP group and the mixture of hydroxy allylic alcohols, **39** and **41**, subjected to preparative tlc on alumina plates. The slower moving material, **39**, crystallized. Hydrolysis of this with methanolic potassium carbonate solution gave (±)-PGE_1 methyl oxime, **42**, which was identical spectrally and on tlc with the methyl oxime prepared from (−)-PGE_1[15] (Scheme III).

A variety of methods were investigated for cleavage of the methyl oxime back to PGE_1. Attention was directed to the nonoxidative procedures used for oximes, *i.e.*, reduction or exchange processes. Reaction in levulinic acid or its ethyl ester containing aqueous mineral acid at 4° effected some conversion to PGE_1. However, the yields were poor, and the process was clearly unsuited for providing adequate quantities of prostaglandin analogs. What was needed was an oxime, which could be cleaved more readily. An unsubstituted oxime would be suitable as many mild

(14) A. J. Speziale and D. E. Bissing, *J. Amer. Chem. Soc.*, **85**, 3878 (1963).

(15) We wish to acknowledge help by Swiss colleagues with this comparison during a stay in Basle in 1967 by Neville Finch. CIBA-GEIGY colleagues, Dr. J. Schmidlin obtained the ir spectra, Dr. H. Hurzeler the mass spectra, and Dr. Neher made the tlc comparisons. Dr. U. Scheidegger (Varian, Zurich) obtained nmr spectra on 2 mg by use of a CAT. A sample of (−)-PGE_1 was kindly provided by Professor D. A. vanDorp (Unilever).

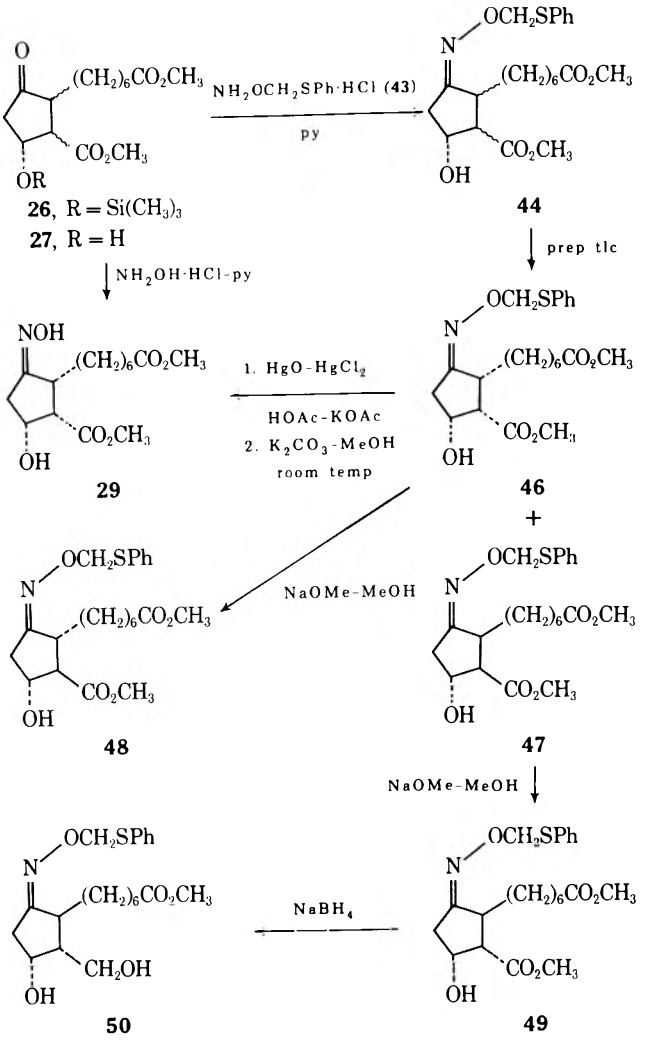
methods are available for conversion of oximes back to ketones.[16] However, unsubstituted oximes will not survive even the mild oxidation conditions of the Moffatt oxidation;[17] so an appropriate protecting group was required. After several investigations[18] one particularly satisfactory reagent was discovered which should have broad applicability for the protection of sensitive ketones, phenylthiomethoxamine **43**. This was prepared and treated with a variety of ketones. The phenylthiomethyl oximes were cleaved back to the unsubstituted oximes in a two-step procedure. Treatment with a mixture of mercuric oxide and mercuric chloride in potassium acetate–acetic acid gave the acetoxymethyl oxime which was unstable and collapsed to the unsubstituted oxime on treatment with methanolic potassium carbonate in the cold.[19]

While this procedure involves multiple operations it is well suited for telescoping, and overall yields are excellent.

The siloxycyclopentanone **26** or the desilylated material **27** reacted with phenylthiomethoxyamine hydrochloride (**43**) in pyridine to give a crystalline product, **44**, in excellent yield. As with other derivatives in this series both isomers had cocrystallized. The major isomer, the all-cis compound **46**, was separated on the first occasion by preparative tlc and fully characterized along with the minor isomer **47**. Application of the cleavage conditions to **46** gave the unsubstituted oxime **29**, which was identical with that obtained as the major product from the reaction of hydroxylamine on the siloxycyclopentanone **26** (Scheme IV). After appropriate experiments on model compounds,[19] to confirm the stability of the new group to oxidation conditions, the scheme proceeded with compound **44** as an intermediate. The epimerization step was first carried out on the separated isomers **46** and **47**. They were separately converted by methanolic sodium methoxide at reflux almost exclusively into epimeric substances (Scheme IV). That the epimerization involved the center α to the carbomethoxy group in both cases was evident from the fact that the minor isomer **47** which was resistant to sodium borohydride reduction was epimerized to **49**. This was smoothly reduced to the crystalline diol ester **50** by sodium borohydride (Scheme IV), thus establishing that the ester and hydroxyl group were cis to one another in **49**. The reverse situation pertained to **46**, as its epimer, **48**, could be converted to a diol ester with sodium borohydride only *via* the THP derivative **51**, which, as we have shown above, is the behavior of a trans arrangement of ester and hydroxyl group.

In view of the lack of stereospecificity in the hydrogenation of the cyclopentenone diester **22** and the absence of a readily purifiable crystalline derivative, such as existed in the methyl oxime sequence, it was clearly necessary to achieve stereochemical homogeneity by means of chromatography. It turned out that separation after epimerization, *i.e.*, of **48** from **49** (Scheme IV)

SCHEME IV



by chromatography, was quite easy. Furthermore as silylation of the cyclopentenone **22** achieved very little in the way of increasing the stereospecificity of the hydrogenation step, it was clear that the process from **22** to **48** could be telescoped (Scheme V). Hydrogenation of **22** with Raney nickel yielded a mixture of the hydroxycyclopentanone, **27**, and its isomer (Scheme II), which was not purified but treated directly with phenylthiomethoxlamine hydrochloride, **43**, in pyridine. The mixture of oximes **46** and **47** (Scheme IV) was epimerized with sodium methoxide and the major isomer, **48**, separated by preparative tlc. **48** was obtained in 48% overall yield from **22**.

A publication by Miyano[20] described an alternative reduction scheme, using zinc and acetic acid, on a related compound. Using this process it was possible to proceed in two steps from hydroxycyclopentenone, **22**, to **48** with approximately the same overall yield. Transformation of **48** into a prostaglandin (Scheme V) proceeded in a manner analogous to that for the methyl oxime **32** (Scheme III). Particular attention was directed at the poor step, *i.e.*, selective borohydride reduction of the esters of the THP ether **51**. Interestingly the ester exchange noted with the analogous process in the methyl oxime case, *i.e.*, **33** to **34** in Scheme

(16) (a) G. H. Timms and E. Wildsmith, *Tetrahedron Lett.*, 195 (1971); (b) A. McKillop, J. D. Hunt, R. D. Naylor, and E. C. Taylor, *J. Amer. Chem. Soc.*, **93**, 4918 (1971); (c) E. J. Corey and J. E. Richman, *ibid.*, **92**, 5276 (1970), and references cited therein.

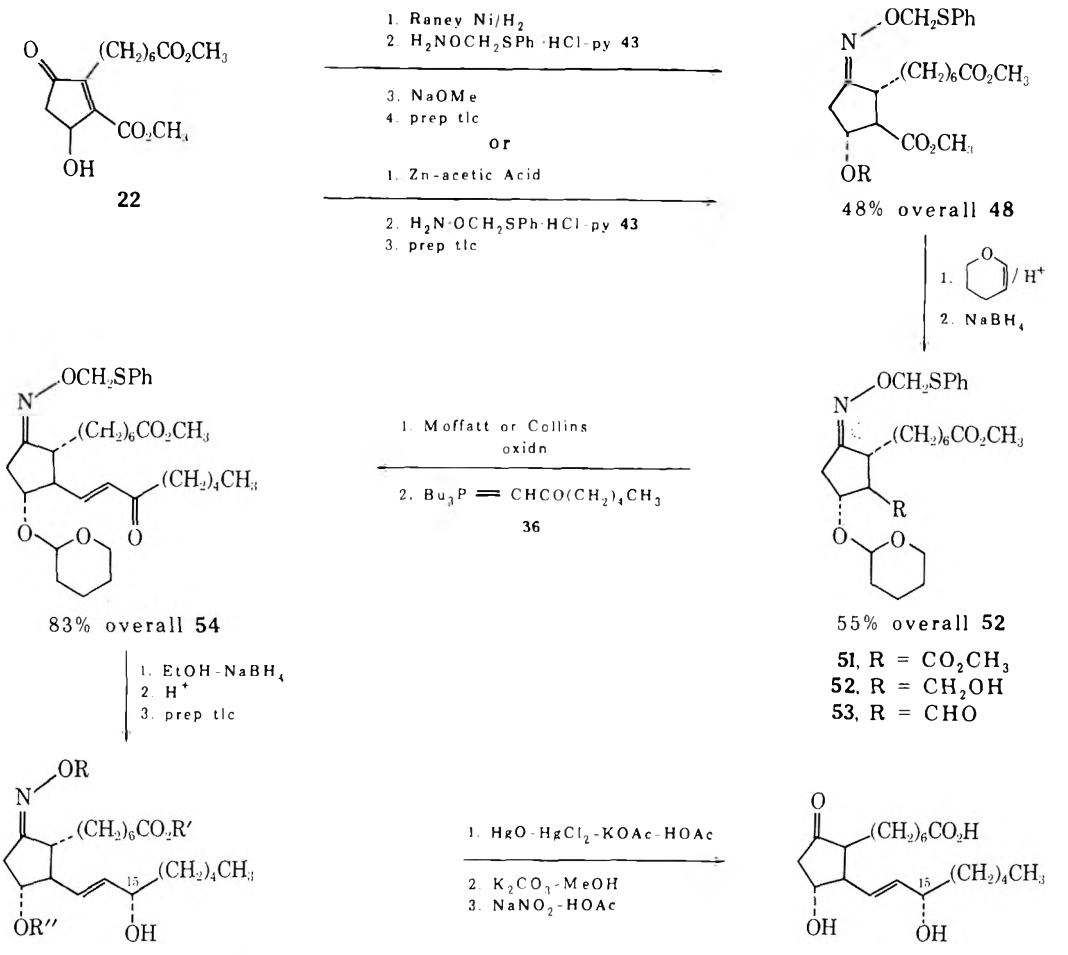
(17) A. H. Fenselau, E. H. Hamamura, and J. G. Moffatt, *J. Org. Chem.*, **35**, 3546 (1970).

(18) N. Finch, U. S. Patent 3,657,328 (1972).

(19) I. Vlattas, L. DellaVecchia, and J. J. Fitt, *J. Org. Chem.*, **38**, 3749 (1973).

(20) M. Miyano, C. R. Dorn, and R. A. Mueller, *J. Org. Chem.*, **37**, 1810 (1972).

SCHEME V



22

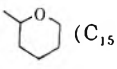
48% overall **48**

83% overall **54**

55% overall **52**

51, R = CO_2CH_3
52, R = CH_2OH
53, R = CHO

36% overall of **56**

55, R = CH_2SPh; R′ = CH_3; R″ =  (C_{15} mixture)

56, R = CH_2SPh; R′ = CH_3; R″ = H
57, R = CH_2SPh; R′ = CH_3; R″ = H (C_{15} epimer)
58, R = CH_2OCOCH_3; R′ = CH_3; R″ = H
59, R = R = H; R′ = CH_3 (*dl*-PGE_1 oxime methyl ester)
60, R = R′ = R″ = H (*dl*-PGE_1 oxime)
62, R = CH_2OCOCH_3; R′ = CH_3; R″ = H (C_{15} epimer)

(*dl*)-PGE_1 **61**, 15% overall yield
(*dl*)-15-epi-PGE_1

III, did not occur in the transformation of **51** to **52**[21] (Scheme V).

The reasons for the absence of exchange in the latter case are not clear. An especially interesting observation was that the "starting material" recovered from the borohydride reduction of the THP ether, **51**, was resistant to further reduction. Nevertheless, cleavage by acid back to the hydroxy diester **48** and re-formation of **51** from this product, yielded material which would again undergo selective reduction of the ester groups, to the extent of about 50%, to yield the carbinol ester **52** (Scheme V). From this we infer that **51** is a 1:1 mixture of epimers only one of which has the geometry suitable for assisting the reduction.

Finally, removal of the ketone protecting group from **56** (Scheme V) proceeded as for the model ketones,[19] *via* the acetoxymethyl oxime **58**. However, cleavage of **58** to the unsubstituted oxime could in this case be accomplished incidental to ester hydrolysis to give (±)-PGE oxime, **60**, directly.

The final step, *i.e.*, nitrosation of (±)-PGE_1 oxime **60** into (±)-PGE_1 **61** was the poorest step in the entire scheme. This was disappointing, especially in view of the claims that oximation was a suitable method for protecting the ketone function of PGE_1.[22] Nevertheless nitrosation provided a clean product which could be crystallized directly. The racemic PGE_1 obtained was identical by spectra (nmr, ir) and tlc behavior[23] with an authentic sample of (−)-PGE_1. Our material showed no depression of melting point on admixture with (±)-PGE_1.[24] Some additional work to improve the conversion of PGE_1 oxime **60** to PGE_1 **61**, using some of the newer procedures,[16] will be undertaken.

(21) E. Schenker in "Newer Methods of Preparative Organic Chemistry," Vol. IV, W. Foerst, Ed., Verlag Chemie, Weinheim, 1968, pp 224–225.

(22) J. E. Pike, F. H. Lincoln, and W. P. Schneider, *J. Org. Chem.*, **34**, 3552 (1969).

(23) K. Grēen and B. Samuelsson, *J. Lipid Res.*, **5**, 117 (1964).

(24) We are indebted to Dr. U. Axen of the Upjohn Co. for a gift of racemic PGE_1.

Experimental Section[25]

Ethyl 2-Cyano-3-ethoxycarbonyl-1,10-decanedioate (1).—Sodium hydride (75.0 g, 3.13 *M* as a 59.8% dispersion in mineral oil) was suspended in 1,2-dimethoxyethane (1.5 l., dried over $LiAlH_4$ and distilled) and ethyl cyanoacetate (352 g, 3.12 *M*) added dropwise over 2 hr. The mixture was refluxed for 1 hr to complete reaction and cooled to room temperature. Ethyl 2-bromoazelate (733 g, 2.27 *M*) was added over a 2.5-hr period and refluxed for 3.5 hr after the addition. The solvent was removed *in vacuo* and the residue slurried in water and acidified with 2 *N* HCl. This was ether extracted and the ether extract washed with water and salt solution. The ether was removed *in vacuo* and the residue distilled to give 1 [670 g (84%), bp 190–205° (0.70 mm)]. Redistillation [bp 144° (0.05 mm)] gave the analytical sample: nmr δ 4.12 (m, 7), 3.07 (m, 1); ir (film) 2225 (w), 1735 (s), 1470 (m), 1375 (m), 1028 cm^{-1} (m).

Anal. Calcd for $C_{18}H_{29}NO_6$: C, 60.82; H, 8.22; N, 3.94. Found: C, 61.15; H, 8.27; N, 4.04

3-Carboxy-1,10-decanedioic Acid (2).—Ethyl 2-cyano-3-ethoxycarbonyl-1,10-decanedioate (1) (10.0 g, 28.2 m*M*) was mixed with concentrated HCl (70 ml) and refluxed for 24 hr. The mixture was filtered to remove an insoluble solid and the filtrate extracted with ethyl acetate. Removal of the ethyl acetate gave a wax that became a white solid on trituration with CH_2Cl_2. Recrystallization from $CHCl_3$ gave the triacid 2: mp 55–58°; ir 1705 (s), 1215 (m), 930 cm^{-1} (m); nmr (DMSO) δ 2.38 (m, 5), 1.41 (m, 10).

Anal. Calcd for $C_{11}H_{18}O_6$: C, 53.65; H, 7.37. Found: C, 53.43; H, 7.42.

Ethyl 3-Ethoxycarbonyl-1,10-decanedioate (3).—The triacid 2 was esterified by reaction in ethanol and benzene with a catalytic amount of H_2SO_4. After work-up the oil was distilled to give the triester 3: bp 217–225° (8.5 mm); ir (film) 1734 (s), 1375 (m), 1030 (m), 858 cm^{-1} (m); nmr δ 4.18 (overlapping quartets, 6), 2.55 (m, 5).

Anal. Calcd for $C_{17}H_{30}O_6$: C, 61.79; H, 9.15 Found: C, 61.63; H, 9.14.

Ethyl 2-Cyano-2-(2-cyanoethyl)-3-ethoxycarbonyl-1,10-decanedioate (4).—Sodium (6.0 g, 0.26 *M*) was allowed to react with anhydrous ethanol (1.5 l.) and cooled to −5° (ice–salt bath). The triester nitrile 1 (1100 g, 3.1 *M*) was added dropwise over 1 hr. Acrylonitrile (200 g, 3.8 *M*) was added dropwise over 1.75 hr with continued cooling and stirring. After addition, the reaction was equilibrated to room temperature and stirred for 18 hr. Examination by tlc (silica gel, benzene–$CHCl_3$ 1:9) indicated that the starting material had been converted to product. The solvent was removed *in vacuo* and the residue shaken between ether and water. The ether extract was washed with water and saturated NaCl solution and dried ($MgSO_4$), and the solvent was removed giving 4 (1230 g, 2.92 *M*, 94% yield). This residue was used for the preparation of the tetraacid 5 without further purification.

A small amount was distilled giving the analytical sample: bp 181–183° (0.10 mm); nmr δ 4.25 (overlapping quartets, 6); ir (film) 2250 (w), 1735 (s), 1370 (m), 1020 (m), 850 cm^{-1} (m).

Anal. Calcd for $C_{21}H_{32}N_2O_6$: C, 61.74; H, 7.90; N, 6.86. Found: C, 61.50; H, 8.01; N, 6.79.

4,5-Dicarboxy-1,12-dodecanedioic Acid (5).—The dicyano triester 4 (660 g, 1.62 *M*) was mixed with concentrated HCl (2.5 l) and heated to reflux, utilizing an air condenser. After 6 hr, an additional 400 ml of concentrated HCl was added, a water condenser attached, and the mixture refluxed 18 hr. The reaction mixture was concentrated to one-third volume *in vacuo* and water added to dissolve the precipitated NH_4Cl. This was extracted with ethyl acetate which was washed with saturated NaCl solution, dried ($MgSO_4$), and evaporated to dryness *in vacuo*. The residue was recrystallized from ethyl acetate–CH_2Cl_2 to give compound 5 (414.5 g, 81%) as a white solid, mp 130–134°. Recrystallization from ethyl acetate gave the analytical sample: mp 143–145°; ir 1712 (s), 1440 (m), 1210 (m), 925 cm^{-1} (m); nmr (NaOD) δ 2.42 (m, 6), 1.48 (m, 12).

Anal. Calcd for $C_{14}H_{22}O_8$: C, 52.82; H, 6.97 Found: C, 53.01; H, 7.09.

Ethyl 4,5-Diethoxycarbonyl-1,12-dodecanedioate (6).—The tetraacid 5 (300 g, 0.945 *M*) was dissolved in anhydrous ethanol (330 ml) and benzene (550 ml) and concentrated H_2SO_4 (5 ml) added. This was heated to reflux and a Dean-Stark water trap attached. After 18 hr, the water was no longer forming and slightly more than the theoretical amount already collected, the heating was discontinued. The solvents were removed *in vacuo* without heating above room temperature. The residue was dissolved in ether and shaken with water and 10% $KHCO_3$ solution. The ether was removed and the residue distilled to give compound 6 [325.1 g (80%), bp 205–210° (0.2 mm)]. Redistillation [bp 192–194° (0.13 mm)] gave the analytical sample: nmr δ 4.16 (overlapping quartets, 8), 2.48 (m, 6); ir (film) 1737 (s), 1380 (m), 1035 (m), 858 cm^{-1} (w); vpc [2% DEGS on Anachrom ABS (110–120 mesh) at 300°] retention time of compound 6 18.4–27.2 min, retention time of compound 3 2.8 min.

Anal. Calcd for $C_{22}H_{38}O_8$: C, 61.37; H, 8.90. Found: C, 62.03; H, 9.05.

Ethyl 2-Ethoxycarbonyl-5-oxocyclopentaneheptanoate (7).—Sodium hydride (38 g, 1.59 *M* as a 57.2% dispersion in mineral oil) was suspended in dry ethyl ether (500 ml) and cooled to 3–4° (cold room). Ethanol (5 ml) was added and after stirring 20 min a cold (3–4°) solution of the tetraester 6 (562.5 g, 1.31 *M*) in dry ether (1.5 l.) was added dropwise over 5 hr. The internal temperature was at 3–4° during the addition and while stirring for an additional 5 days. Hydrochloric acid (400 ml, 2 *N*) was added and the mixture stirred at room temperature for 2 hr. The ether layer was separated, washed with saturated NaCl solution, and removed. The residue from the ether layer (positive $FeCl_3$ test) was mixed with 6.0 *N* HCl (1.0 l.) and refluxed 24 hr. The cooled mixture was extracted with ether, which was washed with saturated NaCl solution. The ether was removed and the residue (negative $FeCl_3$) mixed with benzene (1.6 l.), ethanol (650 ml), and H_2SO_4 (2.5 ml). This was heated to reflux and a Dean-Stark water trap attached. After 48 hr, the solvents were removed *in vacuo*, without heating, and the residue dissolved in ether and shaken with water and $KHCO_3$ solution. The ether was removed and the residue distilled to give compound 7 [376.2 g (92%), bp 201–205° (0.45 mm)], vpc [Supelcoport 80/100, 3% coating SP-2250 at 220°] major retention time 9.3, minor 10.2 (9:1). Redistillation [bp 160–164° (0.10 mm)] gave the analytical sample: nmr δ 4.18 (overlapping quartets, 4), 2.40 (m, 8); ir (film) 1728 (s), 1465 (m), 1378 (m), 1030 (m), 855 cm^{-1} (w).

Anal. Calcd for $C_{17}H_{28}O_5$: C, 65.36; H, 9.03. Found: C, 65.44; H, 9.23.

The semicarbazone 8 of the cyclopentanone diester 7 was prepared and had mp 114–117° (ethanol–water); nmr δ 4.17 (overlapping quartets, 4), 2.45 (m, 7); ir ($CHCl_3$) 3515 (w), 3380 (w), 1735 (s), 1690 (s), 1560 (s), 1380 cm^{-1} (m).

Anal. Calcd for $C_{18}H_{31}N_3O_5$: C, 58.51; H, 8.46; N, 11.37. Found: C, 58.34; H, 8.29; N, 11.16.

2-Carboxy-5-oxocyclopentaneheptanoic Acid (9).—The cyclopentanone diester 7 (10 g) was mixed with 10% aqueous KOH (60 ml), and ethanol was added to effect complete solution. After stirring 18 hr at room temperature the solution was extracted with ether, which was discarded. The aqueous phase was acidified with concentrated HCl and extracted with ether. The ether was shaken with saturated NaCl solution and removed to give 9 as a very viscous oil (7.6 g, 92.5%): nmr δ 2.52 (m, 8), 1.55 (m, 10); ir (film) 1735 (s), 1702 (s), 1405 (m), 1040 (m), 870 cm^{-1} (w).

The thiosemicarbazone, 10, of the cyclopentanone diacid 9 was prepared. The cyclopentanone diacid 9 (550 mg) was dissolved in 50% aqueous acetic acid (10 ml), and thiosemicarbazide (219 mg) was added. The mixture was heated to boiling to obtain a solution; water was added until a slight turbidity persisted. On cooling a white precipitate formed. Recrystallization from water afforded the analytical sample of 10: 510 mg; mp 160–162°; nmr (DMSO) δ 2.59 (m, 4), 2.20 (m, 3); ir 3420 (w), 3140 (m), 1695 (s), 1600 (s), 1510 cm^{-1} (s).

Anal. Calcd for $C_{14}H_{23}N_3O_4S$: C, 51.05; H, 7.04; N, 12.75. Found: C, 51.33; H, 7.00; N, 12.99.

Ethyl 2-Ethoxycarbonyl-5-oxocyclopentaneheptanoate Enol Acetate (12).—The cyclopentanone diester 7 (95.5 g, 0.306 *M*) was dissolved in isopropenyl acetate (61.2 g, 0.612 *M*), and *p*-toluenesulfonic acid (1.0 g) was added. The solution was refluxed for 18 hr, cooled, and added to excess 10% K_2CO_3 solution. This was ether extracted, the ether removed, and the residue

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

distilled. The major fraction [bp 168–175° (0.1 mm)] was the mixture of the enol acetates **12** (92.1 g, 85%): nmr δ 4.15 (pair of quartets, 4), 2.47 (m, 8); ir (film) 1755 (m), 1733 (s), 1375 (m), 1030 (m) cm^{-1}; vpc (2% Degs on Anachrom ABS (110–120 mesh) at 200°) 7.7 and 9.3 min (5:3).

Anal. Calcd for $C_{19}H_{30}O_6$: C, 64.38; H, 8.53. Found: C, 64.86; H, 8.55.

Ethyl 2-Ethoxycarbonyl-5-oxo-1-cyclopenteneheptanoate (13). Formed *via* the Enol Acetate.—The cyclopentanone diester enol acetates **12** (48 g, 0.135 *M*) were dissolved in dry CCl_4 (100 ml, dried by passage through neutral activity I Al_2O_3) and cooled to −5° (ice–salt bath). Bromine (21.6 g, 0.135 *M*) dissolved in dry CCl_4 (100 ml) was added dropwise over 0.5 hr, with continued cooling. The bromine color was discharged immediately on addition. After stirring an additional 0.5 hr, triethylamine (27.3 g, 0.27 *M*) was added, and the mixture was refluxed for 2 hr and stirred overnight at room temperature. The mixture was filtered to remove the precipitated salt. The filtrate was evaporated *in vacuo* and the residue vacuum distilled to give **13** [28.5 g (68%); bp 153–154° (0.1 mm)]: nmr δ 4.18 (overlapping quartets, 4), 2.46 (m, 8); ir (film) 1735–1705 (broad s), 1635 (w), 1375 (m), 1095 (m), 855 (m), 755 cm^{-1} (m); uv λ_{max} (MeOH) 246 mμ (γ 9700).

Anal. Calcd for $C_{17}H_{26}O_5$: C, 65.78; H, 8.44. Found: C, 65.89; H, 8.69.

Ethyl 2-Ethoxycarbonyl-5-oxo-1-cyclopenteneheptanoate (13). Directly from the Cyclopentanone Diester 7.—The cyclopentanone diester **7** (306 g, 0.97 *M*) was dissolved in glacial acetic acid (500 ml) and to it added a solution of bromine (155 g, 0.97 *M*) in glacial acetic acid (250 ml) dropwise over 1.75 hr while stirring at room temperature. After an additional 2 hr, the solvent was removed *in vacuo*. The residue was dissolved in ether and shaken with water and 10% $KHCO_3$ solution. The residue from the ether was dissolved in CCl_4 (1.2 l., dried by passage through neutral activity I Al_2O_3); to it was added triethylamine (101 g, 1.0 *M*). The mixture was refluxed for 8 hr and filtered and the residue from the filtrate vacuum distilled to give **13** [190 g (61%), bp 165–173° (0.3 mm)], which was identical (ir, nmr, vpc) with that obtained from the enol acetate.

The semicarbazone **14** of the cyclopentenone diester **13** was prepared in the usual way and had mp 87–88° (ethanol–water); nmr δ 4.08 (overlapping quartets, 4), 2.47 (m, 8); ir ($CHCl_3$) 3510 (w), 3370 (w), 1720 (s), 1685 (s), 1600 (w), 1560 cm^{-1} (s); uv λ_{max} (MeOH) 298 mμ (ε 23,640).

Anal. Calcd for $C_{18}H_{29}N_3O_5$: C, 58.83; H, 7.96; N, 11.44. Found: C, 58.89; H, 7.99; N, 11.43.

2-Carboxy-5-oxo-1-cyclopenteneheptanoic Acid (15).—The cyclopentenone diester **13** (75.5 g, 0.243 *M*) was dissolved in methanol (800 ml), and 15% K_2CO_3 (800 ml) was added. The mixture was refluxed for 2 hr, cooled, and most of the solvent removed *in vacuo*. The residue was diluted with water and ether extracted. The ether extract was discarded. The aqueous phase was acidified with concentrated HCl, saturated with NaCl, and extracted with ether. The residue from the ether layer was recrystallized from benzene to give **15** [57.6 g (93%), mp 81–83°]. Recrystallization from water afforded the analytical sample: mp 95–96°; nmr δ 2.55 (m, 8), 1.55 (m, 8); ir 1710 (s), 1665 (s), 1215 (s), 905 (m), 720 cm^{-1} (m); uv λ_{max} (MeOH) 245 mμ (ε 12,690).

Anal. Calcd for $C_{13}H_{18}O_5$: C, 61.40; H, 7.14. Found: C, 61.51; H, 7.32.

2-Methoxycarbonyl-5-oxo-1-cyclopenteneheptanoic Acid (16).—The cyclopentenone diacid **15** (5.32 g, 0.021 *M*) was dissolved in ether (200 ml) and to it added ethereal diazomethane (0.0233 *M*) slowly with vigorous stirring. After stirring an additional 0.5 hr the ether solution was extracted with 10% $KHCO_3$ solution. The basic solution was acidified with concentrated HCl, saturated with NaCl, and extracted with ether. The ether was removed to give **16** [3.66 g (65%)] as an oil: nmr δ 3.86 (s, 3), 2.55 (m, 8), 1.53 δ (m, 8).

***N*-Ethyl-2-methoxycarbonyl-5-oxo-1-cyclopenteneheptanoic Acid Amide (17).**—Trisethylaminoboron[26] (600 mg) was dissolved in dry benzene (10 ml, dried over Na wire), and, while stirring at room temperature, a solution of the half-ester acid **16** (1.0 g) in dry benzene (15 ml) was added over a period of 15 min. After stirring 3 days, 1 *N* HCl was added and the benzene layer separated. It was shaken with water and saturated NaCl solution and dried ($MgSO_4$). The residue from the benzene was chromatographed over silica gel and the product eluted as a crystalline solid with methylene chloride–ethyl acetate (1:1). Recrystallization from ether–hexane afforded the analytical sample of **17** (230 mg, mp 57–58°): nmr δ 3.87 (s, 3), 3.31 (m, 2), 1.13 (t, 3); ir (m), 1725 (s), 1705 (s), 1670 (w), 1645 (s), 1555 cm^{-1} (m); uv λ_{max} (MeOH) 246 mμ (ε 13,070).

Anal. Calcd for $C_{16}H_{25}NO_4$: C, 65.06; 8.53; N, 4.74. Found: C, 64.85; H, 8.59; N, 5.05.

***N*-Phenyl-2-carboxy-5-oxo-1-cyclopenteneheptanoic Acid Amide (19).**—The half-ester acid **16** (5.1 g) was dissolved in dry ether (100 ml), and oxalyl chloride (2.5 ml) was added with stirring at room temperature. After 3 hr the solvent and excess oxalyl chloride were removed *in vacuo*. The residue was dissolved in ether (150 ml), and aniline (4 ml) was added with vigorous stirring. After 1 hr the mixture was shaken with water, 1 *N* HCl, and 10% $KHCO_3$ solution. The residue from the ether layer was chromatographed over silica gel and the methyl ester of compound **18** eluted as viscous wax-like oil with ethyl acetate–methylene chloride (1:3) (3.96 g): nmr δ 7.29 (m, 5), 3.84 (s, 3), 2.47 (m, 8); ir (film) 3295 (m), 1728 (s), 1703 (s), 1670 (m), 1620 (s), 1460 (s), 770 (m), 705 cm^{-1} (m).

This half-ester anilide **18** (350 mg) was dissolved in methanol (10 ml) and 10% K_2CO_3 solution (10 ml) and refluxed for 2 hr. After cooling it was diluted with water and extracted with ether. The aqueous phase was acidified with concentrated HCl, saturated with NaCl, and extracted with ether. Removal of the ether gave an oil that crystallized. Recrystallization from ethyl acetate gave the analytical sample of **19** (180 mg): mp 166–168°; nmr (NaOD) δ 7.21 (m, 5), 2.73 (m, 2), 2.23 (m, 6); ir 3304 (w), 1712 (s), 1665 (s), 1602 (m), 1538 (m), 1210 (m), 768 (w), 725 cm^{-1} (w); uv λ_{max} (MeOH) 242 mμ (ε 26,140).

Anal. Calcd for $C_{19}H_{23}NO_4$: C, 69,28; H, 7.04; N, 4.25. Found: C, 69.05; H, 7.14; N, 4.15.

Methyl 2-Methoxycarbonyl-5-oxo-1-cyclopenteneheptanoate (20).—The cyclopentenone diacid **15** (52.5 g, 0.207 *M*) was dissolved in ethyl ether (1.0 l.), and, with stirring at room temperature, ethereal diazomethane added until the yellow color persisted. After 0.5 hr the solution was concentrated to half volume by steam bath. It was shaken with 10% $KHCO_3$ solution. The residue from the ether layer was distilled to give **20** [50.6 g, (87%), bp 146° (0.1 mm)]: nmr δ 3.87 (s, 3), 3.66 (s, 3), 2.49 (m, 8); ir (film) 1735–1700 (s), 1630 (w), 1438 (m), 1095 (w), 753 cm^{-1} (w); uv λ_{max} (MeOH) 246 mμ (ε 9630).

Anal. Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 63.47; H, 7.84.

Methyl 2-Methoxycarbonyl-3-acetoxy-5-oxo-1-cyclopenteneheptanoate (21).—The cyclopentenone dimethyl ester **20** (25.4 g, 0.09 *M*) was dissolved in CCl_4 (225 ml, dried by passage through neutral activity I Al_2O_3), and *N*-bromosuccinimide (19.5 g, 0.11 *M*) was added. A catalyst, 2,2′-azobis(2-methylpropionitrile) (400 mg), was added, and the mixture was refluxed for 1 hr. The floating suspended solid was removed by filtration.

The residue from the filtrate was dissolved in glacial acetic acid (175 ml), and silver acetate (22.6 g, 0.135 *M*) was added. This mixture was refluxed for 1 hr, cooled, and filtered. The filtrate was diluted with ether and extracted with water and 10% $KHCO_3$ solution. The residue from the ether was vacuum distilled to give **21** [17.4 g (47%), bp 169–170° (0.01 mm)]: nmr δ 6.08 (m, 1), 3.88 (s, 3), 3.65 (s, 3), 2.06 (s, 3); ir (film) 1725 (s) 1640 (w), 1440 (m), 1230 cm^{-1} (s); uv λ_{max} (MeOH) 238 mμ (ε 12,830), basified with 0.1 *N* KOH 252 (ε 7710), 422 mμ (ε 8380).[11]

Anal. Calcd for $C_{17}H_{24}O_7$: C, 59.99; H, 7.11. Found: C, 60.38; H, 7.21.

Methyl 2-Methoxycarbonyl-3-hydroxy-5-oxo-1-cyclopenteneheptanoate (22).—The acetoxycyclopentenone diester **21** (32.5 g, 0.0956 *M*) was dissolved in cold 2.4 *N* methanolic HCl (450 ml) and stirred at room temperature. After 4 hr the solvent was removed *in vacuo* and the residue dissolved in ether and shaken with water (until the aqueous washes were neutral). The residue from the ether layer was chromatographed over silica gel and **22** eluted with methylene chloride–ethyl acetate (3:2) [19.0 g (67%), bp 156–158° (0.01 mm)]: nmr δ 5.15 (m, 1), 3.92 (s, 3), 3.66 (s, 3); ir (film) 3460 (m), 1720 (s), 1636 (w), 1440 cm^{-1} (m); uv λ_{max} (MeOH) 237 mμ (ε 11,700).

Anal. Calcd for $C_{15}H_{22}O_6$: C, 60.39; H, 7.43. Found: C, 60.11; H, 7.60.

The semicarbazone, **23**, of the hydroxycyclopentenone diester **22** was prepared: mp 140–141° (methanol–water); ir 3514

(26) D. W. Aubrey and M. F. Lappert, *J. Chem. Soc.*, 2927 (1959).

(w), 3304 (m), 1735 (s), 1715 (s), 1672 (s), 1610 cm^{-1} (m); uv λ_{max} (MeOH) 296 mμ (ε 23,850).

Anal. Calcd for $C_{16}H_{25}N_3O_6$: C, 54.07; H, 7.09; N, 11.83. Found: C, 53.77; H, 7.06; N, 12.07.

The *O*-methyl oxime, **24**, of the hydroxycyclopentenone diacid was prepared by dissolving the ketone in dry pyridine (molecular sieves, type 4A) and adding an excess of methoxyamine hydrochloride. After 2 days at room temperature the solvent was removed *in vacuo*, the residue was dissolved in ether–water, and the ether layer reshaken with water. The residue from the ether was the diester of **24** as a low melting waxy solid.

This wax was dissolved in methanol–10% K_2CO_3 solution (1:1) and refluxed for 1.5 hr. Work-up in the usual manner gave **24**: mp 102–104° (ether–hexane); nmr δ 5.08 (m, 1), 3.98 (s, 3), 2.72 (m, 4), 2.33 (m, 2); ir ($CHCl_3$) 3585 (w), 1685 (s), 1610 (m), 1040 cm^{-1} (s); uv λ_{max} (MeOH) 269 mμ (ε 14,800).

Anal. Calcd for $C_{14}H_{21}NO_6$: C, 56.17; H, 7.07; N, 4.68. Found: C, 56.49; H, 7.39; N, 4.87.

Methyl 2-Methoxycarbonyl-3-trimethylsiloxy-5-oxo-1-cyclopenteneheptanoate (25).—The hydroxycyclopentenone diester **22** (18.9 g, 0.051 *M*) was dissolved in dry ether (500 ml) and mixed with trimethylsilyl chloride (19 ml). With vigorous stirring at room temperature triethylamine (33 ml) was added dropwise causing immediate precipitation of triethylamine hydrochloride. After 2 hr the mixture was filtered. The filtrate was shaken with water and saturated NaCl solution. The residue from the ether layer was chromatograhed over silica gel, and **25**, an oil (21.1 g, 90%), was eluted with ethyl acetate–methylene chloride (1:9): nmr δ 5.15 (m, 1), 3.88 (s, 3), 3.63 (s, 3), 0.18 (s, 9); ir (film) 1722 (s), 1640 (w), 1440 (m), 1258 (s), 845 cm^{-1} (s).

Methyl 2-Methoxycarbonyl-3-trimethylsiloxy-5-oxocyclopentaneheptanoate (26).—The trimethylsiloxycyclopentenone diester **25** (9.8 g, 0.0265 *M*) was dissolved in methanol (125 ml), and Raney nickel catalyst (1.0–2.0 g, wet with methanol) was added. The reduction was conducted at an initial hydrogen pressure of 48 psi, at room temperature. After 3.5 hr slightly more than the theoretical amount of hydrogen was consumed. The mixture was filtered through Celite which was washed well with methanol. Evaporation of the filtrate gave compound **26** (9.21 g, 93.5%) as an oil that crystallized (mp ≈22–24°) on standing in the cold. Although satisfactory microanalysis could not be obtained, the spectra concur with the assigned structure: nmr δ 4.61 (m, 1), 3.69 (s, 3), 3.63 (s, 3), 2.38 (m, 6), 0.14 (s, 9); ir (film) 1738 (s), 1440 (m), 1255 (s), 845 cm^{-1} (s).

Methyl 2-Methoxycarbonyl-3-hydroxy-5-oxocyclopentaneheptanoate (27).—The trimethylsiloxycyclopentanone diester **26** (7.25 g, 0.0195 *M*) was dissolved in methanol (200 ml), and formic acid (1 ml) was added. After stirring 3 hr at room temperature the solvent was removed *in vacuo*. The oily residue (5.72 g, 97.5%), which crystallized on standing, showed two spots on tlc (silica gel, ethyl acetate–methylene chloride 1:4, two developings) a minor R_f 0.565 and a major R_f 0.495. Recrystallization from ether gave a white solid (4.79 g, mp 68–70°) which was predominantly the polar isomer. Further recrystallizations from ether gave pure polar material, the all-cis configuration of **27**: mp 72–73°; nmr δ 4.62 (m, 1), 3.74 (s, 3), 3.68 (s, 3), 3.46 (m, 2); ir ($CHCl_3$) 3480 (w), 1736 (s), 1435 cm^{-1} (m); mass spectrum *m/e* 300 (M), 282 (M − H_2O), 269 (M − OCH_3).

Anal. Calcd for $C_{15}H_{24}O_6$: C, 59.98; H, 8.05. Found: C, 60.26; H, 8.26.

The *O*-Methyl Oxime (28) of the Cyclopentanone Diester 27.—Trimethylsiloxycyclopentanone diester **26** (8.6 g, 0.0231 *M*) was dissolved in pyridine (100 ml, dried over molecular seives), and *O*-methylhydroxylamine hydrochloride (9.8 g) was added. After 24 hr at room temperature the pyridine was removed *in vacuo*. The residue was shaken between ether and water. The residue from the ether layer was recrystallized (ether–hexane) to give compound **28** (5.2 g, 69%). A further recrystallization from hexane gave the analytical sample: mp 46–47°; nmr δ 4.48 (q, 1), 3.84 (s, 3), 3.72 (s, 3), 3.64 (s, 3); ir 3380 (m), 1730 (s), 1655 (w), 1043 cm^{-1} (s); tlc [ethyl acetate–chloroform (1:1 two developings)] R_f 0.635.

Anal. Calcd for $C_{16}H_{27}NO_6$: C, 58.34; H, 8.26; N, 4.25. Found: C, 58.43; H, 8.35; N, 4.24.

The Oxime (29) of the Cyclopentanone Diester 27.—Trimethylsiloxycyclopentanone diester **26** (525 mg) was dissolved in dry pyridine (25 ml), and hydroxylamine hydrochloride (1.5 g) was added. After 24 hr at room temperature the pyridine was removed *in vacuo* and the residue shaken between ether and water. The crystalline residue from the ether layer was recrystallized (benzene–hexane) to give **29** (320 mg): mp 97–98°; nmr δ 4.50 (m, 1), 3.74 (s, 3), 3.67 (s, 3); ir 3390 (m), 3250 (m), 1730 (s), 1190 cm^{-1} (m).

Anal. Calcd for $C_{15}H_{25}NO_6$: C, 57.13; H, 7.99; N, 4.44. Found: C, 57.08; H, 7.73; N, 4.57.

Preparation of *O*-Methyl Oxime 28 from Oxime 29.—Oxime **29** (100 mg) was dissolved in acetonitrile (2 ml, dried by passage through Al_2O_3 neutral activity I) and methyl iodide (3 ml). The solution was warmed to 45° and Ag_2O (11 mg) was added. After 1 hr an additional 11 mg of Ag_2O was added. This process was repeated every hour until a total of 66 mg of Ag_2O was added. After 20 hr, the mixture was diluted with $CHCl_3$ and filtered. The residue from the filtrate was chromatographed over silica gel, and the crystalline solid (48 mg) eluted with methylene chloride–ethyl acetate (4:1) was shown to be the methyl oxime, **28**, by tlc, melting point, and mixture melting point.

Methyl 2-Hydroxymethyl-3-hydroxy-5-methoxyiminocyclopentaneheptanoate (30).—*O*-methyl oxime **28** (3.0 g) was dissolved in ethanol (100 ml), and $NaBH_4$ (2.0 g) was added. After stirring 2 hr, another 1.0 g $NaBH_4$ was added. After an additional 1.5 hr, the ethanol was removed *in vacuo* and the residue shaken between ether and water. The residue from the ether layer was chromatographed over silica gel. Compound **30**, 1.71 g, was eluted with ethyl acetate–methylene chloride (3:2). Recrystallization from ether gave the analytical sample: mp 86–88°; nmr δ 3.83 (s, 3), 3.65 (s, 3); ir 3290 (s), 1735 (s), 1650 (w), 875 cm^{-1} (m).

Anal. Calcd for $C_{15}H_{27}NO_5$: C, 59.78; H, 9.03; N, 4.65. Found: C, 60.09; H, 9.17; N, 4.70.

Methyl 2-Hydroxymethyl-3-hydroxy-5-hydroxyiminocyclopentaneheptanoate (31).—Oxime **29** (630 mg) was dissolved in ethanol (30 ml), and $NaBH_4$ (630 mg) was added. After stirring 2 hr at room temperature an additional 630 mg of $NaBH_4$ was added. After a total of 4.5 hr, the solvent was removed *in vacuo* and the residue shaken between ether and water. The residue from the ether layer was chromatographed over silica gel. Unreacted starting material **29** (350 mg) was eluted with ethyl acetate–methylene chloride (3:7), and compound **31** (180 mg, 71% based on recovered starting material) was eluted with ethyl acetate-methylene chloride (3:2). Recrystallization from ether gave the analytical sample: mp 79–80°; nmr δ 4.48 (m, 1), 3.67 (s, 3); ir 3210 (s), 1730 (s), 1677 cm^{-1} (w).

Anal. Calcd for $C_{14}H_{25}NO_5$: C, 58.51; H, 8.77; N, 4.87. Found: C, 58.83; H, 8.91; N, 4.53.

Epimerization of Methyl Oxime 28 to 32.—Methyl oxime **28** (8.6 g, 0.0261 *M*) was dissolved in methanol (250 ml) and 10% K_2CO_3 solution (250 ml) and refluxed for 2 hr. After cooling to room temperature it was extracted with ether, which was discarded. The aqueous layer was cooled in an ice bath, acidified with concentrated HCl, saturated with $(NH_4)_2SO_4$, and extracted with ether. The residue from the ether layer was dissolved in ether (75 ml) and treated with excess ethereal diazomethane. After 1 hr at room temperature, the solution was extracted with 10% $KHCO_3$ solution, dried over $MgSO_4$, and evaporated to give **32** (7.85 g, 91%), homogeneous on tlc: nmr δ 4.39 (m, 1), 3.82 (s, 3), 3.74 (s, 3), 3.63 (s, 3); ir (film) 3465 (m), 1730 (s), 1650 (w), 1435 (m), 1040 cm^{-1} (s); tlc [ethyl acetate–chloroform (1:1, two developings)] R_f 0.70.

Tetrahydropyranyl Ether (33) of 32.—**32** (2.75 g) was dissolved in methylene chloride (100 ml) and to it added 2,3-dihydro-γ-pyran (1.5 g) and picric acid (50 mg). After 18 hr, the solution was shaken with water and 10% $KHCO_3$ solution. The residue from the methylene chloride layer chromatographed over silica gel and **33** (3.28 g, 95%) eluted with ethyl acetate–methylene chloride (1:9): nmr δ 4.62 (m, 1), 4.36 (m, 1), 3.82 (s, 3), 3.73 (s, 3), 3.64 (s, 3); ir (film) 1732 (s), 1630 (w), 1438 m), 1200 (s), 1170 (s), 1042 cm^{-1} (s).

Borohydride Reduction of 33 to 34.—**33** (10.2 g, 0.0247 *M*) was dissolved in anhydrous ethanol (300 ml) and to it was added $NaBH_4$ (21.5 g) portionwise over 3.5 hr while stirring at room temperature. After that time, the mixture was diluted with water and extracted with ether. The ether layer was reshaken with water and saturated NaCl solution. The residue from the ether layer was chromatographed over silica gel and unreacted starting material (**33**, 2.09 g) eluted with ethyl acetate–methylene chloride (1:4). **34** (4.15 g, 53% based on recovered starting material) was eluted with ethyl acetate–methylene chloride (2:3). Ester exchange occurred during this reaction and **34** was isolated

as the ethyl ester: nmr δ 4.66 (m, 1), 4.12 (q, 2), 3.84 (s,3); ir (film) 3440 (m), 1730 (s), 1650 (w), 1195 (s), 1040 cm^{-1} (s).

Moffatt Oxidation of 34 to 35.—**34** (1.45 g) was dissolved in benzene (20 ml, dried over Na wire) and dimethyl sulfoxide (20 ml, dried over molecular seives) and cooled to 4°. Then dry pyridine (0.47 ml), trifluoroacetic acid (0.26 ml), and 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-*p*-toluenesulfonate (Aldrich No. C-10,640-2) (1.5 g) were added in that order. After stirring 24 hr at 4°, the mixture was poured into ice water and extracted with ether. The ether layer was reshaken with ice water, dried ($MgSO_4$), and evaporated to dryness *in vacuo*, to give **35** [1.35 g (93%)]: nmr δ 9.76 (m, 1), 4.61 (m, 1), 4.13 (q, 2), 3.83 (s, 3); ir (film) 2720 (w), 1725 (s), 1650 (w), 1440 (m), 1030 cm^{-1} (s).

Preparation of 1-Tributylphosphoranylidene-2-heptanone (36).—1-Chloro-2-heptanone[27] (5.0 g, 0.0337 *M*) was added to a solution of tri-*n*-butylphosphine (6.8 g, 0.0337 *M*) in chloroform (35 ml). The mixture was refluxed for 1 hour, and then the solvent was removed. A portion of the residue (5 g, 0.0156 *M*) was slurried in water (100 ml). The water was extracted (ether) and filtered. The clear aqueous solution was basified (15 ml of 2 *N* NaOH), with stirring (5 min) and extracted (ether). The ethereal extracts were dried ($MgSO_4$), and the ether was removed. The residue was distilled. The main fraction, 1-tributylphosphoranylidene-2-heptanone (**36**, 2.4 g, 0.0077 *M*, 49%), had bp 140–143° (0.01 mm); nmr δ 3.14 (s, <1), 2.06 (t, 2); ir (film) 1530 (s), 1470 (m), 1402 (s) cm^{-1}. This substance, **36**, colors rapidly on exposure to air. It was not possible to obtain a satisfactory elemental analysis.

Wittig Reaction of Aldehyde 35 to Enone 37.—**35** (1.35 g) was mixed with-1-tributylphosphoranylidene-2-heptanone **36** (1.3 g) in ether (50 ml) and stirred at room temperature. After 1.5 hr, the solvent was removed and the residue chromatographed over silica gel. The enone **37** [1.24 g (74%)] was eluted with ethyl acetate–methylene chloride (1:19): nmr δ 6.82 (m, 1), 6.1 (m, 1), 4.61 (m, 1), 4.15 (m, 4), 3.83 (s, 3), 0.90 (m, 3); ir (film) 1735 (s), 1695 (m), 1670 (m), 1625 (m), 1030 cm^{-1} (s); uv λ_{max} (MeOH) 225 mμ (ε 15,200).

Hydrolysis of Enone 37 to 38.—**37** (780 mg) was dissolved in methanol (75 ml), and 1 *N* HCl (1 ml) was added. The mixture was stirred at room temperature under a N_2 atmosphere. After 3 hr most of the methanol was removed *in vacuo* at room temperature. The residue was dissolved in ether and shaken with water. The residue from the ether layer was chromatographed on silica gel, and **38** (230 mg) was eluted with ethyl acetate–methylene chloride (1:9). It was homogeneous on tlc: nmr δ 6.76 (m, 1), 6.20 (m, 1), 3.81 (s, 3), 2.45 (complex multiplet, 8), 0.91 (m 3).

Borohydride Reduction of Enone 38 to 39.—**38** (230 mg) was dissolved in ethanol (10 ml) and $NaBH_4$ (440 mg) added. Stirred at room temperature for 2 hr the solvent was removed *in vacuo* at room temperature; the residue was shaken between ether and water. Removal of the ether gave an oil, 195 mg. A major component of this oil was **39** as indicated by tlc [alumina GF, cyclohexane–dioxane–ethyl acetate (7:2.5:0.5)] and nmr.

Borohydride Reduction of Enone 37 to 40.—**37** (3.6 g) was dissolved in ethanol (250 ml), and $NaBH_4$ (7.2 g) was added. After stirring 1.5 hr at room temperature, the mixture was poured into ice water and extracted with ether (three times). The ether layer was reshaken with water and saturated NaCl solution. The residue from the ether layer was chromatographed over silica gel and **40**, 2.54 g, as an oil, eluted with ethyl acetate–methylene chloride (1:9): nmr δ 5.61 (m, 2), 4.69 (m, 1), 3.83 (s, 3), 0.91 (m, 3): ir (film) 3415 (m), 1732 (s), 1650 (w), 1040 cm^{-1} (s).

Hydrolysis of 40 to 39.—**40** (740 mg) was dissolved in methanol (60 ml), and 1 *N* HCl (1 ml) was added. Stirred overnight at room temperature, it was poured into cold water and extracted with ether (twice). The ether layer was reshaken with water and saturated NaCl solution and dried over $MgSO_4$. The residue from the ether layer was preparatively separated [alumina GF, cyclohexane–dioxane–ethyl acetate (7:2.5:0.5)] and two major bands isolated. The nonpolar band, **41**, R_f 0.33, was an oil (220 mg). The polar band gave **39** (228 mg), R_f 0.20, which crystallized on standing in the cold. Recrystallization from ether–pentane gave the analytical sample: mp 67–68°; nmr δ 5.61 (m, 2), 3.82 (s, 2), 2.28 (m, 2), 0.93 (m, 3); ir ($CHCl_3$) 3590 (w), 3375 (m), 1728 (s), 1650 (w), 1465 (m), 1045 cm^{-1} (s); mass spectrum *m/e* 411 (M), 393 (M − H_2O), 380 (M − CH_3O).

Anal. Calcd for $C_{23}H_{41}NO_5$: C, 67.12; H, 10.04; N, 3.40. Found: C, 67.52; H, 10.26; N, 3.31.

***dl*-PGE$_1$ Methyl Oxime (42) from 39.**—**39** (220 mg) was dissolved in methanol (35 ml), and 10% K_2CO_3 solution (35 ml) was added. The mixture was refluxed on the steam bath for 2 hr. On cooling, the reaction was diluted with water and extracted with ether. The aqueous layer was cooled in an ice bath, acidified with 2 *N* HCl, saturated with NaCl, and extracted with ether twice. The ether was dried over $MgSO_4$ and evaporated to dryness *in vacuo* to give *dl*-PGE_1 methyl oxime, **42**, as a solid. Recrystallization from ether–pentane gave the analytical sample (144 mg): mp 97–99°; nmr δ 5.50 (m, 2), 4.05 (m, 1), 3.78 (s, 3), 0.91 (m, 3); ir (CH_2Cl_2) 3610 (m), 3400 (m), 1710 (s), 1044 cm^{-1} (s); mass spectrum *m/e* 383 (M), 365 (M − H_2O), 347 (M − $2H_2O$), 334 (M − H_2O, CH_3O).

Anal. Calcd for $C_{21}H_{37}NO_5$: C, 65.76; H, 9.72; N, 3.65. Found: C, 66.15; H, 9.73; N, 3.62.

PGE_1 was converted to a syn–anti mixture of methyl oximes by aforementioned procedures. The product was chromatographed on Mallinckrodt silicic acid [100–120 mesh, well washed (methanol), and reactivated (120°, 18 hr)] using chloroform–methanol (99:1) as eluent. The faster moving isomer was crystallized [mp 55–57° (aqueous methanol)]. The ir, nmr, and mass spectra of this compound were identical with those of **42** as was its mobility on tlc [silica gel, $CHCl_3$–methanol–acetic acid–H_2O (90:8:1:0.7)].[15]

Cleavage of Methyl Oxime 42.—*dl*-PGE_1 methyl oxime **42** (63 mg) was dissolved in a solution of levulinic acid (0.9 ml) and 13% aqueous $HClO_4$ (0.1 ml), precooled to 3°. After 48 hr at 3° the solution was diluted with cold ether and extracted with cold water (four times). The ether layer was dried ($MgSO_4$) and evaporated to dryness *in vacuo* below room temperature. The residue was chromatographed on silicic acid [100–120 mesh, well washed (methanol), and reactivated (120°, 18 hr)]. An oil (2 mg) eluted with $CHCl_3$–MeOH (97:3) was identical with PGE_1 (R_f 0.27; $CHCl_3$–MeOH–HOAc–H_2O, 90:8:1.0:0.7) on tlc and gave the typical uv shift with base. All attempts to crystallize the oil were unsuccessful.

Phenylthiomethoxyamine Hydrochloride (43).—Thiophenol (110.2 g, 1.0 *M*) and paraformaldehyde (45.0 g, 0.5 *M*) were mixed together and cooled to −15°. Anhydrous HCl gas was bubbled into the mixture and within 5 min the temperature rose to 22°; HCl addition was stopped during the exothermic reaction. When the temperature returned to −15° the HCl addition was continued for 3 hr. The mixture was warmed to room temperature and anhydrous $CaCl_2$ was added with stirring. This mixture was filtered, and the filtrate distilled to give chloromethyl phenyl sulfide (63.4 g, 40% yield): bp 62–63° (0.1 mm) [lit.[28] 106–7° (13 mm)]; nmr δ 7.42 (m, 5), 4.85 (s, 2). *N*-Hydroxyphthalimide (81.5 g, 0.5 *M*), triethylamine (49.6 g, 0.49 *M*), and chloromethyl phenyl sulfide (63.4 g, 0.4 *M*) were mixed together in dry tetrahydrofuran (830 ml) and refluxed for 15 hr. The mixture was filtered and the residue from the filtrate was dissolved in CH_2Cl_2 and shaken with 10% $KHCO_3$ solution (five times) and water. The residue from the CH_2Cl_2 layer was recrystallized from CH_2Cl_2–ether to give *N*-phenylthiomethoxyphthalimide (75.0 g, 66% yield): mp 88–88.5°; nmr δ 7.50 (m, 9), 3.58 (s, 2); ir (KBr) 1785 (w), 1725 (s), 1605 (w), 970 cm^{-1} (m).

Anal. Calcd for $C_{15}H_{11}NO_3S$: C, 63.16; H, 3.89; N, 4.91 Found: C, 62.90; H, 3.91; N, 4.86.

N-Phenylthiomethoxyphthalimide (75.0 g, 0.26 *M*) and hydrazine hydrate (13.5 g, 0.27 *M*) were mixed together in 95% ethanol (600 ml) and refluxed for 4.5 hr. After cooling to room temperature the mixture was filtered. The filtrate was concentrated *in vacuo* to a very small volume, diluted with ether, and cooled to 0°. After 1 hour at 0° it was filtered. The residue from the filtrate was distilled to give phenylthiomethoxyamine (30.2 g, 75% yield): bp 82–94° (0.1 mm); nmr δ 7.35 (m, 5), 5.57 (s, 2), 5.00 (s, 2); ir (film) 3300 (m), 3050 (m), 2910 (m), 1585 (s), 990 cm^{-1} (s).

Anal. Calcd for C_7H_9NOS: C, 54.19; H, 5.85; N, 9.03. Found: C, 54.40; H, 5.99; N, 9.16.

Phenylthiomethoxyamine (3.0 g, 0.0193 *M*) was dissolved in ether (50 ml), and excess ethereal–HCl was added causing the immediate formation of a white precipitate. Filtration gave

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phenylthiomethoxyamine hydrochloride (43, 3.57 g, 96.5%). Recrystallization from ethyl acetate–methanol gave the analytical sample: mp 110–112° dec; nmr (DMSO) δ 7.47 (m, 5), 5.68 (s, 2); ir 2660 (s), 1585 (w), 1570 (w), 1005 (s), 860 cm^{-1} (s).

Anal. Calcd for $C_7H_9NOS \cdot HCl$: C, 43.86; H, 5.26; N, 7.31. Found: C, 43.93; H, 5.39; N, 7.41.

The Phenylthiomethyl Oxime (44) of 27.—The crystalline residue from the preparation of 27 (5.55 g) was dissolved in pyridine (150 ml, dried over molecular sieves), and phenyl mercaptomethylhydroxylamine hydrochloride (43) (4.94 g) was added. After stirring 24 hr at room temperature the pyridine was removed *in vacuo*. The residue was dissolved in ether and shaken with water, 0.2 *N* HCl, and water again. The residue from the ether (8.54 g) crystallized on standing.

A portion of this residue was preparatively separated [silica gel, ethyl acetate–methylene chloride (1:4)] to give the major product 46 (R_f = 0.64), a white crystalline solid: mp 53–55° (ether–hexane); nmr δ 7.33 (m, 5), 5.46 (s, 2), 4;55 (m, 1), 3.70 (s, 3), 3.66 (s, 3), 2.75 (m, 2) 2.28 (m, 2); ir (KBr) 3240 (m), 1731 (s), 1030 cm^{-1} (m); mass spectrum *m/e* 437 (M).

Anal. Calcd for $C_{22}H_{31}NO_6S$: C, 60.40; H, 7.14; N, 3.20. Found: C, 60.62; H, 7.18; N, 3.12.

A minor product, 47, R_f 0.57, was also isolated: nmr δ 7.31 (m, 5), 5.46 (s, 2), 4.49 (m, 1), 3.73 (s, 3), 3.66 (s, 3), 2.65 (m, 2), 2.27 (m, 2).

Anal. Calcd for $C_{22}H_{31}NO_6S$: C, 60.40; H, 7.14; N, 3.20. Found: C, 61.19; H, 7.37; N, 3.32.

Conversion of 46 to Oxime 29.—46 (25 mg) was dissolved in glacial acetic acid (3 ml), and with stirring at room temperature a solution of $HgCl_2$ (105 mg), KOAc (90 mg), and H_2O (44 mg) in 3 ml glacial acetic acid was added. A white precipitate formed after 1 hr, and, after a total of 2.5 hr, the mixture was diluted with acetone and H_2S was bubbled into it until a black precipitate formed. The mixture was filtered through Celite and the filtrate evaporated to dryness *in vacuo*. This residue was dissolved in ether–water. The ether layer was reshaken with water and dried over $MgSO_4$. The residue from the ether layer was dissolved in methanol (4 ml), and 10% K_2CO_3 solution (1 ml) was added. After 35 min at room temperature the solution was diluted with ether and washed with water. The residue from the ether layer was recrystallized from ether to give 29, 12 mg, identical by tlc, melting point, and mixture melting point with the material from oximation of siloxycyclopentanone diester, 26.

Epimerization of 46 to 48.—46 (125 mg) was dissolved in anhydrous methanol (7 ml), and a solution of Na (2 mg) in anhydrous methanol (2 ml) was added. Refluxed for 20 hr under N_2, the solution was cooled, diluted with ether, and shaken with water. The residue from the ether layer was preparatively separated [silica gel, ethyl acetate–methylene chloride (1:4)] to give 48 as an oil (103 mg, R_f 0.605): nmr δ 7.36 (m, 5), 5.45 (s, 2), 4.35 (m, 1), 3.73 (s, 3), 3.65 (s, 3), 2.05–3.4 (complex multiplet, 7).

Anal. Calcd for $C_{22}H_{31}NO_6S$: C, 60.40; H, 7.14; N, 3.20. Found: C, 60.27; H, 7.13; N, 3.11.

Epimerization of 47 to 49.—47 (62 mg) was dissolved in anhydrous methanol (5 ml), and a solution of Na (1.0 mg) in anhydrous methanol (2 ml) was added. Refluxed 20 hr under N_2, the solution was cooled, diluted with ether, and shaken with water. The residue from the ether layer was preparatively separated [silica gel, ethyl acetate–methylene chloride (1:4)] to give 49 as an oil (55 mg, R_f 0.44): nmr δ 7.38 (m, 5), 5.43 (s, 2), 4.37 (m, 1), 3.72 (s, 3), 2.87 (complex multiplet, 5), 2.24 (m, 2).

Anal. Calcd for $C_{22}H_{31}NO_6S$: C, 60.40; H, 7.14; N, 3.20. Found: C, 60.74; H, 7.38; N, 3.28.

Borohydride Reduction of 49 to 50.—49 (710 mg) was dissolved in methanol (35 ml). While stirring at room temperature, $NaBH_4$ (840 mg) was added portionwise over 2 hr. After 2.5 hr, the mixture was poured into ice water and extracted with ether. The ether was shaken with water, dried over $MgSO_4$, and evaporated *in vacuo*. The residue from the ether layer was recrystallized from ether to give 50, 540 mg: mp 56–57°; nmr δ 7.33 (m, 5), 5.42 (s, 2), 3.66 (s, 3), 2.1–2.8 (complex multiplet, 5); ir 3350 (m), 1738 (s), 1020 cm^{-1} (s).

Anal. Calcd for $C_{21}H_{31}NO_5S$: C, 61.59; H, 7.63; N, 3.42. Found: C, 61.67; H, 7.75; N, 3.42.

Preparation of 48 Directly.—The crude crystalline mixture of compounds 46 and 47 (7.0 g) was dissolved in anhydrous methanol (250 ml), and a solution of Na (105 mg) in anhydrous methanol (50 ml) was added. Refluxed for 20 hr under N_2, the solvent was removed *in vacuo*. The residue was dissolved in ether and shaken with water and saturated NaCl solution. The residue was preparatively separated [silica gel, ethyl acetate–methylene chloride (1:4)] to give 48 (3.24 g, 40.5% overall from 22) and 49 (1.21 g, 15% overall from compound 22).

48 by Catalytic Reduction of 22 and a Telescoped Sequence.—22 (9.5 g) was dissolved in methanol (130 ml), and Raney nickel catalyst (2.0–3.0 g, wet with methanol) was added. The mixture was reduced at an initial hydrogen pressure of 47 psi, at room temperature. After 24 hr, slightly more than the theoretical amount of hydrogen absorbed; the mixture was filtered through Celite.

The residue from the filtrate, 27 by ir, nmr, and tlc (8.21 g), was dissolved in pyridine (175 ml, dried over molecular seives) and *O*-phenylmercaptomethylhydroxylamine hydrochloride (43) (7.4 g) was added. After 48 hr at room temperature the pyridine was removed *in vacuo*. The residue was partitioned between ether and water. The ether layer was shaken with 0.1 *N* HCl and water.

The residue from the ether, 44 by ir, nmr, and tlc (12.5 g), was dissolved in anhydrous methanol (400 ml); a solution of Na (150 mg) in anhydrous methanol (15 ml) was added; and the mixture was refluxed 20 hr under a nitrogen atmosphere. Most of the methanol was removed *in vacuo* without heating above room temperature. The residue was dissolved in ether and shaken with water.

The residue from the ether layer (11.7 g) was preparatively separated [silica gel, ethyl acetate–methylene chloride (1:4)] to give 48, identified by tlc and nmr (6.81 g, 48% overall from 22).

The material corresponding to 49 (1.93 g, 14% overall from 22) was also isolated.

48 from 22 by Zinc–Acetic Acid Reduction.—22 (1.0 g) was dissolved in glacial acetic acid (40 ml), and Zn dust (2.0 g) was added. After 20 hr of vigorous stirring at room temperature the mixture was diluted with ether and filtered. The filtrate was evaporated to dryness *in vacuo* without heating above room temperature. The residue was dissolved in ether and shaken with water.

The residue from the ether layer (980 mg) was dissolved in pyridine (50 ml, dried over molecular seives); *O*-phenylmercaptomethylhydroxylamine hydrochloride (43) was added. After 48 hr at room temperature the pyridine was removed *in vacuo*. The residue was partitioned between ether and water. The ether layer was shaken with 0.1 *N* HCl and water.

The residue from the ether layer was preparatively separated [silica gel, ethyl acetate–methylene chloride (1:4)] to give 48 by tlc and nmr (685 mg, 47% overall from 22) and 49 (309 mg, 21% overall from 22).

Tetrahydropyranyl Ether of 48.—48 (3.2 g, 7.34 m*M*) was dissolved in methylene chloride (200 ml, dried over molecular sieves) and to it added 2,3-dihydro-γ-pyran (2.1 ml) and picric acid (210 mg). After stirring 18 hr at room temperature the solution was shaken with water and 10% $KHCO_3$ solution. The residue from the methylene chloride layer was chromatographed over silica gel and 51 (3.76 g, 98.5%) eluted with ethyl acetate–methylene chloride (1:9): nmr δ 7.35 (m, 5), 5.45 (s, 2), 4.61 (m, 1), 3.72 (s, 3), 3.66 (s, 3); ir (film) 1732 (s), 1655 (w), 1585 (s), 1015 cm^{-1} (s).

Borohydride Reduction of 51 to 52.—51 (3.7 g, 7.1 m*M*) was dissolved in ethanol (200 ml), and $NaBH_4$ (4.0 g) was added portionwise over a 4-hr period at a rate of 1.0 g/hr. After 4.5 hr, the solvent was removed *in vacuo* and the residue shaken between ether and water. The residue from the ether layer was preparatively separated (silica gel; ethyl acetate–methylene chloride, 1:4) to give unreacted starting material (1.03 g, R_f 0.86) and 52 (1.44 g, 57% based on recovered starting material, R_f 0.42): nmr δ 7.38 (m, 5), 5.46 (s, 2), 4.65 (m, 1), 3.67 (s, 3); ir (film) 3410 (m), 1730 (s), 1648 (w), 1580 (w), 1010 cm^{-1} (s).

Recyclization of Recovered Material from the Borohydride Reduction of 51.—51 (1.55 g, recovered from the preparation of compound 52) was dissolved in methanol (120 ml), and 1 *N* HCl (3 ml) was added. After stirring 18 hr at room temperature, the solvent was removed *in vacuo* at room temperature, the residue was dissolved in ether, and shaken with water. The residue from the ether layer was chromatographed over silica gel and 48, 880 mg (68%), eluted with ethyl acetate–methylene chloride (1:9).

48 (880 mg) was dissolved in methylene chloride (60 ml), and

2,3-dihydro-γ-pyran (0.6 ml) and picric acid (60 mg) was added. After 18 hr at room temperature the solution was shaken with water and 10% $KHCO_3$ solution. The residue from the methylene chloride layer [**51** by tlc, 1.05 g (100%)] was dissolved in ethanol (50 ml); $NaBH_4$ (1.9 g) was added portionwise over 4 hr with stirring at room temperature. After 4.5 hr most of the solvent was removed *in vacuo* at room temperature. The residue was dissolved in ether–water. The ether layer was reshaken with water (twice). The residue from the ether layer was preparatively separated (silica gel; ethyl acetate–methylene chloride, 1:4) to give unreacted starting material, **51** (420 mg, R_f 0.86) and **52** (435 mg, 73% based on recovered starting material, R_f 0.42).

The Collins Oxidation of 52 to Aldehyde 53.—**52** (305 mg) was dissolved in methylene chloride (40 ml, dried over molecular sieves), and with stirring at room temperature a solution of freshly prepared pyridine dichromate (1.07 g) in dry methylene chloride (150 ml) was added in one portion. After stirring 10 min, the CH_2Cl_2 was decanted into a separatory funnel containing water. The CH_2Cl_2 layer was reshaken with water (twice) and dried over $MgSO_4$. Removal of the solvent gave **53** (290 mg) homogeneous on tlc: nmr δ 9.75 (m, 1), 7.4 (m, 5), 5.4 (s, 3), 4.61 (m, 1), 3.61 (s, 3).

This residue was used immediately without further purification or identification.

The Moffatt Oxidation of 52 to Aldehyde 53.—**52** (725 mg) was dissolved in dimethyl sulfoxide (19 ml, dried over molecular sieves) and benzene (19 ml, dried over sodium wire) and cooled to 4°. Then dry pyridine (175 mg), trifluoroacetic acid (210 mg), and 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-*p*-toluenesulfonate (Aldrich No. C-10,640-2) (2.5 g) were added in that order. After stirring 72 hr at 4°, the reaction mixture was poured into ice water and extracted with ether. The ether was reshaken with water, dried over $MgSO_4$, and evaporated *in vacuo* to give **53** (710 mg), identical with the aldehyde derived from the Collins oxidation by nmr and tlc.

The Wittig Reaction on 53 to Give 54.—**53** (290 mg) and 1-tributylphosphoranylidene-2-heptanone (**43**) (450 mg) were mixed together in ether (20 ml) and stirred at room temperature. After 18 hr, the ether was removed and the residue preparatively separated (silica gel; ethyl acetate–methylene chloride, 1:9) to give **54** [302 mg, 87.5%; R_f 0.83; nmr δ 7.37 (m, 5), 6.77 (m, 1), 6.22 (m, 1), 5.45 (s, 2), 4.61 (m, 1), 3.65 (s, 3), 0.92 (m, 3)] as an oil.

Borohydride Reduction of Enone 54 to 55.—**54** (440 mg) was dissolved in ethanol (30 ml), and $NaBH_4$ (450 mg) was added portionwise over a 5-min period. The mixture was stirred at room temperature for 0.5 hr. The solution was poured into ice water and extracted twice with ether. The ether layer was reshaken with water, dried ($MgSO_4$), and evaporated to dryness *in vacuo*. The residue **55** (430 mg) was used in the next step without further purification or identification.

Hydrolysis of 55 to 56 and 57.—**55** (430 mg) was dissolved in methanol (60 ml), and 0.1 *N* HCl (1.25 ml) was added. Stirred at room temperature 20 hr. The solvent was removed *in vacuo* without heating above room temperature. The residue was dissolved in ether and shaken with water. The residue from the ether layer was preparatively separated [silica gel, ethyl acetate–methylene chloride (3:7), two developings] to give **56** (132 mg) as a crystalline solid (R_f 0.51; ethyl acetate–methylene chloride, 1:1).

Recrystallization from ether–hexane gave the analytical sample: mp 52–54°; nmr δ 7.45 (m), 5.48 (m, 2), 5.42 (s, 2), 3.64 (s, 3), 0.90 (m, 3); ir ($CHCl_3$) 3605 (m), 3415 (m), 1727 (s), 1585 (w), 1018 cm^{-1} (s); mass spectrum *m/e* 505 (M), 473 (M − $HOCH_3$), 366 (M − OCH_2SPh).

Anal. Calcd for $C_{28}H_{43}NO_5S$: C, 66.51; H, 8.57; N, 2.77. Found: C, 66.55; H, 8.51; N, 2.78.

The less polar band was **57** (143 mg as an oil; R_f 0.64, ethyl acetate–methylene chloride, 1:1): nmr δ 7.39 (m, 5), 5.59 (m, 2), 5.45 (s, 2), 3.63 (s, 3), 0.92 (m, 3); ir ($CHCl_3$) 3610 (m), 3450 (w), 1727 (s), 1582 (w), 1020 cm^{-1} (s).

Cleavage of 56 to 58.—**56** (72 mg) was dissolved in glacial acetic acid (5 ml), and a solution of mercuric chloride (230 mg), potassium acetate (210 mg) and mercuric oxide (100 mg) in glacial acetic acid (7.5 ml) was added in one portion. The mixture was stirred at room temperature for 0.5 hr; a white precipitate formed after 10 min. The mixture was diluted with acetone and H_2S bubbled into it until a black precipitate formed. This mixture was filtered through Celite, which was washed well with acetone and ether. The filtrate was evaporated *in vacuo* at room temperature. The residue was dissolved in ether–water. The ether layer was reshaken with water, dried over $MgSO_4$ and evaporated under aspirator pressure to give **58** (61 mg) as an oil: homogeneous on tlc; nmr δ 5.63 (m, 4), 4.00 (m, 2), 3.66 (s, 3), 2.23 (complex multiplet, 7), 0.92 (m, 3).

Formation of the *dl*-PGE$_1$ Oxime Methyl Ester 59 from 58.—**58** (34 mg) was dissolved in methanol (3 ml) and 10% K_2CO_3 solution (0.5 ml) added. Stirred at room temperature for 0.5 hr. Most of the methanol was removed by aspirator; the residue was dissolved in ether and shaken with water and saturated NaCl solution. The ether layer was dried over $MgSO_4$ and evaporated *in vacuo* to give a crystalline residue. Recrystallization from ether–hexane gave the analytical sample of **59** (17 mg): mp 105–107°; nmr δ 5.59 (m, 2), 3.68 (s, 3), 0.98 (m, 3); ir (KBr) 3360 (s), 1738 (m), 1708 (s, internally bonded carbonyl), 1660 (w), 935 cm^{-1} (m); mass spectrum *m/e* 383 (M), 367 (M − O), 366 (M − OH).

Anal. Calcd for $C_{21}H_{37}NO_5$: C, 65.76; H, 9.72; N, 3.65. Found: C, 65.85; H, 9.92; N, 3.75.

***dl*-PGE$_1$ Oxime and *dl*-PGE$_1$ from 58.**—**58** (68 mg) was dissolved in methanol (6.8 ml) and 10% K_2CO_3 solution (1.13 ml) was added; after stirring at room temperature for 4 days, the solvent was removed *in vacuo* at room temperature. The residue was crystallized with ether–methylene chloride to give crystals of *dl*-PGE$_1$ oxime **60**: mp 123–5°; nmr (drop of DMSO added to $CDCl_3$) δ 5.52 (t, 2), 3.10 (d, 1), 2.92 (d, 1); ir (KBr) 3390 (s), 1680 cm^{-1} (s). Spectra and tlc behavior were identical with those of a sample of *l*-PGE$_1$ oxime.

Anal. Calcd for $C_{20}H_{35}NO_5$: C, 65.01; H, 9.55; N, 3.79. Found: C, 64.87; H, 9.78; N, 3.47.

The mother liquor and crystals were recombined and dissolved in glacial acetic acid (3.5 ml) and cooled to 10°. Then 10% aqueous $NaNO_2$ solution (1.5 ml) was added and the reaction was stirred at 10° for 1 hr. An additional 1.5 ml of 10% $NaNO_2$ solution was added and the reaction was allowed to warm to room temperature over 15 min. The mixture was shaken between water and ethyl acetate–ether (3:1). The organic layer was reshaken with water and saturated NaCl solution, dried over $MgSO_4$, and evaporated *in vacuo* at room temperature. The residue was dissolved in ethyl acetate (0.2 ml) and allowed to stand at −5° overnight. *dl*-PGE **61** (8 mg) crystallized out, mp 112–115°, no melting point depression on admixture with authentic *dl*-PGE$_1$.[24] The nmr and ir were identical with those of authentic PGE$_1$. Tlc examination (solvent systems AI and MI[23]) also showed that they were identical.

Cleavage of 57 to 62.—**57** (78 mg) was dissolved in glacial acetic acid (5.5 ml) and a solution of mercuric chloride (250 mg), potassium acetate (2.8 mg), and mercuric oxide (105 mg) in glacial acetic acid (8.0 ml) was added in one portion. After the mixture stirred for 0.5 hr at room temperature, a white precipitate was present. The mixture was diluted with acetone, and H_2S was bubbled into it until a black precipitate formed. It was filtered through Celite, which was washed well with acetone and ether. The filtrate was evaporated in vacuo at room temperature. The residue was dissolved in ether–water. The ether layer was reshaken with water, dried ($MgSO_4$), and evaporated to give **62** (71 mg) as an oil: homogeneous on tlc; nmr δ 5.67 (m, 4), 4.12 (m, 2), 3.67 (s, 3), 2.25 (complex multiplet, 7), 0.91 (m, 3).

***dl*-C$_{15}$-Epi-PGE$_1$ (63) from 62.**—**62** (132 mg) was dissolved in methanol (13.2 ml) and 10% K_2CO_3 solution (2.2 ml) added. After stirring at room temperature for 4 days, the solvent was removed *in vacuo*. The residue was dissolved in glacial acetic acid (6.5 ml) and stirred at 10°. Then 10% aqueous $NaNO_2$ solution (2.75 ml) was added and the solution was stirred at 10° for 1 hr. An additional 2.75 ml of 10% $NaNO_2$ solution was added and the reaction mixture was allowed to warm to room temperature over a 20-min period. The solution was shaken between water and ethyl acetate–ether (3:1). The organic layer was reshaken with water and saturated NaCl solution, dried ($MgSO_4$), and evaporated *in vacuo* at room temperature. The residue from the organic layer was preparatively separated (silica gel; benzene–dioxane–acetic acid, 20:20:1) to give C$_{15}$ *dl*-Epi-PGE$_1$ **63** (21 mg): nmr δ 5.69 (m, 2), 4.16 (m, 2), 2.36 (m, 3), 0.92 (m, 3); homogeneous on tlc (solvent systems AI and MI[23]).

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Registry No.—1, 25407-85-6; 2, 42334-95-2; 3, 42334-96-3; 4, 23166-56-5; 5, 23166-57-6; 6, 23266-13-9; 7, 23166-58-7; 8, 23166-59-8; 9, 42335-01-3; 10, 42335-02-4; 12 4-ene, 26047-64-3; 12 5-ene, 26060-68-4; 13, 23166-53-2; 14, 23166-54-3; 15, 23166-52-1; 16, 42335-08-0; 17, 42335-09-1; 18, 42335-10-4; 19, 42335-11-5; 20, 25346-53-6; 21, 42335-13-7; 22, 42335-14-8; 23, 42335-15-9; 24, 42335-16-0; 25, 42398-33-4; 26, 26258-31-1; 26 epimer, 42447-95-0; 27, 42335-17-1; 27 epimer, 42335-18-2; 28, 25455-39-4; 28 epimer, 42335-20-6; 29, 42335-21-7; 29 epimer, 42398-34-5; 30, 42335-22-8; 31, 42335-23-9; 32, 25348-52-1; 33, 25348-53-2; 34, 25348-54-3; 35, 42335-27-3; 36, 35563-52-1; 37, 25348-56-5; 38, 42335-30-8; 39, 42335-31-9; (*R*)-40, 42335-32-0; (*S*)-40, 42335-33-1; 42, 25455-41-8; 43, 41108-24-1; 46, 42335-36-4; 47, 42335-37-5; 48, 42335-38-6; 49, 42335-39-7; 50, 42398-35-6; 51, 42335-40-0; 52, 42335-41-1; 53, 42335-42-2; 54, 42398-36-7; (*R*)-55, 42335-43-3; (*S*)-55, 42334-36-1; 56, 42334-37-2; 57, 42334-38-3; 58, 42334-39-4; 59, 42334-40-7; 60, 42334-41-8; 61, 20348-58-7; 62, 42334-43-0; 63, 20897-96-5; ethyl 2-bromoazelate, 760-95-2; thiophenol, 108-98-5; chloromethyl phenyl sulfide, 7205-91-6; *N*-hydroxyphthalimide, 524-38-9; *N*-phenylthiomethoxyphthalimide, 41108-32-1; phenylthiomethoxyamine, 41108-23-0.

A General Synthetic Approach to the Eudesmane Class of Sesquiterpenes

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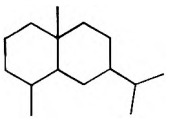
A versatile synthetic approach to the eudesmane class of sesquiterpenes is described. The key intermediate in the synthetic scheme is 6-methoxy-10-methyl-$\Delta^{6,7}$-octal-1-one (4). Elaboration of 4 into precursors which have been used in previous eudesmane sesquiterpene synthesis was accomplished in two manners. Wittig olefination of 4 with methylenetriphenylphosphorane followed by acid hydrolysis gave 1-methylene-10-methyl-6-decalone (10) which has previously been converted to atractylon and isoalantolactone. Incorporation of a carbomethoxy group at C-7 and removal of the carbonyl group at C-6 transformed 4 eventually into 7-carboxy-10-methyl-1-decalone (11) which has previously been converted to β-eudesmol.

The eudesmane class (see **1** for the general substitution pattern) of decalin sesquiterpanes has recently received considerable synthetic attention, especially β-eudesmol (2).[1] As part of our own synthetic studies,



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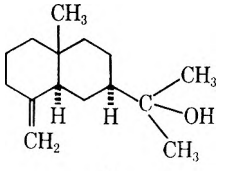

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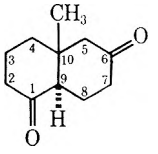
we have developed a general approach which allows elaboration from a common intermediate into diverse members of the eudesmane class. The synthesis of this intermediate and its conversion into compounds used in other eudesmane sesquiterpene syntheses is the subject of this paper.

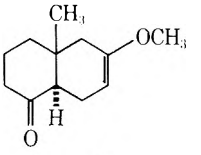
Our scheme was based on the use of a synthon of the diketone **3**. This type of intermediate, properly pro-



3

tected so that the carbonyl functions could be operated on selectively, would allow elaboration at both C-1 and C-7 as is required for the synthesis of the eudesmane sesquiterpenes. Also the presence of the carbonyl groups at C-1 and C-6 would allow stereochemical control of the ring fusion and the group at C-7 by equilibration at these centers. Finally the carbonyl function at C-6 would allow the synthesis of other eudesmane sesquiterpenes, such as the furanosesquiterpene atractylon,[2] not readily accessible by the earlier cited synthetic routes.

Our choice and initial synthetic goal for the protected diketone was the keto–enol ether **4**. This was con-



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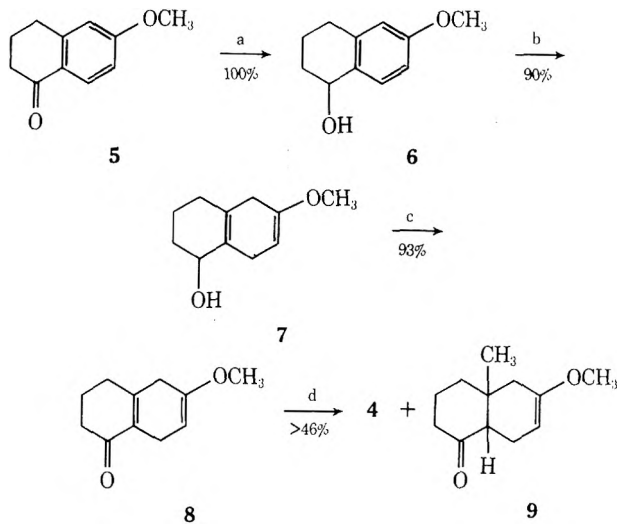
veniently prepared as outlined in Scheme I. Following a modified procedure of Birch,[3a] we prepared keto enol ether **8**[3] in good yield. Birch had suggested that prior reduction of the carbonyl group at C-1 to a hydroxyl group should increase the yield of enol ether–alcohol **7** in the subsequent Birch reduction step. This indeed proved correct as reduction of **5** with sodium borohydride to **6** followed by Birch reduction as previously described[3a] afforded crystalline **7** in 90% yield, whereas direct reduction of **5** gave yields on the order of 60%. Oppenauer oxidation of **7**[3a] gave crystalline enol ether–ketone **8** in yields in excess of 90%. Treatment of **8** with lithium dimethylcopper(I) gave the desired 1,4-addition product as an epimeric mixture at C-9. Under the aqueous work-up conditions the trans-fused product **4** predominated, constituting ~70%

(1) For some previous syntheses of members of the eudesmane class, especially β-eudesmol, see (a) J. A. Marshall, M. T. Pike, and R. D. Carroll, *J. Org. Chem.*, **31**, 2933 (1966); (b) D. C. Humber, A. R. Pinder, and R. A. Williams, *ibid.*, **32**, 2335 (1967); (c) C. H. Heathcock and T. R. Kelly, *Tetrahedron*, **24**, 1801 (1968); (d) J. A. Marshall and M. T. Pike, *J. Org. Chem.*, **33**, 435 (1968); (e) J. W. Huffman and M. L. Mole, *Tetrahedron Lett.*, 501 (1971); *J. Org. Chem.* **37**, 13 (1972); (f) R. G. Carlson and E. G. Zev, *ibid.*, **37**, 2468 (1972).

(2) S. Taki and G. Hongo, *J. Pharm. Soc. Jap.*, **44**, 539 (1925). H. Hikino, Y. Hikino, and I. Yoshioka, *Chem. Pharm. Bull.*, **10**, 641 (1962); **12**, 755 (1964).

(3) (a) A. J. Birch, J. A. K. Quartey, and H. Smight, *J. Chem. Soc.*, 1769 (1952); (b) A. J. Birch, *Proc. Roy. Soc. N. S. W.*, **83**, 245 (1949); (c) N. N. Gaidamovich and I. V. Torgov, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1682 (1961).

SCHEME I[a]

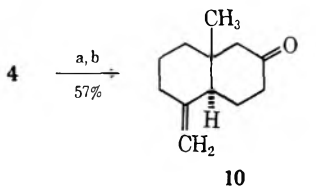


[a] a, $NaBH_4$, MeOH; b, $Na,NH_3(l)$, EtOH; c, $Al(i\text{-}PrO)_3$, CH_3COCH_3, $PhCH_3$; d, $Li(CH_3)_2Cu$, Et_2O.

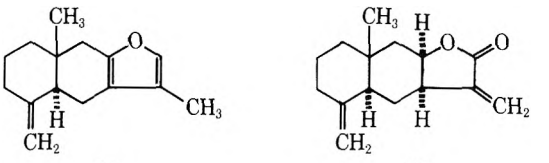
of the 1,4-addition product.[4,5] That the initially obtained product seemed to be the equilibrium mixture was indicated by treatment of the isolated 1,4-addition product with sodium methoxide in methanol to give the same ratio of **4** to **9** as previously observed. Florisil chromatography proved to be an easy method of separation and purification giving **4** in 35% isolated yield.

Despite the somewhat disappointing yield of the lithium dimethylcopper(I) reaction, the ease of preparation and purification of this masked diketone **4** caused us to explore its versatility in the synthesis of eudesmane sesquiterpenes. We investigated two approaches to the use of this compound. First we chose to directly functionalize the carbonyl group at C-1 while leaving the potential carbonyl group at C-6 for later elaboration. This approach, as outlined in Scheme II, led to a compound typified by the exocyclic methylene ketone **10**. This transformation was accomplished by treatment of **4**[6] with methylenetriphenylphosphorane in dimethyl sulfoxide[7] followed by acidic hydrolysis of the crude exocyclic methylene enol ether giving **10** in 57% yield. Compound **10** has been previously synthesized by a rather involved route by Minato[8] and used as a key intermediate in his syntheses of the eudesmane furanosesquiterpene atractylon[8] (**11**) and of the eudesmane sesquiterpene lactone isoalantolactone[9] (**12**).

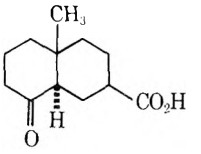
SCHEME II[a]



[a] a, $Ph_3P{=}CH_2$, DMSO; b, H_2O^+.



The second approach using **4** was directed toward the synthesis of the keto acid **13**, an intermediate in many

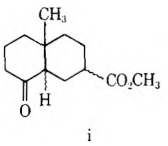


of the previous syntheses of β-eudesmol.[1c,e,f] In this sequence the carbonyl group at C-1 was reduced and protected while the carbonyl group at C-6 was utilized to introduce functionality at C-7. Then, after removal of the C-6 carbonyl group, the C-1 carbonyl group was regenerated. These transformations were carried out as indicated in Scheme III. Reduction of **4** with sodium borohydride followed by acidic hydrolysis of the resulting hydroxy enol ethers gave the epimeric mixture of hydroxy ketone **14** in 73% yield. Treatment of this mixture with sodium hydride in dimethyl carbonate followed by chromatography gave the crystalline keto carbonate ester **15** in 61% isolated yield and a fraction (21% yield) containing what seems to be mainly its C-1 epimer **16**. Although the asymmetry at C-1 would later be destroyed, it was convenient to continue the sequence with the crystalline epimer **15**. The stereochemical assignment of **15** will be discussed later in this paper.

The next transformation involved removal of the C-6 carbonyl group. After attempting several unsuccessful methods, this problem was solved by conversion of **15** to its crystalline thioketal **17** in 95% yield by treatment with ethanedithiol, glacial acetic acid, and a catalytic amount of *p*-toluenesulfonic acid. Desulfurization was accomplished using W-2 Raney nickel[10] in absolute ethanol to give crystalline carbonate ester **18** in 70% yield. Removal of the carbonate group was achieved by subjecting **18** to lithium aluminum hydride reduction to quantitatively afford the crystalline diol **19**. Finally the keto acid **13** was obtained in 53% yield by Jones oxidation[11] of the diol **17**. As **13** has

(4) The isomeric ratio between **4** and **9** was determined by nmr analysis. Carlson (see ref 1f) had shown that in a similar system the angular methyl signal in the cis-fused system occurs at lower field (δ 1.0 ppm in the case of **9**) than that in the trans-fused system (δ 0.75 ppm in the case of **4**).

(5) This isomeric ratio is approximately the same as the total trans:cis ring fusion ratio found by Carlson (see ref 1f) after methoxide equilibration of i.



i

(6) It should be noted that the use of a mixture of **4** and **9** would probably be suitable here in that under the reaction conditions the cis-fused compound **9** would also give **10**. For examples see ref 1a and 1e.

(7) R. Greenwald, M. Chaykovsky, and E. J. Corey, *J. Org. Chem.*, **28**, 128 (1963).

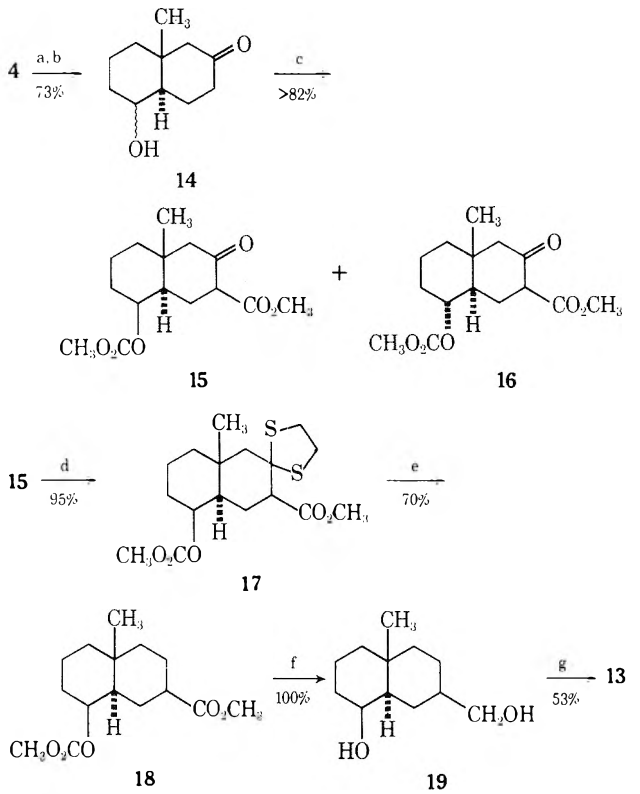
(8) H. Minato and T. Nagasaki, *Chem. Commun.*, 377 (1965).

(9) H. Minato and I. Horibe, *Chem. Commun.*, 531 (1965).

(10) R. Mozingo, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 181.

(11) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

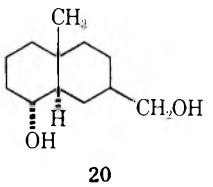
SCHEME III[a]



[a] a, $NaBH_4$, CH_3OH; b, H_3O^+; c, $(CH_3O)_2CO$, NaH; d, $HSCH_2CH_2SH$, HOAc, *p*-TsOH; e, W-2 Raney nickel, EtOH; f, $LiAlH_4$, Et_2O; g, CrO_3, H_2SO_4, CH_3COCH_3.

been previously converted into β-eudesmol,[1c] this constitutes a formal total synthesis of this eudesmane sesquiterpene.

Concerning the stereochemistry[12] of the keto carbonate ester **15**, the assignment was made from the following observations. The trans ring fusion follows from both the starting material **4** and the final product **13** which are known to possess this stereochemistry. The equatorial assignment to the carbomethoxy group at C-7 is consistent with the method of formation and again with transformation into **13**, possessing known equatorial carboxyl stereochemistry. Both of these assignments are predicated on the use of reactions not expected to cause epimerization at the centers of interest. Finally the axial stereochemistry of the carbonate group at C-1 was assigned by comparison of diol **19**, derived from **15** by reactions not involving that position, and diol **20**, obtained by Heathcock[1c] in his



20

synthesis of β-eudesmol. Although the two diols are different (both by nmr and melting point), they are converted to the same keto acid **13** by Jones oxidation.[13]

(12) All compounds in this sequence are *dl* mixtures and only one enantiomeric form is given.

(13) For use of the Jones oxidation procedure for the oxidation of alcohols to enolizable ketones without epimerization of an asymmetry center α to the ketone function, see C. Djerassi, P. A. Hart, and E. J. Warawa, *J. Amer. Chem. Soc.*, **86**, 78 (1964).

Since Heathcock has shown diol **20** to have the equatorial hydroxyl group at C-1, it follows that diol **19** and keto carbonate ester **15** have the axial orientation at that position. This is also consistent with the observation that the position of absorption of the angular methyl group in the nmr is sensitive to the nature of the function at C-1. This variation in angular methyl chemical shift can be seen in Table I. The shift to

TABLE I

Compd	Angular methyl group chemical shift (δ, ppm) CCl_4	CD_3COCO_3	C_5H_5N
13	0.83	0.82	0.77
15	1.08	1.07	1.09
19	*a*	1.12	1.38
20			0.83[b]

[a] Solubility too low to obtain spectrum. [b] From ref 1c.

higher field in going from hydroxyl or carbonate to ketone at C-1 is consistent with a decrease in deshielding by virtue of the 1,3-diaxial interaction which is removed in the keto acid **13**. It can be seen that the angular methyl group in **20** has a high field chemical shift (δ 0.82 ppm) which is consistent with there being no interaction between the equatorial hydroxyl group at C-1 and the angular methyl group.

Experimental Section[14]

6-Methoxy-1-tetralol (**6**).—To a mixture of 53.6 g (304 mmol) of 6-methoxy-1-tetralone[15] in 920 ml of methanol at 0° was slowly added 24.0 g (631 mmol) of sodium borohydride. After stirring the mixture for 3 hr at room temperature, 300 ml of water was added dropwise. The resulting tan solution was concentrated and extracted with ether. The combined ether layers were washed with water and brine, dried, and concentrated to give 54.3 g, quantitative yield, of the crude alcohol **6**: ir (neat) 3400 cm^{-1} (OH); nmr (CCl_4) δ 3.6 (s, 3 H, OCH_3) and 4.4 ppm (m, 1 H, >CHOH). An α-napthylurethane derivative was prepared, mp 130–132° (lit.[16] mp 131–133°).

Formation and Separation of an Isomeric Mixture of 6-Methoxy-10-methyl-$\Delta^{6,7}$-octal-1-one (**4 and 9**).—To 14.6 g (7.68 mmol) of anhydrous copper(I) iodide in 150 ml of anhydrous ether was added 9.5 ml (15.4 mmol) of 1.63 *M* methyllithium at 0°. After 15 min, 0.914 g (5.1 mmol) of **8** in 60 ml of anhydrous ether was added dropwise. The mixture was stirred at 0° for 2 hr; then it was allowed to warm to room temperature as 100 ml of water was added. After filtration, the inorganic salts were crushed and thoroughly washed with ether. The filtrate was extracted with ether. The combined ether layers were washed with water and brine, dried, and concentrated to give 0.854 g of a crude mixture of **4** and **9**. Elution from Florisil with 75% petroleum ether–25% dichloromethane afforded 0.109 g, 11% yield, of **9**: ir (neat) 1710 cm^{-1} (C=O); nmr (CCl_4) δ 1.1 (s, 3 H, angular CH_3), 3.4 (s, 3 H, OCH_3), and 4.5 ppm (m, 1 H, vinyl proton). Further elution from Florisil with 50% petroleum ether–50% dichloromethane afforded 0.348 g, 35% yield, of **4**: ir (neat) 1710 cm^{-1} (C=O); nmr (CCl_4) δ 0.75 (s, 3 H, angular CH_3), 3.4 (s, 3 H, OCH_3), and 4.5 ppm (m, 1 H, vinyl proton); mass spectrum (*m/e*) calcd for $C_{12}H_{18}O_2$ 194.1307, found 194.1285.

Equilibration of 4 and 9.—To a solution resulting from the addition of 0.39 g of sodium to 10 ml of anhydrous methanol was added 4.34 g (2.24 mmol) of a crude mixture of **4** and **9**. This

(14) All melting points are uncorrected. Ir spectra were recorded on a Beckman IR-8 spectrophotometer and nmr spectra were recorded on a Varian A-60A instrument using tetramethylsilane as an internal standard. High-resolution mass spectra were obtained with a Varian M-66 spectrometer. Combustion analyses were done by Chemalytics, Inc., Tempe, Ariz. Petroleum ether used was reagent grade with boiling range 30–60°. All reactions were carried out under a nitrogen atmosphere. Anhydrous sodium sulfate was used as the drying agent. Florisil (60/100A) used for chromatography was purchased from Wilshire Chemical Co., Inc.

(15) Purchased from Aldrich Chemical Co.

(16) L. Long and A. Burger, *J. Org. Chem.*, **6**, 852 (1941).

solution was allowed to stir at room temperature for 48 hr after which water was added and the resulting mixture was extracted with ether. The combined ether layers were washed with water and brine, dried, and concentrated to afford 3.71 g, 85% yield, of a mixture of **4** and **9**. The spectral properties of this mixture were identical with those of the starting mixture, *i.e.*, the initial mixture from the lithium dimethylcopper reaction.

1-Methylene-10-methyl-6-decalone (10).—To 3.55 g (260 mmol) of a 57% mineral oil dispersion of sodium hydride (twice washed with dry pentane) wad added 4.5 ml of anhydrous dimethyl sulfoxide. The mixture was heated to 70° for 30 min after which an additional 8.5 ml of anhydrous dimethyl sulfoxide and 22 g (61.6 mmol) of methyltriphenylphosphonium bromide were added. After 15 min, 6.0 g (30.9 mmol) of **4** was added in 2 ml of anhydrous dimethyl sulfoxide. The dark burgundy solution was stirred at 55° for 18 hr; then it was poured into ice and thoroughly extracted with pentane. The pentane layer was washed with an ice-cold 1:1 mixture of dimethyl sulfoxide–water, ice-cold water, and brine, dried, and concentrated to give 7.5 g of crude product. This material was dissolved in 10 ml of ether and placed in a flask containing 30 ml of 1% aqueous hydrochloric acid. After vigorous sitrring overnight, the mixture was extracted with ether. The combined ether extracts were washed with water and brine, dried, and concentrated to give 6.6 g of crude product. Elution with 25% petroleum ether–75% dichloromethane from Florisil afforded 3.1 g, 57% yield from **4**, of clear oily **10**: ir (neat) 1710 (C=O) and 890 cm^{-1} (C=CH_2); nmr (CCl_4) of δ 0.70 (s, 3 H, angular CH_3), 4.5 (m, 1 H, vinyl proton), and 4.8 ppm (m, 1 H, vinyl proton); mass spectrum (*m/e*) calcd for $C_{12}H_{18}O$ 178.1354, found 178.1357.

Epimeric Mixture of 1-Hydroxy-10-methyl-6-decalone (14).—To 1.61 g (8.3 mmol) of **4** in 20 ml of methanol at 0° was added 0.719 g (18.9 mmol) of sodium borohydride. The mixture was stirred 3 hr as it warmed to room temperature. After adding 15 ml of water, the mixture was concentrated and extracted with ether. The combined ether layers were washed with water and brine, dried, and concentrated to yield 1.56 g, 96% yield, of crude product. This material was dissolved in 5 ml of ether and placed in a flask containing 30 ml of 1% aqueous hydrochloric acid. After vigorous stirring overnight, the mixture was extracted with ether. The combined ether layers were washed with brine, dried, and concentrated to give 1.29 g of crude **14**. Florisil chromatography afforded 1.10 g, 73% overall yield from **4**, of the epimeric mixture **14**: ir (neat) 3460 (OH) and 1710 cm^{-1} (C=O); nmr (CCl_4) δ 1.0 (s, 3 H, angular CH_3) and 3.9 ppm (broad m, 1 H, >CHOH); mass spectrum (*m/e*) calcd for $C_{11}H_{18}O_2$ 182.1307, found 182.1284.

Formation and Separation of an Epimeric Mixture of Methyl 7-Carbomethoxy-10-methyl-6-oxodecalin 1-Carbonate (15 and 16).—To 0.143 g (3.4 mmol) of a 57% mineral oil dispersion of sodium hydride (twice washed with dry pentane) in 2 ml of dry dimethyl carbonate was added 0.305 g (1.68 mmol) of **14** in 15 ml of dimethyl carbonate. The mixture was stirred at 50° for 3 hr after which it was poured into 100 ml of water, acidified, and extracted with ether. The combined ether layers were washed with water and brine, dried, and concentrated to give 0.480 g of a crude mixture of **15** and **16**. Elution with 50% petroleum ether–50% dichloromethane from Florisil afforded 0.107 g, 21% yield, of an oil which was presumed to be mainly **16**. Further elution gave 0.304 g, 61% yield, of crystalline **15**. Recrystallization from petroleum ether gave material with mp 88–89°: ir (CCl_4) 1650 and 1740 cm^{-1} (C=O); nmr (CCl_4) δ 1.08 (s, 3 H, angular CH_3), 3.7 (s, 6 H, OCH_3), and 4.8 ppm (m, 1 H, $-CHOCO_2CH_3$).

Anal. Calcd for $C_{15}H_{22}O_6$: C, 60.39; H, 7.43. Found: C, 60.52; H, 7.26.

Thioketalization of 15.—To 0.308 g (1.03 mmol) of **15** was added 0.2 ml of ethanedithiol, 0.08 g of *p*-toluenesulfonic acid, and 2.5 ml of glacial acetic acid. This mixture was stirred at room temperature for 3 days after which it was poured into ether. The ether layer was washed with 3 *N* sodium hydroxide, water, and brine, dried, and concentrated to give 0.370 g of oily crystals. Recrystallization from ether gave 0.368 g, 95% yield, of crystalline **17**: mp 175–176.5°; ir (CCl_4) 1730 cm^{-1} (C=O); nmr (CCl_4) δ 1.25 (s, 3 H, angular CH_3), 3.20 (m, 4 H, $-SCH_2CH_2S-$), 3.68 (s, 3 H, OCH_3), 3.75 (s, 3 H, OCH_3), and 4.8 ppm (m, 1 H, $>CHOCO_2CH_3$).

Anal. Calcd for $C_{17}H_{26}O_5S_2$: C, 54.52; H, 7.00; S, 17.12. Found: 54.79; H, 6.91; S, 16.50.

Methyl 7-Carbomethoxy-10-methyldecalin 1-Carbonate (18).—To 0.600 g (1.60 mmol) of **17** was added 8.1 g of W-2 Raney nickel[10] in 40 ml of absolute ethanol. The mixture was stirred with the aid of an overhead stirrer for 12 hr at 65° after which the catalyst was removed by filtration and the mixture was concentrated and taken up in ether. The ether layer was washed with brine, dried, and concentrated to give 0.408 g of crude product. Elution with 50% petroleum ether–50% dichloromethane from Florisil afforded 0.316 g, 70% yield, of crystalline **18**. A small sample was recrystallized from petroleum ether: mp 60.5–61.5°; ir (CCl_4) 1730 cm^{-1} (C=O); nmr (CCl_4) δ 1.0 (s, 3 H, angular CH_3), 3.6 (s, 3H, OCH_3), 3.7 (s, 3 H, OCH_3), and 4.7 ppm (m, 1 H, $>CHOCO_2CH_3$).

Anal. Calcd for $C_{15}H_{24}O_5$: C, 63 36; H, 8.51. Found: C, 63.56; H, 8.39.

1-Hydroxy-7-hydroxymethyl-10-methyldecalin (19).—To 0.183 g (0.65 mmol) of **18** was added 0.343 g of lithium aluminum hydride and 10 ml of anhydrous ether. The resulting mixture was stirred at room temperature overnight after which 0.34 ml of water was cautiously added, followed by 0.26 ml of 20% sodium hydroxide then 1 ml of water. After filtration, the resulting salts were rinsed and triturated with ether. The combined ether fractions were concentrated to give 0.128 g, quantitative yield, of crystalline **19**. A small portion was recrystallized from ether: mp 139.5–141°; ir (CH_2Cl_2) 3620 cm^{-1} (OH); nmr (CD_3COCD_3) δ 0.1.12 (s, 3 H, angular CH_3) and 3.1–3.8 ppm (m, 3 H, >CHOH and $>CH_2OH$).

Anal. Calcd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 72.39; H, 10.88

7-Carboxy-10-methyl-1-decalone (13).—To 0.100 g (0.51 mmol) of **19** in 5 ml of reagent grade acetone was added 1.1 ml of Jones reagent.[11] This mixture was stirred for 30 min at room temperature after which it was poured into water and extracted with ether. The ether layer was extracted with saturated aqueous sodium bicarbonate solution. The basic aqueous layer was acidified to pH 2 and extracted with ether. The combined ether extracts were dried and concentrated to give 0.060 g, 57% yield, of **13** as a clear oil which solidified on standing. Recrystallization from ether gave crystalline **13**: mp 123–125° (lit.[1c] mp 124–126°); ir (CCl_4) 2700–3200 (OH) and 1700 cm^{-1} (C=O); nmr (CCl_4) δ 0.83 (s, 3 H, angular CH_3) and 9.70 ppm (s, 1 H, COOH). There was no depression in melting point on admixing with an authentic sample.[17]

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Registry No.—**4**, 42246-03-7; **5**, 1078-19-9; **6**, 42246-05-9; **8**, 42249-32-1; **9**, 42246-06-0; **10**, 42246-07-1; **13**, 42246-08-2; α-OH-**14**, 42246-09-3; β-OH-**14**, 42246-10-6; **15**, 42246-11-7; **16**, 42246-12-8; **17**, 42246-13-9; **18**, 42246-14-0; **19**, 42249-33-2.

(17) We are indebted to Professor Clayton Heathcock for supplying a sample of the keto acid **13**.

The Synthesis of Some 3′,2″-Dioxamethylene-Bridged *p*-Quaterphenyls and Related Compounds[1a]

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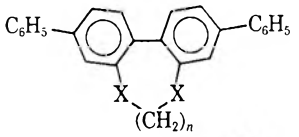
The synthesis of some *p*-quaterphenyls with $-O(CH_2)_nO-$ bridges across the 3′ and 2″ positions having $n = 1$, 2, 3, and 4 is reported. These compounds have been evaluated as liquid scintillator solutes, the results of which are being reported elsewhere. Attempts to prepare analogous compounds with $-NH(CH_2)_nNH-$ bridges across the 3′ and 2″ positions generally were unsuccessful; however, some products related to these are reported. The synthesis of the bridged *p*-quaterphenyls having –O– or –NH– across the 3′ and 2″ positions is also reported.

Earlier work by Taber[2] on the effect of noncoplanarity of some bridged *p*-quaterphenyls on the scintillator efficiency of the compounds prompted the synthesis of the following compounds for further studies.

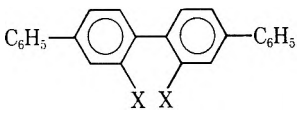


1, X = –O– **2**, X = –NH–
1a, $n = 1$ **2a**, $n = 1$
1b, $n = 2$ **2b**, $n = 2$
1c, $n = 3$ **2c**, $n = 3$
1d, $n = 4$ **2d**, $n = 4$

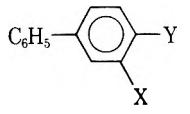
We are reporting the synthesis of the compounds **1a–d** along with attempts to prepare the compounds **2a–d** and certain other related compounds. The dioxepin **1a**, dioxocin **1b**, dioxonin **1c**, and dioxecin **1d** were each obtained from 2″,3′-dihydroxy-*p*-quaterphenyl (**3**) by reaction of the appropriate dihalide with **3** in DMF containing potassium carbonate.[3] Depending on the desired number of methylene groups in the bridge, either methylene iodide, 1,2-dibromoethane, 1,3-dibromopropane, or 1,4-dibromobutane was used to yield the respective bridged diethers **1a–d**.

The 2″,3′-dihydroxy-*p*-quaterphenyl (**3**) was synthesized in several steps starting with commercially available 4-nitrobiphenyl (**4**), which was converted to 2-nitro-5-phenylphenol (**5**) by treatment with potassium hydroxide in diphenyl ether at 95° under an oxygen atmosphere. The yields in this hydroxylation step were quite good, running as high as 80%. Other procedures, such as using potassium hydroxide and toluene or benzene[4] without the oxygen atmosphere, were less successful, the yields generally being less than 20%.

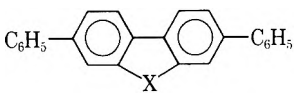
Treatment of crude **5** with dimethyl sulfate and potassium carbonate[5] in anhydrous toluene gave the methyl ether **6** in an 87% yield. Reduction of **6** with



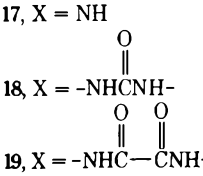
3, X = OH
9, X = OCH_3
12, X = NO_2
13, X = NH_2
15, X = NHTs



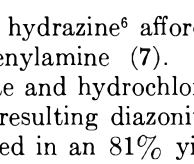
5, X = OH; Y = NO_2
6, X = OCH_3; Y = NO_2
7, X = OCH_3; Y = NH_2
8, X = OCH_3; Y = I
10, X = NO_2; Y = NH_2
11, X = NO_2; Y = I



14, X = O
17, X = NH



18, X = –NHCNH–



19, X = –NHC—CNH–

Raney nickel and hydrazine[6] afforded a 68% yield of 3-methoxy-4-biphenylamine (**7**). Diazotization of **7** with sodium nitrite and hydrochloric acid followed by treatment of the resulting diazonium salt with potassium iodide resulted in an 81% yield of 4-iodo-3-methoxybiphenyl (**8**). Treatment of **8** with copper bronze at 200° afforded a 54% yield of 2″,3′-dimethoxy-*p*-quaterphenyl (**9**), which was cleaved to the desired **3** in 96% yield by refluxing with 57% hydriodic acid in glacial acetic acid. Thus, **3** was prepared in an overall yield of about 20% from 4-nitrobiphenyl (**4**).

Attempts to synthesize the analogous diazepine **2a**, diazocine **2b**, diazonine **2c**, and diazecine **2d** failed; however, several key intermediates and related compounds also of interest to us were prepared as discussed below.

3-Nitro-4-biphenylamine (**10**) prepared from 4-nitrobiphenyl (**4**) by modification of the procedure described by Campbell, Anderson, and Gilmore,[7] was diazotized and treated with potassium iodide to give a 55% yield of 4-iodo-3-nitrobiphenyl (**11**). Ullmann coupling of **11** afforded 2″,3′-dinitro-*p*-quaterphenyl (**12**), which was reduced with hydrazine in the presence of Raney nickel[8] to 2″,3′-diamino-*p*-quaterphenyl (**13**) in 77% overall yield.

Initially it was hoped that diazotization of **13** and treatment of the diazonium salt with water would yield 2″,3′-dihydroxy-*p*-quaterphenyl (**3**); however, the

(1) (a) From the dissertation presented by J. Ernest Simpson to the graduate faculty of the University of New Mexico in partial fulfillment of the requirements for the degree of Doctor of Philosophy. This investigation was supported in part by a Research Grant from the Division of Biology and Medicine of the U. S. Atomic Energy Commission, Contract No. AT-(29-2)915. (b) Graduate Research Assistant, June 1963–Aug 1967. (c) University of New Mexico. (d) Work performed under the auspices of the U. S. Atomic Energy Commission.

(2) R. L. Taber, G. H. Daub, F. N. Hayes, and D. G. Ott, *J. Heterocycl. Chem.*, **2**, 181 (1965).

(3) J. E. Simpson, G. H. Daub, and F. N. Hayes, *J. Org. Chem.*, **38**, 1771 (1973).

(4) J. C. Colbert, W. Meigs, and R. L. Jenkins, *J. Amer. Chem. Soc.*, **59**, 1122 (1937).

(5) B. B. Day, *J. Sci. Ind. Res. (India)*, **3**, 338 (1945); *Chem. Abstr.*, **39**, 4597[9] (1945).

(6) D. Balcom and A. Furst, *J. Amer. Chem. Soc.*, **75**, 4334 (1953).

(7) N. Campbell, W. Anderson, and J. Gilmore, *J. Chem. Soc.*, 446 (1940).

(8) R. E. Moore and A. Furst, *J. Org. Chem.*, **23**, 1504 (1958).

major product isolated in 31% yield proved to be 3,7-diphenyldibenzofuran (**14**). Attempts to cleave **14** to yield 2″,3′-dihydroxy-*p*-quaterphenyl (**3**) proved futile.

Stetter[9] has reported the synthesis of some biphenyl derivatives similar to **2a–d** by treatment of the ditosyl derivative of 2,2′-diaminobiphenyl with dihalides of the type $Br(CH_2)_nBr$ where n = 2, 3, 4, and 5 in *n*-butyl alcohol containing sodium *n*-butoxide. The resulting bridged biphenyl was then hydrolyzed to the corresponding biphenyl with the $-NH(CH_2)_nNH-$ bridge across the 2 and 2′ positions.

In an effort to use Stetter's procedure for the synthesis of **2a–d**, the ditosyl derivative of **13** was prepared by addition of *p*-toluenesulfonyl chloride to a solution of **13** in anhydrous pyridine, affording a 96% yield of *N*,*N*′-ditosyl-2″,3′-diamino-*p*-quaterphenyl (**15**). However, treatment of **15** with sodium, *n*-butyl alcohol, and an appropriate dibromoalkane failed to give any of the desired bridged compounds. Other bases, such as sodium hydride, potassium carbonate, and potassium metal, were tried as well as different solvents, such as *N*,*N*-dimethylformamide, dimethyl sulfoxide, and *n*-amyl alcohol, but without success; however, in one case a 10% yield of the *N*,*N*′-ditosyl derivative (**16**) of 3,11-diphenyl-6,7,8,9-tetrahydro-5*H*-dibenzo[*f*,*h*]-[1,5]diazonine (**2c**) was obtained using *N*,*N*-dimethylformamide and potassium carbonate.

Attempts to remove the tosyl groups from **16** using sodium metal and *n*-amyl alcohol or using concentrated hydrobromic acid and phenol failed to give any of the desired **2c**, only starting material being recovered. Attempts to make the desired bridged compounds using the diamine **13** in a manner similar to that used for the analogous oxygen compounds **1** also failed.

Attention was then turned to some different approaches to the synthesis of **2a–d** and 3,7-diphenylcarbazole (**17**), which would be the nitrogen analog of 3,7-diphenyldibenzofuran (**14**). The carbazole **17** was indeed prepared in 75% yield by heating the diamine **13** with phosphoric acid.[10]

One approach to synthesis of **2a** might be through reduction of the corresponding compound with a carbonyl function at the 6 position. With this in mind 3,9-diphenyl-6-oxo-6,7-dihydro-5*H*-dibenzo[*d*,*f*][1,3]-diazepine (**18**) was prepared by treatment of the diamine **13** with urea[11] at 200°, affording a 91% yield of **18**. Attempts to reduce **18** with lithium aluminum hydride to the desired diazepine **2a** failed, yielding only recovered starting material.

A similar approach to **2b** was made by preparing 3,10-diphenyl-6,7-dioxo-5,6,7,8-tetrahydrodibenzo-[*e*,*g*][1,4]diazocine (**19**) in 82% yield by treatment of the diamine **13** with oxalyl chloride in anhydrous toluene. However, reduction of **19** with lithium aluminum hydride failed to give anything but recovered starting material. Further studies on the synthesis of **2a–d** were abandoned.

Experimental Section[12]

2-Nitro-5-phenylphenol (**5**).—A mixture of 120 ml of diphenyl ether and 170 g of KOH, after mixing in a warm blender, was added to 67.2 g of 4-nitrobiphenyl, mp 113–114°. After stirring in an atmosphere of oxygen at 95° for 28 hr, benzene and water were added to the brick-red mixture. A bright orange solid (70 g) was collected by filtration and dissolved in 1.5 l. of water. Acidification gave 58 g (80%) of **5**, mp 103–104° (lit.[4] mp 103–103.3°).

3-Methoxy-4-nitrobiphenyl (**6**).—A 58-g (0.27 mol) portion of the crude 2-nitro-5-phenylphenol (**5**), mp 103–104°, was dissolved in 1 l. of dry toluene and 37.6 g (0.272 mol) of anhydrous potassium carbonate was added. To this mixture a solution of 41.9 g (0.33 mol) of dimethyl sulfate in 50 ml of dry toluene was added dropwise over 0.5 hr with the temperature maintained between 70 and 90°. The reaction mixture was heated on a steam bath for 24 hr, after which time the mixture had turned to a light orange slurry. The toluene layer was washed with 5% sodium hydroxide and then water. After drying over anhydrous sodium sulfate, the toluene solution was chromatographed through an alumina column (Woelm neutral, activity grade 1 alumina). Removal of the toluene from the eluates gave a light yellow oil which solidified upon cooling, and was recrystallized once from 95% ethanol affording 53.8 g (87% yield) of light yellow solid, mp 62–63.5°. Repeated crystallization from 95% ethanol gave an analytical sample of **6** as light yellow rods, mp 62–63.5°.

Anal. Calcd for $C_{13}H_{11}NO_3$: C, 68.11; H, 4.84. Found: C, 68.03; H, 4.99.

3-Methoxy-4-biphenylamine (**7**).—A 54-g (0.235 mol) portion of 3-methoxy-4-nitrobiphenyl (**6**), mp 62–63.5°, was dissolved in 1 l. of 95% ethanol, and 3–4 teaspoons of fresh Raney nickel mud[13] were added; a solution of 144 ml of anhydrous hydrazine in 75 ml of ethanol was added to this mixture at such a rate so as to maintain gentle reflux. When addition of the hydrazine was complete, the mixture was refluxed on a steam bath for 3 hr, after which the Raney nickel was removed by filtration. The solvent was removed using a rotary evaporator and replaced by dry ether Concentrated HCl (35 ml) was added to the ether solution and the amine hydrochloride separated. After filtering, the solid hydrochloride was dissolved in hot water and filtered, and the cooled aqueous solution was made basic with 10% sodium hydroxide, whereupon the free amine separated. The free amine was filtered, washed well with water, and dried. Recrystallization from cyclohexane afforded 32 g (68% yield) of **7** as tan plates, mp 74–76°. The acetyl derivative of **7** was prepared and recrystallized twice from cyclohexane, giving an analytical sample of 2-methoxy-4-phenylacetanilide, mp 117.5–118.5°.

Anal. Calcd for $C_{15}H_{15}NO_2$: C, 74.67; H, 6.27. Found: C, 74.49; H, 6.34.

4-Iodo-3-methoxybiphenyl (**8**).—A mixture of 32.4 g (0.162 mol) of 3-methoxy-4-biphenylamine (**7**), mp 74–76°, 300 ml of water, and 42 ml of concentrated hydrochloric acid was cooled to 0° and a solution of 11.8 g (0.170 mol) of sodium nitrite in 100 ml of water was added dropwise with stirring over 1.5 hr with the temperature being maintained at 0–2°. After stirring for an additional 1 hr at 2–3°, the excess sodium nitrite was destroyed with sulfamic acid and the diazonium salt was decomposed by the addition of a solution of 134 g (0.81 mol) of potassium iodide in 100 ml of water. The pasty mixture was stirred at 5–10° for 0.75 hr and at room temperature for 1.0 hr. Considerable foaming was encountered, and, after all of the nitrogen had been expelled, the dark brown, oily product was extracted with benzene. The benzene layer was washed successively with 10% aqueous sodium bisulfite, 10% aqueous sodium hydroxide, and water. The benzene solution was dried (potassium carbonate) and chromatographed (Woelm, neutral, activity grade 1 alumina). The benzene was removed from the eluates, and the iodo compound **8** was obtained as a viscous, light yellow oil which was sufficiently pure for the next step. Crystallization from 95% ethanol gave 40.8 g (81% yield), mp 48–50°. Repeated crystallization from 95% ethanol gave an analytical sample of **8** as colorless needles, mp 51–52.5°.

Anal. Calcd for $C_{13}H_{11}OI$: C, 50.34; H, 3.58. Found: C, 50.75; H, 3.82.

2″,3′-Dimethoxy-*p*-quaterphenyl (**9**).—4-Iodo-3-methoxybiphenyl (**8**), 4.4 g (0.014 mol), was heated at 190–210°, and 3.16 g (0.050 mol) of copper bronze (O. Hommel Co., Pittsburgh, Pa.,

(9) H. Stetter, *Chem. Ber.*, **86**, 380 (1953).

(10) E. Tauber, *Chem. Ber.*, **26**, 1703 (1893).

(11) St. von Niementowski, *Chem. Ber.*, **34**, 3325 (1901).

(12) All melting points were taken in Pyrex capillary tubes in a Hoover-Thomas melting point apparatus and are uncorrected.

(13) H. Adkins, "Reactions of Hydrogen with Organic Compounds over Copper Chromium Oxide and Nickel," The University of Wisconsin Press, Madison, Wis., 1937.

5743) was added in small portions over 1.5 hr. The reaction mixture was stirred (dry nitrogen) during the addition and for an additional 4 hr. The reaction mixture was cooled and extracted with hot benzene, and the benzene solution was filtered and chromatographed (Woelm, neutral, activity grade 1 alumina). After removal of the benzene, 1.4 g (54% yield) of fluorescent solid, mp 160–163°, was obtained. Repeated crystallization from ethyl acetate gave an analytical sample of **9** as colorless plates, mp 162.5–163.5°.

Anal. Calcd for $C_{26}H_{22}O_2$: C, 85.22; H, 6.05. Found: C, 85.48; H, 6.28.

2'',3'-Dihydroxy-*p*-quaterphenyl (3).—A mixture of 2.5 g (6.8 mmol) of 2'',3'-dimethoxy-*p*-quaterphenyl (**9**), mp 161.5–163°, 64 ml of 57% hydriodic acid, and 32 ml of glacial acetic acid was refluxed and vigorously agitated for 24 hr, after which time the reaction mixture was poured into ice water. The precipitated solid was collected and dried, affording 2.2 g (96% yield) of colorless product, mp 231–233°. Two recrystallizations from toluene gave an analytical sample of **3**, mp 232–233°.

Anal. Calcd for $C_{24}H_{18}O_2$: C, 85.18; H, 5.36. Found: C, 84.87; H, 5.32.

3,9-Diphenyldibenzo[*d,f*][1,3]dioxepin (1a).—A mixture of 1.5 g (4.5 mmol) of 2'',3'-dihydroxy-*p*-quaterphenyl (**3**), mp 231–233°, and 1.35 g (9.77 mmol) of anhydrous potassium carbonate in 100 ml of dry *N,N*-dimethylformamide was warmed to 80° and a solution of 1.25 g (4.65 mmol) of methylene iodide in 50 ml of dry *N,N*-dimethylformamide was added with stirring over 2.5 hr.[3] The reaction mixture was heated for an additional 22 hr at 80–90° and was then poured into water and extracted with benzene. The benzene layer was washed twice with 5% sodium hydroxide and water, dried (potassium carbonate), and chromatographed (Woelm neutral, activity grade 1 alumina). Concentration of the eluates yielded a colorless solid which upon recrystallization from cyclohexane afforded 0.7 g (44% yield) of **1a** as colorless needles, mp 147.5–149°. Repeated crystallization from cyclohexane gave an analytical sample, mp 148–149°.

Anal. Calcd for $C_{25}H_{18}O_2$: C, 85.69; H, 5.18. Found: C, 85.64; H, 5.08.

3,10-Diphenyl-6,7-dihydrodibenzo[*e,g*][1,4]dioxocin (1b).—The procedure used was essentially the same as that used for **1a** (except that 1,2-dibromoethane replaced the methylene iodide), resulting in a 36% yield of a colorless solid, mp 235–236.5°. An analytical sample of **1b**, mp 235.8–236.8°, was obtained by repeated crystallization fom benzene.

Anal. Calcd for $C_{26}H_{20}O_2$: C, 85.69; H, 5.53. Found: C, 85.81; H, 5.60.

3,11-Diphenyl-7,8-dihydro-6*H*-dibenzo[*f,h*][1,5]dioxonin (1c).—The procedure used was essentially the same as that used for **1a** (but using 1,3-dibromopropane), resulting in a 49% yield of colorless solid, mp 218–220°. Recrystallization from a cyclohexane–benzene solvent pair led to a more insoluble crystalline form, mp 224.5–225.5°, and a more soluble form, mp 218–220°. Repeated crystallization from cyclohexane–benzene yielded analytical samples of both types of melting points, 219–220.5 and 224.5–225.5°. A sample of solid, mp 219–220.5°, was melted, allowed to cool, and remelted, mp 224–224.5°. Thin layer chromatography indicated that both samples were pure and the same. A mixture melting point (222–225°) was taken.

Anal. Calcd for $C_{27}H_{22}O_2$: C, 85.69; H, 5.86. Found (mp 219–220.5°): C, 85.73; H, 5.69. Found (mp 224.5–225.5°): C, 85.84; H, 5.97.

3,12-Diphenyl-6,7,8,9-tetrahydrodibenzo[*g,i*][1,6]dioxecin (1d).—The procedure used was the same as that described for **1a** (using 1,4-dibromobutane), resulting in a 66% yield of colorless solid, mp 185.7–186.5°. Repeated crystallization from a cyclohexane–benzene solvent pair gave an analytical sample of **1d**, mp 186.0–186.5°.

Anal. Calcd for $C_{28}H_{24}O_2$: C, 85.68; H, 6.16. Found: C, 85.54; H, 6.10.

4-Iodo-3-nitrobiphenyl (11).—Concentrated sulfuric acid (75 ml) was cooled to 5° and to this was added gradually 11.7 g (0.170 mol) of sodium nitrite. The resulting solution was warmed to 70° on a steam bath and then cooled to 10°, at which time a hot solution of 33 g (0.154 mol) of 3-nitro-4-biphenylamine (**10**), mp 169–171°, in 600 ml of glacial acetic acid was added with stirring over a 2-hr period, the temperature being maintained between 10 and 15°. The resulting diazonium salt was decomposed by the addition of a solution of 80 g (0.48 mol) of potassium iodide in 80 ml of water over a 15-min period below 15°. Stirring was continued for 16 hr at room temperature, after which time the reaction mixture was diluted with water, and sodium bisulfite was added to reduce any free iodine. The aqueous mixture was extracted with benzene and the benzene layer was washed four times with 75 ml of 10% sodium hydroxide and finally several times with water. After drying (magnesium sulfate), the benzene layer was concentrated and cyclohexane was added to produce a 10:1 ratio of cyclohexane to benzene. This solution was chromatographed (Woelm, neutral, activity grade 1 alumina) and the column was eluted with solutions of increasing benzene concentration. After the solvent was removed from the eluates, the resulting crude yellow solid was recrystallized from methanol, affording 27.7 g (55% yield) of **11** as yellow rods, mp 73–75°. Repeated crystallization gave an analytical sample of **11**, mp 74.5–75° (reported[14] mp 74°).

2'',3'-Dinitro-*p*-quaterphenyl (12).—A Pyrex test tube was charged with 4.67 g (0.0143 mol) of **11**, mp 73–75°, and heated to 190° in a Wood's metal bath. To this melt 2.7 g (0.046 mol) of copper bronze (Hommel 5743) was added with stirring in small portions over 30 min, keeping the reaction temperature between 190 and 205°. The initially fluid reaction mixture gradually solidified with addition of the copper bronze and after an additional 30 min the reaction mixture had turned to a powdery solid. The reaction mixture was cooled and extracted with 200 ml of hot toluene in three portions, and the toluene solution was filtered to remove the excess copper bronze. Concentration of the filtrate afforded 2.36 g (83% yield) of a light-sensitive yellow solid, mp 238.0–239.5°. Repeated crystallization from toluene gave a pure sample of **12**, mp 239.5–241.0° (reported[14] mp 242°).

2'',3'-Diamino-*p*-quaterphenyl (13).—To a stirred mixture of 8.69 g (0.0219 mol) of **12**, mp 238.0–239.5°, and two teaspoons of freshly prepared Raney nickel mud[13] in 950 ml of 95% ethanol was added dropwise 39 ml of 95% hydrazine over a period of 1 hr. The reaction mixture was kept under gentle reflux by warming on a steam bath during the addition of the hydrazine and for an additional 4 hr, after which time the reaction mixture was diluted with 500 ml of ice water. The reaction mixture was filtered and the precipitate was extracted with 300 ml of DMF and filtered to remove the Raney nickel. The filtrate was added to 500 ml of water, whereupon a white solid separated. This crude product was collected, washed well with water, and air dried. The solid was recrystallized from toluene containing a small amount of DMF to give 6.9 g (93% yield) of **13** as colorless plates, mp 225–227°. Repeated crystallization from toluene gave an analytical sample, mp 225.8–227.0° (reported[14] mp 217°).

Anal. Calcd for $C_{24}H_{20}N_2$: C, 85.68; H, 5.99. Found: C, 85.89; H, 5.85.

3,7-Diphenyldibenzofuran (14).—A slurry of 1.68 g (5.0 mmol) of **13**, mp 225–227.0°, in 20 ml of glacial acetic acid was added dropwise to a stirred solution of 0.69 g (10.0 mmol) of sodium nitrite in 5 ml of concentrated sulfuric acid while the temperature was kept between 5 and 12°. After the addition period, the reaction mixture was stirred at 10° for an additional 30 min; 50 ml of water was then added, whereupon the reaction mixture turned to a clear red color. The solution was heated on a steam bath for 10 hr with nitrogen being evolved and a brown solid separating The crude product was filtered, and three recrystallizations from benzene (Norit) afforded 0.5 g (31% yield) of **14** as light pink plates, mp 247.5–249° (reported[15] mp 248°).

3,7-Diphenylcarbazole (17).—The synthesis of **17** was accomplished by heating 1.0 g (3.0 mmol) of **13**, mp 225.5–227.0°, with 3 ml of concentrated phosphoric acid at 190–200° for 3–4 hr. The crude product was recrystallized three times from DMF, affording 0.72 g (75% yield) of an analytical sample of **17**, mp 349.5–351.5°, as fine, colorless needles.

Anal. Calcd for $C_{24}H_{17}N$: C, 90.25; H, 5.37; N, 4.39. Found: C, 90.25; H, 5.64; N, 4.28.

3,9-Diphenyl-6-oxo-6,7-dihydro-5*H*-dibenzo[*d,f*][1,3]diazepine (18).—An intimate mixture of 0.34 g (1.0 mmol) of **13**, mp 225.5–227.0°, and 0.06 g (1.0 mmol) of urea was heated to a melt at 200°. A solid reformed after a minute during which time ammonia was evolved, and after heating for several minutes more, the reaction mixture was cooled. The solid material was

(14) H. O. Wirth, R. Mueller, and W. Kern, *Makromol. Chem.*, **77**, 90 (1964).

(15) H. O. Wirth, G. Waese, and W. Kern, *Makromol. Chem.*, **86**, 139 (1965).

taken up in hot DMF, filtered, and water was added to precipitate the crude product which was collected, affording 0.33 g (91% yield) of a colorless solid, mp 389–391°. Repeated crystallization from DMF–water solvent pair gave an analytical sample of **18**, mp 390–392°.

Anal. Calcd for $C_{25}H_{18}N_2O$: C, 83.13; H, 5.01. Found: C, 82.91; H, 5.02.

An attempt to reduce **18** using lithium aluminum hydride in anhydrous diglyme yielded only unreduced **18** and none of the desired **2a**.

3,10-Diphenyl-6,7-dioxo-5,6,7,8-tetrahydrodibenzo[*e,g*][1,4]-diazocine (19).—Two grams (6.0 mmol) of **13**, mp 225.0–227.0°, was dissolved in 250 ml of anhydrous toluene and to this refluxing solution 0.93 ml (7.5 mmol) of oxalyl chloride in 100 ml of anhydrous toluene was added dropwise with stirring. A colorless solid separated immediately. After refluxing for an additional 30 min, the reaction mixture was cooled, filtered, washed with toluene, and dried at 125° for 24 hr. The product proved to be insoluble in several solvents, and was finally triturated with hot DMF and filtered. This process was repeated twice, affording 1.9 g (82% yield) of **19** as a colorless powder, mp above 400°.

Anal. Calcd for $C_{26}H_{18}N_2O_2$: C, 79.99; H, 4.64. Found: C, 79.65; H, 4.26.

Lithium aluminum hydride reduction of **19** in anhydrous diglyme yielded only recovered **19** and none of the desired reduction product **2b**.

Registry No.—**1a**, 42447-99-4; **1b**, 42448-00-0; **1c**, 42448-01-1; **1d**, 42448-02-2; **3**, 42448-03-3; **5**, 18062-89-0; **6**, 42271-42-1; **7**, 42271-43-2; **7** acetyl derivative, 42271-44-3; **8**, 42271-45-4; **9**, 42271-46-5; **10**, 4085-18-1; **11**, 2499-68-5; **12**, 2499-69-6; **13**, 2499-76-5; **17**, 42448-04-4; **18**, 42448-05-5; **19**, 42448-06-6; diphenyl ether, 101-84-8; 4-nitrobiphenyl, 92-93-3; methylene iodide, 75-11-6; 1,2-dibromoethane, 106-93-4; 1,3-dibromopropane, 109-64-8; 1,4-dibromobutane, 110-52-1.

A New Ring Expansion Reaction. V. The Decomposition of the Magnesium Salts of Various 1-(1-Bromo-1-methylethyl)-1-cycloalkanols. Electrophilic Addition to Isopropylidenecycloalkanes

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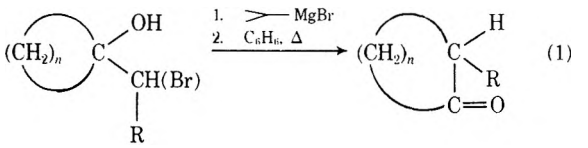
The synthesis of some 2,2-dimethylcycloalkanones is described. They were prepared from the decomposition of the magnesium salts of various halohydrins by a ring-enlargement procedure previously described. The necessary halohydrins were prepared from an electrophilic addition reaction with aqueous NBS and the isopropylidenecycloalkanes. The reasons for the observed selective orientation of the bromo and hydroxyl groups are discussed.

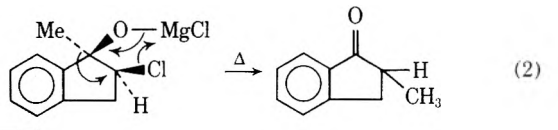
Preliminary papers[1] have reported a new ring-enlargement procedure[2] entailing the decomposition of the magnesium salts of appropriate halohydrins (eq 1).



(1)

R = CH_3 and C_6H_5; n = 4, 5, 6, and 7

Our results were in accord with those of Geissman and Akawie,[3] who extensively studied the reaction producing ketones *via* the decomposition of the magnesium salts of halohydrins. They observed that primary halides rearrange only when a good migrating group is involved but that secondary and tertiary halides rearrange regardless of the migrating group. From their stereochemical studies, they concluded that the halo and hydroxyl groups must be cis (or be able to attain the cis conformation in nonrigid systems) to effect the rearrangement. Trans isomers lead to extensive decomposition, making an epoxide intermediate for the reaction unlikely and leaving as most plausible a pinacol-type mechanism (eq 2).



(2)

This paper describes the synthesis of various 2,2-dimethylcycloalkanones by the new ring-enlargement procedure,[1] as starting materials for which we required halohydrins of the type depicted in **1**. In a preliminary communication,[4] we reported that isopropylidenecyclopentane, when treated with aqueous *N*-bromosuccinimide (NBS), yielded **1** (n = 4), the structural assignment for which was confirmed by the conversion of its magnesium salt to 2,2-dimethylcyclohexanone[5] in 54% overall yield. Additional confirmation has now been furnished by examination of the nmr spectrum, which reveals, from the location of the methyl signal (τ 8.2), that the bromine is indeed attached to the exocyclic carbon atom.[6] It was also reported[4] that isopropylidenecyclohexane, when treated with aqueous NBS, gave a halohydrin **2** *isomeric* with **1** (n = 5). The structure **2** was verified by decomposition of the magnesium salt, which yielded only 1-acetyl-1-methylcyclohexane in 66% overall yield. Further

(1) A. J. Sisti, *J. Org. Chem.*, **33**, 453 (1968); **35**, 2670 (1970).

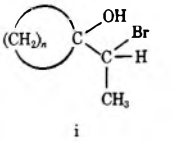
(2) For an excellent recent review, see C. D. Gutsche and D. Redmore, "Carbocyclic Ring Expansion Reactions," Academic Press, New York, N. Y., 1968.

(3) T. A. Geissman and R. I. Akawie, *J. Amer. Chem. Soc.* **73**, 1993 (1951).

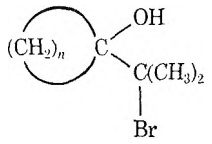
(4) A. J. Sisti, *Tetrchedron Lett.*, 3305 (1970).

(5) The vpc revealed the presence of a 5–10% contaminant, presumably methyl 1-methylcyclopentyl ketone based upon the same retention time as that of an authentic sample [A. J. Sisti and A. C. Vitale, *J. Org. Chem.*, **37** 4090 (1972)] and the nmr spectrum (τ 8.0 and 8.8, two small sharp singlets) It is presumed that the ketone arose from the rearrangement of small amounts of the corresponding epoxide and/or small amounts of the magnesium salt of the halohydrin isomeric with **1** (n = 4).

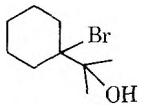
(6) R. M. Silverstein and G. C. Bassler, "Spectrometric Identification of Organic Compounds," Wiley, New York, N. Y., 1967, p 136. Model compounds i show the nmr methyl signal at τ 8.3 (doublet); see A. J. Sisti, *J. Org. Chem.*, **35**, 2670 (1970).



i

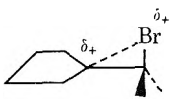


1 (n = 4, 5, and 6)

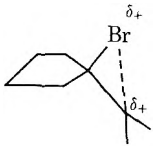


2

data now reported confirm that the hydroxyl group is bound to the exocyclic carbon atom[6] in 2 (CH_3 signal τ 8.6). The striking feature of the reactions of these two olefins is that the addition of the bromo and hydroxyl groups is regiospecifically *opposite* in the two cases. Since the reaction of aqueous NBS with an olefin proceeds *via* the bromonium ion,[7] these results were rationalized by invoking the concepts of *I* strain[8] and the unsymmetrical bromonium ion[9] as follows. Of the two possible unsymmetrical bromonium ions from isopropylidenecyclopentane (**3** and **3a**), the former



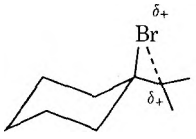
3



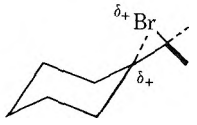
3a

should be the more stable since it would more nearly maintain sp^2 hybridization on the ring carbon in the transition state and thereby avoid or minimize four bond oppositions (two H–Br and two H–isopropyl oppositions) present in **3a**; **3** then reacts with water to yield **1** (n = 4).

In the case of isopropylidenecyclohexane, **4** should be more stable than **4a** since the transition state of the



4



4a

former has essentially sp^3 hybridization on the ring carbon, and thus minimizes the two bond oppositions which are present in **4a** (two adjacent equatorial hydrogens opposed to the isopropyl group); **4** subsequently reacts with water to produce 2.

The present work further examines this rationale and the synthetic utility of our ring-enlargement sequence by extending them to the cycloheptane, cyclooctane, and norbornane systems.

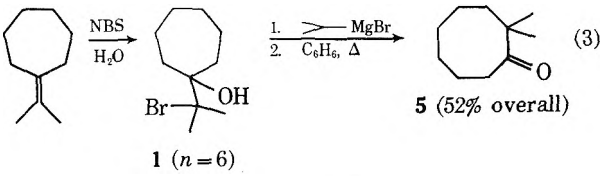
(7) E. E. Van Tamelen and K. B. Sharpless, *Tetrahedron Lett.*, 2655 (1967).

(8) H. C. Brown, R. S. Fletcher, and R. B. Johannesen, *J. Amer. Chem. Soc.*, **73**, 212 (1951).

(9) D. R. Dalton, V. P. Dutta, and D. C. Jones, *J. Amer. Chem. Soc.*, **90**, 5498 (1968).

Results and Discussion

2,2-Dimethylcyclooctanone (5) from Isopropylidenecycloheptane.—The halohydrin[10] **1** (n = 6) was prepared from isopropylidenecycloheptane by treatment with aqueous NBS. The structure for **1** (n = 6) is based upon the nmr spectrum (the methyl signal at τ 8.2 indicates that the bromine is bound to the isopropyl carbon atom[6]), the ir spectrum, and the ring expansion to, almost exclusively, 2,2-dimethylcyclooctanone (**5**) (eq 3). The purity of **5** was established

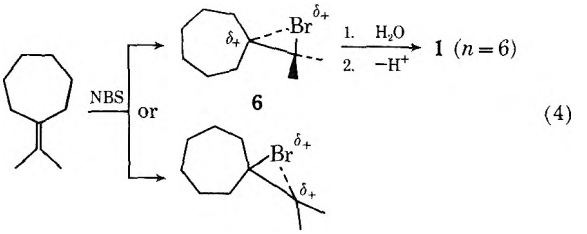


(3)

1 (n = 6) **5** (52% overall)

by vpc and found to be about 90%.[11] The structure for **5** was confirmed by elemental analysis and the ir and nmr spectra.

The orientation observed from the electrophilic addition to isopropylidenecycloheptane was rationalized by the concepts of *I* strain[8] and the unsymmetrical bromonium ion[9] (eq 4). A change in hybridization



(4)

6a

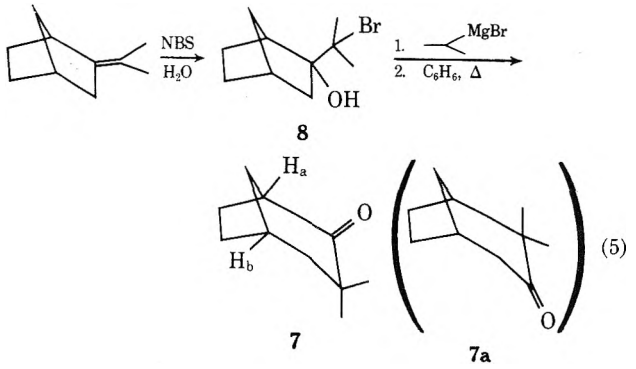
from sp^2 to sp^3 at the site of reaction in a seven-membered ring is beset with bond oppositions and is comparatively disfavored. Therefore, of the two possible unsymmetrical bromonium ions **6** and **6a**, **6** should be the more stable since it would maintain a trigonal or quasitrigonal geometry on the ring carbon in the transition state and thereby avoid or minimize four bond oppositions (two H–Br and two H–isopropyl) present in **6a**; **6** will then yield **1** (n = 6) after nucleophilic attack by water (eq 4).

3,3-Dimethyl[3.2.1]bicyclooctanone-2 (7) from 2-Isopropylidenenorbornane.—The necessary halohydrin[10] **8** was prepared from the olefin with aqueous NBS and was subsequently converted by ring enlargement to the bicyclic ketone **7** in 13% overall yield (eq 5). The poor yield is primarily attributed to the extensive decomposition of **8** during the ring enlargement reaction. The vpc analysis indicated that the product **7** was approximately 85% pure.[12] The structure of **8**

(10) All halohydrins herein were handled under mild conditions during work-up and were used immediately without purification. Undoubtedly, their extreme lability is due to the presence of the tertiary bromo group and the relatively severe bond oppositions in **1**, **2**, and **8**.

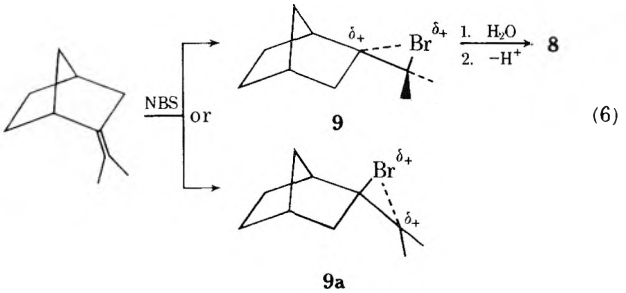
(11) The impurity is probably 1-acetyl-1-methylcycloheptane (as suggested by the observation of two small sharp signals in the nmr spectrum at τ 8.0 and 8.9), probably arising from the rearrangement of the corresponding epoxide and/or small amounts of the magnesium salt of the halohydrin isomeric with **1** (n = 6).

(12) Again the impurity is presumably 2-acetyl-2-methylnorbornane (on the basis of two small sharp signals in the nmr spectrum at τ 8.0 and 8.95) probably arising from rearrangement of small amounts of the corresponding epoxide and/or small amounts of the magnesium salt of the halohydrin isomeric with **8**.



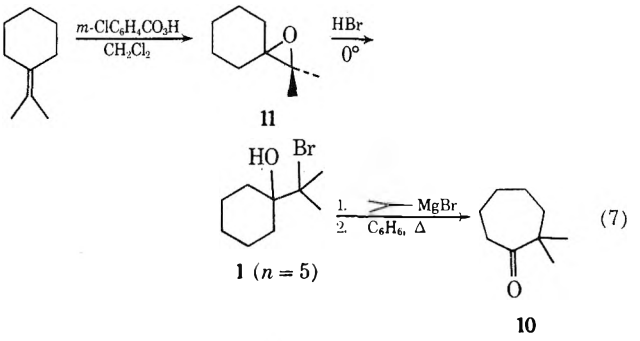
was established from the ir spectrum, the nmr spectrum (signal position for the methyl group at τ 8.28), and conversion to the bicyclic ketone **7** (eq 5). The structure assigned to **7** is based upon the ir spectrum, elemental analysis (2,4-DNP), and the nmr spectrum, which confirmed structure **7** by the presence of signals at τ 7.3–7.4 (H_a multiplet), 7.6–7.7 (H_b multiplet), and 8.9 and 9.0 (the two methyl groups). Model compounds for these signal assignments have already been presented.[13] Additional support for the structural assignment was obtained from a deuterium exchange study. After the bicyclic ketone **7** was treated with trifluoroacetic acid-*d* (10% solution) for 24 hr at 80°, the nmr spectrum revealed that essentially no hydrogens were exchanged [the bicyclic ketone **7a**, the product, if the more substituted C-1–C-2 bond had migrated in **8** (eq 5), should have exchanged two hydrogens]. The reasons for the migratory preference of the less substituted C-2–C-3 bond in **8** have been discussed previously[13] and need not be repeated here.

Since it is known that, in the norbornane system, bond oppositions are present between the groups on C-2 and C-3 and between the groups on C-5 and C-6, *I* strain[8] and the unsymmetrical bromonium ion[9] should adequately explain the production of **8**. Of the two possible unsymmetrical (exo) bromonium ions, **9** and **9a**, **9** is the more stable since it would more nearly maintain the quasitrigonal geometry at C-2 in the transition state and thus avoid or minimize two bond oppositions (H–Br and H–isopropyl) present in **9a**. Subsequent endo attack by water on **9** will yield **8**, the observed product (eq 6).



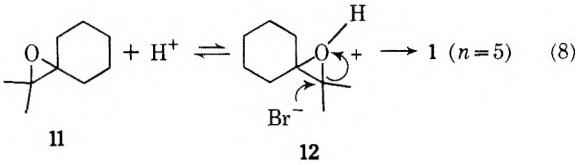
The above arguments presented to account for the orientation observed from all four olefins apply, provided that other effects are excluded or accounted for. Rationalizations based upon polar considerations do not seem fruitful, since both bromo carbonium ions from each olefin would be tertiary and should be of comparable stability. It also seems reasonable to suppose that the symmetrical bromonium ions and the corresponding unsymmetrical bromonium ions (**3**, **4**, **6**, and **9**) should be of comparable stabilities in terms of purely polar considerations. All these results therefore seem best explained by invoking the concepts of *I* strain[8] and the unsymmetrical bromonium ion,[9] as elaborated above.

2,2-Dimethylcycloheptanone (10) from Isopropylidenecyclohexane.—It has already been demonstrated that the desired halohydrin **1** (n = 5) cannot be prepared directly from the olefin with aqueous NBS, since the isomeric halohydrin **2** is produced. Our alternate synthetic approach to the halohydrin **1** (n = 5) involved the hydrogen bromide cleavage of isopropylidenecyclohexane epoxide (**11**) (eq 7). The structure elucidation



for the product **1** (n = 5) was based upon the ir spectrum, the nmr spectrum,[6] and conversion to 2,2-dimethylcycloheptanone (**10**) in 57% overall yield (eq 7). The structure for **10** was assigned from the ir and nmr spectra and conversion to a known derivative. The vpc of **10** established the purity as 85%.[14]

The two most plausible mechanisms for the production of a halohydrin from the epoxide **11** both reasonably lead to **1** (n = 5). If the symmetrical oxonium ion **12** were involved, bromide ion should preferentially attack the exocyclic carbon atom (eq 8), since it is

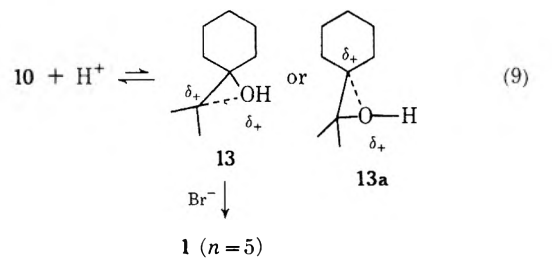


known that SN2 reactions upon the cyclohexyl system are sluggish[15] compared with those upon its acyclic counterpart; alternatively, of the two unsymmetrical oxonium ions, **13** and **13a**, the former should be the more stable since it more nearly maintains the sp^3 hybridization on the ring carbon in the transition state and bond oppositions present in **13a** are thereby avoided or minimized (eq 9); attack by bromide ion on **13** will then yield **1** (n = 5). Attempts to account for the product due to a difference in stability between **13** and **13a** based on polar considerations are unconvincing, since they should be of comparable stability. The

(13) A. J. Sisti, G. M. Rusch, and H. Sukhon, *J. Org. Chem.*, **36**, 2030 (1971); A. J. Sisti, *ibid.*, **35**, 2670 (1970).

(14) The major contaminant is believed to be 1-acetyl-1-methylcyclohexane, confirmation being obtained from the nmr spectrum, which revealed two small sharp signals at τ 8.0 and 8.9; an authentic sample (ref 4) had the same retention time as the impurity. The source of the ketone is probably the rearrangement of small amounts of the corresponding epoxide and/or small amounts of the magnesium salt of the isomeric halohydrin **2**.

(15) E. L. Eliel in "Steric Effects of Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, pp 123–125; P. J. Fierens, *Bull. Soc. Chim. Belg.*, **61**, 427, 609 (1952).



(9)

mechanism involving the unsymmetrical oxonium ion **13** is preferred, because it is known that under acidic conditions highly substituted epoxides undergo cleavage by the SN1 mechanism.[16]

The epoxides from isopropylidenecyclopentane and isopropylidencycloheptane were prepared and subjected to cleavage with 48% hydrogen bromide in an attempt to synthesize the halohydrins isomeric with **1** (n = 4 and 6). However, in each case, extensive decomposition ensued—polymerization (cyclopentane system) and dehydrohalogenation[17] and dehydration (cycloheptyl system)—as evidenced by the ir and nmr spectra.

Presently, other electrophilic and free-radical additions to the isopropylidenecycloalkanes herein mentioned are being undertaken.

Experimental Section[18]

1-(1-Bromo-1-methylethyl)-1-cycloalkanols were prepared from the appropriate isopropylidenecycloalkanes (Columbia Organic Chemicals Co.) (100–150 mmol), an equivalent amount of *N*-bromosuccinimide (NBS), and 100–150 ml of water according to a previously described procedure,[19] except that the reaction temperature was maintained between 10 and 20°, and, after all the NBS had reacted, the mixture was stirred for 5 min. All halohydrins were used immediately without purification.[10]

Halohydrin 1 (n = 4) was a colorless oil: ir 3480 cm^{-1}; nmr τ 8.2 [sharp s, $-C(Br)(CH_3)_2$]; **1** (n = 4) gave an instantaneous precipitate of AgBr when treated with alcoholic $AgNO_3$.

Halohydrin 1 (n = 6) was a light yellow oil: ir 3560 and 3480 cm^{-1}; nmr τ 8.2 [sharp s, $-C(Br)(CH_3)_2$]; **1** (n = 6) gave an instantaneous precipitate of AgBr with alcoholic $AgNO_3$.

Halohydrin 2 was a colorless oil: ir 3540 and 3460 cm^{-1}; nmr ($CDCl_3$) τ 8.6 [sharp s, $-C(OH)(CH_3)_2$]; **2** gave an instantaneous precipitate of AgBr when treated with alcoholic $AgNO_3$.

Halohydrin 8 (prepared from 2-isopropylidenenorbornane[20] by the above procedure) was a dark yellow oil: ir 3550 and 3480 cm^{-1}; nmr τ 8.28 [sharp s, $-C(Br)(CH_3)_2$]; an instantaneous precipitate resulted when **8** was treated with alcoholic $AgNO_3$.

Isopropylidenecyclohexane epoxide 11 was prepared by the dropwise addition of a solution of 20.3 g (100 mmol) of *m*-chloroperbenzoic acid (Aldrich Chemical Co.) dissolved in 200 ml of CH_2Cl_2 to a vigorously stirred solution of 12.4 g (100 mmol) of isopropylidenecyclohexane[21] in 50 ml of CH_2Cl_2 (at room temperature). The reaction mixture was stirred at room temperature overnight. It was then filtered and the filtrate was washed twice with 25 ml of 20% $NaHSO_3$, twice with 50 ml of 10% $NaHCO_3$, and once with 100 ml of saturated aquaous NaCl. The organic solution was dried ($MgSO_4$), filtered, concentrated, and distilled through a 20-cm micro-Vigreux column and there was obtained 12.1 g (87%) of **11** as a colorless liquid: bp 61–62° (12 mm); nmr τ 8.7 (sharp s, 6 H) and 8.2–8.4 (m, 10 H).

Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 77.17; H, 11.51.

Ten grams (72 mmol) of the epoxide **11** was cleaved with 48% HBr at 0°[10] according to the procedure of Traynham.[22] The resulting dense oil **1** (n = 5) gave the following data: ir 3450 cm^{-1}; nmr τ 8.15 [sharp s, $-C(Br)(CH_3)_2$].

Isopropylidenecyclopentane epoxide was prepared from 11.0 g (100 mmol) of isopropylidenecyclopentane[21] and 20.3 g (100 mmol) of *m*-chloroperbenzoic acid as above. Distillation through a 20-cm micro-Vigreux column yielded 7.6 g (60%) of a colorless liquid: bp 56–57° (22 mm); nmr τ 8.7 (sharp s, 6 H) and 8.1–8.2 (m, 8 H).

Anal. Calcd for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 76.28; H, 11.16.

Upon treatment of isopropylidenecyclopentane epoxide with 48% hydrogen bromide according to the procedure of Traynham,[22] extensive decomposition and polymerization occurred immediately[17] along with extreme discoloration. No product characteristic of a halohydrin could be isolated.

Isopropylidenecycloheptane epoxide was prepared with 13.8 g (100 mmol) of isopropylidenecycloheptane (Columbia Organic Chemical Co.) and 20.3 g (100 mmol) of *m*-chloroperbenzoic acid as above. Distillation through a 20-cm micro-Vigreux column afforded 12.3 g (80%) of a colorless liquid: bp 74–75° (9 mm); nmr τ 8.6 (sharp s, 6 H) and 8.1–8.2 (m, 12 H).

Anal. Calcd for $C_{10}H_{18}O$: C, 77.86; H, 11.76. Found: C, 77.67; H, 11.70.

Treatment of isopropylidenecycloheptane epoxide with 48% HBr at 0° according to the procedure of Traynham[22] afforded an unstable oil which spontaneously fumed (HBr):[17] ir 1600 (vinyl hydrogen), 3500 cm^{-1} (w, OH); nmr ($CDCl_3$) τ 3.7–3.9 (m, vinyl hydrogen) and 5.0–5.1 (d, vinyl hydrogen).

2,2-Dimethylcycloalkanones were prepared by the dropwise addition of an equivalent amount of isopropylmagnesium bromide in ether (since the halohydrins were not purified,[10] the quantity of isopropyl bromide used in the formation of the Grignard reagent was equal to the number of moles of olefin employed for the preparation of the halohydrins) to 300 ml of a cooled anhydrous benzene solution of the halohydrin. After the addition, the solution was refluxed for 1 hr and subsequently decomposed with aqueous NH_4Cl. The separated organic portion was washed successively with water, 10% $NaHCO_3$ solution, and water, and then dried ($MgSO_4$), concentrated, and distilled.

2,2-Dimethylcyclohexanone: bp 55–57° (9 mm) (lit.[23] bp 169–170°); 10.2 g (79 mmol, 54% based upon 150 mmol of isopropylidenecyclopentane) isolated; ir 1710 cm^{-1}; nmr τ 8.98 [sharp s, $-COC(CH_3)_2$]; vpc (150°)[18] showed 90–95% purity;[5] 2,4-DNP mp 139–140° (lit.[23] mp 140–142°); mixture melting point produced no depression.

2,2-Dimethylcyclooctanone (5): bp 68–70° (2.5 mm); 8.0 g (52 mmol) isolated (52% based upon 100 mmol of isopropylidenecycloheptane); ir 1700 cm^{-1}; nmr τ 8.98 [sharp s, $-COC(CH_3)_2$]; vpc (200°)[18] demonstrated that **5** was 90% pure.[11]

Anal. Calcd for $C_{10}H_{18}O$: C, 77.92; H, 11.68. Found: C, 77.72; H, 11.50.

The 2,4-DNP was prepared as usual, mp 129–130° (EtOH).

Anal. Calcd for $C_{16}H_{22}N_4O_4$: C, 57.48; H, 6.58, N, 16.76. Found: C, 57.45; H, 6.50; N, 16.66.

2,2-Dimethylcycloheptanone (10): bp 81° (18 mm) [lit.[24] bp 82° (18 mm)]; 6.7 g (47 mmol) (67% based upon 72 mmol of the epoxide **11** or 57% based upon 83 mmol of isopropylidenecyclohexane) isolated; the amount of isopropyl bromide employed in the formation of the Grignard was equal to the number of moles of epoxide **11** used for the formation of the halohydrin **1** (n = 5); ir 1700 cm^{-1}; nmr τ 9.0 [sharp s, $-COC(CH_3)_2$]; vpc (200°)[18] demonstrated that **10** was 85% pure;[14] the semicarbazone had a melting point of 175–176° (lit.[24] mp 175°).

(16) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p 344; see also ref 15, p 112.

(17) It should be noted that the tertiary bromine on the ring carbon atom as opposed to the exocyclic tertiary bromine **1** (n = 4 and 6) would be more labile, since the magnitude of the bond oppositions (five- and seven-membered rings) would be increased and thus provide added impetus for the loss of bromide ion.

(18) All melting points are uncorrected. Infrared spectra, all of pure liquid films, were determined with a Perkin-Elmer Spectracord spectrophotometer. The nmr spectra of CCl_4 solutions, unless otherwise specified, were determined with a Varian A-60 instrument. The vpc analyses were performed with an F & M Scientific Model 720 duel column programmed temperature instrument; a 4-ft column packed with 20% Carbowax 4000 on Chromosorb W was employed at a pressure of 40 psi.

(19) C. O. Guss and R. Rosenthal, *J. Amer. Chem. Soc.*, **77**, 2549 (1955).

(20) J. A. Berson and M. Willcott, *J. Org. Chem.*, **30**, 3569 (1965); F. D. Greene, M. Savitz, F. Osterholtz, H. Law, W. Smith, and P. Zanet, *ibid.*, **28**, 55 (1963).

(21) R. Siegmann, M. Beers, and H. Huisman, *Recl. Trav. Chim. Pays-Bas*, **83**, 67 (1964).

(22) J. G. Traynham and O. Pascual, *Tetrahedron*, **7**, 165 (1959).

(23) P. S. Adamson, A. M. Marlow, and J. L. Simonsen, *J. Chem. Soc.*, 774 (1938).

(24) P. J. Tarbouriech, *C. R. Acad. Sci.*, **156**, 75 (1913).

1-Acetyl-1-methylcyclohexane: bp 68–70° (7 mm) [lit.[25] bp 80–85° (16 mm)]; 13.8 g (66% based upon 150 mmol of olefin) isolated; ir 1700 cm^{-1}; nmr τ 8.0 and 9.0 [sharp s, $H_3CCOCCH_3$]; vpc (130° and 150°)[18] showed a single compound. The 2,4-DNP had a melting point of 131–132° (lit.[26] mp 132°) and the semicarbazone melted at 183–185° (lit.[26] mp 186–187°).

3,3-Dimethyl[3.2.1]bicyclooctanone-2 (7): bp 30–40° (0.3 mm); ir 1710, 3050, and 1610 cm^{-1} (the latter indicated olefinic contamination); vpc (200°)[18] indicated three compounds present. The distillate, dissolved in petroleum ether (bp 30–60°), was placed upon a column containing 30 g of neutral alumina. Elution with petroleum ether yielded an unidentified olefin, ir 3050 and 1610 cm^{-1}, no carbonyl or hydroxyl absorptions present. Elution with 50% (v/v) benzene–petroleum ether yielded 2 g of 7 (13% based upon 100 mmol of 2-isopropylidenenorbornane used): ir 1705 cm^{-1}; vpc (200°)[18] indicated 85% purity;[12] nmr τ 8.9 and 9.0 [d, sharp $-COC(CH_3)_2$]; the 2,4-DNP had a melting point of 103–105° (EtOH).

Anal. Calcd for $C_{16}H_{20}N_4O_4$: C, 57.83; H, 6.02; N, 16.86. Found: C, 57.91; H, 6.16; N, 17.01.

A small amount of 7 was treated with trifluoroacetic acid-*d* (10% solution) at 80° for 24 hr; the nmr of the product showed no deuterium exchange.

Registry No.—1 (n = 4), 42393-47-5; 1 (n = 5), 42393-48-6; 1 (n = 6), 42393-49-7; 2, 42393-50-0; 5, 42393-51-1; 5 2,4-DNP, 42393-52-2; 7, 42393-53-3; 7 2,4-DNP, 42393-54-4; 8, 42393-55-5; 11, 15446-32-9; *m*-chloroperbenzoic acid, 937-14-4; isopropylidenecyclohexane, 5749-72-4; isopropylidenecyclopentane epoxide, 42393-57-7; isopropylidenecyclopentane, 765-83-3; isopropylidenecycloheptane epoxide, 42393-59-9; isopropylidenecycloheptane, 7087-36-7.

(25) O. Sakur, *C. R. Acad. Sci.*, **208**, 1092 (1939).
(26) H. Pines and J. Marechal, *J. Amer. Chem. Soc.*, **77**, 2819 (1955).

Intramolecular Propagation in the Oxidation of *n*-Alkanes. Autoxidation of *n*-Pentane and n-Octane

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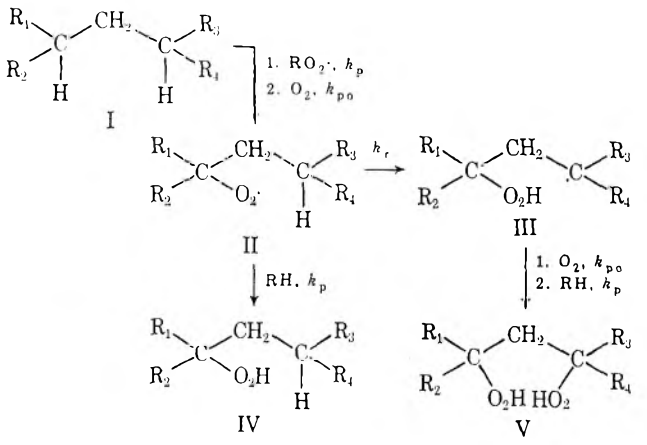
Initiated oxidations of liquid *n*-pentane and *n*-octane at 100 and 125°, respectively, give complex mixtures of products, including 34–76% pentyl hydroperoxides (mostly secondary monohydroperoxides) at <1% conversion and 19–54% octyl hydroperoxides at higher conversions. More cleavage products are found for octane than for pentane at all conversions. Bifunctional products from pentane include dihydroperoxide or diol and ketohydroperoxide with maximum yields of 10% on consumed oxygen. Added *tert*-BuO_2H markedly reduced this yield. Small amounts of octanediols were found following reduction but no reliable estimates of yields were possible. The absolute rate of intramolecular abstraction by *sec*-pentyl peroxy radicals is $^1/_{80}$ of that of 2,4-dimethyl-2-pentylperoxy radical and the ratio of attack by peroxy radicals at secondary and primary CH bonds is 38.5:1.

It was originally demonstrated by Rust[2] that, in the low-temperature liquid-phase oxidation[3] of certain branched alkanes, intramolecular transfer of a hydrogen atom to form bifunctional products is a major reaction path. Thus, good yields of 2,4-dihydroperoxy-2,4-dimethylpentane (Chart I) (R_1–R_4 = CH_3) could be

CHART I



obtained from the oxidation of 2,4-dimethylpentane (2,4-DMP); oxidation of 2,5-dimethylhexane gave a lower yield of the difunctional product. Recent work by Mill and Montorsi[4] showed that, at 100°, over 90% of the oxygen consumed by 2,4-DMP could be accounted for by hydroperoxide and that the ratio of mono- to difunctional hydroperoxide products was 1:7. The apparent generality of intramolecular propagation in the oxidation of alkanes with alternating *tertiary* hydrogens was confirmed by Van Sickle in the oxidation of 2,4,6-trimethylheptane[5] (2,4,6-TMH) [Chart I, R_1–R_3 = CH_3; R_4 = $CH_2CH(CH_3)_2$] where the major oxidation product is 2,4,6-trihydroperoxy-2,4,6-trimethylheptane and the calculated value for the ratio of rate constants of inter- to intramolecular propagation, k_p/k_r, is practically identical with that of 2,4-DMP[4] (0.015 M^{-1} *vs.* 0.013 M^{-1}).

The question now arises as to what proportions of bifunctional reaction products are formed in low-temperature (100–125°) liquid-phase oxidations of *n*-alkanes. *A priori*, one might expect the reaction scheme in Chart I to be valid for the general case where R_1, R_3 = H and R_2, R_4 = any alkyl group. In gas-phase oxidations[6] above 200°, cyclic ethers, expected to arise from III of Chart I, are major products.

Although the liquid-phase oxidation of *n*-alkanes has been reported for various homologs, the results have not been analyzed from the standpoint of intra- intermolecular propagation. We now report the results of an investigation of the oxidation of *n*-pentane at 100° and *n*-octane at 125° where we have searched specifically for bifunctional products expected to be derived from intermediate III of Chart I.

(1) To whom correspondence should be addressed.
(2) F. F. Rust, *J. Amer. Chem. Soc.*, **79**, 4000 (1957).
(3) F. R. Mayo, *Accounts Chem. Res.*, **1**, 193 (1968).
(4) T. Mill and G. Montorsi, *Int. J. Chem. Kinet.*, **5**, 119 (1973).
(5) D. E. Van Sickle, *J. Org. Chem.*, **37**, 755 (1972).
(6) A. Fish, *Advan. Chem. Ser.*, **76**, 69 (1968).

TABLE I

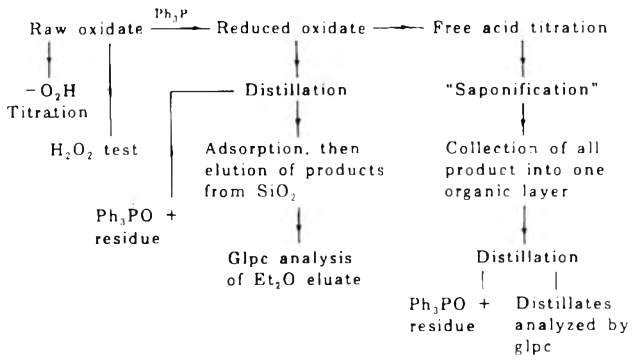
RATES OF OXIDATION OF OCTANE AT 125°

	Run no.									
	92	78	96	108	140	143	126	146	67[a]	74[b]
Time, min	620	470	410	270	320	465	1930	565	600	350
Vol of soln, ml	52.5	56.1	51.3	52.5	52.2	50.5	48.7	50.8	49.0	56.8
$[C_8H_{18}]_0$, mM	5410	5410	5410	5410	4330[c]	3540[c]	2720[c]	2090[c]	5450	5360
$[t\text{-}Bu_2O_2]_0$, mM	4.8	9.2	19.6	47.8	11.4	12.6	13.6	12.0	26.3	18.4
$\Delta[O_2]$, mmol	7.9	6.90	7.2	6.7	2.92	3.15	9.04	2.5	7.4	10.7
R_i,[d] $(M/\text{min}) \times 10^6$	8.2	15.7	33.3	81	19.3	21.5	23.2	20.3	24.6	55.0
R_0,[d] $(M/\text{min}) \times 10^4$	2.4	2.6	3.4	4.7	1.95	1.38	1.33	0.93	1.73	6.25
$R_0/R_i^{1/2}$, $(M/\text{min})^{1/2}$	0.084	0.066	0.059	0.052	0.044	0.029	0.028	0.021	0.035	0.084
$\Delta[O_2]/[C_8H_{18}]_0$, %	2.2	2.3	2.6	2.4	1.3	1.8	6.8	2.4	2.8	3.5
Yield RO_2H, % on O_2		54			54	47	19	36	50	41

[a] 120°. [b] 130°. [c] Benzene solutions. [d] R_i = rate of initiation = $2k_d[t\text{-}Bu_2O_2]$; $k_d = 4.7 \times 10^{-4}$/min at 120°, 8.5×10^{-4}/min at 125°, 1.5×10^{-3}/min at 130°; R_0 = initial rate of oxygen consumption.

CHART II

ANALYSIS OF OCTANE OXIDATION



Experimental Section

Materials.—The *n*-pentane and *n*-octane used were either Phillips Petroleum Co. "Pure Grade" (99%) or "Research Grade" (99.7%) materials. They were distilled and passed over neutral alumina just before use. The $t\text{-}Bu_2O_2$ was distilled (70°, 197 Torr) and stored at −20°; titrations on other samples treated this way have indicated 99+% purity. For solution oxidations, Matheson Coleman and Bell "Chromatoquality" benzene was used directly. Triphenylphosphine (same supplier) was purified by short-path sublimation using a standard sublimation apparatus. All other materials were reagent grade and used directly.

Apparatus and Oxidation Procedure.—Octane oxidations were performed in an apparatus consisting of a heavy glass bulb connected to an oxygen reservoir. The use of this apparatus has been described elsewhere.[7] Solutions of the octane with $t\text{-}Bu_2O_2$, and in some cases benzene, were made up in volumetric flasks before transfer to the reaction bulbs. The bulbs were pressured with oxygen and shaken at the required temperature in a thermostated oil bath, and the drop in pressure was followed. After the desired extent of oxidation had been attained (and in one case after the gas in the void space of the reaction bulb had been sampled for mass spectral analysis), the solutions were cooled and saved for product analysis.

n-Pentane oxidations were done at 100° by a sealed-tube technique similar to that used for isobutane.[8] The reactants were sealed in glass bulbs with a known amount of oxygen and then shaken in the thermostated bath for the indicated time.

Analytical Procedure.—The most elaborate analytical procedure used for octane oxidation analysis is summarized in Chart II; it was used for the 6.6-psia run in Table II. Analyses on some other oxidates were abbreviations of this procedure. The titration procedure[9] was Hercules Method I. The triphenylphosphine-reduced[10] oxidate was divided for different work-ups in order to determine the possible residue-forming effect on the saponification procedure (heating to 100° the mixture of water, added during titration, and oxidate with 2- to 3-mmol excess sodium hydroxide). The distillations of Chart II collected all the materials up to temperatures of 100° at pressures of 0.1 Torr. The amounts of residues remaining, small in comparison with triphenylphosphine oxide, were determined by subtracting the expected quantities of this material. Where desirable, the volatile oxidation products could be isolated from the large quantities of unreacted octane by absorption on silica, followed by elution with ether.

In some experiments, as in procedure A of the 85-psia experiment (Table II), the volatile products were further reduced with sodium borohydride in isopropyl alcohol before glpc analysis on a 15 ft × 0.25 in. column of 15% Carbowax 20M on Chromosorb R; also, in procedure B of the 85-psia experiment, the aqueous layer present from the saponification procedure was separated and continuously extracted with ether after acidification to isolate the product acids for identification. After treatment of the ether extract with diazomethane, only acetic and propionic acids with a trace of butyric acid could be found (as methyl esters) by glpc.

Analysis of the pentane oxidation products was more direct. After the gases in the bulb void space were analyzed on the vacuum line to determine oxygen absorbed and an aliquot was titrated for hydroperoxide yield, an additional aliquot was reduced[11] with triphenylphosphine and analyzed by glpc. Low-boiling products were determined on a 20-ft 20% Carbowax 20M column, first at 100° for 36 min, then programmed at 2°/min to 160°, with toluene as internal standard. High boilers were determined on a 6-ft XE60 on Chromosorb G column (runs 3 and 4) or a 10-ft 2% Carbowax 20M on Chromosorb G column (runs 5 and 6) isothermally at 105° for 12 min, then programmed at 4°/min to 170°. In runs 3 and 4, peaks were estimated relative to toluene; in 5 and 6 the product 1-pentanol was employed as a secondary standard to estimate the relative peak sizes.

Results and Discussion

The rates and products of oxidation of octane are listed in Tables I and II and the same information for pentane is summarized in Table III. The footnotes make the tables mostly self-explanatory.

The equations listed below (Charts III and IV) are believed to be likely and reasonable routes to the products found. They have been grouped according to whether the products are primary or secondary (derived from subsequent attack on the primary products). R represents either a secondary pentyl or octyl radical while R′ and R″ are any primary alkyl radical from methyl to hexyl. Nonfree-radical reactions, which may lead to some of the products found, are not listed but are mentioned in the discussion. Formation of

(7) D. E. Van Sickle, F. R. Mayo, and R. M. Arluck, *J. Amer. Chem. Soc.*, **87**, 4832 (1965).

(8) D. L. Allara, T. Mill, D. G. Hendry, and F. R. Mayo, *Advan. Chem. Ser.*, **76**, 40 (1968).

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

(10) D. B. Denney, W. F. Goodyear, and B. Goldstein, *J. Amer. Chem. Soc.*, **82**, 1393 (1960).

(11) R. Hiatt in "Organic Peroxides," Vol. II, C. D. Swern, Ed., Wiley-Interscience, New York, N. Y., 1971, p 94.

TABLE II

OXIDATION OF *n*-OCTANE (5.41 *M*) AT 125°[q]

Products	$\bar{P}_{O_2}$ = 85 psia, Work-up A	$\bar{P}_{O_2}$ = 85 psia, Work-up B	$P_{O_2} \sim 10$ psia	P_{O_2} = 6.6 psia	$\bar{P}_{O_2}$[a] = 40 psia
$[t\text{-}Bu_2O_2]_0$	12.0	12.0	10.0	11.0	12.6
Time, min	375	375	489	353	465
$\Delta[O_2]$	114	114	187	115	62.4
Titratable $-O_2H$	61.5	61.5	75.3	56.7	30.0
(% on $\Delta[O_2]$)	(54)	(54)	(40)	(49)	(48)
Octanones	*b*	2.5	*b*	7.5,[c] 7.9[d]	0.8
Octanols[e]	34	36	51.8[f]	30,[c] 33.6[d]	16.7
Octanediols[g]	0.7	0	1.6	0	0
CO_2	1.9[h]	1.9[h]	3.2	1.9[h]	1.2[h]
H_2	1.1[h]	1.1[h]	1.8	1.1[h]	0.8[h]
Free acids	12.9	12.9	26.4	12.3[d]	13.5
Esters	3.2	7.1	15.3	10.2[d]	4.0
Unidentified products					
Volatile	6.4[g,i]	16.2[j]	7.0[i]	9.5[c,k]	
Residue				5.2,[c,l] 16.2[d,m]	
C_8H_{18} accounted for[n]	49.2	71.7	93.1	73.6,[c] 88.6[d]	30.2
$[O_2]$ accounted for,[o] %	78 (68)	87 (76)	122 (65)	96,[c] 92[d] (83)(80)	48 (77)
Chain length[p]	13	13	14	14	10

[a] $[C_8H_{18}]_0$ = 3540, benzene diluent. [b] Not determined; converted to octanols by $NaBH_4$ reduction. [c] In the unsaponified aliquot. [d] In the saponified aliquot. [e] After Ph_3P reduction. [f] Product was 2.2, 20.6, 15.5, and 13.5 m*M* in 1-, 2-, 3-, and 4-octanols, respectively. [g] After $NaBH_4$ reduction. [h] Estimated by analogy from 10-psia experiment. [i] Probably butanol, pentanol, or hexanol. [j] 128 mg of material in octane layer plus 112 mg of material extracted from basic aqueous layer. This material is assumed for calculation to be $C_8H_{18}O$. [k] 107 mg of material (four peaks that elute between Et_2O solvent and 4-octanone); assumed mol wt 100. [l] 76 mg; assumed mol wt 130, corresponding to 1 mol of O_2. [m] 238 mg; assumed mol wt 130, corresponding to 1 mol of O_2. [n] Octanols + ketones + esters + unidentified + (lower alcohols + acids + esters)/2. [o] Including accompanying water; $\Delta[O_2]$ = hydroperoxide + octanones + 1.5 CO_2 − 0.5 H_2 + 0.75 acid + 1.5 ester + residue. Volatile unidentified products were not counted in oxygen balance and in the saponified aliquot of the 6.6-psia experiment; ester was not counted in lieu of the higher residue figures. [p] Initial R_0/R_i (see Table I). [q] Concentrations in m*M*.

CHART III

PRIMARY REACTIONS

Initiation

$$t\text{-}Bu_2O_2 \xrightarrow[1]{} 2t\text{-}BuO\cdot \xrightarrow[2]{RH} t\text{-}BuOH + R\cdot$$

Propagation

$$R\cdot + O_2 \xrightarrow[3]{} RO_2\cdot \xrightarrow[4]{RH} RO_2H + R'\cdot \text{ (to 3)}$$

$$R'CH(CH_2)CHR''(O_2H) \xrightarrow[6]{5} R'CH(CH_2)CHR''(O) + HO\cdot \text{ (to 10)}$$

$$R'CH(O_2\cdot)(CH_2)CHR''(O_2H) \xrightarrow{7} \text{(to 4)}$$

$$2RO_2\cdot \xrightarrow[8a]{} 2RO\cdot + O_2 \text{ (to 2)}$$

Termination

$$2RO_2\cdot \xrightarrow[8b]{} \text{nonradical products} + O_2$$

CHART IV

SECONDARY REACTIONS

$$RO_2H \xrightarrow{9} HO\cdot + RO\cdot$$

$$HO\cdot \xrightarrow{RH,\ 10} HOH \text{ or } ROH + R\cdot$$

$$RO\cdot \xrightarrow{11} R'CHO + R''\cdot \text{ (to 3)}$$

$$RO_2H + RO_2\cdot \xrightarrow[12]{} R'C(O_2H)R'' + RO_2H$$

$$R'C(O_2\cdot)R'' \xrightarrow{13} R'C(=O)R'' + HO\cdot \text{ (to 10)}$$

$$R'CHO \xrightarrow[14]{RO_2\cdot \text{ (or } RO\cdot)} R'C\dot{O} + RO_2H \text{ (or ROH)}$$

$$R'C\dot{O} \xrightarrow[15]{O_2} R'CO_3\cdot \xrightarrow[16]{RH} R'CO_3H + R\cdot \text{ (to 3)}$$

alkoxy radicals is depicted as arising both from simple unimolecular decomposition of primary product hydroperoxide, RO_2H (eq 9), although, in actuality, "decomposition" is certainly more complex than this, and from nonterminating interaction of *sec*-peroxy radicals (eq 8); 50–70% of the interactions of *sec*-butyl peroxy radicals have been estimated[12] to be nonterminating at 100–125°.

Rates of Oxidation.—The data of Table I show that, in spite of the product complexity of the reaction, the oxidation of *n*-octane fits the relatively simple rate law

$$\text{initial oxidation rate} = R_0 = (R_i/2k_t)^{1/2} k_p[C_8H_{18}]$$

That the *n*-oxtane oxidation is nearly one-half order in rate of initiation was established by plotting log R_0 *vs.* log $[t\text{-}Bu_2O_2]$ for runs 92, 78, 96, and 108 (Figure 1). Two lines, drawn as limits to the best fit, have slopes of 0.48 and 0.57. If the datum of run 3, Table III, is omitted from a similar log–log plot, the average oxidation rate of *n*-pentane appears to be ~0.68 order in initiation. These results support the idea that termination involves principally the interaction of *sec*-alkyl peroxy radicals.[13]

A plot of the rate of *n*-octane oxidation, corrected to unit initiation, $R_0/R_i^{1/2}$, against hydrocarbon concentra-

(12) T. Mill, D. Allara, F. R. Mayo, H. Richardson, and K. C. Irwin, *J. Amer. Chem. Soc.*, **94**, 6802 (1972).

(13) J. A. Howard, W. J. Schwalm, and K. U. Ingold, *Advan. Chem. Ser.*, **75**, 6 (1967).

TABLE III

OXIDATION OF NEAT *n*-PENTANE (7.44 *M*) AT 100°[g]

	Run 1	2	3	4	5	6[a]
Initial Conditions						
Time, min	2390	3836	4137	200	1444	200
RH, mmol	36.6	35.7	57.8	83.8	43.7	34.0
t-Bu_2O_2	97	50	54	43	9.8	9.8
O_2, mmol	968	369	1062	887	879	1066
Products						
O_2 absorbed ($\Delta[O_2]$)	82	73	47	4.7	10.7	−9.7[b]
RO_2H	28	39	32	1.95	8.2	−60[b]
$RO_2H/\Delta[O_2]$, %	34	54	68	41	76	
2- and 3-AmOH	37	34	23	1.6	5.9	88.3
2- and 3-$C_5H_{10}O$	15	7.8	4.2	0.26	0.51	5.6
n-AmOH		1.2			0.26	2.3
AcH	Trace	0.6	2.5			
EtOH	Trace	0.2	0.9			
$(MeCHOH\text{-})_2CH_2$			2.4	0.21	0.13	0.18
Ac_2CH_2					0.07	
Residue	3–6 mg		9[c]		0.18[c]	
Rates × 10_6, M/min						
R_i[d]	7.5	4.1	4.4	3.5	0.82	
$R_0 = \Delta[O_2]/\Delta t$	34	19	11	24	7.4	
R_0/R_i	4.6	4.5	2.6	6.9	9.1	
$\Delta[O_2]/[AmH]_0$, %	0.9	0.7	0.55	0.065	0.12	
O_2 accounted for, %[e]	52	64	77	47	87	
$k_p/(2k_t)^{1/2} \times 10^3$[f]	1.32	0.99	0.42	1.45	0.97	

[a] 1.81 M t-BuO_2H added initially; RO_2H in products corrected accordingly. [b] Net evolution of O_2 and loss of RO_2H. [c] Estimated mM of unknown product. [d] $R_i = 2k_d[t\text{-}Bu_2O_2]$; $k_d = 4.08 \times 10^{-5}$/min (ref 8). [e] Arbitrarily calculated from RO_2H + mono- and diketones. [f] Calculated from $R_0 = R_i/2a + (R_i/2k_t)^{1/2}k_p[RH]$ with $a = 0.5$ (ref 12). [g] Other concentrations in mM.

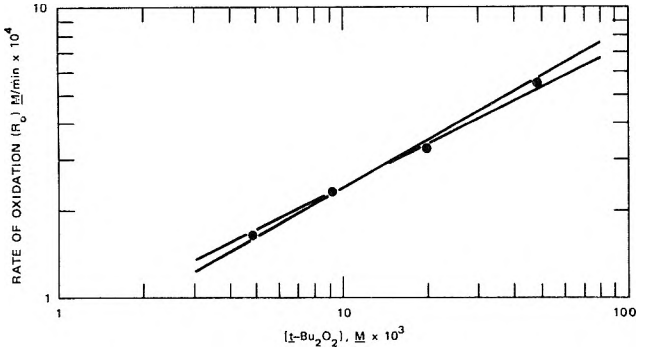


Figure 1.—Plot of log R_0 *vs.* log $[t\text{-}Bu_2O_2]$ for oxidation of *n*-octane at 125°.

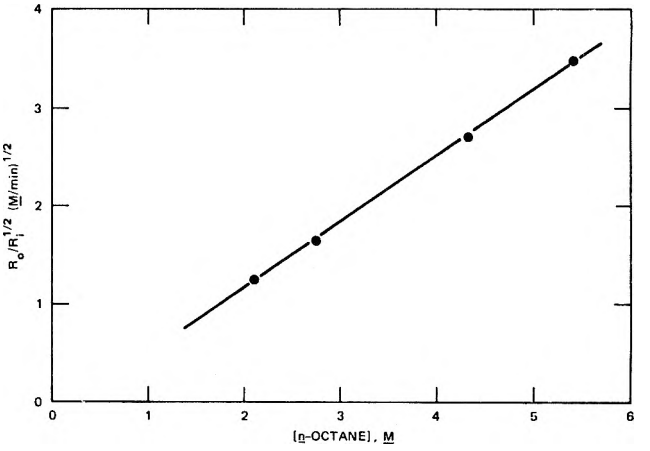


Figure 2.—Plot of $R_0/R_i^{1/2}$ *vs.* [*n*-octane] for oxidation of *n*-octane at 125°.

tion for all 125° runs gives a fairly good straight line, excepting the datum of run 143 (Figure 2). The value of the composite rate constant, $k_p/(2k_t)^{1/2}$, from the slope of the plot is $0.011/(M \text{ min})^{1/2}$; for *n*-butane,[12] the composite rate constant is $0.0028/(M \text{ min})^{1/2}$, which value is 20% lower on a per secondary hydrogen basis and identical within the experimental error.

The limited rate data for oxidation of *n*-pentane at 100° fit the theoretical equation less well than those of octane. (Experiments were done over too small a range of R_i and with chain lengths too short to expect close agreement.) If we assume that the oxidation obeys the extended rate law for oxidation of *n*-butane (eq 9 of ref 12) then an average value for $k_p/(2k_t)^{1/2}$ at 100° is $1.2 \times 10^{-3}/(M \text{ min})^{1/2}$ (excluding runs 3 and 6), in good agreement with the value for *n*-butane of 0.76×10^{-3}, taking into account the difference in numbers of secondary hydrogens.

An attempt to determine the overall energy of activation for octane oxidation from an Arrhenius plot of $R_0/R_i^{1/2}$ *vs.* $1/T$ for runs 67, 92, and 74 gives an unreasonably high value for $E_p - E_t/2$ of 26 kcal/mol. A value of 14–16 kcal/mol is expected.[12] This result suggests that a significant contribution to the rate of initiation is made by decomposition of product octyl hydroperoxides at the higher temperatures (reaction 9) and/or additional complications.

Products.—Unfortunately, in the oxidation of *n*-alkanes larger than *n*-pentane the multiplicity of products is so great and, therefore, the analyses so complex that only qualitative conclusions can be drawn about the relative importance of the postulated steps of the reaction mechanism. One indication of the com-

plications present is the strong inverse dependency of total hydroperoxide yield on conversion. For the *n*-octane oxidations which were carried out at relatively high conversions, hydroperoxide yields range from 54 to 19%. For the pentane oxidations, where all conversions are less than 1%, hydroperoxide yields range from 76 to 34%. Because of analytical difficulties, the lowest conversion *n*-pentane run (4) does not fit the trend. Nonetheless, it seems reasonable to conclude that hydroperoxides are the principal primary products of these oxidations under most conditions.

By the somewhat arbitrary procedure of accounting for oxygen in the products, as detailed in the table footnotes, up to 83% of the consumed oxygen can be accounted for in the 6.6-psi oxidation of *n*-octane. Oxygen balances for other runs are lower. Similarly, for *n*-pentane, where the basis for accounted oxygen has been simplified, products of one run account for 87% of consumed oxygen but other runs are less satisfactory. Part of the problem with oxygen balances lies in the discrepancy between titrated hydroperoxide and octanols or pentanols detected after triphenylphosphine reduction of the oxidates. With the higher conversion octane oxidations, the octanol yields are only about 50% of the hydroperoxide titre while with the pentane oxidations, excepting run 1, the pentanols account for 70–80% of the titrated hydroperoxide. The source of the remaining titrated hydroperoxide is uncertain, although peracids (reaction 16) seem a likely possibility. For most of the octane analyses, the acid found by titration taken with the octanols is still insufficient to account for all of the titrated hydroperoxide.

Turning to the original objective of this work, we find that the yield of readily identifiable bifunctional products from both octane and pentane oxidations is small, in marked contrast to the results for oxidation of 2,4-dimethylpentane[4] and 2,4,6-trimethylheptane,[5] where bi- or polyfunctional products predominate. Further, the yields of the bifunctional products seem to be an erratic function of the conversion, and the oxidation state of the bifunctional products is variable. For runs 3 and 4 of the pentane oxidation, pentanediol is about 10% of pentanols and pentanones, although conversions are substantially different. However, at an intermediate conversion, run 5, the combined yield of pentanediol and pentanedione is only 3.1% of the monofunctional products. The marked reduction of pentanediol yield to 0.2% of the pentanols in run 6 (Table III) made with added *t*-BuO_2H confirms that intramolecular propagation is the source of the small yields of these products in these experiments. The hydroperoxide would be expected to chain transfer[13] efficiently with intermediate II with near elimination of intramolecular propagation. Criegee and Ludwig[14] have shown that in autoxidations of some cyclic hydrocarbons such as 1,4-dimethylcyclohexane, bishydroperoxides can arise from secondary oxidation of monohydroperoxide intermediates but at substantially higher conversions than used here.

Despite the semiquantitative character of these results, we can calculate the approximate ratio of rate constants for intra- and intermolecular hydrogen transfer (k_r/k_p) from the amounts of difunctional (D) and monofunctional (M) pentane products, including diols, keto alcohols and residue and secondary alcohols and ketones, from the equation

$$mk_r/nk_p = \frac{[D][RH]}{[M]}$$

where m and n refer to the number of possible CH bonds available for reaction. For run 5, [D] $\sim$ 0.38 mM, [M] $\sim$ 6.41 mM, and RH = 7.44 M. On a per hydrogen basis, with the assumptions that only the 2-pentyl peroxy radical gives significant intramolecular abstraction at the 4 position and that only *sec*-CH bonds are attacked in intermolecular abstraction, $2k_r/6k_p \sim 0.45\ M$ and $k_r/k_p \sim 1.4\ M$. This may be compared with a value of 83 M for 2,4-dimethylpentane[4]. The absolute value of 48/min for k_r is estimated using a value of $37/M$ min for k_p[15] for pentane.

For octane oxidations product identification and analyses are even less certain than with pentane, but rough calculations of k_r/k_p give values in the same range ($\sim$1 M) as found for pentane; the proportion of intramolecular propagation does not significantly change with chain length.

The detection of 1-pentanol and 1-octanol allows an estimation of relative reactivities of primary and secondary hydrogens by the radicals present. In *n*-pentane, a reliable value of k_p(secondary)/k_p(primary) at 100° obtained from expt 6 (Table III) where the principal chain carrier is *tert*-butylperoxy radical is 88/2.3 = 38.5. Based on the 10-psia octane experiment at 125° (Table II), the ratio seems as low as 11, = (6/12) × [(20.6 + 15.5 + 13.5)/2.2]. Analysis of *n*-butane oxidation[12] gave relative reactivities of secondary and primary hydrogens of *n*-butane toward *sec*-peroxy radicals of 45:1 at 100° while the same ratio for alkoxy radicals was stated to be 8:1 at 100°. The octane result appears to give a low value, even taking into account the higher temperatures, indicating a change to less selective radical chain carriers (such as RO· and HO· radicals) as conversions are increased.

Other investigators[16–18] have reported results similar to our octane experiments in the oxidation of other *n*-alkanes: about 50% of the alkane is converted to hydroperoxide, 10–12% to acids, and 5–15% to ketone. At higher temperature and lower oxygen pressures,[17] small amounts of cyclic ethers can be detected, but, in all cases, the amount of intramolecular propagation, as measured by diols or cyclic ethers, is minor.

In conclusion, the question must be asked as to why the *n*-alkanes give so little intramolecular propagation while 2-4-dimethylpentane and 2,4,6-trimethylheptane give so much under similar conditions. Explanations based on a high degree of reversibility for reaction 5 in the *n*-alkane case do not seem satisfactory.[4] Nor do the pentane data support the idea that, at moderate conversions, the reactive oxidation products, including α hydrogens of *sec*-ROOH, intercept *sec*-RO_2 radicals before they can undergo intramolecular abstraction.

Our previous studies[4,5] together with this one indicate

(14) R. Criegee and P. Ludwig, *Erdoel Kohle*, **15**, 523 (1962).

(15) Estimated from the eooxidation of *n*-BuH and *i*-BuH (ref 12), with the assumption that *sec*-RO_2· is ten times as reactive as *t*-RO_2· toward the same CH bond (private communication from K. U. Ingold).

(16) A. W. Dawkins, *Eur. Chem. News*, *Normal Paraffin Suppl.*, 50 (Dec 2, 1966).

(17) R. D. Boss and R. N. Hazlett, *Can. J. Chem.*, **47**, 4175 (1969); numerous pertinent references to Russian investigators of *n*-alkane oxidations are cited in this article.

(18) G. H. Twigg, *Chem. Eng. Sci., Suppl.*, **3**, 5 (1954).

that only a very limited number of hydrocarbon substrates oxidize with major participation of intramolecular abstraction. Normal and cyclic[14] alkanes may, therefore, be the general case and explanations are required, instead, for the exceptional cases of alternately branched alkanes. We can only speculate at this time that unusual steric factors operate in the alternately branched alkanes which promote reaction 5 by a favored orientation–restricted chain rotation mechanism. Partial screening of the reactive tertiary hydrogens of the substrate from external attack (reaction 4) by the clusters of methyl groups present must also be a factor.[4]

Acknowledgments.—This study was supported by several chemical and petroleum companies as part of SRI's Oxidation Program.

Registry No.—*n*-Pentane, 109-66-0; *n*-octane, 111-65-9.

A Kinetic Investigation of the Configurational Isomerization of Geometrically Isomeric Nitrones[1a]

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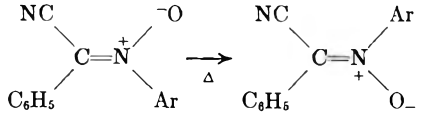
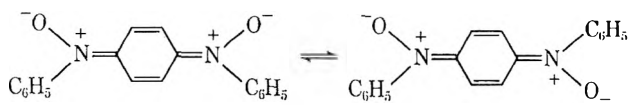
The *Z* and *E* isomers of *N*-methyl-α-(*p*-tolyl)-α-phenyl nitrone (**7a** and **8a**) and the *Z* and *E* isomers of *N*-benzyl-α-(*p*-tolyl)-α-phenyl nitrone (**9a** and **10**) were prepared. Alkylations of isomeric oxime anions and the reaction of *N*-benzylhydroxylamine (**13**) with 1,1-dichloro-4′-methyldiphenylmethane (**14**) were employed in the syntheses. The first-order rates for thermal approach to geometric equilibrium of **7a**, **8a**, **9a**, and **10** were determined in degassed *tert*-butyl alcohol solutions. Activation parameters for the isomerization of **9a** were determined in the same solvent and are $\Delta E^{\pm} = 33.6 \pm 1.4$ kcal/mol; $\Delta S^{\pm} = -4 \pm 4$ eu. The energy barrier to isomerization is substantially larger than would be anticipated from the limited data available from previous studies of geometric isomerizations of nitrones. These results are briefly discussed.

The existence of separate geometric isomers of unsymmetrical nitrones has been reported on several occasions. A modest configurational stability of α,α-diaryl-*N*-methyl nitrones has been inferred from the apparent absence of geometric isomerization during recrystallizations and upon melting.[2,3] By contrast, Barrow and Thorneycroft[4] observed that the cis isomers (**1**) of some *N*-aryl-α-phenyl nitrones slowly isomerized to the trans isomers (**2**) during melting



1 **2**

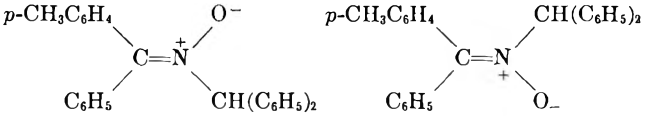
point determinations. Koyano and Tanaka[5] investigated this isomerization in *n*-butyl alcohol. The activation energy for the cis to trans isomerization of *N*,α-diphenyl-α-cyano nitrone (**1** → **2**; Ar = C_6H_5) was found to be 24.6 kcal/mol. Layer and Carman[6] have reported a study of the geometric isomerization of *N*,*N*′-diphenyl-*p*-benzoquinonediimine *N*,*N*′-dioxide (**3a** and **3b**). The pmr study in deuteriochloroform



3a **3b**

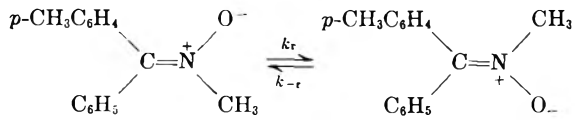
provided an estimate of the energy barrier ($\Delta F^{\pm}$ below room temperature) of about 12 kcal/mol from data obtained at the coalescence temperature. More recently Boyle, Peagram, and Whitham estimated the rate constant for the "configurational exchange" of the vinyl protons for *N*-(1-ethylcyclohexyl) nitrone (**4**) by pmr methods.[7] From the first-order rate constant at 180°, a free energy of activation of 23.2 kcal/mol was calculated.

Our interest in obtaining rates and activation energies for the geometric isomerization of certain nitrones derives from our investigation of the stereochemical course of the N to O rearrangements of (*Z*)- (**5**) and (*E*)- (**6**) *N*-benzhydryl-α-(*p*-tolyl)-α-phenyl nitrone.[8]



5 **6**

Evidence was obtained[8] that these rearrangements proceed *via* intermediate benzhydryl and rapidly interconverting iminoxy radicals. Since it was also discovered that these radicals recombine at nitrogen as well as oxygen, this provided a potential route to the geometric isomerization of **5** and **6** which was observed during the course of the N to O rearrangements.[8] To estimate the rates of the pure torsional isomerizations, the configurational isomerizations of two pairs of isomeric nitrones which do not appear to dissociate to alkyl and iminoxy radicals were investigated. The nitrones chosen for this study were the *Z* and *E* isomers of *N*-methyl-α-(*p*-tolyl)-α-phenyl nitrone (**7a** and



7a **8a**

(1) (a) Taken in part from the Ph.D. Thesis of Thomas S. Dobashi, California State University, San Diego, and the University of California, San Diego, 1973. (b) NDEA Fellow, 1967–1971. (c) NSF College Teacher Reseasch Participant, summer, 1971.

(2) O. L. Brady and R. P. Mehta, *J. Chem. Soc.*, 2297 (1924).

(3) L. Semper and L. Lichtenstadt, *Chem. Ber.*, **51**, 928 (1918).

(4) F. Barrow and F. J. Thorneycroft. *J. Chem. Soc.*, 722 (1934); 769 (1939).

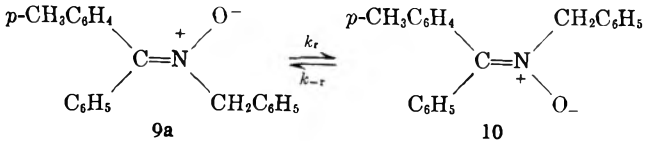
(5) K. Koyano and I. Tanaka, *J. Phys. Chem.*, **69**, 2545 (1965).

(6) R. W. Layer and C. J. Carman, *Tetrahedron Lett.*, 1285 (1968).

(7) L. W. Boyle, M. J. Peagram, and G. H. Whitham, *J. Chem. Soc. B*, 1728 (1971).

(8) T. S. Dobashi and E. J. Grubbs, *J. Amer. Chem. Soc.*, **95**, 5070 (1973).

8a, respectively) and the corresponding isomers of *N*-benzyl-α-(*p*-tolyl)-α-phenyl nitrone (**9a** and **10**,

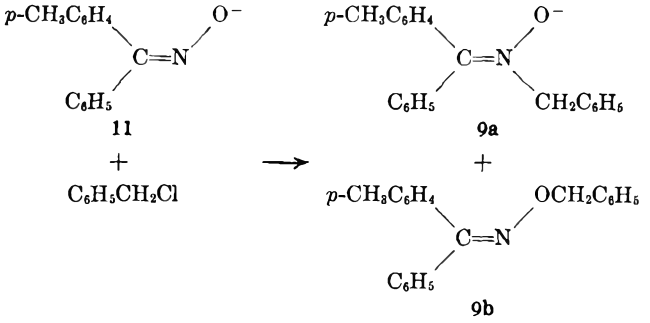


9a **10**

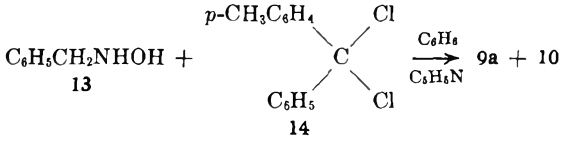
respectively). The rates of approach to equilibrium in these systems are easily measured by use of pmr, since within each isomeric pair the chemical shifts of the methyl singlets differ sufficiently.

Results and Discussion

The nitrones **7a** and **8a** (along with the corresponding *O*-methyl oximes) were obtained by the dimethyl sulfate alkylations of (*Z*)- (**11**) and (*E*)- (**12**) 4-methyl-



benzophenone oximates.[3] The *N*-benzyl nitrone **9a** was first prepared by the reaction of **11** with benzyl chloride in ethanol. A mixture of the two *N*-benzyl nitrones **9a** and **10** was prepared by the reaction of *N*-benzylhydroxylamine (**13**) with 1,1-dichloro-4′-methyldiphenylmethane (**14**). Geometric assignments for the



pure separated nitrones were made by a pmr method based upon the multiplicity characteristics of the ortho protons of the α-aryl rings cis to the oxygen atom.[9,10]

The rate constants for approach to equilibrium (assuming a reversible first-order rate law) were determined in degassed *tert*-butyl alcohol solutions. The rate constants, k_r (rotation), along with probable errors, are listed in Table I.

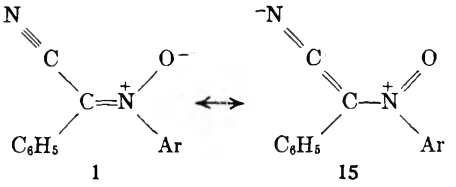
The activation parameters for the isomerization of the *N*-benzyl nitrone **9a** calculated from the last six entries of Table I are $E_a = 33.6 \pm 1.4$ kcal/mol, $\Delta S^{\pm} = -4 \pm 4$ eu. This energy barrier is much larger than that determined for the cis to trans isomerization of *N*,α-diphenyl-α-cyano nitrone.[5] It is also considerably larger than those which might be estimated (assuming small entropies of activation) for the **3a** to **3b** isomerization or for the "configurational exchange" of vinyl protons in **4**. The barrier for the α-cyano derivative may be low (compared with **9a**) because of the reduction of C=N double bond character through contributions of resonance forms such as **15** to the

TABLE I

FIRST-ORDER RATE CONSTANTS FOR THE THERMAL GEOMETRIC ISOMERIZATION OF SOME *N*-ALKYL-α-(*p*-TOLYL)-α-PHENYL NITRONES IN *tert*-BUTYL ALCOHOL

Nitrone	Temp, °C	$k_r \times 10^6$, sec^{-1}
7a[a]	144	4.3 ± 0.4
7a[a]	144	3.6 ± 0.4
7a[b]	144	3.5 ± 0.2
7a[b]	144	3.1 ± 0.1
7a[c]	144	3.7 ± 0.7
7a[c]	144	3.5 ± 0.2
8a	144	3.6 ± 0.4[d]
10	144	7.2 ± 0.3[d]
10	144	7.2 ± 0.2[d]
9a	160	30.1 ± 3.3
9a	160	30.3 ± 1.0
9a	144	8.8 ± 0.9
9a	144	7.4 ± 0.4
9a	135	2.4 ± 0.1
9a	135	2.9 ± 0.1

[a–c] Nitrone concentrations: 9.2×10^{-3} *M*;[a] 4.6×10^{-2} *M*;[b] 9.2×10^{-2} *M*;[c] all other runs, 3.3×10^{-2} *M*. [d] *E* to *Z* isomerization, k_{-r}.



1 **15**

hybrid. Similar delocalization effects could account for the low rotational barriers to the **3a** ⇌ **3b** isomerization, but no such explanation appears reasonable for the relatively low barrier associated with the pmr observed rotational process in **4**. Since it was reported[7] that decomposition occurred at the elevated temperatures employed in the study, the possibility of catalysis by some by-product is a reasonable concern.

In interpreting the stereochemical results of the cycloaddition of α-phenyl-*N*-methyl nitrone to norbornene, it was concluded (on the basis of the rate of "isomerization" of **4**) that at 85° the rate of geometric isomerization of this aldonitrone is reasonably rapid compared with the rate of the cycloaddition.[7] While this may be true, in light of our results it would appear that a study of the rates and interconversion barriers for aldoxime geometric isomerizations would be well justified; and the illusiveness of *E* isomers of aldonitrones may prove to be more a reflection of the difficulty in isolating them from mixtures overwhelmingly predominated by the *Z* isomers, rather than because of rapid thermal interconversion.[11]

An approximately twofold isomerization rate increase is observed when the *N*-methyl group (compounds **7a** and **8a**) is changed to *N*-benzyl (nitrones **9a** and **10**, Table I). This difference is probably due to increased ground-state energies of **9a** and **10** caused by larger nonbonded interactions between the benzyl and α-phenyl groups. The importance of such interactions in influencing electronic spectra of nitrones has been discussed.[12] Indeed, when benzyl (nitrone **9a** or **10**) is replaced by benzhydryl (nitrone **5** or **6**), the

(9) K. Koyano and H. Suzuki, *Bull. Chem. Soc. Jap.*, **42**, 3306 (1969).
(10) F. J. Grubbs, R. J. Milligan, and M. H. Goodrow, *J. Org. Chem.*, **36**, 1780 (1971).
(11) E. Buehler, *J. Org. Chem.*, **32**, 261 (1967).
(12) T. Kubota, M. Yamakawa, and Y. Mori, *Bull. Chem. Soc. Jap.*, **36**, 1552 (1963).

observed first-order rate constant (under the same conditions) jumps to approximately 2.0×10^{-5} sec^{-1}.[13] However, in this case the torsional process is, no doubt, accompanied by isomerization *via* intermediate isomerizing iminoxy radicals. Thus, this latter figure represents a maximum limiting value for the rotational rate constants for interconversion of **5** and **6**.

A comprehensive study of solvent effects upon the rates of geometric isomerization of these nitrones has not yet been conducted. However, one observation may be suggestive of the potential magnitude of such effects. The first-order rate constant for the isomerization of **10** to **9a** was determined in a degassed solution of diethylcarbitol (diethylene glycol diethyl ether) at 135°. The observed rate constant is $9.5 \pm 0.5 \times 10^{-5}$ sec^{-1} (duplicate, $9.1 \pm 0.5 \times 10^{-5}$ sec^{-1}). A comparison of this rate constant with that for the **9a** to **10** isomerization in *tert*-butyl alcohol (approximately 2.65×10^{-6}; see Table I) at this temperature indicates that the rate is approximately 35 times slower in *tert*-butyl alcohol. Alcohols reportedly hydrogen bond to nitrones[14] (presumably at the nitrone oxygen atom). It is possible that this type of hydrogen bonding may increase the double-bond character of the α-carbon to nitrogen bond, thereby inhibiting the torsional isomerization. However, additional experimental work will be necessary to elucidate the nature of such solvent effects.

Experimental Section

All melting points are uncorrected. The nmr spectra were obtained with a Varian Model A-60 spectrometer. Absorptions are reported in parts per million relative to internal TMS. Infrared spectra were obtained on a Perkin-Elmer 621 grating spectrophotometer, and uv spectra on a Cary Model 14 recording spectrophotometer. Analyses were performed by M. H. W. Laboratories.

(*Z*)-*N*-**Methyl-α-(*p*-tolyl)-α-phenyl Nitrone (7a).**—This nitrone was prepared by the dimethyl sulfate methylation of (*Z*)-*p*-methylbenzophenone oxime using a method previously described by Semper and Lichtenstadt.[3] The initially obtained product is a mixture of unreacted oxime, **7a**, and the corresponding (*Z*)-*O*-methyl-*p*-methylbenzophenone oxime (**7b**). The nitrone and the *O*-methyl derivative were isolated (in low yields) by a combination of crystallization and chromatography (silica gel). The nitrone **7a** was obtained as colorless crystals, mp 90.5–91.5° (lit.[3] mp 91–92°), and showed the following spectral characteristics: pmr ($CDCl_3$) δ 7.92 (d, 2, aromatic), 6.95–7.73 (m, 7, aromatic), 3.69 (s, 3, NMe), 2.34 (s, 3, *p*-Me); uv (heptane) λ_{max} 305 nm (ε 15,520); ir (KBr disk) 1255 cm^{-1} (N → O stretch). The *O*-methyl oxime **7b** was obtained as colorless crystals, mp 70.5–71.5° (lit.[3] mp 70.5–72°), and showed the following spectral features: pmr ($CDCl_3$) δ 7.62–7.17 (m, 9, aromatic), 3.97 (s, 3, OCH_3), and 2.38 (s, 3, *p*-CH_3); uv (C_2H_5OH) λ_{max} 261.5 nm (ε 11,180).

(*E*)-*N*-**Methyl-α-(*p*-tolyl)-α-phenyl Nitrone (8a).**—The isomeric nitrone **8a** was prepared as described above [starting from pure (*E*)-*p*-methylbenzophenone oxime] and was isolated as colorless crystals, mp 111–112.5° (lit.[3] mp 113–114°). The spectral features of **8a** are as follows: pmr ($CDCl_3$) δ 7.82–8.20 (m, 2, aromatic), 7.06–7.68 (m, 7, aromatic), 3.73 (s, 3, NMe), 2.44 (s, 3, *p*-CH_3); uv (C_2H_5OH) λ_{max} 303 nm (ε 14,310); ir (KBr disk) 1250 cm^{-1} (N → O stretch). The corresponding *O*-methyl oxime **8b** was chromatographically separated from the reaction mixture and remained a colorless oil with the following spectral features: pmr ($CDCl_3$) δ 7.54 (m, 9, aromatic), 3.97 (s, 3, OCH_3), 2.34 (s, 3, *p*-CH_3); uv (C_2H_5OH) λ_{max} 265.5 nm (ε 11,980).

(*Z*)-*N*-**Benzyl-α-phenyl-α-(*p*-tolyl) Nitrone (9a).**—To 23 ml of absolute ethanol was added 0.490 g (0.0125 g-atom) of freshly cut potassium. Pure (*Z*)-4-methylbenzophenone oxime (2.64 g, 0.0125 mol) and then 2.14 g (0.0125 mol) of benzyl chloride were added. The mixture was stirred at room temperature for 48 hr. The reaction mixture was concentrated under dry nitrogen and the products were separated from KBr by extraction with chloroform. The chloroform extract was concentrated to a pale yellow oil. The crude product mixture (3.76 g) was chromatographed on 100 g of silica gel (60–200 mesh). Elution with hexane containing 50–75% methylene chloride afforded 2.52 g (67%) of (*Z*)-*O*-benzyl-*p*-methylbenzophenone oxime (**9b**), mp 85–86.5°. Recrystallization from hexane afforded 2.19 g of **9b** as colorless needles, mp 86–86.5°. Spectral characterization of **9b** revealed the following: pmr (CCl_4) δ 6.95–7.55 (m, 14, aromatic), 5.13 (s, 2, CH_2), 2.36 (s, 3, *p*-CH_3); uv (C_2H_5OH) λ_{max} 263 nm (ε 12,830), 236 (16,280).

Anal. Calcd for $C_{21}H_{19}NO$: C, 83.69; H, 6.35; N, 4.65. Found: C, 83.78, 83.97; H, 6.34, 6.30; N, 4.60, 4.75.

Further elution with 10–25% ether in methylene chloride yielded approximately 10% unreacted oxime. Elution with 50% ether in methylene chloride, ether, and 2% methanol in ether afforded the crude nitrone **9a** (contaminated with approximately 6% of its geometric isomer **10**) as a white solid, mp 82–90°. Recrystallization first from 10% ether in hexane and then from hexane provided 0.56 g (15%) of **9a** as colorless crystals, mp 91.5–92.5°. The pmr spectrum (in CCl_4) revealed no evidence for the presence of **10** and showed the following absorptions: δ 7.88 (d, 2, aromatic), 6.85–7.50 (m, 12, aromatic), 4.83 (s, 2, CH_2), 2.31 (s, 3, *p*-CH_3).

Anal. Calcd for $C_{21}H_{19}NO$: C, 83.69; H, 6.35; N, 4.65. Found: C, 83.52, 83.71; H, 6.21, 6.28; N, 4.63, 4.63.

In a second preparation conducted as described above, the (*Z*)-*O*-benzyl oxime **9b** obtained possessed a melting point of 84–85°, but the melting point of nitrone **9a** was 106.5–108°. In all other respects (*i.e.*, spectral comparisons), this nitrone appeared identical with the lower melting sample. The source of this discrepancy in melting points is not yet clear.

(*Z*)- (**9a**) **and** (*E*)- (**10**) ***N*-Benzyl-α-phenyl-α-(*p*-tolyl) Nitrone.** A mixture of the isomeric nitrones was prepared by the reaction of *N*-benzylhydroxylamine (**13**) with 1,1-dichloro-4′-methyl-diphenylmethane (**14**). The dichloride **14** was prepared as follows. A mixture of 4.48 g (0.0228 mol) of 4-methylbenzophenone, 4.85 g (0.0234 mol) of phosphorus pentachloride, and 25 mg of di-*tert*-butylphenol was stirred under nitrogen at 80°. The bath temperature was increased to 95–100°, whereupon the solution began to evolve gas and became darker yellow in color. The phosphorus oxychloride was removed under reduced pressure and the straw-colored product **14** (4.69 g, 82%) was obtained by a short-path distillation, bp 116–122° (0.1 mm). The pmr spectrum (CCl_4) exhibited the following absorptions: δ 6.9–7.7 (*m*, 9, aromatic), 2.35 (s, 3, *p*-CH_3). Weak absorption peaks in the ir spectrum characteristic of the starting ketone and a small peak at δ 2.40 in the pmr spectrum indicated the presence of approximately 3% of *p*-methylbenzophenone.

In a dry-nitrogen atmosphere, 1.2 g (0.0098 mol) of *N*-benzylhydroxylamine (**33**) (prepared by the method of Jones and Sneed[16]) was dissolved in a solution of 5 ml of benzene and 2.5 ml of pyridine. With continuous stirring, 2.4 g (0.0096 mol) of the above-described dichloride **14** was added over a 30-min period.[16] After 6 hr at room temperature, the reaction mixture had separated into two phases. The mixture was heated to 70°, but, after 15 min, considerable darkening of both layers occurred and heating was terminated. The top layer was separated and the lower phase (which had then solidified) was washed thoroughly with benzene. The combined upper phase and benzene extract was concentrated under reduced pressure to 2.70 g of a dark orange semisolid. This residue was chromatographed on 100 g of silica gel (60–80 mesh). Elution with pentane–methylene chloride mixtures and finally with 10% ether in methylene chloride removed 4-methylbenzophenone (and possibly other side products) from the column. Elution with 25–75% ether in methylene chloride, followed by concentration of the fractions, afforded 1.48 g of a mixture of the isomeric nitrones **9a** and **10** as a yellow oil. Repeated chromatography on silica gel and Florisil and repeated crystallization attempts from many common solvents failed to

(13) T. S. Dobashi and E. J. Grubbs, unpublished data.

(14) J. Hamer and A. Macaluso, *Chem. Rev.*, **64**, 473 (1964).

(15) L. W. Jones and M. C. Sneed, *J. Amer. Chem. Soc.*, **39**, 674 (1917).

(16) During this time, the temperature of the reaction mixture increased approximately 2° (from 23–25°). However, on a fivefold scale-up, the reaction was vigorously exothermic and external cooling was required.

produce a solid. A crystalline product, mp 116–118°, was finally obtained when a small sample of the oily mixture of nitrones (in methanol) was seeded with a mixture of **9a** and **9b** obtained from the above oxime-alkylation reaction. This crystalline sample provided seed crystals for fractional crystallizations employing hexane and ether–hexane mixtures. In these solvents **9a** and **10** cocrystallize, but **9a** mainly as needles and **10** mainly as hemispheres. The two were separated mechanically. Two final recrystallizations of **10** from 10% ether in hexane afforded 0.345 g (15%) of **10** as nearly colorless crystals, mp 118.0–118.7°. The spectral features of **10** are as follows: pmr (CCl_4) δ 7.87–8.10 (m, 2, aromatic), 7.05–7.30 (m, 12, aromatic), 4.87 (s, 2, CH_2), 2.42 (s, 3, *p*-CH_3); uv (C_2H_5OH) λ_{max} 300 nm (ϵ 12,730).

Anal. Calcd for $C_{21}H_{19}NO$: C, 83.69; H, 6.35; N, 4.65. Found: C, 84.09; H, 6.30; N, 4.63.

Mechanically separated samples of the isomeric nitrone **9a** were combined with corresponding samples from a second preparation and recrystallized from 1:1 ether–hexane yielding pure **9a**, mp 107–108°. The yield of **9a** in the first preparation was only approximately 5%.

Kinetics of the Thermal Configurational Isomerization of Nitrones 7a, 8a, 9a, and 10 in *tert*-Butyl Alcohol.—Control experiments demonstrated that, under the conditions of the kinetic measurements, decomposition of the nitrones (to unidentified products) occurred to an extent less than 2%. Kinetic measurements were performed as follows. Samples of the nitrones in *tert*-butyl alcohol were thoroughly degassed and sealed in Pyrex tubes under reduced pressure. The sample tubes were placed in a constant-temperature bath at the appropriate temperature maintained at ±0.05° of the values cited in Table I. Samples were periodically removed, quenched at low temperature, opened, and concentrated to oils. The nmr spectra were then determined in deuteriochloroform. The isomeric composition of each sample was determined from the relative areas of the two methyl proton absorptions. In all cases, the equilibrium constant was 1.0 ± ~0.08. With the above data and assuming a first-order reversible rate law, the rate constants shown in Table I were calculated. Rate constants for the isomerization of **7a** were unaffected by a tenfold change in concentration.

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Registry No.—**7a**, 42449-48-9; **7b**, 42449-49-0; **8a**, 42449-50-3; **8b**, 42449-51-4; **9a**, 42449-52-5; **9b**, 42449-53-6; **10**, 42449-54-7; **13**, 622-30-0; **14**, 42449-55-8; (*Z*)-4-methylbenzophenone oxime, 2998-92-7; benzyl chloride, 100-44-7.

Notes

Metal-Catalyzed Electrophilic Substitution and Coupling of Naphthalene. Kinetic and Catalytic Considerations

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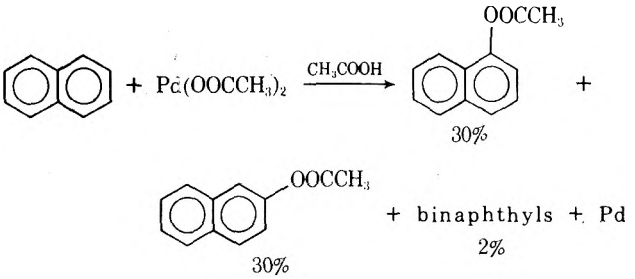
Reactions of benzene and its derivatives with palladium salts have been studied by a number of investigators in recent years.[1] Acetoxylation and/or oxidation of these aromatics in a manner analogous to the Wacker process have apparently not been developed as yet to the status of industrial processes. In that respect, little notice has been given to similar reactions of condensed aromatic ring systems. The present report concerns the results of our study of the acetoxylation of naphthalene under catalytic conditions employing $Pd(CH_3COO)_2$ and other metal salts. Of particular interest was the isomer distribution, since from the preparative standpoint a process yielding predominantly one isomer would be desirable.

Results and Discussion

A reaction stoichiometric with respect to Pd^{2+} was carried out with a mixture of $Pd(CH_3COO)_2$, $C_{10}H_8$, and CH_3COONa at a molar ratio of ~1:1.2:1 in glacial acetic acid. At the reflux temperature of the solvent the reaction appeared to proceed at a faster rate than the analogous benzene reactions. The reaction was essentially complete within 4 hr. The products and the corresponding yields based on Pd^{2+}, are shown in the following Scheme I. Decomposition of $Pd(CH_3COO)_2$

SCHEME I



also occurs with formation of CO_2, which was detected mass spectroscopically, and partially accounts for the low overall yield. The naphthyl acetates are readily hydrolyzed in mildly alkaline solutions. Naphthols found in the products are most probably entirely formed during the work-up, which involved treatment with saturated aqueous $NaHCO_3$ and ethyl ether, but some direct production from the small amount of water present in the reaction mixture cannot be ruled out.

Following completion of this work, a communication appeared[2] in which the same reaction was claimed to yield oxidation products having an isomer ratio of 1:1, in agreement with our results.

In conventional Wacker-type processes, the reoxida-

(1) (a) O. R. Van Helden and G. Verberg, *Recl. Trav. Chim. Pays-Bas*, **84**, 1263 (1965); (b) J. M. Davidson and C. Triggs, *J. Chem. Soc. A*, 1324 (1968); (c) K. Ichikawa, S. Vemura, and T. Okada, *Nippon Kaga Ku Zasshi*, **20**, 212, (1969); (d) P. M. Henry, *J. Org. Chem.*, **36**, 1886 (1971).

(2) L. Eberson and L. Gomez-Gonzales, *Chem. Commun.*, 263 (1971).

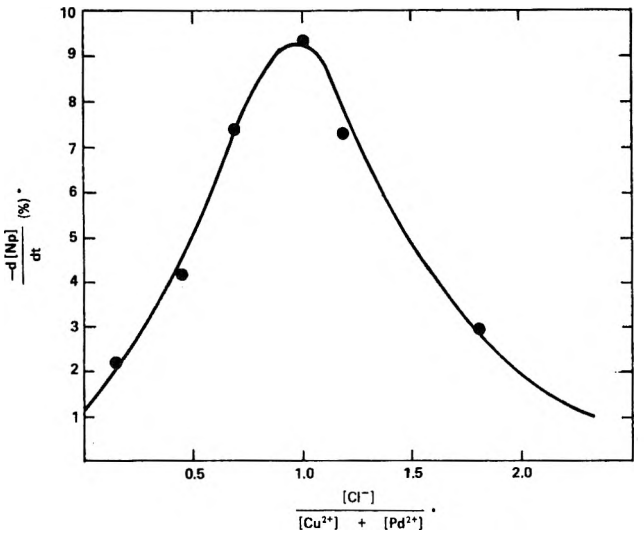


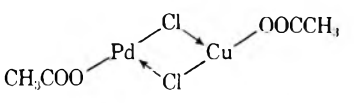
Figure 1.—Average rate of naphthalene consumption as a function of the $[Cl^-]/([Cu^{2+}] + [Pd^{2+}])$ ratio.

tion of Pd to give a catalytic reaction is accomplished by the use of redox systems such as Cu^{+2}/Cu^+ or Fe^{3+}/Fe^{2+}, *e.g.*

$$2CuX_2 + Pd \longrightarrow PdX_2 + 2CuX$$
$$2CuX + 2HX + {}^1/_2O_2 \longrightarrow 2CuX_2 + H_2O$$
$$Pd + 2HX + {}^1/_2O_2 \longrightarrow PdX_2 + H_2O$$

A number of experiments were conducted using several redox systems to investigate the catalytic possibilities of aromatic acetoxylation. The results are presented in Table I.

These investigations indicate that the success of this step depends on the nature of the anion, X, and on the relative concentrations of the metal ions and X in the solution. Acetates of Cu^{2+}, Fe^{3+}, and UO_2^+ were largely ineffective under atmospheric pressure of oxygen and only slightly effective under high pressures of oxygen. Similar conclusions were reached by other investigators.[3] The addition of another nucleophile, especially a halide ion, to the $Cu(CH_3COO)_2/Pd(CH_3COO)_2$ system promotes the reoxidation of Pd and makes the reaction catalytic with respect to Pd even at atmospheric pressure. The highest rate for the reoxidation of Pd, as measured by the rate of $C_{10}H_8$ consumption over the first 4 hr, occurs at a $[Cl^-]/([Cu^{2+}] + [Pd^{2+}])$ ratio equal to 1 and falls off rapidly as this ratio approaches either 0 or 2 (Figure 1). This relationship suggests that the active catalytic species may be a halide bridged complex of the form I.



I

Similar species have been suggested by various authors as intermediates in Wacker-type processes.[4] The inherent problem in the addition of another nucleophile to the system is that it functions not only to promote reoxidation of Pd, but also participates in product formation, *i.e.*, chloronaphthalene. The relative yields of naphthyl acetate and chloronaphthalene are significantly affected by changing the $[OAc^-]/[Cl^-]$ ratio. At a 2.30 ratio the highest recorded[5] yields during the course of the reaction were 21% α-naphthyl acetate and 30% α-chloronaphthalene, whereas at 3.39 the yields were 39 and 11%, respectively. In a typical run using a 7:1 molar ratio of $C_{10}H_8$ to $Pd(OOCCH_3)_2$ and under the optimum redox conditions, the highest combined yield of α-chloronaphthalene and α-acetoxynaphthalene, 25% of naphthalene consumed, is found after ~4 hr and falls over longer time periods. The bulk of naphthalene is eventually converted to binaphthyl, multisubstituted naphthalenes, and acetoxy- and chloro-substituted polynuclear products containing palladium. Water (10% in glacial acetic acid) further reduces the yield of the monomeric products.

Of the other reoxidant systems employed in conjunction with oxygen, quinones, *e.g.*, chloranil, were ineffective, but an $Fe(NO_3)_3/LiCl$ system did promote a reaction catalytic with respect to Pd.

The effects of the different $[CH_3COO^-]/[Cl^-]$ ratio on the rate is seen to be minimal. For the first 6 to 8 hr the reaction is first order in naphthalene. A control experiment was carried out without $Pd(OOCCH_3)_2$ (see Experimental Section). The rate of naphthalene consumption ($k \simeq 1.2 \times 10^{-5}$ sec^{-1}) was approximately one third that in the run with $Pd(OOCCH_3)_2$ under the same reagent concentrations and conditions. In the control experiment only traces of substituted products were found by vpc; coupling[6] and oxidation to quinonic derivatives appeared to be the predominant reaction routes. Binaphthyls were identified by vpc and the polymeric product of the reaction showed characteristic quinonic ir absorption. Acetoxy and chloro substituents appeared to be absent.

A redox system such as Cu^{2+}/Cu^+ is necessary for reoxidation of Pd under mild conditions and the achievement of a catalytic acetoxylation. However, the direct participation of Cu^{2+} in the oxidation of the organic substrate to coupled products (either of naphthalene or of the monosubstituted products) results in loss of selectivity.

An interesting effect observed in the runs incorporating both Cu and Pd and Cl^- ion is the nearly exclusive selectivity for α substitution in contrast to the 50:50% α:β substitution pattern obtained using $Pd(OOCCH_3)_2$ alone. The reason for this behavior might be electronic given the differences in structure between Cl^- bridged complexes, such as I, and $Pd(OOCCH_3)_2$.[7] The stoichiometric reaction of naphthalene with $Pd(OOCCF_3)_2$ results in exclusive α substitution.[8]

(3) M. Tamura and T. Yasui, *Kogyo Kaga Ku Zasshi*, **71**, 1858 (1968).

(4) See, *e.g.*, R. G. Schultz and D. E. Gross in "Homogeneous Catalysis," *Advan. Chem. Series*, **70**, 97 (1968).

(5) The participation of α-chloronaphthalene and α-naphthyl acetate in secondary coupling reactions under catalytic conditions results in loss of directly measurable yield of these products. This reaction sequence is shown by (a) the isolation of 1,1,-binaphthyl 4,4′-diacetate in the first 4 to 6 hr of the experiment and (b) vpc monitoring of the reaction; the yield of monosubstituted products increases gradually during the first 5 hr and then decreases exponentially. This behavior is in line with participation of the initial products in secondary reaction schemes. The pattern applies generally to all catalytic runs, with only small rate variations, attributable to the different reactant ratios.

(6) Cupric halides are well-known halogenating agents for aromatic systems and in certain occasions may act as coupling agents as well. See, *e.g.*, D. C. Nonhebel and J. A. Russel, *Tetrahedron*, **25**, 3493 (1969). $CuCl_2$ acts as an exclusive coupling agent in our reactions, as deduced by the absence of chlorinated products and the formation of coupled naphthalene derivatives.

(7) A. C. Skapski and M. L. Smart, *Chem. Commun.*, 658 (1970).

(8) G. G. Arzoumanidis, F. C. Rauch, and G. Blank, Abstracts of Papers, 163rd National Meeting of the American Chemical Society, Boston, Mass., April 1972, No. 73 (Inorg.).

Experimental Section

Materials.—Palladium acetate was purchased by Engelhard Industries. Absence of nitrate ions in the compound was confirmed by ir. Reagent grade chemicals were used without further purification.

Rate Studies.—The rate of naphthalene consumption and product formation was followed by vpc. A Hewlett-Packard Model 5750 research chromatograph, equipped with a flame ionization detector and a 6-ft column of 10% Apiezon L on Chromosorb W maintained at 220°, was employed. Products were identified by vpc retention time and ir comparison with authentic samples.

Acetoxylation of Naphthalene.—$Pd(OOCCH_3)_2$ [1.485 g (6.6 mmol)], $C_{10}H_8$ [1.024 g (8.0 mmol)], and CH_3COONa [0.584 g (7.1 mmol)] were dissolved in 10 ml of 99% glacial acetic acid and allowed to react at the reflux temperature of the solvent. The mixture assumed a dark color after 10 min and the reaction continued for 4 hr.

The Pd black isolated (0.725 g) indicated quantitative conversion. The acetic acid filtrate was suspended in ether–aqueous $NaHCO_3$, and the ether extract was evaporated to obtain the products. Vpc analysis of the solid products indicated the following compounds to be present (yields): α-naphthylacetate (25%), β-naphthylacetate (25%), α-naphthol (6%), β-naphthol (6%), and binaphthyls (2%).

A Typical Catalytic Reaction.—$C_{10}H_8$ [2.096 g (16.4 mmol)], $Pd(CH_3COO)_2$ [0.498 g (2.2 mmol)], $Cu(CH_3COO)_2 \cdot H_2O$ [0.890 g (4.5 mmol)], $LiOOCCH_3 \cdot 2H_2O$ [1.356 g (13.3 mmol)], and LiCl [0.291 g (6.9 mmol)] were suspended in 15 ml of CH_3COOH in a 100-ml, three-neck flask. The mixture was heated at the reflux temperature for 12 hr while oxygen was sparged through the solution. The yield (based on Pd^{2+}) of isolable[5] monomeric products was highest in about 4 hr after the start of the experiment: α-naphthylacetate (39%) and α-chloronaphthalene (11%).

Control Run.—The above reaction was repeated without $Pd(CH_3COO)_2$. Only traces of monosubstituted products could be detected *via* vpc.

Registry No.—$Pd(OOCCH_3)_2$, 3375-31-3; naphthalene, 91-20-3.

Supplementary Material Available.—A table containing 14 oxidative reactions of naphthalene in the presence of $Pd(OOCCH_3)_2$ with various redox systems and three kinetic figures depicting two of the runs will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 20× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-73-4443.

Kinetics and Mechanism of the Reactions of Allyl Halides with Silver Nitrate in Acetonitrile

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Kinetic studies of the reactions of methyl, primary, and secondary alkyl halides with acetonitrile solutions of silver nitrate have indicated a mechanism in which electrophilic assistance by the silver ion is accompanied, in the rate-determining step, by nucleophilic attack by nitrate ion.[1,2] Alkyl halides found to exhibit these characteristics include methyl,[1] ethyl,[1,3] neopentyl,[1] and isopropyl[1] iodides, 1-octyl and 2-octyl bromides,[2] and 2-octyl chloride.[2] For concentrations of silver salt within the range 0.002–0.2 *M* the overall kinetic order approximates 2.5, first order in alkyl halide, first order in silver ion, and one-half order in nitrate ion.[2]

If the reasonably nucleophilic nitrate ion is replaced by the weakly nucleophilic perchlorate ion, the rate of precipitation of silver halide is considerably reduced; for example, with 0.03 *M* silver salt at 44.6°, silver nitrate reacts with 2-octyl bromide 80 times faster than silver perchlorate.[4] Additional evidence for S_N2 character in the rate-determining step comes from a considerably slower reaction for the appreciably sterically hindered neopentyl iodide than for the considerably less hindered, but also primary, ethyl iodide.[1]

A reconsideration[1,2] of product data obtained for reactions of silver nitrate with ethyl iodide in ethanol[5,6] suggested that an ion pair containing the carbonium ion and the nitrate ion is formed, which then either collapses to product or undergoes solvolysis. A recent study of the reactions of 1-adamantyl halides with silver nitrate in ethanol[7] also implicated such an ion pair. The complex kinetics and the variation observed for the product partitioning between solvolysis and anion exchange with changing identity of the halogen suggested that, in the product-determining step, the halide ion is still in the vicinity of the carbonium ion. They may well be contained within an ion quadruplet or an even more complex aggregate.[7]

While it is reasonable to suppose that the scheme postulated for reactions in ethanol[1,2,7] can also be extended to reactions in other solvents, it should be emphasized that there is no *direct* evidence for formation of ion pairs between a carbonium ion and the anion of the silver salt during reactions in acetonitrile. An argument developed earlier[1] in favor of such an ion pair within reactions of alkyl iodides with silver perchlorate was based on the assumption that covalent alkyl perchlorates would not be solvolyzed by acetonitrile. It has, however, been shown that 2-octyl perchlorate has, in acetonitrile at 25.0°, a half-life of less than 1 min.[8] Nucleophilic attack within the rate-determining step and intermediate ion-pair formation has also been suggested for the reaction in acetonitrile between *tert*-butyl bromide and silver *p*-toluenesulfonate.[9]

A study of the reactions of the tertiary α-halogenated ketone, α-bromo-*p*-phenylisobutyrophenone, with silver salts in acetonitrile[10] also suggested nucleophilic participation by nitrate ion within the rate-determining step of the reaction with silver nitrate.

Previous studies of silver ion assisted reactions of allylic halides have usually been interpreted (in the Hughes–Ingold terminology[11]) as S_N1 Ag^+ reactions, involving in the rate-determining step an electrophili-

(1) G. S. Hammond, M. F. Hawthorne, J. H. Waters, and B. M. Graybill, *J. Amer. Chem. Soc.*, **82**, 704 (1960).

(2) Y. Pocker and D. N. Kevill, *J. Amer. Chem. Soc.*, **87**, 4760 (1965).

(3) F. G. Donnan and H. E. Potts, *J. Chem. Soc.*, **97**, 882 (1910); for a reassessment of these data see ref 2.

(4) Y. Pocker and D. N. Kevill, *J. Amer. Chem. Soc.*, **87**, 4771 (1965).

(5) A. K. Burke and F. G. Donnan, *J. Chem. Soc.*, **85**, 555 (1904).

(6) F. G. Donnan and A. K. Burke, *Z. Phys. Chem. (Leipzig)*, **69**, 148 (1909).

(7) D. N. Kevill and V. M. Horvath, *Tetrahedron Lett.*, 711 (1971).

(8) Y. Pocker and D. N. Kevill, *J. Amer. Chem. Soc.*, **87**, 5060 (1965).

(9) H. M. R. Hoffmann, *J. Chem. Soc.*, 6748 (1965).

(10) D. N. Kevill and N. H. Cromwell, *J. Org. Chem.*, **29**, 499 (1964).

(11) See, for example, C. K. Ingold, "Structure and Mechanism in Organic Chemistry," 2nd ed, Cornell University Press, Ithaca, N. Y., 1969, pp 479–483.

TABLE I

AVERAGE VALUES FOR THE INTEGRATED 2.5-ORDER RATE COEFFICIENTS,[a] $k_{2.5}$ ($M^{-1.5}$ sec^{-1}), FOR REACTION OF ALLYL BROMIDE WITH SILVER NITRATE OR SILVER PERCHLORATE IN ACETONITRILE AT VARIOUS TEMPERATURES

$[C_3H_5Br]$	$[AgNO_3]$	$[AgClO_4]$	Temp, °C	$10^3 k_{2.5}$
0.0400	0.00500		45.0	29.9 ± 1.1
0.0400	0.0100		45.0	26.1 ± 0.8
0.0400	0.0200		45.0	30.0 ± 2.0
0.0400	0.0400		45.0	28.4 ± 0.7[b]
0.0800	0.0400		45.0	26.7 ± 1.1
0.160	0.0400		45.0	25.1 ± 2.1
0.0400	0.0800		45.0	23.0 ± 1.5
0.0800	0.160		45.0	22.1 ± 0.6
0.0800	0.0400		25.0	5.3 ± 0.2
0.0812	0.0406		35.0	9.5 ± 0.5
0.0766	0.0383		55.0	65.7 ± 2.5
0.0400		0.0435	45.0	0.0159 ± 0.0010
0.200		0.0435	45.0	0.0171 ± 0.0009
0.200		0.0870	45.0	0.0164 ± 0.0005

[a] Calculated from appropriate integrated form of $-d[Ag^+]/dt = k_{2.5}[C_3H_5Br][AgX]^{1.5}$, where X = NO_3 or ClO_4. [b] A solution initially 0.0800 M in both reactants and allowed to react to 50%, with precipitation of silver bromide, before start of run (35 min) gave an essentially identical value of 0.0268 ± 0.0021 $M^{-1.5}$ sec^{-1}.

cally assisted ionization. Systems which have been interpreted in this way include reactions with silver acetate in acetic acid,[12] silver oxide suspended in water,[13] and silver nitrate in water[14] or ethanol.[15] The present investigation was undertaken to determine whether reactions of allyl halides with silver nitrate in acetonitrile follow the SN1 Ag^+ type mechanism previously postulated for silver ion assisted reactions of allylic halides or the alternate type of mechanism with concurrent nucleophilic assistance, previously postulated for reactions of acetonitrile solutions of silver nitrate with a variety of organic halides.

It is known that acetonitrile solutions of silver nitrate react with the analogous 2-methallyl chloride to give the replacement product, 2-methallyl nitrate.[16] Silver ion assisted solvolytic reaction (Ritter reaction[17]) could to some extent compete with collapse to nitrate ester. Such reaction would produce an imidoyl nitrate which on addition to moist acetone would be rapidly hydrolyzed to *N*-allylacetamide plus an equivalent amount of nitric acid. Any elimination reaction to give allene would also produce an equivalent amount of nitric acid. An acetonitrile solution, 0.08 M in allyl bromide and 0.16 M in silver nitrate, was allowed to react to completion and acid–base titration after addition to moist acetone indicated less than 0.2% acid development; presumably, allyl nitrate is formed in better than 99.8% yield based on allyl bromide consumed.

The kinetics of the reaction of allyl bromide with silver salts in acetonitrile was analyzed in terms of integrated 2.5-order rate coefficients. The reactions of alkyl bromides with silver perchlorate in acetonitrile have been shown to exhibit complex and variable kinetic orders[4] but at the concentrations of silver perchlorate employed (0.04–0.08 M) the kinetic order closely approximates 1.5 in silver salt and unity in alkyl or allyl bromide. The averages of the integrated rate coefficients (with standard deviations) are shown in Table I. Corresponding rate coefficients for reaction of allyl chloride with silver nitrate in acetonitrile at 45.0°, together with the ratio of the rate coefficients for allyl bromide (from Table I) relative to those for allyl chloride at each silver nitrate concentration, are shown in Table II.

TABLE II

AVERAGE VALUES FOR THE INTEGRATED 2.5-ORDER RATE COEFFICIENTS,[a] $k_{2.5}$ ($M^{-1.5}$ sec^{-1}), FOR REACTION OF ALLYL CHLORIDE WITH SILVER NITRATE IN ACETONITRILE AT 45.0° AND COMPARISON OF THESE COEFFICIENTS WITH THOSE FOR REACTION OF IDENTICAL CONCENTRATIONS OF SILVER NITRATE WITH ALLYL BROMIDE

$[C_3H_5Cl]$	$[AgNO_3]$	$10^5 k_{2.5}$	$k_{2.5}^{Br}/k_{2.5}^{Cl}$
0.0800	0.0100	10.8 ± 0.5	242
0.0800	0.0200	8.7 ± 0.8	345
0.0800	0.0400	10.3 ± 0.4	259
0.0800	0.0800	9.1 ± 0.6	253
0.0800	0.160	6.8 ± 0.7	324

[a] Calculated from appropriate integrated form of $-d[Ag^+]/dt = k_{2.5}[C_3H_5Cl][AgNO_3]^{1.5}$.

Reaction of both allyl chloride and allyl bromide with 0.005–0.16 M silver nitrate in acetonitrile shows essentially the same overall 2.5-order kinetics as previously observed[2] for identical reaction of 1-octyl and 2-octyl halides and, presumably, a mechanism is operating which is closely related to that which was previously proposed (Scheme I).[2]

SCHEME I

$$RX + Ag^+ \rightleftharpoons (RX \cdots Ag)^+ \quad (1)$$

$$NO_3^- + (RX \cdots Ag)^+ \overset{\text{r.d.}}{\rightleftharpoons} (NO_3^- R^+ X^- Ag^+) \quad (2)$$

$$(NO_3^- R^+ X^- Ag^+) \longrightarrow O_2NOR + AgX$$
$$(NO_3^- R^+ X^- Ag^+) \longrightarrow HNO_3 + \text{alkenes} + AgX$$
$$(NO_3^- R^+ X^- Ag^+) \xrightarrow[CH_3CN]{CH_3CN} CH_3CNH^+NO_3^- + \text{alkenes} + AgX \quad (3)$$

There does appear to be, in the present investigation, a tendency for the 2.5-order rate coefficients to fall off slightly in value at the higher silver nitrate concentrations.

From Table I, it can be seen that, for reaction at 45.0° with approximately 0.04 M silver salt, allyl bromide reacts with silver nitrate some 1600 times faster than with silver perchlorate. This can be compared with data available for 2-octyl bromide where, at 44.6°, reaction with silver nitrate is governed[2] by a 2.5-order rate coefficient of 3.27×10^{-3} $M^{-1.5}$ sec^{-1} and reactions with silver perchlorate[4] have initial second-order rate coefficients of 0.578×10^{-5} M^{-1} sec^{-1} at 0.0155 M salt and 0.715×10^{-5} M^{-1} sec^{-1} at 0.0310 M salt. These second-order rate coefficients correspond to 2.5-order rate coefficients of 4.65×10^{-5} $M^{-1.5}$ sec^{-1} and 4.06×10^{-5} $M^{-1.5}$ sec^{-1}, respectively. For 0.03 M silver salt at 44.6°, silver nitrate reacts with 2-octyl

(12) J. D. Roberts, W. G. Young, and S. Winstein, *J. Amer. Chem. Soc.*, **64**, 2157 (1942).
(13) W. G. Young and L. J. Andrews, *J. Amer. Chem. Soc.*, **66**, 421 (1944).
(14) W. G. Young, S. H. Sharman, and S. Winstein, *J. Amer. Chem. Soc.*, **82**, 1376 (1960).
(15) S. Oae and C. A. Vanderwerf, *J. Amer. Chem. Soc.*, **75**, 2724 (1953).
(16) A. F. Ferris, K. W. McLean, I. G. Marks, and W. D. Emmons, *J. Amer. Chem. Soc.*, **75**, 4078 (1953).
(17) J. J. Ritter and P. Minieir, *J. Amer. Chem. Soc.*, **70**, 4045 (1948).

TABLE III

A. Temp, 45.0°; 5-ml aliquots; [C_3H_5Br], 0.0400 M; [$AgNO_3$], 0.0100 M; Titers, ml of 0.00625 M KCl

Time, min	0	10.15	15.20	20.34	24.95
Titer	7.88	7.40	7.19	7.02	6.85
$10^2 k_{2.5}$, $M^{-1.5}$ sec^{-1}		2.64	2.60	2.47	2.53
Time, min	30.51	40.02	49.90		
Titer	6.57	6.22	5.92		
$10^2 k_{2.5}$, $M^{-1.5}$ sec^{-1}	2.67	2.69	2.66		

B. Temp, 45.0°; 5-ml aliquots; [C_3H_5Br], 0.0800 M; [$AgNO_3$], 0.160 M; Titers, ml of 0.100 M KCl

Time, min	0	1.30	2.03	2.66	3.28
Titer	7.70	7.30	7.12	7.00	6.83
$10^2 k_{2.5}$, $M^{-1.5}$ sec^{-1}		2.29	2.22	2.11	2.23
Time, min	3.96	4.54	5.18		
Titer	6.71	6.57	6.50		
$10^2 k_{2.5}$, $M^{-1.5}$ sec^{-1}	2.18	2.26	2.15		

C. Temp, 45.0°; 5-ml aliquots; [C_3H_5Br], 0.200 M; [$AgClO_4$], 0.087 M; Titers, ml of 0.0500 M KCl

Time, min	0	1343	2835	4215	5630
Titer	8.70	8.05	7.48	7.04	6.58
$10^5 k_{2.5}$, $M^{-1.5}$ sec^{-1}		1.70	1.62	1.57	1.60
Time, min	9970	11458	12903	14393	
Titer	5.38	5.17	4.84	4.60	
$10^5 k_{2.5}$, $M^{-1.5}$ sec^{-1}	1.63	1.64	1.69	1.69	

D. Temp, 45.0°; 5-ml aliquots; [C_3H_5Cl], 0.0800 M; [$AgNO_3$], 0.0400 M; Titers, ml of 0.0250 M KCl

Time, min	0	1452	2897	4282	8649
Titer	8.04	7.00	6.23	5.50	4.32
$10^4 k_{2.5}$, $M^{-1.5}$ sec^{-1}		0.97	1.03	1.12	1.02
Time, min	10077	11511	12953	14363	
Titer	3.98	3.70	3.48	3.28	
$10^4 k_{2.5}$, $M^{-1.5}$ sec^{-1}	1.03	1.03	1.02	1.01	

bromide 80 times faster than silver perchlorate. The corresponding ratio of 1600 for allyl bromide is some 20 times larger and this suggests that in reaction with silver nitrate nucleophilic assistance is more pronounced for allyl bromide than for the secondary 2-octyl bromide or the tertiary α-brominated ketone, α-bromo-p-phenylisobutyrophenone, where, at 74.0° and for reaction with 0.16 M salt, a ratio of 130 was observed.[10]

The leaving-group effect (Table II) has an average value of 285, which can be compared to a corresponding bromide/chloride ratio of 467 for reaction of 2-octyl halides.[2] While the difference between these ratios is quite small, its direction is consistent with the proposal of more pronounced nucleophilic assistance (less SN1 character) for reaction of the allyl bromide.

At 45°, silver nitrate reacts with allyl bromide about eight times faster than with 2-octyl bromide. Streitwieser[18] reports that, on the average, allyl derivatives react under SN2 conditions some 1600 times faster than isopropyl derivatives; the rates of isopropyl derivatives can be considered to represent an upper limit for the possible SN2 rates of 2-octyl derivatives. In the presence of accompanying electrophilic assistance, the spread between the rates of nucleophilic attack upon allyl bromide and secondary bromides is considerably reduced.

Experimental Section

Materials.—Allyl chloride and allyl bromide were purified by fractional distillation. Silver nitrate was used as received. Acetonitrile and silver perchlorate were purified as described previously.[2]

Kinetic Procedures.—Potentiometric titration to determine the concentration of silver ion remaining in solution and titration of developed acid, in the presence of silver ion, were carried out as described previously.[2] Reaction solutions were prepared by appropriate dilution of concentrated stock solutions within 50-ml volumetric flasks and, after shaking and temperature equilibration, 5-ml aliquots of solution were removed at appropriate time intervals. Heterogeneous catalysis by precipitated silver bromide was shown to be unimportant by allowing a solution initially 0.08 M in both allyl bromide and silver nitrate to react to 50% completion and then showing the subsequent kinetics to be identical with those of a solution initially 0.04 M in each reactant. Integrated 2.5-order rate coefficients were calculated using the appropriate form for the integrated rate equation.[2,19] Four illustrative runs are reported in Table III.

Registry No.—Allyl bromide, 106-95-6; allyl chloride, 107-05-1; silver nitrate, 7761-88-8; silver perchlorate, 7783-93-9; acetonitrile, 75-05-8.

(18) A. Streitwieser, Jr., *Chem. Rev.*, **56**, 571 (1956).

(19) We wish to thank Mr. K. C. Kolwyck for writing a computer program for this operation and Mr. A. Wang for applying the program to the experimental results.

Onium Ions. VIII.[1] Selenonium and Telluronium Ions and Their Comparison with Oxonium and Sulfonium Ions

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A series of trialkyl(aryl)selenonium and telluronium ions are known.[2] However, neither were acidic selenonium (telluronium) ions previously obtained, nor

(1) Part VII: G. A. Olah, J. R. DeMember, Y. K. Mo, J. J. Svoboda, P. Schilling, and J. A. Olah, *J. Amer. Chem. Soc.*, in press.

(2) For a summary and references see H. Reinboldt in "Houben-Weyl Methoden der Organischen Chemie," Vol. 9, Georg Thieme Verlag, Stuttgart, 1955, pp 1034, 1975.

TABLE I
PMR PARAMETERS OF SELENONIUM IONS AND PARENT SELENIDES[b]

Registry no.		Solvent	SeH	H_1	H_2
7783-07-5	H_2Se	CS_2	−0.25		
42423-18-7	H_3Se^+	HF (excess)–BF_3	5.80 (s)		
593-79-3	$(CH_3)_2Se$	SO_2		1.66	
42423-19-8	$(CH_3)_2SeH^+$	FSO_3H–SbF_5–SO_2	4.50 (sp)	2.96 (d, J = 7.0 Hz)	
7101-31-7	$(CH_3)_2Se_2$	SO_2		2.26	
42493-34-5	$(CH_3)_3Se^+$ [a]	SO_2		2.70	
627-53-2	$(CH_3CH_2)_2Se$	SO_2		2.41 (q)	1.30 (t, J = 7 Hz)
42423-22-3	$(CH_3CH_2)_2SeH^+$	FSO_3H–SbF_5–SO_2	4.40 (p)	3.77 (p)	2.00 (t)
42493-35-6	$(CH_3CH_2)_3Se^+$ [a]	SO_2		3.20 (q)	1.40 (t)

[a] As fluorosulfate salts. [b] s = singlet, d = doublet, t = triplet, q = quartet, p = pentuplet, sp = septuplet.

were any of these onium ions studied by nmr spectroscopy.

To extend our study of onium ions, we prepared and studied the selenonium ion (H_3Se^+), as well as a series of acidic secondary alkylselenonium and telluronium ions $R_2Se(Te)H^+$ in superacid solution. We also prepared and isolated a series of trialkylselenonium and -telluronium ions as well as trialkylsulfonium ions as their fluorosulfate salts. A comparative study of all onium ions by pmr spectroscopy was carried out.

Results and Discussion

Hydrogen selenide is very easily oxidized to elemental selenium. As a result, fluoroantimonic acid (HF–SbF_5) and "Magic Acid" (FSO_3H–SbF_5), generally used in preparation of acidic onium ions, cannot be used, since they both oxidize hydrogen selenide. We have found, however, that hydrogen selenide can be protonated without oxidation by HF–BF_3, in excess HF solution.

$$H_2Se + HF + BF_3 \longrightarrow H_3Se^+BF_4^-$$

The selenonium ion formed in this way at −70° showed a singlet pmr absorption at δ 5.8, deshielded by 6.1 ppm from the absorption of parent H_2Se.

Hydrogen selenide used in the preparation of the selenonium ion was obtained by the hydrolysis of aluminum selenide, Al_2Se_3.

Alkyl selenides are much more stable to oxidation than hydrogen selenide, and can be protonated in FSO_3H–SbF_5–SO_2 solution. The dimethylselenonium

$$R_2Se \xrightarrow[SO_2,\ -60°]{FSO_3H\text{–}SbF_5} R_2SeH^+$$

ion (protonated dimethyl selenide) shows in its pmr spectrum the methyl doublet at δ 2.90 (J = 7.0 Hz) and the SeH septet at δ 4.50 (J = 7.0 Hz). A double irradiation experiment showed that the doublet and septet are coupled. The pmr spectrum also shows an unidentified small doublet at δ 3.50 and a singlet at δ 3.80 for the $(CH_3)_2Se$–SbF_5 complex (see subsequent discussion). The diethylselenonium ion shows the methyl triplet at δ 2.00 (J = 7.0 Hz), the methylene quintet at δ 3.77, and the SeH quintet at δ 4.40. Pmr data of the parent selenium compounds and the corresponding selenonium ions are summarized in Table I.

The pmr spectrum of dimethyl selenide in SbF_5–SO_2ClF solution at −60° shows a singlet at δ 3.85 of the donor–acceptor complex, $(CH_3)_2Se$–SbF_5.

The acidic, secondary alkyl selenonium ions are remarkably stable. The pmr spectra showed no significant change from −60 to 65°.

Trialkylselenonium fluorosulfates are conveniently prepared by the reaction of dialkyl selenide and alkyl fluorosulfate, using 1,1,2-trichlorotrifluoroethane as the reaction solvent. Trimethyl selenonium fluorosul-

$$R_2Se + ROSO_2F \longrightarrow R_3Se^+FSO_3^- \ (R = CH_3, C_2H_5)$$

fate thus prepared is a stable, white solid, mp 83–85°, which, when dissolved in liquid sulfur dioxide, exhibits a singlet proton nmr absorption at δ 2.7. Triethylselenonium fluorosulfate was also prepared in the same way. It is also a stable, white solid, mp 25–28°. When dissolved in liquid sulfur dioxide, triethylselenonium fluorosulfate shows the methylene protons at δ 3.2 (quartet) and the methyl protons at δ 1.4 (triplet).

The parent telluronium ion, H_3Te^+, could not be observed in superacid solution of hydrogen telluride, under conditions where the selenonium ion is observed. Alkyl tellurides in FSO_3H–SbF_5 solution using SO_2 as a diluent at −60° show deshielded alkyl proton chemical shifts, as compared with the corresponding dialkyl tellurides themselves in SO_2. This indicates that in this medium the tellurides are protonated, but neither the proton on tellurium nor its coupling was seen. Using HF–BF_3 in excess HF solution both the >TeH^+ proton and its coupling in secondary alkyl telluronium ions can be observed.

$$R_2Te + HF + BF_3 \longrightarrow R_2TeH^+, BF_4^-$$

Alkyltelluronium ions show well-resolved pmr spectra (Table II). The dimethyltelluronium ion (protonated dimethyl telluride) shows the methyl doublet at δ 2.7 ppm (J = 7 Hz) and the TeH septet at δ 1.6 ppm. Similarly, the diethyltelluronium ion (protonated diethyl telluride) shows the methyl triplet at δ 1.9 ppm, the methylene quintet at δ 3.4 ppm, and the TeH multiplet, partially overlapping the methyl triplet, at δ 1.6 ppm.

Trialkyltelluronium fluorosulfates were prepared similarly to the trialkylselenonium salts from dialkyl telluride and alkyl fluorosulfate. Trimethyltelluro-

$$(CH_3)_2Te + CH_3OSO_2F \longrightarrow (CH_3)_3Te^+FSO_3^-$$

nium fluorosulfate prepared in this way is a stable, light yellow salt, mp 130°, which, when dissolved in liquid sulfur dioxide, exhibits a singlet ^1H nmr signal at δ 2.3 ppm. The triethyltelluronium salt could not be isolated, although prepared in solution it is also quite

TABLE II

PMR PARAMETERS OF ALKYLTELLURONIUM IONS AND THEIR PARENT TELLURIDES[a]

Registry no.		Solvent	TeH	H_1	H_2	H_3	H_4
593-80-6	$(CH_3)_2Te$	SO_2		1.60 (s)			
42422-95-7	$(CH_3)_2TeH^+$	FSO_3H–SbF_5–SO_2		3.55 (s)			
	$(CH_3)_2TeH^+$	HF–BF_3	1.6 (sp, J = 7 Hz)	2.70 (d, J = 7 Hz)			
42493-33-4	$(CH_3)_3Te^+OSO_2F^-$	SO_2		2.30 (s)			
627-54-3	$(CH_3CH_2)_2Te$	SO_2		2.40 (q, J = 7.5 Hz)	1.30 (t, J = 7.5 Hz)		
42422-97-9	$(CH_3CH_2)_2TeH^+$	FSO_3H–SbF_5–SO_2		4.35 (q, J = 7.5 Hz)	2.33 (t, J = 7.5 Hz)		
	$(CH_3CH_2)_2TeH^+$	HF–BF_3	1.6 (m)	3.4 (m)	1.9 (t)		
38788-38-4	$(CH_3CH_2CH_2CH_2)_2Te$	SO_2		2.48 (t, J = 7.3 Hz)	1.46 (m)	1.46 (m)	0.80 (t, J = 7.3 Hz)
42422-99-1	$(CH_3CH_2CH_2CH_2)_2TeH^+$	FSO_3H–SbF_5–SO_2		4.33 (t, J = 7.5 Hz)	2.40 (m)	1.96 (m)	1.40 (t, J = 7.5 Hz)

[a] Chemical shifts are in parts per million from external TMS. Coupling constants in hertz are given in parentheses following the multiplicities: s = singlet, t = triplet, q = quartet, sp = septuplet, m = multiplet.

TABLE III

COMPARISON OF PMR PARAMETERS OF RELATED OXONIUM,[e] SULFONIUM,[e] SELENONIUM, AND TELLURONIUM IONS[a]

Registry no.		^+XH	H_1	H_2	$J_{H-\overset{+}{X}H}$
13968-08-6	H_3O^+	10.2			
18155-21-0	H_3S^+	6.60			
	H_3Se^+ [b]	5.80			
17009-82-4	$(CH_3)_2OH^+$	9.05 (sp, J = 3.4 Hz)	4.49 (d)		3.4
18683-32-4	$(CH_3)_2SH^+$	6.52 (sp, J = 8.0 Hz)	3.08 (d)		8.0
	$(CH_3)_2SeH^+$	4.50 (sp, J = 7.0 Hz)	2.96 (d)		7.0
	$(CH_3)_2TeH^+$ [b]	1.6 (sp)	2.70 (d)		7
17009-83-5	$(CH_3CH_2)_2OH^+$	8.61 (p, J = 3.6 Hz)	4.73 (o)	1.53 (t)	3.6
18682-84-3	$(CH_3CH_2)_2SH^+$	6.23 (p, J = 8.0 Hz)	3.57 (p)	1.67 (t)	8.0
	$(CH_3CH_2)_2SeH^+$	4.40 (p, J = 7.0 Hz)	3.77 (p)	2.00 (t)	7.0
	$(CH_3CH_2)_2TeH^+$ [b]	1.6 (m)	3.4 (m)	1.9 (t)	
12116-05-1	$(CH_3)_3O^+$ [c]		4.12 (s)		
42423-04-1	$(CH_3)_3S^+$ [d]		3.90 (s)		
	$(CH_3)_3Se^+$ [d]		2.7 (s)		
	$(CH_3)_3Te^+$ [d]		2.3 (s)		
17950-40-2	$(CH_3CH_2)_3O^+$ [c]		5.1 (q)	2.0 (t)	
42423-05-2	$(CH_3CH_2)_3S^+$ [d]		3.4 (q)	1.8 (t)	
	$(CH_3CH_2)_3Se^+$ [d]		3.2 (q)	1.4 (t)	

[a] In FSO_3H–SbF_5–SO_2 solution at −60°, from capillary TMS. Figures in parentheses show multiplicity of peaks: s = singlet, d = doublet, t = triplet, q = quartet, p = pentuplet, sp = septuplet, o = octet, m = multiplet. [b] In HF (excess)–BF_3 at −60°. [c] In SO_2 at −60° as the hexafluorophosphate salt. [d] In SO_2 at −60° as the fluorosulfate salt. [e] Data summarized in G. A. Olah, A. M. White, and D. H. O'Brien, *Chem. Rev.*, **70**, 561 (1970), and references cited therein.

stable. No cleavage of the ions in solution is observed up to 65°.

The proton on selenium in selenonium ions and on tellurium in telluronium ions is considerably more shielded than the proton on oxygen in the related oxonium ions (δ 7.88–9.21) and the proton on sulfur in the corresponding sulfonium ions (δ 5.80–6.52). For comparison, the chemical shifts of the corresponding oxonium, sulfonium, selenonium, and telluronium ions are summarized in Table III. There is a consistent trend of increasing shielding going from related oxonium to sulfonium to selenonium to telluronium ions (which is particularly significant when considering the directly observed protons on heteroatoms). Charge delocalization and shielding by increasingly heavier atoms is thus indicated.

Experimental Section

Protonation of Dialkyl Selenides and Tellurides in FSO_3H–SbF_5–SO_2.—*Ca.* 200 mg of corresponding dialkyl selenide (telluride) was dissolved in about 2 ml of liquid sulfur dioxide and added, with good stirring, to a solution of 2 ml of 1:1:4 FSO_3H–SbF_5–SO_2 (at about −70°). Part of the resultant solution was transferred by precooled pipette to the nmr tube. A TMS capillary was inserted and pmr spectra were obtained on a Varian Associates Model 56/60A spectrometer.

Protonation of H_2Se in HF–BF_3.—Approximately 100 mg of

H_2Se (prepared in a side-arm test tube by hydrolysis of Al_2Se_3 and condensed in dry N_2 atmosphere directly into the nmr tube) contained in a quartz nmr tube was cooled to −78° in a Dry Ice–acetone bath. To the nmr tube was added 1 ml of anhydrous hydrogen fluoride and the mixture was agitated to form a clear solution. The solution was then saturated with boron trifluoride. A TMS capillary was inserted and the pmr spectrum was obtained at −80°.

Protonation of Alkyl Tellurides in HF–BF_3.—Approximately 1 ml of anhydrous hydrogen fluoride was placed into a quartz nmr tube and cooled to −78° in a Dry Ice–acetone bath. To the nmr tube was added 100 mg of alkyl telluride and the mixture was agitated to form a clear solution. The solution was then saturated with boron trifluoride. A TMS capillary was inserted and the pmr spectrum was obtained at −80°.

Trimethylselenonium Fluorosulfate.—To a solution of 11.4 g (0.1 mol) of methyl fluorosulfate in 50 ml of anhydrous 1,1,2-trichlorotrifluoroethane was added a solution of 9.4 g (0.1 mol) of dimethyl selenide in 50 ml of anhydrous 1,1,2-trichlorotrifluoroethane at room temperature. The mixture was agitated for 10 min and the white precipitate was filtered off. The product was twice washed with 1,1,2-trichlorotrifluoroethane and dried in a stream of dry N_2, mp 83–85°.

Triethylselenonium Fluorosulfate.—The procedure was similar to that used for the preparation of trimethylselenonium fluorosulfate except that 12.8 g (0.1 mol) of ethyl fluorosulfate and 10.8 g (0.1 mol) of diethyl selenide were used. In order to isolate the product it was necessary to extend the reaction time at 0° to 1 hr, after which the white precipitated triethyl selenonium ion was isolated as before, mp 25–28°.

Trimethyltelluronium Fluorosulfate.—The procedure was similar to that used for the preparation of trimethylselenonium fluorosulfate except that 14.3 g (0.1 mol) of dimethyl telluride was used, mp 128–130°. All melting points were determined in sealed capillary tubes. They are dependent on rate of heating (2°/min in the melting range, after having determined it by 10°/min).

Trimethylsulfonium Fluorosulfate and Triethylsulfonium Fluorosulfate.—The preparations used were similar to those of the corresponding selenonium ions, using dimethyl and diethyl sulfide, respectively. $(CH_3)_3S^+SO_3F^-$ had mp 174–176° and $(C_2H_5)_3S^+SO_3F^-$ had mp 25°.

All isolated onium fluorosulfate salts gave correct elemental analyses.

Acknowledgment.—Support of our work by the National Institutes of Health is gratefully acknowledged.

Registry No.—Methyl fluorosulfate, 421-20-5; ethyl fluorosulfate, 371-69-7; dimethyl sulfide, 75-18-3; diethyl sulfide, 352-93-2.

Regiospecific Alkylation of Organocopper Enolates

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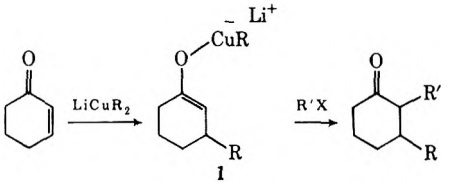
Regiospecific alkylation of lithium and magnesium enolates, generated from enol acetates[1] or the 1,4 addition of Grignard reagents,[2] has been known for some time. The latter process allows the introduction of two different alkyl groups in one synthetic operation. However, to varying degrees, these methods suffer from problems of polyalkylation resulting from proton transfer. A recent paper by Grieco and coworkers prompts us to report our studies in this area.[2d]

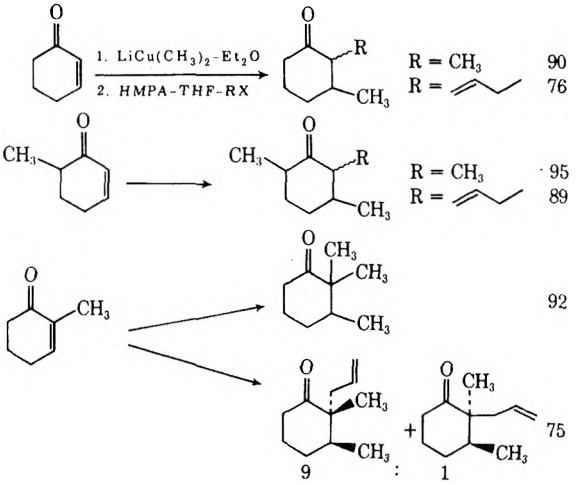
The organocopper enolates (**1**) generated by the addition of lithium dialkylcuprates to enones offer the possibility of eliminating the problems of polyalkylation since these are presumably highly covalent and, therefore, less likely to undergo proton transfer. One also can take advantage of the higher stereoselectivity and generally higher yields of 1,4-addition products produced with the organocopper reagents. We would like to report that these intermediate enolates may be alkylated regiospecifically in unhindered cases without significant amounts of polyalkylation occurring. There has been no direct evidence reported as to the structure of the intermediate (**1**), but in our experience, as



1

well as others,[2e] the unreactivity of **1** under the normal alkylation conditions (methyl iodide, ether, 25°) indicates that the structure is best interpreted as an organocopper enolate. A representative group of cyclohexenones (Table I) which was studied showed that

TABLE I

Reactions	Yield,[a,b] %
	

[a] Distilled yields. [b] Analysis by vpc compared with independently prepared samples.

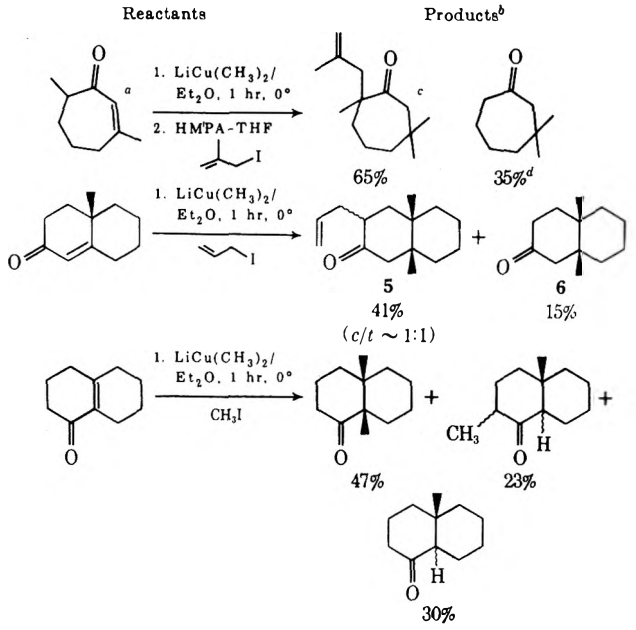
alkylation can be accomplished regiospecifically and in high yield under mild conditions. Significantly, no evidence of polyalkylation was found even in the presence of excess allyl halides.

One limitation of this method (and presumably that of the magnesium enolate also) was encountered. The preservation of enolate regiospecificity during alkylation requires that the rate of alkylation be significantly greater than proton transfer. In the case of β,β-disubstituted enones this criterion is not met. Treatment of β,β-disubstituted enones under the usual conditions for 1,4 addition followed by alkylation resulted in varying amounts of equilibration prior to alkylation. As can be seen (Table II), it appears that reduction

(1) H. O. House and B. M. Trost, *J. Org. Chem.*, **30**, 2502 (1968).

(2) (a) G. Stork, G. L. Nelson, F. Rouesac, and O. Gringore, *J. Amer. Chem. Soc.*, **93**, 3091 (1971); (b) G. Stork, *Pure Appl. Chem.*, **17**, 383 (1968); (c) P. Hudrlik, Ph.D. Dissertation, Columbia University, 1969; (d) P. A. Grieco and R. Finkelhor, *J. Org. Chem.*, **38**, 2100 (1973); (e) G. H. Posner and J. J. Sterling, *J. Amer. Chem. Soc.*, **95**, 3076 (1973).

TABLE II

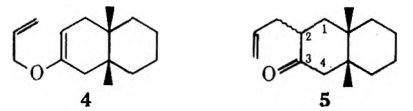


[a] Method of synthesis; see ref 6. [b] Analysis by vpc, compared with independently synthesized samples. [c] Structure assigned by nmr $(CH_3)_2CCH_2C(=O)C(CH_3)CH_2C(=CH_2)CH_3$ protons α to carbonyl, δ 2.61 (1, d, J = 12 Hz), 2.17 (1, d, J = 12 Hz). [d] Isolated yields.

in the size of the alkyl halide increases the ratio of alkylation to equilibration. This suggests that the problem lies in steric hindrance retarding the alkylation rate rather than the covalent nature of the organocopper enolate. To investigate this hypothesis the lithium enolate **2** was generated from enol acetate **3**[3]

2 **3**

(methyllithium, dimethoxyethane, 0°).[1] This enolate was unreactive when treated with excess allyl iodide even in the presence of small amounts of hexamethylphosphoric triamide (HMPA) (~20%). If the medium is made sufficiently polar (~50% HMPA) exclusive O-alkylation results producing enol ether **4** (80%). The structure of **4** was determined by subjecting the enol ether to Claisen rearrangement (at reflux in pyridine) to produce the epimeric **5** (1:1 α/β), identical



4 **5**

with the product of the trapping experiment, whose structure was verified by independent synthesis.[4] This suggests that, when β substitution is present, enolate equilibration, resulting in loss of regiospecificity, will be a major, if not the exclusive, process. This result is not altogether surprising considering the steric conjestion in **2** which hinders approach of reagents to C-4.[5]

(3) J. A. Marshall and A. Hochstetler, *J. Amer. Chem. Soc.*, **91**, 648 (1969).

(4) Prepared by carbomethoxylation of ketone **6**, alkylation ($NaH/CH_2{=}CHCH_2I$), decarbomethoxylation ($LiI \cdot 3H_2O$/collidine); see Experimental Section.

(5) One must also recognize that other steric factors in the fused-ring *cis*-decalin system undoubtedly contribute to the inability to alkylate enolate **2**.

Further studies will be reported elsewhere concerning the reactivity of copper enolates with vinyl ketones.

Experimental Section

All boiling points are uncorrected. Ir spectra were recorded on a Perkin-Elmer IR-257 and are reported in cm^{-1}; nmr spectra were recorded on a Varian T-60 spectrometer and are reported on ppm (δ) downfield from TMS. Tetrahydrofuran (THF), *p*-dioxane, and 1,2-dimethoxyethane (DME) were dried by distillation from lithium aluminum hydride, hexamethylphosphoric triamide by distillation under reduced pressure from calcium hydride, and pyridine from barium oxide.

Representative Alkylation Procedure. Preparation of 2,2,3-Trimethylcyclohexanone.—A solution of lithium dimethylcuprate in anhydrous ether (20 ml) was prepared from purified cuprous iodide (Alfa) (760 mg, 4.0 mmol) and 2.3 *M* methyllithium (Ventron) in ether (3.5 ml, 8.0 mmol). After 15 min at 0°, 2-methyl-2-cyclohexen-1-one[7] (220 mg, 2.0 mmol) in 2 ml of dry Et_2O was added. The mixture was maintained at 0° with stirring for 1 hr. A solution of 5 ml of anhydrous THF and 5 ml of anhydrous HMPA was added, followed by rapid addition of excess methyl iodide (1 ml). The mixture was allowed to warm to room temperature and stirred for 3 hr. The reaction mixture was poured into a 10% aqueous ammonium hydroxide solution, and the organic layer was separated, washed successively with 10% ammonium hydroxide, water, and saturated brine, and dried over magnesium sulfate. Evaporation of the solvent and distillation (Kugelrohr oven 80°) at 24 mm afforded 250 mg (92%) of colorless 2,2,3-trimethylcyclohexanone (lit.[8] bp 90–100° at 100 mm): ir 1705; nmr 1.06 (s, 3), 1.03 (s, 3), 1.02 (broad doublet, 3); vpc[9] analysis indicated ≥97% purity (single peak, retention time 23 min).

Preparation of *cis*- and *trans*-3-Allyl-*cis*-9,10-dimethyl-2-decalone (5).—*cis*-9,10-Dimethyl-2-decalone[3] (180 mg, 1.0 mmol) in 20 ml of anhydrous *p*-dioxane was treated with sodium hydride (washed) (96 mg, 4.0 mmol) and 2.0 ml (23.0 mmol) of dimethyl carbonate. The mixture was heated at 85° for 18 hr under nitrogen, during which time the solution became deep red. The cooled reaction mixture was acidified with aqueous acetic acid and poured into water. After extraction with ether (three times), the combined organic layers were washed with water, dried over magnesium sulfate, and evaporated to an orange oily β-keto ester (204 mg) which exhibited a positive ferric chloride test: ir 1745, 1715, 1655, 1615.

A sample of the crude β-keto ester (473 mg, 1.9 mmol) in anhydrous *p*-dioxane (5 ml) was added to a suspension of sodium hydride (48 mg, 2.0 mmol) in 8 ml of dry dioxane. After gas evolution ceased (35 min), the deep red solution was treated with excess allyl iodide (504 mg, 3.0 mmol), and the mixture was heated at 85° for 3 hr under nitrogen. The products were isolated by ether extraction and dried over magnesium sulfate. Evaporation of the solvent gave 492 mg of crude β-keto ester: ir 1740, 1710, 1640; nmr 6.20–4.80 (m, 3), 3.73 (s, 3), 1.0 (s, 6).

The crude alkylated β-keto ester (492 mg) was added dropwise to a hot (~120°) solution of lithium iodide trihydrate (564 mg, 3.0 mmol) in 30 ml of collidine, and the mixture was heated at reflux under nitrogen for 5 hr. The organic products were isolated by ether extraction as usual to afford a dark oil. A short path distillation (Kugelrohr) at 100° (0.5 mm) gave 318 mg of colorless **5**: ir 1710, 1640, 915; nmr 6.20–4.80 (m, 3), 1.13, 1.00, 0.97, 0.78 (C-9, 10 methyl); mass spectrum P^+ calcd 230.3620, found 230.3615. The spectral data and vpc behavior[10] were identical with the product of the enolate trapping experiment.

***cis*-9,10-Dimethyl-$\Delta^{1,2}$-octal-2-ol Acetate (3).**—A solution of lithium dimethylcuprate, from 11.4 g (60 mmol) of cuprous iodide and 72 ml (120 mmol) of 1.67 *M* methyllithium in 150 ml of anhydrous ether at 0° under nitrogen, was treated with 10-methyl-$\Delta^{1,9}$-octal-2-one (4.92 g, 30 mmol) in 20 ml of anhydrous ether and stirred for 1 hr at 0°. Acetyl chloride (10 ml, excess)

(6) G. Stork, M. Nassim, and B. August, *Tetrahedron Suppl.*, **8**, Part I, 105 (1966).

(7) W. S. Johnson, D. G. Martin, and E. W. Warnhoff, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 161.

(8) E. C. Horning, M. G. Horning, and E. J. Platt, *J. Amer. Chem. Soc.*, **71**, 1771 (1949).

(9) 20% SE-30, 6 ft, 100°.

(10) 20% SE-30, 6 ft, 170°.

was rapidly added at 0° *via* syringe (foaming) and the mixture was warmed to room temperature and stirred (3 hr).

The crude mixture was filtered free of salts and evaporated. Benzene was added and evaporated to remove the last traces of acetyl chloride. Distillation of the residue under reduced pressure [Kugelrohr oven temperature 100° (0.5 mm)][3] afforded 6.2 g (93%) of colorless **3**: ir 1750, 1685; nmr 5.10 (t, J = 2 Hz, 1), 2.20 (s, 3), 1.10 (s, 6).

***cis*-9,10-Dimethyl-$\Delta^{2,3}$-octal-2-ol Allyl Ether (4).**—A solution of methyllithium (1.2 ml of 1.67 M solution, 2.0 mmol) was evaporated under nitrogen stream and 5 ml of anhydrous DME added along with a small amount of triphenylmethane as indicator. A solution of 444 mg (2.0 ml) of **3** in 2 ml of DME was added dropwise at 0° (pale pink color remains). Anhydrous HMPA (5 ml) was added followed by 1 ml (excess) of allyl iodide at room temperature.

The usual ether–water work-up afforded after chromatography on silica gel (10 g) and elution with hexane–benzene (9:1) 325 mg of enol ether **4** (80%): ir 1665, 1645; nmr 6.20–4.80 (m, 4), 1.12 (s, 6); mass spectrum P^+ calcd 230.3620, found 230.3627.

Rearrangement of Enol Ether (4).—Enol ether **4** (30 mg) was heated at reflux in 1 ml of anhydrous pyridine for 20 hr under nitrogen. The pyridine was evaporated *in vacuo* and residue taken up in ether, filtered, and evaporated to afford a yellow oil (25 mg). Analysis of the material by vpc[10] and tlc (silica gel; benzene) established the identity of the major product with allyl ketone (**5**).

Acknowledgments.—Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

Registry No.—**3**, 22738-17-6; **4**, 42449-61-6; *cis*-**5**, 42449-62-7; *trans*-**5**, 42449-63-8; 2,2,3-trimethylcyclohexanone, 39257-08-4; 2-methyl-2-cyclohexen-1-one, 1121-18-2; methyl iodide, 74-88-4; *cis*-9,10-dimethyl-2-decalone, 5523-99-9; allyl iodide, 556-56-9; 10-methyl-$\Delta^{1,9}$-octal-2-one, 826-56-2; acetyl chloride, 75-36-5.

Palladium(II)-π-Allyl Complexes. An Improved Synthesis of Di-μ-chlorobis(1,3,4,5,6-pentamethylbicyclo[2.2.0]hexa-2,5-diene)palladium(II)

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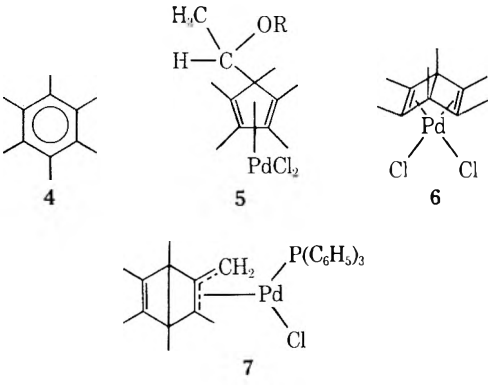
The title compound **1**,[1] derived from hexamethylbicyclo[2.2.0]hexa-2,5-diene (**2**), is unique among π-allyl complexes insofar as it contains two cyclobutene rings.[2] Even so, a convenient synthesis of **1** has not yet been developed. The general procedure of Hüttel and Christ for preparing π-allyl–palladium(II) complexes is not applicable to the synthesis of **1**, since the starting alkene must be heated with palladium(II) chloride (**3**) in 50% aqueous acetic acid containing hydrochloric acid.[3] When **2** is allowed to react with palladium(II) salts and complexes under homogeneous conditions in the presence of hydroxylic solvents, it is either isomerized to hexamethylbenzene (**4**) (neutral media)[4] or converted to cyclopentadiene complexes of general structure **5** (acid media).[5] Shaw and Shaw studied the action of methanolic sodium methoxide on hexamethylbicyclo[2.2.0]hexa-2,5-dienepalladium(II) chloride (**6**) and isolated **1** in low yield (0.41 g of **6** → 0.05 g of **1**).[1] However, this approach to **1** is not only inefficient but hinges on the manipulation of a highly unstable precursor.[6]

We have found that π-allyl complex **1** can be isolated in gram quantities by adherence to a simple procedure: a solution of **2** (commercially available and thermally stable[7]) in dichloromethane is allowed to stir heterogeneously with anhydrous **3** at room temperature, the critical reaction variable being time. In one experiment, 10.0 g of **2** and 2.0 g of **3** gave, after *504* hr and column chromatography on alumina, 2.3 g of **1**, a 62% yield of that complex based on starting palladous chloride.

The structure of **1** was confirmed by its elemental composition (C, H, Cl), by comparison of its spectral parameters (ir, nmr) with those published for the authentic compound,[1] and by its known conversion to triphenylphosphine complex **7**.[1]

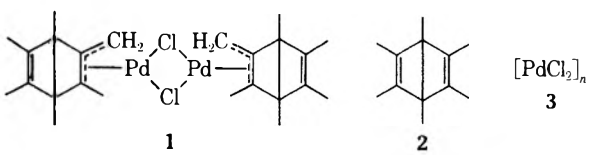


4 **5** **6**

7

The formation of **1** proceeds simultaneously with some aromatization of **2** and with reduction of some Pd(II) to Pd(0). Material balances and descriptions of chromatography fractions for two runs are given in Table I. Run 1 was monitored by nmr spectroscopy, and the relative quantities (based on 100 mol %) of **1**, **2**, and **4** as a function of time were determined; the results are displayed in Figure 1. After about 300 hr both the aromatization of **2** and the formation of **1** were nearly complete, presumably because all starting palladous chloride had been consumed.

It seems plausible that π-allyl complex **1** arises *via* loss of hydrogen chloride from intermediate complex **8**[8] while aromatization of **2** is promoted by "monomeric" palladium(II) chloride.



1 **2** **3**

(1) B. L. Shaw and G. Shaw, *J. Chem. Soc. A*, 602 (1969).

(2) The structure, synthesis, and chemistry of palladium(II)–π-allyl complexes have been reviewed in detail; see P. M. Maitlis, "The Organic Chemistry of Palladium," Academic Press, New York, N. Y., 1971, pp 175–252.

(3) See ref 2, pp 176–177.

(4) C. J. Attridge and S. J. Maddock, *J. Organometal. Chem.*, **26**, C65 (1971).

(5) P. V. Balakrishnan and P. M. Maitlis, *J. Chem. Soc. A*, 1721 (1971).

(6) H. Dietl and P. M. Maitlis, *Chem. Commun.*, 759 (1967).

(7) W. Schäfer and H. Hellman, *Angew. Chem., Int. Ed. Engl.*, **6**, 518 (1967).

(8) See ref 2, p 112, for a discussion of Pd(II) complexes of this structural type.

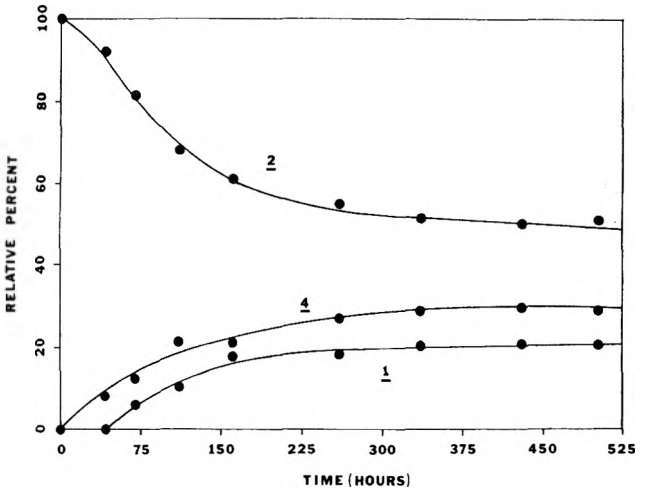
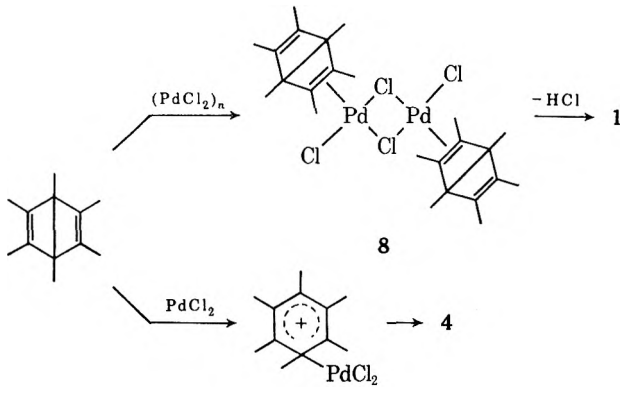


Figure 1.—Relative mole per cents of π-allyl complex 1, hexamethyl (Dewar benzene) (2), and hexamethylbenzene (4) as a function of time.

TABLE I

Fraction	Solvent	Compd	Appearance	Run 1[a] yield, g	Run 2[b] yield, g
A	Pentane	2	Clear liquid	2.20	2.42
B	Pentane	4	White solid	1.46	3.69
C	Methanol	Unknown	Orange oil	0.63	2.10
D	Methanol	1	Yellow solid	0.33	0.40
E	Dichloromethane	1	Yellow solid	1.0	1.93
F		Pd(0)	Black solid	0.09	0.19

[a] 5.0 g of hexamethyl (Dewar benzene); 1.0 g of palladous chloride. [b] 10.0 g of hexamethyl (Dewar benzene); 2.0 g of palladous chloride.



Experimental Section

General.—Nmr spectra were recorded on a Varian Model A-60 nmr spectrometer relative to internal TMS. Melting points are uncorrected. The elemental composition of 1 was determined by Galbraith Laboratories, Inc., Knoxville, Tenn. Hexamethylbicyclo[2.2.0]hexa-2,5-diene was obtained from K & K Laboratories and palladous chloride from Alpha Inorganics.

Reaction of Hexamethylbicyclo[2.2.0]hexa-2,5-diene (2) with Palladous Chloride. Run 1.—A mixture of 5.0 g (30.9 mmol) of 2 in 25 ml of dichloromethane and 1.0 g (5.6 mmol) of anhydrous palladium(II) chloride was allowed to stir for 502 hr at room temperature. At periodic intervals, aliquots were removed for nmr analysis and the relative mole per cents of 1, 2, and 4 were determined by integration of appropriate proton resonances. Each aliquot was returned to the reaction vessel immediately after its nmr spectrum had been recorded. At the end of this time, the reaction mixture was centrifuged, and 0.09 g (15%) of Pd(0) was isolated. The supernatant liquid was subsequently concentrated (30°, 75 mm) to a crude oil (5.78 g) which was resolved by column chromatography on *ca.* 120 g of basic alumina (refer to Table I).

Run 2.—A mixture of 10.0 g (61.8 mmol) of 2 in 50 ml of dichloromethane and 2.0 g (11.2 mmol) of anhydrous palladium(II) chloride was allowed to stir undisturbed for 504 hr at room temperature and worked up as described above. Products and yields are summarized in Table I.

Characterization of Di-μ-chlorobis(1,3,4,5,6-pentamethylbicyclo[2.2.0]hexa-2,5-diene)palladium(II) (1).—π-Allyl complex 1 was recrystallized from benzene–petroleum ether (bp 30–60°) to give yellow crystals: mp 159–160° (lit.[1] mp 170–174°); ir (KBr) 1685 cm^{-1} (C=C); nmr (C_6H_6, TMS) τ 6.22 (d, 1), 8.45 (s, 3), 8.55 (m, 3), 8.66 (s, 3), 8.72 (m, 3), 8.75 (s, 3).

Anal. Calcd for $[C_{12}H_{17}PdCl]_2$: C, 47.60; H, 5.62; Cl, 11.73. Found: C, 47.60; H, 5.74; Cl, 11.96.

Reaction of 1 with Triphenylphosphine.—A solution of 0.30 g (0.5 mmol) of 1 and 0.26 g (1 mmol) of triphenylphosphine in 20 ml of dichloromethane was allowed to stir for 1 hr at room temperature. The solvent was subsequently removed *in vacuo*, and the crude product (0.40 g) was recrystallized from dichloromethane–petroleum ether to give 7 as pale yellow crystals: mp 145–147° (lit.[1] mp 150–158°); nmr (C_6D_6) τ 7.1 (d, 1), 7.37 (d, 1), 8.10–8.25 (m, 6), 8.45 (m, 3), 8.64 (m, 3), 8.81 (s, 3). The nmr spectrum compares favorably with that reported for 7 in ref 1.

Registry No.—1, 33111-51-2; 2, 7641-77-2; 3, 7647-10-1.

Synthesis and Stereochemistry of Arylidenepyruvic Acids and Derived *trans*-α-Bromocinnamic Acids[1]

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New arylidenepyruvic acids (**1a–f**) were prepared through their salts.[2a] The appropriate aldehyde condensed rapidly with pyruvic acid in the presence of base. Table I lists the yellow acids and their methyl esters. Furylidenepyruvic acid formed polymeric brown tars on heating and on dry storage.

Reimer and coworkers[3] concluded that their phenyl-substituted benzylidenepyruvic acids all had the trans configuration, since, on oxidation with hydrogen peroxide in basic solution, *trans*-cinnamic acids were the only products. Our nmr evidence supports the trans structure of 1, Ar = C_6H_5.

The acids 1 readily formed crystalline, somewhat unstable dibromides (2) (only one enantiomer shown). By analogy with *trans*-cinnamic acid dibromide (6), we assume them to be erythro compounds.[4] When the dibromides 2 are heated with water, hydrogen bromide is lost with the formation of stable, colorless β-bromoenol lactones (3). Lacking uv and ir spectra, Reimer identified these as their less stable yellow β-bromo keto

(1) Acknowledgment is made to the National Science Foundation for Undergraduate Research Participation Summer Grants, and to the National Cancer Institute, Columbia University, New York, N. Y., for grants in support of this research.

(2) (a) E. D. Stecher and H. F. Ryder, *J. Amer. Chem. Soc.*, **74**, 4392 (1952); (b) E. D. Stecher and A. Clements, *ibid.*, **76**, 503 (1954); (c) E. D. Stecher, F. Dunn, and E. Gelblum, *ibid.*, **79**, 4748 (1957); (d) E. D. Stecher and E. Gelblum, *J. Org. Chem.*, **26**, 2693 (1961); (e) E. D. Stecher, A. Waldman, and D. Fabiny, *ibid.*, **30**, 1800 (1965).

(3) M. Reimer, *et al.*, *J. Amer. Chem. Soc.* (1926–1941). See Table III for specific references.

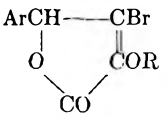
(4) (a) E. Grovenstein, Jr., and D. E. Lee, *J. Amer. Chem. Soc.*, **75**, 2640 (1953); (b) S. J. Cristol and W. P. Norris, *ibid.*, **75**, 632, 2645 (1953).

TABLE I

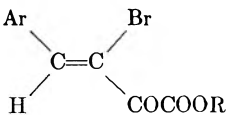
Registry no.	Ar	Mp, °C	Formula	Calcd, % C	Calcd, % H	Calcd, % Hal or S	Found, % C	Found, % H	Found, % Hal or S
			ArCH=CHCOCOOH[a]						
42393-06-6	4-ClC_6H_4[b]	139–140	$C_{10}H_7ClO_3$	57.02	3.35	16.84	57.00	3.24	16.98
42393-07-7	2,4-$Cl_2C_6H_3$	138–139	$C_{10}H_6Cl_2O_3$	49.01	2.47	28.93	48.92	2.63	28.94
42393-08-8	3,4-$Cl_2C_6H_3$	135–136	$C_{10}H_6Cl_2O_3$	49.01	2.47	28.93	49.26	2.83	28.64
42393-09-9	2-C_4H_3O[c]	114–115	$C_8H_6O_4$	57.83	3.64		57.77	3.77	
42393-10-2	2-C_4H_3S[d]	127–128	$C_8H_6O_3S$	52.74	3.31	17.60	52.61	3.33	17.55
			ArCH=CHCOCOOCH$_3$[a]						
42393-11-3	4-ClC_6H_4	116–117	$C_{11}H_9ClO_3$	58.81	4.04	15.78	59.09	4.05	16.02
42393-12-4	2,4-$Cl_2C_6H_3$	83–84.5	$C_{11}H_8Cl_2O_3$	50.99	3.11	27.37	50.92	3.10	27.41
42393-13-5	3,4-$Cl_2C_6H_3$	119–121	$C_{11}H_8Cl_2O_3$	50.99	3.11	27.37	51.03	3.38	27.60
42393-14-6	2-C_4H_3O	64.5–65.5	$C_9H_8O_4$	60.00	4.48		60.58	4.56	
42393-15-7	2-C_4H_3S	111–113.5	$C_9H_8O_3S$	55.09	4.11	16.34	55.28	4.02	16.40

[a] All compounds are yellow and have characteristic spectra.[2b,d,e] 4-Nitrobenzylidenepyruvic acid and ester have already been described by us.[2c] [b] S. Bodforss, *Justus Liebigs Ann. Chem.*, 609, 117 (1957), analyzed a monohydrate. No melting point was given. [c] E. Friedmann, *Helv. Chim. Acta*, 14, 783 (1931), reported and analyzed this acid, mp 112°. He found it to decompose unless protected from light. [d] R. E. Miller and F. F. Nord, *J. Org. Chem.*, 16, 1720 (1951), analyzed a hydrate which when dry melted at 128–128.5°.

TABLE II[a]



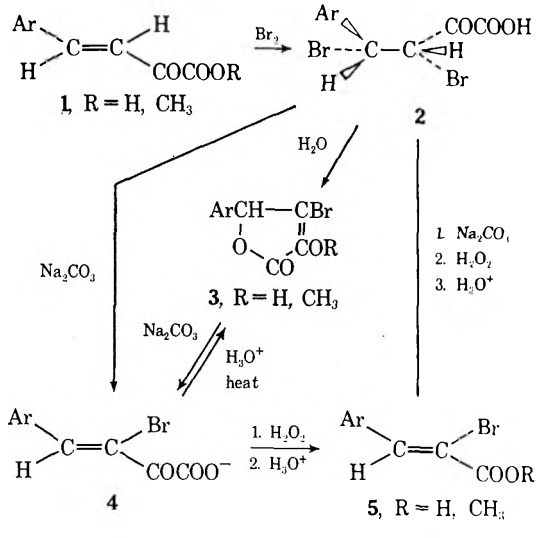
A (R = H, CH_3)



B (R = H, CH_3)

Registry no.	Ar	Compd	R	Mp, °C	Formula	Calcd, % C	Calcd, % H	Calcd, % Hal	Found, % C	Found, % H	Found, % Hal
42393-16-8	4-ClC_6H_4	A	H	140–140.5	$C_{10}H_6BrClO_3$	41.48	2.09	39.85	41.76	2.19	39.74
42393-17-9	4-ClC_6H_4	A	CH_3	95.5–96.5	$C_{11}H_8BrClO_3$	43.52	2.66	38.00	43.41	2.43	38.01
42393-18-0	2,4-$Cl_2C_6H_3$	A	H	145–146	$C_{10}H_5BrCl_2O_3$	37.07	1.55	46.56	37.12	1.77	46.48
42393-19-1	2,4-$Cl_2C_6H_3$	A	CH_3	135–136.5	$C_{11}H_7BrCl_2O_3$	39.09	2.09	44.62	39.30	2.02	44.55
42393-20-4	3,4-$Cl_2C_6H_3$	A	H	145–147.5	$C_{10}H_5BrCl_2O_3$	37.07	1.55	46.56	37.37	1.68	
42393-21-5	3,4-$Cl_2C_6H_3$	A	CH_3	126–127	$C_{11}H_7BrCl_2O_3$	39.09	2.09	44.62	38.97	2.18	44.70
42393-22-6	4-$CH_3OC_6H_4$	A	CH_3	78.5–80	$C_{12}H_{11}BrO_4$	48.19	3.71	26.72	48.46	3.94	26.70
42393-23-7	4-$CH_3OC_6H_4$	B	CH_3	77–77.5	$C_{12}H_{11}BrO_4$	48.19	3.71	26.72	48.52	3.72	
42393-24-8	2-C_4H_3S	B	CH_3	77–79.5	$C_9H_7BrO_3S$	39.15	2.92	28.94	39.45	2.84	29.18
42393-25-9	4-$NO_2C_6H_4$	A	H	161–161.5	$C_{10}H_6BrNO_5$	40.02	2.02	26.64	40.24	2.12	26.67
42393-26-0	4-$NO_2C_6H_4$	A	CH_3	115–116	$C_{11}H_8BrNO_5$	42.17	2.53	25.45	41.98	2.50	25.22
42393-27-1	4-$NO_2C_6H_4$	B	CH_3	100.5–101	$C_{11}H_8BrNO_5$	42.17	2.53	25.45	42.10	2.47	25.30

[a] β-Bromoenols and enol ethers (A) are colorless. For the ethers, uv max (CH_3OH) 223–230 nm (ε 15,000–20,000), ir ($CHCl_3$) *ca.* 1785 cm^{-1} (lactone C=O). Bromo keto esters (B) are pale yellow, uv max (CH_3OH) 340–347 nm (ε 17,000–21,000), ir ($CHCl_3$) *ca.* 1680 (C=O) and 1725 cm^{-1} (ester C=O).



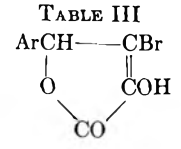
a, Ar = 4-ClC_6H_4 d, Ar = 4-$NO_2C_6H_4$
b, Ar = 2,4-$Cl_2C_6H_3$ e, Ar = 2-C_4H_3O
c, Ar = 3,4-$Cl_2C_6H_3$ f, Ar = 2-C_4H_3S

acid tautomers (**4**, acid form). The latter may be the first products formed, and then may change rapidly in the hot acid solution to the less soluble lactones. We separated the tautomer mixture by extraction of an ether solution with pH 7.2 phosphate buffer to remove the stronger keto acid. The methyl esters of the β-bromobenzylidenepyruvic acids are stable compounds, and were prepared by the action of diazomethane on the few stable acids, or by long boiling of the lactones with methanol–hydrogen chloride. The lactone ethers are also stable (see Table II).

In 1954[2b] we offered clear physical proof (uv and ir spectra and pK values) of the tautomeric structures (**3** and **4**, acid form) both of which had been isolated by Reimer in the *p*-bromo and *p*-ethoxy series. Because the erroneous β-bromobenzylidenepyruvic acid structures still appear in the reference literature (Beilstein, Chemical Abstracts, 1926–1941), we have listed in Table III corrected structures for Reimer's compounds, with specific references.

Reimer isolated two pure sodium enolates (**3**, Ar = 4-BrC_6H_4, 4-$C_2H_5OC_6H_4$; R = Na) which were not oxidized directly by hydrogen peroxide. In weak base their solutions slowly turned yellow and, on acidification, pure β-bromobenzylidenepyruvic acids were recovered. These were then oxidized rapidly by hydrogen peroxide at pH 8.5 to *trans*-α-bromocinnamic acids

TABLE III

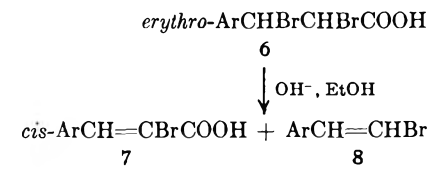


Registry no.	Ar[a]	Mp, °C
42393-28-2	C_6H_5[b]	131–132
42393-29-3	4-$CH_3OC_6H_4$[b]	136
42393-30-6	2-$CH_3OC_6H_4$[c]	173
42393-31-7	3-$CH_3OC_7H_4$[d]	166–167
42393-32-8	3,4-$(CH_3O)_2C_6H_3$[e]	158
32544-95-9	4-$CH_3C_6H_4$[f]	182
42393-34-0	4-BrC_6H_4[g]	144–145
42393-35-1	4-$C_2H_5OC_6H_4$[h]	148–149
42393-36-2	5-Br, 2-CH_3O-C_6H_3[c]	210
42393-37-3	6-Br, 3-CH_3O-C_6H_3[d]	137–139
42393-38-4	6-Br, 3,4-$(CH_3O)_2$-C_6H_2[e]	162–164

[a] These enol lactone structures replace the tautomeric β-bromobenzylidenepyruvic acid structures erroneously assigned by Reimer. See footnote 2b. [b] M. Reimer, *J. Amer. Chem. Soc.*, **48**, 2454 (1926); **58**, 1108 (1936). [c] M. Reimer and M. Howard, *ibid.*, **50**, 2508 (1928). [d] M. Reimer and H. Kamerling, *ibid.*, **55**, 4646 (1933). [e] M. Reimer, E. Tobin, and M. Schaffner, *ibid.*, **57**, 212 (1935). [f] M. Riemer and E. Chase, *ibid.*, **60**, 2470 (1938). [g] M. Reimer and E. Tobin, *ibid.*, **62**, 2518 (1940). [h] M. Reimer and A. L. Morrison, *ibid.*, **63**, 238 (1941).

(**5**) as the sole products. Although the mechanism of lactone formation and opening to **4** is still obscure, the above results indicate that **4** is the species which is oxidized with preservation of its trans configuration.

By this method Reimer and coworkers prepared the α-bromocinnamic acids (**5**) from most of the lactones in Table III. To justify the assignment of trans structure they were often able to prepare the corresponding cis acids (lower melting point)[5] by the method of Sudborough and Thompson.[6] These authors used potassium hydroxide in 95% ethanol to eliminate hydrogen bromide from *erythro*-2,3-dibromo-3-phenylbutyric acid (*trans*-cinnamic acid dibromide) (**6**, Ar = C_6H_5). *cis*-α-Bromocinnamic acid (**7**) predominated in a ratio of 7:1, a result explicable by a trans E2 elimination of hydrogen bromide. A competing reaction, and at times



the only one, was the concerted elimination of carbon dioxide and hydrogen bromide from **6** to form β-bromostyrene (**8**). The mechanism of styrene formation has since been worked out in detail[4] and will be discussed later.

In new experiments we converted benzylidenepyruvic acid dibromides (**2**) directly to *trans*-α-bromocinnamic acids (**5**) without the isolation of lactone as intermediate. Thus **2**, Ar = 4-$CH_3OC_6H_4$, in dilute sodium carbonate solution, after standing for 1 day or after heating at 80° for 1 hr, was oxidized with hydrogen peroxide. The sole product, *trans*-4-methoxy-α-bromocinnamic acid, was the same as that obtained from the corresponding lactone under the same conditions (mp 189–190°).[7] A concerted trans E2 elimination of hydrogen bromide from **2** in basic solution would have formed the cis isomer of **4**, which on oxidation and acidification would have yielded the *cis*-α-bromocinnamic acid as the only product. To explain our results we suggest tentatively that in dilute aqueous base a bromide ion is lost from **2** (E1 mechanism) forming the carbonium ion intermediate (4-$CH_3OC_6H_4C^+HCHBr$-$COCOO^-$) which then loses a proton to form the more stable trans anion (**4**, Ar = 4-$CH_3OC_6H_4$). This is then oxidized to the trans acid **5**.

We observed that *trans*-α-bromocinnamic acids containing strong electron-withdrawing groups (**5**, Ar = 2,4-$Cl_2C_6H_3$, 3,4-$Cl_2C_6H_3$, and 4-$NO_2C_6H_4$) prepared in this way (Table IV) were not as pure as those in which Ar = C_6H_5 or 4-$CH_3OC_6H_4$, and were probably contaminated by cis isomer. We proved that *trans*-4-nitro-α-bromocinnamic acid was accompanied by 31% of the cis isomer. We suggest that strong electron-withdrawing groups render the intermediate carbonium ion less stable, so that some trans E2 elimination takes place even in the aqueous medium, forming the cis acid.

Further research is needed to substantiate this mechanism, but some support is offered by striking parallels with results in the conversion of **6**, Ar = C_6H_5 (sodium salt), to β-bromostyrene (**8**). In detailed studies two teams of investigators[4] found that nonpolar solvents favored a concerted trans elimination of bromide ion and carbon dioxide with 75–100% of the styrene product present as the cis isomer of **8**. In aqueous solutions 80% of the styrene product was trans isomer. To explain the latter, both teams postulate the loss of a bromide ion to form a carbonium ion intermediate ($C_6H_5C^+HCHBrCOO^-$), which then loses carbon dioxide. As in our experiments, electron-withdrawing substituents on benzene, such as the nitro group, reversed the stereochemistry, forming the pure cis isomer. They explained this result as due to the effect of the nitro group in causing carbonium ion destabilization, thus favoring concerted trans elimination even in aqueous solution.

Experimental Section[8]

Potassium Arylidenepyruvates.—These yellow salts were prepared[2a] from 1 equiv each of purified pyruvic acid and of aldehyde and 1.5 equiv of KOH in 50% aqueous CH_3OH. For the more soluble salts formed from liquid aldehydes, the solvent was pure CH_3OH. Sodium carbonate in 50% CH_3OH was used for the preparation of sodium 4-nitrobenzylidenepyruvate as was done previously for the 3-nitro salt.[2e] Purity (85–100%) was determined in pH 7.5 phosphate buffer (0.1 *M*) at the uv max (300–337 nm). Yields were 60–85%. Contaminants were potassium pyruvate and the less reactive chloroaldehydes. After one recrystallization from 50% CH_3OH the purity was 95–100%.

Arylidenepyruvic Acids (**1**, **Table I**).—These were prepared in 90% yield from the alkali salts.[2e] Recrystallization was from

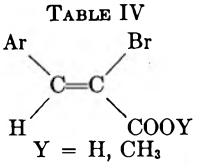
(5) The configurations of *cis*- and *trans*-α-bromocinnamic acids have been well established by physical and chemical reactions. Reference 4a includes a literature review. J. Klein and S. Zitrin, *J. Org. Chem.*, **35**, 666 (1970), report the following uv spectra: trans acid, λ_{max}^{EtOH} 273 mμ (ε 19,000), 217 (17,000); cis acid, λ_{max}^{EtOH} 254 mμ (ε 9600), 210 (12,000).

(6) J. J. Sudborough and K. J. Thompson, *J. Chem. Soc.*, **83**, 673 (1903).

(7) M. Reimer, *J. Amer. Chem. Soc.*, **48**, 2454 (1926); **58**, 1108 (1936).

(8) Most melting points are corrected and were determined in a Herschberg total immersion apparatus, or a Thomas-Hoover apparatus, with the sample inserted 15° below the melting point. Analyses were by Micro-Tech, Skokie, Ill. Uv spectra were obtained on a Beckman DU or DBG instrument, ir spectra on a Beckman IR-5. Nmr spectra were taken on a Varian T-60 instrument, using TMS as internal standard.

TABLE IV



Y = H, CH_3

Registry no.	Ar	Y	Mp, °C	Formula	Calcd, % C	Calcd, % H	Calcd, % Hal	Found, % C	Found, % H	Found, % Hal
42393-39-5	4-ClC_6H_4	H[a]	203–204	$C_9H_6BrClO_2$	41.34	2.31	44.14	41.24	2.45	43.91
42393-40-8	4-ClC_6H_4	CH_3[a]	74–75	$C_{10}H_8BrClO_2$	43.61	2.93	41.91	43.81	2.82	42.01
42393-41-9	2,4-$Cl_2C_6H_3$	H	223–223.5	$C_9H_5BrCl_2O_2$	36.52	1.70	50.95	36.50	1.78	50.85
42393-42-0	2,4-$Cl_2C_6H_3$	CH_3	74.5–75.5	$C_{10}H_7BrCl_2O_2$	38.73	2.28	48.65	38.80	2.36	48.47
42393-43-1	3,4-$Cl_2C_6H_3$	H	188–189	$C_9H_5BrCl_2O_2$	36.52	1.70	50.95	36.93	1.79	50.90
42393-44-2	3,4-$Cl_2C_6H_3$	CH_3	102.5–104	$C_{10}H_7BrCl_2O_2$	38.73	2.28	48.65	38.56	2.34	48.87
42393-45-3	4-$NO_2C_6H_4$	H[b]	211.5–212	$C_9H_6BrNO_4$	39.72	2.22	29.36	39.84	2.26	29.38
42393-46-4	4-$NO_2C_6H_4$	CH_3[b]	126.5–127	$C_{10}H_8BrNO_4$	41.97	2.82	27.93	42.23	2.88	27.97

[a] S. Reich, J. Araus, J. Potok, and H. Tempel, *Helv. Chim. Acta*, **3**, 798 (1920), reported an acid, mp 256°, methyl ester mp 82°. [b] P. Pfeiffer, *Ber.*, **47**, 1758 (1914), reported a yellow acid, mp 210°, and an off-white methyl ester, mp 131–132°.

benzene or benzene–acetone. As furylidenepyruvic acid formed tars in concentrated solution it was crystallized from a dilute ether–petroleum ether (bp 30–60°) mixture: uv max (CH_3OH) 300–333 nm (ε 15,000–20,000); ir ($CHCl_3$) *ca.* 1680 (C=O), 1770 cm^{-1} (acid C=O); nmr (CCl_4) δ 7.6 (d, 1, J = 16 Hz), 6.4 (d, 1, J = 16 Hz), trans protons in **1**, Ar = C_6H_5.

Methyl Arylidenepyruvates (1, R = CH_3, Table I).—These yellow esters were prepared with diazomethane in ether solution.[2e] A second method for all except methyl furylidenepyruvate was to reflux the acid or its salt for 30 min with CH_3OH–3% HCl: uv max (CH_3OH) 313–348 nm (ε 13,000–22,000); ir ($CHCl_3$) *ca.* 1680 (C=O), 1740 cm^{-1} (ester C=O).

3,4-Dibromo-4-aryl-2-oxobutyric Acids (2).—The acids **1** added bromine rapidly[2e] in a stirred, dry $CHCl_3$ or ether solution or suspension at 30°. One half of the solvent was blown off with dry N_2 and the rest was removed below 40° in a vacuum evaporator. The oily residue crystallized slowly on adding a little benzene or hexane. Products were often unstable to recrystallization, and some decomposed rapidly in moist air and more slowly on dry storage. Yields were 60–88% and the melting point varied with the speed of heating. Occasionally, when the dibromide did not crystallize overnight, the oil was dehydrobrominated directly.

3-Bromo-2,4-dihydroxy-4-arylcrotonic Acid γ-Lactones (3, Table II).—These colorless compounds were prepared as previously described[2b,c] by stirring the melt of the dibromides **2** in water at 75° for 30–60 min. The suspension was cooled slowly and left overnight to increase conversion of the less stable keto acid (**4**, acid form) to the lactone. Isolation of the anhydrous product was best achieved by transfer to ether solution and removal of the stronger keto acid[2b] with pH 7.2 buffer (0.1 M KH_2PO_4–Na_2HPO_4). This acid was then recovered separately by acidification and extraction into ether. Lactone fractions gave red colors with $FeCl_3$ solution, and keto acid and keto ester fractions gave 2,4-dinitrophenylhydrazone precipitates.[9] Spectra were characteristic[2b] (see Table II). Ether solutions were dried ($MgSO_4$), evaporated, and then dried azeotropically with benzene on a rotating vacuum evaporator. Crystallization was from benzene–petroleum ether. The yellow keto acid tautomer was more soluble and less stable to heat than the colorless lactone. Typical yields follow: Ar = 4-ClC_6H_4, 75% lactone + 12.5% keto acid; 2,4-$Cl_2C_6H_3$, 38% lactone + 27.5% keto acid; 4-$NO_2C_6H_4$, 34.6% lactone + 19% keto acid.

3-Bromo-4-hydroxy-2-methoxy-4-arylcrotonic Acid γ-Lactones (Table II).—The β-bromoenol lactones were easily converted to colorless lactone ethers with diazomethane in ether or THF solution. Brief treatment of the lactone with CH_3OH–3% HCl had no effect, but boiling for 1 hr with this reagent produced the methyl β-bromobenzylidenepyruvate. Recrystallization was from benzene or benzene–petroleum ether; uv spectra in CH_3OH had a maximum from 223 to 230 nm (ε 15,000–20,000); ir spectra in CH_3CN included a single lactone C=O band at about 1785 cm^{-1}. These are characteristic.[2b]

β-Bromobenzylidenepyruvic Acids (4 Acid Form, Table II).—These were prepared from the benzylidenepyruvic acid dibromides **2** or from the lactones **3** by heating at 80° for 1 hr in dilute 2% Na_2CO_3 solution at pH 8.5 or on standing at 30° for 1–3 days. The deep yellow solutions were cooled, extracted once with ether to remove a trace of insoluble β-bromostyrene, and then acidified with HCl in the presence of fresh ether. The acids were isolated as usual using a vacuum evaporator, and were crystallized from benzene or benzene–petroleum ether. These pale yellow acids are less stable than the corresponding enol lactone tautomers. Reimer isolated the *p*-bromo and *p*-ethoxy acids but found that they were converted to the lactones on heating above the melting point, or on dry storage, or on standing in acid solution. We found that *p*-methoxy-β-bromobenzylidenepyruvic acid, obtained by hydrolysis of its methyl ester, changed gradually to pure lactone during isolation and recrystallization from benzene.

Crude *p*-chloro-β-bromobenzylidenepyruvic acid was obtained in 69% yield and melted at 133.5–135°. It was oxidized without further purification to the *trans*-α-bromocinnamic acid. The crude *p*-nitro acid was formed in 53.5% yield and melted at 139.5–141°. After recrystallization the melting point was 144.5–145.5°, but the analysis, though satisfactory in N, was 1% high in C and 1% low in Br. The methyl ester analyzed correctly.

Methyl β-Bromobenzylidenepyruvates (Table II).—These yellow esters were prepared from the few stable β-bromo keto acids, with diazomethane in ether solution, or preferably from the lactones **3** boiled for 1 hr with CH_3OH–3% HCl. Those prepared by the latter method were transferred to ether and washed free of reagents. Uv spectra in CH_3OH have a maximum at 340–347 nm (ε 17,000–21,000); ir spectra have two strong C=O bands at about 1730 and 1680 cm^{-1}. These are characteristic.[2b,c]

***trans*-α-Bromocinnamic Acids (5, Table IV). A. From the Lactones 3.**—One gram of lactone was dissolved in 45 ml of 1.5% K_2CO_3 solution and heated for 1 hr at 75° to convert it to **4**. After cooling to 30°, 15 ml of 3% H_2O_2 solution neutralized with K_2CO_3 was added. The yellow solution paled rapidly, and after 2–16 hr when no further paling took place on adding 10% more H_2O_2, it was acidified with HCl. Yields were 60–80% and in most cases the melting point indicated high purity of the *trans*-α-bromocinnamic acid formed.

B. From the β-Bromobenzylidenepyruvic Acids.—When these could be isolated in stable form, they were dissolved in 1.5% K_2CO_3 solution and oxidation with 3% H_2O_2 as above took place rapidly without previous heating.

C. From the Dibromides 2.—It was found possible to omit isolation of an intermediate bromo keto acid or lactone. In a typical preparation 10 g (0.027 mol) of *p*-chlorobenzylidenepyruvic acid dibromide in 210 ml of 2% K_2CO_3 solution was heated at 75° for 1 hr. Then, at 30°, 150 ml of neutral 3% H_2O_2 was added. After 15 hr there was sometimes a small precipitate of the sodium cinnamate combined with a trace of 4-chloro-β-bromostyrene. The whole product was transferred to ether with HCl and eventually crystallized from benzene, yield 3.05 g, mp 203–204°, with a second crop of 1.05 g, mp 200.5–201.5° (total yield 53%), of pure *trans*-4-chloro-α-bromocinnamic acid as the sole product. By contrast, the *trans*-3,4-dichloro acid separated as a pure first crop (39%, mp 184–186°) and an impure second crop (21%, mp 138–139°). Similar results were obtained

(9) Reference 2e, footnote 9.

with 2,4-dichloro-α-bromocinnamic acid. *trans*-4-Nitro-α-bromocinnamic acid separated as a pure yellow first crop (56.5%, mp 211–212°) and impure further crops which contained off-white cis isomer. The acids could not be separated by further recrystallization or by column chromatography. Smooth separation of the two isomers in the form of their methyl esters (prepared by diazomethane in ether solution) was effected on a SiO_2 column, using benzene as eluting solvent. Thus a 17.5% yield of the cis isomer was recovered (31% of the total product) as the methyl ester, mp 79–80.[10]

Anal. Calcd for $C_{10}H_8BrNO_4$: C, 41.97; H, 2.82; Br, 27.93. Found: C, 41.94; H, 2.70; Br, 27.79.

Methyl *trans*-α-Bromocinnamates (Table IV).—These were prepared from the acids with diazomethane in ether solution; ir spectra in $CHCl_3$ contained a single C=O band at 1730–1715 cm^{-1}.

(10) P. Pfeiffer (Table IV, footnote *b*) reports mp 79–81°.

Isolation of 2-(4-Hydroxybenzyl)malic Acid from *Petalostemon gattingeri*

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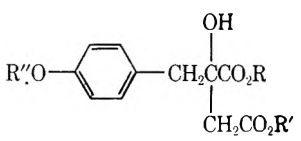
Petalostemon gattingeri (Heller) Heller (Leguminosae) is endemic to cedar glades and codominant in open glade communities.[1] In these glades, certain plant species display a degree of exclusion from the vicinity of *Petalostemon* that might be attributable, at least in part, to metabolites of the plant or to decomposition products of plant litter. Such a pattern is particularly noticeable in the case of *Arenaria patula* Michx., germination of which, under experimental conditions, was reduced by an aqueous extract of *Petalostemon* shoot material. Various aspects of the ecological relationship between *Petalostemon* and *Arenaria* in the cedar glade ecosystem, including allelopathic effects, have been studied and will be reported elsewhere. An effort has been made to isolate and characterize the inhibitory compound(s) from shoot material of *Petalostemon*, results of which are presented here.

An extract of shoots of *Petalostemon gattingeri* was washed with ether and subjected to acidic treatment in order to cleave glycosidic and other labile linkages. Column chromatography on silica gel of ether-soluble material obtained from the hydrolysis gave a crystalline solid, mp 167–168°, which has been assigned structure **1** on the basis of spectral and chemical evidence.



1, R = R′ = R″ = H
2, R = R′ = CH_3; R″ = H
3, R = R′ = R″ = CH_3
9, R = R″ = CH_3; R′ = H

(1) E. Quarterman, *Ecology*, **31**, 234 (1950).

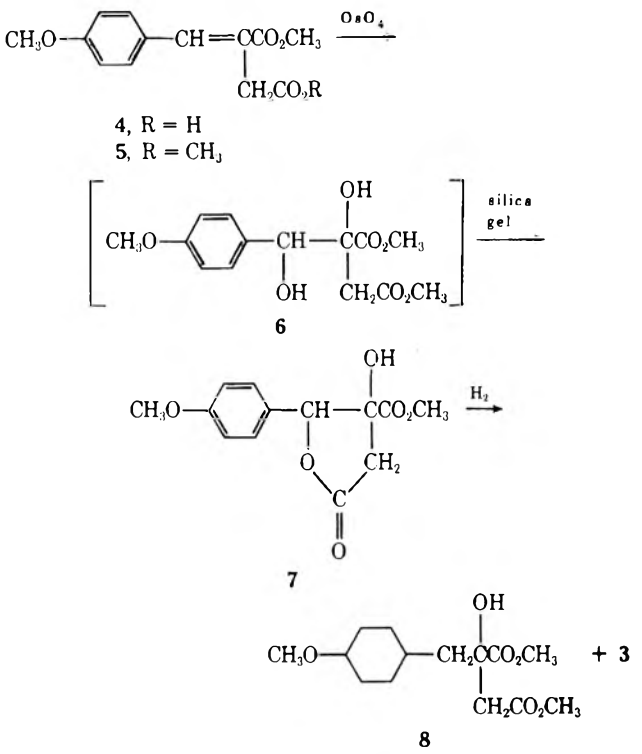
The ultraviolet spectrum of **1** closely resembled that of *p*-cresol. The infrared spectrum suggested the presence of carboxyl (1725 cm^{-1}) and hydroxyl (3110–3480 cm^{-1}) groups. A molecular ion was observed at *m/e* 240 in the mass spectrum; high-resolution mass measurement indicated the molecular formula $C_{11}H_{12}O_6$. The base peak of the spectrum (*m/e* 107) corresponded to hydroxybenzyl (or hydroxytropylium) ion. The nmr spectrum contained an AA′XX′ pattern, indicating that the compound contained a para-substituted ring. The aromatic protons of *p*-cresol produce a similar pattern. The nmr spectrum of **1** also contained a broad hydroxyl resonance at δ 6.33 ppm, representing four protons, and two methylene resonances. One of these was essentially a singlet (δ 3.03), whereas the other appeared as an AB pair of doublets (δ 2.54 and 2.94) with a coupling constant (geminal) of 16 Hz. Both pairs of methylene protons must have diastereotopic environments resulting from the presence of a chiral center in the molecule, although it is only clearly observed in the latter case. These data account for all of the protons and functionality of **1** and can be accommodated only by that assignment.

Additional proof of the structure was obtained chemically. Compound **1** was shown to be a dibasic acid by formation of diester **2** on treatment with diazomethane. The mass spectrum of **2** indicated that two methyl groups had been added (*m/e* 268, $m \cdot^+$). The nmr spectrum of **2** confirmed that two of the hydroxyl groups had been transformed into methoxyls. Treatment of **2** with methyl iodide and potassium carbonate gave phenolic ether **3** (*m/e* 282, $m \cdot^+$). Attempted derivatization of the tertiary hydroxyl group was unsuccessful. Acetic anhydride in pyridine failed to give the acetate derivative. Furthermore, **3** was not dehydrated by methanolic hydrogen chloride, *p*-toluenesulfonic acid, or potassium acid sulfate.

An independent synthesis of **3** was undertaken for a final confirmation of the structure of **1**. Ester acid **4**, obtained by a Stobbe condensation,[2] was treated with diazomethane to give diester **5**. Oxidation of **5** with osmium tetroxide gave glycol **6**, which proved to be unstable, lactonizing to **7** during chromatography on silica gel. Hydrogenolysis, catalyzed by palladium on charcoal, proceeded very slowly in methanol; the reaction gave a mixture of two products. Repeated efforts to resolve this mixture by liquid chromatography were unsuccessful. However, an adequate separation was obtained by glc; direct introduction of the glc effluent into the mass spectrometer revealed that one of the components was the desired ester **3** and was identical with **3** prepared from **1**. The other reduction product was tentatively assigned as hexahydroaryl derivative **8**. The nmr and ultraviolet spectra of the unresolved mixture of **3** and **8** confirmed these assignments. The latter spectrum indicated that **3** and **8** were present in approximately a 60:40 ratio.

It is surprising that hydrogenolysis gave diester **3** instead of ester acid **9**. A probable explanation is traces of acid in the palladium on charcoal catalyzed esterification, methanol being the solvent. Hydrogenolysis of benzylic alcohols and their esters can often be accomplished without subsequent reduction of the

(2) A. M. El-Abbady and L. S. El-Assal, *J. Chem. Soc.*, 1024 (1959).



4, R = H
5, R = CH_3

6

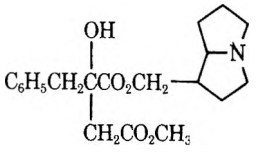
7

8

aromatic ring;[3] however, in the present case the rate of the initial reduction was not favorable.

Compound **1** was assayed for germination inhibition with seeds of *Arenaria patula*. A 0.4 m*M* aqueous solution of **1** produced no inhibition of germination, but a 5 m*M* solution caused 70% inhibition. It is somewhat less efficacious than the crude plant extract, suggesting that a glycoside or other conjugate of **1** is more inhibitory than **1** itself, or that other inhibitory compounds are present in the plant. No evidence is available to indicate whether **1** is conjugated with a sugar or with some other moiety. Several other fractions of the plant extract inhibited germination of *Arenaria*, but their compositions have not been determined.

2-Benzylmalic acid has been postulated as an intermediate in the biosynthesis of gluconasturtiin;[4] phalaenopsin (**10**), which is a conjugate of 2-benzylmalic acid with an alkaloid, has been isolated.[5]



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Experimental Section

Melting points were taken with open capillaries. Nmr spectra were obtained with a 60-MHz Varian A-60 spectrometer. Low-resolution mass spectra were determined with an LKB-9000 mass spectrometer using direct insertion and glc inlet systems; high-resolution mass measurements were performed by the Mass Spectrometry Laboratory, Battelle Memorial Institute, Columbus, Ohio. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Isolation of 2-(4-Hydroxybenzyl)malic Acid (1).—The shoots of *Petalostemon gattingeri* (600 g), gathered in June 1969 and 1970, from a cedar glade near Lavergne, Tenn.,[6] were cut into small pieces and ground with 750 ml of H_2O in a Waring Blendor for 5 min. The mixture was filtered through cloth and then through Celite. The resulting solution was washed with three 200-ml portions of Et_2O and refluxed for 2 hr in the presence of 30 g of the acidic form of Dowex 50 W-X8 ion exchange resin. The mixture was cooled, filtered, and extracted with Et_2O for 48 hr in a continuous extractor. The ethereal solution was dried ($MgSO_4$) and evaporated *in vacuo*. The residual brown oil (0.7 g) was partitioned on silica gel. Elution with hexane containing increasing amounts of Et_2O gave a number of minor components followed by the major one, a greenish white solid (0.295 g). Rechromatography of the solid gave 0.195 g of 2-(4-hydroxybenzyl)malic acid (**1**): mp 161–166 and 167–168° after recrystallization from Et_2O–hexane; ν (KBr) 3480–3100, 1725 cm^{-1}; λ_{max} (95% EtOH) 228 nm (ϵ 9630), 276 (2490), 282 (2480), 320 (830); nmr (CD_3COCD_3) δ 2.54 (1 H, d, J = 16 Hz, 3- or α-CH_2), 2.94 (2 H, approx s, α- or 3-CH_2), 3.03 (1 H, d, J = 16 Hz, 3- or α-CH_2), 6.33 (4 H, broad, hydroxyls), 6.66–7.20 (4 H, AA′XX′ multiplet, p-C_6H_4); mass spectrum m/e 240 (1.9%, m·+), 222 (1.0), 150 (1.6), 132 (2.2), 131 (2.7), 107 (100), 94 (2.2), 77 (17.3), 51 (5.9), 43 (8.1); mass measurement by high-resolution mass spectroscopy m/e 240.0633 (calcd for $C_{11}H_{12}O_6$, m/e 240.0633). The crystals were dried at 25° (0.5 mm) over P_2O_5 prior to elemental analysis; the analysis indicated the presence of residual H_2O.

Anal. Calcd for $C_{11}H_{12}O_6$: C, 55.00; H, 5.04. Calcd for $C_{11}H_{12}O_6 \cdot {}^1/_3H_2O$: C, 53.66; H, 5.19. Found: C, 53.60; H, 5.18.

The Et_2O wash of the original aqueous plant extract was shown by nmr and glc-mass spectroscopy to contain terpenes; diacid **1** was not detected.

Treatment of 1 with CH_2N_2.—A solution of **1** (10.5 mg, 0.044 mmol) in Et_2O was treated for 15 min with excess CH_2N_2. Chromatography of the product on silica gel (Et_2O–hexane elution) gave dimethyl 2-(4-hydroxybenzyl)malate (**2**) as an oil (8.1 mg, 70%): ν (neat) 1750–1730 cm^{-1}; nmr[7] ($CDCl_3$) δ 2.68 (1 H, d, J = 16 Hz, 3- or α-CH_2), 2.95 (2 H, ~s, α- or 3-CH_2), 3.08 (1 H, d, J = 16 Hz, 3- or α-CH_2), 3.69 (3 H, s, OCH_3), 3.77 (3 H, s, OCH_3), 6.69–7.16 (4 H, AA′XX′ multiplet, p-C_6H_4); mass spectrum m/e 268 (0.8%, m·+), 250 (45), 218 (3.1), 209 (17), 191 (3.3), 177 (7.8), 161 (9.0), 135 (11), 107 (100), 101 (22), 77 (22), 69 (4.8), 59 (14).

Treatment of 2 with CH_3I.—Diester **2** (60 mg, 0.22 mmol), CH_3I (150 mg), and anhydrous K_2CO_3 (100 mg) were refluxed in 5 ml of acetone for 7 hr to give, after microdistillation [bp 100° (0.04 mm)], 60.6 mg (95%) of dimethyl 2-(4-methoxybenzyl)-malate (**3**) as an oil: ν (CCl_4) 1745 cm^{-1}; λ_{max} (CH_3OH) 225 nm (ϵ 10,200), 276 (1700), and 283 (1500); nmr[7] ($CDCl_3$) δ 2.64 (1 H, d, J = 16 Hz, 3- or α-CH_2), 2.94 (2 H, s, α- or 3-CH_2), 3.07 (1 H, d, J = 16 Hz, 3- or α-CH_2), 3.68 (3, s, OCH_3), 3.75 (3, s, OCH_3), 3.79 (3 H, s, OCH_3), and 6.76–7.23 (4 H, AA′XX′ multiplet, p-C_6H_4); mass spectrum m/e 282 (1.4%, m·+), 264 (5.6), 223 (2.8), 191 (1.4), 149 (1.4), 121 (100), 101 (2.2), 91 (2.6), 77 (4.2), 59 (2.5).

Anal. Calcd for $C_{14}H_{18}O_6$: C, 59.57; H, 6.43. Found: C, 59.22; H, 6.42.

Oxidation of 5 with OsO_4.—Diester **5** (1.04 g, 3.94 mmol), prepared by esterification of **4**[2] with CH_2N_2, was treated with OsO_4 (1.0 g, 3.94 mmol) in C_6H_5N (30 ml) for 22 hr at 20°. The adduct was decomposed by treatment with $NaHSO_3$ (1.9 g) in aqueous pyridine. The mixture was diluted with H_2O and extracted with $CHCl_3$. The extract was dried ($MgSO_4$) and evaporated. Chromatography of the residue on silica gel (Et_2O–hexane elution) gave 0.889 g (86%) of 3-carbomethoxy-3-hydroxy-4-(4-methoxyphenyl)butyrolactone (**7**) as a glass that crystallized on lengthy standing at 5°: mp 80–87 and 88.5–90° after recrystallization from CH_2Cl_2–pentane; ν (KBr) 1740 cm^{-1}; λ_{max} (EtOH) 228 nm (ϵ 11,600), 274 (1370), 282 (11,700); nmr ($CDCl_3$) δ 2.88 (1 H, d, J = 18 Hz, CH_2), 3.23 (1 H, d, J = 18 Hz, CH_2), 3.48 (3 H, s, OCH_3), 3.79 (3 H, s, OCH_3), 4.36 (1, s, OH), 5.42 (1 H, s, CH), 6.76–7.27 (4 H, AA′XX′ multiplet, p-C_6H_4); mass spectrum m/e 266 (5.6, m·+), 207 (1.4),

(3) J. F. W. McOmie in "Advances in Organic Chemistry: Methods and Results," Vol. 3, R. A. Raphael, E. C. Taylor, and H. Wynberg, Ed., Interscience, New York, N. Y., 1963, pp 191–294.

(4) T. Geissman and D. H. G. Crout, "Organic Chemistry of Secondary Plant Metabolism," Freeman, Cooper & Co., San Francisco, Calif., 1969, p 91.

(5) S. Brandage and B. Luning, *Acta Chem. Scand.*, **23**, 1151 (1969); S. Brandage, I. Granelli, and B. Luning, *ibid.*, **24**, 354 (1970).

(6) Comparable specimens are located in the Vanderbilt University herbarium.

(7) The sample was too small to observe the hydroxyl signal(s).

179 (2.9), 137 (100), 136 (15), 135 (22), 130 (7.1), 109 (5.8), 102 (12), 77 (5.7); mass measurement by high-resolution mass spectroscopy *m/e* 266.0807 (calcd for $C_{13}H_{14}O_6$, 266.0790).

Anal. Calcd for $C_{13}H_{14}O_6$: C, 58.65; H, 5.30. Found: C, 58.80; H, 5.43.

Hydrogenolysis of 7.—Lactone **7** (889 mg, 3.3 mmol) and 300 mg of 10% Pd/C in CH_3OH (50 ml) was treated with H_2 (3.7 atm) for 9 days. The solution was filtered and evaporated *in vacuo*. Chromatography of the residue on silica gel (Et_2O–hexane elution) gave 586 mg of an oil which, although homogeneous by tlc, was shown by nmr and uv spectra to be a mixture of **3** and another component, provisionally assigned as **8**. Preparative tlc, preparative glc, distillation, and further column chromatography failed to separate the components, but an adequate separation on an analytical scale could be obtained by glc. Direct introduction of the glc column effluent into the mass spectrometer gave spectra of the two components.[8] The spectrum of **3** was identical with the spectrum of trimethylated **1**. The spectrum of the second component was consistent with the assignment as dimethyl 2-(4-methoxycyclohexylmethyl)malate (**8**): mass spectrum *m/e* 288 (0.9%, $m^{\cdot+}$), 270 (1.3), 256 (13), 229 (15), 197 (77), 179 (15), 165 (16), 161 (16), 123 (72), 117 (36), 101 (34), 95 (55), 81 (100), 71 (78).

Assay of Germination Inhibition.—The test consisted of placing 100 *Arenaria patula* seeds on Whatman No. 1 filter paper in each of three Petri plates. Each plate was moistened with 5 ml of an aqueous solution of **1**. Controls employed 5 ml of distilled, deionized H_2O. After 2 weeks at 20° under a 12/12 photoperiod, germination counts were made. In a test using a 0.4 m*M* solution of **1**, germination in both the control and the test samples was 75%; however, with a 5 m*M* solution of **1**, 22% germination was observed as compared with 73% in the control samples. The latter represents an inhibition of 70%.

Acknowledgment.—This work was supported by a grant (GB-12439) from the National Science Foundation.

Registry No.—**1**, 42151-32-6; **2**, 42151-33-7; **3**, 42151-34-8; **4**, 42151-35-9; **5**, 42151-36-0; **7**, 42151-37-1; **8**, 42151-38-2; CH_2N_2, 334-88-3; CH_3I, 74-88-4; OsO_4, 20816-12-0.

(8) A trace of a third component (*m/e* 296) was observed; it is probably an ethyl analog of **7**.

A Short Nonannelation Approach to Synthesis of Oxygenated Eudesmane Sesquiterpenes

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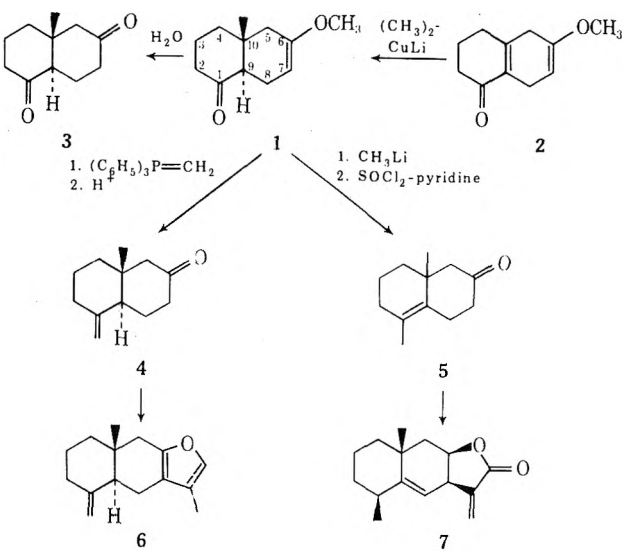
Many syntheses of eudesmane sesquiterpenes have been accomplished within the past 10 years.[1] Most approaches have involved constructing the bicyclic carbon framework of the decalin system *via* Robinson annelation reactions.[2] Although such annelation reactions have been thoroughly studied and reviewed, they are often low-yield procedures which require substantial experimentation before optimum conditions can be achieved, and they may be subject to stereochemical complications when substituents are present in either the Michael donor or the Michael acceptor. Recently β-eudesmol, a simple member of the eudesmane class of sesquiterpenes, has been prepared *via* a stereoselective nonannelation approach starting with a naphthalene derivative.[3] We have extended and generalized this type of approach so that various oxygenated (*e.g.*, furan and lactone) eudesmane sesquiterpenes can be prepared stereoselectively from naphthalene precursors.

SCHEME I



Our primary synthetic effort involved developing a direct nonannelation synthesis of keto enol ether **1**. This compound was attractive for several reasons: (1) the C-1 carbonyl group would allow epimerization (and possibly alkylation) at C-9; (2) the C-1 carbonyl group could be easily transformed into a variety of other functional groups (*e.g.*, methylene or tertiary alcohol); (3) the masked C-6 carbonyl group would allow regioselective alkylation of the *trans*-decalin system at C-7; and (4) the C-6 oxygen atom could be removed or incorporated into furan or lactone rings as, for example, in atractylon (**6**)[4] or alantolactone (**7**).[5] We selected dienone **2** as immediate precursor to keto enol ether **1** because dienone **2** is easily prepared from 6-methoxy-1-tetralone,[6] and it was expected to undergo a conjugate addition reaction with lithium dimethylcuprate(I) to produce enol ether **1** (Scheme I).[7]

Dienone **2**, prepared in 40% yield from 6-methoxy-

(1) (a) J. A. Marshall, M. T. Pike, and R. D. Carroll, *J. Org. Chem.*, **31**, 2933 (1966); (b) D. C. Humber, A. O. Pinder, and R. A. Williams, *ibid.*, **32**, 2335 (1967); (c) R. K. Mathur and A. S. Rao, *Tetrahedron*, **23**, 1259 (1967); (d) C. H. Heathcock and T. R. Kelly, *ibid.*, **24**, 1801 (1968); (e) D. L. Robinson and D. W. Theobald, *ibid.*, **24**, 5227 (1968); (f) J. A. Marshall and M. T. Pike, *J. Org. Chem.*, **33**, 435 (1968); (g) H. Minato and T. Nagasaki, *J. Chem. Soc. C*, 622 (1968); (h) J. Naemura and M. Nagasaki, *Tetrahedron Lett.*, 33 (1969); (i) for stereochemical relationships in the eudesmane group of sesquiterpenes, see W. Cocker and B. H. McMurry, *Tetrahedron*, **8**, 181 (1960); (j) for a review of synthetic approaches to decalin sesquiterpenes, see J. M. Mellor and S. Munavelli, *Quart. Rev., Chem. Soc.*, **18**, 270 (1964).

(2) (a) E. C. DuFeu, F. J. McQuillin, and R. Robinson, *J. Chem. Soc.*, 53 (1937); (b) E. D. Bergmann, D. Ginsburg, and R. Pappo, *Org. React.*, **10**, 179; (c) J. A. Marshall and W. I. Fanta, *J. Org. Chem.*, **29**, 2501 (1964); (d) B. P. Mundy, *J. Chem. Educ.*, **50**, 110 (1973).

(3) (a) J. W. Huffman and M. L. Mole, *J. Org. Chem.*, **37**, 13 (1972). (b) See also R. G. Carlson and E. G. Zey, *ibid.*, **37**, 2468 (1972), for a similar approach. (c) After submission of this manuscript, we learned that Professor R. B. Miller was also pursuing this approach: R. B. Miller and R. D. Nash, *J. Org. Chem.* **38**, 4424 (1973).

(4) (a) H. Minato and I. Horibe, *J. Chem. Soc. C*, 1575 (1967); (b) H. Minato and T. Nagasaki, *ibid.*, 1866 (1966); (c) H. Minato and T. Nagasaki, *Chem. Commun.*, 377 (1965).

(5) J. A. Marshall, N. Cohen, and A. R. Hochstetler, *J. Amer. Chem. Soc.*, **88**, 3408 (1966).

(6) (a) A. J. Birch, J. A. K. Quartey, and H. Smith, *J. Chem. Soc.*, 1768 (1952); (b) H. O. House and R. W. Bashe, II, *J. Org. Chem.*, **30**, 2942 (1965).

(7) G. H. Posner, *Org. React.*, **19**, 1 (1972).

1-tetralone,[6] was found to be contaminated by about 6% of a conjugated dienone.[8,9]

Conjugate addition reactions of organocopper reagents have been used effectively to attach a wide variety of hydrocarbon groups to the β-carbon atom of many types of α,β-ethylenic ketones.[7,10] Dienone **2**, however, poses an unusual problem; the C-5 hydrogen atoms, which are allylic and vinylogously α to the C-1 carbonyl group, may be sufficiently acidic to be abstracted by the organocopper reagent. It was gratifying, therefore, that reaction of dienone **2** with a large excess of lithium dimethylcuprate produced conjugate adduct **1**, which was isolated in approximately 50% yield by preparative tlc using pH 7 buffered plates. The nature of the remaining material formed in this reaction was elusive; deuterium oxide quenching of the reaction in the hope of recovering deuterated dienone **2** led to adduct **1** and an unstable oil and treating the crude reaction products with lithium dimethylcuprate led to no dramatic increase in the amount of conjugate adduct **1**. It should be noted that enolate ions formed *via* organocopper conjugate addition to enones have been trapped as enol acetates and enol silyl ethers[10f,11] which can be converted to lithium enolates;[11b,12] thus indirect alkylation at C-9 may be possible.[13,14]

To confirm the gross structure of conjugate adduct **1**, this liquid enol ether was hydrolyzed in good yield to crystalline diketone **3**. 1,6-Decaldione **3** has not been reported previously.

Treating conjugate adduct **1** with methylenetriphenylphosphorane[15] led upon acidic work-up directly to enone **4**, which had spectral properties identical with those of enone **4** prepared previously by Minato and Horibe.[4,16] Reaction of adduct **1** with methyllithium and then thionyl chloride in pyridine[17] led directly to enone **5**, which had spectral data identical with those of enone **5** prepared previously by Marshall, Cohen, and Hochstetler.[5,18]

The stereochemistry of conjugate adduct **1**, of the corresponding diketone **3**, and of methylene derivative **4** was determined by nuclear magnetic resonance (nmr) spectral data according to the method of Williamson, Howell, and Spencer.[19] The data are summarized in Table I. Since the $\Delta W_{1/2}$ values are substantially larger than 0.25 associated with *cis*-9-methyldecalins and are in the range of those reported for *trans*-9-methyldecalins, the methyldecalins **1**, **3**, and **4** are assigned trans ring fusions. It is noteworthy that *trans*-10-methyldecalin (**1**) is formed stereoselectively under the conditions of the conjugate addition reaction.

TABLE I
NMR DATA FOR ANGULAR METHYL GROUPS IN KETONES **1**, **3**, AND **4**

Ketone	Chemical shift, ppm	$\Delta W_{1/2}$,[a] Hz
1	0.80	1.01
3	0.78	1.58
4	0.72	1.05

[a] The $\Delta W_{1/2}$ values were determined by using the formula $\Delta W_{1/2} = W_{1/2}(CH_3) - W_{1/2}(TMS)$, where $W_{1/2}(CH_3)$ is the half band width of the angular methyl group and $W_{1/2}(TMS)$ is the half band width of the TMS signal.

Because enone **4** has previously been converted to isoalantolactone and atractylon (**6**)[4] and enone **5** has previously been transformed to telekin and alantolactone (**7**),[5] our synthesis of **4** and **5** constitutes a formal total synthesis of these four furanoeudesmane and eudesmanolide sesquiterpenes. In addition, keto enol ether **1** might be a useful intermediate in synthesis of other sesquiterpenes containing the 10-methyl-1,6-decaldione functionality or derivatives thereof.

Experimental Section

General.—Melting points are uncorrected. The ir spectra were determined with a Perkin-Elmer Model 457 ir spectrophotometer. Nmr spectra were determined with either a Varian A-60 or a Jeol MH-100 spectrometer. The mass spectra were determined on a Hitachi Model RMU6 high-resolution mass spectrometer. Microanalyses were performed by Chemalytics, Inc., Tempe, Ariz. Analytical gas–liquid chromatography utilized a Varian Model 1200 gas chromatograph with flame ionization detector. Preparative gas–liquid chromatography utilized a Varian Model 90-P gas chromatograph with a thermal conductivity detector. Thin layer chromatography plates were prepared from silica gel PF-254 which was obtained from EM Laboratories, Inc.

Methyllithium was obtained as a ~2.0 *M* solution in ether from Alpha Inorganics and was titrated[20] before each use. Cuprous iodide was obtained from Fisher Scientific Co. and was extracted with tetrahydrofuran and then dried *in vacuo* before use. Triphenylmethylphosphonium bromide was obtained from Aldrich Chemical Co. and was used without further purification. Potassium *tert*-butoxide was obtained from Alpha Inorganics and was sublimed before use.

Preparation of Keto Enol Ether 1.—To a 50-ml three-neck flask fitted with two serum stoppers and a T-joint with a nitrogen filled balloon attached was added 5.05 g (26.8 mmol) of cuprous iodide. The flask was alternately evacuated while being flamed and purged with nitrogen from the balloon. To the flask was added 19.0 ml of anhydrous ether *via* hypodermic syringe and the flask was cooled to 0°. To this stirred suspension of cuprous iodide in ether was added 27.0 ml of a 1.98 *M* (53.6 mmol) methyllithium, followed by 600 mg (3.37 mmol) of enone **2** in 2.0 ml of anhydrous ether. The reaction mixture was allowed to

(8) A. J. Birch and K. P. Dastur, *Tetrahedron Lett.*, 4195 (1972).

(9) M. V. R. Koteswara Rao, G. S. Khrishna Rao, and S. Dev, *Tetrahedron*, **22**, 1977 (1966).

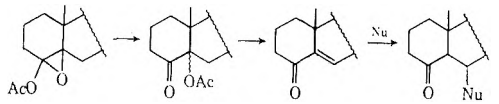
(10) Several organocopper conjugate additions to octalones have been reported: (a) A. J. Birch and R. Robinson, *J. Chem. Soc.*, 501 (1943); (b) A. J. Birch and M. Smith, *Proc. Chem. Soc., London*, 356 (1962); (c) J. A. Marshall and H. Roebke, *J. Org. Chem.*, **33**, 840 (1968); (d) J. A. Marshall, W. I. Fanta, and H. Roebke, *ibid.*, **37**, 1016 (1966); (e) R. E. Ireland, M. I. Dawson, J. Bordner, and R. E. Dickerson, *J. Amer. Chem. Soc.*, **92**, 2568 (1970); (f) E. Piers, W. de Waal, and R. Britton, *ibid.*, **93**, 5113 (1971); (g) R. S. Matthews and R. E. Meteyer, *Chem. Commun.*, 1576 (1971).

(11) (a) K. Heusler, J. Kebrle, C. Meystre, H. Ueberwasser, P. Wieland, G. Anner, and A. Wettstein, *Helv. Chim. Acta*, **42**, 2043 (1959); (b) G. Stork and F. Hudrlick, *J. Amer. Chem. Soc.*, **90**, 4462 (1968).

(12) (a) H. O. House, "Modern Synthetic Reactions," 2nd ed, W. A. Benjamin, New York, N. Y., 1972, Chapter 9; (b) H. O. House, M. Gall, and H. O. Ohmstead, *J. Org. Chem.*, **36**, 2361 (1971), and references therein.

(13) Depending on the stereochemistry of C-9 alkylation, an entry might be available into the *cis*-9,10-dimethyldecalin system, which is characteristic of valerane sesquiterpenes.

(14) Epoxidation of the initial enol acetate, rearrangement, and elimination of HOAc might lead ultimately to C-8 functionalized decalins.



(15) M. Schlosser and K. F. Christmann, *Angew. Chem., Int. Ed. Engl.*, **3**, 636 (1964).

(16) We thank Professor Minato for providing us with a copy of his ir spectrum of enone **4**.

(17) Thionyl chloride in pyridine is known to favor formation of endocyclic rather than exocyclic olefins: R. M. Coates and R. L. Sowerby, *J. Amer. Chem. Soc.*, **94**, 5386 (1972).

(18) We thank Professor Marshall for providing us with copies of his ir and nmr spectra of enone **5**.

(19) K. L. Williamson, T. Howell, and T. Spencer, *J. Amer. Chem. Soc.*, **88**, 325 (1966).

(20) G. M. Whitesides, C. P. Casey, and J. K. Krieger, *J. Amer. Chem. Soc.*, **93**, 1379 (1971).

stir for 2.0 hr at 0° after which time it was quenched by cautiously pouring it into 100 ml of saturated aqueous sodium bicarbonate. The entire mixture was vacuum filtered to remove all solids, the ether layer was separated, and the aqueous portion was extracted with two additional 20-ml portions of ether. The combined ethereal solutions were washed with 50 ml of brine, dried (anhydrous potassium carbonate), and concentrated *in vacuo* to afford 654 mg of a yellow oil. Preparative tlc on pH 7 buffered silica plates[21] eluted with 9:1 carbon tetrachloride:ethyl acetate gave three distinct bands. The fastest migrating band ($R_f \approx 0.5$) was collected to afford 307 mg (48%) of ketone **1** as a pale yellow oil. This material was not further purified for use in subsequent reactions: nmr ($CDCl_3$) δ 0.80 (s, 3 H), 1.20–2.80 (m, 11 H), 3.45 (s, 3 H), 4.52 (unresolved m, 1 H); ir ($CHCl_3$) 1715 cm^{-1} (C=O).

10-Methyldecal-1,6-dione (3).—Preparative tlc of ketone **1** on a nonbuffered silica plate yielded white crystalline material of mp 74–77°. Three recrystallizations from hexane containing a trace of ether afforded an analytical sample of dione **3** as white needles: mp 84–85°; ir ($CHCl_3$) 1710 (C=O), 1378 (CH_3 bend) cm^{-1}; nmr ($CDCl_3$) δ 0.78 (s, 3 H), 1.50–2.82 (m, 13 H); mass spectrum (70 eV) *m/e* 180 (M^+), 165 ($M^+ - CH_3$), 137 (165 − CO), 124, 111, 96, 95, 55.

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.32; H, 8.98.

Preparation of Ketone 4.—In a 10-ml three-neck flask 555 mg (1.55 mmol) of triphenylmethylphosphonium bromide and 150 mg (1.34 mmol) of freshly sublimed potassium *tert*-butoxide were intimately mixed under a nitrogen atmosphere. Anhydrous ether (6.0 ml) was introduced and the mixture turned bright yellow. To this solution of methylene triphenylphosphorane was added 60 mg (0.31 mmol) of ketone **1** in 3.0 ml of anhydrous ether and the reaction was allowed to stir at room temperature for 10 hr. The reaction was quenched by the addition of 5 ml of 1 *N* hydrochloric acid followed by 5 ml of water. The ether layer was separated and the aqueous portion was washed with two additional portions of ether. The combined ethereal extracts were washed with saturated aqueous bicarbonate and brine, dried (magnesium sulfate), and concentrated *in vacuo* to afford 293 mg of an oil with traces of solid.[22] The yield of ketone **4** as determined by glpc[23] using hexadecane as an added calibrated internal standard was 48%. A pure sample (24 mg, 43% yield) was obtained by preparative silica gel tlc which was eluted with 9:1 hexane:ether ($R_f \approx 0.30$): ir (thin film) 3090, 1713, 1645, 895, 887 cm^{-1}; nmr (CCl_4) δ 4.48 (s, 1 H), 4.78 (s, 1 H), 0.72 (s, 3 H), 2.5–0.90 (m, all other protons); mass spectrum (70 eV) *m/e* 178 (M^+, base), 163 ($M^+ - CH_3$), 150 (M^+ − CO), 135, 79.

Preparation of Ketone 5.—Into a 10-ml three-neck flask in which a nitrogen atmosphere was maintained was introduced 60 mg (0.31 mmol) of ketone **1** in 2.0 ml of anhydrous ether. The solution was cooled to 0° and 0.5 ml of 2.0 *M* (1.0 mmol) methyllithium was added. After stirring for 20 min at 0°, the reaction was allowed to warm to room temperature, and 5.0 ml of saturated aqueous sodium bicarbonate was cautiously added. An additional 10 ml of ether was added and the organic layer was separated. The aqueous phase was extracted with two additional 10-ml portions of ether. The combined extracts were washed with 10 ml of brine, dried (anhydrous potassium carbonate), and concentrated *in vacuo* to afford 64 mg of an oil. This crude methyllithium adduct was dissolved in 2.0 ml of freshly dried pyridine and to this solution was added 2.0 ml of a solution made from 0.4 ml of thionyl chloride in 20 ml of pyridine. The reaction mixture was allowed to stir at room temperature for 15 min after which time it was poured into 15 g of ice and acidified with 1 *N* hydrochloric acid to pH 2. The mixture was extracted with two 15-ml portions of ether. The combined ether extracts were washed with water, saturated aqueous sodium bicarbonate, and brine, dried (magnesium sulfate), and concentrated *in vacuo* to afford 35 mg (70%) of ketone **5** as an oil. A pure sample of **5** was obtained *via* preparative gas–liquid chromatography:[24] nmr (CCl_4) δ 1.70 (s, CH_3), 1.00 (s, CH_3); ir (thin film) 1712, 1455, 1265; mass spectrum (70 eV) *m/e* 178 (M^+), 163 ($M^+ - CH_3$), 150 ($M^+ - CO$), 135, 121, 107, 105, 93, 79.

(21) Plates were prepared in the standard manner except that an aqueous solution containing 1% of a standard pH 7 buffer solution was used in place of pure water. These plates were dried at room temperature for at least 24 hr prior to use.

(22) Most of this crude material consists of phosphine oxides.

(23) In a 7 ft × 1/8 in. SE-30 column at 160° with a helium flow rate of 45 ml/min.

(24) In a 20 × 5/8 in. QF-1 column at 175° with a helium flow rate of 100 ml/min. A smaller peak (<10%) was also detected but was not isolated.

Acknowledgment.—This work was supported by Public Health Service Research Grant No. 1 RO1 CA-12658 from the National Cancer Institute.

Registry No.—**1**, 42246-15-1; **2**, 2844-80-6; **3**, 42246-17-3; **4**, 3241-65-4; **5**, 2658-95-9.

Chemistry of Heterocyclic Compounds. 12. Preparation and Reactions of 2-Pyridylacetylenes[1]

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The preparation of 2-pyridylacetylenes has been besieged by sporadic results; for example, dehydrobromination of stilbazole dibromide (**2a**) has been shown to give stilbazole, bromostilbazole, and/or 2-phenylethynylpyridine, depending upon reaction conditions. Scheuing and Winterhalder[2] were the first to isolate 2-phenylethynylpyridine (**3a**) by treatment of the dibromide **2a** with refluxing ethanolic potassium hydroxide. Attempted repetition of this reaction afforded, in one case,[3] only stilbazole (**1a**) and an unstipulated bromostilbazole, whereas others[4] obtained **3a**, bromostilbazole, and α-(2-pyridyl)acetophenone.[5] Recently, Acheson and Bridson,[7] utilizing these reaction conditions,[2] obtained 2-phenylethynylpyridine (**3a**) containing at best approximately 30% of bromostilbazole, which was identified as 2-(1-bromo-*cis*-2-phenylvinyl)pyridine. The pure acetylene **3a** was prepared[7] (83%) by using potassium *tert*-butoxide, as the dehydrobromination reagent, in refluxing *tert*-butyl alcohol.

During the course of our studies, we needed the previously prepared di(2-pyridyl)acetylene (**7a**)[8] and di(6-methyl-2-pyridyl)acetylene (**7b**). We herein describe the preparation of pure **7**, as well as the structural determination of the major side products, which arise when more rigorous conditions[2] are utilized.

(1) This research has been supported by Public Health Service Grant No. 5-RO1-MS-09930 from the National Institute of Neurological Diseases and Stroke, the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the Research Corp.

(2) G. Scheuing and L. Winterhalder, *Justus Liebigs Ann. Chem.*, **473**, 126 (1929).

(3) J. W. Blood and B. D. Shaw, *J. Chem. Soc.*, 504 (1930).

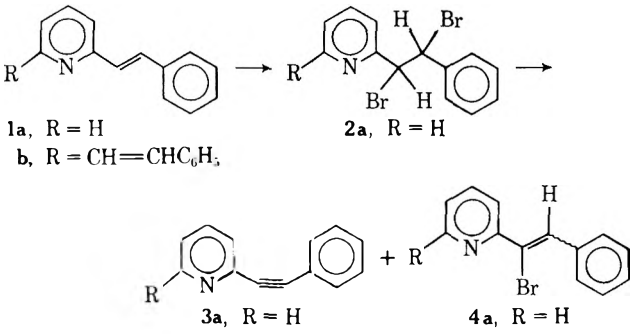
(4) T. Katsumoto and A. Honda, *J. Chem. Soc. Jap.*, **84**, 527 (1963).

(5) Preparations of other phenylethynyl heterocycles[6] have utiliized the original, or slightly modified, procedure of Scheuing and Winterhalder.[2] Analyses of the acetylenic products are generally outside the acceptable analytical limits, which are indicative of halogenated contaminants.

(6) (a) J. M. Smith, Jr., H. W. Stewart, B. Roth, and E. H. Northey, *J. Amer. Chem. Soc.*, **70**, 3997 (1948); (b) K. Schofield and T. Swain, *J. Chem. Soc.*, 2393 (1949); (c) H. C. Beyerman, W. Eveleens, and Y. M. F. Muller, *Recl. Trav. Chim. Pays-Bas*, **75**, 63 (1956); (d) T. Nakashima, *Yakugaku Zasshi*, **77**, 1298 (1957); (e) A. I. Kiprianov and G. G. Dyadyusha, *Zh. Obshch. Khim.*, **30**, 3647 (1960); (f) I. Ernest, *Collect. Czech. Chem. Commun.*, **26**, 748 (1960).

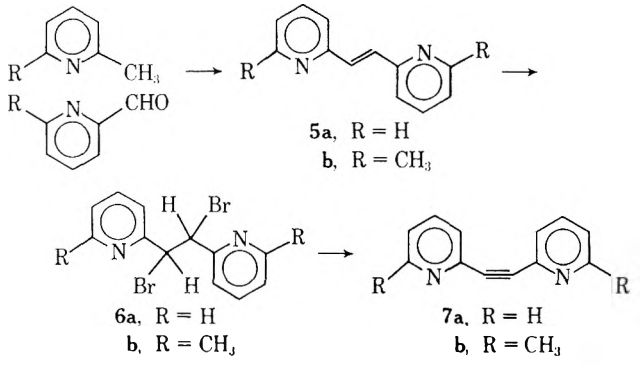
(7) R. M. Acheson and J. N. Bridson, *J. Chem. Soc. C*, 1143 (1969).

(8) D. Jerchel and W. Melloh, *Justus Liebigs Ann. Chem.*, **622**, 53 (1959).



Preparation of the di(2-pyridyl)acetylenes basically follows the procedure shown in Scheme I. Condensa-

SCHEME I



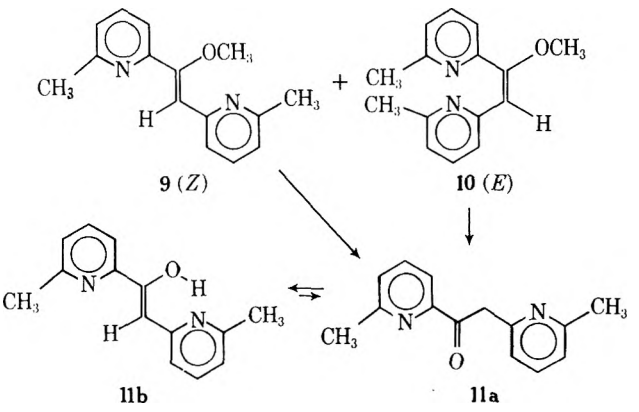
tion of picoline with pyridinecarboxaldehyde gave **5a**, and lutidine with 6-methyl-2-pyridinecarboxaldehyde afforded **5b** along with a 2:1 product **8** whose trans,trans configuration can now be assigned on the basis of the 16.5-Hz coupling constant (220 MHz nmr). Bromination of **5a** and **5b** in chloroform or acetic acid gave (79%) the dibromides **6a**[9] and **6b**,[10] respectively. Owing to the insolubility of **6**, deuterated dimethyl sulfoxide was used in an attempt to obtain their nmr spectra; however, upon warming to 100°, facile debromination occurred, affording the starting olefin **5** with only traces of the dibromide.

Dehydrobromination of **6** is extremely sensitive to the reaction conditions, *with the best conditions being the rapid addition of small quantities of the dibromide to refluxing methanolic potassium hydroxide*, followed by a *brief* 20–30-min reflux period. After the standard work-up procedure, yield data in the range of 90–96% can be realized. Monobromide products, such as experienced in the dehydrobromination of **2**, were not detected under these reaction conditions. Deviation, *e.g.*, a single addition of **6b**, from this procedure resulted in increased quantities of starting olefin, whereas, under prolonged reflux periods, acetylene **7b** underwent addition of solvent (methanol) forming isomeric enol ethers **9** and **10**. With calcium carbonate in dimethylacetamide, **6b** was recovered unchanged after 12 hr at 60°, but at 90–100° debromination occurred exclusively.

The configurations of the enol ethers were assigned on the basis of their nmr spectra. In **9**, the trans aryl groups approach coplanarity with the double bond; thus the 6-methyl substituents (δ 2.56 and 2.58) are

(9) G. Harris and G. H. Lénért, *Justus Liebigs Ann. Chem.*, **410**, 95 (1915).
(10) W. Baker, K. M. Buggle, J. F. W. McOmie, and D. A. M. Watkins, *J. Chem. Soc.*, 3594 (1958).

6b → 7b →



subjected to approximately the same environment. Coplanarity of the cis aryl groups in **10** is not possible owing to steric interactions; therefore, one of the 6-methyl groups (δ 2.42 and 2.53) is shifted owing to the anisotropy of the neighboring pyridyl ring. The chemical shifts of the vinyl proton [**9** (in aromatic region), **10** (δ 6.08)] and the methoxyl group [**9** (δ 3.73), **10** (δ 3.88)] further substantiate the structural assignments.

Hydrolysis of **9** and **10** with dilute acid gave the expected enol, **11b**, which was synthesized according to the method of Goldberg, *et al.*,[11] from methyl 6-methylpicolinate and 6-methyl-2-picolyllithium. Hydrolysis of **10** was essentially complete after 8 hr, whereas **9** was only partially (33%) hydrolyzed under identical conditions. These chemical data are consistent with the assigned configuration of the enol ethers.[12]

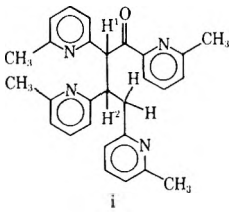
Experimental Section[13]

(*E*)-1,2-Di(6-methyl-2-pyridyl)ethene (5b).—A mixture of 6-methylpyridinecarboxaldehyde (50 g, 0.413 mol, Aldrich Chemical Co.), redistilled lutidine (150 ml), and acetic anhydride (60 ml) was refluxed for 4 hr. The volatile unreacted starting materials were removed *in vacuo* and the residue was vacuum distilled, affording the crude olefin **5b**, bp 136–140° (0.5 mm). Recrystallization from benzene–cyclohexane gave 44 g (48%) of the colorless, crystalline olefin: mp 110–112° (lit.[10] mp 111–113°); nmr ($CDCl_3$) δ 7.7 (HC=CH, s), 2.58 (6-pyr-Me, s).

The residue from the above vacuum distillation afforded, upon crystallization from benzene, 1.5 g (2%) of (*E,E*)-2,6-di[2-(6-methyl-2-pyridyl)vinyl]pyridine: mp 132–135° (lit.[10] mp 129–133°); nmr ($CDCl_3$, 220 MHz) δ 2.57 (6-pyr-Me, s, 6 H), 7.03 (H_5, d, J = 7.8 Hz, 2 H), 7.30 and 7.305 (H_3, H_3', H_5', d, J = 7.8 Hz, 4 H), 7.55 and 7.59 (H_4 and H_4', t, J = 7.8 Hz, 3 H), 7.59 and 7.78 (trans HC=CH, d, J = 16.5 Hz, 4 H).

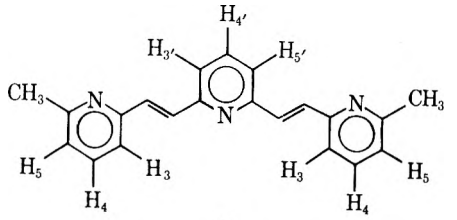
(11) N. N. Goldberg, L. B. Barkley, and R. Levine, *J. Amer. Chem. Soc.*, **73**, 4301 (1951).

(12) Hydrolysis of a mixture of enol ethers **9** and **10** and olefin **5b** gave a condensation product (i), based on its spectral and analytical data. Attempted repetition of the hydrolysis conditions failed to afford additional quantities of i.



i

(13) Infrared spectra were recorded with a Perkin-Elmer 237B grating spectrometer. Nmr spectra were obtained with a Varian A-60A or HR-220 (220-MHz) spectrometer and are reported in δ units (parts per million) relative to tetramethylsilane as the internal standard. Elemental analyses were performed by Mr. Seab in our laboratories. Melting points and boiling points are uncorrected.



8

(*E*)-1,2-Di(2-pyridyl)ethene (5a) was prepared in an identical manner, bp 160–180° (1–2 mm), mp 117–119° (lit.[9] mp 118–119°).

Bromination of (*E*)-1,2-Di(6-methyl-2-pyridyl)ethene. Method A.—To a stirred suspension of 1 g (4.8 mmol) of (*E*)-1,2-di(6-methyl-2-pyridyl)ethene in 10 ml of chloroform, a solution of bromine (770 mg, 4.8 mmol) in 10 ml of chloroform was added dropwise over 1 hr. During the addition, the crude dibromide slowly crystallized, yield 1.4 g (79%), mp 193–195° dec. Recrystallization of 6b from ethanol increased the melting point to 208–209° dec (lit.[10] mp 194–196°).

Method B.—Bromination was identical except that acetic acid was used as solvent, yield 1.4 g (79%), mp 184–185° dec. Recrystallization of 6b from ethanol increased the melting point to 202–203° dec.

1,2-Di(2-pyridyl)1,2-dibromoethane (6a) was prepared (92%) by method A, mp 149–150° (lit.[9] mp 153–154°).

Di(6-methyl-2-pyridyl)acetylene (7b).—To a refluxing solution of potassium hydroxide (3 g) in absolute methanol (20 ml), the above *solid* dibromide 6b (1.0 g) was rapidly added in 50-mg (or less) quantities. Potassium bromide instantaneously precipitated. The suspension was refluxed for 30 min after completion of addition. The solvent was removed *in vacuo*. The residue was dissolved in ice–water and the organic material was extracted with ether, washed with a saturated salt solution, dried, and concentrated, affording the crude acetylene. Recrystallization from cyclohexane afforded 550 mg (95%) of the white, crystalline acetylene: mp 138–139°; nmr ($CDCl_3$) δ 2.56 (6-pyr-**Me**, s, 3 H), 7.1–7.9 (pyr H, m, 4 H); Raman (solid) 2215 cm^{-1} (*sym*-acetylene).

Anal. Calcd for $C_{14}H_{12}N_2$: C, 80.74; H, 5.81; N, 13.45. Found: C, 80.45; H, 5.78; N, 13.35.

Di(2-pyridyl)acetylene (7a) was prepared in an identical manner in 93% yield, mp 69–71° (lit.[8] mp 69–70°).

Di(6-methyl-2-pyridyl)acetylene. Rapid Addition and Extended Reflux Times.—The solid dibromide 6b (4.5 g, 12.2 mmol) was added rapidly to a refluxing methanolic potassium hydroxide solution (6 g/20 ml). The reaction mixture was refluxed for 6 hr and cooled, and the potassium bromide precipitate [2.8 g (2.9 g theoretical weight)] was removed by filtration. The solvent was removed *in vacuo* and ice–water was added; the residue was extracted with ether, washed with a saturated salt solution, dried, and concentrated, affording a yellow oil, 2.9 g. Upon standing, the starting olefin **5b** crystallized as white needles, yield 350 mg, mp 110–113° (recrystallized from low-boiling petroleum ether, mp 112–113°).

The crude oil (2.55 g) was distilled, affording three major fractions, bp 134–148° (0.6 mm), all of which possess different percentages, as quantitatively determined by vpc (10% OV 101 on Gas-Chrom Q 100–120 mesh, 6 ft × 0.125 in.), of four major components, which were isolated by thick layer chromatography (Brinkmann silica gel PF, 50% ethyl acetate–50% cyclohexane, 500 mg).

The fastest moving component was the starting olefin **5b**: R_f 0.50; yield 165 mg (33%), 35% *via* vpc; mp 111–113°; nmr ($CDCl_3$) δ 2.58 (6-pyr-**Me**, s) and 7.7 (trans **HC**=**CH**, s).

The second component was (*Z*)-1-methoxy-1,2-di(6-methyl-2-pyridyl)ethene (9): R_f 0.42; yield 200 mg (40%), 45% *via* vpc; nmr ($CDCl_3$) δ 2.56 and 2.58 (6-pyr-**Me**, 2 s, 6 H), 3.73 (–OMe, s, 3 H), 6.82–8.02 (pyr H and >C=CH, m, 7 H); ir (neat) 1640, 1580, 1460, 1330, 1310, 1080, 1020 cm^{-1}.

The third component was di(6-methyl-2-pyridyl)acetylene (7b): R_f 0.25; yield 5 mg (1%), 1% *via* vpc: mp 133–137°.

The fourth component was (*E*)-1-methoxy-1,2-di(6-methyl-2-pyridyl)ethene (10): R_f 0.06; yield 65 mg (13%), 14% *via* vpc; nmr ($CDCl_3$) δ 2.42 (6-pyr-**Me**, s, 3 H), 2.53 (6-pyr-**Me**, s, 3 H), 3.88 (–OMe, 3 H), 6.08 (>C=CH, s, 1 H), 6.44–7.6 (pyr H, m, 6 H); ir (neat) 1640, 1580, 1450, 1210, 1140 cm^{-1}.

Anal. Calcd for $C_{15}H_{16}N_2O$ (ethers): C, 74.97; H, 6.71; N, 11.66. Found: C, 74.86; H, 6.89; N, 11.58.

Hydrolysis of (*E*)-1-Methoxy-1,2-di(6-methyl-2-pyridyl)ethene (10).—A solution of the *E* vinyl ether (55 mg, 0.23 mmol) in methanol (10 ml) and 5 *N* HCl (5 ml) was refluxed for 8 hr. The solution was cooled, basified with a saturated sodium carbonate solution, and extracted with ether. The extract was washed with a saturated salt solution, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*, giving (100%) the yellow crystalline ketone (as enol): mp 122–123°; nmr ($CDCl_3$) δ 2.50 and 2.56 (6-pyr-**Me**, 2 s, 6 H), 6.7–7.8 (pyr H, m, 7 H); ir (KBr) 2500–3500 (–OH, broad), 1645, 1600, 1560, 1455, 1305, 830, 805, 765 cm^{-1}.

Anal. Calcd for $C_{14}H_{14}N_2O$: C, 74.31; H, 6.24; N, 12.38. Found: C, 74.33; H, 6.21; N, 12.40.

Hydrolysis of (*Z*)-1-methoxy-1,2-di(6-methyl-2-pyridyl)ethene (9) under identical conditions as above afforded the ketone, mp 122–123°, in 33% (nmr and isolated) yield and the unreacted *Z* enol ether.

Hydrolysis of the enol ethers 9 and 10 in the presence of olefin 5b under identical conditions as above initially afforded a viscous oil, which gave colorless crystals upon standing overnight. The crystals were recrystallized from ether–petroleum ether (bp 30–60°), affording an analytical sample of the tetrapyridyl ketone:[12] mp 178–179°; R_f 0.1 (50% ethyl acetate–50% cyclohexane); nmr ($CDCl_3$) δ 2.22, 2.41, 2.51, 2.59 (6-pyr-**Me**, 4 s, 3 H each), 2.9–3.15 (–CH_2–, J = 7, 11 Hz, 2 H), 4.3–4.8 (>CH^2–, J = 7, 7 Hz, 1 H), 6.4 (>CH^1CO–, J = 7 Hz, d, 1 H, exchanged slowly with D_2O), and 6.6–7.7 (pyr H, m, 12 H); ir (KBr) 1706 (>C=O), 1592, 1575, 1457, 1378, 1328, 1292, 1263, 1152, 1093, 992 cm^{-1}.

Anal. Calcd for $C_{28}H_{28}N_4O$: C, 77.04; H, 6.47; N, 12.83. Found: C, 76.83; H, 6.72; N, 12.75.

1,2-Di(6-methyl-2-pyridyl)ethanone (11) was prepared (20.6%) according to the method of Goldberg, *et al.*,[11] from methyl 6-methylpicolinate[14] and 6-methyl-2-picolyllithium, mp 122–123° (cyclohexane). The mother liquor afforded, after chromatography with cyclohexane–ethyl acetate (3:1), 1,2,3-tri(6-methyl-2-pyridyl)propan-1-ol:[15] bp 167–169° (1.2 mm); nmr ($CDCl_3$) δ 2.40 [1,3-(2-pyr-**Me**), s, 6 H], 2.45 [2-(2-pyr-**Me**), s, 3 H], 3.25 (–CH_2–, d, J = 11 Hz), 3.56 (–CH_2–, d, J = 11 Hz), and 6.7–7.5 (pyr H, m, 9 H).

Registry No.—**5a**, 13341-40-7; **5b**, 16552-23-1; **6a**, 42296-31-1; **6b**, 42296-32-2; **7a**, 28790-65-0; **7b**, 42296-34-4; **8**, 39689-97-9; **9**, 42296-37-7; **10**, 42296-38-8; **11b**, 42296-39-9; i, 42296-36-6; 6-methylpyridine-2-carboxaldehyde, 1122-72-1; 2,6-butadiene, 108-48-5; 2-picoline, 109-06-8; 2-pyridenecarboxaldehyde, 1121-60-4; 1,2,3-tri(6-methyl-2-pyridyl)propan-1-ol, 42447-96-1.

(14) W. Mathes, W. Sauermilch, and T. Klein, *Chem. Ber.*, **86**, 584 (1953).

(15) Attempted further purification was thwarted by decomposition to lutidine and 1,2-di(6-methyl-2-pyridyl)ethanone. Additional evidence on this point will be presented in a subsequent communication.

Preparation of Cis and Trans Isomers of 4-Phenylcyclohexyl and 4-Cyclohexylcyclohexyl Bromides

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Substituted cyclohexane compounds have been extensively used in the investigation of steric and conformational properties of functional groups, and for the elucidation of certain mechanistic aspects of chemical reactions. For a number of these investigations, bulky, inert functional groups having a strong prefer-

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ence for equatorial bonding to the cyclohexane ring in cases of 1,4 substitution such as *tert*-butyl have been utilized. 1,4-Substituted cyclohexanes containing either the phenyl or cyclohexyl group provide another such set of potentially useful compounds. In particular, the syntheses and assignments of the stereochemistry of the cis and trans isomers of 4-phenylcyclohexyl and 4-cyclohexylcyclohexyl bromides have been accomplished. These compounds possess a reactive bromide atom which permits ready access to other 4-phenyl and 4-cyclohexyl substituted cyclohexanes, especially by way of organometallic syntheses. Only mixtures of 4-phenylcyclohexyl bromides,[2a] and 4-cyclohexylcyclohexyl bromides,[2b] have been reported.

Results[3]

The route initially attempted for the preparation of the 4-phenylcyclohexyl bromide isomers was the reaction of Br_2–CCl_4 with the silver salt of *trans*-4-phenylcyclohexanoic acid,[4] but only para aromatic ring bromination occurred to produce 4-(4-bromophenyl)cyclohexanoic acid (**1**), mp 266–267°.

The successful route was the conversion of *trans*-4-phenylcyclohexanol (**2a**) to a 4-phenylcyclohexyl halide, although this was far more difficult than expected. (Reaction with hydriodic acid, hydrobromic acid, anhydrous HI, $SOCl_2$, $SOBr_2$, PBr_5, PCl_5, $POCl_3$ or PCl_3 produced the inorganic esters or starting material.)

Successful reaction of **2a** to produce mainly *cis*-4-phenylcyclohexyl bromide (**3b**) in 82% yield was only accomplished with PBr_3 at 80° for 34 hr with intermittent addition of excess HBr gas. (*trans*-4-*tert*-Butylcyclohexanol responded readily at room temperature with PBr_3.) The trans bromide **3a** could only be obtained pure and in reasonable amounts by reaction of *trans*-4-phenylcyclohexylmercuric bromide (**4a**) with Br_2–pyridine complex. This reaction has been shown to be stereospecific by Jensen and Gale.[5] **4a** was prepared by recrystallization from benzene of the mixture of 4-phenylcyclohexylmercuric bromides (**4a** and **4b**) obtained by reaction of $HgBr_2$ with the Grignard from pure **3b** or the crude bromide product mixture from the PBr_3 reaction. (This 4-phenylcyclohexylmercuric bromide mixture was 88% **4a** and 12% **4b**.) Pure *cis*-4-phenylcyclohexylmercuric bromide (**4b**) was obtained by recrystallization and chromatography of the residue from the benzene mother liquors formed in the isolation of **4a**. **4b** was cleaved by Br_2–pyridine to give the previously obtained cis bromide **3b**. The infrared spectra were the same, and the mixture melting point was not depressed for **3b** bromides from both sources.

The Grignard reagents from trans bromide **3a** and from cis bromide **3b** were carbonated, and the resultant acid mixture was esterified with diazomethane and analyzed by glc. **3a** gave 99.8% methyl *trans*-4-phenylcyclohexanoate (**5a**), and **3b** gave 98.2% trans methyl ester (**5a**). **5a** had the same infrared spectra with no depression of the mixture melting point with authentic methyl *trans*-4-phenylcyclohexanoate prepared from the trans acid.[4]

3a (trans) and **3b** (cis) were both reduced selectively in glacial acetic acid with H_2–PtO_2 to *trans*-4-cyclohexylcyclohexyl bromide (**6a**) and *cis*-4-cyclohexylcyclohexyl bromide (**6b**), respectively. (Infrared spectra showed no aromatic hydrogen present in the products.) The reaction of an authentic sample of *cis*-4-cyclohexylcyclohexanol (**7b**) with PBr_3 gave the trans bromide **6a**. The same reaction with authentic trans alcohol **7a** gave the cis bromide **6b**.

6b (cis) and **6a** (trans) bromides produced by reaction with PBr_3 had the same ir, nmr, and physical properties as the corresponding **6b** and **6a** produced by the reduction of the **3b** (cis) and **3a** (trans) bromides.

The nmr absorptions of the bromide carbon methine hydrogen are summarized in the Experimental Section for the cyclohexyl bromides prepared in this investigation, and as expected the cis isomers show this hydrogen as a singlet downfield compared to the multiplet found for the trans isomers by Jensen and Berlin.[6]

Discussion

The cis–trans interrelationship of the two 4-phenylcyclohexyl bromide isomers and the two 4-cyclohexylcyclohexyl bromide isomers was shown by interconversion using organometallic derivatives and comparisons with authentic compounds.

The high preference of the Grignard should be noted for equatorial bonding considering that the *trans*-4-phenylcyclohexanoic acid was formed in 98.2% or higher purity by the generally accepted stereospecific carbonation reaction. The corresponding reaction with $HgBr_2$ gave 88% trans isomer, but there are a number of possible intermediates formed during reaction that can explain this slightly lower preference.

Experimental Section

General.—All melting points are uncorrected. Nmr spectra were run in CS_2 with a Varian Model HR-60 nmr spectrometer. Ir spectra were obtained with a Beckman IR-4 recording spectrometer. Microanalyses were performed by the Microanalysis Laboratory, Department of Chemistry, University of California, Berkeley. Glc analyses were carried out on a 10 ft × 0.25 in. column packed with 10% DEGS on 60–80 mesh Chromosorb W. All ir spectra were consistent with structure. 4-Cyclohexylcyclohexanol and 4-*tert*-butylcyclohexanol were donated by Dow Chemical Co. All solvents were reagent grade unless otherwise stated.

***cis*-4-Phenylcyclohexyl Bromide (3b).**—To 248.3 g (1.410 mol) of *trans*-4-phenylcyelohexol[7] at −70° was added 134 ml (1.410 mol) of PBr_3. The mixture was stirred, initially warmed to 80°, and maintained at this temperature for 34 hr with intermittent addition of HBr gas. The reaction mixture was cooled and poured into ice–isopentane. The isopentane solution was washed with concentrated H_2SO_4, aqueous $NaHCO_3$, and H_2O, then dried over anhydrous $MgSO_4$ and filtered. The solvent was removed to give 276.8 g (1.20 mol), 82% yield, of impure 4-phenylcyclohexyl bromide (cis was the predominant isomer). **3b** was obtained pure by seven recrystallizations from pentane: mp 46.2–46.4°; ν_{max} 687 cm^{-1} (C–Br); nmr (CS_2) δ 5.54 (s, =CBrH). *Anal.* Calcd for $C_{12}H_{15}Br$: C, 60.28; H, 6.32; Br, 33.40. Found: C, 60.19; H, 6.27; Br, 33.41.

***trans*-4-Phenylcyclohexylmercuric Bromide (4a).**—Triply sub-

(2) (a) M. A. Carissimi, A. Cattaneo, R. D'Ambrosio, E. Grumelli, E. Milla, and F. Ravenna, *Formaco, Ed. Sci.*, **20** (2), 106 (1965); *Chem. Abstr.*, **62**, 14559*h* (1965). (b) J. V. Braun, G. Irmisch, and J. Nelles, *Ber.*, **66B**, 1471 (1933).

(3) Taken from the dissertation of W. N. Smith, University of California, Berkeley, 1963.

(4) H. E. Zimmerman and H. J. Giallombardo, *J. Amer. Chem. Soc.*, **78**, 6259 (1956).

(5) F. R. Jensen and L. Gale, *J. Amer. Chem. Soc.*, **82**, 148 (1960).

(6) F. R. Jensen and A. Berlin, unpublished results.

(7) H. E. Ungnade, *J. Org. Chem.*, **13**, 361 (1948).

limed Mg (43.7 g, 1.80 mol) and 200 ml of purified Et_2O under argon were stirred while 348 g (1.46 mol) of **3b** in 800 ml of purified Et_2O was added at such a rate as to maintain reflux. The solution was stirred for 30 min after addition and then filtered. The Grignard solution was added slowly to 548 g (1.60 mol) of $HgBr_2$ in 200 ml of purified Et_2O and stirred overnight. (The slurry had the consistency of paste at this point.) The slurry was then poured into a large excess of H_2O and filtered, and the solid was air dried. The Et_2O filtrate was distilled, and the solid remaining was combined with the precipitate. The material was divided into two batches, and each was recrystallized from *ca.* 15 l. of benzene. The first crops were pure **4a**, mp 182.1–183.0° dec (sealed tube), and weighed 158 g (0.36 mol). The benzene solution was evaporated down in stages, taking various crops, and the final residue of 90 g was discarded. The last crops were recrystallized from EtOH to yield 130 g (0.226 mol) of impure **4b**, mp 109–111°. There was also isolated 158 g (0.360 mol) of additional impure **4a**. The total yield was 70% based on **3b**. *Anal.* Calcd for $C_{12}H_{15}HgBr$: C, 32.75; H, 3.44. Found: C, 32.47; H, 3.48.

cis-**4-Phenylcyclohexylmercuric Bromide (4b).**—Impure **4b** from above was recrystallized from EtOH until the melting point was 120°. The material was then chromatographed using Woelm activity I neutral Al_2O_3 with Et_2O–benzene as eluent, followed by recrystallization from EtOH, mp 134.0–134.3°. *Anal.* Calcd for $C_{12}H_{15}HgBr$: C, 32.75; H, 3.44. Found: C, 32.71; H, 3.44.

trans-**4-Phenylcyclohexyl Bromide (3a).**—After 132.2 g (0.301 mol) of **4a** was dissolved in 500 ml of pyridine, a solution of 15.5 ml (0.301 mol) of Br_2 in 100 ml of pyridine was added slowly with stirring over a 15-min period at 25° with cooling. The solution was cooled to 15° for 1 hr and then poured into a mixture of ice, 200 ml of pentane, and 1200 ml of 6 *N* HCl. The organic layer was separated, washed with $NaHSO_3$ solution, washed several times with H_2O, and dried over anhydrous $MgSO_4$. After removal of the pentane, 54.2 g (76% yield) was obtained. After recrystallization from pentane, the melting point was 62.8–63.2°, ν_{max} 687 cm^{-1} (C–Br), nmr δ 4.66 (m, =CBrH). *Anal.* Calcd for $C_{12}H_{15}Br$: C, 60.28; H, 6.32; Br, 33.40. Found: C, 60.04; H, 6.45; Br, 33.43.

Reaction of the Grignard Reagent Prepared from Pure *cis*-4-Phenylcyclohexyl Bromide (3b) with Mercuric Bromide.—**3b** (12.0 g, 0.0502 mol) in 40 ml of Et_2O was added slowly to just maintain reflux to 1.80 g (0.0741 mol) of sublimed Mg and 25 ml of Et_2O under N_2. The soln. was refluxed for 1 hr after addition. The Grignard formed in 69% yield. This solution was added to 22.6 g (0.0618 mol) of $HgBr_2$ in 50 ml of Et_2O. After the mixture was stirred for 20 hr, 40 ml of H_2O was added, and the precipitate was dissolved in benzene, washed with H_2O, dried, and filtered. After the volume of the filtrate was reduced to 75 ml, 5.28 g of **4a** was isolated and recrystallized, mp 182.5–184.0° dec. The impure residue, 5.6 g, was chromatographed over Woelm activity I neutral Al_2O_3 with Et_2O–benzene eluent. The combination of the latter fractions gave 1.22 g of **4b**, mp 133–134°. The total weight of 4-phenylcyclohexylmercuric bromide obtained from the Grignard reaction was 10.9 g (72%). **4b**, therefore, constituted 12% of the alkylmercuric bromide compounds formed.

Carbonation of the Grignard Reagent from *cis*-4-Phenylcyclohexyl Bromide (3b).—Sublimed Mg (0.35 g, 0.0144 mol) in 12 ml of purified Et_2O was refluxed and stirred under N_2, while 2.00 g (0.0084 mol) of **3b** in 22 ml of purified Et_2O was added slowly. The reaction mixture was refluxed for 1.75 hr and poured into an Et_2O–Dry Ice mixture. This mixture was acidified and CH_2Cl_2 was added. The organic layer was washed several times with H_2O and dried over anhydrous Na_2SO_4; the solvent was removed to give 1.59 g (93% yield) of the acids. The ir showed the mixture to be only carboxylic acids. After esterification with CH_2N_2, the ester mixture was analyzed by glc. **5a** was found to be 98.2% of the total methyl ester mixture. The glc retention time and the ir spectra of authentic samples corresponded with those obtained by the Grignard carbonation. Pure **5a** was obtained by recrystallization from pentane, mp 29–31°. The same Grignard formation and carbonation procedure using *trans*-4-phenylcyclohexyl bromide (**3a**) gave 99.8% **5a** after esterification followed by glc analyses.

cis-**4-Cyclohexylcyclohexyl Bromide (6b).**—**7a** was obtained by the recrystallization of commercial 4-cyclohexylcyclohexanol from cyclohexane until the melting point was 103.8–104.2° (lit.[3] mp 103–104°).

To 4.00 g (0.022 mol) of **7a** was added 5.96 g (0.022 mol) PBr_3 at −40°. The solution was warmed slowly to room temperature and stirred for 3 days. The solution was then poured over ice–isopentane. (A large amount of phosphite ester was still present, indicating that the reaction had not gone to completion.) The yield was 1.81 g (35%), mp 29–32°. *Anal.* Calcd for $C_{12}H_{21}Br$: C, 58.87; H, 8.66. Found: C, 58.76; H, 8.61.

trans-**4-Cyclohexylcyclohexyl Bromide (6a).**—**7b** was prepared by the reduction of 21.0 g (0.124 mol) of *p*-phenylphenol in 150 ml of HOAc with H_2 and Rh–Al_2O_3, at 50 psi and 70°. After H_2 absorption ceased, the solution was cooled and poured into H_2O. The precipitate was dissolved in CH_2Cl_2, washed with aqueous base, and dried over anhydrous $MgSO_4$ and the solvent was removed to yield 19.2 g (85%) of impure **7b**. A small amount of this alcohol was chromatographed over Woelm activity II neutral Al_2O_3 with pentane–Et_2O eluent, mp 94.0–94.5° (lit.[3] mp 92–93°).

To 1.05 g (0.0058 mol) of **7b** at −40° was added 1.60 g (0.0059 mol) of PBr_3 and the solution was stirred for 3 days at room temperature. The solution was poured into ice–pentane, washed with concentrated H_2SO_4 and H_2O, and then dried over anhydrous $MgSO_4$. After the solvent was removed, 0.49 g (0.0020 mol) of **6a** was obtained (35% yield). The material could not be crystallized at room temperature. *Anal.* Calcd for $C_{12}H_{21}Br$: C, 58.87; H, 8.66. Found: C, 59.17; H, 8.87.

Reduction of the *cis*- and *trans*-4-Phenylcyclohexyl Bromides (3b and 3a).—To 30 ml of HOAc were added 0.300 g (0.0013 mol) of **3a** and 0.088 g of PtO_2. The H_2 pressure was kept at 40 mm for 12 hr. The ir spectrum showed complete reduction of **3a** bromide, and was identical with that prepared using **7b**. The material could not be crystallized at room temperature, nmr δ 4.56 (m, =CBrH).

The same procedure was used with **3b**. The ir spectrum was identical with that of the cis bromide **6b** prepared from **7a** and the mixture melting point was not depressed. The yield was 54%, mp 33–34°, nmr δ 5.40 (s, =CBrH).

Summary of Nmr. Bromide-Substituted Carbon Methine Absorption for Cyclohexyl Bromides: *cis*-4-phenylcyclohexyl bromide (**3b**), 5.54 (s); *trans*-4-phenylcyclohexyl bromide (**3a**), 4.66 (m); *cis*-4-cyclohexylcyclohexyl bromide (**6b**), 5.40 (s); *trans*-4-cyclohexylcyclohexyl bromide (**6a**), 4.56 (m); axial methine in cyclohexyl bromide at −81°, 4.70[8] (m)[6]; equatorial methine in cyclohexyl bromide at −81°, 5.56[8] (s).[6]

Acknowledgment.—I wish to thank Professor F. R. Jensen for his guidance and support during the course of this research.

Registry No.—**2a**, 5769-13-1; **3a**, 42367-11-3; **3b**, 42367-12-4; **4a**, 42367-13-5; **4b**, 42367-14-6; **5a**, 36296-69-2; **6a**, 42367-15-7; **6b**, 42367-16-8; **7a**, 7335-42-4; **7b**, 7335-11-7.

(8) A. J. Berlin and F. R. Jensen, *Chem. Ind. (London)*, 998 (1960).

The Addition of Dichloroketene to 2-Aryl-Δ^2-oxazolines

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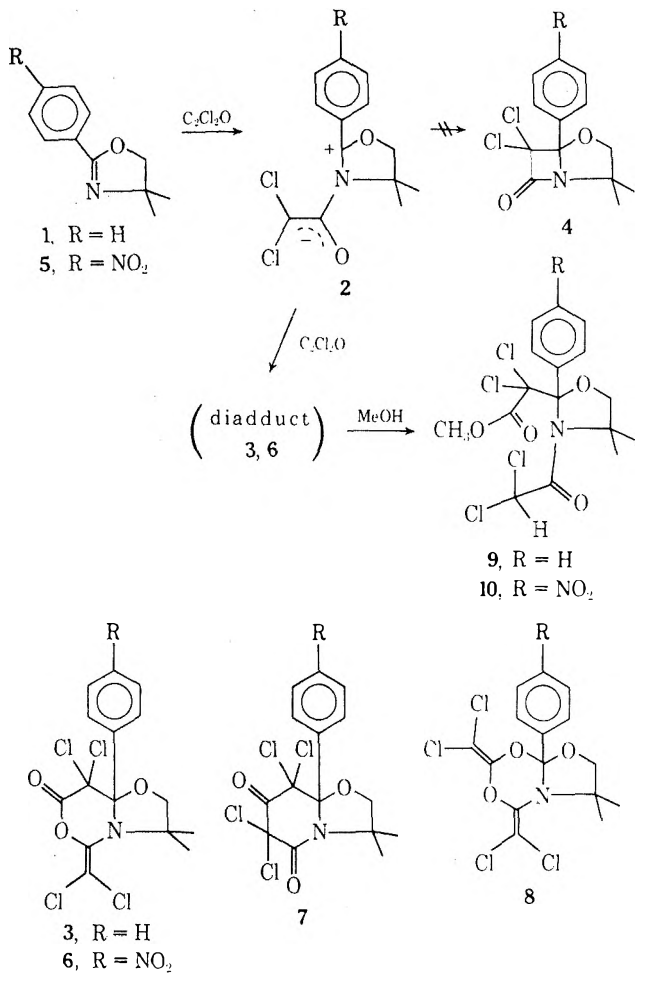
Dichloroketene formed by the *in situ* dehydrohalogenation of dichloroacetyl chloride[1] has been shown[2] to react with many Schiff bases to form α,α-dichloro-β-lactams. In our hands, however, many variations of this reaction with the substrate 4,4-dimethyl-2-phenyl-Δ^2-oxazoline (**1**) have not produced the desired oxygen-containing penicillin-like lactam, **4**, but rather a 2:1 ketene diadduct, **3**.

(1) L. Ghosez, R. Montaigne, and D. Mollet, *Tetrahedron Lett.*, 135 (1966); W. T. Brady, H. G. Liddell, and W. L. Vaughn, *J. Org. Chem.*, **31**, 626 (1966).
(2) F. Duran and L. Ghosez, *Tetrahedron Lett.*, 245 (1970).

SCHEME I

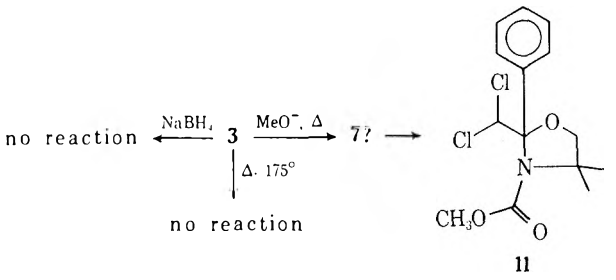


Determination of the structure of **3** was complicated by the possible formation of a number of other isomers, chiefly **7** and **8**. While the absence of protons on the ketene dimer portion of the molecule hindered the structure assignment, the infrared spectra provided some information. The presence of a carbonyl absorption in the ir at 1809 cm^{-1} can be rationalized[3] only in terms of structures **3** or **7**, not **8**. Also the formation of ester **9** (Scheme I) by solvolysis of the ketene diadduct in warm methanol could result from either isomer **3** or **7**. The inertness of the diadduct to sodium borohydride (Scheme II) in warm ether for 5 days, however, suggests structure **3**, as the ketone group in **7** would be expected to be reduced to an alcohol under the conditions employed.

Neither changes in the stoichiometry nor alteration of the order of reactant addition affected the formation of **3**, which was the only observed product of either 1:1 or 2:1 ratios of ketene precursors to substrate and of reaction conditions ranging from −78° to reflux in cyclohexane, ether, THF, and THF–DMF. When 1:1 ratios were used, oxazoline **1** could be recovered from the reaction mixtures.

Consideration of the reaction mechanism which, reportedly,[4,5] involves zwitterion **2** led to the idea that

SCHEME II



destabilization of the benzylic carbonium ion could encourage collapse of **2** to give β-lactam **4** in preference to attack by the intermediate on a second molecule of ketene. When dichloroketene was treated with oxazoline **5**, the *p*-nitrophenyl derivative of **1**, under varying conditions as mentioned above, only product **6** was observed, in direct analogy to the unsubstituted oxazoline.

Dimethyl- and diphenylketene have been reported[6,7] to react with some Schiff bases to form the tetrasubstituted ketene dimers analogous to **3**. These have been shown[6] to undergo a base-catalyzed rearrangement to yield piperidinediones analogous to ketene dimer **7**. Attempts to rearrange compound **3** to **7** using sodium methoxide in refluxing benzene, however, gave only methyl ester **11** rather than the expected dione **7**, although **7** may have served as an intermediate in this reaction. Isomer **3** was found to be thermally stable to 175° in the absence of sodium methoxide.

Experimental Section

Melting points were taken with a Thomas-Hoover Uni-Melt apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 457 grating instrument, while nmr data were collected on a JOEL MH 100 spectrometer utilizing TMS as internal standard. Mass spectra were taken with a Hitachi RMU6-D mass spectrometer. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

4,4-Dimethyl-2-phenyl-Δ^2-oxazoline (**1**) and 4,4-dimethyl-2-*p*-nitrophenyl-Δ^2-oxazoline (**5**) were prepared by the method of Boyd and Hansen,[8] and gave satisfactory spectral data.

Synthesis of 8,8-Dichloro-5-dichlorovinylidene-3,3-dimethyl-8a-phenyltetrahydrooxazolo[3,2-*a*]oxazin-7-one (3) and *p*-Nitrophenyl Analog 6.—Either oxazoline **1** or **5** (0.01 mol) was placed in a dry flask equipped with magnetic stirrer, addition funnel, condenser, and drying tube. One or two equivalents of freshly distilled triethylamine was then added along with 100 ml of dry solvent (either, cyclohexane, THF, or THF–DMF). The solution was brought to the desired temperature, at which time 1 or 2 equiv of dichloroacetyl chloride was added slowly. A white precipitate, amine hydrochloride, became immediately evident. After addition, the mixture was stirred for an additional 1 hr, at which time a theoretical yield of amine salt was recovered by vacuum filtration. About 90% of the solvent was removed from the filtrate *in vacuo*, and the resulting liquid was triturated with hexane to cause precipitation of the diadduct after 1 hr at 0°. Sublimation of the product afforded analytically pure material.

For compound **3**: yield 90% (average for 0.01–0.03-mol scale); mp 91–92°; ir (CCl_4) 1809, 1660, and 1182 cm^{-1}; nmr (CCl_4) δ 1.08 (s, 3), 1.37 (s, 3), 3.66 (AB pattern, 2), 7.28–7.85 (aromatic, 5); mass spectrum[9] (70 eV) parent ion at *m/e* 397; chlorine isotope ratio shows four chlorines.

(3) For a recent article dealing with the controversy of diadduct formation in ketene addition reactions to imines see A. Hassner and M. J. Haddadin, *J. Org. Chem.*, **38**, 2650 (1973).

(4) H. B. Kagan and J. L. Luche, *Tetrahedron Lett.*, 3093 (1968).

(5) R. Huisgen, B. A. Davis, and M. Morikawa, *Angew. Chem.*, **80**, 802 (1968); *Angew. Chem., Int. Ed. Engl.*, **7**, 826 (1968); W. T. Brady and E. D. Dorsey, *J. Org. Chem.*, **35**, 2737 (1970).

(6) A. Hassner, M. J. Haddadin, and A. B. Levy, *Tetrahedron Lett.*, 1015 (1973).

(7) J. C. Martin, K. C. Brannock, R. D. Burpitt, P. G. Gott, and V. A. Hoyle, *J. Org. Chem.*, **36**, 2211 (1971).

(8) R. N. Boyd and R. H. Hansen, *J. Amer. Chem. Soc.*, **75**, 5896 (1953).

(9) We thank Dr. C. Fenslau of The Johns Hopkins School of Hygiene and Public Health for providing us with this spectrum.

Anal. Calcd for $C_{15}H_{13}Cl_4NO_3$: C, 45.37; H, 3.30; N, 3.53. Found: C, 45.37; H, 3.28; N, 3.53.

For 6: yield 85% (average for 0.01–0.03-mol scale); mp 154–155°; ir (CCl_4) 1809, 1658, 1535, 1350, 1175 cm^{-1}; nmr ($CDCl_3$) δ 1.10 (s, 3,), 1.46 (s, 3), 3.65 (AB pattern, 2), 7.62–7.92 and 8.10–8.32 (aromatic, 4).

Preparation of 3-Dichloroacetyl-4,4-dimethyl-2-(methyldichloroacetoxy)-2-phenyloxazolidine (9) and *p*-Nitrophenyl Analog 10.—Diadduct **3** or **6** was placed under gentle reflux in an excess of methanol for 3 hr. Addition of warm water precipitated the methyl esters, which were purified by recrystallization from methanol–water.

For oxazolidine 9: yield >95% on 0.01-mol scale; mp 192–193°; ir (CCl_4) 1755, 1674, 1401, 1070 cm^{-1}; nmr (CCl_4) δ 1.39 (s, 3), 1.73 (s, 3), 3.60 (s, 3), 3.76 (AB pattern, 2), 6.34 (s, 1), 7.20–7.64 (aromatic, 5); mass spectrum (70 eV) no parent ion, *m/e* 285 ($-C_2Cl_2O$), 181, 104.

Anal. Calcd for $C_{16}H_{17}Cl_4NO_4$: C, 44.78; H, 3.99; N, 3.26; Cl, 33.05. Found: C, 44.90; H, 3.93; N, 3.17; Cl, 33.16.

For 10: yield >95% on 0.01-mol scale; mp 229°; ir (CCl_4) 1756, 1670, 1525, 1415, 1350, 1250 cm^{-1}; nmr (CCl_4) δ 1.40 (s, 3), 1.76 (s, 3), 3.68 (s, 3), 3.80 (AB pattern, 2), 6.38 (s, 1), 7.67–8.32 (aromatic, 4).

Anal. Calcd for $C_{16}H_{16}Cl_4N_2O_6$: C, 40.53; H, 3.41; N, 5.91. Found: C, 40.40; H, 3.25; N, 5.79.

Methyl-2-dichloromethyl-4,4-dimethyl-2-phenyloxazolidine-3-carboxylic Acid (11).—Compound **3** (0.01 mol) was placed in 50 ml of dry benzene and brought to reflux. One equivalent of sodium methoxide in methanol was added *via* syringe and the reflux was continued for 1 hr. The solvent was removed *in vacuo*, and the remaining solid was recrystallized from methanol–water. For 11: yield 70%; mp 142–143°; ir (CCl_4) 1691, 1450, 1380, 1260 cm^{-1}; nmr ($CDCl_3$) δ 1.65 (s, 6, broad), 3.48 (s, 3), 3.66 (AB pattern, 2), 6.05 (s, 1), 7.38–7.61 (aromatic, 5). The mass spectrum (70 eV) shows a parent ion at *m/e* 317 containing two chlorines (isotope ratio).

Anal. Calcd for $C_{14}H_{17}Cl_2NO_3$: C, 52.84; H, 5.38; N, 4.43. Found: C, 52.97; H, 5.26; N, 4.36.

Ester 9 was also formed in 10% yield from this reaction.

Acknowledgment.—We thank the National Institutes of Health for support for this work.

Registry No.—1, 19312-06-2; **3**, 42449-39-8; **5**, 42407-05-6; **6**, 42449-40-1; **9**, 42449-41-2; **10**, 42449-42-3; **11**, 42449-43-4; dichloroketene, 4591-28-0.

Author Index TO VOLUME 38, 1973

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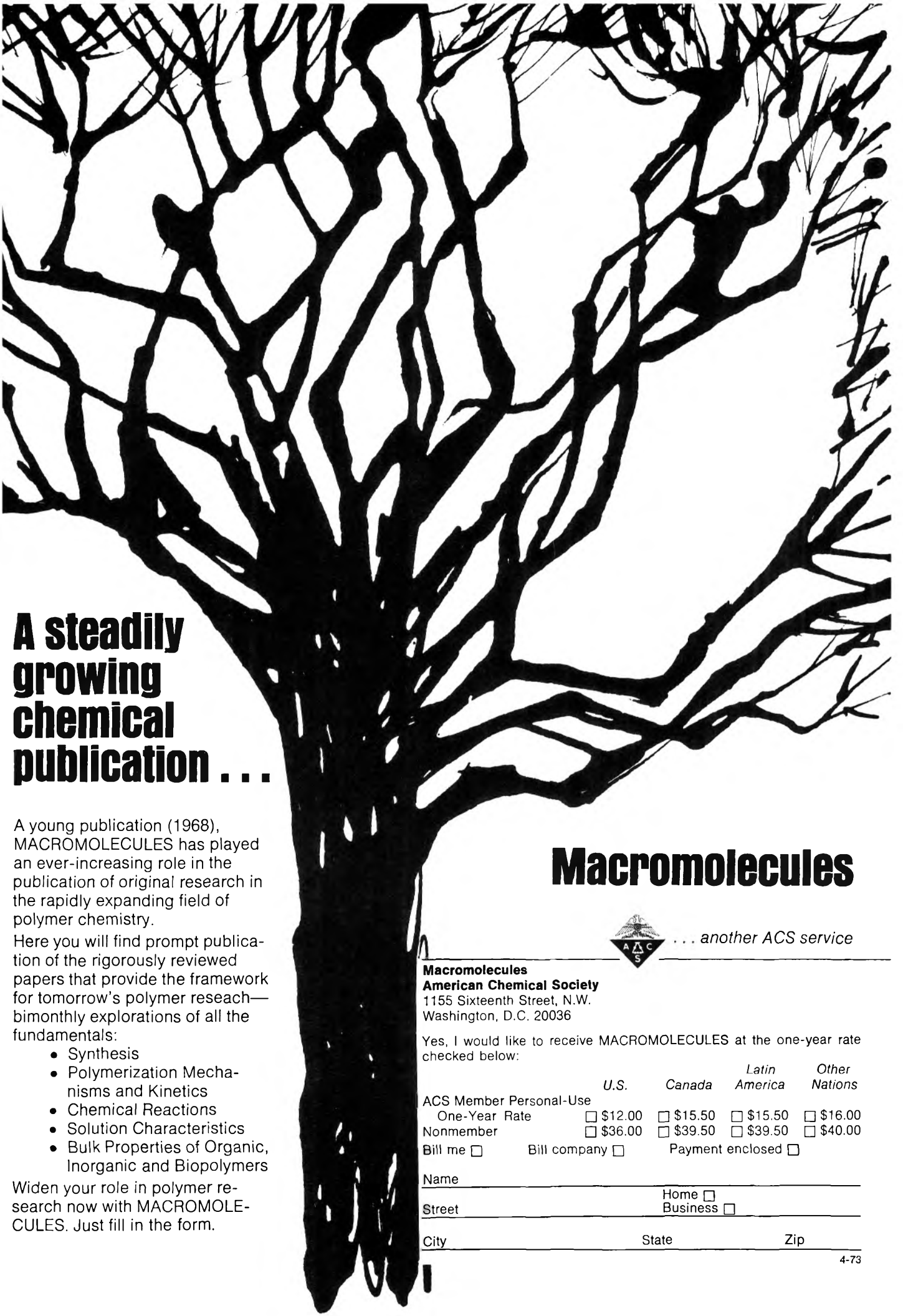
Keyword Index TO VOLUME 38, 1973



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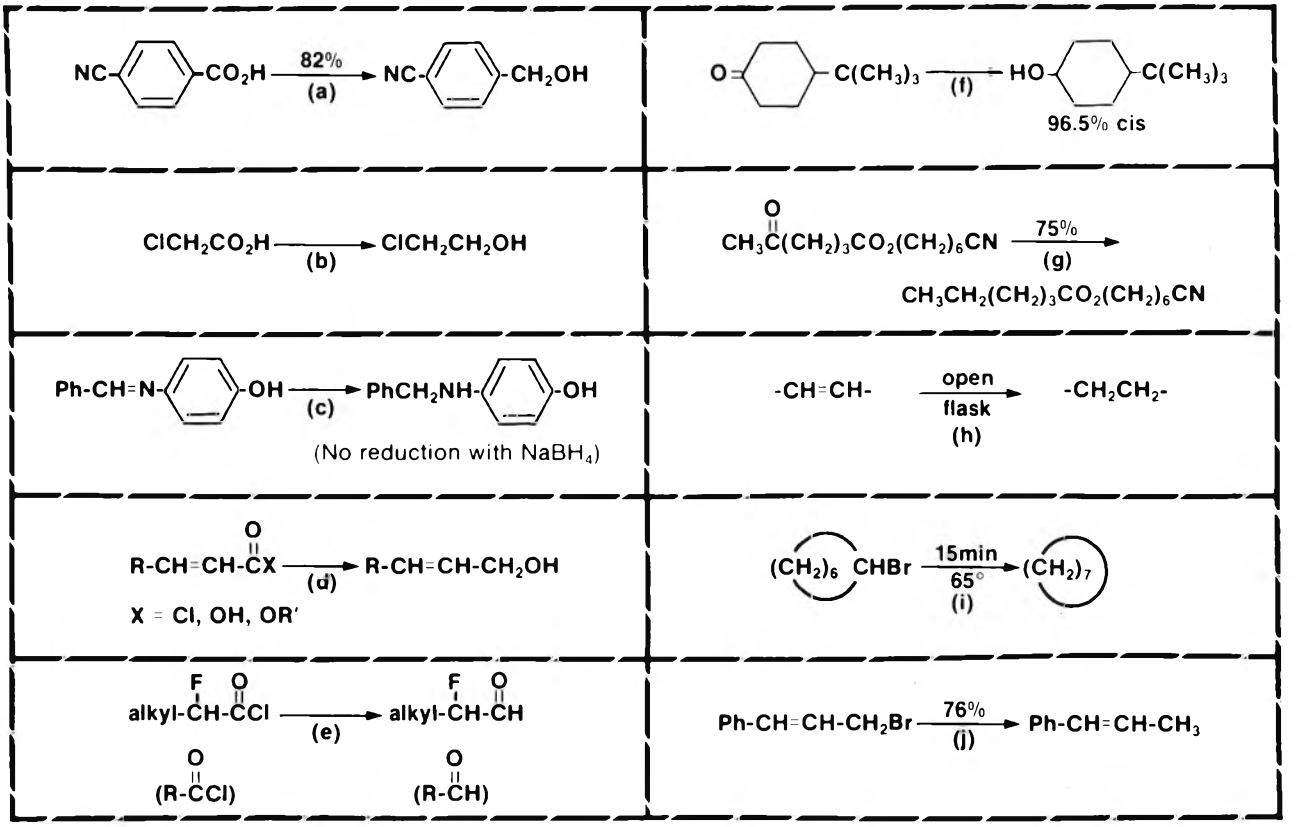
4-73

Aldrich asks...

How would you reduce ?



Answers: (a) $BH_3 \cdot THF$, (b) $(CH_3)_2S \cdot BH_3$ or $BH_3 \cdot THF$, (c) $(CH_3)_2$-$NH \cdot BH_3$, (d) Red-Al®, (e) LiAlH(O-*t*-Bu)$_3$, (f) L-Selectride™, (g) *p*-Toluenesulfonhydrazide + $NaBH_3CN$ in DMF-sulfolane, (h) Polymethylhydrogensiloxane + Pd/C, (i) Super-Hydride™, (j) $NaBH_3CN$.

The above reactions were taken from the chemical literature and are examples of the regioselective and stereoselective reductions possible with our reducing reagents. Please write for a data sheet giving a detailed comparison of and references for all of our reducing reagents.

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7924 Steinheim am Albuch
Germany

18,023-8	**Borane·dimethylamine complex**	**25g $8.00; 100g $25.00**
17,982-5	**Borane·methyl sulfide complex** (Neat liquid, d = 0.80, 80g = *ca* 1mole)	**80g $32.00**
17,619-2	**Borane·tetrahydrofuran complex** (1*M* in THF, 900g = *ca* 1 l)	**900g $37.50**
L290-4	**Lithium aluminum tri-*tert*-butoxyhydride**	**25g $14.30**
17,849-7	**L-Selectride™** [$LiBH(sec\text{-}Bu)_3$] (1*M* in THF, 900g = *ca* 1 l)	**900g $35.00**
17,620-6	**Polymethylhydrogensiloxane**	**50g $4.75; 250g $15.00**
15,109-2	**Red-Al®** [$NaAlH_2(OCH_2CH_2OCH_3)_2$], 70% in benzene	**250g $9.75; 1kg $32.00**
15,615-9	**Sodium cyanoborohydride**	**6.3g† $4.25; 10g $5.50**
		50g $22.50; 62.8g† $27.50
17,972-8	**Super-Hydride™** [$LiBH(Et)_3$] (1*M* in THF, 900g = *ca* 1 l)	**900g $34.00**
13,200-4	***p*-Toluenesulfonhydrazide**	**100g $11.25; 186.2g† $18.00**

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