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NOTES

COMMUNICATIONS

There is no supplementary material for this issue.

* In papers with more than one author, the asterisk indicates the name of the author to whom inquiries about the paper should be addressed.

AUTHOR INDEX

THE JOURNAL OF Organic Chemistry®

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NOVEMBER 14, 1975

Photochemical Formation of 12-Methylene-*cis*-bicyclo[8.2.0]dodecan-1-ol from 2-Methylenecyclododecanone. Restricted Rotation in a Biradical Intermediate

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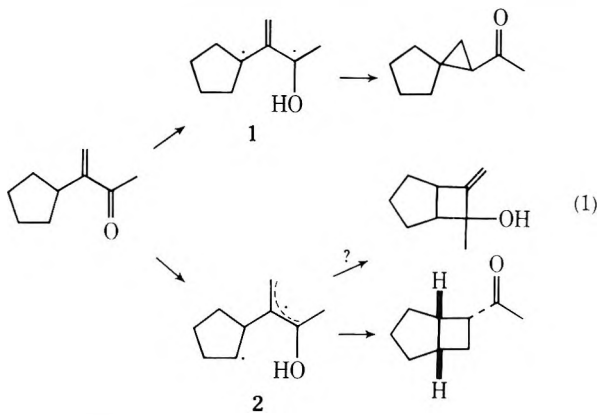
Received July 2, 1975

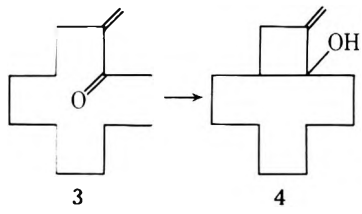
Irradiation of 2-methylenecyclododecanone (**3**) leads to 12-methylene-*cis*-bicyclo[8.2.0]dodecan-1-ol (**11**) in 87% yield, unaccompanied by the cyclobutyl or cyclopropyl ketones usually formed photochemically from α-methylene ketones. Pyrolysis of **11** leads to enone **15** and bicyclic ketone **14**, which is the cyclobutyl ketone anomalously absent from irradiation of **3**. The structures of **11**, **14**, and **15** are supported by spectroscopic and chemical data. Restricted rotation about the C(α)–C(β) bond in biradical intermediate **13** is advanced as an explanation for the exceptional behavior of **3**. These results suggest the importance of conformational mobility of a short-lived biradical in determining the products formed on photolysis of α-methylene ketones.

Photochemical isomerization of a variety of α-methylene ketones leads to cyclobutyl ketones, accompanied in some cases by related cyclopropyl ketones and methylenecyclobutanols.[1] Equation 1 gives a typical example in which all three types of products are found. There is good evidence



(1)

that the cyclopropyl and cyclobutyl ketones arise by way of biradical intermediates in which β hydrogen (**1**, for cyclopropyl ketones) or γ hydrogen (**2**, for cyclobutyl ketones) has been abstracted by the carbonyl oxygen.[2] It is quite likely that the methylenecyclobutanols also arise by way of biradical intermediates (as **2**), although there is no direct evidence for this, and the possibility remains open that these alcohols represent a concerted $[_\sigma 2 + _\pi 2]$ cycloaddition[3] of the γ carbon–hydrogen bond with the carbonyl group. The major photoproduct is cyclobutyl ketone in most cases, and frequently no methylenecyclobutanol is found at all. An exception to this generalization is the photolysis of 2-methylenecyclododecanone (**3**), which furnishes solely a single isomer of the related methylenecyclobutanol **4** in high yield (eq 2).[1] Ketone **3** is the only medium- or

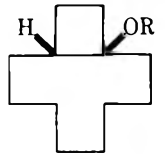


(2)

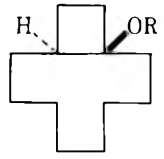
large-ring compound investigated, and its exceptional photochemical behavior presumably is related to this structural feature. Our purpose in the present study was to investigate this isomerization of **3** in more detail; in this connection we have determined the stereochemistry of **4** and carried out sensitization and quenching experiments on its formation from **3**. In addition we have studied the thermolysis of **4** and succeeded thereby in preparing the cyclobutyl ketone which is anomalously absent in photolysis of **3**. The results are discussed in detail below; they permit us to offer a reasonable explanation for the behavior of **3** in terms of restricted rotation in a biradical intermediate, thus providing an instructive example of conformational control over the fate of a short-lived intermediate.

The convenient availability of both isomers of bicyclo[8.2.0]dodecan-1-ol, **5** and **6**, from photolysis of cyclododecanone[4] suggested that a simple proof of the stereochemistry of **4** would involve its correlation with one of these known alcohols. This approach was successful in demonstrating a cis ring fusion in **4**, and the structural formulas showing the degradation incorporate this result for convenience. Before removing the exo methylene group of **4** we first protected the hydroxyl function as the methyl ether. Reaction[5] of **4** with sodium hydride in tetrahydrofuran containing methyl sulfate yielded methyl ether **7** as the only product. As we discuss in a later paragraph, use of a different solvent here can lead to molecular rearrangement

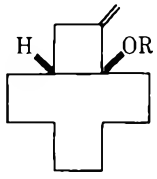
rather than simple etherification. Oxidation of **7**, first with osmium tetroxide in pyridine[6] and then directly with aqueous sodium periodate, furnished the α-methoxy ketone **8**. Attempts to combine these two steps through use of a catalytic amount of osmium tetroxide in the presence of periodate[7] were unsuccessful and apparently led to overoxidation. Wolff–Kishner reduction of **8** then gave the desired simple methyl ether **9**.[8] This degradation product was identical with an authentic sample of **9** prepared from the cis alcohol **5**, and it was readily distinguishable from the trans ether **10** prepared from **6**. The methylenecyclobutanol from irradiation of **3** accordingly is 12-methylene-*cis*-bicyclo[8.2.0]dodecan-1-ol (**11**).



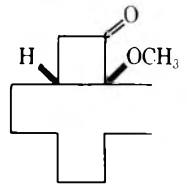
5, R = H
9, R = CH_3



6, R = H
10, R = CH_3



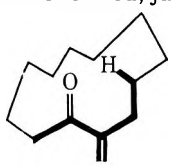
7, R = CH_3
11, R = H



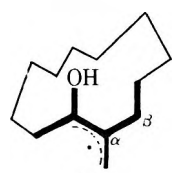
8

We next turned attention to investigation of the reactive excited state in the photoisomerization of **3** through sensitization and quenching experiments. In connection with understanding the unusual photochemical behavior of **3** it was important to determine whether this was due to some unexpected change in behavior of its excited states. We found that rearrangement of **3**, like that of the previously examined α-methylene ketones,[2] could be neither quenched nor sensitized. Isomerization of **11** proceeded equally well in benzene and in benzene containing 4 *M* 2,3-dimethyl-1,3-butadiene, and irradiation of a benzene solution of **3** and sufficient propiophenone to absorb 90% of the incident radiation gave no evidence for sensitized formation of **11**. Previous experiments have shown that the simple α-methylene ketone chromophore can indeed accept triplet energy from propiophenone.[2] Thus, **3** is in no apparent way different from other α-methylene ketones[2] which yield cyclobutyl ketones, cyclopropyl ketones, and little or no methylenecyclobutanol; there is no indication that the unique photochemical behavior of **3** is the consequence of a change in the multiplicity of the reactive excited state.[9]

There are two features of this photoisomerization requiring explanation, the formation of only the cis isomer of the methylenecyclobutanol (that is, **11**) and the total lack of any ketonic product. The unique steric situation in **3** provides an attractive explanation for both points. The unstrained geometry necessary for hydrogen transfer from the γ carbon to oxygen in **3** is shown in **12**.[10] We assume that biradical **13** is formed, just as has been demonstrated to be



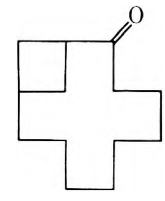
12



13

the case for α-methylene ketones which isomerize to cyclobutyl ketones.[2] In **13**, however, rotation about the C(α)–C(β) bond is severely impeded by the methylene chain constituting the remainder of the molecule, and the probability of bringing the α-methylene group into position for closure to cyclobutyl ketone enol is greatly reduced. Now, as noted above, the observed product **11** very probably arises by way of the alternative collapse of biradical **13** at the carbon bearing oxygen, a cyclization that can take place without prior C(α)–C(β) bond rotation. Not only are such delocalized biradicals already clearly implicated[2] in the photochemistry of other α-methylene ketones, but also there is evidence that singlet hydrogen transfer reactions of saturated alkanones involve analogous biradical intermediates.[11] Whatever the path to **11**, however, the reduced probability of C(α)–C(β) bond rotation in **13** can enhance formation of **11**. If **13** is an intermediate leading to **11**, competition for its collapse to the observed product is decreased; on the other hand, if **11** originates only in a concerted cycloaddition, the obvious path available to **13** is reverse transfer of hydrogen with regeneration of starting ketone **12** in its ground state.[12] It also follows from the geometry of **12** and **13** that the cis isomer of the product will be favored on steric grounds. Cyclization to form a trans-fused bicyclo[8.2.0]dodecane would require that the hydroxyl group be thrust into the methylene chain as the new carbon–carbon bond is formed. This unfavorable interaction does not occur during closure to the cis isomer **11**. The same effect is apparent in the photolysis of cyclododecanone; there the cis alcohol **5** predominates, but a minor amount of trans isomer **6** is also found.[4]

In this investigation we have also studied the thermolysis of **11** and succeeded in preparing by this route cyclobutyl ketone **14**, the "normal" photochemical product not observed on photolysis of **3**. Liquid-phase pyrolysis of **11** at 250° for 4 hr led to essentially complete destruction of starting material with formation of ketones **14** and **15**. The



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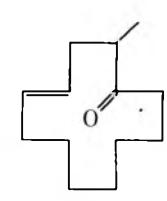

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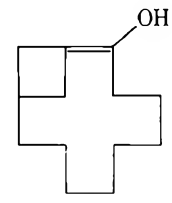
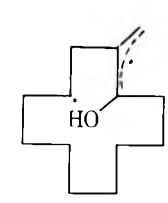
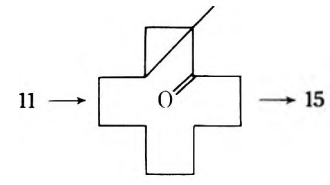


16



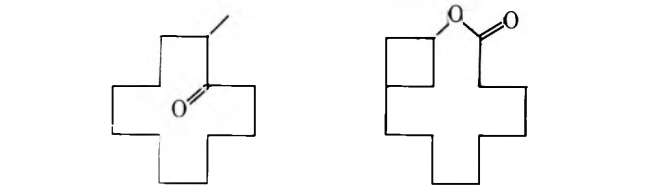
17



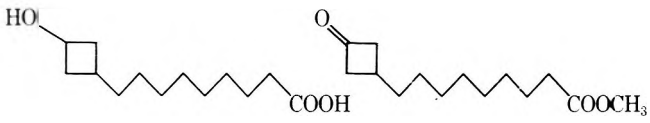
18

isomerization leading to **14** undoubtedly involves a [1,3] shift in the methylenecyclobutane to give initially enol **16** which then ketonizes. This type of rearrangement was not observed in an earlier study of thermal reactions of 2-methylenecyclobutanols,[13] although it has good analogy in the degenerate rearrangement of simple methylenecyclobutanes.[14] It could involve the same 1,4 biradical **17** (≡ **13**) expected on irradiation of 2-methylenecyclododecanone (**3**). If so, the fact that **17** leads to ketone **14** when formed

thermally but not when generated photochemically from **3** can be attributed to the higher temperature involved, which permits in the thermal process the very rotation discussed above as being restricted in the photochemical reaction. This attractive similarity of the two processes may be only a formal one, however, since a labeling study has shown that at least a portion of the methylenecyclobutane automerization follows a symmetry allowed course which is antarafacial in the allylic component.[14] Formation of **15**, on the other hand, can be rationalized by the intermediacy of **18**; that is to say, **11** undergoes ring contraction followed by opening of the cyclopropane, as shown in eq 3. The first step is a known thermal reaction of 2-methylenecyclobutanols,[13] while the pyrolytic ring opening is familiar in other 2-alkylcyclopropyl ketones.[1,15] The structure of **15**, including the trans geometry of the double bond, is based on spectroscopic properties, mechanistic considerations, and its mild catalytic hydrogenation to yield 2-methylcyclododecanone (**19**), an authentic sample of which was available from hydrogenation of **3**. The structure of **14** is defined by the following chemical evidence. Baeyer–Villiger oxidation of **14** furnished lactone **20**, which was hydrolyzed to hydroxy acid **21**. Esterification and oxidation then gave keto ester **22**, which was fully characterized. The ir and NMR



19 **20**



21 **22**

$PhCH_2CH{=}CH_2$ $PhCH{=}CHCH_3$

23 **24**

spectra of **22** show that it contains a 3-alkylcyclobutanone, a carbomethoxy group, and an unbranched aliphatic chain, thus requiring the structure assigned. If **14** indeed arises by way of its enol **16**, ketonization probably should yield a mixture of cis and trans isomers. Comparison of the 220-MHz NMR spectrum of **14** with the spectra of several simple cis and trans 3-substituted cyclobutyl methyl ketones[1] suggested that this was the case.[16]

It is interesting that when the etherification of **11** was carried out using sodium hydride in hexamethylphosphoramide rather than in tetrahydrofuran, rearrangement of **11** to **15** occurred. Further experiments showed that the presence of the methylating agent (methyl iodide or sulfate) was unnecessary, but that the yield of **15** was capricious and varied between 0 and 30%, apparently depending on the history of the solvent. The same cyclopropyl ketone intermediate (**18**) can be invoked in this case as was discussed above in the thermal conversion of **11** to **15**. In simple cases, however, it has been noted previously that the ring contraction of 2-methylenecyclobutanols (as **11** → **18**) does not occur in base.[13] It is possible that the transformation here is related to the curious rearrangement of 3-phenylpropene (**23**) to 1-phenylpropene (**24**) which occurs without evolution of hydrogen in hexamethylphosphoramide containing sodium hydride.[17]

A variety of factors undoubtedly influences the course of the photochemical rearrangement of α-methylene ketones. This investigation of the anomalous photochemical behavior of **3** provides evidence that the relative amounts of cyclobutyl ketone and methylenecyclobutanol formed can be controlled by conformational mobility. In most examples of these transformations rotation about the C(α)–C(β) bond is relatively free, and the delocalized biradical (corresponding to **2** or **13**) couples preferentially at the α-methylene group, furnishing cyclobutyl ketone enol.[1,2] This preference for coupling after rotation exists despite the simpler alternative possibility of direct collapse, without rotation about the C(α)–C(β) bond, to form methylenecyclobutanol. Selective formation of ketone from the biradical can be attributed most simply to a steric effect, with more rapid closure on the unsubstituted α-methylene carbon than on the disubstituted carbonyl carbon. This suggestion finds support in the recent demonstration that the rate of intramolecular radical addition to a double bond is strongly influenced by the degree of substitution at the site of reaction.[18] Only in a substrate such as **3**, with restricted rotation about the C(α)–C(β) bond, does formation of a methylenecyclobutanol become the predominant mode of photochemical rearrangement.

Experimental Section

Materials and Equipment. All VPC was carried out using a Varian Aerograph Model A-90-P3 with one of the following columns: A, 30% Carbowax 20M, 10 ft × 0.375 in.; B, 15% XF-1150, 5 ft × 0.25 in.; C, 20% DEGS, 5 ft × 0.25 in.; D, 25% DEGS, 20 ft × 0.25 in.; E, 10% Carbowax 20M, 5 ft × 0.25 in.; F, 25% QF-1, 15 ft × 0.375 in.; G, 25% QF-1, 10 ft × 0.25 in.; H, 25% QF-1, 50 ft × 0.25 in. Column B was prepared using 60–80 Chromosorb W in stainless steel tubing; all other columns employed 45–60 Chromosorb W in aluminum tubing. The column oven was operated at 68–205°, and the helium carrier gas flow rate was 100–200 ml/min. Tetrahydrofuran (THF) and dioxane were distilled from $LiAlH_4$; hexamethylphosphoramide (HMPA) was distilled from CaH_2. These solvents and reagent grade pyridine were stored over molecular sieves. Unless otherwise noted, ir and NMR spectra were obtained for CCl_4 solutions, the former on a Perkin-Elmer Model 237B spectrophotometer and the latter on a Varian T-60A (60 MHz) or HR-220 (220 MHz) spectrometer. Solutions were dried over anhydrous $MgSO_4$; melting points are corrected. Unless otherwise noted, all solvents were removed in vacuo with a rotary evaporator. Unless otherwise noted, all products were obtained as colorless oils.

Photolysis of Cyclododecanone. A solution of cyclododecanone (3 g) in cyclohexane (65 ml) in a toroidal vessel was irradiated with a Hanovia 450-W medium-pressure mercury lamp in a quartz immersion well using a Pyrex filter for 5 days. The solution was flushed with dry nitrogen for 20 min prior to irradiation and kept under nitrogen during photolysis. The solvent was removed, and the resulting oil was analyzed by VPC on column A to yield two major products in a ratio of 1:5, as previously reported.[4] The first and minor of these was an oil, *trans*-bicyclo[8.2.0]dodecan-1-ol (**6**): ir 3590 (m), 3450 (w), 2920 (s), 2845 (m), 1475 (m), 1440 (m), and 910 cm^{-1} (m); NMR (220 MHz) δ 2.55–2.29 (m, 1 H), 1.97–1.04 (m, 21 H).

Anal. Calcd for $C_{12}H_{22}O$: C, 78.83; H, 12.19. Found: C, 79.06; H, 12.16.

The second major peak was a solid, mp 45.8–47.8° (lit.[4] 47–49°), *cis*-bicyclo[8.2.0]dodecan-1-ol (**5**), and had ir and NMR (60 MHz) spectra that compared favorably with the published data.

A similar photolysis of a 0.1 *M* solution of cyclododecanone in benzene quenched with 2.0 *M* 1,3-pentadiene afforded only the cis isomer **5**, as shown by VPC on column A.

1-Methoxy-*cis*-bicyclo[8.2.0]dodecane (9). This compound was prepared by treatment of cis alcohol **5** (264 mg, 1.45 mmol) with sodium hydride (75 mg of a 53% mineral oil dispersion, 1.66 mmol) and methyl iodide (237 mg, 1.67 mmol) in dimethyl sulfoxide. Work-up followed by bulb-to-bulb distillation afforded 192 mg of a clear oil, approximately 40% of which was the desired ether. Further purification was accomplished by VPC on column A, and the major peak was collected to yield **9**: ir 3005 (m), 2950 (s), 2875 (s), 2845 (m), 1470 (m), 1435 (m), 1265 (w), 1180 (w), 1090 (m), and 1070 cm^{-1} (m); NMR (220 MHz) δ 3.02 (s, 3 H), 2.39–2.22 (br, 1 H), 1.95–1.15 (m, 20 H).

Anal. Calcd for $C_{13}H_{24}O$: C, 79.53; H, 12.32. Found: C, 79.55; H, 12.41.

1-Methoxy-*trans*-bicyclo[8.2.0]dodecane (10). This ether was

prepared according to the method of Brown et al.[5] using trans alcohol **6** (157 mg, 0.86 mmol) with dimethyl sulfate as the methylating agent.

The crude reaction product (162 mg) after work-up was purified on column A to yield **10**: ir 2960 (m), 2920 (s), 2850 (m), 2805 (m), 1470 (m), 1440 (m), and 1065 cm^{-1} (m); NMR (220 MHz) δ 3.07 (s, 3 H), 2.51–2.32 (m, 1 H), 2.12–1.78 (m, 5 H), 1.67–1.21 (m, 14 H), 1.21–1.02 (m, 1 H).

Anal. Calcd for $C_{13}H_{24}O$: C, 79.53; H, 12.32. Found: C, 79.38; H, 12.38.

2-Methylenecyclododecanone (3). A mixture of cyclododecanone (18.2 g, 0.10 mol), diethylamine hydrochloride (10.96 g, 0.10 mol), paraformaldehyde (3.0 g, 0.10 mmol), and absolute ethanol (4 ml) was heated to reflux on a steam bath. After 1 hr, an additional 3.0 g (0.10 mol) of paraformaldehyde was added, and the resulting mixture was similarly heated overnight. The solution was then acidified with 10% HCl and diluted with water. The mixture was extracted with ether, and the organic phase was washed with brine. After drying, the ether was removed to yield a yellow oil. This oil was distilled under high vacuum to yield 4.46 g (23% yield) of clear oil. In general, this material was pure enough for preparative photolyses. For the quenching and sensitization experiments, the oil was purified by VPC on column A to give crystalline 2-methylenecyclododecanone (**3**) identical with material from an alternative synthesis.[10]

Hydrogenation of 2-Methylenecyclododecanone (3). A solution of **3** (188 mg) in methanol containing ~10 mg of 5% Pd/C was hydrogenated at atmospheric pressure for 2 hr. The catalyst was removed by suction filtration, and the solvent was removed. The resulting oil was purified by VPC on column B to yield 97 mg of 2-methylcyclododecanone (**19**):[19] ir 2920 (s), 2855 (m), 1710 (s), 1460 (m), 1440 (m), 1375 (w), and 1110 cm^{-1} (m); NMR (220 MHz) δ 2.70–2.50 (m, 2 H), 2.22 (ddd, J = 16, 8, 4 Hz, 1 H), 1.75–1.42 (m, 5 H), 1.40–1.04 (br s, 13 H), 1.01 (d, J = 7 Hz, 3 H).

12-Methylene-*cis*-bicyclo[8.2.0]dodecan-1-ol (11). This compound was prepared photochemically from **3** using a Rayonet RPR-100 reactor equipped with 16 RPR-3000 Å lamps. Work-up gave **11** (87%) identical with that previously reported.[1]

1-Methoxy-12-methylene-*cis*-bicyclo[8.2.0]dodecane (7). This ether was prepared from **11** (1.24 g, 6.4 mmol) as described above for **10**. The crude reaction product after work-up was purified by column chromatography on neutral alumina (activity III); pentane was used to elute the desired product and minor contaminents (177 mg, 13% yield). Elution with increasing concentrations of diethyl ether afforded the starting material, which could be recycled. Further purification was accomplished by VPC on column D, and the major peak was collected to yield **7**: ir 3105 (w), 2955 (s), 2880 (m), 2845 (w), 1665 (w), 1470 (m), 1435 (w), 1080 (m), and 875 cm^{-1} (m); NMR (220 MHz) δ 4.85–4.79 (m, 2 H), 3.14 (s, 3 H), 2.69–2.54 (m, 1 H), 2.50–2.35 (m, 1 H), 2.02–1.87 (m, 1 H), 1.78–1.14 (m, 16 H).

Anal. Calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 80.84; H, 11.79.

10-Methoxy-*cis*-bicyclo[8.2.0]dodecan-11-one (8). A solution of **7** (135 mg, 0.65 mmol) in pyridine (10 ml) was added to a cooled solution of osmium tetroxide (177 mg, 0.70 mmol) in pyridine (1.5 ml) and washed in with an additional 2 × 0.5 ml of pyridine. The reaction mixture was stirred at room temperature for 7 hr. A solution of $NaHSO_4$ (306 mg) in water (3.65 ml) and pyridine (2.7 ml) was added and the reaction mixture was stirred for 1 hr. The mixture was extracted with chloroform; the extract was washed with dilute HCl to remove pyridine, saturated $NaHCO_3$, water, and brine. After removal of solvent, 188.5 mg of yellow oil was obtained: ir 3485 (br, w); transparent at 875 cm^{-1}.

Solid sodium metaperiodate (167 mg, 0.78 mmol) was added to a suspension of the crude diol in dioxane (6 ml) and water (2 ml) and was stirred at room temperature overnight. The mixture was poured into water and extracted with ether. The ether extracts were washed with saturated $NaHCO_3$, water, and brine. Removal of the solvent gave 124 mg of a yellow oil which was purified by VPC on column E to yield **8**: ir 2920 (s), 2845 (m), 1775 (s), 1475 (m), 1445 (m), 1385 (w), 1110 (m), and 1045 (m) cm^{-1}; NMR (220 MHz) δ 3.29 (s, 3 H), 3.07–2.88 (m, 1 H), 2.51–2.30 (m, 2 H), 1.92–0.72 (m, 16 H).

Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.28; H, 10.76.

Wolff–Kishner Reduction of 8. A mixture of **8** (100 mg, 0.475 mmol), hydrazine (1.6 ml of a 97% solution, 47.5 mmol), and a solution of ethylene glycolate derived from 3 ml of dry ethylene glycol and sodium hydride (109 mg, 4.75 mmol) was heated in an evacuated sealed tube overnight. The reaction product was poured into water and extracted with pentane. The organic extracts were washed with water and brine. After drying, the solvent was removed through a Vigreux column to yield a clear oil. VPC on column D yielded 11.9 mg of clear oil whose 220-MHz NMR and ir spectra and VPC retention time were identical with those of the authentic material **9**.

Quenching and Sensitization Experiments. Solutions of 0.013 M 2-methylenecyclododecanone in benzene containing 0.1–4.0 M of a mixture of *cis*- and *trans*-1,3-pentadiene were irradiated in Pyrex tubes in a Rayonet RPR-100 reactor equipped with 3500 Å lamps for 24 hr. The solutions were degassed with nitrogen for 10 min prior to irradiation. The extent of conversion of **3** to **11**, as assessed by VPC on column G, was 47%; the same value was obtained for a simultaneously irradiated ("merry-go-round" apparatus) sample containing no 1,3-pentadiene.

Attempts to form **11** in the presence of a triplet sensitizer were unsuccessful. Solutions of **3** (0.019 M) in benzene containing 3.7 or 8.9 molar equiv of propiophenone were irradiated as above in a RPR-204 reactor for 21 hr. The final ratios of **11** to **3**, as assessed by VPC on column G, were 0.097:1 and 0.072:1, respectively, as compared to 0.23:1 for a simultaneously irradiated control solution.

Irradiation of a 0.019 M solution of **3** in cyclohexane containing 0.051 M *cis*-1,3-pentadiene as above for 3 hr produced as much *trans*-1,3-pentadiene (<5%) as a simultaneously irradiated 0.051 M *cis*-1,3-pentadiene solution (assessed by VPC on column H). Formation of **11** was not suppressed (~3.5% yield), as observed with the mixture of *cis*- and *trans*-pentadienes. A similar experiment containing 0.05 M ketone **3** and 0.91 M *cis*-1,3-pentadiene gave equivalent results.

***trans*-2-Methylcyclododec-4-enone (15).** In a dry flask under nitrogen, THF (2 ml) and HMPA (2 ml) were added to sodium hydride (9 mg, 0.375 mmol). To this was added a solution of **11** (30 mg, 0.155 mmol) in THF (0.5 ml). The reaction mixture was heated overnight at 45–50°. The excess NaH was carefully destroyed with methanol and water. This solution was extracted with ether. The organic extracts were washed with 1% HCl, water, and brine. After drying, the solvent was removed to yield 12 mg of yellow oil. Purification by VPC on column D yielded *trans*-2-methylcyclododec-4-enone (**15**): ir 3015 (w), 2920 (s), 2850 (m), 1715 (s), 1455 (m), 1430 (m), 1410 (w), 970 (m), and 710 cm^{-1} (w); NMR (220 MHz) δ 5.42–5.32 (m, 2 H), 2.68–2.50 (m, 1 H), 2.50–2.30 (m, 1 H), 2.30–1.53 (m, 6 H), 1.53–0.91 (m, 9 H), 0.97 (d, J = 7 Hz, 3 H); mass spectrum m/e 194.1663 (M^+, calcd for $C_{13}H_{22}O$, 194.1670).

Similar results were obtained when *tert*-butyl alcohol or dimethyl sulfate was present in the reaction mixture. In the latter case, there was also evidence by VPC for the presence of **7**.

Hydrogenation of **15** (53 mg) as described above for **3** yielded, after VPC on column B, a material whose 220-MHz NMR and ir spectra were identical with those of 2-methylcyclododecanone (**19**) as prepared above.

Pyrolysis of 12-Methylene-*cis*-bicyclo[8.2.0]dodecan-1-ol (11). A 606-mg sample of **11** was heated in a sealed evacuated tube in a Wood's metal bath at 245° for 4 hr. Bulb-to-bulb distillation of the resulting semisolid under high vacuum yielded 255 mg of clear oil. Analysis by VPC on column F indicated the presence of two significant products. The first-eluted product was collected and was found to have ir and 220-MHz NMR spectra identical with those of **15**.

The second eluted major product was similarly purified and collected to yield bicyclo[9.1.1]tridecan-2-one (**14**): ir 2920 (s), 2850 (m), 1700 (s), 1465 (m), 1440 (m), and 1350 cm^{-1} (m); NMR (220 MHz) δ 2.94–2.69 (m, 1 H), 2.50–2.26 (m, 3 H), 2.26–2.05 (m, 3 H), 1.86–1.69 (m, 3 H), 1.48–1.14 (m, 12 H); mass spectrum m/e 194.1668 (M^+, calcd for $C_{13}H_{22}O$, 194.1670).

A sample of **14** was equilibrated in 0.5 ml of 2 M methanolic KOH at room temperature for 3 hr. Extractive work-up with pentane yielded a yellow residue whose 220-MHz NMR spectrum was identical with that of the VPC-collected material above.

Conversion of 14 to Methyl 9-(3-oxocyclobutane)nonanoate (22). A pertrifluoroacetic acid solution was prepared[20] using trifluoroacetic anhydride (0.2 ml, 1.44 mmol) and 75% H_2O_2 (27 μl, 0.788 mmol) in methylene chloride (1.0 ml). The peracid solution was added to an ice-cooled, magnetically stirred suspension of bicyclo[9.1.1]tridecan-2-one (**14**, 100 mg, 0.52 mmol) and sodium dihydrogen phosphate (292 mg) in methylene chloride (1.5 ml) with the aid of an additional 0.5 ml of methylene chloride. The reaction mixture was heated to gentle reflux (50°C) for 3.5 hr. At the end of this time, more CH_2Cl_2 was added and the reaction mixture was

washed with water, 10% Na_2CO_3, water, and brine. After drying, the solvent was removed to yield 107 mg of a pale yellow oil (**20**) whose ir spectrum indicated the absence of starting material: ir 2940 (s), 2865 (s), 1780 (m), 1730 (s), 1455 (m), 1250 (s), 1220 (s), 1165 (s), 1140 (s), and 1015 cm^{-1} (m).

Without further purification, the crude lactone mixture **20** was hydrolyzed with 5% methanolic KOH (10 ml) and water (1 ml) for 1 day. The reaction mixture was diluted with water and extracted with ether to remove neutral materials. The aqueous phase was acidified and extracted with ether. The organic extracts were dried, and solvent was removed to yield 104 mg of a white solid, mp 80–82.5°, **21**: ir (KBr) 3470 (m), 1690 cm^{-1} (s). A portion of the crude **21** (86 mg, 0.38 mmol) was esterified with diazomethane to yield 106 mg of an oil which was used without further purification: ir 3585 (m), 3410 (br), 1740 cm^{-1} (s). This hydroxy ester was oxidized with CrO_3–pyridine according to the procedure of Ratcliff and Rodehorst[21] to yield 62 mg of oil, which was purified by VPC on column C to yield 22: ir 2920 (s), 2845 (s), 1785 (s), 1745 (s), 1460 (m), 1435 (m), 1385 (m), 1360 (m), 1245 (m), 1195 (m), 1170 (m), 1110 (m), and 1085 cm^{-1} (m); NMR (220 MHz) δ 3.61 (s, 3 H), 3.15–2.97 (m, 2 H), 2.67–2.49 (m, 2 H), 2.36–2.21 (m, 1 H), 2.22 (t, J = 6 Hz, 2 H), 1.69–1.47 (m, 4 H), 1.39–1.21 (s, 10 H).

Anal. Calcd for $C_{14}H_{24}O_3$: C, 69.96; H, 10.07. Found: C, 69.94; H, 9.89.

Registry No.—**3**, 3045-76-9; **5**, 35522-56-6; **6**, 35522-60-2; **7**, 56468-02-1; **8**, 56468-03-2; **9**, 56468-04-3; **10**, 56498-05-6; **11**, 56498-06-7; **14**, 56468-05-4; **15**, 16837-94-8; **19**, 56468-06-5; **20**, 56468-07-6; **22**, 56468-08-7; cyclododecanone, 830-13-7.

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(9) An important point in this regard is that we find that on irradiation in benzene neither **3** nor the previously investigated[2] α-methylene ketones cause isomerization of 0.05 *M* *cis*-piperylene [see G. S. Hammond, P. A. Leermakers, and N. J. Turro, *J. Am. Chem. Soc.*, **83**, 2396 (1961)]. This result is contrary to our earlier report.[2] Thus, while there is no quenching of these rearrangements even by 4 *M* diene, there is no evidence that any triplets are being quenched at all. These observations have no effect on the present demonstration that **3** behaves like other α-methylene ketones, and the available data still support the earlier conclusion[2] that these are singlet reactions.
(10) Examination of ir and NMR spectra of various α-methylene ketones has led to the conclusion that **3** exists largely in an s-trans conformation, which is that required for γ-hydrogen abstraction as depicted in **12**: M. Mühlstädt, L. Zach, and H. Becwar-Reinhardt, *J. Prakt. Chem.*, **29**, 158 (1965); M. Mühlstädt, H. J. Kohler, D. Porzig, and M. Scholz, *ibid.*, **312**, 292 (1970).
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Bicyclo[4.2.1]non-3-en-2-one. A Convenient Synthesis and Evidence for a Boat Conformation in the Seven-Membered Ring[1,2]

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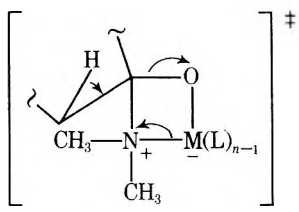
The cycloaddition reaction of 2-(*N,N*-dimethylamino)bicyclo[2.2.1]heptene, prepared from bicyclo[2.2.1]heptan-2-one and dimethylamine with stannic chloride, with ethyl propynoate in refluxing toluene produced ethyl 2-(*N,N*-dimethylamino)bicyclo[4.2.1]nona-2,4-diene-3-carboxylate. Acid hydrolysis of the amino carboxylate derivative produced bicyclo[4.2.1]non-3-en-2-one in 41% overall yield, based on bicyclo[2.2.1]heptan-2-one. The NMR data for the title compound are best understood in terms of a boat conformation in the seven-membered ring, in contrast to the evidence available for the parent hydrocarbon.

Synthetic routes into the bicyclo[4.2.1]nonane ring system are relatively few in number.[3–9] Many of these involve low-yield reactions and/or multistep sequences which are synthetically unattractive. We were particularly interested in developing an efficient route to bicyclo[4.2.1]non-3-en-2-one (**1**), an important intermediate in some of our work. Also, the four-carbon bridge of this ring system seems to us a potentially interesting scaffolding for stereochemical and mechanistic studies. The best example of the methods we wished to improve upon is the reported synthesis of the 3-bromo derivative of **1**.[8] Although the bicyclo[2.2.1]heptane system would seem to be a logical starting point for such a synthesis, there is only one report of its use in the synthesis of the [4.2.1]bicyclic system.[5] We wish to report our successful scheme, based on the commercially available bicyclo[2.2.1]heptan-2-one (2-norbornanone) (**2**).

It is well known that cycloaddition reactions of ethyl propyncate with the enamines of cyclic ketones lead ultimately to bishomologated ketones.[10,11] Thus, we sought to prepare the enamine derivative of **2**. Enamine preparation was at first problematical owing, presumably, to the strain associated with introduction of a double bond into the bicycloheptyl system.[12] The classical method[13] (pyrrolidine and *p*-toluenesulfonic acid) was not at all fruitful. We chose dimethylamine as the base and investigated the various catalysts previously employed. Anhydrous calcium chloride[14] gave only trace amounts of the desired product **3**. Stannic chloride,[15] on the other hand, proved to be most

satisfactory. We originally ascribed this to more efficient water scavenging by stannic chloride. Recently[16] 3 has been prepared using tris(dimethylamino)borane. This result, when considered along with the apparent reaction between dimethylamine and stannic chloride, suggests that for 2-norbornanone the crucial factor for enamine formation is simultaneous incorporation of the amine and a carbonyl-polarizing function within the same complex, i.e.

M = B; $n = 3$; L = $(CH_3)_2N-$
M = Sn; $n = 4$; L = $(CH_3)_2N-$

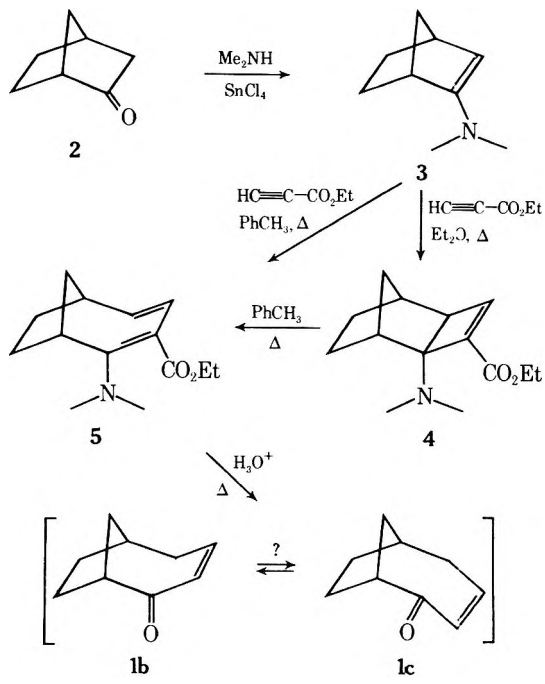


Cycloaddition[10,11] of the enamine **3** and ethyl propynoate leads smoothly and exothermally to the cyclobutene adduct **4** in ether. Actually under the reaction conditions (refluxing for 20 hr) it was anticipated that **5** would be the direct product. **4** was identified by the olefinic portion of the NMR spectrum. A singlet corresponding to one vinyl proton appears at δ 6.54. Such a signal is to be expected, since the dihedral angle between the vinyl proton and the bridgehead proton is approximately 90°.[10,17] Refluxing of **4** in toluene yields **5**. The cyclobutene adduct **4** exhibits unusual thermal stability, since most of the adducts[10] formed from other enamines are only stable below room temperature and undergo ring opening when refluxed in ether. Refluxing in ether for 20 hr leaves **4** unchanged. If the cycloaddition is carried out in refluxing toluene, the intermediate **4** is not isolated, since it is converted directly to **5**. One can, therefore, isolate **5** in a straightforward manner. Finally, acid-catalyzed hydrolysis of **5** produces the desired bicyclic unsaturated ketone **1** in 71% yield from the enamine **3**. This final step accomplishes four separate reactions in situ—hydrolysis of the enamine, hydrolysis of the ester, decarboxylation, and isomerization of the carbon–carbon double bond to the α,β position. These reactions are summarized in Scheme I.

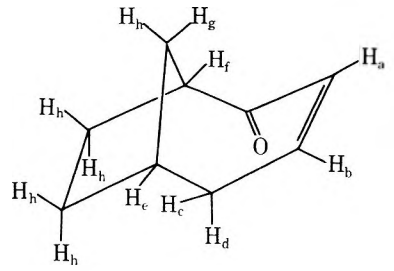
The preparation is accomplished in three steps with an overall yield of 41%. No intermediate product in the sequence need be purified. In fact, one obtains a better overall yield if intermediate purification is neglected owing to the sensitivity of the amino derivatives, **3**, **4**, and **5**. In addition, the final step can be affected essentially by a change of solvent. The product at the end of the synthetic route, bicyclo[4.2.1]non-3-en-2-one (**1**), has the added advantage of sufficient functionality for further adaptations on the four-carbon bridge.

We have indicated in Scheme I the possibility of a chair–boat equilibrium for **1**, using the seven-membered ring as the reference ring. Most, if not all, representations of the bicyclo[4.2.1] system presume a chair conformation.[3-9] Molecular mechanics calculations for the saturated hydrocarbon indicate a preference for the chair form by 1.8 or 0.3 kcal/mol, depending upon the details of the force field employed.[18] Indeed, this preference may be predicted from Dreiding models, based on torsional effects. No such preference, on the other hand, may be deduced for **1** from models. The ^{1}H NMR spectra of **1**, conversely, contain features that suggest a predominance of the boat form. A discussion of the ^{1}H NMR results is appropriate, as it highlights the particular strengths and weaknesses of current 100- and 300-MHz spectrometers in routine conformational analysis.

Scheme I

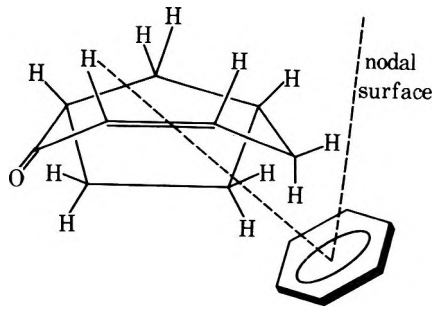


We have employed the proton labeling scheme for the boat indicated below, noting that protons c and d should be reversed in stereochemistry for the chair conformation, i.e., c = endo, d = exo.

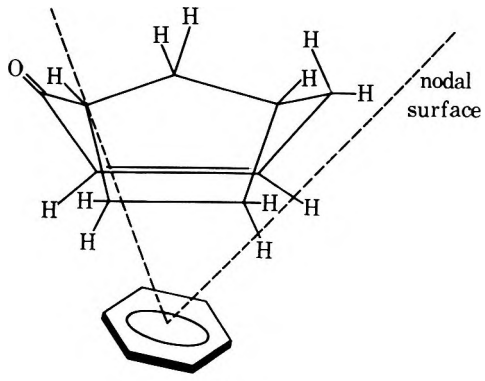


When the ^{1}H NMR spectrum of **1** is taken in deuteriochloroform at 100 MHz, the signals for four protons are sufficiently separated for identification. The apparent doublet of quartets at δ 5.82 (1 H) is assigned to H_a, while H_b appears as an apparent doublet of quartets of doublets at δ 6.21 (1 H). The multiplet at δ 2.98 (1 H) was assigned to H_f. The only other unique feature was a multiplet at δ 1.62 (1 H) clearly distinct from the complex signal arising from the remaining aliphatic protons. This last signal could only be understood in terms of a boat conformation for which H_g is directly above, and shielded by, the carbon–carbon double bond. We sought further evidence for the boat form of **1** by considering the aromatic solvent-induced shift (ASIS) for its protons, defined as $\Delta = \delta_{CDCl_3} - \delta_{C_6D_6}$.[19] Unfortunately, in perdeuteriobenzene the signal for H_g could not be unequivocally identified at 100 MHz; hence we obtained 300 MHz spectra in both chloroform-d_1 and benzene-d_6.

It is generally held[20] that ketones tend to form collision complexes with benzene, though the precise geometry of such complexes is currently unsettled. It *is* clear, nonetheless, that the π system of the benzene ring interacts with the positive end of the carbonyl dipole. Examination of models suggests that in either the chair or boat form of **1** this association may best take place on the endo face of the molecule. This is due primarily to adverse interactions with the 9-syn hydrogen (H_g). Our "best guess" regarding the approximate geometries of the two complexes is shown below.



1b



1c

The pertinent ^{1}H NMR data for 1 are collected in Table I. Let us focus first on the solvent shift data. If the collision complex for **1c** is even approximately as shown, we would anticipate rather different ASIS values for H_b vs. H_c and H_d. Models do not permit prediction of an ASIS value for H_g since the 9-syn proton appears to be too far from the benzene ring for significant shielding to occur. The collision complex for **1b**, on the other hand, can permit near-equal shielding of H_b, H_c, and H_d. In addition, close approach of the benzene molecule to these protons will bring the 9-syn proton within a region of finite shielding. For these reasons, we consider **1b** to be the preferred conformation.

Table I
Selected NMR Data for Bicyclo[4.2.1]non-3-en-2-one

Proton	δ (CDCl3)	δ (C_6D_6)	Δ = [δ (CDCl3) − δ (C_6D_6)]
H_a	5.82[a,b]	5.86[a,b]	−0.04[a,b]
H_b	6.21[a,b]	5.59[a,b]	+0.62[a,b]
H_c	2.62[b]	2.02[b]	+0.60[b]
H_d	2.56[b]	1.92[b]	+0.64[b]
H_f	2.98[a,b]	2.93[a,b]	+0.05[a,b]
H_g	1.62[a,b]	1.25[b]	+0.37[b]

Coupling constants, hertz:[a] J_{ab} = 12.9; J_{bc} = 4.7; J_{bd} = 3.4; J_{be} = 1.3; $J_{ac} \approx J_{ad} \approx J_{af} \approx$ 2.0.

[a] Observed at 100 MHz. [b] Observed at 300 MHz.

Since the shielding of the 9-syn proton was the original basis for considering the boat conformation, it is important to consider the predicted shielding by the double bond for the boat form and the carbonyl group for the chair form. The observed shielding is ~0.3 ppm. This value is within the range predicted from the long-range shielding contour maps[21] for the double bond based on either the Tillieu[22] or Pople[23] values for the principal susceptibilities. Tillieu's values lead to a predicted shielding of ~0.2 ppm while those of Pople predict shielding to the extent of ~0.4 ppm. In the chair conformation only the carbonyl group is close enough to affect the chemical shift of the 9-syn proton. Using shielding plots for the carbonyl group,[24] derived from Pople's values,[23] we find that the predicted value is only ~0.08 ppm, indicating that the carbonyl group is too far removed from the 9-syn proton to shield it significantly.

First order analysis of the olefinic multiplets observed at 100 MHz permitted the evaluation of some of the relevant coupling constants (Table I). These multiplets were only partially resolved at 300 MHz. The vinylic coupling constants J_{bc} and J_{bd} merit some comment. Dreiding models predict the following dihedral angles: $\omega(H_b–C_4–C_5–H_c)$ 0°; $\omega(H_b–C_4–C_5–H_d) \approx 110°$. Using the equations for vinylic coupling constants of Garbisch[25a] and Sayed,[25b] we find that J_{bc} (4.7 Hz) is smaller than expected. The value for J_{bd} (3.4 Hz), while corresponding approximately to the predicted value from the Garbisch equation, is significantly larger than the Sayed prediction. These findings suggest either a chair–boat equilibrium (predominantly boat) or a somewhat flattened boat. We cannot at this time distinguish between these two possibilities, but the ultraviolet spectrum is consistent with a flattened boat. The observed uv maximum [λ_{max} (EtOH) 229.5 nm (ε 10060)] is close to that predicted by Woodward rules[26] (227 nm), suggesting that conjugation between the carbonyl and vinylic groups is not significantly different from that in cyclohexenone derivatives.

Experimental Section

The ir data were taken on a Perkin-Elmer Model 257 grating spectrometer. The spectrometers used for ^{1}H NMR spectra are as follows: 60 MHz, Varian T-60; 100 MHz, Varian XL-100; 300 MHz, Varian HR300. The 300-MHz spectra were obtained through the NMR Center, Institute of Polymer Science, University of Akron, Akron, Ohio.

***N,N*-Dimethylbicyclo[2.2.1]hept-2-en-2-amine (3).** $SnCl_4$ (89.1 g, 0.342 mol) in 40 ml of dry pentane was added dropwise to a mechanically stirred solution of 58.20 g (0.528 mol) of 2-bicyclo[2.2.1]heptanone (2) and 141.5 g (3.14 mol) of dimethylamine in 1.05 l. of dry pentane under nitrogen at 0°C. The reaction mixture was stoppered and stirred under nitrogen at room temperature for 72 hr. The solids were removed by filtration of the reaction mixture on a medium porosity glass funnel. The solid was rinsed with hot, dry pentane, and the combined pentane solutions were fractionally distilled to remove all of the pentane. Crude enamine (49.45 g, ~86% pure by NMR) remained (58% yield). Because of its sensitivity to moisture and air the enamine was used directly in the preparation of the cyclobutene adduct 4: ir (neat) 3070, 2950, 2860, 2780, 1605, 1446, 1363, 1104 cm^{-1}; NMR ($CDCl_3$, 60 MHz) δ 1.5 (m, C-5, C-6, C-7 H), 2.9 (m, C-1, C-4 H), 2.62 (s, 2 CH_3), 4.42 (d of d, J = 2.2, ~1 Hz, C-3 H) [lit.[16] ir (neat) 3080, 2950, 2860, 2800, 1610, 1450, 1370, 1100 cm^{-1}].

Ethyl 2-(*N,N*-Dimethylamino)tricyclo[4.2.1.0^{2,5}]non-3-ene-3-carboxylate (4). Crude enamine 3 (0.1 mol) in 45 ml of anhydrous ether was stirred while 9.81 g (0.1 mol) of ethyl propynoate in 15 ml of ether was added dropwise over a 1-hr period. When addition was complete and when the exothermic reaction had subsided, the solution was refluxed for 20 hr. Removal of ether in vacuo left an oil corresponding to the cyclobutene 4: NMR ($CDCl_3$, 60 MHz) δ 1.6 (m, C-7, C-8, C-9 H), 1.27 (t superimposed on m, J = 6.5 Hz, $-OCH_2CH_3$), 2.32 [s, $N(CH_3)_2$], 3.0 (m, C-1, C-6 H), 3.28 (s, C-5 H), 4.17 (q, J = 6.5 Hz, OCH_2CH_3), 6.54 (s, C-4 H).

The oil 4 was dissolved in 30 ml of toluene and refluxed for 15 hr. The toluene was removed in vacuo leaving **5**, which solidified as a glass.

Ethyl 2-(*N,N*-Dimethylamino)bicyclo[4.2.1]nona-2,4-diene-3-carboxylate (5). To 49.32 g of the crude enamine 3 (86% pure) (~0.31 mol) in 93 ml of anhydrous toluene (distilled from CaH_2) was added 33.4 g (0.34 mol) of ethyl propynoate with stirring. After addition was complete the solution was stirred for 1 hr under nitrogen at room temperature and then at reflux for 15 hr. The toluene was removed in vacuo, leaving a viscous oil 5 which was used directly in the preparation of bicyclo[4.2.1]non-3-en-2-one (1): NMR ($CDCl_3$, 60 MHz) δ 1.27 (t, 3, J = 6.5 Hz, $-OCH_2CH_3$), 1.9 (m, 6, C-7, C-8, C-9 H), 2.9 (m, 2, C-1, C-6 H), 2.90 [s superimposed on m, 6, $N(CH_3)_2$], 4.15 (q, 2, J = 6.5 Hz, OCH_2CH_3), 5.38 (d of d of d, 1, J = 12.5, 7, 1.5 Hz, C-5 H), 6.31 (d, 1, J = 12.5 Hz, C-4 H).

Bicyclo[4.2.1]non-3-en-2-one (1). The crude ethyl 2-(*N,N*-dimethylamino)bicyclo[4.2.1]nona-2,4-diene-3-carboxylate (5) in

121 ml of glacial acetic acid was refluxed for 12 hr with 39.7 ml of concentrated HCl and 33 ml of water. The reaction mixture was poured into 300 ml of water and extracted with three 200-ml portions of ether. The ether solution was divided into two portions. Each portion was washed with 100-ml portions of 10% NaOH until basic, with another 50 ml of 10% NaOH, and with 50 ml of saturated NaCl solution. The ether was dried over $MgSO_4$ and removed in vacuo leaving a dark oil, which was fractionally distilled yielding 29.62 g of **5** (71% yield from the enamine **2**). Analytical samples were prepared by preparative VPC on a 6-ft 15% Apiezon L–Chromosorb P column (column temperature 134°, carrier flow rate 182 ml/min, retention time 21.0 min): bp 89.5–90° (6 mm); $n^{23}D$ 1.5244; uv λ_{max} (95% EtOH) 229.5 nm (ϵ 10060); NMR ($CDCl_3$, 100 MHz) δ 1.62 (m, 1, H_g), 1.95 (m, 5, H_h), 2.6 (m, 3, $H_c + H_d + H_e$), 2.98 (m, 1, H_f), 5.82 (d of d of d of d, 1, $J_{ab} = 12.9$, $J_{ad} = J_{ac} = J_{ac} = J_{af} = 2.0$ Hz, H_a), 6.21 (d of d of d of d, 1, $J_{ab} = 12.9$, $J_{bc} = 4.7$, $J_{bd} = 3.4$, $J_{be} = 1.3$ Hz, H_b); ir (neat) 3017, 2940, 2871, 1661, 1450, 1418, 1402, 1340, 1283, 1223, 1129, 898, 819 cm^{-1}.

Anal. Calcd mass for $C_9H_{12}O$: 136.0887. Measured mass: 136.0894.

Registry No.—**1**, 56533-25-6; **2**, 497-38-1; **3**, 41455-23-6; **4**, 56533-26-7; **5**, 56533-27-8; dimethylamine, 124-40-3.

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Molecular Design by Cycloaddition Reactions. XXIII.[1] Synthesis of Some Highly Strained Bridged Polycyclic Hydrocarbons

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Addition of dichlorocarbene (DCC) in aqueous medium to basketene, snoutene, and bullvalene gave the homobasketene, homosnoutene, and trishomobullvalene skeletons, respectively. Similar DCC addition of bicyclo[4.2.2]deca-2,4,7,9-tetraene afforded the formal 1:2 adduct of DCC to tetracyclodecadiene. Possible mechanisms for the reactions are also discussed.

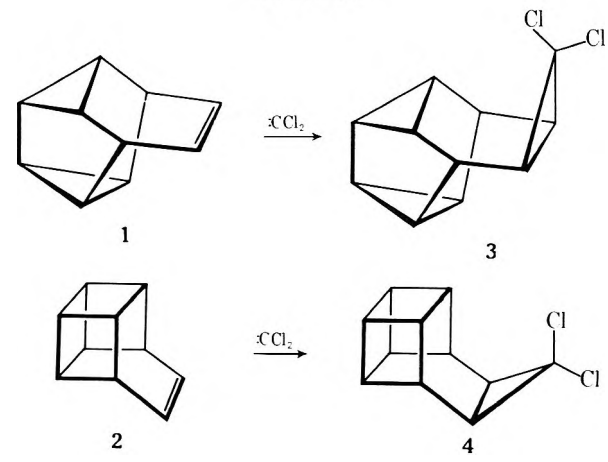
The synthesis of strained bridged polycyclic hydrocarbons is of considerable interest and continues to be a challenging objective to organic chemists.

As a continuation of our previous reports for providing a synthetic entry for new carbon-skeleton construction and further additional data for understanding the capability of a phase transfer catalyzed carbene addition[2] to some strained unsaturated compounds, we examined the carbene addition reactions of snoutene (**1**), basketene (**2**), bullvalene (**6**), and bicyclo[4.2.2]deca-2,4,7,9-tetraene (**11**), all of which are theoretically important $(CH)_{10}$ isomers connected on an energy surface with other $(CH)_{10}$ isomers.[3]

Results and Discussion

The reactions of snoutene (**1**)[4] and basketene (**2**)[5] with a 20-fold molar excess of dichlorocarbene (DCC) prepared at room temperature from chloroform in the presence of 50% aqueous sodium hydroxide–benzene with triethylbenzylammonium chloride (TEBA) as a catalyst afforded 1:1 adducts **3** and **4** in 45 and 60% yields, respectively (Scheme I). However, similar carbene addition reaction of **1** or **2** with excess phenyl(trichloromethyl)mercury gave only tarry materials and the 1:1 adduct could not be detected.

Scheme I



The NMR spectrum consisted of bridgehead protons at δ 2.87 (m, 2 H), cyclopropyl protons at δ 1.93 (m, 6 H), and characteristic dichlorocyclopropyl ring protons at δ 1.57 (s, 2 H) in compound **3**, and of two peaks of dichlorocyclopro-

Table I
DCC Addition to Bullvalene under Various Reagents

Reagent	Product distribution, % yield 1:1 (7)[a]	1:2 (8 + 9)	1:3 (10)
$CHCl_3$ + 50% NaOH in $PhCH_2\overset{+}{N}(Et)_3\ Cl^-$	0	50	10
$CHCl_3$ + $KOC(Me)_3$	60	0	0

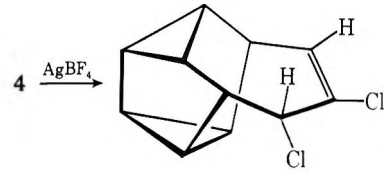
[a] See ref 9.

pyl ring protons as a singlet at δ 1.74 (2 H) and bridgehead protons as a broad singlet at δ 3.15 (8 H) in compound **4**.

These results indicate that the carbene addition reactions of **1** and **2** afforded the corresponding homosnoutene and homobasketene skeletons without skeletal rearrangement and insertion reaction. In this connection, cycloaddition reaction of basketene (**2**) with the skeletal rearrangement ([$_\pi$2 + $_\sigma$2 + $_\sigma$2]) is well known.[6]

The carbene addition to the polycyclic bridged hydrocarbons such as adamantane and adamantene gave the dichlorocarbene insertion products.[7,8] On the other hand, silver ion catalyzed skeletal rearrangement of basketene (**2**) into snoutene (**1**) is also reported.[4] Thus, the silver ion catalyzed rearrangement of **4** into **3** was carried out. When an acetone solution of **4** was refluxed with catalytic amounts of silver fluoroborate for several hours, compound **5** was obtained in a quantitative yield instead of an expected compound **3** (Scheme II).

Scheme II



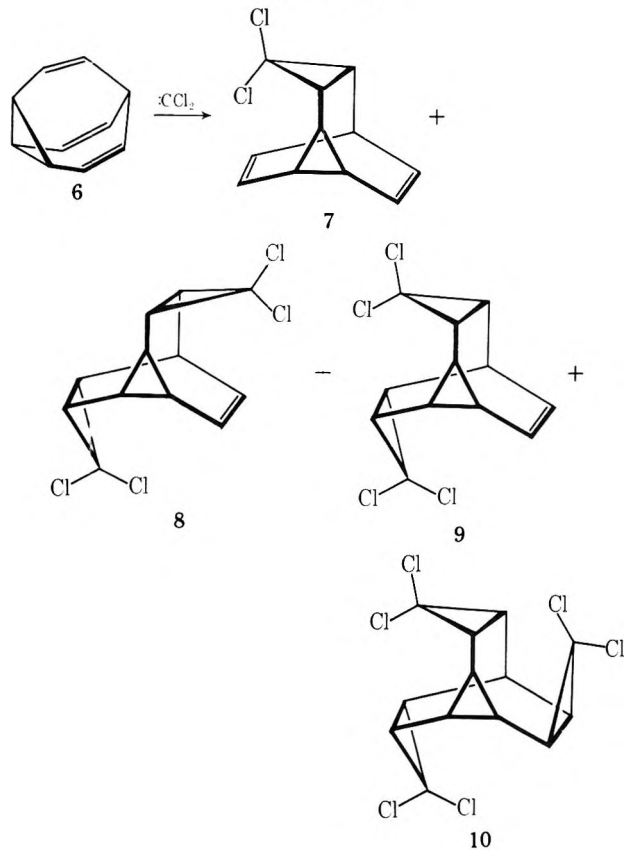
5

The NMR spectrum of **5** exhibits one olefinic proton at δ 6.28 (d, 1 H), an allylic methine proton at δ 4.61 (d, 1 H), and bridgehead protons at δ 2.87 (m, 2 H) and 2.0 (m, 6 H). Compound **5** was also identical with that of the thermal isomerization of **3** by GLC inspection (see Experimental Section).

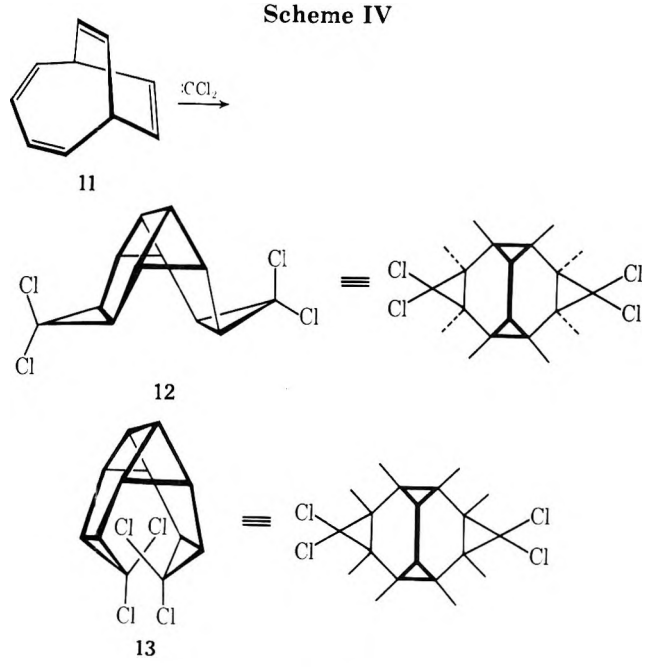
DCC addition to bullvalene (**6**)[9] under the same conditions gave a mixture of 1:2 isomers **8** and **9** (50% yield) together with a 1:3 adduct **10** (10% yield) (Table I). Further treatment of the 1:2 adducts with DCC afforded **10** mixed with recovered remaining isomeric adduct, but the mixture was difficult to purify (see Experimental Section). These results demonstrate that the reaction of **6** with DCC gave the 1:2 adducts **8** and **9** in a regioselective manner, and the formation of the 1:3 adduct **10** was only derived from the isomeric 1:2 adduct **9**, as suggested by an examination of molecular models. However, addition of bullvalene (**6**) to DCC prepared at room temperature from chloroform and potassium *tert*-butoxide afforded only a 1:1 adduct **7**,[9] from which no 1:2 and 1:3 adducts could be detected even with the use of excess DCC (Scheme III).

Similar DCC addition to bicyclo[4.2.2]deca-2,4,7,9-tetraene (**11**)[10] in the dark gave compound **12** in 40% yield (Scheme IV). The structural assignment for **12** was made on the basis of the analytical and NMR data. Surprisingly, the NMR spectrum of **12** shows no olefinic proton signals and the appearance of a characteristic sharp singlet signal of four bridgehead protons in the dichlorocyclopropyl ring

Scheme III



Scheme IV



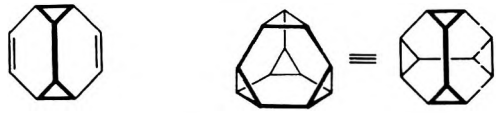
at δ 1.77, and of six equivalent cyclopropyl protons at δ 1.23 as a sharp singlet; the relevant dihedral angles in **12** are shown from molecular models to be approximately 80°, indicating the "extended" conformer rather than the "folded" counterpart **13** and, therefore, the spin-spin coupling constant in **12** should be 0 Hz.

It is interesting that this intriguing structure **12** is the formal 1:2 adduct of DCC to tetracyclo[4.4.0.0^{2,10}0^{5,7}]deca-3,8-diene (**14**) (Chart I), an often-cited (but unisolated) key intermediate in some interconversions of $(CH)_{10}$ isomers,[3] which is easily interconverted with **6** and/or **11** under thermal and photochemical conditions.[3,11] However, compound **14** seems not to be the precursor of the 1:2 adduct **12**. To

Table II
NMR Data for Products

Compd	Chemical shifts, δ (J, Hz)
3	2.87 (m, 2 H, bridgehead), 1.93 (m, 6 H, cyclopropyl), 1.57 (s, 2 H, halocyclopropyl)
4	3.15 (broad s, 8 H), 1.74 (s, 2 H, halocyclopropyl)
5	6.28 (d, J = 8.0, 1 H, olefinic), 4.61 (d, J = 4.0, 1 H, allylic), 2.87 (m, 2 H, bridgehead), 2.0 (m, 6 H, cyclopropyl)
10	1.4–1.5 (m, 10 H)
12	1.77 (s, 4 H, halocyclopropyl), 1.23 (s, 6 H, cyclopropyl)
22	6.07 (dd, $J_{8,7}$ = 11.3, $J_{8,9}$ = 5.1, 1 H, H_8), 5.69 (dd, $J_{7,6}$ = 7.5, 1 H, H_7), 3.0–3.5 (m, 2 H, H_1, H_6), 2.4–2.9 (m, 3 H, H_2, H_5, H_9), 1.96 (s, 2 H, H_3, H_4), 1.85 (dd, $J_{10,9}$ = 9.8, $J_{10,1}$ = 2.0, 1 H, H_{10})
23	6.2–6.5 (m, 2 H, H_3, H_4), 6.10 (dd, $J_{8,7}$ = 12.0, $J_{8,9}$ = 6.0, 1 H, H_8), 5.63 (dd, $J_{7,6}$ = 8.0, 1 H, H_7), 3.2–3.8 (m, 2 H, H_1, H_6), 2.4–3.1 (m, 3 H, H_2, H_5, H_9), 1.1–2.4 (complex m, 5 H, H_{10}, 2 H_{11}, 2 H_{12})
24	6.12 (dd, $J_{8,7}$ = 11.7, $J_{8,9}$ = 5.7, 1 H, H_8), 5.55 (dd, $J_{7,6}$ = 7.5, 1 H, H_7), 3.4–3.9 (m, 2 H, H_1, H_6), 2.4–3.0 (m, 3 H, H_2, H_5, H_9), 1.92 (d, J = 2.0, 2 H, H_2, H_4), 1.8 (dd, 1 H, H_{10}), 1.8–2.4 (m, 4 H, 2 H_{11}, 2 H_{12})

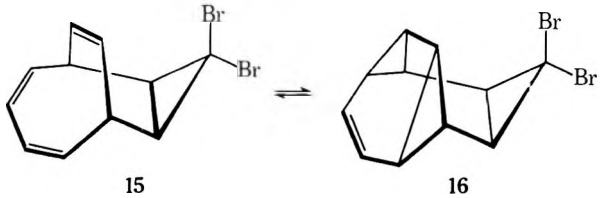
Chart I



14 19

our surprise, Schröder et al. have recently reported the isolation of 1:1 adduct **15** by the reaction of **11** with dibromocarbene (DBC) prepared at room temperature from bromoform and potassium *tert*-butoxide, which is shown to exist as an equilibrium mixture of **15** and **16** (Scheme V) in the ratios of 16:84 at 35° and 50:50 at 221.5° by NMR inspection.[12] Under the above conditions, no 1:2 adduct could be detected even with the use of excess DBC or DCC.

Scheme V

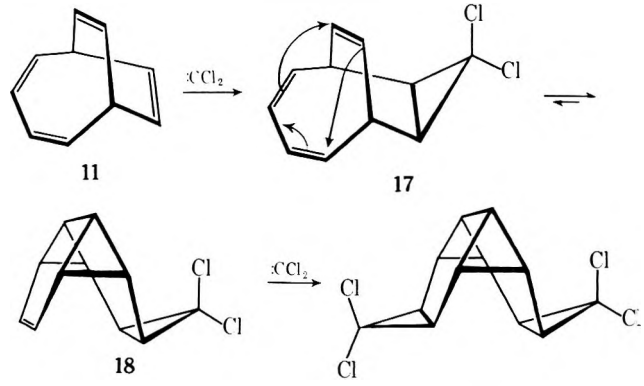


15 16

From the facts, it is concluded that the reaction of **11** with DCC by the phase transfer method initially afforded the 1:1 adduct **17** and successive DCC addition will occur after transformation by intramolecular [4 + 2] cycloaddition of **17** leading uniquely to **12**, quite close to truncated tetrahedran molecule **19** (Chart I). The reaction mechanism for **12** is shown in Scheme VI.

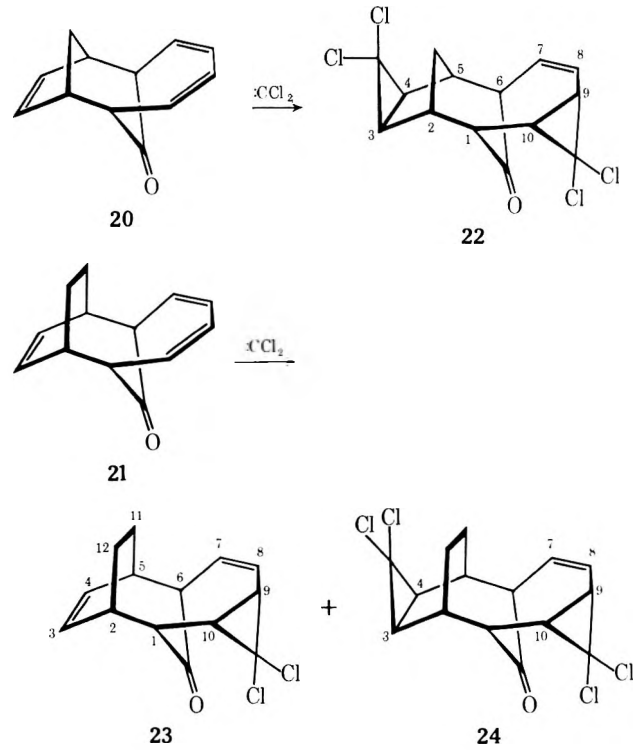
Finally, another type of compounds **20** and **21** was examined to the DCC additivity by the phase transfer method. DCC addition to **20**[13] and **21**[14] under the same conditions gave a 1:2 adducts in 40 and 5% yields, respectively (Scheme VII). However, further treatment of **23** even with

Scheme VI



11 17 18 12

Scheme VII



20 22 21 23 24

the use of excess DCC gave only a small amount of **24**, suggesting a result of steric hindrance of the ethano bridge in **21**. The NMR spectra for these adducts are summarized in Table II.

As a conclusion, the generation of DCC by this catalytic method (phase transfer),[15] compared with other procedures,[16] is quite useful for the synthesis of the new highly strained bridged polycyclic hydrocarbons, which promised a synthetic approach to the truncated tetrahedran **19**[17] and will be the subject of further report.

Experimental Section

The melting points were measured with a Yanagimoto micro-melting point apparatus and are uncorrected. Microanalyses were performed on a Perkin-Elmer 240 elemental analyzer. The NMR spectra were taken with a Jeol C-60-XL recording spectrometer with tetramethylsilane as an internal standard and the chemical shifts are expressed in δ values. GLC analyses were performed on a Varian gas chromatograph, Model 1400 (silicon SE-30). The ir spectra were taken with a Jasco Model IRA-1 grating infrared spectrophotometer.

General Procedure for Dichlorocarbene Addition Reactions in Aqueous Medium. In a 100-ml, three-necked flask fitted with a dropping funnel and a mechanical stirrer, a mixture of the unsaturated compound (0.01 mol), 50% (w/w) aqueous sodium hy-

droxide (0.4 mol, 21.3 ml), benzene (5–10 ml), and triethylbenzylammonium chloride (0.0005 mol, 0.114 g) was vigorously stirred at room temperature. Then the stirring was continued, and chloroform (0.2 mol, 16 ml) was added slowly to the mixture for several hours. The brown slurry was poured into water, and the mixture was extracted with chloroform or benzene. The extract was dried and evaporated to give a dark brownish oil. It was purified by silica gel chromatography and recrystallization.

Reaction of Snoutene (1) with DCC. Compound **3** was obtained as colorless needles in 45% yield, mp 95–97° (from MeOH).

Anal. Calcd for $C_{11}H_{10}Cl_2$: C, 62.00; H, 4.73. Found: C, 62.12; H, 4.93.

Reaction of Basketene (2) with DCC. Compound **4** was obtained as colorless needles in 60% yield, mp 87–89° (from MeOH).

Anal. Calcd for $C_{11}H_{10}Cl_2$: C, 62.00; H, 4.73. Found: C, 62.09; H, 4.80.

Silver Ion Induced Bond Rearrangement of Homobasketene (4). A solution of **4** (0.2 g) and catalytic amounts of silver fluoroborate in acetone (10 ml) was heated at reflux for several hours. The cooled solution was filtered to remove the silver salt; elution with acetone and recrystallization from EtOH gave **5** as colorless needles in a quantitative yield, mp 131–133°. This compound was identical with the thermal rearrangement product of **3**, which passed at 150° through GLC packed with 3% SE-30.

Anal. Calcd for $C_{11}H_{10}Cl_2$: C, 62.00; H, 4.73. Found: C, 62.08; H, 4.71.

Reaction of Bullvalene (6) with DCC.[18] Reaction products **8** and **9** were obtained as a mixture in 50% yield, and **10** in 10% yield.

A mixture of **8** and **9** had mp 116–119° (from EtOH). The NMR spectrum of the mixture exhibited complex signals in the region of δ 1.5–2.5 (m), centered at 3.6 (m) and 5.8 (m, olefinic protons). However, the mixture could not be purified.

Anal. Calcd for $C_{12}H_{10}Cl_4$: C, 48.69; H, 3.40. Found: C, 48.65; H, 3.32.

Compound **10** had mp 269–270° (from MeOH).

Anal. Calcd for $C_{13}H_{10}Cl_6$: C, 41.21; H, 2.66. Found: C, 41.41; H, 2.80.

Reaction of Bicyclo[4.2.2]deca-2,4,7,9-tetraene (11) with DCC. Under the dark reaction conditions, compound **12** was obtained as colorless needles in 40% yield, mp 218–219° (from benzene–*n*-hexane).

Anal. Calcd for $C_{12}H_{10}Cl_4$: C, 48.69; H, 3.41. Found: C, 48.49; H, 3.32.

Reaction of Tricyclo[4.4.1.1^{2,5}]dodeca-3,7,9-trien-11-one (20) with DCC. Compound **22** was obtained as colorless needles in 50% yield: mp 159–161° (from acetone); ir (KBr) 1710 cm^{-1} (C=O).

Anal. Calcd for $C_{14}H_{12}OCl_4$: C, 49.74; H, 3.58. Found: C, 49.61; H, 3.61.

Reaction of Tricyclo[4.4.1.2^{2,5}]trideca-3,7,9-trien-11-one (21) with DCC. Reaction products **23** and **24** were obtained as a mixture. The mixture was purified by silica gel chromatography with *n*-hexane–benzene as an eluent.

Compound **23** was obtained as colorless needles in 40% yield: mp 119–120° (from *n*-hexane); ir (KBr) 1710 cm^{-1} (C=O).

Anal. Calcd for $C_{14}H_{14}OCl_2$: C, 62.47; H, 5.24. Found: C, 62.37; H, 5.31.

Compound **24** was obtained as colorless needles in 5% yield: mp 220–223.5° (from *n*-hexane); ir (KBr) 1708 cm^{-1} (C=O).

Anal. Calcd for $C_{15}H_{14}OCl_4$: C, 51.17; H, 4.01. Found: C, 51.21; H, 3.97.

Registry No.—**1**, 26934-61-2; **2**, 5603-34-9; **3**, 56571-98-3; **4**, 56571-99-4; **5**, 56572-00-0; **6**, 1005-51-2; **8**, 56572-01-1; **9**, 56613-91-3; **10**, 56572-02-2; **11**, 15677-13-1; **12**, 56572-03-3; **20**, 4668-70-6; **21**, 35522-47-5; **22**, 56572-04-4; **23**, 56572-05-5; **24**, 56572-06-6; dichlorocarbene, 1605-72-7; $AgBF_4$, 14104-20-2.

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(17) See also end paper, J. B. Hendrickson, D. J. Cram, and G. S. Hammond, "Organic Chemistry", 3rd ed, McGraw-Hill, New York, N.Y., 1970.
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Foiled Electrocyclic Rearrangement of Cyclopropyl Cations

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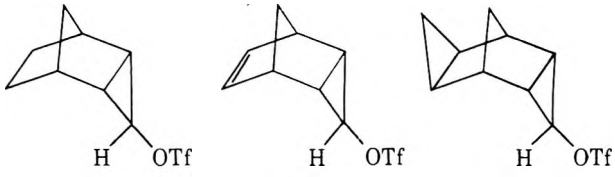
endo-Tricyclo[3.2.1.$0^{2,4}$]oct-*exo*-3-yl triflate (1), has been prepared along with the unsaturated and cyclopropyl analogs *endo*-tricyclo[3.2.1.$0^{2,4}$]oct-6-ene-*exo*-3-yl triflate (2) and *endo,exo*-tetracyclo[3.3.1.$0^{2,4}$.$0^{6,8}$]non-*exo*-3-yl triflate (3). Acetolysis rates and solvolytic product analyses indicate olefinic and cyclopropyl participation in the ionization of 2 and 3, respectively. Relative rates are 1.0, 81, and 7.1, respectively. Rates of solvolysis of 1 are enhanced by steric repulsion due to the endo-6,7 hydrogens. Triflate 1 gave both *exo*- and *endo*-bicyclo[3.2.1]oct-3-en-2-yl acetate on solvolysis. These products suggest a descrete cyclopropyl cationic intermediate. Whereas 1 gave olefinic products, 2 and 3 gave only saturated products on solvolysis, consistent with long-range olefinic and cyclopropyl participation during ionization.

The phenomenon of neighboring group participation to incipient carbocationic centers is well documented.[1] When the center is cyclopropyl, the usual mode of assistance arises via the electrocyclic cyclopropyl to allylic cation rearrangement.[2] The unopened cyclopropyl cation is involved as a discrete intermediate only when strongly stabilizing groups are substituted on the cationic center.[3] It has been shown that a small ring fused to a cyclopropyl system and a leaving group in the exo position in such a system discourages electrocyclic cyclopropyl opening.[4] The smaller the fused ring, the more closely the intermediate should resemble the discrete cyclopropyl cation. In order to further test this hypothesis, the behavior of triflate 1 under solvolytic conditions has been examined.[5] Triflates 2 and 3 have also been prepared in an attempt to observe anchimeric assistance to the developing cationic center in the system where electrocyclic rearrangement has been blocked.

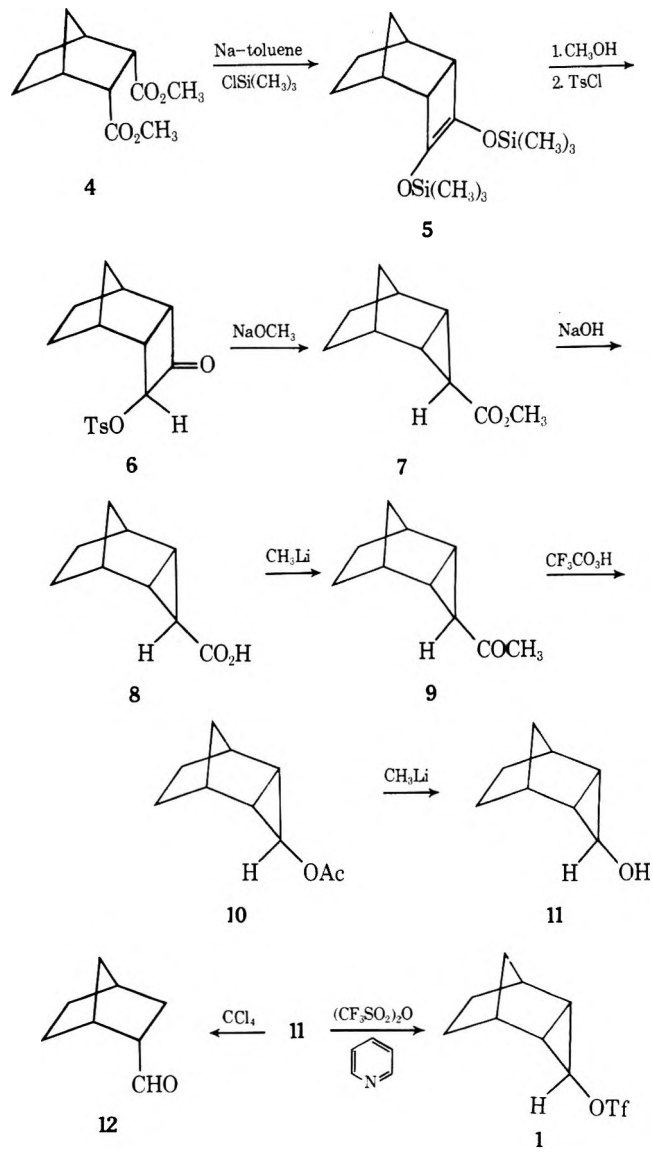


1 2 3

Syntheses. One of the major synthetic difficulties to be overcome was the incorporation of the endo-cyclopropyl group in 1. Carbene additions to norbornene occur exclusively from the exo direction.[6] Hence the acyloin condensation was used to incorporate the endo ring system. Cyclization of diester 4 using the method of Schräpler and Rühlmann[7] gave bistrimethylsilyl ether 5 in 92% yield. Methanolysis was followed by conversion of the hydroxy ketone to tosylate 6. Favorskii rearrangement gave the ring-contracted ester 7.[8] The initial rearrangement product has the carbomethoxy group in the endo position. Epimerization to the desired ester 7 occurs readily under the reaction conditions. The completion of the synthesis was straightforward as outlined in Scheme I. Alcohol 11 (precursor to 1) proved to be relatively unstable. Rearrangement to aldehyde 12 occurs when 11 is warmed in carbon tetrachloride. However treatment with triflic anhydride in pyridine successfully transformed 11 into 1.

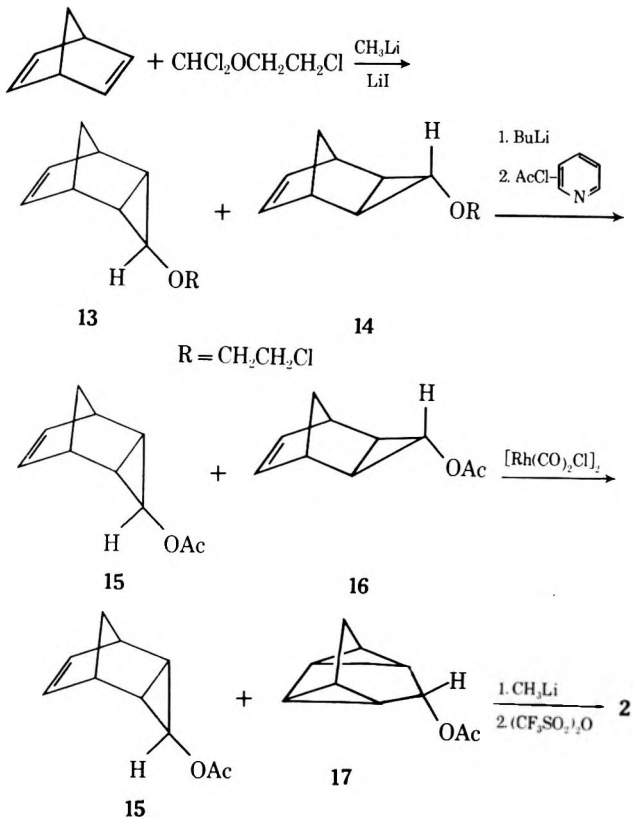
An analogous approach to unsaturated triflate 2 was not attempted owing to anticipated difficulties in maintaining unsaturation in the Baeyer–Villiger oxidation step. The procedure of Schöllkopf[9] was employed as shown in Scheme II. This procedure makes use of the fact that carbene additions to norbornadiene give some endo as well as exo adducts. Treatment of norbornadiene with dichloromethyl chloroethyl ether and methyllithium gave an unsta-

Scheme I

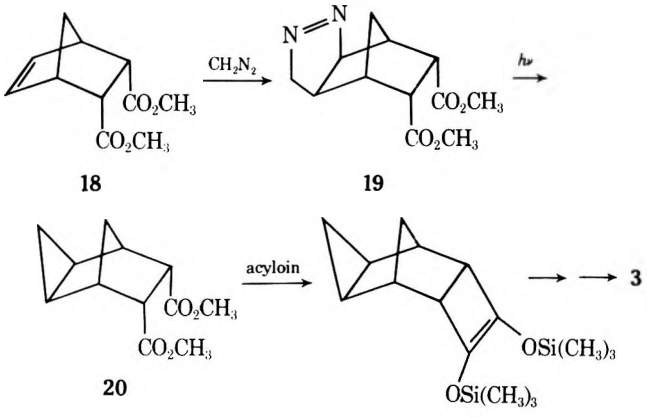


ble mixture of chloro ethers 13 and 14 (Scheme II). Cleavage of this mixture with butyllithium followed by treatment of the crude alcohol mixture with acetyl chloride–pyridine in ether gave a 50% yield (based on dichloromethyl chloroethyl ether) of acetates 15 and 16 in a ratio of 0.41:1. Treatment of the acetate mixture with rhodium dicarbonyl chloride dimer isomerizes exo isomer 16 to 17 while leaving 15 unscathed.[10] When this new acetate mixture (15 and 17) is converted to the corresponding triflates,

Scheme II



Scheme III



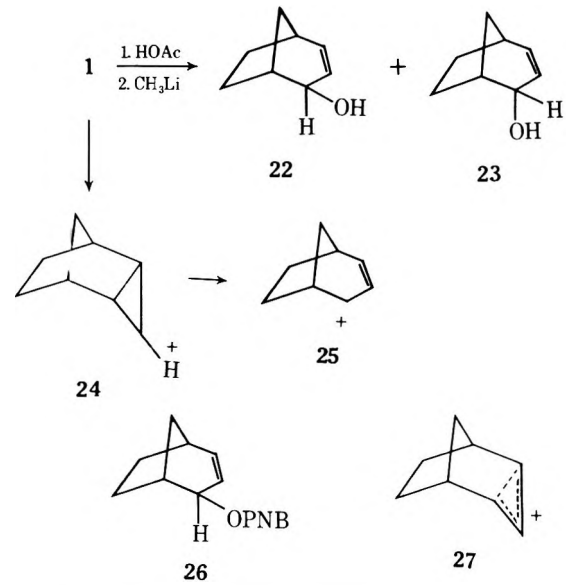
only **2** survives. The triflate derived from **17** is expected to be extremely reactive and no trace of this system is seen.

The synthesis of **3** was analogous to that of **1**. The prerequisite ester, **20**, necessary for cyclization was prepared by photolysis of the pyrazoline **19** derived from the unsaturated diester **18** (Scheme III). (Various Simmons–Smith procedures using **18** gave only small amounts of **20** in a very slow reaction. This lack of Simmons–Smith reactivity is apparently due to an electron-deficient olefinic linkage in **18**, a feature which leads to enhanced rates of pyrazoline formation.) Acyloin cyclization of **20** gives a 75% yield of the tetracyclic system **22**. The remainder of the synthetic sequence to **3** was completely analogous to Scheme I.

Results and Discussion

Solvolysis of 1. Acetolysis of **1** gave, after cleavage of the acetate products with methyllithium, a 91% yield of alcohols **22** and **23** in a ratio of 2.3:1 with exo alcohol **22** predominating.[11,12] No trace of acetate with retained tricyclic structure could be detected. The unexpected appearance of endo alcohol **23** is in contrast to the behavior of **26**, which gives exclusive exo alcohol **22** on solvolysis.[13] A product stability study showed that the exo acetate (precursor to **22**) isomerized under the reaction conditions[14] to give an identical acetate mixture with that obtained in the solvolysis study.

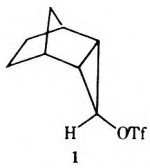
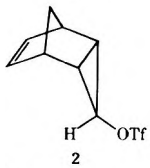
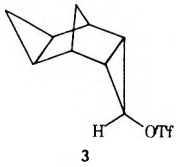
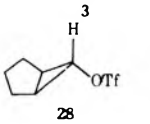
The lack of formation of acetate **10** (which was not convertible to the acetate derivatives of **22** and **23** under the reaction conditions) argues against a "partially opened allylic cation"[4b,15] as suggested by Schleyer, Schöllkopf, Pople et al. in the solvolysis of *exo*-bicyclo[4.1.0]hept-7-yl tosylate and bicyclo[3.1.0]hex-6-yl triflate (**28**). If solvent capture of such a cation, **27**, occurred, substantial amounts of product with retained tricyclic structure should be produced. This is due to the significant positive charge localized on carbon 3 in the partially opened ion **27**. This process would be analogous to the formation of *exo*-bicyclo[4.1.0]hept-7-yl acetate from *exo*-bicyclo[4.1.0]hept-7-yl tosylate. The allylic alcohol products suggest that one actually attains the cyclopropyl cation **24** as a descrete intermediate.[16] The rearrangement of **24** to **25**, which accounts for the observed products, is now allowed, and is expected to occur rapidly.[17] The acetolysis of **1** hence points to an extremely rare case of a solvolytically generated unsubstituted cyclopropyl cation.[19]



Consider next the rates of acetolysis of **1**. Kinetic data (Table I) imply that solvolysis of **1** is enhanced. The basis of this conclusion is the following. Triflate **1** undergoes acetolysis 4.6 times faster than *exo*-bicyclo[3.1.0]hex-6-yl triflate (**28**),[4c] despite the greater ring strain in the former. Because of the effectively "smaller" fused ring in **1**,[20] acetolysis is expected to be slower than in **28**. Additionally, **28** solvolyses *faster* than predicted on the basis of the carbonyl stretching frequency of cyclopropanone.[21] This fact, along with the fact that **28** leads to a partially opened ion, suggests that the acetolysis rate of **28** is enhanced relative to its "unassisted rate". Since **1** solvolyses even faster than **28**, the conclusion must be that **1** is considerably enhanced. The source of this rate enhancement is thought to be steric repulsion[22] due to the endo 6,7 hydrogens which is relieved as **1** proceeds to **24**.

Solvolysis of 2. Acetolysis rates indicate that ionization of **2** is greatly assisted by long-range olefinic participation. Because **1** is itself largely enhanced, its absolute rate is not a good model for the unassisted solvolysis of **2**. Triflate **2** undergoes acetolysis 81 times faster than **1** despite the ex-

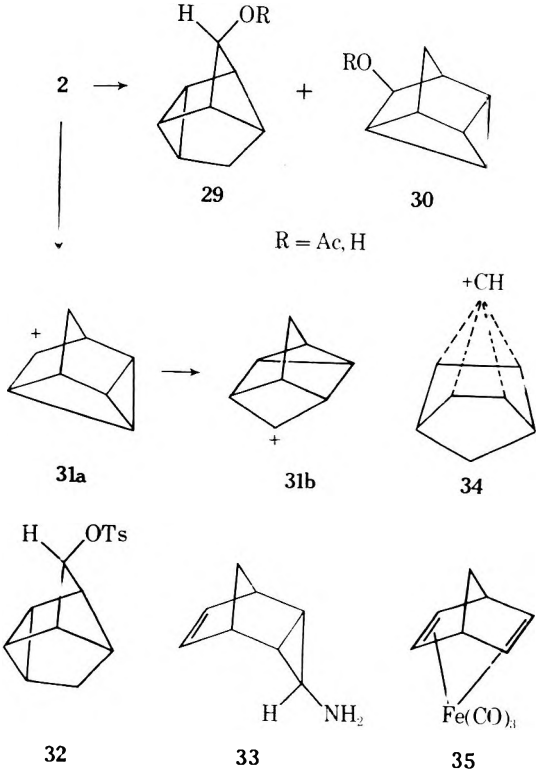
Table I
Rates of Solvolysis in Acetic Acid–0.1 *M* Sodium Acetate

Compd	Temp, °C	k, sec^{-1}	$\Delta H^{\ddagger}$, kcal	$\Delta S^{\ddagger}$, eu	k_{rel} (100°)
 1	140.0	(4.20 ± 0.01) × 10^{-5}	32.7	−0.1	
	150.0	(1.10 ± 0.03) × 10^{-4}			
	160.0	(2.73 ± 0.04) × 10^{-4}			1
	100.0[a]	5.31 × 10^{-7}			
 2	100.0	(4.32 ± 0.02) × 10^{-5}	28.1	−3.6	81
	110.0	(1.19 ± 0.03) × 10^{-4}			
	120.0	(3.13 ± 0.01) × 10^{-4}			
 3	120.0	(3.52 ± 0.03) × 10^{-5}	31.8	1.4	
	130.0	(9.73 ± 0.02) × 10^{-5}			
	140.0	(2.66 ± 0.03) × 10^{-4}			7.1
	100.0[a]	3.75 × 10^{-6}			
 28	150.0[b]	2.23 × 10^{-5}	32.3	−4.3	
	175.0[b]	2.01 × 10^{-4}			
	100.0[a,b]	1.15 × 10^{-7}			0.22

[a] Calculated from data at other temperatures. [b] Data of Su, Sliwinski, and Schleyer, ref 4c.

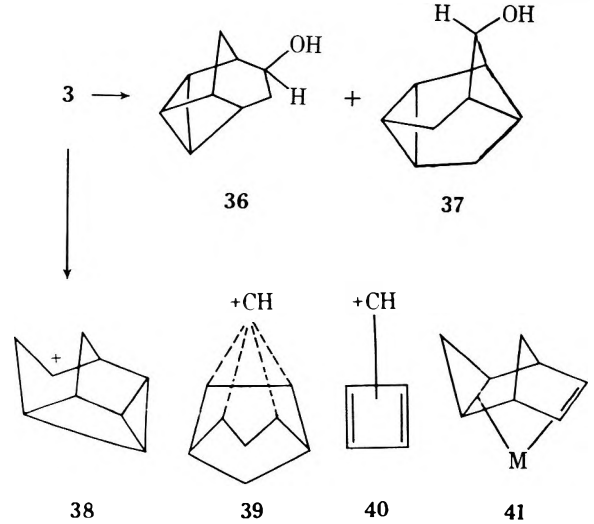
pected rate-retarding inductive effect of the double bond[23] and the lack of steric acceleration in **2**. Anchimeric assistance in **2** is therefore *much greater than*[24] the observed 81 difference in rate between **1** and **2**.

Product studies also bear out the involvement of the unsaturated center in the ionization of **2**. Acetolysis leads to a 55% yield of acetates **29**-OAc and **30**-OAc in a ratio of 1:1. In 65% aqueous acetone, **2** gives a 77% yield of the corresponding alcohols **29**-OH and **30**-OH in a ratio of 1.1:1.[25] No olefinic products were obtained. The same products were found by Coates[26] in acetolysis of **32** and recently by Masamune[27] in the aqueous deamination of **33**. The similarity in products implies a common intermediate or series of intermediates, represented by **31**. The more delocalized ion conceptically derived from **2**, ion **34**, has been generated by Masamune[27] under stable ion conditions. This ion and derivatives[28] can be considered cationic analogs of the well known norbornadiene–iron tricarbonyl complex, **35**.[29]



Solvolysis of 3. Significant long-range cyclopropyl participation in the ionization of **3** is also inferred by rate data. Despite the expected decrease in steric acceleration (relative to **1**) and the rate-retarding cyclopropyl inductive effect,[30] **3** still solvolyzed 7.1 times faster than **1**. Cyclopropyl enhancements in **3**, although slightly less than olefinic enhancements in **3**, must therefore be a real and large factor.

For product studies, solvolysis of **3** was carried out in 65% aqueous acetone containing triethylamine to neutralize liberated triflic acid. Structural assignment of the hydrolysis products proved to be quite formidable. A mixture of at least four alcohols was produced. Spectral data showed the lack of olefinic linkages in the two major isomeric alcohols produced and the presence of cyclopropyl hydrogens. Only alcohols **36** and **37** have structures consistent with the spectral properties of these two major alcohols. Of these two, the major alcohol is assigned structure



36 on the basis of the observed triplet at δ 4.00 (J = 8 Hz) in the carbinyl region of the NMR spectrum. The minor alcohol, assigned structure **37**, shows a broad singlet at δ 3.94 in the carbinyl region. The other products, produced in minor amounts, remained uncharacterized.

The two major products, as well as kinetic evidence, point to a long-range cyclopropyl-assisted ionization, leading to **38**. The more delocalized ion, **39**, conceptionally derived from **3**, is the trishomo analog of square pyrimidal cation **40**,[31] and the cationic analog of metal–tricyclo[3.2.1.$0^{2,4}$]octene complexes, **41**.[10a,b]

Experimental Section

NMR spectra were recorded on a Varian A-60A spectrometer. Data are reported in δ (parts per million) relative to tetramethylsilane. Mass spectra were recorded on an AEI Scientific Apparatus MS902 spectrometer. Infrared spectra were recorded on a Perkin-Elmer Infracord spectrometer. Elemental analyses were performed by Midwest Microlab, Ltd.

Acyloin Condensation of *endo-cis*-2,3-Dicarbomethoxynorbornane (4). Sodium (37 g) was dispersed in 1300 ml of dry refluxing toluene using a wire stirrer and 170 g of chlorotrimethylsilane was added. A solution of 60.6 g of diester **4** in 700 ml of toluene was added dropwise to the stirred, refluxing solution over a 14-hr period. Refluxing was continued for an additional 8 hr. The mixture was cooled and filtered through Celite, and solvent was removed from the filtrate by distillation through a Vigreux column at reduced pressure. The residue was distilled through a Vigreux column to give 78.5 g (92%) of bistrimethylsilyl ether **5**: bp 75–80° (0.3 mm); NMR (CCl_4) δ 0.15 (18 H, s), 1.31 (4 H, broad s), 1.58 (2 H, m), 2.08 (2 H, m), 2.67 (2 H, doublet of doublets).

Anal. Calcd for $C_{15}H_{28}O_2Si_2$: C, 60.75; H, 9.52. Found: C, 60.61; H, 9.62.

Methanolysis of 5. Absolute methanol (160 ml, distilled from magnesium) was added to 32 g of bistrimethylsilyl ether **5** under nitrogen. The solution was refluxed for 7 hr. Solvent was removed under vacuum and the crude residue was slurried in pentane. The product was collected, washed well with pentane, and air dried. A white solid weighing 15.6 (95%) was obtained: mp 105–140°; NMR ($CDCl_3$) δ 1.60 (6 H, m), 2.58 (2 H, m), 3.16 (2 H, m), 4.16 (1 H, s, exchanges with D_2O), 4.81 (1 H, doublet of doublets, J = 9, 4 Hz).

Anal. Calcd for $C_9H_{12}O_2$: *m/e* 152.0837. Found: *m/e* 152.0858.

Preparation of 6. The crude hydroxy ketone obtained above (15.6 g) was dissolved in 80 ml of pyridine and the solution was cooled to 0°. With stirring, 21.9 g of *p*-toluenesulfonyl chloride was added in portions. The mixture was stored at 0° for 24 hr and then taken up in water and methylene chloride. The methylene chloride extract was washed with dilute hydrochloric acid to remove pyridine and with sodium carbonate solution, and dried over anhydrous sodium sulfate. The solvent was removed by rotary evaporator. The yield of crude tosylate 6 was 28.5 g (91%), mp 96–100°. An analytical sample was recrystallized from methanol: mp 100–102°; NMR ($CDCl_3$) δ 1.50 (6 H, br s), 2.30 (2 H, m), 2.46 (3 H, s), 3.12 (2 H, m), 5.28 (1 H, doublet of doublets, J = 9, 3 Hz), 7.66 (4 H, doublet of doublets, aromatic).

Anal. Calcd for $C_{16}H_{18}O_4S$: C, 62.72; H, 5.92; S, 10.47. Found: C, 62.44; H, 6.07; S, 10.68.

Favorskii Rearrangement of 6. Sodium methoxide was prepared by dissolving 7.26 g of sodium in 145 ml of absolute methanol. The solution was cooled in ice under nitrogen while 9.07 g of tosylate **6** was added in portions. The mixture was brought to reflux and heating was continued for 2 hr. The mixture was then cooled and 19 g of acetic acid was added. The mixture was then taken up in low-boiling petroleum ether and water. The aqueous phase was extracted with an additional portion of petroleum ether. The combined extracts were washed with water and dried over anhydrous sodium sulfate. The solvent was removed by distillation through a glass helice packed column and the residue was distilled through a short-path condenser. The yield of ester **7** was 1.98 g (40%): bp 67–69° (0.7 mm); NMR (CCl_4) δ 1.0–1.6 (6 H, m), 1.8–2.1 (3 H, m), 2.40 (2 H, m), 3.57 (3 H, s).

Anal. Calcd for $C_{10}H_{14}O_2$: *m/e* 166.0994. Found: *m/e* 166.1019.

Saponification of 7. A 2.24-g sample of ester **7** was dissolved in 10 ml of methanol and a solution of 1.84 g of potassium hydroxide in water was added. The mixture was refluxed for 2 hr and the volume was reduced to 10 ml by distillation at reduced pressure. The residue was acidified with dilute hydrochloric acid and the solid acid **8** was collected, washed with water, and dried under vacuum. The yield of crude acid **8** was 1.66 g (81%). A sample was purified by sublimation at 0.3 mm, mp 114–116°.

Anal. Calcd for $C_9H_{12}O_2$: *m/e* 152.0837. Found: *m/e* 152.0829.

Preparation of 9. A 1.66-g sample of acid **8** was dissolved in 40 ml of dry ether. A 14-ml aliquot of 1.7 *M* methyllithium in ether was diluted to 25 ml with ether and added dropwise to the stirred solution. Upon completion of the addition, the mixture, from which salts had precipitated, was refluxed for 1 hr. The mixture was then cooled and poured into ice water and the ether phase was separated. After washing with saturated sodium chloride solution, the ether phase was dried over anhydrous sodium sulfate and filtered and the solvent was removed by distillation through a Vigreux column. The residue was distilled to give 1.39 g (84%) of ketone **9**, bp 57–59° (0.6 mm), which crystallized on standing: NMR ($CDCl_3$) δ 0.9–1.7 (6 H, m), 1.75–2.1 (3 H, m), 2.17 (3 H, s), 2.37 (2 H, m).

Anal. Calcd for $C_{10}H_{14}O$: *m/e* 150.1045. Found: *m/e* 150.1047.

Baeyer–Villiger Oxidation of 9. Peroxytrifluoroacetic acid was prepared from 1.08 g of 90% hydrogen peroxide and 10.1 g of trifluoroacetic anhydride in 10 ml of methylene chloride. A 1.6-g sample of ketone **9** was dissolved in 23 ml of methylene chloride and 18.7 g of dibasic potassium phosphate was added. The peracid solution was added dropwise to the cooled mixture with vigorous stirring. Upon completion of the addition, the mixture was refluxed for 1.75 hr. The mixture was taken up into ether and water. The organic phase was washed with potassium carbonate solution and saturated sodium chloride solution and dried over anhydrous sodium sulfate. Solvents were removed by distillation through a Vigreux column. The residue was distilled to give 1.27 g (72%) of acetate **10**: bp 49–50° (0.4 mm); NMR (CCl_4) δ 1.0–1.4 (6 H, m), 1.4–1.7 (3 H, m) 1.90 (3 H, s), 2.39 (2 H, m), 4.00 (1 H, s).

Anal. Calcd for $C_{10}H_{14}O_2$: *m/e* 166.0994. Found: *m/e* 166.0975.

Formation and Isomerization of 11. A 1.15-g sample of acetate **10** was dissolved in 10 ml of ether and 10 ml of 1.7 *M* methyllithium in ether was added dropwise to the solution cooled in an ice bath. The mixture was stirred at 15° for 15 min and cooled to −78°, and 15 ml of water was added dropwise. The ice was allowed to melt and the ether phase was separated, washed with water and saturated sodium chloride solution, and dried over sodium sulfate. After filtration, the solvent was removed under vacuum. The crude residue showed the following NMR (CCl_4): δ 1.0–1.8 (8 H, m), 2.33 (2 H, m), 3.29 (1 H, s). No trace of the aldehyde proton of **12** at δ 10.02 was detected. When the NMR sample was warmed at 65° for 15 min, no trace of the carbinyl proton at δ 3.29 remained. A sharp singlet appeared at δ 10.02. A sample of aldehyde **12** was isolated by distillation of the NMR sample. The infrared showed an aldehydic C–H stretch at 3.64 μ and a carbonyl stretch at 5.80 μ.

Formation of 1. The above procedure for the preparation of alcohol **11** was followed using 0.90 g of acetate **10** and 7 ml of 1.7 *M* methyllithium. The crude alcohol **11** was dissolved in 3 ml of ether and added to a solution of 3.1 g of trifluoromethanesulfonic anhydride in 9 ml of pyridine held at 0°. The mixture was stored at 0° for 8 hr. The mixture was then poured into water and extracted with two portions of pentane. The combined organic extracts were washed with acetic acid solution to remove pyridine, with water, and with potassium carbonate solution and dried over anhydrous sodium sulfate. The pentane was removed by distillation through a Vigreux column and the residue was distilled to give 0.923 g (67%) of colorless triflate **1**: bp 48–50° (0.45 mm); NMR (CCl_4) δ 1.1–1.8 (6 H, m), 1.95 (2 H, m), 2.55 (2 H, m), 4.25 (1 H, s).

Anal. Calcd for $C_9H_{11}F_3O_3S$: *m/e* 256.0381. Found: *m/e* 256.0366.

Formation of 15 and 16. A 10-g sample of dichloromethyl chloroethyl ether and 69 g of norbornadiene were placed in a flask and cooled to 0°. Methyllithium (84 ml of 1.08 *M* solution) prepared from methyl iodide in ether was added dropwise to the stirred solution over a 20-min period. After stirring at 0° for 15 min under nitrogen, ice water was added. The organic phase was separated rapidly and washed with cold sodium thiosulfate solution and sodium hydroxide solution. The organic phase was dried over sodium sulfate and filtered and solvents were removed under vacuum. The entire procedure was carried out rapidly under nitrogen. The crude residue (**13** and **14**) was dissolved in 60 ml of ether and 80 ml of 2.3 *M* butylllithium in hexane was added to the cold solution over 15 min. After stirring for 15 min, the solution was cooled to −78° and 1.5 g of methanol in 20 ml of ether was added. This cold mixture was then added via syringe to a slurry of 20 g of acetyl chloride and 33 g of pyridine in 200 ml of ether at 0°. The mixture was then stirred at room temperature for 8 hr. After filtering through Celite, the filtrate was poured into water and worked up in a standard

manner. The solvents were removed by distillation through a Vigreux column. The residue was distilled and the fraction of bp 55–59° (0.45 mm) was collected. The yield of the acetate mixture (**15** and **16**) was 4.99 g (50%). The NMR spectrum of **16** (CCl_4) shows an olefinic triplet at δ 6.35 (J = 2 Hz) and a carbinyl broad singlet at δ 4.66. Acetate **15** shows an olefinic triplet at δ 5.83 (J = 2 Hz) and a carbinyl broad singlet at δ 3.48. The ratio of **16** to **15** determined by NMR integration was 2.4:1.

Rhodium(I)-Catalyzed Isomerization of 16. A solution of 4.7 g of acetates **15** and **16** and 0.64 g of rhodium dicarbonyl chloride dimer in 3 g of carbon tetrachloride was heated (sealed tube) at 80° for 2 hr. The mixture was diluted with pentane and filtered through Celite and the filtrate was washed with potassium carbonate solution. The pentane extract was dried over sodium sulfate and filtered and the solvent was removed by distillation. The residue was distilled to give 3.38 g (72%) of recovered acetates, bp 52–55° (0.7 mm). The NMR spectrum shows no trace of **16**. The carbinyl proton of **17** appears at δ 4.29. Small amounts of olefinic products are present along with **15**.

Formation of 2. A 3.39-g sample of acetate mixture **15** and **17** was dissolved in 25 ml of ether and cooled in an ice bath. Methyllithium (26 ml, 1.7 M in ether) was added dropwise and stirring was continued for 15 min. The work-up procedure was the same as in the preparation of **11**. The crude mixture of alcohols was dissolved in 5 ml of ether and added dropwise to a cold solution of 11.45 g of trifluoromethanesulfonic anhydride in 35 ml of pyridine. The mixture was kept at 0° for 10 hr. Isolation of **2** was accomplished in the same manner as **1**. The yield of **2** was 1.212 g (23% based on starting acetates): bp 47–50° (0.45 mm); NMR (CCl_4) δ 1.65 (2 H, q, J = 1.5 Hz), 2.00 (2 H, t, J = 2 Hz), 3.11 (2 H, m), 5.37 (2 H, t, J = 2 Hz).

Anal. Calcd for $C_9H_9F_3O_3S$: m/e 254.0224. Found: m/e 254.0253.

Formation of 20. Diazomethane was prepared from 200 g of Diazald (Aldrich Chemical Co.) in 1 l. of ether, 52 g of potassium hydroxide, and 250 ml of 95% ethanol.[32] Unsaturated diester **18** (60 g) was added to the diazomethane solution and the mixture was stored at room temperature for 50 hr. Gas chromatographic analysis shows only a trace (less than 1%) of starting ester **18**. The excess diazomethane was removed by distillation and an additional 30 g of **18** was added to the recovered diazomethane. After 3 days, most of the diester **18** had reacted. Solvents were removed from the pyrazoline **19** under reduced pressure with the last traces being removed under a vacuum of 0.5 mm. Pyrazoline **19** shows $\nu_{N=N}$ at 6.47 μ in the infrared.

Approximately 15-g portions of the crude **19** were dissolved in 350 ml of acetone and irradiated with a 450-W Hanovia lamp using a quartz immersion well. Irradiation was continued until nitrogen evolution ceased (approximately 8 hr for each portion). At the end of the irradiation, acetone was removed by rotary evaporator. The combined photolytes were distilled at 0.3 mm. The distillate contained unsaturated diester **18**, tricyclic diester **20**, and small amounts of other lower boiling impurities. The entire distillate was dissolved in 250 ml of methanol and ozonized exhaustively at −78°. The mixture (from which **20** had crystallized) was warmed to room temperature and a solution of 20 g of sodium carbonate, 50 ml of 30% hydrogen peroxide, and 150 ml of water was added. After stirring for 5 min, the mixture was taken up into ether and water. After a standard work-up, the residue was distilled to give 37.2 g (39%) of solid diester **20**, bp 108–112° (0.3 mm). A sublimed sample gave mp 69–73°; NMR (CCl_4) δ −0.19 to 0.65 (2 H, m), 0.80 (1 H, m), 1.06–1.33 (3 H, m), 2.59 (2 H, m), 2.95 (s H, m), 3.60 (6 H, s).

Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.49; H, 7.34.

Acyloin Condensation of 20. The procedure was analogous to the cyclization of diester **4**. Diester **20** (37.0 g), 22.5 g of sodium, and 99 g of chlorotrimethylsilane gave 38.17 g (75%) of bistrimethylsilyl ether **21**: bp 86–88° (0.2 mm); NMR (CCl_4) δ 0.17 (18 H, s), 0.17–0.95 (4 H, m), 0.95–1.5 (2 H, m), 2.05 (2 H, m), 2.61 (2 H, d, J = 3 Hz).

Anal. Calcd for $C_{16}H_{28}O_2Si_2$: m/e 308.1628. Found: m/e 308.1653.

Kinetics Procedure. A known amount (80–100 mg) of a given triflate was diluted to 10 ml with 0.10 M sodium acetate in anhydrous acetic acid containing 1% acetic anhydride. The solution was divided into eight aliquots and heated in sealed tubes at a particular temperature. One-milliliter aliquots were titrated at given times with 0.02 M perchloric acid in anhydrous acetic acid using either a Metrohm E576 automatic recording titrator or manual potentiometric titration for end-point determinations. All rate constants were determined using an infinity titer which agreed well with calculated values. Rate constants were determined by the method of least squares as calculated by computer. All solvolytic runs gave excellent first-order plots through greater than 75% reaction.

Solvolysis of 1. Product Analysis. A 0.309-g sample of **1** was dissolved in 15 ml of 0.1 M sodium acetate in acetic acid–1% acetic anhydride and the mixture was heated (sealed tube) for 16 hr at 150–153°. The mixture was taken up into ether and water. After a standard work-up, excess methyllithium was added to the acetates dissolved in ether. Samples of alcohols **22** and **23** were isolated by preparative gas chromatography using a 6-ft, 15% Carbowax 20M on Chromosorb P column at 130°. Identification was made by NMR and infrared spectral comparison with authentic samples. In a separate run, the yield of acetates was determined by gas chromatography vs. an internal standard. The ratio of alcohols **22** to **23** was also determined by gas chromatography, after cleavage of the acetates with excess methyllithium.

Solvolysis of 2. Product Analysis. A 0.3005-g sample of **2** was dissolved in 14 ml of 0.1 M sodium acetate in acetic acid–1% acetic anhydride and the mixture was heated (sealed tube) at 110° for 16 hr. After a standard work-up, the products were isolated by distillation. The yield of **29**-OAc and **30**-OAc was 0.1067 g (55%). In addition, 0.037 g of higher boiling products (probably diacetates) was obtained. The carbinyl proton of **29**-OAc is a singlet at δ 4.67, in **30**-OAc a doublet (J = 2.6 Hz) at δ 4.49.

A 0.2570-g sample of **2** was dissolved in 7.5 ml of acetone, and 4 ml of water and 0.155 g of triethylamine were added. The mixture was heated (sealed tube) at 100° for 35 hr. After a standard work-up, the alcohol products were isolated by distillation which gave 0.095 g (77%) of alcohols **29**-OH and **30**-OH. The alcohols were inseparable by gas chromatography. Identification of the components of the mixture was made by infrared and NMR spectral comparison with authentic samples.[21] The carbinyl proton of **29**-OH is a singlet at δ 4.11, in **30**-OH, a doublet (J = 2.6 Hz) at δ 3.77. The alcohol ratio was 1.1:1 by integration of the carbinyl protons.

Solvolysis of 3. Product Analysis. A 0.3024-g sample of **3** was dissolved in 7.5 ml of acetone, and 3.7 ml of water and 0.221 g of triethylamine were added. The mixture was heated (sealed tube) at 130° for 20 hr. After a standard work-up, the sample was analyzed by gas chromatography using a 6-ft, 15% Carbowax 20M on Chromosorb P column at 160°. Four products were observed. The two major products were isomeric alcohols (calcd m/e for $C_9H_{12}O$: 136.0888. Found: 136.0884) and were isolated by preparative gas chromatography using a 6-ft, 15% Carbowax 20M on Chromosorb P column at 160°. NMR analysis of each alcohol showed no olefinic protons and the presence of cyclopropyl protons. The major product, **36**, showed a triplet at δ 4.00 (J = 8 Hz) in the carbinyl region of the spectrum. The minor alcohol, **37**, showed a broad singlet at δ 3.94 in the carbinyl region.

Registry No.—**1**, 56514-04-6; **2**, 56514-05-7; **3**, 56514-06-8; **4**, 4098-47-9; **5**, 56514-07-9; **6**, 56514-08-0; **6** free alcohol, 56514-09-1; **7**, 56514-10-4; **8**, 56552-96-6; **9**, 56552-97-7; **10**, 56514-11-5; **11**, 56514-12-6; **12**, 3574-54-7; **15**, 56514-13-7; **16**, 56552-98-8; **17**, 56514-14-8; **18**, 832-56-4; **19**, 56086-40-9; **20**, 56514-15-9; **21**, 56514-16-0; **22**, 4802-43-1; **23**, 32222-49-4; **28**, 25327-17-7; **29** (R = Ac), 38311-35-2; **29** (R = OH), 38311-30-7; **30** (R = Ac), 38311-36-3; **30** (R = H), 56613-90-1; **36**, 56514-17-1; **37**, 56514-18-2; chlorotrimethylsilane, 75-77-4; p-toluenesulfonyl chloride, 98-59-9; methyllithium, 917-54-4; peroxytrifluoroacetic acid, 359-48-8; trifluoromethanesulfonic anhydride, 358-23-6; norbornadiene, 121-46-0; rhodium dicarbonyl chloride dimer, 14523-22-9; diazomethane, 334-88-3.

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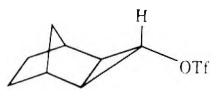

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Substituent, Reagent, and Solvent Effects on the Steric Course of Additions Initiated by Electrophilic Bromine to 3-Bromocyclohexene. A Comparison with the Stereoselectivity of Epoxidation and the Regioselectivity of Ring Opening of Epoxides

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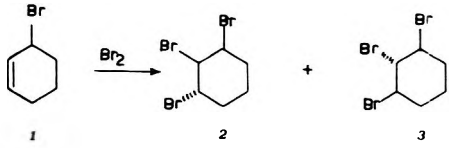
The steric course of the addition of bromine, pyridine perbromide, and acetyl hypobromite to 3-bromocyclohexene in several low polarity nonprotic solvents has been investigated. The bromination always produces nonequilibrium mixtures of two 1,2,3-tribromocyclohexanes resulting from anti addition, in ratios which are markedly affected by the solvent. The addition of pyridine perbromide gives, besides the same tribromo derivatives, a bromo–pyridinium adduct arising from electrophilic attack by bromine anti to the allylic substituent followed by nucleophilic attack by pyridine at C_1. The addition of acetyl hypobromite affords three isomeric anti bromo–acetate adducts, whose distribution is almost solvent independent. The comparison of the stereo- and regioselectivity of the last addition reaction with those of the epoxidation of 3-bromocyclohexene and of the hydrogen bromide opening of its cis and trans epoxides shows a stringent analogy. In both cases the electrophilic attack occurs preferentially (80–90%) anti to the allylic bromine atom; moreover, both the nucleophilic attack by bromide on the protonated epoxides and that by acetate on the epibromonium ions, which are assumed as intermediates for the addition reaction, occur exclusively or with very high preference at the ring carbon which is farther from the substituent. The steric course of the addition of bromine in the presence of bases (like pyridine or ethyl ether) is rationalized on the basis of a ionic two-stage mechanism involving product control by steric, electronic, and conformational factors during the nucleophilic rather than the electrophilic step.

The steric course of halogen additions to 3-substituted cyclohexenes has been shown to markedly depend both on the reagent and solvent employed and on the nature of the allylic substituent.[1-3] Whereas alkyl groups exert mainly a steric effect in both the electrophilic and nucleophilic step of the additions, a polar substituent may also affect the stereo- and regioselectivity in several additional ways. For instance, the product distribution found in the bromination of some 2-cyclohexen-1-ol derivatives has been interpreted[3] on the basis of a syn directive effect of a hydroxy (or methoxy) group, operating in the electrophilic step, in conjunction with an inductive effect, operating in the nucleophilic one. As a part of a research program concerning the stereochemistry and the mechanism of electrophilic additions to alkenes, we extended our investigation to 3-halogenocyclohexenes, starting with the bromo derivative **1**.

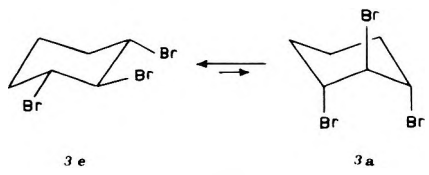
Results

Addition of Bromine. The addition of bromine to 3-bromocyclohexene (1) in chloroform at 0° gave a mixture of two diastereoisomeric tribromocyclohexanes (2 and 3), which was separated by column chromatography into a liquid and a solid component.



1 2 3

The relative configurations of tribromides 2 and 3 had already been attributed by chemical methods[4] and that of 3 also by electron diffraction.[5] They were confirmed in this work on the basis of NMR spectra and equilibration experiments. Although the two diastereoisomeric adducts could not be identified through their 60-MHz NMR spectra run in CCl_4, $CDCl_3$, CD_3COCD_3 and Me_2SO-d_6 owing to overlap of the signals relative to the α protons, which appeared in every case as unresolved and rather narrow multiplets, their identification was easily made in C_6D_6. In the latter solvent the signals of the protons α to halogens were still overlapping and narrow for the liquid compound, but became much broader and showed considerable fine structure for the solid one, which was therefore regarded as diastereoisomer 3 in its triequatorial conformation. This conclusion was confirmed by the 100-MHz spectrum of 3 in C_6D_6, which showed for H(2) a distorted triplet with J = 10 Hz and for the two chemically equivalent protons H(1) and H(3) a rough doublet of triplets (W = 25.4 Hz). Since a value of 10.4 Hz has been given[6] for the coupling constant between two vicinal protons α to equatorial bromine atoms in rigid *trans*-1,2-dibromocyclohexanes, the value of $J_{1,2}$ is consistent with a strong preference for conformation **3e** over **3a**. This shows that, at least in benzene as the solvent,



3e 3a

a bromine–bromine 1,3-diaxial repulsive interaction, present in the triaxial conformation **3a**, is much stronger than the gauche dipole–dipole repulsions between vicinal equatorial halogens present in conformation **3e**. An interaction of the latter type is responsible for the preferential diaxial conformation in *trans*-1,2-dihalogenocyclohexanes.[7] The conformational preference of 3 could not be evaluated in other solvents, such as $CDCl_3$, CCl_4, or Me_2SO-d_6, owing to extensive overlap of the signals of the α protons; however, the rather narrow shape of the multiplets would suggest a contribution by triaxial or twist conformations. It can be observed that the conformational population of 3 in the gas phase has been estimated by electron diffraction[5] to involve 19 ± 5% of triaxial conformer. However, benzene as the solvent has been found to stabilize the diequatorial (or gauche) conformers in a number of *trans*-1,2-dihalogenocyclohexanes[7d] and -cyclopentanes[8] and in open-chain dihalides.[9]

The trans relationship between two vicinal bromine atoms in each component of the diastereoisomeric couple 2–3 was also confirmed by their thermal interconversion through the well-known 1,2-interchange mechanism,[10-12] requiring anti-oriented halogen atoms. The equilibrium ratio at 150° between tribromides 2 and 3 was 87:13, in agreement with the expectedly lower stability of diastereoisomer 3 due to repulsive interactions between three equatorial bromine atoms. On the basis of the different reaction rates of 2 and 3 with sodium hydroxide Cornubert had reported[4] an equilibrium ratio of 95:5 after refluxing at 135° (12 mm).

The ratios between the dibromo adducts 2 and 3 obtained by addition of bromine to 3-bromocyclohexene in several solvents at 0° are reported in Table I.

Table I
Ratios between the Two Trans Diastereoisomeric Adducts Obtained by Addition of Bromine to 1

Solvent	Ratio 2:3	Solvent	Ratio 2:3
CH_2Cl_2	20:80	CCl_4	42:58
CH_2Cl_2[a]	23:77	CCl_4[a]	43:57
C_6H_6	28:72	Et_2O	67:33
$CHCl_3$	28:72	Et_2O[a]	69:31
$CHCl_3$[a]	28:72		

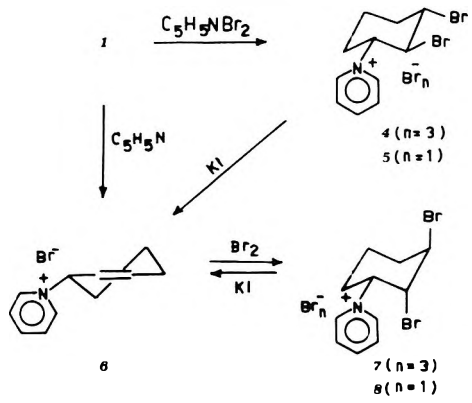
[a] Additions carried out in the presence of di-*tert*-butylcresol.

To avoid the formation of mixed adducts arising from nucleophilic attack by solvent, only low-polarity nonprotic solvents were employed. The product distributions were determined by GLC: only the peaks corresponding to the trans dibromo adducts 2 and 3 were detected in every case. Runs performed either in the absence or in the presence of di-*tert*-butylcresol, a typical free-radical inhibitor, gave very similar results, providing strong evidence against a free-radical addition mechanism. The data of Table I show that the product distribution was considerably affected by the solvent. A similar, although less marked, solvent effect had previously been observed[1] also in the bromination of 3-alkyl-substituted cyclohexenes.

Addition of Pyridine Perbromide. When a chloroform solution of 3-bromocyclohexene was stirred with a 100% molar excess of pyridine perbromide at 0°, a crystalline, red precipitate was slowly formed, besides a mixture of the dibromo adducts 2 and 3 in a 67:33 ratio (GLC). The yield of the red product increased and that of the dibromo adducts decreased when the reaction was carried out in pyridine as the solvent. However, the 2:3 ratio remained practically unchanged. Elemental analysis showed that the red crystals arose from the combination of one bromocyclohexene, one pyridine, and two bromine molecules. Stirring a suspension of the red adduct in chloroform with cyclohexene converted it into a white, crystalline product, *trans*-1,2-dibromocyclohexane being concurrently formed. Elemental analysis of the white adduct showed it to consist of one bromocyclohexene, one pyridine, and one bromine molecule. The presence of a pyridinium cation was inferred from the typical downfield NMR signals[13] in both the red and the white products. On the other hand, a bromide salt structure was suggested by the immediate precipitation of silver bromide on treatment of the latter adduct with silver nitrate solution. All these data indicated that the crystalline adduct was formed by addition of a bromine atom and a pyridine molecule to the double bond to give a pyridinium cation, whose counterion was a tribromide ion in the red compound and a bromide ion in the white one. Structures 4 and 5 were proposed for these adducts on the basis of the evidence outlined in Scheme I.

The pyridinium salt 6, obtained from 3-bromocyclohexene and pyridine, gave on bromination a different red adduct, which was regarded as isomer 7 and was transformed into the white salt 8 on treatment with cyclohexene. This demonstrated that the reaction of 1 with pyridine perbromide does not proceed through the formation of 6 as an

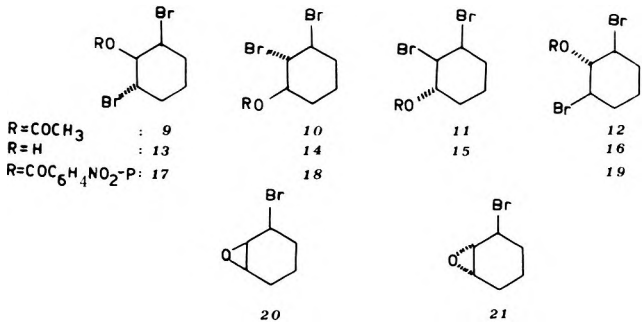
Scheme I



intermediate, but rather involves an electrophilic attack by bromine on the double bond of **1**, followed by a nucleophilic one by pyridine. The vicinal position as well as the trans relationship of the two bromine atoms in both **5** and **8** was shown by their conversion into **6** by heating with potassium iodide.

Configurations and conformations given in Scheme I were confirmed by the examination of the medium-field part of the 100-MHz NMR spectra of the bromo–pyridinium adducts, in which the signals of the cyclohexane protons α to the halogen atoms and to the pyridinium substituent could be sufficiently separated by a proper choice of the solvent (see Experimental Section). While the shapes and widths of these signals in **8** indicated one axial and two equatorial α protons, in **4** and **5** they were clearly consistent with three axial α protons. No evidence was found for the formation of any diastereoisomer of **4** in the reaction of **1** with pyridine perbromide both in chloroform and in pyridine: the ir and NMR spectra of the crude precipitates were identical with those of pure **4**. It is also to underline that the **2:3** ratio found in both reactions, which was the same in spite of the very different total yields of dibromo adducts, was quite different from that obtained with free bromine in chloroform but similar to that found in ethyl ether (Table I).

Addition of Acetyl Hypobromite. The treatment of a carbon tetrachloride solution of 3-bromocyclohexene with a ca. 0.1 *M* solution of acetyl hypobromite in the same solvent gave a complex mixture containing three isomeric acetate esters of dibromocyclohexanols besides very small amounts of the tribromo derivatives **2** and **3**. On heating with methanolic sulfuric acid the esters were cleanly converted into the corresponding dibromo alcohols, which were more easily analyzed by GLC. Three isomeric dibromocyclohexanols were detected. The major isomer was identified as **14** by comparison of its *p*-nitrobenzoate (**18**) with that of the minor product obtained from the bromination of cyclohex-2-en-1-ol.[3] The treatment of the same crude mixture of dibromocyclohexanols with sodium hydroxide in 2-propanol led to two isomeric 3-bromo-1,2-epoxycyclohexanes (**20** and **21**) in a 80:20 ratio. The cis con-



figuration **20** was assigned to the main product, which was separated by fractional distillation, since it should arise from the main dibromo alcohol **14**. On the other hand, epoxidation of 3-bromocyclohexene with *p*-nitroperoxybenzoic acid afforded a 10:90 mixture of the same epoxides **20** and **21**. Pure **21** was obtained by preparative GLC.

The opening of **20** with hydrogen bromide in chloroform afforded practically only one dibromocyclohexanol which was different from **14** and was therefore regarded as the alternative product of trans opening **13**. This was confirmed by the NMR spectrum of the *p*-nitrobenzoyl derivative **17**, which showed three medium-field signals, the one at lowest field, attributable to the hydrogen α to the *p*-nitrobenzoate group, appearing as a doublet of doublets due to coupling with two nonequivalent protons α to the bromine atoms. On the other hand, the opening of the trans epoxide **21** gave two products in a 97:3 ratio (GLC). The main product was easily identified as **16** since the NMR spectrum of its *p*-nitrobenzoyl derivative **19** showed for the hydrogen α to the *p*-nitrobenzoate group a triplet (J = 10 Hz) due to coupling of one axial proton with two chemically equivalent axial protons α to the bromine atoms. The minor product of opening of **21**, which was formed in too small amount to permit its isolation, was therefore regarded as the alternative product of trans ring opening, **15**. The comparison of the GLC retention times of all four dibromo alcohols **13–16** with those of the mixtures obtained by addition of acetyl hypobromite to 3-bromocyclohexene in different solvents followed by deacetylation permitted us to deduce that the above addition reactions gave compounds **9**, **10**, and **11** in the ratios reported in Table II, the fourth possible adduct, **12**, being not formed in appreciable amount.

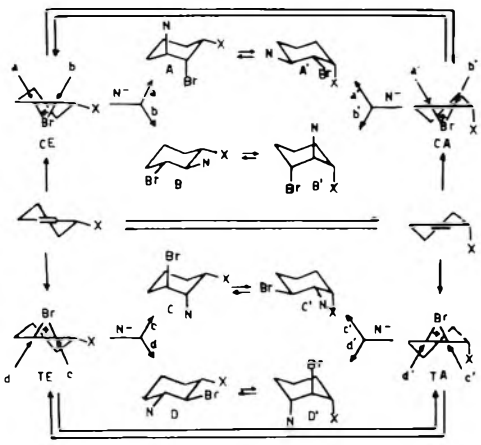
Table II
Product Distribution in the Addition of Acetyl Hypobromite to 3-Bromocyclohexene

Solvent	Products, % 9	10	11
CCl_4	4	77	19
CH_2Cl_2	8	75	17
Et_2O	6	75	19

Discussion

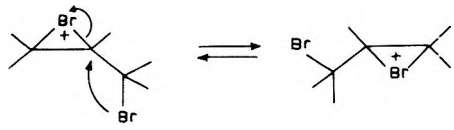
On the basis of the evidence reported above for the brominations and of literature reports about the addition of acetyl hypobromite[14] the usual two-step ionic mechanism[15] will be assumed for all additions under discussion. For the sake of simplicity the intermediates formed in the electrophilic step will be represented as epibromonium ions, as generally assumed for the bromination of nonconjugated alkenes, but it must be kept in mind that probably the distribution of positive charge on the three-membered ring is not symmetrical, owing to the presence of the adjacent electron-withdrawing halogen atom. Furthermore, ion pairing of the cationic intermediates (which in Scheme II are simply represented as free ions) with the anionic nucleophile is almost certainly involved in the nonpolar solvents employed. The alternative pathways leading from the two half-chair conformers of a 3-halogenocyclohexene to two pairs of conformationally isomeric bromonium ions (CE–CA and TE–TA) and to four pairs of adducts (A–A′, B–B′, C–C′, and D–D′) are represented in Scheme II (where X = Br). Paths a, b′, c, and d′ correspond to antiparallel attacks[16] by the nucleophile N^- and involve chair-like transition states, whereas paths a′, b, c′, and d consist in parallel attacks,[16] passing through boat-like transition states.

Scheme II



Owing to the symmetry of the reagent and to the conformational mobility of the alkene as well as of the resulting cis and trans epibromonium ions, the bromine addition (where N^- is Br^- or Br_3^-) is difficult to interpret, since four routes to each of the two diastereoisomeric trans dibromo adducts are available (a, a′, c, and c′ on one hand, b, b′, d and d′ on the other). The situation is less complicated when N^- is an acetate anion. In this case only two routes are available for the formation of each of the four possible diastereoisomeric trans adducts, and, even if the conformational aspects of the reaction pathways cannot be unambiguously distinguished, the stereoselectivity of the electrophilic attack as well as the regioselectivity of the nucleophilic one can be directly inferred from the product distribution.

A further complication could be in the fact that halonium ions with a halogen in the 3 position (**22**) could rearrange to isomeric ions (**23**) through intramolecular electrophilic attack, as found, for instance, in some electrophilic additions to allyl halides.[17-20]



22 **23**

However, although it is not possible to verify the occurrence of such a rearrangement in the ionic intermediates formed in the additions initiated by electrophilic bromine to 3-bromocyclohexene, it is irrelevant for the present discussion, since in the trans ion it would just result in the conformational inversion TA ⇄ TE, whereas in the cis ion, in the very unlikely case that it were possible, it would simply cause the conversion to its enantiomer.

The data of Table III show a striking similarity between the electrophilic step of the addition of acetyl hypobromite in different solvents and the epoxidation of 3-bromocyclohexene, the allylic bromine atom exerting a remarkably strong anti directing effect in both reactions, which could be due to a number of electronic and steric effects which have been discussed in a previous paper.[3] This preference for anti attack is remarkably high, particularly in the epoxidation reaction, if compared for instance to the epoxidation of 3-methoxycyclohexene, where the syn/anti ratio is 37:63.[21] The known preference for pseudo-axial bromine in 3-bromocyclohexene[22] may be the cause for this anti stereoselectivity of the electrophilic attack.

Also the regioselectivity of the nucleophilic attack by the acetate anion on the intermediates TE–TA and CE–CA and that of the attack by bromide on the protonated forms

Table III
Stereoselectivity and Regioselectivity of the Addition of Acetyl Hypobromite Compared with Epoxidation and HBr Opening of the Epoxides from 3-Bromocyclohexene

Reagent (solvent)	Stereoselectivity of the electrophilic attack syn/anti ratio	Regioselectivity of the nucleophilic attack a(a′)/b(b′)	c(c′)/d(d′)
AcOBr (CCl_4)[a]	19:81	100:0	5:95
AcOBr (CH_2Cl_2)[a]	17:83	100:0	10:90
AcOBr (Et_2O)[a]	19:81	100:0	7:93
PNPBA ($CHCl_3$)[b]	10:90	100:0	3:97

[a] With reference to Scheme II, N^- being AcO^-. [b] With reference to Scheme II, Br being replaced by OH, N by Br.

of epoxides **21** and **20** are very similar (Table III), the ring opening occurring with high preference at C_1 through path d or d′ in the trans epibromonium ion and trans epoxide, and exclusively at C_1, presumably through the antiparallel path a, in the cis ion and cis epoxide. The observed regioselectivity, which is similar but even more marked than that found for the analogous reactions of 3-methoxy substituted compounds,[23,24] is consistent with a strong inductive effect of the electron-withdrawing substituent, which should decrease the rate of nucleophilic attack on the nearer epoxide or bromonium ring carbon, provided that bond breaking is more important than bond making. Moreover, also stereoelectronic and conformational factors favor the opening of the cis epibromonium ion and cis epoxide through path a, while steric and electrostatic repulsions between the attacking anion and the polarized halogen substituent can hinder the opening of the trans ion and trans epoxide via c in favor of paths d′ or d, especially if the attack is collinear with the direction of the breaking C–Br or C–O bond.[21] Such a geometric requirement has been assumed recently for the nucleophilic opening of epoxides.[25]

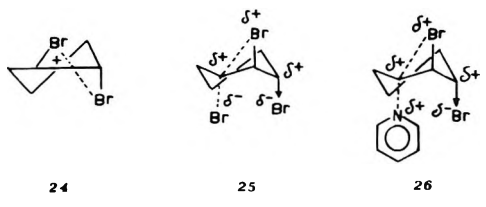
When compared with the strong solvent dependence of the addition of bromine to **1**, the absence of appreciable solvent effect in the addition of acetyl hypobromite is quite surprising. Perhaps it could be related to the different polarizability and capability of interaction with the solvent of the two electrophilic reagents. Anyway, previous work on additions to 3-substituted cyclohexenes initiated by electrophilic bromine[21,26] has shown that the changes in product distribution with changing reagent and solvent are mainly determined by a different stereoselectivity of the electrophilic step, the regioselectivity of the nucleophilic attack on the intermediate epibromonium ions being fairly constant in all conditions and similar to that of the hydrogen bromide opening of the corresponding epoxides. On this basis, if also the partition of the reaction intermediates CE–CA and TE–TA derived from 3-bromocyclohexene between the possible nucleophilic paths is assumed to be roughly constant and reagent and solvent independent, the changes in the ratios between tribromides **2** and **3** obtained in the various solvents (Table I) must be attributed to a different contribution of the two epibromonium ions. If one assumes for the cis ion an exclusive opening at C_1 and a mean value of 93:7 for the ratio of the opening at C_1 to that at C_2 in the trans ion (Table III), one can elaborate the data in Table I to give the following values for the ratio of syn to anti attack in the electrophilic step of the bromine addition in the various solvents: CH_2Cl_2, 14:86; $CHCl_3$ and C_6H_6, 23:77; CCl_4, 38:62; Et_2O, 65:35. Although these data must be taken as a rather crude approximation, they indicate a predominant contribution of TE–TA in all solvents,

except ethyl ether, in which the situation is practically reversed.

Since no reason can be seen for the preference for irreversible syn electrophilic attack in the latter solvent, the already proposed hypothesis[1] that in the presence of a basic solvent this step can be reversible seems therefore to be valid also in the present case. Under these conditions the product distribution would be determined mostly by steric, electronic, and conformational factors during the nucleophilic step. The inductive effect of the 3 substituent disfavors paths b, b′, c, and c′. On the other hand, path a involves a stereoelectronically favorable antiparallel attack leading to the product in its stable conformation A (Scheme II), while path d involves a stereoelectronically adverse parallel attack leading to the product in a twist conformation (which only subsequently passes to the stable form D) and path d′ an antiparallel attack leading to the product in its less stable triaxial conformation D′. Provided that the transition state of the nucleophilic attack is more similar to the products than to the epibromonium ions, as proposed for the attack on protonated epoxides,[27] path a should therefore be expected to be favored and **2** should be the main product. This is actually found in the bromination of 3-bromocyclohexene in ethyl ether.

The incorporation of pyridine in additions to alkenes initiated by electrophilic halogens has been previously observed with dipyridine bromine(I) perchlorate in dichloromethane[28] and with iodonium nitrate in chloroform–pyridine as the solvent.[29] In all cases the formation of halogeno–pyridinium salts has been related to the stability of the halonium or β-halogeno-α-carbenium ions formed in the electrophilic stage, those alkenes leading to more stable ionic intermediates favoring the attack by pyridine. It was also shown[29c] that an allylic hydroxy group causes an increase in the yield of pyridinium adducts with respect to the parent alkene in the reaction with iodonium nitrate in chloroform–pyridine. This was attributed to an increased stabilization of the intermediate iodonium ion by hydroxy group participation.

No pyridinium adducts are formed in the bromination of cyclohexene itself or its 3-alkyl derivatives with pyridine perbromide in chloroform,[1] and only when pyridine is used as the solvent[30] it successfully competes with the more nucleophilic[31] bromide ions for the nucleophilic attack. In contrast, appreciable amounts of pyridinium adducts are formed in the reaction of 3-bromocyclohexene with pyridine perbromide even in chloroform, when equal amounts of pyridine and bromine are present in the reaction medium. However, only the trans ion TE–TA appears to be susceptible to attack by the weaker nucleophile, since compound **4** is the only bromo–pyridinium adduct obtained. This would be consistent with the requirement of stabilization through neighboring group participation by the halogen, as shown in **24**, but would not explain the regiospecificity of the reaction, since nucleophilic attack occurs exclusively at C_1 whereas the positive charge would be stabilized on C_2. An alternative explanation of the ability of pyridine to compete with bromide ions in attacking the intermediate TA through path d′ when X is bromine could be found in the different interactions which develop in transition states **25** and **26**. Whereas the attack by a negatively charged nucleophile may be slowed down by electrostatic repulsions with the C–Br bond dipole in transition state **25**, the attack by a neutral nucleophile like pyridine in **26** could be facilitated, in spite of its lower nucleophilicity, by a favorable interaction between the partial negative charge on halogen and the incipient positive charge on nitrogen. An attractive interaction between vicinal iodo and pyridinium groups has been previously shown[29d] in iodoalkyl pyridinium salts.



24 25 26

As far as the tribromide distribution is concerned, the stringent similarity between the **2:3** ratio obtained with pyridine perbromide and with bromine in ethyl ether suggests that also with the former reagent the electrophilic step be reversible. In fact, since the dibromo adduct **3** as well as the bromo–pyridinium adduct **4** arise from the trans and the dibromo adduct **2** should arise mostly from the cis bromonium ion, an about 4:3 preference for CE–CA over TE–TA can be deduced (see Experimental Section) for the addition of pyridine perbromide to 3-bromocyclohexene in chloroform. Moreover, the **2:3** ratio does not change also when the addition is carried out in pyridine as the solvent, although in these conditions about 65% of the trans bromonium ion is substracted by reaction with the solvent to give **4**. The constancy in the **2:3** ratio obtained in the brominations performed in the above conditions rules out an irreversible formation of the bromonium ions and brings a further stringent evidence for the equilibration between intermediates CE–CA and TE–TA and for product control during the nucleophilic step.

In conclusion, the results reported in this paper confirm the great importance of the effect of an electronegative 3 substituent on the steric course of electrophilic additions to cyclohexenes as well as of the opening of the corresponding epoxides. Furthermore they are also consistent with the interpretation previously proposed[1,2] to explain the preferential formation of diaxial adducts in additions to 3-substituted cyclohexenes when bromine is coordinated by a basic atom, like nitrogen or oxygen.

Experimental Section

Melting points were determined on a Kofler block and are uncorrected. NMR spectra were registered with a Jeol C-60 HL and a Jeol PS-100 spectrometer using Me_4Si as internal standard. GLC analyses of tribromides **2** and **3** and of dibromo alcohols **13–16** were performed on a Perkin-Elmer Model F11 instrument fitted with a 2-m glass column, 2.5 mm i.d., packed with 3% neopentyl glycol succinate on sylanized Chromosorb W 80–100 mesh (column 140°, evaporator 160°, detectors 160°, nitrogen flow 30 ml/min). The mixtures of epoxides **20** and **21** were analyzed with a C. Erba Fractovap Model G.V. gas chromatograph, equipped with a 1.5-m glass column, 2 mm i.d., packed with 15% Carbowax 20M on sylanized Chromosorb W 80–100 mesh (column 80°, evaporator 130°, detectors 150°, nitrogen flow 30 ml/min). The preparative separation of **20** and **21** was achieved with a Perkin-Elmer F21 instrument fitted with a 2-m column, 8 mm i.d., packed with 5% OV 17 on sylanized Chromosorb G 60–80 mesh (column 110°, evaporator 150°, nitrogen flow 250 ml/min). $MgSO_4$ was always used as the drying agent. Evaporations were made in vacuo (rotating evaporator) at 30°. Petroleum ether refers to the fraction of boiling range 40–60°.

Starting Materials. 3-Bromocyclohexene was obtained from cyclohexene and *N*-bromosuccinimide.[32] Bromine was purified by refluxing with $CaBr_2$ and distillation. Pyridine perbromide was prepared immediately before use from bromine and dry pyridine in carbon tetrachloride.[33] Dichloromethane was refluxed over P_2O_5 and rectified. Chloroform was purified by washing with 2 *N* NaOH, concentrated H_2SO_4, and water, drying with K_2CO_3, and distillation and was immediately used. Carbon tetrachloride was Rudi Pont spectroanalyzed reagent grade. Benzene was washed with H_2SO_4, refluxed on sodium, and distilled. Ethyl ether was freed from peroxides by washing with a solution of ferrous sulfate.

1,*c*-2,*t*-3-Tribromocyclohexane (2) and 1,*t*-2,*c*-3-Tribromocyclohexane (3). A solution of bromine (1.9 g, 0.012 mol) in $CHCl_3$ (5 ml) was added dropwise with stirring to a solution of **1**

(1.6 g, 0.01 mol) in the same solvent (5 ml) at 0°. After 10 min the reaction mixture was diluted with $CHCl_3$ (10 ml), washed with saturated aqueous $NaHSO_3$ and water, dried, and evaporated to give a viscous oil (3.0 g). Chromatography of this oil on a neutral silica gel column with petroleum ether as the eluent gave pure **2**, oil: $n^{17}D$ 1.5990; NMR (60 MHz) in $CDCl_3$ δ 4.47–4.90 (–CHBr–, 3 overlapping m, 3 H), in C_6D_6 δ 4.25–4.65 ppm (–CHBr–, 3 overlapping m, 3 H).

Anal. Calcd for $C_6H_9Br_3$: C, 22.46; H, 2.83; Br, 74.71. Found: C, 22.34; H, 2.81; Br, 74.80.

Further elution with petroleum ether gave mixtures of **2** and **3** and then pure **3**: mp 50–51° (from petroleum ether) (lit.[4] mp 51°); NMR (60 MHz) in $CDCl_3$ δ 4.21 (–CHBr–, 2 overlapping m, $W_{1/4}$ = 13 Hz, 3 H), in CCl_4 δ 4.17 ($W_{1/4}$ = 12.7 Hz), in Me_2SO-d_6 δ 4.42 ($W_{1/4}$ = 12.7 Hz), in acetone-d_6 δ 4.34 ppm ($W_{1/4}$ = 13.5 Hz).

Thermal Equilibrations of 2 and 3. Samples of each pure diastereoisomer (0.01 g) were sealed in Pyrex tubes and heated into a thermostatted bath at 150 ± 2°. Samples were withdrawn at intervals, cooled, and analyzed by GLC. The results are summarized in Table IV.

Table IV
Equilibration of 2–3

Time, min	Ratio 2:3	Time, min	Ratio 2:3
0	0:100	960	87:13
10	9:91	0	100:0
20	18.5:81.5	360	87.5:12.5
31	25:75	900	87:13
360	82.5:17.5		

Bromination of 1 in Different Solvents. Stirred solutions of 1 mmol of **1** in 3 ml of the appropriate solvent at 0° were treated dropwise with a 20% excess of 1 *M* solutions of Br_2 in the same solvent. For the bromination in ethyl ether a solution of Br_2 in a different solvent (CCl_4) was employed. After the additions were complete, the reaction mixtures were left at room temperature for 15 min, then washed with saturated aqueous $NaHSO_3$ and water, dried, and evaporated. For each solvent a reaction in the presence of di-*tert*-butylcresol (10 mg) was also carried out with the same procedure. The reaction mixtures were directly analyzed by GLC. The relative retention times of the tribromo derivatives **2** and **3** were 1:2. The average values listed in Table I were obtained from at least four reactions and were reproducible within ±2%.

Additions of $C_5H_5NBr_2$ to 1. A. In $CHCl_3$. A solution of **1** (3.2 g, 0.02 mol) in $CHCl_3$ (60 ml) was cooled at 0° and treated with freshly prepared $C_5H_5NBr_2$ (9.6 g, 0.04 mol). The mixture was stirred at 0° for 30 min, in which time a red precipitate of **4** was formed, and left overnight at −20°. The red salt **4** was collected (1.5 g, 13% yield): NMR (100 MHz) in C_5D_5N δ 4.66 (–CHBr–, m, W = 26.7 Hz, 1 H), 5.41 (–CHBr–, t, $J \simeq$ 10.5 Hz, 1 H), 5.70 (–$CHN^+C_5H_5$, m, W = 26.5 Hz, 1 H), 8.44, 8.80, 9.79 ppm (–$N^+C_5H_5$, 3 m, 5 H). The mother liquors were diluted with petroleum ether and cooled at −20°. After several hours a second crop consisting of unreacted $C_5H_5NBr_2$ (1.5 g) was collected. The mother liquors were then washed with 10% aqueous $NaHSO_3$, 2 *N* aqueous HCl, and water, dried, and evaporated to give a mixture of **2** and **3** (4.7 g, 73% yield) in a ratio of 67:33 (GLC). A sample of **4** crystallized twice from acetic acid had mp 170–172°, and ir and NMR spectra identical with those of the crude product.

Anal. Calcd for $C_{11}H_{14}Br_5N$: C, 23.60; H, 2.52; Br, 71.37. Found: C, 23.98; H, 2.35; Br, 69.90.

Another sample of **4** (1.0 g) was suspended in $CHCl_3$ (5 ml), cyclohexene (2 ml) was added, and the mixture was stirred for 30 min. During this time the red color disappeared and a white, crystalline solid consisting of **5** remained (0.7 g): NMR (100 MHz) in CF_3CO_2H δ 4.35 (–CHBr–, m, W = 24 Hz, 1 H), 4.68 (–CHBr–, t, J = 10 Hz, 1 H), 4.98 (–$CHN^+C_5H_5$, m, W = 26 Hz, 1 H), 8.10, 8.57, 8.95 ppm (–$N^+C_5H_5$, 3 m, 5 H). After crystallization from methanol–benzene **5** had mp 209–210° and ir and NMR spectra identical with those of the crude product.

Anal. Calcd for $C_{11}H_{14}Br_3N$: C, 33.03; H, 3.53; Br, 59.93. Found: C, 32.98; H, 3.51; Br, 59.67.

GLC analysis of the chloroformic solution from which crude **5** was collected showed the presence of *trans*-1,2-dibromocyclohexane.

B. In C_5H_5N. 3-Bromocyclohexene (1.0 g, 6.2 mmol) was dissolved with cooling in dry pyridine (3 ml) and immediately added to a solution of $C_5H_5NBr_2$ (3.0 g, 12.4 mmol) in pyridine (3 ml) cooled at 0°. The mixture was stirred at 0° for 30 min, left overnight at −20°, and then diluted with $CHCl_3$ (50 ml). After storing at −20° for several hours a red precipitate of **4** (2.25 g, 65% yield) was collected, having ir and NMR spectra identical with those of the red product obtained in A. Further dilution did not cause any precipitation. The light yellow mother liquors were washed with 10% aqueous $NaHSO_3$, 2 *N* aqueous HCl, and water, dried, and evaporated to give a mixture of **2** and **3** (0.24 g, 12% yield) in a 66:34 ratio (GLC). Stirring of **4** with cyclohexene in $CHCl_3$ quantitatively converted it into **5**, having ir and NMR spectra identical with those of the white product obtained with procedure A.

Bromination of 6. Equimolar amounts of **1** and dry pyridine were mixed and left at 0° overnight, during which time a low melting, hygroscopic product (**6**) was formed. A sample of this product was dissolved in ethanol and treated with an equimolar amount of sodium tetraphenylboron. The white precipitate was collected and crystallized from ethanol to give pure *N*-cyclohex-2-enyl pyridinium tetraphenylboron, mp 159–160°.

Anal. Calcd for $C_{35}H_{34}BN$: C, 87.67; H, 7.15; N, 2.92. Found: C, 87.54; H, 6.96; N, 2.75.

Another sample of **6** (0.24 g, 1 mmol) was suspended in $CHCl_3$ (5 ml) and treated at 0° with a 1 *M* chloroform solution of bromine (2 ml). The mixture was stirred for 30 min, during which time a red, crystalline solid consisting of **7** (0.5 g) was formed. After two crystallizations from acetic acid **7** had mp 138–140°.

Anal. Calcd for $C_{11}H_{14}Br_5N$: C, 23.60; H, 2.52; Br, 71.37. Found: C, 23.48; H, 2.50; Br, 71.83.

A suspension of **7** (0.5 g) in $CHCl_3$ (5 ml) containing cyclohexene (1 ml) was stirred for 2 hr and then filtered off. The white product **8** so obtained (0.3 g) crystallized from methanol–benzene had mp 169–170°, NMR (100 MHz) in CF_3CO_2H δ 4.96 (–CHBr–, 2 overlapping m, $W_{1/4}$ = 7.7 Hz, 2 H), 5.74 (–$CHN^+C_5H_5$, d of m, J = 11.5 Hz, 1 H), 8.14, 8.74, 8.97 ppm (–$N^+C_5H_5$, 3 m, 5 H).

Anal. Calcd for $C_{11}H_{14}Br_3N$: C, 33.03; H, 3.53; Br, 59.93. Found: C, 32.97; H, 3.51; Br, 60.12.

Debromination of 5 and 8. A. A mixture of **5** (0.2 g) and potassium iodide (0.2 g) in ethanol (2 ml) was sealed in a Pyrex tube, heated at 100° for 48 hr, and then evaporated. The residue, dissolved in water and treated with an excess of aqueous solution of sodium tetraphenylboron, gave a white precipitate which was collected, washed with water, and crystallized from methanol to yield *N*-cyclohex-2-enyl pyridinium tetraphenylboron, with ir and NMR spectra identical with those of the product previously obtained from 3-bromocyclohexene, pyridine, and sodium tetraphenylboron.

B. A mixture of **8** (0.2 g) and potassium iodide (0.2 g) in ethanol (2 ml) was heated at 100° in a sealed tube for 30 hr. After the treatment described under A, *N*-cyclohex-2-enyl pyridinium tetraphenylboron was obtained.

***trans*-3-Bromo-1,2-epoxycyclohexane (21).** *p*-Nitroperoxybenzoic acid (2.2 g, 0.012 mol) was added to a solution of **1** (1.6 g, 0.01 mol) in $CHCl_3$ (30 ml) and the mixture was left at 0–5° for 3 days. *p*-Nitrobenzoic acid was then filtered off and the solution was washed with 3% aqueous Na_2CO_3 and water, dried, and evaporated to give a liquid residue (1.0 g) consisting of epoxides **20** and **21** in a ratio of 10:90 (GLC, relative retention times 2.55:1). The main component **21** was separated by preparative GLC: NMR (60 MHz) in CCl_4 δ 3.24 and 3.33 (epoxy H, 2 overlapping m, 2 H), 4.50 ppm (–CHBr–, m, $W_{1/2}$ = 10.5 Hz, 1 H).

Anal. Calcd for C_6H_9BrO: C, 40.70; H, 5.12; Br, 45.13. Found: C, 40.53; H, 5.15; Br, 45.03.

***cis*-3-Bromo-1,2-epoxycyclohexane (20).** A 0.1 *M* carbon tetrachloride solution of acetyl hypobromite[34] (300 ml) was added dropwise at 0° to a solution of **1** (4.0 g, 0.025 mol) in the same solvent (40 ml). After the addition was complete, the solution was stirred at 0° for 1 hr and left for another 1 hr at room temperature, then washed with saturated aqueous $NaHSO_3$ and water, dried, and evaporated. The residue (6.3 g), whose ir spectrum showed a strong carbonyl band at 5.75 μ, was dissolved in 2.5% methanolic sulfuric acid, refluxed for 2.5 hr, and then poured into water and extracted with petroleum ether. The extracts, washed with water, dried, and evaporated, gave an oily residue (4.6 g) the ir spectrum of which did not show the carbonyl band but showed a strong hydroxyl band near 3 μ. This oil was dissolved in 2-propanol (50 ml) and titrated with 1 *N* aqueous NaOH at room temperature, with phenolphthalein as indicator. The consumption of base was slow and amounted to 17 ml (theoretical 18 ml). The mixture was then diluted with water and extracted with petroleum ether. The ex-

tracts, washed with water, dried, and evaporated, yielded a mixture of epoxides **20** and **21** (2.8 g) in a ratio of 80:20 (GLC), which was distilled to give the following fractions: I (0.4 g), bp 102–104° (20 mm), **20:21** ratio 56:44; II (0.6 g), bp 104–108° (20 mm), **20:21** ratio 72:28; III (1.1 g), bp 108–120° (20 mm), **20:21** ratio 91:9; IV (0.4 g), bp 120° (20 mm), pure **20**, NMR (60 MHz) in CCl_4 δ 3.3 (epoxy H, 2 overlapping m, $W_{1/2}$ = 4 Hz, 2 H), 4.37 ppm (–CHBr–, m, $W_{1/2}$ = 17 Hz, 1 H).

Anal. Calcd for C_6H_9BrO: C, 40.70; H, 5.12; Br, 45.13. Found: C, 40.56; H, 5.18; Br, 45.06.

Opening of 21 with HBr. Dry HBr was bubbled for 5 min into a solution of **21** (0.5 g) in $CHCl_3$ (15 ml) at room temperature. The reaction mixture was then washed with water and 3% aqueous $NaHCO_3$, dried, and evaporated to give a solid residue (0.65 g) consisting of **16** and **15** in a ratio of 97:3 (GLC, relative retention times 1:1.3). Crystallization from petroleum ether gave pure **16**, mp 95.5–96.5°, NMR (60 MHz) in $CDCl_3$ δ 3.8 ppm (–CHBr– and –CHOH–, 2 overlapping m, $W_{1/4}$ = 19.5 Hz, 3 H).

Anal. Calcd for $C_6H_{10}Br_2O$: C, 27.93; H, 3.91. Found: C, 28.13; H, 4.13.

A sample of **16** (0.1 g) was dissolved in dry pyridine (2 ml) and treated with *p*-nitrobenzoyl chloride (0.1 g). After several hours the reaction mixture was diluted with $CHCl_3$, washed with 10% aqueous H_2SO_4 and water, dried, and evaporated to give the *p*-nitrobenzoate **19** which, after crystallization from methanol, had mp 202–204°, NMR (60 MHz) in $CDCl_3$ δ 4.05 (–CHBr–, m, W = 26.5 Hz, 2 equivalent H), 5.55 (–CHO–, t, J = 10.1 Hz, 1 H), 8.37 ppm ($-C_6H_4NO_2$, s, 4 H).

Anal. Calcd for $C_{13}H_{13}Br_2NO_4$: C, 38.35; H, 3.22; N, 3.44. Found: C, 38.58; H, 3.21; N, 3.51.

Opening of 20 with HBr. The opening of **20** under the same conditions described for the isomer **21** gave pure **13** (GLC) as an oil. Treatment with *p*-nitrobenzoyl chloride as reported above afforded the *p*-nitrobenzoate **17**, mp 103–105° (from ethanol), NMR (100 MHz) in $CDCl_3$ δ 4.60 (–CHBr–, m, $W_{1/4}$ = 24 Hz, 1 H), 4.90 (–CHBr–, m, $W_{1/4}$ = 16 Hz, 1 H), 5.25 (–CHO–, d of d, J = 3.15 and 8.60 Hz, 1 H), 8.37 ppm ($-C_6H_4-NO_2$, s, 4 H).

Anal. Calcd for $C_{13}H_{13}Br_2NO_4$: C, 38.35; H, 3.22; N, 3.44. Found: C, 38.53; H, 3.14; N, 3.36.

Additions of Acetyl Hypobromite to 1. A 10% excess of a 0.1 *M* solution of acetyl hypobromite in carbon tetrachloride[34] was added dropwise to a stirred solution of **1** (2.5 mmol) in the appropriate solvent (10 ml) at 0°. After the addition was complete the reaction mixture was left for 15 min at 0° and then poured into saturated aqueous $NaHSO_3$. The organic layer was washed with water, dried, and evaporated and the residue was dissolved into 1.5% methanolic sulfuric acid (20 ml), refluxed for 2.5 hr, and then diluted with water and repeatedly extracted with petroleum ether. The extracts, washed with water, dried, and evaporated, gave mixtures of **13, 14,** and **15** accompanied by traces of tribromides **2** and **3**, which were analyzed by GLC. The dibromo alcohols **13, 14,** and **15** were identified by comparison of their retention times with those of authentic samples. Furthermore, the treatment of one of these mixtures (0.5 g) with *p*-nitrobenzoyl chloride (0.5 g) in dry pyridine (10 ml) gave, after crystallization of the crude product from ethanol, pure **18** (0.3 g), mp 108–110° (lit.[3] mp 103–105°).

The percentages of the addition products **9, 10,** and **11**, assumed to be equal to those of **13, 14,** and **15**, are reported in Table II and were reproducible within ±2%. Equal product distributions were found in the addition performed in ethyl ether by increasing the volume of solvent to 25 ml. Control experiments with mixtures of **13, 14,** and **15** showed that their composition remained unchanged after treatment with methanolic sulfuric acid under the above conditions.

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Electron Transfer with Aliphatic Substrates. Oxidations of Cycloaliphatic Substrates with Cobalt(III) and Manganese(III) Ions Alone and in the Presence of Oxygen

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The oxidation of cycloaliphatic substrates with cobaltic and manganic acetates was investigated. Hydrocarbons studied include cyclohexane, methylcyclohexane, 1,1-dimethylcyclohexane, *cis*-1,2-dimethylcyclohexane, ethylcyclohexane, and cyclohexene. Reaction products include the corresponding ketones, alcohols, esters (ROAc and RCH_2OAc), geminate diesters, keto esters, dimers, and some acids. Their selectivity depends on the metal ion oxidant, experimental conditions, and the structure of the substrate. Added nucleophiles (KOAc or NaOAc) had no effect on product distribution in the cobalt system, but in combination with manganese gave rise to radical derived products (RCH_2OAc and RCH_2COOH) which increased with rising concentration of added acetate. In both bases, oxidation rates were enhanced. Added cupric acetate oxidizes intermediate cyclohexyl radicals to cyclohexene which reacts further to form cyclohexenyl acetates as major products. The use of Co–Cu and Mn–Cu ion combinations may present a route to olefinic derivatives from saturated substrates. With cobalt and in the presence of oxygen, dicarboxylic acids are formed predominantly, but with manganese this reaction is not favored. Pronounced selectivity with cobalt is attributed to steric factors which limit the attack of bulky and heavy-liganded cobaltic ions to noncrowded sites.

Oxidations of alkylbenzenes with Co(III),[1-3] Mn(III),[3] and Ce(IV)[4] salts in acetic acid or acetonitrile were reported to proceed via radical cation intermediates. This mechanism, however, was proposed for π systems exclusively. Earlier we reported results on the oxidation of *n*-butane[5] and cyclohexane[6] in the cobalt system. Reactions of these paraffins followed a pattern identical with that observed in the oxidation of aromatics. We concluded that σ bonds per se were able to donate electrons to metal ions. This paper deals with the oxidation of cyclohexane with cobaltic and manganic acetates in greater detail, showing participation of various mechanisms depending on experimental conditions. Additional substrates studied include methylcyclohexane, 1,1-dimethylcyclohexane, and *cis*-1,2-dimethylcyclohexane. In the presence of both cobalt and oxygen, methylcyclohexane, ethylcyclohexane, 1,1-dimethylcyclohexane, as well as several oxygenated methylcyclohexane derivatives (ketones and alcohol), were also briefly studied.

Results

Experiments with metal salts in the presence or absence of oxygen are summarized in Tables I–V. The reaction was followed in each case by analyzing the neutral residue (~60–75% of product) after removing solvents and unreacted substrate by conventional procedures. In some experiments acidic products were isolated and characterized. Material balance on Co(III) ions consumed ranged from 45 to 70%. Cobaltic salts were prepared either from cobaltous acetate and *tert*-butyl hydroperoxide (method 1) or cobaltous acetate and MEK–O_2 (method 2), affording essentially identical results. Most reactions with metal salts were carried out under nitrogen. Experiment 2, however, was run with exposure to air, with essentially no effect on the selectivity of the reaction.

Oxidation of Cyclohexane with Cobaltic Acetate. The oxidation of cyclohexane with cobaltic acetate, prepared by either of the two methods, afforded three major products in the neutral fraction: cyclohexylmethyl acetate, cyclohexyl acetate, and 2-acetoxycyclohexanone in molar ratios of 50, 32, and 10%, respectively (65% of total product). Minor products consisted of varying amounts of cyclohexylidene diacetate, cyclohexanone, cyclohexanol, and bicyclohexyl and dicyclohexylmethane dimers. Occasionally some cyclohexylmethanol and several unidentified compounds were formed in small amounts. Acidic materials (35% of total product) consisted largely of cyclohexylacetic acid and some cyclohexanecarboxylic acid in a 4:1 or higher ratio. Products isolated accounted for 55% of Co(III) ions consumed.

Table I
Oxidation Products of Cyclohexane[a]

Expt no.	Reactants, *M* C_6H_{12}	$Co(OAc)_3$	$Cu(OAc)_2 \cdot H_2O$	KOAc	NaOAc·$3H_2O$	Rxn time, days[b]	Product distribution, molar ratio[c] C_6H_{11}-OAc	C_6H_{11}-CH_2-OAc	Misc[g]
1	1.5	0.4				2.1[i]	26	51	23
2[d]	1.5	0.4		0.6		1.2	23	54	23
3	1.5	0.4		1.6		0.8	26	58	16
4	1.3	0.16[e]				3.9	34	53	13
5	1.3	0.16[e]	0.16			3.9	4		96[h]
6	1.3	0.16	0.0011			1.7	6		94[h]
7	0.9	0.16[f]				0.8	37	47	16
8	0.9	0.16[f]			0.7	0.8	34	50	16
9	0.9	0.16	0.16			0.8	8		92[h]
10	1.6	0.16	3.3			0.7	2		98[a]
11	0.9		0.4			5.3			

[a] 80°, ~99% HOAc, under N_2. [b] Reaction followed visually; color of solution changes from dark green to pink. [c] Neutral products only (60–80% of total). [d] Reaction exposed to air. [e] Cobaltic acetate prepared from cobaltous acetate and *tert*-butyl hydroperoxide. [f] Cobaltic acetate prepared from cobaltous acetate, MEK, and oxygen. Results with Co(III) oxidants prepared by two methods appear identical. Thus, both methods of preparation were used interchangably. [g] Products in varying amounts include 2-acetoxycyclohexanone, cyclohexylidene diacetate, $C_{12}H_{22}$ and $C_{13}H_{24}$ dimers, cyclohexanol, cyclohexanone, and occasionally cyclohexylmethanol. [h] Products in the presence of Cu(II) consist of 3-cyclohexenyl acetate (~98+%) and 1-cyclohexenyl acetate. [i] In absence of RH, Co(III) solutions were stable from 4 to 6 days under reaction conditions.

Oxidation of Methylcyclohexane with Cobaltic Acetate. Major product types in this reaction were the corresponding ROAc, RCH_2OAc, methylcyclohexanones, and cyclohexanols in molar ratios of 40, 20, 15, and 20%, respec-

Table II
Oxidation Products of Cyclohexane[a]

Expt no.	Reactants, M: C_6H_{12}	$Mn(OAc)_3$	$Cu(OAc)_2 \cdot H_2O$	KOAc	$NaOAc \cdot 3H_2O$	Rxn time, days[b]	Product distribution, molar ratio[c]: $C_6H_{11}OAc$	$C_6H_{11}CH_2OAc$	Misc[d]
12	1.8	0.5				12.8[f]	86	3	11
13	1.8	0.5		0.7		10.8	76	19	5
14	1.8	0.5		1.9		7.1	52	41	7
15	1.4	0.15	0.16			14.3[g]	63		37
16	1.3	0.4	0.16		0.6	14[g]	30	3	67[e]

[a] 80°, ~99% HOAc, under N_2. [b] Reaction followed visually; color of solution changes from dark brown to almost colorless. [c] Neutral products only. Some runs contained detectable amount of cyclohexylacetic acid and cyclohexylcarboxylic acid which were qualitatively identified. [d] Products in varying amounts include 2-acetoxycyclohexanone, cyclohexanol, cyclohexanone, and $C_{12}H_{22}$. [e] Products in the presence of Cu(II) consist largely of 3-cyclohexenyl acetate (98+%). [f] In absence of RH, Mn(III) solutions were stable for about 14 days under reaction conditions. [g] Arbitrary reaction time.

Table III
Oxidation Products of Cycloaliphatic Substrates[a]

Expt no.	Substrate, M	Oxidant, Co^{3+} or Mn^{3+}, M	$Cu(OAc)_2 \cdot H_2O$, M	KOAc, M	$NaOAc \cdot 3H_2O$,	Product distribution, molar ratio[b,c]: ROAc	RCH_2OAc	Misc	Remarks
17	MCH, 1.3	Co(III), 0.2		0.6		39	20[d]	41	Misc = alcohols, ketones, etc.
18	MCH, 0.7	Co(III), 0.12	0.15			12		88	82% methylcyclohexenyl acetates
19	1,1-DMCH, 0.8	Co(III), 0.13			1.0	66	7	27	Alcohols, ketones
20	1,1-DMCH, 0.6	Co(III), 0.13	0.15			23		77	68% dimethylcyclohexenyl acetates, several unknowns
21	MCH, 1.2	Mn(III), 0.3		1.6		36	10	44	
22	*cis*-1,2-DMCH, 1.5	Co(III),[e] 0.5		1.3		40	8	52	Alcohols, ketones, and several unknowns

[a] 80-90°, ~98% HOAc, under N_2. Reactions were followed visually by a change in color of solution. [b] Neutral products only. No attempt was made to isolate acidic product formed (if any). [c] Isomeric distribution of products not determined. [d] $=CHCH_2OAc/=CCH_3CH_2OAc$ ratio, ~3; i.e., 25% attack at the tertiary carbon. [e] Cobaltic acetylacetonate (The Harshaw Chemical Co.).

tively. GLC analysis of the product mixture showed the predominance of the 3-methyl- and the 4-methylcyclohexyl derivatives. Based on the ratio of the 3.8- and 4.0-ppm peaks in the NMR spectrum ($=CHCH_2OAc$ vs. $=CCH_3CH_2OAc$), 20–25% of the initial attack on RH occurred at the tertiary hydrogen site. Treatment of product with $LiAlH_4$ gave methylcyclohexanols (4-, 37%; 3-, 19%; 2-, 20%; and 1-, 24%), representing 70% of product.

Oxidation of *cis*-1,2-Dimethylcyclohexane with Cobaltic Acetylacetonate. The reaction of this substrate with $Co(acac)_3$ (Harshaw Chemical Co.) gave three major products: ROAc, ROH, and RCH_2OAc (molar ratios of 40, 46, and 8%, respectively). Treating the mixture with acetyl chloride converted alcohol to ROAc, doubling the amount of the latter on the chromatogram. The presence of RCH_2OAc adduct was detected by NMR. No attempt was made to determine the isomeric composition of products as standards were not readily available.

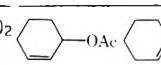
Oxidation of 1,1-Dimethylcyclohexane with Cobaltic Acetate. This substrate on oxidation gave ROAc and RCH_2OAc as identifiable products in molar ratios of 67 and 8%, respectively. The remainder of neutral fraction consisted of dimethylcyclohexanones, and several unidentified compounds which are thought to be dimethylcyclohexylidene diacetates and acetoxydimethylcyclohexanones, in analogy to the products of cyclohexane oxidation. Standards to determine the isomeric composition of products were not available. Likewise, acidic products formed, if any, were not determined.

Oxidation of Cyclohexene with Cobaltic Acetate. Reaction of olefin with cobaltic acetate gave 3-cyclohexenyl acetate as the major product (~80%), along with an unknown (~20%), which is thought to be the unsaturated ketocyclohexyl acetate ($C_8H_{10}O_3$, *m/e* 154.0626).

Oxidation of Cyclohexane with Manganic Acetate. Reaction of cyclohexane with manganic acetate afforded three major products: cyclohexyl acetate (~86%), 2-acetoxycyclohexanone (~9%), and cyclohexylmethyl acetate (~3%). Minor products included traces of cyclohexanol, cyclohexanone, and bicyclohexyl. Products are identical with those obtained with cobalt salts, but their selectivities are different. Cyclohexylacetic acid formed in this experiment was only qualitatively detected.

Effect of Added Acetate Ions. Oxidation of cyclohexane with cobaltic acetate in the presence of added KOAc or NaOAc (expt 2, 3, 8) decreased the time required for reduction of the oxidant, but had no effect on selectivity. With manganic acetate, however, addition of KOAc (expt 13, 14) not only reduced the reaction time, but also changed product selectivity. The magnitude of both effects was a function of the concentration of added nucleophile.

Table IV
Oxidation Products of Cyclohexene[a]

Expt no.	Reactants, M: C_6H_{10}	$Co(OAc)_3$	$NaOAc \cdot 3H_2O$	$Cu(OAc)_2 \cdot 2H_2O$	Product distribution, molar ratio[b]: 	Misc
23	0.5	0.12	0.35		78	2	20[c]
24	0.5	0.12		0.12	98	2	

[a] 80–85°, 98–99% HOAc, under N_2. [b] No acidic products were detected. Products isolated accounted for 45% of Co(III) consumed. [c] Unsaturated keto ester; *m/e* 154.0626 ($C_8H_{10}O_3$).

Effect of Added Cupric Acetate. The presence of cupric acetate in the oxidation of cycloaliphatic substrates with either Co(III) or Mn(III) acetates led in all instances to a dramatic change in the nature of the product. Products obtained were largely the saturated esters, which are normally derived from the oxidation of olefinic substrates only.

Oxidation of Cycloaliphatic Substrates with Cobalt Salts and Oxygen. Oxidation of cyclohexane in this system was earlier reported to give adipic acid. Methylcyclo-

Table V
Oxidation of Cycloaliphatic Substrates with Cobalt Salts and Oxygen[a,b]

Expt no.	Substrate	3-Methyl-adipic acid	2-Methyl-adipic acid	Adipic acid	3-Methyl-glutaric acid	2-Methyl-glutaric acid	Glutaric acid	Methyl-succinic acid	Succinic acid
25	Methylcyclohexane[c]	51.1	12.8	Trace	6.9	3.6	5.1	10.1	2.4
26	2-Methyl-cyclohexanone		22.8			11.7	20.3	23.8	11.4
27	3-Methyl-cyclohexanone	45.3	15.9		(17.1)			3.2	7.3
28	4-Methyl-cyclohexanone	67.3							
29	3-Methyl-cyclohexanol	51.5	22.7		(12.1)			Trace	Trace
30	1,1-Dimethyl-cyclohexane	52.9[d]	21.4[e]						
31	Ethylcyclohexane[c]	51.8[f]	10.3[g]	10.3			12.2		12.0

[a] 100–105°, 20 atm O_2, 1–3 hr. [b] Only major products were identified (wt %). They accounted for 77–91% of unrecovered substrate. [c] In the presence of a cooxidant, *n*-butane or *n*-pentane. RH conversions ranged from 35 to 51%. [d] 3,3-Dimethyl isomer. [e] 2,2-Dimethyl isomer. [f] 3-Ethyl isomer. [g] 2-Ethyl isomer.

hexane, 1,1-dimethylcyclohexane, and ethylcyclohexane were oxidized in the same system in present work to give the corresponding adipic acids as major products. 2-Methyl-, 3-methyl-, and 4-methylcyclohexanone and 3-methylcyclohexanol were also included in this study.

Oxidation of Cyclohexane with Manganese Salts and Oxygen. The reaction of cyclohexane with manganous acetate and oxygen, under conditions employed with cobalt, did not proceed readily. The reaction started, but after only 10–15 min, oxygen adsorption stopped. Analysis showed only traces of adipic acid. The major product was a mixture of neutral compounds consisting of cyclohexanone (~6%), cyclohexanol (~50%), cyclohexyl acetate (~35%), and smaller amounts of unidentified materials, corresponding to a cyclohexane conversion of <1%. It appears, therefore, that manganese salts are not effective oxidants for conversion of hydrocarbons to carboxylic acids under our mild conditions.

Discussion

Liquid phase oxidations of aliphatic hydrocarbons with oxygen, in the presence of large amounts of cobalt salt dissolved in acetic acid, proceed at higher rates and lower temperatures than observed in classical autoxidations. Products of reaction are the corresponding carboxylic acids which contribute little to the understanding of the reaction mechanism. Interest in optimizing the oxidation of cyclohexane to adipic acid with cobalt acetate and oxygen led us to study the reaction of cyclohexane with Co(III) and also Mn(III) salts alone. Similar ρ values for the reaction of alkylaromatics with cobaltic acetate in the presence or absence of oxygen (−2.4[1] vs. −2.66[8]) indicate identical rate-controlling steps in both systems. A similar situation was expected to exist in cycloaliphatic series on the basis of identical reactivities in the presence or absence of oxygen (Table VI).

Cycloaliphatic substrates react with metal oxidants to afford the corresponding ketones, alcohols, keto esters, geminate diesters, esters, some acids, and dimeric products. The ratio of products depend on the substrate, metal oxidant, and experimental conditions. Several mechanisms by which these products could arise have been previously reported.[6] We have now established cyclohexylmethyl acetate as the major product of the reaction between cyclohexane and cobaltic acetate. This ester ($C_9H_{16}O_2$, *m/e* 156.1134) was isolated by chromatography and characterized by NMR and ir by comparing the spectra with those of an authentic sample [CCl_4, Me_4Si: 3.85 ppm (d, 2 H, $-CH_2O-$), 2.0 (s, 3 H, $-OAc$), and 0.7–1.9 (m, 11 H, ring protons)]. 2-Acetoxycyclohexanone, earlier believed to be the major product, is also present, but only as a minor component ($C_8H_{12}O_3$, *m/e* 156.0794). In contrast, oxidation of cyclohexane with manganic acetate produced mostly cyclohexyl acetate with only minor amounts of RCH_2OAc adduct, indicative of different pathways with the two salts.

Cyclohexylacetic acid and some cyclohexanecarboxylic acid constituted the acid product isolated from cyclohexane oxidation with cobalt or manganese salts. Their mechanism of formation is in question. Coupling of cyclohexyl and carboxymethyl radicals is one possibility.[22]

Isolation and identification of most of the reaction products allows a reasonable conclusion to be made with regards to reaction mechanism. Based on the literature, the following steps appear reasonable with manganic acetate as oxidant.

$$Mn(OAc)_3 \xrightarrow{heat} Mn(OAc)_2 + \cdot CH_2COOH^{9-11} \quad (1)$$

$$RH + \cdot CH_2COOH \longrightarrow R\cdot + HOAc \quad (2)$$

$$2R\cdot \longrightarrow R{-}R \quad (3)$$

$$R\cdot + Mn(III) \longrightarrow R^+ + Mn(II) \quad (4)$$

$$R^+ + OAc^- \longrightarrow ROAc \quad (5)$$

$$R\cdot + \cdot CH_2COOH \longrightarrow RCH_2COOH \quad (6)$$

$$RCH_2COOH + Mn(OAc)_3 \longrightarrow RCH_2COOMn(OAc)_2 + HOAc \quad (7)$$

$$RCH_2COOMn(OAc)_2 \xrightarrow{heat} RCH_2\cdot + CO_2 + Mn(OAc)_2 \quad (8)$$

$$RCH_2\cdot + Mn(III) \longrightarrow RCH_2^+ + Mn(II) \quad (9)$$

$$RCH_2^+ + OAc^- \longrightarrow RCH_2OAc \quad (10)$$

$$RCH_2\cdot + R\cdot \longrightarrow RCH_2R, \text{ etc.} \quad (11)$$

Similar reactions could occur with the cobalt oxidant, but involving thermolysis of a different nature.[1]

$$Co(OAc)_3 \longrightarrow Co(OAc)_2 + CH_3\cdot + CO_2 \quad (12)$$

$$CH_3\cdot + HOAc \longrightarrow CH_4 + \cdot CH_2COOH \quad (13)$$

These mechanisms are controlled by thermolysis, consistent with results from manganese salt reactions in which oxidation rates parallel those of thermolysis. With an acetic acid solution of 0.4 *M* Mn(III) and 1.5 *M* C_6H_{12}, for exam-

Table VI
Relative Reactivities per Molecule[a]

Substrate	Co(III), 78°	Co(III), O_2, 100°, 20 atm
Ethylbenzene	1.2 (1.3)[c]	1.2
cis-1,2-Dimethylcyclohexane		1.1
Toluene[b]	1.0	1.0
1,1-Dimethylcyclohexane	0.8	
trans-1,2-Dimethylcyclohexane		0.6
Cyclohexane	0.5	0.5
Cyclohexane-d_{12}	~0.4 (0.4)[d]	
Cumene	(0.3)[c]	0.2
Methylcyclohexane	0.2	0.2
trans-1,4-Dimethylcyclohexane		~0.1

[a] Reactivities obtained by competitive oxidations earlier described.[8] Rates were based on disappearance of RH and related to toluene by $k_a/k_b = \log([A]_f/[A]_i)/\log([B]_f/[B]_i)$, where [A] and [B] refer to concentrations of the two substrates before and after the reaction in wt % [~0.4 *M* Co(III)/HOAc, 0.8 *M* RH, and 0.4 *M* chlorobenzene as internal standard.] [b] Assumed standard, reactivity 1.0. [c] From ref 1, 65°. [d] In the presence of 0.2 *M* $Cu(OAc)_2 \cdot H_2O$, 70°.

ple, it required 13 days for the oxidant to be consumed (80°), approximately the same time as in the absence of RH. With cobalt acetate, however, reactions 12 and 13 cannot be the sole or major contributors, as oxidation are at least twice as fast as thermolysis. It took only 2 days for a 0.4 *M* Co(III) solution to be reduced in the presence of C_6H_{12} (1.4 *M*), while 4–6 days were needed for complete reduction without substrate. While the data could be consistent with a free-radical pathway, propagation through cobalt cannot be excluded (eq 14).

$$C_6H_{12} + Co^{3+} \longrightarrow C_6H_{11}\cdot + Co^{2+} + H^+ \qquad (14)$$

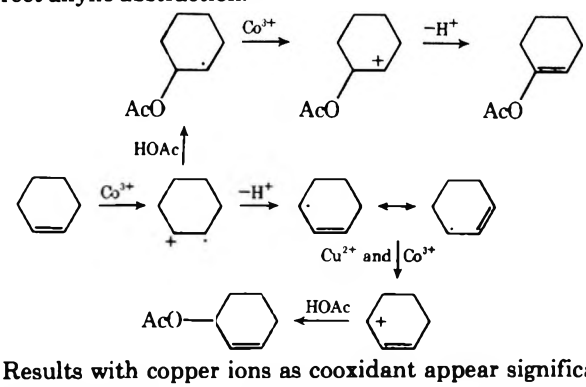
In addition to thermolysis, electron transfer may also be assumed, leading to products identical with those from thermolysis. Waters et al.[23] found the oxidation of cyclohexane with Co(III) ions and oxygen to follow the same rate law as simple alkylbenzenes,[8] with rates being of comparable order. This is believed to be indicative of σ-bond involvement as condensed polycyclic aromatics—biphenyl, naphthalene, and phenanthrene—reacted at rates several orders of magnitude greater than toluene, most likely involving π electrons instead. The rates of Co(III) disappearance and oxygen consumption in this system for the cycloaliphatic[7] and alkylaromatic[14] substrates both followed the expression $-d[Co(III)]/dt = k_1[RH][Co(III)]^2/[Co(II)]$ and $-d[O_2]/dt = k_2[RH][Co(III)]^2/[Co(II)]$. Since electron transfer is now an accepted concept for the oxidation of aromatic substrates, to assume the same for cycloaliphatic hydrocarbons is not considered unreasonable.[24]

Results in Tables I and II show that oxidation of cyclohexane with manganic acetate is more selective than with cobalt. We confirm that cyclohexyl acetate is the major product from cyclohexane oxidation with manganic acetate.[12] Selectivity is attributed to slow formation of radicals with manganic acetate (reaction 1). Cobaltic acetate is a more powerful oxidant and therefore less selective. With Co(III), radicals can be generated by both electron transfer and thermolysis at higher rates and in higher concentrations than with manganese to afford a more complex product. Increasing the concentration of radicals in the manganese system through addition of nucleophiles causes product ratios to approach those with cobalt. Addition of acetates (KOAc or NaOAc) in cyclohexane oxidations with Co(III) led to rate enhancement, but had no appreciable effect on product distribution. With manganese, however, both rate and amount of RCH_2OAc adduct increased with rising acetate ion concentration. Such an effect was earlier reported for oxidations of alkylbenzenes with both cobalt and manganese. Results are comparable to those with the cycloaliphatic substrates. They are in agreement with an electron transfer pathway for cobalt, and a free-radical one for manganese. In analogy to work reported with lead salts,[13] a $Mn(OAc)_4^-$ complex was suggested in the presence of added acetate ions, assumed to be more active than $Mn(OAc)_3$ alone.[10] The same is also true of cobalt.[14]

We also compared cyclohexane oxidations with cobalt to those with manganese salts in the presence of cupric acetate. Cu(II) ions were earlier shown to be effective radical terminators, the rate of termination of simple alkyl radicals being diffusion controlled. Copper oxidizes stable radicals (allyl, benzyl, and *tert*-butyl) to carbonium ions, and converts less stable radicals to olefins.[15] If thermolysis were involved in initiation with cobalt, methyl radicals produced would be trapped by Cu(II), as no products of cyclohexane can be formed. Initiation by electron transfer, however, produces cyclohexyl radicals directly which can be oxidized by Cu(II) to form cyclohexane-derived products. On this basis, data in Tables I–III suggest electron transfer as the sole or dominating mechanism operating in cyclohexane oxidation with cobaltic acetate. Electron transfer in oxidation of cyclohexane with manganic acetate is a probable contributor, at least in experiments with added nucleophiles. Increased formation of cyclohexylmethyl acetate in the absence of copper, and olefin formation in its presence, can be rationalized by assuming this pathway.

The most pronounced effect of copper on the course of reaction is elimination of the RCH_2OAc adduct and formation of unsaturated esters with both cobalt and manganese. Oxidation of cyclohexane with cobaltic acetate and copper led to the formation of 3-cyclohexenyl acetate (~94%), 1-cyclohexenyl acetate (~2%), and cyclohexyl acetate (~4%). With manganese and copper, however, 3-cyclohexenyl acetate and cyclohexyl acetate were formed in 37 and 61% yield, respectively. Unlike with cobalt, considerable amounts of cyclohexyl acetate are still formed with added cupric acetate when manganic acetate is the oxidant. This suggests an additional pathway immune to the radical scavenger, and as yet not elucidated.

Formation of unsaturated esters in the presence of copper proceeds through cyclohexene. With cobaltic acetate, reaction involves radical cations,[16] but with manganese, a direct allylic abstraction.[17]



Results with copper ions as cooxidant appear significant from a practical as well as theoretical point of view. Conversion of aliphatic substrates to olefinic derivatives by this route may have general preparative value.

Conclusion

Our postulate that electron transfer is at least a contributing and most likely the dominant mechanism in the oxi-

Table VII
Characterization of Major Products[b]

Compd	Formula	Mol wt P+, m/e[c]	NMR (CCl_4, Me_4Si)
Cyclohexylmethyl acetate	$C_9H_{16}O_2$	156.1150 156.1134	3.85 (d, 2 H, CH_2O), 2.0 (s, 3 H,OAc), 0.7–1.9 (m, 11 H, ring)
Cyclohexyl acetate	$C_8H_{14}O_2$	142.0994 142.0982	4.7 (s, 1 H, =CHO); 2.0 (s, 3 H, OAc), 1.0–1.9 (m, 10 H, ring)
2-Acetoxycyclohexanone	$C_8H_{12}O_3$	156.0786 156.0794	4.85–5.4 (m, 1 H, =CHO–), 2.3 (m, 2 H, CH_2CO), 2.1 (s, 3 H, OAc), 1.3–2.0 (m, 6 H, ring)
Cyclohexylacetic acid	$C_8H_{14}O_2$	142.0994 142.0987	(Me_2SO-d_6, Me_4Si): 1.0–2.7 (broad multiplet with some fine structure)
Cyclohexanecarboxylic acid	$C_7H_{12}O_2$	128.0837 128.0858	0.6–2.6 (broad multiplet with some fine structure, 11 H, ring). 11.6 (s, 1 H, COOH, exchangeable)
3-Cyclohexenyl acetate[a]	$C_8H_{12}O_2$	140.0837 140.0842	5.9 (m, 2 H, olefin), 5.3 (s, 1 H, =CHO), 2.0 (s, 3 H, OAc), 1.0–1.9 (m, 6 H, ring)

[a] Major product isolated from a comparable run in the presence of 0.001 *M* $Cu(OAc)_2$. [b] Minor products were detected by doping with standards. They included cyclohexanone, cyclohexanol, cyclohexylidene diacetate, and some dimers. [c] Calculated over found.

dation of cycloaliphatic substrates with cobalt is based on manifestations such as high rates at low temperature, high product selectivity, and relative inactivity of tertiary hydrogen, observations among others closely paralleling those with aromatic substrates. Free-radical processes must also occur and experimental conditions will determine their contribution. The extent to which electron transfer contributes will depend on the oxidation potential of the metal ion couple, the ionization potential of RH, experimental conditions in general, and, in the presence of oxygen, on the ability to regenerate the higher valency state of the metal. The requirements for electron transfer to operate with cycloaliphatics and cobalt appear to be well met in the light of these criticalities.

Experimental Section

Oxidations at elevated pressure were carried out in a 1-l., 316 stainless steel, magnetically stirred autoclave which was equipped with a Dispersomax stirrer, a heating mantle, and cooling coils (Autoclave Engineers, Inc., Erie, Pa.). Molecular oxygen was used as the oxidant, introduced into the reactor through a medium porosity, 2-in. o.d., stainless steel sparger and was supplied at the rate at which it was consumed. Experiments with metal salts alone were carried out in standard laboratory glassware under nitrogen. Concentrations of metal ions were determined by iodometric titration. Products of reaction were analyzed by GLC by doping with standards and confirmed by mass spectrometry. Carboxylic acids were analyzed as trimethylsilyl derivatives on Varian 1520, T. C. detector, chromatograph (6 ft × 0.25 in., OV-1 column, programmed from 50 to 275° at 10°/min). Other analyses were carried out on a 5 ft × 0.25 in. 20% Carbowax 20M column at 65°. The NMR spectra were obtained on a Varian T-60 spectrometer. Chemical shifts are in δ units, in parts per million.

Cobaltic Acetate (Method 1). This oxidant was prepared from cobaltous acetate and *tert*-butyl hydroperoxide. To 100 g of $Co(OAc)_2 \cdot 4H_2O$ in 2 l. of methanol, heated under reflux, was added with stirring over a 1-hr period 38 g of 90% *t*-BuOOH (Lucidol). Reaction was continued for an additional 1 hr and methanol solvent was stripped off on a rotary evaporator and replaced with 1.5 l. of acetic acid. The resulting solution was concentrated to ~350 ml, which was 0.37 *N* Co(III), or 32%.

Cobaltic Acetate (Method 2). This oxidant was prepared from cobaltous acetate, MEK, and oxygen. A mixture containing 100 g of $Co(OAc)_2 \cdot 4H_2O$ and 15 g of water in 1 l. of acetic acid was heated to 90°. With oxygen being passed through a medium porosity sparger immersed in the solution (~1–2 l./hr), 350 ml of MEK was added over a period of 1 hr. Reaction was continued for 6 hr and the mixture was concentrated to about 360 ml. Titration showed it to be 0.34 *N* Co(III).

Oxidation of Cyclohexane with Cobaltic Acetate. Material Balance Run. In a typical experiment a 1.2 *M* cyclohexane solution containing 150 mmol of sodium acetate trihydrate, and 100 mmol of cobaltic acetate [28% Co(III)] in 520 ml of acetic acid was heated at 80° (N_2 atmosphere, 28 hr) until the color of solution changed from dark green to purple. The reaction mixture was cooled and then 3.5 mmol of cyclohexyl chloride was added as an internal standard. The solution was diluted with 500 ml of ethyl ether and extracted three times with cold water (400–500-ml portions), once with 5% $NaHCO_3$ solution, and water. After drying the organic layer over magnesium sulfate and filtering, the mixture was concentrated in a rotary evaporator and analyzed by GLC. Analysis showed the sample to contain 1.6 mmol of cyclohexylmethyl acetate, 1.3 mmol of cyclohexyl acetate, and 0.6 mmol of 2-acetoxycyclohexanone. The aqueous layer was evaporated to dryness, treated with 25 ml of concentrated hydrochloric acid to release any acidic products tied up with the cobalt, and evaporated to dryness. After adding 3.5 mmol of octanoic acid as internal standard, the residue was extracted with acetone, dried over magnesium sulfate, filtered, and analyzed by GLC. Analysis showed the sample to contain 1.8 mmol of cyclohexylacetic acid and 0.35 mmol of cyclohexanecarboxylic acid. The products thus isolated account for about 65% of Co(III) ions consumed. The aqueous layer contained additional products (cyclohexanone and cyclohexanol) in trace amounts, but these were not isolated.

Identification of products was carried out by GLC by comparing relative retention times to those of authentic samples. Most authentic samples were commercially available. Cyclohexylmethyl acetate and 3-cyclohexenyl acetate were synthesized by a standard acetylation procedure employing acetyl chloride and the commercially available cyclohexylmethanol and 3-cyclohexen-1-ol.

Major components in a product mixture were also collected off the gas chromatographic column and further characterized by mass spectrum, NMR (Table VII), and ir.

Attempted Oxidation of Methylcyclohexane. A mixture consisting of 20 g of $Co(OAc)_2 \cdot 4H_2O$, 20 g of MEK, 60 g of hydrocarbon, and 400 g of acetic acid was treated with oxygen (105°, 20 atm total pressure, 4 hr) under conditions earlier employed to prepare adipic acid from cyclohexane.[6] Reaction starts as noted by oxygen uptake, but after about 30 min of reaction, whenever MEK is consumed, reaction stops. Continued heating up to 48 hr showed no evidence of any reaction of the substrate.

Cooxidation of Methylcyclohexane and *n*-Butane. The above experiment was repeated in the presence of 95 g of butane (105°, 20 atm, 3 hr) to afford 563 g of liquid reaction product. This mixture was diluted with 500 ml of water, recovering unreacted methylcyclohexane by decanting, and then evaporated to dryness in a rotary evaporator. The residue was extracted several times with acetone to afford 42.2 g of dicarboxylic acids. Analysis by GLC showed methyladipic acids (63.9% efficiency), methylglutaric acids (10.5%), and methylsuccinic acid (10.1%) to be major products. Minor products included glutaric acid and succinic acid, but no adipic acid. Conversion of methylcyclohexane was estimated at ~50%. The ratio of the 3-methyladipic acid to its 2-methyladipic isomer was 4:1, and with glutaric acids it was 1.9:1. No material balance on butane was obtained in this experiment. Results were assumed to be comparable to those of our earlier study.[5]

Oxidation of 4-Methylcyclohexanone. Forty grams of this ketone was oxidized as above in absence of butane (104°, 17 atm, 1.5 hr) to afford 488 g of liquid product. This product was diluted with

200 ml of water, heated on a steam bath until the color of solution had turned from dark green to pink, and then it was evaporated to dryness. Extraction of residue with acetone gave 41.3 g of product. Analysis by VPC showed this material to be 92% 3-methyladipic acid (67% yield). None of the 2-methyl isomer was detected. Recrystallization from benzene afforded pure product [mp 91–92° (lit.[18] mp 89–91°)]: NMR (Me_2SO-d_6, Me_4Si) 0.9 (d, 3, CH_3), 1.5 (m, 2, CH_2CH_2COOH), 1.8–2.6 (m, 5, -CH=, CH_2COOH); neut equiv, 80.8 (calcd, 80).

Preparation and Dehydration of 3,3-Dimethylcyclohexanol. About 100 g (0.7 mol) of 5,5-dimethyl-1,3-cyclohexanedione in 600 ml of methanol was reduced in the presence of 20 g of nickel 0104P catalyst (Harshaw) in a 1-l., 316 stainless steel autoclave (200°, 100 atm H_2, 6 hr). The crude reaction mixture was filtered to recover the catalyst and methanol was distilled off to give 95 g of colorless liquid product which was mostly alcohol by ir: n^{20}D 1.4625 [lit.[19] bp 80–81° (16 mm), n^{25}D 1.4569]; NMR (CCl_4, Me_4Si) 0.89 (s, 3, CH_3), 0.93 (s, 3, CH_3), 1.1–2.1 (m, 8, CH_2), 3.1 (s, 1, exchangeable proton, OH), 3.62 ppm (m, 1, =CH-).

The reaction product was transferred to a 200-ml flask and distilled in the presence of 5 g of *p*-toluenesulfonic acid. The product distilling in the temperature range of 85–130° was collected, separated from water, dried ($MgSO_4$), and redistilled to give 56 g (71%) of ~35:65 mixture of 3,3- and 4,4-dimethylcyclohexene, bp 114–118° (lit.[20] bp 115.2–116.2°).

Preparation of 1,1-Dimethylcyclohexane. About 98 g of olefinic mixture prepared by the above procedure was hydrogenated in the presence of 20 g of nickel 0104P catalyst in 600 ml of methanol (145°, 95 atm, 2 hr). The reaction mixture was filtered, but isolation of 1,1-dimethylcyclohexane by distillation was not successful. Instead, the reaction mixture was diluted with ~2 l. of water and the organic layer was separated, dried ($MgSO_4$), and redistilled to give 86 g (87%) of 1,1-dimethylcyclohexane: bp 116–119° (lit.[21] bp 119.65°); NMR (CCl_4, Me_4Si) 0.88 (s, 6, CH_3), 1.1–1.6 (m, 10, CH_2).

Oxidation of 1,1-Dimethylcyclohexane. A mixture consisting of 20 g of cobaltous acetate tetrahydrate, 400 g of acetic acid, 20 g of MEK, and 60 g of 1,1-dimethylcyclohexane was oxidized to afford 537 g of crude reaction mixture (106°, 20 atm, 3 hr). This mixture was diluted with 1 l. of water to recover unreacted substrate, heated on a steam bath until solution had turned from dark green to pink, and evaporated to dryness. The residue was extracted with acetone to afford 43 g of acids. Analysis by NMR and VPC showed 3,3-dimethyl- and 2,2-dimethyladipic acid (3:1 ratio, based on areas of two singlet *gem*-dimethyl groups at 1.05 and 1.18 ppm, respectively) to be the major products of reaction (73%, 57% conversion). Minor products were not characterized.

Other substrates such as ethylcyclohexane, 3-methylcyclohexanone and 3-methylcyclohexanol, and 2-methylcyclohexanone were oxidized under similar conditions and are summarized in Table V.

Oxidation with Cobaltic and Manganic Salts. Experiments with metal salts alone were carried out in standard laboratory glassware. Conditions employed, substrates oxidized, and the results obtained are summarized in Tables I–III. After termination of reaction, noted by a change in color resulting solution (green to pink for cobalt, and brown to colorless for manganese), the mixture was taken up in ethyl ether and repeatedly extracted with cold water. The organic layer was dried ($MgSO_4$) and filtered, and the ether was evaporated. After carefully stripping off the unreacted substrate in a rotary evaporator, the residue was subjected to chromatographic analysis. Products of reaction were confirmed by doping with standards whenever possible as well as by mass spectrometry. Manganic acetate was prepared by a published procedure.[3] Concentrations of metal ions were determined by iodometric titration.

Oxidation of Cyclohexane with Manganic Acetate and Oxygen. A mixture of 20 g of $Mn(OAc)_3$-$4H_2O$, 20 g of MEK, and 60 g of cyclohexane in 400 g of acetic acid was treated with oxygen (115°, 20 atm) for 3 hr. The autoclave was cooled, depressured, and its content of 505 g withdrawn. This mixture was diluted with an equal volume of cold water, recovering 38 g of unreacted substrate by decanting, and extracted with ethyl ether. The organic layer was washed three times with water and once with dilute sodium bicarbonate solution, and dried over $MgSO_4$. On evaporation to dryness, about 1 g of organic residue was recovered. Analysis by GLC showed cyclohexanone (6%), cyclohexanol (50%), cyclohexyl acetate (35%), and smaller amounts of cyclohexylidene diacetate, 2-acetoxycyclohexanone, and several unidentified compounds to be in the residue. The initial aqueous layer was also evaporated to dryness, but the residue from this treatment contained only a trace of adipic acid. For practical purposes, therefore, no reaction occurred. This of course is in contrast to excellent results obtained with cyclohexane in the cobalt system.

Reactivity Data. Reactivities were determined by a competitive oxidation procedure.[6] Oxidations with cobaltic acetate were carried out under nitrogen in sealed ampoules [0.4 *M* Co(III)/HOAc, 0.8 *M* RH, and 0.4 *M* chlorobenzene as internal standard]. Reactivities under oxygen pressure were carried out in an autoclave, generating Co(III) ions in situ from reaction of cobaltous acetate and MEK in the presence of oxygen. A typical charge consisted of 20 g of $Co(OAc)_2$-$4H_2O$, 20 g of MEK, 60 g of *n*-butane, and 10–15 g of each RH in 450 g of acetic acid. After an induction period of ~30 min at 100° and 20 atm, reaction was continued for ~5 min. Reactivities were based on the disappearance of RH and were related to toluene, an assumed standard.

Registry No.—Cobaltic acetate, 917-69-1; cobaltous acetate, 71-48-7; *tert*-butyl hydroperoxide, 75-91-2; MEK, 78-93-3; oxygen, 7782-44-7; cyclohexane, 110-82-7; cyclohexylmethyl acetate, 937-55-3; cyclohexyl acetate, 622-45-7; 2-acetoxycyclohexanone, 17472-04-7; cyclohexylacetic acid, 5292-21-7; cyclohexanecarboxylic acid, 98-89-5; 3-cyclohexenyl acetate, 10437-78-2; methylcyclohexane, 108-87-2; *n*-butane, 106-97-8; 4-methylcyclohexanone, 589-92-4; 3-methyladipic acid, 3058-01-3; 3,3-dimethylcyclohexanol, 767-12-4; 5,5-dimethyl-1,3-cyclohexanedione, 126-81-8; 3,3-dimethylcyclohexene, 695-28-3; 4,4-dimethylcyclohexene, 14072-86-7; 1,1-dimethylcyclohexane, 590-66-9; ethylcyclohexane, 1678-91-7; 3-methylcyclohexanone, 591-24-2; 3-methylcyclohexanol, 591-23-1; 2-methylcyclohexanone, 583-60-8; $Mn(OAc)_3$, 993-02-2; Co^{3+}, 22541-63-5; Mn^{3+}, 14546-48-6; $Mn(OAc)_2$, 638-38-0.

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Reaction of Nitrosyl Chloride with Phenylmagnesium Bromide[1a]

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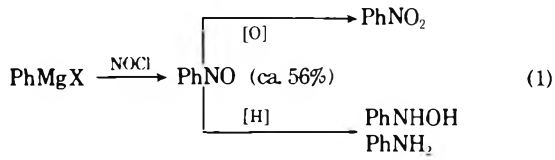
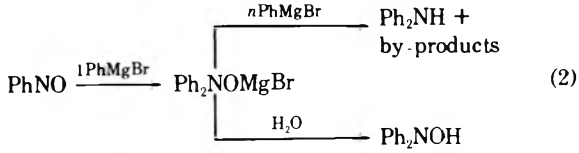
The reaction between nitrosyl chloride and phenylmagnesium bromide in dilute diethyl ether solution was studied at −78°. The predominant volatile product was diphenylamine, and not nitrosobenzene as reported in the earlier literature. Under varying reaction conditions the yield of the secondary amine ranged between 0 and 31%. A mechanistic study included an investigation of the reaction between nitrosobenzene and phenylmagnesium bromide. Contrary to the literature, a 1:1 stoichiometry was evident and several heretofore proposed reaction paths were disproved. The overall reaction occurs via a 2:1 NOCl–Grignard stoichiometry and involves nitrosobenzene and probably diphenylnitric oxide as reaction intermediates.

The thought of developing a simple, relatively mild method for introducing nitrogen functionality into the aromatic nucleus prompted us to explore the reactions of certain nitrogen-containing electrophiles with organometallic compounds. Of primary interest was the possible reaction between Grignard reagents and nitrosyl chloride, since in 1908 Oddo[2] had reported a 56% yield of nitrosobenzene from the reaction of phenylmagnesium bromide and NOCl. If nitroso products were indeed formed, synthesis of any nitrogen derivative would be possible (eq 1).



(1)

However, in apparent contradiction of Oddo's work, Wieland and Roseeu[3a] showed that phenylmagnesium bromide underwent a rapid addition reaction with nitrosobenzene, yielding the magnesium salt of diphenylhydroxylamine. This compound was then quickly converted to diphenylamine, the final product (eq 2).



(2)

where $n = 1-2$

Both Wieland and Roseeu,[3b] and later Gilman and McCracken,[4] presented somewhat differing, but apparently sound mechanisms for the formation of the diarylamine product.

Consideration of the above reports caused us to reinvestigate the reaction between nitrosyl chloride and phenylmagnesium bromide.

Results

Reaction of Nitrosyl Chloride and Phenylmagnesium Bromide. Volatile Products. Phenylmagnesium bromide and NOCl, reacting under a variety of experimental conditions at −78°, produced diphenylamine in yields of 0 to 31%, based on Grignard reagent. Five other products were isolated in lesser yields. They were identified as nitrosobenzene, phenol, biphenyl, phenylmethylcarbinol, and 4-nitrodiphenylamine. The results of these reactions are listed in Table I.

From Table I it is evident that the major volatile product in most cases was diphenylamine. Moreover, nitrosobenzene was detected as a reaction product only once and then in a quite minor amount. Repeated attempts to prepare nitrosobenzene under Oddo's conditions (reaction 8, Table I) yielded only diphenylamine.

Nonvolatile Products. Since ca. 75% of the starting materials could not be accounted for in the reactions of Table I, a search for the nonvolatile products was conducted. Assuming that the nonvolatiles were formed by a further reaction of NOCl with diphenylamine, inverse addition reactions similar to reaction 10, Table I, were carried out under conditions of a large excess of NOCl. From these reactions a large amount of various nitroso- and nitro-substituted diphenylamine products was obtained. Separation of the complex mixture was not attempted, but one product, 2,2′-dinitro-4,4′-dichlorodiphenylamine, was isolated (7.5%) in nearly pure form owing to its relative insolubility in all common solvents.

The above reactions also involved DCl or D_2O hydrolysis steps in an attempt to ascertain the origin of the diphenylamine proton. In all cases the isolated diarylamine was the H_{11} species.

Reaction of Nitrosobenzene and Phenylmagnesium Bromide. Since nitrosobenzene was the expected intermediate of the reactions listed in Table I, its course of action with phenyl Grignard reagent was studied. The reaction was run in two different ways. In the first an ether solution of nitrosobenzene was added to ethereal phenylmagnesium bromide at −78°. Analysis of the product mixture showed a 49.2% yield of diphenylamine plus seven other compounds (see Table II, reaction 1).

The second mode of reaction involved the addition of ethereal phenylmagnesium bromide in incremental amounts to a solution of nitrosobenzene at −78°. The results for this series of Grignard additions are listed as reactions 2–7, Table II.

Table II shows that the major volatile products of the nitrosobenzene–phenyl Grignard reaction are diphenylamine and benzene. Although these results indicate that the nitrosobenzene from the nitrosyl chloride–phenylmagnesium bromide reaction most certainly reacts with more Grignard reagent, other possible fates of the nitroso intermediate are possible and were therefore investigated.

Reaction of Nitrosobenzene with Nitrosyl Chloride. Although earlier work in our laboratory had determined that 0.1 *M* nitrosobenzene in ether was unaffected by large amounts of NOCl at both −78 and 0°, the reactants were tested under more extreme conditions. At 27° nitrosobenzene and NOCl yielded small amounts of nitrobenzene, benzene, phenol, and biphenyl. No quantitative analyses of these volatile products were attempted owing to their low yield.

It was simultaneously noted that virtually no decomposition of nitrosobenzene had taken place, since the well-documented products of that reaction were not found.[6]

Table I
Volatile Products from the Reaction of Nitrosyl Chloride and Phenylmagnesium Bromide

Reaction	Mode of addition[a]	Solvent	Hydrolysis conditions	Mole ratio Grig/NOCl	PhNO[c]	Ph_2NH	PhOH[c]	% yields[b] Ph_2	PhMeCHOH[c]	$(4\text{-}NO_2)$-PhNHPh[c]
1	NOCl (soln), to PhMgBr	Et_2O	NH_4Cl	1.9	0.0	16.8[c]	1.7	1.3	3.7	1.8
2	NOCl (soln) to PhMgBr	Et_2O	NaOH–$NaHCO_3$	1.5	2.0	31.0[c]	0.1			
3	NOCl (soln) to PhMgBr	Et_2O	NaOH–$NaHCO_3$	5.3	0.0	0.0[d]				
4	NOCl (soln) to PhMgBr	Et_2O	NaOH–$NaHCO_3$	2.8	0.0	9.3[d]				
5	NOCl (soln) to PhMgBr	Et_2O	NaOH–$NaHCO_3$	1.9	0.0	24.3[d]				
6	NOCl (soln) to PhMgBr	Et_2O	NaOH–$NaHCO_3$	0.8	0.0	18.8[d]				
7	NOCl (soln) to PhMgBr	THF	NH_4Cl	1.4	0.0	6.6[c]	5.6	0.6	0.0	
8	NOCl (g) to PhMgBr	Et_2O	NH_4Cl		0.0	13.5[d]				
9	NOCl (soln) and PhMgBr to Et_2O	Et_2O	NaOH–$NaHCO_3$	2.1	0.0	9.5[d]				
10	PhMgBr to NOCl (soln)	Et_2O	NH_4Cl	1.5	0.0	3.7[c]	0.4	1.5		6.6

[a] Reaction temperature −76°C. [b] Yield values for PhNO are based on NOCl; other products on PhMgBr. A blank indicates no analysis. [c] Yields by VPC analysis, after correction for starting material impurities. [d] Isolated yields of HBr salt.

Table II
Results of the Nitrosobenzene–Phenylmagnesium Bromide Reaction

Reaction	Mole ratio Grig/PhNO	PhNO reacted[a]	PhMgBr reacted[a]	Ph_2NH formed[a]	PhH formed[a,b]	% yield Ph_2NH[c]
1[d]	1.38	25.4	45.0	12.5	17.1	49.2
2[e]	0.33	3.2	5.0	1.0	1.0[f]	59.4
3[e]	0.68	8.0	10.0	4.6	1.6[f]	55.1
4[e]	1.03	12.2	15.0	6.8	7.0	59.0
5[e]	1.38	12.3	20.0	7.8	9.4	63.4
6[e]	1.74	13.3[f]	25.0	7.7	17.2	57.9
7[e]	2.10	13.9[f]	30.0	7.9	26.7	56.8

[a] Values in millimoles, ±2%, by VPC analysis. [b] Corrected for PhH in Grignard solution. [c] Percent yields based on reacted PhNO, ±2%, [d] PhNO added to PhMgBr; other isolated products were $PhNO_2$ (5.9%), PhOH (4.5%), azoxybenzene (9.2%), PhMeCHOH (2.2%), and PhPh (1.3%). [e] PhMgBr added to PhNO. The Gilman test[5] for active Grignard was negative after each addition of PhMgBr. [f] These values ±15% owing to integration imprecision at low signal to noise ratio.

Reaction of Nitrosyl Chloride with Diethyl Ether and Diphenylamine. At room temperature diethyl ether proved to be essentially inert toward NOCl. However, after a 15-min reaction time, diphenylamine and NOCl produced a 30% yield of 4-nitro-*N*-nitrosodiphenylamine.

Discussion

Reaction of Nitrosyl Chloride with Phenylmagnesium Bromide. Reaction Products. The low (or zero) yields of nitrosobenzene place Oddo's conclusions[2] in doubt. It would seem unlikely, based on our collective experiments, including repeated duplications of Oddo's conditions (reaction 8, Table I), that nitrosobenzene[7] was ever isolated as the major product from the reaction[8] of NOCl and phenylmagnesium bromide.

Of course, diphenylamine was the major volatile product in all reactions. However, a change of solvent from diethyl ether to THF produced a substantial lowering of the diphenylamine yield. An explanation for this could be that since NOCl is 20 times more soluble in THF than in ether,[9] the rate of further nitrosation steps, as mentioned above, would be increased.

A factor which increased amine yield was the change to a basic hydrolyzing medium. The presence of a base would minimize the above-mentioned nitrosation and/or chlorination of diphenylamine which might occur during the hydrolysis step.

The mole ratio of reagents also obviously affected the yield of diphenylamine. Reactions 3–6 (Table I) were patterned after the style of Gilman,[4] who used optimized yields in his mechanistic arguments. From our results it is clear that as the Grignard/NOCl mole ratio is varied from ca. 2:1, the yield of diphenylamine is reduced. This reduction is especially severe when the ratio is large. This fact would seem to indicate that before hydrolysis the amine precursor can react in a different manner with excess Grignard reagent. Of course, the yield of diphenylamine is also lowered when the Grignard/NOCl ratio is very small for reasons already mentioned.

An attempt to reduce side reactions by maintaining a 2:1 Grignard/NOCl ratio throughout the reaction (reaction 9, Table I) apparently failed. Although the solutions were added together in a constant 2:1 ratio, the yield of amine dropped to 9.5%. One possible explanation is that the first step of the reaction, i.e., between Grignard and NOCl, is much faster than the later step(s). Thus the simultaneous addition of phenylmagnesium bromide and NOCl approximates the condition of excess Grignard, e.g., reactions 3 and 4, Table I.

The small yields of phenol and biphenyl are probably the result of the normal amount of oxygenation and coupling which accompany most Grignard reactions. Certainly these yields contradict the proposed mechanisms of Wieland[3] and Gilman[4] for the latter steps of the overall mechanism (see the nitrosobenzene–Grignard discussion).

The yield of phenylmethylcarbinol (3.7%) obtained in reaction 1 (Table I) is normal for ethereal phenyl Grignard

reactions. There are two proposed mechanisms for its formation,[10,11] and neither predicts any phenylmethylcarbinol when the solvent is changed to THF, as was the case in reaction 7 (Table I).

The formation of 4-nitrodiphenylamine in reaction 1 and reaction 10 (Table I) most certainly arises from para nitrosation of diphenylamine by NOCl, since this reaction was examined,[12] found to be very fast, and declared to be the final step of the Fischer–Hepp rearrangement.[13] Under conditions of excess NOCl (reaction 10, Table I), this process is accordingly more dominant. Further oxidation is most likely caused by the hydrolysis mixture of any excess nitrosyl chloride (eq 3).[14]

$$3NOCl + 2H_2O \longrightarrow HNO_3 + 2NO + 3HCl \quad (3)$$

The 30% yield of 4-nitro-*N*-nitrosodiphenylamine from diphenylamine and NOCl strengthens the above mechanistic interpretation.

Thus the probable fate of much of the diphenylamine in the reactions of Table I was repeated nitrosation and oxidation, forming a myriad of expected nitrosated and/or nitrated products.[13,15]

Competing Reactions. The results of the thermal decomposition of nitrosobenzene suggest that this process does not occur to any significant extent during the reaction of NOCl and phenyl Grignard reagent. Neither azoxybenzene nor nitrobenzene, the major decomposition products, were detected in the latter reaction. Likewise the nitrosobenzene-NOCl reaction seems unimportant.

Reaction of Nitrosobenzene with Phenylmagnesium Bromide. Since nitrosobenzene was the expected primary intermediate of the NOCl–Grignard reaction, and since the literature[3,4] is at odds as to the exact mechanism of the nitrosobenzene–Grignard reaction, a decision was made to investigate this step of the overall reaction.

Wieland,[3a] Gilman,[4] and later Maruyama[16] showed that the reaction of nitrosobenzene with phenyl Grignard reagent produces, initially, the magnesium sale of diphenylhydroxylamine (eq 2). Although the salt is reportedly[3,4] reactive toward more Grignard reagent, it apparently can be isolated in pure form and upon hydrolysis yields large amounts[16] of diphenylhydroxylamine. The fact that the hydroxylamine was never isolated or detected during our studies and isolated only once by Gilman[4] reflects its extreme sensitivity to the work-up procedure.[17]

Wieland[3b] explained the formation of diphenylamine as resulting from a reaction between the magnesium salt of diphenylhydroxylamine and excess Grignard reagent (eq 4).

$$PhNO + PhMgBr \longrightarrow Ph_2NOMgBr \xrightarrow{PhMgBr}$$

$$Ph_2NMgBr + PhOMgBr \xrightarrow{H_2O} Ph_2NH + PhOH \quad (4)$$

Support for this explanation came from the fact that relatively large amounts of phenol were isolated from the product mixture and also that an apparent 2:1 Grignard–nitrosobenzene ratio was needed for optimum diphenylamine yield.

Gilman[4] discounted the above explanation when during his studies of the reaction he noticed formation of a significant amount of biphenyl but *no* phenol. This fact, coupled to his observation that a mole ratio of 3 Grignard to 1 nitrosobenzene was necessary to give a positive test[5] for active Grignard reagent, led him to a different mechanism (eq 5).

$$PhNO + PhMgBr \longrightarrow Ph_2NOMgBr \xrightarrow{2PhMgBr}$$

$$Ph_2NMgBr + Ph_2 + O(MgBr)_2 \xrightarrow{H_2O} Ph_2NH \quad (5)$$

Our results appear to disprove both Wieland's and Gilman's mechanisms. Like Gilman we found very little phenol in the product mixture.[18] The low yield of this product could suggest that either a small amount of O_2 was present in the reaction atmosphere, or that Wieland's mechanism (eq 4) does play a minor role. Likewise, the finding of only minuscule amounts of biphenyl (Tables I and II) from both the NOCl–Grignard and nitrosobenzene–Grignard reactions seriously jeopardizes the validity of Gilman's hypothesis (eq 5).[19] The small amount of the hydrocarbon which was found may indicate the relative unimportance of the free radical Grignard species[20] in this particular case.

Besides not finding phenol or biphenyl in significant amounts, our results (Table II) clearly rule out a 3:1 or 2:1 Grignard–nitrosobenzene stoichiometry. In fact, Table II shows that the Grignard reagent reacts in a 1:1 fashion with nitrosobenzene until the concentration of the latter has been significantly reduced. At this point the Grignard reagent continues to react (negative Gilman tests[5]) but resulting mainly in the production of benzene. Moreover, the fact that the yield of benzene is negligible until over half of the nitrosobenzene has reacted, and over three-quarters of the diphenylamine has been formed, indicates that its formation[21] is not involved in the production of the diarylamine.

Another point of this particular reaction deserves mentioning. The amount of diphenylamine produced (Table II) was consistently near 50% of the amount of nitrosobenzene reacted. This result is not only evident from our work, but Gilman[4] also achieved isolated (distillation) yields of only 30–40%. Moreover, in perhaps the most definitive reaction studied by Gilman, the author realized only a 40% isolated yield of diphenylamine starting with diphenylhydroxylamine.[22] Now, since the first step of this reaction should certainly be quantitative,[23] it remains that the conversion of the magnesium salt of diphenylhydroxylamine to diphenylamine may be limited to a ca. 50% yield on mechanistic grounds.

Diphenylnitric Oxide. An obvious solution to the above puzzle would involve some type of disproportion step in the overall process. Fortunately, such a step is available if one assumes the importance of diphenylnitric oxide as a viable reaction intermediate. In this connection Maruyama[16] proved that the initial products from the reaction of nitrosobenzene and phenylmagnesium bromide consist of an equilibrium mixture of diphenylnitric oxide and bound magnesium salt (eq 6).

$$PhNO + (PhMgBr)_n \quad (6)$$

$$\downarrow$$

$$Ph_2NO\cdot + \cdot MgBr(PhMgBr)_{n-1} \rightleftharpoons (Ph_2NOMgBr)(PhMgBr)_{n-1}$$

Under conditions of excess Grignard reagent the equilibrium lay far to the right, whereas a mole ratio of 1.0 produced a 77% yield of the radical species at equilibrium.[24] This same radical, diphenylnitric oxide, first prepared in 1914 by Wieland[25a] and later studied by the same group,[25b] had been shown to decompose quickly in the presence of dilute mineral acid and "sometimes in pure ether" into diphenylamine and "quinoneanil oxide" (eq 7).

$$2Ph_2NO\cdot \longrightarrow Ph_2NH + \text{O=C}_6\text{H}_4\text{=N—Ph} \quad (7)$$

(O)

By combining the various aspects of the above discussion, a likely mechanism for the nitrosobenzene–phenylmagnesium bromide reaction can be formulated. The process most certainly involves a 1:1 addition of Grignard reagent to the nitroso π bond, including equilibration between radical and ionic species. This is followed by a rapid

disproportion of the diphenylnitric oxide to diphenylamine and oxidized quinoidal-type molecule, thereby giving a 50% theoretical yield for the secondary amine under conditions where eq 6 lies far to the left.[26] Although the oxidized species was never isolated, the isolation techniques would probably cause rapid polymerization of this type of molecule, thereby producing some of the nonvolatile materials commonly formed in these reactions.

Additional evidence for the above mechanism is the failure of the reaction to incorporate any deuterium into the diphenylamine product.[27] Certainly this fact would require formation of the secondary amine *before* hydrolysis, whereas Wieland[3b] and Gilman[4] had assumed that protonation occurred *during* hydrolysis (eq 4 and 5).

Nitrosyl Chloride and Phenylmagnesium Bromide. Reaction Mechanism. The present study did not investigate the first step of the reaction of nitrosyl chloride with phenylmagnesium bromide. If the nitroso cation were involved, one would expect a simple and highly exothermic bonding with the very nucleophilic carbon of the Grignard reagent. On the other hand, the reaction of covalent nitrosyl chloride might be compared to the analogous reaction of acid halides with Grignard reagents.[28]

The remaining steps of the overall reaction, i.e., the reaction between nitrosobenzene and phenyl Grignard reagent, probably involve the sequence already outlined above. The entire mechanism is summarized below.

$$PhMgBr + NOCl \longrightarrow [PhNO] + MgClBr$$

$$PhNO + PhMgBr \longrightarrow Ph_2NO\cdot + \cdot MgBr$$

$$2Ph_2NO\cdot \longrightarrow Ph_2NH + O{=}C_6H_4{=}NPh \quad (8)$$

(O)

$$\cdot MgBr \longrightarrow Mg^0 + MgBr_2$$

$$O{=}C_6H_4{=}NPh \longrightarrow \text{polymer}$$

(O)

The third and fourth steps of the above mechanism, although not proven, seem justified based on the nature of the reacting species.

Experimental Section

Melting points were taken on a Mel-Temp melting point apparatus and are uncorrected. All gas chromatography work was done with a Varian 1700 gas chromatograph. Infrared, nuclear magnetic resonance, electron spin resonance, and mass spectral data were recorded on the Beckman IR-33, Varian HA-60, Varian E-3, and Varian Mat-111 instruments, respectively. Elemental analyses were performed by Meade Microanalytical Laboratory, Amherst, Mass., and Galbraith Laboratories, Inc., Knoxville, Tenn.

Reaction of Nitrosyl Chloride with Phenylmagnesium Bromide. Volatile Products. In a typical reaction (reaction 1, Table I) magnesium (3.64 g, 150 mmol) and naphthalene (2.45 g, 19.1 mmol) were added to 250 ml of dry ether in a 1-l., three-neck flask. Under N_2 the reaction was initiated with a small amount of 1,2-dibromoethane, following which 8.32 g (53.0 mmol) of bromobenzene in 250 ml of dry ether was added dropwise. After the addition was complete, the reaction mixture was heated under reflux for 2 hr and the Grignard solution then filtered under N_2 through glass wool. Two aliquots were removed and hydrolyzed with a saturated NH_4Cl solution. VPC analysis (10 ft × 0.125 in. 10% SE-30 column) of the ether extracts of the hydrolysis mixtures showed a 97% conversion to phenylmagnesium bromide. Naphthalene was used as the internal standard and the amount of benzene produced during hydrolysis was corrected for the trace amount present in a flash distillate of the Grignard solution.

One hundred milliliters of a 0.237 *M* (determined by standard iodiometric titrations) solution of NOCl (Matheson Gas Products), bp −5.8°, in dry ether was cooled to −78° in a jacketed pressure-equalizing dropping funnel and added dropwise to the stirred Grignard solution (0.137 *M*, 44.6 mmol), also at −78°. After addition, the suspension was stirred for 3 hr at −78° and then hydrolyzed with 150 ml of a saturated NH_4Cl solution. The dark red ethereal layer was separated and added to two ether extracts of the aqueous phase, now at pH 7–8. The ether solution was further washed with saturated NH_4Cl and dried over $MgSO_4$. VPC analysis (10% SE-30 column) showed the presence of 633 mg (3.74 mmol, 16.8%) of diphenylamine: VPC coinjection with known compound on 10% SE-30 and 10 ft × 0.25 in. 10% Carbowax 20M columns; ir (melt) of VPC effluent identical with spectrum of known Ph_2NH.

VPC analysis of the above solution showed a total of 14 volatile products. The major products were identified by the VPC coinjection technique and comparison of the ir spectra of the VPC collected compounds with known spectra. These products included, in order of elution, benzene (yield undetermined), phenol (0.77 mmol, 1.7%), phenylmethylcarbinol (0.28 mmol, 1.3%), diphenylamine (see above), and 4-nitrodiphenylamine (0.40 mmol, 1.8%): ir identical with Sadtler Spectrum[29] no. 34522. The other eight products were not present in sufficient quantity to permit VPC collection and structure assignment.

Several variations of the above procedure were carried out. In the first (reaction 2, Table I), an NOCl solution (29.0 mmol) was quickly added to the unfiltered Grignard mixture (43.1 mmol) and the hydrolyzing medium was changed to a pH 10 NaOH–$NaHCO_3$ solution. After filtration, tetralin was added as an internal VPC standard and the solution worked up as before. The light green ether extracts of the acidified aqueous layer suggested the presence of nitrosobenzene. VPC analysis (10% SE-30 column) of the combined ether solutions showed a 6.68-mmol (31.0%) yield of diphenylamine as well as 0.04 mmol (0.09%) of phenol and 0.85 mmol (2.0%) of nitrosobenzene. Products were again identified by the VPC coinjection technique and comparison of their respective ir spectra with spectra of the known compounds. None of the other volatile components were identified.

A second variation of the original procedure involved the use of THF as the reaction solvent (reaction 7, Table I). Thus, 46.0 mmol of Grignard and 33.1 mmol of NOCl yielded diphenylamine (1.53 mmol, 6.6%), phenol (2.57 mmol, 5.6%), and biphenyl (0.28 mmol, 0.6%). No phenylmethylcarbinol was detected.

A third experimental variation (reaction 10, Table I) involved the inverse addition of reagents. Thus 37.0 mmol of Grignard was added dropwise to 29.0 mmol of NOCl in ether. Analysis of the hydrolyzed product mixture showed 0.68 mmol (3.7%) of diphenylamine, 0.13 mmol (0.35%) of phenol, 0.28 mmol (1.5%) of biphenyl, and 1.23 mmol (6.6%) of 4-nitrodiphenylamine.

A fourth experimental variation (reaction 9, Table I) involved the simultaneous addition of reagents. The filtered Grignard reagent (85.2 mmol) and NOCl solution (41.2 mmol) were added simultaneously at −78° to 200 ml of dry ether. The two rates of addition were adjusted such that a constant 2:1 Grignard–NOCl ratio was maintained throughout the reaction. After addition, the orange slurry was stirred for an additional 1 hr and worked up in the usual fashion, except that steam distillation was used to remove the reaction volatiles after hydrolysis, and the diphenylamine was precipitated from an ether extract of the steam distillate by conversion to its HBr salt with dry HBr gas. Diphenylamine hydrobromide (4.04 mmol, 9.5%) was isolated and identified by ir and reconversion to diphenylamine with hot NaOH. The product mixture was not further analyzed.

The last experimental variation of this series (reaction 8, Table I) was an attempt to duplicate exactly Oddo's[2] reaction conditions. Thus, gaseous NOCl was bubbled through 50.9 mmol of Grignard reagent at 0° until no further color changes appeared to take place. Hydrolysis and steam distillation gave only an orange-brown distillate (PhNO gives a brilliant green distillate), and VPC analysis of an ether extract showed no nitrosobenzene, whereas treatment with dry HBr yielded 3.44 mmol (13.5%) of diphenylamine hydrobromide.

Nonvolatile Products. Several reactions were run after which only the nonvolatile products were analyzed. Thus, using inverse addition, i.e., adding Grignard to NOCl, 24 mmol of filtered phenylmagnesium bromide in 200 ml of Et_2O at −78° was slowly added to 72 mmol of NOCl in 300 ml of Et_2O at −78°. Following addition and hydrolysis (H_2O, pH 7), the ether layer was dried and evaporated in vacuo, causing a pungent reddish-brown gas to appear. The remaining dark red oil (4.25 g) showed a complex mixture of nitroso- and nitro-substituted diphenylamines in its ir and NMR spectra. After multiple recrystallizations from acetone, the oil yielded 0.30 g (7.5%) of 2,2′-dinitro-4,4′-dichlorodiphenylamine:

mp 248.8–249.9° from acetone; ir (KBr) 3290, 3100, 1507, 1338, 1253, and 816 cm^{-1};[30] MS *m/e* 327 (2 Cl), 281, 280, 264, and 235; NMR (Me_2SO-d_6) δ 7.7 (AB q, J = 9.0 and 2.3 Hz, 2); 8.3 (d, J = 2.3 Hz, 1); uv, see below.[31]

λ_{max}, nm (ϵ) in acetonitrile	Plus KOH	Plus CO_2
235 (20000)	245 (25300)	238 (20000)
261 (22000)	274 (15500)	261 (22400)
299 (14000)	342 (12100)	298 (14700)
440 (11700)	576 (8950)	440 (12600)

Anal. Calcd for $C_{12}H_7N_3O_4Cl_2$: C, 43.93; H, 2.15; Cl, 21.61; N, 12.81. Found: C, 42.54; H, 3.06; Cl, 19.80; N, 12.74.

Hydrolysis by D_2O or DCl. The above reaction was repeated twice more with the hope of incorporating deuterium into the product via D_2O or DCl hydrolysis. Thus, 78.5 and 44.3 mmol of Grignard reacted with 240 and 250 mmol of NOCl, respectively, by D_2O and PCl_3–D_2O[32] hydrolyses, to yield 2.07 and 2.81 g, respectively, of an unknown white crystalline compound: mp 180.2–181.1° from acetone; ir (KBr) 3360, 3060, 1580, 1510, 1320, 870, and 800 cm^{-1}; NMR ($CDCl_3$) δ 7.25–7.75 (m, ~15), 6.30 (broad s, ~1); MS m/e 486 (4 Br); uv λ_{max} (ϵ) 243 (10500) and 293 (19500) in EtOH and no shift with KOH, etc.

Anal. Calcd for $C_{24}H_{14}N_2OBr_7$: C, 31.82; H, 1.56; Br, 61.75; N, 3.09; O, 1.77. Found: C, 31.96; H, 1.54; Br, 58.70; N, 3.10; O, 1.83.

The filtrates from the isolations of the unknown compound yielded a black oil when the solvent was removed. An ir spectrum of the oil showed practically pure diphenylamine, H_{11} in each case. Not only did the spectrum not show any N–D stretch, but the very distinctive N–D bending and C–N stretching bands of *N*-deuteriodiphenylamine[33] were completely absent.

Diphenylamine, H_{10}, was prepared by stirring the amine overnight in a dioxane–D_2O solution.[34] The solvent was removed and the ir spectrum of a melt of the crystals (NaCl plate) was recorded. The spectrum agreed completely with a literature[33] spectrum for the N-deuterated compound. The crystals were allowed to stand in air room temperature for 2 days and the ir spectrum rerun. The new spectrum was essentially unchanged.

Yield Optimization of Diphenylamine. In a series of reactions between phenylmagnesium bromide and NOCl (reactions 3–6, Table I) the mole ratio of Grignard reagent to NOCl was systematically changed and the yields of diphenylamine HBr salt noted. Thus, using basic hydrolysis conditions and the "normal" mode of addition (NOCl to PhMgBr), mole ratios (Grignard–NOCl) of 5.3, 2.8, 1.9, and 0.8 produced yields of diphenylamine corresponding to 0.0, 9.3, 24.3, and 18.8%, respectively. No other products were isolated or identified.

Reaction of Nitrosobenzene with Phenylmagnesium Bromide. Nitrosobenzene (32.5 mmol) in ether was added dropwise at −78° to a stirred ether solution of phenylmagnesium bromide (44.9 mmol) containing naphthalene as an internal VPC standard. After addition (under N_2) the brown slurry was stirred for 2 hr and hydrolyzed with a saturated NH_4Cl solution. Analysis of the organic phase by VPC (10 ft × 0.25 in. SE-30) showed benzene (17.1 mmol), diphenylamine (12.5 mmol), nitrosobenzene (7.1 mmol), phenol (2.0 mmol), nitrobenzene (1.9 mmol), azoxybenzene (1.5 mmol), phenylmethylcarbinol (1.0 mmol), and biphenyl (0.3 mmol). All products were identified by coinjection with known compounds and ir analysis. Prior to that reaction a portion of hydrolyzed Grignard solution failed to show any phenol, phenylmethylcarbinol, or biphenyl by VPC analysis.

A second reaction between nitrosobenzene and phenylmagnesium bromide was carried out in which the Grignard reagent was added in 5-mmol portions to a stirred Et_2O solution of nitrosobenzene (15 mmol) at −78°. After each addition the mixture was stirred for 2 hr and a 10-ml aliquot withdrawn. Five milliliters of the aliquot was flash distilled and the distillate analyzed (VPC) for benzene. The remaining 5 ml was hydrolyzed with a saturated NH_4Cl solution and analyzed (VPC) only for diphenylamine, benzene, and nitrosobenzene. Throughout the course of additions and aliquot withdrawals the Gilman test[5] for the presence of active Grignard reagent was negative. Also, a flash distillation of a sample of the Grignard solution gave a distillate containing ca. 0.2 mmol of benzene per 10 ml of aliquot. The calculated benzene yields were accordingly adjusted. The product yields of the above reactions are listed in Tables II and III.

Thermal Decomposition of Nitrosobenzene. A solid mixture containing 2.848 g (26.6 mmol) of nitrosobenzene and 1.263 g (9.9 mmol) of napthalene was sealed under vacuum in a glass tube at −78°. The tube was heated at 73° for 45 min and the contents dissolved in benzene. VPC analysis of the solution on 10 ft × 0.25 in. SE-30 and QF-1 columns showed six products, accounting for 99.3% of the decomposed nitrosobenzene. By coinjection with known compounds on the two columns and ir analysis of the collected compounds from a 10 ft × 0.375 in. 20% SE-30 column, the products were identified as azoxybenzene (78.6%), nitrobenzene (14.1%), azobenzene (2.7%), aniline (0.5%), and two unknown compounds (3.4%, based on assumed molecular weights from VPC retention values).

Reaction of Nitrosyl Chloride with Nitrosobenzene. To a pressure bottle containing 100 ml of a saturated ether solution of NOCl (24 mmol) was added 1.772 g (16.6 mmol) of nitrosobenzene and 1.136 g (8.9 mmol) of naphthalene. The bottle was capped and shaken for 1.5 hr, by which time a large amount of white crystals had precipitated. The crystals were highly reactive in air, forming quickly a dark red liquid and producing small explosions upon gentle heating. The reaction mixture was cooled to 0° and saturated again with NOCl gas. The brown slurry was shaken for an additional 1 hr and added to ice water, and the highly acidic aqueous phase was adjusted to pH 8 with NaOH. VPC analysis of the dried ether layer showed small amounts of nitrobenzene, benzene, phenol, and biphenyl. A quantitative analysis of the product mixture was not performed owing to the large amount of tarry material formed. Previous work had shown that 0.06–0.12 *M* solutions of nitrosobenzene were unaffected by NOCl at both −78 and 0°.

Reaction of Nitrosyl Chloride with Diphenylamine. Diphenylamine (1.69 g, 10.0 mmol) was dissolved in 100 ml of dry ether at room temperature and the solution was saturated with NOCl gas (ca. 24 mmol). After 15 min the reaction mixture was poured into 50 ml of a pH 10 buffered hydrolyzing solution. After evaporation of solvent, the dried ethereal layer yielded 2.08 g of an oily yellow solid which upon recrystallization from ether–pentane gave 0.73 g (3.0 mmol, 30%) of 4-nitro-*N*-nitrosodiphenylamine: mp 111° dec from ether–pentane (lit.[15] mp 132–133°); ir (KBr) identical with known spectrum;[35] NMR ($CDCl_3$) δ 8.27 (m, 2), 7.53 (m, 4), 7.03 (m, 3).

Anal. Calcd for $C_{12}H_9N_3O_3$: C, 59.26; H, 3.73; N, 17.28; O, 19.74. Found: C, 59.14; H, 3.64; N, 17.03; O, 20.19.

The product, 4-nitro-*N*-nitrosodiphenylamine, exhibited the same color change with KOH as did 2,2′-dinitro-4,4′-dichlorodiphenylamine. The change back from purple was affected by CO_2 or O_3 but not O_2.

Reaction of Nitrosyl Chloride with Ether. After saturating 100 ml of dry Et_2O with NOCl at room temperature the solution was allowed to stand for 1 hr and the volatiles removed. Only a small amount (ca. 1%) of high molecular weight material remained.

Registry No.—Nitrosyl chloride, 2696-92-6; phenyl bromide, 108-86-1; diphenylamine, 122-39-4; 2,2′-dinitro-4,4′-dichlorodiphenylamine, 56553-63-0; nitrosobenzene, 586-96-9; 4-nitro-*N*-nitrosodiphenylamine, 3665-70-1; Et_2O, 60-29-7.

References and Notes

(1) (a) This research was supported by the National Science Foundation, Grant GP-18317, Water Resources Research Center Grant 983, and the University of Montana Foundation, Grants 941-0/0 and 840-9/K. A preliminary report of this work has been published: P. G. Marsh and W. L. Waters, *Proc. Mont. Acad. Sci.*, **31**, 141 (1971), and parts have been presented at the 26th Annual NWRACS Meeting, Bozeman, Mont., June 1971, and the 27th Annual NWRACS Meeting, Corvallis, Oreg., June 1972. (b) In partial fulfillment of the requirements for the Ph.D. degree, University of Montana. Department of Chemistry, University of Calgary, Calgary, Alberta, Canada.

(2) B. Oddo, *Gazz. Chim. Ital.*, **39**, 659 (1909).

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(4) H. Gilman and R. McCracken, *J. Am. Chem. Soc.*, **49**, 1052 (1927).

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(6) See Experimental Section. Our results parallel nicely the work done by Bamberger on the thermal and photochemical decomposition of nitrosobenzene: E. Bamberger, *Ber.*, **35**, 1606 (1902).

(7) In this connection Oddo did not mention the green distillate of steam distilled nitrosobenzene. The reported melting point and carbon–hydrogen data combined are unique for nitrosobenzene, however; the first matches biphenyl and *N*-nitrodiphenylamine and the second fits 2- or 4-nitrodiphenylamine and is approximate for *N*-nitrosodiphenylamine.

(8) The actual identity of NOCl in Oddo's paper is unclear, and a real possibility exists that the gaseous reagent used was something other than NOCl. Also, neither Oddo nor we ourselves assigned any limiting percent values for transition metal impurities in the magnesium used for Grignard preparation. Hence the product discrepancies might be the result of small differences in metal purity.

(9) W. L. Waters and P. G. Marsh, unpublished results. The fact that Gri-

gnard reagents are monomeric in THF may also be important.
(10) See, for example, H. Hock, H. Kropf, and F. Ernst, *Angew. Chem.*, 541 (1951); K. C. Bass, M. J. Cape, and D. Collings, *Chem Ind. (London)*, 326 (1969), and references cited therein.
(11) H. Gilman and A. Wood, *J. Am. Chem. Soc.*, **48**, 806 (1926).
(12) B. T. Baliga, *J. Org. Chem.*, **35**, 2031 (1970), and references cited therein.
(13) O. Fischer and E. Hepp, *Ber.*, **19**, 2291 (1886).
(14) Air Products and Chemicals, Inc., "Nitrosyl Chloride, an Annotated Bibliography", 1970.
(15) H. Ryan and P. Ryan, *Proc. R. Ir. Acad.*, **34**, 212 (1919). Chlorination most probably occurred during hydrolysis, when, upon removal of NO, HNO_3 and HCl (eq 3) give rise to Cl_2, H_2O, and more NOCl.[13]
(16) K. Maruyama, *Bull. Chem. Soc. Jpn.*, **37**, 1013 (1964).
(17) H. Gilman and L. Heck, *Recl. Trav. Chim. Pays-Bas*, **50**, 522 (1931). Gilman found that just the presence of magnesium and magnesium halide would catalyze the decomposition of the hydroxylamine to diphenylamine and other unidentified products.
(18) Actually Gilman (ref 4) did not allow for the formation of *any* phenol during the reaction, and proposed that the small amount found was in the stock solution of Grignard reagent. The use of VPC techniques in the present study has verified a small yield of this product.
(19) It should be pointed out that while our reaction temperature was fairly similar to Wieland's (−78 vs. −15°), Gilman worked at room temperature. The formation of biphenyl and thus a different mechanism for diphenylamine formation may be real at higher temperatures. Gilman (ref 4) denied that such a temperature effect exists.
(20) See, for example, K. Maruyama, *Bull. Chem. Soc. Jpn.*, **37**, 897 (1964).
(21) The formation of a parent hydrocarbon from Grignard reagent plus nitrosobenzene has been noted before: H. Gilman and R. E. Fothergill, *J. Am. Chem. Soc.*, **49**, 2815 (1927). The authors reported 1.09 "active hydrogens" present in nitrosobenzene as a result of the amount of ethane liberated from the mixing of nitrosobenzene and ethylmagnesium bromide.
(22) Gilman assumed that 2 mol of Grignard reagent was necessary to convert the magnesium salt to diphenylamine, since only after the third molar equivalent of phenylmagnesium bromide was added to the hydroxylamine did a positive test for active Grignard result.
(23) Gilman indicated an instant reaction during the addition of the first equivalent of Grignard reagent.
(24) Maruyama also showed that the initial product of the reaction was diphenyl nitric oxide and *not* the magnesium salt.
(25) (a) H. Wieland and M. Offenbacher, *Ber.* **47**, 2111 (1914); (b) H. Wieland and K. Roth, *ibid.*, **53**, 210 (1920).
(26) Equation 6 predicts decreasing diphenylamine yields as the Grignard–NOCl ratio is raised over 2:1 (Table I). However, the alternate product, diphenylhydroxylamine, was not isolated or even detected by VPC, perhaps owing to its instability (ref 3 and 4). All attempts at preparing the pure intermediate failed.
(27) Hydrogen exchange during work-up cannot be completely ruled out. Although diphenylamine, D_1, did not exchange when kept neat at room temperature for 2 days (see Experimental Section), the obviously acidic nature of these work-up conditions could possibly cause an exchange process.
(28) J. March, "Advanced Organic Chemistry: Reactions, Mechanisms, and Structure", McGraw-Hill, New York, N.Y., 1968 p 688. The reaction might also be the result of direct substitution of the phenyl moiety for chlorine as recently suggested in the study of the NOCl–arylthallium system. See E. C. Taylor and R. H. Danforth, *J. Org. Chem.*, **38**, 2088 (1973).
(29) "Sadtler Standard Spectra", Sadtler Research Laboratories, Philadelphia, Pa.
(30) Of all the possible nitroso- and nitro-substituted diphenylamines (see ref 34), only 2,2′-dinitrodiphenylamine exhibits an ir spectrum similar to that of the dichloro derivative.
(31) In absolute EtOH, λ_{max} 428 nm. This agrees closely with the value for 2,2′-dinitrodiphenylamine. See W. A. Schroeder, E. W. Malmberg, L. L. Fond, K. N. Trueblood, J. D. Landerl, and E. Hoerger, *Ind. Eng. Chem.*, **41**, 2818 (1949).
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(33) D. Hadzi and M. Skrbljak, *J. Chem. Soc.*, 843 (1957).
(34) H. Levitsky, G. Norvitz, and D. E. Chasan, *Appl. Spectrosc.*, **22**, 493 (1968).
(35) Spectrum No. 7, Document 10027, ADI Auxiliary Publications Project, Photoduplication Service, Library of Congress, Washington, D.C.

Synthesis of Symmetrical Diarylamines[1a]

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A relatively simple preparation of di-*o*-, *m*-, and *p*-tolylamines and di-*p*-anisylamine is described. The procedure involves the reaction of the corresponding aryl Grignard reagent with nitrosyl chloride. Although yields are not high by this method (≤28%), the secondary amines are uncontaminated by isomeric impurities and easy to isolate. The attempted synthesis of dimesitylamine failed, producing mainly nitrosomesitylene.

Several routes to symmetrically substituted diarylamines exist in the literature. Various procedures include acid, alumina, or acid–alumina catalyzed condensations of aniline derivatives at 300–500°,[2] condensation of 1,1-diarylhydrazines with dichlorocarbene,[3] and iodine-catalyzed condensation of aniline derivatives at normal reflux temperatures.[4] Of all the synthetic methods, the latter appears to be the simplest and one of the best suited for small-scale laboratory preparation.

As an alternate to the above procedures, we decided to extend[5] our investigation of the phenyl Grignard–nitrosyl chloride reaction,[1a] since the major product of the reaction proved to be diphenylamine (eq 1).

$$\mathrm{PhMgBr} + \mathrm{NOCl} \xrightarrow[\mathrm{Et_2O}]{-78^\circ} \mathrm{Ph_2NH} \quad 31\% \qquad (1)$$

Thus, the ethereal Grignard reagents from *o*-, *m*-, and *p*-bromotoluene, *p*-bromoanisole, bromomesitylene, and 1- and 2-bromonaphthalene were allowed to react with nitrosyl chloride at −78°. After hydrolysis and steam distillation the respective amine product was isolated either as the HBr salt or as the free amine. Product identification was made by spectral analysis as well as by melting point correlation with literature values.

Results

Table I outlines the volatile products isolated from NOCl addition to various aryl Grignard reagents.

As noted in the above table, *o*- and *p*-bromotoluene yielded only the respective diarylamine product. In the case of the para isomer steam distillation gave a solid amine product and isolation was simple. Steam distillation of the o-bromotoluene product, however, gave an oil which necessitated conversion to the HBr salt. This done, later reconversion to the free amine with NaOH gave the amine in high purity.

Diarylamine products were also formed from *m*-bromotoluene and *p*-bromoanisole, but their production was accompanied by significant yields of the corresponding nitroso derivatives. In addition, the *p*-anisyl Grignard reagent gave the parent ether, anisole, as well as a 5% yield of methyl-cleaved *p*-nitrosophenol.

The mesityl and naphthyl Grignard reagents failed to give any diarylamine product. The first produced a relatively large amount of nitrosomesitylene and a secondary product which we have tentatively identified as trimesitylhydrazine. The second, both the α and the β isomers, gave mostly intractable tars in addition to ca. 20% yields (or recoveries) of the parent hydrocarbon, naphthalene.

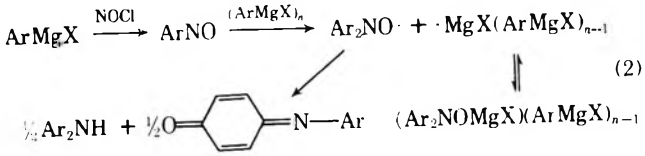
Table I

Aryl halide	Diarylamine yield, %[a,b]	Other products	Yield, %[a]
o-Bromotoluene	23.8[c]		
m-Bromotoluene	11.6[c]	*m*-Nitrosotoluene	1.4
p-Bromotoluene	28.4		
p-Bromoanisole	16.7	Anisole	18.0
		p-Nitrosoanisole	10.4
		p-Nitrosophenol	5.0
Bromomesitylene	0.0	Nitrosomesitylene	22.8
		Trimesitylhydrazine	11.7
α- and β-Bromonaphthalene	0.0	Naphthalene	21.0

[a] Yields are based on aryl Grignard Reagent. [b] A 2:1 Grignard–NOCl stoichiometry is assumed; see ref 1a. [c] Calculations are based on isolated HBr salt.

Discussion

The mechanism of the phenylmagnesium bromide–nitrosyl chloride reaction has already been discussed.[1a] From the results described above this mechanism would seemingly hold for the substituted phenyl Grignards as well. Thus the nitroso and nitric oxide intermediates[1a] are involved in the present reactions (eq 2).



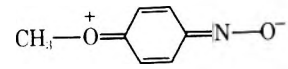
(2)

Although the hydroxylamine was never isolated by us and only once by Gilman,[1a,6] its presence was certainly proven by Wieland[7] and Maruyama.[8] Its conversion to diarylamine does not require excess NOCl or Grignard reagent and apparently occurs via its dissociated radical form.[1a]

Diarylamine Formation. While the three bromotoluenes and *p*-bromoanisole gave significant yields of diarylamine, the corresponding mesityl compound gave none of the product. One would assume that this result reflects the steric requirements of the second step in eq 2.[9] In support of this argument it is noted that in the mesityl case the yield of nitroso product was correspondingly high. The fact that no diarylamine was formed from the naphthyl Grignard reagents was probably due to the peculiar physical nature of these reagents in diethyl ether as mentioned earlier. Modification of the reaction conditions, e.g., solvent, etc., would perhaps allow formation of diarylamine.

Nitrosoarene Formation. The two cases in which no nitroso products were isolated (excluding α- and β-naphthalene) are the two instances of highest amine production (Table I). It would appear, therefore, that the second step in eq 2 is relatively fast compared to the first for compounds like the o- and *p*-tolyl Grignards. Although a more detailed kinetic argument could be advanced here to explain the results with the tolyl Grignards—especially the ortho and para isomers vs. the meta isomer—it would be risky to do so based on yield data alone, especially when 75% of the starting material was not accounted for.

The apparent stability of nitrosomesitylene and *p*-nitrosoanisole certainly deserves some mention. As noted above, the first probably owes its unreactivity toward more Grignard reagent to an ortho steric effect. The second, however, must be purely electronic in nature, and could perhaps be related to a resonance structure such as 1. Contribution of 1 would make *p*-nitrosoanisole less likely to undergo addition across the N–O bond for ground state reasons. The effect of such a resonance contribution to the transition state of the second step in eq 2 is, of course, speculative since the exact nature of that step has not yet been determined. However, no obvious destabilization is apparent.



1

Reaction By-products. In addition to the amine and nitroso products the reaction of *p*-anisylmagnesium bromide with NOCl gave substantial amounts of anisole and *p*-nitrosophenol. Although it was first suspected that anisole was the result of unreacted Grignard reagent, a Gilman test shortly before hydrolysis showed the absence of any organomagnesium compound. Also, previous work with phenylmagnesium bromide and nitrosobenzene[1a] showed that the production of benzene began only after the yield of diarylamine had already peaked, and was therefore not connected with the conversion to the amine. Clearly, then, the formation of anisole must be a competing reaction which the Grignard reagent can undergo after the concentration of NOCl has been sufficiently lowered. The exact mechanism of its formation, i.e., the source of the acidic hydrogen, has not yet been discovered.

The by-product *p*-nitrosophenol is probably the result of the well-known alkyl cleavage reaction of aryl alkyl ethers by Grignard reagents.[10] *p*-Nitrosoanisole should be especially susceptible to this type of cleavage owing to participation of resonance structure 1.

Finally, the formation of trimesitylhydrazine from mesitylmagnesium bromide and NOCl rates some attention. Based on Bamberger's hypothesis that nitrosobenzene slowly disproportionates to nitrobenzene and phenylhydroxylamine,[11] and Busch and Hobein's observation that the reaction of phenylhydroxylamine and phenylmagnesium bromide gives triphenylhydrazine as the major isolated product,[12] it is supposed that a similar path occurs for nitrosomesitylene. The fact that such hydrazine-type products were not isolated in the other reactions may be explained by their facile oxidation to a radical species and subsequent dimerization.[13]

Conclusion

The reaction of aryl Grignard reagents with nitrosyl chloride is definitely a convenient laboratory method for the preparation of symmetrical diarylamines. Although yields are not high by this method, the secondary amines are uncontaminated by isomeric impurities and easy to isolate. Future investigations will include the formation of unsymmetrical diarylamines via the preformed nitroso compound and various phenyl-substituted Grignard reagents.

Experimental Section

Melting points were taken on a Mel-Temp melting point apparatus and are uncorrected. All gas chromatography work was done on a Varian 1700 gas chromatograph. Infrared, nuclear magnetic resonance, electron spin resonance, and mass spectral data were recorded on the Beckman IR-33, Varian HA-60, Varian E-3, and Varian MAT-111 instruments, respectively. Elemental analyses were performed by Meade Microanalytical Laboratory, Amherst, Mass., and Galbraith Laboratories, Inc., Knoxville, Tenn.

Reaction of NOCl with Aryl Grignard Reagents. General Procedure. In a typical reaction 100 mmol of aryl bromide was treated under a nitrogen atmosphere with 100 mmol of 1,2-dibromoethane and 600 mmol of magnesium in a total of 500 ml of dry diethyl ether. After addition of the bromide, the mixture was heated under reflux for 2 hr. A measured aliquot was then removed and hydrolyzed, and the dried ether solution was analyzed by VPC in the presence of tetralin (VPC internal standard). By comparing

the amount of benzene in the solution with that in a flash-distilled aliquot of Grignard solution, it was determined that 95–97% conversions of aryl bromide to arylmagnesium bromide usually occurred.

The unfiltered Grignard solution was next cooled to −78° under a nitrogen atmosphere. To this, 45 mmol of NOCl in 150 ml of dry ether was added in a dropwise fashion over several hours. The solution was stirred for an additional 2 hr and then hydrolyzed with a minimum of pH 10 buffer solution ($NaOH-Na_2CO_3$). The orange ethereal phase was separated, the solid was washed three times with 25-ml portions of ether, and the combined solutions were steam distilled. Concentration of an ether extract of the 5-l. distillate usually afforded the crystalline amine. In cases where the amine had a low melting point, HBr was bubbled through the ether extract and the precipitated salt collected. Regeneration of the amine with hot NaOH solution and subsequent recrystallization from ligroin gave solid amine.

p-Tolylmagnesium bromide (83.8 mmol) was allowed to react with 45 mmol of NOCl at −78° as described above. An ether extract of the steam distillate yielded 2.34 g (11.9 mmol, 28.4%) of di-*p*-tolylamine: mp 77–78° (lit.[4] mp 79°); ir (melt) 3400, 3030, 2920, 1800, 1510, 1520, 1100, and 800 cm^{-1}; NMR δ ($CDCl_3$) 2.28 (s, 6), 5.4 (s, broad, 1), 6.89 (d, J = 9.0 Hz, 4), and 7.09 (d, J = 9.0 Hz, 4).

o-Tolylmagnesium bromide (93.5 mmol) and 45 mmol of NOCl yielded only an oil upon evaporation of the ether extract. HBr treatment gave 3.10 g (111 mmol, 23.8%) of di-o-tolylamine hydrobromide: mp 197–202°; ir (KBr) 2860–2440, 1480, 760, and 740 cm^{-1}. Di-o-tolylamine, mp 48.5–9.5° (lit.[14] mp 52–53°), was regenerated from the amine salt with hot NaOH and subsequent crystallization from ligroin. Spectra were as follows: ir (melt) 3430, 3020, 1480, 1290, 1140, 740, and 710 cm^{-1}; NMR δ ($CDCl_3$) 2.09 (s, 6), 5.0 (s, broad, 1), 6.9 (s, 8).

m-Tolylmagnesium bromide (89.2 mmol) and 45 mmol of NOCl yielded 1.3 g of a green oil as the first portion of the steam distillate. Upon standing at 0° the oil precipitated 150 mg (1.2 mmol, 1.4%) of *m*-nitrosotoluene: mp 48–50°, white crystals to green melt (lit.[15] mp 53.5°); ir (melt) 3040, 2900, 1400, 1380, 780, and 680 cm^{-1}.

Continuation of the steam distillation gave 3.1 g of an orange-red oil which upon HBr treatment yielded 1.45 g (5.10 mmol, 11.6%) of di-*m*-tolylamine hydrobromide: mp 192–196°; ir (KBr) 2860–2420, 1560, and 725 cm^{-1}. Conversion to the free amine with NaOH gave di-*m*-tolylamine: oil (lit.[15] mp <−12°); ir (neat) 3370, 3015, 2900, 1590, 1570, 1470, 1300, 760, and 680 cm^{-1}.

The steam distillation pot residue was extracted with ether, yielding 4.2 g of brownish-black oil. No attempt was made to identify this material.

p-Anisylmagnesium bromide (79.2 mmol) and 45 mmol of NOCl were allowed to react in the usual manner, but stirred for an additional 3 days. The first 125-ml portion of steam distillate yielded 2.66 g of a green oil which was shown to be 58% anisole and 42% *p*-nitrosoanisole by weight (GC, 10 ft × 0.125 in. 10% FFAP, tetralin standard). Thus the oil contained 1.54 g (14.2 mmol, 18.0%) of anisole (GC coinjection with known anisole, ir and NMR comparison with known anisole) and 1.12 g (8.21 mmol, 10.4%) of *p*-nitrosoanisole: ir (neat) 1410, 1265, 1110, and 835 cm^{-1}; NMR δ ($CDCl_3$) 3.70 (s, 3), 6.80 (d, J = 9.1 Hz, 2), and 7.75 (d, J = 9.1 Hz, 2).

The second 750 ml of the steam distillate yielded 490 mg (3.98 mmol, 5.0%) of *p*-nitrosophenol: mp 130° dec from Et_2O–hexane (lit.[16] mp 132–134° dec); ir identical with Sadtler[17] Spectrum No. 23689; NMR δ ($DCDl_3$) 6.60 (d, J = 10.0 Hz, 2) and 7.64 (d, J = 10.0 Hz, 2); MS M^+ m/e 123. Anal. Calcd for $C_6H_5NO_2$: C, 58.53; H, 4.10; N, 11.38. Found: C, 58.24; H, 3.71; N, 11.20.

The final 15-l. portion of the steam distillate and the pot residue yielded a total of 1.51 g (6.59 mmol, 16.7%) of di-*p*-anisylamine: mp 93–96° from hexane (lit.[18] mp 96.8°); ir identical with Coblentz[19] Spectrum No. 2521; NMR δ ($CDCl_3$) 2.8 (s, broad, 1), 3.75 (s, 6), and 6.9 (m, 8); MS M^+ m/e 229, base 214.

Mesitylmagnesium bromide (90.4 mmol) and 45 mmol of NOCl yielded a yellow crystalline precipitate upon hydrolysis of the reaction mixture. Extraction of these crystals with excess Et_2O gave 3.07 g (20.6 mmol, 22.8%) of nitrosomesitylene: mp 117–117.5° white crystals to green melt, from EtOH (lit.[20] mp 122–123°); ir agreement with literature;[21] NMR δ (CS_2) 2.38 (s, 3), 2.43 (s, 3), 2.67 (s, 3), 6.99 (m, 2); MS M^+ m/e 140, 134, 119, and 104.

The ethereal mother liquors from the above isolation yielded 4.7 g of tarry material, from which 1.38 g of ether insoluble brown powder (mp 235° dec from CCl_4–hexane) was obtained. The material was tentatively identified as trimesitylhydrazine: MS M^+ m/e 386, 385, 267, 252, and 134; NMR δ ($CDCl_3$) 2.02 (s, broad, 6), 2.30 (s, broad, 3), 6.90 (m, 2); ir (KBr) 3400, 2920, 1595, 1480, 1315, and 860 cm^{-1}; ESR unsymmetrical multiplet at ~G = 2.003.

α- or β-naphthylmagnesium bromide (ca. 100 mmol) and 45 mmol of NOCl did not yield any isolable product besides 2.69 g of naphthalene (21.0 mmol, 21.0%): mp 65–72° (lit.[14] mp 80.5°); ir identical with Sadtler[17] Spectrum No. 865. Excessive high molecular weight tars were formed by the reaction, probably owing to the extreme heterogeneous nature of the naphthyl Grignard reagents at even room temperature.

Registry No.—NOCl, 2696-92-6; *p*-tolyl bromide, 106-38-7; di-*p*-tolylamine, 620-93-9; *o*-tolyl bromide, 95-46-5; di-*o*-tolylamine HBr, 56553-64-1; di-*o*-tolylamine, 617-00-5; *m*-tolyl bromide, 591-17-3; *m*-nitrosotoluene, 620-26-8; di-*m*-tolylamine HBr, 56553-65-2; di-*m*-tolylamine, 626-13-1; *p*-anisyl bromide, 104-92-7; *p*-nitroanisole, 100-17-4; *p*-nitrosophenol, 104-91-6; di-*p*-anisylamine, 101-70-2; mesityl bromide, 576-83-0; nitrosomesitylene, 1196-12-9; trimesitylhydrazine, 56553-66-3; α-naphthyl bromide, 90-11-9; β-naphthyl bromide, 580-13-2.

References and Notes

(1) (a) See W. L. Waters and P. G. Marsh, *J. Org. Chem.*, preceding paper in this issue. This work was supported in part by the National Science Foundation, NSF Grant GP-18317, Water Resources Research Center Grant 983, and the University of Montana Foundation, Grants 841-0/0 and 840-9/K. (b) In partial fulfillment of the requirements of the Ph.D. degree, University of Montana. Department of Chemistry, University of Calgary, Calgary, Alberta, Canada.

(2) See for example, A. Rieche and R. Moeller, *J. Prakt. Chem.*, **15**, 24 (1961); S. Ogasawara, K. Hamaya, and Y. Kitajima, *J. Catal.*, **25**, 105 (1972).

(3) N. Koga and J. F. Anselme, *Tetrahedron*, **26**, 1909 (1970).

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(5) A preliminary report of this work has been made: P. G. Marsh and W. L. Waters, "A Simple Approach to Secondary Diarylamines", 29th Annual Northwest Regional Meeting of the American Chemical Society, Pullman, Wash., June 1973.

(6) H. Gilman and R. McCraken, *J. Am. Chem Soc.*, **49**, 1052 (1927).

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(10) See, for example, R. L. Burwell, *Chem. Rev.*, **54**, 615 (1954).

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(17) "Sadtler Standard Spectra", Sadtler Research Laboratories, Philadelphia, Pa.

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(19) "Coblentz Society Spectra", cross-referenced by Sadtler Research Laboratories, Philadelphia, Pa. The authors are grateful to F. R. Jensen, University of California, Berkeley, for a copy of this spectrum.

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C-Glycosyl Nucleosides. VIII.[1] Synthesis of 3-Methylshowdomycin

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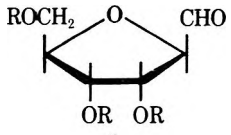
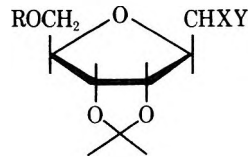
The preparation of 1-carbamoylethylidenedimethylphenylphosphorane (10) has been achieved by treatment of the corresponding phosphonium salt with either 1,5-diazabicyclo[4.3.0]non-5-ene or sodium hydride. The reaction of this ylide with methyl phenylglyoxylate leads to modest yields of 3-methyl-2-phenylmaleimide and methyl 3-methyl-2-phenylfumaramate. The reaction of 10 with methyl 3,6-anhydro-4,5,7-tri-*O*-benzyl-D-*allo*-heptulosonate gives a 30% yield of crystalline 3-methyl-2-(2,3,5-tri-*O*-benzyl-β-D-ribofuranosyl)maleimide, which can be debenzylated with boron trichloride giving 3-methylshowdomycin. The condensation of triphenylphosphine with *N*-bromoacetylurea readily gives a phosphonium salt that can be converted to crystalline *N*-carbamoylcarbamoylmethylenetriphenylphosphorane (20). The condensation of 20 with methyl pyruvate gives methyl *N*-carbamoyl-2-methylfumaramate, while reaction with methyl phenylglyoxylate gives methyl *N*-carbamoyl-2-phenylfumaramate and 2-phenylmaleimide, the latter via thermal decarbamoylation.

In previous papers in this series we have outlined our general interest in the synthesis of *C*-glycosyl nucleosides. Much of this work has centered about the elaboration of *C*-β-D-ribofuranosyl heterocycles using derivatives of 2,5-anhydro-D-allose (1)[3] as starting materials. So far we have described routes for the preparation of maleimide,[4] pyrazole,[5,1] isoxazole,[6] and oxadiazole[1] *C*-glycosides using these generally useful starting materials. In addition, we have developed routes for the stereochemically controlled synthesis of other functionalized *C*-glycosides of general structure 2[7] (X, Y = H, CO_2Me, CN) which open pathways to yet further heterocyclic systems.

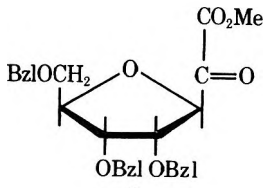


1



2

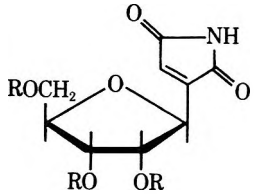
Included in the above work was a facile synthesis of the nucleoside antibiotic showdomycin (5b) via the reaction of methyl 3,6-anhydro-4,5,7-tri-*O*-benzyl-D-*allo*-heptulosonate (3) with carbamoylmethylenetriphenylphosphorane (4) followed by debenzylation of the resulting maleimide (5a).[4]



3

$Ph_3P{=}CHCONH_2$

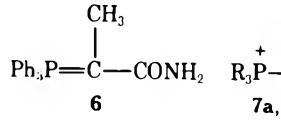
4



5a, R = Bzl
b, R = H

This synthetic route seems capable of extension to the preparation of showdomycin analogs bearing substituents at C_3 of the maleimide ring via the corresponding reactions of 3 with carbon-substituted derivatives of the phosphorane 4. In this paper we describe the synthesis of 3-methyl-2-β-D-ribofuranosylmaleimide (3-methylshowdomycin, 15a) via such a route.

The simplest appropriate phosphorane would be 1-carbamoylethylidenetriphenylphosphorane (6), but, as yet, the synthesis of this compound or its related phosphonium salt (7a) has eluded us. Thus, all our attempts to react 2-chloropropionamide[8] with triphenylphosphine in diverse solvents, or in the absence of solvent, at 100–150°, failed to yield the desired phosphonium salt. The comparable reaction using chloroacetamide, however, readily provides the phosphonium precursor of 4.[9] On the other hand, the more reactive 2-bromopropionamide[10] reacted readily with triphenylphosphine in acetonitrile under nitrogen at 40–50°, giving triphenylphosphine oxide and hydrogen bromide. This reaction presumably proceeds by way of the enolphosphonium salt 8 in a way similar to that shown for more highly halogenated amides,[11] and reminiscent of the Perkow reaction.[12]



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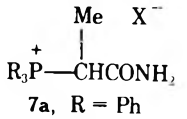
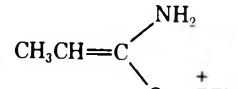
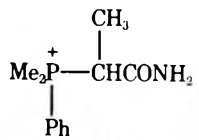


7a, R = Ph
b, R = Bu

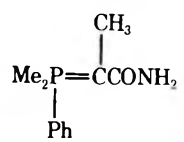


8

The above reaction could, however, be successfully accomplished using more highly nucleophilic phosphines. Thus 2-bromopropionamide reacted readily with tributylphosphine and with dimethylphenylphosphine in acetonitrile at 50–60° to form the corresponding crystalline phosphonium salts (7b and 9) in yields of 44 and 81%, respectively. In view of the higher yield achieved in the preparation of 9, the rest of our work has been done using that compound. The conversion of 9 to the ylide 1-carbamoylethylidenedimethylphenylphosphorane (10) has been in-



9



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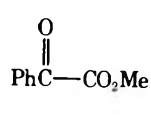

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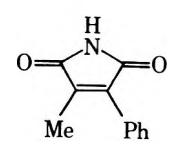

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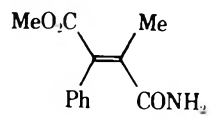


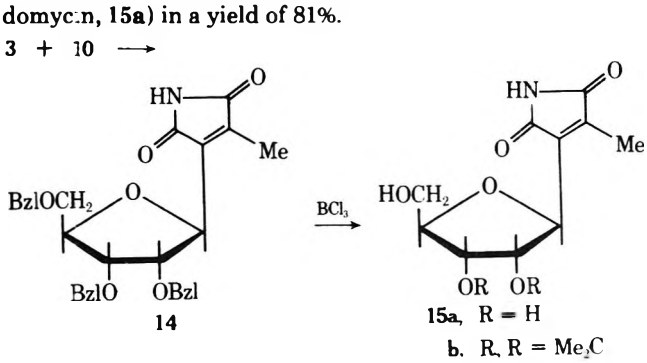
13

vestigated under a number of conditions. As expected, 10 was much less stable than 4 and its attempted preparation by treating 9 with aqueous sodium hydroxide led only to dimethylphenylphosphine oxide.[13] The ylide could, how-

ever, be generated by treatment of **9** with 1,5-diazabicyclo-[4.3.0]non-5-ene (DBN) in a mixture of chloroform and dimethyl sulfoxide. Its formation was confirmed by its reaction at 65° with methyl phenylglyoxylate (**11**), which led to the isolation of crystalline 3-methyl-2-phenylmaleimide (**12**) and methyl 3-methyl-2-phenylfumaramate (**13**) in yields of 17 and 18%, respectively. The structures of these products were clear from their elemental analyses and NMR spectra. Variations in the reaction temperature and solvent did not improve the above yields. The formation of roughly equal amounts of **12** and **13** is quite consistent with what was observed earlier from the reaction of **4** and **10** and indicates little steric preference in the initial formation of **13** and its *Z* isomer.

Attempted direct extension of the above model to the desired reaction of **10** with the *C*-glycosyl keto ester **3** led to only traces of product with a TLC mobility close to that of **5a.** Because of this and the rather low yields of **12** and **13** obtained following generation of the ylide with DBN, we considered other methods for the conversion of **9** to **10** but were unsuccessful using sodamide or butyllithium in ether.[14] Treatment of **9** with slightly less than 1 equiv of sodium hydride in dimethyl sulfoxide at room temperature, however, led to the quite rapid formation of the ylide **10** as a yellow solution. Separately the keto ester **3** was prepared, as previously described,[4] by oxidation of an epimeric mixture of the corresponding hydroxy esters with dimethyl sulfoxide and dicyclohexylcarbodiimide in the presence of dichloroacetic acid.[15] In view of the lability of **3**, this compound was added, without any purification, to the ylide solution above and allowed to react at room temperature. By TLC it could be shown that a fairly rapid reaction ensued with formation of dimethylphenylphosphine oxide and a nucleoside with the expected mobility just greater than that of **5a.** By chromatography of the products on a column of silicic acid crystalline 3-methyl-2-(2,3,5-tri-*O*-benzyl-β-D-ribofuranosyl)maleimide (**14**) was isolated in an overall yield of 30% from the mixed hydroxy esters. Debenzylation of **14** was readily achieved upon treatment with boron trichloride in methylene chloride at −78° for 2 hr. Following destruction of the excess boron trichloride with methanol and removal of the volatile methyl borate a crystalline residue was obtained. Direct recrystallization then gave pure 3-methyl-2-β-D-ribofuranosylmaleimide (3-methylshowdomycin, **15a**) in a yield of 81%.

3 + 10 ⟶



14 **15a**, R = H; **b**, R, R = Me_2C

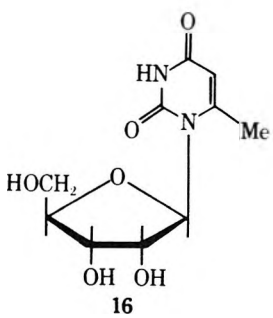
The ^1H NMR spectra of **15a** and of showdomycin (**5b**) are generally similar although $C_{2'}H$ and $C_{3'}H$ are deshielded by 0.17 and 0.16 ppm in **15a.** The most significant feature of the spectrum of **15a** is, of course, the absence of a vinyl proton at C_3 of the maleimide ring and the presence of a three-proton singlet at 1.99 ppm. The absence of C_3H also leads to the appearance of $C_{1'}H$ as a doublet while that in showdomycin is a doublet of doublets due to allylic coupling. The mass spectrum of **15a** was quite typical of other *C*-glycosides[16] and showed major fragments corresponding to loss of water from the molecular ion, and cleavage of the sugar ring giving a B + 30 ion. To our surprise **15a** showed a negative rotation ($[\alpha]_D$ −39.5°) and a negative optical rotatory dispersion spectrum centered about 286 nm, while showdomycin is dextrorotatory[17] and shows a positive Cotton effect ($[\Phi]^{pk}_{309}$ 1000°, $[\Phi]_{288}$ 0°, $[\Phi]^{tr}_{254}$ −7,600°). We have previously shown[4] that no epimerization accompanies the preparation of **3** under the oxidative conditions used for its synthesis. Also, since only 0.87 molar equiv of sodium hydride was used relative to the crystalline phosphonium salt (**9**) during preparation of **10,** basic conditions which could lead to epimerization giving an α-nucleoside were avoided. While the rather large value of $J_{1',2'}$ (6.8 Hz) does not allow an assignment of anomeric configuration, the observed chemical shift of $C_{1'}H$ strongly suggests that **15a** has the desired β configuration. Thus, it is well known that in *N*-glycosides $C_{1'}H$ occurs roughly 0.5 ppm upfield in β-D-ribofuranosyl nucleosides relative to their α anomers.[18] The same is generally true for the known anomeric pairs of *C*-glycosyl nucleosides, $C_{1'}H$ in β-pseudouridine[19] and β-pyrazomycin[20] appearing 0.2–0.3 ppm upfield of the same proton in the α anomers. Since in Me_2SO-d_6–D_2O $C_{1'}H$ of **15a** appears at 4.60 ppm, which is very close to that of showdomycin itself (4.53 ppm), it is quite unlikely that we are dealing with an α anomer. A very similar argument was used earlier in assigning the β configuration to showdomycin.[19a]

In an effort to provide unequivocal assignment of anomeric configuration, **15a** was converted in 96% yield into its 2′,3′-*O*-isopropylidene derivative (**15b**). Unfortunately the ^1H NMR spectra of **15b** in several solvents failed to resolve $C_{1'}H$ from $C_{2'}H$ and $C_{3'}H$ and hence it was not possible to observe a value of $J_{1',2'}$ sufficiently small to permit unequivocal assignment of the β configuration.[18] Several lines of supporting evidence were, however, available from an examination of the ^{13}C NMR spectra of **15b** and of 2′,3′-*O*-isopropylideneshowdomycin[17] prepared by the same route. Previous work has shown that the chemical shift of the anomeric carbon can be used to distinguish between α- and β-furanosides in *O*-glycosides,[21a] *N*-glycosides,[21b] and a few *C*-glycosides.[21c] In each case the isomer having the aglycone and the $C_{2'}$-oxygen function in a cis relationship (α-D-ribo) showed $C_{1'}$ at higher field. Recent work from this laboratory[7] has extended this work to a variety of *C*-glycosides with similar results, C_1 of the C_1–C_2 cis isomers appearing 2–4 ppm upfield of those in the trans counterparts. As expected,[22] the presence of the C_3-methyl group in **15b** led to significant α and β shifts of C_2 and C_3 relative to 2′,3′-*O*-isopropylideneshowdomycin while the other carbons had very similar chemical shifts (see Experimental Section). The cis C_3-methyl would also be expected to lead to a modest (several parts per million) upfield γ shift of $C_{1'}$ in **15b.** Based upon earlier work,[7,21c] if **15b** were to have an α configuration an additional upfield shift of 2–4 ppm would be observed owing to the cis relationship of C_2 and $C_{2'}$-OH. In fact, the chemical shift of $C_{1'}$ in **15b** (78.86 ppm) is only 1.5 ppm upfield of that in 2′,3′-*O*-isopropylideneshowdomycin, a fact which further supports the β configuration. The assignments for individual carbons were confirmed by both off-resonance and single-frequency decoupling techniques.[22]

Still further confirmation comes from consideration of the ^{13}C and ^1H NMR signals of the isopropylidene function in **15b.** Thus the proton chemical shift difference between the isopropylidene methyl signals in **15b** was found to be 24 Hz, a figure that is compatible with a β configuration but far in excess of that for an α nucleoside.[23] Finally, we have recently pointed out that the ^{13}C chemical shifts for the methyl groups in the 2′,3′-*O*-isopropylidene derivatives of a

variety of C-glycosides appear at 25.5 ± 0.2 and 27.5 ± 0.2 ppm while those in the α anomers are at 24.9 ± 0.3 and 26.3 ± 0.2 ppm, respectively.[7] The observed figures for **15b** are 25.49 and 27.83 ppm, while those for 2′,3′-*O*-isopropylideneshowdomycin are 25.43 and 27.60 ppm, both in good agreement with the β configuration. The chemical shifts for the central isopropylidene carbon in a variety of C-glycosides are somewhat more variable but, after exclusion of one anomalous pair (compounds **10e** and **11e** in ref 22), occur at 114.20 ± 1.0 and 112.88 ± 0.5 ppm for the C_1-C_2-trans and C_1-C_2-cis isomers, respectively.[7] Once again, the observed values of 114.53 ppm for **15b** and of 114.92 ppm for 2′,3′-*O*-isopropylideneshowdomycin are compatible only with the β configuration. Taken together, the various NMR parameters of **15a** and **15b** would appear to provide convincing evidence that the β isomer expected from the method of synthesis is indeed present.

We interpret the inverted optical rotatory properties of **15a** as compared to showdomycin as an indication that the presence of the C_3-methyl group leads to an inversion of the normal anti glycosyl conformation. This situation is very similar to that shown by 6-methyluridine (**16**), which is known to have an opposite ORD spectrum to that of uridine or 5-methyluridine.[24] On the basis of NMR studies,[24b]



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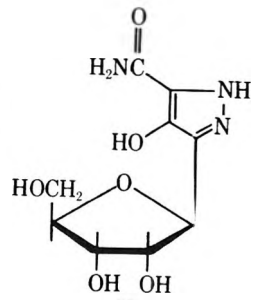

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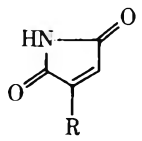
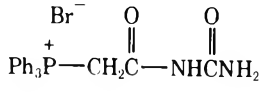


18a, R = Me
b, R = Ph

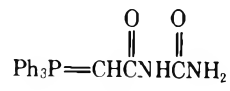
dipole moment measurements,[25] and X-ray crystallography,[26] 6-methyluridine, unlike its 5-methyl counterpart, has been shown to adopt the syn conformation, which is responsible for the optical effects referred to above. A similar syn conformation for 3-methylshowdomycin (**15**) would explain not only the observed optical properties but also the deshielding of C_2′H and C_3′H relative to the same protons in showdomycin, this same effect being noted in 6-methyluridine.[24b] It might also be pointed out that the antibiotic pyrazomycin (**17**), which is known to adopt a syn conformation in the crystal state,[27] also shows a negative Cotton effect in its circular dichroism spectrum.[20] Taken in concert, the above observations make us confident that 3-methylshowdomycin represents a further example of a nucleoside possessing a stable syn conformation.

A recent paper by Titani and Tsuruta[28] has discussed the various biological characteristics of showdomycin relative to those of the model compounds *N*-ethylmaleimide (NEM) and citraconimide **18a**). While marked similarities exist between showdomycin and NEM with respect to radiosensitization and reaction with thiols, citraconimide (**18a**), although a much closer structural analog, was much less active. 3-Methylshowdomycin is something of a structural hybrid of **5b** and **18** and it is interesting to note that, at least with respect to antibacterial activity, **15a** showed a marked reduction in activity with respect to showdomycin itself.[29]

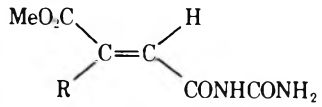
Finally, we have briefly investigated the preparation of *N*-carbamoylcarbamoylmethylenetriphenylphosphorane (**20**), an ylide that appeared to offer a facile route to *N*-carbamoylmaleimides. The reaction of triphenylphosphine with *N*-bromoacetylurea[30] took place readily in acetonitrile at 50°, giving the crystalline phosphonium salt **19** in 75% yield. Treatment of **19** with aqueous sodium hydroxide led to the direct crystallization of the rather stable ylide **20** in almost quantitative yield. A reaction between **20** and methyl phenylglyoxylate (**11**) in chloroform under reflux gave, as its major product, a 35% yield of crystalline methyl *N*-carbamoyl-2-phenylfumaramate (**21a**) together with 15% of 2-phenylmaleimide (**18b**). The assignment of the *E* config-



19



20



21a, R = Ph
b, R = Me

uration to **21a** is based largely upon analogy with the previously described reactions of **11** with **4** and **10**, the product with the *Z* configuration in each case undergoing spontaneous cyclization to a maleimide. In the present case the initially formed *N*-carbamoyl-2-phenylmaleimide appears to have undergone very mild thermal loss of the carbamoyl group giving **18b**, a reaction for which there is ample precedent.[31] A comparable reaction between **20** and methyl pyruvate in chloroform at room temperature led to the formation of only one significant product in addition to triphenylphosphine oxide. Separation of these compounds by chromatography on silicic acid was not complete but crystallization of the pure fractions gave methyl *N*-carbamoyl-2-methylfumaramate (**21b**) in 67% yield. Once again the *E* configuration is assumed because of the previously reported predominant formation of methyl 2-methylfumaramate from **4** and methyl pyruvate. Support for the configurations of both **21a** and **21b** comes from an examination of their NMR spectra.[32] Thus the single vinyl protons in **21a** and **21b** appear at 7.17 and at 6.95 ppm, respectively, in Me_2SO-d_6. These chemical shifts are very close to those that we have found for the related *E* compounds methyl 2-methylfumaramate (6.80 ppm) and methyl 2-phenylfumaramate (7.04 ppm) in $CDCl_3$[4] and that others have shown for dimethyl 2-methylfumarate (6.71 ppm).[33] They are quite different, however, from the chemical shift of the vinyl proton in dimethyl 2-methylmaleate (*Z* configuration, 5.77 ppm).[33] In general, the anisotropic effects of amide and ester functions are quite similar and differences in solvent would not be expected to lead to anything approaching chemical shift differences of 1 ppm. Hence we feel confident that the *E* stereochemistry of **21a,b** is correct and that, as with simple amides, formation of the *Z* amido esters leads to spontaneous cyclization to an N-substituted maleimide. In view of the ready decarbamoylation of *N*-carbamoylmaleimides mentioned above, the reaction of **3** and **20** has not been explored.

By extension of the above work to the preparation of other types of 2-substituted carbamoylmethylene ylides it would appear possible to develop syntheses of various 2,3-

substituted maleimides. In particular, the preparation of other 3-substituted derivatives of showdomycin would be of interest and is being considered.

Experimental Section

General Methods. The general methods used are the same as those described previously.[4]

Tri-*n*-butyl-1-carbamoylethylphosphonium Bromide (7b). A mixture of 2-bromopropionamide (300 mg, 2 mmol)[10] and tributylphosphine (400 mg, 2 mmol) in acetonitrile (5 ml) was stirred under nitrogen at 60° for 6 hr and then at room temperature overnight. The solution was diluted with ethyl acetate (50 ml) and extracted with water (25 ml). The aqueous phase was evaporated to dryness and the residue was coevaporated with toluene, leaving a clear syrup that crystallized upon treatment with ether, giving 310 mg (44%) of **7b**: mp 126–128°; NMR ($CDCl_3$) 1.0 (m, 9, CH_3), 1.57 (dd, 3, $J_{H,H}$ = 8, $J_{P,H}$ = 18 Hz, $PCHCH_3$), 1.5 (m, 12, CH_2's), 2.3 (m, 6, PCH_2), 4.90 ppm (dq, 1, $J_{H,H}$ = 8, $J_{P,H}$ = 12 Hz, PCHCO).

Anal. Calcd for $C_{15}H_{33}BrNOP$ (354.34): C, 50.85; H, 9.39; N, 3.95; Br, 22.55. Found: C, 50.97; H, 9.51; N, 3.81; Br, 22.37.

1-Carbamoylethylidenedimethylphenylphosphonium Bromide (9). Dimethylphenylphosphine (10.35 g, 75 mmol) was added dropwise under nitrogen to a solution of 2-bromopropionamide (11.4 g, 75 mmol) in acetonitrile (150 ml) at 50° and then held at 50° for 3 hr. The mixture was diluted with ethyl acetate and the resulting suspension was extracted with water. Following evaporation of the water the residue was coevaporated with toluene and crystallized twice from acetonitrile–ethyl acetate, giving 18.34 g (81%) of **9**: mp 188.5–190°; NMR (Me_2SO-d_6) 1.35 (dd, 3, $J_{H,H}$ = 7, $J_{P,H}$ = 18 Hz, $PCHCH_3$), 2.32 (dd, 6, J_{PCH} = 14, $J_{H,PCH}$ = 2 Hz, PMe_2), 4.00 (m, 1, PCHCO), 7.55 (br s, 2, $CONH_2$), 7.6–8.1 (m, 5, Ar).

Anal. Calcd for $C_{11}H_{17}BrNOP$ (290.17): C, 45.53; H, 5.91; N, 4.83; Br, 27.54. Found: C, 45.58; H, 5.91; N, 4.58; Br, 27.35.

Generation of Ylide 10 and Reaction with Methyl Phenylglyoxylate (11). A solution of 1,5-diazabicyclo[4.3.0]non-5-ene in chloroform (0.5 ml of 1 *M*, 0.5 mmol) was added to a solution of the phosphonium salt (**9**, 160 mg, 0.55 mmol) in dimethyl sulfoxide (1 ml) and stored under nitrogen for 30 min. The resulting solution was added to a solution of **11** (82 mg, 0.5 mmol) in chloroform and heated at 65° for 20 min. The mixture was cooled, diluted with ethyl acetate, washed three times with water, dried, and evaporated, leaving a syrup. The latter was chromatographed on a 1.5 × 18 cm column of silicic acid using hexane–ether (2:1) which separated dimethylphenylphosphine oxide from two more polar products. The faster, fluorescent product (36 mg) was crystallized from chloroform–hexane giving 16 mg (17%) of 3-methyl-2-phenylmaleimide (**12**): mp 177–178.5°; λ_{max} (MeOH) 223 nm (ϵ 18900), 252 (sh, 7900), 322 (4000); ν_{max} (KBr) 3225 (NH), 1710, 1770 cm^{-1} (imide); NMR ($CDCl_3$) 2.14 (s, 3, CH_3), 7.45 ppm (m, 6, Ar and NH).

Anal. Calcd for $C_{11}H_9NO_2$ (187.20): C, 70.58; H, 4.85; N, 7.48. Found: C, 70.57; H, 4.84; N, 7.35.

The most polar product (31 mg) was crystallized from chloroform–hexane, giving 20 mg (18%) of methyl 3-methyl-2-phenylfumaramate (**13**): mp 155–155.5°; λ_{max} (MeOH) only broad end absorption with a shoulder (ϵ 6700) at 244 nm; ν_{max} (KBr) 3370 (NH), 1725 (CO_2Me), 1635, 1585 cm^{-1} (CONH); NMR ($CDCl_3$) 2.19 (s, 3, CH_3), 3.75 (s, 3, CO_2Me), 5.0 and 5.3 (br s, 1, NH_2), 7.33 ppm (s, 5, Ar).

Anal. Calcd for $C_{12}H_{13}NO_3$ (219.24): C, 65.74; H, 5.98; N, 6.39. Found C, 65.96; H, 6.06; N, 6.30.

3-Methyl-2-(2,3,5-tri-*O*-benzyl-β-D-ribofuranosyl)maleimide (14). Dichloroacetic acid (0.205 ml, 2.5 mmol) was added to a stirred solution of a mixture of methyl 3,6-anhydro-4,5,7-tri-*O*-benzyl-D-*glycero*-D-*allo*-heptonate and its D-glycero-D-altro isomer (2.25 g, 4.56 mmol)[4] and dicyclohexylcarbodiimide (2.6 g, 12.5 mmol) in dimethyl sulfoxide (25 ml) and benzene (25 ml) at 0°. The mixture was then stored at room temperature for 40 min and a solution of oxalic acid (950 mg, 7.5 mmol) in water (25 ml) was added portionwise. After stirring for 20 min the mixture was diluted with ethyl acetate (100 ml) and filtered. The organic phase was washed four times with saturated aqueous sodium chloride, dried ($MgSO_4$), and evaporated to a syrup. The latter was dissolved in ethanol (25 ml), filtered, evaporated, and coevaporated three times with benzene (10 ml).

Separately, benzene-washed sodium hydride (240 mg, 10 mmol) was added in a drybox under nitrogen to a suspension of **9** (4.5 g, 11.5 mmol) in anhydrous dimethyl sulfoxide (12 ml) and stored at room temperature for 2 hr. The resulting yellow solution was then added to a solution of the keto ester **3** prepared as above in benzene (100 ml) and stirred at room temperature for 1.5 hr. The mixture was then diluted with benzene (200 ml), filtered, and washed four times with saturated aqueous sodium chloride and then with water, dried ($MgSO_4$), and evaporated, leaving 1.7 g of a syrup. This material was purified by preparative TLC using two developments with ether–hexane (1:1). Elution of the major band gave 710 mg (30%) of **14** as a TLC homogeneous crystalline product: mp 86–87° from ether–hexane; λ_{max} (MeOH) 209 nm (ϵ 31100), 227 (sh, 14200); $[\alpha]^{23}D$ −6.0° (*c* 0.14, $CHCl_3$); NMR ($CDCl_3$) 1.94 (s, 3, CH_3), 3.51 (dd, 1, J_{gem} = 12, $J_{4',5'a}$ = 2 Hz, $C_{5'a}H$), 3.69 (dd, 1, $J_{4',5'b}$ = 2 Hz, $C_{5'b}H$), 4.01 (dd, 1, $J_{2',3'}$ = $J_{3',4'}$ = 5 Hz, $C_{3'}H$), 4.3 (m, 2, $C_{2'}H$, $C_{4'}H$), 4.45–4.75 (m, 6, OCH_2Ar), 4.91 (d, 1, $J_{1',2'}$ = 6 Hz, $C_{1'}H$), 7.3 ppm (m, 15, Ar).

Anal. Calcd for $C_{31}H_{31}NO_6$ (513.60): C, 72.50; H, 6.08; N, 2.73. Found: C, 72.46; H, 6.20; N, 2.82.

3-Methyl-2-β-D-ribofuranosylmaleimide (15a). A chilled solution of **14** (500 mg, 0.97 mmol) in methylene chloride (5 ml) was gradually added through a septum to a solution of boron trichloride (~4 g) in methylene chloride (40 ml) at −78°. After 2 hr at −78° the cooling bath was removed and a mixture of methanol and methylene chloride (1:1, 35 ml) was added dropwise. The solvents were then evaporated in vacuo and the residue was coevaporated four times with methanol (30 ml), leaving a crystalline residue. Recrystallization from acetone–benzene gave 190 mg (81%) of **15a**: mp 165–166°; λ_{max} 223 nm (ϵ 14100); $[\alpha]^{23}D$ −39.5° (*c* 1.0, MeOH); ORD (MeOH) $[\Phi]^{H}_{308}$ −4200°, $[\Phi]_{286}$ 0°, $[\Phi]^{pk}_{240}$ 6500°; mass spectrum (70 eV) *m/e* 244 (M^+ + H), 225 (M^+ − H_2O), 140 (base + CH_2O); NMR (Me_2SO-d_6–D_2O) 1.99 (s, 3, CH_3), 3.55 (m, 2, $C_{5'}H_2$), 3.81 (m, 1, $C_{4'}H$), 3.93 (dd, 1, $J_{2',3'}$ = 5, $J_{3',4'}$ = 3.5 Hz, $C_{3'}H$), 4.11 (dd, 1, $J_{1',2'}$ = 6.8 Hz, $C_{2'}H$), 4.60 ppm (d, 1, $C_{1'}H$).

Anal. Calcd for $C_{10}H_{13}NO_6$ (243.22): C, 49.38; H, 5.39; N, 5.76. Found: C, 49.54; H, 5.49; N, 5.94.

2-(2,3-*O*-Isopropylidene-β-D-ribofuranosyl)-3-methylmaleimide (15b). Perchloric acid (0.05 ml, 70%) was added to a solution of **15a** (45 mg, 0.185 mmol) in acetone (10 ml) and 2,2-dimethoxypropane (0.5 ml). After 15 min at room temperature the mixture was neutralized to pH 7 by careful addition of methanolic ammonia and the solvent was removed in vacuo. The residue was partitioned between ethyl acetate and water and the organic phase was dried ($MgSO_4$) and evaporated. The residue was freed from acetone polymers by preparative TLC using chloroform–methanol (19:1), elution of the major band giving 50 mg (96%) of **15b** as a foam: λ_{max} (MeOH) 223 nm (ϵ 14800); $[\alpha]^{23}D$ −72.3° (*c* 0.3, $CHCl_3$); ^1H NMR ($CDCl_3$–D_2O) 1.35 and 1.59 (s, 3, CMe_2), 2.05 (s, 3, CH_3), 3.67 (dd, 1, J_{gem} = 12, $J_{4',5'a}$ = 2 Hz, $C_{5'a}H$), 3.85 (dd, 1, $J_{4',5'b}$ = 2 Hz, $C_{5'b}H$), 4.30 (ddd, 1, $J_{3',4'}$ = 2 Hz, $C_{4'}H$), 4.28–4.47 ppm (m, 3, $C_{1'}H$, $C_{2'}H$, $C_{3'}H$); ^{13}C NMR ($CDCl_3$) 8.77 (C_3 CH_3), 25.49 and 27.83 (CMe_2), 63.00 ($C_{5'}$), 78.86 ($C_{1'}$), 82.77 ($C_{3'}$), 84.04 ($C_{2'}$), 85.11 ($C_{4'}$), 114.53 (CMe_2), 136.96 (C_3), 142.72 (C_2), 170.38, and 170.84 ppm (C=O).

Anal. Calcd for $C_{13}H_{17}NO_6$ (283.29): C, 55.12; H, 6.05; N, 4.95. Found: C, 54.98; H, 6.30; N, 4.69.

2',3'-*O*-Isopropylideneshowdomycin. Showdomycin (100 mg, 0.44 mmol) was treated as above for **15b**. Following preparative TLC the product could be crystallized from ethyl acetate, giving 75 mg (64%) of 2',3'-*O*-isopropylideneshowdomycin with mp 138–139° (reported[17] mp 140.5–141°); ^1H NMR ($CDCl_3$) 1.37 and 1.59 (s, 3, CMe_2), 3.68 (dd, 1, J_{gem} = 12, $J_{4',5'a}$ = 2.5 Hz, $C_{5'a}H$), 3.87 (dd, 1, $J_{4',5'b}$ = 2.5 Hz, $C_{5'b}H$), 4.27 (ddd, $J_{3',4'}$ = 2.5 Hz, $C_{4'}H$), 4.7–4.9 (m, 3, $C_{1'}H$, $C_{2'}H$, $C_{3'}H$), 6.62 ppm (s, 1, C_3H); ^{13}C NMR ($CDCl_3$) 25.43 and 27.60 (CMe_2), 62.87 ($C_{5'}$), 80.36 ($C_{1'}$), 82.35 ($C_{3'}$), 84.13 ($C_{2'}$), 85.37 ($C_{4'}$), 114.92 (CMe_2), 130.39 (C_3), 146.52 (C_2), 169.57 and 170.48 ppm (C=O).

***N*-Carbamoylcarbamoylmethyltriphenylphosphonium Bromide (19).** A solution of triphenylphosphine (26.2 g, 0.1 mol) and *N*-bromoacetylurea (18.1 g, 0.1 mol)[27] in acetonitrile (500 ml) was heated under nitrogen at 50° for 6 hr. Upon cooling to 0°, 33 g (75%) of crystalline **19** was obtained. An analytical sample from acetonitrile had mp 119–121°; ν_{max} (KBr) 3410, 3240, 3130, 1720, 1685, and 1580 cm^{-1}; NMR (Me_2SO-d_6) 5.33 (d, 2, $J_{P,H}$ = 14 Hz, exchanges with D_2O, $^+PCH_2CO$), 7.22 (br s, 2, $CONH_2$), 7.5–8.0 (m, 15, Ar), 10.53 ppm (br s, 1 CONHCO).

Anal. Calcd for $C_{21}H_{20}BrN_2O_2P$ (443.31): C, 56.90; H, 4.55; N, 6.32; Br, 18.03. Found: C, 57.04; H, 4.59; N, 6.16; Br, 17.80.

***N*-Carbamoylcarbamoylmethylenetriphenylphosphorane (20).** A solution of the phosphonium salt **19** (22.15 g, 50 mmol) in water (4 l.) was cooled to 0° and to it was added 50 ml of 1 *N* sodium hydroxide (50 mmol). The resulting crystalline product was immediately collected by filtration and dried in vacuo over phos-

phorus pentoxide, giving 16.5 g (92%) of **20** that was suitable for direct use. A portion was recrystallized from chloroform–hexane: mp 190–192°; ν_{max} (KBr) 1685, 1590, 1580, 1560 cm^{-1}; NMR ($CDCl_3$) 3.10 (br s, 1, exchanged with D_2O, P=CH), 7.3–7.7 (m, 15, Ar), 8.17 ppm (br s, 2, NH_2).

Anal. Calcd for $C_{21}H_{19}N_2O_2P$ (362.38): C, 69.90; H, 5.28; N, 7.73. Found: C, 69.63; H, 5.25; N, 7.83.

Reaction of 20 with Methyl Phenylglyoxylate (11). A solution of **11** (330 mg, 2 mmol) and **20** (750 mg, 2 mmol) in chloroform (25 ml) was heated under reflux for 20 hr and then evaporated to dryness. The residue was chromatographed on a column of silicic acid using hexane–ether (2:1), which eluted unreacted **11** followed by 2-phenylmaleimide (**18b**). Crystallization from chloroform–hexane gave 52 mg (15%) of **18b** with mp 164° which was identical with an authentic sample[4] by TLC and NMR analysis. Continued elution with chloroform–ethyl acetate (1:1) gave triphenylphosphine oxide followed by a second material that was crystallized from chloroform–methanol giving 174 mg (35%) of **21a** as white plates that partially decomposed at 182–186° and melted at 193–196°, unchanged upon recrystallization: ν_{max} (KBr) 3480, 3360 (NH), 1712 (COOMe), 1630, 1570 cm^{-1} (CONH); NMR (Me_2SO-d_6) 3.70 (s, 3, CO_2Me), 7.17 (s, 1, C_3H), 7.25 (m, 7, Ar, and NH_2), 10.43 ppm (br s, 1, NH).

Anal. Calcd for $C_{12}H_{12}N_2O_4$ (248.25): C, 58.06; H, 4.87; N, 11.29. Found: C, 58.56; H, 4.94; N, 11.32.

Methyl *N*-Carbamoyl-2-methylfumaramate (21b). A solution of **20** (725 mg, 2 mmol) and methyl pyruvate (205 mg, 2 mmol) in anhydrous chloroform (25 ml) was stirred at room temperature for 20 hr and then evaporated to dryness. The residue was chromatographed on a 4 × 30 cm column of silicic acid using ethyl acetate–chloroform (1:1) which largely separated triphenylphosphine oxide from the slightly more polar product. Crystallization of the product from chloroform gave 248 mg (67%) of **21b** which started to decompose at 180° and melted at 183–185°: ν_{max} (KBr) 3420, 3365 (NH), 1730 (CO_2Me), 1685, 1575 cm^{-1} (CONH); NMR (Me_2SO-d_6) 2.18 (d, 3, $J_{allylic}$ = 1.5 Hz, CH_3), 3.73 (s, 3, CO_2Me), 6.95 (q, 1, $J_{allylic}$ = 1.5 Hz, C_3H), 7.25, 7.65, and 10.45 ppm (br s, 1, NH).

Anal. Calcd for $C_7H_{10}N_2O_4$ (186.18): C, 45.16; H, 5.41; N, 15.05. Found: C, 45.41; H, 5.35; N, 15.10.

Registry No.—**7b**, 56629-80-2; **9**, 53296-04-1; **11**, 15206-55-0; **12**, 5109-46-6; **13**, 56629-73-3; **14**, 56629-74-4; **15a**, 56629-75-5; **15b**, 56629-76-6; **18b**, 34900-45-3; **19**, 53296-07-4; **20**, 53296-08-5; **21a**, 56629-77-7; **21b**, 56629-78-8; 2-bromopropionamide, 5875-25-2; tributylphosphine, 998-40-3; dimethylphenylphosphine, 672-66-2; 1,5-diazabicyclo[4.3.0]non-5-ene, 3001-72-7; methyl 3,6-anhydro-4,5,7-tri-*O*-benzyl-D-*glycero*-D-*allo*-heptonate, 38821-09-9; methyl 3,6-anhydro-4,5,7-tri-*O*-benzyl-D-*glycero*-D-*altro*-heptonate, 38821-08-8; 2,2-dimethoxypropane, 77-76-9; 2′,3′-*O*-isopropylideneshowdomycin, 19254-15-0; triphenylphosphine, 603-35-0; *N*-bromoacetylurea, 6333-87-5.

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Synthesis of Macrolide Antibiotics. II.[1] Stereoselective Synthesis of Methyl 4,6-*O*-Benzylidene-2-deoxy-2-*C*,3-*O*-dimethyl-α-D-glucopyranoside. Stereochemistry of Hydrogenation of the C-2 Methylene Group of Methyl 4,6-*O*-Benzylidene-2-deoxy-2-*C*-methylene-3-*O*-methyl-α- and -β-D-*arabino*-hexopyranoside

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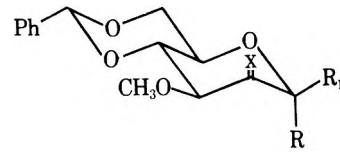
Methyl 4,6-*O*-benzylidene-2-deoxy-2-*C*,3-*O*-dimethyl-α-D-glucopyranoside (**13**) was stereoselectively synthesized by catalytic hydrogenation of methyl 4,6-*O*-benzylidene-2-deoxy-2-*C*-methylene-3-*O*-methyl-α-D-*arabino*-hexopyranoside (**9**) using W-8 Raney nickel as the catalyst and isooctane as the solvent. 2-Deoxy-2-*C*-methylene unsaturated sugar **9** (and its β anomer **10**) was obtained by treating methyl 4,6-*O*-benzylidene-3-*O*-methyl-α-D-*arabino*-hexopyranosid-2-ulose (**1**) (or its β anomer **2**) with triphenylmethylenephosphorane in toluene at 95°. The optimal reaction conditions for the reaction of triphenylmethylenephosphorane and **1** were investigated. The dependence of the stereochemistry of catalytic hydrogenation of unsaturated 2-deoxy-2-*C*-methylene hexopyranosides upon the anomeric configuration, the nature of the catalyst, and the solvent has been studied.

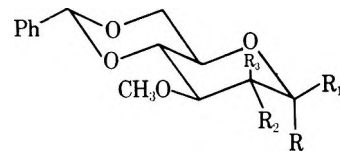
In a previous publication[2] we have reported that sodium borohydride reduction of the C-2 keto group of a methyl D-*arabino*-hexopyranosid-2-ulose derivative is highly stereoselective and strongly depends upon the anomeric configuration of the 2-ulose: the α anomer (**1**) yielded the corresponding D-gluco derivative (**3**) as the only product, whereas the β anomer (**2**) gave a 19:1 mixture of the D-manno (**4**) and D-gluco (**3**) derivatives. It has also been observed that the catalytic hydrogenation of methyl β-D-*arabino*-hexopyranosid-2-ulose (**5**)[3] and its 3,4,6-tri-*O*-benzyl derivative **6**[4] is also highly stereoselective, giving methyl β-D-mannopyranosides **7** and **8** as the predominant products (the manno to gluco ratio was 19:1 in both cases).

In an attempt to stereoselectively synthesize methyl 4,6-*O*-benzylidene-2-deoxy-2-*C*,3-*O*-dimethyl-α-D-glucopyranoside (**13**), an intermediate in the stereoselective synthesis of erythronolides A and B, wherein the C-2 carbon will correspond to the C-2 and/or C-10 carbon of erythronolides A and B, we have undertaken a study on whether the torsional strain and/or nonbonding steric interactions between the C-1 methoxy group and the catalyst in the transition state or its vicinity can be utilized to control the stereochemistry of catalytic hydrogenation of the C-2 methylene group of methyl 4,6-*O*-benzylidene-2-deoxy-2-C-methylene-3-*O*-methyl-α-D-*arabino*-hexopyranoside (**9**). Such interactions have been recently postulated as a possible explanation for the high stereoselectivity observed in the addition reactions to the C-4[1] or the C-2[2] carbonyl carbon atom, as well as for the reactivity of the C-2 methyl sulfonate toward the nucleophilic displacement.[5]

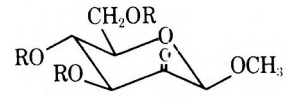
The synthesis of methyl 4,6-*O*-benzylidene-2-deoxy-2-*C*-methylene-3-*O*-methyl-α-D-*arabino*-hexopyranoside (**9**) from methyl 4,6-*O*-benzylidene-3-*O*-methyl-α-D-*arabino*-hexopyranosid-2-ulose (**1**) and triphenylmethylenephosphorane[5] was investigated first. In refluxing ether the reaction of **1** with triphenylmethylenephosphorane gave after 15 hr two products: 2-deoxy-2-*C*-methylene sugar derivative **9** in ca. 25% yield and the elimination product methyl 4-deoxy-3-*O*-methyl-α-D-*glycero*-hex-3-enopyranosid-2-ulose (**11**)[7] in ca. 10% yield. The starting material **1** has also been recovered from the reaction mixture (26%). When dimethyl sulfoxide was used as the solvent, the yield of 2-deoxy-2-*C*-methylene sugar **9** decreased to 17%, whereas the yield of the elimination product **11** increased to 58%, irrespective of the reaction temperature. No starting material could be, however, isolated from the reaction mixture. The increase in the formation of the unsaturated sugar **11** with the increase of the polarity of the solvent used (ϵ_{ether} 4.335 and ϵ_{Me_2SO} 46.68) indicated that in very polar solvents (e.g., dimethyl sulfoxide) the rate of deprotonation at the C-3 carbon of **1** followed by β-elimination of the 4,6-*O*-benzylidene group[8] is a considerably faster reaction than the addition of triphenylmethylenephosphorane to the C-2



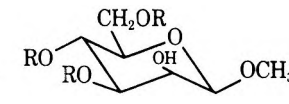
1, R = CH_3O; R_1 = H; X = O
2, R = H; R_1 = CH_3O; X = O
9, R = CH_3O; R_1 = H; X = CH_2
10, R = H; R_1 = CH_3O; X = CH_2



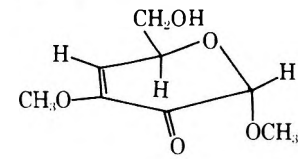
3, R = CH_3O; R_1 = R_3 = H; R_2 = OH
4, R = R_2 = H; R_1 = CH_3O; R_3 = OH
12, R = R_2 = H; R_1 = CH_3O; R_3 = CH_3
13, R = CH_3O; R_1 = R_3 = H; R_2 = CH_3
14, R = CH_3O; R_1 = R_2 = H; R_3 = CH_3



5, R = H
6, R = $C_6H_5CH_2$



7, R = H
8, R = $C_6H_5CH_2$



11

carbonyl carbon of **1**. It has been therefore concluded that the deprotonation at the C-3 carbon of **1** should be considerably slower in solvents less polar than either (e.g., toluene, ϵ 2.379) and that the β-elimination of the 4,6-*O*-benzylidene group to give **11** should be greatly impeded in such solvents. Indeed, when methyl 4,6-*O*-benzylidene-3-*O*-methyl-α-D-*arabino*-hexopyranosid-2-ulose (**1**) was treated at room temperature with triphenylmethylenephosphorane in a toluene solution for 17 hr, 2-deoxy-2-*C*-methylene sugar **9** was isolated in 74% yield. Since the addition of triphenylmethylenephosphorane to the C-2 carbonyl carbon was evidently the rate-limiting step of the Wittig reaction,[6b] we raised the reaction temperature with intention to avoid prolonged contact of **1** with a base (triphenylmethylenephosphorane) which may result in deprotonation of the C-3 carbon and β-elimination of the 4,6-*O*-benzylidene group. Thus by treating **1** with triphenylmethylenephosphorane at 95° not only was the reaction time shortened (the reaction was over in 20 min), but the yield of **9** was increased as well (85%).

Whereas the catalytic hydrogenation of methyl 4,6-*O*-benzylidene-2-deoxy-2-*C*-methylene-3-*O*-methyl-β-D-*arabino*-hexopyranoside (**10**) proceeded stereoselectively giving the corresponding 2-deoxy-2-*C*-methyl-D-mannopyranoside **12** as the only reaction product (84%), the stereoselectivity of the catalytic hydrogenation of methyl 4,6-*O*-benzylidene-2-deoxy-2-*C*-methylene-3-*O*-methyl-α-D-*arabino*-hexopyranoside (**9**) was, contrary to expectations, not very high and depended upon the nature of the catalyst and the solvent used (Table I). Raney nickel and nonpolar solvents favored the formation of the 2-deoxy-2-*C*-methyl-D-gluco derivative **13** (the gluco to manno ratio was 2.9:1), whereas platinum and polar solvents favored the formation of the 2-deoxy-2-*C*-methyl-D-manno derivative **14** (the gluco to manno ratio was 1:3.1). When glacial acetic acid (containing 5% acetic anhydride) was used as the solvent, the overall yield of **13** and **14** was considerably lower (86% with 10% Pt/C and 66% with 10% Pd/C) probably owing to the extensive debenzylidenation. Similarly, large amounts of catalyst (e.g., expt 13) apparently also facilitate debenzylidenation. It is interesting to note that methyl 4,6-*O*-benzylidene-2-deoxy-2-*C*,3-*O*-dimethyl-α-D-mannopyranoside (**14**) is more susceptible to debenzylidenation than **13**, which would explain the fact that the **13**:**14** ratio was higher than expected in expt 1, 2, and 13.

Experimental Section

General. The silica gel used for all column chromatography was M. Woelm (Eschwege, Germany) silica gel, particle size <0.063 mm. The melting points are uncorrected. Optical rotations were determined with a Cary 60 spectropolarimeter in a 1.0-cm cell. The ir spectra were recorded with a Perkin-Elmer infrared spectrophotometer, Model 267. The uv spectra were recorded with a Cary 15 uv-visible spectrophotometer. The proton NMR spectra were recorded with a Varian T-60 spectrometer using tetramethylsilane as an internal standard. The chemical shifts (δ) are expressed in parts per million (ppm). The carbon-13 NMR spectra of compounds **12**, **13**, and **14** were reported elsewhere.[10]

All Wittig reactions were performed in a nitrogen atmosphere using three-necked round-bottom flasks equipped with rubber stopples and a reflux condenser. All solutions were introduced in the reaction flask via syringe. The stirring was effected with a magnetic stirrer.

Reaction of Methyl 4,6-*O*-Benzylidene-3-*O*-methyl-α-D-*arabino*-hexopyranosid-2-ulose (1) with Triphenylmethylenephosphorane in Ether. To a suspension of methyltriphenylphosphonium bromide (179 mg, 0.5 mmol) in absolute ether (20 ml) a 2 *M* hexane solution of *n*-butyllithium (0.25 ml, 0.5 mmol) was added and the reaction mixture was stirred at room temperature for 4 hr. An ethereal solution (10 ml) of methyl 4,6-*O*-benzylidene-3-*O*-methyl-α-D-*arabino*-hexopyranosid-2-ulose (**1**, 162 mg, 0.55 mmol) was then added and the reaction mixture was heated at reflux for 15 hr. The precipitate was filtered off and washed with several portions of benzene and the combined filtrate was evaporated in vacuo. The oily residue (370 mg) was chromatographed on silica gel (18 g). Elution with 3:1 hexane–acetone gave four fractions. The most polar and the only chromatographically pure fraction (10 mg, 9.6%) was the elimination product **11** whereas the other three fractions, being impure, were rechromatographed. By chromatography of the first fraction (49 mg) on silica gel (5 g) using 9:1 benzene–ethyl acetate as eluent pure **9** (40 mg, 24.8%) was obtained, whereas chromatography of the second fraction (38 mg) on silica gel (4 g) using 4:1 benzene–ethyl acetate gave pure starting material **1** (32 mg, 19.7%). Finally, the chromatography of the third fraction (34 mg) on silica gel gave an additional amount of starting material (4.5 mg), raising thus the total amount of recovered **1** to 26.2% (42.5 mg). The other two fractions (12 and 7 mg) except for the fact that they did have the 4,6-*O*-benzylidene group (according to their NMR spectra) were not further investigated.

Reaction of Methyl 4,6-*O*-Benzylidene-3-*O*-methyl-α-D-*arabino*-hexopyranosid-2-ulose (1) with Triphenylmethylenephosphorane in Dimethyl Sulfoxide. To sodium hydride (21 mg of 57% oil suspension) washed with several portions of hexane, dry and freshly distilled dimethyl sulfoxide (6 ml) was added and the suspension was heated at 75–80° for 45 min, whereby a pale greenish solution was obtained. The solution was then cooled to room temperature, methyltriphenylphosphonium bromide (179 mg, 0.5 mmol) was added, and the obtained solution, after stirring at room temperature for 10 min, was heated to 55–60°. Methyl 4,6-*O*-benzylidene-3-*O*-methyl-α-D-*arabino*-hexopyranosid-2-ulose (167 mg, 0.57 mmol) in dimethyl sulfoxide (6 ml) was added and the reaction mixture was kept at 55–60° for 7 hr, at which time the starting material was completely consumed (monitored by TLC). The dimethyl sulfoxide was then removed in vacuo and the residue was chromatographed on silica gel (12 g). Elution with 1:1 benzene–ethyl acetate gave two fractions. The first fraction (29 mg, 17%) was pure methyl 4,6-*O*-benzylidene-2-deoxy-2-*C*-methylene-3-*O*-methyl-α-D-*arabino*-hexopyranoside (**9**), whereas the second fraction (62 mg, 58%) was pure methyl 4-deoxy-3-*O*-methyl-α-D-*glycero*-hex-3-enopyranosid-2-ulose (**11**). The analytical sample of **11** was obtained by recrystallization from acetone–hexane: needles, mp 96–96.5°; NMR ($CDCl_3$) δ 5.83 (d, $J_{4,5}$ = 2.0 Hz, 1, H-4), 4.87 (s, 1, H-1), 4.79 (m, $J_{4,5}$ = 2.0, $J_{5,6}$ = 5.0 Hz, 1, H-5) 3.81 (broad d, $J_{5,6}$ = 5.0 Hz, 2, H-6 and H′-6), 3.63 and 3.53 (two s, 6, methyl from C-1 and C-3 methoxy groups).

Anal. Calcd for $C_8H_{12}O_5$: C, 51.06; H, 6.43. Found: C, 51.19, H. 6.41.

Reaction of Methyl 4,6-*O*-Benzylidene-3-*O*-methyl-α-D-*arabino*-hexopyranosid-2-ulose (1) with Triphenylmethylenephosphorane in Toluene at Room Temperature. To a stirred suspension of methyltriphenylphosphonium bromide (714 mg, 2 mmol) in dry toluene (20 ml) a 2 *M* hexane solution of *n*-butyllithium (1 ml, 2 mmol) was added. After the reaction mixture was stirred at room temperature for 30 min, a toluene solution (10 ml) of methyl 4,6-*O*-benzylidene-3-*O*-methyl-α-D-*arabino*-hexopyranosid-2-ulose (**1**, 294 mg, 1 mmol) was added and stirring at room temperature was continued for another 17 hr. The reaction mixture was then filtered through a layer of Celite, the precipitate was washed with several portions of benzene, and the filtrate was evaporated in vacuo. The crystalline residue (625 mg) was chromatographed on silica gel (180 g). Elution with 95:5 benzene–ethyl acetate gave pure **9** (217 mg, 74%).

Reaction of Methyl 4,6-*O*-Benzylidene-3-*O*-methyl-α-D-*arabino*-hexopyranosid-2-ulose (1) with Triphenylmethylenephosphorane in Toluene at 95°. To a stirred suspension of methyltriphenylphosphonium bromide (7.14 g, 20 mmol) in dry toluene (150 ml) a 2 *M* hexane solution of *n*-butyllithium (10 ml, 20 mmol) was added, and the reaction mixture was stirred at room temperature for 15 min. The temperature was then raised to 95° and a toluene solution (30 ml) of methyl 4,6-*O*-benzylidene-3-*O*-methyl-α-D-*arabino*-hexopyranosid-2-ulose (**1**, 2.940 g, 10 mmol) was added during 2 min. The reaction mixture was stirred at 95° for another 5 min, the heating bath was removed, and stirring was continued for another 15 min. Acetone was then added dropwise until the yellow color of the reaction mixture disappeared, indicating that the excess of triphenylmethylenephosphorane was destroyed and the stirring was continued for 30 min. The suspension was filtered through a layer of Celite, the precipitate was washed with several portions of benzene, and the combined filtrate was evaporated in vacuo. The yellow crystalline residue was chromatographed on silica gel (50 g). Elution with 95:5 benzene–ethyl ace-

Table I
Catalytic Hydrogenation of Methyl 4,6-*O*-Benzylidene-2-deoxy-2-*C*-methylene-3-*O*-methyl-α-D-*arabino*-hexopyranoside (9)

Expt	Solvent	Catalyst	Substrate/catalyst ratio	13, %	14, %	13/14 ratio	Total yield, %
1	CH_3COOH + 5% Ac_2O	10% Pt/C	3:1	25.2	60.9	0.4	86.1
2	CH_3COOH + 5% Ac_2O	10% Pd/C	3:1	36.4	29.8	1.2	66.2
3	2:1 dioxane–water	10% Pt/C	3:1	23.8	74.1	0.3	97.9
4	2:1 dioxane–water	10% Pd/C	3:1	47.0	50.3	0.9	97.3
5	2:1 dioxane–water	Raney Ni (W-1)	~3:1	62.2	36.4	1.7	98.6
6	Dioxane	Raney Ni (W-8)	~3:1	55.6	43.0	1.3	98.6
7	Toluene	10% Pt/C	3:1	41.0	59.0	0.7	100.0
8	Toluene	10% Pd/C	3:1	62.2	37.7	1.6	99.9
9	Toluene	Raney Ni (W-1)	~3:1	66.2	32.4	2.0	98.6
10	Toluene	10% Pd/C	30:1	55.6	43.0	1.3	98.6
11	Toluene	10% Pd/C	1:1.7	59.6	38.4	1.5	98.0
12	Toluene	Raney Ni (W-8)	1:1.2	70.8	29.1	2.4	99.9
13	Toluene	Raney Ni (W-8)	1:5	68.8	22.5	3.0	91.3
14	Isooctane	Raney Ni (W-8)	1:1.2	73.5	25.2	2.9	98.7

tate gave pure methyl 4,6-*O*-benzylidene-2-deoxy-2-C-methylene-3-*O*-methyl-α-D-*arabino*-hexopyranoside (**9**, 2.500 g, 85%). An analytical sample was obtained by recrystallization from acetone–isopropyl ether as needles: mp 151–151.5°; $[\alpha]^{27}D$ +57° (c 1.0, $CHCl_3$); NMR ($CDCl_3$) δ 7.6–7.2 (m, 5, phenyl), 5.55 (s, 1, methine H from benzylidene group), 5.37 and 5.18 (two m, $J_{gem} \sim 2$ Hz, 2, olefinic protons from the C-2 methylene group), 5.01 (s, 1, H-1), 4.43–3.63 (m, 5, H-3, H-4, H-5, H-6, H′-6), 3.59 and 3.37 (two s, 6, methyl from C-1 and C-3 methoxy groups).

Anal. Calcd for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 65.97; H, 7.05.

Methyl 4,6-*O*-Benzylidene-2-deoxy-2-*C*-methylene-3-*O*-methyl-β-D-*arabino*-hexopyranoside (10). To a suspension of methyltriphenylphosphonium bromide (357 mg, 1 mmol) in absolute toluene (20 ml) a 2 *M* solution of *n*-butyllithium in hexane (0.5 ml, 1 mmol) was added and the mixture was stirred at room temperature for 5 hr. A toluene solution (20 ml) of methyl 4,6-*O*-benzylidene-3-*O*-methyl-β-D-*arabino*-hexopyranosid-2-ulose (**2**, 293 mg, 1 mmol) was then added, and the reaction mixture was stirred for 1 hr at room temperature and then at 70° for 4 hr. The precipitate was filtered off and washed with two 20-ml portions of benzene and the combined filtrate was evaporated in vacuo. The residue (351 mg) was chromatographed on silica gel (17 g). Elution with 7:1 benzene–ethyl acetate gave pure crystalline **10** (172 mg, 59%). An analytical sample was obtained by recrystallization from acetone–isopropyl ether: mp 156°; $[\alpha]^{27}D$ − 100° (c 0.9, $CHCl_3$); NMR ($CDCl_3$) δ 7.6–7.3 (m, 5, phenyl), 5.55 (s, 1, methine H from benzylidene group), 5.50 and 5.43 (two d, J_{gem} = 2.0 Hz, 2, olefinic protons from C-2 methylene group), 4.80 (broad s, 1, H-1), 3.58 and 3.55 (two s, 6, methyl from C-1 and C-3 methoxy groups).

Anal. Calcd for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 65.91; H, 6.90.

Catalytic Hydrogenation of Methyl 4,6-*O*-Benzylidene-2-deoxy-2-*C*-methylene-3-*O*-methyl-α-D-*arabino*-hexopyranoside (9). A solution (20 ml) of **9** (150 mg, 0.5 mmol) in various solvents was hydrogenated at atmospheric pressure and room temperature using different catalysts (see Table I). The hydrogenation was interrupted when the consumption of hydrogen ceased. The catalyst was then filtered off and washed with several portions of the solvent which was used for the particular hydrogenation, and the combined filtrate was evaporated in vacuo. The residue was chromatographed on silica gel (the silica gel:substance ratio was always 200:1) using 98:2 benzene–ethyl acetate as eluent. Those fractions which were mixture of C-2 epimers **13** and **14** were rechromatographed on silica gel using again 200:1 silica gel to substance ratio and 98:2 benzene–ethyl acetate as eluent. The results are given in Table I.

An analytical sample of **13** was obtained by recrystallization from *n*-hexane: mp 97°; $[\alpha]^{27}D$ +125° (c 0.94, $CHCl_3$); NMR ($CDCl_3$) δ 7.6–7.2 (m, 5, phenyl), 5.58 (s, 1, methine H from benzylidene group), 4.56 (d, $J_{1,2}$ = 3.6 Hz, 1, H-1), 4.4–3.2 (m, 5, H-3, H-4, H-5, H-6, H′-6), 3.57 and 3.32 (two s, 6 methyl from C-1 and C-3 methoxy groups), 2.1–1.5 (m, 1, H-2), 1.05 (d, J = 6.0 Hz, 3, C-2 methyl group).

Anal. Calcd for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53. Found: C, 65.47; H, 7.54.

Pure 2-deoxy-2-methyl manno derivative **14** was an oil: $[\alpha]^{27}D$ +57° (c 0.43, $CHCl_3$); NMR ($CDCl_3$) δ 7.6–7.2 (m, 5, phenyl), 5.55 (s, 1, methine H from benzylidene group), 4.53 (broad s, 1, H-1), 4.3–3.5 (m, 5, H-3, H-4, H-5, H-6, H′-6), 3.38 and 3.30 (two s, 6, methyl from C-1 and C-3 methoxy groups), 2.7–2.2 (m, 1, H-2), 1.05 (d, J = 6.6 Hz, 3, C-2 methyl group).

Anal. Calcd for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53. Found: C, 65.36; H, 7.49.

Hydrogenation of Methyl 4,6-*O*-Benzylidene-2-deoxy-2-*C*-methylene-3-*O*-methyl-β-D-*arabino*-hexopyranoside (10). An ethyl acetate solution (10 ml) of **10** (177 mg, 0.6 mmol) containing 10% Pt/C as the catalyst (40 mg) was hydrogenated at 0° and atmospheric pressure. After 15 min the consumption of hydrogen ceased and the hydrogenation was interrupted. The catalyst was filtered off and washed with several portions of ethyl acetate, and the combined filtrate was evaporated in vacuo. The residue (172 mg) was chromatographed on silica gel (35 g). Elution with 9:1 benzene–ethyl acetate gave pure **12** as an amorphous solid (150 mg, 84%): $[\alpha]^{27}D$ −60° (c 1.12, $CHCl_3$); NMR ($CDCl_3$) δ 7.6–7.2 (m, 5, phenyl), 5.53 (s, 1, methine H from benzylidene group), 4.46 (d, $J_{1,2}$ = 2.2 Hz, 1, H-1), 3.47 and 3.40 (two s, 6, methyl from C-1 and C-3 methoxy groups), ca. 2.45 (m, 1, H-2), 1.00 (d, J = 6.8 Hz, 3, C-2 methyl group).

Anal. Calcd for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53. Found: C, 65.46; H, 7.50.

Registry No.—**1**, 29774-59-2; **2**, 29774-60-5; **9**, 56614-98-3; **10**, 56614-99-4; **11**, 56615-00-0; **12**, 53011-02-2; **13**, 53011-00-0; **14**, 53011-01-1; methyltriphenylphosphonium bromide, 1779-49-3.

References and Notes

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Optical Resolution of *N*-Acyl-DL-amino Acids by Preferential Crystallization Procedure. Preparation of L-DOPA and L-α-Methyl DOPA[1]

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To develop the practical method for the production of L-DOPA and L-α-methyl DOPA, the optical resolution of their precursors, *N*-acetyl-DL-3-(3,4-methylenedioxyphenyl)alanine and *N*-acetyl-DL-3-(3,4-methylenedioxyphenyl)-2-methylalanine, was studied. The di-*n*-butylamine salt of *N*-acetyl-DL-3-(3,4-methylenedioxyphenyl)alanine and the hydrazine salt of *N*-acetyl-DL-3-(3,4-methylenedioxyphenyl)-2-methylalanine were resolved by preferential crystallization procedures, and optically pure isomers of both amino acids were obtained in good yield. The present simple resolution method using amine salts is expected to be applied more generally for resolution of *N*-acyl-DL-amino acids.

L-3-(3,4-Dihydroxyphenyl)alanine (L-DOPA) and L-3-(3,4-dihydroxyphenyl)-2-methylalanine (L-α-methyl DOPA) are important substances in biochemical and pharmaceutical fields,[2,3] and their markets have been expanding rapidly in recent years. It is therefore desirable to establish practical methods for the production of optically active DOPA and α-methyl DOPA.

Generally, optical resolution of the synthesized DL amino acids is more facile and practical for the production of optically active amino acids than the asymmetric synthesis of amino acids, because the latter method has not yet reached the stage of practicability and is still in a state of investigation. Among the various techniques for optical resolution of DL amino acids,[4] the preferential crystallization procedure[5] is considered to be one of the most useful for industrial application since it enables the desired optically active isomer to crystallize preferentially from a supersaturated solution of DL amino acid. However, it has the disadvantage that it cannot be applied to all kinds of amino acids because most amino acids form racemic compounds and are not suitable for this resolution method. In order to resolve this problem, a method of resolution using aromatic sulfonic acid has recently been developed by us and reported in the previous papers.[6-9] In this manner optical resolution of DL-DOPA and DL-3-(3,4-methylenedioxyphenyl)-2-methylalanine (DL-MDPMA), α-methyl DOPA precursor, became possible as the salts with 2-naphthol-6-sulfonic acid and *p*-phenolsulfonic acid, respectively.[9]

On the other hand, the synthetic route via acyl derivatives has often been used for the synthesis of DL amino acids. For example, DL-DOPA is synthesized in good yield via *N*-acetyl-DL-3-(3,4-methylenedioxyphenyl)alanine (*N*-Ac-DL-MDPA) from piperonal and acetylglycine.[10] In such cases, it is more desirable that an intermediate in the process of amino acid synthesis be easily resolved into the optical antipodes, and the undesired antipode be easily racemized to the DL form and then reused for the resolution step. In this study, therefore, the optical resolution of *N*-Ac-DL-MDPA and *N*-acetyl-DL-3-(3,4-methylenedioxyphenyl)-2-methylalanine (*N*-Ac-DL-MDPMA) have been investigated as a first approach to establish the general method for the optical resolution of *N*-acyl-DL-amino acids by preferential crystallization procedure.

Until now, the ammonium salts of the acyl derivatives of certain amino acids, including DL-tryptophan,[11] DL-phenylalanine,[12] DL-valine,[12] DL-methionine,[12] DL-serine,[13] DL-phenylglycine,[14] and DL-MDPA,[15] have been resolved by the preferential crystallization procedure. Although this type of resolution using the ammonium salts is very valuable, its application is restricted to a limited number of amino acids. In fact, the ammonium salt of *N*-Ac-DL-MDPMA could not be resolved since it formed a racemic compound. With respect to the ammonium salt of *N*-Ac-DL-MDPA, it formed a racemic mixture and was resolvable. However, the operation was not so easy in practice and the resolution results was unsatisfactory since the form of the crystals was unsuitable for the filtration process after crystallization.[1] Generally speaking, even though the ammonium salts of acyl derivatives are resolvable, the practical resolution is often difficult in cases where the salts have no adequate solubility and no suitable characteristics for easy handling.

Therefore, we attempted the optical resolution of the acylamino acids in the form of their salts with commercially available (optically inactive) amines instead of the ammonium salts. This idea is similar to that in our previous method using aromatic sulfonates. Namely, amines vary greatly in their properties and readily form salts with all kinds of *N*-acylamino acids, so that it becomes very easy to screen the salts suitable for the preferential crystallization procedure. Thus, we prepared a wide variety of amine salts of *N*-Ac-DL-MDPA and of *N*-Ac-DL-MDPMA, and screened the salts forming racemic mixtures by comparing the infrared spectrum, melting point, and solubility relationships of the racemic modifications and the optically active isomers.[8] As a result, it was found that the di-*n*-butylamine salt of *N*-Ac-DL-MDPA (*N*-Ac-DL-MDPA·DBA) and the hydrazine salt of *N*-Ac-DL-MDPMA (*N*-Ac-DL-MDPMA·HZ) readily crystallize as a racemic mixture from water, and the crystals have adequate solubility and suitable characteristics for easy handling. Then both salts were resolved by the usual manner described in our previous reports[8,9] and in the Experimental Section (see Tables I and II).

The optically active *N*-Ac-MDPA·DBA and *N*-Ac-MDPMA·HZ obtained above had an optical purity of about 98% on the average. When the optical purity is not satisfactory and further purification is required, the optically impure crystals can be purified without loss of the optically active isomer using the property of a saturated solution of the racemic mixture that it no longer dissolved the optically active isomer. Thus obtained optically active *N*-Ac-MDPA·DBA and *N*-Ac-MDPMA·HZ were decomposed with HCl to yield optically active *N*-Ac-MDPA and *N*-Ac-MDPMA quantitatively. The undesired *N*-Ac-D-MDPA was completely racemized by melting and the resulting *N*-Ac-DL-MDPA was reused for the resolution. However, *N*-Ac-D-MDPMA cannot be racemized in the usual way used for *N*-acylamino acids, because of the character of substitution at the optically active α position. The optically active *N*-Ac derivatives were converted to L-DOPA and L-α-methyl DOPA by the usual hydrolysis.

Table I
Successive Resoluions of N-Ac-DL-MDPA·DBA[a]

Expt	Amount of addition: DL form, g	Amount of addition: Active form, g	Composition of solution: DL form, g	Composition of solution: Active form, g	Separated crystals: Yield, g	Separated crystals: Optical purity,[b] %
1 (L)	37.50	4.00	37.50	4.00	8.95	97.8
2 (D)	9.23		36.85[c]	4.65[c]	7.93	97.7
3 (L)	8.18		38.50[c]	3.00[c]	8.36	97.5
4 (D)	8.62		36.45[c]	5.05[c]	7.81	98.2
5 (L)	8.05		38.98[c]	2.52[c]	8.27	97.5
6 (D)	8.53		36.06[c]	5.44[c]	8.12	97.6
Mean	8.52		37.39[c]	4.11[c]	8.24	97.7

[a] Resolutions were carried out at 35° on a 50-ml scale. Crystallization time was 90 min in every case. [b] The optical purity was calculated with the assumption that the specific rotation of the pure sample is $[\alpha]^{25}D \pm 42.4°$ (c 2, water). [c] Values calculated theoretically from analysis of separated crystals.

Table II
Successive Resolutions of DL-N-Ac-MDPMA·HZ[a]

Expt	Amount of addition: DL form, g	Amount of addition: Active form, g	Composition of solution: DL form, g	Composition of solution: Active form, g	Separated crystals: Yield, g	Separated crystals: Optical purity,[b] %
1 (L)	16.50	2.00	16.50	2.00	3.96	100
2 (D)	4.00		16.59[c]	1.91[c]	4.03	97.5
3 (L)	4.08		16.53[c]	1.97[c]	4.11	96.8
4 (D)	4.24		16.54[c]	1.96[c]	4.05	98.2
Mean	4.11		16.54[c]	1.96[c]	4.04	98.1

[a] Resolutions were carried out at 25° on a 50-ml scale. Crystallization time was 60 min in every case. [b] The optical purity was calculated with the assumption that the specific rotation of the pure sample is $[\alpha]^{25}D \pm 87.8°$ (c 0.5, MeOH). [c] Values calculated theoretically from analysis of separated crystals.

The optical resolution methods now presented are very advantageous providing the optical isomers are available because they require neither an optically active resolving agent nor conversion of the intermediates into complicated derivatives, the yield per unit volume is very high, and the operation is so simple that all processes are expected to be operated automatically in a sequence control system. Therefore, application of the present method for the industrial production of L-DOPA and L-α-methyl DOPA is considered to be very promising if combined with a proper synthetic method for N-Ac-DL-MDPA and N-Ac-DL-MDPMA.

Furthermore, although we cannot find a guiding rule that predicts the kind of amine salts which can be resolved by the preferential crystallization procedure, it becomes very easy to screen the suitable salts by the use of various amines. Therefore, the present simple resolution method using amine salts is expected to be applied more generally for resolution of synthetic acylamino acids.

Experimental Section

Materials. N-Ac-DL-MDPA was prepared in our laboratory from piperonal and N-acetylglycine via the azlactone as usual,[10,16] colorless needles, mp 180–182° (lit.[16] mp 178–180°). Anal. Calcd for $C_{12}H_{13}NO_5$: C, 57.37; H, 5.22; N, 5.58. Found: C, 57.22; H, 5.32; N, 5.67. A small amount of N-Ac-D-MDPA used for initial seed crystals was obtained by the optical resolution of N-Ac-DL-MDPA by asymmetric hydrolysis using a mold aminoacylase preparation.[16] The optically active N-Ac-L- and -D-MDPA used for seed crystals were obtained by the present preferential crystallization procedure. N-Ac-L-MDPA: colorless needles, $[\alpha]^{20}D$ +53.9° (c 1.5, EtOH), mp 158–159° [lit.[16] $[\alpha]^{13}D$ +53.4° (c 2.262, EtOH), mp 158–159°]. N-Ac-D-MDPA: colorless needles, $[\alpha]^{20}D$ −53.9° (c 1.5, EtOH), mp 158–159° [lit.[16] $[\alpha]^{18}D$ −53.4° (c 1.841, EtOH), mp 158–159°].

N-Ac-L-, -D-, and -DL-MDPMA were obtained as usual[17] by acetylating L-, D-, and DL-MDPMA, which were used in the previous report.[9] N-Ac-L-MDPMA: colorless needles, $[\alpha]^{20}D$ −58.8° (c 0.5, MeOH), mp 219–220° [lit.[17] $[\alpha]^{20}D$ −58.0° (c 0.5, MeOH), mp 214–215°]. N-Ac-D-MDPMA: colorless needles, $[\alpha]^{20}D$ +58.8° (c 0.5, MeOH), mp 219–220° [lit.[17] $[\alpha]^{20}D$ +58.0° (c 0.5, MeOH), mp 214–215°]. N-Ac-DL-MDPMA: colorless needles, mp 191–192° (lit.[17] mp 189–191°). Anal. Calcd for $C_{13}H_{15}NO_5$: C, 58.86; H, 5.70; N, 5.28. Found: C, 58.78; H, 5.65; N, 5.30. Di-n-butylamine and hydrazine hydrate were obtained from Katayama Chemical Industries Co., Ltd.

Analyses. All samples were dried overnight at 45–50° unless otherwise noted. Melting points were measured with a Yamato MP-21 melting point apparatus in an unsealed capillary tube and are uncorrected. Infrared spectra of samples were determined in KBr disks using a Shimadzu infrared spectrophotometer, Model IR-27G. Optical rotations were measured with a Perkin-Elmer 141 automatic polarimeter. Elemental analyses were performed with a Perkin-Elmer 240 elemental analyzer. Solubility was determined by approaching saturation equilibrium from both undersaturation and supersaturation. Solute concentration was measured with a Karl Zeiss immersion refractometer.

Preparation of N-Ac-L-, -D-, and -DL-MDPA·DBA. Di-n-butylamine (133.0 g, 1.03 mol) and water (350 ml) were added to N-Ac-DL-MDPA (251.2 g, 1 mol). The mixture was heated, treated with charcoal, and filtered. The filtrate was allowed to stand in a refrigerator overnight. The precipitate was collected, washed with cold water, and dried in vacuo to give N-Ac-DL-MDPA·DBA (267.4 g), mp 142–145°. A second crop was obtained by successive concentrations of the combined filtrates. The total yield was 355.2 g (93.4%). The products were almost pure and could be used for optical resolution without further purification. Recrystallization from water gave colorless prisms, mp 143–145°. Anal. Calcd for $C_{20}H_{32}N_2O_5$: C, 63.14; H, 8.48; N, 7.36. Found: C, 62.83; H, 8.50; N, 7.18. Solubility in water (g/100 ml): 22.8 (15°), 26.5 (25°), 38.3 (35°).

The optically active N-Ac-L- and -D-MDPA·DBA were prepared from N-Ac-L- and -D-MDPA, respectively, in the same way as described above. The L isomer: $[\alpha]^{25}D$ +42.4° (c 2, H_2O); mp 160–162°. Anal. Found: C, 62.96; H, 8.68; N, 7.14. Solubility in water (g/100 ml): 12.7 (15°), 13.3 (25°), 16.6 (35°). The D isomer: $[\alpha]^{25}D$ −42.4° (c 2, water); mp 160–162°. The infrared spectra of N-Ac-L-, -D-, and -DL-MDPA·DBA in KBr were identical: ir (KBr) 3225, 3050, 2950, 2870, 2500–2100, 1625, 1590–1550, 1500, 1445, 1380, 1300, 1240, 1193, 1035, 930, 855, 823, 812, 735 cm^{-1}.

Optical Resolution of N-Ac-DL-MDPA·DBA. In a typical experiment, N-Ac-DL-MDPA·DBA (37.50 g) and N-Ac-L-MDPA·DBA (4.00 g) were dissolved in water (50 ml) at elevated temperature. The solution was cooled to 35°, seeded with fine pulverized crystals of N-Ac-L-MDPA·DBA (0.10 g), and stirred for 90 min at the same temperature. The precipitated crystals were collected by filtration, washed with a small amount of cold water (2 ml), and dried to give N-Ac-L-MDPA·DBA (8.95 g). Its optical purity was 97.8%, $[\alpha]^{25}D$ +41.4° (c 2, H_2O).

After the separation of the L isomer, N-Ac-DL-MDPA·DBA (9.23 g) and a small amount of water were added to the mother liquor in order to prepare the supersaturated solution of almost the same composition as in the previous resolution except that the predominant isomer was D isomer. The amounts of the addition were adjusted by refractometric measurement and weighing according to a standard curve previously constructed. The solution thus obtained was cooled to 35°, seeded with N-Ac-D-MDPA·DBA (0.10 g), and stirred. After 90 min, the precipitated crystals were treated in the same manner as described above to yield N-Ac-D-MDPA·DBA (7.93 g), which had 97.7% optical purity. By repeating these procedures, L and D isomers were successively obtained. The examples of the several runs are shown in Table I.

Purification of Optically Impure N-Ac-MDPA·DBA. The optical isomers separated by the above procedure are practically pure. When further purification is necessary, it can easily be performed by ordinary recrystallization. On the other hand, optically impure N-Ac-L-MDPA·DBA could be purified without loss of op-

tically active isomer as follows. Optically impure *N*-Ac-L-MDPA·DBA (8.53 g, optical purity 85.0%) was dissolved at elevated temperature in a solution comprised of water (3.3 ml) and a saturated solution of *N*-Ac-DL-MDPA·DBA (appropriate amount 10 ml). The mixture was then stirred for 1 hr at 35°. The resulting crystals were collected by filtration, washed with a small amount of water, and dried to give *N*-Ac-L-MDPA·DBA (7.29 g), $[\alpha]^{25}D$ +42.0° (c 2, H_2O), optical purity 99.1%. Recrystallization from water gave optically pure *N*-Ac-L-MDPA·DBA, $[\alpha]^{25}D$ +42.4° (c 2, H_2O), mp 160–162°.

Optically Active *N*-Ac-L- and -D-MDPA from the Corresponding Di-n-butylamine Salts. Optically pure *N*-Ac-L-MDPA·DBA (10.00 g) was dissolved in hot water (25 ml) and decomposed with a slight excess of 5 *N* HCl to liberate the *N*-Ac-L-MDPA. The mixture was allowed to stand in a refrigerator overnight. The precipitate was filtered off, washed with water, and dried to give *N*-Ac-L-MDPA (6.28 g, 95.1%), $[\alpha]^{20}D$ +53.9° (c 1.5, EtOH), mp 158–159° [lit.[16] $[\alpha]^{13}D$ +53.4° (c 2.262, EtOH), mp 158–159°].

N-Ac-D-MDPA was obtained similarly from *N*-Ac-D-MDPA·DBA and had $[\alpha]^{20}D$ −53.9° (c 1.5, EtOH), mp 158–159° [lit.[16] $[\alpha]^{18}D$ −53.4° (c 1.841, EtOH), mp 158–159°]. Their specific optical rotations and melting points did not change after recrystallization from water. From the filtrate, di-*n*-butylamine satisfactory for reuse was recovered in 90% yield.

Racemization of *N*-Ac-D-MDPA and Preparation of *N*-Ac-DL-MDPA·DBA. *N*-Ac-D-MDPA (1.00 g) was melted in an unsealed tube by heating at 160–165°. After 15 min, to the solidified crystals, an equivalent amounts of di-*n*-butylamine (0.53 g) and water (5 ml) were added. The mixture was dissolved at elevated temperature, treated with charcoal, and concentrated nearly to dryness. The residual crystals were suspended in acetone, filtered, and dried in vacuo to give *N*-Ac-DL-MDPA·DBA (1.38 g), mp 138–142°. The product could be reused for the resolution step. Recrystallization from water gave pure *N*-Ac-DL-MDPA·DBA as colorless prisms, $[\alpha]^{25}D$ 0.0° (c 2, H_2O), mp 142–145°. This sample was found to be identical by admixture and ir comparison with the authentic sample prepared from the starting material.

Preparation of L-DOPA. *N*-Ac-L-MDPA (2.00 g) obtained above was added to a mixture of 20% HCl (40 ml) and phenol (2.0 g). The mixture was refluxed for 17 hr under stirring. After filtration, the filtrate was treated with charcoal and concentrated to dryness to remove excess HCl. The residue was taken up in water (10 ml) and the solution was treated with charcoal, adjusted to pH 5 with 5 *N* NH_4OH containing a small amount of sodium bisulfite, and allowed to stand in a refrigerator overnight. The precipitate was filtered and washed with cold water to give crude L-DOPA (1.12 g, 71.4%). Recrystallization from a diluted sulfurous acid solution afforded colorless needles, $[\alpha]^{20}D$ −12.2° (c 4, 1 *N* HCl), mp 278–279° dec [lit.[18] $[\alpha]^{20}D$ −12.1° (c 4, 1 *N* HCl)]. Anal. Calcd for $C_9H_{11}NO_4$: C, 54.82; H, 5.62; N, 7.10. Found: C, 54.85; H, 5.59; N, 7.08.

Preparation of *N*-Ac-L-, -D-, and -DL-MDPMA·HZ. *N*-Ac-DL-MDPMA·HZ was obtained from *N*-Ac-DL-MDPMA (265.1 g, 1 mol) and hydrazine hydrate (52.6 g, 1.05 mol) in the same way as *N*-Ac-DL-MDPA·DBA. Total yield was 216.7 g (97.5%). The products were almost pure and could be used for optical resolution without further purification. Recrystallization from water gave colorless needles, mp 189–190° dec. Anal. Calcd for $C_{13}H_{19}N_3O_5$: C, 52.51; H, 6.44; N, 14.13. Found: C, 52.61; H, 6.51; N, 14.01. Solubility in water (g/100 ml): 17.0 (10°), 21.1 (25°), 31.7 (40°).

The optically active forms were prepared in the same way. The L isomer: $[\alpha]^{25}D$ +87.8° (c 0.5, MeOH), mp 206–207° dec. Anal. Found: C, 52.59; H, 6.54; N, 14.15. Solubility in water (g/100 ml): 10.6 (10°), 12.8 (25°), 17.3 (40°). The D isomer: $[\alpha]^{25}D$ −87.8° (c 0.5, MeOH), mp 206–207° dec. The infrared spectra of *N*-Ac-L-, -D-, and -DL-MDPMA·HZ in KBr were identical: ir (KBr) 3320, 3120, 2120, 1650, 1625, 1565–1490, 1440, 1395, 1365, 1255, 1230, 1190, 1100, 1035, 930, 825, 705, 645 cm^{-1}.

Optical Resolution of *N*-Ac-DL-MDPMA·HZ. *N*-Ac-DL-MDPMA·HZ (16.50 g) and *N*-Ac-L-MDPMA·HZ (2.00 g) were dissolved in water (50 ml) at elevated temperature. The solution was cooled to 25°, seeded with *N*-Ac-L-MDPMA·HZ (0.05 g), and stirred at the same temperature. After 60 min, the precipitated crystals were filtered and washed with cold water (2 ml). *N*-Ac-L-MDPMA·HZ (3.96 g) thus obtained was optically pure, $[\alpha]^{25}D$ +87.8° (c 0.5, MeOH).

After the separation of the L isomer, *N*-Ac-DL-MDPMA·HZ (4.00 g) and a small amount of water were added to the mother liquor in the same way as described in the case of *N*-Ac-MDPA·DBA. The solution was cooled to 25°, seeded with *N*-Ac-D-MDPMA·HZ (0.05 g), and stirred for 60 min. The precipitated crystals were treated as described above to yield *N*-Ac-D-MDPMA·HZ (4.03 g), which had 97.5% optical purity, $[\alpha]^{25}D$ −85.6° (c 0.5, MeOH). The first several runs on a 50-ml scale are given in Table II.

Purification of Optically Impure *N*-Ac-MDPMA·HZ. *N*-Ac-L-MDPMA·HZ (10.00 g, optical purity 56.5%) was dissolved in water (21 ml) by heating. The solution was then stirred for 3 hr at 25°. The precipitated crystals were collected by filtration to give optically pure *N*-Ac-L-MDPMA·HZ (5.52 g), $[\alpha]^{25}D$ +87.8° (c 0.5, MeOH), mp 205–206° dec.

Optically Active *N*-Ac-L- and -D-MDPMA from the Corresponding Hydrazine Salts. The optically pure *N*-Ac-L-MDPMA·HZ (5.00 g) obtained above was dissolved in hot water (50 ml) and decomposed with excess 6 *N* HCl to liberate the *N*-Ac-L-MDPMA. After the mixture was allowed to stand in a refrigerator overnight, the precipitate was filtered, washed with water, and dried in vacuo to yield *N*-Ac-L-MDPMA (4.39, 98.5%), showing $[\alpha]^{25}D$ −58.6° (c 0.5, MeOH), mp 218–219°. Recrystallization from MeOH afforded colorless needles, $[\alpha]^{20}D$ −58.8° (c 0.5, MeOH), mp 219–220° [lit.[17] $[\alpha]^{20}D$ −58.0° (c 0.5, MeOH), mp 214–215°].

N-Ac-D-MDPMA was obtained similarly from *N*-Ac-D-MDPMA·HZ and had $[\alpha]^{20}D$ +58.8° (c 0.5, MeOH), mp 219–220° [lit.[17] $[\alpha]^{20}D$ +58.0° (c 0.5, MeOH), mp 214–215°].

Preparation of L-α-Methyl DOPA. The *N*-Ac-L-MDPMA (4.00 g) obtained above was hydrolyzed with 20% HCl in the presence of phenol in the same way as described in the preparation of L-DOPA from *N*-Ac-L-MDPA. The total yield of L-α-methyl DOPA·$\frac{3}{2}H_2O$ was 2.57 g (71.5%). Recrystallization from a sulfurous acid solution (0.5%) gave a white powder of L-α-methyl DOPA·$\frac{3}{2}H_2O$, and drying of the sesquihydrate in vacuo at 100° gave the anhydrous form, $[\alpha]^{25}D$ −5.2°, $[\alpha]^{25}_{578}$ −5.5° (c 2, 0.1 *N* HCl), mp 306–307° dec [lit.[19] $[\alpha]^{25}D$ −4° (c 2, 0.1 *N* HCl) and $[\alpha]^{25}_{578}$ +5.5° (c 2, 0.1 *N* HCl) for D-α-methyl DOPA]. Anal. Calcd for $C_{10}H_{13}NO_4$: C, 56.86; H, 6.20; N, 6.63. Found: C, 56.75; H, 6.23; N, 6.58.

Registry No.—*N*-Ac-DL-MDPA, 30657-34-2; piperonal, 120-57-0; *N*-acetylglycine, 543-24-8; *N*-Ac-L-MDPA, 28104-71-4; *N*-Ac-D-MDPA, 55629-70-4; *N*-Ac-DL-MDPMA, 23541-10-8; dibutylamine, 111-92-2; *N*-Ac-DL-MDPA·DBA, 55657-00-6; *N*-Ac-L-MDPA·DBA, 55656-80-9; *N*-Ac-D-MDPA·DBA, 55657-01-7; L-DOPA, 59-92-7; *N*-Ac-DL-MDPMA·HZ, 56599-11-2; hydrazine, 302-01-2; *N*-Ac-L-MDPMA·HZ, 56599-12-3; *N*-Ac-D-MDPMA·HZ, 56599-13-4; *N*-Ac-L-MDPMA, 23402-51-9; *N*-Ac-D-MDPMA, 24951-50-6; L-α-methyl DOPA, 555-30-6.

References and Notes

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Orbital Symmetry Control in the Thermal and Photoinduced Pericyclic Reactions of Some 1,2-Dihydropyrazines with Dimethyl Acetylenedicarboxylate[1a]

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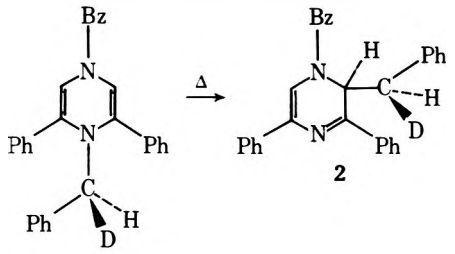
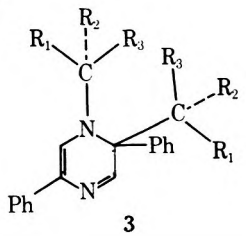
Reaction of several 1,2-dialkyl-2,5-diphenyl-1,2-dihydropyrazines **3** with dimethyl acetylenedicarboxylate (**4**) affords a series of dimethyl 1,2-dialkyl-2,5-diphenyl-3,8-dihydroazetidino[3,2-*b*]pyridine-6,7-dicarboxylates (**6**) the structures of which were proven by specific deuterium labeling. Thermolysis of chiral examples of the latter leads to sequential valence tautomerism via the 1,2-dihydro-1,4-diazocine **7**, [1,3] sigmatropic (C → N) alkyl shift with inversion of configuration, and cycloreversion of an intermediate 1,4-dihydro-1,4-diazocine **11** to pyrroles **10** and ketenimine **12**; the latter was isolated as the chiral amide **14**. Photolysis of chiral **6g** and **6h** takes a parallel chemical pathway except that the analogous [1,3] sigmatropic shift now displays the predicted orbital symmetry allowed retention. Reaction of **6i** with excess of **4** traps **11** to produce the 1,6-diazecines **25** (which in contrast to **11** is stable up to 150°) in addition to the azepines **26**. The latter provides evidence for intermediate **7** since it plausibly arises by trapping of **7**, [1,3]-sigmatropic shift and cycloreversion of the isomeric 1,4-diazecine **24**.

We have recently prepared 1,4-dibenzyl-2,6-diphenyl-1,4-dihydropyrazine (**1**) and have shown that it undergoes a stereospecific thermally induced suprafacial [1,3] sigmatropic benzyl shift with inversion of configuration to give the corresponding 1,2-dihydropyrazine **2** with a 12 ± 6% contribution from a radical dissociation–recombination mechanism.[2,3] Relatively few reports exist of stereochemical investigations of the applicability of the orbital symmetry rules to [1,3] shifts. Elegant examples by Berson,[4] Doering,[5] Masamune,[6] and Baldwin[7] all involve highly strained molecules. In view of the sensitivity of the stereochemical course of certain examples of [1,3] sigmatropic shifts to molecular environment[8] and the predicted dependence on substituent effects[9] it was of interest to examine the stereochemistry of the corresponding rearrangements of the 1,4-dialkyl-2,5-diphenyl-1,4-dihydropyrazines which proceeds regiospecifically to the 1,2-dihydropyrazines **3**.[10]



1

2



3

Since chiral examples of **3** proved resistant to the degradative procedures developed for investigating the absolute configuration of **2**,[3,11] a different approach was adopted. We report that the reactions of 1,2-dihydropyrazines **3** with dimethyl acetylenedicarboxylate (**4**) leading to a series of novel pericyclic reactions[12] permits the establishment of the stereochemistry of [1,3] alkyl sigmatropic shifts in both directions (N → C and C → N) and under both thermal and photochemical conditions and thus permits a detailed examination of these processes. In addition a number of novel nitrogen heterocycles become accessible.

Treatment of 1,2-dicyclohexyl-1,2-dihydro-2,5-diphenylpyrazine (**3a**) with 1 equiv of **4** at room temperature for 3 days in tetrahydrofuran afforded a 1:1 adduct **6a**, formulated as dimethyl 1,2-dicyclohexyl-2,5-diphenyl-3,5-dihydroazetidino[3,2-*b*]pyridine-6,7-dicarboxylate (see Scheme I and Table II). The ring expansion of enamine systems with acetylenic esters has several literature precedents.[13] Structure proof for **6a** is provided by a parallel experiment with 6-deuterio-**3b** (95% *d*) (prepared by the self-condensation of $C_6H_5COCD_2NHC_6H_{11}$ in which the 3 deuteron is selectively exchanged during work-up) which gives **6b** in which the methine AB quartet exhibited by **6a** was simplified to a broad singlet at δ 4.64. In view of the marked propensity for reversibility of the [1,3] sigmatropic shifts noted below, this key experiment permits the exclusion of an alternative mechanism for the formation of compounds of type **6** (see Scheme II) which would have resulted in label scrambling through the intermediate **8**.

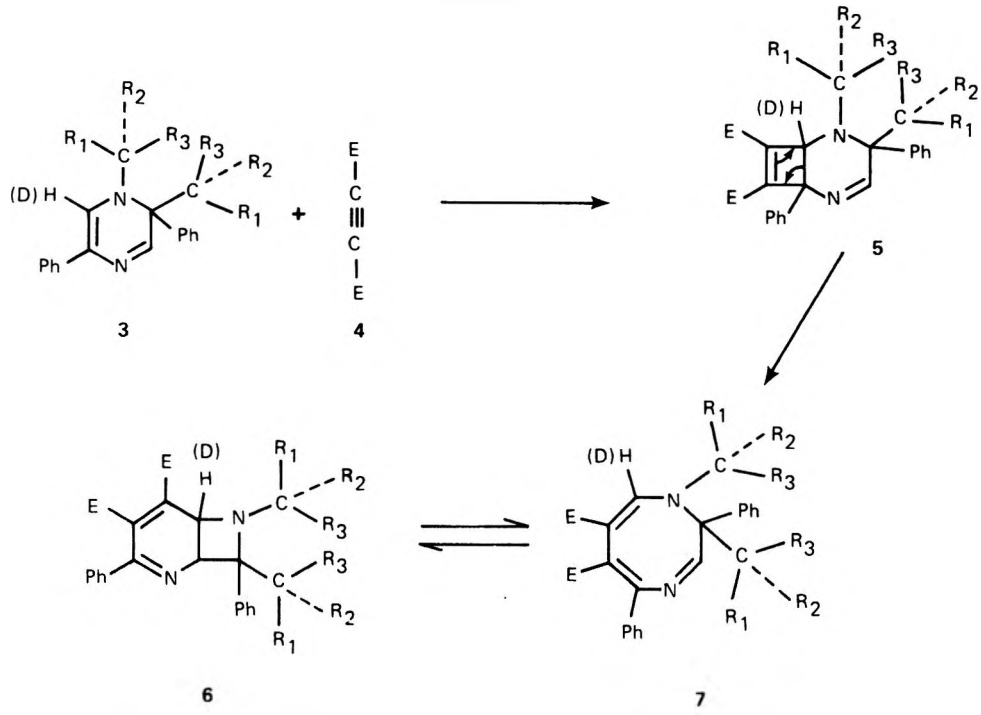
Analytical and spectral data for a series of similarly prepared 1,2-dialkyl-2,5-diphenyl-3,8-dihydroazetidino[3,2-*b*]pyridine-6,7-dicarboxylates are summarized in Table I.

Table I
1,2-Dialkyl-1,2-dihydro-2,5-diphenylpyrazines 3

Compd	Yield, %	δ ($CDCl_3$)
3c(d)[a] (oil)	77	0.17[(d, 3 H, J = 6.5 Hz, $-CH(CH_3)$], 1.39 [d, 3 H, J = 6.5, Hz, $-NCH(CH_3)$], 1.92–2.30[m, 1 H, $-CH(CH_3)$], 2.54–3.21 (m, 4 H, $-CH_2Ph$), 3.82–4.41 [(m, 1 H, $-NCH-(CH_3)$], and 6.69–7.81 (m, 12 H, aromatic and C_3H and C_5H)
3e(f)[a] (oil)	81	1.21 (d, 3 H, J = 6.5 Hz, $CHCH_3$), 1.53 (d, 3 H, J = 6.5 Hz, $-NCHCH_3$), 1.87–2.35 (q, J = 6.5 Hz, $-CH-$), 3.86–4.31 (q, 1 H, $-CH-$), 6.82 (s, 1 H, C_6H), and 7.04–7.71 (m, 20 H, aromatics)
3g(h)[a] (oil)	86	0.52–0.89 [m, 8 $CH(CH_3)$, (C_2H_5)], 1.22–1.85 [m, 8 H, $NC(CH_3)$, (C_2H_5)], 2.51–2.94 [m, 1 H, $-CH(CH_3)(C_2H_5)$], 3.71–4.11 [m, 1 H, $NCH(CH_3)(C_2H_5)$], 6.79 (s, 1H, C_6H) and 7.31–7.87 (m, 1 H, aromatic and C_3H)

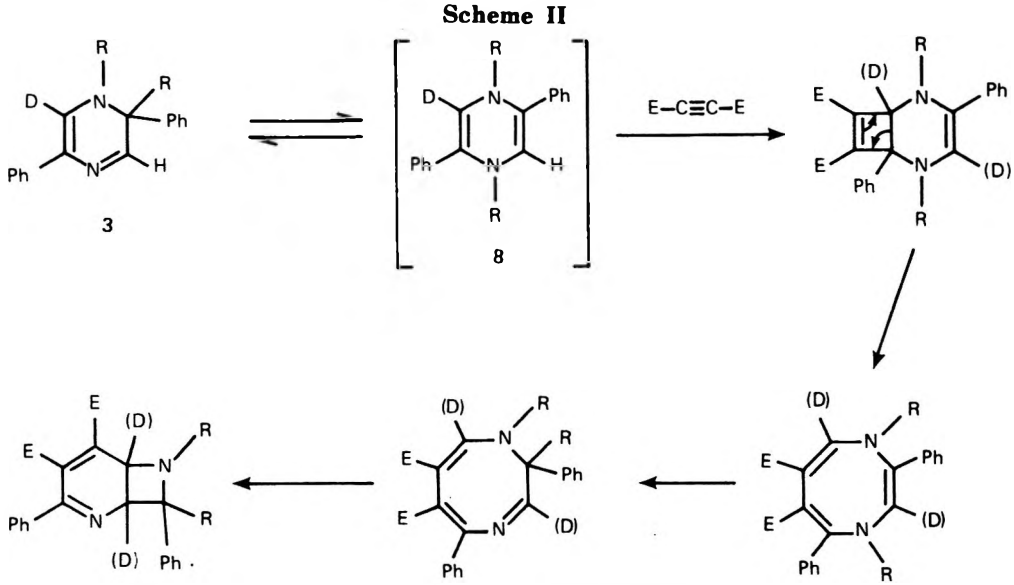
[a] Satisfactory combustion analytical data for C, H, N (±0.3%) and "exact mass" mass spectral data were provided for these compounds. Ed.

Scheme I



a, R_1 = H; R_2, R_3 = C_5H_{10}
b, R_1 = H; R_2, R_3 = C_5H_{10}; H_5 = D
c, R_1 = $PhCH_2$; R_2 = H; R_3 = CH_3
d, R_1 = CH_3; R_2 = H, R_3 = $PhCH_2$
e, R_1 = Ph; R_2 = H; R_3 = CH_3
f, R_1 = CH_3; R_2 = H; R_3 = Ph
g, R_1 = CH_3CH_2; R_2 = CH_3; R_3 = H
h, R_1 = CH_3; R_2 = CH_3CH_2; R_3 = H
i, R_1 = CH_3 R_2 = CH_3; R_3 = CH_3
j, R_1 = CH_3; R_2 = CH_3; R_3 = H
k, R_1 = H; R_2, R_3 = c-$C_{12}H_{23}$

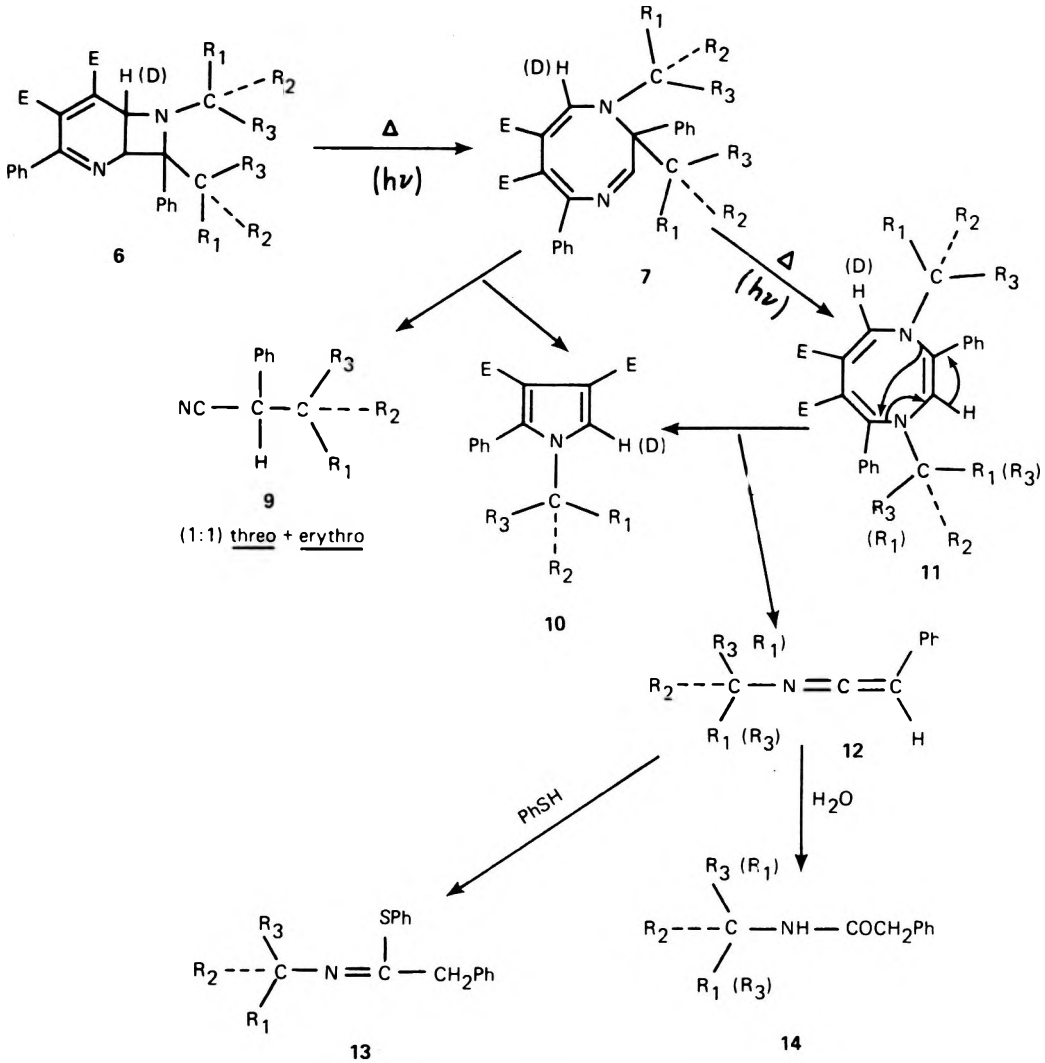
Scheme II



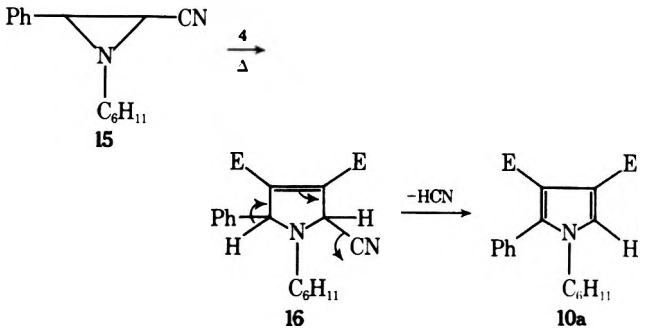
The conversion of **6** to **7** in Scheme I is represented as a reversible valence tautomerism,[14] since **6** upon heating briefly in benzene gave pyrroles **10** and ketenimines **12** in approximately equal quantities. The progress of the thermolysis of **6i** was conveniently followed by NMR and is rationalized as shown in Scheme III as sequential valence tautomerism of **6** to **7**, regiospecific [1,3] sigmatropic (C → N) alkyl shift to **11** followed by a formal orbital symmetry allowed [$_\pi6_s$ + $_\pi4_s$] cycloreversion[15] with an accompanying 1,2-hydride shift to give **10** and **12**.[16] Ketenimine **12i** was isolated during photolysis and characterized spectroscopically (see below) but all the ketenimines readily added water (e.g., during alumina column chromatography) to form the amides **14** which were identified by comparison with authentic samples. Further evidence for the intermediacy of the ketenimines is provided by their trapping with thiophenol to give a pseudothiourea **13** (see Scheme III).

The structure of the pyrrole products was proven in the case of **10a** by a 1,3-dipolar addition of **4** to the aziridine

Scheme III



The stereochemical pathway adopted upon photolysis is indicated in parenthesis.



15[17] followed by 1,4 elimination of hydrogen cyanide from **16**. Additional evidence in support of the proposed mode of cleavage of **11** in Scheme III is provided by the parallel experiment with 8-deuterio-**6b** which gave **10b** in which the 5 position was completely deuterated and **12b** in which the allenic proton was clearly visible in the NMR at δ 4.72. Substituted pyrroles produced by the thermolysis of compound **6** are summarized in Table III and the corresponding amides are reported in Table IV.

Stereochemistry of Thermal [1,3] Sigmatropic Shifts. The transformations in Schemes I and III provide the means for examining the stereochemistry of the [1,3] migrations, since the chiral center of interest is conveniently isolated in the amide **14**. Several examples of **3** containing chiral groups were prepared and treated with **4** (Scheme IV). Starting with **17c**, (−)-(*R*)-amphetamine,[18] the product **6c** (with one [1,3] sigmatropic shift during its formation via **19**) upon thermolysis affords pyrrole (*R*)-**10c** in 100% yield (required retention of configuration at position of 1 of **10c** by comparison with an authentic chiral compound) and amide *N*-(*R*)-**14c** in 100% yield (corresponding to 82% overall retention for the two successive [1,3] sigmatropic shifts during preparation, reaction with **4**, and subsequent cleavage). The comparable result from the (+)-(*S*)-amphetamine derivative **6d** corresponds to 82.5% overall retention in the double [1,3] sigmatropic shift (see Scheme III).

An experiment was performed with chiral (*S*)-(−)-α-methylbenzylamine (**17c**) which allowed a decision between the possible allowed double suprafacial inversion or disallowed double suprafacial retention. In this example **6f** upon thermolysis afforded products **9f** and **10f** (the structure of which was proven by independent synthesis) corresponding to the direct cleavage of **7c** [i.e., prior to the (C → N) [1,3] sigmatropic shift] thereby permitting the establishment of the stereochemistry of a single [1,3] alkyl shift (see Scheme III). The stereochemical results are summarized in Table V. The configuration of the known *erythro*-(*R*)-(−)-2,3-diphenylbutyronitrile (**9f**, $[\alpha]^{26}D$ −24°, C_6H_6)[19] has been correlated with that of (*R*)-(+)-α-phenethyl chloride by SN2 inversion, which in turn has been correlated with both (*R*)-(+)-glyceraldehyde[20] and (*S*)-(−)α-methylbenzylamine.[20]

Compound **9f** was formed in an approximately equal

Scheme IV

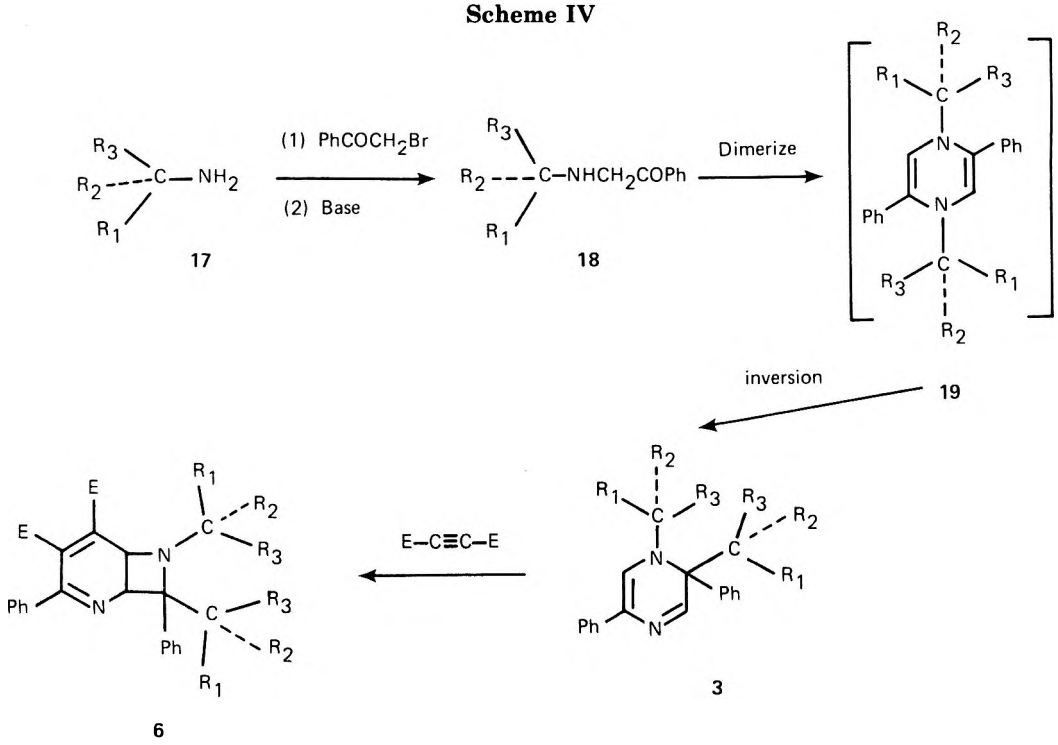


Table II
Dimethyl 1,2-Dialkyl-2,5-diphenyl-3,8-dihydroazetidino[3,2-*b*]pyridine-6,7-dicarboxylates 6

Compd	Mp, °C	Yield %	H_3, H_3 AB q	J_{38}	Ester methyl	1,2-Alkyl groups	Alkyl methine
6a[a]	144–145.5	87	4.18, 4.64	4.0	3.27, 3.86	0.51–1.95	2.05–2.49 2.67–3.17
6b[a]	144–145.5	87	4.18 (br s)		3.27, 3.86	0.50–1.96	2.05–2.49
6c,d[a]	Oil	72	4.18, 4.67	4.0	3.23, 3.83	0.67–1.33 (CH_3) 1.82–2.21 ($-CH_2$) 2.51–2.93 ($-CH_2$)	3.43–3.82 4.21–4.64
6e,f[a]	Oil	75	4.11, 4.61	4.5	3.27, 3.88	0.97–1.31	3.37–3.73 4.16–4.48
6g,h[a]	127–129	85	4.13, 4.62	4.2	3.28, 3.88	0.52–1.51	2.12–2.62 2.82–3.33
6i[a]	1.5–137	91	4.17, 4.76	4.5	3.25, 3.90	0.82, 1.03 (s)	
6j[a]	.18–119	88	4.14, 4.61	4.2	3.27, 3.86	0.36–1.18	2.36–2.91 3.01–3.59
6k[a]	122–123.5	73	3.98, 4.60	4.2	3.40, 3.90	0.77–2.01	2.89–3.41

[a] See footnote *a*, Table I.

mixture of threo and erythro diastereomers implying little or no asymmetric induction during the cleavage of **7f** to **9f**. The isolated and purified erythro diastereomer, mp 135° from **9c** ($[\alpha]^{25}D$ – 21.85, C_6H_6),[21] therefore corresponds to 91.3% overall inversion (i.e., a single inversion in the step **19** to **3** and retention in the step **7** to **9**). We conclude that formation of **14** in 82% overall retention corresponds to two successive N → C (**19** to **3**) and C → N (**7** to **11**) allowed suprafacial [1,3] sigmatropic shifts, i.e., double inversion.

As we reported previously, the analogous [1,3] sigmatropic shift **1** to **2** proceeded with 95% stereospecific inversion of configuration and also in the absence of a scavenger exhibits a 12 ± 6% contribution from the parallel radical dissociation–recombination mechanism[11] which probably accounts for the loss of 18% optical activity observed here. In support of this contention it was observed that thermolysis of **6e** or **6f** at a higher temperature produced some 2,3-diphenylbutane from α-methylbenzyl coupling in addition to **10e** and **14e**. To that extent example **6f** is not ideal and may not be typical of the behavior of this system. A better model is provided by chiral *sec*-butyl, which would have less tendency to form radicals either under photolytic or thermolytic conditions (see below).

The 3,8-dihydroazetidino[3,2-*b*]pyridines **6** contain three chiral carbons and a nitrogen which may be inverting rather slowly. The influence of the relative stereochemistry of the groups in **6** on the stereochemical outcome of the processes described above remains to be investigated. Also the fortuitous formation of **9** rather than **12** in the case of α-methylbenzyl derivatives is currently being investigated employing a range of model compounds to see if the division of reaction pathways in Scheme III may be attributed to steric factors, for example.

Stereochemistry of Photoinduced [1,3] Sigmatropic Shifts. It was now necessary to ascertain the behavior of these systems upon photolysis. It was by no means obvious that [1,3] sigmatropic shifts, if they could be induced to proceed under photolytic conditions, would do so with the predicted retention of configuration. For example, Cookson and Kemp have reported that the photoisomerization of **20**

Table III
Dimethyl 1-Alkyl-2-phenylpyrrole-3,4-dicarboxylates 10

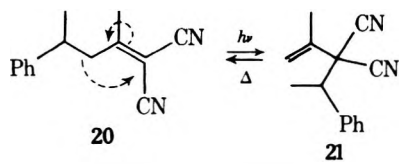
Compd	Mp, °C	Yield, %	CO_2CH_3	Alkyl	Alkyl methine	Ir spectrum [$CHCl_3$ (C=O)] cm^{-1}
10[a]	Oil	89	3.63 3.84	0.85–2.23 (m, 10 H, cyclohexyl)	3.46–4.07	1720 (b)
10c,d[a]	94–95	88	3.56 3.82	1.28 (d, 3 h, J = 6.5 Hz, CH_3), 2.55–3.15 (m, 2 H, CH_2Ph)	3.80–4.46 (m, 1 H)	1720 (b)
10e,f[a]	Oil	89	3.59 3.75	1.67 (d, 3 H, J = 7.0 Hz, CH_3)	5.05–5.40 (q, 1 H, J = 7.0 Hz)	1715 (b)
10g,h[a]	118–119.5	94	3.63 3.81	1.33 (d, 3 H, J = 6.5 Hz, CH_3) 0.71 (t, 3 H, J = 7.0 Hz, CH_2CH_3)	3.36–4.15	1720 (b)
10i[a]	92–93	92	3.55 3.82	1.43 [s, 3 H, $-C(CH_3)_3$]		1715 (b)
10j[a]	145–146.5	92	3.64 3.85	1.35 (d, 6 H, J = 7.0 Hz, CH_3)	3.88–4.58 (1 H, septet J = 7.0 Hz)	1720 (b)
10k[a]	106–107.5	87	3.66 3.65	0.72–2.21 (m, 22 H, cyclooctyl)	3.71–4.31	1720 (b)

[a] See footnote *a*, Table I.

Table IV
***N*-Alkyl-2-phenylacetamides[a] 14**

Compd	Mp, °C	Found molecular ion (mass spectrum)	Calcd molecular ion (mass spectrum)	δ ($CDCl_3$)
14a	132–133.5	217.1461	217.1464	0.85–2.08 (m, 10 H, cyclohexyl), 3.53 (s, 2 H, CH_2), 3.47–4.15 (br, 1 H, methine), 5.17–5.73 (br s, 1 H, NH, D_2O exchangeable), and 7.29 (s, 5 H, aromatic)
14c(d)	90–91.5 (lit. mp 95°[25])	215.1416	253.1419	1.04 (d, 3 H, J = 6.5 Hz, CH_3), 2.62 (d, 2 H, J = 6.7 Hz, $-CH_2Ph$), 3.43 (s, 2 H, $PhCH_2$), 3.78–4.47 (m, 1 H, –CH), 5.64–6.09 (br, 1 H, exchangeable with D_2O, NH), 6.91–7.63 (m, 10 H, aromatic)
14g(h)	57–58.5	191.1308	191.1306	0.83 (t, 3 H, J = 6.5 Hz, $-CH_2CH_3$), 1.08 (d, 3 H, J = 6.5 Hz, CH_3), 1.06–1.54 (m, 2 H, $-CH_2CH_3$), 3.58 (s, 2 H, CH_2), 3.62–4.15 (m, 1 H, methine), 5.31–5.92 (br, 1 H, NH, exchangeable with D_2O), and 7.33 (s, 5 H, aromatics)
14i	135–136.5	191.1304	191.1306	1.30 [s, 9 H, $C(CH_3)_3$], 3.50 (s, 2 H, CH_2), 5.11–5.47 (br, 1 H, exchangeable with D_2O), 7.30 (s, 5 H, aromatics)
14j	102–103.5	177.1159	177.1156	1.67 (d, 6 H, J = 6.5 Hz, CH_3), 3.50 (s, 2 H, $C_6H_5CH_2$), 3.69–4.38 (septet, 1 H, –CH–), 5.82–6.31 (br, 1 H, NH, D_2O exchangeable), and 7.30 (s, 5 H, aromatics)
14k	134–135	301.2504	301.2498	1.61 (br s, 22 H, cyclododecyl), 3.52 (s, 2 H, CH_2), 3.74–4.31 (br, 1 H, methine), 4.95–5.61 (br, 1 H, D_2O exchangeable, NH), and 7.28 (s, 5 H, aromatic)

[a] Authentic sample was prepared in each case by treating phenylacetyl chloride with the appropriate amine.



20 21

to **21** takes place with ca. 85% retention of configuration.[8] However, thermal reversion of the rearrangement occurred with >90% retention and also with ≈10% inversion. In the latter process the concerted suprafacial [1,3] shift with retention may therefore have become sufficiently allowed to permit it to compete successfully with the sterically more strained route with inversion. Cookson therefore warns against uncritical extension of the orbital symmetry rules from the parent system to which they apply to strongly perturbed analogs in which, e.g., substituent electronic effects, the introduction of heteroatoms, and steric strain operate.

In the event photolysis of the dihydroazetidino[3,2-*b*]pyridines both in benzene at room temperature and in ether at −70° with a 200-W Hanovia medium-pressure lamp gave clean products of pyrroles and ketenimines in good isolated yields (i.e., ketenimines isolated as the amides). Next the chiral 1,2-dihydropyrazine **3g** was prepared in 74% yield from (*S*)-(+)-*sec*-butylamine (29% enantiomeric excess). Treatment of 1-(*S*)-2-(*R*)-**3g** with **4** in tetrahydrofuran gave 1-(*S*)-2-(*R*)-**6g**, mp 128–128.5°, in 85% yield. Photolysis of **6g** at −78° in ether afforded chiral 1-(*S*)-pyrrole **10g**

Table V
Optical Activity of Products from Reaction of Chiral 1,2-Dihydropyrazines 3 and Dimethyl Acetylenedicarboxylate under Thermal Conditions, $[\alpha]^{25}D$ (C_6H_6)

General structure	Chiral amine employed			
	(−)-(*R*)-17c	(+)-(*S*)-17d	(−)-(*S*)-17f	(+)-(*R*)-17e
3	−105.6	+108.8	−76.4	+72.8
6	−70.7	+74.3	−85.40	+88.9
9[a]			−21.85	+20.95
9[b]			−22.40	
10[c]	−77.8	+75.6	−57.25	+57.80
10[d]			−59.80	
14[c]	+6.55 (82%)[e]	−6.85 (82.5%)	−54.30[f]	+53.80[f]
14[d]	+7.9	−8.45	−55.5	+55.60

[a] Purified erythro diastereomers. [b] Value in presence of scavenger *n*-BuSH. [c] Product from thermolysis. [d] Authentic synthetic sample. [e] % overall retention. [f] Isolated in 2–3% yield.

Table VI
Optical Activity of Products from Reaction of Chiral 1,2-Dihydropyrazines 3 and Dimethyl Acetylenedicarboxylate under Thermal and Photolytic Conditions, $[\alpha]^{25}D$ (C_6H_6)

General structure	Mp, C	Chiral amine	
		(*S*)-(+)-17g	(*R*)-(−)-17h
3	Oil	+5.65	−5.85
6	128–8.5	+4.95	−5.15
10[a]	118–119	+3.6	−3.8
10[b]	118.5–119.5	+3.2	−3.3
14[c]	57–58.5	+4.95	−5.2
14[a]	55–56.5	+4.7 (95%)[d]	−4.9 (94%)[e]
14[b]	56–57.5	−3.8 (77%)[e]	+3.7 (71%)[e]

[a] Product from thermolysis. [b] Product from photolysis. [c] Authentic synthetic sample. [d] % overall retention. [e] % overall inversion.

in 73% yield and the *N*-(*R*)-ketenimine **12h** (80% yield as estimated by NMR). The latter was isolated as the chiral *N*-(*R*)-**14h**, mp 55–56.5°, in 67% yield, with an optical purity which corresponded to about 80% retention of configuration in the [1,3] sigmatropic rearrangement by comparison with an authentic sample. By contrast, thermolysis of **6g** affords chiral *N*-(*S*)-**14g** with 95% overall retention from two successive suprafacial [1,3] sigmatropic shifts.

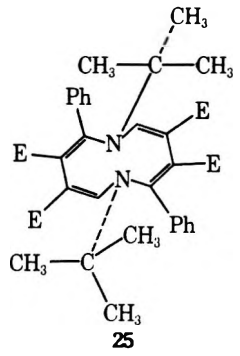
Parallel experiments were performed with *R*-(−)-*sec*-butylamine with comparable results. The isolated pyrroles **10g** and 10h showed 100% retention of configuration of the *N*-*sec*-butyl group in both cases. The stereochemical results are summarized in Table VI.

Trapping of Diazocine Reaction Intermediates. The photolysis of **6** (R = *t*-Bu, see Scheme V) at −70° produced a small quantity of an isomer as a yellow oil. The NMR spectrum shows absence of the AB quartet characteristic of the methine hydrogens in **6** confirming that the 3–8 bond has been broken. Comparison with the known lability and chemical reactivity of compound **11** points to structure **7** (R = *t*-Bu) for this isolated intermediate, although the small quantities available prevented further characterization.

Efforts were now made to obtain more direct evidence for the existence of intermediates **7** and **11** by trapping experiments using **4**. Trapping of **7** or **11** as dienes was possible, or if [1,3] migration from **7** to **11** proved competitive, the latter could conceivably be trapped as an enamine. In the event, reaction of **6** (R = *t*-Bu) or **6** (R = C_6H_{11}) with 1 equiv of **4** thermally succeeded in trapping the enamine moiety of **11** to form the 1,6-diazecines **25** (R = *t*-Bu) and **25** (R = C_6H_{11}), respectively, plausibly via **22**. Compound **25** was isolated in low yield as a yellow oil together with the corresponding pyrrole **10e** and amide **14**. Formation of **25** thus parallels the initial formation of intermediate **5** from the enamine moiety of **3** reacting with **4**. In the presence of a large excess of the ester **4** (as solvent) the facile thermal cycloreversion of **11** to pyrrole and ketenimine is somewhat suppressed and a higher yield of **25i** may be obtained together with substantial amounts of the crystalline tetramer of **4**.[22]

Evidence in support of structure **25** (R = *t*-Bu) is the composition as determined by mass spectroscopy and the NMR spectrum, which shows two equivalent *tert*-butyl groups at δ 1.45, two different methyl ester peaks at δ 3.62 and 3.68, and two equivalent vinyl protons at δ 6.97. The NMR data are consistent with the molecular environments predicted for these groups from a model. The trans disposition of the large *tert*-butyl substituents may also explain the reluctance of **25** to undergo catalytic hydrogenation, since they would be expected to interfere with absorption on the catalyst surface.

Supporting evidence for the formation of **25** is provided by a control reaction of the dihydroazetidino[3,2-*b*]pyridine from α-methylbenzylamine. Previous work had established this compound upon thermolysis to undergo valence tautomerism and then selective cleavage to pyrrole and nitrile only, to the exclusion of the [1,3] (C → N) sigmatropic shift. Reaction with an excess of **4** therefore permitted discrimination between species **7** and **11** as reactants with **4** to yield **25**. In this experiment the corresponding **9e** and **10e** were obtained from cycloreversion of **7** and no product corresponding to **25** was observed. A second control experiment between the ketenimine **12** (R = *t*-Bu) and **4** gave no reaction. Although the formal orbital symmetry allowed [$_\pi6_s$ + $_\pi4_s$] thermal cycloreversion of **11** to **10** and **12** proceeds smoothly, the vinylog of **11**, compound **25**, is thermally stable up to 150°. It is tempting to suggest that the analogous cycloreversion here to the pyrrole would be a [$_\pi6_s$ + $_\pi6_s$] process and is precluded since it is predicted to be thermally disallowed.

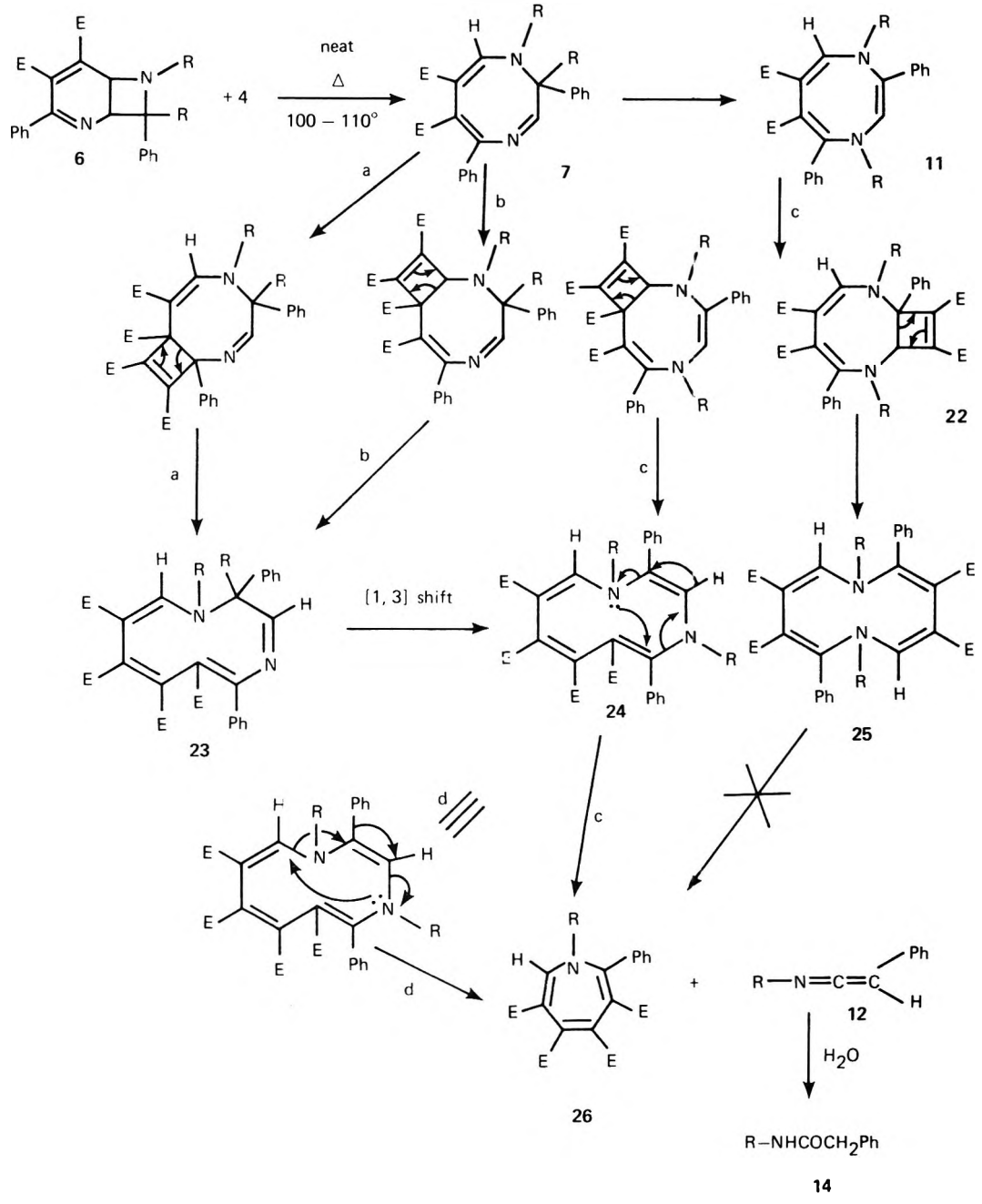


25

An alternative mode of addition of **4** to the valence tautomer of the azetidinopyridine requiring the formation and cycloreversion of an isomeric 1,4-diazecine was uncovered. Reaction of **6** (R = *sec*-Bu) with in **4** as solvent at 100–110° afforded the azepine **26** (R = *sec*-Bu) and the corresponding amide **14**. Several possible pathways to these products may be formulated, some of the alternatives being given in Scheme V.

The nature of the products requires a reverse C → N [1,3] sigmatropic shift in one of the intermediates prior to cycloreversion. Paths a and b are indistinguishable. Pathway c is likely in view of precedents given in Scheme III representing then the vinylog of the cycloreversion of, e.g.,

Scheme V



11 to 10 and 12. Pathway d is unlikely since it requires the postulation of a 1,2-phenyl shift.

The Cope rearrangement that occurs with 7 is evidently not favored for intermediate 23 presumably because this would produce a bridgehead phenyl group.

It is evident that in this first report on these novel and complex reactions the mechanisms proposed can only be viewed as tentative at this stage. The detailed investigation is being continued.

Experimental Section

Melting points were determined on a Fisher-Johns apparatus and are uncorrected. The ir spectra were recorded on a Perkin-Elmer Model 421 spectrophotometer, and only the principal, sharply defined peaks are reported. The NMR spectra were recorded on Varian A-60 and A-100 analytical spectrometers. The spectra were measured on approximately 10–15% (w/v) solutions in $CDCl_3$, with tetramethylsilane as a standard. Line positions are reported in parts per million from the reference. Mass spectra were determined on an Associated Electrical Industries MS-9 double-focusing high-resolution mass spectrometer. The ionization energy, in general, was 70 eV. Peak measurements were made by comparison with perfluorotributylamine at a resolving power of 15000. Kieselgel DF-5 (Camag, Switzerland) and Eastman Kodak precoated sheets were used for thin layer chromatography. Microanalyses were carried out by Mrs. D. Mahlow of this department.

Materials. The amines, *d*- and *l*-α-methylbenzylamine and *d*- and *l*-α-methylphenethylamine, were available commercially (Aldrich Chemical Co.). The *d*- and *l*-*sec*-butylamines were prepared in 29% enantiomeric excess by resolving the *dl*-*sec*-butylamine into diastereomeric tartrate salts and subsequent regeneration of the enantiomeric amines according to the described procedure.[23] The (*S*)-*sec*-butylamine had $[\alpha]^{25}D$ +2.14° (neat) compared with $[\alpha]^{25}D$ +7.44° for enantiomerically pure compound.[23]

1,2-Dialkyl-2,5-diphenyl-1,2-dihydropyrazines 3. Representative examples of the preparation are given; thereafter the physical data of other compounds similarly prepared are summarized in Table I.

6-Deuterio-1,2-dicyclohexyl-2,5-diphenyl-1,2-dihydropyrazine (3b). A mixture of 10 g (5 mmol) of α,α-dideuterio-2-bromoacetophenone (prepared from bromination of acetophenone-d_3) and 10 g (10 mmol) of cyclohexylamine-*N*-d_2 (prepared by repeated deuterium oxide exchange of cyclohexylamine) in dry benzene was stirred at room temperature for 6 hr, then heated at reflux

temperature for 8 hr. The precipitated salt was collected, the filtrate was washed with deuterium oxide (2 × 10 ml) and dried ($MgSO_4$), and the solvent was removed to give a yellow oil. The oil on trituration with methanol deposited 13.5 g (67% yield) of the 1,2-dihydropyrazine **3b**, mp 97–98.5°. During the work-up with methanol the 3-deuterium atom is preferentially exchanged as shown by the NMR spectrum: δ_{Me_4Si} ($CDCl_3$) 0.72–2.04 (br, 20 H, C_6H_{11}), 2.33–2.83 (br, 1 H, methine), 3.47–4.01 (br, 1 H, *N*-methine), and 7.18–7.85 (m, 11 H, aromatic and C_3H).

Anal. Calcd for $C_{28}H_{33}N_2D$: mol wt 399.2728. Found: mol wt, 399.2724 (mass spectrum).

1-(*S*)-2-(*R*)-Di-*sec*-butyl-2,5-diphenyl-1,2-dihydropyrazine (3g). (*S*)-(+)-*sec*-Butylamine, $[\alpha]^{25}D$ 2.14° (neat) (4.54 g, 60 mmol), was added to a benzene solution of 5.0 g (25 mmol) of α-bromoacetophenone, and the mixture was stirred at room temperature for 2 hr, then heated under reflux for 16 hr. Upon cooling, the resulting *sec*-butylamine hydrobromide was removed by filtration. The filtrate was washed with cold water and dried ($MgSO_4$) and the solvent was removed in vacuo to give a reddish-orange oil which was purified by chromatography on B. D. H. alumina. Elution with hexane–benzene (3:1) gave **3g** as an orange oil which resisted crystallization: 3.2 g (74% yield); $[\alpha]^{25}D$ +5.67° (c 9.37, C_6H_6); NMR δ_{Me_4Si} ($CDCl_3$) 0.5–0.98 [m, 11 H, $-CH(C_2H_5)$, CH_3, $-CH_2CH_3$], 1.33 (d, 3 H, J = 6.5 Hz, $-NCHC_2H_5CH_3$) 1.12–1.67 [m, 2 H, $-NCH(CH_2CH_3)CH_3$], 2.51–2.85 (m, 1 H, methine), 3.57–4.16 (m, 1 H, *N*-methine), 6.77 (s, 1 H, C_3H), and 7.02–7.86 (m, 11 H, C_3H aromatics); absorption spectrum λ_{max} (CH_3CN) 265 nm (log ε 4.23).

Anal. Calcd for $C_{24}H_{30}N_2$: mol wt, 346.2409. Found: mol wt, 346.2415 (mass spectrum).

Dimethyl 1,2-Dialkyl-2,5-diphenyl-3,8-dihydroazetidino[3,2-*b*]pyridine-6,7-dicarboxylate (6). A representative preparation of one example is given; thereafter the physical data on other compounds similarly prepared are summarized in Table II.

(+)-Dimethyl-1-(*S*)-2-(*R*)-di-*sec*-butyl-2,5-diphenyl-3,8-dihydroazetidino[3,2-*b*]pyridine-6,7-dicarboxylate (6g). A solution of 2.6 g (7.5 mmol) of the 1,2-dihydropyrazine **3f**, $[\alpha]^{25}D$ +5.67°, in 15 ml of dry tetrahydrofuran and 1.15 g (8 mmol) of **4** was stirred at room temperature for 6 days. Removal of the solvent gave a dark oil which was subjected to chromatography on 80 g of B. D. H. alumina. Elution with hexane–benzene (1:3) gave as the main fraction an oil, 2.94 g (85% yield), which on trituration with hexane deposited the azetidinopyridine **6g** as a white solid: mp 127–128.5°; $[\alpha]^{25}D$ +4.95° (c 8.35, C_6H_6); NMR δ_{Me_4Si} ($CDCl_3$) 0.37–1.83 (m, 16 H, CH_3, C_2H_5), 2.03–2.71 (m, 1 , H, methine), 2.48–2.81 (m, 1 H, methine), 3.33 (s, 3 H, CO_2CH_3), 3.92 (s, 3 H, CO_2CH_3), 4.13 (d, 1 H, J = 4.0 Hz, C_3H), 4.63 (d, 1 H, J = 4.0 Hz, C_8H), and 7.11–7.76 (m, 10 H, aromatic); absorption spectrum λ_{max} (CH_3CN) 314 nm (log ε 3.26).

Anal. Calcd for $C_{30}H_{36}N_2O_4$ (mol wt 488.2846): C, 73.55; H, 7.34; N, 5.75. Found (mol wt 488.2840, mass spectrum): C, 73.41; H, 7.47; N, 5.81.

Dimethyl 8-Deuterio-1,2-dicyclohexyl-2,5-diphenyl-3,8-dihydroazetidino[3,2-*b*]pyridine-6,7-dicarboxylate (6b). A solution of 8.0 g (20 mmol) of the 6-deuterio-1,2-dihydropyrazine **3b** in 35 ml of dry tetrahydrofuran and 2.9 g (20 mmol) of **4** was set aside at room temperature for 4 days. Removal of the solvent gave a yellow oil which in trituration with hexanes deposited yellowish-white crystals of the pyridine **6b**: 9.3 g (86% yield); mp 144–146°; NMR δ_{Me_4Si} ($CDCl_3$) 0.51–1.95 (m, 20 H, cyclohexyl), 2.05–2.49 (br, 1 H, methine), 2.67–3.18 (br, 1 H, methine), 3.28 (s, 3 H, CO_2CH_3), 3.86 (s, 3 H, CO_2CH_3), 4.18 (t, 1 H, C_3H), and 7.11–7.78 (m, 10 H, aromatic).

Anal. Calcd for $C_{34}H_{39}DN_2O_4$: mol wt, 541.2208. Found: mol wt, 541.2210 (mass spectrum).

Thermolysis of Dimethyl 8-Deuterio-1,2-dicyclohexyl-2,5-diphenyl-3,8-dihydroazetidino[3,2-*b*]pyridine-6,7-dicarboxylate (6b). A solution of 1.35 g (2.5 mmol) of the azetidinopyridine **6b** in dry toluene was heated under reflux for 10 hr. Removal of the solvent in vacuo gave a light yellow oil, the NMR spectrum of which exhibited the allenic proton of the ketenimine at δ 4.72. Chromatography of the oil on B. D. H. alumina afforded dimethyl *N*-(*cyclohexyl*)-2-phenyl-5-deuteriopyrrole-3,4-dicarboxylate (**10b**, 0.704 g, 82% yield) which was compared with an authentic sample of **10a**: NMR δ_{Me_4Si} ($CDCl_3$) 0.95–1.30 (br, 10 H, cyclohexyl), 3.65 (s, 3 H, CO_2CH_3), 3.83 (s, 3 H, CO_2CH_3), 3.4–4.05 (br, 1 H, methine), 7.32–7.59 (m, 5 H, aromatics).

Anal. Calcd for $C_{20}H_{22}DNO_4$: mol wt, 342.1688. Found: mol wt, 342.1676 (mass spectrum).

Further elution with benzene–chloroform gave the amide *N*-cyclohexyl-2-phenylacetamide (**14b**, 0.48 g, 90% yield), mp 131–132.5°; mixture melting point with an authentic sample was undepressed; NMR δ_{Me_4Si} ($CDCl_3$) 0.8–2.08 (br, 10 H, cyclohexyl), 3.53 (s, 2 H, $-CH_2C_6H_5$), 3.48–4.15 (br, 1 H, methine), 5.17–5.73 (br, 1 H, NH, D_2O exchangeable), and 7.29 (s, 5 H, aromatic).

Synthesis of Dimethyl *N*-(*S*)-(−)-α-Methylbenzyl]-2-phenylpyrrole-3,4-dicarboxylate (10f). The title compound was prepared by the following sequence of reactions.

A. 1-(*S*)-α-Methylbenzyl-3-cyano-2-phenylaziridine (15). To a solution of 4.35 g (15 mmol) of 1,2-dibromo-1-cyano-2-phenylethane[24] in 200 ml of dry benzene stirred at 0–5° was added dropwise a solution of 7.2 g (0.06 mol) of (*S*)-(−)-α-methylbenzylamine, $[\alpha]^{25}D$ −39° (neat), in 50 ml of benzene. The solution was then stirred at room temperature for a period of 10 days. The precipitated α-methylbenzylamine hydrobromide was collected and the yellow filtrate was concentrated in vacuo and subjected to chromatography on 100 g of B. D. H. alumina. Removal of the solvent from the main fraction gave 1-(*S*)-α-methylbenzyl-3-cyano-2-phenylaziridine as a white solid: mp 135–137.5° (67%); NMR δ ($CDCl_3$) 1.42 (d, 3 H, $-CH_3$, J = 6.5 Hz), AB quartet centered at 2.32 and 3.08 (J = 6.0 Hz, 2 H and 2, 3 ring protons), 2.89 (q, 1 H, J = 6.5 Hz, methine), and 7.27–7.70 (multiplet, 10 H, aryl protons); $[\alpha]^{25}D$ +18.5° (c 5.5, C_6H_6); mass spectrum (70 eV) *m/e* 248.1309 (calcd for $C_{17}H_{16}N_2$, 248.1314); ν_{max} ($CHCl_3$) 2250 cm^{-1} (C≡N).

Anal. Calcd for $C_{17}H_{16}N_2$: C, 82.25; H, 6.45; N, 11.30. Found: C, 82.41; H, 6.51; N, 10.99.

B. Reaction of 1-(*S*)-(+)-α-Methylbenzyl-3-cyano-2-phenylaziridine with 4. A solution of 0.5 g (2 mmol) of the chiral aziridine and 0.285 g (2 mmol) of **4** was heated under reflux in xylene for 24 hr. The yellow solution was cooled and solvent removed in vacuo, giving a yellow oil. The oil was subjected to chromatography on 50 g of B. D. H. alumina to give *N*-[(*S*)-(−)-α-methylbenzyl]-2-phenylpyrrole-3,4-dicarboxylate (**10f**): 0.54 g (74%); $[\alpha]^{25}D$ −59.80° (c 10.01, C_6H_6); NMR δ ($CDCl_3$) 1.68 (d, 3 H, J = 6.5 Hz, $-CH_3$), 3.59 (s, 3 H, CO_2CH_3), 3.75 (s, 3 H, CO_2CH_3), 5.21 (q, 1 H, J = 6.5 Hz, methine), 6.65–7.31 (m, 10 H, aromatics), and 7.43 (s, 1 H, C_5 H); mass spectrum *m/e* 363.1484 (calcd for $C_{22}H_{21}NO_4$, 363.1471).

Anal Calcd for $C_{22}H_{21}NO_4$: C, 72.72; H, 5.78; N, 3.86. Found: C, 72.94; H, 5.62; N, 4.01.

Dimethyl *N*-Cyclohexyl-2-phenylpyrrole-3,4-dicarboxylate (10a). A solution of 0.45 g (2 mmol) of 1-cyclohexyl-2-cyano-3-phenylaziridine[17] and 0.285 g (2 mmol) of **4** was heated under reflux in 35 ml of xylene for 24 hr. Removal of the solvent in vacuo and chromatography on 50 g of B. D. H. alumina eluting with benzene–hexane (1:4) gave **10a** as a light yellow oil which resisted crystallization: 0.58 g (85%); NMR δ ($CDCl_3$) 0.87–2.15 (m, 10 H, cyclohexyl methylenes), 3.63 (s, 3 H, CO_2CH_3), 3.82 (s, 3 H, CO_2CH_3), 3.45–4.01 (br, 1 H, cyclohexyl methine), and 7.32–7.54 (m, 5 H, aromatic and C_5H); mass spectrum *m/e* 341.1616 (calcd for $C_{20}H_{23}NO_4$, 341.1627).

Anal. Calcd for $C_{20}H_{23}NO_4$: C, 70.38; H, 6.74; N, 4.10. Found: C, 70.47; H, 6.43; N, 4.09.

Thermolysis of Dimethyl 1-(*R*)-2-(*S*)-Di(α-methylphenethyl)-2,5-diphenyl-3,8-dihydroazetidino[3,2-*b*]pyridine-6,7-dicarboxylate (6c) in the presence of Thiophenol. A solution of 1.25 g (2 mmol) of the pyridine **6c** and 0.330 g (3 mmol) of the thiophenol in 75 ml of dry toluene was heated under reflux for 10 hr. Removal of the solvent in vacuo gave a light yellow oil which was subjected to chromatography on B. D. H. alumina. Elution with hexane–benzene (2:1) afforded the pseudothioure **13c**, 0.593 g (86% yield), as a yellow oil: NMR δ_{Me_4Si} ($CDCl_3$) 1.30 (d, 3 H, J = 6.0 Hz, $-CH_3$), 2.91–3.14 [m, 2 H, $-CH(CH_2Ph)$], 3.58 (s, 2 H, $-CH_2Ph$), 3.90–4.65 (m, 1 H, methine), and 6.68–7.54 (m, 15 H, aromatics); ν_{max} ($CHCl_3$) 1665 cm^{-1} (C=N).

Anal. Calcd for $C_{23}H_{23}NS$ ($M^+ - C_6H_5S$, $C_{17}H_{18}N$, 236.1439): C, 80.01; H, 6.67; N, 4.05. Found ($C_{17}H_{18}N$ 236.1450, mass spectrum): C, 79.93; H, 6.42; N, 4.33.

Further elution with benzene gave dimethyl *N*-[(*R*)-α-methylphenethyl]-2-phenylpyrrole-3,4-dicarboxylate (**10c**, 0.670 g, 89% yield) as a pale yellow oil which on trituration with hexane deposited yellowish-white crystals, mp 93–95.5°. Repeated crystallization from methanol and petroleum ether gave an analytical sample: mp 94.5–95.5°; $[\alpha]^{25}D$ −78.5° (c 10.1, C_6H_6); NMR δ_{Me_4Si} ($CDCl_3$) 1.28 (d, 3 H, J = 6.5 Hz, $-CH_3$), 2.55–3.15 (m, 2 H, CH_2Ph), 3.56 (s, 3 H, CO_2CH_3), 3.82 (s, 3 H, CO_2CH_3), 3.80–4.46 (m, 1 H, methine), 6.67–7.41 (m, 10 H, aromatic), and 7.45 (s, 1 H, C_5H).

Anal. Calcd for $C_{23}H_{23}NO_4$ (mol wt 377.1813): C, 73.19; H, 6.10; N, 3.72. Found (mol wt 377.1804, mass spectrum): C, 73.17; H, 6.48; N, 3.81.

Thermolysis of Dimethyl 1-(*S*)-2-(*R*)-Di(α-methylbenzyl)-2,5-diphenyl-3,8-dihydroazetidino[3,2-*b*]pyridine-6,7-dicarboxylate (6f). A solution of 1.8 g (3 mmol) of the pyridine **6f** in 75 ml of dry toluene was heated under reflux for 10 hr. Removal of the solvent in vacuo gave a light yellow oil which was subjected to chromatography on B. D. H. alumina. Elution with hexane–benzene (4:1) gave as a yellow oil a mixture of *threo*- and *erythro*-(*R*)-2,3-diphenylbutyronitriles **9f** in a ratio of 1:1 as estimated by NMR: δ_{Me_4Si} ($CDCl_3$) 1.33 (d, 3 H, J = 6.5 Hz, CH_3), 1.45 (d, 3 H, J = 6.5 Hz CH_3), 2.93–3.48 (m, 2 H, methine, C_3H), 3.98 (d, 2 H, J = 6.5 Hz, C_2H), and 7.12–7.47 (m, 20 H, aromatics); infrared ν_{max} ($CHCl_3$) 2230 cm^{-1} (C≡N). The oil on trituration and repeated recrystallization from hot ethanol gave the pure *erythro*-(*R*)-(−)-2,3-diphenylbutyronitrile **9f** as a white solid: mp 132–133.5° (lit.[19] mp 133–134.5°); $[\alpha]^{25}D$ −21.85° (c 8.9, C_6H_6); NMR δ_{Me_4Si} ($CDCl_3$) 1.43 (d, 4 H, J = 6.5 Hz, CH_3), 302–3.50 (quintuplet, 1 H, J_{23} = 6.5, J_{CH_3-H} = 6.5 Hz, C_3H), 3.98 (d, 1 H, J = 6.5 Hz, C_2H), and 7.09–7.48 (m, 10 H, aromatics); infrared ν_{max} ($CHCl_3$) 2235 cm^{-1} (C≡N).

Further elution with benzene gave dimethyl *N*-[(*S*)-(−)-α-methylbenzyl]-2-phenylpyrrole-3,4-dicarboxylate (**10f**, 0.95 g, 86% yield) as a yellow oil: $[\alpha]^{25}D$ = −57.25° (c 10.5, C_6H_6); authentic sample $[\alpha]^{25}D$ −59.80° (c 10.8, C_6H_6); NMR δ_{Me_4Si} ($CDCl_3$) 1.72 (d, 3 H, J = 7.0 Hz, CH_3), 3.65 (s, 3 H, CO_2CH_3), 3.82 (s, 3 H, CO_2CH_3), 5.07–5.42 (q, 1 H, J = 7.0 Hz, methine), 6.92–7.41 (m, 5 H, aromatics), and 7.45 (s, 1 H, C_5H).

Anal. Calcd for $C_{22}H_{21}NO_4$ (mol wt, 363.1471): C, 70.21; H, 5.78; N, 3.85. Found (mol wt, 363.1459, mass spectrum): C, 70.09; H, 5.54; N, 4.01.

Thermolysis of (+)-Dimethyl 1-(*S*)-2-(*R*)-Di-*sec*-butyl-2,5-diphenyl-3,8-dihydroazetidino[3,2-*b*]pyridine-6,7-dicarboxylate (6g). A solution of 0.987 g (2 mmol) of the chiral azetidinopyridine **6g** in 50 ml of dry toluene was heated under reflux for 10 hr. Removal of the solvent in vacuo gave a light orange oil which on trituration with hexanes deposited yellowish-white crystals of dimethyl *N*-[1-(*S*)-*sec*-butyl]-2-phenylpyrrole-3,4-dicarboxylate (**10g**, 0.597 g, 94% yield): mp 118–119.5° (MeOH–petroleum ether); NMR δ_{Me_4Si} ($CDCl_3$) 0.71 (t, 3 H, J = 7.0 Hz, $-CH_2CH_3$), 1.33 (d, 3 H, J = 6.5 Hz, $-CH_3$), 1.01–1.86 (m, 2 H, $-CH_2CH_3$), 3.63 (s, 3 H, $-CO_2CH_3$), 3.81 (s, 3 H, CO_2CH_3), 3.36–4.15 (br, 1 H, methine), and 7.17–7.65 (m, 6 H, aromatic and C_5H); absorption spectrum λ_{max} (CH_3CN) 255 nm (log ε 4.04); $[\alpha]^{25}D$ +3.6° (c 9.91, C_6H_6).

Anal. Calcd for $C_{18}H_{21}NO_4$ (mol wt 315.1470): C, 68.55; H, 6.71; N, 4.44. Found (mol wt, 315.1460, mass spectrum): C, 68.44; H, 6.79; N, 4.42.

The filtrate on evaporation gave a yellow oil which was subjected to chromatography on 30 g of B. D. H. alumina. Elution with benzene–chloroform (4:1) gave a light yellow oil, 0.277 g (78% yield), which on trituration with hexanes and on cooling deposited *N*-[*S*-(+)-*sec*-butyl]-2-phenylacetamide (**14g**): mp 57–58.5°; mixture melting point with an authentic sample was undepressed; $[\alpha]^{25}D$ +4.75° (c 10.2, C_6H_6); NMR δ_{Me_4Si} ($CDCl_3$) 0.83 (t, 3 H, J = 6.5 Hz, CH_2CH_3), 1.08 (d, 3 H, J = 6.5 Hz, $-CH_3$), 1.06–1.54 (m, 2 H, $-CH_2CH_3$), 3.58 (s, 2 H, $-CH_2C_6H_5$), 3.62–4.15 (m, 1 H, $-CH_2CH_3$), 5.31–5.92 (br, 1 H, NH, exchangeable with D_2O), and 7.33 (s, 5 H, aromatic); infrared ν_{max} ($CHCl_3$) 1667 cm^{-1} (=O); absorption spectrum (CH_3CN) ν_{max} 270 nm (log ε 2.38), 266 (2.56), and 248 (2.49).

Anal. Calcd for $C_{12}H_{17}NO$: mol wt, 191.1306. Found: mol wt, 191.1308 (mass spectrum).

***N*-[(*S*)-(+)-*sec*-Butyl]-2-phenylacetamide (14g).** To a cold benzene solution of 1.65 g (1 mmol) of phenacyl chloride was added dropwise a benzene solution of 1.62 g (2 mmol) of (*S*)-(+)-*sec*-butylamine **17g** during 30 min. The reaction mixture was set aside at room temperature for 2 hr and then diluted with cold water. The organic layer was washed twice with cold water and dried ($MgSO_4$) and the solvent was removed to give a pale yellow oil. Trituration with hexane and cooling deposited *N*-[(*S*)-(+)-*sec*-butyl]-2-phenylacetamide (**14g**) as white needles: mp 57–58°; $[\alpha]^{25}D$ +4.95° (c 9.95, C_6H_6); NMR δ_{Me_4Si} ($CDCl_3$) 0.83 (t, 3 H, J = 6.5 Hz, CH_2CH_3), 1.07 (d, 3 H, J = 6.5 Hz, $-CH_3$), 1.06–1.54 (m, 2 H, $-CH_2CH_3$), 3.58 (s, 2 H, $-CH_2C_6H_5$), 3.62–4.15 (m, 1 H, $-CH_2CH_3$), 5.31–5.92 (br, 1 H, NH, exchangeable with D_2O), and 7.33 (s, 5 H, aromatic).

Photolysis of (+)-Dimethyl 1-(*S*)-2-(*R*)-Di-*sec*-butyl-2,5-diphenyl-3,8-dihydroazetidino[3,2-*b*]pyridine-6,7-dicarboxylate (6g). An ethereal solution of 1.0 g (2 mmol) of the azetidinopyridine **6g**, $[\alpha]^{25}D$ 4.95° (c 8.35, C_6H_6), in 100 ml of dry ether was cooled in an acetone–Dry Ice bath at −70 to −80° and irradiated with a 200-W Hanovia medium-pressure lamp for 2.25 hr. The progress of the reaction was followed by thin layer chromatography [Eastman alumina fluorescence coated plate using benzene–hexane (1:2) solution] by following the disappearance of the pyridine. Removal of the solvent in vacuo gave a yellow oil which was chromatographed on 50 g of B. D. H. alumina. Elution with hexane–benzene (1:2) gave a light yellow oil (0.603 g) which on trituration with hexane deposited yellowish white crystals (0.503 g, 80% yield) of dimethyl *N*-[(*S*)-(+)-*sec*-butyl]-2-phenylpyrrole-3,4-dicarboxylate (**10g**), mp 118.5–119°, $[\alpha]^{25}D$ +3.2° (c 10.1, C_6H_6).

Continued elution with benzene–chloroform (4:1) gave a light yellow oil (0.201 g, 52% yield) which on trituration with hexanes and on cooling deposited *N*-[(*R*)-*sec*-butyl]-2-phenylacetamide (**14h**), mp 57–58°, $[\alpha]^{25}D$ −3.8° (c 9.95, C_6H_6). A similar experiment was performed with dimethyl 1-(*R*)-1-(*S*)-di-*sec*-butyl-2,5-diphenyl-3,8-dihydroazetidino[3,2-*b*]pyridine-6,7-dicarboxylate (**6h**) giving comparable results (see Table IV).

Photolysis of Dimethyl 2,3-Di-*sec*-butyl-2,5-diphenyl-3,8-dihydroazetidino[3,2-*b*]pyridine-6,7-dicarboxylate [6g(h)]. An ethereal solution of 0.200 g of the racemic azetidinopyridine **6g(h)** in 100 ml of ether was cooled in an acetone–Dry Ice bath (−70 to −80°) and irradiated under N_2 with a 200-W Hanovia medium-pressure lamp for 30 min. Removal of the solvent in vacuo at 15–18° gave a yellow oil which was chromatographed on B. D. H. alumina. Elution with hexane–benzene (4:1) gave a reddish-yellow oil (35 mg) which resisted crystallization and which is assigned structure **7g(h)** tentatively: NMR ($CDCl_3$) δ 0.75–1.84 [m, 14 H, $-CH(CH_3)(CH_2CH_3)$], 2.35–3.31 (m, 4 H, $-CHCH_2CH_3$), 3.76 (s, 6 H, $-CO_2CH_3$), and 7.02–7.68 (m, 12 H, aromatics, two ring protons); ν_{max} ($CHCl_3$) 1710 cm^{-1} (C=O).

Anal. Calcd for $C_{30}H_{36}N_2O_4$: mol wt, 488.2675. Found: mol wt, 488.2665 (mass spectrum).

Further elution with hexane–benzene (1:2) gave dimethyl *N*-*sec*-butyl-2-phenylpyrrole-3,4-dicarboxylate [**10g(h)**], mp 117–119° (60%), and continued elution with benzene–chloroform gave *N*-*sec*-butyl-2-phenylacetamide [**14g(h)**], mp 55–57° (52%).

Thermolysis of Dimethyl1,2-di-*tert*-butyl-2,5-diphenyl-3,8-dihydroazetidino[3,2-*b*]pyridine-6,7-dicarboxylate (6i) in Excess of Dimethyl Acetylenedicarboxylate. A suspension of 0.97 g (2 mmol) of the azetidinopyridine **6i** and 14.2 g (0.1 mol) of **4** was maintained at 75 ± 2° under a nitrogen atmosphere. The solid slowly dissolved and the mixture was then heated for 10 hr. Upon cooling and removing the excess of **4** a dark oil was obtained, which on trituration with methanol deposited the tetramer of **4** (**18**). The latter was collected and the filtrate concentrated and subjected to chromatography on 100 g of B. D. H. alumina. Elution with hexane–benzene (4:1) gave tetramethyl 1,6-di-*tert*-butyl-2,7-diphenyl-1,6-diazecine-3,4,8,9-tetracarboxylate (**25i**), 0.869 g (69% yield), as a light yellow oil: NMR δ_{Me_4Si} ($CDCl_3$) 1.45 [s, 18 h, $C(CH_3)_3$], 3.62 (s, 6 H, CO_2CH_3), 3.68 (s, 6 H, CO_2CH_3), 6.97 (s, 2 H, C_2H and C_7H), and 7.17–7.42 (m, 10 H, aromatic); ν_{max} ($CHCl_3$) 1673 cm^{-1} (ester C=O); mass spectrum *m/e* 630.2962 (calcd for $C_{36}H_{42}N_2O_8$, 630.2941).

Anal. Calcd for $C_{35}H_{42}N_2O_8$: N, 4.42. Found: N, 4.08.

Further elution with benzene gave 0.157 g (25% yield) of the pyrrole **10i**.

Thermolysis of Dimethyl 1,2-Dicyclohexyl-2,5-diphenyl-3,8-dihydroazetidino[3,2-*b*]pyridine-6,7-dicarboxylate (6a) with Excess of Dimethyl Acetylenedicarboxylate. A suspension of 1.10 g (2 mmol) of the pyridine **6a** and 14.2 g (0.1 mol) of **4** was maintained at 100 ± 2° under nitrogen atmosphere. The solid slowly dissolved and the resulting reaction mixture was heated for 14 hr. Removal of the excess of **4** gave a dark red oil, which on trituration with methanol precipitated the tetramer of **4** as a white solid, mp 109–110.5°. The latter was removed by filtration, the filtrate was concentrated, and the residual oil was subjected to chromatography on 100 g of B. D. H. alumina. Elution with hexane–benzene (4:1) gave tetramethyl 1,6-dicyclohexyl-2,7-diphenyl-1,6-diazecine-3,4,8,9-tetracarboxylate (**25b**) as a light yellow oil: 0.35 g (25% yield); NMR δ ($CDCl_3$) 0.82–2.04 (m, 20 H, cyclohexyl), 3.61 (s, 6 H, CO_2CH_3), 3.67 (s, 3 H, CO_2CH_3), 6.90–7.92 (m, 12 H, aromatic, C_2H and C-H).

Anal. Calcd for $C_{40}H_{46}N_2O_8$: mol wt, 682.3588. Found: *mol wt*, 682.3582 (mass spectrum).

Further elution with hexane–benzene (1:3) gave dimethyl *N*-(cyclohexyl)-2-phenyl-5-deuteriopyrrole-3,4-dicarboxylate (**10b**),

0.381 g (56% yield). Continued elution with benzene–chloroform (2:1) gave *N*-cyclohexyl-2-phenylacetamide (**14a**), mp 130–132°, 0.261 g (60% yield).

Reaction of 1,2-Di-*tert*-butyl-2,5-diphenyl-1,2-dihydropyrazine (3i) with Excess of Dimethyl Acetylenedicarboxylate. A suspension of 0.7 g (2 mmol) of dihydropyrazine **3i** and 7.1 g (50 mmol) of **4** was heated at 75 ± 2° for 10 hr. Removal of the excess of **4** in vacuo gave a dark oil which was subjected to chromatography on B. D. H. alumina. Elution with hexane–benzene (4:1) gave the diazecine **25i**, 0.13 g (11% yield).

Further elution with benzene gave 0.38 g (60% yield) of the pyrrole **10i**. Continued elution with benzene–chloroform (9:1) gave *N*-(*tert*-butyl)-2-phenylacetamide (**14i**), 0.195 g (50% yield). Further elution with benzene–chloroform (3:1) gave unreacted dihydropyrazine **3i**, 0.153 g (20% yield).

Thermal Decomposition of Dimethyl 1,2-Di-*tert*-butyl-3,8-dihydroazetidino[3,2-*b*]pyridine-6,7-dicarboxylate with 1 Equiv of Dimethyl Acetylenedicarboxylate. A solution of 0.97 g (2 mmol) of the pyridine **6i** and 0.285 g (2 mmol) of **4** in benzene was heated under reflux for 10 hr. Removal of the solvent and chromatography on B. D. H. alumina gave the diazecine **25i** as a light yellow oil, 52 mg (4% yield). Further elution gave the pyrrole **10i**, 0.54 g (85.7% yield), and *N*-(*tert*-butyl)-2-phenylacetamide (**14i**), 0.273 g (71% yield).

Thermolysis of Dimethyl 1,2-Di-*sec*-butyl-2,5-diphenyl-3,8-dihydroazetidino[3,2-*b*]pyridine-6,7-dicarboxylate with Excess of Dimethyl Acetylenedicarboxylate 6g(h). A suspension of 1.0 g of the racemic pyridine **6g(h)** and 14.2 g of **4** was maintained at 100° under N_2 atmosphere. The solid slowly dissolved and the resulting mixture was heated for 12 hr. Removal of the excess **4** in vacuo gave a dark red oil which on trituration with methanol deposited the tetramer of **4**, mp 108–110°.[22] The latter was removed by filtration, the filtrate concentrated, and the oil was subjected to chromatography on B. D. H. (150 g) alumina. Elution with hexane–benzene (3:1) gave a light yellow oil, 0.302 g (32%), which on trituration and on standing for 1 week deposited yellow solid, mp 135–137°, of tetramethyl 1-*sec*-butyl-2-phenylazepine-3,4,5,6-tetracarboxylate [**26g(h)**]: NMR ($CDCl_3$) δ 0.91 (t, 3 H, J = 6.5 Hz, $-CHCH_2CH_3$), 1.17 (d, 3 H, J = 6.2 Hz, $-CHCH_3$), 1.35–1.81 (m, 2 H, $-CHCH_2CH_3$), 3.15–3.56 (br, 1 H, –CH–), 3.42 (s, 6 H, $-CO_2CH_3$), 3.83 (s, 6 H, $-CO_2CH_3$), and 6.82–7.48 (m, 6 H, aromatic and C_6H); ir ($CHCl_3$) ν_{max} 1715 cm^{-1} (–C=O ester).

Anal. Calcd for $C_{24}H_{27}NO_8$: mol wt, 457.1737. Found: mol wt, 457.1757 (mass spectrum).

Further elution with hexane–benzene (1:2) gave dimethyl *N*-*sec*-butyl-2-phenylpyrrole-3,4-dicarboxylate [**10g(h)**], mp 117–118.5° (51% yield), and continued elution with benzene–chloroform gave *N*-*sec*-butyl-2-phenylacetamide, [**14g(h)**], mp 56–58.5° (46%).

Isolation of *N*-*tert*-Butyl-3-phenylketenimine (12i). Photolysis of dimethyl 2,3-di-*tert*-butyl-2,5-diphenyl-3,8-azetidino[3,2-*b*]pyridine-6,7-dicarboxylate (**6i**) in the manner described for **6g** and distillation of the oil obtained gave the ketenimine **12i**: bp ~100° (0.01 mmHg); NMR ($CDCl_3$) δ 1.28 (s, 9 H, *t*-Bu), 4.74 (s, 1 H, =CH), and 6.90–7.28 (m, 5 H, aromatic); ν_{max} 2020 cm^{-1} (N=C).

Registry No.—**3b**, 56572-07-7; **3c(d)**, 52168-80-6; **3e(f)**, 52168-81-7; **3g(h)**, 56572-08-8; **3i**, 40312-86-5; **4**, 762-42-5; **6a**, 51909-23-0; **6b**, 51852-18-7; **6c(d)**, 52168-82-8; **6e(f)**, 52168-83-9; **6g(h)**, 56572-09-9; **6i**, 51852-19-8; **6j**, 56572-10-2; **6k**, 50743-06-1; **7g(h)**, 56572-11-3; *threo*-(*R*)-**9f**, 56648-88-5; *erythro*-(*R*)-**9f**, 52195-01-4; **10a**, 50743-12-9; **10b**, 56572-12-4; **10c**, 52168-84-0; **10c(d)**, 56613-92-4; **10e(f)**, 56613-93-5; **10f**, 52168-86-2; **10g**, 56572-13-5; **10g(h)**, 56613-94-6; **10i**, 50743-08-3; **10j**, 56572-14-6; **10k**, 50743-07-2; **12i**, 50743-11-8; **13c**, 56572-15-7; **14a**, 10264-08-1; **14c(d)**, 56613-95-7; **14g**, 56572-16-8; **14g(h)**, 56649-69-5; **14h**, 56572-17-9; **14i**, 6941-21-5; **14j**, 5215-54-3; **14k**, 56572-18-0; **15a** (R = C_6H_{11}), 19521-14-3; **15f** (R = α-methylbenzyl), 56572-19-1; **17c**, 156-34-3; **17d**, 51-64-9; **17e**, 3886-69-9; **17f**, 2627-86-3; **17g**, 513-49-5; **25b**, 56572-20-4; **25i**, 56572-21-5; **26g(h)**, 56572-22-6; α,α-dideuterio-2-bromoacetophenone, 56572-23-7; cyclohexylamine-N-d_2, 2523-32-2; α-bromoacetophenone, 70-11-1; 1,2-dibromo-1-cyano-2-phenylethane, 19521-13-2.

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Imidazo[1,5-a]pyrazines. IV. Aromatic Substitution Reactions[1,2]

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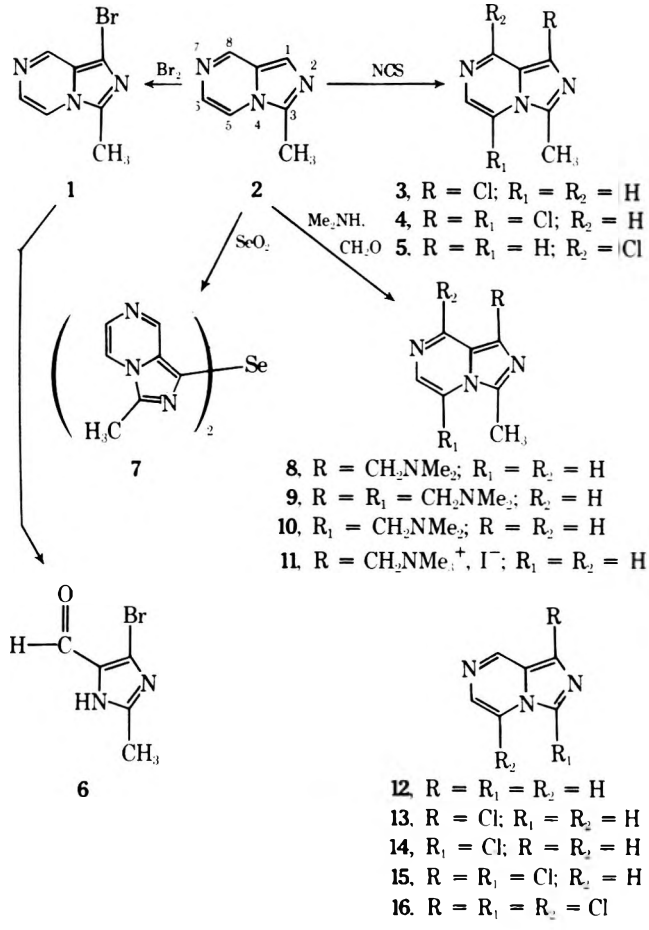
Aromatic substitution reactions on the imidazo[1,5-a]pyrazine nucleus were studied using a variety of electrophilic reagents. Three positions, namely, C-1, C-3 (when there is no substituent), and C-5, were found amenable to electrophilic attack. Chlorination of 3-methylimidazo[1,5-a]pyrazine (2) furnished the 1-chloro derivative (3) as well as the 1,5-dichloro derivative (4). Similarly chlorination of the parent nucleus 12 furnished four derivatives, 13–16, which involved substitution at the C-1, C-3, and (by analogy with 4) C-5. The positions of these substituents were confirmed by ^1H and ^{13}C NMR studies. Other reactions studied included bromination, reaction with selenium dioxide, and the Mannich reaction; in the latter case, the C-5 substitution position in 9 and 10 was assigned by analogy to the chlorination reaction.

Previous papers in this series have described approaches to synthesis of functionally substituted imidazo[1,5-a]pyrazines by way of cyclization of appropriate molecules. A more direct method of functionalization of the heterocyclic system would seem to be available via aromatic substitution reactions on the parent nucleus; this paper describes such studies.

Treatment of the 3-methyl derivative (2)[3] with a limited amount of *N*-chlorosuccinimide (NCS) in carbon tetrachloride with benzoyl peroxide present gave a mixture of two products which could be separated chromatographically. The major product was identified as the 1-chloro-3-methyl derivative (3) by the disappearance of the signal for the C-1 proton[3] from the ^1H NMR spectrum. The second product was the 1,5-dichloro-3-methyl derivative (4) as was shown by analysis of the ^{13}C NMR spectrum (vide infra). The reaction of 2 with iodosobenzene dichloride and with NCS in ethanol also yielded 3, suggesting that the substitution reaction was a normal, electrophilic substitution and that the benzoyl peroxide employed in the initial experiments did not influence the results.

The reaction of 2 with bromine in carbon tetrachloride at ice temperature gave a reasonable yield of the 1-bromo derivative (1); more vigorous conditions led to a mixture of polybrominated products that could not be readily separated. In an effort to prepare a dibromo derivative of 2, the 1-bromo compound (1) was treated with bromine in water and the acid generated was neutralized with excess dilute sodium hydroxide solution. The only product isolated was the imidazole carboxaldehyde (6) presumably resulting from the addition of water across the 7,8 double bond followed by alkaline decomposition of the carbinolamine. Both the chlorine substituent in 3 and the bromine substituent in 1 were resistant to nucleophilic substitution by azide and thiocyanate ions, ammonia, thiourea, or hydrazine. At higher temperatures hydrazine appeared to give ring-opened compounds that could not be characterized. This contrasts with the reactivity of the 8-chloro substituent in 5 which reacted readily with thiourea to give the corresponding thione.[4]

The Mannich reaction[5] was investigated in another attempt to functionalize 2. Reaction with formaldehyde and dimethylamine gave a mixture of products that could be separated chromatographically. The major product was the 1-dimethylaminomethyl derivative (8), isolated as an oil and characterized as its crystalline methiodide, 11. A very small amount of another monosubstituted derivative was separated as well as a disubstituted product and these have



been assigned tentatively the 5 and 1,5 structures (10 and 9, respectively) by analogy with the substitution pattern noted in the dichloro derivative (4).

In an attempt to oxidize the 3-methyl substituent of 2 to a formyl group, the compound was treated with selenium dioxide but the product was that of a substitution reaction, namely the diselenide (7).

The parent compound, imidazo[1,5-a]pyrazine (12), was treated with *N*-chlorosuccinimide in a mixture of chloroform and carbon tetrachloride to give a complex mixture of products that was separated by chromatography. The major products could be identified, on the basis of ^1H NMR spectra, as the 1-chloro compound (13), the 3-chloro compound (14), and the 1,3-dichloro derivative (15). A small amount of a trichloro derivative was isolated and its

Table I
^{13}C NMR Data[a]

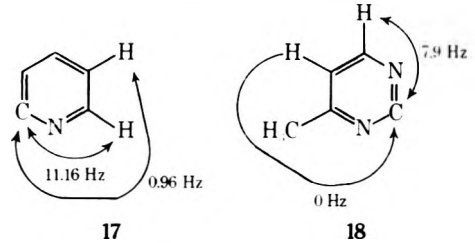
Compd	C_1	C_3	C_5	C_6	C_8	C_9	CH_3
2	123.4 (194, H-1)	136.8	113.5 (186.2, H-5;11.1, H-6)	128.0 (185.1, H-6;5.1, H-5; 12.7, H-8)	145.9 (185, H-8;10.5, H-6)	126.4	12.0
3		135.6	113.6 (188, H-5;13, H-6)	129.2 (186.8, H-6;5, H-5; 13, H-8)	145.3 (188, H-8; second order H-6)	121.8	12.0
4		137.4 (8, CH_3)		128.3 (190, H-6;14, H-8)	143.5 (198, H-8;11, H-6)	124.2	17.0
5	124.6		112.7	126.6			12.5

[a] Chemical shifts are expressed in parts per million downfield from Me_4Si. Data in parentheses refer to coupling constants, in hertz, between the carbon and the indicated proton.

structure is written as the 1,3,5 derivative (16) by analogy with the results of the similar chlorination of 2.

NMR Spectra.[6] The small difference in chemical shift between H-5 and H-6 and the multiplicities of the signal in 2 did not permit an unambiguous assignment, based on ^1H NMR data, of the dichloro product from 2 to the 1,5-dichloro-3-methyl or to the 1,6-dichloro-3-methyl structure, although the 1,8-dichloro-3-methyl structure could be eliminated with confidence. Fortunately, the use of ^{13}C NMR data permitted the compound to be assigned as 1,5-dichloro-3-methylimidazo[1,5-*a*]pyrazine (4). The ^{13}C NMR data of compounds 2–5 are summarized in Table I. Chemical shift assignments in compound 2 were based on chemical transformations as well as analogies with similar compounds. Differences in peak intensities clearly identify quaternary carbons C-9 and C-3 at 126.4 and 136.8 ppm, respectively. Distinction between these two absorptions came from the spectrum of compound 4, where careful decoupling studies were made and which showed a quaternary carbon as a quartet at 137.4 ppm, identifiable as C-3. Absorptions at 123.4 and 145.9 ppm were assigned to C-1 and C-8. These signals were absent in the spectra of compounds 3 and 5, respectively. These two carbons are quaternary in 3 and 5, respectively, and do not experience the full nuclear Overhauser enhancement which exists in the parent compound 2.

The signals at 113.5 and 128.0 ppm were assigned to C-5 and C-6, respectively, based upon the magnitude of the coupling constants between these two absorptions and H-8 (Table I). The higher field absorption showed no detectable coupling while the lower field signal had a coupling constant ($^3J_{C,H}$) of 12.7 Hz. These data find analogy in both the pyridine and pyrimidine systems (17 and 18)



17 18

where $^3J_{C,H}$ and $^4J_{C,H}$ in pyridine were 11 and 1 Hz, respectively,[7] and the same splittings in 4-methylpyrimidine were of similar magnitudes.[8]

The complete assignment of ^{13}C chemical shifts allowed unambiguous determination of the structure of the dichloro compound as 4. The noise decoupled spectrum of this compound lacked the 113.5-ppm signal. In addition a downfield shift (+5.0 ppm) of the C-3 methyl group was observed. This can be attributed to steric interactions between the C-3 and C-5 substituents in a manner similar to that reported for the 4-methyl group (+3.3 ppm) in 1,4,8-trimethyl-5-fluorophenanthrene.[9] A similar shift (+5.9 ppm) was observed for the methyl group in 1-methylnaphthalene[10] when another methyl group was introduced at C-8.[11]

Experimental Section

Melting points (uncorrected) were determined with a Thomas-Hoover capillary apparatus. ^1H NMR spectra were determined on a Varian A-60 apparatus or on a JEOLCO C-60-HL instrument using $CDCl_3$ and Me_4Si unless otherwise noted. ^{13}C NMR spectra were obtained on a Varian CFT-20 NMR spectrometer. Mass spectral molecular weights were obtained from either a Perkin-Elmer RMV-6E or a CEC 24-104 spectrometer. Microanalyses were performed by Microanalysis, Inc., Marshallton, Del. All evaporations were carried out in vacuo using a water aspirator or a water pump and solutions were dried over anhydrous sodium sulfate unless otherwise noted.

1-Bromo-3-methylimidazo[1,5-*a*]pyrazine (1). To a stirred solution of 0.27 g (2 mmol) of 3-methylimidazo[1,5-*a*]pyrazine (2)[1] in 50 ml of carbon tetrachloride at 0° was added, over a period of 5 min, a solution of 0.48 g (3 mmol) of bromine in 50 ml of carbon tetrachloride. After the mixture had been stirred for 10 min the solvent was evaporated and the residue dissolved in 5 ml of water. The aqueous solution was neutralized with 20% aqueous sodium hydroxide and the solution was extracted with three 50-ml portions of chloroform. Evaporation of the dried extracts left a residue that was crystallized from hexane–acetone to give 0.30 g (62%) of 1: mp 119–120°; ^1H NMR δ 2.7 (CH_3, 3 H, s), 7.6 (H-5 and H-6, 2 H, m), 8.8 (H-8, 1 H, broad s).

Anal. Calcd for $C_7H_6BrN_3$: C, 39.62; H, 2.83; N, 19.81; Br, 37.73. Found: C, 39.84; H, 2.90; N, 19.66; Br, 37.80.

1-Chloro-3-methylimidazo[1,5-*a*]pyrazine (3). A mixture of 0.67 g (5.0 mmol) of 2, 0.80 g (6.0 mmol) of *N*-chlorosuccinimide, 0.015 g of benzoyl peroxide, and 100 ml of carbon tetrachloride was heated, with stirring, at reflux for 45 min, then cooled to 0° and filtered to separate the succinimide. The filtrate was evaporated and the residue was transferred to a dry alumina (75 g) column, eluting with dichloromethane. The first fraction yielded 0.015 g (1.5%) of 1,5-dichloro-3-methylimidazo[1,5-*a*]pyrazine (4) and was followed by 0.48 g (56%) of 1-chloro-3-methylimidazo[1,5-*a*]pyrazine (3), which was recrystallized from hexane: mp 102°; ^1H NMR δ 2.6 (CH_3, 3 H, s), 7.5 (H-5 and H-6, 2 H, m), 8.8 (H-8, 1 H, broad s).

Anal. Calcd for $C_7H_6ClN_3$: C, 50.15; H, 3.58; N, 25.07; Cl, 21.19. Found: C, 50.19; H, 3.87; N, 24.95; Cl, 21.13.

1,5-Dichloro-3-methylimidazo[1,5-*a*]pyrazine (4). The above procedure was repeated using 0.5 mmol of 2, 1.1 mmol of NCS, 5 mg of benzoyl peroxide, and 20 ml of carbon tetrachloride. The chromatographic separation yielded 15% of 3 and 20% of 4, which was recrystallized from hexane: mp 90–91°; ^1H NMR δ 3.0 (CH_3, 3 H, s), 7.5 (H-6, 1 H, s), 8.8 (H-8, 1 H, s).

Anal. Calcd for $C_7H_5Cl_2N_5$: C, 41.58; H, 2.47; N, 20.8; Cl, 35.15. Found: C, 41.57; H, 2.61; N, 20.91; Cl, 35.10.

4(5)-Bromo-5(4)-formyl-2-methylimidazole (6). To 0.21 g (1.0 mmol) of 1-bromo-3-methylimidazo[1,5-*a*]pyrazine (1) dissolved in 1 ml of water was added a solution of 0.32 g (2.0 mmol) of

bromine in 20 ml of water. The reaction mixture was then brought to pH 11 by the dropwise addition of 10% aqueous sodium hydroxide solution. The solution was extracted with four 75-ml portions of chloroform–methanol (9:1), and the extracts were dried over potassium carbonate and then evaporated to give a residue which was recrystallized twice from acetone–hexane (1:4) to furnish 0.058 g (31%) of the aldehyde **5**: mp 222–223° dec; ^{1}H NMR δ 2.4 (CH_3, 3 H, s), 9.6 (O=CH, 1 H, s), 13.3 (–NH, 1 H, broad, D_2O exchangeable).

Anal. Calcd for $C_5H_5BrN_2O$: C, 31.77; H, 2.67; N, 14.82; Br, 42.28. Found: C, 32.10; H, 2.75; N, 14.70; Br, 42.86.

1,1′-Selenobis(3-methylimidazo[1,5-*a*]pyrazine) (7). Freshly sublimed selenium oxide (1.11 g, 10.0 mmol) was added to a stirred solution of 1.33 g (10 mmol) of **2** in glacial acetic acid and the reaction mixture was heated under reflux for 2.5 hr. The mixture was cooled and evaporated, giving a residue that was extracted with five 20-ml portions of hot chloroform. The extracts were evaporated and the residue applied to a dry alumina (80 g) column, eluting with chloroform–methanol (99:1). The first fraction yielded 0.20 g of starting material **2** and was followed by 0.60 g (40%) of **7** which was recrystallized from 50% aqueous ethanol: mp 239–240°; ^{1}H NMR δ 2.63 (CH_3, 3 H, s), 7.57 (H-5 and H-6, 2 H, m), 9.13 (H-8, 1 H, broad s).

Anal. Calcd for $C_{14}H_{12}SeN_6$: C, 48.98; H, 3.50; N, 24.65. Found: C, 48.73, H, 3.50; N, 24.48.

Mannich Reaction with 2. A solution of the Mannich reagent was prepared by mixing with mild agitation 45 ml (0.12 mol) of 35% aqueous dimethylamine (precooled to 5°), 15.5 g (0.26 mol) of glacial acetic acid (precooled to 5°), and 20 ml (0.10 mol) of 40% aqueous formaldehyde (precooled to 5°). This solution was added to 9.3 g (0.07 mol) of 3-methylimidazo[1,5-*a*]pyrazine (**2**) contained in the pressure vessel of a low-pressure Parr hydrogenator. The reaction mixture was heated on a steam bath for 2 hr, cooled, and treated with more of the Mannich reagent, prepared as above, from 15 ml of 35% aqueous dimethylamine, 5.2 g of acetic acid, and 6 ml of 40% aqueous formaldehyde. The solution was again heated on the steam bath for 1.5 hr, then cooled and brought to neutrality with 20% aqueous sodium hydroxide. The solution was extracted with five 200-ml portions of chloroform and the extract was dried and evaporated to give 12 g of residue which was applied to a dry alumina (800 g) column using ethyl acetate as the eluent. The first fraction contained 0.090 g (0.07% yield) of an oil, identified by ^{1}H NMR spectrum as 5-dimethylaminomethyl-3-methylimidazo[1,5-*a*]pyrazine (**10**): ^{1}H NMR δ 2.3 (CH_3, 6 H, s), 3.1 (heterocyclic CH_3, 3 H, s), 3.6 (CH_2, 2 H, s), 7.3 (H-6, 1 H, s), 7.8 (H-1, 1 H, s), 8.8 (H-8, 1 H, s); *m/e* 190 (parent), 145 (base). The second fraction afforded 1.3 g (7.5%) of an oil, considered, on the basis of its ^{1}H NMR spectrum, to be 1,5-bis(dimethylaminomethyl)-3-methylimidazo[1,5-*a*]pyrazine (**9**): ^{1}H NMR δ 2.28 (CH_3, 6 H, s), 2.3 (CH_3, 6 H, s), 3.0 (heterocyclic CH_3, 3 H, s), 3.6 (CH_2, 2 H, s), 3.8 (CH_2, 2 H, s), 7.3 (H-6, 1 H, broad s), 9.0 (H-8, 1 H, broad s); *m/e* 247 (parent), 58 (base). The third fraction furnished 5.02 g (38%) of 1-dimethylaminomethyl-3-methylimidazo[1,5-*a*]pyrazine (**8**), again as an oil: ^{1}H NMR δ 2.3 (CH_3, 6 H, s), 2.7 (heterocyclic CH_3, 3 H, s), 3.8 (CH_2, 2 H, s), 7.6 (H-6, 1 H, d, $J_{5,6}$ = 5 Hz), 7.7 (H-5, 1 H, q, $J_{5,6}$ = 5, $J_{5,8}$ = 1.5 Hz), 9.1 (H-8, 1 H, d, $J_{5,8}$ = 1.5 Hz); *m/e* 190 (parent), 147 (base).

(3-Methylimidazo[1,5-*a*]pyrazinyl-1-methyl)trimethylammonium Iodide (11). To a solution of 2.01 g (10.6 mmol) of **8** in 100 ml of acetone was added 4.3 g (30 mmol) of iodomethane. A precipitate formed rapidly and, after 5 min, was separated by filtration and recrystallized from ethanol to give 1.52 g (43%) of **11**: mp 214–215° dec; ^{1}H NMR (Me_2SO-d_6) δ 2.7 (heterocyclic CH_3, 3 H, s), 3.2 (CH_3, 9 H, s), 5.0 (CH_2, 2 H, s), 7.7 (H-6, 1 H, d, $J_{5,6}$ = 5 Hz), 8.3 (H-5, 1 H, q, $J_{5,6}$ = 5, $J_{5,8}$ = 2 Hz), 9.5 (H-8, 1 H, d, $J_{5,8}$ = 2 Hz).

Anal. Calcd for $C_{12}H_{17}IN_4$: C, 39.75; H, 5.10; N, 16.86. Found: C, 39.89; H, 5.10; N, 16.60.

Chlorination of Imidazo[1,5-a]pyrazine (12). A mixture of 5.95 g (0.05 mol) of imidazo[1,5-*a*]pyrazine (**12**), 7.5 g (0.055 mol) of NCS, 100 mg of benzoyl peroxide, 100 ml of chloroform, and 100 ml of carbon tetrachloride was heated at reflux, with stirring, for 10 min, then processed as in the chlorination of **2**. The residue was separated by chromatography on dry alumina (400 g) using dichloromethane as eluent. The first fraction consisted of 1.9 g (23%) of 1,3-dichloroimidazo[1,5-*a*]pyrazine (**15**) which melted at 109° after recrystallization from hexane: ^{1}H NMR δ 7.8 (H-5 and H-6, 2 H, s), 9.0 (H-8, 1 H, broad s).

Anal. Calcd for $C_5H_3Cl_2N_3$: C, 38.30; H, 1.60; N, 22.34; Cl, 37.77. Found: C, 38.56; H, 1.87; N, 22.31; Cl, 38.10.

The second fraction (2.3 g) was a mixture of 1-chloroimidazo[1,5-*a*]pyrazine (**13**) and 3-chloroimidazo[1,5-*a*]pyrazine (**14**) which was separated by preparative thin layer chromatogaphy on alumina using hexane–chloroform (3:2) as eluent. There was obtained 1.2 g (18%) of **14** which was recrystallized from hexane to give mp 136–137° and 0.6 g (9%) of **13** which was recrystallized from acetone–hexane to give mp 128–129°; ^{1}H NMR (for **13**) δ 7.8 (H-6, 1 H, d, $J_{5,6}$ = 5 Hz), 8.0 (H-5, 1 H, q, $J_{5,6}$ = 5, $J_{5,8}$ = 2 Hz), 8.3 (H-3, 1 H, s), 9.0 (H-8, 1 H, broad s); for **14** 7.8 (H-1, H-5, H-6, 3 H, m), 9.0 (H-8, 1 H, broad s).

Anal. Calcd for $C_6H_4ClN_3$: C, 46.91; H, 2.61; N, 27.36; Cl, 23.13. Found (for **13**): C, 47.15; H, 2.90; N, 27.24; Cl, 23.23. Found (for **14**): C, 47.15; H, 2.66; N, 27.31; Cl, 23.07.

The final fraction, eluted with chloroform, consisted of 0.8 g of recovered **12**.

When the chlorination was repeated as above but with 2 molar equiv of NCS, there was obtained, from the first chromatography fraction, a 14% yield of 1,3,5-trichloroimidazo[1,5-*a*]pyrazine (**16**) which was recrystallized from hexane to give mp 89°; ^{1}H NMR δ 7.6 (H-6, 1 H, s), 8.8 (H-8, 1 H, s).

Anal. Calcd for $C_5H_2Cl_3N_3$: C, 32.36; H, 0.90; N, 18.88; Cl, 47.86. Found: C, 32.51; H, 1.18; N, 19.14; Cl, 47.66.

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Registry No.—**1**, 56481-29-9; **2**, 39204-53-0; **3**, 56481-30-2; **4**, 56481-31-3; **6**, 56481-32-4; **7**, 56481-33-5; **8**, 56481-34-6; **9**, 56481-35-7; **10**, 56481-36-8; **11**, 56481-37-9; **12**, 274-49-7; **13**, 56481-38-0; **14**, 56481-39-1; **15**, 56481-40-4; **16**, 56481-41-5; bromine, 7726-95-6; *N*-chlorosuccinimide, 128-09-6; selenium oxide, 7446-08-4; iodomethane, 74-88-4.

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Imidazo[1,5-*a*]pyrazines. V. Electrophilic Addition, a Novel Reissert-Like Reaction[1-3]

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The reaction of imidazo[1,5-*a*]pyrazine (**1a**) and its 3-methyl derivative (**1b**) with acid chlorides and acid anhydrides resulted in addition rather than substitution reactions. Addition was shown to take place at the N-7, C-8 imine bond and in a manner analogous to the Reissert reaction. By varying the acylating reagents and quenching agents a variety of adducts (**3**) were prepared. Structure proof of the adducts was derived by converting **3a** and **3b** to the corresponding 8-chloro derivatives (**9**), which were shown to be susceptible to nucleophilic displacement with thiourea. In one instance the imidazo[1,5-*a*]pyrazine system was also found to be susceptible to hydrolytic cleavage to form imidazole carboxaldehydes. A possible mechanism for the addition and cleavage reactions is presented.

Electrophilic substitutions of the imidazo[1,5-*a*]pyrazine system were visualized as a convenient route for the functionalization of the nucleus. Previous studies[2] on this system have shown it, like other related systems,[4] to be susceptible to such reactions. This work describes the extension of these reactions to acid chlorides and anhydrides where a novel Reissert-like addition, rather than substitution, reaction has taken place.

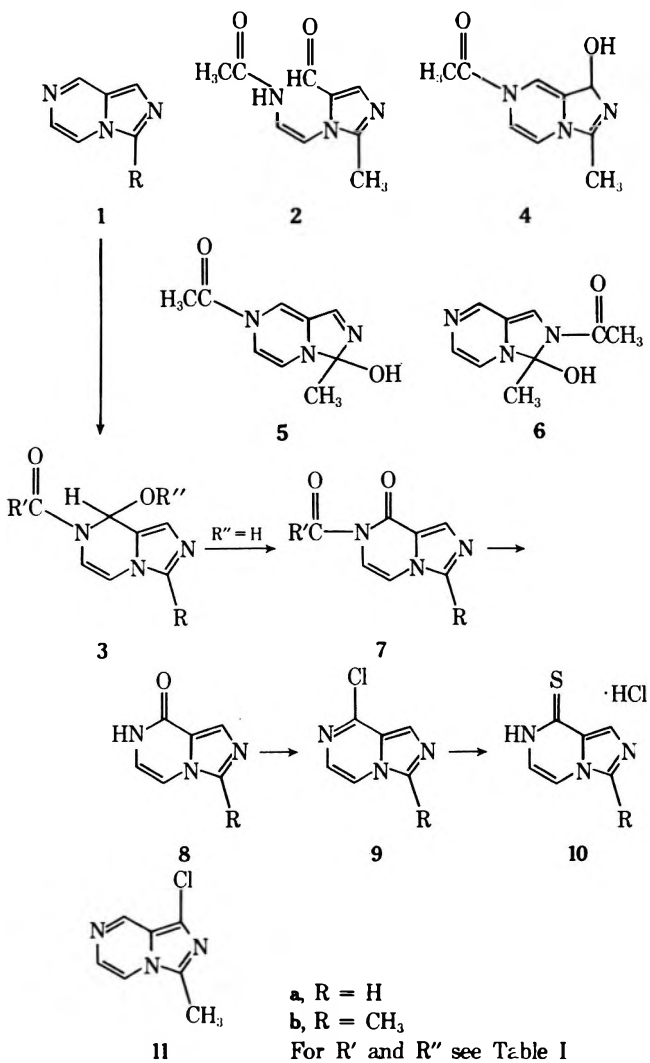
When compound **1b** was treated with acetyl chloride, or acetic anhydride, followed by aqueous work-up, the product isolated, in moderate yields, did not exhibit the spectral properties expected of an acetyl-substituted imidazo[1,5-*a*]pyrazine. The product had two methyl groups and a carbonyl band in the ^{1}H NMR and ir spectra, respectively. Its mass spectrum as well as elemental analysis indicated that the product obtained was an adduct of acetic acid to the starting material.

Five possible structures (**2–6**) can be written for this adduct (Scheme I). One of these (**2**) can be ruled out from the NMR data since no aldehydic proton was observed. Differentiation between the four remaining structures (**3–6**) came from further chemical transformations outlined in Scheme I. Jones oxidation of the adducts (**3a** or **3b**) afforded products (**7a** and **7b**) whose mass spectrum showed a molecular ion two units less than that of the parent compounds.[5] This, along with other physical data, clearly showed that formulas **5** and **6** could not represent the correct structure of the adducts.

Final confirmation of the structure as **3** rather than **4** came from converting the oxidation product to the chloro compounds (**9a** and **9b**). Alcoholysis of the imides (**7**) furnished the lactams (**8**) which were identical with those obtained from the rearrangement of the 7-oxides.[6] Treatment with phosphoryl chloride gave chloro derivatives (**9**) whose spectral and chemical properties were different from those of the known 1-chloro compounds (**11**).[2]

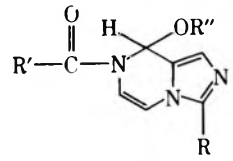
This novel addition finds analogy in the Reissert reaction.[7] Initial formation of an amide results in the generation of a carbonium ion (**12**) which is quenched by water to form the product. Cyanide ion failed to generate the corresponding cyano derivative. Preferential reactivity at N-7 rather than at C-1 as was previously observed[2] can best be explained by assuming that generation of **12** is kinetically favored over **13** as in electrophilic substitution at C-1. However, in the case of other electrophiles [(Cl_2, *N*-chlorosuccinimide (NCS), Br_2, $CH_2{=}N^+(CH_3)_2$)], the initial formation of a carbonium ion at C-8 (**14**) is in equilibrium

Scheme I



with the starting material, thus allowing the thermodynamic products to be formed. In an attempt to trap **14** (X = Cl), compound **1** was treated with 1 equiv of NCS in methanol. An unstable product was formed as evidenced by thin layer chromatography. However, upon the addition of 2 equiv of NCS a product was isolated in very poor yield whose NMR and mass spectral data strongly support the assigned diad-

Table I

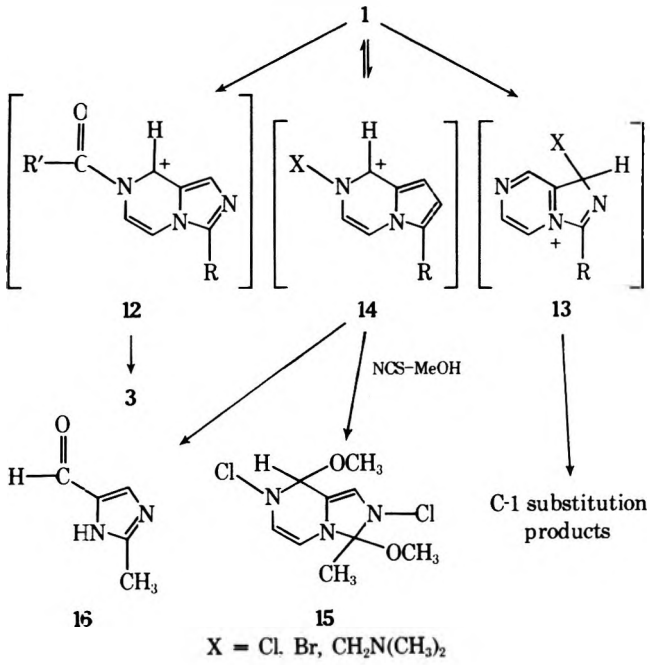


3

Compd (% yield)[a]	R	R′	R″	Mp, °C (solvent)	Elemental analysis found (calcd) C	H	N
3a (91)	H	OC_2H_5	H	163–165 (Me_2SO–H_2O)	51.56 (51.67)	5.46 (5.26)	19.97 (20.10)
3b (41)	CH_3	CH_3	H	168–169 (MeOH–ether)	56.27 (55.96)	5.85 (5.70)	21.50 (21.76)
3c (58)	CH_3	CH_3	CH_3	129–131 ($CHCl_3$–hexane)	57.89 (57.97)	6.35 (6.28)	20.02 (20.29)
3d (42)	CH_3	CH_3	C_2H_5	96–97 (ether–hexane)	59.51 (59.73)	6.75 (6.79)	18.46 (19.00)
3e (51)	CH_3	OC_2H_5	H	208 dec (Me_2SO)	53.80 (53.81)	5.82 (5.83)	18.54 (18.83)
3f (30)	CH_3	OC_2H_5	CH_3	103–105 (hexane–$CHCl_3$)	55.52) (55.70)	6.46) (6.33)	17.66 (17.72)
3g (15)	CH_3	OC_2H_5	C_2H_5	97–98 (ether–hexane)	57.59 (57.37)	6.59 (6.77)	16.53 (16.73)
3h (65)	CH_3	*p*-$NO_2C_6H_4$	H	166–167 (MeOH–$CHCl_3$)	56.24 (56.00)	4.04 (4.00)	18.35 (18.63)
3i (50)	CH_3	*p*-$NO_2C_6H_4$	C_2H_5	145–147[b]	58.27 (58.54)	4.71 (4.88)	17.08 (17.07)
3j (50)	CH_3	*p*-$NO_2C_6H_4$	*p*-$NO_2C_6H_4CO$	153–155 (MeOH)[c]	55.89 (56.12)	3.62 (3.34)	15.64 (15.59)

[a] Yield of purified product. [b] Purified by silica gel chromatography. [c] Assumed to be formed from 3h with excess acylating reagent.

Scheme II



duct structure (**15**). The compound was not stable enough for elemental analysis. The trapping experiment was repeated using aqueous sodium hypochlorite. In this case cleavage of the pyrazine ring took place to form the known aldehyde **16**.[8] This cleavage offers a new and useful approach to the synthesis of substituted imidazole carboxaldehydes (Scheme II).[9]

Further support for the proposed rationalization can be derived from both ^1H and ^{13}C NMR data, which showed H-8[6] as well as C-8[2] as the most deshielded nuclei in the imidazo[1,5-*a*]pyrazine nucleus. This strongly suggests that N-7 is more electronegative than either N-2 or N-4. Similar observations in related systems have been reported recently.[10]

The generality of this reaction is shown by the variety of compounds prepared using various acylating agents and quenching compounds and tabulated in Table I.

Unlike previously prepared chloroimidazo[1,5-*a*]pyrazines,[2] the 8-chloro derivatives are amenable to nucleophilic attack. Mild treatment of **9a** and **9b** with thiourea furnished the corresponding 8-thiones (**10a** and **10b**) in good yields. This displacement clearly demonstrates the utility of this method for the preparation of other C-8 derivatives.

Experimental Section

Melting points (uncorrected) were determined with a Thomas-Hoover capillary apparatus. ^1H NMR spectra were determined on a Varian A-60 or on a JEOLCO C-60-HL spectrometer using $CDCl_3$ and Me_4Si unless otherwise indicated. Mass spectral fragmentations were obtained from either a Perkin-Elmer RMV-6E or CEC 24-104 mass spectrometer. Microanalyses were performed by MicroAnalysis, Inc., Marshallton, Del. All evaporations were carried out in vacuo using a water aspirator and solutions were dried over anhydrous magnesium sulfate unless otherwise noted. In the NMR spectra resonances were assigned whenever possible.

7-Acetyl-8-hydroxy-3-methyl-7,8-dihydroimidazo[1,5-*a*]pyrazine (3b). *The preparation of this compound serves as a general procedure for all adducts* (*3*). To 3-methylimidazo[1,5-*a*]pyrazine (**1b**, 1.33 g, 10 mmol) in dichloromethane (25 ml) was added acetic anhydride (2 ml) (or acetyl chloride) dropwise and with stirring. After a few minutes water (25 ml) was added and stirring was continued for 0.5 hr. Evaporation of the organic solvent was followed by the addition of water (50 ml) and neutralization with sodium bicarbonate. Extraction with an 8% methanol–chloroform mixture (100 ml × 3) and subsequent work-up gave the product: ^1H NMR δ 2.40 (CH_3, 6 H, s), 3.21–3.31 (CH_3, 3 H, broad, s),

6.31–7.11 (H-1, H-5, H-6, and H-8, 4 H, m); ir (KBr) 1670 cm^{-1}; mass spectrum *m/e* (rel intensity) 193 (M^+, 32), 176 (10), 151 (25), 134 (100).

When methanol or ethanol were used to quench the reaction, the corresponding 8-methoxy (**3c**) and 8-ethoxy (**3d**) derivatives were obtained.

7-Acetyl-3-methylimidazo[1,5-*a*]pyrazin-8(7*H*)-one (7b, R′ = CH_3). To 7-acetyl-8-hydroxy-3-methyl-7,8-dihydroimidazo[1,5-*a*]pyrazine (**3b**, 0.19 g, 1 mmol) suspended in cold (10°) acetone (20 ml) was added Jones reagent[11] (0.4 ml) dropwise with vigorous stirring. After 5 min the reaction mixture was concentrated under reduced pressure to small volume and mixed with ice (5 g). The water solution was extracted with chloroform (50 ml × 5). The residue obtained on evaporation of chloroform was filtered through a short silica gel column with chloroform as eluent to give the product as a white, crystalline solid (0.08 g, 42% yield): mp 174–176°; ^1H NMR δ 2.47 (CH_3, 3 H, s), 2.53 (CH_3, 3 H, s), 6.68 and 7.40 (H-5 and H-6, 2 H, doublets, J = 6 Hz), and 7.83 (H-1, 1 H, s); ir (KBr) 1740, 1720, and 1690 cm^{-1} (C=O); mass spectrum m/e (rel intensity) 191 (M^+, 20), 150 (12), 149 ($M^+ - CH_2{=}C{=}O$, 100), 148 (12), 122 (8), and 109 (8).

Anal. Calcd for $C_9H_9N_3O_2$: C, 56.54; H, 4.71; N, 21.98. Found: C, 56.79; H, 4.94; N, 21.79.

7-Carboethoxyimidazo[1,5-*a*]pyrazin-8(7*H*)-one (7a, R′ = OEt). The procedure followed was essentially that for preparation of **7b**. Thus, 7-carboethoxy-8-hydroxy-7,8-dihydroimidazo[1,5-*a*]pyrazine (**3a**, 0.93 g, 4.4 mmol) was mixed with Jones reagent (1.6 ml). Upon work-up a white, crystalline solid (0.37 g, 40% yield) was obtained: mp 171–172°; ^1H NMR δ 1.47 (CH_3, 3 H, t), 4.50 (CH_2, 2 H, q), 7.17 and 7.29 (H-5 and H-6, 2 H, doublets, J = 6 Hz), 7.93 and 8.05 (H-1 and H-3, 2 H, s); ir (KBr) 3100, 1750, and 1680 cm^{-1} (C=O).

Anal. Calcd for $C_9H_9N_3O_3$: C, 52.17; H, 4.35; N, 20.29. Found: C, 52.34; H, 4.28; N, 20.28.

Imidazo[1,5-*a*]pyrazin-8(7*H*)-one (8a). The imide (**7a**, R′ = OEt) (0.3 g, 1.45 mmol) was dissolved in ethanol (10 ml), refluxed for 1 hr, and the solution evaporated to dryness. The residue, washed once with dichloromethane–ethyl ether (1:3) (50 ml), was filtered through a short silica gel column with chloroform–methanol (92:8) as eluent to give the product as a white, crystalline solid (0.18 g, 91% yield): mp 270° dec; ^1H NMR (Me_2SO-d_6) δ 6.75 (1 H, m), 7.5 (1 H, d), 7.87 and 8.35 (H-1 and H-3, 2 H, s), and 10.67 (broad, 1 H, deuterium oxide exchangeable).

Anal. Calcd for $C_6H_5N_3O$: C, 53.33; H, 3.70; N, 31.11. Found: C, 53.08; H, 3.87; N, 30.95.

3-Methylimidazo[1,5-*a*]pyrazin-8(7*H*)-one (8b). This was prepared as indicated for **8a** from **7b** (R′ = CH_3) (0.48 g, 2.5 mmol) in quantitative yield: mass spectrum *m/e* (rel intensity) 149 (M^+, 100), 122 (8), 109 (10), 81 (15), 80 (20), and 153 (45); mp 280° dec.

Anal. Calcd for $C_7H_7N_3O$: C, 56.38; H, 4.70; N, 28.19. Found: C, 56.48; H, 4.89; N, 28.06.

8-Chloroimidazo[1,5-*a*]pyrazine (9a). The lactam **8a** (0.4 g, 2.9 mmol) was added to phosphoryl chloride (25 ml) and heated on an oil bath (135°) for 1 hr. The residue after evaporation was dissolved in ice water (10 ml). The water solution was neutralized with 5% sodium bicarbonate and extracted with dichloromethane (50 ml × 5). Evaporation of the dried dichloromethane extract gave the product as a slightly orange solid (0.21 g, 47% yield), mp 100–103°. The analytical sample was obtained by recrystallization from ether–hexane as needles: mp 105–106°; ^1H NMR δ 7.48 and 7.91 (H-5 and H-6, 2 H, doublets, J = 6 Hz), 7.97 (H-1, 1 H, broad), 8.38 (H-3, 1 H, broad); uv (EtOH) λ_{max} 268 nm (ε 2000), 278 (2500), 289 (2200), and 350 (1700); ir ($CHCl_3$) 2950, 1600, 1500, 1450, 1430, and 1340 cm^{-1}; mass spectrum *m/e* (rel intensity) 155 (33), 153 (100), 156 (3), 154 (9), 128 (3), 126 (7), 118 (14), 117 (32), 101 (9), and 99 (18).

Anal. Calcd for $C_6H_4ClN_3$: C, 46.91; H, 2.61; N, 27.36; Cl, 23.13. Found: C, 46.98; H, 2.79; N, 27.27; Cl, 23.33.

8-Chloro-3-methylimidazo[1,5-*a*]pyrazine (9b). This was prepared from **8b** (0.3 g, 2.1 mmol) in a manner similar to that for **9a** in 74% yield, mp 126–127°.

Anal. Calcd for $C_7H_6ClN_3$: C, 50.15; H, 3.58; N, 25.07; Cl, 21.19. Found: C, 50.40; H, 3.81; N, 24.89; Cl, 21.15.

3-Methylimidazo[1,5-*a*]pyrazine-8(7*H*)-thione Hydrochloride (10b). An ethanol solution (10 ml) of 8-chloro-3-methylimidazo[1,5-*a*]pyrazine (**9b**, 85 mg, 0.5 mmol) and thiourea (40 mg, 0.5 mmol) was refluxed for 10 min. Upon cooling the product crystallized and was filtered (74 mg, 75% yield): mp 305°; ^1H NMR (CF_3COOH) δ 2.98 (CH_3, 3 H, s), 7.07 (1 H, d, J = 6 Hz), 7.45 (1 H, m, J = 6 Hz), and 8.26 (H-1, 1 H, s).

Anal. Calcd for $C_7H_8ClN_3S$: C, 41.69; H, 3.97; N, 20.84. Found: C, 42.24; H, 4.06; N, 20.61.

Imidazo[1,5-*a*]pyrazine-8(7*H*)-thione Hydrochloride (10a). This was prepared from **9a** as in the preparation of **10b** to give a 94% yield of yellow needles, mp >310°.

Anal. Calcd for $C_6H_6ClN_3S$: C, 38.40; H, 3.20; N, 22.40. Found: C, 38.49; H, 3.17; N, 22.59.

2,7-Dichloro-3,8-dimethoxy-3-methyl-2,3,7,8-tetrahydroimidazo[1,5-*a*]pyrazine (15). A solution of 3-methylimidazo[1,5-*a*]pyrazine (**3b**, 0.55 g, 5 mmol) and *N*-chlorosuccinimide (1.34 g, 10 mmol) in methanol (50 ml) was allowed to stand at room temperature for 3 days. Evaporation of the methanol followed by dry column chromatography (silica gel, 5% methanol in chloroform as eluent) gave a yellow gum which was mainly a mixture of two compounds as indicated by thin layer chromatography (silica gel, using 4% methanol in chloroform). A small quantity (19 mg) of the compound (R_f 0.63] was obtained from several TLC plates and appeared as a yellow gum, which could not be further purified owing to decomposition: ^1H NMR δ 2.71 (CH_3, 3 H, s), 3.53 (CH_3, 3 H, s), 4.02 (CH_3, 3 H, s), 4.65 (1 H, s), 5.34 (1 H, d, J = 1 Hz), 6.07 (1 H, d, J = 1 Hz), and 7.43 (1 H, s); ir ($CHCl_3$) 2950, 1630, and 1330 cm^{-1}; mass spectrum *m/e* (rel intensity) 267 (2), 265 (2.5), 236 (10), 234 (17), 231 (30), 229 (82), 216 (33), 214 (100), 194 (50.

The second spot (R_f 0.58) was insufficient for characterization.

2-Methylimidazole-4(5)-carboxaldehyde (16). To an ice-cooled solution of 3-methylimidazo[1,5-*a*]pyrazine (**3b**, 0.53 g, 4 mmol) in water (10 ml) was added 5% sodium hypochlorite solution (30 ml) with stirring. After 5 min the ice bath was removed and the reaction mixture was stirred for another 5 min. The water solution was washed with ether (30 ml) and evaporated to dryness. The residue was heated with methanol (20 ml) and the insoluble material was discarded. Evaporation of the methanol solution followed by filtration through a short silica gel column with chloroform–methanol (92:8) as eluent gave a white, crystalline solid (156 mg, 40% yield): mp 159° dec; ir (KBr) 3130 (–NH), 3040, 2900, 2750 (CH), and 1670 cm^{-1} (C=O); ^1H NMR (Me_2SO-d_6) δ 1.35 (CH_3, 3 H, s), 7.83 (2 H, broad, s, one is D_2O exchangeable), and 9.65 (1 H, s). This material agrees in spectral characteristic and physical properties with the product from irradiation of 2-methylpyrimidine *N*-oxide (lit.[8] mp 160–162°).

Registry No.—**1b**, 39204-53-0; **3a**, 56468-09-8; **3b**, 56468-10-1; **3c**, 56468-11-2; **3d**, 56468-12-3; **3e**, 56468-13-4; **3f**, 56468-14-5; **3g**, 56468-15-6; **3h**, 56468-16-7; **3i**, 56468-17-8; **3j**, 56468-18-9; **7a** (R′ = OEt), 56468-19-0; **7b** (R′ = CH_3), 56468-20-3; **8a**, 56468-21-4; **8b**, 56468-22-5; **9a**, 56468-23-6; **9b**, 56468-24-7; **10a**, 56468-25-8; **10b**, 56468-26-9; **15**, 56468-27-0; **16**, 35034-22-1; phosphoryl chloride, 10025-87-3; *N*-bromosuccinimide, 128-08-5.

References and Notes

(1) This work was supported by Contract NIH-71-2312 from the Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, Department of Health, Education and Welfare.

(2) Part IV: E. Abushanab, A. P. Bindra, D.-Y. Lee, and L. Goodman, *J. Org. Chem.*, preceding paper in this issue.

(3) Taken in part from the Ph.D. Thesis of D.-Y. Lee, University of Rhode Island, 1975.

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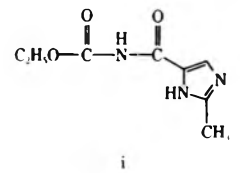

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Imidazo[1,5-a]pyrazines. VI. 3-Thio Derivatives[1,2]

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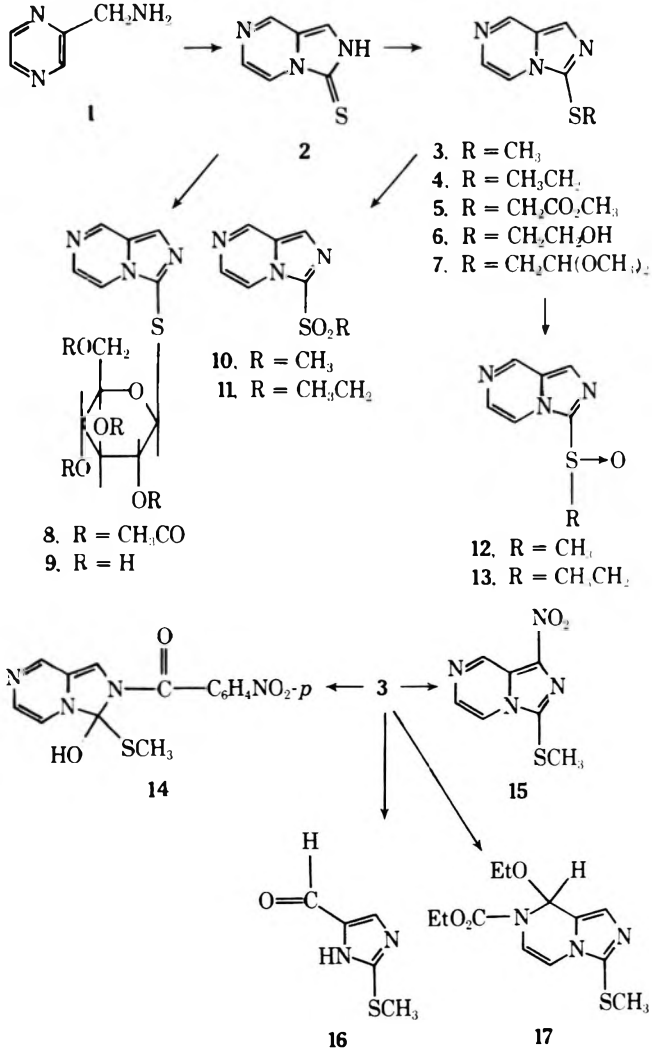
The imidazo[1,5-a]pyrazinthione 2 is prepared from pyrazinemethanamine and CS_2. A number of alkylthioimidazopyrazines and derivatives are described.

Previous papers in this series have described our efforts to prepare functionalized derivatives of the imidazo[1,5-a]pyrazine system. In a continuation of these studies a number of 3-thioimidazo[1,5-a]pyrazines were prepared both for their intrinsic interest as possible antitumor agents and for study as substrates in nucleophilic displacements reactions for further modification of the heterocyclic system.

The parent compound **2** was prepared in excellent yield by reaction of the amine **1**[3] with carbon disulfide. This reaction was patterned after the work of Albert and Ohta,[4] who reported that the reaction of carbon disulfide with 2-amino-3-aminomethylpyrazine yielded 8-aminoimidazo-[1,5]pyrazine-3-thiol. Alkylation of **2** proceeded smoothly to give high yields of **3–7**. Efforts to form a tricyclic compound from **7**, after acid hydrolysis, did not lead to a characterizable product. The alkylated derivatives (**3** and **4**) did not react with *n*-butylamine, cyanide ion, or azide ion in attempted displacement reactions and the oxidized derivatives (**10–13**), prepared with *m*-chloroperbenzoic acid, were also unreactive tc these reagents. That oxidation had taken place at sulfur rather than nitrogen in **10–13** was evident both from NMR and mass spectral data. Thus there was the expected downfield shift of the methyl groups in the sulfoxide **12** and the sulfone **10** accompanied by a large deshielding effect on the H-5 proton. The mass spectra of **12** showed the typical M − 15 peak characteristic of methyl sulfoxides[8] while lacking the characteristic peak due to loss of oxygen in *N*-oxides;[9] the mass spectrum of **10** showed a major loss of the CH_3SO_2 moiety. Alkylation of **2** with acetobromoglucose gave a reasonable yield of the nucleoside-like compound **8** whose structure is written on the basis of the "trans rule".[10] Deacetylation with methanolic sodium methoxide afforded **9**.



A brief study was made of the reaction of the methyl sulfide (**3**) with electrophilic reagents. Reaction with nitrosonium tetrafluoroborate in acetonitrile gave a low yield of the 1-nitro derivative (**15**) apparently as the result of further oxidation of an initially formed 1-nitroso compound. There is literature precedent for such a reaction.[11] The reaction of **3** with aqueous nitrous acid resulted in pyrazine ring cleavage to give a low yield of the aldehyde **16**. Apparently the initial attack of the electrophilic agent occurred by reaction at the N-7–C-8 double bond. Indeed, when **3** was treated with ethyl chloroformate and the reaction mixture quenched with ethanol the product was the addition product **17**, completely analogous to the addition products noted with similar reactions of imidazo[1,5-a]pyrazine and 3-methylimidazo[1,5-a]pyrazine.[2] Curiously, when **3** was treated with *p*-nitrobenzoyl chloride and the reaction mixture was quenched with water the product resulted from addition across the N-2–C-3 double bond to give **14** whose aromatic protons did not experience the usual upfield shift when addition takes place at N-7–C-8[2]. Rather, their chemical shifts and coupling constants were very similar to those of the methyl sulfide **3**.

Experimental Section

Melting points (uncorrected) were determined with a Thomas-Hoover capillary apparatus. Ultraviolet data were obtained on a Cary 15 spectrophotometer in ethanol. NMR spectra were determined on a Varian A-60 or a JEOLCO C-60-HL instrument using deuteriochloroform, unless otherwise noted, and tetramethylsilane as the internal standard. Mass spectral data were obtained from a CEC 24-104 spectrometer. Microanalyses were performed by MicroAnalysis, Inc., Marshallton, Del. All evaporations were carried out in vacuo using a water aspirator or a vacuum pump and solutions were dried over anhydrous potassium carbonate unless otherwise noted. Only pertinent spectral data for key compounds are included in the experimental details.

Imidazo[1,5-a]pyrazine-3(2*H*)-thione (2). To the amine **1** [freshly generated from its hydrochloride (5 g, 34.4 mmol) and triethylamine (5.2 ml, 36 mmol)] in 100 ml of methanol was added 15

ml of carbon disulfide and the reaction mixture was heated at reflux for 12 hr. Evaporation of the solvent furnished a residue which was dissolved in 0.5 *N* aqueous sodium hydroxide (100 ml) and the solution was filtered. The filtrate was adjusted to pH 7 with 6 *N* hydrochloric acid and the precipitate (4.1 g, 80%) after washing with water and acetone, was collected by filtration: mp 209° dec; uv (95% EtOH) 245 nm (ε 9400), 298 (9870), 308 (s), 400 (1350); ^{1}H NMR (Me_2SO-d_6) δ 7.88 (H-6, 1 H, d, $J_{5,6}$ = 5 Hz), 7.87 (H-1, 1 H, s), 7.95 (H-5, 1 H, m), 8.91 (H-8, 1 H, d, $J_{5,8}$ = 2 Hz).

Anal. Calcd for $C_6H_5N_3S$: C, 47.66; H, 3.31; N, 27.81; S, 21.19. Found: C, 47.72; H, 3.42; N, 27.49; S, 21.04.

3-Methylthioimidazo[1,5-*a*]pyrazine (3). A solution of the sodium salt of **2** was prepared by mixing 12.08 g (80 mmol) of **2** and 6.0 g (80 mmol) of 85% potassium hydroxide in 300 ml of methanol with stirring to dissolve the solids. Methyl iodide (12.0 g, 84 mmol) was added and the solution was stirred at room temperature for 12 hr, then evaporated. The residue was extracted with four 100-ml portions of ether, the extracts dried and evaporated, and the residue distilled in vacuo to give 11 g (85%) of distillate as a yellow oil that turned reddish on standing, bp 102–105° (0.05 mm). The oil solidified on cooling: mp 34–35°; uv (95% EtOH) 275 nm (s), 285 (ε 7590), 295 (6435), 345 (1690); ^{1}H NMR δ 2.68 (CH_3, 3 H, s), 7.71 (H-6, 1 H, d, $J_{5,6}$ = 5 Hz), 7.93 (H-5, 1 H, m), 8.0 (H-1, 1 H, s), 9.10 (H-8, 1 H, d, $J_{5,8}$ = 2 Hz); MS *m/e* (rel intensity) M^+ 165 (82), 150 ($M^+ - CH_3$, 87), 106 ($M^+ - C_2H_3S$, 100).

Anal. Calcd for $C_7H_7N_3S$: C, 50.89; H, 4.27; N, 25.43; S, 19.41. Found: 50.64; H, 4.15; N, 25.32; S, 19.47.

3-Ethylthioimidazo[1,5-*a*]pyrazine (4). The preparation was conducted as above using 3.02 g (20 mmol) of **2** and giving 4.3 g (90%) of **4** as a yellow oil, bp 97–98° (0.01 mm), that solidified on standing, mp 35–36°.

Anal. Calcd for $C_8H_9N_3S$: C, 53.61; H, 5.06; N, 23.44; S, 17.89. Found: C, 53.82; H, 5.03; N, 23.29; S, 17.62.

3-(Carbomethoxymethyl)thioimidazo[1,5-*a*]pyrazine (5). The preparation was conducted as for **3** using 2.27 g (15 mmol) of **2** and 2.30 g (15 mmol) of methyl bromoacetate to give, after crystallization from hexane, 1.99 g (59%) of **5**, mp 81–82°.

Anal. Calcd for $C_9H_9N_3O_2S$: C, 48.42; H, 4.06; N, 18.82; S, 14.37. Found: C, 48.82; H, 4.08; N, 18.43; S, 13.93.

3-(2-Hydroxyethyl)thioimidazo[1,5-*a*]pyrazine (6). Reaction, as above, of 1.51 g (10 mmol) of **2** and 1.38 g (11 mmol) of bromoethanol gave, after crystallization from acetone–hexane, 1.5 g (77%) of **6**, mp 99–100°.

Anal. Calcd for $C_8H_9N_3OS$: C, 49.23; H, 4.61; N, 21.54; S, 16.41. Found: C, 49.38; H, 4.82; N, 21.23; S, 16.15.

3-(2,2′-Dimethoxyethyl)thioimidazo[1,5-*a*]pyrazine (7). Reaction, as above, of 3.02 g (20 mmol) of **2** and 3.72 g (22 mmol) of bromoacetaldehyde dimethyl acetal gave 3.95 g (83%) of **7** as a yellow oil, bp 130° (0.01 mm).

Anal. Calcd for $C_{10}H_{13}N_3O_2S$: C, 50.23; H, 5.44; N, 17.58; S, 13.41. Found: C, 50.01; H, 5.69; N, 17.49; S, 13.16.

Imidazo[1,5-*a*]pyrazin-3-yl 1-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)sulfide (8). To a filtered solution of 0.66 g (10 mmol) of 85% potassium hydroxide in 50 ml of methanol was added 1.7 g (11.3 mmol) of **2**, and the solution was stirred at room temperature for 6 hr, then evaporated. The residue was suspended in 15 ml of water and the aqueous mixture extracted with five 100-ml portions of chloroform. The combined extracts were washed with 50 ml of water, dried, and evaporated to give 2.5 g (52%) of yellow needles, mp 144–146°. Three recrystallizations from acetone–hexane gave the analytical sample, mp 153–154°.

Anal. Calcd for $C_{20}H_{23}N_3O_9S$: C, 49.89; H, 4.82; N, 8.73; S, 6.66. Found: C, 50.12; H, 4.69; N, 8.64; S, 6.41.

Imidazo[1,5-*a*]pyrazin-3-yl 1-(β-D-Glucopyranosyl)sulfide (9). To a solution of 0.48 g (1 mmol) of **8** in 30 ml of methanol was added 2 mg of sodium and the mixture was stirred at room temperature for 12 hr. Ammonium chloride (2 mg) was added, the solvent was evaporated, and the residue was triturated with 2 ml of cold (0°) water, filtered, and dried to give 0.32 g (100%) of **9**, mp 112–116°.

Anal. Calcd for $C_{12}H_{15}N_3O_5S$: C, 46.00; H, 4.83; N, 13.41; S, 10.23. Found: C, 46.29; H, 4.91; N, 13.21; S, 10.00.

3-Methylsulfonylimidazo[1,5-*a*]pyrazine (10). A solution of *m*-chloroperbenzoic acid (15.0 g, 75 mmol) in 150 ml of chloroform was added to a stirred solution of **3** (4.13 g, 25 mmol) in 100 ml of chloroform. The mixture was stirred at room temperature for 1.5 hr, washed with two 50-ml portions of saturated aqueous sodium bicarbonate, dried, and evaporated. The residue was crystallized from acetone–hexane to give 2.5 g (50%) of **10**: mp 138–139°; ^{1}H NMR (Me_2SO-d_6) δ 3.63 (CH_3, 3 H, s), 8.30 (H-1, 1 H, d, $J_{1,5}$ = 1 Hz), 8.10 (H-6, 1 H, d, $J_{5,6}$ = 5 Hz), 8.90 (H-5, 1 H, m), 9.53 (H-8, 1 H, d, $J_{5,8}$ = 2 Hz); MS *m/e* (rel intensity) M^+ 197 (100), 118 ($M^+ - CH_3SO_2$, 100, confirmed by m* 70.6).

Anal. Calcd for $C_7H_7N_3O_2S$: C, 42.63; H, 3.58; N, 21.31. Found: C, 42.68; H, 3.63; N, 21.32.

3-Ethylsulfonylimidazo[1,5-*a*]pyrazine (11). Using essentially the same procedure as above and purifying the residue by dry column chromatography (Woelm alumina, 18 × 1 in. column) with 2% methanol in chloroform as eluent, there was obtained 4.7 g (74%) of **11**, mp 63–64° after recrystallization from acetone–hexane.

Anal. Calcd for $C_8H_9N_3O_2S$: C, 45.50; H, 4.26; N, 19.90; S, 15.17. Found: C, 45.50; H, 4.40; N, 19.79; S, 15.20.

3-Methysulfinylimidazo[1,5-*a*]pyrazine (12). A solution of *m*-chloroperbenzoic acid (4.67 g, 23 mmol) in 150 ml of chloroform was added dropwise to a stirred, chilled (0°) solution of **3** (3.3 g, 20 mmol) in 50 ml of chloroform over a period of 5 min. The reaction mixture was allowed to stir for 1 hr in the ice bath, washed with three 20-ml portions of saturated aqueous sodium bicarbonate solution, dried, and evaporated. The residue, after crystallization from acetone–hexane, furnished 2.1 g (59%) of **12**: mp 76–77°; ^{1}H NMR δ 3.31 (CH_3, 3 H, s), 8.03 (H-1, 1 H, d, $J_{1,5}$ = 1 Hz), 7.87 (H-6, 1 H, d, $J_{5,6}$ = 5 Hz), 8.78 (H-5, 1 H, m), 9.27 (H-8, 1 H, d, $J_{5,8}$ = 2 Hz); MS *m/e* (rel intensity) M^+ 181 (35), 166 ($M^+ - CH_3$, 100), 118 ($M^+ - CH_3SO$, 35).

Anal. Calcd for $C_7H_7N_3OS$: C, 46.40; H, 3.89; N, 23.19. Found: C, 46.30; H, 3.69; N, 23.24.

3-Ethylsulfinylimidazo[1,5-*a*]pyrazine (13). Using the same procedure and proportions of reagents as above, there was obtained a 97% yield of **13**, mp 81–82° after recrystallization from chloroform–hexane.

Anal. Calcd for $C_8H_9N_3OS$: C, 49.23; H, 4.62; N, 21.54; S, 16.41. Found: C, 49.00; H, 4.64; N, 21.41; S, 16.11.

3-Hydroxy-3-methylthio-2-*p*-nitrobenzoyl-2,3-dihydroimidazo[1,5-*a*]pyrazine (14). Potassium cyanide (0.39 g, 6 mmol) was added to a solution of **3** (0.33 g, 2 mmol) in 25 ml of dichloromethane which contained 0.5 ml of water. A solution of *p*-nitrobenzoyl chloride (0.74 g, 4 mmol) in 10 ml of dichloromethane was added dropwise to the stirred reaction mixture over a period of 10 min and stirring was continued for 2 hr. The mixture was filtered, and the precipitate was washed with water and crystallized from dimethyl sulfoxide–water to give 0.28 g (41%) of **14**: mp 163°; ^{1}H NMR (Me_2SO-d_6) δ 2.7 (CH_3, 3 H, s), 7.8 (H-6, 1 H, d, $J_{5,6}$ = 5 Hz), 8.16 (H-1, 1 H, s), 8.0–8.5 (5 H, m), 9.25 (H-8, 1 H, d, $J_{5,8}$ = 2 Hz)

Anal. Calcd for $C_{14}H_{12}N_4O_4S$: C, 50.60; H, 3.64; N, 16.86; S, 9.65. Found: C, 50.33; H, 3.66; N, 16.68; S, 9.86.

3-Methylthio-1-nitroimidazo[1,5-*a*]pyrazine (15). To a stirred solution of nitrosonium fluoroborate (2.9 g, 25 mmol) in 20 ml of anhydrous acetonitrile, under nitrogen, was added a solution of 1.4 g (8.5 mmol) of **3** in 20 ml of dry acetonitrile. The mixture was stirred at room temperature for 3 hr, the excess nitrosonium salt was decomposed with 1 ml of methanol, and the solvent was evaporated. The residue was chromatographed over alumina (Woelm dry column 12 × 1 in.) using acetonitrile as eluent. The first 100 ml eluted yielded 0.45 g (32% based on recovered **3**) of **15** and 0.35 g of **3**. Recrystallization from acetonitrile–ether gave yellow needles: mp 180–181°; ^{1}H NMR (Me_2SO-d_6) δ 2.76 (CH_3, 3 H, s), 8.23 (H-6, 1 H, d, $J_{5,6}$ = 5 Hz), 8.6 (H-5, 1 H, q, $J_{5,6}$ = 5, $J_{5,8}$ = 2 Hz), 9.76 (H-8, 1 H, d, $J_{5,8}$ = 2 Hz).

Anal. Calcd for $C_7H_6N_4O_2S$: C, 39.99; H, 2.88; N, 26.65; S, 15.35. Found: C, 40.24; H, 2.92; N, 26.34; S, 15.35.

2-Methylthio-4(5)-formylimidazole (16). To a stirred, chilled (0°) solution of **3** (2.0 g, 12 mmol) in concentrated hydrochloric acid (5 ml) and water (10 ml) was added a solution of sodium nitrite (2.0 g, 29 mmol) in 5 ml of water over a period of 10 min. The mixture was stirred in the cold for 15 min and at room temperature for 1 hr. It was evaporated to a volume of about 5 ml, brought to pH 10 with dilute aqueous sodium hydroxide, and extracted with three 50-ml portions of chloroform. The combined extracts were dried and evaporated and the residue sublimed (120°, 0.15 mm) to furnish 0.12 g (7%) of **16** as a colorless solid mp 125°; ^{1}H NMR (Me_2SO-d_6) δ 2.72 (CH_3, 3 H, s), 8.13 (H-5, 1 H, s), 9.83 (HC=O, 1 H, s), 13.3 (NH, 1 H, broad, D_2O exchangeable).

Anal. Calcd for $C_5H_6N_2OS$: C, 42.24; H, 4.25; N, 19.70; S, 22.55. Found: C, 42.08; H, 4.46; N, 19.55; S, 22.50.

7-Carboethoxy-8-ethoxy-3-methylthio-7,8-dihydroimidazo-[1,5-*a*]pyrazine (17). To a solution of **3** (0.495 g, 3.0 mmol) in

methylene chloride (5 ml) was added a solution of ethyl chloroformate (0.325 g, 3.0 mmol) in methylene chloride (10 ml). After 10 min the reaction mixture was quenched with ethanol (2 ml). The product (0.4 g, 48%) was obtained as an oil by dry column chromatography of the residue, obtained after evaporation, on alumina eluting with chloroform: ^{1}H NMR δ 1.15 (CH_3, 3 H, t), 1.35 (CH_3, 3 H, t), 2.56 (CH_3, 3 H, s), 3.55 (CH_2, 2 H, q), 4.33 (CH_2, 2 H, q), 6.5–6.8 (H-5, H-6, and H-8, m), 7.13 (H-1, 1 H, s); significantly, there was no characteristically low-field absorption for an aromatic-type H-8.

Anal. Calcd for $C_{12}H_{17}N_3O_3S$: C, 50.87; H, 6.05; N, 14.83; S, 11.31. Found: C, 50.60; H, 6.07; N, 14.71; S, 11.57.

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Registry No.—**1**, 20010-99-5; **2**, 56488-16-5; **3**, 56488-17-6; **4**, 56488-18-7; **5**, 56488-19-8; **6**, 56488-20-1; **7**, 56488-21-2; **8**, 56488-22-3; **9**, 56488-23-4; **10**, 56488-24-5; **11**, 56488-25-6; **12**, 56488-26-7; **13**, 56488-27-8; **14**, 56488-28-9; **15**, 56488-29-0; **16**, 56488-30-3; **17**, 56488-31-4; carbon disulfide, 75-15-0; methyl iodide, 74-88-4; methyl bromoacetate 96-32-2; 2-bromoethanol, 540-51-2; bromoacetaldehyde dimethyl acetal, 7252-83-7; *p*-nitrobenzoyl chloride, 122-04-3.

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Solvolysis of Isothiazole Analogs of Cumyl Chloride. Determination of the Brown Electrophilic Substituent Constants for Isothiazole Derivatives

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Rates of solvolysis in 80% ethanol have been determined for 2-(3-isothiazolyl)-2-chloropropane, 2-(4-isothiazolyl)-2-chloropropane, and 2-(5-isothiazolyl)-2-chloropropane. From these rates and the rates of solvolysis of cumyl chlorides bearing electron-withdrawing substituents σ^+ values appropriate for the replacement of the benzene ring by an isothiazolyl moiety have been determined.

The chemistry of isothiazole, which was first prepared in 1956,[2] has recently been reviewed.[3] Electrophilic substitution occurs preferentially in the 4 position, including nitration and halogenation, but relatively few quantitative indices of the reactivity of the system are available. Nitration of phenylisothiazoles leads to substitution in the phenyl moiety.[4,5] The latter authors observed that the phenyl ring is strongly deactivated by the isothiazole ring, which is, of course, protonated by the concentrated acid of the nitration mixture.

In competitive nitrations, Dou and Metzger et al.[6] observed the following relative reactivities for the 4 position of various isothiazoles: 3-methylisothiazole, 1.0; 5-methylisothiazole, 1.7; isothiazole, 0.43. The isothiazoles were substantially less reactive than 2,4-dimethylthiazole.

The most quantitative studies are by Katritzky and his coworkers and include examination of nitration and hydrogen exchange.[7] The acid-catalyzed hydrogen–deuterium exchange of 3,4-dimethylisothiazole showed a change in the slope of the rate–acidity profile at $D_0 = -6.0$.[7] The authors concluded that the reaction at low acidities occurs on the free base and at high acidities on the conjugate acid; they estimated that the free base was 10^8 times more reactive than the conjugate acid. Hydrogen–deuterium exchange in D_2SO_4 of isothiazole and isoxazole and their 3- and 5-methyl derivatives was also studied.[8] Exchange was observed only in the 4 position. Heating with D_2SO_4 of various concentrations did not lead to any observable exchange in the 3 and 5 positions for any conditions under which the compounds were stable. Standard k_0 values for exchange at pH 0 at 100° were calculated as before,[9] with the assumption that pK_a values for isothiazoles follow the same relationship for temperature variation as pyridine. For isothiazole the calculated log k_0 value was −7.5. The authors calculated a log partial rate factor of 3.6 which, with their ρ value of −7.5, corresponds to a replacement σ_{Ar}^+ value[11] for the 4-isothiazolyl group of −0.48. In contrast to their earlier estimation,[7] the order of reactivity for the 4 positions of the 1,2-azoles is found to be pyrazole ≫ isoxazole > isothiazole (> phenyl).

Obviously, the question of the relative electrophilic reactivity of the isothiazoles is far from closed. The available quantitative data show that isothiazole's 4 position is more reactive than a phenyl position and less reactive than the 4-pyrazolyl position[8] or the 5-thiazolyl position.[6] Direct indications of the relative electrophilic reactivity of the 3 and 4 positions are absent, although it is clear that they are both significantly less reactive than the 4 position. Extrapolation from the substitution patterns of 4-substituted isothiazoles would suggest a greater reactivity for the 5 posi-

Table I
Rate Constants for Solvolysis of 2-(x-Isothiazolyl)-2-propyl Chlorides in 80% Ethanol

Compd solvolyzed	Temp, °C	$10^5 k$, sec^{-1} [a]	σ_{Ar}^+
2-(3-Isothiazolyl)-2-propyl chloride	45.65	20.6 ± 0.2	
	45.65	20.6 ± 0.3	
	57.5	86.9 ± 0.8	
	57.7	88.6 ± 0.7	
	74.80	343 ± 3	
	74.80	350 ± 3	
	75.00	377[b]	0.65
2-(4-Isothiazolyl)-2-propyl chloride	0.00	125 ± 2	
	0.00	127 ± 1	
	18.67	1150 ± 10	
	18.67	1150 ± 10[c]	
	25.08	2220 ± 30	
	25.08	2340 ± 50	
	75.00	211000[b]	−0.04
2-(5-Isothiazolyl)-2-propyl chloride	45.08	15.85 ± 0.06	
	45.10	16.14 ± 0.07	
	57.70	58.8 ± 0.5	
	59.00	63.2 ± 0.2	
	73.63	271. ± 1.0	
	73.63	274. ± 0.6	
	75.00	305[b]	0.67

[a] Determined at constant pH 7.5. [b] Extrapolated from measurements at other temperature. [c] Constant pH 10.

tion relative to the 3, but such a statement is subject to the pitfall of incomplete understanding of substituent effects in the isothiazole system.

We have approached this problem by examining the solvolytic reactivities of the isothiazolyl analogs of cumyl chloride, as we have done for pyridine[12] and thiazole systems.[11] Such an approach is particularly advantageous in the present circumstances as it avoids the severe series of extrapolations which Katritzky and his coworkers found necessary. It further makes accessible a reactivity index for all three of the positions of isothiazole.

Results

The results of the rate measurements in 80% ethanol are given in Table I.

From the measured rates extrapolated to 75° we calculate the replacement σ_{Ar}^+ values[11] given in the last column of Table I using the correlation equation determined earlier[12] from reactivities of some cumyl chlorides with deactivating substituents. The 4-isothiazolyl moiety is very slightly activating, while both of the other isomers are strongly deactivating compared to phenyl. These relationships are roughly similar to those observed by Katritzky et al.[8] However, there is a *significant* quantitative difference in the magnitude of the activation exerted by the 4-isothiazolyl moiety. It is the opinion of the present authors that our direct determination of a σ_{Ar}^+ value through solvolysis rate measurements is a better guide than Katritzky's value because of the necessarily severe extrapolations required in his studies. It should be noted that his extrapolation procedure gives a value[10] for thiophene (2-thienyl position, $\sigma_{Ar}^+ = -1.15$) which is very substantially more negative than the value determined from a large number of other studies.[13,14]

Experimental Section

General. All melting points and boiling points are uncorrected. Elemental analyses and high-resolution mass spectra were determined by the Analytical Services Laboratory, College of Chemistry, University of California, Berkeley, Calif. NMR spectra were recorded using a Varian T-60 spectrometer with Me_4Si as internal standard.

Isothiazole-4-carboxylic acid was prepared following the procedure of Adams and Slack,[15] mp 159–160° (lit.[15] mp 162°), and was converted to the methyl ester; mp 55° (lit.[15] mp 55°); NMR ($CDCl_3$) δ 9.18 (s, 1, H_5), 8.80 (s, 1, H_3), 3.88 (s, 3, OCH_3).

2-(4-Isothiazolyl)-2-propanol. To a stirred solution of 7.5 mmol (2.5 ml of a 3 *M* solution in ether) of methylmagnesium bromide in 30 ml of anhydrous ether, which was cooled in an ice bath, was added slowly 0.5 g (3.5 mmol) of methyl isothiazole-4-carboxylate in 10 ml of anhydrous ether. After addition was complete, the ice bath was removed, and the reaction mixture was allowed to stir at room temperature for 1 hr. The white precipitate was hydrolyzed with 20 ml of saturated ammonium chloride solution. The layers were separated, and the aqueous layer was extracted repeatedly with dichloromethane. The organic layers were combined and dried with magnesium sulfate. The solvents were evaporated to yield 0.4 g (80%) of 2-(4-isothiazolyl)-2-propanol: NMR (CCl_4) δ 8.33 (s, 1, H_5), 8.30 (s, 1, H_3), 3.95 (broad s, 1, –OH), 1.55 (s, 6, methyl protons); mass spectrum calcd for C_6H_9NOS, 143.04075; found, 143.0385.

2-(4-Isothiazolyl)-2-chloropropane. To a stirred solution of thionyl chloride (0.12 g, 1 mmol) in 12 ml of 1,2-dichloroethane was added dropwise 0.1 g (0.7 mmol) of 2-(4-isothiazolyl)-2-propanol in 6 ml of the solvent. The solution was stirred at room temperature for 1.5 hr, then the solvent and excess thionyl chloride were removed on the rotary evaporator. The residue, 0.12 g, was taken up in 2 ml of carbon tetrachloride, separated from a small amount of insoluble material, and utilized for kinetic studies without further purification: NMR (CCl_4) δ 8.42 (s, 1, H_5), 8.37 (s, 1, H_3), 1.97 (s, 6, CH_3).

2-(5-Isothiazolyl)-2-propanol. In a flame-dried flask equipped with a nitrogen inlet, a reflux condenser and drying tube, and a dropping funnel, a solution of 10 g (0.117 mol) of isothiazole in 124 ml of anhydrous ether was cooled with stirring in an ice bath. As stirring continued, 75 ml of a 2 *M* solution of butyllithium in hexane mixed with 50 ml of anhydrous ether was added dropwise. After the 1-hr addition period, the ice bath was removed, and stirring was continued for an additional 2 hr. The solution was then cooled, and 8.8 g (0.15 mol) of acetone was added cautiously. The mixture was stirred for 0.5 hr. Saturated ammonium chloride solution (100 ml) was added, and stirring was continued until both layers became clear. The layers were separated and the aqueous layer was extracted repeatedly with chloroform. The organic layers were combined and dried. The solvents were evaporated, and the residue was distilled under vacuum to yield 3.35 g (20%) of 2-(5-isothiazolyl)-2-propanol: NMR (CCl_4) δ 8.10 (d, J = 2 Hz, 1, H_3), 6.93 (d, J = 2 Hz, 1, H_4), 5.30 (br s, 1, 1 H), 1.60 [s, 6, $(CH_3)_2$-COH–]; mass spectrum calcd for C_6H_9NOS, 143.04075; found, 143.0391.

2-(5-Isothiazolyl)-2-propyl Chloride. A solution of 0.72 g (0.005 mol) of 2-(5-isothiazolyl)-2-propanol in 5 ml of carbon tetrachloride was added cautiously to a stirred solution of 0.6 g (0.005 mol) of thionyl chloride in 10 ml of carbon tetrachloride. A white precipitate formed immediately. The mixture was stirred overnight at room temperature resulting in a yellow solution with a brown suspended liquid. To this was added 0.5 g (0.005 mol) of triethylamine. After a few minutes of additional stirring, the mixture was cooled thoroughly. The mixture was filtered and the solvent was removed to yield 0.72–0.80 g (82–99%) of the desired chloride which was shown by NMR to contain a trace of the alkene but no unreacted alcohol. 2-(5-Isothiazolyl)-2-propyl chloride was used for kinetic measurements without further purification: NMR (CCl_4) δ 8.15 (d, J = 2 Hz, 1, H_3), 7.02 (d, J = 2 Hz, 1, H_4), 2.00 [s, 6, $(CH_3)_2CCl$–].

3-Tribromomethylisothiazole. 3-Methylisothiazole was prepared from commercial 5-amino-3-methylisothiazole hydrochloride by the procedure of Buttimore et al.:[16] bp 134–136° (lit.[15] bp 135–136°); NMR (CCl_4) δ 8.48 (d, J = 4 Hz, 1, H_5), 6.95 (d, J = 4 Hz, 1, H_4), 2.45 (s, 3, C_3CH_3).

A mixture of 2.5 g (0.025 mol) of 3-methylisothiazole and 14.5 g (0.77 mol) of *N*-bromosuccinimide in carbon tetrachloride (50 ml) was heated under reflux with 0.5 g of benzoyl peroxide. Heating was continued for 48 hr. At the end of this period the solution was cooled and filtered. The solvent was evaporated to yield a mixture which by NMR was shown to contain 3-tribromomethylisothiazole (95%) and 5% 3-dibromomethylisothiazole: NMR (CCl_4) 3-tribromomethylisothiazole δ 8.70 (d, J = 4 Hz, 1, H_5), 7.61 (d, J = 4 Hz,

1, H_4). 3-Dibromomethylisothiazole: δ 8.60 (d, J = 5 Hz, 1, H_5), 7.53 (d, J = 5 Hz, 1, H_4), 6.73 (s, 1, $-CHBr_2$).

Ethyl Isothiazole-3-carboxylate. The reaction residue from above, containing predominantly 3-tribromomethylisothiazole, was mixed with 25 ml of ethanol. The mixture was stirred and warmed as 0.077 mol of silver nitrate, dissolved in a minimum amount of water, was added. After 20 min heating was discontinued and the mixture was cooled. The precipitated silver bromide was removed by filtration. Sodium chloride was added to saturate the solution, and the small amount of additional precipitate was removed. The resulting solution was extracted repeatedly with methylene chloride. The organic layers were washed with 5% aqueous sodium bicarbonate solution and dried over magnesium sulfate. The solvents were evaporated, and the residue was distilled to yield 2.5 g (64% based on 3-methylisothiazole) of ethyl isothiazole-3-carboxylate: bp 140–145° (5 Torr); NMR ($CDCl_3$) δ 8.77 (d, J = 5 Hz, 1, H_5), 7.73 (d, J = 5 Hz, 1, H_4), 4.40 (q. J = 6 Hz, 2, $-COOCH_2CH_3$), 1.43 (t, J = 6 Hz, 3, $-COOCH_2CH_3$).

2-(3-Isothiazolyl)-2-propanol. To a stirred, cooled solution of 7.5 mmol of methylmagnesium bromide (2.5 ml of a 3 M solution in ether) in 20 ml of anhydrous ether was cautiously added 0.5 g (3.2 mmol) of ethyl isothiazole-3-carboxylate in 5 ml of anhydrous ether. The reaction mixture was stirred at room temperature for 0.5 hr. At the end of this period, 15 ml of saturated ammonium chloride solution was added. The layers were separated and the aqueous layer was extracted with four 20-ml portions of chloroform. The organic layers were dried over magnesium sulfate. The solvents were evaporated to yield 0.35 g (77%) of 2-(3-isothiazolyl)-2-propanol which contained a trace of nonaromatic impurity. Part of the product (0.15 g) was purified by column chromatography (chloroform and alumina) and submitted for high-resolution mass determination: NMR ($CDCl_3$) δ 8.48 (d, J = 4 Hz, 1, H_5), 7.18 (d, J = 4 Hz, 1, H_4), 6.6 (broad s, 1, –OH), 1.63 [s, 6, $-C(CH_3)_2OH$]; mass spectrum calcd for C_6H_9NOS, 143.04075; found, 143.0396.

2-(3-Isothiazolyl)-2-chloropropane. The procedure used in the preparation of 2-(5-isothiazolyl)-2-chloropropane was utilized without variation. Upon work-up, the reaction was found to yield the desired product and about 30% (by NMR) of the alkene. This mixture was solvolyzed without further purification. NMR showed multiplets in the aromatic region corresponding to the superimposed signals of the chloride and the alkene; however, the signal of the methyl protons was well resolved and occurred at δ 1.87.

Kinetic Techniques. Rate measurements were performed in 80% ethanol–water which had been prepared by dilution of four volumes of dry ethanol with one volume of water. The ethanol was dried by distillation from magnesium ethoxide according to the method of Lund and Bjerrum.[17] The water utilized was redistilled laboratory distilled water. Volumes were measured at room temperature.

Rates of all compounds were followed at constant pH maintained through automatic, recorded neutralization of generated acid with 0.3 M potassium hydroxide in 80% ethanol. Between 0.6 and 0.8 mmol of substrate was used for each run.

The apparatus was a radiometer automatic titrator consisting of a TITlc automatic titrator, and ABUlc autoburette (with a 2.5-ml burette), and TTA3c titrator assembly and an SBR2c recorder. Radiometer electrodes, K401 calomel and 202c glass, were used.

Best least squares rate constants were determined using the LSKIN-I program.[18]

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Registry No.—2-(3-Isothiazolyl)-2-propyl chloride, 56615-15-7; 2-(4-isothiazolyl)-2-propyl chloride, 56615-16-8; 2-(5-isothiazolyl)-2-propyl chloride, 56615-17-9; isothiazole-4-carboxylic acid methyl ester, 56133-37-0; 2-(4-isothiazolyl)-2-propanol, 56615-18-0; methyl bromide, 74-83-9; 2-(5-isothiazolyl)-2-propanol, 56615-19-1; isothiazole, 288-16-4; acetone, 67-64-1; 3-tribromomethylisothiazole, 56615-20-4; N-bromosuccinimide, 128-08-5; 3-dibromomethylisothiazole, 56615-21-5; ethyl isothiazole-3-carboxylate, 23244-32-8; 2-(3-isothiazolyl)-2-propanol, 56615-22-6.

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Synthesis and Tautomeric Properties of Some Potential 2-Hydroxythieno[3,2-*b*]thiophenes and 2-Hydroxythieno[2,3-*b*]thiophenes

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Several alkyl- and aryl-substituted potential 2-hydroxythieno[3,2-*b*]thiophenes and 2-hydroxythieno[2,3-*b*]thiophenes have been prepared by the hydrogen peroxide oxidation of the corresponding boronic acids; the structures of the compounds obtained have been determined by NMR spectroscopy. In no case could evidences be found for the presence of the hydroxy form of these compounds which instead exist as thiolactones; in the case of the thieno[2,3-*b*]thiophene system all of the compounds examined have the structure of thieno[2,3-*b*]thiophen-2(3*H*)-ones, while in the case of the thieno[3,2-*b*]thiophene the two isomeric thieno[3,2-*b*]thiophen-2(3*H*)-ones (B) and the thieno[3,2-*b*]thiophen-2(5*H*)-ones (D) could be identified. Compounds having the structure B were in every case those first obtained from the oxidation mixtures, but they sometimes isomerized to a mixture of B and D whose composition was influenced by the presence of substituents. The effects of the nature and of the position of substituents on the tautomeric equilibria have been explored; it was found that the isomers D were favored by the presence, in the 3 position, of substituents which could conjugate or hyperconjugate with the condensed thieno ring. The syntheses of a large number of thienothiophene derivatives, which were necessary as intermediates, are also described.

The properties of compounds having in principle the structure of hydroxythiophenes have been carefully investigated by Hörnfeldt and Gronowitz and by Lawesson, who have also developed easily available synthetic procedures which have made possible the study of the tautomeric properties of several differently substituted derivatives.[2] It has been observed that all the 2-hydroxythiophenes exist as thiolen-2-ones, with the exception of those holding substituents which can chelate with the OH function, which are instead true hydroxy heterocycles;[3] the enol form can also be observed in some aryl-substituted thiophenes.[4] 3-Hydroxythiophenes generally exist as a mixture of 4-thiolen-3-ones and 3-hydroxythiophenes[5] and also in this case chelation with electron-attracting groups causes these products to exist as intramolecularly hydrogen-bonded hydroxythiophenes.[6] Benzo[*b*]thiophenes exist exclusively as the benzo[*b*]thiophen-2(3*H*)-one and the benzo[*b*]thiophen-3(2*H*)-one, respectively.[7] Similar investigations have not been carried out with thienothiophenes; the few data available concern the cyclization of the 2- and 3-thienylthioacetic acids which both afforded the thieno[3,2-*b*]thiophen-3(2*H*)-one with no evidence of other tautomers.[8] In connection with ESR studies of nitroxides and radical anions of thienothiophene derivatives[9] and thieno[3,2-*b*]thiophene-2,5-diones[10] we have studied the tautomeric equilibria of some potential 2-hydroxy derivatives of thieno[3,2-*b*]thiophene and thieno[2,3-*b*]thiophene.[11]

All the products described in the present investigation were obtained through the hydrogen peroxide oxidation of the boronic acids of thienothiophenes, as described by Hörnfeldt and Gronowitz,[12] according to the following reactions.

$$\text{Ar-Br} \xrightarrow{n\text{-BuLi}} \text{Ar-Li} \xrightarrow{B(OC_4H_9)_3} \text{Ar-B(OH)}_2 \xrightarrow{H_2O_2} [\text{Ar-OH}]$$

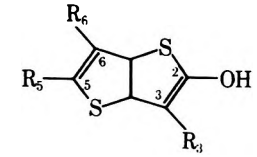
Ar = 2-thieno[3,2-*b*]thienyl and 2-thieno[2,3-*b*]thienyl

In one case the *p*-toluenesulfonic acid catalyzed dealkylation[13] of the *tert*-butoxythienothiophene was also employed. The products prepared and investigated are collected in Scheme I.

Compounds **7**, **8**, **14**, **15**, **17**, and **18** were not prepared with the general methods described above, but were obtained as by-products from the syntheses of the corresponding 2,5-dihydroxythienothiophenes which will be reported in a forthcoming paper;[10] their physical and spectral data and their tautomeric properties will, however, be described in this paper.

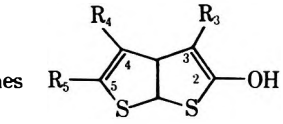
Scheme I

2-Hydroxythieno[3,2-*b*]thiophenes



1, $R_5 = R_3 = R_5 = H$
2, $R_3 = CH_3$; $R_3 = R_6 = H$
3, $R_3 = CH_2CH_3$; $R_5 = R_6 = H$
4, $R_3 = C_6H_5$; $R_5 = R_6 = H$
5, $R_5 = CH_3$; $R_3 = R_6 = H$
6, $R_3 = R_5 = CH_3$; $R_6 = H$
7, $R_6 = C(CH_3)_3$; $R_3 = R_5 = H$
8, $R_6 = C_6H_5$; $R_5 = R_5 = H$
9, $R_6 = CH_3$; $R_4 = R_5 = H$
10, $R_3 = R_5 = CH_3$; $R_6 = H$

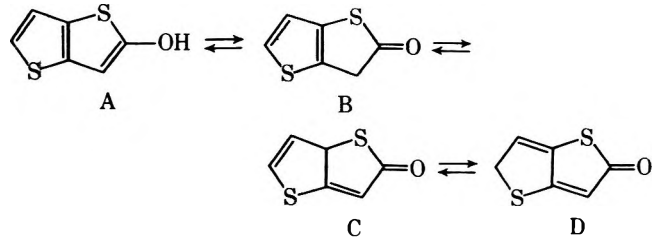
2-Hydroxythieno[2,3-*b*]thiophenes



11, $R_3 = R_4 = R_5 = H$
12, $R_3 = CH_3$; $R_4 = R_5 = H$
13, $R_5 = C_6H_5$; $R_4 = R_5 = H$
14, $R_4 = C(CH_3)_3$; $R_3 = R_5 = H$
15, $R_4 = C_6H_5$; $R_3 = R_5 = H$
16, $R_5 = CH_3$; $R_3 = R_4 = H$
17, $R_3 = R_4 = CH_3$; $R_5 = H$
18, $R_3 = R_4 = C_6H_5$; $R_5 = H$

2-Hydroxythieno[3,2-*b*]thiophenes. For this series of compounds the following four tautomeric forms can in principle be written (Scheme II).

Scheme II

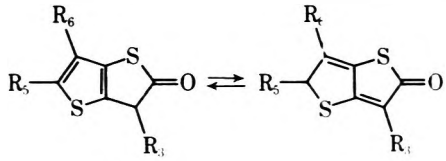


A B C D

The equilibrium compositions, in CS_2, for the tautomers of the variously substituted thieno[3,2-*b*]thiophen-2-ones, **1**–**10**, were established by NMR spectroscopy and are collected in Table I.

From the oxidation of the 2-thieno[3,2-*b*]thienylboronic

Table I
Equilibrium Compositions for the Tautomer of the Thieno[3,2-*b*]thiophen-2-ones 1–10 in CS_2



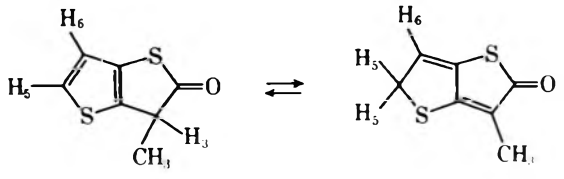
B D

	B	D
1, $R_3 = R_5 = R_6 = H$	100	
2, $R_3 = CH_3$; $R_5 = R_6 = H$	40	60
3, $R_3 = C_2H_5$; $R_5 = R_6 = H$	75	25
4, $R_3 = C_6H_5$; $R_5 = R_6 = H$	10	90
5, $R_5 = CH_3$; $R_3 = R_6 = H$	100	
6, $R_3 = R_5 = CH_3$; $R_6 = H$	100	
7, $R_6 = C(CH_3)_3$; $R_3 = R_5 = H$	100	
8, $R_6 = C_6H_5$; $R_3 = R_5 = H$	100	
9, $R_6 = CH_3$; $R_3 = R_5 = H$	85	15
10, $R_3 = R_6 = CH_3$; $R_5 = H$		100

acid a single crystalline product was obtained in good yield whose NMR spectrum, in CS_2, presented absorptions at δ 7.35 (1 H, doublet of triplets, J = 5.25 and 1.1 Hz), 6.9 (1 H, doublet of triplets, J = 5.25 and 0.5 Hz), and 3.78 (2 H, two doublets, J = 1.1 and 0.5 Hz). No other absorptions were detected and attempts to produce modifications by treatment with traces of acids or bases, which are known to catalyze the isomerization of hydroxythiophenes,[4] did not give any appreciable change. These results indicate that we are dealing with a single, relatively stable tautomer, to whom the structure of thieno[3,2-*b*]thiophen-2(3*H*)-one, (**1b**) can be confidently assigned; this attribution is also confirmed by the strong band at 1725 cm^{-1} in the ir spectrum and by the absence of the characteristic[14] uv spectrum of the thieno[3,2-*b*]thiophene ring.

The oxidation of the 3-methylthieno[3,2-*b*]thienylboronic acid afforded a reaction mixture in which only one isomer was present; the structure of the 3-methylthieno[3,2-*b*]thiophen-2(3*H*)-one (**2b**) was assigned to this compound on the basis of its NMR spectrum (Scheme III). After

Scheme III



40% 60%

2b **2d**

δ_{CH_3} = 1.41, J_{3-6} = 0.45 Hz
δ_3 = 3.78, J_{3-5} = 1.1 Hz
δ_6 = 6.9, J_{5-6} = 5.25 Hz
δ_5 = 7.35, J_{5-CH_3} = 7.5 H

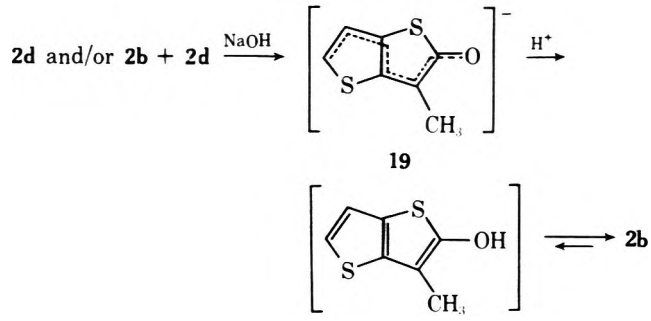
δ_{CH_3} = 1.87, J_{6-CH_3} = 0.45 Hz
δ_6 = 6.52 J_{5-CH_3} = 1.3 Hz
δ_5 = 4.25, J_{5-6} = 3.2 Hz

standing at room temperature or attempted purification by distillation or by column chromatography, this oily product invariably afforded a mixture with a second compound, which from the NMR spectrum is 3-methylthieno[3,2-*b*]thiophen-2(5*H*)-one (**2d**).

The ir spectra are in agreement with the proposed structures, the carbonyl stretching vibrations occurring at 1725 cm^{-1} for **2b** and at 1695 cm^{-1} for the isomer **2d** in which the carbonyl group is conjugated. Absorptions at 3450 and 3370 cm^{-1} observed for **2b** and **2d**, respectively, are attributed to the first overtone of the carbonyl stretching,[15] rather than to the presence of traces of hydroxy form **2a**. Integration of the NMR spectrum in CS_2 indicated an equilibrium composition of the two isomers **2b** and **2d** in the ratio of 40:60 ± 5. Equilibration could be greatly accelerated by the presence of catalytic amounts of gaseous HCl, triethylamine, or pyridine and the composition remained unchanged; the same equilibrium mixture was obtained starting from both pure **2b** or pure **2d** which could be prepared as described below.

The more stable form **2d** (or the tautomeric mixture) can be converted to the pure thieno[3,2-*b*]thiophen-2(3*H*)-one (**2b**) by the base-extraction method;[16] for this purpose, it was dissolved in cold dilute NaOH and the solution acidified in the presence of ether so that the lactones could be extracted in the organic phase as soon as they form (Scheme IV). The behavior of the 3-methyl-2-hydroxy-

Scheme IV

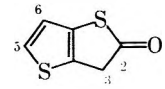


19

thieno[3,2-*b*]thiophene parallels that of 5-alkyl-substituted thiolen-2-ones,[4] studied by Hörnfeldt, and is in agreement with Ingold's rule[4] that in the protonation of a mesomeric anion of a weakly acidic tautomer, like **19**, the thermodynamically less stable tautomer is formed first.[17] The protonation of the mesomeric anion **19** should be an exothermic process in which the main factor governing the direction of attack by the proton will be the charge distribution in the anion; owing to its closer proximity to the electron-withdrawing oxygen atom, position 3 is thought to have the higher charge density and therefore the isomer **2b** will be formed more rapidly under conditions of kinetic control.[17]

Pure 3-methylthieno[3,2-*b*]thiophen-2(5*H*)-one (**2d**) can be obtained by taking advantage of its lower solubility. Treatment of the tautomeric mixture (or pure **2b**), dissolved in the minimum amount of ethanol, with a few drops of pyridine caused crystallization of **2d**. Thus the introduction of a methyl group in the 3 position of the thieno[3,2-*b*]thiophene nucleus increases the relative stability of conjugated form **2d** owing to hyperconjugation with the CH_3 group. This structure, which is not present at the equilibrium in the parent compound, becomes more stable than the thieno[3,2-*b*]thiophen-2(3*H*)-one (**2b**), in which one thiophene ring is still preserved. This modification is not unprecedented, since similar effect caused by the introduction of a methyl group in the 3 position was also observed in the simpler thiolen-2-ones.[4]

Table II[a]
Physical and Spectral (NMR in CS_2 and Ir in CCl_4) Data of the Thieno[3,2-*b*]thiophen-2(3*H*)-ones



Compd	Mp or bp, °C (mm)	>C=O, cm^{-1}	Chemical shifts, δ				Coupling constants, Hz			
			3	6	5	3'	J_{3-6}	J_{3-5}	J_{5-6}	$J_{3-3'}$
1b	94–95	1725	3.78	6.9	7.35		0.5	1.1	5.25	
2b	95–97 (1)	1725	3.78	6.9	7.35	1.41[b]	0.45	1.1	5.25	7.5
3b	98–100 (1)	1725	3.62	6.9	7.35	1.88,[c] 0.95[b]	0.45	1.1	5.25	5.5,[d] 6.6,[d] 7.5[e]
4b	*h*	1730	4.75	6.9	7.35	7.2[f]	0.45	1.1	5.25	
5b	82–84	1725	3.73	6.6	2.52[b]		0.5	1.1	1.1	
6b	32–34	1720	3.65	6.55	2.48[b]	1.41[b]	0.4	1.1	1.1	7.5
7b[i]	53–55	1730	3.72	1.29[g]	6.92			1.05		
8b[i]	70–71	1730	3.82	7.32[f]	7.26			1.05		
9b	61–62	1725	3.78	2.22[b]	6.9		0.3	1.1	1.1	
10b	*h*	1725	3.75	2.21[b]	6.88	1.45[b]	0.3	1.1	1.1	7.5

[a] Satisfactory analytical data were reported for all the compounds listed in the table. [b] Methyl group. [c] CH_2 of the ethyl group. [d] Coupling constants between the H_3 and the two geminal hydrogens of the ethyl group. [e] $J_{CH_2-CH_3}$. [f] Phenyl group. [g] *tert*-Butyl group. [h] Not isolated (the NMR and ir data were determined from the mixture with the -2(5*H*)-one isomer). [i] Obtained as a by-product from the synthesis of the corresponding 2,5-dihydroxythieno[3,2-*b*]thiophene.

The enolic form **2a** and the thiolactonic compound, **2c**, which is conceivably less stable than **2b** and **2d**, could never be evidenced in the experiments described above.

Oxidation of the 3-ethylthieno[3,2-*b*]thienylboronic acid also afforded as the first-formed compound the pure 3-ethylthieno[3,2-*b*]thiophen-2(3*H*)-one (**3b**); this, however, rapidly isomerized to a mixture of the **3b** and **3d** forms in the ratio of 75:25, respectively, in agreement with the lower hyperconjugative effect of the ethyl in respect to the methyl group. Compound **3b** showed the peculiarity, which also constituted a proof of its structure, of giving an NMR pattern due to two magnetically different geminal hydrogens in the ethyl group indicating that it is linked to a chiral center; the different staggered conformations of the rotating ethyl group are not equally populated, thus making the two methylene protons nonequivalent. This is clearly revealed in the multiplicity shown by the H_3 proton which allowed the coupling constants reported in Table II to be determined; a complete analysis of the ethyl group was not undertaken.

Also in this case the base-extraction method applied to the pure isomers or to a tautomeric mixture afforded the kinetically favored tautomer **3b** in pure state.

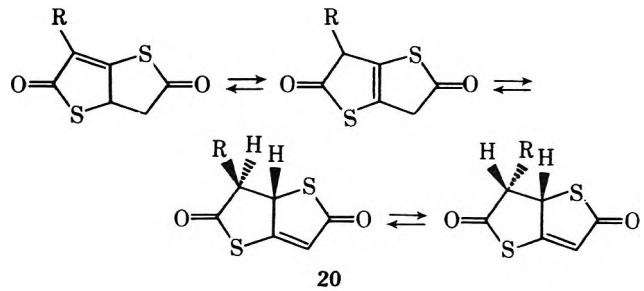
On passing to the 3-phenyl-substituted compound, **4**, the picture is modified in the expected way. The first-formed tautomer is still the kinetically favored 3-phenylthieno[3,2-*b*]thiophen-2(3*H*)-one (**4b**), but this is easily and rapidly isomerized to a mixture in which the 3-phenylthieno[3,2-*b*]thiophen-2(5*H*)-one (**4d**) largely predominates (**4b:4d** 10:90), a result which can be anticipated on the basis of the conjugation of the phenyl group with the carbon–carbon double bonds.

In this case the treatment of an alkaline solution of **4d** with acid did not give pure **4b** but a mixture in almost equimolecular amounts of the two, indicating that the base-extraction method is not so efficient to avoid a partial isomerization of **4b** to **4d** to occur; as a consequence a pure sample of the 3-phenylthieno[3,2-*b*]thiophen-2(3*H*)-one could not be obtained and analyzed.

Substituents in the 5 position cannot obviously contribute to the stabilization of the -2(5*H*)-one forms (D), whereas they can conjugate or hyperconjugate with the thiophene ring in the -2(3*H*)-one structures (B); accordingly only this latter tautomer is expected. Actually, the oxidation of the 5-methylthieno[3,2-*b*]thienylboronic acid afforded the 5-methylthieno[3,2-*b*]thiophen-2(3*H*)-one (**5b**); no indication of the formation of other tautomers could be found on attempted equilibration with acids or after treatment with alkali.

The strong stabilization of the thiophenic structure (B) by the methyl group in the 5 position is clearly demonstrated also in the case of 3,5-dimethylthieno[3,2-*b*]thiophen-2-one (**6**), where, notwithstanding the presence of a methyl group in 3, the fully conjugated tautomer (D) could not be detected and the only product obtained was 3,5-dimethylthieno[3,2-*b*]thiophen-2(3*H*)-one (**6b**).

The effect of substituents in the 6 position cannot easily be predicted and a rather complex situation should result from the fact that from this position they can exert their stabilizing properties on both the -2(3*H*)-one and the -2(5*H*)-one tautomers; the relative stability of the two isomers should reflect the balance of these effects for the various substituents. The first two compounds of this group investigated were the 6-*tert*-butyl (**7**) and the 6-phenyl (**8**), which were formed as by-products from the synthesis of the corresponding 2,5-dihydroxythieno[3,2-*b*]thiophenes (**20**), in connection with a parallel investigation of their tautomeric properties,[10] and their oxidation to the diones **21**.



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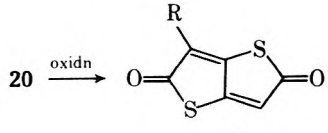
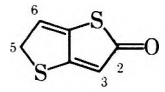


21

Both compounds **7** and **8** exist exclusively as thieno[3,2-*b*]thiophen-2(3*H*)-ones (B) and no indication of the pres-

Table III[a]
Physical and Spectral (NMR in CS_2, Ir in CCl_4) Data of the Thieno[3,2-*b*]thiophen-2(5*H*)-ones



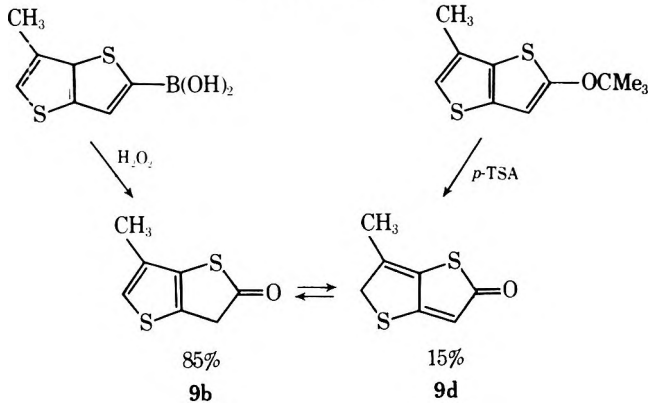
Compd	Mp, °C	>C=O, cm^{-1}	Chemical shifts, δ				Coupling constants, Hz			
			3	6	5		J_{3-6}	J_{3-5}	J_{5-6}	
2d	109–110	1695	1.87[b]	6.52	4.25		0.4	1.3	3.2	
3d	98–99	1695	2.3[c]	6.38	4.25	1.1[b]		1.0	3.2	7.5[d]
4d	101–102	1695	7.55–7.2[e]	6.47	4.30				3.3	
9d	*g*	1695	5.8	2.15[b]	4.15		0.4	1.35	1.35	
10d[f]	127–128	1690	1.82[b]	2.13[b]	4.1		0.4	1.2	1.4	

[a] Satisfactory analytical data were reported for all the compounds listed in the table. [b] Methyl group. [c] CH_2 of the ethyl group. [d] $J_{CH_2-CH_3}$. [e] Phenyl group. [f] The attribution has been made with reference to the chemical shifts of the methyl group in compounds **2b** and **9b**. [g] Not isolated (the NMR and ir data were determined from the mixture with the -2(3*H*)-one isomer).

ence of the -2(5*H*)-one form could be found on attempted isomerization with acids or bases.

The oxidation of 6-methylthieno[3,2-*b*]thienylboronic acid afforded instead a mixture of the two isomers **9b** and **9d** in the ratio of 85:15; only the -2(3*H*)-one **9b** isomer could, however, be obtained after work-up of the reaction mixture. Essentially the same results were obtained when the *p*-toluenesulfonic acid catalyzed dealkylation of the 2-*tert*-butoxy-6-methylthieno[3,2-*b*]thiophene (**22**) was utilized for the synthesis of the potential hydroxy derivative (Scheme V).

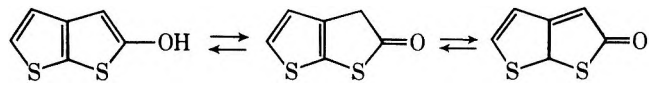
Scheme V



9b **9d**

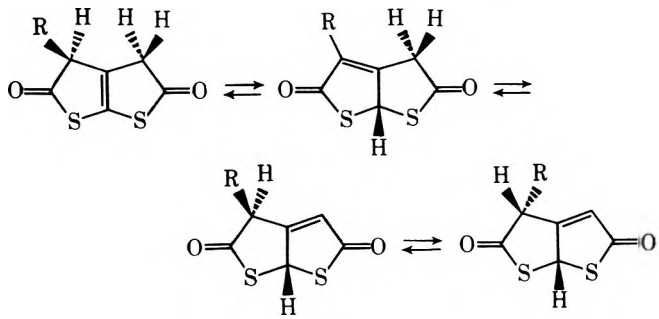
A similar mixture of the two tautomers was also obtained by the base-extraction method applied to **9b**. These results indicate that a methyl group stabilizes to a certain extent the -2(5*H*)-one tautomeric form (D) also when it is present in the 6 position and, as a final example of this group of compounds, the 3,6-dimethyl derivative, **10**, was synthetized with the expectation that in this case the carbonyl conjugated form (D) should have a much greater stability than the isomeric -2(3*H*)-one, **10b**. Actually the 3,6-dimethylthieno[3,2-*b*]thiophen-2(3*H*)-one (**10b**), which exclusively formed from the oxidation of the boronic acid, very easily isomerized completely to the more stable 3,6-dimethylthieno[3,2-*b*]thiophen-2(5*H*)-one (**10d**). When **10d** was dissolved in alkali and then acidified in the presence of ether a mixture of the two tautomers was obtained in which **10d** predominated (**10b:10d** 20:80); this mixture, on standing or on attempted manipulation, afforded pure **10d**.

2-Hydroxythieno[2,3-*b*]thiophenes. The following three tautomeric structures can in principle be expected for this class of compounds. The synthesis of these compounds has been carried out in the usual way by the oxidation of



A B C

the corresponding boronic acids; several of them were, however, formed as by-products[10] in the preparation of the 2,5-dihydroxythieno[2,3-*b*]thiophenes (**23**). All the potential 2-hydroxythieno[2,3-*b*]thiophenes investigated existed as a single product which remained unchanged on treatment with acids or bases; dissolution of these compounds in alkali followed by acidification in the presence of ether afforded the starting products without any evidence of the formation of other tautomers. NMR and ir data (see Table IV) indicated that these compounds have the structure of thieno[2,3-*b*]thiophen-2(3*H*)-ones (B).



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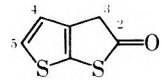
In this case, therefore, at variance with what is observed in the thieno[3,2-*b*]thiophenes, the condensed thieno ring is not involved in the tautomeric equilibrium, notwithstanding that in the thieno[2,3-*b*]thiophen-2(7*H*)-one structure (C) the carbonyl group could conjugate with the two carbon–carbon double bonds as in the case of the thieno[3,2-*b*]thiophen-2(5*H*)-ones; ring strain effects, which will prevent the two rings from reaching complete coplanarity, are probably responsible for the unstability of the tautomeric -2(7*H*)-one structure (C).

In order to test their chemical behavior, few reactions have been carried out with some of the potential 2-hydroxythienothiophenes here described with the expectation that derivatives could be obtained both from the enol and from the thiolactone forms; the reactions with acyl chlorides, aldehydes, ketones, and diazoalkanes indeed occurred at the oxygen and/or at the carbon atoms holding the active methylene groups. The results of these experiments are discussed in the accompanying paper.

Compounds 11–18 as well as 1–10 in both the tautomeric

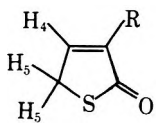
Table IV[a]
Physical and Spectral (NMR in CS_2 and Ir in CCl_4) Data of the Thieno[2,3-*b*]thiophen-2(3*H*)-ones



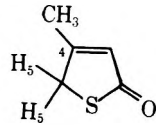
Compd	Mp or bp, °C (mm)	>C=O, cm^{-1}	Chemical shifts, δ				Coupling constants, Hz			
			3	4	5	3'	J_{3-4}	J_{3-5}	J_{4-5}	$J_{3-3'}$
11	84–86	1735	3.70	6.90	7.21		0.5	0.2	5.2	
12	94–96 (0.8)	1730	3.61	6.88	7.18	1.41[b]	0.5	0.2	5.2	7.5
13	102–104	1730	4.65	6.7	7.13	7.05[c]	0.5	0.2	5.2	
14[e]	143–145 (1.5)	1735	3.65	1.25[d]	6.70			*f*		
15[e]	106–107	1735	3.70	7.1[c]	6.95			*f*		
16	109–110	1730	3.59	6.55	2.49[b]		0.5	0.2	1.1	
17[e]	95–96 (0.5)	1730	3.55	2.24[b]	6.76	1.46[b]		*f*	1.1	7.5
18[e]	86–88	1735	4.55	6.88	7.0[c]	6.88[c]		*f*		

[a] Satisfactory analytical data were recorded for all the compounds listed in the table. [b] Methyl group. [c] Phenyl group. [d] *tert*-Butyl group. [e] Obtained as a by-product from the synthesis of the corresponding 2,5-dihydroxythieno[2,3-*b*]thiophene. [f] Not resolved.

forms B and D give rise to NMR spectra which can be easily interpreted by first-order treatment and which are extremely useful in the structural assignments. Thus the aromatic protons or the methyl groups in positions 4 and 5 in the series of the thieno[2,3-*b*]thiophen-2(3*H*)-ones or in the 5 and 6 positions of the thieno[3,2-*b*]thiophen-2(3*H*)-ones have chemical shifts and coupling constants in excellent agreement with the values expected for a 2,3-disubstituted thiophene or methylthiophene. The same groups in the thieno[3,2-*b*]thiophen-2(5*H*)-ones (D) have J_{5-6} coupling constants of 3.2–3.3 Hz which become 1.4 Hz when a methyl group is present in the 6 position; these values are quite similar to those reported by Hörnfeldt and Gronowitz[4] for the coupling between the protons in the 5 and 4 positions of the 3-thiolen-2-one **24** (J_{5-4} = 3–3.4 Hz) and of the 4-methyl-3-thiolen-2-one **25** ($J_{5\text{-}CH_3}$ = 1.5 Hz).



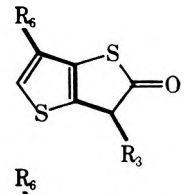
24



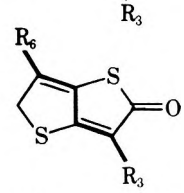
25

Interesting long-range couplings are observed in the thieno[3,2-*b*]thiophen-2-ones between protons in the 3 position and those in the 5 and 6 positions in both the systems of the -2(3*H*)-one (B) and of -2(5*H*)-one (D) (Scheme VI). J_{3-6} is 0.4–0.5 Hz in the thieno[3,2-*b*]thiophen-2(3*H*)-ones **1b–6b** and becomes 0.3 Hz when a methyl group is placed in 6 position (**9b** and **10b**); a 0.4-Hz coupling is also observed in the thieno[3,2-*b*]thiophen-2(5*H*)-ones holding a methyl group in the 3 position, **2d**, or in the 6 position, **9d**, and this coupling remains of the same magnitude even in compound **10d**, where two methyls are present at the two extreme carbon atoms. A 0.4-Hz coupling is also observed[10] in 3-methylthieno[3,2-*b*]thiophene-2,5-dione (**26**), which is structurally very similar to the corresponding -2(5*H*)-ones. The J_{3-6} observed in these compounds may be related to the J_{3-6} observed in the thieno[3,2-*b*]thiophene[18] or its 2-bromo[18] or 2-methyl[19] derivatives, which have couplings of 0.7, 0.69, and 0.5 Hz, respectively; a J_{3-6} = 0.6 Hz is also found in the 2-bromo-5-methylthieno[3,2-*b*]thiophene described in the present paper. A similar coupling has been reported for benzo[*b*]thiophene[20] between the protons in the 3 and 7 positions. The 0.4-Hz coupling between the two methyl groups of **10d** represents an example of coupling over as many as seven bonds which has previously been observed only in a few cases such as the polyacetylenic compounds[21] and 5-methyl-3-acetonylidene-4-thiolen-2-one (**27**).[4]

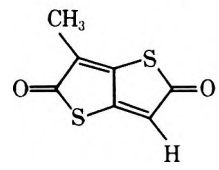
Scheme VI



$R_3 = R_6 = H$; J_{3-6} = 0.4–0.5 Hz
$R_3 = R_6 = CH_3$; J_{3-6} = 0.3 Hz

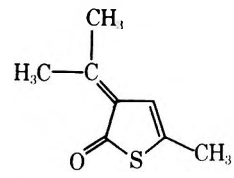


$R_3 = CH_3$, $R_6 = H$; J_{3-6} = 0.4 Hz
$R_3 = H$, $R_6 = CH_3$; J_{3-6} = 0.4 Hz
$R_3 = R_6 = CH_3$; J_{3-6} = 0.4 Hz



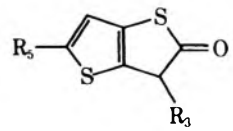
J_{3-6} = 0.4 Hz

26

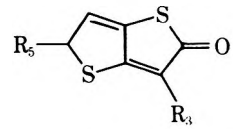


J = 0.7–0.8 Hz

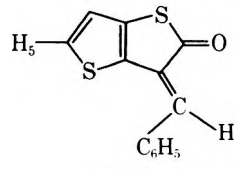
27



$R_3 = R_5 = H$; J_{3-5} = 1.1 Hz
$R_3 = H$, $R_5 = CH_3$; J_{3-5} = 1.1 Hz



$R_3 = R_5 = H$; J_{3-5} = 1.35 Hz
$R_3 = CH_3$, $R_5 = H$; J_{3-5} = 1.2–1.35 Hz



J_{CH-5} = 0.7 Hz

28

A long-range coupling is also observed in the lactones of the thieno[3,2-*b*] series between protons in positions 3 and 5. In the thieno[3,2-*b*]thiophene this coupling is small and negative;[18] in the products here described J_{3-5} has the value of 1.0–1.1 Hz in the -2(3*H*)-ones (B) and of 1.2–1.3 Hz in the -2(5*H*)-ones (D); in both cases the coupling remains practically unaffected when a hydrogen linked to the unsaturated carbon [R_5 in the -2(3*H*)-ones and R_3 in the -2(5*H*)-ones] is replaced by a methyl group. A similar long-range coupling (0.7 Hz) was also detected[22] in compound **28** between the benzylidene proton and the ring proton in position 5. The fact that the magnitude of the proton–proton coupling constants, J_{3-5} and J_{3-6}, remains practically unchanged when an olefinic or ring proton is substituted by a methyl group can be taken as an indication of a π-electron transmitted interaction.[21,23]

Finally, in the case of 3-ethylthieno[3,2-*b*]thiophen-2(5*H*)-one (**3d**), the J_{3-6} becomes so small that it could not be resolved and the J_{3-5} was reduced to 1 Hz; this can probably be associated with the conformational requirements of the ethyl group which causes the C–CH_3 bond to lie preferentially perpendicular to the molecular plane. A similarly interpretable decrease of the hyperfine splitting constant of the alkyl protons was observed in the radical anions of the thieno[3,2-*b*]thiophene-2,5-diones on passing from the 3-methyl to the 3-ethyl derivatives.[10]

Experimental Section[24]

2-Bromothieno[3,2-*b*]thiophene (**29**) and 2-bromothieno[2,3-*b*]thiophene (**30**) were prepared as described in the literature.[25]

2-Bromo-3-methylthieno[3,2-*b*]thiophene (31). To a solution of 3-methylthieno[3,2-*b*]thiophene[26] (4.2 g) in acetic acid (100 ml), *N*-bromosuccinimide (NBS, 4.9 g) was added in small portions and the mixture was stirred at room temperature for 2 hr. The solution was poured on water and extracted with chloroform several times; the organic layer was separated, washed with water and $NaHCO_3$ solution, and dried. The solvent was evaporated and the residue distilled: bp 106–108° (1 mm) (5.5 g); NMR (CS_2) δ_{CH_3} 2.25, δ_5 7.25, δ_6 7.01, J_{5-6} = 5.2 Hz.

Anal. Calcd for $C_7H_5BrS_2$: C, 36.06; H, 2.16; Br, 34.28; S, 27.50. Found: C, 36.02; H, 2.23; Br, 35.0; S, 27.35.

3-Acetylthieno[3,2-*b*]thiophene (32). To a solution of *n*-butyllithium (prepared from 0.85 g of lithium) in ether cooled at −70°, 3-bromothieno[3,2-*b*]thiophene[25] (12 g) was added and the mixture was stirred for 1 hr. Then *N*,*N*-dimethylacetamide (12 ml) dissolved in ether was added dropwise and the reaction mixture was stirred at −70° for 3 hr and then overnight at room temperature. Water was added and the ether layer was treated with dilute HCl, washed with water, dried, and evaporated. The solid residue (11 g) was chromatographed through silica gel with light petroleum–ether (9:1) as eluent. A solid product was collected which melted at 81–82° after crystallization from ethanol. NMR (CS_2) δ_2 7.95, δ_5 7.4, δ_6 7.1, δ_{COCH_3} 2.45, J_{5-6} = 5.1, J_{2-5} = 1.6 Hz.

Anal. Calcd for $C_8H_6OS_2$: C, 52.72; H, 3.32; S, 35.18. Found: C, 52.75; H, 3.29; S, 35.10.

3-Ethylthieno[3,2-*b*]thiophene (33). A mixture of **32** (7 g), 85% hydrazine (3.5 ml), KOH (4.4 g), and diethylene glycol (35 ml) was refluxed for 2 hr and the water formed slowly distilled off. The resulting mixture was boiled for 3 hr more and then poured on water and extracted with ether. The organic solution was washed with water, dried, and evaporated. The residue was distilled to give 4.5 g of **33**: bp 85–86° (0.3 mm); NMR (CS_2) δ_2 6.82, δ_5 7.16, δ_6 7.05, δ_{CH_2} 2.62, δ_{CH_3} 1.29, $J_{CH_2-CH_3}$ = 7.5, J_{2-CH_2} = 1.1, J_{2-5} = 1.5, J_{5-6} = 5.2 Hz.

Anal. Calcd for $C_8H_8S_2$: C, 57.10; H, 4.79; S, 38.11. Found: C, 57.04; H, 4.80; S, 38.21.

2-Bromo-3-ethylthieno[3,2-*b*]thiophene (34) and 2,5-Dibromo-3-ethylthieno[3,2-*b*]thiophene (35). Treatment of **33** (4.5 g) with NBS (2.67 g) as described above for **31** afforded a mixture (3.5 g) of mono- and dibromo derivatives together with some unreacted **33** which was separated by column chromatography through silica gel with light petroleum as eluent. The dibromo compound was eluted first: NMR (CS_2) δ_6 7.02, δ_{CH_2} 2.68, δ_{CH_3} 1.24, $J_{CH_2-CH_3}$ = 7.5 Hz. This was not further analyzed. Then the desired product **34** was obtained as an oil: bp 115° (1 mm); NMR (CS_2) δ_5 7.25, δ_6 7.02, δ_{CH_2} 2.69, δ_{CH_3} 1.25, $J_{CH_2-CH_3}$ = 7.5, J_{5-6} = 5.1 Hz.

Anal. Calcd for $C_8H_7BrS_2$: C, 38.87; H, 2.85; S, 25.94; Br, 32.33. Found: C, 39.0, H, 2.85; S, 26.05; Br, 32.80.

2-Bromo-3-phenylthieno[3,2-*b*]thiophene (36). Treatment of 3-phenylthieno[3,2-*b*]thiophene[7] (2.16 g) with NBS (1.78 g) as described above for **31** afforded a product which was purified by column chromatography on silica gel, using light petroleum as eluent. Pure **36** (3.15 g) melted at 77–78°; NMR (CS_2) δ_5 7.3, δ_6 7.05, $\delta_{C_6H_5}$ 7.4, J_{5-6} = 5.1 Hz.

Anal. Calcd for $C_{12}H_7BrS_2$: C, 48.82; H, 2.39; Br, 27.07, S, 21.72. Found: C, 48.9; H, 2.45; Br, 27.25; S, 22.00.

2-Bromo-5-methylthieno[3,2-*b*]thiophene (37). Treatment of 2-methylthieno[3,2-*b*]thiophene[19] (4.3 g) with NBS (4.9 g) in CH_3COOH (90 ml) as described above for **31** afforded the desired product (6 g) with mp 128–129° after crystallization from ethanol; NMR (CS_2) δ_{CH_3} 2.52, J_{3-6} = 0.6 and J_{CH_3-6} = 1.1 Hz.

Anal. Calcd for $C_7H_5BrS_2$: C, 36.06; H, 2.16; Br, 34.28; S, 27.50. Found: C, 36.17; H, 2.16; Br, 34.24; S, 27.60.

3,5-Dimethylthieno[3,2-*b*]thiophene (38). To a solution of *n*-butyllithium (prepared from 0.35 g of lithium) cooled at −70°, 3-bromo-5-methylthiophene[27] (4 g) was added dropwise and the mixture was kept at this temperature for 30 min. Sulfur (1 g) was then added and the temperature was allowed to gradually rise to −10°; to this solution containing the lithium salt of the 5-methyl-3-mercaptothiophene chloroacetone (3 g) was added and the mixture was stirred at room temperature overnight. The mixture was poured on water and the ether layer was washed, dried, and evaporated. The residue was distilled to afford (5-methyl-3-thienylthio)acetone (**39**) (3.5 g): bp 125–126° (1 mm); NMR (CS_2) δ 2.15 (t, 3 H, CH_3CO, J = 0.3 Hz), 2.41 (d, 3 H, CH_3 in 5, J = 1.1 Hz), 3.38 (g, 2 H, CH_2CO, J = 0.3 Hz), 6.53 (d, q, 1 H, J = 1.5, J' = 1.1 Hz), 6.78 (d, 1 H, J = 1.5 Hz).

Anal. Calcd for $C_8H_{10}OS_2$: C, 51.58; H, 5.41; S, 34.42. Found: C, 51.49, H, 5.47; S, 34.86.

To a stirred mixture of $AlCl_3$ (3 g) and CS_2 (60 ml) a solution of **39** (3.2 g) in CS_2 was added and the mixture was stirred at room temperature for 24 hr. Water was added and the organic layer was separated, washed and dried. Evaporation of the solvent afforded an oil which was distilled under vacuum to afford 2 g of **38**: bp 98–100° (2 mm); NMR (CS_2) δ_3 2.21, δ_5 2.46, δ_6 6.65, δ_2 6.67, J_{2-3} = 1.2, J_{6-5} = 1.2, and J_{2-5} = 0.3 Hz.

Anal. Calcd for $C_8H_8S_2$: C, 57.10; H, 4.79; S, 38.11. Found: C, 57.19; H, 4.74; S, 38.20.

2-Bromo-3,5-dimethylthieno[3,2-*b*]thiophene (40) and 2,6-Dibromo-3,5-dimethylthieno[3,2-*b*]thiophene (41). Treatment of **38** (1.7 g) with NBS (1.8 g) in CH_3COOH (30 ml) afforded a mixture of products which was separated by column chromatography on Florisil using hexane as eluent. Compound **41** was eluted first (0.4 g), mp 127–129° from ethanol, NMR (CS_2) δ_3 2.22, δ_5 2.45.

Anal. Calcd for $C_8H_6Br_2S_2$: C, 29.47; H, 1.85; S, 19.66. Found: C, 30.21; H, 1.90; S, 20.01.

A second fraction contained the monobromo derivative **40** (1.7 g), bp 148–150° (2 mm), NMR (CS_2) δ_3 2.18, δ_5 2.48, δ_6 6.65, J_{5-6} = 1.1 Hz.

Anal. Calcd for $C_8H_7BrS_2$: C, 38.87; H, 2.85; Br, 32.33; S, 25.94. Found: C, 38.76; H, 2.90; Br, 32.71; S, 26.02.

2-Bromo-6-formylthieno[3,2-*b*]thiophene (42). Treatment of 3-formylthieno[3,2-*b*]thiophene[28] (2 g) with NBS (1.9 g) as described above for **31** afforded a solid product (2.9 g) which was purified by chromatography on silica gel using a 1:1 mixture of light petroleum–ether as eluent, mp 104–105°, NMR (CS_2) δ_{CHO} 9.89 (s), δ_5 8.2 (s), δ_3 7.25 (s).

Anal. Calcd for $C_7H_3BrS_2O$: C, 34.02; H, 1.22; Br, 32.34; S, 25.95. Found: C, 34.10; H, 1.22; Br, 32.28; S, 25.70.

2-Bromo-6-methylthieno[3,2-*b*]thiophene (43). A mixture of **42** (3.5 g), diethylene glycol (12 ml), KOH (1.9 g), and 85% hydrazine (1.2 ml) was refluxed for 1 hr and the water formed distilled off. The temperature was raised to 170–180° and the mixture was stirred at this temperature for 3 hr and then poured on water. Extraction with ether afforded, after evaporation of the solvent, an oil which was purified by distillation: bp 120° (2 mm) (1.3 g); NMR (CS_2) δ_3 7.06, δ_5 6.85, δ_{CH_3} 2.26, J_{CH_3-5} = 1.1 Hz.

2,3,5-Tribromo-6-methylthieno[3,2-*b*]thiophene (44). To a solution of 3-methylthieno[3,2-*b*]thiophene[26] (1.54 g) in CS_2 (15 ml), bromine (5.3 g) in CS_2 (5 ml) was added dropwise and the resulting mixture was stirred at room temperature for 14 hr and then poured on 2 *N* NaOH solution. More CS_2 was added and the organic layer was separated, washed, and dried. A solid compound

was obtained (3.25 g), mp 179–180° from chloroform, NMR (CS_2) δ_{CH_3} 2.25.

Anal. Calcd for $C_7H_3Br_3S_2$: C, 21.50; H, 0.77; Br, 61.32; S, 16.40. Found: C, 21.48; H, 0.75; Br, 60.95; S, 16.42.

3,5-Dibromo-2-*tert*-butoxy-6-methylthieno[3,2-*b*]thiophene (45) and 3,5-Dibromo-6-methylthieno[3,2-*b*]thiophene (46). A solution of *n*-butyllithium (from 0.6 g of lithium) in ether was added dropwise to a suspension of **44** (11.7 g) in ether cooled at −70° and the mixture was kept at this temperature for 30 min and then at −30° for 1 hr. A 0.5 *M* solution of $MgBr_2$ in ether (100 ml) was added and the mixture was left to reach room temperature during 1 hr. After cooling at 0° a solution of *tert*-butyl perbenzoate (5 g) in ether was added and the solution was stirred for 3 hr. The mixture was poured on dilute HCl and the organic layer was washed with water and 10% NaOH solution and finally washed neutral with water and dried. The ether was removed and the residue was purified by column chromatography on Florisil using light petroleum as eluent. The first fractions contained **46** (1 g), mp 86–87°, NMR (CS_2) δ_2 7.17, δ_{CH_3} 2.27.

Anal. Calcd for $C_7H_4Br_2S_2$: C, 26.94; H, 1.29; Br, 51.22; S, 20.55. Found: C, 27.04; H, 1.39; Br, 51.07; S, 20.42.

The desired product **45** was then eluted (4.9 g), mp 65–66°, NMR (CS_2) δ_{CH_3} 2.18, $\delta_{C(CH_3)_3}$ 1.42.

Anal. Calcd for $C_{11}H_{12}Br_2OS_2$: C, 34.39; H, 3.15; Br, 41.61; S, 16.69. Found: C, 34.37; H, 3.18; Br, 41.82; S, 16.59.

2-*tert*-Butoxy-6-methylthieno[3,2-*b*]thiophene (22). To a solution of *n*-butyllithium (from 0.5 g of lithium), cooled at −70°, a solution of **45** (2.95 g) in ether was added and the mixture was kept at −50° for 30 min. Water was added and the ether layer was separated, washed, dried, and evaporated. The residue was purified on silica gel using light petroleum as eluent to afford **22** (1 g), mp 39–40°, NMR (CS_2) δ_5 6.7, δ_3 6.4, δ_{CH_3} 2.25, $\delta_{C(CH_3)_3}$ 1.37, $J_{CH_3\text{-}5}$ = 1.1 Hz.

Anal. Calcd for $C_{11}H_{14}OS_2$: C, 58.37; H, 6.24; S, 28.33. Found: C, 58.92; H, 6.33; S, 29.02.

3,6-Dimethylthieno[3,2-*b*]thiophene (48). Reaction of 3-bromo-4-methylthiophene[29] (4 g) with *n*-butyllithium (from 0.35 g of Li), sulfur (1 g), and chloroacetone (3 g), carried out as described above for **39,** afforded the (4-methyl-3-thienylthio)acetone, **47** (3.5 g), bp 95° (0.2 mm).

Anal. Calcd for $C_8H_{10}OS_2$: C, 51.58; H, 5.41; S, 34.42. Found: C, 51.69, H, 5.36; S, 34.05.

To a stirred mixture of $AlCl_3$ (3 g) and CS_2 (60 ml) a solution of **47** (3.2 g) in CS_2 was added and the mixture was worked up as described above for **38.** The solid product **48** was purified by crystallization from pentane, mp 88–89°, NMR (CS_2) δ_{CH_3} 2.3, δ_2 6.87, $J_{2\text{-}CH_3}$ = 1.1 Hz.

2-Bromo-3,6-dimethylthieno[3,2-*b*]thiophene (49) and 2,5-Dibromo-3,6-dimethylthieno[3,2-*b*]thiophene (50). Treatment of 48 (1.7 g) with NBS (1.8 g) in CH_3COOH (50 ml) as described above for **31** afforded a mixture of **50, 49,** and **48,** which were eluted in order from a silica gel column using light petroleum as eluent. The dibromo derivative **50** (0.3 g) melted at 140–142°, NMR (CS_2) δ_{CH_3} 2.22.

Anal. Calcd for $C_8H_6Br_2S_2$: C, 29.47; H, 1.85; Br, 49.02; S, 19.66. Found: C, 29.72; H, 1.97; Br, 48.86; S, 20.02.

The desired product **49** (2.1 g) had mp 47–48°, NMR (CS_2) δ_5 6.83, δ_3 2.27, δ_6 2.2, $J_{5\text{-}6}$ = 1.1 Hz.

Anal. Calcd for $C_8H_7BrS_2$: C, 38.87; H, 2.85; Br, 32.33; S, 25.94. Found: C, 39.02; H, 2.84; Br, 32.50; S, 26.05.

2-Bromo-3-methylthieno[2,3-*b*]thiophene (51). Treatment of 3-methylthieno[2,3-*b*]thiophene[28] (2.1 g) with NBS (2.4 g) in CH_3COOH (40 ml) as described above for **31** afforded **51** as an oil (3 g), bp 112–113° (0.8 mm), NMR (CS_2) δ_5 7.32, δ_4 7.05, δ_{CH_3} 2.25, $J_{4\text{-}5}$ = 5.25 Hz.

Anal. Calcd for $C_7H_5BrS_2$: C, 36.06; H, 2.16; Br, 34.28; S, 27.50. Found: C, 36.50; H, 2.22; Br, 34.31; S, 27.46.

2-Bromo-3-phenylthieno[2,3-*b*]thiophene (52). Treatment of 3-phenylthieno[2,3-*b*]thiophene[7] (2.24 g) with NBS (1.85 g) in acetic acid (60 ml) as described for **31** afforded an oil, bp 176–178° (0.8 mm) (3 g).

Anal. Calcd for $C_{12}H_7BrS_2$: C, 48.82; H, 2.37; Br, 27.07; S, 21.72. Found: C, 48.86; H, 2.31; Br, 27.40; S, 21.82.

2-Bromo-5-methylthieno[2,3-*b*]thiophene (53). Treatment of 2-methylthieno[2,3-*b*]thiophene[19] (4.3 g) with NBS (4.9 g) in CH_3COOH (90 ml) afforded a solid product (5.6 g) which was purified by column chromatography on silica gel using light petroleum as eluent, mp 79–80°, NMR (CS_2) δ_3 6.72, δ_4 6.98, δ_{CH_3} 2.53, $J_{3\text{-}CH_3}$ = 1.2 Hz.

Syntheses of the Thieno[3,2-*b*]thiophen-2-ones. The syntheses of these compounds have been carried out according to the general procedure described below for the parent compound **1b.** Details of preparations are also reported for the single products, whose physical and spectral data are collected in Tables II and III. In these tables data are also reported for compounds **7b** and **8b,** which were not prepared as described for **1b,** but were isolated as by-products from the syntheses of the corresponding 2,5-diones which will be described in a forthcoming paper.

Thieno[3,2-*b*]thiophen-2(3H)-one (1b). To a stirred solution of *n*-butyllithium (prepared from 0.45 g of Li) in ether, cooled at −70°, an ethereal solution of the 2-bromothieno[3,2-*b*]thiophene **29** (6.5 g) was added dropwise; the resulting solution of the 2-thieno[3,2-*b*]thienyllithium compound was stirred for 1 hr at −70° and then treated with *n*-butyl borate (9.2 g). The mixture was left to gradually reach room temperature during 5 hr and then shaken with 2 *N* HCl (25 ml). The layers were separated and the aqueous phase extracted with ether. The ethereal solution was extracted with three portions of 100 ml of cold 2 *N* NaOH and the alkaline solution was acidified with cold 2 *N* H_2SO_4; the separating boronic acid was dissolved in ether and 35% hydrogen peroxide (25 ml) was added. The mixture was vigorously stirred, under nitrogen, for 12 hr. The ethereal solution was washed several times with water and dried over Na_2SO_4, and the solvent was evaporated under nitrogen. A solid residue was obtained (2.1 g), which was purified by column chromatography. The physical and spectral data of **1b** are collected in Table II.

3-Methylthieno[3,2-*b*]thiophen-2(3*H*)-one (2b) and 3-Methylthieno[3,2-*b*]thiophen-2(5*H*)-one (2d). Treatment of **31** (7.8 g) as described above for **1b** afforded an oil (4 g), which was shown by NMR to be pure **2b.** Distillation of this product, bp 95–97° (1 mm), or elution through a silica gel column afforded a mixture of **2b** and **2d;** a mixture of the two isomers was also obtained when the oil was left to stand at room temperature for few hours. The isomerization was rapidly obtained if gaseous HCl was bubbled into the solutions of pure **2b** or **2d,** prepared as described below, or if a few drops of triethyllamine were added; the equilibrium composition, in CS_2, determined by NMR was **2b:2d** 40:60 ± 5.

Pure **2b** could be obtained with the base-extraction method. Pure **2d,** or a mixture of the two isomers, was dissolved in an excess of cold 2 *N* NaOH solution and ether was added; the mixture was vigorously stirred in an ice bath and acidified by the dropwise addition of a cold 2 *N* H_2SO_4 solution. The ether layer was separated, washed, dried, and evaporated under nitrogen; the oily residue consisted of pure **2b.**

Pure **2d** was obtained when to a saturated methanolic solution of **2b,** or a mixture of the two isomers, a few drops of pyridine were added; the **2d** which crystallized down from the solution was filtered and washed with cold methanol (mp 109–110°).

3-Ethylthieno[3,2-*b*]thiophen-2(3*H*)-one (3b) and 3-Ethylthieno[3,2-*b*]thiophen-2(5*H*)-one (3d). Treatment of **33** (5.2 g) as described above for **1b** afforded an oil (2.8 g) which consisted of pure **3b,** as shown by NMR. A mixture of **3b** and **3d** was obtained after chromatography on silica gel using light petroleum–ether (8:2) as eluent; fractions could be obtained in which pure **3d** was present (mp 98–99°). Pure **3b** could be regenerated by dissolving the mixture in alkali and acidifying in the presence of ether. The acid- or base-catalyzed equilibrium mixture in CS_2 contained **3b** and **3d** in the ratio of 75:25.

3-Phenylthieno[3,2-*b*]thiophen-2(3*H*)-one (4b) and 3-Phenylthieno[3,2-*b*]thiophen-2(5*H*)-one (4d). The oxidation of the boronic acid obtained from **36** (3 g) as described for **1b** afforded **4b** (1.6 g) as an oil which on attempted distillation gave rise to a mixture with the isomeric **4d;** the isomerization occurred also on standing or when passing the product through a silica gel column. At the equilibrium the mixture contained **4b** and **4d** in the ratio of 10:90. The base extraction method in this case did not give pure **4b** but a mixture in approximately equimolecular amounts.

5-Methylthieno[3,2-*b*]thiophen-2(3*H*)-one (5b). This compound was obtained in 70% yield starting from **37** (5.8 g) according to the usual procedure. The solid compound, mp 82–84°, did not suffer isomerization on crystallization or on treatment with acids or bases.

3,5-Dimethylthieno[3,2-*b*]thiophen-2(3*H*)-one (6b). This product was prepared in 65% yield from **40** (1.3 g) and could be distilled without suffering isomerization, bp 118° (1 mm). No changes were observed after treatment with acids or bases.

6-Methylthieno[3,2-*b*]thiophen-2(3*H*)-one (9b) and 6-Methylthieno[3,2-*b*]thiophen-2(5*H*)-one (9d). A. Treatment of **43** (3.5 g) as described above for **1b** afforded a residue (2 g) which was shown by NMR to contain 85% of **9b** and 15% of **9d.** Column chro-

matography of the reaction mixture on silica gel afforded pure **9b**, mp 61–62°. When this product was dissolved in alkali and the solution acidified in the presence of ether a mixture of the two isomers, **9b** and **9d**, in the ratio of 85:15 was obtained.

B. 2-*tert*-Butoxy-6-methylthieno[3,2-*b*]thiophene (**22**, 0.9 g) was warmed at 65°, under nitrogen, for 5 hr in the presence of traces of *p*-toluenesulfonic acid. The cooled mixture was dissolved in CS_2 and the NMR spectrum recorded; a mixture of **9b** and **9d** in the ratio of 30:20 was obtained. Column chromatography on silica gel of this mixture afforded pure **9b**, mp 61–62°.

3,6-Dimethylthieno[3,2-*b*]thiophen-2(3*H*)-one (10b) and 3,6-Dimethylthieno[3,2-*b*]thiophen-2(5*H*)-one (10d). From the oxidation of the boronic acid obtained from **49** (2.8 g), according to the procedure reported above for **1b**, an oily residue was obtained which was identified from its NMR spectrum as the pure tautomer **10b**. This compound spontaneously isomerized very rapidly to the isomeric **10d**; the transformation occurred almost instantaneously when HCl was bubbled into the CS_2 solution of **10b**. Column chromatography on silica gel of the reaction mixture gave rise to the pure 3,6-dimethylthieno[3,2-*b*]thiophen-2(5*H*)-one (**10d**), mp 127–128°. An alkaline solution of **10d**, treated with sulfuric acid in the presence of ether in the usual way, afforded a mixture of **10b** and **10d** in the ratio 30:70.

Syntheses of Thieno[2,3-*b*]thiophen-2-ones. The preparation of compounds **11**, **12**, **13**, and **16** from the bromo derivatives **38**, **51**, **52**, and **53**, respectively, was carried out according to the procedure described above for **1b** and their physical and spectral data are collected in Table IV. This table also contains the data concerning the products **14**, **15**, **17**, and **18**, which were obtained as by-products from the syntheses of the corresponding 2,5-diones.[10]

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Registry No.—**1b**, 56411-71-3; **2b**, 56411-72-4; **2d**, 56411-73-5; **3b**, 56411-74-6; **3d**, 56411-75-7; **4b**, 56411-76-8; **4d**, 56411-77-9; **5b**, 56411-78-0; **6b**, 56411-79-1; **7b**, 56411-80-4; **8b**, 56411-81-5; **9b**, 56411-82-6; **9d**, 56411-83-7; **10b**, 56411-84-8; **10d**, 56411-85-9; **11**, 56411-86-0; **12**, 56411-87-1; **13**, 56411-88-2; **14**, 56411-89-3; **15**, 56411-90-6; **16**, 56411-91-7; **17**, 56411-92-8; **18**, 56411-93-9; **22**, 56411-94-0; **29**, 25121-82-8; **31**, 56411-95-1; **32**, 56411-96-2; **33**, 56411-97-3; **34**, 56411-98-4; **35**, 56411-99-5; **36**, 56412-00-1; **37**, 56412-01-2; **38**, 31486-84-7; **39**, 56412-02-3; **40**, 56412-03-4; **41**, 56412-04-5; **42**, 56412-05-6; **43**, 56412-06-7; **44**, 56412-07-8; **45**, 56412-08-9; **46**, 56412-09-0; **47**, 56412-10-3; **48**, 56412-11-4; **49**, 56412-12-5; **50**, 56412-13-6; **51**, 56412-14-7; **52**, 56412-15-8; **53**, 56412-16-9; 3-methylthieno[3,2-*b*]thiophene, 1723-34-8; 3-bromothieno[3,2-*b*]thiophene, 25121-83-9; *N,N*-dimethylacetamide, 127-19-5; 3-phenylthieno[3,2-*b*]thiophene, 35022-15-2; 2-methylthieno[3,2-*b*]thiophene, 13393-75-4; 3-formylthieno[3,2-*b*]thiophene, 31486-88-1; 3-bromo-4-methylthiophene, 30318-99-1; chloroacetone, 78-95-5; 3-methylthieno[2,3-*b*]thiophene, 5911-97-7; 3-phenylthieno[2,3-*b*]thiophene, 35022-13-0; 2-methylthieno[2,3-*b*]thiophene, 26238-22-2.

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(1) (a) Laboratorio del CNR dei composti del carbonio contenenti eteroatomi, Ozzano-Emilia-Bologna, Italy. (b) University of Bari. (c) Istituto di Chimica Organica dell'Università-Viale Risorgimento, 4 Bologna, Italy.
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(17) Charge distributions have been calculated for the anions derived from compounds **1**, **2**, **9**, and **10** by using the CNDO/2 method and in every case it was found that the 3 position has a charge density considerably higher than the 5 position; position 7 also resulted to be slightly negative. The difference between charge densities in the 3 and 5 positions becomes less pronounced in compound **10**. The most relevant data were as follows: **1**, C_3 −0.1826, C_5 −0.1121, C_7 −0.0652; **2**, C_3 −0.1401, C_5 −0.1087, C_7 −0.0624; **9**, C_3 −0.1826, C_5 −0.1256, C_7 −0.0758; **10**, C_3 −0.1391, C_5 −0.1234, C_7 −0.0717. A CNDO/2 study was also carried out in order to investigate the influence of substituents on the relative stability of the two tautomers B and D; in qualitative agreement with the experimental results, it was found that, while in the unsubstituted product **1** form B is 4.33 kcal/mol more stable than **1d**, the introduction of a methyl group in the 3 position renders the form **2d** 4.71 kcal/mol more stable than **2b**, the effect becoming even more pronounced (5.13 kcal/mol) in the case of compound **10**, in which two methyl groups are present in the 3 and 6 position. In compound **9** the -2(3*H*)-one structure (B) is 1.56 kcal/mol more stable than the -2(5*H*)-one isomer (D). Details on calculations will be supplied on request.
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The Coupling of Thieno[3,2-*b*]thiophen-2-ones with Diazoalkanes

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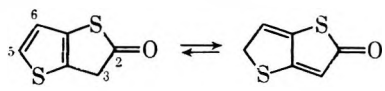
Thieno[3,2-*b*]thiophen-2(3*H*)-one reacted with diazoethane, in ether, to give the 3-ethylhydrazone of the thieno[3,2-*b*]thiophene-2,3-dione, the 2-ethoxythieno[3,2-*b*]thiophene, and the 3,3′-diethylthieno[3,2-*b*]thiophen-2-one; the hydrazone can further react with diazoalkanes to give the 2-alkoxy-3-ethylazothieno[3,2-*b*]thiophene. Reaction of diazoethane with 3-methylthieno[3,2-*b*]thiophen-2(3*H*)-one afforded only 2-ethoxy-3-methylthieno[3,2-*b*]thiophene and 3-methyl-3′-ethylthieno[3,2-*b*]thiophene; the same two products were formed starting from the tautomeric 3-methylthieno[3,2-*b*]thiophen-2(5*H*)-one. The formation of the reaction products is tentatively explained assuming the intermediate presence of the ethyldiazonium 2-thieno[3,2-*b*]thiophenate ion pair; decomposition within the ion pair should lead to O-alkylation or C-alkylation products, while the electrophilic attack of the diazonium cation on the anion would ultimately produce the ethylhydrazone. Some reactions of thieno[3,2-*b*]thiophen-2-ones and thieno[2,3-*b*]thiophen-2-ones with benzoyl chloride and carbonyl compounds also showed the property of these compounds of giving derivatives of the enol form as well as condensation products owing to the presence of active methylene groups.

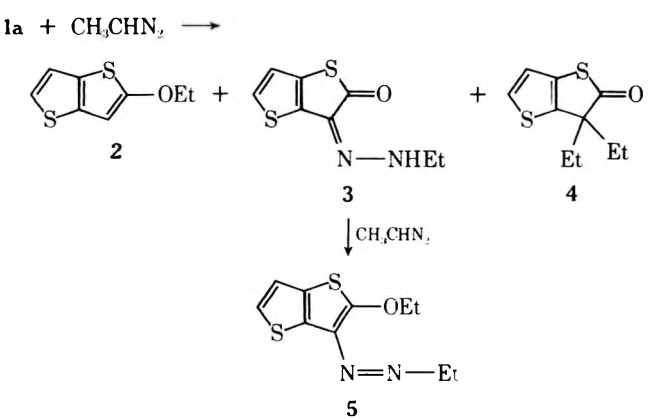
It has been shown that the 2-hydroxy derivatives of thieno[3,2-*b*]thiophene and of thieno[2.3-*b*]thiophene do not exist as enols but have the structure of thiolactones;[2] in the case of the [2,3-*b*] compound only the thieno[2,3-*b*]thiophen-2(3*H*)-one form could be identified while in the thieno[3,2-*b*]thiophene series an equilibrium exists between the two tautomeric structures thieno[3,2-*b*]thiophen-2(3*H*)-one (**1a**) and thieno[3,2-*b*]thiophen-2(5*H*)-one (**1b**). The equilibrium is strongly influenced by substituents; thus structure b becomes more stable when substituents in the 3 and/or 6 positions can conjugate or hyperconjugate with the carbon–carbon double bonds.



1a **1b**

In order to test their chemical behavior, a few reactions have been carried out with some of these potential 2-hydroxythienothiophenes with the expectation that derivatives could be obtained both from the enol and the thiolactone forms. The reactions investigated were those with diazoalkanes, carbonyl compounds, and acyl chlorides.

The reaction of **1a** with diazoethane in ether occurred smoothly at room temperature and afforded a mixture of compounds which could be separated by column chromatography. They were identified as 2-ethoxythieno[3,2-*b*]thiophene (**2**), thieno[3,2-*b*]thiophene-2,3-dione 3-ethylhydrazone (**3**), 3,3′-diethylthieno[3,2-*b*]thiophen-2-one (**4**), and 2-ethoxy-3-ethylazothieno[3,2-*b*]thiophene (**5**), which was formed in traces.

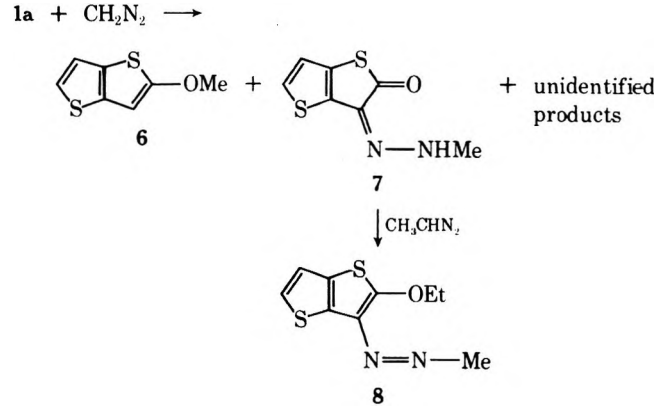


Product **2** was identified by comparison with an authentic sample prepared independently. Structure **3** was assigned to the main reaction product on the basis of its spectral and analytical data; the NMR spectrum in CS_2 showed a broad absorption at δ 11.25 (NH), two doublets at δ 7.18 and 6.83 (J = 5.25 Hz), respectively, due to the 5 and 6 protons of the thiophene ring, a quartet (J = 7.25 Hz) of doublets (J = 4.5 Hz) at δ 3.60 assigned to the CH_2 of the ethyl group, which is also coupled with the NH proton, and finally a triplet (J = 7.25 Hz) at δ 1.34 due to the CH_3 protons of the ethyl group; the infrared spectrum showed characteristic absorptions at 3220 (ν_{N-H}) and at 1635 cm^{-1} ($\nu_{C=N}$ + $\nu_{C=O}$) in agreement with the proposed structure.

The NMR spectrum of **4**, in CS_2, showed two doublets at δ 7.23 and 6.84 (J = 5.25 Hz) due to the two aromatic protons, a triplet (six hydrogens) at δ 0.7 (J = 7.2 Hz), and a complex spectral pattern (four hydrogens) centered at δ 1.75. This latter multiplet is ascribable to the methylenic protons which, being in nonequivalent environments, are diastereotopic; a complete analysis of the ABX_3 system was not attempted. A very similar multiplet is given by the methylene group of compound **11** described below.

As confirmed by independent synthesis, compound **5** forms through the reaction of **3** with excess diazoethane. Its structure is clearly demonstrated by the NMR spectrum, the chemical shifts of protons 5 and 6 being those expected for a thieno[3,2-*b*]thiophene derivative.[2,3]

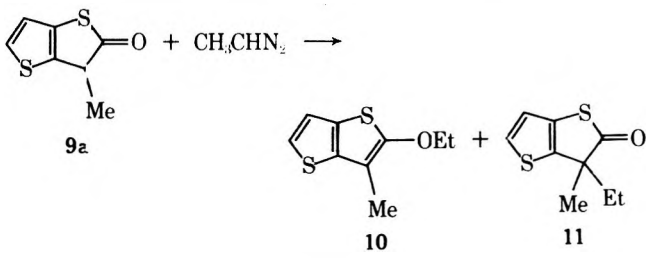
Thieno[3,2-*b*]thiophen-2(3*H*)-one also reacts with diazomethane, but the separation of the reaction products is more difficult. The two main compounds formed from this reaction were 2-methoxythieno[3,2-*b*]thiophene (**6**) and thieno[3,2-*b*]thiophene-2,3-dione 3-methylhydrazone (**7**).



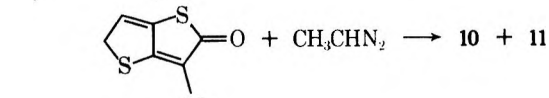
Compound **7**, like **3**, can react further with diazoalkanes to give the 2-alkoxy-3-alkylazothieno[3,2-*b*]thiophenes.

The treatment of **7** with diazoethane afforded 2-ethoxy-3-methylazothieno[3,2-*b*]thiophene (**8**).

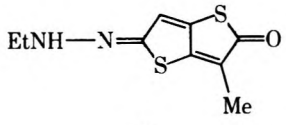
Reaction of diazoethane with 3-methylthieno[3,2-*b*]thiophen-2(3*H*)-one (**9a**) gave only two products identified as 2-ethoxy-3-methylthieno[3,2-*b*]-thiophene (**10**) and 3-methyl-3′-ethylthieno[3,2-*b*]thiophen-2-one (**11**). Compound **11** showed a special NMR pattern due to two different geminal hydrogens in the ethyl group. This is expected on the basis of the proposed structure where the ethyl group is linked to a chiral center. The NMR spectrum at 60 MHz was rather complex in the methylene region, which was very similar to that of compound **4**; the NMR spectrum was also recorded at 100 MHz and the different δ and J values of the ABX_3 system were calculated by use of the standard LAOCOON 3 program. The same mixture of **10** and **11** was obtained when the tautomer 3-methylthieno[3,2-*b*]thiophen-2(5*H*)-one (**9b**) was treated with diazoethane, suggesting that the two reactions probably proceed through a common intermediate. No evidence could be found for the 5-ethylhydrazone **12**, which could be expected to form by analogy with the reaction of **1a**.



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



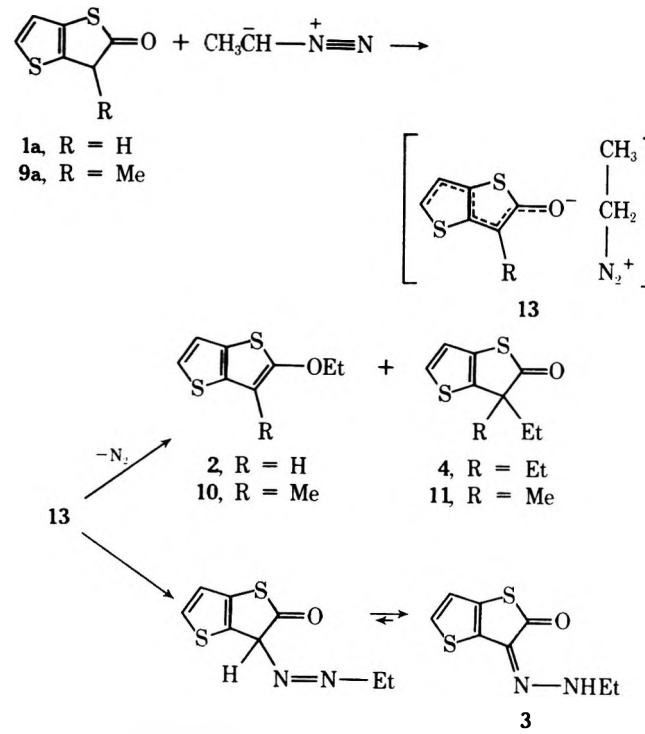
9b



12

A rationalization of the experimental results assumes that, in the ethereal solvent in which these reactions take place, an interaction occurs between the basic diazoalkane and the acidic thieno[3,2-*b*]thiophen-2-one to afford an ion pair, **13**, constituted by alkyldiazonium cation and the mesomeric 2-thieno[3,2-*b*]thiophenate anion; this ion pair represents the intermediate from which the products originate. Decomposition within the ion pair should lead to the products of O- and C-alkylation with evolution of nitrogen, by nucleophilic attack of the bident anion on the carbon atom holding the diazo group; a similar mechanism was proposed by Huisgen and Rüchardt[4,5] to explain the reaction of benzoic acid with diazo-*n*-propane in ether. Another reaction path open to the ion pair is the electrophilic attack of the diazonium cation on the mesomeric anion; this is a coupling reaction which ultimately would lead to the hydrazones. Although the coupling of an aromatic diazonium salt with compounds bearing activated carbon–hydrogen bonds is well documented,[6] this reaction is very seldom encountered with aliphatic diazonium salts. Examples are, however, known of coupling of diazomethane with carbonyl activated methylenic groups.[7,8]

The same mesomeric anion, and hence the same ion pair **13**, should obviously result from the interaction of diazoethane with either **9a** or **9b**. C-Monoalkylation products



1a, R = H
9a, R = Me

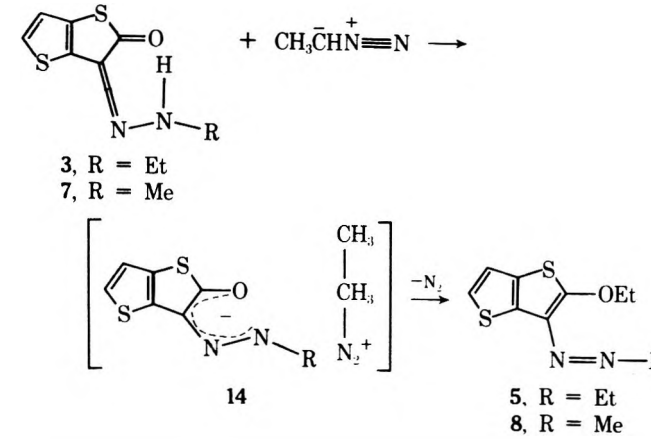
13

2, R = H
10, R = Me

4, R = Et
11, R = Me

3

were not isolated from the reaction of the unsubstituted compound **1a**, but the identification of compound **4** clearly indicates their intermediate formation; the 3-ethylthieno-[3,2-*b*]thiophen-2(3*H*)-one is not very stable[2] and it probably decomposes during the several column chromatography operations necessary to effect a complete separation of the various components. Compounds **3** and **7** still contain an acidic hydrogen atom which can react with the diazoalkane to afford a new ion pair, **14**, to which only the O-alkylation path, which regenerates the aromaticity of the thienothiophene system, is now open and products **5** or **8** are obtained.



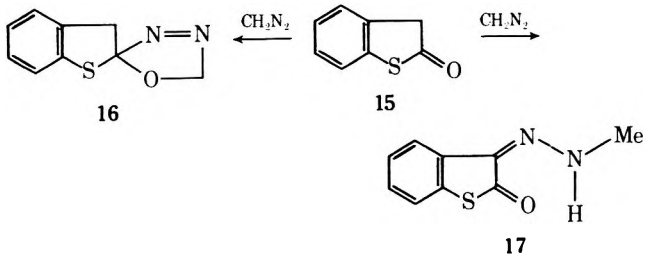
3, R = Et
7, R = Me

14

5, R = Et
8, R = Me

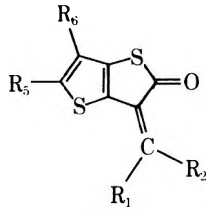
The coupling of the diazonium ion with the mesomeric anion and the C-alkylation reaction occur exclusively at the 3 position; position 5 is never involved. This is in agreement with greater electron density at the 3 than at the 5 position as determined by CNDO/2 calculations carried out on these anions.[2] As seen below, however, *reactions* do occur in the 5 position when attack at C-3 is blocked.

Conflicting results are reported in the literature concerning the structure of the reaction product of diazomethane and benzo[*b*]thiophen-2(3*H*)-one (**15**). Hawthorne and Porter[9] have reported the formation of the spirooxadiazoline **16**, while Schmiechen[8] has more recently suggested the hydrazone structure **17**. In the light of our results with thieno[3,2-*b*]thiophen-2-ones, the hydrazone structure seems more probable.

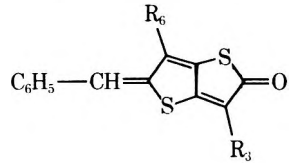


16 15 17

Reactions of the thieno[3,2-*b*]thiophene system with benzaldehyde and acetone led to compounds **18–22.**



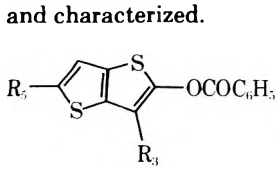
18, $R_1 = R_3 = R_4 = H$; $R_2 = C_6H_5$
19, $R_1 = R_2 = R_3 = Me$; $R_4 = H$
20, $R_1 = R_2 = Me$; $R_3 = H$; $R_4 = CMe_3$



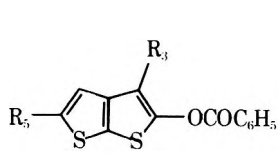
21, $R_3 = Me$; $R_4 = H$
22, $R_3 = R_4 = Me$

These compounds can be easily obtained in good yields by treating the solution of the appropriate thiolactone and acetone or benzaldehyde with gaseous hydrogen chloride; similar reactions were also given by the simpler thiolen-2-ones under the same experimental conditions.[10] Compounds **19** and **20** could also be obtained by simply passing 5-methylthieno[3,2-*b*]thiophen-2(3*H*)-one and 6-*tert*-butylthieno[3,2-*b*]thiophen-2(3*H*)-one, respectively, through an alumina column using a mixture of light petroleum and acetone as eluent. The condensations occur at the 3 position unless a substituent is present, in which case the reaction takes place at the 5 position, as is observed in compounds **21** and **22.**

Reactions which exclusively occur at the oxygen atom of the mesomeric anion are those with acyl chlorides which obviously afford the corresponding esters of the enol form; thus the 2-benzoyloxythieno[3,2-*b*]thiophenes or the 2-benzoyloxythieno[2,3-*b*]thiophenes can be conveniently obtained from the reaction of benzoyl chloride with an alkaline solution of the corresponding thienothiophen-2-ones. The following benzoyloxy derivatives, **23–28,** were prepared and characterized.



23, $R_3 = R_5 = H$
24, $R_3 = Me$; $R_5 = H$
25, $R_3 = H$; $R_5 = Me$



26, $R_3 = R_5 = H$
27, $R_3 = Me$; $R_5 = H$
28, $R_3 = H$; $R_5 = Me$

Experimental Section[11]

The thieno[3,2-*b*]thiophen-2(3*H*)-ones, thieno[3,2-*b*]thiophen-2(5*H*)-ones, and thieno[2,3-*b*]thiophen-2(3*H*)-ones were prepared as described in the previous paper.[2]

2-Methoxythieno[3,2-*b*]thiophene (6). A mixture of 2-bromothieno[3,2-*b*]thiophene[2] (1.95 g), sodium iodide (0.1 g), sodium methoxide (1.3 g), and CuO (0.35 g) in methanol (20 ml) was refluxed for 4 days; the solvent was distilled and the residue dissolved in ether and washed with water. The solvent was evaporated and the residue distilled to afford **6** (1 g): bp 80–81° (0.3 mm); NMR (CS_2) δ_{CH_3} 3.85, δ_3 6.29, δ_6 6.94, δ_5 7.03, J_{5-6} = 5.25, J_{3-6} = 0.4 Hz.

Anal. Calcd for $C_7H_6OS_2$: C, 49.38; H, 3.55; S, 37.66. Found: C, 49.17; H, 3.55; S, 37.66.

2-Ethoxythieno[3,2-*b*]thiophene (2). This compound was prepared as described above for **6** using sodium ethoxide and ethanol as solvent. The oily residue was chromatographed through a silica gel column using pentane as eluent. The desired product was obtained as a solid: mp 38–39°; NMR (CS_2) δ_{CH_3} 1.39, δ_{CH_2} 4.03, δ_3 6.28, δ_6 6.93, δ_5 6.96, $J_{CH_2CH_3}$ = 7.0, J_{5-6} = 5.25 Hz, J_{3-6} = 0.4 Hz.

Anal. Calcd for $C_8H_8OS_2$: C, 52.14; H, 4.38; S, 34.80. Found: C, 52.31; H, 4.44; S, 34.54.

2-Ethoxy-3-methylthieno[3,2-*b*]thiophene (10). The synthesis of this compound was carried out as described above for compound **2,** starting from the 2-bromo-3-methylthieno[3,2-*b*]thiophene.[2] The desired product was purified by distillation: bp 108° (0.7 mm); NMR (CS_2) $\delta_{CH_2CH_3}$ 1.35, δ_{CH_3} 2.13, $\delta_{CH_2CH_3}$ 4.01, δ_6 6.95, δ_5 7.02, $J_{CH_2CH_3}$ 7.0, J_{5-6} = 5.25 Hz.

Anal. Calcd for $C_9H_{10}OS_2$: C, 54.51; H, 5.08; S, 32.34. Found: C, 54.81; H, 5.0; S, 32.11.

Reaction of Thieno[3,2-*b*]thiophen-2(3*H*)-one (1a) with Diazoethane. A solution of thieno[3,2-*b*]thiophen-2(3*H*)-one (**1a,** 4 g) and diazoethane (5.5 g) in ether was stirred at room temperature for 2 hr and the solvent evaporated. The residue was chromatographed through a silica gel column using a mixture of light petroleum and benzene (4:1) as eluent. The first fractions contained 2-ethoxythieno[3,2-*b*]thiophene (**2,** 0.6 g), identical with the authentic sample, and 3,3′-diethylthieno[3,2-*b*]thiophen-2-one (**4,** 0.4 g), bp 70–72° (0.3 mm); ir (CCl_4) 1720 cm^{-1} (C=O).

Anal. Calcd for $C_{10}H_{12}OS_2$: C, 56.57; H, 5.70; S, 30.20. Found: C, 56.37; H, 5.80; S, 30.10.

The complete separation of the two compounds was obtained after a second column chromatography.

The following fractions contained a mixture of compounds which could be separated by repeated column chromatography on silica gel using light petroleum–ether (9:1) as eluent; after this treatment 2-ethoxy-3-ethylazothieno[3,2-*b*]thiophene (**5**) was obtained as an oil (0.1 g), identical with the product prepared independently as described below. A second compound was then isolated (2.2 g) which was identified as thieno[3,2-*b*]thiophene-2,3 dione 3-ethylhydrazone (**3**), mp 101–102°, yellow needles from ethanol.

Anal. Calcd for $C_8H_8N_2OS_2$: C, 45.26; H, 3.80; N, 13.20; S, 30.22. Found: C, 45.16; H, 3.55; N, 12.94; S, 30.67.

The spectroscopic data for compounds **3** and **4** are reported in the text.

Reaction of Thieno[3,2-*b*]thiophen-2(3*H*)-one (1a) with Diazomethane. A solution of **1a** (0.8 g) and diazomethane (1.9 g) in ether was stirred at room temperature for 2 hr; an amorphous precipitate was formed which was insoluble in the usual organic solvents and which could not be identified. The filtered solution was evaporated and the residue chromatographed through a silica gel column using light petroleum–ether (9:1) as eluent. The first fractions contained 2-methoxythieno[3,2-*b*]thiophene (**6,** 0.1 g), identical with the authentic compound; the following fractions contained the yellow thieno[3,2-*b*]thiophen-2,3-dione 3-methylhydrazone (**7,** 0.4 g) which was purified by crystallization from ethanol: mp 119–120°; NMR (CS_2) δ_5 7.23, δ_6 6.90, δ_{CH_3} 3.41, δ_{NH} 11.18, J_{5-6} = 5.25, J_{NH-CH_3} = 4.5 Hz; ir (CCl_4) 3220 (NH), 1635 cm^{-1} (C=N, C=O).

Anal. Calcd for $C_7H_6N_2OS_2$: C, 42.4; H, 3.05; N, 14.13; S, 32.34. Found: C, 42.42; H, 3.06; N, 14.03; S, 32.26.

Reaction of 3-Methylthieno[3,2-*b*]thiophen-2(3*H*)-one (9a) with Diazoethane. A solution of **9a** (7 g) and diazoethane (4 g) in ether was stirred at room temperature for 3 hr and the solvent evaporated. The residue was chromatographed through a silica gel column to afford a first fraction containing two compounds and other fractions in which unidentified oily products were present. The two compounds present in the first fractions were separated by chromatography on Florisil using light petroleum as eluent. The first component was identified as 2-ethoxy-3-methylthieno[3,2-*b*]thiophene (**10,** 2.1 g) by comparison with the authentic compound. The second product was attributed the structure of 3-methyl-3′-ethylthieno[3,2-*b*]thiophen-2-one (**11,** 1.2 g): bp 76–77° (0.3 mm); ir (CCl_4) 1720 cm^{-1}; NMR (CS_2) δ_5 7.32, δ_6 6.93, δ_{CH_3} 1.40, $\delta_{CH_2CH_3}$ 1.83, 1.74, $\delta_{CH_2CH_3}$ 0.78, J_{5-6} = 5.25, $J_{CH_2CH_3}$ 7.4 Hz. (The ABX_3 system given by the ethyl group has been reconstruct-

ed for the spectrum recorded at 100 MHz. The following values accurately reproduced the experimental spectrum: δ_{Me} 73.92 ± 0.05 Hz, δ_{H_a} 187.27 ± 0.034 Hz, δ_{H_b} 167.74 ± 0.035 Hz, $J_{H_aX_3}$ 7.18 ± 0.034 Hz, $J_{H_bX_3}$ = 7.22 ± 0.037 Hz, J_{gem} = −13.27 ± 0.044 Hz.)

Anal. Calcd for $C_9H_{10}OS_2$: C, 54.51; H, 5.08; S, 32.34. Found: C, 55.05; H, 5.10; S, 31.94.

Reaction of 3-Methylthieno[3,2-*b*]thiophen-2(5*H*)-one (9b) with Diazoethane. A solution of **9b** (3.3 g) and diazoethane (2 g) in ether was stirred at room temperature for 9 hr and then worked up as described above for compound **9a**. The two identified products were **10** and **11**; other compounds were formed in minute amounts and their identification was not possible.

2-Ethoxy-3-ethylazothieno[3,2-*b*]thiophene (5). A solution of thieno[3,2-*b*]thiophene-2,3-dione 3-ethylhydrazone (**3**, 1 g) in ether was treated with excess diazoethane and stirred at room temperature for 2 hr. The solvent was evaporated and the residue was chromatographed through silica gel using light petroleum–ether (9:1) as eluent. The product obtained (0.9 g) was purified by distillation: bp 137° (0.5 mm); NMR (CS_2) δ_5 7.10, δ_6 6.90, $\delta_{OCH_2CH_3}$ 4.46, $\delta_{NCH_2CH_3}$ 3.98, $\delta_{OCH_2CH_3}$ 1.48, $\delta_{NCH_2CH_3}$ 1.39, J_{5-6} = 5.25, $J_{OCH_2CH_3}$ = 7.0, $J_{NCH_2CH_3}$ = 7.5 Hz.

Anal. Calcd for $C_{10}H_{12}N_2OS_2$: C, 49.97; H, 5.03; N, 11.66; S, 26.68. Found: C, 50.40; H, 5.03; N, 11.66; S, 26.48.

2-Ethoxy-3-methylazothieno[3,2-*b*]thiophene (8). A solution of thieno[3,2-*b*]thiophene-2,3-dione 3-methylhydrazone (**7**, 0.3 g) was treated with excess diazoethane and the reaction mixture worked up as described above for **5**. The azo compound was obtained as an oil, which was purified by distillation: bp 125° (0.5 mm); NMR (CS_2) δ_5 7.15, δ_6 6.95, $\delta_{CH_2CH_3}$ 4.5, $\delta_{CH_2CH_3}$ 1.5, δ_{NCH_3} 3.93. J_{5-6} = 5.25, $J_{CH_2CH_3}$ = 7.0 Hz.

Anal. Calcd for $C_9H_{10}N_2OS_2$: C, 47.76; H, 4.45; N, 12.38; S, 28.33. Found: C, 47.90; H, 4.25; N, 12.50; S, 28.10.

3-Benzylidenethieno[3,2-*b*]thiophen-2-one (18). A stirred solution of thieno[3,2-*b*]thiophen-2(3*H*)-one (**1a**, 0.6 g) and benzaldehyde (0.4 g) in ethanol (10 ml), cooled in an ice bath, was treated with gaseous HCl. A yellow product precipitated after a few minutes and stirring was continued for 30 min. The solid was filtered off and crystallized from ethanol to give 0.7 g of **18**: mp 107–108°; NMR (CS_2) δ_5 7.24, δ_6 6.93, $\delta_{=CH}$ 7.30, $\delta_{C_6H_5}$ 7.32–7.75, J_{5-6} = 5.25, $J_{=CH-5}$ = 0.7 Hz; ir (CCl_4) 1700 cm^{-1} (C=O).

Anal. Calcd for $C_{13}H_8OS_2$: C, 63, 91; H, 3.30; S, 26.24. Found: C, 64.09; H, 3.28; S, 26.07.

3-Acetonylidene-5-methylthieno[3,2-*b*]thiophen-2-one (19). This compound was obtained as a yellow solid melting at 118–119°, after crystallization from ethanol, when 5-methylthieno[3,2-*b*]thiophen-2(3*H*)-one[2] was chromatographed through an alumina column and a mixture (3:1) of light petroleum and acetone was used as eluent: NMR (CS_2) δ_5 6.52, δ_5 2.57, δ_{CH_3-1} 2.23, δ_{CH_3-2} 2.40, J_{5-6} = 1.1 Hz; ir (CCl_4) 1690 cm^{-1} (C=O).

Anal. Calcd for $C_{10}H_{10}OS_2$: C, 57.11; H, 4.79; S, 30.49. Found: C, 57.09; H, 4.80; S, 30.36.

3-Acetonyliden-6-*tert*-butylthieno[3,2-*b*]thiophen-2-one (20). This product was obtained from 6-*tert*-butylthieno[3,2-*b*]thiophen-2(3*H*)-one[2] following the procedure described above for **19**: mp 83–85° from ethanol; NMR (CS_2) δ_5 6.87, δ_6 1.3, δ_{CH_3-1} 2.22, δ_{CH_3-2} 2.38; ir (CCl_4) 1690 cm^{-1} (C=O).

Anal. Calcd for $C_{13}H_{16}OS_2$: C, 61.86; H, 6.39; S, 25.41. Found: C, 61.16; H, 6.53; S, 25.75.

5-Benzylidene-3-methylthieno[3,2-*b*]thiophen-2-one (21). This compound was prepared from **9b** or **9a** following the procedure reported above for **18**: mp 128–129° from ethanol; NMR (CS_2) $\delta_{C_5H_5}$ 7.1–7.6, δ_6 6.72, $\delta_{=CH-}$ 6.92, δ_{CH_3} 1.96; ir (CCl_4) 1685 cm^{-1} (C=O).

Anal. Calcd for $C_{14}H_{10}OS_2$: C, 65.08; H, 3.90; S, 24.82. Found: C, 65.17; H, 3.80; S, 24.69.

5-Benzylidene-3,6-dimethylthieno[3,2-*b*]thiophen-2-one (22). This compound was obtained from 3,6-dimethylthieno[3,2-*b*]thiophen-2(5*H*)-one[2] according to the procedure reported above for **18**: mp 196–197° from ethanol; NMR (CS_2) $\delta_{C_6H_5}$ 7.2–7.7, $\delta_{=CH-}$ 7.0, δ_5 2.31, δ_3 2.03; ir (CCl_4) 1690 cm^{-1} (C=O).

Anal. Calcd for $C_{15}H_{12}OS_2$: C, 66.14; H, 4.44; S, 23.54. Found: C, 65.94; H, 4.60; S, 23.58.

2-Benzoyloxythieno[3,2-*b*]thiophene (23). A solution of thieno[3,2-*b*]thiophen-2(3*H*)-one (**1a**, 0.16 g) in 10% NaOH (1.5 ml) was treated with benzoyl chloride (0.15 g). A precipitate was formed which was extracted with ether. Evaporation of the solvent left a solid compound which was purified by crystallization from ethanol: mp 113–114°; NMR (CS_2) δ 8.18–8.01 (2 H, ortho protons), 7.6–7.35 (3 H, meta and para protons), δ_3 6.99, δ_6 7.08, δ_5 7.20, J_{5-6} = 5.2, J_{3-6} = 0.7 Hz; ir (CCl_4) 1760–1740 cm^{-1} (C=O).

Anal. Calcd for $C_{13}H_8O_2S_2$: C, 59.98; H, 3.10; S, 24.63. Found: C, 58.80; H, 3.13; S, 24.30.

2-Benzoyloxy-3-methylthieno[3,2-*b*]thiophene (24). This compound was prepared in 55% yield from either **9b** or **9a**, according to the procedure reported above for **23**: mp 89–90° from ethanol; NMR (CS_2) δ 8.20–8.03 (2 H, ortho protons), 7.6–7.3 (3 H, meta and para protons), δ_6 7.08, δ_5 7.18, δ_{CH_3} 2.28, J_{5-6} = 5.2 Hz; ir (CCl_4) 1760–1740 cm^{-1} (C=O).

Anal. Calcd for $C_{14}H_{10}O_2S_2$: C, 61.29; H, 3.67; S, 23.37. Found: C, 61.30; H, 3.53; S, 23.28.

2-Benzoyloxy-5-methylthieno[3,2-*b*]thiophene (25). This compound was obtained in 45% yield from 5-methylthieno[3,2-*b*]thiophen-2(3*H*)-one[2] after treatment with benzoyl chloride as described above for **23**: mp 130–131° from ethanol; NMR (CS_2) δ 8.2–8.0 (2 H, ortho protons), 7.6–7.3 (3 H, meta and para protons), δ_3 6.88, δ_6 6.73, δ_{CH_3} 2.55, J_{3-6} = 0.6, J_{6-CH_3} = 1.2 Hz; ir (CCl_4) 1760–1740 cm^{-1} (C=O).

Anal. Calcd for $C_{14}H_{10}O_2S_2$: C, 61.29; H, 3.67; S, 23.37. Found: C, 61.20; H, 3.79; S, 23.51.

2-Benzoyloxythieno[2,3-*b*]thiophene (26). This compound was obtained in 60% yield from thieno[2,3-*b*]thiophen-2(3*H*)-one[2] after treatment with benzoyl chloride as described above for **23**: mp 109–110° from ethanol; NMR (CS_2) δ 8.18–8.0 (2 H, ortho protons), 7.6–7.35 (3 H, meta and para protons), δ_3 6.95, δ_4 7.09, δ_5 7.23, J_{4-5} = 5.2 Hz; ir (CCl_4) 1760–1740 cm^{-1} (C=O).

Anal. Calcd for $C_{13}H_8O_2S_2$: C, 59.98, H, 3.10; S, 24.63. Found: C, 59.10; H, 3.15; S, 24.95.

2-Benzoyloxy-3-methylthieno[2,3-*b*]thiophene (27). The product was prepared in 52% yield from 3-methylthieno[2,3-*b*]thiophen-2(3*H*)-one[2] according to the procedure reported above for **23**: mp 95–96° from ethanol; NMR (CS_2) δ 8.18–8.0 (2 H, ortho protons), 7.6–7.3 (3 H, meta and para protons), δ_5 7.20, δ_4 7.02, δ_{CH_3} 2.29, J_{4-5} = 5.2 Hz; ir (CCl_4) 1760–1740 cm^{-1} (C=O).

Anal. Calcd for $C_{14}H_{10}O_2S_2$: C, 61.29; H, 3.67; S, 23.37. Found: C, 61.27; H, 3.81; S, 23.29.

2-Benzoyloxy-5-methylthieno[2,3-*b*]thiophene (28). This product was obtained in 50% yield from 5-methylthieno[2,3-*b*]thiophen-2(3*H*)-one[2] according to the procedure reported above for **23**: mp 146–148° from ethanol; NMR (CS_2) δ 8.18–8.0 (2 H, ortho protons), 7.6–7.3 (3 H, meta and para protons), δ_3 6.68, δ_4 6.74, δ_{CH_3} 2.55, J_{CH_3-4} = 1.1 Hz; ir (CCl_4) 1760–1740 cm^{-1} (C=O).

Anal. Calcd for $C_{14}H_{10}O_2S_2$: C, 61.29; H, 3.67; S, 23.37. Found: C, 60.59; H, 3.97; S, 23.85.

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Registry No.—**1a**, 56411-71-3; **2**, 56412-20-5; **3**, 56412-21-6; **4**, 56412-22-7; **5**, 56412-23-8; **6**, 56412-24-9; **7**, 56412-25-0; **8**, 56412-26-1; **9a**, 56411-72-4; **9b**, 56411-73-5; **10**, 56412-27-2; **11**, 56412-28-3; **18**, 56412-29-4; **19**, 56412-30-9; **20**, 56412-31-8; **21**, 56412-32-9; **22**, 56412-33-0; **23**, 56412-34-1; **24**, 56412-35-2; **25**, 56412-36-3; **26**, 56412-37-4; **27**, 56412-38-5; **28**, 56412-39-6; 2-bromothieno[3,2-*b*]thiophene, 25121-82-8; sodium methoxide, 124-41-4; sodium ethoxide, 141-52-6; 2-bromo-3-methylthieno[3,2-*b*]thiophene, 56411-95-1; diazoethane, 1117-96-0; diazomethane, 334-88-3; benzaldehyde, 100-52-7; 5-methylthieno[3,2-*b*]thiophen-2(3*H*)-one, 56411-78-0; 6-*tert*-butylthieno[3,2-*b*]thiophen-2(3*H*)-one, 56411-80-4; 3,6-dimethylthieno[3,2-*b*]thiophen-2(5*H*)-one, 56411-85-9; benzoyl chloride, 98-88-4; thieno[2,3-*b*]thiophen-2(3*H*)-one, 56411-86-0; 3-methylthieno[2,3-*b*]thiophen-2(3*H*)-one, 56411-87-1; 5-methylthieno[2,3-*b*]thiophen-2(3*H*)-one, 56411-91-7.

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Thermolysis of Ethyl Azidoformate in 2,3-Dimethyl-2-butene. An Example of a Simple Olefin Giving a Dominant 1,2,3-Δ^2-Triazoline Intermediate

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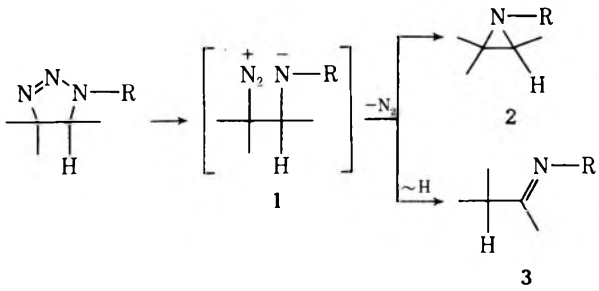
The thermolysis of ethyl azidoformate in refluxing 2,3-dimethyl-2-butene proceeds through competitive 1,2,3-Δ^2-triazoline and carbethoxynitrene routes. The triazoline route dominates by a factor of about 2–3. The main products are 3,3-dimethyl-2-butylidene ethyl carbamate (62%), 1-carbethoxy-2,2,3,3-tetramethylaziridine (36%), and *N*-1-(2,3-dimethyl-2-butenyl)ethyl carbamate (2.5%).

The thermolysis of alkyl azidoformates in many simple olefins proceeds by rate-determining loss of nitrogen to give carbalkoxynitrene intermediates.[1] The ultimate product is mainly the aziridine adduct of the olefin. However, the reaction can follow a different course with so-called activated olefins, that is olefins which are either strained[2–5] or contain strong electron-donating groups such as alkoxy[6] and amino[7] substituents. With such olefins, 1,3-dipolar cycloaddition becomes important, giving 1,2,3-Δ^2-triazoline intermediates. Similar trends have been observed with aryl azides.[8] A kinetic study of aryl azide cycloadditions to norbornene led Scheiner to propose a transition state for triazoline formation where some positive charge has developed at the olefinic carbon atom.[9]

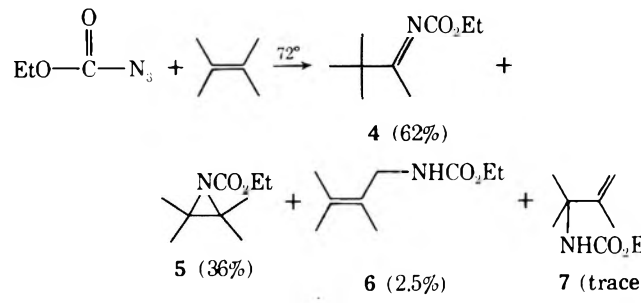
Differences in product distribution are among those features which distinguish between triazoline and nitrene intermediates. Like nitrenes, triazolines can give aziridines. However, unlike nitrenes, triazolines also produce anils, and these are usually the dominant products.[2,5,6,9–11] The often-proposed route to the anils involves a diazonium–betaine intermediate (**1**) which partitions between the aziridine **2** and the anil **3** on loss of nitrogen (Scheme I).

Scheme I



This paper describes the thermolysis of ethyl azidoformate in 2,3-dimethyl-2-butene. It appears to be the first report of a dominant 1,2,3-Δ^2-triazoline route for the thermolysis of an alkyl azidoformate in a simple olefin. The evidence further suggests that this is a borderline case of competitive nitrene and triazoline formation.

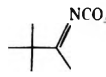
Thermolysis of ethyl azidoformate in refluxing 2,3-dimethyl-2-butene carried to about 90% conversion gives a quantitative yield of three carbamates. These are 3,3-dimethyl-2-butylidine ethyl carbamate (**4**), 1-carbethoxy-2,2,3,3-tetramethylaziridine (**5**), and *N*-1-(2,3-dimethyl-2-butenyl)ethyl carbamate (**6**). It is possible that a very small amount of *N*-3-(2,3-dimethyl-1-butenyl)ethyl carbamate (**7**) might also be present but is not completely resolved from the imide **4** under our VPC conditions. The imide **4** is not a product of the aziridine **5**. Repeating this reaction in the presence of labeled aziridine, 1-carbethoxy-2-methyl-d_1-2,3,3-trimethylaziridine (**8**) (Table I), gives negligible label in the imide **4**. Essentially all of the added label is accounted for as unconverted aziridine. Furthermore, forcing the thermal rearrangement of **5** at 150° (neat) gives only the carbamate **7** in a first-order reaction with $k_1 = 0.0207$ hr^{-1} ($\sigma = 2 \times 10^{-4}$), $t_{1/2} = 34$ hr.



The dominance of the imide **4** in the product distribution from the thermolysis of ethyl azidoformate in 2,3-dimethyl-2-butene suggests that the major route for this reaction is through 1-carbethoxy-4,4,5,5-tetramethyl-1,2,3-Δ^2-triazoline (**9**). This could decompose to the imide **4** through a methide shift analogous to the hydride shift in Scheme I. To confirm that the imide **4** does not result from an anomalous reaction of carbethoxynitrene, we generated authentic carbethoxynitrene in 2,3-dimethyl-2-butene by both α-elimination from *N*-*p*-nitrobenzenesulfonoxyurethane[12] (**10**) and photolysis of ethyl azidoformate.[13] The results show that the reaction of carbethoxynitrene with 2,3-dimethyl-2-butene is typical of carbethoxynitrene–olefin reactions. The expected aziridine **5** is, in fact, the dominant product with only small amounts of imide **4** being present.

There remains the question of whether any of the aziridine **5** from the thermolysis of ethyl azidoformate in 2,3-dimethyl-2-butene comes from a competing carbethoxynitrene route. The presence of carbamate **6** suggests that it does. Assuming that the mole ratio, **5/6**, from the α-elimination reaction (Table II) can serve as an approximate index of carbethoxynitrene-derived products, one can estimate that about 60% of the aziridine **5** from ethyl azidoformate thermolysis is produced in this way. This also means that triazoline formation is about three times faster than carbethoxynitrene formation. To test this prediction, a comparison was made between the observed first-order rate constant for ethyl azidoformate thermolysis in 2,3-dimethyl-2-butene and that in 2,3-dimethylbutane and cyclohexane (Table III). Only carbethoxynitrene formation can be rate determining in these two saturated C_6 hydrocarbons. Since the rate of azidoformate thermolysis is highly insensitive to solvent polarity,[1] such a comparison might serve as a useful test. From the above relative rate esti-

Table I
Thermolysis of 0.34 *M* Ethyl Azidoformate in 2,3-Dimethyl-2-butene with Added 1-Carbethoxy-2-methyl-d_1-2,3,3-trimethylaziridine

	Products, mmol			
				
Reactants (mmol)	$-d_0$	$-d_1$	$-d_0$	$-d_1$
1. EtO—C(=O)—N_3 (6.87)	3.84		2.24	
2. EtO—C(=O)—N_3 (6.87) 5 (0.22) 8 (1.87)	3.92	0.08 (σ = 0.07)	2.70	1.73

mate, thermolysis in 2,3-dimethyl-2-butene is expected to be about four times faster than in the saturated hydrocarbons. While there is a rate enhancement in 2,3-dimethyl-2-butene, it is only by a factor of 2.0–2.4 rather than 4. This is in better agreement with the 2.6-fold rate enhancement expected if all the aziridine **5** were produced through carbethoxynitrene. Thus, these two estimates of the carbethoxynitrene component in ethyl azidoformate thermolysis are not in good agreement. They bracket the nitrene contribution at between 60 and 100% of the aziridine **5** produced. The reason is unclear. Possibly the high sensitivity of the predicted relative rate to small errors in the analysis of a minor component, the carbamate **6**, is responsible. Nevertheless, both estimates support carbethoxynitrene as an important source of the aziridine **5**.

Therefore, it seems that four methyl substituents on a double bond provide sufficient charge stabilization in the triazoline-forming transition state[9] to make it the dominant reaction. This raises the interesting question of whether this chemistry of ethyl azidoformate is peculiar to 2,3-dimethyl-2-butene or fairly general for tetraalkyl-substituted olefins.

Experimental Section

Reagents. Ethyl azidoformate was prepared according to the method of Lwowski and Mattingly[14] and *N*-*p*-nitrobenzenesulfonoxyurethane (**10**) was prepared by the method of Lwowski and Maricich.[12] 2,3-Dimethyl-2-butene (99%) was purchased from Chemical Samples Co., Columbus, Ohio, and distilled from Na–K under nitrogen. A middle fraction was taken and shown by VPC to be >99.9% pure.

Thermolysis of Ethyl Azidoformate in 2,3-Dimethyl-2-butene. Preparative Scale. A 250-ml, three-neck flask was fitted with a water-cooled condenser, a gas dispersion tube, and a magnetic stirring bar. The opening at the top of the condenser was directed into a shallow mercury well with tubing. The apparatus was flame dried under nitrogen and charged with 5.94 g (0.0517 mol) of ethyl azidoformate and 150 ml of 2,3-dimethyl-2-butene. The stirred solution was purged with nitrogen, then heated, under nitrogen, at gentle reflux for 310 hr. This corresponds to about 90% conversion as measured by the disappearance of the 2140-cm^{-1} band in ethyl azidoformate. The product was distilled on a spinning band column, giving aziridine **5**: bp 59° (1.5 mm); ir (neat) no NH, 1705 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.26 ppm (t, 3, J = 7 Hz), 1.28 ppm (s, 12), 4.13 (q, 2, J = 7 Hz); mass spectrum parent ion m/e 171.

Anal. Calcd for $C_9H_{17}NO_2$: C, 63.12; H, 10.01; N, 8.18. Found: C, 63.32; H, 9.83; N, 8.28.

Imide **4**: bp 69–70° (1.8 mm); ir (neat) no NH, 1717 (C=O), 1660 cm^{-1} (C=N); NMR ($CDCl_3$) δ 1.16 (s, 9), 1.32 (t, 3, J = 7 Hz), 1.97 (s, 3), 4.24 ppm (q, 2, J = 7 Hz); mass spectrum parent ion m/e 171.

Anal. Calcd for $C_9H_{17}NO_2$: C, 63.12; H, 10.01; N, 8.18. Found: C, 62.20; H, 9.91; N, 8.10.

Table II
Product Distributions from the Reaction of Carbethoxynitrene with 2,3-Dimethyl-2-butene

	Products, % yield			
Method	4	5	6	7
α-Elimination (10)[a]	0.5	59.	6.9	1.0
Photolysis (EtO—C(=O)—N_3)[b]	1.	54.	8.8	0.9

[a] Dichloromethane used as cosolvent (45% v/v); reaction carried out at 42°. [b] Reaction carried out at 0°.

Table III
Kinetics of Ethyl Azidoformate Decomposition at 70° in C_6 Hydrocarbon Solvents

Solvent	Concn, *M*	$k \times 10^3$, hr^{-1}	$\sigma \times 10^3$	$k(>=<)/k$
2,3-Dimethyl-2-butene	0.23	5.3	0.11	1.0
2,3-Dimethylbutane	0.18	2.7	0.01	2.0
Cyclohexane	0.23	2.2	0.06	2.4

The carbamate **6** was not isolated but identified by comparing its VPC retention time and normalized mass spectrometric fragmentation pattern with those of authentic material. Carbamate **6**: bp 81–82° (0.35 mm); ir (neat) 3340 (NH), 1695 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.23 (t, 3, J = 7 Hz), 1.68 (broad s, 9), 3.78 (d, 2, J = 6 Hz), 4.12 (q, 2, J = 7 Hz), 4.7 ppm (broad, 1).

Analytical Scale. A two-neck, 25-ml flask was fitted with a water-cooled condenser and a gas inlet tube. The opening at the top of the condenser was directed into a shallow mercury well with tubing. The apparatus was flame dried under nitrogen and charged with 0.790 g (0.0068[7] mol) of ethyl azidoformate and 20 ml of 2,3-dimethyl-2-butene. The system was purged with 600 ml of nitrogen, then heated at gentle reflux for 310 hr. The reaction mixture was cooled, transferred into a container having a known quantity of naphthalene (internal VPC standard), and analyzed by VPC. Quantitative analysis was performed on a calibrated 5 ft × 0.25 in. column packed with 20% Ucon 50 HB5100 on 70/80 mesh Anakrom U. A glass sleeve was used in the injection port, which was maintained at 190–200°.

Photolysis of Ethyl Azidoformate. A PCQ9G-1 photochemical immersion lamp, Ultraviolet Products, Inc., with a 2537-cm^{-1} peak intensity at 2.5 W was housed in a reaction vessel prepared from a 7.5-in. length of 18-mm Pyrex tubing. The reactor contained a gas inlet and outlet tube. It was charged with 0.88 g (7.6 mmol) of ethyl azidoformate and 21 ml of 2,3-dimethyl-2-butene. The solutions was purged with 400 ml of nitrogen through a 6-in. needle, cooled in an ice bath, and irradiated for 18 hr. Quantitative analysis was performed by VPC in the usual way. Distillation gave 0.53 g (41%) of aziridine **5**.

α-Elimination in *N*-*p*-Nitrobenzenesulfonoxyurethane (10). A three-neck, 50-ml flask was fitted with a nitrogen inlet, a rubber septum, a magnetic stirring bar, and a water-cooled condenser. The opening at the top of the condenser was directed to a shallow mercury well with tubing. The apparatus was flame dried under nitrogen, then charged with 0.770 g (2.65 mmol) of **10**, 11.7 ml of 2,3-dimethyl-2-butene, and 9.5 ml of dichloromethane. The system was purged with about 400 ml of nitrogen and heated to gentle reflux. Triethylamine (0.42 ml) was then added through a syringe over a 5-min period. Triethylammonium *p*-nitrobenzenesulfonate precipitates during the addition. After addition was complete, the mixture was stirred at gentle reflux for an additional 2 hr and cooled, and the solution was decanted from the precipitate into a bottle containing naphthalene, the VPC internal standard. The precipitate was rinsed twice with 2,3-dimethyl-2-butene and the rinse combined with the decanted solution. The mixture was then chilled and shaken with 15 ml of cold water. The organic phase was decanted off, chilled to −13° to crystallize residual water, and analyzed by VPC in the usual way. The purpose of this water extraction step is to remove small amounts of dissolved triethylammonium *p*-nitrobenzenesulfonate. This can catalyze some rearrange-

ment of the aziridine 5 to the carbamate 7 in the injection port of the gas chromatograph. For example, analysis of the chilled reaction mixture without the water extraction step gives 4 (0.8%), 5 (55%), 6 (7.0%), and 7 (2.8%).

1-Chloro-2,3-dimethyl-2-butene-4-d_1 (11). DCl was generated from 566 g (4.02 mol) of benzoyl chloride and 16.1 g (0.805 mol) of D_2O according to the method of Brown and Groot.[15] This was directed through a gas dispersion tube into a stirred, three-neck, 250-ml flask containing 120.1 g (1.46 mol) of 2,3-dimethyl-1,3-butadiene cooled to −80°.[16] After DCl generation was complete, the contents were purged with nitrogen and allowed to warm to room temperature and stand for 3 days. Distillation gave three fractions, 30.0 g (0.253 mol) of 3-chloro-2,3-dimethyl-1-butene-4-d_1 (12), bp 35° (45 mm) [lit.[16] bp 32° (45 mm)], 97 g of an unknown fraction, bp 37–53° (45 mm), and 48.6 g (0.410 mol) of the chloride 11, bp 53–55° (45 mm) [lit.[16] bp 57.7° (45 mm)]. Mass spectra: 11, 7% d_0, 88% d_1, 5% d_2; 12, 7% d_0, 89% d_1, 4% d_2.

2,3-Dimethyl-2-butene-d_1 (13). The chloride 11 was reduced using the method of Brown and Bell.[17] A three-neck 1-l flask was fitted with an addition funnel, a magnetic stirring bar, a thermometer, and a water-cooled condenser. It was charged with 390 ml of glyme, 210 ml of water, and 24 g (0.60 mol) of sodium hydroxide. The mixture was stirred and heated to 55°. To this was added 90.6 g (2.40 mol) of sodium borohydride. When dissolved, 8.75 g (0.0739 mol) of the chloride 11 was added over a 15-min period. Some cooling was necessary to maintain the temperature at 50–55°. There was considerable gas evolution. The mixture was allowed to cool and stirred overnight. It was then extracted with two 400-ml aliquots of water. The organic phase was then dried over $CaSO_4$ and distilled on a spinning band column giving 11.6 g (46%) of 13, bp 71–72°, NMR ($CDCl_3$) 1.63 ppm (s).

1-Carbethoxy-2-methyl-d_1-2,3,3-trimethylaziridine (8). A solution of 1.57 g (13.6 mmol) of ethyl azidoformate in 2[illegible] ml of the butene 13 was photolyzed in the usual way. Distillation gave 1.14 g (49%) of aziridine 8: NMR ($CDCl_3$) same as that of aziridine 5; mass spectrum, 10% d_0 (σ 1.3), 85% d_1 (σ 1.4), 5% d_2 (σ 1.2).

Kinetics of 1-Carbethoxy-2,2,3,3-tetramethylaziridine (5) Thermolysis. This experiment was carried out by proton NMR using a sealed 30-μl Kontes microcell charged with aziridine 5. The cell was placed in a constant-temperature bath at 150° and periodically removed for analysis. The rate of carbamate 7 formation was followed by measuring the change in the combined area of the two vinylic protons in 7 relative to the total area of the methylene quartet of the ethoxy groups present. The final spectrum, at 88% conversion, was that of the carbamate 7.

Kinetics of Ethyl Azidoformate Thermolysis. Cyclohexane and 2,3-dimethylbutane were purchased and further purified by distillation from Na–K under nitrogen. Solutions of ethyl azidoformate were prepared, charged into several 7-mm glass tubes, evacuated, and sealed with a torch. These were placed in a constant-temperature bath and individual samples taken periodically for analysis. The rate of ethyl azidoformate decomposition was followed by infrared using the disappearance of the 2140-cm^{-1} band.

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Registry No.—4, 56488-01-8; 5, 56488-02-9; 6, 1611-51-4; 8, 56488-03-0; 10, 2955-74-0; 11, 56488-04-1; 12, 56488-05-2; 13, 56488-06-3; ethyl azidoformate, 817-87-8; 2,3-dimethyl-2-butene, 563-79-1; DCl, 7698-05-7; 2,3-dimethyl-1,3-butadiene, 513-81-5.

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Dehydrogenation of Heterohelicenes by a Scholl Type Reaction. The Dehydrohelicenes[1]

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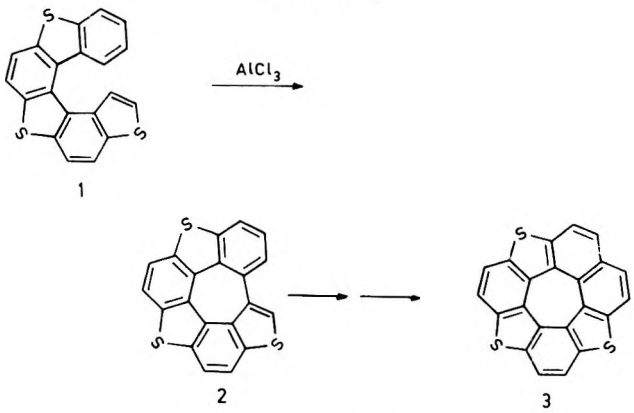
The reaction of seven heterohelicenes with $AlCl_3$ is described. The products are compounds in which the two helical termini of a helicene are connected by a σ bond. They are called dehydrohelicenes. The intramolecular ring closure is limited to hetero[5]- and -[6]helicenes. In addition to the synthesis, the spectral properties of dehydrohelicenes are discussed.

In our study of the synthesis, resolution, and chemistry of heterohelicenes,[2] the preparation of dehydrohelicenes by a Scholl reaction became of importance. The Scholl reaction has been defined by Balaban and Nenitzescu[3] as the elimination of two aryl-bound hydrogens accompanied by the formation of an aryl–aryl bond under the influence of Friedel–Crafts catalysts. Groen and Wynberg used this reaction in preparing 2 in low yield from the heterohexahelicene 1[4] (Scheme I). The conversion of 2 to the [7]heterocirculene 3[5] prompted us to undertake a more systematic study of the Scholl reaction of heterohelicenes. Compounds such as 2, in which the two helical termini of a helicene are connected by a σ bond, will be called dehydrohelicenes.[6]

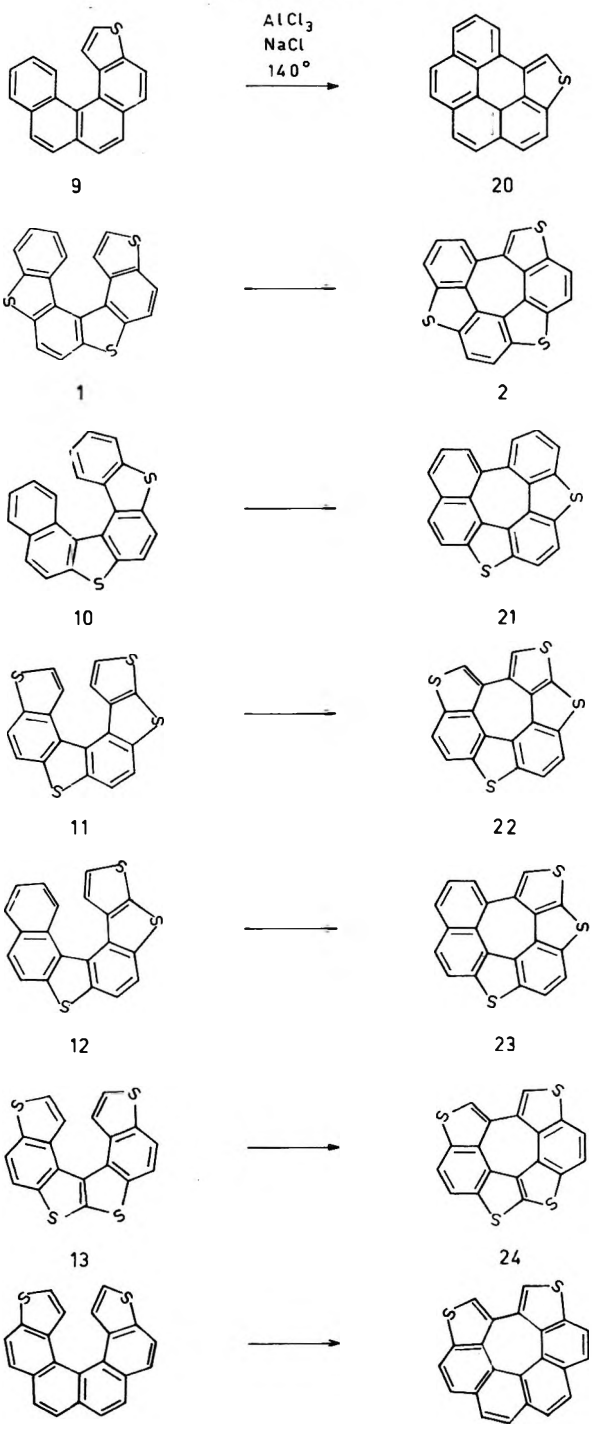
Results

Most of the heterohelicenes used in this study (Schemes II and III) have been described previously.[4,7] The new compounds 4, 6, 7, 9, and 16 were prepared by standard methods.[1] In the original "Scholl" method employed by Groen,[4] 1 was dissolved in benzene at room temperature and to this solution an excess of $AlCl_3$ was added. The mixture was allowed to stand for 24 hr prior to isolating 2. This method is improved when a mixture of $AlCl_3$ and NaCl is used.[8] When 1, $AlCl_3$, and NaCl were mixed together and heated to 140°, a black melt was formed immediately. After hydrolysis of this melt 2 was obtained in 95% yield. The other dehydrohelicenes were obtained in a similar manner. A

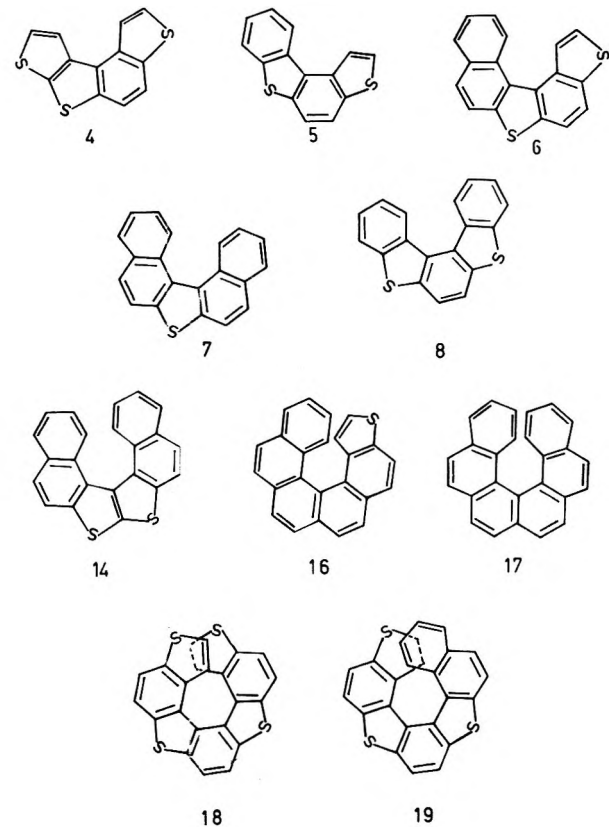
Scheme I



Scheme II



Scheme III



summary of the successful ring closures is given in Scheme II. Clearly, the reaction is limited to hetero[5]- and -[6]helicenes.

The helicenes **4–8, 14, 16, 17,**[9] **18,** and **19** (Scheme III) when subjected to similar reaction conditions gave no well-defined products.

Attempts to perform the Scholl reaction with proton acids as catalysts[3,10] were unsuccessful. Treatment of **13** with FSO_3H or 98% H_2SO_4 yielded only water-soluble products, presumably resulting from sulfonation of the helicene. No reaction could be obtained with 40% HF, benzenesulfonic acid, trifluoroacetic acid, 5% H_2SO_4 in THF, or liquid hydrochloric acid. This might be due to the inhomogeneity of the medium or to the insufficient acidity of the acids used.

Properties of Dehydrohelicenes. The dehydrohelicenes are extremely insoluble in most organic solvents. In benzene and carbon disulfide they are sparingly soluble. They dissolve in $AsCl_3$ under the formation of paramagnetic species. They crystallize from *p*-xylene in long needles and have high melting points. In solution they fluoresce weakly. Owing to their extreme insolubility no well-resolved NMR spectra could be obtained. The mass spectra of the dehydrohelicenes resemble those of the corresponding helicenes.[4,7] In addition to high-intensity singly and double charged molecular ions, only small-intensity fragments were observed. The results are collected in Table I.

The uv spectra of the dehydrohelicenes are drawn in Figure 1. In these spectra a large shift of the α band (± 30 nm) is observed when compared with the uv spectra of the corresponding helicenes. In contradistinction to the α band, only a small shift of the p band is observed. Those dehydrohelicenes (**22–24**) containing a thieno[2,3-*b*]thiophene moiety **26** behave differently.[7] Relative to the corresponding helicenes (**11–13**) there is only a moderate red shift of the longest wavelength band. The red shift depends upon the place of **26** in the molecule. In order to understand this

Table I
Mass Spectra of the Dehydrohelicenes, Relative Abundance (M^+ = 100)

Compd	$-S^+$	$-H_2S^+$	$-CS^+$	$-CHS^+$	$-CHS_2^+$	$-C_2S_2^+$	M^{2+}	$M-C_2S_2^{2+}$
20			8	12			32	
2	4	6	4	10	2		32	
21							40	
23	5	5	5	10	10	4	20	5
25	7	10		10			28	
22			10	10	3	10	15	10
24			10	10	4	10	30	15

phenomenon in a more quantitative way, the uv spectra of **2**, **22**, and **24** were calculated by PPP type of semiemperical SCF-MO calculations.[11] The results are given in Tables II and III.

Table II
Experimental and Calculated Transitions of the Dehydrohelicenes 2, 22, and 24

Dehydrohelicene	Experimental, nm (log ε)		Calculated, nm (*f*)		
2	413 (2.88),	392 (3.32),	384 (0.05),	350 (0.10),	332 (0.74),
	372 (3.56),	356 (3.89),	320 (0.33),	299 (0.09),	285 (0.46),
	343 (4.07),	334 (4.36),	280 (0.65),	269 (0.54),	265 (0.03),
	321 (4.19),	309 (4.07),	258 (0.56),	250 (0.39),	246 (0.01),
			235 (0.03),	223 (0.10)	
22	376 (4.00),	359 (3.91),	360 (0.29),	341 (0.10),	310 (0.39),
	343 (4.14),	328 (4.12)	309 (0.20),	294 (0.33),	277 (0.86),
			271 (0.11),	267 (0.33),	259 (0.59),
			256 (0.01),	247 (0.41),	241 (0.05),
			235 (0.11),	230 (0.00)	
24	363 (4.00),	347 (4.08),	350 (0.49),	325 (0.51),	319 (0.10),
	333 (4.00),	312 (4.09),	304 (0.08),	288 (0.05),	286 (0.01),
	300 (4.12)		269 (0.09),	262 (0.79),	258 (1.48),
			254 (0.02),	250 (0.01),	239 (0.27),
			232 (0.20),	231 (0.03)	

All absorptions calculated by this PPP method gave energies higher than those observed. Only an approximate correspondence between calculated and experimental data was obtained.

Experimental Section

All reagents were purified where necessary by standard methods. For column chromatography neutral alumina (Merck A1) for silica gel (B. D. H.) was used. Melting points (corrected) up to 300° were determined on a Mettler FP_1 microscope and between 300 and 350° (uncorrected) on a Reichert hot-stage apparatus.

Uv spectra were measured on a Zeiss PMQ 11 or recorded with a Beckman DB-G grating spectrophotometer. Mass spectra were obtained with a AEI MS 902 instrument and recorded by Mr. A. Kiewiet. Elemental analysis were carried out by Mr. H. Draayer, Mr. J. Ebels, and Mr. J. Vos in the microanalytical department of this laboratory.

The preparation of dehydrohelicenes is illustrated by a detailed procedure for the preparation of **24**.

6,7-Epithio-2,5,10-trithiabenz[1.8]azuleno[4,5,6,7-*jkl*]-*as*-indacene (24). To a mixture of **13** (100 mg, 0.28 mmol) and sodium chloride (300 mg, 5.1 mmol) was added as quick as possible 1500 mg (11.2 mmol) of finely powdered aluminum chloride. The three compounds were mixed thoroughly, the reaction flask was provided with a $CaCl_2$ drying tube, and the flask was inserted into an oil bath preheated to 140°. Immediately the flask contents turned black and after 5 min the mixture started to melt. As soon as the melt was completed (10 min) the flask was taken out of the oil bath and the reaction mixture was hydrolyzed directly with distilled water. A slightly yellow precipitate was formed, which was filtered off and washed with water until neutral. After drying in vacuo over P_2O_5 the mixture was taken up in a minimum amount of benzene and chromatographed on alumina with benzene as eluting agent. In this way 92 mg (92%) of pure **24** was obtained. An analytically pure sample of **24** (mp 318° dec) was obtained by recrystallization from *p*-xylene, from which it crystallizes in long white needles.

Anal. Calcd for $C_{18}H_6S_4$: C, 61.69; H, 1.73; S, 36.59. Found: C, 61.8; H, 1.9; S, 36.4.

Pyreno[5,4,3-*cde*]benzo[*b*]thiophene (20). The pyrenobenzo[*b*]thiophene **20** was obtained by treatment of **9** (100 mg, 0.35 mmol) with sodium chloride (300 mg, 5.1 mmol) and aluminum chloride (1500 mg, 11.2 mmol). After hydrolysis of the melt and working up of the reaction mixture a yellow-orange precipitate was formed which was taken up in benzene (200 ml). The benzene layer was washed with water and $NaHCO_3$ solution and dried over $MgSO_4$. After filtering and evaporation of the solvent the residue was chromatographed on alumina with benzene. After removal of the solvent the residue was recrystallized twice from methylcyclohexane. The analytically pure compound (long orange yellow needles) melted at 298–299°. The yield was 95 mg (95%).

Table III
The Red Shift of the Longest Wavelength Absorption of the Dehydrohelicenes Relative to the Corresponding Helicenes

Compd	Observed, nm	Calculated, nm
1 → 2	29	29
11 → 22	10	13
13 → 24	24	13

Anal. Calcd for $C_{20}H_{10}S$: C, 85.09; H, 3.57; S, 11.35. Found: C, 85.0; H, 3.8; S, 11.4.

1,11-Etheno-2,5,10-trithiabenz[1.8]azuleno[4,5,6,7-*jkl*]-*as*-indacene (2). The dehydrohelicene **2** was obtained by treatment of **1** (262 mg, 0.76 mmol) with sodium chloride (800 mg, 13.6 mmol) and aluminum chloride (4 g, 30 mmol). After hydrolysis of the melt a yellow precipitate was formed which was filtered, washed, and dried. After drying the product was sublimed in vacuo (220°/0.001 mm) and recrystallized from benzene. The yield of analytically pure **2** (mp 344–345°, lit.[4] 359–363°) was 180 mg (69%).

Anal. Calcd for $C_{20}H_8S_3$: C, 69.73; H, 2.34; S, 27.92. Found: C, 69.7; H, 2.3; S, 27.8.

4,7-Dithianaphth[2′,1′,8′:3,4,5]azuleno[1,8,7,6-*cdef*]fluorene (21). The dehydrohelicene **21** was obtained by treatment of **10** (300 mg, 0.88 mmol) with sodium chloride (900 mg, 15.2 mmol) and aluminum chloride (4.5 g, 33.6 mmol). After hydrolysis of the melt a brown-yellow precipitate was formed which was taken up in 200 ml of benzene. The benzene solution was washed with water and sodium bicarbonate solution and dried over $MgSO_4$. After evaporation

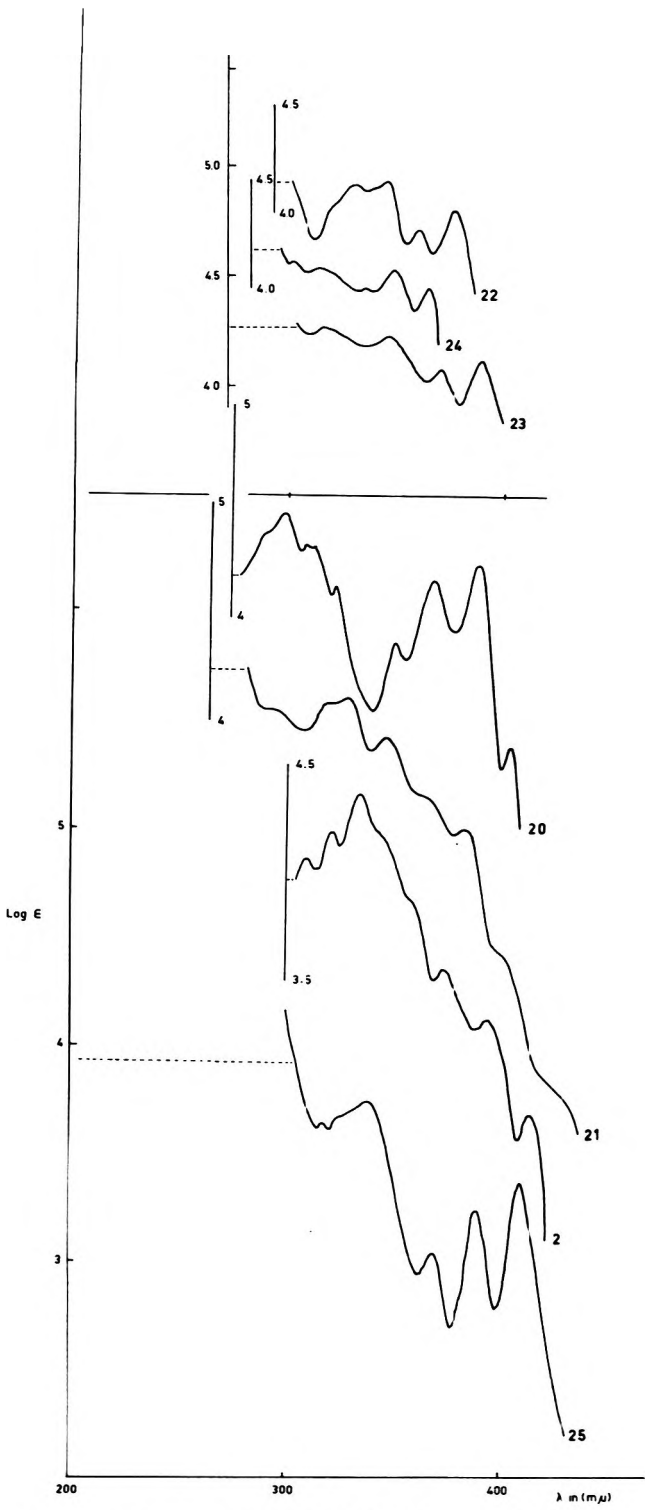


Figure 1. The uv spectra of the dehydrohelicenes in C_6H_6.

of the solvent the yellow residue was taken up in a minimum of hot *p*-xylene and chromatographed on alumina with benzene. After removal of the solvent the yellow residue (105 mg, 35%) was recrystallized from methylcyclohexane. The analytically pure compound melted at 284–290° (lit.[4] 267–280°).

Anal. Calcd for $C_{22}H_{10}S_2$: C, 78.07; H, 2.98; S, 18.95. Found: C, 77.9; H, 3.2; S, 18.8.

5,6:9,10-Diepithio-2,11-dithiabenz[7.8]azuleno[4,5,6-*cd*]indene (22). The dehydrohelicene **22** was obtained by treatment of **11** (262 mg, 0.74 mmol) with sodium chloride (1 g, 17.1 mmol) and aluminum chloride (4 g, 30 mmol). After hydrolysis of the melt a slightly green precipitate was formed which was filtered, washed, and dried. The product was taken up in a minimum of hot *p*-xylene and chromatographed on alumina with benzene. After removal of the solvent the residue was recrystallized from *p*-xylene. In this way 241 g (92%) of analytically pure **38** (mp 347–350° dec) was obtained.

Anal. Calcd for $C_{18}H_6S_4$: C, 61.69; H, 1.73; S, 36.59. Found: C, 61.8; H, 1.9; S, 36.1.

7,8-Etheno-2,5,6-trithiabenz[4.5]azuleno[1,8,7,6-*ijkl*]-*as*-indacene (23). The dehydrohelicene **23** was obtained by treatment of **12** (280 mg, 0.81 mmol) with sodium chloride (1.04 g, 17.7 mmol) and aluminum chloride (5.0 g, 37.4 mmol). After hydrolysis of the melt a yellow-brown precipitate was formed which was filtered, washed, and dried. After drying the product was chromatographed on alumina with benzene. After removal of the solvent the yellow residue (223 mg, 80%) was recrystallized from methylcyclohexane. The analytically pure compound sublimed between 250 and 300° and decomposed slowly above 290°.

Anal. Calcd for $C_{20}H_8S_3$: C, 69.73; H, 2.34; S, 27.92. Found: C, 69.7; H, 2.5; S, 27.9.

5,6-Etheno-2,11-dithianaphth[2′,1′,8′:3,4,5]azuleno[8,7,6-*cd*]indene (25). The dehydrohelicene **25** was obtained by treatment of **15** (150 mg, 0.44 mmol) with sodium chloride (450 mg, 7.6 mmol) and aluminum chloride (2.25 g, 16.8 mmol). After hydrolysis of the melt a yellow precipitate was formed which was filtered, washed, and dried. After drying the product was taken up in a minimum of hot *p*-xylene and chromatographed on alumina with benzene–chloroform (1:1). After removal of the solvent the yellow residue (139 mg, 93%) was recrystallized from benzene. The analytically pure compound sublimed between 280 and 290° and decomposed slowly at 348–354°.

Anal. Calcd for $C_{22}H_{10}S_2$: C, 78.07; H, 2.98. Found: C, 77.6; H, 3.1.

Registry No.—**1**, 24132-27-2; **2**, 30689-70-4; **9**, 56488-32-5; **10**, 20841-66-1; **11**, 41784-95-6; **12**, 41784-96-7; **13**, 41784-97-8; **15**, 41784-99-0; **20**, 54844-63-2; **21**, 30689-69-1; **22**, 54844-57-4; **23**, 54844-60-9; **24**, 54844-54-1; **25**, 54844-52-9; aluminum chloride, 7446-70-0.

References and Notes

(1) Taken in part from J. H. Dopper, Ph.D. Thesis, Groningen, 1974.
(2) H. Wynberg, *Acc. Chem. Res.*, **4**, 65 (1971), and earlier references.
(3) C. D. Nenitzescu and A. T. Balaban, "Friedel-Crafts and Related Reactions", Vol. II, G. A. Olah, Ed., Interscience, New York, N.Y., 1964, p 979.
(4) M. B. Groen, H. Schadenberg, and H. Wynberg, *J. Org. Chem.*, **36**, 2797 (1971); M. B. Groen, Ph.D. Thesis, Groningen, 1970.
(5) (a) J. H. Dopper and H. Wynberg, *Tetrahedron Lett.*, 763 (1972); (b) *J. Org. Chem.*, **40**, 1957 (1975).
(6) We prefer this nomenclature because these molecules are in fact dehydrogenated helicenes. However, we realize that the use of the word helicenes for almost planar molecules may be somewhat confusing.
(7) J. H. Dopper, D. Cudman, and H. Wynberg, *J. Am. Chem. Soc.*, **95**, 3692 (1973).
(8) M. Zander and W. F. Franke, *Chem. Ber.*, **102**, 2728 (1969).
(9) Recently, the dehydro[6]helicene has been prepared: P. J. Jessup and J. A. Reiss, *Tetrahedron Lett.*, 1453 (1975).
(10) C. D. Nenitzescu and A. Balaban, *Chem. Ber.*, **91**, 2109 (1958), and references cited therein.
(11) For details of the calculations see ref 5b. They were carried out by Dr. P. B. Koster of this laboratory.

Heterocyclic *N*-Oxides as Synthetic Intermediates. III.[1] Conversion of 1,3,4-Oxadiazin-6-one 4-Oxides to Substituted Butenolides[2]

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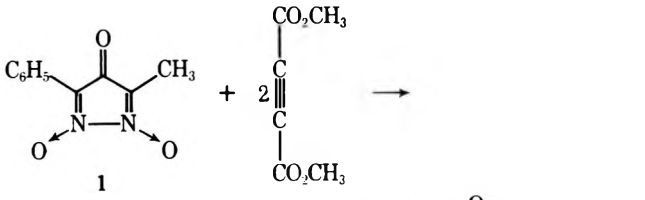
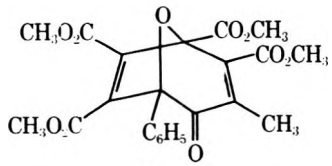
Cycloaddition of acetylenes and acetylenic esters to 1,3,4-oxadiazin-6-one 4-oxides (3) produces 3- and/or 5-acyl butenolides (4 and 5) in good yields. The degradation of these acyl lactones by bases to the parent lactones and succinic acid derivatives is described. A mechanism for the transformation involving a rearrangement of the primary cycloadduct, a fused Δ^4-isoxazoline, and subsequently a novel acyl migration step is proposed.

We have reported two reactions in which heterocyclic *N*-oxides undergo deep-seated transformations during cycloaddition with acetylenic dipolarophiles to produce new heterocycles. Treatment of 2-methyl-5-phenyl-3,4-diazacyclopentadienone 3,4-dioxide (1) with dimethyl acetylenedicarboxylate produced the bicyclic enone 2.[1a]

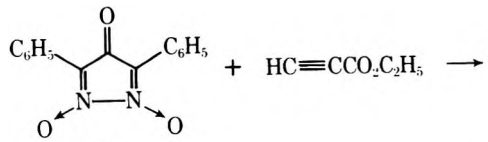


1

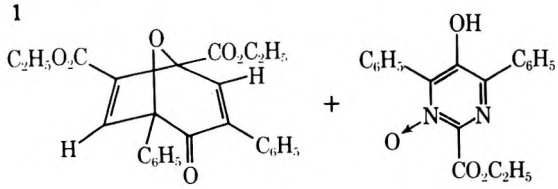


2

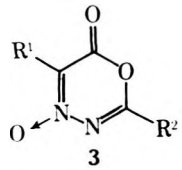
When the 2,5-diphenyl analog of 1 was treated with ethyl propiolate, an enone analogous to 2 was obtained, but in addition a pyrimidine derivative was also produced.[1b]



1



Synthesis of Butenolides. We have now found that 1,3,4-oxadiazin-6-one 4-oxides,[4] 3, react with a variety of acetylenes to produce acyl butenolides, 4 and 5, the exact



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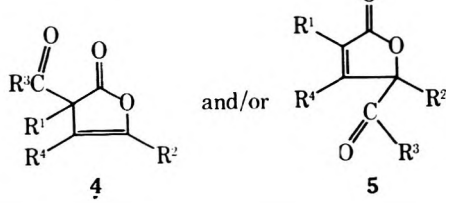
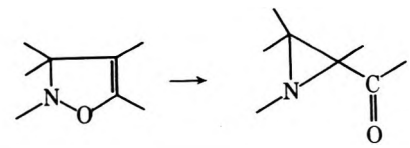


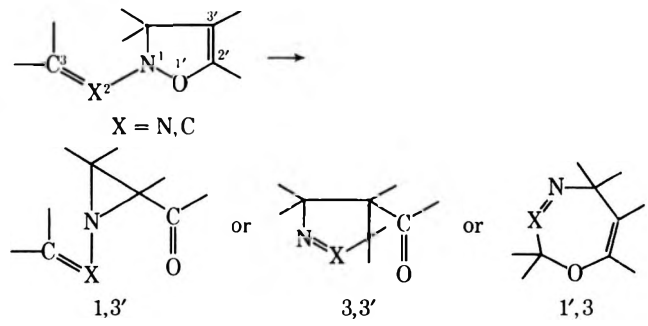
4 and/or 5

structure of which apparently is dependent upon the nature of the substituents in both the heterocycle and the acetylene (Table I). The structures of the butenolides are based on elemental analyses, spectral information (see Experimental Section), chemical degradation, and independent synthesis of degradation products. It should be noted that this reaction appears to be a general reaction of acetylenes and is not limited to those with electron-withdrawing groups.

Mechanism of Formation. The transformations previously reported[1] and the present conversion of the oxadiazinone oxides to acylbutenolides can be understood in terms of rearrangements of a first-formed Δ^4-isoxazoline. Baldwin and his coworkers[5] have shown that simple Δ^4-isoxazolines can isomerize to ketoaziridines. Recently there



have been reports of cycloaddition reactions of complex heterocyclic *N*-oxides which probably involve variations of this simple process.[6,7] Analogously N-unsaturated derivatives form heterologs of a Cope system.[8] Pyridine and quinoline *N*-oxides undergo reactions with acetylenes and benzyne that appear to involve a 1,5 shift after formation of a bicyclic Δ^4-isoxazoline.[9]



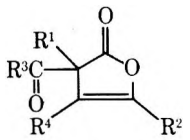
X = N, C

1,3′ or 3,3′ or 1′,3

In the present case the Δ^4-isoxazoline intermediate 6 is thermally labile and rearranges in a fashion analogous to the Cope rearrangement of 1,5-dienes. The stereochemistry illustrated in 7 is that expected from a concerted 3,3-sigmatropic rearrangement. The products (4 and/or 5) can then result from the loss of nitrogen and the migration of the acyl group[10] to either of the two carbons formerly attached to nitrogen in 7. The trends in this migration can be explained by assuming the intermediacy of a dipolar intermediate 8.

First it should be noted that an acyl group always migrates in preference to carbalkoxy.[11] Then the nature of R^1 and R^3 play an important role in the migratory outcome. Migration of the acyl group (R^3CO) to the negative end of

Table I
Properties of Butenolides[f]



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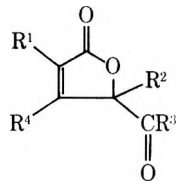
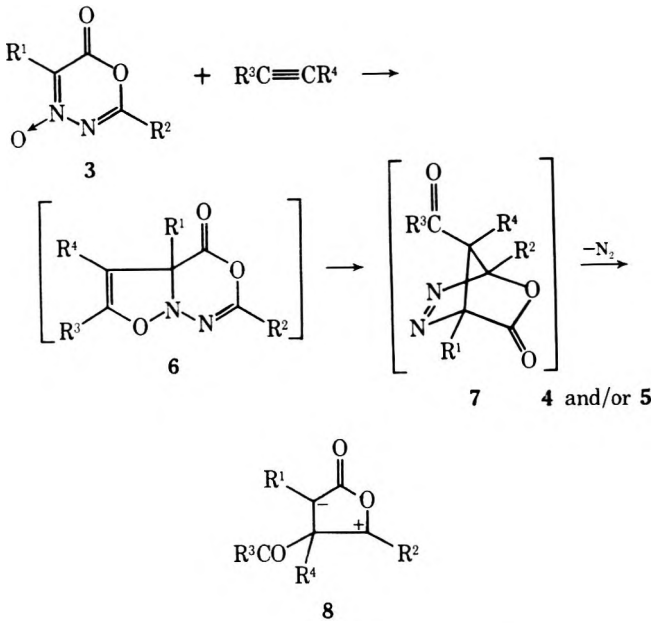


5

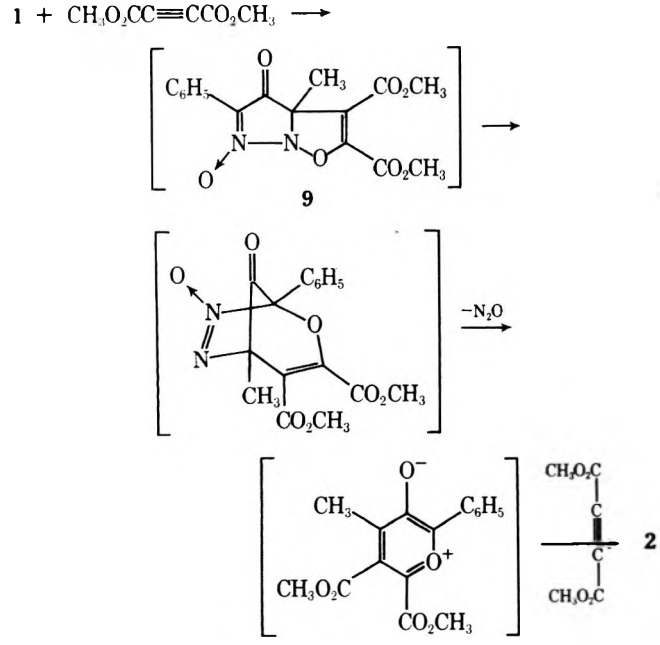
Compd	R^1	R^2	R^3	R^4	Mp, °C	Yield, %	Solvent	Procedure and reaction time, hr	Ir, cm^{-1} [a] Lactone C=O	Ir, cm^{-1} [a] Enol C=C	NMR, δ [b] Ester CH_3 (R^4)	NMR, δ [b] R^1	NMR, δ [b] Misc
4a	C_6H_5	C_6H_5	CO_2CH_3	CO_2CH_3	169–170 (CH_3OH)	75	Benzene	A-24	1810	1620	3.65		O=CCO$_2$CH$_3$, 3.85
4b	CH_3	C_6H_5	CO_2CH_3	CO_2CH_3	103–104 (hexane)	92	Heptane	A-24	1805	1625	3.66	1.7, s, 3	O=CCO$_2$CH$_3$, 3.81
4c	C_2H_5	C_6H_5	CO_2CH_3	CO_2CH_3	*c*	98	Heptane	B-24	1805	1625	3.65	2.22, q, 2 0.90, t, 3	O=CCO$_2$CH$_3$, 3.79
4e	CH_3	C_6H_5	C_6H_5	CO_2CH_3	100–103 (CCl_4)	90[d]	Heptane	B-60	1805	1600	3.58	1.90, s, 3	
5e	CH_3	C_6H_5	C_6H_5	CO_2CH_3	100–102 (CH_3OH)				1780		3.79	2.24, s, 3	
5d	C_6H_5	C_6H_5	C_6H_5	CO_2CH_3	146–148 (CH_3OH)	60	*p*-Xylene	A-60	1780		3.72		
5f	C_6H_5	C_6H_5	C_6H_5	$CO_2C_2H_5$	143–145 (CH_3OH)	55	*p*-Xylene	B-24	1780				
4g	CH_3	C_6H_5	C_2H_5	C_2H_5	*c*	34	Heptane	C-120	1805			1.58, s, 3	
5g	CH_3	C_6H_5	C_2H_5	C_2H_5	*c*	12			1775			1.86, s, 3	
4h	CH_3	C_6H_5	C_6H_5	H	65–67 (pentane)	32 13	Heptane	B-48	1805			1.76, s, 3	H(R^4) 6.03, s
5h	CH_3	C_6H_5	C_6H_5	H	*c*				1775			1.94, d (J = 1.5 Hz), 3; H (R^4) 7.63, q (J = 1.5 Hz)	
4i	CH_3	C_6H_5	CH_3	CH_3	*c*	33	Heptane	C-168	1805			1.53, s, 3	1.9, s, 3 2.2, s, 3
5i	CH_3	C_6H_5	CH_3	CH_3	*c*	*e*						1.83, s, 3	2.01, s, 3 2.25, s, 3
16[18]	H	H, H		CO_2CH_3	82				1785		3.88	6.65, t (J = 2 Hz), 1; ring CH_2, 4.99, d (J = 2 Hz), 2	
10	C_6H_5, H	C_6H_5		CO_2CH_3	105–106				1805	1635	3.56	4.85, s	

[a] Measured in KBr disks, except 4b (Nujol mull) and 4c (CCl_4). [b] Measured in $CDCl_3$, Me_4Si standard, 60 MHz. [c] Viscous oil purified by column chromatography. [d] Overall yield of mixture comprised of 86% 4e, 14% 5e. [e] 5i was not isolated pure. [f] All compounds gave satisfactory elemental analyses.



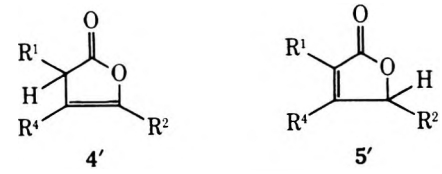
the dipole in 8 is dominant when the acyl group is highly electrophilic. Thus compounds with the electrophilic methoxalyl groups yield exclusively the β,γ-unsaturated butenolides **4a–c**. The less electrophilic benzoyl group migrated exclusively to the opposite center to yield **5d**. These results reflect a trend in the product formation as a function of the electrophilicity of the acyl group. This trend, however, is complicated by the ability of R^1 to accommodate negative charge in 8; there seems to be increased migration to that center when R^1 = methyl as contrasted to phenyl. Because of limitations on the synthesis of the oxadiazinones,[4] the effect of R^2 is more difficult to delineate.

The thermal rearrangement of 6 is similar to that of the Δ^4-isoxazoline 9 presumed to be an intermediate in the diazacyclopentadienone reaction[1a] except that in that case a 1′,3 rearrangement must occur; a 3,3′ rearrangement would require formation of a strained, four-membered ring. These



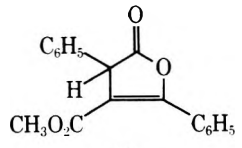
reactions and others previously reported suggest that N-unsaturated Δ^4-isoxazolines should prove to be useful intermediates for the synthesis of a variety of heterocycles.

Reactions of the Acylbutenolides. Chemical Evidence. The butenolides 4 and 5 are labile to both acids and bases owing to retro-Claisen cleavage of the acyl group.

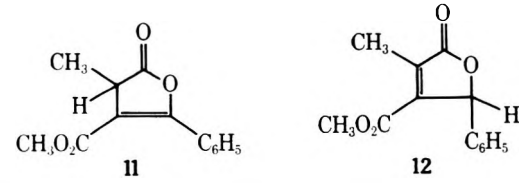


The product is either the β,γ-unsaturated lactone 4′ or the α,β-unsaturated lactone 5′, the more stable isomer.[13,14] With bases, the retro-Claisen product reacts further to yield ring-opened products which will be discussed later.

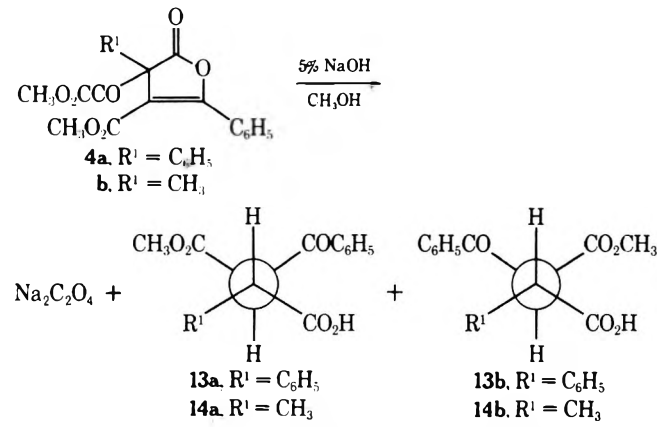
The retro-Claisen products from "mild" acid treatment could be isolated in some cases; lactone **10** was isolated



from the filtrate upon recrystallization of **4a** from wet (but not anhydrous) methanol. Partial deacylation of **4b** occurred on a silica gel column to yield principally lactone **11** and traces of **12** along with unaffected **4b**. These structures were assigned on the basis of their spectra and the isomerization of **11** to **12**.

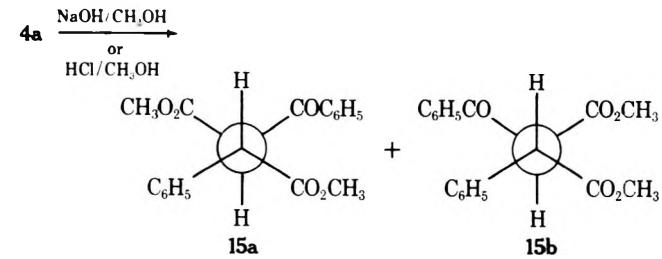


Treatment of **4a, b** with base under mild conditions yielded the appropriate deacylated half-ester as a 1:1 mixture of diastereomers (NMR analysis). Treatment of **5d**

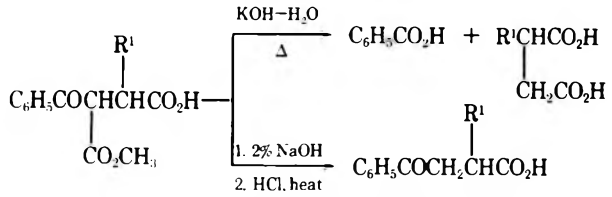


and **10** under the same conditions also yielded **13a** and **13b**; benzoic acid was also isolated from the degradation of **5d**. When R^1 was phenyl, one of the two diastereomers, **13a**, could be separated from the mixture. Treatment of pure **13a** with diazomethane yielded one diastereomer which was assigned as **15a** based upon the shielding effect on the methyl ester (see Experimental Section).

A mixture of the diesters **15a** and **15b** could also be obtained by the following reactions.



The structures of **13** and **14** were supported by their degradation to known compounds. These degradations involved the β-keto ester functional group as depicted below.



The structures of these degradation products were verified by comparison with known physical properties. (See Experimental Section.) The appropriate γ-keto acids were also isolated from the base hydrolysis of **4a** and **4c**. The deacylated succinate half-esters are probably intermediates in this transformation. These degradations therefore established the positions of R_1, R_2, and R_4 in **4** and **5**.

Experimental Section

General. Infrared spectra were recorded on a Perkin-Elmer Model 137-A Infracord. NMR spectra were measured on a Varian A-60A spectrometer. Mass spectra were measured with an A. E. I. MS 902 mass spectrometer at 70 eV. We are indebted to Mr. Donald Schifferl for these measurements. The elemental analyses were done by Midwest Microlab.

J. T. Baker silica gel (60–200 mesh) was dried at 135° for 4 hr before use and the column chromatography was monitored by TLC on Baker-flex sheets (silica gel 1B-F) using benzene as the developing solvent.

2,5-Diphenyl-1,3,4-oxadiazin-6-one 4-Oxide (3a).[4] To a stirred suspension of 23.4 g (92.9 mmol) of 1,4-dihydroxy-3,5-diphenylpyrazole[16] in 700 ml of CH_2Cl_2 and 40 ml of anhydrous CH_3OH at 0° was added 41 g of *m*-chloroperbenzoic acid. Stirring was continued for 4 days in a refrigerator. The mixture was filtered to remove a gold solid and the filtrate was concentrated to half its volume and an equal volume of CH_3OH was added. The solid that separated was filtered, combined with the first crop, and recrystallized from CH_2Cl_2–CH_3OH to give **3a** as yellow needles: mp 243–244°; yield 15.6–17.8 g (63–72%); ir (KBr) 1755, 1595, 1560 cm^{-1}; NMR ($CDCl_3$, Me_4Si) δ 8.12 (m, 4 H). 7.52 (m, 6); MS *m/e* (rel intensity) 266 (42), 105 (100), 77 (49), 51 (10).

Anal. Calcd for $C_{15}H_{10}N_2O_3$: C, 67.67; H, 3.79; N, 10.52. Found: C, 67.56; H, 3.81; N, 10.36.

5-Methyl-2-phenyl-1,3,4-oxadiazin-6-one 4-Oxide (3b).[4] To a stirred solution of 23.4 g (0.123 mol) of 1,4-dihydroxy-5-methyl-3-phenylpyrazole[16] in 130 ml of anhydrous ether and 35 ml of anhydrous CH_3OH at 0° was added 45 g of *m*-chloroperbenzoic acid in 240 ml of anhydrous ether. The dark red solution was stirred in a refrigerator for 1 day, 13.5 g of fresh peracid in 50 ml of ether was added, and stirring was continued in the cold for 2 days. The solid product was isolated as in **3a** above. The combined solid product was recrystallized from anhydrous C_2H_5OH to give **3b** as white flakes: mp 174–175°; yield 5.1–6.5 g (20–26%); ir (KBr) 1755, 1600 cm^{-1}; uv max (95% C_2H_5OH) 257 nm (ϵ 14700), 297 (12000); NMR ($CDCl_3$, Me_4Si) δ 2.38 (s, 3 H), 7.60 (m, 3 H), 8.20 (m, 2 H); MS *m/e* (rel intensity) 204 (29), 160 (15), 105 (100), 103 (41), 77 (43), 44 (26).

Anal. Calcd for $C_{10}H_8N_2O_3$: C, 58.82; H, 3.95; N, 13.72. Found: C, 59.06; H. 4.10; N, 13.59.

5-Ethyl-2-phenyl-1,3,4-oxadiazin-6-one 4-Oxide (3c).[4] **3c** was prepared by the same procedure as **3b**: mp 177–178° (CH_2Cl_2–hexane); yield 30%; ir (Nujol) 1760, 1600, 1560 cm^{-1}; NMR ($CDCl_3$, Me_4Si) δ 1.21 (t, 3 H), 2.84 (q, 2 H), 7.61 (m, 3 H), 8.15 (m, 2 H); MS *m/e* (rel intensity) 218 (36), 105 (100), 77 (44), 57 (12), 51 (16), 39 (12).

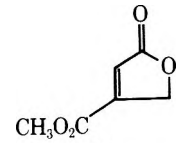
Anal. Calcd for $C_{11}H_{10}N_2O_3$: C, 60.55; H, 4.62; N, 12.84. Found: C, 60.80; H, 4.54; N, 12.59.

Cycloaddition Reactions. Procedure A. A suspension of 5–10 mmol of **3** in 50 ml of dry heptane containing 10–20 mmol of acetylene was stirred under reflux for 1 day. The residue from evaporation of the solvent[17] was recrystallized from hot CCl_4 or CH_3OH.

Procedure B. After the reflux period of procedure A, the oily residue was chromatographed on silica gel using benzene or CH_2Cl_2 as eluent. Fractions of similar R_f value was combined and crystallized from the appropriate solvent (Table I). Only **5h** could not be obtained crystalline by this procedure.

Procedure C. A suspension of 2 mmol of **3b** in 5 ml of dry heptane containing 1.5–2 ml of acetylene was heated in a Fischer-Porter sealed tube for 5–7 days at 100–120°. The tarry residue was washed from the tube with CH_2Cl_2 and concentrated to yield an oil that was chromatographed on silica gel using benzene as eluent. Fractions of similar R_f values were combined and concentrated to yield the two isomers.

Spectral Properties of Butenolides (Table I). Infrared. The position of the double bond in the butenolides is easily determined by the carbonyl band of the lactone and in some cases the presence or absence of the enol stretching band.[13] The β,γ-unsaturated lactones (**4**) showed carbonyl absorption at 1800–1795 cm^{-1} while the α,β isomers (**5**) usually absorbed around 1775 cm^{-1}. The infrared spectrum of methyl aconate[18] (**16**) was also used as a model for band assignments.

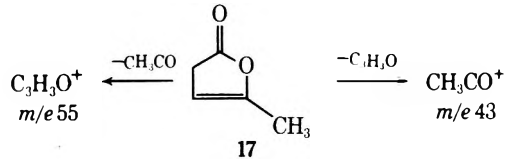


16

NMR. The spectra of **4** and **5** were consistent with the structure assignments, but the simplicity of the spectra limited their utility. Some points stand out, however. The chemical shifts of the ester methyl group of the 4-carbomethoxy substituents are rather different in the two ring systems (**4** and **5**). In the β,γ isomer the group is shielded (δ 3.57–3.66) as compared to the α,β isomer (δ 3.72–3.88), probably because the 4 position is enriched in electron density by the lactone oxygen in **4** and diminished by the lactone carbonyl group in **5**.

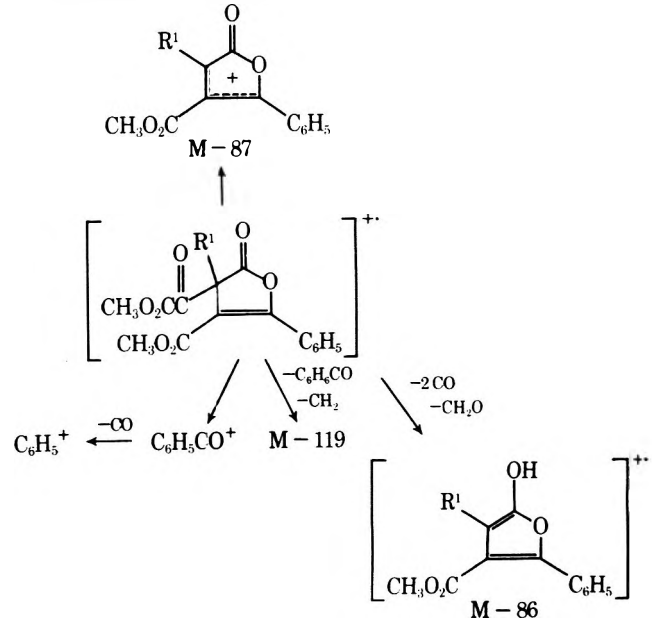
The chemical shifts of the pendant methyl group ($R^1 = CH_3$) in **4** and **5** reflect the differences in the hybridization at C-3 in the two isomers. The variations in shift of the methyl group in **4** can be attributed to the differential shielding effects of the acyl groups at C-3.

Mass Spectra. The cracking patterns of these butenolides bear a close resemblance to known spectra[19] in this series. In particular, the main fragmentation of α-angelica lactone[19b] (**17**) results from the cleavage

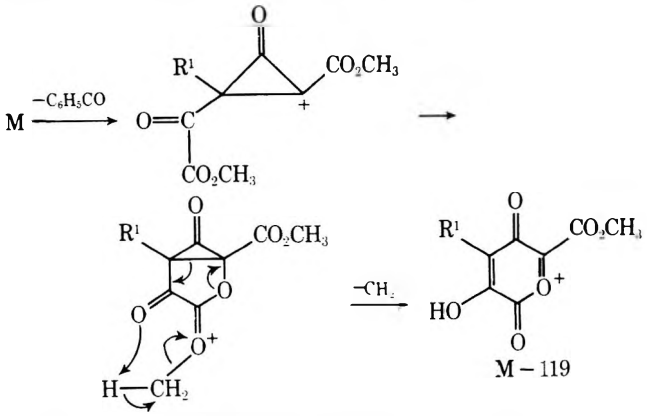


17

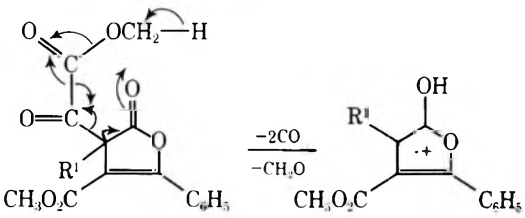
Extensive rearrangement was evident for the ion of mass 55 which was the base peak. In **4a–c, e, h, 5e, f,** and **10** the base ion was 105 ($C_6H_5C{\equiv}O^+$), which results from an analogous fragmentation. The molecular ions were also present; their cracking pattern is illustrated below for **4a–c**.



The M − 105 ion is not apparent but might have been expected by comparison with the cracking pattern of **17**. However, the M − 119 ion might result from this ion in the following manner.



The presence of methoxalyl group in the mass spectra of **4a–c** is also apparent in the formation of the M − 86 ion as shown below.

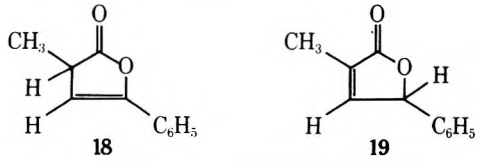


4-Carbomethoxy-3,5-diphenyl-2,3-dihydro-2-furanone (10). Lactone **4a** was prepared by procedure A. The filtrate from recrystallization of **4a** from technical grade methanol was evaporated in vacuo to yield a white solid.[20] Recrystallization of this solid from hexane gave white needles of **10**: mp 105–106°; ir and NMR, Table I; MS *m/e* (rel intensity) 294 (39), 265 (23), 235 (15), 206 (14), 189 (27), 178 (14), 129 (14), 105 (100), 77 (48).

The infrared spectrum of **10** is similar to its precursor except for the absence of the methoxalyl group. In its NMR spectrum the observed chemical shift of the methine proton (δ 4.85) agreed with the calculated value (δ 4.95)[21] and the chemical shift of the ester methyl protons is analogous to that expected from the spectra of the acyl butenolides (see Experimental Section). Its mass spectrum was similar to that of its precursor except the molecular ion was more prominent. The M − 119 ion was also absent but the M − 105 ion was very prominent which supports the mechanism suggested for the formation of the M − 119 ion.

4-Carbomethoxy-3-methyl-5-phenyl-2,5-dihydro-2-furanone (12). Lactone **4b** (0.156 g, 0.49 mmol) was washed through a silica gel column (10 g) with benzene. Evaporation of the solvent yielded 0.11 g (97%) of a yellow oil that was a mixture of **11** and **12**: ir (neat) 1810, 1775, 1725 cm^{-1}; NMR (CCl_4, Me_4Si) δ 1.45 (d, J = 7.5 Hz, 3 H), 2.2 (d, J = 2 Hz, 3 H).

This mixture was stirred in 6 ml of benzene containing 3 drops of $(C_2H_5)_3N$ at 25° for 1 day. The solution was washed with H_2O, dried, and concentrated to give an oil that was purified by chromatography on silica gel using $CHCl_3$ as eluent to give **12** as a yellow oil: ir (neat) 1775, 1725 cm^{-1}; NMR (CCl_4, Me_4Si) δ 2.21 (d, J = 2 Hz, 3 H), 3.68 (s, 3 H), 5.88 (q, J = 2 Hz, 1 H), 7.25 (s, 5 H). The spectra[22] of the model compounds **18** and **19** were used to assign the isomeric structures **11** and **12**.



Alkaline Hydrolysis of 4a. Formation of α-Phenyl-β-benzoyl-β-carbomethoxypropionic Acid (13a and 13b). A solution of 0.65 g (1.7 mmol) of **4a** and 6.5 ml of 5% NaOH in 25 ml of CH_3OH was stirred at 25° for 1 hr. The original bright yellow solution faded to a pale yellow. The solution was neutralized (5% HCl) and a white solid that had separated was removed by filtration and identified as sodium oxalate. The filtrate was acidified (5% HCl), diluted with 30 ml of H_2O, and extracted with 3 × 50 ml of ether. The ether extracts were washed, dried, and concentrated to yield 0.51 g (96%) of a yellow oil, a mixture of acids **13a** and **13b**. This oily mixture was dissolved in the minimal amount of hot benzene and hexane was added to turbidity. Upon cooling 0.13 g of ***RS*(*SR*)-β-benzoyl-β-carbomethoxy-α-phenylpropionic acid (13a)** separated as white needles: mp 156–157°; ir (Nujol) 2650, 1740, 1700, 1680 cm^{-1}; NMR ($CDCl_3$, Me_4Si) δ 3.33 (s, 3 H), 4.63 (d, J = 11.5 Hz, 1 H), 5.07 (d, J = 11.5 Hz, 1 H, 7.2–7.6 (m, 8 H), 7.95–8.15 (m, 2 H), 9.88 (br s, 1 H); MS *m/e* (rel intensity) 312 (1), 294 (24), 163 (25), 131 (34), 105 (100), 103 (28), 77 (54), 51 (37).

Anal. Calcd for $C_{18}H_{16}O_5$: C, 69.22, H, 5.16. Found: C, 69.63, H, 5.27.

The structure of **13a** is assigned on the basis of the selective chemical shift of the methyl group of the β-carbomethoxy group (δ 3.33) compared to that of **13b**, δ 3.65 (present in the original oily mixture). In the preferred and apparently predominant conformation of diastereomer **13a**, this methyl group is in the shielding cone of the α-phenyl group. The large coupling constant between the vicinal hydrogens (11.5 Hz) suggests a high population for this conformation. Similar shielding effects were seen in **14a** and **15a** as compared to **14b** and **15b**.

13a also appeared to be the more stable isomer as base equilibration of the two yielded a 2.6:1 mixture of **13a:13b**.

α-Phenyl-β-benzoylpropionic Acid. Treatment of the mixture of **13a** and **13b** with 2% aqueous NaOH for 1 day followed by acidification, heating on a steam bath, and cooling yielded a tan solid that gave white plates of α-phenyl-β-benzoylpropionic acid, mp 153–155°, which was not depressed upon admixture with an authentic sample.[23] Pure **13a** gave analogous results. **4a** could be converted directly to this acid by the same method.

α-Phenylsuccinic Acid. A mixture of **13a** and **13b** (261 mg) was heated under reflux with 10 g of KOH in 20 ml of H_2O. The product, isolated after acidification and extraction with ether, was purified by slurrying in benzene (to remove benzoic acid). The residue was recrystallized from ether–hexane to yield white needles of α-phenylsuccinic acid, mp 162–163°, which was not depressed upon admixture with an authentic sample,[24] yield 66 mg (41%).

Alkaline Hydrolysis of 5-Benzoyl-4-carbomethoxy-3,5-diphenyl-2,5-dihydro-2-furanone (5d). Using the same procedure as for **4a**, a crude solid residue was obtained. Benzoic acid (49% yield) was sublimed from this solid at 70° (2 Torr). The oily residue was identified as a mixture of **13a** and **13b** by NMR analysis.

***erythro*-Dimethyl α-Phenyl-β-benzoylsuccinate (15a).** To a solution of 0.1 g (3.16 mmol) of **13a** in 10 ml of ether was added dropwise an ethereal solution of diazomethane until the yellow color persisted. Evaporation of the ether yielded a clear oil that deposited white beads of **15a** from hexane: mp 86–87°; ir (KBr) 1740, 1680, 1290, 1230, 1190, 1175, 760, 708, 687 cm^{-1}; NMR (CCl_4, Me_4Si) δ 3.33 (s, 3 H), 3.58 (s, 3 H), 4.50 (d, J = 11.5 Hz, 1 H), 5.03 (d, J = 11.5 Hz, 1 H), 7.2–7.6 (m, 8 H), 8.0–8.2 (m, 2 H).

Anal. Calcd for $C_{19}H_{18}O_5$: C, 69.94; H, 5.52. Found: C, 69.79, H, 5.61.

Acid-Catalyzed Methanolysis of 4a. To a suspension of 0.25 g (0.66 mmol) of **4a** in 30 ml of 1:1 v/v aqueous methanol was added 5 ml of concentrated HCl. This mixture was heated under reflux for 10 min and extracted with ether. The dried ether extracts were concentrated to an oil that was chromatographed on silica gel to yield a mixture of **15a** and **15b**. The NMR spectrum of this mixture showed the ester methyl hydrogens of **15b** as a six-proton singlet at δ 3.67 in addition to the singlets at δ 3.33 and 3.58 for **15a**.

Alkaline Hydrolysis of 4b. Formation of α-Methyl-β-benzoylpropionic Acid. Treatment of 1 g of **4b** with aqeuous methanolic NaOH at room temperature for 1 hr yielded 0.77 g of a yellow oil, a mixture of **14a** and **14b**. With no α-phenyl substituents the ester methyl groups of both diastereomers are at δ 3.64. However, the α-methyl group of one isomer is at higher field (δ 1.17) than the other (δ 1.33). Since the preferred conformation of **14b** has methyl and benzoyl groups syn to each other, it is suggested that **14b** is the isomer with the higher field methyl signal.

When this mixture was stirred in 2% aqueous NaOH at 25° for 1 day, then acidified with 5% HCl, heated on a steam bath for 30 min, and then cooled, long, white needles separated and were recrystallized from C_2H_5OH–H_2O to yield α-methyl-β-benzoylpropionic acid, mp 139–140° (lit.[25] mp 139–140°), NMR spectrum, ref 22.

α-Methylsuccinic Acid. Treatment of the mixture of **14a** and **14b** with a hot mixture of 10 g of KOH and 20 ml of H_2O for 4 hr gave, after the same work-up as for the formation of α-phenylsuccinic acid, a tan solid that yielded white needles (ether–benzene) of α-methylsuccinic acid, mp 109–111° (lit.[26] mp 110–111°), NMR spectrum, ref 27.

Alkaline Hydrolysis of 4c. Formation of α-Ethyl-β-benzoylpropionic Acid. A mixture of **4c** (0.4 g) and 20 ml of 2% NaOH was stirred at 25° for 1 day. The mixture was acidified with 5% HCl, heated on a steam bath for 30 min, and cooled to yield a white solid. Recrystallization from petroleum ether produced white needles of α-ethyl-β-benzoylpropionic acid: mp 86–87° (lit.[28] mp 85°); ir (KBr) 2650, 1680, 757, 688 cm^{-1}; NMR ($CDCl_3$ Me_4Si) δ 1.00 (t, J = 7 Hz, 3 H), 1.68 (q, 2 H), 2.8–3.8 (m, 3 H), 7.3–7.7 (m, 3 H), 7.9–8.1 (m, 2 H), 10.7 (s, 1 H).

Registry No.—**2** (R^3 = R^4 = CO_2CH_3), 762-42-5; **2** (R^3 = C_6H_5; R^4 = CO_2CH_3), 4891-38-7; **2** (R^3 = C_6H_5; R^4 = $CO_2C_2H_5$), 2216-94-6; **2** (R^3 = R^4 = C_2H_5), 928-49-4; **2** (R^3 = C_6H_5; R^4 = H), 536-74-3; **2** (R^3 = R^4 = CH_3), 503-17-3; **3a**, 28969-37-1; **3b**, 28969-38-2; **3c**, 28969-39-3; **4a**, 56615-23-7; **4b**, 56615-24-8; **4c**, 56615-25-9; **4e**, 56615-26-0; **4g**, 56615-27-1; **4h**, 56615-28-2; **4i**, 56615-29-3; **5d**, 56615-30-6; **5e**, 56615-31-7; **5f**, 56615-32-8; **5g**, 56615-33-9; **5h**, 56615-34-0; **5i**, 56615-35-1; **10**, 56615-36-2; **11**, 56615-37-3; **12**, 28970-27-6; **13a**, 56615-38-4; **13b**, 56615-39-5; **14a**, 56615-40-8; **14b**, 56615-41-9; **15a**, 56615-42-0; **15b**, 56615-43-1; 1,4-dihydroxy-3,5-diphenylpyrazole, 17953-00-3; *m*-chloroperbenzoic acid, 937-14-4; 1,4-dihydroxy-5-methyl-3-phenylpyrazole, 56615-44-2; α-phenyl-β-benzoylpropionic acid 4370-96-1; α-phenylsuccinic acid, 635-51-8; diazomethane, 334-88-3; α-methyl-β-benzoylpropionic acid, 1771-65-9; α-methylsuccinic acid, 498-21-5; α-ethyl-β-benzoylpropionic acid, 56615-45-3.

References and Notes

(1) (a) Part I: J. P. Freeman and M. J. Hoare, *J. Org. Chem.*, **36**, 19 (1971). (b) Part II: J. P. Freeman, E. G. Duthie, M. J. O'Hare, and J. F. Hansen, *J. Org. Chem.*, **37**, 2756 (1972).
(2) This research was supported by a grant from the National Cancer Institute of the National Institutes of Health CA-10742.
(3) Reilly Fellow, 1973–1974.
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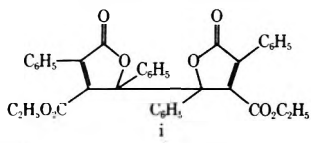

i

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Chemistry of o-Amino Aldehydes. Reactions of 2-Aminonicotinaldehyde and Cyclohexanediones

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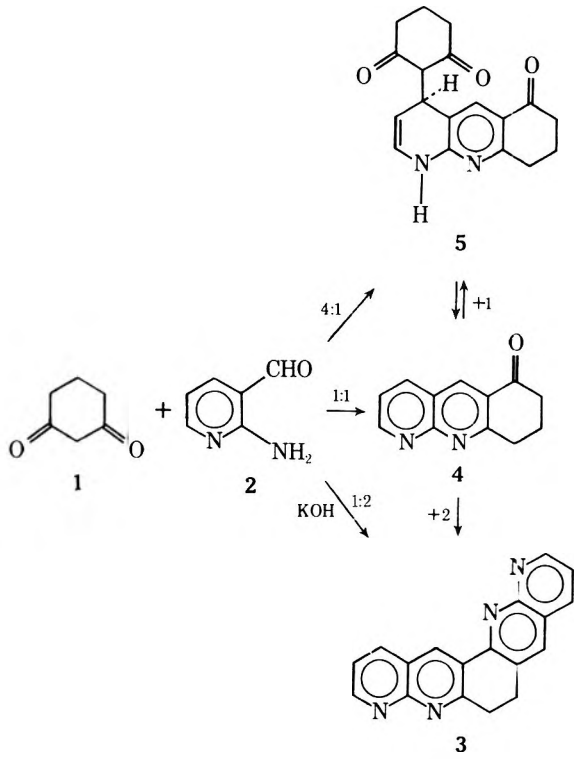
1,3-Cyclohexanedione and 2-aminonicotinaldehyde form 6,7-dihydrodipyrido[2,3-*b*:2,3-*j*]-1,7-phenanthroline (**3**) or 6-oxo-6,7,8,9-tetrahydrobenzo[*b*]-1,8-naphthyridine (**4**) depending on the molar ratio of reagents. Excess 1,3-cyclohexanedione, on the other hand, results in a 2:1 addition product (**5**). Similar reactions with 1,4-cyclohexanedione were not successful; a series of addition–elimination steps in toluene results in the formation of 7-oxo-6,7,8,9-tetrahydrobenzo[*b*]-1,8-naphthyridine (**12**) and 6,7-dihydrodipyrido[3,2-*b*:2,3-*j*]-4,7-phenanthroline (**13**), demonstrating the feasibility of uncatalyzed Friedländer condensations. The isomeric pentacyclic systems are readily dehydrogenated to their fully aromatic analogs. 1,2-Cyclohexanedione gives the highly unreactive 6,7-dihydrodipyrido[2,3-*b*:2,3-*j*]-1,10-phenanthroline (**14**). The mechanism of the actual ring closing step in Friedländer condensation reactions of 2-aminonicotinaldehydes and ketomethylenes is discussed.

The incorporation of the 1,8-naphthyridine heterocyclic system into a polycyclic framework is of interest in view of the unusual stability and properties of "black orlon" obtained from poly(acrylonitrile) by controlled pyrolysis. A linearly annelated sequence of partially oxygenated 1,8-naphthyridine units has been proposed for this remarkable material.[1] The Friedländer condensation of *o*-amino aldehydes seemed a most promising synthetic sequence for the construction of such systems, since fully aromatic substrates without amino or oxo substituents are obtained and the direction of annelation is unequivocally determined by the location of the functional groups in the substrate. This paper deals with the reaction of 2-aminonicotinaldehyde and cyclohexanediones leading to three isomeric pentacyclic systems containing two 1,8-naphthyridine units.

The reaction of 1,3-cyclohexanedione (**1**) and excess 2-

aminonicotinaldehyde (2) in refluxing ethanol containing a few drops of methanolic KOH resulted in the formation of 6,7-dihydrodipyrido[2,3-*b*:2,3-*j*]-1,7-phenanthroline (3) in nearly quantitative yield. On the other hand, refluxing an ethanolic solution of 1 and 2 in a 1:1 molar ratio, in the absence of base, gave the monocondensation product, 6-oxo-6,7,8,9-tetrahydrobenzo[*b*]-1,8-naphthyridine (4) in 90% yield, uncontaminated by 3. This ketone is easily converted into 3 by base-catalyzed (KOH and MeOH) condensation with 2.

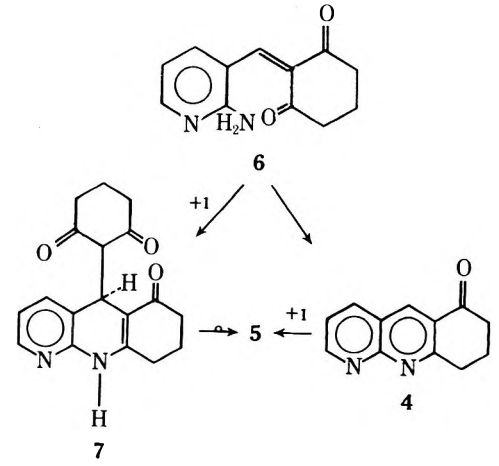


The great reactivity of the central methylene group of 1 seems to favor formation of the monocondensation product under neutral conditions. However, during the course of the reaction leading to 4 a precipitate formed and then slowly disappeared as the reaction progressed. Isolation (maximum yield amounted to 20% under the experimental conditions employed in the synthesis of 4) proved it to be a 2:1 addition product of 1,3-cyclohexanedione and the amino aldehyde, with loss of 2 mol of water. It is not surprising, therefore, that heating an ethanolic solution of 1 and 2 in a 4:1 molar ratio resulted in the formation of the adduct 5 in 90% yield. Its composition is reminiscent of addition products of aldehydes and dimedone; in the present case, the second molecule of water would be eliminated by intramolecular condensation with the amine function. A pronounced molecular ion at *m/e* 310 is observed in the mass spectrometer, with principal fragmentations resulting from either loss of a hydrogen atom or 1,3-cyclohexanedione moiety; the latter fragmentation is more pronounced and is followed by loss of a hydrogen atom with formation of the ion *m/e* 198, identical with the molecular ion obtained from the ketone 4. Such fragmentation pattern is typical for compounds containing a dihydropyridine structure.[2] Characteristic strong absorptions in the ir spectrum for NH and C=O functional groups, observed at 3185 and at 1670, 1640, and 1615–1565 cm^{-1}, are in agreement with a 1,3-cyclohexanedione substituted dihydropyridine structure for 5. Its simple mode of formation and the known tendency of aldehydes to form adducts with 2 mol of 1 seemed to suggest such a dihydro structure for the central pyridine ring of 5. However, its NMR spectrum[3] does not show the characteristic absorptions (doublet of doublets) in the aromatic region for a 2,3-disubstituted pyridine ring. On the contrary, a sharp singlet is observed at δ 8.19, with a proton count of one. A structure wherein the dione moiety resides on the outer pyridine ring is in agreement with this observation.

Absorptions at δ 6.74 (m, 1), 5.70 (m, 1), and 4.4 (m, 1) further substantiate this structure; the latter absorption was assigned to the methine proton on the carbon containing the 1,3-dione moiety, whereas the former are in the characteristic region for vinyl protons. Both the NH and enolic proton of the 1,3-dione moiety are exchanged by dissolving 5 in $CDCl_3$. Addition of a few drops of D_2O to this solution removed the absorption at δ 6.74. The same total exchange of three protons was observed in the spectrum obtained in deuterated acetic acid. Such facile exchange is in agreement with the proposed 1,4-dihydro structure for 5, which contains an enamine structure, in equilibrium with the tautomeric azomethine.

The concurrent formation of 4 and 5 from 2-aminonicotinaldehyde and 1,3-cyclohexanedione seemed to suggest a possible route to the addition product. Indeed, an equimolar solution of 4 and 1, in ethanol at 65°, slowly formed a precipitate (43%) identical in all respects with the addition product isolated from 1 and 2. It is apparent therefore that 5 arises from nucleophilic addition of the 1,3-dione on the outer pyridine ring of 4. As mentioned earlier, 5 is slowly converted to 4 in refluxing ethanol. This elimination is greatly accelerated by the addition of base or by brief treatment with dilute mineral acid. Two reaction mechanisms leading to 4 and ultimately to 5 can be envisioned. Aldol condensation of 1 and 2 followed by dehydration of the aldol results in an α,β-unsaturated carbonyl system (6). Intramolecular Schiff base formation can lead to 4, which then further reacts with a second molecule of 1,3-dione, as discussed earlier.

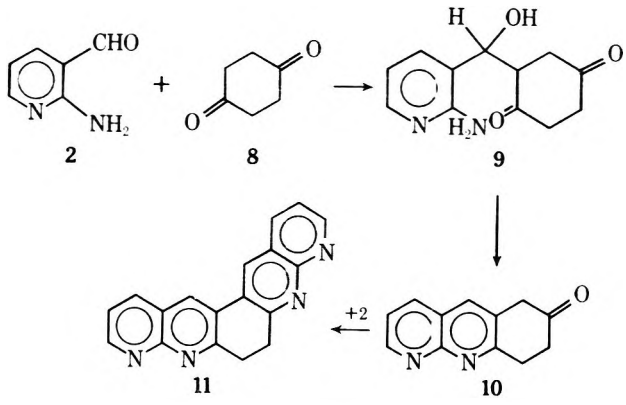
The alternative pathway, based on the known tendency of 1,3-cyclohexanedione to form 2:1 addition products with aldehydes, cannot be excluded. Michael addition of 1 and 6, followed by ring closing, would lead to 7, which would then rearrange to its thermodynamically more stable isomer 5, via dissociation into 4 and 1. The facile elimination



of the 1,3-dione moiety from 5 is indicative of the possibility for such isomerization. However, attempts to isolate 7 from the reaction of 1 and 2 were not successful. The second molecule of 1,3-cyclohexanedione required in both reaction pathways can be readily supplied by retroaldol condensation.

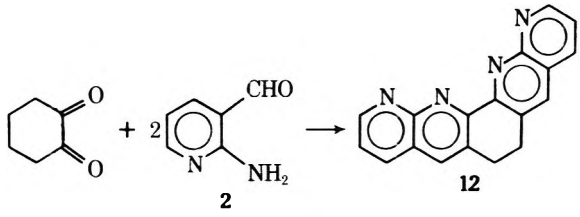
The attempted condensation of 1,4-cyclohexanedione (8) and 2-aminonicotinaldehyde under conditions similar to those utilized in the synthesis of 3 resulted in untractable,

highly colored products. After considerable experimentation a step by step sequence of addition and ring closing reactions proved successful.

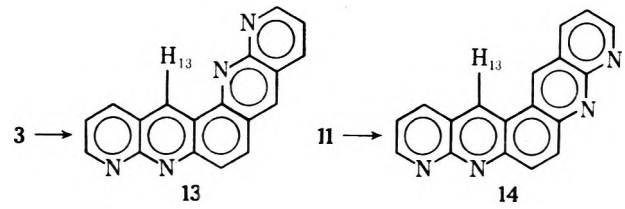


A solution of **2** and 8 (1:1 molar ratio) in ethanol was treated with piperidine at room temperature. A white precipitate was formed slowly and was isolated in 60% yield. Analysis indicated a simple addition product without loss of water, while the infrared spectrum shows the characteristic absorptions for OH and a primary amine (3530, 3450, 3340, and 3220 cm^{-1}). The monoaldol structure **9** is consistent with these data. Its isolation is fortunate since it provides evidence that aldol condensation precedes Schiff base formation in Friedländer condensations of **2** and ketones. The opposite sequence of events has been proposed for condensations of *o*-aminobenzaldehyde and ketones, although no intermediates analogous to **9** were isolated in condensations utilizing this *o*-amino aldehyde.[4] Ring closure of **9** could be effected almost quantitatively by dissolving it in boiling toluene; 2 mol of water was eliminated by this treatment with formation of 7-oxo-6,7,8,9-tetrahydrobenzo[*b*]-1,8-naphthyridine (**10**). Formation of 6,7-dihydrodipyrido[3,2-*b*:2,3-*j*]-4,7-phenanthroline (**11**) from **2** and **10** was not successful under conventional Friedländer conditions;[5] it was obtained instead in very good yield by refluxing both reagents in toluene with azeotropic removal of water. This condensation is unique in that it represents a first example of a Friedländer reaction in a hydrocarbon solvent. Although **10** could lead to a linear annelation product in the above reaction, this was not observed; the singlet in the NMR spectrum of **11** at δ 8.60 is characteristic of the angular structure (see further).

The base-catalyzed reaction of **2** and 1,2-cyclohexanedione in a 2:1 molar ratio resulted in the formation of 6,7-dihydrodipyrido[2,3-*b*:2,3-*j*]-1,10-phenanthroline (**12**) in moderate yield. Yields could not be increased under a variety of experimental conditions.



The recognition that Friedländer condensations on cyclohexanediones invariably result in dihydro derivatives of polycyclic systems prompted us to explore the transformation of the three isomeric pentacyclic dihydro compounds into their fully aromatic analogs. Selenium oxide in ethanol proved to be the method of choice for the dehydrogenation of **3** and **11** leading to dipyrido[2,3-*b*:2,3-*j*]-1,7-phenanthroline (**13**) and dipyrido[3,2-*b*:2,3-*j*]-4,7-phenanthroline (**14**), respectively. It is totally ineffective, however, in the dehydrogenation of **12**. This is not surprising since **12** does not contain activated carbon–hydrogen bonds.[6] However, dehydrogenation could not be effected even under drastic conditions such as SeO_2 in boiling nitrobenzene, Pd/C in high-boiling hydrocarbon solvents, sulfur, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in acetic acid. Both **13** and **14** are white, crystalline compounds soluble in common organic solvents; **14** is soluble in water.



The isomeric pentacyclic compounds described herein all contain two 1,8-naphthyridine units interconnected in different modes, but structured on the same angular building principle. The different magnetic environment on the "bay"[7] side of these molecules provided us with a basis for the interpretation of their NMR spectra (see Experimental Section). The absence of symmetry in **3** and **13** gives rise to rather complicated absorptions for protons H_2–H_{10} and H_3–H_{11}, recognized as two sets of doublets of doublets. As expected, protons on the bay side (four in **11** and **14**, two in **3** and **13**, none in **12**) absorb downfield from identical protons on the opposing side (H-12 and H-4 in **3**); protons on the bay side in the proximity of the nitrogen atoms absorb downfield from protons in the same relative position but only under the influence of an aromatic ring (H-13 in **3** and **11**).[8] A comparison of the bay protons, especially H-13, in the fully aromatic compounds and their dihydro analogs is of interest. Dehydrogenation of **3** results in a downfield shift for H-13 of 0.85 ppm, while oxidation of **11** produces a similar shift for H-13 of 0.89 ppm. The slightly lower value in going from **3** to **13** is the result of a concurrent upfield shift due to the increased distance separating H-13 and the electron pair on N-14 in **13**. The fact that very similar shifts are observed for both systems indicates that the diamagnetic anisotropy of the electron pair of N-14 is already maximized at the dihydro stage, implying a near planar arrangement for the bay side of the dihydro pentacyclic systems. This is substantiated by the ultraviolet spectra of these compounds. It is noteworthy that the three isomers differ in their absorption maximum: 361, 357, and 350 nm for **12**, **3**, and **11**, respectively. This seems to reflect steric interaction between H-13 and the electron pair on N-14 in **3** and between H-13 and H-14 in **11**, resulting in decreased conjugation between the two 1,8-naphthyridine moieties.

Experimental Section

General. NMR spectra were recorded with a Varian A-60 and/or Varian XL-100 with FT spectrometer in $CDCl_3$ as solvent using Me_4Si as an internal standard. Mass spectra were obtained on a Hitachi Perkin-Elmer RMU6E instrument; infrared spectra were recorded on a Perkin-Elmer Model 137 spectrophotometer and uv spectra on a Cary 15 instrument. All melting points are uncorrected. Microanalyses were done by Galbraith Laboratories, Inc., Knoxville, Tenn.

6,7-Dihydrodipyrido[2,3-*b*:2,3-*j*]-1,7-phenanthroline (3). To a refluxing solution of 2.0 g (17 mmol) of 1,3-cyclohexanedione and 5.0 g (41 mmol) of 2-aminonicotinaldehyde[9] in 50 ml of ethanol was added 10 drops of methanolic KOH (20%). Reflux was continued for 72 hr. The product crystallized upon cooling (4.6 g, 90%): mp 233; ir (Nujol) 1590, 1540, 1470, 1225, 1140, 990, 935, 915, 805, 800, 780, 735, 715 cm^{-1}; NMR δ 9.55 (H-13, 1, s), 9.12 (H-2 and H-10, 2, dd, $J_{\alpha-\beta}$ = 4.3, $J_{\alpha-\gamma}$ = 2 Hz), 8.34 (H-12, 1, dd, $J_{\beta-\gamma}$ = 8.1 Hz), 8.19 (H-4, 1, dd), 8.09 (H-5, 1, s), 7.50 and 7.49 (H-3 and H-11, 2, two sets of dd), 3.54–3.33 (H-6 and H-7, 4, m); uv (MeOH) 357 nm (ϵ 28830), 343 (25260), 236 (46850); mass spectrum M^+ *m/e* 284.

Anal. Calcd for $C_{18}H_{12}N_4$: C, 76.03; H, 4.25; N, 19.71. Found: C, 75.94; H, 4.17; N, 19.80.

6-Oxo-6,7,8,9-tetrahydrobenzo[*b*]-1,8-naphthyridine (4). A solution of 6.0 g (51 mmol) of 1 and 6.3 g (51 mmol) of 2 in 150 ml of ethanol was heated at 80° for 24 hr and then refluxed for 48 hr. The cooled mixture was filtered and the filtrate evaporated to dryness. Extraction with benzene gave 9.0 g (89%) of product: mp 165° dec; ir (Nujol) 1670, 1590, 1540, 1450, 1410, 1285, 1280, 1250, 1220, 1190, 1175, 1160, 1110, 1020, 1005, 990, 970, 910, 885, 815, 787 cm^{-1}; NMR δ 9.18 (H-2, 1, dd, $J_{\alpha-\beta}$ = 4, $J_{\alpha-\gamma}$ = 2 Hz), 8.81 (H-5, 1, s), 8.30 (H-4, 1, dd, $J_{\beta-\gamma}$ = 8 Hz), 7.50 (H-3, 1, dd), 3.39 (H-9, 2, t, $J_{H\text{-}8,H\text{-}9}$ = 6 Hz), 2.81 (H-7, 2, t, $J_{H\text{-}7,H\text{-}8}$ = 6 Hz), 2.31 (H-8, 2, m); uv (MeOH) 327 nm (ϵ 6590), 318 (6520), 276 (6210), 226 (50460); mass spectrum M^+ *m/e* 198 (75%), 170 (100%).

Anal. Calcd for $C_{12}H_{10}N_2O$; C, 72.71; H, 5.08; N, 14.13. Found: C, 72.70; H, 4.95; N, 14.17.

4-(2′,6′-Dioxocyclohexyl)-6-oxo-1,4,6,7,8,9-hexahydrobenzo[*b*]-1,8-naphthyridine (5). Method A. A mixture of 0.250 g (2 mmol) of 2 and 0.920 g (8 mmol) of 1 in 50 ml of ethanol was stirred at 65° for 48 hr. The white precipitate was washed extensively with ethanol to yield 0.540 g (87%) of 5: mp 203–204°; ir (Nujol) 3185, 1670, 1640, 1615–1565, 1520, 1410, 1320, 1275, 1266, 1225, 1175, 1150, 1110, 1055, 1020, 950, 925, 910, 820, 795, 740–720 cm^{-1}; NMR (CD_3–COOD) δ 8.27 (s, 1, H-5) 6.00 (s, 1, H-2) 4.24 (s, 1, H-4) 3.04 (unresolved triplet, 2, H-9) 2.72–1.92 (unresolved multiplet, 10, remaining aliphatic protons); NMR ($CDCl_3$) δ 8.19 (s, 1, H-5) 6.74 (unresolved m, 1, H-3), 5.70 (distorted dt, 1, H-2, J_{2-3} = 7.2, J_{2-4} = 2.3 Hz), 4.4 (unresolved m, 1, H-4), 2.90 (t, 2, H-9, J_{H8-H9} = 6 Hz), 2.59 (t, 2, H-7, J_{H7-H8} = 6 Hz), 2.46–1.90 (unresolved m, 8, remaining aliphatic protons); mass spectrum M^+ *m/e* 310. Since 5 could not be recrystallized from any solvent without change, an analytical sample was prepared by multiple washings of the crude reaction mixture at room temperature.

Anal. Calcd for $C_{18}H_{18}N_2O_3$: C, 69.65; H, 5.84; N, 9.03. Found: C, 69.33, H, 5.71; N, 9.00.

Method B. A mixture of 0.407 g (2 mmol) of 4 and 0.230 g (2 mmol) of 1 in 15 ml of ethanol was stirred at 65° for 3 days. The white precipitate was collected and characterized as described under method A.

[3-(2-Aminopyridyl)][2′-(1′,4′-dioxocyclohexyl)]methanol (9). To a solution of 8.0 g (65 mmol) of 2 and 6.0 g (54 mmol) of 1,4-cyclohexanedione in 50 ml of ethanol was added 30 drops of piperidine. The mixture was stirred at room temperature for 6 hr. The white precipitate was filtered and washed extensively: yield 6.8 g (59%); mp 125° dec; ir (Nujol) 3530, 3450, 3340, 3220, 3100, 3080, 1690, 1600, 1585, 1520, 1440, 1310, 1300, 1265, 1220, 1140, 1130, 1110, 1090, 1080, 1035, 1005, 980, 940, 820, 805, 780 cm^{-1}. Since 9 could not be recrystallized from any solvent without change, an analytical sample was prepared by multiple washings of the crude reaction product at room temperature.

Anal. Calcd for $C_{12}H_{14}N_2O_3$: C, 61.54; H, 5.98; N, 11.96. Found: C, 61.88; H, 6.06; N, 11.73.

7-Oxo-6,7,8,9-tetrahydrobenzo[*b*]-1,8-naphthyridine (10). 9 (6.8 g) was refluxed in 500 ml of toluene until a clear solution was obtained (~1 hr). The solution was cooled and filtered and the filtrate was evaporated to yield 5.4 g (94%) of product: mp 150° dec; ir (Nujol) 1710, 1625, 1605, 1560, 1480, 1420, 1305, 1290, 1220, 1180, 1160, 1100, 1020, 985, 955, 940, 915, 795, 750, 725 cm^{-1}; NMR δ 9.11 (H-2, 1, dd, $J_{\alpha-\beta}$ = 4, $J_{\alpha-\gamma}$ = 2 Hz), 8.18 (H-4, 1, dd, $J_{\beta-\gamma}$ = 8 Hz), 7.95 (H-5, 1, t, J_{5-6} = 1 Hz), 7.50 (H-3, 1, dd), 3.86 (H-6, 2, d), 3.57 (H-9, 2, t, J_{H8-H9} = 7 Hz), 2.75 (H-8, 2, t); uv (MeOH) 317 nm (ϵ 9510), 307 (9030), 264 (6020); mass spectrum M^+ *m/e* 198.

Anal. Calcd for $C_{12}H_{10}N_2O$: C, 72.71; H, 5.08; N, 14.13. Found: C, 72.73; H, 5.30; N, 14.09.

6,7-Dihydrodipyrido[3.2-*b*:2,3-*j*]-4,7-phenanthroline (11). A mixture of 2.0 g (1 mmol) of 10 and 4.0 g (3 mmol) of 2 in 75 ml of toluene was refluxed for 48 hr with continuous water removal. The precipitate was collected to give 2.5 (89%) of product: mp 242; ir (Nujol) 1605, 1538, 1470, 1275, 1225, 1190, 1175, 1150, 1140, 925, 905, 895, 810, 800, 795, 780 cm^{-1}; NMR δ 9.10 (H-3 and H-10, 2, dd, $J_{\alpha-\beta}$ = 4.2, $J_{\alpha-\gamma}$ = 2 Hz), 8.60 (H-13 and H-14, 2, s), 8.27 (H-1 and H-12, 2, dd, $J_{\beta-\gamma}$ = 8.2 Hz), 7.50 (H-2 and H-11, 2, dd), 3.58 (H-6 and H-7, 4, s); uv (MeOH) 350 nm (ϵ 26720), 338 (sh, 24140), 243 (45690), 231 (sh, 41380); mass spectrum M^+ *m/e* 284.

Anal. Calcd for $C_{18}H_{12}N_4$: C, 76.03; H, 4.25; N, 19.71. Found: C, 75.98; H, 4.25; N, 19.64.

6,7-Dihydrodipyrido[2,3-*b*:3,2-*j*]-1,10-phenanthroline (12). To a solution of 2.0 g (16 mmol) of 1,2-cyclohexanedione and 5.0 g (41 mmol) of 2 in 100 ml of ethanol was added 25 drops of methanolic KOH (20%). The solution was refluxed for 48 hr. The precipitate was collected and recrystallized (H_2O) to yield 2.1 g (44%) of 12: mp 315°; ir (Nujol) 1615, 1590, 1550, 1538, 1450, 1285, 1190, 1125, 1025, 900, 833, 810, 800, 770, 725, 715 cm^{-1}; NMR δ 9.23 (H-2 and H-11, 2, dd, $J_{\alpha-\beta}$ = 4.2, $J_{\alpha-\gamma}$ = 1.9 Hz), 8.18 (H-4 and H-9, 2, dd, $J_{\beta-\gamma}$ = 8.2 Hz), 8.12 (H-5 and H-8, 2, s), 7.50 (H-3 and H-10, 2, dd), 3.31 (H-5 and H-6, 4, s); uv (MeOH) 361 nm (ϵ 26130), 346 (22520), 233 (44140); mass spectrum M^+ *m/e* 284.

Anal. Calcd for $C_{18}H_{12}N_4$: C, 76.03; H, 4.25; N, 19.71. Found: C, 75.96; H, 4.37; N, 19.56.

Dipyrido[2,3-*b*:2,3-*j*]-1,7-phenanthroline (13). A mixture of 1.0 g (3.5 mmol) of 3 and 0.4 g (3.6 mmol) of SeO_2 was refluxed for 3 hr. The reaction mixture was filtered hot and the filtrate evaporated to dryness. The residue was dissolved in chloroform and percolated through a column of alumina to give 0.8 g (87%) of white product: mp 325–326°; ir (Nujol) 1620, 1610, 1590, 1560, 1390, 1175, 925, 910, 820, 810, 765 cm^{-1}; NMR δ 10.40 (H-13, 1, s), 9.32 and 9.30 (H-2 and H-10, 2, two sets of dd, $J_{\alpha-\beta}$ = 4.2, $J_{\alpha-\gamma}$ = 2.1 Hz), 8.69 (H-5, 1, s), 8.55 (H-12, 1, dd, $J_{\beta-\gamma}$ = 8.4 Hz), 8.42 (H-4, 1, dd), 8.11 (H-7, 1, distorted doublet), 8.05 (H-6, 1, distorted doublet, J_{H6-H7} = 9.5 Hz), 7.60 and 7.59 (H-3 and H-11, 2, two sets of dd); mass spectrum M^+ *m/e* 282 (100) and *m/2e* 141 (45); uv (MeOH) 228 nm (ϵ 51887), 278 (18870), 289 (19810), 327 (51890), 342 sh (33000), 377 (2360), 395 (800).

Anal. Calcd for $C_{18}H_{10}N_4$: C, 76.57; H, 3.58; N, 19.86. Found: C, 76.37; H, 3.46; N, 19.80.

Dipyrido[3.2-*b*:2,3-*j*]-4,7-phenanthroline (14). A mixture of 2.0 g (7 mmol) of 11 and 0.78 g (7 mmol) of SeO_2 in 200 ml of ethanol was heated slowly to reflux. At this point heating was continued for 0.5 hr. The cooled mixture was filtered and the filtrate concentrated to give 1.5 g (77%) of 14, mp 342–344°. An analytical sample was prepared by sublimation (200°, 1 mmHg): ir (Nujol) 1610, 1540, 1495, 1300, 1220, 1040, 930, 835, 810, 780, 730 cm^{-1}; NMR δ 9.49 (H-13 and H-14, 2, s), 9.32 (H-3 and H-10, 2, dd, $J_{\alpha-\beta}$ = 4.2, $J_{\alpha-\gamma}$ = 2 Hz), 8.51 (H-1 and H_{12}, 2, dd, $J_{\beta-\gamma}$ = 8.3 Hz), 8.42 (H-6 and H-7, 2, s), 7.63 (H-2 and H-11, 2, dd); mass spectrum M^+ *m/e* 282; uv (MeOH) 230 nm (ϵ 54500), 274 (24000), 284 (26800), 326 (49000), 341 sh (34000), 357 sh (14000), 372 (5400), 380 (1850), 391 (4200).

Anal. Calcd for $C_{18}H_{10}N_4$: C, 76.57; H, 3.58; N, 19.86. Found: C, 76.35; H, 3.70; N, 19.60.

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Registry No.—1, 504-02-9; 2, 7521-41-7; 3, 56488-07-4; 4, 56488-08-5; 5, 56488-09-5; 9, 56488-10-9; 10, 56488-11-0; 11, 56488-12-1; 12, 56488-13-2; 13, 56488-14-3; 14, 56488-15-4; 1,4-cyclohexanedione, 637-88-7; 1,2-cyclohexanedione, 765-87-7.

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Benzanthracene Derivatives via the Stobbe Condensation. Synthesis of 3,9-Dihydroxybenz[a]anthracene

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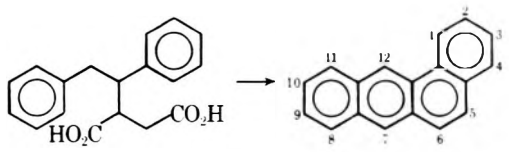
The synthesis of 3,9-dihydroxybenz[a]anthracene is described. The Stobbe condensation of deoxyanisoin 1 with dimethyl succinate was successful when the reaction was performed in refluxing diglyme. The resultant γ-(*p*-methoxyphenyl)-γ-(*p*-methoxybenzylidene)methylsuccinic acid (2) was reduced by Raney nickel to the saturated diacid 3, which was readily converted to its anhydride 4 in refluxing acetyl chloride. Aluminum chloride catalyzed Friedel–Crafts reaction of the anhydride in *sym*-tetrachloroethane containing 20% nitrobenzene gave 1-oxo-3-(*p*-methoxyphenyl)-7-methoxy-1,2,3,4-tetrahydro-2-naphthylacetic acid (5), whose structure was proven by eventual conversion to 3-(*p*-methoxyphenyl)-7-methoxy-2-naphthylacetic acid (6b). The infrared spectrum of the latter unambiguously supports the structural assignment of 5. Attempted cyclization of the keto acid 5 resulted instead in the formation of an undesired enol lactone 11; therefore the ketone function was first reduced under Clemmensen conditions to the tricyclic acid 6. Anhydrous HF readily cyclized this intermediate to the hexahydrobenz[a]anthracene derivative 7. The 5-keto function was reduced either under Clemmensen or Wolff–Kishner conditions to give the deoxo derivative 8, which was aromatized with DDQ to 3,9-dimethoxybenz[a]anthracene (9a). The 3,9-diol 9b was obtained via BBr_3 cleavage of the ether, and was further characterized by conversion to the diacetate 9c. The estrogenic activities and possible carcinogenic properties of these compounds are currently under investigation.

The identification of polar metabolites of carcinogenic polycyclic hydrocarbons has been hampered by the unavailability of authentic hydroxy derivatives of these compounds. Attempts to elucidate the mechanism by which certain hydrocarbons behave as carcinogens have been limited to correlations with a meager supply of fortuitously available derivatives[2] with the exception of the easily obtainable hydroxy derivatives substituted at the 7,12 positions. No other dihydroxy derivatives of benz[a]anthracene of unequivocal structure have been reported.

Many of the polar metabolites of polycyclic hydrocarbons remain unidentified owing to the noncoincidence of these derivatives with available compounds on radiochemical scans of thin layer chromatograms. In the case of 7,12-dimethylbenz[a]anthracene, for example, a full third of the metabolites from rat liver and breast tissue incubations are more polar than the known monohydroxy derivatives of this hydrocarbon and probably contain two or more hydroxy groups.[3]

Of particular interest in this laboratory is the 3,9-diol of benz[a]anthracene, since models of this compound show that the hydroxy groups are superimposable with those of 17β-estradiol and diethyl stilbestrol, and the possibility exists that this polycyclic hydrocarbon diol may have estrogenic properties. One attractive route toward the acquisition of the benzanthracene ring system is that which has been explored by Newman.[4] This route involves the ring closure of the reduced Stobbe condensation product derived from methyl succinate and either deoxybenzoin or its methyl derivatives.



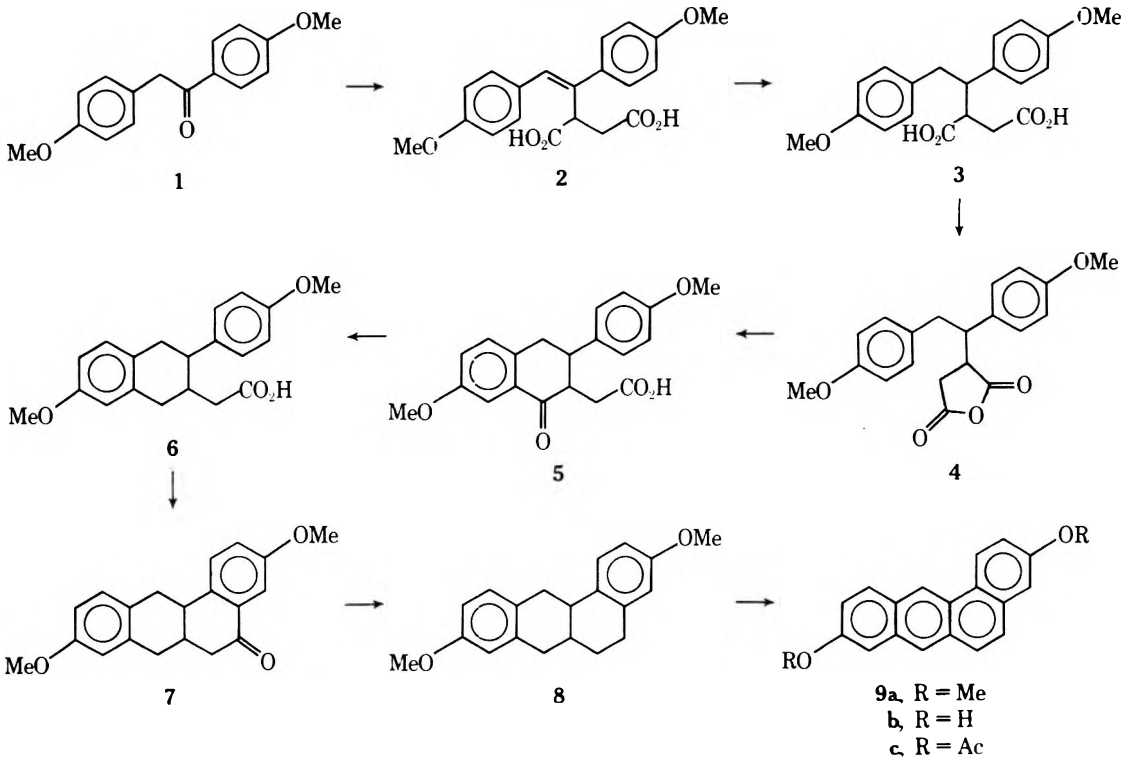
It was presumed that selection of methoxylated deoxybenzoins would yield, by similar reactions, the substituted tetracyclic benzanthracene ring system. Such an application with deoxyanisoin (1) would thus lead to the desired 3,9-dihydroxybenz[a]anthracene (9b). The expected Stobbe condensation of deoxyanisoin with dimethyl succinate, however, failed to occur under those conventional conditions[5] utilizing sodium ethoxide in ethanol or ether, sodium methoxide in ether, or potassium *tert*-butoxide in *tert*-butyl alcohol. The relative insolubility of deoxyanisoin in dimethyl succinate precluded implementation of the conditions utilized by Newman and Hart in which a solution of deoxybenzoin in dimethyl succinate was added to the hot catalyst[4].

By refluxing the reagents in diglyme and sodium methoxide, the reaction was successful, owing in part to the higher temperature of the reaction and the greater solubilizing characteristics of the solvent (see Chart I). The unsaturated acid 2 was reduced with Raney nickel in hot 10% NaOH to give saturated acid 3, mp 190–193°, and a minor isomeric saturated acid, mp 148–150°. The higher melting compound was treated with anhydrous HF in an attempt to bring about partial cyclization to compound 5 or full cyclization corresponding to the tetracyclic benz[a]anthracene ring system. The related succinic acid derivative in which the methoxyl groups are not present does indeed provide a mixture of mono- and dicyclized products under these conditions.[4] In the present case, infrared spectra of the products of the reactions gave no absorption peaks consistent with those expected from cyclic ketones. Instead, the sole product of this reaction was found to be the anhydride 4. Crude anhydride 4 was also obtained exclusively by treatment of the diacid 2 with polyphosphoric acid. Only degradation was noted by treatment of the acid 2 with either concentrated sulfuric acid or phosphorus pentachloride.

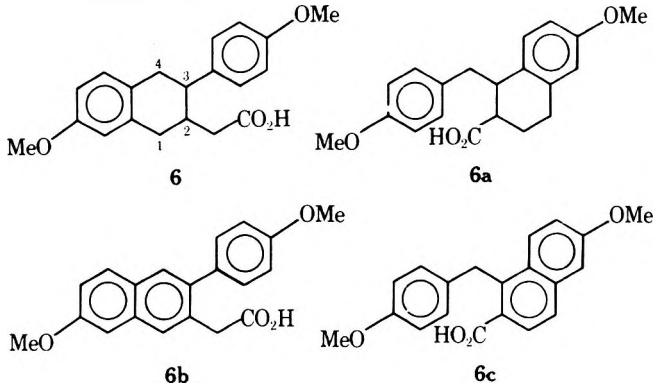
For preparative purposes, anhydride formation was most efficiently performed in refluxing acetyl chloride.[6] Cyclization of the anhydride was accomplished by aluminum chloride in *sym*-tetrachloroethane containing 20% nitrobenzene[7] to form the tricyclic keto acid 5. The assigned structure is consistent with that of the unsubstituted keto acid prepared from deoxybenzoin by Newman. To confirm the structure, it was decided to utilize the next compound in the synthetic sequence (6 in Chart I). The structural alternatives are the tetrahydronaphthylacetic acid 6 or its isomer, tetrahydronaphthoic acid 6a.

Attempts at establishing structure 6 instead of the isomer 6a by off-resonance coupling of the ^{13}C NMR spectrum of the material at hand were frustrated by the presence of a small amount of a stereoisomer at C-2 of the tetrahydronaphthalene moiety. The NMR results were equivocal in permitting assignment of a methylene vs. a

Chart I

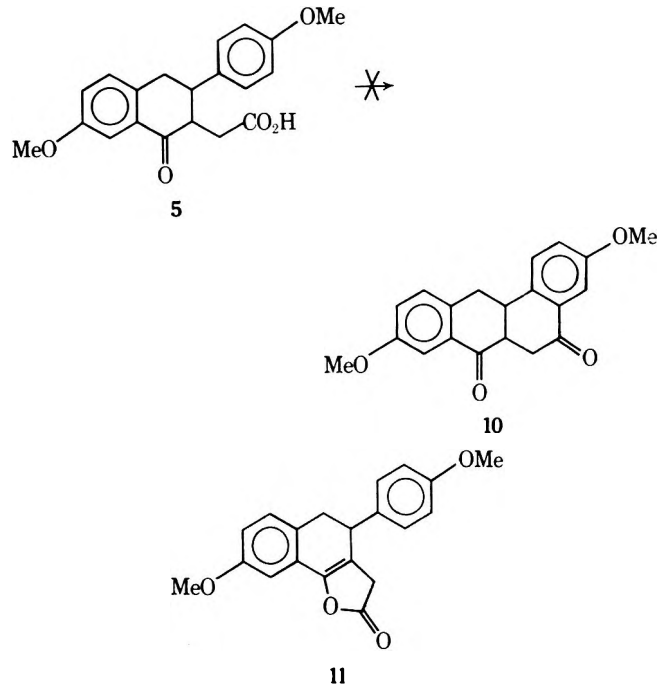


methine carbon α to the carboxyl function. Therefore, the compound was totally aromatized to give the naphthylacetic acid **6b**, as confirmed by its arylacetic acid carbonyl frequency of 1710 cm^{-1}.[8] The alternative structure **6c** is ruled out, since being a naphthoic acid, its ir carbonyl frequency would be expected to be at 1680 cm^{-1}. For purposes of comparison, spectra of 4-methoxyphenylacetic acid and 2-naphthoic acid were obtained on our instrument and showed the expected carbonyl frequencies of 1720 and 1680 cm^{-1}, respectively.



A second closure of the remaining carboxy group to form the tetracyclic benzanthracene dione **10** was attempted with thionyl chloride followed by aluminum chloride, with polyphosphoric acid, and with anhydrous HF. All of these treatments instead resulted in a compound which showed disappearance of the acid and ketone carbonyl functions (1715 and 1680 cm^{-1}, respectively) and the appearance of a single sharp peak at 1810 cm^{-1} which presumably represents the enol lactone **11**, which was not further studied.

Wolff–Kishner reduction of the keto acid **5** resulted in the formation of a single high-melting (235–239°) product which showed spectral characteristics inconsistent with the expected acid **6**. The compound was refractive to both acid and base hydrolysis and is probably a cyclic hydrazide derivative similar to those which have been demonstrated to form under these conditions with other keto acids.[9]



Clemmensen reduction successfully yielded the saturated acid **6** which easily cyclized to the tetracyclic ketone **7** with anhydrous HF. Clemmensen reduction of compound **7** gave the dimethoxyhexahydrobenz[*a*]anthracene derivative **8**. Aromatization of compound **8** to the dimethyl ether of benz[*a*]anthracene-3,9-diol **9a** was accomplished with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in refluxing benzene[10] after it was found that only fragmentation occurred during attempted high-temperature dehydrogenation with palladium on carbon, or with selenium. The final step in the sequence was the ether cleavage with boron tribromide[11] to 3,9-dihydroxybenz[*a*]anthracene **9b**, which was further characterized by conversion to the diacetate **9c**. The estrogenic activities and the possible carcinogenic properties of the synthetic compounds described in this report are currently under investigation.

Experimental Section[12]

γ-(p-Methoxyphenyl)-γ-(p-methoxybenzylidene)methylsuccinic Acid (2). A mixture of 100 g (0.39 mol) of deoxyanisoin **1** [p-methoxy-α-(p-methoxyphenyl)acetophenone], 57 g (0.39 mol) of dimethyl succinate, and 42.2 g (0.78 mol) of sodium methoxidein 1 L of diglyme (2-methoxyethyl ether) was heated under reflux for 2 hr while protected from moisture with a Drierite tube. The solution was then allowed to cool to room temperature and stirred overnight. The reaction mixture was poured onto crushed ice and extracted with ether. The ether solution was extracted with a total of 1 l. of 5% NaOH. The base extracts were combined with the original aqueous phase and set up for distillation to remove residual ether. When a distillation temperature of 95° was attained, the distillation head was removed and replaced with a reflux condenser and reflux was continued for 3 hr.

The reaction solution was cooled in an ice bath, acidified with concentrated HCl, and extracted with ether. The ethereal solution was washed with water and saturated NaCl solution, dried ($MgSO_4$), and concentrated in vacuo to give 99.2 g of the crude diacid **2** as a dark glass. Crystallization from benzene afforded 48.7 g of crystals, mp 115–116°, in the first crop, and 7.64 g, mp 82–85°, in the second crop, for a total yield of 56.3 g (40.4%) of the crystalline diacid **2**. Recrystallization of the higher melting crop from benzene afforded the analytical sample: mp 116–118°; ir (KBr) CO_2H, 1705; Ar, 1610; $-CH_3$, 1030 cm^{-1}. Anal. Calcd for $C_{20}H_{20}O_6$: C, 67.40; H, 5.65. Found: C, 67.66; H, 5.67.

γ-(p-Methoxyphenyl)-γ-(p-methoxybenzyl)methylsuccinic Acid (3). To a mechanically stirred solution of 15.1 g (42.4 mmol) of diacid **2** in 500 ml of 10% NaOH on a steam bath was added 45 g of Raney nickel in small portions. When the reaction had subsided, the reaction mixture was allowed to cool to room temperature and the nickel residue was removed by filtration. The filtrate was cooled in an ice bath, stirred with a mechanical paddle-stirrer, and acidified with concentrated HCl to pH 1. The remaining white solid was separated by filtration and washed with copious amounts of cold water. The solid was dried overnight at room temperature and then at 100° over P_2O_5, and gave 14.1 g (93%) of saturated diacid **3**, mp 180–183°. Crystallization from ethanol afforded the analytical sample: mp 198–200°; ir (KBr) CO_2H, 1695; Ar, 1610; $-OCH_3$, 1035 cm^{-1}. Anal. Calcd for $C_{20}H_{22}O_6$: C, 67.04; H, 6.19. Found: C, 67.23; H, 6.15.

The mother liquors also yielded a small amount of a lower melting isomer in some runs. This isomer, mp 148–150°, had ir spectrum which was virtually superimposable with that of the higher melting isomer, with minor differences in the fingerprint region. Anal. Calcd for $C_{20}H_{22}O_6$: C, 67.04; H, 6.19. Found: C, 67.12; H, 6.20.

γ-(p-Methoxyphenyl)-γ-(p-methoxybenzyl)methylsuccinic Anhydride (4). A mixture of 20.0 g (55.8 mmol) of higher melting diacid **3** and 40 ml of acetyl chloride was refluxed for 1 hr. The excess acid chloride was removed in vacuo and the last traces of acetic acid were removed azeotropically with benzene. The remaining yellow glass of crude anhydride was used directly in the Friedel–Crafts reaction: ir ($CHCl_3$) anhydride C=O, 1870, 1780; Ar, 1620; $-OCH_3$, 1030 cm^{-1}.

1-Oxo-3-(p-methoxyphenyl)-7-methoxy-1,2,3,4-tetrahydro-2-naphthylacetic acid (5). To a stirred, ice-cold solution of 11.1 g (83 mmol) of $AlCl_3$ in 120 ml of *sym*-tetrachloroethane and 30 ml of nitrobenzene was added a solution of 14.1 g (40.3 mmol) of anhydride **4** in the same solvent mixture as above. The addition was performed in a dropwise fashion over a period of 50 min. The mixture was stirred at 0–5° for 2 hr and then allowed to warm to room temperature overnight. The dark brown reaction mixture was poured onto a mixture of 10% HCl and crushed ice, and extracted with chloroform. The organic phase was extracted with 5% NaOH; the latter was cooled to 0° and acidified with concentrated HCl. The precipitated oil was extracted into chloroform, washed with water, dried ($MgSO_4$), and concentrated in vacuo gave 12.7 g (89.5%) of crude tricyclic keto acid **5**. Crystallization from benzene–hexane afforded the analytical sample: mp 151–152°; ir (KBr) CO_2H, 1705; C=O, 1675; Ar, 1610; $-OCH_3$, 1038 cm^{-1}; NMR ($CDCl_3$)δ 2.4–3.3 m. 6 H), 3.82 (s, 3 H), 3.85 (s, 3 H), 6.8–7.6 (m, 7 H). Anal. Calcd for $C_{20}H_{20}O_5$: C, 70.57; H, 5.92. Found: C, 70.66; H, 5.93.

3-(p-Methoxyphenyl)-7-methoxy-1,2,3,4-tetrahydro-2-naphthylacetic Acid (6). Amalgamated zinc was prepared by swirling 30 g of mossy zinc granules with 3.0 g of $HgCl_2$, 1.5 ml of concentrated HCl, and 38 ml of H_2O for 5 min. The solvent was decanted, and to the residual amalgamated zinc was added 18 ml of H_2O, 40 ml of concentrated HCl, and a solution of 9.02 g (25.5 mmol) of keto acid **5** in 100 ml of toluene. The reaction mixture was stirred under reflux for 69 hr. During the course of the reaction, seven 10-ml portions of concentrated HCl were added at intervals. The reaction mixture was cooled in an ice bath, and the biphasic solution was decanted from the residual metal and extracted with benzene. The organic solution was extracted with two 100-ml portions of 5% NaOH; to the base solution was added 10 ml $(CH_3)_2SO_4$ and the mixture was stirred at room temperature for 1 hr. The reaction mixture was cooled in an ice bath, acidified with concentrated HCl, extracted with chloroform, washed with water, washed with saturated NaCl solution, dried ($MgSO_4$), and concentrated in vacuo to give 7.61 g (88%) of crude acid **6** as a light yellow glass. Crystallization from benzene gave a solid, mp 147–156°, which on recrystallization afforded the analytical sample: mp 153–156°; ir (KBr) CO_2H, 1700; Ar, 1610; $-OCH_3$, 1035 cm^{-1}; NMR ($CDCl_3$) δ 2.2–3.0 (m, 8 H), 3.74 (s, 6 H), 6.56–7.33 (m, 7 H). Anal. Calcd for $C_{20}H_{22}O_4$: C, 73.6; H, 6.79. Found: C, 73.53; H. 6.80.

3-(p-Methoxyphenyl)-7-methoxy-2-naphthylacetic Acid (6b). A solution of 1.0 g (3.06 mmol) of acid **6** and 2.09 g (9.18 mmol) of DDQ in 50 ml of anhydrous benzene was refluxed for 18.5 hr while protected from moisture with a Drierite tube. The reaction mixture was cooled to room temperature, and the suspended precipitate was removed by filtration and washed with benzene. The filtrate was passed through a column (45 × 90 mm) of activated alumina (80–225 mesh, MCB) and eluted with ethyl acetate (2 × 500 ml) and 5% CH_3CO_2H in ethyl acetate (2 × 500 ml). Concentration of the combined eluates gave 0.80 g of tan foam whose ir spectrum showed, in addition to the expected 1710-cm^{-1} acid peak, an ester peak at 1765 cm^{-1}, presumably due to transesterification by ethyl acetate on the activated alumina column. The material was therefore refluxed in 10% NaOH (50 ml) for 4 hr, cooled in an ice bath, and acidified with concentrated HCl to give a tan solid. This was separated by filtration, washed with water, and dried in vacuo at room temperature over P_2O_5 to give 0.75 g of crude naphthylacetic acid **6b**. Recrystallization from methanol afforded the analytical sample: mp 218–220°; ir ($CHCl_3$) $-CO_2H$, 1710; Ar, 1630, 1620; $-OCH_3$, 1030 cm^{-1}; NMR ($CDCl_3$) δ 3.77 (s, 2 H), 3.86 (s, 3 H), 3.94 (s, 3 H), 6.78–7.85 (m, 9 H). Anal. Calcd for $C_{20}H_{18}O_4$: C, 74.52; H, 5.63. Found: C, 74.25; H, 5.61.

3,9-Dimethoxy-5-keto-5,6,6a,7,12,12a-Hexahydrobenz[a]anthracene (7). A 4.64-g (14.2 mmol) sample of the naphthylacetic acid **6** was dissolved in 60 ml of anhydrous HF and allowed to evaporate overnight. The crystalline residue was partitioned between chloroform and water, washed with 5% NaOH solution, washed with water, dried ($MgSO_4$), and concentrated in vacuo to give 4.44 g of a greenish glass. The infrared spectrum of this material showed, in addition to the desired 1680-cm^{-1} carbonyl absorption of the tetracyclic ketone **7**, a minor ester peak at 1725 cm^{-1}. To remove the latter contaminant, the above material was refluxed with 25 ml of 10% NaOH and 30 ml of ethanol for 1 hr. The reaction mixture was cooled in an ice bath and the suspended solid was separated by filtration, washed with water, and dried in vacuo at 100° over P_2O_5 to give 2.69 g of tetracyclic ketone **7**. The mother liquors yielded another 0.57 g of material for a total of 3.26 g (74.3%). Recrystallization from methanol provided the analytical sample: mp 145–147°; ir ($CHCl_3$) C=O, 1680; Ar, 1620; $-OCH_3$, 1027 cm^{-1}; NMR ($CDCl_3$) δ 2.12–3.68 (m, 8 H), 3.79 (s, 3 H), 3.86 (s, 3 H). 6.60–7.63 (m, 6 H). Anal. Calcd for $C_{20}H_{20}O_3$: C, 77.9; H, 6.54. Found: C, 77.94; H, 6.56.

3,9-Dimethoxy-5,6,6a,7,12,12a-Hexahydrobenz[a]anthracene (8). A. Via Clemmensen Reduction. Amalgamated zinc was prepared from 7 g of mossy zinc, 0.7 g of $HgCl_2$, 1.2 ml of concentrated HCl, and 10 ml of H_2O in the usual fashion. To the amalgamated metal was added 5 ml of H_2O, 13 ml of concentrated HCl, and a solution of 1.90 g (6.17 mmol) of the tetracyclic ketone **7** in 100 ml of toluene. The mixture was refluxed with stirring for 21 hr, during which period five 5-ml portions of concentrated HCl were added at intervals. The reaction mixture was cooled to room temperature, partitioned between benzene and water, washed with saturated NaCl solution, dried ($MgSO_4$), and concentrated in vacuo gave 1.85 g of crude solid tetracyclic compound **8**. Recrystallization from benzene–hexane afforded the analytical sample: 1.19 g (66%); mp 130–131°; ir($CHCl_3$) no C=O; Ar, 1610, 1580; $-OCH_3$, 1030 cm^{-1}. Anal. Calcd for $C_{20}H_{22}O_2$: C, 81.60; H, 7.53. Found: C, 81.55; H, 7.55.

B. Via Wolff–Kishner Reduction. A mixture of 3.26 g (10.6 mmol) of tetracyclic ketone **7**, 2.78 g (86.7 mmol) of anhydrous hydrazine, and 3.01 g (53 mmol) of KOH in 100 ml of diethylene glycol was refluxed with stirring for 4 hr and left to stir overnight at

room temperature. The reaction mixture, which contained a suspended solid, was diluted with water and acidified with concentrated HCl. The solid was separated by filtration and washed with water. Recrystallization from benzene gave 1.35 g (43.3%) of material, mp 109–112°, which on further recrystallization gave material identical with that obtained from Clemmensen reduction: NMR ($CDCl_3$) δ 1.42–3.55 (m, 10 H), 3.88 (s, 6 H), 6.58–7.40 (m, 6 H).

3,9-Dimethoxybenz[*a*]anthracene (9a). A solution of 200 mg (0.678 mmol) of the hexahydro compound **8** and 930 mg (4.07 mmol) of DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) in 60 ml of benzene was refluxed for 16 hr. The reaction mixture was cooled to room temperature, filtered through an alumina column, and eluted with benzene. The colorless eluate on concentration gave 190 mg of white crystals, fluorescent in ultraviolet light, mp 175–176°. Recrystallization from benzene–hexane afforded the analytical sample of **9a** as colorless needles: mp 190–192°; ir (KBr) Ar, 1625, 1590; $-OCH_3$, 1025 cm^{-1}; NMR ($CDCl_3$) δ 3.98 (s,6 H), 7.24–8.94 (m, 10 H). Anal. Calcd for $C_{20}H_{16}O_2$: C, 83.31; H, 5.59. Found: C, 83.05; H, 5.67.

3,9-Dihydroxybenz[*a*]anthracene (9b). To a heated, stirred solution of 394 mg (1.36 mmol) of 3,9-dimethoxybenz[*a*]anthracene (**9a**) in 30 ml of benzene was added a solution of 3 ml of BBr_3 in 10 ml of benzene. Initially, during the dropwise addition of the latter, a precipitate was formed which redissolved on further heating. The solution was refluxed for 3 hr protected from moisture with a Drierite tube, then cooled to room temperature, poured onto crushed ice, and extracted with ether. The organic solution was washed with water and extracted with 10% NaOH (3 × 35 ml). The fluorescent yellow base solution was cooled to 0°, acidified with concentrated HCl, and extracted with ethyl acetate. The organic extract was washed with water, dried ($MgSO_4$), and concentrated in vacuo to give 370 mg of brown solid, mp >250° dec. High vacuum sublimation of this material at 255° afforded analytically pure diol **9b** as a yellow solid: mp 265–270° dec; ir (KBr) –OH, 3100; Ar, 1620, 1595 cm^{-1}. Anal. Calcd for $C_{18}H_{12}O_2$: C, 83.06; H, 4.65. Found: C, 82.89; H, 4.68.

3,9-Diacetoxybenz[*a*]anthracene (9c). A 125-mg sample of the dihydroxy compound **9b** was dissolved in 5 ml each of acetic anhydride and pyridine, and left overnight at room temperature. The usual work-up afforded analytically pure diacetate **9c** as white platelets: mp 200–201°; ir (KBr) C=O, 1760; Ar, 1620, 1590 cm^{-1}; NMR ($CDCl_3$) δ 2.38 (s, 6 H), 7.18–9.10 (m, 10 H). Anal. Calcd for $C_{22}H_{16}O_4$: C, 76.73; H, 4.68. Found: C, 76.56; H, 4.70.

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Registry No.—**1**, 120-44-5; **2**, 56554-10-0; **3**, 56554-11-1; **4**, 56554-12-2; **5**, 56554-13-3; **6**, 56554-14-4; **6b**, 56554-15-5; **7**, 56554-16-6; **8**, 56554-17-7; **9a**, 56554-18-8; **9b**, 56614-97-2; **9c**, 56554-19-9; dimethyl succinate, 196-65-0.

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Synthesis of 1-Substituted and 1,3-Disubstituted 5-Hydantoincarboxylates[1]

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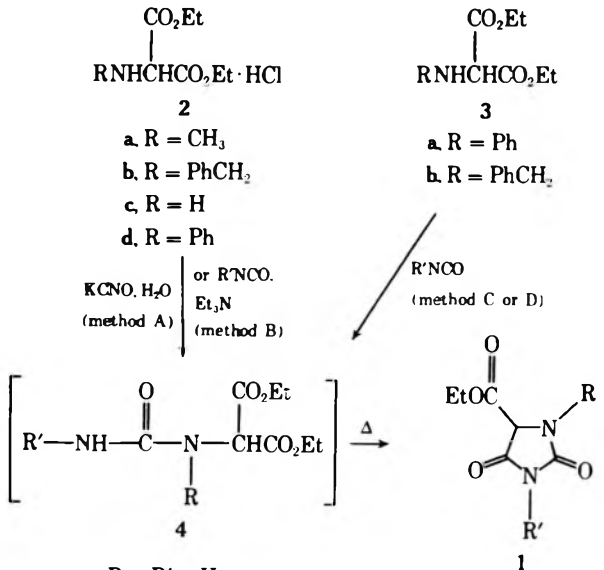
N-Substituted aminomalonates react with KCNO or isocyanates to give directly 1-substituted or 1,3-disubstituted 5-hydantoincarboxylates. The initial products, i.e., the hitherto unknown N-substituted or N,N′-disubstituted ureidomalonates, cyclize spontaneously on heating under the experimental conditions. This behavior is in contrast to that of ureidomalonate and N′-substituted ureidomalonates, which require base catalysis for cyclization. The benzylic protons of 1-benzyl-5-hydantoincarboxylates display chemical shift nonequivalence.

In a synthetic program for 8-hydroxypurines, it was necessary to prepare ethyl 1-substituted 5-hydantoincarboxylates. A literature search has not revealed a description of any 1-substituted or 1,3-disubstituted 5-hydantoincarboxylates,[2] although 3-substituted 5-hydantoincarboxylates[3,4] are known. We wish to report a facile general synthesis of the title 5-hydantoincarboxylates by the cyclization of N-substituted and N,N′-disubstituted ureidomalonates.

5-Hydantoincarboxylate (**1k**) and many 3-substituted 5-hydantoincarboxylates are known and can be prepared by base-catalyzed cyclization of ureidomalonate (**4a**) and N′-substituted ureidomalonates.[3-5] However, under no circumstances can the cyclization be effected simply by heating. Gatewood[2h] reported that **4b** failed to cyclize to **1j** under various conditions, including heating at its melting point for varying lengths of time. We noted that **4a** behaved similarly. Heating **4a** beyond its melting point, e.g., at 200°, caused gas evolution and numerous products were formed, as indicated by the TLC of the residue. An apparent route to 1-substituted 5-hydantoincarboxylates would be, therefore, the base-catalyzed cyclization of N-substituted ureidomalonates.

1-Substituted 5-Hydantoincarboxylates. Heating *N*-methyl- (**2a**) and *N*-benzylaminomalonate hydrochloride (**2b**) with KCNO in water produced directly 1-methyl- (**1a**) and 1-benzyl-5-hydantoincarboxylate (**1e**), respectively (method A). The initial products, i.e., the N-substituted ureidomalonates **4c** and **4d**, apparently cyclized spontaneously under the experimental conditions. This result is surprising in view of the fact that the reaction of amino-



a, R = R′ = H
b, R = H; R′ = Ph
c, R = CH_3; R′ = H
d, R = $PhCH_2$; R′ = H
e, R = Ph; R′ = H
f, R = R′ = Ph

a, R = CH_3; R′ = H
b, R = R′ = CH_3
c, R = CH_3; R′ = $PhCH_2$
d, R = CH_3; R′ = Ph
e, R = $PhCH_2$; R′ = H
f, R = $PhCH_2$; R′ = CH_3
g, R = $PhCH_2$; R′ = Ph
h, R = Ph; R′ = CH_3
i, R = R′ = Ph
j, R = H; R′ = Ph
k, R = R′ = H

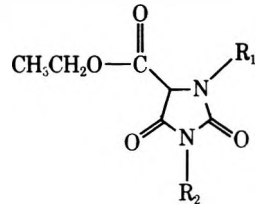
malonate hydrochloride (**2c**) and KCNO is known to afford the urea **4a**.[3,4,6,7] Anilinomalonate hydrochloride (**2d**) failed to form the ureidomalonate **4e** by reacting with KCNO under the same conditions and the free amine **3a** was recovered quantitatively.

1,3-Disubstituted 5-Hydantoincarboxylates. Heating an N-substituted aminomalonate hydrochloride **2** or the corresponding free amine **3** and an isocyanate, such as methyl, benzyl, or phenyl isocyanate, with or without a solvent produced 1,3-disubstituted 5-hydantoincarboxylates with equal success (methods B–D, see Table I). Owing to the ease of formation of the desired hydantoins **1**, no attempt was made to isolate the urea intermediates **4** except in one case. In the reaction of **3a** and PhNCO, the product was shown to be the urea **4f** by ir and NMR spectroscopy. The urea **4f** did cyclize to the hydantoin **1i** just by heating, although much higher temperatures were needed. The urea **4f** is the first known N,N′-disubstituted ureidomalonate. Although the reaction of aminomalonate hydrochloride (**2c**) with isocyanates to form N′-substituted ureidomalonates is well documented,[2h,3,4,6] there is no description of any N-substituted or N,N′-disubstituted ureidomalonates in the literature.

Whereas N′-substituted ureidomalonates, **4** (R = H; R′ = H, alkyl, aryl), are quite resistant to heat[8] and are readily cyclized to hydantoins upon base catalysis,[3,4] the results of this work clearly show that the presence of a substituent at the ureido nitrogen drastically changes the chemical properties of the ureidomalonates, **4** (R = alkyl or aryl; R′ = H, alkyl, aryl). These N-substituted and N,N′-disubstituted ureidomalonates cyclize spontaneously to hydantoins simply on heating without the need of base catalysis.

The two benzylic protons of the 1-benzyl-5-hydantoin-

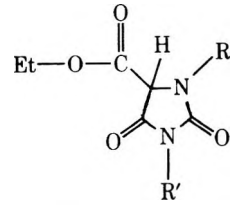
Table I
Ethyl 5-Hydantoincarboxylates



Compd	R_1	R_2	Formula	Method	Yield,[a] %	Mp, °C (recrystn solvent)	Bp,[b] °C (mm)	C, % Calcd	C, % Found	H, % Calcd	H, % Found	N, % Calcd	N, % Found
1a	CH_3	H	$C_7H_{10}N_2O_4$	A	80.6	85–87 (Et_2O)		45.16	45.03	5.41	5.50	15.05	15.07
1b	CH_3	CH_3	$C_8H_{12}N_2O_4$	B	88		75–78 (5×10^{-3})	47.99	47.75	6.04	5.96	13.99	13.72
1c	CH_3	$PhCH_2$	$C_{14}H_{16}N_2O_4$	B	97	67–70[c]	114–115 (3×10^{-4})	60.86	61.05	5.84	5.80	10.14	10.07
1d	CH_3	Ph	$C_{13}H_{14}N_2O_4$	B	90		118 (6×10^{-4})	59.54	59.54	5.38	5.36	10.68	10.57
1e	$PhCH_2$	H	$C_{13}H_{14}N_2O_4$	A	42	137.5–138.5 (EtOAc)		59.54	59.50	5.38	5.31	10.68	10.79
1f	$PhCH_2$	CH_3	$C_{14}H_{16}N_2O_4$	C	90		120–125 (5×10^{-4})	60.86	61.11	5.84	5.81	10.14	10.27
1g	$PhCH_2$	Ph	$C_{19}H_{18}N_2O_4$	B C	47 80	63–68[c]	160–165 (7×10^{-4})	67.45	67.55	5.36	5.29	8.28	8.48
1h	Ph	CH_3	$C_{13}H_{14}N_2O_4$	D	50	120–121 (EtOAc)		59.54	59.57	5.38	5.32	10.68	10.77
1i	Ph	Ph	$C_{18}H_{16}N_2O_4$	D	73.4	131–132.5 (EtOH)	180–190 (8×10^{-4})	66.66	66.88	4.97	5.00	8.64	8.73

[a] Yield of purified product. Some of the reactions were conducted only once and the yields of products were not optimized. [b] These are not real boiling points. The given temperatures are the air-bath temperatures at which the compounds were collected during short-path distillation. [c] Melting point of solidified material.

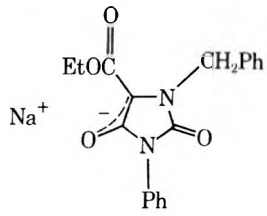
Table II
Ir and NMR[a] Spectral Data of Ethyl 5-Hydantoincarboxylates



Compd	Ir, μ ($\nu_{C=O}$)	NMR, δ			
		Solvent	H	R	R'
1a	(Nujol) 3.16 (NH), 5.61, 5.75, 5.84	$CDCl_3$	4.67	CH_3, 3.0 (s)	H, 9.5 (br s)
1b	(Neat) 5.61, 5.81 (br)	CCl_4	4.54	CH_3, 2.94 (s)	CH_3, 2.94 (s)
1c	(Neat or Nujol) 5.6, 5.8 (br)	$CDCl_3$	4.58	CH_3, 2.97 (s)	CH_2, 4.67 (s); Ph, 7.2–7.58 (m)
1d	(Neat) 5.59, 5.79 (br)	$CDCl_3$	4.65	CH_3, 2.95 (s)	Ph, 7.37 (s)
1e	(Nujol) 3.14 (NH), 5.61, 5.72, 5.86	Me_2SO-d_6[b]	4.66	CH_2, 4.34 and 4.54 (AB q, J_{AB} = 14.3 Hz),[d] Ph, 7.27 (s)	H, 11.36 (br s)
1f	(Neat) 5.6, 5.8 (br)	$CDCl_3$[c]	4.35	CH_2, 4.21 and 4.93 (AB q, J_{AB} = 14.5 Hz),[d] Ph, 7.24 (s)	CH_3, 3.0 (s)
1g	(Neat) 5.6, 5.79 (br)	$CDCl_3$[c]	4.48	CH_2, 4.28 and 5.0 (AB q, J_{AB} = 14.6 Hz),[d] Ph, 7.28 (s)	Ph, 7.4 (s)
1h	(Nujol) 5.66, 5.73, 5.86	$CDCl_3$	5.11	Ph, 7.02–7.6 (m)	CH_3, 3.11 (s)
1i	(Neat or Nujol) 5.59, 5.79 (br)	$CDCl_3$	5.23	Ph, 6.95–7.65 (m)	Ph, 7.41 (s)

[a] Spectra were recorded on a Perkin-Elmer Hitachi Model R-24 60-MHz NMR spectrometer at probe temperature 40°. [b] Concentration 15% w/v. [c] Concentration 25% w/v. [d] ν_A, ν_B, $|\nu_A - \nu_B|$, and $|J_{AB}|$ are calculated on the basis of the observed four absorption lines of the AB quartets.

carboxylates **1e–g** are diastereotopic[9] and hence show chemical shift nonequivalence. They appear as AB quartets (Table II). Under the given experimental conditions, the magnitude of the difference in chemical shift of the two benzylic protons in **1f** and **1g** is considerably large (0.72 ppm). Destroying the asymmetric center at carbon 5 by converting **1g** to the enolate salt **5**[10] leads to the expected



5

coalescence of the signals of the benzylic protons. However, the two benzylic protons in the 3-benzyl-5-hydantoincarboxylate **1c** show a singlet.

Experimental Section

Materials. The ethanol used throughout this work was denatured alcohol formula 12A. Diethyl *N*-methylaminomalonate was synthesized after Hardegger and Corrodi[11] and isolated as the hydrochloride **2a**, mp 118–119°. Diethyl anilinomalonate (**3a**) and benzyl isocyanate were prepared according to O'Brien et al.[12] and Haworth et al.,[13] respectively.

Diethyl *N,N*-Dibenzylaminomalonate Hydrochloride (6). Diethyl bromomalonate (technical grade, 95.6 g, 0.4 mol) was added slowly into dibenzylamine (158 g, 0.8 mol) with stirring. The mixture was heated on a steam bath with occasional swirling for 2 hr, cooled, and extracted with Et_2O. The white crystals of $(PhCH_2)_2NH$·HBr were removed by filtration, and the ethereal filtrate was washed with water, dried (Na_2SO_4), cooled in ice, and saturated with HCl gas. The crystals of **6** were collected, washed well with Et_2O, and air dried, mp 95–98° dec, yield 103.6 g (66%).

The free amine could readily be purified on a silica gel column, using CH_2Cl_2–EtOAc (8:2 v/v) as eluting solvent. An analytical specimen of **6** prepared from a chromatographically purified amine had the following physical data: mp 103–104° (EtOH); ir (Nujol) 3.6–4.45 ($^+$NH), 5.7 μ (C=O).

Anal. Calcd for $C_{21}H_{25}NO_4$·HCl: C, 64.36; H, 6.69; N, 3.57; Cl, 9.05. Found: C, 64.32; H, 6.54; N, 3.65; Cl, 8.89.

Diethyl *N*-Benzylaminomalonate Hydrochloride (2b). Compound **6** (3.9 g, 0.01 mol) was dissolved in EtOH (20 ml) and hydrogenated in the presence of 10% Pd/C catalyst (0.2 g) at 22° and atmospheric pressure. The hydrogenolysis was stopped after 1 molar equiv of H_2 was taken up. Removal of the catalyst and the solvent in vacuo afforded a pale syrup which crystallized upon standing. Triturating the crystalline residue with Et_2O and collecting the solid gave **2b** (2.7 g, 90% yield), mp 142–143° dec.

A portion of the above material was recrystallized from EtOH–Et_2O to give an analytical specimen as white granules: mp 153° dec; ir (Nujol) 5.69, 5.75 μ; NMR ($CDCl_3$) δ 1.3 (t, J = 7 Hz, 6, CH_3–), 4.26 (q, J = 7 Hz, 4, $-CH_2O-$), 4.43 (s, 1, CH), 4.56 (s, 2, $-CH_2N^+-$), 7.26–7.84 (m, 5, Ph protons), 10.92 (br s, 2, $^+NH_2$).

Anal. Calcd for $C_{14}H_{19}NO_4$·HCl: C, 55.72; H, 6.68; N, 4.64; Cl, 11.75. Found: C, 55.86; H, 6.61; N, 4.66; Cl, 11.75.

Compound **2b** was also obtained by direct alkylation of benzylamine with diethyl bromomalonate with or without using EtOH as solvent, followed by treatment with HCl gas. However, the yield of **2b** was about 9% (isolated and purified product). The reaction appeared to be complicated by aminolysis of the malonate, especially when no solvent was used. The product in this case showed an amide absorption at 5.94 μ.

Diethyl *N*-Benzylaminomalonate (3b). The amine **3b** was readily obtainable by washing a solution of the hydrochloride **2b** in CH_2Cl_2 with dilute NaOH and then with water, drying (Na_2SO_4), and evaporating to dryness in vacuo, as a pale oil which was homo-

geneous on TLC: ir (neat) 2.96 (NH), 5.73 μ (C=O); NMR ($CDCl_3$) δ 1.28 (t, J = 7 Hz, 6, CH_3-), 2.53 (br s, 1, NH), 3.94 (s, 2, $-CH_2-N-$), 4.17 (s, 1, CH), 4.34 (q, J = 7 Hz, 4, $-CH_2O-$), 7.54 (s, 5, Ph protons).

Ethyl 1-Substituted 5-Hydantoincarboxylates. General Method A. A solution of **2** (0.01–0.02 mol) in H_2O (30 ml) and a solution of KCNO (0.011–0.022 mol) in a minimum amount of H_2O were mixed, stoppered, vigorously stirred at ambient temperature for 0.5–2 hr, and then heated with stirring on a steam bath for 0.5–2 hr. After cooling, the reaction mixture was extracted with CH_2Cl_2. Drying the extract (Na_2SO_4) followed by evaporating to dryness in vacuo afforded the product as a solid residue, which was recrystallized from an appropriate solvent.

Ethyl 1,3-Disubstituted 5-Hydantoincarboxylates. General Method B. To a solution of **2** (0.01–0.05 mol) in $CHCl_3$ (25–50 ml) were added in turn an isocyanate (0.011–0.053 mol) and Et_3N or pyridine[14] (0.011–0.055 mol). The resulting solution was heated at reflux for 2–3 hr and then evaporated to dryness in vacuo until any excess isocyanate was removed. The residue was redissolved in CH_2Cl_2, washed with H_2O, dried (Na_2SO_4), and evaporated to dryness in vacuo to give the crude product, which was purified by short-path distillation in a Kugelrohr apparatus.

General Method C. An isocyanate (0.011–0.022 mol) was added to a solution of **3b** (0.01–0.02 mol) in C_6H_6 (25–40 ml). The resulting solution was heated at reflux for 2 hr and then evaporated in vacuo until any excess isocyanate was removed. The residue was distilled in a Kugelrohr apparatus to give the product.

General Method D. A mixture of **3a** (0.02–0.03 mol) and an isocyanate (0.022–0.033 mol) was heated at reflux in an oil bath at 90–110° for 2–6 hr. The reaction temperature and duration were varied appropriately according to the boiling point and reactivity of the isocyanate. In the reaction of **3a** and CH_3NCO, the reaction mixture solidified upon cooling and was therefore recrystallized from EtOAc to give pure **1h**.

In the reaction of **3a** and PhNCO, the reaction mixture became an orange-colored syrup, the spectral data of which indicated that it was largely the urea **4f** containing a very small amount of **1i**: ir (neat) 2.95 (m, NH), 5.74 (s, ester C=O), 5.94 μ (s, urea C=O); NMR ($CDCl_3$) δ 1.18 (t, CH_3–), 4.17 (q, $-CH_2O-$), 5.56 (s, methine proton), 6.35 (br s, NH), 6.8–7.8 (m, Ph protons). The methyl, methylene, and methine protons of **1i** appeared at δ 1.25 (t), 4.25 (q), and 5.24 (s), respectively. Upon heating during short-path distillation at 180–190°, the above material afforded the hydantoincarboxylate **1i**, which no longer showed absorptions at 2.95 and 5.94 μ but exhibited one of the hydantoin characteristic C=O bands at 5.59 μ.

Registry No.—**1a**, 56598-90-4; **1b**, 56598-91-5; **1c**, 56598-92-6; **1d**, 3531-91-7; **1e**, 56598-93-7; **1f**, 56598-94-8; **1g**, 56598-95-9; **1h**, 56598-96-0; **1i**, 56598-97-1; **2a**, 56598-98-2; **2b**, 56598-99-3; **3a**, 6414-58-0; **3b**, 56599-00-9; **4f**, 56599-01-0; **6**, 56599-02-1; isocyanic acid potassium salt, 15586-00-2; methyl isocynate, 624-83-9; benzyl isocyanate, 3173-56-6; phenyl isocyanate, 103-71-9; diethyl bromomalonate, 685-87-0; dibenzylamine, 103-49-1; benzylamine, 100-46-9.

References and Notes

(1) This work was performed under the auspices of the Division of Cancer Treatment, National Cancer Institute, Department of Health, Education and Welfare, Contract No. N01-CM-23706. The opinions expressed in this article are those of the author and not necessarily those of the NCI.
(2) 1-Methyl- and 3-methyl-5-hydantoincarboxylic acid and various 5-hydantoincarboxamides have been obtained as degradation products of nitrogen-substituted purines, mainly uric acids: (a) E. Fischer, *Justus Liebigs Ann. Chem.*, **215**, 253 (1882); (b) H. Biltz, *Ber.*, **43**, 1600, 1618 (1910); *ibid.*, **46**, 3407 (1913); (c) H. Biltz and M. Bergius, *Justus Liebigs Ann. Chem.*, **414**, 54 (1917); (d) H. Biltz and F. Max, *ibid.*, **414**, 68 (1917); (e) H. Biltz and R. Lemberg, *ibid.*, **432**, 137 (1923); H. Biltz and P. Nachtweg, *Ber.*, **64**, 1974 (1931); (g) E. S. Gatewood, *J. Am. Chem. Soc.*, **45**, 3056 (1923); (h) *ibid.*, **47**, 2175 (1925); (i) *ibid.*, **47**, 2181 (1925).
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(7) T. B. Johnson and B. H. Nicolet, *J. Am. Chem. Soc.*, **36**, 345 (1914).
(8) It is of interest that diethyl (*N'*-phenylthioureido)malonate cyclizes to ethyl 3-phenyl-2-thio-5-hydantoincarboxylate upon heatng in water (see ref 3).
(9) For a detailed discussion on symmetry criteria in NMR spectroscopy, see K. Mislow and M. Raban, *Top. Stereochem.*, **1**, 1 (1967).
(10) To a solution of **1g** in $CDCl_3$ in an NMR tube was added a solution of CD_3ONa in CD_3OD. The resulting solution was orange-yellow in color.
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(12) D. E. O'Brien, F. Baiocchi, R. K. Robbins, and C. C. Cheng, *J. Med Pharm. Chem.*, **5**, 1085 (1962).
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(14) Triethylamine permitted simpler work-up and generally gave better results.

Halogenated Ketenes. XXVIII. Mixed Dimerizations of Halogenated Ketenes and Nonhalogenated Ketenes[1]

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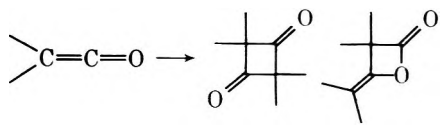
Alkylhaloketenes and dialkylketenes undergo a codimerization to yield the unsymmetrical 1,3-cyclobutanediones. These mixed dimers have been prepared by several different methods. Some of the ketenes employed are methylchloro-, ethylchloro-, *tert*-butylchloro-, dimethyl-, diethyl-, and pentamethyleneketenes. In certain systems some 2-oxetanone mixed dimer was formed.

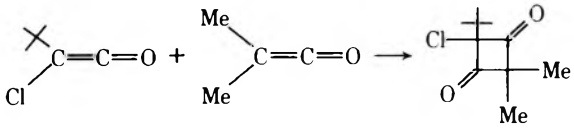
Most all ketenes are very susceptible to dimerization when heated or when allowed to stand at room temperature for a sufficient length of time.[2] The dimerization produces a 1,3-cyclobutanedione and/or a 2-oxetanone. Mixed dimers of ketenes have rarely been studied, because in addition to the mixed ketene dimers the two homodimers are produced. However, recently England and Krespan have described mixed dimers of bis(trifluoromethyl)ketene.[3] This ketene does not thermally homodimerize and forms mixed dimers with various other ketenes in good yield. Both dimers of the 1,3-cyclobutanedione structure and 2-oxetanones have been observed. The 2-oxetanone dimers were derived only from cycloaddition to the carbon–carbon double bond and not to the carbon–oxygen double bond of the nonfluorinated ketene.



Halogenated ketenes are quite labile but undergo in situ cycloaddition reactions to produce a variety of cycloadducts. We have made numerous attempts to homodimerize halogenated ketenes with no success; only α-halovinyl esters are produced and/or polymeric material. However, we

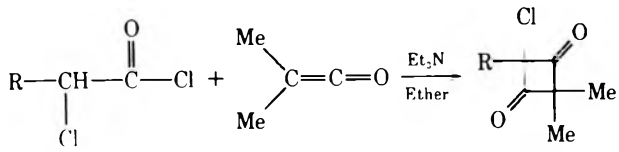
have recently discovered that halogenated ketenes will undergo a mixed dimerization with nonhalogenated ketenes, and the purpose of this paper is to describe these mixed dimerizations. A preliminary report of this work has appeared.[4]

A chloroform solution of *tert*-butylchloroketene was prepared by the triethylamine dehydrochlorination of 2-chloro-3,3-dimethylbutanoyl chloride.[1] An ether solution of dimethylketene was added and a 40% yield of the mixed dimer was obtained in about 3 hr. The 1,3-cyclobutanedione was characterized by elemental analysis, infrared, and NMR spectroscopy. This reaction was accompanied by some polymer from the halogenated ketene and by less than 10% of the homodimer of dimethylketene.[5]



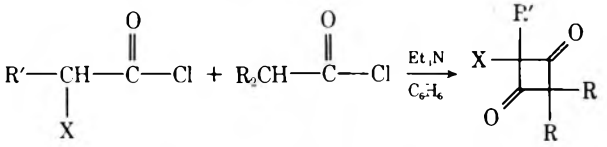
I

Mixed dimerizations involving other alkylhaloketenes were accomplished by generating the alkylhaloketene in the presence of dimethylketene, i.e., an in situ cycloaddition reaction. The alkylchloroketenes were prepared by the triethylamine dehydrochlorination of α-chloro acid chlorides in the presence of dimethylketene in ether solution. The 1,3-cyclobutanedione mixed dimers were produced in 1–2 hr in yields up to 55%. Some halogenated ketene polymer and a small amount of homodimer of dimethylketene was also produced. The attempted mixed dimerizations of diphenylketene and methylchloro- and ethylchloroketene in a similar manner were not successful. Only a small amount of the mixed 1,3-cyclobutanedione dimer was produced as evidenced by NMR.



I, R = *t*-Bu
II, R = Et
III, R = Me

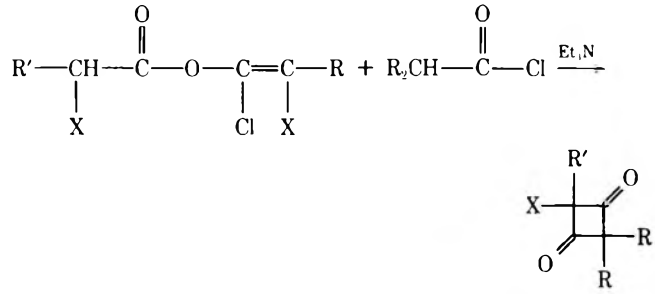
The most successful method for preparing the mixed dimers involves a simultaneous generation of the halogenated ketene and the dialkylketene from the respective acid halides. This method is generally illustrated below.



The unsymmetrical halogenated cyclobutanediones prepared by this method are illustrated in Table I.

The cyclobutanediones were all characterized by a band in the infrared spectrum at 1750–1760 cm^{-1} and NMR and elemental analysis. These reactions were all accompanied by some polymeric material of the halogenated ketenes and some homodimer of the dialkylketenes (<10%). The reaction time is very dependent upon the particular dialkylketene selected. Pentamethyleneketene and diethylketene are formed very slowly from the respective acid halides and thus the reaction time is usually several days to obtain the optimum yield of the mixed dimer. Conversely, dimethylketene is formed very rapidly and the reaction time for the mixed dimerization with this ketene is about 1–3 hr.

It is well known that certain α-halo acid halides react with triethylamine to yield α-halovinyl esters.[6] These vinyl esters were found in some of the reactions described above. The α-halovinyl esters will react with triethylamine to generate halogenated ketenes. An α-halovinyl ester could be used in place of the α-halo acid chloride as a source of the halogenated ketene with those dialkylketenes which formed slowly, i.e., pentamethyleneketene and diethylketene.



The attempted mixed dimerization of methylchloroketene and ethylketene by the generation of these ketenes from the respective acid halides resulted in only the 2-oxetanone homodimer of ethylketene. Efforts to codimerize two different halogenated ketenes were unsuccessful as only polymer resulted. Also, the aldoketene, methylketene, could not be codimerized with methylchloro- or *tert*-butylchloroketene.

Several of the mixed dimerizations described above to produce unsymmetrical cyclobutanediones were accompanied by another type of mixed dimerization which produced a 2-oxetanone. Two such 2-oxetanones are possible depending upon whether cycloaddition occurs across the carbon–oxygen bond of the halogenated ketene or the dialkylketene. The 2-oxetanone exhibited bands in the infrared at 1887, 1828 (C=O), and 1712 cm^{-1} (C=C). Methanolysis was used to determine which of the above 2-oxetanones were produced. The distinction was made on the basis of the α-hydrogen. The β-keto ester produced revealed a proton in the NMR at δ 4.4. We synthesized meth-

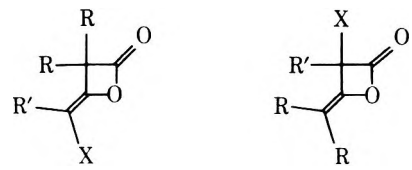
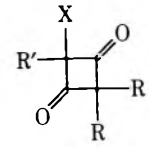
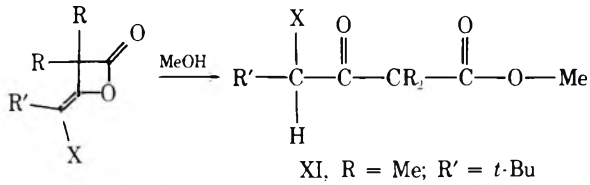


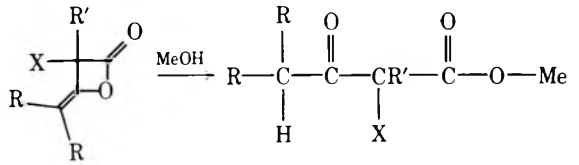
Table I
Unsymmetrical Halogenated Cyclobutanediones



Compd	R	R′	X	Yield, %
III	Me	Me	Cl	34
IV	Et	Me	Cl	63
V	$-(CH_2)_5-$	Me	Cl	62
VI	Et	Et	Cl	51
VII	$-(CH_2)_5-$	Et	Cl	35
II	Me	Et	Cl	41
VIII	Me	*i*-Pr	Cl	40
I	Me	*t*-Bu	Cl	56
IX	Et	*t*-Bu	Cl	43
X	$-(CH_2)_5-$	*t*-Bu	Br	36



XI, R = Me; R′ = *t*-Bu
XII, R = Me; R′ = *i*-Pr
XIII, R = R′ = Et



yl 3-keto-2,2,4-trimethylpentanoate from tetramethylcyclobutanedione for comparison purposes and found that the α hydrogen was revealed in the NMR at δ 2.8.[7] Since the β-keto ester produced had a δ value of 4.4, we conclude that 2-oxetanone was produced whereby cycloaddition occurred only across the carbon–oxygen linkage of the halogenated ketene. This is consistent with what England and Krespan found for bis(trifluoromethyl)ketene.

The mixed dimerizations with pentamethyleneketene did not form any 2-oxetanones. In most of the other cases the 2-oxetanones were produced but in yields of less than 10%.

Since it is known that 1,3-cyclobutanedione dimers of ketenes can isomerize to the 2-oxetanone dimers, it seemed necessary to demonstrate whether isomerization of any kind was occurring in the reaction mixtures.[8] It was found that a mixture of the 1,3-cyclobutanedione mixed dimer of dimethylketene and isopropylchloroketene and the 2-oxetanone mixed dimer upon refluxing in hexane containing triethylamine and triethylammonium chloride for 24 hr underwent no change. Consequently, it is concluded that no isomerization occurred under our reaction conditions and the mixed dimer ratios observed in the reaction mixtures do in fact represent the actual cycloaddition results.

Experimental Section

Proton NMR spectra were recorded on a Jeolco PS-100 NMR spectrometer employing tetramethylsilane as an internal standard and CCl_4 as the solvent. All solvents and triethylamine were dried by distillation from sodium. VPC was performed on an F & M Scientific Model 700 gas chromatograph with 10 ft × 0.25 in. columns packed with 10% SE-30 and Carbowax 20M on an acid-washed Chromosorb W (80/100). Dimethylketene was prepared by the pyrolysis of tetramethylcyclobutanedione.

General Methods for Mixed Dimerizations. Method A. To a stirred solution of 0.05 mol of dimethylketene and 0.05 mol of triethylamine in 50 ml of ether was added to a solution of 0.05 mol of α-chloro acid chloride in 10 ml of ether at room temperature. Stirring was continued for 2 hr and then the amine salt was removed by filtration. The solvent was removed from the filtrate with a rotatory evaporator and the residue vacuum distilled.

Method B. To a refluxing solution of 0.1 mol of α-halo acid chloride and 0.1 mol of isobutyryl chloride, α-ethylbutyryl chloride, or cyclohexanecarboxyl chloride in 150 ml of benzene was added dropwise with stirring 0.25 mol of triethylamine in 15 ml of benzene. The reaction mixture was stirred from 1 hr to 4 days, the salt was removed by filtration, and the filtrate was concentrated with a rotatory evaporator and vacuum distilled. Other solvents which could be used include hexane, acetonitrile, chloroform, and ether.

Method C. To a refluxing solution of 0.05 mol of 1,2-dichloropropenyl 2-chloropropanoate or 1,2-dichlorobutenyl 2-chlorobutanoate and 0.1 mol of triethylamine in 100 ml of benzene was added dropwise 0.05 mol of cyclohexanecarboxyl chloride in 15 ml of benzene. Refluxing was continued for several days as the reaction was monitored by VPC analysis until the reaction was complete. The amine salt was removed by filtration, the solvent was removed by evaporation on a rotatory evaporator, and the mixed dimer was vacuum distilled.

2-Chloro-2-*tert*-butyl-4,4-dimethyl-1,3-cyclobutanedione (I). Method A. A 50% yield of mixed dimer was produced.

Method B. The reaction mixture was stirred for 24 hr and a 56% yield of dione and a 13% yield of 2-oxetanone was produced.

This mixed dimer was also prepared directly from the two ketenes as described below. A solution of 0.05 mol of 2-chloro-3,3-dimethylbutanoyl chloride in 10 ml of chloroform was added dropwise to a stirred solution of 0.05 mol of triethylamine in 100 ml of chloroform at 0–5°. The ketene band in the infrared at 2110 cm^{-1} reached a maximum intensity within about 4 hr. At this time, a solution of 0.07 mol of dimethylketene in 10 ml of ether was added over a period of about 3 hr. The solution was concentrated on a rotatory evaporator and 100 ml of hexane was added to precipitate the amine salt. After removal of the salt by filtration, the filtrate was concentrated and the mixed dimer distilled at 39–40° (0.025 mm) to give a 40% yield: ir 1750 cm^{-1}; NMR δ 1.19 (s, 9 H), 1.28 (s, 3 H), 1.60 (s, 3 H).

Anal. Calcd for $C_{10}H_{15}ClO_2$: C, 59.26; H, 7.41; Cl, 17.53. Found: C, 59.09; H, 7.20; Cl, 17.29.

2-Chloro-2-ethyl-3,3-dimethyl-1,3-cyclobutanedione (II). Method A. A 55% yield was obtained.

Method B. The reaction mixture was refluxed for 3 hr and then stirred for an additional 3 hr to produce a 41% yield of the dione and a 13% yield of the vinyl ester, 1,2-dichlorobutenyl 2-chlorobutanoate. The dione had bp 54–55° (0.25 mm); ir 1755 cm^{-1}; NMR δ 1.14 (t, 3 H), 1.34 (s, 3 H), 1.54 (s, 3 H), and 2.40 (q, 2 H).

Anal. Calcd for $C_8H_{11}ClO_2$: C, 55.01; H, 6.30; Cl, 20.34. Found: C, 55.20; H, 6.39; Cl, 20.06.

2-Chloro-2-methyl-4,4-dimethyl-1,3-cyclobutanedione (III). Method A. A 42% yield was obtained along with a small amount of 1,2-dichloropropenyl 2-chloropropanoate.

Method B. As soon as the addition was completed at reflux, the reaction mixture was cooled over a period of 1 hr. Vacuum distillation afforded the mixed dimer at 70° (0.25 mm) which crystallized from ether giving a 34% yield and a small amount of the vinyl ester. The dione had mp 78–80°; ir 1750 cm^{-1}; NMR δ 1.36 (s, 3 H), 1.52 (s, 3 H), and 1.70 (s, 3 H).

Anal. Calcd for $C_7H_9ClO_2$: C, 52.34; H, 5.61; Cl, 22.12. Found: C, 52.52; H, 5.75; Cl, 21.63.

2-Chloro-2-methyl-4,4-diethyl-1,3-cyclobutanedione (IV). Method B. The reaction mixture was refluxed for 24 hr; a 63% yield was obtained at 43° (0.05 mm); ir 1750 cm^{-1}; NMR δ 1.08 (2 t, 6 H), 1.72 (s, 3 H), 1.96 (m, 4 H).

Anal. Calcd for $C_9H_{13}ClO_2$: C, 57.29; H, 6.90; Cl, 18.83. Found: C, 57.44; H, 7.04; Cl, 18.71.

2-Chloro-2-methylspiro[3.5]nona-1,3-dione (V). Method B. Refluxed for 24 hr; bp 67–70° (0.025 mm), then recrystallized from alcohol, mp 67–69° (62%).

Method C. After 48 hr, the reaction was complete (63%): ir 1750 cm^{-1}; NMR a multiplet centered at δ 1.80 out of which there was a singlet at δ 1.70.

Anal. Calcd for $C_{10}H_{13}ClO_2$: C, 59.85; H, 6.48; Cl, 17.70. Found: C, 59.60; H, 6.65; Cl, 17.45.

2-Chloro-2,4,4-triethyl-1,3-cyclobutanedione (VI). Method B. Refluxed for 4 days, 51% yield of dione and 7% yield of vinyl ester. The dione had bp of 41–43° (0.025 mm); ir 1750 cm^{-1}; NMR δ 1.04 (m, 9 H), 1.84 (m, 6 H).

Anal. Calcd for $C_{10}H_{15}ClO_2$: C, 59.26; H, 7.41; Cl, 17.53. Found: C, 59.17; H, 7.46; Cl, 17.29.

2-Chloro-2-ethylspiro[3.5]nona-1,3-dione (VII). Method B and Method C. Refluxed for 2–3 days, 35% yield of dione and 14% yield of vinyl ester. The dione had bp 60–62° (0.1 mm); ir 1750 cm^{-1}; NMR δ 1.16 (t, 3 H) and 1.84 (m, 12 H).

Anal. Calcd for $C_{11}H_{15}ClO_2$: Cl, 16.55. Found: Cl, 16.72.

2-Chloro-2-isopropyl-4,4-dimethyl-1,3-cyclobutanedione (VIII). Method B. Refluxed for 20 hr (40%), bp 40–43° (0.05 mm); ir 1750 cm^{-1}; NMR δ 1.20 (d, 6 H), 1.34 (s, 3 H), 1.52 (s, 3 H), and 2.40 (heptet, 1 H).

Anal. Calcd for $C_9H_{13}ClO_2$: C, 57.29; H, 6.90; Cl, 18.83. Found: C, 57.63; H, 7.03; Cl, 18.36.

2-Chloro-2-*tert*-butyl-4,4-diethyl-1,3-cyclobutanedione (IX). Method B. Stirred for 2 days at room temperature in $CHCl_3$ (43%), bp 52° (0.1 mm) and mp 43–45°; ir 1750 cm^{-1}; NMR δ 1.08 (t, 6 H), 1.16 (s, 9 H), 1.80 and 2.10 (2 q, 4 H).

Anal. Calcd for $C_{12}H_{19}ClO_2$: C, 62.47; H, 8.24. Found: C, 62.10; H, 8.46.

2-Bromo-2-*tert*-butylspiro[3.5]nona-1,3-dione (X). Method B. Refluxed for 2 days (36%); bp 32–34° (0.25 mm); recrystallized

from ethanol, mp 77–78°; ir 1760 cm^{-1}; NMR δ 1.10 (s, 9 H) and 1.60 (m, 10 H).

Anal. Calcd for $C_{13}H_{19}BrO_2$: C, 54.36; H, 6.68; Br, 27.82. Found: C, 54.33; H, 6.82; Br, 27.45.

General Procedure for Methanolysis of 2-Oxetanones. The 2-oxetanones could not be easily separated from the diones but were observable by ir bands at 1887, 1828, and 1712 $cm.^{-1}$ Methanolysis of the mixture of dione and 2-oxetanone was accomplished by refluxing this mixture with methanol for 1.5 hr. The β-keto ester revealed bands in the ir at 1748 and 1718 $cm.^{-1}$ Methanolysis of the 1,3-cyclobutanediones required a much longer (1–3 days) reflux period.

Methyl 4-Chloro-3-keto-2,2,5,5-tetramethylhexanoate (XI): bp 90–92° (0.1 mm); NMR δ 1.12 (s, 9 H), 1.40 (s, 3 H), 1.52 (s, 3 H), 3.74 (s, 3 H), and 4.42 (s, 1 H).

Anal. Calcd for $C_{11}H_{19}ClO_3$: C, 56.29; H, 8.10; Cl, 15.14. Found: C, 56.53; H, 8.40; Cl, 15.20.

Methyl 4-Chloro-3-keto-2,2,5-trimethylhexanoate (XIII): bp 57–59° (0.5 mm); NMR δ 1.00 (2 d, 6 H), 1.44 (s, 3 H), 1.52 (s, 3 H), 2.40 (m, 1 H), 3.83 (s, 3 H), and 4.40 (d, 1 H).

Anal. Calcd for $C_{10}H_{17}ClO_3$: C, 54.42; H, 7.71; Cl, 16.09. Found: C, 54.65; H, 7.80; Cl, 15.52.

Methyl 4-Chloro-2,2-diethyl-3-ketohexanoate (XIII): bp 52–54° (0.05 mm); NMR δ 0.90 (m, 9 H), 2.00 (m, 6 H), 3.76 (s, 3 H), 4.40 (t, 1 H).

Anal. Calcd for $C_{11}H_{19}ClO_3$: C, 56.29; H, 8.10; Cl, 15.14. Found: C, 56.64; H, 8.21; Cl, 14.72.

Attempted Isomerization of a 1,3-Cyclobutanedione and a 2-Oxetanone. A 1.0-g portion of a mixture of VIII and the 2-oxetanone obtained from the preparation of VIII was refluxed in hexane for 24 hr. No change in the isomer distribution was observed. The addition of triethylamine and triethylammonium chloride and continued reflux for another 24 hr also caused no change in the isomer distribution.

Acknowledgments. The authors wish to express appreciation to the Robert A. Welch Foundation and the North Texas State University Faculty Research Fund for support of this investigation.

Registry No.—I, 56513-91-8; II, 56513-92-9; III, 56513-93-0; IV, 54363-24-5; V, 54363-23-4; VI, 54363-25-6; VII, 56513-94-1; VIII, 56513-95-2; IX, 56513-96-3; X, 56513-97-4; XI, 56513-98-5; XII, 56513-99-6; XIII, 56514-00-2; dimethyl ketene, 598-26-5; 2-chloro-3,3-dimethylbutanoyl chloride, 52920-18-0; 2-chlorobutanoyl chloride, 7623-11-2; 2-chloropropanoyl chloride, 7623-09-8; 2-bromo-3,3-dimethylbutanoyl chloride, 29336-30-9; isobutyryl chloride, 79-30-1; α-ethylbutyryl chloride, 2736-40-5; cyclohexanecarboxyl chloride, 2719-27-9; 1,2-dichloropropenyl 2-chloropropanoate, 52920-13-5; 1,2-dichlorobutenyl 2-chlorobutanoate, 23649-91-4; 4-chloro-3,3-dimethyl-4-*tert*-butyl-2-oxetanone, 56514-01-3; 4-chloro-3,3-dimethyl-4-isopropyl-2-oxetanone, 56514-02-4; 4-chloro-3,3,4-triethyl-2-oxetanone, 56514-03-5.

References and Notes

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An Efficient α-Halogenation of Acyl Chlorides by *N*-Bromosuccinimide, *N*-Chlorosuccinimide, and Molecular Iodine[1]

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Received April 15, 1975

An efficient procedure (yields ~75%) for the α-halogenation of acyl halides has been demonstrated using *N*-bromosuccinimide, *N*-chlorosuccinimide, and molecular iodine. Thionyl chloride was found to be the most effective solvent for all halogenation reactions and necessary for α-iodination. Various anomalies and possible mechanisms are discussed.

The halogenation of carboxylic acids can be carried out either by free-radical[2] or acid-catalyzed reactions.[3] The former occurs with random orientation and the latter, via the Hell–Volhard–Zelinsky (HVZ) procedure,[3] gives exclusively α-halogenated products only in the case of bromination, but variable selectivity in chlorination, and no reaction at all in iodination.[4]

In an effort to develop new and efficient methods for preparing α-halo acid chlorides, from which a wide variety of compounds may be obtained by replacing both the halogen on the α carbon and on the acyl function, a study was undertaken of the ability of *N*-bromosuccinimide (NBS), *N*-chlorosuccinimide (NCS), and molecular iodine as α-halogenating agents.

Results and Discussion

α-Bromo acids can be prepared by a multistep procedure, involving alkylation, bromination, deacylation, and hydrolysis.[5] In the more direct method (HVZ),[3] carboxylic acids are treated with free bromine in the presence of a catalyst which can be phosphorus trichloride or phosphorus itself. However, the experimental conditions are sometimes strenuous, often involving high temperature and extended reaction times.

Although NBS is well known as a brominating agent,[6a] there appears to be no report of this reagent being employed to directly brominate acyl chlorides.

We have found that NBS α-brominates a variety of acyl chlorides (formed in situ by the reaction of thionyl chloride[6b] with carboxylic acids, Table I) in good yield.[7] NBS is not only easy to handle but also α-brominates more rapidly and efficiently than molecular bromine, as shown by a comparative study. After 2 hr at 54°, the reaction of *n*-hexanoyl chloride (1) with NBS was almost complete, whereas that with free bromine had only occurred to an extent of ca. 60% (Figure 1). Furthermore, bromination reactions with Br_2 often do not proceed past ca. 80% completion. At 85°, the reaction with NBS was complete after 1.5 hr.[8]

Table I[a]

Compd	Reaction time, hr	Temp,[b] °C	Product	Bp (mm) or mp, °C	Yield, %[c]
1 $CH_3(CH_2)_4COCl$	1.25	85	1a $CH_3(CH_2)_3CH(Cl)COCl$[d]	174–176 (760)[e]	87
	1.50	85	1b $CH_3(CH_2)_3CH(Br)COCl$[f]	45–47 (1.5)	80
	1.50	130	1c $CH_3(CH_2)_3CH(I)COCl$	62–64 (0.5)	80
2 $C_6H_5CH_2CH_2COCl$	2.00	95	2a $C_6H_5CH_2CH(Cl)COCl$[g]	70–71 (0.2)	84
	3.0	85	2b $C_6H_5CH_2CH(Br)COCl$[h]	88–89 (0.35)	71
	3.0	130	2c $C_6H_5CH_2CH(I)COCl$[i]	83–84 (0.5)	75
4 $C_6H_5CH_2COCl$	3.0	85	4a $C_6H_5CH(Br)COCl$	100–102 (5)[j]	75
5 $CH_3(CH_2)_2COCl$	1.50	85	5a $CH_3CH_2CH(Br)COCl$	57–59 (26)[k]	75
	1.50	130	5b $CH_3CH_2CH(I)COCl$[l]	23 (0.1)	69
6 c-$C_6H_{11}COCl$	4.5	85	6a $C_6H_{10}(Br)COCl$	82–85 (5)[m]	58 (70)[n]
7 $CH_3(CH_2)_2CHCOCl$	2.50	85	7a $CH_3(CH_2)_2CCH_3(Cl)COCl$	47–48 (1.0)	79
CH_3					
	0.75	130	7b $CH_3(CH_2)_2CCH_3(I)COCl$	45–46 (0.35)	80[o]
8 $(CH_3)_2CHCOCl$	2.50	85	8a $(CH_3)_2C(Cl)COCl$[p]	58–59 (80)[q]	70
	0.75	130	8b $(CH_3)_2C(I)COCl$[r]	59–60 (0.17)	80[o]
9 $ClCH_2CH_2COCl$	4.0	85	9a $ClCH_2CH(Cl)COCl$[s]	52–54 (16)[t]	70
	2.0	85	9b $ClCH_2CH(Br)COCl$	45 (9)	70
10 $CH_2(CH_2COCl)_2$	1.0	85	10a $CH_2[CH(Br)COCl]_2$		75
11 $(CH_2CH_2COCl)_2$	1.0	85	11a $[CH_2CH(Br)COCl]_2$		60
12 $(C_6H_5)_2CHCOCl$	1.25	85	12a $(C_6H_5)_2C(Cl)COCl$	52–53[u]	82

[a] Typical procedures for each type of halogenation are given in the Experimental Section. Ratio of substrate vs. halogenating agent and solvent was the same in a given type; only the temperature might be changed. [b] Temperatures were that of the heating bath; actual temperatures of the reaction mixture were much lower; for example, they were 85 and 70° for bath temperatures of 130 and 85°, respectively. [c] Yields were based on distilled or recrystallized products; the reactions were complete as per NMR measurement, unless stated otherwise. [d] Amide, mp 56–57° (lit.[13] 57.8–58.2°); anilide, mp 195–197°. [e] Lit.[14] bp 174–176°. [f] Free acid, bp 64–66° (0.075 mm) [lit.[15] 132–140° (15 mm)]. [g] Free acid, mp 48–49°. [h] Amide, mp 125–126° (lit.[16] 126.5–128.5°); methyl ester, bp 92–95° (0.05 mm) [lit.[17] 147–148° (14 mm)]; benzyl ester, bp 143–145° (0.025 mm). [i] Free acid, mp 74.5–75°. [j] Lit.[18] 117° (20 mm). [k] Lit.[19a] 150–152° (760 mm). [l] Free acid, mp 39–39.5° (lit.[20a] 41–42°). [m] Lit.[21] 129–131° (29 mm). [n] Isolated as amide. [o] The reaction was stopped when α-chloro product started to appear; yield was based on the amount of consumed starting material. [p] Free acid, mp 30–31° (lit.[19b] 31°). [q] Lit.[22] 126–127° (113–114 mm). [r] Anilide, mp 126–126.5°. [s] Amide, mp 106–107° (lit.[22] 103°). [t] Lit.[23] 140–144° (720 mm). [u] Lit.[19c] 50–51°.

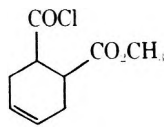
$$CH_3(CH_2)_4CH_2COCl + NBS \xrightarrow{H^+} CH_3(CH_2)_4CHBrCOCl$$
1 1b

Another advantage of the present method is that NBS specifically α-brominates acyl halides and is not reactive toward benzylic-type protons. Thus, 3-phenylpropanoyl chloride (2) reacts with NBS to give 2-bromo-3-phenylpropanoyl chloride (**2b**), and none of the 3-bromo derivative.[9]

Similarly, the protons of a carboxylic ester are not replaceable by this reaction. When ethyl acetate was treated with NBS, no reaction had occurred after 20 hr at 80°. In the case of the acid chloride of methyl succinate, NBS selectively brominated the carbon atom α to the acyl group.

$$CH_3OOCCH_2CH_2COCl + NBS \xrightarrow{H^+} CH_3OOCCH_2\underset{\displaystyle Br}{\underset{|}{C}}HCOCl$$

Finally, the NMR spectrum of the reaction mixture of the polyfunctional derivative **3** indicated that the acyl chloride



3

function was α-brominated first and the carbon–carbon double bond was brominated much later.

The results obtained with NBS led us to extend the method to the α-chlorination of acyl chlorides using *N*-chlorosuccinimide (NCS). Under the same conditions as for NBS, NCS reacted less rapidly.[10] Fortunately, the reaction time was decreased by using a larger amount of NCS and enough thionyl chloride to dissolve NCS completely[11] (Table I).

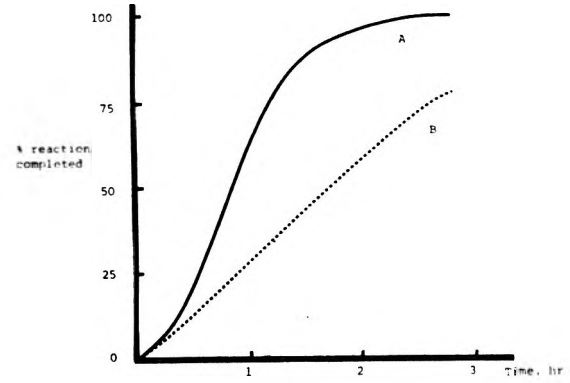


Figure 1. Comparative bromination of *n*-hexanoyl chloride (1) at 54°C: (A) by NBS; (B) by Br_2.

NCS proved to be a very useful chlorinating agent, since it not only gave good yields (70–87%) with various substrates, but was also selective for protons α to the acyl chloride group (for example, **2** gave exclusively **2a**). Therefore NCS is superior to the previously employed reactions involving molecular chlorine, which lead not only to α-chloro acids but in some instances to chlorination in various other positions to an appreciable extent.[2d,6b,12]

The fact that benzylic protons, which normally are very susceptible to radical halogenation, are not replaced in the present methods (NBS and NCS) favors an ionic mechanism. The addition of a trace of mineral acid has a strong accelerative effect on the bromination of phenylacetyl chloride (**4**), while the addition of benzoyl peroxide, a free-radical initiator, considerably suppressed the rate[7a] (Figure 2).

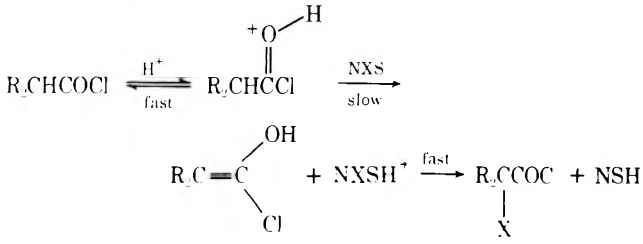
The function of the acid is presumably to enhance the formation of a complex (vide supra).[10] The complex may then undergo halogenation.

The structure of the acyl chloride also has a marked influence on the rate of the reaction. With straight-chain substrates, the time required for the completion of the reaction is essentially the same. Thus, *n*-butanoyl and *n*-hexanoyl chlorides (**5** and **1**, respectively) were completely α-brominated after 1.5 hr. However, when there is a substituent on the α carbon, the reaction is considerably retarded. Cyclohexyl carbonyl and phenylacetyl chlorides (**6** and **4**) required 4.5 and 3.0 hr, respectively, to complete the bromination. Similarly, both 2-methylpentanoyl and 2-methylpropanoyl chlorides (**7** and **8**) were completely chlorinated in 2.5 hr, whereas their straight-chain isomers **1** and **5** needed only 1.25 and 1.50 hr, respectively. It is interesting to note that both functions of a diacyl chloride are α-brominated rapidly. For example, pentyl- and hexyldicarbonyl chlorides (**10** and **11**) required only 1 hr. This might be explained by stabilization of the intermediate complex (vide infra)[10] by internal hydrogen bonding.

It has been assumed and established in some cases that the HVZ method, similar to the acid-catalyzed halogenation of ketones,[24] involves a slow enolization of the acyl chloride (formed in situ), followed by a rapid attack of the halogens on the enol.[25] This entails an independence of the reaction rate on the concentration of halogen.

In the present system it might appear that enolization is not involved in the rate-determining step in that the rate of the reaction depends on the nature of the halogenating agent (NBS reacts faster than NCS) as well as on its concentration (for example, the extent of α-chlorination of diphenylacetyl chloride by 2 equiv of NCS was 80% after 1 hr heating in a 105° bath; when the concentration of NCS was halved, there was only 60% reaction after 1.3 hr.) In addition, an α-alkyl substituted substrate would be expected to more rapidly form an enol and undergo halogenation faster than its straight-chain isomer would; however, the opposite was found to be true.

There are a number of possible rationalizations for these apparent anomalies. The mechanism could involve the *N*-halosuccinimide acting as a base to remove the α hydrogen to form the enol intermediate in the slow step.[10] The enol



would then be halogenated in a rapid step. This proposal would be in accord with the rate dependence on the presence of acid, the nature of the halogenating agent (the highly electron-withdrawing chlorine of NCS would retard the ability of NCS to compete as a base relative to NBS). Further, increasing the substitution around the α position could serve to retard the reaction by hindering the approach of the bulky *N*-halosuccinimide. That NBS is more reactive than either Br_2 or NCS is understandable; the bromine atom of NBS is more positive, therefore more electrophilic, than either Br in molecular bromine or Cl in NCS, based on the relative polarizabilities of the bonds involved.

Another possibility has definition from a proposal made some years ago by Kwart and Scalzi.[10] On the basis of a steric and deuterium isotope study, these authors proposed that the intermediate in the halogenation of acid chlorides

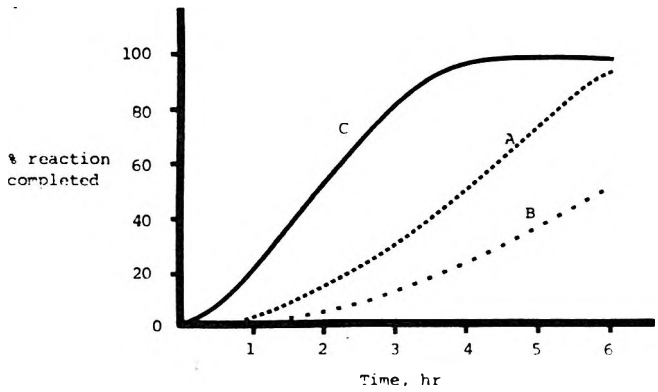
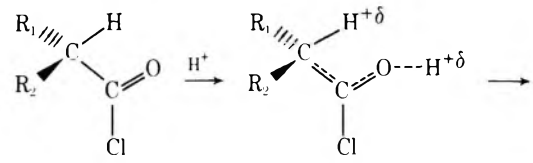


Figure 2. Bromination of phenylacetyl chloride (**4**), 75°: (A) refluxing carbon tetrachloride (1 *M*); (B) as A, benzoyl peroxide added; (C) as A, 1 drop of HBr–HOAc added.

is a cationic complex **13** in which the C_α–H bond of the conjugate acid is highly ionized, yet the proton is still associated with the now-rehybridized α carbon (see **14**). In this



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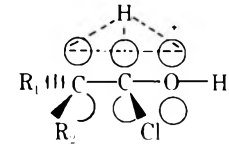


14

proposal the rate-determining step would be that of an unusual electrophilic displacement of a proton on the complex **14** by NXS, according to a bimolecular mechanism. This mechanism might explain the steric effect of the α substituent as well as the dependence of the reaction rate on the nature and the concentration of the halogenating agent. Only further study will permit a distinction of these possibilities.

No direct iodination of acyl halides has been reported in literature up to the present time.[26a,b] The classical HVZ method is not applicable to iodine and α-iodo acids are prepared by metathesis from α-bromo acids, the bromide being displaced by iodide ion in aqueous or acetone solution.[26c] However, when a higher bath temperature (130°) is applied and when thionyl chloride is used as solvent (instead of the usual CCl_4) direct iodination results. Attempts to perform the reaction in other polar solvents (e.g., acetonitrile) were not successful even after heating periods up to 5 days. Thionyl chloride presents a special advantage in the iodination procedure reacting instantaneously with hydrogen iodide to give iodine and sulfur.[27] Therefore, in the course of these iodinations there is no net evolution of hydrogen iodide.

Substrates without an α-methyl or phenyl substituent undergo α-iodination smoothly and in good yield (Table I). The reaction was once again selective for protons α to the acyl chloride group (e.g., **2** gave only **2c**). α-Iodoacyl chlorides, in parallel with their bromo and chloro counterparts, are easily transformed into a variety of derivatives under very mild conditions.

When the substrate possesses an α-methyl or a second α-phenyl group, iodination is followed by another interesting transformation. For example, the iodination of 2-

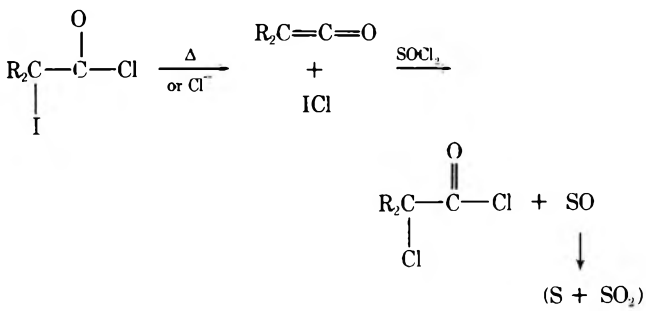
methylpropanoyl chloride (8) gave rise to the following observations (NMR). The spectrum of 8 presents a heptet (δ_{SOCl_2} 2.97, J = 8 Hz, 1 H) and a doublet (δ 1.21, J = 8 Hz, 6 H). When 8 was treated under the usual conditions, a singlet appeared at δ 2.17, which was later shown to correspond to 2-iodo-2-methylpropanoyl chloride (**8b**) (43% after 45-min reaction). Subsequently, the amount of **8b** decreased while another singlet at δ 1.86, shown to be that of 2-chloro-2-methylpropanoyl chloride (**8a**), appeared and grew at the expense of **8b** (35% of **8b** and 19% of **8a** were present in the reaction mixture after 1.5 hr). Finally, 8 and **8b** disappeared completely (10 hr) to leave **8a** as the major product.[28]

The same transformation from the α-iodo to the α-chloro derivatives was observed with 2-methylpentanoyl chloride (**7**) and diphenylacetyl chloride (**12**). In the latter case, the transformation was so rapid that the α-iodo derivatives could not be isolated, even when the reaction was slowed down by being carried out at lower temperature (70°). An intermediate involving iodine was necessary, however, since when 12 was heated with thionyl chloride in a 110° bath for 1 hr, no reaction occurred.[29]

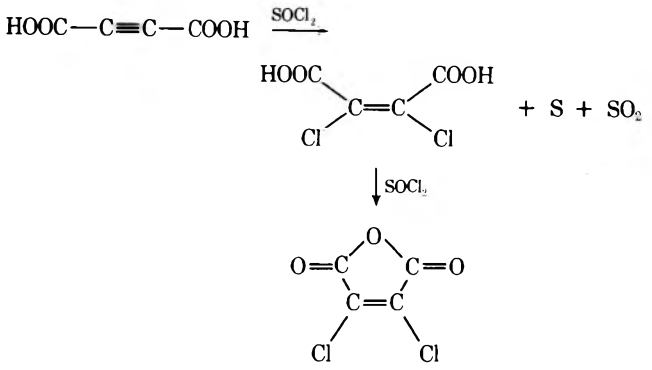
It is clear that the starting acyl chlorides are first α-iodinated in the normal way, then the α-iodo compounds are converted into the α-chloro derivatives, possibly by one of the following mechanisms.

Conceivably iodine was displaced by chloride anions present in the reaction mixture as hydrogen chloride (from the reaction of the starting acid and thionyl chloride). Chloride anion is known to react more rapidly than I^- in aprotic solvents.[30] However, this possibility is not likely, since the reaction would most probably follow an SN2-type displacement rather than an SN1 mechanism (the carbonyl group would destabilize a carbonium ion formed at the α carbon), hence a reaction would be virtually precluded by α-branching. Experimentally, the opposite was found. Moreover, when pure **8b** was dissolved in carbon tetrachloride (without added $SOCl_2$), and the reaction mixture was refluxed with gaseous HCl bubbled through it for 94 hr, no detectable amount of 2-chloro derivative was formed.[31] However, when 2 equiv of thionyl chloride was added to the reaction mixture, a fair amount of **8a** appeared after 3.5 hr at 80°; the transformation was about 40% complete after 26 hr. The reaction was faster when a larger amount of $SOCl_2$ was used. Thus thionyl chloride must actively participate in the reaction.

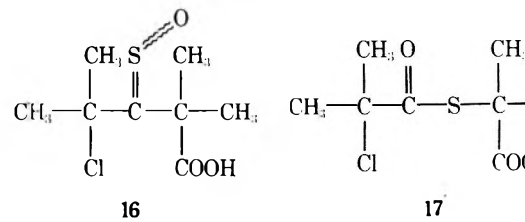
A mechanism which can account for the above facts involves the formation of a ketene, favored by α-branching. The ketene thus formed reacts with thionyl chloride to afford 2-chloroacyl chloride with elimination of SO, the latter being unstable and disproportionating to sulfur[27b] and SO_2.



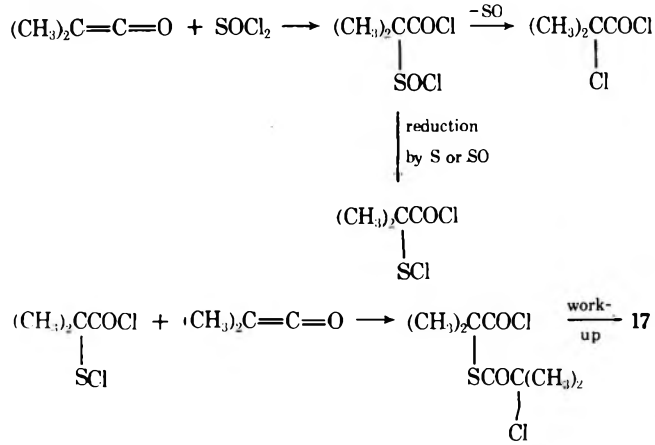
Indeed, when pure diphenylketene (generated by the dehalogenation of 2-bromo-2,2-diphenylacetyl chloride with triphenylphosphine[32] and distilled in vacuo) was treated with $SOCl_2$, there was an exothermic reaction and the final product was identified as the 2-chloro compound **12a**. A similar addition of thionyl chloride to a multiple bond has been reported in the literature.[33] Acetylenedicarboxylic acid reacts with thionyl chloride in dimethylformamide to give dichloromaleic anhydride, a product of cis chlorination.



A minor product was isolated in 3% yield from the iodination of 8. Spectral data were consistent with either of the isomeric structures, sulfine **16**, or thiol ester **17** (see Experimental Section). When **8a** was treated with 2-methyl-2-mercaptopropanoic acid (**18**), a crystalline product was isolated in 95% yield and was found to be identical in all respects (mixture melting point, NMR, ir) with **17**. Attempts



to generate the acyl chloride of **18** from 8 and elemental sulfur in CCl_4, however, were not successful. It is possible that **17**, is formed via a ketene according to the following scheme.[34]



When **1a** and **1b** were treated with NCS or NBS, respectively, for a prolonged period (up to 34 hr), there was no significant change. This further illustrates the specificity of the α-monohalogenation reaction. Iodo derivatives are somewhat more reactive. When **5** was treated with 2 equiv of iodine in thionyl chloride, **5b** was formed first and re-

mained unreactive for ca. 6 hr. Finally, it appeared to undergo diiodination, then dehydroiodination, to a mixture whose NMR was consistent with a mixture of *E* and *Z* vinyl iodides.

In summary, acyl halides can be directly α-halogenated with efficiency and selectivity by means of NBS, NCS, and molecular iodine. In the case of α-methyl- or α-phenyl-substituted substrates, an interesting transformation of the iodo to the chloro compounds occurs.

Experimental Section

Melting points were taken on a Gallenkamp apparatus and are uncorrected. Boiling points are uncorrected. Infrared measurements were performed on a Perkin-Elmer 257 grating spectrophotometer; liquid samples were measured neat on NaCl plates, solid samples as KBr pellets. Mass spectra were recorded at 70 eV on an AEI-MS 902 mass spectrometer. Proton NMR spectra were recorded on a Varian T60 instrument, employing tetramethylsilane as internal standard. Gas chromatographic analyses were carried out on an F & M 5750 research chromatograph, flame ionization detector, SE-30 column. Elemental analyses were performed by MicroAnalyses, Montreal. (Abbreviations: m, medium; s, strong; vw, very weak; w, weak).

2-Chlorohexanoyl Chloride (1a). Hexanoic acid (11.6 g, 0.1 mol) and thionyl chloride (28.8 ml, 0.4 mol) were placed in a 250-ml flask equipped with a magnetic stirring bar, and a condenser with a drying tube. The reaction mixture was stirred and heated in a 70° oil bath. After 0.5 hr, an aliquot of the reaction mixture was submitted to NMR measurement, which showed the disappearance of the triplet at δ 2.40 ($-CH_2COOH$) and the emergence of a new triplet at δ 2.87 ($-CH_2COCl$). The flask was removed from the oil bath and cooled to room temperature. To the reaction mixture were added successively finely powdered NCS (26.7 g, 0.2 mol), $SOCl_2$ (20 ml), and concentrated HCl (7 drops). The flask was then returned to the oil bath, the temperature of which was raised to 85°. The actual temperature of the reaction mixture was 70°. After 1.25 hr, the reaction was over, as indicated by the disappearance of the triplet at δ 2.87 and the emergence of a system of two doublets at δ 4.77–4.55 (–CHClCOCl). The solvent was removed under reduced pressure and the solid (succinimide) was collected and washed with CCl_4. The filtrate was fractionally distilled to give 14.7 g (87%) of **1a**: bp 174–176° (760 mm); n_D 1.4458; ir (neat) 1787 vs, 1721 cm^{-1} (shoulder); NMR (neat) δ 4.51 (2 d, J = 5.5 and 6 Hz, 1 H, –CHClCOCl); MS *m/e* 170, 168 w (P^+), 135, 133 w ($P - Cl$)$^+$, 41 base peak ($HC{\equiv}C{=}O$)$^+$. Anal. Calcd for $C_6H_{10}ClO$: C, 42.62; H, 5.97; Cl, 41.93. Found: C, 42.62; H, 6.07; Cl, 42.25.

The amidation of **1a** (0.8 g, 4.7 mmol) was performed by bubbling dry NH_3 into its anhydrous ether solution (10 ml) at 10° with stirring, until there was a basic reaction to pH paper (10 min). Ether was evaporated, and the white precipitate (0.7 g, quantitative) was washed with ice-cold water, then sublimed at 30° (0.05 mm): mp 56–57° (lit.[13] 57.8–58.2°); NMR δ 7.4 (s, 1 H), 6.53 (s, 1 H), 4.11 (2 d, J = 6 and 8 Hz, 1 H, –CHClCO–); MS *m/e* 151, 149 w ($P - Cl$)$^+$, 44 base peak, ($H_2N{=}C{=}O$)$^+$.

Anilidation was performed on 0.72 g (4.2 mmol) of **1a**, using 0.4 g (4.3 mmol) of aniline, to give 0.66 g (70%) of the product which was sublimed at 90° (1.25 mm), mp 195–197°.

2-Bromohexanoyl Chloride (1b). The mixture of hexanoic acid (11.6 g, 0.1 mol), CCl_4 (10 ml), and $SOCl_2$ (28.8 ml, 0.4 mol) was stirred at 65° for 0.5 hr. NBS (21.4 g, 0.12 mol), CCl_4 (50 ml), and 48% HBr (7 drops) were added to the mixture. The flask was heated at 70° for 10 min, then at 85° for 1.5 hr. After work-up and fractional distillation in vacuo, **1b** was obtained as a clear, slightly yellow oil (17.1 g, 80%), bp 44–47° (1.5 mm). The decoloration of the product was achieved by using 1.5 ml of a freshly prepared $Na_2S_2O_3$ solution. After distillation, **1b** was obtained (15.75 g, 92% for the decoloration step): bp 45–47° (1.5 mm); $n^{22}D$ 1.4706; d^{24} 1.4017; ir (neat) 1785 cm^{-1}, vs; NMR (neat) δ 4.54 (t, J = 6 Hz, 1 H, –CHBrCOCl); MS *m/e* 179, 177 ($P - Cl$)$^+$. Anal. Calcd for $C_6H_{10}BrClO$: C, 33.75; H, 4.72; Br, 37.42; Cl, 16.60. Found C, 33.42; H, 4.77; Br, 37.29; Cl, 16.74.

The hydrolysis of **1b** (10.28 g, 48.2 mmol) was achieved by treating its acetone (92 ml) solution with 115 ml of a saturated sodium bicarbonate solution (ca. 115 mmol) at 10°. After acidification by concentrated HCl, extraction by $CHCl_3$, and drying over anhydrous $MgSO_4$, the solvent was removed in vacuo to give a colorless liquid (9.36 g, 99.5% yield, 96% pure by gas chromatography). Fractional distillation gave 7.76 g (83%) of 2-bromohexanoic acid, bp 64–66° (0.075 mm) [lit.[15] 132–140° (15 mm)], which was homogeneous by gas chromatography.

Table II

Measurement	Time, hr	NBS % reaction	Br_2, % reaction
1	0.25	6.7	5.2
2	0.50	23.3	15.2
3	0.75	42.6	20.0
4	1.00	64.4	29.3
5	1.25	78.2	37.0
6	1.50	88.9	46.3
7	1.75	93.7	54.1
8	2.08	97.4	60.7
9	2.42	99.3	70.7
10	2.75	100.0	77.0

Comparative Bromination of Hexanoyl Chloride (1) by NBS vs. Molecular Bromine. Hexanoyl chloride (1) was prepared as described above from hexanoic acid (11.6 g, 0.1 mol), carbon tetrachloride (10 ml), and thionyl chloride (28.8 ml, 0.4 mol). To the mixture was added 1.5 ml of xylene which was practically inert to the experimental conditions and used as internal standard. The mixture was then divided into two equal fractions which were placed in two separate flasks. The latter were cooled in an ice bath. Into one of them were introduced bromine (9.6 g, 0.06 mol), CCl_4 (25 ml), and concentrated HBr (3 drops). In the other flask were placed NBS (10.7 g, 0.06 mol), CCl_4 (25 ml), and HBr (3 drops). Condensers with drying tubes were attached and the flasks were placed in the same oil bath (54°). At known intervals of time, aliquots of the reaction mixtures were removed from the flasks and placed in NMR tubes which were dipped in an ice bath to quench the reactions. NMR spectra were recorded, and from the integration curve, the area of the triplet of the product at ca. δ 4.54 (–CHBrCOCl) was compared to that of the aromatic signal of xylene. The ratio was proportional to the extent of the reactions. This ratio increased with time, and at a certain point remained unchanged; the reactions were then considered complete. The results are recorded in Table II.

2-Iodohexanoyl Chloride (1c). Hexanoic acid (11.61 g, 0.1 mol), resublimed iodine (15.23 g, 0.12 g-atom), and thionyl chloride (40 ml, 0.55 mol) were placed in a round-bottom flask equipped with an efficient condenser and a drying tube. The mixture was magnetically stirred and the heating bath was adjusted to 130°. When the reflux was steady, the actual temperature of the reaction mixture was 85°. The reaction was complete after 1.5 hr, as indicated by NMR measurement which was performed and analyzed in the same way as in the preparation of **1a** and **1b**. Thionyl chloride was evaporated under reduced pressure; excess iodine was filtered and washed with carbon tetrachloride. The filtrate was shaken with concentrated $Na_2S_2O_3$ to remove the remaining iodine. The organic layer was separated and dried over anhydrous $MgSO_4$. After solvent evaporation, the product was distilled to yield 21.0 g (80%) of **1c**: bp 62–64° (0.5 mm); $n^{21}D$ 1.5179; NMR (neat) δ 4.94 (t, J = 8 Hz, 1 H, –CHClCOCl); MS *m/e* 260 w (cluster of P^+), 98 s ($P - I - Cl$)$^+$, 41 s ($HC{\equiv}C{=}O$)$^+$. Anal. Calcd for $C_6H_{10}ClIO$: C, 27.66; H, 3.87; Cl, 13.61; I, 48.72. Found: C, 27.38; H, 3.68; Cl, 13.77; I, 49.10.

2-Chloro-3-phenylpropanoyl Chloride (2a). The procedure was the same as that described for **1a**, except that the temperature was 95°. Thus 7.51 g (0.05 mol) of 3-phenylpropanoic acid gave, after 2.0-hr reaction followed by work-up, 8.51 g (84%) of **2a**, bp 70–71° (0.2 mm), as a clear slightly yellow oil: n_D 1.5340; ir (neat) 1785 vs, 1720 cm^{-1} (shoulder); NMR (neat) δ 7.2 (s, 5 H), 4.59 (2 d, J = 6 and 7 Hz, 1 H, –CHClCOCl), 3.5–2.84 (m, 2 H, $C_6H_5CH_2$–); MS *m/e* 202 vw (cluster P^+), 131 s ($P - HCl - Cl$)$^+$, 91 base peak (C_7H_7)$^+$, 77 m (C_6H_5)$^+$. Anal. Calcd for $C_9H_8Cl_2O$: C, 52.95; H, 3.70; Cl, 35.15. Found: C, 53.23; H, 3.97; Cl, 34.92.

The hydrolysis of 2a (1 g, 5 mmol) by 1 ml of H_2O was performed by stirring the mixture at room temperature overnight. The mixture was cooled in a Dry Ice bath and then allowed to warm up to room temperature. White crystals were formed and recrystallized from CCl_4–hexane to give 0.94 g (quantitative) of 2-chloro-3-phenylpropanoic acid: mp 48–49°; NMR (neat) δ 12.0 (s, 1 H), 7.30 (s, 5 H), 4.49 (2 d, J = 6.5 and 8 Hz, 1 H), 3.59–2.94 (m, 2 H); MS *m/e* 186, 184 vw (P^+), 149 w ($P - Cl$)$^+$, 91 base peak

($C_7H_7^+$), 77 m ($C_6H_5^+$). Anal. Calcd for $C_9H_9ClO_2$: C, 58.53; H, 4.92. Found: C, 58.14; H, 4.71.

2-Bromo-3-phenylpropanoyl Chloride (2b). The procedure was the same as that for **1b**. The bromination of 15.0 g (0.1 mol) of 3-phenylpropanoic acid gave 17.5 g (71%) of **2b**: bp 88–89° (0.35 mm); ir (neat) 1775 vs, 1720 cm^{-1} (shoulder); NMR (neat) δ 7.17 (s, 5 H), 4.57 (t, J = 8 Hz, 1 H), 3.54–2.84 (m, 2 H); MS m/e 246 w (cluster P^+), 131 s $(P - HCl - Br)^+$, 91 base peak ($C_7H_7^+$), 77 m ($C_6H_5^+$). Anal. Calcd for C_9H_8BrClO: C, 43.67; H, 3.26; Br, 32.28. Found: C, 43.31; H, 3.42; Br, 32.34.

The esterification of **2b** (1.6 g, 6.3 mmol) in CCl_4 (3 ml) by benzyl alcohol (0.7 g, 6.3 mmol) in CCl_4 (3 ml) at room temperature gave 1.565 g (76%) of the ester: bp 144–145° (0.025 mm); NMR (CCl_4) δ 7.17 (s, 5 H), 7.0 (s, 5 H), 4.94 (s, 2 H), 4.3 (t, J = 8 Hz, 1 H), 3.54–2.84 (m, 2 H). The methyl ester was prepared in the same way: bp 92–95° (0.05 mm); $n^{23}D$ 1.5370 [lit.[17] 147–148° (14 mm), $n^{20}D$ 1.5391]; NMR (neat) δ 7.24 (s, 5 H), 4.5 (t, J = 8 Hz, 1 H), 3.5 (s, 3 H), 3.67–3.10 (m, 2 H).

The amide was obtained by bubbling NH_3 for 15 min into a solution of **2b** (2.54 g, 10 mmol) in dry ether (20 ml). The product was recrystallized from aqueous ethanol to give leaves (2.17 g, 89%): mp 125–126° (lit.[16] 126.5–128.5°); ir (KBr) 3420 m, 3280 m, 3180 m, 1675 vs, 1605 cm^{-1}, s; NMR (Me_2SO-d_6) δ 7.9 (s, 1 H), 7.5 (s, 6 H), 4.77 (t, J = 8 Hz, 1 H), 3.75–3.02 (m, 2 H); MS m/e 227, 229 w (P^+), 148 base peak $(P - Br)^+$, 131 s $(C_6H_5CH_2C{=}C{=}O)^+$, 103 s $(C_6H_5CH{=}CH)^+$, 91 s ($C_7H_7^+$), 77 m ($C_6H_5^+$), 44 m $(H_2NC{\equiv}O)^+$. Anal. Calcd for $C_9H_{10}BrNO$: C, 47.39; H, 4.42; N, 6.14. Found: C, 47.45; H, 4.37; N, 5.86.

2-Iodo-3-phenylpropanoyl Chloride (2c). 3-Phenylpropanoic acid (7.5 g, 0.05 mol) was iodinated by the procedure described above for **1c**. After a 3-hr reaction followed by work-up, 11.0 g (75%) of **2c** was obtained: bp 83–84° (0.05 mm); NMR (neat) δ 7.24 (s, 5 H), 4.84 (t, J = 8 Hz, 1 H), 3.6–4.57 (m, 2 H).

When the reaction was repeated, using only a stoichiometric amount of thionyl chloride (3.6 ml, 0.05 mol) for 7.5 g (0.05 mol) of 3-phenylpropanoic acid and 6.34 g (0.05 g-atom) of iodine in 20 ml of CCl_4, there was no α-iodination, as indicated by the absence of the triplet at δ 4.84 after a heating period of 24 hr. Some side reaction occurred, giving signals upfield from the benzylic proton. No attempt was made to identify the components.

Hydrolysis of **2c** (1.0 g, 3.4 mmol) was performed by the $NaHCO_3$ method as described for **1b**. When solvent was removed on the rotary evaporator, an oily residue remained which solidified on cooling to Dry Ice temperature. The solid was recrystallized from a CCl_4–hexane mixture (1:1) to give 0.9 g (95%) of 2-iodo-3-phenylpropanoic acid: mp 74.5–75°; NMR (CCl_4) δ 11.91 (s, 1 H), 7.42 (s, 5 H), 4.59 (t, J = 8 Hz, 1 H), 3.74–3.02 (m, 2 H); MS m/e 276 w (P^+), 131 s $(P - H_2O - I)^+$, 103 s $(P - HI - COOH)^+$, 91 base peak ($C_7H_7^+$), 77 s ($C_6H_5^+$). Anal. Calcd for $C_9H_9IO_2$: C, 39.15; H, 3.28; I, 45.96. Found: C, 39.09; H, 3.32; I, 45.72.

2-Bromobutanoyl Chloride (5a). Butanoic acid (9.7 g, 0.11 mol) was brominated by NBS in the usual way. The reaction was complete after 1.5 hr. Distillation under reduced pressure gave 15.2 g (75%) of **5a**: bp 57–59° (26 mm) [lit.[19a] 150–152° (760 mm)]; NMR (neat) δ 4.5 (t, J = 8 Hz, 1 H, –CHBrCOCl).

2-Iodobutanoyl Chloride (5b). The iodination of butanoic acid (4.4 g, 0.05 mol) was complete in 1.5 hr, giving 7.9 g (69%) of **5b**: bp 23° (0.1 mm); NMR (CCl_4) δ 4.59 (t, J = 8 Hz, 1 H).

Hydrolysis was performed on 1.0 g (4.3 mmol) of **5b** to give 0.81 g (90%) of 2-iodobutanoic acid which was sublimed at room temperature (0.05 mm) as colorless needles: mp 39–39.5° (lit.[20a] 41–42°); NMR ($CDCl_3$) δ 12.08 (s, 1 H), 4.30 (t, J = 8 Hz, 1 H); MS m/e 214 vw (P^+), 87 m $(P - I)^+$, 41 base peak $(HC{=}C{=}O)^+$. Anal. Calcd for $C_4H_7IO_2$: C, 22.45; H, 3.30. Found: C, 21.91; H, 3.37.

2-Chloro-2-methylpentanoyl Chloride (7a). This compound was obtained in two ways: by the action of NCS or via prolonged iodination.

A. NCS Method. The procedure described for **1a** was used. 2-Methylpentanoic acid (11.6 g, 0.1 mol) was treated with NCS (26.7 g, 0.2 mol), thionyl chloride (40 ml, 0.55 mol), and HCl (7 drops) for 2.5 hr to give 13.35 g (79%) of **7a**: bp 47–48° (1.0 mm); $n^{29}D$ 1.4420; ir (neat) 1775 cm^{-1} vs; NMR (CCl_4) δ 1.84 (s, 3 H). Anal. Calcd for $C_6H_{10}Cl_2O$: C, 42.63; H, 5.96; Cl, 41.94. Found: C, 42.90; H, 6.35; Cl, 41.90.

B. Via Iodination. The starting acid (5.8 g, 0.05 mol) was submitted to α-iodination in the same way as that for **1c**, but the reaction time was increased to 10 hr. NMR measurement showed that the transformation from **7b**, characterized by the singlet at δ_{SOCl_2} 2.16, to **7a** (δ_{SOCl_2} 1.83, s, 3 H), was practically complete. Thionyl chloride was removed, and iodine was filtered and washed with CCl_4. The filtrate was fractionally distilled to give 6.3 g (75%) of an oil, identical in every way with the compound obtained by the NCS method.

2-Iodo-2-methylpentanoyl Chloride (7b). 2-Methylpentanoic acid (11.6 g, 0.1 mol) was iodinated as above, but the reaction was stopped after 0.75 hr, when **7a** started to appear as indicated by the emergence of the singlet at δ 1.83. The mixture was worked up as usual and fractionally distilled to give 7.6 g of **7** and 8.9 g of **7b** (80% yield, based on the amount of consumed starting material): bp 45–46° (0.35 mm); $n^{29}D$ 1.5175; ir (neat) 1760 cm^{-1} vs; NMR (neat) δ 2.04 (s, 3 H). Anal. Calcd for $C_6H_{10}ClIO$: C, 27.66; H, 3.87; Cl, 13.61; I, 48.73. Found: C, 27.88; H, 4.09; Cl, 13.98; I, 49.23.

2-Chloro-2-methylpropanoyl Chloride (8a). This compound was also obtained by two methods.

A. NCS Method. 2-Methylpropanoic acid (4.4 g, 0.05 mol) gave 4.9 g (70%) of **8a**: bp 58–59° (80 mm) [lit.[31] 126–127° (113–114 mm)]; $n^{25}D$ 1.4328; NMR (neat) δ 2.0 (s); ir (CCl_4) 1772 vs, 1740 cm^{-1} (shoulder). Anal. Calcd for $C_4H_6Cl_2O$: C, 34.07; H, 4.29; Cl, 50.29. Found: C, 33.62; H, 4.27, Cl, 49.90.

The corresponding free acid was obtained by hydrolysis, mp 30–31° (lit.[19b] 31°). Anal. Calcd for $C_4H_7ClO_2$: C, 39.20; H, 5.76; Cl, 28.93. Found: C, 38.63; H, 5.34; Cl, 29.28.

B. Via Iodination. The procedure has been described for **7a**. Thus 4.4 g (0.05 mol) of 2-methylpropanoic acid gave 4.7 g (67%) of **8a**, which was identified by spectral data and by its anilide, which sublimed at room temperature (0.025 mm): mp 67–68° (lit.[29b] 67–68°, 69–70°); NMR (CCl_4) δ 9.07 (s, 1 H), 8.24–7.57 (m, 5 H), 8.0 (s, 6 H); MS m/e 199, 197 vw (P^+), 120 base peak $(C_6H_5NHC{\equiv}O)^+$, 77 s ($C_6H_5^+$). Anal Calcd for $C_{10}H_{12}ClNO{\cdot}\frac{1}{2}H_2O$: C, 58.11; H, 6.34; N, 6.78. Found: C, 58.42; H, 5.97; N, 6.82.

During the distillation of **8a**, a white solid was obtained (**17**) at 74° (0.2 mm) in 3% yield: mp 133–134°; ir (KBr) 1700 s, 1670 cm^{-1} s; NMR (CCl_4) δ 10.88 (s, 1 H), 1.74 (s, 6 H), 1.04 (s, 6 H); MS m/e 226, 224 w, 198, 196 w, 147 m, 87 s, 77 base peak, 41 s. Exact mass measurement: calcd 224.0273, found 224.0290. Anal. Calcd for $C_8H_{13}OClS$: C, 42.76; H, 5.83; Cl, 15.78; S, 14.27. Found: C, 42.70; H, 5.41; Cl, 15.54; S, 14.42.

Preparation of Thiol Ester 17. In a 100-ml flask equipped with a magnetic stirring bar, a reflux condenser, and a drying tube were placed 2-mercapto-2-methylpropanoic acid (**18**, 1.0 g, 8.3 mmol), 2-chloro-2-methylpropanoyl chloride (**8a**), and CCl_4 (40 ml). The mixture was refluxed in an 80° oil bath overnight. The solvent was removed on the rotary evaporator to give a white solid which was then recrystallized from CCl_4, 1.95 g (95%). This compound was identical with **17** (mixture melting point, ir, NMR).

2-Iodo-2-methylpropanoyl Chloride (8b). The iodination of 2-methylpropanoic acid (4.4 g, 0.05 mol) was stopped when the singlet at δ 1.86 of **8a** started to appear (ca. 0.75 hr). After work-up, fractional distillation gave 4 g (80%) based on the amount of consumed starting material of **8b**: bp 59–60° (0.17 mm); NMR (neat) δ 2.37 (s). Anal. Calcd for C_4H_6ClIO: C, 20.67; H, 2.60; Cl, 15.25; I, 54.59. Found: C, 20.46; H, 2.51; Cl, 15.53; I, 54.19.

The anilidation was performed on a solution of **8b** (0.781 g, 3.36 mmol) in ether (5 ml) by aniline (0.313 g, 3.36 mmol) dissolved in ether (5 ml). When aniline was added dropwise to the starting material, a dark blue color appeared, then turned to dark orange. The precipitate formed was filtered and washed with ether. Ether was removed from the filtrate, and the solid residue was recrystallized from CCl_4 to give long needles (0.84 g, 86%) of anilide: mp 126–126.5°; NMR (acetone-d_6) δ 9.67 (s, 1 H), 8.34–7.57 (m, 5 H), 2.4 (s, 6 H); MS m/e 289 s (P^+), 169 w $[(CH_3)_2CI]^+$, 162 w $(P - I)^+$, 92 w $(C_6H_5NH)^+$, 77 w ($C_6H_5^+$), 70 m $[(CH_3)_2C{=}C{=}O]^+$, 41 s $(CH_3C{=}CH_2)^+$. Anal. Calcd for $C_{10}H_{12}INO$: C, 41.54; H, 4.18; I, 43.89; N, 4.84. Found: C, 41.78; H, 4.19; I, 43.31; N, 5.10.

Attempted Iodination of 8 in Acetonitrile. 2-Methylpropanoic acid (4.4 g, 0.05 mol), thionyl chloride (3.6 ml, 0.05 mol), and CCl_4 (5 ml) were refluxed for 0.5 hr. NMR measurement showed a complete transformation to **8**. To the reaction mixture was added iodine (6.35 g, 0.05 g-atom), acetonitrile (25 ml), and HI (5 drops). The mixture was refluxed in a 85° oil bath. NMR measurement showed that the doublet signal (δ 8.72, J = 6 Hz) of the methyl group of **8** remained almost unchanged, for 114 hr, indicating no α-halogenation.

Attempted Transformation of 8b by HCl in the Absence of $SOCl_2$. Dry HCl was bubbled into a solution of **8b** (1 g, 4.2 mmol) in CCl_4 (10 ml). The solution was heated to 85°. After 94 hr, no detectable amount of **8a** was formed as evidenced by NMR measurement.

Transformation of 8b into 8a by $SOCl_2$ in the Absence of HCl. Dry nitrogen was passed through a solution of **8b** (1 g, 4.2

mmol) in CCl_4 (10 ml) for 5 hr to flush any HCl which might be present. Thionyl chloride (20 ml) was added to the solution which was then heated to 85°. After 26 hr, ca. 40% of **8b** was transformed to **8a**, as per NMR measurement.

2,3-Dichloropropanoyl Chloride (9a). This compound was prepared by the procedure described for **1a**. Thus 3-chloropropanoic acid (5.4 g, 0.05 mol) gave 5.6 g (70%) of **9a**: bp 52–54° (16 mm) [lit.[23] 140–144° (720 mm)]; $n^{20}D$ 1.4764; NMR (neat) δ 4.87 (2 d, J = 5 and 6.5 Hz, 1 H, –CHClCOCl). Its amide was prepared by the usual method: mp 106–107° (lit.[22] 103°); NMR (acetone-d_6) δ 7.04 (broad s, 2 H), 4.54 (t, J = 5 Hz, 1 H); MS *m/e* 141 (cluster P^+), 108, 106 m $(P - Cl)^+$, 89 w $(P - Cl - OH)^+$, 62 s $(P - Cl - CONH_2)^+$, 44 base peak $(H_2NC{=}O)^+$. Anal. Calcd for $C_3H_5Cl_2O$: C, 25.38; H, 3.55; N, 9.86. Found: C, 25.03; H, 3.61; N, 10.11.

2-Chlorodiphenylacetyl Chloride (12a). This compound was prepared by two different routes.

A. NCS Method. The usual procedure was followed. The proton signal was shifted from δ 5.0 (starting acid) to δ 5.25 (acyl chloride). The latter signal disappeared after a heating period of 1.5 hr at 85°. After work-up, the product was obtained and recrystallized from CCl_4 to give 21.8 g of **12a** (82% yield from 21.2 g, 0.1 mol of diphenylacetic acid): mp 52–53° (lit.[19] 50–51°); NMR ($CDCl_3$) δ 7.4 (s).

B. Via Iodination. The usual procedure of iodination was performed on 5.3 g (0.025 mol) of diphenylacetic acid at 130° (bath temperature). After 1.3 hr, the reaction was complete; the NMR spectrum of the reaction mixture was very clean and showed only one singlet at δ 7.4. Iodine was filtered (2.2 g of iodine was recovered from the starting amount of 3.7 g). After work-up, 7.0 g of a white solid was obtained which was identified as **12a**: mp 52–53°; ir (KBr) 1765 cm^{-1} s; MS *m/e* 266, 264 (P^+), 201, 203 s $(P - COCl)^+$, 194 s $(C_6H_5)_2C{=}C{=}O)^+$, 166 s $(C_{13}H_{10}^+)$, 165 base peak. Anal. Calcd for $C_{14}H_{10}Cl_2O$: C, 63.42; H, 3.80; Cl, 26.74. Found: C, 63.51; H, 3.62; Cl, 26.85.

The reaction was repeated, but the temperature was lowered to 70°. When about half of the starting material had reacted (ca. 5 hr) the reaction was stopped and worked up, but no iodo derivative could be isolated.

C. Via the Reaction of Ketene and Thionyl Chloride. Diphenylketene was generated from the reaction of 2-bromodiphenylacetyl chloride (30.8 g, 0.1 mol) and triphenylphosphine (30.0 g, 0.11 mol) in dry benzene.[31] The ketene was distilled in vacuo to give 12.6 g (65%) of an orange liquid: bp 73–75° (0.1 mm) [lit.[31] 95–96° (0.5 mm)]; ir (neat) 2095 vs, 2054 cm^{-1} w; NMR (CCl_4) δ 7.17.

Diphenylketene (9.4 g, 0.48 mol) was added rapidly into $SOCl_2$ (15 ml). An exothermic reaction took place and the orange color of ketene faded. The solution was refluxed for 3 hr. Work-up was performed as described above, to give 8.9 g (70%) of a product which was identical with **12a** by spectral data.

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Registry No.—**1**, 142-61-0; **1a**, 43056-19-5; **1b**, 42768-46-7; **1c**, 54468-31-4; **2a**, 54468-36-9; **2b**, 42762-86-7; **2c**, 54468-37-0; **4a**, 19078-72-9; **5a**, 22118-12-3; **5b**, 54468-34-7; **6a**, 29548-87-6; **7a**, 54468-32-5; **7b**, 54468-33-6; **8a**, 13222-26-9; **8b**, 54468-35-8; **9a**, 7623-13-4; **9b**, 29548-84-3; **10a**, 29548-85-4; **11a**, 29548-86-5; **12a**, 2902-98-9; **17**, 56348-63-1; **18**, 4695-31-2; hexanoic acid, 142-62-1; 2-chlorohexanamide, 56348-64-2; 2-chlorohexananilide, 56348-65-3; *N*-bromosuccinimide, 128-08-5; *N*-chlorosuccinimide, 128-09-6; 2-bromohexanoic acid, 616-05-7; iodine, 7553-56-2; 3-phenylpropionic acid, 501-52-0; 2-chloro-3-phenylpropanoic acid, 20334-70-7; benzyl 2-bromo-3-phenylpropionate, 56348-66-4; methyl 2-bromo-3-phenylpropionate, 3196-22-3; 2-bromo-3-phenylpropionamide, 56348-67-5; 2-iodo-3-phenylpropanoic acid, 54468-38-1; butanoic acid, 107-92-6; 2-iodobutanoic acid, 7435-10-1; 2-methylpropanoic acid, 97-61-0; 3-methylpropanoic acid, 79-31-2; 2-chloro-2-methylpropanoic acid, 594-58-1; 2-chloro-2-methylpropionanilide, 2322-58-9; 2-iodo-2-methylpropionanilide, 54468-39-2; 3-chloropropanoic acid, 107-94-8; diphenylacetic acid, 117-34-0; diphenylketene, 525-06-4.

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(9) This was demonstrated as follows. The side chain protons $(-CH_2CH_2-)$ of the starting material **2** form an A_2B_2 system (δ 3.23–7.35) which was transformed into an ABX system $(-CH_2CHBr-)$ in the product and could be analyzed by first-order splitting: δ (CCl_4) 4.65 (H_X), 3.71 (H_A), and 3.18 (H_B), $J_{AX} = J_{BX} = 7$, $J_{AB} = 14$ Hz. The mass spectrum of the product was characterized by a peak at *m/e* 91 (base peak, $C_7H_7^+$).[9b] The absence of $C_7H_6Br^+$, which would give a pair of peaks of equal intensity at *m/e* 169 and 171, was further demonstrated. (b) This ion could be the benzylium or tropilium ion: J. Winkler and F. W. McLafferty, *J. Am. Chem. Soc.*, **95**, 7533 (1973). (c) When the HVZ method was applied to **2**, followed by esterification, a mixture of α- and β-bromo compounds was formed but could not be separated by fractional distillation.[17]

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$$2SOCl_2 + 4HI \rightarrow S^0 + SO_2 + 2I_2 + 4HCl$$

(b) The presence of sulfur was shown by its reaction with triphenylphosphine to give triphenylphosphine sulfide.

(28) There is no similar transformation from α-bromo to α-chloro derivatives, e.g., when **8** is brominated by Br_2 or NBS in thionyl chloride.

(29) In order to ascertain whether or not diphenyacetic acid was chlorinated

directly by thionyl chloride, the following experiment was performed. The starting acid (5.3 g, 0.025 mol) was treated with $SOCl_2$ (10 ml) at 110°. After 1.5 hr the NMR spectrum of the reaction mixture showed that the α proton was not replaced. Therefore **12a** could not be obtained in the absence of iodine. At a higher temperature (130°) and upon a longer period of heating (overnight) there was ca. 40% α-chlorination.

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Hydroxylation of Carbonyl Compounds via Silyl Enol Ethers[1a]

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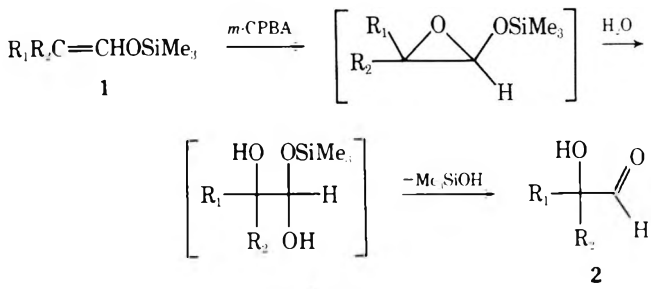
Silyl enol ethers **1**, which are readily available from the corresponding aldehydes, react rapidly with *m*-chloroperbenzoic acid to afford the protected α-hydroxy aldehydes **3** in good yield. Treatment of **3** with acetic anhydride and triethylamine produces α-acetoxy aldehydes **5**. This sequence provides a simple procedure for α-hydroxylation of aldehydes. Silyl enol ethers of ketones **10** are converted directly to α-siloxy ketones **11** with *m*-chloroperbenzoic acid representing a significant improvement over the usual enol ether or acetate procedure.

The effectiveness of trimsyl[1d] enol ethers **1** as masked aldehydes, ketones, and even acids or esters in reactions with electrophiles such as halogens or NOCl has recently been demonstrated.[2] We have now examined the reaction of **1** with peracids, as a potential route to siloxy epoxides or to α-hydroxy carbonyl compounds[3] which are of current interest in sugar synthesis and as precursors to β-hydroxy-α-amino acids.[4] Until recently there were no satisfactory methods available for the synthesis of α-hydroxy aldehydes.[5a] Several procedures have now been described, but they represent homologation reactions.[4,5]

A simple operation was envisioned which would proceed via the epoxidation of trimsyl enol ethers **1** with *m*-chloroperbenzoic acid (*m*-CPBA) followed by hydrolysis and β-cleavage of trimsyl alcohol[6] to afford the desired product **2** as shown in Scheme I. However, the observed product was

Scheme I



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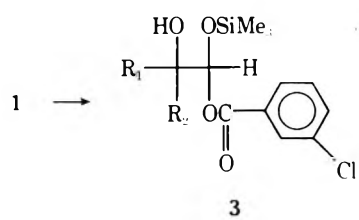
not the hydroxy aldehyde **2**, but the acetal derivative **3**, which is probably generated by opening of the intermediate epoxide by *m*-chlorobenzoic acid or by trapping of an intermediate cation by this acid. The in situ ring opening of α-



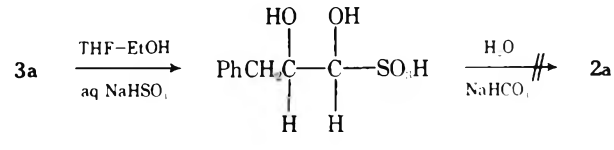
3

alkoxy epoxides, derived from vinyl ethers, by carboxylic acids is a well-known reaction.[7] Attempts to trap the epoxide as the aldehyde by reaction in aqueous THF and as the dimethyl acetal by reaction in methanol afforded uncharacterized mixtures. Hydrogen peroxide (30%) in THF produced only the parent aldehyde via hydrolysis.

Equimolar amounts of **1** and *m*-chloroperbenzoic acid reacted rapidly at room temperature in dichloromethane. After 1 hr, work-up yielded **3** in high yield (Table I). The structure of the product was confirmed by ir, NMR, and mass spectral data. The technique is applicable to a wide range of aldehydes. Thus, R may be alkyl, aryl, or hydrogen. Particularly noteworthy is the presence of a double bond (entry **1f**) and an ester function (**1c**).

It is well known that α-hydroxy aldehydes **2** are quite unstable and rapidly rearrange to hydroxy ketones, dimerize, and polymerize.[5] Generally, compounds **2** are generated in a protected form such as an acetal and converted to the parent **2** only with difficulty.[5] Similar difficulties were encountered in this work. Thus, when **3a** was treated with fluoride ion in Me_2SO or THF,[7] hydrochloric acid in methanol, or aqueous sodium hydroxide in THF, the desired aldehyde **2a** was not obtained. Pyrolysis of **3a** also failed to produce **2a** by expulsion of trimsyl *m*-chlorobenzoate. Finally, an effort to convert **3a** to the siloxy derivative of **2a** by generation of the alkoxide ion by LiH followed by intramolecular silicon transfer also failed. No effort was made to determine the course of these reactions once it was found that the desired transformation was not occurring.

An uncharacterized red oil was obtained from phenylhydrazine and **3e** rather than the desire osazone.[9a] Treatment of **3a** with a standard solution of sodium bisulfite afforded sulfonate **4**.[9b] However, when **4** was stirred with aqueous



4

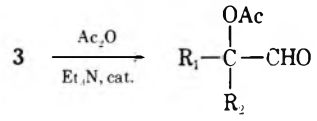
sodium bicarbonate, **2a** was not obtained, but instead an uncharacterized mixture which appeared to contain mostly the dimer of **2a** was recovered. Attempted protection of the hydroxyl function of **3** as an *O*-methyl ether by reaction with methyl Meerwein reagent or methyl iodide and silver oxide or sodium hydride resulted in polymeric products.

Successful deblocking of **3** to generate acetoxy aldehyde

Table I
Synthesis of Protected α-Hydroxy Aldehydes 3 from Silyl Enol Ethers 1

Entry	R_1	R_2	% yield of 3
1a	Ph	Me	85
1b	$PhCH_2$	H	72
1c	$-CH_2CH_2CH_2CH(CO_2Et)CH_2-$		93
1d	Me	Me	74
1e	C_8H_{17}	H	84
1f	$-CH_2CH_2CH{=}CHCH_2-$		79

5 was achieved by reaction with excess acetic anhydride and triethylamine in the presence of a catalytic amount of 4-pyrrolidinopyridine.[10] Presumably, this represents an ac-

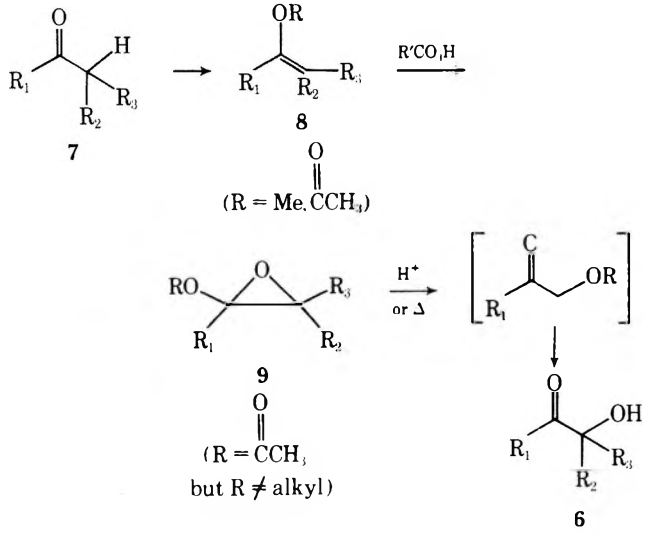


5

ylation followed by deblocking of the aldehyde. The percent conversion of 1 to 5 is only modest but related synthetic procedures for conversion of aldehydes to their α-hydroxy derivatives do not appear to be available.[11] Table II shows the results of the direct conversion of silyl enol ether 1 to acetoxy aldehyde 5 without isolation of the intermediate 3.

There are several synthetic procedures available for α-hydroxy ketones. The acyloin reaction[12] is the best known, but there are several other homologation reactions.[13] Some ketones with an α carbon bearing only one hydrogen can be converted to the corresponding α-hydroxy derivative upon treatment with base and oxygen followed by reduction of the intermediate hydroperoxide with zinc or trialkyl phosphites.[14] With most ketones this procedure results in α diketones and α-cleavage products.

A convenient procedure for regiospecific synthesis of α-hydroxy ketones 6 from the parent ketones 7 is the reaction of enol ether or acetate derivatives 8 of the ketone with peracids.[14] The intermediate epoxides 9 can be converted to the desired 6 by acid or heat followed by hydrolysis.



Since regioselective formation of 8 can readily be achieved, the procedure represents a regioselective synthesis of the desired hydroxy ketone 6. A further convenient hydroxylation of enolates using MoO_5 has recently been reported.[15]

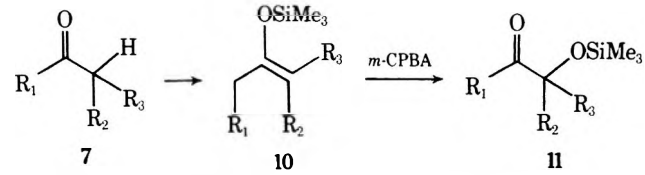
We have observed that extention of the peroxidation procedure to silyl enol ethers of ketones 10[3] allows the hydroxylation of 7 to 6 to be carried out much more conveniently, since the α-siloxy ketones 11 are obtained directly (Table III).[16] Furthermore, the transformation of ketones to 10 can be accomplished regiospecifically in high yields,[17] and silyl ethers are more readily hydrolyzed to alcohols than acetates or ethers.

Table II
Synthesis of α-Acetoxy Aldehydes 5 from Silyl Enol Ethers 1

Entry	R_1	R_2	% yield of 5
1b	$PhCH_2$	H	42
1c	$-CH_2CH_2CH_2CH(CO_2Et)CH_2-$		45
1e	C_8H_{17}	H	46
1f	$-CH_2CH_2CH{=}CHCH_2-$		39

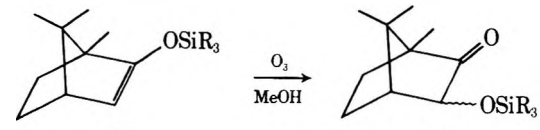
Table III
Synthesis of α-Siloxy Ketones 11 from Silyl Enol Ethers 10

Entry	R_1	R_2	R_3	% yield of 11
10a	Ph	Me	H	90
10b	Et	Me	H	75
10c	*t*-Bu	H	H	73



7 10 11

A related reaction has been observed by Heathcock.[18] Treatment of silyl enol ethers with ozone generally results in cleavage of the olefinic double bond as expected. However, when 12 was treated with ozone rearrangement occurred to afford α-siloxy ketone 13. Similar transformations were also reported for ketene silyl acetals.



12 13

Experimental Section[19]

Preparation of Silyl Enol Ethers. The procedure by House[17a] employing trimsyl chloride and triethylamine in DMF was used to afford products in 60–80% yield.

Epoxidation of Silyl Enol Ethers 1. To a stirred solution of 1 in dichloromethane was added portionwise over several minutes 1.1 equiv of 85% *m*-chloroperbenzoic acid (Aldrich). In the synthesis of some α-siloxy ketones the addition of solid $NaHCO_3$ avoids hydrolysis of the silyl group. After the resulting solution was stirred for 1 hr, aqueous Na_2SO_3 was added to destroy excess peroxide. The solution was washed with aqueous $NaHCO_3$, and the organic layer was dried and concentrated in vacuo. The hydroxy aldehyde derivatives 3 are difficult to purify and were converted to 5 as described below, while the siloxy ketones 11 were purified by bulb-to-bulb distillation. Though these compounds are difficult to obtain analytically pure, elemental analysis was performed on representative samples (5e and 11a) and NMR and mass spectral data as well as analogous reports on α-hydroxy ketones[3] are consistent with the assigned structures.

1-Trimethylsiloxy-1-*m*-chlorobenzoxy-2-phenyl-2-propanol (3a). From 1.03 g (5 mmol) of 1a was obtained 1.60 g (85%) of colorless, viscous oil 3a as a 7:3 erythro/threo mixture: ir (neat) 3500 (OH), 1720 cm^{-1} (ester); NMR ($CDCl_3$) δ 0.1 (s, 9, $SiMe_3$), 1.8 (s, 3, Me), 3.3 (s, 1, OH), 6.3 (s, 1, CH), 7.5 (m, 7, aromatic), 8.0 (m, 2, aromatic); 0.3 (s, 9, $SiMe_3$), 1.6 (s, 3, Me), 3.3 (s, 1, OH), 6.4 (s, 1, CH), 7.5 (m. 7, aromatic), 8.0 (m, 2, aromatic).

1-Trimethylsiloxy-1-*m*-chlorobenzoxy-3-phenyl-2-propanol (3b). From 1.03 g (5 mmol) of **1b** was obtained 1.35 g (72%) of colorless, viscous oil **3b:** NMR ($CDCl_3$) δ 0.1 (s, 9, $SiMe_3$), 2.3 (s, 1, OH), 2.8 (m, 2, CH_2), 3.8 (m, 1, CH), 6.10 (d, 1, CH), 7.2 (s, 5, Ph), 7.4 (m, 2, Ph), 7.9 (m, 2, Ph).

Ethyl [3-Hydroxy-3-(trimethylsiloxy-*m*-chlorobenzoxy)-methyl]cyclohexanecarboxylate (3c). From 1.38 g (5 mmol) of **1c** was obtained 2.0 g (93%) of colorless, viscous oil **3c:** NMR ($CDCl_3$) δ 0.1 (s, 9, $SiMe_3$), 1.2 (t, 3, CH_3), 1.5 (m, 9, ring protons), 2.5 (s, 1, OH), 4.1 (q, 2, CH_2), 5.9 (s, 1, CH), 7.5 (m, 2, aromatic), 8.0 (m, 2, aromatic).

1-Trimethylsiloxy-1-*m*-chlorobenzoxy-2-methyl-2-propanol (3d). From 0.72 g (5 mmol) of **1d** was obtained 1.17 g (74%) of colorless, viscous oil **3d:** NMR ($CDCl_3$) δ 0.1 (s, 9, $SiMe_3$), 1.2 (s, 6, Me_2C), 2.5 (s, 1, OH), 5.9 (s, 1, CH), 7.4 (m, 2, aromatic), 8.4 (m, 2, aromatic).

1-Trimethylsiloxy-1-*m*-chlorobenzoxy-2-decanol (3e). From 1.14 g (5 mmol) of **1e** was obtained 1.68 g (84%) of viscous, colorless oil **3c:** NMR ($CDCl_3$) δ 0.1 (s, 9, $SiMe_3$), 0.9 (m, 3, Me), 1.2 [m, 14, $(CH_2)_7$], 2.8 (s, 1, OH), 3.6 (m, 1, CH), 6.0 (d, 1, CH), 7.4 (m, 2, aromatic), 7.9 (m, 2, aromatic).

4-Hydroxy-4-(trimethylsiloxy-*m*-chlorobenzoxy)methylcyclohexene (3f). From 0.91 g (5 mmol) of **1f** was obtained 1.40 g (79%) of viscous, colorless oil **3f:** NMR ($CDCl_3$) δ 0.1 (s, 9, $SiMe_3$), 1.5–2.5 (broad, 6, ring protons), 2.4 (s, 1, OH), 5.6 (m, 2, –CH=CH–), 5.9 (s, 1, CH), 7.4 (m, 2, aromatic), 7.9 (m, 2, aromatic).

Synthesis of α-Acetoxy Aldehydes 5. The crude products **3** from above were dissolved in dry ether and 1 ml of acetic anhydride, 2 ml of triethylamine, and 0.02 g of 4-pyrrolidinopyridine[10] were added. After stirring for 15 min methanol was added to destroy excess acetic anhydride. The solution was washed with aqueous saturated sodium bicarbonate, 1.5 *M* aqueous hydrochloric acid, and water. The ether was dried (K_2CO_3) and concentrated in vacuo to afford crude **5,** which was purified by bulb-to-bulb distillation.

2-Acetoxy-3-phenylpropanol (5b). From 1.03 g (5 mmol) of **1b** was obtained 0.45 g (42%) of colorless oil **5b:** bp 110° (0.1 Torr); ir (neat) 1730 cm^{-1} (C=O); NMR ($CDCl_3$) δ 2.0 (s, 3, CH_3), 2.9 (d of d, 2, CH_2), 5.2 (d of d, 1, CH), 7.3 (s, 5, Ph), 9.5 (s, 1, CHO).

Ethyl 3-Acetoxy-3-formylcyclohexanecarboxylate (5c). From 1.38 g (5 mmol) of **1c** was obtained 0.55 g (45%) of colorless oil **5c:** bp 100° (0.1 Torr); NMR ($CDCl_3$) δ 1.2 (t, 3, CH_3), 1.0–3.0 (m, 9, ring protons), 2.2 (s, 3, CH_3), 4.1 (q, 2, CH_2), 9.4 (s, 1, CHO).

2-Acetoxydecanal (5e). From 1.14 g (5 mmol) of **1e** was obtained 0.55 g (51%) of colorless oil **5e:** bp 100° (0.1 Torr); NMR ($CDCl_3$) δ 0.9 (t, 3, CH_3), 1.0–2.0 [br, 14, $(CH_2)_2$], 2.1 (s, 3, CH_3), 4.9 (t, 1, CH), 9.4 (s, 1, CHO). Anal. Calcd for $C_{12}H_{22}O_3$: C, 67.26; H, 10.35. Found: C, 67.18; H, 10.35.

4-Acetoxy-4-formylcyclohexene (5f). From 0.91 g of **1f** was obtained 0.33 g (39%) of colorless oil **5f:** bp 90° (0.1 Torr); NMR ($CDCl_3$) δ 1.4–2.8 (m, 6, ring protons), 2.1 (s, 3, CH_3), 5.65 (s, 2, –CH=CH–), 9.5 (s, 1, CHO).

α-Trimethylsiloxypropiophenone (11a). From 1.03 g (5 mmol) of **10a** was obtained 0.96 g (90%) of colorless oil **11a:** bp 85° (0.6 Torr); NMR ($CDCl_3$) δ 0.1 (s, 9, $SiMe_3$), 1.4 (d, 3, CH_3), 5.0 (q, 1, CH), 7.4 (M, 3, aromatic), 8.0 (m, 2, aromatic). Anal. Calcd for $C_{12}H_{18}O_2Si$: C, 64.82; H, 8.16. Found: C, 64.92; H, 8.15. Calcd for $C_{12}O_{18}O_2Si$: M^+ 222.107. Found: 222.085.

2-Trimethylsiloxy-3-pentanone (11b). From 0.80 g (5 mmol) of **10b** was obtained 0.65 g (75%) of colorless **11b:** bp 80° (8 Torr); NMR ($CDCl_3$) δ 0.1 (s, 9, $SiMe_3$), 1.0 (t, 3, CH_3), 1.2 (d, 3, CH_3), 2.5 (q, 2, CH_2), 4.05 (q, 2, CH).

1-Trimethylsiloxy-3,3-dimethyl-2-butanone (11c). From 0.86 g (5 mmol) of **10c** was obtained 0.69 g (73%) of colorless oil **11c:** bp 70° (10 Torr); NMR ($CDCl_3$) δ 0.1 (s, 9, $SiMe_3$), 1.15 (s, 9, *t*-Bu), 4.35 (s, 2, CH_2).

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Registry No.—**1a**, 51075-23-1; **1b**, 51075-22-0; **1c**, 55638-14-7; **1d**, 6651-34-9; **1e**, 51075-24-2; **1f**, 51075-25-3; *erythro*-**3a**, 55638-15-8; *threo*-**3a**, 55638-16-9; **3b**, 55638-17-0; **3c**, 55638-18-1; **3d**, 55638-19-2; **3e**, 55638-20-5; **3f**, 55368-21-6; **5b**, 38559-23-8; **5c**, 55638-22-7; **5e**, 55638-23-8; **5f**, 55638-24-9; **10a**, 37471-46-8; **10b**, 17510-47-3; **10c**, 17510-46-2; **11a**, 55638-25-0; **11b**, 55638-26-1; **11c**, 55638-27-2; *m*-chloroperbenzoic acid, 937-14-4; acetic anhydride, 108-24-7.

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Use of Achiral Shift Reagents to Indicate Relative Stabilities of Diastereomeric Solvates

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In the presence of chiral aryl perfluoroalkylcarbinols, the NMR spectra of sulfoxide enantiomers are nonequivalent. Addition of an achiral lanthanide shift reagent, $Eu(fod)_3$, alters the magnitude and sometimes the sense of this nonequivalence. Mechanisms underlying this "alteration" are discussed and the shape of the nonequivalence vs. $Eu(fod)_3$ curves is related to nonidentical energies of solvation of the sulfoxide enantiomers by the chiral carbinol. These energy differences are in turn related to the structure and stereochemistry of the sulfoxides via specific carbinol–sulfoxide solvation models. The application of chiral solvent–achiral shift reagent systems to the determination of the absolute configurations of enantiomeric solutes is considered.

A continuing interest in the mechanisms by which chiral molecules distinguish between enantiomers has prompted us to explore new methods of obtaining information regarding the strengths of diastereomeric interactions between chiral molecules. Such information is essential to rational design of asymmetric induction reactions and to the direct chromatographic resolution of enantiomers. We now describe a method employing chiral solvents and achiral shift reagents which not only provides this information but also affords results relevant to the question of whether chiral solvent–achiral shift reagent systems can be used to determine absolute configurations in a manner analogous to that used for chiral solvents alone.[1-4]

Mixed chiral solvent–achiral shift reagent systems have been reported[5] by Jennison and Mackay to enhance NMR spectral nonequivalence for enantiomeric solute molecules beyond that observed in the chiral solvent alone. The mechanism underlying this enhancement was not delineated, however. Similarly, Whitesides et al have reported[6] that the addition of $Eu(fod)_3$ to a solution of resolved *N*-methyl-1-phenylethylamine containing partially resolved 1-phenylethylamine produces enantiomeric nonequivalence in the ^1H NMR spectra of the latter. These authors present data to support the contention that this nonequivalence stems from formation of spectrally dissimilar rapidly exchanging diastereomeric 1:1:1 complexes of $Eu(fod)_3$, chiral *N*-methyl-1-phenylethylamine and 1-phenylethylamine. Considered and excluded as the source of the nonequivalence was an alternate mechanism in which $Eu(fod)_3$ preferentially complexes whichever of the 1-phenylethylamine enantiomers that most weakly interacts with the chiral *N*-methyl-1-phenylethylamine. Even more recently, Ajisaka and Kainosho have reported that partially resolved α-phenylethylamine shows enantiomeric ^1H NMR nonequivalence upon addition of $Eu(fod)_3$.[7] These workers suggest that such nonequivalence originates from the formation of transient diastereomeric 2:1 amine–$Eu(fod)_3$ complexes having nonidentical chemical shifts. This mechanism is very similar to that espoused by Whitesides.[6] Ajisaka and Kainosho also rule out[8] the alternate mechanism earlier considered and excluded by Whitesides.[6]

Although apparently unimportant among the systems studied by Whitesides et al.[6] or by Ajisaka and Kainosho,[7] this latter type of mechanism is fundamentally reasonable and seems more likely to be observed for strong diastereomeric interactions than for weak ones. Prior studies of the interactions of chiral solvents with enantiomeric solutes suggest several such systems, and evidence is herein presented that dissimilar stabilities of diastereomeric solvates can be demonstrated through the agency of achiral lanthanide shift reagents.

Using the terms R and S to designate the solute enantiomers, C to represent the chiral solvent, and L to represent the achiral lanthanide shift reagent, eq 1–7 represent reactions which play a role in determining the time-averaged chemical shifts of the solute enantiomers. Other reactions

$$R + C \overset{K_1}{\rightleftharpoons} RC \quad (1)$$

$$S + C \overset{K_2}{\rightleftharpoons} SC \quad (2)$$

$$R + L \overset{K_3}{\rightleftharpoons} RL \quad (3)$$

$$S + L \overset{K_3}{\rightleftharpoons} SL \quad (4)$$

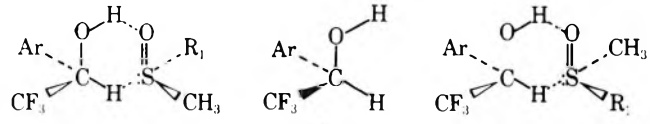
$$RC + L \overset{K_4}{\rightleftharpoons} RCL \quad (5)$$

$$SC + L \overset{K_5}{\rightleftharpoons} SCL \quad (6)$$

$$C + L \overset{K_6}{\rightleftharpoons} CL \quad (7)$$

occur and can be described (e.g., $2L \rightleftharpoons L_2$; $2R + L \rightleftharpoons R_2L$; $2S + L \rightleftharpoons S_2L$; $R + S + L \rightleftharpoons RSL$; $2C \rightleftharpoons C_2$; $2S \rightleftharpoons S_2$; $2R \rightleftharpoons R_2$; $R + S \rightleftharpoons RS$) but will be considered as unimportant to the bulk of the subsequent discussion, even though some of them are essential to the Ajisaka–Kainosho mechanism.[7]

Chiral type 1 alcohols have been proposed[1] to interact with sulfoxide enantiomers to afford two rapidly exchanging diastereomeric 1:1 solvates which spend a significant fraction of time in the chelate-like conformations **2a** and **2b**. Although these diastereomeric solvates may have nonidentical formation constants, K_1 and K_2, the strength of these principle interactions ensures that essentially all of both sulfoxide enantiomers will be hydrogen bonded *if a severalfold excess of the alcohol is used.* Under these conditions, spectral differences between enantiomers arise not from differential degrees of solvation but rather from intrinsic spectral nonidentity of the conformers, **2a** and **2b**. In the stereochemical situation depicted, the resonance of the sulfinyl methyl will, owing to shielding by the cis aryl group, occur at higher field for the enantiomer incorporated into **2b** than for the one in **2a**. The converse holds for the substituent R_1. During the subsequent discussion, nonequivalence arising via this mechanism will be termed "type A" nonequivalence.



2a **1** **2b**

Type 1 alcohols are fairly acidic and, while they solvate the basic sulfoxides strongly, they interact only weakly

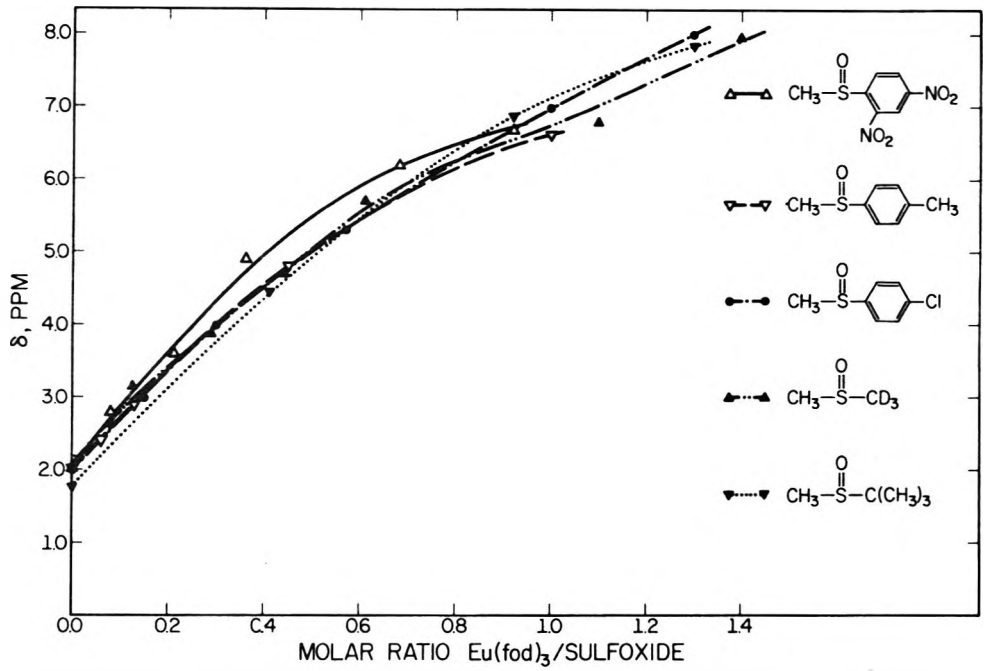


Figure 1. The influence of $Eu(fod)_3$ concentration upon the chemical shifts of the sulfinyl methyls of several methyl sulfoxides. Samples are ca. 0.2 *M* in sulfoxide and 0.6 *M* in chiral carbinols **4** or **5**.

with $Eu(fod)_3$ (i.e., K_6 is small) as evidenced by the small chemical shifts induced by addition of the latter. $Eu(fod)_3$ is a strong Lewis acid and, again judging by induced shifts, interacts more strongly with sulfoxides than do type 1 alcohols (i.e., $K_3 > K_1$ or K_2).[9] If the $Eu(fod)_3$ preferentially strips enantiomeric sulfoxide from the least stable of the diastereomeric alcohol–sulfoxide solvates, then that sulfoxide enantiomer will tend to have its time averaged chemical shifts at lower field than those of the enantiomer incorporated into the more stable solvate (type B nonequivalence). This will be true *regardless of the initial relative chemical shift positions of the enantiomers observed in the chiral solvent alone.* By relating type B nonequivalence to the nonidentical formation constants (K_1 and K_2) of the two diastereomeric alcohol–sulfoxide solvates, one predicts that, in situations where no difference in stability exists (K_1 equals K_2), the addition of the lanthanide reagent will simply attenuate the type A nonequivalence initially induced by the chiral alcohol. This situation will obtain for many meso compounds and for compounds enantiomeric by virtue of isotopic substitution.[10] Further, addition of sufficient shift reagent to strip all sulfoxide from the chiral alcohol should cause type B nonequivalence to vanish. These predictions differ from the results expected via the mechanism operative in the work reported by Whitesides.[6] For example, if nonequivalence stemmed solely from formation of spectrally nonidentical diastereomeric 1:1:1 complexes of shift reagent, sulfoxide, and chiral solvent (type C nonequivalence), one would not expect excess (relative to sulfoxide) $Eu(fod)_3$ to cause nonequivalence to vanish and one would expect to see nonequivalence for meso and isotopically chiral molecules. Moreover, the possibility that these 1:1:1 diastereomeric complexes may be formed to different extents provides additional mechanisms for nonequivalence even if the 1:1:1 diastereomers have identical spectra. If addition of the chiral alcohol to a 1:1 sulfoxide–$Eu(fod)_3$ complex increases the coordination number of the europium ion, spectral changes can be expected to occur for bound ligands. In general, limiting shifts for 2:1 solute–lanthanide complexes are not as great as those of the 1:1 complexes.[11] Hence, differential extents of formation of diastereomeric 1:1:1 complexes may cause nonequivalence of the sulfoxide enantiomers. These concentration differences can result either from nonidentical formation constants ($K_4 \neq K_5$; type D nonequivalence) or, even if K_4 equals K_5, nonidentical K_1 and K_2 values will result in nonidentical concentrations of the 1:1:1 complexes. In this event, the nonequivalence thus induced (type E) will be opposite in sense to that of the type B mechanism. Realistically, one should expect simultaneous contributions from all nonequivalence mechanisms. However, for a given system, the relative contribution of each mechanism will be concentration and temperature dependent.

Consider a sample containing (*R*)-enriched methyl sulfoxide, CCl_4, and a threefold excess of (*R*)-2,2,2-trifluoro-1-(10-bromo-9-anthryl)ethanol (**3**).[12] Under these type A conditions, the sulfinyl methyl resonance of the *S* enantiomer occurs at higher field than that of the *R* enantiomer. Subsequent progressive addition of $Eu(fod)_3$ shifts all the sulfoxide resonances downfield, the sulfinyl methyl resonances being most strongly shifted (Figure 1). The initial increments of $Eu(fod)_3$ can either strip sulfoxide from the chiral alcohol ($K_3 > K_1$ or K_2, $K_3 > K_4$ or K_5) or add to the 1:1 solvates to form 1:1:1 complexes ($K_3 < K_4$ or K_5). If the first situation prevails, then, for a sulfoxide where K_1 equals K_2 and K_4 equals K_5, an experimental plot of observed nonequivalence vs. the concentration of $Eu(fod)_3$ should be approximately a straight line which reaches zero and remains there when the $Eu(fod)_3$ concentration equals or exceeds that of the sulfoxide. This is essentially the case with methyl trideuteromethyl sulfoxide (Figure 2). Note that the nonequivalence initially shown by the enantiomers of this sulfoxide is attenuated by the addition of $Eu(fod)_3$ and reaches zero after the lanthanide:sulfoxide ratio exceeds 1:1. This is in accord with the proposed requirement that the diastereomeric solvates be of different stability in order that nonequivalence of types B, D, or E be observable. Here, such stability difference would be isotopic in origin and quite small. This result also suggests that type C nonequivalence makes little contribution in this instance. If 2:1 (rather than 1:1) complexes of Me_2SO–$Eu(fod)_3$ were being formed to an appreciable extent, the nonequivalence should, within the framework of the assumptions involved in this model, be observed to diminish to zero at $Eu(fod)_3$–

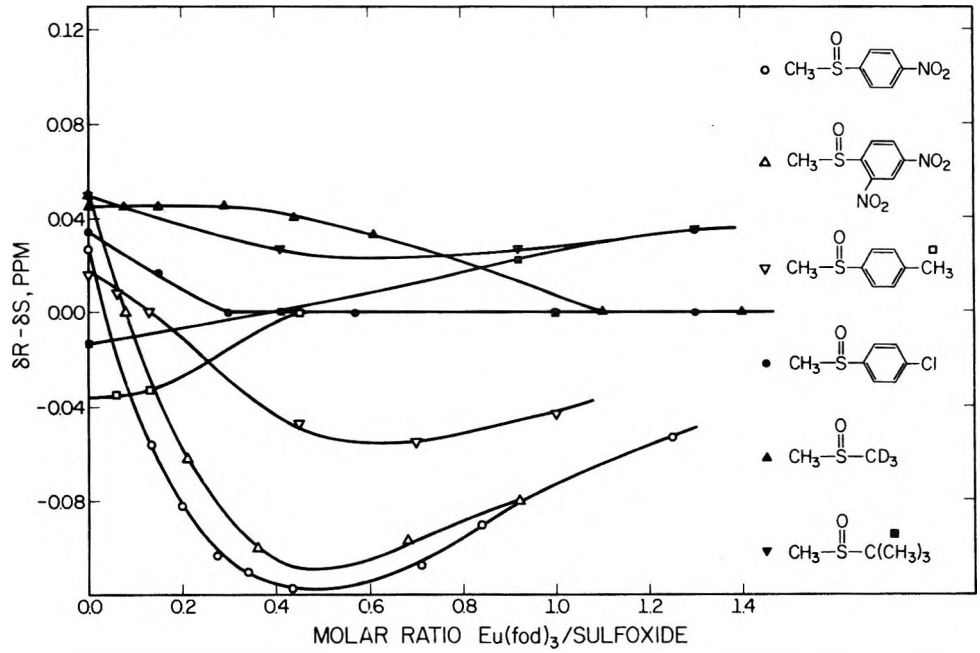


Figure 2. The influence of $Eu(fod)_3$ concentration upon the magnitudes and senses of nonequivalence of several methyl sulfoxides (0.2 *M*) in the presence of *R* carbinols **4** or **5** (0.6 *M*).

Me_2SO ratios of less than unity. While formation of diastereomeric 2:1 sulfoxide–$Eu(fod)_3$ complexes could, in principle, afford nonequivalence for partially resolved sulfoxides via the Ajisaka–Kainosho mechanism,[7] such nonequivalence would, in the case of methyl trideuteriomethyl sulfoxide, be isotopic in origin. No such nonequivalence is noted in the absence of chiral alcohol **3**.

In the case of methyl *tert*-butyl sulfoxide, solvate **2b** (R_1 = *tert*-butyl) is expected on steric grounds to be more stable than solvate **2a** in which the bulky anthryl and *tert*-butyl groups are cis. If this situation obtains, the type B model predicts that the sign of the *tert*-butyl (but not the sulfinyl methyl) nonequivalence will invert and that the magnitudes of both nonequivalences will approach zero with increasing lanthanide concentration. Initially, these predictions are borne out. However, high lanthanide:sulfoxide ratios do not cause nonequivalence magnitudes to become zero, presumably as a consequence of the occurrence of significant type D (and perhaps type C) nonequivalence in this concentration range. Nonequivalence of the Ajisaka–Kainosho type would also disappear at high lanthanide:sulfoxide ratios.[7] The extent to which the type E mechanism occurs and counteracts the type B mechanism will depend upon the magnitudes of several equilibrium constants (K_1–K_5). A priori, it seems unlikely that the type E mechanism can dominate the type B mechanism, since type I carbinols coordinate but weakly to $Eu(fod)_3$. Moreover, the ratio of the E/B contributions is smaller at low $Eu(fod)_3$/sulfoxide ratios owing to the effect of mass action.

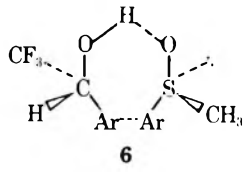
In the case of methyl *p*-tolyl sulfoxide, the a priori prediction of the stability order (**2a** vs. **2b**) of the diastereomeric solvates is complicated by considerations of steric vs. electronic interactions. Solvate **2b**, in which the 10-bromo anthryl substituent of the alcohol is cis to the *p*-tolyl group, will be the most stable provided that the electronic effects of π–π bonding and trifluoromethyl–*p*-tolyl repulsion[13] dominate possible steric repulsion between the two aryl groups. This is apparently the case since addition of $Eu(fod)_3$ causes inversion in the sign of the sulfinyl methyl nonequivalence. Addition of 0.5 molar equiv of $Eu(fod)_3$ to a 30% enriched sample of this sulfoxide in carbon tetrachloride affords no Ajisaka–Kainosho-type nonequivalence. Similarly, no nonequivalence is afforded upon subsequent addition of racemic carbinol **4**. Clearly, the presence of the chiral carbinol is essential for the observation of nonequivalence in these systems.

Methyl *p*-chlorophenyl sulfoxide behaves approximately as does methyl *p*-tolyl sulfoxide but does not actually show inversion of the sense of nonequivalence of the sulfinyl methyl, presumably as a consequence of the increasing importance of offsetting type C, D, and/or E contributions as the $Eu(fod)_3$ concentration is increased. However, the rate of increase of the observed nonequivalence is initially too rapid to be simply attenuation of the type A contribution.

To amplify energy differences between diastereomeric solvates, a system comprised of slightly enriched (*S*)-(−)-methyl 2,4-dinitrophenyl sulfoxide (**4**) and (*R*)-2,2,2-trifluoro(10-methyl-9-anthryl)ethanol (**5**)[12] was chosen. In this case, the assignment of absolute configuration to the sulfoxide. Since type B nonequivalence stems from the nonidentity of K_1 and K_2, the increased amplitude of the signment leads to a curve of the same general shape as that observed for the configurationally known methyl *p*-tolyl sulfoxide. Since type B nonequivalence stems from the nonidentity of K_1 and K_2, the increased amplitude of the curve bespeaks a larger energy difference between these diastereomeric solvates. Mixtures of this sulfoxide and alcohol **5** are red, consistent with the formation of π–π complexes, as is the inverse temperature dependence of the intensity of this red color. Note also that the change of slope which occurs at a lanthanide:sulfoxide ratio of ca. 0.5 is especially indicative of the type B mechanism, since it is at just this value that maximum type B nonequivalence should occur for a *racemic solute*.[14]

Finally, it should be noted that crystallization of racemic methyl 2,4-dinitrophenyl sulfoxide from a carbon tetrachloride solution of (*R*)-2,2,2-trifluoro(10-methyl-9-anthryl)ethanol affords mother liquors enriched in the enantiomer showing low-field type A nonequivalence. The crystalline material is oppositely enriched. This enrichment is consistent with the existence of energetically dissimilar diastereomeric solvates; the enantiomer preferentially retained (complexed) in the mother liquors *is the one predicted by the solvation model.* Since similar results ob-

tained either on crystallization of racemic 4 from or dissolution in solutions containing (*R*)-2,2,2-trifluoro(9-anthryl)ethanol,[12] it appears that the enrichment is thermodynamic rather than kinetic in origin. Although the extent of enantiomeric enrichment of the mother liquors is appreciable (ca. 10%), it is not so great as to suggest that only one enantiomer of 4 can simultaneously hydrogen bond and π complex to the carbinol. Because of the presumed greater strength of the π complex (in this instance) than the carbinyl hydrogen bonding interaction, it is deemed likely that solvation energy differences reflect the presence of the carbinyl hydrogen bonding interaction in one diastereomer but not the other. In this event, conformer **2a** remains the important conformer for the *R* sulfoxide but conformer **6** may now be the important conformer for the solvate derived from *R* alcohol and *S* sulfoxide. Supportive of this



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point is the observation that racemic methyl *p*-nitrophenyl sulfoxide and carbinol **5** afford a curve very similar to that of dinitrophenyl sulfoxide **4**,[15] if one accepts the configurational assignments based upon the sense of the type A nonequivalence. In the case of (−)-methyl 2,4-dinitrophenyl sulfoxide, the *S* configuration follows from the sense of the type A nonequivalence and from the similarity of curve shape (Figure 2) obtained using this assignment to those of the configurationally known methyl *p*-tolyl and methyl *p*-chlorophenyl sulfoxides.

In principle, the six equilibrium constants (eq 1–7) can be obtained for a sulfoxide via an iterative computational process which matches calculated and experimental curves. Additional curves obtained at other concentration levels would facilitate this matching. Even without computation, however, one can roughly equate the depth of the minimum shown by the curves in Figure 2 with the stability differences between the diastereomeric solvates. Such comparison requires that all the curves be obtained under similar conditions and that one *assume* that the R_1 substituent has a negligible effect upon the chemical shifts of the sulfinyl methyls in the sulfoxide containing species present. The similarity of the curves in Figure 1 show this not to be an unreasonable approximation.

In view of the several nonequivalence mechanisms potentially operable, it is clear that *generalized* correlations between the senses of nonequivalence observed in chiral solvent–achiral shift reagent systems and the absolute configurations of the solutes are unwarranted. However, in systems where solvent–solute interactions are understood, the spectral perturbations attending the addition of achiral shift reagents can provide supportive data for assignment of absolute configurations.

It is manifest from the preceding discussions that addition of an achiral shift reagent to a partially resolved solute is potentially capable of producing enantiomeric spectral nonequivalence by a mechanism other than that of Ajisaka and Kainosho.[7] Indeed, both types of nonequivalence, arising as it were from the partially resolved solute serving as a chiral solvent, could also occur for *chiral* lanthanide shift reagents and thus either counteract or reinforce any nonequivalence stemming from the chirality of the shift reagent. Such contributions further complicate the assignment of absolute configuration through the use of chiral lanthanide shift reagents.[16–19]

One obvious application for NMR experiments of this kind is the screening of compounds potentially useful as chiral stationary phases for the direct chromatographic resolution of enantiomers. The chiral compound being screened need not be capable of inducing type A nonequivalence for this approach to succeed.

Experimental Section

General NMR Procedure. Samples of the sulfoxide and the chiral alcohol were weighed into an NMR tube and dissolved in 0.5 ml of CCl_4. The spectrum of this solution was determined before and after successive additions of solid $Eu(fod)_3$. Relative concentrations were determined through comparison of the integrals of the *tert*-butyl ligand resonance and the sulfinyl methyl resonances.

$Eu(fod)_3$ was used as obtained from Aldrich Chemical Co. and the CCl_4 (J. T. Baker reagent grade) was used without further purification. All spectra were taken on a Varian A-60A spectrometer at 44°C.

Sulfoxides. Partially resolved samples of the *tert*-butyl, trideuteriomethyl, *p*-tolyl, and *p*-chlorophenyl methyl sulfoxides were prepared by the method of Andersen and have been previously reported.[20,21,22] Partially resolved nitro-substituted aryl methyl sulfoxides are not readily obtained by Andersen's approach owing to reaction of nitro groups with Grignard reagents. However, racemic *p*-nitrophenyl[23] and 2,4-dinitrophenyl methyl[24] sulfoxides have been reported.

Partial Resolution of 2,4-Dinitrophenyl Methyl Sulfoxide. The solution obtained by stirring 30 mg of racemic sulfoxide and 25 mg of (*S*)-(+) − **5** in 1 ml of carbon tetrachloride for 4 hr at 25° was filtered to remove undissolved sulfoxide and found to be enriched (ca. 10% e.e.) in the sulfoxide enantiomer showing a low field sense of sulfinyl methyl nonequivalence. Similar results are obtained by allowing the sulfoxide to crystallize from an initially hot solution of similar composition. A partially resolved *S*-enriched sample of the sulfoxide of 17% enantiomeric purity, obtained in an alternate manner, shows $[\alpha]^{25}D$ −15.4° (*c* 0.49, dichloromethane).

Acknowledgment. This work has been partially supported by the National Institutes of Health through Research Grant GM 14518.

Registry No.—Methyl 2,4-dinitrophenyl sulfoxide, 56454-35-4; methyl *p*-tolyl sulfoxide, 39066-80-3; methyl *p*-chlorophenyl sulfoxide, 56487-58-2; methyl trideuteriomethyl sulfoxide, 56487-59-3; methyl *tert*-butyl sulfoxide, 49775-44-2; methyl *p*-nitrophenyl sulfoxide, 56454-34-3

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(8) Although it is probably correct to consider this alternate mechanism as relatively unimportant *in this case*, the grounds for excluding it seem less than rigorous. The experimental demonstration that racemic and enantiomerically pure α-phenylethylamine are isochronous does not necessarily demonstrate the absence of strong diastereomeric solute–solute interactions.
(9) Infrared measurements show that the association constant between Me_2SO and 2,2,2-trifluoro-1-phenylethanol is ca. 200 in carbon tetrachloride whereas the association constant for 1:1 interaction between Me_2SO and $Eu(fod)_3$ in CCl_4 has been reported to be 625. See J. Reuben, *J. Am. Chem. Soc.*, **95**, 3534 (1973).
(10) For meso compounds containing but one group complexable by $Eu(fod)_3$ or the chiral solvent (e.g., 2-propanol), type B nonequivalence cannot be observed in principle. However, for meso compounds of the type $R(CH_2)_nS$, where R and S are enantiotopic and contain complexable groups, nonequivalence originating from the formation of 1:1:1 complexes can result but is of type C or D. Jennison and Mackay report[5] several instances where meso compounds fail to show perceptible nonequivalence in chiral solvent–achiral shift reagent systems.
(11) It has been noted [D. F. Evans and M. Wyatt, *J. Chem. Soc., Dalton Trans.*, 765 (1974)] that the limiting shifts of 2:1 solute–lanthanide complexes are smaller than those of the 1:1 complexes. In particular, the limiting shift of the 2:1 Me_2SO–$Eu(fod)_3$ complex is 3.48 ppm whereas that of the 1:1 adduct is 6.58 ppm. It should be clear that the 2:1 complexes discussed are restricted to those where the lanthanide ion is di-

rectly coordinated to the solutes. A referee has correctly observed that limiting shifts depend upon the geometry of the complexes and that the generalization, while possibly true for sulfoxides, is not necessarily true for all other substrates.

(12) The synthesis, resolution, and assignment of absolute configuration for this alcohol is being reported elsewhere.

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(14) The position of the minimum should reflect the enantiomeric purity of the solute provided types C and D nonequivalence make negligible contributions.

(15) The Ajisaka–Kainosho mechanism[7] cannot be operative for racemic solutes. Hence, the observation of nonequivalence for racemic **4**, racemic methyl *p*-nitrophenyl sulfoxide, and unlabeled Me_2SO must have a different origin.

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Carbon-13 Nuclear Magnetic Resonance Studies of Organoboranes The Relative Importance of Mesomeric B–C π-Bonding Forms in Alkenyl- and Alkynylboranes[1]

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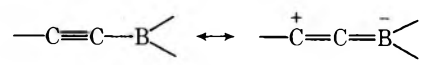
The ^{13}C NMR spectra have been obtained for trialkylboranes, dialkylborinates, alkylboronates, dialkylchloroboranes, alkenylboranes, and alkynylboron derivatives. In the alkenyl- and alkynylboranes, it is concluded on the basis of the ^{13}C NMR chemical shifts that π interaction between the π-electron system and the vacant p orbital of the boron atom exists to a certain extent, and that the mesomeric B–C π-bonding forms contribute to the ground state of these α,β-unsaturated compounds.

The question of B–C π bonding in alkenylboranes has presented chemists with an intriguing problem (eq 1).[3]

(1)

Though a substantial body of evidence now exists supporting π interaction between the π-electron system and the vacant p orbital of boron in an alkenylborane,[3] objection against such π bonding has also been raised.[3a] The large volume of experimental data gathered so far has been obtained by infrared,[4–10] Raman,[10] ultraviolet,[7,8,11] ^1H NMR,[8] ^{11}B NMR,[7,8] ^{19}F NMR,[7,12,13] and photoelectron[14] spectroscopic techniques, data which seem to provide mainly indirect evidence. The question has also been the subject of LCAO–MO–SCF,[11] CNDO,[15,16] and INDO[17] calculations. However, ^{13}C NMR spectra have not as yet been obtained, despite the superior advantage that their chemical shifts can more directly provide insight into the bonding situations.[18,19]

Alkynylboranes may also exist in the mesomeric allenyl form (eq 2),[3a] though to our knowledge there is no literature evidence for such B–C π bonding. In this paper, we report in full on the ^{13}C NMR spectra and the bonding situation of alkenyl- and alkynylboranes.



(2)

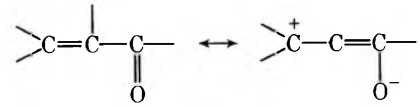
Experimental Section

All boranes were prepared as previously described.[20] ^{13}C NMR spectra were measured on a Varian XL-100-15 spectrometer operating in the Fourier transform mode at 25.2 MHz. All spectra were determined with noise-modulated proton decoupling. Single-frequency off-resonance decoupled spectra were used to assign the resonances in questionable cases. The spectra were taken in benzene-d_6 (ca. 50% concentration), except where otherwise indicated, in 12-mm sample tubes, and were calibrated using the solvent resonances as secondary standards.

Results and Discussion

The chemical shifts obtained from the ^{13}C NMR spectra of alkenyl- (**1–5**), alkynyl- (**6** and **7**), and alkylboron derivatives (**8–14**), and those of the corresponding alkenes, alkynes, and alkanes are listed in Tables I–III. Assignments of ^{13}C signals were made on the basis of (1) off-resonance decoupling spectra, (2) consistency with other shift data,[18,19] and (3) broadening and weakening of the peak corresponding to the ^{13}C nuclei directly attached to boron. The last phenomenon was generally observed for the alkyl- and alkenylboranes, and is presumably due to large carbon–boron couplings which are incompletely relaxed by the quadrupole mechanism.[21,22] In the case of the alkynylboranes, the absorption of the α carbon had completely disappeared.

As is apparent from Table I, the chemical shifts at C_1 and C_2 of **1** are similar to those of acrylic acid (δ C_1 128.0, δ C_2 131.9).[18] Also, the shifts in the other alkenylboranes show an analogous trend to those in α,β-unsaturated carbonyl compounds, where the contribution of enolate form is important (eq 3).[18,19]

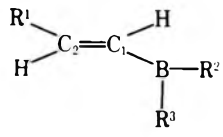


(3)

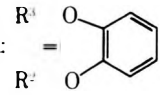
This phenomenon is highly interesting in connection with the relationship between the ^{13}C shielding and the chemical reactivity of boron derivatives, since the suggestion that many reactions of aldehydes and ketones have counterparts in the reactions of trialkylboranes has already been presented.[23]

The $^{13}C_2$–H coupling constants of di-*n*-butylvinylboronate (**1**) were 158 and 164 Hz, indicating that the C_2 has a normal sp^2 hybridization. The coupling constant of di-*n*-butylacetyleneboronate (**6**) was 240 Hz, demonstrating that the C_2 has a normal sp hybridization. The $^{13}C_2$–H coupling constant of *n*-butylboronate (**9**) was 124 Hz, indicating here also that the C_2 has a normal sp^3 hybridization.

Table I
^{13}C Chemical Shifts for Alkenylboranes (1-5)[a]



1. $R^1 = H$; $R^2 = R^3 = O\text{-}n\text{-}Bu$
2. $R^1 = n\text{-}Bu$; $R^2 = CH{=}CH\text{-}n\text{-}Bu$; $R^3 = Cl$
3. $R^1 = n\text{-}Bu$; $R^2 = CH{=}CH\text{-}n\text{-}Bu$; $R^3 = OCH_3$
4. $R^1 = n\text{-}Bu$; $R^2 = R^3 = CH(CH_3)CH(CH_3)_2$
5. $R^1 = n\text{-}Bu$:



Borane	Alkenyl δ C_1	δ C_2	δ C_3	δ C_4	δ C_5	δ C_6	Other
1	*b*	135.5					δ OCH_2 64.4, δ C_2 35.3, δ C_3 20.7, δ CH_3 15.1
1[c]	127.8	134.1					δ OCH_2 63.3 δ C_2 34.0 δ C_3 19.2, δ CH_3 13.9
2	133.0	160.9	37.1	31.8	23.8	15.2	
3	129.1	153.8	37.3	32.4	23.8	15.3	δ OCH_3 52.3
4	134.6	155.2	37.6	32.3	23.9	15.4	δ CH_3 14.9, 14.9, 14.5, δ CH 32.5, δ B–CH 38.5
5	114.3	158.2	37.0	31.8	23.7	15.1	δ C_1 149.6, δ C_2 113.3, δ C_3 123.4
Ethene[d]	122.8	122.8					
1-Hexene	113.4	137.8	33.6	31.3	22.1	13.4	

[a] In parts per million (±0.1) (downfield positive) from Me_4Si, converted using δ_C (C_6D_6) 128.7. [b] The absorption is not obvious, owing to overlap with that of C_6D_6. [c] Using $CDCl_3$ as a solvent with an internal standard of Me_4Si. [d] References 18 and 19.

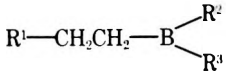
Table II
^{13}C Chemical Shifts for Alkynylboranes (6 and 7)[a]

$R^1{-}C{\equiv}C{-}B(O\text{-}n\text{-}Bu)_2$ 6. $R^1 = H$; 7. $R^1 = n\text{-}Bu$

Borane	Alkynyl δ C_1	δ C_2	δ C_3	δ C_4	δ C_5	δ C_6	Other
6	*b*	91.4					δ OCH_2 64.2, δ C_2 35.1, δ C_3 20.4 δ C_4 15.0
7	*b*	104.9	20.5	32.0	23.2	14.7	δ OCH_2 64.1, δ C_2 35.2, δ C_3 20.5 δ C_4 15.0
Acetylene[c]	70	70					
1-Hexyne[c]	68.6	84.0	18.6	31.1	22.4	14.1	

[a] See footnotes to Table I. [b] The absorption is not obvious, owing to the neighboring boron. [c] Reference 18.

Table III
^{13}C Chemical Shifts for Alkylboranes (8-14)[a]

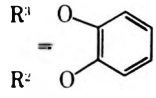


8. $R^1 = H$; $R^2R^3 =$

9. $R^1 = Et$; $R^2R^3 =$

10. $R^1 = n\text{-}Bu$; $R^2 = n\text{-}hexyl$; $R^3 = Cl$

11. $R^1 = n\text{-}Bu$; $R^2 = n\text{-}hexyl$; $R^3 = OCH_3$
12. $R^1 = H$; $R^2 = R^3 = Et$
13. $R^1 = Et$; $R^2 = R^3 = n\text{-}Bu$
14. $R^1 = n\text{-}Bu$:

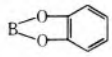


Borane	δ C_1	δ C_2	δ C_3	δ C_4	δ C_5	δ C_6	Other
8	8.6	8.6					δ OCH_2 62.4, δ CH_2 29.0
9	16.4	27.8	26.8	15.1			δ OCH_2 62.5, δ CH_2 29.1
10	30.4	26.0	33.4	33.4	24.1	15.4	
11	21.3	25.5	34.0[b]	33.4[b]	24.1	15.3	δ OCH_3 53.8
12	20.8	9.3					
13	29.8	28.4	27.5	15.3			
14	12.2	25.2	33.4[b]	33.2[b]	24.0	15.3	δ C_1 149.6, δ C_2 113.2, δ C_3 123.3
Ethane[c]	5.9	5.9					
Butane[c]	13.2	25.0	25.0	13.2			
Hexane[c]	13.9	22.9	32.0	32.0	22.9	13.9	

[a] See footnotes to Table I. [b] There is a possibility that the assignments should be interchanged. [c] Reference 18.

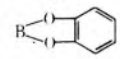
The data presented in Table IV demonstrate the effects of substituent groups on the boron in the alkenyl- and alkynylboron derivatives. The substituent effect ($\Delta\delta$ C_1) at C_1 in the alkynylboranes are unknown, because of disappearance of the α carbon in 6 and 7 (Table II). However, from the data for the alkenyl (5.0 or 0.9 ppm from Table IV) and alkyl (2.7, 3.2, or −1.7 ppm from Table V) derivatives, it appears that the α effect of the boronate group on the triple bond is estimated to be at most ca. 5 ppm, since the α effect of the boronate group is generally slight, as shown in

Table IV
Substituent Effects on ^{13}C Chemical Shifts of Boron-Substituted Alkenes and Alkynes[a]

Substituent	$\Delta\delta C_1$	$\Delta\delta C_2$	$\Delta\delta C_3$
Boron-substituted alkene			
$B(O\text{-}n\text{-}Bu)_2$	5.0	11.3	
$BR'Cl$[b]	19.6	23.1	3.5
$BR'OCH_3$[b]	15.7	16.0	3.7
$B(Sia)_2$[c]	21.2	17.4	4.0
	0.9	20.4	3.4
Boron-substituted alkyne			
$B(O\text{-}n\text{-}Bu)_2$[d]		21.4	
$B(O\text{-}n\text{-}Bu)_2$[e]		20.9	1.9

[a] In parts per million with respect to the corresponding hydrocarbons (ethene, 1-hexene, acetylene, and 1-hexyne). Higher values correspond to lower shielding. [b] R′ = 1-hexenyl. [c] Sia = $CH(CH_3)\text{-}CH(CH_3)_2$. [d] Substituent effect for 6. [e] Substituent effect for 7.

Table V
Substituent Effects on ^{13}C Chemical Shifts of Boron-Substituted Alkanes[a]

Substituent	$\Delta\delta C_1$	$\Delta\delta C_2$	$\Delta\delta C_3$
$B(OR)_2$ (for **8**)	2.7	2.7	
$B(OR)_2$ =			
$B(OR)_2$ (for **9**)	3.2	2.8	1.8
$BR'Cl$[b]	16.5	3.1	1.4
$BR'OCH_3$[b]	7.4	2.6	2.0
BR_2; R = Et	14.9	3.4	
BR_2; R = *n*-Bu	16.6	3.4	2.5
	−1.7	2.3	1.4

[a] In parts per million with respect to the corresponding hydrocarbons (ethane, butane, and hexane). Higher values correspond to lower shielding. [b] R′ = *n*-hexyl.

Tables IV and V, and the difference in α effect between alkenes and alkynes may be not great.[24]

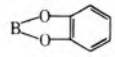
Table V contains data on substituent effects in the alkylboranes, where the effect of BR_2 (R = Et or *n*-Bu) is determined from the shift data (Table III) of triethyl- (**12**) and tributyl- (**13**) boranes. That these data are somewhat, but not essentially, different from the reported values[22] must be due to the differences in experimental conditions.[25]

Comparison of the data in Tables IV and V leads to a conclusion that the α effect ($\Delta\delta$ C_1) in unsaturated boranes show ranges comparable to those in saturated boranes. However, for the β carbons, the substituent effects ($\Delta\delta$ C_2) exhibit a much wider range of shifts than those observed in saturated boranes. The comparisons are summarized in Table VI, being made on the assumption that the following pairs of groups are equivalent: (1) $B(O\text{-}n\text{-}Bu)_2$ and $B(OR)_2$ (see Table V), (2) 1-hexenyl and *n*-hexyl in $BR'Cl$ and $BR'OCH_3$,[26] and (3) $B(Sia)_2$ and $B(n\text{-}Bu)_2$. The difference at C_1 ($\Delta\Delta\delta$ C_1) for acetylene is estimated to be of the same order of magnitude as that for alkene.

Evidently, the substituent effect is more strongly felt at the β positions than at the point of substitution. This clearly indicates that in all cases (1–7) there is some contribution of the mesomeric B–C π-bonding forms shown in eq 1 or 2.[18,19,24]

To roughly estimate the relative contribution of the mesomeric B–C π-bonding form in **2**, we have chosen the isopropyl cation[27] as a model for the C_β carbon in the mesomeric form, where the chemical shift of the central carbon

Table VI
Difference in Substituent Effect between Unsaturated and Saturated Boranes[a]

Substituent	$\Delta\Delta\delta C_1$	$\Delta\Delta\delta C_2$	$\Delta\Delta\delta C_3$
Alkene			
$B(OR)_2$	2.3	8.6	
$BR'Cl$	3.1	20.0	2.1
$BR'OCH_3$	8.3	13.4	1.7
BR_2	4.6	14.0	1.5
	2.6	18.1	2.0
Acetylene			
$B(OR)_2$		19.7(18.1)[b]	0.1[b]

[a] $\Delta\Delta\delta$ C_n = $\Delta\delta$ C_n (alkenyl or alkynylboranes) − $\Delta\delta$ C_n (alkylboranes), where n = 1, 2, and 3, R = alkyl, and R′ = 1-hexenyl and *n*-hexyl, on the assumption 1, 2, 3. [b] The value for 7.

is 319.6 ppm from Me_4Si,[18] and have chosen 2-hexene as a model for the C_β carbon without such π interaction, where the chemical shift of C_3 carbon is 129.8 ppm from Me_4Si.[18] Experimentally the C_β of **2** is deshielded by 160.9 ppm relative to Me_4Si, the relative contribution of the B–C π-bonding form consequently being about 16%.

Conclusion

There is much circumstantial evidence for the B–C π bonding, but there is also an argument that most if not all such data, taken individually, are inconclusive.[3a] The present results clearly indicate a certain degree of B–C π bonding in alkenylboranes. Also the ^{13}C shift data demonstrate for the first time the presence of B–C π bonding in alkynylboranes.

Acknowledgment. Y.Y. wishes to express gratitude to Dr. K. Lee and Mr. M. Doi of the Department of Chemistry, Faculty of Science, Osaka University, for measuring the ^{13}C NMR spectra.

Registry No.—**1**, 6336-45-4; **2**, 55168-90-6; **3**, 55168-91-7; **4**, 55168-92-8; **5**, 56554-20-2; **6**, 24215-39-2; **7**, 56070-64-5; **8**, 56554-21-3; **9**, 30169-71-2; **10**, 18379-62-9; **11**, 2344-22-1; **12**, 97-94-9; **13**, 122-56-5; **14**, 56554-22-4.

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(26) The assumption 2 may be unpardonable. However, the preparation of RCH=CHB(R')Cl (R' = alkyl) is highly difficult. Other assumptions, 1 and 2, are reasonable.
(27) A referee suggests that the comparison to an isopropyl cation is oversimplified. Both electron density and bond order contribute heavily to the paramagnetic term of the ^{13}C screening constant. The downfield shifts of C_2 must be due not only to decreased electron density but also to decreased π bond order.

Nuclear Magnetic Resonance Studies. IV.[1] The Carbon and Phosphorus Nuclear Magnetic Resonance of Phosphine Oxides and Related Compounds

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The ^{13}C and ^{31}P NMR of 16 phosphine oxides and sulfides are examined. Changes in the ^{13}C and ^{31}P NMR of triphenylphosphine oxide, sulfide, and selenide with respect to changes in the P–X bond are discussed. Perturbations on the ^{13}C–^{31}P nuclear spin coupling are examined for this series of compounds and various alkyl-substituted diphenylphosphine oxides. Support is given for the theory of competitive dπ–pπ overlap with the PO bond for phenyl and vinyl substituted phosphine oxides.

Phosphorus, a second row atom, possesses empty d orbitals which may overlap with filled p orbitals on an adjacent atom. Thus the following resonance structures may be considered.

$$\underset{\textbf{1a}}{R_3\overset{+}{P}-\overset{-}{X}} \longleftrightarrow \underset{\textbf{1b}}{R_3P=X}$$
$$X = O, S, Se$$

The formal PX double bond in **1b** is expected to be quite different from a normal pπ–pπ double bond of, for example, a carbonyl group. The d orbitals are diffuse and more directional than 3p orbitals and most of the electron density in a pπ–dπ bond is expected to lie in the vicinity of the X atom.[2] The physical evidence which has been used to imply dπ–pπ overlap in the phosphoryl bond is quite persuasive and includes X-ray fluorescence,[3] basicity data,[4] ^{13}C–H nuclear spin coupling,[5] bond dissociation energies,[2,6] bond lengths,[7] dipole moments,[8] NQR measurements,[4] and photoelectron spectra.[10] This is further corroborated by semiempirical[11] and ab initio[12] molecular orbital calculations. There is less evidence of multiple PX bonding for phosphine sulfides and selenides. The general view, however, seems to be that the P–S (and analogously, P–Se) bond is weaker and there is less π bonding than in the PO bond. Bond dissociation energies,[13] ir force constant calculations,[14] and semiempirical molecular orbital calculations[11] lend support for this notion.

It has been considered that an important consequence of a strong, multiple PX bond is that competitive π bonding from an additional, weaker π donor is diminished (e.g., a vinyl or phenyl group). Various physical techniques, especially ^{19}F NMR, have given support for this notion.[15] Thus, in a vinyl phosphine oxide the dπ–pπ contribution from the PO bond will decrease dπ–pπ bonding from the vinyl group to phosphorus. In vinyl phosphonium salts the ^{13}C and ^{31}P NMR data strongly suggest dπ–pπ overlap between the vinyl group and phosphorus.[16] These differences will be examined in this context.

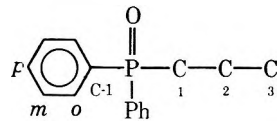
Results and Discussion

The values of the ^{13}C chemical shifts, ^{31}P–^{13}C coupling constants, and ^{31}P chemical shifts are given in Tables I and II. The ^{13}C chemical shifts previously reported[17] for tri-*n*-butylphosphine oxide and sulfide agree with the values reported in Table I. The ^{13}C chemical shifts and couplings reported for triphenylphosphine oxide also agree with those previously reported by Gray.[18] The values of the ^{31}P chemical shift and ^{31}P–^{77}Se coupling agree with those given by Stec and coworkers.[19]

Quin noted[17] that the close proximity of the ^{13}C resonances for carbons 2 and 3 in tri-*n*-butylphosphine oxide and sulfide are difficult to assign and are subject to adjustment. We have reexamined this problem and make our assignments based on spectra determined at two different field strengths. Additionally, in the case of tri-n-butylphosphine oxide, T_1 values were determined by the inversion–recovery technique.[20] The T_1 values for a $CDCl_3$ solution (not degassed) of the four carbons are found to be 1.2, 1.7, 2.4, and 3.0 ± 0.6 sec, respectively, for carbons 1–4. This is the normal sequence for saturated alkyl chains.[21] Moreover, the closely spaced inner lines of the four-line pattern due to C-2 and C-3 in tri-*n*-butylphosphine oxide were readily assigned by careful adjustment of the delay time in the inversion–recovery sequence so that the two low-field lines due to C-3 where inverted while the two high-field lines were upright.[22] On this basis the assignments given by Quin[17] were confirmed, but a value of $^2J_{P-C} = 3.9 \pm 0.1$ Hz was found instead of the reported $^2J_{P-C} = 5$ Hz.

The ^{31}P chemical shift of triphenylphosphine sulfide (**3**) is deshielded by 13.9 ppm from triphenylphosphine oxide (**2**). This is consistent with an expected smaller contribution of resonance structure **1b** for the sulfide. Likewise, the ^{31}P resonance of **2** is shielded by 27.9 ppm from its phosphonium salt analog **16**, while the ^{31}P resonance of **3** is virtually unaffected upon protonation to 17.[23] However, in triphenylphosphine selenide (**4**), the ^{31}P chemical shift is deshielded by only 6.5 ppm from the oxide **2** and is shielded by 7.4 ppm with respect to the sulfide **3**. This irregularity in the ^{31}P chemical shift of the selenide is not in accord with the expected changes in the P–Se bond as compared to the P–S and P–O bonds. For example, an ir force constant study gave the strengths of the P–X bond, and hence the order of contribution of resonance structure **1b**, as P–O > P–S ≫ P–Se.[25] Therefore, a straightforward interpreta-

Table I
Carbon and Phosphorus Chemical Shifts[a]



Compd	Registry no.	Compd no.	Carbon, ppm 1	2	3	4	C-1	o	m	p	^{31}P, ppm
$Ph_3P{=}O$	791-28-6	2					132.8	132.1	128.5	131.8	29.3
$Ph_3P{=}S$	3878-45-3	3					133.0	132.2	128.5	131.5	43.2
$Ph_3P{=}Se$	3878-44-2	4					131.9	132.7	128.5	131.5	35.8
$Ph_2P(=O)Me$	2129-89-7	5	16.5				134.3	130.4	128.5	131.6	28.7
$PhP(=O)Me_2$	10311-08-7	6	18.0				135.0	129.6	128.6	131.5	32.5
$Me_3P{=}O$	676-96-0	7	18.6[b]								41.0[d]
$Ph_2P(=O)$—Et	1733-57-9	8	22.7	5.5			133.1	130.8	128.6	131.6	32.8
$Ph_2P(=O)$-*i*-Pr	2959-75-3	9	26.9	15.2			132.4	130.8	128.5	131.4	36.2
$Ph_2P(=O)$-*t*-Bu	56598-35-7	10	33.8	25.1			131.3	132.0	128.2	131.3	38.8
$PhP(=O)Cl_2$	824-72-6	11					134.2	130.1	129.7	134.7	34.9
$(n\text{-}Bu)_3P{=}O$	814-29-9	12	27.9	23.9	24.3	13.7					46.9
$(n\text{-}Bu)_3P{=}S$	3084-50-2	13	30.8	24.5	23.9	13.6					48.1
$Ph_2P(=O)$—$CH{=}CH_2$	2096-78-8	14	131.3	134.4			132.4	131.1	128.5	131.8	22.4
$Ph_2P(=O)$—$C{\equiv}CH$[c]	6104-48-9	15	77.9	95.3							
$Ph_3\overset{+}{P}$—OH HSO_4^-	56648-89-6 56598-36-8	16					120.0	131.1	129.0	132.8	57.2
$Ph_3\overset{+}{P}$—SH HSO_4^-	56598-38-0 56598-39-1	17					119.3	132.6	129.8	135.2	42.6
$Ph_3\overset{+}{P}$—$CH{=}CH_2$ Br^-	5044-520	18	119.2	145.2			117.2	133.9	130.7	135.5	19.3
$Ph_2\overset{+}{P}(Me)(CH{=}CH_2)$ I^- (Me = 3, $CH{=}CH_2$ = 1, 2)	56598-40-4	19	119.3	143.7	9.9		118.1	132.9	130.2	135.0	17.3

[a] All compounds were run in $CDCl_3$ solution and are referenced with respect to Me_4Si in the carbon NMR. The ^{31}P NMR are referenced with respect to external 85% H_3PO_4 with resonances deshielded from H_3PO_4 being reported as positive values. Compounds 16 and 17 were run in 3:1 concentrated sulfuric acid-glacial acetic acid solutions using external Me_2SO-d_6 as a deuterium lock and Me_4Si as the reference. [b] Values taken from G. A. Gray and S. E. Cremer, *J. Org. Chem.*, 37, 3458 (1972). [c] Values taken from R. M. Lequan, M. J. Pouet, and M. P. Simonnin, *J. Chem. Soc., Chem. Commun.*, 475 (1974). [d] Value taken from H. Schmidbauer, W. Buchner, and D. Scheutzow, *Chem. Ber.*, 106, 1251 (1973).

tion of the ^{31}P chemical shifts of these compounds is not possible at this time.

The two phosphonium salts of triphenylphosphine oxide and sulfide (16 and 17) exhibit C-1 phenyl carbon resonances that are shielded by 15.6 and 14.7 ppm, respectively, from their precursors, 2 and 3. A similar effect has been noted for the C-1 phenyl carbons in P–C and P–N ylides with respect to their phosphonium salts.[1] In addition, the carbon α to the carbon or nitrogen bearing the formal negative charge in these compounds is also deshielded, compared to their phosphonium salts.[1] A similar situation occurs with carbons α to a sulfoxide group.[26] The anisotropy of the sulfoxide group has been studied by ^1H NMR;[27] however, anisotropy is expected to contribute no more than 4–5 ppm to the ^{13}C chemical shift.[28] It is possible that these shifts may be due in part to an electric field effect, since the PX bond is polar.[29] However, the important fact is that this effect is always observed in compounds capable of resonance interactions such as 1a and 1b.

In Table II, it is seen that $^1J_{P\text{-}C}$ for the C-1 phenyl carbons decreases regularly in the order 2 > 3 > 4. The corresponding couplings in the phosphonium salts 16 and 17 are also larger than those in the respective parent compounds, 2 and 3. This is consistent with the idea that the electronegativity of the X substituent determines, in part, the magnitude of P–C coupling to the C-1 phenyl carbon. The alkyl carbon 1 couplings of tri-*n*-butylphosphine oxide and sulfide (12 and 13) also follow this trend. Furthermore, replacement of two phenyl groups with electronegative chlorine atoms in phenylphosphoryl chloride (11) dramatically increases the C-1 phenyl coupling to 158.7 Hz. This phenomenon has been found to be a common feature in the one-bonded P–C couplings in phosphonium salts.[16]

Various studies[3b,30] have revealed that phosphorus becomes more positively charged and, hence, more electronegative when methyl or other alkyl groups are replaced by phenyl groups. In Table I and the ^{13}C chemical shifts of the methyl carbons in going from methyl diphenylphosphine oxide (5) to dimethyl phenylphosphine oxide (6) and trimethylphosphine (7) are increasingly deshielded. Furthermore, these methyl carbons are all deshielded with respect to a methyl carbon directly bonded to a phosphonium group (e.g., carbon 3 in 19). If one assumes the argument that increased charge withdrawal by α substituents results in deshielding the ^{13}C chemical shifts, then the shifts of the methyl carbons in this series are not in accord with changes of the charge on phosphorus. Effects, other than electronic in origin, as discussed previously, and steric factors may be

Table II
^{13}C-^{31}P Coupling Constants[a]

Compd	No.	Carbon, Hz 1	2	3	4	C-1	o	m	p
$Ph_3P{=}O$	2					103.5	9.8	17.7	2.4
$Ph_3P{=}S$	3					85.0	10.6	12.7	2.8
$Ph_3P{=}Se$	4		(J_{P-Se} = 732.4)			70.8	9.8	12.2	3.7
$Ph_2P(=O)$—Me	5	73.5	(J_{C-H} = 127.4)			100.9	9.7	11.8	2.8
$PhP(=O)Me_2$	6	70.8	(J_{C-H} = 128.0)			98.0	9.6	11.6	2.8
$Me_3P{=}O$	7	68.3[b]	(J_{C-H} = 129)[c]						
$Ph_2P(=O)Et$	8	73.0	4.7			98.4	9.0	11.5	2.7
$Ph_2P(=O)$-*i*-Pr	9	72.8	2.7			94.3	8.5	11.3	2.7
$Ph_2P(=O)$-*t*-Bu	10	70.8	*			89.9	8.1	10.8	2.6
$PhP(=O)Cl_2$	11					158.7	13.8	18.4	3.8
$(n\text{-}Bu)_3P{=}O$	12	65.1	3.9	13.9	*				
$(n\text{-}Bu)_3P{=}S$	13	50.5	3.8	15.4	*				
$Ph_2P(=O)$—$CH{=}CH_2$	14	97.8	*			104.6	10.0	12.0	2.9
$Ph_2P(=O)$—$C{\equiv}CH$[b]	15	164.6	29						
$Ph_3\overset{+}{P}$—OH HSO_4^-	16					107.4	9.8	12.2	*
$Ph_3\overset{+}{P}$—SH HSO_4^-	17					85.4	11.0	14.6	*
$Ph_3\overset{+}{P}$—$CH{=}CH_2$ Br^-	18	80.3	*			90.3	10.5	12.9	3.2
$Ph_2\overset{+}{P}(Me)(CH{=}CH_2)$ I^- (3; 1 2)	19	80.6	*	56.2		89.4	11.2	12.7	*

[a] The numbering system used is the same as in Table I. The digital resolution was ±0.1 Hz, except for compounds 16 and 17, where the high viscosity of the solution prohibited resolution beyond ±2.4 Hz. The digital resolution used in the determination of the C-H coupling was ±0.6 Hz. An asterisk indicates unresolved coupling. [b] Values taken from references listed in Table I. [c] Value taken from P. Haake, W. B. Miller, and D. A. Tyssee, *J. Am. Chem. Soc.*, 86, 3577 (1964).

operative in this case. The same situation is also present for the C-1 phenyl chemical shifts.

The phosphorus–methyl carbon couplings decrease regularly in **5**, **6**, and **7**; also, the P–C couplings to the C-1 phenyl carbons decrease in the order **2** > **5** > **6**. It might be argued that changes in the effective nuclear charge on phosphorus are consistent with this trend, if the nuclear charge on **2** is greater than on **7**. However, the C–H couplings of the methyl groups in **5**, **6**, and **7** are nearly identical. In **4** the C–H coupling has been reported to be 129 Hz.[30] We have found the C–H coupling for the methyl groups in **5** and **6** to be 127.4 and 128.0 ± 0.6 Hz, respectively, whereas the C–H coupling for the tetramethylphosphonium salt has been given as 134 Hz.[30] If the C–H coupling can be taken as a reflection of the electronegativity of the substituent on the methyl group,[28] then our data suggest than there is little change in the amount of positive charge on phosphorus for **2**, **5**, **6**, and **7**. There may be changes in bond lengths and/or bond angles as the number of phenyl groups around phosphorus is increased, so that it is not possible at this time to effect a quantitative separation of the factors responsible for the changes of J_{P-C} in this series of compounds.

The replacement of hydrogen atoms with methyl groups in going from methyl to *tert*-butyldiphenylphosphine oxide (compounds **5**, **8**, **9**, and **10**) causes a decrease in the P–C coupling to the carbon 1 of the alkyl group concomitantly with a decrease in the coupling to the C-1 phenyl carbon. This effect has also been found for an analogous series of alkyl-substituted triphenylphosphonium salts.[16] The reduction of $^1J_{PC}$ for the alkyl carbon 1 in **10** compared to **5** is consistent with the notion that the C–C–C bond angles in **10** increase as a result of nonbonded interactions between the methyl C–H bonds. Therefore, the percent s character in the central carbon hybrid orbitals comprising the C–C (or C–H) bonds must increase in **10** compared to **5** at the expense of decreasing the percent s character of the carbon hybrid making up the P–C bond. Alternatively, the P–C bond distance may increase in **10** compared to **5** as a result of steric interactions between the methyl and phenyl groups. Both rationales lead to the same conclusion, namely, a decrease in the $^1J_{P-C}$ coupling for the alkyl carbon in **10** compared to **5**. Similarly, as the percent s character of the carbon hybrid comprising the P–C bond decreases or as the P–C bond length increases, the electronegativity of this substituent decreases[31] causing the $^1J_{P-C}$ for the C-1 phenyl carbon to decrease.

In Figure 1 the ^{31}P chemical shifts of a series of alkyl-substituted diphenylphosphine oxides [$Ph_2P(O)R$] are plotted against the ^{13}C chemical shifts of the methyl carbons in an analogous series of alkanes (Me–R). Similar relationships have been found for the ^{31}P chemical shifts in alkyl-substituted phosphonium salts[16] and ^{15}N chemical shifts in aliphatic amines.[32] This has been assumed to mean that the same factors influencing ^{13}C chemical shifts are also present in the ^{31}P and ^{15}N chemical shifts for these two series of compounds. In the present case this relationship also implies that there is little change in the nature of the PO bond among the alkyldiphenylphosphine oxides.

In Figure 1 it is apparent that triphenylphosphine oxide (**2**) and vinyldiphenylphosphine oxide (**14**) are shielded by 6.7 and 11.6 ppm, respectively, from what would be expected if the relationship between ^{13}C and ^{31}P chemical shifts was linear. The transfer of charge from a π donor onto phosphorus, presumably via d orbitals, has previously been shown to cause the ^{31}P resonance to become more

shielded.[16,33] This factor may contribute in the present case. However, inspection of the ^{13}C chemical shifts for carbon 2 in **14** and **18** reveals that the β vinyl carbon for the phosphine oxide **14** is shielded by 10.8 ppm from the β vinyl carbon of the phosphonium salt **18**. Likewise, replacement of the methyl group in methylvinyldiphenylphosphonium iodide (**19**) with an oxygen atom (**14**) results in the β vinyl carbon becoming shielded by 9.3 ppm. The para phenyl carbons of the phosphine oxides in Table I are also shielded in comparison to their phosphonium salt analogs[16,18] (compounds **18** and **19** are typical examples). If the ^{13}C chemical shifts for these vinyl carbons are taken as being at least in part exemplary of the differences in the electronic distribution for these carbons, then a model can be proposed for these phosphine oxides, in which there is diminished interaction between the vinyl or phenyl groups and phosphorus. Thus, this model is consistent with competitive $d\pi$–$p\pi$ overlap as developed by other physical methods and discussed in the introduction. Carbon 2 for ethynyldiphenylphosphine oxide (**15**) is also shielded compared to its phosphonium salt analog.[16] The fact that carbon 1 for the vinyl and ethynyl carbons in **14** and **15** are deshielded with respect to most substituted ethylenes and acetylenes[28] is taken to be a consequence of the previously noted effect of carbons α to the PO bond. Therefore, the shielding of the ^{31}P resonances for **2** and **14** in Figure 1 are

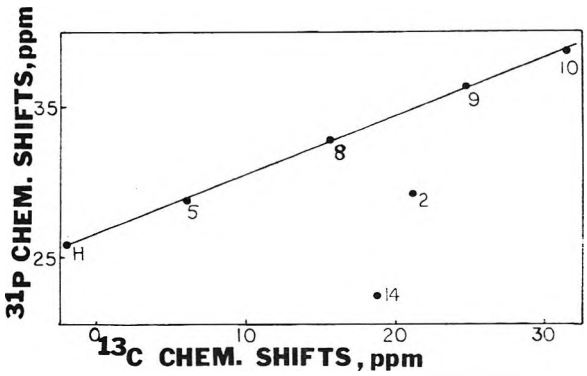


Figure 1. Comparison of the ^{31}P chemical shifts of $Ph_2P(O)R$ vs. the ^{13}C chemical shifts of **Me**–R. The numbers refer to compounds listed in Table I. The point labeled H refers to R = H; the ^{31}P chemical shift was taken from ref 34. The correlation coefficient for this data was 0.9996, not including **2** and **14**.

probably not simply a result of $d\pi$–$p\pi$ interactions between the vinyl and phenyl groups and phosphorus. Another factor of importance is that these two groups are more electronegative than an alkyl group[31] and, therefore, the contraction of the d orbitals on phosphorus is facilitated along with increased $d\pi$–$p\pi$ overlap between the oxygen atom and phosphorus.[2] Thus, a portion of the shielding of the ^{31}P resonance for **2** and **14** can be ascribed to increased multiple bonding in the PO fragment.

In Table II $^1J_{PC}$ for carbon 1 of the substituent increases from 73.0 Hz for **8** to 97.8 and 164.6 Hz for **14** and **15**, respectively. This phenomenon has also been observed for phosphonium salts[16] and phosphonates.[34] This is probably a reflection of increased s character of the substituent (assuming the Fermi contact term to be dominant). It also should be noted that the coupling of phosphorus to the C-1 phenyl carbon is larger in vinyldiphenylphosphine and triphenylphosphine oxides (**14** and **2**) compared to any of the other alkyldiphenylphosphine oxides, which is consistent with the notion previously developed for the dependence of $^1J_{PC}$ for the C-1 phenyl carbon and the electronegativity of the other substituents.

Conclusions

A unified description of the factors influencing ^{13}C, ^{31}P, and P–C couplings for the phosphine oxides is likely to be quite complex. Part of the difficulty is by a lack of quantitative information on how the PO (or PS) bond is perturbed upon changing the other substituents around phosphorus. Reliable theoretical techniques may shed light on this situation. It does appear that the changes of the ^{13}C chemical shifts for phosphine oxides are compatible with competitive $d\pi$–$p\pi$ overlap. Electronegative and steric effects are reflected in the P–C couplings. It should be possible to relate the factors responsible for ^{31}P chemical shifts of alkyl-substituted phosphine oxides to the ^{13}C chemical shifts of analogs. Finally, the data presented here for replacement of alkyl with phenyl groups in the phosphine oxides cast doubt on the interpretation by others that the phosphorus is becoming more positively charged. It appears that the situation is much more complex. Other physical information, such as the energy of the PO bond for this series, would be most useful.

Experimental Section

The spectra were obtained on a Bruker HFX-90 spectrometer equipped for Fourier transform pulsed NMR with a Nicolet 1085 data system as previously described.[16] The ^{31}P and ^{13}C data were taken at operating frequencies of 36.43 and 22.63 MHz, respectively. ^{13}C NMR data were also obtained for **12** and **13** on a Varian CFT-20 at 20.0 MHz. The ^{31}P chemical shifts are reported as referenced to external 85% H_3PO_4 with resonances deshielded from the reference being reported as positive. The ^{13}C chemical shifts are reported with respect to internal Me_4Si. All samples were run as 0.25–0.50 *M* solutions of $CDCl_3$, except as noted in Table I, with broad band ^1H decoupling. Spectral assignments were made with comparisons of the ^{13}C chemical shifts and the magnitudes of P–C coupling constants to previously reported compounds.[16-18] The phosphine oxides and sulfides were prepared by standard methods[35] and triphenylphosphine selenide was purchased from Aldrich Chemicals. *tert*-Butyldiphenylphosphine oxide (**10**) was prepared by heating 5.0 g (0.0112 mol) of *tert*-butyltriphenylphosphonium iodide[36] at 80°C with 100 ml of 20% NaOH–H_2O solution overnight. The mixture was extracted with chloroform and dried over anhydrous magnesium sulfate. Recrystallization gave 2.3 g (80% yield) of **10**: mp 131–132°C; ^1H NMR δ 1.2 (d,[2] J_{P-H} = 15.0 Hz, 9 H), 7.25–8.3 (m, 10 H). An exact mass determination by mass spectrometry gave mass 258.11734 (calcd, 258.11599).

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Thallium in Organic Synthesis. XXXIX. A Convenient Synthesis of Nitroaryl Iodides[1,2]

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A method is described for the conversion of aromatic substrates to nitroaryl iodides by (1) thallation with thallium(III) trifluoroacetate (TTFA) in trifluoroacetic acid (TFA), (2) nitration of the isolated arylthallium ditrifluoroacetate with acetyl nitrate, and (3) treatment of the resulting nitroarylthallium intermediate with iodine in chloroform. Nitration occurs meta to the thallium substituent, and iodine enters the ring at the position formerly occupied by thallium.

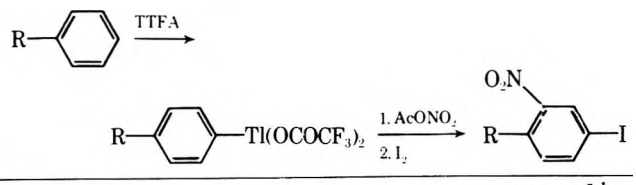
The classic route to nitroaryl iodides from aromatic substrates comprises a sequence of reactions involving nitration or dinitration, selective reduction of one of the nitro groups to an amine, diazotization, and subsequent replacement of the diazonium group with iodine utilizing potassium iodide.[3] Alternatively, nitroarenes can be iodinated with molecular iodine in various media.[4-6] The drawbacks of the former approach are the multiple reaction steps required and the frequently observed iodine atom migration which occurs under acidic conditions;[7] a disadvantage of the latter synthesis is the occasional occurrence of polyiodination when 20% oleum–iodine is employed.[4]

We describe a facile conversion of aromatic substrates to nitroaryl iodides via arylthallium ditrifluoroacetates. The appropriate arene is first thallated with thallium(III) trifluoroacetate (TTFA) in trifluoroacetic acid (TFA).[8] The *isolated* arylthallium ditrifluoroacetate is then nitrated with acetyl nitrate[9] (conveniently generated in situ by adding 70% nitric acid to an excess of acetic anhydride) in the presence of concentrated sulfuric acid, and the intermediate nitroarylthallium derivative is then refluxed with molecular iodine in chloroform. In the resulting nitroaryl iodide, the iodine atom enters the ring at the position formerly occupied by thallium; i.e., the position which is generally most reactive to electrophilic substitution. The nitro substituent is almost invariably meta to the iodine atom. Since nitration and iodination of the arylthallium ditrifluoroacetate can be achieved without isolation of the intermediate nitroarylthallium species, this overall procedure constitutes a two-step synthesis of nitroaryl iodides from arenes. Furthermore, the requisite arylthallium ditrifluoroacetate intermediates are readily prepared from the precursor arenes utilizing TTFA in TFA,[8] and are stable, crystalline solids which can be kept indefinitely.

Representative yields of nitroaryl iodides prepared by this technique are listed in Table I.

Varying amounts of sulfuric acid were employed to promote the nitration of the above arylthallium ditrifluoroacetates, the amount of sulfuric acid being determined by the reactivity of the latter intermediates to electrophilic substitution.[9] Arylthallium ditrifluoroacetates substituted with electron-withdrawing groups are not nitrated satisfactorily under the above conditions. For example, 4-chlorophenylthallium ditrifluoroacetate gives only very small amounts of ring nitration with acetyl nitrate, even in the presence of a large excess of concentrated sulfuric acid.[15]

Table I
Synthesis of Nitroaryl Iodides



Starting material	Product	Yield, %[a,b]
Benzene	3-Nitroiodobenzene	87[c]
Toluene	2-Nitro-4-iodotoluene	90[d]
Ethylbenzene	2-Nitro-4-iodoethylbenzene	92
Mesitylene	Nitroiodomesitylene	94[e]
Anisole	2-Nitro-4-iodoanisole	98[f]
m-Xylene	4-Nitro-6-iodo-*m*-xylene	99[g]
Biphenyl	4-Nitro-4′-iodobiphenyl	55[h]
	2-Nitro-4′-iodobiphenyl	45

[a] Yields were determined by GLC analysis of the crude product and are based on the weight of isolated arylthallium ditrifluoroacetate. [b] In some cases, it was possible to isolate the major isomer by simple crystallization of the crude product from ethanol. [c] Contains 14% 2-nitroiodobenzene and 5% nitrobenzene. [d] Contains 5% 2-iodo-4-nitrotoluene, 3% 2-nitro-6-iodotoluene, 1% 2-nitrotoluene, 1% 4-nitrotoluene, and 2% of an unidentified material. [e] Contains 5% dinitromesitylene. [f] Contains 8% 2-iodo-4-nitroanisole. [g] Contains 27% 2-nitro-4-iodo-*m*-xylene. [h] Contains 3% 4-nitrobiphenyl.

It seems probable that the actual substrate undergoing nitration may, at least in some instances, be the corresponding diarylthallium trifluoroacetate, formed in situ by "disproportionation" of the initial arylthallium ditrifluoroacetate.[16] For example, treatment of phenylthallium ditrifluoroacetate with acetyl nitrate in the absence of concentrated sulfuric acid led to the formation of small amounts of diphenylthallium trifluoroacetate. In a subsequent experiment, it could be shown that this latter compound was readily converted with acetyl nitrate and sulfuric acid (followed by iodine) to the same mixture of nitroaryl iodides obtained from phenylthallium ditrifluoroacetate itself. Furthermore, di-2-tolylthallium trifluoroacetate under the same conditions gave (in 99% yield) a mixture of nitroiodotoluenes consisting of 2-iodo-4-nitrotoluene (61%) and 2-nitro-6-iodotoluene (39%). Since, however, we have been able to show in an independent study that diarylthallium trifluoroacetates appear to undergo all of the thallium displacement reactions exhibited by arylthallium ditrifluoroacetates[17] (again with the new substituent entering the ring at the position previously occupied by thallium), such in situ disproportionation under the above nitration conditions is of no practical concern.

The formation of 2-nitroiodobenzene (see footnote *c*, Table I) from phenylthallium ditrifluoroacetate or diphenylthallium trifluoroacetate under the above conditions is unexpected, but consistent with the well-documented ability of the electron-deficient thallium(III) atom to complex with Lewis bases.[18,19] Thus complexation of thallium (and mercury)[20] electrophiles by electron-rich substituents on aromatic rings, which is followed by intramolecular delivery of the electrophile to the ortho position, is thoroughly documented. It would thus appear that the above ortho nitration probably arises by complexation of thallium with acetyl nitrate. It is interesting to note that attempted thallation of nitrobenzene with TTFA in refluxing TFA, although only 15% complete after 7 days, resulted in significant thallation ortho to the nitro group (41% of the total thallation which occurred; see Experimental Section). Once again, this high percentage of ortho thallation is undoubtedly due to complexation of TTFA by the substituent nitro group, followed by intramolecular delivery of the thallium electrophile. It is significant that no para thallation was observed.

Experimental Section[21]

General Procedure for Nitration–Iodination of Arylthallium Ditrifluoroacetates. The general procedure is illustrated below with 2,4-dimethylphenylthallium ditrifluoroacetate.

Acetic anhydride (25 ml) was placed in a 100-ml round-bottomed flask immersed in an ice bath, and stirred until the temperature had fallen to 15°. Nitric acid (70%) was then added cautiously until the temperature of the stirred solution rose to approximately 20°.[22] During the nitric acid addition, the temperature must be maintained between 15 and 20°. After the requisite amount (3.60 g, 0.04 mol) had been added, the temperature of the reaction mixture was allowed to fall to 2°, and 0.50 g of concentrated sulfuric acid was carefully added while maintaining the temperature below 10°. When the temperature had again fallen to 2°, 5.35 g (0.01 mol) of 2,4-dimethylphenylthallium ditrifluoroacetate was added rapidly, and the stirred reaction mixture was allowed to warm to room temperature. After 2.5 hr, the reaction mixture was cooled, and ice was added to destroy any unreacted acetyl nitrate. Distilled water (25 ml) was then added cautiously, and the reaction mixture was then transferred to a 500-ml round-bottomed flask. The pH was adjusted to 6 with 6 *M* aqueous sodium hydroxide while maintaining the temperature below 35°, and 4.00 g (0.0157 mol) of iodine in 80 ml of chloroform was added. The two-phase reaction mixture was then stirred under reflux for 12 hr, cooled, and 10.0 g (0.052 mol) of sodium metabisulfite added. Thallium(I) iodide was then removed by filtration through Celite, and the chloroform layer in the filtrate was separated, extracted with distilled water, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. The residual oil (2.81 g) consisted of 2.75 g (99%) of two isomeric nitroiodo-*m*-xylenes (GLC analysis), each of which was isolated by preparative gas chromatography. 4-Iodo-6-nitro-*m*-xylene (73%): mp 84–86° (lit.[23] mp 87°); NMR δ 2.43 (3, s), 2.52 (3, s), 7.23 (1, $J \simeq 0$ Hz), and 8.43 (1, $J \simeq 0$ Hz). 2-Nitro-4-iodo-*m*-xylene (27%): mp 68–70°; NMR δ 2.24 (3, s), 2.39 (3, s), 6.87 (1, d, $J = 8$ Hz), and 7.85 (1, d, $J = 8$ Hz).

Anal. Calcd for $C_8H_8INO_2$: C, 34.68; H, 2.91; N, 5.06. Found: C, 34.92; H, 3.02; N, 4.74.

Evidence for Disproportionation of Phenylthallium Ditrifluoroacetate in Acetic Anhydride–70% Nitric Acid. Acetyl nitrate was prepared from 3.60 g (0.04 mol) of 70% nitric acid and 25 ml of acetic anhydride as described above. Phenylthallium ditrifluoroacetate (5.07 g, 0.01 mol) was then rapidly added, and the stirred solution was maintained for 12 hr at room temperature. After destruction of unreacted acetyl nitrate and adjustment of the pH to 8 with 6 *M* aqueous sodium hydroxide, the ivory-colored solid which had separated was collected by filtration, washed with distilled water, and dried, yield, 2.88 g. A suspension of 0.5 g of this material was suspended in 5 ml of distilled water and 5 ml of TFA, stirred for 15 min at room temperature, diluted with 10 ml of distilled water, and filtered to give 0.15 g of diphenylthallium trifluoroacetate, mp 265–270°. This material was identical with an authentic sample of diphenylthallium trifluoroacetate.[16]

Nitration–Iodination of Di-2-tolylthallium Trifluoroacetate. Preparation of 2-Iodo-4-nitrotoluene and 2-Nitro-6-iodotoluene. The general procedure detailed above for nitration–iodination was employed for di-2-tolylthallium trifluoroacetate (1.25 g, 0.0025 mol), the amounts of the various reagents (acetic anhydride, iodine, etc.) being proportionally reduced. The weight of concentrated sulfuric acid employed was 0.38 g, and the stirred nitration mixture was kept at room temperature for 2.5 hr before proceeding with the iodination step (vide supra). Upon completion of the iodination, an oil (1.37 g) was obtained which was shown by GLC to contain two nitroiodotoluenes (1.31 g, 99%). These were isolated from the GLC column to give 2-iodo-4-nitrotoluene (61%), mp 50–52° (lit.[24] mp 54°), and 2-nitro-6-iodotoluene (39%), mp 34–35° (lit.[25] mp 34–36°).

Thallation of Nitrobenzene. A solution of 4.07 g (0.033 mol) of nitrobenzene in 25 ml of a 0.88 *M* TTFA–TFA solution (0.022 mol) was heated under reflux for 7 days. TFA was then removed by distillation under reduced pressure, and a solution of 7.80 g (0.03 mol) of iodine in 30 ml of chloroform was added to the residual red syrup. The resulting mixture was heated under reflux for 4 hr and cooled, and a solution of 10.0 g (0.052 mol) of sodium metabisulfite in 20 ml of distilled water was added. After 15 min of vigorous stirring, the precipitated thallium(I) iodide was removed by filtration

through Celite and the chloroform layer in the filtrate was extracted with distilled water, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure to give 4.18 g of an orange liquid. GLC analysis indicated the formation (15%) of a mixture of nitroiodobenzenes, consisting of 41% of 2-nitroiodobenzene and 59% of 3-nitroiodobenzene (GLC and ir analysis, and comparison with authentic samples). No 4-nitroiodobenzene could be detected.

4-Biphenylthallium Ditrifluoroacetate. A solution of 3.73 g (0.024 mol) of biphenyl in 25 ml of an 0.88 *M* TTFA–TFA solution (0.022 mol) was stirred at room temperature for 13 hr, the TFA was removed by evaporation under reduced pressure, and the residual gray solid was dissolved in a minimal amount of diethyl ether–1,2-dichloroethane (1:1). These solvents were then evaporated under reduced pressure, and the procedure was repeated once again. The residual gray solid was then suspended in 50 ml of 1,2-dichloroethane, cooled to 0°, and filtered to give 4.90 g (38%) of 4-biphenylthallium ditrifluoroacetate, mp 210–220° dec. Treatment of this intermediate with aqueous potassium iodide as previously described[8] gave 0.48 g (99%) of 4-iodobiphenyl, mp 109–112° (lit. mp 113°),[26] pure by GLC analysis. Thus, thallation had occurred only in the para position of biphenyl.

4-Biphenylthallium ditrifluoroacetate could be obtained as a white solid, mp 228–231° dec, by recrystallization from 1,2-dichloroethane.

Anal. Calcd for $C_{16}H_9F_6O_4Tl$: C, 32.93; H, 1.55. Found: C, 32.90, H, 1.90.

Registry No.—Benzene, 71-43-2; toluene, 108-88-3; ethylbenzene, 100-41-4; mesitylene, 108-67-8; aniscle, 100-66-3; *m*-xylene, 108-38-3; biphenyl, 92-52-4; TTFA, 23586-53-0; $AcONO_2$, 591-09-3; I_2, 7553-56-2; 2,4-dimethylphenylthallium ditrifluoroacetate, 34202-98-7; 4-iodo-6-nitro-*m*-xylene, 4102-38-9; 2-nitro-4-iodo-*m*-xylene, 56404-21-8; phenylthallium ditrifluoroacetate, 23586-54-1; di-2-tolylthallium, trifluoroacetate, 27675-18-9; nitrobenzene, 98-95-3; 4-biphenylthallium ditrifluoroacetate. 55341-42-9.

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Notes

Cyclopropylmethyl Dihydrogen Phosphate. Preparation and Use in the Phosphorylation of Nucleosides

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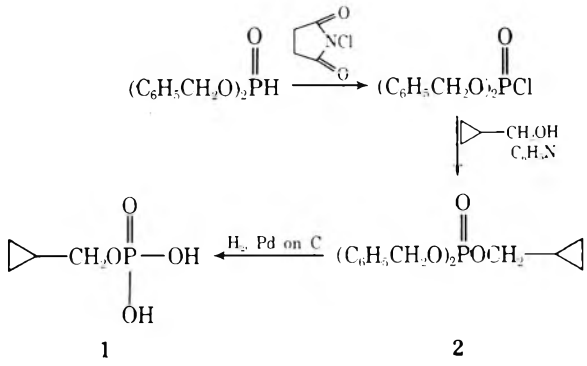
Many methods have been developed for phosphorylating nucleosides. The main types are condensations brought about by dialkylcarbodiimides and direct use of phosphorus oxychloride or its suitably activated derivatives, such as the phosphorochloridates.[1] The direct use of phosphorus oxychloride in trialkyl phosphate solvent has been shown to yield nucleotides in good yield.[2] A widely used method[3] is that of Tener,[4] who effected phosphorylation of blocked nucleosides with hydracrylonitrile dihydrogen phosphate and dicyclohexylcarbodiimide (DCC) in dry pyridine. The present study offers a convenient alternative to the latter procedure.

Acyclic organophosphodiesters generally undergo hydrolysis and other displacement reactions more slowly than phosphomonoesters and triesters containing similar substituents.[5-7] This behavior is particularly important when considering synthetic routes to nucleotides involving hydrolytic cleavage of ester blocking groups.[8,9] Simple alkyl and aryl substituted phosphorylating agents are rarely used in nucleotide preparations.[10] Even *p*-nitrophenyl nucleotide diesters require strong alkaline hydrolysis to remove the blocking group.[11] A notable advance was made by introduction of the 2-cyanoethyl blocking group[12] and its application to nucleotide syntheses.[4] The 2-cyanoethyl group is very sensitive to alkaline treatment, with 2-cyanoethyl phosphodiesters being more labile than hydracrylonitrile dihydrogen phosphate.

The cyclopropylmethyl blocking group has been employed in the synthesis of phosphomonoesters and nucleotides.[13] Facile hydrolytic removal of the cyclopropylmethyl group from phosphate esters was anticipated, similar to the rapid solvolyses of cyclopropylmethyl benzenesulfonate[14,15] and chloromethylcyclopropane.[16] Bis(cyclopropylmethyl) phosphorochloridate has been used to prepare bis(cyclopropylmethyl) nucleoside phosphates.[13] However, conditions necessary for hydrolysis of both blocking groups to give nucleotides produced considerable glycosidic cleavage. Rearrangement to less reactive cyclobutyl esters was shown to interfere with facile hydrolysis.[13] Therefore, attention was focused on Tener's method, but utilizing the cyclopropylmethyl blocking group instead of the 2-cyanoethyl group.

In this study phosphorylations of blocked nucleosides with cyclopropylmethyl dihydrogen phosphate (1) were carried out in a manner similar to those involving hydracrylonitrile dihydrogen phosphate. Preparation of 1 according to the methods used for hydracrylonitrile dihydrogen phosphate appeared unattractive, however, owing to the aqueous work-ups required.[4] Phosphomonoesters have been prepared directly from an alcohol, orthophosphate, and DCC.[4,17,18] However, the monoesters initially formed underwent further reaction with DCC and gave diesters.[17] The route chosen for the preparation of 1 is shown below.



1 2

Commercial dibenzyl phosphonate was converted with *N*-chlorosuccinimide[19] to bis(benzyl) phosphorochloridate and the product esterified with cyclopropanemethanol, which provided dibenzyl cyclopropylmethyl phosphate (2). Catalytic hydrogenolysis of 2 using 10% palladium on charcoal in ethyl acetate or ethanol, followed by filtration and treatment with pyridine, yielded the pyridinium salt of 1. Addition of gaseous ammonia to a solution of 1 in ethyl acetate gave the crystalline ammonium salt of 1. Since 1 decomposed slowly at room temperature, it was best prepared just before it was to be used in a phosphorylation reaction. Also, it was best converted to the pyridinium salt immediately after the hydrogenolysis reaction.

As illustrations of the use of 1 in nucleotide syntheses, 2′,3′-*O*-isopropylideneuridine, 2′,3′-*O*-isopropylideneadenosine, and 2′,3′-*O*-isopropylideneguanosine were converted to uridine 5′-phosphate (UMP), adenosine 5′-phosphate (AMP), and guanosine 5′-phosphate (GMP). As observed in the case of hydracrylonitrile dihydrogen phosphate,[4] the blocked adenosine nucleoside required a fourfold excess of 1 to give extensive phosphorylation. Hydrolysis of the cyclopropylmethyl and isopropylidene blocking groups was accomplished in refluxing water at pH 2.5–2.8. Data showing yields of nucleotides and reaction conditions are summarized in Table I. The purine nucleotides were hydrolyzed for shorter periods in order to avoid extensive glycosyl cleavage.

Table I
Nucleotides from Cyclopropylmethyl Dihydrogen Phosphate

Nucleoside precursor	Registry no.	Nucleotide	Yield, %	Phosphodiester hydrolysis time, hr
2′,3′-*O*-Isopropylideneuridine	362-43-6	UMP	61	3.0
2′,3′-*O*-Isopropylideneadenosine	362-75-4	AMP	36	1.5
2′,3′-*O*-Isopropylideneguanosine	362-76-5	GMP	35	1.5

The main advantage of the present method, compared with Tener's method,[4] is that the reagent 1 used in the phosphorylations is readily synthesized from 2 in an anhydrous condition. Storage of 2 for over 1 year at room temperature gave little decomposition. If only acid-labile blocking groups are employed, all blocking groups may be removed in a single hydrolysis step.

Experimental Section

NMR spectra were obtained using a Bruker HX-60 spectrometer. All peak positions are in δ (parts per million) from internal tetramethylsilane reference. Pyridine was dried over calcium hydride before use. All evaporations were performed under vacuum below 40°.

Cyclopropanemethanol, obtained commercially (Aldrich Chemical Co.), was fractionated using a Vigreux column. The fraction boiling at 125° was used for syntheses below. Microanalysis was by Galbraith Laboratories, Knoxville, Tenn.

Dibenzyl Cyclopropylmethyl Phosphate (2). Dibenzyl phosphonate was prepared according to the literature[20] and was used undistilled (but free of benzyl chloride) to prepare bis(benzyl) phosphorochloridate by the *N*-chlorosuccinimide method.[19] A solution of 20.1 g of bis(benzyl) phosphorochloridate (68.6 mmol) in 75 ml of ether was added dropwise over a 15-min period to 5.44 g (70 mmol) of cyclopropanemethanol and 5.93 (75 mmol) of pyridine in 100 ml of ether at 0°. Pyridine hydrochloride precipitated from the solution immediately. The mixture was stirred at room temperature for 18 hr. Filtration of the pyridine hydrochloride and evaporation of the ether left 19.9 g of a clear oil (88%): NMR (CCl_4) δ 0.33 (m, 4 H, CH_2CH_2), 1.03 (m, 1 H, CH), 3.73 (dd, 2 H, CH_2), 4.97 (d, 4 H, $ArCH_2$), 7.25 (s, 10 H, ArH). Attempted distillation of **2** at reduced pressure resulted in decomposition.

Cyclopropylmethyl Dihydrogen Phosphate (1). A solution of 1.20 g (3.6 mmol) of **2** was dissolved in 30 ml of dry absolute ethanol and 0.5 g of 10% palladium on charcoal was added. The mixture was hydrogenated for 30 min at 20–30 psi using a Parr hydrogenator. The catalyst was filtered and the solvent evaporated, affording 0.24 g of an oil (91%): NMR (Me_2SO-d_6) δ 0.46 (m, 4 H, CH_2CH_2), 1.17 (m, 1 H, CH), 3.77 (m, 2 H, CH_2), 11.1 (broad s, 2 H, OH).

Treatment of the solution obtained after hydrogenolysis and filtration followed by treatment with ammonia gave the ammonium salt, mp 160–164°.

Anal. Calcd for $C_4H_{12}NO_4P$: C, 28.41; H, 7.15; N, 8.28; P, 18.32. Found: C, 28.57; H, 7.33; N, 8.42; P, 18.40.

Uridine 5′-Phosphate.[21] Cyclopropylmethyl dihydrogen phosphate (from 1.61 g of **2**) was converted to the pyridinium salt by addition of 5 ml of pyridine to the filtered ethanol solution from above. The solution was evaporated and the residue dissolved in 10 ml of pyridine. After addition of 0.284 g (1.0 mmol) of 2′,3′-*O*-isopropylideneuridine, the solution was treated with 2.06 g (10 mmol) of DCC. The mixture was kept at room temperature for 2 days, followed by treatment with 2 ml of water. The mixture was allowed to stand for an additional 1 hr. The solvents were evaporated and the residue treated with 10 ml of water and evaporated to dryness. The residue was treated with 75 ml of water and the mixture was filtered. The filter cake was washed with 50 ml of water. The filtrate and washings were poured through an Amberlite 120 H^+ column. The column was washed with water until the effluent was neutral. The final volume of solution was adjusted to 500 ml and the pH was 2.6. The solution was refluxed for 3 hr. The cooled solution was then reduced to a volume of 50 ml and the pH was adjusted to 7.5–8.0 with saturated barium hydroxide solution. The barium phosphate was removed by centrifugation. The salt was washed well with water and the filtrate and washings (150 ml) were treated with 300 ml of ethanol to precipitate the barium salt of uridine 5′-phosphate. The solid was collected using a centrifuge, washed with water–ethanol, 1:2 (v/v), ethanol, and ether, and dried over P_2O_5 at 0.1 mm for 4 hr. The dry powder was calculated to be the hexahydrate of UMP using uv analysis at 262 nm of a sample dissolved in 0.01 *N* HCl. The product weighed 0.345 g (61%). Chromatographic analysis was performed as reported previously.[13]

Registry No.—**1**, 56599-14-5; **1** NH_3, 56599-15-6; **2**, 56599-16-7; UMP, 58-97-9; AMP, 61-19-8; GMP, 85-32-5; bis(benzyl) phosphorochloridate, 538-37-4; cyclopropanemethanol, 2516-33-8.

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Use of Hydrazides of Heterocyclic Carboxylic Acids for the Resolution of Z-DL-Alanine during Papain Catalysis

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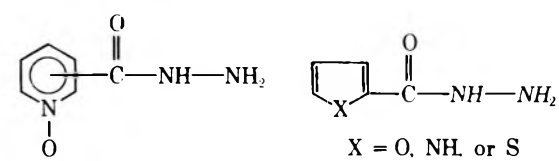
Numerous arenecarboxylic hydrazides have been demonstrated to be effective amino bases for papain-catalyzed reactions with N-blocked amino acids.[1] We have now focused attention on the behavior of a few hydrazides which incorporate a heterocyclic nucleus and a single hydrazide function toward Z-amino acids under papain catalysis.[2] A substantial number of such hydrazides have been prepared in conjunction with a systematic investigation of their antituberculin activity.[3]

The first hydrazides used in the current study contained a pyridine nucleus. These were picolinic hydrazide, nicotinic hydrazide, and isonicotinic hydrazide. When subjected to proper conditions for papain catalysis of reactions with *N*-acylamino acids, all three failed to respond. With the conjecture that the difficulty might be attributed to the basic nature of the heterocyclic nitrogen, this nitrogen was blocked with oxygen. Picolinic *N*-oxide, nicotinic *N*-oxide, and isonicotinic *N*-oxide hydrazides (I) were then examined. In addition, the study was extended to three compounds with representative five-membered heterocycles, namely, 2-furoic, 2-pyrrolecarboxylic, and 2-thiophenecarboxylic hydrazides (II).



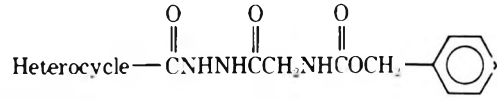
I II

When Z-glycine was the *N*-acylamino acid reactant, all six hydrazides yielded the unsymmetrical, achiral N^1,N^2-

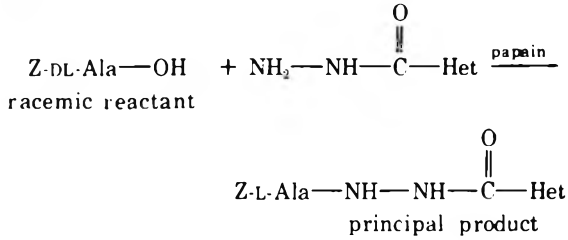
Table I
Properties of Unsymmetrical N^1,N^2-Diacylhydrazines Formed by Papain Catalysis

Name of product		pH optimum for reaction	% N Calcd	% N Found	$[\alpha]^{25}D$ in pyridine	Mp, °C	% L enantiomer in product
N^1-(2-Furoyl)-							
N^2-(Z-glycyl)hydrazine[a]	FGH[b]	3.75	13.24	13.46	Achiral	219–220	Achiral
N^2-(Z-L-alanyl)hydrazine	FLH		12.68	12.62	−50.9°	248–249	100
N^2-(Z-alanyl)hydrazine[c]	FAH		12.68[e]		−50.3°	248–252	99.4
N^1-(2-Thiophenecarboxylyl)-							
N^2-(Z-glycyl)hydrazine	TGH	4.25	12.61	12.88	Achiral	145–146	Achiral
N^2-(Z-L-alanyl)hydrazine	TLH		12.09	12.19	−55.4°	215–216	100
N^2-(Z-alanyl)hydrazine[c]	TAH		12.09[e]		−52.3°	219–220	97.2
N^1-(2-Pyrrolecarboxylyl)-							
N^2-(Z-glycyl)hydrazine	PyGH	4.00[d]	12.71	12.40	Achiral	194.5–195.5	Achiral
N^2-(Z-L-alanyl)hydrazine	PyLH		12.96	12.90	−51.1°	191–193	100
N^2-(Z-alanyl)hydrazine[c]	PyAH		12.96[e]		−49.1°	191–193	98.0
N^1-(Picolinyl N-oxide)-							
N^2-(Z-glycyl)hydrazine	PiGH	4.25	16.18	16.24	Achiral	199–200	Achiral
N^1-(Nicotinyl N-oxide)-							
N^2-(Z-glycyl)hydrazine	NGH	4.00	16.18	15.98	Achiral	216–217	Achiral
N^1-(Isonicotinyl N-oxide)-							
N^2-(Z-glycyl)hydrazine	IGH	4.25	16.18	16.18	Achiral	218–220	Achiral
N^2-(Z-L-alanyl)hydrazine	ILH		15.63	15.45	−51.0°	239–244	100
N^2-(Z-alanyl)hydrazine[c]	IAH		15.63	15.79	−30.8°	240–242	80.2

[a] Z is the accepted abbreviation for N-(benzyloxycarbonyl). [b] Abbreviations for products used in the Experimental Section. [c] Products from Z-DL-alanine contain some D enantiomer; hence Z-L-alanyl cannot be used. [d] Median pH of all other reactions with Z-glycine was used here. [e] Mixture melting point with product from Z-L-alanine showed no change or depression.



diacylhydrazines. Four of the hydrazides reacted with Z-L-alanine, and these same four hydrazides effectively resolved Z-DL-alanine. This represents another example of



racemic reactant

principal product

the power of papain to exert stereochemical preference during catalyzed reactions.[4] Results of these experiments are itemized in Table I. The extent of resolution, as calculated from optical rotations of products, varied from about 80 to 99%, also shown in Table I. Neither picolinic N-oxide hydrazide nor nicotinic N-oxide hydrazide underwent reactions with the Z-alanines.

The pH dependence of yield was determined for reactions between Z-glycine and five of the hydrazides; pH optima are given in Table I. The median optimum pH was 4.00. This was used satisfactorily for all reactions of the sixth hydrazide, 2-pyrrolecarboxylic hydrazide.

Experimental Section

***Preparation* of Active Papain.** Dried papaya latex, imported from the African Congo region, was donated by the Wallerstein Co., Deerfield, Ill. Activation, isolation, and drying of the papain over P_2O_5 have been described previously.[5]

Preparation of the Three Methyl Pyridinecarboxylate *N*-Oxides. Higher yields of the N-oxides than previously reported were obtained by using 40% peracetic acid in acetic acid. After the reactions, excess acetic acid was removed in a rotatory evaporator under very low pressure, with the use of an oil pump.

Picolinic acid N-oxide[6,7] was obtained in 57% yield as brown crystals, mp 158–160°. Dry HCl was passed into an absolute methanolic solution of the acid. After evaporation, treatment with Na_2CO_3 solution, extraction into chloroform, drying, and evaporation, recrystallization from toluene gave a 75% yield of colorless crystals of methyl picolinate N-oxide,[8] mp 73–74°.

Methyl nicotinate and methyl isonicotinate were converted into their N-oxides[4,9] by means of 40% peracetic acid. Recrystallization from 95% ethanol gave an 88% yield of methyl nicotinate N-oxide, mp 95–97°, and a 75% yield of methyl isonicotinate N-oxide, mp 118–120°.

Preparation of the Three Pyridinecarboxylic *N*-Oxide Hydrazides. More concentrated hydrazine than used in some of the earlier research was available for conversion of the esters to the hydrazides. Direct addition of methyl picolinate N-oxide to 95% hydrazine produced picolinic N-oxide hydrazide, mp 147–149°, in 82% yield (lit.[10] 148–148.5°).

Methyl nicotinate N-oxide was heated with 95% hydrazine in methanol. Rotatory evaporation was followed by treatment with activated charcoal in 95% ethanol. Subsequent work-up produced a 95% yield of the hydrazide as yellow needles, mp 225–227°. The literature[10] reported a substantially lower yield, with mp 222°. Methyl isonicotinate N-oxide and 95% hydrazine in absolute ethanol were refluxed for 2.5 hr on a steam bath and then cooled. Recrystallization from ethanol and carbon black yielded white needles of the hydrazide[3] in 75% yield, mp 228–229°. One literature value[10] was 227°.

2-Thiophenecarboxylic Hydrazide. Ethyl 2-thiophenecarboxylate was heated for 5 hr with 95% hydrazine in 95% ethanol. The hydrazide was treated with hot methanol and carbon black, and recrystallized in 75% yield, mp 134–136°. This melting point agrees with the early literature[9] but a more recent report[11] gives mp 138°.

2-Pyrrolecarboxylic Hydrazide. 2-Pyrrolecarboxylic acid was converted into the acid chloride with PCl_5, followed by treatment with methanol.[12] When the isolated ester was treated with 95% hydrazine in the refrigerator overnight, it yielded the crude hydrazide, mp 210–214°. The literature indicates mp 231–232°. It was used successfully without further purification for all papain-catalyzed reactions.

pH Dependence of Yield for Reactions between Z-Glycine and Hydrazides of Heterocyclic Carboxylic Acids. Furoic hydrazide was commercially available. The general procedure for determining the pH dependence of yield has been described previously.[4] Buffered solutions, 0.50 M buffer, were used at intervals of 0.25 pH units from pH 3.0 to 6.0. Solutions for a given hydrazide contained an equal molal quantity of Z-glycine, plus equal weights of L-cysteine·HCl·H_2O and activated papain from a common stock

solution. Adjustment of quantities was necessary for a specific hydrazide. Time of incubation at 40° was generally 24 hr, with the exception of 2-thiophenecarboxylic hydrazide, for which the time was reduced to 1.5 hr. Removal of products by suction filtration was followed by washing with water, drying, and weighing. For 2-pyrrolecarboxylic hydrazide, only the median optimum pH for the other five reactions, pH 4.00, was used to obtain the product from Z-glycine. pH optima are summarized in Table I. For nitrogen analyses and melting point determinations, products were dissolved in hot methanol, treated with decolorizing carbon, and suction filtered four or five times with thorough washing of any solid on the filter paper with fresh methanol into the filtrate each time to remove soluble solid. The final filtration involved a glass funnel with a fritted disk. The solvent was then removed by evaporation under the hood, with subsequent drying of solid.

Reactions between Hydrazides of Heterocyclic Carboxylic Acids and Z-L-Alanine and Z-DL-Alanine. Buffer, 0.50 *M*, at the pH optimum for the reaction between Z-glycine and a given hydrazide was used for these reactions. For 2-pyrrolecarboxylic hydrazide, pH 4.00 was again used. Quantities of solutes are all relative to a total of 100 ml of resultant buffered solution. For reactions or attempted reactions involving Z-DL-alanine and a hydrazide, 5 ml of hexamethylphosphortriamide was added as a solubilizing agent, with the exception of isonicotinic *N*-oxide hydrazide and 2-furoic hydrazide. In recording results, first an abbreviation of a reaction product from Table I is given. Second, the weight of L-cysteine·HCl·H_2O and therefore active papain is recorded. Third, the moles of hydrazide are immediately followed by the moles of *N*-acylamino acid. Fourth, the periods of incubation at 40° are given. Fifth, the weights of products obtained for each incubation period are indicated. Sixth, weights of recrystallized products from combined incubation periods that were dissolved in sufficient Eastman Spectrograde pyridine to produce 5.00 ml of solution at 25° precede the observed optical rotation at 25° in a Rudolph Model 80 high precision polarimeter, in a 2-dm polarimeter tube.

Recrystallized products, by means of essentially the same method as for products from Z-glycine, were used for nitrogen analyses, melting points, and mixture melting points, as well as optical rotations. Details are given in Table I.

FLH: 0.500 g; 0.0100 mol, 0.0100 mol; 0–24, 24–48 hr; 0.33 g, 0.075 g; 0.0901 g for α_{obsd} −1.834°.

FAH: 0.417 g; 0.0133 mol, 0.0133 mol; 0–24, 24–48 hr; 1.05 g, 0.100 g; 0.1090 g for α_{obsd} −2.194°.

TLH: 0.400 g; 0.0100 mol, 0.0100 mol; 0–24 hr; 1.31 g; 0.1691 g for α_{obsd} −3.750°.

TAH: 0.400 g; 0.0100 mol, 0.0200 mol; 0–24 hr; 1.29 g; 0.1000 g for α_{obsd} −2.092°.

PyLH: 0.500 g; 0.0100 mol, 0.0200 mol; 0–24 hr; 0.26 g; 0.1000 g for α_{obsd} −2.045°.

PyAH: 0.500 g; 0.0100 mol, 0.0200 mol; 0–24 hr; 0.25 g; 0.1000 g for α_{obsd} −1.962°.

ILH: 0.600 g; 0.0100 mol, 0.0100 mol; 0–72 hr; 0.35 g; 0.1103 g for α_{obsd} −2.250°.

IAH: 0.461 g; 0.0123 mol, 0.0123 mol; 0–72 hr; 0.31 g; 0.1126 g for α_{obsd} −1.386°.

Acknowledgments. The Squibb Institute for Medical Research supplied a sample of isonicotinic *N*-oxide hydrazide for preliminary experimentation. The Wallerstein Co., Deerfield, Ill., donated the dried papaya latex. This research was supported by grants from the Society of the Sigma Xi and a Federick Gardner Cottrell grant from the Research Corporation. Mr. C. F. Geiger, Ontario, Calif., ran the nitrogen analyses.

Registry No.—Papain, 9001-73-4; picolinic acid *N*-oxide, 824-40-8; picolinic acid, 98-98-6; peracetic acid, 79-21-0; methyl picolinate *N*-oxide, 38195-81-2; methyl nicotinate, 93-60-7; methyl isonicotinate, 2459-09-8; methyl nicotinate *N*-oxide, 15905-18-7; methyl isonicotinate *N*-oxide, 3783-38-8; hydrazine, 302-01-2; picolinic *N*-oxide hydrazide, 54633-17-9; nicotinic *N*-oxide hydrazide, 23597-85-5; isonicotinic *N*-oxide hydrazide, 6975-73-1; 2-thiophenecarboxylic hydrazide, 2361-27-5; ethyl 2-thiophenecarboxylate, 2810-04-0; 2-pyrrolecarboxylic hydrazide, 50269-95-9; 2-pyrrolecarboxylic acid, 634-97-9; Z-glycine, 1138-80-3; furoic hydrazide, 3326-71-4; Z-L-alanine, 1142-20-7; Z-DL-alanine, 4132-86-9; FGH 56587-73-6; FLH, 56587-74-7; TGH, 56587-75-8; TLH, 56587-76-9; PyGH, 56587-77-0; PyLH, 56587-78-1; PiGH, 56587-79-2; NGH, 56587-80-5; IGH, 56587-81-6; ILH, 56587-82-7.

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The Circular Dichroism Spectra of Folic Acid and 10-Thiafolic Acid and the Problem of Racemization in the Synthesis of Analogs of Folic Acid through the Cyclization of Substituted 2-Amino-3-cyanopyrazines[1]

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In view of the central role of derivatives of folic acid in cellular metabolism[2] and the usefulness of analogs of folic acid in the treatment of neoplastic disease,[3,4] a great deal of effort has been expended on searching for improved syntheses of molecules related to folic acid.

A relatively simple synthesis of 6-substituted pteridines was introduced by Taylor and his coworkers.[5-7] The reaction of aminomalononitrile with α-ketoaldoximes yields 2-amino-3-cyano-5-substituted pyrazine 1-oxides, deoxygenation and guanidine cyclization of which yields pteridines. This procedure, like some older but more cumbersome syntheses,[8,9] has the advantage of avoiding ambiguity in the positioning of the side chain and, in addition, delays the problems introduced by the extreme insolubility of pteridines until the final stages of the synthetic sequence. Recently, this synthesis was applied to the preparation of analogs of the antineoplastic agent methotrexate by Chaykovsky and his coworkers,[10] while our laboratory explored the usefulness of this approach in synthesizing 10-thiafolic acid, 10-thiapteroic acid, and related compounds.[11]

To prepare the latter group of compounds two synthetic routes were followed (Figure 1). In the first approach, reaction of 2-amino-3-cyano-5-chloromethylpyrazine[6] with ethyl 4-thiobenzoate, followed by cyclization with guanidine, yielded the ethyl ester of the 4-amino derivative of 10-thiapteroic acid. Mild hydrolysis led to the formation of 10-thiapteroic acid from which 10-thiafolic acid could be prepared using condensation with diethyl L-glutamate via the mixed anhydride method.

Alternatively, the complete side chain could be formed before addition to the pyrazine ring. In this approach, diethyl 4-thio-*N*-benzoyl-L-glutamate[11] was permitted to react with 2-amino-3-cyano-5-chloromethylpyrazine. Cyclization with guanidine, followed by mild hydrolysis, led to the formation of 4-amino-4-deoxy-10-thia-10-deazafolic acid or 10-thiaaminopterin.

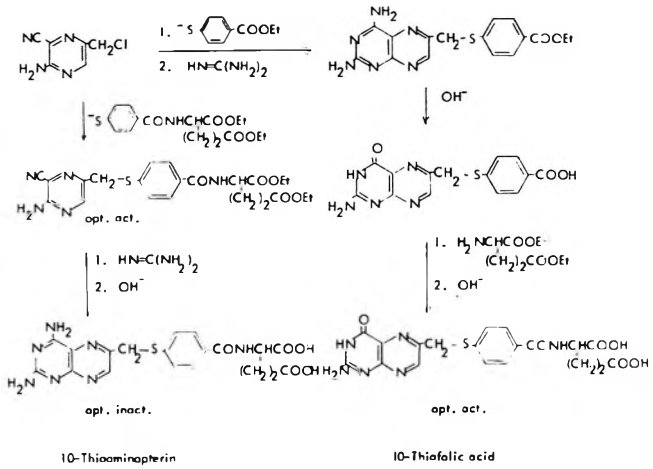

Figure 1.

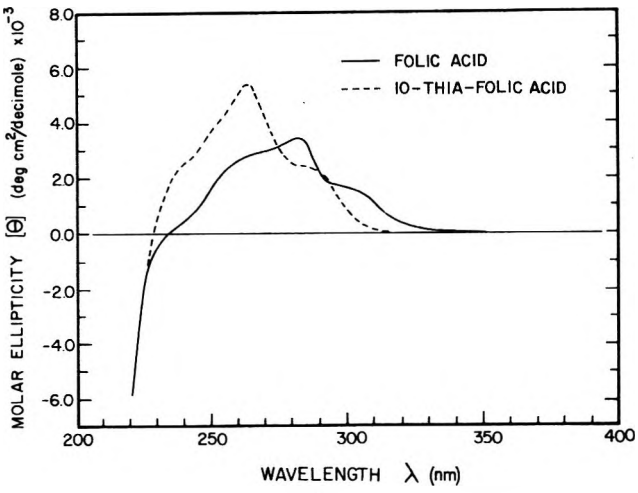

Figure 2. CD spectrum (0.01 *N* NaOH) of 10-thiafolic acid compared with that of folic acid.

In comparing the CD spectra of folic acid and of its 10-thia analog, it was noted that while the shapes of the absorption curves were similar, a considerable hypsochromic shift is seen in the 10-thia as compared to the 10-amino compound (Figure 2). Presumably, resonance involving the interaction of the heteroatom with the benzene ring is favored to a greater extent in the aminophenyl than in the thiophenyl compound. It should be noted that, while the CD spectra of methylenetetrahydrofolates have been measured,[12] the CD spectrum of folic acid has not been reported previously.

In contrast to the compounds discussed above, 10-thiaaminopterin proved to be optically inactive. This indicated that the *p*-aminobenzoyl-L-glutamyl side chain had racemized during the very basic conditions of the guanidine cyclization. An attempt was made to minimize racemization during the guanidine cyclization by heating the reaction mixture for 3.5 hr at 80° instead of refluxing it overnight. Analysis using TLC showed that cyclization was less than half complete, while the product has racemized totally, indicating that racemization is faster than cyclization.

Aminopterin synthesized by the addition of *p*-aminobenzoyl-L-glutamic acid to 2-amino-3-cyano-5-chloromethylpyrazine, followed by guanidine cyclization, also proved to be racemic. Both in the synthesis of aminopterin and the synthesis of 10-thiaaminopterin the intermediate 5-substituted 2-amino-3-cyanopyrazines retained full optical activity.

The problem of side-chain racemization during the guanidine cyclization cannot be ignored since it affects the biological interactions of the products. In the analog of methotrexate carrying a D-glutamic acid rather than an L-glutamic acid residue, ability to inhibit the growth of L-1210 leukemia cells is lowered considerably.[13] In addition, it was noted, using NMR spectroscopy, that the orientation of the aromatic rings of *p*-aminobenzoyl-L-glutamate and *p*-aminobenzoyl-D-glutamate on being bound to dihydrofolic acid reductase is quite different.[14]

The racemization problem in synthesizing folic acid analogs by the use of the Taylor synthesis can be avoided by carrying out the cyclization at the pteroic acid level and then forming the amide carrying the optically active substituent. No racemization takes place during the relatively mild conditions used to hydrolize esters of folic or related compounds.

Experimental Section

Materials. 2-Amino-3-cyano-5-chloromethylpyrazine was synthesized by the procedure of Taylor and Kobayashi.[6] 10-Thia-10-deazafolic acid and 10-thia-10-deaza-4-amino-4-deoxyfolic acid were prepared by a synthesis described elsewhere.[10]

CD Spectra. The spectra shown in Figure 2 were obtained with a Jasco J-20 automatic recording spectropolarimeter.

Acknowledgments. We are indebted to the National Cancer Institute for a grant in support of this work (CA-12186). Thanks are expressed to Dr. John Gollogly and Mr. Stephen F. Currier for their help in obtaining the CD spectra.

Registry No.—Folic acid, 59-30-3; 10-thiafolic acid, 54931-98-5.

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Reaction of *n*-Butyllithium and 2,2,6,6-Tetramethylpiperidine Nitroxyl[1]

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Stable nitroxyl radicals[2-4] are widely used as radical scavengers[4] and as probes for certain types of molecular motion.[5] In the course of other problems that utilized ni-

Table I
Products from Reaction of *n*-Butyllithium and 2,2,6,6-Tetramethylpiperidine Nitroxyl (TEMPO)

Product	Yield, %[a] Based on BuLi	Based on TEMPO
Butane	13	
Butene	4	
Octane	1	
Di-*n*-butyl ether	2	
n-Butyl alcohol	14	
TEMPOBu	65	46
TEMP		11
TEMPOH[b]		11
$TEMPOCH_3$[c]		33
Total	99	101

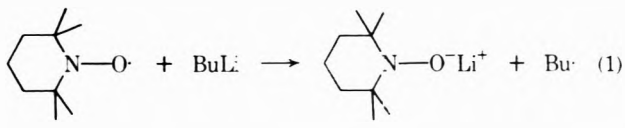
[a] The reaction for which these products are reported consumed 1.27 mmol of *n*-butyllithium and 1.80 mmol of TEMPO. [b] TEMPOH was detected by GLC as the quantitative conversion of TEMPOH to TEMPO in the injection port of the GLC was demonstrated using authentic TEMPOH. [c] $TEMPOCH_3$ is formed from $TEMPOLi^+$ by alkylation with dimethyl sulfate.

troxyl radicals in these applications, we required a procedure for destroying these radicals rapidly and quantitatively at low temperature in hydrocarbon solution. Here we report that the reaction of *n*-butyllithium with nitroxyl radicals is an effective method for accomplishing this objective, and describe the products of a representative reaction.

Results and Discussion

Addition of *n*-butyllithium (1.6 mmol, an excess) to a solution of 1.8 mmol of 2,2,6,6-tetramethylpiperidine nitroxyl[2,3,6] in *n*-hexane solution at −70° resulted in rapid disappearance (<1 min) of the characteristic red color of the stable radical. The resulting mixture was treated with 1,2-dibromoethane in order to convert excess *n*-butyllithium to *n*-butyl bromide. An aliquot of this reaction mixture was hydrolyzed and analyzed by GLC. A second aliquot was first treated with dimethyl sulfate to O-methylate lithium 2,2,6,6-tetramethylpiperidine nitroxide and facilitate its analysis by GLC, then hydrolyzed and analyzed. Table I summarizes the observed yields of products. These yields are corrected for the quantities of butane and butenes present in the starting *n*-butyllithium solution, and for the presence of 0.33 mmol of *n*-butyl bromide—representing unreacted *n*-butyllithium—among the products. They therefore represent the products of a reaction that consumed 1.27 mmol of *n*-butyllithium and 1.80 mmol of the nitroxyl radical. For convenience, the starting nitroxyl radical and the products derived from it are abbreviated as derivatives of tetramethylpiperidine (TEMP): thus, the nitroxyl radical is abbreviated TEMPO·, *N*-*n*-butoxytetramethylpiperidine is abbreviated TEMPOBu, and similar abbreviations are used for related compounds.

A detailed examination of the mechanisms leading to those products has not been carried out. A plausible sequence leading to the major products starts with one-electron oxidation of *n*-butyllithium by TEMPO·,[7,8] followed by coupling of a second equivalent of TEMPO· with the resulting *n*-butyl radical (eq 1 and 2). The extent of aggregation of the *n*-butyllithium may play a role in this reaction,[9] but has not been explored. It is ignored in this formulation.



(1)

(TEMPO·)

$$Bu\cdot + TEMPO\cdot \longrightarrow TEMPOBu \quad (2)$$

The variety of other products formed in the reaction clarifies the deviation of the stoichiometry of the reaction from the 2TEMPO:1BuLi expected on the basis of these two equations. Most of these products can be rationalized using straightforward reactions (eq 3–6).

$$Bu\cdot + Et_2O \longrightarrow BuH + CH_2\dot{C}HOEt \quad (3)$$

$$Bu\cdot + RH \longrightarrow BuH + R\cdot \quad (4)$$

$$BuLi + TEMPOBu \longrightarrow BuOBu + TEMP^-Li^+ \quad (5)$$

$$BuLi + TEMPO^-Li^+ \longrightarrow TEMP^-Li^+ + BuOLi \quad (6)$$

Reactions 5 and 6 are similar to the well-established cleavage of the oxygen–oxygen bond of dialkyl peroxides and lithium hydroperoxides by organolithium reagents.[9-11] Since these reactions appear to involve intermediate free alkyl radicals,[11] they may also contribute to other products formed. The observation among the products of a small quantity of a substance not alkylated by dimethyl sulfate and listed in Table I as TEMPOH is difficult to explain, and is probably an artifact. Independent experiments established that the conversion of authentic $TEMPO^-Li^+$ to $TEMPOCH_3$ by dimethyl sulfate was quantitative under the conditions employed in this assay. The presence of a derivative of TEMPO· that was not alkylated by dimethyl sulfate is compatible with its formulation as TEMPOH, but incompatible with the presence of a species having an acidic OH group in a solution containing butyllithium. It seems possible that $TEMPO^-Li^+$ present in this reaction mixture is less reactive than that in a solution containing only $TEMPO^-Li^+$ by virtue of its complexation with other species present in the mixture. In this event, the quantity of $TEMPO^-Li^+$ actually produced in the reaction should be considered to be the sum of the entries in Table I for TEMPOH and $TEMPOCH_3$.

The small quantities of butene and octane formed do not merit discussion, other than to note that the bimolecular reaction of butyl radicals would be expected to yield butene (by disproportionation) and octane (by coupling) in a ratio of approximately 1:7.[12] Thus, most of the butene and butane are formed by reactions other than bimolecular radical–radical disproportionation of *n*-butyl radicals. The coupling of TEMPO· and *n*-butyl radical generates little butane or butene (<5%).[8] Hence the majority of the butane formed in the reaction of butyllithium and TEMPO· probably results from hydrogen abstraction from some other component of the reaction system, probably by *n*-butyl radicals. The major hydrogen donor has not been identified.

Attempts to reduce the importance of reaction 2, and thereby to increase the probability of reaction between butyllithium and butyl radicals, by adding TEMPO· very slowly to an excess of butyllithium were only partially successful. The yield of TEMPOBu was decreased from 46 to 25% under the best conditions examined, and the relative yield of butane was significantly increased. The product balance in these experiments was not, however, sufficiently high to justify development of this system as a method of generating alkyl radicals in the presence of alkyllithium reagents.

In summary, the reaction of butyllithium with TEMPO· (and with other nitroxyl radicals examined) provides a rapid method of converting the radical to diamagnetic products.[14] The reaction mechanism has not been established in any detail, but the reaction products are compatible with initial one-electron oxidation of the organolithium reagent by the nitroxyl radical.

Experimental Section

Organometallic reagents were manipulated using standard procedures.[15] GLC analyses were carried out using an F & M Model 810 instrument and flame ionization detection, by unexceptional internal standard techniques. Butane and butene analyses utilized a 3-ft 3% Apiezon on alumina column; other analyses utilized an 8-ft 20% UC-W98 silicone rubber on Chromosorb P column. *n*-Hexane was purified by distillation under nitrogen from a suspension of sodium benzophenone ketyl. THF was distilled from $LiAlH_4$, and DME from disodium benzophenone dianion. TEMPO· was prepared by oxidation of TEMP with hydrogen peroxide catalyzed by sodium phosphotungstate;[6] it had mp 34–35° (lit.[6] mp 39°). Reagent dimethyl sulfate was purified by washing with cold saturated sodium bicarbonate solution and drying over potassium carbonate.[16] The dry solution was transferred to a Schlenk tube and traces of methanol were removed by a vacuum of 0.05 Torr. The dimethyl sulfate was stored in the Schlenk tube under prepurified nitrogen. It was reevacuated before use. Organolithium reagents were supplied by Foote Mineral Co., and were analyzed by the Gilman double titration method.[17]

***N*-Methoxy-2,2,6,6-tetramethylpiperidine (TEMPOCH$_3$).** DME (50 ml), 0.147 g (6.4 mg-atoms) of sodium metal, and 0.885 g (5.67 mmol) of freshly sublimed 2,2,6,6-tetramethylpiperidine nitroxyl were added to a flame-dried round-bottomed flask equipped with a condenser and a magnetic stirring bar and stoppered with a serum cap. The mixture was stirred under nitrogen at ambient temperature for 8 hr. Iodomethane (0.805 g, 5.67 mmol) was added to the resulting pale yellow solution of $TEMPO^-Na^+$, and the solution was stirred for an additional 4 hr under nitrogen. The reaction solution was saturated with sodium chloride, extracted with 50 ml of ether, and washed with distilled water and saturated sodium chloride solution. The ether was dried ($MgSO_4$) and concentrated to give a crude oil which was purified by column chromatography. The product was eluted from 6 g of silica gel G with 40 ml of cyclohexane followed by 40 ml of benzene, to give 0.4 g (41%) of *N*-methoxy-2,2,6,6-tetramethylpiperidine, having ir (CCl_4) 2980, 2930, 2810, 1475, 1385, 1355, 1060 cm^{-1}; NMR (CCl_4) δ 3.6 (s, 3 H, OCH_3), 1.0–1.5, multiplet (18 H); mass spectrum (70 eV) *m/e* (rel intensity) 171 (10.5), 156 (100), 88 (17), 69 (16), 55 (15), 41 (17).

***N*-Butoxy-2,2,6,6-tetramethylpiperidine (TEMPOBu).** The procedure for synthesizing $TEMPOCH_3$ was repeated using 1-iodobutane instead of 1-iodomethane, yielding 0.196 g (19%) of *N*-butoxy-2,2,6,6-tetramethylpiperidine, a colorless liquid, having ir (CCl_4) 2990, 2980, 2970, 2810, 1450, 1380, 1365, 1260, 1250, 1210, 1190, 1140, 1070, 1050 cm^{-1}. This ir spectrum was indistinguishable from that of TEMPOBu collected by GLC from a typical reaction of 2,2,6,6-tetramethylpiperidine and *n*-butyllithium. TEMPOBu had NMR (CCl_4) δ 3.6 (t, 2 H, J = 7 Hz, OCH_2–), 1.0–1.8 (m, 25 H).

Anal. Calcd for $C_{13}H_{27}NO$: C, 73.20; H, 12.74; N, 6.57. Found: C, 73.06; H, 12.62; N, 6.44.

Lithium 2,2,6,6-Tetramethylpiperidine Nitroxide. A solution of 0.03 g (0.192 mmol) of TEMPO· in 3 ml of DME was titrated to a colorless end point with 0.47 *M* lithium naphthalenide in DME, giving lithium 2,2,6,6-tetramethylpiperidine nitroxide and naphthalene. Hydrolysis of this solution afforded *N*-hydroxy-2,2,6,6-tetramethylpiperidine. Treatment with dimethyl sulfate yielded $TEMPOCH_3$ in quantitative yield.

Reaction between *n*-Butyllithium and 2,2,6,6-Tetramethylpiperidine Nitroxyl. Typical Procedure. Freshly sublimed TEMPO· (0.278 g, 1.8 mmol) and ca. 10 ml of *n*-hexane were added under nitrogen to a dry, stoppered, 40-ml centrifuge tube. *n*-Dodecane (104 mg) and *n*-pentane (28 mg) were added as internal GLC standards, and the solution was cooled to −78° in a Dry Ice–isopropyl alcohol bath. One milliliter of 1.60 *M* *n*-butyllithium was added to the mixture by syringe. When the reaction was complete, excess *n*-butyllithium was quenched with ca. 100 mg (0.535 mmol, 0.05 ml) of 1,2-dibromoethane. Five milliliters of the resulting solution was transferred to another dry centrifuge tube and hydrolyzed with 0.5 ml of distilled water. The remaining solution was treated with 0.2 ml (excess) of dimethyl sulfate, and shaken vigorously for 1 min. The products were analyzed by GLC. The hydrolyzed sample was used for butane, butene, and 2,2,6,6-tetramethylpiperidine analyses, the alkylated sample for all others. The results of this and similar reactions are summarized in Table I.

Registry No.—$TEMPOCH_3$, 34672-84-9; 2,2,6,6-tetramethylpiperidine nitroxyl (TEMPO), 2564-83-2; iodomethane, 74-88-4; TEMPOBu, 56514-19-3; 1-iodobutane, 542-69-8; *n*-buty lithium, 109-72-8.

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A Mild Oxidation of Alkyl Halides to Aldehyde Derivatives

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There have been several reports of the oxidation of alkyl halides to ketones or aldehydes.[1] None of these methods offer the direct conversion of an alkyl halide to a protected aldehyde (ketone). This type of transformation has synthetic utility especially in the case of labile aldehydes.

Hydrazones have not been widely used for protection of aldehydes or ketones,[2] probably owing to the widespread belief that they are difficult to cleave. Recently, however, several methods of mild hydrolytic cleavage for hydrazones and substituted hydrazones have been developed,[2,3] making the use of this group a viable means of carbonyl protection.

In this communication we wish to report a high-yield synthesis of acyl hydrazones from alkyl halides. This reac-

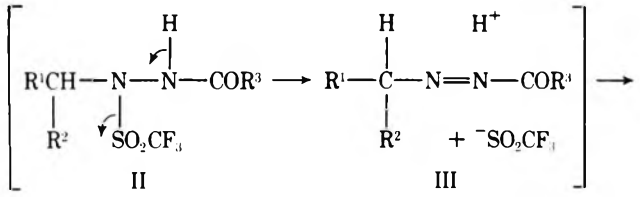
Table I
Acylhydrazone Synthesis

Alkyl halide	Registry no.	Temp, time	Yield of hydrazone derivative of		Mp, °C	Authentic sample mp,[a] °C
		A. From $C_6H_5CONHNHSO_2CF_3$[d]				
$C_6H_5CH_2Br$	100-39-0	Room temp, overnight	90%	C_6H_5CHO	210–212	207–208
C_2H_5I	75-03-6	Reflux, overnight	96%	CH_3CHO	159–162	162
$C_6H_5CHBrCH_3$	585-71-7	Reflux, 48 hr	70%	$C_6H_5COCH_3$	152–153	153
$C_6H_5(CH_2)_3ONs$	56572-24-8	Room temp, 48 hr	87%	$C_6H_5(CH_2)_2CHO$	119–121	119–120
$CH_2=CHCH_2Br$	106-95-6	Room temp, overnight	86%	$CH_2=CHCHO$	146–148	175–177[b]
c-$C_6H_{11}OTs$	953-91-3	No reaction				
		B. From $(CH_3)_3COCONHNHSO_2CF_3$[e]				
$C_6H_5CH_2Br$		Room temp, 48 hr	85%	C_6H_5CHO	184–185	185–186
$C_6H_5CHBrCH_3$		Room temp, 48 hr	43%	$C_6H_5COCH_3$	168–169	169–170
C_2H_5I		Room temp, 48 hr	96%	CH_3CHO	Oil	Oil
$C_6H_5(CH_2)_3Br$	637-59-2	60°, 42 hr[c]	80%	$C_6H_5(CH_2)_2CHO$	135–137	139–140

[a] Authentic samples were prepared from the corresponding aldehyde (ketone) and $C_6H_5CONHNH_2$ or $(CH_3)_3COCONHNH_2$. [b] There is some doubt as to whether this value is correct. On repeating the literature procedure[7] with $C_6H_5CONHNH_2$ and freshly distilled acrolein a compound that melted at 165–168° was isolated. The NMR spectrum of this compound showed no absorptions in the olefin region whereas the compound we prepared from I and allyl bromide exhibited satisfactory elemental analysis (C, H, N) and spectral data (NMR, ir, MS).[8] [c] A catalytic amount of KI was added. [d] Registry no., 41804-90-4. [e] Registry no., 56572-25-9

$$R^1CHX + R^3CONHNHSO_2CF_3 \xrightarrow[CH_3CN]{K_2CO_3} \underset{R^2}{R^1CHX}$$

I



II III

$$R^1C{=}N{-}NHCOR^3 \quad (1)$$
$$R^2$$

tion involves the alkylation of an *N*-acyl-*N'*-trifylhydrazine, subsequent elimination of triflinate ($SO_2CF_3^-$), and tautomerization to an acylhydrazone (eq 1).[4] The alkylation appears to be the rate-limiting step, for neither the alkylated trifyl hydrazide (II) nor the alkyl acyl azo compound (III) could be isolated. The hydrazone formation is postulated to occur by elimination of triflinate via removal of the amide N–H followed by tautomerization, rather than by the direct cleavage of the C–H bond, since alkylated triflamides without relatively acidic β hydrogen fail to undergo triflinate elimination even under more vigorous conditions [e.g., PhN(Tf)-*n*-Bu is unreactive even on treatment with *tert*-butyllithium in refluxing benzene[5]].

The reaction proceeds at room temperature for activated primary halides or unactivated nosylates, but requires refluxing and KI catalysis for unactivated primary halides or activated secondary halides. The reaction does not occur with unactivated secondary halides. Examples demonstrating the scope of the reaction are collected in Table I.

Tertiary-butoxycarbonyl (*t*-BOC) protected hydrazones are also available in good yield by this route (Table I). These compounds are potentially useful in forming specific alkyl hydrazones (N-alkylation followed by *t*-BOC removal[6]), mixed azines (*t*-BOC removal in the presence of another carbonyl compound), or other hydrazone derivatives.

Analogous attempts to form tosylhydrazones by alkylating TsNHNHTf were unsuccessful (eq 2). Apparently elimination of toluenesulfinate occurred faster than alkylation

$$TsNHNHTf \xrightarrow[C_6H_5COCH_2Br]{K_2CO_3} C_6H_5COCH{=}NNHTs \quad (2)$$
$$\downarrow$$
$$N_2 + Tf^-K^+ + Ts^-K^+ \xrightarrow{PhCOCH_2Br} PhCOCH_2Ts$$

of the triflamide, for only toluene sulfones were isolated (formed by alkylation of Ts^-); however, tosylhydrazones are potentially available from the *t*-BOC protected hydrazones.

Our examination of two representative acyl substituents [i.e., C_6H_5CO–, $(CH_3)_3COCO$–] indicates that the reaction is probably amenable to the synthesis of a wide variety of acylhydrazones under mild conditions.

Experimental Section

All melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. NMR spectra were recorded on a Varian Model A-60A spectrometer. Ir spectra were recorded on a Perkin-Elmer Infracord, Model 137 spectrophotometer. Elemental analyses were carried out by Galbraith Laboratories, Inc., Knoxville, Tenn. The CH_3CN was distilled from CaH_2 and stored over 3 Å molecular sieves. Anhydrous K_2CO_3 was activated before each use by heating over a Fisher burner for 0.5 hr.

***N*-Benzoyl-*N'*-trifylhydrazine.** Benzoylhydrazine (Aldrich) (5.44 g, 0.04 mol) was added portionwise to a solution of triflic anhydride[9] (5.64 g, 0.02 mol) in methylene chloride (150 ml) at −78°, with stirring. The reaction mixture was allowed to warm to room temperature and stirred for an additional 1 hr, then evaporated in vacuo, taken up in ether, and filtered and the ether was evaporated in vacuo to yield 5.00 g (93%) of a white solid which melted at 156–158°. An analytically pure sample (sublimed at 140°, 60 μ) melted at 159–160°: ir (KBr) 2.95 m, 3.30 m, 6.00 s, 8.13–8.29 μ s (three absorptions); NMR (CD_3CN) δ 9.22 (s, 1 H), 7.94–7.49 (m, 6 H).

Anal. Calcd for $C_8H_7F_3N_2O_3S$: C, 35.83; H, 2.63. Found: C, 35.91; H, 2.70.

***N*-*tert*-Butoxycarbonyl-*N'*-trifylhydrazine.** Triflic anhydride (5.64 g, 20.0 mmol) in CH_2Cl_2 (20 ml) was added dropwise to a solution of *tert*-butyl carbazate (Aldrich) (2.64 g, 20.0 mmol) and triethylamine (2.22 g, 22.0 mmol) in CH_2Cl_2 (100 ml) at −78° with stirring. The reaction mixture was allowed to warm to room temperature and stirred for a total of 2 hr, then washed twice with H_2O, once with 5% HCl, and once with H_2O and dried (Na_2SO_4) and the solvent was evaporated in vacuo. This residue crystallized on cooling (0°) overnight. Two recrystallizations from CH_2Cl_2–hexane afforded 2.67 g (50%) of colorless crystals: mp 92–94°; ir (KBr) 2.84 m, 3.03 m, 5.74 s, 7.20 s, 8.12 s, 8.28 s, 8.63 μ s; NMR ($CDCl_3$) δ 7.99 (broad s, 1 H), 6.94 (broad s, 1 H), 1.47 (s, 9 H).

Anal. Calcd for $C_6H_{11}F_3N_2O_4S$: C, 27.28; H, 4.20. Found: C, 27.34; H, 4.10.

General Procedure for the Formation of Acylhydrazones. The reaction times and temperatures are found in Table I. A solution of 1 equiv each of the alkyl halide and the trifyl hydrazide was stirred in dry CH_3CN with 2 equiv of anhydrous K_2CO_3. The reaction was monitored by TLC. A typical work-up involved filtration of the reaction mixture and evaporation of the solvent in vacuo followed by trituration of the residue with several portions of hot CH_2Cl_2. The acylhydrazones were obtained on evaporation of the CH_2Cl_2 in vacuo and were recrystallized from ethanol or CH_2Cl_2–hexane.

Registry No.—Benzaldehyde benzoylhydrazone, 956-07-0; acetaldehyde benzoylhydrazone, 1483-22-3; acetophenone benzoylhydrazone, 1219-41-6; benzenepropanal benzoxylhydrazone, 56572-26-0; 2-propenal benzoylhydrazone, 6631-27-2; benzaldehyde *tert*-butoxycarbonylhydrazone, 24469-50-9; acetophenone *tert*-butoxycarbonylhydrazone, 56572-27-1; acetaldehyde *tert*-butoxycarbonylhydrazone, 56572-28-2; benzenepropanal *tert*-butoxycarbonylhydrazone, 56572-29-3; benzoylhydrazine, 613-94-5; triflic anhydride, 358-23-6; *tert*-butyl carbazate, 870-46-2.

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(8) The data for $C_6H_5CONHN{=}CHCH{=}CH_2$ are as follows: NMR (CD_3CN,$CDCl_3$) δ 10.0 (broad s, 1 H), 7.98–7.30 (m, 6 H), 6.90–6.25 (m, 1 H), 5.76–5.66 (m, 1 H), 5.58–5.40 (m, 1 H); ir 3260, 3100, 1650, 1550 cm^{-1}; MS parent molecular ion *m/e* 174. Anal. Calcd for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.96; H, 5.93; N, 16.07.

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Regio- and Stereospecificity in the Addition of Hydrogen Bromide to Some Cyclic Allenes

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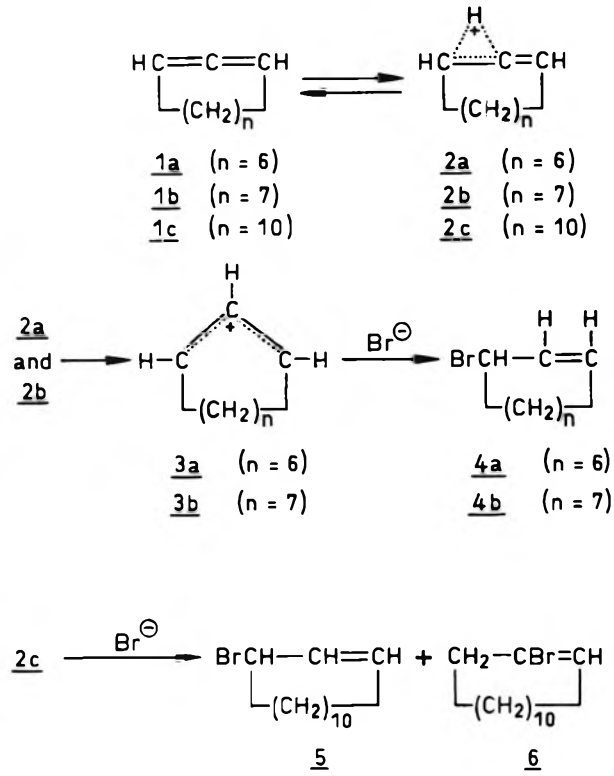
Addition of an unsymmetrical electrophilic reagent to an allenic bond is attractive as the system has more than one center for electrophilic attack. Many unsymmetrical electrophilic reagents such as hydrogen halides, water, mercuric acetate, 2,4-dinitrobenzenesulfenyl chloride, and organoboranes have been added to cyclic allenes.[2] However, the addition of hydrogen halides to cyclic allenes has not been systematically examined. Gardner et al.[3] have shown that hydrogen chloride gas adds to 1,2-cyclononadiene (**1a**) at −70° to form 3-chlorocyclononene. A similar regiospecificity has been observed in the addition of hydrogen bromide to **1a**.[4] Therefore, we thought that it would be interesting to examine the addition of hydrogen bromide to different cyclic allenes to know the effect of ring size on the regio- and stereospecificity of addition. We report here our work on the addition of hydrogen bromide to 1,2-cyclononadiene (**1a**), 1,2-cyclodecadiene (**1b**), and 1,2-cyclotridecadiene (**1c**) (Scheme I).

Scheme I



The addition of hydrogen bromide in acetic acid to 1,2-cyclononadiene (**1a**) in 1:1 mole ratio at ca. 20° gave only *cis*-3-bromocyclononene (**4a**) in 86% yield. Careful GLC analysis on a silicone rubber column indicated it to be pure. Its ir spectrum had absorptions at 2018, 1635, and 710 cm^{-1}. There was no ir absorption in the region 960 cm^{-1}, suggesting the cis configuration for the double bond. The NMR spectrum of **4a** showed two olefinic protons at δ 5.60, one methine proton at 5.00, and 12 methylene protons from 1.00 to 2.40 as multiplets. The identity was further confirmed by comparison of GLC retention times, ir, and NMR spectra with those of an authentic sample prepared from *cis*-cyclononene and *N*-bromosuccinimide.[5] Furthermore, the addition of deuterium bromide to **1a** gave *cis*-3-bromocyclononene-2-*d*. Its NMR spectrum exhibited one olefinic proton at δ 5.60, one methine proton at 5.00, and 12 methylene protons from 1.00 to 2.40. The mass spectrum showed characteristic molecular ion peaks of almost equal intensity at *m/e* 203 and 205. These results rule out the possibility of initial isomerization of **1a** to 1,3-cyclononadiene prior to addition to hydrogen bromide, and also suggest that the possible isomerization of the initially formed *trans*-3-bromocyclononene to the observed product, **4a**, is less likely. Finally, the addition of hydrogen bromide to **1a** was unaffected in the presence of a free radical inhibitor which excludes free radical addition.

In a similar manner, the addition of hydrogen bromide to 1,2-cyclodecadiene (**1b**) occurred to yield *cis*-3-bromocyclodecene (**4b**, 75%) as the sole product whose identity was established using an authentic sample prepared from *cis*-cyclodecene.[5] Hydrobromination of 1,2-cyclotridecadiene (**1c**), on the other hand, provided a mixture of 1-bromocyclotridecene (**5**) and 3-bromocyclotridecene (**6**), in a ratio 45:55. The regioisomers were separated by preparative GLC, and their structures secured by elemental analysis and comparison of GLC retention times and spectral properties with those of authentic samples.[5,6] Our attempts to separate the possible stereoisomers of **5** or **6** by GLC were not successful.

Our results demonstrate that hydrogen bromide addition to **1a** and **1b** is regiospecific as well as stereospecific, whereas the addition of **1c** is nonregiospecific. The most convincing rationale of our results is depicted in Scheme I. We suggest that **1a** or **1b** reacts with hydrogen bromide in a reversible process to form the corresponding unstable π-proton complex (**2a** or **2b**), which readily breaks up to form a planar resonance stabilized π-allylic cation (**3a** or **3b**). The addition of bromide anion to **3a** or **3b** can give rise to the observed allylic bromide (**4a** or **4b**) in each case. The stereospecificity observed can be explained as the cis configuration of **3a** or **3b** is much more stable than its trans configuration in a nine- or ten-membered ring. In the case of **1c** we argue that the π-proton complex (**2c**) is stable, and it is attacked by the nucleophile (Br^-) both at central and terminal centers to form 1-bromocyclotridecene (**5**) and 3-bromocyclotridecene (**6**), respectively. However, the possibility of the formation of the observed products (**5** and **6**) via nonplanar allylic and vinylic cations cannot be ruled out completely.

In conclusion, the reactions reported here represent the first example of change of orientation of hydrogen bromide addition with change in the ring size. The mode of addition of hydrogen bromide to strain-free 1,2-cyclotridecadiene (**1c**) resembles that of simple 1,3-disubstituted acyclic allenes.[7] We propose that the strain factor could be responsible for the observed difference in behavior of C-9 or C-10 as compared to C-13 allene in hydrogen bromide addition.

Experimental Section

All boiling points are uncorrected. Ir spectra were recorded on a Perkin-Elmer IR-137 using neat liquids. NMR spectra were recorded on a Varian Model A-60 NMR spectrometer relative to internal standard Me_4Si. The mass spectral measurements were performed by the Mass Spectrometry Laboratory, National Chemical Laboratory, Poona, India. The gas–liquid chromatography utilized a Varian Model 90-P gas chromatograph with a thermal conductivity detector. Elemental analyses were performed by the Microanalysis Laboratory, Department of Chemistry, Indian Institute of Technology, Kanpur 208016, India.

General Procedure for the Addition of Hydrogen Bromide to Cyclic Allenes. The cyclic allene (0.05 mol) was taken in a three-necked round-bottomed flask and cooled to around 15–20° in a nitrogen atmosphere. Hydrogen bromide solution in acetic acid (40% w/v, 12.0 ml, 0.055 mol) was added dropwise with magnetic stirring over a period of 30 min. After the addition was over, it was allowed to stir for another 2 hr. The reaction mixture was poured into 200 ml of water, neutralized carefully with sodium bicarbonate, and extracted with petroleum ether (bp 40–60°). The combined extract was washed thoroughly with water and dried over anhydrous $MgSO_4$. Removal of solvent and distillation under vacuum gave the monobromo adduct.

Addition of Hydrogen Bromide to 1,2-Cyclononadiene. From 1,2-cyclononadiene (6.1 g, 0.05 mol) and hydrogen bromide (0.055 mol), there was obtained 8.8 g (86%) of *cis*-3-bromocyclononene: bp 87–88° (5 mm) [lit.[5] bp 34–35° (0.05 mm)]; ir (neat) 2018, 1635, and 710 cm^{-1}; NMR ($CDCl_3$) δ 5.60 (m, 2 H), 5.00 (br m, 1 H), and 1.00–2.40 (m, 12 H).

Anal. Calcd for $C_9H_{15}Br$: C, 53.20; H, 7.39. Found: C, 53.41; H, 7.21.

Addition of Deuterium Bromide to 1,2-Cyclononadiene. Following the general procedure, the treatment of 1,2-cyclononadiene (1.22 g, 0.01 mol) with deuterium bromide (0.012 mol) in acetic acid-*d* provided 1.5 g (74%) of 3-bromocyclononene-2-*d*: bp 90° (5 mm); ir (neat) 2020, 1636, and 712 cm^{-1}; NMR ($CDCl_3$) δ 5.60 (m, 1 H), 5.00 (br m, 1 H), and 1.00–2.40 (m, 12 H); mass spectrum *m/e* 203 and 205 (M^+) of almost equal intensity.

Addition of Hydrogen Bromide to 1,2-Cyclodecadiene. Treatment of 1,2-cyclodecadiene (6.8 g, 0.05 mol) with hydrogen bromide (0.055 mol) in acetic acid gave 8.0 g (75%) of *cis*-3-bromocyclodecene: bp 91–92° (5 mm) [lit.[5] bp 86–87° (3 mm)]; ir (neat) 2018, 1634, and 712 cm^{-1}; NMR ($CDCl_3$) δ 5.58 (m, 2 H), 5.00 (br m, 1 H), and 1.00–2.42 (m, 14 H).

Anal. Calcd for $C_{10}H_{17}Br$: C, 55.30; H, 7.83. Found: C, 55.13; H, 7.71.

Addition of Hydrogen Bromide to 1,2-Cyclotridecadiene. 1,2-Cyclotridecadiene (9.0 g, 0.05 mol) was treated with hydrogen bromide (0.055 mol) to yield 9.0 g (70%) of a mixture of 3-bromocyclotridecene and 1-bromocyclotridecene, bp 93–101° (1 mm). Careful GLC analysis (10% silicone rubber SE-30, 5 ft × 0.25 in., 100°, 30 ml/min N_2) of the reaction product showed two closely situated peaks having 1-bromocyclotridecene (shorter retention time) and 3-bromocyclotridecene in the ratio 45:55. The two components were separated by GLC and compared with authentic samples.[5,6]

An authentic sample of 3-bromocyclotridecene was prepared from cyclotridecene (cis and trans mixture) and *N*-bromosuccinimide:[5] ir (neat) 2014, 1636, 970, and 710 cm^{-1}; NMR ($CDCl_3$) δ 5.56 (m, 2 H), 4.96 (br m, 1 H), and 0.96–2.45 (m, 20 H). An authentic sample of 1-bromocyclotridecene was made by lithium aluminum hydride reduction of 2,3-dibromocyclotridecene:[6] ir (neat) 2016, 1636, 850, and 820 cm^{-1}; NMR ($CDCl_3$) δ 5.50 (t, J = 7.0 Hz, 1 H) and 0.98–2.54 (m, 22 H).

Anal. Calcd for $C_{13}H_{23}Br$: C, 60.23; H, 8.88. Found: C, 59.98; H, 8.50.

Registry No.—**1a**, 1123-11-1; **1b**, 4415-98-9; **1c**, 5601-67-2; **4a**, 33332-75-1; **4b**, 56412-17-0; **5**, 56412-18-1; **6**, 38916-95-9; hydrogen bromide, 10035-10-6; deuterium bromide, 13536-59-9; 3-bromocyclononene-2-*d*, 56412-19-2; *cis*-cyclotridecene, 2484-66-4; *trans*-cyclotridecene, 2484-65-3; 2,3-dibromocyclotridecene, 34833-29-9; *N*-bromosuccinimide, 128-08-5.

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Sodium Borohydride–Carboxylic Acid Systems. Useful Reagents for the Alkylation of Amines

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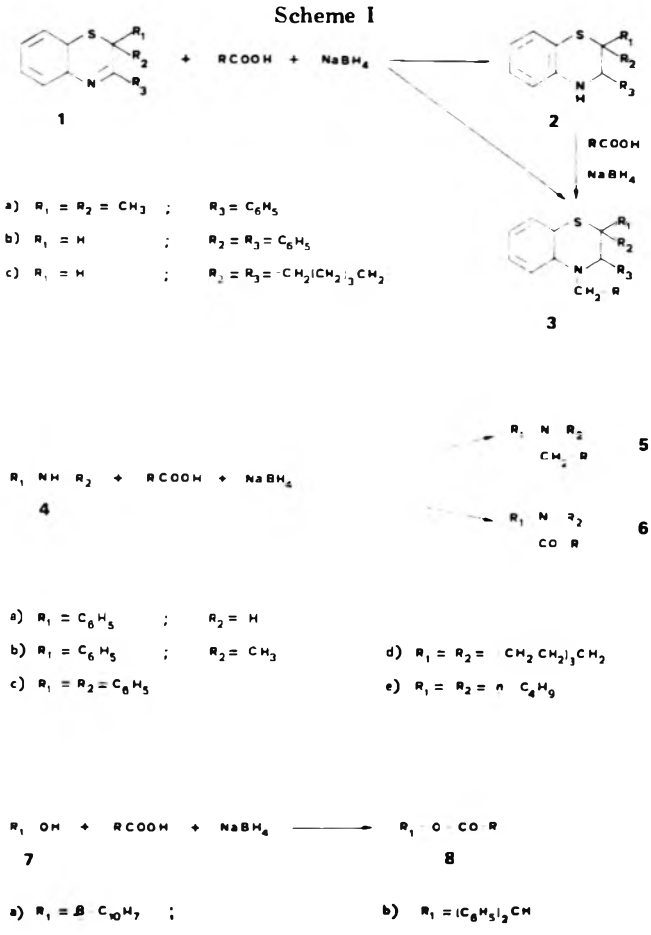
The recent paper by Gribble et al.[1] concerning the alkylation of aromatic amines with liquid carboxylic acids and sodium tetrahydroborate has prompted us to publish our own data on the same reaction, since they not only support the findings of the authors cited, but extend the scope of the reaction to the N-alkylation of amines with *solid* carboxylic acids, and provide further insight on the possible reaction pathway.

In the course of an investigation aimed at determining the reactivity of some 1,4-benzothiazines of structure **1**[2] we observed that their treatment with $NaBH_4$, in neat acetic acid as solvent, gave rise to the expected dihydro-1,4-benzothiazines **2** or to the corresponding *N*-ethyl derivatives **3** (R = CH_3) (Scheme I) depending on the amount of $NaBH_4$ added. The unexpected formation of *N*-alkyl derivatives prompted us to extend the reaction to a number of primary and secondary amines, both aliphatic and aromatic, and to

Scheme I



several liquid carboxylic acids; invariably the corresponding *N*-alkyl derivatives were obtained (Table I).

We noticed that by adding the amine to the $NaBH_4$–carboxylic acid mixture previously refluxed for 3 hr, further heating for a period of 3 hr leads to the formation of *N*-acyl derivatives **6**; addition of an alcohol or a phenol (**7**), in the place of the amine, yields, under the same conditions, the corresponding esters **8**.

In separate experiments, the volume of H_2[1,3] evolved on addition of $NaBH_4$ to neat acetic acid was measured. The results of a number of experiments indicate that 3 mol of H_2 per mole of $NaBH_4$ is immediately evolved at 20°, while approximately a fourth mole of H_2 is evolved very slowly at 20°, and more rapidly on heating at 80°.

The remarkable ease and usefulness of this direct method of alkylating amines by means of the corresponding carboxylic acid has induced us to study the possibility of performing N-alkylations even with solid carboxylic acids dissolved in suitable solvents. In fact, it is clear from what has been reported so far that the method appeared limited to the use of liquid carboxylic acids. It was first checked that the stoichiometry of the evolution of hydrogen was not changed when $NaBH_4$ and carboxylic acid in the molar ratio 1:5 were allowed to react in solvents such as benzene or toluene; in fact, 3 mol of hydrogen per mole of $NaBH_4$ was evolved at 20°, and approximately a fourth mole on heating under reflux. A certain number of reactions have therefore been performed in benzene yielding the *N*-alkyl derivatives **5** (Table II).

The addition of $NaBH_4$ to solutions of the acids in benzene causes, in general, the formation of insoluble compounds very sensitive to moisture. We have isolated those from formic, acetic, monochloroacetic, and benzoic acid; these are high-melting solids (except that obtained from monochloroacetic acid, which decomposes at 120–125°); their ir spectrum exhibits a B–H band between 2480 and 2530 cm^{-1} and two bands in the carbonyl zone. By treatment with water, they rapidly evolve H_2, and yield the carboxylic acid and boric acid in the molar ratio of 2:1, as shown by volumetric[5] and potentiometric[6] titrations; a third mole of carboxylic acid can be freed by addition of strong acids to the hydrolysis reaction mixture.

These products are capable of carrying out N-alkylation reactions, when reacted with amines in solvents such as toluene or benzene (Table III).

Table I
Results Obtained According to Procedure A

Reactants			
Substrate	Carboxylic acid	Reaction products	Yield, %
1a	Acetic	2a	60
1b	Acetic	2b	95
1a	Acetic	3a (R = CH_3)	95
1c	Acetic	3c (R = CH_3)	75
2a	Acetic	3a (R = CH_3)	95
2c	Formic	3c (R = H)	70
4c	Acetic	5c (R = CH_3)	95
4d	Acetic	5d (R = CH_3)	60
4e	Acetic	5e (R = CH_3)	80
4a	Propionic	6a (R = C_2H_5)	95
4c	Acetic	6c (R = CH_3)	40
4d	Propionic	6d (R = C_2H_5)	60
7a	Acetic	8a (R = CH_3)	50
7b	Acetic	8b (R = CH_3)	95

Table II
Results Obtained According to Procedure B

Reactants			
Substrate	Carboxylic acid	Reaction products	Yield, %
4a	Acetic	5a (R = CH_3)	30
4a	Propionic	5a (R = C_2H_5)	60
4a	Propionic	5 (R = C_2H_5, R_1 = C_2H_5, R_2 = n-C_3H_7)	90[a]
4b	Propionic	5b (R = C_2H_5)	65
4b	Palmitic	5b (R = $C_{15}H_{31}$)	70
4b	Benzoic	5b (R = C_6H_5)	20
4c	Acetic	5c (R = CH_3)	70
4c	Propionic	5c (R = C_2H_5)	35
4c	Palmitic	5c (R = $C_{15}H_{31}$)	25
4c	Monochloroacetic	5c (R = CH_2Cl)	35
4c	Monochloroacetic	5c (R = CH_2Cl)	90[b]

[a] Reaction carried out with a molar ratio BH_4^-:substrate of 10:1. [b] Molar ratio BH_4^-:substrate 5:1.

Table III
Results Obtained According to Procedure C

Reactants			
Substrate	Carboxylic acid	Reaction products	Yield, %
4b	Benzoic	5b (R = C_6H_5)	90[a]
4c	Acetic	5c (R = CH_3)	80
4c	Monochloroacetic	5c (R = CH_2Cl)	100
2,2′-Dithiodianiline	Acetic	*N*,*N*′-Diethyl derivative	90[b]
2,2′-Dithiodianiline	Benzoic	*N*,*N*′-Dibenzyl derivative	70[b]

[a] Reaction carried out in toluene under reflux for 15 hr. [b] Reaction carried out with a molar ratio BH_4^-:substrate of 10:1.

While the results so far available can hardly be regarded as conclusive, we feel that the experimental data support the assignment of the triacyloxymonohydroborate structure $Na[(RCOO)_3BH]$ (**9**) to the N-alkylating species we have isolated. This structure agrees with the results of the hydrolysis: in fact, it is obvious that on treatment with water 1 mol of **9** necessarily gives 1 mol of H_2, 1 mol of boric acid, 2 mol of carboxylic acid, and 1 mol of the sodium salt of the carboxylic acid and therefore that the addition of a strong acid is required to displace the third mole of carboxylic acid from the sodium salt. Furthermore, the structure **9** fits the ir spectroscopic data. In particular, the observed high frequency of B–H stretching bands seems appropriate for borohydrides, that can be looked at as adducts of poor Lewis acids like the acyloxyboranes of the present case. This interpretation is consistent with the results in the paper by Rice et al.,[7] correlating the increase in B–H stretching frequency of borane adducts with their lowered stability.

Species **9** can form an aldehyde by intra- or intermolecular hydride reduction; indeed, we have obtained benzyl alcohol on refluxing **9** ($R = C_6H_5$) for 20 hr in toluene and β-monochloroethyl monochloroacetate on refluxing **9** ($R = CH_2Cl$) for 6 hr in benzene. Furthermore, we found that all species isolated from $NaBH_4$ and carboxylic acids are capable of reducing iminium cations. These results seem to support the reaction pathway suggested by Gribble et al.[1]

Concerning the nature of acylating species, the evolution of 4 mol of H_2 per mole of $NaBH_4$ can be reasonably ascribed to the formation of a tetracyloxyborate $Na[B(OCOR)_4]$, **10**.

However, under the experimental conditions used, it is possible that species such as **10** decompose into RCOONa and $B(OCOR)_3$, whose acylating ability has been reported.[1,8]

Experimental Section[9]

N-Alkylation Reactions in Neat Carboxylic Acids. Procedure A. $NaBH_4$ (0.1 mol) was added portionwise to neat carboxylic acid (30 ml), the temperature being kept at 20°; when the lively evolution of H_2 had ceased, the amine (0.02 mol) was added. The reaction mixture was heated at 80° for 3 hr, cooled at room temperature, made alkaline with 2 *N* NaOH, and extracted with CH_2Cl_2. The organic layer was separated, dried (Na_2SO_4), and evaporated; PLC of the residue [light petroleum ether–ethyl acetate (9:1) as solvent] gave the corresponding *N*-alkyl derivative. The results obtained are reported in Table I.

4-Ethyl-2,2-dimethyl-3-phenyl-3,4-dihydro-2*H*-benzo[*b*]-[1,4]thiazine (3a, R = CH_3): mp 103–104° (2-propanol); NMR ($CDCl_3$) δ 7.6–6.6 (group of signals, 9 H, aromatic H), 4.27 (s, 1 H, C_3 H), 3.8–3.0 (m, 2 H, CH_2), 1.52 (s, 3 H, C_2 CH_3), 1.12 (s, 3 H, C_2 CH_3), and 1.12 ppm (t, 3 H, CH_3).

11-Ethyl-5a,6,7,8,9,10,10a,11-octahydrobenzo[*b*]cyclohepta[*e*][1,4]thiazine (3c, R = CH_3): bp 120–122° (0.05 Torr); NMR (CCl_4) δ 7.3–6.4 (group of signals, 4 H, aromatic H), 3.7–3.0 (group of signals, 4 H, NCH_2 + C_{5a} H + C_{10a} H), and 2.5–0.8 ppm [group of signals, 13 H, CH_3 + $(CH_2)_5$].

11-Methyl-5a,6,7,8,9,10,10a,11-octahydrobenzo[*b*]cyclohepta[*e*][1.4]thiazine (3c, R = H): mp 56–57° (EtOH); NMR (CCl_4) δ 7.2–6.5 (group of signals, 4 H, aromatic H), 3.8–3.5 (m, 1, C_{10a} H), 3.5–3.3 (m, 1 H, C_{5a} H), 2.87 (s, 3 H, CH_3), and 2.4–1.2 ppm [group of signals, 10 H, $(CH_2)_5$].

In the case of the imines **1**, if the above procedure (A) is modified by allowing $NaBH_4$ and benzothiazine to react in the molar ratio 1:1 and reducing the heating time to 1 hr, the reaction products are the dihydro derivatives **2**.[2]

The reaction of $NaBH_4$ with neat carboxylic acids at 20° was explored in order to determine the amount of H_2 evolved. In several experiments, it was found that 3.0 ± 0.1 mol of H_2 per mole of $NaBH_4$ was formed. In a typical run, $NaBH_4$ (0.079 g, 2.1 mmol) was added to neat acetic acid (0.8 ml) at 20°; 6.4 mmol of H_2 was immediately evolved.

Acylation Reactions in Neat Carboxylic Acids. $NaBH_4$ (0.1 mol) was added portionwise to neat carboxylic acid (30 ml), the reaction mixture was refluxed for 3 hr, the amine, the alcohol, or the phenol (0.02 mol) was added, and the reflux was prolonged for an additional 3 hr. By working up as above, the corresponding amide or ester was isolated. The results of these reactions are reported in Table I.

The reaction of $NaBH_4$ with liquid carboxylic acids under reflux was explored in order to determine the amount of H_2 evolved. In several experiments it was found that 3.8 ± 0.1 mol of H_2 per mole of $NaBH_4$ was formed. In a typical run, $NaBH_4$ (0.125 g, 3.3 mmol) was added to neat acetic acid (1.5 ml); after reflux for 3 hr, 12.7 mmol of H_2 was evolved.

N-Alkylation Reactions in Benzene Solution. Procedure B. $NaBH_4$ (0.1 mol) was added to a solution of the carboxylic acid (0.33 mol) in dry benzene (50 ml), the temperature being kept at 20°. When the evolution of H_2 had ceased, the amine (0.05 mol) was added, and the reaction mixture was refluxed for 3 hr, cooled at room temperature, and shaken with 2 *N* NaOH. The organic layer was separated, dried (Na_2SO_4), and evaporated; PLC of the residue [light petroleum ether–ethyl acetate (9:1) as solvent] gave the corresponding *N*-alkyl derivative. The results obtained are reported in Table II. It should be noted that the reported yields were not optimized; in fact, better yields can be attained by raising the BH_4^-:substrate molar ratio and/or the refluxing time, as shown in the case of **5c** ($R = CH_2Cl$), which was obtained in 90% yield using a molar ratio BH_4^-:substrate of 5:1.

***N*-(2-Chloroethyl)-*N*-phenylaniline (5c, R = CH_2Cl):** bp 110–112° (0.1 Torr); NMR (CCl_4) δ 7.2–6.9 (group of signals, 10 H, aromatic H) and 4.2–3.5 ppm (group of signals, 4 H, $-CH_2CH_2-$).

***N*-Hexadecyl-*N*-phenylaniline (5c, R = $C_{15}H_{31}$):** mp 43–44° (EtOH); NMR (CCl_4) δ 7.6–6.9 (group of signals, 10 H, aromatic H), 3.78 (t, 2 H, NCH_2), and 2.0–0.6 ppm (group of signals, 31 H, aliphatic H).

The reaction of $NaBH_4$ with solutions of carboxylic acids in dry benzene or toluene at 20° was explored in order to determine the amount of H_2 evolved. In several experiments, it was found that 3.0 ± 0.1 mol of H_2 per mole of $NaBH_4$ was formed. In a typical run, $NaBH_4$ (0.144 g, 3.8 mmol) was added to a solution of acetic acid (1.5 ml) in dry toluene (10 ml) at 20°; 11.1 mmol of H_2 was evolved.

Sodium Triacyloxymonohydroborates, 9. $NaBH_4$ (0.1 mol) was added portionwise to a solution of the carboxylic acid (0.33 mol) in dry benzene (1 l.), the temperature being kept at 20°. After hydrogen evolution, the precipitate **9** was rapidly collected by suction, washed with ethyl ether, and dried under vacuum. Compounds **9** do not melt up to 300°, except for **9** ($R = CH_2Cl$), which decomposes at 120–125°.

9 ($R = CH_2Cl$): ir 2530 (B–H) and 1735, 1685 cm^{-1} (C=O).

9 (R = H): ir 2480 (B–H) and 1680 cm^{-1} (broad band, C=O).

9 ($R = CH_3$): ir 2480 (B–H) and 1660 cm^{-1} (broad band, C=O).

9 ($R = C_6H_5$): ir 2490 (B–H) and 1670, 1635 cm^{-1} (C=O).

A suspension of **9** ($R = C_6H_5$) in dry toluene (50 ml) was refluxed for 20 hr and cooled at room temperature, and the solid was filtered off. The presence of benzyl alcohol in the filtrate was monitored by vapor phase chromatography. Similarly, β-monochloroethyl monochloroacetate was formed by refluxing a suspension of **9** ($R = CH_2Cl$) in dry benzene for 6 hr, and monitored by vapor phase chromatography.

Compounds **9** are capable of reducing imonium cations. In a typical run, **9** ($R = CH_3$) (0.22 g) was added to a stirred suspension of **1a HCl** (0.29 g) in dry benzene (50 ml) at room temperature. After 10 min, the reaction mixture was shaken with 2 *N* NaOH, and the organic layer was separated, dried (Na_2SO_4), and evaporated to give **2a** (0.25 g).

Hydrolysis of the Triacyloxymonohydroborates 9. On reaction with an excess of water, **9** promptly release hydrogen; in a typical run, 0.400 g of **9** ($R = C_6H_5$) (1.00 mmol) evolves 0.98 mmol of H_2.

The hydrolysis mixtures were examined by potentiometric titration with 0.1 *N* NaOH; a molar ratio of carboxylic acid to boric acid of 1.95 ± 0.05:1 was determined.

In the case of benzoic acid derivative (**9**, $R = C_6H_5$) a gravimetric determination was also accomplished. **9** ($R = C_6H_5$) (3.91 g) was hydrolyzed in hot water (150 ml); after cooling, the reaction mixture was extracted with CCl_4, and the organic layer was separated, dried (Na_2SO_4), and evaporated; a residue of benzoic acid (2.26 g) was obtained. The aqueous layer was strongly acidified with HCl, and extracted with CCl_4; the organic phase was separated, dried (Na_2SO_4), and evaporated; a residue of benzoic acid (1.25 g) was obtained.

N-Alkylation Reactions Carried Out with 9. Procedure C.

The amine and 9 in the molar ratio 1:5 were refluxed in dry benzene for 6 hr. By working up as for the above procedure (B) the corresponding *N*-alkyl derivatives were isolated. The results obtained are reported in Table III.

Acknowledgment. The authors are grateful to Professor V. Carelli for his helpful suggestions. This work was supported by a research grant from CNR, Rome, Italy.

Registry No.—**1a**, 49634-65-3; **1b**, 19195-32-5; **1c**, 25069-59-4; **2a**, 49634-66-4; **2b**, 25069-68-5; **2c**, 25069-64-1; **3a** (R = CH_3), 56553-67-4; **3c** (R = H), 49634-64-2; **3c** (R = CH_3), 56553-68-5; **4a**, 62-53-3; **4b**, 100-61-8; **4c**, 122-39-4; **4d**, 110-89-4; **4e**, 111-92-2; **5** (R = Et; R_1 = Ph; R_2 = Pr), 2217-07-4; **5a** (R = CH_3), 103-69-5; **5a** (R = C_2H_5), 622-80-0; **5b** (R = C_2H_5), 13395-54-5; **5b** (R = C_6H_5), 614-30-2; **5b** (R = $C_{15}H_{31}$), 56553-69-6; **5c** (R = CH_3), 606-99-5; **5c** (R = CH_2Cl), 42393-65-7; **5c** (R = $C_{15}H_{31}$), 51580-76-8; **5d** (R = CH_3), 766-09-6; **5e** (R = CH_3), 4458-33-7; **6a** (R = C_2H_5), 620-71-3; **6c** (R = CH_3), 519-87-9; **6d** (R = C_2H_5), 14045-28-4; **7a**, 135-19-3; **7b**, 91-01-0; **8a** (R = CH_3), 1523-11-1; **8b** (R = CH_3), 954-67-6; **9** (R = H), 56553-59-4; **9** (R = CH_3), 56553-60-7; **9** (R = CH_2Cl), 56553-61-8; **9** (R = C_6H_5), 56553-62-9; acetic acid, 64-19-7; formic acid, 64-18-6; propionic acid, 79-09-4; palmitic acid, 57-10-3; benzoic acid, 65-85-0; monochloroacetic acid, 79-11-8; 2,2′-dithiodianiline, 1141-88-4; *N*,*N*′-diethyl-2,2′-dithiodianiline, 56553-70-9; *N*,*N*′-dibenzyl-2,2′-dithiodianiline, 56553-71-0.

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Synthesis of 3,11-Dimethyl-2-nonacosanone, a Contact Courting Pheromone of the German Cockroach[1]

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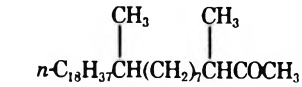
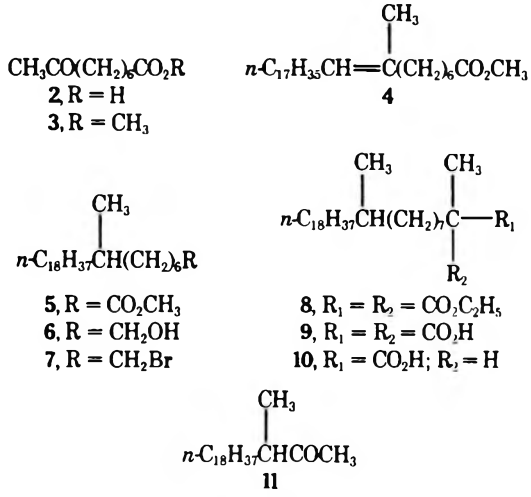
From the cuticle of sexually mature female German cockroaches (*Blattella germanica*), Ishii and coworkers recently isolated a contact chemoreceptive agent, identified as 3,11-dimethyl-2-nonacosanone (1), which was shown to elicit typical courting behavior, including wing raising, in males.[2] As part of a program of research on the properties and functions of cockroach pheromones,[3] we undertook and now describe a synthesis of 1. After completion and submission of this work for publication, an account with limited experimental details of a synthesis of 1 along somewhat similar lines by Ishii and coworkers appeared.[4]



1

As starting material in our synthesis we employed 8-oxononanoic acid (2), prepared from ϵ-caprolactone by modifications of the route of Kameoka et al.[5] via 6-bromohexanoic acid, esterification, and acetoacetic ester synthesis. Treatment of the methyl ester 3 in polar solvent with the Wittig reagent derived from octadecyltriphenylphosphonium bromide gave, in 48% yield, methyl 8-methyl-8-hexacosenoate (4), apparently mainly (by GLC) the *Z* isomer.[6] Hydrogenation of 4 afforded the saturated ester 5, which, after $LiAlH_4$ reduction to the corresponding alcohol 6 and conversion into the bromide 7, was used to alkylate diethyl methylmalonate. Hydrolysis of the resulting diester 8 and decarboxylation of the acid 9 gave 2,10-dimethyloctacosanoic acid (10), which, with two widely separated asymmetric centers, was undoubtedly a mixture of the two possible diastereoisomers. Treatment of 10 with 2 mol of methyllithium then furnished the desired ketone 1, mp 28–31° (lit.[4] 29–31°), in 50% overall yield from the Wittig product 4.



2, R = H
3, R = CH_3

4

5, R = CO_2CH_3
6, R = CH_2OH
7, R = CH_2Br

8, R_1 = R_2 = $CO_2C_2H_5$
9, R_1 = R_2 = CO_2H
10, R_1 = CO_2H; R_2 = H

11

Although spectral data indicate that the synthetic and natural ketones are structurally identical, our method of synthesis, like that of Ishii and coworkers,[4] undoubtedly afforded a mixture of the two possible diastereoisomers of 1. It is not surprising, therefore, that the natural product has a different melting point (45–46°), even though it appears to be optically inactive.[2,4]

Previous studies have shown that courting behavior in the German cockroach includes antennation (antennal stroking) of the female by the male, presumably allowing the latter to perceive sex pheromone on the cuticular surface of the female.[7] In our bioassay of synthetic 1 we used antennae ablated from American cockroaches (*Periplaneta americana*) to eliminate any possible stimuli associated with German cockroach antennae. Control antennae, dipped only in carbon tetrachloride, evoked no response. Antennae dipped in a 70 μg/ml solution of synthetic 1 in carbon tetrachloride elicited typical wing raising and other features of courting display[7] in 5% of a group of males (n = 60) kept isolated from females. At a higher concentration of 500 μg/ml the response was 70% in a group of isolated

males (n = 40) showing 80% response when presented with a mature virgin female.

These findings are comparable to those of Ishii and coworkers,[2,4] who reported that purified natural ketone **1** exhibited "distinct activity" in antennal testing at a concentration as low as 50 μg/ml in carbon tetrachloride. Interestingly, we found a lower molecular weight analog of **1**, 3-methyl-2-heneicosanone (**11**), to be completely devoid of activity. Moreover, synthetic **1** failed to excite male American (*Periplaneta americana*) or Cuban (*Byrsotria fumigata*) cockroaches.

Experimental Section

Melting points and boiling points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 137B Infracord or a Beckman IR-5 spectrophotometer. Proton magnetic resonance (^{1}H NMR) spectra were taken on a Varian A-60A or HA-100 instrument in carbon tetrachloride with tetramethylsilane as internal reference except where noted otherwise. Electron impact mass spectra were obtained at 70 eV with a Varian CH-5 spectrometer by Mr. Robert Drake, University of Kansas Department of Chemistry. Decolorizations were done with Nuchar C-190N. Anhydrous magnesium sulfate was used for drying organic extracts. "Pentane" and "hexane" refer to dry, redistilled Skellysolve F (bp 39–50°) and Skellysolve B (bp 64–68°), respectively. Homogeneity assays were made by TLC (silica gel 60F-254) or GLC (Varian A90-P3 instrument, 8-ft glass column packed with 10% SE-30 on 60–80 Gas-Chrom Q). Elemental analyses were run on an F & M 185 CHN analyzer by Mr. Dennis Eisele, University of Kansas Department of Medicinal Chemistry microanalyst.

8-Oxononanoic Acid (2). The route of Kameoka et al.[5] was modified to give a 3.25-fold improvement in overall yield. A mixture of 400 g (3.50 mol) of ε-caprolactone (Aldrich Chemical Co.), 600 ml of 48% hydrobromic acid, and 185 ml of concentrated sulfuric acid was refluxed for 5.5 hr and cooled to 15°. After separation of the upper layer, the lower layer was treated with 600 ml of saturated sodium chloride solution and extracted with three 150-ml portions of ether. The combined dark ether extracts and original upper layer were washed with four 200-ml portions of 20% aqueous sodium chloride solution and once with 200 ml of saturated sodium chloride solution. The ether layer was then decolorized and dried. Filtration and concentration afforded 641 g of crude 6-bromohexanoic acid, which was distilled rapidly at 1 mm; the fraction boiling at 139–140° [lit.[5] bp 150–152° (13 mm)] was collected to yield 533 g (78%) of purified acid, mp 36–38° (lit.[8] mp 35°). Esterification of 460 g (2.36 mol) of this acid with 1150 ml of absolute ethanol and 9.2 ml of concentrated sulfuric acid as catalyst gave, after removal of excess ethanol, extraction into methylene chloride, and distillation, 476 g (90%) of ethyl 6-bromohexanoate, bp 87–88° (0.75 mm) [lit.[5] bp 117–120° (4 mm)]. This ester (450 g, 2.02 mol) was added dropwise at 25–30° to a mechanically stirred solution of the sodium enolate of 276 g (2.12 mol) of ethyl acetoacetate [generated at 10–15° in a suspension of 50.5 g (2.12 mol) of sodium hydride] in 2 l. of dry benzene and 0.5 l. of dimethylformamide under an inert (argon) atmosphere. After stirring for 41 hr at 55° the mixture was concentrated under reduced pressure to ca. 1 l. and stirred for 2 hr longer. Aqueous work-up followed by extraction with benzene and distillation furnished 417 g (76%) of alkylated ethyl acetoacetate, bp 149–150° (1 mm). For conversion into **2**, 310 g (1.14 mol) of this ester was dissolved in 700 ml of acetic acid to which was added 450 ml of water and 82 ml of concentrated sulfuric acid. The mixture was refluxed vigorously with stirring for 2.75 hr and cooled to 5°, after which it was poured into 2 l. of ice water saturated with sodium chloride. The oily product was extracted with three 200-ml portions of ether, washed twice with an equal volume of saturated sodium chloride solution, and dried. The solution was concentrated at 45° under water aspirator vacuum and the residue was taken up in 400 ml of 1:1 ether–hexane, after which it was decolorized, filtered, and slowly cooled, with stirring, to ca. −25°. After crystallization was complete, rapid collection of the colorless, fine plates on a precooled Büchner funnel gave 119 g (61%) of 8-oxononanoic acid (**2**), mp 39–40.5° (lit.[5] mp 40°). Further hydrolysis and decarboxylation of the vacuum-distilled mother liquors (52 g) afforded an additional 19 g (mp 35–39°) of this acid, making the total yield 70%.

Methyl 8-Oxononanoate (3). Esterification of 100 g (0.58 mol) of acid **2** with ethereal diazomethane at 5° gave 103 g (95%) of distilled **3**, bp 95° (0.65 mm) [lit.[9] bp 104° (3 mm)]. Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.56; H, 9.78.

Methyl 8-Methyl-8-hexacosenoate (4). Triphenyloctadecylidenephosphorane (0.100 mol) was generated in 100 ml of dimethyl sulfoxide by the method of Greenwald, Chaykovsky, and Corey[10] from octadecyltriphenylphosphonium bromide (mp 93–95°, prepared in refluxing xylene). To this deep orange, slightly soluble ylide was added, with stirring, 100 ml each of dry dimethylformamide and tetrahydrofuran, followed by slow addition at 25° of 18.6 g (0.100 mol) of methyl 8-oxononanoate (**3**). After stirring under argon for 36 hr at 25°, the mixture was poured into 1.5 l. of 15% aqueous sodium chloride solution and extracted with five 100-ml portions of pentane. The combined pentane extracts were washed with three 100-ml portions of water and 200 ml of saturated sodium chloride solution, dried, cooled to 0°, filtered through 15 mm of alumina (Alcoa F-20, 45 g), and evaporated to give 26.2 g (62%) of crude **4** containing small amounts of recovered **3** and traces of triphenylphosphine oxide. Elution of 15.0 g of this product from 200 g of neutral alumina (Woelm, activity grade 2.5) with 1.2 l. of pentane gave 11.7 g (48%) of analytically pure methyl 8-methyl-8-hexacosenoate (**4**), apparently mainly the Z isomer by GLC analysis: ir (thin film) 3050 (=CH, very weak), 1740 (ester), no absorption at 1715 cm^{-1}; ^{1}H NMR δ 5.11 (1 H, t, J = 7.5 Hz, =CH–), 3.60 (3 H, s, –OCH_3); mass spectrum m/e (rel intensity) 422 (1.6, M^+), 152 (78), 137 (71), 129 (86), 111 (64), 97 (100, base), 71 (43), 69 (93), 57 (71), 55 (64). Anal. Calcd for $C_{28}H_{54}O_2$: C, 79.56; H, 12.88. Found: C, 79.77; H, 12.95.

Methyl 8-Methylhexacosanoate (5). The above ester (11.7 g, 27.6 mmol) was hydrogenated at 1 atm in 150 ml of acetic acid with 400 mg of prereduced platinum oxide until hydrogen uptake was complete (ca. 3 hr) The filtered solution was concentrated at the aspirator to 30 ml, diluted with 100 ml of pentane, and washed successively with 100-ml portions of water, 2% sodium bicarbonate, and saturated sodium chloride. After drying, the solution was evaporated to yield 11.7 g (99%) of **5** as a colorless oil which slowly solidified (mp 31–33°). An analytical sample crystallized from pentane at −10° had mp 33–34°; ir (thin film) 1740 cm^{-1} (ester); ^{1}H NMR δ 3.61 (3 H, s, –OCH_3), 2.22 (2 H, t, J = 7.2 Hz, –$CH_2CH_2CO_2$–); mass spectrum m/e (rel intensity) 424 (2.1 M^+), 423 (37), 310 (33), 143 (100, base), 87 (57), 75 (43), 74 (76), 57 (39), 55(71), 43 (27). Anal. Calcd for $C_{28}H_{58}O_2$: C, 79.18, H, 13.29. Found: C, 79.27; H, 13.48.

8-Methyl-1-hexacosanol (6). A solution of 11.3 g (25.6 mmol) of ester **5** was stirred at 25° for 6 hr with 1.5 g of lithium aluminum hydride in 100 ml of dry ether. After acidic work-up, extraction of the product into hexane, concentration of the dried extracts to 40 ml, and cooling to −10°, 10.0 g (98%) of nearly pure alcohol **6**, mp 51–53°, was isolated. Recrystallization from hexane gave an analytical sample: mp 52–53°; ir (CCl_4) 3600–3400 (–OH), no absorption at 1740, 1050 cm^{-1} (C–O); ^{1}H NMR δ 3.55 (2 H, 5, J = 7.0 Hz, –CH_2CH_2O–), 3.02 (1 H, s, –OH); mass spectrum m/e (rel intensity) 396 (0.04, M^+), 125 (48), 97 (44), 85 (37), 83 (56), 71 (56), 69 (74), 57 (100, base), 43 (41), 28 (56). Anal. Calcd for $C_{27}H_{56}O$: C, 81.74; H, 14.23. Found: C, 81.84; H, 14.33.

1-Bromo-8-methylhexacosane (7). A mixture of 10.0 g (25.2 mmol) of **6**, 16 ml of 48% hydrobromic acid, and 2.8 ml of concentrated sulfuric acid was stirred vigorously under reflux for 5 hr. The mixture was then cooled, diluted with 150 ml of water, and extracted with ether. After drying and evaporation of the ether extracts, the product was purified by elution with pentane from 100 g of alumina (Alcoa F-20) to give 10.1 g (88%) of bromide **7**, 94% pure by GLC: ir (thin film) no absorption at 3600–3500 cm^{-1}; ^{1}H NMR δ 3.30 (2 H, 5, J = 6.8 Hz, –CH_2CH_2Br); mass spectrum m/e (rel intensity) 460 (0.4, M^+ + 2), 458 (0.43, M^+), 125 (21), 99 (22), 97 (26), 85 (47), 83 (42), 71 (68), 69 (47), 57 (100, base), 55 (31), 43 (38), 29 (58). Anal. (after molecular distillation, 0.5 mm). Calcd for $C_{27}H_{55}Br$: C, 70.55 H, 12.06. Found: C, 70.96; H, 12.24.

2,10-Dimethyloctacosanoic Acid (10). To 27.8 mmol of the sodio derivative of diethyl methylmalonate (Aldrich Chemical Co., generated with sodium hydride) in 30 ml of 1:1 benzene–dimethylformamide was added over 15 min, with stirring, 4.50 g (9.80 mmol) of bromide **7**. The mixture was stirred under argon for 36 hr at 55°, cooled to 15°, poured into 250 ml of cold 2% acetic acid, and extracted with three 50-ml portions of ether. The combined extracts were washed and concentrated to yield a mixture of diester **8** and recovered diethyl methylmalonate, which was refluxed for 3 hr in 60 ml of 10% ethanolic potassium hydroxide with efficient stirring. After cooling, the mixture was acidified and extracted with ether to yield the crude diacid **9**, used without further purification (mp 64–67° after crystallization from acetone). When heated to

180–185° for 45 min under mild aspirator vacuum, 9 furnished 3.34 g (75% yield from 7) of 2,10-dimethyloctacosanoic acid (10) as a colorless, waxy solid: mp 49–51° (after crystallization from acetone); ir (CCl_4) 3500–2400 and 1712 cm^{-1} (carboxyl); ^1H NMR δ 12.30 (1 H, s, $-CO_2H$), 2.33 (1 H, m, >CHCO–); mass spectrum *m/e* (rel intensity) 452 (42, M^+), 143 (21), 130 (26), 97 (22), 87 (43), 74 (100, base), 71 (47), 69 (43), 57 (67), 43 (21). Anal. (vacuum sublimed sample). Calcd for $C_{30}H_{60}O_2$: C, 79.58; H, 13.36. Found: C, 79.77; H, 13.63.

3,11-Dimethyl-2-nonacosanone (1). Over a period of 45 min, 9.0 ml of 1.26 *M* methyllithium in ether was added under argon to a rapidly stirred solution of 2.50 g (5.53 mmol) of acid **10** in 35 ml of dry ether cooled to −10°. The mixture was stirred at −10 to −5° for 20 min and then at 25° for 4 hr, after which it was poured slowly, with stirring, into 100 ml of ice-cold 5% hydrochloric acid. Extraction with two 50-ml portions of ether followed by washing with 5% sodium bicarbonate, saturated sodium chloride, decolorization, drying, and evaporation yielded 2.25 g of colorless and nearly pure (by TLC and GLC) ketone **1**, which partially solidified at 25° (mp 24–28°). For purification, 2.20 g of this product was chromatographed on 150 g of silica (Mallinckrodt SilicAR CC-7). After elution with 200 ml of hexane, 1.91 g (78%) of purified **1** (homogeneous by TLC and GLC) was collected with 600 ml of 5% ether in hexane as a waxy solid with a very faint, thionyl chloride-like odor: mp 28–31° (lit.[4] 29–31°); ir (CCl_4) 1723 cm^{-1} (ketone); ^1H NMR ($CDCl_3$) and ^{13}C NMR (Bruker HX-90, $CDCl_3$) spectra indistinguishable from those reported[2,4] for the natural pheromone; mass spectrum *m/e* (rel intensity) 450 (3, M^+), 85 (9), 72 (100, base), 71 (6), 69 (5), 57 (11), 55 (6), 43 (14). Anal. (after evaporative distillation, 0.5 mm). Calcd for $C_{31}H_{62}O$: C, C, 82.59; H, 13.86. Found: C, 82.81; H, 14.13.

The 2,4-DNP of **1** crystallized from methanol–ethyl acetate in fine yellow needle clusters, mp 56–62° (lit.[4] mp of natural pheromone 2,4-DNP, 55–56°). Anal. Calcd for $C_{37}H_{66}N_4O_4$: C, 70.43; H, 10.54; N, 8.88. Found: C, 70.20; H, 10.65; N, 8.89.

3-Methyl-2-heneicosanone (11) (with David C. Clymer). Under the same conditions used to prepare ketone **1** from acid **10**, 3.00 g (9.20 mmol) of 2-methyleicosanoic acid[11] [mp 60–61° (lit.[11] mp 61.5–62°)] in 125 ml of ether was allowed to react with 16.3 ml of 1.25 *M* methyllithium in ether to yield 2.44 g (78%) of chromatographed ketone **11**: mp 29–29.5°; ir (CCl_4) 1723 cm^{-1} (ketone); ^1H NMR δ 2.39 (1 H, m, J = 6.8 Hz, >CHCO–) 2.01 (3 H, s, CH_3CO–), 1.02 (3 H, d, J = 6.8 Hz, CH_3CHCO–); mass spectrum *m/e* (rel intensity) 324 (1.3, M^+), 85 (13), 72 (100, base), 57 (15), 55 (10), 43 (15), 28 (19). Anal. (after evaporative distillation, 0.5 mm). Calcd for $C_{22}H_{44}O$: C, 81.41; H, 13.66. Found: C, 81.38; H, 13.87.

The 2,4-DNP of **11** crystallized from ethanol in yellow spores, mp 77–78°. Anal. Calcd for $C_{28}H_{48}N_4O_4$: C, 66.63; H, 9.59. Found C, 66.68; H, 9.97.

Acknowledgments. We thank Dr. B. A. Pearson, Department of Chemistry, The University of Iowa, for the ^{13}C NMR spectrum and Professor R. G. Carlson, Department of Chemistry, The University of Kansas, for helpful suggestions and advice. We also thank Messrs. David J. Clymer and Chung Shih for experimental assistance and Professor S. Ishii for information concerning his investigations.

Registry No.—**1**, 53623-10-2; **1** 2,4-DNP, 56629-71-3; **2**, 25542-64-7; **3**, 34455-70-4; **4**, 56599-03-2; **5**, 56599-04-3; **6**, 56599-05-4; **7**, 55590-34-6; **9**, 56599-06-5; **10**, 56599-07-6; **11**, 56599-08-7; **11** 2,4-DNP, 56599-09-8; 2-methyleicosanoic acid, 56599-10-1.

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Synthesis of Aflatoxin Q_1

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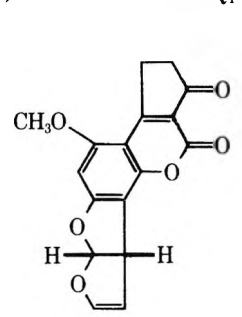
To interpret differences in susceptibility of various animal species to the carcinogenic effects of aflatoxin B_1 (1) a knowledge of its metabolic fate is of much importance.[1] The in vitro metabolism of the carcinogen by liver homogenates of duck, rat, mouse, monkey, and human has been investigated and a major, new metabolite called aflatoxin Q_1 (2) was isolated and identified structurally by three groups of investigators using monkey[2,3] and human liver.[4] To decide whether the hydroxylation of B_1 (1) represents an activation or a detoxification mechanism substantial quantities of Q_1 (2) are needed for physiological evaluation. We have developed two simple chemical methods which transform B_1 (1) to the metabolite Q_1 (2).



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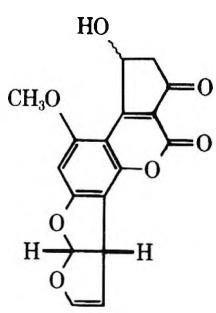

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The presence of the enol ether function in the starting material **1** made most presently known methods unsuitable for direct hydroxylation and our efforts, accordingly, centered about oxidation of carbanions, derived from starting material by proton abstraction. Small, but detectable amounts of Q_1 (2) were formed by oxidation of B_1 (1) in *tert*-butyl alcohol solution with oxygen, *tert*-butyl hydroperoxide, or hydrogen peroxide in the presence of potassium *tert*-butoxide. Oxidation of a lithium diisopropylamide generated anion with MoO_5·Py·HMPA[5] afforded similar results. Substantial quantities of Q_1 (2) were produced when solutions of B_1 (1) in methylene chloride–methanol containing aqueous sodium hydroxide were exposed to either silver(II) or -(I) oxide. Efforts to replace silver oxide with copper(I) or -(II) species, manganese dioxide, and thallium(III) nitrate failed and as a result the reaction parameters of the silver oxide oxidation were examined in some detail with the more readily available model compound **3**.[6] Silver(I) oxide proved to be superior and gave the alcohol **5** in 38% yield while 17% of the starting material **3** was recoverable by chromatography. The structure of the alcohol **5** was determined by NMR spectroscopy and catalytic hydrogenation, proceeding with the consumption of 3 equiv of hydrogen, to 5,7-dimethoxycyclopenteno[2,3-*c*]coumarin (**4**).

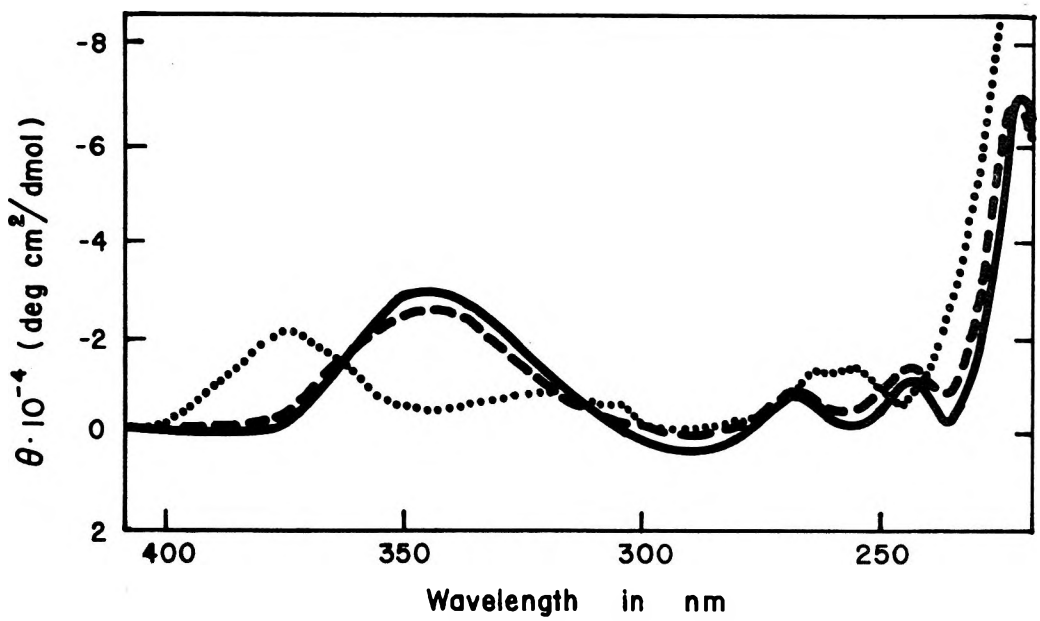
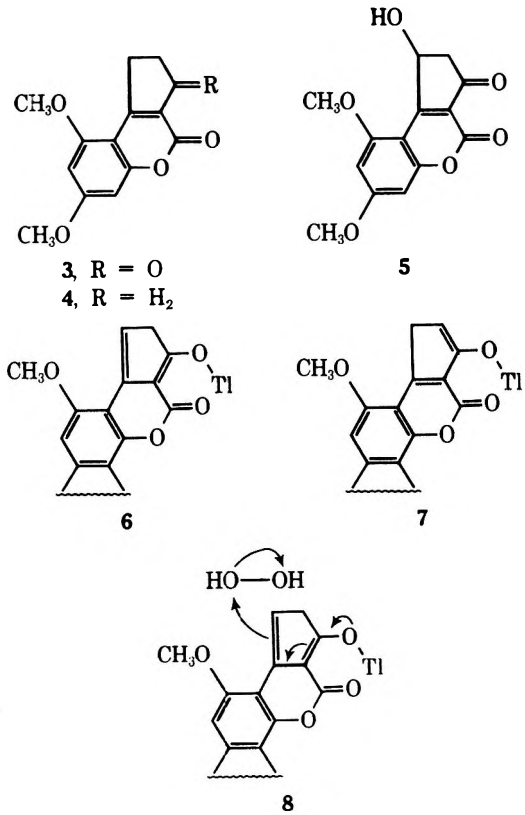


Figure 1. CD spectra of natural aflatoxin Q_1 (—), synthetic aflatoxin Q_1 (natural epimer - - -), and synthetic aflatoxin Q_1 (unnatural epimer · · · ·).

Oxidation of a thallium complex prepared from B_1 (1) and thallium(I) ethoxide[7] in methylene chloride–methanol with 95% hydrogen peroxide represents the most practicable synthesis of aflatoxin Q_1 (2). Excess hydrogen peroxide and 1 equiv of thallium(I) ethoxide at 0° afford optimal yield of both Q_1 (2) and the model compound 5. Oxidation



is fast at the beginning but comes to a halt long before the starting material has been consumed and aqueous work-up leads to the recovery of as much as 50% of B_1 (1). Possibly two thallium enolates 6 and 7 are formed irreversibly. The less stable isomer 6 combines rapidly with hydrogen peroxide (arrows in 8) to produce Q_1 (2), with regeneration of the coumarin ring, while the more stable isomer 7 is transformed more slowly to hitherto unidentified, highly polar products.

Not unexpectedly chemical oxidation of B_1 (1) led to a mixture of two diastereomeric alcohols 2 (59% yield based on B_1 consumed) which was separated from starting material (56%) by chromatography. One aflatoxin Q_1 (2) epimer, mp 265° dec, identical with natural material, crystallized from methylene chloride–methanol–hexane in 41% yield. A second crystalline crop contained both epimers as revealed by the appearance of two acetal proton doublets at δ 8.5 in the NMR spectrum when measured in Me_2SO-d_6. After repeated chromatography of the remaining mother liquor the unnatural epimer, mp 235° dec, crystallized from the same solvent mixture. The proton spectra of the two epimers showed only small differences but circular dichroism (Figure 1) provided an easy means of differentiation. Conformational assignment to the secondary hydroxyl group will only be possible when a closely related alcohol of known configuration becomes available.

Experimental Section

Melting points are corrected. The following spectrometers were used: ir, Perkin-Elmer 247; ultraviolet, Perkin-Elmer 202 or Cary 14; NMR, Varian HA-100 or Hitachi Perkin-Elmer R-22 90 MHz; MS, Hitachi Perkin-Elmer RMU-6; CD, Cary 60.

Oxidation of Aflatoxin B_1 (1). A. Hydrogen Peroxide–Thallium(I) Ethoxide. To a solution of aflatoxin B_1 (1, 521 mg, 1.67 mmol) in 150 ml of methylene chloride at 0° a solution of thallium(I) ethoxide (382 mg, 1.54 mmol) in 38 ml of methylene chloride was added followed by a solution of 95–100% hydrogen peroxide (293 mg, 8.6 mmol) in 47 ml of methanol. After stirring at 0° for 47 hr the dark brown reaction mixture was filtered through a silica gel column (50 g) eluting with 500 ml of methylene chloride–methanol (3:1 v/v). The solvent was evaporated and the residue chromatographed (10 20 × 20 × 0.1 cm Analtech silica gel chromatoplates) eluting with chloroform–ethanol–hexane (10:2:1 v/v/v) to afford 293 mg (56%) of TLC-pure, crystalline aflatoxin B_1 (1) and 141 mg (26%) of TLC-pure mixture of epimeric aflatoxins Q_1 (2).

B. Silver(I) Oxide–Sodium Hydroxide. To a solution of aflatoxin B_1 (1, 100 mg, 0.32 mmol) in 53 ml of methylene chloride–methanol–water (27:22:4 v/v/v) at 0° silver(I) oxide (232 mg, 1 mmol) was added and then 1.2 ml of 0.5 *N* aqueous sodium hydroxide (0.6 mmol). After stirring at 0° for 160 min the mixture was filtered through a silica gel column (15 g) eluting with 200 ml of methylene chloride–methanol (3:1 v/v). The eluate was diluted with 350 ml of methylene chloride and extracted once with 4 *N* aqueous ammonium chloride and once with water. The organic

phase was diluted with 100 ml of dry benzene and evaporated to dryness. Chromatography (completely analogous to A) afforded 36 mg (36%) of the TLC-pure aflatoxin B_1 (1) and 32 mg (30%) of TLC-pure mixture of epimeric aflatoxins Q_1 (2).

Separation of Epimeric Aflatoxins Q_1 (2). A mixture of epimeric aflatoxins Q_1 (2, 341 mg, obtained mainly by procedure A) was dissolved in methylene chloride–methanol–hexane. Upon concentration 141 mg (41%) of the natural epimer crystallized as very fine needles in two crops. A third crystalline crop (98 mg, 29%) obtained from the same solvent mixture turned out to be a mixture (mainly unnatural epimer) of the two epimers as judged by the NMR spectrum in Me_2SO-d_6. The remaining mother liquor was rechromatographed twice [1. chromatography: 2 20 × 20 × 0.1 cm Analtech silica gel chromatoplates, eluted with chloroform–ethanol–hexane (10:2:1 v/v/v); 2. chromatography 2 20 × 20 × 0.1 cm Analtech silica gel chromatoplates, eluted with methylene chloride–ethyl acetate (2:1 v/v), R_f 0.15] to yield 55 mg of solid residue from which 38 mg (11%) of pure (as judged by the NMR in Me_2SO-d_6) unnatural epimer of aflatoxin Q_1 (2) crystallized from the solvent mixture used above. The two epimers showed the following physical properties.

Aflatoxin Q_1: mp 265° dec; uv max (100% C_2H_5OH) 223, 242 (sh), 267, 366 nm (ϵ 22250, 10800, 11800, 18700); uv min (100% C_2H_5OH) 252, 286 nm (ϵ 8600, 1000); ir ($CHCl_3$) 3600, 1780, 1710, 1640, 1610, 1575 cm^{-1}; MS (70 eV) *m/e* (rel intensity) 329 (23), 328 (100, M^+), 313 (7), 312 (15), 310 (7), 299 (9); NMR, 90 MHz (Me_2SO-d_6) δ 2.21 (A part of ABX, 1, J_{AB} = 18, $J_{AX} \approx$ 1.5 Hz), 2.77 (B part of ABX, 1, J_{AB} = 18, J_{BX} = 6.5 Hz), 3.19 (s, H_2O from the solvent, exchanging with ROH of the substance), 3.85 (s, 3), 4.69 (d, 1, J = 7 Hz, of t, J = 2 Hz), 5.29 (t, 1, J = 2 Hz) overlapping with 5.38 (doubletoid m, X part of AEX, 1), 6.62 (t, 1, J = 2 Hz) overlapping with 6.65 (s, 1), 6.84 (d, 1, J = 7 Hz); CD (100% C_2H_5OH) 222, 236, 244, 255, 269, 290, 347 nm (θ −72200, −9500, −15300, −4100, − 10200, ±0, −26700), estimated absolute error in θ ±2500 deg cm^2/dmol.

Epiaflatoxin Q_1: mp 235° dec; uv max (100% C_2H_5OH) 224, 243 (sh), 267, 366 nm (ϵ 18200, 8400, 10000, 16500); uv min (100% C_2H_5OH) 252, 286 nm (ϵ 7300, 1200); ir ($CHCl_3$) 3600, 1775, 1710, 1635, 1605, 1575 cm^{-1}; MS (70 eV) *m/e* (rel intensity) 329 (25), 328 (100, M^+), 326 (24), 313 (9), 312 (21), 310 (7), 299 (10); NMR, 90 MHz (Me_2SO-d_6) δ 2.24 (A part of ABX, 1, J_{AB} = 18, J_{AX} = 1.5 Hz), 2.80 (B part of ABX, 1, J_{AB} = 18, J_{BX} = 7 Hz), 3.23 (s, H_2O from solvent, exchanging with ROH of the substance), 3.86 (s, 3), 4.71 (d, 1, J = 7 Hz, of t, J = 2 Hz), 5.34 (t 1, J = 2 Hz) overlapping with 5.41 (doubletoid m, X part of ABX, 1), 6.65 (t, 1, J = 2 Hz) overlapping with 6.68 (s, 1), 6.85 (d, 1, J = 7 Hz); CD (100% C_2H_5OH) 222, 244, 257, 292, 321, 345, 375 nm (θ −10600, −7200, −15500, ±0, −9600, −3000, −21500), estimated absolute error in θ ±2500 deg cm^2/dmol.

11-Hydroxy-5,7-dimethoxycyclopenteno[2,3-*c*]coumarin (5) (Silver(I) Oxide–Sodium Hydroxide Reaction). To a stirred solution of 3 (26 mg, 0.1 mmol) in dichloromethane–methanol–water (11 ml, 4:4:1 v/v/v) in an ice bath was added in succession silver(I) oxide (70 mg, 0.3 mmol) and aqueous sodium hydroxide (0.5 ml, 0.4 *N*, 0.2 mmol). The reaction mixture was filtered through a silica gel column (6 g) after 2.5 hr, and the column washed with 250 ml of chloroform–methanol (3:1 v/v). The resulting solution was diluted with 500 ml of chloroform and washed once with 4 *N* aqueous ammonium chloride (300 ml) and once with distilled water (300 ml). The resulting organic phase was diluted with benzene (100 ml) and evaporated to dryness under reduced pressure. The residue was chromatographed (one 20 × 20 × 0.05 cm Analtech silica gel chromatoplate, chloroform–ethanol–hexanes, 10:2:1 v/v/v) to afford 3 (4.4 mg of a solid, R_f 0.73, 17% recovered) and 5 (10.2 mg of a solid, R_f 0.59, 46% based on amount of 3 reacted). Recrystallization of 5 from chloroform–ethanol–hexane gave pale yellow needles: mp 217–218°; ir (KBr) 3460, 2956, 1750, 1680, 1610, 1065 cm^{-1}; MS (70 eV) *m/e* (rel intensity) 276 (M^+, 100), 230 (24), 245 (16), 233 (39), 205 (16), 69 (19); NMR (Me_2SO-d_6) δ 6.6 (AB pattern, 2, protons on C-6 and C-8), 5.45 (m, 1, proton on C-11), 3.96, 3.92 (two s, 6, $-OCH_3$), 3.32 (broad s, 1, –OH), 2.90 (d of d, 1, J = 6 and 18 Hz, C-9), 2.30 (d of d, 1, J = 2 and 18 Hz, C-9); uv max (100% C_2H_5OH) 216, 240 (sh), 248 (sh), 258 (sh), 357 nm (ϵ 23600, 13960, 13250, 11300, 27000).

11-Hydroxy-5,7-dimethoxycyclopenteno[2,3-*c*]coumarin (5) (Thallous Ethoxide–Hydrogen Peroxide Reaction). To a solution of 3 (24.3 mg, 0.09 mmol) in dichloromethane (8 ml) in an ice bath was added a solution of thallous ethoxide (27.3 mg, 0.11 mmol) in dichloromethane (2 ml) and a solution of hydrogen peroxide (98%, 16.8 mg, 0.48 mmol) in methanol (3 ml). After 72 hr the reaction mixture was filtered through a silica gel column (6 g), and the column was washed with 300 ml of chloroform–methanol mixture (3:1 v/v). The resulting solution was evaporated and the residue chromatographed (one 20 × 20 × 0.05 cm Analtech silica gel chromatoplate, chloroform–ethanol–hexanes, 10:2:1 v/v/v) to afford 3 (13.6 mg, R_f 0.73, 56% recovered) and 5 (8.1 mg, R_f 0.59, 71% based on amount of 3 reacted).

Hydrogenation of 3. Compound 3 (4.8 mg, 0.0185 mmol) in absolute ethanol (6 ml) was hydrogenated in a Hösli microhydrogenator using a 10% Pd/C catalyst (30 mg) at 22° (730 mm). Hydrogen absorption was complete after an uptake of 0.91 ml (270 min). The catalyst was collected on a Celite filter pad and washed with chloroform. The combined filtrates were evaporated to dryness and the residue was chromatographed using a 0.25 mm silica gel thin layer chromatoplate (Analtech Co.) and chloroform–ethyl acetate (2:1 v/v) as the solvent. The major product, 5,7-dimethoxycyclopenteno[2,3-c]coumarin (4, 3.5 mg, 77%), was located by visualizing under long wavelength ultraviolet light (pale blue fluorescence), and eluted off the silica gel with chloroform–methanol (3:1 v/v). Ir, uv, and melting point were identical with those of an authentic sample; MS (70 eV) *m/e* 246 (molecular ion); mp 183–184° after one recrystallization from ethanol. A mixture melting point with an authentic sample showed no depression. Uv max (C_2H_5OH) 248, 257, and 325 nm (ϵ 7700, 7000, 16100); ir ($CHCl_3$) 1706, 1608, and 1567 cm^{-1}.

Hydrogenation and Hydrogenolysis of 5. Compound 5 (4.6 mg, 0.016 mmol) in absolute ethanol (6 ml) was hydrogenated in a Hösli microhydrogenator using a 10% Pd/C catalyst (30 mg) at 22° (730 mm). Hydrogen absorption became very slow after an uptake of 1.0 ml (4.5 hr, 80% of theoretical value). The 5,7-dimethoxycyclopenteno[2,3-c]coumarin (4) was isolated as described for the hydrogenation of 3, yield 3.2 mg (78%); ir, uv, and melting point identical with those of the authentic sample.

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Registry No.—1, 1162-65-8; 2 natural, 52819-96-2; 2 epimer, 56648-94-3; 3, 1150-42-1; 4, 1146-71-0; 5, 56599-31-6; thallium(I) ethoxide, 20398-06-5; silver(I) oxide, 1301-96-8.

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Geometric Isomers of 11,12-Dehydro-15-demethyl-β-axerophtene. New Geometric Isomers of Vitamin A and Carotenoids III[1]

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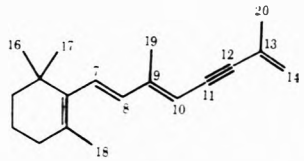
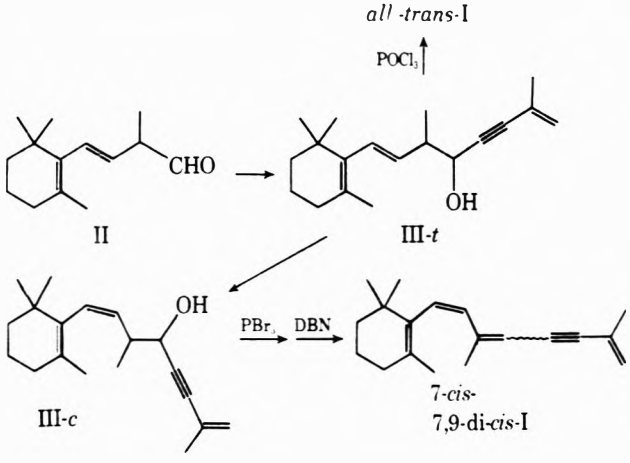
In connection with the photochemical studies of the polyenes in the vitamin A series,[3] we were in need of a complete set of geometric isomers of such a pentaene. The compound 11,12-dehydro-15-demethyl-β-axerophtene (I) was chosen because it has only four isomers and a procedure to the all-trans isomer is in the literature.[4] A modification of



I

this procedure may lead to the other isomers. The preparation and spectroscopic properties of all four isomers of I including the two sterically crowded 7-cis isomers, are now described here.

Aldehyde II, known as the iso-C_{14} aldehyde, was prepared according to the literature procedure.[5] Reaction of II, instead of the conjugated C_{14} aldehyde,[4] with the Grignard of 3-methyl-3-buten-1-yne gave the C_{19} alcohol III-*t* as the only product in high yield [ir 3400 (OH) and 960 cm^{-1} (trans C=C); NMR $J_{7,8}$ = 16 Hz (trans)]. Because of the introduction of a second asymmetric carbon through the Grignard reaction, the presence of diastereomers in III-*t* was expected. This is clearly shown by its NMR spectrum, in which H-8, H-10, and CH_3-19 all appear as doublets (in addition to splittings due to spin–spin coupling).



Dehydration of III-*t* with $POCl_3$–pyridine gave a yellow oil. Similar to the reaction from an isomer of III-*t* from C_{14} aldehyde,[4] this reaction appears to give only *all-trans*-I [ir 2200 (C≡C), 970 (trans C=C), 820 cm^{-1} (trisubstituted double bond); NMR (Table I)]. The absence of detectable amounts of the 9-cis isomer in the dehydration reaction is somewhat surprising but appears often in vitamin A synthesis.[6]

One-way sensitized irradiation[3] of the C_{19} alcohol (III-*t*) with β-acetonaphthone gave the 7-cis isomer (III-*c*) in quantitative yield. The cis geometry is revealed by the magnitude of the vinyl coupling constant ($J_{7,8}$ = 12.0 Hz) in NMR and the 730-cm^{-1} band in ir. Alternatively, the compound was also obtained by reaction of 7-cis-iso-C_{14} aldehyde (II-*c*) with the Grignard from 3-methyl-3-buten-1-yne.

Dehydration of the more hindered III-*c* presented some difficulties. With reagents such as proton acids or $POCl_3$ molecular rearrangements occurred, giving complex mixtures. Therefore, instead, dehydration was accomplished in two steps via the intermediacy of the corresponding bromide which was prepared by reaction of III-*c* with PBr_3. To avoid possible electrocyclization of the product at elevated temperatures, the mild dehydrobrominating reagent diazabicyclo[4.3.0]nonene (DBN)[7] was used.

The mass spectrum of the product (*m/e* for M = 254) agrees with that of a $C_{19}H_{26}$ hydrocarbon. Its ir spectrum indicates the retention of the 7-cis geometry (720 cm^{-1}) with no noticeable absorption between 960 and 980 cm^{-1} for 7-trans products. Its NMR spectrum is also in agreement with the presence of the 7-cis geometry only. However, it also shows the presence of two isomers in a relative ratio of 3:2. Although the isomers have not yet been isolated, the key NMR signals, even in a mixture, are sufficiently well resolved for assignments (Table I). The major product was assigned with the 7,9-di-cis geometry. The 7-cis geometry is evident from the coupling constant and the high field shift of CH_3-13.[8] The assignment of the 9-cis geometry was based on the low-field H-8 signal as a result of deshielding by steric polarization by the cis ethynyl group.[9] This downfield shift is in fact characteristic of all 9-cis isomers in the vitamin A series.[9,10] The minor isomer with a higher field H-8 signal therefore must have the 7-cis geometry.

Table I
NMR Spectral Characteristics of Geometric Isomers of 11,12-Dehydro-15-demethyl-3-axerophtene[a]

Isomer	H_7	H_8	H_{10}	CH_3-20	CH_3-19	CH_3-13[b]	$J_{7,8}$[c]
all-trans	6.20	6.08	5.51	2.04	1.86	1.68	14.5
7-*cis*	5.97	6.07	5.64	1.99	1.93	1.54	12.0
9-*cis*	6.21	6.73	5.32	1.86	1.84	1.68	15.0
7,9-Di-*cis*	5.95	6.74	5.46	1.95	1.76	1.54	12.2

[a] HA-100, solvent $CDCl_3$-Me_4Si. [b] Chemical shifts in parts per million. [c] Coupling constants in hertz.

These two isomers exhibit expected photochemical properties for polyenes in this series[3b] in that upon photosensitized irradiation (with benzanthrone or benzo[*a*]pyrene and light >400 nm) they were completely converted to the less hindered 7-trans isomers. The major product in the stationary state mixture (~55% by NMR) is *all-trans*-I. The minor product (~45%) shows NMR characteristics (Table I) only consistent with 9-*cis*-I, i.e., low-field H-8 (9-cis) and a large $J_{7,8}$ (7-trans).

The reaction sequence described above for 7-cis isomers of I suggests a promising route to the unknown 7,11-di-cis isomers of vitamin A[11] by replacing the C_5 enyne with isomers of 3-methyl-2-penten-4-yn-1-ol (cis/trans "pentol"). This and other routes to such new isomers are actively being studied in our laboratory.

Experimental Section

All NMR spectra were recorded on a Varian HA-100 spectrometer with $CDCl_3$ as solvent and Me_4Si as internal standard. Ir spectra were recorded on a Beckman IR-10 and MS on a Hitachi Perkin-Elmer RMU-6D unit.

Preparation of Iso-C_{14}-aldehyde II. The trans isomer was prepared from β-ionone by a modified procedure[3b] of that of Oediger and Eiter.[5] The cis isomer was obtained by sensitized irradiation as reported earlier.[3b]

Preparation of C_{19} Alcohol III-*t*. To an ether solution of ethylmagnesium bromide, prepared from 30 g of ethyl bromide and 6 g of Mg, was added 20 g of 3-methyl-3-buten-1-yne diluted with 30 ml of ether. After 4 hr, 30 g of II-*t* was added dropwise. After completion the solution was heated to 50°C for 1 hr and then allowed to stand for 8 hr. The mixture was worked up with a saturated NH_4Cl solution. Extraction with ether, drying over $MgSO_4$, and evaporation of ether gave the C_{19} alcohol III-*t* [ir 3400 (OH), 960 (trans C=C), 895 cm^{-1} (exo CH_2); NMR 1.02 (s, CH_3-16, 17), 1.15, 1.16 (s, d, CH_3-19, diastereomers), 1.68 (s, CH_3-18), 5.39, 5.31 (d, d, J = 16.0 Hz, H-8), 5.97 ppm (d, J = 16.0 Hz, H-7)].

Preparation of III-*c*. It was prepared either by sensitized irradiation of III-*t*[3b] or by a similar procedure as described above for III-*t* except using II-*c* instead. [III-*c*: ir 3400 (OH), 895 (exo CH_2), 730 cm^{-1} (cis C=C); NMR 1.02 (s, CH_3-16, 17), 1.10 (s, CH_3-19), 1.60 (s, CH_3-18), 5.58, 5.45 (d, d, J = 11.5, H-8), 5.67 ppm (d, J = 11.5 Hz, H-7)].

Preparation of *all-trans*-II. A solution of 2 g of III-*t* in 6 ml of toluene was added to 1.2 g of $POCl_3$ in 4 ml of pyridine and 10 ml of toluene. The mixture was refluxed for 45 min, cooled, and

poured over ice, then extracted with ether. The ether solution was dried over $MgSO_4$ and solvent evaporated to give crude *all-trans*-I. The product was purified by passing through a short silica gel column using benzene–hexane solvent mixture [ir 2200 (C≡C), 1620 (conjugated double bonds), 970 (trans C=C), 895 (exo CH_2), and 820 cm^{-1} (trisubstituted double bond); NMR (Table I)]. These data are in agreement with those published for I-*t*.[5]

Preparation of 7-Cis Isomers of I. To 2 g of III-c in 20 ml of ether was added at 0° a solution of 2 g of PBr_3 in 10 ml of ether. The mixture was stirred at room temperature for 2 hr, then poured over ice and extracted with ether. Upon evaporation of solvent, the crude bromide was obtained [MS *m/e* (M) 335, ir no OH].

Without further purification the bromide was taken in 20 ml of benzene, previously distilled over Na. To this was added 3 ml of DBN in 10 ml of benzene. The mixture was stirred at 50°C for 1 hr followed by 12 hr at room temperature. Then the mixture was poured over ice and extracted with ether. Upon evaporation of ether, a yellow oil was obtained. It was chromatographed over silica gel using petroleum ether (bp 30–60°) as solvent. The early fractions contained mixtures of 7-*cis*- and 7,9-di-*cis*-I [ir 2200 (C≡C), 895 (exo CH_2), 820 (trisubstituted C=C), and 720 cm^{-1} (cis C=C); NMR (Table I)].

Acknowledgment. The work was partially supported by grants from the Public Health Services (EY00918, AM17806).

Registry No.—*all-trans*-I, 56744-00-4; 7-*cis*-I, 56744-01-5; 9-*cis*-I, 56744-02-6; 7,9-di-*cis*-I, 56744-03-7; *cis*-II, 56013-06-0; *trans*-II, 56013-05-9; III NS isomer, 56744-04-8; 3-methyl-3-buten-1-yne, 78-80-8.

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Vicinal Chlorination of Alkyl Chlorides with Molybdenum(V) Chloride[1]

Summary: The reaction of alkyl chlorides with an excess of molybdenum(V) chloride leads to vicinal chlorination in fair to excellent yields.

Sir: We wish to report that alkyl chlorides and haloalkanes in general react with an excess of molybdenum(V) chloride under mild conditions to produce vicinal dichloroalkanes in fair to excellent yields.[2] The preparation of 2,3-dichlorobutane illustrates a typical procedure. A solution of 2-chlorobutane (0.47 g, 5.0 mmol) in methylene chloride (7 ml) was added over an 8-min period to a vigorously stirred solution of molybdenum(V) chloride[3] (3.46 g, 12.7 mmol) in methylene chloride (6 ml) at room temperature with the rigorous exclusion of moisture and oxygen.[4] The resulting mixture was stirred for 8 hr. Direct chromatography of the reaction mixture over low activity alumina followed by analysis indicated the presence of *dl*-2,3-dichlorobutane (58%) and *meso*-2,3-dichlorobutane (38%). Results obtained on treatment of other representative halides are given in Table I.

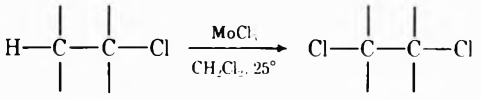

Table I
Vicinal Chlorination of Various Alkyl Halides with $MoCl_5$[a]

Alkyl halide (concn, *M*)	Products	Yield, %[b] (recovered RX, %)
2-Chlorobutane (0.4)	*meso*-2,3-Dichlorobutane	38
	dl-2,3-Dichlorobutane	58
Chlorocyclopentane (0.5)	*cis*-1,2-Dichlorocyclopentane	88
	trans-1,2-Dichlorocyclohexane	<1
Chlorocyclohexane (0.5)	*cis*-1,2-Dichlorocyclohexane	75
	trans-1,2-Dichlorocyclohexane	<1
3-Chloro-2-methylpentane (0.5)	2,3-Dichloro-2-methylpentane	46
2-Chloro-2,3-dimethylbutane (0.5)	2,3-Dichloro-2,3-dimethylbutane	40
1-Chlorooctane (0.5)	1,2-Dichlorooctane	<5 (>90)
2-Chlorohexane (0.4)	*erythro*-2,3-Dichlorohexane	1
	threo-2,3-Dichlorohexane	36
	dl-3,4-Dichlorohexane	14
	meso-3,4-Dichlorohexane	2
2-Bromobutane (0.3)	*meso*-2,3-Dichlorobutane	38
	dl-2,3-Dichlorobutane	54

[a] Unless otherwise indicated all additions were carried out in CH_2Cl_2 solution at room temperature under an inert atmosphere of dry nitrogen. The concentration of molybdenum(V) chloride was ~1.0 *M*. [b] Yields were determined by quantitative vapor phase chromatography and are based on alkyl halide.

This reaction sequence seems applicable to the vicinal chlorination of secondary and tertiary alkyl halides containing either a secondary or tertiary vicinal carbon. Primary alkyl chlorides are not chlorinated under these conditions.

Several specific points concerning the data in Table I deserve brief comment.

First, chlorination of alkyl chlorides appears to be regiospecific. Substitution is virtually exclusively vicinal and highly selective: tertiary vicinal carbons are chlorinated in exclusive preference to secondary vicinal carbons which in turn undergo chlorination in exclusive preference to primary vicinal carbons.

Second, chlorination is stereospecific. Cyclopentyl and cyclohexyl chloride yield exclusively *cis*-1,2-dichlorocyclopentane and *cis*-1,2-dichlorocyclohexane, respectively.

Third, vicinal chlorination is not limited to alkyl chlorides. Similar results, accompanied by halide–chloride exchange,[2] are obtained with alkyl bromides.

Fourth, the products of these reactions provide convincing evidence that vicinal chlorination with molybdenum(V) chloride does *not* proceed via the free-radical pathway characteristically observed in the chlorination of alkyl halides with molecular halogens and related halogenating agents. Specifically, chlorination with molybdenum(V) chloride occurs essentially exclusively at the carbon α to the halogen-bearing carbon.[5] In addition, vicinal chlorination of cyclopentyl and cyclohexyl chloride is unaccompanied by the formation of the respective *trans*-1,2-dichlorocycloalkane, typically observed when vicinal halogenation is performed using molecular halogen.[9,10]

Finally, chlorination of 2-chlorohexane yields, in addition to 2,3-dichlorohexanes, a substantial fraction of 3,4-dichlorohexane, indicating that, at least in this instance, chlorine migration has occurred. Such migration is reminiscent of the hydrogen migration observed during certain transition metal catalyzed olefin hydrogenations[11] and the thermal decomposition of certain transition metal alkyls.[12] These processes are believed to involve repetitive metal hydride elimination and addition steps. An analogous sequence of metal *halide* elimination and addition[13] may be involved in the overall reaction sequence leading to the formation of 3,4-dichlorohexane.

Further observations relative to the mechanism of these reactions will be presented in later papers.

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(1) Supported by the Research Corporation and the donors of the Petroleum Research Fund, administered by the American Chemical Society.
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(5) The relative reactivities of alkyl fluorides, chlorides, and bromides toward free-radical halogenation vary with the nature of the halide and the structure of the alkyl moiety. However, in general, carbons vicinal to the halogen-containing carbon are characterized by a *diminished* relative reactivity.[6] A particular exception is the free-radical bromination of alkyl bromides in which vicinal bromination is actually favored.[7,8]
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(14) Exxon Summer Research Fellow, 1974.

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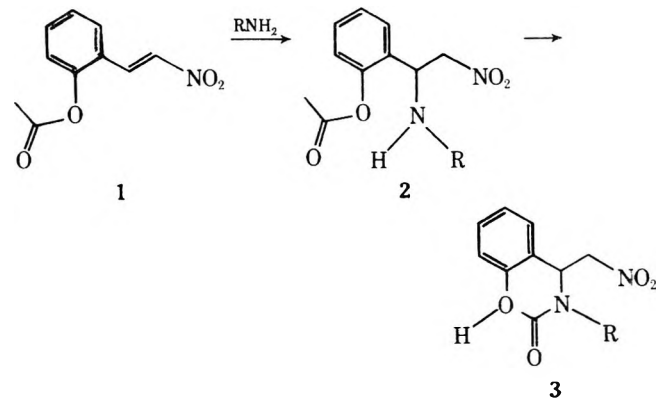
Anomalously Large Steric Inhibition of Intramolecular *O,N*-Acyl Transfer to Amino Acid Esters

Summary: Michael adducts of o-acetoxy-β-nitrostyrene and amino acid esters are found to undergo quantitative intramolecular, *O,N*-acyl transfer at anomalously slow rates; a model which rationalizes slow intramolecular acyl transfer to hindered amino acid derivatives is proposed.

Sir: Earlier,[1] we reported experiments demonstrating amide formation by intramolecular acyl transfer to an amine, trapped by a prior reaction with an electrophilic site. In the accompanying communication,[2] we apply this principle to peptide synthesis. Here we demonstrate and rationalize an unexpected, large steric inhibition of intramolecular *O,N*-acyl transfer which defines the scope of the principle.

In our earlier study, carbonyl functions were employed as amine trapping sites, and unwanted *O*-acyl transfer and dehydration were observed. To avoid these complications, we have investigated nitrostyrene derivatives. Reactions of **1** with primary amines yield Michael adducts in nearly quantitative yield;[3] rate constants fell in the range of 0.2 to 4 M^{-1} min^{-1}.[4]

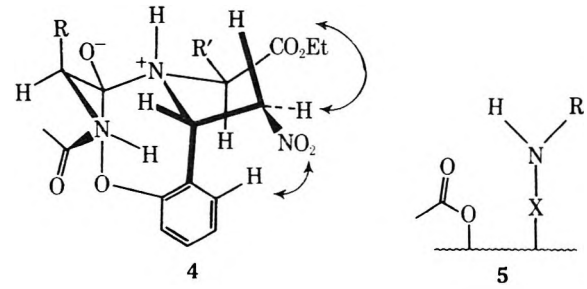
Most strikingly, the intramolecular *O,N*-acyl transfer, **2** → **3**, which can occur via an apparently favorable cyclic six-atom linkage, is slow and is subject to an exceedingly large steric effect. Thus, in acetonitrile a rate constant of 0.02 min^{-1} is observed at 25° for NH_2—R′=HGlyOEt, while for methyl esters of Ala, Phe, and Val, respective values of 2×10^{-4}, 7×10^{-5}, and 2×10^{-5} min^{-1} are observed. The rate ratios of 100 for Gly/Ala and 1000 for Gly/Val may be contrasted with the respective values of 4 and 10, observed for



the corresponding intermolecular aminolysis of *p*-nitrophenyl esters.[5]

Replacing acetoxy by carbobenzoxyglycyl resulted in no systematic change in acyl migration rate. More surprisingly, an attempt to buttress the acyloxy group by using 3,5-dibromo-2-acetoxynitrostyrene did not result in a significant change in acyl transfer rate or rate span. With alanine methyl ester **1** reacts to give two diastereomers, **2**, which rearrange to **3** at rates differing only by a factor of two.

A model which rationalizes the anomalous steric effect can be built from a successful model for steric effects on rates of aminolysis of peptide *p*-nitrophenyl esters.[5] Substitution of the additional linkages of **2** into the latter model yields **4** or a diastereomer as the structure of the



transition state for the conversion **2** → **3**. Steric interactions not shared with **2** or **3** arise in **4** between the nitromethylene group and the ester or alkyl substituent of the amine component. Stabilization of **4** through conformational changes is not possible, since the immediate environment of the carbon of the benzylamine moiety is bounded by the 3-H of the aromatic function, the alkyl substituent of the acyloxy function, and the nitromethylene group. The latter group encounters an interaction of the type found in a 1,3-diaxially substituted cyclohexane for any transition state **4** except that derived from glycine.

From this model, one predicts that anomalous steric sensitivity is expected for acyl transfer in all derivatives **5** except those in which the electrophilic site X is small and minimally substituted; e.g., for X equal to sulfur, methylene, or sp^2 carbon. In the accompanying communication we report normal transfer rates for a methylene system. [An attempt to prepare and study a sulfur case (derived from 1-acetoxy-2-chlorosulfenyl-4-chloronaphthalene) resulted in very slow transfer rates in an unhindered case (3×10^{-4} min^{-1} for HGlyOEt).]

Although it is difficult to envisage a practical reversible trapping involving an sp^2 electrophile, it was of interest to study acyl transfer in such a system, and ethyl esters of *N*-(2-acetoxyphenyl)glycine, alanine, and valine were prepared and studied.[6] Most surprisingly, *O,N*-acyl transfer in the unhindered Gly case is exceedingly sluggish, showing rate constants of 5.5×10^{-4} ($CDCl_3$), 5.0×10^{-4} (PhH),

and 2.0×10^{-4} min^{-1} (CD_3CN). The Gly/Ala rate ratios are 2.8 ($CDCl_3$) and 3.3 (PhH), and the Gly/Val rate ratios are 8 (CD_3CN) and 22 ($CDCl_3$); they are thus comparable with the intermolecular cases.[7]

A successful intramolecular amide synthesis must exhibit (1) a rapid intramolecular *O,N*-acyl transfer in nonhindered cases and (2) a small sensitivity to steric effects. Our model has successfully rationalized and predicted steric sensitivity. We lack a satisfactory means of predicting nonhindered acyl transfer rates.[10] In this study, nearly a 10^6-fold range of rate constants have been observed for acyl transfer via cyclic five- or six-atom linkages, the noteworthy cases being the sluggish 5-ring acyl transfers observed for *o*-aminophenyl derivatives (low nucleophilicity of N and strain in the intermediate are important contributors)[11] and the very rapid 6- and 7-ring acyl transfers to carbinolamines.[1]

Although *O,O*-acyl transfers are well documented and almost invariably rapid,[10] the more interesting *O,N*-acyl shifts are rarer, and rapid cases are unusual. Despite the advanced state of knowledge concerning the principles of acyl transfer in biological systems, there remains a remarkable disparity between the facility of enzymatic acyl transfer and the ease with which it can be achieved in model systems.

Acknowledgment. Financial support from the National Institutes of Health (GM 13453) is gratefully acknowledged.

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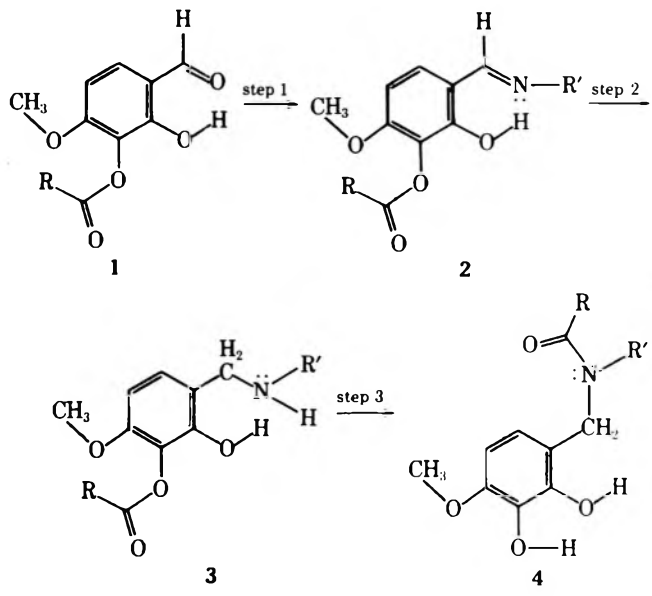
Peptide Bond Formation by the Prior Amine Capture Principle

Summary: Amino acid esters react with 4-methoxy-3-acyloxy-2-hydroxybenzaldehydes to form imines, which upon reduction undergo intramolecular acyl transfer to form *N*-4-methoxy-2,3-dihydroxybenzyl amides, useful in peptide synthesis.

Scheme I



Sir: As outlined in Scheme I, we wish to report the feasibility of peptide bond formation through a new principle of intramolecular acylation which is preceded by amine capture.[1]

Step 1—Amine Capture. Imine formation from salicylaldehydes occurs with unusually large rate and equilibrium constants.[2] Thus, **1**[3] (R = ZGly) reacts with methyl esters of Ala, Leu, or Phe (CH_3CN, 25°, 0.2–0.3 *M*) with half-times of 4–5 min. Only small rate changes result from variation of R ($t_{1/2}$ = 5–6 min for R = ZAla, R′ = HAlaOMe; R = HPhe, R′ = HValOMe). From two cases, rates appear to be ~10 times as fast as in DMSO.

Step 2—Reduction. As a reducing agent for **2**, pyridine borane in acetic acid[4] is mild, rapid, and quantitative. With a 1:1 molar stoichiometry, reaction is complete in <3 min; somewhat slower, complete reaction is also observed with 0.5 equiv of borane. In practice, solvent is removed from **2**, which is dissolved without purification in acetic acid, followed by pyridine borane. Disappearance of the yellow color of **2** indicates complete reaction, whereupon solvent is removed, and **3** is isolated by partitioning between an organic solvent and aqueous bicarbonate.

Step 3—Acyl Transfer. Although the unimolecular[5] isomerization, **3** → **4**, is somewhat retarded by polar solvents (slow in DMSO),[6] it occurs with half-times in the range of 0.2–4 hr in other media, including neat **3**. Thus for **3** (R = ZGly) transfer to captured Ala, Leu, and Phe occurs with half-times of 15, 40, and 70 min, respectively ($CDCl_3$, 25°). For **1** (R = ZPhe or ZAla) transfer to Ala gives $t_{1/2}$ values of 120 and 70 min. Steric effects at the amine substitution site are normal[7] (the Val/Gly rate ratio appears to be ~10). Preparatively, reaction times of 12 hr were convenient.

The yield for the conversion of **1** (R = ZGly) and 1 equiv of DL-HPheOEt to **4** was 85%.[8] Reaction of **1** (R = ZGly) with HLeuGlyOH tetramethylguanidine salt (DMSO, 25°, 5 min), followed by precipitation with ether, reduction, and isomerization, resulted in an isolated yield of 92% **4**.

Step 4—Cleavage. Cleavage of this **4** with *HBr/HOAc* yielded 84% HGly-L-LeuGlyOH, after neutralization. With trifluoroacetic acid in the presence of the trapping agent resorcinol, the 4-methoxy-2,3-dihydroxybenzyl moiety (DHMB) could be selectively cleaved.[9] Treatment of PhthGly(N-DHMB)PheOEt with Tfa (1 hr, 25°, 5 equiv of resorcinol) generated 100% PhthGlyPheOEt. A similar

treatment of ZGly(N-DHMB)PheOEt gave 83.3% ZGly-PheOEt and 11% HGlyPheOEt; the half-time for DHMB cleavage is 12 min in Tfa and in 3:1 Tfa–CH_2Cl_2.[10] The N-DHMB group is resistant to hydrogenation (Pd, 1 atm, 3 hr).[9]

Other Issues. 1. Racemization. Scheme I is expected to minimize normal racemization processes or other side reactions which occur at the acyl site,[11] but it is potentially vulnerable to epimerization at the amino site of **2**. To test the extent of this problem, we applied our isotopic dilution assay.[11] Reaction of **1** (R = Z-2-^{14}C-Gly) with H-L-Phe-GlyOEt was followed by conversion to **4** and treatment with Tfa, without purification of intermediates. Reaction times for **1** → **2** of 1.5 and 14 hr (0.2 *M*, CH_3CN) gave 0.1 and 0.3% DL tripeptide, respectively.[12] **2. Diketopiperazines.** The sequence HGlyProX readily forms diketopiperazines.[13] A similar problem is observed for HGly(N-DHMB)XY. When ZGly(N-DHMB)PheOEt was hydrogenolyzed (3 hr, Pd, HOAc), 62% diketopiperazine was isolated. The tripeptide HGly(N-DHMB)-L-LeuGlyOH formed diketopiperazine and HGlyOH slowly in DMSO solution. **3. Solubility.** As noted by Weygand,[9] substitution of *N*-benzyl groups on the amide backbone markedly increases peptide solubility. Unlike their counterparts which lack the N-DHMB group, ZGly(N-DHMB)-L-LeuGlyOH is soluble in chloroform and HGly(N-DHMB)-L-LeuGlyOH is soluble in DMSO. The solubilizing effect in these two cases appears to be at least an order of magnitude. **4. Protection of 1.** In order to be useful as a "safety catch" activated group, **1** must be convertible to an unreactive derivative. Reaction of **1** (R = ZGly) with NaH/DMF and benzyl bromide, followed by acidic ethyl orthoformate, generates 4-methoxy-3-ZGlyO-2-benzyloxybenzaldehyde diethyl acetal, which aminolyzes very slowly with peptide nucleophiles (with HGlyOEt in CH_3CN, $k_2 = 5 \times 10^{-6}$ sec^{-1}, 25°) and which is reconverted to **1** by treatment with Tfa for 1 hr.

Summary. The potential virtues of amide formation by prior amine capture and intramolecular acylation have been summarized previously.[1] Several of these (diminished steric effects on rate, first-order acylation rate, solubilization) have been demonstrated in this system; others are likely but remain to be proved. Although its feasibility awaits testing, the following scheme can be envisaged from the results here obtained. The amino acid ester of **1**, blocked by benzylation and acetal formation, could be introduced at the C terminus of a medium-sized peptide acid by conventional amide-forming reagents. Liberation of **1** at some later stage by Tfa treatment would permit a fragment condensation to yield a peptide bearing the solubilizing N-DHMB group at an N site of its amide backbone. A critical question concerns the minimum ratio of DHMB amide to secondary amide which is required for useful solubility effects. Until these questions are resolved, the importance of Scheme I is the demonstration of the feasibility of a new approach to amide synthesis.

Acknowledgment. Financial support from the National Institutes of Health (GM 13453) is gratefully acknowledged.

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(5) Although **3** is a catechol monoester, it is hindered. No aminolysis of the more activated **2** was observed over 24 hr in the presence of excess amine, nor were concentration effects on aminolysis seen. Rate constants were obtained from NMR measurements.
(6) Strikingly, this result is the opposite of that seen for intermolecular phenyl ester aminolysis.
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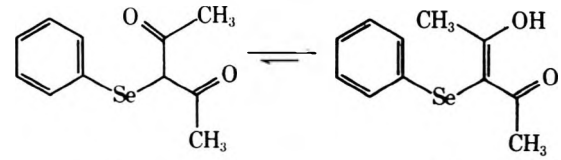
Heteroatom Directed Photoarylation. Photochemistry of an Organoselenide

Summary: Aryl selenide **1** undergoes photocyclization–rearrangement to give benzoselenophene **4**.

Sir: While the existence of carbonyl and thiocarbonyl ylides has been established,[1] the generation of selenocarbonyl ylides has not been reported.[2] In this paper, we communicate preliminary results concerning possible generation and rearrangement of a selenocarbonyl ylide and describe the first preparative organoselenium photoreaction.[3]

Recent success with photogeneration of carbonyl[4] and thiocarbonyl ylides[5] from 2-aryloxyenones and 2-thioaryloxyenones, with subsequent rearrangement to dihydrofurans and dihydrothiophenes, suggested that selenocarbonyl ylides might be generated from similarly structured 2-selenoaryloxyenones. Because of the known propensity of selenides to eject elemental selenium on exposure to light,[6] we initiated the investigation with aryl selenide **1**, which via enolic form **1b** was expected to give a relatively stable photoproduct, i.e., **4**.

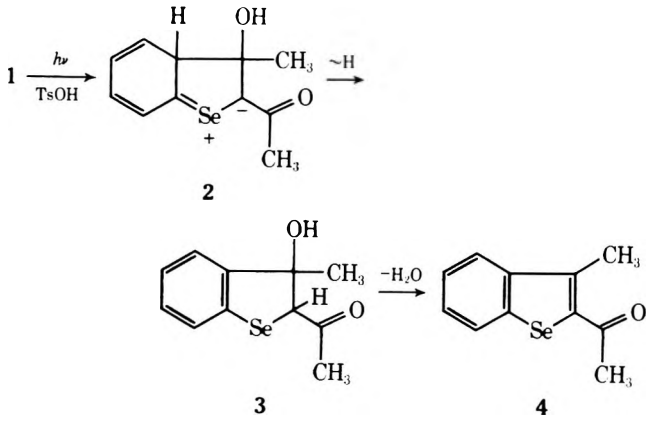


1a **1b**

The elegant method for α-arylselenenylation of ketone enolates developed principally by Sharpless[7] and Reich[8] was used to prepare **1**. Reaction of a suspension of the sodium enolate of acetylacetone in tetrahydrofuran with benzene selenyl bromide gave the required phenyl selenide (**1**), which exists predominately in enolic form **1b** (NMR analysis, 4 *M* **1** in $CDCl_3$, ratio of **1a**:**1b** = 1:9).

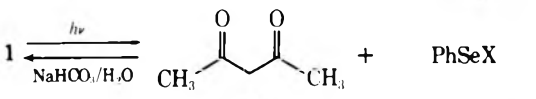
Preparative-scale Pyrex-filtered irradiation of **1** in benzene solution (0.05 *M*) saturated with *p*-toluenesulfonic acid at ~15° while purged with argon gave 2-acetyl-3-methylbenzo[*b*]selenophene (**4**) in 60% isolated yield (mp 93–95°, lit.[9] mp 94°). The mechanism[10] for the transformation **1** → **4** presumably involves photocyclization of **1b** to selenocarbonyl ylide (**2**), which undergoes rearrangement

to β-hydroxy ketone **3**; acid-catalyzed dehydration of **3** would give benzoselenophene (**4**).



That **3** actually is an intermediate in the conversion of **1** → **4** was demonstrated by photolysis of **1** in benzene-d_6 containing acetic acid (1 equiv) in a degassed[11] NMR tube; extended irradiation led to a mixture of products (vide supra), a major component (~30%) of which gave NMR singlets at δ 1.92 (3 protons), 2.31 (3 protons), and 4.86 (1 proton) and has been assigned structure **3** on the basis of chemical reactivity. Thus, treatment of the photolysis mixture with a catalytic amount of *p*-toluenesulfonic acid resulted in rapid disappearance of the three NMR singlets attributable to **3** together with an enhancement of absorptions due to the methyl resonances of benzoselenophene **4** (δ 2.60 and 2.73).

The photochemistry of **1** also includes cleavage of carbon–selenium bonds. Photoreaction of **1** in benzene-d_6 with *p*-toluenesulfonic acid was carefully monitored by NMR spectroscopy;[11] after brief irradiation, NMR analysis above δ 6.00 revealed that **1** (19%), benzoselenophene (**4**, 54%), and acetylacetone (**5**, 27%) were present. Interestingly, treatment of the crude photoreaction with aqueous sodium bicarbonate solution resulted in the disappearance of acetylacetone with concomitant formation of selenide **1**. Thus, a portion of photoexcited **1** must undergo carbon–selenium bond cleavage to generate acetylacetone (**5**) and PhSeX (**6**); on treatment with base, **1** is regenerated from **5** and **6**.[12] Formation of considerable acetylacetone occurred when **1** was irradiated in benzene–acetic acid sclution, and in pure benzene photocleavage was the predominant reaction.



5 **6**. X = OTs, OH

The high yield obtained in the conversion of **1** → **4** suggests that analogous photoreactions may be useful for synthesis of a variety of aryl annelated selenophenes. Perhaps more importantly, it is clear that appropriately structured organoselenium compounds may undergo interesting and synthetically useful photoreactions. Work in this area will continue.

Acknowledgment. This work was supported by the National Institutes of Health (Grant No. GM 21159-01).

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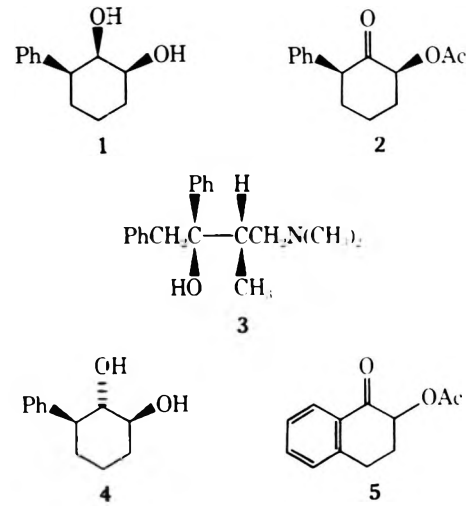
Asymmetric Synthesis and Absolute Stereochemistry of Some Cis and Trans Diols

Summary: A general method for the preparation of optically active cis and trans diols by asymmetric reduction of α-acetoxy ketones using a 2:1 Darvon–lithium aluminum hydride complex, is described. The absolute stereochemistry of these diols has been established by chemical methods.

Sir: In the course of some studies on the absolute stereochemistry of a variety of metabolites, cis dihydrodiols[1a] obtained from the microbial metabolism of aromatic substrates and trans dihydrodiols prepared by enzymatic hydration of arene oxides,[1b] we encountered difficulties in obtaining sufficient quantities of these compounds. Therefore, we have developed chemical methods for preparing optically active dihydro derivatives of several metabolites. The absolute stereochemistry of these compounds has been determined by chemical transformations to substances of known absolute stereochemistry.

We first chose the asymmetric synthesis of **1**, a dihydro derivative of a metabolite of biphenyl[2] by a species of *Beijerinckia*. Our approach focused on the chiral reduction of



the appropriate cis α-acetoxy ketone **2** which was prepared by mercuric acetate oxidation of 2-phenyl cyclohexanone;[3] it was reduced under conditions in which the molar ratios of ketone:$LiAlH_4$:*l*-Darvon (**3**) were 1:1.5:3, at 0°C for 16 hr in diethyl ether as described by Yamaguchi and Mosher,[4] to yield a mixture of cis,cis and trans,trans diols (38, 21%, respectively) **1** and **4**, which were separated by thick layer chromatography on silica gel using 40% ethyl acetate–hexane. An examination of the NMR spectrum (220 MHz) of **1** {$[\alpha]^{25}D$ +33.8° (*c* 2.16, methanol)} in the presence of the chiral shift reagent tris(3-heptafluorobutyryl-*d*-camphorato)europium(III) showed the enantiomeric excess to be 64% (Δ 0.23 ppm, Eu/S 0.16, $CDCl_3$). This enantiomeric excess was confirmed, and the absolute stereochemistry determined as (1*S*,2*R*)-dihydroxy-3(*S*)-phenylcyclohexane, by oxidizing **1** (sodium periodate in 70% aqueous ethanol, followed by bromine water in the presence of calcium carbonate), to (+)-2(*S*)-phenyladipic acid of known absolute stereochemistry.[5] Attempts to determine the enantiomeric excess present in the trans,trans diol **4** {$[\alpha]^{25}D$ +23.1° (*c* 3.21, methanol)} using Eu(hfbc)$_3$ and Eu(hfc)$_3$ were unsuccessful. A minimum value of 77% for the enantiomeric excess, as well as its absolute stereochemistry [(1*R*,2*R*)-dihydroxy-3(*R*)-phenylcyclohexane], was determined by oxidation to (−)-2(*R*)-phenyladipic acid.

The large enantiomeric excess present in the above compounds and our interest in the absolute stereochemistry of a variety of aromatic metabolites prompted us to examine this route for the preparation of the dihydro derivatives of the cis and trans 1,2-dihydro diols from naphthalene.[6] The intermediate **5**[7,8] was reduced with a 2:1 Darvon–lithium aluminum hydride complex to yield primarily (~30%) (−)-cis diol, **6** {$[\alpha]^{25}D$ −15.0° (*c* 2.43, methanol)}. Examination of its NMR spectrum in the presence of the above-mentioned chiral shift reagent showed a 20% enantiomeric excess (Δ 0.18 ppm, Eu/S 0.3, $CDCl_3$). The enantiomeric excess of the minor product [5%, (+)-trans diol **7**] was 62% {$[\alpha]^{25}D$ +70° (*c* 0.39, $CHCl_3$)} based on the value reported by Nakazaki et al.,[6b] who has established its absolute stereochemistry as (1*R*,2*R*)-dihydroxytetrahydronaphthalene. The absolute stereochemistry of **6** was established as *cis*-(1*R*,2*S*)-dihydroxy-1,2,3,4-tetrahydronaphthalene by conversion (acetylation and hydrogenolysis) to the known (−) - 2(*S*) - acetoxy - 1,2,3,4 - tetrahydronaphthalene.[9] Although the absolute stereochemistry of the metabolite was previously reported,[6a] that of the dihydro derivative was not.[11]

Work is currently in progress on extending this approach toward the synthesis of a variety of dihydro derivatives of metabolites from polycyclic hydrocarbons.

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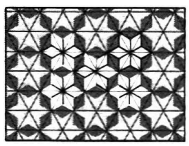

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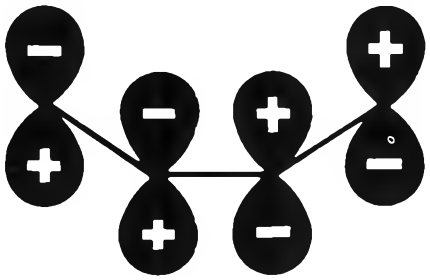

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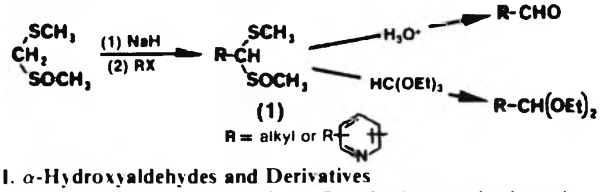
Methyl methylthiomethyl sulfoxide (MMTS, FAMSO)

A masked formaldehyde reagent

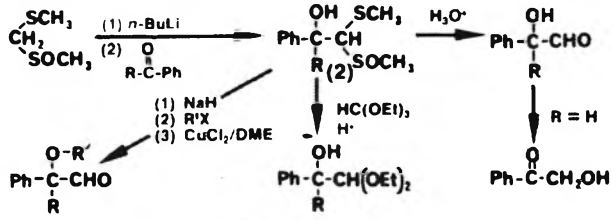
I. Aldehydes and Acetals

The carbanion derived from **methyl methylthiomethyl sulfoxide (MMTS, FAMSO)** reacts with alkyl halides to give aldehyde dimethylmercaptal *S*-oxides **(1)** which are readily hydrolyzed in acid to produce the corresponding aldehydes in excellent overa l yields.[1] As an aldehyde equivalent, **1** affords directly the diethyl acetal of the corresponding aldehyde upon treatment with ethyl ort noformate.[1] This scheme has been used successfully to prepare subs ituted pyridinecarboxaldehydes, whereas other methods fail.[2] This synthesis is especially suitable for labile aldehydes and is superior to the 1,3-dithiane method since the carbanion is easily generated and the hydrolysis of **1** can be accomplished under mild conditions.[1] Homologation of aromatic aldehydes can be achieved using MMTS.[3]



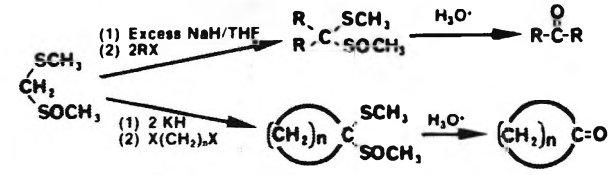
II. α-Hydroxyaldehydes and Derivatives

Treatment of the carbanion of MMTS with ketones leads to the α-hydroxyaldehyde dimethylmercaptal *S*-oxides **(2)** which can be similarly hydrolyzed to the corresponding ketones or converted to the ketals.[4] The intermediate **2** can also be formed by $NaBH_4$ reduction of a ketone compound **4** (*vide infra*).[5] Protected hydroxyaldehydes can be produced by methylation or benzylation of **2** followed by treatment with cupric chloride dihydrate in 1,2-dimethoxyethane (DME).



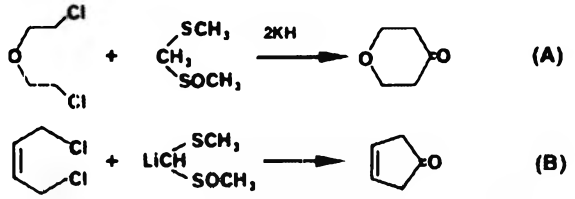
III. Dialkyl Ketones and Cyclic Ketones

In reactions analogous to the aldehyde synthesis, symmetrical dialkyl ketones,[6] substituted cyclobutanones,[7] and other cyclic ketones[8] can be prepared from MMTS.



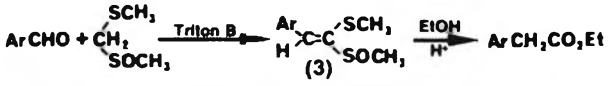
X = Br or TsO; n=2,3,4,5,6

The versatility of this method is further demonstrated by the synthesis of tetrahydro-γ-pyrone from bis(2-chloroethyl) ether (eq A) and the synthesis of 3-cyclopentenone from *cis*-1,4-dichloro-2-butene (eq B).

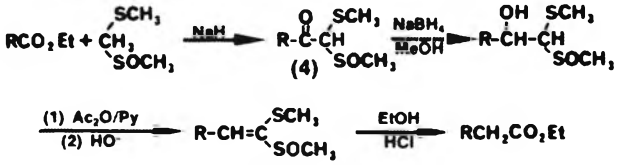


IV. Synthesis of Phenylacetic Acid Derivatives and Homologation of Esters

MMTS and aromatic aldehydes undergo Knoevenagel-type condensation to give 1-methylsulfinyl-1-methylthio-2-arylethylenes **(3)**. Acid-catalyzed ethanolysis of **3** produces ethyl arylacetates in hig yields.[9]

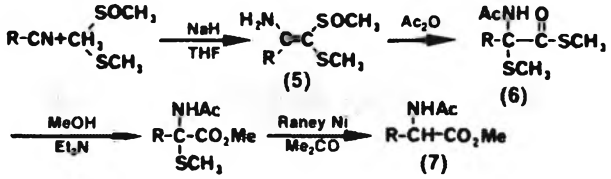


Homologation of esters can be achieved by the following sequence of reactions.[5]



V. Synthesis of α-Amino Acids from Nitriles

The carbanion of MMTS reacts with nitriles to form enaminosulfoxides **(5)** which, upon treatment with Ac_2O, afford the unusual rearranged product **6**. Ester exchange of **6** followed by desulfurization leads to the *N*-acetylamino acid ester **7**.[10] The synthesis of the methyl ester of DL-*N*-acetyl-5-hydroxytryptophan by this method is a remarkable example.[10]



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